A retrospective study of the clinical management and treatment outcomes of patients established on antiretroviral therapy who are newly diagnosed with tuberculosis in the public sector, KwaZulu-Natal

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Thesis presented in partial fulfilment of the requirements for the degree of
Master of Science in the Faculty of Nursing at Stellenbosch University

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March 2013

Declaration

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March 2013

Abstract

Taking into consideration the long duration of standard treatment for *Mycobacterium tuberculosis* (TB), the high prevalence of HIV co-infection and the growing prevalence of drug-resistant TB, there is an urgent need for improved treatment approaches for TB and HIV. However, there is inadequate information regarding the burden being placed on the Department of Health (DOH) systems by the current treatment of patients established on Antiretroviral Therapy (ART) who are newly diagnosed with TB, and by their clinical management.

The aim of the study was to determine what proportion of patients established on ART were newly diagnosed with TB, and what their clinical and treatment outcomes were in different public sector settings in the eThekwini Region, KwaZulu-Natal (KZN). Approval for the study was obtained from the Human Research Committee of Stellenbosch University and from the Biomedical Research Committee, KZN.

The study used a retrospective, quantitative, cohort technique at both TB and ART clinics at three sites in the eThekwini region, KZN. These sites were DOH clinics and were selected as they all had a TB clinic and a DOH-registered ART clinic. The study focused on a period of one year prior to a patient established on ART developed TB. The study population comprised all TB patients who attended the selected DOH clinics.

A data collection tool was developed and pilot-tested. A small sample of patient files (n=15, representing 2% of the study population) was randomly selected; five from each site. The files and data were excluded from the main study.

A total of 1824 files (579 from the TB clinics and 1245 from the ART clinics) were reviewed. The data were captured into an electronic database (EpiData Version 3.3) and analyzed using STATA (Version 11.0) with the assistance of a statistician.

The findings show that of the study sample from the TB clinics (N=579), 78% (454/579) were newly diagnosed with TB. Of the new TB cases, 90% (409/454) had pulmonary TB and 71% (413/579) were HIV-positive. Nearly 50% (68/137) of the patients had commenced ART prior to TB diagnosis and treatment, and 14% (19/137) had commenced ART after TB. Of those who commenced ART prior to TB diagnosis and treatment, 29% (20/68) had commenced ART more than three months prior to acquiring TB.

The findings from the ART clinics show that of the files (N=1245) reviewed, 40% (501/1245) had TB, and of these 8% (42/501) developed TB after three months or more of ART.

Missing data in the patient medical files was a major challenge. The lack of recorded data about ART in the TB clinics and about TB in the ART clinics suggests suboptimal clinical management and poor integration of HIV and TB services. It was therefore not possible to derive a combined HIV-TB outcome measure.

Recommendations to promote and implement the integration of TB and HIV services included policy changes and implementation, management and practice suggestions, education and training to integrate TB/HIV services and increase research to identify gaps in clinical management and to improve integration of services.

Opsomming

Met inagneming van die lang duur van die standaard behandeling vir *Mycobacterium* tuberkulose (TB), hoë voorkoms van MIV-infeksie en die groeiende voorkoms van dwelmweerstandige TB, is daar ’n dringende behoefte aan verbeterde behandelingbenaderings vir TB en MIV. Daar is egter ’n gebrek aan inligting oor die las geplaas op die Departement van Gesondheid (DvG) se stelsels deur die huidige behandeling van pasiënte op antiretrovirale terapie (ART) wat gediagnoseer is met TB en deur hul kliniese bestuur.

Die doel van die studie was om vas te stel watter persentasie van pasiënte wat op ART gevestig is, wel met TB gediagnoseer is, en wat hul kliniese en behandeling-uitkomste was in verskillende openbare-sektorinstellings in die eThekwini-streek, KwaZulu-Natal (KZN). Goedkeuring vir die studie is verkry van die Menslike Navorsingskomitee van die Universiteit van Stellenbosch en van die Biomediese Navorsingskomitee, KZN.

Die studie het gebruik gemaak van ’n retrospektiewe, kwantitatiewe ‘cohort’-tegniek by beide TB en ARB-klinieke op drie plekke in die eThekwini-streek, KZN. Hierdie terreine was DvG-klinieke en is gekies omdat hulle almal oor ’n TB-kliniek en 'n DvG-geregistreerde ART-kliniek beskik. Die studie het gefokus op ’n tydperk van een jaar voor ’n pasiënt wat op ART is, TB ontwikkel het. Die studiepopulasie bestaan uit alle TB-pasiënte wat die geselekteerde DvG-klinieke bygewoon het.

’n Data-insamelinginstrument is ontwikkel en getoets. ’n Klein voorbeeld van die pasiëntlêers (n = 15, 2% van die studie bevolking verteenwoordig) is ewekansig gekies: vyf uit elke plek, en die data is vervat in ’n elektroniese databasis (EpiData Version 3,3).

’n Totaal van 1824 lêers (579 in die TB-klinieke en 1245 lêers in die ART-klinieke) is ondersoek. Die data is ontleed deur gebruik te maak van Stata (weergawe 11,0) met die hulp van ’n statistikus.

Die bevindinge toon dat van die studiemonster in die TB-klinieke (N = 579), 78% (454/579) met TB gediagnoseer is. Van die nuwe TB-gevalle, het 90% (409/454) pulmonêre TB gehad en was 71% (413/579) MIV-positief. Byna 50% (68/137) van die pasiënte het ART begin vóór hulle TB-diagnose en -behandeling, en 14% (19/137) ART ná TB. Van dié wat ART voor TB-diagnose en -behandeling begin het, het 29% (20/68) meer as drie maande voor die opdoen van TB met ART begin. Die bevindinge van die ART-klinieke toon dat van die lêers (N = 1245) wat bestudeer is, 40% (501/1245) TB het, en hiervan het 8% (42/501) TB na drie of meer maande van ART ontwikkel.

Ontbrekende data in die pasiënt se mediese lêers was ’n groot uitdaging. Die gebrek aan aangetekende data oor ART in die TB-klinieke en oor TB in die ART-klinieke dui op suboptimale kliniese bestuur en swak integrasie van MIV- en TB-dienste. Dit was dus nie moontlik om ’n gesamentlike MIV-TB uitkomsmaatreël af te lei nie.

Aanbevelings om die integrasie van TB- en MIV-dienste te bevorder en te implementer, het beleidveranderinge en -implementering ingesluit, asook bestuur- en praktykvoorstelle, onderwys en opleiding om TB-/MIV-dienste by DvG-vlak te integreer en meer navorsing om gapings in die kliniese bestuur te identifiseer en die integrasie van dienste te verbeter.

Acknowledgements

I would like to acknowledge and express my sincere thanks to:

my husband, Manogren, and son, Vyshun, for their patience and support;

my late parents for their spiritual support;

my research supervisor, Dr Frederick Marais, for his unfailing support and encouragement throughout this process;

my research co-supervisor, Dr Alex Pym;

Ms Tarylee Reddy, for statistical analysis and guidance during this project; and

the staff of the DOH clinics, for their assistance and cooperation during data collection;

Ms. Yagen Naidoo, Khareen Pech and Elizabeth le Sueur for their language and technical editing and proofreading.

Dedication

I dedicate this thesis to my late mother, who instilled in me the need for progress and to never give up.

List of tables and diagrams

Abbreviations and acronyms

3TC	Lamuvidine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
ANOVA	Analysis of variance
AZT	Zidovudine
BREC	Biomedical Research Ethics Committee
CD4	CD4 cell or T4 ‘helper’ lymphocyte
Cr	Creatinine
CPT	Cotrimoxazole preventive therapy
ddI	Didanosine
d4T	Stavudine
DOH	Department of Health
E	Ethambutol
EFV	Efavirenz
EPTB	Extrapulmonary tuberculosis
FTC	Emtracitabine
HCT	HIV Counselling and Testing
HIV	Human Immune Virus
INH	Isoniazid
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
KMPC	Kwa Mashu Poly Clinic
LPV/r	Lopinavir/Ritonavir
MDG	Millennium Development Goals
MDR	Multidrug-Resistant
MRC	Medical Research Council
NIMART	Nurse Initiated and Managed ART

PCHC	Phoenix Community Health Centre
PI	Protease Inhibitor
PTB	Pulmonary tuberculosis
QA	Quality Assurance
SAPIT	Starting antiretroviral therapy at three points In tuberculosis therapy
SANAC	South African National AIDS Council
SAMRC	South African Medical Research Council.
TB	Tuberculosis
TCHC	Tongaat Community Health Centre
UNAIDS	Joint United Nations Program on HIV/AIDS
XDR-TB	Extensively drugresistant TB
NVP	Nevirapine
TDF	Tenofovir
VL	Viral load (HIV)
WHO	World Health Organisation

Definitions used in the study

Clinical management: the process of leading and directing the care and treatment of a patient or groups of patients (Home-Health Solutions, no date).

Clinical characteristics: the distinguishing or representative observation of a particular condition pertaining to treatment, practice, observation or diagnosis (English Collins Dictionary Online, n.d.).

Clinical outcome: the results of any health care intervention, including the entire range of activities performed. Clinical outcomes are the end result of any therapeutic interventions applied to patients (Patient-Centred Acute Case Training, n.d.).

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CHAPTER 1

SCIENTIFIC FOUNDATION OF THE STUDY

1.1 Introduction

Chapter 1 provides a brief overview of the rationale for, as well as the aims and objectives of, the study. The chapter also introduces the research methodology and the ethical considerations applied in the undertaking of the study. Finally, the chapter offers an outline of the respective chapters in the thesis.

1.2 Rationale and background literature

Mycobacterium tuberculosis (TB) is an opportunistic infection of Acquired Immune Deficiency Syndrome (AIDS) in Human Immune Virus (HIV)-infected persons (WHO, 2009: 1). According to El-Sadr and Tsiouris (2008:525), “the marriage of these two deadly infections creates huge challenges for patients, communities, and health systems”. Individually, TB and HIV are two of the world's greatest ongoing public health threats. In combination, the two diseases can be even more devastating. HIV significantly increases an individual's chances of reactivation of latent TB infection and progression to active TB disease (El-Sadr & Tsiouris, 2008:29).

TB is the major cause of death in individuals infected with HIV, and the combination of both illnesses creates treatment challenges for providers. HIV infection progressively increases immunodeficiency and susceptibility to infections, especially TB. As the HIV infection progresses and CD4 declines, the immune system weakens thus contributing to the progress of TB infection to TB disease. In HIV-seronegative patients with TB infection only about 10% develop active TB during their lifetime, and in HIV-seropositive patients about 50% will develop active TB disease (DOH, 2009:9).

Globally, TB is a significant cause of illness and death, accounting for an estimated 9.27 million incident cases in 2007. Of these cases, the African region accounts for an estimated 31% (WHO, 2009:411). Among the 9.27 million incident cases of TB globally, an

estimated 15% were HIV-seropositive and 79% of these were from the African region (WHO, 2009:1).

Southern Africa continues to bear the brunt of the global burden of HIV. In 2007, South Africa accounted for 31% of the estimated 79% of HIV seropositive TB cases in the African region(WHO, 2009:1).The current HIV prevalence amongst antenatal women in South Africa shows that KwaZulu-Natal (KZN) has the highest seroprevalence of HIV (DoH, 2009:9). KZN is the province with the highest HIV burden in South Africa. KZN also has a rapidly progressing TB epidemic (DOH, 2009:9). The 2006 statistics in the National Tuberculosis Management Guidelines (DOH, 2009:9) show that in KZN the TB (all cases) incident rate was 1076/100 000 population and TB prevalence was 907/100 000 population (DOH, 2009:9).

Since identifying the TB/HIV co-infection epidemic globally, providers have been making concentrated efforts to promote the integration of HIV care and treatment into the TB programme. In order to deliver integrated HIV and TB treatment, it is important to determine the burden placed on the Department of Health (DOH) by people requiring both Antiretroviral Therapy (ART) and TB treatment, as well as identifying strategies toward improving the clinical management and treatment outcomes of HIV/TB co-infected patients. A recent survey carried out by the Medical Research Council of South Africa (SAMRC) at several DOH facilities in the eThekwini and uThungulu districts of KZN, demonstrated the high percentage of patients co-infected with TB/HIV. The survey found that 74% (699/945) of all TB patients either tested HIV-seropositive or were known to be seropositive. Of these, 14% were already on ART as per the CD4 requirement of the DOH (Dilraj & Rustomjee, 2009). A study undertaken at a hospital in Johannesburg South Africa showed that of a total of 467 TB patients counselled, laboratory data were retrievable for 373. Of this data, 284 (76%) of HIV results were retrieved. 270 (95%) of the 284 TB patients had concurrent HIV infection (John, Menezes, Chita, Sanne & Grobusch, 2007:795)

Despite the widespread availability of TB treatment, TB/HIV co-infected patients in Africa had an annual mortality rate of 25% to 40% before the introduction of ART (Mukadi, Maher

& Harries, 2001:143). This mortality was attributable to both complications from overwhelming TB disease and immunosuppression from advanced HIV disease (Murray, Sonnenberg, Shearer & Godfrey-Faussett, 1999:733) . Thus, efforts to reduce mortality in TB/HIV-co infected patients must focus on both improving TB treatment completion rates and on providing HIV care and ART (Maher, Harries & Getahun, 2005: 734). .

HIV and TB co-infection is associated with high mortality rates and one of the main challenges is the integration of combined treatment of HIV and TB. Combining HIV and TB treatment is critical for reducing the mortality rate and this has been recently confirmed by the SAPIT trial (Abdool Karim, Baxter, et al., 2010:808) in which HIV- positive patients with TB who initiated ART during TB therapy had a significant reduction in mortality when compared with patients who deferred ART until after TB treatment was complete(Abdool Karim, Abdool Karim et al. 2010:808). As a result South African DOH guidelines have elevated the CD4 count below which TB patients should initiate concomitant ART, from 200 to 350 cells/mm^3 (DOH, 2010:8).

This change in guidelines is also due to mounting evidence that problems of immune-reconstitution inflammatory syndrome (IRIS), toxicity, drug/drug interaction, and poor adherence to treatment have not prevented first line TB-HIV treatment in the form of Efavirenz-based ART and short course TB therapy (isoniazid, rifampicin, pyrazinamide and ethambutol) from obtaining good clinical outcomes (Novak, Richardson et al. 2012: np). However, there are very few data on the outcomes of combining second line ART with TB treatment. Second-line ART combines a Protease inhibitor (PI) with two nucleoside analogues and patients are switched following signs of virological, immunological or clinical failure of first-line therapy. Combining PIs with rifampicin is more problematic as the dose of the PI has to be increased, or super boosted with additional ritonavir. These increased PI doses are associated with hepatotoxicity and severe gastrointestinal intolerability (DOH, 2009:75).

Based on the literature review undertaken for the study, there is a paucity of research conducted in South Africa on the clinical outcomes and management of patients on TB therapy and second line ART. The number of patients on ART who develop TB remains

unclear. Amongst these it is unknown how many are failing ART, and of those failing therapy, there are little data on how these patients are being investigated and managed. This situation exposes the need to investigate the proportion of all patients with TB who were established on ART at the time of diagnosis, and their clinical and treatment outcomes.

Taking into consideration the long (six-month) duration of standard TB treatment, the high prevalence of HIV co-infection and the growing prevalence of drug resistant TB, there is an urgent need for improved, more effective, and integrated approaches for TB and HIV treatment. According to the Tuberculosis Strategic Plan for South Africa (DOH, 2009:20) the challenge of implementing integrated TB/HIV services lies in the inadequate detail and written formal guidelines on how this collaboration is to be achieved. Limited integration of services at health facilities is due to inadequate technical support, guidelines and registers for monitoring and evaluation of integrated TB and HIV services (DOH, 2009:20).

1.3 Research problem

The duration of standard TB treatment, coupled with the high prevalence of HIV co-infection and the growing prevalence of drug resistant TB in South Africa (DOH, 2009:80) reveal the urgency for improved, more effective, and integrated approaches for TB and HIV treatment. Based on the findings from the literature review, one aspect of TB and HIV co-treatment that has not been extensively studied in South Africa is the combination of second line ART and TB treatment at the programmatic level. Importantly, there is inadequate information as to the number of patients who require second-line ART and TB treatment. For example how many patients are there who are established on ART and are subsequently diagnosed with TB? Preliminary data obtained from a study conducted by the SAMRC suggest this is a significant proportion of all TB cases (Dilraj & Rustomjee, 2009). Furthermore, there is inadequate information concerning the clinical management and treatment outcomes of these patients and to what extent second-line ART is being used.

1.4 Significance of the study

The study was undertaken in the context that the TB epidemic is adding to the burden of the existing HIV burden placed on the DOH services (DOH, 2009:9). The study was done to evaluate the percentage of patients who develop TB after three months or more of ART, and to determine the clinical and treatment outcomes of these patients in order to understand the need for better management of patients combining second-line ART with rifampicin. The secondary goal was to show the need for integration and closer follow-up of clients on ART for early detection and management of TB and the use of second line treatment.

1.5 Research question

The study focused on public health care facilities in the eThekwini Region in KZN. The study sought to answer the following questions:

(a) What proportion of patients with TB were on ART at the time of their TB diagnosis?

(b) How were these patients, established on ART at time of TB diagnosis, managed at both the TB and ART clinics?

(c) What were the clinical and treatment outcomes of those patients established on ART and newly diagnosed with TB?

For the purpose of the study 'newly diagnosed TB' was defined as a patient being treated for TB for the first time, independent of the diagnostic test, and 'established on ART' as having taken ART for more than three months consecutively.

1.6 Research aim

The aim of the study was to determine:

(a) the proportion of TB patients established on ART at the time of their TB diagnosis; and

(b) the clinical and treatment outcomes of these TB patients in different public health care facilities in the eThekwini region of KZN.

1.7 Research objectives

The objectives of the study were as follows:

(a) To determine the proportion of all patients with TB who were established on ART at the time of TB diagnosis;

(b) To establish the clinical characteristics of patients established on ART who were newly diagnosed with TB;

(c) To evaluate the clinical management of patients established on ART who were newly diagnosed with TB; and

(d) To evaluate the TB and HIV treatment outcomes of patients established on ART who developed TB.

1.8 Research methodology

The research methodology applied in the study will be discussed briefly in the following subsections: research approach and design, population and sampling, data collection tool, pilot test, validity and reliability, data collection, data analysis, and ethical considerations.

1.8.1 Research approach and design

This was a retrospective cohort study undertaken at both TB and ART clinics at three DOH health care facility sites in the EThekwini region in KZN. The study focused on a period up to one year prior to commencement of data collection. The rationale for collecting data during this timeframe was that it allowed for clinical TB and HIV follow-up and outcome data to be collected through an audit of the medical files of patients included in the study sample.

1.8.2 Population and sampling

It was envisaged that due to poor integration of TB and HIV services it would be necessary to look at both clinical systems. There were two study populations for the purpose of the study corresponding to TB clinics and ART clinics. In TB clinics it was all patients initiating TB therapy regardless of diagnosis. In ART clinics it was all TB patients who had received

at least three months of ART prior to their diagnosis of TB. Only clinics in the Northern region of eThekwini were selected corresponding to the region where the SAMRC has well-established collaborative links. There were a total of 115 DOH clinics in the eThekwini region that had a TB component, but only 15 (13%) of these provided on-site TB treatment and ART initiation. Of these 15 clinics, 3 were located in the Northern region of eThekwini. Accordingly, the study included all the clinics (n=3) for data collection.

1.8.3 Sample size

A statistician from the Biostatistics Department, SAMRC KZN, was consulted to determine the appropriate sample size of patient medical files to be selected from the TB and ART clinics for audit (there was no direct patient contact in the study).

1.8.3.1 Proportion of TB patients established on ART at the time of TB diagnosis at the TB clinic

It was estimated that 15% of all patients with TB in the eThekwini Region are on ART. This information was gained by personal communication from a researcher at the SAMRC (Dilraj & Rustomjee, 2009). At the time of communication these data were not published. With a 95% confidence level and 5% margin of error, a sample size of 589 was required, at a power of 90% to determine the proportion of TB patients on ART at the time of TB diagnosis Accordingly, a total minimum of 600 medical files were selected at the TB clinic for audit.

1.8.3.2 Proportion of TB patients established on ART at the time of TB diagnosis at the ARV clinic

A combined HIV and TB favourable clinical and treatment outcome at six months was adopted as a measure of treatment outcome. It was estimated that 75% of patients would have had a favourable TB outcome (cure or completion) and of these 66% would have had a favourable HIV outcome (undetectable viral load). Therefore, it was estimated that with a combined favourable HIV and TB outcome of 50% and a 7% error, a sample size of 532 medical files was required for a 95% confidence at a power of 90% to determine treatment

outcome in the cohort at the ARV clinic. A total of 1121 patient medical files from the TB and ART clinics would thus be sufficient for this purpose.

1.8.4 Inclusion criteria

1.8.4.1 TB clinic

The study sampled the medical files of all adult patients diagnosed with TB by symptoms, positive sputum smears and cultures and/or chest x-ray, entered onto the TB register, and treated at any of the selected sites 12 months prior to initiation of the study and those aged 15 years and older.

1.8.4.2 ART clinic

The study sampled the medical files of all adult patients: diagnosed with HIV, entered onto the ART register, and treated for TB at any of the selected sites for at least three months prior to initiation of TB treatment and those aged 15 years and older.

1.8.5 Exclusion criteria

1.8.5.1 TB clinic

The study excluded the medical files of patients: aged less than 15 years; who had more than one month's TB treatment at a different institution and transferred to the study site to continue TB treatment and those treated for drug-resistant TB.

1.8.5.2 ART clinic

The study excluded the medical files of patients aged less than 15 years and those who had less than three months of ART at the time of commencing TB treatment.

1.8.6 Data collection tool

Data were extracted using a structured data collection tool (Appendix 1). The tool was developed by the researcher based on the findings from the literature, recommendations from experts in the field (Dr Alex Pym, SAMRC KZN, and Dr Frederick Marais,

Stellenbosch University). A statistician from SAMRC KZN advised on the study. The data captured included demographics, laboratory results (such as sputum smear and culture, CD4 and viral load counts) and clinical variables (such as TB symptoms, TB and ART treatment, and treatment outcomes at two and six months).

1.8.7 Pilot test

Prior to the empirical phase, the data collection tool was tested in order to validate its applicability. A small sample of patient medical files (n=15), representing 2% of the study population was randomly selected; five from each study site and their data captured. These clinics were evaluated by the researcher for data available for capture. Subsequent changes to the tool and variables were made to ensure appropriate and quality data capturing. The manually captured data were entered into an electronic database (EpiData, version 3.3) by the researcher, and used by the statistician (Dr Kabera, MRC KZN) to test the data analysis method. The validation files and data were excluded from the empirical study.

1.8.8 Validity and reliability

The data collection tool was evaluated for face validity and applicability by means of the pilot test. Content validity was supported by findings from the literature and evaluative input from experts in the field (Dr Pym, SAMRC and Dr Marais, Stellenbosch University) and a statistician of the SAMRC. Table 1 provides an overview of how content validity was determined. Face validity was supported by entering the pilot data onto the electronic database and testing to see if data collected met the target variable.

Table 1: Content validity of the data collection tool

Study objectives	Questions	Literature
To determine the proportion of all patients with TB who were established on ART at the time of TB diagnosis.	**Q3-8:** HIV/CD4 status (Appendix A)	HIV and TB co-infection is associated with high mortality rates. One of the main challenges is the integration of combined treatment of HIV and TB in the public sector (Abdool Karim,, et al., 2010:808). TB epidemic is adding to the burden of the existing HIV burden placed on the DOH services (DOH, 2009:9).
To establish the clinical characteristics of patients established on ART who were newly diagnosed with TB.	Q-8: CD4 and viral loads data of TB Patients. Q-14: Current TB (Appendix A)	Literature review revealed lack of published evidence on the clinical characteristics of patients established on ART who were newly diagnosed with TB. In 2009, the government raised the CD4 treatment initiation threshold from 200 to 350 cells/mm^3, to be in line with the latest WHO guidelines (DOH 2010:4).Initiating treatment below 350 cells/mm^3 was implemented on the basis that it would improve the mortality rate amongst those that were HIV infected. This change was implemented and substantiated by the SAPIT trial (Abdool Karim et al. 2010:808)

objectives	Questions	Literature
To evaluate the clinical management of patients established on ART who were newly diagnosed with TB.	Q-8: CD4 and Viral loads data.Q-9:.ARV therapy Q-10: TB diagnosis Q-11: Sputum collection Q-15: TB therapy – (Appendix A)	Effective TB management requires early detection and prompt commencement of treatment (DOH,2009:34).The aims of TB treatment are to cure the client of TB, decrease transmission of TB to others, prevent drug resistance or relapse by ensuring adherence and follow up, and prevent deaths from TB or its complications(DOH,2009:34). Literature review revealed lack of published evidence on the clinical management of patients established on ART who were newly diagnosed with TB.
To evaluate the TB and HIV treatment outcomes of patients established on ART who developed TB.	Q-17: Treatment outcome (Appendix A)	Literature review revealed lack of published evidence on TB and HIV treatment outcomes of patients established on ART who developed TB.

Reliability was enhanced by means of the pilot test to ensure capture of all the required data to meet the stated objectives. Reliability was further enhanced by the researcher who undertook all the data collection and one trained research fieldworker from the SAMRC KZN who assisted with file location and return of files. Collection of the medical files sampled for the study was systematic to ensure complete data capture. In addition, based on data yielded from the pilot test, the statistician evaluated and confirmed the feasibility of the data collection tool and the method of data analysis.

1.8.9 Data collection

Data collection was undertaken by the researcher and the research fieldworker at both the TB and ART clinics. Using the data collection tool, data were extracted manually from the sampled files. Data extraction was done at the site. Prior arrangement was made with the site staff to ensure no interference in the sites daily routine and space was allocated to the researcher. Extraction was done during site working hours from 08h30 to 16h30. Data collection differed as it was dependent on the availability of the file for data collection. Some files where archived and lost and the researcher and fieldworker had to search for and locate these files.

1.8.10 Data management and analysis

Quality control and assurance of the data were undertaken by the researcher on a daily basis. The completed data collection records were compared against corresponding registers and medical files, and missing data and errors corrected immediately.

The collected data were captured into an electronic database (EpiData Version 3.3) by a trained data encoder from the SAMRC KZN. Double entry was completed to verify and validate the data captured. The database, reflecting the variables and categories of the data collection tool, was presented to and approved by the statistician of the SAMRC KZN.

The data were analyzed using STATA (version 11.0) with the assistance of a statistician, at the SAMRC KZN. Data were presented in tables for descriptive statistics. Statistics reported were proportions and means and standard deviations. The analysis of categorical variables is presented using cross tabulations with frequencies and percentages reported. Means and standard deviations were only used to summarize the age distribution of participants within each site.

1.8.10.1 Primary outcome

The following was the main endpoint or outcome of the study.

1.8.10.1.1 Proportion of patients established on ART at the time of TB diagnosis

The proportion of patients established on ART who were newly diagnosed with TB, calculated as a proportion of all TB patients on ART for greater than three months at initiation of TB treatment.

1.8.10.1.2 Treatment outcome

The proportion of patients with combined favourable TB and HIV outcomes at six months after initiation or on completion of TB treatment.

1.8.10.2 Secondary outcomes

These outcomes were additional data that were collected for analysis to assess other effects and outcomes.

1.8.10.2.1 Tuberculosis

The proportion of TB patients established on at least three months of ART at time of TB diagnosis:

- who were smear-positive;
- tested for HIV;
- tested for HIV and CD4;
- with CD4 less than 200/350 on ART, depending on when ART commenced, as per the new DOH guidelines;
- with favourable TB outcomes at two months (e.g. smear conversion);
- on ART with viral loads and CD4 after diagnosis of TB;
- on ART with a CD4 above 200 at the time of TB diagnosis;
- with documented ART and TB treatment adherence problems.

1.8.10.2.2 HIV

The proportion of patients established on at least three months of ART at time of TB diagnosis:

• on TB treatment who switch from first-line ART therapy to second-line ART therapy;

• whose CD4 was below 200 at the time of TB diagnosis;

• who had CD4 and viral loads within three months of TB diagnosis;

• with viral load undetected at the time of TB diagnosis;

• with an increase in CD4 and decrease in viral load from baseline;

• on ART with favourable TB outcomes at two and six months;

• with favourable HIV outcomes as determined by undetectable viral loads at the end of TB treatment;

• annual rated newly diagnosed TB in patients three months after initiating ART therapy;

• Mortality rate in subjects initiated on TB treatment who have been on ART therapy for more than three months.

1.9 Ethical considerations

Ethical approval for the study was obtained from the Human Research Committee of Stellenbosch University (Appendix B), Biomedical Research Committee (BREC) of KZN (Appendix C), and the Health Research Committee of the DOH KZN (Appendix D). Written permission was obtained from the Medical Superintendents of the selected study sites to gain access to the clinics and medical files of the patients sampled for the study (Appendix E). Permission was granted by means of e-mail or telephonic consent.

This was a retrospective study with no patient contact. Data were collected from medical files and registers. Data collected were identified by study, register numbers and initials. No full names were used and there was no link between names and numbers. Since no patients were directly involved in the study, application was made and granted for a waiver of consent.

Data collection was undertaken at a time and place that did not impede patient care at the selected study sites and data were kept securely in a locked filing cabinet at the office of the researcher. Any queries or uncertainty about the study by staff was dealt with by the researcher who was contactable by cell phone.

1.10 Time fame

The data collection was completed over a period of six months.

1.11 Chapter outline of the thesis

Chapter 1: Scientific foundation of the study

Chapter 1 provides a brief overview of the rationale for, aims and objectives of, and the methodology used in, the study.

Chapter 2: Literature review

Chapter 2 presents the findings from the literature review.

Chapter 3: Research methodology

Chapter 3 describes the research design and methodology applied in the study.

Chapter 4: Data analysis, interpretation, and discussion

Chapter 4 describes and discusses the study findings.

Chapter 5: Conclusion and recommendations

Chapter 5 summarizes the achievement of the study objectives, discusses certain limitations, offers recommendations based on the findings of the study, and draws together the final study conclusions.

1.12 Conclusion

Chapter 1 briefly outlined the issues of TB and HIV epidemic in South Africa and especially in KZN. There is inadequate information regarding the burden being placed on the DOH systems by the number of patients established on ART who are being treated for newly

diagnosed TB. Furthermore, there is inadequate information concerning the clinical management and treatment outcomes of these patients.

The main aim of the study was to fully understand the burden and clinical outcome TB and HIV has on the current health system in order to make suggestions and recommendations with regards to integration of services toward improved clinical management and treatment outcomes.

The lack of information demonstrates the need for research which investigates the integration of both the HIV and TB services in the DOH centres in order to promote a holistic approach to the HIV/TB co-infection epidemic.

Chapter 2 will present findings from a review of the pertinent literature that supports the rationale for the study.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

Chapter 2 presents findings from a review of the pertinent literature relevant to the study. The review offers insights into two key areas: The TB and HIV epidemics at both global and local levels; and the need for the integration of TB and HIV clinical management to improve patient treatment outcomes.

2.2 Selecting and reviewing the literature

Literature was selected in terms of the conception of the research proposal. The review was started at the conception of the research phase and continued until writing the thesis so that the study would include the latest, pertinent literature. Literature was identified and selected from multiple electronic databases, Pubmed, Cochrane Library, and Google Scholar, periodicals, journals, books, e-books and websites (DOH, NIH, WHO).

The review is drawn from literature on the following:

- TB and HIV epidemiology at the global level as well as in South Africa and KZN;
- DOH standards and requirements for the clinical management of HIV and TB;
- The need for integrated HIV and TB management, treatment and management of TB and HIV; and
- The challenges of integrating the two services.

2.3 Organisation of findings from review of the literature

The findings from the literature review are described under the following main headings:

- Clinical overview of TB;
- Clinical overview of HIV;
- TB epidemiology at the global level as well as in South Africa and KZN;
- HIV epidemiology at the global level as well as in South Africa and KZN;

- TB/HIV co-infection challenges;
- Challenges for TB control; and
- Clinical management of TB, HIV and TB/HIV co-infection.

Referencing throughout the thesis is presented in accordance with the Harvard style (Harvard 2009). The findings from the literature for the study are presented below.

2.4 Clinical overview of TB And HIV

2.4.1 TB

TB is a chronic, progressive infection caused by the tubercle bacilli, Mycobacterium tuberculosis (TB) which mainly affects the lungs but may progress to other pART of the body e.g. meninges, kidneys, bones and lymph (Brunner, Smeltzer, Bare, Hinkle & Cheever, 2009)

2.4.1.1 Pathophysiology

The onset of TB occurs when a susceptible person inhales the mycobacterium bacilli and becomes infected. The bacteria are transmitted through the airways to the alveoli where they are deposited and begin to multiply (Brunner, Smeltzer, Bare, Hinkle & Cheever, 2009). The bacilli may also be transported via the lymph system to other pART of the body. The immune system initiates an inflammatory reaction resulting in the accumulation of exudates in the alveoli. Initial infection usually occurs two to ten weeks after exposure. Tubercle bacilli initially cause a primary infection, which most often is asymptomatic. In most cases, after about three weeks of uninhibited growth, the immune system suppresses bacillary replication before symptoms or signs develop. In about 10% of immune-competent patients, latent infection develops into active disease (Brunner et al., 2009:644).

2.4.1.2 Transmission

TB is an airborne infection. Larger droplets settle and smaller droplets remain suspended. TB infection results mainly from inhalation of airborne particles and is transmitted from person to person by talking, coughing, sneezing and laughing (Basavanthappa, 2008:745)

2.4.1.3 Risk factors

A number of factors have been associated with an individual's risk of infection *(*Brunner et al., 2009:644). These include:

(a) the extent of exposure to the infected airborne particles

(b) personal (genetic) susceptibility to the infection

(c) close contact with active TB

(d) immune compromised status, e.g. HIV

(e) substance abuse

(f) pre-existing medical conditions e.g. diabetes, chronic renal failure, etc.

(g) overcrowding and poor housing

(h) profession, e.g. healthcare workers

(i) poor infection prevention control at healthcare level.

2.4.1.4 Signs and symptoms

Common signs and symptoms of TB include fever, cough (can be productive or non productive), night sweats, fatigue, weight loss and haemoptysis (Brunner et al., 2009:644). Not all patients will present with the above signs and symptoms. Any patient who presents with any of the above symptoms warrants further investigation for prompt commencement of TB treatment.

2.4.1.5 Diagnosis

TB is usually diagnosed by detection of mycobacterium either by sputum microscopy, culture of sputum or using a nucleic acid amplification test (NAAT). Other tests including interferon gamma release assay (IGRA), a Tuberculin skin test, or chest X-Ray, are also used in conjunction with physical examination and assessment (DoH, 2009:18).

2.4.2 HIV

HIV infection results from one of two similar retroviruses (HIV-1 and HIV-2) that are transmitted through body fluids (blood, seminal fluid and vaginal secretions). These viruses destroy $CD4^+$ lymphocytes and impair cell-mediated immunity which increases the risk of certain infections and cancers *(*Basavanthappa, 2008: 317).

2.4.2.1 Pathophysiology

HIV is a retrovirus that carries its genetic material in the form of RNA. It attaches itself to the uninfected CD4 cell surface and fuses with the cell membrane. The viral core contents are emptied into the host cell. HIV's enzyme reverse transcriptase copies the genetic material from the RNA to a double stranded DNA. The double-stranded DNA merges with the cellular DNA (Provirus). The cell uses the provirus to make new viral proteins and viral RNA. These new viral proteins join the viral RNA and create new viral particles. New viral particles bud from the cell and start the process all over *(*Brunner et al., 2009:1821).

2.4.2.2 Transmission

HIV may be transmitted through unsafe sex (seminal/vaginal fluid), from mother to child (breast feeding, transplacental), by drug abuse (sharing of infected needles) and blood (blood transfusion, inflammation/breaks in the skin) *(*Brunner et al., 2009:1821).

2.4.2.3 Risk factors

The risk factors associated with HIV infection are unsafe sex, multiple sexual partners, substance users, poverty (multiple partners for financial gain), poor education (lack of knowledge on the HIV epidemic and consequences thereof, and cultural factors (promote multiple partners) (Beers & Porter, 2006).

2.4.2.4 Diagnosis

Diagnosis is made by rapid test at HIV counseling and testing (HCT).This is a finger prick blood test that shows positive or negative status. The result is confirmed by the detection of antibodies to HIV or by detecting HIV RNA in the blood (DOH, 2009:74).

2.4.3 TB epidemiology

TB epidemiology is the scientific and medical study of the causes and transmission TB and distribution in a given population (Dorland, 1901).

2.4.3.1 TB at global level

TB is known to man since the time of Hippocrates and may even go beyond if one had to look at Indian and Chinese literature (Basavanthappa BP, 2008:713). In 1952 anti-TB medication was introduced and in combination with vaccines and improving living standards, led to a noticeable decrease in and control of TB infection in the US and some developing countries (Brunner et al., 2009:643). With the successful implementation and progress of vaccine programmes throughout the world there was hope that TB would be eliminated. However, by the late 1980s there was a resurgence of TB due to the emerging HIV epidemic and multidrug resistant (MDR) TB. The emergence of MDR TB was mainly due to failure to complete TB therapy (Dilraj & Rustomjee, 2009). MDR-TB is defined as TB disease caused by strains that are resistant, in vitro, to both rifampicin and isoniazid, with or without resistance to other drugs (DoH, 2009:80).

The rapidly growing TB epidemic globally, and especially in Africa, creates an immense burden compounded by the increasing HIV co-infection rate. In 2011, there were an estimated 8.7 million new cases of TB globally (13% co-infected with HIV); 79% of these HIV-positive TB cases were in the African Region. In the same time period approximately 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430 000 among people who were HIV-positive (WHO, 2012: 1).

India and China make up for almost 40% of the world's TB cases. About 60% of cases are in the South-East Asia and Western Pacific regions. The African Region has 24% of the world's cases, and the highest rates of cases and deaths per capita (WHO, 2012:2).

2.4.3.2 TB in South Africa

South Africa ranked fifth out of the 22 WHO-identified high-burden countries as per the number of reported TB cases in 2007 (Lonnroth & Raviglione, 2008:481). The latest statistics for the five high-burden countries is shown in Table 1. Since then the WHO 2010

report places South Africa third on list of the five countries with the largest number of incident cases. “Ninety-five per cent of all cases and 99 % of deaths occur in developing countries, with the greatest burden being in sub-Saharan Africa” (Lonnroth & Raviglione, 2008:481).

TB is a major public health problem in South Africa. According to WHO Global TB Report 2009, South Africa reported nearly 460,000 new TB cases in 2007. The incidence rate was an estimated 948 cases per 100,000 population. This is a major increase from 338 cases per 100,000 population in 1998 (WHO 2009:7).

Table 2: Estimated epidemiological burden of TB, 2011: all forms 100 000 pop/year

Country	Incidence (Includes TB in people with HIV)	Prevalence (Includes TB in people with HIV)	Mortality	HIV Prevalence in Incident TB (%)	HIV-Positive Incident TB Cases (No. in 1000’s)
India	199	346	35	5.2	120
China	85	119	36	1.7	17
Indonesia	222	489	48	4.2	20
Nigeria	204	382	40	26	86
South Africa	1180	1250	87	66	390

(WHO 2012:10)

HIV has contributed significantly to the re-introduction and increase in TB both globally and especially in Southern Africa. Southern Africa continues to bear the brunt of the global burden of HIV as reported below in Table 2. Thirty-five percent of HIV infections and 38% of AIDS deaths in Southern Africa occurred in 2007 (WHO 2008:32). In 2007, South Africa accounted for 31% of the estimated 79% of HIV positive TB cases in the African region (DOH, 2009:10).

2.4.3.3 TB in KwaZulu-Natal (KZN)

In 2006, KwaZulu-Natal had the highest total TB caseload, as shown in Table 3, and this accounted for 31% of all TB cases nationally (DOH, 2009:9). KZN in South Africa is the

province with the highest HIV burden and a rapidly progressing TB epidemic (DOH, 2009:9).

Table 3: TB cases in South Africa: 2006

	All TB Cases	PTB Cases	New Smear Positive PTB Cases	Retreatment Smear Positive PTB Cases	Smear Negative PTB Cases	No Smear PTB Cases	Children 0-7 years	EPTB Cases	Incidence All TB cases per 100 ,000	Incidence PTB cases per 100,000
Eastern Cape	48,512	41,558	19,527	8,473	3,615	9,943	2,805	6,954	687	589
Free State	23,374	19,058	9,553	2,840	2,479	4,186	2,295	4,316	789	643
Gauteng	46,093	34,290	20,609	4,188	2,915	6,578	4,155	11,803	501	372
KZN	104,705	88,271	32,855	9,527	20,547	25,342	8,593	16,434	1076	907
Limpopo	17,301	14,118	7,574	1,323	1,305	3,916	1,069	3,183	305	249
Mpumalanga	15,035	13,496	7,216	1,081	859	4,340	7,55	1,539	463	416
North West	28,421	24,519	12,539	2,954	1,764	7,262	2,156	3,902	738	637
Northern Cape	8,631	7,951	3,583	1,482	901	1,986	1,018	680	950	875
Western Cape	49,093	43,296	17,644	8,563	8,366	8,723	6,955	5,797	1,033	911
South Africa	**341,165**	**286,557**	**131,100**	**40,431**	**42,751**	**72,276**	**29,801**	**54,608**	**720**	**605**

(DOH,2009: 9)

2.4.4 HIV epidemiology

The HIV epidemiology will be discussed at the global level and in South Africa as well as in KZN.

2.4.4.1 Global level and in South Africa

Sub-Saharan Africa is still the largest contributor to the global HIV burden (UNAIDS, 2010:26). Although the rate of new HIV infections has decreased, the total number of

people living with HIV continues to rise. In 2009, South Africa had 22.5 million people living with HIV. This was an estimated 68% of the global total (UNAIDS, 2010: 26).

The HIV incidence appears to have peaked in the mid-1990s, with evidence of declines in incidence in several countries in sub-Saharan Africa. Between 2001 and 2009, the incidence of HIV infection declined by more than 25% in the estimated 22 countries (UNAIDS, 2010: 27), but South Africa's epidemic remains the largest in the world.

2.4.4.2 HIV epidemiology in KZN

As shown in Table 4 below, despite a decrease from 2006 but KZN still had the highest HIV prevalence rate in 2011, based on the prevalence amongst antenatal women in South Africa (DOH, 2011:11).

Table 4: HIV prevalence among antenatal women by province, South Africa, 2006 to 2011

	HIV Prevalence 2006	HIV Prevalence 2007	HIV Prevalence 2008	HIV Prevalence 2010	HIV Prevalence 2011
Eastern Cape	28.6	28.8	27.6	16.0	16.02
Free State	31.1	31.5	32.9	19.47	19.58
Gauteng	30.8	30.5	29.9	16.0	16.09
KZN	39.1	38.7	38.7	24.59	24.11
Limpopo	20.6	20.4	20.7	12.9	12.92
Mpumalanga	32.1	34.6	35.5	23.94	24.11
North West	29.0	30.6	31.0	18.83	18.89
Northern Cape	15.6	16.5	16.2	9.2	9.23
Western Cape	15.1	15.3	16.1	4.72	4.75
South Africa	29.1	29.4	29.3	17.3	17.3

(DOH, 2011:11).

2.4.5 TB/HIV co-infection

It is estimated that more than 65% of all TB patients in Africa are co-infected with HIV, and TB is the leading cause of morbidity and mortality among HIV-infected patients. Despite

the widespread availability of TB treatment, TB/HIV co-infected patients in Africa had an annual mortality rate of 25% to 40% before the introduction of ART therapy (Mukadi, Maher & Harries, 2001: 143). This mortality was attributable to complications from overwhelming TB disease as well as immunosuppression from advanced HIV disease (Murray, Sonnenberg, Shearer & Godfrey-Faussett, 1999:733).

In 2007, South Africa, with 0.7% of the world's population, had 17% of the global burden of HIV infection, and one of the world's worst TB epidemics, aggravated by increasing drug resistance and HIV co-infection (Maher & Raviglione, 2005:167) .Individually, TB and HIV are two of the world's greatest on-going public health threats. In combination, the two diseases can be even more devastating. HIV significantly increases an individual's chances of reactivation of latent TB infection and progression to active TB disease. TB is the major cause of death in individuals infected with HIV, and the combination of both illnesses creates treatment challenges for providers. Magnifying these challenges even further is the fact that much of the burden of TB/HIV co-infection exists in some of the world's most resource-limited settings. Concerted efforts are needed to identify effective and feasible strategies to manage both conditions in the co-infected patient (El-Sadr & Tsiouris 2008:29).

2.4.5.1 Integrated TB/HIV management

Currently HIV is considered the greatest risk factor for TB infection progressing to disease and TB is the most common life threatening opportunistic infection associated with HIV. In areas with high rates of HIV, TB is increasing rapidly (DOH, 2009:10).

HIV and TB co-infection is associated with high mortality rates. One of the main challenges is the integration of combined treatment of HIV and TB in the public sector (Abdool Karim, Baxter, et al., 2010:808). Integration of HIV and TB treatment is critical in reducing the mortality rate and this has been confirmed by the SAPIT trial (Abdool Karim, Abdool Karim, Baxter, et al., 2010:808). This study looked at HIV-positive patients on TB treatment who initiated ART therapy. This type of management had a significant reduction in mortality, compared to patients who deferred ART until after TB treatment was complete. As a result,

South African DOH guidelines have elevated the CD4 count from 200 to 350 below which TB patients should initiate concomitant ART (DOH, 2008:10).

2.4.6 Challenges of TB Control

Global TB control is facing major challenges. The main contributory factor is HIV and immune system compromise. Due to poor treatment compliance by patients, there is an increase in Multi-Drug Resistance (MDR) and Extreme Drug Resistance (XDR) TB. The rising HIV and TB rates are increasing the health care burden on an already overburdened health system. Poverty and poor access to health care especially in rural areas further compound the challenges of TB control and contribute to the increase in MDR and XDR (DOH, 2009:10).

In South Africa, poverty and poor access to health care, especially in rural areas, further compound the challenges of TB control, and contribute to the increase in MDR and XDR (DOH, 2009:10).

Reports produced by the South African National Department of Health have shown that health workers in the study sites did not adequately follow up on patients' progress after starting TB treatment due to lack of resources (DOH, 2009:10).

2.4.6.1 WHO targets for global control of TB

WHO's goals for global TB control is that the incidence should be falling and prevalence and death rates should be halved by 2015. By then at least 70% of incident sputum smear-positive cases should be detected and treated in DOTS programmes and 85% should be successfully treated (WHO 2009:1).

2.4.6.2 The South African National Tuberculosis Programme

The South African National Tuberculosis Programme (DOH, 2009:34) has outlined a strategic plan to control the TB growth rate and to meet the Millennium Development Goals.

2.4.7 Clinical management

Effective TB management requires early detection and prompt commencement of treatment. The aims of TB treatment are to cure the client of TB, decrease transmission of TB to others, prevent drug resistance or relapse by ensuring adherence and follow up, and prevent deaths from TB or its complications (DOH,2009:34).

2.4.7.1 TB

TB treatment at the DOH clinics is adhered to as per the National Tuberculosis Management Guidelines. These guidelines have set out standard regimens of treatment for patients with TB. The use of standard treatment regimens decreases prescription errors, reduces cost, simplifies training, and facilitates access to drugs when patients change health facilities. (DOH, 2009:35).

The drugs used in TB treatment as stipulated by the National Tuberculosis Management Guidelines are: R-rifampicin, H-isoniazid, Z-pyrazinamide, E-ethambutol and S-streptomycin. Regimen 1 (standard regimen) is made up of two months of intensive phase and four months of continuation phase. Regimen 2 is made up of three months of intensive phase and 5 months of continuation-phase (DoH, 2009:35).

2.4.7.1.1 New cases

A new case is defined as a patient newly diagnosed and never treated for TB in the past, or who had taken TB treatment for less than four weeks. Such patients are commenced on the standard regimen i.e. months of isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) in the intensive phase and months months of isoniazid and rifampicin-4 (HR) in the continuation phase (DOH,2009:35).

2.4.7.1.2 Retreatment cases

A retreatment case is a TB patient treated for 4 weeks or more in the past, and who are diagnosed for TB again due to treatment failure, defaulted treatment or those patients that relapse. Such patients are commenced on two months of isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin and 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol in the intensive phase and 5 months of isoniazid, rifampicin and ethambutol in continuation phase (DOH, 2009:35).

Effective treatment of TB requires a patient to strictly adhere to the treatment regimen. In order to ensure patient adherence there must be adequate health infrastructures and access to health facilities for all. Primary health care staff, who are specifically TB trained, to work in TB clinics. There should be continuous training and update of staff. The level of TB awareness should be raised at primary health care and community level by educating patients and family members about TB (prevention and cure) and the need to support family/community members infected with TB, side-effects of TB medication, adherence and importance of reporting to health facility and continuing treatment (DOH,2009:35).

2.4.7.2 HIV

ART therapy is indicated in the following instances irrespective of CD4 count:

WHO clinical stage 4, severe HIV-related disorders such as Immune thrombocytopenia, thrombotic thrombocytopenia, polymyositis, lymphocytic interstitial pneumonitis and non HIV-related disorders, e.g. Malignancies, Hepatitis B, Hepatitis C. ART is also indicated when CD4+ counts are below 200 cells/mm^3 and between 200 cells/mm^3 to 350 cells/mm^3. Baseline investigations are recommended in all patients prior to initiating ART, These include liver function tests (LFT), full blood count (FBC), serum creatinine, urinalysis for proteinuria, hepatitis B surface antigen(DoH 2009:8).

ART therapy should only be commenced when patients are fully prepared to commit themselves to long-term treatment and to maintaining good adherence and follow up for treatment. Patients must attend at least three educational sessions prior to commencing

ART therapy. Patients must show knowledge and understanding that ART therapy is a life time therapy and adherence is of utmost importance. They must be informed about side effects, active depression and substance abuse. Patients must be encouraged to disclose their HIV status as this is a contributory factor to adherence (DOH, 2009: 8).

The patients' attendance to at least three educational sessions is used to establish the patients' commitment to treatment, adherence and follow up. Once a patient is deemed ready ART therapy is commenced (DOH, 2009: 8).Table 5 outlines the National guidelines for HIV management.

Table 5: Standardized National ART Regimens for Adults and Adolescents

1st Line		
All new patients needing treatment	TDF(Tenofovir) + 3TC(Lamivudine)/FTC(Emtricitabine) + EFV(Efavirenz)/NVP(Nevirapine)	For TB co-infection EFV is preferred. For pregnant women or women of child-bearing age, not on reliable contraception, NVP is preferred.
Currently on d4T-based regimen with no side effects	d4T(Stavudine) + 3TC + EFV/NVP	Remain on d4T if well tolerated. Early switch with any toxicity. Substitute TDF if at high risk of toxicity (high BMI, older, female, TB treatment)
Contraindication to TDF: renal disease	AZT(Zidovudine)+ 3TC +EFV/NVP	
2nd Line		
Failing on a d4T or AZT-based 1st line regimen	TDF + 3TC/FTC + LPV/r(Lopinavir/Ritonavir)	Virological failure must be followed by intensive adherence management, as resuppression is often possible. If repeat VL remains >1000 in three months despite adherence intervention, switch.
Failing on a TDF-based 1st line regimen	AZT + 3TC + LPV/r	Virological failure must be followed by intensive adherence management, as resuppression is often possible. If repeat VL remains >1000 in 3 months despite adherence intervention, switch.

Salvage Therapy		
Failing any 2nd line regimen	Specialist referral	Virological failure on protease inhibitors is almost always due to non-adherence. Intensively exploring and addressing issues relating to causes of non-adherence will most often lead to resuppression. If VL remains high, refer where possible, but maintain on failing regimen.

(DOH,2009:8)

2.4.7.3 Management of TB patients on ART therapy

Patients diagnosed with HIV should be educated and counselled health care staff and community health workers about the signs and symptoms of TB and the severity of TB/HIV co infection. They should be encouraged to present early to the nearest health facility when any of the TB symptoms are recognized or suspected. They should encourage other community members who present with such symptoms to visit their local health centres for a TB/HIV assessment. All HIV-positive patients with no signs and symptoms of TB, or a PTB contact are eligible for TB prophylaxis (DoH, 2009: 71).

The standard regimen for TB preventive therapy is: Adults: Isoniazid (INH) 5 mg/kg/day (maximum 300 mg per day) and Vitamin B6 (pyridoxine) 25 mg per day (DoH, 2010:29). The national HIV and AIDS Policy Guideline recommends trimethoprim/ sulphamethoxazole (cotrimoxazole) 160/800mg (960mg) daily for all HIV-positive adults whether they have TB or not. The standardized treatment for HIV management for South Africa and when to switch treatment is shown in table 3 (DOH,2010: 20).

Patients who present with TB before commencing ART therapy should complete two to a maximum of eight weeks of TB therapy before commencing ART therapy if the patient has a CD4 count of less than 350 cells/mm^3. ART therapy should be initiated as soon as the patient is tolerating their TB therapy and this is usually within 2-4 weeks. Efavirenz-based

regimens are generally preferred in patients with active TB, however, other regimens may be considered for use by the clinician/specialist. Patients who develop tuberculosis while on ART should continue ART throughout the TB treatment phase. Patients on Lopinavir/Ritonavir should have their dose doubled slowly over two weeks (to 800/200 mg twice a day); all other regimens can be continued unmodified. Continue these changes to Lopinavir/Ritonavir until two weeks after completion of TB treatment. These patients must be monitored and investigated closely for hepatotoxicity symptoms (DOH 2010:29).

2.4.7.4 Side-effects

TB therapy and ART carries significant side-effects, and attention by health care workers is important to manage patients effectively and holistically. Table 6 outlines some of the common side effects experienced with use of TB treatment and ART (DOH, 2009:24).

Table 6. Common shared side-effects of TB and ART

Side-effects	ART	Tuberculosis Treatment
Nausea	Didanosine, Zidovudine, protease inhibitors	Pyrazinamide
Hepatitis	Nevirapine, Efavirenz	Rifampicin, Isoniazid, Pyrazinamide
Peripheral neuropathy	Stavudine, Didanosine	Isoniazid
Rash	Nevirapine, Efavirenz	Rifampicin, Isoniazid, Pyrazinamide

2.5 Conceptual framework

In 2009 9.4 million incident TB cases were reported globally. An estimated 11–13% of incident cases were HIV-positive and the African Region accounted for approximately 80% of these cases (WHO, 2010:1). According to the WHO (2010:1) new data from 15 countries show that efforts by national TB programmes (NTPs) to engage all care providers in TB control can be a particularly effective way to increase the Case Detection Rate (WHO, 2010:1).

Based on the literature review undertaken for the study, there is a paucity of research conducted in South Africa on the clinical outcomes and management of patients on TB therapy and second line ART. The number of patients on ART who develop TB remains unclear. Amongst these it is unknown how many are failing ART, and of those failing therapy, there are few data on how these patients are being investigated and managed. This situation exposes the need to investigate the proportion of all patients with TB who were established on ART at the time of diagnosis, and their clinical and treatment outcomes.

Random visits by the researcher during the preparatory phase of the study of DOH facilities showed that they had both a TB and a HIV (VCT) clinic that functioned independently of each other. Each clinic kept separate files and logs with referral of patients across clinics. Those primary Health Care facilities that did not have a dispensary, did not initiate ART therapy, so patients with TB requiring ART needed to be referred out to be commenced and stabilized on ART and then referred back to the PHC facility for follow up management. TB and HIV cannot be treated as separate conditions rather as a whole to ensure control is gained of the rapidly progressing epidemic of co-infection (Abdool Karim, Churchyard, Abdool Karim & Lawn, 2009:921) .

In order to control TB in high HIV settings, collaborative TB/HIV programmes need to be implemented in South Africa (DoH, 2009: 71). The main objective of TB/HIV programmes must be to create a mechanism of collaboration between TB and HIV/AIDS management units, thus reducing the burden of TB among people living with HIV/AIDS and reducing the burden of HIV among TB patients .

2.6 Conclusion

This chapter described the literature reviewed in order to support the research question and rationale, and to demonstrate the need for the proposed study. It reviews the epidemiology of TB, its association with HIV and how TB has been exacerbated by the increase in HIV. Despite the stepping up of programmes and changes in guidelines the TB/HIV epidemic is still a major issue in South Africa. The various studies and reports reviewed in this chapter bring to the fore the need for integration of the two services but to

date limited progress has been made in the government institutions in this respect. All the trials show association of TB and HIV as the major contributor to the increasing morbidity and mortality rates in South Africa and the dire need for the integration of TB and HIV management services.

Having identified from the literature review that integration of TB and HIV is essential in curbing the TB/HIV scourge the researcher was brought to the realization that: Firstly it is not clear currently how many patients on ART develop TB. It is unknown how many of these are failing ART and of those failing therapy, there are few data available on how these patients are being investigated and managed and this led to the conceptualization and aim of the study. The basis of the research proposal is to describe a cohort of patients established on ART therapy who develop TB. The aim is to determine what proportion of all tuberculosis patients are established on ART at the time of TB diagnosis, and what their clinical and treatment outcomes are in different public sector settings in the EThekwini region, KZN.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Introduction

Chapter 3 describes the methodology applied to the study. This chapter gives in depth information regarding the methodology used to determine the sample size, collect and analyze data required to meet the study objectives.

3.2 Research aim

The aim of the study was to determine:

(a) the proportion of TB patients established on ART at the time of their TB diagnosis; and

(b) the clinical and treatment outcomes of these TB patients in different public health care facilities in the eThekwini region of KZN.

3.3 Research objectives

The objectives of the study were as follows:

(a) To determine the proportion of all patients with TB who were established on ART at the time of TB diagnosis;

(b) To establish the clinical characteristics of patients established on ART who were newly diagnosed with TB;

(c) To evaluate the clinical management of patients established on ART who were newly diagnosed with TB; and

(d) To evaluate the TB and HIV treatment outcomes of patients established on ART who developed TB.

3.4 Research methodology

The research methodology of the study is described under the following subsections: research approach and design; population and sampling; data collection tool; pilot study; validity and reliability; data collection; data management and analysis, and Ethical considerations.

3.4.1 Research approach and design

A retrospective design was chosen as a suitable design for the study. A retrospective study investigates a phenomenon, situation, problem or issue that has happened in the past. Usually that which has happened in the past and based on the data available for that period (Kumar,R. 2005:99). In accordance with the study objectives, the chosen study design enabled measurement of the management and clinical outcomes of a cohort of patients once commenced on TB treatment and ART. The study required review of clinical chART and required data three months post-RT to six months post-TB treatment. This could only be achieved retrospectively. It was also a feasible and cost-effective means of obtaining sufficient data to answer the objectives and managing a large sample size. The study focused on a period of one year prior to patients having commenced and been established on ART who developed TB. This timeframe allowed for the collection of clinical HIV follow-up and outcome data by means of an audit of the medical files of patients included in the study sample.

3.4.1.1 Population and sampling

This section describes the criteria of the study population and sample included in the study.

3.4.1.2 Study population

The study population comprised all TB patients who attended selected DOH clinics in the northern part of the eThekwini region in KZN. The reason was that the South African Medical Research Council (SAMRC), the place of work of the researcher, had well-established collaborative links with them.

A total of 115 DOH clinics in the eThekwini region had a TB component. At the time of the study, only 13% (n=15) of the clinics provided comprehensive on-site TB treatment and ART initiation. Of these 15 clinics, three were located in the Northern region of eThekwini. Accordingly, the study included all three clinics since they had a TB clinic and a DOH-registered ART clinic. All the clinics served both rural and urban/semi-urban populations.

Initially an additional clinic was also included. This additional site only had an HIV clinic, and no TB clinic. It was included because of the large number of patients with follow-up for ART therapy. However, this site was later excluded from the study because their internal Clinics' Ethical Board declined inclusion on the basis that the clinic did not have sufficient numbers to meet the study population requirements.

3.4.1.2.1 Study population in TB Clinics

According to policy and protocol guidelines set by the DoH (DoH, 2009:22), suspect TB patients who present at the Primary Health Care Department are diagnosed by X-ray and then referred to the TB clinic for further investigation and sputum collection. In this study, all TB patients at the clinics were included, regardless of the means of TB diagnoses. These included patients: (a) who had started empirically on treatment; (b) diagnosed by X-Ray and had been assessed by the clinician and started TB treatment; (c) diagnosed by sputum smear (2x positive sputum smear results) and who had commenced treatment by the Primary Health Care nurse; (d) TB positive patients who had commenced treatment and were entered into a TB register; (e) with TB symptoms and negative sputum smear results who were commenced on antibiotics and who awaited sputum culture results before commencement of TB treatment; (f) on TB treatment (six months) who had been followed up on a weekly basis in the intensive phase of treatment (two months) and then monthly during the continuation phase (four months); and (g) who were followed up until their TB treatment was completed or they were cured (DOH, 2009:22).

From personal observation by the researcher it was noticed that follow up schedules could differ at the respective clinics and also could be altered to suit patients' availability, as long as the patient had sufficient TB medication until the next scheduled visit.

Some patients were transferred between facilities for continuation of TB treatment. All patients that were transferred into the research site, who had more than one month of treatment at the former institution were excluded from the study because data on commencement of treatment were not obtainable. Patients transferred out of the

clinic after initiation of therapy were also excluded as no TB outcome data could be obtained from these patients.

Information regarding ART was poorly captured in the TB files. It was difficult to link patients in the TB clinic with registers in the ART clinic as numbers at both clinics were different.

3.4.1.2.2 Study population at ART clinics

In line with the guidelines of the DOH (DOH, 2010:23), all patients at the ART clinics were screened for TB at their baseline visit, prior to initiation of ART. Suspect TB patients (diagnosed by signs and symptoms) or those diagnosed by X-rays were referred to the TB clinic for further investigation. Patients with confirmed TB started TB treatment and were then referred back to the ART clinic for reassessment and commencement of ART. Patients then had to go to the TB clinic for TB treatment and the ART clinic for ART on separate days, unless the patient arranged with the clinic staff to adjust the appointments so that they coincided (DOH, 2010:23).

Few data relating to TB had been captured in the ART files. Patients could not easily be traced back to the TB clinic because the patient numbers were different at each clinic, and these numbers were also not recorded.

3.5 Specific sampling criteria

3.5.1 Inclusion criteria

TB clinic

The study sampled the medical files of all adult patients: diagnosed with TB by symptoms, positive sputum smears and cultures and/or chest x-ray, entered onto the TB register, and treated at any of the selected sites 12 months prior to initiation of the study; and those aged 15 years and older.

ART clinic

The study sampled the medical files of all adult patients: diagnosed with HIV, entered onto the ART register, and treated for TB at any of the selected sites for at least three months prior to initiation of TB treatment and those aged 15 years and older.

3.5.2 Exclusion criteria

TB clinic

The study excluded the medical files of patients: aged less than 15 years; those who had more than one month's TB treatment at a different institution and transferred to the study site to continue TB treatment and those treated for drug-resistant TB.

ART clinic

The study excluded the medical files of patients: aged less than 15 years; and those who had less than three months of ART at the time of commencing TB treatment.

The study was aimed at investigating patients who potentially required second-line ART. These are a different population to patients who develop immune reconstitution inflammatory syndrome (IRIS) after initiating TB-HIV therapy, an important clinical problem that has been extensively studied. IRIS occurs in the first few weeks after initiating ART, and is rare after three months of ART. The rationale for excluding patients on less than three months ART treatment was therefore to ensure that IRIS patients were not included. The evaluation of childhood HIV and TB clinical management is distinct and different from that of adults, and was therefore not a focus of the study. Accordingly those aged less than 15 years were excluded.

3.5.3 Study sample

When doing a study it may not be possible to access the entire population and findings may be based on a subset of participants (Goddard & Melville, 2004). This study used a retrospective, quantitative, cohort technique. The study sample was selected in the following manner: Having gained prior permission from the study sites the PI scheduled dates and times to be spent at each clinic. The PI accessed the clinic TB register, identified all TB patients and entered them onto a screening log. The files of eligible

patients were reviewed to ensure the data met the inclusion criteria of the study. Data of all patients who met the study criteria were entered into the data collection tool (Appendix 1).

3.5.3.1 Study sample: TB clinic

At the TB clinics, a total of 600 medical files were to be reviewed. This sample size was based on prior knowledge from a study conducted by the SAMRC. From the latter study, it was known that an estimated 15% of all TB patients in the eThekwini Region were on ART. With a 95% confidence level and 5% margin of error, a sample size of 589 was required, at a power of 90% to estimate this proportion.

The 600 files to be reviewed were divided equally between the three study sites. The actual total of 579 (96.5%) files was reviewed. Older files, that had been poorly archived, were not easily traced. Difficulties in accessing these files resulted in the sample size falling short of the intended 600 files. The file review was completed within the time frame of January 2010 and May 2010. The researcher maintained this timeframe at all sites as this ensured availability of files and access to information.

3.5.3.2 Study sample: ART clinic

The primary end point of the study at the ART clinics was combined HIV and TB favourable outcomes at six months. Based on prior knowledge from the study conducted by the SAMRC (Dilraj & Rustomjee, 2009) it was estimated that 75% of patients would have had a favourable TB outcome (cure or completion) and of these 66% would have had a favourable HIV outcome (undetectable viral load). Therefore, it was estimated that with a combined favourable HIV and TB outcome of 50% and a 7% error, a sample size of 532 was required for 95% confidence at a power of 90%.

A total of 1245 ART files were reviewed across the three study sites. Of these, 501 were identified with TB. In line with the inclusion criteria (section 3.4.1.2) the researcher further reviewed these files to extract data for only those (n=42) that had three months or more of ART at the time of commencement of TB treatment.

3.6 Data collection tool

Data were extracted using a structured data collection tool (Appendix 1). The tool was developed by the researcher, based on the findings from the literature and recommendations from experts in the field (Dr Pym, MRC KZN, and Dr Marais, Stellenbosch University) as well as advice from a statistician at SAMRC KZN).

This tool was pre-printed, and quality control and quality assurance of the completed data forms were undertaken by the researcher (as explained in section 1.11). The data from each patient file were entered manually onto a separate data form. Since data were collected from both the TB and ART clinics, using the same data collection tool, the researcher differentiated the tool by colour coding and using white or yellow paper respectively. This was to ensure that the data from the separate clinics were not mixed. Completed data forms were filed per clinic site and kept in a locked cupboard in the researcher's office.

3.6.1 DEMOGRAPHIC profile

Data were collected on the age and sex of all patients. The initial intent was also to collect data on ethnicity. The pilot test revealed that ethnicity was not being captured in the patient files, and it was not possible or ethical to determine ethnicity from names.

3.6.2 HIV-related results

This data included known HIV status, VCT and patients who did not want to be tested for HIV. Baseline CD4, viral loads and repeat tests data were also captured.

3.6.3 ART

Data included were the starting date and regimen of ART. These data helped to identify those patients who had three months or more of ART, prior to starting TB treatment.

3.6.4 SPUTUM results

This data included all sputum TB smears and cultures that had been recorded. This information was used to determine baseline smears and outcome of smear results at two and three months of TB treatment.

3.6.5 TB diagnosis

This data captured the common diagnostic method used to detect and treat TB. Delays in turnaround time for sputum results from the National Health Laboratory Services may have resulted in delays in commencement of TB treatment.

3.6.6 Previous TB

This data outlined whether the patient had been previously diagnosed with TB and had received treatment.

3.6.7 Current TB

This data showed the dates of TB diagnoses and the start of TB treatment. It also showed the regimen used and any change in medication as well as the reason for changing medication. It also captured completion or default of treatment.

3.6.8 OUTCOME

Outcome data were collected to measure the TB treatment outcome at six months after the commencement of treatment. At this stage, the patient was assessed for completion of treatment, sputum smear conversion and TB symptoms resolved, for example, whether the X-ray was normal, and the patient was discharged from the TB clinic. HIV outcomes could not be measured as data on ART. Progress was not fully captured in patient files in both the TB and ART clinics. HIV outcome was to be measured using CD4 count and viral loads. These tests were either not both done or they were recorded inconsistently in patient files.

3.6.9 Pilot test

A pilot test is a small-scale version of the major study. Unforeseen problems may arise during a study. By doing a pilot test, the researcher can identify and address relevant issues and make adjustments to ensure the smooth running of the actual study (Brink et al., 2005:54).

Prior to the empirical phase, the tool was tested in order to validate its applicability. A small sample of patient files (15 files, representing 2% of the study population) was randomly selected. Five files were identified from the TB register in the past 6 months at time of pilot study. The file that could be located was used to capture the data from each site. The data were captured electronically by the SAMRC-designated data capturer.

Based on the findings from the pilot test, some adjustments were made to the data collection tool. In the demography section, ethnicity was omitted as this was not being captured on the clinic files. The clinics serve a multi ethnic community and it would be biased to determine ethnicity based on name alone. CD4 details were captured based on date rather than monthly interval as CD4 was not done at absolute specific dates. TB symptoms were omitted as it was not being collected on all patients and was not required for any of the outcome results. The sputum collection format was changed to capture data of two sputum samples and the interval was replaced by date as sputum samples were not collected at specific intervals (e.g. two weeks, three months, six months) , instead collected as client presented at the clinic. The outcome at six months was changed to represent the outcome that appeared on the patients file and TB registers. The manually captured data were entered into an electronic database (EpiData, version 3.3) by the researcher, and used by the statistician to test the data analysis method. The validation files and data were excluded from the empirical study. The manually captured data were entered into an electronic database (EpiData, version 3.3) by the researcher. The statistician used the database to test the data analysis method. The validation files and data were excluded from the empirical study.

3.7 Validity and reliability

This was a retrospective study. There was no patient contact and therefore the data collection tool was not in the form of a questionnaire. The tool was designed to collect data from patients' files that were required to meet the study objectives. The face and content validity of the data collection tool was validated by experts in the field as mentioned previously in section 3.8. The applicability of the tool was validated in the pilot test prior to the empirical phase in order to ensure that it captured all the required information to achieve the objectives of the study. Data yielded from the pilot test was used to validate the tool and to test the data analysis method. All the data were collected by the researcher who is a Registered Nurse with seven years of research experience. The researcher used the assistance of an experienced research fieldworker employed by the SAMRC. The fieldworker was used to trace and collect files from the clinics for data capture by the researcher. The fieldworker did not capture any data. Collection of the files of the study sample was systematic; it followed the sequence of the file numbers and the timeframe of January 2010 to May 2010 to ensure complete data were collected for all patients. Quality control and assurance (QC/QA) of the captured data was undertaken daily by the researcher. The data were compared and checked against registers and patient medical files. Missing data and errors were corrected immediately. A QC/QA check was also done by a qualified data encoder with many years of research experience. Missing data were marked and any errors or omitted information was brought to the researchers attention, and the respective corrections were made. Data were double-entered by the biostatistician to ensure reliability of data capture.

3.8 Data collection

The researcher undertook the data collection on her own as funding was limited and the researcher was capable of completing the task alone. Using the data collection tool, the data were extracted manually from the sampled files. Attention to collection of all files for the various samples was systematic to ensure complete data capture. All patient files at the selected clinics were reviewed from date of start of study to a period of one year prior to study.

3.9 Data management and analysis

The collected data were captured into an electronic database (EpiData Version 3.3) by the data encoder. Double-entry was completed by the statistician who also verified and validated the data captured. There were few inconsistencies that were rectified by the researcher. The database which reflected the variables and categories of the data collection tool was presented to and approved by the statistician.

The data were analyzed using STATA (version 11.0) with the assistance of the statistician from SAMRC KZN. The data were presented in tables for descriptive statistics. This was deemed the appropriate method due to the large number missing variables i.e. incomplete data entry in the patient medical files. Statistics reported were proportions and means and standard deviations. The analysis of categorical variables is presented using cross tabulations with frequencies and percentages reported. Means and standard deviations were only used to summarize the age distribution of participants within each site.

3.10 Conclusion

Chapter 3 presented an in-depth description of the methodology employed in the study. The study used a retrospective cohort research design. Patients' files were accessed, and data relevant to the study objectives were extracted and entered into a data collection tool. Data were extracted from the TB and ART registers and patients' files.

Data collection at the DOH facilities was made difficult by missing files, incomplete data in the files and poor correlation of data between TB register and patient files. The researcher was presented with many challenges that will be expanded upon in Chapter 5. However, despite these problems, sufficient data were obtained to effectively address the principal objectives of the study.

CHAPTER 4

DATA ANALYSIS, INTEPRETATION AND DISCUSSION

4.1 Introduction

Chapter 4 presents, interprets, and discusses the results of the data analyzed for this study. The study was retrospective and quantitative in nature. The data analysis was descriptive, and the results are presented in the form of frequency tables and proportions.

4.2 Presentation and discussion of the study findings

The results of the study will be presented and discussed by site and for the total cohort. The results will be discussed for the TB and HIV cohort under the following sections: demographic data, age, gender, HIV and ART analysis, HIV related tests, diagnosis, TB treatment and outcome. Results are reported only for those data that were found to be statistically significant ($p \leq 0.05$).

4.2.1 TB clinic cohort

A flow chart was used to show the breakdown of the cohort to give clarity on the type of TB and identify the number of TB cases initiating chemotherapy. The sample (N=579) is analyzed and depicted in Diagram 1.1 showing previously treated and new TB as well as the type of TB.

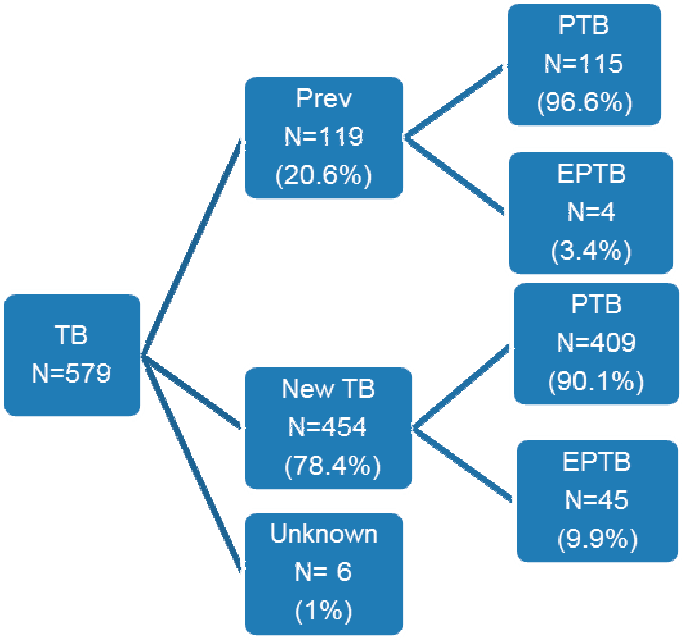

Diagram 1: Characteristics of TB clinic cohort in terms of type of TB and history of previous treatment

The study sample (N=579) shows that 78.4% (454/579) of patients were newly diagnosed with TB, 20.6%. (119/579) had a previous episode of TB of which 3.4% (4/119) had extra pulmonary TB (EPTB). Of the new TB cases, 90.1% (409/454) had Pulmonary Tuberculosis (PTB) and 9.9% (45/454) had extra pulmonary TB.

4.2.2 Demographic data

The demographic data collected from the three research sites for the purpose of the study included gender and age. Ethnic group was not captured on patient files and therefore could not be used to determine ethnic distribution. The findings are presented in Tables 6 and 7.

Table 7 Gender of patients by site: TB clinics

Gender	Site A N=212	Site B N=162	Site C N=205	Total N=579
Male	n=109 (51.4%)	n=82 (14.2%)	n=102 (17.6%)	293 (50.6%)
Female	n=102 (48.1%)	n=80 (13.8%)	n=103 (17.8%)	285 (49.2%)
Missing Data	n=1 (0.5%)	0	0	1 (0.2%)

Table 8 Age of patients by site: TB Clinics

Age	Site A N=212	Site B N=162	Site C N=205	Total N=579
15-30	n=79 (39.5%)	n=54 (27%)	n=67 (33.5%)	200 (34.5%)
31-45	n=85 (32.2%)	n=82 (31.1%)	n=97 (36.7%)	264 (45.6%)
46-60	n=40 (48.8%)	n=16 (19.5%)	n=26 (31.7%)	82 (14.2%)
>60	n=6 (20%)	n=10 (33.3%)	n=14 (46.7%)	30 (5.2%)
Unknown	n=2 (66.7%)	n=0	n=1 (33.3%)	3 (0.5%)

The demographic data of the sample show a relatively even distribution in gender. Total male were 50.6% (293/579) and female were 49.2% (285/579). Mean age is reflected at 36 years across all sites. All ages from 15 years and above were included in the study.

4.2.3 HIV and ART analysis

The primary TB objective was to determine the proportion of all TB patients in the study who had developed TB after three months or more of ART treatment. Therefore the TB analysis was further broken down in Diagram 2 to show the percentage of patients that developed TB after having had three months or more of ART treatment.

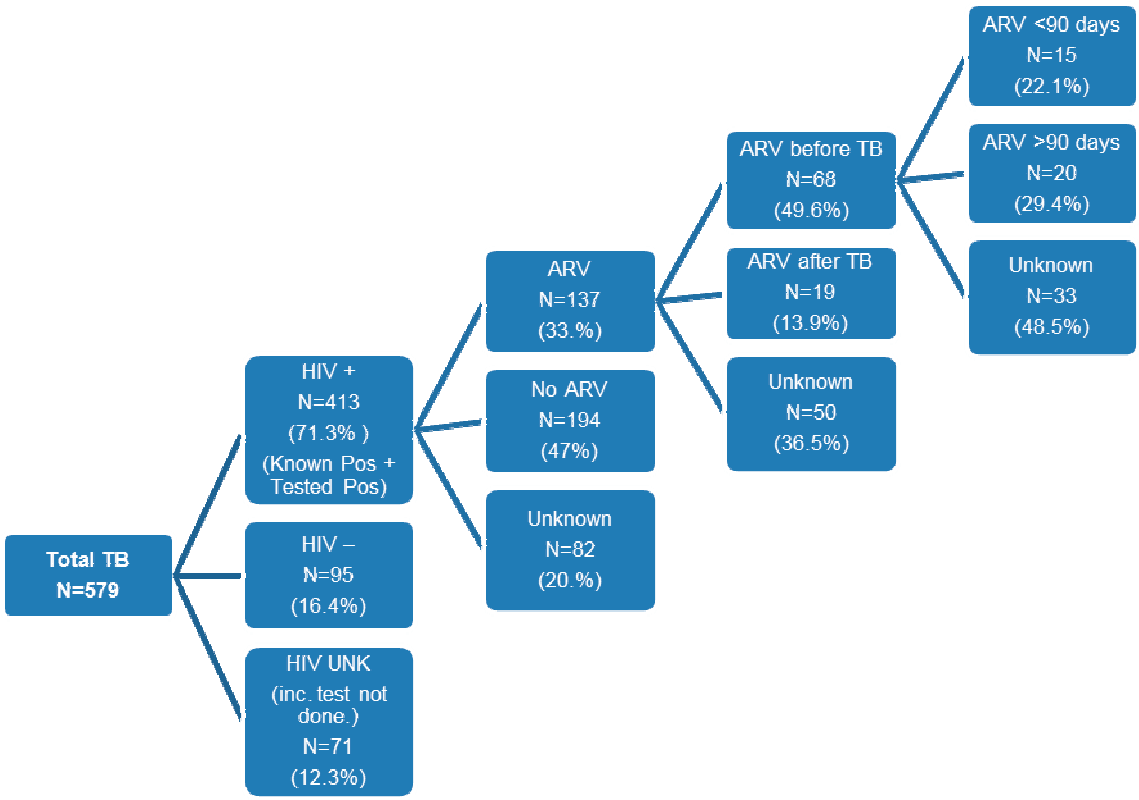

Diagram 2: TB Analysis showing percentage of patients that developed TB 3 months after ART

Of all the medical files of TB patients reviewed, 71.3% (413/579) were HIV-positive. The HIV positive patients included those who knew their HIV status (Known positive) 51.6% (299/579) and those who tested positive 20.2% (117/579) and 16.4% (95/579) were negative at time of TB diagnosis. 12.3% (71/579) of the medical files had missing data and were categorized as unknown. These include those that did not have a HIV test or no record of test done or results in patient medical file. Of the 413 HIV-positive patients, 33.2% (137/413) had commenced ART, 47% (194/413) were not on ART and the ART status was unknown for 20% (82/413). Nearly 50% (68/137) patients on ART had

commenced ART prior to TB diagnosis and treatment and 13.9% (19/137) had commenced ART after TB. Of the 137 patients on ART, 36.5% (50/137) had no records in the patient files of whether ART were commenced prior to TB or after. The notes usually just indicated 'ART commenced'. Of the 68 who commenced ART prior to TB diagnosis and treatment, 29.4% (20/68) had commenced ART more than 3 months prior to acquiring TB, 22.1% (15/68) commenced ART less than 3 months prior to TB, and 48.5% (33/68) were unknown due to missing data in patient files. The 48.5% of missing data could have significantly increased the number of patients that commenced ART prior to TB. This was a retrospective study where data were only collected from the TB register and patient medical files, missing data could not be rectified or filled in, but had to be captured as missing information. The biggest challenge for this study was that of missing data. Information that was current and required for the treatment of the patients' current problems, i.e. TB, were captured fully and fields related to HIV, CD4, viral loads and ART were often left blank or filled incompletely. In the TB clinic all TB information was completed fully but HIV and ART information was sparse and vice-versa in the ART clinic.

4.2.3.1 HIV-related tests

These tests included HIV rapid tests, ELISA when available, as well as CD4 and viral loads.

4.2.3.1.1 HIV status

Table 9 shows the HIV status of TB patients at the time of TB diagnosis. The table reflects HIV testing and status by site and in total.

Table 9 HIV status at the time of TB diagnosis

HIV Test done	Site A N=212	Site B N=162	Site C N=205	Total N=579
Yes	n=78 (36.6%)	n=50 (23.5%)	n=85 (39.9%)	n=213 (36.9%)
No	n=21 (38.9%)	n= 6 (11.1%)	n=27 (50%)	n=54 (9.3%)
Known positive	n=111 (37.1%)	n=104 (34.8%)	n=84 (28.1%)	n=299 (51.6%)
Unknown	n= 2 (15.4%)	n= 2 (15.4%)	n= 9 (69.2%)	n=13 (2.2%)

The findings reveal that of all patients, 51.6% (299/579) was aware of their HIV positive status at the time of TB diagnosis, and 46.1% (267/579) were not tested. Of these267, 79.8% (213/267) agreed to be tested and 20.2% (54/267) were not tested. Those not tested included those that refused to be tested and defaulters. Of this data there was 2.2% (13/579) that had missing data and is shown as unknown in Table 9. Missing data refers to data that were not recorded on the patients' medical files.

In keeping with the emphasis on HIV Counselling and Testing (HCT) at local clinics and institutions, analysis of the sample shows that more patients knew their HIV status than those that did not know their status but agreed to testing after counselling. However 20.2 % (54/579) of patients did not know their status and had not been tested. The numbers that were not tested included patients who refused testing, needed time to think about VCT, and did not go back to be tested. Of the 213 that tested, 54.9% (117/213) were HIV positive, 44.6% (95/213) negative, and 1 missing data (no data in patients' file). The South African Government launched a

major HIV counselling and testing campaign (HCT) in 2010 (South African Government Information. 2010). Since implementation in 2010, the HCT campaign has had a notable impact on the availability and uptake of HIV testing and treatment.

4.2.3.1.2 CD4 status

In 2009, the government raised the CD4 treatment initiation threshold from 200 to 350 cells/mm^3, to be in line with the latest WHO guidelines (DOH 2010:4).Initiating treatment below 350 cells/$mm^3$was implemented on the basis that it would improve the mortality rate amongst those that were HIV-infected. This change was implemented and substantiated by the SAPIT trial (Abdool Karim et al. 2010)mentioned in Chapter 2.

However, raising the threshold neglects the fact that most patients start treatment long after becoming eligible as shown in the data above. Patients generally start treatment only when they become seriously ill especially after presenting with TB symptoms or other serious AIDS associated conditions. Of the 579 TB patients 47% (194/579) were not on ART at time of TB diagnosis and 14% (19/194) of those that were on ART commenced after being diagnosed with TB. The following results on CD4, ART start date, and TB start date illustrate the late start of ART. Table 9 outlines baseline CD4 done for all patients who were HIV positive. Baseline CD4 for the purpose of the study was identified as the first CD4 test done. It was not restricted to any timeframe.

Table 10: Testing for CD4 lymphocyte count

CD4 Test Done	Site A N=158	Site B N=112	Site C N=141	Total N=411
Yes	n=127 (40.8%)	n=80 (25.7%)	n=104 (33.5%)	n=311 (75.7%)
No	n= 6 (37.5%)	n= 8 (50%)	n= 2 (12.5%)	n=16 (3.9%)
Unknown	n= 25 (29.8%)	n= 24 (28.6%)	n= 35 (41.6%)	n= 84 (20.4%)

Of all the TB patients, 53.7% (311/579) had CD4 tests recorded at baseline (that is first CD4 test done), 2.8% (16/579) did not and 29% (168/579) had an unknown CD4 count. Unknown included missing data (incomplete notes) in patient case notes. Written notes were minimal and when possible CD4 results and comments on whether CD4 was done or not were captured from notes. The baseline CD4 count for those tested is tabulated in Table 10 by site to show the percentage of patients at the various levels of CD4 ranging from below 50 cells/mm^3 to greater than 350 cells/mm^3, at time of TB diagnosis.

Table 11: CD4 lymphocyte count results

CD4	Site A N=95	Site B N=72	Site C N=95	Total N=262
<50	n=12 (34.3%)	n=9 (25.7%)	n=14 (40%)	n=35 (13.4%)
50-99	n=16 (39%)	n=7 (17.1%)	n=18 (43.9%)	n=41 (15.6%)
100 - 199	n=28 (39.4%)	n=18 (25.4%)	n=25 (35.2%)	n=71 (27.1%)
200-350	n=20 (29%)	n=25 (36.2%)	n=24 (34.8%)	n=69 (26.4%)
>350	n=19 (41.3%)	n=13 (28.3%)	n=14 (30.4%)	n=46 (17.5%)

'Test done' in Table 9 shows 311 but the above breakdown only reflects 262. The reason for this difference is that 49 of the 311 files had missing results. That means the question 'was CD4 done' in the patient medical files stated 'yes' but there was no results recorded in the patient medical files. Of 262 files, 13.4% (35/262) had CD4 below 50 cells/mm^3, 15.6% (41/262) were between 50 and 99, 27.1% (71/262) between 100 and 199, 26.4% (69/262) between 200 and 350 and 18% (46/262) had cd4 above 350 cells/mm^3. The proportion of patients with CD4 count less than 200/350cells/mm^3at time of TB diagnosis (secondary objective) was 37.3% (216) of 579 or as a percentage of those that had CD4 done was 69.5% (216) of 311.

4.2.4 Diagnosis

As per DOH guidelines (DoH, 2010:18), diagnosis of TB and commencement of treatment can be based on various forms of diagnosis rather than on sputum results alone. Table 6 gives an overview of the method of TB diagnosis of 579 patients. Type of diagnosis was analyzed on total sample size and not per clinic.

Table 12: Diagnosis method of tuberculosis

X-Ray	Mantoux	Sputum Smear	Sputum Culture	Other
n=300 (51.8%)	n=1 (1%)	n=216 (37.5%)	n=22 (3.7%)	n=35 (6%)

The common method for TB diagnosis was X-rays as shown in table 12, 51.8% (300/ 579) were diagnosed with TB based on X-rays and treatment commenced prior to sputum results, 37.5% (216/579) on sputum smears, 3.7% (22/579) on sputum culture as sputum smears were negative or indeterminate and 1% (1) on Mantoux. The 35(6%) results that are shown as 'other' include diagnoses by means of biopsies, ultrasound, pleural aspiration, and scans. These diagnoses are used to diagnose extra pulmonary TB. A study done by Y. Hanifa showed that 'CXR improved sensitivity substantially and allowed rapid treatment initiation' and suggested that it should be routine, where available, pending better point-of-care diagnostics(Hanifa, Fielding, Charalambous, et al., 2012:1252).

4.2.4.1 Baseline smear and culture results.

According to DOH guidelines each patient should produce two sputum samples for diagnosis (DOH, 2010: 18). The specimen is usually an early morning and a random spot specimen. Based on either positive specimen results treatment may be commenced. Two specimens were not collected in all cases. Also we must take into consideration that diagnosis of TB and treatment is not only based on positive smear results. A smear is a diagnostic tool used to determine if a patient has TB. According to Dorland's Medical Dictionary (Dorland, 1901) a sputum specimen is spread on a glass slide, stained, washed in acid solution and examined to detect acid fast bacilli (AFB) in a specimen. According to WHO (WHO, 2010), the revised definition of a new sputum smear-positive pulmonary TB case is based on the detection of acid fast bacilli (AFB+) in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system . The breakdown shown in Table 7 is smear and culture for specimen 1 and 2.

Table 13: Sputum AFB smear and culture results

Smear	Positive	Negative	Unknown	Total
1	n=210 (36.3%)	n=323 (55.8%)	n=46 (7.9%)	N=579
2	n=88 (15.2%)	n=205 (35.4%)	n=286 49.4%)	N=579
Culture				
1	n=26 (70.3%)	n=11 (29.7%)	0	N=37
2	n=3 (100%)	0	0	N=3

The results shown in Table 13 are based on the first sputum specimen (Smear 1) collected from the patient. Of all the TB patients 36.3% (210/579) had at least one acid fast bacilli (AFB+) in at least one sputum sample. All results recorded were either Positive or Positive (+, ++, +++). Smears for sample one, 55.8% (323/579) were negative, and 7.9 % (46/579) had an unknown result. For sample two, 15.2% (88/579) were positive smear, 35.4% (205/579) were negative and 49.4% (286/579) of results were unknown. The category 'unknown' includes missing data, unrecorded results, sputum not collected, or sputum collected after TB treatment had commenced. Not all specimens had cultures done. In line with policy (DOH, 2009: 21) a culture may be requested if there are indeterminate smear results or if diagnosis is made on X-ray and smear results are negative. As a result the breakdown of the culture results in Table 12 is not reflective of the entire sample (579). Only 6.4% (37) had cultures done on smear 1. Of these, 89.2% (33/37) were culture positive and 10.8% (4/37) were negative. Only 3 (0.5%) of smear 2 had cultures done and all 3(100%) cultures were positive.

4.2.5 TB Treatment

Once a patient is diagnosed for TB the patient is commenced on TB treatment and the duration and medication is based on whether the TB is new (first diagnosis of TB) or old (previous TB infection or treatment for more than a month with chemotherapy).

4.2.5.1 Previous TB

The data collected on previous TB revealed 95% (113/119) patients were treated for TB previously. The other 5% (6/119) can be accounted for as unknown or missing data. Previous TB data are not being fully captured by the clinic staff. Most often just a date and if treatment was taken is recorded. This again shows that significance of data capture is given to current condition and previous history is being ignored or seen as insignificant.

4.2.5.2 Current TB

All of the patients were commenced on TB treatment on diagnosis of TB, of which 76% (441/579) completed treatment and15.4% (89/579) had defaulted treatment. Defaulters included those people that defaulted treatment and when traced was found to be deceased. 8.5% (49/579) had missing or incomplete data in patient files.

Streptomycin is prescribed for patients that have had previous TB (DoH 2009: 36). The prescription of streptomycin for patients who have had previous TB varies at each site. If a patient reports to have had previous Streptomycin, any allergies to Streptomycin or refuses daily injections then Streptomycin is omitted. Therefore, as per data collected, only 37.8% (45/119) previous TB patients received Streptomycin.

Pyridoxine (Vitamin B6) 50mg daily is suggested for patients taking isoniazid to prevent peripheral neuritis however it may not be given routinely. It should be given to TB patients who are alcohol abusers, pregnant, diabetic or epileptic (DOH, 2009: 39). Complete details on Pyridoxine were not collected as prescription and issue of pyridoxine was not properly recorded in patients' files. Recording in patient chART were very sparse and often important information was omitted, as a result data could not be collected. Based on observation by the PI often pre-printed information in patient files are completed e.g. the regimen, but information that needs to be written in e.g. Pyridoxine, is omitted. This is the reason for large chunks of missing data from patient files.

4.2.5.3 Outcome

Outcome of TB treatment is assessed after six months of TB treatment based on the smear results, chest X-rays or completion of TB treatment (DOH, 2009: 41). The following definitions are used to describe the outcome of TB treatment:

Cured - A patient who was initially sputum smear-positive and who was sputum smear-negative in the last month of treatment and on at least one previous occasion.

Completed treatment - A patient who completed treatment but did not meet the criteria for cure or failure. This definition applies to sputum smear-positive and sputum smear-negative patients with pulmonary TB and to patients with extrapulmonary disease.

Died - A patient who died from any cause during treatment.

Failed - A patient who was initially sputum smear-positive and who remained sputum smear-positive at month 5 or later during treatment.

Defaulted - A patient whose treatment was interrupted for two consecutive months or more.

Not evaluated/Other - A patient whose treatment outcome is not known.

Cured - A patient who was cured or who completed treatment.

Table 14 shows the outcome after six months of TB treatment.

Table 14: TB outcome after six months of TB treatment

Outcome	Site A N= 210	Site B N=161	Site C N=205	Total N=579
Cured	n=79 (39.9%)	n=76 (38.4%)	n=43 (21.7%)	n=198 (34.2%)
Treatment Completed	n=74 (30.1%)	n=63 (25.6%)	n=109 (44.3%)	n=246 (42.5%)
Defaulted	n=46 (51.7%)	n=11 (12.3%)	n=32 (36%)	n=89 (15.4%)
Treatment Failure	0	0	0	0
Deceased	n=7 (20.6%)	n=6 (17.6%)	n=21 (61.8%)	n=34 (5.9%)
Other	n=4 (33.4%)	n=5 (41.6%)	n=3 (25%)	n=12 (2%)

Of all the medical files reviewed of patients on TB treatment, 34.2% (198/579) were cured, and 42.5% (246/579) had completed TB treatment. In total 76.7% (444/579) had successfully completed six months of treatment, 15.4% (89/579) had defaulted treatment and 5.9% (34/579) died. The other 2% (12/579) included unknown outcome due to incomplete information on patient chART and those that treatment was on-going at time of data collection. A set timeframe of 12 months was allocated thus ensuring patients commenced on treatment would have completed treatment and there would be outcome results. However due to defaulting, treatment is extended and sometimes restarted as a result treatment was still on-going at time of data collection. Treatment could be extended up to 18 months or even two years when retreating or relapse of TB as seen in patient case files.

4.2.6 ART cohort

The primary end point of the study was combined HIV and TB favourable clinical and treatment outcomes at six months. It was estimated that 75% of patients would have had a favourable TB outcome (cure and completion) and of these 66% would have had a favourable HIV outcome (undetectable viral load). Therefore it was estimated that with a combined favourable HIV and TB outcome of 50% and a 7% error, a sample size of 532 medical files was required for a 95% confidence at a power of 90%.

Based on the above assumption the researcher was to identify 532 patients in the ART clinic that had developed TB and data to be collected of those that had ART for three months or more at time of TB diagnosis. After the pilot study and random overviews of the ART clinics at the three sites it was realized that this will not be possible. The researcher instead reviewed patient files at the three sites between the period of January and May 2010, the same period that was used to collect all of the TB data at the TB clinics.

The researcher reviewed a total of 1245 patient medical files across the three sites. Patients' medical files were identified from the TB register and systematically extracted and reviewed for the period of January 2010 to May 2010. At two of the three clinics all files for this period were reviewed as the filing system and registers were systematic and easily accessible. At one clinic this was not possible. This site serves a larger community, however the researcher only managed to access 353 files. Files were being used daily and return of files to the filing room had a poor turnaround time. Also there was a poor filing system which made access and locating files difficult. Table 10 and Flow Chart 3 below gives a breakdown of what was obtained from these sites.

Table 15: ART data per site

	Site A N=353	Site B N=435	Site C N=457	Total N=1245
TB	n=204 (40.8%)	n=135 (26.9%)	n=162 (32.3%)	n=501 (40.2%)
No TB	n=110 (20.1%)	n=220 (40.3%)	n=216 (39.6%)	n=546 (43.9%)
UNK	n=39 (19.7%)	n=80 (40.4%)	n=79 (39.9%)	n=198 (15.9%)
	N=204	N=135	N=162	N=501
TB Prior to ART	n=164 (38.2%)	n=114 (26.6%)	n=151 (35.2%)	n=429 (85.6%)
TB 0-3 mths after ART	n=12 (40%)	n=11 (36.7%)	n=7 (23.3%)	n=30 (6%)
TB after 3 mths of ART	N=28 (14%)	N=10 (7%)	N=4 (2%)	42 (8.4%)

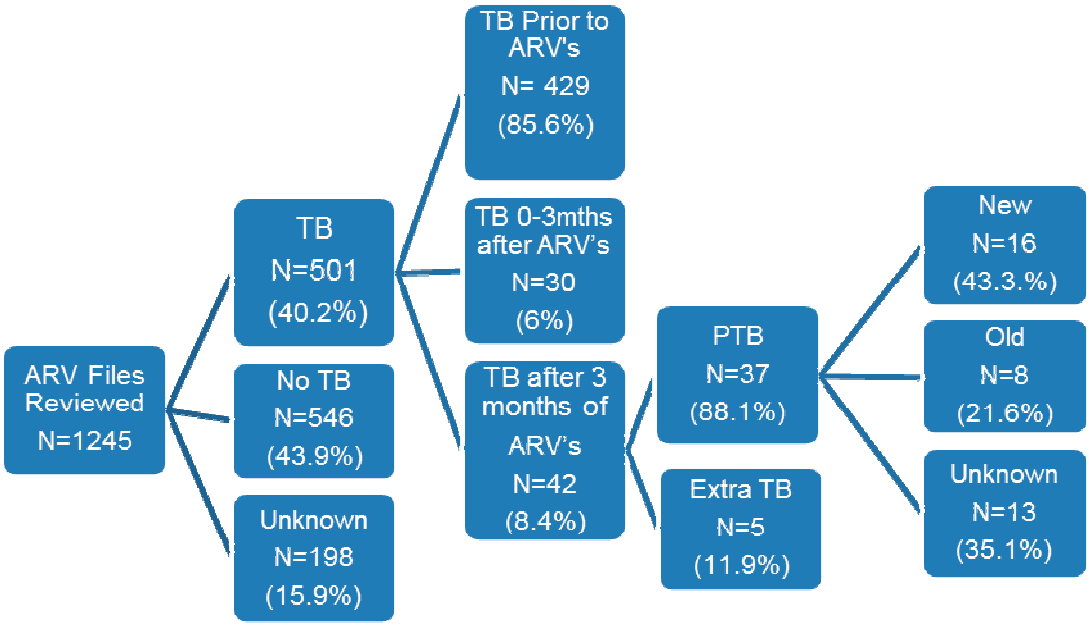

Diagram 3. ART Clinic Analysis.

Of all the medical files of patients on ART between January and May 2010 reviewed, 40.2% (501/1245) had TB and 43.9% (546/1245) had not had TB. 15.9% (198/145) of files reviewed had missing data and were recorded as 'unknown'. Of the 40.2% (501) of patients who had TB, 6% (30/501) were diagnosed with TB within three months of commencing ART, and 8.4% (42/501) after three months or more of ART.

In order to identify the primary objective 'patients that were newly diagnosed with TB three months or more after commencing ART', the 8.4% (42) patients who fitted this criterion were further analyzed. This breakdown is shown in Table 16.

Table16: Details of patients diagnosed with TB after three months or more of ART.

Site	TB			Extra-TB	Total
	New	Previous	Unknown		
	N=16	N=8	N=13	N=5	N=42
A	n=12 (42.85%)	n=4 (14.3%)	n =9 (32.1%)	n=3 (10.7%)	N=28 (66.7%)
B	n=3 (30%)	n=2 (20%)	n=3 (30%)	n=2 (20%)	n=10 (23.8%)
C	n=1 (25%)	n =2 (50%)	n=1 (25%)	n=0	N=4 (9.5%)

Amongst the patients that had TB after 3months or more of ART, 38.1% (16/42) were new TB cases, 19% (8/42) had previous TB, 30.9% (13/42) had missing data (Unknown) and 11.9 % (5/42) had extrapulmonary TB.

4.2.6.1 Gender

Of the patients that had TB three months or more after commencing ART, 61.9% (26/42) where women and 38.1% (16/42) were men.

4.2.6.2 HIV status at the time of TB diagnosis

97.6% (41/42) were known positive (i.e. they knew their HIV status at time of TB diagnosis and treatment). The other 2.4% (1/42) was counselled and tested positive.

4.2.6.3 CD4 and viral load

CD4 tests were done on 92.8% (39/42) patients that had TB after three months or more of ART therapy and the other 7.1% (3/42) had missing data (unknown). Data for viral load were recorded for only 9.5% (4/42) patients.

Table 17 shows the percentage of patients at the various levels of CD4 ranging from below 50 cells/mm^3 to greater than 350 cells/mm^3 at time of TB diagnosis.

Table 17: CD4 levels and patient percentage.

CD4	Total
<50	N=9 (21.4%)
50-99	N=8 (19%)
100 - 199	N=20 (47.7%)
200-350	N=2 (4.8%)
>350	N=3 (7.1%)
Total	42

Of the 42 patients that had TB after 3 months or more of ART therapy 21.4% (9/42) had CD4 counts below 50cells/mm^3,19% (8/42) were between 50 and 99cells/mm^3, 47.7% (20/42) had CD4 between 100 and 199, 4.8% (2/42) had CD4 between 200 and 350cells/mm^3 and 7.1% (3/42) had CD4 above 350cells/mm^3.

4.2.6.4 Outcome

TB outcome for the 42 patients that had TB after three months or more of ART therapy could not be measured as TB outcome was not recorded in patients ART files. On rare occasion a note was made on completion of TB medication. No dates or actual outcome was recorded. As mentioned previously, only data that were specific to that clinic that was required to treat the patients' current condition were captured. The lack of coordination of the TB and HIV outcomes between clinics is a reflection of the poor integration of HIV and

TB services. It was therefore not possible to derive a combined HIV-TB outcome measure as articulated in the protocol.

4.3 Conclusion

Chapter 4 presented and discussed the results of the study, using several tables and flow chART highlighting the primary objectives and giving breakdowns of collected data that represent the secondary objectives. The analysis brings to the fore many challenges and gaps that are apparent when patients conditions are treated separately, i.e. TB is managed but HIV status and ART management are ignored. Also the findings show that there is an uptake of ART only after TB diagnosis. Patients after HCT are not followed up for CD4 counts and start of ART. As a result patients present at the clinic only when they are very ill with TB symptoms and have very low CD4 counts. Table 5 shows 216 (82.4%) patients had CD4 below 350 cells/mm^3 at time of TB diagnosis and 147 (56%) had CD4 counts below 200 µcells.

Chapter 5 will highlight challenges and limitations of the study and draw final conclusion of data that was analyzed.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

5.1 Introduction

Chapter 5 draws conclusions based on the specific study objectives as outlined in Chapter 3. In addition there are some more general conclusions derived from the experience of carrying out the survey in DOH clinics that relate to burden of TB as well as TB/HIV co-infection, and from the state of clinical services providing for these conditions. In addition since both the TB clinics and ART clinics were visited certain conclusions can be drawn concerning the integration of the two services.

Field research at the clinics revealed a lack of adequate data recorded in patient medical files and poor filling systems. Consequently, large amounts of laboratory results and findings were not filed or recorded. For this reason, the study objectives were only partly realizable. The very lack of adequate data highlights the need to integrate TB and HIV services. This will be explained in more detail below. In addition some recommendations for the provision of integrated TB/HIV services are offered. These recommendations are in line with the current National Tuberculosis and ART Guidelines presented by the South African government.

5.2 Achievement of the study aims and objectives

The aims of the study were to determine what proportion of all patients with TB were established on ART at the time of TB diagnosis, and what their clinical and treatment outcomes were in different public health care facilities in the eThekwini region of KZN. Underlying this aim was the requirement for a better understanding of the potential need to treat these patients with second-line ART.

5.2.1 Objective 1

The first objective was to determine the proportion of all patients with TB who were established on ART at the time of TB diagnosis. The findings concluded that out of 137

patients who received ART: 49.6% (68/137) had commenced ART prior to TB diagnosis and treatment; 29.4% (20/68) had commenced ART more than three months prior to acquiring TB; and 22.1% (15/68) commenced ART less than three months prior to TB. However the above figures are not reflective of the desired objective due to missing data in patient medical files. Thirty-three files (48.5%) had inadequate data on ART treatment.

However, it is possible to gain an idea of the proportion of all TB patients who are on ART for more than three months at the time of TB diagnosis if one excludes the proportion of patients who have missing data. This obviously assumes that having a missing value is not associated with a particular variable. If this is done then one can determine that 81.3% (413/508) patients were HIV-positive.

Of the 413 HIV positive patients, 137 were taking ART of which 49.6% (68/137) had initiated before starting TB therapy and 43% had done so for more than three months. This gives a figure of 11% of all TB patients who are on ART for more than three months at the time of TB diagnosis. This is a significant proportion of all TB patients and underlines how important it is to determine if these patients are failing ART therapy and therefore developing TB. If so these patients would need to be started on second-line ART therapy.

5.2.2 Objective 2

The second objective was to establish the clinical characteristics of patients established on ART who were newly diagnosed with TB. This objective was only partly achieved where clinical characteristics could be established for CD4 counts. However, there was much missing data in the patient medical files.

Of the data available for the CD4 count it was established that:

- 13.4 (35/262) had CD4 counts below 50-cells/mm^{3}';
- 15.6 (41/262) were between 50 and 99;
- 27.1% (71/262) were between 100 and 199;
- 26.3 (69/262) were between 200 and 350; and
- 17.6 (46/262) had CD4 counts above 350-cells/mm^{3}.

The percentage of patients who had CD4 tests was 69.5% (216/311). It can be seen that patients who present with an opportunistic illness, in this instance TB, have their CD4 tested only at baseline. Repeat CD4 tests were either not done or results not recorded. In order to determine the clinical characteristics of patients established on ART repeat CD4 data is required at intervals to determine the improvement or regression of the CD4 count. It was therefore not possible to determine outcomes of therapy in terms of CD4 count.

5.2.3 Objective 3

The third objective was to evaluate the clinical management of patients established on ART who were newly diagnosed with TB.

This objective was not possible to achieve because little or no data were recorded in the patient medical files with regards to the clinical management of ART in the TB patient files, and with regard to the clinical management of TB in the patients ART files. As mentioned in Chapter 4, only data relevant to managing the patients' condition specific to the clinic were collected and entered into the files. At the TB clinic, all relevant TB data were collected and very few data on ART treatment were entered; only a basic 'yes/no' or a date was recorded. The opposite was relevant at the ART clinic: only data relevant to ART were collected. When a patient was diagnosed with TB or referred from the TB clinic for commencement of ART, only a note was recorded in the patients' medical files.

When a patient who had been established on ART (i.e. three months or more of ART) was diagnosed or suspected of having TB, the patient was referred to the TB clinic and a note was recorded on the ART file. There was no follow up information on confirmation of TB, commencement/completion of TB regimen or outcome of TB. Again lack of CD4 results or repeat CD4 counts not done made this objective less achievable.

The lack of data was therefore the biggest challenge in meeting the objectives of the study. TB and ART clinics were separate from each other; separate files and numbers were kept for each patient. There was no cross reference of patient file numbers so there was no way of tracing patients between the clinics to update or collect missing data.

5.2.4 Objective 4

The fourth objective was to evaluate the TB and HIV treatment outcomes of patients established on ART who developed TB.

While TB outcomes could be measured, they could not be related to HIV outcomes. TB outcomes could not be measured against improvements in CD4 counts because TB patients could not be traced back to the ART clinic or vice versa.Of the 579 medical files reviewed for patients on TB treatment, 34.2% (198/579) were recorded as cured and 42.5% (246/579) as TB treatment completed. In total out of all the TB patients 76.7% (444/579) had successfully completed their six months of treatment; 15.4% (89/579) had defaulted on their treatment; 5.9% (34/579) patients died; and outcomes were unknown for the remaining 2.1% (12/579) due to incomplete information on patients' chART, or treatment had not yet been completed at the time of data collection.

The above data provide a clear picture of successful outcomes of TB treatment despite its long duration of six months. However, it would be helpful to be able to associate the TB outcomes with ART treatment/outcomes in order to draw conclusions and make recommendations in respect of TB/HIV co-infection and the need to integrate TB/HIV services.

Secondary outcomes for the TB cohort were more achievable than the HIV cohort as shown below.

<u>TB</u>

a. Proportion of patients who were smear positive on smear 1 was 3.62% (21/579) and on second smear was 15.2% (88/579).
b. Proportion of patients tested for HIV was 86.7% (502/579), which included those that knew their status and those that were tested.
c. Proportion of patients tested for HIV and CD4; was 75.7% (311/411).
d. Proportion of patients with CD4 less than 200/350 depending on when ART were commenced as per the new DOH guidelines, was 69.5% (216/311).

e. Proportions of patients with favourable TB outcomes at two months (e.g. smear conversion): this was not achieved as sputum smear was not collected for all patients at a precise two-month interval. Any sample that was collected after the two-month interval was recorded as the two-month result.

f. Proportion of patients on ART with viral loads and CD4 after diagnosis of TB, was 31.5% (98/311).

g. Proportion of patients on ART with a CD4 above 200 at time of TB diagnosis was 14.8% (46/311).

h. Proportion of patients with documented ART and TB treatment-adherence problems was 15.4% (89/579).

HIV

a. Proportion of patients on TB treatment who switch from first line ART therapy to second-line ART therapy: there was no documented evidence of this in the patients' medical files.

b. Proportion of patients whose CD4 was below 200 at time of TB diagnosis was 88.1% (37/42).

c. Proportion of patients who had CD4 and viral loads within three months of TB diagnosis: no data were available in patients' medical files of repeat CD4 or viral loads after TB.

d. Proportion of patients with viral load undetected at time of TB diagnosis: no data were recorded in patients' files of viral load results.

e. Proportion of patient with increase in CD4 and decrease in viral load from baseline: no data were available to determine CD4 and viral load outcomes.

f. Proportion of patients on ART with favourable TB outcomes at two and six months: TB outcomes were not recorded in patients' ART medical file.

g. Proportion of patients with favourable HIV outcomes as determined by undetectable viral loads at the end of TB treatment: no data were available.

5.3 Limitations of the study

The study was retrospective; data were collected from registers as well as patient medical files. The study was therefore subject to several limitations which may be classified and explained in the following way:

5.3.1 Infrastructure

Inadequate space for filing and archiving meant that patient medical files could not be located or were lost. PI used all available resources to trace and recover patient medical file to the best of her ability.

5.3.2 Patient registers

Both the TB and ART clinics kept registers but these were not completed. The TB register had ART, HIV, CD4 data missing and the ART register had TB information missing. These files could not be cross referenced to trace patients from the TB clinic to the ART clinic, or vice versa.

5.3.3 Patients' medical files

Patients' files consisted of pre-printed forms aimed at collecting relevant TB information. These forms only established: whether the patient is on ART, the start date of ART treatment and the CD4 count. This information was often not completed. The same lack of data applies in the ART clinic. Where TB data were required, the form was often left blank. This was the reason for the large gap of missing data in the analysis. Where ever possible the researcher gathered as much data from the patients' medical files.

It was not possible to derive a combined HIV and TB outcome due to the large amount of missing data in the patient medical files. The TB clinic did not capture ART data and management and the ART clinic did not capture TB data and management despite the pre printed files and documents that contained question pertaining to ART or TB. The lack of recorded data about ART in the TB clinic and TB in the ART clinic is a reflection of poor

integration of HIV and TB services and a result contributing to suboptimal management of the co-infection.

5.3.4 Access to files at study sites

All the study sites were very busy DOH clinics. This meant that files were either being used or were not filed, thus accessing the files was challenging. The PI continuously followed up on outstanding files to ensure adequate data were collected.

From the above outcomes it is evident that due to the lack of data it is difficult to draw conclusions and make adequate recommendations. Being able to draw accurate information from clinics ensures that researchers can identify gaps and loopholes in our current management strategy and assist the DOH to better understand the HIV/TB co infection problem. Researchers may then confidently and without bias make recommendations and suggestions to properly address the crisis and contribute positively towards overcoming the current disease burden on our population.

5.4 Recommendations

Recommendations were made in regard to policies, management and practice, education and research.

5.4.1 Recommendations from the literature

From the literature review described in Chapter 2, it is known that there is a strong increase in TB in South Africa and that this increase is associated with HIV co-infection. “Infection with HIV is the most powerful known risk factor predisposing for Mycobacterium tuberculosis infection and progression to active disease, which increases the risk of latent TB reactivation 20-fold” (Pawlowski et al. 2012:np). Due to this and the fact that HIV continues to pose a threat, TB/HIV co-infection is a grave concern.

Since gaining additional evidence from randomized controlled trials, observational studies, operational research and best practices from programmatic implementation of the

collaborative TB/HIV activities WHO recognized the need for integration of TB and HIV services and established a policy that emphasizes the need to establish mechanisms for delivering integrated TB and HIV services, preferably at the same time and location (WHO. 2012:8).

According to the WHO Guidelines (WHO, 2012), TB/HIV collaborated clinics need to achieve the following goals:

a) To establish and strengthen the mechanisms of collaboration and joint management between HIV programmes and TB-control programmes for delivering integrated TB and HIV services, preferably at the same time and location;

b) To reduce the burden of TB in people living with HIV, their families and communities by ensuring the delivery of Intensified TB case findings and Isoniazid preventive therapy and Infection control for TB and the early initiation of ART in line with WHO guidelines;

c) To reduce the burden of HIV in patients with presumptive and diagnosed TB, their families and communities by providing HIV prevention, diagnosis and treatment. (WHO.2012:14)

5.4.2 Recommendations from the study

5.4.2.1 Policy

From the data presented in Chapter 4 and observations made by the PI: those patients that developed TB prior to ART as well as those that were on ART and who were newly diagnosed with TB; needed to be referred to the ART and TB clinics respectively for commencement of co-treatment.

The recommendation would be for DOH to draw up protocols and guidelines to implement and promote the integration of services. Integrating the two services would ensure a holistic approach to the HIV/TB co-infection epidemic.

Health care should always be aimed at holistic treatment of an individual. By separating the two infections and managing them separately other important factors are being neglected, for example psychosocial impact of co-infection and managing the intake of two medication regimens and their side effects.

By integrating the services DOH can address a major issue that the health system is being faced with currently. That is the economic factor of the health system and its effects on the patient and the health care system.

Having to visit two different clinics on two different dates can have financial implications and to a worker many constraints on getting so many days sick leave. Integrated services are easier for the patient to access in one visit. When health care is holistic and easily accessible it puts the patient into a comfort zone and the patient would want to access such a service.

5.4.2.2 Management/practice

It is important that TB clinics are able to initiate ART treatment and that ART clinics are able to screen and initiate TB treatment so that the services are integrated. This would mean that a client can access both services in one clinic. Staff can address issues related to both problems and give advice and refer as required. It promotes a holistic approach to the patients well being. Such integrated services will also help to reduce the challenge of defaulters. Once patients are started on TB treatment they may feel better and as a result if not educated well will feel there is no need to continue with ART and as a result default. Also the side effects of both drug regimens or the large intake of medication may cause a client to default treatment. As a result patients may have TB relapse or present with stage-4 AIDS.

Integrated services may lead to an increase in the uptake of TB and ART treatment due to the comprehensive management of the patient at one department. Patients that are referred to TB clinic may not go to the clinic due to, lack of knowledge, time and work constraints and inaccessibility of the clinic.

Integration will ensure that registers and notification of infections is not duplicated. Integrated patient records will ensure capture of accurate data for both infections. One of the challenges faced by the PI was the accessing of files. Due to space issues filling and archiving was poor. This may be eliminated in an integrated service as there will be no duplication of patient files, thus removing the strain on the filing systems and the need for space to keep two files for each patient. It will ensure easy access of patient information and data from which the institution can draw for monitoring and evaluation of its services.

5.4.2.3 Education

All nurses working at the clinics are Primary Health Care trained and able to identify and manage both infections, but due to specialisation and delegation only manage the infection that is specific to that clinic. All nurses should be able to deal with both infections on all levels. Nurses at both clinics need to be given refresher courses on the integrated management of HIV and TB. Nurses need to be constantly updated on the progress and outcomes of the integration of services. The importance of data collection and record keeping must be emphasized. With the roll out of Nurse Initiated and Management of ART(NIMART) all nurses should be afforded the training thus ensuring that nurses at the TB clinic can initiate ART rather than refer to the ART clinic for further management.

Community awareness has mainly been focused on HIV and the uptake of ART. An extensive awareness campaign needs to be implemented to make the community aware of the TB/HIV co-infection and the importance of ensuring both infections are treated simultaneously. More emphasis and education of communities should be placed on TB and the importance of completion of TB treatment while continuing ART.

5.4.2.4 Research

Nurses must be afforded the opportunity to analyse data that is collected and taught how to interpret their analysis. This will give them the opportunity to understand the need for research and how to use outcome results to monitor and evaluate their service. Research results may also be used by nurses to make recommendations to the DOH and use evidence based arguments to improve their services.

Table 18 gives an outline of the recommendations in the various areas discussed above.

Table 18: Outline of recommendations.

Area	Recommendations
Policy	1. Draw policies for integration of services. 2. Draw guidelines for implementation of integrated services. 3. Draw guidelines for monitoring and evaluation of integrated services.
gement and Practice.	**1.** Implement integrated services. **2.** Draw up integrated patient medical files. **3.** Ensure patient records are simple and user friendly to capture integrated data of both infections. **4.** Introduce integrated patient registers and notification. **5.** Introduce adequate filing and archiving systems for easy access and follow up. **6.** Implement monitoring and evaluation strategies to ensure adequate provision of integrated services.
tion	**1.** Train all clinical staff in management of both infections. **2.** Train all clinical staff on data collection and reporting. **3.** Train all clinical staff in Good Clinical Practice.
rch	**1.** DOH to build relationships with research organizations. Feedback from research conducted will assist in identifying issues and challenges.

5.5 Conclusion

Chapter 5 has explained to what extent the aim and objectives of the study were achieved. The study findings suggest that there are inadequacies in the current health system based on separate management of TB and HIV/AIDS, two serious diseases that are often found to co-exist.

The findings of the study reflect the degree of service provision for TB and HIV as well as the loopholes in effectively managing or researching TB and HIV when these diseases are treated as separate entities. The PI recognizes there are certain limitations that presented

problems during the study. However, where possible such problems were accounted for and strategies were employed to minimize their potential impact, as in the case of missing data in patient files. In the latter case, there was an attempt to recover data from registers, patient case notes and laboratory results.

The study reflects that there is a need for further research and data collection to determine the actual burden of the TB/HIV co-infection and to assess whether the introduction of TB/HIV integrated services significantly contributes to the reduction of HIV and TB rates.

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Appendix A

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

Demographics:	
1.Gender:	**Male** ❑ **Female** ❑
2.Age	_____yrs

HIV/CD4 STATUS	**Date Unknown =Nk/Nk/Nk Unk = Unknown**
4.HIV Test Done : **Yes** ❑ **No** ❑ **Known Positive** ❑ **UNK** ❑	
5.If Yes, date collected: _____ / _____ / _____ (dd/mon/yyyy)	
6.Results **Neg.** ❑ **Pos** ❑	
7.CD4 Test Done : **Yes** ❑ **No** ❑ **Unk** ❑ 8.Viral Load Test Done : **Yes** ❑ **No** ❑ **Unk** ❑	

9.CD4/Viral Load				
Interval	**CD4**		**Viral Load**	
	Date	**Results**	**Date**	**Results**

Signature _____ Date ____/_____/_____

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

1				
2				
3				
4				
Comments :				

10.ARV Therapy

ARV's commenced **Yes** ❑ Comment :

No ❑

UNK ❑

TDF= Tenofovir 3TC= Lamuvidine FTC= Emtracitabine EFV=Efavirenz NVP= Nevirapine d4T= Stavudine AZT= Zidovudine LPV/r= Lopinavir/Ritonavir.

ARV Drug	Start Date	Stop Date	Reason for Switch	Comment
TDF				
3TC				
FTC				
EFV				
NVP				
d4T				

Signature _____ Date ____/_____/_____

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

AZT				
Bactrim				
DDC				
LPV/R				
Other				
Unspecified ARV				

11.TB Diagnosis	
X-Ray	❑
Sputum Smear	❑
Sputum Culture	❑
CSF	❑
Other	❑ **Specify :**

Signature _____ Date ____/_____/_____

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

12.Sputum Collection

Culture Done Yes ❑ No ❑ UNK ❑

Visit	Date	Smear		Culture		DST	HAIN
		Specimen 1	Specimen 2	Specimen 1	Specimen 2		
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							

Signature _____ Date ____/_____/_____

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

12. TB History (Previous TB)

Did the patient have previous TB **Yes** ❑ **No** ❑ **Unk** ❑

Type of TB.

12.1 Pulmonary **Yes** ❑ **NO** ❑

12.2 Extra Pulmonary **Yes** ❑ **No** ❑

If12. 2 Identify (Tick Appropriate Condition)

Lymph Nodes ❑

Kidney ❑

Bone ❑

Spine ❑

Cardiac(Pericarditis) ❑

Abdomen (Peritonitis) ❑

Brain (Meningitis) ❑

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

13.TB Therapy (Previous)

TB Treatment **Yes** ❑ Comment:

No ❑

Unk ❑

H=Isoniazid ,R= Rifampicin ,Z=Pyrizinamide ,E= Ethambutol,S=Streptomycin

Outcome – Completed ,Defaulted , Unknown

TB DRUGS	Start Date	Stop Date	Outcome	Drug Resistance
Isoniazid				
Rifampicin				
Pyrizinamide				
Ethambutol				
Streptomycin				
Pyridoxine				
Other				

Signature _____ Date ____/_____/_____

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

15. Current TB

Current TB

Yes ❑ **No** ❑ **Unk** ❑ (If yes please tick new/old)

Old ❑

New ❑

Unk ❑

Type of TB.

15.1 Pulmonary **Yes** ❑ **NO** ❑

15.2 Extra Pulmonary **Yes** ❑ **No** ❑

If 15.2 Identify (Tick Appropriate Condition)

Lymph Nodes ❑

Kidney ❑

Bone ❑

Spine ❑

Cardiac(Pericarditis) ❑

Abdomen (Peritonitis) ❑

Brain (Meningitis) ❑

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

16.TB Therapy (Current)

9.TB Treatment commenced **Yes** ❑ Comment:

No ❑

Unk ❑

H=Isoniazid ,R= Rifampicin ,Z=Pyrizinamide ,E= Ethambutol,S=Streptomycin

Outcome – Completed -1,Defaulted -2 , Unknown-3, Ongoing -4

Regimen 1	Start Date	Stop Date	Outcome	Drug Resistance
Isoniazid				
Rifampicin				
Pyrizinamide				
Ethambutol				
Other(List)				
Multivitamin				

14.Weight

Visit	Date	Weight
Baseline		
1		
2		
3		

Signature _____ Date ____/_____/_____

ARV/TB DATA

Site Identification: ___ ___ ___ Reg.No _ _ _ _ _ _ Subject Initials: _____

Study No: ---------- Clinic_____

4		
5		
6		
7		
8		
9		
10		

17.Outcome: 6 Months	
Cured ❑	**Date of Outcome --/--/----**
Treatment Completed ❑	
Treatment Defaulted ❑	**Date of Last Visit --/--/----**
Treatment Failure ❑	
Deceased ❑	**Date of Death --/--/----**
Other ❑	
If Other Explain:	

Signature _____ Date ____/_____/_____

Appendix B

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot • your knowledge partner

10 September 2010 **MAILED**

Mrs S Veerasami
Department of Nursing
2nd Floor
Teaching Block

Dear Mrs Veerasami

Clinical management and treatment outcome of patients on both TB and antiretroviral therapy in the public sector, KwaZulu-Natal.

ETHICS REFERENCE NO: N10/08/255

RE : APPROVED

It is a pleasure to inform you that a review panel of the Health Research Ethics Committee has approved the above-mentioned project on 6 September 2010, including the ethical aspects involved, for a period of one year from this date.

This project is therefore now registered and you can proceed with the work. Please quote the above-mentioned project number in ALL future correspondence. You may start with the project. Notwithstanding this approval, the Committee can request that work on this project be halted temporarily in anticipation of more information that they might deem necessary.

Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly and subjected to an external audit.

Translations of the consent document in the languages applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Please note that for research at primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Hélène Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

Approval Date: 6 September 2010 Expiry Date: 6 September 2011

Fakulteit Gesondheidswetenskappe · Faculty of Health Sciences

Verbind tot Optimale Gesondheid · Committed to Optimal Health
Afdeling Navorsingsontwikkeling en -steun · Division of Research Development and Support
Posbus/PO Box 19063 · Tygerberg 7505 · Suid-Afrika/South Africa
Tel.: +27 21 938 9075 · Faks/Fax: +27 21 931 3352

Yours faithfully

MRS MERTRUDE DAVIDS
RESEARCH DEVELOPMENT AND SUPPORT
Tel: 021 938 9207 / E-mail: mertrude@sun.ac.za
Fax: 021 931 3352

Appendix C

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

14 January 2011

Dr. Alexander Pym
Medical Research Council, 491 Ridge Road
Overport
Durban
4041

Dear Dr Pym

PROTOCOL: An investigation into the management of patients established on antiretrovirals who are newly diagnosed with tuberculosis in the public Health Sector. REF: BE134/010

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received by BREC on 22 June 2010.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 14 January 2011 to queries raised on 11 November 2010 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 14 January 2011.

This approval is valid for one year from **14 January 2011.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** at a full sitting of the Biomedical Research Ethics Committee meeting to be held on **08 February 2011.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

25/Jan/14

Appendix D

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

TB RESEARCH UNIT (TBRU): CLINICAL AND BIOMEDICAL

491 & 460 Ridge Road, Overport, Durban, 4091
P.O. Box 70380, Overport, 4067, South Africa
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Dr. Mtshali
Phoenix Community Health Centre
32/36 Brookstone Place
Whetstone
Phoenix

Dear Sir

Re- Application for Permission to conduct Study.

Title: Clinical management and treatment outcome of patients on both TB and antiretroviral therapy in the public sector, KwaZulu-Natal

We would like to apply for permission to conduct the above study at the Phoenix Community Health Centre. It is a retrospective cohort study that will capture data from registers and case notes of patients from both the TB and ARV clinic respectively.

Your assistance would be greatly appreciated.

Thank you,
Yours Sincerely

Mrs. S. Veerasami. (Registered Nurse)
South African Medical Research Council,
Unit for Clinical and Biomedical Tuberculosis Research
sveerasami@mrc.ac.za
Tel: +27 31 2034918
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Dr. BM Roopsingh
7 Sanele Nxumalo Lane
Tongaat
4349

Dear Sir

Re- Application for Permission to conduct Study.

Title: Clinical management and treatment outcome of patients on both TB and antiretroviral therapy in the public sector, KwaZulu-Natal

We would like to apply for permission to conduct the above study at the Tongaat Community Health Centre. It is a retrospective cohort study that will capture data from registers and case notes of patients from both the TB and ARV clinic respectively.

Your assistance would be greatly appreciated.

Thank you,
Yours Sincerely

Mrs. S. Veerasami. (Registered Nurse)
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Unit for Clinical and Biomedical Tuberculosis Research
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Dr. Hadebe
Kwa Mashu Poly Clinic
P/Bag X013
Kwa Mashu
4360

Dear Sir

Re- Application for Permission to conduct Study.

Title: Clinical management and treatment outcome of patients on both TB and antiretroviral therapy in the public sector, KwaZulu-Natal

We would like to apply for permission to conduct the above study at the Kwa Mashu Poly Clinic. It is a retrospective cohort study that will capture data from registers and case notes of patients from both the TB and ARV clinic respectively.

Your assistance would be greatly appreciated.

Thank you,
Yours Sincerely

Mrs. S. Veerasami. (Registered Nurse)
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Appendix E

HEALTH
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www.kznhealth.gov.za

Reference : HRKM200/10
Enquiries : Mrs G Khumalo
Telephone : 033 – 3953189

11 January 2011

Dear Mrs S Veerasami

Subject: Approval of a Research Proposal

1. The research proposal titled **'Clinical management and treatment outcome of patients established on antiretroviral therapy who are newly diagnosed with TB in the public sector, KwaZulu-Natal'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at **KwaMashu Polyclinic, Tongaat & Phoenix Community Health Centres.** Please seek support to conduct your study at **Sinikithemba clinic** from eThekwini Municipality as this is not a public clinic.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mrs G Khumalo on 033-3953189.

Yours Sincerely

Mrs E Snyman
Interim Chairperson, Health Research Committee
KwaZulu-Natal Department of Health
Date: 13/01/2011

Appendix F

ELIZABETH LE SUEUR
Language practitioner
for expert wordwork

editburo@gmail.com 073-254-4995

AFFIDAVIT

This is to certify that I, the undersigned, have completed the language editing of the M.Health Sciences thesis of Sowbagium Veerasami, titled:

A retrospective study of the clinical management and treatment outcomes of patients established on antiretroviral therapy who are newly diagnosed with tuberculosis in the public sector, KwaZulu-Natal.

I am satisfied that the academic style and language usage are of very high standard.

ELIZABETH LE SUEUR (BA Hons)
EDITBURO

20 Forest Drive
PINELANDS
7405

20 February 2013

Yagen Naidoo
Technical Editor

Yagennaidoo15@gmail.com 074 786 0579

AFFIDAVIT

This is to certify that I, the undersigned, have completed the technical editing of the M.Health Sciences thesis of Sowbagium Veerasami, titled:

A retrospective study of the clinical management and treatment outcomes of patients established on antiretroviral therapy who are newly diagnosed with tuberculosis in the public sector, KwaZulu-Natal.

I am satisfied that the technical editing are of very high standard.

YAGEN NAIDOO
SHAHJU BUSINESS SOLUTIONS

69 Cardgrove Place
Grove End
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DURBAN
4058

20 February 2013