PATTERN OF TUBERCULOSIS INFECTION AND ADHERENCE TO DIRECTLY OBSERVED TREATMENT STRATEGY AT LAGOS UNIVERSITY TEACHING HOSPITAL, NIGERIA

BY

AKINSOLA, OLUWATOSIN JONADAB

B.Sc. (Hons) Statistics, 2001

M.Sc Biostatistics, 2008

Matric No: 88323

A Dissertation Submitted to

Department of Epidemiology and Medical Statistics,

Faculty of Public Health, College of Medicine, University of Ibadan, Nigeria

In Partial Fulfillment of the award of

MPhil (Biostatistics)

July 2nd, 2014

DECLARATION

I hereby declare that this work is original otherwise acknowledged. The work has neither been presented to any other College for an academic award nor has it been submitted elsewhere for other purpose.

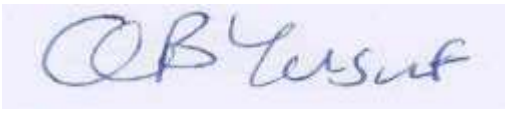
……..

Oluwatosin Jonadab Akinsola

B.Sc (Statistics), M.Sc (Biostatistics), Ibadan

CERTIFICATION

I certify that this work was carried out by research work was carried out by **Oluwatosin Jonadab Akinsola** in the department of Epidemiology and Medical Statistics, Faculty of Public Health, University of Ibadan under my supervision.



……

Supervisor
Dr. Oyindamola B. YUSUF
B.Sc. (Statistics), MSc., PhD (Biostatistics), Ibadan
Department of Epidemiology and Medical Statistics
Faculty of Public Health
University of Ibadan

ACKNOWLEDGEMENTS

I am greatly indebted to many people too numerous to mention, who have contributed their expertise in specific area and participated in the development of technical contents of this study.

At first, I sincerely appreciate my supervisors Dr. Bidemi Yusuf and Dr Onoja Akpa for their unwavering courage; unflinching supports and constructive criticisms which made this work a successful one. I pray that God almighty will grant them sound health and splendid minds to continue to steer the ship of Biostatistics in Nigeria. I am indebted to Dr. Ikeoluwapo Ajayi, the Head of Department who provided administrative support in finishing this programme. I would ever remain grateful to Dr. Fawole the former head of department, who gave me moral support and encouragement in completing this work. I also appreciate the self-sacrificing spirit of my former Faculty sub-dean (Dr. Fatiregun) for his meticulous and painstaking time and effort in making my abstract to get approval. God will reward you for your assistance.

I remember lecturers in the department of Epidemiology and Medical Statistics whose contributions and suggestions enhance the quality of this work. They include; Dr. M. D. Dairo, Dr. A. S. Adebowale, Dr. B. O. Adedokun, Dr. O. Akinyemi, Dr. Fagbamigbe for their encouragement, helpful guidance in the process and computational advice during statistical analysis. The non-academic staff of the department also substantially assisted in their capacities too. I appreciate the kind gesture and support of Mr. Taiwo Abiona in Community Medicine department, who accommodated me in his office during report writing and typing. May God meet you at the point of your need.

Finally, I thank the God Almighty, my creator, the giver of knowledge and understanding for his protection, provision and infinite grace throughout my educational career. Father, for making this dream a reality I will serve Him till the rest of my life.

Abstract

Tuberculosis is one of the leading causes of morbidity in developing countries and Nigeria ranks fifth among the countries with high burden of the disease. Understanding the distribution pattern of tuberculosis infection as well as adherence to treatment guidelines could help to strengthen existing policy aimed at reducing morbidity associated with the disease. This study was carried out to assess the pattern of sputum smear–positive tuberculosis infection and adherence to Directly Observed Treatment Strategy (DOTS) at Lagos University Teaching Hospital (LUTH), Lagos.

This was a retrospective cohort study involving 210 sputum smear-positive tuberculosis patients with complete data out of 226 that underwent DOTS at LUTH from January 2008 to June 2011. Variables extracted from the patients DOTS follow-up register included, socio-demographic characteristics, proximity of patients' residence to the hospital, family support received, anatomical location of lesion, HIV status and treatment outcomes, including conversion time to smear-negative sputum. Adherence was defined as the number of days a patient took the drugs divided by the number of days expected to have taken the drugs. Patients that had >0.5 of the fraction were regarded as having adhered to treatment. Data were analysed using descriptive statistics, Chi-square and Log-rank tests at 5% level of significance.

Mean age of patients was 39.1±10.4 years, 67.6% were males, 40.7% were Yoruba and 73.1% were married. Sixty-nine of the patients had ever smoked, out of which 60.7% were current smokers. The percentage of patients who had family support was 83.0%. About two-third of patients (66.2%) were HIV positive and 75.9% had pulmonary tuberculosis. The proximity of residence to the hospital was ≤25km for majority (65.7%) of the patients. About three-quarter (75.9%) of the patients adhered with DOTS. Treatment outcomes included 72.5% cured, 8.6% dead and 12.4% defaulted. Median sputum conversion time was 67 (range: 63 – 71) days. Patients who resided ≤25km to the hospital (65.7%) significantly adhered to treatment compared to those who lived >25km (31.6%). Also, patients who received family support significantly adhered to therapy (83.0%) compared to those who did not (14.6%). Median conversion time was lower among those who adhered to treatment [58 (range: 54 – 63) days] compared to those who did not [73 (range: 69 – 77) days].

Majority of smear-positive tuberculosis infected patients were males and their level of adherence was high. Family support received was identified to influence adherence. Integration of family support with directly observed treatment strategy as well as location of treatment centres close to patients residence could enhance effectiveness of the strategy.

Keywords: Directly Observed Treatment Strategy, Sputum Conversion Time, Tuberculosis Infection

Word count: 413

TABLE OF CONTENTS

List of Abbreviations

DOTS	Directly Observed Treatment Strategy
TB	Tuberculosis
HIV	Human Immuno-Deficiency Vrus
LFU	Losses to Follow Up
MDR	Multi – Drug Resistant
K–M	Kaplan Meier
NTBLCP	National Tuberculosis and Leprosy Control Programme
RNTCP	Revised National Tuberculosis Control Programme
CDC	Centre for Disease and Control
WHO	World Health Organization
WHA	World Health Assembly
LUTH	Lagos University Teaching Hospital

CHAPTER ONE

INTRODUCTION

1.1 BURDEN OF TUBERCULOSIS

Tuberculosis ranks as the 2nd leading cause of death from an infectious disease worldwide, after human immune-deficiency virus (WHO Tuberculosis Report 2012) and the scale of the global TB epidemic demands urgent and effective action. Tuberculosis remains a major cause of morbidity and mortality in many countries and a significant public health problem worldwide. The global incidence of TB was estimated to be 136 cases per 100,000 populations per year in 2005, ranging from 39 per 100,000 per year in the WHO Region of the Americas to 343 per 100,000 per year in the WHO African Region. This represents a total of 8.8 million new cases of TB and 1.6 million deaths from TB every year (WHO, 2008). The 22 high-burden countries as defined by WHO are those countries that cover 63% of the world's population and that account for approximately 80% of the estimated number of new TB cases occurring worldwide each year (WHO, 2007).

However, based on surveillance and survey data, 9.2 million new cases of TB occurred in 2006 (139 per 100,000) including 4.1 million (62 per 100,000) new smear-positive cases which include TB in HIV-positive people. India, China, Indonesia, South Africa and Nigeria rank first to fifth respectively in terms of incident cases of the 22 high burden countries (WHO, 2007; WHO, 2008). Also, more than 90 million TB patients were reported to WHO between 1980 and 2005; 26.5 million patients were notified by Directly Observed Treatment Strategy (DOTS) programmes between 1995 and 2005 and 10.8 million new smear-positive cases were registered for treatment by DOTS programmes between 1994 and 2004 (WHO, 2007).

DOTS which underpins the Stop TB Strategy was being applied in 187 countries in 2005; 89% of the world's population lived in areas where DOTS had been implemented by public health services. In addition, a total of 199 countries/areas reported 5 million episodes of TB in 2005 (new patients and relapses); 2.3 million new pulmonary smear-positive patients were reported by DOTS programmes in 2005 and 2.1 million were registered for treatment in 2004 (WHO Report

2007). If properly implemented, DOTS is projected to give a cure rate of about 85%. It is a panacea for addressing drug resistance in the management of tuberculosis.

Although in the past decade there has been substantial progress in the development and implementation of the strategies necessary for effective tuberculosis control, the disease remains an enormous and growing global health problem (WHO, 2005). One-third of the world's population is infected with *M. tuberculosis*, mostly in developing countries, where 95% of cases occur. In 2003, there was an estimated 8.8 million new cases of tuberculosis, of which 3.9 million were sputum smear-positive (Corbett *et al*, 2003).

The number of tuberculosis cases that occur in the world each year is still growing, although the rate of increase is slowing. In the African region, the tuberculosis case rate continues to increase, both because of the epidemic of HIV infection in sub-Saharan African countries and the poor or absent primary care services in parts of the region (WHO Report, 2005). In many other countries, because of incomplete application of effective care and control measures, tuberculosis case rates are either stagnant or decreasing more slowly than should be expected (WHO Report 2009).

The latest available figures show that the global TB incidence rate is diminishing or stabilizing while prevalence and death rates are falling. WHO calculates that the expansion of the WHO-recommended DOTS strategy between 1990 and 2003 led to a fall in the global TB prevalence rate from 309 to 245 per 100,000 (including HIV-positive patients), including a 5% fall between 2002 and 2003.

Globally there are almost 9 million new cases of tuberculosis each year and each person with active TB infects 10 to 15 persons yearly (WHO, 2009). Tuberculosis kills about two million people every year, 33% of which are HIV positive (WHO, 2009) and 95% of the cases are found in the developing world with the majority in Sub-Saharan Africa (WHO, 2005). Tuberculosis is said to make up 2.6% of the disease burden in middle and low income countries, making it the ninth leading cause of death and disability worldwide. This estimate does not include tuberculosis in the context of HIV infection (Lopez AD *et al*, 2006).

1.1.1 DOTS STRATEGY

The Directly Observed Treatment Short course (DOTS) strategy was launched in 1994 (WHO/TB/94.179), to meet the targets set and to address the problem of TB globally. DOTS implementation helped countries to improve their National TB Control Programmes (NTPs) and also make major progress in TB control. By 2004, more than 20 million patients had been treated in DOTS programmes worldwide out of which more than 16 million were cured (WHO-Stop TB Partnership) Mortality due to TB has been declining and incidence diminishing or stabilizing in all the regions of the world except in Sub-Saharan Africa and to some extent Eastern Europe. The global treatment success rate among new smear-positive TB cases reached 83% by 2003 just short of the World Health Assembly (WHA) target of 85% by 2005) and in 2004 the case detection rate was 53% (against the target of 70% by 2005), (WHO report, 2005).

To meet the challenges of the Millennium Development Goals (MDGs), the DOTS strategy was extended to the Stop TB Strategy in early 2006. The Stop TB strategy was designed to address three major challenges in tuberculosis control which are; continuing DOTS expansion, dealing with emerging types of tuberculosis like HIV-TB and multi drug resistant tuberculosis (MDR-TB) and engaging the broader health system including the private sector (Reviglione and Upleker, 2006). The Stop TB programme enables existing achievements to be sustained, effectively addresses the remaining constraints and challenges, and underpins efforts to strengthen the health systems, thereby alleviating poverty and advancing human rights (WHO-Stop TB Partnership, 2005).

Moreover, the most important recent changes in the natural history of TB have been the impact of the HIV epidemic and the emergence of resistance to anti-TB drugs. HIV infection exacerbates the TB epidemic through its impact on susceptibility to Mycobacterium tuberculosis infection and progression from infection to active disease. HIV infection increases the rate at which Mycobacterium tuberculosis infections are acquired and increases the likelihood that people who are already infected will develop active TB disease. The impact of HIV has been greatest in countries of southern and eastern Africa, where up to 40% of adults may be infected with HIV and where the incidence of TB has increased to 4-5 fold within 10 years (Dye *et al* 1999). Other significant risk factors that may also have an important impact at population level includes overcrowding, tobacco smoking, diabetes, and severe malnutrition. In developing countries, tuberculosis is not uncommon which also constitutes a leading killer of people infected

with HIV. In a study in Oshogbo, Nigeria, sputum smear was positive in 20.0% of patients with TB (Fayemiwo *et al* 2003). Also, in another study on the prevalence of sputum smear-positive tuberculosis among patients at University of Maiduguri Teaching Hospital, the overall prevalence was 12.8% (Zailani *et al* 2005). This study seeks to determine the pattern of sputum smear-positive TB and compliance to Directly Observed Treatment Strategy (DOTS) among patients in a tertiary hospital in South-Western Nigeria.

1.1.2 TB CONTROL IN NIGERIA

Nigeria adopted and commenced the implementation of DOTS in 1993 through the National Tuberculosis and Leprosy Control Programme (NTBLCP), (FMOH, Abuja, 2008). At present, at least two health facilities in each Local Government Area (LGA) have fully functional DOTS services (WHO Report, 2009). The targets of the National TB programme are:

- to detect at least 70% of the estimated smear positive TB cases,
- to achieve at least 85% cure rate of the smear positives,
- to halve by 2015 the prevalence and the mortality due to TB relative to 1990 levels;
- to eliminate TB as a public health problem by 2050 (FMOH Abuja, 2008).

So far the National programme has achieved a case detection rate of 30% and treatment success rate of 79% (WHO Report, 2007). These achievements still fall below the respective global targets of detecting 70% of smear positive TB cases and a cure rate of 85%. Collaborative TB/HIV activities are being scaled up and 32% of TB cases are screened for HIV at major health facilities (WHO Report, 2009). Failure to expand DOTS to the private sector was identified as one of the main reasons militating against the attainment of the targets as the private sector is a major health care provider estimated to contribute 60% of the health expenditure in Nigeria (WHO Report, 2007). Thus, in line with the WHO recommendation, Nigeria's TB programme has advocated promotion of the public private mix to expand coverage and improve case detection (FMOH Abuja, 2008).

1.2 STATEMENT OF PROBLEM

Tuberculosis is still a major public health problem, with Africa having a disproportionate burden of the disease. Although the continent is only 11% of the world's population, it has more than 25% of the global burden of TB (WHO, 2005). Over 34 African countries have notification rates of at least 300 cases per 100,000 population, compared to less than 15 per 100,000 population in developed countries (ATM, 2006). The situation is worsening due to the high prevalence of HIV as approximately 35% of all TB patients in Sub Saharan Africa are co-infected with HIV, in comparison with the global average of 8%. This makes TB the commonest cause of morbidity and mortality among people living with HIV in the Sub-region (Styblo and Bumgarner, 1991). Recognizing that the TB epidemic had more than quadrupled since 1990 in Africa, Africa Ministers of Health in 2005 declared TB a regional emergency and affirmed their commitment to ensuring universal access to treatment, care and support by 2015 (AMH2, 2005).

Although the exact burden of tuberculosis is not known in Nigeria, the WHO estimates that there are about 435,000 new cases of pulmonary tuberculosis (311 per 100,000 population), about 184,000 new smear positive cases (131 per 100,000 population) and 745,000 cases of all forms of TB (521 per 100,000 population). Multi drug resistant TB (MDR-TB) among new TB cases is 1.8% while it is 9.4% among those previously treated for TB and the annual deaths due to all form of TB in Nigeria is about 130,000 (93 per 100,000 population). These figures place Nigeria fourth among the 22 high burden countries in the world (WHO, 2006).

In 1991, a World Health Assembly (WHA) resolution set a global target of cure for 85% of smear positive patients under treatment and detection of 70% of cases by the year 2000. These targets were based on epidemiological modelling, which suggested that achievement of an 85% cure rate and 70% case detection will reduce not only the prevalence of infectious (smear-positive) TB cases, but also the number of infected contacts and the incidence of infectious cases (WHO, 2005). Furthermore, achievement of these targets for case detection and cure is also expected to reduce the annual TB incidence rate by 7–12% per year, in the absence of HIV co-infection globally (Dye and Williams, 2000). However by 1998, it had become apparent that the targets would not be met by the specified date and in 2000, the fifty-third WHA therefore postponed the target year to 2005.

1.3 JUSTIFICATION

Understanding how to lower disease transmission, morbidity and mortality of Tuberculosis was an important part of the 2010 International Union Against Tuberculosis and Lung Disease Conference on Lung Health. The World Conference calls for increase in the development and implementation of strategies necessary for effective tuberculosis control. The World Conference also specifies the enormous investment in resources required to meet this challenge. This has prompted governments of nations to spend resources on programmes that aim at reducing its morbidity.

In Nigeria today, where free medication is available, many patients are not successfully treated (Fayemiwo *et al*, 2003), incomplete treatment may result in prolonged excretion of bacteria that may also acquire resistance to drugs and cause transmission of disease leading to increased morbidity and mortality. Considering the incidence and prevalence of TB world-wide (especially Africa), a study on the treatment outcomes, factors determining it and compliance to DOTS are necessary for effective management of the infection. In a study on the factors influencing compliance in patients with Tuberculosis on DOTS at Ile-Ife, Nigeria, 158 (73.0%) of the study group complied and all of them were cured (Erhabor *et al*, 2000). Also, in a study on DOTS compliance by tuberculosis patients in District Raipur (Chhattisgarh), 65.9% of patients complied with DOTS therapy while 33.45 were non-compliant (Singha *et al*, 2010).

1.4 AIM AND OBJECTIVES

General

- To assess the pattern of sputum-smear positive tuberculosis infection and adherence to Directly Observed Treatment Strategy (DOTS) at Lagos University Teaching Hospital (LUTH), Lagos.

Specific Objectives

1. To describe the age distribution, socio-economic and demographic characteristics of Sputum smear-positive TB patients accessing DOTS programme in LUTH, Lagos
2. To assess the level of adherence with DOTS
3. To identify factors influencing adherence to DOTS
4. To assess sputum conversion rates of patients

CHAPTER TWO

LITERATURE REVIEW

2.1 EPIDEMIOLOGY OF TUBERCULOSIS

Transmission of TB is through air borne spread of infectious droplets-nuclei, which are generated when infected persons cough, sneeze, talk or spit. Transmission generally occurs indoors where droplet nuclei can stay in air for a long time. An individual's risk of infection depends on the concentration of the droplet nuclei in contaminated air, the length of time the individual is exposed to the contaminated air and the susceptibility of the individual to the infection which is linked to the standard of living, the nutritional level of the exposed person and presence of immune-suppressive illness like HIV (WHO, 1996).

Tuberculosis affects people between 15 – 49 years (WHO/UNAID, 2001). A Nigerian study revealed that TB in South West Nigeria affects predominantly individuals below 40 years of age with peak age frequency between 21 to 30 years. More females are affected with TB with twice as many females as males being affected in the reproductive years. Deaths from tuberculosis were highest in the age group zero to 10 years, with deaths in all age groups being due to disseminated TB and TB meningitis (Nwachokor & Thomas , 2000).

2.2 PATHOGENESIS OF TUBERCULOSIS

About 90% of those infected with Mycobacterium tuberculosis have asymptomatic, latent TB infection (sometimes called LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease. However, if untreated, the death rate for these active TB cases is more than 50% (Onyebujoh *et al,* 2006). TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within alveolar macrophages (Houben *et al,* 2006). The primary site of infection in the lungs is called the *Ghon focus*. Bacteria are picked up by dendritic cells, which do not allow replication, although these cells can transport the bacilli to local lymph nodes. Further spread is through the blood stream to other tissues and organs where secondary TB lesions can develop in other parts of the lung, peripheral lymph nodes, kidneys, brain and bone. All parts of the body can be affected by the disease, though it rarely affects the heart, skeletal muscles, pancreas and thyroid (AMH2, 2005).

Pleural effusion may occur at any time after the initial infection. Effusions that are most common are caused by the release of a small amount of tuberculoprotein from an unapparent form within the lung into the pleural space. This in turn causes an inflammatory reaction and the accumulation of clear, protein-rich fluid. During the initial infection, regional, hilar, and mediastinal lymph nodes are always seeded with bacilli and other lymph nodes may be seeded also. The infection in these nodes may progress directly to clinical disease and this may become active after many years or may never become apparent.

In a normal host the immunologic response to infection with the tubercle bacillus provides a degree of protection against additional tubercle bacilli that may be inhaled subsequently in droplet nuclei. The likelihood of re-infection is a function of the risk of re-exposure, the intensity of such exposure, and the integrity of the host's immune system. Furthermore, in an otherwise healthy, previously infected person, any organisms that are deposited in the alveoli are likely to be killed by the cell-mediated immune response. Exceptions may occur, but clinical and laboratory evidence indicates that disease produced by the inhalation of a second infecting strain is uncommon.

2.3 SYMPTOMS OF TUBERCULOSIS

Symptoms include chest pain, coughing up blood (hemoptysis), and productive, prolonged cough for more than three weeks. Systemic symptoms include fever, chills, night sweats, appetite loss, weight loss, and often a tendency to fatigue easily (WHO, 2006). In the other 25% of active cases, the infection moves from the lungs, causing other kinds of TB. This occurs more commonly in immune-suppressed persons and young children. Although extra-pulmonary TB is not contagious, it may co-exist with pulmonary TB, which is contagious (CDC, 2000). Once infected with M. tuberculosis a person is infected for many years. The vast majority (90%) of people who are infected do not develop tuberculosis. Precipitating factors leading to active disease following primary infection include the onset of diabetes mellitus, corticosteroid therapy, poor nutrition, inter-current disease, stress and HIV infection. Adults are at the greatest risk of developing active disease within three years of primary infection. HIV infected individuals however develop primary TB within a few months of exposure to an infectious patient (WHO, 1996).

2.4 NATURAL HISTORY OF UNTREATED TUBERCULOSIS

Without treatment after five years, 50% of patients with pulmonary TB will be dead, 25% would be cured spontaneously and 25% will remain with chronic infectious TB (FMOH 2008, Abuja). Left untreated, each person with active TB will infect on the average, between 10-15 people every year and only 5%-10% of people who are infected with TB become sick or infectious at some time during their life (WHO, 2002).

2.5 HOST FACTORS PREDISPOSING TO TUBERCULOSIS

2.5.1 Age and Sex: Tuberculosis affects all ages in developing countries; however in developed countries, the disease is more common in the elderly; there is a low resistance in babies and young children because they do not have any passive immunity from their mothers. Resistance is also low in adolescence, in women who have repeated pregnancies and in old age due to breakdown of body defenses (Parks, 2007)

2.5.2 Heredity/Immunity: Several studies suggest that genetic factors play a key role in innate resistance to infection with M. tuberculosis. The existence of this resistance is suggested by the differing degree of susceptibility to TB in different population (Okochi AC, 2005)

2.5.3 Nutrition: Malnutrition is widely believed to predispose to TB. During World War 11, TB rates increased in European countries affected by the war, particularly in some special groups such as the German camps (WHO Report, 2010), and in Warsaw ghetto (WHO Report 2012). Improvement of sanitation status may alter the probability of those who are infected from developing clinical tuberculosis, and it may decrease the break down rate from infection to disease (Murray C *et al*, 1993).

2.5.4 Blood Group: In a study done in the Far East, persons with blood group O have been found to be relatively resistant to TB whereas those with blood group AB showed an increased risk of developing tuberculosis (WHO Report, 2009).

2.5.5 HIV Infection: Human immunodeficiency virus (HIV) predispose to tuberculosis. In 2008, new data from direct measurements of the proportion of TB cases that are co-infected with HIV in 64 countries suggest that HIV-positive people are about 20 times more likely than HIV-negative people to develop TB in countries with a generalized HIV epidemic (compared with a previous estimate of six) and between 26 and 37 times more likely to develop TB in countries where HIV prevalence is lower (compared with a previous estimate of 30) (Youmans *et al*, 1980)

in some countries in sub-Saharan Africa, up to 70% of patients with smear positive pulmonary TB are HIV-positive (WHO, 2003). HIV fuels the tuberculosis epidemic in several ways. It promotes progression to active TB both in people with recently acquired diseases and those with latent M tuberculosis infections. HIV is the most powerful known risk factor for reactivation of latent tuberculosis infection to active disease. HIV infected people are more susceptible to be TB infected when they are exposed to M tuberculosis (WHO, 2003).

The annual risk of developing TB in a PLHA who is co-infected with M tuberculosis ranges from 5 to 15%. In Kinshasa, Zaire, HIV positive women had a 26-fold increased risk of developing TB compared with HIV sero-negative women after a median follow up of 32 months (Braun *et al*, 1991). In Nigeria, an increasing association between HIV and TB has been observed. The HIV sero-prevalence rate among TB patients increased over the years from 2.2% in 1991 to about 30% in 2006, a situation indicating that the TB situation in the country will continue to be HIV driven (FMOH 2008, Abuja).

2.6 Social Factors Predisposing to Tuberculosis

Tuberculosis is described as a social disease with medical manifestations (Parks, 2007). Non medical factors such as poor quality of life, poor housing, overcrowding, under-nutrition, lack of education, lack of awareness of the cause of illness have contributed to the occurrence and spread of the disease (Mangtani *et al*, 1995) and it has been described as the barometer for social welfare (Parks, 2007). In Nigeria, a larger percentage of the people are poor and as such the disease is able to thrive and cause severe public health consequences (Oyarabu, 2000). Socio-economic factors have been found to also affect the health seeking behaviour of patients with tuberculosis. In Zambia, the mean diagnostic delay for TB treatment was associated with low socio-economic status (Needham *et al*, 2001). The economic burden for tuberculosis on patients creates barriers to prompt diagnosis, which may lead to continuing transmission of the infection (Needham *et al*, 1998).

In England and Wales in the 19th century before the introduction of effective anti-tubercle therapy, improvements in socio-economic conditions and fair distribution of wealth, brought about improvement in the nutrition of the general population and a fall in the incidence of tuberculosis (Davies *et al*, 1993). Tuberculosis has long ceased to be a purely medical problem, it is a socio-political challenge and any strict medical approach to TB eradication will fail. Medical

intervention must be set within, and be supported by a strong social and political network (Lyndon Barends, 1997).

2.7 Risk Factors of Tuberculosis

People with prolonged, frequent, or intense contact are at particular high risk of becoming infected, with an estimated 22% infection rate. There are a number of known factors that make people more susceptible to TB infection: worldwide the most important of these is HIV. Co-infection with HIV is a particular problem in Sub-Saharan Africa, due to the high incidence of HIV in these countries. Smoking more than 20 cigarettes a day also increases the risk of TB by two to four times (WHO, 2006). Diabetes mellitus is also an important risk factor that is growing in importance in developing countries (Nwachokor & Thomas, 2000). In addition, Overcrowding and Malnutrition are also known risk factors for tuberculosis (Ali & Olowokere , 1998).

2.8 Diagnosis of Tuberculosis

A complete medical evaluation for TB must include a medical history, a chest X-ray, and physical examination. Tuberculosis radiology is used in the diagnosis of TB. It may also include a tuberculin skin test, a serological test, microbiological smears and cultures. The interpretation of the tuberculin skin test depends upon the person's risk factors for infection and progression to TB disease, such as exposure to other cases of TB or immune-suppression (CDC, 2000).

There are four steps in diagnosing TB disease:

2.8.1 The Medical History: A medical history is the part of a patient's life history that is important for diagnosing and treating the patient's medical condition. It includes social, family, medical, and occupational information about the patient. To obtain a medical history, the clinician should ask whether the patient has been exposed to a person who has infectious TB, has Symptoms of TB disease, has had TB infection, TB disease before, or has risk factors for developing TB disease. Clinicians should suspect TB disease in patients with any of these factors.

2.8.2 The Tuberculin Skin Test: Patients with symptoms of TB disease are often given a tuberculin skin test. However, they should always be evaluated for TB disease, regardless of their skin test results. Furthermore, clinicians should not wait for tuberculin skin test results when evaluating patients who have symptoms of TB disease. Instead, they should give the patient a tuberculin skin test at the same time as they start the other steps in the diagnosis of TB disease.

2.8.3 The Chest X-ray: If the patient has TB disease in the lungs, the chest x-ray usually shows signs of TB disease.

2.8.4 The Bacteriologic Examination: This is the examination and the culture (growth) of clinical specimens (for example, sputum or urine) in the laboratory. The bacteriologic examination has four parts: Obtaining a specimen, examining the specimen under a microscope, culturing the specimen and doing drug susceptibility testing on positive cultures.

2.8.5 Prevention

TB prevention and control takes two parallel approaches. In the first, people with TB and their contacts are identified and then treated. Identification of infection often involves testing high-risk groups for TB. In the second approach, children are vaccinated to protect them from TB. Unfortunately, no vaccine is available that provides reliable protection for adults. However, in tropical areas where the levels of other species of mycobacteria are high, exposure to nontuberculous mycobacteria gives some protection against TB (WHO Report, 2006)

2.8.6 Vaccines

Many countries use Bacillus Calmette-Gerin (BCG) vaccine as part of their TB control programmes, especially for infants. This was the first vaccine for TB and developed at the Pasteur Institute in France between 1905 and 1921. According to the WHO, this is the most often used vaccine worldwide, with 85.0% of infants in 172 countries immunized in 1993 (WHO, 1995). However, mass vaccination with BCG did not start until after World War II (Constock, 1994) The protective efficacy of BCG for preventing serious forms of TB (e.g. meningitis) in children is greater than 80.0%; its protective efficacy for preventing pulmonary TB in adolescents and adults is variable, ranging from 0.0 to 80.0% (Bannon, 1999).

In South Africa, the country with the highest prevalence of TB, BCG is given to all children under age three (WHO/UNICEF, 2006). However, BCG is less effective in areas where mycobacteria are less prevalent; therefore BCG is not given to the entire population in these countries. In the USA, for example, BCG vaccine is not recommended except for people who meet specific criteria;

1. Infants or children with negative skin test results who are continually exposed to untreated or ineffectively treated patients or will be continually exposed to multidrug-resistant TB.

2. Health workers considered on an individual basis in settings in which a high percentage of MDR-TB patients has been found, transmission of MDR-TB is likely, and TB control precautions have been implemented and were not successful (CDC, 2005).

BCG provides some protection against severe forms of pediatric TB, but has been shown to be unreliable against adult pulmonary TB, which accounts for most of the disease burden worldwide. As it is now, there are more cases of TB on the planet than at any other time in history and most agree there is an urgent need for a newer, more effective vaccine that would prevent all forms of TB including drug resistant strains (in all age groups and among people with HIV) (Sadoff, 2006).

Several new vaccines to prevent TB infection are being developed. The first recombinant tuberculosis vaccine entered clinical trial in the United States in 2004, sponsored by the National Institute of Allegry of Infectious Diseases (NIAID) (NIAID, 2007). A 2005 study showed that a DNA TB vaccine given with conventional chemotherapy can accelerate the disappearance of bacteria as well as protect against re-infection in mice; it may take four to five years to be available in humans (Ha *et al*, 2005). A very promising TB vaccine, MVA85A, is currently in phase II trials in South Africa by a group led by Oxford University (Dye & Williams, 2000) and is based on a genetically modified vaccine virus. Many other strategies are also being used to develop novel vaccines. In order to encourage further discovery, researchers and policy makers are promoting new economic models of vaccine development including prizes, tax incentives and advance market commitments (WHO, 2000).

The Bill and Melinda Gates Foundation has been a strong supporter of new TB vaccine development. Most recently, they announced a $200 million grant to the areas Global TB Vaccine Foundation for clinical trials on up to six different TB vaccines candidates currently in the pipeline. It is believed that these vaccines when finally developed and applicable to man will go a long way in eradicating TB.

CHAPTER THREE

MATERIALS AND METHODS

3.1 STUDY SITE

The study utilized secondary data collected at the Directly Observed Treatment Strategy (DOTS) centre, Lagos University Teaching Hospital, Idi-Araba. LUTH is one of the two tertiary health institutions in Lagos state that was established in 1962 to cater for the needs of the teeming population of Lagos at the tertiary level. The Directly Observed Treatment Strategy (DOTS) centre was established in 2008 as a unit in response to address remaining constraints and challenges to TB control – an expansion that is critical to achievement of the Millennium Development Goals and related Stop TB Partnership targets for TB control.

3.2 STUDY POPULATION

The study involved 210 sputum smear-positive tuberculosis patients with complete data out of 226 that underwent DOTS at LUTH from January 2008 – June 2011. A review of records of these sputum smear-positive TB patients was carried out in January 2012.

3.3 DATA COLLECTION METHODS

The study utilized secondary data collected from patients Directly Observed Treatment Strategy (DOTS) at Lagos University Teaching Hospital, Idi-Araba, Lagos. A pre-coded data collection form was used to retrieve data from the case files of patients. Variables extracted from the patients DOTS follow-up register included: socio-demographic characteristics, proximity of patients' residence to the hospital, family support received, distance to the hospital e.g <=25km and >25km (Erhabor 2000, *et al*) HIV status and treatment outcomes, including conversion to smear-negative sputum and loss to follow-up of the patients. Also, information on availability of treatment partner was sought from the patients (by telephone contact). Each data collection form was given an identification number same as that on the case file of the patients. This facilitated easy cross-checking and verification during the process of data verification and validation.

3.4 DATA MANAGEMENT AND ANALYSIS

Descriptive statistics such as means, medians, ranges and standard deviations were used to summarize quantitative variables such as patients' characteristics while categorical variables such as level of adherence were summarized with proportions and percentages. Bivariate analysis such as Chi-square test was used to investigate the association between compliance and the selected variables. Logistic regression was further used to determine the factors that may be significantly associated with compliance of the patients. Model fit was assessed using the Hosmer Lemeshow goodness of fit test. A univariate comparison of proportions and percentages using chi-square test was also done for relevant variables. Due to the likely presence of censored observations, the median time to smear conversion and loss to follow up were estimated using the Kaplan-Meier method of survival analysis. The logrank test statistic was used to compare estimates of the hazard functions of the different subgroups at each observed event time. Cox Proportional hazard model was used to determine the relationship between the variables and time to smear conversion. All analysis was carried out using Statistical Packages for Social Sciences (SPSS), version 17.0.

3.5 OPERATIONAL DEFINITION OF VARIABLES

1. Loss to Follow-up

Lost to follow-up refers to patients who at one point in time were actively honoring their appointments at the DOTS clinic but have become lost (either being incommunicado or by being unreachable) at the point of data collection of the research study. These patients can become lost for many reasons i.e. *without properly informing the Health Care Worker in the DOTS clinic about the situation of their treatment regimen they may have opted to withdraw or discontinue treatment, moved away from the particular study site during their treatment period* or *become ill and unable to communicate* or *are deceased*.

2. Adherence

A patient was regarded as being adhered if he/she takes the drugs for at least 40 days out of the 60 days (i.e. two months period). If the total number of days a patient takes the drugs is >= 40 {Patients that had >0.5 of the fraction were regarded as having adhered to treatment} days which excludes Saturdays and Sundays for two months it was regarded as Yes (Adhered) otherwise.

3. Conversion Rate

Conversion rate is the rate at which all smear positive patients become negative. In this context, the conversion rate is defined as the number of negative results divided by the number of smear-positive patients for whom the 2 months follow-up examination was completed.

Rate = (No of negative results/No of smear-positive patients) x 100%

4. Treatment Failure

Treatment failure is defined as the proportion of patients with potentially bacteriological unsuccessful outcomes (failure, default, died transferred out). In this context, this is a patient who is sputum smear-positive at 2 months or later during treatment.

5. Cured

These are patients who finished treatment and with negative bacteriology result at the end of treatment. In this context, this is a patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion.

6. Defaulter

Any patient who has interrupted treatment for 8 consecutive weeks or more after the date of the last attendance during the course of treatment.

7. Treatment Outcome

This encompasses the following: Cure, Transferred out, Treatment completed, Treatment Not Complete, Died and Defaulted

8. CAT I

This involve 6 months Regimen; Smear positive patients should be examined at end of 2nd Months, 5th months and 6 months.

9. CAT II

This involve 8 months Regimen; Smear positive patients should be examined at the end of 3rd months, 5th months and 7th months.

3.6 STATISTICAL METHODS

3.6.1 The Chi-square test of association

The chi-square test is used to test the significance of association between any two categorical variables. It is a parametric test that demands that the observations be expressed as frequencies and presented in contingency tables. The size of a contingency table is determined by the number of categories of each classifying nominal variables. A specific feature of the chi-square tests is its dependence on the degree of freedom. A rXc contingency table has (r-1) X (c-1) degree of freedom.

Suppose that in a particular sample, a set of possible events E_1, E_2,…….E_k are observed to occur with frequencies o_1, o_2,…..o_k called observed frequencies and that occurring to probability rules, they are expected to occur with frequencies e_1, e_2,…..e_k called expected or theoretical frequencies. Often we wish to know whether the observed frequencies differ significantly from the expected frequencies.

Event	E_1	E_2	.	.	E_k	
Observed frequency	O_1	O_2	.	.	O_k	N
Expected frequency	E_1	E_2	.	.	E_k	N

A measure of the discrepancy existing between the observed and expected frequencies is given by the statistic χ^2, $\chi^2 = \sum_{j=1}^{k} \frac{(Oj - ej)2}{ej}$

Where if the total frequency is N, $\Sigma O_j = \Sigma E_j = N$

The greater the value of χ^2 the greater is the discrepancy.

In practice, the expected frequencies are computed on the basis of a hypothesis H_o. if under this hypothesis, the computed value of χ^2 is greater than some critical value ($\chi^2_{0.95}$ or $\chi^2_{0.99}$), we conclude that the observed frequencies differ significantly from the expected frequencies and would reject H_o at the corresponding level of significance, otherwise we would accept it.

3.6.2 Logistic Regression

Logistic regression is a predictive analysis which involves prediction of dichotomous outcome variables using specified explanatory variables. A specific form of the logistic regression model is given by:

$$P(x) = \frac{\exp(bo + b_1 x)}{1 + \exp(bo + b_1 x)}$$

The logit transformation of the model in terms of P(x) is defined as:

$g(x) = \text{Ln}\,[P(x)/1 - P(x)]$

After simplification, we have; $g(x) = \beta_0 + \beta_1 x$

The logit, g(x) is linear in its parameters and may be continuous, and may range from $-\infty$ to $+\infty$ depending on the range of X.

In order to estimate the parameters of this logit model, the method of maximum likelihood estimation is used. This method yields values for the unknown parameters which maximizes the probability of obtaining the observed data. To apply this method, a function called likelihood function is constructed. This function expresses the probability of the observed data as a function of the unknown parameters. The maximum likelihood estimates of these parameters are chosen to be those values which maximize this function. Thus, the resulting estimates are those which agree most closely with the observed data.

In logistic regression, comparison of observed to predicted values is based on the log of the likelihood function. The ML method calculates the fitting function without using the predictor x and then recalculates it using what we know about x. The result is a difference in goodness of fit. The fit should increase with the addition of the predictor variable x.

The conceptual formula looks like the expression below where G stand for "goodness of fit"

G = likelihood without predictor – likelihood with the predictor

G = -2Ln {likelihood without the variable/likelihood with the variable}

Under the hypothesis that β_1 is equal to zero, the statistic G follows a chi-square distribution with 1 degree of freedom. The calculation of the log likelihood is a standard feature of any good logistic regression package. In SPSS, G as stated above is referred to as "-2 log likelihood".

3.6.3 Multiple Logistic Regression

The logit of this multiple logistic regression model is given by the equation

$$g(x) = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots + \beta_k X_k$$

in which case $p(x) = e^{g(x)}/(1 + e^{g(x)})$

Most logistic regression software will generate the design variables, and some programs have a choice of different methods. Specifically, if a nominal scales variable has k possible values, then k-1 dummy variables will be needed. The method of estimation used in the multivariate case is the same as in the univariate – maximum likelihood.

3.6.4 Fitting a Multiple Logistic Regression Model

The strength of a modeling technique lies in its ability to model many variables, some of which may be on different measurement scales. When a collection of say, p such independent variables are involved, the logit of this multiple logistic regression model is given by the equation

$$g(x) = \beta_o + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots + \beta_k X_k$$

in which case $p(x) = e^{g(x)}/(1 + e^{g(x)})$

Most logistic regression software will generate the design variables, and some programs have a choice of different methods. Specifically, if a nominal scales variable has k possible values, then k-1 dummy variables will be needed. The method of estimation used in the multivariate case is the same as in the univariate – maximum likelihood.

3.6.5 Cox Regression

The regression method introduced by Cox (1972) is used widely when it is desired to investigate several variables at the same time when the outcome variable is a *time to event variable*. It is also known as proportional hazards regression analysis. Cox's method is a 'semi-parametric' approach – no particular type of distribution is assumed for the survival times, but a strong assumption is made that the effects of the different variables on survival are constant over time and are additive in a particular scale.

The hazard function is closely related to the survival curve, representing the risk of having the event in a very short time interval after a given time, assuming survival thus far. It can therefore be interpreted as the risk of the event at time *t*. Cox's method is equivalent in its capability to multiple regression analysis except that the dependent variable is the hazard at a given time. If we have several independent variables of interest, say X_1 to X_p, we can express the hazard at time *t*, h(t), as

$$h(t) = h_o(t) \times \exp(b_1X_1 + b_2X_2 + \ldots\ldots + b_pX_p).$$

The quantity $h_o(t)$ in the equation is estimated from the data, and clearly corresponds to the hazard when all the variables are zero (because $e^0 = 1$). It is called the baseline or underlying hazard function. The regression coefficients, b_1 to b_p, also have to be estimated. If we have just one variable of interest, such as age, then we have

$$h(t) = h_o(t) \times \exp(b_{age} \times age)$$

Under this model a proportional change in age, such as a 50% increase from 40 to 60 years, results in a proportional change in the log of the hazard. In practice, the proportional hazards regression model is often found very suitable for modeling survival data, but the assumption of proportional hazards can and should be tested. The hazard gives the risk of the event at time *t*. so we can add all the hazards up to time *t* to get the risk of the event between time 0 and time *t*; this is called the **cumulative hazard**, H(t). It is defined as

$$H(t) = H_o(t) \times \exp(b_1X_1 + b_2X_2 + \ldots\ldots + b_pX_p)$$

where $H_o(t)$ is the cumulative underlying hazard function. Because of the way H(t) is calculated it can be shown that the probability of surviving to time *t*, S(t) can be estimated by exp [- H(t)]. We can thus estimate the survival probability for any individual with specific values of the variables in the model.

3.6.6 Kaplan – Meier Survival Curve

The Kaplan-Meier Method is a method for estimating the survival rate from ungrouped survival data. It is a method of estimating time-to-event models in the presence of censored cases. The Kaplan-Meier model is based on estimating conditional probabilities at each time point when an event occurs and taking the product limit of those probabilities to estimate the survival rate at each point in time.

This method is suitable for determining the rate of losses to follow up (LFU) in this study. This is because the concept of LFU is similar to the concept of survival in follow studies.

In this study, the event of interest (death in survival parlance) is "lost to follow up". Patients who died after recruitment into the DOTS program or those still being followed up and those that have been up for 15 months are treated as censored.

To determine the K-M estimate of the rate of LFU:

the period of observation is divided into series of time intervals such that one death is contained in each interval. The death is taken to occur at the start of the interval.

Specifically, let $t_{(1)}$, $t_{(2)}$, and $t_{(3)}$ be 3 survival times in ranked order so that $t_{(1)} < t_{(2)} < t_{(3)}$, c is a censored survival time between $t_{(2)}$ and $t_{(3)}$

The intervals begin at $t_{(1)}$, $t_{(2)}$, and $t_{(3)}$. Each interval includes one death.

There could be more than one subject dying at any survival time.

No interval begins at a censored survival time.

$t_{(0)}$ is time origin

Suppose there are k such intervals and that there are n individuals with observed survival times $t_1, t_2, t_3 \ldots\ldots t_n$ of which some are censored and that there may be more than one subject with the same observed survival times;

So we have r deaths with r <= n and with ordered survival times

$t_{(1)} < t_{(2)} < t_{(3)} < t_{(R)}$

The jth death is at time $t_{(j)}$

Let the number alive at $t_{(j)}$ is d_j.

Consider the time interval t_{j-d} to t_j where *d* is very small. The probability of survival through this interval is $\frac{n_j - d_j}{n_j}$

If censored survival time occurs at the same time with a death time, the censored time is taken to occur immediately after the death time.

Thus $(n_j - d_j)/n_j$ is an estimate of the probability of surviving from t_j to t_{j+1}.

Thus, the K-M estimate of the survival rate S(t) is

$$S(t) = \prod_{j=1}^{k} pj \quad \text{----------(1)}$$

for K = 1, 2, ------, r where pj = (nj - dj)/nj is the estimated probability that an individual survives through the time interval which begins at t(j) , j = 1, 2, -----, r

S_t is the probability that an individual survives (from LFU) longer than time t.

S_t = P (an individual survives longer than t)

= P (T > t)

= 1 – P (an individual fails (or LFU) before time t)

= 1 – P (T <= t)

$= 1 - F(t)$

$F(t) = 1 - S(t)$

F(t) = probability (proportion) of individuals failing (or lost to follow up) before time t.

F(t) as described above represent the rate of losses to follow up (LFU).

3.6.7 The Logrank Test

The logrank test is a non-parametric method for testing the null hypothesis that the groups being compared are samples from the same population as regards survival experience. The log rank test compares the overall survival experience of the (two) groups. The method assumes that the hypothesis being tested is whether the (two) survival curves are equal or whether one is consistently better than the other. If the (two) survival curves cross, the test needs to be interpreted with caution.

Rationale for the log rank test

Consider separately each death time in the two groups (Adherence and Non-Adherence).
Suppose there are r distinct death times

$t(1)<t(2) < \ldots\ldots\ldots\ldots t(r)$ across the two groups.

The null hypothesis that there is no difference in the survival experiences of individuals between the two groups at time t(j) can be tested by the usual χ^2 test. This test can be repeated for each of the death times then we need to find a way to summarize this series of tests by combining the information from the r individual 2 x 2 tables. ***a method of doing this is the Mantel-Haenszel procedure.***

3.6.8 Analysis Models

The logistic regression model of the multivariate equation is of the form:

$$\mathbf{Log[P/(1-P)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n}$$

In this equation, X_1, X_2,…X_n are independent variables, which include; sex, age, level of education, level of income, marital status, treatment partner status and distance to the hospital. While the dependent variable (level of compliance) was dichotomized as Yes or No status. Where P is the probability or the proportion of outcome variable. In order to dichotomize the level of compliance of patients, the number of days that a patient takes the drug divided by the number of days expected to have taken the dug were disaggregated into two categories (*e.g. for those patients in intensive phase who were expected to take the drugs once daily for the first two months under the supervision of health worker in the health facility, except weekends when the drugs for Saturday and Sunday are given to the patients to take home*). If the total number of days a patient takes the drugs is >= 40 days which excludes Saturdays and Sundays for two months it was regarded as Yes (complied) or *otherwise*.

Also, the Cox regression model, otherwise known as proportional hazard model works as described below.

Let there be n subjects with data provided.

Let $\mathbf{h_i(t)}$ be the hazard of the i-th subject at time t.

Let X be an indicator variable such that $X_i = 1$ if the i^{th} individual has a particular attribute and

$X_i = 0$ if otherwise.

In general, if the hazard of an event (rate of loss to follow-up) at a particular time depends on the values of X_1, X_2, X_3,…,X_p of p explanatory variables recorded at the time origin (the beginning of the interval). Let $h_o(t)$ be the hazard function for an individual whom the values of all the p explanatory variables are zero. Then for i^{th} individual, the hazard function is $h_i(t) = \psi(x_i)h_o(t)$.

Where $\psi(x_i)$ is a function of the explanatory variables for the i^{th} individual.

That is $\psi(x_i) = \beta_1 X_{1i} + \beta_2 X_{2i} + \ldots + \beta_p X_{pi}$

The hazard model of the multivariate equation is of the form

$$\text{Log}\left[\frac{hi(t)}{ho(t)}\right] = \beta_1 X_{1i} + \beta_2 X_{2i} + \ldots + \beta_p X_{pi}$$

$$= \sum_{j=1}^{p} \beta j X j i$$

Where X_{1i}, X_{2i},…, X_{pi} are independent variables which would include socio-demographic variables like sex, age, level of education, level of income, marital status, treatment partner status and distance to the hospital.

CHAPTER FOUR

RESULTS

Table 1 shows the socio-demographic characteristics of the patients included in this study. Their mean age was 39.1±10.4 years. The youngest patient was 20 years while the oldest was 65 years. About one-third of the patients (31.4%) were aged between 30 to 39 years. The sex ratio was 2.1 given a larger proportion of male gender (68.6%), while (32.4%) were females. Majority (75.7%) of them were married. Most of the respondents (40.3%) were Yorubas. A larger percentage of the patients (36.3%) have primary only education.

Table 1: Socio-demographic characteristics of patients included in the study.

Age group (years)	**Frequency**	**Percentage**	**Cumulative Frequency**
20-29	47	20.8	20.8
30-39	71	31.4	52.2
40-49	58	25.7	77.9
45-59	30	13.3	91.2
>=60	4	1.8	93.0
Missing	16	7.0	**100.0**
Total	**226**	**100.0**	
Sex			
Male	155	68.6	68.6
Female	71	31.4	**100.0**
Total	**226**	**100.0**	
Marital Status			
Single	33	14.6	14.6
Married	171	75.7	90.3
Widow/Widower	8	3.5	93.8
Separated	14	6.2	**100.0**
Total	**226**	**100.0**	

Ethnicity			
Yoruba	91	40.3	40.3
Hausa	42	18.6	58.9
Igbo	54	23.9	82.8
Others	26	11.5	94.3
Missing	13	5.8	**100.0**
Total	**226**	**100.0**	
Level of Education			
None	33	14.6	14.6
Primary	82	36.3	50.9
Secondary	78	34.5	85.4
Tertiary	24	10.6	96.0
Missing	9	4.0	**100.0**
Total	**226**	**100.0**	

Table 2 shows that over one-third of the patients (38.6%) engage in one form of business or the other. A larger percentage of the patients (57.9%) practice Christianity. Majority of the patients (47.3%) income ranges between 18,000-29,999 naira. More than three-quarters of the patients (83.2%) have Treatment partner while a larger proportion of the patients (61.1%) live within 25 kilometers from the health facility.

Table 2: Distribution of Patients' Occupation, Religion, Level of income, Treatment partner status and Distance.

Variable	Frequency	Percentage	Cumulative Frequency
Occupation			
Artisan	39	17.3	17.3
Business	86	38.6	55.9
Civil/Public Servant	31	13.7	69.6
Trading	53	23.5	93.1
Others	17	6.9	**100.0**
Total	**226**	**100.0**	
Religion			
Christianity	131	57.9	57.9
Islam	89	39.4	97.3
Traditional	6	2.7	**100.0**
Total	**226**	**100.0**	
Level of Income			
<18,000	62	27.4	27.4
18,000-29,999	107	47.3	74.7
>=30,000	45	19.9	94.6
Missing	12	5.3	**100.0**
Total	**226**	**100.0**	
Treatment partner status			
Yes	188	83.2	83.2
No	23	10.2	93.4
Missing	15	6.6	**100.0**
Total	**226**	**100.0**	
Distance to the hospital			
<=25km	138	61.1	61.1
>25km	76	33.6	94.7
Missing	12	5.3	**100.0**
Total	**226**	**100.0**	

Table 3 summarizes the distribution of lifestyle history, disease type, treatment outcome and level of adherence of the patients. One-third of the patients (35.8%) have ever smoked, about two-third of them (64.2%) are currently smoking while less than one-fifth (16.4%) have missing cases. Also, less than two-third of the patients (57.5%) has ever taken alcohol, two-fifth of them (55.4%) are currently taking alcohol while about more than ten percent (12.9%) have missing cases. A paltry proportion of the patients (7.9%) are diabetic while less than one-third (29.6%) have missing cases. Of the total of 226 patients, about three-quarter of the patients (74.9%) are new pulmonary tuberculosis cases, 5% of the patients are Extra-pulmonary tuberculosis cases while about ten-percent of the patients (9.3%) are Re-treatment cases. The cure rate of the patients was about two-third (66.4%) of the cohort. In addition, majority (80.5%) of the patients adhered with DOTs while (26.1%) was lost to follow-up. The cure and treatment success rates among the smear-positive were 75.9% and 78.3% respectively. Moreover, the median conversion time observed in this study was similar among males and females of [70 (range: 66 – 75) days] days each.

Table 3: Distribution of life style history, disease type, treatment outcome and level of adherence of patients.

Variable	Frequency	Percentage	Cumulative Frequency
Have you ever smoked?			
Yes	81	35.8	35.8
No	108	47.8	83.6
Missing	37	16.4	**100.0**
Total	**226**	**100.0**	
Are you currently smoking?			
Yes	52	64.2	64.2
No	23	28.4	92.6
Missing	6	7.4	**100.0**
Total	**81**	**100.0**	
Have you ever taken alcohol?			
Yes	130	57.5	57.5
No	67	29.6	87.1
Missing	29	12.9	**100.0**
Total	**226**	**100.0**	

Are you currently taking alcohol?			
Yes	72	55.4	55.4
No	41	31.5	86.9
Missing	17	13.1	**100.0**
Total	**130**	**100.0**	
Diabetes Mellitus			
Present	18	7.9	7.9
Absent	141	62.5	70.4
Missing	67	29.6	**100.0**
Total	**226**	**100.0**	
Type of Disease			
New pulmonary	192	84.9	84.9
Extra-pulmonary	13	5.8	90.7
Re-treatment	21	9.3	**100.0**
Total	**226**	**100.0**	
Treatment category			
Cat I	145	64.2	64.2
Cat II	81	35.8	**100.0**
Total	**226**	**100.0**	
Treatment outcome			
Cure	150	66.4	66.4
Transferred out	12	5.3	71.7
Treatment completed	7	3.1	74.8
Treatment Not complete	12	5.3	80.1
Died	24	10.6	90.7
Defaulted	21	9.3	**100.0**
Total	**226**	**100.0**	
HIV status			
Positive	158	69.9	69.9
Negative	55	24.4	94.3
Missing	13	5.7	**100.0**
Total	**226**	**100.0**	
Level of adherence			
Yes	182	80.5	80.5
No	29	12.8	93.3
Missing	15	6.6	**100.0**
Total	**226**	**100.0**	

Factors influencing adherence to DOTS

The result in table 4a shows the associations between Adherence to DOTS and socio-demographic variables. More males adhered with DOTS than the females (73.6% vs 26.4%, p=0.031). Level of adherence appeared to increase with increasing age; however this increase was not statistically significant. (p=0.810). Adherence was highest among patients with primary education (37.9%) and lowest among those with tertiary education (9.3%). However, these differentials in educational level were not statistically significant at 5% level. Furthermore, adherence was highest among the traders (83.9%), followed by those in business (39.6%) and lowest among the other categories of occupation (6.6%) (p=0.358). Results in table 4b showed the associations between adherence to DOTS with ethnicity, level of income, treatment partner and distance to the hospital. Adherence to DOTS was significantly higher among those with treatment partner (90.7%) compared with those without treatment partner (9.3%) (p=0.027). Patients that live close to the health facility adhered more than those who live far away (66.5% vs 33.5%, p=0.031). However, there were no significant associations between adherence and ethnicity (p=0.122), and level of income (p=0.458).

Table 4a: Factors influencing adherence to DOTS.

Variable	**Level of Adherence**		χ^2	**P-value**
	Yes	**No**		
Sex of patients			4.337	0.031**
Male	134(73.6)	21(72.4)		
Female	48(26.4)	8(27.6)		
Total	**182(100.0)**	**29(100.0)**		
Age of patients (years)			1.655	0.810
20-29	38(20.9)	9(31.0)		
30-39	56(30.8)	15(51.7)		
40-49	48(26.3)	10(34.5)		
50-59	24(13.2)	6(20.7)		
>=60	3(1.6)	1(3.4)		
Total	**182(100.0)**	**29(100.0)**		

Educational level of patients			1.515	0.638
None	27(14.8)	6(20.7)		
Primary	69(37.9)	13(44.8)		
Secondary	67(36.8)	11(37.9)		
Tertiary	17(9.3)	7(24.1)		
Total	**182(100.0)**	**29(100.0)**		
Marital status of patients			2.196	0.427
Single	24(13.2)	9(31.0)		
Married	139(76.4)	17(58.6)		
Widow/Widower	7(3.8)	1(3.4)		
Separated	12(6.6)	2(6.9)		
Total	**182(100.0)**	**29(100.0)**		
Occupation of patients			4.652	0.358
Artisan	31(17.0)	8(27.6)		
Business	72(39.6)	14(48.3)		
Civil/Public servant	22(12.1)	9(31.0)		
Trading	46(25.3)	7(24.1)		
Others	12(6.6)	5(17.2)		
Total	**182(100.0)**	**29(100.0)**		
Religion of patients			1.773	0.389
Christianity	107(58.8)	24(82.8)		
Islam	78(42.9)	11(37.9)		
Traditional	4(2.2)	2(6.9)		
Total	**182(100.0)**	**29(100.0)**		

****** significant at 5%

Table 4b: Factors influencing adherence to DOTS.

Variable	Level of Adherence		χ^2	P-value
	Yes	No		
Ethnicity of patients			5.816	0.114
Yoruba	78(42.9)	13(44.8)		
Hausa	37(20.3)	5(17.2)		
Igbo	39(21.4)	15(51.7)		
Others	18(9.9)	7(24.1)		
Total	**182(100.0)**	**29(100.0)**		
Level of Income of patients			1.672	0.438
<18,000	53(29.1)	9(31.0)		
18,000 – 29,999	89(48.9)	18(62.1)		
>=30,000	35(19.2)	10(34.5)		
Total	**182(100.0)**	**29(100.0)**		
Treatment partner status			4.763	0.027**
Yes	165(90.7)	23(79.3)		
No	17(9.3)	6(20.7)		
Total	**182(100.0)**	**29(100.0)**		
Distance to the hospital			4.638	0.031**
<=25 Km	121(66.5)	17(58.6)		
>25 Km	61(33.5)	12(41.4)		
Total	**182(100.0)**	**29(100.0)**		

****** significant at 5%

Multivariate Analysis (Logistic Regression) for factors influencing Adherence to DOTS

The factors identified to be significantly associated with adherence to DOTS in bivariate analysis were harvested and subjected to multivariate analysis. The result of the multiple logistic regression analysis for adherence to DOTS is shown in tables 5. The dependent variable in table 5 is adherence to DOTS, a Yes-or-No outcome. Male patients were about two times more likely to (OR=1.832, p=0.042, 95% CI: 1.02, 3.3) adhere with DOTS than the female patients. {Also, patients who have treatment partner are two times more likely (OR=2.069, p=0.089, 95% CI: 0.61, 1.92) to adhere with DOTS than those without treatment partner}. However, patients' treatment partner (p=0.782) distance to the hospital p=(0.188) were not significant predictors of adherence in the analysis. The model was a good fit as Hosmer and Lemeshow goodness of fit was not significant ($\chi 2 = 3.601$, p= 0.463).

Table 5: Logistic Regression Analysis of Factors influencing adherence to DOTS

Variables	Odds Ratio	SE	Wald Statistic	P-value	95% CI
Sex					
Male	1.832	0.298	4.124	0.042*	(1.021, 3.289)
Female*					

* reference category

Sputum Conversion of Patients

Table 6 shows the results of the Cox proportional hazard model for Sputum Conversion of patients. In this analysis, an event was defined as time to sputum conversion. Sex, Treatment partner and Distance to the hospital and Level of adherence were investigated as determinants of the outcome [time to sputum conversion]. The estimated rate of sputum conversion was higher among Female patients compared to Male patients (HR=2.83, p=0.000, 95% CI: 2.143, 3.765). The risk of sputum conversion was lower among patients who have treatment partner compared to patients who do not have treatment partner (HR=0.205, p=0.04, 95% CI: 0.628, 0.939). {Also, the risk of sputum conversion was higher among patients who live <=25Km distance to the health facility compared to patients with >25Km proximity (HR=1.69, p=0.188, 95% CI: 0.774, 3.682)}. In addition, the risk of sputum conversion was lower among patients who adhered compared to non-adhered patients (HR=0.266, p=0.003, 95% CI: 0.113, 0.628).

Table 6: Determinants of Time to Sputum Conversion

Variables	B	SE	Wald Statistic	P-value	Hazard Ratio	95% CI
Sex						
Female	1.043	0.145	52.761	0.000*	2.837	(2.143, 3.765)
Male*						
Treatment partner	-1.584	0.294	0.065	0.024*	0.205	(0.628, 0.939)
Yes						
No*						
Level of Adherence	-1.324	0.438	15.756	0.003*	0.266	(0.113, 0.628)
Yes						
No*						

* reference category

Table 7 shows the summary statistics of sputum conversion time. The Median sputum conversion time of those who adhered was 58 (range: 54 – 63) days and 73 (range: 69 – 77) days among those who did not. The Median sputum conversion time of patients in category I was 72 (range: 66 – 78) days compared to 75 (range: 69 – 82) days in category II. Moreover, the Median sputum conversion time among the HIV positive patients was 79 (range: 73 – 84) days compared to 53 (range: 48 – 57) days in HIV negative patients.

Table 7: Comparison of sputum conversion time among the prognostic variables

Group	Number of cases	Number of events	Number censored	Median sputum conversion time (days)	P value (log-rank test)
Level of adherence					0.05**
Yes	192	8	184	58 (range: 54 – 63)	
No	14	5	9	73 (range: 69 – 77)	
HIV Status					0.011**
Positive	162	10	152	79 (range: 73 – 84)	
Negative	91	18	73	53 (range: 48 –57)	

****** significant at 5%

Loss to follow up of Patients

The result of the K-M estimates of survival from loss to follow up is presented in table 8. The percentages of patients retained in care are (98.4%) at 3 months and (74.0%) at 15 months respectively. Also, the percentages of LFU at 3 months and 15 months are (1.9%) and (25.9%) respectively.

Table 8: Kaplan-Meier Estimates of Survival (from lost to follow-up)

Time (Months)	No Remaining	Cum. Event (LFU)	Cum. Survival [S_t]	SE	Cum. F_t = 1 - S_t
0 –	226	-	-	-	-
3 Months –	210	27	0.9842	0.0293	0.0187
6 Months –	206	48	0.9813	0.0315	0.0158
9 Months –	200	41	0.9126	0.0372	0.0874
12 Months –	195	40	0.8442	0.414	0.1558
15 Months –	188	36	0.7403	0.0436	0.2597

In Kaplan-Meier Survival Plots were displayed in Figures 1.1 to 1.4. Level of adherence (P = 0.05) and HIV status (P = 0.011) was significantly associated with sputum conversion of patients while Treatment categories (P = 0.861) of patients were not associated with sputum conversion. Overall, there was no significant difference (P = 0.329) in the sputum conversion of patients.

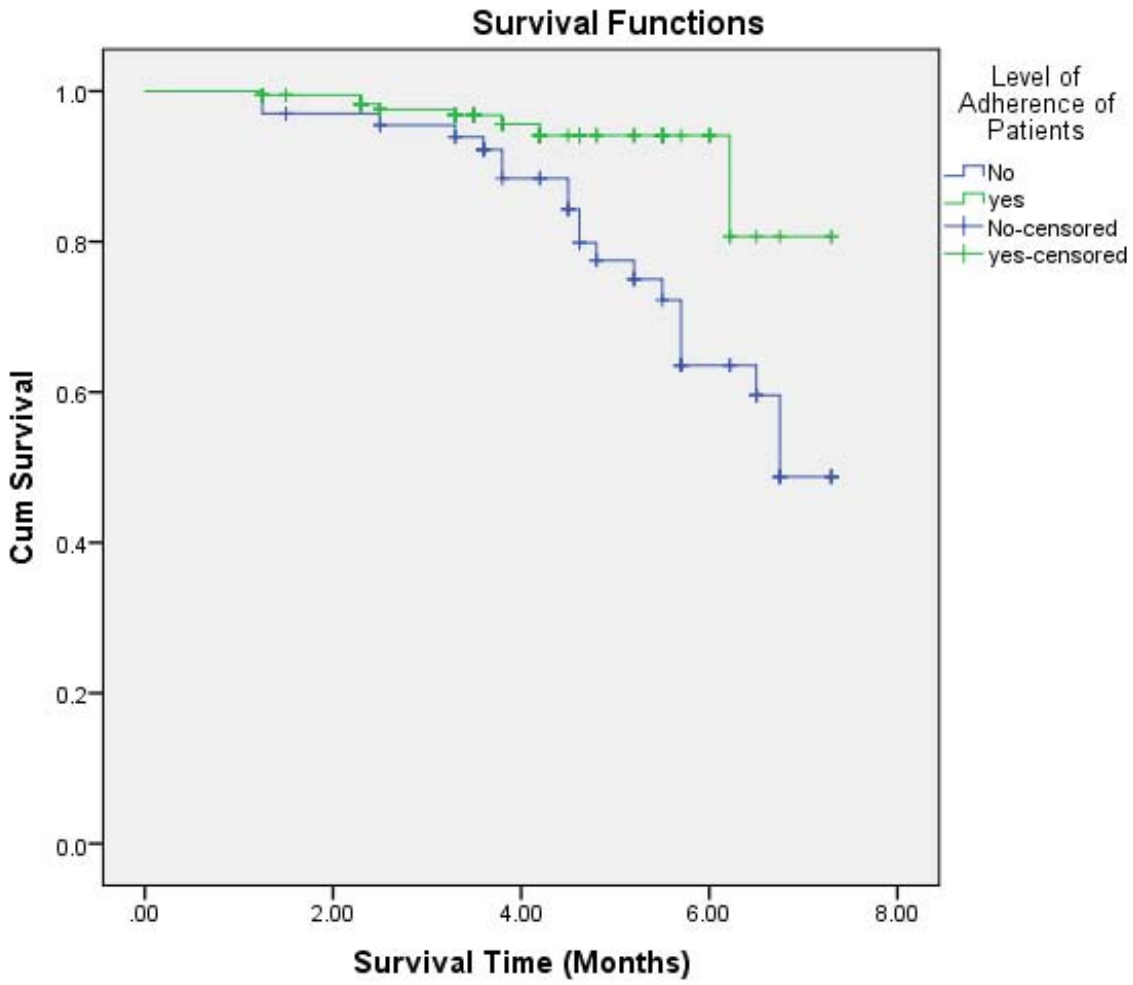


Figure 1.1: K-M plot for time to Sputum conversion by Level of Adherence of patients

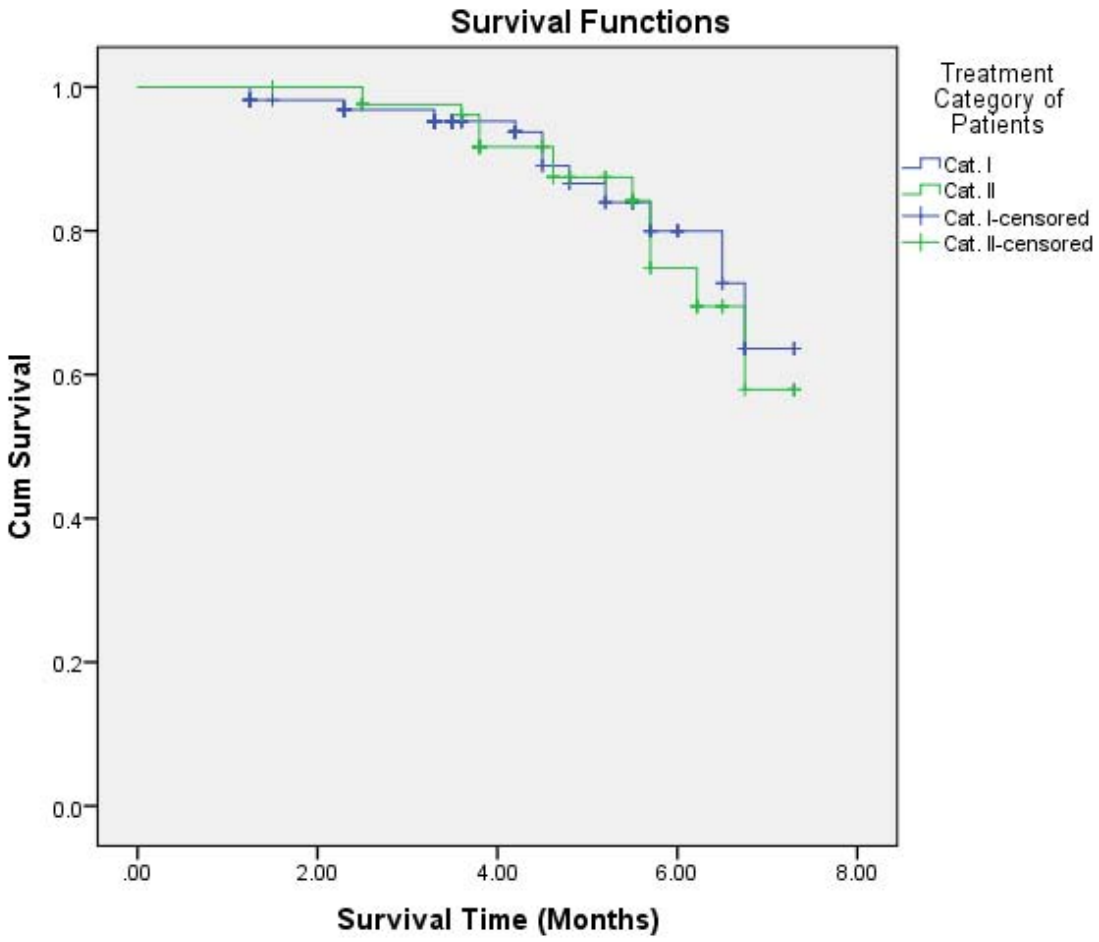


Figure 1.2: K-M plot for time to Sputum conversion by Treatment Categories of patients

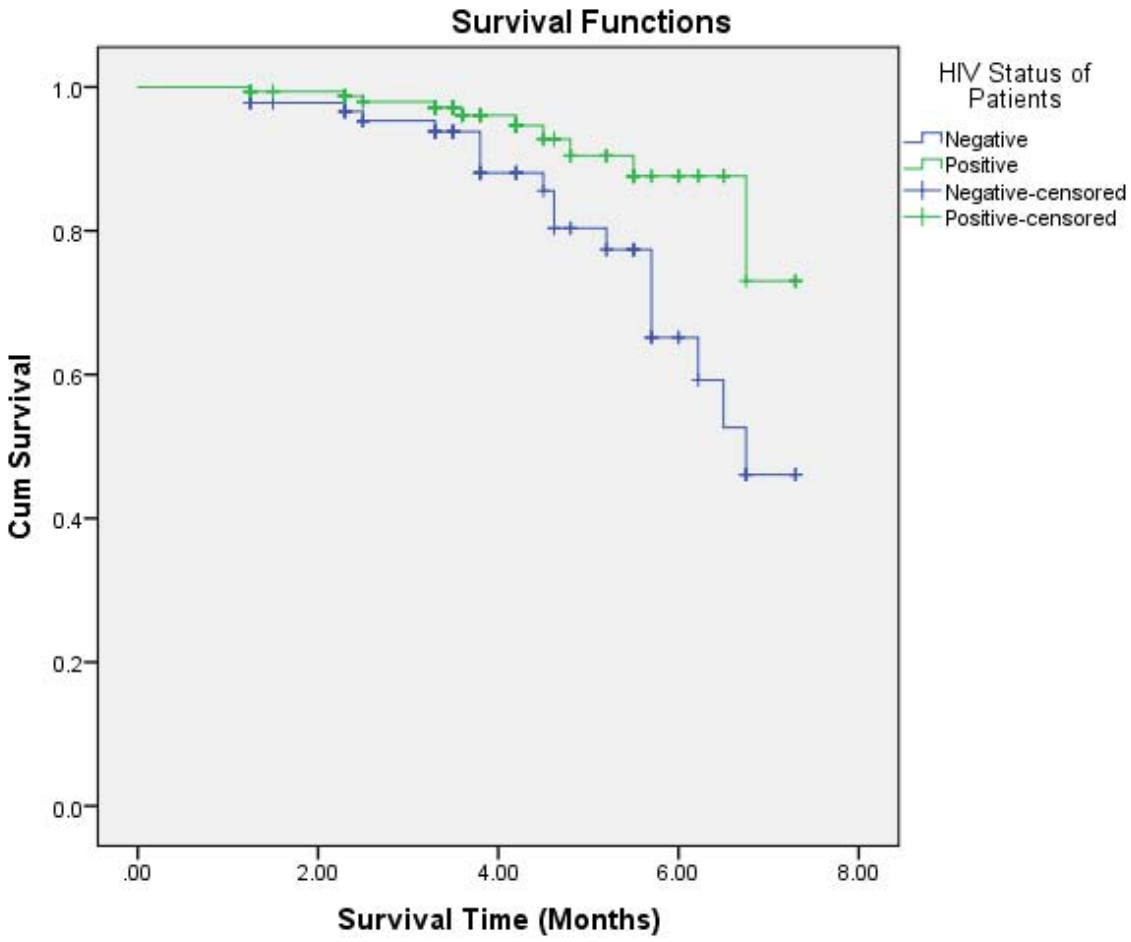


Figure 1.3: K-M plot for time to Sputum conversion by HIV Status of patients

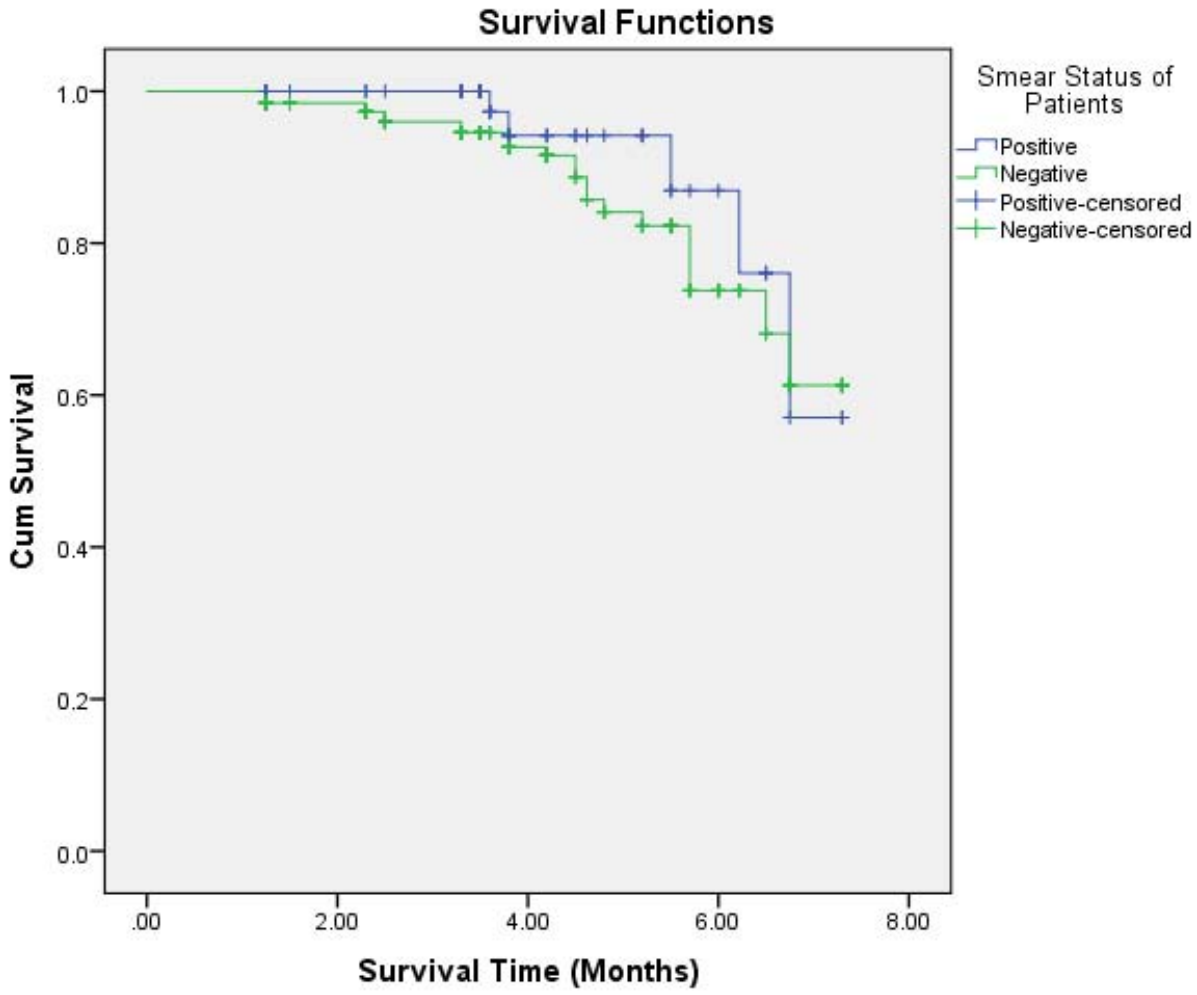


Figure 1.4 Overall Survival Function for Sputum conversion of patients

CHAPTER FIVE

DISCUSSIONS, CONCLUSION AND RECOMMENDATION

5.1 INTRODUCTION

This study has revealed the pattern of sputum smear-positive tuberculosis infection and compliance to Directly Observed Treatment Strategy (DOTS). It also identified socio-demographic factors influencing level of compliance and survival status. In this section, the discussions and conclusions emanating from the results presented in the preceding chapters are made. Relevant recommendations on the basis of the results and discussions are also included.

5.2 DISCUSSION

Studies on Tuberculosis have been conducted at different times in Lagos State and other locations in Nigeria. However, the present study revealed socio-economic factors and patterns of sputum smear-positive tuberculosis infection and adherence to Directly Observed Treatment Strategy (DOTS) at LUTH, Idi-Araba, Lagos. In this study, cure and treatment success rates among smear positive patients were 75.9% and 78.3% respectively. Although these figures are lower than the 85% cure rate set by WHO, They are however comparable to the results obtained in studies in Poland, Mexico, Iran and Egypt. These countries have lower prevalence of TB compared to Nigeria.

In the study period, higher proportion of males were diagnosed and treated, giving the sex ratio of 2.1. The study of Kehinde *et al*, (2006) a 10 year review (1996 – 2005) of TB treatment at the University College Hospital (UCH), Ibadan, reported a higher proportion of males. The study of Fahettin *et al* (2007), conducted in Turkey reported a higher proportion of males. These suggest that there is an apparent higher prevalence of TB among the males to females. However, Nwachoko and Thomas (2000), a 30 year review of TB treatment in University College Hospital (UCH), Ibadan, reported a higher prevalence among females than males (a female to male ratio of 2:1).

The mean age of patients treated within the period under study was 39.1, this shows that most of the patients were between the ages of 20 and 65 years. This is in contrast to the observation of

Nwachoko and Thomas, 2000 in a study conducted at the University College Hospital, Ibadan, they observed that TB infection was predominant in individuals below 40 years of age. Fahrettin *et al*, 2007 also observed a mean age of 32.5 ± 13.2 years.

The observed cure and treatment success rate was higher in males than in females. And this is in disagreement with Fahrettin *et al* who found a higher treatment success in females than males, (61.0% and 58.1%) respectively. This discrepancy may be attributed to the fact that majority of the respondents are predominantly male gender.

Also, there were sharp differences in the failure rates between [adhered and non-adhered] groups (4.7% and 8.9%) and default rates between [adhered and non-adhered] groups (8.3% and 12.5%) respectively. This would also underscore the importance of evaluating multi-drug resistance more carefully. Treatment success was lowest among patients in age group 60 and above. This may be attributed to the fact that the highest death rates (22.2%) occurred in this age group. Fahrettin *et al*, 2007, also observed a low treatment success in patients above 46 years of age. It is possible that this age group may be a risk factor for deaths if the life expectancy in the country is taken into consideration. However, this may not be unconnected with other causes of death such as chronic diseases, old age among others which are common among this age group but could not be determined in this study due to unavailability of data.

The rate of loss to follow-up in this study was higher in males (17.1%) than in females (5.8%). This is in consonance with the study of Fahrettin *et al*, 2007; where 6.5% and 0% were reported among males and females respectively. Deil and Neimann (2003) determined that being male is a risk factor for default. They observed that females were more eager to go to clinic to receive their treatment and use their drugs more regularly than the males. Treatment default is very important in TB treatment as it can easily lead to drug resistance and increase the risk of infection.

The median time to initial smear conversion observed in this study was 68 days for all cases respectively. This is apparently lower than the 83 days conversion time observed by Holtz *et al*, (2006). The median conversion time observed in this study was similar among males and females; 70 days each. The median sputum conversion time was lower among the adhered patients compared to non-adhered patients. The effect of the DOTS therapy may probably be adduced to this shorter time to conversion. The sputum conversion time was higher among the

HIV positive patients compared to HIV negative patients. The delayed sputum conversion may be attributed to the co-infection between HIV and TB. The treatment categories of patients did not have any effect on the smear sputum conversion of the patients.

According to Ige *et al*, 2004, about 90.0% smear conversion was achieved among treatment patients. A slower conversion rate was observed among the Re-treatment cases compared to New treatment patients (69 and 120 days respectively). This may be related to the fact that default or re-treatment increases the chance of becoming resistant to anti-TB drugs. Results also showed that patient category was significantly associated with smear conversion time. Within 30 days, about 13 (6.1%) converted to smear negative 28 (11.0%) patients converted within 2 months. The majority however converted after two months. The clinical implication of these can be attributed to a high drug adherence of the TB patients.

Sputum conversion time has very important public health implication as it determines the risk of infection among the public. According to Holtz et al, (2006), achieving a more rapid smear conversion can simplify a patient therapy and increase comfort by reducing the amount of time he or she is giving an injectable drug. Sputum culture conversion is used routinely as an indicator of treatment progress in multi-drug resistant TB despite little evidence to justify its use or provide a benchmark against which a program can be measured. While median conversion time was lower among those who adhered to treatment compared to those who did not, the survival rates in this study were found to be 90.0% in category I and 85.2% in category II. This is similar to the survival rates reported in another study (Geeta Pardeshi, 2009) were 93.0% in category I and 88.0% in category II respectively. The implication of this is that patients in category I are more likely to get acute TB while category II are likely of having chronic TB which are functions of survival status. In this study, mortality is higher among category I smear-positive patients than category II smear-positive patients. In a study of survival analysis and risk factors for deaths in tuberculosis patients on DOTS (Geeta Pardeshi, 2009), out of the total 41 deaths in patients of tuberculosis, 11 deaths occurred in category I smear-positive patients; and remaining 30 deaths, in category II smear-positive patients. Also, in another study conducted in the state of Delhi, mortality due to tuberculosis was considerably reduced among new sputum-positive cases with the implementation of Revised National Tuberculosis Control Programme (RNTCP), but mortality among smear-negative and new extra-pulmonary and re-treatment cases did not show any significant decline (Dhingra VK *et al*, 2009). While in a study of survival analysis and risk factors for deaths in tuberculosis patients on Directly Observed treatment Short course, a lower

survival rate at the end of the intensive phase was noted in re-treatment cases (category II) compared to category I (Geeta Pardeshi, 2009).

Finally, results of the Kaplan-Meier estimate of survival from losses to follow up (or succinctly, DOTS follow up continuation rate) showed that majority of the patients survived LFU (or are continuing with DOTS follow up care) at 3 months. While about three-quarter of them were continuing with DOTS care and follow up at 15 months post discharge, the cumulative rate of LFU (DOTS follow up discontinuation rate) ranges from 1.87% at 3 months to 25.97% at 15 months.

5.3 CONCLUSION

In conclusion, this study attempted to determine the patterns of sputum smear-positive TB infection and compliance to DOTS at LUTH, Idi-Araba, Lagos. The study revealed high cure and treatment success rate among New and Re-treatment cases. Majority of smear-positive tuberculosis infected patients were males and their level of adherence was high. Family support received and proximity of patients' residence to the hospital were factors identified to influence adherence. Integration of family support with Directly Observed Treatment Strategy could enhance effectiveness of the strategy. Similar median conversion times were observed for both males and females and treatment categories. Level of adherence and HIV status of patients showed significant differences in the median sputum conversion times.

5.4 RECOMMENDATIONS

1. The study observed a long initial time to smear conversion (about 64 days). It was observed that the patients' sputum smear observations were done at two or three months interval. This interval may be too long to enable effective monitoring of the sputum conversion time. Although this is a resource limited setting, a more frequent sputum smear examination (if possible on monthly basis) will be more appropriate for better patient monitoring.

2. In the course of the study, it was observed that some patients were given radiologic examinations (X – ray) whose records were not available; who were subjected to sputum examination. These patients could not be certified as cured but only as having completed treatment. We suggest that radiologic examination should be combined with sputum examination with detailed documented reports so that the true outcome of the patients' treatment can be ascertained.

REFERENCES

AFRICAN UNION UPDATE ON TUBERCULOSIS CONTROL IN AFRICA.Special Summit of the African Union on HIV/AIDS, Tuberculosis and Malaria (ATM).Sp/Ex.CL/ATM/4 (1) 2006Abuja.

AMH. (2005). African Union Sustainable Access to treatment and care for the achievement of the millennium development goals: Gaborone Declaration on HIV/AIDS, TB and Malaria. 2nd ordinary session of the conference of Africa Ministers of Health (AMH2), 10-14 October 2005. Gaborone, Botswana.

Braun A. (1991). A retrospective cohort study of the risk of tuberculosis among women of child bearing age with HIV infection in Zarie.Am Rev Respir Dis. 143: 501-504.

Dye C., Suzanne M.S. (1999). Global burden of tuberculosis: Estimated Incidence, Prevalence, and Mortality by Country. JAMA, 1999; 282: 677 – 686.

Cosivi O., Grange J.M. (1998). Zoonotic Tuberculosis due to Mycobacterium bovis in developing countries: emerging Infectious Diseases Vol. 4, No. 1, January – March.

Davies R.P. (1999).Historical declines in Tuberculosis in England and Wales; improving social conditions or natural selection. Int. J. Tuberc Lung Dis;3:105-54.

Dye C., Williams B.G. (2000).Criteria for the control of drug resistance tuberculosis.Proceedings of the National Academy of Sciences. 97:8180-8185.

Erhabor G.E. (2000). Factors Influencing Compliance in patients with Tuberculosis on Directly Observed Therapy at Ile-Ife, Nigeria.East African Medical Journal Vol. 77. No 5,

Fayemiwo S.A., Taiwo S.S. (2004). Epidemiology of tuberculosis and HIV Infection in Oshogbo, Nigeria.

FMOH. (2008). Public-Private Mix in Tuberculosis Control: Implementation Guidelines.

Hauser S.L., Longo D.L., Jameson J.L. (1998). Harrison's Principles of internal medicine.15th edition USA.McGraw-Hill Companies inc.1024-1035.

Jain R.C. (1970). ABO Blood Group and Pulmonary Tuberculosis.Tubercle. 51: 322-323.

Khatri G.R., Frieden T.R. (2002).Controlling tuberculosis in India.N Engl J Med. 347:1420-5.

Lopez A.D. (2006). Global and regional burden of disease and risk factors; Systematic analysis of population health data.Lancet. 367: 1747-1757.

Barends L. (1997). DOTS in Action for African Health.

Mangtani P., Watson J.M., Rodrigues L.C. (1995).Socio-economic deprivation and notification rates for tuberculosis in London during 1982-1991. BMJ. 310: 953-960.

Marioc R., Richard O. (2004). Tuberculosis Jn, Braunwaid E, Fausi A.S, Kasper DL

Murray C. (1993).*et al*. Disease control priorities in developing countries. Oxford medical publications.The World Bank. New York.

Needham D.M., Godfrey–Fausette P., Foster S.D. (2001). Socio-economic, gender and health services factors affecting diagnostic delay for tuberculosis patients in urban Zambia. Trop Med Int. Health. 6(4):256-9.

Needham D.M, Godfrey–Fausette P, Fosta SD. (1998). Barriers to tuberculosis control in urban Zambia. The economic impact and burden on patient prior to diagnosis. Int. J. Tuber Lung Dis. 2(10): 811-817.

Nwachokor F.N., Thomas J.O. (2000). Tuberculosis in Ibadan, Nigeria: A 30 year review. Central African Journal of Medicine. 46(11): 289-292

Oyarabu K.A. (2000). Poverty, Homelessness and water supply: Public health consequences in Nigeria. Archives of Ibadan medicine.Vol 1 (2) supplement.

Parks K. (2007).Tuberculosis in Parks Textbook of preventive and social medicine.19th edition. India. M/s BanasidasBhandt Publishers.137-51.

Reviglione M.C, Upleker MW. (2006). WHO's New Stop TB strategy. Lancet.367: 952- 953.

Sarmiento A.G. (1990). Operational Assessment of the case finding and treatment aspects of the Strengthened National Tuberculosis Control Programme. Department of Health, The Philippines. Manila.

Singh V. (2002) TB control, poverty, and vulnerability in Delhi, India.Trop Med Int Health.**7:**693–700.

Styblo K., Bumgarmer J.R. (1991). Tuberculosis can be controlled with existing technologies: evidence. Tuberculosis Surveillance Research Unit progress report 1991, 2: 60-72

WHO Report. (1992). Secular Trend of Tuberculosis in Western Europe: Epidemiological situation in countries. WHO/TB/1992.170. Geneva.

WHO Report. (1994). Tuberculosis Programme: framework for effective tuberculosis control. (WHO/TB/94.179).Geneva

WHO Report. (1996). TB/HIV.A Clinical Manual.

WHO Report. (1999). What is DOTS: A guide to understanding the WHO- recommended TB control strategy known as DOTS. 1999. WHO/CDS/CPC/TB/99.270.

WHO Report. (2000). Resolution WHA 53.1. Stop Tuberculosis Initiative. Fifty-third World Health Assembly. Geneva. Resolution and decisions. World Health Organization 2000 (WHA 53/2000/REC/1) Annex 1-2.

WHO Report. (2002).An expanded DOTS framework for effective tuberculosis control 2002.WHO/CDS/TB/2002.297.Geneva.

WHO Report. (2003). Guidelines for implementing collaborative TB and HIV programme activities. WHO/CDC/TB/2003.319. Geneva

WHO Report. (2005). Global tuberculosis control, Surveillance, Planning and Financing.World Health Organization (WHO/HTM/TB/2005.349).Geneva.

WHO-Stop TB Partnership. (2005). The Stop TB strategy: building and enhancing DOTS to meet the TB related millennium developmental goals.

WHO Report.(2006). Global Tuberculosis Control, Surveillance, Planning and Financing, STOP TB department, Geneva.

WHO Report. (2007). Global tuberculosis control: Surveillance, Planning and Financing;

WHO Report. (2008). Global tuberculosis control: Surveillance, Planning and Financing.

WHO Report. (2009). Global Tuberculosis Control: A short update to the 2009 report. (WHO/HTM/TB/2009.426) Geneva.

WHO Report. (2012). Global tuberculosis report.

Youmans G.P., Paterson P.Y, Sommers H.M. (1980).The biologic and clinical basis of infectious diseases 2nd edition. Saunders USA.

APPENDIX I

Standardized Treatment Categories

Treatment categories are basically divided into two: category 1 and category 2 (WHO, 2003).

TB treatment category	Patients
Category 1	New sputum smears positive PTB
	Newly diagnosed seriously ill patient with severe form of TB
Category 2	Relapse
	Treatment failure
	Return after default

Monitoring of TB treatment

Monitoring progress of tuberculosis patients while on treatment is an essential part of the case management. This is to ascertain the effectiveness of treatment in killing M. Tuberculosis as well as assessing improvement in the patient's clinical state. Monitoring is done through the following methods: (WHO, 2003)

- Sputum microscopy: Looking for AFB in sputum at specified intervals.
- Clinical: Regular clinical assessment including weight monitoring
- Drug intake: Through assessment of patient's records for regularity.

Follow up of patients using Sputum Microscopy

- Two sputa smear examinations (taken as two early morning samples within 2 days) at different points during the treatment.
- For smear positive patients, collection and examination of sputum should be done at the end of 2nd month for new cases or 3rd month for re-treatment cases, at the end of the 5th and 7th month
- For smear negative patients, collection and examination of sputum should be done only at the end of the 2nd month.

- If the direct smear is positive at the end of the 2nd month for new cases, the intensive treatment with daily RHZE will be continued as a rule for a maximum of 4 more weeks.
- If the intensive phase is prolonged by 1 month because sputum examination was positive at the end of the second month, then the continuation phase should last five months (WHO, 2003).

INTERNATIONAL STANDARD FOR TUBERCULOSIS CARE

The International Standards for Tuberculosis Care (ISTC) describe a widely endorsed level of care that all practitioners should seek to achieve in managing individuals who have, or are suspected of having tuberculosis. The document is intended to engage all care providers in delivering high quality care for patients of all ages, including those with smear-positive, smear-negative, and extra-pulmonary tuberculosis caused by drug-resistant Mycobacterium tuberculosis complex, and tuberculosis combined with HIV infection (Sarmiento A.G., 1990).

Standards for Diagnosis

The Standards are also intended to serve as a companion to and support for the patients' Charter for Tuberculosis care

1. All persons with otherwise unexplained productive cough lasting two-three weeks or more should be evaluated for tuberculosis

2. All patients (adults, adolescents, and children who are capable of producing sputum) suspected of having pulmonary tuberculosis should have at least two, and preferably three, sputum specimens obtained for microscopic examination.

3. For all patients suspected of having Extra-pulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for microscopy and where facilities and resources are available, for culture and histo-pathological examination.

4. All persons with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination.

5. The diagnosis of sputum smear-negative pulmonary tuberculosis should be based on the following criteria: at least three negative sputum smears (including at least one early morning specimen); chest radiography findings consistent with tuberculosis; and lack of response to a trial of broad spectrum antimicrobial agents. In persons with known or suspected HIV infection, the diagnostic evaluation should be expedited.

6. The diagnosis of intra-thoracic (i.e. pulmonary, pleural, and mediastinal or hilar lymph node) tuberculosis in symptomatic children with negative sputum smears should be based on the findings of chest radiographic abnormalities consistent with tuberculosis and either a history of exposure to an infectious case or evidence of tuberculosis infection infection (positive tuberculin skin test).

Standards for Treatment

1. Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility. To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen but, also, be capable of assessing the adherence of the patient to the regimen and addressing poor adherence when it occurs. By so doing, the provider will be able to ensure adherence to the regimen until treatment is completed.

2. All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability. The initial phase should consist of two months of isoniazid, rifampicin, pyrazinamide, and ethambutol. The preferred continuation phase consists of isoniazid and rifampicin given for four months. Isoniazid and ethambutol given for six months is an alternative continuation phase regimen that may be used when adherence cannot be assessed, but it is associated with a higher rate of failure and relapse, especially in patients with HIV infection. The doses of antituberculosis drugs used should conform to international recommendations. Fixed-dose combinations of two (isoniazid and rifampicin, three (isoniazid and rifampicin, and pyrazinamide), and four (isoniazid and rifampicin, and pyrazinamide, and ethambutol) drugs are highly recommended, especially when medication ingestion is not observed.

3. To foster and assess adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients. Supervision and support should be gender-sensitive and age-specific and should draw on the full range of recommended interventions and available support services, including patient counseling and education.

4. All patients should be monitored for response to therapy, best judged in patients with pulmonary tuberculosis by follow-up sputum microscopy (two specimens) at least at the time of completion of the initial phase of treatment (two months), at five months, and at the end of treatment. Patients who have positive smears during the fifth month of treatment should be considered as treatment failures and have therapy modified appropriately, (see Standards 8 and 9). In patients with extrapulmonary tuberculosis and in children, the response to treatment is best assessed clinically. Follow-up radiographic examinations are usually unnecessary and may be misleading.

5. A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

6. In areas with a high prevalence of HIV infection in the general population and where tuberculosis and HIV infection are likely to co-exist, HIV counseling and testing is indicated for all tuberculosis patients as part of their routine management. In areas with lower prevalence rates of HIV, HIV counseling and testing is indicated for tuberculosis patients with symptoms and/or signs of HIV-related conditions and in tuberculosis patients having a history suggestive of high risk of HIV exposure.

7. All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of antituberculosis treatment and antiretroviral therapy, consultation with a physician who is expert in this area is recommended before initiation of concurrent treatment for tuberculosis and HIV infection, regardless of which disease appeared first. However, initiation of treatment for tuberculosis should not be delayed.

8. An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance, should be obtained for all patients. Patients who fail treatment and chronic cases should always be assessed for possible drug resistance. For patients in whom drug resistance is considered to be likely, culture and drug susceptibility testing for isoniazid, rifampicin, and ethambutol should be performed promptly.

9. Patients with tuberculosis caused by drug-resistant (especially multiple drug resistant [MDR]) organisms should be treated with specialized regimens containing second-line anti-TB drugs. At least four drugs to which the organisms are known or presumed to be susceptible should be used, and treatment should be given for at least 18 months. Patient centered measures are required to ensure adherence (ISTC, 2006).