DISPARITIES IN TUBERCULOSIS INCIDENCE AND TREATMENT OUTCOMES IN RURAL AND URBAN SETTINGS IN ZAMBIA: EPIDEMIOLOGICAL APPROACH FOR TARGETED TUBERCULOSIS CONTROL

by

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ABSTRACT

Statement of the problem: Tuberculosis is the one of the leading causes of death among infectious diseases in the world. Although the TB epidemic is generally higher in Sub-Sahara Africa, it is not uniform among all the populations in this region. It is not known whether incidence of TB and TB treatment outcomes are similar between rural and urban settings in Sub-Sahara Africa.

Goal: The main goal of our study is to improve TB control by describing the incidence and TB treatment outcomes in rural and urban Zambia

Methods: In the first 2 specific aims we performed a retrospective cohort analysis of data from the TB control program in southern Zambia. We assessed the association between unfavorable TB treatment outcomes and rural/urban setting among new and recurrent TB patients. In the third aim we compared the incidence of TB between rural and urban settings among HIV seropositive individuals on ART in Zambia.

Results: Among 21,057 new TB patients' rural health setting was associated with death (aOR: 1.3; 95% CI; 1.0 1.5). Similarly, in recurrent TB in rural areas were more likely to die during the time of TB treatment than their counterparts in the urban settings ((aOR: 1.7; 95% CI: 1.0 - 2.7).

There was no difference in TB incidence among HIV seropositive individuals on ART between rural and urban settings ((aHR =1.4, 95% CI: 0.4 – 1.7). The overall incidence rate was high in both rural and urban settings (IR: 2.07/1000PYO; 95% CI: 1.8–3.7).

Conclusion

Rural setting was associated with poor TB treatment outcomes. The incidence of TB was high in both rural and urban settings. TB control officers must adapt TB control strategies according to the setting.

INDEX WORDS: Tuberculosis treatment outcome incidence rural urban HIV ART

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DEDICATION

To Nelo Mutembo my mom and Dickson Mutembo my dad I dedicate this dissertation. Your love and dedication to excellence has carried me through even after your death in my teenage years. Although you never had a chance to attend school beyond middle primary school, you did all you could to teach me how to read. Your unwavering belief that a person who can read can solve any social or scientific problem on earth made me develop passion for knowledge and wisdom. Rest in eternal peace.

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CHAPTER 1 : INTRODUCTION

Public Health Significance of TB

Tuberculosis (TB) has existed for decades and remains a major global health problem. In 2015 it was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease[1].

Based on the global case reports for 2015, there were 10.4 million new TB cases (including 1.2 million among HIV-positive people), of which 5.9 million were among men, 3.5 million among women and 1.0 million among children. The report estimates that there were 1.4 million TB deaths, and an additional 0.4 million deaths resulting from TB disease among HIV-positive people[1].

TB problem in Sub-Sahara Africa

Although the global trends in TB incidence, prevalence and mortality declined over the past 20 years, the number of new TB cases did not reduce as expected[2]. The decline is slowest in resource constrained countries particularly Sub- Sahara Africa. Of the cases reported in the 2015 World Health Organization (WHO) global TB report, 85% of the new TB cases occurred in Africa and Asia with incidence rates of more than 300 cases per 100,000[1].

In Sub-Sahara Africa, the burden of TB is compounded by Human Immunodeficiency virus (HIV) co-infection. Nearly 1.2 million of the 8.7 new TB cases are co-infected with HIV1 and estimates suggest that TB disease claimed 1.4 million lives of which about 400,000 were HIV positive. Nearly 89% of these deaths occurred in Sub-Sahara Africa.

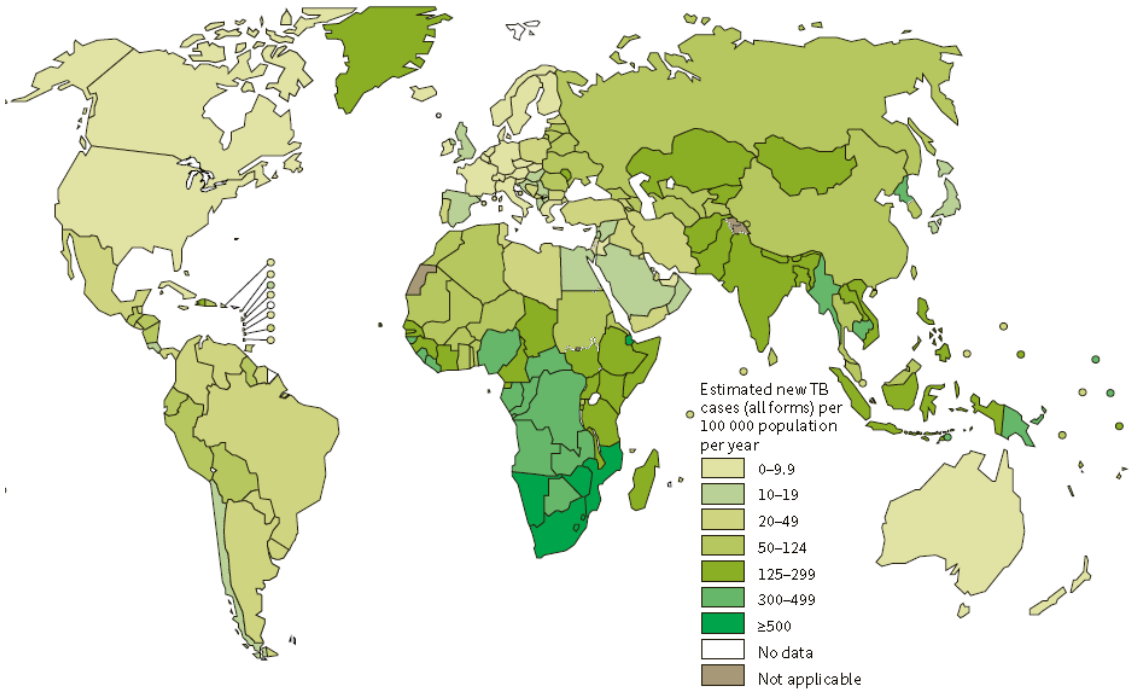

Figure 1-1:Estimated Global Incidence of all forms of TB

Source: WHO Global TB report 2015

TB problem in Zambia

Zambia is one of the Sub-Saharan African countries that is hard hit by TB and HIV epidemics and ranks among the thirty (30) high burden countries in the world3. TB is ranked among the top 5 causes of morbidity and mortality especially among the young and economically productive adults aged 15 -49 years[3].

The incidence rate of all forms of TB is estimated to be 433 per 100,000 population[4]. The TB notification rate had been increasing since the early 1980s until 2005 when it began to decline [5]. The changes in case detection are not clearly explained. Anecdotally, these changes can be attributed to either the population changes or deterioration or improvements in case detection or the true changes in TB cases and the dynamics of the HIV epidemic.

The first national TB prevalence survey was conducted in 2013/2014 and the initial results show that the prevalence of TB in the general population was actually higher than the estimates[6]. The prevalence for culture positive TB was 568 per 100,000 adult population[3]. From a nationwide representative sample of 296 symptomatic cases only 7% of the cases were on TB treatment at the time of the study[3]. In Zambia the dual HIV and TB burden pose a serious danger with 27% of all TB cases being HIV positive[6]. Zambia has an extraordinarily high prevalence of HIV among TB patients[7].

Core of the current TB control program

The World Health Organization (WHO) has developed a strategy to end the global TB epidemic but this can only be accomplished by acceleration of early diagnosis of TB, treatment of all patients with active TB and preventive treatment of LTBI in those at risk of progressing to disease.[8] The core element of the global TB control program is effective diagnosis of active TB cases and initiate effective therapy promptly. The goal of this strategy is to reduce morbidity and mortality at the individual level, reduce further transmission and prevent the development of drug resistance *M.tuberculosis*[9,10]. Through the stop TB strategy, the WHO recommends Directly Observed Therapy Strategy (DOTs) as the standard TB control strategy. Under the DOTS strategy, the national TB control programs (NTPs) target to detect at least 70% of new smear positive TB cases and cure 85% of these cases of TB disease. The strategy is widely adopted and implemented by NTPs and follows a passive case finding approach accompanied by bacteriological diagnosis and chemotherapy. Despite the availability of chemotherapy the passive case finding approach has not been very effective in controlling the TB epidemic in low-income countries[2]. This strategy has followed a passive disease surveillance and except in high incomes countries treatment for LTBI has lagged.

Tuberculosis control in Zambia

The Zambia National TB program (NTP) adopted the WHO DOT strategy in 1994. Since then the DOT strategy has been expanded and by 2003 the NTP had achieved a 100 percent DOTS coverage.[4] All patients are assessed for TB disease at the health facilities of choice. For smear positive patients, treatment is initiated at the health facility were the diagnosis of TB disease is made. This group of patients can access treatment from the nearest health facility known as a treatment center if they so wish. TB registers are kept both at the treatment and diagnostic centers. All treatment is ambulatory, and hospital admission is only done if there are other clinical indications. Daily treatment is carried out under DOTs which is either observed at the health center or by trained community treatment supporters/relatives. The Zambia NTP aims to reduce the burden of TB through 4 strategic areas which are: Strengthening and expanding quality DOTs services, improving collaboration between TB and HIV/AIDS programs at the provincial and district levels, improving laboratory systems, with activities such as supply and specimen management, increasing community involvement and awareness of TB, expanding private public partnerships and enabling research.[11]

Shortfalls of current approach and inadequate implementation of active case finding

Despite the demonstrated benefits of active case finding, Passive case finding of disease is the mainstay of TB control advocated by WHO DOTs [12]. This approach to TB control is limited because it does not interrupt the development of new cases as it waits for patients to go to the health care at their own volition.[13] By the time we make the diagnosis of TB and treat, the index case has already transmitted to the next generation of TB cases. Under this approach TB cases have a long duration to live with the disease and continue to transmit *M. tuberculosis* to the contacts in their network. In other words, there is a large pool of individuals with undetected active TB disease who continue to transmit *M. tuberculosis* for a long period of time before they present to the health care system.

Another important short fall of the TB control programs in low- and middle-income countries is failure to identify and treat latent TB infection (LTBI) which has potential to progress to active disease. Diagnosis and treatment of LTBI is important because approximately 5–10% of people with LTBI will develop active TB over the course of their lives[14]. This risk of disease is magnified in HIV seropositive persons, especially when immunosuppressed, where progression to disease is about 3% per year. Although unnoticed, the global burden of LTBI is high. It is estimated that 23% of the global population is infected with *Mycobacterium tuberculosis* (MTB).[15,16] This creates an extraordinarily large pool of people with LTBI who are at risk for disease progression. To make matters worse, of those with LTBI, less than 5% are diagnosed and treated.[15,16]

Mycobacterium TB transmission and the role of high incidence in the TB epidemic

M.tuberculosis is an air-borne pathogen that is expelled when an infected individual coughs it up and infects new individuals within proximity upon inhalation with some probability[17]. The transmission of TB mainly depends on the duration and intensity of exposure as well as susceptible host characteristics and the virulence of the infecting organism. Based on this it is reasonable to conclude that transmission is enhanced by the long duration of exposure of susceptible individuals to infectious individuals.

Epidemics of TB grow using the replacement principle of TB[13,18]. This principle is based on the reproductive number (R_0) in epidemic theory. According to the epidemic theory, epidemics of TB grow and are sustained when one infectious case is replaced by another case in the population[13]. New cases of TB disease do not necessarily develop immediately after infection with *M. tuberculosis* but may develop months or even years after a long latent period. When an index case develops TB disease either as a primary progressive disease or reactivation, the infectious index case transmits the infection before the diagnosis and/or treatment. The current control strategy focuses on treating index cases when they go to the health care system at their own volition. Treatment of an index case is essential but is not adequate to control an epidemic[13,18].

To control an epidemic, we need to reduce the R_0 to less than one (1) by preventing new cases. This can be achieved by preventing infection in the first place or prevent development of disease in those who are infected[13]. BCG and treatment of LTBI is used for the prevention of TB disease in those who are already infected. Strategies that are implemented to prevent new infection include improved ventilation and infection prevention practices in the health care setting[18]. Apart from these strategies prompt case identification can interrupt transmission in the community by reducing the duration of infectiousness and hence reduce the number of new cases. Despite this overwhelming knowledge we do not have an efficient strategy of promptly identifying infectious cases in the community and mitigating transmission. Additionally, not every patient who is started on TB treatment is able to achieve cure or successfully complete treatment.

The problem of undetected cases of TB disease

Undetected cases of TB disease pose a major problem for TB control because they perpetuate transmission because of the prolonged period of infectivity[19]. Globally it is estimated that nearly one-third of active TB disease cases remain undiagnosed[20]. In a recent nationwide population based TB prevalence survey in Zambia 97% of the 296 symptomatic survey cases were not on treatment at the time of the survey[3]. Only 7 (3%) of the 296 symptomatic cases were on TB treatment. This evidence suggests that a substantial pool of prevalent TB cases remain undiagnosed and serves as a source of ongoing TB transmission in the community. Previous studies have estimated that each undetected case of TB can result in 8-15 new infections in a year depending on the background prevalence[21]. Based on this evidence and the high number of undetected cases of TB in Zambia, it is difficult to control TB using the current approaches alone.

The problem of unfavorable TB treatment outcomes

A recent report by the WHO suggests that countries in sub-Sahara will not achieve the TB elimination goals by 2020.[22] In part because of the high number of TB patients who do not

successfully complete anti-TB treatment and continue transmitting *mycobacterium* TB and end up developing multi-drug TB (MDR-TB). The core element of the global TB control program is effective diagnosis of active TB cases and initiating effective therapy promptly. Since prompt diagnosis and treatment successful treatment of TB cases is the core strategy for the control of TB in most countries, suboptimal anti-TB treatment can result unfavorable anti-treatment outcomes which can further affect the transmission of TB at a large scale and the development of MDR-TB. These anti-TB treatment outcomes are likely to vary depending on the set up of the health care system and other demographic characteristics.

There is paucity of data on the effectiveness of TB control in most rural and urban parts of sub-Sahara Africa especially in countries where the HIV prevalence is high. It is not clear whether rural areas form a pocket of poor anti-TB outcomes and hence create a high potential of TB transmission and MDR-TB.

The problem of high TB incidence

Based on basic principles of epidemiology, prevalence of a disease is driven by the incidence rate and the duration of the disease.[23] When the duration of the disease is held constant and the incidence rate is high the prevalence of the disease is likely to increase. [23]From epidemic theory, we know that tuberculosis epidemics, or any epidemic in general, are perpetuated when one index case is replaced by one or more cases among contacts during their lifetimes.[23]Therefore to control the TB epidemic we must prevent new TB cases and hence reduce the incidence of TB. Firstly, new cases can be prevented by reducing or interrupting transmission through case detection and treatment in high-risk settings or using environmental controls. Secondly, we can prevent new cases by reducing the likelihood of disease progression from LTBI to active TB.

Purpose of the study and the underlying theory

The main goal of our study is to improve TB control by describing the incidence and TB treatment outcomes in rural and urban Zambia. We will refine and use epidemiological methods to describe anti-TB treatment outcomes according to geographical locations and therefore identify settings that have a potential of nesting TB cases for longer durations and high risk for MDR-TB. Then we will evaluate the incidence of TB disease and therefore identify the setting with high risk of new TB cases.

The incidence and prevalence of TB is variable between rural and urban settings. Within an urban area, or city, the distribution of TB incidence is variable, and outcomes of TB treatment may vary. Apart from the characteristics of the disease, distribution of the disease and TB treatment outcomes may be influenced by demographic characteristics and health care set up. Health care service delivery is better in urban populations because health facilities are easy to reach while in rural populations, patients must travel long distances. [24,25] Additionally, urban settings have more skilled health care providers with greater clinical experience in the management of TB and HIV and better diagnostics. In contrast, most TB patients in urban settings are from deprived communities and socially disadvantaged areas such as slums which may contribute to poorer TB treatment outcomes. [24,25]

Therefore, TB treatment outcomes also vary between different subpopulations. Subpopulations with poor treatment outcomes are not only at increased risk of mortality but act as reservoir for *M. Tuberculosis* transmission. If these communities or subpopulations can be identified they can be targets for heightened clinical and public health interventions

Our study is built on fundamental principles of infectious disease epidemiology. These principles are: 1) Transmission of TB occurs in geographical clusters. 2) TB cases are more likely to transmit *M. tuberculosis* to persons whom they share social and domestic gatherings. 3) Epidemics of infectious diseases including TB disease are propagated when one case replaces another. 4) Long duration of TB disease before and after diagnosis implies long duration of infectivity. A

combination of these factors with host and environmental factors increase the probability of *M. tuberculosis* transmission in the community. Alteration to any one of these fundamentals can play a substantial role in the control of TB.

We hypothesize TB treatment outcomes vary between different subpopulations;

Poor TB treatment outcomes occur in certain population groups and account for and account for disproportionately high mortality and longer duration of infectivity.

If we identify these population groups, they will be targets of heightened TB control activities: This will reduce mortality, the duration of infectiousness, contact rate between the infectious source and the susceptible host hence the probability of infection given contact. In figure 2 we present the conceptual impact of target TB control approaches following identification of settings with high transmission potential.

Gaps in the literature

There is paucity of data on the effectiveness of TB control in most rural and urban parts of sub-Sahara Africa especially in countries where the HIV prevalence is high. It is not clear whether rural areas form a pocket of poor TB treatment outcomes and hence create a high potential for further TB transmission and emergence of MDR-TB. Additionally, it is not known if the incidence of TB is homogenous between rural and urban settings among HIV+ patients accessing cART in these 2 settings. To our knowledge, a study designed to asses TB treatment outcomes and incidence of TB in HIV seropositive individuals on ART between the 2 settings has never been conducted in Zambia.

Specific aims of the study

To address the specific aims two (2) interrelated studies will be performed, each with its own aims.

Part 1: This is a retrospective cohort study of TB treatment outcomes among TB patient treated for TB in the southern province of Zambia between 2006 and 2013:

***Specific aim 1*:** To estimate and compare the risk of death between rural and urban settings for new TB patients treated for TB in Southern province, Zambia.

Hypothesis*:* We hypothesize that patients who live in urban settings have better treatment outcomes as compared to patients in rural areas who have difficulties in accessing health care.

***Specific aim 2*:** To estimate and compare the risk of death between rural and urban settings for TB retreatment patients treated with first line TB treatment in Southern province, Zambia.

Hypothesis*:* We hypothesize that patients who live in urban settings have better treatment outcomes as compared to TB retreatment patients in rural areas who have difficulties in accessing health care.

Part 2: This is a retrospective cohort study of TB incidence among patients receiving combination Anti-Retroviral Treatment (ART) in the Zambia national ART program.

Specific aim 3: To estimate and compare the incidence of TB disease among HIV patients receiving HAART in rural versus urban settings.

Hypothesis*:* The risk of developing TB disease in HIV patients receiving HAART is higher in patients seen rural clinics as compared to those in urban clinics.

Study designs

To address our specific aims, we will conduct two inter-related studies. The first study is a retrospective cohort study which will utilize data collected by the Ministry of Health in Southern province as part of TB monitoring and evaluation. The goal of this study is to examine tuberculosis treatment outcomes in patients notified in the national TB program between 2006 and 2013.

The second will address the third aim of this propose. It is a retrospective cohort analysis of data from the National AIDS Program Outcome and Impact Evaluation (NAPOIE). The NAPOIE was a nationwide evaluation of the HIV treatment program in Zambia for patients treated with cART between 2005 and 2014.

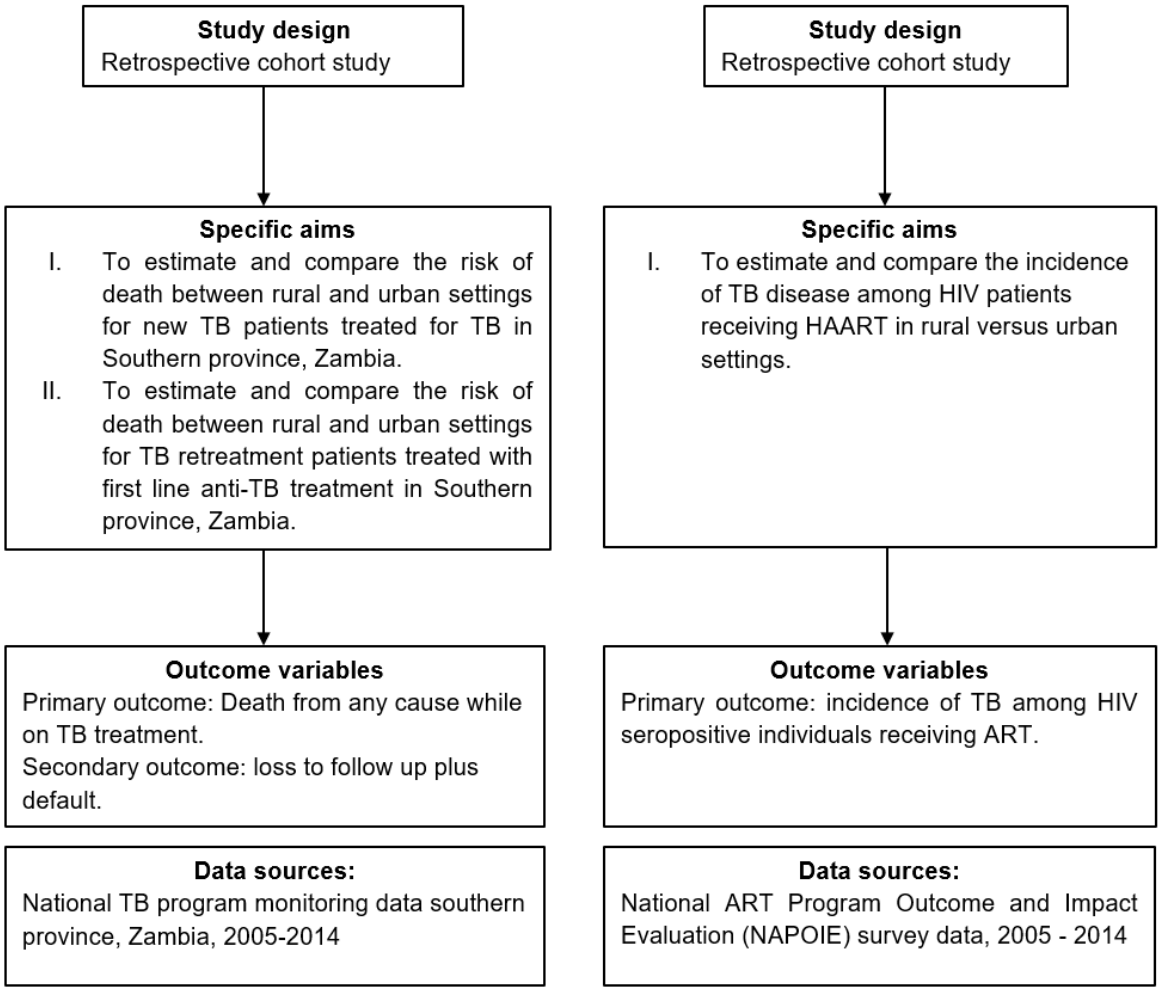

Figure 1-2: Flow diagram showing summary of the study design

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CHAPTER 2 : LITERATURE REVIEW

This chapter provides a critical review of the state of existing literature on identifying the geographical locations for tuberculosis transmission within the community especially in Sub-Saharan Africa and the difference in the incidence and TB treatment outcomes between rural and urban settings. Firstly, we will provide a brief description of the natural history of TB. Secondly will talk about the Global TB control strategies. Lastly, we provide a critical review of the published literature on the risk created by every setting in sustaining the TB epidemic and provide a perspective on how this study will address the gap in literature.

Methods of Literature Search

A search was performed in Pubmed, Embase, Global Health and Web of Science databases for relevant articles. Journal articles published in English between 2005 and 2017 were mostly included. The following phrases were used in conjunction with 'tuberculosis': 'case detection', 'case finding', 'household contact tracing', 'household contact investigation', 'transmission', 'hotspot', 'systematic case finding', 'locations of transmission, 'treatment outcomes', 'incidence',' recurrent', 'targets of control', 'community follow up', 'adherence strategies'.

The Natural History of tuberculosis

Tuberculosis (TB) is a preventable and curable infectious disease that nonetheless remains a significant cause of morbidity and mortality in resource-poor nations[1]. Eighty (80) percent of the cases of TB are caused by *Mycobacterium tuberculosis complex (MTC)* [2]. MTC refers to a group of species (*Mycobacterium tuberculosis, Mycobacterium canettii, Mycobacterium africanum, Mycobacterium microti, Mycobacterium bovis, Mycobacterium caprae* and *Mycobacterium pinnipedii)* that are genetically similar[3]. Of these *M. tuberculosis* is

the most well-known, infecting more than one-third of the world's human population[3]. Other species within the MTC, such as *Mycobacterium africanum*, and *Mycobacterium bovis*, are also known to cause TB in humans[4].

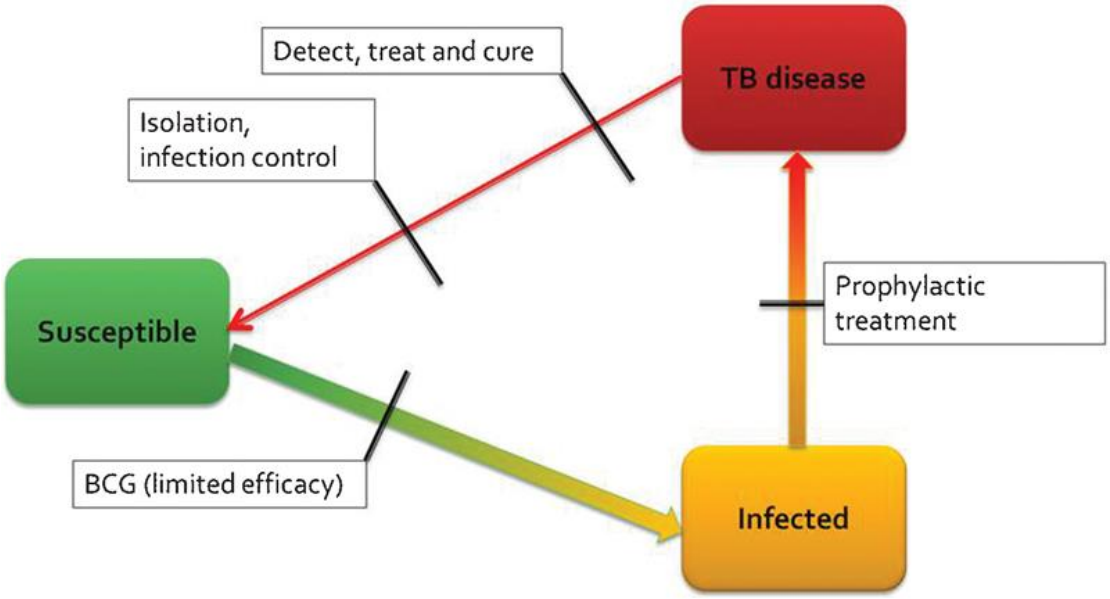
The organism is spread from human to human through airborne droplets when a person with active TB disease coughs or laughs or sneezes. Exposure to such persons with active disease results into the inhalation of infected droplets and may result into infection in 10-30% of individuals[5]. Of the individuals who acquire TB infection only about 10% develop active TB disease within the first year of acquiring infection known as primary progressive disease[5]. In the other 90% TB infection does not progress to disease and the body's immune system is able to either kill the bacteria or suppress it to the state of dormancy known as Latent TB Infection (LTBI)[6]. LTBI is asymptomatic in humans. It is not detected both bacteriologically and radiologically. However, it can be detected using Tuberculin Skin Test (TST) and interferon gamma. After a period of latency active TB may develop following disruption of the immune system and this form of TB is known as reactivation TB. For a person with an intact immune system the lifetime risk of developing TB is about 10%[7]. When there is disruption of the immune system as is the case in HIV, the risk of TB disease in persons with TB infection is dramatically increased. It is estimated that in this select group of individuals the risk of TB disease is as high as 10% per year[8]. Isoniazid preventive therapy and life time antiretroviral treatment is highly effective in reducing the incidence of TB disease in these individuals[9].

TB disease can occur through the reactivation or primary progressive pathway. If treated with anti-TB chemotherapy most of the individuals are cured within 6-8 months. If left untreated, it is estimated that 70% of sputum positive individuals will either self-cure or die within 2-3 years[10].

Tuberculosis control strategies

The control strategy for TB which is being implemented by WHO and its member countries is known as "end TB strategy"[11]. The target of this strategy is to reduce the number of TB deaths by 90% and reduce TB incidence rate by 80% by 2030. This strategy is designed around three

pillars which are: 1)Integrated patient-centered TB care and prevention, 2)Bold policies and supportive systems 3)intensified research and innovation[12]. In our review we will discuss the scientific methods/principles used to control TB which are mainly implemented in the first pillar of the end TB strategy. We will discuss these strategies under the following sub headings: Case detection, treatment/cure, vaccination, prophylactic treatment of Latent tuberculosis (LTBI) and other TB control strategies. Figure 4 summarizes the principles of the stopping TB and the points at which all these strategies act.



Source: Respiratory critical care medicine 2013;34(01):003-016

Note: TB control is based on preventing susceptible individuals from becoming infected using vaccination, preventing infected individuals from developing the disease using prophylactic treatment, preventing individuals with TB from having contact with susceptible individuals through early detection and cure, isolation, and infection control measures[13].

Figure 2-1: Principles for controlling the TB epidemic.

Case detection

The main case detection strategy in the WHO end TB strategy is based on evidence from the Directly Observed Therapy (DOTs) studies[14]. In this strategy the index case patients present to the health care system for diagnosis at their own volition. This may take several days or even

years from the onset of symptoms before the patient can present to the health care system. The case detection strategy of TB disease is an example of the passive disease surveillance and is not adequate to interrupt transmission. Under this strategy the NTP should detect at least 70% of the estimated new smear positive cases and successfully treat 85% of these cases each year[12]. Recent updates of the strategy recommend screening of household members of sputum positive patients and systematic screening of high risk groups such as individuals living with HIV[15].

Early case detection and prompt initiation of effective TB treatment is the principle means of controlling transmission and reducing TB incidence[16]. Globally the overall estimated case detection rate (CDR) is 63% (range, 60% - 66%)[17]. CDR is calculated as the total number of new and relapse cases notified divided by the estimated number of incident cases of TB that year[17]. When the CDR is expressed as a percentage it gives an indication of the proportion of all incident TB cases that are diagnosed and reported to the NTPs or national surveillance systems. Since the 1990s global CDR has been increasing in all the WHO regions with the greatest increase in the countries with multiple sources of TB data and effective TB control programs such as China and Cambodia. These same countries have experienced enormous declines in the incidence of TB[13]. However in most High Burden Countries (HBC) the increase in CDR and the decline in the incidence of TB disease has not been dramatic enough to achieve the targets of the end TB strategy[13]. The suboptimal trends observed in HBCs are mainly because of the gap in the early detection of TB.

Treatment and cure

The dominant method of TB control at the moment is the treatment of active disease by chemotherapy[18]. The impact of drug treatment in forcing down incidence depends critically on the incremental increase in case detection and cure rates. If a cure rate of 85% is achieved with a detection rate of 70% the incidence rate of TB would be reduced by an average of 4% annually for the first decade of the control[19]. A reduction of this magnitude, and on a large geographical

scale, would be a substantial achievement for public health, but it leaves an incidence rate in 2050 that is still far above the elimination target of 1 per million[19].

Besides drug treatment for active TB there are, in principle, two other possible approaches to control: the first is to prevent infection by (pre-exposure) vaccination, and the second is to stop the progression from latent infection to active disease (reactivation) through preventive drug therapy or post-exposure vaccination

Vaccination

Bacillus Calmette-Guerin (BCG) vaccination is the primary prevention strategy. BCG vaccine has existed for over 80 years and is one of the most widely used of all current vaccines. In countries where it is part of the national childhood immunization program the coverage is usually over 80% of neonates and infants. The vaccine is given at birth and offers protection against severe forms of the childhood TB.[20] Randomized controlled trials and case-control studies have shown consistently high efficacy of BCG vaccination against severe forms of childhood tuberculosis, principally miliary disease and meningitis, but variable efficacy against pulmonary tuberculosis in adults.[21]. BCG has a summary protective effect of 51% according to a metanalysis published by Colditz et al. [21].

The impact of BCG vaccination on transmission of M. tuberculosis is limited. This is as a result of wide variation in preventing primary infection and, more importantly, it does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community.[22]

Prophylactic treatment of Latent tuberculosis

Treatment of LTBI is a form of secondary prevention of TB. An individual who is infected with *M.tuberculosis* is treated with one or more anti-tuberculosis drugs to prevent the development of active TB[23]. Treatment of LTBI is considered an essential component of TB control programs in several industrialized countries and is being used in selected situations in developing

countries[24]. Persons with LTBI have a positive skin test but no evidence of active disease[25]. Treatment of LTBI with a course of antibiotics to prevent reactivation tuberculosis is major goal of the national strategy for elimination of TB in the USA[25].

The WHO recommends isoniazid preventive therapy for all HIV infected patients because they are at a high risk of developing TB disease. Several efficacy and effectiveness studies have demonstrated the benefit of isoniazid in this select group of patients [26,27]. However, isoniazid preventive therapy has not been widely used in HIV patients in most countries with a high double burden of HIV and TB. In most places frequent interruptions of isoniazid supply has been the main reason for the low utilization of Isoniazid preventive therapy[28].

Other control strategies

Infection control through work practice and administrative measures has the greatest impact on preventing TB transmission in healthcare settings[29]. The goal is to prevent TB exposure to health workers and patients, reduce the spread of infection by ensuring rapid diagnostic investigation and treatment for those suspected or known to have TB. Environmental control measures including the use of N95 personal respirators, negative pressure ventilation, ultraviolet lights in TB wards and clinics, constitute a second line of defense in health settings. They all have been shown to have some benefit in preventing the spread of TB to health workers and among patients in hospital settings[30,31]. However most of these measures have limited use in the developing countries.

Studies describing TB according to geographical setting

Studies and program evaluations have been conducted in different parts of the world to asses TB treatment outcomes among different population groups which include HIV+ individuals.[32-34] The most comprehensive of these studies have been in high income countries.[35] Studies which have described TB treatment outcomes and the incidence of TB disease have not tried compared rural and urban settings.[36-39] However, several studies have studies have explored

transmission between different settings. These studies have found that the potential for transmission differs from place to place.

The gap in the transmission of tuberculosis in the community can partly be explained by the fact that the problem of tuberculosis transmission is vast, and the methods of measuring transmission are expensive to be incorporated in the routine TB control programs especially in settings with a high burden. Although it has always been known that TB is a clustered disease, it was not until the 1980's when new methods of genotyping where applied to TB transmission that we were able to infer transmission to a localized setting. In 1986 in Boston Massachusetts a group of scientists investigated an outbreak of TB and were able to show that most of the cases of TB that were diagnosed in a homeless shelter were a result of recent transmission from a single source[40].

Following the Boston TB outbreak investigation, several studies have been conducted using molecular epidemiology techniques to understand transmission dynamics. In these studies, more advanced laboratory techniques such as restriction fragment length polymorphism (RFLP), Spoligotyping and mycobacterial interspersed repetitive-unit-variable number tandem repeat (MIRU-VNTR) were used. In these studies, recent transmission of *M. tuberculosis* accounted for more disease in the community [41-44]. These techniques have become standard practice in the TB reference laboratories and TB outbreak investigations in the developed world. However, the methods are still not feasible for most of the low-income countries which bear the biggest proportion of the TB disease [44].

These new techniques and the results from studies have led to change in the focus of understanding the dynamics of TB transmission. Previously household contact investigation was the focus of studies which attempted to interrupt the transmission of TB in the community [45-47]. The approach is reasonable because it is since an infectious case in the household makes a household an intense site for *M. tuberculosis* transmission. However recent studies show that household transmission only accounts for 15-25% of TB transmission in the community [48,49]. With

this data research focus has moved to supplement the household transmission evidence with estimates of transmission away from the household.

Several studies have shown that transmission is localized to very specific areas within the community and some studies have explored the settings in which the risk of transmission is highest [40,50-52]. In a study aimed at identifying possible transmission hotspots in Tokyo Japan, the concept of activity space which is based on studying the place where patients spend most of their time was used in combination with molecular genotyping techniques. Activity space spatial analysis suggested possible transmission around the major railway station[52].

In another study in Cape Town South Africa researchers analyzed data from time activity diaries and CO_2 concentration in different locations and established that children got the infection from schools and adults from work environments. Transmission in home environments was uniform across all age groups[53]. In another community transmission study in Cape Town to identify risk factors for ongoing *M. Tuberculosis* the incidence and proportion of genotypically clustered cases in this city was higher than reported elsewhere. As a result of the overwhelming levels of ongoing transmission in the whole study area, the study failed to establish any localized geographical associations with genotype clustering[54].

In Uganda another Sub-Saharan country with a high burden of tuberculosis Chamie etal showed that the most likely sites for TB transmission were the health and social settings in rural areas [51]. In this study they employed social network analysis methods, GIS and molecular epidemiology. The multidisciplinary methods used by Chamie have been applied by other researchers to understand TB transmission dynamics and we have learned that recent transmission of *M. tuberculosis* accounts for more disease than it has always been thought. Following this a mathematic modeling study was conducted in Brazil to demonstrate the effect of achieving TB control targets in *M. tuberculosis* transmission hotspot containing 6% of the city's population. Achieving TB control targets in the hotspot containing 6% of the city's population will

result in similar impact on the city wide incidence of TB as achieving the same targets throughout the remaining community[55].

In addition to understanding the settings of *M. tuberculosis* transmission several studies have been conducted on the diagnostic pathways and delays to TB diagnosis [56-59]. It is important to understand this in relation to place because the longer a patient life with active disease and spends more time at a place the higher the likelihood of his contacts at that place to get infected. The "TB diagnosis delay studies" have increased the depth of knowledge about the duration of infectiousness from the time that TB patients notice the symptoms. Through a meta-analysis of studies from different parts of the world we have learned that the median delay time from the onset of symptoms to diagnosis by the health care ranges between 25-185 days with the highest delays being in the low and middle income countries (LMMC)[56]. From a recent cohort study of Index case mobility, there are about 32,000 person years of follow up time for potential *M.tuberculosis* transmission in multiple settings before an individual sought care from the professional health care system[59].

Despite the remarkable progress towards understanding settings of transmission and the long duration that TB patients continue to transmit *M. tuberculosis*, there is a missing link in physically identifying the geographical locale in the community where *M. tuberculosis* transmission is highest. As a result of this gap it has been difficulty to develop geographically targeted systematic TB control interventions. Secondly it is not known whether treatment outcomes for anti-TB treatment follow a similar pattern as the transmission potential described in this section.

Studies describing TB treatment outcomes in rural and urban settings

In this section we summarize the findings of studies that attempted to compare TB treatment outcomes between rural and urban settings. The first study that we summarize was conducted in Uganda a Sub-Sahara African country with a high burden of TB and HIV.[60] Of 191 rural patients that were enrolled in this study, 66.7% achieved treatment success compared to

81.1% of 213 urban patients. Adjusted analysis revealed higher average treatment success in urban patients than in rural patients (OR 3.95, 95%CI 2.70–5.78). Loss to follow-up was higher and follow-up sputum smear results were less frequently recorded in TB clinic registers among rural patients. In this study patients receiving treatment at higher-level facilities such as hospitals in rural settings had greater odds of treatment success, while patients receiving treatment at lower level facilities such as rural health centers had lower odds of treatment success. The major reason cited for this was frequent drug stock-outs at the lower level. As can be seen this study enrolled very small numbers to draw conclusions that can be inferred to other settings.

Many studies have described TB treatment outcomes for population of TB patients on treatment or for either urban or rural setting but never made a comparison between the 2 settings.[61-63] Most of the programs in these studies reported good TB treatment outcomes. One thing which is common among TB programs with good TB treatment outcomes is an effective community follow up program using strategies such as DOT.[64-66]

Incidence of TB in HIV seropositive individuals in Sub-Sahara Africa

Studies conducted in Sub-Sahara Africa and other parts of the world have consistently shown that incidence of TB among HIV patients is higher than comparable groups of HIV seronegative individuals. [1,32,36,39]

To measure incidence of TB among HIV patients a receiving ART a community-based cohort in Cape Town were analysed.[67] 1544 patients with a median follow-up of 5.0 years (IQR 2.4-5.8) were included in the analysis. 484 episodes of incident TB (73.6% culture-confirmed) were diagnosed in 424 patients for 6506 person-years (PYs) of follow-up. In this study the TB incidence rate during the first year of ART was 12.4 (95% CI 10.8-14.4) cases/100PYs and decreased to 4.92 (95% CI 3.64-8.62) cases/100PYs between 5 and 8 years of ART. The study concluded that the incidence of TB was higher among HIV seropositive individuals even after introducing ART as compared to the general population. The incidence was highest in the first year of starting ART and waned off with time.[67]

In another study in Johannesburg, South Africa during 13,416 person-years of follow-up, 501 TB cases occurred among 7536 individuals, corresponding to an overall incidence rate of 4.2 cases/100 person-years.[39] The highest incidence rate (21.7 per 100 person-years) was observed in the first 3 months of ART among people with CD4 count below 50 cells/mm3. Low baseline CD4 count, anemia, and low body mass index were the strongest risk factors for early incident TB. Low updated CD4 count, low updated body mass index, anemia, and high viral load on ART were strong risk factors for late incident TB. Severe immune suppression at the time of starting ART was the major reason for early incidence of TB.[39]

Although these studies adequately describe the incidence of TB in HIV seropositive individuals on ART and the associated risk factors, none of them studied the relationship between incidence of TB among HIV seropositive individuals and rural/urban setting.

Differences in rural and urban living conditions

The rural and urban setting has marked differences in the living conditions. These differences in living conditions have potential to affect health outcomes including TB incidence and TB treatment outcomes. Therefore, these two unique settings provide a platform for targeted approaches to TB control or at least TB control approaches that are tailored to the setting. In this section we briefly describe the rural and urban set up in Zambia in terms of population distribution and living conditions.

Zambia has a population of just over 17 million people based on the 2010 estimate of 14.3 million people in 2010 and a 3.3% annual growth rate.[68] Of this population 40% live in urban areas.[68] The proportion of the urban population varies by province, from 13 percent in Eastern and Western provinces to 85 percent in Lusaka.[68] Average population density by province in 2010 ranged from a high of 100 people per square kilometer in Lusaka to a low of six people per square kilometer in North Western.[69] In short rural areas had the lowest population density per square kilometer.

Zambia has a mixed economy consisting of a rural agricultural sector and a modern urban sector that, geographically, follows the rail line.[69] Currently, construction sector contributes 14 percent of the gross domestic product (GDP), agriculture contributes 9 percent of the GDP, manufacturing sector and mining each contribute 8 percent of the GDP. According to the Living Conditions Monitoring Survey 2010, 60 percent of Zambians are classified as poor.[70] In the Zambian context, poverty is defined as lack of access to income, employment opportunities, and entitlements, including freely determined consumption of goods and services, shelter, and other basic needs.[70] As of 2010, poverty continued to be more prevalent among rural than urban residents (78 percent and 28 percent, respectively).[70]

Potential application of the concept of targeted tuberculosis control

There is enough evidence that social and environmental factors play a critical role in the epidemiology of disease. Understanding the epidemiology of a disease in a setting where it is prevalent, or endemic is critical in developing interventions that are appropriate for that setting. In this case the epidemiology of TB is likely to be different between rural and urban settings in Zambia because of the differences in the social and physical environment of the two settings. Understanding the epidemiology of TB in these settings is important because it provides a platform for scientists to develop interventions that are appropriately tailored for each setting. In our approach we will endeavor to firstly understand epidemiological differences in TB treatment outcomes between rural and urban settings. Secondly, we will explore the relationship between TB incidence among HIV seropositive individuals and rural/urban setting.

Therefore, we will not only be measuring the incidence of TB and TB treatment outcomes for the entire population but breaking it down between rural and urban setting. If this approach is successful, we can develop interventions that are appropriate for each setting using modern technological advances such as mobile phones and short-term TB preventive treatment. With this approach we hope to improve the promptness of TB detection, effectiveness of follow up of

patients on treatment and hence reduce the duration of infectiousness among TB patients and improve TB treatment outcomes.

Gaps in literature

There is little knowledge as to whether TB incidence and TB treatment outcomes follow the pattern of TB transmission potential that have been adequately described by many researchers. There is generally lack of data on the effectiveness of TB control in most rural and urban parts of sub-Sahara Africa especially in countries where the HIV prevalence is high. It is not clear whether rural areas form a pocket of poor TB treatment outcomes and hence create a high potential for further TB transmission and emergence of MDR-TB. Additionally, it is not known if the incidence of TB is homogenous between rural and urban settings among HIV+ patients accessing cART in these 2 settings. To our knowledge, a study designed to asses TB treatment outcomes and incidence of TB in HIV seropositive individuals on ART between the 2 settings has never been conducted in Zambia.

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CHAPTER 3 : METHODS

Overview of study design

To address our specific aims, we will conduct two inter-related studies (Figure 1). The first study is a retrospective cohort study which will utilize data collected by the Ministry of Health in Southern province as part of TB monitoring and evaluation. The goal of this study is to examine TB treatment outcomes in patients notified in the national TB program between 2006 and 2014.

The second study will address the third aim of this propose. It is a retrospective cohort analysis of data from the National AIDS Program Outcome and Impact Evaluation (NAPOIE). The NAPOIE was a nationwide evaluation of the HIV treatment program in Zambia for patients treated with ART between 2006 and 2014.

We now present the methodological details of our study under 3 specific aims before discussing the ethical review and human subjects' requirements.

Specific aim 1

Specific aim 1: The aim was to estimate and compare the risk of death between rural and urban settings for new TB patients treated for TB in Southern province, Zambia.

Study design

We conducted a multicenter retrospective cohort review of new TB patients who were treated for TB in Southern Province, Zambia between January 2006 and January 2014.

A. Map of Africa showing the position of Zambia

B. Up close map of Zambia showing the site of the study

Figure 3-1: Show the map of Zambia and the site of our study

Study setting

Southern province is located in the southern part of Zambia and has a population of 1,806, 187 with an annual growth rate of 2.7%.[1] The province is predominantly rural with over 75% of the population living in rural settings and engaged in peasant farming.[1] Demographic characteristics are summarized in table 1. The prevalence of HIV is generally high and is estimated at 13.4% in the adult general population.[2] Generally, HIV prevalence is higher in the urban settings as compared to the rural settings.[2] In 2015, 3464 TB cases were reported in southern province translating into a notification rate of 187/100,000 population. This notification rate is higher than the national average of 219/100,000 population.

Study population

The study was conducted within the National TB Control Program (NTP) in June 2014 by abstracting patient level data from the NTP registers in southern province of Zambia.

Inclusion criteria: All patients in the cohort were screened for inclusion into separate “new” and “retreatment” TB sub cohorts. A new TB patient was defined as an individual who was diagnosed

with TB disease by a clinician and was never treated for TB before this episode or has never taken TB drugs for more than 1 month.[3] In this analysis the study population is new TB patients.

Table 3-1: Summary of the key demographic characteristics of the study population

Population	2,077,229
Female population	1,047,442 (50.4%)
Age distribution	N (%)
0 - 14	987,068 (45.7%)
15 - 24	419,618 (20.2%)
24 – 44	461,475 (22.2%)
45 – 54	102,629 (4.9%)
Over 55	106,439 (5.1%)
Fertility rate	6.2 births/woman
HIV prevalence	13.3%
Number of TB cases notified in 2015	3464
TB notification rate in 2015/100,000	187/100,000

Exclusion criteria: New TB patients who transferred to other facilities and their status at the end of treatment could not be verified were excluded from the analysis.

Study outcome(s)

The primary outcome was death from TB disease or any other cause before the patient completed anti-TB treatment or was confirmed cured.

Secondary outcome was a composite of default and treatment failure. Default was defined as a patient having missed more than 2 months of consecutive doses and treatment failure was

defined as a patient being smear positive after more than 5 months of treatment and was not detected as having MDR-TB.[3]

Study exposure

The main exposure was place of TB treatment dichotomously classified as rural health setting or urban health setting. Rural health setting was defined as receiving TB treatment at clinics or hospitals that served a catchment population of up to 30,000 and located in a place where the source of livelihood for at least 75% of the population is agriculture and agriculture allied activities.[4] While Urban health setting is defined as receiving TB treatment at clinics or hospitals located in an urban area and where the facility serves a catchment population of over 30,000.[4] Classification of rural and urban health facilities was based on the Ministry of Health and Central Statistical Office of Zambia 2010 census classification and definitions.[1] All the health facilities provided anti-TB treatment within the framework of the NTP which is adapted from the WHO TB treatment guidelines.[5,6]

Covariates, Confounders

We assessed demographic and clinical risk factors that were associated with death among TB patients treated for TB. The following were included in the analysis as covariates and potential confounders: age, sex, weight at the start of treatment and end of follow up, sputum smear results, type of TB disease, anti-TB treatment delay, year of starting anti-TB treatment and HIV status. For HIV positive patients the role of cART and Cotrimoxazole prophylaxis was further evaluated. The type of health facility classified as health center or clinic and hospital was a potential confounder of the relationship between rural/urban and death.

Type of TB disease was classified into: Clinical pulmonary TB, bacteriologically confirmed pulmonary TB and extrapulmonary TB. Clinical Pulmonary TB was a situation where the attending clinician made a diagnosis of pulmonary TB and decided to give the patient a full course of anti-TB treatment without bacteriological confirmation; Bacteriologically confirmed pulmonary TB was

when the diagnosis and treatment was supported by laboratory confirmation such as Acid-Alcohol Fast Bacilli (AAFB) smear microscopy, culture or GeneXpert. And extrapulmonary TB was defined as any case of TB disease with involvement of organs other than the lungs.[3]

Potential confounders

Based on pre-existing knowledge we assessed for the potential confounding effects of HIV on TB treatment outcomes among new TB patients. It is known that HIV seropositive individuals have a high risk of poor TB treatment outcomes as compared to HIV seronegative individuals.[7] It has also been established that the prevalence of HIV is higher in the urban settings as compared to the rural settings.[8] HIV therefore met the criteria for a confounder because: 1) It is associated with the outcome which is TB treatment outcome; 2) HIV as a variable is in a non-casual way associated with rural and urban setting; 3) HIV is not an intermediate variable in the cause pathway between TB treatment outcomes and rural-urban setting. Figure 3 illustrates the Directed Acyclic Graph constructed to explore covariates and potential confounders of the relationship between rural and urban setting with TB treatment outcomes among new TB patients.

Clinical Management of TB

Before 2010, adult and adolescent TB patients received a 2-month rifampicin regimen. The intensive phase comprised of Isoniazid, Ethambutol, Rifampicin and Pyrazinamide while the continuation phase was for 6 months and was comprised of Isoniazid and Ethambutol.[6] For children below the age of 10 or 25kg body weight, in the 2 months of intensive phase they treated with Isoniazid, Rifampicin and Pyrazinamide. The 4-month continuation phase was comprised of Isoniazid and Rifampicin.[9]

Since 2010 new adult and adolescent TB patients received a regimen containing 6 months of rifampicin. The intensive phase comprises 2 months of Isoniazid and Rifampicin, Pyrazinamide and Ethambutol. The 4 months continuation phase comprised of Rifampicin and Isoniazid.[5]

Data Integrity

Clinical information of TB patients is recorded in the NTP register at every patient visit which includes the start of anti-TB treatment, at end of the intensive phase and at the end of treatment. Clinical and demographic data at all these critical stages of TB treatment was abstracted into an excel database. Because the NTP register is prone to high levels of incompleteness it was cross referenced to the TB patient care cards where possible. Anonymized database entries were subjected to quality control, including removal of duplicate data entries, outliers for continuous variables or date parameters and ambiguous or erroneous entries. Verification of extracted records with source data was done in a randomly selected subset of 10 patients for every 100 entries from each site. After quality control, all available records for TB patients registered at the participating health centers between January 2006 and January 2013 were screened for inclusion.

Analytic strategy

Data were described using frequency counts and percentages for categorical variables, means and standard deviations for continuous variables. We performed a correlation analysis using the spearman correlation for categorical variables Pearson correlation for continuous variables.[10]

In the primary analysis Odds Ratio (OR) for the association between death and the risk factors was estimated. Firstly, stratified analysis was conducted to determine the occurrence of interaction and confounding. The estimated OR for the relationship between covariates and death was stratified by rural/urban health setting. If the stratum specific OR were similar but different from the crude estimate by 10% or more, the variable was considered as potential confounder.[11] If the stratum specific estimates were different from each other, interaction was considered. An Interaction term was used in the multivariable analysis to confirm interaction in the stratified analysis.

We then assessed for associations between explanatory variables and the primary and secondary outcomes using a univariable mixed effects logistic regression to estimate the odds ratios (OR) and 95% confidence intervals.[12] We used this method to account for clustering within districts. TB treatment outcome is modelled by rural/urban setting as follows:

$$Y_{ij=b_0} + \sum_{k=1}^{p} b_k x_{ijk} + v_{i0} + \sum_{k=1}^{q} v_{ik} z_{ijk} + e_{ij}$$

Where:

Y= death (yes or no)

$X = (X_1, X_2, ..., X_k)$ be a set of explanatory variables which can be discrete, continuous, or a combination. X_i is the observed value of the explanatory variables for observation *i*

A multivariable model was fitted for the effects of all factors significant at the 0.05 significance level in the univariable analysis. Variables that were considered potential confounders or effect modifiers in the stratified analysis were included in the multivariable model. The model was built one step at a time following the forward selection method.

In the secondary analysis OR for the association between unfavorable treatment outcomes and risk factors was estimated using the same procedures described above. In both the primary and secondary analysis, we assessed for potential confounders and interactions based on scientific knowledge and findings from the stratified analysis. A sensitivity analysis was performed to compare demographic and clinical characteristics of patients who were excluded from the analysis because their treatment outcomes could not be verified. A sample chi-square test was used to compare those who were included and those who were excluded. The data were cleaned and analyzed using Stata v.14.

Specific aim 2

The second aim of this study was to estimate and compare the risk of death between rural and urban settings for recurrent TB patients treated with first line TB drugs in Southern province, Zambia.

Study design

A retrospective cohort study was conducted by analyzing data collected in the NTP in southern province of Zambia.

Study Setting

The study setting has been described above in specific aim 1.

Study population

Inclusion criteria: All adults and children who were treated for recurrent TB between January 2006 and June 2014 were included in the analysis. Recurrent TB was defined as a case of TB disease diagnosed in a patient who had been treated before for more than 1 month with TB drugs.[3]

Exclusion criteria: Recurrent TB patients who transferred to other health facilities and their TB treatment outcomes could not be verified were excluded from the analysis.

Study outcomes

The primary outcome for recurrent TB patients on TB treatment was death from TB disease or any other cause before the patient completed treatment or being confirmed microbiologically cured. Cure is achieved when a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment is smear- or culture-negative in the last month of treatment and on at least one previous occasion.[3] While completed treatment is when TB patient completes treatment without symptoms of failure but with no record to show 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 or because results are unavailable.[3] The secondary outcome was a composite of: loss to follow up which was defined as a patient having missed more than

two months of consecutive doses and treatment failure which was defined as patient being smear positive after more than 5 months of treatment and was not determined to have MDR-TB.[3] We further evaluated TB treatment outcomes according the WHO criteria were treatment success is a sum of treatment completion and cure.

Study exposure

The study assessed factors associated death among patients treated for recurrent TB. The main exposure was health facility location classified as either rural or urban. The definition of rural or urban was based on the Ministry of health and Central Statistical Office of Zambia classification of health facilities. [4] Rural Health facilities are health facilities that serve catchment population of up to 30,000 where the source of livelihood for at least 75% of the population is agriculture and agriculture allied activities.[4] Urban health facilities are facilities that are located in urban settings and serve catchment populations of over 30,000. [4]

Covariates and confounders

The following clinical and demographic characteristics were evaluated as risk factors for death: age, sex, HIV status, cART and Cotrimoxazole prophylaxis in TB/HIV co-infected patients, treatment delay, calendar year of treatment, type of health facility, site of disease and bacteriological confirmation.

Site of disease and bacteriological confirmation was combined and categorized as: Clinical Pulmonary TB in a situation where the attending clinician made a diagnosis of pulmonary TB and decided to give the patient a full course of anti-TB treatment without bacteriological confirmation; Bacteriologically confirmed TB when the diagnosis and treatment was supported by biological specimen such as by Acid-Alcohol Fast Bacilli (AAFB) smear microscopy, culture or GeneXpert; and as Extrapulmonary defined as any case of TB disease with involvement of organs other than the lungs.[3]

The reason why patients were retreated for TB was another important covariate. Reason for retreatment was classified by the outcome of the patients most recent course of TB treatment: relapse patients, treatment after failure patients, treatment after loss to follow patients and other previously treated patients.[3]

Relapse patients were defined as individuals who had previously been treated for TB, were declared microbiologically cured or treatment completed at the end of their most recent course of TB treatment and were diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).[3,13] Treatment after failure patients are those who were previously treated for TB and whose TB treatment failed at the end of their most recent course of TB treatment.[3] Treatment after loss to follow-up were patients who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of TB treatment.[3] Other recurrent cases are those who were previously treated for TB but whose outcome after their most recent course of TB treatment is unknown or undocumented.[3]

Potential confounders

HIV status of the recurrent TB patients was a potential confounder because it met the 3 criteria required for a variable to be a potential confounder[14] : 1) It is associated with the outcome which is TB treatment outcome; 2) HIV as a variable is in a non- casual way associated with rural and urban setting; 3) HIV is not an intermediate variable in the cause pathway between TB treatment outcomes and rural-urban setting.

Clinical management of recurrent tuberculosis

The NTP treatment guidelines for recurrent TB were adapted from the Global Plan to Stop TB which had set a target of all recurrent cases having access to Drug Susceptibility Testing (DST) at the beginning of treatment by 2015.[5] According to these guidelines sputum specimens must be obtained for culture and/or DST from all recurrent TB cases at the start of anti-TB treatment.[15] Sputum specimens for culture and DST were collected on all recurrent cases and

analyzed at the National Chest Diseases Reference Laboratory in the capital of Zambia. The recurrent TB regimen comprised first line drugs: Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Streptomycin (2HRZES/1HRZE/5HRE).[5]

Data collection and data integrity

We abstracted clinical and demographic data on the TB cases that had been recorded in the NTP register at every outpatient visit. All of patients were screened for inclusion into separate "new" and "recurrent TB cases" sub cohorts. Medical record data collected in the NTP register during clinical care, consisted of age, sex, weight at the start of treatment and end of follow up, sputum smear results, site of TB disease, TB treatment history, place of clinical care, HIV test results, cART and Cotrimoxazole prophylaxis prescription history for HIV positive patients and associated dates. Data entries were subjected to quality control, including removal of duplicate data entries, outliers in continuous variables, date parameters and ambiguous or erroneous entries in categorical entries. Verification of extracted records with source data was done in a randomly selected subset of 10 patients for every 100 entries from each site. After quality control, all available records for TB patients registered at the participating health centers between January 2006 and January 2013 were screened for inclusion.

Statistical analysis

To address the second aim, we implemented the following analytic steps:

I. Exploratory data analysis

After the data cleaning steps, we performed item analysis for each variable. In the item analysis, we assessed for data completeness, distribution, pattern of missingness and out of range variables. Data were described using frequency counts and percentages for categorical variables, means and standard deviations for continuous variables. During this step we checked if there was violation of the assumptions of binomial logistic regression.

II. Correlation assessment

We then performed a correlation analysis using the spearman correlation for categorical variables and Pearson correlation for continuous variables. We excluded or combined some variables based on the strength of correlation i.e. high correlation coefficients and lack of variability.

III. Univariable analysis

We performed a univariable analysis cross tabulating each variable against the outcome and each variable against the main exposure. Chi square tests were used for categorical variables and student t-test for continuous variables.

IV. Stratified analysis

A stratified analysis was conducted to determine the occurrence of interaction and confounding. We estimated the OR for the relationship between covariates and death stratified by rural/urban location. If the stratum specific OR were similar but different from the crude estimate by 10% or more, the variable was considered as potential confounder. If the stratum specific estimates were different interaction term was used in the multivariable analysis to confirm effect of interaction.

V. Univariable binomial logistic regression

We then assessed for associations between explanatory variables and the primary and secondary outcomes using a univariable binomial logistic regression to estimate the odds ratios (OR) and 95% confidence intervals (CI).[16]

A multivariable model was fitted for the effects of all factors significant at the 0.05 significance level in the univariable analysis. Variables that were considered significant in the univariable analysis were entered in the multivariable model one at a time. Variables that were considered potential confounders or effect modifiers were included in the stratified analysis were included in the multivariable model.

The formula for this model was written as[16]:

$$Y = \beta_0 + \beta_{xi1} + \cdots + \beta_{xik}$$

Where: Y=categorical outcome of either death or alive.

$X = (X_1, X_2, \ldots, X_k)$ be a set of explanatory variables which can be discrete, continuous, or a combination. X_i is the observed value of the explanatory variables for observation *i*.

VI. Sensitivity analysis

A sensitivity analysis was performed to assess the effect of patients who transferred out and therefore were excluded from the analysis. In this sensitivity analysis, we compared the baseline clinical and demographic characteristics of the patients who transferred out to the patients who were included in the analysis. The data were cleaned and analyzed using Stata v.14.

Specific aim 3

The third aim of this study was to estimate and compare the incidence of TB disease between rural and urban settings among HIV patients receiving ART.

Study design

We conducted a retrospective cohort study by analyzing HIV treatment program data for HIV positive individuals who started ART between January 1, 2005 and December 31, 2014 in Zambia. The data was collected as part of the National ART Program Outcome and Impact Evaluation (NAPOIE). The NAPOIE was a national wide HIV treatment, facility-based survey conducted between June 1 and October 19, 2016 whose aim was to evaluate retention, immunological and clinical outcomes of pediatric and adult HIV patients treated with ART.

Study setting

The study was conducted in 19 rural and 33 urban health facilities providing cART distributed in all the 10 provinces of Zambia. Zambia has a population of just over 17 million people in 2017 (based on the 2010 census estimates), of which live 40% reside in rural areas.[17]

The HIV prevalence is 12.3% in the adult population between 15 - 59 which means about 980 000 are living with HIV.[2] In 2015, over 85% of the population that know their HIV status self-reported being on ART.[2] Bacteriologically confirmed TB prevalence is 638/100,000 in the general population.[8] Among HIV seropositive individuals in the general population the prevalence of bacteriologically confirmed TB is 887/100,000 population.[8]

Study population

In this study we analyzed data for patients accessing HIV treatment in both rural and urban health facilities. Rural Health facilities were defined as health services providers which serve catchment populations of up to 30,000 in an area where the source of livelihood for at least 75% of the population is agriculture and agriculture allied activities.[4] Whereas, Urban health facilities are located in urban settings and serve catchment populations of over 30,000.[4]

Inclusion criteria: The analysis included randomly selected adult HIV patients above the age of 15 who started ART between January 1, 2005 and December 31, 2014.

Exclusion criteria: All HIV positive patients who were not on ART at the time of the evaluation; any patients with missing information on both birth date and age, missing cART initiation date and any patients whose record could not be traced. Data for Pediatric patients was abstracted and analyzed separately.

Study outcomes

The primary outcome of this analysis was incidence of TB disease in a cohort of HIV patients started on ART in public health facilities in Zambia. Incident TB was defined as the occurrence of an episode of TB disease more than 1 month after initiation of ART diagnosed by a clinician and were a patient is commenced on a full course of anti-TB treatment. If TB was diagnosed at the time of starting cART or within 1 month of starting ART, then the case was classified as prevalent TB. Person Years of Follow-Up (PYFU) were calculated from the date of starting ART until the date of TB diagnosis. Patients who did not develop TB were censored on the last date of clinic visit.

Study exposure

The study assessed factors associated with TB incidence. Place of ART and TB treatment classified as either rural or urban was the primary exposure. The definition of rural or urban was based on the Ministry of health and Central Statistical Office of Zambia classification of health facilities as defined above. [4] Rural Health facilities are health facilities that serve catchment population of up to 30,000 where the source of livelihood for at least 75% of the population is agriculture and agriculture allied activities.[4] Urban health facilities are facilities that are located in urban settings and serve catchment populations of over 30,000. [4]

Covariates and confounders

The following clinical and demographic characteristics at start of cART were considered as covariates: sex, age, marital status, treatment support, Cotrimoxazole prophylaxis, WHO staging of HIV, Body Mass Index (BMI), screening for TB at ART initiation, baseline $CD4^+$ count and diagnosis of TB at baseline.

Statistical issues

Sample size

In the NAPOIE study a two-stage cluster sampling strategy was used to select patient records eligible for the analysis. In the first step patients on cART were separated into 2 clusters: rural and urban. In each cluster health facilities were selected based on the probability of selection proportion to the number of patients receiving cART at each facility. Assuming a conservative retention rate of 50% at 12 months after initiation of cART and a design effect of 1.5, a 95% confidence interval equal to the sample proportion of + 3%, the sample size was estimated to be a minimum of 1599 for adult patients. The sample size was generated to achieve equal weights across the strata.

Analytic strategy

I. Exploratory data analysis

After cleaning the data, we performed item analysis. In this step we checked for data completeness, distribution of the data using different plots and variability.

II. Correlation analysis

Pearson correlation analysis for continuous variables and Spearman correlation for category variables was performed. The helped the select the variables to include in the analysis or combine based on the degree of correlation.

III. Univariable analysis

We analyzed each of the variables and cross tabulated the exposure variable and each covariate against the outcome. We cross tabulated each covariate against the exposure variable. Baseline demographics were characterized using standard descriptive statistics. In the second part of this step and as part of the main analysis Person Years of Follow-Up (PYFU) was calculated from the date of starting cART to the date of TB diagnosis. Patients who did not develop TB were censored on the last date of clinic visit or October 19,2016 which ever occurred first. The reasons for censoring were death, loss to follow-up (LTFU) and close of the survey before TB was diagnosed. Incidence rates of TB and the confidence intervals were calculated were Person-time at risk of TB was accrued from the date of starting cART until diagnosis of TB. Person time accrued during treatment of prevalent TB was excluded in the person time at risk for TB when calculating TB incident rates.

IV. Stratified analysis

For stratified analysis we plotted Kaplan Meier survival curves. The survival curves were stratified by rural and urban setting. We then plotted survival distributions at 1^{st}, 2^{nd},3^{rd} and 5^{th} year of starting cART. Because most cases of TB were diagnosed in the early days of starting cART, the Kaplan Meier curves were compared by the Wilcoxon rank statistic test which applies more weight to the earlier events.

V. Univariable cox proportion hazard regression

Cox proportion hazard model was used to estimate the baseline hazard for risk factors associated with death. In the first stage we performed a univariable cox proportion hazard regression for the exposure variable and each covariate. Univariable cox proportion hazard is represented by the following equation:

$$h(t) = h_0(t)\, exp(b_1X_1 + b_2X_2 + \cdots + b_iX_i)$$

Where h = hazard of TB disease at time t; X = (x_1, x_2..... x_i) are the predictor variables i.e. rural/urban setting, age, sex, BMI and CD4+ count.

To control for effects of confounding on the main outcome we performed a multivariable Cox proportion hazard modelling. All variables in the univariable analysis which were significant at the 0.05 significance level were included in the multivariable model. [18]We tested the Proportion Hazard Model assumption using the goodness of fit approach and the graphical approach (Log-log plots). In the graphical approach we compared the log – log survival curves. To have a test statistic for us to decide on the violation of the assumption we used the goodness of fit approach to supplement the graphical methods.[18]

In model building we first put into the model rural/urban setting and assed how this compared with other variables. In the subsequent steps we added one variable one at a time. We used the AIC to select the best fit model.

We then assessed for confounding by adding potential confounders. To assess for confounding we looked at the difference the crude hazard ratio and the hazard ratio after adding the potential confounder. We used 10% change as a rule of thumb to decide. This method of model building is known as forward selection. Since our model was small, we tested for all possible interactions. And there were no interactions. Data analysis was performed with STATA version 14.

Data Integrity

NAPOIE was a retrospective cohort analysis of programmatic and treatment outcomes for HIV seropositive patients on ART. Data was abstracted from patient records which were either paper based or electronic. Demographic and clinical information was abstracted at the time point of ART initiation and at window periods of 6, 12 and 24 months of being on ART. Before the beginning of data abstraction data collectors were trained on the study procedures for 5 days. Data abstraction was carried out by a team of 3: 2 data abstractors and a team leader who was responsible for checking the completeness of all entries. At each site, sampling frame was determined by dividing the total number of patient files at the site by 50. The first file for review was selected (N) by randomly selecting a number between 1 and X (sampling interval). Data abstractors selected the Nth file and proceed with selecting file N+X as first consecutive record for review and continued by adding X until the quota for that site was reached. To ensure data quality the study team leader re-abstracted 10% of the records selected at the site.

Clinical management

All the HIV patients who formed the cohort for our analysis were treated with ART according to national ART guidelines for management of HIV adapted from WHO guidelines.[7,19] In this cohort, TB screening was conducted according to the WHO guidelines for Intensified case finding.[20] Patients where regularly screened for TB using a clinical algorithm at every visit at a health facility or contact with a health worker. Any patient with one of the four symptoms (current cough, fever, weight loss or night sweats) were evaluated for TB and other diseases. Patients who were diagnosed with TB were commenced on a full course of anti-TB treatment according to national TB treatment guidelines.[21] Isoniazid preventive therapy in patients were active TB was ruled out was not routinely prescribed to this cohort.

Limitations and alternative approaches

The major limitation of this analysis is that we were analyzing data collected for clinical purposes in a resource limited setting and hence had high potential for missing data. To address

this the design of the data abstraction was comprehensive to minimize missingness. Secondly in our analysis we performed sensitivity analysis where we noticed that key variables had a high proportion of missingness and there was potential of bias in the interpretation of our findings.

Ethical considerations

Ethical approval was obtained from Macha Research Trust in Zambia, the University of Georgia and the Zambia National Health Research Authority.

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CHAPTER 4 : TITLE: DISPARITIES IN TB TREATMENT OUTCOMES BETWEEN RURAL AND URBAN POPULATIONS IN SOUTHERN ZAMBIA AMONG PATIENTS TREATED FOR THE INITIAL EPISODE OF TB[1]

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Abstract

Background

The difference in tuberculosis (TB) treatment outcomes between rural and urban settings is not known. We compared TB treatment outcomes between rural and urban settings in southern province of Zambia and identified risk factors associated with unfavorable TB treatment outcomes.

Methods

In a retrospective cohort study of new TB patients, we evaluated the association of location of TB treatment and all-cause mortality using mixed effects logistic regression. We performed a secondary analysis to assess the impact of location on the Odds of TB treatment failure and loss to follow up.

Results

We analyzed 21,057 new TB cases, of whom 65% were in urban settings. HIV was diagnosed in 11,053 (43%). Unfavorable TB treatment outcomes occurred in 2,617 (12%). Of these 41% occurred in rural health settings. Unfavorable outcomes were caused by death (41%), loss to follow up (36%) and treatment failure (23%). Rural health setting was associated with death (aOR: 1.3; 95% CI; 1.0 1.7). Treatment delay greater than14 days increased mortality by 60% (aOR: 1.6; 95% CI 1.3 2.1). Rural setting was associated with loss to follow up (aOR 1.3; 95% CI 1.1 1.8).

Conclusion

The risk of death and loss to follow up was higher in rural settings than urban settings. Delay in starting TB beyond 14 days was associated with a higher risk of death.

Keywords

Tuberculosis, mortality, loss to follow up, TB treatment failure, rural, urban, TB treatment outcomes

Introduction

Tuberculosis (TB) is one of the leading causes of mortality and morbidity in most parts of the world.[1] It is one of the top 10 causes of death worldwide, ranking above Acquired Immunodeficiency Syndrome (AIDS) as one of the leading causes of death from an infectious disease.[1] In 2017, there were 10 million new TB cases and 9% of these cases were among people living with HIV.[2] In the same year 1.6 million died while on TB treatment. Among those who died 0.3 million were HIV seropositive. Sub-Sahara Africa and Asia accounted for 87% of global TB cases.[2]

Zambia is one of the Sub-Sahara African countries that is hit hard by TB and HIV epidemics and ranks among the thirty (30) highest TB burden countries in the world.[3] TB is ranked among the top 5 causes of morbidity and mortality especially among the young and economically productive adults aged 15 - 49 years.[4] In the general population, the prevalence of bacteriologically confirmed TB is 568/100,000 population.[4]

With this high prevalence of TB, Zambia faces many challenges in controlling the TB epidemic. One of them is the divide between urban and rural health care. In Zambia, 39.5% of the population live in urban settings, and therefore has access to modern health care centers, whereas 60.5% live in rural settings where there are barriers to care.[5,6] The burden of TB disease is generally considered to be higher in urban settings than rural settings of overcrowding, high HIV prevalence and occupational transmission in urban settings.[4] However, health care service delivery is better in urban populations because health facilities are easy to reach while in rural populations, patients must travel long distances.[7,8] Additionally, urban settings have more skilled health care providers with greater clinical experience in the management of TB and HIV. On the other hand, most TB patients in urban settings are from deprived communities and socially disadvantage areas. This scenario in urban settings can negatively impact follow up and adherence and ultimately impact TB treatment outcomes.[7]

This study was undertaken to assess whether a difference exists in TB treatment outcomes between urban and rural populations and identify risk factors associated with unfavorable TB treatment outcomes.

Methods

Study design

We conducted a multicenter retrospective cohort study of new TB patients who were treated for TB in Southern Province, Zambia between January 2006 and June 2014.

Study setting and population

The study was conducted within the National TB Control Program (NTP) in July 2014 by abstracting patient level data from the NTP registers. All patient's data were screened for inclusion into separate "new" and "retreatment" TB sub-cohorts. A new TB patient was defined as an individual who was diagnosed with TB disease (pulmonary or extrapulmonary) by a clinician and has neither been treated for TB nor taken TB drugs for more than 1 month.[9] In this analysis the study population is new TB patients. New TB patients who transferred to other facilities and their status at the end of treatment could not be verified were excluded from the analysis.

A new case of TB was classified as clinical pulmonary TB, bacteriologically confirmed pulmonary TB or extrapulmonary TB. Clinical Pulmonary TB was a case where the attending clinician made a diagnosis of pulmonary TB and treated the patient without bacteriological confirmation; bacteriologically confirmed pulmonary TB was when the diagnosis and treatment was supported by laboratory confirmation such as Acid-Alcohol Fast Bacilli (AAFB) smear microscopy, culture or GeneXpert. Extrapulmonary TB was defined as any case of TB disease with involvement of organs other than the lungs.[9]

Study exposure

The main exposure was place of TB treatment classified as either rural health setting or urban health setting. Rural health setting was when an individual received treatment at a health facility located in a place where the source of livelihood for at least 75% of the population was

agriculture and agriculture allied activities and served a catchment population of up to 30,000 people.[10] While urban health setting is when a patient was treated for TB at clinics or hospitals located in an urban area and where the facility serves a catchment population of over 30,000.[10] Classification of rural and urban health facility was based on the Ministry of Health and Central Statistical Office of Zambia 2010 census classification and definitions.[11] All the health facilities provided TB treatment within the framework of the NTP which is adapted from the World Health Organization (WHO) TB treatment guidelines.[12-14]

Study outcome(s)

The primary outcome was all-cause mortality defined as death from TB disease or any other cause before the patient completed TB treatment. Death was verified and confirmed by the attending clinicians either from a death certificate or verbal report from the TB treatment supporter or the next of kin.

Secondary outcome was loss-to-follow-up plus treatment failure. Loss-to-follow-up was when a patient missed more than 2 months of consecutive doses.[9] Treatment failure was defined when a patient was sputum smear-positive after more than 5 months of treatment and was not detected as having Multi Drug Resistance TB (MDR-TB).[9]

Covariates, Confounders

We assessed demographic and clinical risk factors that were associated with death among TB patients. The following were included in the analysis as covariates: age, sex, weight at the start of treatment and end of follow-up, sputum smear results at baseline, type of TB disease, TB treatment delay, year of starting TB treatment and HIV status and type of health facility. For HIV seropositive patients the role of ART and Cotrimoxazole prophylaxis was adjusted for.

Analytic strategy

Data were described using frequency counts and percentages for categorical variables, means and standard deviations for continuous variables. We performed a correlation analysis using Pearson correlation for continuous data and ranked data using the spearman correlation.

In the primary analysis we estimated the odds ratio and the 95% confidence intervals for death among rural cases compared with urban cases. We first estimated the crude odds ratio and then stratified to assess for confounding and interaction. For associations between explanatory variables and the primary and secondary outcomes we used mixed effects logistic regression accounting for clustering by district.

To evaluate selection bias as a result of missing data a sensitivity analysis was performed. We compared demographic and clinical characteristics of patients who were excluded from the analysis because their treatment outcomes could not be verified. A 2-sample chi-square test was used to compare those who were included and those who were excluded. The data were cleaned and analyzed using Stata v.14.

Ethical considerations

The study was approved by Macha Research Trust and University of Georgia Institutional Review Board and National Health Research Authority. Informed consent was not required because the study was retrospective and analyzed previously collected anonymized data.

Results

Data from 25,533 TB patients were obtained, of whom 16,791 (66%) attended 8 health facilities in urban settings and 8,742 (34%) attended 22 health facilities in rural settings (Figure 4-1). After applying the inclusion and exclusion criteria 21,057 patients were included in the analysis, of whom 13,668 (65%) attended urban health facilities (Figure 4-1). In the entire study population, the mean age was 33 years (Standard Deviation (SD) =17) and 54% were male. Clinical and demographic characteristics of patients excluded from the analysis (N = 1027) were similar to those who were included in the analysis. (Table 4-5).

Forty-three per cent (n = 11,053) of the TB patients were co-infected with HIV and 9,715 (88%) of these were commenced on ART either before or while on TB treatment (Table 4-1). Of those who were treated in the urban settings 8085 (48%) were TB-HIV co-infected, whereas in rural settings, 2968 (33%) were TB-HIV co-infected.

Unfavorable outcomes which is a sum of death, loss to follow up and TB treatment failure occurred in 2,617 (12%) patients, of which 1,075 (41%) were in rural settings. Overall, 41% of unfavorable outcomes were attributed to death (n = 1,091); for the other unfavorable outcomes, 577 (22%) were attributed to treatment failure and 949 (36%) to loss-to-follow-up (Table 4-2). Of the 1,091 deaths 610 (56%) occurred among those who were HIV seropositive, 227 (21%) among those who were HIV seronegative and for the remainder of the deaths the HIV status was unknown. Of the overall number of TB treatment outcomes in rural areas 410 (6%) were due to all-cause mortality, 560 (8%) were caused by loss to follow up. In urban areas 681(5%) was due to all-cause mortality and Loss to follow up occurred in 389 (3%) (Figure 4-2).

In the crude analysis, death was not associated with the setting of treatment, whether rural or urban (OR 1.3; 95% CI: 0.7 – 3.1). After adjusting for age, sex, type of TB disease, health facility type (hospital or health center), calendar year of treatment and HIV status, the aOR for death was 1.3 (95% CI: 1.0 - 1.7), indicating that the odds of death were 30% greater among patients treated in rural as compared to urban settings (table 4-3). Place of treatment was not the only important driver of mortality. TB patients treated in health centers were twice more likely to experience mortality when compared to those treated in hospitals (aOR 1.9; 95% CI 1.8-2.3). Among the 11,053 patients who were co-infected with HIV and TB, Cotrimoxazole prophylaxis reduced the odds of death by 30% in this population group (aOR 0.7; 95% CI 0.4 – 0.9) (Table 4-7). Similarly, HIV-TB co-infected patients who were on ART had a 40% reduction in mortality as compared to HIV-TB co-infected patients who were not commenced on ART while on TB treatment (aOR 0.6; 95% CI 0.5 - 0.8) (Table 4-7).

We analyzed loss to follow up and TB treatment failure as separate secondary outcomes. After adjusting for age, calendar year of treatment, treatment delay, HIV and HIV treatment status loss to follow up was associated with rural setting (aOR 1.3, 95% CI: 1.1 1.6) (Table 4-4). Patients who started treated more than 14 days after first registration at the TB clinic were 80% more likely to be lost to follow up (aOR 1.8, 95% CI: 1.6 2.3). For treatment failure (table 4-5), there was no

statistically significant association between location and treatment failure. (aOR 0.8, 95% CI: 0.6 1.1). Patients treated at clinics were 10 times more likely to fail TB treatment when compared to those getting treatment at hospitals (aOR 10.7, 95% CI: 8.1 14.3).

Discussion

Our study assessed the effect of geographical setting on TB treatment outcomes in a middle-income country with high prevalence of HIV. The risk of death was 30% higher in rural than urban setting. The risk of loss to follow up was 30% higher in rural setting as compared to urban setting. Delay in starting TB treatment beyond 14 days were associated with loss to follow up. And patients treated at clinics were 10 times more likely to experience treatment failure when compared to those treated at hospitals.

We found higher risk of mortality in rural settings as compared to urban settings. Higher risk of mortality among TB cases in rural setting is likely due to poor cases management of TB in rural settings in challenges in community follow up of these patients. We theorize that high loss to follow is a surrogate of poor community follow of TB patients. Community follow up and support of TB patients organized around the Directly Observed Therapy strategy (DOTs) is a critical component of TB case management. Inadequate patient follow up is associated with poor treatment adherence which directly and may lead to death, recurrence and MDR-TB. In this study, loss to follow-up was associated with rural setting. A high loss-to-follow-up among TB cases in rural settings is consistent with findings in Uganda, a low-income country with a high prevalence of HIV.[15] Other studies have reported low loss-to-follow-up rates and generally good treatment outcomes in both rural and urban settings.[16,17] Programs which have reported low loss to follow up rates have well-organized community tracing activities that promote successful treatment such as DOTs.[16-18]

In our study, loss to follow up was 30% more likely in rural settings as compared to urban settings. In studies conducted among TB/HIV coinfected patients in sub-Sahara Africa, TB treatment success rate among rural clinics was lower than what was reported in urban clinics.[15]

In these studies differences in TB treatment outcomes were related to patient characteristics and health care organization.[19-21] Patients in rural areas were more likely to live far away from the health facilities and therefore present late to health care providers.[22-24] In contrast, studies in high income countries showed no difference in treatment outcomes between rural and urban settings.[7] Patients who delayed TB treatment for more than 14 days from the time that they registered in the NTP clinic were more likely to be lost to follow up. Delay was defined as a time interval between the date of seeking health care from a health care provider and the date of initiating TB treatment.[25] The mean delay from registration to initiation of TB treatment was 4 days in the urban settings while in the rural settings it was 8 days. Previous studies have shown that delay to initiate treatment depend on patient, societal and health care factors.[25]

Another interesting finding was higher risk of mortality in clinics and health center as compared to hospitals. We expect mortality to be higher in hospital settings because of referral bias. That is severe cases of disease which are likely to die are referred and treated in hospitals. On the contrary we found that mortality was higher in the clinics than hospital settings. This scenario requires further investigation. In both rural and urban settings, Cotrimoxazole prophylaxis was associated with reduction in mortality and a generally better in TB treatment outcomes. This finding has been extensively documented in previous studies.[28-30]

Limitations

As in any real-world data or observational studies this study has some limitations. An obvious limitation in program data are errors in recording of data which cannot be validated and are therefore regarded as missing. However, with a large sample size the proportion of missing (less than 5%) was small and less likely to influence the precision of our estimates. To address this potential selection bias we compared patient baseline characteristics to those that were exclude and those included in the analysis. We found that the two populations had similar characteristics (supplementary material Table 4-6). TB treatment regimen was changed from the 8 month combination to the more efficacious 6 month regimen in 2010.[12,13] This significant change

in regimen may have introduced temporal bias in the outcomes of TB treatment. To address this temporal effect, calendar year of starting TB treated was adjusted for in the multivariable analysis.

Policy implications

This study demonstrated disparity between rural and urban setting in terms of TB treatment outcomes. It offers a unique perspective on the outcomes of TB treatment between rural and urban settings using patient level data from a TB control program. The study demonstrates how program data can be utilized in TB control to identify populations needing supplemental efforts. Most importantly it shows that mortality was higher in the rural setting than urban setting. Policy implications are that methods for following up patients using various approaches must be streamlined according to the setting to avoid treatment delay and maintain people on treatment until they successfully complete treatment or are cured. Tailoring the TB control program particularly follow up of TB patients differently between rural and urban setting may provide an effective answer to this disparity. To enhance community, follow up and support of TB patients the TB program can take advantage of the expanding use of mobile phone technology in both rural and urban settings as an adjunct to current strategies to address this gap.

Conclusion

Patients with TB disease in the rural settings have poorer TB treatment outcomes than patients in urban areas. Our findings reinforce the need to improve TB diagnostics, treatment access and patient follow up strategies in rural areas.

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Figures

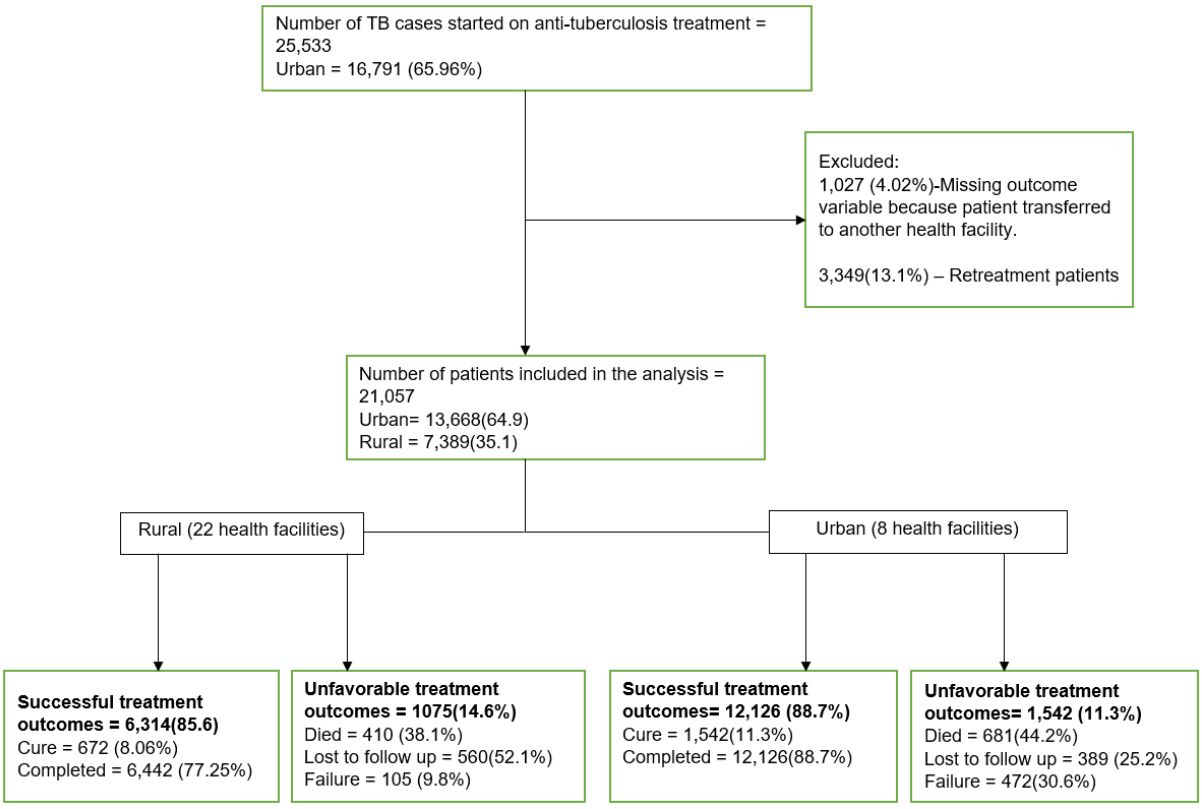

Figure 4-1: Case enrolment, distribution of cases, tuberculosis treatment outcomes by urban-rural area.

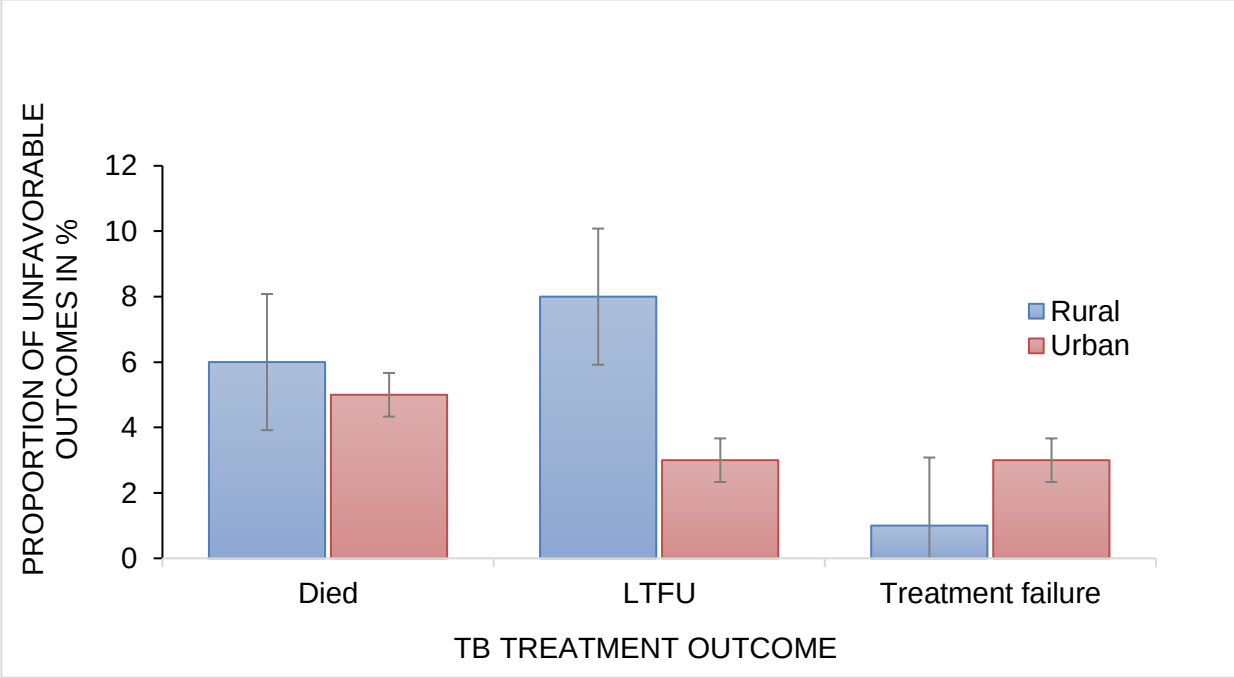

Figure 4-2: Showing reasons for unfavorable outcomes stratified according to setting of receiving TB treatment

Tables

Table 4-1: Demographic and clinical characteristics of the patients who were treated with TB therapy in 30 rural and urban health facilities in southern province, Zambia (2006-2014).

Variable	**category**		**Total**	**Urban**	**Rural**	
N (%)		n = 21,057	13,668	(65%)	7,389	(35)
Sex*	Female	9,616	6027	(44.3)	3589	(49.2)
	Male	11,253	7551	(55.6)	3702	(50.7)
Weight in Kg	mean (+/- SD)	47.4 (16.1)	46.8	(16.3)	47.9	(16.8)
Age in years	mean(+/-SD)	32.6(16)	32.2	(16.3)	33	(17.7)
	Below 18	16408	2152	(15.7)	1204	(16.3)
	19 - 55	15,575	10329	(75.6)	5246	(71)
	56 and older	2,125	1187	(8.7)	938	(12.6)
Health facility	Hospital	9,363	5,019	(36.7)	4,344	(58.8)
	Health Center	11,694	8,649	(63.2)	3,045	(41.2)
Treatment delay	14 days & less	17,816	12,563	(91.9)	5,253	(71.1)
	15 days and more	3,241	1,105	(8.1)	2,136	(28.9)
Calendar year of start of anti-TB treatment	After 2010	8,306	5,739	(43)	2,567	(35)
	Before 2010	12,284	7,462	(57)	4,822	(65)
Clinical classification of TB	Clinical Pulmonary TB	10,997	6449	(47.1)	4548	(61.5)
	Microbiology confirmed pulmonary TB	5,986	4170	(30.5)	1816	(24.6)
	Extrapulmonary TB	4,074	3049	(22.3)	1025	(13.9)
HIV status	negative	10,004	3,258	(23.8)	1,088	(14.7)
	positive	11,053	8,085	(48.1)	2,968	(33.1)
ART for HIV+ patients	ART	9,717	7055	(87.2)	2662	(89.7)
	No ART	1,336	1030	(12.7)	306	(10.3)
Cotrimoxazole prophylaxis for HIV+ patients	Cotrimoxazole	7,126	5,143	(64)	1,983	(67)
	No Cotrimoxazole	3,927	2,942	(36)	985	(33)
*0.8% missing data on sex						

Table 4-2: Estimates of Reasons for Unfavorable TB Treatment Outcomes in Rural and Urban Settings of Southern Province, Zambia

		Urban				Rural			
Characteristic	**level**	**Total**	**Failure %**	**Died %**	**loss to follow up %**	**Total**	**Failure %**	**Died %**	**Loss to follow up %**
Age group	Below 18	78	32.05	47.44	20.51	71	14.08	33.8	52.11
	19 - 55	1,280	30.08	44.53	25.39	867	6.57	38.18	55.25
	56 and older	153	23.53	47.71	28.76	103	12.62	51.46	35.92
HIV status	Positive	643	27.53	41.52	30.95	748	9.09	28.61	62.3
	Negative	898	32.85	46.1	21.05	327	11.31	59.94	28.75
	no result	1	0	0	100				
cART for HIV+ patients	cART	707	24.75	51.63	23.62	318	10.69	61.01	28.3
	No cART	191	62.83	25.65	11.52	9	33.33	22.22	44.44
Cotrimoxazole prophylaxis	Cotrimoxazole	206	37.86	41.75	20.39	145	11.03	67.59	21.38
	No Cotrimoxazole	692	31.36	47.4	21.24	182	11.54	53.85	34.62
Clinical classification of TB	Clinical Pulmonary TB	680	28.53	45.59	25.88	689	6.24	30.19	63.57
	Microbiology confirmed pTB	629	37.36	40.54	22.1	274	18.98	50	31.02
	Extrapulmonary TB	233	18.45	49.79	31.76	112	8.93	58.04	33.04
Sex	Female	768	30.08	46.09	23.83	618	9.71	38.67	51.62
	Male	770	31.04	42.34	26.62	453	9.71	37.31	52.98

Table 4-3: Estimates of the risk of death (OR) according to clinical and demographic characteristics among new TB patients in southern province of Zambia (2006-2014).

			Crude		Adjusted	
Characteristic	**Total number**	**Number of deaths**	**OR**	**95% CI**	**OR**	**95% CI**
Area						
urban	13668	681	1		1	
rural	7389	410	1.3	(0.7 3.1)	1.3	(1.0 1.7)
Sex						
Male	9616	593	1			
Female	11253	495	0.68	(0.6 0.8)	0.85	(0.7 1.1)
Calendar year						
after 2010	8306	520	1		1	
before 2010	12284	575	1.3	(0.8 1.4)	1.0	(0.8 1.2)
Age group*						
Below 18 year	3357	64	1			
19 – 55 years	15575	901	1.2	(0.8 1.4)		
above 55 years	2125	126	1.2	(0.8 1.5)		
Health facility level						
Hospital	9363	308	1.0		1.0	
Health center	11694	783	1.4	(1.2 1.8)	1.9	(1.8 2.3)
Treatment delay						
<14 days	17816	1010	1		1	
> 14 days	3141	81	1.8	(1.6 2.7)	1.1	(0.9 2.1)
Clinical classification of TB						
Clinical pulmonary TB	10997	518	1		1	
Microscopically confirmed TB	5986	392	1.2	(1.0 1.4)	1.0	(0.7 1.1)
Extra pulmonary TB	4074	181	0.9	(0.7 1.1)	1.0	(0.8 1.2)
HIV status						
HIV negative	10004	367	1.0		1	
HIV+ on ART	9717	610	1.7	(1.2 4.8)	1.7	(1.4 3.7)
HIV+ no ART	1336	114	2.3	(1.8 5.8)	2.3	(1.8 6.0)

*There only 2 outcomes below 10 years so we collapsed it into the less than 18 years.

Table 4-4:Estimates of risk of Loss to follow up (OR) according to clinical and demographic characteristics among new TB patients in southern province of Zambia between 2006-2014

Characteristic	total	LTFU	Crude OR (95% CI)	Adjusted OR (95% CI)
Setting				
Urban	13668	560	1.0	1.0
Rural	7,389	389	1.3 (1.1 1.6)	1.3 (1.1 1.5)
Sex				
Male	11,253	445	1.0	
Female	9,616	502	0.8 (0.4 1.2)	
Age group				
Below 18 years	3,357	64	1.0	
18 - 55	15,575	804	2.2 (1.8 3.0)	
Above 55	2,125	81	1.4 (1.0 1.9)	
Calendar year				
Before 2010	12,284	672	1.0	1.0
After 2010	8,773	277	0.7 (0.6 0.9)	0.8 (0.7 1.0)
Type of health facility				
Hospital	9363	562		
Clinic	11,694	387	1.0 (0.8 1.2)	
Treatment delay				
Less than 14 days	17,816	559	1.0	
14 days and more	3,241	390	2.2 (1.8 2.6)	1.8 (1.6 2.3)
Classification of TB				
clinical	15,071	725	1.0	
Microbiology confirmed	5,986	224	0.9 (0.7 1.1)	
HIV and ART status				
HIV negative	10,004	500	1.0	1.0
HIV seropositive on ART	6,290	185	0.4 (0.3 0.7)	0.4 (0.3 0.7)
HIV seropositive no ART	4,763	264	1.1 (0.7 1.3)	1.1 (0.7 1.3)

Table 4-5: Estimates of risk of TB treatment failure (OR) according to clinical and demographic characteristics among new TB patients in southern province of Zambia (2006-2014).

Characteristic	Total	Treatment failure	Crude OR (95% CI)	Adjusted OR (95% CI)
Setting				
Rural	7,389	105	1.0	1.0
Urban	13,668	472	0.8 (0.5 1.1)	0.8 (0.6 1.1)
Sex				
Male	11,253	283	1.0	
Female	9,616	291	0.8 (0.7 0.9)	
Age group				
Below 18 years	3,357	86	1.0	
18 - 55	15,575	442	1.1 (0.9 1.5)	
Above 55	2,125	49	1.1 (0.7 1.6)	
Calendar year				
Before 2010	12,284	320	1.0	1.0
After 2010	8,773	257	1.2 (0.4 1.3)	1.1 (0.7 1.3)
Type of health facility				
Hospital	9363	74		1.0
Clinic	11,694	503	11.3 (8.5 14.0)	10.7 (8.1 14.3)
Treatment delay				
Less than 14 days	17,816	458		
14 days and more	3,241	119	2.5 (2.1 3.1)	
Classification of TB				
clinical	15,071	290		1.0
Microbiology confirmed	5,986	287	2.3 (1.9 2.7)	1.5 (1.3 1.8)
HIV and ART status				
HIV negative	10,004	245	1.0	
HIV seropositive on ART	6,290	287	0.9 (0.8 1.1)	
HIV seropositive no ART	4,763	45	1.6 (1.4 2.0)	

Supplementary material

Table 4-6: Supplementary table – Comparison of the Characteristics of the analytic sample and the excluded sample using a 2-sample t-test.

	Analytic sample		Excluded sample		
Sex	**n**	**%**	**n**	**%**	**p - value**
Female	9,581	46.04	439	50.93	0.8
Male	11,227	53.96	423	49.07	
health facility level					0.09
Hospital	9,314	44.46	361	41.54	
Health Center or clinic	11,637	55.54	508	58.46	
Classification of TB based on site of disease					0.75
pulmonary	16,416	78.73	678	78.29	
Extrapulmonary	4,435	21.27	188	21.71	
location					
urban area	13,602	64.92	528	60.76	
rural area	7,349	35.08	341	39.24	
HIV status					0.97
Negative	4,317	20.61	138	15.88	
positive	11,020	52.6	519	59.72	
refused	17	0.08	1	0.12	
result not available	5,597	26.71	211	24.28	
Treatment delay					0.06
14 days & less	17,767	84.8	17,767	84.8	
15 days and more	3,184	15.2	3,184	15.2	
Classification based on sputum					
Pulmonary sputum negative	10,861	52	462	53.35	
Pulmonary low smear positive	3,217	15.4	111	12.82	
Pulmonary High smear positive	2,740	13.12	118	13.63	
Extrapulmonary	4,070	19.48	175	20.21	
ART status for HIV+ patients					0.16
HIV+, on ART	4,939	32.2	250	38.05	
HIV+, not on ART	1,331	8.68	33	5.02	
HIV+, no ART	4,750	30.97	236	35.92	
	mean	SD	mean	SD	
Age in years	32	17	36	14	<0.001
Weight at the start of TB treatment in Kg	47	16	49	15	0.05

Table 4-7: Supplementary table - Estimates of the risk of death (OR) according to clinical and demographic characteristics among new TB patients in southern province of Zambia who were HIV seropositive at the time of starting TB treatment

Variable	Total	died	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
Area						
urban	8085	414	1		1	
rural	2968	196	1.2	(0.8 1.5)	1.2	(0.9 1.6)
Age group*						
Below 18 years	1195	17	3.2	(1.7 4.8)	2.9	(2.5 7.9)
19 – 55 years	9080	564	3.6	(2.2 5.0)	3.9	(1.7 5.4)
56 & older	578	33	3.5	(2.1 5.0)	3.3	(2.0 5.8)
Sex						
male	5213	272	1			
female	5785	336	0.7	(0.6 0.8)	0.7	(0.6 0.8)
Clinical classification of TB						
clinical pulmonary TB	5647	324				
microbiology confirmed pulmonary TB	2941	171	1	(0.8 1.3)		
extrapulmonary TB, modify	2465	115	0.9	(0.7 1.1)		
Treatment delay						
less than 14 days	10288	566	1			
more than 14 days	825	44	0.9	(0.7 1.2)		
Cotrimoxazole prophylaxis						
No	3927	426	1		1	
Yes	7126	184	0.5	(0.4 0.8)	0.7	(0.4 0.9)
ART						
Yes	9717	351	1		1	
No	1336	51	1.7	(1.2 3.2)	1.6	(1.2 2.8)
Type of facility						
Health center or clinic	4926	401	1			
hospital	6127	209	1.1	(0.7 1.4)		

*There were only 2 deaths in the age group below 10 years. Because of the small number of outcomes in this age group we categorized the referent group from 0 – 18 years.

Table 4-8: Estimates of risk of Loss to follow up plus treatment failure (OR) according to clinical and demographic characteristics among new TB patients in southern province of Zambia between 2006-2014

			Crude		Adjusted	
Variable	**Total number**	**Treatment failure and loss to follow up**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Area						
urban	13668	861	1.0		1.0	
rural	7389	665	1.3	(1.0 1.5)	1.28	(1.1 1.8)
Sex						
male	9616	728	1.0		1.0	
female	11253	793	0.8	(0.7 0.9)	0.6	(0.5 0.7)
Treatment delay						
<14 days	17816	1017	1.0		1.0	
> 14 days	3214	509	2.4	(2.1 2.7)	1.6	(1.3 2.1)
Age group						
0 - 10	2524	62	1.0		1.0	
10 - 18	833	88	3.6	(2.6 5.2)	2.7	(1.2 6.0)
19 - 55	15575	1246	3.0	(2.3 3.7)	4.1	(2.5 6.9)
above 55	2125	130	2.7	(1.9 3.7)	3.8	(2.1 7.2)
Health facility level						
Hospital	9363	636				
Health center or clinic	11694	890	1.7	(1.4 2.6)	1.8	(1.4 2.6)
HIV status						
HIV negative	10004	910	1.0		1.0	
HIV+ on ART	9717	15	0.006	(0.004 0.7)	0.61	(0.004 0.9)
HIV+ no ART	1336	600	4.9	(2.5 5.8)	4.8	(2.7 5.7)

CHAPTER 5 : URBAN-RURAL DISPARITIES IN TB TREATMENT OUTCOMES AMONG RECURRENT TB CASES IN SOUTHERN PROVINCE, ZAMBIA[2]

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Abstract

Background

Recurrent tuberculosis (TB) infections comprise between 13 – 20% of all TB cases reported globally. Understanding the magnitude of recurrent TB and its treatment outcomes is critical because recurrent TB increase the risk of Multi-Drug Resistant TB (MDR-TB). We examined the prevalence of recurrent TB among TB cases and compared the risk factors of unfavorable treatment outcomes between rural and urban settings in Zambia.

Methods

We conducted a multicenter retrospective cohort study of TB program data routinely collected between 2006 – 2014 in a setting with a high prevalence of both HIV and TB. To assess for associations between explanatory and outcome variables, we used binomial logistic regression. The primary outcome was all-cause mortality and the main exposure was location classified as either rural or urban.

Results

Of the 25,533 TB cases 3,566 (13.9%) were recurrent TB cases. The prevalence of recurrent TB cases was 15.3% in urban and 11.3% in rural areas among all TB cases. Fifty-seven percent were male and median age was 36.3 (SD: 14.8). The causes of recurrent TB were relapse (77%), loss to follow up (1%), failure (1%) and uncertain (21%). In urban areas 66.7% of recurrent TB cases were HIV positive and 46.6% HIV positive in the rural.

For subsequent treatment outcomes, 7.5% were cured, 80.9% completed treatment, 5.5% died, 2.9% were lost to follow, and 3.2% experienced treatment failure. In both the univariable and multivariable analyses, rural area was associated with death (Adjusted OR: 1.7; 95% CI: 1.2 - 2.7). Males had 40% reduction in the odds of death (adjusted OR 0.6; 95% CI: 0.4 - 1.0). Among cases with HIV, those not initiated on Anti-Retroviral Treatment (ART) were twice likely to die (adjusted OR: 2.2; 95% CI: 1.2 – 3.1).

Conclusion

Recurrent TB was high in both rural and urban with rural areas having worse treatment outcomes. A well-organized patient-monitoring system adapted to each setting such as effectively administered Directly Observed Therapy (DOT) and improve early detection of recurrent cases and case management.

Introduction

Tuberculosis (TB) remains a major problem in the world and leading killer among infectious diseases.[1] In 2017 there were 10 million cases of TB and 1.6 million deaths among TB cases.[1] Multi-Drug Resistant TB (MDR-TB) poses a big threat to TB control because of the expensive and limited treatment options and high mortality. MDR-TB is common among patients with recurrent TB - that is individuals who were previously treated with TB drugs for more than one month and once again have been diagnosed with TB disease.[2]

It is estimated that 13% of all the TB cases reported to the World Health Organization (WHO) in 2017 were due to recurrent TB.[3] In areas heavily burdened by Human Immunodeficiency Virus (HIV), recurrence rates are even higher reaching 20% following standard treatment.[4,5] Recurrent TB can result from reactivation of the original *Mycobacterium tuberculosis* or from reinfection with a different strain.[6]

Zambia is a country with a high prevalence of TB (455 cases per 100,000 population) and a high prevalence of HIV infection (12% among adults between 15 – 59 years).[7,8] The extent of recurrent TB and treatment outcomes of recurrent TB cases have not been fully described for this area. Moreover, it is uncertain whether the distribution of recurrent cases is homogenous in rural and urban settings and whether cases in rural settings are at an increased risk of poor outcomes as compared to urban settings. Understanding the magnitude of recurrent TB and its treatment outcomes is critical because recurrent TB is a strong determinant of MDR-TB.[3] Recurrent TB is associated with lower rates of cure than new TB cases.[5,9] Distinctions must be made between

new and recurrent cases as well as the subgroups of recurrent cases because they are essential for monitoring the TB epidemic and TB program performance.[10]

The burden of TB disease is generally considered to be higher in urban settings than rural settings due to overcrowding, high HIV prevalence and occupational transmission.[7] However, health care service delivery is better in urban populations because health facilities are easy to reach whereas rural patients must travel long distances.[11,12] Additionally, urban settings have more skilled health care providers with more clinical experience in the management of TB and HIV and access to better diagnostics. In contrast, most TB patients in urban settings are from deprived communities and social disadvantages such as slums which may contribute to poorer TB treatment outcomes.[11]

In a multicenter retrospective review, we examined the prevalence of recurrent TB among TB cases notified to the National TB Program (NTP) in southern province of Zambia. We assessed for risk factors associated with death, loss to follow up and failure in rural and urban settings.

Methods

Study design

A retrospective cohort study was conducted by analyzing data collected in the NTP in southern province of Zambia.

Study Setting and population

The study was conducted in a predominantly rural setting (85%) with a high TB case notification rate (>300 cases per 100,000 population per year).[13]

All adults and children who were treated for recurrent TB between January 2006 and June 2013 were included in the analysis. Recurrent TB was defined as a case of TB disease diagnosed in a patient who had been treated before for more than 1 month with TB drugs.[2]

Study exposure

The study assessed factors associated with death, treatment failure and loss to follow up among patients treated for recurrent TB. The main exposure was health facility location classified

as either rural or urban. The definition of rural or urban was based on the Ministry of health and Central Statistical Office of Zambia classification of health facilities. [14] A rural area is a location where the source of livelihood for at least 75% of the population is agriculture and agriculture allied activities and the health facility in the area serve a catchment population of less than 30,000.[14] Urban health facilities are facilities that are located in urban settings and serve catchment populations of over 30,000.[14]

Study outcomes

The primary outcome was all-cause mortality which is death from TB disease or any other cause before the patient successfully completed treatment. Death was verified by the attending physician through death certificate or verbal report from treatment supporters or the patient's next of kin.

The secondary outcome was a composite of: loss to follow up which was defined as a patient having missed more than two months of consecutive doses and treatment failure which was defined as patient being smear positive after more than 5 months of treatment.[2] We further evaluated TB treatment outcomes according the WHO criteria were treatment success is a sum of treatment completion and cure.

Another outcome was successful completion which is either "cure" or "clinical treatment completion" without bacteriological evidence of *mycobacterium* tuberculosis clearance. Cure is achieved when a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment is smear- or culture-negative in the last month of treatment and on at least one previous occasion. Clinical treatment completion is when a TB patient completes TB treatment course without symptoms of failure but with no record to show sputum smear or culture results in the last month of treatment either because tests were not done or because results are unavailable.[2]

Covariates

The following clinical and demographic characteristics were evaluated as risk factors for death: age, sex, HIV status, cART and Cotrimoxazole prophylaxis in TB/HIV co-infected patients, treatment delay, calendar year of treatment, type of health facility, site of disease and bacteriological confirmation.

We further classified TB according to Site of disease and bacteriological confirmation. Clinical Pulmonary TB was a situation where the attending clinician made a diagnosis of pulmonary TB and decided to give the patient a full course of anti-TB treatment without bacteriological confirmation; Bacteriologically confirmed TB was when the diagnosis and treatment was supported by biological specimen such as by Acid-Alcohol Fast Bacilli (AAFB) smear microscopy, culture or GeneXpert; and as extrapulmonary TB was defined as any case of TB disease with involvement of organs other than the lungs.[2]

The reason why patients were retreated for TB was another important covariate. Reason for retreatment was classified by the outcome of the patients' most recent course of TB treatment: TB relapse patients, TB treatment failure patients, treatment after loss to follow-up patients and others.[2]

Relapse patients were defined by meeting the following criteria: as individuals who had previously been treated for TB; were declared microbiologically cured or treatment completed at the end of their most recent course of TB treatment; and were diagnosed with another episode of TB (either a true relapse or a new episode of TB caused by reinfection).[2,15] Treatment after failure patients are those who were previously treated for TB and whose TB treatment failed at the end of their most recent course of TB treatment.[2] Treatment after loss to follow-up were patients who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of TB treatment.[2] Other recurrent cases are those who were previously treated for

TB but whose outcome after their most recent course of TB treatment is unknown or undocumented.[2]

Clinical management of recurrent tuberculosis

The NTP treatment guidelines for recurrent TB were adapted from the Global Plan to Stop TB has set a target of all recurrent cases having access to Drug Susceptibility Testing (DST) at the beginning of treatment by 2015.[10] According to these guidelines sputum specimens must be obtained from all recurrent TB cases at the start of TB treatment.[3] Sputum specimens for culture and DST were collected on all recurrent cases and analyzed at the National Chest Diseases Reference Laboratory in the capital of Zambia. The recurrent TB regimen comprised first line drugs: Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Streptomycin (2HRZES/1HRZE/5HRE).[10]

Data collection and data integrity

We abstracted clinical and demographic data on the TB cases that had been recorded in the NTP register at every outpatient visit. Medical record data collected in the NTP register during clinical care consisted of age, sex, weight at the start of treatment and end of follow up, sputum smear results, site of TB disease, TB treatment history, place of clinical care, HIV test results, cART and Cotrimoxazole prophylaxis prescription history for HIV positive patients and associated dates. Data entries were subjected to quality control, including removal of duplicate data entries, outliers in continuous variables, date parameters and ambiguous or erroneous entries in categorical entries. Verification of extracted records with source data was done in a randomly selected subset of 10 patients for every 100 entries from each site. After quality control, all available records for TB patients registered at the participating health centers between January 2006 and January 2013 were screened for inclusion.

Statistical analysis

Data were described using frequency counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables. We performed a correlation analysis using the spearman correlation (Table 5-5).

In the primary analysis we estimated the odds ratio and the 95% confidence intervals for death among rural cases compared with urban cases. We first estimated the crude odds ratio and then stratified to assess for confounding and interaction. For associations between explanatory variables and the primary and secondary outcomes we used mixed effects logistic regression accounting for clustering by district. The data were cleaned and analyzed using Stata v.14.

Ethical considerations

Ethical approval was obtained from the Macha Research Trust ethics committee, the University of Georgia institutional review board and regulatory authority from the Zambia National Health Research Authority.

Results

Case enrollment

Data from 25,533 tuberculosis patients was obtained, of whom 3,566 (13.9%) were recurrent TB cases. Of these recurrent TB cases 2,573 (72.2.3%) were in urban areas and 992 (27.8%) in rural areas (Figure 5-1). After excluding recurrent TB cases whose treatment outcome were not documented because they transferred to another facility before the end of treatment, there were 2,565 (72.1%) recurrent TB cases in urban areas and 990 (27.9%) in rural areas.

Prevalence of recurrence among TB cases

The overall prevalence of recurrent TB was 14% (95% CI; 13.5 14.4). In urban setting the prevalence was 15.3% (n = 2,573; 95% CI: 14.8 15.9) and 11.3% (n = 992; 95% CI: 10.7 12.0) in rural areas (Table 5-1). TB recurrence in HIV negative TB cases was 10.0% (n = 499; 95% CI:

9.2 10.9) and 16.1% (n = 2,216; 95% CI: 15.5 16.7) in HIV seropositive positive recurrent TB cases. In males' prevalence of recurrent TB was 13% (n = 1506; 95% CI: 12.4 13.6) and 14.9% (n = 2,049; 95% CI: 14.3 15.5).

Demographic and clinical characteristics

The mean age was 36.3 (Standard deviation (SD) = 14.8) and most of the recurrent TB cases were male (n = 2,019; percent = 56.9%) Of the total cases 2,745(77%) were recurrent cases due to relapse, 31 (0.9%) were recurrence after loss to follow up, 29 (0.8%) were recurrence after failure and 106 (3.0%) were classified as others (Table 5-2).

In urban setting, 2,126 (82.9%) of the cases were relapse while in the rural setting 619 (62.5%) were classified as relapse cases. Most patients received treatment within the first 14 days of registering in the TB clinic (n=3,135; 88.2%). In urban areas, 1,712 (66.7%) of the recurrent TB cases were HIV positive, and in 456 (17.8%) cases, the HIV status was unknown. In rural areas, 461 (46.6%) cases were HIV positive, and in 427 (43.1%) cases, the HIV status was unknown. Among HIV positive cases, 829 (48.4%) were on cART in the urban areas while in the rural areas, 358 (77.7%) were on cART. (Table 5-2).

Treatment outcomes

Of the 3,555 patients who were included in the analysis 265 (7.5%) were cured and 2,877 (80.9%) completed treatment (Table 5-3). Four-hundred and thirteen (11.6%) had unfavorable outcomes which are treatment failure, lost to follow-up and death. In the urban areas 95 (3.7%) of the unfavorable outcomes was a result of TB treatment failure, 52 (2.0%) were lost to follow-up, and 111 (4.3%) died. In the rural areas 18 (1.8%) of unfavorable outcomes were caused by TB treatment failure, 51 (5.2%) were lost to follow-up and 86 (8.7%) died.

Univariable and multivariable analysis results

In both the univariable and multivariable analysis place of TB treatment was statistically associated with all-cause mortality (Table 5-4). After adjusting for sex, age group, microbiological confirmation, health facility type and HIV status, recurrent TB cases treated in the rural settings

were 70% more likely to die while on TB treatment. (aOR: 1.7, 95% CI: 1.2 2.7). Recurrent TB patients treated at health centers were 30% more likely to experience death than those treated at hospitals (aOR: 1.3, 95% CI: 0.9 2.1). HIV negative patients were 50% less likely to die when compared to HIV positive patients (OR 0.5; 95% CI: 0.4 - 0.8).

For secondary outcomes of lost to follow up and TB treatment failure analyzed separately rural areas had worse TB treatment outcomes. After adjusting for calendar year of treatment, HIV and ART status recurrent TB patients in the rural areas where twice more likely to be lost to follow up as compare to those in urban areas (aOR 2.0, 95% CI: 1.3 3.0) (Table 5-5). For recurrent TB treatment failure, patients in rural areas were 70% more likely to experience treatment failure (aOR 1.7, 95% CI: 0.7 5.1) (Table 5-6). Recurrent TB patients treated at clinics were 13 times more likely to experience recurrent TB treatment failure as compared to the urban area counterparts (aOR 13, 95% CI: 6.2 27.3).

Discussion

In this retrospective cohort of TB patients, the overall prevalence of recurrent TB of 14% is high and similar to other sub-Sahara Africa countries.[16] It is higher in urban (15.3%) than in rural areas (11.3%). Recurrent TB cases receiving treatment in rural areas were 70% more likely to experience death when compared to patients treated in urban areas. The risk of both treatment failure and loss to follow up was higher in the rural areas than urban areas. A large proportion of cases (70.9%) had no bacteriological evidence of *M. tuberculosis* at the start of treatment to adequately support the diagnosis of TB.

Overall the prevalence of recurrent TB was high and similar to other sub-Saharan African settings with high HIV prevalence.[4] The prevalence was slightly higher in urban areas than rural areas. High prevalence of recurrent TB can be driven by either a high rate of exogenous reinfection or high rate of relapse of the initial *M. tuberculosis* infection. In this study, high prevalence of TB in the general population and among HIV seropositive individuals provides a suitable environment for high exposure to *M. tuberculosis* and consequently a high potential of

reinfection. Because of the limited laboratory capacity, distinction between exogenous reinfection and true relapse cases could not be made. However, previous molecular studies in similar settings have demonstrated that a large proportion of recurrent TB cases among HIV patients are caused by exogenous reinfection. In a cohort of South African gold-mine workers, HIV-1 infection was strongly associated with reinfection but not with relapse. This finding has programmatic and public health consequences because even with effective TB treatment regimens TB recurrence can be more common in population with high HIV prevalence as long as exposure to *M. tuberculosis* is high.[4,17]. Another study in Uganda showed that recurrent TB occurring more than 2 years after completing TB treatment was mainly due to reinfection whereas recurrence occurring within 2 years of treatment was due to relapse. Unfortunately, the NTP registers do not capture the dates when the last TB treatment was completed and hence it was not possible to ascertain the time interval between TB episodes.[16].

In this retrospective cohort study, risk of death was higher in rural areas than urban areas. Generally, patients in rural areas have worse TB treatment outcomes than patients in the urban areas.[11,18] Most studies that have looked at TB treatment outcomes in rural and urban sub-Saharan Africa among new TB patients have assessed unfavorable outcomes as a composite of death, failure and loss to follow up. Our study presents data on recurrent TB patient and provides a valid assessment recurrent TB treatment outcome separately for death, treatment failure and loss to follow up. Based on evidence from these studies urban areas generally have better outcomes because of better organized patient follow up systems and relatively easy access to health care services.[19-21] A qualitative study conducted in Uganda highlighted geographical barriers in rural areas as one of the barriers for delivery of routine TB diagnostic and treatment services.[20] Interviews highlighted physical remoteness of their homes from the clinic and the tough terrain encountered during travel as the principal barrier to accessing timely TB evaluation and treatment.[20] Challenges in accessing diagnostic and treatment services have potential of influencing TB treatment outcomes and increasing mortality among TB patients. Additionally,

urban settings have a high prevalence of TB and HIV and have more healthcare providers as compared to rural settings.[12] Therefore health workers in the urban areas have more clinical experience in managing TB and HIV.

Another interesting finding of this study is the high risk of recurrent TB treatment failure among patients treated at clinics as compared to hospitals. This finding requires further investigation. However, most of the patients did not have adequate laboratory results to make definitive conclusion of treatment failure.

The strength of this study is that it describes recurrent TB cases from a large cohort of TB cases at multiple rural and urban sites in a setting with high prevalence of both TB and HIV.[7] This paper presents data on the burden of recurrent TB from the NTP and evaluates treatment outcomes of this select group of patients who if not adequately treated are at high risk of developing MDR-TB. This is in stark contrast to previous studies which were conducted in places with low background prevalence of TB.[5] Additionally, the data highlight some of the gaps in the program and clinical case management of recurrent TB. The gaps herein highlighted are likely to be found in most NTPs in sub-Saharan Africa.

Limitations

As in any real-world data or observational studies our analysis was subject to some limitations. An obvious weakness of this analysis was errors in the recorded data and missing which could not be validated. This may affect the precision of our estimates. However, since we were dealing with a large sample and the proportions of missing data was less than 5%, the precision of our estimates is unlikely to be affected.

Public health relevance

We have shown that recurrent rates of TB are high in both rural and urban settings with rural areas having worse treatment outcomes as compared to urban areas. Therefore, a well-organized patient monitoring system such as effectively administered DOTS can help early detection of recurrent cases and improve clinical patient follow up and case management. Patient

follow up can take advantage of modern advances in technology such as use of mobile phones and video DOTS in addition to current strategies. The follow up and monitoring of patients must be adapted to the setting.

Adequate bacteriological confirmation of *M. tuberculosis* and drug susceptibility tests are critical for correct diagnosis and appropriate clinical management of recurrent TB. Highlighted in this paper is the low bacteriological confirmation of *M. tuberculosis* and the lack of culture and drug susceptibility testing. More effort is needed to ensure that every patient with recurrent TB has a bacteriological confirmation of *M. tuberculosis* and a drug susceptibility test especially with the wider use of rapid molecular assays such as Xpert MTB/RIF assay.[22]

Conclusion

The burden of recurrent tuberculosis is generally high in both rural and urban areas in the southern part of Zambia, a setting with a high prevalence of HIV. The burden is higher in urban areas than rural areas. However, TB recurrent cases in rural areas experience more mortality and worse treatment outcomes as compare to patients in urban areas. We strongly recommend effective patient monitoring systems to prevent recurrence and improve early detection of recurrent cases.

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Figures

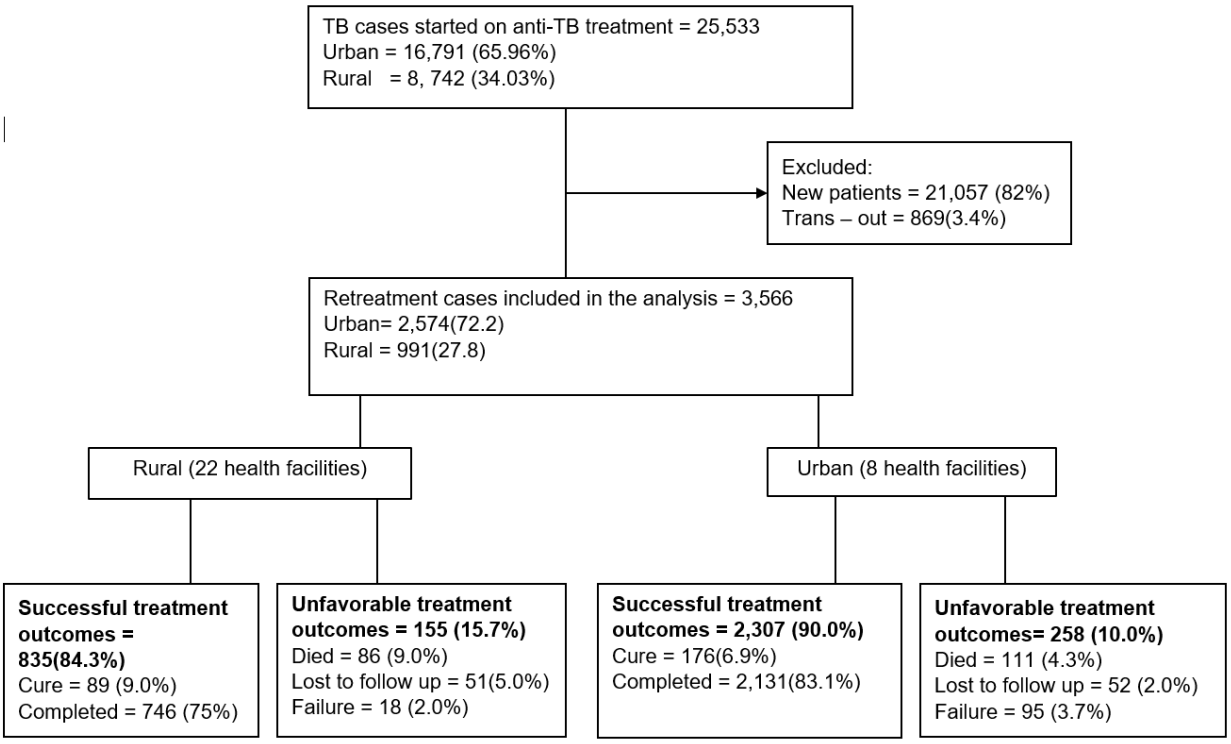

Figure 5-1: Consort diagram showing the selection of retreatment TB patients and a summary of TB treatment outcomes

Tables

Table 5-1: Prevalence of Tuberculosis retreatment cases by different characteristics among patients who were treated for tuberculosis

Patient characteristics	**total number of TB cases**	**retreatment cases**	**Prevalence in % (95% CI)**
Overall	25,533	3,566	14.0 (13.5 14.4)
Urban site	16,791	2,574	15.3 (14.8 15.9)
Rural site	8,742	992	11.3 (10.7 12.0)
Age			
10 & below	3,259	280	8.6 (7.7 9.6)
11 - 18	2,641	272	10.3 (9.1 11.5)
19 - 55	16,835	2,614	15.5 (15 16.1)
56 &older	2,769	400	14.5 (13.1 15.8)
Sex			
Female	11,569	1506	13 (12.4 13.6)
Male	13,726	2,049	14.9 (14.3 15.5)
HIV status			
negative	4,963	499	10.1 (9.2 10.9)
positive	13,795	2,216	16.1 (15.5 16.7)
unknown	6,746	857	12.7 (11.9 13.5)
Note: In this table we estimate the prevalence using the overall number of cases before excluding cases who did not have the outcomes of interest at the end of follow (patients who transferred out and the TB treatment outcome was not documented.			

Table 5-2: Clinical and demographic characteristics of recurrent TB cases treated for drug susceptible TB in Zambia, southern province

Characteristic	**Level**	**Total**	**Urban areas**	**Rural areas**
		n (percent)	n (percent)	n (percent)
Sex	Female	1,482 (41.7)	1045 (40.7)	437 (44.1)
	male	2,019 (56.9)	1473 (57.4)	546 (55.2)
	Missing	54 (1.52)	47 (1.8)	7 (0.7)
Age group*	10 & below	128 (3.6)	93 (3.6)	35 (3.5)
	11 – 18	140 (3.9)	103 (4.0)	37 (3.7)
	19 - 55	2,185 (79.2)	2064 (80.5)	751 (75.9)
	56 & older	403 (11.3)	259 (10.1)	144 (14.6)
	Missing	69 (1.9)	46 (1.8)	23 (2.3)
Microbiological confirmation	clinical	2,519 (70.9)	1874 (73.1)	639 (64.6)
	confirmed	1,036 (29.1)	689 (26.9)	347 (35.1)
Reason for retreatment	Relapse patients	2,745 (77.2)	2126 (82.9)	619 (62.5)
	Other	644 (18.1)	330 (12.9)	314 (31.7)
	Treatment after default patients	31 (0.8)	28 (1.1)	3 (0.3)
	Treatment after failure patients	29 (0.82)	15 (0.6)	14 (1.4)
	Missing	106 (3.0)	66 (2.6)	40 (4.0)
Site of disease	Pulmonary	2,937 (82.6)	2086 (81.3)	851 (86.0)
	Extra-pulmonary	537 (15.1)	418 (16.3)	119 (12.0)
	Missing	81 (2.3)	61 (2.4)	20 (2.0)
Delay	14 days & less	3,135 (88.2)	2286 (89.1)	849 (85.8)
	15 days and more	420 (11.8)	279 (10.9)	141 (14.2)
Calendar year	<2010	1,884 (53)	1336 (52.1)	548 (55.4)
	2010 & after	1,671 (47)	1229 (47.9)	442 (44.7)
Facility type	Hospital	1,353 (38.1)	926 (36.1)	427 (43.1)

	Health Center or clinic	2,202 (61.9)	1639 (63.9)	563 (56.9)
HIV status	negative	499 (14.0)	397 (15.5)	102 (10.3)
	positive	2,173 (61.1)	1712 (66.7)	461 (46.6)
	unknown	883 (24.8)	456 (17.8)	427 (43.1)
ART	No ART	986 (45.4)	883 (51.6)	103 (22.3)
	Yes ART	1,187 (54.6)	829 (48.4)	358 (77.7)
Cotrimoxazole prophylaxis	Cotrimoxazole	1,285 (59.1)	1056 (61.7)	229 (49.7)
	No Cotrimoxazole	888 (40.9)	656 (38.3)	232 (50.9)
*Age group (<10, 11 – 18, 19 – 55 and > 55) classification was based a WHO pediatric treatment guidelines and other previous studies of anti-TB treatment outcomes[23,24]				

Table 5-3: TB treatment outcomes among recurrent TB cases in rural and urban settings in southern province, Zambia

		Urban	**Rural**
Treatment outcomes	Total number	n (percent)	n (percent)
Cure	265	176 (6.9)	89 (9.0)
Completed	2,877	2131 (83.1)	746 (75.4)
Failure	113	95 (3.7)	18 (1.8)
Died	197	111 (4.3)	86 (8.7)
Default	103	52 (2.0)	51 (5.2)

Table 5-4: Estimates of the risk of death (OR) in recurrent TB patients in southern province Zambia according to demographic and clinical characteristics.

			Crude		Adjusted	
Characteristics	**Total**	**Died**	**OR**	**95% CI**	**OR**	**(95% CI)**
Location						
Urban	2,574	111	1		1	
Rural	991	86	2.1	(1.5 2.8)	1.7	(1.2 2.7)
Sex						
Female	1,482	112	1		1	
Male	2,019	85	0.5	(0.4 0.7)	0.6	(0.4 1.0)
Age group*						
Below 55	2721	171	1			
>55	403	26	1.0	(0.8 1.3)		
Microbiological confirmation						
clinical	2519	62	1			
confirmed	1036	135	1.1	(0.8 1.5)	0.6	(0.4 1.0)
Reason for retreatment						
Relapse patients	2,745		1			
Transfer in TB patients	644	36	0.9	(0.7 1.4)		
Treatment after default patients	31	3	1.8	(0.3 5.9)		
Treatment after failure patients	29	0	0	(0 2.2)		
Site of disease						
pulmonary	2937	169	1			
Extra-pulmonary	537	24	0.8	(0.5 1.2)		
Delay						
<=14 days	3135	174	1			
>15 days	420	23	1.2	(0.6 1.5)		
Facility type						
hospital	1353	54	1			
health center	2202	143	1.7	(1.2 2.3)	1.3	(0.9 2.1)
Calendar						
<=2010	1884	106	1			
>2010	1671	91	0.9	(0.7 1.3)		
HIV test						
Positive	2173		1			
Negative	499	99	0.7	(0.4 1.0)	0.5	(0.4 0.8)
unknown	883	64	1.1	(0.7 1.7)	0.4	(0.1 0.9)
ART for HIV+ individuals						
Yes ART	1187	98	1			

no ART	986	71	2.2	(1.4 3.4)	2.0	(1.2 3.1)
Cotrimoxazole prophylaxis for HIV+						
Cotrimoxazole	1285	59	1			
No Cotrimoxazole	88	40	1.2	(0.4 4.8)		
*age group was categorized into 2 age strata because there were no outcomes in the younger age groups below the age of 18 years.						

Table 5-5: Estimates of the risk of loss to follow up (OR) in recurrent TB patients in southern province Zambia according to demographic and clinical characteristics.

Characteristic	total	LTFU	Crude OR (95% CI)	Adjusted OR (95% CI)
Setting				
Urban	2,565	52	1.0	
Rural	990	51	1.9 (1.1 3.4)	2.0 (1.3 3.0)
Sex				
Male	2,019	53	1.0	
Female	1,482	50	0.8 (0.5 1.2)	
Age group				
Below 55	2721	90	1.0	
Above 55	403	13	0.9 (0.8 12)	
Calendar year				
Before 2010	1,884	53	1.0	
After 2010	1,671	50	0.99 (0.7 1.5)	1.1 (0.7 1.5)
Type of health facility				
Hospital	1,353	31	1.0	
Clinic	2,202	72	1.2 (0.7 2.0)	
Treatment delay				
Less than 14 days	3,135	92	1.0	
14 days and more	420	11	0.8 (0.4 1.4)	
Classification of TB				
Microbiology confirmed	1,036	40	1.0	
clinical	2,460	63		
HIV and ART status				
HIV negative	1,382	57	1.0	
HIV seropositive on ART	1,187	39	0.9 (0.6 1.3)	0.8 (0.5 1.2)
HIV seropositive no ART	986	7	0.9 (0.7 1.4)	0.9 (0.8 1.4)

Table 5-6: Estimates of the risk of treatment failure (OR) in recurrent TB patients in southern province Zambia according to demographic and clinical characteristics.

Characteristic	total	Treatment failure	Crude OR (95% CI)	Adjusted OR (95% CI)
Setting				
Urban	2,565	95	1.0	
Rural	990	18	1.4 (0.5 3.9)	1.7 (0.7 5.1)
Sex				
Male	2,019	60		
Female	1,482	50	0.8 (0.5 1.2)	
Age group				
Below 18 years	268	10	1.0	
18 - 55	2,815	86	0.7 (0.4 1.5)	
Above 55	403	17	1.3 (0.5 2.9)	
Calendar year				
Before 2010	1,884	54	1.0	
After 2010	1,671	59	1.2 (0.8 1.8)	
Type of health facility				
Hospital	1,353	9		
Clinic	2,202	104	15.1 (7.4 31)	13 (6.2 27.3)
Treatment delay				
Less than 14 days	3,135	90		
14 days and more	420	23	2.1 (1.2 3.4)	1.7 (0.9 2.4)
Classification of TB				
Microbiology confirmed	1,036	63		
clinical	2,460	50	0.3 (0.2 0.4)	0.4 (0.2 0.6)
HIV and ART status				
HIV negative	1,382	45	1.0	
HIV seropositive on ART	1,187	27	0.7 (0.5 1.4)	0.7 (0.4 1.2)
HIV seropositive no ART	986	41	0.8 (0.4 1.2)	1.0 (0.6 1.7)

Supplementary materials

Table 5-7: Supplementary table spearman correlation analysis

year	sex	age startw~t en	haart	urbanr~l	facili~e	sputum~c	treatm~t		delaycat	bactrim2	sputum1	diseas~e
year	1											
sex	0.0479	1										
age	-0.0109	0.1478	1									
startweigh	0.0184	0.3012	0.1686	1.0000								
endweight	-0.0013	0.2684	0.1537	0.8837	1.0000							
lastsputur	0.3298	0.0153	-0.0744	-0.0263	-0.0700	1.0000						
haart	-0.1464	0.0725	-0.0900	0.0	1							
urbanrura	-0.2039	-0.06	0.1468	-0.0	-0.0145	1.0000						
facilitype	0.0037	0.032	0.0270	-0.0	-0.0682	-0.1655	1.0000					
sputumse	0.0612	0.0488	-0.0157	-0.0	-0.0777	-0.0561	0.0706	1.0000				
treatment	-0.0061	-0.0435	-0.0215	-0.0	-0.0102	-0.0251	0.0281	-0.0138	1.0000			
delaycat	-0.1724	0.0086	-0.0002	0.0	-0.0790	-0.1406	0.2200	0.0402	0.0453	1		
bactrim2	0.3366	-0.0255	0.0727	0.0	-0.0955	0.1564	-0.2288	-0.0460	-0.0473	-0.3553	1	
sputum1	0.0771	0.0608	-0.0454	0.0	-0.0047	-0.0467	-0.1281	0.0564	-0.0110	-0.0664	0.0454	1
diseasetyp	0.0246	-0.0005	-0.0712	-0.0	-0.0047	-0.0221	-0.0670	0.1209	0.0001	-0.0547	0.0184	0.6910	1.0000

Table 5-8: Supplementary table-Estimates of the risk of death (Odds Ratio) according to demographic characteristics in recurrent TB patients stratified by urban (n = 111) and rural (n = 86) setting

Variable	**Rural**			**Urban**		
	OR	**95% CI**		**OR**	**95% CI**	
Sex	0.7	0.5	0.8	0.8	0.7	0.9
Age						
Below 55	0.8	0.4	1.1	0.7	0.4	1.8
>55	1.0					
HIV status						
positive	1.0					
negative	0.6	0.5	0.7	1.0	0.8	1
ART						
Yes	1.0					
no	1.9	0.1	0.4	2.1	1.7	2.4
Bactrim						
no	1.0					
yes	0.6	0.4	0.7	2.1	1.7	2.4
Microbiology confirmation						
yes	1.0			1.0		
no	0.7	0.5	0.8	0.7	0.8	0.7
delay						
>14 days	1.0			1.0		
>=14 days	1.6	1.4	1.7	1.4	1.2	1.6
Facility type						
hospital	1.0			1.0		
health center	1.3	1.2	1.5	1.7	1.5	1.9

Table 5-9: Estimates of the risk of loss to follow up and treatment failure (OR) in recurrent TB patients in southern province Zambia according to demographic and clinical characteristics

Characteristic		total	Lost to follow up and treatment failure	OR (95% CI)	OR (95% CI
Area	Urban	2,574	147	1	1
	Rural	991	69	1.2 (0.8 1.7)	1.4 (0.9 1.9)
Sex	Female	1,482	100	1.0	1.0
	male	2,019	113	0.8 (0.5 1.6)	0.7 (0.6 2.0)
Type of health facility	Hospital	1353	40	1.0	1.0
	Health Center	2202	176	2.9 (2.1 3.4)	2.8 (2.0 4.0)
Delay	<14	3135	182	1.0	
	=>15 days	420	34	1.4 (0.7 1.6)	
Bacteriological confirmation	clinical	2519		1.0	1.0
	confirmed	1036		2.3 (1.9 2.5)	2.2 (1.6 3.0)
Calendar	<2010	1884	107	1.0	
	2010 & after	1671	109	1.2 (0.8 1.6)	
Site of disease	pulmonary	2937	188	1.0	
	Extra-pulmonary	537	25	0.7 (0.4 1.5)	
Reason for retreatment	Treatment after relapse	2,745	172	1.0	
	Treatment after default patients	644	3	1.6 (0.3 2.5)	
	Treatment after failure patients	31	1	0.5 (0.1 1.8)	
	others	29	40	0.8 (0.4 2.3)	
Age group	Below 18	268	11	1.0	
	19 - 55	2185	175	1.4 (0.3 4.9)	
	56 above	403	30	2.5 (0.6 4.7)	
HIV status	positive		114	1.0	1.0
	negative		56	0.7 (0.5 0.9)	0.5 (0.5 0.8)
	unknown		883	1.1 (0.9 1.3)	0.3 (0.2 1.3)

CHAPTER 6 : INCIDENCE OF TUBERCULOSIS IN HIV SEROPOSITIVE PATIENTS TREATED WITH ART IN ZAMBIA[3].

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Abstract:

Background

Tuberculosis (TB) is the leading cause of morbidity and mortality among Human Immunodeficiency Virus (HIV+) patients. The risk of TB among patients on Anti-Retroviral Therapy (ART) is heterogeneous depending on the timing of ART. However, it is not known whether there are differences in the risk of TB among HIV+ patients accessing ART in rural and urban health settings in sub-Sahara Africa.

In urban settings, high TB incidence is sustained by the high HIV prevalence and crowded living conditions. Rural settings have distinct challenges which drive the TB and HIV epidemic. These include poor health care access, lack of diagnostics and severe shortage of health care providers. Therefore, it is important to understand differences in the risk of TB between these 2 populations.

To address this knowledge gap, we evaluated the risk of TB among HIV seropositive individuals receiving ART in rural and urban settings of Zambia.

Methods

We performed a retrospective cohort study on a sample of HIV patients who started ART between 2005 and 2014 within the Zambia National ART Program. We estimated the Incidence Rates (IR) of TB were person-time at risk of TB was accrued from the date of starting ART until diagnosis of TB. To assess the risk factors associated with incident TB, Cox proportion hazard regression was performed.

Results

Overall 1,518 patients met the eligibility criteria (rural: 33%; urban: 67%). At the time of initiating ART 82 patients (5.4%) were diagnosed with prevalent TB. New cases of TB were diagnosed for 37 patients (2.8%) over 21,209 person-years of observation (PYO). The overall IR was 2.6/1000PYO (95% CI: 1.8–3.7). The IR was 2.4/1000PYO (95% CI: 1.6–4.4) in urban health settings and 3.4/1000PYO (95%: 1.3–2.7) in the rural health settings. Within the first year of ART

the IR was 7.6/1000PYO (95% CI: 5.3–10.7), and then dropped to 1.9/1000PYO (95% CI: 0.8–4.2) in the second year and 0.43/1000PYO (95% CI: 0.2–1.1) after 5 years.

In the adjusted analysis, the incidence of TB was not associated with rural/urban health care setting (aHR =1.4, 95% CI: 0.4 – 1.7) (table 1). New cases of TB were 90% more likely than recurrent TB during follow up on ART (aHR = 1.9, 95% CI: 0.4 – 1.7). For both new and recurrent TB the incidence was highest in the first year of ART.

Conclusion

Incidence of TB is substantially high in both rural and urban HIV care settings especially during the first year of ART. HIV treatment programs must develop effective TB screening mechanisms and robust use of preventive therapy.

Introduction

Tuberculosis (TB) is one of the leading causes of morbidity and mortality in the world.[25] As the HIV epidemic evolves and more people living with Human Immunodeficiency Virus (HIV) gain access to Anti-retroviral therapy (ART), the risk of dual infection with HIV and *mycobacterium* TB is still substantial.[26] Of the 10.4 million cases of TB reported to the World Health Organization in 2016, 1.2 million cases were among HIV positive patients and 400,000 TB-HIV coinfected individuals died because of TB.[25] Africa accounted for 74% of the cases of TB among people living with HIV.[25]

Zambia is one of the African countries hard hit by the dual burden of TB and HIV.[7] In a population of over 17 million people, the adult HIV prevalence is 12% and the prevalence of bacteriologically confirmed TB in the general population is 638/100,000 population.[7,27] Among people living with HIV in the general population the prevalence of TB is 887/100,000 population.[7]

HIV confers the greatest known risk for TB because of its damaging effect of the host cellular immunity which is critical for protection against *mycobacterium* TB.[28] Additionally, once HIV patients develop TB, they are at increased risk of death even after starting ART.[26] With the relative restoration of immunity by use of ART, there is a reduction in the risk of TB.[29,30] However, the risk of TB remains, and one study reported substantial incidence after 5 years of ART.[31] Since ART potentially restores or improves the life expectancy of HIV patients, this prolonged life could have unfavorable impact on the control of TB because of the sustained high risk of TB transmission driven by high TB incidence even when individuals with HIV are on ART.

Numerous studies have estimated the risk of TB and evaluated the underlying risk factors, but these studies have not estimated the variations in the risk of TB among individuals living with HIV between rural and urban settings in low and middle-income countries, especially countries with a high dual burden of HIV and TB.[32-35] We performed a retrospective cohort analysis of national data for HIV patients on ART in Zambia to estimate the risk of TB, assess factors

associated with this risk and asses the difference in TB incidence between rural and urban settings.

Methods

Study design

In a retrospective cohort study design we analyzed HIV treatment program data for a nationally representative sample of 1,600 HIV positive individuals who started ART between January 1, 2005 and December 31, 2014 in Zambia. The data was collected as part of the National ART Program Outcome and Impact Evaluation (NAPOIE). The NAPOIE was a national wide HIV treatment, facility-based survey conducted between June 1 and October 19, 2016 whose aim was to evaluate retention, immunological and clinical outcomes of pediatric and adult HIV patients treated with ART.

Study setting and population

The study was conducted in 19 rural and 33 urban health facilities providing ART. Rural Health facilities serve catchment populations of up to 30,000 and were in places where the source of livelihood for at least 75% of the population is agriculture and agriculture allied activities. Urban health facilities are located in urban settings and serve catchment populations of over 30,000. [14]The analysis included randomly selected adult HIV patients above the age of 15 who started ART between January 1, 2005 and December 31, 2014The random selection of patient records followed a two-stage random sampling technical. The following were excluded from the study: all HIV positive patients who were not on ART at the time of the evaluation; any patients with missing information on both birth date and age, missing ART initiation date and any patients whose record could not be traced. Data for Pediatric patients was abstracted and analyzed separately.

Study outcomes

The primary outcome of this analysis was incidence of active TB disease in a cohort of HIV patients started on ART in public health facilities in Zambia. Incident TB was defined as the occurrence of an episode of TB disease diagnosed by a clinician more than 1 month after initiation

of ART and where the patient was commenced on a full course of TB treatment. If TB was diagnosed at the time of starting ART or within 1 month of starting ART, then the case was classified as prevalent TB. TB diagnosed in a prevalent TB case after completing TB treatment was regarded as recurrent TB was not included in the measure for incident TB. Person Years of Follow-Up (PYFU) were calculated from the date of starting ART until the date of TB diagnosis. Patients who did not develop TB were censored on the last date of clinic visit.

Study exposure

The study assessed factors associated with TB incidence. Place of ART and TB treatment classified as either rural or urban was the exposure. The definition of rural or urban was based on the Ministry of health and Central Statistical Office of Zambia classification of health facilities as defined above.[14] Rural health setting if the health facility was located in a place where the source of livelihood for at least 75% of the population was agriculture and agriculture allied activities and served a catchment population of up to 30,000 people.[14] While urban health setting is when a patient was treated for TB at a clinic or hospital located in an urban area and where the facility served a catchment population of over 30,000.[14]

Covariates and confounders

The following clinical and demographic characteristics at start of ART were considered as covariates: sex, age, marital status, treatment support, Cotrimoxazole prophylaxis, WHO staging of HIV, Body Mass Index (BMI), screening for TB at ART initiation and baseline $CD4^+$ count.

Sample size

A two-stage random sampling was used to select patient records eligible for the analysis in NAPOIE (CDC, Epi Info 2008, version 7, Atlanta, Georgia, USA). In the first step patients on ART were separated into 2 strata: rural and urban. In each stratum health facilities were selected based on the probability proportionate to the number of patients receiving ART at each facility. Assuming a conservative retention rate of 50% at 12 months after initiation of ART and a design effect of 1.5, a 95% confidence interval equal to the sample proportion of + 3%, the sample size

was estimated to be a minimum of 1599 for adult patients. The sample size was generated to achieve equal weights across the strata.

Analytic strategy

Baseline demographic characteristics were characterized using standard descriptive statistics. Pearson correlation analysis for continuous variables and Spearman correlation for nominal category variables was performed. In the first part of the main analysis PYFU was calculated from the date of starting ART to the date of TB diagnosis. Patients who did not develop TB were censored on the last date of clinic visit or October 19, 2016 which ever occurred first. The reasons for censoring were death from any cause, loss to follow-up (LTFU) and close of the survey before TB was diagnosed. Incidence rates of TB and the confidence intervals were calculated were Person-time at risk of TB was accrued from the date of starting ART until diagnosis of TB. Person time accrued during treatment of prevalent TB was excluded in the person time at risk for TB when calculating TB incident rates. Kaplan Meier (KM) curves comparing disease free distributions between rural and urban settings and between various classes of covariates and potential confounders were plotted. Because most cases of TB were diagnosed in the early days of starting ART, KM curves were compared by the Wilcoxon rank statistic test which applies more weight to the earlier events. The KM curves were tested for the Proportion Hazard Model assumption using the goodness of fit approach and the graphical approach (Log-log plots).

To assess the risk factors associated with incident TB univariate Cox proportion hazard regression was performed. All statistically significant variables ($p<0.05$) were included in the multivariate model. We used the forward selection method to build the final model. Since our model was small, we tested for all possible interactions. And no interactions were identified. Data analysis was performed with STATA version 14.

Data Integrity

NAPOIE was a retrospective cohort analysis of programmatic and treatment outcomes for ART patients. Data was abstracted from patient records which were either paper based or electronic. Demographic and clinical information was abstracted at the start of ART and at window periods of 6, 12 and 24 months of being on treatment. Before beginning data abstraction, data collectors were trained on the study procedures for 5 days. Systematic random sampling was used to select patient patients eligible for the evaluation at each site. To ensure data quality the study team leader re-abstracted 10% of the records selected at the site.

Clinical management

All the HIV patients who formed the cohort for our analysis were treated with ART according to national ART guidelines for management of HIV adapted from WHO guidelines.[36,37] In this cohort, TB screening was conducted according to the WHO guidelines for Intensified case finding.[38] Patients where regularly screened for TB using a clinical algorithm at every visit at a health facility or contact with a health worker. Any patient with one of the four symptoms (current cough, fever, weight loss or night sweats) were evaluated for TB and other diseases. Patients who were diagnosed with TB were commenced on a full course of TB treatment according to national TB treatment guidelines.[39]

Ethics

Ethical approval was obtained from the University of Zambia ethics committee and regulatory authority from the Zambia National Health Research Authority. Permission to publish these findings was obtained from the Ministry of Health in Lusaka.

Results

Study population and follow up

Overall, 1,600 patient records were reviewed. And of these 1,518 (95%) patient records that were successfully abstracted (Rural: n = 508, percent = 33%) (Figure 6-1). At the time of ART initiation 82 (5.4%) of these patients were diagnosed with TB and commenced on TB treatment

and we call this prevalent TB (Table 6-1). Most of the patients receiving ART were female (n=926; percent = 61%). Of the overall number of patients started on ART 78.7% were classified as having been screened for TB symptoms at the start of ART. Among those who were screened for TB symptoms 629(41.4%) of the total patients had at least one symptom suggestive of TB. At the close of the survey 753 (53%) individuals were TB disease free and alive whereas 80 (5.6%) had died and 593 (41.3%) were either lost to follow up or transferred to another facility (Figure 6-1).

Incident TB cases

New episodes of TB were diagnosed among 37 patients (2.4%) after starting ART (table 6-2). Of these new cases of TB, 26 (70%) were in urban health settings and 11(30%) in rural settings. Most cases (n = 25, Percent = 68%) were diagnosed within the first year of starting ART and only one cases was diagnosed after 5 years of ART (Table 6-2). Of the remaining cases 6(16%) occurred in the second year, 4 (10%) in the third and fourth year of ART. Most of cases (n=25, percent = 68%) occurred in individuals with CD4+ count less than 250 cells/mm^3.

In this cohort of 1518 individuals 13905 person-year of observation (PYO) was accrued over a period of 9 years. The overall incidence rate of TB was 2.6/1000PYO (95% CI: 1.7 - 3.7). In the urban setting the incidence rate of TB was 2.4/1000PYO (95% CI: 1.6 - 3.6) and 3.4/1000PYO (95%: 1.6 - 3.6) in the rural health settings (Table 6-2A). Although, not statistically significant, the incidence was consistently higher in rural areas than urban areas (first 6 months: IRR 1.2, 95% CI 0.4 - 3.1; 7-12 months: IRR 0.9, 95% CI 0.2 4.8; 12 – 18 months: IRR 1.1, 95% CI 0.1 10; after 18 months: IRR 1.4, 95% CI 0.3 - 6.8) (table 6-2B).

The incidence rate was 7.6/1000PYO (95% CI: 5.3 - 10.7) within the first year, 1.9/1000PYO (95% CI: 0.85 – 4.2) in the second year and was 0.4/1000PYO (95% CI: 0.2 – 1.1) after 5 years of ART (Figure 6-2).

Risk factors for incident cases of tuberculosis

We used KM curves to analyze the association between place of treatment and TB incidence including time at risk before developing TB (Figure 6-3a). The median time of follow up

in the population that developed TB was 179 PYO (IQR: 90.5 - 583). The median time of observation in the population that did not develop TB while on ART was 1405 PYO (IQR: 620 - 2257). When we plotted the KM survival curves for occurrence of TB in the rural and urban areas, there was no difference in the cumulative incidence for the 2 curves (Wilcoxon rank p=0.54) (Figure 3b).

In the multivariable Cox proportion Hazard model, although there was no statistical significance, the incidence of TB in rural areas was 40% higher than urban areas (HR =1.4; 95% CI: 0.4 - 1.7) after adjusting for $CD4^+$ count and TB symptom screening (Table 6-3). Patients who were started on ART at CD4+ count greater than 250 cells/mm^3 were 20% less likely to develop active TB (HR = 0.8; 95% CI: 0.3 - 1.0).

We checked the Cox proportion Hazard assumption using the goodness of fit and the log-log plots graphical approaches. There was no violation of the Cox proportion hazard assumption.

Discussion

The overall incidence of TB was 2.9 cases/1,000 PYO. Although not statistically significant, the Hazard of TB incidence was 40% higher in the rural areas than urban areas. This study presents a nationally representative measure of incidence of TB for patients on ART in a country with a high prevalence of both HIV and TB and where a high proportion of these patients have access to ART.[7,27]

The fact that there is 40% difference in the incidence of TB among HIV patients receiving ART in rural settings and those in urban settings is notable. However, there is not enough statistical evidence to support the precision of this measure of effect. In theory it is expected that the incidence rate of TB must be higher in urban settings because of the high prevalence of both TB and HIV in urban settings and congested living conditions.[11] It is important to recognize that; previous studies did not document the incidence of TB comparing the two settings. What is known about these 2 settings are prevalence estimates from nationwide population-based TB prevalence surveys and TB program reports.[7,40] In Zambia and other sub-Sahara African countries the

prevalence of TB is generally high across different population groups. When we compare the prevalence in the rural and urban settings in Zambia, it is twice higher in the urban population (993 versus 460/100,000 population).[7]

High incidence rates of TB among HIV patients in both rural and urban settings implies that the burden of TB poses a big threat to the control of TB among HIV patients and the general population. Based on basic principles of epidemiology, prevalence of a disease is driven by the incidence rate and the duration of the disease.[41] When the duration of the disease is held constant and the incidence rate is high the prevalence of the disease is likely to increase. Therefore, if incidence rate of TB among HIV patients in the rural areas remain as high as that in urban settings the prevalence of TB is likely to increase in rural settings as well. A high prevalence of TB in rural settings is a problem to the TB control program because in rural settings the diagnostic and TB/HIV case management capacity is not adequately developed and prepared to handle large numbers of TB cases.

Overall the incidence rate of TB was high in this cohort of patients being treated for HIV but was not as high as other sub-Sahara settings such as South Africa and Uganda.[29,32] The incidence was highest in the first year of ART and progressively reduced and by the 5th year of treatment we had very few cases. Previous studies in sub-Sahara Africa found higher incidence rates of TB among patients receiving ART and it is generally accepted that TB incidence is higher in HIV patients as compared to the general population.[29,32] In these studies incidence rates were highest within the first six months of starting ART and waned downed with prolonged ART.[42] However, one study in South Africa showed a high incidence even after 5 years of ART.[31]

Several reasons may contribute to the high incidence of TB within the first year of ART initiation. In this cohort the high incidence rate during the first year of ART can be explained by 2 theories. The first one being detection bias which resulted from some cases of TB may have been misdiagnosed partly because of clinician related factors, patient's degree of immunosuppression and sensitivity and specificity properties of the TB screening algorithm. In this case patients with

TB are misclassified as not having TB. These misclassified cases paradoxically got worse with introduction of ART plus the accompanying restoration of immunity hence being diagnosed later. Or maybe since these patients where now in HIV care and frequent clinical visits signs and symptoms of TB that were missed at baseline were picked later.

Because of these reported variations with the use of the TB symptom screening tool, we hypothesize that TB may have been underdiagnosed at the start of ART. In this cohort symptom screening was conducted using the WHO TB symptom screening algorithm. The WHO TB symptom screening algorithm has been used in different parts of the world with different levels of precision being reported.[43] In a study conducted in South Africa among HIV patients to evaluate the performance of strategies to exclude active TB, the sensitivity of active TB disease symptom screen algorithm was 59%, specificity was 76% and negative predictive value was 97%. From a sample of 899 cases, 44 definitive cases of TB were identified of which 18 (41%) were missed by the symptom screening algorithm questionnaire.[44] In a recent study to assess optimal means of conducting TB screening among HIV patients, the presence of cough, fever of any duration and night sweats lasting more than 3 weeks had a sensitivity of 93%, specificity of 35% and a negative predictive value of 97 % at 5% TB prevalence.[45] This paper concludes that a combination of these 3 symptoms accurately rules out TB and allows for safe initiation of Isoniazid preventive therapy and ART.[45]. Under diagnosis of TB at the start of ART has been reported in most resource constrained settings resulting in higher morbidity and mortality among HIV patients after starting ART.[46]

The second probable reason for high incidence rate of TB during the first year of ART was unmasking of Latent TB Infection(LTBI).[46] TB symptom screening cannot identify LTBI. In this cohort of HIV patients screening for LTBI was not part of the minimum standard of care. However, it is known that in the worst-affected communities of southern Africa, as many as 50% of 15-year-olds and 77–89% of adults have evidence of LTBI confirmed by Tuberculin Skin Test (TST).[47-49] It is also well established that HIV-infected patients with positive TST have a substantially higher

risk of LTBI progressing to active TB than do those with a negative TST.[50] In HIV negative individuals the life-time risk for developing TB disease for individuals with LTBI is 10% while for HIV positive individuals with LTBI, one-year risk may exceed 10% depending on the level of immunosuppression and prevailing economic factors.[51] The high background prevalence of undetected LTBI in this population of HIV patients plus the introduction of ART at lower $CD4^+$ count may have played a major role in the incidence of TB in the first year of ART.

Limitations

We acknowledge the limitations of the study and subsequent analysis. The NAPOIE was powered to defect the effect of loss to follow up among HIV seropositive individuals on ART in Zambia and not incidence of TB in this population. However, this data base provides a nationally representative database from which the incidence of TB in this population can be estimated with good precision.

Public health implications

Based on the findings of high incidence rate of TB within the first year of starting ART we make tow critical recommendations which have been shown to be effective but are not adequately implemented in most TB control programs. Firstly, we recommend that TB control program managers in sub-Sahara Africa must develop strategies to fully implement intensified TB case finding in both rural and urban settings in HIV treatment clinics. Patients with one at least one symptom must receive further evaluation for TB. The TB symptom screening algorithm if combined with further evaluation using TB diagnostics in symptomatic patients achieves a balance between limited resources and the risk of false negative results.[45]

Secondly, for those in whom active TB has been ruled out we recommend screening for LTBI using tuberculin skin testing or IGRA. Individuals with LTBI will benefit from availability short course LTBI preventive therapy.[52] Effective screening for LTBI and early case detection is critical in the control of TB because it reduces rates of morbidity, mortality and *M.tuberculosis* transmission rates by interrupting progression of LTBI to active TB.

Conclusion

TB incidence rate among individuals living with HIV in rural and urban Zambia is generally high in both settings. It is highest within the first six months of starting ART. We recommend intensified screening for TB among individuals living with HIV at the time of initiating ART is critical screening for LTBI followed with treated LTBI.

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Tables

Table 6-1: Patient demographic and clinical characteristics at the time of starting ART.

Patient characteristic		**Rural**	**Urban**
		n (%)	n (%)
	Overall n =1518	508 (33)	1010 (67)
Median age (IQR)	35(29 - 44)	36 (29 - 43)	34 (28 - 41)
Gender			
female	926 (61)	303 (59.7)	623 (61.7)
male	592 (39)	205 (40.3)	387 (38.3)
marital status			
divorced	163 (10.7)	59 (11.6)	104 (10.3)
married	875 (57.6)	310 (61.0)	565 (56.0)
single never married	316 (20.8)	73 (14.4)	243 (24.1)
widowed	164 (10.8)	66 (13)	98 (9.7)
HIV status Disclosure			
friend	11 (0.72)	4 (0.79)	7 (0.7)
none	504 (33.2)	154 (30.3)	350 (34.6)
family member	510 (33.6)	187 (36.8)	323 (32.0)
spouse	493 (32.5)	163 (32.1)	330 (32.7)
TB at ART initiation*			
no	1398 (92.1)	471(92.7)	927 (91.8)
yes	82 (5.4)	19 (3.7)	63 (6.2)
WHO HIV staging			
stage 1	343 (23.1)	149 (29.3)	194 (19.2)
stage 2	158 (10.5)	71 (14.0)	87 (8.6)
stage 3	947 (61.7)	267 (52.6)	680 (67.3)
stage 4	70 (4.9)	21 (4.1)	49 (4.9)
Body Mass Index**			
underweight(<18.5kg)	466 (30.7)	160 (31.5)	306 (30.3)
normal weight (18.5-24.99kg)	885 (58.3)	299 (58.9)	586 (58.0)
overweight(25-29.99kg)	83 (5.5)	22 (4.3)	61 (6.0)
obese(>30Kg)	16 (1.1)	4 (0.79)	12 (1.2)
TB symptom screening at ART initiation			
yes	1195(78.7)	421(82.9)	774 (76.6)
no	323 (21.3)	87 (17.1)	236 (23.4)
Presence of 1 or more symptoms suggestive of TB[1]			
yes	629(41.4)	221 (43.5)	408 (40.4)
no	889(58.6)	287 (56.5)	602 (59.6)
Year in which ART was started			

2004 - 2009	621 (40.9)	169(33.3)	452 (44.8)
2010 -2014	897(59.1)	339 (66.7)	558 (55.2)
Median CD4+ count at baseline (IQR)	151(70-287)	152(75- 320)	150(70- 289)
Asterisk (*) indicates 38 (2.5%) individuals missing data on diagnosis of TB at the time of ART initiation. Asterisks (**) indicate 68(4.5%) individual missing data required to estimate BMI. [1]presence of anyone of these symptoms requires further evaluation for TB: fever, productive or non-productive cough, night sweats, weight loss, and hemoptysis.			

Table 6-2: Incidence rate of tuberculosis by demographic and clinical characteristics

Patient characteristic	# of new TB cases	PYO	Rate(n/1000)	95%CI
Overall	37	13905	2.6	(1.7 3.7)
location				
rural	11	3282	3.4	(1.8 – 6.1)
urban	26	10623	2.4	(1.6 – 3.6)
Duration on ART		0		
First year	19	3803	7.6	(5.3 – 11)
Second year	6	3162	1.9	(0.9 – 4.2)
Third year	4	3518	1.14	(0.4 – 3.0)
Fourth year	8	1393	0.72	(0.1 – 5.1)
Fifth year and after	1	9333	0.39	(0.1 – 1.1)
Gender		0		
female	22	8021	2.7	(1.8 – 4.1)
male	15	5884	2.5	(1.3 – 3.3)
Marital Status		0		
divorced	3	781	3.8	(1.2 – 12)
married	19	7337	2.6	(1.7 – 4.1)
single never married	10	4096	2.4	(1.4 – 4.6)
widowed	5	1691	2.9	(1.2 – 7.1)
Age group				
15 - 30	12	5789	5.8	(1.1 – 3.6)
31 - 40	17	6261	6.3	(1.6 – 4.3)
older than 41	8	1855	4.3	(2.1 – 8.6)
BMI				
Underweight (<18.5kg)	13	3318	3.3	(1.9 – 5.7)
normal weight (18.5-24.99kg)	22	7340	2.9	(1.9 – 4.5)
Overweight (25-29.99)	0			
Obese (>30Kg)	0			
CD4 count at baseline				
50 and below	17	5837	2.9	(1.8 – 4.6)
51-250	8	3950	2.0	(1.0 – 4.0)
251-350	7	1927	3.6	(1.7 – 7.6)
above 350	5	2191	2.2	(0.9 – 5.4)
HIV status Disclosure				
no	10	5128	1.9	(1.0 – 3.6)
yes	27	8777	3.1	(2.1 – 4.5)
TB symptom screening at ART initiation				
yes	16	5859	2.7	(1.7 – 4.4)

no	21	8046	**2.6**	(1.7 – 4.0)
Presence of 1 or more symptoms suggestive of TB				
yes	23	1316	**1.7**	(1.2 – 2.6)
no	21	8046	**2.6**	(1.7 – 4.0)
WHO HIV staging				
stage 1	2	1026	**1.9**	(0.5 – 7.8)
stage 2	2	593	**3.3**	(0.8 – 13.5)
stage 3	33	12286	**2.6**	(1.9 – 3.7)

Table 6-3: Estimates of the incidence rate ratios of TB disease between rural and urban areas according to duration on ART

Time on ART	**Rural**			**Urban**			**IRR (95% CI)**
in months	**TB cases**	**PYO**	**IR (per 1000)**	**TB cases**	**PYO**	**IR**	
< 6	6	480	12.5	13	1211	10.7	1.2 (0.4 3.1)
7 - 12	2	583	3.4	4	1027	3.9	0.9 (0.2 4.8)
12 - 18	1	416	2.4	3	1343	2.2	1.1 (0.1 10)
> 18	2	1803	1.1	6	7042	0.8	1.4 (0.3 6.8)

Table 6-4: Risk factors for new episode of tuberculosis among HIV positive individuals on ART: Crude HR, adjusted HR

			Unadjusted		adjusted	
Patient characteristics	**# of new cases**	**PYO**	**HR**	**95% CI**	**HR**	**95% CI**
Location						
rural	11	3282	1.0			
urban	26	10623	1.2	(0.6 2.5)	1.4	(0.4 1.7)
Age						
Sex						
female	22	8021				
male	15	5884	1.1	(0.6 2.2)		
Marital Status						
divorced	3	781	1.0			
married	19	7337	1.1	(0.3 3.7)		
single	10	4096	1.7	(0.4 6.4)		
widowed	5	1691	1.5	(0.3 6.6)		
HIV status Disclosure						
no	10	5128	1.0			
yes	27	8777	1.2	(0.6 2.6)		
WHO staging at baseline						
stage 1	2	1026	1.0			
stage 2	2	593	2.1	(0.3 15)		
stage 3	33	12286	6.5	(1.6 27)		
stage 4	0	-	-	-		
Body Mass Index						
under weight	13	3318	1.0			
normal weight	22	7340	0.8	(0.4 1.6)		
Overweight	0	-	-	-		
Obese	0	-	-	-		
CD4 count at start of ART						
0 - 250 cells/mm^3	25	9787	1.0			
greater than 250 cells/mm3	12	4118	0.7	(0.3 1.0)	0.9	(0.8 1.0)
TB symptom screening at ART initiation						
no	10	5128	1.0			
yes	27	8777	1.3	(0.6 2.8)	1.6	(0.7 3.2)
Presence of 1 or more symptoms suggestive of TB						
yes	23	1316	1.0			
no	21	8046	0.9	(0.4 1.7)		

Figures

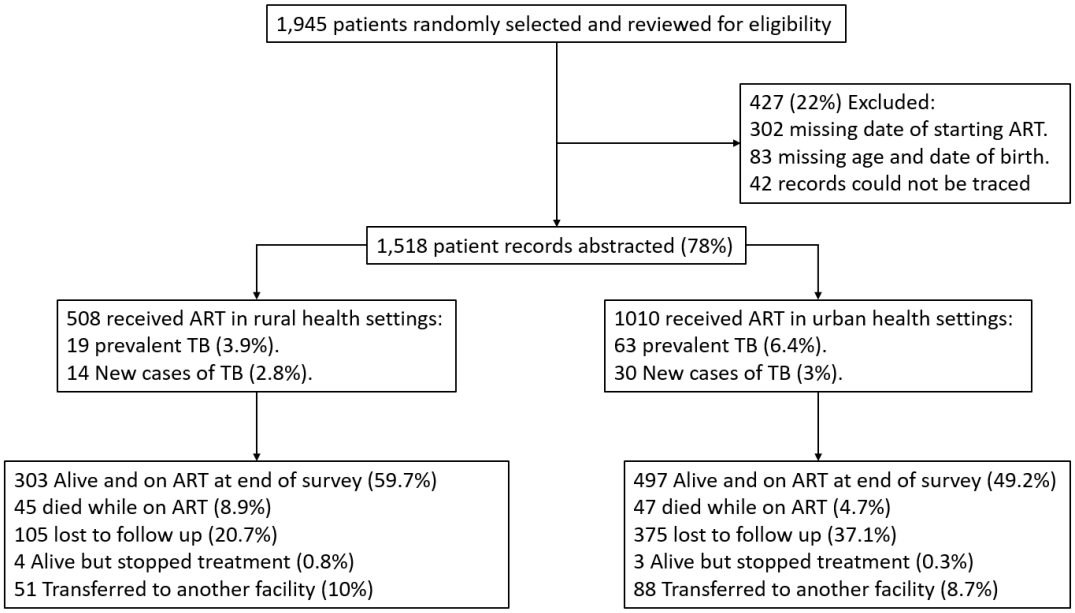


Figure 6-1: Consort diagram showing patient records that made it into the analytic sample and other reasons for censoring

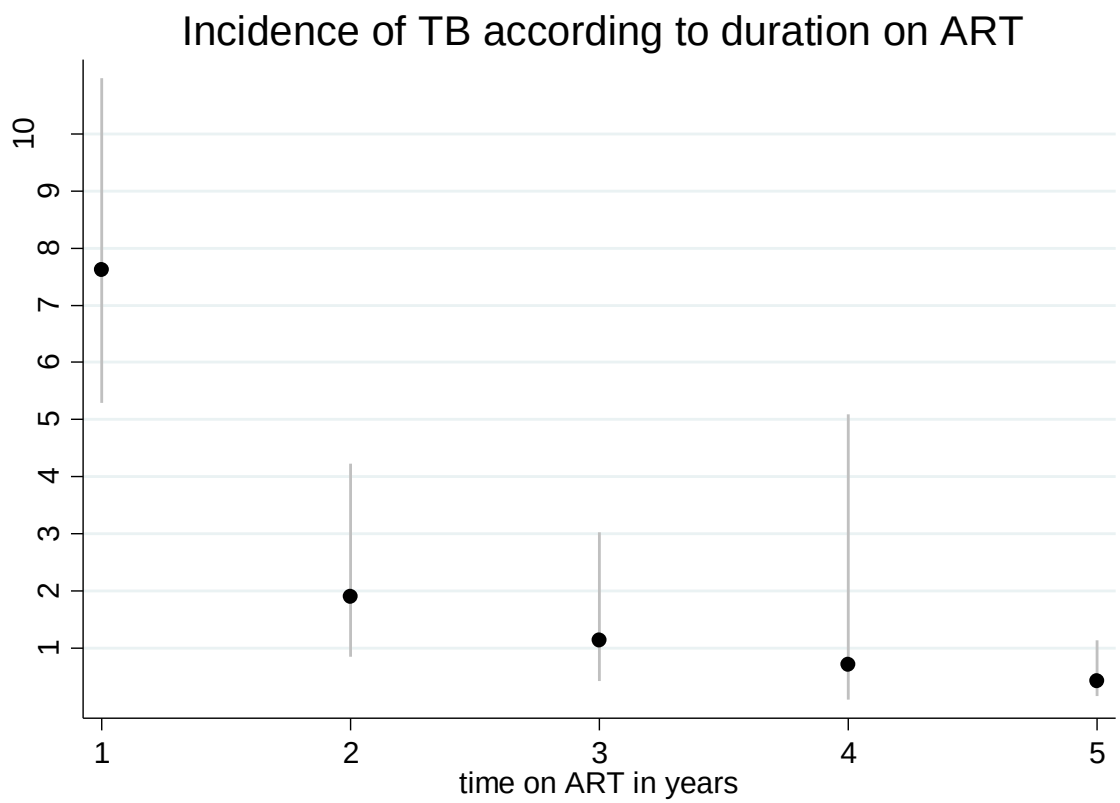


Figure 6-2: Incidence rate of TB among individuals receiving ART. The highest rate was observed in the first year of ART.

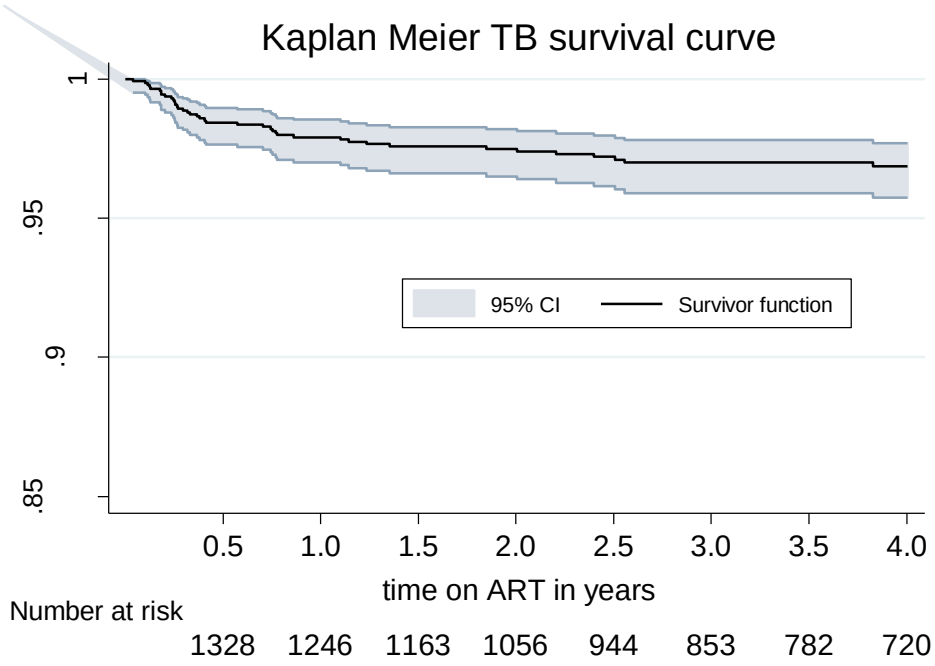


Figure 6-3: KM time to event plots for TB patients developed TB while on ART

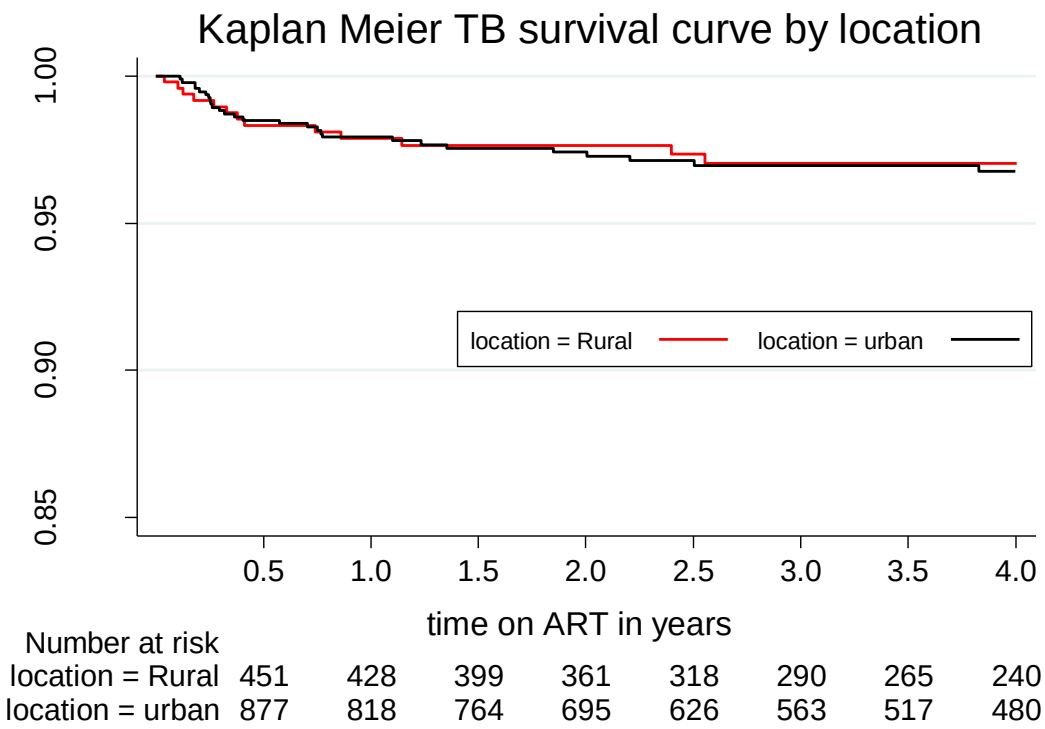


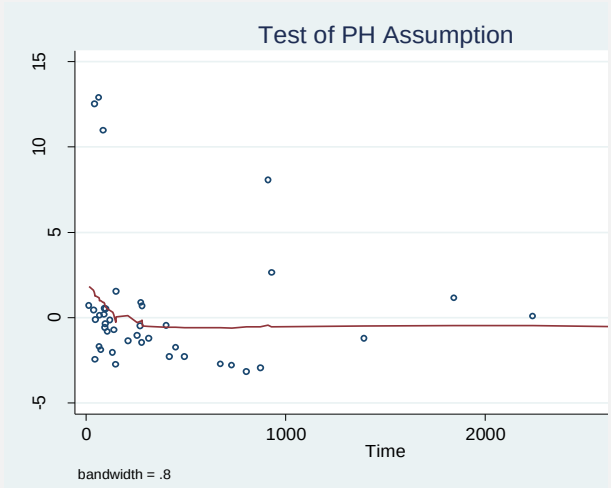
Figure 6-4: Time to event KM curve comparing urban and rural setting.

Supplementary materials

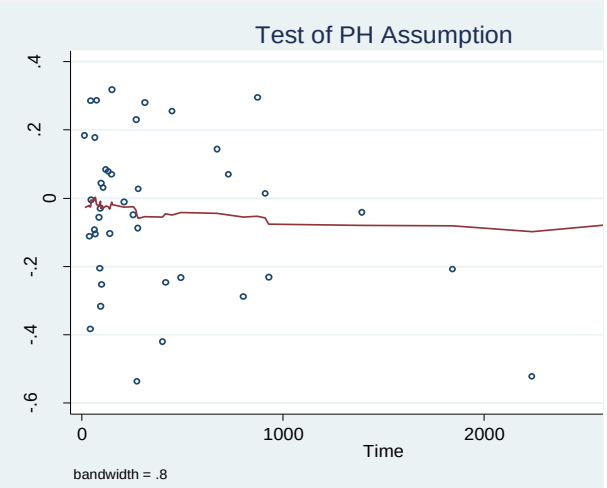
Table 6-5: supplementary table testing the Cox proportion hazard proportion assumption using the goodness of fit testing approach.

	rho	chi2	df	Prob>chi2
location	-0.04582	0.09	1	0.7695
base_cd4	-0.13663	0.58	1	0.4466
bmi	-0.23255	1.18	1	0.2769
yrart	0.0857	0.3	1	0.5856
global test		4.83	6	0.5656

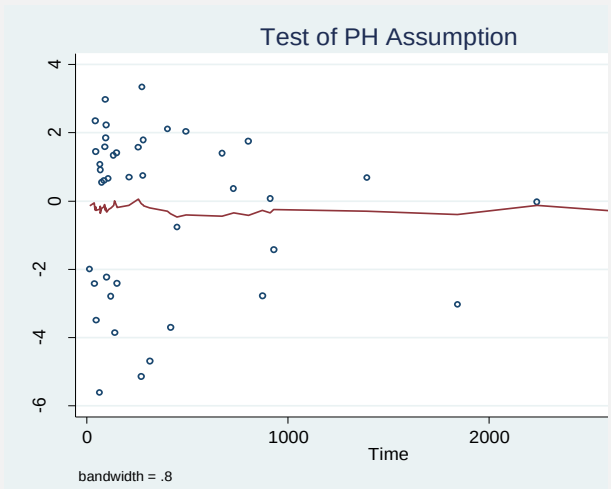
BMI

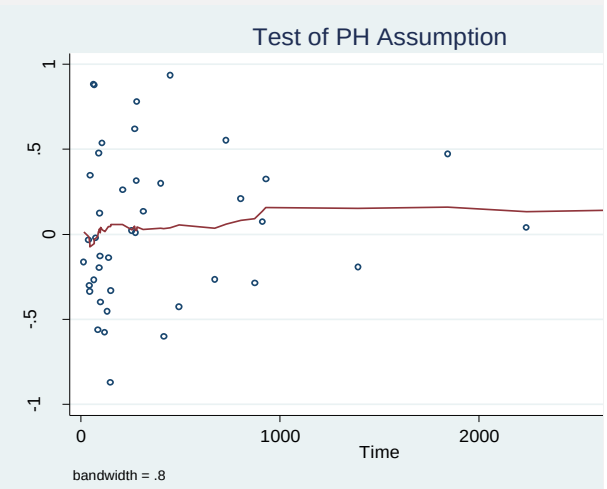


Calendar year



location





CD4 count

Figure 6-5: supplementary material - Testing the Cox proportion hazard assumption using graphical methods. All of them appear like strait lines.

CHAPTER 7 : SYNTHESIS

Overview

Based on program reports and data from national TB prevalence surveys prevalence and incidence of TB is higher in urban settings than rural settings in Zambia and this situation is similar in most countries in Sub-Sahara Africa.[1-4] High burden of TB in the urban setting is driven in part by ongoing community transmission. [1] In contrast to rural settings most of the population in urban settings live in crowded conditions which provide a good environment for M. TB transmission. [5,6] Additionally, occupation exposure predisposes urban populations to M.TB. For instance, in Zambia particularly on the Copperbelt province most of the population work in underground mines which are known to be a high-risk place for M. TB transmission.[7] These workers are exposed to high levels of silicon and asbestos which increase the risk of TB disease.[7] Apart from living conditions and occupational exposure, HIV prevalence is higher in the urban settings than the rural settings.[8] It is known that the incidence of TB is higher in HIV seropositive individuals.[9] With a high HIV prevalence in the urban areas as compared to rural areas, this plays a significant role in TB incidence and prevalence in urban settings.

The prevalence and incidence of TB is heterogeneous even in a defined location. For instance, in most urban settings the prevalence is different between high population density and low population density residential areas. However, there is close proximity between these different settings such that individuals in the high-density locations have social interactions with people of the low-density settings. In much the same way there is cross movement between rural and urban populations. In this study some of the outcomes we reported for patients in urban areas may have been for patients who reside in rural settings but for unknown reasons decided to get treatment in urban health facilities. This may result in exposure misclassification

and may bias our results. However, the TB control program is designed in such a way that TB patients are encouraged to get treatment from the health facility nearest there home. This follows upon the concepts of the DOTS which require a health work or community health observing the patient swallow the pills. Based on the DOTS guidelines all TB patients must be registered at the health center near their home for easy of follow up and refill of TB drugs.

TB treatment outcomes are documented at the facility where the patient get the TB drugs. Therefore, it was not possible to accurately ascertain the place of death especially for patients who reside in rural areas. This is because all TB treatment outcomes are recorded in the TB register where the patient was getting the treatment even if the patient was referred to the hospital and later died at the hospital. Despite of this the place where the patient was receiving treatment is a better proxy for the measure of place where the patient resides. If we were assessing quality of care, it would be best to document the place of death. For our analysis the many goal was not to measure the quality of clinical care at various levels of health care provision.

Although the scientific world has a clear picture of the burden of TB in rural and urban settings no studies have been conducted to assess the difference in TB treatment outcomes between rural and urban settings in Zambia and most parts of Sub-Sahara Africa.[1] To our knowledge there are no studies which have compared the incidence rates of TB between rural and urban settings in Sub-Sahara Africa. Under 3 specific aims we endeavored to address this gap in scientific knowledge. In the next passages we will summarize: 1) our main findings and conclusions from two interrelated studies; 2) what our findings contribute to science and public health and 3) Future direction of this research.

Main findings and conclusions

Specific Aim 1: To estimate and compare the risk of death between rural and urban settings in new TB patients treated for TB in Southern province, Zambia.

Major findings and conclusion

Achieving a high cure and completion rate of TB treatment remains a key target for the TB control program.[10] Cure and completion are regarded as successful treatment outcomes. [11] According to the WHO end TB targets every country must achieve 85% successful TB treatment outcomes per annum to be on track to achieving the TB elimination goal.[12] On the hand every TB program must aim at reducing death, lost to follow up and treatment failure.[12] These three outcomes of TB treatment are regarded as unfavorable TB outcomes.

In this study we evaluated the risk of unfavorable outcomes among TB patients treated in urban and rural settings of southern province in Zambia. Southern province is a predominantly a rural province with approximately 85% of the population living in the rural settings.[13]

We found that unfavorable outcomes occurred in 12% of the patients that were treated for the first episode of TB. This translates into 88% successful treatment outcomes which is higher than the target of 85% set by the WHO. Death occurred in 41% of the patients with unfavorable outcomes whereas 36% were lost to follow up and 22% failed treatment. Patients who were treated in the rural areas were 30% more likely to die or be lost to follow and fail treatment than the urban setting counter parts. The poor treatment outcomes in the rural settings may potentially be because of the suboptimal follow up of patients when they are on treatment. We conclude that unfavorable outcomes may have been influenced suboptimal community follow up of patients because of the higher loss to follow up in the rural population when compared to urban. Previous studies have shown that patients in rural areas were more likely to live far away from the health facilities and therefore present late to health and this creates a challenge in accessing health care.[14-16] Coupled with the issues of distance in the rural settings there are few qualified health workers and inadequate community structures to provide DOTs and follow up pf patients.

Another important finding under this aim was the longer duration in the time it took for some patients to get treatment after the diagnosis of TB. Delay was higher in the rural settings as compared to urban settings. Delay between diagnosis and start of treatment measures the efficiency of the TB program at the health facility level.[17] Again, this disparity in efficiency of the TB program may explain the difference in death, loss to follow up and default between rural and urban settings.

Public health implication

Public health implications of our findings are that methods for following up patients must use various approaches that are streamlined according to the setting to avoid treatment delay and maintain people on treatment until they successfully complete treatment or are cured. To address the disparity in the treatment outcomes between rural and urban settings programs must understand the population dynamics and the TB epidemiology of the different settings. With that knowledge delivery models for the TB control must be tailored to suit the local epidemiology and population dynamics. One size fits all approach will not result in achieving the TB elimination targets.

Specific aim 2: To estimate and compare the risk of death between rural and urban settings for recurrent TB patients treated with first line anti-TB treatment in Southern province, Zambia.

Major findings and conclusion

It is estimated that at least 13% of the cases reported to the WHO annually are recurrent cases of TB and among TB patients who are HIV seropositive recurrence can be as high as 20%.[18-20] In this study, we examined the prevalence of recurrent TB among TB cases notified to the National TB Program (NTP) in southern province of Zambia. We assessed for risk factors associated with death, loss to follow up and failure in rural and urban settings among recurrent TB patients. In this multi-center retrospective cohort of TB patients, the overall prevalence of recurrent TB was high in both rural (11.3%) and urban (15.3%) settings. Favorable treatment outcomes (cure plus completing treatment) were recorded in 90% of the urban cases and 84.3%

of the rural cases. Although the rate of favorable outcomes was high, a large proportion of cases (70.9%) had no bacteriological evidence of *M. tuberculosis* at the start of treatment to adequately support the diagnosis of TB. Most importantly we found that cases receiving treatment in rural settings were 70% more likely to die during the period of treatment when compared to patients treated in urban areas.

The prevalence of recurrent TB was generally high. This is similar to what is prevailing in other Sub-Sahara Africa settings.[19] However, the diagnostic capacity of this program was suboptimal to allow us to differentiate between recurrent drug sensitive TB and MDR-TB. It is critical to evaluate for drug sensitivity because patients who are treated for recurrent TB have a high risk of MDR-TB.[11] Having a definitive diagnosis and drug sensitivity results will assist clinicians to prescribe correct treatment. Otherwise, wrong treatment may result in MDR-TB patients living and transmitting resistant bugs for a longer period. Additionally, we could not differentiate between reinfection and relapse. A search for culture, microscopy and sensitivity results were in vain. If optimal treatment must be provided to these patients, there is a critical need by program managers and policy makers to invest in the laboratory services for the TB program.

Public health implication

Our findings raise the flag for a well-organized patient monitoring system such as effectively administered DOTs. Patient follow up and monitoring strategies must be tailored according to the setting that they are being implemented in. Use of modern technology such as mobile phones can help with the DOTs program. An improved DOTs program will not only help early detection of recurrent cases but improve clinical patient follow up and case management in the initial episode of TB. With good adherence we are likely to avoid recurrence and consequently MDR-TB. Patient follow up can take advantage of modern advances in technology such as use of mobile phones and video DOTS in addition to current strategies.[21,22] The follow up and monitoring of patients must be adapted to the setting.

A major weakness of our findings and the management of this TB control program is a lack of bacteriological confirmation of *M. tuberculosis* and drug susceptibility tests. These are critical for correct diagnosis and appropriate clinical management of recurrent TB. Highlighted in this paper is the low bacteriological confirmation of *M. tuberculosis* and the lack of culture and drug susceptibility testing. More effort is needed to ensure that every patient with recurrent TB has a bacteriological confirmation of *M. tuberculosis* and a drug susceptibility test especially with the wider use of rapid molecular assays such as Xpert MTB/RIF assay.[23]

Specific aim 3: To estimate and compare the incidence of TB disease among HIV patients receiving HAART in rural versus urban settings.

Major findings and conclusion

The incidence of TB is high among HIV patients even after the introduction of ART as compared to the general population.[24,25] We performed a retrospective cohort analysis of data for HIV patients on lifelong ART in Zambia to estimate the incidence of TB and assess factors associated with this incidence. The incidence of TB was high in both rural (1.9/1000PYO) and urban (2.6/1000PYO) settings. In the adjusted analysis there was a difference in the hazard of TB among HIV patients between rural and urban setting. An interesting finding was the high incidence of TB in the first year of starting ART. The incidence reduced over time and by the 5th of ART we did not have enough outcomes to calculate the incidence rate. The fact that there is no difference in the incidence of TB among HIV patients receiving cART in rural settings and those in urban settings has important public health consequences. In theory it is expected that the incidence rate of TB is higher in urban settings because of the high prevalence of both TB and HIV in urban settings and congested living conditions.[5] If incidence rate of TB among HIV patients in the rural areas remains as high as that in urban settings the prevalence of TB is likely to increase in rural settings as well. A high incidence of TB in rural settings is a problem to the TB control program because in rural settings the diagnostic and TB/HIV case management capacity is not adequately developed and prepared to handle large numbers of TB cases.

Public health implication

Based on the findings of high incidence rate of TB in both rural and urban settings more especially within the first year of starting ART we recommend to program managers in sub-Sahara Africa to develop effective strategies to fully implement intensified TB case finding in both rural and urban settings in HIV treatment clinics. Secondly, we strongly recommend implementation of screening for LTBI and treatment of LTBI using new short course therapy which have been shown to be effective in most settings where they have been tried.[26]

Contributions of this study to science

What was known before this study?

It was generally known and accepted that the burden of TB disease is higher in urban settings than rural settings due to overcrowding, high HIV prevalence and high occupational transmission in urban settings.[1] This scenario is true for most Sub-Sahara Africa countries but may be different in some other parts of the world especially high-income countries.[5] As result of better economic opportunities, infrastructure and other social amenities health care service delivery is better in urban than rural settings.[27] Although patient physician levels in both urban and rural settings are below the recommended standards, urban settings have more skilled health care providers with greater clinical experience in the management of TB and HIV and have better diagnostics. Additionally, health facilities are easy to reach while in rural settings, patients travel long distances to access usually poorly equipped and staffed health facilities.[5,6] In contrast, most TB patients in urban settings are from deprived communities and socially disadvantaged areas such as slums which may contribute to poorer anti-TB treatment outcomes.[5]

Incidence of TB in the general population in Sub-Sahara Africa is high as compared to other parts of the world.[28] Apart from the livings environment the health care system is not fully developed to promptly identify TB cases and LTBI and provide treatment thereby interrupting further transmission. [29,30] Efficacious drugs to treat TB disease and LTBI are available but require a very organized health care system because they are taken over a long period of time. It is

important to mention that most countries including Zambia has been achieving good treatment outcomes with the use of these drugs based on the TB treatment targets of having 85% successful treatment outcomes per annum.[28]

Except for the Africa region the incidence of TB has been declining globally. Even in the African region the increase in TB incidence has been rising less rapidly each year.[28] It is important to measure Incidence (cases arising in each time period) as it gives an indication of the burden of TB in a population, and of the size of the task faced by a national TB control program.[31]

It is known that the incidence of TB is higher in HIV seropositive individuals than in the general.[9]The incidence of TB is highest in the first few months after starting ART most probably because of immune reconstitution syndrome.[32] The incidence of TB in HIV seropositive patients is high because they have a higher probably of progressing from LTBI to active TB since their cellular immunity is impaired.[33] Screening for LTBI in this select population has been studied extensively.[34] Treatment of LTBI has been shown to prevent progression of LTBI to active TB in both HIV seropositive and HIV seronegative.[26] Unfortunately, most countries with a high dual burden of TB and HIV have not been fully implemented screening and treatment of LTBI including Zambia.

<u>What this study adds to science and public health</u>

This study is important to public health because before this study, it was not known whether TB treatment outcomes in urban setting were similar to TB treatment outcomes in rural settings in Zambia. It was always thought that since the burden of TB was higher in urban setting it is implied that urban settings had worse TB treatment outcomes than rural settings. This study shows results to the contrary. TB treatment outcomes were worse off in the rural setting for both new TB patients and recurrent TB patients than in urban setting. The main driver of the poor TB treatment outcomes was inadequate patient follow up approaches. Although our study did not endeavor to study community follow up of the patients who were treated for TB, it was observed that loss to follow up was higher in the rural settings than urban settings. A high

loss to follow up implies that the TB program in the rural setting did not have strong community TB control activities like the programs in urban settings. The DOTs program in rural is probably not be as well organized as the ones in the urban setting or may be organized on the same principles as the ones in the urban areas. However, because the demographics are different in the rural areas the rural DOTs program does not achieve the intended results. Although the numbers of patients may be smaller in the rural settings the challenges are unique and require special approaches tailored to rural settings.

Another potential reason for poorer TB treatment outcomes in rural areas when compared to urban setting was sub-optimal clinical management at rural health facilities. This is exemplified by the delay in starting TB treatment which was associated with rural health setting. This difference in delay of initiating TB treatment shows health system delay in the rural areas. In other words, it shows inefficiencies in health care management at rural health care facilities. However, in studying treatment outcomes we analyzed data from southern province of Zambia were over 85% of the population reside in rural areas. The question which arises from this analysis is: “Will we get similar results if we conducted this study in a different part of Zambia where the majority of the population reside in urbanized settings and the minority is found in rural settings?” This question needs further exploration. One thing which this study brings out is that it is important to understand the epidemiology of TB in terms of transmission and TB outcomes for different settings so that TB control programs can tailor the responses according to the setting.

Incidence of TB among HIV seropositive individuals on ART has been widely studied.[35-38] However, none of the studies looked at the difference in the incidence of TB between rural and urban areas. Our study showed that among HIV seropositive individuals the incidence of TB was not different between rural and urban settings. Our expectation was that the incidence will be higher in urban setting because of their being a higher prevalence of both HIV and TB. Surprisingly In both settings the incidence of TB was generally high and no different between

the 2 settings. It was highest in the first 6 months of ART. Perhaps the major reasons for the high incidence of TB in this population is immune reconstitution syndrome and missed diagnosis of TB at the beginning of ART which eventually get worse when the patients are on ART. In this program HIV seropositive patients were screened for TB disease using TB symptom screening algorithm but there was no screening for LTBI. If screening for LTBI was done most of the cases of TB would potentially be prevented.

Future directions

This study has 3 major finding which are potential areas of research and intervention:

1. A high risk of unfavorable TB treatment outcomes in the rural settings as compared to urban settings in southern province.
2. High incidence of TB among HIV seropositive patients receiving ART in Zambia more especially in the first year of treatment.
3. Poor laboratory diagnostic capabilities of the laboratory of the TB program. Although we did not set out to investigate this it was a major limitation in the management of patients being treated for recurrent TB and poses a high risk of missing MDR-TB.

Upon graduation from the PhD program the first and second key findings will form the focus of my public health work in TB and HIV research. Below, I briefly describe the overarching plan for each of the key finding as future focus areas.

Focus area 1: A high risk of unfavorable TB treatment outcomes in the rural settings as compared to urban settings in southern province.

The major factor that may be associated with a high rate of poor outcomes in rural settings is suboptimal follow up of TB patients and challenges in delivering treatment as close to the household as possible. Currently all community activities for TB patients are built on a standard DOTs approach. We will study models of implementing TB community activities and efficient methods of DOT using mobile technology such as phone reminders and video DOTs.

These approaches have been used in other settings with success and are less costly. Currently cell phone use and penetration has been growing at a rapid rate in both rural and urban settings of Sub-Sahara Africa.

Focus area 2: High incidence of TB among HIV seropositive patients receiving ART in Zambia more especially in the first year of treatment.

To address this gap in TB control we plan to develop studies and programs to strengthen screening for TB disease an approach known as intensified case finding and introduce screening for LTBI. To prevent progression of LTBI to active TB we will propose to treat LTBI infections within the HIV treatment clinics. Preventive therapy for LTBI has been shown to reduce incidence of active TB. However, this affective approach to TB control is not routinely implemented in TB endemic settings because of the challenges associated with treatment of LTBI. With develop of short course regimens for treating LTBI, we will propose to evaluate the effectiveness and feasibility of treating LTBI in an endemic setting using new short course regimens which have recently been approved by the WHO. This will form the first phase of my epidemiology and implementation science research work after graduating. From this we hope to develop models to deliver this efficacious intervention. In the second phase or the long-term goal of this intervention is to scale up screening of TB disease and LTBI among household contacts of TB cases. In all this we will strengthen intensified case finding and infection prevention procedures which are already being implemented. For the community component of this project we will be riding on the approaches already described above which include use of mobile technology such as mobile phone reminders and video DOTs.

Recommendations

Policy makers

These recommendations are for policy makers at national, region and global level.

1. Develop clear policy guidelines on screening and treatment of active TB – intensified case finding.

2. Mobilize adequate resources and have budget allocations for intensified case finding among HIV seropositive individuals receiving ART
3. Adopt LTBI screening using TST or IGRA and preventive treatment of LTBI using newly available short course regimens.
4. Advocate or negotiate with pharmaceutical companies for the reduction in the cost short course drugs particularly Rifapentine.
5. Develop guidelines for operational research for local program managers to understand the epidemiology of TB in their local setting.
6. Develop policy guidelines for the diagnosis of TB using modern laboratory techniques which can report culture results and drug sensitivity.

Program managers

1. Streamline implementation of intensified case finding in the HIV treatment clinics.
2. Develop LTBI screening and LTBI preventive treatment programs according to the prevailing national guidelines.
3. Conduct operational research to understand the population dynamics of the region they are operating in.
4. Develop community programs for follow up of patients such as video DOTS or DOTs based on the existing community structure such as local leadership structures.
5. Plan and purchase laboratory equipment to meet the current challenges of the NTP.

Researchers

1. Conduct research into models of delivering different TB control packages
2. Conduct research for short course acting active TB and preventive treatment of LTBI drugs.
3. Cheaper and faster laboratory methods for the diagnosis of TB.

TB control funding agencies

1. Mobilize resources for research into short course treatment regimens for TB disease and LTBI.
2. Mobilize resources Research into effective models for delivery of different packages of TB control.
3. Mobilize resources to provide laboratory services required for an effective control of TB and prevention of emergency of MDR-TB.

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