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RESEARCH REPORT

TITLE

OUTCOME OF HAART IN PATIENTS WITH TUBERCULOSIS IN THE THEMBA LETHU CLINICAL COHORT.

Submitted in partial fulfillment of the requirements for the Degree; Master of Science in Medicine (MSc Med) in the field of Epidemiology and Biostatistics for the 2007/2008 academic Year.

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CHAPTER ONE

GENERAL INTRODUCTION

1.1 INTRODUCTION:

The burden of disease due to HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome) and tuberculosis (TB) remains great for many countries around the world. Continuing attention must be devoted to these epidemics if we ever hope to one day contain their devastating effects on humankind. An estimated 38.6 million people worldwide were living with HIV in 2005. It is estimated that 4.1 million people were newly infected with HIV and 2.8 million lost their lives to AIDS (1). In the past 25 years, HIV has spread rapidly from a few locations to virtually every country in the world, infecting an estimated 65million people and killing 25 million worldwide(1).

HIV/AIDS on its own has created more than 13 million orphans in the world with Sub-Saharan Africa (SSA) bearing the greatest burden of the crisis. In this region, (which is home to less than 10% of the world's population) there are 25.3 million people with HIV/AIDS, i.e. 70% of all cases globally. In 2000 there were 3.8 million new HIV infections in sub-Saharan Africa alone and 2.4 million people died of HIV/AIDS, representing 80% of all deaths attributed to AIDS (2).

Additionally, SSA carries the greatest burden of HIV-associated TB (3). TB is a disease that has caused significant morbidity and mortality to mankind throughout history. It is believed to have been around for almost 20,000 yrs (4) and, as a rule, has affected the poorest groups of society. Over the years,

more devastating forms of the disease have developed (5). In 1999 there were estimated to be 8.4 million new cases of TB in the world (6). By 2004, an estimated one-third of the global population, around 2,000million people (7), was infected with the microorganism, known as Koch's bacillus. This represents the largest reservoir of healthy, infected carriers for any given infectious disease (5).

The WHO report of 2002 declared that HIV fuels the TB epidemic and that nearly three-quarters of people infected with both HIV and Mycobacterium tuberculosis (MTB) live in SSA (8). It is known that HIV results in the reactivation of latent TB, and promotes progression to active TB both in people with recently acquired (9) and latent (10) MTB infections. It has been estimated in 1997 that global prevalence of MTB infection was 32% (1.86 billion) (11), whereas 0.18% of the world population (10.7 million people) had MTB and HIV co-infection, and 640 000 incident TB cases (8%) had HIV infection. The great majority of incident TB cases were found in the South-east Asian and African countries with the highest overlapping HIV and TB epidemiology (12). In 2005, the WHO estimated that 6.5million people living in resource-poor countries were in urgent need of antiretroviral treatment ART (13). This ever-increasing number will certainly result in more HIV -related illnesses, in particular, TB, resulting in greater mortality/negative outcomes.

The Themba Lethu Clinic (TLC), an ARV rollout site based at Helen Joseph Hospital in Johannesburg, Gauteng, currently provides antiretroviral (ARV) treatment to about 7000 HIV infected patients. Some of these patients are co-infected with TB. This study will look at the differences in HIV outcomes according to TB status of patients.

1.2 Background and Information on Place of Study:

TLC was introduced in 2004 to take care of HIV-infected patients. It functions as an HIV clinic providing HAART and is affiliated to the Right to Care and the Clinical HIV Research Unit and this to the University of the Witwatersrand. TLC is also partnered to the Gauteng Province which ensures the sustainability of the clinic.

TLC is found in the premises of the Helen Joseph Hospital (HJH), in the city of Johannesburg, Gauteng province, South Africa. A Government ARV role out center, TLC is considered the flagship of National ARV rollout sites and supported by the right to care- the President's Emergency Plan for AIDS Relief (PEPFAR). Situated within a Wits University teaching hospital HJH, it serves as a good training site for health students and healthcare workers. TLC has strong links to the medical unit of HJH ensuring easy admission for the 10 to 20 patients per week, needing specialist care (14).

The clinic is made up of health care workers with more than 10 years experience in treating HIV patients. These workers include nurses, doctors, laboratory scientists and other auxiliary staff who make up a total number of ±65persons (14). Three registrars from the hospital, from the medical unit of the HJH, work in rotation for 3hours per week carrying out consultations at the clinic (14). Approximately 50 HIV tests are conducted a day based on clinical analysis and patients requests.

TLC could count no less than 4300patients by March 23rd of 2006, registering 30 – 40 patients per week all under 3 basic ARV regimens. By October 2006, TLC had registered approximately 6,200 patients on ARV, was initiating 150

–200 new patients per month and seeing about 200 patients per day from Monday to Thursday (14). Today the clinic can boast of a staggering no less than 8000patients in their data base.

Enrollment into the programme follows the National ARV Rollout guidelines, which in turn follows WHO recommendations in providing ARV (this states that clinical Stage 4 disease or those with CD4 count less than 200 are initiated on HAART) (15).

With its primary aim the care of HIV patients, TLC has a good system of capturing patient information. Patient information/Data at the TLC is stored on TherapyEdge-HIV™ which is an interactive data base. This provides a good opportunity for research and analysis.

This study will analyze three years' worth of data/information from April 2004 to April 2007 of the TherapyEdge-HIV™ data base for patients on HAART at TLC who meet the inclusion criteria.

1.3 Problem Statement:

HIV/AIDS and TB are two of the world's major pandemics, with most of their effects felt in sub-Saharan Africa. In trying to control these pandemics, efforts have been largely aimed at prevention with little attention given to care (2). Treatment of patients with both HIV/AIDS and TB is a major challenge in the care and control of HIV/AIDS. The ever increasing numbers infected with both diseases, makes it imperative for health scientists and researchers to redefine their position and goals in combating these diseases. The global burden of TB remains enormous because there are insufficient TB control programmes and higher rates of TB and HIV co-infection (12).

The WHO's '3 by 5' initiative has stirred up many developing countries to make antiretroviral therapy available to their HIV infected patients (16). This development raises questions about when it is appropriate to start ARV therapy in those dually infected with HIV/AIDS and TB, the difference in effect of ARV therapy between those only infected with HIV and those dually infected with HIV and TB is also unclear and requires careful research.

With so much literature available universally on HIV and TB, how they interact and inter-relate, very little literature can be ascertain to be available for the differences in outcome in ARVs in HIV patients with TB and those without TB. A major reason for such limited literature could be that, ARVs in most African countries have only recently become available. The issue of ARVs is generally new in most African societies or at least not that old and so too is information and data on such a population/ patients. Studies on the action of ARV drugs, its outcome in HIV-TB positives and HIV-TB negatives must consider the fact that while a substantial burden of the dual infection of HIV and TB is also experienced by children, the majority of the burden is borne by adults (17).

Research Question: What are the differences in HIV/AIDS outcomes comparing adult HIV infected patients of the TLC with and without TB, who have at least 1 follow up clinical visit post initiation in the period April 2004 to April 2007?

1.4 Justification/ motivation:

Keeping in mind that HIV/AIDS increases the incidence of TB, when you consider the estimates of June 2005 that 6.5 million people living in resource-limited settings were in urgent need of ARVs (13), and that other estimates in

2004 showed populations in the developing world account for 95% of all cases of HIV-infection, more than 99% of HIV-related deaths, about 95% of all TB cases, and about 98% of TB-related deaths (18) it becomes clear that more has to be done in both research and care actions.

Despite adequate antituberculous therapy, many individuals co-infected with TB and HIV have an accelerated course of HIV disease and shortened survival (19). The introduction of HAART has greatly increased the survival probability of HIV patients and decreased the probability of opportunistic infections in these patients (20). The same is expected of TB infected HIV patients but the problem here is the potential for complex drug interactions, overlapping adverse reactions, noncompliance due to the pill burden of multidrug therapy, and drug malabsorbtion (21). Thus the introduction and adequate follow up of such persons may be of utmost importance as to timing, urgency and survival of these patients.

The availability of data and the fact that one could show an aspect of the provision of ARV that could impact on its provision and action provides motivation for the completion of the study.

1.5 OBJECTIVES

1.51 General Objective:

To evaluate and compare cohort treatment outcomes of HIV infected TB patients and HIV infected non-TB patients treated with HAART at baseline, 3-month, 6-month and 12-month intervals at the TLC between April 2004 and April 2007.

1.52 Specific Objectives:

- To measure and identify differences in the following outcomes: CD_4 gain, undetectable viral load, death, loss to follow up and weight gain in HIV patients on HAART at the TLC at baseline, three months, six months and twelve months after initiation of HAART in the period of April 2004 to April 2007.
- To measure the effect of confounders on outcomes of ARV/HAART in TB+ and non-TB patients with at least one follow up visit in the period April 2004 to April 2007 at the TLC.
- To show regression, repeated measure and survival analysis of endpoints in TB+ and TB- patients of the TLC.

1.6 Literature review:

Introduction and Effect of HIV and TB

TB although known for more than thousands of years (>6,000 years) now, has had its control and eradication only becoming possible after the introduction of multi-drug chemotherapy in the 20th century (22). The number of cases of TB has increased exponentially worldwide during the last two decades. This has in part been accredited to the HIV pandemics, since HIV coinfection significantly changes the natural balance between man and the Koch bacillus (23, 24).

TB kills 2 million people every year globally. It was declared by WHO in 1993 "a global emergency" (25). The global epidemic is growing and becoming more dangerous. The emergence of multidrug resistant TB (MDR-TB) and extreme drug resistant (XDR-TB), and the spread of HIV are contributing to the worsening impact of the disease (26).

Other Related Studies

Few studies have so far been carried out in places like the UK, Thailand, Taiwan and Malawi, trying to show differing outcomes of ARV/HAART between TB+ patients and TB- patients. Generally most of these studies have used cohort designs. In Sub-Saharan Africa, up to early 2007 to the best of my knowledge there was no such study comparing outcomes of TB and non TB HIV patients in the post ARV era. The studies in Malawi seem to be the first around this region and this research should be the first of its kind in South Africa.

In principle, HIV-positive TB patients should benefit from ART, which leads to a reduction in HIV-related mortality and HIV-related recurrence of TB disease. So too in principle should HIV-positive non TB patients show better out comes when put on ARVs since they are on a single type of treatment and as such should present with better respond and adherence.

Two studies carried out in Malawi tried to compare outcomes of ART on patients who had TB and those that did not have TB. The first of this studies was more or less a general one considering data/information registered in the ART master cards and ART registers of patients who have been initiated into the ARV role out scheme of the country. Between 2004 and prior to the carrying out of the research, health facilities in Malawi were gradually becoming accredited and starting ART delivery services, and by March 2006, 66 sites were accredited and were delivering ART using the national standardized systems. Using a retrospective cohort study design Makombe, Haies et al selected a sample of 6967 non TB HIV patients and 938 HIV with

TB patients (total sample of 7905) and compared their 6months cohort outcomes.

This Malawi study (16) showed that HIV/AIDS patients with TB had a slight bigger proportion with better outcomes than those without TB. The study showed that a greater proportion of HIV/AIDS patients without TB died, defaulted or stopped treatment or were transferred when compared with patients with TB. Approximately 75% of HIV-positive TB patients were alive and on ART 6–12 months after starting ART compared to 71.5% for HIV-patients without TB. And if we had to consider that patients who were transferred or stop treatment were still alive at the 12^{th} month, then the proportion of HIV-positive TB patients who are alive at 6 and 12 months after starting ART would increase to approximately 80% as opposed to 78% for HIV-positive non TB patients.

This findings are in line with statements from Okwera et al. (27) who reported that cure rates are higher among HIV-infected TB patients while death (28; 29) and recurrence rates are lower (30; 31) with rifampicin containing than with non-rifampicin-containing regimens. Controversially, malabsorption of rifampicin and isoniazid has been reported in HIV-infected TB patients, resulting in reduced drug concentrations in tissues and blood and possibly worse treatment outcomes (32).

A second study carried out just along side the above in Malawi tried to compare such outcomes of ARV among children, (17). This study was aimed to determine outcomes of HIV-infected children at Mzulu Central Hospital, North Malawi who were started on antiretroviral therapy (ART) because of either active TB or a past history of TB within the two years prior to the

research and comparing them to those children with HIV but no history of present or past TB. This study showed no clear difference in outcomes in HIV infected children with or without TB and in fact, suggested that good outcomes are potentially achievable in HIV infected children on HAART both with TB and without TB. This study compared outcomes for children less than 14years of age at 6-month and at 12-month by using survival probability. It was noticed that at 6-month, survival probabilities for the groups though not the same were very close and high. The 6-month probability of survival was 0.86 for children with active TB, 0.94 for children with a past history of TB and 0.89 for children with a non-TB diagnosis. At 12 months the corresponding probability of survival was 0.86 for children with active TB, 0.86 for children with a past history of TB and 0.88 for children with a non-TB diagnosis. There was no significant difference in the outcomes for the three groups up to 12 months (log-rank test, P _ 0.59) (17). This study is in some way contradictory to the one by Makombe et al (16) which suggested better outcomes in HIV-TB patients than HIV-non TB patients. In this study comparing outcomes in children by Bong, Chen et al (17), there is no clear difference amongst the groups. Being the first and only available such study on children in Sub-Saharan Africa, the repeatability of this results cannot be ascertained but the same results have been shown by studies undertaken involving adults in other parts of the world.

The study comparing out comes of HIV/HAART in children (<14years of age) in Malawi is in line with a study carried out in 2003 by Hung, Chen, Hsiao et al in Taiwan (12). This study was structured to demonstrate the impact of ART on outcomes of HIV-infected TB patients in a consecutive

cohort of 716 HIV-infected patients receiving medical care from June 1994 to June 2002 at a University Hospital there in Taiwan (12). Using various statistical models, determining survival probabilities and adjusting for age, sex, year TB diagnosis or enrollement, baseline CD_4 cell count, and presence of concurrent AIDS-associated illness at TB diagnosis or enrollment, use of ART, and type of ART (HAART versus two NRTIs versus no antiretroviral therapy) the study showed differences in crude mortality rates of 14.31 per 100 person-years for TB-infected patients and 9.98 per person-years for the non-TB patients but showed similar risk of death among the two groups. The adjusted hazard ratio of the two groups of patients was 1.05 (95% CI, 0.73 – 1.49) and was similar in the two groups before and after the introduction of HAART. This hazard ratio was 1.18 (0.65, 2.14) before HAART and 0.89 (0.57, 1.69) after HAART for both groups of patients showing their similar outcomes of survival and death (12).

Research carried out in London by Keertan Dheda, et al (33) comparing outcomes of HIV-TB infected patients before and after the introduction of HAART shows a mark improvement in survival of patients infected by both TB and HIV. Comparing outcomes in patients starting TB treatment during the pre-HAART era (before 1996) with those patients starting treatment during the HAART era (during or after 1996) they came out with results that showed that HAART substantially reduces new AIDS events and death in co-infected patients. Those with a CD_4+ cell count !100 cells/mm3 have a high event risk during the intensive phase of anti-TB treatment as such recommended that such results should be taken into account when deciding to

delay HAART in co-infected patients with CD_4+ cell counts !100 cells/mm3 because it could be a very vital aspect of their survival (33).

Looking at the limited available literature on this subject, it becomes clear that one cannot confidently declare what the outcomes are like comparing HIV-infected TB patients and HIV- non infected TB patients. Studies carried out pre ARV/HAART era all showed very negative results in the out comes of patients treated/cared for with co-infection of HIV and TB. Many studies in South Africa and the world that look at outcomes of HIV co-infection with TB pre ARV era were done studying pregnant women or maternal mortality data. One of such studies carried out in South Africa in 2001 studying maternal mortality associated with TB and HIV-1 co-infection by M. Khana, et al, came out with staggering mortality rates/ death rates (34). Of a total of 50 518 deliveries, 101 maternal deaths were recorded. Of these deaths, 29.7% (30/101) were HIV-1 infected. The overall mortality rate was 200/100 000; for HIV-1-infected women this was 323.3/100 000, HIV-1-negative mothers, 148.6/100 000 live births. The attributable fraction of overall deaths as a result of HIV-1 was 15.9%. Fourteen of the 15 mothers with tuberculosis were HIV-1 co-infected. The mortality rate for tuberculosis and HIV-1 co-infection was 121.7/1000; for tuberculosis without HIV-1 co-infection, mortality was 38.5/1000 (34). This study in South Africa was in line with many other studies carried out in Africa before 2004 (before the introduction of ARVs by most countries) showing negative outcomes of HIV and TB co-infection going long ways to strengthen the notion that HIV combined with TB in an absence of ARV has more devastating effects. This is understandably and clearly seen when the clinical issues related with coinfection are studied. That is knowing

the precise problem of drug interaction, pathogenesis and immune reconstitution in HIV, TB coinfection. In an ARV era, comparing patients with those that are just HIV positive but free of TB.

Clinical Issues of HIV, TB and coinfection

TB and HIV infection have important and bidirectional interactions that impact on the epidemiology, natural history, clinical presentation, and management of each pathogen. (35)

Following successful transmission of HIV from one individual to another, the course of subsequent infection is quite variable and dependent on a number of factors. These factors include characteristics unique to the virus itself as well as a variety of cellular immune responses and other features of the host.(36) Acute or primary HIV infection (PHI) is followed by a variable period of time during which viral replication persists and an inexorable progressive immunologic decline results. Throughout most of this period, the patient may be entirely asymptomatic. However, the end result of consequent immunologic deterioration is a state of profound immune suppression that renders the infected individual susceptible to a multitude of opportunistic infections and malignancies (36). The degree of viral replication at this stage is the prime determinant of time necessary to progress from HIV infection to AIDS. Potential symptoms of HIV infection include fever, fatigue, headache, diarrhea, nausea and vomiting, weight loss, neurologic symptoms, sore throat, myalgias, arthralgias, night sweats and signs like Lymphadenopathy, Pharyngitis, with or without exudates, rash usually maculopapular, thrush, Hepatosplenomegaly, Oral ulcers and Genital ulcers (36). Initiation of ARV in HIV infected persons is generally influenced by the CD_4 count that decreases

with stage, level of HIV/AIDS and some opportunistic infections. With the knowledge that TB could also cause CD4 to reduce, the problem of actually determining the unset of ARV in co infection patients is highlighted.

Classic pulmonary TB, with upper-lobe infiltrates and cavitary lesions, may occur in HIV-infected persons with relatively intact immunity. As CD_4 cell counts decrease, TB is more likely to manifest atypically in the chest (without cavitary disease, or with lower-lobe disease, adenopathy, pleural effusions, or interstitial or miliary infiltrates), as extra-pulmonary disease.(37).

Tubercle bacilli incite an inflammatory response known as granulomatous inflammation Cell-mediated immunity and hypersensitivity reactions contribute to TB infection (38). TB bacilli enter the alveoli and are surrounded and engulfed by macrophages. Followed by the development of single, circumscribed granulomatous lesion called Ghon's focus (TB bacilli, modified macrophages, and other immune cells) (38). Ghon's focus undergoes necrosis within 2 to 3 weeks. This occurs at about the time that the tuberculin test becomes positive, suggesting that the necrosis is caused by the cell-mediated hypersensitivity immune response. At the same time, tubercle bacilli drain along the lymph channels to the tracheobronchial lymph nodes of affected lung causing caseous granuloma (38). First-line TB drugs identified include; Isoniazid, Rifampin, Rifabutin, Rifapentine, Pyrazinamide, Ethambutol and Second-line drugs; Cycloserine, Ethionamide, Streptomycin, Amikacin/kanamycin, Capreomycin, P-Amniosalicylic acid, Levofloxacin, Moxifloxacin, Gatifloxacin (38). With the amount and type of medication that is taken as anti TB, co infection registers another crisis of potential over medication and possible drug interactions when ARV is considered. Apart

from these considerations, there are reasons to avoid initiating antiretroviral therapy in patients with active TB, including avoidance of potential drug interactions and toxicities and avoidance of the "paradoxical response" or "immune reconstitution inflammatory syndrome" to anti-TB therapy that can be caused by immune reconstitution under antiretroviral therapy. This response, which has been observed soon after initiation of antiretroviral therapy, is characterized by persistent or increasing fever, severe pulmonary inflammation, and lymphadenopathy (14). But it has also been noticed the number of deaths that can be prevented when ARVs are commenced early in HIV/AIDS patients (CD_4 counts < 200) whether with or with out TB.

A biologic synergy exists between these infections and treatment: HIV-induced immunosuppression increases susceptibility to TB infection, and active TB infection enhances HIV replication through immunologic stimulation. The populations infected by these 2 pathogens overlap in many respects, creating epidemiologic synergy (37). Therefore actively caring and providing better wats to care for the two conditions is vital and until proven other wise most be done simultaneously. Trying to ascertain best possible period and differences that exist in outcome as a result of time when ARV was introduced is and shall play a very important role in going through this dilemma. Research and clinical studies that look into these aspects of HIV and TB need to be multiplied and supported. Recent guideline for treatment of co infection is; when not eligible for ART treat TB, when eligible for ART but CD4 > 200, treat TB first and defer initiation of ART until rifampin-containing regimen completes. But when eligible for ART and CD4 <200, treat TB and HIV at the same time (39).

CHAPTER 2

METHODOLOGY

2.1 STUDY DESIGN:

The study is a prospective cohort study. Data on patients on HAART at the TLC (At Helen Joseph Hospital) who have at least 1 follow up clinic visit in the period April 2004 to April 2007 is to be analyzed. Analysis will involve regression, survival and repeated measures analysis.

2.1.1 ABOUT THE TLC COHORT AND DESIGN OF THE COHORT

Started in April 2004 with the government role out date, the Themba Lethu Clinical cohort has been growing ever since. Today, TLC shows more than 9000 patients. These patients are followed up for ARV compliance and adherence, changes in HIV state, opportunistic infections and wellness programmes. The cohort is not designed particularly for research purposes, it is designed for the care of patients but since data/information that is collected from patients is well organized, managed and stored it serves as a good material for research and analysis. Information/data in TLC is collected systematically, prospectively and continually. A patient after initiation and first laboratory test will follow a monthly programme of re-visit to the clinic for collection of ARVs and weight verification. At certain months during these monthly visits, patients will carry out test like CD_4 counts, viral load examinations, hemoglobin counts, liver function tests, subjective opportunistic infection test amongst others.

Data/information that are stored on patients are collected using consultation forms, laboratory request and results forms, nurses clerking forms and also directly in a computer data base designed to enter patient information the

TherapyEdge-HIV™. Information on patients is confidential and visited by only designated staff members of the clinic and the Clinical HIV Research Unit CHRU.

The TLC cohort receives and follows up patients from any location of the country. It involves a variety of race even thought the black race is far more dominant. It cares for men and women, adults and children. Enrollment into the role out and programme for patients doesn't demand any specific requirements but for HIV sero-positivity.

2.1.2 STUDY POPULATION:

The study is a retrospective analysis of a cohort of appxoximately 6,000 patients who met the inclusion criteria and enrolled at the Themba Lethu Clinic between 31 April 2004 and February 2007. After data cleaning an estimated 5500 patients over the age of 18 years are expected to be available for analysis.

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2.1.3 QUESTIONNAIRE DESIGN

Apart from the forms (consultation, laboratory request and results forms) filled at initiation and at consultations, a computer based questionnaire is used to fill in required information obtained from patients either at consultation, ARV collection visits and from laboratory examinations. It is a four page TherapyEdge-HIV™ questionnaire that can be easily printed from the TherapyEdge-HIV™ data entry programme. It includes payment requisition forms and follow-up visit forms which are easily and directly linked with previously collected data in the data base using patient unique identifiers like

file id, pool id or id_patients. This computer base data entry form is in English and serves all purposes of data collection and entry at TLC.

2.1.4 WORK AT CLINIC/ FIELD WORK

Data/information on patients at the clinic is collected by an average of 60 trained health personnel; doctors, nurses, pharmacists and pharmacy attendants by means of consultations and laboratory test. Data used for this study will be information collect on patients between April 2004 and April 2007. Such information are collected each working week day where by patients come in for initiation, ARV collection and laboratory test. Data collection is systematic, continuous and repeated for each patient post initiation.

2.1.5 DATA PROCESSING

Data used for the study is information obtained from initiation, consultations and observations conducted during routine visits of patients for ARV on roll outs at the TLC. The data collection tools used here are basically patient's clinic files/forms filled by nurses and doctors. These information, are entered almost immediately into the TherapyEdge-HIV™ data management programme using the built in questionnaire. Information and data are also obtained from routine physical and laboratory examinations carried out on these patients when they come in at particular visits. From the TherapyEdge-HIV™, data is later transferred and managed using the SAS software package. Data entries are done by the personnel of the clinic. All data obtained is stored as a computerized data set and backed up in documents. These are only consulted by authorized personnel. Information/data on patients for this

research are management and obtained from the epidemiologist/data manager of the CHRU at the TLC-Helen Joseph Hospital.

The collection of the various variables is not simultaneous. Weight is collected every visit as patients come in for ARV clinical visits. CD_4 counts are carried out at baseline (day of initiation of treatment), 4^{th} month, 10^{th} month visits and each subsequent 6months visit. Viral load is done at 4months after starting ARV and repeated at intervals as for the CD_4.

All demographic and socioeconomic variables are entered in the form filled by patients at initiation visit.

2.1.6 QUALITY CONTROL

Information/data on patients of the TLC is constantly controlled for its quality. The data manager in place constantly checks and manages data. For the purpose of this research, most variables which where thought of as partially or poorly collected, where left out at analysis. Having information stored in patient files gives room of a recheck to make sure that an entry was rightly done.

2.3 STUDY SUBJECTS:

Patients' information/data from clinic (TLC) visits and examinations are studied for potential outcome differences in HIV infected patients with TB (HIV+TB+) compared to HIV infected patients without TB (HIV+TB-). In this study, There are actually 4 groups of patients: (i) those who never had TB; (ii) those with TB at ARV initiation + history of past TB; (iii) those with TB at ARV initiation + no history of past TB; (iv) those with no TB at ARV initiation + history of past TB [Another group which we shall not talk about in

this study are those that get TB while on ARV (either early or late)]. We will basically compare ii and iii (test group) against i and iv (control).

- ***Inclusion Criteria***:

- All study participants must be patients enrolled for ARV rollout or care at the TLC.

- Patients must have at least 1 follow up clinic visit after initiation, and must have been enrolled at clinic between 1st April 2004 and 1st April 2007 and are on regimen 1A which is the friendly most common regimen.

- All patients must be of age 18 and above.

- All patients must be on HAART, specifically, regimen 1A at initiation.

- ***Exclusion Criteria***:

- Any person with no follow up post initiation.

- Patients below 18years of age.

- Any person not on ARV or treatment regimen other than regimen 1A at initiation.

2.4 KEY WORDS:

- ***TB positive (TB+):*** All those on treatment for tuberculosis (Mycobacterium tuberculosis) at the time of ARV initiation whether diagnosed by laboratory examination or on clinical grounds.
- ***TB negative (TB-):*** All those without a current diagnosis of tuberculosis (No M. tuberculosis).
- ***HIV/AIDS Patient:*** Infected with HIV (40). AIDS is when an HIV patient has a CD_4 count less than 200 (41) and is infected/ becomes sick from opportunistic infections.

- ***HIV/HAART End Points (outcomes):*** Terminal or gateway. Those variables compared to determine differences among the various groups of patients, HIV+TB+ and HIV+TB-.

- ***ARV regimen 1A***: Regimen 1A is a combination of ARVs (lamivudine, stavudine and efavirenz) given to HIV infected patients with CD_4 counts below 200 as laid down in the CCMT guidelines. (42).

- **Case of TB**: The study considered every individual/patient on ARV regimen 1A at the Themba Lethu clinic who has been diagnosed with TB and was with TB/TB medication during the start of ARV.

2.5 VARIABLES OF INTEREST (Exposure & Outcome Variables):

2.5.1 *EXPOSURE/ EXPLANATORY VARIABLES*

Variables the study will use are those available in the data base. These variables include demographics, clinical investigations, laboratory examinations, and socioeconomic status.

a. Demographic and Socioeconomic Status.
   - Age of patient
   - Ethnicity/Race
   - Gender and employment status

b. Clinical Investigations
   - Visits to clinic
   - Weight

c. Laboratory examinations
   - CD_4 Counts
   - Viral Loads
   - Hemoglobin levels
   - TB status and liver function.

2.5.2 *OUTCOME VARIABLES*:

HAART/ARV endpoints/ out come variables will include:

- ***Viral load***: Detectable or undetectable from laboratory examinations.
- ***CD_4 count***: Determined from laboratory investigations at baseline, 4-6months and at 10-12months to determine an increase or decrease in counts.
- ***Weight***: This was measured to determine weight gains or loss as a result of

  continuous treatment. Measurement was done monthly.
- ***Hemoglobin counts/level***: Carried out by laboratory examinations to check for changes in blood counts. Measurement here will be considered at base and 1month.
- ***Died/loss to follow up:*** at any stage post start of ARV therapy (1, 3, 6, 9 & 12month).
- ***Liver function:*** Laboratory test will help in indicating adherence to medications.

2.6 HYPOTHESIS:

Anti tuberculosis medication has negative effects on the effectiveness and outcome of highly active antiretroviral therapy in HIV/AIDS patients.

2.7 Scope and Limitations.

As a prospective and secondary data analysis study, the investigation has a number of limitations. These are listed below;

a). The use of already collected data in itself meant that the researcher could not manipulate or amend any variable or collection tool. The researcher has to use what is available to him.

b). Some variables which could act as potential confounders like occupation/ wealth index are not examined due to their absence in the data set. Other variables in the data set could not be used because of partiality at collection phase.

c). As analysis is restricted to information/data on data set, biases such as measurement bias, recall biases which are more probably a concern to the study are not considered in analysis or in data cleaning.

This study relies on data captured at the clinic on TherapyEdge-HIV™. Some of this information does not match with the patient and some are incomplete. Even thought these draw backs exist, in all, TherapyEdge-HIV™ has greatly improved on data capture time and the follow up of patients. It has also improved data output and the transfer (export) of data to SAS. In all, the fact that data was readily available made it possible and realistic to carry out such a research.

2.8 PLANS FOR THE DISSEMINATION OF RESULTS

This study on approval and completion will be made available to the TLC, suggestions on how to improve on data and patients care will be addressed. Also the study will be made available for educational and research purposes for students and others who could need information. A plan for a poster or a publication is envisaged in order to keep the information as widely available as possible.

2.9 ETHICAL CONSIDERATIONS

Secondary data collected from patients on ARV treatment at the TLC will be analyzed in this study. Data is obtained already de-identifiable (coded) and as a computerized data set. Before obtaining the data from TLC, a form of the Standard Operating Procedure, norms and principles was read and signed by the student researcher declaring to keep data/information confidential and will be used for the sole purpose for which it was granted. This signed document acts as a prerequisite to obtaining information (data) and is also needed for TLC to provide a consent/go ahead for the data to be used for a study.

Study was ascertained to be in line with principles of non-maleficence, beneficence, and autonomy.

Ethical approval was obtained from the University of the Witwatersrand Ethical Committee.

2.10 DATA MANAGEMENT

Permission to use the Themba Lethu Clinical cohort data was obtained from the Helen Joseph Hospital according to protocol. That is an ethical clearance was first obtained for the study before authorization to use data could be granted. The data was downloaded from the TherapyEdge-HIV™ information software into SAS. This was done by the epidemiologist and data manager of the Themba Lethu Clinic/ CHRU. The imported data in SAS was de-identifiable. The data was checked for the complete collection of some variables and was then stored in five separate CSV datasheets (demographics, doctors visits, laboratory, conditions and pharmacy visits).

Further data management, cleaning and recoding was done using the statistical software package STATA 9.1 by importing and linking the CSV files in this

software package. A total of 52 variables were imported into STATA including variables mentioned in section 2.5.1 and 2.5.2 and other variables necessary to create them or necessary for multivariate analysis. Other variables created for survival analysis purposes included; treatment outcome which denotes those who defaulted and those who are continuing their ARV medications, BMI gain which shows success (a gain of more than 1uniy of BMI) and failure (anything less than 1unit BMI gain), weight gain with failure being any gain of 2kg (which is actually a positive outcome). Other variables include CD_4good which was a failure when an individual/patients CD_4 rose to greater than 200, astgood and altgood which were variables created to model survival analysis of the incidence and failures of liver function test (above 40 being failures), viral good which was a success (failure) when a patients viral load counts dropped to below 400. The last variable created purposely for survival and repeated data analysis was hbgood which showed failure (clinically positive) as when a patient registered a positive change in hemoglobin counts. The number of observations at this stage varied depending on the variables but was for a total number of 5818 HIV patients on ARV. These numbers of patients represent all the adults above 18years of age who were enrolled between the 1st of April 2004 and the 1st of April 2007 and who are regimen 1A of ARVs at the Themba Lethu Clinic.

A total of more than 3000 patients were excluded either because they were under 18years of age, not on regimen 1A, had no age attached to their observations or were not on ARVs. Some variables that were planned to be analyzed were dropped due to incompleteness in collection and very poor response. Employment status/profession was dropped because it was noticed

from investigations that most of the patients did not report their true employment status in fear of not being treated for free or at a lower cost. Generally the data was made usable in STATA and the variables used altogether had a response rate and or completion of more than 90%.

2.11 DATA ANALYSIS

Data set obtained from the TLC in SAS format was analyzed in STATA a conversion that passed through CSV data format. This conversion was done due to the researchers experience and knowledge in working with STATA.

Some continuous variables were categorized prior to analysis in order to ease the analysis process. These variables include: age at enrollment into the TLC ARV roll-out programme was categorized into five groups, all those18 and more but less than or equal to 25 fell in the first category 18 – 25, all those greater than 25 but less than or equal to 35 are in the group 26 – 35. Those in the group 36 – 45 were more than 35years old but less than or equal to 45, the group 46 – 55 was made up of those greater than 45 years of age but less than or equal to 55 and the last group those older than 55 years (>55). Ethnic group like other variables was re-categorized into four groups; Blacks, Asian, coloured and white. This was done by combining certain response that showed to be close or same. Other variables like Conditions were generated from infections and then re- categorized into either having TB or not (0 = TB & 1 = NonTB). The outcome condition dead was categorized into either Yes for someone who died and No for any individual still alive. A new variable was also created to use in analysis known as tbgroup. This variable shows the interval when individuals were reported of having TB that is before, during

(had TB before the start of ARV and recovered after ARV onset) or after the start of ARVs and those who never had TB. Another variable arvstatus shows three potential outcomes; defaulters, loss to follow up and those still adhering to their drugs. From arvstatus, loss to follow up was created to comprise of all defaulters and those loss to follow up. At TLC, patients are called 'defaulters' if they have failed to keep an appointment within a month and 'lost to follow up' after three months. Such patients are actively traced by telephone and home visits but many remain untraceable. It is generally believed that most of the defaulters and those loss to follow up either were receiving treatment in other health centers or were dead. Generally, the mean follow up time for all those lost to follow up was about 248days while the total mean follow up of all patients was 422.5days. All laboratory outcomes; CD_4 counts, viral load, HB, AST, ALT were maintained and analyzed as continuous variables. These variables were cleaned by removing extreme observations. Variables like weight was measured in kg and cleaned while height was measured in centimeters after some cleaning had been done. A variable for BMI (bmi) was generated to actually see and differentiate the changes in body mass index over time in our two groups of patients. At this stage most of the non-required variables from the original data set were dropped and each data set was left to contain demographics and the important variables of the category.

Analysis carried out using already collected computerized data from the TLC was done in three levels. Data analysis involved all eligible HIV infected patients on ARV therapy at the TLC from April 2004 to April 2007.

The three levels of data analysis started with descriptive data analysis which was carried out describing the distribution of CD4 counts at base, 3 months,

6months and 12months, viral loads, weight, BMI, liver function (AST & ALT) and hemoglobin levels, describing any differences among patients who had TB and those without TB/ who have never had TB. At this stage results are shown as frequencies, means, proportions and standard deviations. These results are shown in tables and graphs histograms and pie charts.

At the Second level of analysis, univariate and bivariate analysis was carried out, trying to ascertain relationships between any of the explanatory variables and the outcome variables. Cross tabulations, Relative risk, p values, and confidence intervals and associated chi-square values are shown as necessary.

In the third level of analysis, Linear Regressions and multivariate analysis was done to quantify relationships and show estimated changes over time. At this stage, survival and repeated measures analysis was also carried out and results are shown in tables, graphs and plots for curves. Through out the analysis process, to see and show the effect of the duration and or time a patient had TB, most models were modeled to take into consideration the tbgroup. At other points differences are ascertained by gender and age group. Assumptions were checked by using histograms, and other parameters to acknowledge distribution of results.

After all analysis was carried out, a comparison between the different groups of HIV patients was done to show, see and outline differences in the outcomes of HAART among TB patients and non-TB patients.

CHAPTER THREE

RESULTS

3.1 CHARACTERISTICS OF COHORT PARTICIPANTS

The study had as main objective to show and evaluate the differences in outcomes and ARV response in patients of two different groups that is, those HIV patients who at a point in time presented with TB against those who have never had TB. With age considered at 18 years and above and regimen 1a considered as ARV therapy of choice, the study cohort had 5818 participants, 36.04% of which were males (2,097) and 63.96% females (3,721). There was a general average of 422.51 days of follow up while those lost to follow up had in average 248 days of follow up. This chapter shall actually try to statistically determine such differences in TB and non TB patients. This shall be done by carrying out several statistical models. As regarding the distribution of TB and Non TB patients, it was noticed that 19.23% (1,048) of the patients had been diagnosed with TB at some point in time while 80.77% (4,770) had never been diagnosed with TB. Figure 3.1 shows a pie chart of the distribution of patients followed up at TLC between 01st April 2004 and 01st April 2007 by gender.

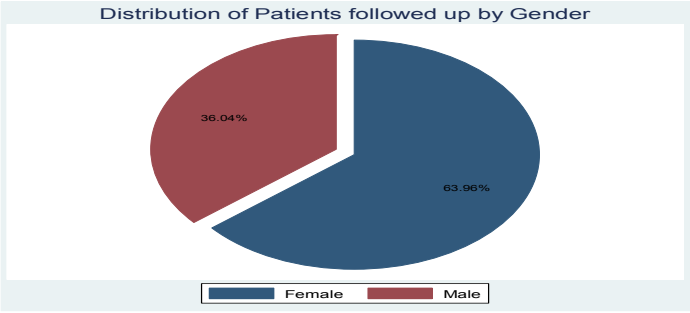


Fig 3.1: Percentage distribution of Patients by Gender

By April 1st 2007, a total number of 269 (4.62%) patients had been reported dead from the cohort and a further 1,278 (21.99%) had stopped receiving ARV (loss to follow up). With the assumption that any other person was still alive, the study had more than 73% of its participants surviving to the censoring date of April 1st 2007. Figure 3.2 below shows distribution of deaths among the two groups of patients, where 4.96% of all TB patients are shown to have died while death amongst those who never had TB was 4.32%.

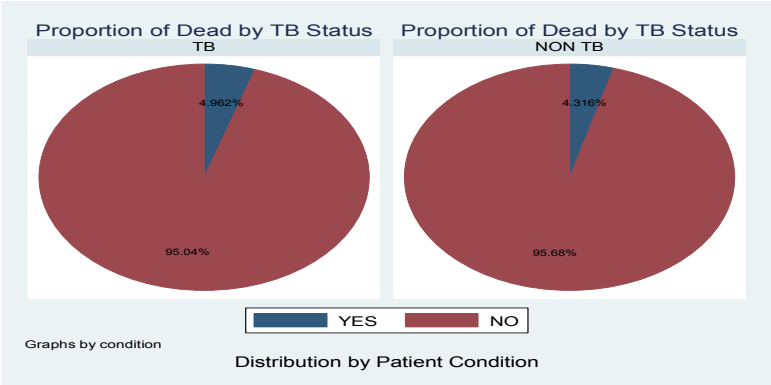


Fig 3.2: percentage distribution of deaths by TB Status

Table 3.1 below shows cohort patient distributions by some demographic factors, physical and health status/states. In the general population of the cohort 78% of the patients were between 26 to 45 years old ascertaining literature that shows this age group as one with the greatest incidence and prevalence of HIV. This age interval was also noticed to be the interval accounting for the greatest number of deaths and default/loss to follow up.

Many demographic variables on patients from the TLC cohort were not available for analysis. These variables such as residence, economic status, profession, religion and marital status were either very poorly collected or were not collected at all during regular patient visits for ARV collection or physical/ laboratory examinations. The TLC cohort patients presented as more

of females (63.96%) than males (36.04%) with 95.68% of

Table 3.1: Numbers and proportions for some variables in the cohort

No.	Variable	Category	Frequency (%)	
1.	Age group	18 – 25	265	4.55
		26 – 35	2,355	40.48
		36 – 45	2,193	37.69
		46 – 55	808	13.89
		>55	197	3.39
2.	Ethnic Group	African (Black)	5,556	95.68
		Asian	14	0.24
		Coloured/Hispanic	213	3.67
		White	24	0.41
3.	Gender/Sex	Male	2,097	36.04
		Female	3,721	63.96
4.	TB State	Non TB	4,770	81.99
		TB	1,048	18.01
5.	Time of occurrence TB	Before ARV start	346	5.95
		During ARV	632	10.86
		After	39	0.67
		Never had TB	4,770	81.99
6.	Treatment Status	Loss to follow up	1,278	21.99
		Continuing treatment	4,264	73.38
		Dead	269	4.63

the patients considering them selves as blacks and less than 5% being either Asians, whites or coloureds. Amongst those who started treatment (ARV) between April 1st 2004 and April 1st 2007 at the TLC, 21.99% either defaulted or had a loss to follow up in that same 3years period of time. In the 78% that presumably continued treatment, a number of them died. The total number of

patients who died in the cohort amount 269 (4.63%)

Considering those loss to follow up and deaths, we had 4264patients who were alive at the end of 1st of April 2007.

Table 3.2: Distribution of Demographic categories by TB status

No.	Variable	Category	Frequency (%)			
			Non TB	%	TB	%
1.	Age group	18 – 25	213	80.38	52	19.62
		26 – 35	1,892	80.34	463	19.66
		36 – 45	1,801	82.12	392	17.88
		46 – 55	687	85.02	121	14.98
		>55	177	89.85	20	10.15
2.	Ethnic Group	Black	4,556	82.00	1,000	18.00
		Asian	10	71.43	4	28.57
		Coloured	173	81.22	40	18.78
		White	21	87.50	3	12.50
3.	Gender/Sex	Male	1,640	78.21	457	21.79
		Female	3,130	84.12	591	15.88
4.	Treatment Status	Loss to follow up	1,031	80.67	247	19.33
		Continuing treatment	3,517	82.48	747	17.52
		Deaths	217	80.67	52	19.33

Table 3.2 above shows the distribution of various conditions and or states by patient record of TB. That is, if a patient ever presented with TB or not.

The TLC cohort shows a greater proportion of the young adults developing TB in HIV than the aged. Those below 35years of age presented with no less than 18% of their population with TB at one point of their sero-positive state. Skeptically, we see that of all the deaths, only 19.33% were ever TB infected while 80.67% had never been infected. Males in this cohort seem to be more

predisposed to developing TB as those who developed TB at one point in time make up 21.79% of the male population while for females; only 15.88% of them ever developed TB. The ethnic group with the highest proportion of TB by percentage is the Asians who had a total 28.57% of their general number presenting with TB. However the total number is small. They are followed by the coloureds and Africans with 18.78% and 18.00% of their total population respectively presenting with TB. For viral load which is not on the table, it was noticed that baseline observations showed that 88.83% of non TB patients had first viral loads below or equal to 400 while 11.17% presented with viral loads greater than 400. Amongst the TB patients, 89.34% of them had first viral load counts less than or equal to 400 and 10.66% of them presented with viral load counts greater than 400.

As regards the summary of continues variables, the cohort noticed and compared means of several variables including BMI, age, CD_4 counts, hemoglobin counts, weight, and the liver function tests of ALT and AST.

Table 3.3 below, shows studentised t-test mean of some baseline outcome variables by patient's TB status. From the table we notice that the mean of ALT one of the LFT in both groups of patients (TB and Non TB) stayed at clinically acceptable figures between 5 and 40. With the other LFT AST, figures are higher in both TB and non TB patients, and are significantly different in both groups. Differences in means among those who have ever been TB infected and those who have never had TB are also noticed when considering their various BMI. The figures of 22.58 and 20.76 for non TB and TB infected patients respectively could signify that those with TB either do loss more weight than non TB patients by the onset of ART.

Table 3.3: Comparing means of first observations by TB Status-ttest distribution

No.	Variable	TB Status	Mean	Std. dev	ttest 95% CI	Obs.	p. value
1.	BMI	Non TB	22.58	4.83	22.42 - 22.75	3187	<0.0001
		TB	20.76	3.87	20.56 - 20.95	1462	
2.	Weight	Non TB	60.30	12.80	59.88 - 60.72	3538	<0.0001
		TB	55.97	10.60	55.44 - 56.50	1566	
3.	CD_4	Non TB	113.47	104.68	107.41 - 119.52	1151	<0.0001
		TB	88.85	75.68	82.48 - 95.22	545	
4.	Hemoglobin	Non TB	11.90	2.34	11.15 - 11.42	1186	
		TB	10.51	2.20	10.33 - 10.70	562	<0.0001
5.	Log Viral Load	Non TB	4.48	1.09	4.41 - 4.55	913	0.8237
		TB	4.50	1.11	4.39 - 4.60	469	
6.	ALT	Non TB	31.34	33.80	29.43 - 33.25	1205	
		TB	35.80	48.28	31.89 - 39.70	590	<0.0001
7.	AST	Non TB	44.19	42.05	41.82 - 46.57	1206	<0.0001
		TB	55.18	50.58	51.09 - 59.27	589	
8.	AGE	Non TB	37.37		37.13 - 37.62	4770	<0.0001
		TB	36.20		35.72 - 36.68	1048	

The same trend is noticed with weights of the two groups of patients where the baseline mean is higher in those who have never had TB than those who at a point in time have had TB. This trend also repeats it self with means of CD_4 and Hemoglobin counts which are higher in Non TB than in one time TB patients. The mean viral load (considered as a continuous variable) is higher in any time TB patients than those who never had TB, 171.23 and 165.90 respectively. What is evident here is the fact that baseline mean viral load is far below 400. This is so because TLC has as protocol to check viral loads

only three months after the start of ARV and could prompt us to arguably say those who never develop TB do better when it comes to viral load decreasing. All these means also have some trends when we examine them by the time of

Table 3.4: Distribution of change in outcome means by Months After Initiation of ARV

No.	Var.	TB G.	Mean (Std. Dev) by Months of test post initiation on ARV				
			Baseline	3	6	9	12
1.	CD_4	Non TB	103.23 (102.58)	+109.02 (142.14)	+117.80 (125.05)	+127.82 (131.54)	+179.60 (140.60)
		TB	78.35 (71.91)	+101.81 (112.49)	+142.29 (131.34)	+161.56 (128.49)	+179.55 (136.67)
2.	Weight	Non TB	60.46 (12.46)	+0.98 (13.15)	+3.88 (12.51)	+4.99 (12.75)	+6.30 (12.38)
		TB	56.66 (11.05)	+0.63 (11.52)	+3.92 (11.54)	+6.16 (12.57)	+7.99 (12.68)
3.	BMI	Non TB	22.66 (4.65)	+0.41 (4.92)	+1.46 (4.62)	+1.92 (4.98)	+2.47 (4.66)
		TB	21.04 (4.07)	+0.25 (4.31)	+1.44 (4.16)	+2.22 (4.61)	+3.05 (4.67)
4.	ALT	Non TB	34.98 (37.81)	-3.87 (25.25)	-3.86 (23.90)	-4.91 (21.30)	-4.81 (21.63)
		TB	37.74 (35.12)	+3.84 (41.32)	-4.1 (39.48)	-8.26 (22.38)	-6.48 (25.32)
5.	AST	Non TB	48.21 (58.90)	-9.12 (23.00)	-9.99 (24.95)	-11.05 (27.57)	-11.53 (24.06)
		TB	56.98 (44.02)	-4.08 (33.95)	- 14.77(23.69)	-17.49 (24.62)	-17.51 (30.32)
6.	Hb	Non TB	11.22 (2.14)	+0.55 (2.19)	+1.25 (2.06)	+1.09 (2.10)	+1.74 (2.02)
		TB	10.30 (2.13)	+0.66 (1.96)	+1.99 (1.98)	+2.24 (1.86)	+2.59 (2.38)

occurrence of TB (table 3.4). Figures and trends are shown in table 3.4 above. From table 3.4 above it should be noted that baseline for CD_4 is considered as 2months prior to and 1month after start of ARV. Other baselines values are taken within 1month of start of ARV.

Figures 3.3, shows graphical distribution of weight among four groups of patients. Those who had TB and was cured before they started ARV (before), those who had TB and started ARV while still treating their TB (during), those who had TB long after they had started ARV medication (after) and lastly those who never had TB (never).

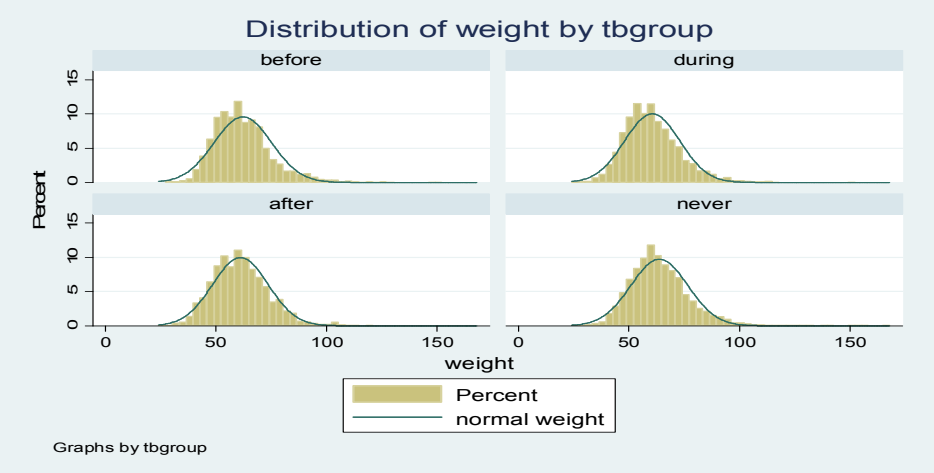


Fig.3.3 Distribution of weight by TB group

The distribution of weight as seen in figure 3.3 looks to be fairly symmetrical. The same symmetry is seen in figure 3.4 where Hb distribution is shown by TB group. On the other hand, figure 3.13 (appendix) shows graphical distribution of CD_4 counts and looks asymmetrical in the four groups.

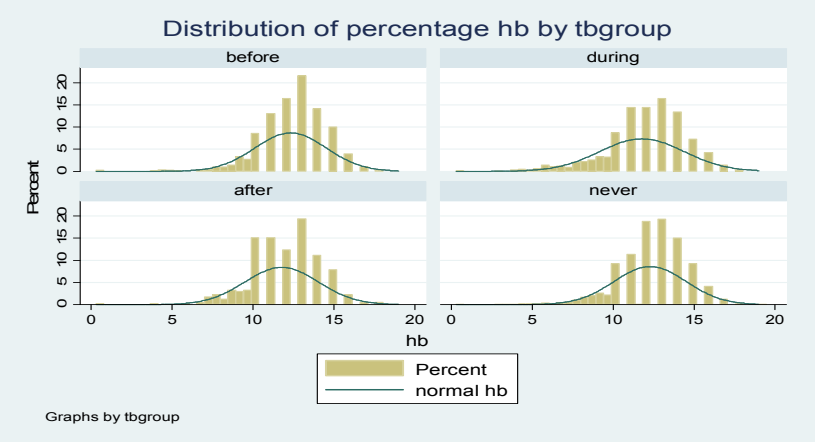


Fig.3.4 Distribution of hemoglobin counts by TB group

The distribution of weight and BMI over time also shows some clear signs of a trend (Table 3.4). These trends are better evident when looking at weight change over time among patients who have never presented with TB. The mean weight for this group moves from 60.46 at baseline to 61.44 in the third month of starting ARV, 64.34 by the sixth month, then 65.45 and 66.76 for the , 9^{th} and 12^{th} month of ARV initiation respectively. The trend of weight for those who have presented with TB follows same and increases over time. This is also true when BMI is considered were there is a constant increase in average BMI over time for both groups of patients.

3.2 BIVARIABLE ANALYSIS

Table 3.5 shows risk ratios of patients who had ever had TB (exposed) against those who have never had TB (unexposed). The risk among those who had TB of dying is 49.62deaths per 1000persons who have TB while that for those who never had TB is 45.49deaths per 1000persons without TB. This is also shown by some demographic factors sex, ethnic group, and age group. The

risk ratio is of two types, risk of dying (death) and the risk of defaulting/loss to follow up.

Table 3.5: Bivariate Analysis of TB status Risk Ratio of dying by Possible Confounders

No.	Variables	Category	RR of dying	Confidence Interval	P. value
1.	General		1.09	0.81 - 1.47	0.5647
2.	Sex	Female	1.13	0.76 - 1.69	
		Male	1.00	0.64 - 1.56	0.6860
3.	Age group	18 – 25	1.12	0.32 - 3.86	
		26 – 35	1.38	0.87 - 2.19	
		36 – 45	1.14	0.72 - 1.79	0.5490
		46 – 55	0.50	0.16 - 1.61	
		>55	0.59	0.08 - 4.23	
4.	Ethnic group	Black/African	1.02	0.74 - 1.39	
		Asian	_		
		Coloured	1.57	0.53 - 4.68	0.4474
		White	_		

Tables 3.6 below, shows bivariate risk ratio for patients, whether exposed or not, who default or are lost to follow up. Exposure is having TB at any point in time while those who never had TB are the unexposed. In both tables 3.5and 3.6, there is no statistical evidence to say for sure that a particular group of persons or categories of persons have a higher risk of dying or defaulting as all confidence intervals contain 1. The only exception of this is noticed among those aged 18 – 25 where they show 1.51times more likely to default. Still the overall p value is far from significant.

Table 3.6: Bivariate Analysis of TB RR for Loss to Follow up by Possible Confounders

No.	Variables	Category	RR Loss to follow up	95% CI	P. value
1.	General		1.06	0.95 – 1.20	0.3051
2.	Sex	Female	1.08	0.92 – 1.26	
		Male	1.01	0.85 – 1.20	0.6009
3.	Age group	18 - 25	1.51	1.01 – 2.25	
		26 - 35	1.15	0.97 – 1.36	
		36 - 45	0.98	0.79 – 1.20	0.1775
		46 - 55	0.82	0.55 – 1.21	
		>55	0.94	0.42 – 2.09	
4.	Ethnic group	Black/African	1.08	0.96 – 1.21	
		Asian	0.83	0.12 – 5.82	
		Coloured	0.91	0.48 – 1.70	0.8683
		White	0.64	0.12 – 3.32	

3.3 LEVELS AND DIFFERENTIALS (random effect linear regressions)

To have an idea and make reasonable statistical inferences on different outcome variables relating to their changes over time after the start of ARV at the TLC, we plot regression models to evaluate this relationship between these variables by TB state or history of the patient. Table 3.7 shows coefficients, corresponding 95% confidence intervals and p. values for the relationship of various outcome variables with time. That is the trend of this outcome variables are studied to compare changes in the two groups of patients (TB and Non TB) over time (time after initiation of ARV and time is in Months).

With all statistically significant coefficients, constants, and likelihood ratio statistic (likelihood ratio chi2- LR chi2), the progress of these outcome variables over the period post the start of ARV is shown to be slightly different among the two groups of patients- TB and non TB patients. The regression models plotted considered time in months after the start of ARV. Among patients who have ever been tested with TB, we could fit a model;

$$y_{it} = \beta_0 + \beta_1 \text{periodstart} + u_i + e_{it}$$

Where "periodstart", is number of months after the start of ARV therapy.

Table 3.7: Regression Coefficients for relationship of Outcome variables with Time

No.	Variables	TB group	Constant	Coefficients	Conf. Interval	P. value
1.	BMI	Non TB	23.12	0.06	0.06 - 0.07	< 0.001
		TB	21.53	0.11	0.10 - 0.11	< 0.001
2.	Weight	Non TB	61.63	0.17	0.16 - 0.18	< 0.001
		TB	57.96	0.30	0.28 - 0.31	< 0.001
3.	CD_4	Non TB	194.25	7.56	7.22 - 7.91	< 0.001
		TB	186.92	6.92	6.46 - 7.37	< 0.001
4.	Hb	Non TB	12.22	0.04	0.035 - 0.045	< 0.001
		TB	11.88	0.06	0.05 - 0.07	< 0.001
5.	ALT	Non TB	31.96	-0.26	-0.33 - -0.19	< 0.001
		TB	33.98	-0.21	-0.32 - -0.10	< 0.001
6.	AST	Non TB	41.15	-0.53	-0.61 - -0.45	< 0.001
		TB	47.19	-0.64	-0.74 - -0.54	< 0.001

From this equation, we can see that with every unitary increase of periodstart that is every 1 additional month that passes sees average CD_4 counts for non TB patients increasing by almost 7.56 while that of those who at a point in time have been TB positive have lower increases of 6.92 with every additional month that passes post ARV initiation. BMI, weight and hemoglobin averages are greater in non TB patients than in TB patients at start of ARV. In both groups the is a very slow increase as months go by but these increases are very slightly higher in any time TB patients than those who have never had TB. These is clear as coefficients are less than 1 and are always higher in TB patients for these variables. Also all coefficients, constants and LR chi2 are statistically significant with p. values < 0.05.

The linear model that requested the maximum likelihood estimator also shows a decreasing number of liver function test counts with increasing months. With negative coefficients, AST decreases slightly faster in those who have had TB at some point than those who have never had TB. If their coefficients are fitted in the model equation that takes into account the structure of observations, the decrease is noticed to be slightly bigger in TB patients than non TB patients as the latter have bigger negative coefficients. The trend in ALT is a faster decrease among non TB patients than those who have ever had TB. Generally, we notice that ALT, Hemoglobin, weight and BMI start up with average mean values that are clinically acceptable for persons aged 18 and above. With AST, those who have never had TB had as mean 41.15 (when we fit 0 to the equation) at start of ARV which is clinically unacceptable (5 – 40). Also, those who had TB at some point before or after the start of ARVs had greater and clinically unacceptable means for AST.

3.4 SURVIVAL ANALYSIS

Data was analysed using survival analysis in two ways. Analysis was done on demographics and the more binomial/categorical out come variables as death and ARV status. Survival analysis here was done as a simple one subject to one out come survival analysis; start time being the date when a patient started ARV medications at TLC and censored at April 01st 2007. An individual here had either survived or failed. In the second survival analysis, repeated data analysis was carried out. This involved longitudinally collected data and had as end points levels of CD_4 count, viral load, hemoglobin counts, AST and ALT levels, weight and BMI changes and gains. Survival or failure is determined by the occurrence of an event adopted at levels determined for each variable. Since patients start ARV when the CD_4 counts drops to < 200 a CD_4 count greater than 200 was considered to be an event. For viral load the event was a viral load <400 (the lower limit of delectability in the assay used). For the test of liver function AST and ALT, failure occurs when an individual test scores above 40.. Failure with regard to hemoglobin occurs when an individual registers a negative change in hemoglobin. In regard to BMI and weight, failure and or success is achieved when an individual gains more than 1 BMI point or gains more than 5% of weight respectively for the two variables. Even though these end points are positive results we use them as 'failures' in the syntax of STATA survival analysis. Table 3.8 shows incidence rates per 100 patient years of the occurrence of the above 'failure' events while Table 3.9 shows RR obtained from multivariate models; Mantel-Haenszel survival time/rates having controlled for sex, age group, ethnic group and time from start of AVR (startgorup).

Table 3.8: Incidence rate and ratio of failures in specified end point Variables

No.	Variables	Inc. Rate Ratio	Inc. RR 95% CI	Inc. TB	Inc. Non TB
1.	BMI	1.25	1.21 - 1.28	382.96	307.25
2.	Weight	1.40	1.35 - 1.45	291.25	208.08
3.	CD_4	0.94	0.85 - 1.03	124.88	133.21
4.	Viral load	1.02	0.93 - 1.11	173.93	171.23
5.	Hb	0.77	0.63 - 0.94	24.54	31.70
6.	ALT	1.20	1.01 - 1.42	46.46	38.86
7.	AST	1.35	1.17 - 1.56	66.77	49.42
8.	Dead	0.93	0.66 - 1.28	3.84	4.16
9.	Loss to follow up	0.54	0.44 - 0.66	06.14	11.40

The incidence rate of dead among those patients whom at one point after being sero-positive developed TB is at 3.84 deaths per 100 patient years while among those who never had TB its 4.16 deaths per 100 patient years giving a rate ratio of 0.93. This difference of a greater incidence of deaths among non TB patients is not statistically proven if we consider that the confidence interval of the rate ratio does includes 1. Regarding loss to follow up, that is whether an individual defaulted treatment or stopped coming for ARV, we notice that those who never had TB presented with higher incidence rates. They are 46% more likely to default than those who at one point have had TB (RR 0.54). The non TB patients have an incidence rate of 133.21 patients reaching CD_4 counts greater than 200 per 100 patient years. This rate compares those who have had TB (124.88) with a rate ratio of 0.94 and CI

0.85 - 1.03. Looking at this rate and CI, we notice there is no real difference in changes of CD_4 count between non TB patients and those who had TB. The same trend is noticed when comparing viral load between the two groups of patients where we notice that there is also no clear difference in patients reaching viral load test counts of 400 and below. The incidence rate of a patient having a positive gain in hemoglobin is statistically higher among non TB patients than those who had TB with a rate ratio of 0.77 comparing TB against non TB patients with CI 0.63 - 0.94. In the test for liver function, those patients who ever had TB presented with greater incidence of poor liver function (AST and ALT results of more than 40). In both AST and ALT results, rate ratio which are 1.35 and 1.20 respectively present with statistically significant CI which do not include 1. This shows that failure is higher when considering liver function test among TB patients than non TB patients. When it comes to body gains, it is noticed that TB patients seem to gain BMI more than non TB patients. The incidence of patients gaining more than 1unit of BMI is higher among TB patients than among non TB patients. This is the same trend noticed with weight where more onetime TB patients have higher incidences of more than 2kg gain of weight than non TB patients.

In line with the incidences on table 3.8, survival and failure curves show graphically differences and similarities as seen. Figure 3.5, shows how there is a possible difference in deaths between TB and non TB patients. The survival curves for deaths in both HIV groups are close to each other. On checking for differences using Log Rank Test for equality of survival functions a p. value less than 0.0001 was obtained but a hazard function graph of the two patient

groups shows non parallel lines. This denies any assumption of similarity in the two groups with respect to incidence of deaths (Appendix B)

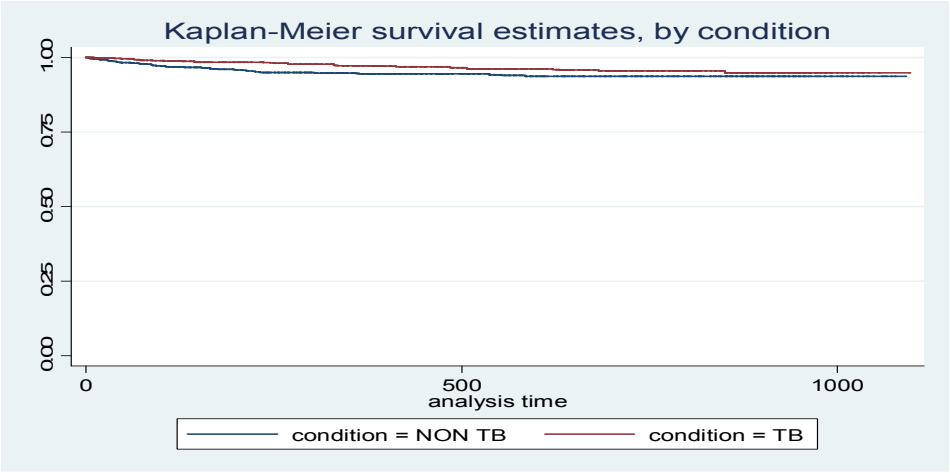


Fig.3.5 KM Survival curve for deaths by person days in cohort

Figure 3.6, shows possible difference in out come of BMI between TB and non TB patients. It shows how fast every body gains more than 2kg in the cohort. Its failure curve at the appendix B shows the incidence of gaining 2kg in the cohort.

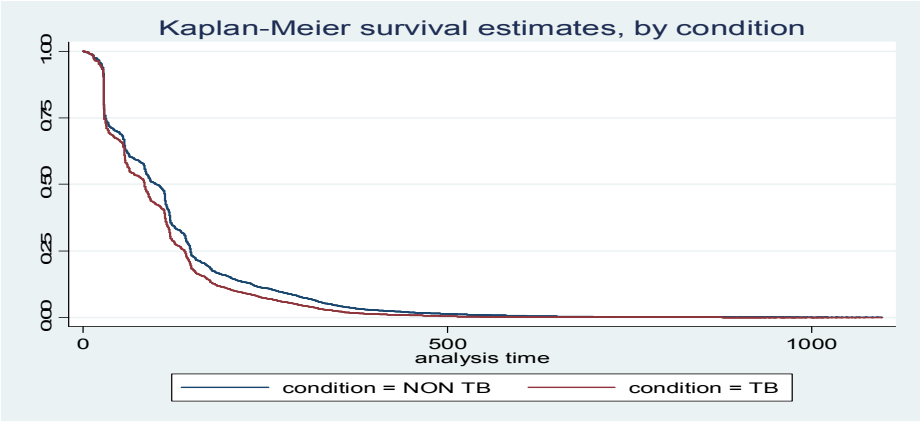


Fig.3.6 KM Survival curve in attaining +2kg in the cohort

This difference in BMI in the two groups is statistically evident as a hazard function graph shows parallel lines for the two groups (figure 3.7) and log rank test presents with p.value 0.0001. Log rank test of equality of survival curves are for other outcome variables are shown in appendix B.

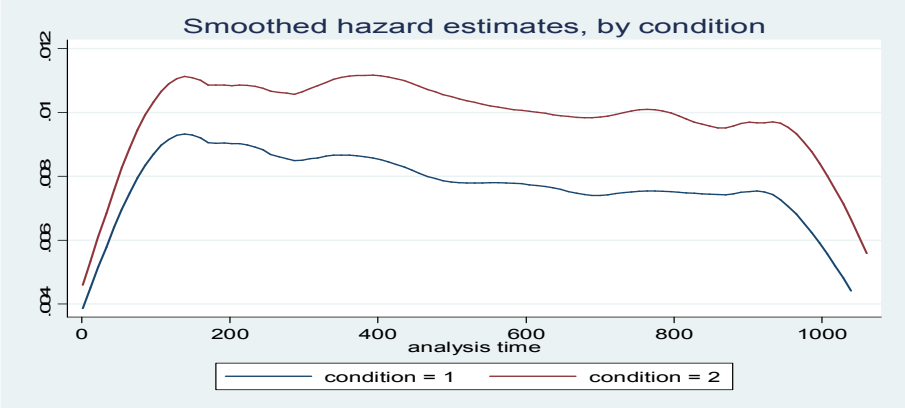


Fig. 3.7 Smooth hazard estimates of weight gain

Where condition 1= Non TB and Condition 2= TB

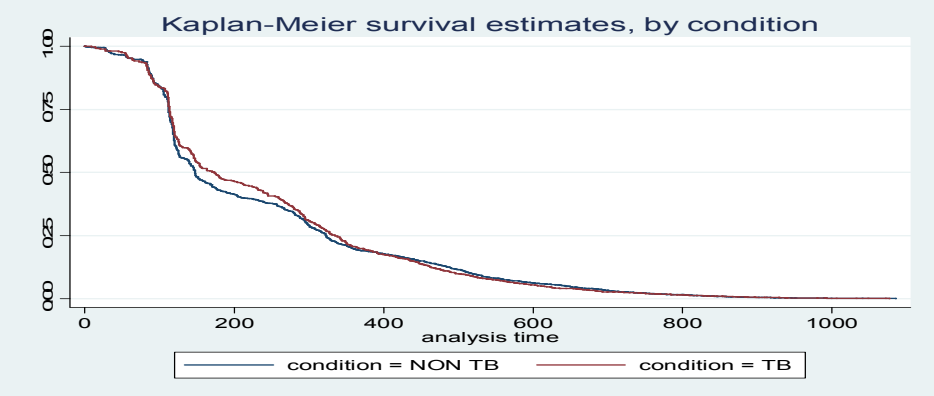


Fig.3.8 Survival curve showing proportion of viral load <=400

Figure 3.8 above shows how survival event which in this case shows almost every individual attaining viral load <=400 are reached by patient group TB and non TB. From the graph, no clear difference is noticed. This supported by the log rant test p value 0.83 which shows no significant difference in survival outcomes of attaining undetectable viral loads (<400) in the two patient groups. Failure curve for viral load shows proportion of patients attaining viral loads <=400 with person time (Appendix B.)

Figure 3.9 below shows survival curve of loss to follow up. It gives the probability for an individual to still be in the cohort with time (days).

From the graph it is almost clear that loss to follow up is not similar in both groups of patients. In appendix B failure estimates, which is the probability of failing or of dropping out of the cohort are shown for the two patient groups with log rank test of equality of survival curves. The test shows a difference in the two groups with p.value < 0.0001 and a smoothed hazard curve with parallel lines. This probability does not consider those who died.

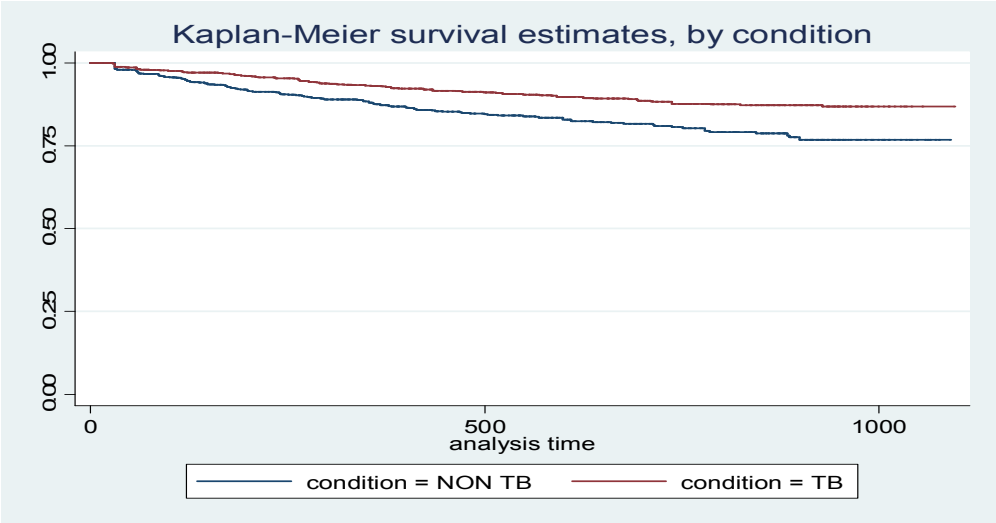


Fig.3.9 survival curve those who stayed in the cohort

3.4 MULTIVARIATE SURVIVAL ANALYSIS

In an attempt to explain the effects on the rate ratio of the study end points, models were fitted that take in to consideration sex, age group, ethnic group, and start group (month in which test or observation was done post ARV initiation). Table 3.9 below shows this multivariate analysis by the various survival end points. In this analysis having considered possible and available confounders as gender, age, ethnic group and interval from when a patient started ARV we noticed different outcomes. A negative confounding effect

was noticed of these confounders when we looked at the incidence rate ratio of deaths in the two groups of patients. In the multivariate analysis, the was no

Table 3.9: Multivariate survival analysis for RR of outcomes considering demographics

No.	Variables	Rate Ratio	RR 95% CI	Chi2	P. value
1.	BMI	1.29	1.25 - 1.32	301.31	< 0.001
2.	Weight	1.43	1.38 - 1.48	443.17	< 0.001
3.	CD_4	0.96	0.87 - 1.06	0.74	0.391
4.	Viral load	1.00	0.91 - 1.10	0.00	0.990
5.	Hemoglobin	0.81	0.67 - 0.995	4.05	0.044
6.	ALT	1.17	0.98 - 1.39	3.17	0.075
7.	AST	1.36	1.17 - 1.57	16.42	< 0.001
8.	Dead	1.41	0.66 - 1.52	1.21	0.272
9.	Loss to follow up	0.76	0.60 - 0.95	5.80	0.016

difference in the incidence of deaths among HIV TB patients and HIV non TB patients as they showed an RR CI including 1. This effect was also found to be non significant with p.value> 0.05. Among the defaulters (Loss to follow up), a statistically significant negative confounding effect was found. Controlling for age, sex, ethnic groups and time increased the RR to 0.76 [p.value = 0.016]. This shows that though reduced, many more non TB patients defaulted than those who had TB at one point. The HIV patients without TB are 24% more likely to default. Difference in defaulting in the two groups of patients was also supported by parallel smoothed hazard curve lines and log rank test with p value < 0.0001. Negative confounding effects were

also noticed in the out comes of AST, Hemoglobin, and BMI with all significant results. With AST and BMI, it was noticed that incidence of positive results was higher among TB patients while more non TB patients gained Hemoglobin values faster. A positive confounding effect was noticed when a model for weight outcome was done. Here it was more likely for non TB patients than TB patients to gain 2kg of body weight. Multivariate models for CD4, viral loads and ALT were not significant.

Multivariate models that tried to control for baseline CD4 for the incidence of deaths and defaulting in the two groups of patients all proved to be statistically insignificant with RR of 2.15 [p.value = 0.114], CI 0.81 – 5.67 when comparing defaulters in the two groups.

CHAPTER 4

DISCUSSION

The main objective of this study is to show differences in two different groups of HIV patients. That is those who had or have TB against those who have never had TB. The study compares these two groups of patients using statistical output comparisons of their summary statistics, regression models, survival and repeated data analysis models. Summary statistics shows numerical and proportional differences in the TB patients (that is those who at some point after being HIV positive were tested or diagnosed of TB) against non TB patients (those who have never had TB). The regression models fits changes in the outcome variables over time (months before and after the start of ARV). Survival and repeated data analysis shows incidences, rate ratio and survival, failures and hazard function curves. In an over view of the results, in most outcomes, there is no statistical evidence of a difference between the two groups of patients TB and non TB. In a few other outcomes like changes in BMI, weight, liver function and hemoglobin it is seen that those who at some stage had TB have a faster rate of improving on this outcomes.

4.1 LIMITATIONS OF THE STUDY

In view with the findings of this study, it is important that we acknowledge some limitations. These limitations are noticed to be of different sources. They could be results of errors and or practices at data collection phase, analysis, data entry, institutional rules and procedures and patients behaviour and honesty.

The positive outcome of very few deaths in the time period of the study which showed good reaction to ARV of the patients is in a way one of the analysis crisis. This is so because an analysis comparing death in the two groups of patients always certainly gives non-statistically significant results. Nonetheless, the sample of the study was quite exhaustive in number and in groups.

Another limitation of the study is the issue of data collection and entry. Issues of dates entered wrongly as could be noticed in the dates of registration and start of ARV, dates not captured as in defaulters/loss to follow up, measurements which do not make mathematical sense (weights and heights captured as meters and centimeters in one variable, CD_4, and LFT which do not reflect the tests) and observations which are not in sequence with presumable dates of event makes for poor statistical modeling and results. This aspect of the study causes it to be less as strong as it ought to be in bringing out differences and in it reliability. One thing to bear in mind though is the fact that cleaning of the TLC cohort is an ongoing activity – one day the will be a better cleaner dataset from the start.

The absence of information for socio-economic status; wealth index, employment and or profession (which at onset of analysis was dropped due to proof of bias entries) which in literature is sure related to disease states, death, treatment adherence and efficacy makes certain important comparisons impossible to carry out. This problem is further compounded by the fact that data is secondary and the researcher cannot go back in time to modify any data collection tool or verify some of the responses/ observations.

Another limitation noticed is the fact that the study is unlikely to confidently compare outcomes taking into consideration ethnic groups alone as this variable is not at all representative of what is thought of the general public. The sample ethnic distribution is predominantly black with very few whites and coloureds.

4.2 LEVELS AND DIFFERENTIALS

4.2.1 Deaths

There are very slight differences that are statistically proven in the study between TB and non TB patients. Such differences are seen in changes in weight, BMI, liver function (ALT and AST), hemoglobin and those who stopped (defaulted). Meanwhile, differences are not evident in deaths, CD4 counts changes and viral load changes. This non statistical evidence of differences in deaths, CD_4 and viral load is supported by a study carried out in Malawi on adults after initiation on ARV (16). The same non significance is observed when looking at deaths by various groups; sex, age group and ethnic group. Rate ratio of all groups and general model shows to have p value greater than 0.05.

4.2.2 Stopped Treatment/Defaulters

In contrast to the number of deaths, the number of those who stopped following up on their ARV medications or defaulted is not small and shows some statistical differences between the two groups of patients as shown by the rate of defaulting. This result is contrary to studies in Malawi (16) and Taiwan (12) which both found non-significant (p. values >0.05) differences in HIV TB patients and HIV non TB patients. Both studies concluded that there

were no differences in the drop out or defaulting rate in the two groups of patients.

4.2.3 Viral Load

Outcomes of viral load are not evident of any differences in the two groups of patients. At the first viral load test post ARV initiations; most of the patients had undetectable viral loads. This is so because viral loads are only checked for three months post start of ARV. In a continuous form, mean viral load are not significantly higher among TB patients than non TB patients. Survival analysis of the incidence of undetectable levels of viral load, we find that there are no differences in the two groups of patients in attaining undetectable viral loads as RR is approximately 1. This finding of no difference is supported by studies carried out in Taiwan (12), and Malawi (17) were in both cases 95% CI of RR contained 1 and p. values were greater than 0.05. Considering log viral loads we still notice that there is no difference in the two groups.

4.2.4 Weight and BMI

The cohort shows differences in mean values of weight and BMI at particular points in time significantly different between the two groups of patients TB and non TB. It is noticed that non TB patients generally have greater weights and BMI but the gradient of change with time is significantly higher with TB patients than non TB patients. This is supported by the survival and incidence rate at which patients gain 2kg of weight or 1unit of BMI which is higher in TB than in non TB patients. Basically it is biologically and physiologically correct for the mean values of weight and BMI at baseline to be higher in HIV non TB patients than in HIV TB patients and for this weight and BMI to

increase faster when in treatment for those who medically should have loose more the HIV TB patients.

4.2.5 CD_4 Counts

Statistically there is no difference noticed in CD_4 count change among the two groups of patients. In both cases though as clinically expected, there is a gradient of rising CD_4 counts over time in ARV medication. Still, no true difference is evident in this rise of the CD_4 over time in TB and non TB patients. These results of similarity in CD_4 change in both groups of patients are in line with studies carried out in Malawi among children under 14years of age (17) and in Taiwan (12) that both show similar outcomes of CD_4 counts in the two groups of patients.

4.2.6 Hemoglobin Counts

In a test of the means of baseline hemoglobin records for TB and non TB patients, it is noticed that there actually exist a difference among the two groups of patients at the onset of ARV. This difference is supported by regression analysis that shows changes with time in the two patient groups. In both cases, hemoglobin seems to increase with increasing time of receiving ARV. But the increase or change is not similar in both patient groups as those who at one point had TB even though start at baseline with lower hemoglobin (Hb) have a greater gradient in the rise of their hemoglobin with time. These findings are theoretically correct in that those who tend to be sicker had Hb levels dropping lower and so need to gain them faster to attain medically required states. Generally other studies of this nature rarely used Hb as one of the outcomes and so do not report on their differences in HIV TB patients against HIV TB-negative patients.

4.2.7 Liver Function Test- LFT (AST and ALT)

Liver function test (LFT), which in this study is also used to compare differences in outcomes of HIV TB patients on ARV with HIV TB-negative patients also on ARV is not as direct in its interpretation as it can vary by gender, ethnicity, exercise and alcohol intake (43). In this study we notice that AST and ALT that are used to measure liver functioning here tend to decrease over time. High figures usually above 40 indicate poor function and possible cirrhosis and or tissue damage. The decrease with time of AST and ALT is noticed in both patient groups. But the incidence of values over 40 for AST and ALT is higher among TB patients than those who have never had TB in univariate models. When we take into considerations other demographic characters (gender, ethnic group, age) we notice that there are no clear differences in ALT outcomes in both groups even though AST values statistically differ in the two groups of patients. Also noticed with changes over time is the faster decrease among non TB patients of both AST and ALT. To note is the fact that difference in AST above could be more due to another embedding disease than to TB as other studies like one carried out in Italy have shown no significant difference in liver function test between a range of different groups of patients (44).

4.3 Predictors of failures or successes in Outcome variables

In an attempt to view effects of confounders and determine other predictors for outcome results, we find out that all of our available demographic factors were not significant confounders to outcomes in HIV TB and HIV non TB patients. They were not as a group characteristics related to differences between the two groups of patients. An exception of this could be suspected

with ALT out comes which proves not significant at multivariate models even though significant at univariate level.

With the absence of important demographic information like profession, income, and general socio-economic class much is believed to have been left out as concerns possible predictors. Outcomes of CD_4, Hb, weight/BMI and others are expected to have a relationship with nutrition, standard of living and daily physical activities.

Overall, a factor which almost certainly blunted the differences between TB and non-TB patients, as defined in this study, was that the TB group contained all patients who had *ever* been exposed to the condition. Thus the TB group included patients who had had TB and who had completed TB treatment prior to presenting with AIDS, some in whom TB was part of an AIDS defining condition but had completed TB treatment prior to ARV, some who were on overlapping HAART and anti-tuberculous therapy for varying periods and some who had developed TB after starting ARV/HAART, either as part of the Immune Reconstitution Inflammatory Syndrome (IRIS-TB) or as incident TB. These different groups are an important source of bias in the present study and will obviously have to be taken into account in a more detailed analysis than was appropriate here. Never-the-less, the findings that the groups, as defined in this study, differed is of interest as a first step towards further analysis.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

This study was designed to evaluate and compare differences in outcomes among HIV patients who have been diagnosed with TB against those HIV patients who have never had TB. Results from summary statistics, regressions student t-test, chi-squared test survival and repeated data analysis show generally fewer than thought of differences. An important reason for this maybe the inhomogeneous nature of the TB group. Slight significant differences were noticed in the weights and BMI of the two groups of patients where those without TB tended to have greater weights/BMI than those who had TB. But here too it was noticed that the gradient of increase of weight and BMI are very slightly greater in those with baseline lower weights/BMI (those who had TB) than those whose weight and BMI were already high. In the same way was small statistically evident differences noticed with outcomes of Hb, and AST.

The lack of association between the social/demographic factors and ARV outcomes can be associated with the fact that individuals of all gender, race, social class and age are becoming more and more aware of the problems and challenges of HIV and TB and by so take better care of themselves while striving to achieve better health. Also the fact that the burden of such conditions have been seen to be of so much disadvantage to states/countries that treatment have become virtually free in both diseases in most countries.

5.2 RECOMMENDATIONS

With the difficulties obtained in managing and reporting data, information from TLC can be priceless if data capture and entry were to be improved upon. Nonetheless, with the major outcomes of ARV (CD_4 and viral load), not significantly different in both groups of patients and both groups experiencing significant improvements in their health states, it is all but normal to propagate for a wider coverage of HIV infected individuals with prompt initiation to ARV.

The fact that some important data was missing like occupation and socio-economics factors due to respondent fear of their effects on their treatment cost should serve as a boost to provide cheap, equal and passionate care to all persons no matter their social class. This could help in improving research findings and assumptions.

The South African government guidelines do not include base-line viral load measurements and the first viral loads are usually collected four to six months post ART initiation. This makes it difficult, in all but a few cases, to assess the rate of viral load decline as most of the patients would have attained undetectable viral loads before their first test post ARV initiation.

Further analysis of the TLCC data is needed where the timing of the diagnosis of TB with respect to the diagnosis of AIDS and the initiation of both TB treatment and HAART are taken into account.

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APPENDIX B

Graphs of Summary and Survival statistics including Log rank test of equality of survival curves

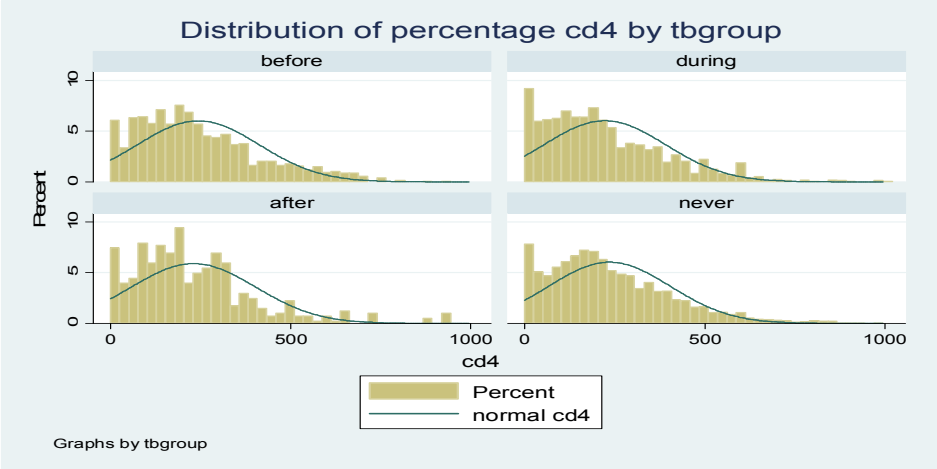


Fig.3.10 Distribution of CD_4 counts by TB groups

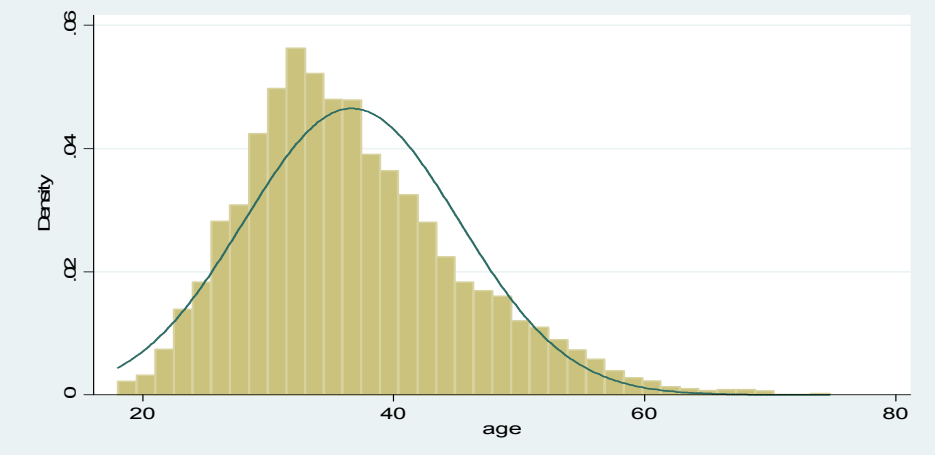
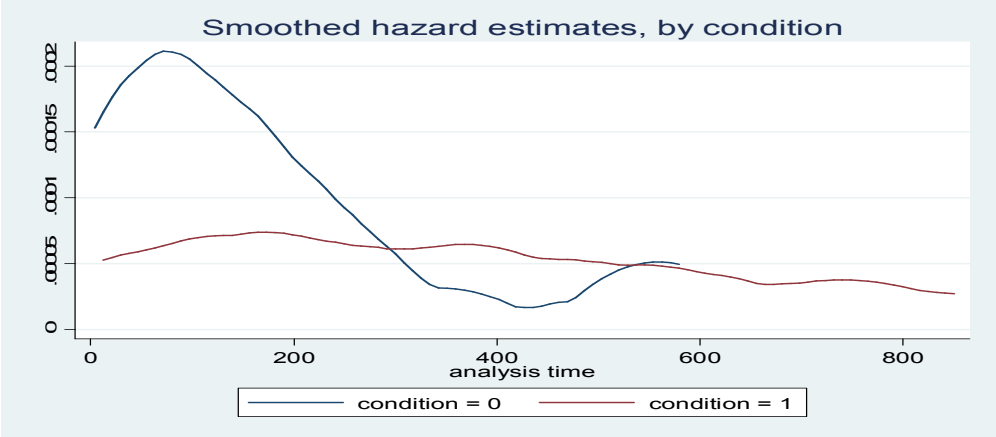


Fig.3.11 Structural distribution of Age

Graphs and information on deaths



Smooth hazard curve of those who died in the cohort

Log-rank test for equality of survivor functions

condition	Events observed	Events expected
NON TB	48	32.85
TB	139	154.15
Total	187	187.00
	chi2(1) =	8.51
	Pr>chi2 =	0.0035

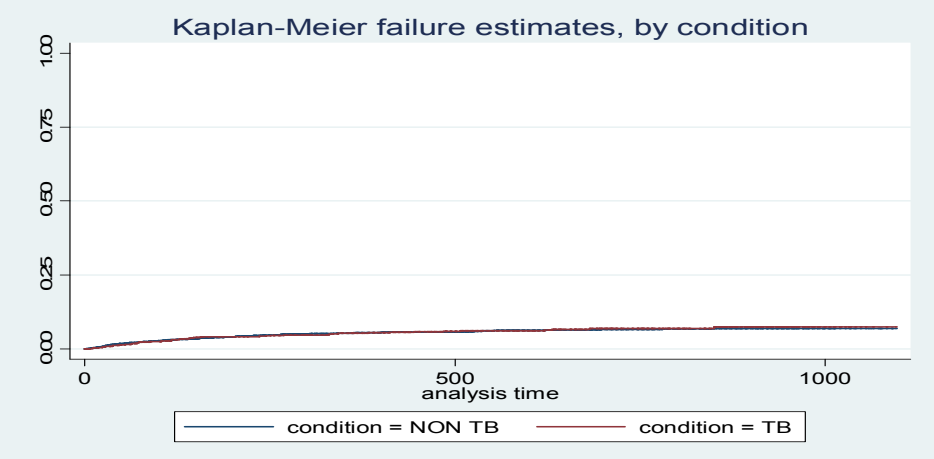


Fig.3.12 KM Incidence of deaths by person days in the cohort

Graph and information on Weight

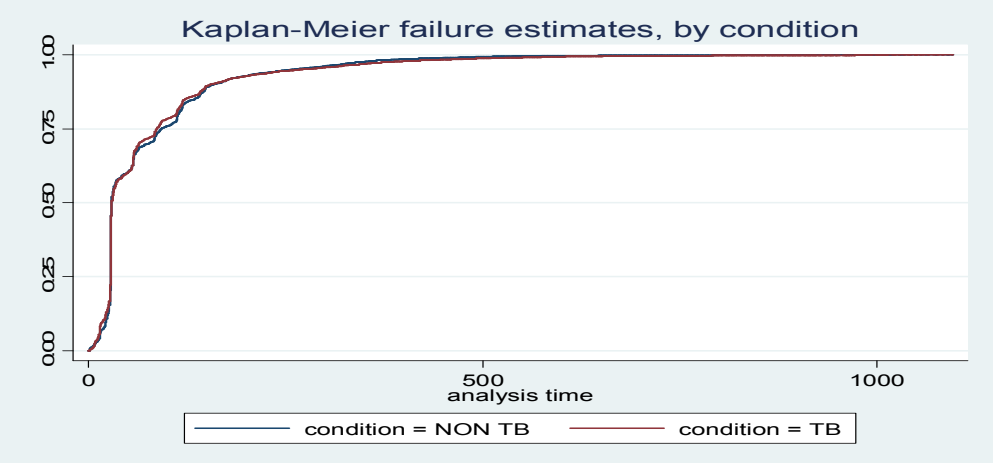


Fig. 3.13 Failures showing incidence of patients gaining >=2kg weight

Log-rank test for equality of survivor functions

condition	Events observed	Events expected
NON TB	13505	12939.37
TB	7123	7688.63
Total	20628	20628.00

chi2(1) = 69.23 Pr>chi2 = 0.0000

Graph and information on Viral Load

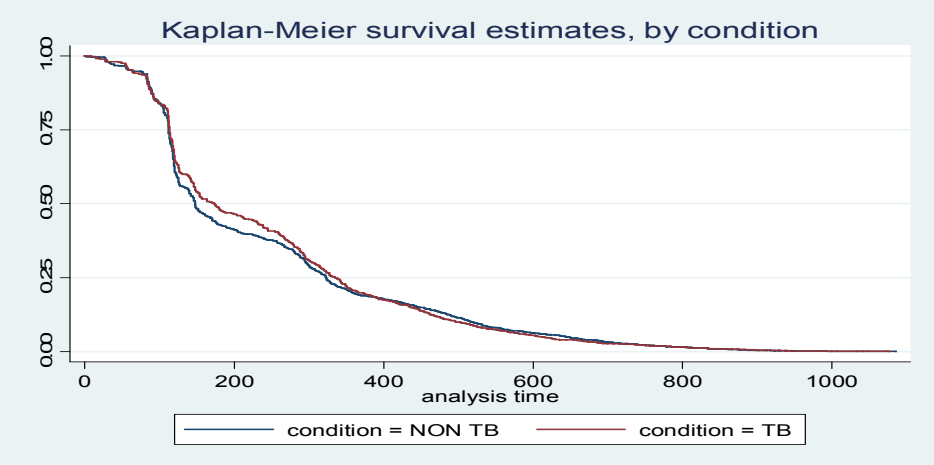


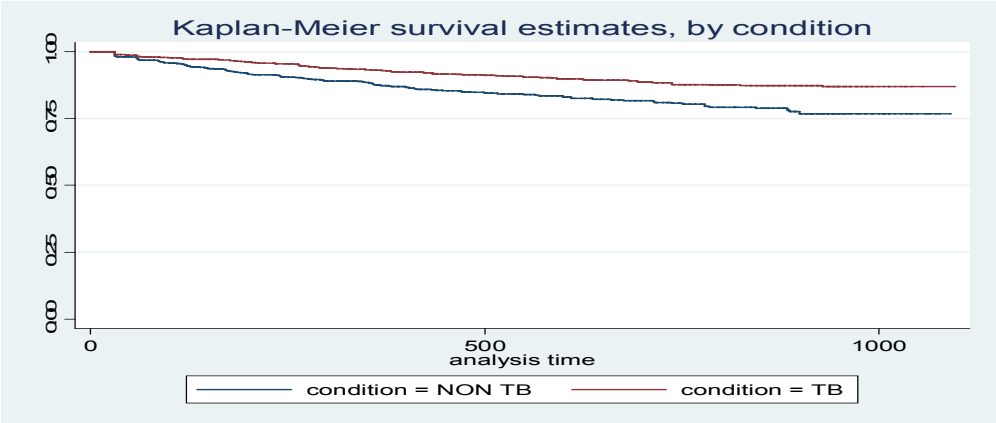
Fig.3.14 survival curve showing proportion not attaining viral load <=400

Log-rank test for equality of survivor functions

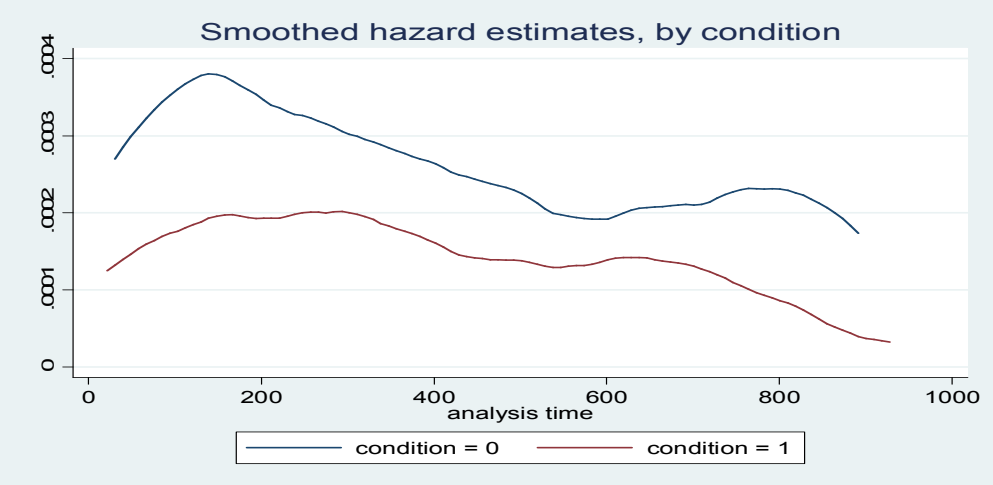
condition	Events observed	Events expected
NON TB	1185	1189.46
TB	757	752.54
Total	1942	1942.00

chi2(1) = 0.04 Pr>chi2 = 0.8345

Graph and information on Loss to follow up



KM survival curve of loss to follow up

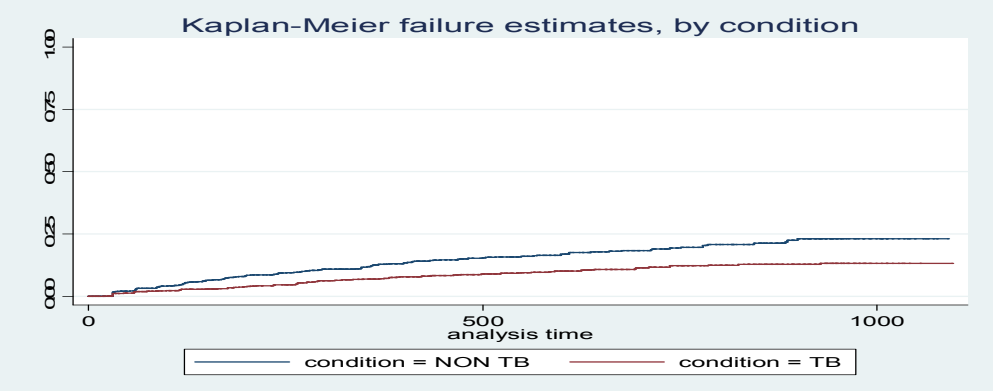


Smoothed Hazard curve for loss to follow up

Log-rank test for equality of survivor functions

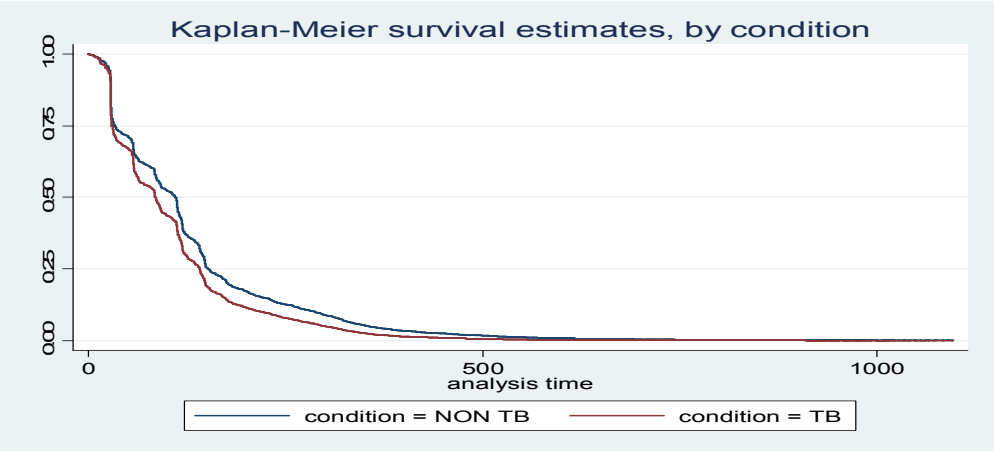
condition	Events observed	Events expected
NON TB	141	89.28
TB	374	425.72
Total	515	515.00

chi2(1) = 36.43
Pr>chi2 = 0.0000



Failure curve showing percentage loss to follow up

Graphs and information on BMI

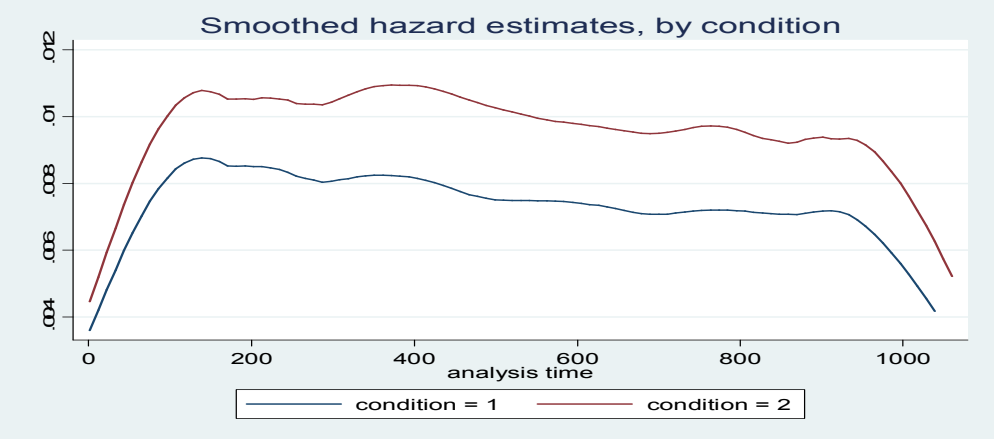


KM Survival curve of gaining 1 and more BMI units

Bmi Log-rank test for equality of survivor functions

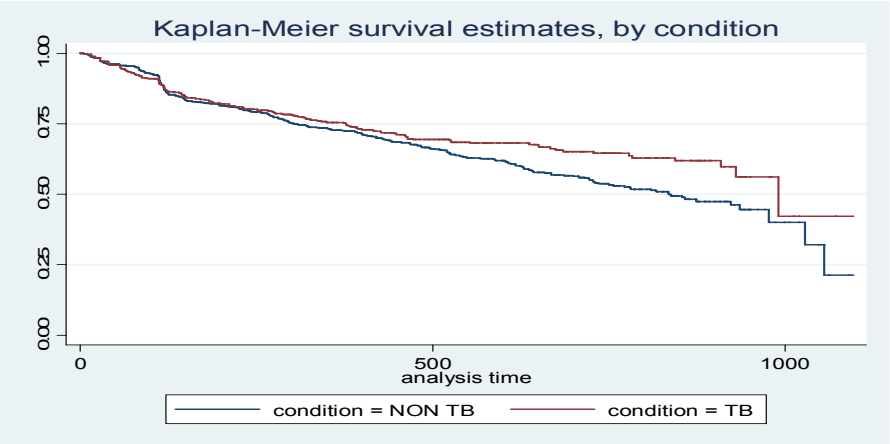
| Events | Events
condition	observed	expected
NON TB	11281	12333.13
TB	8643	7590.87
Total	19924	19924.00

chi2(1) = 240.50 Pr>chi2 = 0.0000



Hazard estimates by condition for BMI

Graphs and information on Hemoglobin

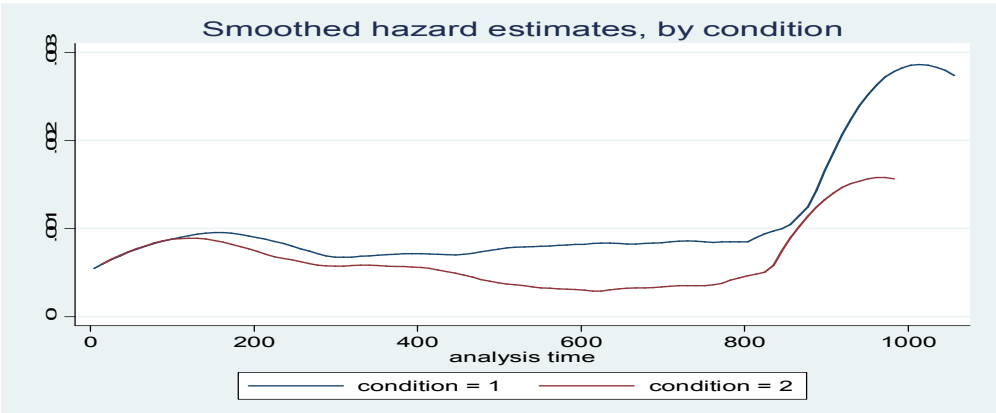


KM Survival curve for positive change of hemoglobin

Log-rank test for equality of survivor functions

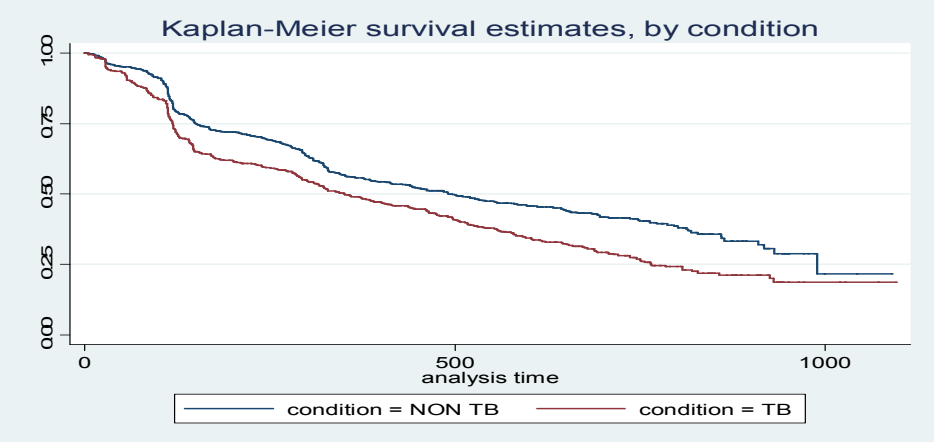
condition	Events observed	Events expected
NON TB	299	274.90
TB	149	173.10
Total	448	448.00

chi2(1) = 5.50 Pr>chi2 = 0.0191



Hazard function curve of failing by having positive Hb gains

Graphs and information on AST

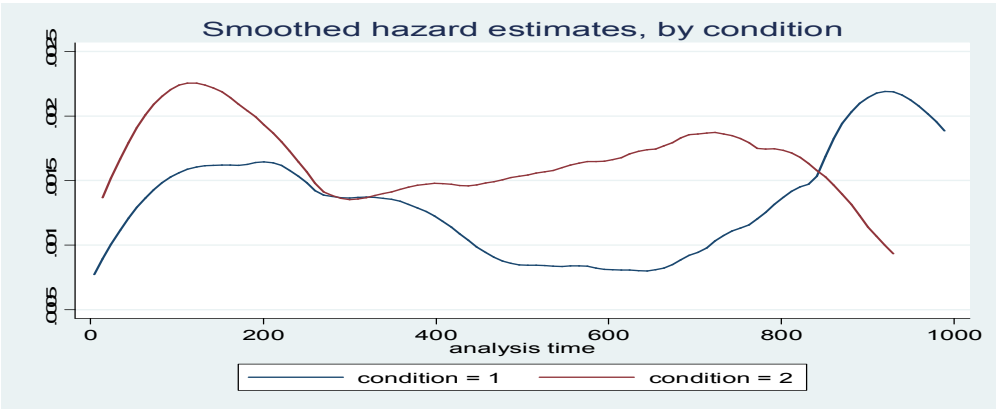


KM survival curve of developing negative AST scores (>40)

Log-rank test for equality of survivor functions

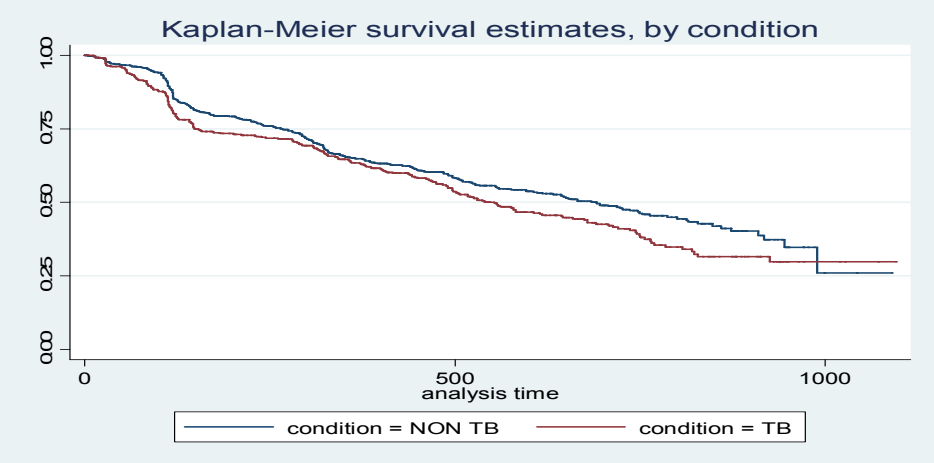
condition	Events observed	Events expected
NON TB	411	468.63
TB	349	291.37
Total	760	760.00

chi2(1) = 18.60 Pr>chi2 = 0.0000



Hazard estimates by condition for AST

Graphs and information on ALT

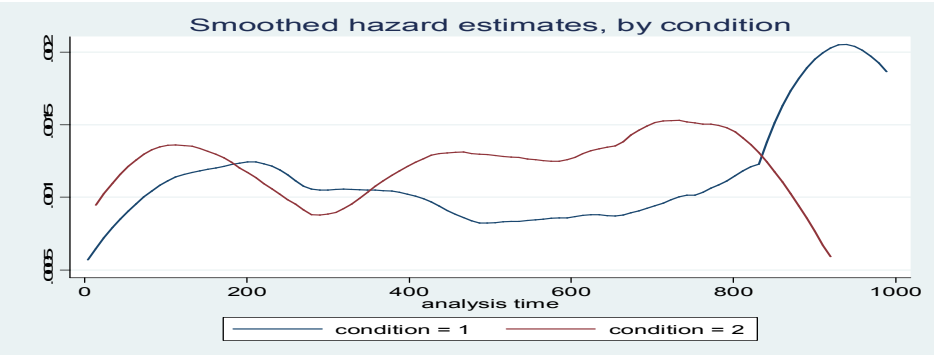


Survival curve for those who do not develop ALT scores >40

Log-rank test for equality of survivor functions

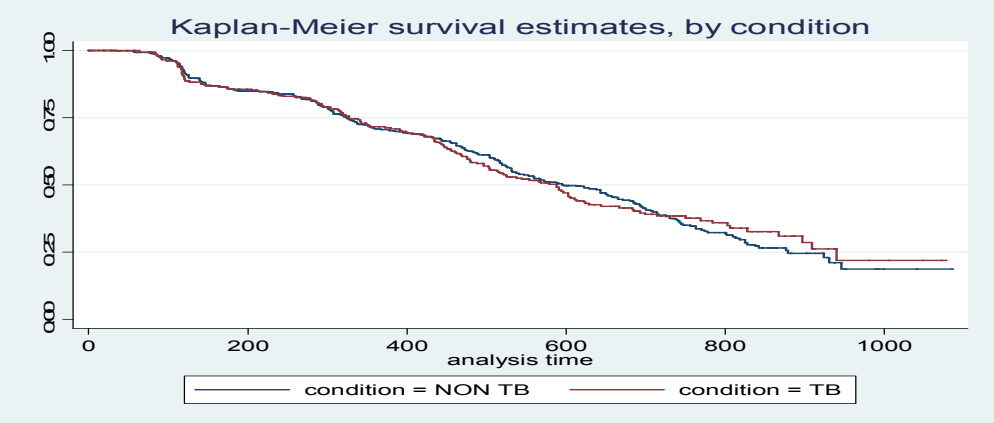
	Events	Events
condition	observed	expected
NON TB	329	354.49
TB	244	218.51
Total	573	573.00

chi2(1) = 4.83 Pr>chi2 = 0.0279



Hazard estimates by condition for ALT

Graphs and Information on Viral load

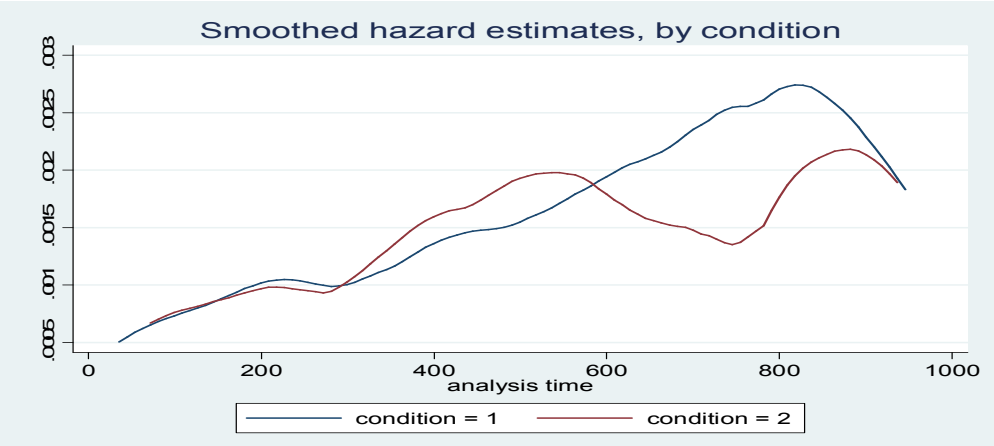


Survival curve for those who develope viral load less than 400

Log-rank test for equality of survivor functions

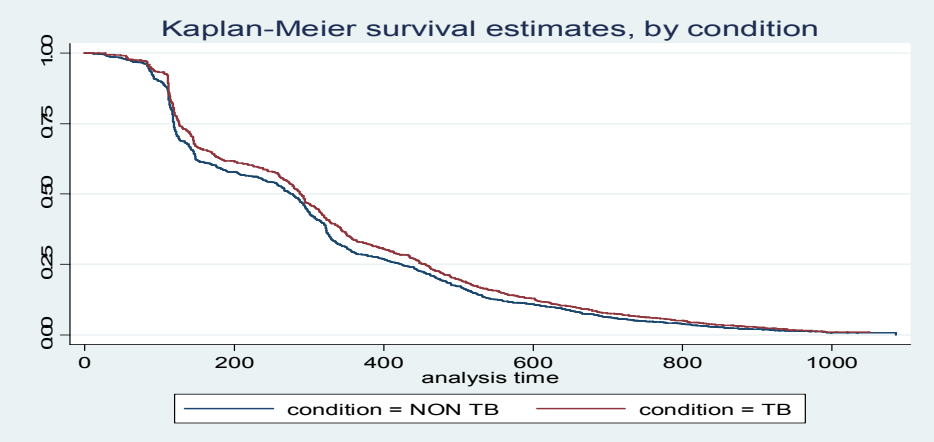
condition	Events observed	Events expected
NON TB	1185	1189.46
TB	757	752.54
Total	1942	1942.00

chi2(1) = 0.04 Pr>chi2 =0.8345



Harzard estimates for failing by attaining viral load <=400 (undetectable)

Graphs and information for CD_4 counts

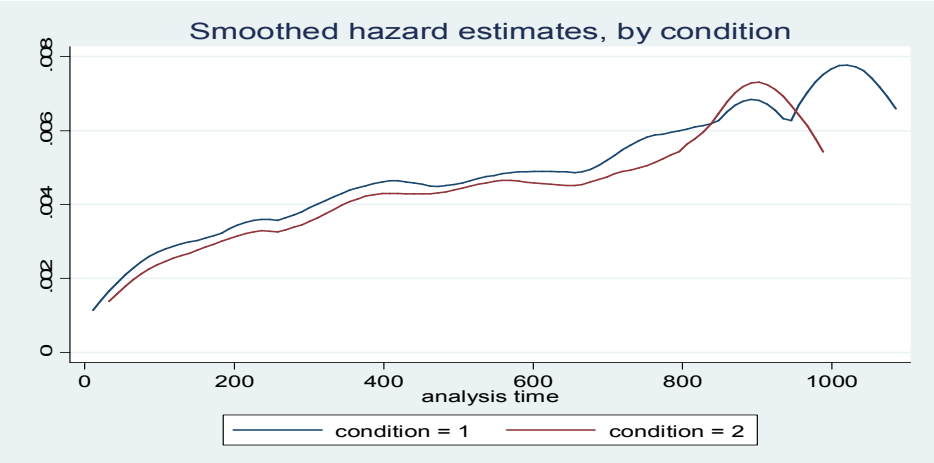


Survival curve showing probability of not developing CD4 over 200

Log-rank test for equality of survivor functions (CD_4)

condition	Events observed	Events expected
NON TB	1235	1195.88
TB	706	745.12
Total	1941	1941.00

chi2(1) = 3.36 Pr>chi2 = 0.0666



Hazard estimates of failing by developing CD_4 above 200

APPENDIX C

Plan of Movement on patient arrival at the Themba Lethu Clinic

