PREDICTORS OF UNFAVORABLE TUBERCULOSIS TREATMENT OUTCOMES: PROSPECTIVE COHORT STUDY AMONG NOTIFIED CASES IN VIHIGA COUNTY, KENYA

BY

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DEDICATION

To my family for their unwavering support throughout this journey.

ABSTRACT

Each year, tuberculosis (TB) causes an estimated 10 million illnesses and 1.4 deaths globally. Kenya, one of 30 high-TB burden countries, has made progress in identifying more TB cases, but achieving the global treatment success rate target of >90% has remained a challenge. With TB mortality rate of 13% and treatment interruption rate of >5%, Vihiga is one of the counties with highest rates of unfavorable TB treatment outcomes in Kenya. Understanding their predictors is critical for improving TB epidemiology and advancing the global zero TB epidemic targets. A prospective cohort study was conducted among 291 notified TB patients from 20 health facilities in Vihiga County to: describe distribution of TB disease and treatment outcomes by patients' characteristics; identify determinants of treatment interruption; and investigate factors associated with survival distribution and the occurrence of mortality. Baseline and follow-up data were gathered using questionnaires, while qualitative data was obtained using treatment interruption tracing form and the mortality audit tool. Patients' demographic, socioeconomic, behavioral, and clinical characteristics were summarized descriptively, while probabilities of treatment completion, survival, and event-time intervals were estimated using Kaplan-Meier estimator. Log-rank test was used to quantify statistical differences in survival probability based on univariable patients' characteristics. Cox proportional hazard model was fitted to identify determinants of TB treatment interruption and factors associated with the occurrence of all-cause mortality through the calculation of hazard ratios (HR) at 95% Confidence Intervals (CI) and $p \leq 0.05$. Qualitatively, reasons for treatment interruption were identified thematically while causes of mortality, and associated circumstances were categorized by HIV status. Of the 291 patients, 72% were male, and nearly half were aged 25-34 years (23.4%) and 35-44 years (23.4%). During follow-up, 32 (11%) patients interrupted treatment while 45 (15%) died. Higher incidences of treatment interruption (59%, $p < 0.001$) and mortality (78%, $p < 0.001$) occurred during the intensive phase of treatment. Alcohol consumption (HR = 9.2, 95% CI; 2.6–32.5, $p < 0.001$); being female (HR = 5.01, 95% CI; 1.68–15.0, $p = 0.004$) and; having primary or lower of education level (HR = 3.09, 95% CI; 1.13–8.49, $p < 0.029$) increased risk for treatment interruption, while having a treatment supporter (HR = 0.33, 95% CI; 0.14–0.76, $p = 0.009$) was protective. The main reasons for treatment interruption were feeling better soon after beginning treatment and alcohol use. Severe illness (HR = 5.06, 95% CI; 1.59–16.1, $p = 0.006$); HIV coinfection (HR = 2.56, 95% CI; 1.28–5.12, $p = 0.008$); comorbidities (HR = 2.72, 95% CI; 1.36–5.44, $p = 0.005$); and smoking (HR = 2.79, 95% CI; 1.01–7.75, $p = 0.049$) were associated with increased risk of occurrence of mortality. Mortality among HIV-negative patients was ascribed to lung complications while advanced HIV disease was the leading cause of mortality among the HIV-positive. This study's findings indicate that interruption of treatment and mortality from TB remain problematic and occur early in the treatment. The study also acknowledges the important role person's characteristics play in the distribution of TB disease and predicting unfavorable treatment outcomes. Comprehensive public health interventions using multisectoral approach may help reduce rates of unfavorable TB treatment outcomes.

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LIST OF ABBREVIATIONS AND ACRONYMS

AFB: Acid-First Bacillus test

AHD: Advanced HIV disease

AIC: Akaike information criterion

AIDS: Acquired Immunodeficiency Syndrome

ART: Antiretroviral Therapy

CDC: Centre for Disease Control and Prevention

CHVs: Community Health Volunteers

CPHM: Cox Proportional Hazard Model

CPT: Cotrimoxazole Preventive Therapy

CTLC: County tuberculosis, leprosy and lung disease coordinator

DOTS: Directly observed therapy short-course

DRTB: Drug-Resistant tuberculosis

EPTB: Extra-Pulmonary tuberculosis

FBOs: Faith-Based Organizations

HC: Health Centre

HCWs: Healthcare Workers

HIV: Human Immunodeficiency Virus

IQR: Interquartile Range

LTBI: Latent Tuberculosis Infection

MOH: Ministry of Health

NTLDP: National Tuberculosis, Leprosy and Lung Disease Program

PLWHIV: People living with HIV

PTB: Pulmonary tuberculosis

SCH: Sub County Hospital

SCTLC: Sub County Tuberculosis, Leprosy, and Lung Disease Coordinator

SDGs: Sustainable Development Goals

TB: Tuberculosis

TLF: Treatment After Lost to Follow-up

TPT: TB Preventive Therapy

TSR: Treatment Success Rate

UNAIDS: Joint United Nations Program on HIV/AIDS

VCRH: Vihiga County Referral Hospital

WHO: World Health Organization

OPERATIONAL DEFINITION OF TERMS

Advanced HIV disease: A HIV positive patient who has CD4 cell count less than 200 cells/mm^3 or WHO clinical stage III or IV.

Akaike information criterion: A criteria which is the basis of cox proportional hazard model selection rank. Better fitting models will have a higher log-likelihood value and lower number of parameters, resulting in a lower value of the Akaike information criterion. It helps in selection of the best fitting CPH model.

All-cause mortality: Death from any cause of a patient receiving TB treatment and follow-up. Death of A TB patient can be TB or non-TB related.

ART Naïve: People living with HIV who have never been on antiretroviral therapy.

Bacilli: A bacteria that causes tuberculosis, *Mycobacterium tuberculosis*

Bacteriologically confirmed TB case: A patient whose biological specimen contains *Mycobacterium tuberculosis* as determined by smear microscopy, molecular, culture, or other WHO-approved rapid diagnostics.

Cadre: A group of people unified by a specific training in health science, e.g., nursing, public health or clinical medicine.

Cases: Patients with TB

Chemotherapy: Treatment of TB using a combination of several antibiotic agents.

Clinical condition: The patient's general clinical features, categorized as stable or severely ill. In this study, stable patients had mild signs and symptoms and could fully support themselves, whereas the severely ill patients were very sick. They exhibited severe signs and symptoms such as "respiratory rate > 30/min, temperature > 39 °C, heart rate > 120/min, inability to walk unaided, or severe malnutrition" at the time of treatment initiation.

Clinically diagnosed TB case: A patient who has been diagnosed with active tuberculosis by a clinician based on clinical parameters and other diagnostics but without bacteriological confirmation. Clinicians typically prescribe a complete course of TB treatment for such patients.

Clinicians: Health care workers including clinical officers, nurses, and medical officers. They offer TB diagnosis, treatment and follow-up.

Community Health Volunteer(s) (CHVs): Individuals who have been selected by community members to serve them. They are frequently given basic health care training in order to enable them provide disease prevention, health promotion, screening, and referral services.

Community Health Assistants/Officers (CHAs/CHOs): A health care professional who is engaged by the government or another organization to serve the community. They provide health promotion, disease prevention, basic curative services and referral.

Community health personnel: Comprises of community health volunteers and community health assistants/officers.

Comorbidity/Comorbid conditions: Includes all underlying medical conditions/diseases among TB patients apart from HIV, alcoholism and smoking.

Continuation phase of TB treatment: the four-month TB treatment period, which is typically preceded by two-months intensive phase.

Cured Rate: Proportion of bacteriologically confirmed PTB patients who were notified in a specified period that have completed a course of TB treatment and have negative second/fifth-month and sixth-month microscopy or culture sputum result, among the total bacteriologically confirmed PTB patients notified during the same reporting period.

Differentiated service delivery: client centres approach that simplifies and adapts health care services across cascade to reflect patients' preferences, expectations and needs of people while reducing unnecessary burden on patients and the health care system.

End TB strategy: A plan with elaborate milestones to end the TB epidemic, formulated by the World Health Organization to be implemented by all countries.

Extrapulmonary tuberculosis: any TB instance where organs other than the lungs are affected. The pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, and meninges are examples of these organs.

Faith-Based Organizations: Health care facilities sponsored by religious organizations.

Gene-xpert: Molecular-based test which, through polymerase chain reaction detects *Mycobacterium tuberculosis,* a bacillus associated with TB disease among human beings. The test also detects rifampicin resistance. Rifampicin is one of the most potent first line TB drugs.

Health care facility: Institution that offers diagnostic and treatment services

Health care workers/Health staff: All people offering wide range of health care services in health care facilities and the community

Health system: These are a combination of resources, organization, financing, staff and management that culminate in the delivery of health services to the population.

Infection: The entry, development, or multiplication of an infectious agent in the body of a man or an animal. An infection does not always result in illness, such as a latent TB infection.

Infection prevention and control: All measures aimed at ensuring the protection of persons who might be at risk of infection. These measures can be applied in health facilities and at the community.

Intensive phase: The first two months of TB treatment. Intensive phase treatment typically precedes the continuation phase for another four months.

Latent tuberculosis infection: A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest TB

Mycobacterium tuberculosis*:* Rode shaped, acid-fast bacteria that causes tuberculosis in human population.

National guideline: Integrated guideline for the management of TB, leprosy, and other lung diseases. It is the national resource that guides healthcare workers in all health facilities in Kenya in the management of TB.

New TB patient: A patient who has never been treated for TB or has been on anti-TB drugs for less than 1 month.

Notified TB patients: These are TB patients who have been recorded by health care providers (clinicians) in facility data collection tools, e.g., TB treatment registers and patient record cards, and also registered in the national electronic data base (TIBU) by sub-county TB, leprosy, and lung disease coordinators (SCTLCs), for care and follow up.

Nutritional category: An outcome of nutritional assessment e.g., severe malnutrition, moderate malnutrition, normal nutrition or overweight.

Predictors: These are demographic, socioeconomic, behavioral and clinical characteristics of TB patients that are likely to influence TB treatment outcomes.

Presumptive TB case: A patient who exhibits signs and symptoms of TB. Investigations are required to rule out TB.

Previously treated TB patient: A TB patient who has previously taken anti-TB medication for one or more months.

Public health facilities: These are institutions owned by the government where patients or individuals visit to receive, diagnostic, promotive, curative and rehabilitative health care services.

Pulmonary tuberculosis: Any case of TB, including miliary TB, that involves the tracheobronchial tree or the lung parenchyma.

Risk: This is a function of the probability of an adverse health effect and the severity of that effect, consequential to an infection and individual or any other characteristic(s).

Survival Analysis: Techniques used in the analysis of time to event censored data.

TB treatment sites: Health facilities where TB patients receive treatment and follow up services

TB/HIV coinfected: Patients who have TB disease and HIV infection

TB death/TB mortality: Patients who die during TB treatment due to any cause, also known as all-cause mortality.

TB treatment interruption: Programmatically known as **lost to follow up**, occurs if a TB patient fails to show up for their medication for up to two months since the last day they showed up. Such patients are continuously the source of TB transmission while they are also at increased risk of developing drug resistance and death.

TIBU: It is a national tuberculosis, leprosy and lung disease program central data management tool. TIBU a web-based solution integrated with mobile tablet technology developed and introduced in Kenya in the year 2012 with inter-sector support.

Tuberculosis: Mostly abbreviated as TB. It is a chronic infectious disease caused primarily by bacillus *Mycobacterium tuberculosis*.

Transmission: The process by which an infectious agent is spread or passed from a source to a susceptible host. Tuberculosis is transmitted from person to person through respiratory tract.

Treatment completed: 'Treatment completed' refers to TB patients who have completed treatment without evidence of failure but have no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done, results are unavailable or the patient was clinically diagnosed.

Treatment outcome: An even that constitutes termination of treatment which is confirmed and assigned by attending clinician during follow-up of TB patients. TB treatment outcomes include treatment success (cure & treatment completion), death and treatment interruption (lost to follow up). Treatment outcome may also include treatment failure and discontinuation by heath care provider due to any reason.

Treatment success rate: Proportion of TB patients who were notified in a specified period that were cured or completed treatment, among the total TB patients notified during the same reporting period.

Treatment supporter: A household member, workmate, or health care provider who is acceptable and accountable to the patient and provides directly observed therapy (DOT) and any other support to the patient.

Unfavorable TB treatment outcomes: These are adverse or unwanted TB treatment outcomes. They include mortality and TB treatment interruption.

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CHAPTER ONE

INTRODUCTION

1.1 Background information

Tuberculosis (TB) is a chronic infectious disease caused by the bacillus, *Mycobacterium tuberculosis*, which is spread through the respiratory tract and primarily affects the lungs (Ministry of Health, 2021). Tuberculosis is the most prevalent infectious disease in the world and is the leading cause of death due to a single infectious disease agent. In 2019, there were an estimated 10 million cases of TB worldwide, with 1.4 million fatalities (World Health Organization, 2020). Each year, over two-thirds of TB cases occur in Southeast Asia (44%) and Africa (25%), with lesser frequencies being observed in the Eastern Mediterranean (7%), Europe (3%), and the Americas (3%) (World Health Organization, 2021a). The diverse worldwide TB epidemiology is mostly contextual, with varying attributable risks.

Despite being removed from the list of high burden drug-resistant TB countries, Kenya remains one of the 30 high burden countries for TB and TB/HIV, with Gabon and Uganda joining the list (World Health Organization, 2021c). Kenya's national TB prevalence survey (Ministry of Health, 2016) indicated a tuberculosis prevalence of 558 cases per 100,000 adult population and revealed that the surveillance system misses roughly 40% of TB cases annually. Tuberculosis is also responsible for the total disability-adjusted life years (DALYs) of 4.8% and an annual mortality rate of 6.3% (Kipruto *et al.,* 2015; Ministry of Health, 2020a). Whereas Kenya has made remarkable progress in detection and notification of TB cases from 84,879 in 2017 to 94,544 in 2018, as a result of the implementation of facility-based active TB case finding approach, the treatment success rate (TSR) for all forms of TB has plateaued, only slightly improving from 82.4% in the 2017 cohort to 84.9% in the 2018 cohort (Bigogo *et al.*, 2018; Ministry of Health,

2019). Additionally, Kenya's TB TSR still falls short of the global TSR target of >90% (MacNeil *et al.,* 2020). In the 2017 cohort, Vihiga County had a lower TSR of 81.6%, owing to two key unfavourable TB treatment outcomes: treatment interruption (>5%) and mortality (13%). Moreover, while the cumulative rate of unfavorable TB treatment outcomes in Vihiga County (18%) is virtually comparable to that of Siaya County (16%), it is considerably higher than that of other neighboring counties, including Kakamega (13%), Nandi (13%), and Kisumu (14%). Understanding predictors of unfavorable TB treatment outcomes is critical for improving TB epidemiology, and this may help in designing programs and interventions aimed at achieving the global zero TB epidemic milestones and targets.

The coexistence of HIV and other diseases in high-TB burden settings, along with a high poverty index and weak health systems, presents a difficult hindrance in achieving the global TSR target of >90% (Al Abri *et al.,* 2020; Chimeh *et al.,* 2020; MacNeil *et al.,* 2020). In such settings, TB disproportionately affects the socioeconomically vulnerable population and is particularly linked to persons' characteristics and health disparities. Besides, the majority of TB cases in such settings show substantial clustering tendencies that vary greatly in the spatiotemporal dimension (Lee-Rodriguez *et al.,* 2020; Maore *et al.,* 2017; Shaweno *et al.,* 2018). To guide intervention strategies across countries, it is vital to understand the patterns of TB epidemic and distribution of TB disease and treatment outcomes by patient characteristics. While routine treatment and follow-up surveillance data is an effective monitoring tool, accuracy, completeness, and the exclusion of important socioeconomic characteristics make it difficult for explicit interpretation (Kimani *et al.,* 2021; Masini *et al.,* 2016)**.**

Elimination of source of TB infection from the population, prevention of drug resistance, enhancement of the quality of life, and reduction of related mortality all necessitate universal

access to prompt diagnosis and successful treatment of TB (MacNeil *et al.*, 2020; Vesga *et al.*, 2019; World Health Organization, 2021a). The most difficult obstacle to achieving the global TB treatment success rate target, a TB incidence reduction initiative, is the interruption of treatment. Adherence to a long course of TB chemotherapy is a complicated and dynamic phenomenon that is influenced by a wide variety of circumstances (Munro *et al.,* 2007). This emphasizes the need for evidence-based quality care, patient linkage, and retention. Understanding the causal pathways by which broader issues such as demographic, socioeconomic, behavioral, and clinical factors influence individuals' experiences with TB disease, as well as their interactions which culminate in an increased risk of TB treatment interruption, can result in more innovative public health actions and clinical interventions that may improve TB treatment success as envisioned by global policies. While some previous studies (Chimeh *et al.,* 2020; Kimani *et al.,* 2021; Nisar, 2018) have attempted to investigate TB treatment interruption, relatively few have either considered event time or allowed for qualitative interrogation of patients who interrupt treatment to reveal reasons for treatment interruption.

Ending the worldwide TB epidemic, which is a public health concern, is a common goal of the WHO's End TB Strategy and the third United Nations' Sustainable Development Goal (SDG-3). In comparison to 2015 figures, the milestones and targets include a 90% reduction in TB mortality and an 80% decrease in TB incidence by 2030, and a 95% reduction in TB mortality, and a 90% reduction in TB incidence by 2035 (Floyd *et al.*, 2018; World Health Organization, 2015c). Despite rigorous intervention efforts, slow progress towards these milestones remains a key impediment in high-TB-burden countries such as Kenya (Murray *et al.,* 2018). Although several studies (Azeez *et al.*, 2019; Bukundi *et al.,* 2021; Chung *et al.*, 2021; Kosgei *et al.,* 2020; Wekunda *et al.,* 2017) concur on the need for interventions to eliminate TB related mortality, there was still

a paucity of information on the reasons for commonly observed survival distributions and causes of increased mortality risk among TB patients. Besides, because of differences in survival and mortality rates, as well as variation in risks of mortality, between people living with HIV (PLWHIV) and the HIV-negative population, knowledge of specific causes of death and associated circumstances among TB patients based on HIV status may be useful in predicting risks and the occurrence of mortality with greater accuracy. In high-TB-burden context, this could lead to more cost-effective mortality reduction interventions and improved TB surveillance.

The goal of this study was therefore to identify and characterize predictors that were more likely to be linked to increased risks of the occurrence of unfavorable treatment outcomes among notified TB patients receiving routine therapy.

1.2 Statement of the problem

The primary component of the global TB incidence and mortality reduction strategy is effective treatment of active TB cases. To enhance this, Kenya's national tuberculosis program offers free TB diagnosis and treatment in all public and faith-based health care facilities. Additionally, Kenya has implemented active TB case finding, a relatively new routine initiative, which has enabled the country net more TB cases. However, achieving optimal treatment success remains a challenge. Kenya’s treatment success rate (TSR) of 84% falls short of the global TSR target of >90%, and with a lower TSR of 81.6%, treatment interruption rate of >5% and mortality rate of 13%, Vihiga is one of Kenya's counties with the highest rates of unfavorable TB treatment outcomes. Higher rates of unfavorable TB treatment outcomes in the county have raised concern among stakeholders because patients who interrupt TB treatment remain infectious for an extended period of time, are more likely to develop drug resistance, and are at higher risk of severe complications and death

from TB. Besides, high rate of mortality among TB patients is a serious impediment to achieving the End TB Epidemic and SDG milestones and targets. Despite this, the associated factors and reasons for underperformance are still unknown.

While there could be challenges in providing standardized care and follow-up, patients' characteristics may be responsible for frequently observed patterns in the distribution of TB disease and the risks of unfavorable treatment outcomes. It was therefore necessary to comprehend the causal pathways through which broader demographic, socioeconomic, behavioral, and clinical characteristics influence individuals' experiences with TB disease, as well as their interactions that are likely to culminate in elevated risks of treatment interruption and mortality.

This study followed up on a cohort of TB patients on routine care to describe epidemiological pattern of TB disease and outline the distribution and determinants of treatment interruption and mortality by patients' characteristics using both quantitative and qualitative methods. The findings of this study may help in the formulation and implementation of programs to identify and reduce the risks of treatment interruption and mortality. In addition, this study's findings may provide data for a better understanding of TB epidemiology in the local context.

1.3 Objectives

1.3.1 Main objective

To identify predictors of unfavorable tuberculosis treatment outcomes among notified patients in Vihiga County

1.3.2 Specific objectives

1. To describe the distribution of tuberculosis disease and treatment outcomes in Vihiga County based on characteristics of notified patients.

2. To identify determinants of tuberculosis treatment interruption among notified patients in Vihiga County

3. To investigate factors associated with survival distribution and the occurrence of all-cause mortality among notified tuberculosis patients in Vihiga County.

1.3.3 Research questions

1. Based on the characteristics of notified patients, how is tuberculosis disease and treatment outcomes distributed in Vihiga County?

2. What are the determinants of tuberculosis treatment interruption among notified cases in Vihiga County?

3. What factors influence survival distribution and the occurrence of all-cause mortality among Vihiga County tuberculosis patients?

1.4 Justification

Vihiga, being one of Kenya's counties with the highest rates of unfavorable TB treatment outcomes, offered a suitable context for this study. It was necessary to investigate the patterns and distribution of TB disease, the transition hazards at which patients move to the next stage identified by their treatment outcomes, sources and determinants of treatment interruption and mortality, as well as their potential impact on strategic TB prevention and control decisions in Kenya. This may help identify and mitigate the driving forces of negative trends, the vulnerability of subgroups, and risk factors for unfavorable TB treatment outcomes.

While routine secondary data obtained during diagnosis, treatment and follow-up of TB patients is an effective monitoring and evaluation tool, issues of accuracy, completeness, and exclusion of

important patient characteristics such as income, education, disease severity, alcohol abuse, and smoking make it difficult to identify covariates and characterize their interactions. As a result, analyzing and interpreting such data might be difficult, resulting in inconclusive findings. This necessitated the deployment of a study design that permitted the collection and utilization of primary baseline and follow up data.

Additionally, data on TB treatment and follow-up is typically skewed in distribution and is frequently subject to repeated measurement, which is likely to alter assumptions about the risk of survival and the probability of treatment completion. A statistical technique that takes into account survival time and an individual's reliance on repeated events allowed for more accurate judgments. Also, the difference in survival and mortality rates between HIV positive and HIV negative TB patients justified the subpopulation mortality analysis. Furthermore, qualitative analysis of patients who experienced treatment interruption or mortality, may provide additional information on the patients' experiences, attitudes and perceptions of TB disease and its consequences. This may result in more contextual data and tools for comprehensive population-based surveillance systems and other public health interventions related to TB prevention and control in high-TB-burden settings.

1.5 Significance

This study highlights epidemiological patterns of TB disease and outlines the distribution and determinants of unfavorable treatment outcomes based on patients' characteristics. The use of both quantitative and qualitative methods, provides a more comprehensive evaluation of TB treatment interruption and mortality in a routine health care setting where programmatic gaps exist and complex data analysis is not feasible. The findings of this study have improved the understanding of TB epidemiology, and as a result, health care service providers, county and national health

managers, and other stakeholders may design and implement innovative interventions and programs that are likely to improve treatment success. The findings of this study have also improved understanding of patient characteristics, attitudes, and perceptions that are likely to increase the risk of occurrence of unfavorable TB treatment outcomes. This may improve quality of patient care, retention & linkage. Ultimately, the findings of this study may help to advance the global End TB and SDG strategic goals.

1.6 Limitations of the study

This study has some limitations. First, the study design required recruiting of TB patients over a six-month period. This increased the possibility that confounders and extraneous variables would enter the study and cause measurement errors. Nevertheless, this study was carried out in a routine health care setting where standard guidelines are consistently implemented, while Cox proportional hazard model was used to adjust for confounders. Second, patients from facilities with a low TB case load were omitted from the study, potentially leading to bias. Nonetheless, the study was designed to mimic typical healthcare scenario. Thirdly, the findings of this study are dependent on patient characteristics at the onset of treatment. Routine interventions such as counselling may have modified some patient characteristics, such as alcohol use and smoking, in the course of follow-up.

CHAPTER TWO

LITERATURE REVIEW

2.1 Scope of the study

The termination of the global TB epidemic hinges on a better understanding of TB epidemiology through monitoring and evaluation of TB treatment outcomes. This can help improve the identification and comprehensive care of patients who are at risk of unfavorable TB treatment outcomes. In a semi-urban cluster, this study focused on the extensive description of patients' demographic, socioeconomic, behavioral, and clinical characteristics and the influence these characteristics have on distribution of TB disease, TB treatment interruption and mortality. Qualitatively, reasons for treatment interruption as well as causes and conditions contributing to mortality have also been highlighted.

2.2 Natural history and Epidemiology of tuberculosis

Tuberculosis is a chronic communicable disease caused by a rod-shaped spore-forming aerobic bacteria known as *Mycobacterium tuberculosis*, which is transmitted from person to person through the respiratory tract. Tuberculosis mostly affects the lungs, although it can affect any other part of the body (World Health Organization, 2020).

The source of TB infection is usually an infectious case of pulmonary TB (PTB) (Adane *et al.*, 2020; Laghari *et al.*, 2019). When the infectious case of PTB coughs, sneezes, laughs, talks, sings, or spits, droplets are generated, dispersed and suspended in air for extended period of time. Epidemiological studies have established that transmission of TB requires the presence of a susceptible host, an infectious case of TB, environment and frequency or duration of exposure (Martinez *et al.*, 2017). Therefore, the risk of transmission increases when a susceptible host is

exposed more frequently or for a longer period of time to an infectious case of PTB in a poorly ventilated environment. Rapid identification and successful treatment of infectious cases of TB is critical for sterilizing them and thereby eliminating the source of infection from the population (Vesga *et al.*, 2019). Treatment interruption, on the other hand, allows patients to transmit TB for a longer time and increases the risk of developing drug resistance and mortality.

Once droplet nuclei containing TB bacilli are inhaled by a susceptible host, they enter the alveoli, the smallest unit of the lung, usually in the lower parts of upper lobes or upper parts of lower lobes of the lungs, and multiply there while some spread throughout the body through blood (Heemskerk *et al.*, 2015). The body's immune response, usually cellular, occur within 2-10 weeks, during which specialized white blood cells known as *macrophages* and *antigen-specific T-cells* produce a hard shell around the TB bacteria called the *Ghon focus*, which keeps the bacteria contained (Todar, 2022). This phenomenon is known as latent TB infection (LTBI), and it can last a person's entire life without progressing to TB disease. Over a quarter of the world's population have latent TB infection (Floyd *et al.*, 2018). Latent tuberculosis infection is asymptomatic and non-infectious, although it can be detected with a *Tuberculin skin test* (TST) or *Interferon-gamma release assays* (IGRA) (Kiazyk & Ball, 2017).

Tuberculosis disease occurs if the body's immune system fails to contain the TB bacteria, allowing them to multiply rapidly. The body's immune system may fail due to multiple factors including HIV, malignancies, heavy alcohol use, and malnutrition (Lawn & Churchyard, 2009; Shimeles *et al.*, 2019). Tuberculosis disease can develop as a result of the initial course of tuberculosis infection or due to the reactivation of a previously latent TB infection (Heemskerk *et al.*, 2015; Kiazyk & Ball, 2017). Without treatment, 33% of TB patients die within two years, 50% die within five

years, and roughly 25% remain ill beyond five year period (World Health Organization, 2017). Tuberculosis prevention and control strategies can be targeted at different stages of the disease's natural history, such as eliminating infectious cases through prompt diagnosis and treatment, reducing host susceptibility through improved socioeconomic status and general health, and reducing transmission through environmental control and respiratory protection (Martinez *et al.,* 2017).

Tuberculosis remains an important global public health problem. Annually, it causes an estimated 10 million illnesses and 1.4 deaths globally (World Health Organization, 2020). The common goal of the WHO's End TB Strategy and the United Nation's third Sustainable Development Goal (SDG-3) is to end the global TB epidemic by 2030/2035 by establishing a clear route and milestones for lowering TB incidence, deaths, and catastrophic costs in comparison to 2015 figures (Floyd *et al.,* 2018; World Health Organization, 2015c). However, a slow global decline in tuberculosis incidence of 2% per year between 2015 and 2020 resulted in a cumulative incidence reduction of 11%, only slightly more than halfway to the End TB Strategy milestone of a 20% decrease in TB incidence between 2015 and 2020 (MacNeil *et al.,* 2020; World Health Organization, 2021a). Additionally, while the European region was on track to achieve a 2020 TB related mortality reduction milestone of 35% by achieving 31% mortality reduction, African region achieved only 19% TB mortality reduction in the same period (Fukunaga *et al.,* 2021). On the global scale, the pace of progress lagged and the 2020 milestones were missed. The success of ending the global TB epidemic is particularly challenging in contexts of socioeconomic and health disparities, where TB disproportionately affects socio-economically disadvantaged and vulnerable populations resulting in a higher prevalence of unfavorable TB treatment outcomes; treatment interruption, and mortality (Murray *et al.,* 2018; World Health Organization, 2021a). Kenya has a

high prevalence of TB, 558 cases per 100,000 adult population (Ministry of Health, 2016), while many incidences of unfavorable treatment outcomes have been reported in some regions including Vihiga County (Ministry of Health, 2019; Wekunda *et al.,* 2017). However, few studies have comprehensively highlighted predictors of unfavorable TB treatment outcomes in a routine health care setting. As a result, more innovative patient care models, as well as treatment interruption and mortality reduction measures, remain difficult to execute.

2.3 Management of tuberculosis patients in Kenya

Tuberculosis diagnosis, care, and follow-up services are based on the first pillar of the WHO's End TB Strategy, which calls for integrated, patient-centered care and prevention (World Health Organization, 2015a). Early diagnosis of TB patients, clinical evaluation, prompt treatment, and follow-up are all essential components of TB management. Patients with TB should not only have unrestricted access to comprehensive and affordable services, but they should also be able to participate in their care.

2.3.1 Diagnosis of tuberculosis

Diagnosis of TB allows sick individuals to receive further care, and this is vital in reducing TB incidence and mortality (Floyd *et al.,* 2018). Mop-up of TB cases from the community and provision of quality health care minimizes the likelihood of continuous transmission of TB in the population. However, the findings of the 2015/2016 Kenya TB prevalence survey revealed that the country fails to identify up to 40% of TB cases annually (Masini *et al.,* 2018). As a result, Kenya has strengthened its surveillance system to ensure prompt TB diagnosis by implementing integrated diagnostic algorithms and expanding the use of WHO-recommended molecular diagnostic technologies such as *gene xpert MTB/RIF* (Ministry of Health, 2021). Health facilities

have also prioritized and implemented facility-based active TB case finding approach that includes a systematic TB screening of all persons who visit health care facilities, regardless of their presenting concerns (Bigogo *et al.,* 2018; Ministry of Health, 2019). Targeted community outreach and contact management are other case-finding strategies being utilized (Laghari *et al.,* 2019; Murray *et al.,* 2018). However, diagnostic delays remain common due to poor health seeking behavior among patients and health system gaps (Masini *et al.*, 2018). Delays in diagnosis are most often associated with unfavorable TB treatment outcomes (Bukundi *et al.,* 2021; Takarinda *et al.,* 2015; Wekunda *et al.,* 2017)

2.3.2 Treatment of drug-susceptible tuberculosis patients

A complete clinical evaluation of newly diagnosed TB patients allows rapid identification and management of comorbidities, nutritional deficits and other risk factors (Ministry of Health, 2021). Treatment of TB is an important aspect of public health because it allows patients to be cured, thus removing the source of TB infection from the population. Treatment also prevents complications of TB, improves the quality of life, and reduces risk of drug resistance and mortality (CDC, 2016). Majority of TB patients are treated for six months with TB chemotherapy. Nonetheless, patients with TB of the central nervous system and skeletal system are typically treated for twelve months, while treatment for drug-resistant TB varies depending on the resistance pattern. The six-month TB treatment comprises of an intensive phase that lasts two months after treatment begins, followed by a four-month continuation phase (Ministry of Health, 2021). The intensive phase aims at reducing the bacterial burden by swiftly eliminating actively multiplying bacilli (McIlleron & Chirehwa, 2019). This is accomplished by use of a mixture of antimicrobials, including rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E), all of which work together to eliminate TB symptoms and minimize infectiousness. During the continuation phase, two drugs, rifampicin

(R) and isoniazid (H) are administered to eliminate any remaining or dormant bacilli, effectively curing the TB patient. The dosage of TB medications is regulated by the patient's body weight and is given orally in a fixed-dose combination (World Health Organization, 2021b). Majority of patients are treated ambulatory, which means they obtain their drugs from healthcare facilities and take them while at home. To enhance their immunity and minimize peripheral neuropathy, all TB patients also receive vitamin A and vitamin B6 (pyridoxine), respectively (Prasad *et al.,* 2019). To boost TB treatment adherence, a DOTS (directly observed therapy short-course) strategy was adopted and involves observation of drug intake by a treatment supporter (Nganda *et al.,* 2003; Salehitali *et al.,* 2019). A treatment supporters can be medical personnel, community health volunteers, co-workers, or family members. More recent studies have shown that 'Wirelessly Observed Therapy' initiative is gaining traction and may be superior to DOTS in supporting confirmed daily adherence to TB medications during the continuation phase of TB treatment and is preferred by patients (Browne *et al.,* 2019).

2.3.3 Monitoring and follow up of patients on tuberculosis treatment

Before starting therapy, many patient-level covariates such as demographic and clinical characteristics as well as contact information are collected and analyzed. Routine TB data gathering tools, on the other hand, overlook important behavioral and socioeconomic factors such as patients' education level, alcohol consumption, and income (Kimani *et al.,* 2021; Masini *et al.,* 2016). Excluding these crucial covariates from data analysis can lead to erroneous conclusions. Tuberculosis patients are monitored in health care facilities until their treatment is completed or until an event that constitutes termination of treatment, such as treatment interruption or mortality, occurs. Although many health care facilities implement a differentiated care model when managing TB patients, the patients typically visit their respective health facilities once a week

during the intensive phase and twice a month during the continuation phase, where they are clinically evaluated and given medicine (Ministry of Health, 2021). Acid Fast Bacilli (AFB) smear microscopy is performed on samples from bacteriologically confirmed pulmonary tuberculosis (PTB) patients in the second, fifth, and sixth months of treatment, and any patients that tests positive is further examined for drug resistance (World Health Organization, 2021b). A treatment outcome is assigned at the end of six months therapy or following an event that constitutes termination of treatment. A recent systematic review of TB treatment outcomes suggested that studying contextual covariates by utilizing prospective study designs may provide more accurate assumptions (Teferi *et al.,* 2021).

2.4 Tuberculosis treatment outcomes

2.4.1 Tuberculosis treatment Success

The goal of TB treatment is to cure patients and strict adherence to treatment is essential for this to happen (CDC, 2016). Treatment success rate (TSR) is the proportion of TB patients who were notified in a specific period that were cured or completed treatment, among the total TB patients notified during the same reporting period. Treatment success is the most desirable and anticipated therapeutic outcome for tuberculosis. The World Health Organization has established a TSR target of >90%. Nevertheless, the global TSR was 83% in 2018 (World Health Organization, 2020), Kenya had an 84% TSR during the same period, whereas Vihiga County had a TSR of 81% (Ministry of Health, 2018a). Comparatively, counties neighboring Vihiga such as Kakamega, Nandi, and Kisumu, had higher TSRs of 87%, 87%, and 86%, respectively. Understanding factors that are likely to influence TB treatment success is a critical step toward lowering the global TB epidemic.

2.4.2 Unfavorable tuberculosis treatment outcomes

2.4.2.1 Tuberculosis treatment interruption

Interruption of TB treatment is frequently accompanied by poor adherence, resulting in treatment failure, prolonged TB transmission, and drug resistance (Kigozi *et al.,* 2017). Patients who miss any weekly clinic appointments during intensive phase or twice monthly appointments during continuation phase should be listed, traced, and returned to treatment as soon as possible, preferably within one day of the missed appointment (Ministry of Health, 2021). Tracing of TB patients is achieved by utilizing the contact information previously recorded during their enrollment. However, it is not clear when patients who interrupt treatment are contacted. Patients who miss clinic appointment and medication for more than two months are considered lost to follow up (treatment interrupters) and pose a serious public health risk. They should be tracked down and reintroduced to treatment, albeit this almost always results in a missed opportunity and wasted resources.

In Kenya, the cumulative incidence of treatment interruption is 4.5% for the new TB patients, and 8.5% for previously treated patients (Masini *et al.,* 2016). Previous research (Kimani *et al.,* 2021; Masini *et al.,* 2016; Muture *et al.,* 2011; Shargie & Lindtjørn, 2007) has shown that the cumulative incidence of TB treatment interruption increases more rapidly over the first two to three months of TB treatment. Treatment interruption has been associated with patients feeling better after treatment commencement (Kaona *et al,* 2004), traveling long distances to health facilities, staff attitude, long waiting time, inadequate food, ignorance (Muture *et al.,* 2011), migration, drug side effects, and previous treatment (Masini *et al.,* 2016; Wohlleben *et al.,* 2017). A prospective cohort study design that incorporates survival analytic techniques and includes socioeconomic and behavioral covariates such as education, income, treatment supporter, alcohol use, and smoking

may provide a more accurate understanding of the determinants of TB treatment interruption. Furthermore, qualitative assessment of patients who discontinue treatment might help in understanding of patients' attitudes, beliefs and sentiments regarding the importance of adhering to TB therapy.

2.4.2.2 Tuberculosis related mortality

Despite the widespread availability of chemotherapy, tuberculosis related mortality remains one of the most common unfavorable TB treatment outcomes (Floyd *et al.,* 2018). Tuberculosis-related mortality is all-cause mortality occurring during treatment phases (Ministry of Health, 2021). While Kenya's TB case fatality was 6.3% in 2018, Vihiga County had a death rate of 13%, placing it second among Kenya's counties with the highest TB-related mortality (Ministry of Health, 2018a). Previous studies (Ali *et al.,* 2016; Garcia-Basteiro *et al.*, 2016; Geleso, 2020; Wekunda *et al.,* 2017) have indicated that TB mortality is highest during the intensive phase of treatment and is linked to advancing age, co-infection with HIV, and malnutrition. Poor access to ART and TB treatment delays have also been identified as key contributors to mortality (Adamu *et al.,* 2017; Wen *et al.,* 2018). Based on current evidence, effective identification and quantification of factors associated with survival and occurrence of mortality among TB patients may be achieved by incorporating survival times and censoring using prospective studies beyond the scope of monitoring (Moolphate *et al.,* 2011). Moreover, specific causes of mortality and conditions that contribute to mortality in distinct subgroups of the population may highlight the need for interventions that incorporate socioeconomic determinants in health care settings, in addition to a patient-centered approach.

2.5 Predictors of unfavorable tuberculosis treatment outcomes

Although there has been an improvement in TB TSR at the global level, it is still below the target of >90% (Chaves Torres *et al.*, 2019). Ending TB epidemic should therefore be focused not only on finding people who have TB and treating them but also identifying, quantifying and addressing social and other predictors of TB disease and treatment outcomes (Chakaya *et al.*, 2021). To support TB prevention and control program, there has been substantial investment in health system, and this has improved TB diagnostics using rapid and molecular tests, TB treatment using short course therapy, and monitoring of patients using differentiated service delivery model. Also, healthcare service delivery in Kenya is administered using the national guidelines and standard operating procedures, and this has ensured that health care services are consistent across health facilities (Ministry of Health, 2021). Despite this, unfavorable TB treatment outcomes remain high in some regions, implying that variations in patients' characteristics most likely predict the occurrence of unfavorable TB treatment outcomes. Therefore, this study investigates the distribution of tuberculosis diseases based on patients' demographic, socioeconomic, behavioral, and clinical characteristics as well as the influence these characteristics have on the unfavorable TB treatment outcomes.

2.5.1 Demographic characteristics of patients associated with distribution of tuberculosis and unfavorable treatment outcomes

2.5.1.1 Age of tuberculosis patients

Age is an essential factor in tuberculosis prevention and control since it influences TB transmission and may predict unfavorable TB treatment outcomes (Cui *et al.*, 2020; Glynn & Moss, 2020). Globally, the TB burden is higher among people aged 25-34 years (World Health Organization, 2020). High TB burden countries such as India (Mundra *et al.*, 2017), Indonesia (Muliawan &

Sawitri, 2016), and South Africa (Yoko *et al.,* 2017) exhibit a similar picture, while China, Thailand, and Vietnam have a higher proportion of TB patients over the 65years (Hoa *et al.,* 2011). Pakistan, on the other hand, has higher TB rates among adolescents aged 15-24 years (Javed *et al.,* 2017). Kenya has the highest TB burden within age groups, 25-34 and 45-54 (716 and 607 per 100,000 population respectively), and the lowest burden in the age group of 15-24 (360 per 100,000 population) (Ministry of Health, 2016). Age has also been previously associated with unfavorable TB treatment outcomes. Studies in South Africa (Kigozi *et al.,* 2017) and Madagascar (Comolet *et al.,* 1998) have indicated that TB patients younger than 25 years are more likely to interrupt TB treatment while advancing age has been shown to predict mortality among patients on TB treatment (Moolphate *et al.,* 2011; Wekunda *et al.,* 2017). The differences in age of TB patients and associated treatment outcomes suggest specific cluster variation.

2.5.1.2 Gender of tuberculosis patients

Worldwide, gender has modified the distribution of TB over time and has been shown to influence TB treatment outcomes (World Health Organization, 2019, 2020). The prevalence of TB in male is persistently high, and there is substantial evidence that male are underserved in terms of access to TB care (Horton *et al.*, 2016). Besides, high burden of TB among male have been attributed to males' health-risk behavior and outgoing nature (Kimani *et al.,* 2021) while recent evidence suggest that biological factors also plays a role. Nevertheless, a fairly equal gender distribution of TB cases has been observed in Gondar town, Ethiopia (Bogale *et al.*, 2017). Regarding unfavorable treatment outcomes, male gender has been linked to an increased risk of treatment interruption (Kimani *et al.,* 2021; Masini *et al.,* 2016; Muture *et al.,* 2011) and mortality (Chung *et al.,* 2021; Garcia-Basteiro *et al.,* 2016) while bacteriologically confirmed PTB and HIV coinfected women have a lower risk of dying compared to men (Kosgei *et al.,* 2020). Contrary, several studies

(Amuha *et al.,* 2009; Kigozi *et al.,* 2017; Krasniqi *et al.,* 2017; Mekonnen & Azagew, 2018; Sang *et al.,* 2017) have found that there is no gender difference in unfavorable TB treatment outcomes. This suggests that the influence of gender on unfavorable TB treatment outcomes varies, most likely by context, emphasizing the need to consider local experiences as potential sources of heterogeneity in the frequency of occurrence and distribution of unfavorable TB treatment outcomes. It is noteworthy, however, that secondary data may include some observations with recording errors while the exclusion of important covariates such as alcohol consumption and smoking, which are known to vary between gender, may result in confounding during analysis (Nascimento do Prado *et al.,* 2017). Cox proportional hazard modeling may account for the effect of confounding variables.

2.5.1.3 Marital status of tuberculosis patients

Both epidemiological and social studies have consistently demonstrated a strong connection between marriage and health (Mikucka *et al.,* 2021). This has been attributable to the fact that people in marriage are likely to enjoy better psychosocial support, nutritional care, and directly observed therapy compared to those without such unions. In many high TB burden countries including Kenya, the relationship marriage has on the burden of TB as well as unfavorable treatment outcomes has not been well explored. In Northern Mexico, a study conducted to establish the "effects of socioeconomic status, clinical factors, and genetic ancestry on pulmonary TB" revealed that the disease is less frequent among the married or those in a civil union (Young *et al.,* 2014). Similarly Mitku and others indicated that patients who are not married are 3 times more likely to suffer from TB compared to those who are married in the Amhara region of Ethiopia (Mitku *et al.,* 2016). Contrary, the married have a 10 times higher chance of acquiring TB compared to unmarried in Punjab Pakistan (Javed *et al.,* 2017). Furthermore, although Shargie &

Lindtjørn, (2007) have argued that marital status doesn't predict treatment interruption among bacteriologically confirmed TB patients, other studies have associated marital status with TB treatment interruption and TB mortality (Fang *et al.,* 2019; Muture *et al.,* 2011).

2.5.1.4 Residence of tuberculosis patients

Whereas the prevalence of TB is higher among the urban dwellers in Kenya (Ministry of Health, 2016), it is not yet explicit whether the residence of TB cases has a considerable hazard in TB treatment interruption and mortality. Previous studies have shown that although the place of residence is not a significant predictor of TB status (Young *et al.,* 2014), residents of rural areas may experience pronounced delays in diagnosis (Bogale *et al.,* 2017) and have higher risk of unfavorable treatment outcomes (Thuy *et al.,* 2007). A study in a semi-urban setting is likely to provide more insight.

2.5.2 Socioeconomic characteristics of patients associated with distribution of tuberculosis and unfavorable treatment outcomes

Several postulates have been advanced to indicate that TB disproportionately affects socio-economically disadvantaged and vulnerable populations (World Health Organization, 2021a). Socio-economic characteristics also influence TB distribution in the population, transmission patterns and treatment outcomes (Young *et al.,* 2014).

2.5.2.1 Educational level of tuberculosis patients

Epidemiologists and socio-scientists have linked education advancement to better health outcomes (Dilmaghani, 2020). Education has consistently been associated with higher income and improved socio-economic status, better overall self-awareness on personal health, healthy lifestyles and making healthcare more accessible (Raghupathi & Raghupathi, 2020). Population with low-level

education faces health disparities in disease burden and clinical outcomes. In Kenya, the prevalence of TB among people with primary level education, 1421 TB cases per 100,000 population, is higher than the national average prevalence of 558 TB cases per 100,000 adult population (Ministry of Health, 2016). Several other studies have shown that less than secondary level education is linked to a higher risk of developing TB disease, delaying TB diagnosis, and significantly contributes to treatment interruption and mortality (Bogale *et al.,* 2017; Dodd *et al.,* 2017; Lackey *et al.,* 2015; Muture *et al.,* 2011). On the contrary, other studies (Krasniqi *et al.,* 2017) have revealed that education level does not influence TB treatment outcomes. Variations in the findings may suggest need to control for confounding covariates using Cox proportional hazard modeling. This may provide a better understanding, and may aid in consideration of education level in TB prevention and control initiatives.

2.5.2.2 Income of tuberculosis patients

Existing global epidemiologic evidence suggest an important association between low income and TB disease (Djibuti *et al.,* 2014; Murray *et al.,* 2018). Low income means that patients have financial limitations, lack food, lack transport to treatment sites, and lack social support (Tola *et al.,* 2015). Low income also exposes patients to high catastrophic costs and income loss (Erlinger *et al.,* 2019; Nana *et al.,* 2014; World Health Organization, 2015a). A study conducted in Nairobi, Kenya postulated that income less than 10,000 Kenya shillings (Ksh) is predictive of TB treatment interruption (Muture *et al.,* 2011). However, it is noteworthy that retrospectives studies have issues of recall bias (Bonita *et al.,* 2006) while categorization of income may also lead to bias. Description of income of TB patients and effects it has on unfavorable treatment outcomes in a semi-urban location may provide baseline information for interventions that cushion TB patients from catastrophic costs and also enhance their income.

2.5.2.3 Employment status among tuberculosis patients

Employment likely determines the health status of the population, probably due to the income it provides. Employment have also been associated with increased or decreased risks of exposure to specific occupational hazards. For instance, people working in the silica industry have enhanced risk of acquiring TB infection, developing TB disease, and suffering long-term complications of TB (Kuyinu *et al.*, 2016). Also, previous studies have indicated that compared to the employed, TB disease is more common among the unemployed and informal employees (Ministry of Health, 2016; Woldeyohannes & Abera, 2015). Nevertheless, it has not been explicit whether employment status has an increased hazard rate for TB treatment interruption, patient survival, and related mortality. Such knowledge is amenable to designing and implementing specific interventions toward the improvement of TB treatment success rates.

2.5.2.4 Family Size of tuberculosis patients

A retrospective review of the medical records and patient interviews in a high TB burden country (Natesan *et al.*, 2015) has indicated that a family with less than five members is protective against patient delay in seeking TB treatment and offers directly observed treatment (Salehitali *et al.*, 2019), hence the likelihood of successful treatment. Other studies have indicated that the family size of TB patients doesn't influence TB treatment outcomes (Ali & Prins, 2016). In Kenya, there is little evidence concerning the relationship between family size and treatment interruption, patients' survival, and the occurrence of mortality.

2.5.2.5 Treatment supporters

Adherence to TB chemotherapy and successful treatment requires social support from the family and the community (MacIntyre *et al.*, 2003; Tola *et al.*, 2015). "A treatment supporter is a

household member, workmate or health care provider who is acceptable and accountable to the patient and provides directly observed therapy (DOT) and any other support to the patient" (Ministry of Health, 2021). The concept of treatment supporters and or treatment buddies has been used in the management of diseases that require long-term medication, including communicable diseases such as HIV and TB. While interventions using treatment supporters have shown varied effects on TB treatment interruption and related mortality (Pradipta *et al.,* 2020), studies in rural and urban settings in Kenya (Ong'ang'o *et al.,* 2014), Hadiya Zone, South Ethiopia (Billoro & Nunemo, 2019), and Windhoek District, Namibia (Endjala *et al.*, 2017) have indicated that treatment supporters are critical mitigation for treatment interruption. In Tanzania Bukundi and others (Bukundi *et al.,* 2021) have favored home-based DOT supporters since hospital-based DOT is associated with higher mortality. Besides, treatment supporters selected by patients and the community are more appropriate in developing countries where the TB burden is high because they are often readily available and are more cost-effective (Newell *et al.,* 2006). Most of these studies are based on routine TB surveillance data; hence, they have generated scanty information on the uptake and the role of treatment supporters in TB treatment interruption and mortality.

2.5.3 Behavioural characteristics of patients associated with distribution of tuberculosis and unfavourable treatment outcomes

2.5.3.1 Health seeking behavior

For successful treatment of TB, timely detection of patients and initiation of treatment remains critical (Getnet *et al.,* 2017). This means patients should learn to visit a health care facility for investigation soon after exhibiting initial signs and symptoms of TB, since this is likely to mitigate long-term lung damage (Bello *et al.,* 2019). Whereas the Kenya TB prevalence survey has underscored missed opportunities in the health system (Masini *et al.,* 2018), there still exists

scantly information concerning the time patients take to visit health facilities after experiencing their symptoms. In many high TB burden countries, patients exhibit health risk behaviors that heighten the risk for unfavorable treatment outcomes such as treatment interruption and mortality (Spring *et al.,* 2012). Natesan and others have demonstrated that patients take up to 36 days while suffering before they seek healthcare service (Natesan *et al.,* 2015). These delays have led to delays in TB treatment initiation (Yazdani-Charati *et al.,* 2017), treatment interruption (Kaona *et al.,* 2004; Naing *et al.,* 2001), and mortality (Garcia-Basteiro *et al.,* 2016; Javed *et al.,* 2017). A prospective cohort design and survival statistical technique would aid in improved understanding of TB patients' health-seeking behavior, associated survival probability, and risk of treatment interruption and mortality.

2.5.3.2 Smoking, alcohol consumption, and substance abuse among tuberculosis patients

Regardless of socio-economic factors and alcohol use, smoking is a serious risk factor for TB disease (Young *et al.*, 2014). Globally, 0.8 million TB cases are attributable to cigarette smoking (World Health Organization, 2017) while previous or current smoking with use of alcohol and other substances increases the risk of death from TB (Thomas *et al.,* 2019). Previous studies have also demonstrated that excess alcohol consumption impairs the immune system, amplifies TB transmission, and constitutes a risk for TB incidence and re-infection (Fiske *et al.,* 2009; Rehm *et al.,* 2009). Alcohol has also been shown to predict TB treatment interruption (Imtiaz *et al.,* 2017; Muture *et al.,* 2011; Sang *et al.,* 2017) and mortality (Ragan *et al.*, 2020).

Although efforts to prevent smoking, alcohol use, and drug abuse could substantially reduce the burden of TB (Murray *et al.,* 2018), locally, there is a dearth of evidence supporting smoking,

alcohol consumption, and substance abuse cessation programs, owing to a paucity of data on their prevalence among TB patients and their impact on TB treatment outcomes.

2.5.4 Clinical characteristics of patients associated with distribution of tuberculosis and unfavorable treatment outcomes

2.5.4.1 Tuberculosis and HIV coinfection

Human Immunodeficiency Virus (HIV) is known to accelerate TB transmission, worsen disease progression, and alter treatment outcomes, notably TB-related mortality. The global TB and HIV coinfection rate (12%) is lower than that of the African region (39%) (World Health Organization, 2015b). In Kenya, there has been a gradual decline in the TB/HIV co-infection rate among notified TB cases from 45% in 2008 to 33% in 2015 (Kipruto *et al.,* 2015). The 2016 national TB prevalence survey indicated a lower TB/HIV co-infection rate of 16% (Ministry of Health, 2016). This means that HIV interventions are working well. Antiretroviral therapy (ART), one of the most important HIV interventions, has enabled people living with HIV to live longer, healthier lives with fewer risks. However, according to WHO, people living with HIV, including those on antiretroviral therapy, are 16 to 27 times more likely to develop tuberculosis than people who do not have HIV (World Health Organization, 2019). Additionally, HIV has been frequently associated with increased rates of mortality (Fukunaga *et al.,* 2021). This suggests that TB and HIV collaborative activities, such as intensive TB case finding among people living with HIV, HIV testing for all TB patients, integration of TB and HIV care and treatment efforts, TB preventive therapy for people living with HIV, immediate ART for TB/HIV coinfected patients, and improved infection prevention and control, should be strengthened. HIV infection remains a key risk factor for mortality among TB patients in Vihiga County (Wekunda *et al.,* 2017). However, little is known about the distribution and influence of certain HIV-related covariates

such CD4 count, viral load, and ART adherence. Besides, subgroup analysis of survival distribution and mortality is important because, first, there could be heterogeneity in clinical characteristics between people living with HIV and those without HIV. Secondly, previous studies have elicited a substantial difference in mortality rates between people living with HIV and those without HIV.

2.5.4.2 Comorbidities among tuberculosis patients

In Kenya, there is a progressive increase in the incidence of three major non-communicable diseases; diabetes, hypertension, and cancer (Ministry of Health, 2014). Many TB patients have underlying comorbid conditions which are rarely recognized and managed (Puchner *et al.*, 2019). Current evidence indicates that comorbidity with diabetes may increase tuberculosis rates as much as co-infection with HIV (Jeon & Murray, 2008; Ponce-De-Leon *et al.*, 2004; Raghuraman *et al.*, 2014). Although pulmonary TB patients who have diabetes have higher pre-treatment bacillary load, they "achieve slightly higher sputum conversion by the end of 3 months of treatment compared to non-diabetic patients and diabetes does not alter the final TB treatment outcome among pulmonary TB patients" (Singla *et al.*, 2006). Also, individuals suffering from cancer are nine times more likely to suffer from TB than those without cancer (Cheng *et al.*, 2017). This means TB screening and TB preventive therapy can be a great boon to patients suffering from a wide range of comorbidities. Knowledge of the burden of comorbidities among TB patients as well as its effect on treatment outcomes in the local context is important for better planning and service delivery.

2.5.4.3 Nutritional status of tuberculosis patients

Globally, an estimated 1.9 million TB cases are attributable to undernourishment (World Health Organization, 2017). In high TB burden countries such as India (Pai & Memish, 2017), Thailand (Moolphate *et al.*, 2011), Indonesia (Rondags *et al.*, 2014), and South Africa (Gafar *et al.*, 2014), malnutrition is one of the major social determinants that drive TB epidemic. In Kenya, the proportion of malnutrition is higher among males than females (Ministry of Health, 2016). Lackey and others (Lackey *et al.*, 2015) indicated that TB patients with BMI under 18.5Kg/M^2 are more likely to die but unlikely to interrupt TB treatment. Identifying the burden of malnutrition and its influence on TB treatment outcomes in the local context can enable the health managers and other stakeholders to effectively plan for micro-and macro-nutrient supplementation among patients suffering from TB.

2.5.4.4 Severe illness among tuberculosis patients

Severe illness among TB patients is not common, but mortality is usually high (Muthu *et al.*, 2018). Due to the chronicity of TB disease, severe illness may indicate a longer duration of the disease, resulting from delay in diagnosis and timely anti-TB therapy due to poor health-seeking behavior and health system delays (Natesan *et al.*, 2015). This is a possible cause of uncontrolled multiplication and dissemination of TB bacilli leading to death. Locally, adequate pretreatment evaluation, risk stratification, and patient care prioritization have remained difficult due to the unknown prevalence of severe illness among TB patients and its impact on unfavorable TB treatment outcomes.

2.6 Analysis of tuberculosis treatment outcomes

When TB patients begin treatment, their baseline characteristics are documented, and the patients are followed up until they complete treatment or until an event that constitutes termination of treatment such as treatment interruption or mortality occurs. Therefore, when analyzing unfavorable TB treatment outcomes, it is important to include baseline covariates, unfavorable TB treatment outcome (event), and the time to the unfavorable TB treatment outcome variable (Asar *et al.,* 2015). Typically, regular statistical approaches that do not account for both the event and time elements are incapable of handling such data (Hagar & Dukic, 2015). Survival analysis technique is more suitable for analyzing TB treatment and follow up data because it takes into account the duration between two occurrences, or more broadly, the durations of transition between different states or circumstances (Leung *et al.,* 1997). To determine the survival time, two-time points are defined: the time of origin and the time of failure. In TB treatment and follow up data, the time of origin refers to when TB treatment began, whereas the time of failure refers to time point when a specific unfavorable treatment outcome, treatment interruption, or mortality occurred. As a result, the time to an event has been defined as the number of days between the start of treatment and the occurrence of unfavorable TB treatment outcome. A variety of demographic, socioeconomic, behavioral, and clinical characteristics are typically examined during TB treatment and follow-up to establish whether specific unfavorable treatment outcomes occur due to diverse reasons. The non-parametric (Kaplan Meier) approach and semi-parametric (Cox proportional hazard models) method are among the techniques used to perform survival analysis.

2.6.1 Censoring

When there is insufficient information on a person's surviving time, censoring occurs (Kartsonaki, 2016). In survival analysis, right censoring is the most used way of censoring. When an incident

does not occur during an individual's follow-up, right censoring is considered. During TB treatment and follow-up, a large number of patients complete their treatment, but some may die or interrupt their treatment. This means that after a patient's treatment is terminated, follow-up is stopped. Administrative censorship is considered when a patient undergoes the entire duration of TB treatment without experiencing the event of interest. Patients that encounter a different event other than the event of interest are also censored, for instance, if the event of interest is mortality, patients who interrupt or fail treatment are censored, and vice versa.

2.6.2 Survival function

Survival function *S(t)* gives an understanding of whether or not a TB patient survives beyond a specific time. In survival analysis, follow-up time and event of interest are used to estimate survival function (Kartsonaki, 2016). In the context of TB treatment and follow up, survival function is interpreted as the probability that TB patients will survive or the proportion of TB patients surviving unfavorable events (mortality or treatment interruption) beyond specific time in days, months, or treatment phases. Thus, the survival function can be represented as;

$$S(t) = P(T>t)$$

When TB treatment is initiated, the survival probability is 1 and typically reduces during follow-up. The survival function (S*(t)*) describes the probability that event of interest will occur (George *et al.*, 2014). Specifically, the survival function shows that the event of interest has not yet occurred by a specified time. Thus, if T denotes the time until an unfavorable TB treatment outcome, *S(t)* denotes the probability of surviving beyond the time of the specific event. Survival function may be influenced by variety of patients' characteristics.

2.6.2.1 The Kaplan-Meier Estimator

The Kaplan-Meier (or product-limit) estimator is a non-parametric estimator of the survival function (Kaplan & Meier, 1958). The Kaplan-Meier estimator is applied where there is no assumption regarding the distribution of hazard rate with time (Prinja *et al.*, 2010); every time an individual is censored, he/she is excluded from the denominator. The advantage of Kaplan-Meir over lifetable is that each time an event of interest occurs it re-estimates survival probability. The Kaplan-Meier approach can be used to estimate the probability of experiencing an unfavorable TB treatment outcome during the treatment and follow-up of TB patients, and survival probabilities are comparable across TB patients recruited early or late into the study. With this approach, each time an event occurs, the survival probability is computed using;

$$S_{t+1} = S_t((N_{t+1}-D_{t+1})/N_{t+1}),$$

Where;

- S_{t+1} is survival probability during time t,
- S_t is the survival probability during the preceding time,
- D_{t+1} is the number of TB cases suffering a specific unfavorable TB treatment outcome while
- N_{t+1} is the number of TB cases at risk of suffering the specific event, which is also equal to $N_t-D_{t+1}-C_t$, where N_t is the number who are event-free and considered at risk during time t and C_t is the number censored during the time t.

Survival curves based on Kaplan-Meier estimates can be plotted to compare the survival times of different groups of people (Kartsonaki, 2016). One example in treatment and follow up of TB patients is contrasting survival times of TB patients who are HIV positive to those who are HIV

negative. Two survival curves can be outlined, one for HIV positive and another one for HIV negative.

2.6.2.2 Comparing event times (survival curves) among TB patients

During follow-up of TB patients, it may be important to statistically compare the survival times of two or more groups of TB patients. A popular method used to achieve this is the Log-Rank or Mantel-Haenszel test (Qian & Zhou, 2022). The Log-Rank statistic can be used to quantify statistical differences in survival probability (survival curves) between different groups of people being studied. For example, the null hypothesis that there is no difference in six-month survival probability between HIV positive and HIV negative patients on TB therapy might be examined. The Kaplan-Meir approach can be used to calculate the survival probability for HIV-negative and HIV-positive TB patients independently, while the Log-Rank test can be used to statistically compare the survival probabilities between the two groups of TB patients. When computing the Log-Rank test, the sums of the observed and expected number of events of interest are computed for each time of the event and summed for each comparison group (e.g., HIV negative and HIV positive). Since the Log Rank test is a statistical hypothesis test, a p-value is usually calculated at the end of it (Bland & Altman, 2004). Although p-values are often set at 0.05 (5%), deriving a p-value together with confidence interval and effect size estimate yields stronger statistical and epidemiological support (Homa-bonell, 2023). If the calculated p-value is greater than 0.05, the null hypothesis is not rejected. This implies that, based on the available data, both groups, e.g., HIV-positive and HIV-negative populations, have the same survival probability distribution. If the p-value is less than 0.05, the null hypothesis is rejected and it is assumed that the two groups have statistically different survival probabilities.

2.6.3 The hazard function

The instantaneous rate at which an event of interest will occur is represented by the hazard function (h(t)) (Kartsonaki, 2016). The hazard function can also be used to represent the relationship between the probability density function P(t) and the survival function S(t), which is given by:

$$h(t) = P(t)/S(t)$$

During treatment and follow up of TB patients, the hazard function can be the instantaneous probability of experiencing unfavorable TB treatment outcomes in the next time interval conditional upon having survived till that time *'t'*.

2.6.3.1 Cox proportional hazards model

Cox proportional hazards model (CPHM) is a semi-parametric regression technique for survival analysis used to measure the effect of hazard function (Cox, 1972). Cox proportional hazard model may take the univariable form; $h(t) = h_0(t) \times \exp(b_1X_1)$ where only one variable is included e.g., HIV status or multivariable form; $h(t) = h_0(t) \times \exp(b_1X_1+b_2X_2+...+b_pX_p)$, in which several covariates e.g., alcohol consumption, HIV status and gender of TB patients are included in the model to adjust for the effect of each covariate.

In the univariable and multivariable forms;

- t represents the survival time
- h(t) is the hazard function determined by a set of p covariates (X_1 X_2..., Xp)
- The coefficients (b_1, b_2..., bp) measure the impact (i.e., the effect size) of covariates.
- The term (h_0) is called the baseline hazard. It corresponds to the value of the hazard if all the X_i are equal to zero (the quantity exp (0) equals 1). The "t" in h(t) indicates that the hazard may vary over time.

- $X_1X_2…X_p$ are covariates (predictors) that have a multiplicative or proportional effect on the predicted hazard. In TB treatment and follow up data, this can be demographic characteristics e.g., sex, socioeconomic characteristics e.g., education level, clinical characteristics e.g., HIV status, and behavioral characteristics e.g., alcohol consumption.

When studying TB patients on treatment and follow up, the association between the predictor covariates ($X_1X_2…Xp$) and outcomes variables (unfavorable TB treatment outcomes) are quantified by the regression coefficients (b1, b2, ..., bp). The estimated coefficients represent the change in the expected log of the hazard ratio relative to a one-unit change in a specific predictor, holding all other predictors constant. The predicted hazard or the rate of suffering the unfavorable TB treatment outcomes is the product of the baseline hazard ($h_0(t)$) and the exponential function of the linear combination of the predictor covariates. Exponentiation ensures that the hazard is positive and this is achieved by taking the natural logarithm (ln) of each side of the Cox proportional hazards regression model. This produces the log of the relative hazard to a linear function of the predictors.

In most situations, groups of TB patients can be compared with respect to their hazards using the hazard ratio. The hazard ratio is the ratio of the hazard function to the baseline hazard i.e., two expected hazards: $h_0(t)\exp(b_{1a})/ h_0(t)\exp(b_{1b}) = \exp(b_{1(a-b)})$ which does not depend on time. This is an important CPHM assumption known as the proportional hazards assumption, which refers to the fact that the hazard ratio is constant over time (Xue *et al.*, 2013). The proportional hazard assumption is tested using statistical tests and graphical diagnostics based on scaled Schoenfeld residuals. When Schoenfeld residuals are plotted against time, a significant relationship ($p \leq 0.05$) between the residual and time indicates that the proportional hazard assumption has been violated,

and the violation can be corrected by stratifying the offending covariate. Additionally, each covariate is assumed to contribute linearly to the CPHM and has an additive effect on the natural logarithm of the hazard ratio.

2.6.4 Qualitative analysis of unfavorable tuberculosis treatment outcomes

The most basic definition of qualitative research is that "it uses words as data" (Braun & Clarke, 2013). Qualitative analysis generates rich, nuanced, and complex accounts from each participant, and can be analyzed thematically to reveal patterns related to data (Boyatzis, 1998; Braun & Clarke, 2006). The use of qualitative methods among patients who experience unfavorable TB treatment outcomes may allow them to clarify their own reality, attitudes or specific behaviors that are likely to cause preventable unfavorable TB treatment outcomes, while also allowing researchers to learn how people experience and define their conditions or how interventions are tailored to specific settings (Doyle *et al.*, 2009). Previously, qualitative approaches have rarely been used on patients who experience unfavorable TB treatment outcomes, making it difficult to obtain more information that could be used to improve TB treatment success. In-depth interviews can be used to elicit reasons for treatment stoppage from patients who interrupt treatment, whereas a mortality audit can be used to investigate causes and circumstances that contribute to mortality through a focus group discussion. This can be accomplished by soliciting opinions from experienced clinicians, obtaining narratives from care givers of diseased patients, and reviewing patients' medical records.

2.7 Conceptual framework

The conceptual framework in Figure 2.1 displays interaction between the predictor and outcome variables in the present study (Table 3.2). The premise of this study is that the predictor covariates (patients' characteristics) predict the occurrence of the outcome variables (unfavourable TB

treatment outcomes). Tuberculosis can be effectively prevented and controlled through interventions that take patients' characteristics into consideration. The predictor variables considered for this study include baseline patients' characteristics i.e., demographic characteristics (e.g., age and gender), socio-economic characteristics (e.g., education level and employment), behavioural characteristics (e.g., alcohol and smoking), and clinical characteristics (e.g., HIV status, clinical condition and comorbidity). Health system factors such as timely diagnosis, clinical care of patients and follow up protocols, represent extraneous variables that play an important role in modifying the unfavourable treatment outcomes. Patients' knowledge, perceptions, attitudes, and personalities are among the intervening variables in this study.

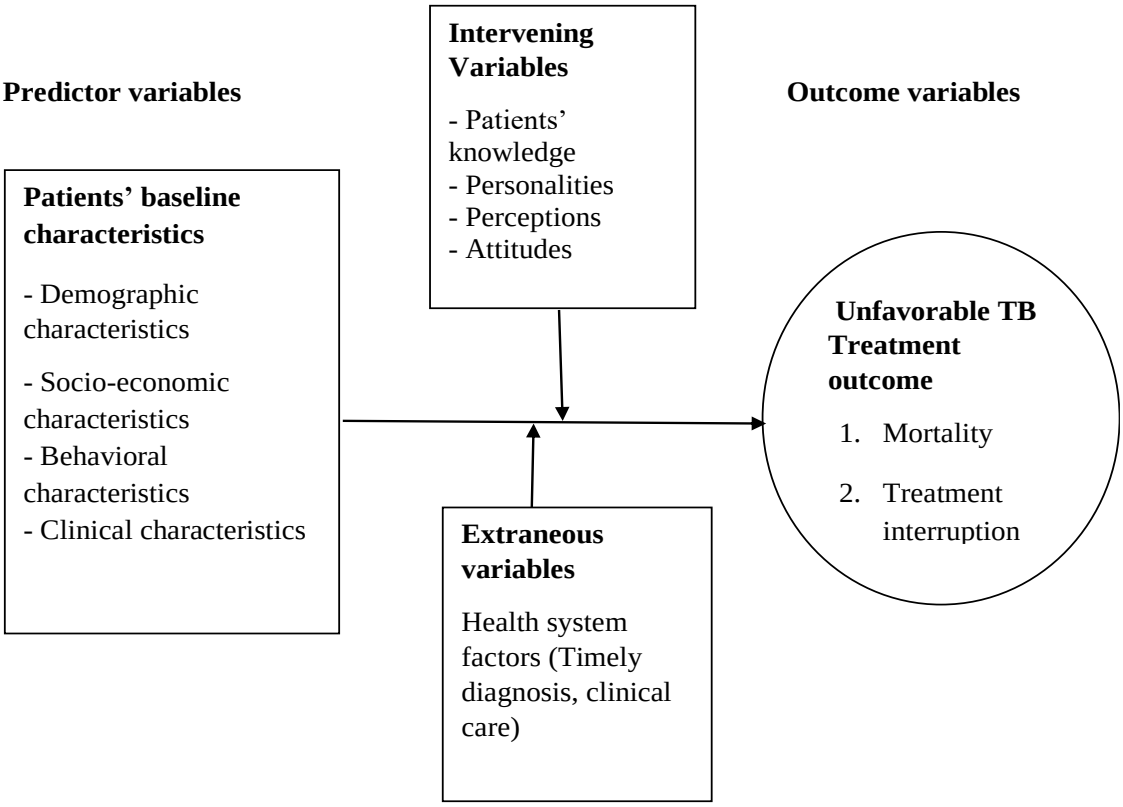

Figure 2.1: Conceptual framework (Patient care & follow-up; Ministry of Health, 2021)

CHAPTER THREE

METHODOLOGY

3.1 Introduction

This chapter outlines the methods and procedures used to carry out the study. The chapter focuses on the study's design, study area, and study population. The chapter also describes in detail how the sample size was depicted, how it was distributed in selected health care facilities, and how study participants were selected. The chapter also covers data collection instruments and data gathering strategies, key variables, and data analysis techniques. The chapter then discusses the study's ethical considerations and approvals.

3.2 Study design

This study utilized a prospective cohort design. A cohort of patients who commenced TB treatment between July and December 2019 was considered in to the study. The patients' apparent demographic, socioeconomic, behavioral and clinical characteristics were depicted in baseline data, gathered within two weeks of treatment commencement. Each patient was observed for six months or until an event that constituted treatment termination, such as mortality or treatment interruption occurred. The follow-up observation was conducted in conjunction with the routine follow-up schedules, which were once a week during the intensive phase and twice a month during the continuation phase. Patients who interrupted treatment were identified and physically traced, and the reasons for their interruption were documented. All patients who died while receiving treatment were subjected to a mortality audit. This made it possible to document the causes of mortality and circumstances that contributed to mortality.

3.3 Study area

This study was carried out in Vihiga county (Figure 3.1) which is located in the western region of Kenya. The county has a population of 590,013 with a male/female ratio of 0.9:1 (Kenya National Bureau of Statistics, 2019). The county's annual fertility rate is 5.1%, with 49% of the population aged 15 to 64 years. Age categories 0-14 years and >65 years account for 45% and 6% of the total population, respectively. Vihiga County is fully covered by community health strategy, i.e., all households are overseen by community health personnel; the Community Health Assistants (CHAs) and Community Health Volunteers (CHVs). The county has four TB treatment zones; Emuhaya, Vihiga, Sabatia and Hamisi (Ministry of Health, 2020a). As of 2019, the county had 111 health care facilities, including 65 public, 9 faith-based, and 37 private facilities. Sixty-two health facilities provide TB management services, of which, thirty-one health facilities provide TB diagnosis, treatment, and follow-up services, whereas the remaining thirty-one solely provide TB treatment and follow-up services. Across the county is a robust sample networking initiative in which, twenty contracted and trained riders traverse the county to collect samples from non-diagnostic health facilities and deliver them to health facilities with molecular and/or AFB microscopy capabilities for TB diagnosis. For molecular testing, Vihiga County Referral Hospital, Emuhaya Sub County Hospital, and Hamisi Sub County Hospital each has one *GeneXpert* machine. The *GeneXpert* technique simultaneously detects the presence of *Mycobacterium tuberculosis* bacteria in a sample as well as resistance to Rifampicin, one of the most potent anti-TB medicines (Horne *et al.,* 2019). In the 2018 cohort, the county reported TB case notification rate of 119 per 100,000 population. The county has also consistently reported high rates of treatment interruption and mortality. Vihiga is placed second among Kenyan counties with the highest TB-related mortality (Ministry of Health, 2019).

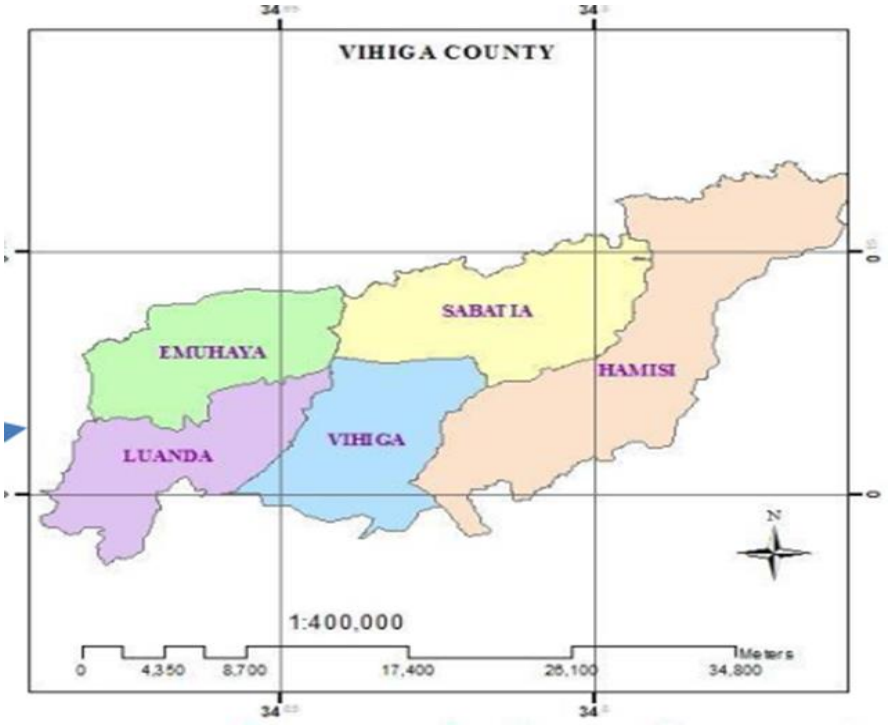

Figure 3.1: Map of Vihiga County (Source: Vihiga CIDP 2018-2022)

3.4 Study population

This study's population consisted of patients who had been diagnosed with tuberculosis, started treatment, and had been notified. Vihiga County notifies 850 TB patients annually on average, with 90% of patients being 15 years or older (Ministry of Health, 2017, 2018a, 2019). More than 85% of TB patients receive their care and follow-up from county's twenty health facilities (Table 3.1). Patients with TB have a variety of inherent demographic characteristics, socio-economic, behavioral and clinical characteristics that are likely to influence their treatment outcomes.

3.4.1 Inclusion criteria

This study included the following participants:

i. Male and female patients, 15 years and older, who had commenced a six months TB treatment.

ii. Patients who had been notified in the health facility TB patients record cards and TB treatment registers as well as in the TIBU database.

iii. Patients who were starting the treatment or whose treatment has lasted less than two weeks

iv. Patients who provided a written consent or assent to participate in the study.

3.4.2 Exclusion criteria

i. Patients with TB involving meninges, bones, and or joints

ii. Patients with drug-resistant TB

iii. Patients who were referred out to or opt to get their TB treatment in a different health facility

3.5 Sample size determination

The sample size for the current study was calculated using the Cochrane equation (Cochran, 1977)**.** For populations that are large, or infinite, Cochran developed an equation to yield a representative sample for proportions.

$$\mathbf{n = z^2pq / e^2}$$

Where;

- ***n*** is the sample size,
- $\boldsymbol{z^2}$ is the selected critical value of desired confidence level
- ***e*** is the desired level of precision,
- ***p*** is the estimated proportion of an attribute that is present in the population, and
- ***q*** is 1-p

Assuming the maximum variability of 50% (p=0.5) and taking a 95% confidence level with 0.05 precision, the required sample will be calculated as follows;

$$[(1.96)^2(0.5)\ (0.5)] / (0.05)^2 = 384$$

However, Cochran indicated that if the accessible population is finite, the sample size can be reduced slightly using the following correction formula.

$$\mathbf{n} = n_o / 1 + [(n_o - 1)/N]$$

Where n is the sample size, n_o is the sample size for an infinite population (384) at a 95% confidence level and N is the size of the accessible population

The accessible population for this study was finite, i.e., the average annual (2012-2018) number of notified TB cases in Vihiga County was 850 (Ministry of Health, 2017, 2018a, 2019)**.** If n_o/N (384/850) is negligible then n_o is a satisfactory approximation of the sample size (Cochran, 1977). In this study, the sample size of 384 exceeds 5% of the population size (850). Therefore, using the correction formula, the sample size for the study was calculated as follows:

$$\mathbf{n} = 384/ 1 + [(384 - 1)/850] \mathbf{= 265}$$

To compensate for TB cases the researcher would be unable to contact, 10% of the calculated sample size (265) was added resulting in the total sample (n) size of **291.**

3.6 Sampling procedure

3.6.1 Selection of study health facilities and allocation of the sample

Twenty health facilities that account for >85% of TB cases in Vihiga County (Ministry of Health, 2017, 2018a, 2019) were purposively selected, five from each of the four TB treatment zones. The proportionate allocation of sample size to the selected health facilities is presented in Table 3.1. First, the sample of 291 was proportionately distributed to four TB treatment zones based on their annual TB caseload. For instance, Vihiga treatment zone was assigned a sample size of 99 TB patients (34/100*291=99) since it accounts for 34% of all TB cases in Vihiga County. Secondly, similarly, the sample from each treatment zone was proportionately distributed to five health

facilities within that zone based on their annual TB caseload. This is consistent with a congregation of TB disease in particular locations, patient facility access (Maore *et al.,* 2017), and user preferences (Munch *et al.,* 2003). This strategy also offered an opportunity to net in more TB patients per given zone as well as to precisely capture patients' diverse characteristics.

Table 3.1: Proportionate sample size allocation to treatment zones and health facilities

Treatment Zone	Percentage Contribution of TB Cases, 2012-2018	Allocated Sample size (n)	Health facilities	Percentage Contribution of TB cases, 2012-2018	Allocated Sample size (n)
Sabatia	14	40	Sabatia SCH	48	19
			Kegondi HC	16	6
			Givudimbuli HC	14	6
			Bugina HC	13	5
			Nadanya Dis	9	4
Vihiga	34	99	Vihiga CRH	60	59
			Mbale rural HC	17	17
			Vihiga HC	12	12
			Lyanaginga HC	8	8
			Iduku Dispensary	3	3
Emuhaya	26	76	Coptic Hospital	44	33
			Emuhaya SCH	23	18
			Ipali HC	13	10
			Ebusiratsi HC	12	9
			Esiarambatsi HC	8	6
Hamisi	26	76	Serem HC	29	22
			Kaimosi Hospital	18	14
			Tigoi HC	18	14
			Hamisi SCH	18	14
			Kaptech Dispensary	17	12
Total		**291**			**291**

HC = Health Centre; Dis = Dispensary; SCH = Sub County Hospital; CRTH = County Referral Hospital Proportions extracted from TIBU with permission from NTLP

3.6.2 Selection of study participants

For each selected health care facility, eligible participants (TB patients) were selected sequentially until the sample size allocated to it was accrued. The selection of eligible patients took place between July and December, 2019.

3.7 Data collection instruments/tools and approaches

Three data collection instruments were used in this study; the questionnaire, the treatment interruption tracing form, and the mortality audit tool.

3.7.1 Questionnaire

A structured questionnaire (Appendix 1) was primarily used to collect demographic, socioeconomic, behavioural, and clinical data that could potentially predict treatment interruption or mortality at the beginning of treatment (baseline or time zero). Before administering questionnaires, eligible patients were asked for their voluntary consent/assent (Appendices 2 & 3). Questionnaires were administered through face-to-face interviews by the principal investigator and clinical officers or nurses, each from a participating health facility. Additional clinical data was obtained from patients' medical records (files). Each study participant was followed-up throughout his or her treatment period. A treatment outcome was assigned whenever an event of interest (treatment interruption or mortality) or censoring event (treatment completion, treatment failure, or treatment discontinuation) occurred. The principal investigator, who traversed around the field throughout the data collection period, ensured that the data quality was maintained. Furthermore, the principal investigator was always available to resolve any issues raised by the research assistants. Before being accepted for analysis, questionnaires were checked for completeness and clarity.

3.7.2 Treatment interruption tracing form

The treatment interruption tracing form (Appendix 4) was adapted and customized for this study from a nationally recognized TB treatment interruption tracing form. The TB treatment interruption tracing form was used to gather qualitative data depicting reasons for treatment

interruption among patients who had interrupted their treatment. The treatment interruption tracing form was administered by community health volunteers (CHVs). Data for treatment interruption tracing form was gathered through administration of an in-depth open answer question, 'tell me the reason why you stopped taking TB medicines before the required time of six months?'. The entire patient's response was recorded, after which patients were counseled and referred back to the health facilities for treatment re-initiation. For those patients who were not found during tracing, explanations for their absence were also recorded in the treatment interruption tracing form.

3.7.3 Mortality audit tool

The customized section five of the national TB mortality audit tool (Appendix 5) was used to obtain qualitative data on the causes and circumstances that contributed to mortality for all patients who died during follow-up. The mortality audit was carried out using a focus group discussion with a team of clinicians managing patients in various health facilities, the SCTLC(s), and the principal investigator. The mortality audit included a review of patients' medical data as well as an appraisal of narrative from attending clinicians and patients' care takers. The principal investigator recorded causes of death and conditions that contributed to death, which were subsequently categorized by patients' HIV status.

3.7.4 Reliability and validity of data collection instruments

To ensure reliability and validity, the questionnaires were pretested to identify any errors that may have occurred during the instrument's construction. Pre-tests were carried out on twenty TB patients from health facilities that were not selected to participate in this study. Returned pre-test questionnaires were checked and discussed by the enumerators, TB management experts

(SCTLCs) and the principal investigator. Questions with unclear language or content were reformulated until a clearer version of the questionnaire was arrived at. The treatment interruption tracing form and mortality audit tool are national TB surveillance and data management tools that have been pre-validated and standardized for use in routine care and follow-up of TB patients. They were, however, modified and tailored for this study.

3.8 Recruitment and training of research assistants

3.8.1 Research assistants for administration of questionnaires

Twenty research assistants, each from a participating health facility, were recruited to collect data for questionnaires. The research assistants included clinical officers and nurses (clinicians) offering health care services in TB and HIV clinics. This group of health care professionals is well-versed in TB patient care, treatment, and follow-up. They also comprehend English, Kiswahili, and, to a large extent, local languages in the study area. The research assistants were led through all questions in the questionnaires, and any concerns they expressed were addressed. Before pretesting, the research assistants did simulation face-to-face interviews among themselves. Post-simulation evaluation and discussion were undertaken to address any arising issues.

3.8.2 Research assistants for administration of treatment interruption tracing form

Twenty community health volunteers (CHVs), one from each participating health facility, administered treatment interruption tracing forms to patients who had interrupted treatment. The CHVs provide a wide range of health care services to the community, and their practice is guided by the Kenya Community Health Policy 2020-2030 (Ministry of Health, 2020b). The CHVs who participated in the present study were fluent in English, Kiswahili, and the local language, and they had previously undergone training on the community TB package, which included management

of TB contacts and TB treatment interrupters. However, before taking part in this study, the CHVs were reoriented on the management of TB treatment interruption. The CHVs used previously obtained patients' physical addresses and contact information to track patients who had interrupted treatment.

3.9 Variable definition

Variables for this study are defined in Table 3.2. The outcome variables for this study are two; treatment interruption (yes or no) or mortality/death (yes or no). The outcome of 'treatment interruption' was assigned to patients who missed their clinic appointment for at least two months. A physical search of patients who interrupted treatment was usually initiated using the previously obtained physical address and contact information (Ministry of Health, 2021). The death of a TB patient was all-cause mortality confirmed by the clinical team who explicitly recorded the death in patient record cards and TB registers. The follow-up time for the study was the total time elapsed starting from the day a TB patient started treatment until he/she completed the treatment (180 days) (programmatically six months). Time to event was defined as the time in days until treatment interruption or death. Censoring occurred when information about the survival time of some patients was incomplete. If the event of interest was treatment interruption, then censored patients included those who died, discontinued treatment, failed treatment, or completed their treatment; if the event of interest was death, then censored patients included those who interrupted treatment, discontinued treatment, failed treatment, and completed their treatment. Predictor variables considered in this study included demographic, socio-economic, behavioural, and clinical characteristics of TB patients.

Table 3.2: Variable Definition

Variable name	Variable level	Definition of variable	Measurement
Treatment interruption	Nominal	Interrupting TB treatment for at least two months; yes or no	Patient records
Died	Nominal	If a TB patient died due to any cause; yes or no	Patient records
Time to Event	Numeric	Time in days from treatment initiation to treatment outcome	Patient records
Zone	Nominal	TB treatment zone where facility is located; Vihiga, Emuhaya, Hamisi or Sabatia	Administrative records
Sector	Nominal	Type of health facility, Public or Faith-based	Administrative records
Gender	Nominal	Gender of TB patients, Male or Female	Self-reported
Age	Numeric	Chronological age of TB patients in years	Identity card/facility records
Occupation	Nominal	Status of Employment of TB patients; Employed or not employed	Self-reported
Marital status	Nominal	Marital status of a TB patient, married or not married	Self-reported
Monthly-income	Nominal	Monthly income of TB patients in Kenya shillings	Self-reported
Family size	Numeric	Number of family members for TB patients	Self-reported
Education level	Nominal	Education level of TB patients: Primary or lower; Secondary; post-secondary	Self-reported
Duration of illness	Nominal	Duration in weeks from the day patients started experiencing signs and symptoms of TB to the date they visited a health facility: 1-2 weeks, 2-4 weeks or more than 4 weeks	Self-reported
First sector visited	Nominal	Sector/Type of health facility a patient visited first for consultation: Chemist, faith based, Herbal, private or public	Self-reported
Treatment supporter	Nominal	A person who reminds the TB patient on health appointment, observe the patient take drugs and supports the patients in any other way; yes or no	Self-reported
Smoking	Nominal	Smoking status before or as at TB diagnosis; yes or no	Self-reported
Alcohol consumption	Nominal	Alcohol consumption status before or as at TB diagnosis; yes or no	Self-reported
Substance abuse	Nominal	Abuse of any other illicit drugs apart from cigarette and alcohol before or as at TB diagnosis; yes or no	Self-reported
No. visits	Numeric	Number of times the patient visited health facility before TB diagnosis	Self-reported
Clinical Condition	Nominal	If the patient is unable to walk, has respiratory rate >30/min, heartrate >110/min or temperature $>39^0$C then he/she is severely ill, otherwise stable; yes or no	Clinic records/clinical appearance
Type of TB	Nominal	If TB involves the lung, it is PTB otherwise EPTB	Clinic records
Clinical TB Classification	Nominal	If TB was confirmed using a biological specimen e.g., sputum, it is bacteriologically confirmed if not, it is clinically diagnosed	Clinic records
Type of patient	Nominal	New is a patient who has never been on TB treatment, Relapse successfully completed TB treatment but has TB again while TLF interrupted previous TB treatment	Clinic Records; self-report
TPT for HIV positive	Nominal	Whether TB/HIV co-infected patient has ever been on TB preventive therapy (TPT); yes or no	Clinic Records/ self-report
HIV status	Nominal	HIV status of TB patient; HIV positive or HIV negative	Clinic Records
Viral Suppression	Nominal	Viral suppression status among TB & HIV coinfected patients: new, not done, not suppressed or suppressed	Clinic Records
Ever stopped taking ART	Nominal	If the TB/HIV coinfected patient has ever interrupted antiretroviral therapy (ART); yes, no or is a ART naïve	Clinic Records
Nutritional category	Nominal	Severely malnourished Body mass index (BMI) <16; Moderate BMI =16-18.49; normal – BMI = 18.5-24.9; Overweight- BMI = 25-30	Clinic records; BMI assessment at time of visit
Food support	Nominal	Whether on food by prescription; yes or no	Clinical report/ self-reported
Comorbidities	Nominal	If a TB patient has any other condition apart from HIV, alcohol abuse or smoking, yes or no	Abstracted from clinic records/ self-reported

3.10 Data analysis

Data for the current study was analyzed using *R* software version 4.1.0. To describe characteristics of tuberculosis patients by their treatment outcomes in Vihiga County, standard descriptive statistics; proportions, median (interquartile range (IQR)), and mean (standard deviation (SD)) were calculated to demonstrate the demographic, socio-economic, and clinical factors and characterize their distributions.

To identify determinants of tuberculosis treatment interruption among notified patients, Kaplan Meier (KM) estimator was used to obtain univariable descriptive statistics for time to treatment interruption, including estimation of probabilities of treatment completion by patient characteristics and determining time intervals. The Log-rank test for the equality of survival distributions was used to analyze the statistical significance of differences in probability of treatment completion among patients based on their characteristics. Cox proportional hazard (CPH) model, was fitted to identify determinants of TB treatment interruption through the calculation of hazard ratios with a 95% Confidence Intervals (CIs). Reasons for treatment interruption from patients who interrupted treatment were identified thematically.

To investigate factors associated with survival distribution and occurrence of all-cause mortality among notified TB patients, the Kaplan Meier (KM) estimator was used to obtain univariable descriptive statistics for time to mortality, including estimation of survival probabilities by patient characteristics and determine time intervals. The Log-rank test for the equality of survival distributions was used to analyze the significance of survival differences among categorical variables and the overall differences between estimated survival curves of patients by their characteristics. Cox proportional hazard model was fitted to analyze factors associated with

mortality through the calculation of hazard ratios (HR) with a 95% CIs. Due to variations in mortality rates between TB/HIV coinfected patients and HIV negative patients, the sample size was further separated into two subgroups depending on patients' HIV status, and each subgroup was analyzed independently. Kaplan Meier (KM) estimator was calculated to estimate survival probabilities by patient characteristics in each subgroup while the CPH model, was fitted to identify predictors of all-cause mortality through the calculation of hazard ratios at a 95% CI. Causes of mortality and conditions contributing to mortality among patients who died during follow-up were identified from the mortality audit and categorized by HIV status.

For multivariable analyses, variables with a p-value < 0.05 and universal demographic covariates such as age and sex were included in the CPH model. Before fitting the covariates into the CPH model, the proportional hazard assumption was tested by plotting Schoenfeld residuals against time to test for time and residual independence. The covariates that failed to satisfy this criterion were stratified. A backward stepwise strategy was used to help identify the models with the lowest AIC while the statistical significance was set at p 0.05 for all variable analyses.

3.11 Ethical consideration

3.11.1 Ethical approval

This study was ethically approved by Maseno University Ethical Review Committee (MUERC) (Ref: MSU/DRPI/MUERC/00707/19) and the National Commission for Science, Technology & Innovation (NACOSTI) (License no.: NACOSTI/P/19/1618) and was conducted in accordance with the Helsinki's declaration, a 'statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data' (World Medical Association, 2013).

3.11.2 Administrative approval, entry and participant recruitment process

The principal investigator entered participating health facilities through the office of the county director of health services who administratively permitted the implementation of this study. The in charges of selected health facilities were informed through the county health director's office. The principal investigator oversaw the recruitment of the study participants (patients). Those patients who were selected and appropriately consented/assented were listed for the administration of questionnaires and follow-up during their subsequent clinic appointment days.

3.11.3 Participants' consent/assent and confidentiality

Written informed consent/assent was obtained from all participants and confidentiality was ensured throughout the study. For the participants below 16 years, the parents/guardians provided assent. The consent/assent indicated that participating in the study was voluntary, would not yield any financial benefits and those who wished to opt out of the study could be allowed to do so unconditionally. To ensure participants' confidentiality, their names did not appear on data collection tools, instead, every participant was assigned a unique code to ensure anonymity, but allowed the researcher to link individuals to their data in case of need for mandatory notification.

3.11.4 Safety of principal investigator and research assistants

To ensure safety of the principal investigator and the research assistants, this study was conducted alongside daytime routine care and treatment of TB patients and was guided by Ministry of health policies, guidelines, and standard operating procedures. To prevent TB transmission, routine infection prevention and control techniques such as environmental management and respiratory protection were utilized.

CHAPTER FOUR

RESULTS

4.1 Introduction

The results for this study are presented in three sections: distribution of tuberculosis disease and treatment outcomes by characteristics of notified tuberculosis patients, determinants of TB treatment interruption, and factors associated with survival probability distribution and all-cause mortality among patients on TB treatment in Vihiga County. Two hundred and ninety-one patients were followed up for at most 180 days. Two hundred and twelve (73%) TB patients completed their treatment, 32 (11%) interrupted their treatment, 45 (15%) died, one failed treatment, and another one discontinued treatment because he developed adverse drug reactions.

4.2 Distribution of tuberculosis disease and treatment outcomes in Vihiga County based on characteristics of notified patients

4.2.1 Demographic and socio-economic characteristics of TB patients by treatment interruption, mortality, and successful treatment

Demographic and socio-economic characteristics of TB patients by treatment interruption, mortality, and successful treatment are summarized in Table 4.1. Of the 291 TB patients under observation, slightly more than a third (34%) were from the Vihiga treatment zone. Overall, 241 (83%) were from public health facilities, and the male sex comprised of majority (n=209, 72%) of the patients. Nearly half of the TB patients in the study were in the age categories 25–34 years (23.4%) and 35–44 years (23.4%), with just 11% aged 15–24 years. Treatment interruption was more common in age groups 25–34 years (16.2%), 65+ years (16%), and 45-54 years (15.8%), whereas mortality was more common in age groups 65+ years (24%), and 55-64 years (20%). The age category 15-24 years had the lowest proportion of mortality (9%), while non interrupted TB

treatment in the age category 55-64 years. The highest TSR was recorded among patients aged 15-24 years, whereas the lowest TSR was observed among patients aged 65 years or older. The median monthly income for TB patients was 3000 shillings (IQR = 1500-5000). Only 19 (6.5%) patients had a formal employment and two among them died while none of the employed patients interrupted treatment. Overall, the treatment success rate (TSR) was almost 90% among the employed group compared to 72% among the unemployed patients. Almost 62% of TB patients under study were not married and lower proportion of the unmarried (68%) successfully completed their treatment compared to those who were married (80%). Also, the proportion of patients who interrupted treatment and died was higher among the unmarried (14% and 17%) compared to the patients who were married (6% and 13%). Of the 291 patients under observation, 172 (59%) had primary education or lower. Slightly more (61%) male TB patients had primary level education or lower compared to females (56%). Twenty-six (15%) patients with primary or lower-level education interrupted treatment while 31 (18%) died. Also, patients with primary or lower-level education had the lowest treatment success (66%) in the category of education level. One hundred and fifty-three (53%) patients under observation reported to be consuming alcohol. The prevalence of alcohol consumption was higher among male (68%) compared to female (11%) patients. Treatment success rate for patients who never consumed alcohol was higher (86%) than those who consumed alcohol (61%). Sixteen percent (16%) of patients who consumed alcohol died while 10% of those who never consumed alcohol died. Also, a higher proportion (26%) of patients who consumed alcohol interrupted their treatment compared to patients (4%) who never consumed alcohol. Similarly, a lower proportion of patients who smoked (58%) and those who abused drugs (58%) completed their treatment compared to those who never smoked (86%) and those who never abused drugs (75%), respectively. Of the 291 patients under observation, 183 (63%) experienced

illness from TB for at least four weeks before they sought healthcare services. The reason for delay in seeking health care services among 54% of patients who delayed seeking health care service for at least two weeks was a perception that the initial signs and symptoms they experienced were not severe enough. One hundred and forty-one patients (48.5%) did not have a treatment supporter and their TSR was 63.8% while TSR for patients with a treatment supporter was 81.3%. Treatment interruption rate was 5% among patients with a treatment supporter and 17% among those without a treatment supporter.

Table 4.1: Demographic, socio-economic & behavioral characteristics of tuberculosis patients by treatment outcomes

label	Levels	Frequency (%)	Interrupted treatment (%)	Died (%)	Successfully treated (%)
TB treatment zone	Vihiga	101 (34.7)	9 (8.3)	18 (17.8)	73 (72.3)
	Emuhaya	87 (29.9)	11 (12.6)	13 (14.9)	63 (72.4)
	Hamisi	63 (21.6)	8 (12.7)	9 (14.2)	46 (73)
	Sabatia	40 (13.7)	4 (10)	5 (12.5)	30 (75)
Health sector	Faith Based	50 (17)	4 (8.2)	11 (22)	34 (68)
	Public	241 (83)	28 (11.6)	34 (14)	178 (74)
Sex	Male	209 (71.8)	24 (11.5)	32 (15.3)	151 (72.2)
	Female	82 (28.2)	8 (9.8)	13 (15.8)	61 (74.4)
Age Category	15-24	33 (11.3)	2 (6)	3 (9)	28 (85)
	25-34	68 (23.4)	11 (16.2)	9 (13.2)	47 (69)
	35-44	68 (23.4)	6 (9)	10 (14.7)	51 (75%)
	45-54	57 (19.6)	9 (15.8)	9 (15.8)	39 (68.4)
	55-64	40 (13.9)	0	8 (20)	32 (80)
	65+	25 (8.6)	4 (16)	6 (24)	15 (60)
Employment status	Employed	19 (6.5)	0	2 (10.5)	17 (89.5)
	Not Employed	272 (93.5)	32 (11.8)	43 (15.8)	195 (71.6)
Married	Married	111 (38.1)	7 (6.4)	14 (12.6)	89 (80.2)
	Not married	180 (61.8)	25 (13.8)	31 (17.2)	123 (68.3)
Monthly income (KSH)	Median (IQR)	3000 (1500-5000)	3000 (1425-4000)	3000 (1500-4000)	3000 (1500-5000)
Family size	Mean (SD)	4.1 (1.9)	4.2 (2.3)	4.2 (1.4)	4 (1.9)
Education level	Secondary	95 (32.6)	5 (5.3)	12 (12.6)	78 (82.1)
	Post-Secondary	24 (8.2)	1 (4.2)	2 (8.3)	20 (83.3)
	Primary or lower	172 (59.1)	26 (15.1)	31 (17.9)	114 (66.3)
Alcohol consumption	Yes	153 (52.6)	27 (17.6)	31 (20.3)	93 (60.8)
	No	138 (47.4)	5 (3.6)	14 (10.1)	119 (86.2)
Drug/substance abuse	Yes	31 (10.7)	8 (25.8)	5 (16.1)	18 (58.1)
	No	260 (89.3)	24 (9.2)	40 (15.4)	194 (74.6)
Smoking	Yes	136 (46.7)	25 (18.4)	31 (22.8)	79 (58.1)
	No	155 (53.3)	7 (4.5)	14 (9)	133 (85.8)
Duration of symptoms before visiting health facility	1-2 weeks	39 (13.4)	2 (5.1)	4 (10.3)	33 (84.6)
	2-4 weeks	69 (23.7)	5 (7.2)	6 (8.7)	58 (84.1)
	>4 weeks	183 (62.9)	25 (13.7)	35 (19.1)	121 (66.1)
First health sector visited	Public facility	137 (47.1)	12 (8.6)	18 (13.1)	105 (76.6)
	Private facility	47 (16.2)	4 (8.5)	7 (14.9)	36 (76.6)
	Chemist	73 (25.1)	12 (16.4)	14 (19.2)	47 (64.4)
	Faith based	24 (8.2)	3 (12.5)	4 (16.7)	17 (70.8)
	Herbal	10 (3.4)	1 (10)	2 (20)	7 (70)
No. visits to facilities before TB diagnosis	Mean (SD)	2.8 (1.6)	2.4 (0.9)	2.9 (1.4)	2.8 (1.7)
Treatment supporter	Yes	150 (51.5)	8 (5.3)	19 (12.7)	122 (81.3)
	No	141 (48.5)	24 (17)	26 (18.4)	90 (63.8)

IQR=Interquartile range; SD =Standard deviation; KSH =Kenya shillings, No. = Number

4.2.2 Clinical characteristics of TB patients by treatment interruption, mortality, and successful treatment

Clinical characteristics of TB patients under observation with their correspondent treatment outcomes (treatment interruption, death, and treatment success) are presented in Table 4.2. Of the 291 patients on follow-up, 136 (47%) were severely ill at the time of treatment commencement while 155 (53%) were clinically stable. Among the severely ill patients, 41 (30%) died during follow up while only 4 (3%) clinically stable patients died. Of the total patients under observation, 269 (92%) had Pulmonary TB (PTB); treatment success rate among the PTB patients was 74% while a TSR of 60% was recorded among the patients with Extra pulmonary TB (EPTB). This excluded patients with TB affecting bones, joints and the central nervous system. Pulmonary TB patients had slightly higher (n=30, 11%) treatment interruption rate than EPTB (n=2, 9%) while death rate was higher (n=9, 32%) among EPTB patients than PTB patients (n=38, 14%). Regarding clinical categorization, the majority (n=227, 78%) of the TB patients were bacteriologically confirmed. Higher death (n=17, 27%) and lower treatment success rate (n=39, 61%) were observed among the clinically diagnosed TB patients compared to the bacteriologically confirmed (death = 12%, TSR = 76% respectively). Four (30.8%) of 13 patients who previously interrupted treatment (TLF) interrupted treatment again during follow-up. One hundred and one (35%) patients under observation were HIV positive (TB/HIV coinfected). Among them, the majority (n = 65, 64%) were newly diagnosed with HIV while (n=36, 36%) were already living with HIV at the time of TB diagnosis. Of the 101 TB/HIV coinfected patients, 77 (76%) had CD4 results with a median CD4 count of 125 cells/ml (IQR = 57-239) and a range of 4-748 cells/ml. Among 27 (75%) TB/HIV coinfected patients who had viral load results, 9(33%) had suppressed viral load while 18 (67%) had an unsuppressed viral load. The death rate was higher among patients with

unsuppressed viral load (n=9, 50%) compared to TB/HIV patients with a suppressed viral load (n=3, 33%). All 101 HIV-positive patients were on cotrimoxazole preventive therapy while 97 (96%) patients were on antiretroviral therapy (ART). Among patients on ART, 94 were on first-line ART while 3 were on second-line ART. Of the 36 patients who were living with HIV infection at the time of TB diagnosis, 30 (83%) reported to have previously stopped taking ART and among them, 13 (43%) died during follow up while only one patient who had never stopped taking ART died. Cumulatively, the death rate among TB/HIV coinfected patients was higher (n =27, 27%) compared to death rate among the HIV negative TB patients (n =18, 10%). Furthermore, 75 (26%) of patients under observation were severely malnourished and only 11 (15%) of severely malnourished were put on food support. Severe malnutrition comprised the highest death rate (n=28, 37%) and lowest treatment success rate (n=42, 56%) in the nutritional category. Thirty-six patients (12%) had comorbidities and 16 (44%) with comorbidities died during follow-up.

Table 4.2: Clinical characteristics of tuberculosis patients by treatment outcomes in Vihiga County

label	Levels	Frequency (%)	Interrupted treatment (%)	Died (%)	Successfully treated (%)
Clinical condition	Stable	155 (53.3)	18 (11.6)	4 (2.6)	131 (84.5)
	Severely ill	136 (46.7)	14 (10.3)	41 (30.1)	81 (59.6)
Type TB	PTB	269 (92.4)	30 (11.2)	38 (14.1)	199 (74)
	EPTB	22 (7.6)	2 (9.1)	7 (31.8)	13 (59.1)
Clinical TB classification	Bact – confirmed	227 (78.0)	24 (10.6)	28 (12.3)	173 (76.2)
	Clinically diagnosed	64 (22.0)	8 (12.5)	17 (26.6)	39 (60.9)
Type of patient	New	246 (84.5)	26 (10.6)	40 (16.3)	179 (72.9)
	Relapse	30 (10.3)	2 (6.7)	4 (13.3)	23 (76.9)
	TLF	13 (4.5)	4 (30.8)	1 (7.7)	8 (61.5)
	Failure	2 (0.7)	0	0	2 (100)
TPT for HIV Pos	Yes	22 (7.6)	2 (9.1)	10 (45.5)	10 (45.5)
	No	14 (4.8)	0	5 (35.7)	9 (64.3)
	New	65 (22.3)	8 (12.3)	12 (18.5)	45 (69.2)
HIV status	Pos	101 (34.7)	10 (9.9)	27 (26.7)	64 (63.4)
	Neg	190 (65.3)	22 (11.6)	18 (9.5)	148 (77.9)
Viral Suppression	Suppressed	9 (9)	1 (11.1)	3 (33.3)	5 (55.6)
	Not Suppressed	18 (18)	1 (5.6)	9 (50%)	8 (44.8)
	Not done	7 (6)	0	2 (28.6)	5 (71.4)
	New	67 (67)	8 (11.9)	13 (18.4)	46 (68.7)
Ever stopped ART	Yes	30 (30)	2 (6.7)	13 (43.3)	15 (50)
	No	6 (5)	0	1 (16.7)	5 (83.3)
	Starting	65 (65)	8 (12.3)	13 (20)	44 (67.4)
Nutritional Category	Severe malnutrition	75 (25.8)	5 (6.7)	28 (37.3)	42 (56)
	Moderate malnutrition	99 (34.0)	13 (13.1)	9 (9.1)	76 (76.8)
	Normal	105 (36.1)	13 (12.4)	7 (6.7)	84 (80)
	Overweight	12 (4.1)	1 (8.3)	1 (8.3)	10 (83.3)
Comorbidities	Yes	36 (12.4)	2 (5.6)	16 (44.4)	17 (47.2)
	No	255 (87.6)	30 (11.7)	29 (11.4)	195 (76.5)

TLF=Treatment after lost to follow up (previously interrupted treatment), Bact = Bacteriologically; PTB = Pulmonary TB; EPTB =Extra pulmonary TB

4.3 Determinants of tuberculosis treatment interruption among notified cases in Vihiga County

4.3.1 Demographic and socio-economic characteristics of TB patients by treatment interruption and probability of treatment completion

Eleven percent (11%, n = 32) of the 291 TB on follow up interrupted their treatment. During analysis; patients who completed treatment, died, failed treatment or discontinued treatment due to medical reason were censored. Using Kaplan Meier method, the overall probability of treatment completion (survival) among the TB patients was 0.877, (95% CI = 0.838 - 0.918). Statistically (log-rank $p<0.001$) more (59%) incidences of treatment interruption occurred during intensive phase of TB treatment. Demographic and socio-economic characteristics associated with TB treatment interruption, probability of completing treatment and difference in probabilities of treatment completion within groups is presented in Table 4.3. A P-value equal or less than 0.05 implies that, the groups under study have statistically different probability of treatment completion, hence the null hypothesis was rejected. The results show that almost 12% of male TB patients interrupted treatment compared to about 10% of female TB patients. Although there was no difference in probability of treatment completion (p value = 0.74), male patients had slightly lower probability of treatment completion (0.87) compared to female (0.89). Probability of treatment completion was significantly lower among TB patients who had primary or lower education (primary of lower-level education (0.83 (95% CI = 0.77-0.89); secondary education = 0.94 (95% CI = 0.89-0.99), post-secondary education = 0.96 (95% CI = 0.88-1); p = 0.02); not married (not married = 0.84 (95% CI = 0.79-0.90), married = 0.93 (95% CI = 0.88-0.98) p = 0.030); those without a treatment supporter (no = 0.81 (95% CI = 0.74-0.88), yes = 0.94 (95% CI = 0.91-0.98) $p < 0.001$); those who consumed alcohol (yes = 0.79 (95% CI = 0.73-0.87) , no = 0.96 (95% CI =

0.93-0.99); p = <0.001); those who abused drugs/substance abuse (yes = 0.72 (95% CI = 0.56-0.7), no = 0.89 (95% CI = 0.86-0.94); p = 0.007) and the smokers (yes = 0.78 (95% CI = 0.71-0.86), no = 0.95(95% CI = 0.92-0.99); p<0.001).

Table 4.3: Demographic and socio-economic characteristics of tuberculosis patients by treatment interruption and probability of treatment completion

Character	Category	Frequency (%) or median (IQR)	Number (%) Interrupted treatment	Probability of treatment completion (95%CI)	Log rank p-value
Zone	Vihiga	101 (34.7)	9 (8.3)	0.90 (0.84-0.96)	0.811
	Emuhaya	87 (29.9)	11 (12.6)	0.86 (0.79-0.94)	
	Hamisi	63 (21.6)	8 (12.7)	0.86 (0.77-0.95)	
	Sabatia	40 (13.7)	4 (10)	0.89 (0.79-0.99)	
Health Sector	Faith based	49 (16.8)	4 (8.2)	0.90 (0.81-0.99)	0.640
	Public	242 (83.2)	28 (11.6)	0.87 (0.82-0.92)	
Gender	Male	209 (71.8)	24 (11.5)	0.87 (0.82-0.92)	0.740
	Female	82 (28.2)	8 (9.8)	0.89 (0.82-0.97)	
Age in years	Median (IQR)	40 (32-53)	38.5 (32-49)	-	**0.042**
Occupation	Employed	19 (6.5)	0	1	0.111
	Not Employed	272 (93.5)	32 (11.8)	0.87 (0.83-0.91)	
Marital status	Married	110 (37.8)	7 (6.4)	0.93 (0.88-0.98)	**0.029**
	Not married	181 (62.2)	25 (13.8)	0.84 (0.79-0.90)	
Monthly income (KSH)	Median (IQR)	3000 (1500-5000)	3000 (1425-4000)	-	0.078
Family size	Mean (SD)	4.2 (1.9)	4.2 (2.3)	-	0.121
Education	Primary or lower	172 (59.1)	26 (15.1)	0.83 (0.77-0.89)	**0.018**
	Secondary	95 (32.6)	5 (5.3)	0.94 (0.89-0.99)	
	Post-secondary	24 (8.2)	1 (4.2)	0.96 (0.88-1)	
Treatment supporter	Yes	150 (51.5)	8 (5.3)	0.94 (0.91-0.98)	**<0.001**
	No	141 (48.5)	24 (17)	0.81 (0.74-0.88)	
Alcohol consumption	Yes	153 (52.6)	27 (17.6)	0.79 (0.73-0.87)	**<0.001**
	No	138 (47.4)	5 (3.6)	0.96 (0.93-0.99)	
Drug/Substance abuse	Yes	31 (10.7)	8 (25.8)	0.72 (0.56-0.7)	**0.007**
	No	260 (89.3)	24 (9.2)	0.89 (0.86-0.94)	
Smoking	Yes	136 (46.7)	25 (18.4)	0.78 (0.71-0.86)	**<0.001**
	No	155 (53.3)	7 (4.5)	0.95(0.92-0.99)	
Duration of symptoms before visiting health facility	1-2 weeks	39 (13.4)	2 (5.1)	0.94 (0.88-1)	0.131
	2-4 weeks	69 (23.7)	5 (7.2)	0.92 (0.86-0.99)	
	>4 weeks	183 (62.9)	25 (13.7)	0.84 (0.79-0.90)	
First health sector visited	Public facility	137 (47.1)	12 (8.6)	0.90 (0.85-0.96)	0.452
	Private facility	47 (16.2)	4 (8.5)	0.90 (0.82-0.99)	
	Chemist	73 (25.1)	12 (16.4)	0.80 (0.72-0.91)	
	Faith based	24 (8.2)	3 (12.5)	0.85 (0.72-1)	
	Herbal	10 (3.4)	1 (10)	0.90 (0.73-1)	
No. visits to facilities before TB diagnosis	Mean (SD)	2.8 (1.6)	2.4 (0.9)	-	0.141

IQR = Interquartile range; SD = Standard deviation; KSH = Kenya shillings; Note: Null hypothesis that there is no difference in probability of treatment completion among different groups of TB patients was rejected at log rank p value ≤0.05

Figure 4.1 is a box-plot for age of TB patients, related to treatment interruption. The results show that median age of patients who interrupted TB treatment (38.5 years (IQR = 32-49)) was lower than patients who did not interrupt their treatment (40 years (IQR = 33-54)).

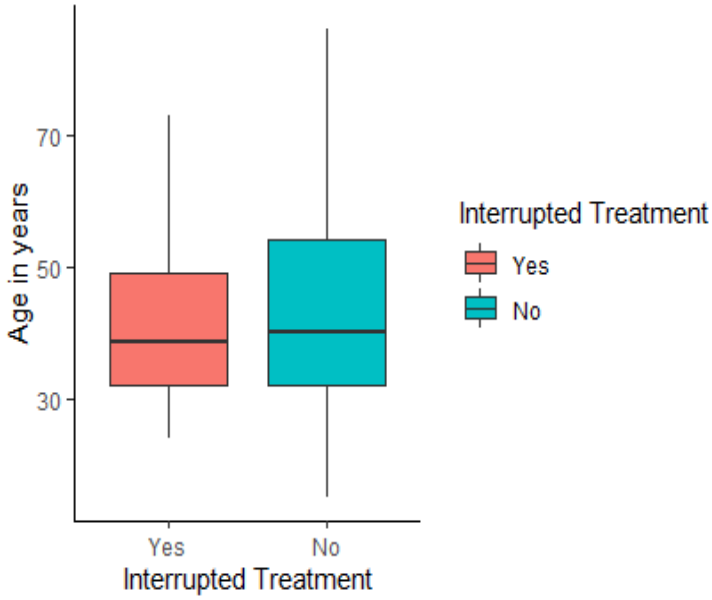

Figure 4.1: Age of tuberculosis patients by treatment interruption

4.3.2 Clinical characteristics of TB patients by treatment interruption and probability of treatment completion

Table 4.4 highlights clinical characteristics of TB patients by treatment interruption, probabilities of treatment completion and differences in probabilities of treatment completion within distinct groups. Patients who previously interrupted TB treatment had significantly lower probability of treatment completion (TLF = 0.66 (0.45-0.99), new = 0.88 (0.84-0.93), relapse = 0.92 (0.83-1.0), p= 0.05).

Table 4.4: Clinical characteristics of tuberculosis patients by treatment interruption and probability of treatment completion

Character	Category	Total number (%) or median (IQR)	Number (%) Interrupted treatment	Probability of treatment completion (95%CI)	Log rank p value
Clinical condition	Stable	155 (53.3)	18 (11.6)	0.88 (0.83-0.93)	0.821
	Severely ill	136 (46.7)	14 (10.3)	0.87 (0.81-0.94)	
Type of TB	PTB	269 (92.4)	30 (11.2)	0.88 (0.84-0.92)	0.910
	EPTB	22 (7.6)	2 (9.1)	0.89 (0.75-1.0)	
Clinical TB category	Bact confirmed	227 (78.0)	24 (10.6)	0.88 (0.84-0.93)	0.481
	Clinically Dx	64 (22.0)	8 (12.5)	0.86 (0.77-0.95)	
Type of TB patient	New	246 (84.5)	26 (10.6)	0.88 (0.84-0.93)	**0.054**
	Relapse	30 (10.3)	2 (6.7)	0.92 (0.83-1.0)	
	TLF	13 (4.5)	4 (30.8)	0.66 (0.45-0.99)	
TPT for HIV Pos	Yes	22 (7.6)	2 (9.1)	0.86 (0.66-1)	0.682
	No	14 (4.8)	0	1	
	New	65 (22.3)	8 (12.3)	0.86 (0.77-0.97)	
HIV Status	Positive	101 (34.7)	10 (9.9)	0.88 (0.81-0.95)	0.971
	Negative	190 (65.3)	22 (11.6)	0.88 (0.83-0.93)	
Viral Suppression	Suppressed	9 (3.1)	1 (11.1)	0.83 (0.58-1)	0.920
	Not Suppressed	18 (6.2)	1 (5.6)	0.91 (0.75-1)	
	Not done	7 (2.4)	0	1	
	New	67 (23.0)	8 (11.9)	0.86 (0.78-0.96)	
Ever stopped taking ART	Yes	30 (10.3)	2 (6.7)	0.89 (0.75-1)	0.811
	No	6 (2.1)	0	1	
	Starting	65 (22.3)	8 (12.3)	0.86 (0.77-0.95)	
Nutritional Category	Severe malnutrition	75 (25.8)	5 (6.7)	0.90 (0.83-0.99)	0.862
	Moderate malnutrition	99 (34.0)	13 (13.1)	0.86 (0.79-0.93)	
	Normal	105 (36.1)	13 (12.4)	0.87 (0.81-0.94)	
	Overweight	12 (4.1)	1 (8.3)	0.92 (0.77-1)	
Comorbidities	Yes	36 (12.4)	2 (5.6)	0.54 (0.40-0.74)	0.491
	No	255 (87.6)	30 (11.7)	0.88 (0.84-0.92)	

PTB = Pulmonary TB; EPTB= Extra pulmonary TB; Bact = bacteriologically; Dx = diagnosed; TLF= treatment after lost to follow up; TPT=TB preventive Therapy; ART=Antiretroviral therapy; Comorbidities = underlying non-communicable diseases; Note: Null hypothesis that there is no difference in probability of treatment completion among different groups of TB patients was rejected at log rank p value ≤0.05

4.3.3 Time of tuberculosis treatment interruption

The time of treatment interruption is depicted in Figure 4.2. The results show that there was sharp rise in the incidences of treatment interruption in the first two months (intensive phase) of TB treatment, after which they started reducing steadily. Overall, 59% of 32 patients who interrupted

treatment did so during intensive phase of TB treatment, while cumulatively, 88% of the incidences of treatment interruption occurred at the third month of follow-up.

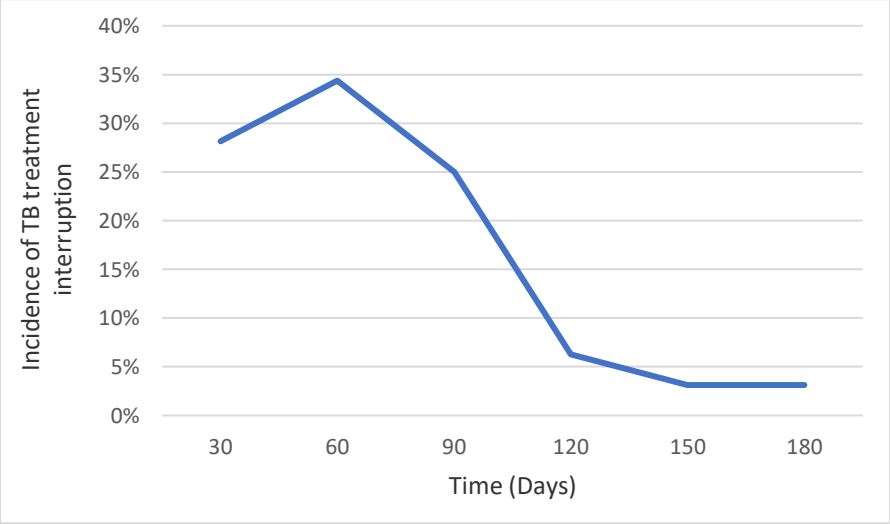

Figure 4.2: Incidence of tuberculosis treatment interruption by time

4.3.4 Kaplan Meier curves showing univariable factors associated with reduced probability of treatment completion due to treatment interruption

Kaplan Meier curves showing factors significantly associated with a reduced probability of treatment completion on univariable analysis are presented in Figure 4.3. For each characteristic, the lower curve indicates a factor significantly associated with a reduced probability of treatment completion with a corresponding log-rank p-value. Factors significantly associated with a reduced probability of successful treatment as a result of treatment interruption included primary or lower-level education (log Rank p = 0.02), not having a treatment supporter (log-rank p <0.001), alcohol consumption (log-rank p <0.001), being unmarried (log-rank p<0.029), drug/substance abuse (log-rank p<0.007), having previously interrupted treatment (log-rank p<0.001) and smoking (log-rank p<0.001).

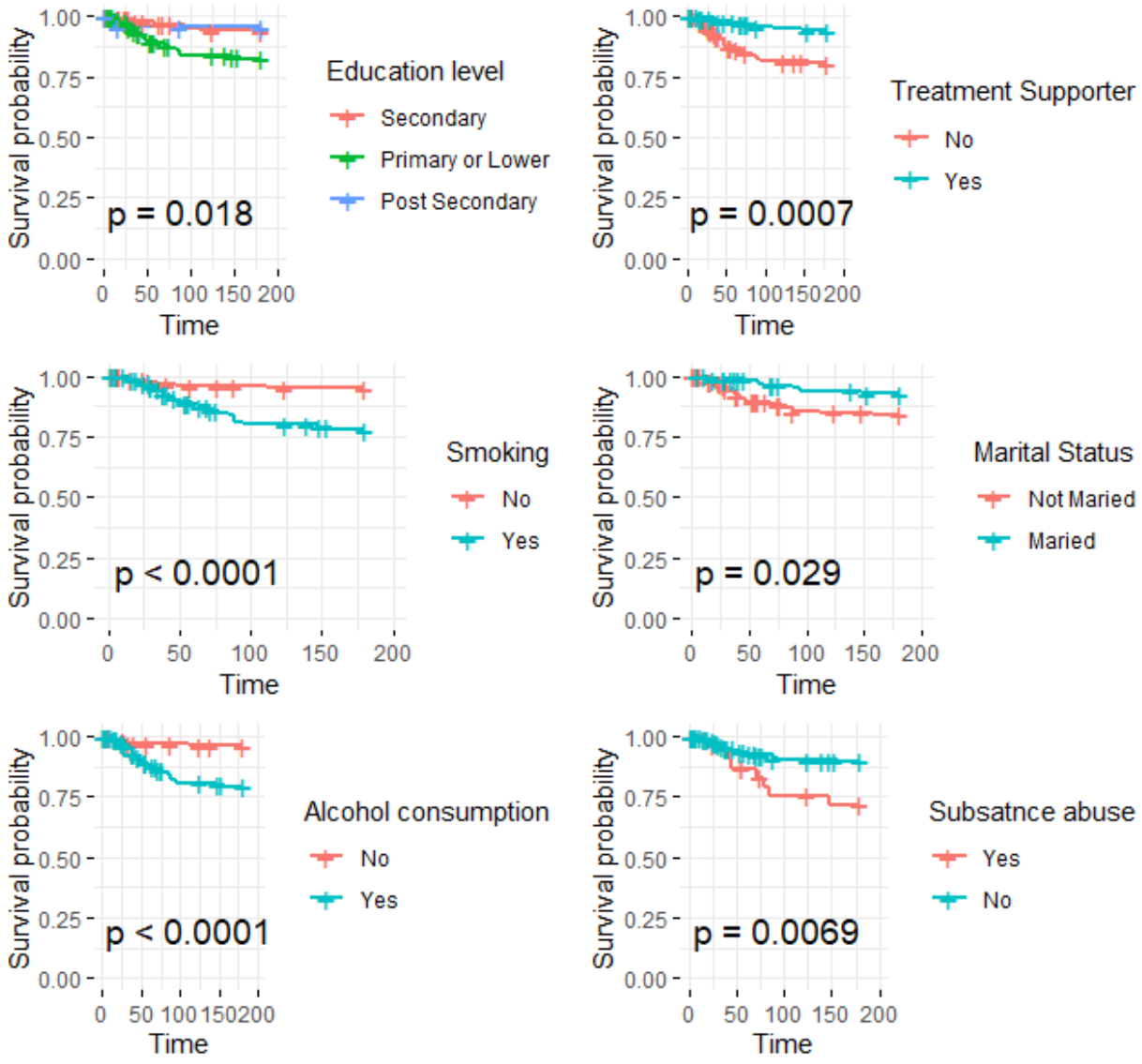

Figure 4.3: Kaplan Meier curves showing univariable factors significantly associated with a reduced probability of treatment completion due to treatment interruption

4.3.5 Multivariable analysis of determinants of tuberculosis treatment interruption

In the Cox proportional hazard (CPH) model, the proportional hazard assumption was examined using graphical diagnostics based on the scaled Schoenfeld residuals. Schoenfeld residuals were plotted against time and the "smoking" covariate was found to significantly (p = 0.03) differ from zero at a 5% significant level. The final CPH model was corrected by stratifying "smoking" and

the results are presented in Table 4.5. Tuberculosis patients who consumed alcohol were 9 times (HR = 9.2, 95% CI; 2.6–32.5, p < 0.001) more likely to interrupt treatment compared to patients who did not consume alcohol. Regarding gender, female patients were 5 times (HR = 5.01, 95% CI; 1.68– 15.0, p = 0.004) more likely to interrupt treatment compared to male patients. Also, patients with primary or lower education levels were 3 times (HR = 3.09, 95% CI; 1.15 - 8.37, p < 0.026) more likely to interrupt their treatment compared to those with post-secondary education. Contrary, TB patients who had a treatment supporter were 67% (HR = 0.33, 95% CI; 0.14–0.76, p = 0.009) less likely to interrupt treatment compared to patients who did not have a treatment supporter.

Table 4.5: Multivariable Cox regression analysis of determinants of tuberculosis treatment interruption among TB patients in Vihiga County

Characteristic	Category	HR[1]	95% CI[1]	p-value
Gender	Male	Reference	—	
	Female	5.01	1.68 -15.0	**0.004**
Age in Years	Age	0.99	0.96 - 1.02	0.412
Education Level	Post-secondary	Reference	—	
	Secondary	1.65	0.17 - 19.0	0.562
	Primary or Lower	3.09	1.15 - 8.37	**0.026**
Monthly income (KSH)	Monthly income	1	1.00 - 1.00	0.797
Treatment supporter	No	Reference	—	
	Yes	0.33	0.14 - 0.76	**0.009**
Alcohol consumption	No	Reference	—	
	Yes	9.2	2.60 - 32.5	**<0.001**
Clinical Condition	Stable	Reference	—	
	Severely ill	0.69	0.31 - 1.53	0.363
Clinical TB Category	Bact confirmed	Reference	—	
	Clinically Diagnosed	2.43	0.91 - 6.53	0.077
HIV status	Negative	Reference	—	
	Positive	0.64	0.28 - 1.49	0.299
Type of TB	PTB	Reference	—	
	EPTB	0.84	0.16 - 4.43	0.836
Type of patient	New	Reference	—	
	Relapse	0.55	0.13 - 2.40	0.426
	TLF	3.11	0.96 - 10.1	0.058

[1]HR = Hazard Ratio; CI = Confidence Interval; TLF = treatment after lost to follow up (treatment after treatment interruption); Bact = bacteriologically; KSH = Kenya shillings; Note: Null hypothesis was rejected at p value ≤0.05

4.3.6 Reasons for tuberculosis treatment interruption

Thirty-two patients who interrupted treatment for more than two months were physically searched using previously obtained physical locator information. Of the 32 patients, 27 (84%) were found, two were not known in the locality while three patients had migrated. All patients who were found were counselled and referred back to health facilities for treatment. For those patients who were found, a single open-ended question was posed: “tell me the reason why you stopped taking your drugs before the required time of six months?” Reasons for TB treatment interruption were categorized and presented in Table 4.6 with an associated quote from the patients. Slightly more than a quarter of patients who interrupted treatment cited “feeling well soon after treatment initiation” as the reason for stopping their treatment. Nineteen percent blamed “alcoholism” for their stoppage, 15% cited “difficulty reaching the health facility”, 15% perceived “stigma”, 11% thought they didn’t have TB, 7% had many other pills (pill burden) and 7 cited “lack of food” as the reason for stopping their TB treatment.

Table 4.6: Reasons for tuberculosis treatment interruption (From traced patients)

Reason for treatment interruption	Percent of patients found (n=27)	Associated quotes from patients who interrupted treatment
Felt well soon after treatment initiation	26%	*"I stopped the drugs because I was told that my sputum tested negative at two months and I no longer cough, feel cold nor feel tired"*
Alcohol use	19%	*"This son of mine is never at home. He wakes up early and goes straight to chang'aa* den where he drinks until evening. When he comes back, he is always too drunk to swallow medicine. We got tired of him".* This was a mother referring to her son who was also present.
Difficulty reaching a health facility	15%	*"My legs are weak; I am not able to walk to the facility"*
Stigma	15%	*"I recently came from Nairobi sick and weak, if I come to HIV clinic, people will say 'he brought HIV from Nairobi"*
Perception of not having TB	11%	*"My sputum tested negative for TB; how then do you tell me that I have TB?"*
Pill burden	7%	*"I'm taking too many drugs. I'm taking ARVs, TB drugs, and drugs for hypertension. I had to stop taking TB drugs because they are too many and big"*
Lack of food	7%	*"I feel terrible when I swallow the medicine on empty stomach. I discontinued the medicine because I don't have enough food"*

**chang'aa = Locally prepared alcoholic drink*

Note: Patients who missed treatment appointment for more than two months were considered treatment interrupters (lost to follow up) and were physically traced using locator information that was already in patients' records

4.4 Factors associated with survival distribution and occurrence of all-cause mortality among notified TB patients in Vihiga County

Of the 291 patients under observation, 45 (15%) patients died comprising a mortality rate of 32.2 (95% CI; 23.5 - 43.1) deaths per 1000 person-months. Overall, 78% (log-rank = <0.001) of incidences of death occurred during the intensive phase of treatment.

4.4.1 Survival probability of patients on tuberculosis treatment

4.4.1.1 Overall survival probability

During analysis; patients who completed treatment, interrupted treatment, failed treatment or discontinued treatment were censored. The overall six-month (or 180 days) survival probability of patients on TB treatment is depicted in Figure 4.4. The vertical axis represents survival probability, whereas the horizontal axis represents time in days. The overall survival probability of TB patients under study was 0.84 (95% CI: 0.79-0.88).

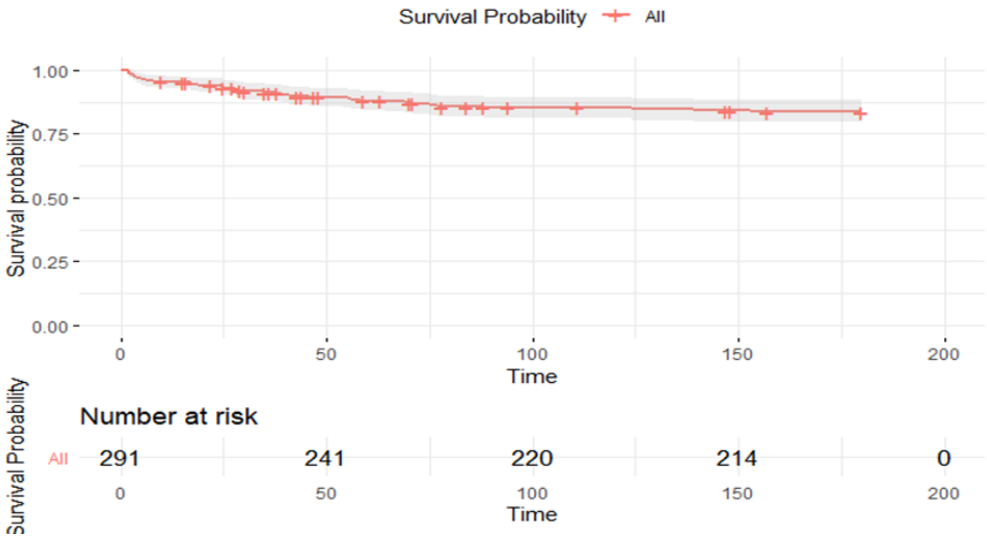

Figure 4.4: Overall survival probability for patients on tuberculosis treatment in Vihiga County

4.4.1.2 Survival probability distribution by demographic and socioeconomic characteristics of TB patients

Table 4.7 presents demographic and socio-economic characteristics, 6-months survival probability and differences in survival between sub-groups. A P-value equal or less than 0.05 implies that, the groups under study have statistically different survival probabilities, hence, the null hypothesis is rejected. The results show significantly lower survival among patients who consume alcohol (yes = 0.78 (95% CI = 0.72-0.85), no = 0.9 (95% CI = 0.85-0.94); p = 0.01) and smokers (yes=0.75 (95% CI = 0.68-0.83), no = 0.91 (95% CI = 0.86-0.96); p = <0.001). Additionally, the median age of patients who died (45 years, IQR = 34-59) was significantly higher (p = 0.01) than median age of all patients (40 years, IQR = 32-53) under observation. These factors are also highlighted by Kaplan Meier curves in Figure 4.5.

Table 4.7: Survival probability of TB patients by patients' demographic and socio-economic characteristics

Socio-demographic characteristics		Sample (n=291)	Died (%)	6-Month survival probability	Log Rank (p-value)
Zone	Emuhaya	87	13 (15%)	0.84 (0.77-0.92)	0.881
	Hamisi	63	9 (14%)	0.85 (0.77-0.95)	
	Sabatia	40	5(13%)	0.87 (0.77-0.98)	
	Vihiga	101	18 (18%)	0.81 (0.74-0.89)	
Sector	Faith Based	50	11 (22%)	0.76 (0.66-0.90	0.121
	Public	241	34 (14%)	0.85 (0.81-0.89)	
Age	Median (IQR)	40(32-53)	45 (34-59)	-	**0.008**
sex	Female	82	13 (16%)	0.83 (0.75-0.92)	0.860
	Male	209	32 (15%)	0.84 (0.79-0.89	
Occupation	Employed	19	2 (11%)	0.89 (0.77-1)	0.484
	Not Employed	272	43 (16%)	0.83 (0.79-0.88)	
Marital Status	Married	111	14 (13%)	0.87 (0.81-0.94)	0.221
	Not married	180	31 (17%)	0.82 (0.76-0.88)	
Monthly income (KSH)	Median (IQR)	3000 (1500-5000)		-	0.341
Family size	Mean (SD)	4.2 (1.9)		-	0.142
Education	Post-secondary	24	2 (8%)	0.91 (0.8-1)	0.262
	Secondary	95	12 (13%)	0.87 (0.81-0.94)	
	Primary or Lower	172	31 (18%)	0.81 (0.75-0.87)	
Duration of illness	1-2 weeks	39	4 (10%)	0.89 (0.80-0.99)	0.077
	2-4 weeks	69	6 (9%)	0.91 (0.85-0.98)	
	More than four weeks	183	35 (19%)	0.79 (0.74-0.86)	
First sector visited	Chemist	73	14 (19%)	0.8 (0.71-0.89)	0.781
	Faith based facility	24	4 (17%)	0.83 (0.69-0.99)	
	Herbal	10	2 (20%)	0.78 (0.55-1)	
	Private facility	47	7 (15%)	0.84 (0.74-0.96)	
	Public facility	137	18 (13%)	0.86 (0.81-0.92)	
Treatment Supporter	Yes	150	19 (13%)	0.87 (0.82-0.93)	0.120
	No	141	26 (18%)	0.8 (0.74-0.87)	
Smoking	Yes	136	31 (23%)	0.75 (0.68-0.83)	**<0.001**
	No	155	14 (9%)	0.91 (0.86-0.96)	
Alcohol consumption	Yes	156	31 (20%)	0.78 (0.72-0.85)	**0.011**
	No	135	14 (10%)	0.9 (0.85-0.94)	
Substance abuse	Yes	260	5 (16%)	0.81 (0.67-0.97)	0.912
	No	31	40 (15%)	0.84 (0.79-0.89)	
No. visits to facilities before TB diagnosis	Mean (SD)	2.8 (1.6)	2.9 (1.4)	-	0.161

IQR = Interquartile range; SD = Standard deviation; KSH = Kenya shillings; Note: Null hypothesis that there is no difference in survival probability among different groups of TB patients was rejected at log rank p value ≤0.05

4.4.1.3 Survival probability distribution by clinical characteristics of TB patients

Cumulative incidences of death, 6-months survival probability and survival differences by patients' clinical characteristics are presented in Table 4.8, while Figure 4.5 presents Kaplan Meier curves showing all patients' characteristics that are associated with reduced survival probability among TB patients. Significantly lower survival was observed among severely ill patients (severely ill = 0.68 (95% CI = 0.61-0.77), clinically stable = 0.97 (95% CI = 0.95-0.99); p <0.001)), Extra pulmonary TB (EPTB) patients (EPTB = 0.67 (95% CI = 0.49-0.7), PTB = 0.85 (95% CI = 0.81-0.89); p = 0.03)); clinically diagnosed TB patients (clinically diagnosed = 0.71 (95% CI = 0.6-0.84), bacteriologically confirmed = 0.87 (95% CI = 0.83-0.92); p = 0.005)); HIV infection (pos = 0.72 (95% CI = 0.64-0.82), neg = 0.9 (95% CI = 0.86-0.94); p<0.001)); severely malnourished (severe malnutrition = 0.62 (95% CI = 0.52-0.74), normal = 0.93 (95% CI = 0.88-0.98), moderate malnutrition = 0.9 (95% CI = 0.84-0.97), overweight = 0.91 (95% CI = 0.75-1); p <0.001)); and having comorbid conditions (yes = 0.54 (95% CI = 0.39-0.74), no = 0.88 (95% CI = 0.84-0.92); p <0.001)).

Table 4.8: Survival probability of TB patients by their clinical characteristics

Clinical Characteristics		Frequency	Died (%)	6-month's survival probability	Log Rank (p-value)
Clinical Condition	Stable	155	4 (3%)	0.97 (0.95-0.99)	**<0.001**
	Severely ill	136	41 (30%)	0.68 (0.61-0.77)	
Type of TB	[1]EPTB	22	7 (32%)	0.67 (0.49-0.70)	**0.031**
	PTB	269	38 (14%)	0.85 (0.81-0.89)	
Type of TB case	[2]Bact confirmed	227	28 (12%)	0.87 (0.83-0.92)	**0.005**
	Clinically Diagnosed	64	17 (27%)	0.71 (0.60-0.84)	
Type of patient	New	246	40 (16%)	0.83 (0.78-0.88)	0.811
	Relapse	30	4 (13%)	0.86 (0.74-0.99)	
	[3]TLF	13	1 (8%)	0.92 (0.79-1)	
[4]TPT for HIV positive	Yes	22	10 (45%)	0.54 (0.36-0.80)	**<0.001**
	No	15	5 (33%)	0.64 (0.44-0.95)	
	New	64	12 (19%)	0.81 (0.71-0.91)	
HIV Status	Neg	190	18 (9%)	0.9 (0.86-0.94)	**<0.001**
	Pos	101	27(27%)	0.72 (0.64-0.82)	
Viral Suppression	Suppressed	9	3 (33%)	0.67 (0.42-1)	**<0.001**
	Not Suppressed	18	9 (50%)	0.49 (0.30-0.79)	
	Starting	67	13 (19%)	0.79 (0.86-0.94)	
	Not done	7	2 (29%)	0.71 (0.45-1)	
Ever stopped taking ART	Yes	30	13 (43%)	0.56 (0.41-0.77)	**<0.001**
	No	6	1 (17%)	0.83 (0.58-1)	
	ART Naïve	65	13 (20%)	0.79 (0.69-0.89)	
Nutritional category	Severe Malnutrition	75	28 (37%)	0.62 (0.52-0.74)	**<0.001**
	Moderate Malnutrition	99	11 (11%)	0.9 (0.84-0.97)	
	Normal	105	7 (7%)	0.93 (0.88-0.98)	
	Over weight	12	1 (7%)	0.91 (0.75-1)	
[*]Comorbidities	Yes	36	16 (44%)	0.54 (0.39-0.74)	**<0.001**
	No	255	29 (11%)	0.88 (0.84-0.92)	

*[1]EPTB = Extrapulmonary TB; [2]Bact = Bacteriologically; PTB = Pulmonary TB; EPTB= Extra pulmonary; [3]TLF = Treatment after loss to follow up; [4]TPT = TB preventive therapy; [5]ART = Antiretroviral Therapy; *Comorbidities = underlying non-communicable diseases. Note: Null hypothesis that there is no difference in survival probability among different groups of TB patients was rejected at log rank p value ≤0.05*

4.4.1.4 Kaplan Meier curves showing univariable factors associated with reduced survival probability among TB patients

On univariable analysis, patient characteristics that are significantly associated with survival probability among TB patients were identified and are presented in Figure 4.5 as Kaplan Meier

curves. For each characteristic, the lower curve indicates a factor significantly associated with reduced survival probability with a corresponding log rank p-value. The patients' characteristics associated with lower survival probability include; being severely ill, alcohol consumption, having Extra pulmonary TB, severe malnutrition, clinically diagnosed TB, having a comorbidity, HIV positive and smoking.

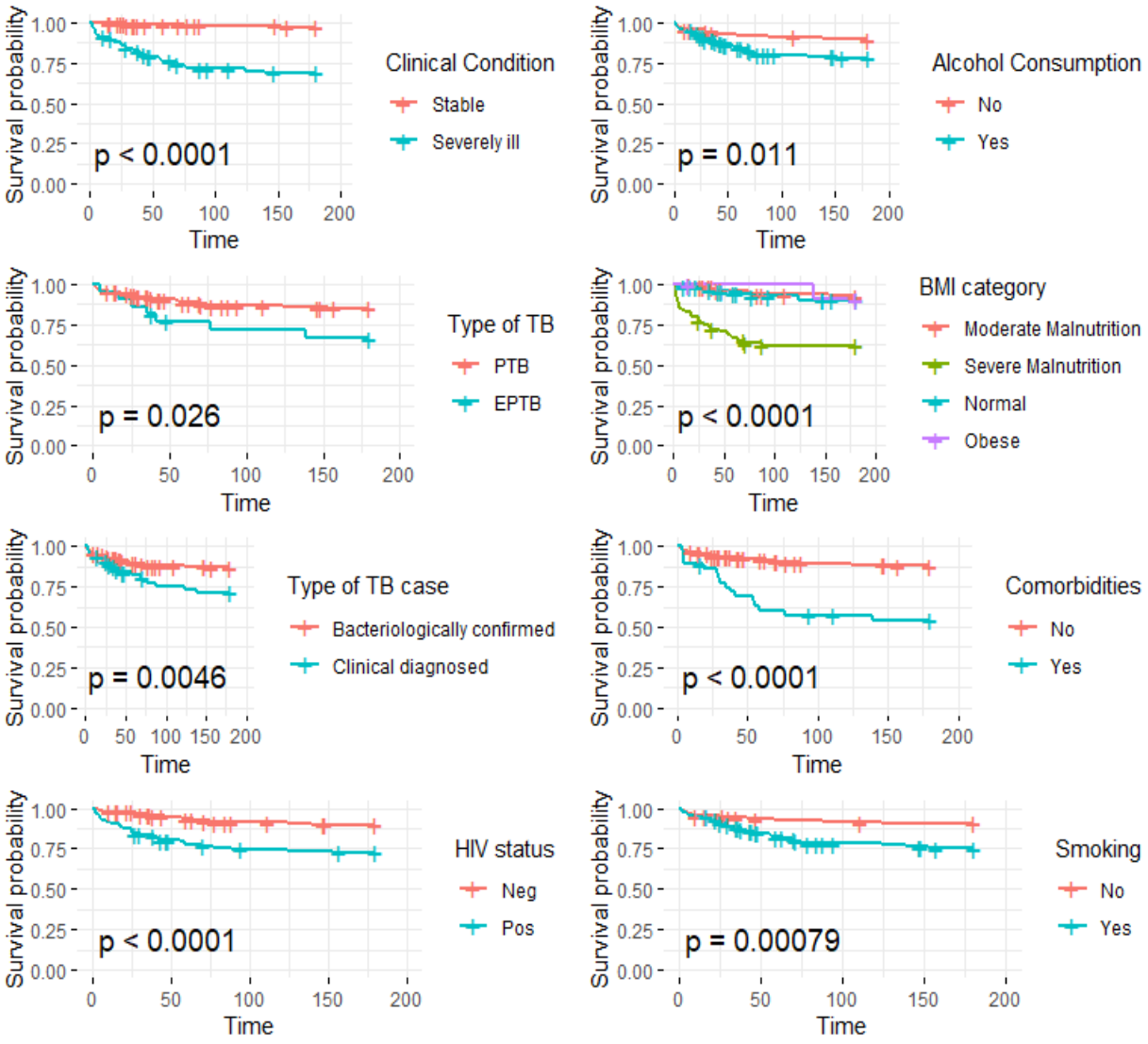

Figure 4.5: Kaplan Meier curves; factors significantly associated with reduced survival probability among TB patients

4.4.2 Factors associated with all-cause mortality among TB patients in Vihiga County

In the Cox proportional hazard model, the proportional hazard assumption was examined using graphical diagnostics based on the scaled Schoenfeld residuals. Schoenfeld residuals were plotted against time and the "Nutritional category" covariate was found to significantly ($p = 0.021$) differ from zero at a 5% significant level. The final CPH model was corrected by stratifying the "Nutritional category" and presented in Table 4.9. TB patients with underlying comorbidities were almost 3 times (HR = 2.72, 95% CI; 1.36–5.44, $p = 0.005$) more likely to die compared to patients without comorbidities. Besides, Patients who were severely ill during treatment initiation were five times (HR = 5.06, 95% CI; 1.59–16.1, $p = 0.006$) more likely to die compared to clinically stable patients. Additionally, TB and HIV coinfected patients were two and a half times (HR = 2.56, 95% CI; 1.28–5.12, $p = 0.008$) more likely to die compared to patients not infected with HIV, while those who smoked were almost 3 times (HR = 2.79, 95% CI; 1.01–7.75, $p = 0.049$) more likely to die compared to those who did not smoke.

Table 4.9: Factors associated with mortality among tuberculosis patients

Characteristic		HR[1]	95% CI[1]	p-value
Age	Age in years	1.01	0.99, 1.03	0.434
Sex	Male	—	—	
	Female	0.7	0.6, 4.82	0.316
Education level	Post-secondary	—	—	
	Secondary	1.19	0.23, 6.26	0.837
	Primary or lower	0.98	0.46, 2.06	0.955
Occupation	Employed	—	—	
	Not employed	0.47	0.09, 2.41	0.361
Symptom duration	1-2 weeks	—	—	
	2-4 weeks	1.23	0.29, 5.33	0.777
	>4 weeks	1.86	0.56, 6.16	0.308
Alcohol consumption	No	—	—	
	Yes	1.12	0.38, 3.31	0.831
Smoking	No	—	—	
	Yes	2.79	1.01, 7.75	**0.049**
Clinical Condition	Stable	—	—	
	Severely ill	5.06	1.59, 16.1	**0.006**
HIV Status	Neg	—	—	
	Pos	2.56	1.28, 5.12	**0.008**
Type of TB	PTB	—	—	
	EPTB	1.33	0.53, 0.31	0.541
Comorbidities	No	—	—	
	Yes	2.72	1.36, 5.44	**0.005**

[1] HR = Hazard Ratio, CI = Confidence Interval, PTB=Pulmonary TB, EPTB=Extra pulmonary TB; Note; Null hypothesis was rejected at p value ≤0.05

4.4.3 Analysis of HIV - positive and HIV - negative subgroups

Cumulatively, of 101 TB/HIV coinfected patients, 27 (27%) died comprising a mortality rate of 61.7 (95% CI; 40.6 – 89.7) deaths per 1000 person-months. Among the 190 HIV-negative TB patients, 18 (9.5%) died comprising a mortality rate of 18.7 (95% CI; 11.1 – 29.6) deaths per 1000 person-months.

4.4.3.1 Univariable and multivariable analysis of HIV-negative and HIV-positive subgroups

Among HIV negative TB patients, significantly lower survival probability was observed among those who consume alcohol (yes=0.84, no=0.95: Log Rank p = <0.024), smokers (yes=0.82, no=0.96: Log Rank p = <0.005), the severely malnourished (severe malnutrition = 0.68, overweight = 0.88, moderate malnutrition = 0.96; Log Rank p <0.001); severely ill (severely ill = 0.76, clinically stable = 0.96; Log Rank p <0.001), clinically diagnosed (clinically diagnosed = 0.73, bacteriologically confirmed = 0.93; Log Rank p = 0.001), extra pulmonary TB (EPTB) patients (EPTB = 0.67, PTB = 0.91; Log Rank p = 0.01), and those with comorbidities (no = 0.93, yes = 0.58; Log Rank p <0.001). On multivariable analysis, stratified by smoking, HIV negative TB patients with underlying comorbidities were almost 4 times more likely to die (HR = 4.25, 95% CI; 1.15-15.7, p = 0.03) compared to patients without comorbidities. Besides, clinically diagnosed patients were almost five times more likely to die (HR = 4.8, 95% CI; 1.43-16, P = 0.01) compared to bacteriologically confirmed TB patients.

Factors associated with reduced survival probability among TB/HIV coinfected patients included, smoking (Yes=0.62, No=0.81: Log Rank p = <0.03), severe malnutrition (severe malnutrition = 0.54, moderate malnutrition = 0.79, normal = 0.84; Log Rank p <0.003), severe illness (severely ill = 0.61, stable = 0.94; Log Rank p <0.001), being previously on TPT (Yes=0.54, No=0.78: Log Rank p = <0.03), having unsuppressed viral load (not suppressed = 0.48, suppressed = 0.66, not done = 0.78, ART Naïve = 0.79; Log Rank = 0.05), previous ART interruption (Yes = 0.56, No = 0.83, ART Naïve = 0.79; Log Rank = 0.04), and comorbidity (no = 0.78, yes = 0.50; Log Rank p <0.01). On multivariable analysis of TB/HIV coinfected patients, smokers were four times more likely to die (HR = 4.05, 95% CI;1.03-16.0, P = 0.04) compared to non-smokers. Also, severely

ill patients were almost 6 times more likely to die (HR = 5.84, 95% CI; 1.08-31.6, P = 0.04) compared to clinically stable while severely malnourished patients were five times more likely to die (HR = 4.56, 95% CI; 1.33-15.6, P = 0.01) compared to normally nourished patients. Besides, patients with comorbidities were three times more likely to die (HR = 3.04, 95% CI; 1.03-8.97, p = 0.04) compared to patients without comorbidities.

4.4.3.2 Causes of mortality among TB patients by HIV status

A mortality audit was conducted for 45 patients who died while on TB treatment. Specific causes of death were categorized based on patients' HIV status and are summarized in Table 4.10. Majority (72% (TB pneumonia = 44%, lung collapse = 17%, lung fibrosis = 11%)) of HIV Negative TB patients died due to lung disease while more than a half (52%) deaths among HIV positive patients were attributable to advanced HIV disease. Sixteen percent of deaths among HIV-positive patients were due to opportunistic infections while 22% of mortality in this group were linked to TB-related pneumonia.

Table 4.10: Causes of death among TB patients by HIV status

HIV status	Cause of death	No. died	Percent
HIV Negative	TB Pneumonia	8	44%
	Lung collapse	3	17%
	Lung fibrosis	2	11%
	Status Asthmaticas	1	6%
	Diabetes ketoacidosis	1	6%
	Injury	1	6%
	Liver disease	1	6%
	Lung Cancer	1	6%
HIV Positive	Advanced HIV disease	14	52%
	TB Pneumonia	6	22%
	Liver disease	2	7%
	Cryptococcal Meningitis	1	4%
	Immune reconstitution inflammatory syndrome	1	4%
	Kaposi's Sarcoma	1	4%
	Injury	1	4%
	Pneumocystis jiroveci pneumonia	1	4%

4.4.3.3 Circumstances contributing to the mortality among TB patients by HIV status

Figure 4.6 shows conditions that contributed to mortality, but may not be related to the disease or condition causing the mortality, categorized by HIV status of patients. Forty-four percent of mortality among HIV-negative patients was attributable to delayed diagnosis while a third died due to multiple factors. For the HIV positive, mortality was exacerbated by poor adherence to ART (37%) and delayed diagnosis (33%). 'Multifactor' are conditions that constituted patients' factors, social factors, and health system factors. Patient factors included poor health-seeking behavior, the frailty of a patient, multiple comorbidities, alcohol consumption, and drug abuse while on treatment. Social factors included lack of family support, stigma, and discrimination while health system factors comprised hidden travel and referral costs and gaps in diagnosis and treatment.

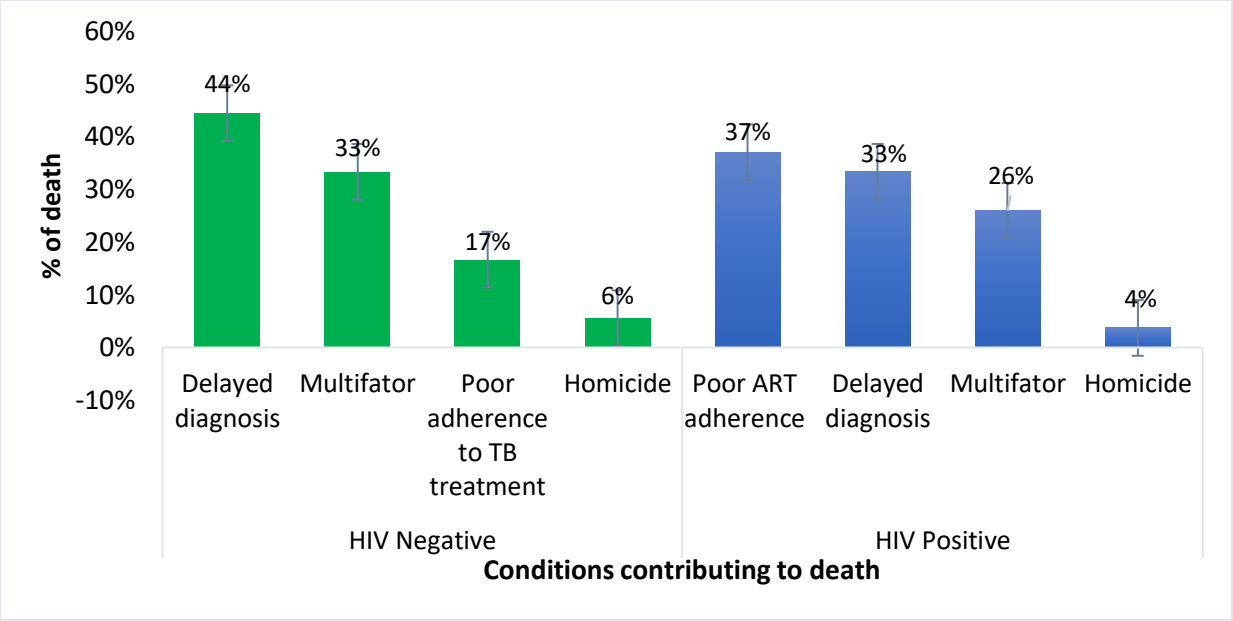

Figure 4.6: Circumstances contributing to the mortality among TB patients by their HIV status

CHAPTER FIVE

DISCUSSION

5.1 Introduction

This chapter discusses the distribution of tuberculosis disease and treatment outcomes based on the characteristics of TB patients. The chapter also discusses the determinants of TB treatment interruption and reasons the patients gave for prematurely discontinuing their treatment. Finally, the chapter covers factors associated with survival distribution and the occurrence of all-cause mortality, as well as specific causes of mortality and circumstances that contributed to mortality among notified tuberculosis patients in Vihiga County.

5.2 Distribution of tuberculosis disease and treatment outcomes by characteristics of notified patients

Understanding the distribution of tuberculosis disease and treatment outcomes by person is important in enhancing knowledge about TB transmission patterns and identifying the most vulnerable groups for the disease and unfavorable treatment outcomes. While prior research has made this possible, there is often worldwide and within-country variation in the burden of tuberculosis disease in the population (World Health Organization, 2021a). The findings of this study have indicated that almost three-quarters of notified TB patients are male. Whereas a study conducted in Gondar, Ethiopia (Bogale *et al.,* 2017) indicated a roughly equal proportion of TB cases in both gender, males have generally had a higher TB burden globally (World Health Organization, 2019, 2020, 2021a). Although high TB burden in male have been attributed to their susceptibility owing to their social behavior such as smoking, alcohol misuse and high mobility (Kimani *et al.,* 2021; Thomas *et al.,* 2019), the "gender difference apparent in the tuberculosis case notification is real and not due to socio-cultural barriers leading to under-diagnosis of TB in

females" (Hamid Salim *et al.*, 2004). Additionally, even though male patients interrupted treatment at a slightly higher proportion compared to females, the mortality rate appeared similar within the gender. Susceptibility of male gender to tuberculosis disease suggests the need to prioritize gender in TB case finding efforts and management.

This study also found that age categories 25-34 and 35-44 accounted for nearly half of all notified TB patients, whereas age groups 15-24 and over 65 years constituted 11% and 9% of all the patients, respectively. This is congruent with the findings of the Ministry of Health's 2016 Kenya TB prevalence survey, which indicated that people aged 25-34 and 45-54 have the highest TB burden (716 and 607 TB cases per 100,000 population), respectively, while people aged 15-24 have the lowest TB burden (360 TB cases per 100,000 population). This hints that locally and nationally, tuberculosis is more prevalent in age groups that are critical in economic development hence the need for enhanced surveillance, prevention and control. Furthermore, considering the mobility of these age groups (Masini *et al.*, 2018) and the fact that the infectious form, bacteriologically confirmed PTB, is the most frequent (78%) in the study area, it is quite possible that active transmission of TB is ongoing. Despite the fact that only 9% of TB patients were 65 or older, this implies a significant TB burden among the elderly, given that only 6% of the entire population in the study area is 65 or older (Kenya National Bureau of Statistics, 2019). This study also demonstrates vulnerability of the elderly to tuberculosis, as observed by low treatment success rates and high rates of treatment interruption and mortality. Age distribution among TB patients varies widely around the world. In high-TB-burden countries like India (Mundra *et al.*, 2017), Indonesia (Muliawan & Sawitri, 2016), and South Africa (Yoko *et al.*, 2017), a distribution comparable to this study has been observed. On the contrary, 65 years and older population seem to bear a higher burden of TB in Vietnam and China (Hoa *et al.*, 2011) while a higher burden of

TB has been observed in adolescents between 15-24 years in Pakistan (Javed *et al.*, 2017). The variation in age distribution in the burden of TB and treatment outcomes suggests the need for context-specific prioritization of TB prevention and control interventions.

A higher proportion of patients with a low education level, low income, and unemployment, as observed in this study, indicate a serious socioeconomic vulnerability among TB patients. Previous studies have also found that low socioeconomic status is a common characteristic of TB patients (Chung *et al.*, 2021; Masini *et al.*, 2018; Prado *et al.*, 2017), with vulnerable people likely to cluster in poverty-laden regions which lack social and economic risk protection (Floyd *et al.*, 2018). Although most health facilities provide free TB diagnosis and treatment, high catastrophic costs such as payment for transport, differential diagnosis, and treatment are likely to place further economic strain on already-stressed patients (Erlinger *et al.*, 2019; Ministry of Health, 2018b). This may result in financial constraints, poor living conditions, lack of food, lack of transport to treatment facilities, and a lack of social support (Tola *et al.*, 2015), which is likely to amplify TB transmission and result in poor health-seeking behavior and delay in diagnosis, as observed in this study. Interventions aimed at reducing TB incidence and improving treatment outcomes must include safeguards that protect patients from catastrophic costs, as well as unconditional access to nutritious food and financial incentives for the socioeconomically vulnerable patients while on TB treatment. Additionally, necessary policies and guidelines that enable primordial prevention of TB and other communicable diseases are feasible through interventions that improve the socioeconomic status of the population. Social support from family and community is also extremely important for adherence to TB treatment (Tola *et al.*, 2015). For the strict accomplishment of TB treatment, there is a need for a patient-responsive treatment supporter within the TB control program. This study, however, found that nearly half of TB patients did not

have treatment supporters, signifying a lack of social support and DOTs among TB patients. Considering low cost and easy accessibility of patient-selected family and community treatment supporters (Dogah *et al.,* 2021; Thiam *et al.,* 2007), institutionalizing and supporting patient-selected treatment supporters is feasible may result in improved outcomes. Alcohol, smoking, and substance abuse have been previously linked to increased TB transmission, development of disease, and unfavorable TB treatment outcome (Imtiaz *et al.,* 2017; Ministry of Health, 2021; Muture *et al.,* 2011; Sang *et al.,* 2017; World Health Organization, 2021a). The pronounced burden of smoking and alcohol abuse among males in this study represents poor coping mechanisms, which may further enhance pre-existing vulnerabilities.

Clinically, the TB/HIV coinfection rate of 35% in this study is higher than the national TB/HIV co-infection rate of 16% (Ministry of Health, 2016) and the global TB/HIV co-infection rate of 12% (Murray *et al.,* 2018). Higher TB and HIV coinfection in this study may imply that the study area probably has higher HIV prevalence or that TB case finding is concentrated in HIV care clinics. Longer exposure to ART, poor adherence to ART, as well as ART treatment failure, have been positively and significantly associated with amplified transmission and development of TB disease and unfavorable outcomes (Bayu *et al.,* 2017; World Health Organization, 2019). Comprehensive HIV risk assessment, clinical care, and monitoring are required for risk prevention and reduction. However, according to this study, only three-quarters of eligible TB/HIV coinfected patients had CD4 and/or viral load tests, respectively. In addition, the study found a high rate of ART interruption among patients who were already on HIV follow-up at the time of TB diagnosis. This suggests the need to strengthen TB and HIV collaborative efforts. Contrary to a previous study which indicated that severe illness is less common among TB patients (Muthu *et al.,* 2018), the results of this study have shown that nearly half of TB patients were severely ill. Severe illness

may reflect a delay in TB diagnosis since nearly two-thirds of patients in this study took more than four weeks before visiting health facilities, while it required the patients an average of three visits to health facilities before they were diagnosed with TB. Furthermore, the high proportion of malnourished patients indicates a complex and dynamic interaction of factors; low socioeconomic status and delay in diagnosis and treatment of TB. Synergetic effect between HIV, TB, and malnutrition could also result in deterioration of patients' general health. Apart from TB and HIV collaborative efforts, nutritional assessment and intervention remain critical in the management of TB. Despite this, this study found that only 11% of severely malnourished patients were put on therapeutic dietary supplementation. Even though only 12% of patients in this study had comorbidities, the proportion of mortality was high among this group. Comorbidity with conditions such as diabetes may increase TB rates as much as co-infection with HIV (Singla *et al.*, 2006; Jeon & Murray, 2008; Ponce-De-Leon *et al.*, 2004; Raghuraman *et al.*, 2014). Also, individuals suffering from cancer are nine times more likely to suffer from TB than those without cancer (Cheng *et al.*, 2017).

The findings of this study imply that the distribution of TB disease and treatment outcomes is substantially based on patients' demographic, socioeconomic, behavioral, and clinical characteristics; hence, tuberculosis seems to be more of a socioeconomic and demographic issue than a solely medical condition. Although patient centered approach is often advocated for, a paradigm shift from individual patient treatment to more comprehensive social interventions in a multisectoral approach is required, as this can present a unique opportunity for improvement. This can be accomplished by strengthening collaboration among biomedical personnel, patients and their families, community health personnel, and community administration.

5.3 Determinants of tuberculosis treatment interruption

Interrupting TB treatment poses a serious public health risk because, in addition to raising the risk of drug resistance and mortality, it causes patients to transmit TB for a longer period of time. Current interventions to manage patients who interrupt TB treatment include timely identification, listing, tracking, and counseling the patients to return to treatment. Despite this, the findings of this study indicate that approximately one in every ten (11%) TB patients interrupted their treatment, most often within the first two months of treatment. Nationally, 4.5% of new TB patients and 8.5% of previously treated patients interrupt their treatment (Masini *et al.*, 2016), while higher rates of treatment interruption have been observed in Kiambu county, Kenya (20.9%) (Kimani *et al.*, 2021), Ethiopia (21.21%) (Zegeye *et al.*, 2019) and Mbarara hospital, Uganda (25%) (Amuha *et al.*, 2009). Despite variations in the operational definition of 'treatment interruption' in previous studies, consistent high rates of TB treatment interruption represent a widespread regional problem. This scenario constitutes a serious setback in achieving the global treatment success rate target of >90%, which is a critical milestone in eliminating the global TB epidemic. Adherence to the six-month course of TB chemotherapy is a complex and dynamic phenomenon that is influenced by a wide range of factors (Munro *et al.*, 2007). In a survival multivariable model, this study identified primary or lower education level, female gender, and alcohol consumption as key determinants of TB treatment interruption while having a treatment supporter was found to mitigate treatment interruption.

Previous studies in Kenya (Muture *et al.*, 2011; Sang *et al.*, 2017), Sudan (Ali & Prins, 2016), and Ethiopia (Zegeye *et al.*, 2019) have similarly indicated that low education and illiteracy contribute to TB treatment interruption. Although patient experiences and perceptions are likely to vary with operational guidelines (Omondi Aduda & Mkhize, 2014), low literacy levels may have contributed

to negative perceptions of patients who interrupt treatment. Simplified structured baseline and continuous health education and adherence counselling targeting low educated patients should therefore be encouraged.

Cumulatively more than half of TB patients in this study reported to consume alcohol, and burden of alcohol use appeared higher in male than female patients. Also, many patients who interrupted treatment described alcohol misuse as one of the primary reasons for their stoppage of treatment. Previous studies in Kenya (Muture *et al.,* 2011; Sang *et al.,* 2017) and other African regions (Imtiaz *et al.,* 2017; Rehm *et al.,* 2009) have consistently associated alcohol consumption with treatment interruption and poor adherence. Interventions that reduce hazardous alcohol consumption in the population should be operationalized while continuous alcohol, smoking, and substance abuse cessation counselling and support need to be intensified during TB patient care and follow-up.

A unique finding in the present study was that female patients were at a higher risk of TB treatment interruption compared to males. Several previous studies (Kimani *et al.,* 2021; Masini *et al.,* 2016; Muture *et al.,* 2011) have found male patients to be at high risk of interrupting treatment, while other studies have indicated that there is no gender difference in treatment interruption (Amuha *et al.,* 2009; Kigozi *et al.,* 2017; Krasniqi *et al.,* 2017; Mekonnen & Azagew, 2018; Sang *et al.,* 2017). Modelling in this study reduced possibility of confounders. The study also included variables that are often not considered in routine surveillance data such as alcohol use, education, and smoking, which had wide between gender variation. Nevertheless, further investigation should be instituted to elucidate this finding.

This study found that while only slightly more than half of patients under observation had a treatment supporter, the patients who had treatment supporters were less likely to interrupt their treatment. Studies in "rural and urban settings in Kenya" (Ong'ang'o *et al.,* 2014), Hadiya Zone,

South Ethiopia (Billoro & Nunemo, 2019), and Windhoek District, Namibia (Endjala *et al.*, 2017) concur with this finding. The concept of treatment supporters have been widely used in TB case management and although this intervention has shown varying effects on TB treatment outcomes (Pradipta *et al.*, 2020), allowing TB patients to choose their own treatment supporters is more appropriate and cost-effective, especially in the context of high TB burden settings (MacIntyre *et al.*, 2003; Thiam *et al.*, 2007). Although there was a difference that did not reach statistical significance, compared to new patients, patients who previously interrupted TB treatment (LTFU) were more likely to interrupt their treatment again. This should be examined further in a larger study. Additionally, the previous treatment interrupters should be considered high-risk, and their care should be prioritized.

High proportion of patients who were tracked and returned back to health facilities after interrupting TB treatment suggests that it is feasible to prevent treatment interruption, a major unfavourable TB treatment outcome. However, delay in in identification and tracking of the patients who interrupted their medication demonstrates a severe health-care system deficit despite adequate community health coverage and robust clinical structures. Interventions that reduce time taken to trace treatment interrupters could eliminate treatment interruption, enhance programmatic treatment success rates and shorten the duration of TB transmission in the community. Reorientation of health care providers on the need for accurate documentation, rapid identification, listing and immediate tracking of treatment interrupters is advocated for. During qualitative interviews, patients who were found indicated the following reasons for interrupting their treatment: feeling well soon after treatment initiation, alcohol misuse, difficulty reaching the health facility, stigma, perception of not having TB, pill burden and lack of food. Similarly, previous studies have associated treatment interruption with patients feeling better after treatment

commencement (Kaona *et al*, 2004), traveling long distances to health facilities, inadequate food, ignorance (Muture *et al.,* 2011), migration, and previous TB treatment (Masini *et al.,* 2016; Wohlleben *et al.*, 2017). These explanations are mostly perceptual, socioeconomic, ignorance, and behavioural lifestyle risk factors, implying a systemic issue further confining programming gaps due to an emphasis on curative rather than preventive approaches in management of TB treatment interruption. Baseline and continuous health promotion and education efforts, as well as a well-designed social support network, are all essential in prevention of treatment interruption. Furthermore, employing a person-centred approach in a multidisciplinary environment is frequently advocated for since it enables for the construction of interventions that are individually tailored to the patients' ongoing treatment, monitoring, and psychosocial support needs (Fang *et al.*, 2019). A few possibilities include assigning case managers, targeted adherence counselling, psychosocial support groups, and appointment reminders. However, the efficacy of these approaches in routine public healthcare settings needs to be evaluated further.

5.4 Factors associated with survival probability and mortality among tuberculosis patients

Ending the global TB epidemic requires a substantial reduction in TB incidence and mortality (MacNeil *et al.,* 2020). However, this study found a cumulative mortality incidence of 15%, predominantly occurring during the intensive phase of treatment. The mortality rate in this study is slightly higher than previously reported, and it is higher than the national average of 6.3% (Ministry of Health, 2019), Kilifi County (5.5%) (Abdullahi *et al.,* 2019), and Tanzania (3.6%) (Bukundi *et al.*, 2021). Similar or higher rates of mortality have been observed in other high TB burden countries such as Uganda (15%) (Musaazi *et al.*, 2019), Nigeria (16.6%) (Adamu *et al.*, 2017), and Zimbabwe (20%) (Takarinda *et al.*, 2017). This suggests the need for the public health approaches that meet multi-dimensional patient needs. Examining factors associated with survival probability distribution and all-cause mortality among patients on TB treatment as well as causes, and circumstances contributing to mortality have implications for a better understanding of TB epidemiology and more accurate prediction of risks and occurrence of mortality. In high-TB-burden settings, this could allow for more cost-effective intervention techniques and increased surveillance. This study found older age, smoking, alcohol consumption, severe illness, extra pulmonary TB, clinically diagnosed TB, TB and HIV coinfection, severe malnutrition and comorbidities to be associated with reduced survival probability among patients on TB treatment. On multivariable model, comorbidities, severe illness, TB and HIV coinfection, and smoking were all associated with occurrence of mortality. Although only slightly more than a third of TB patients had one or more comorbid conditions, patients with comorbidities had a considerably worse chance of survival and were independently linked to all-cause mortality in the study population and in both HIV positive and HIV negative subgroups. Comorbidities including diabetes mellitus, cardiovascular diseases, malignancies, chronic respiratory conditions, mental health illnesses, liver

diseases, and chronic kidney diseases are common among TB patients and significantly increase the risk of mortality (Azeez *et al.*, 2019; Podalirio *et al.*, 2018; Puchner *et al.*, 2019). A bidirectional negative association between TB and comorbidities suggests the need for holistic health care of patients. Universal screening of TB patients for comorbid conditions and vice-versa may result in early detection, better management, and improved treatment outcomes.

Previous studies (Duro *et al.*, 2017; Muthu *et al.*, 2018) indicate that severe illness is not common among TB patients but the associated mortality is high. Whereas the severely ill patients constituted nearly a half of all TB patients in this study, similarly, high mortality and reduced survival probability were observed. Severe illness among TB patients, characterized by "respiratory rate > 30/min, temperature > 39 °C, heart rate > 120/min, inability to walk unaided and severe malnutrition" (World Health Organization, 2015d), is likely indicative of a delay in diagnosis and treatment of TB. The delay, as observed in this study, could be occasioned by patients' poor health-seeking behavior and/or health care systems gaps. This necessitates long-term, cost-effective efforts to reduce time to diagnosis via existing programmatic interventions such as community and health care facility active TB case finding.

This study also found that smoking increases the risk of mortality and dramatically diminishes the survival probability of TB patients. Studies in Malaysia (Khan *et al.*, 2020), Brazil (Ranzani *et al.*, 2020), India (Thomas *et al.*, 2019), and South Africa (Azeez *et al.*, 2019) as well as systematic reviews (Wang *et al.*, 2020) have similarly indicated that smoking is associated with mortality and thus, a substantial barrier to TB treatment success. Smoking is a risk factor for the development of TB disease (Thomas *et al.*, 2019), reduces lung function, and predisposes patients to other conditions such as lung cancer, chronic obstructive airway disease, and bronchitis (Murray *et al.*, 2018; World Health Organization, 2021d). Pollack and others (Pollack *et al.*, 2017) demonstrated

that smoking is likely to exacerbate immunodeficiency in TB and HIV coinfected patients by increasing the probability of having a high HIV viral load by one and a half to two times. Even though passive and active smoking were measured, this study did not quantify the pack-year index consumed. Nevertheless, incorporating smoking cessation into TB and HIV prevention and control programs may help to reduce TB incidence and mortality.

Although global reports have shown declining mortality among TB and HIV coinfected patients (Floyd *et al.,* 2018; World Health Organization, 2021a), people living with HIV continue to be at high risk for TB transmission, developing TB disease, and mortality (World Health Organization, 2019). The results of this study have shown a higher TB and HIV coinfection rate of 35% compared to the national average of 16% (Ministry of Health, 2016) and the global average of 12% (Murray *et al.,* 2018). HIV has also been associated with reduced survival probability and increased the risk of mortality among patients on TB treatment. Previous studies within Kenya (Kosgei *et al.,* 2020; Onyango *et al.,* 2017; Wekunda *et al.,* 2017) and other high TB burden countries such as Tanzania (Bukundi *et al.,* 2021), Zimbabwe (Takarinda *et al.,* 2017) and South Africa (Heunis *et al.,* 2017) have also indicated that HIV is a serious mortality risk among TB patients. Smoking, severe malnutrition, severe illness, and comorbidities were all associated with mortality in the TB/HIV coinfected patients. Almost all of these factors point to advanced HIV infection. According to the mortality audit, advanced HIV disease was the leading cause of death among TB/HIV coinfected individuals, with TB pneumonia accounting for fewer than a quarter of deaths. Immune reconstitution inflammatory syndrome and opportunistic infections such pneumocystis jiroveci pneumonia, cryptococcal meningitis, and Kaposi's sarcoma are among other causes of death in TB/HIV coinfected patients, with previous ART interruption and delays in diagnosis playing a pivotal role. Previous studies (Lin *et al.,* 2014; Simonovska *et al.,* 2015) have congruently

attributed death among HIV positive TB patients to non-TB causes. Comprehensive HIV care and prevention offer a unique opportunity to improve TB treatment outcomes. However, more research is needed to understand why TB/HIV coinfected individuals previously on TB preventative therapy (TPT) had a lower survival probability, as observed in this study. Within the HIV-negative group, patients with comorbidities and those clinically diagnosed had an increased risk of occurrence of mortality. This suggests the need for more accurate evaluation of clinically diagnosed TB cases to rule out other underlying factors associated with mortality. Also, the mortality audit revealed that lung related illnesses such as pneumonia, lung fibrosis and lung collapse were top causes of death among HIV-negative patients. The conditions that contributed to death among HIV negative subset appeared to be linked to patients' socio-behavioral characteristics and health-care system flaws that can be addressed by regular sensitization of the healthcare providers on the need for rapid and accurate diagnosis, comorbidity management, patient education, and adherence counseling. Community health personnel can intensify their TB prevention and control role through health education and promotion as well as screening families and promptly referring the sick to available health care facilities.

CHAPTER SIX

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

6.1 Summary

Tuberculosis remains serious public health problem. Globally, TB causes 10 million illnesses and 1.4 million deaths annually. Efforts to end global TB epidemic by 2035 are ongoing and include specific targets and milestones. Diagnosis and successful treatment of TB patients remains the best intervention in achieving the End TB targets. However, high rates of unfavorable TB treatment outcomes, mortality and treatment interruption, continue to present a difficult hindrance towards ending TB epidemic. Although previous studies have attempted to describe factors associated with unfavorable treatment outcomes, few have applied survival analytic techniques to investigate the predictors of unfavorable TB treatment outcomes. Besides, scanty have qualitatively characterized patients who experience the unfavorable TB treatment outcomes. Through a prospective cohort design, as well as quantitative and qualitative methods, this study identified and characterized predictors of unfavorable TB treatment outcomes in Vihiga County which is located in Western region of Kenya and is among counties with the highest rates of unfavorable TB treatment outcomes in the Kenya. The present study has demonstrated that the infectious form of TB, bacteriologically confirmed PTB, is the most common type of TB in the study area, and given that TB affects the most productive age group, this suggests an ongoing transmission. The male, people with low education, those who abuse alcohol, and smokers were found to bear heavy burden of TB with adverse consequences. Alcohol consumption, female gender, and primary or lower-level education were found to increase the risk of TB treatment interruption. Contrary, having a treatment supporter was found to mitigate treatment interruption. This study also established a serious health system delay in identifying and tracking patients who interrupt TB treatment. This

implies that it is possible to reduce or entirely prevent TB treatment interruption. The explanations the patients gave for interrupting their treatment were perceptual, socioeconomic, and behavioral lifestyle risk factors which can be addressed through health promotion, education, economic cushioning and psychosocial counseling using multisectoral approach. HIV coinfection, severe illness, smoking, and underlying comorbid illnesses were all linked to TB mortality. Smoking, severe malnutrition, severe illness, and comorbidities were all found to increase the risk of mortality among the TB/HIV coinfected patients while comorbidities and being clinically diagnosed increased the risk of mortality among the HIV negative TB patients. The mortality audit indicated that advanced HIV disease was the leading cause of death among TB/HIV coinfected individuals, whereas lung related complications resulted in majority of mortality among the HIV negative group. These findings indicate that predictors of unfavorable TB treatment outcomes are multidimensional and suggest the need for interventions that not only target individual patients but also the environment in which they live and receive healthcare services in a multisectoral approach.

6.2 Conclusions

1. Tuberculosis disproportionately impacts the male individuals, economically productive adults, people with low socioeconomic status and those with risky behaviours such as alcohol consumption and smoking, characteristics that also contribute to unfavourable treatment outcomes. The most frequent form of TB, bacteriologically confirmed PTB, indicates active ongoing transmission of TB in the study area while the burden of HIV coinfection remains high. The apparent distribution of TB disease and treatment outcomes based on patients' characteristics suggests that TB is more of a demographic, socioeconomic and behavioural issue than being regarded as a strict medical condition.

2. The rate of TB treatment interruption in Vihiga County is higher than previously reported, and it occurs predominantly during the intensive phase of treatment. The determinants of treatment interruption include alcohol consumption, being female, and having lower education level, while having a treatment supporter was found to mitigate TB treatment interruption. There is a serious health system delay in the identification and tracking of patients who interrupt TB treatment. The reasons patients gave for interrupting TB treatment including feeling well soon after beginning treatment, alcohol use, difficulty reaching health facilities, stigma, perception of not having TB, pill burden, and lack of food, are mostly perceptual, socioeconomic, ignorance, and behavioural lifestyle risk factors further compounding existing gaps.

3. The mortality rate among TB patients in Vihiga County is high and increasingly occurs during the intensive phase of treatment. Factors associated with reduced survival probability include older age, smoking, alcohol consumption, severe illness, EPTB, clinically diagnosed TB, HIV positive, severe malnutrition and comorbidities. Factors associated with all-cause mortality include comorbidities, severe illness, HIV coinfection, and smoking. Specific causes of mortality as well as conditions contributing to mortality differ by HIV status; advanced HIV disease is the leading cause of mortality among TB/HIV coinfected patients, while TB-related lung disease is the leading cause of death among HIV-negative individuals. Patient, social, and healthcare system factors play a role in the occurrence of mortality.

6.3 Recommendations

1. Addressing socioeconomic conditions, a distal health determinant, through appropriate policies may aid in the prevention and control of tuberculosis at the individual, family, and community levels. Although patients centred management is advocated for, a paradigm shift

from individual patient treatment to more comprehensive social interventions in a multisectoral approach is essential, as this presents a unique opportunity for advancing global zero TB targets. This can be accomplished by improving collaboration among biomedical personnel, patients and their families, community health personnel, and community administrators.

2. Interventions that help to reduce TB treatment interruptions should be encouraged. This may include rolling out behaviour change communication to address alcohol use, smoking, and substance abuse, as well as targeting low-educated patients. Preventive measures such as assigning treatment supporters to all patients, establishing psychosocial support groups, and enhancing appointment management are also possible. Health care providers need to be reoriented on the need for prompt identification and tracking of patients who interrupt TB treatment.

3. To reduce TB-related mortality, deliberate efforts should be availed to identify high-risk patients and prioritize their care through integrated social and health service strategies. Strengthening existing facility-based and community-based active TB case-finding activities, as well as clinical care, referral, and follow-up services, may help ensure timely diagnosis and treatment of TB patients. Also, revamping comprehensive care for people living with HIV could offer a once-in-a-lifetime opportunity to reduce TB mortality.

6.4 Recommendations for further studies

1. Further investigation with a larger sample size should be instituted to establish reasons why female patients have higher risk of treatment interruption.

2. A further interventional study should be conducted to establish efficacy of case managers, psychosocial support groups, and appointment reminders in prevention of treatment interruption.

3. Lengthier cohort studies, particularly those that persist beyond treatment completion, are required to evaluate the long-term survival of TB patients.

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APPENDICES

Appendix 1: Questionnaire for notified tuberculosis cases

Maseno University
School of Public Health and Community Development
Doctor of Philosophy in Public Health (Epidemiology & Population Health)

Predictors of unfavorable tuberculosis treatment outcomes: Prospective cohort study among notified cases in Vihiga County, Kenya

This questionnaire focuses on risk factors associated with management of tuberculosis and treatment outcomes among notified cases in Vihiga County. The main objective is to describe tuberculosis treatment outcomes, identify their predictors and related distribution patterns as well as determine survival time until occurrence of the unfavorable events among notified cases in Vihiga County. The purpose of the study is to understand modifiable factors in order to improve delivery of interventions in routine practice of TB control. You are therefore kindly requested to respond to the following questions

(Please indicate a tick in the brackets provided depending on patient's response).

Questionnaire code : …….

Interview Date: …….

Participant code: …….....

Name of supervisor: …….

a) Demographic and socio-economic characteristics

1. Treatment zone: Emuhaya [] Hamisi [] Sabatia [] Vihiga []
2. Sector: Faith based [] Public []
3. Where do you come from? Ward _____ Sub Location_____ Village_____
4. What is your gender? Female [] Male []

5. What is your date of birth _____ (Age in years_____
6. Are employed? Employment [] Not employed []
7. What is your marital status? Married [] Not married []
8. Approximately what is your monthly income in Kenya shillings? _____
9. How many people do you live with in your household? _____
10. What is your education level? Primary or lower [] Secondary [] Post-secondary []
11. Do you currently consume alcohol? Yes [] No []
12. Do you abuse any other substance(s) (Bhang, Miraa, cocaine, heroin etc.)? Yes [] No []
13. Do you smoke (currently, in past six months or passive)? Yes [] No []
14. How long (in weeks) had you been suffering from your symptoms before seeking medical attention? 1-2 weeks [] 2-4 Weeks [] More than four weeks []

    If 1-2 weeks skip question 16
15. Tell me why it took you so long with signs and symptoms before visiting the health facility?
16. Which health sector did you visit first after experiencing your symptoms? Chemist [] Faith based facility [] Herbal [] Private facility [] Public facility []
17. Approximately how many times did you visit health facility or facilities before you were diagnosed with TB _____
18. Is there someone who supports you (observe/reminds you take your drugs, reminds you of clinic appointment and cares for your needs)? Yes [] No []

b) Clinical characteristics of notified tuberculosis cases (Documented/Observed or subject declaration)

1. Date TB diagnosed_____
2. Date TB treatment initiated_____

3. What is the type of TB? Pulmonary [] Extra pulmonary []
4. What is clinical condition of the TB patient? Stable (Supports him/herself and or mild signs and symptoms [] Unstable (inability to walk unsupported or severe signs and symptoms e.g., fever of 39^0C, fast breathing >30/min, BMI <16 []
5. What is the clinical classification of TB case? Bacteriologically confirmed [] Clinically diagnosed []
6. What is the type of patient? New [] Relapse [] Treatment after lost to follow up (TLF) (previous treatment interruption) []
7. HIV test: Negative [] Positive [] Patient declined [] Not done []
8. Date HIV test done_____

   If HIV negative, patient declined or not done go to question 24.
9. Are you taking Cotrimoxazole preventive therapy (CPT)? Yes [] No []
10. Date CPT started_____
11. Are you on Anti-retro viral therapy (ART)? Yes [] No []
12. Date started HAART_____ Regimen_____
13. If HIV positive and not on ART, why? _____
14. CD4 count_____
15. Current viral load_____
16. Have you ever stopped taking ART? No [] Yes []
17. Have you ever taken TB preventive therapy (TPT)? Yes [] No []
18. Weight _____Height _____ Body mass index or z score_____
19. Food Support (RUTF or FBF): No [] Yes []

20. Do you suffer from any other disease (comorbidity)? Yes [] No [] If No, skip questions 21 and 22.
21. If yes, which disease? Diabetes [] RBS_____ Hypertension [] (Blood pressure) _____ Cancer [] Other specify (List the diseases that the patient suffers from) _____
22. How long have you suffered from the disease? Newly diagnosed [] Pre-existing []

THANKS FOR YOUR TIME

c) Follow up after initiation of treatment

Follow up month one

1. Date_____
2. Weight_____ Body mass index or z score_____
3. What is the clinical condition of TB patient/ treatment outcome?

   Still on treatment and stable [] Still on treatment but unstable [] Interrupted treatment []

   Died []
4. Date of treatment outcome_____
5. Any other significant observation_____

Follow up month two

1. Date_____
2. Weight_____ Body mass index or z score_____
3. If bacteriologically confirmed, what is the follow up smear microscopy results?

   Positive [] Negative []

4. If smear microscopy result is positive what is the;

a) Gene xpert result: Positive RR [] Positive RS [] Negative [] Not done []

b) Culture results: Positive with resistance [] Positive without resistance [] Negative [] Not done []

5. What is the clinical condition of TB patient/ treatment outcome?

   Still on treatment and stable [] Still on treatment and unstable [] Interrupted treatment []

   Died []

6. Date of treatment outcome_____

7. Any other significant observation_____

Follow up month three

1. Date_____
2. Weight_____ Body mass index or z score_____
3. If bacteriologically confirmed, what is the follow up smear microscopy results?

   Positive [] Negative [] Not Applicable []

4. If smear microscopy result is positive what is the;

   a) Gene xpert result: Positive RR [] Positive RS [] Negative [] Not done []

   b) Culture results: Positive with resistance [] Positive without resistance [] Negative [] Not done []

5. What is the clinical condition of TB patient/ treatment outcome?

   Still on treatment and stable [] Still on treatment but unstable [] Interrupted treatment []

   Died []

6. Date of treatment outcome_____
7. Any other significant observation_____

Follow up at month four

1. Date _____
2. Weight_____ Body mass index or z score_____
3. If bacteriologically confirmed, what is the follow up smear microscopy results?

   Positive [] Negative [] Not Applicable []
4. If smear microscopy result is positive what is the;
   a) Gene xpert result: Positive RR [] Positive RS [] Negative [] Not done []
   b) Culture results: Positive with resistance [] Positive without resistance [] Negative [] Not done []
5. What is the clinical condition of TB patient/treatment outcome?

   Still on treatment and stable [] Still on treatment but unstable [] Interrupted treatment []

   Died []
6. Date of treatment outcome_____
7. Any other significant observation_____

Follow up at month five

1. Date _____
2. Weight_____ Body mass index or z score_____
3. If bacteriologically confirmed, what is the follow up smear microscopy results? Positive [] Negative []
4. If smear microscopy result is positive what is the;
   a) Gene xpert result: Positive RR [] Positive RS [] Negative [] Not done []
   b) Culture results: Positive with resistance [] Positive without resistance [] Negative [] Not done []

5. What is the clinical condition of TB patient/treatment outcome?

   Still on treatment and Stable [] Still on treatment but Unstable [] Interrupted treatment [] Died [] Failed treatment []

6. Date of treatment outcome_____

7. Any other significant observation_____

Follow up at month six

1. Date _____

2. Weight_____ Body mass index or z score_____

3. If bacteriologically confirmed, what is the follow up smear microscopy results? Positive [] Negative []

4. If smear microscopy result is positive what is the;

   c) Gene xpert result: Positive RR [] Positive RS [] Negative [] Not done []

   d) Culture results: Positive with resistance [] Positive without resistance [] Negative [] Not done []

5. What is the clinical condition of TB patient/treatment outcome?

   Interrupted treatment [] Died [] Failed treatment [] Completed treatment/Cured []

6. Date of treatment outcome_____

7. Any other significant observation_____

Appendix 2: Consent for notified tuberculosis patients

Principal Investigator
Paul Waliaula Wekunda
Contact: P.O Box, 1069 Maragoli.
Email: wekundapaul@gmail.com

Approving institution
Maseno University Ethics Review Committee (MUERC)
P.O Box, Private bag, Maseno. Phone: +254721543976/ +254733230878

Hello, my name is Paul Wekunda. I'm a student in the department of Public Health at the School of Public Health and Community Development in Maseno University. I am inviting you to participate in research titled, 'Predictors of unfavorable tuberculosis treatment outcomes: Prospective cohort study among notified cases in Vihiga County, Kenya'. You have been selected as a possible participant because you were diagnosed with TB and you are taking your therapy from this facility.

The study will take approximately six months from the time you were diagnosed with TB. However, you can ask questions about the study at any time and if you decide anytime not to finish, you can ask to stop. In other words, you will be asked to answer some questions today for around 45 minutes, and then monthly throughout the remainder of the period. These inquiries could be about your personal life, health, or conduct. However, you are assured that all the information you give will NOT be shared by any unauthorized persons apart from the research assistant and principal investigator, who will only access your responses. Also, this study is observational hence no risk is anticipated. It is important for you to know that participation in the study is voluntary and may not yield direct benefits for you, however, the findings may help improve service delivery to TB patients as well as prevention and control of TB. If you agree to participate in the study, you will be required to provide information and sign the following consent.

Consent form
I (Participant code) ……consent to participate in the study titled predictors of tuberculosis treatment outcomes and survive time among notified patients in Vihiga County.

Sign…… Date……
Or
Thumb print…… Date……

Appendix 3: Assent for tuberculosis patients between 15-18 years

Principal Investigator
Paul Waliaula Wekunda
Contact: P.O Box, 1069 Maragoli.
Email: wekundapaul@gmail.com

Approving institution
Maseno University Ethics Review Committee (MUERC)
P.O Box, Private bag, Maseno. Phone: +254721543976/ +254733230878

Hello, my name is Paul Wekunda. I'm a student in the department of public health at the School of Public Health and Community Development in Maseno University. I am inviting you to participate in research titled, 'Predictors of unfavorable tuberculosis treatment outcomes: Prospective cohort study among notified cases in Vihiga County, Kenya'. Your parents/guardians know we are talking with you about the study. This form will tell you about the study to help you decide whether or not you want to take part in it at will.

The study will take around six months from the time you were diagnosed with TB. However, you can ask questions about the study at any time and if you decide anytime not to finish, you can ask to stop. In other words, you will be asked to answer some questions today for around 45 minutes, and then monthly throughout the remainder of the period. Your parent/guardian may help you in answering questions that may be difficult for you. The inquiries could be about your personal life, health, or conduct. However, you are assured that all the information you give will NOT be shared by any unauthorized persons apart from the research assistant and principal investigator, who will only access your responses. Please note also that this study is observational hence no risk is anticipated. It is important for you to know that participation in the study is voluntary and may not yield direct benefits for you, however, the findings may help improve service health delivery to patients as well as prevention and control of TB. If you agree to participate in the study, you will be required to complete the following consent.

Your signature _____ Date _____

Code_____

Signature of person obtaining assent _____Date_____

Appendix 4: Treatment interruption tracing form

Maseno University
School of Public Health and Community Development

Doctor of Philosophy in Public Health (Epidemiology & Population Health)

Predictors of tuberculosis treatment outcomes: Prospective cohort study among notified cases in Vihiga County

Section A contains patient's details. To be filled by the attending clinician

1. Date…….
2. Name of the health facility …….
3. Questionnaire code…….……. (Refer to the questionnaire)
4. Participant (patient's) code: ……..... (Refer to the questionnaire)
5. Name of patient's village……. (Refer to the questionnaire)
6. Nearest land mark…….……. (Refer to the questionnaire)
7. Phone contacts of the next of kin (if applicable) ……
8. Relationship with patient……

Section B to be filled by the person tracing the patient

1. Interviewer's code: …….....
2. Date of physical tracing: …….
3. Was the patient found during tracing? Yes [], No []
4. If the patient was found, ask this question and; Tell me the reason why you stopped taking TB medicines before the required time of six months?
   (Write the answer in the provided paper in patient's own words)
5. Was the patient counselled to return to treatment? Yes [] No []
6. Was the patient referred back to the health facility? Yes [] No []
7. If the patient was not found, indicate the reason for his/her missing ……

Appendix 5: Mortality audit tool

Maseno University
School of Public Health and Community Development
Doctor of Philosophy in Public Health (Epidemiology & Population Health)

Predictors of tuberculosis treatment outcomes: Prospective cohort study among notified cases in Vihiga County

Section A: Details of the diseased

1. Name of the health facility …….
2. Questionnaire code…….……. (Refer to the questionnaire)
3. Participant (patient's) code: ……..... (Refer to the questionnaire)
4. Phone contacts of the next of kin ……. ……
5. Relationship with patient……

Section B: Causes of mortality and associated circumstances. This section is filled by the principal investigator in a multidisciplinary focus group discussion. The data is obtained from patient's treatment records, narration from attending clinicians and patient's kin.

1. Date of mortality occurred…….
2. Where did mortality occur?
3. Was the patient diagnosed with any other opportunistic infection in the 12 months prior to death?
4. Did the patient have any comorbidity prior to mortality?
5. What were the possible contributors of mortality?
6. What is the probable cause of mortality?
    a) **Immediate** cause; disease or condition directly leading to mortality?
    b) **Antecedent** morbid conditions, if any, giving rise to the IMMEDIATE cause?
    c) Any other **underlying condition** last?
    d) **Other significant conditions** contributing to the mortality, but not related to the disease or condition causing it?

Appendix 6: Approvals

MASENO UNIVERSITY
SCHOOL OF GRADUATE STUDIES

Office of the Dean

Our Ref: PHD/PH/00092/016

Private Bag, MASENO, KENYA
Tel:(057)351 22/351008/351011
FAX: 254-057-351153/351221
Email: sgs@maseno.ac.ke

Date: 9th April, 2019

TO WHOM IT MAY CONCERN

RE: PROPOSAL APPROVAL FOR WEKUNDA PAUL WALIAULA — PHD/PH/00092/2016

The above named is registered in the Doctor of Philosophy Programme in the School of Public Health and Community Development, Maseno University. This is to confirm that his research proposal titled "Predictors of Tuberculosis Treatment Outcomes and Survival Time among Notified Cases in Vihiga County" has been approved for conduct of research subject to obtaining all other permissions/clearances that may be required beforehand.

MASENO UNIVERSITY
29 APR 2019
DEAN SCHOOL OF GRADUATE STUDIES
PRIVATE BAG MASENO

Prof. J.O. Agure
DEAN, SCHOOL OF GRADUATE STUDIES

MASENO UNIVERSITY ETHICS REVIEW COMMITTEE

Tel: +254 057 351 622 Ext: 3050
Fax: +254 057 351 221
Private Bag – 40105, Maseno, Kenya
Email: muerc-secretariate@maseno.ac.ke

FROM: Secretary - MUERC

DATE: 19th July, 2019

REF: MSU/DRPI/MUERC/00707/19

TO: Paul Waliaula Wekunda
PG/PHD/PH/00092/2016
Department of Public Health
School of Public Health and Community Development
Maseno University
P. O. Box, Private Bag, Maseno, Kenya

RE: Predictors of Tuberculosis Treatment Outcomes: Prospective Cohort Study among Notified Cases in Vihiga County. Proposal Reference Number MSU/DRPI/MUERC/00707/19

This is to inform you that the Maseno University Ethics Review Committee (MUERC) determined that the ethics issues were adequately addressed in the initial proposal. Consequently, the study is granted approval for implementation effective this 19th day of July, 2019 for a period of one (1) year. This is subject to getting approvals from NACOSTI and other relevant authorities.

Please note that authorization to conduct this study will automatically expire on 18th July, 2020. If you plan to continue with the study beyond this date, please submit an application for continuation approval to the MUERC Secretariat by 15th June, 2020.

Approval for continuation of the study will be subject to successful submission of an annual progress report that is to reach the MUERC Secretariat by 15th June, 2020.

Please note that any unanticipated problems resulting from the conduct of this study must be reported to MUERC. You are required to submit any proposed changes to this study to MUERC for review and approval prior to initiation. Please advice MUERC when the study is completed or discontinued.

Thank you.

MASENO UNIVERSITY SECRETARY 19 JUL 2019 ETHICS REVIEW COMMITTEE

Dr. Bernard Guyah
Ag. Secretary,
Maseno University Ethics Review Committee.

Cc: Chairman,
Maseno University Ethics Review Committee.

REPUBLIC OF KENYA

NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Ref No: **192517**

Date of Issue: **30/September/2019**

RESEARCH LICENSE

This is to Certify that Mr.. Paul Wekunda of Maseno University, has been licensed to conduct research in Vihiga on the topic: Predictors of Tuberculosis Treatment outcomes: Prospective Cohort Study among Notified cases in Vihiga County for the period ending : 30/September/2020.

License No: **NACOSTI/P/19/1618**

192517

Applicant Identification Number

Director General
NATIONAL COMMISSION FOR SCIENCE,TECHNOLOGY & INNOVATION

Verification QR Code

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Appendix 7: Publications

RESEARCH ARTICLE

Determinants of tuberculosis treatment interruption among patients in Vihiga County, Kenya

Paul Waliaula Wekunda[1]*, Dickens S. Omondi Aduda[2], Bernard Guyah[3]

1 Department of Health, Tuberculosis, Leprosy and Lung Disease Control, Vihiga County, Kenya, 2 Directorate of Research, Innovation and Partnerships, School of Health Sciences, Jaramogi Oginga Odinga University of Science and Technology, Bondo, Kenya, 3 Department of Biomedical Sciences, Maseno University, Kisumu, Kenya

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OPEN ACCESS

Citation: Wekunda PW, Aduda DSO, Guyah B (2021) Determinants of tuberculosis treatment interruption among patients in Vihiga County, Kenya. PLoS ONE 16(12): e0260669. https://doi.org/10.1371/journal.pone.0260669

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Background

Despite robust Tuberculosis (TB) program with effective chemotherapy and high coverage, treatment interruption remains a serious problem. Interrupting TB treatment means that patients remain infectious for longer time and are at risk of developing drug resistance and death. This study was conducted to identify and describe predictors of TB treatment interruption.

Methods

A cohort of 291 notified TB patients from 20 selected health facilities in Vihiga County were enrolled in to the study and followed up until the end of treatment. Patient characteristics that potentially predict treatment interruption were recorded during treatment initiation using structured questionnaires. Patients who interrupted treatment were traced and reasons for stoppage of treatment recorded. Kaplan Meier method was used to estimate probabilities of treatment interruption by patient characteristics and determine time intervals. The Log rank test for the equality of survival distributions analyzed significance of survival differences among categorical variables. For multivariable analysis, Cox proportional hazard model, was fitted to identify predictors of TB treatment interruption through calculation of hazard ratios with 95% Confidence Intervals (CIs). For variable analysis, statistical significance was set at $P \leq 0.05$. Reasons for treatment interruption were categorized according to most recurrent behavioral or experiential characteristics.

Results

Participants' median age was 40 years (IQR = 32–53) and 72% were male. Of the 291 patients, 11% (n = 32) interrupted treatment. Incidences of treatment interruption significantly occurred during intensive phase of treatment. Independent predictors of treatment interruption included alcohol consumption (HR = 9.2, 95% CI; 2.6–32.5, p < 0.001), being female (HR = 5.01, 95% CI; 1.68–15.0, p = 0.004), having primary or lower education level

Predictors of mortality and survival probability distribution among patients on tuberculosis treatment in Vihiga County, Kenya

Paul Waliaula Wekunda[1], Dickens S Omondi Aduda[2], Bernard Guyah[3], James Odongo[4]

1. Department of Health; Vihiga County Government, Kenya.
2. School of Health Sciences: Directorate of Research, Innovation and Partnerships; Jaramogi Oginga Odinga University of Science and Technology.
3. Department of Biomedical Sciences; Maseno University.
4. Department of Mathematics and applied sciences; Ramogi Institute of Advanced Technology.

Abstract

Background: Tuberculosis (TB) related mortality remains a serious impediment in ending TB epidemic.

Objective: To estimate survival probability and identify predictors, causes and conditions contributing to mortality among TB patients in Vihiga County.

Methods: A cohort of 291 patients from 20 purposively selected health facilities were prospectively considered. Data was obtained by validated questionnaires through face-to-face interviews. Survival probabilities were estimated using Kaplan-Meier method while Cox proportional hazard model identified predictors of TB mortality through calculation of hazard ratios at 95% confidence intervals. Mortality audit data was qualitatively categorized to elicit causes and conditions contributing to mortality.

Results: 209 (72%) were male, median age was 40 (IQR=32-53) years while TB/HIV coinfection rate was 35%. Overall, 45 (15%) patients died, majority (78% (log rank<0.001)) during intensive phase. The overall mortality rate was 32.2 (95% CI 23.5 - 43.1) deaths per 1000 person months and six months' survival probability was 0.838 (95% CI, 0.796-0.883). Mortality was higher (27%) among HIV positive than HIV negative (9%) TB patients. Independent predictors of mortality included; comorbidities (HR = 2.72, 95% CI,1.36–5.44, p< 0.005), severe illness (HR=5.06, 95% CI,1.59–16.1, p=0.006), HIV infection (HR=2.56, 95% CI,1.28–5.12, p=0.008) and smoking (HR=2.79, 95% CI,1.01–7.75, p=0.049). Independent predictors of mortality among HIV negative patients included; comorbidities (HR = 4.25, 95% CI; 1.15-15.7, p = 0.03) and being clinically diagnosed (HR = 4.8, 95% CI; 1.43-16, P = 0.01) while among HIV positive; they included smoking (HR = 4.05, 95% CI;1.03-16.0, P = 0.04), severe illness (HR = 5.84, 95% CI; 1.08-31.6, P = 0.04), severe malnutrition (HR = 4.56, 95% CI; 1.33-15.6, P = 0.01) and comorbidities (HR = 3.04, 95% CI; 1.03-8.97, p = 0.04). More than a half (52%) of mortality among HIV positive were ascribed to advanced HIV diseases while majority of (72%) of HIV negative patients died to TB related lung disease. Conditions contributing to mortality were largely patient and health system related.

Conclusion: Risk of TB mortality is high and is attributable to comorbidities, severe illness, HIV and smoking. Causes and conditions contributing to TB mortality are multifaceted but modifiable. Improving TB/HIV care could reduce mortality in this setting.

Keywords: TB mortality; survival distributions; treatment outcomes; Vihiga.

DOI: https://dx.doi.org/10.4314/ahs.v23i1.24

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Introduction

Whereas tuberculosis (TB) is preventable and curable, it remains a leading cause of mortality from single infectious disease agent [1]. In 2019, an estimated 10 million people fell ill with TB globally and a total of 1.7 million died [2]. More than two thirds of TB cases occur in south-east Asia (44%) and Africa (25%) while lower incidences are observed in the Eastern Mediterranean region (7%), the European region (3%) and the region of the Americas (3%) [2]. Although Kenya has been removed from the list of high burden drug resistant TB countries, it remains

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