EFFECTIVENESS OF EARLY INITIATION OF ANTIRETROVIRAL THERAPY IN ADULTS WITH HIV ASSOCIATED TUBERCULOSIS IN LESOTHO IN 2012

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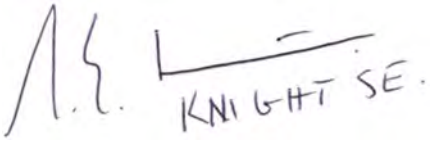
Signature: 

Dr Stephen Knight

Purpose of Research Study

This research study is for my Master of Public Health qualification. The research project contributes 50% of the qualification. This dissertation is presented in the traditional master-level format.

Declaration

I, Maletsatsi Lenela declare that:

(i) The research reported in this dissertation, except where otherwise indicated, is my original research.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other personsôdata, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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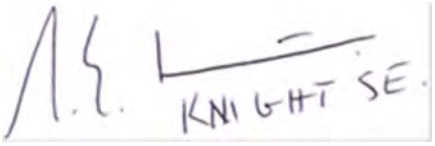

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Table of Contents

List of Figures

List of Tables

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Acronyms & Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ATT	Anti-tuberculosis Treatment
BREC	Biomedical Research Ethics Committee
CHAL	Christian Health Association of Lesotho
CI	Confidence Interval
CPT	Cotrimoxazole Preventive Therapy
EPTB	Extra-pulmonary Tuberculosis
HIV	Human Immunodeficiency Virus
IERB	Institutional Ethical Review Board
IRD	Immune Reconstitution Disease
MDR-TB	Multidrug resistant tuberculosis
MOHSW	Ministry of Health and Social Welfare
PLHIV	People Living with HIV and AIDS
PR	Prevalence Ratio
OR	Odds Ratio
PTB	Pulmonary Tuberculosis
RCU	Research Coordinating Unit
TB	Tuberculosis

WHO	World Health Organization
XDR-TB	Extensive Drug Resistant Tuberculosis

Abstract

Background

Today Africa is confronted with a huge burden of Human Immunodeficiency Virus (HIV) associated tuberculosis (TB). In 2010, 77% of the TB in Lesotho was HIV associated.

The problem is intensified by many factors, such as the timing of initiation of antiretroviral therapy (ART), separation of HIV and TB services that discourages people from seeking care and the policies governing the treatment of HIV and TB.

Aim

The aim of this study is to compare the effectiveness of late versus early commencement of ART in adults living with HIV associated TB in Lesotho in 2012.

Method

An observational, analytic cross-sectional study design was conducted. Three out of 17 hospitals were randomly selected and data for patients with HIV-associated TB who had completed TB therapy during the study period (January to March 2012) was extracted from the hospitalsôTB registers.

Results

Of the 247 adults living with HIV associated TB, 80 (32%) were started on ART early (4 weeks or less), 100 (41%) were started late (after 4 weeks) and 67 (27%) received no ART at all. The unadjusted results show that early initiators were 6 times more likely to have a successful TB outcome (OR 6.2: 95%CI: 3.7 to 27.5)

relative to the group who had no ART. The difference was statistically significant ($p<0.001$). Interestingly those who commenced ART late also were six times more likely to have a successful TB outcome (OR 5.6: 95% CI: 2.8 to 11.2) relative to the group who had no ART.

Discussion

This study provides evidence that in Lesotho, early initiation of ART in adults living with HIV associated TB has not been fully implemented. Only a third were commenced on ART early after starting TB treatment. This study demonstrated however, that even those who commenced ART late performed much better than those who were not prescribed ART. This therefore highlighted that successful TB treatment outcomes were not dependent on when ART was initiated.

Recommendations

The Lesotho Ministry of Health should ensure early initiation of ART in people living with HIV associated TB in order to improve their TB outcomes.

1 CHAPTER ONE: INTRODUCTION

Human Immunodeficiency Virus (HIV) associated tuberculosis (TB) constitutes one of the leading causes of death in Africa. Lesotho, as an independent nation, is no exception. It has experienced high levels of mortality due to TB, occurring in people living with HIV and Acquired Immunodeficiency Syndrome (AIDS) (PLHIV). Research has shown that TB is more likely to occur in those infected with HIV than in those who remain uninfected. [1] In 2010, 77% of the TB in Lesotho was HIV associated, and there has arisen a demand for action aimed at ensuring those co-infected both survive and achieve better TB outcomes.

Lesotho is faced with high levels of mortality and poor TB outcomes, occurring in people living with HIV associated TB. Furthermore, initiation of antiretroviral therapy (ART) within a month of TB treatment commencement among adults with HIV associated TB the policy in Lesotho.[a] The problem is important because the economically active population (15 to 64 year olds) is the most affected sector and this exerts adverse impact on the economy of the country. The study will contribute evidence that will enable the authorities to be aware of the problem and the need to commence ART in people living with HIV associated TB early as it has been found to be efficacious in experimental studies.

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[a] The policy since April 2011 in Lesotho, is that all people living with HIV associated TB on TB treatment are initiated on ART within a month of commencing TB therapy regardless of their CD4 count. [2]

Before implementation of early initiation of ART in adults living with HIV associated TB, initiation of ART was based on their CD4 count and this approach did not yield favourable results. [2] The TB and HIV services were not user-friendly as those co-infected could not gain access to all services under one roof, and this factor discouraged their seeking appropriate treatment and care.[2] In 2011, Lesotho revised the national guidelines for TB and HIV co-management, incorporating the new recommendations of the World Health Organization (WHO). These National Antiretroviral Therapy Guidelines (Guidelines) recommended that those individuals living with HIV associated TB be initiated on ART immediately (i.e. within two to four weeks) after commencing TB treatment. [2] The Guidelines also indicated that all facilities should integrate TB and HIV services in order to ensure effective TB and HIV co-management, which includes early initiation of ART and other necessary services for PLHIV associated TB. [2]

In this opening chapter, I will describe the background to this study on assessing the effectiveness of HIV-associated TB in Lesotho. The aim of this study, objectives of the study, type of research, the definitions of words and phrases, statement of the problem and the present state of knowledge and expertise are all vital factors that will be described.

1.1 Aim

The aim of this study is to compare the effectiveness of late versus early commencement of ART in adults living with HIV associated TB in three hospitals in Lesotho in 2012.

1.2 Objective

The objectives of this study are:

- To describe the profile of people living with HIV associated TB;
- To measure TB outcomes in PLHIV associated TB initiated both early and late on ART;
- To identify predictors associated with the effectiveness of early initiation of ART in adults living with HIV associated TB; and
- To make recommendations to authorities as to how the programme can be improved.

1.3 Type of research

This is health systems research.

1.4 Definitions

- **HIV associated TB,** occurs when an individual is co-infected with both TB and HIV.

- **Early initiation of ART,** involves initiation of ART for people living with HIV associated TB within two to four weeks after starting TB treatment.

- **Late initiation of ART** is when ART is only commenced for people living with HIV associated TB any time after four weeks of starting TB treatment.

- The **Type of TB patient** is categorised as to whether the patient is diagnosed with TB for the first time, after defaulting, after failing the first course of TB treatment, after relapsing or for any other cause excluding the mentioned ones.

- **Treatment category,** refers to whether a patient is in category one (I) or two (II) depending on whether the person infected with TB receives (I) the standard TB treatment regimen for those diagnosed with TB for first time or whether they received (II) the alternate TB treatment regimen reserved for those who have been treated for TB before.

- **Treatment outcome** is the end result of every PLHIV associated TB who commences TB treatment.

1.5 Statement of the problem

Lesotho had a population of 1 880 661 and 13 520 cases of TB were notified in 2010.[2] Out of these cases, 76% were living with HIV associated TB. Lesotho, like other low income countries has been greatly affected by TB and HIV and this has further led to high levels of mortality related to these two infections and which negatively affects the health service.[2] Consequently, the reported annual TB notification incidence risk was 640 per 100 000 population in 2009. The high levels of HIV associated TB are the primary reason contributing to the reduction in life expectancy at birth, declining to 35 years in the country in 2010. [2] Moreover, the Lesotho Ministry of Health and Social Welfare (MOHSW) reported that in 2011, HIV testing had occurred in 82% of TB patients of which 76% were found to be living with HIV.[3] Amongst those that were living with HIV (irrespective of whether they were infected with TB or not), 90% were started on cotrimoxazole and 40% were initiated on ART in 2011.[3]

In 2011, the MOHSW adopted a policy of initiating people with HIV associated TB on ART within a month of commencing TB therapy, which should increase their survival. [2] Increased survival has been reported in other countries such as its Rwanda, where both improved TB treatment outcomes and the CD4 count in adults living with HIV

associated TB that were initiated on ART within a month of commencing TB treatment occurred.[4] The efficacy of early initiation of ART in people living with HIV associated TB is around 90%, a positive development, which strongly implies that people living with HIV associated TB are started on ART early. [5]

1.6 What is known so far?

A renewed epidemic of TB has been present in Lesotho commencing in 1985. [7] There is strong evidence that HIV is the underlying factor fueling the epidemic. A condition where both diseases have infected an individual (HIV associated TB) is now common in sub-Saharan Africa, a serious public health development, which has resulted in high levels of mortality in those co-infected. [7] The issue is, where there is HIV associated TB, the CD4 count decreases and viral load accordingly increases, leading to the worsening of AIDS. [7]

Early initiation of ART serves as one of the strategies that have been proven to be effective in improving survival in people living with HIV associated TB. [5] Survival was increased by 60% to 90% among people living with HIV associated TB in countries where early initiation of ART was introduced.[5] The study that was conducted in South Africa in 2006 by the International Center for AIDS Care and Treatment Programs (ICAP) recommended that people living with HIV associated TB should be started on ART within four weeks as mortality is reduced by early initiation of therapy.[6]

Additionally, Colebunders & Lambert (2002) allude to the fact that ñabout a third of the 36 million people living with HIV worldwide are co-infected with *Mycobacterium tuberculosis*; 70% of those co-infected live in sub-Saharan Africa.ò[5] Sub-Saharan African countries have about 70% of those globally with HIV associated TB.[5] For this reason, knowledge about the condition is important, a vital instrument allowing the remedy and solution of problem.

1.7 Organisation of the report

The dissertation is divided into eight chapters**:**

In Chapter 1: Introduction, the background to the topic is described briefly, the purpose of the research and the specific objectives are outlined.

The literature review in Chapter 2 provides an analysis of the existing literature on the timing of ART in patients with HIV associated TB and the TB treatment outcomes.

In Chapter 3: Materials and Methods, the study design, study population, data sources, sampling methods, variables and statistical analysis applied in this study are further explored. The reliability and validity of the study and handling of bias and limitations are also described.

In Chapter 4, the results are presented.

In Chapter 5: Discussion of the results is undertaken.

In Chapter 6, conclusion and recommendations based on the results of the study are described.

In Chapter 7: References to all materials used are shown.

Chapter 8 contains the appendices, which include the data collection tool used, permission letters to hospitals, permission to conduct the research obtained from the KwaZulu-Natal Biomedical Research Ethics Committee (BREC) and letter of registration of the project with the School of nursing and Public health Research and Higher Degrees Committee.

1.8 Summary of the chapter

The introductory chapter gives a background to HIV associated TB and the effectiveness of its treatment. HIV associated TB is a major problem facing Africa today and Lesotho constitutes no exception. It has been shown that survival and TB outcomes were much improved when ART was initiated early in people living with HIV associated TB. It is important to measure the effectiveness of this intervention in a low income country with a large HIV associated burden such as Lesotho.

2 CHAPTER TWO: LITERATURE REVIEW

In this chapter, and issues related to access of early initiation of antiretroviral therapy, clinical improvement with early initiation of ART, changes in CD4 and viral load (immunity) and challenges of early initiation of ART are explored. It will reflect purpose of the literature review; the scope of what has already been studied and research that has been undertaken and reported in the scientific literature.

2.1 Purpose of the literature review

The purpose of this literature review was to establish:

- What is currently documented about effectiveness of early initiation of ART in PLHIV and TB globally, in the African continent and in South Africa;
- Challenges and successes encountered in implementing the guidelines relating to early initiation of ART in PLHIV and TB;
- Outcomes related to early initiation of ART in PLHIV and TB conducted in different study settings.

2.2 Scope of literature review

The literature was searched using a number of databases ï Medline, PubMed, PLOS Medicine, Journal of Acquired Immune Deficiency Syndromes, and Google scholar and Google search engine. The key terms ñearly initiation of ART in PLHIV and TBò, ñearly ART initiationò, ñTB and HIV co-infectionòand ñHIV and TBòwere used in the literature search. However, some material such as the Lesotho TB and guidelines was accessed from the Ministry of Health.

2.3 Problem framework

Figure 1 below shows the problem framework that was considered for effectiveness

of early ART initiation. It has four components namely individual factors, facility factors, national factors and the assessment of the study. Lastly, at the center of the diagram there is a descriptor, which summarizes the study title.

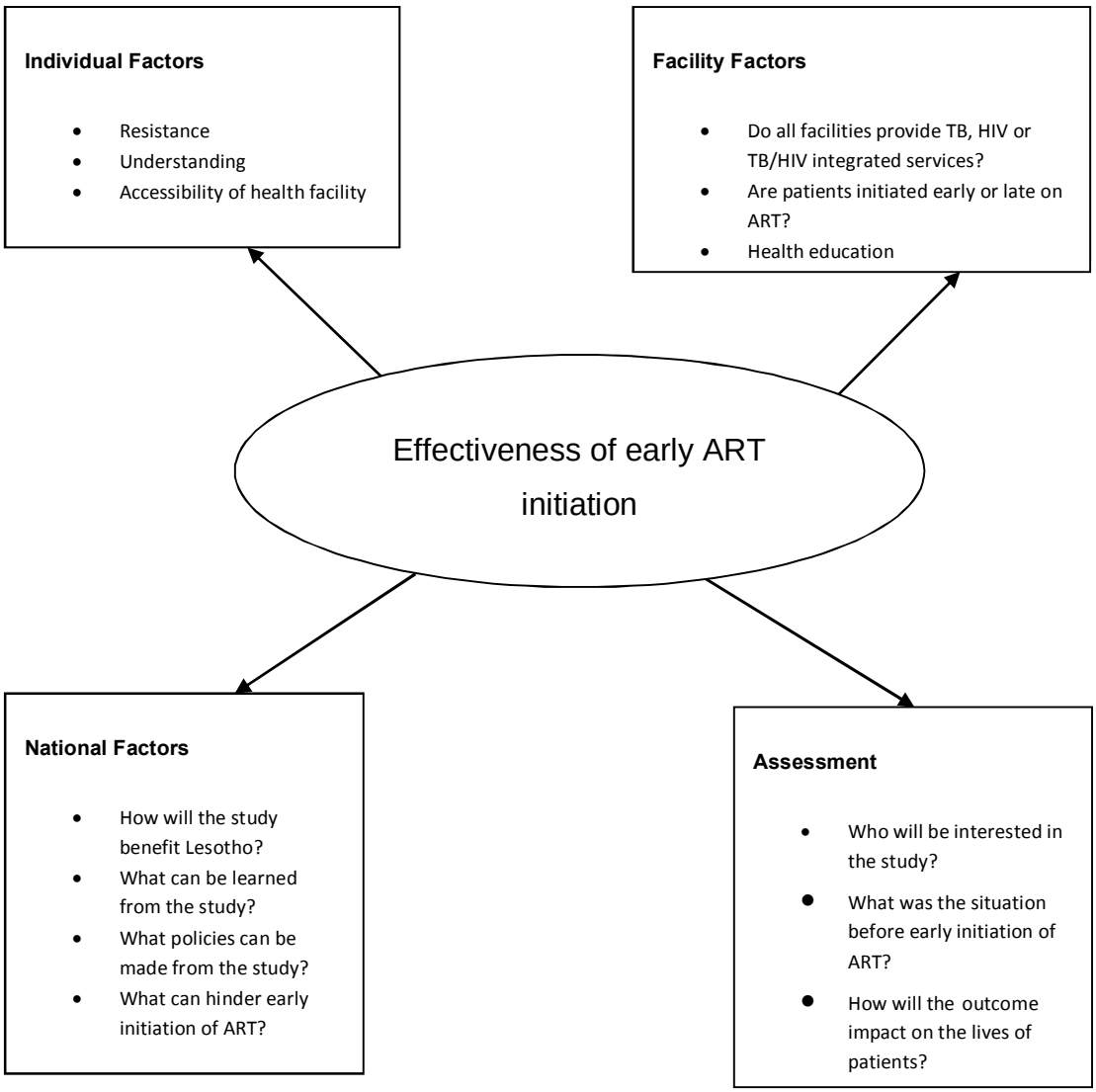

Figure 1: Conceptual framework

2.4 Access of early initiation of ART in people with HIV associated TB

It is important to establish whether people living with HIV and TB in different settings have access to ART and TB services. Many factors could hinder access and this will be elaborated further by studies discussed below.

An observational, cross-sectional study conducted in India in 2005 on this particular question of HIV associated TB showed that timely initiation of ART markedly improved the outcomes of people living with this specific combination of diseases .[1] Furthermore, it was reported that although there had been no prior evidence of the appropriate time to initiate ART in people living with HIV associated TB, this retrospective study demonstrated that early initiation of ART was associated with reduced mortality and disease progression.

In 2002, a study conducted in London among 347 HIV-1 patients presenting with culture proven TB confirmed that most people living with HIV associated TB who died with low CD4 counts were not prescribed ART. Furthermore, some were only started on ART a few months prior to death.[8] The study showed the importance of early initiation of ART in people living with HIV associated TB, as it improves survival.

A retrospective study conducted in Iran between 2002 and 2006 revealed that, among 69 hospitalized patients living with HIV associated TB, 28% of those who started ART eight weeks after commencing TB treatment died, while only 4.5% died, in those who were started two weeks after commencing TB therapy.[9] Results from this study also confirmed that early initiation of ART in people living with HIV associated TB is better than late initiation.

Additionally, early initiation of ART in people living with HIV associated TB may not only lead to improved treatment outcomes but it may also assist in faster sputum conversion.[10] The Indian Council of Medical Research, reported the following insight:

ñEarly initiation reduces mortality and morbidity due to HIV and tuberculosis with faster sputum conversion. The Starting Antiretrovirals at Three Points in Tuberculosis Therapy trial reported a 56% lower mortality among 214 patients who commenced ART during tuberculosis treatment, compared with 215 patients who waited until TB therapy had been completed.[10]

Furthermore, it has been pointed out that ñCollaboration between TB and HIV & AIDS programmes in making ART available to HIV-positive TB patients will contribute to speeding up progress towards achieving the ó3 by 5ôtarget (3 million people on ART by 2005).ò[11] As soon as a TB patient tests positive for HIV, he/she must be started on Cotrimoxazole Preventive Therapy (CPT). These patients must now also be started on ART within two months of commencing their TB treatment.[12]

A retrospective cohort study conducted in Thailand among 1003 patients living with HIV associated TB between January 2000 and December 2004, revealed that, ñAntiretroviral therapy substantially reduces mortality rate among HIV/TB-co infected patients. Initiation of ART within 6 months of TB diagnosis is associated with greater survival.ò[13] This observational study showed high levels of survival, which ranged between 88% and 96% in people living with HIV associated TB who began ART and low levels of survival of about 9% to 44% of those not on ART.[13]

The WHO revised the HIV guidelines in 2010 and indicated that people living with HIV associated TB must be started on ART within two to four weeks after commencing TB treatment. [2] Thus, clinical improvement with early initiation of ART in people living with HIV associated TB should also be an important subject of study as it reflects the true picture of treatment outcomes. [2]

A clinical trial conducted in Lesotho in 2013 among 444 HIV associated TB patients indicated that there is evidence that people living with HIV associated TB have better

survival rates when started on ART early. [14] However, the country is still faced with the challenge of people who do not start ART within the recommended time while others simply do not remain in care. [14]

As shown by the studies above, early initiation of ART in people living with HIV associated TB reduces mortality and improves TB treatment outcomes. The evidence suggests that the most appropriate time of ART initiation is soon after commencing TB therapy.

2.5 Clinical Improvement with early initiation of ART in people with HIV associated TB

In this section, studies relating to clinical improvement due to early initiation of ART in people living with HIV associated TB will be discussed. The focus will be onCD4 cell count, weight gain and sputum conversion.

A prospective study conducted in 5 hospitals in Cambodia (2006 to 2009) where 661 patients (332 receiving early ART and 329 receiving late ART) were enrolled and demonstrated that there were fewer new AIDS-defining illnesses due to early initiation of ART in adults living with HIV associated TB. Only 16% of the patients receiving earlier ART compared with 27% of the patients receiving later ART developed a new AIDS-defining illness or died (Incidence Rate Risk 95% CI: 1.5 to 20.5; p = 0.02).ò[15]

A study conducted in Durban showed that initiating ART early in people living with HIV associated TB improves survival, even in patients with low CD4 counts. This report, based on the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPiT) trial, compared early ART initiation (within 4 weeks of commencing TB therapy) and late initiation of ART (between 4 and 12 weeks of commencing TB

treatment) among 642 South Africans infected with HIV and having smear-positive pulmonary TB confirmed the efficacy of early initiation. The incidence of AIDS or occurrence of death among patients with a CD4 count less than 50 cell/µ was 8.5 and 26.3 cases per person-years (incidence-rate ratio 0.32; 95% CI: 0.07 to 1.13; p = 0.06) in the early and late ART initiation groups respectively.[16]

In Hong Kong, another study confirmed that improved survival was associated with early initiation of ART in patients with HIV associated TB. In this study involving 260 patients living with HIV associated TB, 32 were started on ART within two months of commencing TB treatment (early group). Results revealed early initiation of ART was associated with favourable outcomes (cure or treatment completion without relapse) at 24 months (91% v 67%; p=0.007) compared to those who were only started on ART at a later stage (beyond two months of starting TB treatment).[17]

A study conducted in Boston in 2011 reported that among 806 individuals enrolled from 26 sites on 4 continents, 405 received immediate ART (median of 10 days) while 406 received early ART (within 10 weeks from start of TB treatment).[16] The median start ART time for the immediate group was 10 days and that of the early ART was 40 days. Results showed that only 13% of those who received immediate ART experienced AIDS or death at 48 weeks and this figure was 16% for the early ART group.[18] This further revealed that the earlier ART was initiated, there were improved TB treatment outcomes.

In Lesotho in 2012, a study conducted on 134 confirmed MDR-TB patients with 94 (70%) being co-infected with HIV, showed that the time to death for patients not on ART was notably shorter than that of those on ART. [19] Out of 134 HIV confirmed MDR-TB patients, 83(62%) were cured or completed treatment, 46(34%) died, 3(2%) transferred, 1(1%) defaulted and 1(1%) failed treatment. [19] Among the 94 (70%) patients with HIV co-infection, 53% were already on (ART) before MDR-TB treatment

and 43% started ART a median of 16 days after the start of the MDR-TB regimen. Among HIV co-infected patients who died, those who had not started ART had a shorter median time to death (80 days vs. 138 days, $p = 0.065$). [19] The importance of early initiation of ART was highlighted, even though PLHIV severely immunosuppressed may take longer to show a benefit from ART. [19]

In Cape Town in 2005, a study reported that the frequency of extra-pulmonary disease in people living with HIV associated TB started early on ART was reduced.[20] There were however, indications that paradoxical reactions were associated with early initiation of ART in people living with HIV associated TB.[20] These paradoxical reactions were significantly associated with starting ART within six weeks after beginning TB treatment ($p= 0.03$).[21]

2.6 Changes in CD4 count and viral load

Changes have been noted in the CD4 count and viral load depending on stage of initiation of ART in people living with HIV associated TB. A study conducted in Cape Town in 2005 revealed that early initiation of ART in people living with HIV associated TB has been associated with viral load suppression which then leads to reconstitution of the immune system. [20] The study showed that the CD4 cell count for patients who were diagnosed with TB who had already started on ART was significantly higher than the level of CD4 count for patients who did not receive ART at the time their TB was diagnosed. This finding suggests that substantial restoration of CD4 cell numbers had occurred among the patients receiving ART at the time TB was diagnosed.

2.7 Challenges of early initiation of ART

People living with HIV associated TB may not have access to TB and HIV services for a variety of reasons that may differ from country to country. In a rural district in Malawi, acceptance of ART was low and was associated with scarce availability of transport and high transport costs to the hospital. Hospitals providing ART at the time were centralized.[22] The following factors were also reported as hindrances to early initiation of ART in HIV associated TB:

- ART is deferred until the continuation phase of tuberculosis treatment when the sickest patients might have died and survivors feel well enough not to start ART.
- In the continuation phase, tuberculosis treatment was decentralized whereas ART often still remained centralized, a negative factor requiring several visits to different facilities to obtain antiretroviral medications.
- Tuberculosis and ART services operate in a vertical manner in many health facilities, making access to ART difficult for patients con-infected with tuberculosis.
- There are specific clinical challenges of combined TB and ART management, including the following: optimum time to start ART; how best to combine rifampicin-containing regimens with first-line and second-line ART; consideration of rifabutin instead of rifampicin; management of immune reconstitution disease; and the role of isoniazid preventive therapy after completion of tuberculosis treatment.
- Inadequate empowerment of patients and community groups on the benefits of combined ART and tuberculosis treatment.[23]

In Lesotho, access to health care is limited because of poor health infrastructure which is inadequately staffed; this has been a problem especially for PLHIV and TB.[24] In some cases, patients would go to the dilapidated health centers, wait on the queue for the whole day and go home without obtaining healthcare. [24] However, in 2015 the Millennium Challenge Corporation (MCC) through its partnership with Millennium Challenge Account ï Lesotho (MCA) has intervened by addressing health sector challenges through $122,000 million investment in health infrastructure and health system. [24]

A study conducted in Lesotho in 2009 among 13 243 PLHIV enrolled in HIV care between 2006 and 2008, showed that the government of Lesotho was committed to addressing HIV/AIDS and TB but there are persisting health care delivery problems including major health resource constraints. [25] There is a dire shortage of health professionals Lesotho has just 5 doctors and 62 nurses per 100 000 inhabitants as compared South Africa with 74 doctors and 393 doctors per 100 000 inhabitants. [25]

2.8 Summary of the chapter

The literature review showed that there exists an association between survival and early initiation of ART in PLHIV associated TB. CD4 count and viral load also showed improvements where ART was initiated early. There were however, adverse effects such as development of Immune Reconstitution Inflammatory Syndrome (IRIS) in some people living with HIV associated TB who were started early on ART. In some settings, challenges to access of ART to people living with HIV associated TB included high transport costs to hospitals, long distances to clinics, long queues at hospitals which discourage or deter patients to seek appropriate treatment. There is however strong evidence that countries should commence PLHIV associated TB early on ART.

3 CHAPTER THREE: RESEARCH METHODS

In this section, the research methods employed in this study to show whether early initiation of ART in adults living with HIV associated TB in Lesotho in 2012 have proved effective or not will be described. The chapter includes information on the study setting, study design, target population, study population, sampling and data processing and analysis.

3.1 Study setting

The study was conducted in three selected hospitals in Lesotho, namely Berea, Ntsekhe and Scott hospitals[b].

3.2 Study design

An observational, analytic cross-sectional study design was used.

3.3 Target population

The target population is focused on adults living with HIV associated TB and can be generalized to similar populations from other comparable hospitals and areas throughout Lesotho.

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[b] Berea Hospital is a government hospital which serves about 251 169 people in its catchment area. It has an integrated TB and HIV programme where people are served under one roof. Ntsekhe Hospital is also a government hospital which serves about 175 497 people in its catchment area. It also offers TB and HIV services under one roof. On the other hand, Scott is a Christian Hospital Association of Lesotho (CHAL) hospital which serves about 13 275 people in its catchment area. It also has an integrated TB and HIV programme where people living with HIV and TB are served under one roof.

3.4 Study population

The study population consisted of adults living with HIV associated drug-sensitive TB (both pulmonary and extra-pulmonary) and who commenced TB treatment in Lesotho at Berea, Ntsekhe and Scott Hospitals from January to March (first quarter) 2012.[c] The plan was to assess treatment outcomes of a cohort of people living with HIV associated TB one year after all the participants had commenced TB therapy and had completed therapy in April 2013, since all such patients would have had their treatment outcomes and mortality recorded. Consequently, the effectiveness of therapy could be measured. However, there were delays in finalizing the protocol. This meant that the evaluation of participants was only done in July 2013, but on the same cohort of people living with HIV associated TB proposed in the protocol.

3.4.1 Inclusion / exclusion criteria

Inclusion and exclusion criteria were considered in this study.

3.4.1.1 Inclusion criteria

All people aged 15 years and above of both sexes were included in this study as they are considered to be ‘adults’ in Lesotho. The inclusion criteria included all those living with HIV at the commencement of TB treatment, but who were not already on ART

[c] Patients with both pulmonary and extra-pulmonary TB were included, but those with multi-drug resistant (MDR-TB) and extensive-drug resistant (XDR-TB) TB were excluded, as they are not enrolled into the TB programme at district level in Lesotho. Patients with drug resistant TB receive care from the XDR-TB and MDR-TB treatment centre located in Maseru the capital of Lesotho where all such patients are managed.

when diagnosed with TB. These included adults started on TB treatment who had come to the hospital with an already known HIV positive status as well as those who tested positive at the commencement of TB treatment.

3.4.1.2 Exclusion criteria

The exclusion criteria included all people living with HIV associated TB who commenced TB treatment and were already on ART when commencing TB treatment. In addition, patients who were ôTransferred Outôto another TB care centre, specifically patients with MDR-TB and XDR-TB strains of the disease were excluded from the study population.

3.5 Study sample

The study sample comprised 247 patients with HIV associated TB, selected from three out of the 17 hospitals in Lesotho. There were to be 70 participants from Berea, 64 from Scott and 113 from Ntsekhe Hospital.

3.5.1 Size of sample

A software package called Survey Random Calculator provided by Custom Insight was used to determine the sample size required to give an estimate with 95% confidence interval and 5% margin of error. The study sample size required was 245. The study population comprised 302 people living with HIV associated TB who qualified to participate in the study recorded in the TB registers during the study period, of which 75 were identified at Berea Hospital, 72 at Scott Hospital and 155 from Ntsekhe Hospital. The proportional study sample size from each hospital was determined to be 63 from Berea Hospital, 72 for Scott Hospital and 110 for Ntsekhe Hospital. However, during data collection, the Scott Hospital study sample size dropped from 72 to 64 as it was found at the time of data collection that some

patients had been ódouble enteredôinto the hospital TB register. The number of patients obtained from Berea and Ntsekhe was increased from 63 to 70 and 110 to 113 respectively to compensate for fewer patients being available from Scott Hospital giving a total of 247 patients that comprised the study sample.

3.5.2 Method of selecting sample

A multi-stage stratified random sampling process was used. Lesotho has 17 hospitals (seven belong to the Christian Health Association for Lesotho (CHAL) and ten government hospitals) and these were the primary sampling units. In order to obtain a representative sample, the first stage of this process involved selecting three of the 17 (18%) hospitals randomly without replacement from a list of all hospitals (both government and CHAL).

The second stage of sample selection occurred at the hospital level, where all TB patients who commenced TB therapy during the review period (January to March 2012) were selected from the TB register. The third stage of sample selection was where 70 participants were selected from Berea, 64 from Scott and 113 from Ntsekhe Hospital using simple random sampling without replacement.

3.6 Data sources

The TB registers kept at the hospitals were used as the primary source of data for each participant included in the study sample. Where possible, TB treatment cards which were available at the hospital TB clinic were used to verify the data from the TB register and obtain data missing from the TB registers.[d]

[d] In Lesotho, TB patients have 2 treatment cards opened once they are commenced on TB treatment;

3.6.1 Measurement instruments / Data collection techniques

A data collation sheet was completed by the researcher to enter the data required from each of the participants for the study including type of TB, TB treatment regimen, timing of ART initiation, CD4 count results and the TB treatment outcomes. [e]

3.7 Measures to ensure validity

In order to ensure validity in this study, internal and external bias was reduced as far as possible.

3.8 Internal validity

The internal validity was improved by reducing selection and information bias.

3.8.1 Selection bias

Selection bias was reduced by clearly defining the study population, giving careful attention to sampling and proper identification of people living with HIV associated TB who started ART early and those who had begun it late.

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one is left at the facility and the other one is kept by the patient. Both cards are updated every time the patients come to the facility for care.

[e] Viral load has been excluded as a variable because in Lesotho, the test is done only for serious cases, due to the cost of the test and its affordability in Lesotho.

3.8.2 Information bias

Information bias was reduced by using standardized measures for each variable. At each hospital, the same CD4 cell count machine was used for all patients, the same weight scale was used and TB and HIV treatment provided was the same, depending upon the needs of all patients and given according to the Lesotho Standard Treatment Guidelines. The process of standardising the data collation was assisted by maintaining a data collation form and having this collected and collated by one person, namely the principal investigator.

3.9 External validity / Generalisability

In this study, adults living with HIV associated TB of both sexes were included in the study population. This was done so that the results obtained could be generalized to other hospitals and areas in Lesotho with a similar population and environmental conditions.

3.10 Pilot study

The initial plan was to conduct a pilot study prior to the actual research study but the researcher was restricted by time factors and could therefore not undertake a pilot study.

3.11 List of variables

There were specific variables that were measured in this study. The TB outcome variables collected were the standard TB treatment outcomes used in Lesotho and recommended by the WHO. The exposure variables used concerns the question of whether the patient received early initiation of ART (less than 4 weeks from commencing TB therapy), late initiation of ART (four or more weeks from

commencing TB therapy) or no ART. These variables were used as the purpose of the study was to assess the effectiveness of the stage of ART initiation in those patients living with HIV associated TB on their TB outcomes.

3.12 Plan for data collection

Data was collected in July 2013 at the time that all participants had completed their TB treatment and the measurable outcomes were available and would have been recorded in the relevant hospital TB registers.

3.13 Plan for data handling/processing

Clear procedures were followed in this study to ensure proper data handling. Consequently, data collected and used in this study was accessed by the researcher only, in order to ensure confidentiality. The researcher captured data into the computer that only authorized personnel possessed access to even during statistical processing of the data. Moreover, participantsô names were not captured; instead, codes were given to each participant for confidentiality reasons. Different letters were used to identify patients according to their hospitals. Participants from Scott Hospital had their code starting with ñSò, those from Berea Hospital started with ñBòand lastly those from Ntsekhe Hospital had their code starting with ñMò

3.14 Statistical methods

Statistical methods used in this study were descriptive and analytic.

3.14.1 Descriptive statistics

Descriptive statistics methods were used to organise, summarise and describe data. In this study, categorical data was summarised using appropriate frequency distribution tables and graphs.

3.14.2 Analytic statistics

Multivariable models were used to draw inferential conclusions on the data. These showed how the outcome was associated with the exposure variables being measured after controlling for confounding variables. SPSS was the statistical software package used to calculate measures of associations and the chi-squared test.

3.15 List of possible confounding factors

The possible confounders in this study included age, sex, TB site (pulmonary or extra-pulmonary), hospital ownership and treatment category. To control for confounding, stratification and multivariable models were considered for all variables that were likely to complicate the estimation of the measures of association between exposures and outcomes.

Each predictor was tested bivariately against the TB outcomes using a logistic regression. Variables significant at $p<0.2$ level were selected for entry into the final multivariable model. The link test was also performed to check model specification. Multivariable model fit was assessed using the Hosmer and Lemeshow's goodness of fit statistic. A classification table was also produced relating observed versus predicted outcomes from the model, i.e. predictive power. Multicollinearity between predictors was also assessed as this factor can erroneously affect the coefficient values. This was assessed using the variance inflation factor (VIF). As a general rule of thumb, the VIF should not exceed 10, though some sources of literature suggest this cut-off should be lower i.e. 5.

3.16 List of associations to be measured

The measures of association that were calculated in this study to determine whether there was an association between the exposed and the un-exposed variables relative

to the outcome were prevalence ratio and odds ratio. These were measured to assess the exposure and outcome relationship in the variables being evaluated and to check the strength of association between the variables. The exposure variables evaluated were hospital, type of TB, site of TB, CD4 count cell/mm^3, age, sex and time of ART initiation.

3.17 Ethical considerations

An expedited ethical review process was followed as this study involved processing and analysing data collected from patient records. There was no direct patient contact.

3.17.1 Institutional ethical review board

Lesotho has a Research Coordinating Unit (RCU) that needs to give approval before any research is commenced. Thus, the Lesotho RCU was consulted prior to this study, being carried out and approval was granted. Expedited ethical approval was also obtained from the College of Health Sciences, Biomedical Research Ethics Committee at the University of KwaZulu-Natal (BREC No.: BE300/12).

3.17.2 Permissions

The study obtained data from the TB registers in the hospitals and prior to extracting the data from the TB registers gate-permission was obtained the hospital management.

3.17.3 Informed consent

Adults living with HIV associated TB being studied did not have a direct benefit from

this study. Thus, it was not necessary to obtain informed consent and information from the subjects.[f]

3.18 Summary of the chapter

This study used an observational analytic cross-sectional design and was conducted in three hospitals in Lesotho namely Berea, Ntsekhe and Scott Hospitals. The target population would be adults living with HIV associated TB in similar hospital to those selected in Lesotho. The study sample comprised 247 participants and TB registers were used to obtain data using a custom designed data collection tool. The statistical software utilised to process and analyse data was SPSS. Associations measured included prevalence and odds ratios. Regarding ethical considerations, the Lesotho Research Coordinating Unit was consulted and approval was granted. The College of Health Sciences, Biomedical Research Ethics Committee at the University of KwaZulu-Natal granted an expedited ethical approval for the study as well. Lastly, permission was sought from the management at three hospitals to conduct the study.

[f] Participants did not have a direct benefit in respect of the flat that, the researcher was interested in the outcomes of TB patients and only those enrolled after the study is completed will benefit because the recommendations will be shared with the Lesotho MOHSW. Data was collected from hospital registers and not directly from patients hence informed consent was not necessary.

4 CHAPTER FOUR: RESULTS

4.1 Introduction

In this chapter of the dissertation, I will present the results of the study. In the first section, the study sample characteristics are described. In the second section timing of antiretroviral therapy is presented. The TB outcomes are presented in the third and fourth section of the results chapter. In the third section, associations between the standard WHO TB outcomes and the timing of ART commencement are assessed using prevalence ratios. In the fourth section the TB outcomes are dichotomised as ósuccessfulô or not and using logistic regression a multivariable model is developed.

4.2 The study sample

There were 247 participants living with HIV associated TB who were enrolled in the study of which, 70 (28%) were from Berea Hospital, 64 (26%) from Scott Hospital and 113 (46%) from Ntsekhe Hospital. Slightly more than half (54%) of participants were males. There were more males (42/70 - 60%: 95% Confidence Interval (CI): 48 to 71) in Berea Hospital compared to the other two hospitals. The difference was not statistically significant (p = 0.22). Only in Ntsekhe Hospital were there recorded more females than males. The difference was not statistically significant (p = 0.37) (Table 1).

A slightly higher proportion of females (109/114 - 96%; 95% CI: 90 to 98) comprised of new TB cases compared to males (120/133 - 90%; 95% CI: 84 to 94). There was a 2.4 times increased risk of females being new cases compared to males (Odds Ratio (OR) 2.4; 95%CI: 0.8 to 6.8) but this factor was not statistically significant (p = 0.11) (Table 1).

Regarding site of disease and gender, males are 1.6 more likely to get pulmonary TB compared to females. (OR 1.6; 95% CI: 0.7 to 4.0). This is confirmed by results which further show that it is more likely for males (124/133 - 93%: 95% CI: 87 to 97) to have pulmonary TB than females (102/114 - 90%; 95% CI: 82 to 94). The association was not statistically significant (p = 0.29) (Table 1).

Only 86 (65%) males and 86 (75%) females had a known CD4 count result recorded in the TB register. In the participants who had a result a similar proportion of males (49/86 - 57%; 95% CI: 46 to 68) recorded a CD4 count below 200 cell/mm^3 to females (48/86 - 56%; 95% CI: 45 to 66) (Table 1).

Overall, only 180 of the 247 (73%) people with HIV associated TB had commenced antiretroviral therapy. A greater proportion of females (87/114 - 76%; 95% CI: 67 to 84) than males (93/133 - 70%; 95% CI: 61 to 77) were on ART. Females were more likely to have been initiated on ART late (more than 4 weeks after commencing TB therapy) (49/114 - 43%; 95% CI: 34 to 53) compared to males (51/133 - 38%; 95% CI: 30 to 47) (Table 1).

Table 1: Gender of adult patients living with HIV associated TB in three hospitals, by type and site of TB, CD4 count, age and stage ART was initiated in Lesotho, 2012.

		Males n (%) 95%CI	Females n (%) 95%CI	Total (%)
Hospital	Berea	42 (60.0%) 47.6 to 71.3	28 (40.0%) 28.7 to 52.4	**70 (28.3%)**
	Scott	37 (57.8%) 44.8 to 69.8	27 (42.2%) 30.2 to 55.2	**64 (25.9%)**
	Ntsekhe	54 (47.8%) 38.4 to 57.5	59 (52.2%) 42.7 to 61.6	**113 (45.7%)**
Type TB	New	120 (90.2%) 83.6 to 94.5	109 (95.6%) 89.6 to 98.4	**229 (92.7%)**
	Other	13 (9.8%) 5.5 to 16.5	5 (4.4%) 1.6 to 10.4	**18 (7.3%)**
Site of TB	Pulmonary	124 (93.2%) 87.2 to 96.7	102 (89.5%) 82.0 to 94.2	**226 (91.5%)**
	Extra-Pulmonary	9 (6.8%) 3.3 to 12.8	12 (10.5%) 5.8 to 18.0	**21 (8.5%)**
CD 4 Count cell/mm^3	Known CD4	86 (64.7%) 55.8 to 72.6	86 (75.4%) 66.3 to 82.8	**172 (69.6%)**
	<200	49 (57.0 %) 45.9 to 67.5	48 (55.8%) 44.7 to 66.4	**97 (39.3%)**
	200+	37 (43.0%) 32.5 to 54.1	38 (44.2 %) 33.6 to 55.3	**34 (13.8%)**
	Unknown CD4	47 (35.3%) 27.4 to 44.2	28 (24.6%) 17.2 to 33.7	**75 (30.4%)**
Age	< 30 years	31 (23.3%) 16.6 to 31.6	43 (37.7%) 29.0 to 47.3	**74 (30.0%)**
	30 + years	102 (76.7%) 68.4 to 83.4	71 (62.3) 52.7 to 71.0	**174 (70.0%)**
ART Initiation Stage	Early Ò4 weeks	42 (31.6%) 24.0 to 40.3	38 (33.3%) 25.0 to 42.9	**80 (32.4%)**
	Late >4 weeks	51 (38.3%) 30.2 to 47.2	49 (43.0%) 33.9 to 52.6	**100 (40.5%)**
	No Treatment	40 (30.1%) 22.6 to 38.7	27 (23.7%) 16.4 to 32.7	**67 (27.1%)**
	Total	**133 (53.8%) 47.4 to 60.2**	**114 (46.2%) 39.8 to 52.6**	**247 (100.0%)**

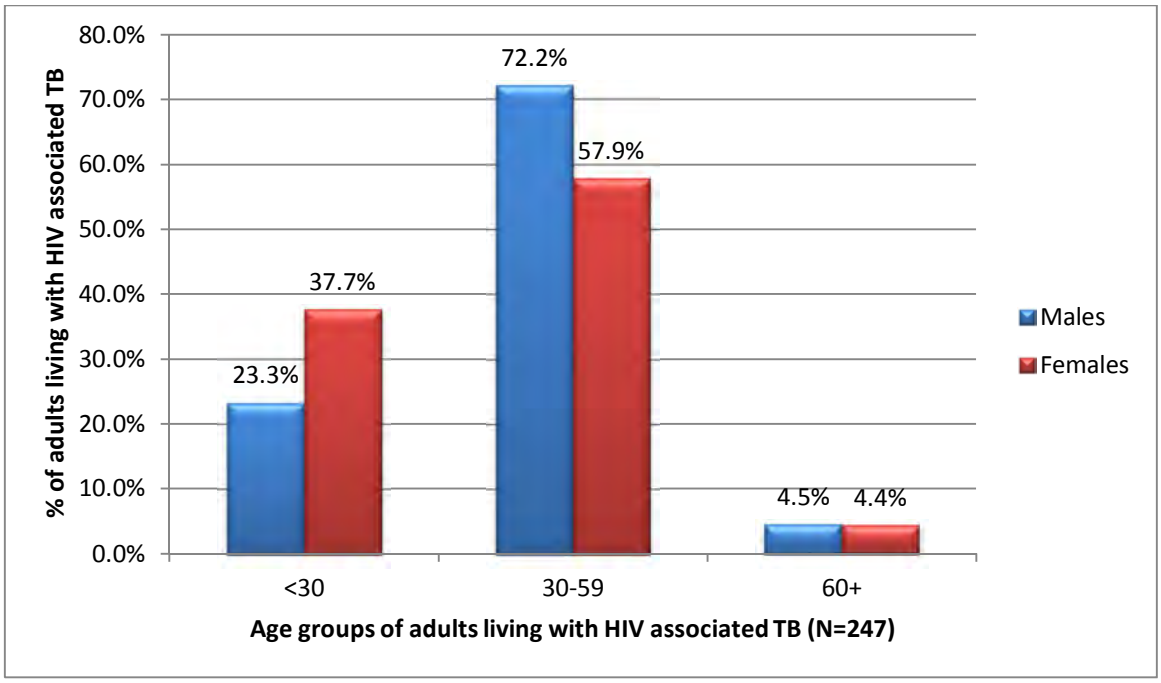

Figure 2: **Age and gender of adults living with HIV associated TB in three hospitals Lesotho, 2012**

In this study, all participants were aged 15 years and above. A greater proportion (43/114 - 38%; 95% CI: 29 to 47) of females were less than 30 years of age compared to 31 of 133 (23%; 95% CI: 16 to 31) who were males (Figure 2). This difference was statistically significant ($p < 0.05$). This gender ratio was reversed in those older than 30 years, with males comprising 72% (96/133 - 95% CI: 64 to 79) and females 58% (66/114 - 95% CI: 48 to 67).

Of the 247 participants, 229 (93%) received the basic and first line Category 1 treatment regimen. All of these patients had newly diagnosed TB. The 18 (7%) who were received the Category 2 regimen were all patients with HIV associated TB who were receiving repeat TB treatment (Table 2).

Table 2: Treatment category and patient type for adults living with HIV associated TB in Lesotho, 2012.

Treatment Category	Patient Type		Total
	New	**Other**	
Category 1	229 (100.0%)	0 (0.0%)	229 (92.7%)
Category 2	0 (0.0%)	18 (100.0%)	18 (7.3%)
Total	**229 (100.0%)**	**18 (100.0%)**	**247 (100.0%)**

4.3 Timing of antiretroviral therapy initiation

About 31% of those with HIV associated TB who did not commence ART were less than 30 years of age (23/74 - 31%; 95% CI: 21 to 43). This factor was not statistically significant (p = 0.20). There was no statistical difference in the proportion who initiated ART early or late according to age, the prevalence ratio being 0.9 in early initiators (95%CI: 0.6 to 1.5), 1.3 in late initiators (95% CI: 0.8 to 2.0) in those less than 30 years and 1.3 in early initiators (95% CI: 0.8 to 12.2) and 1.6 in late initiators (95% CI: 1.0 to 2.5) in those aged 30 years or more (Table 3).

Table 3: Early and late ART initiators by age for adults with HIV associated TB in three hospitals in Lesotho, 2012.

	Age Group				
ART Initiation	**<30 years n (%) 95%CI**	**Prevalence Ratio (95%CI)**	**30+ years n (%) 95%CI**	**Prevalence Ratio (95%CI)**	**Total %**
Early Initiation[g]	21 (28.4%) 18.8 to 40.2	0.9 (0.6 to 1.5)	59 (34.1%) 27.2 to 41.7	1.3 (0.8 to 2.2)	**80 32.4%**
Late Initiation	30 (40.5%) 29.3 to 51.7	1.3 (0.8 to 2.0)	70 (40.5%) 33.2 to 48.2	1.6 (1.04 to 2.5)	**100 40.5%**
No ART	23 (31.1%) 21.1 to 43.0	Reference	44 (25.4%) 19.2 to 32.7	Reference	**67 27.1%**
Total	**74 (100.0%)**		**173 (100.0%)**		**247 100.0**

Ninety seven participants (97/247 - 39%; 95% CI: 33 to 46) recorded CD4 count less than 200 cell/mm^3 and 75 a CD4 count 200 cell/mm3 and above (75/247 - 30%; 95% CI: 25 to 37) or had an unknown CD4 count (75/247 - 30%; 95% CI: 25 to 37). The difference was not statistically significant ($p < 0.25$) (Table 4).

Most (48/67; 72%; 95% CI: 59 to 82) of those who did not have a CD4 count were not on ART.

Participants with a CD4 count less than 200 cell/mm^3 (PR 6.5; 95% CI: 3.0 to 14.4) were more likely to be initiated early on ART compared to those with CD4 of 200 cell/mm^3 and above and those with no CD4 count (PR 1.7; 95% CI: 0.1 to 3.1 and PR

[g] Early initiation of ART refers to participants initiated on ART four or less weeks after commencing TB treatment and late initiation were those started late more than four weeks

0.1; 95% CI: 0.4 to 0.2 respectively). Similarly, those with CD4 count less than 200 cell/mm^3 were 4.9 times (PR 4.9; 95% CI: 2.2 to 10.6) of being initiated late on ART compared to those with CD4 of 200 cell/mm^3 and above and those with no CD4 count (PR 1.8; 95% CI: 1.0 to 3.2 and PR 0.3; 95% CI: 0.2 to 04 respectively) (Table 4).

Table4: Early and late ART initiators by CD4 count for adults with HIV associated TB in three hospitals in Lesotho in 2012.

ART Initiation	<200 n (%) 95%CI	Prevalence Ratio 95% CI	200+ n (%) 95%CI	Prevalence Ratio 95% CI	Unknown CD4	Prevalence Ratio 95% CI	Total %
Early Initiation[h]	47 (58.8%) 47.2 to 69.5	6.5 (3.0 to 14.4)	27 (33.7%) 23.8 to 45.3	1.7 (0.1 to 3.1)	6 (7.5%) 3.1 to 16.2	0.1 (0.0 to 0.2)	**80 32.4%**
Late Initiation	44 (44.0%) 34.2 to 54.3	4.9 (2.2 to 10.6)	35 (35.0%) 25.9 to 45.3	1.8 (1.0 to 3.2)	21 (21.0%) 13.8 to 30.5	0.3 (0.2 to 0.4)	**100 40.5%**
No ART	6 (9.0%) 3.7 to 19.2	Reference	13 (19.4%) 11.1 to 31.2	Reference	48 (71.6%) 59.1 to 81.7	Reference	**67 27.1%**
Total	**97 (39.2%) 33.2 to 45.7**		**75 (30.4%) 24.8 to 36.6**		**75 (30.4%) 24.8 to 36.6**		**247 100.0%**

[h] Early initiation of ART refers to participants initiated on ART four or less weeks after commencing TB treatment and late initiation were those started late more than four weeks

4.4 TB outcomes depending on stage of antiretroviral therapy initiation.

The outcomes were calculated for each of the WHO standard TB outcome indicators (Table 3). In this section, the association between each outcome and stage of ART initiation was calculated as prevalence ratios. The cure and completed treatment outcomes were both better in those who commenced ART late (prevalence ratio (PR) 3.3; 95% CI: 1.9 to 5.7 and PR 2.6; 95% CI: 1.5 to 4.8 respectively) compared to the early initiators (PR 1.7; 95% CI: 0.9 to 3.2 and PR 2.5; 95% CI: 1.3 to 4.5 respectively) relative to those not commenced on ART.

When the cure and completed outcomes were aggregated as õsuccessfulò the outcomes were also both better in those who commenced ART late (PR 1.9; 95% CI: 1.4 to 2.5 compared to the early initiators (PR 1.9; 95% CI: 0.9 to 3.2) relative to those not commenced on ART. The deaths and defaulter outcomes were both much worse in those who did not have any ART relative to both late (PR 0.4; 95% CI: 0.3 to 0.6 and PR 0.5; 95% CI: 0.3 to 0.8) and early initiators (PR 0.3; 95% CI: 0.2 to 0.5 and PR 0.4; 95% CI: 0.3 to 0.7). None of these differences were statistically significant (Table 5).

Table5: TB treatment outcomes and prevalence ratios (PR) for different stages of ART initiation in people living with HIV associated TB in three hospitals in Lesotho, 2012

	TB Treatment Outcomes (WHO)													
ART Initiation	**Cured**		**Completed**		**Successful**		**Died**		**Defaulted**		**Failed**		**TOTAL**	
	n %	**PR 95%CI**	**n %**	**PR 95%CI**	**n %**	**PR 95%CI**	**n %**	**PR 95%CI**	**n %**	**PR 95%CI**	**n %**	**PR 95%CI**	**N %**	**PR 95%CI**
≤4 weeks	12 28.6%	1.7 0.9 - 3.2	54 40.3%	2.5 1.3 - 4.5	**66 82.5%**	**1.91 1.4 - 2.6**	5 19.2%	0.3 0.2 - 0.5	9 21.4%	0.4 0.3 - 0.7	0 0.0%	0.0	**80 32.4%**	**1.2 0.9 - 1.6**
>4 weeks	23 54.8%	3.3 1.9 - 5.7	58 43.3%	2.6 1.5 - 4.8	**81 81.0%**	**1.87 1.4 - 2.5**	6 23.1%	0.4 0.3 - 0.6	11 26.2%	0.5 0.3 - 0.8	2 66.7%	2.0 1.4 - 2.8	**100 40.5%**	**1.5 1.1 - 2.0**
No ART	7 16.6%	Ref.	22 16.4%	Ref.	**29 43.3%**	**Ref.**	15 57.7%	Ref.	22 52.4%	Ref.	1 33.3%	Ref.	**67 27.1%**	Ref.
Total	**42 17.0%**		**134 54.3%**		**176**		**26 10.5%**		**42 17.0%**		**3 1.2%**		**247 100.0%**	

Successful Outcome = Cured +Completed treatment. TOTAL = Successful + Died + Defaulted + Failed

4.5 Factors associated with TB treatment outcomes

In this section, the factors associated with TB treatment outcomes were analysed using logistic regression and the unadjusted and adjusted results presented. Those patients with HIV associated TB who were cured and completed were aggregated together as having a ósuccessfulô outcome.

4.5.1 Unadjusted findings

Ages of those with HIV associated TB, which hospital they were being managed at, gender, site of TB, type of TB and CD4 count were the factors (independent variables) analysed and the outcome was ósuccessfulô (cured and completed) TB treatment.

Participants aged below 30 years were 1.1 times more likely to have successful TB treatment outcome (OR 1.1: 95% CI: 0.6 to 2.1) than those aged 30 years and above. The difference was not statistically significant (p=0.696) (Table 6).

Participants with HIV associated TB from Berea Hospital had less chances of having successful TB outcomes (OR 0.5: 95%CI: 0.3 to 1.0) relative to those from Scott Hospital and the difference was marginally statistically significant (p=0.063). On the other hand, HIV associated TB participants from Ntsekhe Hospital were 0.9 times less likely to obtain successful TB outcomes (OR: 0.9: 95% CI: 0.4 to 2.0) and the difference was not statistically significant (p=0.741) (Table 6).

Slightly more males (97/133; 73%; 95% CI: 64 to 80) had successful TB outcomes compared to females (79/114; 69%; 95% CI: 60 to 77). The unadjusted OR of 0.8 (95% CI: 0.5 to 1.5) indicated that females were 0.8 times less likely to have successful TB outcomes than males and the difference was not statistically significant (p=0.529) (Table 6).

Those with extra pulmonary TB were 1.8 times more likely (OR 1.8: 95% CI: 0.6 to 5.5) to have a successful TB outcomes. The difference was not statistically significant (p=0.310). Additionally, patients who were taking TB therapy for the first time were 0.6 times less likely (OR 0.6: 95% CI: 0.2 to 1.6) to have successful TB outcomes than those repeating a course of TB therapy for whatever cause. The difference was not statistically significant (p=0.327) (Table 6).

Not all the sample had a record of having had a CD4 count. Successful TB outcomes were not dependent on CD4 count. Participants with a CD4 count less than 200 cell/mm^3 had less chances of having successful TB outcomes (OR: 0.9: 95% CI: 0.2 to 1.6) relative to those with no CD4 count and the difference was statistically significant (p=0.011). Similarly, those with a CD4 count of 200 cell/mm^3 and above were 0.8 times less likely to obtain successful TB outcomes (OR 0.8 95% CI: 0.4 to 1.6) and the difference was not statistically significant (p=0.493) (Table 6).

Out of 247 adults living with HIV associated TB, 80 (32%) were started on ART early (4 weeks or less), 100 (41%) were started late (after 4 weeks) and 67 (27%) received no ART at all. The unadjusted results show that early initiators were 6 times more likely to have a successful TB outcome (OR 6.2: 95%CI: 3.7 to 27.5) relative to the group who had no ART. This difference was statistically significant (p<0.001) (Table 6). Interestingly those who commenced ART late also had a six times more likely to have a successful TB outcome (OR 5.6: 95% CI: 2.8 to 11.2) relative to the group who had no ART.[i]

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[i] The Odds Ratio overestimates the association between timing of ART initiation and successful outcome. The OR was 6.2 in early initiators and 5.6 in late initiators relative to those who did not commence ART. The prevalence ratio was 1.91 and 1.87 for the same exposures and outcomes. The Odds Ratio is

4.5.2 Adjusted findings

After the bivariate regression, some predictors, namely hospital, CD4 count and stage when initiated on ART remained significant and therefore were included into the multivariable analysis. However, age and sex by virtue of being confounders were also included into the multivariable model even though they were not significant. In the final model, hospital (OR 0.4: 95% CI: 0.2 to 1.0) and stage when initiated on ART (OR 10.1: 95% CI: 3.7 to 27.5) were the two predictors that remained statistically significant as revealed by the p-values p=0.040 and p<0.001 respectively. Nonetheless, age and sex were closer to being significant in the multivariable analysis with p=0.212 and p=0.288 respectively than in the bivariate analysis with p=0.696 and 0.529 respectively. Regarding age, the p-value dropped from p= 0.696 to p=0.212 while the p-value for sex moved from p=0.529 to p=0.288 (Table 6).

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overestimated when the occurrence of the outcome variable is greater than 0.1. It is however much easier to calculate the adjusted Odds Ratio using logistic regression, and this finding is commonly reported in cross-sectional studies where prevalence is the measure of disease occurrence measured.

Table 6: Successful TB outcomes by stage of ART Initiation, hospital, age, sex, CD4 count, site of TB and type of TB & AIDS service for adults living with HIV associated TB in three hospitals in Lesotho, 2012.

Predictor	n/N	Unadjusted			Adjusted		
		Odd Ratio	95% CI	*P* value	Odd Ratio	95% CI	*P* value
Age: 30+ years	122/173	1 (Ref.)					
<30 years	54/74	1.13	0.61 to 2.07	0.696	0.64	0.32 to 1.29	0.212
Hospital: Scott	50/64	1 (Ref.)					
Ntsekhe	73/113	0.87	0.39 to 1.95	0.741	0.44	0.20 to 0.96	0.040
Berea	53/70	0.51	0.25 to 1.04	0.063	0.61	0.24 to 1.61	0.333
Sex: Male	97/133	1 (Ref.)					
Female	79/114	0.84	0.48 to 1.46	0.529	1.41	0.75 to 2.65	0.288
Site: PulmonaryTB	159/226	1 (Ref.)					
Extra-PTB	17/21	1.79	0.58 to 5.52	0.310	-	-	-
Type: Repeat TB	11/18	1 (Ref.)					
New TB	165/229	0.61	0.23 to 1.64	0.327	-	-	-
CD4: Unknown	47/75	1 (Ref.)					
<200	78/97	0.89	0.21 to 1.59	0.011	0.76	0.28 to 2.01	0.578
200+	54/75	0.79	0.40	0.493	0.49	0.19 to 1.25	0.136
Stage ART initiated							
No ART	29/67	1 (Ref.)					
Early (<4 week)	66/80	6.18	2.91 to 13.1	0.000	10.07	3.69 to 27.48	0.000
Late (4+ weeks)	81/100	5.59	2.79 to 11.2	0.000	8.39	3.42 to 20.6	0.000

4.6 Summary of the chapter

In this study the effectiveness of TB outcomes in patients living with HIV associated TB in Lesotho was assessed. There was duplication of records found at one hospital. Only 70% had a CD4 count. About 1/3 of the participants had no ART, 1/3 had early ART and 1/3 had late ART. Those not on ART were much worse off. There was no difference between early and late initiators of ART as shown by adjusted analysis.

5 CHAPTER FIVE: DISCUSSION

5.1 Introduction

In this chapter the results obtained in the study will be discussed in relation to the existing literature on the topic of TB outcomes in relation to those living with HIV associated TB in Lesotho in 2013. The discussion contains five sub-sections, namely the study sample; factors associated with timing of antiretroviral therapy initiation, TB outcomes depending on the stage of antiretroviral therapy initiation, factors associated with treatment outcomes, to get the with two sub headings, unadjusted findings and adjusted findings and, finally, the limitations.

5.2 The study sample

There were slightly more males (54%) than females (46%) living with HIV associated TB in this study. Females were however generally younger than their male counterparts. A study conducted in Hong Kong in 2013 evaluating the optimal time for initiating ART in 260 patients with HIV associated TB had 228 (88%) males and 32 (12%) females and the average age for males was 40 years, while that of females was 34 years. [17] Those with HIV associated TB in low income countries such as Lesotho have a very different demographic profile than in high income countries. Our participants confirmed much to that of the participants in the SAPiT trial conducted in Durban in 2010, which reported that gender distribution of their 642 participants was equal.[27]

It is probable that the demographic profile at Ntsekhe Hospital, which recorded more females than the other two hospitals could have resulted from a Prevention of Mother-to-Child programme at the hospital. Most females in this hospital are routinely HIV tested and those who test positive at the antenatal clinic were referred to the ART clinic unlike the prevailing in other hospitals where relatively few women are HIV tested. The

essential fact is that, the two hospitals, namely Berea and Scott, are not the only hospitals in their districts. This explains why some women go elsewhere for antenatal services.

Out of 229 new TB cases, more than half (52%) were males. Although a study conducted in Pakistan revealed a contrary situation where there were more new female TB cases being notified.[28] This study however, showed results similar to most countries, including America, nations in South-East Asia and in Europe, the opposite phenomenon is observed where more male cases were notified with TB. [28]

All the newly diagnosed TB patients were receiving treatment that is the recommended first line TB therapy type and those who had repeat TB infection were on the standard second-line therapy. The practice in Lesotho is similar to what is being done in South Africa. [29] The 2009 National Tuberculosis Management Guidelines of the Department of Health in South Africa recommended that the newly diagnosed (treatment naïve) TB patients should be on standard first-line TB therapy. [29] The guidelines further recommend that those with TB who are repeating treatment for TB should be on a standard second-line therapy regimen, but that sputum should be sent for culture and drug susceptibility testing. [29]

Slightly more of the male PLHIV (55%) in this study had HIV associated pulmonary TB. This is different from the nature of that found in a study conducted in Uganda in 2002 where more females (109 out of 214; 51%) were reported to have PTB. [30]

A disappointing factor concerning the matters that only (70%) of the participants in this study had a recorded a CD4 count. Of those who had a CD4 count result, 44% had a CD4 count greater than 200 cell/mm^3. In Durban in 2012, 1% of HIV associated TB patients had no CD4 count, and in those who reported a CD4 count, it was less than 50 cell/mm^3 in 48%, 51 to 100 in 26%, 101 to -200 in 24% and greater than 200 cell/mm^3 in

only 3%.[31] PLHIV in LIC are diagnosed with HIV associated TB, they are sicker and their CD4 counts are found to have CD4 count below 200 cell/mm^3. [31]

There were no significant differences in age between male (54%) and female (46%) participants in our study. There were more PLHIV in Lesotho aged above 30 years. A study in Durban in 2012 demonstrated a similar situation where, in 458 patients with HIV associated TB, the median age was calculated as 35 years and the interquartile range was 30 to 42 years. [31]

More males (52%) were on ART. Such a phenomenon is similar to that which was observed in a study of 69 PLHIV associated TB conducted in Iran in 2009, where more males (68%) were started on ART than females. [9] The results obtained were similar to what was found in Durban in 2012. [31] The study had 458 participants, who weren't divided into three (3) groups, namely the immediate (66%), early (19%) and late initiators (15%). In all the groups, males comprised a greater proportion thereof, constituting 52%, 51% and 51% respectively. [31]

5.3 Timing of antiretroviral therapy initiation

Age was not a significant factor in respect of whether these PLHIV associated TB commenced ART or not. A study in 2006, in relation to those with newly registered PLHIV associated TB conducted in Malawi, revealed that age was not a statistically significant (p=0.09) predictor of initiating ART. [22] The study recorded two age categories, those of less or equal to 35 and above 35 years, a factor which was similar to that prevailing in our study (less than 30 and 30 years and above). [22] In our study, most participants commencing ART were older than 30 years.

Slightly more of the early initiators (59%) had a CD4 count less than 200 cells/mm^3. Nearly three quarters of those without a CD4 count were not on ART, although PLHIV associated TB were not supposed to commence ART, dependent on their CD4 count. A

study in Iran showed a different scenario where early ART initiation was dependent on the CD4 count. [28]Those whose CD4 count was less than 100 cells/mm^3 were on early ART initiation and late initiation was on those whose CD4 count was between 101 and 200 cells/mm^3. In our study, participants with a CD4 count below 200 cells/mm^3 constituted the largest proportion (56%). Likewise, a study conducted in Durban in 2012 also had more participants with a CD4 less than 200 cells/mm^3. [31] Participants with CD4 count less than 200 cells/mm^3 dominated in all groups of immediate initiators, early initiators and delayed initiators when compared to those with CD4 count above 200 cells/mm^3.[31]

5.4 TB outcomes depending on stage of antiretroviral therapy initiation

This study provides the important observation, that in Lesotho, the implementation of ART initiation policy in adults living with HIV associated TB is sub-optimal. About three quarters of those living with HIV and AIDS were on ART whilst only one third were initiated on ART early. This occurred in spite of HIV and TB services being provided under one roof. Health care workers responsible for TB and HIV services reported that some of the reasons for a delay in starting ART involved the shortage of ARVs and a of training among some nurses who were designated to provide integrated HIV and TB care. The Lesotho National Antiretroviral Therapy Guidelines recommends that those living with HIV associated TB be initiated on ART immediately (within two to four weeks) after commencing TB treatment. [2] This latter finding in our study is of a similar nature to which was reported in Durban in 2013, where late initiators were 6/100 per-year compared with early initiators were 5.7/100 per-year.[16] On the other hand, the Lesotho finding was contrary to what was observed in a study conducted in Thailand in 2012, where more than half (79 out of 156; 51%) of the patients living with HIV associated TB were started on ART early. [26]

This study, however demonstrated that the phenomenon of favourable treatment

outcomes was not dependent on initiating ART early. There was no difference in TB outcomes between early (Prevalence Ratio 1.97) and late ART initiation (Prevalence Ratio 1.87). However, there were discrepancies in the Odds Ratio and prevalence ratio for the same exposure and outcomes. The Odds Ratio overestimates the association between timing of ART initiation and a successful outcome. The OR was 6.2 in early initiators and 5.6 in late initiators relative to those who did not commence ART. The prevalence ratio was 1.91 and 1.87 for the same exposures and outcomes. The Odds Ratio is overestimated when the occurrence of the outcome variable is greater than 0.1 which was the case in our study. It is, however, much easier to calculate the adjusted Odds Ratio using logistic regression, and this finding is commonly reported in cross-sectional studies where prevalence is the measure of disease occurrence measured.

Moreover, when assessing association between the stage when ART commenced and successful TB treatment, results showed that there existed a significant statistical difference in those started early on ART and those who started late (OR 2.4: 95% CI: 1.3 to 4.7). In a study conducted in Durban in 2012, the opposite phenomenon was observed, where timing of initiation of ART was not statistically associated with either increased survival or decreased mortality. [31]

Previous studies have demonstrated that early initiation of ART in people living with HIV associated TB increased survival and improvement of CD4 cell count, weight and suppression of viral load. Nevertheless, the variable which was measured in this study was CD4 count and the opposite was observed in Lesotho, where there was no association (p=0.07). A study conducted in Durban in 2013 confirmed that initiating ART early in people living with HIV associated TB improves survival even in patients with low CD4 counts. [16] This particular report, based on the SAPiT trial compared early ART initiation (within 4 weeks of commencing TB therapy) and late initiation of ART (between 4 and 12 weeks of commencing TB treatment) among 642 South Africans infected with

HIV and smear-positive pulmonary TB confirmed the efficacy of early initiation. [16] There was however, with a marginal significance in the incidence of AIDS or occurrence of death among patients with CD4 count less than 50 cell/µ of 8.5 and 26.3 cases per person-years (incidence-rate ratio 0.32; 95% CI: 0.07 to 1.13; p=0.06) in the early and late ART initiation groups respectively.[16]

Moreover, results revealed that there were more males (54%) than females (46%) who participated in the study. However, there was no association between sex and successful TB treatment (p=0.37). Regarding age, the group of 30 and above was more frequent (173/247, 70%). The finding in our study is similar to that obtained in a study conducted in Durban in 2012 where the common age was 35 in those initiated on ART immediately, early and late. There was however no statistical significance (p=0.59). [31] Concerning association of age and successful TB outcomes, results showed that there was no statistical significance (p=0.50).

Participants who were confirmed with TB for the first time and were classified as category 1 constituted above 90% of all participants. There was, however no statistical difference between type of patient and successful TB outcome (p=0.35). The results further revealed that Pulmonary TB, was more common (226/247, 91%) than extra-pulmonary TB the latter which constituted only 21(9%) participants. Although participants with Pulmonary TB and those with extra-pulmonary TB retained equal chances of having successful TB outcomes, there was no statistical significance (p=0.26).

5.5 Factors associated with treatment outcomes

Logistic regression was used to assess factors associated with TB treatment outcomes and the output resulted in unadjusted and adjusted results.

5.5.1 Unadjusted findings

A bivariate analysis was conducted to assess individual association of the explanatory variables namely age, hospital, gender, site of TB, type of TB, CD4 count and stage where ART was initiated with the response variable successful treatment where the two outcomes; completed and cured were aggregated. The output revealed that hospital was marginally significant (p=0.063) and CD4 count and stage ART were highly significant as shown by *p*-value p=0.011 and p<0.001 respectively. The rest of the variables were not statistically significant. This is similar to what was illustrated by a study in Durban, where CD4 count and ART initiation were statistically significant; p<0.001 and p<0.001 respectively; when associated with timing of ART initiation.[31]

5.5.2 Adjusted findings

On multivariate analysis, which was mainly for controlling of confounders, only hospital (p=0.04) and stage ART initiated (p<0.001) were independently associated with successful TB treatment outcomes. In this analysis, age and gender were included by virtue of being confounders even though they were not significant in the univariate analysis. This finding continues to confirm that it remains important to initiate PLHIV associated TB on ART. A similar finding was observed in a study conducted in India in 2010 where researchers reported a 50% lower mortality among patients who started ART during tuberculosis treatment, compared with those among patients who waited until TB therapy had been completed. [10] There were also limitations in this study that have been elaborated below.

5.6 Limitations

The study had a number of limitations which included selection bias, information bias, confounding and precision problems.

5.6.1 Selection bias

There was some selection bias inherent in the study. The study sample comprised only three out of 17 hospitals in Lesotho and all the selected hospitals are situated in the lowland areas of Lesotho. Access to health care services for people in the highlands is more of a challenge and highland hospitals could have had worse TB outcomes.

The required sample size from one of the hospitals (Scott) was not achieved because of duplication of patientsôdata in the TB register. The total sample size was maintained by increasing the sample size from another hospital thus, but this could have reduced the representivity of the results in favour of the hospital that was over-represented.

The response rate was high as this was a record review, so there was no participation refusal. In this study we included participants from the age of 15 years as this is the age an adult is defined in Lesotho and not 18 years as in most other countries in Africa. Consequently, for comparison purposes, this was a limitation. However, only 2 of the 247 (0.8%) participants were aged between 15 and 18 years so this contributed little to selection bias.

5.6.2 Information bias

Measures were observed in this study to minimize information bias. All the participants were one the same TB and HIV therapy according to the national guidelines.

This was a record review and, as a result, results were dependent on the quality of the data recorded by clinicians and data collectors who are not researchers and may not have had rigor of categorization, collection and recording that one would have preferably desired.

In the period under review, Lesotho encountered a national problem of running out for

re-agents used for obtaining CD4 count for people living with HIV. This inadequacy, as a result, affected even the study participants. The health care workers reported that the problem occurred due to constraints with the national budget. Some participants, therefore, reported CD4 count results, which were not obtained from hospitals where they were initiated on ART. This factor also was a limitation, in that, different machines were used and so there was no standardization when measuring CD4 count.

There was also a plan to carry out a pilot study before the main data collection but this was not possible for the researcher to do due to time constraint. This, however, affected the result adversely because the researcher only learned during data analysis that range of age categories was wrong. Thus, if a proper pilot study had been conducted and its data had been processed, the researcher could have picked up that something was wrong with age categories. It was however, a lesson for a researcher and such a mistake will not be repeated. In addition, weight results were also not found in the registers and it was clarified that they were recorded in the TB patient cards, which they take home with them. Had there been a pilot study, the researcher could have noticed this defect and such a problem could have been rectified.

5.6.3 Precision problems

The required sample size for the study was ascertained by a biostatistician prior to commencing the study. Because of resources constraints this was limited. Due to a sub-optimal sample size, the confidence intervals were wide thereby affecting the precision of the study. Thus, the dependency on this study is likely to be questioned due to this limitation which was caused by insufficient resources.

5.6.4 Confounding problems

The study had confounders, such as viral load and weight, which were not measured because they were not available in the TB register. However, health care workers reported that viral load tests are not undertaken for everyone in Lesotho unless there is an imperative need because they are expensive; the consequence was that all participants did not have viral load results. This adversely affected the results in that the association between the patientsôviral load, weight and when ART was initiated was not determined.

6 CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

This chapter presents conclusions based on the findings and discussions made on each issue explored in the study.

6.1 Conclusion

This study contributed to the assessment as to whether health services in Lesotho are initiating people living with HIV associated TB on ART at the appropriate times after commencing TB treatment and whether the TB treatment outcomes are affected by ART timing. The study found that whether patients were initiated on ART early or late, they were more likely to have a successful TB treatment outcome than if not initiated on ART. There was not difference whether initiated early or late. This is contrary to other studies, which suggested early initiation of ART after TB treatment was associated with better survival and favourable outcomes.[9] There was no statistical difference in timing of ART initiation and successful TB treatment outcomes even after adjustment for potential confounders including age, CD4 count and gender.

Not all confounders were measured. This included obtaining the patients viral load and weight, which were not routinely recorded in the TB register and thus could not be collected. As a result a measure of clinical improvement could not be ascertained. The improvement in the health status of participants was not an outcome measure used in this study.

The study sample was obtained from three hospitals in Lesotho. This however was a limitation in itself because if more hospitals were sampled, they could have been more representivity of all hospitals in Lesotho. Participants included both sexes from the age of 15, they had different types of TB; either new categories or other categories. The site

of TB was different also, it was either PTB or EPTB and they had different CD4 count results. Of all the above mentioned factors, only those concerning hospital, CD4 count and stage ART initiated were statistically significant in univariate analysis were associated with successful TB treatment outcomes. In multivariate analysis, only hospital and stage ART initiated remained statistically significant.

6.2 Recommendations

6.2.1 The Lesotho Ministry of Health should enforce early initiation of ART in people with HIV associated TB in order to have even better results. This can be done by hiring monitoring and evaluation officers for all hospitals and they will be responsible for regular reporting so that when there are problems, they can be addressed at early stage. This can also be achieved by the high level involvement of organizations that deal with TB and HIV programs such as ICAP Lesotho.

6.2.2 There should be improvement in record keeping especially in the TB registers so that data Lesotho can have access to reliable data.

6.2.3 For more effectiveness, on-going education through media and community campaigns will be imperative as more successful outcomes can be expected.

7 CHAPTER SEVEN: REFERENCES

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8 CHAPTER EIGHT: APPENDIX

8.1 Appendix 1: Data collation sheet

District ☐ **Hospital** ☐ **Date** ☐

Name of person completing the form:

Checked by: _____

Patient study number: _____

Date TB treatment started: _____

A. Hospital service delivery

1. Is this a government or CHAL hospital? Gov ☐ CHAL ☐

2. Are TB and HIV offered under one roof? Yes ☐ No ☐

B. General information about the patient

3. Sex: Male ☐ Female ☐

4. Age: 15-19 ☐ 20-29 ☐ 30-59 ☐ 60+ ☐

C. TB and HIV patient Information

5. Type of patient

New ☐

Relapse ☐

Treatment after default ☐

Treatment after failure ☐

Other ☐

6. Treatment Category

Cat I ☐ Cat II ☐

7. ART Initiation

Date ART initiated	Tick (√)
a) < 2 weeks after starting TB treatment	
b) 2-4 weeks after starting TB treatment	
c) > 4 weeks but less than 2 months after starting TB treatment	
d) 2 months or more after starting TB treatment	
e) Not initiated on ART at all	

8. Clinical Features

a) CD4 Count	Specify
CD4 at the start of TB treatment	
b) Weight in Kilograms	**Specify**
Weight at the start of TB treatment	

9. TB Treatment Outcomes

TB treatment outcome if started early on ART	**Tick (√)**	**TB treatment outcome if started late on ART**	**Tick (√)**
Cured		Cured	
Completed		Completed	
Died		Died	
Defaulted		Defaulted	
Failure		Failure	
Transferred out		Transferred out	

8.2 Appendix 2: Request for permission letter from Ntsekhe Hospital

P.O. Box 13136
Maseru 100
Lesotho
25th May 2012

The Chairperson
Ntsekhe Hospital Management
P.O. Box 29
Mohaleôs Hoek 800

Dear Sir/Madam

RE: PERMISSION TO UNDERTAKE A STUDY AT THE HOSPITAL

I am a student at the University of KwaZulu-Natal studying Masters of Public Health and I hereby request your permission to undertake a study on ñEffectiveness of early initiation of ART in adults with HIV associated TB in Lesotho in 2012ò at your hospital. Ntsekhe hospital is among the three hospitals in Lesotho that have been selected to represent the country.

The purpose of the study is to complete the above mentioned degree as it contributes 50% of the evaluation. The areas of focus will be TB clinic and ART corner where the patientsôfiles will be reviewed as a way of data collection. The TB registers will however be used as the primary source of data as I will be looking at HIV positive adults started on TB treatment. Data collection will commence in April 2013 as the study will be looking at the cohort of January to March 2012 whose treatment outcomes will be obtainable by April 2013. Final results will definitely be shared with the hospital.

I hope my plea will be approved in your favourable office and I humbly ask that you write a letter of acceptance that I can produce at the beginning of the study during data collection.

Yours sincerely,

Maletsatsi Lenela (mlenela@gmail.com, Cell: +26658003751)

8.3 Appendix 3: Request for permission letter from Berea Hospital

P.O. Box 13136
Maseru 100
Lesotho
25th May 2012

The Chairperson
Berea Hospital Management
P.O. Box 4
Berea 200
Dear Sir/Madam

RE: PERMISSION TO UNDERTAKE A STUDY AT THE HOSPITAL

I am a student at the University of KwaZulu-Natal studying Masters of Public Health and I hereby request your permission to undertake a study on ñEffectiveness of early initiation of ART in adults with HIV associated TB in Lesotho in 2012ò at your hospital. Berea hospital is among the three hospitals in Lesotho that have been selected to represent the country.

The purpose of the study is to complete the above mentioned degree as it contributes 50% of the evaluation. The areas of focus will be TB clinic and ART corner where the patientsô files will be reviewed as a way of data collection. The TB registers will however be used as the primary source of data as I will be looking at HIV positive adults started on TB treatment. Data collection will commence in April 2013 as the study will be looking at the cohort of January to March 2012 whose treatment outcomes will be obtainable by April 2013. Final results will definitely be shared with the hospital.

I hope my plea will be approved in your favourable office and I humbly ask that you write a letter of acceptance that I can produce at the beginning of the study during data collection.

Yours sincerely,

Maletsatsi Lenela (mlenela@gmail.com, Cell: +26658003751)

8.4 Appendix 4: Request for permission letter from Scott Hospital

P.O. Box 13136
Maseru 100
Lesotho
25th May 2012

The Chairperson
Scott Hospital Management
Private Bag 190
Morija, Lesotho
Dear Sir/Madam

RE: PERMISSION TO UNDERTAKE A STUDY AT THE HOSPITAL

I am a student at the University of KwaZulu-Natal studying Masters of Public Health and I hereby request your permission to undertake a study on ñEffectiveness of early initiation of ART in adults with HIV associated TB in Lesotho in 2012ò at your hospital. Scott hospital is among the three hospitals in Lesotho that have been selected to represent the country. The purpose of the study is to complete the above mentioned degree as it contributes 50% of the evaluation. The areas of focus will be TB clinic and ART corner where the patientsô files will be reviewed as a way of data collection. The TB registers will however be used as the primary source of data as I will be looking at HIV positive adults started on TB treatment. Data collection will commence in April 2013 as the study will be looking at the cohort of January to March 2012 whose treatment outcomes will be obtainable by April 2013. Final results will definitely be shared with the hospital. I hope my plea will be approved in your favourable office and I humbly ask that you write a letter of acceptance that I can produce at the beginning of the study during data collection.

Yours sincerely,

Maletsatsi Lenela (mlenela@gmail.com, Cell: +26658003751)

8.5 Appendix 5: BREC approval

8.6 Appendix 6: Registration of the project with the school of nursing and public health research and higher degrees committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

20 August 2014

To whom it may concern,

Re: MALETSATSI LENELA – STUDENT NO. 211538728

This is to confirm that Ms M Lenela is currently registered as a student at the University of Kwazulu-Natal. She is registered for the Research Project in the Masters of Public Health (MPh) Degree.

Yours sincerely,

Michelle Ramlal
Admin Officer
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20 August 2014

Ms. M Lenela
Department of Public Health Medicine
School of Nursing and Public Health
Howard College Campus
University of KwaZulu-Natal

PROTOCOL: Effectiveness of early initiation of antiretroviral therapy in adults with HIV associated Tuberculosis in Lesotho in 2012: BE300/12

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	18 June 2014
Expiration of Ethical Approval:	17 June 2015

I wish to advise you that your application for Recertification received on 15 August 2014 for the above protocol has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

This approval will be **ratified** by a full Committee at its next meeting taking place on **09 September 2014.**

Yours sincerely

Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics