SPUTUM SMEAR CONVERSION IN PULMONARY TUBERCULOSIS: AN INTENSIVE PHASE MONITORING OF SPUTUM SMEAR POSITIVE PATIENTS IN ZARIA, NIGERIA

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September 2012

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A DISSERTATION SUBMITTED TO THE POSTGRADUATE SCHOOL, AHMADU

BELLO UNIVERSITY, ZARIA NIGERIA

IN PARTIAL FULFILMENT FOR THE AWARD OF MASTER IN PUBLIC HEALTH IN FIELD EPIDEMIOLOGY

DEPARTMENT OF COMMUNITY MEDICINE

AHMADU BELLO UNIVERSITY, ZARIA

NIGERIA

September 2012

CERTIFICATION

This dissertation entitled "SPUTUM SMEAR CONVERSION IN PULMONARY TUBERCULOSIS: AN INTENSIVE PHASE MONITORING OF SPUTUM SMEAR POSITIVE PATIENTS IN ZARIA, NIGERIA" by Dr Tolough Geoffrey Ingyoroko meets the regulations governing the award of the degree of Masters in Public Health of Ahmadu Bello University, Zaria, and is approved for its contribution to knowledge and literary presentation.

_____ _____

Chairman, Supervisory Committee Date

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Member, Supervisory Committee Date

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Member, Supervisory Committee Date

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Dean, Postgraduate School Date

ATTESTATION

I declare that the work in the dissertation entitled "Sputum Smear Conversion in Pulmonary Tuberculosis: An Intensive Phase Monitoring of Sputum Smear Positive Patients in Zaria, Nigeria" has been performed by me in the Department of Community Medicine under the supervision of Dr Saad Aliyu Ahmed.

The information derived from the literature has been duly acknowledged in the text and a list of references provided. No part of this dissertation was previously presented for another degree or diploma at any university.

Dr Tolough Geoffrey Ingyoroko September 2012

_____ _____ _____

Name of student Signature Date

ACKNOWLEDGEMENTS

Project supervisor: Dr Saad Aliyu Ahmed (MBBS, MPH, FMCPath, FICS), for directing through constructive criticisms, provision of useful journal articles and great interest in this topic.

Dr Gidado Mansu: of NTBLTC Zaria; for initial guidance and interest on this research topic at the field site.

Project team members:

Isiyaku Ahmadu: project supervisor and check-microscopist.

Paul Maro: lead microscopist.

Wale Amoo: for documentation and records.

Esther Dimlong: patient preparation and education.

Baba Aliyu: slide preparation.

NTBLTC Management: for creating an enabling field site to carry out this research and waiving the cost of all the investigations.

ABU/UI: for providing quality teachers to impart knowledge.

FMOH/FMOAWR: for actualizing NFELTP through CDC.

AFENET: for this project grant and timely disbursement of funds for field activities and monthly stipend.

CDC Atlanta: for initiating this training program, (Field Epidemiology and Laboratory Training Program in Nigeria: NFELTP)

Dr Oladayo Biya: for creating the maps.

To my wife: Mrs. Felicia Tolough, for taking over completely the management of 'Home Affairs' enabling me to focus more on this demanding program.

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LIST OF ACRONYMS

AFB: Acid-fast bacilli

AFENET: African Field Epidemiology Network

AIDS: Acquired immuno deficiency syndrome

CD4+: Cluster of differentiation antigen 4

CDC: Centers for Disease Control and Prevention

DOTS: Directly observed treatment short course

FMOAWR: Federal Ministry of Agriculture and Water Resources

FMOH: Federal Ministry of Health

HIV: Human immunodeficiency virus

IUATLD: International Union Against Tuberculosis and Lung Disease

MDG: Millennium development goals

MDR-TB: Multi-drug resistant tuberculosis

NTBLCP: National Tuberculosis and Leprosy Control Program

NTBLTC: National Tuberculosis and Leprosy Training Center

PCR: Polymerase chain reaction

TEPHINET: Training Programs in Epidemiology and Public Health Intervention Network.

PTB: Pulmonary tuberculosis

TB: Tuberculosis

USAID: United States Agency for International Development

WHA: World Health Assembly

WHO: World Health Organization

X^2: Chi square

XDR-TB: Extensively drug resistant tuberculosis

ZN: Ziehl Neelsen

Time to sputum conversion means the time at which sputum becomes negative for acid-fast bacilli while on anti-TB drugs.

Sputum smear conversion means a positive sputum smear for acid fast-bacilli becoming negative by the action of appropriate anti-TB drugs.

Patient category refers to whether the patient is new and has not started anti-TB drugs before (category 1) or has started anti-TB drugs but defaulted, relapsed or a case of treatment failure (category 2).

SUMMARY

Tuberculosis (TB) is a high burden global problem. Nigeria ranks fifth among the 22 high burden TB countries globally and first in Africa. Directly observed treatment short-course (DOTS) is central to all TB control programs. One indicator of assessing the effectiveness of DOTS is through sputum smear conversion rates at the end of intensive phase. Whether some of the patients become smear negative early during the intensive phase has not been investigated. There is lack of data to clarify this research question. The rate and time to sputum smear conversion were determined as well as the relationship between baseline sputum smear grades and time to sputum smear conversion described.

A longitudinal study at National Tuberculosis and Leprosy Training Center, (NTBLTC) Zaria was employed from January-June 2010. Data collection was by laboratory method using Ziehl Neelsen staining technique for grading the bacillary load in the sputum at diagnosis and weekly follow-up specimens. HIV status of each patient was determined and 2007-2009 records analyzed. Data was entered and analyzed by Epi-Info version 3.5.1

Of the 62 patients analyzed, 67.7% were males with male/female ratio of 2:1. The productive age group constituted 88.7% of those affected with median age of 32 years. About 75.8% were HIV negative with TB/HIV co-infection of 24.2%; 79% were new TB patients. Overall, Zaria and her immediate neighboring LGAs had 82.3% of patients.

Of the 58 patients that converted, the mean time to sputum smear conversion was 2.7 ± 1.3 weeks, standard error (SE), 0.2 (95% confidence interval 2.3-3.1). Sputum smear conversion rate peaked in week three with 71%. By the end of intensive phase, conversion rate was 93.5%. At univariate analysis, by first week, 90% of sputum smear grade of ≤ 1+ converted but none among sputum grade of 3+. Being HIV positive was not associated with early conversion at bivariate analysis with p-value of 0.31 by Fisher's exact. Of the 611 records analyzed for 2007-2009, the average sputum conversion rate was 82%. When conversion rate was categorized by sputum grade, it was statistically significant (X^2 15.5 df 4 and p-value 0.003), indicating that sputum smear grade is a strong predictor of sputum smear conversion.

It was concluded that sputum smear conversion rate during the intensive phase was high and peaked early. This may offer a rethink of duration of admission policy or isolation and a reduction of routine time for assessing sputum conversion from seventh week to the fifth week at least at NTBLTC, Zaria. A national survey on sputum smear conversion is recommended in a further study for wider national application.

Key words: Tuberculosis, Sputum, Conversion, intensive phase, acid fast bacilli

Chapter 1 **INTRODUCTION**

1.1 Background

Tuberculosis (TB), long known to be a major cause of morbidity and mortality throughout the world has for the past several decades been a neglected disease in both the industrialized and developing countries. Robert Koch in his presentation on the 24th March 1882 to the Physiological Society of Berlin on the discovery of *Mycobacterium tuberculosis*, an acid-fast bacillus that causes tuberculosis stated thus: "If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those much feared infectious diseases, plague, cholera and the like. One in seven of all human beings die from tuberculosis. If one considers the productive middle-age groups, tuberculosis carries away one-third and often more". That burden still persists today and was thus declared as "global emergency" by World Health Organization (WHO). [1]

The burden of TB of 1990 as a baseline for the global TB situation in the world has the following estimates: Approximately, one third of the world's population is infected with Mycobacterium tuberculosis. An estimated eight million developed tuberculosis worldwide and 2.6 to 2.9 million died. [2, 3] Co-infection with human immunodeficiency virus (HIV) and multidrug resistant TB has dramatically fueled the burden of TB. [3]

Nigeria ranks fourth among the 22 high burden TB countries globally and first among nine African countries that are part of the 22 high burden countries. [4] In 2007, annual

estimated data is as follows: 460,000 were estimated new TB cases out of which 195,000 (42%) were sputum smear positive. Prevalence was 521/100,000 and mortality at 93/100,000 population. MDR-TB among all new cases of TB was 1.8%. HIV infection, a strong force in awakening latent TB is put at prevalence of 4.6%, of which 3.1% affects age group, 15 to 49 years. TB/HIV co-infection is 27%. Case detection rate is unfortunately the lowest among the high TB burden countries, (23%), but with an encouraging treatment success rate of 76%.

Based on the global TB situation in the world, with reference to 1990 baseline, the global efforts to control TB were reinvigorated in 1991, when the World Health Assembly (WHA) resolution recognized TB as a major public heath problem. Two targets for TB control were established as part of this resolution—detection of 70% of new sputum smear positive cases and cure of 85% of such cases by the year 2000. [5] In 1994 the internationally recommended control strategy, short-course chemotherapy (SCC), later named directly observed treatment short-course (DOTS) was launched. [6, 7]

According to WHO TB program, all countries with a TB problem must provide standardized SCC to at least all sputum smear positive TB patients. This effectively cures the disease and prevents future transmission of the TB bacilli. One of the treatment indicators to measure progress of this target is successful treatment of detected cases, among which is sputum smear conversion rate at the end of two months or intensive phase of treatment. [6] It provides an early assessment to the effectiveness of treatment/treatment services provided in the intensive phase. Sputum smear conversion

rate is the proportion of new sputum smear patients who were negative at the end of the second month of the intensive phase of short-course chemotherapy out of which all new smear positive cases registered in the respective time period. [6] This uses a simple tool: the Ziehl Neelsen staining technique. [8, 9]

Limited information is available to predict the length of time required for a patient to achieve sputum conversion after starting therapy for pulmonary tuberculosis in days or weeks. [10, 11] The available information are those on the research carried out on monthly basis during the intensive phase of management, that is, at the end of first and second months. Most researchers concentrate on factors that predict time to sputum smear conversion and conversion rate at the end of intensive phase. Many factors are therefore associated with time to sputum smear conversion and conversion rates, notably, grades or quantification of baseline sputum smears. The higher the sputum bacillary loads the longer the conversion time. Others are lung cavitations, duration of the illness, age, sex, nutritional status, co-morbidities e.g. HIV infection, diabetes, cancer or influence of drugs. [12, 15-18]

In Nigeria, information on sputum smear conversion rate and time to sputum smear conversion are assessed at the end of intensive phase. The 5th month is set aside to check for treatment failure and 7th month to assess cure as stipulated in the National guidelines on TB management.[19] No detailed research information is available on this topic.

1.2 Statement of the Problem

Routinely, sputum smear conversion testing is carried out at the seventh week of intensive phase while on treatment using DOTS for each sputum smear positive patient as

specified by the National Tuberculosis and Leprosy Control Program (NTBLCP) of Nigeria. Whether some of the patients become sputum smear negative earlier during the intensive treatment phase has not been investigated. When really, a patient on appropriate anti-TB drugs does converts? Further individual case management depends on the smear conversion status of the patient at the end of the intensive phase. This is very clear as the patient moves to the continuation phase if such a one converts or one additional month if sputum is still positive for AFB.

1.3 Justification of the Study.

There is lack of data to clarify when sputum smear positive patients converts on weekly basis during intensive phase of treatment. This study will analyze the timelines of conversion to smear negativity for TB patients under DOTS to provide data that will be helpful for TB case management in terms of admission policy of the patients. Information gathered from this research will also be used for public education, to assure TB patients and those who care for them. This study therefore sets out to establish detail time to sputum conversion in weeks which serves as an assessment tool for DOTS program in NTBLTC Zaria and NTBLCP.

1.4 Research Questions

According to the American guideline on controlling TB by the American Thoracic Society, Centers for Disease Control and Prevention and Infectious Diseases Society of America, patients become non-infectious while on two to three weeks of standard

treatment regimen. This is still a subject of controversy when it comes to issues of isolation and duration of admission for sputum smear positive pulmonary TB. Does all the different baseline AFB quantification or grades at diagnosis convert within two to three weeks of treatment? This research will determine the timeline of sputum smear conversion week by week during the eight weeks of intensive phase to pinpoint when infectiousness will be over given the various sputum smear grades. The research will help in planning for hospital admissions relating it to initial sputum smear grade at diagnosis and expected time of sputum conversion.

1.5 Objectives of the Study

1.5.1 General objective

The overall objective of the study is to assess Nigeria DOTS program based on sputum smear conversion during the intensive phase treatment.

1.5.2 Specific objectives

1. To determine the time to sputum smear conversion for smear-positive PTB patients in weeks during intensive phase.
2. To describe the relationship between sputum smear grade at baseline and time to sputum smear conversion during intensive phase.
3. To determine the relationship between HIV status and time to sputum smear conversion during the intensive phase.
4. To analyze the existing data at NTBLTC from 2007-2009 to determine the number of smear-positive that converted to smear negative at the end of the intensive phase for comparison.

Chapter 2 **LITERATURE REVIEW**

2.1 TB Microbiology

Taxonomically, the causal agents for TB belong to the order *Actinomycetales* and the family *Mycobacteriaceae.* TB is caused by *Mycobacterium tuberculosis*, an acid-fast bacillus. It was discovered by Robert Koch on March 24th 1882, a day which is set aside as World TB Day, to educate the public about the devastating health and economic consequences of TB, its effect on developing countries, and its impact on global health. *Mycobacterium tuberculosis* complex consist of M. tuberculosis, M. africanum and M. microti affecting humans. M. bovis is a zoonotic disease, affecting humans when unpasteurized milk in affected animals are consumed.

2.1.1 Cell wall structure and characteristics

Mycobacterium tuberculosis has a unique cell wall structure which is the major determinant of virulence for the bacterium but lacks a cerulean capsule. About 60% of the cell is lipid with three major components: mycolic acids, cord factor and wax-D. It also has peptidoglycan. *Mycobacterium tuberculosis* is protected from the host by a unique cell wall through mycolic acid portion by protecting the cell against phagocytic granules, oxygen radicals, lysozyme and cationic proteins.

The following properties are associated with high lipid content:

- Impermeability to staining process
- Resistance to antibiotics

- Resistance to acidic and alkaline disinfectants
- Resistance to osmotic lysis via complement deposition
- Resistance to lethal oxidation and survival inside of microphages .

2.2 TB Epidemiology

This comprises two major parts: the detailed analysis of the state of the epidemic in the world and the epidemiological chain of transmission as well as factors influencing it.

2. 2.1. The state of the epidemic in the world today

TB remains the most important infectious disease worldwide. The current global situation of TB reflects the enormous economical and social differences among countries.

The International Burden of TB

The distribution of most of the estimated number of cases in 2008 occurred in Asia (55%) and Africa (30%) with small proportions of cases in the Eastern Mediterranean Region (7%), the European Region (5%) and the Region of the Americas (3%). The 22 high-burden countries (HBCs, defined as the countries that that rank first to 22nd in terms of absolute numbers of cases and which have received particular attention at the global level since 2000) account for 80% of all estimated cases worldwide. The five countries that rank first to fifth in terms of total numbers of incident cases in 2008 are India (1.6–2.4 million), China (1.0–1.6 million), South Africa (0.38-0.57 million) (0.38–0.57 million), Nigeria (0.37–0.55 million) and Indonesia (0.34–0.52 million). India and China alone

account for an estimated 35% of TB cases worldwide. Of the 9.4 million incident cases in 2008, an estimated 1.2–1.6 million (13–16%) were HIV-positive, with a best estimate of 1.4 million (15%) Of these HIV-positive cases, 78% were in the African Region and 13% were in the South-East Asia Region. [4]

Prevalence

There were an estimated 11.1 million (range, 9.6–13.3 million) prevalent cases of TB in 2008 equivalent to 164 cases per 100 000 population.

Mortality

The number of TB deaths per 100 000 population among HIV-negative people plus the estimated TB deaths among HIV-positive people equates to a best estimate of 28 deaths per 100 000 population at least one case of XDR -TB.

2.2.2. The Epidemiological chain of transmission

Causal agent

M. tuberculosis is a bacillary-shaped (i.e., rod-like) microorganism and a strict aerobe. Its growth depends on the presence of oxygen and the surrounding pH level. It is highly resistant to cold, freezing, and drying, and is very sensitive to heat, sunlight, and ultraviolet radiation. Under adverse metabolic conditions, the bacterium enters a latent or dormant state, and multiplication can be postponed from days to many years. These characteristics have clearly helped the microorganism to survive in humans.

Source of infection

Humans (healthy and infected or diseased) are the fundamental reservoir or host for *M. tuberculosis*. The most infectious presentations correspond to pulmonary TB, where the host capacity to spread bacteria is greatest relative to highest bacterial loads. Such patients show cavities on chest radiographs or have positive smear microscopy results.

Mechanism of transmission

The airborne route is responsible for almost all cases of TB transmission.

When speaking, singing, laughing, sneezing, and especially coughing, the infected patient expels microdroplets into the air, which contain the mycobacteria.

The microdroplets that measure 1 to 5micrometer in diameter contain 1 to 5 bacilli per microdroplet. These microdroplets are highly infectious since they can be deposited within the alveolar spaces, particularly at the best-ventilated region of the lungs where conditions are ideal for multiplication. Initially, the macrophages, followed by the lymphocytes, migrate towards this region, and in the majority of cases are able to arrest microbial multiplication. However, when this initial defense mechanism is impaired, primary TB develops. The potential of a patient to infect others depends on the following factors:

1. *The extent of disease*

Patients with positive smear microscopy and those presenting radiographic evidence of pulmonary cavitations are regarded as highly infectious.

2. *The severity and frequency of coughing*

Infected patients who cough frequently are more contagious, since the microdroplets expelled are smaller.

3. *The quality and volume of the respiratory secretions*

Scantly viscous sputum often constitutes an ideal aerosol vehicle, and is therefore more contagious.

4. *The antituberculous chemotherapy provided*

Patients who receive such therapy are 50 times less infective than those who do not receive therapy. It is generally accepted that a patient is no longer infective after 2 weeks of treatment, although confirmation is not possible until smear microscopy results are negative. The characteristics of exposure: i) the concentration of bacilli in the atmosphere, with the greatest transmission potential being found in small, closed rooms where the smear microscopy-positive TB patient spends many hours; ii) room ventilation, with fewer bacilli being found in the air of well-ventilated rooms; and iii) the duration of exposure to the infectious TB patient, where the risk of transmission increases with close and prolonged contact.

2.2.3 The susceptible host: risk factors

Children under the age of 5 years and elderly subjects older than 65 to 70 years are more vulnerable to TB, partly because immunity is slightly reduced at these ages. It is not known, however, why children between the ages of 6 and 14 years are less susceptible.

Worldwide, TB affects men more often than it does women (60-70%). This higher prevalence has been attributed to differences in social habits. Not all individuals are at the

same risk of developing TB disease once infected. Several risk factors have been identified that are known to facilitate the development of the disease. These factors imply a greater or lesser degree of immune deficiency, with up to a 1000-fold increase in the risk of developing TB as compared with normal, immune-competent individuals. For example, the relative risk of developing active TB is 50-100 in HIV infection while in heavy smokers is about 2-4; silicosis is 8-34 compared to normal population.

2.3 Sputum Smear Conversion

Sputum smear conversion refers to a condition when a pulmonary TB patient who is positive for acid fast-bacilli becomes negative by the action of appropriate anti-TB drugs. Smear microscopy remains the first priority for diagnostic services within national TB programs in high-prevalence countries where resources are typically limited. [21] Studies have however shown that in countries where limited culture and sensitivity studies for mycobacteria are available, sputum microscopy at two months may be a critical determinant of high and low risk patients for treatment failure. Monitoring tuberculosis patients during treatment is vital in order to establish patients' treatment outcomes and to measure the national program effectiveness.

Sputum smear conversion may be carried out either by sputum culture, as in developed nations or sputum smear microscopy, in low resource settings. The correlation between sputum AFB smear and culture is generally good, although there are reports on the poor correlation of smear and culture during treatment and the unreliability of smear for declaration of failure. [22, 23] One researcher recommended the correlation of sputum smear conversion studies with sputum culture to review the impact of treatment in near future.[16]

More of such culture studies had been carried out in the last few years instead of smear conversions or in combination. [24, 25, 26]

Being a programmatic requirement in monitoring treatment at the end of intensive phase, when important decisions are taken on whether to proceed to the next phase of treatment or add additional four weeks for the intensive phase, or even predict the outcome of treatment success in a cohort of patients, many studies on sputum smear conversion have been carried out. Most of these studies are based on computing the rates, time to sputum smear conversion at various points during intensive phase and factors affecting conversion. One thing that is quite clear is that among sputum positive pulmonary tuberculosis patients, persistent sputum positivity at the end of the initial two months of treatment can predict adverse outcomes. [23, 27-29] On the other hand, after conversion to a negative smear the patient is unlikely to transmit tuberculosis to contacts therefore the conversion rate may be used to determine the period whereby the patient remains potentially infectious. [19, 28, 29]

2. 3.1. Time to sputum smear conversion

Time to sputum smear conversion refers to when an individual or cohort of sputum smear positive patients become negative by the administration of appropriate anti-TB drugs. Time to sputum smear conversion is considered generally during intensive phase at two months or at three months when those who failed to convert at two months are further given additional one month. Not many studies are designed to monitor conversion on weekly basis.

2.3.2 Factors affecting sputum smear conversion

Different studies have demonstrated that specific circumstances or factors, including baseline sputum smear grades lung cavitation, smoking, a prolonged course of symptoms, larynx involvement, age of the patient , and incorrect treatment, increase the time to sputum conversion. Others are sex of the patient, presence of a BCG scar, erythrocyte sedimentation rate. [30] Some of these factors are seen as confounders by some authors when subjected to multivariate or other statistical analysis. In order words they can independently delay sputum conversion and are closely associated with other exposures that are known to cause the delay but by themselves, are not in causal pathway of sputum smear conversions. [12, 16]

Baseline sputum smear grade

This is by far the most consistent factor in sputum smear conversion studies that has been known to have a strong association with time to sputum smear conversion. In Nigeria, Lawson in a randomized controlled trial of zinc and vitamin A, as co-adjuvants for the treatment of pulmonary tuberculosis, significant predictors of time to sputum conversion were sputum smear grade and others like lung abnormality score, age, and serum C-reactive protein. [31] Kidola in Tanzania, found out that sputum grading of 3+ was a significant factor in conversion. [30] Another study in Cameroon revealed that the presence of numerous bacilli (3+) on initial pre-treatment sputum smears was also an independent predictor of non conversion of positive sputum smears after two months of anti-TB therapy. [32] In The Gambia, after two months of intensive phase, the low baseline sputum smear was noted to increase the rate.[33] Another study stated that a high Ziehl-Neelsen

stain score was an independent predictive factor in sputum smear conversion after two months [34]. Wang concluded that patients with higher smear grading had a longer time to sputum smear conversion. [35] Singla noted that numerous bacilli on initial sputum smear examination was a significant factor associated with persistent sputum positivity at the end of 2 months of treatment. [36] A study on sputum culture also revealed that smear grading predicted second month culture conversion, relapse and also recurrence. [25]

Lung cavities

During active disease, the granuloma center become liquefied (necrosis or abscess) by an unknown process forming cavities, which then serves as a rich medium in which the now revived bacteria can replicate in an uncontrolled manner. Some cavities are joined by the air passages, bronchi, and this material can be coughed up. [37] These events flourish in conditions where immune system becomes weakened by immunosuppressive drugs, HIV infection, malnutrition, aging, or other factors.[10, 16, 25, 26, 29, 38]

In one study, there was no association even though half of the patients had cavities in their lungs. The association of cavitations and sputum conversion rate at two months was not statistically significant. [16] However, several other studies found that the presence of lung cavities in patients with pulmonary tuberculosis was associated with the delayed sputum rate or persistent smear positivity following DOTS. [11, 34, 36, 39] Similarly, two researchers in South Africa, in sputum culture, found the statistical association in extensive parenchymal involvement and cavities as predicting sputum conversion. [25, 26]

Smokers

Smoking rates are highest among poorer and less educated communities where members are less likely to seek early medical care leading to chronic cough and thus cavitary disease. [40] Smokers are more likely to have clinical symptoms of tuberculosis such as cough and dyspnoea, as well as cavitary lesions, compared with non-smokers. [24, 41, 42]

2.3.3 Sputum smear conversion Rates

According to National TB Control Program of Nigeria, Sputum smear conversion is used as a tool to monitor or measure early success of treatment at seventh or 12th week of intensive phase during DOTS, when sputum conversion rate is calculated. At the 20th week of treatment, if a patient failed to covert, such a patient is then categorized as treatment failure. Sputum smear conversion rate is thus a useful treatment indicator during intensive phase. The conversion rate is defined as the number of negative results divided by the number of new smear-positive patients for whom the 2-month follow-up examination was performed. [6, 19] A lot of researches had been done in sputum smear conversion globally but more in high burden TB countries.

In some Asian countries, India for example, sputum smear conversion rate by was 74.2% for new sputum smear positive cases and 76.1% in all cases or category II, while 91% was the rate obtained in another. [43, 44] In Bangladesh, 85% converted during DOTS. [27]

In Oman, South West Asia, it was 78.6% after intensive phase. [16]

In the Leningrad Region of the Russian Federation, conversion rate at the end of intensive phase was 82.8%. [45]

In the Sub-Saharan Africa, the east African countries of Uganda and Tanzania had the following conversion rates, 76% and 72.9%kidola respectively. [12, 18]

Studies in some West African countries like Burkina Faso had conversion rate of 80.3% in 2003 while The Gambia had 90% in a data analysis. [17, 33]

Nigeria recorded after eight weeks of treatment, 68% sputum smear conversion, and the median conversion time was 6.5 weeks. [31]

Sputum smear conversion rates in HIV Co-infection

Most researchers on sputum smear conversion in HIV co-infected patients showed that there was no difference in conversion rates with HIV negative PTB patients. At week eight, a research in Tanzania had 98.6% in HIV positive and 97.0% in HIV negative though with a slight variation at week two at 72.8% and 66.5%. [39] Again, in Tanzania, another study conclude that there was no association as HIV positive had 81.5%, while HIV negative was 72.9%. [12] In Uganda, among HIV seronegative patients, conversion to a negative smear status occurred in 76% persons compared to 78% in HIV seropositive patients. This difference was not statistically significant.[18] However Dominguez-Castellano, had higher conversion rate in HIV co-infection, associated with a shorter time to sputum conversion and statistically significant. [29]

In Togo, HIV infected TB patients were more susceptible to treatment in the first six weeks of intensive phase than the HIV negative patients: 87.4% and 24.5% in week two while in week six, it was 94% and 61.8% but 100% and 96.7% in week eight respectively for each of the stated weeks. [46]

In Nigeria, at Infectious Disease Hospital Kano, Mukhtar determined sputum smear conversion rate in only HIV positive patient, being an important inclusion criteria, with a 91% conversion rate at two months of intensive phase. [47]

2.4 Staining Technique

2.4.1 ZN staining technique

Sputum smear positive patients are the most potent sources of transmission of *M. tuberculosis* in the community. The sensitivity (proportion of actual cases identified) of sputum smear microscopy in the diagnosis of pulmonary tuberculosis is far from perfect. With a diligent technique, over two thirds of all adults with culture-confirmed pulmonary tuberculosis can be identified in this way in routine services in high-prevalence countries, but the proportion may be lower among patients co-infected with the human immunodeficiency virus (HIV), and is always substantially lower among young children. However, its sensitivity in identifying transmitters of tubercle bacilli is in excess of 80%, whatever the setting, as sputum smear-positive patients are much more likely to transmit *M. tuberculosis* than patients negative on sputum smear examination. Thus, sputum smear microscopy is one of the most effective and efficient tools for case finding in national tuberculosis control program: it identifies the cases that should have the highest priority in tuberculosis control. Moreover, sputum smear microscopy is highly specific in identifying acid-fast bacilli, which in high-prevalence countries are almost always diagnostic of tuberculosis.

In most areas of the world, direct microscopy for acid-fast bacilli (AFB microscopy) is the primary diagnostic tool for the detection and control of tuberculosis (TB). The Ziehl Neelsen technique, performed directly on pulmonary specimens, is an effective method to detect TB cases, assess response to treatment and monitor cure rates. [8]

The standard for the collection, storage and transport of sputum specimens and for the examination of sputum smears by direct microscopy must be strictly followed to arrive at reliable results.

As a crucial component of TB control, direct AFB microscopy must be performed appropriately using standard methods to accurately determine and report whether a patient is acid-fast smear positive or negative. To ensure that this diagnostic test is accessible to as many patients as possible, direct AFB microscopy is performed in many rural and urban peripheral laboratories and IUALTD/WHO guidelines on scoring the AFB grades. [9, 48]

The principle of the test is based on the fact that primary stain penetrates cell wall and intense decolorization does not release primary stain from the cell wall of AFB. Color of AFB is based on primary stain while counterstain provides contrasting background.

Mycobacterial cell walls contain a waxy substance composed of mycolic acids. These are ß-hydroxy carboxylic acids with chain lengths of up to 90 carbon atoms. The property of acid

fastness is related to the carbon chain length of the mycolic acid found in any particular species.

Basic fuchsin binds to negatively charged groups in bacteria. The mycolic acid (and other cell wall lipids) presents a barrier to dye entry as well as elusion (washing out with solvent) and this is partly overcome by adding a lipophilic agent to a concentrated aqueous solution of basic fuchsin and partly by heating.

2.4.2 Fluorescence microscopy with auramine O

Fluorescence staining utilises the same approach as Ziehl-Neelsen staining, and if the number of daily specimens to be examined exceeds 30 per technician, and if electricity is continuously available, fluorescence microscopy is indicated. It has a slightly better sensitivity and the same specificity as Ziehl-Neelsen staining, in detection of specimens with a positive culture. The main advantage of fluorescence staining is that slides can be examined at a lower magnification, allowing the examination of a much larger area per unit of time. Therefore, the technician is less fatigued, often resulting in a higher sensitivity especially when the workload is high or the smears contain few acid-fast bacilli. Its main disadvantage is its cost: a fluorescence microscope costs at least five times as much as a bright-field microscope. [8]

2.5 Impact of HIV Infection on TB

Undoubtedly, HIV infection has greatly complicated the problem of TB control in the world. The virus selectively destroys or alters the function of those immune cells that defend the host against TB bacillus. It is estimated that substantial areas of the poorest countries will lose their youngest populations in the coming decades.

Africa has 28% of all TB/HIV case globally and contributes 33% of all cases in Africa. Epidemics of HIV/AIDS have increased the tuberculosis (TB) case-load by five or more times in East Africa and southern Africa. WHO gave a measure indicating that HIV-positive people are about 20 times more likely than HIV-negative people to develop TB in countries with a generalized HIV epidemic.

TB and HIV are difficult to separate from each other as both have an impact on one another. While HIV increases the risk of developing active TB, TB on other hand adds to the risk of progression from HIV to AIDS. Dual infection with HIV/AIDS and TB has contributed largely to an increase in number of new TB cases worldwide and remains a major cause of death in an HIV infected person. [4,49]

Researches across Nigeria shows that in Ibadan, 32.8% HIV-positive patients had active pulmonary TB. In Zaria, 30% of HIV-positive patient had PTB. At national level, Nigeria has 27% TB/HIV co-infection. [50, 51]

2.6 TB Control

The recognition of TB burden and declaration as an emergency marked the beginning of a new approach to the control of TB, when the World Health Assembly (WHA) resolution recognized TB as a major public heath problem. [5]

2.6.1 Launching DOTS 1994

A WHO report with clear objective to reduce mortality, morbidity and disease transmission while averting the development of resistance. The strategy to achieve this is through the provision of short-course chemotherapy, under direct observation, to at least all identified smear positive cases (the source of the infection). Two targets were set: 85% cure rate and 70% detection rate of sputum smear positive PTB. The framework has a policy package of five elements: government commitment and sustained financing; case detection by predominantly passive case-finding through quality assured bacteriology; standardized short-course chemotherapy, to at least all confirmed sputum smear-positive provided under proper case management conditions; a system of regular drug supply; and a monitoring system for program supervision and evaluation. [6]

The slow progress of DOTS implementation in most countries with a high burden of TB was a concern. A comprehensive multi-sectoral approach to TB control was recommended. Subsequently, in late 1998, a global partnership was launched linking

health, social and economic sectors in the fight against TB: the partnership, called "Stop TB Initiative", In the year 2000, a high level Ministerial Conference of Ministers of Health and Finance of the top 20 high burden countries endorsed the "Stop TB Partnership" in what is called the "Amsterdam Declaration. [52]

The increasing impact of HIV on the incidence of TB especially in Sub-Saharan Africa calls for new partnerships and approaches. A surge in drug-resistant forms of TB in the former Soviet Union and several other parts of the world requires effective implementation of the DOTS strategy to prevent occurrence of new multidrug-resistant (MDR-TB) cases as well as measures to cure existing MDR-TB cases. General public health services need to enhance their capacity to sustain and expand DOTS implementation without compromising the quality of case detection and treatment. Community involvement in TB care and a patient-centered approach need emphasis and promotion to improve both access to and utilization of health services. Collaboration and synergy among the public, private, and voluntary sectors are essential to ensure accessible and quality-assured TB diagnosis and treatment. All these challenges called for the update and expansion of the framework known as expanded DOTS framework with reinforcement of the five elements of DOTS.[7] There is also DOTS Plus for the management of multidrug resistant TB (MDR). [53] The success story of DOTS over the years since it was first lunched in 1995 is reflected in the reductions in disease burden. A cumulative total of 36 million TB patients were successfully treated in DOTS programs, and up to 8 million deaths were averted. [4] The global detection rate under DOTS was 63 per cent in 2007 and its success rate for treatment was 85 per cent in 2006.

2.6.2 Stop TB Strategy 2006:

"Building on and enhancing DOTS to meet the TB-related Millennium Development Goals" The new Stop TB Strategy is merely the successor of DOTS. It was launched in 2006 to build on and enhance on what DOTS is doing to meet the TB-related Millennium Development Goals through 'The global plan Stop TB 2006-2015'. It has a six-point strategy: DOTS expansion and enhancement; addresses TB/HIV, MDR-TB and needs of poor and vulnerable groups; health system strengthening based on PHC; engage all care providers, (Private-Public mix); empower people and communities with TB through partnership; and enable and promote research.

The Millennium Development Goal (MDG) number six and target eight is meant to halt and begin to reverse the incidence of TB by 2015 relative to 1990. [54]

This goal is linked to Stop TB Partnership targets: by 2005, detect at least 70% of new sputum smear-positive cases and cure 85% of such cases; by 2015, reduce TB prevalence and deaths by 50% relative to 1990; and eliminate TB by 2050 as a public health problem, (1/1,000,000). Factors known to be also important to this endemic disease form part of MDG and are important to be addressed as well.

Of these factors, only improvement in socioeconomic conditions (affording an annual reduction in infection risk of 4-6%) and adequately administered anti-TB therapy (offering an additional annual risk reduction of 7-9%) have been shown to halt the progression of TB. In contrast, poverty, HIV, massive immigration from highly endemic zones, the non-existence or ineffective establishment of National Tuberculosis Control Programs, and demographic growth increase the prevalence of TB in many parts of the

world. In short, the Stop TB Initiative is hinged around the Stop TB Strategy with DOTS at its centre while the MDG and Stop TB Partnership are programs enhancing it. [54]

2.6.3 Stop TB Partnership

The Stop TB Partnership was established by WHO in 1998 as a broad-based social movement to combat TB. Over 200 organizations are now signed up to the Partnership. In 2001 it launched the Global Plan to Stop TB and set targets to eliminate the disease. These are to identify 70 per cent of all people with infectious TB and ensure that 85 per cent of those detected are successfully treated, by the end of 2005, using the Directly Observed Treatment Short-Course (DOTS) strategy. [55]

2.7 TB Control in Nigeria

TB control is through NTBLCP, which was established in 1989 to provide framework for the control of TB and Leprosy in Nigeria and lunched in 1991. DOTS (1993) and Stop TB Strategy (2006) had been adopted for the control of TB in Nigeria.

A lot of progress has been made through DOTS expansion scale up plan 2006-2010:

1. All the 774 LGAs in Nigeria are implementing DOTS strategy by 2008.

2. Of the 1138 laboratories expected to provide access to AFB microscopy, 900 (79%) has been achieved in 2008.

3. Of the 5081 DOTS centres expected in 2008, 2472 (54%) have been established.

4. There are 304 (42%) DOTS centres with HIV/TB collaborative activities in 2008.

5. There is only one reference laboratory of the expected eight by the year 2008.

6. Of the 75, 372 new smear positive expected, 61% was detected in 2008.

7. Of the 150, 744 TB cases expected, 60%was diagnosed in 2008.

While treatment success rate is impressive, Nigeria remains, unfortunately, the only country among the 22 high burden TB countries with lowest case detection rate (CDR) with grave implication in her efforts to effectively control TB epidemic.

Chapter 3 **METHODS AND MATERIALS**

3.1 Description of the Study Area

The National Tuberculosis and Leprosy Training Centre, Zaria is about four kilometers from Zaria town, along the old Zaria – Kaduna road, at a village called Saye in Dutse Aba council ward of Zaria Local Government Area (LGA). The Centre was established in January, 1991 to perform functions in respect of the National Tuberculosis and Leprosy Control Program (NTBLTCP). The functions are manpower training, case management (140-bed hospital) and operational research, all relating to TB and leprosy.

For example, in 2007, from records review, a total of 1611 TB suspects attended Chest Unit out of which 447 (27.7%) TB patients were diagnosed as having all forms of TB. Of the 447 TB patients, 20 were cases of extra-pulmonary TB patients. Of the 427 PTB patients, 242(56.7 %) patients were smear-positive while 185 (43.3%) were smear-negative.[13]

Kaduna State is located in the North-West geopolitical zone of Nigeria. The State occupies an area of approximately 48,473.2 square kilometers and has a population of more than 6 million (2006 census). Zaria, the second largest city in Kaduna state after Kaduna, comprises two local government areas (LGA), namely Zaria and Sabon Gari. Zaria has the Ahmadu Bello University and its Teaching Hospital at Shika as a tertiary health institution.

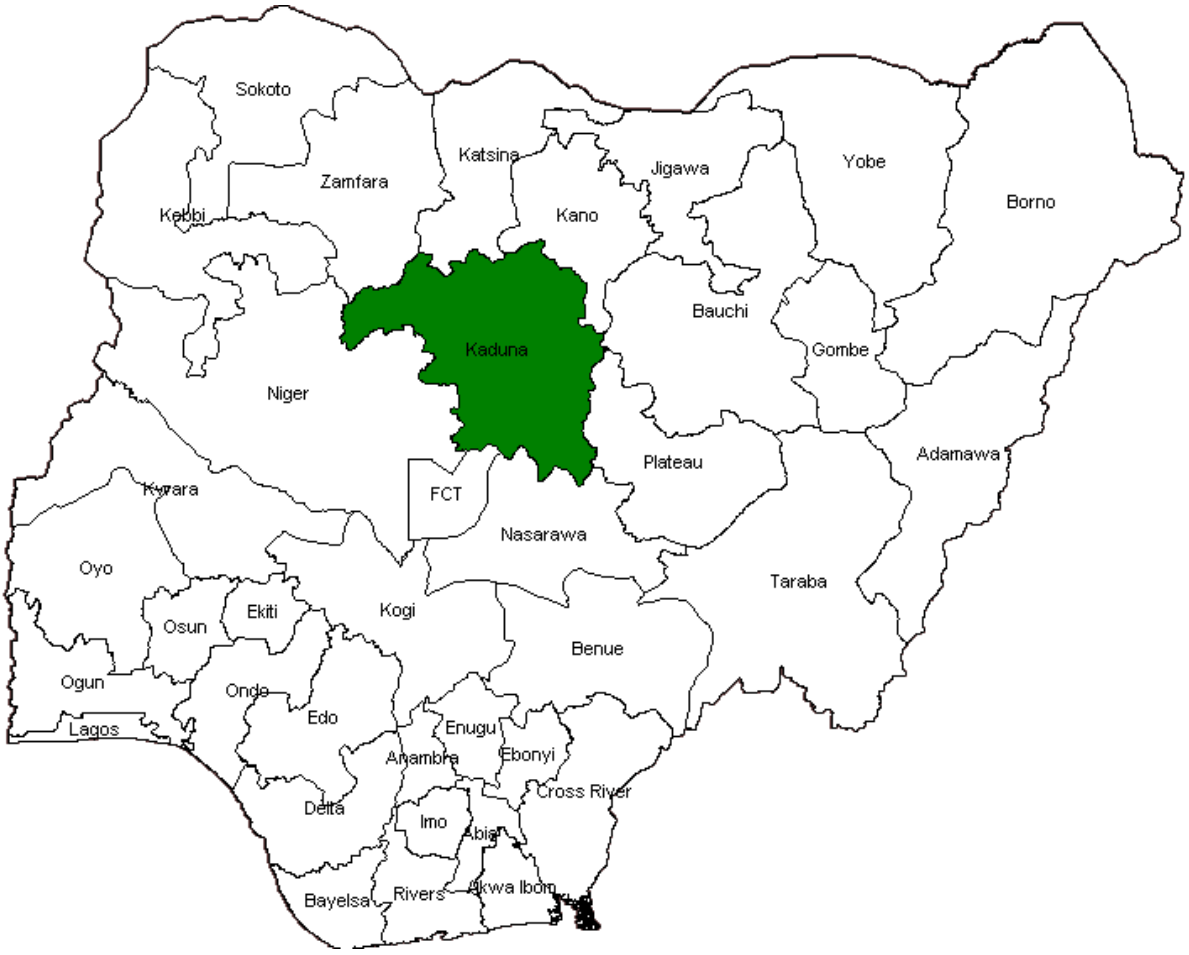


Fig 1: Map of Nigeria Highlighting Kaduna State

Zaria LGA has a projected population of about 459, 431 (2010) and was created from the old Zaria LGA along with Sabon-Gari in 1991. The predominant tribe is the Hausa and Fulani and predominant occupation is farming, producing both commercial and sustenance crops. Islam is the major religion. The Zaria city is the seat to the Emir of

Zazzau emirate. There are several gates (Kofar in Hausa) leading into Zaria city, connoting that it was once a fortified city. The most popular of them is kofar Doka, which leads to the emir's palace and LGA secretariat. Others are kofar Gayan, Jatau, Kibo, kona and Kuyanbana.

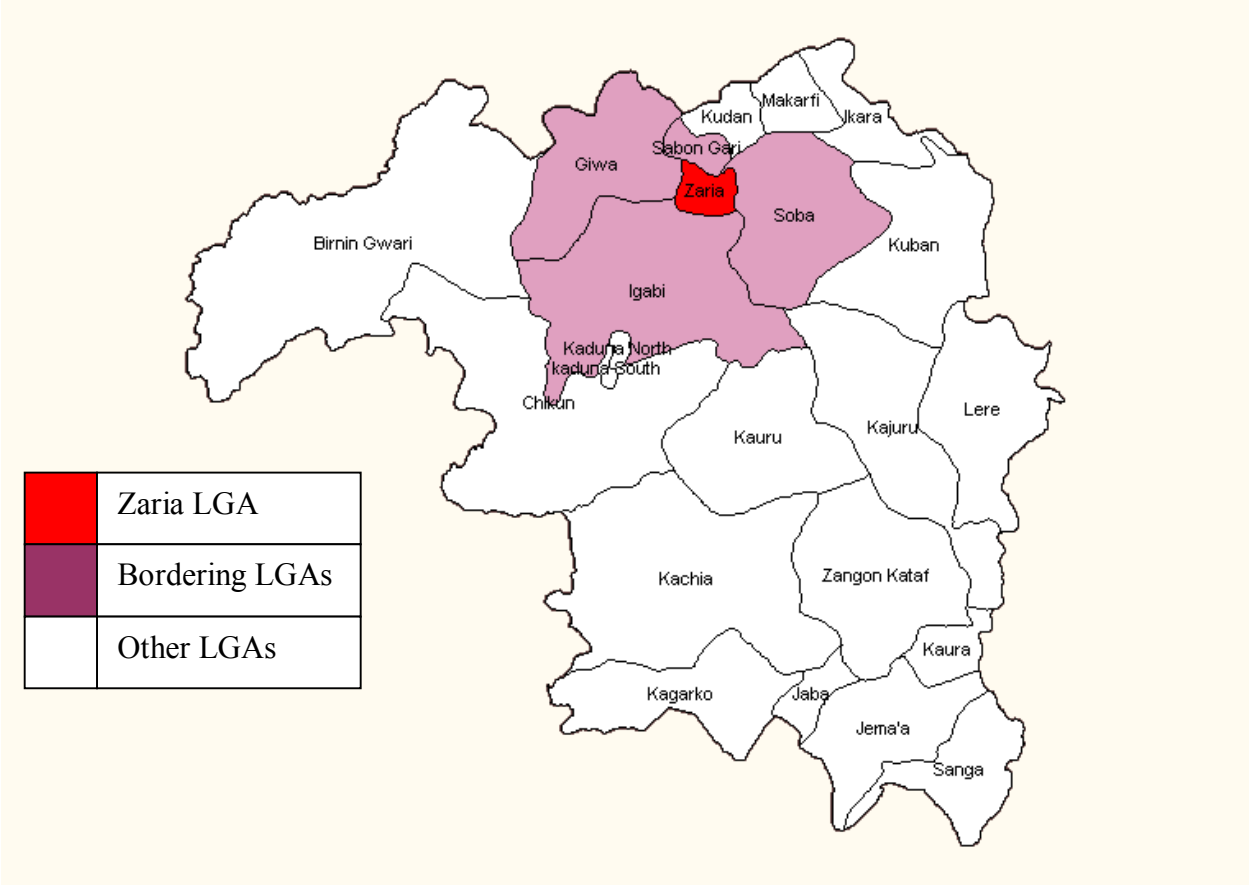


Fig 2: Map of Kaduna State Highlighting Zaria LGA and her Immediate Neighbors

There are seven DOTS centers in Zaria LGA; NTBLTC is among five which have TB microscopy facility. These are: NTBLTC Saye, TB annex, ABUTH Zaria, Gambo Sawaba General Hospital Kofar Gayan, Zaria Clinic and Muslim Specialist Hospital, Dan

Magaji. NTBLTC Saye was selected for this study through simple random sampling by balloting.

3.2 The Study Design

A longitudinal design was used for this study.

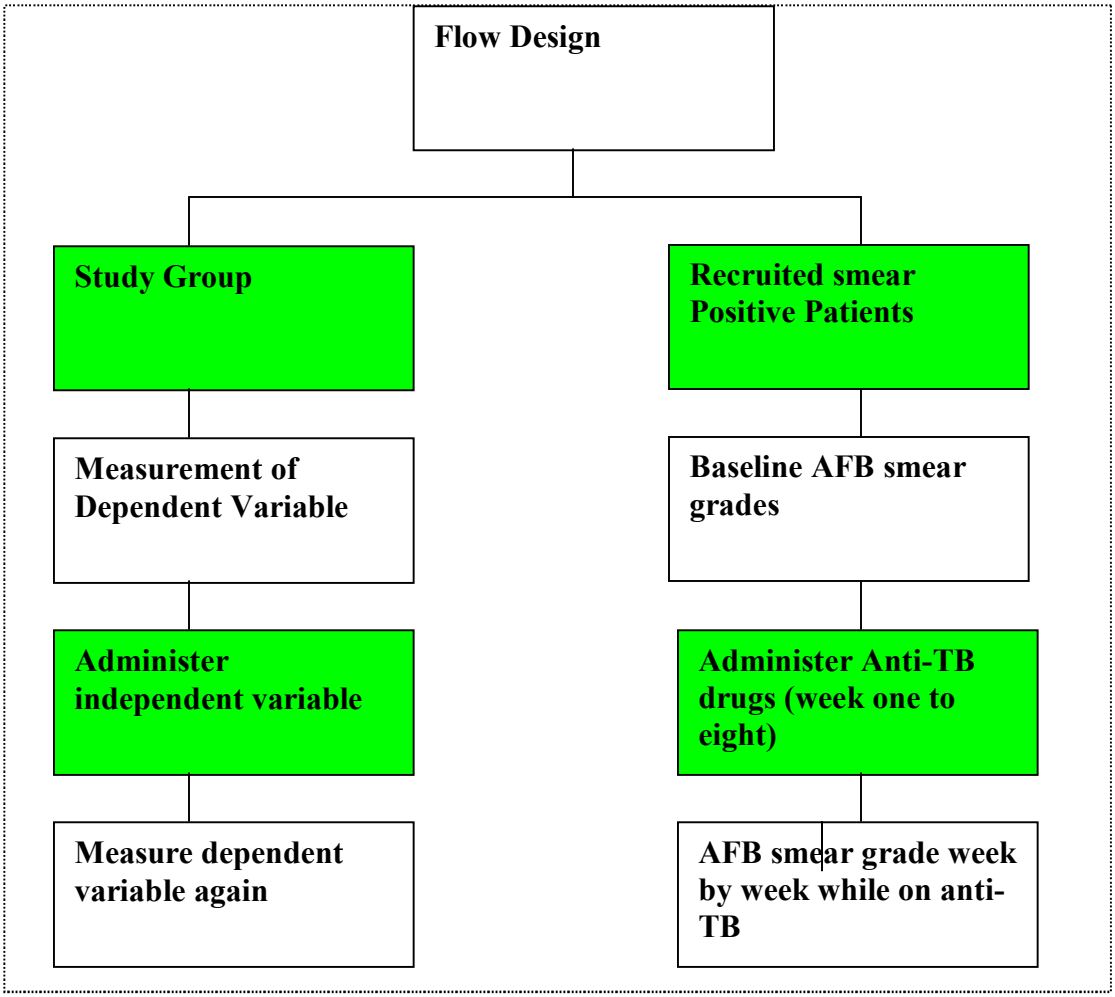


Fig 3: Schematic flow design of the study

3.3 Study Population

3.3.1 Inclusion criteria

TB sputum smear positive patients were recruited in this study in the first half of 2010. They were patients above 10 years who were clinically observed in NTBLTC Zaria.

3.3.2 Exclusion criteria

Patients transferred out, those that absconded and children who were 10 years and below, who may not be able to produce satisfactory sputum specimen were not included.

3.4 Sample Size Estimation

3.4.1 Using sample size formula

A study population of 447 TB patients was noted in the same study site [13]. In a similar university dissertation in Tanzania the proportion that converted to sputum smear negative at the end of intensive treatment phase was 76%. [12]

By applying the study population of 447, proportion of 76% and finite population correction factor: N - n/ N-1 [14]

Solving for $n = z^2 pq / d^2 + (z^2 pq / N)$

Where:

z = reliability coefficient (1.96)

n = is sample size to be calculated,

N = study population

d = absolute precision (10%) [56]

p = is the proportion having the characteristic being measured

q = (1-p) is the proportion that lacks it.

$n = 3.84x0.76x0.24/ 0.1^2 + (3.84x0.76x0.24/ 447) = 0.7/0.0115 = 60.86 \approx 61.$

Therefore the sample size became 61 + 6 (10% attrition rate) = **67**

3.5 Sampling Technique

Being a longitudinal cross-sectional study, all the sputum smear pulmonary TB patients that satisfied inclusion criteria were recruited into the research. This took place between January – June 2010 to achieve the sample size of 67 patients

3.6 Study Instruments

Sputum smear conversion was measured by AFB in smears stained by ZN staining technique. Data analysis through patients' records: case notes and laboratory. Details of study instruments are further stated in the following data collection procedures.

3.7 Data Collection Procedures: Laboratory

Each patient was followed-up for the period of intensive phase (eight weeks) until such a patient converted by two consecutive weekly negative sputum results. All TB patients were on DOTS. Data collection commenced from January to June 2010. Patients were recruited on weekly basis though subsequent or weekly follow-up samples were collected with reference to the first date of anti-TB commencement..

3.7.1 Making a diagnosis

Sputum specimens were collected for diagnosis and follow-up as stated in the NTBLCP worker's manual. For diagnosis three samples were required: 'on the spot' sputum sample on first day, 'early morning sample' from home the next day and the third 'on the spot' sample while at the health facility. The 'on the spot' samples are supervised. Patients who were sputum smear positive regardless of their HIV status and category were enrolled into this study. Using Ziehl Neelsen staining procedure, smear results were reported as "0" if there were no AFB seen per 100 fields. If 1-9 are found in 100 fields, record the exact figure. "1+" if AFB seen were 10-99 per 100 fields, "2+" if AFB seen per field were 1-10 and "3+" if AFB seen per field were more than 10 [19,48].

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3.7.2 Follow-up samples

Follow-up samples were collected weekly for eight weeks to determine when sputum smear conversion occurs from the commencement of treatment on diagnosis through two consecutive early morning samples.

3.7.3 HIV screening

Additionally, HIV counseling and testing was done on all recruited participants. Participants were then requested, after an informed consent, to provide blood for rapid HIV screening, collected using ethylene diamine-tetra-acetic acid (EDTA) tubes. Test kits, determine with high sensitivity and Unigold, with high specificity were used in serial algorithm. Stat park was used as tiebreaker when there is discordant sample,

3.7.4 The 2007-2009 records analysis

Records analysis for three years, 2007-2009, was carried out to determine sputum smear conversion rates for each year and then cumulatively for the three years. Laboratory records and patients' case notes were used.

3.8 Data Analysis

Longitudinal study design was conducted among the recruited patients at NTBLTC Zaria from January-June 2010. Continuous variables were summarized by means, medians and standard deviation, while categorical by percentages. Statistical tests of significance such as chi square (X^2) and Fisher's exact test were applied appropriately. Univariate, bivariate, p-values and 95% confidence intervals were applied. Data entry and analysis was through Epi-Info version 3.5.1.

3.9 Ethical Considerations

Ethical clearance for this project was sought and obtained through the Ahmadu Bello University Committee on Ethics. Oral or written consent were explained and agreed by all participants and confidentiality assured by proper storage of data away from unauthorized persons or disclosure of such information other than the intended use.

3.10 Limitations

1. ZN staining technique is not very sensitive; bacillary load of 5,000-10,000/ml of sputum may be missed. This is an inherent problem of the technique. However, well trained microscopists were used for this research to minimize wrong conversion time.

2. No follow-up for those who failed to convert during the eight weeks of intensive phase for additional four weeks due to initial plan to terminate this study by eight weeks of intensive phase to meet the strict timeline for the submission of this thesis to the university. However they were routinely followed up as recommended by the National TB Control program by the hospital management team.

Chapter 4 **RESULTS**

4.1 Baseline Socio-demographic Characteristics of the Patients

Sixty seven sputum smear positive pulmonary tuberculosis patient were recruited into this study between January and June 2010, patients were from National Tuberculosis and Leprosy Training Center Saye village, Zaria. Of the 67 patients, five died before the end of intensive phase of treatment and were excluded; three of them died of extensive pulmonary complication in the second week while the remaining two co-infected patients died of poor response to treatment. The remaining 62 were finally subjected to analysis. Four patients failed to convert at the end of eight weeks of intensive phase.

Table 1 Socio-demographic Characteristics of the Study Group, NTBLTC Zaria Jan-June 2010

Variable	Category	Percent
Sex	Male	42 (67.7)
	Female	20 (32.3)
Location (LGA)	Zaria	21 (33.9)
	Sabon Gari	15 (24.2)
	Soba	6 (9.7)
	Igabi	6 (9.7)
	Giwa	3 (4.8)
	Other LGAs of Kaduna State	3 (4.8)
	Other States including Abuja	8 (12.9)
Religion	Islam	50 (80.6)
	Christianity	12 (19.4)
Occupation	Farming	23 (37.1)
	House wife	18 (29.0)
	Schooling	10 (16.1)
	Trading	4 (6.5)
	Civil Service	3 (4.8)
	Others	4 (6.5)
HIV Status	HIV Negative	47 (75.8)
	HIV Positive	15 (24.2)
Patient Category	Category 1	49 (79)
	Category 2	13 (21)

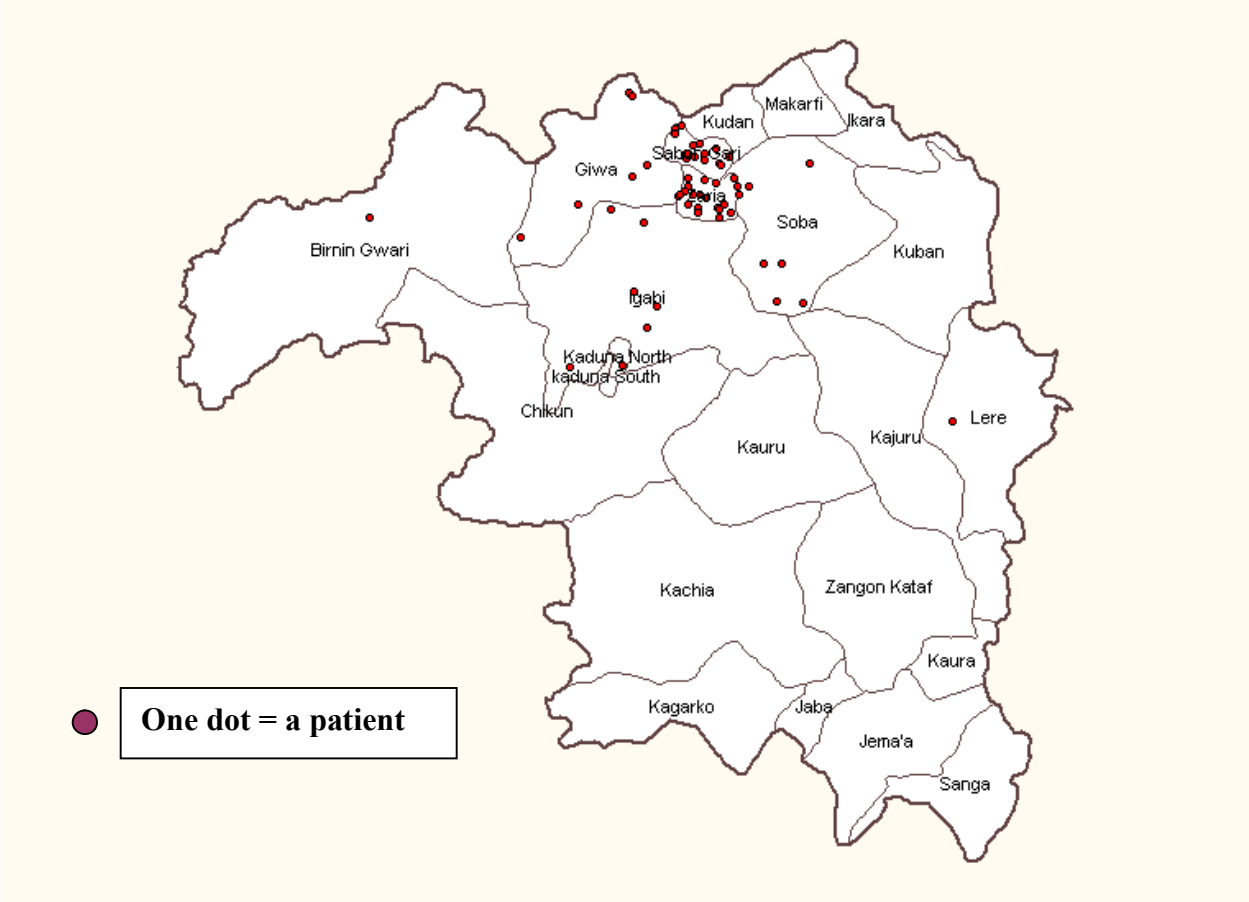


Fig 4: Map of Kaduna State Showing Distribution of Patients by LGAs, Jan-Jun 2010

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More than half (58.1%) of the patients came from Zaria municipal which is Zaria and Sabon Gari LGAs as noted by concentration of dots in these areas, (see Table 1)

Table 2 Age Distribution of the Study Group, NTBLTC Zaria, Jan-June 2010

Age Group	Freq (%)	Cum. %
16-20	11 (17.7)	17.7
21-25	8 (12.9)	30.6
25-30	11 (17.7)	48.4
31-35	8 (12.9)	61.3
36-40	12 (19.4)	80.6
41-45	5 (8.1)	88.7
46-50	2 (3.2)	91.9
=>50	5 (8.1)	100
Total	62 (100)	-

The productive age group (16-45 years) formed 88.7% of the patients.

Table 3: Cumulative Rate of Conversion by Weeks, NTBLTC Zaria, Jan-June 2010

Week	Cum. Freq	Conversion rate (cum.)
Week 1	10	15.1
Week 2	26	41.9
Week 3	44	70.9
Week 4	54	87
Week 5	57	91.9
Week 6	57	91.9
Week 7	57	91.9
Week 8	58	93.5

The peak rate of conversion was achieved by week 3; better depicted in Fig 5, the next page.

Of the 58 patients that converted, the mean time from the initiation of appropriate anti-TB drugs to sputum smear conversion was 2.7 ± 1.3 weeks, standard error (SE), 0.2 (95% confidence interval 2.3-3.1).

The overall conversion rate was 93.5%

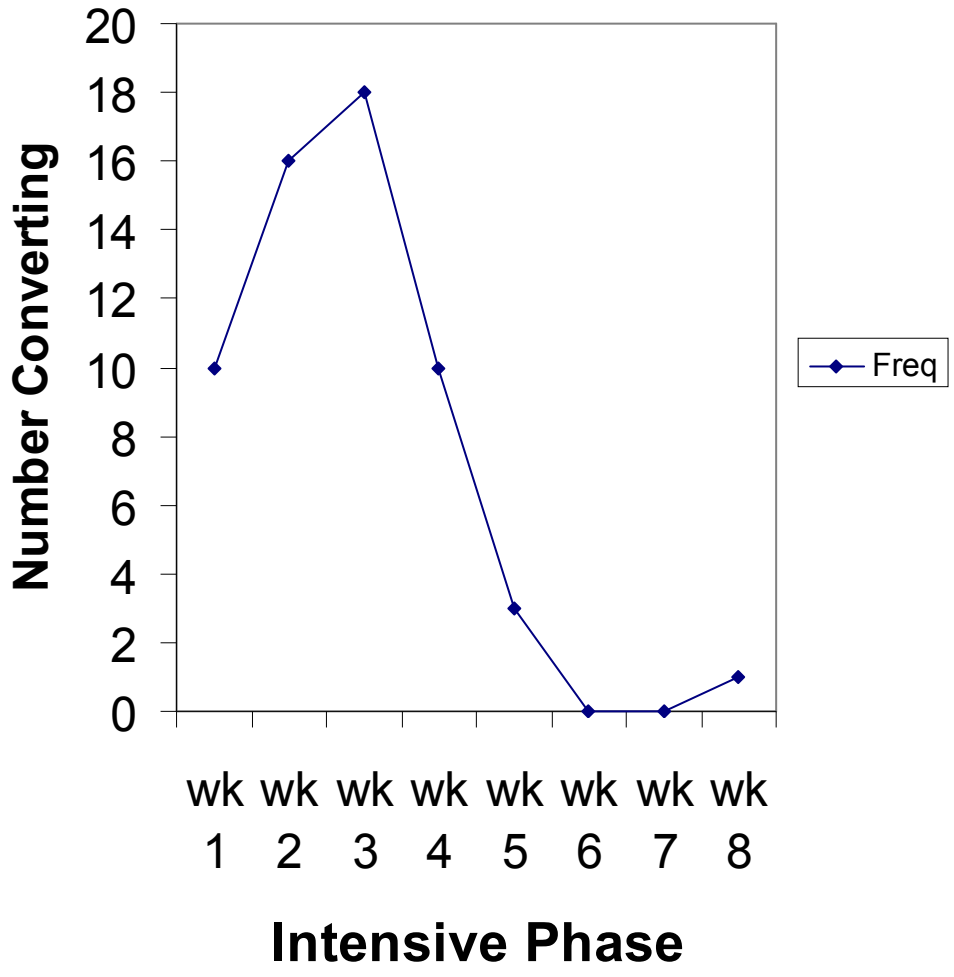


Fig 5: Weekly trend of sputum smear conversion

Note: The peak of sputum smear conversion was attained in week three at 71%. Week five represents a turning point of this study, providing sufficient answers to research questions and forming the basis for the recommendations.

Table 4: Relationship between Sputum Grades and Number converting each Week, NTBLTC Zaria, Jan-June 2010

Sputum	Number of patients converting weekly					Total
grade	Week 1	week 2	week 3	Week 4	Week 5	
≤ 1+	9	2	-	-	-	11
2 +	1	11	5	1	-	18
3 +	0	3	13	9	3	28
Total	10	16	18	10	3	**57***

* One patient that converted in week 8 was not shown on the table.
Note the effect of sputum smear grade on conversion especially in week 1 and the length of time required by various grades to achieve maximum conversion.

Table 5: Relationship between HIV Status and Conversion, NTBLTC Zaria, Jan-June 2010

HIV Status	Converted	Did not covert	% Converted
HIV Positive	15	0	100
HIV Negative	43	4	91.5
Total	58	4	--

Note: At bivariate analysis, being HIV positive or not was not statistically significant; p-value of 0.31 by Fisher's exact.

Table 6: Yearly Conversion Rates from Records Analysis, NTBLTC Zaria, 2007-2009

Year	Sputum smear conversion	
	Converted (%)	Did not convert
2007	177 (80.8)	42
2008	160 (77.2)	47
2009	162 (87.5)	23
Average	499 (81.6)	112

Note: Although there was high sputum conversion rate each year, this centre was upgraded to National Reference Laboratory with expert training in sputum microscopy and improved anti-TB logistics management system as reflected in a higher conversion rate in 2009.

Table 7: Baseline Sputum Grade and Conversion Rates from Records analysis, NTBLTC Zaria, 2007-2009

Sputum smear grade	Sputum smear conversion	
	Converted (%)	Did not convert (%)
≤ 1+	98 (89.0)	12 (11)
2+	146 (87.4)	21 (12.6)
3+	225 (74.1)	79 (26.9)

Note: The differences in proportions in various sputum smear grades were compared using chi square test (X^2) of 15.5 at degree of freedom 4, a significant statistical association with p value 0.003, was obtained indicating that sputum smear grade is a strong predictor of sputum smear conversion.

Chapter 5 **DISCUSSIONS**

There were three key findings in this study. Firstly, time to sputum smear conversion peaked at week three on appropriate anti-TB drugs. Secondly, time to sputum smear conversion was dependent on sputum grade at diagnosis. Thirdly, high sputum smear conversion rate was achieved in this study just as the review of records in the same study site. The duration of infectiousness and the consequent period of isolation which are still subjects of discussion once appropriate anti-TB is initiated as stated by some researchers have been addressed by this work. [29, 39]

Sputum smear conversion peaked at week three on appropriate anti-TB drugs. This is the hallmark of this project which sought to answer the research question about what goes on at the early weeks of intensive phase of TB management in particular and week by week account through out the eight weeks of intensive phase in general. This is closely in line with the finding by Senkoro in Dar es Salaam, Tanzania, where conversion peaked at week two. [39] **(**Table 3 and Fig 5).

In Togo, even though a comparative sputum smear conversion was done between HIV positive and negative cases, at week two of intensive phase of treatment very high conversion rate of 84.7% was recorded in HIV positive cases as against 24.5% in HIV negatives. [46] Again this finding is in line with another result which has also shown that conversion to a negative test of smear positive pulmonary tuberculosis patients during therapy does occur rapidly in most patients. [38] Similarly, the high rate of conversion achieved in week two (72.8%) by Senkoro was also recorded in this research at week

three (71%). It has been proven from this research finding and support from the work of Senkoro that about 30% of patients remained potentially infectious contrary to the belief that patients become non-infectious while on two to three weeks of standard treatment regimen as stated in the American guideline on controlling TB. [57] This study in Zaria, Nigeria and Dar es Salaam, Tanzania are the most recent researches on time to sputum smear conversion in which strikingly similar mean time to sputum smear conversion around two and three weeks on initiating appropriate anti-TB drugs was recorded

The mean time to sputum smear conversion recorded in this study was the lowest when compared with other researchers (2.7 weeks or 19 days), indicating early sputum smear conversion. The closest to this study was that work done by Edward Telzak in New York whose mean time to sputum smear was 23 days while Dominguez-Castellano was at 22 days. An earlier study in Nigeria had the highest mean time of 6.5 weeks followed by another study in Spain with 5.6 weeks. [10, 11, 29, 31]

The uniqueness of this project work has been that of offering weekly account of the conversion rates unlike the work of some researchers who looked at conversion rates grossly at first and second month. [15, 16] The fifth week of treatment has therefore thrown more light on time to sputum smear conversion as almost all the patients, 91.9%, converted. Weeks six and seven did not produce any patient converting and just one in week eight. It may be tempting to caution here that the last patient who converted in week eight may be an anomaly as a case of non-conversion after all, as the study has as one of its limitations of not exceeding eight weeks, thereby making an important point for

week five in this study. This could be a turning point in the study between early and late findings on weekly basis to press forward a hypothesis that most patients during the intensive phase of treatment convert by week five.

Bwari in India and Dembele in Burkina Faso considered the high rate of conversion in their separate studies as been the result of effectiveness of DOTS. [15, 17] In the study group, the conversion rate was similar with a study conducted in Bosnia, 93% and 91% in India.[44,58] Strikingly too, is very close result in Infectious Disease Hospital (IDH) Kano, Nigeria, where 91% of solely HIV positive patients converted at the end of intensive phase. [47] It is logical to argue here that at week eight of intensive phase, the difference in sputum conversion between HIV positive and negative cases is not significant as exemplified in a study in Togo and Tanzania [39, 46] Improvements in case management under Nigerian DOTS may be a reason for even a much higher rate of sputum smear conversion noted at the end of intensive phase, 93.5% when compared to any of the conversion rate in the three year records review in the same facility. One of such recent improvement is the Logistic Management Information System (LMIS) which provides adequate information on consumption and distribution of TB drugs at all levels, leading to adequate and uninterrupted distribution of supplies thereby addressing the rampant stock-outs syndrome in DOTS centers. The LMIS is among the USAID program achievements in Nigeria TB control. [59] Secondly, the NTBLTC Zaria laboratory was upgraded in 2007 to the status of National Reference Laboratory with the provision of expertise and equipments by Center for Disease Control and Prevention Atlanta and Institute of Human Virology Maryland United States of America. Gains from this may be

seen as reflected by improvement from the 2009 data review with conversion rate of 88% and that of this project work in 2010 being 93.5%.

Baseline sputum smear grades are noted to affect the time to sputum smear conversion, relating inversely with conversion. The heavier the sputum smear with AFB at time of diagnosis, the lower the time to conversion and vice versa. This was well illustrated in this research work. Almost all patients on the baseline sputum grade of ≤1+ converted by week one, just one converted in the 2+ and none for the 3+ categories. By week two, all those patients with ≤1+ baseline grade had converted while those with 3+ category all converted lately by week five. Similarly, the rate of conversion was noted to be higher (90%) at lower sputum grade of ≤1+ by week one while an even lower conversion rate (72.3%) was achieved by week three for the sputum grade of 3+. Thus a graphic explanation by the findings in this study group at univariate analysis, backing baseline sputum AFB grades as a determinant of time or rate of conversion has been presented, (Table 4.6). This study shares similar view with other researchers who noted that sputum conversion rate is affected by the baseline sputum smear grade. [10, 11, 16] Horne David in USA noted that the initial smear grade was the strongest predictor of time to sputum smear and culture conversion in pulmonary TB patients and concluded that it may be a useful predictor for programmatic planning especially isolation and patient counseling. [60] Similarly, a host of other researchers implicated sputum smear pre-treatment grades as a significant and independent predictor of sputum smear conversion and the outcome of treatment success.[25,30,31,34-36] Apart from initial baseline sputum grade, and other researchers went ahead to implicate other factors that influence time or rate of conversion

as duration of illness and lung cavitations. These two factors will actually determine the sputum AFB quantification at diagnosis[10, 11, 29 38] The process of cavity formation for example, is due to extensive necrosis of lung parenchyma eroding into bronchi of caseous material with high bacillary load and coughed up as sputum which in turn is a function of duration of illness. [37]

The HIV status, as it relates to sputum smear conversion, was found in this study as not being a statistically significant determinant for sputum smear conversion rate at bivariate analysis. However, at univariate analysis, the 100% conversion rate for the HIV positive patients was significant when compared to 91.4% for the HIV negative patients. This was comparable to the work of Senkoro in Tanzania, who also had a significant result at univariate analysis but not at multivariate analysis. [39] Bwire, in South-East Uganda, also had similar result where 76% conversion rate in HIV negative and 78% rate in HIV positive patients was not statistically significant. [18] In Kinshasa, Zaire, no difference was observed in sputum smear conversion rate between HIV seropositive and HIV seronegative patients (87.6% vs 88.5% after two months. [61] In Togo, the difference was great in HIV positive and HIV negative in week two at 87.4% to 24.5% but virtually vanished by week eight at 100% and 96.7% [46]

Another researcher however came to conclusion that HIV positive patients tend to have a higher conversion rate as judged by the radiological evidence that they have less lung cavitations. [29]

The data analysis at NTBLTC, Zaria for 2007, 2008 and 2009 revealed the corresponding conversion rates of approximately 81%, 77% and 88% respectively. The high sputum

smear conversion rate recorded in the data analysis was similar to some retrospective research work. For instance, the conversion rate of 81% for 2007 was comparable to 82.9% in Burkina Faso and 82.8% in Russia Federation [17, 45] but lower than 84%, a finding in India. [15] The 2008 record review was similar to the work by Kidola and Panjakar in which the conversion rate was 76% and 78.6% respectively. [12, 16] In like manner, the 2009 data review though slightly higher, was comparable with the finding in Bosnia when 1998 record review had 89.5% and to the finding in Bangladesh at 85%.[27, 45] Thus the data analysis for three years in same project site revealed a high sputum smear conversion rates with an average of 82%, but short of 93.5% for the this project work. Reasons could be higher number of subjects involved in data analysis resulting in a more representative analysis. Secondary, the high conversion rate could be accounted for by prepositioned quality anti-TB drugs to forestall occasional stock-outs, patient compliance and no defaults. During stock-outs, patients shop for anti-TB drugs in the open market, often ending up with sub-standard drugs. Thirdly, the author of this project in his previous data analysis in the study site came out with high rate of unfavorable treatment outcome for TB management. In particular, the high default rate of 14.9% out of the total 32.2% of unfavorable outcomes was recorded. [13] This is known to impact negatively by causing drug resistance and then poor conversion rates. Treatment default was not recorded in this study.

Chapter 6 **CONCLUSION AND RECOMMENDATIONS**

6.1 Conclusion

This study offers new insights into the time to sputum smear conversion, especially as it occurs early and at high percent by third week and almost complete by the fifth week with overall high sputum smear conversion rate of 93.5%. These are good outcomes of effectiveness of the DOTS program in this study and may offer a rethink of duration of admission policy or isolation and a tool for patients counseling during the intensive phase of DOTS for TB control, at least, in this health institution.

6.2 Recommendations

1. FMOH/NTBLCP: A national survey to determine the time to sputum smear conversion is necessary in a further study to substantiate the thoughts on reducing the duration of DOTS to five weeks for TB control in the country
2. NTBLTC Zaria: As an institution charged with the responsibilities of case management and operational research relevant to TB control and prevention, the management should plan and individualize hospital stay according to baseline sputum grades for each patient.
3. Similarly, NTBLTC Zaria should routinely carry out conversion test by the end of fifth week instead of the seventh week to pave way for early discharge and linkage to DOTS centers closer to these patients.

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