INCIDENCE OF TUBERCULOSIS AMONGST HIV POSITIVE CLIENTS WHO RECEIVED ISONIAZID PREVENTIVE THERAPY (IPT)

by

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submitted in accordance with the requirements for the degree of

MASTER OF PUBLIC HEALTH

at the

UNIVERSITY OF SOUTH AFRICA

SUPERVISOR: PROF L ROETS

FEBRUARY 2015
DECLARATION

I declare that INCIDENCE OF TUBERCULOSIS AMONGST HIV POSITIVE CLIENTS WHO RECEIVED ISONIAZID PREVENTIVE THERAPY (IPT) is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

SIGNATURE

Full names: Emmanuel Ikechukwu Okoli

DATE

14 February 2015
INCIDENCE OF TUBERCULOSIS AMONGST HIV POSITIVE CLIENTS WHO RECEIVED ISONIAZID PREVENTIVE THERAPY (IPT)

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ABSTRACT

The research objectives were to describe the age and gender of adult HIV positive clients on ART who received IPT; the incidence of tuberculosis among clients that received IPT and the defaulter rate among those that were commenced on IPT. Quantitative non-experimental descriptive retrospective cohort study was undertaken to ascertain the incidence of tuberculosis among adult HIV positive clients who received IPT. 104 clinic records of HIV positive adult clients accessing care at Isithebe Clinic, iLembe-South Africa who were commenced on IPT between 01 July 2010 and 30 November 2011 were analysed. The study found that 66 of 104 (63.5%) study respondents completed the course of IPT and the majority of those that defaulted were due to poor quality of care. Gender was statistically found to have played a role on whether a patient completes IPT. None of the study respondents that completed IPT was diagnosed with TB disease.

KEY CONCEPTS

AIDS; viral load; CD4+ cells; adherence; adult; antiretroviral therapy; Human immunodeficiency virus (HIV); Isoniazid preventive therapy (IPT); tuberculosis; incidence; demographic characteristics.
ACKNOWLEDGEMENTS

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CHAPTER 1

Orientation to the study

1.1 INTRODUCTION

With an estimated 5.6 million people living with HIV in 2011, South Africa’s epidemic remains the largest in the world (National Department of Health [NDOH] 2012). South Africa is also the country with the third highest tuberculosis (TB) burden globally, only lagging behind China and India, which have significantly larger populations (NDOH, 2011:4). The World Health Organization (WHO) (2012:151) reported that an estimated 500 000 people living in South Africa, including ones who were HIV positive, contracted TB in 2011.

Infection with human immunodeficiency virus (HIV) has been identified as the strongest risk factor in the reactivation of latent or new Mycobacterium tuberculosis infection to active TB disease. TB is also the commonest cause of morbidity and mortality among the HIV-infected population in South Africa and studies have shown that TB accelerates HIV disease progression (NDOH 2010b:2).

Isoniazid preventive therapy (IPT) is one of the interventions recommended by the WHO and the South African NDOH for the prevention of progression to active TB disease in people living with HIV (PLHIV). However, no known scientific study has been undertaken in iLembe district regarding the incidence of TB among HIV-positive clients who received IPT.

1.2 BACKGROUND TO THE RESEARCH PROBLEM

Since the first report of HIV/AIDS was made by two physicians in the United States of America (USA), the number of people living with the disease has steadily increased and the epidemic moved into a generalised state impacting on many segments of society. An estimated 34 million people were living with HIV at the end of 2011 (UNAIDS, 2012:4). The Joint United Nations Programme on HIV and AIDS (UNAIDS) further
indicates that sub-Saharan Africa still bears an inordinate share of the global HIV burden. An estimated 69% of people living with HIV (PLHIV) globally reside in sub-Saharan Africa. With an estimated 5.6 million people living with HIV in 2011, South Africa’s epidemic remains the largest in the world (NDOH 2012). KwaZulu-Natal province has consistently recorded the highest provincial HIV prevalence since 1990 (NDOH 2010a:43).

The population of iLembe District where the study was conducted grew from 568 498 in 2006 (Enterprise iLembe [s.a.]:13) to 606 809 in the latest census report (SSA 2012:117). Only about 28% of the population were formally and informally employed at the end of the second quarter in 2011. In this district, the not-economically active persons account for 64.2% of the district population (Enterprise iLembe [s.a.]:17). The reported high unemployment and resulting poverty noted in the district has been shown to be associated with increased exposure to HIV and other sexually transmitted infections (STIs) (Buvé, Bishikwabo-Nsarhaza & Mutangadura 2002:2014). HIV prevalence among antenatal women was 35.4% in 2011 (NDOH 2012:17) while the HIV prevalence for the entire iLembe population was 16.6% as in the first quarter of 2011 according to Enterprise iLembe.

TB has existed in the world for centuries. The incidence of TB was generally on the decline in the world until the early 1980s (FPD 2010a:151). The Foundation for Professional Development (FPD) indicates that from the mid 1980’s, an increase of cases was reported in the USA, parts of South East Asia, and East, Central, West and Southern Africa. While various factors contributed to the upsurge in the world TB burden, the groups with the greatest increase in TB were also the groups with the highest HIV rates (FPD 2010a:151).

From a recorded 7-8 million cases in 1993 when the WHO declared TB a global public health emergency, the spread of TB increased to about 9 million new cases in 2011 (WHO 2011b:3; 2012:3). TB is the second leading cause of death from an infectious disease worldwide after HIV, accounting for an estimated 1.4 million deaths in 2011. This included an estimated 430 000 deaths from TB among PLHIV (WHO 2012:3).

South Africa is the world’s third largest TB burdened country in the world, lagging behind China and India, which have significantly larger populations (NDOH 2011a:4).
South Africa has the fifth-largest DR-TB burden in the world due largely to the high prevalence of HIV in the country and inadequate management of TB (NDOH 2011b:4). An estimated 500 000 people in South Africa contracted TB in 2011 with 66% of them occurring in PLHIV (WHO 2012:151). The WHO further indicates that about 25 000 of the deaths that occurred in the country in 2011 were due to TB disease which has an incidence rate of 993 per 100 000 people.

ILembe District in KwaZulu-Natal where the study was carried out also has a high TB burden. According to a report emanating from the KwaZulu-Natal Tuberculosis Programme, a total of 3643 PLHIV were diagnosed with TB disease in the district in 2012 (KZN Tuberculosis Programme 2012). This figure represents 62.1% of the absolute number of clients diagnosed with TB disease in the district. However, 13% of them are yet to test for HIV.

HIV is the strongest risk factor yet recognised in the reactivation of latent or new Mycobacterium tuberculosis infection to active TB disease (WHO, 2011a:1). The increased risk of active TB occurs soon after HIV sero conversion and doubles by the end of the first year of HIV infection (Granich, Akolo, Gunneberg, Getahun, Williams & Williams 2010:S215). In 2011, about 1.1 million PLHIV were newly diagnosed with TB, representing 12.4% of the global total number of PLHIV (UNAIDS 2012:54).

The WHO (2011a:1) has provided clear recommendations about interventions needed to prevent, diagnose and treat TB in PLHIV. The recommendations are collectively referred to as “collaborative TB/HIV activities”. They include HIV testing of TB patients, provision of ART and Cotrimoxazole Preventive Therapy (CPT) to TB patients living with HIV, HIV-preventive services for TB patients, intensified TB case-finding among people living with HIV, Isoniazid preventive therapy (IPT) for PLHIV who do not have active TB and infection control in healthcare and assembly settings. Active TB screening offers the opportunity to provide preventive therapy for those who do not have symptoms and signs of TB.

IPT refers to the intake of isoniazid by individuals with latent infection with Mycobacterium tuberculosis in order to prevent the progression to active TB disease amongst People Living with HIV (NDOH 2010b:2). Adults and adolescents living with HIV who have an unknown or positive tuberculin skin test (TST) status and who are
unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care (WHO 2011a:6). The WHO strongly recommends with high quality of evidence that IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women. In practice however, TST which identifies people with latent TB infection often constitutes an impediment for the provision of IPT. It is no longer required compulsorily to identify people eligible for IPT in the South African public health setting (NDOH 2010b:4). IPT is thus one of the interventions recommended by the WHO that reduce the morbidity and mortality from TB in PLHIV (WHO 2011b:1). The protective effect of TB preventive therapy is expected to last for approximately 18 months and therefore, the therapy should be given once only within this period (NDOH 2010b:5).

The theoretical foundation of the study is based on the submission by WHO (2011:71) that high quality of evidence exists to the fact that provision of IPT reduces incidence of active TB disease in individuals affected by HIV/AIDS. The study was thus carried out to ascertain the veracity of this theory in a rural setting located in iLembe district, South Africa.

1.3 RESEARCH PROBLEM

There is a need for scientific evidence regarding the incidence of TB among HIV-positive clients who received IPT in Isithebe Primary Healthcare Centre (PHC) within the 18-month period that the protective effect of IPT is expected to last. Accordingly, the researcher undertook this evidence-based study to explore and reveal the impact of isoniazid as a preventive therapy meant to protect HIV-positive patients.

1.4 AIM

The aim of the study was to describe the incidence of TB amongst HIV-positive clients who received IPT in Isithebe PHC.

1.5 RESEARCH OBJECTIVES

The research objectives were to describe the
• demographic characteristics (age and gender) of adult HIV-positive clients on antiretroviral therapy who received isoniazid preventive therapy
• incidence of TB among clients who completed a 6-month course of isoniazid preventive therapy
• defaulter rate for adult clients who commenced isoniazid preventive therapy

1.6 RESEARCH DESIGN AND METHODOLOGY

1.6.1 Research design

A research design refers to the overall structure or plan for the research (Bowling 2009:158). The researcher chose a quantitative non-experimental descriptive retrospective cohort study to ascertain the incidence of TB among adult HIV-positive clients who received a six-month course of IPT at the clinic between July 2010 and November 2011. A non-experimental design was considered appropriate for the study because there was no manipulation of the independent variables, no intervention, and the setting was not controlled (Brink, Van der Walt & Van Rensburg 2012:112).

A descriptive study refers to a simple description of the health status of a community based on routinely available data or on data obtained in special surveys (Bonita et al 2006:40) therefore the study was descriptive. In studies with retrospective designs a phenomenon existing in the present is linked to phenomena that occurred in the past (Polit & Beck 2012:224). The study was retrospective as data for the study was collected from records of HIV-positive patients who accessed IPT from Isithebe Clinic between July 2010 and November 2011. The study thus aimed to explore whether TB in the study population was linked to their intake of IPT within the designated period. A cohort study was chosen because the records of a group of people who share certain characteristics, which in this case were HIV-positive clients commenced on IPT, were followed during and after treatment (Joubert & Ehrlich 2007:79). The variables were not manipulated (Grove, Burns & Gray 2013:215) (see chapter 3 for discussion).

1.6.2 Research setting

The study was carried out at Isithebe Clinic located in iLembe Health District, KwaZulu-Natal Province, South Africa.
1.6.3 Population

A research population refers to the whole collection of cases in which a researcher is interested while the accessible population is the cases that conform to the set study criteria and are available for the study (Polit & Beck 2012:273).

The accessible population for the study were the 104 clinic records of HIV-positive patients accessing care at Isithebe Clinic who were aged over 18 and were started on IPT between 01 July 2010 and 30 November 2011. Chapter 3 discusses the population fully.

The target population is the aggregate of cases that the study generalised and in this study were the entire HIV-positive adult clients that received IPT in iLembe district.

1.6.4 Sampling

All the patients’ records that met the inclusion criteria were used for the study. They were 104 HIV-positive patients that were enrolled on IPT within the period being studied according to the daily clinic register after data cleaning.

To be included in the study, the patients had to be HIV-positive adults aged 18 and older, to have been screened for TB and commenced on IPT within the stated period.

The records of patients who were stopped from continuing IPT due to adverse drug reactions; died before completing the therapy; transferred out of the clinic within the period under review, or were lost to follow-up were excluded.

1.6.5 Research technique

The researcher used a data-gathering sheet to compile information from the identified clinic records and registers. The data included the patient’s age at the commencement of IPT; gender; date of commencement of IPT; monthly collection of INH for IPT; indication of whether patient completed the full course of IPT; any other co-morbidity; any diagnosis of TB after the IPT, and an indication of when the diagnosis of TB
disease was made, where appropriate. The compilation of the data was done solely by the researcher (see chapter 3 for detailed discussion).

1.6.6 Data collection

The daily clinic attendance registers, IPT register and the folders of the patients were the patients’ records utilised for the study. The choice of review of records was to minimise cost and time, yield data that could not be influenced by the project and also allow for comparison. Where there was incomplete data, other clinic or laboratory records were used as much as possible (Katzenellenbogen & Joubert 2007:108). For the purpose of this study, incomplete information regarding the TB treatment was sourced from the TB register. The electronic ART patient records maintained at the facility were also used to access information regarding treatment of the patient missing from the aforementioned records. Strict confidentiality was maintained while collecting the data and the names of the patients were replaced with unique letters on the data capture sheet.

1.6.7 Data analysis

1.6.7.1 Data handling

Before full analysis, issues concerning data collection process were reviewed. Information regarding the extent of missing data, data on the characteristics of respondents and data on the setting in which the information was collected were properly reviewed (Katzenellenbogen & Joubert 2007:117).

1.6.7.2 Statistical processing

Descriptive statistics was used to summarize and describe the data in a concise form (Joubert 2007:137). The clinic records of all the clients who commenced IPT between 01 July 2010 and 30 November 2011 and met the inclusion criteria were analysed. Their records up to 15-30 months of commencing IPT were followed and the proportion of those diagnosed with TB before the end of that period was indicated. The percentage of the participants who were male or female and the percentage of patients who adhered
to their medications and those who did not go to the clinic to collect the full 6-month course of IPT were analysed.

Analysis of the data was done using the Statistical Package for the Social Sciences (SPSS). The test statistic was calculated by applying the appropriate statistical formula using the sample data collected from the study. Analysis was undertaken to measure the associations between intake of IPT and incidence of TB among the study participants with the assistance of a statistician.

1.6.8 Validity and reliability

The quality of a research instrument is determined by its validity and reliability (see chapter 3).

1.6.8.1 Reliability of the data-collection instrument

Reliability is the extent to which measures are consistent or repeatable over time (Brink et al 2012:157). The reliability of the instrument is the consistency with which it measures the target attributes (Polit & Beck 2012:331). It was assumed that the precision and sensitivity of the laboratory equipment used in conducting HIV screening, TB and CD4 testing had been taken care of by the relevant authorities at National Health Laboratory Service at Stanger Provincial Hospital. Thus repeated administration of the data-collection instrument was not expected to change the responses from the records. The file clerk, data capturer and ART nursing staff assisted in retrieving the clinic records of the identified patients. They were not remunerated though the researcher provided them with refreshments. The data entries were made solely by the researcher. This ensured reliable data capturing.

1.6.8.2 Measures to ensure validity

Polit and Beck (2012:336) describe validity as “the degree to which an instrument measures what it is supposed to measure”. In this study, the researcher applied face, content, construct and criterion validity (see table 3.9).
1.6.8.2.1 Internal validity

In order to ensure internal validity, the researcher made every effort to reduce bias, including selection and information bias. Efforts were made to avoid any form of bias that could invalidate the results of the study. A biased study result suggests one that does not represent the truth (Myer & Karim 2007:160). The researcher under guidance from the supervisor as well as a scientific committee in the Department of Health Studies at UNISA checked the data-collection instrument before commencing the study. Similar responses should be expected to ensure internal validity of the collection instrument.

The clinic records of the clients who received IPT within the indicated period and met the selection criteria were utilised for the study. This eliminated selection bias as sampling was not used to select the clinic records used for the study. All the records that fulfilled the requirements were used.

Information bias was avoided by ensuring that the variables are measured in the same way (Myer & Karim 2007:163). The researcher who collated the data did not have a working knowledge about the participants. Prior to data analysis, the District Data Coordinator was approached to cross-check the entries made.

1.6.8.2.2 External validity

External validity refers to the extent to which study findings can be generalised beyond the sample used in the study (Grove et al 2013:202). Polit and Beck (2012:250) indicate that external validity concerns the extent to which it can be inferred that the research findings hold true over variations in people, conditions and settings. Due to the study population which was far less than the population of South African adults that received IPT and the difference in the study setting when compared to other areas of the country, the results of the study cannot be generalised to the entire population of adults aged over 18 that received IPT from other centres in the country. However, in patients that access care in areas with similar developmental status in the province, the outcome of the study can be generalised to them.
1.6.9 Ethical considerations

Ethics deals with matters of right and wrong. Ethical considerations are essential to the design of any research involving human subjects in order to protect the rights of the participants.

Ethical approval for the study was obtained from the Higher Degrees Committee of the Department of Health Studies (Research Ethics Committee), University of South Africa (see Annexure D). Permission for the study was also obtained from the KwaZulu-Natal Department of Health, iLembe District Department of Health and the Management of Isithebe Clinic before embarking on the study (see Annexures C and E). In order to maintain anonymity and confidentiality, the actual names of the participants whose records were used for the study were not indicated in the data-collection sheet. In place of the actual names, a code was used for identification. All the documents relating to the study will be stored away from public access for at least five years. The electronic data will be password-protected to ensure denial of access to the data by unauthorised individuals.

1.7 SCOPE OF THE STUDY

The study focused on the adult HIV-positive clients that received IPT in Isithebe Clinic between July 2010 and November 2011. The findings of the study will be used to describe their demographic characteristics and the incidence of TB among those who completed IPT. The defaulter rate to IPT was also ascertained.

1.8 SIGNIFICANCE OF THE STUDY

The outcome of the study will be shared with the relevant stakeholders including the facilities where the study was conducted, the District and the provincial department of Health. It is expected that this will encourage clinicians working at the various clinics to intensify the use of IPT as a form of protection against TB infection. This is important since no known scientific study has been carried out in iLembe regarding the efficacy of IPT. Strategies aimed at controlling TB among HIV-positive clients that will be recommended to the health authorities will assist in strengthening existing IPT policy. It
is envisaged that the findings of the study when shared with HIV-positive patients will further encourage them to accept IPT and ensure adherence to the medication.

1.9 DEFINITION OF CONCEPTS

Acquired Immune Deficiency Syndrome (AIDS)

AIDS refers to the symptoms and sicknesses that people infected with human immunodeficiency virus (HIV) eventually develop because of their weakened immune systems (Wilkins 2010:386).

Viral load

Viral load means the concentration of HIV ribonucleic acid (RNA) in the blood plasma (Wilson, Cotton, Bekker, Meyers, Venter & Maartens 2008:48). It indicates how much HIV there is in the blood, how quickly it is replicating, and how quickly a patient is progressing towards AIDS and subsequent death.

CD4+ cells

CD4+ cells refer to those T-lymphocyte components of white blood cells that are directly and indirectly destroyed by HIV (Wilson et al 2008:49). Wilson et al (2008:49) further indicate that the CD4+ cells play a central stimulatory role in the immune system and their count indicates the stage of the disease. When their numbers fall due to the exhaustion of the regenerative capacity of the immune system occasioned by prolonged destruction by HIV, the affected individual is suppressed immunologically.

Adherence

Haynes, Ackloo, Sahota, McDonald and Yao (2005:2) define adherence as how patients follow the instructions they are given regarding intake of prescribed treatments. Zuurmond (2008:5) describes adherence as taking the doses of drugs and sticking to the treatment plan thus taking the correct dose of drugs at the correct time and in the correct way.
Adult

Adult means a fully grown person who is legally responsible for their actions (*Oxford Advanced Learner’s Dictionary* 2010a:20).

**Antiretroviral therapy**

Antiretroviral therapy refers to the use of at least 3 drugs in combination in order to keep viral load suppressed (Wilson et al 2008:469). Wilson et al (2008:469) add that the therapy is life-long as it reverses the progression of HIV disease by reducing the HIV viral load in the blood and does not cure HIV. Treatment-naive patients are usually initiated on triple therapy, which consists of one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitor (NRTI) in combination (NDOH 2010c:13). The NDOH (2010c:20) further indicates that a third class of drug known as protease inhibitor (PI) is introduced to replace the NNRTI as part of the second-line treatment for patients failing first-line regimen.

**Human Immunodeficiency Virus (HIV)**

HIV is a single-stranded ribonucleic acid (RNA) retrovirus of the Lentivirus family that causes AIDS. After mucosal exposure, the virus infects the CD4 cell resulting in the attrition of the CD4 cell population which are pivotal in orchestrating the immune system of the body. The depletion of the CD4 cells renders the body susceptible to various opportunistic infections (Wilkins 2010:387).

**Isoniazid preventive therapy (IPT)**

This refers to the intake of isoniazid by individuals with latent infection with *Mycobacterium tuberculosis* in order to prevent the progression to active TB disease (FPD 2010b:127). Isoniazid is a drug used in the treatment of TB when combined with other drugs and for prophylaxis of TB when used alone (SAMF 2010:317).
Tuberculosis (TB)

Tuberculosis is an infectious disease caused by infection with a microorganism called *Mycobacterium tuberculosis* (Reid 2010:688). *Mycobacterium tuberculosis* is spread by the inhalation of aerosolised droplet nuclei from other infected patients.

**Incidence**

The incidence of a disease represents the rate of occurrence of new cases arising in a given period in a given population at a given point in time (Bonita, Beaglehole & Kjellström 2006:18).

**Demographic characteristics**

Demographic characteristics refer to the features of populations and include all aspects of population structure and changes which can be measured numerically (Joubert & Ehrlich 2007:24).

**1.10 OPERATIONAL DEFINITION OF CONCEPTS**

**Acquired Immune Deficiency Syndrome (AIDS)**

Where the records used for the study indicated AIDS, it meant that the patient had symptoms and sicknesses that people infected with human immunodeficiency virus (HIV) eventually develop because of their weakened immune systems (Wilkins 2010:386).

**Viral load**

According to the South African guidelines which were used throughout the study, it is deemed undetectable when the count is less than 400 copies/ml of blood (NDOH 2010c:19).
CD4+ cells

The readings recorded for CD4 cell count were those reported by the National Health Laboratory Service in Stanger Hospital where the tests were done.

Adherence

A research participant whose record was utilized for the study was deemed to have adhered to a course of IPT if not more than one treatment interruption was recorded during treatment and the 6-month therapy was taken within a 9-month period (NDOH 2010b:7).

Adult

For the purpose of the study, adult referred to the category of HIV patients who received IPT at Isithebe Clinic within the designated period who were 18 years and older.

Antiretroviral therapy

Antiretroviral therapy refers to the triple therapy, which consists of one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitor (NRTI) in combination, that was commenced on the patients for management of HIV disease (NDOH 2010c:13). The NDOH (2010c:20) indicates further that a third class of drug known as protease inhibitor (PI) is introduced to replace the NNRTI as part of the second-line treatment for patients failing first-line regimen.

Human Immunodeficiency Virus (HIV)

In the facility where the study was conducted, a patient was deemed to be positive for HIV if the initial ELISA test performed was positive and a second test with another ELISA from a different manufacturer was used to confirm the diagnosis and exclude possible technical errors (Regensberg & Dunn 2012:7). This practice is also available in other public health facilities in South Africa.
Isoniazid preventive therapy (IPT)

IPT refers to the intake of 300 mg of isoniazid daily by individuals with latent infection with *Mycobacterium tuberculosis* in order to prevent the progression to active TB disease (FPD 2010b:127).

Tuberculosis (TB)

For the purpose of the study, a patient was said to be diagnosed with TB when the acid and alkaline fast bacilli (AAFB) was demonstrated directly in the sputum, based on the clinical presentation or by TB culture (FPD 2010a:65).

Incidence

Incidence in the context of this study implied the counting of the number of clients diagnosed with TB disease in the population of HIV clients who received IPT in Isithebe PHC clinic between July 2010 and February 2011 and were used for the study.

Demographic characteristics

The demographic characteristics that were recorded and measured during the course of the study are the sex, age of the accessible population that commenced IPT.

1.11 STRUCTURE OF THE DISSERTATION

Chapter 1 presents an overview of the study.

Chapter 2 discusses the literature review on TB and HIV.

Chapter 3 describes the research design and methodology.

Chapter 4 covers the data analysis and interpretation, and results.
Chapter 5 concludes the study, briefly describes its significance and limitations and makes recommendations for practice and further research.

1.12 CONCLUSION

This chapter described the research problem, research design and methodology, significance and scope of the study, and ethical considerations and defined key concepts.

Chapter 2 discusses the literature review conducted for the study.
CHAPTER 2

Literature review

2.1 INTRODUCTION

This chapter discusses the literature review on HIV/AIDS, TB, HIV/TB co-infection and TB preventive therapy conducted for the study. With the upsurge in the global TB burden, the greatest increase in terms of the incidence of TB disease was noted among the population of people with the highest HIV rates. Africa has the highest prevalence and mortality rate associated with TB disease (WHO 2013c:9).

Literature indicates that HIV is the strongest risk factor recognised in the reactivation of latent or new Mycobacterium tuberculosis infection to active TB disease (FPD 2012:25; Wilson et al 2008:35). The researcher explored the literature to highlight the clinical features and current management guidelines of HIV, TB and TB preventive therapy. Various databases (Google scholar, Pubmed, Medline, WHO) were searched and the words tuberculosis, isoniazid preventive therapy, HIV/AIDS, adherence, MDR-TB, antiretroviral therapy and HIV infection were used to search for applicable literature. Relevant sections of Internal Medicine textbooks and reports/guidelines released by the National Department of Health, South Africa were also perused.

2.2 HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Sub-Saharan Africa still bears an inordinate share of the global HIV burden (UNAIDS 2010:25). Furthermore, although the rate of new HIV infections has decreased, the total number of people living with HIV in the region continues to rise. In 2009, that number reached 22.5 million which represents 68% of the global total which was estimated to be 33.3 million at the end of 2009. Recent statistics indicate that there were more people living with HIV in 2011 than ever before due to expanding treatment access and subsequent declining death rates. Globally, this figure was put at 35.3 million in 2012 (UNAIDS 2013:4). The UNAIDS also indicates that in sub-Saharan Africa where the need for treatment with antiretroviral therapy (ART) is the greatest, more than half the
people needing treatment, were receiving it in 2011, and 22% more people were receiving the treatment in 2011 than a year earlier. The number of deaths due to AIDS also decreased from an estimated 2.3 million in 2005 to about 1.6 million in 2012 (UNAIDS 2013:4).

South Africa has one of the largest Anti-Retroviral Therapy (ART) programmes in the world (Padayatchi, Naidoo, Dawood, Kharsany & Karim 2010:88) but in South Africa, having unprotected sex with multiple partners remains the greatest risk factor for HIV. With an estimated 5.575 million PLHIV in 2010 (NDOH 2011b) and about 6.1 million people in 2012, South Africa's epidemic remains the highest in the world followed by Nigeria with 3.4 million HIV-infected individuals and India with an estimated 2.1 million PLHIV (UNAIDS 2013:A15). The NDOH (2011b) further indicates that the national HIV prevalence estimate among antenatal women in 2010 was 30.2% while in KwaZulu-Natal, the figure was 39.5%. KwaZulu-Natal province has consistently recorded the highest provincial HIV prevalence since 1990 (NDOH 2010a:43).

In the iLembe district, where the study was conducted, the HIV prevalence was 42.3% in 2011 making it the district with the highest prevalence of HIV among antenatal women throughout the country (NDOH 2011b). However, statistics from 2012 indicate that the prevalence had declined to 35.4% (NDOH 2012:17). The HIV prevalence for the entire iLembe population was 16.6% at the first quarter of 2011 (Enterprise iLembe [s.a.]:13).

2.2.1 Pathogenesis of HIV

HIV is a single-stranded RNA retrovirus from the genus lentivirus of the family retroviridae (Wilson et al 2008:16).

Two types of HIV exist, namely:

- HIV Type 1 (HIV-1): This type is responsible for the global pandemic.
- HIV Type 2 (HIV-2): This type is less pathogenic than HIV-1. It exists mainly in West Africa with limited spread to other countries largely due to migration (Wilson et al 2008:16).
HIV 1 is morphologically similar to HIV2 but only differs in the course of the disease and treatment method in which case the transmission rate for HIV2 is usually lower compared to HIV1 (Tadoka & Kavathekar 2013:315).

HIV-1 is a rapidly evolving virus with a high viral turnover due to the nature of the reverse transcriptase. The inherent ability of adapting rapidly enables it to develop drug resistance; escape detection by the immune system, and affect possible use of vaccine and accurate diagnosis using viral assays (Wilson et al 2008:16).

Upon entry into a cell mainly through mucosal exposure, HIV is transported to the lymph nodes via dendritic CD4 T lymphocytes or Langerhans cells where infection becomes established (Wilkins 2010:387). Also referred to as T-helper cells, the CD4 T lymphocytes are white blood cells that are an essential part of the human immune system that send signals to other types of immune cells like CD8 cells to destroy the infecting virus. The gut-associated lymphoid tissue also plays a major role in the establishment of infection and initial depletion of the memory CD4 T cells (Fauci 2009:601). Fauci indicates further that the hallmark of HIV disease is the immunodeficiency that results from a progressive deficiency of the CD4 cells. This occurs following failure of the host immunity system to control viral replications. The replications occur when the viral RNA genome is transcribed into double-stranded DNA by a virally encoded reverse transcriptase that is present in the HIV particle. The resultant viral DNA migrates to the cell nucleus and integrates into the host cell (Manda 2009:35). HIV transmission is also influenced by the viral load of the infected person.

2.2.2 Transmission of HIV

Transmission of HIV infection is dependent on the viral load which determines the degree of infectiousness of the HIV-infected individual and susceptibility of the uninfected partner, especially during acute HIV infection (Kamps & Hoffman 2007:24). Viral load, phenotypic factors, and the existence of co-infections like sexually transmitted infections (STIs) affect the degree of infectiousness while hereditary, innate or acquired resistance in addition to existence of co-infections like TB affect the susceptibility of an individual to contracting HIV (Naicker 2010:1).
HIV is present in the blood and other body fluids, such as breast milk, semen, vaginal fluid and saliva. Individuals can contract HIV which eventually results in AIDS through various ways as described below.

2.2.2.1 Unprotected sexual practices

HIV could be transmitted through sexual practices like oral, anal, homosexual and heterosexual intercourse when done in an unprotected manner. HIV transmission through unprotected heterosexual intercourse is the leading mode of HIV infection worldwide (Simon, Ho & Karim 2006:490). The presence of STIs, especially genital ulcer, cervical atrophy, non-circumcision, and rectal or vaginal trauma, menstruation and increased number of partners increases the chances of HIV infection (Wilkins 2010:387). The spread of HIV through unprotected sexual practices is determined largely by the viral load of the individual and breach of the genital mucosal barrier. This is because the plasma viral load in HIV-infected individuals correlates with the HIV load shed in genital secretions (Galvin & Cohen 2004:3). Therefore with higher plasma viral load, there is an increased likelihood of spreading HIV. Also, the breach in genital mucosal barrier that occurs as a result of genital trauma and STIs increases susceptibility of individuals to HIV. This is because areas of inflammation as a result of ulcer render the mucosa more susceptible to viral entrance as they provide direct entrance for the virus into the bloodstream and the CD4 cells attracted to the areas following the inflammation render the area more susceptible since the virus is attached to CD4 cells (FPD 2012:17). Sexually transmitted infections in both men and women have also been associated with increased genital viral shedding (Galvin & Cohen 2004:3).

2.2.2.2 Parenteral transmission

Parenteral transmission results from blood/body fluid contact during unsafe blood transfusion, injection drug use and occupational injuries (FPD 2012:16). The risk of contracting HIV following a single transfusion of blood from an infected individual is 100% (FPD 2012:15). Increased frequencies of injection drug use increases susceptibility to HIV infection. Also, healthcare workers and laboratory personnel could be infected by HIV while at work with HIV-infected specimens through occupational injuries (Fauci 2009:601).
2.2.2.3 Mother-to-child transmission (MTCT)

Mother-to-child transmission of HIV can occur during pregnancy, childbirth or breastfeeding. Prolonged rupture of membranes, foetal trauma, aggressive suctioning of the baby that could breach the oral mucosa and chorioamnionitis increase perinatal transmission of HIV (Wilkins 2010:387). Breastfeeding accounted for about 360 000 cases of HIV infection in 2005 globally and thus is an important route for MTCT of HIV (Coovadia, Rollins, Bland, Little, Coutsoudis, Bennish & Newell 2007:1107). About 25-45% of infants born to HIV-infected breastfeeding women could be infected with HIV-1 and exclusive breastfeeding with instant weaning after 3-6 months has been found to make breastfeeding safer (Thior, Lockman, Smeaton, Shapiro, Wester, Heyman, Gilbert, Stevens, Peter, Kim, Van Widenfelt, Moffat, Ndase, Arimi, Kebaabetswe, Mazonde, Makhema, McIntosh, Novitsky, Lee, Marlink, Lagahos & Essex 2006:794). Avoidance of breastfeeding prevents transmission of HIV from mother to her baby through breastfeeding. However, the use of infant formula especially where access to clean water is not guaranteed at all times is associated with increased infant morbidity and mortality (Thior et al 2006:795). The risk of perinatal HIV transmission was also noted to be lower with exclusive breastfeeding when compared with mixed feeding as the latter could lead to breach in the gut epithelium of the baby (Coovadia et al 2007:1113). The presence of high viral load in the mother, which occurs in advanced AIDS or during the seroconversion period, increases the rate of HIV transmission from an infected mother to her baby. The rate is further increased with longer duration of breastfeeding, mastitis, and poor breast feeding techniques like poor latching (Wilkins 2010:387).

2.2.3 Diagnosis of HIV

Laboratory diagnosis of HIV has evolved from detecting antibodies of the virus in the blood sample to viral RNA/DNA tests and viral culture which is largely used in reference laboratories for research (Wilson et al 2010:45). In South Africa, the NDOH recommends that people should test for HIV at least on an annual basis. Provider Initiated Counselling and Testing (PICT) for HIV is recommended to be offered to every individual accessing care in all healthcare settings unless the patient opts out. This is in line with the recommendations of the WHO that HIV testing and counselling should be offered as part of package of care to everyone seen in the health facilities in areas with
generalised epidemics (WHO 2013a:70). The US Centres for Disease Control and Prevention (CDC) recommends that healthcare providers should offer assessment care to all patients at health facilities for voluntary screening of HIV (Mahajan, Stemple, Shapiro, King & Cuuningham, 2009:264). However, in areas of concentrated or low-level epidemics, the WHO (2013a:70) recommends that HIV testing and counselling should be offered to those presenting to health facilities with signs and symptoms suggestive of underlying HIV infection. HIV-exposed children are also to be counselled and tested for HIV.

The three testing strategies recommended by the UNAIDS and the WHO for use in screening serum or plasma sample are as follows:

**Strategy I:** Strategy I is recommended for the use in screening blood or body organs meant for donation, surveillance in areas of >10% HIV prevalence and diagnosis of HIV in areas where HIV prevalence is >30% (WHO 2004:6). In this strategy, each serum sample is tested with one ELISA or rapid assay. The serum that tests positive is considered HIV antibody positive while the one that tests negative is considered HIV antibody negative.

**Strategy II:** As illustrated in Table 2.1, strategy II is recommended for use in diagnosing individuals with HIV clinical stage III or IV infection in areas where HIV prevalence <30% as defined by the WHO (WHO 2007b:15). Other scenarios where the use of strategy II is recommended are for surveillance where HIV prevalence is ≤10% and HIV screening for asymptomatic individuals in areas where the prevalence in the population is >10%.

In this strategy, the serum/plasma sample is initially tested with ELISA or rapid assay with subsequent retesting using a different ELISA or rapid test kit if the result is positive. If the result is positive on both tests, the patient is diagnosed as HIV positive. However, if discordant results are noted, the sample is re-tested by either ELISA or rapid assay and if concordant results are noted, it is accepted. When the results remain discordant after the retesting, the test is deemed indeterminate. The WHO (2004:6) recommends repeat testing after two weeks for indeterminate results in asymptomatic individuals and further confirmatory testing if the results remain indeterminate. Discordant results are
accepted as positive if the individual tested has clinical features indicative of HIV Clinical stage III or IV (WHO 2007:16).

**Strategy III**: Strategy III is recommended for use in screening individuals where prevalence of HIV infection is ≤10%. According to the WHO (2004:5), any reactive sample noted using the ELISA or rapid assay is retested using a different assay. While the serum that is negative is not disputed, the reactive sample is retested using both tests and if positive, a third test is carried out. The test is considered HIV antibody positive if reactive on all the three samples while the serum that remains discordant in the second assay or is reactive in the first and second test but negative on the third test is considered as an indeterminate result.

**Table 2.1 HIV testing strategies**

<table>
<thead>
<tr>
<th>Objective of testing</th>
<th>Prevalences of infection</th>
<th>Testing strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion/transplant safety</td>
<td>All prevalences</td>
<td>I</td>
</tr>
<tr>
<td>Surveillance</td>
<td>&gt;10%</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>≤10%</td>
<td>II</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Clinical signs/symptoms of HIV infection</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>&gt;30%</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>≤30%</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>≤10%</td>
<td>III</td>
</tr>
</tbody>
</table>

(WHO 2004:3)

The standard laboratory test in South Africa is the Enzyme Linked Immunosorbent Assay (ELISA) which is about 99.5% sensitive in patients infected with HIV for more than 3 months already (Barlett et al 2008:8). According to the HIV testing algorithm recommended by the NDOH (2010d:23), a rapid test is used to test the blood sample of the individual. If the screening result is non-reactive, the result is reported as negative while if the result is positive, a second rapid test from a different manufacturer is used for HIV testing with a follow-up ELISA test if negative after the initial positive result. The test is considered HIV antibody reactive if positive following the ELISA test. However, if the ELISA is non-reactive, the client is encouraged to live a risk-free life and retest after three months to exclude possibility of a window period. A window period refers to the
period when an individual has not developed antibodies to HIV in the body fluid even though HIV infection has taken place. It could be as early as four weeks (Wilson et al 2009:46) and rarely exceeds six months (Barlett et al 2008:8).

Despite the high sensitivity and specificity of the ELISA test, there are instances where the test result could be incorrect. False negative test results using the ELISA are commonly due to errors committed while carrying out the test or writing up the results and also occur if the test was performed during the window period when the patient has not seroconverted. That explains why individuals with negative antibody test results are advised on risk-free living and repeat of HIV test after three months. However, the presence of auto antibodies, use of HIV vaccines, erroneous reporting of HIV infection with intention to deceive and influenza vaccination are capable of causing false positive results (Barlett et al 2008:9).

The Western blot test could also be used as a confirmatory after ELISA. It detects antibodies to HIV antigens of specific molecular weights (Fauci 2009:603). With the advent of reliable ELISA tests, Western blot is not currently used routinely for the confirmation of HIV infection in the public healthcare system of South Africa due to cost concerns and improvements in the sensitivity and specificity of ELISA tests. Nevertheless, it remains the most reliable confirmatory test for infection with HIV-2 (Wilson et al 2008:44).

Fauci (2009:603) points out that the use of polymerase chain reaction (PCR), branched DNA nucleic-acid based assay (NABBA) or viral culture can detect HIV infection during the window period and beyond. The PCR test could detect a single copy of HIV nucleic acid in the blood sample hence the increasing use of this method for babies who still have their mothers’ antibodies circulating in their blood and by transfusion services. HIV can also be grown in cell culture in which case mononuclear cells from the peripheral blood of uninfected donor are incubated with the sample for testing (Wilson et al 2008:45). Routine testing of HIV using PCR and viral culture is not practised on a large scale due to cost factors. The viral culture is largely used for research in reference laboratories (Wilson et al 2008:45).
2.2.4 Clinical progression of HIV disease

2.2.4.1 Acute HIV infection

Acute HIV infection refers to the initial period following HIV infection, usually within the first 30 days (Naicker 2010:1). In order for infection to become established, HIV needs to cross the epithelial barrier and come into contact with CD4+ immune cells with CCR5 or CXCR4 chemokine receptors (Wilson et al 2008:55). The presence of genital trauma, ulceration or inflammation in addition to the viral load from the source HIV-positive individual enhances HIV infection in both partners (FPD 2012:17; Wilkins 2010:387) (see section 2.2.2 for modes of HIV transmission).

Immune activation during HIV infection is a major contributor to disease progression and is the product of inflammatory responses to HIV-encoded receptors, microbial translocation and homeostatic response to CD4+ T-cell depletion. Immune cells activated during HIV infection include T cells, B cells, natural killer cells, macrophages and plasma cytokines. IL-7, IL-12p40, IL-12p70, IFN-γ and IL-15 are the types of plasma cytokines noted in women with acute infection that have been found to be predictive of long-term HIV disease prognosis (Roberts, Passmore, Williamson, Little, Bebell, Mlisana, Burgers, Van Loggerenberg, Walzl, Djoba Jiawaya, Abdool Karim & Abdool Karim 2010:821). Roberts et al (2010:821) point out that HIV viral loads in plasma and systemic CD4 counts are the widely accepted predictors of HIV disease progression though T-cell proliferative capacity and concentrations of soluble biomarkers such as TNF-rIL, neopterin and β²-microglobulin during chronic infection have also been shown to predict HIV disease progression to AIDS. Neopterin is one of the chemicals synthesised by human macrophages during HIV infection and because their concentrations usually correlate with the extent and activity of HIV, they are used as monitors of the disease progression (Murr, Widner, Wirleitner & Fuchs 2002:175).

Primary infection with HIV could be symptomatic in 70-80% of cases within the first six weeks of infection (Wilkins 2010:389). In about 80% of infected individuals, acute HIV 1 infection is symptomatic (Manda 2009:38). Early HIV infection is characterised by the appearance of viral markers and antibodies in the blood (Cohen, Shaw, McMichael & Haynes 2011:1944). Symptoms at this stage may include fever, influenza-like illness, sore throat, rash, myalgia, mouth sores, and lymphadenopathy among others.
Recognition of HIV infection is important as the initial viraemia makes the infected individual highly infectious and HIV transmission readily occurs within this period. However, in practice, most of the infections at this stage are undiagnosed as the routine antibody tests are negative due to the delay in the production of antibodies to HIV during the acute HIV infection stage. Worldwide, only about 1000 cases have been diagnosed during the first month of infection (Naicker 2010:1). Naicker (2010:1) further indicates that only viral specific diagnostic tests like HIV nucleic acid amplification assay are needed to diagnose the infection prior to the appearance of HIV antibodies. The p24 antigen test is about 89% sensitive, 100% specific and detects HIV infection as early as 2 weeks after infection. However, due to cost factors, the p24 test is not routinely available in the public health system of South Africa.

As depicted in figure 2.1, there is a marked increase in the viral load and sharp decline in CD4 count during this stage. The use of antiretroviral therapy effectively reduces the viral load and slows down extensive damage to the immune system during this period (Hecht, Wang, Collier, Little, Markowitz, Margolick, Kilby, Daar, Conway & Holte 2006:726). This forms the basis of the use of antiretroviral in post exposure prophylaxis.

2.2.4.2 Asymptomatic stage

The asymptomatic stage refers to the period during which the infected patient largely remains well and does not manifest clinical features of retroviral disease except for the occasional occurrence of persistent generalised lymphadenopathy (Wilkins 2010:389). Without the use of ART, this period could last between 2-20 years and is characterised by CD4 decline and viral replication (Naicker 2010:2). Faster progression to CD4+ cell count of 350 cells/µL or less, viral load of at least 1x100000 copies/ml and AIDS has been observed in HIV-1 subtype C when compared to subtypes A and D (Amornkul, Karita, Kanali, Rida, Sanders, Lakhi, Price, Kilembe, Cormier, Anzata, Latka, Bekker, Allen, Gilmour & Fast 2013:2283). This stage is also known as the clinical latency period and is illustrated in figure 2.1. There is progressive decline in CD4 count and gradual increase in viral load. The rate at which these occur could vary from one patient to another.
2.2.4.3 Mildly symptomatic disease stage

The mildly symptomatic disease stage refers to the period in the majority of patients infected with HIV that is characterised by some impairment of cellular immunity which are not AIDS defining (Wilkins 2010:390). Wilkins (2010:390) further indicates that while some patients could be fast or slow progressors, the average interval from infection to the development of symptoms is around 7-10 years.

Symptoms or disease states like recurrent oropharyngeal or vaginal candidiasis, pelvic inflammatory diseases (PID), herpes zoster, chronic diarrhoea, peripheral neuropathy, weight loss and fever could occur during this period with sustained increase in viral load (FPD 2012:81).

2.2.4.4 Advanced HIV disease stage

Advanced HIV disease stage is also referred to as Acquired Immunodeficiency Syndrome (AIDS). This stage occurs in untreated patients or patients with virological failure (Fauci 2009:602). Specific AIDS-defining opportunistic infections, tumours or
presentations occur within this period with decline of CD4+ cell count to levels lower than 200/µL and increase in viral load. This stage is depicted in figure 2.1.

Disease states such as oesophageal candidiasis, meningitis, cerebral toxoplasmosis, CMV retinitis, tuberculosis, pneumocystis jirovecii pneumonia, kaposi sarcoma, lymphoma, invasive cervical cancer amongst others could occur within this period (Wilkins 2010:390). If left untreated, death ultimately occurs. However, drugs have been developed for the treatment of HIV infection and AIDS.

2.2.5 Treatment of HIV infection

The use of antiretroviral treatment (ART) for the management of HIV and AIDS decreases morbidity, mortality and improves the quality of life for many patients all over the world (Formundam & Mathews 2009:2). ART programmes in the developing world where free medication is provided, such as in South Africa, have been found to be effective with viral load suppression rates similar to figures noted in developed countries (Ivers, Kendrick & Doucette 2005:223). In the absence of antiretroviral treatment, HIV infection progresses to AIDS at a medium time of 8-10 years with the median survival time after developing AIDS significantly reduced to only 9.2 months (Kamps & Hoffmann 2007:24).

South Africa has one of the largest ART programmes in the world and provides the medication free of charge to eligible patients across all public health institutions in the country (Padayatchi, Naidoo, Dawood, Kharsany & Karim 2010:88).

The WHO (2013a) provides consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection in susceptible individuals. The NDOH (2013a) developed clinical guidelines for the management of HIV and AIDS in adults and adolescents for South Africa. In addition to several goals, the objectives of the programme are to contribute to strengthening of the public and private health sectors’ capacity to deliver high quality integrated health and wellness services; ensure timely initiation of antiretroviral drugs (ARVs) for treatment and prevention according to the Presidential mandates, and minimise unnecessary drug toxicities (NDOH 2013a:4).
2.2.5.1 **Eligibility criteria for starting ART regimens for adults and adolescents**

Adults diagnosed with HIV in South Africa are eligible for commencement on ART if their CD4 count is ≤350 cells/mm³, irrespective of the WHO clinical stage (NDOH, 2013a:5). The ART treatment protocol is largely based on the recommendations by the WHO (2010c:20) that all adolescents and adults with CD4 count ≤350 cells/mm³ should start ARV irrespective of the existence of clinical symptoms. The NDOH emphasises that patients who are pregnant or breastfeeding are eligible to start ART, irrespective of their CD4 count. This also applies to patients with WHO clinical stage 3 or 4 including those co-infected with any form of TB or cryptococcal meningitis.

Although the focus of the study is on HIV-infected individuals that were commenced on IPT, commencing those with TB on ART has been found to be associated with improved treatment outcomes as TB infection leads to high mortality in HIV-infected individuals (Karim, Naidoo, Grobler, Padayatchi, Baxter, Gray, Gengiah, Nair, Bamber, Singh, Khan, Pienaar, El-Sadr, Friedland & Karim 2010:702).

The NDOH treatment guidelines differ from the current recommendations by the WHO on when to start ART in adults and adolescents. According to WHO (2013a:28), in addition to those eligible for treatment under the South African guidelines, ART should be initiated in all individuals with CD4 count ≤500 cells/mm³ regardless of WHO clinical stage. Serodiscordant couples are also to be commenced on ART to reduce HIV transmission to the uninfected partners.

However, patients who are not yet eligible for ART after clinical and laboratory assessments are transferred to a wellness programme for regular follow-up and repeat clinical assessment/CD4 count testing every six months according to the NDOH guidelines. They are also advised on how to avoid HIV transmission to sexual partners and children, initiated on isoniazid (INH) prophylaxis if asymptomatic for TB and offered contraception and a pap smear (NDOH 2010:6). Initiation on INH is after screening using the screening tool and ascertaining that the patient is not a TB suspect.

Table 2.2 describes the national ART regimen for adults and adolescents in South Africa. Once eligible for commencement on ART, all new adult patients are commenced on the fixed dose combination preparation (FDC) which contains Tenofovir,
Emtricitabine and Efavirenz except where there is contraindication to the use of any of them. When virological failure is diagnosed, the appropriate second-line regimen is used as outlined in table 2.2. Referral to HIV treatment specialist is advised where there is resistance to the second-line regimen.

**Table 2.2  Standardised National ART regimens for adults and adolescents**

<table>
<thead>
<tr>
<th>1st Line</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All new patients needing treatment including pregnant women</td>
<td>TDF+FTC (or 3TC) + EFV FDC preferred</td>
</tr>
<tr>
<td>Contraindications to EFV</td>
<td>TDF + (FTC or 3TC) + NVP</td>
</tr>
<tr>
<td>Contraindication to TDF</td>
<td>AZT + 3TC+ EFV (or NVP)</td>
</tr>
<tr>
<td>Contraindication to TDF and AZT</td>
<td>d4T + 3TC +EFV (or NVP)</td>
</tr>
<tr>
<td>Contraindication to TDF, AZT and d4T</td>
<td>ABC + 3TC+ EFV (or NVP)</td>
</tr>
<tr>
<td>Currently on d4T-based regimen</td>
<td>TDF + FTC (or 3TC) + EFV FTC preferred</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd Line</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of virological failure</td>
<td>If plasma HIV RNA &gt;1000 copies, check for adherence, compliance, tolerability and drug-drug interaction and assess psychological issues. Repeat VL test 2 months later If plasma VL confirmed &gt;1000 copies, change regimen to second line therapy</td>
</tr>
</tbody>
</table>
2.2.5.2 Standardised monitoring of clients on ART

Table 2.3 indicates the standardised monitoring procedures for HIV-positive patients at the initial diagnosis of HIV, at routine follow-up visits, and when they are eligible for ART as outlined in the 2013 Clinical guidelines for the management of HIV & AIDS in adults and adolescents. The entire essence is to ensure best possible and timely care to deserving clients. Compared to previous editions, the 2013 guideline emphasises early commencement of ART and change in the timing of CD4 count tests. As illustrated in table 2.3, after initiation on ART, CD4 count follow-up CD4 count test will now be done at 1 year on ART and then every 12 months as opposed to the 2010 guidelines that required CD4 tests to be done at six months, one year post-initiation and then yearly afterwards (NDOH 2010b:3).

The NDOH (2013a:6) also recommends that viral load monitoring should be done first at 6 months after initiation where it is expected to be undetectable (NDOH 2013a:6).

| Failing on a TDF-based 1st line regimen | AZT + 3TC + LPV/r | Patients with anaemia and renal failure switch to ABC |
| Failing on a d4T-based 1st line regimen | TDF+3TC (or FTC ) and LPV/r | |
| Dyslipidaemia or diarrhoea associated with LPV/r | Switch LPV/r to ATV/r | |
| **3rd Line** | | |
| Failing any 2nd line regimen | Specialist referral | |
| Should be expert and genotype resistance testing based decision and supervised care. Patients failing on second line therapy will be managed by an expert panel. The drugs for third line will be managed centrally. More discussion is required to deal with the modalities | Most likely regimen would be Raltegravir/Darunavir/ Etravirine adjusted according to genotype interpretation. Should be by expert and take into account prior exposure and predictable mutations. | |

(NDOH 2013a:6)

KEY: 3TC-Lamivudine; d4T-Stavudine; ABC-Abacavir; ATV/r-Atazanavir/ritonavir; AZT-Zidovudine; EFV-Efavirenz; FTC-Emtricitabine; LPV/r-Lopinavir/ritonavir; NVP-Nevirapine; RNA-Ribonucleic acid; VL-Viral load.
Repeat viral load is also to be done at 1 year after commencement on ART and yearly afterwards should the values remain undetectable. Should the viral load result read more than 1000 copies/ml, however, the NDOH (2013a:5) recommends that adherence, tolerability and psychological issues should be carefully assessed and the test repeated after two months of providing adherence services to the affected client. Regimen change to second-line therapy is recommended if the viral load remains more than 1000 copies/ml on repeating the test.

**Table 2.3 Standardised national monitoring for adults and adolescents with HIV**

<table>
<thead>
<tr>
<th>At Initial Diagnosis of HIV</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm HIV result with rapid antibody test</td>
<td>Ensure that national testing algorithm has been followed</td>
</tr>
<tr>
<td>Do CD4 count if HIV positive and WHO clinical staging</td>
<td>To assess eligibility for ART</td>
</tr>
<tr>
<td></td>
<td>To assess eligibility for fast-tracking</td>
</tr>
<tr>
<td>Screen for pregnancy or ask if planning to conceive</td>
<td>To identify women who need ART for life or ARV prophylaxis for PMTCT</td>
</tr>
<tr>
<td>Screen for TB symptoms using the WHO questionnaire</td>
<td>To identify TB/HIV co-infected</td>
</tr>
<tr>
<td>Do the CD4 count on the same day</td>
<td>To identify eligibility for ART or ARVs for prophylaxis if pregnant</td>
</tr>
<tr>
<td>Do Hb or FBC if requires AZT</td>
<td>To detect anaemia or neutropenia</td>
</tr>
<tr>
<td>Creatinine if requires TDF</td>
<td>To detect renal insufficiency</td>
</tr>
<tr>
<td>For patients initiated on Nevirapine based regimen, do ALT</td>
<td>To exclude liver disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>On ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 at 1 year on ART</td>
<td>To monitor immune response to ART</td>
</tr>
<tr>
<td>VL at month 6, 1 year on ART and then every 12 months</td>
<td>To identify treatment failures and problems with adherence</td>
</tr>
<tr>
<td>ALT only if on NVP and develops rash or symptoms of hepatitis</td>
<td>To identify NVP toxicity</td>
</tr>
<tr>
<td>FBC at month 3 and 6 if on AZT</td>
<td>To identify AZT toxicity</td>
</tr>
<tr>
<td>Creatinine at month 3 and 6, 1 year then every 12 months if on TDF</td>
<td>To identify TDF toxicity</td>
</tr>
<tr>
<td>Fasting cholesterol and triglycerides at month 3 if on LPV/r</td>
<td>To identify LPV/r toxicity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>At Routine follow-up visits for those not yet eligible on ART</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat CD4 at 6 months</td>
<td>To see if they have become eligible for ART</td>
</tr>
<tr>
<td>WHO clinical staging at every visit</td>
<td>To see if they have become eligible for ART</td>
</tr>
</tbody>
</table>
Screening for TB symptoms should also be done at every visit to any health facility. This is to identify TB/HIV co-infection and institute the appropriate management accordingly. Where no TB symptoms exist and the patient is eligible, Isoniazid preventive therapy (IPT) is commenced to avoid the activation of TB disease.

2.3 TUBERCULOSIS

Tuberculosis is caused by infection with tubercle bacillus known as *Mycobacterium tuberculosis* and can be spread by the inhalation of aerosolised droplet nuclei from other infected people (Reid, 2010:688). This was first demonstrated by Robert Koch in 1882 (Foundation for Professional Development [FPD] 2010a:6).

2.3.1 Pathology and pathogenesis of tuberculosis

The organism that causes TB, *Mycobacterium tuberculosis* lodges in the alveoli once inhaled and thereafter commences the formation of macrophages and lymphocytes. The macrophages undergo transformation into epithelioid and Langhans cells. These merge with the lymphocytes to form tuberculous granuloma, also known as Ghon focus when lots of them aggregate together usually situated in the periphery of the lung. The hilar and paratracheal group of lymph nodes also harbour Ghon lesion (Barlam & Kasper 2009:538). The capsule that encases the lesions limits the spread of the bacilli resulting in latent TB infection.

In situations where the defence system of the body is unable to contain the invading organisms, they multiply and eventually lyse the macrophages. This results in spread to the regional lymph nodes initially with the possibility of spreading throughout the body afterwards (Barlam & Kasper 2009:538). With lymphatic or haematological spread, these lesions could be lodged in other body organs like kidneys, lungs, lymph nodes, bones and liver where they may lie dormant for years.
Detection of infection at this stage is by the existence of delayed-type hypersensitivity reaction to tuberculin which is demonstrated by tuberculin skin testing (FPD 2010a:19). The failure of the aforementioned reparative processes leads to active TB disease. FPD further indicates that the lifetime risk of developing disease after primary infection is 10% in the absence of HIV/AIDS which accelerates this process.

2.3.2 Epidemiology of tuberculosis

The FPD (2010a:5) indicate that TB existed in the world for centuries as an endemic disease among animals long before it affected humans, possibly existing in non-human primates. The incidence of TB had generally been on the decline in the world until the early 1980s when an increase of cases was reported in the USA, parts of South East Asia, East, Central, West and Southern Africa. While various factors contributed to the upsurge in the global TB burden, the groups with the greatest increase in TB were also the groups with the highest HIV rates (Balcells, Thomas, Godfrey-Faussett & Grant 2006:744; FPD 2010a:31).

From an estimated 7-8 million cases in 1993 when the WHO declared TB a global public health emergency, the spread of TB increased to about 8.6 million new cases in 2012 (WHO 2013c:1). Table 2.4 indicates the estimated burden of disease caused by TB in South Africa and across the major regions of the world in 2011.

Table 2.4 Estimated burden of disease caused by TB in 2011

(Rates per 100 000 population)

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (thousand)</th>
<th>Mortality</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>HIV prevalence in incident TB cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best</td>
<td>Low</td>
<td>High</td>
<td>Best</td>
<td>Low</td>
</tr>
<tr>
<td>South Africa</td>
<td>50 460</td>
<td>49</td>
<td>21</td>
<td>87</td>
<td>768</td>
</tr>
<tr>
<td>Africa</td>
<td>857 382</td>
<td>26</td>
<td>21</td>
<td>31</td>
<td>293</td>
</tr>
<tr>
<td>America</td>
<td>943 019</td>
<td>2.2</td>
<td>1.9</td>
<td>2.5</td>
<td>35</td>
</tr>
<tr>
<td>EMR</td>
<td>608 628</td>
<td>16</td>
<td>10</td>
<td>24</td>
<td>170</td>
</tr>
<tr>
<td>EUR</td>
<td>899 500</td>
<td>5.0</td>
<td>4.9</td>
<td>5.1</td>
<td>56</td>
</tr>
<tr>
<td>SEAR</td>
<td>1 830 361</td>
<td>26</td>
<td>19</td>
<td>34</td>
<td>271</td>
</tr>
<tr>
<td>WPR</td>
<td>1 808 797</td>
<td>6.9</td>
<td>5.7</td>
<td>8.3</td>
<td>138</td>
</tr>
<tr>
<td>Global</td>
<td>6 947 687</td>
<td>14</td>
<td>12</td>
<td>17</td>
<td>170</td>
</tr>
</tbody>
</table>

(WHO 2012:10)
Table 2.4 shows that the prevalence of TB disease is the highest in Africa. An estimated incidence rate of 262 per thousand was noted for Africa, which is high when compared to 42 recorded in Europe and other WHO-designated regions of the world. Africa also has the highest prevalence and mortality rate associated with TB disease as well as the highest HIV-positive incident TB cases (WHO 2012:9). The WHO (2011b:3) indicates that South Africa was among the five countries with the highest number of incident TB cases in 2010. South Africa is also one of the 22 high-burden countries that account for 80% of all new TB cases globally and has the second highest TB incidence rate worldwide (Kranzer 2011:418). An estimated 0.40-0.59 million people were diagnosed with TB worldwide in 2010. Globally, TB is the second leading cause of death from an infectious disease after HIV accounting for an estimated 1.4 million deaths in 2012 (WHO 2013c:1). About 300 000 deaths from TB recorded in 2012 occurred among people living with HIV (PLHIV).

A total of 5,868 cases of TB were reported across all health facilities in iLembe, South Africa in 2012 (KZN Tuberculosis Programme, 2012). According to data released by the Tuberculosis programme, this figure includes all forms of TB across all segments of the population and 38.3% of the cases were smear positive.

Various factors are associated with the risk of developing TB disease (FPD 2010a:14-18).

2.3.3 Risk factors for contracting tuberculosis

The major factors that determine the risk of becoming exposed to the TB bacilli include the number of infectious cases in the community, the duration of their infectiousness and the number and nature of interactions between a TB case and a susceptible contact per unit time of infectiousness (FPD 2010b:19). FPD further indicates that the probability of becoming infected with Mycobacterium tuberculosis depends on the concentration of the infectious droplets in the air (infectious particle density) and the duration of exposure of a susceptible individual to the particle density.

The risk of developing active TB following infection is largely endogenous and is determined by the integrity of the cellular system. This implies internal reactivation of the bacilli that has been latent after the initial infection (FPD 2010b:31). Reids and Innes
(2010:689) indicate that a history of close contact with any individual with smear-positive pulmonary TB disease, prolonged infection with the TB bacilli, residence in poorly ventilated areas, extremes of age at which time immunity is low and co-infection with HIV/AIDS are some of the risk factors that accelerate the progression of primary infection to active TB disease. Other diseases like diabetes, silicosis, malignancies, renal failure, immunosuppressive states and malnutrition are also risk factors for development of active disease (FPD 2010a:16). While increased population density and crowded living conditions noted in some urban areas increases transmission of TB disease, poor nutritional status and high HIV prevalence enhances the progression to active TB disease (Lönnroth, Jaramillo, Williams, Dye & Raviglione 2009:2241).

2.3.4 Clinical features of TB disease

The clinical features of TB disease include the various signs and symptoms associated with the disease and are discussed under the various forms of the disease.

2.3.4.1 Primary pulmonary TB

Primary pulmonary TB refers to the infection of a previously uninfected (tuberculin-negative) individual. During this phase, a few patients develop a self-limiting febrile illness while the rest remain asymptomatic after the formation of the primary complex (tuberculous granuloma) described in section 2.3.1. The clinical feature at this stage is usually lymphadenopathy at the hilar and paratracheal areas that could be painless. However, in the immunocompromised individuals, like those living with HIV, spontaneous progression to clinical disease with cavitation and pleural effusions are common (Barlam & Kasper 2009:538).

2.3.4.2 Post primary pulmonary TB

Post pulmonary TB refers to exogenous or endogenous infection in a person who has been sensitised by an earlier exposure to tuberculous bacilli (Reid & Innes 2010:689). The onset is usually insidious and develops slowly over several weeks. Systemic symptoms include fever, night sweat, malaise, loss of appetite, loss of weight, chronic productive cough with occasional haemoptysis (Barlam & Kasper 2009:539). Reid and Innes (2010:689) further indicate that in extensive form of post primary pulmonary TB,
pleural effusion, spontaneous pneumothorax, and unresolved pneumonia could also be noted on examining the affected patient.

### 2.3.4.3 Extra pulmonary TB disease

Extra pulmonary tuberculosis (EPTB) refers to isolated occurrence of TB disease in any other part of the body apart from the lungs and accounts for more than 50% of all cases of TB in HIV-infected individuals (Sharma & Mohan 2004:316). Higher incidence of EPTB has been noted in USA since the AIDS epidemic occurred (Golden & Vikran 2005:1761). Similar trends of rising rates of EPTB have also been reported in other countries of the world with HIV epidemics (WHO 2007:3). The clinical feature depends on the part of the body affected. Any part of the body could be affected with lymph node involvement occurring in more than 40% of the (EPTB) cases (Barlam & Kasper 2009:539). Painless swelling of cervical, supraclavicular, axillary and inguinal group of lymph nodes are typical. The affected nodes, though initially mobile, could become matted with time and discharge through the skin with formation of abscess and sinus.

Symptoms of abdominal TB include abdominal pain, diarrhoea, fever, night sweats, anorexia, weight loss, painful abdominal distension with exudative ascites. Extra pulmonary pericardial TB disease could occur in the form of pericardial effusion and constrictive pericarditis. The presentation is usually acute or sub-acute fever, dull retrosternal pain and pericardial effusion (Balaam & Kasper 2009:540).

In the genitourinary diseases, urinary frequency, dysuria, haematuria and pyuria could occur (FPD 2010b:63). Barlam and Kasper (2009:540) point out that the spine, hip and knees are the most common sites of skeletal TB disease. The vertebral bodies are affected in such cases with collapse of the vertebral bodies and resulting kyphosis and gibbous in extreme cases of the disease.

Miliary disease refers to the form of TB caused by blood-borne spread of the tuberculous bacilli (Reid & Innes 2010:689). Reid and Innes emphasise that while miliary TB could present acutely, more frequently, it is characterised by fever, headache, night sweat, anorexia, weight loss and dry cough. Hepatosplenomegaly,
crackles, anaemia and appearance of small 1-2 mm lesions throughout the lung fields on chest X-ray are other clinical findings that are suggestive of military TB.

Tuberculous meningitis occurs most often in young children and sero-positive adults according to Barlam and Kasper (2009:540). Clinical features of tuberculous meningitis include headache, fever, vomiting, depression, confusion, lethargy, meningism and occasional ocular cranial nerve involvement.

2.3.5 Diagnosis

Diagnosis of TB disease is made by performing a complete clinical assessment that includes a medical history, physical examination, chest X-ray and laboratory tests (Manda 2009:50).

2.3.5.1 Medical history

The NDOH (NDOH, 2013a) recommends that investigation for TB disease be carried out if 2 or more of the following symptoms are present:

- Cough of any duration
- Sputum production (with or without haemoptysis)
- Fever
- Drenching night sweats
- Unexplained weight loss
- Loss of appetite, malaise, tiredness
- Shortness of breath, chest pains
- New palpable lymphadenopathy

In taking the medical history from the patient, questions should be targeted towards ascertaining the existence of the aforementioned symptoms. In addition, past history of TB exposure and disease as well as history of past TB treatment should be probed as resistant TB could occur if past treatment was erratic (FPD 2010b:63). Existence of other disease conditions like HIV infection, diabetes mellitus, renal disease, haematological disease, silicosis and ingestion of immunosuppressive drugs should
also be questioned as these could increase the chances of contracting TB disease (FPD 2012:61).

### 2.3.5.2 Physical examination

A thorough physical examination should be performed on the TB suspect as this could provide more details about the overall condition of the patient and other findings capable of affecting the management plans for the patient (FPD 2010b:61).

Most signs are not specific for TB disease. They include wasting, elevated temperature, tachycardia and deviation of the trachea, bronchial breathing, crackles and dull percussion notes (FPD 2012:62).

### 2.3.5.3 Investigations

Direct microscopy of sputum for detecting the acid-fast bacilli using the Ziehl-Neelsen technique is the commonest method for detecting pulmonary TB. A positive smear is sufficient for the presumptive diagnosis of TB though definitive diagnosis requires culture. In HIV-negative individuals, the sensitivity of Ziehl-Neelsen staining for diagnosis of TB disease is about 80%. This drops to as low as 20% in HIV co-infected individuals who are often smear-negative even though they have TB disease (Peter & Theron 2011:404). Approximately one fourth of HIV-infected persons with pulmonary TB disease have false-negative results (CDC 2009:20). Smear-negative sputum exists because cavities are less common in individuals with HIV with the load of the organism higher in the tissue. It should therefore also be investigated where the constitutional clinical features are present and there is no response to broad spectrum antibiotics (De Kock, Odayar, Page-Shipp & Conradie 2013:8). Smear-negative sputum sent for culture could turn out to be positive as only 10-100 viable organisms are required for diagnosis of TB using culture compared to 5 000-50 000 required in detecting the bacilli using direct microscopy (Reid & Innes 2010:692). FPD further indicates that diagnosis of smear-negative TB is either made with a positive culture result or with suggestive x-ray findings together with a medical decision to start TB treatment. However, this diagnostic method could be challenging due to the likelihood that in more advanced immunosuppression, chest radiography becomes more atypical.
Other diagnostic technologies available for TB detection in addition to the commonly available ZN staining and microscopy are indicated in table 2.5. The turn-around time for the Integrated Nucleic Acid Amplification Tests (see table 2.5), also known as GeneXpert is approximately 90 minutes long, making it the fastest way to diagnose TB disease using sputum. The sensitivity is also more than Ziehl-Neelson or Auramine test. In 2013, the NDOH rolled out GeneXpert to several public health facilities as the preferred method for diagnosing TB. GeneXpert is able to detect the presence or absence of both Mycobacterium tuberculosis complex DNA and rifampicin drug resistance (Peter & Theron 2011:404).

The Xpert MTB/RIF refers to a cartridge-based system that employs an automated real-time nucleic acid amplification technology for rapid and simultaneous detection of *Mycobacterium tuberculosis* and resistance to rifampicin (WHO 2011d:6). Also referred to as Gene Xpert, this test has been rolled out in select health facilities in South Africa and 76 other countries as at the end of 2012 (WHO 2013b). A recent demonstration study in 6648 participants found the sensitivity of a single GeneXpert assay for TB diagnosis to be 97% in smear-positive patients and 76.9% in smear negative TB cases with an overall specificity of 99% (Peter & Theron 2011:404).

Advantages of the test includes quicker turn-around time of 90-120 minutes for TB diagnosis and detection of rifampicin resistant TB when compared with AFB that has a turn-around time of 2-3 days and sputum culture that may takes up to 60 days to diagnose resistant TB. The test can also be performed in any laboratory where smear microscopy can be performed and does not require biosafety cabinets or highly skilled technicians (Conradie 2011:428). Conradie further indicates that the Xpert system is less specific than Hain test, a form of Line Probe Assay (LPA) and confirmation of MDR-TB by culture is still required.

The automated liquid culture systems are available in most South African laboratories and have largely replaced the traditional solid culture methods. Peter and Theron (2011:406) further indicate that though it offers better sensitivity and speed than the solid culture test, it is expensive and requires excellent laboratory infrastructure in order to maintain good quality control. The Microscopic-Observation Drug Susceptibility (MODS) provides a cheaper alternative to culture systems. However, it is labour-
intensive and suitable for research-limited settings with cheaper labour. It requires about 7 days for TB diagnosis.

The Rapid Speciation Line Probe Assay (LPA) is used for rapid genotypic rifampicin and isoniazid drug susceptibility testing. It has high sensitivity for rifampicin resistance. In South Africa, it is routinely available for MDR-TB suspects. Another point of care method for TB diagnosis is the lipoarabinomannan (LAM) rapid test. The test is designed for TB diagnosis in hospitalised HIV and TB co-infected patients with advanced immunosuppression using the urine sample. This method is not yet publicly available in South Africa even though it is cheaper than the GeneXpert.

Table 2.5  Diagnostic technologies for tuberculosis

<table>
<thead>
<tr>
<th>TECHNOLOGY</th>
<th>TURN AROUND</th>
<th>SENSITIVITY GAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziel Neelson (ZN)</td>
<td>2-3 days</td>
<td></td>
</tr>
<tr>
<td>Solid culture</td>
<td>30-60 days</td>
<td>Baseline</td>
</tr>
<tr>
<td>Liquid culture</td>
<td>15-30 days</td>
<td>+10%</td>
</tr>
<tr>
<td>Rapid speciation Line Probe Assay</td>
<td>2-4 days</td>
<td>Compared to LJ</td>
</tr>
<tr>
<td>Liquid culture</td>
<td></td>
<td>Currently smear positive only</td>
</tr>
<tr>
<td>Integrated Nucleic Acid Amplification Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene Xpert MTB/RIF</td>
<td>90 minutes</td>
<td>+40% compared to ZN</td>
</tr>
<tr>
<td>The Microscopic – Observation Drug - Susceptibility (MODS)</td>
<td>7 days</td>
<td>+14% compared to LJ</td>
</tr>
<tr>
<td>T-cell based assays (Interferon – y-based assays)</td>
<td>16-24 days</td>
<td>Overall sensitivity gain</td>
</tr>
<tr>
<td>LED-based fluorescent microscopy</td>
<td>1-2 days</td>
<td>Unknown</td>
</tr>
<tr>
<td>TB Antigen Detection (Lipoarabinomannan- LAM Assay)</td>
<td>3-4 hours</td>
<td>Overall sensitivity gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown; 52% sensitivity in HIV positive patients, specificity 89%</td>
</tr>
</tbody>
</table>

(Naidoo et al 2010:3)
For patients with clinical features suggestive of extra pulmonary TB, needle aspiration or tissue biopsy of skin lesions, lymph nodes, pleural or pericardial fluid should be performed for histopathological examinations (CDC 2009:22). Furthermore, mycobacterial blood cultures might be useful for patients with features of disseminated disease or worsening immunodeficiency. Lumbar puncture for analysis of the cerebrospinal fluid (CSF) is used for diagnosing TB meningitis. There is a predominance of lymphocytes with rise in proteins and fall in CSF glucose levels. Enhanced CT brain may show hydrocephalus, brisk meningeal enhancement or intracranial tuberculoma in patients with TB meningitis (Allen, Lueck & Dennis 2010:1208).

2.3.6 Treatment of tuberculosis in adults

TB disease needs to be treated with multiple drugs to avoid developing resistance. Resistance refers to clinical failure to respond to a prescribed treatment when any strain of the offending organism is unaffected by the medications. The use of more than one drug with different modes of action ensures complete clearance of the offending organism from the body. Drug resistant TB refers to any strain of Mycobacterium tuberculosis that is unaffected by one or more antibacterial drugs. This is purely a laboratory diagnosis (De Kock et al 2013:35). The resistant strain TB results in clinical failure to respond to the first-line anti-TB treatment. However, not all failure to respond to TB treatment implies that the TB strain is drug resistant. In some cases, failure to respond to anti-TB therapy is due to poor adherence, treatment default or direct infection with the resistant strain of the offending organism. These factors could, in turn, lead to development of resistant TB at a later stage.

South Africa was the first country to produce the four-drug fixed drug combinations (FDC) formulation recommended by the WHO for the treatment of TB disease and also became the first country to implement a fully FDC-based treatment regimen (FDP 2012:93). The FDC implies that several drugs are combined to form one single tablet. In South Africa, the combinations used include RHZE, RH (150, 75) and RH (300,150). FDC simplifies treatment, minimises prescription errors and simplifies the management of drug supply (Blomberg as cited in FDP 2012:91). Adherence to the medications among TB patients is also enhanced by the use of FDC as pill count is reduced and patients cannot be selective in the choice of drugs to ingest.
For ease of management, TB patients are classified into new or retreatment patients. New patient is defined as a patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than 4 weeks while retreatment refers to a patient who has taken TB treatment for 4 weeks or more in the past and either relapsed, defaulted or had treatment failure (The Aurum Institute 2012a:31). Figure 2.2 illustrates the FDC regimen for the treatment of new TB cases for adults also referred to as Regimen 1. The pre-treatment body weight, intensive phase and continuation phase treatment schedule is illustrated in the table, based on different weight bands.

The weight-based dosing for management of adult patients who have been previously treated for TB is illustrated in table 2.6. As indicated, a combination of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol in addition to daily injection with Streptomycin should be administered to patients for the first two months according to the pre-treatment body weight. The drugs will be continued in the next one month aside Streptomycin after which Rifampicin, Isoniazid and Ethambutol are used for another five months. Streptomycin should however not be administered to pregnant patients and elderly patients aged over 65 years.

![Figure 2.2 Adult Regimen (Regimen 1): New cases for adults](De Cock et al 2013:39)
Table 2.6  Adult Regimen (Regimen 2): Previously treated

<table>
<thead>
<tr>
<th>Pre-treatment body weight</th>
<th>Intensive phase (7 days a week for 2 months)</th>
<th>Intensive phase (7 days a week for 1 month)</th>
<th>Continuation phase (7 days a week for 5 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZE 150,75,400,275</td>
<td>RHZE 150, 75, 400, 275</td>
<td>RH 150, 75, E 400, RH 300, 150</td>
</tr>
<tr>
<td>30-37</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>38-54</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>55-70</td>
<td>4</td>
<td>4</td>
<td>3, 2</td>
</tr>
<tr>
<td>&gt;70</td>
<td>5</td>
<td>5</td>
<td>3, 2</td>
</tr>
</tbody>
</table>

(The Aurum Institute: A prescribers guide for managing TB & HIV)

Where rapid tests like LPA or Xpert MTB/RIF are available, all previously treated patients diagnosed with sensitive TB must be started on Regimen 1, instead of Regimen 2 while those confirmed as rifampicin resistant must be started on MDR-TB treatment. This implies that Regimen 2 will be phased out over time as scale-up of rapid tests for MDR-TB is implemented.

2.3.7 Drug resistant tuberculosis

Drug resistant TB refers to any strain of *Mycobacterium tuberculosis* that is unaffected by one or more antibacterial drugs and is purely a laboratory diagnosis (De Kock et al 2013:35). Drug-resistant TB results in clinical failure to respond to the first-line anti-TB treatment. However, not all failure to respond to TB treatment implies that the TB strain is drug resistant. In some cases, failure to respond to anti-TB therapy is due to poor adherence, treatment default or direct infection with the resistant strain of the offending organism.

In 2010, the WHO endorsed the use Xpert MTB/RIF (Gene Xpert) for the simultaneous testing for pulmonary TB and Rifampicin resistance (WHO 2013c:59). The GeneXpert test is also used routinely in most health facilities in South Africa as the first-line investigation to diagnose TB disease and it also detects resistance to Rifampicin which is one of the first-line anti-TB drugs. This could happen in either sputum smear positive or smear negative individuals.
Following detection of Rifampicin resistance, another sputum sample is sent for microscopy, culture and phenotypic drug susceptibility testing (DST) for confirmation. While awaiting the outcome of the DST, the patient is registered, notified and commenced on Multi-drug resistant (MDR-TB) treatment.

The outcome of the DST testing determines the next line of management. Diagnosis of MDR-TB is confirmed if resistance to Rifampicin and Isoniazid is detected in which case the management instituted earlier is continued. However, if the result indicates resistance to Rifampicin and susceptibility to Isoniazid, the patient is managed as mono-resistant TB in which case Isoniazid is added to the MDR-TB treatment. MDR-TB treatment is discontinued and substituted with the first-line anti-TB regimen outlined in table 2.7 if isoniazid mono resistance is detected by the DST.

Table 2.7   Intensive phase treatment of MDR-TB for adults and children >8 years

<table>
<thead>
<tr>
<th>Patients weight</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33kg</td>
<td>Kanamycin</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg (children: 7.5-10 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td>33-50kg</td>
<td>Kanamycin</td>
<td>500-750 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1000-1750 mg</td>
</tr>
<tr>
<td>51-70kg</td>
<td>Kanamycin</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1750-2000 mg</td>
</tr>
<tr>
<td>&gt;70kg</td>
<td>Kanamycin</td>
<td>1000 mg</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>2000-2500 mg</td>
</tr>
</tbody>
</table>

(De Kock et al 2013:54)

The duration of the intensive phase in MDR-TB treatment is determined by adding 4 months to the date of collection of the first sputum that turned TB culture negative while the duration the continuation phase will be determined by adding 18 months to the date
of TB culture conversion (De Kock et al 2013:54). Tables 2.7 and 2.8 indicate the MDR-TB treatment regimen for both the intensive and the continuation phases in adults and children older than 8 years. The actual dosing of the medications is determined by the weight of the affected patient. In addition to the standardised regimen, pyridoxine is to be given to patients on terizidone at a daily dose of 150-200 mg.

Table 2.8  Continuation phase treatment of MDR-TB for adults and children >8 years

<table>
<thead>
<tr>
<th>Patients weight</th>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>15-20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40 mg/kg</td>
</tr>
<tr>
<td>33-50kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1000-1750 mg</td>
</tr>
<tr>
<td>51-70kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>1750-2000 mg</td>
</tr>
<tr>
<td>&gt;70kg</td>
<td>Moxifloxacin</td>
<td>400 mg</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Terizidone</td>
<td>750-1000 mg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>2000-2500 mg</td>
</tr>
</tbody>
</table>

(De Kock et al 2013:55)

2.4  TUBERCULOSIS AND HIV CO-INFECTION

HIV is the strongest risk factor yet recognised in the reactivation of latent or new *Mycobacterium tuberculosis* infection to active TB disease (WHO 2011a:1). The increased risk of active TB occurs soon after HIV sero-conversion and doubles by the end of the first year of HIV infection (Granich, Akolo, Gunneberg, Getahun, Williams & Williams 2010:S215).

The lifetime risk of an infected but immune-competent individual developing active TB disease is around 10% with the highest risk in the first two years following infection (WHO as cited in FPD 2010b:14). The risk increases to around 10% per year in an individual infected with HIV (Wilson, Cotton, Bekker, Meyers, Venter & Maartens
Wilson et al. (2008:36) further indicate that while disease caused by the relatively non-virulent non-tuberculous mycobacteria such as *Mycobacterium avium* complex tends to affect those with very low blood CD4 lymphocyte counts, the risk of TB disease increases after HIV seroconversion and is elevated across the full spectrum of immunodeficiency, increasing steeply as the CD4 cell count declines.

A study on HIV-infected South African adults found that whereas ART alone decreased the adjusted risk of TB by 64%, the incidence of the disease remained high at 4.6 cases per 100 person years (Golub et al., 2009:5). This reflects a rate 10 times higher than the overall incidence of TB in the South African population and 1000-fold that in the United States.

In addition to high rates of reactivation TB, HIV-infected persons have also been found to have a heightened susceptibility to new exogenous infection and rapidly progressive primary disease. Genetic fingerprinting studies have shown that high TB recurrence rates are fuelled by a high rate of exogenous reinfection (Wilson et al., 2008:36). The HIV positive individuals that are co-infected with TB are about 21-24 times more likely to develop TB disease compared with those who are HIV negative (WHO, 2011b:61). This is because HIV weakens the immune system of the affected individual and may render it completely defenceless against the invading organism. A study carried out among miners in four mines located in Gauteng, South Africa, revealed that the HIV-positive miners were significantly more likely to develop TB disease than their counterparts who were HIV-negative (Sonnenberg, Glynn, Fielding, Murray, Godfrey-Fausseth & Shearer, 2004:153). The incidence of TB was found to have doubled within the first year and increased four-fold after 2 years among miners that participated in the particular study.

It is estimated that without intensified intervention, 2 million PLHIV will die of TB between 2011 and 2015 (WHO, 2011c:2). The African region accounted for about 82% of the new TB cases among PLHIV in 2010. This translates to an estimated 900,000 people representing 39% of the global 2.3 million HIV-positive individuals diagnosed of TB disease the same year according to the WHO (2011c:2).

About 65% of TB patients are co-infected with HIV compared to the global average of 20% and about 16% for the region of Americas (WHO, 2013c:70). FPD (2010b:127) indicate that TB is the commonest cause of morbidity and mortality among HIV-infected
population in South Africa and has been shown to accelerate HIV disease progression. This explains the recommendation that measures aimed at preventing TB among the HIV-infected should be offered in the package of care for people living with HIV (NDOH 2010b:4).

2.4.1 Clinical features of TB in HIV co-infected individuals

Several clinical features of TB are found in individuals co-infected with HIV. The clinical features of TB in HIV-infected individuals with high CD4 counts are similar to those of non-HIV-infected individuals with active TB disease with progression of deficient immune state associated with an increasing frequency of cutaneous abnormal immune response to purified protein derivative and an increased risk of extra pulmonary forms of TB disease (Wilson et al 2008:36).

The signs and symptoms include cough, profuse night sweats, loss of appetite, pleuritic chest pain, haemoptysis, fever and weight loss (FPD 2010a:154).

2.4.2 Diagnosis of TB in HIV-positive individuals

2.4.2.1 Sputum smear microscopy

The underlying immune status of the HIV-infected TB patient affects the sensitivity sputum smear microscopy result. This is in addition to other factors, such as poor quality of sputum, poor quality of laboratory service, and poor microscopy techniques (FPD 2010a:154). Sputum smear-negative TB is more commonly seen in HIV-infected individuals. Smears are negative in such individuals more often because cavities are less common as the organism load in tissues is higher than in individuals who are not infected with HIV (Peter & Theron 2011:404). In such situations, diagnosis is either made with a positive culture, gene Xpert test or with suggestive x-ray findings together with a medical decision to start TB treatment based on the clinical features.
2.4.2.2 **Xpert MTB/RIF**

The Xpert MTB/RIF test has been found to be 76.9% sensitive in smear negative TB cases which abound in TB/HIV co-infected individuals (Peter & Theron 2011:404). In most health facilities in South Africa, this test has replaced sputum microscopy test for routine use in diagnosing TB in HIV co-infected individuals.

2.4.2.3 **Chest X-ray**

In HIV-infected individuals, the chest x-ray could be used in establishing the diagnosis of TB where only one sputum sample is positive for TB or two negative sputum smears are noted in a patient who continues to cough despite a full course of broad-spectrum antibiotic (FPD 2012:121). FPD indicates further that in the early stages of HIV disease, common x-ray findings may include cavitation, focal infiltrates in the upper chest and hilar regions, hilar adenopathy and pleural or pericardial effusions. The findings may also be atypical with pulmonary infiltrates noted throughout the lungs rather than cavities in the upper lobes of the lungs. The sensitivity and specificity of chest x-ray in the diagnosis of active TB disease is reduced in smear negative mostly HIV-positive individuals due to less pronounced cavities and is operator-dependent (Cleef, Kivihya-Ndugga, Meme, Odihiambo & Klaster 2005:6). However, chest x-ray should not replace TB symptom screening as some chest x-ray findings are not specific to TB disease. The inconsistency in the reading and interpretation of x-ray among clinicians and radiologists further reduces the specificity of the x-ray in the diagnosis of active TB disease (FPD 2012:121). The WHO (2013d:81) recommends the use of chest x-ray as a second screening method for individuals with symptoms suggestive of TB after either sputum smear microscopy or rapid molecular test such as Xpert MTB/RIF. However, individuals with abnormal Chest x-rays suggestive of TB when done prior to the diagnostic tests should be further evaluated.

2.4.2.4 **Sputum culture**

Sputum culture testing is the gold standard for TB diagnosis in both HIV-infected and non-HIV infected individuals as HIV has no effect on the test sensitivity and specificity (De Kock et al 2013:25). This test could be done on any clinical specimen and has high
sensitivity with the added capability of detecting TB cases before they become infectious. Due to the fact that culture is more expensive and requires 2-6 weeks wait for the result, it is not considered as an initial diagnostic test except in settings where resources permit and the health system has sufficient capacity to ensure that patients are followed after the culture results are available (WHO 2013d:81). The long wait for the result could increase the morbidity and mortality associated with active TB disease. The culture may then be used in parallel with or after testing with the Xpert MTB/RIF or sputum-smear microscopy. FPD (2010a:155) indicates that this test is not necessary, however, if sputum microscopy has already tested positive but remains a useful tool for excluding active TB disease in an HIV individual prior to considering IPT. This was deemed important for the study as exclusion of active TB disease is recommended prior to commencing IPT on the patient.

2.4.3 Diagnosis of extra-pulmonary TB

This form of TB disease is more common in HIV-infected individuals, particularly those with low CD4 count. The lymph nodes, pleural cavity and the pericardium are the usual sites of HIV-associated extra-pulmonary TB (FPD 2012:121). Needle aspirations, inspection of biopsied lymph nodes for macroscopic caseation, cultures and direct smears for AFB are some of the methods of establishing diagnosis of extra-pulmonary TB disease. Blood cultures for Mycobacterium tuberculosis could also be used.

2.5 TB PREVENTIVE TREATMENT

2.5.1 Introduction

The WHO (2011a:1) provides clear recommendations about interventions needed to prevent, diagnose and treat TB in PLHIV. The recommendations are collectively referred to as collaborative TB/HIV activities, and include HIV testing of TB patients, provision of anti-retroviral therapy (ART) and CPT to TB patients living with HIV, HIV preventive services for TB patients, intensified TB case-finding among people living with HIV, isoniazid preventive therapy (IPT) for PLHIV who do not have active TB and infection control in healthcare and assembly settings. Active TB screening offers the opportunity to provide preventive therapy for those who do not have symptoms and signs of TB.
Isoniazid Preventive Therapy (IPT) refers to the intake of isoniazid by individuals that have latent infection with *Mycobacterium tuberculosis* in order to prevent the progression to active TB disease. The WHO (2011a:6) recommends that adults and adolescents living with HIV who have an unknown or positive Tuberculin Skin Test (TST) status and who are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care irrespective of the degree of immunosuppression, pregnancy status, whether the patient is on ART or have previously been treated for TB. In practice however, TST which identifies people with latent TB infection often constitutes an impediment for the provision of IPT. This is largely due to shortage of personnel to carry out the test and occasional reluctance of patients to return back to the clinic within 48 hours for the interpretation in addition to possible false positive or negative results. The NDOH (2013a:14) recommends a TST prior to commencing patients with no sign or symptom of TB on IPT. However, if no TST is done, IPT should be continued for six months but efforts should be made to perform TST as soon as possible after commencement on IPT.

Performing TST is important as it guides in determining the length of treatment. However, Rangaka, Wilkinson, Boulle, Glynn, Fielding, Cutsem, Wilkinson, Goliath, Mathee, Goemaere and Maartens (2014:7) revealed that the benefit of IPT on patients on ART was found to be greater in individuals who had negative TST compared to those who were positive and recommended IPT to all eligible patients receiving ART in moderate to high TB incidence areas irrespective of the TST results. According to the study, the finding that in HIV-positive patients with low CD4 count that reside in high prevalence areas tend to have more false negative TST results may have accounted for their finding. The outcome of this study differed from an earlier report by Wilkinson, Kon, Newton, Meintjes, Davidson, Pasvol and Wilkinson (2006:355) which found non-existent efficacy of IPT in TB-exposed individuals with negative TST results and concluded that TST may have been flawed in both sensitivity and specificity. IPT is however one of the interventions recommended by the WHO that reduce the morbidity and mortality from TB in PLHIV (WHO 2011b:1).

### 2.5.2 Mechanism of action of Isoniazid (INH)

INH is an artificial equivalent of pyridoxine that is made as a prodrug which when ingested is activated by a mycobacterial catalase-peroxidase (Howland & Mycek
Once ingested, the drug is activated and inhibits the enzymes that are used for the synthesis of mycolic acid in the mycobacterial cell wall.

Isoniazid exhibits bacteriostatic and highly potent bactericidal action against mycobacterium tuberculosis that causes TB disease (FPD 2010a:95).

### 2.5.2.1 Pharmacokinetics of INH

INH when taken orally is well absorbed though this could be impaired if the drug is taken with food or aluminium-containing antacid preparations (Howland & Mycek 2006:397). The drug penetrates the host cells where it acts against TB bacilli growing within the intracellular space. The inactive metabolic products and unchanged INH are excreted by the kidneys in the urine (Rossiter 2012:320).

### 2.5.2.2 Adverse effects of INH

Neurotoxicity is a notable dose-related adverse effect of INH. It could manifest as peripheral neuropathy, seizures, psychosis and optic neuritis according to Rossiter (2012:320). Peripheral neuropathy manifesting as paraesthesia is the most common adverse effect (Howland & Mycek 2006:397). This is thought to be due to the inhibitory effect of INH on the metabolites of pyridoxine and explains why pyridoxine is routinely prescribed for patients on INH for prevention and treatment of peripheral neuropathy (Lobue & Menzies 2010:609).

Hepatotoxicity in the form of drug induced hepatitis could occur with intake of isoniazid. This is caused by monoacetylhydrazine which is a metabolic product of INH (Howland & Mycek 2006:397). Regular alcohol consumption and age >35 years old are factors that are associated with development of INH-associated hepatotoxicity (Lobue & Menzies 2010:609).

Other possible adverse effects of INH include anaemia, hypersensitivity reactions, thrombocytopenia, neutropenia and hypersensitivity reactions manifesting as fever, chills and rarely arthritis (Rossiter 2012:320).
2.5.2.3 Drug interactions

INH interacts with the metabolism of several drugs. It can potentiate the adverse effects of Phenytoin by inhibiting the metabolism of the drug (Rossiter 2012:230). The adverse effects include nystagmus and ataxia. INH reduces the serum concentrations of Cyclosporine, ketoconazole and oral contraceptives and increases levels of pentamidine, ethosuximide, theophylline, diazepam and carbamazepine (Turner 2010:272).

2.5.3 Possible mechanisms of IPT efficacy

The effect of IPT on the incidence of TB may therefore have been because of treatment of early, subclinical or latent Mycobacterium tuberculosis infection (Zar, Cotton, Strauss, Karpalis, Hussey, Schaaf & Rabie 2006:5). Zar et al (2006:5) further indicate that IPT may have provided primary or secondary prophylaxis against infection. Rangaka et al (2014:7) reported recently that treatment for latent TB with INH alters the body’s immune response to tuberculosis by releasing mycobacterial antigens. Increased numbers of Mycobacterium tuberculosis-specific gamma interferon-producing T-cells was noted after commencing patients on INH (Wilkinson et al 2006:357). INH is a potent anti-TB drug that works by inhibiting mycolic acid synthesis in the bacterial wall and is found to be bactericidal after 24 hours of ingestion (FPD 2010a:95).

2.5.4 Advantages of IPT

In a study in Cape Town, isoniazid prophylaxis was found to have significantly reduced mortality in children with HIV who were living in areas with high prevalence of TB and the incidence of confirmed or probable TB cases by intention to treat analysis was found to be lower in the isoniazid group than in the placebo group (Zar et al 2006:5). Thus, the protective effect of isoniazid on the incidence of TB occurred in all categories of severity of clinical disease in children aged more than one year and in both dose regimen. Ayieko, Abuogi, Simchowitz, Bukusi, Smith and Reingold (2014:9) found that IPT reduces the risk of TB by 59% among children ≤15 years of age and thus confers protective effect against TB among HIV-negative children. Zar et al (2006:5) nevertheless acknowledged that their study lacked sufficient data required to make a definite conclusion on the efficacy of INH in preventing TB in HIV-positive children.
Some level of protection against TB and a reduction in mortality among the TST-positive subjects studied were noted after six months intake of isoniazid (Hawken, Mene, Elliot, Chakaya, Moris, Githui, Juma, Odhiambo, Thiong’o, Kumari, Ngugi, Bwayo, Gills, Plummer, Porter, Nunn & McAdam 1997:881). The study findings were not statistically significant when compared to the group of study population that did not receive isoniazid. Golub, Pronyk, Mohapi, Thsabangu, Moshabela, Struthers, Gray, McIntyre, Chaisson and Martinson (2009:5) also indicate that the combined effect of both IPT and ART was associated with 89% decrease in the adjusted risk for TB with a crude incidence of 1.1 cases per 100 person years following a study they conducted. This implies that in conjunction with ART initiation, widespread use of IPT has the potential to lead to further reductions in TB incidence among the HIV-infected adults in high TB burden settings. Also, 12 months of IPT reduced the incidence of tuberculosis in patients receiving ART by 37% (Rangaka et al 2014:6). A retrospective study of HIV positive patients in Ethiopia revealed that initiating IPT after starting ART resulted in 92% protective effect from active TB disease (Yirdew, Jerene, Gashu, Edginton, Kumar, Letamo, Feleke, Teklu, Zewdu, Weiss & Ruff, 2014:4). However, this group of patients was considered low risk prior to the study as TB disease incidence after their initiation on ART but prior to IPT was 0.2 per 100 person years.

In the public health perspective, INH prophylaxis is cost effective, extends life expectancy, reduces the incidence of TB and promotes savings in medical and social costs in adults with HIV, especially those who are tuberculin skin test positive and INH has also been shown to inhibit the development of malarial parasite (Zar et al 2006:5).

Concerns about implementing IPT programmatically include difficulties in detecting active TB, selection for INH resistance and toxicity and achieving optimal adherence to IPT. Good adherence to IPT appears to be a historical problem with a reported 54% of patients receiving the recommended 6 months of IPT in a study by Golub et al (2009:5).

Active TB can be excluded using relatively simple screening measures and there is little evidence that IPT results in the emergence of drug resistance (Golub, Saraceni, Caucante, Pachebo, Moulton, King, Efron, Moore, Chaisson & Durovni 2007:7). A TB preventive therapy is an effective intervention for HIV-infected individuals and all people living with HIV should be screened for active TB and assessed for their eligibility to be enrolled on ART (NDOH 2013a:14). While those who are eligible for ART should be
started on ART, all PLHIV in whom active TB have been excluded should be started on IPT unless alcohol abuse, adherence to IPT when instituted or possible side effects are of concern in which case counselling should precede IPT according to NDOH.

There has been concerns that intake of IPT could lead to INH-resistant TB (Balcells et al 2006:744). This is one of the reasons adduced for poor uptake of IPT for the prevention of progression to active TB disease in interactions between the researcher and some clinicians. However, the main cause of resistance to anti-tuberculosis medication has been found to be inadequate treatment of active TB disease (Balcells et al 2006:760). Isoniazid resistant-TB was not significantly attributable to previous IPT intake according to Balcells et al (2006:760). TB disease among mostly HIV-infected people who took IPT had treatment outcomes and similar prevalence of isoniazid resistance when compared with findings from similar setting among those that did not take IPT (Van Halsema, Fielding, Chihota, Russel, Lewis, Churchyard & Grant 2010:1054).

Routine diagnosis of isoniazid mono-resistance TB by DST in isolation is not programmatically recommended by the WHO which rather, recommends that DST should be performed after the conventional testing method has detected resistant TB (WHO 2010b:88). In South Africa, DST is required to make a definitive diagnosis of MDR-TB only after the Xpert MTB/RIF has already detected Rifampicin-resistance TB in which case, IPT cannot be implicated as the sole cause of the resistant TB (NDOH, 2011c:36). Routine six to nine months of treatment with regimen of medications used during the intensive phase (Fixed dose combination of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol) is however recommended for Isoniazid mono-resistant TB (De Cock et al 2013:52).

Notwithstanding the absence of definitive evidence from randomised controlled trials on optimal duration of IPT in HIV-infected patients, data from several observational studies demonstrate that IPT is both cost effective and beneficial through combating low bacillary load latent TB which serves as a reservoir for recurrent disease (Naidoo, Naidoo, Padayatchi & Karim 2010:3). Naidoo et al (2010:3) also found that the concurrent administration of ART and IPT has demonstrated a TB risk reduction of 76-89% in observational studies from both SA and Brazil though the protection offered by IPT to those infected with HIV may depend on a number of factors. These factors
include degree of immune suppression of the individual, duration of IPT, adherence to and potency of the regimen as well as general risk of reinfection in that setting.

### 2.5.5 Duration of IPT

Prior to commencing a patient on IPT, both the WHO (2011a:5) and NDOH (2013a:14) recommend that active TB disease should be excluded prior to commencing IPT. The screening entails asking the patients about the existence of symptoms suggestive of active TB disease. The questions are outlined in the screening tool developed by NDOH (see Annexure F) and include existence of cough, loss of weight, night sweat or fever. It is recommended that where any of the symptoms exist, further screening for active TB disease using Xpert MTB/RIF, chest x-ray or sputum culture where indicated should be performed. See Annexure G for the recommended screening algorithm for TB prophylactic therapy.

While more studies are required to establish optimal duration of IPT in HIV-infected patients in high burden TB settings, current data suggest benefits from IPT when used for a period of nine months post-TB therapy (Naidoo et al 2010:3). The recommended dose is 5mg/kg to a maximum of 300mg daily with pyridoxine administered alongside Isoniazid to suppress the side effects (NDOH 2013a). Table 2.9 indicates the NDOH recommendations regarding the duration of IPT. Where no TST is done and the patient is not on ART with a CD4 cell count of >350, IPT should be administered for 6 months with efforts intensified towards performing TST as soon as possible after starting IPT. The same duration of treatment is recommended for patients on ART. However, if the TST done is negative, IPT should be continued for 12 months for those on ART while those not yet on ART with CD4 more than 350 should receive IPT for 6 months. At the same time, where TST done on a patient that qualifies for IPT is positive and the patient is not yet on ART with CD4 count more than 350 or on ART, IPT should be taken for at least 36 months. Table 2.9 illustrates a summary of the NDOH recommendations for the institution of IPT. In the USA, INH is recommended to be taken for 9 months though some public health programmes recommend 6 months, based on cost-effectiveness (Lobue & Menzies 2010:608).
Table 2.9  Summary of NDOH recommendations for IPT administration

<table>
<thead>
<tr>
<th></th>
<th>Pre-ART</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST not done</td>
<td>IPT for 6 months</td>
<td>IPT for 6 months</td>
</tr>
<tr>
<td>TST negative</td>
<td>IPT for 6 months</td>
<td>IPT for 12 months</td>
</tr>
<tr>
<td>TST positive</td>
<td>IPT for at least 36 months</td>
<td>IPT for at least 36 months</td>
</tr>
</tbody>
</table>

(NDOH 2013a:14)

2.6 CONCLUSION

This chapter discussed the literature review undertaken for the study. The literature covered the epidemiology, pathogenesis, transmission, clinical features, current investigation modalities and treatment of TB, HIV, and TB co-existing with HIV. The possible mechanisms of IPT efficacy, advantages and recommended duration of IPT were also discussed. Although the researcher found no literature or data on the incidence of TB disease after intake of IPT in iLembe district and poor adherence to IPT, the literature review guided the researcher in terms of developing the questionnaire.

Chapter 3 describes the research design and methodology.
CHAPTER 3

Research design and methodology

3.1 INTRODUCTION

This chapter discusses the research design and methodology, including the population, sampling and sample, data collection and analysis, data-collection instrument, and ethical considerations.

3.2 RESEARCH DESIGN

A research design refers to the overall structure or plan for the research (Bowling 2009:158). Grove et al (2013:195) define a research design as a blueprint for conducting research which is the entire strategy for the study. The researcher conducted quantitative, non-experimental, descriptive, retrospective cohort study to ascertain the incidence of TB amongst adult HIV-positive clients who received IPT at Isithebe Clinic, KwaZulu-Natal, South Africa.

Protection from TB disease after 6 months duration of IPT declined after 18 months of commencing the therapy (Johnson, Okwera, Hom, Mayanja, Kityo, Nsubuga, Nakibali, Loughlin, Yun, Mugyeni, Vernon, Mugerwa, Ellner & Whalen 2001:2144). Protection from TB disease has been found to last up to 30 months (Aït-Khaled, Alacron, Bissell, Boillot, Caminero, Chiang, Clevenbergh, Dlodlo, Enarson, Enarson, Ferroussier, Fujiwara, Harries, Heldal, Hinderaker, Kim, Lienhardt, Rieder, Rusen, Trébucq, Van Deun & Wilson 2009:930). Given these findings, the researcher chose the duration used for the study to allow for between 15 and 30 months protective action of IPT prior to data collection and analysis. Thus data were collected from clinic records of patients who were commenced on IPT between July, 2010 and November, 2011.

A non-experimental design was appropriate because there was no manipulation of the independent variables, no intervention took place and the setting was not controlled (Brink, Van der Walt & Van Rensburg 2012:112). A descriptive study refers to a simple
description of the health status of a community based on routinely available data or on
data obtained in special surveys thus the study was descriptive in nature (Bonita et al
2006:40).

In studies with a retrospective design like this one, a phenomenon existing in the
present is linked to a phenomenon that occurred in the past (Polit & Beck 2012:224).
Retrospectively, data for this study were collected from records of HIV-positive patients,
who accessed IPT from Isithebe Clinic between July, 2010 and November, 2011. Thus
whether TB occurred among the population under study was linked to their intake of IPT
within the designated period. Both the proposed cause, which is intake of IPT, and the
proposed effect, which in this study refers to occurrence of TB disease in the sample
population, had already occurred and the variables were not manipulated (Grove et al
2013:219). The choice of a cohort study was because the records were for a group of
people who shared certain characteristics, which in this case were HIV-positive clients
commenced on IPT that were followed-up after 6 months of treatment (Joubert & Ehrlich

3.3 RESEARCH SETTING

The research setting refers to the location where a study is conducted (Grove et al
2013:373). A natural (field) setting where the environment was uncontrolled was chosen
for the study. The research was conducted at Isithebe Clinic that falls under the
Mandenki Municipality. Mandeni is a municipality in iLembe Health District of KwaZulu-
Natal Province in South Africa.

Isithebe is an industrial area adjacent to formal urban settlement in Mandeni. It is
therefore classified as an urban area (Statistics South Africa 2004:16). Located in the
northern part of the district (see figure 3.1), the clinic provides the full complement of
HIV/AIDS/TB management to the inhabitants of Mandeni Municipality and others who
attend the clinic.

Services rendered include Provider-initiated Counselling and Testing (PICT); HIV
Counselling and Testing (HCT); wellness clinic; Post Exposure Prophylaxis (PEP); Adult
and Paediatric antiretroviral treatment; Prevention of Mother-to-child transmission
(PMTCT) services; adherence support, assessment and monitoring; TB/HIV care; family
planning and other related services. The clinic attendees are largely semi-skilled and unskilled workers of the Isithebe Industrial Area and their families.

3.4 POPULATION

Population refers to the entire aggregate of cases in which a researcher is interested. The accessible population refers to the cases that conform to the inclusion criteria and are available for the study, and the target population is the aggregate of cases to which the researcher would like to generalise the findings (Polit & Beck 2012:274).

Figure 3.1 Map of iLembe District showing health facilities located in the district (iLembe District Municipality 2014:30)
A total of 441 records were identified for the study according to the daily clinic attendance register that was available. From the 441, 104 clinic records of HIV-infected adult clients managed at Isithebe Clinic met the eligibility criteria for the study and were the sample. The criteria to be included in the study were evidence that the patient tested HIV positive, was more than 18 years old and commenced IPT at Isithebe Clinic. The cut-off enrolment month of November 2011 was chosen because the records of the patient for 15-30 months were followed to ascertain if they developed active TB disease after using IPT. The records of patients enrolled on IPT earlier than July 2010 was not used due to limitation in finances and time constraints.

The number of records used was less than initially anticipated. This was due to the discovery during the data collection stage that many of the patients initially indicated as eligible for the study judging from the entries on the daily clinic register were screened for TB disease but were not eventually enrolled for IPT. Inadequate record keeping also made it difficult to access some of the records while some of the patients whose records initially met the eligibility criteria while the study was proposed no longer qualify for the study. This was because they were no longer accessing care at the facility. It was therefore difficult ascertaining whether they had active TB disease after intake of IPT.

3.5 SAMPLING

The study sample refers to the most basic unit of the population element about which data are collected (Polit & Beck 2012:275). Consecutive sampling was used for the study. The entire 104 patients’ records that met the inclusion criteria were used. According to the daily clinic register, 441 HIV-positive patients were enrolled on IPT within the period being studied. However, during the actual perusal of the identified folders, it was discovered that the majority of them were screened for TB disease but were not eventually commenced on IPT, thus only 104 were included in the study.

3.5.1 Inclusion criteria

The clinic records of patients that were used for the study met the following criteria:

- Evidence that the patient tested positive for HIV.
The patient was 18 years or older. The choice of 18 years is because of the legal requirement of securing consent from parents which could be difficult considering the design of the study. Thus the study was intended for adult population.

IPT was commenced from July, 2010 up to November, 2011.

The therapy was commenced at Isithebe Clinic.

3.5.2 Exclusion criteria

Clinic records were excluded from the study sample if:

- They belonged to patients that were demised before commencement of the study.
- The patients relocated from the area and were therefore transferred out of the facility for ongoing care at another facility at the time the data was collected.
- Patients were lost to follow-up after initial screening.
- IPT was discontinued due to adverse drug reaction.
- The patients were mentally challenged adults commenced on IPT.
- The records were incomplete with key data elements such as gender, age and IPT starting dates and screening to exclude active TB disease missing.

3.6 RESEARCH TECHNIQUE

3.6.1 Data-collection instrument development

The development of the structured data-collection instrument took considerable time. The researcher developed the data-collection sheet after scrutinising literature relevant to the research topic, the problem and the objectives. The data-collection instrument was then submitted to the Supervisor as well as a panel of experts and scientific committee in the Department of Health Studies at UNISA for scrutiny and comment, before the pilot study was conducted.

Table 3.1 describes the variables recorded in the data-collection instrument and their categories of measurement. For the independent variables, age was continuous numerical, gender was nominal categorical; number of months on IPT was discrete
numerical while the TB screening method was numerical categorical. The dependent variables were also described.

**Table 3.1  Research variables and levels of measurement**

<table>
<thead>
<tr>
<th>INDEPENDENT VARIABLES</th>
<th>CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Continuous numerical</td>
</tr>
<tr>
<td>Gender</td>
<td>Nominal categorical</td>
</tr>
<tr>
<td>Number of months on IPT</td>
<td>Discrete numerical</td>
</tr>
<tr>
<td>TB screening method</td>
<td>Numerical categorical</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DEPENDENT VARIABLES</th>
<th>CATEGORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count</td>
<td>Continuous numerical</td>
</tr>
<tr>
<td>Viral load</td>
<td>Continuous numerical</td>
</tr>
<tr>
<td>Diagnosis of TB after IPT</td>
<td>Nominal categorical</td>
</tr>
</tbody>
</table>

The data-collection instrument contained closed questions with numerical values attached to each of them to ensure standardised recording. The choice of closed questions was to ensure easier administration and analysis as well as save time (Polit & Beck 2012:298).

The data-collection instrument was structured into three sections:

- **Section A:** This section contained the biographical data, including the identification code, age (in years), gender and date of commencement on ART, if the patient was already taking ART.
- **Section B:** Section B contained information relating to IPT, including pre-screening for TB disease, method of TB screening used to exclude the disease prior to initiating on IPT, date of commencing IPT, number of months the patient received IPT, completion status, and number of months used to complete a course of IPT. The reason for stopping where indicated in addition to TB-disease status of the patient post-IPT was also included.
- **Section C:** This section contained information pertaining to the last clinic visit of the patient prior to retrieval of the data from the clinic records. The last viral load and CD4 count of the patient, where retrievable, were the last part of this section.
3.6.2 Validity

Validity refers to the extent to which an instrument measures what it is supposed to measure (Polit & Beck, 2013:336). It affirms the appropriateness of the data-collection instrument for the purpose for which it was designed (Grove et al 2013:394). The researcher extensively reviewed the literature and consulted with professional colleagues prior to designing the data-collection instrument. This enhanced the validity of the instrument.

The use of medical records, which were extracted solely by the researcher, eliminated the possibility of influencing respondents’ responses thus enhancing the validity of the data-collection instrument.

3.6.3 Reliability

The reliability of an instrument means the consistency of the measures in the study (Grove et al 2013:389). Similar recordings of same clinic records were observed by different health workers when the data-collection instrument was evaluated during the pilot testing. This ensured the reliability of the instrument. The instrument was also submitted to the supervisor and a panel of research experts for review prior to commencement of the study.

3.6.4 Pilot testing

A pilot test of the data collection instrument was conducted at Isithebe Clinic prior to commencing data collection. The purpose of the pilot study was to evaluate the appropriateness and quality of the instrument. The 20 records used for the pilot study were conveniently selected. They were records of HIV-positive adults who received IPT prior to the period used for the main study. The pilot study did not lead to any further modification of the instrument or the study procedures and the results were not included in the analysis of the data.
3.7 ETHICAL CONSIDERATIONS

Research ethics refers to the moral principles guiding research (Oxford Advanced Learner’s Dictionary 2010b:500). Since the first major international code of ethical principles in medical research referred to as the Declaration of Helsinki was produced by the World Medical Association in 1964, several ethical guidelines have been enacted by various countries, professional bodies and institutions (Barrett & Coleman 2005:556).

In collecting data and other aspects of the study, the researcher maintained sound ethical principles in line with the ethical guidelines of the Department of Health Studies, UNISA and the KwaZulu-Natal Department of Health.

Ethical approval for the study was obtained from the Research Ethics Committee of the Department of Health Studies, University of South Africa (see Annexure D). Permission for the study was also obtained from the KwaZulu-Natal Department of Health, iLembe District Department of Health and from the Management of Isithebe Clinic (see Annexures C and E). In order to maintain anonymity and confidentiality, the actual names of the participants whose records were used for the study were not indicated in the final entries entered onto the statistical software for analysis. In place of the actual names and file numbers, a code was used for identification. All the documents relating to the study were stored away from public access and will remain so for at least 5 years. The electronic data were password-protected to ensure denial of access to the data by unauthorised individuals.

3.7.1 Protecting the rights of the institutions

Permission to carry out the study was granted by the KwaZulu-Natal Department of Health. See Annexures D and E for the responses to the letters requesting permission to conduct the study and the authorisations letters from both the University and KwaZulu-Natal Department of Health.

Authorities at the District Department of Health, iLembe, Sundumbili Community Health Centre and Isithebe Clinic were also assured in writing that sound ethical principles would be upheld by the researcher. This ensured that the confidentiality attached to patient information was not compromised during and after the study. Only the researcher abstracted the required information from the clinic records of the patients.
Data collection occurred during weekends when the patient traffic was lower than that experienced during the week. This ensured minimal disruption of clinic activities and enabled better concentration. The researcher also undertook to share the findings and recommendations of the study with the facility, district and provincial department of health.

3.7.2 Right to self-determination

Self-determination means that the research respondents should be treated as autonomous agents and allowed to voluntarily decide whether to participate in the study (Polit & Beck 2012:154). It also implies that the respondents have the right to withdraw from the study at any time of their choice without any penalty (Grove et al 2013:164).

The study only involved the review of clinic records and therefore no patient was personally involved in this study.

3.7.3 Right to privacy

The right to privacy refers to the right of the research respondent to determine the manner in which personal information will be shared or withheld from another party (Grove et al 2013:69). The researcher was granted access by the Provincial Department of Health as no contact was made with the patients while carrying out the study. Only the researcher had access to the patients’ information prior to coding.

3.7.4 Right to anonymity and confidentiality

Anonymity refers to a situation where the identity of the research respondents and the responses provided during data collection will not be linked back to them by any individual. Confidentiality refers to the proper management of information provided by the research respondents for the purpose of the study such that the information will not be shared or disclosed to others without prior authorisation from them (Grove et al 2013:172). The respondents thus have the right to anonymity in addition to the understanding that the data collected will be kept confidential.
The researcher took the following steps to ensure that breach of anonymity and confidentiality did not occur:

- Collation of the required information from the clinic records was done solely by the researcher.
- Assigning a unique identification code to represent each patient record. This was carried out after data cleaning and prior to commencing analysis.
- Storing the data in a locked cabinet and the soft copies in a password-protected and secured database maintained by the researcher.
- The study findings were reported in a way that the information could not be traced to any individual.

3.7.5 Right to fair treatment

This is based on the ethical principle of justice and dictates that everyone should be treated fairly (Grove et al 2013:173). In upholding this principle during the study, selection of research respondents was based on the requirements for the study and not on their vulnerability (Polit & Beck 2012:155). No one was discriminated against on the basis of their disease status or social standing. Though there was no direct interaction with the research respondents, the researcher demonstrated respect for their different backgrounds. The Provincial Department of Health was also afforded the right to terminate the study at any stage without any litigation.

3.7.6 Right to protection from discomfort or harm

This is based on the ethical principle of beneficence which indicates that the researcher should do well and not harm the respondents (Grove et al 2013:174). Though there was no direct invasion of privacy by the researcher while accessing the records of the respondents, the benefits of the study outweighs the possible harm that could befall the participants. There was no monetary reward to them. However, the findings of the study will be shared with the provincial health authorities with recommendations aimed at enacting more positive intervention strategies in the area of TB disease control.
3.7.7 Scientific integrity of the researcher

The goal of the study is to generate sound scientific knowledge. This is possible through honesty in conducting, reporting and publication of studies (Burns & Grove 2005: 187). The Department of Health Studies, University of South Africa maintains list of events that typifies research misconduct. These include plagiarism, dishonesty, personal accountability, and adhering to the University rules and regulations pertaining to research.

The researcher did not display misconduct during the course of the study by carrying out the following steps:

- Avoided plagiarism and other forms of dishonesty by ensuring proper referencing of ideas, words and findings made by other researchers.
- Undertook the research in such a manner that the values of the environment and the society were not threatened.
- Observed sound ethical principles during all stages of the study, including when the research respondents were selected and when data was extracted from their clinic records.
- Preserved the research data in the prescribed manner and ensured confidentiality at all times.
- Provided an accurate report of the study findings and sound recommendations that will impact positively on society.
- Maintained a fair and open relationship with the Supervisor and the relevant authorities of the university.

3.8 DATA COLLECTION

3.8.1 Data sources

The data for the study was sourced from the clinic records of patients who complied with the inclusion criteria of the study. Sourcing data from pre-existing medical records and documents is advantageous because they enable examination of trends of a phenomenon under study over a period of time especially when data is collected repeatedly (Manda 2009:63). It also eliminates bias which could be introduced into the
study by twisting responses when they are sourced directly from the respondents. Recall biases are also reduced. These could occur when respondents are approached physically to provide information relating to a study by recalling the events that transpired during the period under review.

The researcher did not encounter any uncooperative stance from the participants since the data was sourced from the records (Polit & Beck 2012:190). Polit and Beck (2012:190) further indicate that collection of original data could be time-consuming and expensive. The choice to review records was to minimise cost and time, yield data that could not be influenced by the respondents and also allow for comparison (Katzenellenbogen & Joubert 2007:108).

The clinic records utilised for the study were kept at the facility. Each patient who accessed care at the clinic has a unique identifier that enables better filing and easy retrieval by the Administration Clerk employed by the Provincial DOH. The identifiers are in the form of alphabets and numbers and are clearly written out on the patients’ clinic records.

The identifiers that belong to patients commenced on IPT within the stipulated period were initially extracted from the daily clinic attendance register and IPT register. The daily attendance register supplied centrally by the Province basically contains the identifiers, name of patients, gender, age, date of presentation at the local clinic, diagnosis, treatment given and outcome.

With the assistance of the clerk, the identified folders containing the patients’ medical records were retrieved from the filing section of the facility. The folders contain more detailed information about the patients. Apart from the demographic information, the details of management for the patient at each presentation at the clinic are in the records. These include the date of presentation, brief history of presenting complaints, vital signs, examination findings, diagnosis, and management plans. Hard copies of investigation results, TB screening tools and treatment charts are also enclosed in the folders. Strict confidentiality was maintained while collecting the data and the names of the patients were replaced with unique letters on the data-capture sheet.
The strategy of sourcing data from the records utilised by the researcher was therefore deemed advantageous.

Having worked closely with the facility, the researcher has a good understanding of the various tools and record-keeping procedures used in the facility. However, there were challenges retrieving some of the folders due to incorrect filing. They were not deemed significant enough to affect the findings of the study. The researcher secured the necessary authorisations from the relevant authorities and did not experience difficulty accessing the required data.

3.8.2 Data-collection approach and method

The researcher used a structured data-collection method. This involved the use of a formal written-out data-collection instrument to collect and record information (Polit & Beck 2012:191). After review by a panel of research experts and approval from the Higher Degrees Committee of the Department of Health Studies at UNISA, the researcher sourced the data for the study from the patients’ clinic records that met the inclusion criteria (see section 3.5.1). They were entered onto an electronic spreadsheet (data-collection instrument) that was developed by the researcher. The data-collection instrument contained a pre-determined set of questions that were meant to be answered in a specified sequence. The use of a structured data-collection method ensured that the data were relatively easy to quantify and analyse (Polit & Beck 2012:191). After recording the data, the researcher thoroughly checked the data for completeness before proceeding to analyse them.

3.9 STUDY VALIDITY

Study validity refers to a measure of the accuracy of the research findings. This provides the main basis for the decision regarding aspects of the findings that are deemed sufficiently valid enough as to provide evidence base for practice (Grove et al 2013:197). Threats to validity are the various reasons that will make the findings of a study possibly wrong (Polit & Beck 2012:236).
Types of validity include statistical conclusion validity, internal validity, construct validity and external validity (Grove et al 2013:197). The internal and external validity of this study will be discussed.

3.9.1 Internal validity

Internal validity refers to the extent to which the outcome of the study represents a true reflection of reality rather than due to extraneous variables (Grove et al 2013:199).

The following measures were undertaken by the researcher for the purpose of enhancing the internal validity of the study:

- The review of records not including a respondent enhanced internal validity as it eliminated possible subject attrition. Attrition in the context of a study refers to the fact that some research respondents do not complete the experiment for a variety of reasons, such as failure to participate in all phases of the study (Christensen 2004:204). In selecting the records for the study, there was no interaction with a respondent. All the records that met the inclusion criteria within the stipulated period of the study were used.
- There was no influence on the researcher by the province, fellow health workers or the patients as the researcher personally collated the information from the various clinic records used for the study. This enhanced the internal validity.

3.9.2 External validity

External validity refers to the extent to which the study findings can be generalised beyond the sample used for the study (Grove et al 2013:202). Optimal enhancement of external validity implies that the outcome of the study can be generalised across variations in people, settings, treatments, outcomes and times (Christensen 2004:217).

The clinic records of adult HIV-positive patients aged 18 and above that met the inclusion criteria within the stipulated period were used for the study. Since the patients whose clinic information was used for the study were from an identified target population and setting, the outcome of the study can be generalised to similar groups of people who share the same social characteristics and psychosocial circumstances. The
research respondents were deemed to be representative of the population of HIV-positive patients who access IPT services from state clinics located in the rural/semi-urban areas.

The guidelines used in managing the patients were drawn up by the National Department of Health, South Africa and the KwaZulu-Natal Provincial Department of Health. This maintains uniform approaches to IPT across all the health facilities. There was no identified variability in management protocols in the course of the study at Isithebe Clinic.

The researcher did not interact with patients as only their clinic records were used. This eliminated the possibility of refusal to participate in the study and possible selection bias. This further strengthened the external validity.

3.10 CONCLUSION

This chapter discussed the research design and methodology used in the study. The research methods included population, sampling, data collection and instrument, and the ethical considerations. The measures taken to ensure internal and external validity were also discussed.

Chapter 4 presents the data analysis and interpretation, with reference to the literature review.
CHAPTER 4

Data analysis and interpretation

4.1 INTRODUCTION

This chapter discusses the data analysis and interpretation and the findings.

The research objectives were to describe:

- The demographic characteristics (age and gender) of adult HIV-positive clients on antiretroviral therapy who received isoniazid preventive therapy.
- The incidence of tuberculosis among clients that completed a 6-month course of IPT.
- The defaulter rate for adult clients that were commenced on IPT.

The results of the data analysis extracted from the clinic records of 104 patients who met the inclusion criteria (see chapter 3, section 3.5.1) are discussed.

4.2 DATA MANAGEMENT AND ANALYSIS

Data analysis refers to the process of organising, interpreting and communicating numerical information (Polit & Beck 2013:379). Descriptive and analytic statistics were used to describe and synthesise the data. The researcher engaged the services of a Public Health Practitioner/Statistician who analysed the data, using the IBM SPSS statistical software program version 21. While descriptive statistics were used to describe the demographic characteristics, analytical statistics using the Chi-square test measured the associations between gender and age distributions of the respondents and those that completed IPT at six and nine months. The 95% level of confidence (95% CI) and a probability of p<0.05 were used as the definition of significance while comparing the groups. The study findings are discussed in line with the study objectives and presented in the form of graphs and tables.
In the discussion of the results the following will apply:

N: Capital letter “N” will represent the total number of files audited.
n: Small letter “n” will represent the number of files that were included when a specific issue was audited, thus excluding the files where that information was not available or where only files of one gender were compared with the other gender.
f: Small letter “f” will represent the frequency.
%: The sign % will represent the percentage from either “n” or “N”, where applicable.

4.3 RESEARCH RESULTS

4.3.1 Baseline characteristics of the study population

A total of 104 (N=104) clinic records of HIV-positive adults accessing care at Isithebe Clinic that met the inclusion criteria were abstracted for analysis. Prior to commencing the analysis, the recorded data were crosschecked to ensure correctness. Of the respondents, 63.5% (n=66) were female and 36.5% (n=38) were male (see figure 4.1).

![Gender distribution of research respondents](image)

Figure 4.1 Gender distribution of research respondents
The youngest respondent was 24 and the oldest was 77 years old at the time of reviewing the clinic records. The mean age was 40.95 (standard deviation 8.467). For ease of analysis, the respondents were grouped into six age groups. The researcher used a 10-year interval for age analysis. The age group 38-47 had the highest frequency (39.4%; n=41), followed by 28-37 (36.5%; n=38). Only one respondent was aged between 58 and 67. Figure 4.2 is a bar chart illustrating the respondents’ ages in groups. The highest number of male respondents was in the 28-37 age group while most female respondents were between 38 and 47. In the age groups 18-27 and 68-77, there were only two male respondents in each group.

Figure 4.2 Age distribution of research respondents

The finding of more female respondents is similar to the trend in the HIV epidemic in South Africa where the HIV incidence is higher among women compared to their male counterparts (Rehle, Hallett, Shisana, Pillay-Van Wyk, Zuma, Carrara & Jooste 2010:4). In 2012, the age group with the highest prevalence of HIV among antenatal women was found to be 30-34 followed by 35-39 (NDOH 2013b:26). Rehle, Hallett, Shisana, Pillay-van Wyk, Zuma, Carrara and Jooste (2010:5) found the highest prevalence of men with HIV in the 30-34 years age group. This is similar to the finding of this study though the researcher did not use the exact age grouping as the NDOH and Rehle et al (2010)
4.3.2 Uptake of IPT among research respondents

All the research respondents were screened for TB prior to commencing intake of IPT. This was one of the inclusion criteria. In addition to using the screening tool, 12 of the respondents had their sputum tested for AFB prior to initiation on ART. The sputum testing was because they answered in the affirmative to at least one of the questions in the screening tool. It was therefore important to exclude a diagnosis of TB.

Figure 4.3 indicates that 31.7% (n=33) of the respondents completed IPT at six months. At the end of nine months, 63.5% (n=66) of the respondents completed IPT (see figure 4.4). This was because some respondents missed collecting their medications for some months or the isoniazid used for IPT was out of stock, but they did complete IPT within nine months. Treatment default in the context of TB management refers to a situation where interruption of treatment was recorded for two months or more (WHO 2013e:6). However, according to the IPT guidelines of the NDOH (2010c:5), the six months course of IPT can be completed within nine months. Thus defaulting IPT occurs when the treatment was not completed within nine months of commencement. The remaining 38 of 104 (36.5%) respondents were deemed to have defaulted as they did not complete IPT within nine months (see figure 4.4).

In a least-cost analysis study of IPT for TB in HIV-seropositive patients, Masobe, Lee and Price (1995:77) found an adherence rate of 68.5% in their epidemiological model. However, the index study findings revealed that 63.5% had completed the course of IPT. The proportion noted in this study is slightly higher when compared to Aisu, Raviglione, Van Praag, Eriki, Narain, Barugahare, Tembo, McFarland and Engwau’s (1995:267) finding that 62% of their respondents adhered to IPT. Also, in a study of adherence to TB preventive therapy among HIV-infected persons in Thailand, Ngamvithayapong, Uthaivoravit, Yanai, Akarasewi and Sawanpanyalert (1997:109) reported 69.4% adherence to IPT. Golub et al (2009:4) found an IPT adherence rate of 59%. Compared to the adherence rates of similar studies in various countries, the adherence rate of 68.5% was slightly higher. A more recent study in Addis Ababa Ethiopia found the level of adherence to IPT to be 89.5% (Berhe, Demissie & Tesfaye 2014:3). This adherence was self-reported and was defined as those that took more than 80% of their medications in the preceding one week prior to the study.
Figure 4.5 indicates that of the respondents, 18.4% (n=38) defaulted IPT because the drug was out of stock at the clinic; 13.2% (n=38) who defaulted were lost to follow-up, while 68.4% (n=38) defaulted solely because IPT was not prescribed for them. The exact reason for this was not stated in the clinic records of the affected patients. Thus, out of a total 38 respondents, 86.8% (n=38) defaulted because they did not receive IPT from the clinic for some months despite attending the clinic for their ART.
According to Goudge, Gilson, Russell, Gumede and Mills (2009:15), to ensure quality of care, the needed drugs to prevent TB should always be available to the patient. In this study, it was of concern that 33 out of 38 respondents who did not complete their treatment defaulted because IPT was not available to them: either not prescribed (26) or out of stock (7). This had a negative impact on the quality of care, further compounded by the fact that the clinic the respondents attend is within the catchment area of very low socio-economic class clients.

The reasons why 5 respondents were lost to follow-up were beyond the scope of this study as the reasons were not included in the files of the respondents. However, Ngamvithayapong (1997:110) reported outmigration for job search, HIV-status denial, side-effects of IPT and ignorance of the duration of treatment as the reasons for defaulting IPT. These might or might not be some of the reasons why the respondents in this study were lost to follow-up.
4.3.3 Gender distribution of respondents that completed IPT at six months

Table 4.1 Gender distribution of respondents that completed IPT at six months

<table>
<thead>
<tr>
<th>Completed at 6 months</th>
<th>Female</th>
<th></th>
<th>Male</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>% within gender</td>
<td>Count</td>
<td>% within gender</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>51</td>
<td>77.3</td>
<td>20</td>
<td>52.6</td>
<td>71</td>
<td>68.3</td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>22.7</td>
<td>18</td>
<td>47.4</td>
<td>33</td>
<td>31.7</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>100.0</td>
<td>38</td>
<td>100.0</td>
<td>104</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 4.1 indicates that the analysis of the respondents’ gender distribution revealed that only 22.7% (15 of 66) of the females while 47.4% (18 of 38) of the males completed at six months. Of these respondents, 77.3% (51) of the females and 52.6% (20) of the males did not complete IPT at six months.

It could be deduced from the cross-tabulation that gender plays a role on whether a patient completes IPT at six months (p<0.05) (see table 4.2).

Table 4.2 Chi-square test for gender distribution of respondents that completed IPT at six months

<table>
<thead>
<tr>
<th>Chi-Square Tests</th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>6.759a</td>
<td>1</td>
<td>.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

4.3.4 Gender distribution of respondents that completed IPT at nine months

The number of female respondents who completed IPT within six months increased to 57.6% (n=15) at nine months. This proportion accounted for 36.5% of all the respondents who completed (see table 4.3).

However, 73.7% (n=28) of the male respondents, representing 26.9% of all the respondents, completed IPT at the end of nine months. This represents an increase
compared to 18 males who completed IPT at the end of six months. Though inferential statistics indicate that males are more likely to adhere to the initial six months of IPT, there was no statistical significance between female and male respondents who completed IPT at nine months (see table 4.4).

Table 4.3 Gender distribution of respondents that completed IPT at nine months

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th></th>
<th>Male</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>% within gender</td>
<td>Count</td>
<td>% within gender</td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Completed at 9 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>42.4</td>
<td>10</td>
<td>26.3</td>
<td>38</td>
<td>36.5</td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>57.6</td>
<td>28</td>
<td>73.7</td>
<td>66</td>
<td>63.5</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>100.0</td>
<td>38</td>
<td>100.0</td>
<td>104</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 4.4 Chi-square test for gender distribution of respondents that completed IPT at nine months

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
<th>Exact Sig. (2-sided)</th>
<th>Exact Sig. (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>2.699a</td>
<td>1</td>
<td>.100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of Valid Cases</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. 0 cells (0.0%) have expected count less than 5
b. Computed only for a 2x2 table

Men were found to be more likely to complete a course of IPT at six months while at nine months there was no statistical significance between the male and female respondents who completed IPT. The lower social and economic status of women, which Krishnan, Dunbar, Minnis, Medlin, Gerdts and Padian (2008:102) noted as one of the key drivers of the HIV epidemic, could be responsible for this finding. Women tend to shoulder other domestic responsibilities that keep them away from work. Hence they could prefer stretching their treatment for fear of losing their jobs as they can only collect their medications by absenting themselves from work.

4.3.5 Age distribution of respondents that completed IPT

The age groups of the respondents who completed IPT at six months were analysed. The results indicated that the age group 38-47 recorded the highest number of
respondents who completed IPT at six months (see table 4.5). A total of 19 out of 41 (46.3%) respondents aged 38-47 completed IPT at six months. This proportion was higher than the figures recorded for respondents aged 28-37, the next most populated age group, while 12 out of 38 (31.6%) aged 28-37 completed IPT at six months. The majority of the respondents aged 48-57 did not complete IPT at six months: 18 of 20 (90%) respondents in this age group did not complete IPT at six months. No patients aged 18-27, 58-67 and 68-77 completed IPT at six months.

Table 4.5  Age distribution of respondents that completed IPT at six months

<table>
<thead>
<tr>
<th>Age in group</th>
<th>Completed IPT at six months (Yes/No)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>% within age group</td>
</tr>
<tr>
<td>18-27</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>28-37</td>
<td>12</td>
<td>31.6</td>
</tr>
<tr>
<td>38-47</td>
<td>19</td>
<td>46.3</td>
</tr>
<tr>
<td>48-57</td>
<td>2</td>
<td>10.0</td>
</tr>
<tr>
<td>58-67</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>68-77</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The inferential statistics illustrated in table 4.6 indicate that age groups play a role in determining completion of IPT at six months (p<0.057).

Table 4.6  Chi-square test for age distribution of respondents that completed IPT at six months

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson’s Chi-square</td>
<td>10.725&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>.057</td>
</tr>
<tr>
<td>N of Valid cases</td>
<td>104</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. 6 cells (50.0%) have expected count less than 5.

At the end of nine months on IPT, 80.5% (33 of 41) of the respondents aged 38-47 completed IPT. Table 4.7 indicates that this was the highest proportion for any age group in terms of completion of IPT at nine months as the 33 patients represented 31.7% of all the respondents. At the same time, 65.8% (25 of 38) of the respondents aged 28-37 completed IPT at the end of nine months of treatment with isoniazid. Though the numbers are too few for optimal comparison, it was noted that no patients aged 18-27 and 58-67 completed IPT at nine months. Using the Chi-square test, it was
statistically deduced that age group plays a role in completing IPT at nine months (p0.001) (see table 4.8).

Table 4.7 Age distribution of respondents that completed IPT at nine months

<table>
<thead>
<tr>
<th>Age in group</th>
<th>Completed IPT at nine months (Yes/No)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>% within age group</td>
</tr>
<tr>
<td>18-27</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>28-37</td>
<td>25</td>
<td>65.8</td>
</tr>
<tr>
<td>38-47</td>
<td>33</td>
<td>80.5</td>
</tr>
<tr>
<td>48-57</td>
<td>6</td>
<td>30.0</td>
</tr>
<tr>
<td>58-67</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>68-77</td>
<td>2</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 4.8 Chi-square test for age distribution of respondents that completed IPT at nine months

<table>
<thead>
<tr>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig. (2-sided)</th>
</tr>
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<tbody>
<tr>
<td>Pearson Chi-square</td>
<td>5</td>
<td>.001</td>
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</table>

4.3.6 Incidence of TB disease among research respondents

Information extracted from the clinical records indicated that 1% (1 of 104) of the research respondents (a male) was diagnosed with active TB disease (see figure 4.6). He was aged 48 years and was commenced on IPT on 01 November 2011. He was screened with the approved TB screening tool and answered in the affirmative when asked about cough and weight loss. Sputum AFB test was done afterwards. The result was negative prompting commencement of IPT. Sputum TB culture was not done and GeneXpert test was not available at the facility at that time. He was initially managed with a five-day course of oral antibiotics.

The respondent defaulted IPT after four months. There was no indication in his record that isoniazid was prescribed for him after the initial four months. He continued clinic visits for his ART, however, and was diagnosed with TB disease on 11/01/2013 using the sputum AFB testing method. At the time his clinic record was accessed for data gathering in April 2013, he was on the maintenance phase of anti-TB treatment (see figure 2.2). His last recorded CD4 count (reported on 04/12/2014) was 201 cells/mm³.
while his viral load result (reported 05/12/2012) was lower than detectable. Thus he was virally suppressed and adherent to his ART. Though the study population was relatively small when compared to the disease burden of the district, the result is similar to Golub et al’s (2009:633) finding that men accessing IPT/ART care were more likely to develop TB. This could be related to the general health-seeking behaviour of men. Neglecting symptoms until the disease state reaches an advanced stage was found to be the typical health-seeking pattern of men (Johansson, Long, Diwan & Winkvist 2000:46).

It is evident from research studies that IPT for six months to patients, successfully prevented TB disease. An incidence rate of 0.80 per 100 person-years (Golub et al 2007:15) and 2.3 per 100 person-years (Rangaka et al 2014:3) were reported.

None of the 66 respondents who completed IPT at the end of nine months was diagnosed with TB disease as at the time the study data was gathered.

![Proportion of research respondents diagnosed with TB disease](image)

**Figure 4.6** Proportion of research respondents diagnosed with TB disease

### 4.4 CONCLUSION

The study revealed a preponderance of female research respondents over their male counterparts. The majority of the respondents were aged 38-47 followed by age group 28-37. Less than half of the research respondents completed IPT at six months. This
proportion increased to 66 out of 104 (63.5%) respondents at the end of nine months with 38 (36.5%) of the respondents defaulting IPT.

Gender and age group were found to have played a statistically significant role on the completion of IPT at six months. Age group also played a role in completing IPT at nine months. Only one male respondent who defaulted on IPT was diagnosed with active TB disease within the period the study covered. None of the respondents who completed IPT after 9 months was diagnosed with TB disease within the study period.

Chapter 5 presents findings, briefly describes the limitations, contribution and significance of the study, and makes recommendations for practice and further research.
CHAPTER 5

Contributions, limitations, conclusions and recommendations

5.1 INTRODUCTION

Isoniazid preventive therapy (IPT) is one of the interventions recommended by the WHO for preventing progression of latent TB infection to active TB disease. No known scientific study has been conducted in iLembe district to ascertain uptake of IPT and the efficacy of this intervention.

The purpose of this study of limited scope was to describe the incidence of TB among HIV-positive clients who received IPT in a specific PHC centre in iLembe district in order to recommend positive intervention strategies aimed at improving uptake of IPT. The study also explored the defaulter rate among respondents who were commenced on IPT, in order to recommend ways of optimising adherence to IPT.

Both descriptive and analytical statistics were used in analysing the audited data from the clinic records of the study population.

5.2 CONTRIBUTIONS OF THE STUDY

The finding that most of the research respondents who defaulted IPT did so due to not dispensing revealed a major shortcoming in the healthcare system. The researcher will share the study findings with the facility, the district and the Provincial Department of Health through the provincial Health Research Committee. This will enable the province and the district to act in terms of more efficient drug supply management and implement the recommendations of the researcher.

The study also strengthened the findings of similar local and international studies that IPT is advantageous. Not one respondent who completed IPT developed active TB disease within the period the study covered. This message should be passed on to the entire public at every appropriate forum, such as continuous professional development
sessions, poster presentations and oral presentations at conferences. The researcher will also submit a manuscript for possible publication in the accredited peer reviewed journal, *South African Medical Journal*, to disseminate these results.

5.3 LIMITATIONS OF THE STUDY

Since this study is a dissertation of limited scope, the researcher only used data from one district. This study is only one of the modules in the Master of Public Health degree and the limitations should be seen in this context.

The retrospective design of the study that involved the analysis of the data from clinical records of research respondents was a limiting factor. The information in the clinical records was primarily for the management of the patient. As a result, the researcher could not extract demographical information like socio-economic characteristics, adverse drug reactions, psychosocial issues, pill burden and other reasons that may have influenced IPT intake. The researcher was thus limited in finding the reason for not prescribing IPT to some patients as the study was restricted to reviewing available clinic records which did not provide such information.

The 104 clinic records used for the study are far below the number of adult patients who tested positive for HIV in the clinic and which the researcher thought could have been included. The key finding was that not all of them were screened for TB at each visit and therefore needed to be excluded, thereby contributing to the small sample. It is possible that more cases of TB would have been detected by the researcher if the study population was increased and better sensitive and specific TB testing methods utilised for all the respondents during the period of the study as opposed to the use of the TB screening tool.

5.4 CONCLUSIONS

5.4.1 Gender and adherence

The data revealed that after a six-month period, which is the preferred time for completing the IPT regimen, the percentage of male adherence (47.4%) was much higher than that of females (22.7%). After nine months, which can still be seen as
adherence according to the NDOH (2010c:5), 73.7% of males completed, but only 57.6% of the females did.

**Recommendation**

The Department of Health should consider and explore other ways of getting chronic medications, like IPT across to the deserving patients. Community health care workers should be trained to be the responsible for dispensing IPT to patients at their homes, after official hours or during weekends. Women, who tend to put other domestic responsibilities as well as fear of losing their jobs if they are absent from work, before their own health, will then be able to adhere to the IPT treatment within the six-month period as required. This might contribute to the improvement of adherence to IPT by women. The adherence of males can be further improved if they also receive their medication at home and at work where applicable. Companies that engaged the services of Occupational Nurse could capacitate them to dispense IPT to their deserving members of staff.

**5.4.2 Default due to unavailability of IPT**

Of the respondents, 38 of 104 (36.5%) defaulted intake of IPT, with only 5 due to not attending the clinic, thus only 5 participants were responsible for the default. For all the others who defaulted therefore it seemed as if poor quality of care was the main factor associated with the default. Either IPT was not prescribed for some reason, or was out of stock. The current recording system did not allow the researcher to access whether the IPT was out of stock or was simply not prescribed. It is therefore possible that some healthcare workers have not fully accepted the advantages of IPT in terms of reducing the incidence of active TB, or still harbour reservations about prescribing IPT due to the perceived side effects or development of resistance to INH used for IPT (Rangaka et al, 2014:7; Golub et al, 2007:1442). It also may be that IPT was not available to be prescribed, thus out of stock at the clinic.

**Recommendation**

A system that will ensure timely procurement of medication should be adopted to ensure the provision of quality healthcare service to patients. Each healthcare facility
(clinic or department) should appoint a healthcare worker or workers to take responsibility for procurement of medication. Alternatively, this task should be delegated to a specific healthcare worker who will be held responsible and accountable if the medication is not available for prescription. This responsibility lies with the Pharmacy Assistant in facilities where they are available. The availability of IPT for prescription, as all other medications, should be checked on a chart on a daily basis. This responsibility should be incorporated in the performance appraisal of the personnel and the consequences for neglect should be stipulated. In this way, quality healthcare can be improved and the adherence rate will improve.

Healthcare personnel, especially the doctors who need to prescribe the drug, and the pharmacy assistants/nurses who are responsible for ensuring that the drugs are ordered, need to attend continuous professional development sessions where IPT is addressed. Attending these sessions should also form part of the performance appraisal of these professionals.

Other measures aimed at further reducing the defaulter rate for IPT should be implemented. These include but are not limited to ongoing adherence counselling, regular screening for side effects of IPT, and improving accessibility to IPT.

5.4.3 Incidence of TB among respondents who completed IPT

None of the 66 respondents who completed the course of IPT at the end of nine months was diagnosed with TB disease at the time the study data was gathered. Only one male respondent was diagnosed with TB after he defaulted IPT at four months. The exact reason for defaulting was not stated in the clinic records.

It is evident from the study results that the use of IPT proved to be a successful intervention in preventing HIV-positive patients from developing TB disease. It remains of serious concern that the uptake of IPT was still low despite the advantages of IPT use and the NDOH (2013:14) and WHO (2011a:6; 2011b:1) recommendations.
**Recommendation**

The most current national treatment guidelines in South Africa (DOH 2014:85) recommend the use of tuberculin skin test (TST) prior to commencing IPT. This practice of carrying out TST prior to commencing IPT should be standardised to ensure that the appropriate duration of IPT is adopted. However, if research evidence is to be implemented and evidence-based practice to be delivered to healthcare consumers, the healthcare workers need to take responsibility for the quality of the care that they deliver.

Performance appraisal should include aspects such as timely ordering of medication, accountability for negligence to order medication, attending workshops and continuous professional development sessions. Healthcare professionals who do not comply with their agreed upon performance appraisal should be held accountable for poor quality of healthcare with the necessary action taken against them.

**5.5 GENERAL RECOMMENDATIONS**

The researcher recommends strengthening of the data management system at the clinics to ensure enhanced capturing of dispensed IPT. This includes designing less cumbersome registers; enhancing the data-capturing abilities of the healthcare workers and data capturers; yearly didactic training sessions at the district and mentorship at the institutional level by experienced district information management team who have rich and updated knowledge of the district information system.

A formal mentorship agreement between a senior and a junior colleague to ensure that junior personnel are mentored and supervised should be implemented. The exact reason for not prescribing any medication should be clearly written in the progress notes.

**5.6 RECOMMENDATIONS FOR FURTHER RESEARCH**

Due to the limited scope of the study, only one PHC clinic was included in the study. A national study can be conducted to enable generalisation of the findings so that recommendations can be implemented at national level.
The researcher recommends inclusion of demographic data like monthly income, educational status and the type of accommodation both in the manual and electronic IPT registers. This will enable further studies on the possible impact of demographic characteristics on the uptake of IPT as the utilisation of IPT has already proved advantageous.

5.7 CONCLUDING REMARKS

Gender differences still exist in relation to health-seeking behaviour. The finding of men being more likely to complete a course of IPT within six months collaborates this. It remains a serious concern that inadequacies or incompetence of healthcare providers were the main reasons for defaulting Isoniazid Preventive Therapy as isoniazid was not dispensed to the patients. None of the patients who completed the course of IPT contracted active TB disease during the duration of the study. Intervention strategies to improve uptake of IPT must be advocated.

His experience as a medical doctor and the insight and understanding he gained from the study have enriched the researcher. The findings should benefit policy makers, healthcare professionals, and particularly the patients in need.
LIST OF REFERENCES


98


Peter, J & Theron, G. 2011. The progression of Tb diagnosis in the HIV era: From microscopes to molecules and back to the bedside. Continuing Medical Education 29(10):404-408.


Annexure A

Notification letter of registered research title and appointed supervisor
Annexure B

Institutional approval letter for conducting research
Annexure C

District approval letter for conducting research
Annexure D

Ethical clearance certificate
Annexure E

Provincial approval letter for conducting research
Annexure F

TB screening tool for adults
Annexure G

Screening algorithm for IPT
Annexure H

Data gathering tool
Annexure I

Letter from the editor
ANNEXURE A: NOTIFICATION LETTER OF REGISTERED RESEARCH TITLE
AND APPOINTED SUPERVISOR

Tel: 012-429-6443
Fax: 012-429-6688
E-MAIL: tjolie@unisa.ac.za

Department of Health Studies
PO Box 392
UNISA
0003
28 February 2012

Student number: 4494-108-0

Dr ET Okoli
PO Box 2929
STANGER
4450

Tel no: +27728291020 (Mobile)
Email Address: 44941080@mylife.unisa.ac.za

Dear Student

MPH: DISSERTATION
TITLE: INCIDENT OF TUBERCULOSIS AMONG HIV CLIENTS WHO RECEIVED ISONIAZID PREVENTIVE THERAPY (IPT)

This letter serves as an advance notification of your registered research title and appointed supervisor(s). You will receive official documentation in due course.

The appointed supervisor(s) is/are as follows:

Supervisor: Prof L Roets
Tel: +27 12 4292226 E-mail: roetsl@unisa.ac.za

Joint Supervisor: -
Tel: E-mail: -

In future, direct all correspondence relating to your research project to your supervisor. If you cannot get hold of your supervisor you may consult the joint supervisor. The most convenient means of communication is by e-mail.

The first step is to submit a research proposal. With this at their disposal, your supervisor(s) will guide you further through the process of writing and revising the proposal until it is accepted by the Research and Ethics Committee of the Department of Health Studies. Contact your supervisor for guidance on how to write a research proposal. Consult Tutorial Letter MNJUALL/301/2012.

After the research proposal has been accepted, you will commence with the dissertation. The research proposal will be dispersed into the dissertation. Your supervisor will guide you through the process of planning and executing your research and writing the dissertation. Under no circumstances are you...
allowed to enter the field and collect data without the permission of your supervisor. Permission will only be granted once the relevant chapters of the dissertation, the research methods and the data collection instruments have been approved.

All documentation concerning your proposal and dissertation must be in accordance with the technical and academic stipulations of the MNUALL/301/2012 tutorial letter. Electronic submission via e-mail is preferable. If you send your documents in printed format, you must include an electronic version saved on a memory stick or disk (stiffy). This will enable the supervisor to make some changes to your document and insert electronic comments. NEVER send your documents in an assignment envelope because it will be delivered to the assignment section and not to your supervisor. Remember to make backup copies of all your documents to prevent loss of important data and information.

You need to register annually and pay the full registration fee until your research has been completed and the dissertation has been submitted for examination.

The supervisor will grant permission to submit the dissertation for examination once he or she is convinced that the necessary scientific and technical standards have been met. You will not be allowed to submit without the supervisor’s permission. Once all the chapters, introductory pages, annexures and the bibliography have been approved, the dissertation must be submitted for professional editing. This can be very costly and you are advised to make provision for this expense in your budget.

Wishing you success with your studies.

Yours sincerely

Mrs JE Tjallinks
COORDINATOR: DEPARTMENT OF HEALTH STUDIES
ANNEXURE B: INSTITUTIONAL APPROVAL LETTER FOR CONDUCTING THE RESEARCH

SUNDUMBILI COMMUNITY HEALTH CENTRE
PHSag x 6032
Mandeni
4490
A 6823/3 Mamoahle Rd Sundumbili Township
Sundumbili 4491
Tel 032 4547502. Fax: 032 4547529
Email: nathi.shabane@kznhealth.gov.za
www.kznhealth.gov.za

Reference: Permission to conduct research
Enquiries: Mr J.N. Shabane
Telephone: (032) 4547502
- Monday, September 10, 2012

Attention:
Dr Emmanuel Okoli
P.O. Box 2929
Stanger
4450

RE: REQUEST FOR RESEARCH APPROVAL – MPH UNISA

Your letter dated the 03rd of September 2012 on the above subject has reference. In line with the departmental policy, permission is hereby granted for you to conduct research at Sithebe Clinic which falls under the control of Sundumbili Community Health Centre. Permission is granted subject to compliance with all the ethical considerations for conducting professional research. You are requested to present this letter to the Operational Manager of the clinic on commencement of your research.

Yours sincerely,

J.N. Shabane
Chief Executive Officer
Sundumbili Community Health Centre

Approved / Not approved

Ms S.D. Dube – District Manager – Ilembe Health District

uMnyango Wezempilo. Departement van Gesondheid
Fighting Disease, Fighting Poverty, Giving Hope
Dr Emmanuel Okoli
P.O. BOX 2929
STANGER
4450

RE: PERMISSION TO CONDUCT A STUDY ON THE INCIDENCE OF TUBERCULOSIS AMONG HIV CLIENTS WHO RECEIVED ISONIAZID PREVENTIVE THERAPY (IPT) AT ISITHEBE CLINIC

I have pleasure in informing you that permission has been granted to you by the District Office to conduct a study on the incidence of tuberculosis among HIV clients who received isoniazid preventive therapy (IPT) at Isithebe Clinic.

Please note the following:
1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this study.
2. This study will commence once this Office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Please ensure this Office is informed before you commence your study.
4. The District Office / Facilities will not provide any resources for this study.
5. You will be expected to provide feedback on your findings to the District Office and the hospitals selected for the study.

Thank you,

Ms S D Dube
District Manager
Ilembe Health District
UNISA

UNIVERSITY OF SOUTH AFRICA
Health Studies Higher Degrees Committee
College of Human Sciences
ETHICAL CLEARANCE CERTIFICATE

HSHDC/92/2012

Date: 31 October 2012  Student No: 4494-108-0

Project Title: Incidence of Tuberculosis amongst HIV positive clients who received isoniazid preventative therapy (IPT).

Researcher: Dr EI Okoli

Degree: Masters in Public Health  Code: DIS4986

Supervisor: Prof Loets
Qualification: Phd
Joint Supervisor: -

DECISION OF COMMITTEE

Approved ☑ Conditionally Approved

Prof L Roets
CHAIRPERSON: HEALTH STUDIES HIGHER DEGREES COMMITTEE

Dr MM Moleki
ACTING ACADEMIC CHAIRPERSON: DEPARTMENT OF HEALTH STUDIES

PLEASE QUOTE THE PROJECT NUMBER IN ALL ENQUIRES
Dear Dr El Okoli

Subject: Approval of a Research Proposal

1. The research proposal titled ‘Incidence of Tuberculosis amongst HIV clients who received Isoniazid Preventive Therapy (IPT)’ was reviewed by the KwaZulu-Natal Department of Health.

The proposal is hereby approved for research to be undertaken at Isilhebe 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 Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lütte
Chairperson, Health Research Committee
Date: 30/01/2015
ANNEXURE F: TB SCREENING TOOL FOR ADULTS

**TUBERCULOSIS SCREENING TOOL FOR ADULTS**

Surname: ___________________________  First Name: ___________________________

Address: ___________________________

Contact number: ____________________

Date: ______________________________

Patient record or Folder Number: ______________________________

Reason for screening:
- TB contact
- MDR/XDR TB Contact
- HCT/FMTC/TCT/CCMT/ART

Answer "yes" or "no" on the following questions

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Do you have a cough (24 hours or more)?</td>
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<tr>
<td>Do you have loss of weight?</td>
<td></td>
<td></td>
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<tr>
<td>Do you sweat a lot at night?</td>
<td></td>
<td></td>
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<tr>
<td>Do you have fever?</td>
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If "yes" to one or more of the questions, suspect TB
 Clinically evaluate the patient using national guidelines for diagnosing TB. If required, refer for further investigations, including a sputum for microscopy and culture.

If "no" to all questions, inform the patient of the benefit of IPT (TB preventive therapy) and assess patient eligibility or refer the patient for IPT eligibility.

<table>
<thead>
<tr>
<th>TB suspect?</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Sputum collected?</td>
<td></td>
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<tr>
<td>Do you sweat a lot at night?</td>
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<td>IPT started / referred for IPT</td>
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Patients referred to the clinic
Name of counsellors / health care worker: ___________________________
Facility / contact details: _________________________________________
ANNEXURE G: SCREENING ALGORITHM FOR IPT

Figure 8: Screening Algorithm for TB Prophylactic Therapy (PT)

1. HIV + Client
2. Complete Patient Chart
3. Clinical status and screening for suitability for IPT
   - Alcohol abuse
   - Active Liver disease
   - Not eligible for IPT
4. TB symptoms or signs (use TB screening tool)
5. NO
   - Thorough counselling - Inform patient on benefits of IPT - ask patient consent
   - Commence IPT
   - Client refuses IPT
6. YES
   - Sputum smear & culture
   - Smear Negative
   - Smear Positive or culture
7. Visit 2 FOR SYMPTOMATIC PATIENTS ONLY
   - Follow-up - schedule for smear results then after 6 weeks to allow for culture results to come back. If a positive result is received before then the patient should be contacted immediately and referred for treatment
8. Antibiotics
   - Good response to antibiotics
   - Poor response to antibiotics
   - Refer for further investigations for PTB, EPTB or other possible conditions
   - Reassess and reconsider screening for IPT after 3 months
   - TB Treatment Cotrimoxazole prophylaxis

SCREEN FOR TB REGULARLY AT ALL SUBSEQUENT VISIT
### ANNEXURE H: DATA GATHERING TOOL

<table>
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<tr>
<th>S/NO</th>
<th>AGE (IN YEARS)</th>
<th>GENDER</th>
<th>DATE STARTED ON ART</th>
<th>PRE-Screening for TB Disease Y/N</th>
<th>DATE STARTED ON IPT</th>
<th>MONTH 1</th>
<th>MONTH 2</th>
<th>MONTH 3</th>
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<th>MONTH 4</th>
<th>MONTH 5</th>
<th>MONTH 6</th>
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<th>MONTH 8</th>
<th>MONTH 9</th>
<th>STOPPED IPT Y/N</th>
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<th>REASON</th>
<th>TRANSFERRED OUT</th>
<th>LOST TO FOLLOW UP Y/N</th>
<th>DATE OF LAST VISIT IF Y</th>
<th>COMPLETED IPT Y/N</th>
<th>TOTAL NUMBER OF MONTHS ON IPT</th>
<th>LAST CLINIC VISIT</th>
<th>DIAGNOSED TB Y/N</th>
<th>DATE OF TB DIAGNOSIS</th>
<th>REMARKS</th>
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ANNEXURE I: LETTER FROM THE EDITOR

Cell/Mobile: 073-782-3923
53 Glover Avenue
Doringkloof
0157 Centurion

28 February 2015

TO WHOM IT MAY CONCERN

I hereby certify that I have edited Emmanuel Ikechukwu Okoli’s master’s dissertation, *Incidence of Tuberculosis amongst HIV-positive clients who received Isoniazid Preventive Therapy (IPT)*, for language and content.

IM Cooper

Iauma M Cooper

192-290-4