PREDICTORS OF TUBERCULOSIS TREATMENT OUTCOME AMONG HIV-POSITIVE PATIENTS IN LAGOS STATE, NIGERIA

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ABSTRACT

Background: Tuberculosis is curable if patients with drug susceptible organisms are treated on time and are given sufficient uninterrupted therapy. Despite the fact that TB is treatable and curable, it has proved impossible to eliminate and this has been worsened by HIV/AIDS epidemic. HIV/AIDS is seen to be fueling the prevalence of TB. The aim of this study was to assess the factors associated with the treatment outcomes of TB among HIV-Positive patients in Lagos State.

Methodology: This study was a cross sectional descriptive study to determine factors associated to TB treatment outcomes of Tuberculosis among HIV-Patients in Lagos state. Multistage sampling method was used in this study. A semi-structured, interview-administered questionnaire was used to collect information; the data obtained was analyzed using EPI-INFO statistical software version 7.1

Result: 46.1% were cured as a result of the treatment, 5.12% defaulted on the course of treatment, 9.6% treatment failed, and 4.1% were transferred out to another hospital for further treatment while 34.8% completed their treatment. Thus successful treatment comes to 80.9%.Patients demographic information were taken, like their names, registration numbers, sex, age clinical classification, HIV status, treatment outcome, CD4 count for initial and latest, PCV at initial and their weights. The mean age of respondents is 37.3 ± 10.6, the mean for initial CD4 count is 188.16 ± 171.7, latest CD4 count is 441.3 ± 206.9, initial PCV 33.0 ± 6.9 and weight 55.7 ± 13.5 respectively. from the result of the means, it revealed that initial CD4 count increased from 188 to 441, showing signifying the effectiveness of the treatments that they are being given. Majority (62.2%) of these respondents are females, (40.2%) between the age of 28-

37years. Patients interview shows that 80.1% of respondents claimed that there treatment was not interrupted and 66.6% were of them were married and 43% of them are traders with 45.1% of them having secondary education. More than half of the respondent claimed that the health facility is >5km faraway from their residence.

Conclusion: There is high successful treatment outcome as a result of early initiation of antiretroviral drugs and adherence to drugs, the low unsuccessful treatment outcome results from 5.12% default, 9.6% failure on treatment and 4.1% transferred out to another hospital. .

Recommendation: The Government should design effective HIV/TB treatment centres with good HIV/TB collaborative activities. This will ensure early initiation of anti-retroviral drugs and thus reduce prevalence of TB among HIV-Positive to the same level as HIV-Negative. Other Non-governmental agencies should support government in reducing default rate on both HIV and TB drugs when they start treatment.

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ACRONYMS AND ABBREVIATIONS

AIDS - Acquired Immune Deficiency Syndrome

ART - Antiretroviral Therapy

ARV - Antiretroviral Drug

HIV - Human Immunodeficiency Virus

LGA - Local Government Area

PHC - Primary Health Care

STIs - Sexually Transmitted Infections

TB- Tuberculosis

UNAIDS - Joint United Nations Programme on HIV/AIDS

VCT - Voluntary Counselling and Testing

WHO - World Health Organization

CERTIFICATION

This is to certify that this project is original and my individual, independent work which was supervised by Dr. Dairo M.D. The assistance and contribution received from others has been duly acknowledged.

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Dr. M.D. Dairo
Supervisor

Date

....

Dr. Anthony Ojonimi OMALE
Student

Date

DECLARATION

I, Dr. Omale hereby, declare that this research was carried out by me under the supervision of Dr M.D. Dairo and that it has not been submitted in part or in full for any other examination.

DEDICATION

This research project is dedicated to The Almighty God forHis mercies bestowed upon me and to my wife: Mrs. Adeyemi Anike Omale and to my children: Victoria, Rebecca and Solomon for their prayers, patience and moral support.

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CHAPTER ONE

Introduction

1.1 Background

Tuberculosis (TB) is a curable infectious disease caused by the *Mycobacterium tuberculosis*. It is an airborne infectious disease that primarily affects the lungs (pulmonary) but can affect other parts of the body like the kidneys, lymph nodes, spinal cord and the abdomen (extra pulmonary). (Ofoegbu & Odume, 2015). Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) on the other hand, is a non-curable disease caused by the human immunodeficiency virus (HIV). It is transmitted via body fluids, for example, blood, seminal and vaginal fluids. It affects the human immune system destroying them and impairing their function and progressively diminishing the body's ability to fight infections (Ofoegbu & Odume, 2015).

A steady association between Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) infections has been widely documented. Tuberculosis/HIV co-infection is bi-directional, synergistic and is often designated as the 'cursed duet'.Over nine million new cases of tuberculosis (TB) occur annually throughout the world (Adebimpe *et al.*, 2011). Most cases of tuberculosis can safely and effectively be treated but complications can occur during treatment due to anti-TB drug resistance, poor adherence, drug-drug interactions and also toxicity (Adebimpe et al., 2011). Tuberculosis can either be latent (i.e. inactive) or active. Many people will simply live with latent TB and not even know it but for those with compromised immune systems (be it through general poor health or other infections like HIV), active TB can develop and if untreated will most certainly be fatal (Oliver *et*

al.,2012). An HIV-negative person with latent TB infection has a 10% chance of progressing to active TB over his or her entire lifetime while an HIV-positive person has a 10% chance of developing active TB each year (Babatunde, 2013). Tuberculosis is one of the most common infections that threaten people living with HIV (PLWH) in the developing world. Of the 1.7 million deaths from TB in 2008, almost one-third were people co-infected with HIV or AIDS.In Nigeria the prevalence of HIV among TB patients increased from 2.2% in 1991 to 19.1% in 2001 and 25% in 2010, showing that the TB situation in the country is HIV-driven (Okonko *et.al,* 2012).

Due to the high HIV prevalence among TB patients, WHO recommends the Three *I's*: intensified TB screening among HIV-infected individuals, provision of isoniazid preventive therapy (IPT), and infection control (WHO, 2012). Also, a case detection rate of 70% and a treatment success rate of 85% is currently being recommended by the World Health Organisation for all TB cases(Alobu *et.al*,2014). It is believed that achieving these targets will lead to a reduction in TB prevalence, incidence, transmission and drug resistance to TB. In order to effectively monitor the TB control efforts by TB control programmes, the WHO has recommended a strong indicator which is the proportion of pulmonary TB patients whose sputum smear or culture are positive after 5 months or later during treatment (NTBLCP, 2010).

The individuals are categorized as treatment failure cases. Treatment failure constitutes a major problem for the National TB control programmes because such failed cases tend to have higher morbidity and mortality when compared with cured cases (Alobu *et.al.*, 2014).

Also, treatment failure cases remain infectious for prolonged periods of time and this promotes further transmission of the disease in the community and ultimately leads to high rates of multidrug-resistant TB especially in resource limited settings; hence, the importance of achieving a treatment success rate of 85% as recommended by the WHO. Also, current recommendations by the American Thoracic Society-Centers for Disease Control and Prevention- Infectious Diseases Society of America and the World Health Organization (WHO) are that the standard 6-month therapy should be used for active TB in HIV-positive patients; the former provides clinicians with the option of extending therapy on the basis of clinical judgment. Both guidelines state that intermittent 3-times weekly dosing schedules are acceptable alternatives to daily treatment in HIV-seropositive patients, but WHO specifically recommends against using twice-weekly dosing for HIV-seropositive patients (WHO, 2012).

1.2 Problem statement

The intricate linkage of TB/HIV co-infection for nearly the past three decades has posed a major concern and threat to the international community's effort to achieve the health related United Nations Millennium Development Goals for TB and HIV infection (Ofoegbu, 2015).

The two diseases are a deadly combination and are far more dangerous occurring together than either alone. The HIV/AIDS epidemic in Ogun State which stood at a prevalence of 3.1% as at 2014 and Abeokuta having the second highest prevalence rate (2.7%) has militated against efforts to control TB in the State (Babatunde, 2013).

The prevalence of HIV/TB co-infection in Ogun State stands at 12% and there has being an increase of poor TB treatment outcome among patients living with HIV/AIDS (Oshi*et.al*.,2014). Hence, the TB/HIV co-infections posed diagnostic and therapeutic challenges (Shobowale *et.al*, 1996). The risk of death in HIV infected patients with tuberculosis has been reported to be twice that in HIV infected patients without tuberculosis (Oshi *et.al*,2014). Due to increase in poor treatment outcome of TB among HIV patients, multidrug resistance TB (MDR-TB) among patients living with HIV/AIDS is also on the rise and this has left a resultant negative effect on management and treatment of HIV/TB co-infection (Chaisson, 2007)

1.3 Justification

Tuberculosis is curable if patients with drug susceptible organisms are treated on time and are given sufficient uninterrupted therapy. If untreated, the fatality rate can be between 50% - 80% among patients with smear positive tuberculosis and in poorly implemented TB programme, as many as 30% of patients with smear positive TB die (Ofoegbu & Odume, 2015). Despite the fact that TB is treatable and curable, it has proved impossible to eliminate and this has been worsened by HIV/AIDS epidemic.

The Mainland Hospital Yaba and Lagos General Hospital Marina are the top ranking hospitals in Lagos State with functional and equipped Directly Observed Treatment Short Course (DOTS) and HIV clinics for effective management of tuberculosis and HIV respectively. Evidence abounds from within and outside the National TB programme that HIV impacts negatively to TB treatment outcome and this has made treatment success of

1.4 Research questions

1. What is the success rate of TB treatment among HIV patients in Lagos?
2. What is the cure rate/failure rate of TB treatment among HIV patients in Lagos?
3. What factors affect the success rate of TB treatment among HIV patients in Lagos?

1.5 Aim and Objectives

1.5.1 Aim

To assess the predictors of TB treatment outcomes among HIV-patients in Lagos State.

1.5.2 Specific Objectives

1. To determine the cure rate for TB among HIV patients attending TB treatment sites in Lagos.
2. To determine the failure rate among HIV patients attending TB treatment sites in Lagos who had TB treatment in the past.
3. To determine factors influencing the TB treatment outcome among HIV patients who had TB treatment in the past.

CHAPTER TWO

Literature Review

2.1 Epidemiology of Tuberculosis

Mycobacterium tuberculosis (MTB) was the cause of the "White Plague" of the 17th and 18th centuries in Europe. During this period nearly 100 percent of the European population was infected with MTB, and 25 percent of all adult deaths were caused by MTB (Note: The White Plague is not to be confused with the "Black Plague", which was caused by *Yersinia pestis* and occurred about 3 centuries earlier) (Todar, 2011).

Tuberculosis (TB) is a potentially serious infectious disease that mainly affects the lungs (pulmonary TB) and may also affect other parts of the body (extra-pulmonary TB). It is a bacterial infection caused by *Mycobacterium tuberculosis* which is a member of *Mycobacterium complex* and other members include *Mycobacterium africanum* and *Mycobacterium bovis*(Muller, 2011). It is transmitted from one person to another through tiny droplets released into the air via coughs and sneezes. In West Africa, *Mycobacterium africanum* is the most commonly found as it causes up to a quarter of tuberculosis cases in the Gambia while Mycobacterium bovis is the main cause of tuberculosis in deer, cattle and other mammals (Muller, 2011).

Approximately, one-third of the world's population has been infected with *M. tuberculosis* and new infections occur at a rate of one per second. In 2007 there was an estimated 13.7 million chronic active cases and in 2010 there were 8.8 million new cases, and 1.45 million deaths, mostly in developing countries. 0.35 million of these deaths occur in those co-infected with HIV (WHO, 2012). The epidemiology of tuberculosis varies substantially around the world. The highest rates (≥100/100,000) are observed in sub-Saharan Africa, India, China and the islands of

Southeast Asia and Micronesia (Serafino & Med, 2012). However, tuberculosis is less common in developed countries and it is mainly an urban disease. For example, the national average of tuberculosis in the United Kingdom was 15 per 100,000 in 2007 while the highest incidence rate in Western Europe was 30 per 100.000 in Portugal and Spain. In the United States, the overall tuberculosis case rate was 4 per 100.000 persons in 2007 (WHO, 2010).

Nigeria ranks 10th among the 22 high-burden TB countries in the world with an estimate of 210,000 new cases of all forms of TB occurring in the country in 2010, which is equivalent to 133/100,000 population (Tshikuka et al., 2012). Also, in 2010, there were 320,000 prevalent cases of TB which is equivalent to 199/100,000 cases (prevalence rate).

2.2 Epidemiology of HIV-Related Tuberculosis

The World Health Organization (WHO) estimates that one third of the world's population is infected with *Mycobacterium tuberculosis*, resulting in an estimated nearly 9 million new cases of active TB in 2010. Worldwide, 14.8% of TB patients have HIV co-infection, and as many as 50-80% have HIV co-infection in parts of sub-Saharan Africa (Luetkemeyer, 2013). The incidence of TB associated with HIV is believed to have peaked at 1.39 million in 2005 and is now decreasing. However, globally, TB remains the most common cause of death among patients with AIDS, killing 1 of 3 patients(Okonko *et.al.*, 2012). TB can develop through progression of recently acquired infection (primary disease), reactivation of latent infection, or exogenous reinfection. Infection with M tuberculosis can occur when an individual exposed to an infectious case of TB inhales particles (<5 μm in size) containing the tubercle bacilli. (Alobu *et al.*, 2014). If the bacilli reach the pulmonary alveoli, they may be ingested by alveolar macrophages, the first line of defense against M tuberculosis. Surviving tubercle bacilli multiply

within the macrophage and eventually undergo hematogenous spread to other areas of the body. In HIV infection, defective macrophages function in response to TB infection, which may in part increase susceptibility to TB disease (Luetkemeyer, 2013).

The intricate linkage of tuberculosis (TB) and human immunodeficiency virus (HIV) infection for nearly the past 3 decades poses a major threat to the international community's effort to achieve the health-related United Nations Millennium Development Goals for TB and HIV infection (Ofoegbu & Odume, 2015). These two diseases are a deadly combination and are far more dangerous occurring together than either disease alone. According to the World Health Organization (WHO) TB/HIV co-infection can be referred to as two monsters working against humanity (Ofoegbu & Odume, 2015). Globally, the TB epidemic is fuelled by the HIV epidemic. Even if all new HIV infections were prevented, TB incidence would increase due to the high risk of TB progression among prevalent HIV cases. The highest rates of HIV co-infection in TB patients are in the African Region in contrast to the rates being recorded in the more industrialised parts of the world. In Nigeria, the TB burden is compounded by a high prevalence of HIV in the country which stands at about 4.1% in general population (Alobu et al., 2014). In the individual host the two pathogens, *M. tuberculosis* and HIV, potentiate one another, accelerating the deterioration of immunological functions and resulting in premature death if untreated. Some 14 million individuals worldwide are estimated to be dually infected. Tuberculosis is the largest single cause of death in the setting of AIDS, accounting for about 26% of AIDS-related deaths, 99% of which occur in developing countries (WHO, 2012). Both Tuberculosis and HIV have profound effects on the immune system, as they are capable of disarming the host's immune responses through mechanisms that are not fully understood.

Human Immunodeficiency Virus co-infection is the most powerful known risk factor for progression of *M. tuberculosis* infection to active disease, increasing the risk of latent TB reactivation 20-fold (Pawlowski *et.al.*, 2012). Also, tuberculosis has been reported to exacerbate HIV infection. Various lines of evidence indicate that inborn errors of immunity, as well as genetic polymorphisms, have an impact on susceptibility to TB and HIV (Rottenberg et al., 2012).

2.3 HIV Infection and Susceptibility to Tuberculosis

Human Immunodeficiency Virus (HIV) infected persons are at markedly increased risk for primary or reactivation tuberculosis and for second episodes of tuberculosis from exogenous reinfection (Diane and Barnes, 2011). Susceptibility to tuberculosis is related to the pattern of cytokines produced by T lymphocytes. T1 lymphocytes, which produce interferon-γ, are central to anti-mycobacterial immune defenses and fatal mycobacterial disease develops in children who lack the interferon-γ receptor (Babatunde, 2013). In contrast to T1 lymphocytes, T2 lymphocytes which produce interleukin-4 and interleukin-10 do not contribute to anti-mycobacterial immunity(Fenner et al., 2013). When peripheral blood lymphocytes from HIV-infected patients with tuberculosis are exposed to *Mycobacterium tuberculosis* in vitro, they produce less interferon-γ but similar amounts of interleukin-4 and interleukin-10, as compared with lymphocytes from HIV-negative patients with tuberculosis (Diane and Havlir, 2011). These findings suggest that the reduced T1 response in HIV infected patients contributes to their susceptibility to tuberculosis.

2.4 Clinical Presentation of Tuberculosis

The clinical presentation of pulmonary TB can vary widely in both immune-competent and immune-compromised hosts. In general, the presentation in HIV-infected patients is similar to that seen in HIV-uninfected patients, although the signs and symptoms (such as fevers, weight loss, and malaise) may be attributed to HIV itself and the possibility of TB overlooked. Symptoms usually are present for weeks to months, and an acute onset of fever and cough is more suggestive of a non-mycobacterial pulmonary process. In HIV-infected patients, clinical manifestations of pulmonary TB reflect different levels of immunosuppression. Earlier in the course of HIV disease, TB is more likely to present as classic reactivation-type disease, whereas patients with advanced immunosuppression are more likely to present with findings consistent with primary TB (Luetkemeyer, 2013).

In HIV-positive people with very severe immune damage, TB can spread from the lungs into any part of the body. Often TB affects the lymph nodes, causing them to swell. Other places where TB infection can occur include the gut (causing pain and severe diarrhoea), the spine (causing numbness or tingling), the liver (causing inflammation), or the brain. If TB infection affects the brain, the patient might have symptoms of confusion, change in personality, seizures or difficulty moving parts of the body. If symptoms suggest presence of TB infection in any of these body parts, then extra tests and treatment aside the standard treatment for TB is needed (Babatunde, 2013)

2.5 Stages of Tuberculosis Infection

The stages that will be explained are typically for *Mycobacterium tuberculosis* (MTB) sensitive hosts as only a small percent of tuberculosis infections progress to disease while many remain as

latent TB but the chances of latent TB becoming active TB increases when the hosts' immune system is compromised by co-infections such HIV/AIDS (Affusim et.al.,2012). Disease progression depends on strain of MTB, prior exposure to the organism, infectious dose and immune status of the host. (Babatunde, 2013).

2.5.1 Stage 1

The first stage takes place in the first week after the inhalation of the TB bacillus. After the bacillus reaches the alveoli in the lung, it gets picked up by special cells of the immune system, called macrophages. These macrophages usually sit within the tissue of the alveoli; their duty is to swallow and inactivate any foreign object entering the alveolar space. The macrophages swallow the TB bacillus. The events that follow largely depend on the amount of TB bacilli and the strength of the macrophage. If the amount of TB bacilli is too large, or if the macrophage is not strong enough to resist, the bacilli can reproduce in the macrophage. This ultimately leads to the destruction of the macrophage and the infection of new, nearby macrophages that try to swallow emerging TB bacilli (Muller, 2011). A droplet nuclei contains no more than 3 bacilli. Droplet nuclei are so small that they can remain air-borne for extended periods o0f time. The most effective (infective) droplet nuclei tend to have a diameter of 5 micrometers. Droplet nuclei are generated during talking coughing and sneezing. Coughing generates about 3000 droplet nuclei. Talking for 5 minutes generates 3000 droplet nuclei but singing generates 3000 droplet nuclei in one minute. Sneezing generates the most droplet nuclei by far, which can spread to individuals up to 10 feet away (Chaisson, 2007).

2.5.2 Stage 2

If the macrophage cannot contain the TB bacillus, TB infection enters its second stage after about a week. The TB bacilli start reproducing exponentially, which means that for every initial bacillus two new ones emerge. These two then produce two each and it goes on. This leads to a rapid expansion of the initial TB bacillus, and the macrophages cannot contain the spread anymore. This stage lasts until the third week after initial infection (Muller, 2011). MTB multiplies virtually unrestricted within inactivated macrophages until the macrophages burst. Other macrophages begin to extravagates from peripheral blood. These macrophages also phagocytize MTB but they are also inactivated and hence cannot destroy the bacteria (Getahun et.al., 2010).

2.5.3 Stage 3

After the third week, the bacilli do not grow exponentially anymore, and the infection enters its third stage. At this stage, bacilli growth and destruction by macrophages are balanced. The body brings in more immune cells to stabilize the site, and the infection is under control. At least nine of ten patients infected with mycobacterium tuberculosis stop at stage 3 and do not develop symptoms or physical signs of active disease (Muller, 2011).

2.5.4 Stage 4

Although many activated macrophages can be found surrounding the tubercles, many other macrophages present remain inactivated or poorly activated. Mycobacterium *tuberculosis* uses these macrophages to replicate, and hence, the tubercle grows. The growing tubercle may invade a bronchus. If this happens, MTB infection can spread to other parts of the lung. Similarly the tubercle may invade an artery or other blood supply' line. The hematogenous spread of MTB

may result in extra-pulmonary tuberculosis otherwise known as military tuberculosis. The name "military" is derived from the fact that metastasizing tubercles are about the same size as a millet seed, a grain commonly grown in Africa (Getahun et al., 2010).

2.5.5 Stage 5

For unknown reasons, the gaseous centers of the tubercles liquefy. This liquid is very conducive to MTB growth, and the organism begins to rapidly multiply extracellularly. After time, the large antigen load causes the walls of nearby bronchi to become necrotic and rupture. This results in cavity formation. This also allows MTB to' spill into other airways and rapidly spread to other parts of the lung. As stated previously, only a very small percent of MTB infections result in disease and even a smaller percentage of MTB infections progress to an advanced stage. Usually the host will begin' to control the infection at some point. When the primary lesion heals, it becomes fibrous and calcifies. When this happens the lesion is referred to as the Ghon complex (also known as Ghon focus) named after the Australian pathologist who first described it. Depending on the size and severity, the Ghon complex may never subside. Typically, the Ghon complex is readily visible upon chest X-ray. Small metastatic foci containing low numbers of MTB may also calcify. However, in many cases these foci will contain viable organisms. These foci are referred to Simon foci. The Simon foci are also visible upon chest X-ray and are often the site of disease reactivation. (Godoy et al., 2012).

In summary, there are three ways in which the body reacts to an infection with *Mycobacteriumtuberculosis*:

If the body's immune system is strong, lymphocytes manage to contain the bacteria and the infection does not spread further. This is called asymptomatic primary TB (stages 1 to 3). If the

immune system is weak, the lymphocytes cannot contain the TB bacteria and it rapidly spreads whereby the infected person develops symptoms and falls ill. This is called progressive primary TB (stages 1 to 3, but without the final control over the bacillus). If the immune system is initially strong and contains the TB bacteria, but subsequently weakens and cannot control it any longer, the bacteria first go into a dormant state but then get reactivated and subsequently spread aggressively (stages 4 to 5). This is called secondary TB or reactivation TB. It can also be triggered by a new infection with TB bacteria, which leads to the reactivation of the initial infection (Chaisson, 2007).

2.5.6 General Characteristics of *Mycobacterium tuberculosis*

Mycobacterium tuberculosis is a fairly large non-motile rod-shaped bacterium distantly related to the Actinomycetes. Many non-pathogenic mycobacteria are components of the normal flora of humans, found most often in dry and oily locales. The rods are 2-4 micrometers in length and 0.2-0.5 um in width (Todar, 2011).

Mycobacterium tuberculosis is an obligate aerobe. For this reason, in the classic case of tuberculosis, MTB complexes are always found in the well-aerated upper lobes of the lungs. The bacterium is a facultative intracellular parasite, usually of macrophages, and has a slow generation time of 15-20 hours, which is a physiological characteristic that may contribute to its virulence (Muller, 2011).

Two media are used to grow MTB Middlebrook's medium which is an agar based medium and Lowenstein-Jensen medium which is an egg based medium. MTB colonies are small and buff colored when grown on either medium. Both types of media contain inhibitors to keep contaminants from out-growing MT. It takes 4-6 weeks to get visual colonies on either type of

media. Chains of cells in smears made from in vitro-grown colonies often form distinctive serpentine cords. This observation was first made by Robert Koch who associated cord factor with virulent strains of the bacterium (Todar, 2011).

MTB is not classified as either Gram-positive or Gram-negative because it does not have the chemical characteristics of either, although the bacteria do contain peptidoglycan (murein) in their cell wall. If a Gram stain is performed on MTB, it stains very weakly Gram-positive or not at all (cells referred to as "ghosts")(Adebimpe et al., 2011).

Mycobacterium species, along with members of a related genus *Nocardia*, are classified as acid-fast bacteria due to their impermeability by certain dyes and stains. Despite this, once stained, acid-fast bacteria will retain dyes when heated and treated with acidified organic compounds. One acid-fast staining method for *Mycobacterium tuberculosis* is the Ziehl-Neelsen stain. When this method is used, the MTB smear is fixed, stained with carbol-fuchsin (a pink dye), and decolorized with acid-alcohol. The smear is counterstained with methylene-blue or certain other dyes. Acid-fast bacilli appear pink in a contrasting background (Jassal & Bishai, 2010). In order to detect *Mycobacterium tuberculosis* in a sputum sample, an excess of 10,000 organisms per ml of sputum are needed to visualize the bacilli with a 100X microscope objective (1000X mag). One acid-fast bacillus per slide is regarded as "suspicious" of an MTB infection (Todar, 2011).

The cell wall structure of Mycobacterium tuberculosis deserves special attention because it is unique among procaryotes, and it is a major determinant of virulence for the bacterium. The cell wall complex contains peptidoglycan, but otherwise it is composed of complex lipids. Over 60% of the mycobacterial cell wall is lipid. The lipid fraction of MTB's cell wall consists of three major components, mycolic acids, cord factor, and wax-D (Harries et.al., 2004).

Mycolic acids are unique alpha-branched lipids found in cell walls of Mycobacterium and

Corynebacterium. They make up 50% of the dry weight of the mycobacterial cell envelope. Mycolic acids are strong hydrophobic molecules that form a lipid shell around the organism and affect permeability properties at the cell surface. Mycolic Acids are thought to be a significant determinant of virulence in MTB. Probably, they prevent attack of the mycobacteria by cationic proteins, lysozyme, and oxygen radicals in the phagocytic granule. They also protect extracellular mycobacteria from complement deposition in serum (Jassal & Bishai, 2010). Cord factor is responsible for the serpentine cording mentioned above; it is toxic to mammalian cells and is also an inhibitor of PMN migration. Cord factor is most abundantly produced in virulent strains of MTB while wax-D in the cell envelope is the major component of Freund's Complete Adjuvant (CFA) (Todar, 2011).

The high concentration of lipids in the cell wall of *Mycobacterium tuberculosis* have been associated with these properties of the bacterium: impermeability to stains and dyes, resistance to many antibiotics, resistance to killing by acidic and alkaline compounds resistance to osmotic lysis via complement deposition , resistance to lethal oxidations and survival inside of macrophages (Muller, 2011).

2.6 Diagnosis of Tuberculosis

A diagnosis of active TB can only be confirmed when there is definite evidence of TB bacteria in the person's body. Some of the TB diagnostic tests look directly for TB bacteria. Others such as the chest X-ray look for the effect of the bacteria on the person suspected of having TB. Below are some of the diagnostics tests for detecting tuberculosis.

2.6.1 Sputum smear microscopy

Smear microscopy of sputum is often the first TB test to be used in countries with a high rate of TB infection. Sputum is a thick fluid that is produced in the lungs and the airways leading to the lungs, and a sample of sputum is usually collected from the person coughing. Historically it has been recommended that three sputum specimens are collected on two consecutive days, but in 2007 the World Health Organisation (WHO) recommended that just two specimens could be examined from consecutive days. Now it has been suggested that two specimens can be collected on the same day without any loss of accuracy (Sachdeva, 2015). To do the TB test a very thin layer of the sample is placed on a glass slide, and this is called a smear. A series of special stains are then applied to the sample, and the stained slide is examined under a microscope for signs of the TB bacteria (Falzon et al., 2011). Sputum smear microscopy is inexpensive and simple, and people can be trained to do it relatively quickly and easily. In addition the results are available within hours. The sensitivity though is only about 50-60% (Sachdeva, 2015).

2.6.2 Culture method

Culturing is a method of studying bacteria by growing them on media containing nutrients. Media can be either solid media on culture plates or bottles of liquid media (culture broths). Different media are used to make it as easy as possible for the suspected microorganisms to grow (Sharma et.al., 2005). To isolate a single bacterial species from a mixture of different bacteria, solid media are normally used. Individual cells dividing on the surface do not move away from each other as they would do in liquid, and after many replications they form visible colonies composed of tens of millions of cells all derived from a single cell (Muller, 2011).

Culturing and identification of M. tuberculosis provides a definitive diagnosis of TB and can significantly increase the number of cases found. Culture can also provide drug susceptibility

testing, showing which TB drugs the bacteria are resistant to. It shows if a person has multi-drug resistance (MDR) or extensive drug resistance (XDR) TB. However, culture is much more complex and expensive than microscopy to perform as it requires specific equipment and enhanced laboratory facilities. Diagnosing TB using culture can also take weeks because of the slow growth of TB bacilli. It averages 4 weeks to get a conclusive test result using the most common methods of solid media, with another 4-6 weeks to produce drug susceptibility results (Sachdeva, 2015). Some commonly used culture media include the Löwenstein-Jensen (LJ), Kirchner, Ogawa and Middlebrook media (7H9, 7H10, and 7H11).

2.6.3 GeneXpert test

The Xpert (GeneXpert) *Mycobacterium tuberculosis*/Rifampicin (MTB/RIF) test is a new molecular test for TB which diagnoses TB by detecting the presence of TB bacteria, as well as testing for resistance to the drug Rifampicin. The test is a molecular test which detects the DNA in TB bacteria. It uses a sputum sample and can give a result in less than 2 hours and it can also detect the genetic mutations associated with resistance to the drug Rifampicin (Tsurugi et al., 2011). The Xpert MTB/RIF detects DNA sequences specific for Mycobacterium tuberculosis and rifampicin resistance by polymerase chain reaction. It is based on the Cepheid GeneXpert system, a platform for rapid and simple-to-use nucleic acid amplification tests (NAAT). The Xpert MTB/RIF purifies and concentrates *Mycobacterium tuberculosis* bacilli from sputum samples, isolates genomic material from the captured bacteria by sonication and subsequently amplifies the genomic DNA by PCR. The process identifies all the clinically relevant Rifampicin resistance inducing mutations in the RNA polymerase beta (rpoB) gene in the Mycobacterium tuberculosis genome in a real time format using fluorescent probes called molecular beacons.

Results are obtained from unprocessed sputum samples in 90 minutes, with minimal biohazard and very little technical training required to operate (Sachdeva, 2015). This test was developed as an on-demand near patient technology which could be performed even in a doctor's office if necessary. WHO recommended that the test should be used as the initial diagnosis test in individuals suspected of having MDR TB, or HIV associated TB. They also suggested that it could be used as a follow on test to microscopy in settings where MDR TB and/or HIV is of lesser concern, especially in smear negative specimens, because of the lack of accuracy of smear microscopy (Sharma et al., 2005). The main advantages of the test are, for diagnosis, reliability when compared to sputum microscopy and the speed of getting the result when compared with culture. Although culture gives a definitive diagnosis, to get the result usually takes weeks rather than the hours of the Xpert test. (Tweya et al., 2013).

2.6.4 Tuberculosis skin test

The TB skin test is a widely used diagnostic TB test, and in countries with low rates of TB it is often used to test for latent TB infection. The problem with using it in countries with high rates of TB infection is that the majority of people may have latent TB (Muller, 2011). The TB skin test involves injecting a small amount of fluid (called tuberculin) into the skin in the lower part of the arm. Then the person must return after 48 to 72 hours to have a trained health care worker look at their arm. The health care worker will look for a raised hard area or swelling, and if there is one then they will measure its size. They will not include any general area of redness. The TB skin test result depends on the size of the raised hard area or swelling, and the larger the size of the affected area the greater the likelihood that the person has been infected with TB bacteria at some time in the past. But interpreting the TB skin test result, that is whether it is a positive

result, may also involve considering the lifestyle factors of the person being tested for TB (Sachdeva, 2015).

The Mantoux TB test is the type of TB test most often used, although the Heaf and Tine tests are still used in some countries. None of these TB tests though will guarantee a correct result. False positive results happen with the TB skin test because the person has been infected with a different type of bacteria, rather than the one that causes TB. It can also happen because the person has been vaccinated with the BCG vaccine, and this vaccine is widely used in countries with high rates of TB infection. False negative results particularly happen with children, older people and people with HIV (Sachdeva, 2015).

2.6.5 Chest X-ray as a Tuberculosis test

Acute pulmonary TB can be easily seen on an X-ray. In active pulmonary TB, infiltrates or consolidations and/or cavities are often seen in the upper lungs with or without mediastinal or hilar lymphadenopathy or pleural effusions (tuberculous pleurisy). However, lesions may appear anywhere in the lungs. In disseminated TB a pattern of many tiny nodules throughout the lung fields is common, hence the so-called miliary TB. In HIV and other immunosuppressed persons, any abnormality may indicate TB or the chest X-ray may even appear entirely normal. However, the picture it presents is not specific and a normal chest X-ray cannot exclude extra pulmonary TB (Sachdeva, 2015).

2.6.6 Tuberculosis Interferon gamma release assays

Interferon Gamma Release Assays (IGRAs) are blood tests that measure a person's immune response to the bacteria that cause TB. The immune system mounts a complex response to TB

bacteria, and produces some special molecules called cytokines. These assays work by detecting a cytokine called the interferon gamma cytokine. They are performed in practice by taking a blood sample and mixing it with special substances to identify if the cytokine is present (Muller, 2011), 2011). The advantages of an IGRA TB test includes the fact that it only requires a single patient visit to conduct the TB test, results can be available within 24 hours, and prior BCG vaccination does not cause a false positive result. Disadvantages include the fact that the blood sample must be processed fairly quickly, laboratory facilities are required, and the test is for latent TB. It is also thought that the IGRAs may not be as accurate in people who have HIV (Muller, 2011).

2.6.7 Serological diagnosis of Tuberculosis

This is an immune based test for detection of antibodies to *Mycobacterium tuberculosis* and antigens but none of the existing commercial serological tests show adequate sensitivity and specificity to be recommended for diagnostic use. Interestingly, the WHO recently made a negative recommendation against the use of serological tests for TB, based on data suggesting that these tests could neither replace sputum microscopy nor be used as an add-on test to rule out TB (Padmapriyadarsini et.al., 2011)

2.7 Treatment of Tuberculosis in Tuberculosis and HIV co-infected individuals.

In Nigeria, the treatment of tuberculosis is usually done through the Directly Observed Treatment Short Course (DOTS) therapy. Criteria for assigning treatment include age, history of previous anti TB exposure, pregnancy, HIV status and pre-treatment weight among others. The basic principles of treatment for HIV associated TB are the same as for HIV uninfected

individuals. Certain areas of uncertainty remain, including the regimen duration, dosage and frequency of administration of anti-TB drugs, optimal timing of initiation of ART and optimal anti-TB drug combination for patients on second line treatment (Padmapriyadarsini et al., 2011).

The following first line drugs are used within the NTBLCP for TB treatment:

R: Rifampicin H: Isoniazid E: Ethambuthol Z: Pyrazinamide S: Streptomycin.

These drugs are presented as loose or in fixed-dose combinations (FDC). There are two categories of treatment regimens namely category 1 and 2 (CAT 1 and CAT 2). Category 1 regimen is for treatment of new cases while Category 2 regimen is for treatment of previously treated patients who relapsed or failed (NTBLCP, 2010). The treatment regimen consists of two phases namely:

1. The initial intensive phase: This consists of 2 months of fully supervised daily administration of drugs in new cases (CAT 1). This phase extends to 3 months in retreatment cases (CAT 2).
2. The continuation phase: This consists of 6 months (EH) or 4months (RH) of monthly drug collection for new cases (CAT 1), and is usually self-administered treatment for EH, while patients on RH should be observed daily. For retreatment cases (CAT 2), the continuation phase is 5 months and treatment administration should be supervised daily (NTBLCP, 2010).

For Category 1 regimen, 2 months of Ethambuthol, Isoniazid, Rifampicin and Pyrazinamide followed by 4 months of Isoniazid and Rifampicin (2EHRZ/4HR) is recommended for newly diagnosed TB. This regimen is reinforced with streptomycin (Sm) in the intensive phase and the total duration increased to eight months for retreatment cases - Category 2 (2EHRZS3/1EHRZ3/5EHR3) (Padmapriyadarsini et al., 2011).

Rifampicin plays a key role in the treatment of HIV associated TB because of its ability to destroy both intracellular and intermittently and slowly growing TB bacilli. Non-rifampicin containing regimens are associated with inferior cure rates and prolong the period of treatment (Padmapriyadarsini et al., 2011).

2.8.1 Monitoring of treatment

Monitoring of progress of TB patients while on treatment is an essential part of case management for TB patients. This is to ascertain the effectiveness of treatment in killing the TB bacilli as well as in assessing improvements in the patients' clinical state. Monitoring is done through the following processes

(a) Sputum microscopy: Two sputum smear examinations (taken as two early morning samples within two days) are done at different times during the period of treatment. This is done at the end of the second month and then repeated at the end of 5^{th} and 7^{th} months.

(b) Clinical: Regular (at least monthly) clinical assessment including weight assessment.

(c) Drug intake: Through assessment of patients record for regularity of drug intake.

2.8.2 Resistance to Rifampicin

Rifampin, along with isoniazid, is the mainstay of chemotherapy for treatment of tuberculosis. Rifampin is widely used today in most countries in the world, if not for the entire course of treatment, for at least the initial 2 months of therapy. Without rifampin, 18 to 24 months of therapy is necessary to treat active tuberculosis disease (Tshikuka et al., 2012). Tuberculosis that is resistant to rifampin but susceptible to isoniazid (rifampin-monoresistant tuberculosis) is more common in HIV-infected patients than in immune-competent patients, and most cases arise

independently from mutations in drug susceptible strains, not from extensive transmission of a few rifampin-monoresistant strains (Oluwaseun et.al., 2010). Rifampin is essential to short-course chemotherapy for tuberculosis (i.e., a 6-month regimen). The mechanism of development of rifampin monoresistance in HIV-infected patients is unclear (Oluwaseun et al., n.d.). Rifampin resistance will impact upon the ability of tuberculosis control programs to provide short-course chemotherapy, leading to higher program costs and a larger burden on patients.

2.8.3Multidrug Resistance Tuberculosis and Extensively Drug-Resistant Tuberculosis Resistance to anti-TB drugs can occur when these drugs are misused or mismanaged. Examples include when patients do not complete their full course of treatment; when health-care providers prescribe the wrong treatment, the wrong dose, or length of time for taking the drugs; when the supply of drugs is not always available or when the drugs are of poor quality.

Multidrug-resistant tuberculosis (MDR TB) is TB that is resistant to at least two of the best anti-TB drugs, isoniazid and rifampicin. These drugs are considered first-line drugs and are used to treat all persons with TB disease. Extensively drug resistant TB (XDR TB) is a relatively rare type of MDR TB. XDR TB is defined as TB which is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Due to the resistance of XDR TB to first-line and second-line drugs, patients are left with less effective treatment options, and cases often have worse treatment outcomes (Todar, 2011). Both MDR TB and XDR TB are more common in TB patients that do not take their medicines regularly or as prescribed, or who experience reactivation of TB disease after having taken TB medicine in the past. Persons with HIV infection or other conditions that can compromise the immune system are at highest risk for

MDR TB and XDR TB. They are more likely to develop TB disease once infected and have a higher risk of death from disease (Oluwaseun et al., n.d.).

2.8.4 Chemoprophylaxis

HIV-infected patients with recent or remote *Mycobacterium tuberculosis* infection are at extremely high risk for the development of tuberculosis and the importance of chemoprophylaxis cannot be overestimated (Diane and Havlir, 2011). Once active tuberculosis has been ruled out, chemoprophylaxis is recommended for all HIV infected persons with a positive tuberculin skin test (induration of 5 mm or more in diameter), a previous positive tuberculin skin test without prior chemoprophylaxis against tuberculosis, or recent close contact with potentially infectious patients with tuberculosis (Padmapriyadarsini et al., 2011). Isoniazid chemoprophylaxis for six months reduced the risk of tuberculosis by approximately 70 percent in HIV-infected patients with positive tuberculin skin tests (Diane V. Havlir, 2011).

Rifampin and pyrazinamide administered twice weekly for 2 months and isoniazid administered twice weekly for 6 months were equally effective (Muller, 2011) and preliminary data suggest that the efficacy of daily rifampin and pyrazinamide for 2 months is similar to that of 12 months of isoniazid in tuberculin-positive, HIV-infected patients (Diane V. Havlir, 2011). Currently recommended preventive-therapy regimens for HIV infected patients are nine months of daily or twice-weekly isoniazid, or two months of daily pyrazinamide and either rifampin or rifabutin(Diane V. Havlir, 2011). Chemoprophylaxis for an HIV-infected person exposed to a patient with multidrug-resistant tuberculosis should include at least two drugs with activity against the drug-resistant isolate (Brouwer et.al., 2013). Because HIV-infected patients have defective cell mediated immunity, false negative tuberculin skin tests are common. It has

therefore been recommended that skin testing be performed with tuberculin and other antigens (Dauda, 2010).

2.8.5 Risks for developing Tuberculosis

Persons with silicosis have an approximately 30-fold greater risk for developing TB. Silica particles irritate the respiratory system, causing immunogenic responses such as phagocytosis which consequently results in high lymphatic vessel deposits. It is this interference and blockage of macrophage function which increases the risk of tuberculosis (Falzon et al., 2011). Persons with chronic renal failure who are on hemodialysis also have an increased risk: 10-25 times greater than the general population. Persons with diabetes mellitus have a risk for developing active TB that is two to four times greater than persons without diabetes mellitus, and this risk is likely greater in persons with insulin-dependent or poorly controlled diabetes. Other clinical conditions that have been associated with active TB include gastrectomy with attendant weight loss and malabsorption, jejunoileal bypass, renal and cardiac transplantation, carcinoma of the head or neck, and other neoplasms (e.g., lung cancer, lymphoma, and leukemia) (Gandhi et al., 2012).

Given that silicosis greatly increases the risk of tuberculosis, more research about the effect of various (indoor) air pollutants on the disease would be necessary. Some possible indoor source of silica includes paint, concrete and Portland cement. Crystalline silica is found in concrete, masonry, sandstone, rock, paint, and other abrasives. The cutting, breaking, crushing, drilling, grinding, or abrasive blasting of these materials may produce fine silica dust. It can also be in soil, mortar, plaster, and shingles. When you wear dusty clothing at home or in your car, you

may be carrying silica dust that your family will breathe (Sakamoto, 2012).

Low body weight is associated with risk of tuberculosis as well. A body mass index (BMI) below 18.5 increases the risk by 2-3 times. On the other hand, an increase in body weight lowers the risk. Patients with diabetes mellitus are at increased risk of contracting tuberculosis and they have a poorer response to treatment, possibly due to poorer drug absorption (Nor et.al., 2011). Other conditions that increase risk include intravenous (IV) drug abuse, recent TB infection or a history of inadequately treated TB, chest X-ray suggestive of previous TB which shows fibrotic lesions and nodules, prolonged corticosteroid therapy and other immunosuppressive therapy, Immuno-compromised patients (30-40% of AIDS patients in the world also have TB), hematologic and reticuloendothelial diseases such as leukemia and Hodgkin's disease, kidney disease, intestinal bypass, chronic malabsorption syndromes, vitamin D deficiency and low body weight (Sakamoto, 2012). Some drugs, including rheumatoid arthritis drugs that work by blocking tumor necrosis factor-alpha (an inflammation-causing cytokine), raise the risk of activating a latent infection due to the importance of this cytokine in the immune defense against TB (Nor et al., 2011).

2.9.1 Prevention of Tuberculosis

TB prevention and control takes two parallel approaches. In the first, people with TB and their contacts are identified and then treated. Identification of infections often involves testing high-risk groups for TB. In the second approach, children are vaccinated to protect them from TB. No vaccine is currently available that provides reliable protection for adults, However, in tropical areas where the levels of other species of mycobacteria are high, exposure to non-tuberculosis mycobacteria gives some protection against TB (Chaisson, 2007). Until 2005, school children in

the United Kingdom and most other European countries were given a vaccination against TB, called BCG (Bacillus of Calmette and Guerin, named after the two Frenchmen that developed it). However, this vaccination does not offer complete protection against TB, and there have been cases of people who received the BCG vaccination as a child developing tuberculosis (Serafino & Med, 2012).

People with HIV should not be given the BCG injection as it is a live vaccine and can cause a TB-like illness. One of the best ways of preventing TB in people with HIV is to improve the immune system. Treatment with combinations of effective anti-HIV drugs boosts the immune system, enabling it to fight TB and other infections (Serafino & Med, 2012).

In order to prevent the development of active tuberculosis, people with latent TB are sometimes given anti- TB drug/s and also those who have come in close contact with people who have active TB may be given an anti-TB drug so as to prevent them from getting infected (Martinson et.al., 2011). The drug normally used is called isoniazid, which is given for at least six months. Sometimes a combination of another drug, rifampicin with isoniazid can be given for four months. It is recommended that HIV-positive people who come from communities that have high levels of TB, including people from Africa and those from the Indian sub-continent, are given this prophylactic treatment if their Mantoux test was positive (Shobowale et al., 2015). It is also recommended that HIV positive people who have been in close contact with people who have active TB should receive this treatment (Serafino & Med, 2012).

Eating well, getting an adequate amount of sleep and living in dry, well-ventilated houses help prevent infection with TB and it helps one remain healthy after being exposed to it or in the presence of latent TB. Anyone who comes into close contact with somebody with TB, such as a family member, housemate or friend, should be tested for TB so as to rule out possible infection.

The most important thing a patient can do is to take all of their medications exactly as prescribed by a health care provider. No doses should be missed and treatment should not be stopped early or abruptly. Patients should tell their health care provider if they are having trouble taking the medications. If patients plan to travel, they should talk to their health care providers and make sure they have enough medicine to last while away.

Health care providers can help prevent both TB and MDR TB by quickly diagnosing cases, following recommended treatment guidelines, monitoring patients' response to treatment, and making sure therapy is completed. Persons who work in hospitals or health-care settings where TB patients are likely to be seen should consult infection control or occupational health experts by asking about administrative and environmental procedures for preventing exposure to TB. Once those procedures are implemented, additional measures could include using personal respiratory protective devices.

2.9.2 Treatment outcomes of TB among HIV patients and factors associated with outcomes

A study conducted in two health facilities in Ebonyi State, Southeast Nigeria, between January 2011 and December 2012 showed that 65.8% of TB/HIV patients who registered for TB treatment achieved successful outcomes while 34.2% achieved unsuccessful outcomes (Oshi et.al., 2014). A lower TB treatment success rate of 48.8% was recorded among TB/HIV co-infected patients at the National Hospital, Abuja, Nigeria as compared to a treatment success rate of 78.5% among HIV negative patients. Also, studies done in Oyo and Gombe States in Nigeria showed poor TB treatment outcomes in terms of cure and mortality rates in patients dually infected with HIV and TB compared to those without HIV infection. This provides evidence that TB/HIV co-infection impacts negatively on TB treatment outcome (Ofoegbu & Odume, 2015).

Another study conducted in Chitungwiza district of Zimbabwe, a Southern African country with a high TB/HIV burden achieved a 73% successful treatment outcome of tuberculosis among HIV patients (Takarinda et al., 2012) .

Although the World Health Organisation (WHO) and even the National Tuberculosis and Leprosy Control Programme (NTBLCP) have set a target of 85% treatment success rate for TB, this has not been achieved in Nigeria due to many factors. A study conducted in Ebonyi State of Nigeria, attributed the unsuccessful treatment outcome to default, death and treatment failure. Independent determinants for unsuccessful outcomes were attributed to receiving care at a public facility and non-initiation of anti-retroviral therapy (Oshi et al., 2015). Another study conducted at the Federal Medical Center Ebonyi had 42.3% unsuccessful treatment outcome rate. Determinants for unsuccessful treatment outcome were attributed to high default rate which stood at 67.6%, 19.4% death and 12% transferred out. Unsuccessful treatment was also attributed to old age, rural residence, smear negative pulmonary tuberculosis, HIV sero-positivity and being on re-treatment (Ifebunandu et.al., 2013). In a similar study of factors affecting treatment outcomes of TB among HIV patients carried out in Ido-Ekiti, South-western Nigeria, the treatment failure rate was put at 53.9%. This was due to a high default rate of 30.8% (Babatunde, 2013).

High incidences of failure, death, and default depict poor treatment outcome. The outcome targets of WHO is to achieve a case detection rate of new smear-positive cases of at least 70% and to reach a treatment success rate of at least 85% for such cases. The treatment outcome for Nigeria under the WHO DOTS 2006 cohort was put at cured 65%, treatment completed 11%, died 5.8%, failed 1.9%, defaulted 10%,transfer out 2.2% with a treatment success rate of 76%.The treatment outcome for African region with the WHO DOTS 2006 cohort was cured

65%, treatment completed 10%, died 6.2%, failed 1.2%, defaulted 7.7%, transfer out 4.1% with a treatment success rate of 75% while the global treatment outcome of WHO TB DOTS 2006 cohort was put at cured 78%, treatment completed 6.3%, died 4.2%, failed 1.6%, defaulted 5.0%, transfer out 2.5%, with a treatment success rate of 85% (Nwene, 2009). Also, from the WHO TB DOTS 2006 cohort, Nigeria and African region with TSR of 76% and 75% fell below the WHO recommendation of 85% while the South East Asia Region (87%), West Pacific Region (87%) all fell within the WHO expectations for TB treatment outcome (Nwene, 2009).

CHAPTER THREE

METHODOLOGY

3.1 Study Area

The study Area is Lagos, Lagos State South West Nigeria. Lagos is the most populous city in Nigeria and one of the thirty six states of the Federation, Lagos is the second fastest growing city in Africa and the 7th in the world, Lagos has a population of 17.5 million according to the Lagos State Government after the 2006 census. Lagos has 26 General Hospitals, 2 Teaching Hospitals, 256 Public Health centres, 2,886 Private Hospitals/clinics/Labs/Dental and diagnostic centers. Lagos state has twenty Local Government Areas.

3.2 Study Design

The study is a cross sectional descriptive study of the predictors of Tuberculosis treatment outcomes among HIV-Positive patients attending HIV Clinics in Lagos.

3.3 Study Population

All patients 18 years and above attending HIV clinic in the five selected hospitals from 1st January 2012 to 31st December 2015 with history of tuberculosis treatment within the time frame.

3.3.1 Inclusion Criteria

Adults 18 years and above confirmed HIV positive attending clinic with history of TB treatment between 1st January 2012 to 31st December 2015.

3.3.2 Exclusion Criteria

Critically ill and any patient with history of reaction to ARVS or Anti-TB drugs. Then, new patients on Tuberculosis treatment.

3.4 Sample size determination

Sample size estimation using: $n = \frac{Z^2 p q}{d^2}$

Z= alpha risk expressed in Z-score usually 1.96

P= Expected prevalence

q= 1-p

d= Absolute precision usually 0.05

In a study carried out in Nasarawa state among HIV-Positive clients attending clinic at the Specialist Hospital in Lafia in 2013, TB prevalence was 34.5% (Gyar, Dauda, & Reuben, 2014).

$$n = \frac{1.96^2 \times 0.345 \times 0.655}{0.05^2}$$

$n = 347$

10% of non-response rate is then added to make up total of 382 patients that will be recruited for the study.

3.5 Sampling Technique

Multi-stage sampling technique will be used for the study. First stage, four Local Government areas were randomly selected using balloting out of the twenty LGAs.

Second stage, three public health facilities offering HIV services and TB treatment were identified and selected. Then, two private health facilities offering TB treatment according to the National TB control program and/or HIV services were identified and selected.

The treatment registers at the five facilities were used to identify patients and they were interviewed at the clinics where the receive HIV care.

Finally, patients identified were selected using table of random numbers and proportion to size

was applied. So, 120 patients allocated to Mainland Hospital, 87 patients for Ajeromi General Hospital, 77 patients for General Hospital , Marina Lagos, 56 patients for St Kizito Clinics and 43 patients for St Theresa Clinic.

3.6 Data Collection Method

Data was collected using semi-structured interviewer administered questionnaire; the questionnaire is adapted from previous study of factors affecting Tuberculosis treatment outcomes in Plateau. Three research assistants were trained for a day on how to administer the questionnaire.

3.7 Definition of Terms used in Treatment Outcome

Cured –A TB patient who was smear positive at diagnosis, who completed the course of 6 months treatment and was smear negative at the end of the 5th month of treatment

Completed treatment- Any patient who was smear positive at diagnosis and who completed treatment but in whom smear examination results were not available at the end of treatment. This includes all smear-negative and extra-pulmonary patients who completed treatment.

Default - A TB patient who completed at least one month of treatment and returns after interrupting treatment for two months or more.

Died - Any patient who dies for any reason during the course of his or her treatment.

Treatment failure- A smear positive TB patient who while on the first line of treatment remained or becomes smear positive again 5 months or later after commencement of treatment.

Treatment success - This is the sum total of all the patients that were cured and all those that completed treatment.

3.8 Data management and Analysis

The data was pre-tested in OlabisiOnabanjo University Teaching Hospital and Epi Info 7 was used to analyze and adjust for any findings on the questionnaire.

Finally, data from the study was carefully entered, cleaned and analyzed usingEpi Info 7.Univariate analysis of age, gender, educational level was done and bivariate was also done with the treatment outcomes from the data. Chi square was used for the means and level of significance set at 5%. Statistical tests were carried out testing for association using hypothesis testing along the different possible treatment outcomes.

3.9 Quality Control

All patients' folders were cross checked using the patients' registers are the treatment centres. All selected patients for the study provided the latest weight and height. A research assistant ensured data quality by cross checking the folders. Two others obtained data by interview from selected patients.

3.9.1 Ethical Consideration

Research ethical approval was sought from the Lagos State University Teaching Hospital ethics committee. Consent forms were signed by research assistants that they shall keep all information confidential as they go through the hospital records in the HIV and TB treatment centres in Lagos. Assurance of confidentiality of information was given. Participation was voluntary and written informed consent was given by each of the respondents. All the hospitals' management received letter of Introduction from Lagos State Health Service Commission for Permission to carry out the study and that the outcome of the study will be shared with all the hospitals used for the study.

3.9.2 Limitation

This is a hospital based study; it will be difficult to generalize. Also, poor data management in the hospitals could result in missing data and false negative result of sputum AFB and chest x-ray is a concern.

CHAPTER FOUR

RESULTS

Table 1: Socio-demographic factors of Respondents

	Frequency (n=386)	Percentage
Sex		
Female	240	62.2
Male	146	37.8
Age		
18-27	61	15.8
28-37	153	40.2
38-47	109	28.2
48-57	51	13.2
58 and above	12	3.1
Clinical classification		
New Smear Negative	89	22.0
New Smear Positive	278	72.0
RAD	8	2.1
Relapse	11	2.8
Treatment outcome		
Cured	174	46.1
Defaulted	20	5.2
Failure	37	9.6
Transferred out	16	4.1

atment completed	138	34.8
Hospital use		
General Hospital Ajeromi	88	22.8
General Hospital Lagos	79	20.5
Mainland Hospital	119	30.8
St Kizito Clinic	57	14.8
St Theresa Clinic	43	11.1

Table 1 shows the demographic information of respondents, majority (62.2%) are females, and majorly (40.2%) between the age of 28-37years. The clinical classification is new smear Negative 22%, New smear Positive 72%, RAD 2.1% and Relapse 2.8% respectively. From the table 46.1% were cured as a result of the treatment, 5.12% defaulted on the course of treatment, 9.6% treatment failed, 4.1% were transferred out to another hospital for further treatment while 34.8% completed their treatment.

Table 2: characteristics of Clinical and Laboratory Parameters

	Mean	Std. Deviation
Age	**37.3**	**10.6**
Initial CD4 count	188.16	171.688
Latest CD4 count	441.30	206.966
Initial PVC	33.01	6.930
Weight	55.69	13.499

Table 2 showing mean and standard deviation of different parameters, CD$ count, initial and latest, initial PCV and weight of respondents.

Table 3a: Interview of patients Social Factors

	Frequency (n=386)	Percentage
Did you ever interrupt your treatment		
No	309	80.1
Yes	77	19.0
Marital status		
Divorced	15	3.9
Married	257	66.6
Separated	33	8.5
Single	76	19.7
Applicant/unemployed	**38**	**9.8**
Artisan	50	13.0
Civil Servant	73	18.9
Farming	13	3.4
Others, specify	4	1.0
Schooling	37	9.6
Trading	166	43.0
Education		
No formal education	21	5.4
Post secondary	100	25.9
Primary school	80	20.7
Quran education	5	1.3
Secondary School	174	45.1

Distance of health facility		
< 5 KM	157	40.7
>5Km	224	58.0

Table 3 shows patients interview, 80.1% of respondents claimed that there treatment was not interrupted and 66.6% were of them were married and 43% of them are traders with 45.1% of them having secondary education. More than half of the respondent claimed that the health facility is >5km

Table 4: knowledge of Cause and Transmission of TB

Variables	Frequency (n=386)	Percentage
Cause of TB		
By Germ	132	34.2
Contact with TB patient	149	38.6
Don't Know	44	11.4
From God	11	2.8
Others, specify	2	.5
Witchcraft/Poisoning	41	10.6
How TB spread		
Airborne	351	90.9
Don't know	13	3.4
Through food	9	2.3
Through water	4	1.0
TB can be cured		
Don't know	5	1.3
No	10	2.6
Yes	365	94.6
Treatment can cure TB		
Don't know	3	.8
No	13	3.4
Yes	362	93.8

Duration of treatment		
>6 months	31	8.0
6 months	322	83.4
Don't	5	1.3
Reasons for taking treatment		
Don't have reason for taking the treatment	1	.3
Forced by family members to take the treatment	5	1.3
To avoid spread of the disease	15	3.9
To be cured	359	93.0
Role in the family		
Dependants	72	18.7
House wife	52	13.5
Main bread winner	129	33.4
Not Main Bread winner, but supports family	127	32.9

Respondents (38.6%) said that the cause of TB is contact with Tb patient while 34.2% said it is caused by germ. Majority claimed that Tb can be spread through Airborne and also 96.4% said TB can be cured. They (93.8%) also believed that the treatment they are undergoing now will cure the TB. 83.4% said that TB treatment last for 6months and 93% are taking the Tb treatment to be cured of TB

Table 5: Patients interview on alcohol and tobacco usage.

Variables	Frequency	Percentage
Smoking		
No	330	85.5
Yes	40	10.4
Duration of smoking (in years) (n=40)		
6-11	16	40
1-5	11	27.5
12 and above	13	32.5
Number of sticks per-day		
1-5	24	60
10	4	10
6-11	11	27.5
12 and above	1	2.5
Still smoking		
No	32	8.8
Yes	8	99.1
Stop smoking for how long now (n=32)		
1-5	12	37.5
6-11	7	21.875
12 and above	13	40.625

ver taken alcohol		
No	291	75.4
Yes	95	24.6
Started drinking in (years) (n=95)		
12 and above	4	1.0
1-5	28	.8
6-11	22	2.1
Still drinking alcohol		
No	58	15.0
Yes	32	85.
Stopped drinking (n=58)		
< 6 months	6	1.6
>12 months and above	34	8.8
6 to 12 months	28	89.6
Started ARVs		
No	70	18.1
Yes	316	81.9
Total	386	100.0

Only 40 respondents out 386 claimed that they smoke, 32.5% having smoking for 12years and above and they (60%) said they smoke 1-6 stick per day. 24.6% said also they take alcohol, lastly 81.9% said they have started taking ARVs

Interruption of treatment * Outcome of treatment

Treatment outcome	Interruption of treatment		
	No	Yes	Total
Cured	0	3	3
Cured	145	31	176
Defaulted	6	14	20
Failure	0	1	1
Failure	27	9	36
Transferred out	14	2	16
Treatment completed	118	16	134
Total	**310**	**76**	**386**

From the association table above, using the Chi-square test, it revealed that interruption of treatment affects the outcome of treatment; this is shown by the P-value 0.005 which is less than 0.05 significant levels. So we reject the Null hypothesis and accept the alternative.

Distance * outcome of treatment

Outcome of treatment	Distance		
	< 5 KM	>5Km	**Total**
Cured	0	3	3
Cured	79	97	176
Defaulted	13	7	20
Failure	0	1	1
Failure	12	24	36
Transferred out	8	8	16
Treatment completed	45	89	134
Total	**157**	**229**	**386**

This table shows also that there is a statistically significant association between distance and outcome of treatment, P=0.041

Outcome of treatment * sex

Outcome of treatment	Sex		
	Female	Male	Total
Cured	2	1	3
Cured	118	58	176
Defaulted	10	10	20
Failure	1	0	1
Failure	23	13	36
Transferred out	12	4	16
Treatment completed	74	60	134
Total	**240**	**146**	**386**

This table shows that is no statistically significant association between sex and outcome of treatment, that is sex has nothing to do with outcome of treatment, p=0.270, showing non-significant.

ART * Outcome of treatment

Outcome of treatment	ART		Total
	No	Yes	
Cured	2	1	3
Cured	16	160	176
Defaulted	8	12	20
Failure	0	1	1
Failure	5	31	36
Transferred out	9	7	16
Treatment completed	23	111	134
Total	**63**	**323**	**386**

This table also showed a statistically significant association between ART and outcome of treatment, P=0.000. Here we reject the null hypothesis and accept the alternative.

CPT * outcome of treatment

Outcome of treatment	CPT		
	No	Yes	**Total**
Cured	1	2	3
Cured	58	118	176
Defaulted	11	9	20
Failure	0	1	1
Failure	21	15	36
Transferred out	10	6	16
Treatment completed	72	62	134
Total	**173**	**213**	**386**

This table also showed that there is a relationship between CPT and outcome of treatment, P=0.002.Here we reject the null hypothesis and accept the alternative.

Knowledge * Outcome of treatment

Outcome of treatment	Knowledge		Total
	Good	poor	
Cured	3	0	3
Cured	175	1	176
Defaulted	19	1	20
Failure	1	0	1
Failure	35	1	36
Transferred out	16	0	16
Treatment completed	132	2	134
Total	**381**	**5**	**386**

This table above showed that there is no statistical association between knowledge and outcome of treatment of Tb, P=0.704. Here we fail to reject the null hypothesis.

CHAPTER FIVE

DISCUSSION

The study carried out in Lagos among HIV-positive patients who were treated for TB has results as seen from table 1: 46.1% were cured as a result of the treatment, 5.12% defaulted on the course of treatment, 9.6% treatment failed, 4.1% were transferred out to another hospital for further treatment while 34.8% completed their treatment. Thus successful treatment comes to 80.9% , this higher than the study conducted in two health facilities in Ebonyi State, Southeast Nigeria, between January 2011 and December 2012 showed that 65.8% of TB/HIV patients who registered for TB treatment achieved successful outcomes while 34.2% achieved unsuccessful outcomes (Oshi et.al., 2014).

It is also higher than TB treatment success rate of 48.8% was recorded among TB/HIV co-infected patients at the National Hospital, Abuja, Nigeria as compared to a treatment success rate of 78.5% among HIV negative patients. Thus, successful treatment rate is similar to result got among HIV-negative patients in National Hospital. Also, studies done in Oyo and Gombe States in Nigeria showed poor TB treatment outcomes in terms of cure and mortality rates in patients dually infected with HIV and TB compared to those without HIV infection. This provides evidence that TB/HIV co-infection impacts negatively on TB treatment outcome (Ofoegbu & Odume, 2015).

The result of the study in Lagos is similar to the study conducted in Chitungwiza district of Zimbabwe, a Southern African country with a high TB/HIV burden achieved a 73% successful treatment outcome of tuberculosis among HIV patients (Takarinda et al., 2012) .

Although the World Health Organisation (WHO) and even the National Tuberculosis and Leprosy Control Programme (NTBLCP) have set a target of 85% treatment success rate for TB, this has not been achieved in Nigeria due to many factors.

On the contrary, the result of the study among HIV/TB patients in Lagos is not consistent with A study conducted in Ebonyi State of Nigeria, attributed the unsuccessful treatment outcome to default, death and treatment failure. Independent determinants for unsuccessful outcomes were attributed to receiving care at a public facility and non-initiation of anti-retroviral therapy (Oshi et al., 2015). Another study conducted at the Federal Medical Center Ebonyi had 42.3% unsuccessful treatment outcome rate which is higher than 19.1% in the Lagos study. Determinants for unsuccessful treatment outcome were attributed to high default rate which stood at 67.6%, 19.4% death and 12% transferred out. Unsuccessful treatment was also attributed to old age, rural residence, smear negative pulmonary tuberculosis, HIV sero-positivity and being on re-treatment (Ifebunandu et.al., 2013). In a similar study of factors affecting treatment outcomes of TB among HIV patients carried out in Ido-Ekiti, South-western Nigeria, the treatment failure rate was put at 53.9%. This was due to a high default rate of 30.8% (Babatunde, 2013).

High incidences of failure, death, and default depict poor treatment outcome. The outcome targets of WHO is to achieve a case detection rate of new smear-positive cases of at least 70% and to reach a treatment success rate of at least 85% for such cases. The treatment outcome for Nigeria under the WHO DOTS 2006 cohort was put at cured 65%, treatment completed 11%, died 5.8%, failed 1.9%, defaulted 10%,transfer out 2.2% with a treatment success rate of 76%.The treatment outcome for African region with the WHO DOTS 2006 cohort was cured

65%, treatment completed 10%, died 6.2%, failed 1.2%, defaulted 7.7%, transfer out 4.1% with a treatment success rate of 75% while the global treatment outcome of WHO TB DOTS 2006 cohort was put at cured 78%, treatment completed 6.3%, died 4.2%, failed 1.6%, defaulted 5.0%, transfer out 2.5%, with a treatment success rate of 85% (Nwene, 2009). Also, from the WHO TB DOTS 2006 cohort, Nigeria and African region with TSR of 76% and 75% fell below the WHO recommendation of 85% while the South East Asia Region (87%), West Pacific Region (87%) all fell within the WHO expectations for TB treatment outcome (Nwene, 2009).

Tuberculosis (TB) is a curable infectious disease, but there are factors that affects successful and unsuccessful treatment outcomes, to discover these factors is the reason behind this survey carried out in Lagos State on predictors of tuberculosis treatment outcome among HIV positive patient. This survey took place in five different hospitals namely: General Hospital Ajeromi, General Hospital Lagos, Mainland Hospital, St Kizito Clinic and St Theresa Clinic in Lagos State.

Treatment failure constitutes a major problem for the National TB control programmes because such failed cases tend to have higher morbidity and mortality when compared with cured cases (Alobu *et.al.*, 2014). Also, treatment failure cases remain infectious for prolonged periods of time and this promotes further transmission of the disease in the community and ultimately leads to high rates of multidrug-resistant TB especially in resource limited settings; hence, the importance of achieving a treatment success rate of 85% as recommended by the WHO. Also, current recommendations by the American Thoracic Society-Centers for Disease Control and Prevention- Infectious Diseases Society of America and the World Health Organization (WHO) are that the standard 6-month therapy should be used for active TB in HIV-positive patients; the

former provides clinicians with the option of extending therapy on the basis of clinical judgment. Both guidelines state that intermittent 3-times weekly dosing schedules are acceptable alternatives to daily treatment in HIV-seropositive patients, but WHO specifically recommends against using twice-weekly dosing for HIV-seropositive patients (WHO, 2012).

This study also revealed some of the factors that affecting successful and unsuccessful treatment of TB as interruption of treatment, when treatments are not taken according to prescription, it affects the successful treatment of TB. This is proven by the association table using Chi-square test, it revealed that interruption of treatment affects the outcome of treatment; this is shown by the P-value which is 0.005,it is less than 0.05 significant levels. It shows also that there is a statistically significant association between distance and outcome of treatment, P=0.041. This means that the distance from their place of residence to the various clinic where they are taking treatment is far, thereby discouraging them from continuing for treatment and thereby affect successful treatment of TB.

Overall knowledge of respondent showed that 96.3% of respondents have good knowledge of TB. 38.6% said that the cause of TB is contact with Tb patient while 34.2% said it is caused by germ. Majority claimed that Tb can be spread through Airbone and also 96.4% said TB can be cured. They (93.8%) also believed that the treatment they are undergoing now will cure the TB. 83.4% said that TB treatment last for 6months which is the standard months for TB treatment. Patients demographic information were taken, like their names, registration numbers, sex, age clinical classification, HIV status, treatment out, CD4 count for initial and latest, PCV at initial and their weights. The mean age of respondents is 37.3 ± 10.6, the mean for initial CD4 count is

188.16 ± 171.7, latest CD4 count is 441.3 ± 206.9, initial PCV 33.0 ± 6.9 and weight 55.7 ± 13.5 respectively. from the result of the means, it revealed that initial CD4 count increased from 188 to 441, showing signifying the effectiveness of the treatments that they are being given. Majority (62.2%) of these respondents are females, (40.2%) between the age of 28-37years. Patients interview shows that 80.1% of respondents claimed that there treatment was not interrupted and 66.6% were of them were married and 43% of them are traders with 45.1% of them having secondary education. More than half of the respondent claimed that the health facility is >5km faraway from their residence.

Due to the high HIV prevalence among TB patients, WHO recommends the Three I's: intensified TB screening among HIV-infected individuals, provision of isoniazid preventive therapy (IPT), and infection control (WHO, 2012), a case detection rate of 70% and a treatment success rate of 85% is currently being recommended by the World Health Organisation for all TB cases(Alobu et.al,2014). It is believed that achieving these targets will lead to a reduction in TB prevalence, incidence, transmission and drug resistance to TB. In order to effectively monitor the TB control efforts by TB control programmes, the WHO has recommended a strong indicator which is the proportion of pulmonary TB patients whose sputum smear or culture are positive after 5 months or later during treatment (NTBLCP, 2010). But in this study carried out in Lagos State, there is 46.1% cure rate, 5.12% defaulted on the course of treatment, 9.6% treatment failed, 4.1% were transferred out to another hospital for further treatment while 34.8% completed their treatment.

Conclusion

Tuberculosis is curable if patients with drug susceptible organisms are treated on time and are

given sufficient uninterrupted therapy. Despite the fact that TB is treatable and curable, it has proved impossible to eliminate and this has been worsened by HIV/AIDS epidemic. However, TB/HIV Collaborative activities help to attain high successful outcome.

Recommendations

- To address these challenges, Lagos State government has to strengthen its TB/HIV collaborative activities by ensuring cross referral of TB/HIV patients and timely provision of treatment and care.
- Making sure that TB treatment is readily available to dually infected patients.

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PREDICTORS OF TUBERCULOSIS TREATMENT OUTCOMES AMONG HIV-POSITIVE PATIENTS IN LAGOS

Annex 1: Questionnaire for TB patients with HIV

From Central Register and Treatment card

1. Patient name: ----------

2. Patient Registration number -------/------/-------/----------State/LGA/Year/Patient number

3. Sex of patient

[ ] Female

[ ] Male

4. Age of patient ----------(in years)

5. Clinical classification of patient (Tick one that applies)

[ ] New smear positive

[ ] New smear negative

[ ] Relapse

[ ] Failure

[ ] RAD

[ ] Others

6. HIV status of patient

[ ] HIV Positive

7. Treatment outcome of patient

[ ] Cured (start on question 9)

[ ] Treatment completed (start on question 9)

[ ] Failure (start on question 9)

[ ] Defaulted (start on question 8)

8. CD4 count

Initiation ……

Latest……..

9. PCV at initiation……

10. Weight……

11. ART….. Yes or No

12. CPT …..Yes or No

Section B: Interview of Patients

Interview date (dd/mm/yy) ----/-----/----

Interviewer Name ---------- Sign ----------.

Consent from respondent:

My name is ----------. We are conducting a study on Tuberculosis disease among HIV- positive patients and the services being offered for its control. The aim is to learn ways to organize the services better for TB patients in the state.

We shall ask you some questions and will take 20 to 30 minutes. Your participation is confidential and all information shall be used for the study only.

Your response will help us assess the services and improve on it in Lagos State.

Thank you for giving us audience.

13. Did you ever interrupt your treatment?

[ ] Yes [ ] No

14. Marital status of patient

[ ] single

[ ] married

[ ] divorced

[ ] Separated

15. Occupation of patient

[ ] Farming

[ ] Schooling

[ ] Applicant / unemployed

[ ] Civil servant

[ ] Trading

[ ] Artisan

[ ] Others specify ----------

16. Highest education level attained:

[ ] No formal education

[ ] Primary school

[ ] Secondary school

[ ] Post secondary

[ ] Qur'an education

17. How far is health facility from your home?

[ ] ≤ 5 km [ ] > 5km

18. What do you think cause TB? (Tick all that apply)

[ ] Witch craft/poisoning

[ ] From God

[ ] By germ

[ ] Don't know

[ ] Contact with TB patient

[ ] Others causes please specify ----------

19. How does TB spread? (Tick all that apply)

[ ] Don't Know

[ ] Airborne

[ ] Through food

[ ] Through water

[ ] Don't know

[ ] Others please specify----------

20. Do you think you can be cured of TB?

[ ] Yes

[ ] No

[ ] Don't know

21. Do you think this treatment can cure your TB disease?

[ ] Yes

[ ] No

[ ] Don't know

22. How long are you supposed to take the treatment?

[ ] < 6 months

[ ] 6 months

[ ] > 6 months

[ ] Don't know

23. What are your reasons for taking treatment?

[ ] To avoid spread of disease to others

[ ] To be cured of the disease

[ ] Forced by family member to take drug

[ ] Don't have reason for taking the drugs

[ ] others please specify ----------

24. Which of these roles applies to you in your family?

[ ] Main bread winner

[ ] Not main bread winner but supports family

[ ] House wife

[ ] Dependant

25. Have you ever smoked cigarette?

[ ] Yes

[ ] No (Go to question 25)

26. If "Yes" when did you start smoking the cigarette? ---------- (in years)

27. How many sticks of cigarette do you smoke each day? ---------- (number of sticks)

28. Do you still smoke the cigarette?

[ ] Yes

[ ] No

29. If "No" when did you stop smoking cigarette? ---------- (in months)

30. Have you ever taken alcohol?

[ ] Yes

[ ] No (End of survey)

31. If "Yes" when did you start drinking the alcohol? ----------(in years)

32. Do you still drink alcohol?

[ ] Yes

[ ] No

33. If "No" when did you stop drinking the alcohol?

[ ] < 6 months ago

[ ] 6 to 12 months ago

[ ] > 12 months ago

34. Have started ARVs

[ ] Yes [ ] No

Thank you for participating in the study.