SURVIVAL PATTERN OF TB/HIV PATIENTS ON TREATMENT AT FEDERAL MEDICAL CENTRE, IDO – EKITI. EKITI STATE, NIGERIA.

BY

Ayodeji Theophilus AYODELE

B.Tech. INDUSTRIAL MATHEMATICS (AKURE)

MATRIC NO: 168261

A DISSERTATION IN THE DEPARTMENT OF EPIDEMIOLOGY AND MEDICAL STATISTIC, SUBMITTED TO THE FACULTY OF PUBLIC HEALTH, COLLEGE OF MEDICINE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (MEDICAL STATISTICS) OF THE UNIVERSITY OF IBADAN

MARCH, 2014

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DEDICATION

This research work is dedicated to the Almighty God that gave me the enablement to start and complete this programme in record time and to my Late mother Mrs Beatrice Ayodele.

ACKNOWLEDGEMENT

My Saviour, Jesus Christ, who in His amazing love and unfailing mercy gave me the strength to complete this dissertation. Glory be to Almighty God for his inspiration, protection, provision and grace throughout the course of the programme.

I wish to express my unreserved gratitude to my supervisor Prof. E.A. Bamgboye for not just being a supervisor but also a father. His unrelenting constructive criticism and corrections have unveiled my eyes to the dynamics of research.

So long as the Earth remains, seed time and harvest shall not cease. Even as he has sown seeds of advancement and progression in my life, may God cause him to reap in abundance.

I wish to express my profound gratitude to my beloved wife, Busayo Ayodele, for her understanding and co-operation throughout the duration of this programme. I equally want to appreciate my lovely daughter Gold, for coping with daddy's absence. My appreciation also goes to my parents Mr and Late Mrs Ayodele for their financial assistance and relentless prayers. I can but appreciate my amiable brothers and sisters Moses Ayodele, Kehinde Ayodele, Mr Dickson Idowu, Mrs Betty Ogunniyi and Olori Tayo Ayo – Ajayi for their moral and financial support.

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May God bless as many that their names are not mentioned but contributed to the success of this project.

ABSTRACT

Background: Tuberculosis (TB) and HIV co-infection remains a major public health concern worldwide. In spite of different initiatives implemented to tackle the disease, many countries have not reached TB control targets. One of the major reasons for this failure is attributed to its relationship with HIV infection. The aim of this project is to evaluate effect of ART on the survival of TB patients with HIV co-infection.

Methodology: A retrospective cohort study was conducted to compare the survival between HIV/TB patients with and without ART treatment during a twenty-four month ART period. HIV/TB patients' status was ascertained and followed up for a period of 24months. Death was taken as an outcome of interest. All patients with HIV/TB treatment outcomes other than death were considered as censored. Cox proportional hazard regression model was used to determine the hazard ratio (HR) of death for each baseline predictor.

Result: Three hundred and forty –four TB/HIV co-infected patients were followed up for a period of 24months. Two hundred and eighteen HIV/TB co- infected patients were on ART while one hundred and twenty-six HIV/TB co infected patients were on Cotriomoxazole prophylaxis therapy (Non ART) as the control group. Sixty-seven HIV/TB co- infected patients death occur at the end of the follow up study. Thirty patients were from ART group while the remaining Thirty- seven patients were from Cotriomoxazole group. HIV/TB co-infection patients not on ART were two times more likely to die than those on ART after adjusting for other variables, (adjusted Hazard Ratio (AHR) =1.65, p = 0.013). HIV/TB patients who were not on ART had shorter survival time (Log rank test= 17.34, df= 1, p< 0.001).

Conclusion: Mortality was substantially higher among HIV/TB co- infected patients who were on Cotriomoxazole prophylaxis therapy, especially during the intensive phase. Higher death rate was demonstrated in HIV/TB patients with CD4 counts less than 200. Targeted and comprehensive management of TB and HIV with a strict follow up should be considered through the entire TB and HIV treatment period.

CERTIFICATION

I certify that this project was carried out under my supervision by AYODELE Ayodeji Theophilus, in the Department of Epidemiology and Medical statistics, Faculty of Public Health, University of Ibadan.

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14/8/2014

Supervisor

Prof. E. Afolabi Bamgboye, PhD (Lond.)

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MEANING OF ABBREVIATION

HIV – Human Immune - deficiency Virus

AIDS – Acquired Immune deficiency syndrome

TB – Tuberculosis

WHO – World Health Organization

PLHIV – People living with HIV/AIDS

GHAIN – Global HIV/AIDS Initiative Nigeria

NTBLCP – National TB and Leprosy control Program

DOTS – Direct Observed Therapy Strategy

M & E – Monitoring and Evaluation

ART – Antiretroviral therapy

HTC – HIV testing and counseling

XDR-TB – Extensive drug-resistance TB

DST – Drug Susceptibility

IRS – Immune reconstitution syndrome

PTB – Pulmonary Tuberculosis

CPT – Cotrimoxazole preventive therapy

VCT – Voluntary counseling and Testing

IPT – Isoniazid Preventive Treatment

LGA – Local Government Area

NNRTIs – Non – nucleosides reverse transcriptase inhibitors

PIs – Protease inhibitor

TB – HIV – Tuberculosis and HIV co – infection

CHAPTER ONE

INTRODUCTION

1.1 Background to the study

The relationship between HIV and tuberculosis (TB) epidemics is well established. HIV is a key risk factor for the reactivation of latent Mycobacterium tuberculosis infection and increases the risk of recurrent tuberculosis (Ko-renromp et al, 2003) making TB the leading cause of death among HIV-positive individuals (WHO, 2009). A big challenge is that the majority of people living with HIV who are infected with TB do not know their HIV status and most of those who know their HIV status are not yet accessing antiretroviral therapy (ART). The World Health Organization, 2009 estimates that HIV-positive people are nearly 20 times more likely than HIV-negative people to develop TB in countries with a generalized HIV epidemic. The substantial burden of TB found in Nigeria is not surprising as the country with the largest number of people living with HIV (PLHIV) in the world. Globally, Nigeria ranks fourth in total number of TB cases with nearly half a million in 2007, 27% of whom were co-infected with HIV (WHO, 2009a). Even though HIV is known to affect more females than males, the reverse is the case with TB, available data showing more male infections (Allotey and Gyapong, 2008).

Historically, global and national responses to TB and HIV epidemics have worked separately implementing vertical disease programs. However, the synergy between the two control programmes is increasingly recognized. This dual epidemic of TB and HIV has a better chance of being controlled through combined and coordinated efforts (WHO, 2009a). In response to the gap in integrated TB-HIV programming, the WHO HIV/AIDS and TB departments developed several guidelines and tools on TB-HIV integration. The WHO recommended twelve collaborative TB-HIV actions and 'The Three I's': Isoniazid Preventive Treatment (IPT), intensified case finding for active TB (ICF) and TB infection control (IC), as key public health strategies to decrease the impact of TB on people living with HIV (WHO, 2009b).

1.1.1 TB and HIV service organization prior to GHAIN integration pilot

The National TB Control Program is structured along the three tiers of government at the Federal, State and Local Government Area (LGA) levels, with the National TB and Leprosy

Control Program (NTBLCP) responsible for providing the framework for the control of TB. The Directly Observed Therapy strategy (DOTS) was adopted in 1993. This was later broadened to include the global STOP TB Strategy in 2006. The national level facilitates policy and human resource development, resource mobilization, technical support including monitoring and evaluation (M&E) of state programmes. The state level coordinates TB control activities in each state and also provides technical assistance to LGA level. Although there was a National TB-HIV working group that was functional at the national level, there was little collaboration between HIV and TB programs at the State and LGA levels and at the operational levels within the health facilities. Integration between TB and HIV programs at facility levels were challenged by limited knowledge and experience on TB-HIV collaborative activities by antiretroviral therapy (ART) and DOTS care providers, as well as TB and HIV programme managers. Other barriers included weak referral systems between TB and HIV programs, stigma on the part of TB patients in accessing HIV Testing and Counseling (HTC), and dilapidated infrastructure in DOTS sites. The Global HIV/AIDS Initiative Nigeria (GHAIN) has been a key supporter of TB-HIV integration activities in Nigeria since 2007. Launched as a pilot program in Cross River and Lagos States of Nigeria, the program now supports TB-HIV integration in 186 sites across every state in the country. The wide coverage of the GHAIN was a good leveraging opportunity to provide a one stop access to TB-HIV services, thereby improving very significantly TB case finding amongst people living with HIV/AIDS (PLHIV), and vice versa. The integration of both programs has also added value in information sharing and problem management among the various communities in Nigeria where GHAIN provided support.

1.1.2 HIV testing and counseling for *all* patients known or suspected to have TB

Irrespective of epidemic setting, WHO recommends HIV testing for patients of all ages who present with signs or symptoms that suggest tuberculosis (WHO and UNAIDS, 2007) whether TB is suspected or already confirmed. TB is often the first clinical indication that a person has underlying HIV infection, and TB services can be an extremely important entry point to HIV prevention, care and treatment (Geneva, 2007). In addition, the HIV status of TB patients makes a difference to the impact of their TB treatment. Detecting HIV infection in a TB patient is also critical for the TB patient's household members: HIV-positive TB patients may have household

members who are also living with HIV. Testing and counseling are usually recommended for children and other immediate family members of all people living with HIV to prevent horizontal or vertical transmission of the infections. Within a family-centered approach to HIV testing, once a family member is identified as having HIV, health workers are encouraged to actively facilitate HIV testing for other family members. This could be done, where possible and appropriate, through couples or family testing and counseling services (Geneva and WHO, 2008). Serodiscordant partnerships (in which one partner is HIV-positive and the other is HIV-negative) provide an important opportunity for prevention of HIV transmission (Dunkle KL et al, 2008). Household contacts of an infectious TB case are a high priority for TB screening and treatment, especially if they are living with HIV (Geneva and WHO, 2007), and those who are found to have active TB disease need prompt treatment. Among household contacts, people living with HIV (and children, regardless of their HIV status) who do not have active TB are candidates for isoniazid treatment to prevent the development of active TB (Geneva and WHO, 2008). WHO recommends "provider-initiated" testing, which means that the health care provider recommends HIV testing and counseling as a standard component of care (Geneva and WHO, 2007). For patients known or suspected to have TB, provider-initiated HIV testing can be done at the same time the sputum samples or chest radiographs are obtained. This is more efficient and more likely to result in patients learning their HIV status, than referring them elsewhere for HIV testing and counseling (Geneva and WHO, 2007). As in the case of client-initiated HIV testing, informed consent, counseling and confidentiality are essential. WHO recommends that providers use "opt-out" approaches (Geneva, UNAIDS and WHO, 2007), meaning that individuals must specifically decline the HIV test after receiving pretest information if they do not want the test to be performed. The provision of HIV testing by the same health worker who provides the TB treatment (or the provision of HIV testing in the same facility) has been responsible for facilitating HIV testing for TB patients (Nunn P and De Cock K, 2008). If this is not possible, NTPs should take responsibility for ensuring that any referred individual actually goes for a test.

1.2 PROBLEM STATEMENT

Tuberculosis and HIV is traditionally conceived as a very contagious disease with high mortality rate. Researchers rated Tuberculosis as more dangerous than HIV/AIDS because of its mode of

transmission, an airborne disease. But TB is a more controllable disease than HIV because it has a lasting cure and relatively cheap drug subsided by the government is available (Oluwadare and Oluwasanmi, 2003).

The issue of non-compliance which fuels defaulter rate is rampant across Nigeria. Nigeria currently has 70% defaulter rate (Federal Ministry of Health, 2004). This is probably due to poor treatment regimen. The rural communities are unable to sustain patronage of their clients because of poor quality of health services. This is equally worsened with poor and less educated sub-populations who cannot afford alternative routes of treatment in the good private or in nearby urban centre (Needham et al, 1998). Generally, poor patients lack the means to either travel to the public health facilities or pay for any consultation, prescriptions for drugs (Demissie, 2002).Nair and Chacko (1997) had earlier identified poor knowledge of the treatment process for non compliance in a study in India, Potential patients are not adequately aware of the adherence instructions for the period of treatment thus abandoning treatment at the onset of positive response from chemo therapy.

The treatment of TB in Nigeria is equally hampered by its poor health care delivery system and poor literate population particularly in the rural areas. The urban centres where services exist are also characterized by inadequate good quality service which facilitates the poor survival of people living with HIV and TB. However, there are limited studies on the survival pattern of people infected with both tuberculosis and HIV in Nigeria.

Therefore, the present study will evaluate the survival pattern and effect of therapy on patients receiving treatment for HIV/TB in Ekiti State.

1.3 STUDY RATIONALE/JUSTIFICATION

There have been some studies on the evaluation of treatment of TB patients co infected with HIV but no study has been done yet to see the survival pattern of HIV/TB co-infection on ART treatment at Federal Medical Centre, Ido–Ekiti, Ekiti state. Reliable data on the treatment outcomes and survival pattern of HIV positive patients co infected with tuberculosis and the utilization of the health care delivery services to inform scientific recommendations on TB, HIV and AIDS are scanty. Therefore the results of this study would fill up some gap and assist in the development of appropriate policies to reduce the mortality of patient co-infected with TB and

HIV. This study would also contribute to the body of knowledge in the field of health care delivery services of appropriate effective intervention strategies on HIV/AIDS and tuberculosis.

1.4 OBJECTIVES OF THE STUDY

1.4.1 Broad Objective of the study

The main objective of the study was to determine survival pattern and treatment outcome among patients with HIV/TB co-infection attending Federal Medical Centre, Ido- Ekiti between January 2010 and December 2012.

1.4.2 Specific Objectives of the study

- The study would determine the clinical characteristics of HIV/TB patients who access treatment services for TB, HIV counseling and testing (HCT), Cotriomoxazole prophylaxis therapy (CPT) and antiretroviral therapy (ART) in 2010, 2011 and 2012 at FMC, Ido – Ekiti.
- To describe the socio-demographic characteristics of TB/HIV patients accessing treatment services in FMC, Ido-Ekiti.
- To determine the 24months survival pattern of HIV/TB patients on ART treatment.
- To evaluate the effect of ART on mortality of TB/HIV patients.

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CHARPER TWO

LITERATURE REVIEW

2.1 Introduction

The type of treatment that TB and HIV patients get has been shown to affect the rate of survival of TB patients. A study carried out in Uganda to examine one year survival rate of TB/HIV co-infected patients found that the risk of death in patients on standard treatment which comprise of (streptomycin, Isoniazid and thiacetazone) was 60% higher than in patients who were treated with Rifampcin, Isoniazid and pyrazinamide (Okwera A et al, 1994). In this study it was thought that Rifampcin has an antimicrobial effect on HIV patients with bacterial infection and thiacetazone which was in the other regime was causing more drug reactions which lead to death (Okwera A et al, 1994).

Highly Active antiretroviral Therapy (HAART) is associated with a reduction in death and also new AIDS defining illnesses by 60% (Dheda Keertan, 2004). Nucleoside reverse transcriptase inhibitors non-nucleoside reverse transcriptase inhibitors based treatment regime are highly effective in clearing rapidly replicating virus in African patients dually infected with HIV-1 and TB by 93.8% by day 90 (Edna Cassol et al, 2004). Among TB patients with HIV 94% had undetectable viral load after 3 months of HAART. 97% of patients with TB and HIV were cured of TB compared to 96% of TB patients who were not infected with HIV (Gunsuch et al, 2006). The study by Harries A.D which compared treatment outcome and mortality among 2 study groups showed that there was higher mortality amongst patients who receive intermittent regime of 2R3H3Z3E3/6HE of TB drugs than those who receive established regime of 2SRHZ/6HE.

In the established regime death was at 14% while in the one with intermittent regime death was at 21%. In both groups 40-45% died within the first month of initiation of treatment (Harries A.D et al, 2001).

Bioavailability of mean plasma Rifampicin concentrations at different time points in patient with advanced HIV disease is decreased (Karen Cohen el al, 2008). Protease inhibitors and non nucleotide reverse transcriptase inhibitors interact with Rifampicin by causing decreased plasma concentration of antiretroviral drugs (Centre for Disease Control and prevention update, 2007). Rifabutin could be used as an alternative to Rifampicin as it has least potential for metabolizing ARV but is very expensive for developing countries (Harries A.D et al, 2001).

2.2 Early Initiation of ART

The immune reconstitution syndrome (IRS) may affect the response to TB treatment as well as ART especially if treatment is initiated early in intensive phase of TB treatment. However, ART during TB treatment reduces the risk of death by 80% regardless of CD4 Cell Count (Harries A.D et al, 2001). Initiation of ART within the 2-6months after finishing intensive phase of TB treatment has a mortality of 48/1000 patients compared to 147/1000 patients who are not on ART. ART and TB treatment reduces mortality by 25% from 47.7% to 27.7% (Velasco M, Gasper Gabriel, et al, 2009).

2.3 Lack of HIV and AIDS Interventions in TB patients with HIV

A study at Zomba General Hospital in 1999 found 77% (612 of 793) of TB patients were HIV positive. Deaths among smear negative PTB co-infected with HIV were higher (59%) than smear positive PTB co-infected with HIV (46%). HIV positive patients had 2.5 times the death rate of HIV negative patients who were smear positive patients (Harries et al, 1999). The high death rate observed during this study could be attributed to lack of HIV and AIDS interventions in the NTP program to combat the burden of disease at that time.

Another study in Ntcheu district also found that cure rate amongst HIV positive patient was lower (59%) while in HIV negative patients was 84% and the death rate in HIV positive patient with PTB was higher (29%) than in HIV negative which was 8% (Benerjee A, Moyo S, et al, 1997).

2.4 Quality of Care

The quality of care that TB patients get affects the outcome of patients co-infected with HIV (Chimizi R.B, Harries A.D, et al, 2001). In extreme cases; some of the patients in the hospital die because health care workers are not providing treatment to HIV infected patients and also not reviewing the patients such that patients' complications are not identified in good time to receive proper treatment (Chimizi R.B, Harries A.D, et al, 2001). In a study, 44% of TB patients with HIV complications receiving anti tuberculosis treatment in some hospitals of Malawi were not seen by clinicians because ward rounds were not conducted despite patients receiving TB treatment in the TB ward. Most patients (84%) who had HIV related complications were not provided with treatment for the opportunistic infection (Chimizi R.B, Harries A.D, et al, 2001).

2.5 Access to HIV Services

In Brazil, provision of ART to patients reduced the incidence of TB in people living with AIDS by about 80% (Nunn P, Williams B, et al, 2005). Initiations of patients with ART in primary HIV infection reduces the frequency of opportunistic infection and raises CD4 count cells with less progression to AIDS than delaying treatment (Chimizi R.B and Harries A.D, 2007). Chimzizi R.B. in assessing recommendations by the protest program on prevention, care and support of HIV patients' co infected with TB found low uptake to HIV testing (47%). Lack of supplies was the major barrier to access and patients were not willing to be tested (Chimizi R.B and Harries A.D, 2007).

A study done in Thyolo in 1999 where all registered TB patients were offered VCT and when they tested positive Cotrimoxazole prophylaxis 480mg twice daily for the duration of treatment and indefinitely after wards found out that the use of Cotrimoxazole treatment reduced mortality in all TB patients from 36% to 28%. This shows that if all TB patients who are HIV positive could be receiving Cotrimoxazole preventive Therapy (CPT) mortality rate among TB patients co infected with HIV would be reduced.

However, another study in Ndirande confirms that HIV patients really do have high rates of bacterial infection 78 new events per 100 person years and of whom 15.3% developed TB, but found high resistance rate to Cotrimoxazole of about 76% which was attributed to SP in incidences of Malaria which was at 34.1 per 100 person years.

2.6 Late or Difficult To Diagnose TB

Late diagnosis of TB infected patient could also contribute to poor TB treatment outcome such as death. In Malawi at Queen Elizabeth Central Hospital in 1996, 21% of patients who were smear negative with minimal chest abnormality after 3 months of follow up were found to be positive of mycobacterium tubercle and 47 % developed a TB with abnormal TB chest x-ray (Harries A.D, Wirima J, et al, 1998). In Karonga, the study found high prevalence of HIV in patients presenting with chronic cough; though 70% had not been diagnosed with TB at the end of the follow up 56% of 108 who got tested were HIV positive with half of the HIV positive patients eligible for ART as were in Stage 3 or 4 (Munthali L. et al, 2006).

2.7 Treatment Outcomes

In the pre HIV era when TB cases were low, infectivity was considered to be minimal and treatment outcome was good with standard treatment using drugs like Streptomycin, Isoniazid and Thiacetazone (Briggs I, Rochester W.R. et al, 2007). With HIV it is observed that the cases of TB are increasing and there is an increase in TB case fatality. In Karonga, a proportion of new smear positive cases of tuberculosis rose from 17% in 1988-1990 to 57% in 2000-2001 while TB cases in HIV uninfected people fell from 78 per 100,000 to 45 per 100,000 (Glynn J.R.S et al, 1988-2001 AIDS 2004). There is high case fatality in patients with smear negative than smear positive patients this was attributed to the fact that most patient who are sputum negative PTB patients are HIV positive compared to those who are sputum positive. For smear negative TB patients 1054(25%) died, while for patients who were smear positive, 799 (20%) died (Harries A.D, Benerjee A, et al, 1999).

Other studies have also stated that there is drug to drug reaction in cases where Rifampicin is used in treatment of TB and Nevirapine is used for HIV. Rifampicin is known to be a strong inducer of the drug metabolizing enzyme cytochrome P450 3A4 (CYP3A4) and the drug transporter P-glycoprotein in the Liver, intestinal wall which produces a significant in plasma concentration of Non-nucleoside reverse transcriptase inhibitor (NNRTIs) and protease inhibitors (PIs) (Ribera E, Lopez R, et al, 2007). Other studies have recommended TB patients' co infected with HIV to be treated with Rifabutin rather than Rifampin in treatment of tuberculosis as Rifabutin tend to have clinical cure at 89.4% than Rifampin which was at 82.8% (Vargas A, Clumeck N, et al, 2005).

2.8 Enhancing TB/HIV collaboration

In 2011, 69% of TB patients were tested for HIV in the African Region; up to 3% in 2004 the number of people in HIV care who were screened for TB increased by 39% between 2010 and 2011. Nearly half a million people were provided with isoniazid preventive therapy in 2011, more than double the number who started in 2011. Though there is a significant progress in ART for TB patients known to be living with HIV (48%); courage needs to be doubled to meet WHO recommendation that all TB patients living with HIV are promptly started on ART.

2.9 TB treatment in people living with HIV

Among treated TB patients, death rates are higher in HIV-positive than in HIV-negative patients. Case-fatality is higher in people living with HIV with smear-negative pulmonary and extra-pulmonary TB, as these patients are generally more immunosuppressed than those with smear-positive TB (Geneva and WHO, 2007). The case-fatality rate is reduced in patients who receive concurrent ART. The first priority for HIV-positive TB patients is to initiate TB treatment, followed by the use of co-trimoxazole and ART (Geneva and WHO, 2007).

The new recommendation is based on a systematic review showing that the incidence of relapse and failure among HIV-positive TB patients who were treated with intermittent TB therapy throughout treatment was 2–3 times higher than that in patients who received a daily intensive

phase (Khan FA et al, 2010). In addition, a study in India showed that HIV-positive patients with pulmonary TB are at higher risk of acquired rifampicin resistance, when failing a three times weekly short-course intermittent regimen (Swaminathan S et al, 2009).

2.10 Antiretroviral therapy

Antiretroviral therapy improves survival in HIV-positive patients (Harries AD, Zachariah R and Lawn SD, 2009). In addition, antiretroviral therapy reduces TB rates by up to 90% at an individual level, by 60% at a population level and it reduces TB recurrence rates by 50% (Lawn SD and Churchyard G, 2009). ART is recommended for *all* people living with HIV with active TB disease irrespective of CD4 cell count. It has been found to be of benefit if TB treatment is started before a patient receive ART and this take place preferably within the first 8 weeks of starting TB treatment (Geneva and WHO, 2009).

2.11 Drug susceptibility testing

Several studies have shown that TB treatment outcome may be affected by the drugs the patient received in treating tuberculosis, the immune status of the individual, availability and accessibility to HIV and AIDS services, quality of care and time diagnose of TB. High mortality rates have been reported among people living with HIV who have drug resistant-TB (Geneva and WHO, 2008), and rates can exceed 90% in patients co-infected with extensively drug-resistant TB (XDR-TB) and HIV (Gandhi NR et al, 2006). Prompt initiation of appropriate TB treatment (and subsequent initiation of ART) can reduce mortality among people living with HIV who have drug-resistant TB (Well C.D et al, 2007).

WHO recommends that NTPs undertake DST at the start of TB therapy in all HIV-positive TB patients, to avoid mortality due to unrecognized drug-resistant TB and strongly encourages the use of rapid DST in sputum smear-positive person living with HIV (Karim S.A et al, 2009).

For a country introducing DST, but does not yet have the resources to test all HIV-positive TB patients, initial NTP policy should be to target DST at the start of TB treatment for patients with previously treated TB, who are very likely to be multidrug-resistant. This group includes patients

whose prior TB treatment has failed, who have relapsed or who are ~~returning~~ from default. NTP managers may also choose to target DST for those HIV-positive TB patients with lower CD4 counts (e.g. less than 200 cells/mm3) given their very high risk of death due to unrecognized drug-resistant TB (Geneva and WHO, 2008).

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Introduction

This chapter is organized under the following sub-headings; Research Design, Study Population, Sample size and selection of sample, Data collection Procedure, Method of data analysis, Ethical consideration and Brief Profile of Ekiti Health System.

3.2 Research Design

This is a retrospective cohort study of HIV patients with TB co infection attending a tertiary health care in Ekiti State of Nigeria that were tracked for 24 months after their diagnosis as having TB. The records of each patient were reviewed and relevant data on the patients was collected from patient's registers for 2010, 2011 and 2012.

3.3 Population of the study

The target population of the study comprised of all TB/HIV patients found in the TB/HIV registers in the 2010, 2011 and 2012 in Federal Medical Centre, Ido – Ekiti.

3.4 Sample Size and Selection of Sample

A sample size of 344 was used in the study. These are all patients with HIV/TB co-infection that meet the inclusion criteria for this study.

The inclusion criteria for the study are;

i. HIV/TB co- infected patient with aged greater than 15years.
ii. HIV infected patient who was diagnose suspected to have TB and referred for evaluation at the FMC Ido Ekiti within the period of the study.
iii. Patient who are on TB treatment before the start of ART.

3.5 Data Collection Procedure

The TB/HIV registers at Federal Medical Centre, Ido – Ekiti contains patient identification, medical history, treatment provided and outcome. Data collection involved reviewing files of patients who attended VCT clinics and extracting relevant data of all HIV/TB patients between January 2010 and December 2012 on a data collection form.

3.6 Method of data Analysis

The collected data was checked for completeness and records with incomplete basic information were excluded from entry. The data was entered using the facilities in the SPSS version 20.0.

Subsequently, data was cleaned and checked for coherence and appropriate analysis was carried out using SPSS version 20.0. The main outcome variable was death and its time of occurrence in the two years study period. The survival time was calculated in months using the time interval between date of Antiretroviral Therapy (ART) initiation and

(I) date of event (death)

(ii) Date of transfer out of the clinic or lost to follow-up.

(iii) Date in which patient completed the 24 months of follow up.

Kaplan-Meier and Cox-proportional hazard techniques were used to identify predictors of death. Kaplan-Meier model was used to estimate survival probability after ART initiation and the log rank tests were used to compare survival curves.

Univariate Cox-proportional Hazards model was used to assess the relationship between baseline variables and mortality and to calculate hazard ratios. The baseline variables included in the analysis were sex, age, marital status, CD4 count, TB location and phase duration. Variables statistically significant ($p<0.05$) in the univariate analysis were subsequently included in the multivariate analysis.

All statistical tests were two sided and $p<0.05$ was considered as significant level of association.

3.7 Ethical considerations

This study was approved by the Research Ethics committee of the Department of Community Medicine of the Federal Medical Centre and Ethical clearance with protocol number ERC/2013/04/08/25B was obtained from the ethics committee of the hospital management board. All information collected from patients register were kept strictly confidential and names were not included in the abstracted data.

3.8 Brief Profile of Ekiti Health System

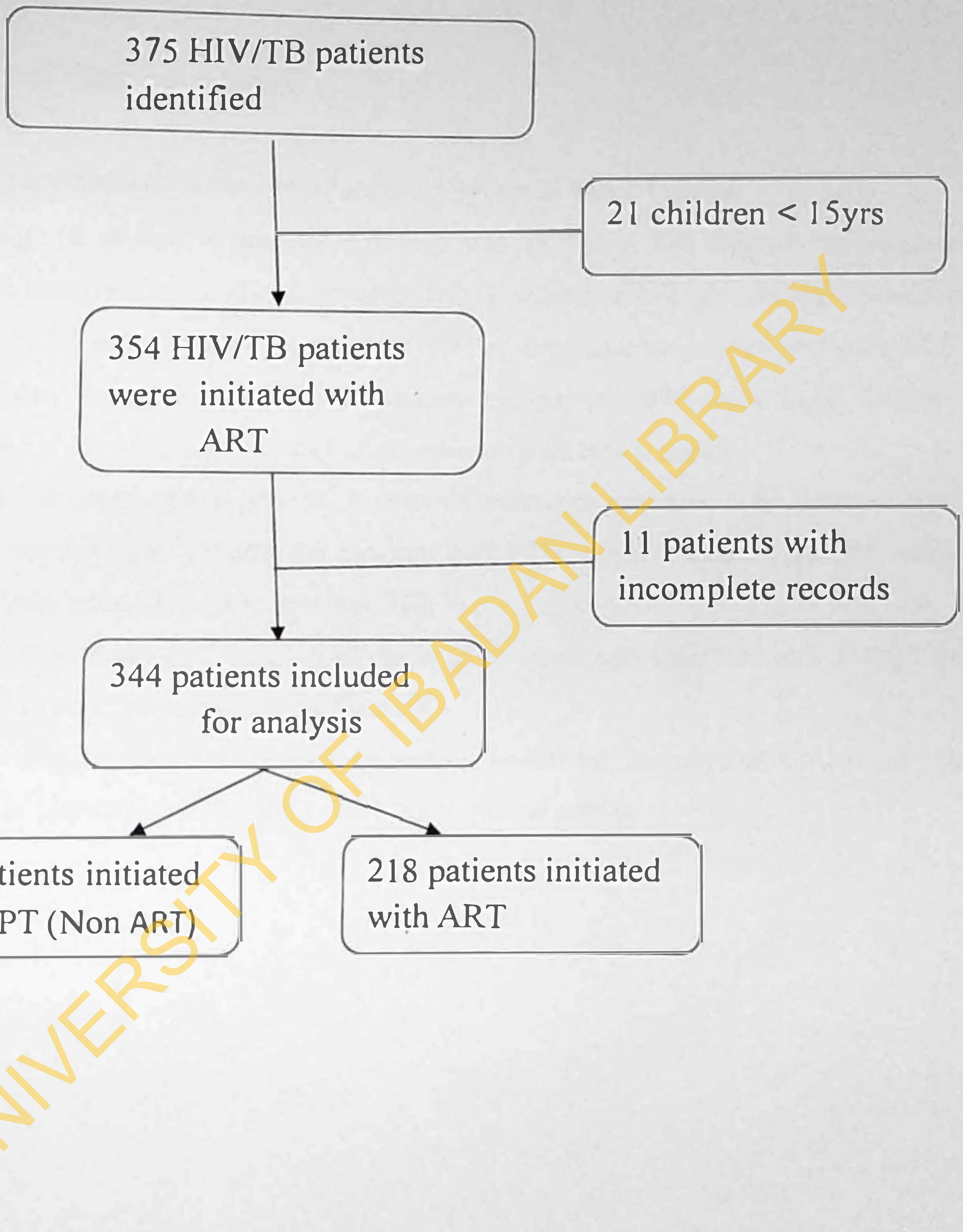
Ekiti state is in the south-west geo-political zone of Nigeria with a population of about two and half million people and annual population growth rate of 3%. There are sixteen local government areas, mostly of less than two hours' drive distance to the state capital (Ado-Ekiti). The basic occupation of the people is agriculture mainly cocoa, coffee, rice, cassava, maize and vegetable cultivation. Roads linking the state capital to local government headquarters are relatively good but those to the remote communities are mostly in disrepair (Ekiti-State 2004). There are about 174 functioning primary health care centres across the state, three state specialist hospitals, seventeen state general hospitals, one state teaching hospital and one federal medical centre. The latter is the highest referral point HIV/AIDS patients in the state for ART. Virtually all the state health structures (buildings and also personnel) were inherited from the old Ondo State with continuous rehabilitation and improvement in facilities (Dare, 2005). There are other private health providers of varying qualities across the State.

TB-DOTS service is also available in all the sixteen local government areas though in reality the quality of the service tends to reduce with increase in distance from the State Capital. This study took place in the Federal Medical Centre having the best HIV and Tuberculosis treatment Centre in the State. The Centre is located in Ido - Ekiti. The Centre has been enjoying the support of Federal Government, WHO and British Council for over a decade.

3.9 Study cohort:

From January 01, 2010 to December 31st, 2010 a total of 375 cases of HIV/TB patients were identified. We included 344 patients over 15 years of age and whose records are complete.

Figure 1: Inclusion of the study cohort for analysis, Federal Medical Centre, Ido – Ekiti. (January 1st – December 31st, 2010) Ekiti State, Nigeria.



CHAPTER FOUR

4.1 RESULT

4.2 Clinical Characteristics

The clinical characteristics of the cohort are summarized in Table I below.

The median age of patients at start of treatment was 28 years. The majority of patients were female (62.6%) and two hundred and four (60.0%) of patients clinically screened were found to have pulmonary TB at the point of diagnoses while the remaining have extra pulmonary TB.

One hundred and twenty four (36.0%) of patients are married, while (7.6%) of patients were either separated or divorced and (56.4%) of the patients have never married.

The median CD4 count of the patients at time of treatment initiation was 204.0cells/μl. One hundred and seventy-nine (52.6%) of patients had CD4 count greater than 200 while the remaining patients have CD4 count less than 200.

Sixty-one (37.9%) of patients on no ART have CD4 count less than 200 and 118(65.9%) of patients on ART had CD4 counts greater than 200.

Almost sixty – four percent of the patients received antiretroviral therapy and the 36% of patients who received no antiretroviral therapy served as the control group.

Table 1: Socio demographic characteristics of HIV/TB patients by ART groups

Characteristics	No ART (%)	ART (%)	Total (%)
Age in Years			
15 – 24	50 (34.2%)	96 (65.8%)	146 (42.9%)
25 – 34	43 (38.1%)	70 (61.9%)	113 (33.2%)
35 – 44	19 (35.8%)	38 (64.2%)	57 (15.6%)
Above 45	10 (35.7%)	18 (64.2%)	28 (8.2%)
Gender			
Male	47 (37.0%)	80 (63.0%)	127 (37.4%)
Female	79 (35.2%)	138 (64.8%)	217 (62.6%)
TB Location			
Pulmonary	69 (33.8%)	139 (66.2%)	208 (60.0%)
Extra pulmonary	53 (39.0%)	83 (61.0%)	136 (40.0%)
Marital Status			
Single	71 (57.3%)	123 (55.9%)	194 (56.4%)
Married	46 (37.1%)	78 (35.5%)	124 (36.0%)
Divorced or separated	7 (5.6%)	19 (8.6%)	26 (7.6%)
Duration			
Intensive Phase	59 (57.8%)	47 (42.2%)	106 (30.0%)
Continuation Phase	63 (26.5%)	175(73.5%)	238 (70.0%)

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Characteristics	No ART (%)	ART (%)	Total (%)
CD4 Count			
CD4 < 200	61 (37.9%)	104 (62.1%)	165 (47.4%)
CD4 > 200	61 (34.1%)	118 (65.9%)	179 (52.6%)
Clinically Screened for TB			
On INH prophylaxis(IPT)	26 (18.4%)	115 (81.6%)	141 (41.5%)
TB suspected & RFE*	39 (53.4%)	36 (46.6%)	75 (21.5)
Currently on TB treatment	47 (48.0%)	51 (52.0%)	98 (28.8%)
Not on TB drug	12 (35.7%)	18 (64.1%)	30 (8.2%)
Follow-up Outcome			
Dead	33 (52.4%)	30 (47.6%)	63 (18.5%)
Alive	25 (13.1%)	139 (86.9%)	164 (47.1%)
Lost	64 (58.2%)	46 (41.8%)	110 (32.4%)
Transfer out	4 (57.1%)	3 (42.9%)	7 (2.1%)
Median CD4 counts		204.0	
Median Age of the patients		28.0	

RFE: Refer for evaluation

4.3 SURVIVAL CHARACTERISTICS

A total of 67 (18.5%) patients out of the 344 HIV/TB patients died within two years of initiation of ART. The majority of the deaths occurred in the intensive phase of follow-up. Thus all other 277 (81.5%) patients' either on ART or non-ART were regarded censored at the end of the follow up period. The minimum follow up period was 1day to 15days with the maximum of 24 months for both groups. The Kaplan Meier survival curve in figure 1 showed that the probability of survival was significantly lower in HIV/TB patients who were not on ART. However, little information was available on the possible causes of death. And table 2 showed the location of TB and the possible causes of death of the only 8 cases with such information.

Table 2: Causes of early death in the intensive phase

Cases	TB location	Causes of death
1	Pulmonary	Respiratory failure(RF)
36	Pulmonary	Liver failure(prior adverse drug reaction)
69	Extra pulmonary	T-cell non-Hodgkin lymphoma in colon and septic shock prior to beginning of anti-TB therapy.
109	Pulmonary	Evidence of radiological progression, RF

Cases	TB location	Causes of death
158	Pulmonary	Metastatic testicular cancer (dead three weeks after discharge).
186	Extra pulmonary	RF**, bronchopneumonia and pleural effusion.
214	Pulmonary	Liver failure, gastrointestinal bleeding.
235	pulmonary	RF**, evidence of radiological progression.

***RF: Respiratory failure*

Figure 1: Kaplan Meier estimate showing the effects of treatment on the probability of survival. The green line depicts cumulative mortality in 218 HIV/TB patients on ART while the blue line depicts cumulative mortality in 126 HIV/TB patients on no ART follow over a period of 24months. Cumulative mortality was higher in patients without ART. (Log rank test =16.0, p<0.001, median of survival for group one is 14months and 18months for group two)

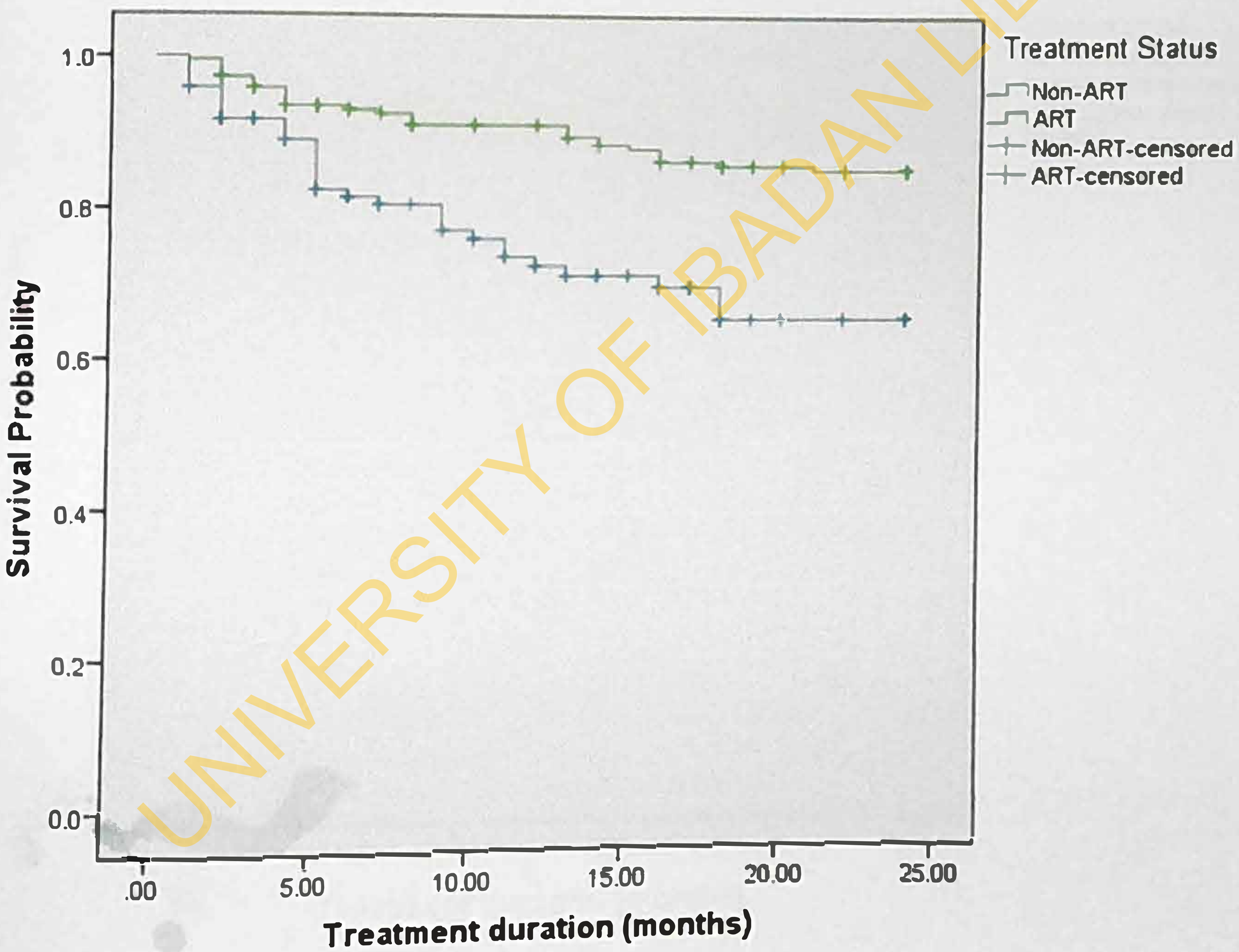


Figure 2: Kaplan Meier estimate showing the effects of dying in the duration phase on the probability of survival. The green line depicts cumulative mortality in 242 HIV/TB patients in continuation phase while the blue line depicts cumulative mortality in 102 HIV/TB patients in the intensive phase follow over a period of 24months. Cumulative mortality was higher in HIV/TB patients in the intensive phase. (Log rank test =188.8, p<0.001). 45(70.3%) of death occur in the intensive phase out of the total number of 65(100%) deaths that occur during the period of 24months of follow up.

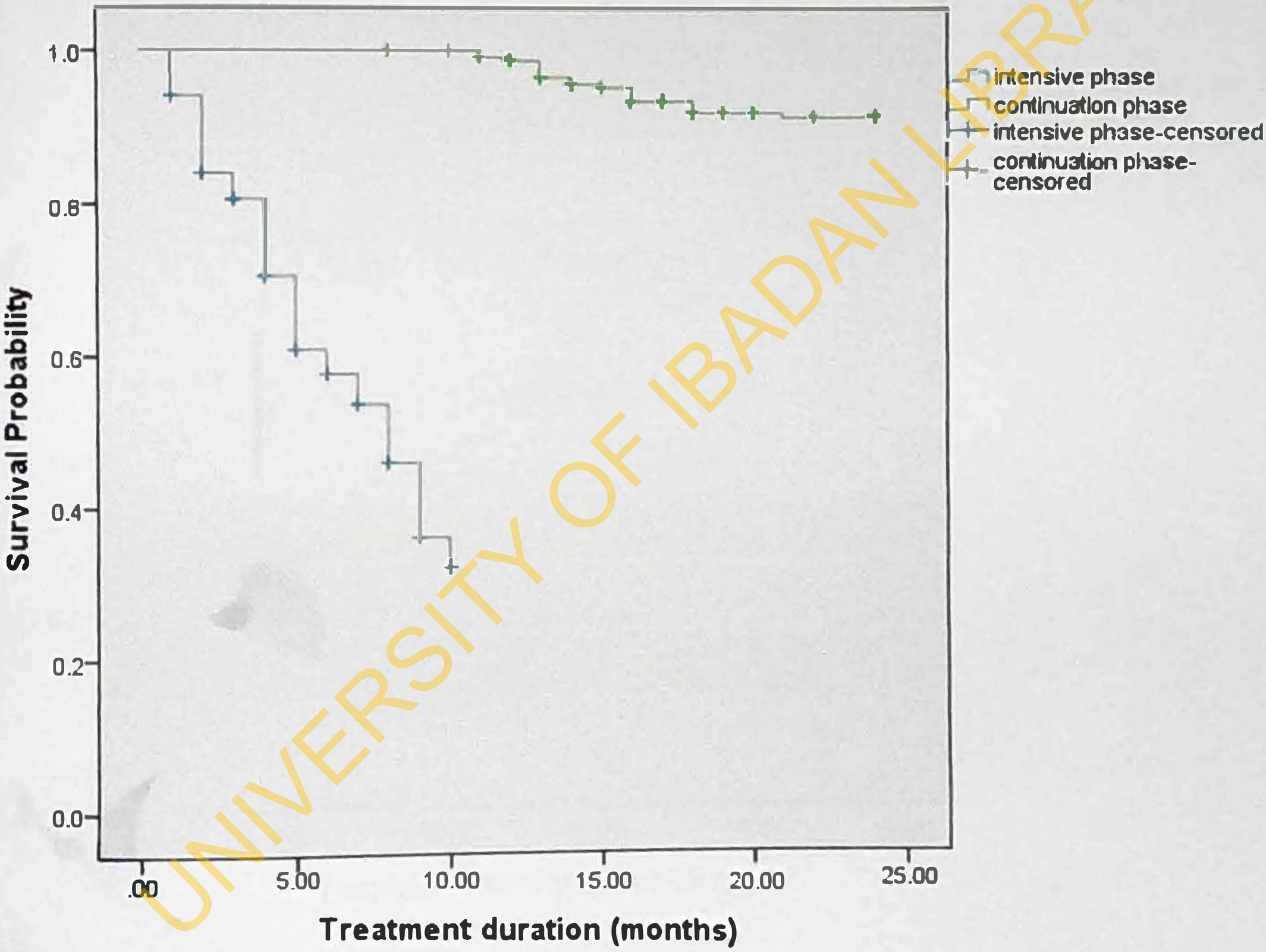
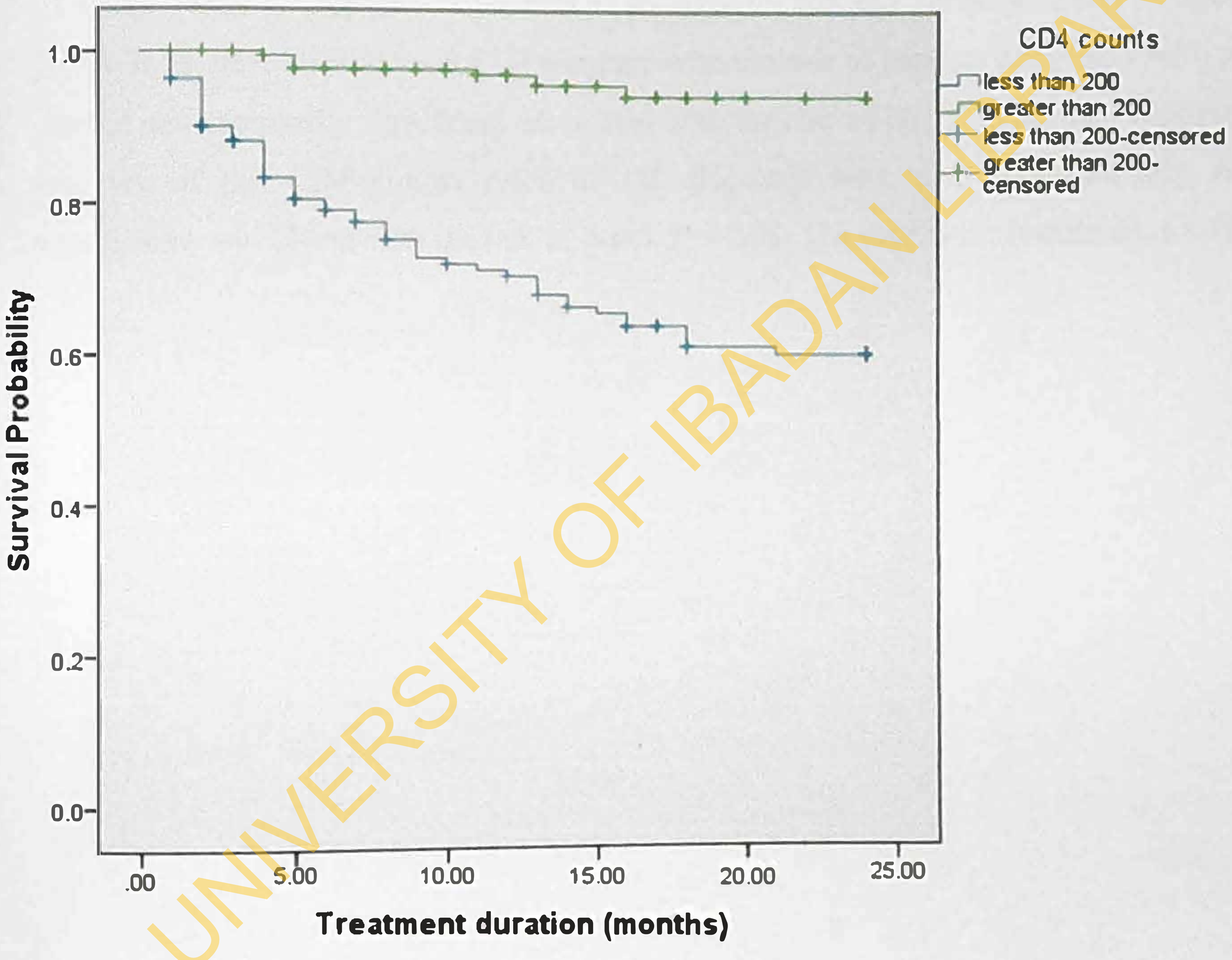


Figure 3: Kaplan Meier estimate showing the effects of CD4 counts on the probability of survival. The green line depicts cumulative mortality in 181 HIV/TB patient with CD4 counts greater than 200 while the blue line depicts cumulative mortality in 163 HIV/TB patients with CD4 counts less than 200 follow over a period of 24months. Cumulative mortality was higher in patients with CD4 counts less than 200. (Log rank test =55.54, df = 1 p<0.001).



4.4 PREDICTOR OF MORTALITY

Table 3 showed that TB location, treatment, Phase duration and CD4 counts were associated with mortality. Age, gender and marital status were not statistically significant risk factors of death. The hazard of death for patients diagnosed with CD4 count less than 200 was higher than those patients whose CD4 counts were greater than 200 (HR: 8.88; 95% CI 4.387 – 17.995).

In the final multivariable model, adjusted for TB location, CD4 counts, Phase duration and Treatment initiation, Phase duration were found to be non-significantly associated with the risk of dying. Patients diagnosed with extra pulmonary TB reduced the relative risk of dying by 53% [AHR: 0.53, 95% CI 0.318 – 0.874] compare with the risk of patients diagnosed with pulmonary TB but not statistically significant associated with the risk of death. Treatment initiation and the category of the CD4 counts prior to TB diagnosis were also independently statistically significantly associated with the risk of death, $P < 0.05$. The results are presented in table 4.

Table 3: Univariate predictors of death among HIV/TB patients on Treatment

Variable	Category	Hazard Ratio (HR)	95% CI	P-Value
Treatment	Without ART(ref)	1		
	With ART	2.649	1.608 - 4.365	0.001
Gender	Male(ref)	1		
	Female	0.973	0.584 – 1.621	0.916
TB Location	Pulmonary(ref)	1		
	Extra pulmonary	0.440	0.268 – 0.722	0.001
Phase duration	Intensive	1		
	Continuation	1383.975	14.018 –13663.457	0.002
Age	15 – 24(ref)	1		
	25 – 34	0.958	0.368 – 2.496	0.931
	35 – 44	1.230	0.467 – 3.236	0.675
	Above 45	1.114	0.381 – 3.260	0.844
Marital status	Single(ref)	1		
	Married	0.597	0.246 – 1.450	0.255
	Sep/divorce	1.256	0.525 – 3.005	0.608
CD4 counts	Less than 200(ref)	1		
	Greater than 200	8.885	4.387 – 17.995	0.001

Table 4: Multivariate predictors of death among HIV/TB patients on Treatment

Variable	Category	Hazard Ratio (HR)	95% CI	P-Value
Treatment				
	With ART(ref)	1		
	Without ART	1.657	0.713 – 2.079	0.013
CD4 counts	Greater than 200	1		
	Less than 200	5.397	2.632 – 11.068	0.001
TB Location	Pulmonary(ref)	1		
	Extra pulmonary	0.528	0.318 – 0.975	0.471
Phase Duration	Intensive(ref)	1		
	Continuation	33129.366	0.001 – 1.150E+042	0.226

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CHAPTER FIVE

5.0 DISCUSSION, CONCLUSION AND RECOMMENDATION

5.1 DISCUSSION

In this retrospective study, HIV/TB co-infected patients without ART were given Cotriomoxazole prophylaxis. The category of patients in this group is TB patients with HIV infection. We found that among HIV/TB co-infected patients who were treated with and without antiretroviral therapy, mortality is consistently higher among HIV/TB co-infected patients on no ART. Multivariate analysis predicted that higher mortality among HIV positive TB patients on no ART were as high as two times increased risk of death (AHA = 1.65).

Many researchers in outside of Nigeria have reported higher mortality in HIV positive TB patient. WHO, (2009) reported higher overall death rates among HIV- positive TB patients as high as four times increased risk of death in a previous report during TB treatment. A study also carried out in Uganda to examine one year survival rate of TB/HIV co-infected patients found that the risk of death in patients on standard treatment which comprise of (streptomycin, Isoniazid and thiacetazone) was 60% higher than in patients who were treated with (Rifampcin, Isoniazid and pyrazinamide) (Okwera A, Mugwera E.J, et al, 1994).

In our study it was thought that treatment with Cotriomoxazole alone could not improve survival of the HIV/TB patients due to other bacterial infections and the HIV infection itself. Almost half of the deaths in HIV positive TB patients were attributed to their HIV infection. If HIV positive TB patients had not been infected by HIV, 50% of the observed deaths would not have occurred.

Information about the time of death among HIV/TB co-infected patients while on treatment could help provide the necessary care on time. In this current study, irrespective of one's HIV status, most of the deaths 45(70.3%) occurred during the intensive phase. This may suggest that late presentation was a major factor for early death than HIV infection itself and that late diagnosis of HIV positive TB patients could also contribute to poor treatment outcome such as death.

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It was also revealed that risk of death among HIV positive TB patients increases in the continuation phase but was not statistically significantly after adjusted for other variables (AHR = 3.31296E+05, P = 0.767). Unlike another study elsewhere, risk of death was not different in the intensive phase between HIV positive and negative TB patients, but significantly higher among the HIV positive TB patients during the continuation phase (Moolphate S, Yamada N, et al). This finding may suggest the self-supervised treatment for a longer period (24 months) by patients co-infected with TB/HIV might have not been able to sustain adherence to treatment regimen.

The median survival time of HIV positive TB patients on either ART or no ART ranges between 14 and 18 months during the 24 months of follow up study. The finding that the Kaplan Meier model showed that HIV/TB patients on ART appears to survive better than those patients with no ART is consistent with many studies from the United States. They showed that the median survival time of patients with TB-HIV, with little or no exposure to ART can range between 16 and 23 months depending upon prior history of other AIDS-defining illnesses (Shafer RW, Dehovitz JD et at, 1996).

Another study from United States (Leroy V, Dequae L, et al, 1997) which included comparable proportions of people with severe immune suppression, extra pulmonary TB and history of AIDS, showed longer survival times than our patients with ART (median17-36 months vs. 14 - 18 months in our series). The difference is remarkable, because use of ART in those studies ranged between 36 to 57% compared to our entire cohort expose to ART. These studies may suggest that those patients have a better prognosis than our patients as a result of other factors such as delay in the diagnosis or treatment of TB and low CD4 counts at the time of diagnosis which might contribute to the greater mortality in our cohort. However, there are few reports from developing countries on the survival time of TB-HIV patients with and without access to ART. Whalen et al, (1996) in Uganda reported a survival time of 26 months (n=191) and a probability of survival at 12 months of 68% (the study did not include CD4+ T cell counts). Garin B, et al, (1997) in the Central African Republic reported a survival time of 15 months among those who died (58%; 81/139) and an overall survival of 42% at 24 months. Connoly et al, (1999) in South Africa reported a 24 month survival of 59% in people cured of TB. These

studies showed that this difference may be as a result of better immune status of Nigeria patients, consistent with the low proportion of AIDS – indicator conditions and extra pulmonary TB.

According to our findings, initiation of Cotriomoxazole prophylaxis therapy is insufficient to improve mortality until antiretroviral therapy treatment has been received by HIV/TB patients. Interestingly, there was no significant difference in the risk of death depending on the degree of TB location and phase duration. The explanation of the observation may lie in the relatively small population used in the comparison (n=344); Moreover, in the context of severe immune suppression (CD4 counts cells/μL) it was observed from our study that the risk of death of HIV positive TB patients with CD4 counts less than 200 increases five times that of HIV positive TB patient with CD4 counts greater than 200 after adjusted for other variables and were statistically significant (AHA = 5.40, $p < 0.001$).

The Kaplan Meier model also estimated that cumulative mortality was higher among HIV/TB patients with CD4 counts less than 200 as compare with HIV/TB patients with CD4 counts greater than 200 and the median survival time of CD4 counts were 204.0cells/uL. These studies suggest that the higher mortality in HIV/TB patients with less CD4 counts is mostly due to other opportunistic infections which occur in the presence of profound immune suppression and presenting late into care with low CD4 + T-cell. However, treatment with antiretroviral therapy and standard anti-tuberculosis regime using DOTS simultaneously could go a long way improving quality of life.

5.2 CONCLUSION

The study showed that HIV/TB co-infected patients with CPT (Non ART) were at higher probability of mortality than those under ART. The impact of AIDS and other opportunistic infection was magnified during intensive phase. Higher death rate was demonstrated in HIV/TB patients with CD4 counts less than 200. Also ART appear to reduce the risk of dying which shows that initiation of ART to HIV/TB co-infected patients is protective.

5.3 RECOMMENDATION

HIV/TB patients need strict follow up not only during the intensive phase but also during the continuation phase. Alongside with the treatment of both infections, HIV positive TB patients should be aware of the danger of presenting late to health care with low CD4 counts. Patients should be encouraged to go for ART. ART is protective and prolong life span

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