INFLUENCE OF HUMAN IMMUNODEFICIENCY VIRUS AND OTHER RISK FACTORS ON TUBERCULOSIS

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ABSTRACT

Introduction

Tuberculosis (TB) notification in South Africa has increased six fold over the last two decades mainly because of the Human Immunodeficiency Virus (HIV) epidemic. Globally, it was estimated that 73% of the TB cases were co-infected with HIV with more than 25% of this global co-infection burden being in South Africa alone. In 2012, globally 1.3 million deaths occurred due to TB; moreover 0.3 million were HIV-associated TB death. In 2010 TB was the leading cause of natural deaths in the population aged 15 to 24 years accounting for 14% of the total deaths in South Africa. In 2013 the proportion of patients with TB who were co-infected with HIV was extremely high at 62%. The outcome of co-infected patients was poorer than the outcome of HIV negative TB patients. However, there is little information available on the risk factors associated with TB treatment outcomes and the influence of co-infection.

Method

A cross sectional study analyzed Electronic TB Register (ETR.net) data from the Metro East Geographic Service Area (GSA) of the Cape Town Metro district. The dataset included adult patients aged 15 years or more, who initiated TB treatment between 1st July 2011 and 30th June 2012. In the descriptive analysis we analysed death separately but for the regression we merged death with unfavourable treatment outcome. Relative risks were used for measures of association. Univariate and multivariate analyses were performed using a generalized linear regression model. Statistically significant variables in the univariate analysis were included in the multivariate analysis.

Findings

TB case notification in Eastern GSA was 922 per 100 000 population. Of the 12672 TB patients registered, 50% were co-infected with HIV. The incidence of death in co-infected was 5% versus 3% in uninfected, treatment success 67% versus 73% and unfavourable treatment outcome 28% versus 24%. The Khayelitsha sub-district had the highest proportion of the TB burden (37%) and of co-infection (65%). Fourteen percent of patients had extra-pulmonary TB (EPTB), 66% of whom were co-infected with HIV.

In the multivariate analysis HIV (RR 1.2), retreatment (RR 1.4) and sputum smear microscopy not done (RR 1.4) were significantly associated with unfavourable treatment outcome. The sub districts Eastern
(RR 0.9) and Northern (RR 0.7) were less likely to develop unfavourable outcome compared to Khayelitsha.

In the stratified analysis, retreatment (RR 1.3) and smear not done (RR 1.3) were significant risk factors for an unfavourable treatment outcome in co-infected patients. Amongst HIV negative patients retreatment (RR 1.6) and smear not done (RR 1.6) were significant risk factors for an unfavourable treatment outcome.

Conclusions

The incidence of TB is extremely high in the Eastern GSA of Cape Town however the prevalence of co-infection varies across the sub-districts. Although treatment outcomes have been improving, co-infection, retreatment and smear microscopy not done pretreatment were factors significantly associated with an unfavourable treatment outcome. Eastern and Northern sub-districts were significantly more likely to have favourable treatment outcomes compared to Khayelitsha, where both TB incidence and HIV co-infection were greatest.
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PART A: PROTOCOL
INTRODUCTION

World Health Organization (WHO) reports show major progress in the reduction of Tuberculosis (TB) cases and deaths in the past 20 years [1]. Even though the Millennium Development Goals (MDGs) to halt and reverse the epidemic of TB by 2015 have been accomplished (new TB cases continued to fall in 2011 at a rate of 2%), the WHO cautions that the global burden of TB remains large. In 2013, there were 1.5 million deaths due to TB globally, 360 000 Human Immunodeficiency Virus (HIV) associated [2]. In 2010 TB was the leading cause of mortality in persons 15-24 years of age, accounting for 14% of all deaths, in South Africa [3]. In 2013 the WHO reported that 62% of TB patients were co-infected in South Africa [4]. Co-infected patients have poorer treatment outcomes than patients who are HIV negative. In 2011 the TB treatment success rate in co-infected patients was 73% and in HIV negative patients 87% [5]. However, there is little information available on the risk factors for outcomes in co-infected patients.

TUBERCULOSIS AND THE BURDEN OF TUBERCULOSIS

Definition and spread of Tuberculosis

TB is defined as an infectious disease caused by the bacillus Mycobacterium tuberculosis. It characteristically affects the lungs, in which case it is referred to as pulmonary TB (PTB). However in up to a third of cases it can affect other sites, in which case it is referred to as extra pulmonary TB (EPTB) [6, 7]. TB is commonly spread through the air when individuals with TB disease expel bacteria, for instance by coughing [7]. Many people acquire TB infection but a competent immune system usually keeps the infection under control in the lung and this is referred to as latent TB. Persons with latent TB are asymptomatic and not infectious [8]. However when the immune system is no longer able to keep the infection under control, active TB or TB occurs, with destruction of the lung. Symptoms include chronic cough, hemoptysis, lethargy, fatigue, loss of appetite, weight loss and night sweats. Patients with TB disease are infectious [9].

Global Tuberculosis burden

TB is one of the leading causes of morbidity and mortality in developing countries, and continues to be a major global health problem. Although much has been done to improve the incidence of TB, with the global rate of TB having decreased by 45% since 1990 [5], it is listed as the second cause of death from
an infectious disease globally, after HIV [5]. According to the World Health Organization (WHO) 2014 TB Report, in 2013 there were 9 million new cases of TB worldwide, with 1.5 million resulting deaths [2].

**Tuberculosis prevalence in South Africa**

TB incidence ranges substantially at country level, and the prevalence was more than 1000 cases per 100 000 in South Africa and Swaziland, and fewer than 10 per 100 000 in parts of America, Australia, Japan, New Zealand and several countries in Western Europe [5].

The TB epidemic has worsened in South Africa over recent times, and the country ranked 7th among the twenty-two high TB burden countries in 2007 and 1st in 2013 [10, 2]. In 2013, 328896 cases of TB were notified in South Africa, and the incidence of all types of TB was 860 per population of 100 000 [2]. The increasing severity of the TB epidemic has been attributed to a number of factors including the socio-environmental conditions such as poverty, poor education, overcrowding, inferior health services for the poor and the migrant labour system [11].

In 2009, 29,478 cases of TB were notified in the Cape Town Metro District and 51% were co-infected with HIV [12]. The incidence of TB varies across sub-districts. The Khayelitsha sub-district had the highest TB case notification and co-infection rates in 2005 whereas the Tygerberg sub-district a high TB notification rate but lower co-infection rate [13]. The TB notification rate in the Western Cape Province has been consistently higher than the rest of the country even though the per capita income is higher than the country average [14, 15, 16].

**TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS**

**HIV infection, AIDS and the spread of HIV**

HIV is most commonly spread via sexual intercourse, through blood or blood products (e.g. transfusions or needle stick injuries) and through vertical transmission from mother to child during pregnancy, delivery or through breast milk. Infection with HIV leads to destruction of the body's immune system resulting in opportunistic infections such as TB. When HIV infection is accompanied by severe opportunistic diseases, the affected person is said to have acquired immunodeficiency syndrome (AIDS) [17].
TB and HIV co-infection

An HIV-infected person has a 17-fold greater risk of developing TB disease compared to HIV negative individuals [12]. This may either be as a result of reactivation of latent infection or due to primary progression following infection [18]. Some studies have suggested that HIV-positive patients may be more prone to developing multi drug-resistant (MDR) TB due to malabsorption of rifampicin but this has not been confirmed [19]. In 2012, approximately 13% of the 8.6 million patients who developed TB were HIV co-infected, and 75% of these cases were in Africa [5].

TB HIV Co-infection in South Africa

South Africa has the largest HIV epidemic in the world. In 2012, there were 6.1 million persons living with HIV, with 240,000 AIDS-related deaths [20]. With over a quarter of the global burden of TB/HIV co-infection, South Africa bears the brunt of these two epidemics [21]. In 2013, the TB incidence rate in persons living with HIV was 520 per 100 000 and in the same year the mortality rate in co-infected persons was 121 per 100 000, more than double the rate of 48 per 100 000 in HIV negative persons in South Africa [4].

HIV co-infection is changing the epidemic of TB across the age groups, as the age distribution of TB disease parallels the age distribution of HIV disease in this population [12].

In 2013, 90% of the HIV related mortality occurring in women was in Africa. TB in HIV co-infected pregnant women increases the risk of maternal and infant mortality by nearly 300% [22]. In Africa the rate of TB 10 times higher in HIV infected women compared to HIV negative women. In South Africa HIV prevalence is higher in women particularly at younger ages and thus the incidence of TB is highest in women aged 15 to 24 years [23].

Diagnosis of Tuberculosis

The diagnosis of TB has traditionally been established by sputum smear microscopy in which stained smears of sputum specimens from TB suspects are examined microscopically. Sputum culture is a more sensitive test compared to sputum smear microscopy, but culture takes several weeks. There are many cases of smear negative culture positive TB [24]. This delays the initiation of treatment and leads to less favourable outcomes.
In the absence of positive bacteriology, clinical signs and symptoms, radiological examination of the chest and response to therapy have been used to diagnose TB. These are non-specific criteria and they may lead to either under or over diagnosis.

The standard of care is to test all patients with active TB for HIV [25]. This has been rapidly implemented in Africa. In 2004 only 4% of TB cases were tested for HIV, but this proportion had increased to 45% in 2008 [25]. From a programmatic perspective, to eliminate both the HIV and TB epidemics, there should be communication and good team work between the TB and AIDS control programs. The WHO introduced guidelines for symptom screening for the detection of TB, but the sensitivity was low, with 10% to 20% of cases being missed [26]. Sputum smear microscopy detected less than one in five cases when used as a screening tool pre-antiretroviral therapy (ART) in a resource-limited setting [26].

**TUBERCULOSIS TREATMENT OUTCOME**

The WHO classifies TB treatment outcomes into one of the six categories: completed, cured, failed, died, defaulted and outcome unknown [1]. The WHO estimates that a treatment completion rate of 85% and a case detection rate of 70% are required to have an impact on the TB epidemic.

Definitions:

- **Cure**: Patient who was smear/culture positive at the beginning of the treatment and is smear/culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior [7].

- **Treatment completed**: Patient who was smear or culture positive at the beginning and has completed treatment but does not have a negative smear/culture in the last month of treatment and on at least one previous occasion more than 30 days prior. The smear examination may not have been done or the results may not be available at the end of treatment [7].

- **Treatment success**: TB treatment success includes both treatment completion and cured [7].

- **Treatment default**: Patient whose treatment was interrupted for two consecutive months or more during the treatment period [7].
- **Treatment failure**: Smear/ culture positive patient who remains or is again smear-positive at 5 months or later during treatment. This definition also includes those patients who are diagnosed with MDR-TB during treatment [7].

- **Died**: A person died because for any reason during TB treatment [7].

- **Unfavourable treatment outcome**: Unfavorable treatment outcome include treatment default, treatment failure and death.

**Tuberculosis Treatment Outcome in HIV Positive and HIV Negation Populations**

The treatment of patients co-infected with HIV requires both anti-TB and ART that have to be taken concurrently. The main challenges are the high pill burden and adherence, drug interactions and synergistic side effects, and immune reconstitution inflammatory syndrome (IRIS). The regimens for TB treatment have different outcomes for HIV positive and HIV negative patients [27].

TB disease has a negative impact on HIV by increasing the risk of HIV-related morbidity and mortality [28]. TB disease increases the replication of HIV cell lines and activation of mononuclear cells, increasing susceptibility to infection, the progression of HIV infection and decreasing the time to AIDS [29]. Studies have revealed that TB impacts on HIV viral load and co-infected patients have viral loads significantly higher than persons with HIV who are not co-infected with TB [29].

Some studies have shown that outcomes are poorer in co-infected persons in terms of mortality [30, 31]. A study from Toronto showed a high treatment failure rate (36%) in co-infected patients and HIV was an independent factor for not completing TB treatment [32]. Another study from Nigeria found a treatment failure rate 27% in HIV co-infected patients compared to 19% in HIV negative patients [33]. Study from South Africa has shown that outcomes of co-infected patients receiving ART during TB treatment were similar to those of HIV-negative patients [34]. However study from India has suggested that treatment outcomes are better in co-infected persons [35]. Further research is required to identify the influence of HIV on TB treatment outcomes.

**RESEARCH QUESTION**

To identify the distribution of HIV and other risk factors among TB patient and their influence on TB treatment outcome
OBJECTIVES

Primary objective is to describe the characteristics of TB patients according to the following variables:

- Demographics
- HIV status
- Tuberculosis Treatment outcome
- Patient registration type (new versus retreatment)
- Disease classification pulmonary, extra pulmonary or both
- Sputum smear microscopy results

The secondary objective is to identify risk factors associated with TB treatment outcomes stratified by HIV status.

METHODS

STUDY DESIGN

This will be a cross sectional study using quantitative research methods and data from the Electronic TB Register (ETR.net). The ETR.Net is an electronic register that monitors all persons treated for TB at public sector health facilities. The register is prospectively completed as the person progresses through their course of TB treatment. The register contains the following information: date of treatment initiation, basic demographics, previous TB treatment, bacteriological test results at initiation, 2 months, 3 months, at completion of treatment. In some facilities data is entered by the clerks manually and the information is then transferred to ETR.Net by data capturers while at other clinics the data are entered directly onto the electronic register. This information is used to generate standard cohort reports and provide data on the quality of services so that the TB strategy and program can be monitored and evaluated.

STUDY SETTING

Data from ETR.net of persons initiated on TB treatment between 1st July 2011 and 30th June 2012 will be analyzed. The district of Cape Town is divided into two Geographic Service Areas (GSAs), East and West. Data for the Metro East GSA will be analyzed in this project. Metro East GSA includes Eastern, Khayelitsha, Northern and Tygerberg sub-districts.
POPULATION

The population will be any person aged 15 years or more who is placed on TB treatment from 1st July 2011 to 30th June 2012 at public sector TB services in Metro East GSA of Cape Town and who is registered on ETR.net for TB treatment initiation.

DEFINITIONS

There are a number of definitions relating to persons with TB in the ETR.net system as per the guidelines for the National TB Control Program [7]. These are:

- Transfer in: a case transferred from outside the metropolitan area.
- Moved in: a case transferred from a facility within the metropolitan area.
- New case: a patient who has never had treatment for TB or who has taken anti-TB drugs for less than four weeks.
- Re-treatment case: a patient who has taken treatment for TB before and either relapsed, defaulted or had treatment failure.
- Treatment after failure: a pulmonary TB patient who is still sputum smear positive at the end of the treatment period.
- Treatment after default: a patient who completed at least one month of treatment and returns after having interrupted treatment for two months or more but still with active TB as judged on clinical and radiological assessment.
- Smear positive pulmonary TB: a direct sputum smear was positive on one or more occasion.
- HIV-status: Patients were defined as HIV-positive if results of positive HIV serology were recorded in the TB register or if the patient was recorded to be currently receiving antiretroviral therapy or co-trimoxazole prophylaxis.
- HIV-negative status was defined by a recorded HIV-negative serology result.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

- Age greater than or equal to 15 years.
- Known HIV status.
- Initiation on TB treatment between 1 July 2011 and 30 June 2012.
• Patient on regime 1 or 2.

**Exclusion Criteria**

• Age less than 15 years.
• Patients not on regimen 1 or 2.
• Patients initiated on treatment before 1 July 2011 or after 30 June 2012.
• Unknown HIV status.
• Transfer in and Moved in
• Transferred out and Moved out

**STUDY SIZE**

The Metropolitan District (City of Cape Town) is divided into two Geographic Service Areas (GSA), each comprising of 4 sub-districts. All TB patients from the Eastern GSA placed on TB treatment from 1 July 2011 and 30 June 2012 will be included.

**SAMPLE SIZE**

In order to calculate the sample size for this study we anticipated the prevalence of TB with known HIV status was 50%.

Anticipated population proportion (p): 50%

For 95% CI: \( z = 1.96 \)

Desired precision (d) 5%

\[
n = \frac{p(1-p)z^2}{d^2} = \frac{0.50(1-.50)1.96^2}{0.05^2} = 384
\]

**DATA MANAGEMENT**

All data from the electronic TB register will be cleaned by the principal investigator under the supervision of the supervisor. The data is captured in Microsoft Excel program. The selected variables will be analyzed according to treatment outcome (treatment success versus unfavourable treatment outcome) as defined above. The following variables will be included in the analysis:

1. Age
2. Gender
3. HIV status
4. Sub district level
5. Patient category
6. Disease classification
7. Sputum smear microscopy and culture results
8. Treatment outcome

QUALITY CONTROL

All the data will be cleaned and double checked by the principal investigator and rechecked by the supervisor to ensure the accuracy of data.

STATISTICAL ANALYSIS

Data will be exported from Microsoft Excel 2010 into STATA version 12.1 (StataCorp Inc, College Station, Texas, USA) for analysis. Pearson’s χ² statistics will be used for the comparison of categorical variables, and a P-value of < 0.05 will be considered statistically significant in all analyses. Relative risks will be used for measure of association and univariate and multivariate analyses will be performed by generalized linear regression model. All significant variables in the univariate analysis will be included in the multivariate analysis. The contribution made to the model by each variable will be evaluated using likelihood ratio χ² tests.

STRENGTHS AND LIMITATIONS OF THE STUDY

Strengths

The major strength is the large database from an area with a high incidence of TB and varying prevalence of HIV. HIV status was confirmed from clinical records rather than self-reported and therefore the accuracy of the data was likely to be good.

Limitations

A major limitation may be missing or incomplete data and this could affect the power of the study. This is a secondary analysis of data already collected and the principal investigator will not be allowed to
trace missing information from the primary clinical records. In addition there may have been recording and data capturing errors that the principal investigator will not be able to correct.

ETHICS AND COMMUNICATION

ETHICAL CONSIDERATIONS

Ethics approval for analysis of data from the electronic TB register will be obtained from the Health Sciences Human Research Ethics Committee at the University of Cape Town. The names and addresses of all participants will have been removed from the data base before the study is conducted.

DISSEMINATION OF RESULTS

These results will provide important information on characteristics associated with the treatment in co-infected patients compared to those who are HIV negative. These results will be presented at the Provincial Research Day and will provide important information for the managers of Metro East GSA that can be used to inform decisions regarding the treatment for patients with TB.

PROJECT MANAGEMENT

Data will be cleaned and analyzed, as soon as ethics approval is obtained from the Health Sciences Human Research Ethics Committee at the University of Cape Town.

BUDGET

No budget is requested.

REFERENCES


PART B: LITERATURE REVIEW
INFLUENCE OF HUMAN IMMUNODEFICIENCY VIRUS AND OTHER RISK FACTORS ON TUBERCULOSIS

OBJECTIVES OF LITERATURE REVIEW

The objectives of this literature review are:

- To explain the overview of Tuberculosis (TB).
- To describe the burden of TB, globally and in South Africa.
- To explain the relationship between TB, the human immunodeficiency virus (HIV) and other risk factors.
- To discuss factors related to TB treatment outcome.
- To discuss TB treatment success and unfavourable outcomes in HIV positive and HIV negative patients.

LITERATURE SEARCH STRATEGY

The platforms used to search the literature in this study were Internet search engines Google Scholar, the electronic journal databases of the University of Cape Town, as well as PubMed. The keywords used included burden of TB; prevalence of TB; TB and HIV, TB and HIV co-infection; TB screening; TB diagnosis; TB treatment; smear positive and negative TB; TB treatment outcomes and HIV. The search was limited to drug sensitivity TB.

LITERATURE REVIEW

BACKGROUND

World Health Organization (WHO) reports show major progress in the reduction of TB cases and deaths in the past 20 years [1]. Even though the Millennium Development Goals (MDG) to halt and reverse the epidemic of TB by 2015 have been accomplished (new cases of TB continue to fall, in 2011 at a rate of 2%), the WHO cautions that the global burden of TB remains large. In 2013, there were 1.5 million deaths due to TB globally, 360 000 HIV associated [2]. In 2010, according to South African data TB was the leading cause of death in persons 15 to 24 years of age, accounting for 14% of all deaths [3]. In 2013 the WHO reported that 62% of TB patients were co-infected in South Africa [4]. Co-infected patients have poorer treatment outcomes than patients who are HIV negative. In 2011 the treatment success rate in co-infected patients was 73% and in HIV negative patients 87% [5]. The reasons could be that HIV
co-infected patients are different; EPTB is 20-70% more common in HIV co-infected therefore it is less likely to be diagnosed at an early stage and the sensitivity of the smear microscopy is lower. HIV positive patients have a greater risk for re-infection or reactivation of TB disease. This literature review discusses the epidemic of TB and HIV co-infection in countries with a high prevalence of HIV, the socio-demographics of persons placed on TB treatment and factors associated with poor treatment outcomes.

**TUBERCULOSIS**

TB is caused by the bacillus Mycobacterium tuberculosis. It characteristically affects the lungs; however in a third of cases it also affects other sites. TB is spread through the air when individuals infected with pulmonary TB (PTB) expel bacteria, for instance by coughing [6, 7]. The acquisition of TB infection is very dependent on the closeness of contact with an infectious person, and the major determinants of TB are poverty, malnutrition, a compromised immune system and overcrowding [8].

TB can also be classified according to the organ involved. PTB refers to disease involving the parenchyma of the lung and extra Pulmonary TB (EPTB) refers to TB of organs other than the lungs [9].

**HIV INFECTION AND AIDS**

HIV is spread via sexual intercourse, through blood or blood products (e.g. transfusions or needle stick injuries) and through vertical transmission from mother to child during pregnancy, delivery or through breast milk. HIV infection may lead to destruction of the body’s immune system, resulting in the development of severe infections and conditions, to which people without HIV usually would not normally be susceptible. When accompanied by severe opportunistic conditions, the affected patient is said to have acquired immunodeficiency syndrome (AIDS) [10].

**TB AND HIV**

Globally TB is the most common opportunistic infection in HIV-infected persons. TB disease has a negative impact on HIV, increasing the risk of HIV-related morbidity and mortality [11] through the increased replication of HIV cell lines and activation of mononuclear cells, increasing susceptibility to infection and progression of HIV infection and decreasing the time to AIDS [12]. Studies have revealed that TB impacts on HIV viral load and co-infected patients have viral loads significantly higher than persons with HIV who are not co-infected with TB [12].
HIV infection affects the microbiological and clinical presentation of TB in several ways. Co-infected patients tend to have paucibacillary TB or lower micro-bacterial colony counts compared to HIV negative patients [13]. This reduction in micro-bacterial count makes the diagnosis of TB by smear microscopy more difficult among co-infected persons [13]. For this reason TB culture has been recommended for diagnosis in co-infected persons [13]. In areas where GeneXpert, a cartridge-based, automated point of care diagnostic test that identifies TB through nucleic acid amplification, has been introduced, this is no longer necessary.

In HIV positive populations, there was a 17-fold increased risk of developing TB disease compared to HIV negative individuals [14]. This may either be as a result of reactivation of latent infection or due to primary progression following infection [15]. Some studies have suggested that HIV-positive patients may be more prone to developing MDR TB due to malabsorption of rifampicin but this has not been confirmed [16].

Approximately 13% of the 8.6 million patients who developed TB worldwide in 2012 were co-infected with HIV, and 75% of these cases were in Africa [5]. In South Africa the initiation of ARVS has decreased the risk of TB disease [17] and thus earlier initiation of ARVs is recommended [18].

GLOBAL EPIDEMIOLOGY OF TUBERCULOSIS AND HIV COINFECTED

Although the incidence of TB disease has decreased in the world since 1990, particularly in developed countries, it remains one of the leading causes of morbidity and mortality in developing countries. TB is the second primary cause of death from an infectious disease globally, after HIV [5].

There is disparity in incidence of TB disease across countries, with 80% of the global TB burden occurring in twenty-two high-burden countries [2]. In 2013 the Western Pacific and South-East Asia collectively accounted for 56% of the global TB burden, with the African Region accounting for over a quarter of TB cases worldwide [2]. TB has been called the disease of poverty and it tends to occur where there are high levels of poverty, weak health systems due to a lack of funds and human resources or precarious political systems [19].

According to the 2014 WHO Global TB Report, in 2013 there were 9 million new cases of TB worldwide, resulting in 1.5 million deaths. AIDS is a comparatively new disease known to man and HIV has spread globally with alarming efficiency. In 2013, approximately 35 million people were living with HIV globally,
and 2.1 million new infections occurred in 2013. In the same year nearly 1.5 million people died due to AIDS-related illness [2].

In 2013 approximately 360,000 death occurred due to HIV-associated TB and 25% of deaths among HIV infected people were due to TB. In the same year there were nearly 1.1 million new TB cases co-infected with HIV, 78% of them were living in Africa [2].

**EPIDEMIOLOGY OF TUBERCULOSIS AND COINFECTION WITH HIV IN SOUTH AFRICA**

In many developing countries the TB epidemic has worsened. South Africa ranked 1st in 2013 among the 22 highest TB burden countries, compared to 7th in 2007 [2, 20]. From 1986 to 2006 there was a fourfold increase in TB notification from 163 cases/100,000 to 628 cases/100,000 populations [21]. In 2013, 328,896 cases of TB were notified in South Africa, and the incidence of all type of TB was 860 per population of 100,000 [2].

South Africa has the largest HIV epidemic globally and in 2012, about 6.1 million people were living with HIV and 240,000 deaths occurred [22]. With around a quarter of the global burden of TB/HIV co-infection, South Africa bears the brunt of these two epidemics [23]. In 2013, TB incidence rate in persons infected with HIV was 520 per 100,000 in South Africa and mortality rate in co-infected persons was 121 per 100,000, more than double the rate of 48 per 100,000 in HIV negative persons [4].

Many people live in poor social and economic circumstances in South Africa. The country is undergoing rapid urbanization [24], with migration to the cities where the poor lived in crowded informal settings where the prevalence of HIV and incidence of TB rates are high [25].

**EPIDEMIOLOGY OF TUBERCULOSIS AND COINFECTION WITH HIV IN THE WESTERN CAPE**

Cape Town is the capital of the Western Cape Province and is a diverse city with approximately 3.7 million residents, many of whom live in poor socio-economic conditions [26]. In 2009, 29,478 cases of TB were notified in the City of Cape Town and 51% were co-infected with HIV [15]. The incidence of TB varies across sub-districts in the City of Cape Town. The Khayelitsha sub-district had the highest TB case notification and co-infection rates in 2005 whereas the Tygerberg sub-district had a high TB notification rate but the lowest co-infection rate [27]. The TB notification rate has been consistently higher in the Western Cape Province compared to other provinces of the country even though the per capita income is higher than country average [28, 29, 30]. Risk factors for TB in the province are many, and studies
combining in-depth anthropological interviews and molecular epidemiology in a high incidence area in the Western Cape, characterized by economic depression and overcrowding, proved that TB was not predominantly transmitted in households [31]. In these areas, social drinking was a prominent leisure activity, and 74% of TB patients drank for about 30 hours per week [31]. This study showed that transmission mostly occurred in informal bars where large amounts of alcohol were consumed. Other studies have also confirmed that this type of socializing with consumption of large amounts of alcohol may contribute to the transmission of TB [32]. The incidence of TB is exceptionally high in the coloured population of Western Cape however the reasons for this are uncertain [33].

RISK FACTORS FOR TUBERCULOSIS AND COINFECTION

Surveillance and research show that the TB burden varies with age. The burden of TB is highest in children under 5 years of age, as this age group is more prone to developing active disease once they are infected (primary TB) [34]. Infection is usually from contact with adults who have TB disease in their households. Children 5 to 14 year of age range are at lower risk, with the risk increasing after 14 years of age with a high burden in adolescents and young adults. The incidence of TB decreases after the age of 35 years in populations with a low prevalence of HIV, and increases once again in the elderly [34].

HIV co-infection is changing the epidemic of TB across the age groups, as the age distribution of TB disease parallels the age distribution of HIV disease in these populations [15]. Among HIV negative individuals from the City of Cape Town there were three peaks in the TB notification rate namely 511, 553, and 628 per 100,000 among 0-4, 20-24, and 45-49 year olds, respectively [15]. TB notification rates among HIV positive individuals were dramatically higher than rates among HIV negative individuals in each age group [15].

Under notification is frequently cited as a factor associated with the disproportionate burden of TB disease among males after childhood in many low- and middle-income countries. Under notification of females is commonly associated with barriers that decrease access to care for females such as lack of access to finances, legal rights, education, lower social status [35], lower prioritization of health [36], feelings of embarrassment or shame [37], and TB clinics being inaccessible by foot [38]. In addition, findings show that certain genetic polymorphisms increase male susceptibility to TB [39, 40]. Mice studies also found that testosterone treatment increased susceptibility to M.marinum and M.intracellulare [41, 42] while oestrogen treatment reduced susceptibility to M.avium [43]. Lastly, males engage in more social interactions than females in some settings, increasing their risk of TB exposure.
and subsequent development of TB disease [44]. All of these factors may explain why adolescent and adult males have a higher burden of TB disease than females in the majority of low and middle income countries who reported sex differences related to TB disease.

In 2013, 90% of the HIV related mortality occurred in women in Africa. TB in HIV co-infected pregnant women increased the risk of maternal and infant mortality by 300% [45]. In Africa the TB rate was 10 times higher in HIV infected women compared to HIV negative women. In South Africa the prevalence of HIV is higher in women particularly at younger ages and the incidence of TB is highest in women aged 15 to 24 years [46].

**DISEASE CLASSIFICATION**

EPTB is more common in HIV co-infected patients and studies show that EPTB occurs in 20 to 70% of co-infected persons with TB [47 48, 60]. According to the WHO report EPTB is more common in HIV co-infected patients than PTB, and having both EPTB and PTB is strongly suggestive of HIV infection. The WHO clinical staging of AIDS classifies EPTB as AIDS defining or stage 4 [49].

**DIAGNOSIS OF TUBERCULOSIS IN SOUTH AFRICA**

According to 2013 WHO global report, 40% of new cases of TB in South Africa was sputum smear positive, 21% were smear negative and in 24% of cases the smear status was unknown and 14% were EPTB [5]. The lower than expected percentage of smear positive patients may be due to HIV-co-infection [50, 51]. Some studies showed that the sensitivity of smears may be as low as 20% in co-infected populations [52].

Prior to the HIV epidemic smear negative TB was more common in children and the elderly and was considered minimal cavitary disease therefore the association of smear negative implied with low infectivity and mortality. Infectivity is unaffected by HIV status but the mortality rate is fourfold higher in co-infected smear negative TB patients compared to HIV negative smear negative patients [53]

**RETREATMENT CASES**

The risk of re-infection or reactivation of the disease is greater in HIV-positive persons although ART decreases the risk of developing TB disease. Studies show that retreatment in HIV negative population is mainly due to poor adherence to treatment whereas reinfection is the commonest reason of retreatment in HIV positive people on ART [54]
FACTORS ASSOCIATED WITH TUBERCULOSIS TREATMENT OUTCOME

The WHO classifies TB treatment outcome into one of the six categories: completed, cured, failed, died, defaulted and outcome unknown [1]. The WHO estimates that a treatment completion rate of 85% and 70% case detection rate is required to have an impact on the TB epidemic [2].

According to South African National TB Guidelines, TB treatment success includes both treatment completion and cured. Therefore the rate of treatment success is the percentage of both new and retreatment TB cases that were registered under a national TB control programme in a given year that completed the treatment successfully, with or without bacteriological confirmation of success [55].

A study from India showed that treatment success was similar in TB patients who were HIV co-infected and those who were not. This might be due to better services for those who are HIV-infected, more integrated and holistic care and the ART adherence support programme. Awareness programmes have also provided co-infected patients with knowledge about their health [56].

A study from Toronto showed a high treatment failure rate (36%) in co-infected patients and HIV was an independent factor for not completing TB treatment [57]. Another study from Nigeria found a treatment failure rate of 27% in HIV co-infected patients compared to 19% in HIV negative patients [58]. A study from South Africa showed that outcomes of co-infected patients receiving ART during TB treatment were similar to those of HIV-negative patients [59].

Treatment outcomes are better in persons with PTB compared to those with EPTB. As EPTB may be more difficult to diagnose there may be a delay in the initiation of treatment. Diagnosis at a later stage often leads to a less favourable treatment outcome. Moreover, specialist care may be required for diagnosis and treatment of EPTB and this may not be widely available [60]. A study from Pakistan showed that the cure rate of EPTB was 41%, and there was no difference between the sexes [61]. A study from Thailand showed that 19% of co-infected persons with EPTB died compared to 16% of co-infected died with PTB [62].

A study from Malawi showed that 35% of smear-negative PTB patients completed treatment compared to 72% of smear positive patients. In addition mortality was higher in smear negative patients. It was not clear whether this was due to HIV co-infection [63]. Another study showed that smear negative TB was associated with hospitalization and there was a greater delay in treatment initiation in smear negative
patients [64]. Another study showed that HIV co-infected TB patients with positive smears were more likely to have an unfavourable treatment outcome [65].

A Ugandan study that enrolled a cohort of 105 male and 109 female co-infected adults with culture confirmed TB identified favourable outcomes as those who were cured or alive and unfavourable outcomes as those not cured or dead. At the end of one year of follow-up there was no difference in the likelihood of experiencing a favourable outcome in men and women (RR 1.02, 95 CI 0.89-1.17) [66].

A study conducted in Agincourt, a rural area in South Africa, from 1992 to 2000 reported higher mortality in co-infected men than women of all ages (RR=2.48, 95% CI 1.53-4.04) [67]. However mortality was significantly higher in men over 25 years of age. The median age of death in co-infected men was 38 years.

A study in Ghana reported that increased age, sputum smear-negative disease, residence in a rural area, prolonged duration of symptom prior to initial diagnosis and defaulting treatment was associated with TB mortality in HIV-infected persons [68]. However a study from Madagascar found no association between age and defaulting treatment [69].

A case control study in Kenya showed that poor knowledge on TB (OR 8.67), low income (OR 5.57), alcohol abuse (OR 4.97), previous default (OR 2.33), co-infection with HIV (OR 1.56) and male sex (OR 1.43) were strongly associated with an unfavourable treatment outcome [70].

Treatment related factors that affect outcomes include the side effects of anti-TB medications. Furthermore as treatment is for at least 6 months, patients tend to default once they start feeling better [71, 72].

Co-infected patients may also experience side effects due to the interaction of TB and HIV medications. Studies show that it is important to treat co-infected patients holistically at integrated services [70, 73]. This will also ensure that any side effects due to the combination of HIV and TB treatments can be monitored closely and that patients are made aware of possible side effects and be supported and encouraged, in particular with regard to the high pill burden [74].
TUBERCULOSIS TREATMENT OUTCOMES IN SOUTH AFRICA

The treatment success rate has increased in South Africa since the introduction of the Directly Observed Therapy (DOT) program in 1996 [75]. In 2013, the treatment success rate was 86% globally and the success rate in South Africa increased to 77% in 2013 from 58% in 1995 [2].

In South Africa there has been an increase in the proportion of TB patients who die on treatment from 6.5% in 2000 to 7.2% in 2009 [76]. According to the South Africa WHO country specific report, in 2013 the mortality rate in HIV negative persons with TB was 48 per 100 000 and in co-infected it was 121 per 100 000. This is supported by evidence from several studies reporting higher mortality in co-infected patients [59, 77, 78]. Mortality rates are particularly high in co-infected persons who have a low CD4 cell count when initiated on ART [79].

CONCLUSIONS

In developing countries TB is still one of the leading causes of morbidity and mortality. The HIV epidemic has had a negative impact on the TB epidemic. Countries like South Africa with a high prevalence of HIV are now facing a dual epidemic with less favourable outcomes due to synergism between these two diseases. HIV-positive patients have a much greater risk of developing TB disease and HIV is one of the major factors responsible for the dramatic increase in the TB epidemic.

The distribution of TB with respect age and sex has changed due to high burden of co-infection. TB is commoner in younger women as they are more prone to HIV. TB is more difficult to diagnose in co-infected patients due to low sensitivity of sputum smear microscopy, asymptomatic clinical presentation and the higher incidence of EPTB. GeneXpert has been introduced in most parts of South Africa and this will provide a more rapid diagnostic test with greater sensitivity.

In terms of treatment outcome, studies showed higher mortality in co-infected patients due to the interaction of these two diseases, a more compromised immune system or late initiation of treatment due to atypical presentation of TB and a high prevalence of smear negative TB and EPTB.

Studies on treatment outcomes were controversial with many studies showing poorer outcomes in co-infected patients while some showed no difference. Further research is required to identity risk factors associated with poor TB outcomes in persons co-infected with HIV.
REFERENCES


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PART C: MANUSCRIPT

INFLUENCE OF HUMAN IMMUNODEFICIENCY VIRUS AND OTHER RISK FACTORS ON TUBERCULOSIS

Journal formatted according to the guidelines required for Bulletin of the World Health Organization.

Variations from journal requirements: For the purpose of dissertation submission, tables and figures are inserted in the text of the manuscript rather than appended at the end of the manuscript.
INFLUENCE OF HUMAN IMMUNODEFICIENCY VIRUS AND OTHER RISK FACTORS ON TUBERCULOSIS

Sana Mahtab

ABSTRACT

Objective: To assess the effect of Human Immunodeficiency Virus (HIV) and other factors on tuberculosis (TB).

Method: A cross-sectional study was used to analyze data from the Cape Town Metro East Geographic Service Area (GSA) Electronic TB Register (ETR.net) including adult patients aged 15 years or more, who initiated TB treatment between 1st July 2011 and 30th June 2012.

Findings: TB case notification in East GSA was 922 per 100,000 population, of the 12672 TB patients registered, 50% were co-infected with HIV. The incidence of death in co-infected patients was 5% versus 3% in HIV-negative patients, treatment success 67% versus 73% and unfavourable treatment outcome 28% versus 24%. The Khayelitsha sub-district had the highest proportion of TB burden (37%) and co-infection (65%). Fourteen percent of patients had extra-pulmonary TB (EPTB), 66% of whom were co-infected with HIV.

In the multivariate analysis HIV (RR 1.2), retreatment (RR 1.4) and sputum smear microscopy not done (RR 1.4) were significantly associated with unfavourable treatment outcome. The Eastern (RR 0.9) and Northern (RR 0.7) sub-districts were less likely to have unfavourable outcomes compared to Khayelitsha.

In the stratified analysis retreatment and smear not done were significant risk factor for an unfavourable treatment outcome in both co-infected and HIV-negative patients.

Conclusion: The burden of both TB and co-infection was high in this community although HIV prevalence varied. Mortality was higher and treatment completion lower in co-infected patients. Co-infection, previous TB treatment and smear not done were significant risk factors for an unfavourable outcome in all patients.
INTRODUCTION

The HIV epidemic in Africa has not only dramatically increased TB incidence in this region, but also increased the TB mortality rate. Co-infected patients are also more likely to die from TB although is a curable disease in HIV-negative patients [1]. The unfavourable treatment outcome rate for HIV-positive PTB patients in some African countries is now as high as 20% for sputum smear positive cases and 50% for sputum smear-negative cases [2, 3]. Deaths from TB represent a significant indicator of the severity of the effect of HIV on tuberculosis epidemiology [1]. EPTB is 20-70% more common in HIV positive patient which also have a risk for factor for unfavourable outcome [4].

In 2013, there were 1.5 million deaths due to TB globally, 360 000 Human Immunodeficiency Virus (HIV) associated [5]. Globally TB is the most common opportunistic infection in HIV-infected patients, due to the compromised immune system. In HIV positive populations, there was a 17-fold increased risk of developing TB disease compared to HIV negative individuals [6]. TB disease has a negative impact on HIV increasing the risk of HIV-related morbidity and mortality [7] through the increased replication of HIV cell lines and activation of mononuclear cells, increasing the progression of HIV infection and susceptibility to other infections and decreasing the time to AIDS [8].

The increased mortality rate of TB patients in high HIV prevalence populations in Africa may change the general perception of TB as a curable disease and threaten the reputation of TB programme. This may have an adverse influence on the willingness of TB suspects to come forward for diagnosis and completing TB treatment [1].

In 2010, according to South African data TB was the leading cause of death in persons 15 to 24 years of age, accounting for 14% of all deaths [9]. In 2013 the WHO reported that 62% of TB patients were co-infected in South Africa [10]. Co-infected patients have poorer treatment outcomes than patients who are HIV negative. In 2011 the treatment success rate globally was 73% in co-infected patients and 87% and in HIV negative patients [11]. In 2013, the incidence of TB in persons co-infected with HIV was 520 per 100 000 in South Africa and mortality was 121 per 100 000, more than double the rate of 48 per 100 000 in HIV negative persons [10].
METHODS

Study design

A cross-sectional study was conducted using quantitative research methods on data from the Electronic TB Register (ETR.net). The ETR.Net is an electronic TB register that monitors all persons treated for drug-sensitive TB at public sector health facilities. The register is prospectively completed as the person progresses through their course of TB treatment. The register contains the following information: date of treatment initiation, basic demographics, previous TB treatment, laboratory test results at initiation, at 2 or 3 months, and at completion of treatment, and HIV status. In most facilities, this information was collected in a paper TB register and then transferred to ETR.Net at sub-district level. This information is used to generate standard reports and provide data on the quality of services so that the TB strategy and program can be monitored and evaluated.

Study Setting

The district of Cape Town is divided into two Geographic Service Areas (GSAs), Metro East and Metro West. Data for the Metro East GSA was analyzed in this project. Metro East GSA includes Eastern, Khayelitsha, Northern and Tygerberg sub-districts.

Population

The study population included persons aged 15 years or more, placed on TB treatment regimens 1 or 2, at public sector TB services in Metro East GSA of Cape Town and who were registered on ETR.net for TB treatment initiation from 1st July 2011 to 30th June 2012. This study only included participants whose HIV status was known.

Ethical approval

Ethics approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town. The names and addresses of all participants were removed from the database before the study was conducted.

Objectives

The primary objective of the study was to describe the socio-demographic and outcome characteristics of TB patients. The secondary objective was to identify risk factors associated with TB treatment outcomes stratified by HIV status.
**Tuberculosis treatment outcome**

The WHO classifies TB treatment outcomes into one of the six categories: completed, cured, failed, died, defaulted and outcome unknown [5].

**Definitions:**

- **Cure:** Patient who was smear/culture positive at the beginning of the treatment and is smear/culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior [5].

- **Treatment completed:** Patient who was smear or culture positive at the beginning and has completed treatment but does not have a negative smear/culture in the last month of treatment and on at least one previous occasion more than 30 days prior. The smear examination may not have been done or the results may not be available at the end of treatment [5].

- **Treatment success:** TB treatment success includes both treatment completion and cured [5].

- **Treatment default:** Patient whose treatment was interrupted for two consecutive months or more during the treatment period [5].

- **Treatment failure:** Smear/culture positive patient who remains or is again smear-positive at 5 months or later during treatment. This definition also includes those patients who are diagnosed with MDR-TB during treatment [5].

- **Died:** A person died because for any reason during TB treatment [5].

- **Unfavourable treatment outcome:** Unfavorable treatment outcome include treatment default, treatment failure and death.

**Data analysis**

All selected data were exported from Microsoft excel into STATA version 12.1 (StataCorp Inc, College Station, Texas, USA) for analysis. A univariate analysis explored the distribution of the dependent and independent variables using frequency tables.
The bivariate analysis identified risk factors that were associated with HIV status and other risk factors and TB treatment outcomes. For the bivariate analysis treatment default, treatment failure and death were merged into one variable, namely unfavourable treatment outcome. The Pearson’s $\chi^2$ statistic was used to compare categorical variables and $P$-values of < 0.05 were considered statistically significant.

Relative risks were used for measures of association. Univariate and multivariate analyses were performed using a generalized linear regression model. Statistically significant variables in the univariate analysis were included in the multivariate analysis. The contribution of each variable to the model was evaluated using likelihood ratio $\chi^2$ tests.

RESULTS

There were 14585 patients aged 15 years or more, initiated on TB treatment between 1 July 2011 and 30 June 2012 and registered on the TB ETR.net in the Metro East GSA. The study sample included 12672 patients after 1913 were excluded because they were not on treatment regimen 1 or 2, their HIV status was not known or because they had been transferred in or out of the district (Figure 1).

Figure 1: Selection of Population included in the Study
Table 1. Demographic characteristics, HIV status, treatment category, site of TB, sub-district where treated and diagnostic sputum smear microscopy results stratified by HIV status of persons initiated on TB treatment in Metro East GSA, Cape Town.

<table>
<thead>
<tr>
<th>Stratified by HIV Status</th>
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</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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</tr>
<tr>
<td>6275 (50)</td>
<td>6397 (50)</td>
<td>12672 (100)</td>
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Variables

Age (Years)

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<th>45-59</th>
<th>&gt;59</th>
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Sex

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<tr>
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<td>3410 (59)</td>
<td>2987 (43)</td>
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<td>5766 (46)</td>
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Sub District

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<th>Eastern</th>
<th>Northern</th>
<th>Tygerberg</th>
<th>Total</th>
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<td>2166 (69)</td>
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</tr>
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<td>1347 (46)</td>
<td>1017 (54)</td>
<td>990 (31)</td>
<td>6921 (51)</td>
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<td></td>
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Outcome

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<th>Treatment unsuccessful</th>
<th>Died</th>
<th>Total</th>
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<td>8870 (70)</td>
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<td>4258 (48)</td>
<td>1799 (55)</td>
<td>340 (66)</td>
<td>3288 (26)</td>
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<td>8870 (70)</td>
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Category

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<td>3856 (30)</td>
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<td>8816 (70)</td>
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Disease Classification

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</thead>
<tbody>
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<td>5575 (53)</td>
<td>4989 (47)</td>
</tr>
</tbody>
</table>


Table 1 presents the demographic characteristics, treatment category, site of TB, sub-district where treated and diagnostic sputum smear microscopy results stratified by HIV status. 77% of patients initiated on TB treatment from 1 July 2011 until 30 June 2012 was between 15 and 44 years of age. The majority was male (54%). The sub-district with the highest proportion of the TB cases in the GSA was Khayelitsha (37%) and the lowest was Northern (15%). 50% of TB patients were co-infected with HIV. Retreatment cases accounted for 30% of all cases. 83% of TB cases were classified as pulmonary TB and 88% had a diagnostic sputum smear microscopy result of which 46% were positive.

40% of persons aged 15 to 29 years, 66% of persons 30 to 34 years, 41% of persons 44 to 59 years and 14% of persons over 59 years of age were co-infected with HIV. 59% of females and 43% of males were co-infected. Khayelitsha had the highest proportion of co-infected patients (65%) and Tygerberg the lowest (31%). Of those who had a successful outcome, 48% were co-infected and of those who died 66% were co-infected. Of those who had a positive sputum smear result only 35% were co-infected with HIV.
Table 2. Demographic characteristics, HIV status, treatment category, site of TB and diagnostic sputum smear microscopy results of persons initiated on TB treatment stratified by treatment outcome in Metro East GSA, Cape Town.

<table>
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<td></td>
<td>Success</td>
<td>Defaulted</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
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<td></td>
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<tr>
<td>15-29</td>
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<td>45-59</td>
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<td>&gt;59</td>
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<td><strong>Gender</strong></td>
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<td>3847 (43)</td>
<td>1264 (38)</td>
<td>255 (50)</td>
</tr>
</tbody>
</table>
70% of all TB patients in the GSA had a successful treatment outcome, 26% were treatment failures and 4% had died. 66% of persons who died and 55% of those who defaulted were co-infected whereas 48% of those with a treatment success outcome were co-infected. Khayelitsha was the district with the highest proportion of unsuccessful outcomes (43%) and deaths (39).

**TB notification case among districts**

Based on the population census of 2011, the TB case notification rate was calculated for Eastern GSA was 922 per 100 000 and for each sub-district is presented in Table 4. The annual HIV sero-prevalence from the antenatal survey and the proportion of co-infected persons is also included. The trend for HIV co-infection across sub-districts matches the sero-prevalence of HIV in antenatal survey.

Table 4. TB case notification case rate, proportion of TB patients co-infected with HIV and HIV prevalence by district in 2011

<table>
<thead>
<tr>
<th>Sub District Level</th>
<th>Khayelitsha</th>
<th>Eastern</th>
<th>Northern</th>
<th>Tygerberg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB Notification Case rate</strong></td>
<td>4683/279212 =1677 per 100000</td>
<td>2941/372344 =790 per 100000</td>
<td>1892/281691 =672 per 100000</td>
<td>3156/441688 =715 per 100000</td>
</tr>
<tr>
<td><strong>Proportion of TB patient with HIV co-infection</strong></td>
<td>3043/4683 =65%</td>
<td>1347/2941 = 45%</td>
<td>1017/1892 =53%</td>
<td>990/3156 =31%</td>
</tr>
<tr>
<td><strong>HIV Prevalence (Antenatal survey 2012)</strong></td>
<td>37.1%</td>
<td>17.9%</td>
<td>26.2%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>
Sputum smear conversion rates at the end of the intensive phase and at the end of treatment stratified by HIV status

In total 11255 patients had a diagnostic sputum smear sent to the laboratory for microscopy and 5889 (52%) were positive and of those who were positive 2063 (35%) were HIV positive and 3826 (65%) were HIV negative.

Figure 2a shows that at the end of the intensive phase 1707 (83%) of those who had a positive sputum smear at initiation had a negative smear, 88 (4%) remained positive and 311 (15%) did not have a smear in HIV positive patients. At the end of the treatment 14 smears (0.7%) remained positive but 703 (34%) did not have a smear.

Figure 2b shows that at the end of the intensive phase 3331 (87%) of those who had a positive sputum smear at initiation had a negative smear, 265 (7%) remained positive and 375 (10%) did not have a smear in HIV negative patients. At the end of the treatment 25 smears (0.7%) remained positive but 1003 (26%) did not have a smear.

Figure 2a. Diagnostic Sputum Smear Result and conversion at the end of Intensive Phase and at the end of the Treatment in HIV positive patients
Sputum smear microscopy and culture results at diagnosis

In Figure 3a, of the 3403 negative sputum smear microscopy results among HIV positive patients, 2333 (69%) also had a culture result and 1364 of these smears (59%) were positive on culture (smear negative TB). Of the 2063 positive sputum smear microscopy results, 1326 (64%) also had a culture result and 1216 of these smears (92%) were confirmed positive on culture. However for 110 of the positive smears (8%) the culture was negative.

In Figure 3b, of the 1963 negative sputum smear microscopy results among HIV negative patients, 1078 (55%) also had a culture result and 783 of these smears (73%) were positive on culture (smear negative TB). Of the 3826 positive sputum smear microscopy results, 1749 (46%) also had a culture result and 1674 of these smears (96%) were confirmed positive on culture. However for 75 of the positive smears (4%) the culture was negative.
Figure 3a. Comparison of diagnostic sputum smear result and sputum culture result at pretreatment in HIV positive patient.

Figure 3b. Comparison of diagnostic sputum smear result and sputum culture result at pretreatment in HIV negative patient.
Risk factors for an unfavourable treatment outcome

In the multivariate analysis HIV co-infection (RR 1.2), retreatment (RR 1.4) and smear not done (RR 1.4) were significant risk factors for an unfavourable treatment outcome.

The sub-districts Eastern (RR 0.9) and Northern (RR 0.7) were less likely to have had an unfavourable treatment outcome compared to Khayelitsha sub-district.

When stratified by HIV status, retreatment patients and smear not done were significantly associated with unfavourable treatment outcomes in HIV-negative TB patients while being from sub-districts Northern and Eastern compared to Khayelitsha was associated with a favourable outcome.

Co-infected patients aged less than 59 years compared to those aged 15-29 years and co-infected patients who had a negative diagnostic smear recorded compared to a positive smear were less likely to have an unfavourable outcome. Patients who had had TB previously (retreatment cases) were significantly more likely to have an unfavourable TB treatment outcome (RR of 1.6 for HIV negative and 1.3 for co-infected persons).

HIV-negative TB patients from sub-districts Eastern and Northern were more likely to have a favourable outcome than those from Khayelitsha while retreatment compared to new patients and those who did not have a smear compared to those who had a positive smear were more likely to have an unfavourable outcome.

Table 5: Risk Factors for unfavourable treatment outcome stratified by HIV Status

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole Population</td>
<td>Whole Population</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>P</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Positive</td>
<td>1.3 (1.2-1.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>30-44</td>
<td>1.1 (1.0-1.2)</td>
<td>0.015</td>
</tr>
</tbody>
</table>
DISCUSSION

Our study showed that the incidence of TB in the Eastern GSA of the Metro was high at 922 per 100 000 and this is alarming. According to the 2014 WHO TB Report, the incidence of TB was 125 per 100 000 population globally, 165 per 100 000 in 22 high burden countries and 860 per 100 000 in South Africa [2]. The incidence in the Western Cape was 885 per 100 000 population [12] and in Cape Town it was
877 per 100,000 population [13]. One of the main reasons for the high incidence is high prevalence of HIV in some of these areas [14].

In the Metro East GSA of Cape Town 97% of TB patients had been tested for HIV. This shows that the recommendation that all TB patients be screened for HIV has been successfully implemented. 50% of TB patients in this study were co-infected with HIV; this high co-infection rate was due to the inclusion of Khayelitsha sub-district which has the highest co-infection rate in the Western Cape [14]. Khayelitsha with the highest antenatal HIV prevalence had both the highest rate of TB and the highest co-infection rate while Tygerberg had a comparatively high TB incidence but the lowest prevalence of co-infection [15]. HIV is thus not the sole reason for this major epidemic of TB. This is seen in other developing countries such as Pakistan, India and China where the prevalence of HIV is low but TB incidence is high [16, 17, 18].

In this study 46% of TB patients were female but 59% were co-infected with HIV compared to 41% in males. Co-infected females were also younger than their male counterparts. The epidemic of TB in terms of sex has changed due to the HIV epidemic. Before the era of HIV the male to female ratio for TB incidence was 2:1 [19], but the high prevalence of HIV in females has led to an increased incidence of TB among females [20]. A number of studies and reports have shown that women of child-bearing age were more likely to develop TB due co-infection with HIV [21, 22].

In this study 14% of persons with TB had EPTB and 66% of them were co-infected. This was similar to other studies that showed that EPTB was more common in co-infected patients [23, 24].

Our study showed more retreatment patients were co-infected. This is similar to another South African study in which 97% of retreatment cases were tested for HIV and 78% were co-infected [25]. A study from India found that retreatment cases were less likely to be co-infected but this was in a low HIV prevalence setting [26].
In the Western GSA smear microscopy should not be the only means of diagnosing TB as 59% of HIV positive patients and 73% of HIV negative patients had smear negative culture positive TB. Culture is the gold standard for the diagnosis of TB but it takes up to 6 weeks and is expensive and therefore sputum smear microscopy is the cornerstone of the diagnosis in many resource-limited settings [27, 28]. Many studies show that smear microscopy has low sensitivity [29, 4]. Recently GeneXpert, a nucleic acid test that produces results within two hours has been used in the majority of clinics in South Africa and this should alleviate the problem of waiting for cultures [30].

Sputum smear microscopy is useful to monitor the progress of disease [26]. According to the TB guidelines sputum smear microscopy should be done before treatment is initiated, at the end of the intensive phase (at two or three months) and at the end of the treatment, particularly in those who had positive bacteriology pretreatment. At end of the three months 8% of patients with smear positive TB had not had a smear done showing that clinics in the Eastern GSA were not following the guidelines. This could have been due to the fact that patients were not able to provide a sputum specimen.

Only 70% of TB patients had a successful outcome in the Eastern GSA, way below the target of 85%. This may explain why the Western Cape Province has the highest TB notification rate in the country [31]. The WHO estimates that a treatment completion rate of 85% and 70% case detection rate is required to have an impact on the TB epidemic in high burden countries [2]. In 2013, the treatment success rate was 86% globally. In the same year, the success rate in South Africa was 77% [2].

The Khayelitsha sub-district had the highest proportion of unsuccessful treatment outcomes. This can be due to the high burden of TB and HIV co-infection on the health system. Khayelitsha is also one of the poorest areas of Cape Town with high unemployment with more than 50% of dwelling being informal [12, 17].
HIV co-infection was associated with an unfavourable treatment outcome. This could be due to the negative impact of HIV on TB, increasing the risk of HIV-related morbidity and mortality [32]. A study from Toronto showed a high treatment failure rate (36%) in co-infected patients and HIV was an independent risk factor for not completing TB treatment [33]. Another study from Nigeria found a treatment failure rate of 27% in HIV co-infected patients compared to 19% in HIV negative patients [34].

Unfavourable outcomes in co-infected patient may be due to a delay in diagnosis because of atypical clinical presentation [35] and it is also known that co-infected patients tend to have paucibacillary TB or lower micro-bacterial colony counts [35]. This reduction in micro-bacterial count makes the diagnosis of TB by smear microscopy more difficult.

Contrary to other studies this study has showed no difference in treatment outcome between sexes [36].

Patients who had had TB previously (retreatment cases) were significantly more likely to have an unfavourable TB treatment outcome. A number of studies showed that retreatment patients are more at risk of having an unfavourable treatment outcome [37]. Retreatment was more common in co-infected patients providing an added risk [38]. Furthermore retreatment patients were more prone to drug resistance TB and loss to follow up and these patients are more likely to have an unfavourable outcome [2, 37].

The absence of sputum smear microscopy at diagnosis was also a significant risk factor for an unfavourable treatment outcome. Sputum smear microscopy might not be requested if there was an atypical clinical presentation of TB such as the absence of a cough and inability to produce sputum. It may also be due to health system related failures. It may be difficult for patients to produce sputum and a physiotherapist is usually not present at clinics to assist. Due to a lack of resources patients or
tardiness on the part of clinical staff, sputum may not be requested, or the results never received by the clinic, or received but never entered in the patient record.

In the case of EPTB, a diagnosis may be confirmed using other bacteriological methods such as cytology and sputum may not be requested to exclude pulmonary TB. A study from Pakistan showed that only 41% of persons with EPTB were cured [39]. Moreover EPTB is more common with worse outcome in co-infected patients; a study from Thailand showed that 19% of co-infected persons with EPTB died compared to 16% co-infected persons with PTB died [40].

Strengths

The major strength was the large database from an area with a high incidence of TB and varying prevalence of HIV, showing both the impact of HIV and other factors. HIV status was confirmed from clinical records rather than self-reported and therefore the accuracy of the data was likely to be good. Only 3% of patients were excluded due to the absence of an HIV test result.

Limitations

A major limitation was missing or incomplete data and this may have affected the power of the study. This was a secondary analysis of data already collected and the principal investigator was not able to trace missing information from the primary clinical records. In addition there may have been recording and data capturing errors that the principal investigator was not able to correct. Moreover, limited information was collected on patients on ETR.Net and thus we could not adjust for the known confounders such as socioeconomic status, education level and marital status. All patients with an unrecorded treatment outcome were regarded as an unfavorable treatment outcome. Persons with an unrecorded HIV status were excluded and this group may have been more or less likely to be co-infected.
CONCLUSIONS

The incidence of TB is extremely high in the Eastern GSA of Cape Town however the prevalence of co-infection varies across the sub-districts. Co-infection, retreatment and smear microscopy not done pretreatment were factors significantly associated with an unfavourable treatment outcome. Eastern and Northern sub-districts were significantly more likely to have favourable treatment outcomes compared to Khayelitsha, where both TB incidence and HIV co-infection were greatest. More research is required to identify other risk factors for unfavourable treatment outcomes.

REFERENCES


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34) Jibrin YB, Ali AB, Saad ST, Kolo PM. Prevalence of Treatment Failure among Pulmonary Tuberculosis Patients in Federal Medical Centre, Gombe, Northeastern Nigeria. ISRN Infectious Diseases [Internet] 2012;2013. DOI:10.5402/2013/461704


PART D: APPENDICES
# APPENDIX 1: DEFINITION OF VARIABLES

The following variables were included in the analysis:

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Smear Microscopy</td>
<td></td>
</tr>
<tr>
<td>Smear positive</td>
<td>Direct sputum smear microscopy was positive</td>
</tr>
<tr>
<td>Smear negative</td>
<td>Direct sputum smear microscopy was negative</td>
</tr>
<tr>
<td>Smear not done</td>
<td>An extra pulmonary TB or pulmonary TB suspect diagnosed with TB without smear microscopy results with or without chest x-ray, or there has been no response to broad-spectrum antibiotics and the HCW has taken the decision to treat with a full course of TB treatment.</td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>Patients were defined as HIV-positive if results of positive HIV serology was recorded in the TB register or if the patient was recorded to be currently receiving antiretroviral therapy or co-trimoxazole prophylaxis</td>
</tr>
<tr>
<td>HIV negative</td>
<td>HIV-negative status was defined by a recorded HIV-negative serology result.</td>
</tr>
<tr>
<td>Patient category:</td>
<td></td>
</tr>
<tr>
<td>New case</td>
<td>A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than four weeks.</td>
</tr>
<tr>
<td>Re-treatment case</td>
<td>A patient who has taken treatment for TB before and either relapsed, defaulted or had treatment failure.</td>
</tr>
<tr>
<td>Disease classification</td>
<td></td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>Refers to disease involving the lung parenchyma.</td>
</tr>
<tr>
<td>Extra Pulmonary TB</td>
<td>Refers to TB of organs other than the lungs: e.g. pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints and bones and meninges</td>
</tr>
<tr>
<td>Both</td>
<td>A patient with both a parenchymal lesion in the lungs (pulmonary TB) and extra-pulmonary TB</td>
</tr>
<tr>
<td>Treatment outcome</td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>Patient who is cured or has completed treatment</td>
</tr>
<tr>
<td>Cure</td>
<td>Patient who was smear/culture positive at the beginning of the treatment and is smear/ culture negative in the last month of treatment and on at least one previous occasion at least 30 days prior.</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>Any person initiated on treatment who completed the treatment. Patient who was smear or culture positive at the beginning and has completed treatment but does</td>
</tr>
<tr>
<td>Scenario</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Treatment unsuccessful</td>
<td>Patient who has treatment failure or died or treatment default or not evaluated</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>Smear/culture positive patient who remains or is smear-positive at 5 months or later during treatment. This definition also includes those patients who are diagnosed with MDR-TB during treatment.</td>
</tr>
<tr>
<td>Died</td>
<td>Patient who died for any reason during the course of TB treatment.</td>
</tr>
<tr>
<td>Treatment Default</td>
<td>Patient whose treatment was interrupted for two consecutive months or more during the treatment period.</td>
</tr>
<tr>
<td>Not Evaluated</td>
<td>Cases that have no outcome at the end of the continuation phase of treatment or who did not complete the full course of treatment.</td>
</tr>
</tbody>
</table>

not have a negative smear/ culture in the last month of treatment and on at least one previous occasion more than 30 days prior. The smear examination may not have been done or the results may not be available at the end of treatment.
## APPENDIX 2: AGE AND SEX DISTRIBUTION BY HIV STATUS

<table>
<thead>
<tr>
<th>HIV NEGATIVE</th>
<th>15-29</th>
<th>30-44</th>
<th>45-59</th>
<th>&gt;59</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENDER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td>1103(46.82%)</td>
<td>615(26.1%)</td>
<td>470(19.95%)</td>
<td>168(7.13%)</td>
<td>2356(100%)</td>
</tr>
<tr>
<td>MALE</td>
<td>1503(38.53%)</td>
<td>1240(31.64%)</td>
<td>935(23.86%)</td>
<td>241(6.15%)</td>
<td>3919(100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2606(41.53%)</td>
<td>1855(29.56%)</td>
<td>1405(22.39%)</td>
<td>409(6.52%)</td>
<td>6275(100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV POSITIVE</th>
<th>15-29</th>
<th>30-44</th>
<th>45-59</th>
<th>&gt;59</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENDER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td>1222(35.84%)</td>
<td>1715(50.29%)</td>
<td>431(12.64%)</td>
<td>42(1.23%)</td>
<td>3410(100%)</td>
</tr>
<tr>
<td>MALE</td>
<td>532(17.81%)</td>
<td>1873(62.71%)</td>
<td>536(17.94%)</td>
<td>46(1.54%)</td>
<td>2987(100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1754(27.42%)</td>
<td>3588(56.09%)</td>
<td>967(15.12%)</td>
<td>88(1.38%)</td>
<td>6397(100%)</td>
</tr>
</tbody>
</table>
APPENDIX 3: LETTER OF APPROVAL FROM UCT FACULTY OF HEALTH SCIENCES

HUMAN RESEARCH ETHICS COMMITTEE
16 October 2014

HREC/REF: 758/2014

Prof D Coetzee
Public Health & Family Medicine
Entrance 5 level 5
Falmouth Building

Dear Prof Coetzee

Project Title: INFLUENCE OF HIV AND OTHER FACTORS ON TUBERCULOSIS OUTCOME (Masters-candidate-Dr S Mahtab)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has formally approved the above mentioned study.

Approval is granted for one year until the 30 October 2015.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

We acknowledge that the following student:- Dr Sana Mahtab is also involved in this project.

Please note that the on-going ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.