OUTCOMES OF TB TREATMENT IN HIV CO-INFECTED TB PATIENTS IN ETHIOPIA

by

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submitted in accordance with the requirements
for the degree of

MASTER OF PUBLIC HEALTH

at the

UNIVERSITY OF SOUTH AFRICA

SUPERVISOR: PROF TR MAVUNDLA

JANUARY 2015
DECLARATION

I declare that 'OUTCOMES OF TB TREATMENT IN HIV CO-INFECTED TB PATIENTS IN ETHIOPIA' is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

Solomon Ahmed Ali January 2015

FULL NAMES DATE
OUTCOMES OF TB TREATMENT IN HIV CO-INFECTED TB PATIENTS IN ETHIOPIA

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ABSTRACT

The purpose of this study was to determine and compare the outcomes of tuberculosis (TB) treatment among Human Immunodeficiency Virus (HIV) co-infected TB patients, and identify factors associated with these outcomes. A quantitative cross-sectional analytic design was used. Patient level secondary data was collected and analysed for the study. A total of 575 TB patients, including 360 non-HIV infected, 169 HIV co-infected and 46 without a documented HIV status, were enrolled. The overall treatment success rate was 91.5%, and HIV co-infected TB patients had a high rate (11.8%) of unfavourable outcomes. The cure rate was significantly lower (10.1% versus 24.2%) and the death rate higher in HIV co-infected patients (8.3% versus 2.5%). Age and TB classification were significantly associated with treatment outcome. No association was found with starting ART, Cotrimoxazole prophylactic treatment or enrolment in HIV care, but 22% of HIV co-infected TB patients were taking ART when they developed TB disease.

Keywords

TB treatment outcome; TB/HIV co-infection; HIV status; treatment success rate; favourable outcomes; unfavourable outcomes; cure rate; death rate; age; TB classification.
# TABLE OF CONTENTS

## CHAPTER 1

### ORIENTATION TO THE STUDY

1.1 INTRODUCTION ............................................................................................................................................... 1

1.2 BACKGROUND INFORMATION ABOUT THE RESEARCH PROBLEM .................................................. 1

1.3 RESEARCH PROBLEM ..................................................................................................................................... 4

1.4 AIM OF THE STUDY .......................................................................................................................................... 5

1.5 RESEARCH QUESTIONS ..................................................................................................................................... 5

1.6 RESEARCH OBJECTIVES ................................................................................................................................. 5

1.7 DEFINITIONS OF TERMS ................................................................................................................................. 6

1.7.1 Conceptual definitions ............................................................................................................................... 6

1.7.1.1 Tuberculosis .............................................................................................................................................. 6

1.7.1.2 HIV infection ............................................................................................................................................ 6

1.7.1.3 Co-infection ................................................................................................................................................ 7

1.7.1.4 Outcome .................................................................................................................................................... 7

1.7.1.5 Patient ........................................................................................................................................................ 9

1.7.1.6 Treatment .................................................................................................................................................. 9

1.7.1.7 Cure ........................................................................................................................................................... 9

1.7.1.8 Default ....................................................................................................................................................... 9

1.7.2 Operational definitions ............................................................................................................................... 9

1.7.2.1 TB infection .............................................................................................................................................. 10

1.7.2.2 Active TB disease .................................................................................................................................... 10

1.7.2.3 Case of tuberculosis ................................................................................................................................ 10

1.7.2.4 HIV infection ............................................................................................................................................ 10

1.7.2.5 TB/HIV co-infection ............................................................................................................................... 10

1.7.2.6 TB treatment outcome ............................................................................................................................. 10

1.7.2.7 Cured ....................................................................................................................................................... 11

1.7.2.8 Treatment completed ............................................................................................................................... 11

1.7.2.9 Treatment failure .................................................................................................................................... 11

1.7.2.10 Defaulter .................................................................................................................................................. 11

1.7.2.11 Died ......................................................................................................................................................... 11

1.7.2.12 Transfer out ............................................................................................................................................. 11

1.7.2.13 Treatment success .................................................................................................................................. 12

1.8 RESEARCH PARADIGM ................................................................................................................................. 12

1.9 STRUCTURE OF THE DISSERTATION ................................................................................................. 12

1.10 CONCLUSION ............................................................................................................................................. 13
CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION ..................................................................................................................................... 14

2.2 TUBERCULOSIS (TB) ............................................................................................................................. 14
  2.2.1 TB infection .............................................................................................................................................. 14
  2.2.2 TB disease ............................................................................................................................................... 15
  2.2.3 TB diagnosis ............................................................................................................................................ 16
  2.2.4 TB treatment ............................................................................................................................................ 16
  2.2.5 TB treatment outcome ............................................................................................................................. 17

2.3 HIV INFECTION ...................................................................................................................................... 18

2.4 AIDS AND OPPORTUNISTIC ILLNESSES ............................................................................................. 19

2.5 TB/HIV CO-INFECTION .......................................................................................................................... 20

2.6 CONCLUSION ......................................................................................................................................... 25

CHAPTER 3

RESEARCH DESIGN AND METHOD

3.1 INTRODUCTION ..................................................................................................................................... 26

3.2 RESEARCH PARADIGM ......................................................................................................................... 26

3.3 RESEARCH DESIGN .............................................................................................................................. 27
  3.3.1 Quantitative aspect of design .................................................................................................................. 27
  3.3.2 Non-experimental aspect of design ......................................................................................................... 28
  3.3.3 Cross-sectional aspect of design ............................................................................................................. 28
  3.3.4 Analytic design ......................................................................................................................................... 29

3.4 RESEARCH METHOD ............................................................................................................................ 29
  3.4.1 Population ................................................................................................................................................ 29
  3.4.2 Sampling .................................................................................................................................................. 30
  3.4.3 Ethical issues related to sampling ............................................................................................................ 32
  3.4.4 Data collection ......................................................................................................................................... 33
    3.4.4.1 Data collection approach and method ..................................................................................................... 33
    3.4.4.2 Development of the data collection instrument ........................................................................................ 33
    3.4.4.3 Characteristics of the data collection instrument ..................................................................................... 33
    3.4.4.3.1 Validity of the data collection instrument .................................................................................................. 34
    3.4.4.3.2 Reliability of the data collection instrument .............................................................................................. 34
  3.4.4.4 Data collection process ............................................................................................................................ 35
  3.4.5 Data analysis ........................................................................................................................................... 36
CHAPTER 4

ANALYSIS, PRESENTATION AND DESCRIPTION OF THE RESEARCH FINDINGS

4.1 INTRODUCTION ................................................................................................................................. 39

4.2 DATA MANAGEMENT AND ANALYSIS ............................................................................................. 39

4.3 RESEARCH RESULTS .......................................................................................................................... 41

4.3.1 Sample characteristics ...................................................................................................................... 41

4.3.1.1 Age distribution ............................................................................................................................... 42

4.3.1.2 Gender distribution .......................................................................................................................... 42

4.3.1.3 HIV status of the study participants ................................................................................................. 42

4.3.2 TB disease characteristics of the study participants ......................................................................... 43

4.3.2.1 TB disease classification .................................................................................................................. 43

4.3.2.2 TB treatment category ..................................................................................................................... 44

4.3.3 Other medical care services received by the study participants ...................................................... 45

4.3.4 Treatment outcomes of the study participants .................................................................................. 45

4.3.5 TB treatment outcomes in relation to HIV status ......................................................................... 47

4.3.6 Other characteristics associated with treatment outcome .............................................................. 49

4.4 CONCLUSION ..................................................................................................................................... 51

CHAPTER 5

CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

5.1 INTRODUCTION .................................................................................................................................... 53

5.2 DISCUSSION OF FINDINGS ................................................................................................................ 53

5.3 LIMITATIONS ....................................................................................................................................... 56

5.4 RECOMMENDATIONS .......................................................................................................................... 57

5.4.1 Practice recommendations ................................................................................................................ 57

5.4.2 Recommendations for further research ............................................................................................ 58

5.4.3 Recommendations for education ..................................................................................................... 58
5.5 CONCLUSIONS .................................................................................................................................................. 59

LIST OF REFERENCES ............................................................................................................................................. 60
LIST OF TABLES

Table 4.1  Age distribution of study participants (N=575) ................................................................. 42
Table 4.2  HIV status of the study participants (N=575)................................................................. 43
Table 4.3  Category of TB treatment of the study participants (N=575) .................................................. 44
Table 4.4  Outcome of TB treatment in the study participants (N=575) ................................................. 46
Table 4.5  Comparison of TB treatment success based on HIV status (N=529) .................................... 47
Table 4.6  Chi-square tests for treatment outcome comparisons based on HIV status ........................ 47
Table 4.7  Comparison of treatment outcomes and HIV status ............................................................ 49
Table 4.8  Results of the binary regression analysis of the association of baseline individual, TB disease and other medical care services characteristics with TB treatment outcome ......................... 50
Table 4.9  Multinomial regression analysis of factors associated with treatment outcome ....................... 51
LIST OF FIGURES

Figure 4.1  Gender distribution of the study sample (N=575).................................................................................. 42

Figure 4.2  TB disease classifications of the study participants (N=575)................................................................ 44

Figure 4.3  Status of other medical care services received by the study participants who have co-infection with HIV (N=169) ............................................................................................................. 45

Figure 4.4  Comparison of treatment outcomes by HIV status (N=529)................................................................. 48

Figure 4.5  Comparison of adverse outcomes by HIV status (N=529).................................................................... 48
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
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<tr>
<td>ART</td>
<td>Anti-Retroviral Treatment</td>
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<td>CATIE</td>
<td>Canadian AIDS Treatment Information Exchange</td>
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<td>CD4</td>
<td>Cluster of differentiation 4</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CHS</td>
<td>College of Human Sciences</td>
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<td>EP</td>
<td>Extra Pulmonary</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>HBC</td>
<td>High Burden Countries</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HSHDC</td>
<td>Health Studies Higher Degrees Committee</td>
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<td>IPT</td>
<td>Isoniazid Prophylactic Treatment</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IRS</td>
<td>Immune Reconstitution Syndrome</td>
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<td>MDR</td>
<td>Multi Drug Resistance</td>
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<tr>
<td>MMWR</td>
<td>Mortality and Morbidity Weekly Report</td>
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<tr>
<td>OI</td>
<td>Opportunistic Infections</td>
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<td>PASW</td>
<td>Predictive Analytics Software</td>
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<tr>
<td>P/pos</td>
<td>Pulmonary Positive</td>
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<td>PCP</td>
<td>Pneumocystis Carinii Pneumonia</td>
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<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
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<td>RHB</td>
<td>Regional Health Bureau</td>
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<td>SPSS</td>
<td>Statistical Package for Social Sciences</td>
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<td>SSA</td>
<td>Sub-aharan Africa</td>
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<td>TB</td>
<td>Tuberculosis</td>
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<td>UCSD</td>
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<td>VR</td>
<td>Vital Registration</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</table>
ANNEXES

Annex I  Approval by the local IRB

Annex II  Request for access to health facilities

Annex III  Approval by UNISA

Annex IV  Standard TB registers - Ethiopia

Annex V  Data collection form

Annex VI  WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV

Annex VII  List of selected health facilities
CHAPTER 1

ORIENTATION TO THE STUDY

1.1 INTRODUCTION

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) are among the most prevalent communicable diseases afflicting the populations of resource poor countries of Africa like Ethiopia (World Health Organization [WHO] 2012a:3). The interaction of the two diseases in the same person is associated with adverse individual patient health outcomes (Chaisson & Martinson 2008:1089-1092). There is scarcity of evidence on the magnitude of the problem and the potential contributing factors that determine these outcomes. This is a study designed to generate evidence on the health outcomes of HIV infected TB patients and to identify determinants of these outcomes in the Ethiopian context. In this dissertation the researcher introduces readers to the background of study, problem statement, research design and methods applied in order to achieve the objectives stated by the researcher.

1.2 BACKGROUND INFORMATION ABOUT THE RESEARCH PROBLEM

TB and HIV are the most prevalent communicable diseases of major public health concern in the populations of sub-Saharan African (SSA) countries including Ethiopia. Co-infection with HIV and TB is very common with an estimated 30% of HIV infected persons having dual infection with TB (Getahun, Gunneberg, Granich & Nunn 2010:[S202-203]). About 80% of the total estimated disease burden of HIV associated TB is found in countries of SSA, and this part of the world has the “highest rates of cases and deaths per capita” attributable to TB disease (WHO 2012a). TB is among the leading causes of morbidity and mortality in HIV infected individuals; and in patients with TB disease, co-infection with HIV significantly complicates both the diagnosis and management of TB disease (Getahun, Gunneberg, Granich & Nunn 2010:[S202-203]).

Many of the countries most severely affected by the two epidemics are resource poor settings with weak health systems (Friedland, Churchyard & Nardell 2007:S1-S3). Through the technical and financial support of donors and other international
development partners, these countries are working to address the problems posed by these health issues (WHO 2010b). Decreasing the burden of disease from both infections among the population and improving the health outcomes of the individual patients attending medical services is of paramount importance to mitigate the adverse impact from these conditions.

TB is one of the most prevalent communicable diseases in the world and a major cause of morbidity and mortality (WHO 2012a). The WHO estimated that, in 2011, there were more than 8.7 million new cases of TB worldwide and that 1.4 million people have died of TB disease in that same year (WHO 2012a). The burden of TB disease is highest in the resource poor countries of Asia and Africa (Chaisson & Martinson 2008:1089-1092). TB is among the top diseases considered as global public health threats, and the WHO declared TB a global public health emergency in 1993 (WHO 2012a).

The high prevalence of the HIV in the early 1990s has contributed to the enormous TB disease burden globally (Chaisson & Martinson 2008:1089-1092). The geographic and population distribution of TB and HIV has shown marked overlap with the highest prevalence of both diseases occurring in the populations of the poor countries of the sub-Saharan Africa (SSA) and Asia (Chaisson & Martinson 2008:1089-1092). The interaction of the two deadly diseases has incurred massive losses to the human assets, socioeconomic growth, and overall development of the countries hardest hit by these diseases. The global TB report by WHO (WHO 2012a) shows that about 1.1 million people with TB disease in 2011 (out of the 8.7 million who developed TB in 2011) were co-infected with HIV, and 79% of these reside in the resource poor countries of Africa. There were also 400,000 HIV associated TB deaths in the same time period.

Early detection of TB disease and prompt initiation of effective treatment with potent anti-TB drug regimens is required to decrease morbidity and mortality from TB disease in HIV infected patients (WHO 2012b). This approach also is critically important for prevention of transmission of TB within the population.

Co-infection with HIV complicates the diagnosis and management of TB disease and greatly increases the mortality risk if both infections are not properly addressed (Padmapriyadarsini, Narendran & Swaminathan 2011:850). Therefore, HIV screening
among TB patients and routine symptom screening of HIV patients with appropriate diagnostic evaluation for those with a positive symptom screen are critical in settings where the two diseases are known to be prevalent (Chaisson & Martinson 2008:1089-1092).

Most infections with the TB bacilli in immune competent individuals remain asymptomatic and become latent infections (Centers for Disease Control and Prevention [CDC] 2012c). In contrast, for HIV infected persons, there is an increased risk for the development of active TB disease. HIV-infected people who have latent TB (asymptomatic TB infection) have a 20-30-fold increased risk of developing active TB disease than those who are non-HIV infected (WHO 2011b).

Furthermore, the clinical presentation of TB disease in HIV infected individuals is different from those without HIV infection. There is more extra pulmonary presentation of TB and non-specific signs, symptoms, and diagnostic features in HIV co-infected TB patients (University of California San Francisco [UCSF] 2013).

The presence of other co-morbidities also complicates the diagnosis and management of TB in these patients. Treatment of active TB disease in HIV co-infected TB patients is complicated due to drug interactions, adverse drug reactions, Immune Reconstitution Syndrome (IRS), and other less favourable patient outcomes (UCSF 2013).

Co-infection with HIV is associated with significantly increased likelihood of mortality from TB disease, and HIV co-infected TB patients have significantly lower cure rates and lower treatment success rates compared to non-HIV infected TB patients (Daniel & Alausa 2006:222-226; WHO 2011b). HIV patients with active TB disease have a probability of dying of 15–20% at one year while those without active TB disease have 7–8% probability of dying at one year (Lawn, Myer, Bekker & Wood 2006:1605-1612). Early detection and prompt treatment are important in reducing morbidity and mortality.

Provision of Isoniazid prophylactic Treatment (IPT) for those co-infected patients with latent TB prevents development of active TB disease (WHO 2011a). Anti-Retroviral Therapy (ART) has been associated with a significantly reduced risk of developing active TB disease and death from TB (Lawn, Kranzer & Wood 2009:685-699; WHO 2012a).
Ethiopia is one of the countries in SSA that is hardest hit by the TB and HIV epidemics. With an estimated national adult prevalence of 1.5%, it is estimated that, in 2013, there were 734,048 adults and children infected with HIV in Ethiopia (Ethiopian Health and Nutrition Research Institute, Federal Ministry of Health 2012). The incidence of TB was 258 cases per 100,000 populations in 2011 (WHO 2012a). The prevalence of HIV among incident TB cases was found to be 17% (WHO 2012a). This indicates that there is a high burden from each disease and a considerable co-infection rate. It is essential and timely to better understand how and why HIV co-infected TB patients have unfavourable outcomes following anti-TB treatment. It is hoped that gaining a better understanding of the reasons for unfavourable outcomes will help identify strategies and standards targeted at improving the medical care of HIV co-infected TB patients.

1.3 RESEARCH PROBLEM

There is high TB and HIV co-infection rate among the population in countries of the Sub-Saharan African region, and this has major adverse public health impact (Chaisson & Martinson 2008:1089-1092; WHO 2012a). Ethiopia is an African country with high burden of both diseases (Ethiopian Health and Nutrition Research Institute, Federal Ministry of Health 2012; WHO 2012a). There is lack of evidence on the individual patient outcomes of co-infected patients with active TB disease receiving anti-TB treatment.

According to the Global TB Report by WHO (WHO 2012a), the health systems of most countries lack the appropriate monitoring system to track, record, and report individual patient outcomes of TB/HIV co-infected patients, and it recommends that “The recording and reporting of the outcomes of TB treatment disaggregated by HIV status needs to be improved.” It is also necessary for country programmes to have reliable information on patient outcomes of co-infected patients to assess progress made towards meeting targets set to decrease the number of TB deaths among HIV-positive people (WHO 2012a; United Nations Development Programme 2014).

TB/HIV co-infected patients have multiple individual, disease specific and treatment related factors that can adversely affect their treatment outcomes (UCSF 2013). Comparison of the outcomes of co-infected TB patients with those without HIV infection
is relevant to understand the magnitude of the problem. Identifying the different factors that are associated with these outcomes would provide the evidence for informing the designing of relevant standards of care for the co-infected patients. Strategies targeted at improving the outcomes of co-infected patients are needed to mitigate the impact of the two deadly diseases. This problem lead to the following aim and research questions:

1.4 AIM OF THE STUDY

The aim of this study is to understand and explain the outcomes of TB treatment in TB patients with respect to their HIV status and the differences in these outcomes among the different groups, and to identify the associated underlying factors that contribute to the occurrence of these outcomes.

1.5 RESEARCH QUESTIONS

The researcher formulated the following research questions in order to summarise the research problem.

- What is the TB treatment outcome among HIV co-infected TB patients?
- Is there a difference in TB treatment outcome in HIV co-infected TB patients?
- What are the risk factors for an adverse TB treatment outcome?

1.6 RESEARCH OBJECTIVES

In this study the researcher wishes to assess the following objectives:

- To assess TB treatment outcomes in HIV co-infected patients in major urban setting in Ethiopia
- To compare the treatment outcomes among HIV co-infected and non-HIV infected TB patients
- To identify determinants of adverse TB treatment outcomes among HIV co-infected TB patients
- To make recommendations for developing or revising the national guidelines for the management of TB and HIV
1.7 DEFINITIONS OF TERMS

In this study, a number of terms are used to identify the different characteristics, processes, and outcomes related to the study subjects, settings or methods. The definitions of the relevant terms used in the study are provided in this section.

1.7.1 Conceptual definitions

1.7.1.1 Tuberculosis

Tuberculosis a usually chronic highly variable disease that is caused by a bacterium of the genus Mycobacterium (M. tuberculosis) and rarely in the United States by a related mycobacterium (M. bovis), is usually communicated by inhalation of the airborne causative agent, affects especially the lungs but may spread to other areas (as the kidney or spinal column) from local lesions or by way of the lymph or blood vessels, and is characterised by fever, cough, difficulty in breathing, inflammatory infiltrations, formation of tubercles, caseation, pleural effusion, and fibrosis — called also TB (Merriam-Webster Inc. 2013b, Sv “tuberculosis”).

The WHO defined tuberculosis as “an infectious bacterial disease caused by Mycobacterium tuberculosis, which most commonly affects the lung [and] is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease” (WHO 2015a).

1.7.1.2 HIV infection

The human immunodeficiency virus (HIV) is a retrovirus that infects cells of the immune system, destroying or impairing their function and is transmitted through unprotected sexual intercourse (anal or vaginal), transfusion of contaminated blood, sharing of contaminated needles, and between a mother and her infant during pregnancy, childbirth and breastfeeding (WHO 2015b).
1.7.1.3 Co-infection

Co-infection simultaneous infection of a cell or organism by separate pathogens (Mosby's Medical Dictionary 2009a, Sv "co-infection").

It is also described as “when a person is living with more than one infection at a time” (CATIE [s.a]).

1.7.1.4 Outcome

The condition of a patient at the end of therapy or a disease process, including the degree of wellness and the need for continuing care, medication, support, counselling, or education (Mosby's Medical Dictionary 2009b, Sv "outcome").

The United States Food and Drug Administration (FDA) has further elaborated and classified outcome with respect to ‘Clinical outcome assessment’ (COA) which is “any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit” (FDA 2015). According to FDA, “COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer”. This is in contrast to measurements that use automated processes, algorithms etc … to ascertain outcomes (for example, biomarkers).

There are four types of COAs in the FDA classification and they are patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, and performance outcome (PerfO) measures.

Clinician-reported outcome (ClinRO) — A ClinRO is based on a report that comes from a trained health-care professional after observation of a patient’s health condition. A ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity).
Observer-reported outcome (ObsRO) — An ObsRO is a measurement based on an observation by someone other than the patient or a health professional. This may be a parent, spouse, or other non-clinical caregiver who is in a position to regularly observe and report on a specific aspect of the patient’s health. An ObsRO measure does not include medical judgment or interpretation. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life.

Patient-reported outcome (PRO) — A PRO is a measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient’s health condition without amendment or interpretation of the patient’s report by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient’s response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others.

Performance outcome (PerfO) — A PerfO is a measurement based on a task(s) performed by a patient according to instructions that is administered by a health care professional. Performance outcomes require patient cooperation and motivation. These include measures of gait speed (e.g., timed 25 foot walk test), memory recall, or other cognitive testing (e.g., digit symbol substitution test).

Proxy-reported outcome — A proxy is a person who reports an outcome as if she/he was the patient him/herself. Proxy reports are not recommended for unobservable symptoms that can be known only by the patient. A proxy-reported outcome is not a PRO but is a measurement based on a report by someone other than the patient reporting as if he or she is the patient. A proxy-reported outcome is not a valid endpoint.

An outcome can also be measured through the use of a biological marker (biomarker) which is described as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (FDA 2015).
1.7.1.5 **Patient**

A sick individual especially when awaiting or under the care and treatment of a physician or surgeon (Merriam-Webster Inc. 2013c, Sv "patient").

1.7.1.6 **Treatment**

The action or manner of treating a patient medically or surgically (Merriam-Webster Inc. 2013d, Sv "treatment").

1.7.1.7 **Cure**

Remission of signs or symptoms of a disease especially during a prolonged period of observation (Merriam-Webster Inc. 2013e, Sv "cure").

1.7.1.8 **Default**

To fail to fulfill an obligation or a promise (Mosby’s Dental Dictionary, 2008, Sv "default").

1.7.2 **Operational definitions**

For conducting a proper scientific study, it is critical that data are collected and used accurately and reliably by all individuals involved in data collection, compilation, summary and/or analysis. That means there should be a uniform and valid understanding of all the variables used in the study, and everyone should be collecting and managing the data in the same way. For this purpose, operational definitions should be made prior to the data collection. “An operational definition describes exactly what the variables are and how they are measured within the context of [the] study” (Cherry 2014).

“An operational definition, when applied to data collection, is a clear, concise detailed definition of a measure” (Operational definition 2014). The following operational definitions are adapted from the Ethiopian National Tuberculosis, Leprosy and TB/HIV prevention and Control Programme Manual, Guidelines for the clinical and

1.7.2.1 TB infection

Infection with mycobacterium tuberculosis bacilli

1.7.2.2 Active TB disease

Presence of signs and symptoms of TB disease in an individual who is infected with mycobacterium tuberculosis bacilli.

1.7.2.3 Case of tuberculosis

A definite case of TB (a pulmonary TB case with one or more initial sputum smear examinations positive for acid-fast bacilli) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment.

1.7.2.4 HIV infection

Infection with the Human Immune-deficiency Virus (HIV) that is confirmed by approved serologic tests.

1.7.2.5 TB/HIV co-infection

The presence of both TB and HIV infection in an individual patient.

1.7.2.6 TB treatment outcome

The final known status of a TB patient who was started on anti-TB treatment.
1.7.2.7 **Cured**

An initially smear-positive patient who is sputum smear-negative at, or one ‘month’ prior to, the completion of TB treatment and on at least one previous occasion (usually at the end of the 2nd or 5th month).

1.7.2.8 **Treatment completed**

A patient who completed anti-TB treatment without evidence of failure but for whom sputum smear or culture results are not available in the last month of treatment and on at least one previous occasion.

1.7.2.9 **Treatment failure**

A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.

1.7.2.10 **Defaulter**

A patient who has been on treatment for at least four weeks and whose treatment was interrupted for 8 or more consecutive weeks

1.7.2.11 **Died**

A patient who dies for any reason during the course of treatment

1.7.2.12 **Transfer out**

A patient who started treatment and has been transferred to another reporting unit and for whom the treatment outcome is not known at the time of evaluation of treatment results.
1.7.2.13 Treatment success

The sum of patients who are declared ‘cured’ and those who have ‘completed’ treatment.

1.8 Research paradigm

This quantitative cross-sectional study is based on the post-positivist paradigm. The main rational behind this philosophy is that it is not possible to make totally independent and objective observations of the world (objective reality), but should make all effort to get as close to the objective reality as possible, at the same time admitting the inherent limitations posed by our own subjectivity and ourselves being part of the reality (Introduction to quantitative research 2010). According to the post-positivist view, research can never be certain and one cannot fully uncover the objective reality. Rather, it emphasises on how much certainty one can have or how much confidence there is in predicting or understanding the objective reality. In this paradigm, "all observation is fallible and has error and that all theory is revisable" (Trochim 2006d). It underlines the importance of having different measures and/or observations. There could be inherent weaknesses in each of these observations and the reconciliation of the different approaches may yield the best approximation of the reality or truth (Trochim 2006d).

1.9 Structure of the dissertation

This dissertation is structured in the following manner:

Chapter 1: Study outline

Chapter 2: Literature review

Chapter 3: Research methodology

Chapter 4: Research findings

Chapter 5: Discussions, limitations, recommendations and conclusions
1.10 CONCLUSION

There is scarcity of evidence on the TB treatment outcomes of HIV co-infected TB patients, particularly so in the Ethiopian context. This is a cross-sectional study designed to provide evidence on the different outcomes of TB treatment and potential underlying factors that affect these outcomes among HIV co-infected TB patients in the Ethiopian context. The findings of the study will have relevance for improving the quality of services provided to co-infected TB patients by informing the formulation of standards of care that are required in the facilities providing these services. The selection of the sites for the study and the retrospective nature of the data collection method may limit the validity of the findings of the study.
CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, the researcher discusses the available body of knowledge, evidence and ideas around the research topic from the relevant literature. Literature review is described as “a ‘re’-view or ‘further look’ at what has previously been written on a particular subject” and is “intended to convey to the reader the current state of knowledge on a given subject along with the strengths and limitations of the underlying research” (Volmink 2007:66). The purpose of literature review is justifying planned research, contextualising new findings, interpreting the findings of the research, and facilitating access to or identifying existing relevant research under the subject being studied (Volmink 2007:66-67).

In reviewing the literature for this study, the following terms or concepts have been used to search for the relevant published literature on the topic: TB, TB infection, TB disease, TB diagnosis, TB treatment, TB treatment outcome, HIV, HIV infection, AIDS and opportunistic illnesses, and TB-HIV co-infection.

2.2 TUBERCULOSIS (TB)

This section will describe the existing evidence and context on TB. The different aspects of the problem of TB with respect to the clinical and programmatic perspectives will be discussed.

2.2.1 TB infection

It is estimated that one third of the world's population is infected with the Tuberculosis bacterium (CDC 2014). TB is one of the most prevalent communicable diseases that is caused by a bacterium called Mycobacterium tuberculosis, and is spread from person to person through the air (air borne infection) by inhaling the bacteria that are released into the air when a person with TB disease of the lungs or throat coughs or sneezes (CDC
Most people who have inhaled the TB bacteria and have become infected can fight and control the infection from multiplying and spreading in their body through their immune system. These individuals do not have symptom and/or signs of TB disease and do not spread the infection to other individuals but the TB bacteria live in their body as latent infection without causing disease. However, the latent TB infection can reactivate and cause active TB disease in these individuals if their immune system can no longer fight the infection due to other concurrent conditions that weaken their immunity, for example co-infection with HIV, underlying diabetes mellitus, and advanced age.

2.2.2 TB disease

When the TB bacterium multiplies and spreads in the body, it causes TB disease that can affect any part of the body but most commonly the lungs (respiratory system), and individuals with active TB disease, particularly those with TB of the lungs, transmit the TB infection to other individuals (CDC 2012b). People who have TB disease are sick and will have symptoms like chronic cough (usually with copious sputum), fever, sweating, weight loss, and other symptoms and signs specific to the organs affected by the disease.

TB disease continues to be a major global health problem; 8.6 million people worldwide are estimated to have developed active TB disease in the year 2012 (1.1 million of these were people co-infected with HIV) and approximately 1.3 million of them have died from the disease (WHO 2013a). Of these TB associated deaths, 320,000 were among those co-infected with HIV. Without effective treatment, TB disease is associated with high mortality rates; studies have shown that as high as 70% of smear positive TB patients (but not infected with HIV) will die in 10 years’ time (CDC 2014). In HIV infected individuals, TB is the leading cause of death (CDC 2012a).

Ethiopia is identified as one of the 22 High Burden Countries (HBC) in the world where 80% of the world’s TB cases are found (CDC 2013). The WHO global TB report for 2013 indicated that there were an estimated 230,000 (251 per 100,000) incident cases of TB in Ethiopia in 2012. There were an estimated 16,000 TB deaths (17 per 100,000) in Ethiopia during the same time period, excluding deaths among those co-infected with
HIV. The report also mentions that there were an estimated 23,000 HIV-positive incident TB cases in Ethiopia in 2012.

2.2.3 TB diagnosis

The diagnosis of TB disease is made through identification of suspected TB cases, and undertaking clinical evaluation and diagnostic tests as appropriate. Symptoms of TB disease that are most commonly used to identify suspected TB cases include cough of two weeks or more duration, fever, night sweating, and weight loss (Federal Democratic Republic of Ethiopia Ministry of Health 2013).

Confirmation of the diagnosis of active TB disease requires different diagnostic methods employing bacteriological, molecular, histo-pathological and/or radiological procedures. All TB suspects must be investigated using one or more of these methods according to the recommendation of nationally adopted standard TB diagnostic algorithms either to confirm or rule out active TB disease.

According to the Ethiopian guideline for the management of TB, a “proven case of TB” is an individual with two sputum smears or culture positive for Mycobacterium tuberculosis while one sputum smear positive is sufficient to confirm the diagnosis of TB in HIV positive patients. Any patient with Mycobacterium tuberculosis complex identified from a clinical specimen (sputum, cerebrospinal fluid, pleural or peritoneal fluid, joint aspirate or biopsy specimens) either by culture or by a newer method such as molecular line probe assay is also considered as a proven/definite case of tuberculosis.

2.2.4 TB treatment

For the treatment of patients diagnosed with active TB disease, chemotherapy with a combination of medications that are effective against TB bacteria is provided for a specified duration. The aims of treatment for TB patients are to cure the TB patient, prevent death from active TB or its complications, restore quality of life and productivity, prevent or decrease transmission of TB infection, prevent the development and transmission of drug resistance, and prevent relapse or recurrence of TB disease (Federal Democratic Republic of Ethiopia Ministry of Health 2013).
TB patients should receive optimal treatment so that these aims are met. Optimal TB treatment rapidly and substantially reduces the number of actively multiplying bacteria, cures TB disease, prevents relapse of active TB disease, and prevents the development of resistance to the drugs. Treatment of TB patients should include an appropriate combination of drugs, be prescribed in the correct dosages, be taken regularly by the patient according to the right schedule, and provided and taken for a sufficient period of time.

The duration of TB treatment consists of two phases: the intensive phase and the continuation phase. The type and number of drugs to be taken by the TB patients and the schedule of TB treatment vary depending on the phase of treatment, category of TB disease, and other concurrent health or physiological conditions of the patients (Federal Democratic Republic of Ethiopia Ministry of Health 2013).

2.2.5 TB treatment outcome

For any person who has been diagnosed with active TB disease and put on a course of anti-TB treatment, his/her last known status with regard to the treatment provided should be documented and reported. This is the outcome of the patient while on or at completion of anti-TB treatment. WHO and national TB programmes use standard definitions for the different possible outcomes of TB treatment for TB patients. The following TB treatment outcome definitions are taken from the Ethiopian national TB programme guideline (Federal Democratic Republic of Ethiopia Ministry of Health 2013:43).

**Cured:** A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

**Treatment completed:** A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
**Treatment failure**: A patient whose sputum smear or culture is positive at 5 months or later during treatment or patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.

**Died**: A patient who dies for any reason during the course of TB treatment.

**Defaulter**: A patient who has been on treatment for at least four weeks and whose treatment was interrupted for eight or more consecutive weeks.

**Transfer out**: A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.

**Treatment success**: A sum of cured and completed treatments.

### 2.3 HIV INFECTION

Human immunodeficiency virus (HIV) is a retrovirus that destroys the lymphocyte cells called CD₄ (cluster of differentiation 4) T lymphocytes in the blood and body, and causes acquired immunodeficiency syndrome (AIDS) in humans (Overview of HIV 2014). HIV was first isolated in 1983, and has two types (HIV-1 and HIV-2) and many subtypes (clades); the two types have distinct geographic, epidemiologic and pathologic features although both are transmitted by similar routes (Corcoran & Meintjes 2009:3).

HIV is transmitted from an infected individual to another individual through percutaneous or mucous membrane exposure to infected body fluids like blood, genital secretions, and breast milk. The probability of transmission varies based on the type of exposure (Kassaye & Levy 2009:39).

There were an estimated 35.3 million people living with HIV throughout the world in 2012, and there were 2.3 million new HIV infections and 1.6 million AIDS deaths in the same year (Joint United Nations Programme on HIV/AIDS 2013). The vast majority of these HIV infections and deaths occurred in resource poor countries of sub-Saharan Africa. In Ethiopia, there were an estimated 793,700 people living with HIV in the year 2013 including more than 200,000 children <15 years of age, and there were
approximately 45,200 AIDS related deaths in the same time period (Federal HIV/AIDS Prevention and Control Office 2014).

The natural course of HIV infection has multiple stages (Maniar, Surjushe & Pande 2009:133). The initial phase of acute HIV infection becomes clinically manifest within about 2-4 weeks of acquiring the virus and has non-specific and variable features that may include fever, rash, lymph node swelling, sore throat, all of which gradually subside without treatment and are rarely severe enough to lead to a visit to a health care provider. Following the acute HIV infection phase, a long period of chronic HIV infection sets in whereby there is slow but progressive decline in the individual’s immune function. This phase of chronic infection is further classified into early, intermediate and late stages. During the early phase of chronic infection, the patient may feel entirely normal though may have swollen lymph nodes if carefully examined. During the late stage of HIV infection, there is advanced immune deficiency and deterioration of the immune system that predisposes the HIV infected individual to infections and other disease conditions, (eg., Tuberculosis, cryptococcal disease, malignancies) (Maniar et al 2009:135).

2.4 AIDS AND OPPORTUNISTIC ILLNESSES

The first cases of AIDS were described in the Morbidity and Mortality Weekly Report (MMWR) by the United States Centers for Disease Control and Prevention (CDC) in 1981 about five cases of Pneumocystis Carinii Pneumonia (PCP) among homosexual men in Los Angeles, USA (CDC 2001).

The WHO has defined AIDS in adults and children with confirmed HIV infection as clinical diagnosis (presumptive or definitive) of any stage 4 condition (see Annex VI); or documented CD4 count less than 200 per mm³, or CD4% <15; or among children aged 12–35 months first ever documented CD4% <20; or among children less than 12 months of age CD4% <25 (WHO 2007b).

Opportunistic infections (OIs) are infections that occur because of advanced immunosuppression in HIV-infected persons and would not cause illness in non-HIV infected persons with intact immune systems (Department of Health and Human Services 2013). These infections are more frequent or more severe in HIV infected
individuals. Among the most common opportunistic infections that occur in HIV infected people are Tuberculosis, Pneumocystis Pneumonia, Toxoplasmosis, and Cryptococcus.

2.5 TB/HIV CO-INFECTION

Co-infection is the “simultaneous infection of a cell or organism by separate pathogens” (Mosby's Medical Dictionary 2009, Sv "co-infection"). TB/HIV co-infection is the concurrent presence of HIV and TB infection in an individual.

According to recent data from the WHO (WHO 2013b), TB is the most common presenting illness among HIV infected individuals coming for care and treatment services, and there were an estimated 1.1 million HIV positive new TB cases in 2012 throughout the world of whom 75% live in the resource-poor countries of the SSA. TB accounts for 20% of HIV-related deaths and is unrivalled as the leading cause of death among people living with HIV (estimated 320,000 people died of HIV-associated TB in 2012). Drug-resistant TB including multi-drug resistant (MDR-TB) and extensively drug resistant TB (XDR-TB) are emerging threats for HIV co-infected patients that may further undermine the TB control efforts in resource-poor countries (Gandhi, Moll, Sturm, Pawinski, Govender, Laloo, Zeller, Andrews & Friedland. 2006:1575-1580).

Among patients with latent TB infection, HIV is the strongest risk factor for TB disease progression and is associated with a 20.6-36.7% increased risk compared to HIV uninfected people with latent TB (Daley 2009:138). In addition to the increased risk of death observed in HIV co-infected patients, there is an increased rate of default and recurrence of TB disease in these patients (Daley 2009:143).

Routine programme reports at national programme level and also those reported to WHO do not specify TB treatment outcomes disaggregated by HIV status. This is clearly described in the 2011 and 2012 WHO Global TB reports. The reports state that “most countries with a high burden of TB lacked national or sample [vital registration] VR systems and few had conducted mortality surveys. TB mortality among HIV-positive people is hard to measure even when VR systems are in place because deaths among HIV-positive people are coded as HIV deaths and contributory causes (such as TB) are often not reliably recorded” (WHO 2012a). The 2011 global report by WHO further states that “Measurements of TB mortality among HIV-positive people from VR data remain scarce and are often unreliable. HIV deaths may be miscoded as TB deaths,
and TB deaths among HIV-positive people may be impossible to quantify because TB is only recorded as a contributory cause of death. About one third of countries submitting aggregated VR data on causes of death to WHO do not report data on contributory causes. Estimates of TB mortality in HIV-infected individuals thus remain highly uncertain” (WHO 2011b).

The same report makes a key recommendation by saying “The recording and reporting of the outcomes of TB treatment disaggregated by HIV status needs to be improved, using WHO-recommended TB registers (which should also be used by HIV service providers including ART clinics)” and further emphasises this with the heading “Better reporting of the outcomes of TB treatment by HIV status is urgently needed”.

There is a critical reason for demanding better information on disaggregated TB treatment outcomes as stated in the report. In their “Stop TB Partnership,” WHO and UNAIDS have set a target of halving the number of TB deaths among HIV-positive people by 2015 compared with 2004 (the year in which TB mortality among HIV-positive people is estimated to have peaked). To assess whether the goal is achieved, data on mortality rates among HIV-positive TB patients during TB treatment are needed. In turn, this requires that treatment outcomes for TB patients are disaggregated by HIV status; that is, outcomes are available for HIV-positive and HIV-negative TB patients separately (WHO 2011b).

According to the WHO Global TB Report for 2013, 96 countries reported TB treatment outcomes disaggregated by HIV status for the year 2011, and among the 41 countries identified as priority countries, only 19 countries reported disaggregated TB treatment outcomes (WHO 2013a). Ethiopia was not among the countries listed as reporting TB treatment outcomes disaggregated by HIV status.

A prospective observational study in a high HIV and TB prevalence region in India to compare the TB treatment clinical response (patient outcomes) of newly diagnosed adult pulmonary TB patients showed that treatment success rates (cured or treatment completed) were significantly lower in HIV positive TB patients than in HIV negative TB patients (66% vs 85%), and 29% of the HIV positive and 1% of the HIV negative patients died during the course of TB treatment (Tripathy, Anand, Inamdar, Manoj, Khillare, Datye, Iyer, Kanoj, Thakar, Kale, Pereira & Risbud 2011:521-528). The follow-
up period for the study lasted for 30 months including 6 months on TB treatment and 24 months of follow up after completion of TB treatment. During the entire period of 30 months in the study, 61 (51%) of the 121 HIV positive patients died but there were only 6 (4%) deaths among HIV negative patients. The study was conducted during the time when ART was not available in the region, and none of the HIV positive study participants received ART or any form of prophylactic treatment during the study follow-up period.

A retrospective cohort study in San Francisco, USA, that evaluated treatment outcomes in HIV co-infected TB patients demonstrated that significantly more HIV co-infected patients died than other TB patients, and HIV co-infected TB patients that were on ART during the course of treatment for TB had a significantly lower mortality when compared with HIV-infected patients who didn't receive ART (Nahid, Gonzalez, Rudoy, Jong, Unger, Kawamura, Osmond, Hopewell & Daley 2007:1199-1206). In addition, those patients who received both TB treatment and ART have a faster sputum smear and culture conversion to negative than those not treated with ART.

A study conducted in a large TB treatment centre in Malawi to compare treatment outcomes among new smear-positive pulmonary TB patients 15 years of age and above, based on HIV status and anti-retroviral treatment (ART) status, showed that HIV co-infected TB patients had worse TB treatment outcomes (Tweya, Feldacker, Phiri, Ben-Smith, Fenner, Jahn, Kalulu, Weigel, Kamba, Banda, Egger & Keiser 2013:e56248). In the study, there was a higher likelihood of a successful treatment outcome in those HIV co-infected TB patients who were on ART.

A recent Nigerian study from a retrospective cohort of pulmonary TB patients in one hospital in Abuja from 2007 to 2012 to determine the differences in TB treatment outcome between patients with TB/HIV co-infection and TB patients without HIV infection showed that HIV co-infected TB patients have a lower treatment success rate (48.8% vs. 78.5%), a higher rate of treatment failure (10.8% vs. 4%), and a higher rate of default (38.6% vs. 17%) than TB patients without HIV infection (Ofoegbu & Odume 2015: 50-56).

Another retrospective review of case records from a tertiary centre in India that assessed the treatment outcomes of co-infected TB patients and the factors related to
poor outcome indicated that the overall rate of favourable outcome (cured or completed treatment) to anti-tuberculosis treatment was 77%, and those with advanced immune suppression (CD4<200/mm3) and those on retreatment had unfavourable outcomes that include death, failure and default (Sharma, Soneja, Prasad & Ranjan 2014:157).

A retrospective cross-sectional study using routine programme report data to compare the outcomes of TB treatment among HIV co-infected and non HIV infected TB patients in a province in India found that treatment successes (cured or treatment completed) were similar between HIV co-infected TB patients and those who have only TB (Shastri, Naik, Shet, Rewari & Costa 2013:4). In this study, while death rates were higher in the co-infection group, rates of default and treatment failure were higher among non HIV infected TB patients.

To date, in Ethiopia, there is serious lack of data that specifically addresses the issue of TB treatment outcomes of HIV co-infected TB patients. A recent retrospective cohort study conducted in north-west Ethiopia to identify predictors of mortality among HIV co-infected TB patients showed that the death rate was 65% lower in TB-HIV co-infected patients treated with ART than those not treated with ART (Sileshi, Deyessa, Girma, Melese & Suarez 2013:297). But, in the study, direct comparisons with non-HIV infected TB patients and data on other TB treatment outcomes is lacking.

Another study with similar retrospective design and looking at a five year cohort of HIV co-infected TB patients (from 2009 to 2013) in western part of Ethiopia showed a treatment success rate of 60.7% over the five year period (Ejeta, Birhanu & Wolde 2014:164-171). The results from the study show that there is progressive improvement in treatment success rate over the five year period from 12.5% in 2009 to 84.3% in 2013. The study identified receiving HIV care, co-trimoxazole and ART as factors associated with treatment success. However, similar to the other study, there was no comparison of the treatment outcomes with non-HIV infected TB patients. The study used a small sample size and also considered the outcome ‘transfer-out’ as a negative outcome (which may not be the case for many patients).

A retrospective study that assessed the “trend of TB and treatment outcomes” in the Gambella region of Ethiopia in the five year period from 2006 to 2010 showed that 63.4% were ‘successfully treated’, 22.9% defaulted their treatment, 3.6% had died,
0.09% had treatment failure and 10% were transferred out to other health facilities (Demeke, Legesse & Bati 2013:130). The study identified patient age above 15 years and the gender of the patients to be associated with treatment success, but it did not look at HIV status of the study participants and had no description of their treatment outcomes by HIV status.

This literature review includes very relevant studies from high disease burden and resource limited settings. It has focused on the published data most importantly from sources that represent the geographic and population profiles of the settings where HIV infection and TB disease are highly prevalent. The studies are observational and most of them are retrospective in design. The review includes studies both from the pre-ART era when HIV co-infected TB patients were not receiving interventions for treating the HIV virus or other concurrent opportunistic illnesses, and also from recent time periods and settings where provision of ART and management of any associated illnesses (for co-infected TB patients) is the standard practice, including prophylactic treatment for opportunistic illnesses. It includes a balanced and appropriate mix of study designs, settings and delivered services, and looked adequately into the existing evidence to enable a fair judgement of what is already known regarding the research questions posed.

Other studies that evaluate the outcome of TB treatment were excluded from the literature review because either their main focus is on programmatic aspects, like mode of service delivery (for example Directly Observed Treatment), method of TB case finding, improving tracking of treatment outcomes etc…, or they do not include disaggregation and comparison by HIV status when evaluating TB treatment outcome. Some studies that looked at TB treatment outcome were focused narrowly on specific issues like hospitalization, or only a sub-set of TB patients (for example, patients with pulmonary TB or extra-pulmonary TB). These studies were also excluded because the specific research questions and the findings they are looking for are significantly different from the ones in this study.

This study attempts to address key questions on TB-HIV co-infected patients who have been put on a course of anti-TB treatment. Similar to the studies described above, the study will determine the TB treatment outcome among HIV co-infected TB patients, and identify any differences in treatment outcome in comparison with non-HIV infected TB
patients. In addition, the study will look for other factors (other than HIV) that are potentially associated with the adverse patient outcomes among HIV co-infected TB patients. Unlike some of the studies mentioned above, since a wide range of comprehensive HIV care and treatment services are currently available in Ethiopia, the HIV co-infected TB patients in the study would have received other related HIV care and treatment services including ART, co-trimoxazole prophylactic treatment, adherence support, nutritional support and other indicated services.

2.6 CONCLUSION

This literature review has elaborated on the wide range of concepts and existing evidence on TB/HIV co-infection and outcomes of TB treatment. Based on this review, various programme reports and some studies on TB treatment outcomes have indicated that the health outcomes of TB/HIV co-infected individuals have been adversely affected by the presence of HIV even after efficacious treatment of TB disease. However, there is lack of reliable data from resource poor countries to fully understand the current scale of the problem and the contributing factors to the unfavourable outcome observed in this group of patients. It is critical to understand the differences in health outcomes among co-infected and non-HIV infected TB patients, and identify potential contributing factors for these adverse outcomes. This proposed study will attempt to address this knowledge gap and potentially inform formulation of strategies and standards of care that will improve the health care service delivery and patient outcomes in HIV co-infected TB patients.
CHAPTER 3

RESEARCH DESIGN AND METHOD

3.1 INTRODUCTION

In this chapter, the research paradigm, the research design and methods used in the study are discussed. A quantitative, non-experimental, cross-sectional, analytic design is used to conduct the study. The study population, the sources for the study data, the sampling techniques and procedures, the data collection tool, and the characteristics of the tools will be described. The types of data analysis, and the tools and procedures for the analysis are outlined. In addition, ethical issues concerning the study are also addressed.

3.2 RESEARCH PARADIGM

The research paradigm for this research is the post-positivist paradigm which underlines that it is not possible to make totally independent and objective observations of the world (objective reality), but should make all effort to get as close to the objective reality as possible, at the same time admitting the inherent limitations posed by our own subjectivity and ourselves being part of the reality (Introduction to quantitative research 2010). According to the post-positivist view, research can never be certain and one cannot fully uncover the objective reality. Rather, it emphasises on how much certainty one can have or how much confidence there is in predicting or understanding the objective reality. In this paradigm, "all observation is fallible and has error and that all theory is revisable" (Trochim 2006d). It underlines the importance of having multiple measures and/or observations which have different types of error inherent to each of them, and using ‘triangulation’ of the information from these multiple sources to reach close to the objective reality. It recognizes that there could be inherent weaknesses in each of the different observations and the reconciliation of the different approaches may yield the best approximation of the reality or truth (Trochim 2006d).
In considering this research paradigm for this study, as will be discussed in the following sections, the researcher recognises the limitations that are inherent in selecting the study sites purposefully, the accessible population used for the study which may have their own unique characteristics in health seeking behaviour, and the fact that determining HIV status of the study participants relies on voluntariness and availability of the services at the time of receiving medical care which have been happening before the beginning of the study. Therefore, this study will provide its own share of evidence to reach to the truth or objective reality in answering the research questions posed to respond to the research problem. It also emphasises that other methods and sources of data, using different settings, and possibly a combination of quantitative and qualitative design will contribute significantly to attaining greater objectivity and answering the research questions satisfactorily.

3.2 RESEARCH DESIGN

A structured approach employed by investigators to answer a specific research question is referred to as research design, and the design determines the sampling techniques and the collection and analysis of the study data (Morroni & Myer 2007:77). The objectives of the research and the specific research questions expected to be answered by the research determine the choice of the research design. The type of research design chosen has implications regarding the ethical issues involved in conducting the research and also on the cost of the research. The research design for this study is a quantitative, non-experimental, cross-sectional, analytic design. The aspects of this design are briefly described in sub-sections below.

3.2.1 Quantitative aspect of design

This study has a quantitative research characteristic. Quantitative research designs are employed to determine the relationship between variables within a defined population (i.e. look at cause and effect), and randomly selected samples (with larger sample sizes that are representative of the target population) are studied with the research data gathered through precise measurements using structured and validated data-collection instruments (Quantitative Methods 2014). In quantitative studies, there are clearly defined research questions at the conception of the studies and the investigator seeks objective answers to these questions. In this type of design, selected specific variables
are studied, and the data analysis is performed to identify statistical relationships. The study data are in the form of numbers and statistics, and are often presented in tables, charts, figures, or other non-textual forms. Throughout the study process objectivity by the researcher is required and all forms of bias are to be avoided. The most common objectives of quantitative research are to describe, explain, &/or predict phenomena. The study findings are commonly reported statistically with correlations, comparisons of means, and statistical significance of findings. The results of a quantitative study design are generalizable and can be applied to other populations or settings. This study compares outcomes of TB treatment and attempts to identify predictors of the differential outcomes among randomly selected study participants using objective research methods. A pre-designed and validated data collection instrument (Annex V) is used to obtain the study data, and data analysis is performed to make comparisons, assess correlations, and test statistical significance.

3.2.2 Non-experimental aspect of design

In non-experimental or observational study designs, the researcher observes or measures the presence or occurrence of exposure and outcome, but does not introduce any form of intervention (Morroni & Myer 2007:77). In this study there is no intervention introduced by the researcher, and all exposure and outcome variables to be used in the study are captured as they existed or happened during the time frame selected for the study.

3.2.3 Cross-sectional aspect of design

A cross-sectional study design is aimed at determining the frequency (or level) of a particular attribute, such as a specific exposure, disease or any other health-related event, in a defined population at a particular point in time; i.e. the required information is obtained from or about the population or the study participants at a fixed point in time (Silva 1999:213-214). Cross-sectional studies can also attempt to go further than just providing information on the frequency (or level) of the attribute of interest (ex. disease outcome) in the study population by collecting information on both the attribute of interest and potential risk factors (predictors) such as socioeconomic status, intravenous drug use, sexual behaviour, etc. Therefore, cross sectional study designs
can be used to investigate and/or analyse associations between an attribute of interest and other underlying risk factors.

In this study, information on outcomes (of TB treatment) and potential risk factors (exposures) are collected at one point in time. The study attempts to investigate associations between outcomes and other risk factors among the study participants in the comparison groups.

3.2.4 Analytic design

Analytic aspect of the design enables the researcher to examine potential association or relationship between an exposure and an outcome (Morroni & Myer 2007:79). In this study, there is comparison of two groups of TB patients (HIV infected versus HIV non-infected) to assess for any differences in treatment outcomes among the two groups and to identify potential predicting factors responsible for the differences. Information on underlying risk factors (exposures) and outcomes of TB treatment for both comparison groups is collected. This information is used to analyse any associations between the outcomes and any of the exposure variables (risk factors).

3.3 RESEARCH METHOD

The research method relates to the systematic procedures employed in selecting the study sample, collecting data, analysing the data and addressing ethical issues relevant for conducting the study. The different components of these procedures are described below.

3.3.1 Population

The group to which the results of the study will be generalised to is called the study population and consists of all the subjects one wants to study (Trochim 2006c). The target population for this study is all patients diagnosed with active TB disease and put on anti-TB treatment regimens. The accessible population is all patients diagnosed with active TB disease and put on anti-TB treatment regimens in the selected health facilities for this study (see Annex VII for list of selected health facilities). The listing of the
The accessible population from which the study sample is drawn is called the sampling frame (Trochim 2006c).

The data source for this study is the TB register (Annex IV) at the TB clinics of the health facilities (health centres and hospitals) where all patients diagnosed with active TB disease are put on anti-TB treatment regimens and monitored throughout the course of their treatment. The TB registers in the TB clinics of these health facilities are used to record all relevant patient level and clinical information for the treatment and monitoring of TB patients, and also for reporting of patient level data based on the national guidelines. Therefore, the sampling frame for this study is the list of all TB patients enrolled (within the selected time frame for the study, which is January 2013 – December 2013) in the selected health facilities at which the study is conducted.

### 3.3.2 Sampling

Sampling is the process of selecting a subset (group of subjects) of the population of interest, and this subset is meant to represent the entire population from which it is selected (Yount 2006:1). This representative subset of a population is called a sample.

A simple random sampling method is used to enrol eligible study participants into the study. The number of study participants to be enrolled from each selected health facility is determined proportionally (based on patient load). A table of random numbers is used to select and enrol study participants into the study sample from the sampling frame at each health facility.

### Inclusion criteria

- Any individual who has been diagnosed with active TB disease based on the Ethiopian national TB guidelines recommendations.
- He or she has been started on a course of anti-TB treatment regimen within the time frame of the study period.
Exclusion criteria

- Any individual who has taken less than four weeks of the course of anti-TB treatment regimen.
- Individuals less than 15 years of age at initiation of anti-TB treatment.

The study sites (health facilities) included in this study are selected based on convenience (geographic accessibility) and patient load among all health centres within the Addis Ababa city administration which is a major urban setting and capital of Ethiopia. Based on the current TB patient load at each site and the number of patients required to meet the sample size, eight health facilities are selected (by convenience) for conducting the study. The reason for selecting the study sites on convenience is due to the limited time available to conduct the study and the challenges of logistics to access potential study sites that would be selected by random sampling method. This is a limitation of the study which can affect the external validity of the study findings (i.e. its generalizability).

Sample size

The sample size calculation is done using the Epi Info 7 statistical software program. Since this is a cross-sectional study and comparison is made in the TB treatment outcomes between HIV co-infected TB patients and non-HIV infected TB patients, the estimated or known proportion of the outcomes for both groups (from similar studies or reports etc.) is taken into consideration to calculate the sample size. The prevalence of HIV in incident TB cases in Ethiopia was estimated at 17% (WHO 2012a). The reported TB treatment success rate for year 2009 indicated in the 2011 WHO global TB report (2011b) shows a TB treatment success rate of 72% and 88% for HIV co-infected and non-HIV infected TB patients respectively. Using these background data as inputs to the epi info 7 statistical software to calculate the sample size, the smallest sample size required for this study is 350 TB patients (61 HIV co-infected, 289 non HIV infected) with a two sided confidence level of 95% and a power of 80%.
3.3.3 Ethical issues related to sampling

In this study, only the individual patient information and clinical data that were obtained during routine medical care provision and had been recorded in the TB clinic registers are abstracted. The abstracted data pool includes only anonymous data without any personal identifiers. No additional information beyond what has already been gathered during the medical care of the study participants is collected. All study participants have completed their treatment follow-up and have received the standard of care based on the national guidelines recommendations by the time they are enrolled in to the study. All data and information collected are handled only by the data collector(s) and the investigator, and are securely protected. All data are held confidentially and will not be used or shared outside the scope of the study. All paper and electronic formats for collecting and processing the research data are kept in a secured locked place, and electronic formats are password protected. This is done to avoid loss of confidentiality of their personal information and to make sure that there is no risk or harm to study participants as a result of their enrolment and participation in the study.

The final version of the study protocol has been submitted and ethical clearance obtained from the local IRB (Annex I) and the UNISA College of Human Sciences (CHS) Health Studies Higher Degrees Committee (HSHDC) [Annex III] prior to commencement of the study. Permission is secured from the head of the selected facilities (sites) for conducting the study prior to the commencement of the data collection for the study (Annex II).

The findings of the study will be shared with the health workers and management team of the health facilities where the study was conducted, and other implementing partners and donors that support the TB/HIV activities in the facilities and the region. It will also be shared with the health governing bodies at regional and national level as appropriate including at national technical working groups. The information gained through the study will be used to improve the delivery of quality medical care services for all TB patients.
3.3.4 Data collection

3.3.4.1 Data collection approach and method

A data collection tool that is pre-designed to capture the relevant individual patient level data is used to abstract data from the TB registers (Annex IV). There is no interaction with study participants. All data collected have already been obtained during routine patient care and recorded in the TB register. The information collected in this data collection tool is subsequently transferred to another data entry electronic data sheet prepared specifically for the purpose of the study.

3.3.4.2 Development of the data collection instrument

A data collection tool that is designed to capture all relevant information and/or variables for the study is developed. This tool was designed in such a way that all patient level and clinical data can be abstracted and entered into the tool easily, clearly and completely. The tool is in paper format for ease of use at the selected sites. An electronic format is used to enter the data for analysis after the data collection has been completed.

3.3.4.3 Characteristics of the data collection instrument

In this study, for the purpose of collecting the required study data, a data collection instrument or tool has been developed by the researcher (Annex V). This tool or instrument is developed based on the standard TB registers that are available at the eligible sites to be included in the study. The data to be collected is secondary data that was extracted and documented on the TB registers during the process of routine medical care provision to these patients by the health care providers at these sites. The data collection instrument is designed to capture these data from the TB registers. Each variable (ex. HIV status, TB category etc.) has a separate space and a box or place where the appropriate response is made. In this way, each variable pertaining to the study participants’ baseline characteristics, disease specific data, medical care received, and the outcome and relevant time-line with respect to starting and terminating medical care and/or follow-up can be abstracted. For each variable all possible values are accounted for and avoid additional measurements, approximations
or inferences. The tool is completed by marking on the given boxes after each applicable given value or documenting a value (ex. age or date). It is simple to use, and all variables are easily understood.

3.3.4.3.1 Validity of the data collection instrument

Validity is “the extent to which a measurement instrument actually measures what it is meant to measure” (Katzenellenbogen & Joubert 2007:117). An instrument is valid only to the extent that the value or score allows making appropriate assessment or inference about a specific group of subjects and for specific purposes (Siegle [s.a.]). Among the different concepts in evaluating validity, content validity and face validity of the tool were evaluated.

Content validity is whether “the measure accounts for all the elements of the variable or concept being investigated” (Katzenellenbogen & Joubert 2007:120). The data collection tool for this study captures baseline demographic information, HIV and TB disease specific and medical care specific patient level data, and TB treatment outcome data. This information is the basis for the objectives in this study and is adequately accounted for in the tool. Two experts in the field of TB/HIV were given the tool for review. They agreed that the tool can account for all the variables required under the objectives of the study.

Face validity is “the extent to which the measure ... makes sense to those knowledgeable about the subject” (Katzenellenbogen & Joubert 2007:120). Experts working in TB programme and TB medical care have been consulted during the development of this protocol and the data collection instrument. All of the experts gave the opinion that the overall study is a relevant and timely undertaking, and the data collection instrument also can effectively accomplish the task for which it is designed.

3.3.4.3.2 Reliability of the data collection instrument

The classical test theory states that any observed score or value obtained by a measuring instrument or tool consists of both the “true” score and “error” in the measurement process; therefore, reducing error in the measurement process is the main focus in developing a valid measuring instrument or tool (Kimberlin & Winterstein
The degree of similarity of the results of repeated measurements by a measurement instrument or tool (ex. on the same item, subject or group) is the reliability or precision of the measuring instrument or tool (Katzenellenbogen & Joubert 2007:117).

Poor reliability of a measuring instrument can be decreased or improved by identifying and addressing the source of the variation between measures. Pretesting or pilot testing of a measuring instrument helps to identify and rectify these sources of variation thereby refining the instrument and minimising measurement error (Kimberlin & Winterstein 2008:2277).

In this study, there is no direct data collection from study participants. All data collected are secondary data that are already collected and documented by health providers during medical care of the TB patients. The tool to collect these data serves as data collection check-list to abstract this secondary data. A copy of the data collection tool and the standard TB register were shared with a statistician (a consultant in a university) for his assessment of the tool and to establish Cronbach alpha score to measure the reliability of the tool. Following his recommendation, the researcher did a pre-test of the tool by abstracting 15 patients’ entries in the TB register (which are not part of the study) to make sure that the check list collects what is intended to be collected and check for consistency.

The pre-test showed that the tool can collect the intended data and was 100% consistent on repeated measurements. The statistician recommended that it is not necessary or applicable to measure the reliability coefficient as the tool is not used for primary data collection. Furthermore, data collected from patient information available in medical records are generally considered more objective “because the reliability and validity of the measures are known, with the error margins and reporting of results meeting generally rigorous standards” (Kimberlin & Winterstein 2008:2277). Therefore, the data collection tool for this study is found to be reliable.

3.3.4.4 Data collection process

The TB registers are used as the sampling frame. The sample is selected from the TB registers using simple random sampling of the TB patients in the register within the
appropriate time frame. A table of random numbers is used for randomly selecting the study participants from the TB registers. The sampling interval is determined based on the patient load at the respective health facility. For those study participants randomly selected using this method, the data collectors abstract the required data from the TB registers to the data collection tool. At the end of each day of data collection, the data collectors check the data for completeness.

3.3.5 Data analysis

The collected study data is entered to an excel sheet and subsequently imported to Statistical Package for Social Sciences (SPSS) (PASW Statistics 18) statistical software for analysis. Data checking is conducted for any errors, missing or strange values and implausible results. Exploratory data analysis using tables and charts is done to further understand the data and detect errors and strange values. Then, the data is summarised and analysed using the statistical software.

Descriptive data is summarised and presented using tables and charts. Odds ratios are calculated for the different groups and sub-groups. Comparison of TB treatment outcomes is performed for HIV co-infected and non-HIV infected individuals (and also between subgroups if appropriate) using chi-square test to see if observed differences between the two groups are significant. Fischer's exact test is used if the numbers in the 2X2 table are very small (where the chi-squared test is not valid). Logistic regression is used to look at associations between individual patient demographic and clinical characteristics and TB treatment outcomes.

3.4 INTERNAL AND EXTERNAL VALIDITY OF THE STUDY

3.4.1 Internal validity

The internal validity of a study is how much confidence will be there to allow choosing among different possible or alternative explanations for the observed results (Trochim 2006b). That is the degree with which it avoids confounding.
In enrolling study participants in to this study, the investigator includes in the sampling frame all patients in the selected facilities who meet the inclusion criteria. Study participants are selected randomly using a table of random numbers and the number of participants from each site is allocated proportional to patient load. The inclusion criteria are broad enough to enable enrolling most of the TB patients in the facilities selected for the study. This enhances the internal validity of the study by avoiding the selective exclusion of TB patients during sample selection.

3.4.2 External validity

External validity refers the generalisability of the findings of the study. This is the degree to which the conclusions made in the study would be applicable to other settings like different geographic area, populations or time periods (Trochim 2006a).

In this study, an adequate sample size is used based on estimations from sample size calculations to maximize the external validity of the study findings. The sample size is calculated based on the expected proportions (of outcomes) under each study group of patients. Probability sampling method is used to select the study participants.

3.4 CONCLUSION

This study is designed to generate evidence on the health outcomes of HIV infected TB patients after a course of standard TB treatment in selected health facilities within the Addis Ababa city administration in Ethiopia. The health outcomes of these co-infected TB patients is compared with that of the non-HIV infected TB patients and the investigator attempts to identify determinants of any differential outcomes among the two groups in the Ethiopian context.

The study has a cross-sectional design and existing data from TB registers in the selected facilities are used. Data are abstracted from these registers by trained data collectors and there is no interaction with the study participants. The sites that participate in this study are selected purposefully but the selection of individual study participants is through probability sampling.
The data are checked for errors and entered into appropriate statistical software for analysis. The data analysis includes descriptive presentation of the data and also further statistical analysis for identifying associations among the different variables and outcomes. The results of the study will be shared and/or disseminated to the participating sites, the local health governing bodies, stakeholders, and other relevant forums as appropriate.
CHAPTER 4

ANALYSIS, PRESENTATION AND DESCRIPTION OF THE RESEARCH FINDINGS

4.1 INTRODUCTION

This chapter describes the process and findings of the analysis of the data collected for the study from the TB registers in the eight TB clinics where the study participants had been following their medical care. The investigator discusses the data management process, the baseline characteristics of the study participants, and the findings in the data analysis with respect to the objectives of the study. The objectives of the study are: (1) to assess TB treatment outcomes in HIV co-infected TB patients; (2) to compare the treatment outcomes among HIV co-infected and non-HIV infected TB patients; and (3) to identify determinants of adverse TB treatment outcomes among HIV co-infected TB patients.

4.2 DATA MANAGEMENT AND ANALYSIS

There were eight purposefully selected health centres in Addis Ababa that were included as sites for this study. The sites were selected based on patient load and accessibility. The investigator went to the respective health facilities (health centres) that were selected for the data collection and presented the support letter (Annex II) he received from the Ethical Clearance Committee of the Regional Health Bureau (RHB) to the head of each facility to gain access to the TB registers at these sites. The head of the respective health facilities granted access to the TB clinics (where TB patient registers are located) and advised the health workers at the TB clinics to facilitate and support the investigator in collecting the data required for the study.

The TB registers used in the TB clinics of Ethiopian health facilities are paper based tools and completed manually by the health workers at the TB clinics. They contain the demographic and medical (disease, treatment and outcome) information of all TB patients attending the specific health facility over a long (up to two years or more) period.
of time. Since the study participants that are to be enrolled in to the study have already completed their course of TB treatment and medical care by the time of the data collection and the required data for the study has already been collected and documented at the TB registers in the course of the medical care of the study participants, a waiver for the informed consent of the study participants has been already obtained from the local IRB. The investigator requested for the TB register that was used during the study period (January – December 2013) at each of the selected facilities. The registers were never removed from the site and remained in an isolated and private area within the TB clinic throughout the data collection process. At the end of the data collection, the TB registers were returned intact to the health worker at the TB clinic of the health facility on the same day. No part of the register or any of the content was copied or photographed. The data collection tool was used to abstract the required data without any personal identifiers.

The investigator identified the appropriate TB registers at the TB clinics in the selected sites and marked the list of TB patients that had been enrolled in the registers within the time frame of the study period (i.e. beginning of January 2013 to end of December 2013). The TB clinics used the Ethiopian calendar in the registers which is different from the European calendar on the dates and year count. The investigator used the Ethiopian calendar used in the TB registers to identify the 12 months of the study period, and there was no drawback encountered in using this approach. TB patients are enrolled in the TB register sequentially with unique TB numbers (Annex IV). The TB register was used as a sampling frame to randomly select the study participants. The investigator used a table of random numbers to select and enrol the study participants into the study. Those study participants who were found not to fulfil the inclusion criteria were excluded from the study sample.

The investigator used the prepared data collection tool to collect the data of randomly selected study participants from the TB registers. Each selected study participant was given a code and no personal identifiers were collected. The tool worked very well in capturing the required data. The health workers at each site supported the data collection by clarifying some ambiguous and/or missing data in the registers. The collected data were checked for completeness and accuracy at the end of the data collection process at each site (using 5% of the collected data and cross-checking with the TB registers).
The collected data were transferred to an electronic format (Excel sheet) that was prepared to capture the study variables from the data collection tool. The data in the Excel electronic format were cleaned. Those study participants with missing data were identified. Study participants without documented TB treatment outcome data (<1% of the sample) were excluded from the study sample as their data cannot be part of the analysis. The most common missing data were baseline HIV status. The commonest reason for undocumented HIV status was unavailability of HIV test kits at the time of enrolment to TB treatment. There was very limited information on patients who declined to be tested for HIV. These study participants with missing HIV status information were kept with the study sample to be part of the data analysis.

The investigator imported the cleaned data to SPSS statistical software (PASW Statistics 18) from the electronic Excel format. The continuous variable age was recoded into age groups for the purpose of the analysis. The treatment outcome was also recoded into two groups. The treatment outcomes ‘Cured’ and ‘Treatment completed’ were grouped together as favourable treatment outcomes or treatment success. The other treatment outcomes were put together as unfavourable treatment outcomes. The following sections discuss the findings of the analysis using tables and graphs as appropriate.

4.3 RESEARCH RESULTS

Under this part, the findings of the study analysis will be presented including the baseline characteristics of the sample, the disease specific and TB treatment specific patient level information of the study participants, and the results of the analysis.

4.3.1 Sample characteristics

In this section, the baseline characteristics of the study participants at the beginning of their course of treatment will be presented.
4.3.1.1 Age distribution

The age of the study participants ranged from 15 years to 90 years with 58.3% in the 25-49 age range. Table 4.1 shows the age distribution of the sample.

Table 4.1 Age distribution of study participants (N=575)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>151</td>
<td>26.3</td>
</tr>
<tr>
<td>25-34</td>
<td>184</td>
<td>32.0</td>
</tr>
<tr>
<td>35-49</td>
<td>151</td>
<td>26.3</td>
</tr>
<tr>
<td>50-64</td>
<td>60</td>
<td>10.4</td>
</tr>
<tr>
<td>64-90</td>
<td>29</td>
<td>5.0</td>
</tr>
<tr>
<td>Total</td>
<td>575</td>
<td>100.0</td>
</tr>
</tbody>
</table>

4.3.1.2 Gender distribution

Male gender accounted for more than half of the study sample as depicted in the pie chart below.

Figure 4.1 Gender distribution of the study sample (N=575)

4.3.1.3 HIV status of the study participants

Among the 575 study participants enrolled in the study sample, 529 (92%) of them had a documented HIV test offered and performed at or prior to the beginning of their course.
of anti-TB treatment. Almost one-third of the study participants have documented HIV co-infection (i.e. HIV positive). This is in contrast to the country report for Ethiopia for 2013 (WHO 2014b) which shows that 71% of TB patients with known HIV status and 11% of these being documented as HIV positive.

Table 4.2  HIV status of the study participants (N=575)

<table>
<thead>
<tr>
<th>HIV status</th>
<th>Number</th>
<th>Percentage</th>
<th>Percentage among tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-reactive (HIV-negative)</td>
<td>360</td>
<td>62.6</td>
<td>68.1</td>
</tr>
<tr>
<td>Reactive (HIV-positive)</td>
<td>169</td>
<td>29.4</td>
<td>31.9</td>
</tr>
<tr>
<td>Missing (not done)</td>
<td>46</td>
<td>8.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>575</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

4.3.2  TB disease characteristics of the study participants

The characteristics of the TB disease in the study participants with respect to the standard categories and disease classification are described in this section.

4.3.2.1  TB disease classification

Most of the study participants were diagnosed with pulmonary tuberculosis (55.8%) and a quarter of all cases of TB were found to have smear-positive pulmonary tuberculosis (P/pos). Extra-Pulmonary (EP) cases accounted for 44% of the total. Figure 4.2 depicts the TB disease classification among the study sample.
4.3.2.2 TB treatment category

The majority of the study participants were new TB patients who started their TB treatment at the health facility where they have completed their course of TB treatment. Twenty patients (3.5%) were put on TB treatment either due to relapsed smear positive pulmonary TB (R), TB treatment failure at the end of the course of TB treatment (F), or re-started on TB treatment after defaulting on their treatment (D). Table 4.3 depicts the distribution of the different categories of TB treatment of the study participants.

Table 4.3 Category of TB treatment of the study participants (N=575)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Default</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Failure</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>New</td>
<td>488</td>
<td>84.9</td>
</tr>
<tr>
<td>Other</td>
<td>51</td>
<td>8.9</td>
</tr>
<tr>
<td>Relapse</td>
<td>17</td>
<td>3.0</td>
</tr>
<tr>
<td>Transfer-in</td>
<td>16</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>575</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
4.3.3 Other medical care services received by the study participants

For those study participants who have co-infection with HIV, other medical services are available and recommended as part of the management of their underlying HIV infection and other associated illnesses. Enrolment in HIV care will enable the study participants to receive relevant HIV care and support services as dictated by their overall health status, for example adherence counselling, nutritional support, screening and treatment or prophylaxis for other opportunistic diseases, etc. Prophylactic treatment with co-trimoxazole is part of the standard of care for HIV co-infected patients receiving TB treatment. It is also recommended that all HIV patients with active TB disease and on a course of TB treatment be started on anti-retroviral treatment (ART). Figure 4.3 shows the documented status of the study participants with respect to the provision of these medical services.

![Figure 4.3 Status of other medical care services received by the study participants who have co-infection with HIV (N=169)](image)

4.3.4 Treatment outcomes of the study participants

Analysis of the study data demonstrates that the outcome of TB treatment for the study participants shows a very high overall treatment success rate (91.5%) defined as either ‘Cured’ or ‘Treatment completed’ after a course of anti-TB treatment. The treatment success rate among all new TB patients was 92.2%, and it was 93.6% among non-HIV infected TB patients. The treatment success rate among HIV co-infected TB patients was 88.2%. This finding persists at 91.9% treatment success rate even after excluding
those study participants with unknown HIV status. Table 4.4 shows the rate of the different treatment outcomes in the study.

Table 4.4  Outcomes of TB treatment in the study participants (N=575)

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>106</td>
<td>18.4</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>420</td>
<td>73.0</td>
</tr>
<tr>
<td>Defaulted</td>
<td>15</td>
<td>2.6</td>
</tr>
<tr>
<td>Died</td>
<td>27</td>
<td>4.7</td>
</tr>
<tr>
<td>Failure</td>
<td>7</td>
<td>1.2</td>
</tr>
<tr>
<td>Total</td>
<td>575</td>
<td>100.0</td>
</tr>
</tbody>
</table>

A prospective observational study in a high HIV and TB prevalence region in India had shown a treatment success rate of 66% for HIV co-infected TB patients compared to 85% in non-HIV infected TB patients (Tripathy et al 2011:521-528). Another retrospective review of case records from a tertiary center in India also showed an overall treatment success rate of 77% (Sharma et al 2014:157). The reported TB treatment success rate for year 2009 indicated in the 2011 WHO global TB report (WHO 2011b) shows a TB treatment success rate of 72% and 88% for HIV co-infected and non-HIV infected TB patients, respectively. From global TB reports by the WHO, the best treatment success rates (95%) were reported from China among all new TB patients (WHO 2014b). The reported treatment success rate for Ethiopia among all new TB cases in 2012 was 91%, which is the highest reported yet for this country and shows a progressively improving trend over the years (WHO 2014b). The same report indicates that the treatment success rate for Ethiopia was less than 80% in the years prior to 2011.

The reason for the high treatment success rate observed in this study could be due to the fact that the study participants for this particular study were selected from health centres which usually provide TB treatment and other medical care services for clinically stable patients. Those patients who are seriously sick and with advanced stage of their illnesses are referred to hospitals, and they receive their treatment at these referral facilities. This could have overestimated the favourable outcomes (treatment success) demonstrated in this study.
4.3.5 TB treatment outcomes in relation to HIV status

HIV co-infected TB patients have a treatment success rate of 88.2%. The analysis of TB treatment outcome disaggregated by HIV status shows that HIV co-infected TB patients have a higher rate (11.8%) of unfavourable treatment outcomes (defined as death, default or failure) compared to those without underlying HIV infection (6.4%) as shown on Table 4.5. This difference was found to be statistically significant using the Chi-Square test (Table 4.6). This finding is consistent with programme reports from countries that show differences in treatment outcomes between those TB patients co-infected with HIV and those without HIV infection. According to the global TB report (WHO 2014b), globally in 2012, HIV co-infected TB patients had 74% favourable treatment outcomes compared with 88% for HIV-negative TB patients, though the difference was smaller in the African region (75% in co-infected versus 83% in non-HIV infected).

Table 4.5 Comparison of TB treatment success based on HIV status (N=529)

<table>
<thead>
<tr>
<th>TB treatment outcome</th>
<th>HIV status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV negative</td>
<td>HIV positive</td>
</tr>
<tr>
<td>Unfavorable outcome</td>
<td>23 (6.4%)</td>
<td>20 (11.8%)</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>337 (93.6%)</td>
<td>149 (88.2%)</td>
</tr>
<tr>
<td>(treatment success)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>360 (100.0%)</td>
<td>169 (100.0%)</td>
</tr>
</tbody>
</table>

Table 4.6 Chi-Square test for treatment outcome comparisons based on HIV status

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson chi-square</td>
<td>4.567a</td>
<td>1</td>
<td>.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity correction</td>
<td>3.867</td>
<td>1</td>
<td>.049</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>4.321</td>
<td>1</td>
<td>.038</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fisher's exact test</td>
<td></td>
<td></td>
<td>.040</td>
<td>.027</td>
<td></td>
</tr>
<tr>
<td>N of valid cases</td>
<td>529</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. 0 cells (0%) have expected count less than 5. The minimum expected count is 13.74.
b. Computed only for a 2x2 table

The cure rate among HIV co-infected TB patients was significantly lower and the death rate significantly higher than that among those without underlying HIV infection (10.1%
versus 24.2% and 8.3% vs 2.5%, respectively). Figure 4.4 shows the different outcomes of TB treatment in the study participants in relation to their HIV status. The Chi-Square test showed that the observed differences in cure and death rates are statistically significant (Table 4.7 and 4.8). Very similar findings were reported in the TB global report (WHO 2014b) which showed the proportion of TB patients that died during treatment was more than three times higher among HIV-co-infected TB patients (11% versus 3.4%). According to this report, in the African Region, HIV-co-infected TB patients were twice as likely to die as HIV-negative TB patients (10% compared with 5%).

Figure 4.4   Comparisons of treatment outcomes by HIV status

Figure 4.5   Comparison of adverse outcomes by HIV status
Table 4.7  
Comparison of treatment outcomes and HIV status

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>HIV -</th>
<th>HIV +</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>87 (24.2%)</td>
<td>17 (10.1%)</td>
<td>2.702</td>
<td>1.542-4.735</td>
<td>0.001</td>
</tr>
<tr>
<td>Defaulted</td>
<td>10 (2.8%)</td>
<td>3 (1.8%)</td>
<td>1.76</td>
<td>0.476-6.505</td>
<td>0.397</td>
</tr>
<tr>
<td>Died</td>
<td>9 (2.5%)</td>
<td>14 (8.3%)</td>
<td>0.339</td>
<td>0.143-0.805</td>
<td>0.014</td>
</tr>
<tr>
<td>Failure</td>
<td>4 (1.1%)</td>
<td>3 (1.8%)</td>
<td>0.704</td>
<td>0.155-3.192</td>
<td>0.649</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>250 (69.4%)</td>
<td>132 (78.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.3.6  
Other characteristics associated with treatment outcome

Further analysis of the study data was performed to identify other factors (variables) that potentially affect the outcome of TB treatment in the study population using binary and multinomial logistic regression analytic methods. This analysis showed that age and TB classification are significantly associated with TB treatment outcome. Table 4.9 provides a detailed account of the results of the analysis. No association was observed between TB treatment outcome and receiving other medical care services like starting ART, co-trimoxazole prophylactic treatment or enrolment in HIV care. These findings are in contrast to results of other studies from other settings which showed that TB patients who were put on ART had more successful treatment outcomes than those not taking ART (Tweya et al 2013:e56248; Vijay, Kumar, Chauhan, Narayan Rao & Vaidyanathan 2011:e21008).

A similar study in HIV co-infected TB patients in Italy showed that there is a marked reduction in death rate in patients who were taking ART during tuberculosis treatment; but patients who were already on ART when they were diagnosed to have tuberculosis had higher risk of death (Girardi, Palmieri, Angeletti, Vanacore, Matteelli, Gori, Carbonara & Ippolito 2012:1-8). Looking at HIV co-infected patients separately, the analysis shows that there were 37 patients (22%) who had been on ART for more than six months when they developed active TB disease. The occurrence of active TB disease in those HIV patients who have been on ART for more than six months could indicate emergence of treatment failure on the ART regimen. This could have dampened the positive effect of ART on TB outcomes. However, a separate analysis comparing the TB treatment outcomes among those who developed active TB disease...
while taking ART for more than six months with the other study participants (who started ART after TB diagnosis or were taking ART less than six months when developing active TB disease) failed to show a significant difference in TB treatment outcome between them (OR=0.613 [0.218-1.726]; P=0.354).

**Table 4.8 Results of the binary regression analysis of the association of baseline individual, TB disease and other medical care services characteristics with TB treatment outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>TB treatment outcome</th>
<th>Total</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No success</td>
<td>Success</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>15-24</td>
<td>9 (6.0%)</td>
<td>142 (94.0%)</td>
<td>151</td>
<td>0.243</td>
<td>0.079-0.747</td>
</tr>
<tr>
<td></td>
<td>25-34</td>
<td>15 (8.2%)</td>
<td>169 (91.8%)</td>
<td>184</td>
<td>0.34</td>
<td>0.120-0.965</td>
</tr>
<tr>
<td></td>
<td>35-49</td>
<td>10 (6.6%)</td>
<td>141 (93.4%)</td>
<td>151</td>
<td>0.272</td>
<td>0.090-0.820</td>
</tr>
<tr>
<td></td>
<td>50-64</td>
<td>9 (15%)</td>
<td>51 (85%)</td>
<td>60</td>
<td>0.676</td>
<td>0.215-2.124</td>
</tr>
<tr>
<td></td>
<td>65-90</td>
<td>6 (20.7%)</td>
<td>23 (79.3%)</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>49 (8.5%)</td>
<td>526 (91.5%)</td>
<td>575</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>22 (8.3%)</td>
<td>242 (91.7%)</td>
<td>264</td>
<td>0.956</td>
<td>0.531-1.722</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>27 (8.7%)</td>
<td>284 (91.3%)</td>
<td>311</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>49 (8.5%)</td>
<td>526 (91.5%)</td>
<td>575</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB classification</td>
<td>EP</td>
<td>17 (6.7%)</td>
<td>236 (93.3%)</td>
<td>253</td>
<td>0.436</td>
<td>0.22-0.863</td>
</tr>
<tr>
<td></td>
<td>P/neg</td>
<td>12 (6.7%)</td>
<td>168 (93.3%)</td>
<td>180</td>
<td>0.432</td>
<td>0.204-0.917</td>
</tr>
<tr>
<td></td>
<td>P/pos</td>
<td>20 (14.2%)</td>
<td>121 (85.8%)</td>
<td>141</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>49 (8.5%)</td>
<td>525 (91.5%)</td>
<td>574</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrollment in HIV care</td>
<td>No</td>
<td>3 (20.0%)</td>
<td>12 (80.0%)</td>
<td>15</td>
<td>2.015</td>
<td>0.516-7.864</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>17 (11.0%)</td>
<td>137 (89%)</td>
<td>154</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>20 (11.8%)</td>
<td>149 (88.2%)</td>
<td>169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-trimoxazole given</td>
<td>No</td>
<td>7 (17.9%)</td>
<td>32 (82.1%)</td>
<td>39</td>
<td>1.969</td>
<td>0.725-5.344</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>13 (10.0%)</td>
<td>117 (90.0%)</td>
<td>130</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>20 (11.8%)</td>
<td>149 (88.2%)</td>
<td>169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART started</td>
<td>No</td>
<td>8 (15.4%)</td>
<td>44 (84.6%)</td>
<td>52</td>
<td>1.591</td>
<td>0.608-4.161</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>12 (10.3%)</td>
<td>105 (89.7%)</td>
<td>117</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>20 (11.8%)</td>
<td>149 (88.2%)</td>
<td>169</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV status</td>
<td>Negative</td>
<td>23 (6.4%)</td>
<td>337 (93.6%)</td>
<td>360</td>
<td>0.508</td>
<td>0.271-0.954</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>20 (11.8%)</td>
<td>149 (88.2%)</td>
<td>169</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>43 (8.1%)</td>
<td>486 (91.9%)</td>
<td>529</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For those factors that showed significant association on initial analysis, multinomial regression analysis was done. The results show that these factors are still significantly
associated with outcomes of TB treatment. Table 4.9 summarises the results of this analysis.

**Table 4.9 Multinomial regression analysis of factors associated with TB treatment outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>TB treatment outcome</th>
<th>Total</th>
<th>OR</th>
<th>AOR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No success</td>
<td>Success</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>15-24</td>
<td>9 (6.0%)</td>
<td>142 (94.0%)</td>
<td>151</td>
<td>0.243</td>
<td>0.150</td>
<td>0.041-0.546</td>
</tr>
<tr>
<td></td>
<td>25-34</td>
<td>15 (8.2%)</td>
<td>169 (91.8%)</td>
<td>184</td>
<td>0.34</td>
<td>0.185</td>
<td>0.055-0.619</td>
</tr>
<tr>
<td></td>
<td>35-49</td>
<td>10 (6.6%)</td>
<td>141 (93.4%)</td>
<td>151</td>
<td>0.272</td>
<td>0.126</td>
<td>0.034-0.468</td>
</tr>
<tr>
<td></td>
<td>50-64</td>
<td>9 (15%)</td>
<td>51 (85%)</td>
<td>60</td>
<td>0.676</td>
<td>0.389</td>
<td>0.104-1.457</td>
</tr>
<tr>
<td></td>
<td>65-90</td>
<td>6 (20.7%)</td>
<td>23 (79.3%)</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>49 (8.5%)</td>
<td>526 (91.5%)</td>
<td>575</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB classification</td>
<td>EP</td>
<td>17 (6.7%)</td>
<td>236 (93.3%)</td>
<td>253</td>
<td>0.436</td>
<td>0.322</td>
<td>0.149-0.697</td>
</tr>
<tr>
<td></td>
<td>P/neg</td>
<td>12 (6.7%)</td>
<td>168 (93.3%)</td>
<td>180</td>
<td>0.432</td>
<td>0.329</td>
<td>0.146-0.744</td>
</tr>
<tr>
<td></td>
<td>P/pos</td>
<td>20 (14.2%)</td>
<td>121 (85.8%)</td>
<td>141</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>49 (8.5%)</td>
<td>525 (91.5%)</td>
<td>574</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV status</td>
<td>Negative</td>
<td>23 (6.4%)</td>
<td>337 (93.6%)</td>
<td>360</td>
<td>0.508</td>
<td>0.367</td>
<td>0.178-0.757</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>20 (11.8%)</td>
<td>149 (88.2%)</td>
<td>169</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>43 (8.1%)</td>
<td>486 (91.9%)</td>
<td>529</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**4.4 CONCLUSION**

This chapter presented and discussed the findings of the analysis of the study data from a random sample of 575 study participants that were taken from the eight health centres in Addis Ababa. The age of the study participants ranged from 15-90 years of age with 58.3% of the participants falling into the age groups 25-49, and males accounted for more than half of the study sample. Ninety two percent of the study participants had documented HIV test result with almost two-third of them tested negative for HIV, but
eight percent of the participants have no documented HIV status (i.e. missing data). The most common reason for missing HIV status information was lack of testing kits.

With respect to TB disease characteristics, 56% of the study participants had pulmonary tuberculosis (PTB), and smear-positive PTB accounted for one-fourth of all TB cases among the study sample. The large majority of these patients were newly diagnosed TB patients who started their treatment at the respective facility where they were enrolled to the study.

The analysis of the outcome of TB treatment for all the study participants showed that the treatment success rate (a sum of 'cured' and 'treatment completed') was 91.5% including for those without a documented HIV status. The treatment success rate was 92.2% for all new TB patients and 93.6% for all non-HIV infected TB patients. HIV co-infected TB patients had 88.2% treatment success rate. This high treatment success rate remained similar (91.9%) when those with missing HIV status information were excluded. There was a lower cure rate and a higher death rate for HIV co-infected TB patients (10.1% and 8.3%, respectively) compared to those without underlying HIV infection (24.2% and 2.5% respectively).

The high rate of treatment success in this study could be attributed to the fact that most patients receiving TB treatment in health centre (lower level health facilities) are relatively clinically stable and the seriously sick patients are referred to higher level facilities.

In addition to co-infection with HIV, age and TB classification (i.e smear-positive PTB, smear-negative PTB, Extra-pulmonary TB) were found to be associated with outcome of TB treatment.

In the next chapter, a detailed discussion of these findings, their interpretation, comparison with evidence from other studies and sources, and the limitations of the study will be presented together with recommendations from the study.
CHAPTER 5

CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

This chapter provides an overview and summary of the study findings together with the interpretation of the findings. Relevant recommendations based on these findings are also discussed. In addition, the limitations of the study and their implications regarding the validity of the findings are pointed out.

5.2 DISCUSSION OF FINDINGS

In this section, the major findings of the analysis of the study data will be presented, and these findings will be interpreted in light of the problem statement, the study questions, and existing evidence from the review of the literature.

The age of the study participants ranged from 15 to 90 years and more than half (58.3%) of them were in the age groups between 25 and 49 years. More than half of the study participants were males. Among the 575 study participants enrolled into the study sample, 529 (92%) have a documented HIV test result, among whom about one-third (1/3) were HIV-positive. These findings are much higher than that reported for Ethiopia for 2013 with just 71% of TB patients having a documented HIV status and only 11% of those with documented status being HIV-positive (WHO 2014b). This high rate of testing for HIV and high rate of positivity in the study could be due to the fact that the study was conducted in the biggest city of the country which has among the highest HIV prevalence rates in the country (Ethiopian Health and Nutrition Research Institute, Federal Ministry of Health 2012). Being located in the major town, the study sites also could have better access to resources for HIV testing supplies compared to other remote sites. Shortage of HIV test kits was one of the major reasons for not being tested for HIV. Other countries have reported high rates of testing for HIV (98% for Rwanda) among TB patients, and very high rate of HIV positivity (74% for Lesotho and Swaziland) among those tested for HIV (WHO 2014b).
Most of the study participants were diagnosed to have pulmonary tuberculosis (55.8%), and a quarter of all cases of TB were found to have smear-positive pulmonary tuberculosis (P/pos). Extra-Pulmonary (EP) cases accounted for 44% of the total. The largest proportion of the study participants (85%) were new TB patients and had started their TB treatment at the health facility where they had completed their course of TB treatment.

In this study, among those study participants who had co-infection with HIV (N=169), 91.1% had been enrolled in HIV care, 76.9% had received co-trimoxazole prophylactic treatment and 69.2% had been regularly receiving ART.

There was a very high rate of treatment success observed in this study. Overall, treatment success rate was 91.5% for all the study participants. It was 92.2% for all new TB patients and 93.6% for all non-HIV infected TB patients. Other similar studies conducted in high prevalence settings showed that the highest treatment success rate (85%) is observed in HIV non-infected TB patients and overall success rate (for both groups combined) is 77% (Tripathy et al 2011:521-528; Sharma et al 2014:157). From global TB reports by the WHO, the best treatment success rates (95%) were reported from China among all new TB patients (WHO 2014b).

The reported treatment success rate for Ethiopia among all new TB cases in 2012 was 91%, which is the highest reported yet for this country and showing a progressively improving trend over the years (WHO 2014b). The same report indicates that the treatment success rate for Ethiopia was less than 80% in the years prior to the year 2011.

This study is conducted in health centres that manage stable patients in contrast to other higher level health facilities (referral hospitals) where seriously sick patients with advanced or complicated disease receive medical care. This could be the reason for the higher than expected rate of treatment success observed in this study.

TB treatment outcome disaggregated by HIV status shows that HIV co-infected TB patients have a higher rate (11.8%) of unfavourable treatment outcomes (defined as death, default or failure) compared to those without underlying HIV infection (6.4%).
cure rate among HIV co-infected TB patients was significantly lower than among those without underlying HIV infection (10.1% versus 24.2%); whereas, the death rate was higher in HIV co-infected TB patients (8.3% versus 2.5%). These findings are consistent with the expected outcomes among HIV co-infected patients including observations from studies and programme reports. According to the global TB report (WHO 2014b), globally in 2012, HIV co-infected TB patients had 74% favourable treatment outcomes compared with 88% for HIV-negative TB patients, though the difference was smaller in the African region (75% in co-infected versus 83% in non-HIV infected). In this same report, there were very similar findings regarding TB patient mortality which showed the proportion of TB patients that died during treatment was more than three times higher among HIV-co-infected TB patients (11% versus 3.4%). In the African Region, the report indicated that HIV-co-infected TB patients were twice as likely to die as HIV-negative TB patients (10% compared with 5%).

In addition to HIV status, age and TB classification were significantly associated with TB treatment outcome in this study. TB patients in the age group above 65 years of age had a higher likelihood of “unfavourable outcome” than those in the other age groups. Other studies have also demonstrated the association of adverse TB treatment outcomes and advanced age. A study conducted in South India (Ananthakrishnan, Kumar, Ganesh, Kumar, Krishnan, Swaminathan, Edginton & Gupta 2013:e67288) showed that TB treatment outcomes were poor among older TB patients and there was an increased risk of unfavourable outcomes in those above the age of 60 years. Another study in Delhi, India also showed a significantly higher rate of death and TB treatment failure among TB patients older than 65 years of age (Gaur, Dhingra, Rajpal, Aggarwal & Meghna 2004:83).

Lower TB treatment success was observed among those patients with smear positive pulmonary TB. This is consistent with the results of other studies in similar settings. A study in India demonstrated that TB disease classification is significantly associated with TB treatment outcome and patients under ‘Pulmonary’ TB classification had “unfavourable outcome” (Vijay et al 2011:e21008). Another Nigerian study showed that those TB patients with smear positive status at diagnosis (i.e. pulmonary positive TB classification) have more adverse TB treatment outcomes (Babatunde, Elegbede, Ayodele, Fadare, Isinjaye, Ibironke & Akinyandenu 2013:210).
The unexpected finding in this study was the absence of association between TB treatment outcome and the other medical care services received by HIV co-infected TB patients, namely starting ART, Cotrimoxazole prophylactic treatment and enrolment in HIV care. These findings are in contrast to results of other studies from other settings which showed that TB patients who were put on ART had more successful treatment outcomes than those not taking ART (Tweya et al 2013:e56248; Vijay et al 2011:e21008). A similar study in HIV co-infected TB patients in Italy showed that there is a marked reduction in death rate in patients who were taking ART during tuberculosis treatment; but patients who were already on ART when they were diagnosed to have tuberculosis had higher risk of death (Girardi et al 2012:1).

Additional analysis of the data showed that 22% of HIV co-infected TB patients were taking ART for more than six months when they were diagnosed to have active TB disease and started on TB treatment. This finding could be indicative of the emergence of treatment failure on the ART regimen these patients were taking. This could have contributed to dampen the positive effect of ART on TB treatment outcomes. However, no difference in treatment outcome was observed between those who developed active TB disease while taking ART for more than six months and the other study participants.

5.3 LIMITATIONS

A major limitation of this study lies in the fact that the sites selected for this study were selected purposefully by their geographic accessibility and patient load. All the sites are within Addis Ababa which is the capital and the largest town of the country. Patients from these facilities might have a different profile from patients residing in other parts of the country including in socio-economic status, education, proximity to health facilities, and access to information, diagnostic and treatment services. The types of the health facilities selected for the study were health centres only. This was because of the design of the national TB programme to enable TB patients to receive their TB medications under direct observation in the health facilities near their residences, and higher level health facilities (hospitals) usually refer the patients they diagnose with TB to health centres for initiating and following TB treatment. Health centres provide medical care to relatively well and stable patients. Patients with advanced disease and more complicated clinical conditions are referred and receive care and treatment...
services at higher level facilities (referral or specialised hospitals). This could have selected patients with better prospects for favourable treatment outcome in this study.

However, an adequate sample size was used to achieve enough power to detect differences among the groups and achieve statistical significance. The study participants were also randomly selected during enrolment into the study. On the other hand, the sample size calculation didn’t take into account the individual factors other than HIV that may affect patient outcome in HIV co-infected TB patients. This might be the reason for the observed absence of differences in outcome between those taking ART and those not taking ART.

Another limitation is that the data collected is retrospective secondary data which in some way proved to have some issues with missing and inaccurate data. It was also not possible to collect additional patient information that potentially could have importance for the analysis. The data collection was restricted to whatever is documented in the TB registers.

5.4 RECOMMENDATIONS

It was necessary for the researcher to make recommendations based on the study findings. The following recommendations are made in terms of practice, research, and education of health care professionals.

5.4.1 Practice recommendations

For patients diagnosed with active TB disease, routine screening for HIV is recommended and the results of this study also confirm this fact. As has been observed in other studies, early identification of both TB and HIV, and prompt initiation of treatment (both TB treatment and ART) gives TB patients the best chance for a favourable treatment outcome or treatment success. Patients in older age groups and those patients with smear positive pulmonary TB have increased likelihood of unfavourable treatment outcome. This group of patients may require more intensive evaluation and follow-up to ensure compliance and identify other medical needs they might have. It is also recommended to assess and improve the quality of the other medical services that are provided to HIV co-infected TB patients. Timely identification
of ART failure and ARV regimen switching could contribute to improved patient outcome and reduce the risk of developing TB while on treatment. Optimal provision of quality care and support services for HIV co-infected TB patients is required so that these TB patients will not succumb to other concomitant illnesses or conditions (ex. malnutrition, opportunistic illnesses).

5.4.2 Recommendations for further research

In this study, it was observed that older TB patients and those patients with smear positive pulmonary TB have increased risk of adverse treatment outcomes. Further studies are required to explore any additional factors that may contribute to the unfavourable treatment outcome among this group of patients. It is also important to study what additional medical interventions (ex. nutritional support, adherence support etc.) may be employed to improve the treatment outcome of these patients.

Provision of additional medical care services to HIV co-infected TB patients did not bring any difference in the treatment outcome among the patients in this study. It will be worthwhile to assess the quality and timeliness of the delivery of these services and identify any gaps so that quality improvement activities can be implemented.

There could be other factors associated with TB treatment outcomes among TB patients in general and HIV co-infected TB patients in particular that were not identified in this study. Prospective studies that can capture more diverse variables (in addition to what is documented in the TB registers only) will be useful to identify these unknown factors. Qualitative studies will also contribute to understanding other patient level and health service level factors that are affecting the treatment outcomes in TB patients.

5.4.3 Recommendations for education

Training health professionals in recording and analysing data for use at the service delivery sites to improve their practice is indispensable. The evidence should be used to implement quality improvement activities and guide clinical practice at service delivery site level.
5.5 CONCLUSIONS

In this study, the review of the TB registers showed that a high proportion of TB patients were tested for HIV and there was a very high rate of co-infection with HIV among patients with active TB disease who were receiving TB treatment in the health facilities selected for the study. In addition, in terms of documents studied or reviewed, there was a high treatment success rate among the study participants in this study. However, there was a higher likelihood of unfavourable outcomes and increased death rate among HIV co-infected TB patients compared with non-HIV infected TB patients. In addition to HIV status, age and TB classification were found to be associated with TB treatment outcome. No association was observed between the other medical services provided to HIV co-infected TB patients and TB treatment outcome, including ART. Of note, a significant proportion of these HIV co-infected TB patients had developed active TB disease after they had been receiving ART for more than six months.

Prospective quantitative studies and qualitative studies are required to further explore additional patient level and service delivery factors that may affect the outcome of TB patients.
LIST OF REFERENCES


CATIE see Canadian AIDS Treatment Information Exchange.


CDC see Centers for Disease Control and Prevention.


Demeke, D, Legesse, M & Bati, J. 2013. Trend of Tuberculosis and Treatment Outcomes in Gambella Region with Special Emphasize on Gambella Regional Hospital, Western Ethiopia. Mycobacterial Diseases 3(2):130.


Ejeta, E, Birhanu, T & Wolde, T. 2014. Tuberculosis treatment outcomes among tuberculosis/human immunodeficiency co-infected cases treated under directly


FDA see Food and Drug Administration.

Food and Drug Administration. 2015. *Clinical Outcome Assessment (COA): Glossary of Terms.*


PASW see Predictive Analytics Software.


UCSF see University of California San Francisco.


WHO see World Health Organization.


Annex I. Approval by the local IRB

<table>
<thead>
<tr>
<th>CRITERIA/ITEM</th>
<th>RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. consent form</td>
<td>☑Yes</td>
</tr>
<tr>
<td>Does the consent contain all the necessary information that the subject should be aware of?</td>
<td>☑Not applicable</td>
</tr>
<tr>
<td></td>
<td>☑Not attached</td>
</tr>
<tr>
<td>2. Are the objectives of the study clearly stated?</td>
<td>☑Yes</td>
</tr>
<tr>
<td></td>
<td>☑No</td>
</tr>
<tr>
<td>3. Are provisions to overcome risks well described and accepted?</td>
<td>☑Yes</td>
</tr>
<tr>
<td>a. Justice</td>
<td>☑No</td>
</tr>
<tr>
<td>b. Beneficence</td>
<td>☑Not well described</td>
</tr>
<tr>
<td>c. Respect for a person</td>
<td>☑Not applicable</td>
</tr>
<tr>
<td>4. Are the safety procedures in the use of vaccines, drugs and other biological Products acceptable?</td>
<td>☑Yes</td>
</tr>
<tr>
<td></td>
<td>☑No</td>
</tr>
<tr>
<td></td>
<td>☑Not applicable</td>
</tr>
<tr>
<td>5. Are the procedures to keep confidentiality well described?</td>
<td>☑Yes</td>
</tr>
<tr>
<td></td>
<td>☑No</td>
</tr>
<tr>
<td></td>
<td>☑Not applicable</td>
</tr>
<tr>
<td>6. Are the proposed researchers competent to carry out the study in a scientifically sound way?</td>
<td>☑Yes</td>
</tr>
<tr>
<td></td>
<td>☑No</td>
</tr>
<tr>
<td></td>
<td>☑Not applicable</td>
</tr>
<tr>
<td></td>
<td>☑Unable to assess</td>
</tr>
<tr>
<td>7. Does it have material transfer agreement?</td>
<td>☑Yes</td>
</tr>
<tr>
<td></td>
<td>☑No</td>
</tr>
<tr>
<td></td>
<td>☑Not applicable</td>
</tr>
<tr>
<td>8. Recommendation</td>
<td>☑Approved with condition</td>
</tr>
<tr>
<td></td>
<td>☑Fully Approved</td>
</tr>
<tr>
<td>9. Remarks</td>
<td></td>
</tr>
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</table>

Ethical Clearance Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. EYOBED KALEB</td>
<td></td>
</tr>
</tbody>
</table>

Reference: [Stamp Image]
Annex II. Request for access to health facilities

To BOLE 17 HEALTH CENTER
WEREDA 9 (NIFAS SILK ) HEALTH CENTER
KOTEBE HEALTH CENTER
SHIROMEDA HEALTH CENTER
YEKA HEALTH CENTER
KAZANCHIS HEALTH CENTER
SESEMEN HEALTH CENTER
ADDIS KETEMA HEALTH CENTER

Addis Ababa

Subject: Request to access Health Facilities to conduct approved research

This letter is to support Dr Solomon Ahmed to conduct research, which is entitled as “OURCOMESOF TB TREATMENT IN HIV CO-INFECTED TB PATIENTS IN ADDIS ABABA.”
The study proposal was duly reviewed and approved by Addis Ababa Health Bureau IRB, and the principal investigator is informed with a copy of this letter to report any changes in the study procedures and submit an activity progress report to the Ethical Committee as required.
Therefore we request the mentioned facilities and staffs to provide support to the Principal investigator.

With Regards
Eyobed Kaleb
Ethical Clearance committee

Cc: - Dr Solomon Ahmed
Addis Ababa
To Ethical Clearance Committee
Addis Ababa
UNIVERSITY OF SOUTH AFRICA
Health Studies Higher Degrees Committee
College of Human Sciences
ETHICAL CLEARANCE CERTIFICATE

HSHDC/217/2013

Date: 16 October 2013  Student No: 4869-816-4

Project Title: Outcomes of TB in HIV co-infected TB patients in Ethiopia.

Researcher: Solomon Ahmed Ali

Degree: Masters in Public Health

Supervisor: Prof TR Mavundla
Qualification: D Cur
Joint Supervisor: -

DECISION OF COMMITTEE

Approved  Conditionally Approved

Prof L Roets
CHAIRPERSON: HEALTH STUDIES HIGHER DEGREES COMMITTEE

Prof MM Moleki
ACADEMIC CHAIRPERSON: DEPARTMENT OF HEALTH STUDIES

PLEASE QUOTE THE PROJECT NUMBER IN ALL ENQUIRES
<table>
<thead>
<tr>
<th>MRN</th>
<th>Unit No.</th>
<th>Name of the patient</th>
<th>Sex</th>
<th>Name of contact person</th>
<th>Smear result</th>
<th>Category</th>
<th>Intensive phase</th>
<th>Treatment started</th>
<th>Intensive phase treatment monitoring chart</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Days: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Address of the patient (Woreda, Kebele, HNc)</td>
<td></td>
<td>Address contact person (Woreda, Kebele, HNc)</td>
<td>Lab no.</td>
<td>P R P N or EP</td>
<td>Drug</td>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Annex V. Outcomes of TB treatment in HIV co-infected TB patients in Ethiopia

Data collection form

Date of data collection: .....................  Serial number/code: ............

Part I: Demographic information

1. Age: ................  2. Gender: Male ○  Female ○

Part II: TB status information

3. TB Smear result:
   Smear positive ○
   Smear negative ○

4. TB disease Classification:
   Pulmonary Positive (P/Pos) ○
   Pulmonary Negative (P/Neg) ○
   Extra Pulmonary (EP) ○

5. TB disease Category:
   New (N) ○
   Relapse (R) ○
   Treatment after Failure (F) ○
   Treatment after Default (D) ○
   Transfer in (T) ○
   Other (O) ○

6. Date of starting TB Treatment: ...........................................

7. Date TB treatment was stopped: ...........................................
Part III: Patient outcome information

8. Outcome of TB treatment:
   - Cured
   - Failure
   - Treatment Completed
   - Defaulted
   - Died
   - Transferred

Part IV: HIV status and care information

9. HIV test result:
   - Reactive (R)
   - Indeterminate (I)
   - Non-Reactive (NR)
   - Not done

10. Enrolled in HIV care: Yes, No

11. Cotrimoxazole given: Yes, No

12. Started on ART: Yes, No  If Yes, Date started on ART
Annex VI. WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection

Clinical stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical stage 2

Moderate unexplained weight loss
(<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections

Clinical stage 3

Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than one month
Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic thrombocytopaenia (<50 × 10^9 per litre)

Clinical stage 4

HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month’s duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi’s sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent non-typhoidal Salmonella bacteraemia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

i Unexplained refers to where the condition is not explained by other causes.
ii Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis]) in the WHO Region of the Americas and disseminated penicilliosis in Asia).

Annex VII. List of selected health facilities

Addis Ketema health center
Bole 17 health Center
Kazanchis health center
Kotebe health center
Semien health center
Shiromeda health center
Wereda 9 (Nifas Silk) health center
Yeka health center