

An evaluation of the difference in the presentation and treatment response of Tuberculosis in HIV and TB sputum positive patients: HAART versus Pre-HAART era.

BY

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Declaration

I, Oladoyinbo Olarotimi Samuel, hereby declare that the work which I hereby submit as partial fulfilment for the degree of MSc (Clinical Epidemiology), on which this thesis is based, is original (except where acknowledgement indicates otherwise) and that neither the whole work nor any part of it has been submitted, or is being submitted, for another degree at this or any other university

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Date 17/02/2010

ABSTRACT

Objective: The objective of this cross sectional study was to compare the clinical presentation and response to treatments, in HIV positive and TB smear positive patients treated during the pre-Highly Active Antiretroviral Therapy (HAART) and Highly Active Antiretroviral Therapy (HAART) era (2004 and 2007), in St Joseph's hospital Roma Lesotho. Comparison was done in terms of age, sex, sputum conversion at 2 months and 6 months end of TB treatment, baseline and 6 months end of TB treatment weight, weight gained and radiological presentation and resolution.

Method: It was a cross sectional study design. Data was captured from the TB/HIV register, for pre-HAART era data of patients registered in the 2004 TB/HIV was captured and for the HAART era data of patients registered in the 2007 TB/HIV was captured. Cases were individuals with sputum smear positive tuberculosis and confirmed HIV infection, presenting in the pre HAART era (2004) and in the HAART era (2007). For inclusion in the HAART era, an individual had to be on HAART for at least 2 weeks or more. A total of 113 Patients were analysed and 85 patients the HAART era. Comparison of continuous measurements was done with a t-test and categorical measurement was done with a chi-square test. Multivariable logistic regression was used to detect differences between the pre-HAART and HAART era

Result: One hundred and thirteen (113) patients were analysed in the pre-HAART era and eighty five (85) in the HAART era. Mean age of presentation was lower in the pre-HAART era 36.1 years compared to HAART era 39.3 years with statistically significant result ($p=0.0362$). Pattern of sex distribution was similar in both era, ($p\text{-value}=0.85$). Sputum conversion showed statistically significant differences at 2 months, 95.2% of the HAART patients had sputum reverted whereas, 83.2% of the pre-HAART had sputum reversion ($p\text{-value}=0.009$), but no statistically significant result was seen at 6 months ($p\text{-value}=0.38$). Weight did not differ significantly between the two time periods, but there was a statistically significant difference in terms of mean weight gained in Haart era. Patients in the HAART era gained 0.92kg at the end of treatment compared to pre HAART era (p -

value=0.001). Radiological presentation and resolution did not differ significantly between the two time periods. (p-value= 0.36).

Conclusion: Smear positive TB/HIV co-infected patients in the HAART era were older at presentation, had better sputum conversion at 2 months and improved weight gain at 6 months end of TB treatment. Comparison with a historical control group alone however does not conclusively prove that this effect is due to HAART.



TABLE OF CONTENTS

CHAPTER 1	1
BACKGROUND AND LITERATURE REVIEW.....	1
EPIDEMIOLOGY	2
HIV AND TB SITUATION IN LESOTHO	2
PROGNOSIS	3
HIV SERO-PREVALENCE IN PATIENTS WITH TB	4
INVESTIGATIONS FOR TUBERCULOSIS IN HIV INFECTED INDIVIDUALS.	4
SMEAR AND CULTURE.....	4
PATHOGENESIS OF TB.....	4
POST-PRIMARY TB.....	5
IMMUNOPATHOGENESIS OF HIV INFECTION	6
HOW HIV DESTROYS THE IMMUNE SYSTEM.....	6
HIV-TB: A BIDIRECTIONAL INTERACTION	6
CLINICAL, RADIOLOGICAL AND PATHOLOGICAL FINDINGS	7
TREATMENT OPTIONS IN HIV/TB CO-INFECTED PATIENTS.....	8
MOTIVATION FOR THE STUDY	9
CHAPTER 2	10
METHODS.....	10
RESEARCH QUESTIONS:.....	10
AIM OF THE STUDY.....	10
OBJECTIVES	10
STUDY DESIGN.....	10
PATIENT SELECTION.....	11
SAMPLING FRAME.....	11
INCLUSION AND EXCLUSION CRITERIA:	12
EXCLUSION CRITERIA.	12
HAART ERA.	13
MEASUREMENTS.	14
DATA TOOLS AND PROCEDURE FOR DATA COLLECTION	15
DATA ANALYSIS.	16
TEST STATISTICS	16
MULTIVARIATE ANALYSIS.	17
ETHICAL CONSIDERATIONS.....	17



CHAPTER 3 19

RESULTS 19

 SOCIO DEMOGRAPHIC CHARACTERISTICS..... 19

 SPUTUM CONVERSION PROPORTIONS..... 19

 WEIGHT..... 19

 RADIOLOGICAL PRESENTATION AND RESOLUTION. 19

 DRUG REGIMEN..... 20

MULTIVARIATE ANALYSIS..... 22

INTERPRETATION OF THIS FINAL MODEL 22

CHAPTER 4 23

DISCUSSION..... 23

STUDY RESULTS IN RELATION TO OTHER STUDY 23

 ISSUES WITH REGARD TO STUDY DESIGN..... 24

 BIAS AND CONFOUNDING. 24

LIMITATIONS OF THIS STUDY..... 25

CONCLUSION..... 26

REFERENCES..... 28

LIST OF TABLES

Table 1.1 Demographic and clinical characteristic of the study population (comparison of pre-HAART and HAART era (mean (sd) and n(%))..... 21

Table 1. 2The pattern of sputum conversion at 2 months among patients in the HAART era based on their antiretroviral drug regimen..... 21

Table 1.3 The final multivariate logistic regression model with HAART era as the outcome..... 22

CHAPTER 1

Background and Literature review

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) pandemic has dramatically changed the epidemiology and natural history of TB. In Sub-Saharan Africa, where the HIV prevalence is highest, TB is the most prevalent opportunistic infection and the leading cause of death in HIV-infected individuals.¹⁻⁵ HIV co-infection is one of the most potent risk factors for TB, increasing the risk of both reactivation of latent infection and progression to active TB following initial exposure to *Mycobacterium tuberculosis* or infection.⁶⁻⁹

Advancing immune suppression as a result of HIV infection is associated with increasing risk of developing TB and also altered clinical presentation of TB. The sputum smear, which is the cornerstone of diagnosis and often the only diagnostic modality in resource-poor settings, is more negative in HIV-associated TB. Furthermore, TB progresses more rapidly in HIV-infected individuals and is associated with important changes in clinical and public health considerations. Although effective treatment available for both HIV infection and TB treatment, co-administration of antiretroviral and antituberculous therapy can result in shared toxicity, drug interaction and immunopathology, complicating treatment decisions for individuals with both infections. Despite these complications, antiretroviral therapy should not be withheld simply because patients are being treated simply for TB.¹⁰ The optimal timing of initiation of antiretroviral therapy in relation to initiation of antituberculous treatment is unclear.

However, the latest development in TB and HIV treatment is the SAPIT trial that will, once it is published, indicate that CD4 counts are not that important for initiation of treatment and that ART and TB treatment should commence simultaneously to prevent 50% less deaths. Patients that are HIV positive might benefit from tuberculosis prophylaxis.¹¹

Epidemiology

Based on surveys of the prevalence of infection and of disease, on the assessments of performance of surveillance systems and on death registrations, there were an estimated 9.2 million new cases of TB in 2006, of which 4.1 million were smear positive.¹² The WHO African region had the highest estimated incidence rate (363 per 100,000 population), but the majority of TB patients lived in the most populous countries in Asia. The global burden of TB is growing, driven largely by the HIV associated TB epidemic in sub-Saharan Africa, while incidence of TB is stable or declining in other regions. In southern African countries, where HIV-infected prevalence is highest, more than half of all the new cases are HIV infected. In rural Malawi the proportion of new smear positive TB cases attributable to HIV-infected increased from 17% in 1998-1999 to 57% in 2000-2001.¹³

Reactivation from latent TB infection is an important mechanism for the development of adult TB. However, there is accumulating evidence from using DNA fingerprinting techniques that has a significant proportion of TB cases are recently acquired due to reinfection or new infection, particularly when HIV prevalence is high. One study in Malawi found that about two-third of cases were clustered, indicating recent transmission and that HIV infection increased the risk of clustering by about fivefold.¹⁴

HIV and TB situation in Lesotho

HIV and TB are major public health problems in Lesotho. The country has the fourth highest estimated TB incidence (696 TB patients per 100,000 population) in the world.¹⁵ The estimated prevalence of TB is 544 per 100,000 population equivalent to 11,968 TB cases at any point in time. The estimated incidence of sputum smear positive cases is 281 per 100,000 population which equals 6,182 cases annually with 75% new cases among age-group 15-44 years. The estimated TB mortality is 107/100,000 annually which equals 2,354. About 80% of TB cases are HIV positive.¹⁵ Lesotho has

the third highest adult HIV prevalence in the world at 23.2%. There are estimated 62 new HIV infections and about 50 deaths due to AIDS each day in the country. An estimated 270,000 people are living with HIV in Lesotho as of the end of 2007 of which 11,801 are infected children while 258,472 are infected adults. Females contribute more to the total number of infected adults than males; 153,581 (57%) infected compared to 116,692 (43%) infected males.¹⁵ However there appear to be slightly downward trend in the HIV prevalence among 15-24 year old young people dropping to 8.9% (7.2-11%) in 2007 from 11% in 2005. The adjusted HIV prevalence among females aged 15-24 was 14.9% compared to 5.9% among males of the same age.¹⁵

Prognosis

The risk of developing TB increases with clinically advanced HIV disease or with declining CD4+ Lymphocyte counts.¹⁶⁻¹⁷ In sub-Saharan Africa, TB in HIV-infected individual occurs across a broad spectrum of CD4+ Lymphocyte counts with about a third cases occurring with CD4+ count <200 cells/ul and a similar proportion among those with CD4+ counts of 200-500 and > 500 cells/ul .¹⁸⁻¹⁹ In the United States and other industrialized countries all form of HIV-associated TB regarded as AIDS-defining illnesses, because they generally occur with lower CD4+ counts (median <200 cells/ul).²³ In the current World Health Organization (WHO) staging system, pulmonary TB is stage 3 and extra-pulmonary TB is stage 4 (equivalent to AIDS).²⁰

In Africa, all forms of TB have a better prognosis than other AIDS-defining illnesses, and the prognosis is similar for extrapulmonary and pulmonary disease.²¹ The prognosis of TB in communities with high TB incidence and HIV prevalence can only be reliably assessed in conjunction with the CD4+ count or other clinical features of HIV disease . There is evidence from cohort studies suggesting that TB accelerates the course of HIV infection.²²⁻²³ The basis for the accelerated HIV disease is thought to be related to prolonged immune activation .²⁴

HIV sero-prevalence in Patients with TB

In sub-Saharan Africa, HIV sero-prevalence rates among patients with TB are high ranging from 24 to 67 per cent.²⁵ In Asia, the rate of HIV infection among TB patients has been lower. Studies from India have reported HIV-sero-positivity rates ranging from 0.4 to 20.1 per cent.²⁵⁻³⁵

Investigations for Tuberculosis in HIV infected individuals.

Diagnosis of pulmonary tuberculosis in HIV co-infected patients currently does not differ from patients with normal immune systems and consist of the following:

Smear and culture

The finding of acid-fast bacilli (AFB) on stained specimen is the corner of diagnosis of TB. It is the only reliable and affordable rapid diagnostic test, and is often the only diagnostic modality available in developing countries. Mycobacterium culture has a higher yield than smear and provide a specific diagnosis. Although there are some contradictory reports, most studies show that the sputum smear is more likely to be negative in patients with HIV infection than those without HIV.³⁶ Nevertheless, sputum smear remains the most important diagnostic test in HIV infected patients with suspected pulmonary TB and has reasonably high yield. At least two or preferably three sputa should be sent for smear and at least one should be early morning sputum. Sputum induction using an ultrasonic nebulizer and hypertonic saline has been shown to improve the yield of smear and culture in patients with pulmonary TB.³⁷

Pathogenesis of TB

Primary infection occurs in people who have not had any previous exposure to tubercle bacilli. Droplet nuclei, which are inhaled into the lungs, are so small that they avoid the mucociliary defences of the bronchi and lodge in the terminal alveoli of the lungs. Infection begins with

multiplication of tubercle bacilli in the lungs. The resulting lesion is the Gohn focus. Lymphatics drain the bacilli in the hilar lymph nodes. The Gohn focus and related hilar lymphadenopathy form the primary complex. Bacilli may spread haematogenously from the primary complex throughout the body. The immune response (delayed hypersensitivity and cellular immunity) develop about 4-6 weeks after the primary infection. The size of the infecting dose of bacilli and the strength of the immune response determine what happens next. In most cases, the immune response stops multiplication of bacilli. However, a few dormant bacilli may persist. A positive tuberculin skin test would be the only evidence of infection. In a small proportion of cases the immune response is not strong enough to prevent multiplication of bacilli and disease occurs within a few months.³⁸

Post-primary TB

Post-primary TB occurs after a latent period of months or years following primary infection. It may occur either by reactivation of the dormant tubercle bacilli acquired from primary infection or by re-infection. Reactivation means that dormant bacilli persisting in tissues for months or years after primary infection start to multiply. This may be in response to a trigger, such as a weakening of the immune system by HIV infection. Re-infection means a repeat infection in a person who has previously had a primary infection.³⁹

The immune response of these patients results in pathological lesions that characteristically localized, often with extensive tissue destruction and cavitations. Post-primary TB usually affects the lungs but can involve any part of the body. The characteristic features of post-primary PTB are the following; extensive lung destruction with cavitations; positive sputum smear; upper lobe involvement, usually no intra-thoracic lymphadenopathy. Patients with these lesions are the main transmitters of infection in the community.⁴⁰

IMMUNOPATHOGENESIS OF HIV INFECTION

How HIV infects cells

HIV infects cells that have the CD4 antigen molecules on their surface, these cells are principally the helper subset of T- lymphocytes, which are central to cell-mediated immunity. They are called CD4+ T- Lymphocytes. In recent years it has also been discovered that HIV needs other molecules, called chemokine, on the cell to gain entry into the cells. Patients who do not have some of these specific chemokines (for example, CCR5) are more resistant to HIV infection. Others who have molecular changes in these chemokines receptors progress more slowly to AIDS.⁴¹

How HIV destroys the immune system

The critical abnormality resulting from HIV infection is a progressive decline in the number of CD4+ T-lymphocytes. These cells are the most important cells in the cell- mediated immune response. In addition the surviving CD4+ T-lymphocytes do not perform their functions as well as they did before infection. Progressive HIV infection therefore causes progressive decline in immunity.⁴²

HIV-TB: A bidirectional interaction

HIV infected persons are at markedly increased risk for progressive disease following primary TB infection². T-helper type immune response characterised by adequate cell-mediated immunity is the crucial host defence against M. Tuberculosis. HIV infection primarily affects the component of the host immune system responsible for cell-mediated immunity. Thus in HIV infected individuals with latent tuberculosis infection, the fine balance between M. Tuberculosis and the host immunity gets tilted in favour of the former, resulting in reactivation.⁴³

Moreover, the infection is poorly contained following reactivation, resulting in widespread dissemination causing pulmonary disease. This is corroborated by experimental findings that when

peripheral blood lymphocytes of patients with HIV-TB are exposed to *M. tuberculosis* in vitro, they produce decrease less T helper type cytokines, as compared with HIV-negative patients with TB.^{43-44.}

CLINICAL, RADIOLOGICAL AND PATHOLOGICAL FINDINGS

Unlike other opportunistic infections which occur at low CD4+ count below 200/mm³, active TB may occur throughout the course of HIV disease.⁴⁵ However, the clinical presentation of TB in HIV-Infected individuals does depend on the level of immune-suppression. Extra-pulmonary tuberculosis (EPTB) becomes increasingly common with greater immunosuppression. In contrast to HIV-negative patients with EPTB, the dissemination involves two or more non-contiguous organs concomitantly, in patients with HIV/AIDS.⁴⁶

Chest radiological findings in patients with advanced HIV disease are characterised by frequent lower lobe involvement, air space consolidation similar to bacterial pneumonia and absence of cavitations, sputum smears are seldom positive.⁴⁷ Intra-thoracic lymphadenopathy is often evident in these patients, resembling primary TB, regardless of the prior TB exposure status. A miliary pattern of involvement is also associated with severe immuno-suppression.⁴⁷ Interestingly, a considerable proportion of patients (10 to 20%) with advanced immuno-suppression may have apparently have normal looking chest radiographs, yet *M tuberculosis* can be demonstrated isolated from their sputum or bronchoalveolar lavage fluid.⁴⁸ However, computed tomography (CT) demonstrated abnormalities such as pulmonary nodules, tuberculoma and intra-thoracic lymphadenopathy in these patients.⁴⁷

In developing countries, extra pulmonary tuberculosis is the commonest cause of pyrexia of unknown origin among HIV infected patients.⁴⁹ In contrast to HIV- negative patients in whom pleural effusion due to TB often resolves spontaneously, it is progressive and remains culture positive for *Mycobacterium tuberculosis* for prolonged period of time in patients with HIV/AIDS.⁵⁰ In addition, pleural fluid shows abundant mesothelial cells in these patients, a finding reflecting poor

inflammatory response due to HIV/AIDS.⁵¹⁻⁵² Severe weight loss is a common presenting feature of HIV-Infected patients presenting with TB.⁵³ Many patients with AIDS, particularly in Africa, develop severe wasting and this has been called “slim disease”.⁵⁴ Since these patients usually have chronic diarrhoea, the condition was thought to be a consequence of HIV-enteropathy. However, at autopsy, nearly half of HIV/AIDS patients who died with “slim disease” were found to have disseminated TB as compared with just over a quarter of those dying without such wasting, suggesting that disseminated/miliary TB may be important cause of wasting in these patients.⁵⁵

Treatment options in HIV/TB co-infected patients

Since co-infection with both Mycobacterium tuberculosis and HIV is common, concurrent treatment of both infections may be needed. In general, treatment of HIV related tuberculosis should follow the general principles for those without HIV. Treatment should include 6 months regimen consisting of isoniazid, rifampicin or rifabutin, ethambutol and pyrazinamide for 2 months followed by isoniazid and rifampicin or rifabutin for 4 months when the infection is due to susceptible organisms. A prolonged treatment of 9 months in patients with a delayed response to treatment is accepted.⁵⁶

The rifamycins are important drugs for the treatment of TB; however they have significant interactions with antiretrovirals. Rifampicin is a very potent inducer of the CYP3A4. The nucleoside reverse transcriptase inhibitors (NRTI) have no interactions with rifamycins, however the non-nucleoside reverse transcriptase inhibitors (NNRTI) and the protease inhibitors (PIs) do interact. In general, rifampicin should not be administered in patients on nelfinavir, saquinavir, amprenavir, atazanavir, lopinavir or tipranavir. Rifabutin at 150mg three times weekly can be given as an alternative. Efavirenz given at the higher dose 800mg daily along with rifampicin has been shown to give adequate levels of both drugs. Nevirapine and rifampicin may be safe, but studies are lacking.^{57,58}

The optimal timing of HAART and TB treatment is unknown. Treatment for tuberculosis should never be delayed because of the risk of transmission and progression of disease. Early administration of HAART may lead to high incidence of side effect and paradoxical reactions. Delaying the initiation of HAART for 4-8 weeks may decrease adverse events and improve adherence. This decision should however be individualized.⁵⁸⁻⁵⁹

Motivation for the study

Tuberculosis is known for its high prevalence and incidence in Southern African countries, especially in the HIV co-infected population. Several studies have demonstrated the beneficial effect of co-administration of antiretroviral and tuberculosis in patients with HIV and TB coinfection, though the optimal timing of initiation of antiretroviral therapy is still a subject of debate. In view of this, different guidelines are used in various countries regarding the recommended CD4 counts when HAART should be started in HIV/TB co-infection patient. There have been several studies comparing the outcomes of the standard 6-months rifampicin-based regimens for the treatment of pulmonary TB in patients with and without HIV. All of the study reported comparable early clinical response to therapy, sputum conversion rate, and rate of treatment failure.⁶⁰⁻⁶¹ However, there is still a knowledge gap on whether antiretroviral therapy modifies clinical and radiological presentation and response to TB treatment, especially in HIV positive and smear TB positive patient. In view of this perceived gap, this project seeks to investigate how antiretroviral treatment modifies presentation and response to TB treatment in this category of patients. It is also hope that the finding of this study will contribute to the bundle of knowledge as per the effect of HAART on HIV/TB smear positive patients.

CHAPTER 2

METHODS

Research questions:

- Does HAART modify the clinical presentation and response to TB treatment in HIV and TB smear positive patients?
- Does HAART modify the radiological presentation and resolution in HIV positive and smear positive patients?

Aim of the study.

The aim of the study was to compare the clinical presentation and response to treatments in HIV positive, TB smear positive patients between pre-HAART (2004) and HAART periods (2007), in St Joseph's hospital Roma Lesotho.

Objectives

- To Compare the following clinical variables; age, sex, sputum conversion at 2months and 6months end of treatment, baseline and end of treatment weight, weight gained at the end of TB treatment (6months) between pre-HAART and HAART era.
- To compare radiological presentation and resolution between both era.

Study design.

This was a cross sectional study design.

Setting.

The study was done at St. Joseph's Hospital Roma, Lesotho. It is a 120 bed district hospital. Roma is a Semi-urban area in the Kingdom of Lesotho with an estimated population of over 14,000. The hospital is located in Roma which is about 45km south of Maseru, the capital of Lesotho. The facility

serves Roma town and its neighbouring villages through 6 primary health care centres located in those villages

Patient selection.

Study population: This is the population of HIV positive with smear positive TB patients, who met the inclusion criteria seen in St Joseph's Hospital Roma in 2004 and 2007.

Targets population: This is the population of HIV positive with smear positive pulmonary TB.

Sampled population: For the pre-HAART era the sampled population was the population of HIV positive and smear positive TB patients treated at St. Joseph's in 2004 before the roll out of HAART in the hospital and for the HAART era this was the population of HIV positive and smears positive TB patients started on HAART and treated for TB at St. Joseph's in 2007.

Sampling frame.

The sampling frame is the register of patients with confirmed TB/HIV diagnosis registered in the TB and HIV registers between the specified periods of 2004 and 2007. The hospital has very sound TB/HIV collaborative activities, so it was not difficult extracting all the information needed from the TB/HIV registers. All patients that met the inclusion criteria were included in the study for the specified time period. No probability sampling method was used. All eligible cases were consecutively selected from the Registers for 2004 and 2007. For the pre HAART era (2004) cases were individuals with confirmed HIV and sputum smear positive tuberculosis. In the HAART era individuals were already on HAART for at least two weeks or more and had confirmed sputum smear positive TB. A total of 113 Patients were analysed from the pre HAART era and 85 patients were analysed from the HAART era.

Inclusion and exclusion criteria:

Pre-HAART era.

- HIV/TB co-infected diagnosed with at least two HIV rapid test and at least one sputum test smear positive for acid fast bacilli (AFB) and a clinical presentation suggestive of tuberculosis.
- Acceptable adherence to TB medications as measured by pills counts marked in the TB treatment cards and documented TB outcome as either cured written in the “outcome column” in the TB register. The term TB treatment cured was used for patients who had bacteriological confirmation of being smear negative after completing TB treatment.
- Patients had to have adequate documentation in the TB/HIV register of baseline and follow up results or investigations such as: baseline, 2 months and end of treatment (6 months) sputum smear results, Baseline and end of treatment (6 months) chest X-ray, baseline weight, end of treatment weight and change in weight over time.
- HIV/TB patients 18 yrs and above were included.
- HIV/TB patient must have completed 6 months of TB Treatment.

Exclusion criteria.

The following categories of patients were excluded from the study;

- Patients who had only TB or HIV infection and not co-infection.
- Patients with medical condition that may impair treatment response: Patients with diabetes, malignancy, chronic liver disease, renal failure, long term steroid usage for any medical condition and chemotherapy were excluded.

- Patients with documented evidence of poor adherence ,<95%, as measured by poor clinic attendance or follow up visit, pills charts showing 9 or more missed doses or declared as TB default(TB default is defined as patient who interrupted TB treatment for 2 months or more)
- Patients with inconclusive HIV/TB diagnosis; that is patients diagnosed only with chest X-ray, but negative sputum test or patients with therapeutic trials of anti-tuberculosis or diagnosed purely on clinical ground with no sputum confirmation were excluded.
- HIV/TB patients less than 18years.

HAART era.

Inclusion and exclusion criteria were essentially the same as for pre-Haart era, except that, for patients to qualify for the HAART era,

- The patient must have been on antiretroviral for at least two weeks, before starting anti-tuberculosis treatment. This was necessary since the focus of the study was to investigate the effect of antiretroviral on clinical and radiological presentation and response in smear positive TB patients. It might be difficult to attribute any effect seen in the HAART era, in those on Antiretroviral therapy less than 2weeks on treatment to the effect of HAART. A major assumption in this study is that all patients in the HAART era, had been on antiretroviral treatment before they developed tuberculosis.
- Patients must have had at least 95% adherence to antiretroviral and must have had documented proof in the TB/HIV register as a case of treatment TB cured. Acceptable adherence pattern to both antiretroviral and tuberculosis medication was measured by pills counts marked in the TB treatment cards and HAART adherence sheets. Acceptable adherence 95% in this study was defined as patients not missing more than 3 doses per month on his or her antiretroviral therapy and adherence for the TB treatment was

considered to be acceptable if the patient did not interrupt or default treatment in the course of his or her TB treatment. All patients who had acceptable adherence to both medications were included in the study. There was a column in the TB/HIV register where adherence for each individual patient was marked, so all patients with 95% or more adherence, were included in this study and any patients with less than 95% adherence were excluded. This was done to minimise the negative effect of poor adherence on the variable of interest in this study. There are several studies that have demonstrated adherence of less than 95% in HIV positive patients on antiretroviral to be associated with poor virological suppression, immunological and clinical response in this category of patients and also TB patients with treatment interruption have also been shown to have poor TB treatment outcome, hence the need to recruit patient with good adherence for both conditions so as to reduced or eliminate the confounding effect of poor adherence in this study.⁶²⁻⁶³

Measurements.

Exposure measurement for pre-HAART: Antituberculosis drug regimen.

Exposure measurement for HAART era: Antiretroviral and antituberculosis drug regimen.

Outcome measurement .

These parameters: age, sex, weight, sputum AFB result, chest X-ray, CD4 counts and drug regimen were collected from the TB/HIV register for patients with adherence of 95% or more.

Baseline outcome measurement : This include; age, sex, weight, AFB results and Chest X-ray (for pre-HAART period) and the HAART period included above variables with addition of CD4 counts and anti-retroviral drug regimen. Radiological presentation was classified as follow;

1= Normal radiological finding

2 =Cavitations in any part of the lung fields

3= Small nodules or pulmonary infiltrates

4= Unilateral pleural effusions.

5= Others radiological picture that did not fit above radiological classification.

Two months outcome measurement.

Pre-HAART era: Sputum AFB.

HAART era: Sputum AFB.

Six months outcome measurement.

Pre-HAART: weight at the end of treatment, weight gain, sputum AFB, end of treatment chest X-ray.

HAART: weight at the end of treatment, weight gain, sputum AFB, end of treatment chest X-ray.

Confounding variables: Adherence pattern, age of presentation, sex, present of other medical conditions, d4 count at the point of entry into programme are considered to be possible confounding variables. This was handled by the inclusion and exclusion criteria set for patients to be included in the study(study design level) and others that could not handled at the design level was handled by statistical modelling and stratification .

Data tools and procedure for data collection .

Data collection tools : TB/HIV register 2004 and 2007. The TB register is a reliable and valid instrument recommended by the WHO for running TB/HIV programmes in all countries. The TB register in Roma was adapted from the WHO TB register/HIV register.

Procedure for data collection: Data were captured from the TB/HIV register, for pre-HAART era data of patients registered in the 2004 TB/HIV was captured and for the HAART era, data of patients

registered in the 2007 TB/HIV was captured. Data were captured into an Excel spread sheet between July –November 2008 following . The following variables were captured from the register;

I. Continuous variables: Age, Baseline weight at the start of TB treatment and 6months end of TB treatment. CD4 count for the HAART era (no record of CD4 count in the pre-HAART era).

II. Categorical variables: , sex, Sputum AFB smear results at baseline, 2months and 6 months, pattern of radiological presentation at baseline and resolution at 6months end of TB treatment and drug regimen for those in the HAART era.

Data management: Data checking was done on all categorical and continuous variables captured for values that were not within plausible range and attempt was also made to check for missing values to authenticate that these values were actually missing (especially the variables on radiological presentation and resolution). Cross checking of variables was also done.

Data analysis.

Data was collected in an Excel spread sheet and imported to STATA version 10 for analysis. Descriptive statistics of sample was done. Comparison of continuous measurements was done with a t-test and categorical measurement was done with a chi-square test. Statistical significance was set at 0.05 Univariate analysis was done on age, sex, sputum conversion at 2nd and 6 months end of treatment, baseline weight at the start of TB treatment and 6months end of TB treatment.

Test statistics

The mean age of presentation, mean baseline weight, mean weight at the end of treatment and mean weight gained or (weight difference) between HAART and pre-HAART was compared by (Independent t-test)

The Proportion of sputum conversion at 2nd month and 6 months end of TB treatment, radiological presentation and resolution between the HAART and pre-HAART era was compared by (Chi-square)

Multivariate analysis.

Multivariable logistic regression was used to detect differences between the pre-HAART and HAART era. Statistical significance was set at 0.05. The initial model contained the following variables; age, sex, sputum conversion at 2months, 6months, baseline weight (w1), weight at the end of treatment (w2), weight difference (w2w1), Baseline and end of treatment chest X-ray. Interaction terms age*sex, age*sputum conversion at 2 months, sex*sputum conversion at 2 months were generated and added to the initial model. Statistically significant results were assessed by the Wald test and likelihood ratio tests (LR test). There was no statistically significant results among the interaction terms generated. Backward hierarchical elimination was carried out on the basis of high p-values and likelihood ratio test was done on each variable, in order to determine if substantial information would be lost, before finally eliminating these variables. None of the variables dropped had significant P-value, when the LR test was done. The final model showed age, sputum conversion at 2 months and mean weight difference to be statistically significant.

The final model showed that patients in the HAART era were older at presentation, had a better sputum conversion rate at 2 months and improved weight gain at 6 months.

Ethical considerations.

Confidentiality of the data collected from the TB/HIV register was maintained and used for the intended purpose. No reference was made to any patient's name or other details that might break confidentiality.

Confidentiality of data collected was maintained through the following process; a separate code number known as patient's identifier was used during data collection, which was kept separately by

me and my data assistant. No reference was made to any patient's name or TB number during data entry or other details that might break confidentiality

II. All data was captured in an Excel spread sheet by the TB data assistants under my supervision and efforts was made to prevent unauthorized access to it, by coding this data in such a way that it was difficult for anyone not participating in the study to be able to interpret unless given the codes

CHAPTER 3

RESULTS

One hundred and thirteen (113) patients were analysed in the pre-HAART era and eighty five (85) in the HAART era. Table 1.1 compared the various variables for pre-HAART and HAART era with the appropriate statistical tests and showed the following findings;

Socio demographic characteristics.

The mean age of presentation was lower in the pre-HAART era 36.1 years compared to HAART era 39.3 years with statistically significant result (p-value=0.036). Pattern of sex distribution was similar in both era, (p-value=0.85).

Sputum conversion proportions.

In-terms of sputum conversion statistically significant result was found, At 2 months 80 (95.2%) of the HAART patients had sputum reverted whereas 94 (83.2%) of the pre-HAART had sputum reversion (p-value=0.009). At 6 months 133(100%) of the patients in the HAART era had sputum reverted and 85(100%) also had sputum reverted in the pre-HAART era (p-value =0.38).

Weight.

Weight did not differ significantly between the two time periods. Baseline weight; pre- HAART era was 52.6kg and HAART era was 50.4 kg (p-value=0.064). End of treatment mean weight pre- HAART was 56.9 kg and HAART was 55.6 kg (p-value=0.24). Statistically significant result was found in terms of mean weight gained. Patients in the HAART era compared to pre-HAART era, gained 0.92kg at the end of treatment (p-value= 0.001).

Radiological presentation and resolution.

Radiological presentation did not differ significantly between the two time periods. However, the following pattern of presentation was noticed; in the pre-HAART era 21.3% of patients who

presented with unilateral pleural effusion, whereas 5.3% of the patients who presented with unilateral pleural effusion in the HAART era. 28.57% of the patient in the pre- HAART era presented with cavitations in the upper lung apices and pulmonary infiltrates respectively. In the HAART era the most common pattern of presentation was pulmonary infiltrates (52.63%), cavitations in the lung apices (26.32%), Normal radiological findings (10.56%) and 5.26% for unilateral pleural effusion. Radiological resolution did not differ significantly between the two time periods. (78.9%) of the Patients in the HAART era showed complete resolution and (21.1%) showed partial resolution, while, radiological resolution in the pre-HAART era showed that (60.7%) had complete resolution,(35.7%) had partial resolution and (3.6%) had no resolution at the end of TB treatment (p-value= 0.36).

Drug regimen

In terms of drug regimen in the HAART era 51(60%) of the patients were on drug regimen 1 (Tenovovir + Lamivudine and Efavirenz), 28(32.94%) were on drug regimen2 (Zidovudine + Lamivudine+ Efavirenz) and 5(7.06%)on drug regimen 3 (Stavudine + Lamivudine + Efavirenz). Of the 95.1% HAART era patients who had sputum conversion at 2 months, 50 (61.7%) were on drug regimen 1, 26 (32.1%) were on drug regimen 2 and 5 (6.2%) were on drug regimen 3, the different antiretroviral regimen did not have any differential effect on the rate of sputum conversion among patients in the HAART era (p-value=0.21). See Table 1.2.

Table 1.1 Demographic and clinical characteristic of the study population (comparison of pre-HAART and HAART era (mean (sd) and n(%))).

Variables	Pre-HAART era	HAART era	p-value
Age (mean age in years)	36.1(10.8)	39.3(10.6)	0.036
Sex			
Male	58(51.3%)	43(50.5%)	0.85
Female	55(48.7%)	42(49.7%)	
Sputum conversion at			
2 months	94(83.2%)	80(95.2%)	0.009
6 months	113(100%)	85(100%)	0.038
Baseline weigh (Kg)	52.6(8.3)	50.4(8.0)	0.064
Mean weight at 6 months end of treatment (Kg)	56.9(8.2)	55.6(7.0)	0.064
Mean weight difference (TB end of treatment weight-baselineTB treatment weight)	4.32(1.5)	5.17(2.1)	0.001
Radiological presentation			
Normal radiological findings	5(17.5%)	2(10.5%)	0.38
Cavitations in the lungs	8(28.6%)	5(26.3%)	
Pulmonary infiltrates/nodules	8(28.6%)	10(52.6%)	
Unilateral pleural effusion	6(21.4%)	1(5.3%)	
Others that did not fit the above radiological picture	1(3.5%)	1(5.3%)	
Radiological resolution			
Complete resolution	17(60.7%)	15(78.9%)	0.36
Partial resolution	10(35.7%)	4(21.1%)	
No resolution	1(3.6%)	0(0%)	

Table 1. 2The pattern of sputum conversion at 2 months among patients in the HAART era based on their antiretroviral drug regimen.

Drug regimen	% Sputum conversion per drug regimen	P-value
1 Tenofovir+lamivudine+Efavirenz	50(61.7%)	0.21
2 Zidovudine+Lamivudine+Efavirenz	26(32.1%)	
3 Stavudine+Lamivudine+Efavirenz	5(6.2%)	

Multivariate analysis

Multivariate logistic regression to detect differences between pre-HAART and HAART era was done. Statistically significant results was assessed by the Wald test and LR test. There was no statistically significant results among parameter estimates included in the initial model. The interaction terms generated also did not show any statistically significant results, hence there was no effect modification. The overall p-value of this initial model was 0.61 and the pseudo R^2 value was 0.128

The final model had a P-value 0.002, pseudo R square test was=0.071, goodness of fit test was 0.55.

Table 1.3 The final multivariate logistic regression model with HAART era as the outcome.

HAART era	Odds ratio	P-value	Confidence Interval
Age	1.02	0.049	1.00-1.06
Sputum conversion at 2months	0.03	0.028	0.10-0.88
Weight difference in Kg.	1.26	0.00	0.00-387

Interpretation of this final model

- The odds of sputum conversion at 2 months increases by 97% among TB patients in the HAART era compared to those in pre-HAART era adjusting for age and weight gain.
- The odds of gaining 1 Kg of weight among TB patients in the HAART era is 1.26 times more than those the pre-HAART era adjusting for age and sputum conversion at 2 months.

CHAPTER 4

DISCUSSION

The main findings in this study showed that smear positive TB/HIV co-infected patients in the HAART era were 3.2 years older at presentation, had a better sputum conversion rate at 2 months and improved weight gain at 6 months.

This study showed statistically significant result in the HAART era, patients in the HAART era were older at presentation, had a better sputum conversion rate at 2 months and improved weight gain at 6 months. Sex distribution was similar in both eras. Baseline weight, end of treatment weight, pattern of radiological presentation and response did not differ significantly between the two time periods.

This study was a cross sectional study, investigating the effect of antiretroviral drugs on the clinical presentation and response in TB/HIV smear positive patients. A two time period comparison was done between the pre-HAART and HAART era.

Study results in relation to other study

The delayed age of presentation seen in the HAART era could be attributed to the major beneficial effect of HAART which result in gradual restoration of pathogen- specific immune response in HIV patients on HAART.⁵⁸⁻⁵⁹ However, some studies have shown that during the initial months of HAART, the reconstitution of immune function can also result in a transient worsening or appearance of new signs, symptoms or radiological manifestations of TB.^{47,58} This could possibly explain the different radiological pattern seen in both eras, though not significant because of small numbers of chest-x-rays films available for review. Previous studies have shown that patients, who have access to HAART and rifampicin containing antituberculosis treatment, demonstrated decreased incidence,

recurrence and mortality rate of TB and improved survival .^{60,61,64.} The use of HAART was also shown by some studies to be associated with 80% reduction in the risk of TB.⁶⁴⁻⁶⁵ Weight gained in the HAART era seen in this study is similar to the pattern seen in other studies.⁶⁶ There is presently no information on the impact of HAART on sputum conversion in the smear positive TB/HIV co-infected patients, hence the uniqueness of this study.

Issues with regard to study design

Cross sectional studies are mostly used to examine the relationship between exposure and outcome. Unlike cohort and case-control studies, a cross sectional study does not assess and compare occurrence of new (incident) cases of disease in two groups. Rather, it assesses and compares the prevalence of disease or exposure across the two groups.

In cross sectional study, the researcher usually selects the sample without reference to exposure or disease; often the sample is drawn at random from a defined population. He or she then measures the presence (or history) of both disease and exposure in each participant in the study. Finally, the researcher compares the prevalence of disease among those exposed to determine if there is a difference in the prevalence of disease according to exposure status. This study was carried out by obtaining a cross-sectional data for pre-HAART and HAART era from the TB/HIV register for 2004 and 2007. The demographics and clinical characteristics of patients in both eras were similar, except for those in the HAART era that had exposure to HAART.

Bias and Confounding.

An attempt to reduce bias was made throughout the study.

- Patients selection : All eligible who met the inclusion criteria were consecutively selected from the Registers for 2004 and 2007 thereby, preventing selection of patients with poorer outcome. (Selection bias)

- With respect to data entry, Different people entered data at different time into the TB register, there could have been some degree of error in the information provided for some of the patients in the register, this could have introduced some degree of measurement bias into the study.
- Adherence pattern, age of presentation, sex, present of other medical conditions, CD4 count of entry into the programme were considered as confounding variables and were these was taken into account in the course of the study. Patients who are HIV positive and smear positive for TB were who has other medical conditions or taken medication that could affect the outcome of the study were excluded. Patient with adherence less than 95% were excluded from the study because of the potential of this category of patients to compromise the outcome of the study. CD4 count of entry into the programme for both era could not be ascertained for the pre-HAART era, so it was difficult to ascertain if degree of immunosuppression was similar or different in both era. If one era has more patients more immunosuppressed patients, this could have an effect on the outcome of interest. In this study it was difficult to control for this, since CD4 count was only available for the HAART era patients.
- At analysis level statistical modelling (multivariate logistic regression) was used to estimate the strength of association while controlling for a number of confounding variables simultaneously.

Limitations of this study.

- This study was only done in HIV positive and smear positive TB patients aged 18yrs and above, hence the finding cannot be extrapolated to HIV positive smear or extrapulmonary TB patients and also caution should be exercised in extrapolating findings to those who are HIV positive and smear positive for TB, but less than 18 years.

- The antiretroviral drugs evaluated in this study were the Nucleoside, non nucleoside and protease inhibitors. None of the patients evaluated was on the newer antiretroviral drugs such as integrase inhibitors and fusion inhibitors , so extrapolation of findings to these set of drugs should be done with caution.
- With regards to study design a randomized control trial with a number of patients in the antiretroviral arm would have been better, although cost and ethical approval would have made it difficult for this study to be carried out.
- A sample of 100 for each time period was considered to be adequate for comparative and regression analysis, but only 85 patients were found eligible in the HAART era. Most of the patients in the HAART era did not have chest X-ray since they were all AFB smeared positive, which did not need further radiological investigation to confirm diagnosis. The non-statistically significant radiological picture seen in terms of patients' radiological presentation and resolution seen in both era, could be due to small number of X-ray films available for review and hence resulting in type2 error.

Conclusion

This study has succeeded in answering the following questions;

1. Does HAART modify the clinical presentation and response to TB treatment in HIV and TB smear positive patients?

- HAART appear to modify or affect the age of presentation in HIV/TB smear positive patient. Patient in the HAART era were older in presentation and the odd of having TB increases by about 2% for every year increase in age in the HAART era.
- HAART does improve sputum conversion at the end of 2months of TB in HIV/TB smear patients by 97% , but not does seem to improve sputum conversion beyond this time.

- HAART does improve weight gained at the end of 6months TB treatment in HIV/TB smear positive patients.

2. Does HAART modify the radiological presentation and resolution in HIV positive and TB smear positive patients?

- This study failed to produce evidence that HAART does modify radiological presentation and resolution in HIV/TB smear positive patient, reason could be attributed to small sample size of the Chest X-rays available for evaluation. In view of this, studies with adequate sample is recommended to answer this question

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