CHAPTER 1: INTRODUCTION

Tuberculosis (TB) is a global health concern, with an estimated 8.9 million new cases world wide in 2004 and two million deaths each year (Dye C, 2006). It is a major contributor to the burden of disease, especially in low and middle-income countries, where it is fuelled by the HIV/AIDS epidemic (Corbett EL et al, 2006)

More than 2 billion people (about one third of the world population) are estimated to be infected. Tuberculosis peaked around 2003 and now appears to be declining slowly (WHO, 2008).

In 2006 the World Health Organization estimated:

- The prevalence of active infection was 14,4 million
- The incidence of new cases was estimated to be 9,2 million
- Twelve of the 22 countries with the highest estimated TB incidence are in Africa
- In 2006 there were 1.7 million deaths from Tuberculosis worldwide, a death rate of 25/100 000. (WHO.2006)

The epidemiology of tuberculosis varies substantially around the world. The highest rate in sub-Saharan Africa, India, China and the islands of South East Asia and Micronesia. Intermediate cases/100 000 occur in Central and South America, Eastern Europe, and Northern Africa. Low rate per inhabitants occur in the united states, Western Europe, Canada, Japan and Australia (Horsburgh R, 2010). Poverty, HIV and drug resistance are major contributors to the resurging global tuberculosis epidemic which occur in developing countries. Approximately 1 in 14 new TB cases occur in individuals who are in Africa (Corbett EL et al, 2006). About 9 million new cases of Tuberculosis occur each year, which includes people who are also infected with HIV/AIDS. The global case load is certainly rising and being driven upwards in sub-saharan Africa by the spread of HIV/AIDS. In 1991, the world health organization assembly set a target for 70 % case finding of smear positive TB and 80 % of those identified cases should complete anti-tuberculosis treatment. The most dramatic increase in the number of reported cases has been in sub-saharan Africa. Between 1984 and 1990, increases of 86 %, 140 %, 154 % and 180 % were

reported in Tanzania, Burundi, Zambia and Malawi respectively (Narain JP and All, 1992)

The impact of HIV on TB prevalence is clearly seen with the increase in prevalence of congenital TB, Paucibacillary or smear negative TB, extra pulmonary tuberculosis and immune reconstitution inflammatory syndrome (IRIS). It has been estimated that a billion people will be newly infected with mycobacterium tuberculosis between 2002 an 2020, unless tuberculosis control is further strengthened. More than 150 million people will develop active disease and 36 million people will die (Kandel TR et al, 2008). The African region has the highest TB prevalence rate (363/100 000 population) and, within the region, South Africa has the highest rate (998/100 000 population). After HIV/AIDS, TB is the second most widespread disease in South Africa. Although TB and HIV frequently co-exist; in 2006 only 32 % of TB patients were tested for HIV. Concern about the number of multi-drug resistance cases is increasing (WHO, 2008).

Tuberculosis is the most common notifiable disease is South Africa. It ranks second among the 22 high-burden TB countries in terms of TB incidence and seventh in terms of overall TB burden (WHO, 2007). The rate of Tuberculosis in South Africa is equivalent to 29 cases of Tuberculosis every hour, with 80 % of the cases occurring in the 15 to 49 year age group, representing one of the highest rates in the world (Weyer K et al, 1999). The seriousness of the epidemic was confirmed in June 1996, when the WHO declared that South Africa had one of the worst recorded TB epidemics in the world because of the impacts of HIV and the emergence of multi-drug resistant tuberculosis. The Tuberculosis epidemic in South Africa is largely due to a conjunction of the following factors: Historical neglect, health service fragmentation and poor management, compounded by one of the fastest growing HIV epidemics ever recorded.

In South Africa, 998 out of 100 000 have tuberculosis. The provinces affected the most are Kwazulu Natal, Western Cape, Eastern Cape and Gauteng, which have 80

% of tuberculosis cases in South Africa. Of these only 54 % are cured and 13 % of patients stop taking prematurely treatment (Kandel TR et al, 2008).

As mentioned above, tuberculosis is one of the serious health problem in South Africa.   According to the stats-SA mortality and causes of death figures, Tuberculosis moved from being the leading cause of death in 4 provinces in 1997 through being the leading cause of death in all 9 provinces in 1999 to being the leading causes of death in 7 provinces in 2001 (second leading cause of death in Limpopo and Free State). According to the same source, 68 % of the country's new smear positive tuberculosis patients successfully complete treatment, 7 % of the remainders dying and 12 % default (Mvusi L, 2005).

The above cure rate of 68 % is still under the target of 80 % fixed by the world health Organization.   Anti- tuberculosis therapy should be administered to the greatest possible number of patients in order to cure them, and thereby interrupt the chain of transmission of tuberculosis within the population.

The most serious problem hindering tuberculosis treatment and control is non compliance of patients. It is believed to delay sputum conversion to smear negative, increase the relapse rate 5-6 times, and help the emergence of resistance mutant strains.

Adherence to treatment requires the active participation of the patient in self management of treatment and cooperation between the patient and health care provider.

The reasons for poor adherence are multifaceted and complex, but include the characteristics of the individual patient and socioeconomic factors such as the availability of drugs, communication between the patients and health care providers, duration and number of medications needed, side effects, cost of treatment, competing demands on time, contradictory norms or expectations of families and

cultural groups, and the poor quality of the Tuberculosis control infrastructure. (Sumartojo E, 1993)

Poor, inconsistent or partial treatment when patients do not take all their medicines regularly for the required period of time because they start to feel better, or the doctors and nurses prescribe incorrect drugs or incorrect combinations of drugs, may lead to multi-drug resistant strains. (MDR-TB). This is a dangerous form of tuberculosis resistant to at least isoniazid (INH) and rifampicin, which are the two most powerful anti-tuberculosis drugs.

Multi-drugs resistant Tuberculosis requires especially lengthy complex and more expensive treatment. In developing nations, nearly all patients are condemned to die because effective treatment to Multi-drugs resistant Tuberculosis is often impossible to afford because it cost 100 times more to cure Multi-drugs resistant Tuberculosis than drugs susceptible tuberculosis. The key elements in tuberculosis control are the individual patient, interrupting transmission of tuberculosis to others, and preventing the tubercle bacilli from becoming drug resistant. Therefore, the highest priority in stopping Multi-drugs resistant Tuberculosis is its prevention through prompt diagnosis of tuberculosis and adequate treatment with supervision.

Compliance to tuberculosis treatment is the cornerstone for the success in the fight against tuberculosis. In our daily practice at Matlala District Hospital, we observed an increasing number of patients defaulting tuberculosis treatment for various reasons. This inspired me to initiate this study to establish the reasons for the interruption of Tuberculosis treatment by patients attending Matlala District Hospital. The results of this research will assist in formulating appropriate recommendations which will help to decrease the default rate in our hospital.

Problem statement and Significance of the study: Despite the availability of highly effective TB drugs and DOTS strategy developed by World Health Organization (WHO), tuberculosis remains widespread public health concern. There is an increase in numbers of patients developing complications, or dying as a result of poor compliance in detected cases of tuberculosis at Matlala hospital. This increase is a great concern to the hospital management including the clinical manager. This study will assist the policy markers in the Sekhukhune district to identify the main reasons for non-compliance among TB patients.

Research Question: Are there any socio-economic and cultural factors contributing to non-compliance among Tuberculosis patients in Matlala hospital?

Aim: The aim of this study was to determine the causes of non-compliance to Tuberculosis treatment in patients seen at Matlala District Hospital.

Objectives:
1. To determine the factors that influence defaulting behavior.
2. To identify the reasons for defaulting treatment.

CHAPTER 2: LITERATURE REVIEW

PATHOPHYSIOLOGY OF TUBERCULOSIS

Tuberculosis has recently re-emerged as a major health concern. Each year, approximately 2 million persons worldwide die of Tuberculosis and 9 million become infected (CDC, 2007). The prevalence of tuberculosis is continuing to increase because of the increased number of patients infected with human immuno deficiency virus, bacterial resistance to medications, increased international travel and immigration from countries with high prevalence, and the growing numbers of homeless people and drugs abusers.

Causative agent

Tuberculosis is an infection caused by the rod-shaped, non-spore forming, aerobic bacterium mycobacterium tuberculosis. Mycobacteria typically measure 0.5 micron millimeter by 3 micron millimeter, are classified as acid-fast bacilli, and have a unique cell wall structure crucial to their survival. The well-developed cell wall contains a considerable amount of a fatty acid, mycolic acid, covalently attached to the underlying peptido glycan-bound polysaccharide arabinogalactan, providing an extraordinary lipid barriers. This barrier is responsible for many of the medically challenging physiological characteristics of tuberculosis, including resistance to antibiotics and host defense mechanisms. The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate (Lee RB et al, 2005). The peptidoglycan polymer confers cell wall rigidity and is just external to the bacterial cell membrane, another contributor to the permeability barrier of mycobacteria. Another important component of the cell wall lipoarabino mannan, a carbohydrate structural antigen on the outside of the organism that is immuno genic and facilitates the survival of mycobacteria within macrophages. The cell wall is key to the survival of mycobacteria, and a more complete understanding of the bio

synthetic pathways and gene functions and the development of antibiotics to prevents formulation of the cell wall are areas of great interest (Joe M et al, 2007).

Transmission

Mycobacterium tuberculosis is spread by small air borne droplets, called droplets nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal tuberculosis. These minuscule droplets can remain airborne for minutes to hours after expectoration. The number of bacilli in the droplets, the virulence of the bacilli, exposure of the bacilli to UV light, degree of ventilation, and occasions for aerosolization all influence transmission. Introduction of Mycobacterium tuberculosis into the lungs leads to infection of the respiratory system, however, the organisms can spread to other organs, such as the lymphatic system, pleura, bones/joints, or meninges, and cause extra pulmonary tuberculosis.

Pathophysiology

Once inhaled, the infectious droplets settle through the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblets cells exist. The mucus produced catches foreign substances and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal. This system provides the body with initial physical defense that prevents infection in most persons exposed to tuberculosis (Knechel A, 2009). Bacteria in droplets then bypass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages, the most abundant immune effector cells present in alveolar spaces. These macrophages, the next line of host defense, are part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection (Van Crevel R, 2002).

Macrophages are readily available phagocytic cells that combat many pathogens without requiring previous exposure to the pathogens. Several mechanisms and

macrophage receptors are involved in uptake of the mycobacteria. The mycobacterial lipo arabino mannan is a key ligand for a macrophage receptor. The complements system also plays a role in the phagocytosis of the bacteria. The complement protein C3 blinds to the cell wall and enhances recognition of the mycobacteria by macrophages. Opsonization by C3 is rapid, even in the air spaces of a host with no previous exposure to mycobacterium tuberculosis (Ferguson JS, 2004). The subsequent phagocytosis by macrophages initiates a cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease, called primary progressive tuberculosis. The outcome is essentially determined by the quality of the host defenses and the balanced that occurs between host defenses and the invading mycobacteria. After being ingested by macrophages, the mycobacterium continues to multiply slowly, with bacterial cell division occurring every 25 to 32 hours.

Regardless of whether the infection becomes controlled or progresses, initial development involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria. Releasing cytokines attract T lymphocytes to the site, the cells that constitue cell mediated immunity. Macrophages then present mycobacterial antigens on their surface to the T cells. The initial immune process continues for 2 to 12 weeks, the microorganisms continue to grow until they reach sufficient numbers to fully elicit the cell-mediated immune response, which can be detected by a skin test. For persons with intact cell-mediated immunity, the next defensive step is formation of granulomas around the mycobacterium tuberculosis organisms.

The nodular-type lesions form an accumulation of activated T lymphocyte and macrophages, which creates a microenvironment that limits replication and the spread of the mycobaterium. (Nicod LP, 2007). This environment destroys macrophages and produces early solid necrosis at the centre of the lesion; however, the bacilli are able to adapt to survive. In fact, Mycobacterium Tuberculosis organisms can change their phenotypic expression, such as protein regulation, to enhance survival.

By 2 or 3 weeks, the necrotic environment resembles soft cheese, often referred to caseous necrosis, and is characterized by low oxygen levels, low PH, and limited nutrients. This condition restricts further growth and establishes latency.

Lesions in persons with an adequate immune system generally undergo fibrosis and calcification, successfully controlling the infection so that, the bacilli are contained in the dormant, healed lesions. Lesions in persons with less effective immune systems progress to primary progressive tuberculosis. For less immunocompetent persons, granuloma formation is initiated yet ultimately is unsuccessful in containing the bacilli. The necrotic tissue undergoes liquefaction, and the fibrous wall loses structural integrity. The semi liquid necrotic material can then drain into a bronchus or nearby blood vessel, leaving an air filled cavity at the original site. In persons infected with Mycobacterium tuberculosis, droplets can be coughed up from the bronchus and infect other persons. If discharge into a vessel occurs, occurrence of extra pulmonary tuberculosis is likely. Bacilli can also drain into the lymphatic system and collect in the tracheo bronchial lymph nodes of the affected lung, where the organisms can form new caseous glamulomas.

DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS

Diagnosis of Tuberculosis

Active tuberculosis may be considered as a possible diagnosis when findings on a chest radiography of a patient being evaluated for respiratory symptoms are abnormal, as occurs in most patients with pulmonary tuberculosis.
The radiographs may show the characteristics findings of infiltrates with cavitation in the upper and middle lobes of the lungs.

However, specific groups of patients, such as the elderly and patients with advanced infection by human immunodeficiency virus, may not have these typical findings.

Compared with other patients, both groups have the classic cavitations less often and may have lower lobe infiltrates as a prominent finding. Although abnormal findings on a chest radiograph may suggest Tuberculosis, they are not diagnostic for the disease.

Traditionally, the first laboratory test used to detect active tuberculosis in a patient with abnormal findings on chest radiographs is examination of a sputum smear for the presence of acid –fast bacilli.

According to the center for disease control and prevention of Atlanta, 3 sputum specimens should be used for detection of   pulmonary tuberculosis, with specimens collected in the morning on consecutive days (CDC, 2007).   However, recently, investigators have questioned the need for 3 specimens.   Leonard and Collaborators concluded that examination of 2 specimens is just as sensitive. For the test; sputum is smeared on a slide, stained, dried, and then treated with alcohol. Any bacilli that are present will remain in red because they will not be stained. The test is not specific for tuberculosis, because other mycobacteria give the same results, but it does provide a quick method to determine if respiratory precautions should be maintained while more definitive testing is performed. Results of sputum smears should be available within 24 hours of the specimen collection.

The standard diagnosis

Definitive diagnosis of tuberculosis requires the identification of mycobacterium tuberculosis in a culture of a diagnostic specimen. The most frequent sample used from a patient with a persistent and productive cough is sputum. Because most mycobacteia grow slowly, 3 to 6 weeks may be required for detectable growth on solid media. However, a newer, alternative method in which high-performance liquid chromatography is used to isolate and differentiate cell wall mycolic acids provide confirmation of the disease in 4 to 14 days.

Other alternative approaches are available if sputum specimens are still inadequate, or the index of suspicion for tuberculosis is still high despite cultures negative for Mycobacterium Tuberculosis. Those tests are not commonly used because of their cost and availability and are as follows:

- Bronchoscopy with bronchial washing or broncho alveolar lavage can provide sputum for diagnosis.
- In patients with involvement of initial thoracic lymph nodes, as indicated by adenopathy suggestive of tuberculosis, who have sputum smear negative for Mycobacterium Tuberculosis, culture of specimens collected by Trans bronchial needle aspiration can be used to accurately and immediately diagnose the disease.
- Newer diagnostic techniques for faster detection of Mycobacterium Tuberculosis include nucleic acid amplification tests.

In these tests, molecular biology method is used to amplify DNA and RNA, facilitating rapid detection of microorganism. One method is the polymerase chain reaction assay (PCR), which can be used to differentiate mycobacterium tuberculosis from other mycobacteria on the basis of generic information and provides results within hours.

MANAGEMENT OF TUBERCULOSIS

Principles of Tuberculosis Treatment

The aims of Tuberculosis Treatment are to:

1. Cure the client of Tuberculosis
2. Decrease transmission of Tuberculosis to others
3. Prevent the development of acquired drug resistance
4. Prevent relapse
5. Prevent death from Tuberculosis or its complications

The key to stopping the spread of Tuberculosis in a community is to start treating clients who are coughing up live TB bacilli (smear or culture positive) as soon as

possible.   Apart from the public health imperative, effective treatment reduces individual morbidity and mortality. For treatment to be effective, it is crucial that the correct drugs are given for the correct period of time. Pulmonary Tuberculosis and Extra Pulmonary Tuberculosis are both treated in the same way: regimen 1 for new cases and regimen 2 for the re-treatment cases.

1.   The Essential Tuberculosis Drugs

TB drugs have varying properties:

- they may be bactericidal, bacteriostatic (Sterilising) or have the ability to prevent resistance.

- They differ in the ability to act against the various populations of bacilli found in a Tuberculosis lesion:

  - Metabolically active bacilli, intermediary active bacilli, semi-dormant bacilli, which undergo spurts of metabolism and dormant bacilli (that may become active)

  - Some Tuberculosis drugs act best in acid environment, others better at more alkaline PH

  - Bacilli occur both in extra cellular spaces where the PH is usually neutral or alkaline and in intra cellular spaces where it is acid.

Table 1: Properties of TB drugs

Drug	Drug Property	Target Bacilli	PH	Site of Action
Isoniazid (H)	Bactericidal after 24h High potency: Kills more than 90 % bacilli in first few days of treatment	Rapid and intermediate growing bacilli	Alkaline and acid media	Intracellular and extra cellular
Rifampicin (R)	Bactericidal within 1 hour High potency Most effective Sterilising agent	All populations including dormant bacilli	Alkaline and acid media	Intracellular and Extra cellular
Pyrazinamide (Z)	Bactericidal with a low potency Achieves its sterilizing action within 2-3 months	Slow growing bacilli	Acid media	Intracellular and Extra cellular
Ethambutol (E)	Bacteriostatic Low Potency Minimises the emergence of drug resistance	All bacterial populations	Alkaline and acid media	Intracellular and Extra cellular
Streptomycin (S)	Bactericidal with a low potency	Rapidly growing bacilli	Alkaline media	Extra cellular bacilli

2. Standard treatment regimens for adults (8 years and Older)

- Standardized treatment regimens have several advantages over individualized treatment:

* Reducing prescription errors

* Facilitating estimates of drugs required and procurement

* Reducing cost

* Facilitation regular drug supply when clients move from one facility to another

* Simplifying training

The total duration of treatment is 6 months with 2 phases

- Initial Phase: 2 Months

- Continuation Phase: 4 months

- 2 (HRZE)/4 (HR).

New recommendations are that treatment is given daily. The exception is where strepromycin injections may be given a minimum of 5 times per week where health services are unavailable on weekends and no alternative plan for daily injection is possible.

New Cases

A new case is a client who has never been treated for Tuberculosis in the past or who has taken TB treatment for less than four weeks. The standard treatment regimen for new cases has an initial (or intensive) phase lasting 2 months. Treatment with 4 drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) in the intensive phase results in rapid killing of tubercle bacilli.

Infectious clients become non-infectious within approximately 2 weeks. Symptoms abate the vast majority of clients with sputum smear-positive TB become smear-negative within 2 months. In the continuation phase, 2 drugs (Isoniazid, Rifampicin) are used for 4 months. The sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse

The Standard treatment regimen for new cases is regimen 1: 2 (HRZE)/ 4 (HR)
- The intensive phase is 2 (HRZE) treatment is with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol in fixed dose combinations given 7 days a week for 2 months.
- The continuation phase is 4 (HR) treatment is with isoniazid and rifampicin in fixed dose combinations given 7 days a week for 4 months
-

<u>Re-treatment cases</u>

Re-treatment client include all TB clients who were treated for 4 weeks or more in the past and who are now smear or culture positive or who have clinically been diagnosed with TB (Failure, relapse, return after default).These cases have a higher

likelihood of resistance that may have been acquired through inadequate prior chemotherapy. The re-treatment regimen has an intensive phase lasting 3 months. For the first 2 months, treatment includes 5 drugs: Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin.

In the 3rd month, treatment is with 4 drugs: Isoniazid, Rifampicin,

Pyrazinamide, Ethambutol. The continuation phase with 3 drugs (Isoniazid, Rifampicin, Ethambutol) lasts 5 months. The standard regimen for re-treatment cases is regimen 2: 2(HRZES)/1 (HRZE)/ 5 (HRE). The intensive phase is 2 (HRZES) / 1 (HRZE) it lasts 3 months in total. For the first 2 months, treatment is with Isiniazid, Rifampicin, Pyrazinamide and Ethambutol in fixed dose combinations given 7 days a week and streptomycin injections given 7 days a week (or a minimum of 5 times a week if daily injections are not possible). In the third month only isoniazid, rifampicin, pyrazinamide and ethambutol in fixed dose combinations is given7 days a week.

The continuation phase is 5 (HRE)

It lasts 5 months treatment is with isoniazid, rifampicin and ethambutol in fixed dose combinations given 7 days a week.

Standard Treatment regimen dosages

Essential TB drug (Abbreviation)	Dose mg/kg	Dose range mg/kg
Refampicin (R)	10	8 – 12
Isoniazid (H)	5	4 – 6
Pyrazinamide (Z)	25	20 – 30
Ethambutol (E)	15	15 – 20
Streptomycin	15	12 - 15

EPIDEMIOLOGY OF TUBERCULOSIS

Global TB epidemiology and burden of disease

Although tuberculosis is a disease of great antiquity, it is likely that it did not occur in epidemic form of rapid urbanization associated with the industrial revolution. Since then an epidemic wave has swept across the world reaching a peak in Europe around 1750, in America and now affecting the developing world. Much of the dramatic decline in tuberculosis in the industrialized world has been ascribed to improved socio-economic conditions and less crowded conditions, and in the developed world TB incidence have now fallen below 20/100 000. The epidemiology of Tuberculosis is complicated by the fact that the etiologic agents, unlike many other infections diseases, causes diseases in only a minority of those infected and had a lifetime potential for activation after infection.

Tuberculosis incidence varies considerably in different populations and geographical regions. The use of routine tuberculosis data, has in 2000 resulted in the identification by the world health organization (WHO) of the 22 countries responsible for roughly 80 % of the global tuberculosis burden (WHO, 2000). Dye et al have estimated that nearly one-third of the global population is infected with mycobacterium tuberculosis and at risk of developing the disease. Over 90 % of global tuberculosis cases and deaths occur in the developing world, where 75 % of cases are in the most economically productive age group (15 -54 years)

Using trends is case notification to update estimates of Tuberculosis incidence, WHO estimated in its 2006 report (World health Organization, 2006) that there were 8,9 million new cases of tuberculosis globally in 2004, of which 3,9 million were smear positive. The global incidence rate of tuberculosis (per capita) was growing at approximately 1, 1 % per year in 1997 but at 0, 6 % by 2004. The growth in cases notifications has been much faster in African countries with high HIV prevalence (3 % per year) and in Eastern Europe (mainly the former Soviet Union), but seems to be slowing in both regions since the mid 1990s. Five countries (India, China, South Africa, Indonesia and Nigeria) accounted over 60 % of additional cases notified in 2004. The ranking of countries by number of tuberculosis cases has drawn attention to 22 countries that account for 80 % of the global tuberculosis burden. Among the 15 high burden countries with the highest estimated TB incidence per capita, 13 are in Africa and, in most, the prevalence of HIV infection among TB patients currently exceeds 40 % (WHO, 2004).

Countries in the southern Africa development region (SADC), in particular face a disaster as far as tuberculosis an HIV are concerned. Four of the highest burden countries are in the SADC region, contributing almost 40 % to the tuberculosis burden in Africa. The incidence of tuberculosis per capita is the highest in Zambia, Zimbabwe, Namibia and Botswana. However, in terms of actual numbers of cases, South Africa currently contributes over 30 % to the total burden of tuberculosis in SADC countries.

TB-HIV joint infection in SADC countries represents more than 30 % of the global TB-HIV co-infected pool, with rates being highest in Botswana, Zimbabwe and South Africa (Weyer, 2003). It is becoming increasingly evident that the joint impact of tuberculosis and HIV in sub-saharan Africa is set to become more devastating over the next few years than has been seen any where else in the world.

Table 2. Estimated incidence of TB in the high-burden countries, 2004 (source: world health organization global tuberculosis control surveillance, planning, financing WHO report 2006 Geneve, Switzerland)

Rank	Country	Population 10005	Incidence Number	Rates
			Number	Rates
1.	India	1 087 124	1 824	168
2.	China	1 307 989	1 325	101
3.	Indonesia	220 077	539	245
4.	Nigeria	128 709	374	290
5.	South Africa	47 208	339	718
6.	Bangladesh	139 215	319	229
7.	Pakistan	154 794	281	181
8.	Ethiopia	75 600	267	353
9.	Philippines	81 617	239	293
10.	Kenya	33 467	207	619
11.	Democratic Republic of	55 853	204	336
12.	Congo	143 899	166	115
13.	Russian Federation	83 123	147	176
14.	Vietnam	37 627	131	347
15.	Tanzania	27 821	112	402
16.	Uganda	183 913	110	60
17.	Brazil	28 574	95	333
18.	Afghanistan	63 694	91	142
19.	Thailand	19 424	89	460
20.	Mozambique	12 936	87	674
21.	Zimbabwe	50 004	85	171
22.	Myanmar	13 798	70	510
23.	Cambodia Total	3 386 642	7 102	178
	GLOBAL	6 386 642	8918	140

* Rate expressed per 100 000 population

Epidemiology of tuberculosis in South Africa

Tuberculosis is a major public health problem in South Africa. South Africa ranked fifth on the list in 22 high-burden tuberculosis countries in the world. According to the world health organization's global TB report 2009, South Africa had nearly 460 000 new TB cases in 2007, with an incidence rate of an estimates 948 cases per 100 000 population, a major increase from 338 cases per 100 000 population in 1998. Since South Africa adopted Direct Observed Treatment Strategy (The internationally recommended strategy for TB control) in 1996. All districts have

implemented the core DOTS components, although coverage varies widely within and among districts.

Despite South Africa's investments in TB control, progress toward reaching program objectives has been slow. However, new data suggest that for the first time, in 2006, South Africa reached (and surpassed) the DOTS case detection target of 70 % and increased to 78 % in 2007. DOTS treatment success increased from 65 % in 2001 to 74 % in 2006, somewhat lower compared with other African Countries that have high HIV/AIDS prevalence rates and few resources. Progress against the TB epidemic in South Africa is likely to be constrained over the next few years due to HIV/AIDS. The TB –HIV/AIDS co-infection rate is high, with an estimated 73 % of new TB patients co-infected with HIV. An estimated 31 % of all TB cases in Africa are in South Africa. Multi drug –resistant (MDR) TB, largely caused by non-adherence to drugs regimens, is further exacerbating the epidemic.

The number of laboratory confirmed cases of MDR-TB more than tripled, from 2000 cases in 2005 to 7 350 in 2007. Since 2007, South Africa has increasingly reported patients with extensively drug-resistant (XDR) TB. A recent study that examined MDR isolates collected from 2004-2007 showed that 5, 6 % (986) of 17615 TB cases were XDR-TB (WHO, 2008). The actual reported cases of XDR-TB have also increased from 74 in 2004 to 536 in 2007 (National Department of Health Report, 2008)

The most critical factor in addressing MDR-TB is primary prevention through excellent basic DOTS management (still poor in many areas) and excellent management of patients requiring re-treatment and treatment with second-line medicines. An unprecedented strengthening of overall TB control (diagnostic, treatment and case-finding) is needed to ensure success in addressing the epidemic.

Country population: 48 577 000
Estimated number of new TB cases: 460 600

Estimated TB incidence (all cases per 100 000 populations): 948

DOTS population coverage (%): 100

Rate of new smear positive cases (per 100 000 populations): 358

DOTS case detection rate (new smear positive) %: 78

DOTS treatment success rate, 2006 (new smear positive) %: 74

Estimated new adult TB cases (HIV) + %: 73

MDR-TB among all new TB cases (%): 1.8

All data are for 2007 except where other noted (WHO Global TB Report 2009).

The rapid rise of HIV in South Africa has played a critical role in the upsurge of TB in recent years, and adverse trends in TB incidence have been especially marked in those provinces most severely affected by the HIV epidemic. The prevalence of HIV infection varies widely among the nine provinces but does not yet coincide with TB incidence as noted earlier.   HIV infection shows the opposite geographical distribution, with provinces to the north more severely affected, suggesting that the full impact of HIV on the TB epidemic in South Africa still has to be felt. A recent MRC survey of HIV prevalence in confirmed TB patients showed that 55, 3 % of Tuberculosis patients, overall also had HIV co-infection (Weyer K et al, 2003)

Table 3: Reported incidence of TB in South Africa, 2005 (source, Directorate TB control, Department of Health, Pretoria, September 2005) (Weyer K, 2007)

Province	All TB Cases			Smear Positive TB Cases	
	Cases	Incidence		Cases	Incidence
		2005	2003		
Limpopo	13 366	237	170	6 854	122
Mpumalanga	10 746	334	234	5 554	172
North West	27 208	711	525	13 419	351
Free State	20 915	708	607	9 508	322
Kwazulu Natal	85 507	886	725	28 938	300
Gauteng	43 990	488	373	21 084	234
Northern Cape	76 33	846	950	3 567	395
Eastern Cape	44 909	638	414	17 984	256
Western Cape	48 193	1037	932	18 550	399
South Africa	302 467	645	513	125 460	267 5

SOCIO-ECONOMIC IMPLICATIONS OF TUBERCULOSIS

The economic implications of Tuberculosis are difficult to estimate and are therefore often overlooked, particular in developing countries. However, more than two-third of TB patients are in the most economically productive years of life. Moreover, the devastation caused by Tuberculosis goes beyond the 1.9 million estimated deaths each year. Tuberculosis undermines economies in a variety of ways. Among its causalities are families and communities that suffer severe economic and social repercussions long after TB patients have died. With the onset of tuberculosis in the family, a ripple effect often begins (Weyer, 2003): firstly, cash income is lost when the wage earner is too ill to work. Often up to five or more dependants are supported in the household by the main income earner, making the loss of wages an immediate hardship for the family.

Next, capital is lost as the family sells land, animals and investments to pay for healers, medicine and hospital bills. Direct costs related to diagnosis and treatment of Tuberculosis can quickly add up to the average annual income in a developing country. Family members must often care for TB patients, resulting in reduced land productivity as families turn to crops that require less intensive farming. Often these are less valuable nutritionally and economically, resulting in a loss of income opportunities and quickly reducing self-sustaining and economically viable families to welfare recipients or beggars on a large scale, the output of industry such as factories and corporations suffers when their employees take considerable time off work. Often, medical and other benefits must be paid and new employees must be trained. Also, patients with tuberculosis often stop earning money which they would have spent and fed back into the economy. Tuberculosis therefore fuels poverty, ironic in the sense that poverty itself leads to increased risk of TB infection and disease. Some segments of the workforce are hit harder by TB than others. TB is also particularly common among migrant workers. When migrants develop Tuberculosis they often remain untreated, as health systems tend to over look mobile individuals. They are then spreading Tuberculosis to others in crowded

temporary housing and can infect otherwise healthy populations as they move through new towns and countries.

Financial data analyzed by WHO from data received from the high-burden Countries (HBCS) indicated that expenditure on TB control for 2002 was between US dollar 834 and US dollar 884 million. Total costs for 2003 were estimated at approximately US dollar 1 billion. In the 14 high burden countries, the cost per patient treated was in the range of US dollar 125 to US dollar 380. For three others (Brazil, South Africa, and the Russian Federation), costs per patients were significantly higher (exceeding US dollar700), largely because of higher labour and capital costs or because of more reliance on inpatient care. 10 factors about cost of Tuberculosis (IVATLD fact sheet, 1999):

- Poverty increases the risk of Tuberculosis, while Tuberculosis impoverishes its victims - 80 % of TB patients are aged between 15 and 49 and are in the most economically productive years of their lives.

- More than 90 % of TB cases and deaths occur in low and middle income countries.

- The estimated cost to poor households is US dollar 12 billion per year.

- Tuberculosis carries an indirect cost to society, the family and community.

- In order to reach the DOTS expansion targets of diagnosing 70 % new cases and treating 85 % of them by the year 2005, the world's governments need to spend US dollars 1,8 billion per year.

- At its creation in July 2001, the Global fund for AIDS, Tuberculosis and Malaria (GFATM) raised US dollar 1, 7 billion for the three diseases.

- The Global drug facility, part of the STOP TB partners forum, reduced the cost of essential drugs to US dollar 10 for a complete six-month course.

THE PROBLEMATIC OF NON-COMPLIANCE WITH TB TREATMENT

Poor case management, often because of non-compliance to treatment, has emerged as the most important factor in the resurgence of Tuberculosis and the appearance of multiple drugs resistant. The prolonged duration of treatment, the need for multiple drugs and socio-economic factors are the main reasons for non-compliance to treatment. The currently recommended minimum duration of treatment is 6 months, which, although much shorter than the previously recommended 12 to 24 months, is still very long. According to the World Health Organization, directly observed therapy (DOTS) ensures successful treatment of patients with Tuberculosis (WHO, 2006)

There are still patients who are not compliant to DOT and default from treatment. Increased morbidity and mortality of Tuberculosis have been blamed on neglect of the human dimension of Tuberculosis control. One of such factors included in human dimension is non-compliance, a behavioral parameter, which has led to the emergence of multi-drugs resistant Tuberculosis, and poor treatment outcome (Erhabor GA et al, 2000).

Defaulting on Tuberculosis treatment is one of the major barriers to effective Tuberculosis control and poses serious challenge to tuberculosis control programmes. The recommended targets of the World Health Organization for Tuberculosis control programmes are to achieve a case detection rate of 70 %, a treatment success rate of 85 % and a defaulter rate of less than 5 % (WHO, 2006). Nine of the world's 22 TB high burden countries are in the African region and the treatment success rate in the regions is said to have remained more or less unchanged at around 70 % since 1998, considerably short of the 85 % target. Treatment default is one of the factors blamed for the low treatment success rate in the world and in the African region.

South Africa is on the nine TB high burden Counties in Africa and during the first six months of 2005, the National cure rate was 54, 9 %. This figure increased to 62,9 %

for the same period in 2006. The National defaulter rate was 8, 8 % for the first quarters of 2006, which was down from 9,7 %for the same period in 2005.

In Limpopo Province, the number of TB cases increased from 6286 in 2000 to 22292 in 2008. The case rate in Limpopo is 62, 4 % with a defaulter rate of 7,6% and a death rate of 9,2%. Unfortunately, the province in particular and the country in general has not been able to reach the WHO target of 85% cure rate and less than 5% defaulter rate (Motsoaledi, 2009).

Factors linked to adherence can be grouped in those related to socio economic circumstances and conditions; those related to the patient, those related to the Health Workers and Health system, and those related to the disease and its treatment. These factors from the literature are summarized in table 4 (Mash R et al, 2009)

Table 4: Factors linked to adherence to Anti-Tuberculosis Treatment

A. Socio-Economic Factors
- Negatively associated factors:
  - Lack of effective social support networks and unstable living circumstances
  - Social Factors such as poverty, unemployment, and migrancy may limit the amount of social support and create instability in people's lives
  - High cost of medication
  - High cost of transport

B. Patients related factors
- Negatively associated factors
  - Cultural beliefs about illness and treatment
  - Ethnicity, gender and age have been linked to adherence in various settings
  - Criminal justice involvement
  - Involvement in drug dealing
  - Mental disorder such as depression, or alcohol abuse

C. Health Care Team/Health System factors

- Negatively associated factors
  - Poorly developed health services
  - Inadequate relationship between health care provider and patient
  - Health care providers who are untrained, overworked, inadequately supervised or unsupported in their tasks

- Positively associated factors:
  - Good relationship between patients and heath care provider
  - Availability of expertise
  - Links with patient support systems
  - Flexibility in the hours of operation of treatment centers

D. Conditions Related factors

- Negatively associated factors:
- Asymptomatic patients
- Complex Treatment regimen
- Adverse effects of medication and toxicity

- Positively Associated Factors:
- Knowledge about TB

There are various reasons for defaulting Tuberculosis treatment as shown by different studies done in South Africa and All over the world.

- A study done by HH CONRADIE in 1986 in HEWU district of Ciskei showed that the high number of TB defaulters were unemployed males patients (Conradie, 1986).
- A study done by PORTWIG GH and COUPER ID in the Wellington area in South Africa showed that the reasons for non-adherence to TB treatment were multifaceted, ranging from the personalities of the patient and the social and economic environment (Portwig et al, 2000)

- A study done by Kandel TR, Mfenyana K and collaborators in Eastern Cape revealed that of the 255 TB patients who attended for treatment, 121 (47, 5 %) had interrupted their treatment. Reasons given for interruption included change of living place (18, 96 %), no money to go to the clinic (15, 52 %), feeling better (13, 78 %), side effects of the drugs (6. 9 %) , did not know the treatment course (5, 17 %), physical disability either old or too sick to collect treatment and nobody to help (5, 17 %), clinic too far (1, 73 %), drugs not available in the clinic (13, 83 %) and no reasons (8, 62 %) (Kandel TR et al, 2008).

- A study done by Mash R et al (2008) in Kwazulu Natal showed that of the 159 TB patients, 105 (66 %) were adherent and 54 (34 %) non-adherent, 47 (30 %) were re-treatment patients. Most (56 %) of the patients were male and nearly all (96 %) lived in the rural areas, thirty-nine (25 %) of the patients reported that they had had no schooling only 4 (2 %) had post-matriculation additional qualifications. Fifty-nine (37 %) of the house holds reported receiving no income and a further 82 (52 %) earned less than R1000 a month.

- A study done in Malawi (Kruyt ML et al, 1998) revealed that of the 1099 patients, 126 (11, 5 %) had been registered as defaulters and two significant characteristics were associated with the defaulters.   They were unmarried, and they did not know the correct duration of anti-tuberculosis treatment.

- A study done in Malaysia showed that of the 118 patients who have followed in their chest clinic, 80 (67, 8 %) completed the prescribed treatment. Compliance with treatment and follow-up was not affected by age, sex, ethnic group, and educational level, occupation, extent of knowledge, Tuberculosis symptoms, and hospitalization for Tuberculosis or duration of the prescribed treatment regimen.   There was a trend toward poor compliance among patients who equated disappearance of Tuberculosis symptoms with cure of the disease (Liam CK et al, 2006)

- A recent study in Brazil shows that of the 341 patients included, 186 (61, 2 %) were considered cured and 67 (22 %) were non-compliant.

The factors associated with non-compliance were:

- Previous anti-TB treatment, prescription of drugs other than the standard first-line regimen proposed by the Brazilian health ministry, the need for hospitalization and non-inclusion in the Hospital's tuberculosis control programme for treatment follow-up (Marcelo F, 2008)

CHAPTER 3: METHOD0LOGY

Study Design: A cross-sectional descriptive study among confirmed TB patients was conducted at Matlala Hospital for a period of (24) twenty four months.

Settings: The study was conducted at the district Hospital, which is located at Sekhukhuni district of the Limpopo Province. The hospital has 250 beds with 11 doctors.

Study population: All Tuberculosis patients presenting to a unit at the Matlala hospital from January 2008 to December 2009 were recruited for the study.   A defaulter was defined as a patient whose treatment was interrupted for two consecutive months or more.

Inclusion criteria: All TB patients above the age of 10 years whose treatment was interrupted for two consecutive months or more and willing to be part of the study

Exclusion criteria: TB patients below 10 years and patients who did not give consent were excluded.

Pilot study: The questionnaire used for the study was piloted at St Ritas hospital which is not far from the study area.

Sampling technique and Sample Size: A minimum sample size of 73 defaulters is required for the study, which was calculated based on: (1) the sampling error of 5%, (2) confidence level of 95%, (3) the population size of 200 (i.e. total number of TB patient getting treatment at Matlala Hospital) and (4) the estimated prevalence of 8% of TB defaulters in South Africa. All the TB patients who came for treatment during the study period were asked to participate in the study.

Data collection: The semi structured questionnaires were given to the study participants to complete. The trained research assistant clarified the questions to

participants who had problems with understanding of some questions. The data for the study was collected from January 2008 to December 2009. The questionnaire for the study had (24) twenty four closed questions (**Appendix A**).

Data Analysis: The data for this study was captured and analyzed using Microsoft excel and EpiInfo, respectively. Frequencies and percentages were used to interpret the data. The data for this study was displayed using bar graphs and pie charts.

Reliability and Validity: The questionnaire for the study was translated into a local language (i.e. Sepedi) back translated into English. It was piloted a St Rites hospital which is next to the study area. No major changes were made on the questionnaire after the pilot study.

Bias: In this study the following bias were expected

Selection bias: selection bias was minimized by including all TB patient presented at Matlala hospital during the study period.
Interview bias: It was minimized by letting the participants to complete the questionnaire on their own.

Ethical Considerations: Ethical approval was obtained from MEDUNSA Research Ethic Committee before commencing the study. Patient confidentiality was maintained through out the study. No patient was identified by name. All study participants were asked to complete a consent form.

Study Limitations: The sample size for the study was very small, which makes it difficult to generalize the findings to the entire population of the TB defaulter's. Another limitation of this study was that no comparism group was available, to compare the defaulters and non-defaulters.

CHAPTER 4: RESULT AND ITS INTEPRETATIONS

Table 1: Distribution of Patients according to their age groups
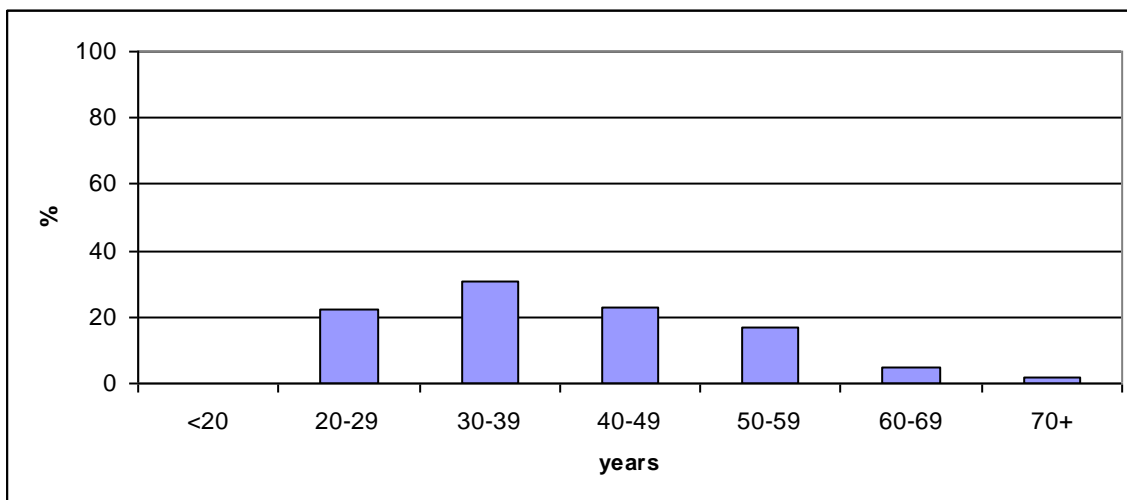
Figure 1: Age distribution of defaulters

During the study period, a total of 430 TB patients were approached to participate. Of these, 64(14.8%) were defaulters. The majority 31% of the defaulters were in the age group 30-39 yrs, followed by 23% and 21% of the defaulters in the age group 40-49 years, and 20-29 years, respectively (**Figure 1**).
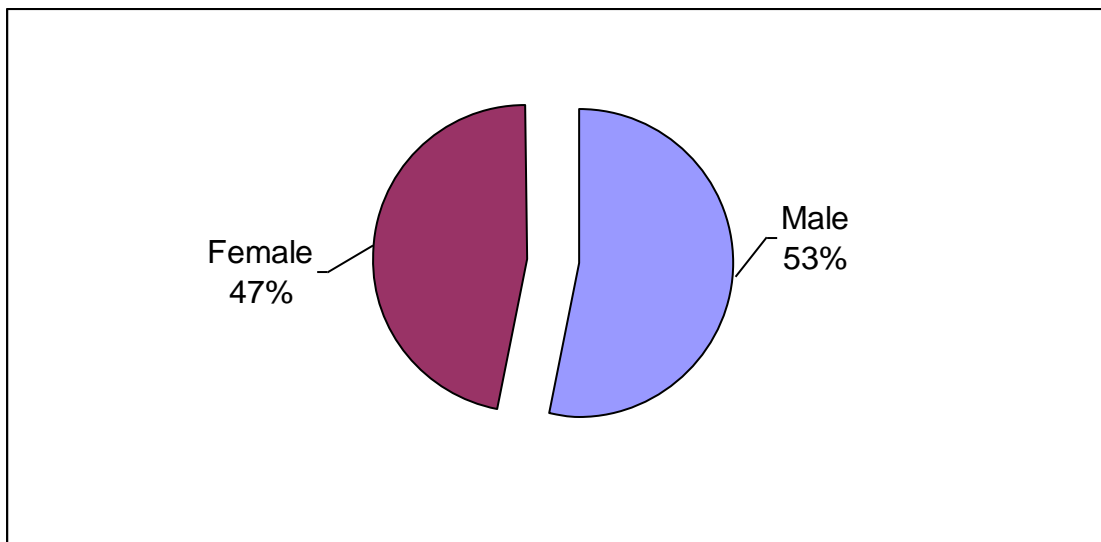

Figure 2: Distribution of gender of defaulters

Figure 2 shows the distribution of defaulter's gender. About 34(53%) of the defaulters were male and 30(47%) were female.
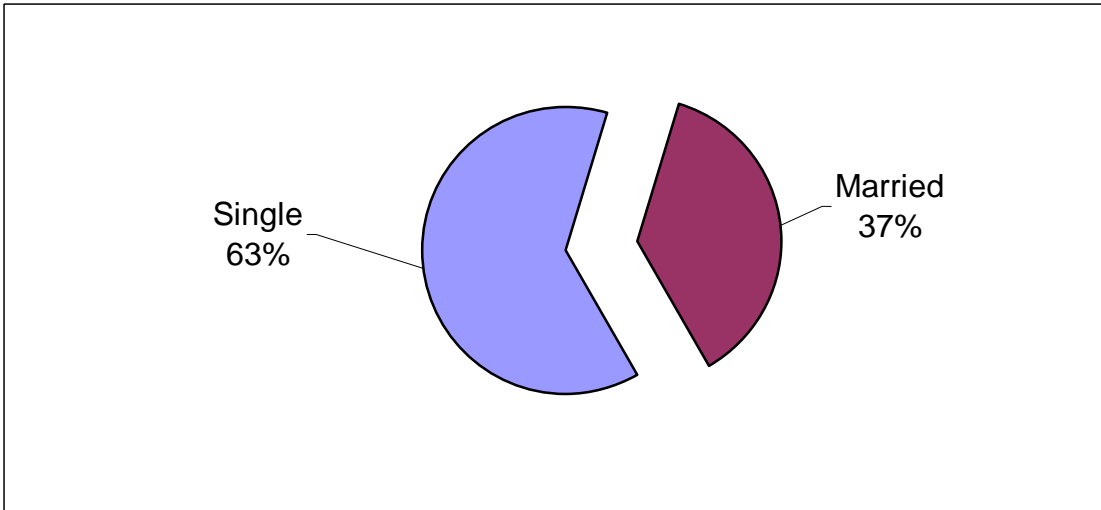
Figure 3: Distribution of defaulter's marital status

The majority 63% of the defaulters were single and only 37% were married (**Figure 3**). About 68 defaulters patients which are 93 % of the defaulters were from other surrounding villages and only 5 over 73 (7 %) were from Tsimanyane village.
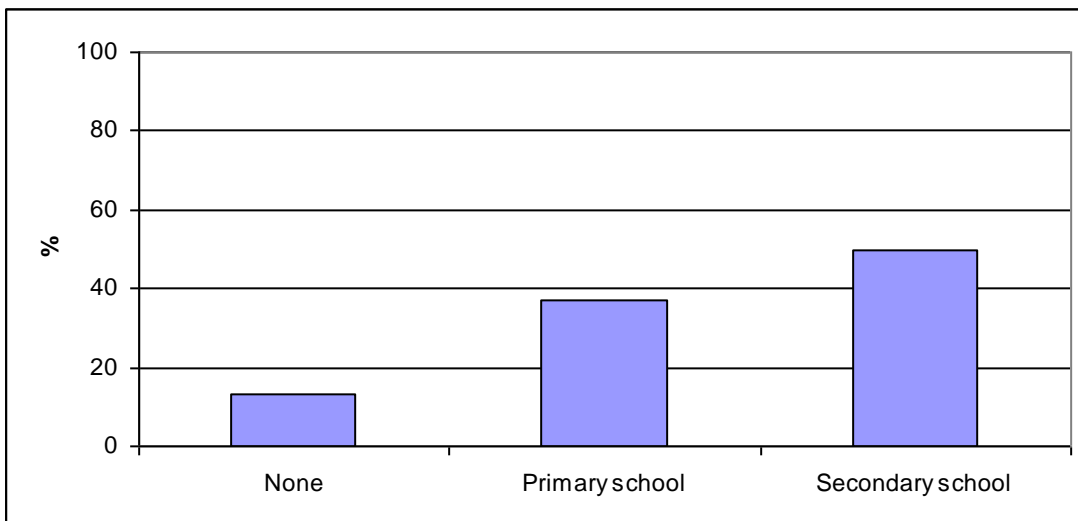
Figure 4: Distribution of defaulter's education status

Fifty percent of the defaulter's had secondary education, 37% had primary education and only 13% had no formal education (**Figure 4**).

Twenty nine (45%) were from Christian religion, 29(45%) were from African black traditional religion, and 5(8%) did not specify their religion. Fifty two (81%) were unemployed.
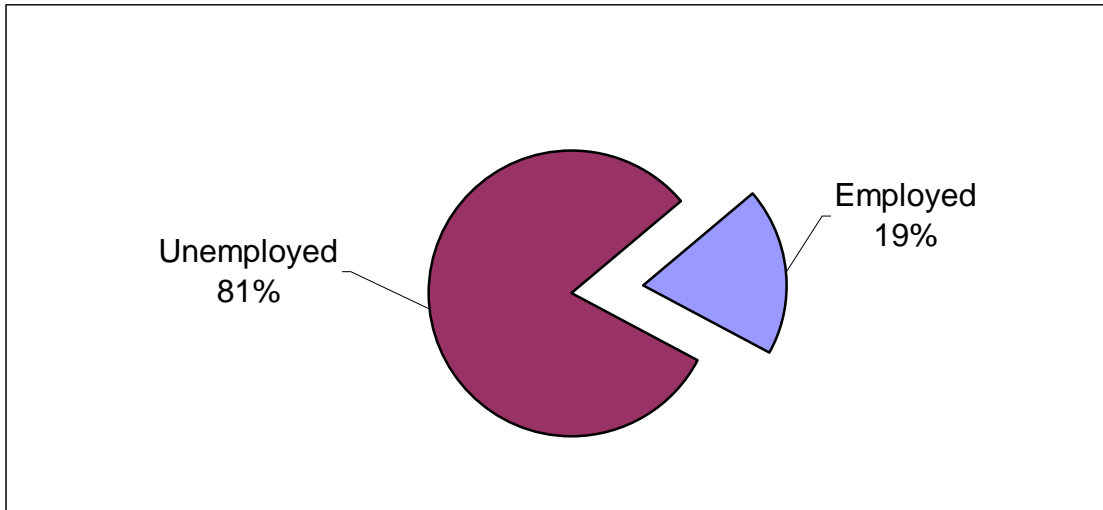
Figure 5: Distribution of defaulters employment status

More than eighty percent of the defaulters were unemployed (**Figure 5**).
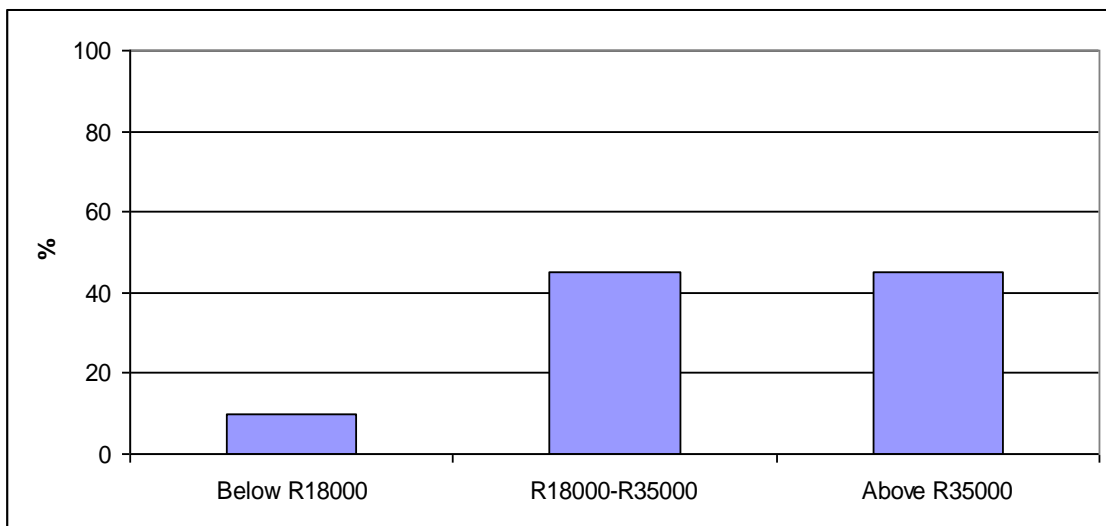
Figure 6: Distribution of defaulters income

Figure 6 shows the distribution of defaulter's income. About 10% of the defaulter's were earning below R 18 000 annual and 45% were earning R18 000-R35 000, and 45 % above R35 000.
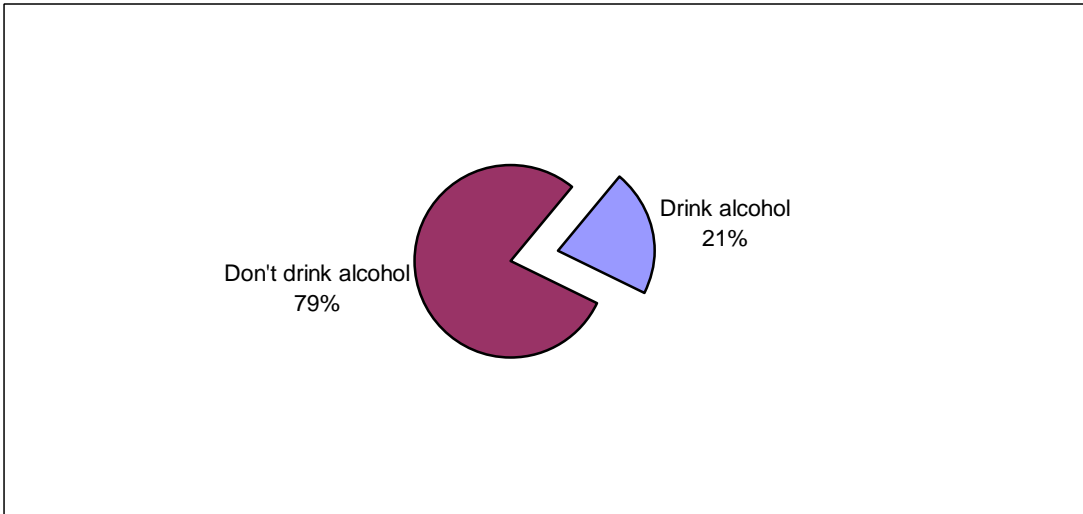
Figure 7: Distribution of defaulters drinking status

Figure 7 shows the distribution of defaulters who drink alcohol. More than seventy percent of the defaulters were not drinking alcohol.
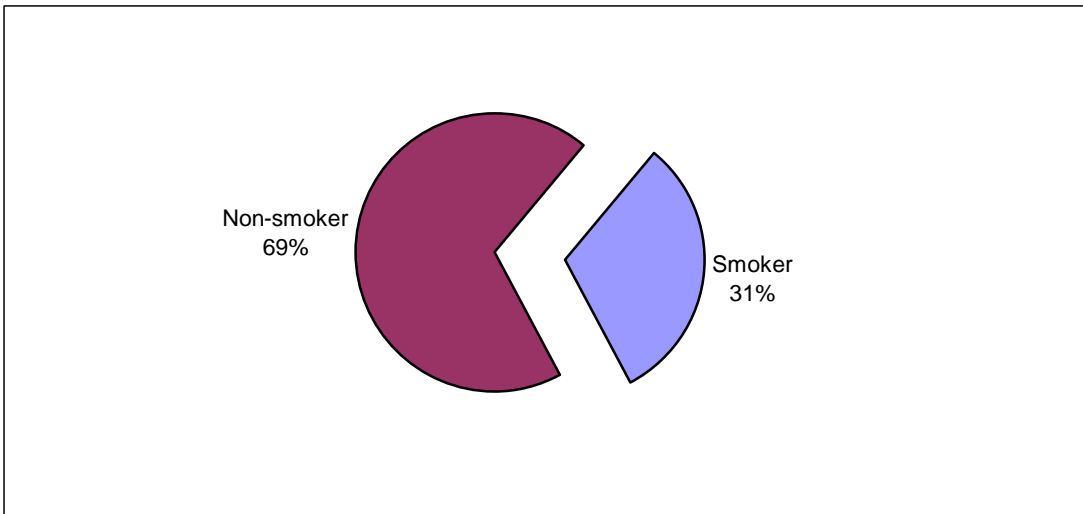

Figure 8: Distribution of defaulters smoking status

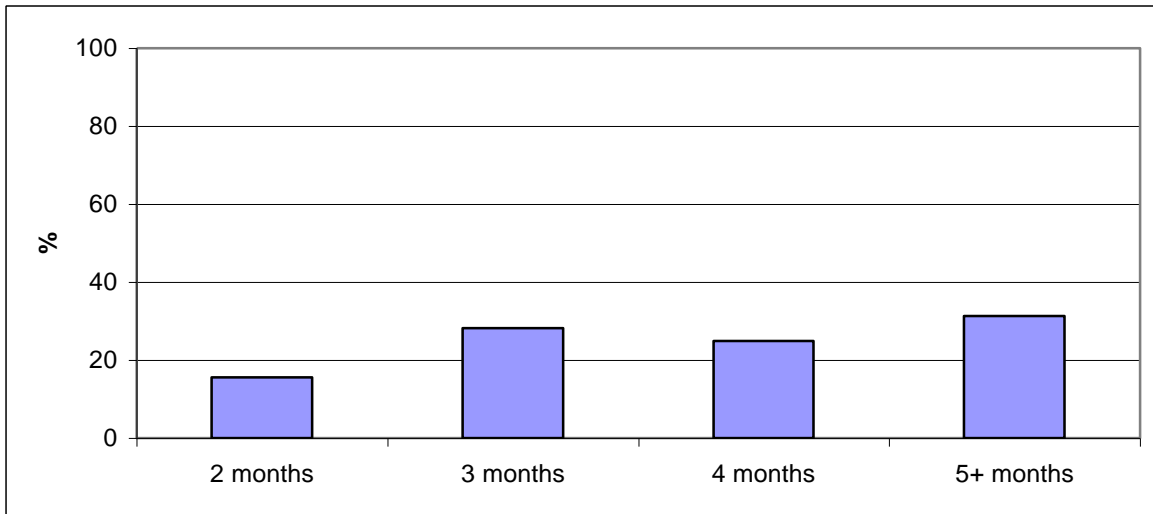The majority of the defaulters were non-smokers (**Figure 8**).

Figure 9: Distribution of defaulters according to time when default occurred

The month of defaulting started at the second month and increased up to 5 months (**Figure 9**). In the second month, 16% defaulters were observed, and increase to 28% in the third month. The majority (31%) of the defaulter's were observed in the fifth month.
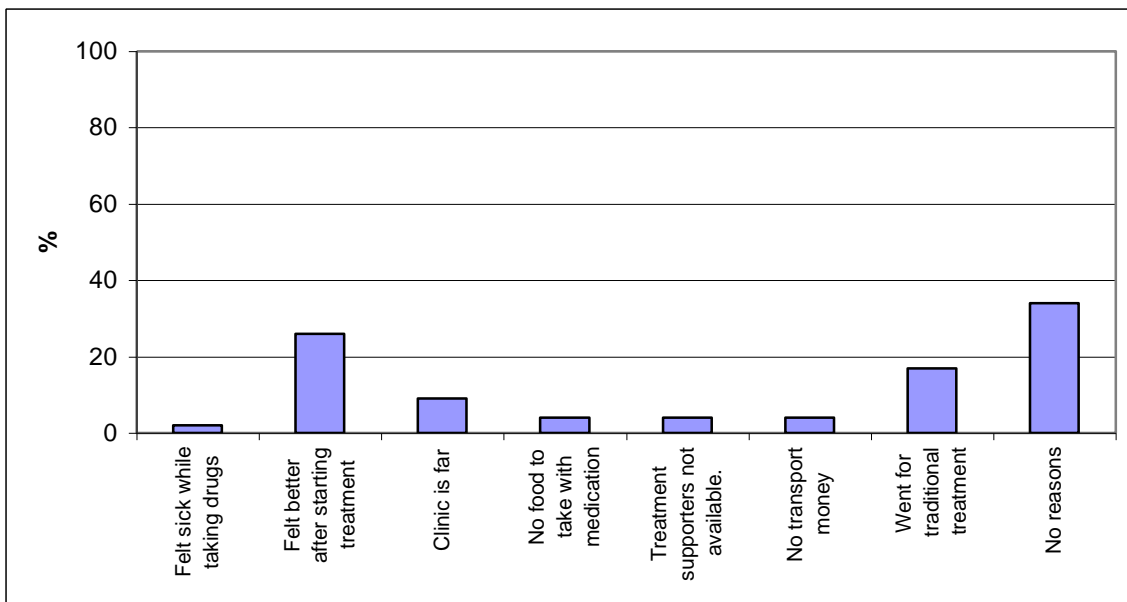

Figure 10: Distribution of defaulters according to reason for default

Figure 10 illustrates the distribution of defaulter's reason for not completing their TB treatment. The majority 34% of the defaulter's indicated that they had no reasons for not completing the treatment. About 26% said they defaulted because

they felt better after starting treatment, 17% went to the traditional treatment and only 9% said the clinic was too far.
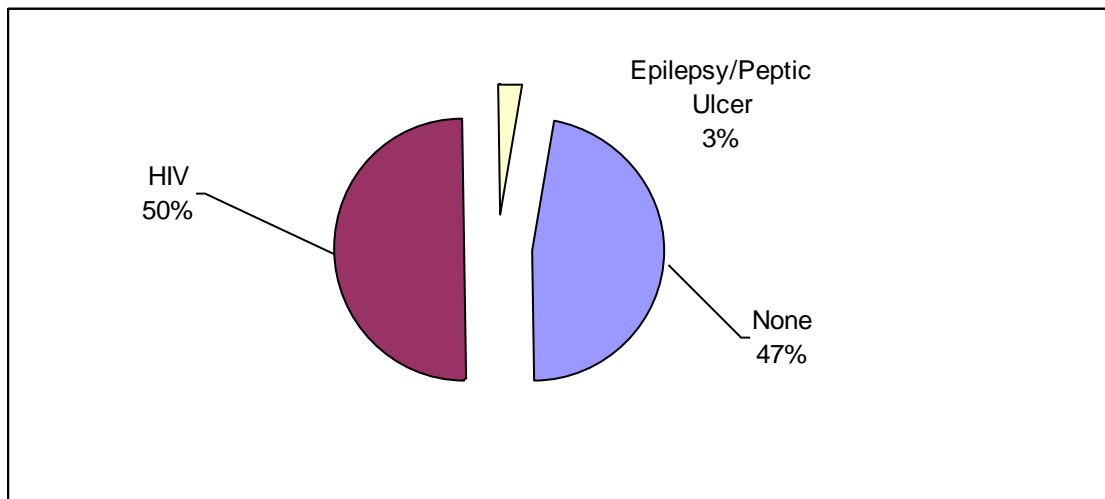

Figure 11: Distribution of defaulter's co-morbidities/sicknesses

Fifty percent of the defaulter's are HIV positive, 47% had no other sicknesses and 3% had epilepsy/peptic ulcer.
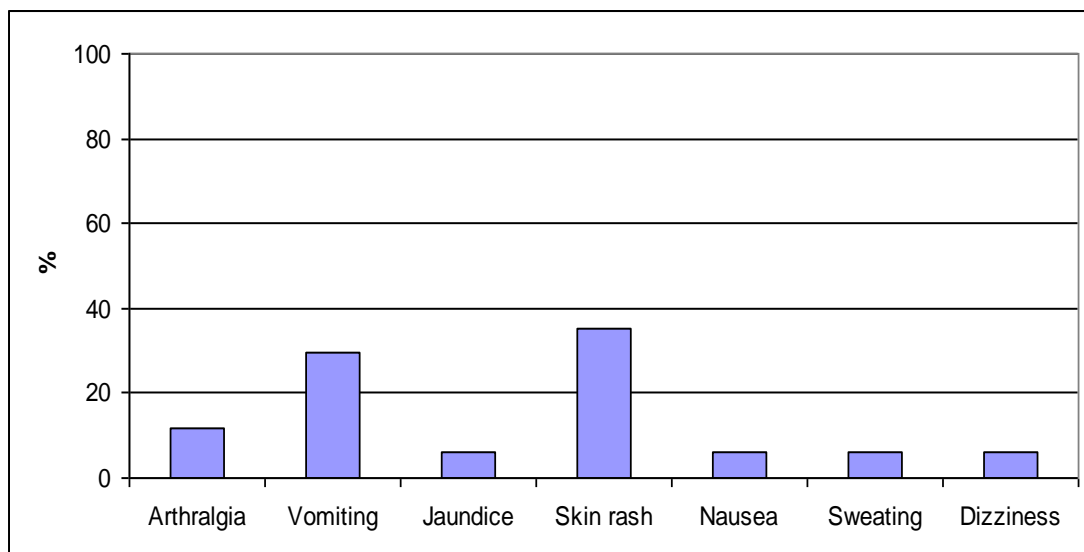

Table 12: Distribution of adverse effects of TB drugs on defaulters

Figure 12 shows the distribution of adverse effects of TB drugs on defaulters. About 17% of the participants had adverse effect and of these, 35% had skin rash, 29% reported vomiting, and 12% had arthralgia.
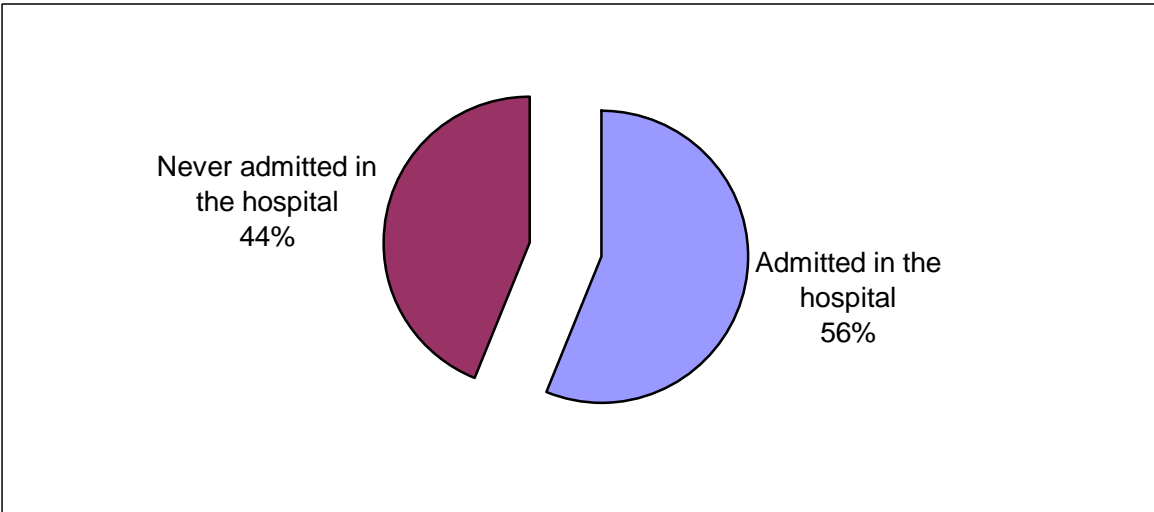
Table 13: Distribution of defaulters admitted in the hospital

About 56% of the defaulters were admitted in the hospital. The main reasons for admission were 58% PTB, 7% diarrhea, 10% injuries, 26% other diseases.

CHAPTER 5: DISCUSSION AND CONCLUSION

In the previous chapter, the findings and the interpretation of the results were presented. In this chapter, the results of this study are discussed. The main purpose of this study was to identify the reason TB patients default treatment.

Based on the findings of this study, the TB patient defaulter rate was less than 15%, which is similar to other studies conducted in developing countries (Dodor, 2004, Lamsal et al, 2009, Kiliman et al, 2010). Previous study has observed a defaulter rate of 21-27% (Chatterjee et al, 2003; Hasker et al, 2008, Janani, et al, 2008).

Some studies have reported defaulters in the following aged group 25-44 years (Dodor, 2004), 30 years and younger (Rakotonirina, et al, 2008), 15-24 years (Abuaku et al, 2010). In the present study we observed the highest default rate was in the age group 30-39 years followed by 20-29 years.

Fifty three percent (53%) of males were defaulting TB treatment in this study. Previous studies have indicated that males tend to default TB treatment (Dobor, 2004, Rakotorina et al, 2008, Abuaku et al, 2010). The study also indicated that default rate was high in single individuals, which was similar to the study conducted in Malawi (Kruyt ML et al, 1998)

Chatterjee et al (2003) reported illiteracy and high income group as the main reason of high default rate. In this study, the highest proportion of defaulters was observed in patients with primary and secondary education and those with low income level.

Studies conducted in different settings indicated unemployment as the main reason for TB treatment default (Hasker et al, 2008, Janani, et al, 2008, Conradie, 1986). In the present study, eighty one percent of the defaulters were unemployed. More than seventy percent of the defaulters were not smoking and drinking alcohol. Previous studies indicated alcohol as the reason for defaulting TB treatment (Lamsal et al, 2009, Hasker et al, 2008, Kiliman et al, 2010). Janani et al, (2008) reported smoking as the main reason for defaulting TB treatment.

In this study the reasons for defaulting TB treatment were: patient felt better after starting treatment, clinic too far, went for traditional treatment. Similar findings were reported by some studies conducted in different countries (Chatterjee et al, 2003, Hasker et al, 2008, Lamsal et al, 2009). More than fifty percent of the defaulters in this study were admitted in the hospital for the following conditions: pulmonary tuberculosis, diarrhea, injuries. Hasker et al, (2008) reported that the majority of the defaulters were hospitalized during treatment.

A retrospective study conducted in Kwazulu-Natal with the aim to determine the outcome of MDR-TB patients has indicated that defaulter rate is high among patients with associated HIV diseases (Brust et al, 2010). In this study, 50% of the patients were HIV positive.

In summary, this study has demonstrated some of the factors that contribute to non-compliance to TB treatment among patients seen at Matlala Hospital. We observed that a large number of the defaulter stop TB treatment due to distance, using traditional healers, and stop treatment when they felt better. With regard to the said reasons, we need to intensify patient education about the need to complete treatment and improve the DOTS support system.

Recommendations:

1. Improve the referral system to the nearest clinic
2. Improve the supervision of patients
3. Provide of food parcels and grant
4. Improve patient education
5. Integrate traditional healers in the management of tuberculosis

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