A RETROSPECTIVE COMPARATIVE STUDY OF ADVERSE DRUG REACTIONS AMONG HIV (+) AND HIV (-) ADULT PATIENTS TAKING ANTITUBERCULAR DRUGS, IN 2006-2007.

BY:

DR. JOHNSON ONGERI MASESE,
SCHOOL OF PHARMACY,
UNIVERSITY OF NAIROBI (KENYA).

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Declaration

This dissertation is my original work and to my knowledge it has not been presented in any other university for a degree.

Principal investigator

Dr. Johnson Ongeri Masese,

Postgraduate student – M.Pharm (Clinical Pharmacy),

School of Pharmacy,

University of Nairobi (Kenya).

Signature..... Date. 18/11/2008..

Supervisor

This dissertation has been submitted with my approval as university supervisor.

1. Dr. Rashid Juma,
   MB.CH.B, M.MED (Internal Medicine),
   Clinical Pharmacologist,
   Centre for Clinical Research,
   Kenya Medical Research Institute (KEMRI).

Signature ..... Date..... 26/11/08

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DEDICATION

To my father Mr. Jeremiah Masese Onyangore and my mother Yunuke Moraa who instilled the value of education and the fundamental skills of life in me.

Post humorously to my grandmother mama Ruth Sagara who layed the stone of education in our family.

To my five brothers and my two dear sisters, for their unconditional love and support during the study period.

LIST OF ABBREVIATIONS

3TC	Lamivudine
ARVs	Antiretroviral drugs
AIDS	Acquired immunodeficiency syndrome
ALT (SGPT)	Alanine aminotransferase
ALP	Alkaline phosphatase
Anti-TB	Anti tuberculosis drugs
AST (SGOT)	Aspartate aminotransferase
AZT	Zidovudine
CDC	Centre for Disease Control and Prevention
CMV	Cytomegalovirus
DOTS	Directly Observed Therapy Short Course
DDI	Didanosine
DDC	Zalcitabine
D4T	Stavudine
E	Ethambutol
EFV	Efavirenz
EPTB	Extra pulmonary TB
H or INH	Isoniazid
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HIV (+)	HIV positive
HIV(-)	HIV negative
LFT	Liver function test
KNH	Kenyatta National Hospital
MDR TB	Multi drug resistance TB
MOH	Ministry of Health, Kenya.
MS ACCESS	Microsoft access package
NVP	Nevirapine
NLTP	National Leprosy and Tuberculosis Programme
NR	Not recorded
OR	Odds ratio
PTB	Pulmonary TB
PI	Protease inhibitor

R or RIF	Rifampicin
RR	Relative risk
SD	Standard deviation
SPSS	Statistical package for the social sciences
SM	Streptomycin
TB	Tuberculosis
TDF	Tenofovir
WHO	World Health Organization
WBC	White blood count
XDR TB	Extreme Drug Resistance TB
Z or PZA	Pyrazinamide

2RHZE/6EH	2 months intensive phase of rifampicin, isoniazid, pyrazinamide and ethambutol then 6 months continuation phase of ethambutol and isoniazid.
2SRHZE/1RHZE/5RHE	2 months intensive phase of streptomycin, rifampicin, isoniazid, pyrazinamide and ethambutol; then 1 month consisting of rifampicin, isoniazid, pyrazinamide and ethambutol; then 5 months of rifampicin, isoniazid and ethambutol.
2RHZ/4RH	2 months intensive phase consisting of rifampicin, isoniazid and pyrazinamide; then 4 months continuation phase consisting of rifampicin and isoniazid.
2SRHZE/4RHZE	2 months of intensive phase consisting of streptomycin, rifampicin, isoniazid and pyrazinamide; then 4 months of continuation phase consisting of rifampicin, isoniazid, pyrazinamide and ethambutol.

Definition of terms

Adverse drug reaction - According to the WHO definition, this is any noxious, unintended, and undesired effect of the drug which occurs at doses used in humans for prophylaxis, diagnosis or therapy.

Tuberculosis - An infectious disease caused by mycobacterium tuberculosis, an acid fast rod shaped bacillus.

Abstract

***Background*:**

Tuberculosis (TB) is an infectious bacterial infection caused by Mycobacterium tuberculosis. It is estimated that a third of the world population is infected, with eight million people progressing to active TB disease each year, two million of whom die of the disease. About one third of people infected with HIV are also infected with TB and 70% of these people live in sub-Saharan Africa. In Kenya, the data for 2006 indicated that the national average HIV prevalence in TB patients was 52%. Although standard TB treatment consisting of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) is effective in treating active TB, it has been associated with many adverse drug reactions (ADRs) more so in HIV (+) patients and poses a significant challenge to completion of treatment, therefore; they need to be carefully monitored.

***Main objective*:**

To determine the prevalence of ADRs among HIV (+) and HIV(-) adult patients taking anti-TB drugs at Kenyatta National Hospital (KNH).

***Study Design*:**

A retrospective cohort study carried out at the medical records department of KNH. Three hundred and fourteen patient files meeting inclusion criteria during the study period January 2006 to December 2007 were selected randomly for inclusion in the study, of which 157 were for adult HIV(+) patients taking anti-TB drugs while 157 were for their HIV(-) counterparts. Data extracted from patient files were analyzed using the Statistical Package for social sciences (SPSS) version 13.0.

Results:

A total of 83 ADRs were recorded among HIV (+) patients compared to 28 ADRs among HIV(-) patients. ADRs were more common in HIV (+) patients 70 (44.6%) compared to HIV (-) patients 26 (16.6%), (OR = 2.692 [1.819 – 3.985], $p<0.001$).

More HIV (+) patients than HIV (-) patients taking anti-TB drugs had more than one ADR; 11 (7%) versus 2 (1.3%), (OR = 5.50 [1.239 – 24.412], $p=0.02$). Seventy two (45.86%) HIV (+) patients were also taking ARVs while on anti-TB drugs.

Overall, the most frequent ADR was gastrointestinal disturbance which was recorded in 34 (21.7%) HIV (+) patients compared to 16 (10.2%) HIV (-) patients, $p=0.006$. Peripheral neuropathy was recorded in 26 (16.6%) HIV (+) patients compared to 7 (4.5%) HIV (-) patients, $p=0.0005$. Cutaneous reactions were more common in HIV (+) patients 10 (6.4%) than HIV (-) patients 2 (1.3%), $p=0.02$. Nine (5.7%) HIV (+) patients compared to 2 (1.3%) HIV (-) patients had hepatotoxicity, $p=0.03$. There were no statistically significant differences between HIV (+) patients

and HIV (-) patients with regard to the prevalence of ocular toxicity (1.9% vs 0.6%, p=0.3) and ototoxicity (0.6% vs 0%, p=0.3).

Interruption of anti-TB treatment occurred in 8 (5.1%) HIV (+) and 4 (2.55%) HIV(-) patients. Although, gastrointestinal disturbances and peripheral neuropathy were the most commonly recorded ADRs in both the HIV (+) and HIV (-) patients, hepatotoxicity was the main cause of TB treatment interruption; 4.46% in HIV (+) and in 1.27% HIV (-) patients.

Conclusion:

ADRs were more likely to occur in adult HIV (+) patients taking anti-TB drugs and on ARVs than their HIV (-) counterparts taking anti-TB drugs alone.

Gastrointestinal disturbances and peripheral neuropathy were the most common ADRs in both HIV(+) and HIV(-) adult patients taking anti-TB drugs. However, hepatotoxicity was the main cause of TB treatment interruption in both the HIV(+) and HIV(-) adult taking anti-TB drugs.

Recommendations:

ADRs surveillance systems should be established in hospitals as they will have a major impact on ADRs monitoring and control.

Clinical monitoring should be done regularly as hepatotoxicity is the main cause of TB treatment interruption.

More studies on the incidence and risk factors for ADRs in Africans are required as they will help to prevent serious adverse effects during TB and combined HIV/TB treatment.

Any future studies should preferably be prospective to overcome the numerous limitations of retrospective studies.

Grading of ADRs will be necessary in future studies to identify serious ADRs.

1.1 Introduction / background

TB Global picture

Tuberculosis disease has re-emerged as a major public health problem in the world. It is estimated that a third of the world population is infected with tubercle bacillus [2, 29] According to a World Health Organization (WHO) report, there were an estimated 8.8 million new TB cases in 2005, 7.4 million in Asia and sub-Sahara Africa [1]. Globally, TB is second only to HIV/AIDS as a cause of illness and death of adults[2, 29, 32]. It accounts for about 13% of all HIV-related deaths worldwide [7].

HIV/AIDS pandemic has caused a resurgence of TB, resulting in increased morbidity and mortality worldwide. HIV and *Mycobacterium tuberculosis* have a synergistic interaction; each accentuates progression of the other[7].

HIV (+) individuals are more susceptible than HIV(-) persons to acquiring TB after exposure to mycobacterium TB and to activation of latent infection. Studies indicate that active TB can cause progression of HIV disease; HIV (+) patients with TB have a shorter survival and a higher tendency to acquire new opportunistic infection than HIV (+) patients who have not had TB, even when matched by the disease stage[34].

Other studies also suggest that the mortality of HIV-infected patients with TB is higher than that of HIV(-) TB patients. The mortality depends upon the type of disease and the degree of underlying immunosuppression[7].

Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do experience adverse effects. HIV in TB infection is associated with an increased risk of adverse drug reactions when on many anti-TB drugs. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly[39].

Sub-Sahara Africa

Although it has only 11% of the world's population, Africa accounts today for more than a quarter of TB global burden with an estimated 2.4 million TB cases and 540,000 TB deaths annually[32].

In the African region a sharp rise in the incidence of TB has been attributed to the high HIV prevalence in this region[2, 31]. About one third of people infected with HIV are also infected with

TB and 70% of these people live in sub-Sahara Africa[19]. Furthermore, HIV (+) patients are more prone to developing ADRs when on anti-TB drugs and need to be monitored carefully [7, 25]

In 2005, the WHO Regional Committee for Africa declared TB an emergency in the African region, as a response to an epidemic that has more than quadrupled the annual number of new TB cases in most African countries since 1990 and that it continues to rise across the continent, killing more than half a million people every year [19, 32].

Tuberculosis is the leading cause of morbidity and mortality. HIV-positive patients have much higher death rates during the time they are being treated for tuberculosis than patients without HIV, about 30% of HIV (+) patients die within 12 months of TB treatment[26, 28].

The Kenyan picture

Kenya is one of the 22 high burdened countries in the world which collectively contribute 80% of the global TB disease burden. It is experiencing a generalized TB epidemic affecting the young economically productive age groups (15-44 year old).[2, 31] In 1994, a national survey to determine the prevalence of HIV among TB patients found that 40% of TB patients were HIV seropositive.[31] By 2006 this had risen to 52%.[3]

According to the National Leprosy Tuberculosis Programme [NLTP] annual report, the number of reported TB cases has increased nine fold from 11,625 in 1990 to 115,234 cases in 2006 (Appendix iv). The average annual increase over the past 10 years is 13% for all forms of TB. However in the last 5 years the annual increase in notified TB cases slowed down to an average of 9%.[3] Although Kenya's TB disease burden is large the cases notified may represent less than half of the incident cases that occur each year[31].

TB chemotherapy and adverse drug reactions

Short course chemotherapy is currently the most effective treatment for most patients with TB[30]. However, the necessity of utilization of multidrug regimens has been associated with increased incidence of side effects. These side effects may be mild or severe. Any severe side effect by one of the primary anti-TB drugs, which leads to the discontinuation of that drug, has several complications including an increased morbidity and mortality. At the same time, use of alternative agents may result in greater problems of toxicity and compliance. In addition, the risk of treatment failure and relapses are higher. Therefore monitoring is crucial, but costly. Awareness of the risk groups may decrease the cost as well as the incidence of serious drug-related adverse effects[4].

While most patients treated for TB experience no problems with the treatment, a few patients may have significant side effects which can threaten life or interfere with the quality of life.[2, 31] It is therefore important that patients are clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary[39].

HIV-infected patients are more prone to developing adverse reactions to anti-TB drugs and need to be carefully monitored[7, 25]. The risk of adverse drug reactions (ADRs) increases with advanced immunosuppression and a majority of the ADRs occur in the first two months of treatment. These include skin rash, usually caused by thiacetazone and sometimes by rifampicin and streptomycin, gastrointestinal disturbances and drug-induced hepatotoxicity. Rifampicin, isoniazid and pyrazinamide are all potentially hepatotoxic. Transient increases in transaminases and bilirubin commonly occur at the start of treatment[13]. Thiacetazone can cause fatal ADRs and hence is contraindicated in HIV-infected patients[7, 25].

Isoniazid may also cause dose dependent peripheral neuropathy, probably due to depletion of vitamin B6; this reaction is rare in recommended doses but certain patient groups e.g. the poorly nourished, alcoholics, diabetics, uraemic patients and pregnant women are at greater risk and should receive pyridoxine supplementation at a dose of 10 -20mg per day.[13] HIV-infected patients are more prone to developing isoniazid-induced peripheral neuropathy and all HIV-TB patients receiving isoniazid should be given pyridoxine supplementation (10-25 mg/day).[7]

Ocular toxicity is by far the most important side-effect of ethambutol. It occurs in fewer than 2% of patients at the usual dose of 15mg/kg but is more common in the elderly and people with renal impairment.[13]

Classification of anti-TB adverse drug reactions

The WHO classifies adverse effects of anti-TB drugs as minor or major. In general, a patient who develops minor adverse drug reactions should continue the TB treatment, sometimes at a reduced dose. The patient also receives symptomatic treatment. In patients developing a major side-effect, the treatment with the offending drug should be stopped. Further management depends on the nature of the adverse reaction. Patients with major adverse reactions should be managed in a hospital[39].

Table 1: WHO classification: Minor and major side effects of anti-TB drugs[39].

Side effect	Drug(s) probably responsible	Management
a. Minor		**Continue anti-TB drugs** **Check drug doses**
Anorexia, nausea, abdominal pain	Pyrazinamide (Z), Isoniazid (H)	Give drug with small meals or as last thing at night.
Joint pains	Pyrazinamide	Aspirin
Burning sensation in feet	Isoniazid	Pyridoxine 100mg daily.
Orange / red urine	Rifampicin (R)	Reassurance. Patient should be told when starting treatment that this commonly happens and is normal.
b. Major		**Stop responsible drug(s)**
Itching	Thioacetazone, Z, S, R, H.	Stop anti-TB drugs.
Deafness (no wax on auroscopy)	Streptomycin (S)	Stop S, Use Ethambutol (E)
Dizziness (vertigo & nystagmus)	Streptomycin	Stop S, Use Ethambutol.
Jaundice (other causes excluded) hepatitis	H, Z, R.	Stop anti-TB.
Confusion (suspect drug-induced acute liver failure of jaundice) present	Most anti-TB drugs	Stop anti-TB drugs. Urgent liver function tests and prothrombin time.
Visual impairment (other causes excluded)	Ethambutol	Stop Ethambutol.
Shock, purpura, acute renal failure	Rifampicin	Stop Rifampicin.

Definition of drug-induced hepatotoxicity

***WHO definition of drug-induced hepatotoxicity.**

Grade 1 (mild): <2.5 · the upper limit of normal (ULN) (ALAT 51–125 U/l).

Grade 2 (mild): 2.6–5 · the ULN (ALAT 126–250 U/l).

Grade 3 (moderate): 5–10 · the ULN (ALAT 251–500 U/l).

Grade 4 (severe): >10 · the ULN (ALAT >500 U/l).

Adapted from reference 15

According to BHIVA [British HIV Association], hepatotoxicity has been defined as:

i. A serum AST or ALT level of more than three times the upper limit of normal in the presence of symptoms, or

ii. A serum AST or ALT greater than five times the upper limit of normal in absence of symptoms.[18]

1.2 Literature review

The ADR definition used in this study is that of the WHO 'Any noxious or unintended response to a drug, which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or for the modification of physiological function[8].

While most patients treated for TB experience no problems with the treatment, a few patients may have significant side effects which can threaten life or interfere with the quality of life[2, 31]. A study of the treatment of HIV/TB co-infection in the era of HAART observed an incidence of significant adverse events of more than 50% with one third of subjects discontinuing anti-TB treatment[9].

Adverse effects of first line antituberculosis drugs occur in both HIV (+) and HIV(-) patients and the patient should be monitored carefully for these. However, side effects of antituberculosis drugs are comparatively more frequent in the HIV (+) tuberculosis patients and very severe and even fatal reactions have been observed according to several studies[25].

In a retrospective study done in London, UK, 2006, the incidence of serious adverse events was compared in 312 individuals treated for TB, of whom 156 were co-infected with HIV. 111 HIV infected individuals (71%) received highly active antiretroviral therapy [HAART] at the same time as anti-TB treatment. The patients were taking rifampicin, pyrazinamide and isoniazid that was co-administered with pyridoxine 10-25 mg daily. (Ethambutol was routinely commenced at North Middlesex and Royal Free but not University College) for 2 months followed by a continuation phase of two drugs dependent on drug sensitivities. Serious adverse events were recorded in 40% HIV infected and 26% HIV uninfected individuals. Peripheral neuropathy and persistent vomiting were more common in HIV co-infected patients. However, the interruption of anti-TB treatment occurred with similar frequency in the two groups (13% in HIV infected patients and 15% in HIV uninfected patients. In 85% of HIV infected patients and 87% of HIV uninfected individuals this was due to hepatotoxicity, which typically presented within 2 months of starting treatment[9].

The study also suggested that only in the black African population did ethnicity appear to be important, with a significantly lower frequency of anti-TB treatment interruption observed in the HIV uninfected group than in the HIV infected group[9].

In a retrospective study conducted in Canada 46 serious adverse reactions occurred among 430 patients treated for active TB, 1990 - 1999, who were taking rifampicin, isoniazid, pyrazinamide and ethambutol. The incidence of serious side effects, especially hepatitis and rash, was highest with PZA, and was associated with female sex, older age, birth in Asia and HIV infection. The consequences of these adverse events included hospitalizations, prolonged therapy, and more clinic and home visits.[8, 37]

In a Ugandan study, only two of the 265 HIV (+) subjects (1%) developed hepatotoxicity during treatment of PTB using (2HRZE/6HR). The same group reported that hepatitis and transaminase elevations did occur during preventive TB treatment in HIV (+) patients and that 0.8% had transaminase level >135u/l.[15]

In the former Zaire, TB drugs (2HRZE/4HR) were well tolerated among 446 TB patients. No hepatitis was reported but increased transaminase levels were occasionally seen.[15]

Schaberg et al, conducted a retrospective study on 519 patients with pulmonary TB in Germany. The patients had taken isoniazid 5mg/kg daily, rifampicin 10mg/kg daily, and pyrazinamide 25-30 mg/kg daily during the study period of 1990 - 1994. They reported that the termination of isoniazid, rifampicin or pyrazinamide because of severe side effects was necessary in 121 out of 519 patients (23%). In this study, the top-three severe side effects leading to the final termination of one drug were hepatotoxicity (11%), exanthema (6%) and arthralgia (2%).[6, 8]

The study by *Schaberg et al,* also indicated that, exanthema due to isoniazid occurred after 13.5 days of treatment, whereas exanthema due to pyrazinamide occurred after only 2 days. Arthralgia due to pyrazinamide was seen after 25 days of treatment.[6]

In addition to combination therapy, there are several other well established risk factors for development of abnormal liver function tests; increasing age, pre-existing liver disease, slow acetylators and continuation of drug after development of hepatic dysfunction.[16]

In an Iranian study done between 2004 and 2005 involving 204 patients with TB given rifampicin, pyrazinamide, isoniazid and ethambutol. 120 patients were females and 84 males. Ninety-two patients (45.10%), including 58 females and 34 males, had at least one ADR induced by anti-TB drugs. Since some patients experienced more than one ADR, a total number of 136 adverse reactions were recorded (38 patients with two and 3 patients with three ADRs). The highest percentage of ADR was observed in the age group of older than 65 years. The top three ADRs were, nausea and vomiting 16.79%, hepatitis 16.06% and pruritus 13.4%. The most frequent system-organ classes affected by ADRs were the gastrointestinal system (36.1%) and

liver and billiary system (25%).[8]

A retrospective study was done in Turkey in 2006, involving 1149 hospital admitted patients over a time period of 15 years (1984-2001). Patients first received primary anti-TB drugs including a combination of 3 or 4 drugs [Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, or Streptomycin during an initial phase of 2 months, followed by a continuation phase of 7 months consisting of INH and RIF. Treatment was given daily, and at least the initial phase administered during hospitalization. Ninety-five patients (8.3%) had side effects, 9 of whom experienced a second adverse reaction. Severe hepatotoxicity was noted in 5 patients (27.8%), who were re-administered anti-TB treatment with the same drug regimen and same doses after hepatotoxicity. The most common drug which had to be terminated due to hepatotoxicity was pyrazinamide. Pyrazinamide was stopped in 7 patients, whereas rifampicin was stopped in only 2 patients. Severe hepatotoxicity was more frequent among younger patients.[4]

The results of the Turkey study, indicate that intolerance of anti-TB standard therapy due to the side effects is still a serious problem in the hospital-treated patients with tuberculosis.[4]

Some ADRs can be increased by HAART, such as peripheral polyneuropathy secondary to isoniazid in combination with didanosine (ddI), zalcitabine (ddC) or stavudine (d4T), and hepatotoxicity related to isoniazid and / or pyrazinamide in combination with nevirapine, efavirenz or protease inhibitors (PIs).[38]

Isoniazid

The incidence of adverse reactions to isoniazid in more than 2,000 patients has been estimated to be 5.4%, with the most prominent reactions being cutaneous eruptions (2%), fever (1.2%), jaundice (0.5 %), and peripheral neuritis (0.6 %).[36]

a. Hepatitis

Isoniazid has been reported to cause severe, and sometimes fatal, age-related hepatitis. If signs and symptoms of hepatotoxicity occur, isoniazid should be discontinued promptly. The incidence of clinical hepatitis in young, healthy adults is 0.3%, but can increase to 2.6% for those who drink alcohol daily, have chronic liver disease, or are elderly. Patients with advanced HIV disease have been reported to have an increased incidence of adverse reactions to antitubercular medications[10]. The risk of hepatitis is higher in older patients, alcohol abusers and Hispanics and black women of child bearing age.[27]

With respect to hepatotoxicity, some rise in serum aspartate transaminase (AST) is common (12% of all cases treated with isoniazid); but severe idiosyncratic reactions are rare. In the 1970s two cases of fatal fulminant hepatic failure secondary to isoniazid were documented, with subsequent reports of 16 fatal cases of rifampicin. Further fatal cases of fulminant hepatic failure secondary to isoniazid have been reported.[16]

Hepatotoxicity due to isoniazid in the general population increases with age occurring in less than 0.3% of those under 35 years against about 2.3% of those older than 50 years[18]. Many studies have stated that slow acetylators would develop more severe hepatotoxicity than rapid acetylators.[22]

b. Peripheral neuritis

Peripheral neuritis, usually preceded by paresthesia of the feet and hands, is the most common adverse effect of isoniazid and occurs most frequently in malnourished patients and those predisposed to neuritis (e.g., alcoholics, diabetics, HIV infection, and renal failure). Rarely, other adverse nervous system effects have also occurred including seizures, toxic encephalopathy, muscle twitching, ataxia, stupor, tinnitus, euphoria, and memory impairment, separation of ideas and reality, loss of self-control, dizziness, and toxic psychosis. Neurotoxic effects may be prevented or relieved by the administration of 10-50 mg of pyridoxine hydrochloride daily during isoniazid therapy, and pyridoxine should be administered in malnourished patients, pregnant women, and those predisposed to neuritis (e.g., HIV-infected individuals).[11, 24, 36]

c. Other adverse drug reactions

Other adverse reactions associated with isoniazid include hypersensitivity reactions, such as acneiform skin rash, effects similar to those of monoamine oxidase inhibitor after the ingestion of such foods as red wine or cheese, and development of antinuclear antibodies or (rarely) overt systemic lupus erythematosus.[27]

Adverse hematologic effects, including agranulocytosis, eosinophilia, thrombocytopenia, methemoglobinemia, and hemolytic, sideroblastic, or aplastic anemia, have occurred in patients receiving isoniazid.[11]

Hypersensitivity reactions produce urticaria, angioneurotic edema, and morbilliform eruptions, which may occasionally progress to exfoliative dermatitis. Other skin lesions noted include xerostomia, nonthrombocytopenic purpura, striae cutis atrophica, pruritis, and erythema.

Acneiform eruptions have been particularly noted in younger patients with a previous history of acne vulgaris.[36]

Adverse effects of Isoniazid can be classified on the basis of their potential clinical significance: [11]

a. Those indicating need for medical attention [11]

Those that are more frequent:

i. *Hepatitis* (dark urine, yellow eyes or skin);

ii. *Hepatitis prodromal symptoms* (loss of appetite, nausea or vomiting, unusual tiredness or weakness);

iii. *Peripheral neuritis* (clumsiness or unsteadiness; numbness, tingling, burning, or pain in hands and feet).

Those that are rare:

i. *Blood dyscrasias* (fever and sore throat, unusual bleeding and bruising, unusual tiredness or weakness);

ii. *Hypersensitivity* (fever, joint pain, skin rash);

iii. *Neurotoxicity* (seizures, mental depression, mood or other mental changes);

iv. *Optic neuritis* (blurred vision or loss of vision, with or without eye pain).

b. Those indicating need for medical attention only if they continue or are bothersome [10]

More frequent:

i. *Gastrointestinal disturbances* (diarrhea, nausea and vomiting, stomach pain).

Incidence not reported

Local irritation at the site of intramuscular injections.

Rifampicin

a. Hepatotoxicity

Rifampicin toxicity is low when administered alone, the hepatotoxicity of rifampicin has been observed in patients with underlying liver disease. Rifampicin is involved in some cases of cholestatic hepatitis. [22, 36]

Rifampicin alone is possibly associated with a lower potential for hepatotoxicity than isoniazid or pyrazinamide.[5, 27]

Serious liver injury due to rifampicin *per se* is rare (and is associated with zone 3 centrilobular necrosis) but rifampicin does increase the hepatotoxicity of isoniazid. This effect is thought to be due to enzyme induction, leading to an increase in hepatotoxic metabolites of isoniazid.[23]

The dose regimen appears to be important; in one series of patients treated with rifampicin and isoniazid, the rate of drug-induced hepatitis was 21% when rifampicin was given daily and 5% when given twice weekly.[23, 27]

b. Gastrointestinal disturbances

Gastrointestinal upset is relatively common in the first few weeks of first line anti- tuberculosis therapy particularly rifampicin, but drugs must not be discontinued because of minor side effects. Dosing with meals and changing the hour of dosing is recommended.[24]

c. Other adverse reactions

Cutaneous reactions with or without a rash may occur in as many as 6% of patients but is generally self limited. Flu-like syndrome may occur in 0.4 -0.7% of patients receiving 600mg twice weekly but not in daily administration of same dose.[24]

Rifampicin therapy causes a harmless red or orange discoloration of the urine and other body fluids and may stain contact lenses. Hypersensitivity reactions, thrombocytopenia, renal failure and flu-like symptoms occur only rarely; however, they seem to occur more frequently with intermittent than with daily administration.

The frequency of reactions varies in different populations but may occur in up to 5% of the patients. Chronic papular acneiform lesions of face and neck were reported in 8 – 24% of African men with genitourinary TB. Withdrawal of the medication led to disappearance of the lesions within 3 weeks. One case of Stevens-Johnson syndrome associated with rifampicin was also reported in one African man. [36]

Adverse effects of rifampicin can be classified on the basis of their potential clinical significance:

a. Those indicating need for medical attention [10]

Less frequent incidences

i. Flu-like" syndrome (chills; difficult breathing; dizziness; fever; headache; muscle and bone pain; shivering);

ii. *Hypersensitivity* (itching; redness; skin rash).

Rare incidences

i. Blood dyscrasias (sore throat; unusual bleeding or bruising);

ii. *Hepatitis* (yellow eyes or skin);

iii. *Hepatitis prodromal symptoms* (loss of appetite; nausea or vomiting; unusual tiredness or weakness);

v. *Interstitial nephritis* (bloody or cloudy urine, greatly decreased frequency of urination or amount of urine).

b. Those indicating need for medical attention only if they continue or are bothersome [10]

More frequent

i. Gastrointestinal disturbances (diarrhea; stomach cramps).

Less frequent

i. Fungal overgrowth (sore mouth or tongue).

c. Those not indicating need for medical attention [10]

More frequent

i. Reddish-orange to reddish-brown discoloration of urine, feces, saliva, sputum, sweat, and tears.

Pyrazinamide

a. Hepatotoxicity

The risk of hepatotoxicity in patients with pre-existing liver disease is greatest with pyrazinamide then rifampicin then isoniazid.[18] *T. Schaberg*, et al reported that Pyrazinamide showed more severe side-effects (15%) than isoniazid (7%) and rifampicin (1.5%).[6]

Pyrazinamide-associated hepatotoxicity is said to be dose dependent, in contrast to the idiosyncratic hepatotoxicity of isoniazid. Pyrazinamide caused fatal hepatitis when it was administered at a dose of 150 mg/kg for treatment of drug-resistant TB, but it was better tolerated at 20–25 mg/kg in multidrug regimens[20] It occurs after several weeks, usually after 2 months[22, 27] About 15% of patients receiving 3 g/day will develop hepatic disease. Of these, 2-3% will have jaundice or death due to hepatic necrosis.[36]

Incidence of major side effects associated with pyrazinamide PZA), is somewhat controversial. Authoritative treatment guidelines have stated that "there does not appear to be significant increase in hepatotoxicity when PZA is added to INH and RIF, based on results from large scale randomized trials". However, studies of patients treated for active disease, or receiving 2 months of RIF and PZA for latent infection, have reported serious adverse events attributable to PZA.[37]

The contribution of pyrazinamide to the development of drug-induced hepatotoxicity during treatment of TB appeared to be controversial in earlier reports. However, later studies or analyses, especially the more recent ones, have been more in favour of pyrazinamide's potential hepatotoxicity, among the various components of a short-course antituberculosis drug regimen.[5]

An Indian study found pyrazinamide was used in addition to isoniazid and rifampicin in a significantly higher percentage of patients with antituberculosis drug-induced hepatitis, as compared with those in the control group (70% vs. 42%).[5] A Turkish study revealed that re-introduction of a regimen including pyrazinamide was more likely to result in recurrence of hepatotoxicity than that without.[5]

In a Singaporean study, all the patients with fatal drug-induced hepatotoxicity had received pyrazinamide- containing regimens.[5]

In a recent analysis undertaken in Canada, the incidence of all major adverse events was 1.48 per 100 person-months of exposure for pyrazinamide as compared with 0.49 for isoniazid, and 0.43 for rifampicin. Pyrazinamide induced adverse events were associated with age >60 years and a birthplace in Asia. The incidence of pyrazinamide-induced hepatotoxicity during treatment for

active TB was thus substantially higher than those attributable to the other first-line antituberculosis drugs and higher than previously recognized. As the hepatotoxicity incurred by pyrazinamide is likely to be dose-related, several authorities now recommend the use of lower daily or thrice-weekly dosages of the drug.[5]

b. Exanthema

Schaberg et al. reported that, most patients developed exanthema directly after the first dose of pyrazinamide. In such cases, an attempt was made to reintroduce pyrazinamide at a reduced dose, which was then increased to the normal dose in the case of tolerance within the following days. Using this approach, most patients with exanthema tolerated pyrazinamide. However, a substantial number of patients also showed severe exanthema with the reduced dose.[6]

c. Other adverse drug reactions

Hypersensitivity reactions and gastrointestinal upset may occur with pyrazinamide. It often produces elevated serum levels of uric acid, although arthralgias occur infrequently, and acute gout is rare[27]. Sensations of burning in the skin and development of reddish-brown discoloration on sun-exposed areas have also been described.[36]

Adverse effects of pyrazinamide can be classified on the basis of their potential clinical significance:

a. Those indicating need for medical attention [10]

More frequent incidences

i. Arthralgia (pain in the large and small joints) — related to hyperuricemia; usually mild and self-limiting.

Incidence rare

i. Gouty arthritis (pain and swelling of joints, especially big toe, ankle, and knee; tense, hot skin over affected joints);

ii. *Hepatotoxicity* (loss of appetite; unusual tiredness or weakness; yellow eyes or skin) — related to large doses, i.e., 40 to 50 mg per kg of body weight per day for prolonged periods of time.

b. Those indicating need for medical attention only if they continue or are bothersome [10]

Rare incidences

i. Itching; skin rash.

Ethambutol

a. Ocular toxicity

Ethambutol toxicity is dose related, in one report of eighteen patients treated with ethambutol at 60mg/kg/day, eight developed toxic optic neuropathy. Patients receiving 25mg/kg/day have a 5% to 6% reported incidence of optic neuropathy. Patients receiving 15mg/kg/day have incidence reportedly less than 1%.[17, 33]

Toxicity generally does not develop until after treatment for at least one and half months. In a series of seven patients, the reported mean interval between onset of therapy and toxic effects was 3.4 months. In another series of ten patients, the mean interval was five months. Manifestations of toxicity can occur as late as twelve months after initiation of therapy[17] The risk is higher at higher doses given daily (18% of patients receiving more than 30mg/kg/day) and in patient with renal insufficiency.[24]

Ocular toxicity is by far the most important side effect of ethambutol. It occurs in fewer than 2% of patients at the usual dosage of 15mg/kg but is more common in elderly and people with renal impairment. Patients may complain of changes in colour vision or visual field which may appear suddenly. The effect is usually reversible on discontinuation but permanent damage may occur if the drug is continued.[13]

Retrobulbar optic neuritis is thought to be dose-related, occurring most frequently with daily doses of 25 mg per kg of body weight (mg/kg) and after 2 months of therapy; however, optic neuritis has occurred after only a few days of treatment. Most cases are reversible after several weeks or months. Visual changes may be unilateral or bilateral; therefore, each eye must be tested separately and both eyes tested together[10] The central fibers of the optic nerve are most commonly affected, causing blurred vision, decreased visual acuity, central scotomas, and often loss of the ability to detect green and sometimes red.[33]

Both anterior and retrobulbar optic neuropathies have been reported, although the retrobulbar form is far more common. Visual loss develops insidiously over weeks or months, particularly affecting colour vision and, later, visual acuity. In cases with unilateral onset, the second eye is usually involved within 1 month.[21]

Ethambutol produces an optic neuritis that progresses to blindness if the drug is not withdrawn. Vision returns virtually to normal after the drug is withdrawn.[17]

The combination of ethambutol and isoniazid for TB meningitis poses a particular risk to vision, as either can produce a toxic optic neuropathy.[21]

b. Other adverse drug reactions

Between 1968 and 1977, there were recorded 108 skin reactions attributed to ethambutol. Hair loss accounted for eight cases, while urticaria, erythema multiforme, angioedema, hyperhidrosis, skin striae, bullous eruptions, and exfoliative dermatitis (one of two cases was lethal) accounted for one to three cases each. Rash and pruritis accounted for *70%* of the cutaneous side effects. Ethambutol induced lichenoid eruption and two cases of acute gouty arthritis were also reported.[36]

Adverse effects of ethambutol can be classified on the basis of their potential clinical significance:

a. Those indicating need for medical attention [10]

Less frequent incidences

i. Gouty arthritis, acute (chills; pain and swelling of joints, especially big toe, ankle, or knee; tense, hot skin over affected joints).

Rare incidences

i. Hypersensitivity (skin rash; fever; joint pain);

ii. *Peripheral neuritis* (numbness, tingling, burning pain, or weakness in hands or feet);

iii. *Retrobulbar optic neuritis* (blurred vision, eye pain, red-green color blindness, or any loss of vision)

b. Those indicating need for medical attention only if they continue or are bothersome [10]

Less frequent incidences

Confusion; *disorientation*; *gastrointestinal disturbances* (abdominal pain; loss of appetite; nausea and vomiting); *headache*.

Streptomycin

Streptomycin is an aminoglycoside antibiotic that interferes with bacterial protein synthesis. It is given by injection, usually intramuscularly, at a daily dose of 15 mg/kg. Ototoxicity and nephrotoxicity are associated with administration of this drug, occurring more frequently in the elderly. Vestibular dysfunction is more common than auditory damage.[27]

Of 515 TB patients treated with streptomycin, 8.2% developed adverse reactions: 50% of these involved the vestibular and auditory function of the eighth cranial nerve. The remaining patients had undetermined dermatitis (2%) and fever (1.4%)." Skin eruptions were reported in as many as 5% of patients treated with this drug, including morbilliform, maculo-papular, erythematous, and urticarial lesions. Pruritis, scaling, lichenoid eosinophilia, lymphadenopathy, mouth ulcers, purpura, and fever may accompany these eruptions. Exfoliative dermatitis occurs in approximately 1% of individuals, and occasionally acute anaphylaxis may follow the administration of any quantity of SM. Toxic erythema with generalized follicular pustules and SM-induced arthritis.[36]

Adverse drug reactions of streptomycin can be classified on the basis of the potential clinical significance.

a. Those indicating need for medical attention [10]

More frequent incidences

i. *Nephrotoxicity* (greatly increased or decreased frequency of urination or amount of urine; increased thirst; loss of appetite; nausea; vomiting).

ii. *Neurotoxicity* (muscle twitching; numbness; seizures; tingling).

iii. *Ototoxicity, auditory* (any loss of hearing; ringing or buzzing or a feeling of fullness in the ears).

iv. *Ototoxicity, vestibular* (clumsiness; dizziness; nausea; vomiting; unsteadiness).

v. *Peripheral neuritis* (burning of face or mouth; numbness; tingling).

Less frequent

i. *Hypersensitivity* (skin itching, redness, rash, or swelling);

ii. *Optic neuritis* (any loss of vision).

Rare incidences

i. *Neuromuscular blockade* (difficulty in breathing; drowsiness; weakness).

b. Those indicating possible ototoxicity, vestibular toxicity, or nephrotoxicity and the need for medical attention if they occur and / or progress after medication is discontinued.[10]

i. Any loss of hearing; clumsiness or unsteadiness; dizziness;

ii. Greatly increased or decreased frequency of urination or amount of urine; increased thirst;

iii. Loss of appetite; nausea or vomiting; ringing or buzzing or a feeling of fullness in the ears.

1.3 Problem statement

TB remains a major cause of morbidity and mortality in Kenya. Kenya is experiencing a generalized TB epidemic affecting the economically productive age groups (15-44 years). The HIV epidemic has increased TB burden and it also complicates TB therapy. Concurrent HIV infection means that the patient has to take several drugs for either treatment of the concurrent infection or prophylaxis of opportunistic infection during anti-TB therapy. Drug interactions and overlapping toxicities are often seen in patients taking first line fixed dose combination therapy during TB therapy.

Most patients complete their treatment without any significant adverse drug reactions. However, a few patients may have significant adverse drug reactions which can threaten life or interfere with the quality of life. HIV-infected patients are more prone to developing adverse reactions to anti-TB drugs. It is therefore important that patients are clinically monitored during treatment so that the adverse drug reactions can be detected promptly and managed properly.

Prevention of adverse drug reactions may increase adherence and treatment success rate which will eventually contribute to TB control. Treatment failures and drug resistance may reduce as patients are not likely to stop taking anti-TB drugs because of adverse drug reactions.

Severe adverse drug reactions can lead to hospital admission and even mortality. The extent of ADRs in HIV (+) and HIV(-) adult patients taking anti-TB drugs is not known in Kenya. Therefore, this study on prevalence of adverse drug reactions in HIV (+) and HIV(-) adult patients taking anti-TB drugs may help in determining the proportion of patients likely to develop severe adverse drug reactions.

1.4 Justification

While most patients treated for TB experience no problems with the treatment, a few patients may have significant side effects which can threaten life or interfere with the quality of life.[2, 31] Adverse effects of anti-TB drugs occur in both HIV (+) and HIV(-) patients. It is therefore important that patients are clinically monitored during treatment so that adverse effects can be detected promptly and managed properly[39]. HIV-infected patients are more prone to developing adverse reactions to anti-TB drugs and need to be carefully monitored[7, 25].

The literature review shows that, there are few comparative studies on adverse drug reactions among HIV (+) and HIV(-) adult patients taking anti-TB drugs. In a study done in London, serious adverse events were recorded in 40% HIV infected and 26% HIV uninfected individuals[9]. However, another study on the treatment of HIV/TB co-infection in the era of HAART observed an incidence of significant adverse events of more than 50%, with one third of subjects discontinuing anti-TB treatment[9].

Most studies on anti-TB drug induced ADRs were conducted in Europe, Southeast Asia and northern America. Studies conducted in Sub-Saharan Africa are limited with a confusing picture as shown by a few studies conducted in East and Central Africa below.

Studies conducted in East Africa reported different prevalence rates of ADR. In a Ugandan study, only two of the 265 HIV (+) patients (1%) developed hepatotoxicity during treatment of PTB using (2HRZE/6HR) [15]. However, in a former Zaire study, TB drugs (2HRZE/4HR) were well tolerated among 446 TB patients. No hepatitis was reported but increased transaminase levels were occasionally seen.[15]

The Kenyan guidelines for the management of patients co-infected with HIV and TB are still evolving which is further complicated by drug interactions and overlapping toxicities. Therefore, the results obtained from the study may be used in advocacy of adverse drug reactions in HIV (+) and HIV(-) adult patients taking anti-TB drugs. In addition to that, the study may recommend regimen changes in TB treatment.

Lastly, from the foregoing, it is clear that further studies are needed to establish the prevalences of ADRs in HIV (+) and HIV(-) adult patients taking anti-TB drugs.

2.0 DESIGN AND METHODOLOGY

2.1 Goal of the study

To improve the management of adult HIV (+) and HIV(-) patients taking anti-TB drugs at Kenyatta National Hospital.

2.2 Study objectives

i. To determine the prevalence of adverse drug reactions among HIV (+) and HIV(-) adult patients taking anti-TB drugs at KNH.
ii. To document the patterns of ADRs among HIV (+) and HIV(-) adult patients taking anti-TB drugs.
iii. To estimate the odds ratio (OR) of developing adverse drug reactions among HIV (+) and HIV(-) adult patients taking anti-TB therapy.

2.3 Research questions

i. Are the odds ratio of developing adverse drug reactions different between HIV (+) and HIV(-) adult patient taking anti-TB drugs?

ii. What is the prevalence of adverse drug reactions among HIV (+) and HIV(-) adult patients taking anti-TB drugs?

iii. What are the patterns of ADRs among HIV (+) and HIV(-) adult patients taking anti-TB drugs?

2.4 Hypothesis of the study

Null hypothesis

There is no difference in the prevalences of ADRs among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

Alternative hypothesis

ADRs are more likely to occur in HIV (+) adult patients taking anti-TB drugs than HIV(-) adult counterparts.

2.5 Area of the study

The study was done at the records department of Kenyatta National Hospital.

2.6 Study design

A retrospective cohort study [hospital based].

2.7 Target population

Both HIV (+) and HIV(-) patients diagnosed with TB and treated with anti-TB drugs.

2.8 Inclusion criteria

i. All adult patient files for either HIV (+) or HIV(-) patients who were diagnosed with TB and started on anti-TB drugs between January 2006 and December 2007.
ii. No other chronic infectious diseases or any other major illness e.g. cardiovascular and renal.
iii. Complete patient files.

2.9 Exclusion criteria

i. Patients less than 18 years on the day of TB diagnosis.
ii. Patients whose HIV status was not documented.
iii. Other chronic infectious diseases or any other major illness e.g. cardiovascular and renal.
iv. Incomplete patient files with missing pages resulting in loss of information.
v. Patient files whose records documented anti-TB treatment duration of less than seven days.

2.10 Ethical considerations

Approval to carry out the study

Approval to carry out the study was obtained from Kenyatta National Hospital Ethics and Research Committee (Appendix 1).

Benefits from the study

There was no direct benefit to patients whose files were used in the study. Future patients may benefit as the results from the study may be used for recommending regimen change so as to minimize ADRs in susceptible patients.

Risks involved

There were no risks involved as no patients were involved in the study.

Confidentiality

Confidentiality of the patients whose files were used was kept by using study numbers and patient file numbers. Patient names were not entered into the data collection form. The data extracted from patient files was stored securely under lock and key.

Voluntariness

Voluntariness was not applicable, as only patient files were reviewed.

Informed consent

Consent explanation and consent forms were also not applicable as only patient files were used for the study. Consent waiver was obtained from the Kenyatta National Hospital Ethics and Research Committee since patients were not involved.

2.11 Sample size and sampling method

Sample size

The prevalences of ADRs for both the HIV (+) and HIV(-) adult patients used in this study for the calculation of sample size are those of a London, retrospective study done by *Breen et al. 2006*. This study made assumptions that similar prevalence rates existed among HIV (+) and HIV(-) adult patients taking anti-TB drugs at Kenyatta National Hospital as those reported in the London study. The incidence of serious adverse events was compared in 312 patients treated for TB, of whom 156 were HIV (+). 111 HIV (+) patients (71%) received highly active antiretroviral therapy [HAART] at the same time as anti-TB treatment. Serious adverse events were recorded in 40% HIV+ and 26% HIV- patients[9].

Calculation of sample size

$$N = \left[\frac{[Z\beta\sqrt{[P_1(1-P_1) + P_2(1-P_2)]} + Z_{1-\alpha/2}\sqrt{2P_2(1-P_2)}}{(P_1-P_2)^2} \right]^2$$

β – Beta = 1- power (82%) (Type II Error)

$Z_{1-\alpha/2}$ – Corresponding value to the 95% confidence interval (Type I Error)

P_1 – Prevalence among HIV+ patients = 40%

P_2 – Prevalence among HIV- patients = 26%

$$N = \left[\frac{0.82\sqrt{[(0.4)(0.6)] + (0.26)(0.74)]} + 1.96\sqrt{2(0.26)(0.74)}}{(0.4 - 0.26)^2} \right]^2$$

= 157 per group.

Sampling method and retrieval of patient files.

Simple random sampling method was applied for each of the two groups in identification of the study files. Three hundred and fourteen patient files meeting the inclusion criteria were included in the study. One hundred and fifty seven of the patient files were for HIV(-) while one hundred and fifty seven of them HIV (+) adult patients taking anti-TB drugs.

The study file numbers for HIV (+) and HIV(-) adult patients treated with anti-TB during the study period (Jan 2006 to Dec 2007) were randomly picked and listed down for each month at the coding section of the medical records department.

The list of patient file numbers was then handed over to the personnel of the medical records department, KNH who retrieved the listed patient files from patient files section.

The retrieved patient files were then taken to the study room of the medical records department where files were separated based on the inclusion criteria of the study. Simple random sampling was then used to identify patient files to be included in the study.

At least 7 patient files were randomly picked for each month for both HIV(+) and HIV(-) adult patient taking anti-TB drugs during the study period (Jan 2006 to Dec 2007). If a given month had less than 7 patient files meeting the inclusion criteria for either the HIV (+) or HIV(-) patients then all the patient files meeting inclusion criteria in that month were sampled and the remaining monthly quota was filled by uniformly increasing the number of patients sampled in the remaining months of the year of study for the particular group.

Data were then extracted from the patient files picked and then transcribed into data collection forms.

2.12 Data collection methods

The data collection forms [Appendix 2] were filled in with data extracted from patient files.

Variables

Independent variables

The independent variables considered in this study were age of the HIV(+) and HIV(-) patients, anti-TB drugs, gender, education level, occupation and marital status.

Dependent variables

The dependent variables considered in this study were peripheral neuropathy, hepatotoxicity, ocular toxicity, gastrointestinal disturbances, cutaneous reactions and ototoxicity / vestibular toxicity.

2.12 Data management and analysis

The data were extracted from the patient files and entered into data collection forms. The data were then keyed into computer database using Microsoft Access package (MS Access). When data entry was completed, data clean-up was done by checking the data entered into the computer database Ms Access against data recorded in the data collection forms. Any errors identified during data clean-up were corrected. The data were then analyzed using the SPSS version 13.0 software.

The independent variables considered during analysis of the results were age, anti-TB drugs, gender, education level, occupation and marital status of the HIV(+) and HIV(-) patients.

The dependent variables considered during analysis of the results were peripheral neuropathy, hepatotoxicity, ocular toxicity, gastrointestinal disturbances, cutaneous reactions and ototoxicity / vestibular toxicity.

The level of significance was set at 0.05 and p values less than 0.05 were considered statistically significant.

2.13 Data quality control

The data collection form was pre-tested before use. This was done by randomly sampling 5 patient files of the HIV (+) and HIV(-) adult patients taking anti-TB drugs. The data collection form was then modified after pre-testing.

The information quality from the study files was assured by using more complete files in the study. Also only patient files meeting the inclusion criteria were included in the study.

After data collection, twenty of the 314 (12.74%) patient files were again reviewed by another pharmacist who also filled separate data collection forms. These were then used to compare with the data collected by the investigator.

After data entry was completed, data cleaning was done before analysis to correct any mistakes that might have occurred during data entry.

3.0 RESULTS

In this study 806 patient files were sampled. Four hundred and ninety two files were excluded from the study. Three hundred and fourteen patient files were reviewed for HIV (+) and HIV(-) adult patients taking anti-TB drugs during the study period, January 2006 to December 2007.

3.1 Demographics of the study groups.

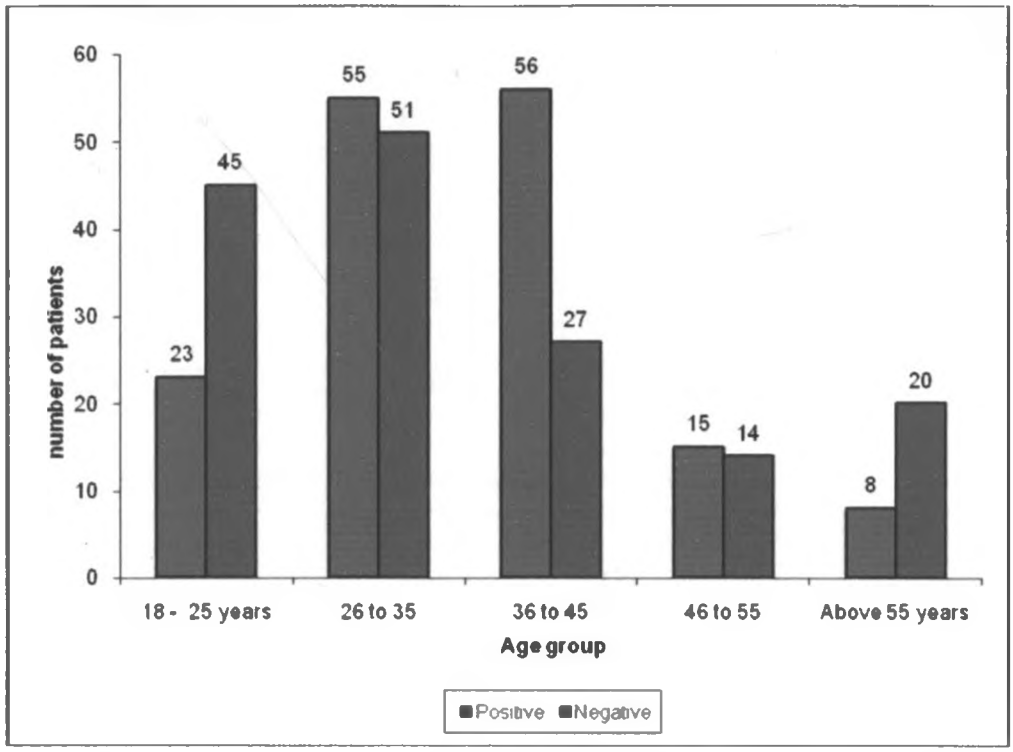
3.1.1 Age distribution of the study population.

The mean age for the HIV (+) patients was 36.78 years with a standard deviation of 9.71. The mean age for the HIV(-) patients was 35.77 years with a standard deviation of 14.98. The median age for the HIV (+) patients was 36 years, with the minimum and maximum ages being 18 and 70 years. The median age for the HIV(-) patients was 31 years, with the minimum and maximum ages being 18 and 82 years respectively.

Table 2: Age distribution of the study population

Age (Yrs)	HIV (+)	HIV(-)	Total
18 – 25	23	45	68
26 – 35	55	51	105
36 – 45	56	27	82
46 – 55	15	14	28
Over 55	8	20	28
Total	**157**	**157**	**314**

Figure 1: Age distribution of the study population



Majority of the patients included in the study were less than 45 years for both the HIV(+) and HIV(-).

3.1.2 Gender distribution of the study population

Seventy three HIV (+) and 99 HIV(-) patients were males; 84 HIV (+) and 58 HIV (-) patients were females.

Figure 2: Comparison of gender of the HIV (+) and HIV(-) patients.

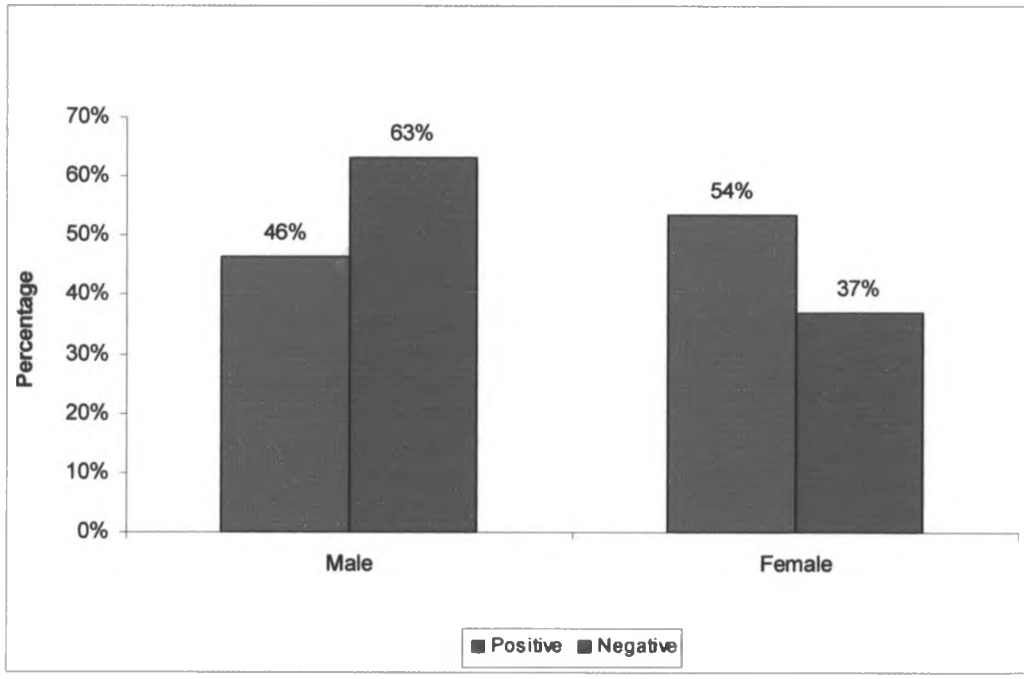
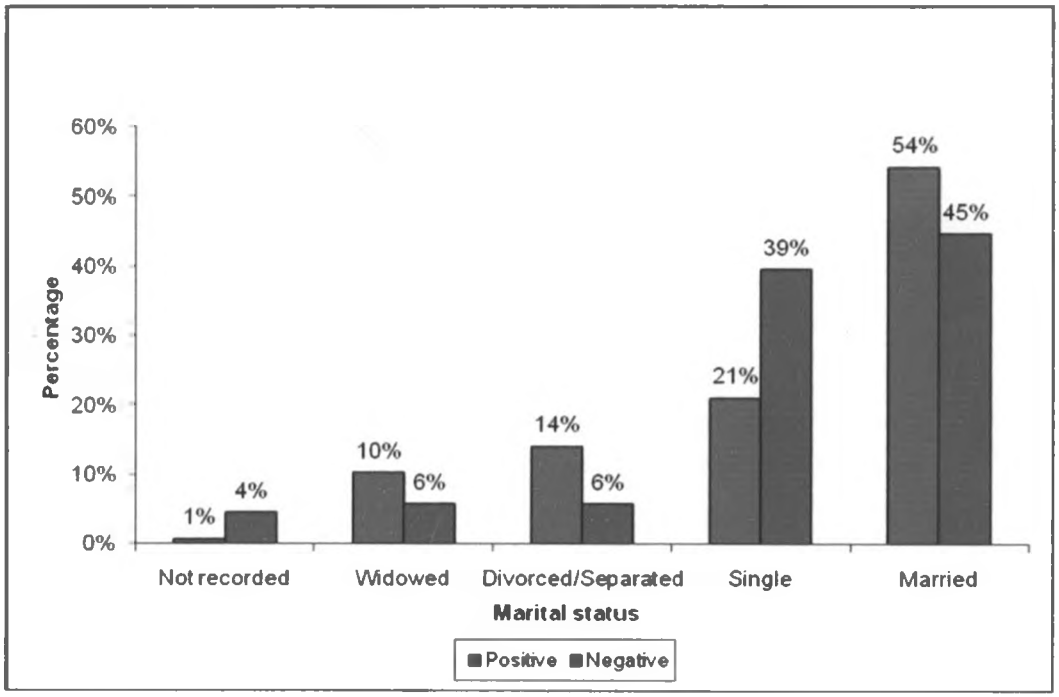


Table 3: The marital status of the HIV (+) and HIV(-) patients.

Marital status	HIV (+)	HIV(-)	Total
Married	85	70	155
Single	33	62	95
Divorce / separated	22	9	31
Widowed	16	9	25
Not recorded	1	7	8
Total	**157**	**157**	**314**

Figure 3: Marital status of the HIV (+) and HIV(-) patients.



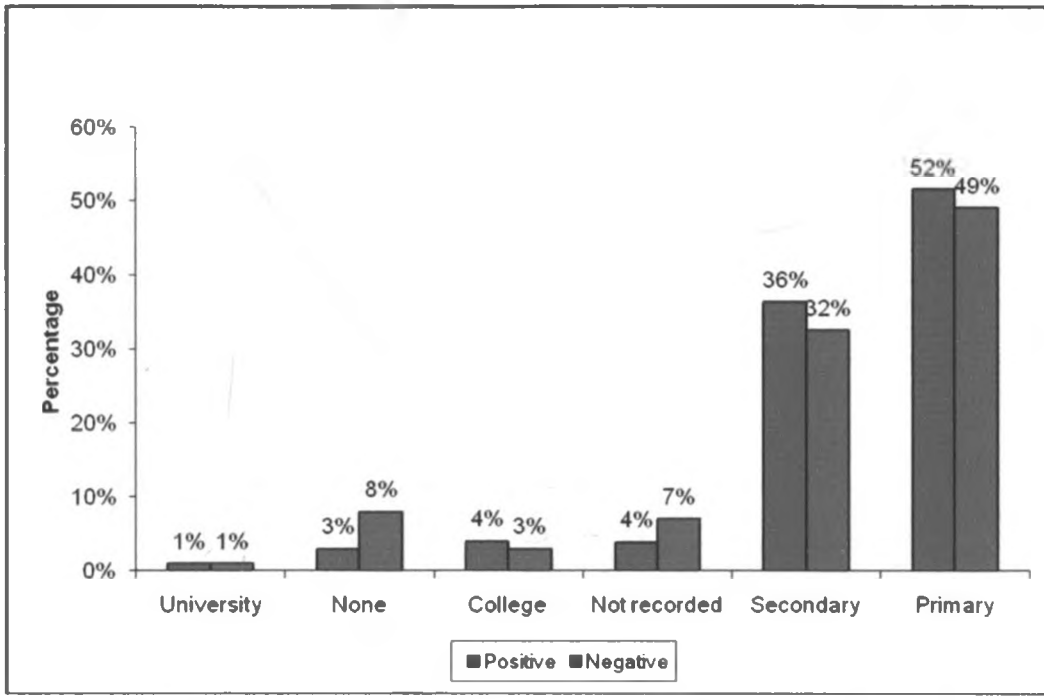
Majority of the patients included in the study were either single or married in both the HIV(+) and HIV(-) adult patients taking anti-TB drugs.

3.1.4 Education levels of the HIV(+) and HIV(-) patients

Table 4: The education levels of the HIV (+) and HIV(-) patients.

Education	HIV (+)	HIV(-)	Total
Primary	81	77	158
Secondary	57	51	108
College	6	4	10
University	2	2	4
None	5	12	17
Not recorded	6	11	17
Total	**157**	**157**	**314**

Figure 4: Education levels of the HIV (+) and HIV(-) patients



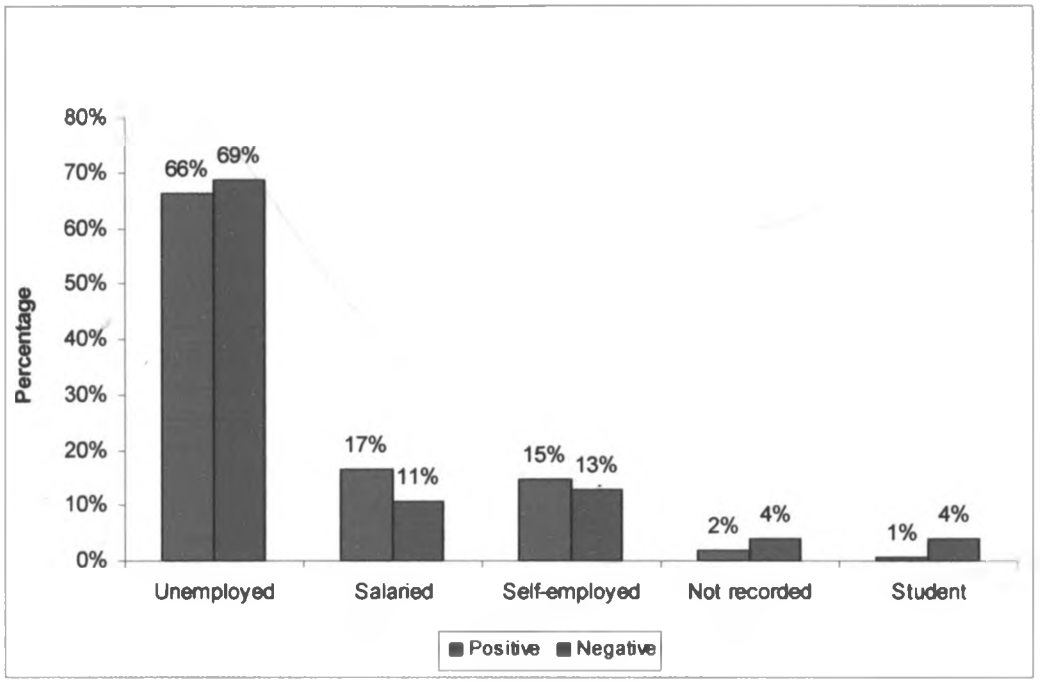
Most of the HIV (+) and HIV(-) patients had either primary or secondary education level.

3.1.5 Occupations of the HIV(+) and HIV(-) patients included in the study.

Table 5: The occupation of the HIV (+) and HIV(-) patients.

Occupation	HIV (+)	HIV(-)	Total
Unemployed	104	108	212
Salaried	26	17	43
Self-employed	23	20	43
Student	1	6	7
Not recorded	3	6	9
Total	**157**	**157**	**314**

Figure 5: Occupations of the HIV (+) and HIV(-) patients

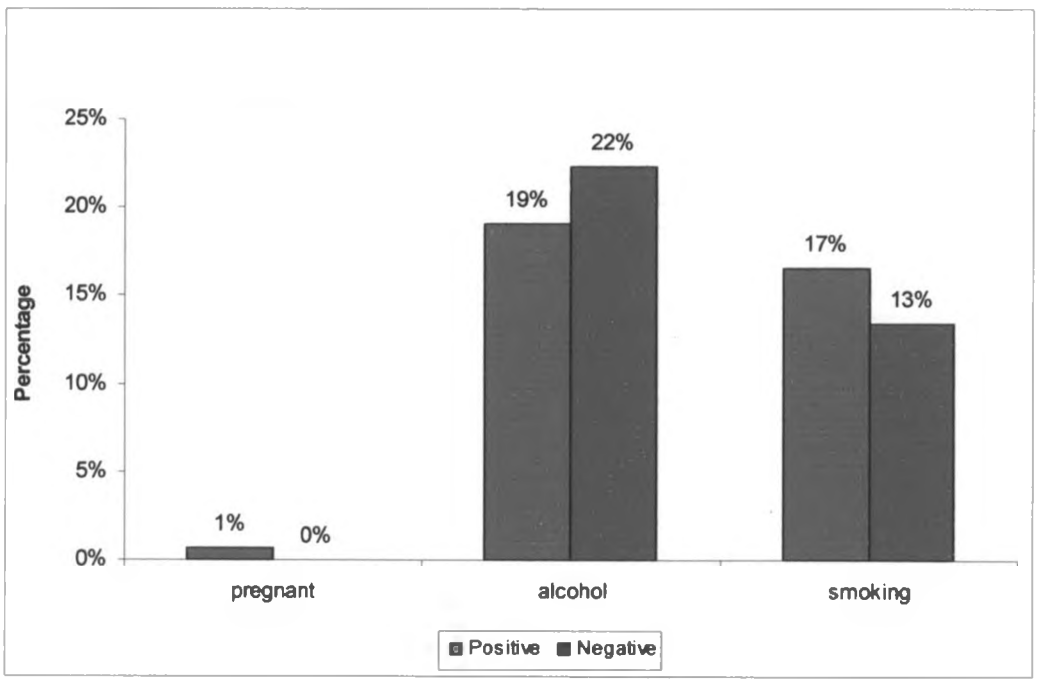


Most of the patients included in the study were unemployed.

3.1.6 Patients pregnant, with positive alcohol use and smoking history.

Pregnancy was recorded only in one (0.06%) HIV(+) patient. Thirty (19.12%) HIV (+) and 35 (22.29%) HIV(-) patients had a positive alcohol use history. Twenty six (16.56%) HIV (+) and 21(13.38%) HIV(-) patients had a positive smoking history.

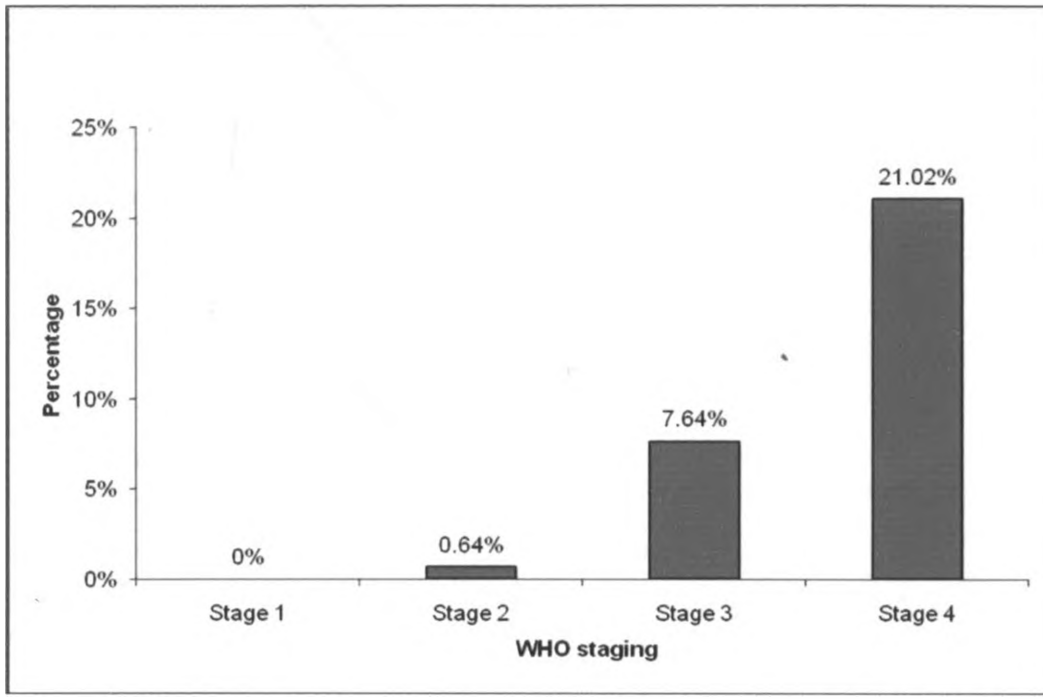
Figure 6: Percentage of patients pregnant, consuming alcohol and smoking



3.1.7 WHO staging for HIV(+) patients

The WHO staging was recorded for only 46 (29.3%) HIV (+) patients and was not recorded for the remaining one hundred and eleven. Stage 2 was recorded in one (0.64%) patient, stage 3 in 12 (7.64%) patients and stage 4 in 33 (21.02%) patients.

Figure 7: Number of HIV (+) patients for whom WHO staging was recorded.



3.1.8 TB types recorded for the HIV(+) and HIV(-) patients.

Table 6: The TB types of the HIV (+) and HIV(-) patients.

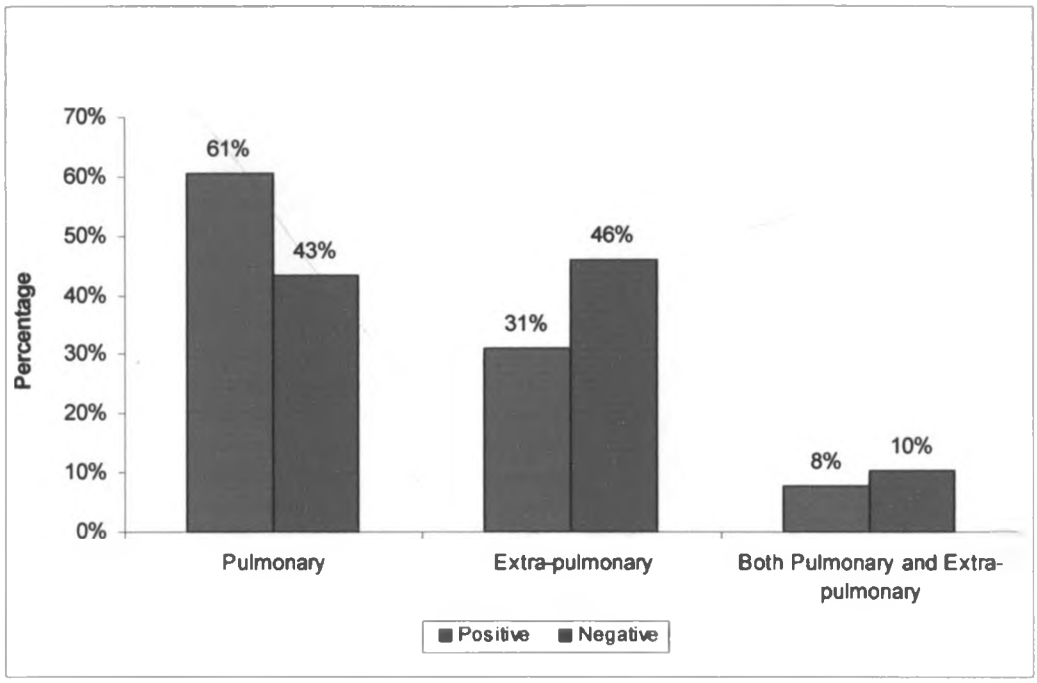
TB Type	HIV Positive	HIV Negative	Total
Pulmonary TB	95	68	163
Extra Pulmonary TB	49	73	122
Both PTB / EPTB	12	16	28
Not recorded	1	0	1
Total	**157**	**157**	**314**

The extra-pulmonary forms of TB recorded for the HIV (+) and HIV(-) patients in the study were as shown in table 7.

Table 7: Extra-Pulmonary forms of TB recorded

Extra-Pulmonary TB	HIV Positive	HIV Negative	Total
TB Meningitis	19	13	32
Miliary TB	18	13	31
TB Spine	2	15	17
Pleural Effusion	4	12	16
TB Peritonitis	1	14	15
TB Adenitis	6	2	8
TB Pericarditis	1	6	7
Tuberculoma	4	3	7
Pericardial Effusion	3	1	4
Miliary TB , TB Meningitis	0	2	2
TB Abdomen	0	2	2
TB Peritonitis , Pleural effusion	0	1	2
Genitourinary Tract TB	0	1	1
Lymphadenitis	1	0	1
Miliary TB , Pericardial Effusion	0	1	1
Pleural Effusion , Miliary TB	1	0	1
Pleural Effusion , Pericardial Effusion	0	1	1
TB Breast	1	0	1
TB Meningitis , TB Spine	0	1	2
TB Miliary , TB Adenitis	0	1	1
Total	**61**	**89**	**152**

Figure 8: TB types recorded for the HIV (+) and HIV(-) patients.



TB of both pulmonary and extra-pulmonary was recorded in twelve HIV (+) and sixteen HIV(-) patients.

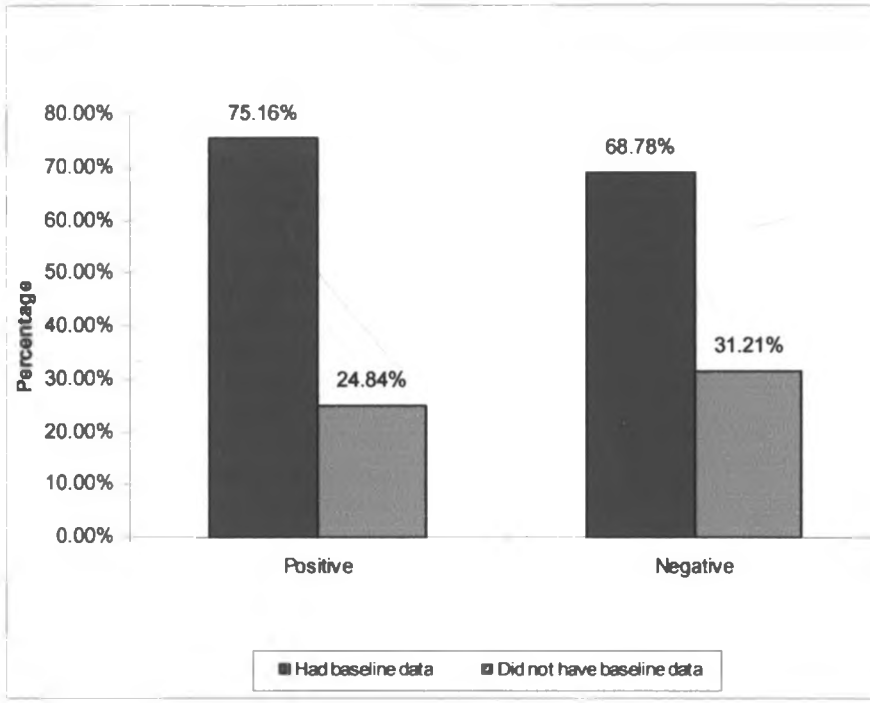
3.1.9 Baseline parameters for the HIV(+) and HIV(-) patients.

The baseline laboratory parameters included liver function tests {Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), total protein, albumin, total bilirubin and conjugated bilirubin}.

Full haemogram included in the study were haemoglobin, WBC and platelet counts. Urea and electrolytes included in the study were sodium, potassium, Creatinine and urea.

Baseline laboratory parameters before starting anti-TB drugs were done for 118 of the157 (75.16%) of the HIV (+) patients while for HIV(-) patients they were done for 108 of the 157 (68.79%).

Figure 9: Baseline laboratory parameters for the HIV (+) and HIV(-) patients.



3.1.10 TB regimens

The TB regimens prescribed for the patients included in the study were as shown in table 8.

Table 8: TB regimens the HIV (+) and HIV(-) patients in the study were taking.

Regimen	HIV Positive	HIV Negative	Total
2RHZE/6EH	129	130	259
2SRHZE/1RHZE/5RHE	21	10	31
2RHZE/4RH	7	16	23
RHZ/RHZE/EH	0	1	1
Total	157	157	314

See appendix: 9.3 TB treatment regimens used in 2006 – Kenya

One HIV(-) patient was on RHZ for 1 month which was then changed to RHZE for 1 month which was later again changed to EH.

There was a significant standard deviation in the mean duration of anti-TB treatment recorded for HIV (+) patients was 99.19 days (SD 91.39) while for HIV(-) patients it was 80.60 days (SD 98.72).

3.1.11 HIV(+) patients taking ARVs while on anti-TB drugs.

Seventy two (45.86%) HIV (+) adult patients taking anti-TB drugs were also taking ARVs.

Table 9: ARV regimens HIV (+) patients were taking while on anti-TB drugs.

ARV regimen	Number of HIV (+) patients
Stavudine / Lamivudine / Efavirenz	55
Zidovudine / Lamivudine / Efavirenz	12
Stavudine / Lamivudine / Nevirapine	4
Tenofovir / Lamivudine / Efavirenz	1
Total	**72**

3.1.12 Opportunistic infections recorded among the HIV(+) and HIV(-) patients

Opportunistic infections were recorded in 82 (52.22%) of HIV (+) patients compared with 9 (5.73%) of HIV(-) patients.

Table 10: Opportunistic infections recorded among the HIV (+) and HIV(-) patients.

Opportunistic infections	HIV Positive	HIV Negative	Total
Oral candidiasis	39	6	45
Diarrhoea	16	1	17
Oropharyngeal candidiasis	6	0	6
Pneumocystis jiroveci pneumonia	5	1	6
Herpes zoster	4	0	4
Cryptococcal meningitis	4	0	4
Kaposi sarcoma	3	0	3
Toxoplasmosis	2	0	2
Herpes labialis	2	1	3
Cytomegalo virus	1	0	1
Total	**82**	**9**	**91**

3.1.13 Other drugs HIV(+) and HIV(-) patients were taking while on anti-Tb drugs.

One hundred and fifty (150) (95.54%) HIV (+) patients and one hundred and thirty (130) (82.8%) HIV(-) patients were taking other drugs in addition to anti-TB drugs.

Table 11: Drugs for opportunistic infections HIV(+) and HIV(-) patients were taking while on anti-Tb drugs.

Drug	HIV Positive	HIV Negative	Total
Co-trimoxazole	118	14	132
Fluconazole	63	8	71
Dapsone	1	0	1
Others	49	55	104

Co-trimoxazole and fluconazole were the most commonly prescribed drugs for both HIV(+) and HIV(-) adult patients taking anti-TB drugs. Oral candidiasis was recorded in 6 HIV(-) patients who were prescribed fluconazole.

Table 12: Other additional drugs that HIV (+) and HIV(-) patients were taking while on anti-TB drugs.

Drug	HIV Positive	HIV Negative	Total
Pyridoxine	92	85	177
Multivitamin	91	43	134
Iron supplements	31	17	48
Herbal	0	0	0

Multivitamin and iron were prescribed for supplementation of vitamins and iron. Pyridoxine was prescribed to prevent peripheral neuropathy in both the adult HIV(+) and HIV(-) patients taking anti-TB drugs.

3.2 Adverse reaction recorded among HIV (+) and HIV(-) adult Patients taking anti-TB drugs.

A total of 83 ADRs were recorded among HIV (+) patients compared to 28 ADRs recorded among HIV(-) adult patients taking anti-TB drugs.

Table 13: Number of ADRs recorded per patient among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

ADRs of Anti-TB drugs	Number of ADRs recorded per patient on Anti-TB drugs	HIV status			
		Positive n = 157		Negative n = 157	
		Number	%	Number	%
	0	87	55.4%	131	83.4%
	1	59	37.6%	24	15.3%
	2	9	5.7%	2	1.3%
	3	2	1.3%	0	.0%
Total		157		157	

ADRs were more common in HIV (+) patients 70 (44.6%) compared to HIV(-) patients 26 (16.6%), (OR = 2.692 [1.819 – 3.985], $p < 0.001$).

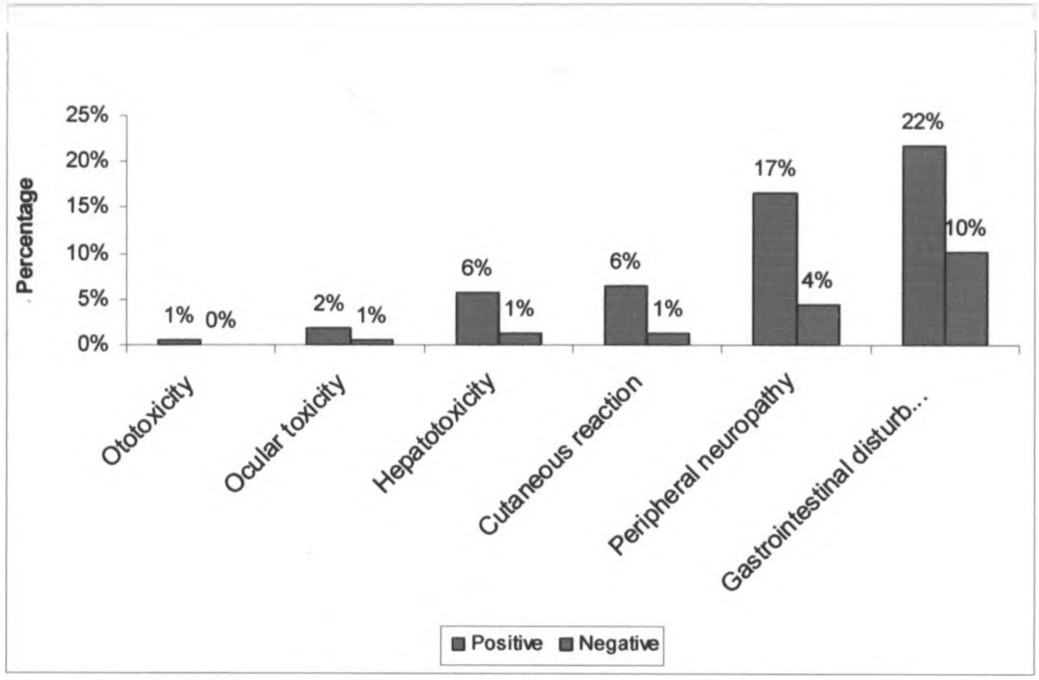
More HIV (+) patients than HIV(-) patients had more than one ADR; 11 (7%) versus 2 (1.3%), (OR = 5.50 [1.239 – 24.412], $p = 0.02$).

Table 14: Prevalence of specific ADRs among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

Specific ADRs of Anti-TB drugs	HIV status				p value
	HIV Positive n = 157		HIV Negative n = 157		
	Number with ADR	%	Number with ADR	%	
Hepatotoxicity	9	5.7%	2	1.3%	0.03
Peripheral neuropathy	26	16.6%	7	4.5%	0.0005
Ocular toxicity	3	1.9%	1	0.6%	0.3
Gastrointestinal disturbances	34	21.7%	16	10.2%	0.006
Cutaneous reactions	10	6.4%	2	1.3%	0.02
Ototoxicity	1	0.6%	0	0%	0.3

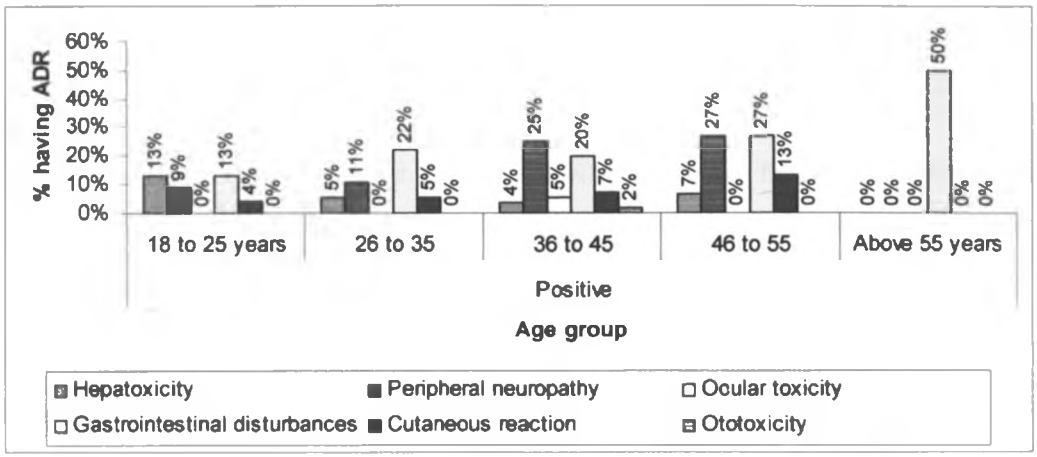
Overall, the most frequent ADR was gastrointestinal disturbance which was recorded in 34 (21.7%) HIV (+) patients compared to 16 (10.2%) HIV(-) patients, p=0.006. Peripheral neuropathy was recorded in 26 (16.6%) HIV (+) patients compared to 7 (4.5%) HIV(-) patients, p=0.0005. Cutaneous reactions were more common in HIV (+) patients 10 (6.4%) than HIV(-) patients 2 (1.3%), p=0.02. Nine (5.7%) HIV (+) patients compared to two (1.3%) HIV(-) patients had hepatotoxicity, p=0.03. There were no statistically significant differences between HIV (+) patients and HIV(-) patients with regard to the prevalence of ocular toxicity (1.9% vs 0.6%, p=0.3) and ototoxicity (0.6% vs 0%, p=0.3).

Figure 10: Prevalence of specific ADRs recorded by HIV status.



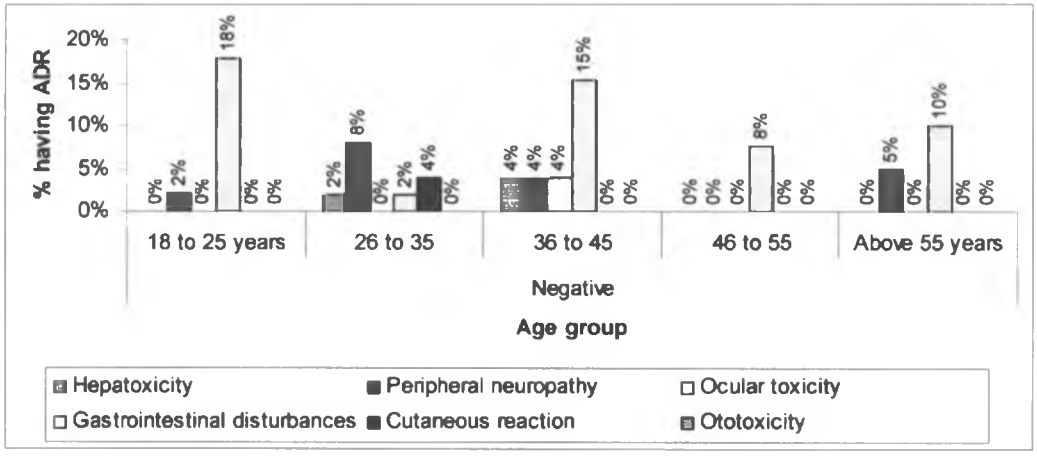
Gastrointestinal disturbances and peripheral neuropathy were the most commonly recorded ADRs in both the HIV(+) and HIV(-) adult patients taking anti-TB drugs.

Figure 11: Prevalence of specific ADRs against age distribution of the HIV (+) patients



Among HIV (+) patients, gastrointestinal disturbances and peripheral neuropathy appear to become more frequent in older patients.

Figure 12: prevalence of specific ADRs against age distribution of the HIV(-) patients



Although a higher proportion of HIV(–) younger patients had gastrointestinal disturbances, its distribution and that of the other ADRs does not appear to change with age.

Interruption of anti-TB treatment occurred in 8 (5.1%) HIV (+) and 4 (2.55%) HIV(-) patients. This was mainly due to hepatotoxicity; 7 (4.46%) in HIV (+) and 2 (1.27%) of HIV(-) patients.

a) Hepatotoxicity

Of the 9 HIV(+) patients who developed hepatotoxicity, jaundice was recorded in 8 patients while abdominal pain was recorded in 2 patients. Other signs / symptoms documented only once were dark yellow urine, loss of appetite, rash and hepatomegally.

Two of the 9 HIV(+) patients were also taking ARVs at the time hepatotoxicity was recorded. The 2 were on (D4T/3TC/NVP) ARV regimen. Viral co-infection (hepatitis B) was recorded for only one HIV (+) patient who developed hepatotoxicity. Only 1 of the 9 HIV (+) patients had a positive alcohol use history.

Anti-TB medication was stopped for 7 of the 157 (4.46%) HIV(+) patients who developed hepatotoxicity. ARVs were discontinued in 2 patients. Anti-TB drugs were re-started in 8 HIV (+) patients who had developed hepatotoxicity. One HIV (+) patient stopped anti-TB drugs. Hepatotoxicity resolved in 6 of the 9 HIV(+) patients while it was not documented for 3 HIV(+) patients.

Of the 2 HIV(-) patients who developed hepatotoxicity, jaundice was recorded in the 2 patients while loss of appetite and general malaise were documented in 1 patient. Viral co-infections (hepatitis B) and alcohol use history were not recorded in any of the 2 HIV(-) patients who had developed hepatotoxicity.

Anti-TB medication was stopped for 2 of the 157 (1.27%) HIV(-) patients who developed hepatotoxicity. Anti-TB drugs were re-started in 1 of the 2 HIV(-) patients who had developed hepatotoxicity. One HIV(-) patient stopped anti-TB drugs. Hepatotoxicity resolved in all the 2 HIV(-) patients.

Adult HIV (+) patients taking anti-TB drugs were at least 4 times more likely to develop hepatotoxicity than their HIV(-) counterparts (OR = 4.71 [1.23-22.17], p=0.03).

b) Peripheral neuropathy

Among the 26 HIV (+) patients who had peripheral neuropathy, numbness was the most frequently recorded symptom of peripheral neuropathy, recorded in 18 of the 26 HIV (+) patients.

Among the 7 HIV(-) patients who had peripheral neuropathy, numbness was the most frequently recorded sign of peripheral neuropathy; recorded in 3 of the 7 HIV(-) patients.

The other symptoms of peripheral neuropathy recorded were shown in the table 15.

Table 15: Recorded symptoms of peripheral neuropathy among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

ADR	Symptoms recorded	HIV Positive n = 157	HIV Negative n = 157
Peripheral neuropathy	Numbness	18	3
	Pain	7	3
	Tingling / burning sensation	7	1
	Weakness of muscles	6	2

Four of the 26 HIV (+) patients who developed peripheral neuropathy had a positive alcohol use history. Twelve of the 26 HIV (+) patients were also taking pyridoxine at the time peripheral neuropathy was recorded. Sixteen of the 26 HIV (+) patients who developed peripheral neuropathy were also taking ARVs while on anti-TB drugs. Twelve HIV(+) patients were on (D4T/3TC/EFV), three were on (D4T/3TC/NVP) while one was on (AZT/3TC/EFV) ARV regimen.

None of the 7 HIV(-) patients who developed peripheral neuropathy had a positive alcohol use history. Only one of the 7 HIV(-) patients was taking pyridoxine at the time peripheral neuropathy was recorded.

Table 16: Interventions taken for patients who developed peripheral neuropathy among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

ADR	Interventions	HIV Positive	HIV Negative
Peripheral neuropathy	Amitriptylline	12	2
	Pyridoxine	10	4
	Neurobione	7	1
	Diclofenac	2	0
	Carbamazepine	1	0

Peripheral neuropathy was mainly managed using amitriptylline, pyridoxine and neurobione for both the HIV (+) and HIV(-) patients. In 2 HIV (+) patients stavudine was substituted with tenofovir and zidovudine respectively.

All the 26 HIV (+) patients who had developed peripheral neuropathy continued taking anti-TB drugs. Two of the 26 HIV (+) patients who had peripheral neuropathy were unable to walk. Peripheral neuropathy was not resolved as per last entries in the records of 19 HIV (+) patients.

Six of the 7 HIV(-) patients who had peripheral neuropathy continued taking anti-TB drugs, while the records for one patient did not indicate if the patient continued taking anti-TB drugs. Peripheral neuropathy was not resolved as per last entries in the records of 5 HIV(-) patients.

Adult HIV (+) patients taking anti-TB drugs were at least 4 times more likely to develop peripheral neuropathy than their HIV(-) counterparts. {OR = 4.25 [1.79-10.12]}, p = 0.0005).

c) Ocular toxicity

Of the 3 HIV(+) patients who had ocular toxicity, blurred vision, photophobia and poor vision were the recorded symptoms. Of the 3 HIV(+) patients, 1 went for ophthalmological review while there was no documentation for 2 HIV(+) patients as to what action was taken. Ocular toxicity was resolved in 2 of the 3 HIV (+) patients while the records did not indicate if it was resolved in one HIV(+) patient.

Ocular toxicity was recorded in only 1 HIV(-) patient, there were no documented symptoms, the patient went for ophthalmological review. The records did not document if ocular toxicity was resolved.

The results suggest that there was no statistically significant difference for ocular toxicity among HIV (+) and HIV(-) adult patients taking anti-TB drugs. {OR = 3.03 [0.313-29.54]}, (p = 0.3).

d) Gastrointestinal disturbances

Gastrointestinal disturbance were recorded in 34 HIV (+) and 16 HIV(-) adult patients taking anti-TB drugs. Vomiting was the most frequently recorded sign, recorded in 33 of the 34 HIV (+) and in all the 16 HIV(-) patients. The other symptoms recorded were shown in table 17.

Table 17: Recorded symptoms of gastrointestinal disturbances among HIV (+) and HIV(-) adults taking anti-TB drugs.

ADR	Symptoms recorded	HIV Positive n = 157	HIV negative n = 157
Gastrointestinal disturbances	Vomiting	33	16
	Diarrhoea	9	3
	Stomach pains	8	2
	Loss of appetite	3	0
	Nausea	1	0
	Generalized body weakness	1	0

Twenty one of the 34 HIV (+) patients who developed gastrointestinal disturbances were also taking ARVs while on anti-TB drugs. Seventeen of whom were on (D4T/3TC/EFV), 3 were on (AZT/3TC/EFV) and one was on (TDF/3TC/EFV) ARV regimen.

Table 18: Interventions taken for patients who developed gastrointestinal disturbances among HIV (+) and HIV(-) adults taking anti-TB drugs.

ADR	Intervention	HIV Positive n = 157	HIV Negative n = 157
Gastrointestinal disturbances	Metoclopamide	25	16
	IV fluids	6	2
	Loperamide	6	0
	Hyoscine butyl bromide	2	1
	Ciprofloxacin	2	0
	Promethazine	1	2
	chlorpromazine	1	0
	Norfloxacin	1	0
	Co-trimoxazole	0	1
	No action recorded	5	4
	Stopped taking anti-TB drugs	0	1

Metoclopamide and intravenous fluids were the most frequently used to manage vomiting in both HIV(+) and HIV(-) patients. Loperamide and fluids were the most frequently used to manage diarrhoea.

Thirty of the 34 HIV (+) patients who had developed gastrointestinal disturbances continued taking anti-TB drugs. The records for 4 HIV (+) patients did not document if the patients continued taking anti-TB drugs. Resolution of gastrointestinal disturbances was recorded in 31 of the 34 HIV (+) while it was not documented as per last entries in the records of 2 HIV(+) patients.

Fifteen of the 16 HIV(-) patients who had developed gastrointestinal disturbances continued taking anti-TB drugs. The records of one HIV(-) patient did not document if the patients continued taking anti-TB drugs. Resolution of gastrointestinal disturbances was documented for 13 of the 16 while it was not documented for 3 HIV(-) patients.

Adult HIV (+) patients taking anti-TB drugs were at least 2 times more likely to develop gastrointestinal disturbances than their HIV(-) counterparts; {OR = 2.44 [1.28 - 4.63]}, (p = 0.006).

e) Cutaneous reactions

Cutaneous reactions were recorded in 10 HIV (+) adult patients taking anti-Tb drugs. Itchiness was the most frequently recorded symptom, recorded in 8 of the 10 HIV (+) patients. Skin rash was recorded in 4 of the 10 HIV (+) patients. Other signs documented only once in the HIV (+) patients were swelling of the body, generalized pruritic rash and skin wetness. Four of the 10 HIV (+) patients who developed cutaneous reactions were also taking ARVs while on anti-TB drugs. Two of the 4 were on (D4T/3TC/EFV) while (AZT/3TC/EFV) and (D4T/3TC/EFV) had one patient each.

Cutaneous reactions were recorded in 2 HIV(-) adult patients taking anti-TB drugs. Itchiness was recorded in 1 of the 2 HIV(-) patients while skin rash was also recorded in one HIV(-) patient.

Table 19: Interventions taken for patients who developed cutaneous reactions among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

ADR	Interventions	HIV (+) n = 157	HIV(-) n = 157
Cutaneous reaction	Chlorpheniramine	5	1
	Corticosteroids	1	1
	Cetrizine	1	0
	No action recorded	2	0
	Stopping anti-TB drugs	1	1
	Regimen change	0	1

Cutaneous reactions were mainly managed using antihistamines (chlorpheniramine and cetrizine). Anti-TB drugs were stopped in 1 of the 10 HIV (+) and 1 of the 2 HIV(-) patients while no actions were documented for two of the 10 HIV (+) patients. However, all the 10 HIV (+) and all the two HIV(-) patients who developed cutaneous reactions later continued taking anti-TB drugs.

Resolution of cutaneous reactions was documented for 5 of the 10 HIV (+) patients while it was not documented for 5 of the 10 HIV(+) and all the 2 HIV(-) patients.

Adult HIV (+) patients taking anti-TB drugs were at least 5 times more likely to develop cutaneous reactions than their HIV(-) counterparts; {OR = 5.27 [1.14-24.47]}, ($p = 0.02$).

f) Ototoxicity

Ototoxicity was recorded in just one (0.6%) HIV (+) patient while none (0%) was recorded for HIV(-) patients.

The only symptom recorded was high tone deafness. Twenty one (13.38%) HIV (+) and 10 (6.37%) HIV(-) patients were on the 2SRHZE / 1RHZE / 5RHE regimen. At the time of ototoxicity the patient was on 2SRHZE / 1RHZE / 5RHE regimen. The patient continued taking anti-TB medication. The records did not document if ototoxicity resolved.

3.3 LIMITATIONS OF THE STUDY

The study had the following limitations; first, it was difficulty to formally assess the adherence and compliance of patients to the treatment regimens. Secondly, lack of baseline laboratory investigations and incomplete patient records. Thirdly, some adverse drug reactions may not have been recorded. However, rates of under-reporting should have been similar regardless of HIV status.

Fourthly, insufficient funds, time and design biases. The results are limited to ADRs in HIV (+) and HIV(-) adult patients taking anti-TB drugs and may not be applicable to ADRs in HIV (+) and HIV(-) children taking anti-TB drugs.

Finally, it was difficulty to assign the side effects to a particular drug since the drugs have similar side effect profile. Also the use of pyridoxine prophylaxis might have resulted in lower peripheral neuropathy prevalence than expected.

4.1 DISCUSSION

In this study, the mean ages in the two groups did not differ significantly. The study population falls within the age group (15-44) that is greatly affected by the TB epidemic.[2] This was similar to a 2006 annual report by NLTP that showed the age group with the highest TB notification in 2005 to be 25-34 years in both males and females which has been the trend over the last decade. This is the same age category with a high HIV sero-prevalence.[3]

In this study, TB treatment was associated with greater prevalence of ADRs in HIV (+) patients than in HIV(-) adult patients taking anti-TB drugs; (44.6% vs 16.6%). Although, gastrointestinal disturbances and peripheral neuropathy were the most commonly recorded ADRs among both the HIV (+) and HIV(-) patients, hepatotoxicity was the main cause of TB treatment interruption; 4.46% in HIV (+) and in 1.27% HIV(-) patients.

Literature review showed there are few comparative studies on adverse drug reactions among HIV (+) and HIV(-) adult patients taking anti-TB drugs. In a retrospective study reported in London, UK, by *Breen et al. 2006*; the incidence of serious adverse events was compared in 312 patients treated for TB of whom 156 were HIV (+). Serious adverse events (grade III / IV) were recorded in 40% HIV (+) and 26% HIV(-) individuals. Peripheral neuropathy and persistent vomiting were more common among HIV (+) patients.[9] In our study, TB treatment was also associated with greater prevalence of ADRs in HIV (+) patients than in HIV(-) patients; (44.6% vs 16.6%).

The difference in study results above might reflect the different criteria used. In the retrospective study done in London by *Breen et al. 2006*; 5 ADR variables (hepatotoxicity, peripheral neuropathy, rash, persistent vomiting and arthralgia) and only serious ADRs (grade III and IV), were considered. In this study 6 ADR variables (hepatotoxicity, peripheral neuropathy, ocular toxicity, gastrointestinal disturbances, cutaneous reactions and ototoxicity) were considered, no grading of ADRs was done which might have led to higher figures. However, the ADR prevalence rates of our study; (44.6% vs 16.6%) were comparable to the reported ADR prevalence rates among HIV(+) (18 - 39%) and HIV(-) (3 - 22%) patients taking anti-Tb drugs.(*Gillian et al.2002*)[40]

Studies conducted in East Africa reported different prevalence rates of ADRs. In a Ugandan study, only two of the 265 HIV (+) patients (1%) developed hepatotoxicity during treatment of PTB using (2HRZE/6HR) [15]. However, in the former Zaire study, using TB drugs, (2HRZE/4HR) were well tolerated among 446 TB patients[15]

In this study, results suggest that HIV (+) patients were more prone to developing adverse reactions to anti-TB drugs and need to be carefully monitored. This is in line with other previous studies.[7, 9, 25, 39] *Zumla et al. 2000*; also reported that ADRs of anti-TB drugs were comparatively more frequent in the HIV(+) patients taking anti-TB drugs[25]. In the retrospective study done in London by *Breen et al. 2006*; serious ADRs (grade III/IV) among HIV(+) were more compared to HIV(-) patients taking anti-TB drugs, (40% vs 26%) [9].

Although this study also identified hepatotoxicity as the main cause of TB treatment interruption, the rates of TB treatment interruption were low when compared with the *Breen et al. 2006*; retrospective study, which reported interruption of anti-TB treatment was the same in the two groups (13% in HIV (+) patients and 15% in HIV(-) patients;).[9]

The *Breen et al. 2006*; retrospective study, further suggested that only in the black African population did ethnicity appear to be important, with a significantly lower frequency of anti-TB treatment interruption observed in the HIV(-) than in the HIV (+) patients. Data on the impact of ethnicity on anti-TB treatment are limited. This study did not assess the impact of ethnicity on anti-TB treatment interruption; therefore, these findings might not represent the impact of ethnicity on anti-TB treatment interruption.

There are several reasons for the apparent low rates of treatment interruption in this study; firstly, in this study patients were not regularly followed during treatment; this might have led to fewer recorded cases of hepatotoxicity. Secondly, the patient treatment files were not designed to document hepatotoxicity.

Studies have reported that many of the ADRs occur within the first 2 months of starting TB therapy[40]. However, this study did not establish the time duration from starting anti-TB drugs to development of ADRs. Firstly, the patients were not regularly followed; therefore the exact time of ADRs development might not have been recorded. Secondly, anti-TB and ARV therapy have overlapping toxicities; therefore, it was difficult to pin-point which drug caused a particular ADR.

a. Hepatotoxicity

In this study, hepatotoxicity was recorded in nine (5.7%) HIV (+) patients compared to two (1.3%) HIV(-) patients. Jaundice was the most frequently recorded sign of hepatotoxicity for both HIV (+) and HIV(-) patients who experienced hepatotoxicity.

The prevalence of hepatotoxicity induced by anti-TB drugs has been variably reported as between 2% and 11% (*Dossing et al. 1996; Schaberg et al. 1996; Yee et al. 2003; Fernandez-Villar et al. 2004*). This rate depends on the investigators' definition of hepatotoxicity as well as the population studied. Most studies on hepatotoxicity induced by anti-TB drugs were performed in Europe, Southeast Asia and northern America. Data on sub-Saharan Africa are limited. This is probably due to the fact that transaminases are not measured routinely and hepatotoxicity is often diagnosed clinically by the occurrence of jaundice.[15] This is in contrast to the retrospective study by *Breen et al. 2006*; whereby liver function was routinely checked at baseline (along with assessment of hepatitis B and C status) and repeated at 2 weeks. In patients with normal test results, further blood tests were performed only in the event of new symptoms[9].

The low prevalence of hepatotoxicity induced by anti-TB drugs in this study is consistent with other previous studies. In a Ugandan study, only two of the 265 HIV (+) patients (1%) developed hepatotoxicity during treatment of PTB using (2HRZE/6HR) [15]. In a former Zaire study, TB drugs (2HRZE/4HR) were well tolerated among 446 TB patients. No hepatitis was reported but increased transaminase levels were occasionally seen[15] In a Malawian randomized clinical trial on co-trimoxazole prophylaxis in 579 HIV (+) adult pulmonary TB patients; about 2% of the patients developed grade 2 or 3 hepatotoxicity during TB treatment, according to WHO definitions. None of the patients received antiretroviral treatment[15] However, these studies did not compare the prevalence of hepatotoxicity among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

These studies[15] and our study suggest a low prevalence of anti-TB drug induced hepatotoxicity in adults in sub- Saharan Africa. This is unexpected, because risk factors such as HIV, hepatitis B and C infections are highly prevalent in this region. There are several possible reasons for this apparently low incidence of anti-TB drug induced hepatotoxicity. First, the available studies were not designed to record anti-TB drug induced hepatotoxicity. Cases of mild or transient hepatotoxicity might have been missed[15] Secondly, in our study patients were not regularly followed during treatment; this might have led to fewer recorded cases of hepatotoxicity.

Previous studies have reported a number of risk factors for anti-TB drugs induced hepatotoxicity; alcohol use, underlying liver disease, elderly patients, patients with advanced

HIV disease and black women of child bearing age.[5, 10, 16, 18, 22, 27] In this study, both groups had a low prevalence of chronic viral hepatitis; which made assessment of this risk factor unfeasible. This study did not assess the impact of underlying liver disease, extent of HIV disease and black women of child bearing potential. In both groups, the use of alcohol and herbal medications were poorly recorded, therefore, findings based on incomplete data might be misleading.

Many studies have stated that slow acetylators would develop more severe hepatotoxicity than rapid acetylators[22] The dose regimen has also been reported to be important; in one series of patients treated with rifampicin and isoniazid, the rate of drug-induced hepatitis was 21% when rifampicin was given daily and 5% when given twice weekly[23, 27] However, this study did not assess the impact of different dose regimens.

In our study, it was difficulty to assign hepatotoxicity to a particular drug, since; rifampicin, isoniazid and pyrazinamide can all cause the condition. However, it is well documented that the risk of hepatotoxicity is greatest with pyrazinamide then rifampicin then isoniazid.[5, 18] *T. Schaberg; et al.1996;* reported that Pyrazinamide showed more severe side-effects (15%) than isoniazid (7%) and rifampicin (1.5%) [b] Pyrazinamide-associated hepatotoxicity is thought to be dose dependent, in contrast to the idiosyncratic hepatotoxicity of isoniazid. Pyrazinamide was reported to cause fatal hepatitis when it was administered at a dose of 150 mg/kg for treatment of drug-resistant TB, but it was better tolerated at 20–25 mg/kg in multidrug regimens[20]

Previous studies have observed increased prevalence rates of hepatotoxicity related to isoniazid and / or pyrazinamide in combination with nevirapine, efavirenz or Protease inhibitors (PIs) [38] In our study, 2 of the 9 (22.22%) HIV (+) patients who developed hepatotoxicity were also taking ARVs at the time hepatotoxicity was recorded. Anti-TB and ARV therapy can both cause this condition; therefore, it was difficult to pin-point which particular drug(s) caused hepatotoxicity. Consequently, more studies are required to establish the impact of HAART on hepatotoxicity among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

In this study, eight HIV (+) and one HIV(-) patients who had hepatotoxicity discontinued anti-TB drugs, they were later re-started and continued taking anti-TB drugs. This was in line with the NLTP guidelines.[2]

In this study, the study results suggest that adult HIV (+) patients taking anti-TB drugs were more likely to develop hepatotoxicity compared to their HIV(-) counterparts. This is in contrast to the retrospective study by *Breen et al. 2006*; that reported no difference in the prevalence of hepatotoxicity (13%) among HIV (+) and HIV(-) adult patients taking anti-TB drugs[9]

b. Peripheral neuropathy

In this study, peripheral neuropathy was recorded in 16.6% HIV (+) compared to 4.5% HIV (-) adult patients on anti-TB medication. Similar prevalence rates were reported in the London retrospective study by *Breen et al. 2006*; peripheral neuropathy was reported in 22 (14%) HIV+) patients compared to 3 (2%) HIV(-) patients[9] However, in the *Breen et al, 2006*; study, only serious (grade III and IV) were considered while in our study, there was no grading of ADRs, therefore, the cases might have been fewer if ADR grading was done.

In this study, the results suggest that HIV (+) adult patients taking anti-TB drugs were more likely to develop peripheral neuropathy compared to their HIV(-) counterparts. This is in agreement with other previous studies which also suggest that HIV (+) patients were more prone to developing isoniazid-induced peripheral neuropathy and all HIV-TB patients taking isoniazid should be given pyridoxine supplementation (10-25 mg/day) [2, 7].

Previous studies have identified a number of risk factors for isoniazid induced peripheral neuropathy including the poorly nourished, extent of disease, alcoholics, diabetics, uraemic patients and pregnant women are at greater risk [2, 13]. In this study, both groups had a low prevalence of alcohol use and pregnant women; which made assessment of these risk factors unfeasible. This study did not assess the impact of nutrition, extent of disease, diabetes mellitus and uraemia.

As observed by previous studies; nucleoside analogues didanosine, zalcitabine and stavudine (D4T) may all cause peripheral neuropathy and an additive toxicity of isoniazid when used with D4T has been demonstrated[18] In this study, 61.54% HIV (+) patients who developed peripheral neuropathy were also taking ARVs, majority of who were on stavudine containing regimens. Therefore, it was difficult to assign all the cases of peripheral neuropathy to anti-TB drugs. Lastly, more studies are required to establish the impact of HAART on peripheral neuropathy among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

c. Ocular toxicity

Data on comparative studies on ocular toxicity among HIV (+) and HIV(-) adult patients taking anti-TB drugs are limited. In this study, ocular toxicity was documented in 3 (1.9%) HIV (+) patients and 1 (0.6%) HIV(-) patient.

Previous studies have reported that ocular toxicity occurs in fewer than 2% of patients at the usual dosage of ethambutol 15mg/kg but is more common in elderly and people with renal impairment. Patients may complain of changes in colour vision or visual field which may appear suddenly. The effect is usually reversible on discontinuation but permanent damage may occur if the drug is continued[13, 17] However, none of these studies compared the prevalence of ocular toxicity among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

It is well documented that ethambutol toxicity is dose related, patients receiving 25mg/kg/day have a 5% to 6% reported incidence of optic neuropathy. Patients receiving 15mg/kg/day have incidence reportedly less than 1% [17, 33] The risk is higher at higher doses given daily (18% of patients receiving more than 30mg/kg/day) and in patient with renal insufficiency[24] In this study, the impact of various doses of ethambutol on ocular toxicity was not assessed. Further more, this study did not include patients with renal failure, therefore, these findings may not represent the prevalence rates of ocular toxicity in such patients.

There are potential limitations of this study in the evaluation of ethambutol ocular toxicity. First, routine visual field examinations before starting anti-TB drugs were not done. Secondly, there is usually no single simple diagnostic test that can be performed, even by an ophthalmologist that is confirming or diagnostic for ethambutol toxicity[33]

As observed by other studies, ocular toxicity is uncommon [2, 10, 13, 17, 33] Due to the rare occurrence of the condition, studies investigating this ADR would require large sample sizes. However, in this study, the results suggest that there was no difference in odds ratio for ocular toxicity among HIV (+) and HIV(-) adult patients taking anti-TB drugs. These findings should, however, be interpreted with caution, and confirmation from other cohort studies is needed.

d. Gastrointestinal disturbances

In this study, gastrointestinal disturbances was the most commonly recorded ADR in both HIV(+) and HIV(-) adult patients taking anti-TB drugs. They were recorded in 21.7% HIV (+) patients and in 10.2% HIV(-) patients. Five gastrointestinal disturbance variables (vomiting, abdominal pains, nausea, loss of appetite and diarrhea) were considered in our study. This was in contrast to the retrospective study by *Breen et al. 2006*; which reported lower prevalence rates of gastrointestinal disturbances. However, it only considered one gastrointestinal disturbance variable (persistent vomiting) which occurred in 15 (10%) of HIV (+) and 3 (2%) of HIV(-) patients[9] Therefore, the differences in number of variables considered might explain the differences in the reported prevalence rates.

In an Iranian study by *Javadi et al.2007,* done between 2004 and 2005 involving 204 TB patients treated using rifampicin, pyrazinamide, isoniazid and ethambutol, 120 patients were females and 84 males. Nausea and vomiting was reported in 16.79% of the patients. The most frequent systems affected by ADRs were the gastrointestinal system (36.1%) and liver and billiary system (25%) [8] Although the Iranian study did not compare the prevalence of gastrointestinal disturbances among HIV (+) and HIV(-) adult patients taking anti-TB drugs, it also reported gastrointestinal system as the most frequently system affected by ADRs. This was in line with the findings of our study.

Gastrointestinal disturbances have been reported to be common especially in the first few weeks after starting antituberculosis therapy[18, 24]. However, our study did not assess the time duration from starting anti-TB drugs to the development of this condition.

This study was unable to assign all cases of gastrointestinal disturbances to anti-TB drugs; this was because of the following reasons. Firstly, there was high prevalence of co-morbidities and opportunistic infections which might have also caused gastrointestinal disturbances. Secondly, this study was unable to establish the extent of use of herbal drugs and other over the counter medication. Thirdly, the patients were not regularly followed during anti-TB treatment; hence some cases might not have been documented. However, this might have occurred equally for the two groups. Lastly, other likely causes of gastrointestinal disturbances, food and water hygiene were not assessed by this study. Further more, in this study 62% of the HIV(+) patients who developed this condition were also taking ARVs. Consequently, more studies are required to establish the impact of HAART on gastrointestinal disturbances among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

This study findings suggest that, adult HIV (+) patients taking anti-TB drugs were more likely to develop gastrointestinal disturbances compared to adult HIV(-) patients taking anti-TB drugs.

e. Cutaneous reactions

Data on comparative studies on cutaneous reactions among HIV (+) and HIV(-) adult patients taking anti-TB drugs are limited. In this study, cutaneous reactions were recorded in 6.4% of HIV (+) adult patients and 1.3% HIV(-) adult patients taking anti-TB drugs. This study considered the following symptoms; skin rash, itchiness, wetness, and generalized pruritic rash. These prevalence rates were unexpectedly low, in contrast to the *Breen et al. 2006*; which only considered rash which occurred in 20 (13%) of HIV (+) and 13 (8%) of HIV(-) patients. Further more, the retrospective study by *Breen et al. 2006*; only considered grade (III / IV) reactions[9].

All drugs used in treating TB have been reported that they can cause a skin rash[24]. Consequently, it was difficult to pinpoint a particular drug as the cause of cutaneous reaction. Further more, in this study, 4 of the 10 HIV(+) patients who developed this condition were also taking ARVs. Therefore, it was difficult to assign all the cases of cutaneous reactions to anti-TB drugs. Lastly, more studies are required to assess the impact of HAART on cutaneous reactions among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

This study results suggest that adult HIV (+) patients taking anti-TB drugs were more likely to develop cutaneous reactions compared to their HIV(-) counterparts.

f. Ototoxicity / vestibular toxicity

In this study, 13.38% HIV (+) and 6.37% HIV(-) patients were on the 2SRHZE / 1RHZE / 5RHE regimen. The small number of patients on this regimen made it impossible to assess risk estimate for ototoxicity among HIV (+) and HIV(-) adult patients taking anti-TB drugs.

As observed in other studies[36], ototoxicity is uncommon and only one case was recorded in our study. Any conclusions based on one case might be misleading and therefore more studies are required to establish the extent of ototoxicity in HIV (+) and HIV(-) adult patients taking anti-TB drugs. Due to the rare occurrence of this ADR, studies investigating this ADR would require very large sample sizes.

4.2 CONCLUSIONS

Hepatotoxicity, peripheral neuropathy, gastrointestinal disturbances and cutaneous reactions occurred in both HIV(+) and HIV(-) patients but they were more likely in adult HIV(+) than in adult HIV(-) patients on anti-TB medication.

Gastrointestinal disturbances and peripheral neuropathy were the most commonly recorded ADRs among both the HIV (+) and HIV (-) adult patients taking anti-TB drugs.

Hepatotoxicity was the main cause of TB treatment interruption in both the HIV(+) and HIV(-) adult patients taking anti-TB drugs.

There were no statistically significant differences between HIV (+) patients and HIV (-) patients with regard to the prevalence of ocular toxicity and ototoxicity.

ADRs were more likely to occur in adult HIV (+) patients compared to adult HIV(-) patients taking anti-TB drugs.

4.3 RECOMMENDATIONS

ADRs surveillance systems should be established in hospitals as they will have a major impact on ADRs monitoring and control.

Clinical monitoring should be done regularly as hepatotoxicity is the main cause of TB treatment interruption.

More studies on the incidence and risk factors for ADRs in Africans are required as they will help to prevent serious ADRs during TB and combined HIV/TB treatment.

Any future studies should preferably be prospective to overcome the numerous limitations of retrospective studies.

Grading of ADRs will be necessary in future studies to identify serious ADRs.

REFERENCES

1. WHO. *Global Tuberculosis Control: surveillance, planning, financing*. WHO Report; **2007**.
2. Ministry of Health [Kenya]. *National Leprosy and Tuberculosis Program [NLTP] Guidelines*. August **2006**.
3. The Republic of Kenya, Ministry of Health. *Annual report;* National Leprosy Tuberculosis Programme, **2006**.
4. Banu Eris- Gu¨lbay, O¨zlem Ural Gu¨rkan, O¨znur Akkoca Yıldız, et al. *Side Effects due to Primary Antituberculosis Drugs During the Initial Phase of Therapy in 1149 Hospitalized Patients for Tuberculosis.* Respiratory Medicine **2006**; 100: 1834–1842.
5. Yew WW, Leung CC. *Antituberculosis drugs and hepatotoxicity.* Respirology **2006**; 11: 699–707.
6. T. Schaberg, K. Rebhan, H. Lode. *Risk factors for side-effects of isoniazid, rifampicin and pyrazinamide in patients hospitalized for pulmonary tuberculosis*. European Respiratory Journal **1996**; 9: 2026–2030.
7. S.K. Sharma, Alladi Mohan & Tamilarasu Kadhiravan. *HIV-TB co-infection: Epidemiology, diagnosis & management*. Indian Journal of Medical Research: **2005**; 121 (4): 550-567.
8. Mohammad Reza Javadi, Gloria Shalviri, Kheirollah Gholami, et al. A*dverse reactions of anti-tuberculosis drugs in hospitalized patients: incidence, severity and risk factors*. Pharmacoepidemiology and drug safety **2007**; 16: 1104–1110.
9. R. A. M Breen, R. F. Miller, T. Gorsuch, et al. *Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection*. Thorax **2006**; 61:791–794.
10. USP DI Drug Information for the Health Care Professional, *Micromedex,* Englewood, [Teton software] **2004**, 24th Edition.
11. AHFS Drug Information, American Society of Health System Pharmacists, USA, [Teton software] **2004.**
12. Jason Lazarou, Bruce H. Pomeranz, Paul N. Corey. *Incidence of Adverse Drug Reactions in Hospitalized Patients - A Meta analysis of prospective studies*. JAMA **1998**; 279: 1200 - 1205.
13. Roger Walker, Clive Edwards. *Clinical Pharmacy and Therapeutics*, Churchill Livingstone, London, UK **2003**; 3rd Edition, Chapter 38, 583 - 593.
14. Dermot Maher, Anthony Harries and Haileyesus Getahun. *Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies.* Tropical Medicine and International Health **2005**; 10 (8): 734–742.
15. A. Tostmann, M. J. Boeree1, A. D. Harries, et al. *A short communication: antituberculosis drug induced hepatotoxicity is unexpectedly low in HIV-infected pulmonary tuberculosis patients in Malawi.* Tropical Medicine and International Health **2007**; 12 (7): 852–855.

16. Imogen Mitshell, Julia Wendon, Sarah Fitt, et al. *Anti- Tuberculosis therapy and liver failure. Lancet* **1995**; 345: 555-556.
17. Alex Melamud, Gregory S. Kosmorsky and Michael S. Lee. *Case Report: Ocular Ethambutol Toxicity*. Mayo Clinic proceedings **2003**; 78: 1409-1411.
18. AL Pozniak, RF Miller, MCI Lipman, et al, (on behalf of the BHIVA Guidelines Writing Committee). *British HIV Association (BHIVA) treatment guidelines for tuberculosis (TB)/HIV infection.* HIV Medicine **2005**; 6 (Suppl.2): 62-83.
19. Philip Onyebujoh, Alimuddin Zumla, Isabella Ribeiro, et al. *Public health reviews; Treatment of Tuberculosis: present status and future prospects*. Bulletin of World Health Organization **2005**; 83 (11): 857-865.
20. Kashef Ijaz, John A. Jereb, Lauren A. Lambert, et al. *Severe or Fatal Liver Injury in 50 Patients in the United States Taking Rifampicin and Pyrazinamide for Latent Tuberculosis Infection*. CID **2006**; 42 (1 February): 346-347.
21. S. Hadjikoutisa, J. E. Morganb, J. M. Wildc, et al. *Ocular complications of neurological therapy.* European Journal of Neurology **2005**; 12: 499–507.
22. Elisabeth Kimmoun and Didier Samuel. *Conference proceedings; Antituberculous drugs in patients with chronic liver disease.* Journal of Gastroenterology and Hepatology **2002**; 7: S408 – S412.
23. N.P. Thompson, M.E. Caplin, M.I. Hamilton, et al. *Anti-tuberculosis medication and the liver: dangers and recommendations in management*. European Respiratory Journal **1995**; 8: 1384–1388.
24. American Thoracic Society / Centers for Disease Control and Prevention / Infectious Diseases Society of America. *Treatment of Tuberculosis*. American Journal of Respiratory and critical care **2003;** 167: 603 – 663.
25. Alimuddin Zumla, Patrick Malon, Jane Henderson, et al. Reviews: *Impact of HIV infection on tuberculosis*. Postgrad Med J **2000**; 76: 259–268.
26. Motasim Badri, Douglas Wilson, Robin Wood. *Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: A cohort study*. Lancet ***2002;*** 359: 2059–64.
27. Earl Hershfield. *Tuberculosis: 9. Treatment.* Canadian Medical Association Journal **1999;** 161 (4): 405 - 411.
28. Anthony D Harries, Nicola J Hargreaves, Julia Kemp, et al. *Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1*. Lancet **2000;** 357: 1519–23.
29. Bert Schreuder, Jan Visschedijk, Peter Gondrie, et al. *Viewpoint: Why and how tuberculosis control should be included in health sector reviews.* Tropical Medicine and International Health **2004**; 9 (8): 910–916.
30. Christopher Dye, Geoffrey P Garnett, Karen Sleeman, et al. *Prospects for Worldwide tuberculosis control under the WHO DOTS strategy*. Lancet **1998**; 352: 1886–91.
31. Ministry of Health (Kenya). W*hat health care workers need to know about implementing TB*

/ *HIV collaborative activities*. TB / HIV guidelines **2006**; pp 1 - 47.

32. WHO. *WHO declares TB an emergency in Africa Call for "urgent and extraordinary actions" to halt worsening epidemic*. **2005**.
33. David E. Griffith, Barbara A. Brown-Elliott, Sara Shepherd, et al. *Ethambutol Ocular Toxicity in Treatment Regimens for Mycobacterium avium Complex Lung Disease*. Am J Respir Crit Care Med **2005**; 172: 250–253.
34. Jensa C. Bell, David N. Rose, Henry S. Sacks. *Tuberculosis preventive therapy for HIV-infected people in Sub-Saharan Africa is cost effective*. AIDS **1999**, 13: 1549-1556.
35. Jeffrey Glassroth. *Tuberculosis 2004, Challenges and opportunities*. Transactions of the American clinical and climatological association **2005**; 116: 293-311.
36. Mack R. Holdiness. *Review: Adverse Cutaneous Reactions to Antituberculosis Drugs*. International Journal of Dermatology **1985;** 24: 280-286.
37. Daphne Yee, Chantal Valiquette, Marthe Pelletier, et al. *Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis*. Am J Respir Crit Care Med **2003**; 167: 1472–1477.
38. L. Aaron, D. Saadoun, I. Calatroni, et al. *Tuberculosis in HIV-infected patients: A comprehensive review*. Clinical Microbiology and Infection, **May 2004**; 10: 388-398.
39. WHO. *Treatment of Tuberculosis. Guidelines for National programmes*, 3rd edition, **2003**.
40. Gillian L. Dean, Simon G. Edwards, Natalie J. Ives et al. *Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy*. AIDS **2002**; 16: 75 – 83.

APPENDICES:

Appendix 1: Study approval

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref: KNH-ERC/ 01/ 243

7th March 2008

Dr. Johnson Masese
Dept. of Clinical Pharmacy
School of Pharmacy
University of Nairobi

Dear Dr. Masese

RESEARCH PROPOSAL: "A RETROSPECTIVE COMPARATIVE STUDY OF ADVERSE DRUG REACTIONS AMONG HIV (+) AND HIV (-) ADULT PATIENTS TAKING ANTITUBERCULAR DRUGS, IN 2006-2007" (P15/1/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above cited research proposal for the period 7th March 2008 – 4th March 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY. KNH-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Pharmacy, UON
Supervisor: Dr. Rashid Juma, KEMRI

Appendix 2: Data collection form

Study No……

IP / OP No……..... Date……....

1. Patient bio-data

Date of birth---------- Sex -------- Residence----------

Marital status: (Tick where appropriate)

Single------- [ ]

Married----- [ ]

Divorced---- [ ]

Widowed--- [ ]

Occupation: (Tick where appropriate)

Unemployed -------- [ ]

Salaried ---------- [ ]

Self employed------- [ ]

Student ---------- [ ]

Highest level of education: (Tick where appropriate)

None ---------- [ ]

Primary---------- [ ]

Secondary------- [ ]

College----------[ ]

University-------- [ ]

Date of TB diagnosis ---------- Pulmonary [ ] or Extra pulmonary [ ]…

Specify----------

2. Parameters at the start of anti-TB treatment

Pregnancy-----[Y] / [N] Alcohol----[Y] / [N] [NR]

Smoking----[Y] / [N] [NR] Weight (kg) ----------

HIV status: Positive [ ] Negative [ ]

WHO staging [I]

[II]

[III]

[IV]

[NR]

CD4 count (cells/mm^3) [*if done*] ----------.

Other co-morbid disease: [Y] / [N]

If Yes above, specify----------.

3. Laboratory parameters before starting anti-TB treatment

a. Liver function tests (LFT)

	at baseline	**Reference**
ALT (U/L)		
AST (U/L)		
ALP (U/L)		
Total protein g/L		
Albumin (g/L)		
T. Bilirubin (umol/L)		
D. Bilirubin (umol/L)		

b. Full haemogram

	At baseline	**Reference**
Haemoglobin (g/dl)		
WBC (10^9)		
Platelet (10^9)		

c. Urea and electrolytes

	At baseline	**Reference**
Na+ (mmol/L)		
K+ (mmol/L)		
Creatinine (umol/L)		
Urea (mmol/L)		

4. Drug History

Date started anti TB Drugs ---------- To ----------

(Last date recorded in the file)

The total number of months patient has taken Anti TB drugs ----------.

Regimen patient is on ----------.

Patient on Intensive [ ] or Continuation Phase [ ]

Has the patient been on ARVs? [Y] [N]

If yes

i. Date started on ARVs ----------

ii. ARV drugs the patient was on at the time of ADR

	Drug	Dose	Frequency
1.			
2.			
3.			
4.			
5.			

Other drugs currently being used by the patient (at the time of ADR)– [Y] [N]

Cotrimoxazole ---------- ---------- [ ]

Corticosteroid ---------- [ ]

Dapsone---------- [ ]

Herbal medication---------- [ ]

Fluconazole ---------- [ ]

Iron supplements ---------- [ ]

Multivitamin ---------- [ ]

Pyridoxine ---------- [ ]

Other drugs ---------- [ ] specify if other----------

5. Viral co-infections - hepatitis A/B/C --------- [Y] [N]

If yes specify ----------

6. Opportunistic infections [at the time of ADR]

CMV---------- [ ]

Diarrhoea ---------- [ ]

Herpes zoster ---------- [ ]

Kaposi sarcoma ---------- [ ]

PJP (Pneumocystis jiroveci pneumonia -------- [ ]

Any other ---------- [ ] specify ----------.

7. Adverse drug reaction recorded in the patient file

a. Hepatotoxicity

Hepatotoxicity [Y] [N] Date of ADR [if recorded] ----------

Which of the following signs are recorded? (Tick where appropriate)

	Present	**Date**
Jaundice (yellow eyes)		
Nausea /vomiting		
Abdominal pain		
Hematemesis		
Rash		

Any other----------.

Are there any laboratory tests done at the time of ADR or after ADR resolved?

Lab test	**Lab at the time of ADR**	**Reference**	**Lab at time of ADR resolution**
ALT (U/L)			
AST (U/L)			
ALP (U/L)			
Total protein g/L			
Albumin (g/L)			
T. Bilirubin (umol/L)			
D. Bilirubin (umol/L)			

Action taken

Regimen change---------- [ ]

Admission---------- [ ]

Stopping of medication---- [ ]

None---------- [ ]

Addition of non anti-TB drug [ ] specify ----------.

Patient outcomes

Continued taking anti-TB drugs [ ]

Cessation of anti-TB drugs [ ]

Significant disability [ ] specify ----------.

Death [ ]

Time taken for ADR to resolve

Did the ADR resolve? [Y] [N]

If Yes, time taken to resolve (months) ----------.

If No, fate of the ADR: ----------

b. Peripheral neuropathy

Peripheral neuropathy [Y] [N] Date of ADR [if recorded] ----------

Which of the following signs are recorded? (Tick where appropriate)

	Present	**Date**
Pain		
Numbness		
Weakness of muscles		
Tingling / burning sensation		

Action taken

Regimen change---------- [ ]

Admission---------- [ ]

Stopping of medication-------- [ ]

None---------- [ ]

Addition of non anti-TB drug [ ] specify ----------.

Patient outcomes

Continued taking anti-TB drugs [ ]

Cessation of anti-TB drugs [ ]

Significant disability [ ] specify ----------.

Death [ ]

Time taken for ADR to resolve

Did the ADR resolve? [Y] [N]

If Yes, time taken to resolve (months) ----------.

If No, fate of the ADR: ----------

c. Ocular toxicity

Ocular toxicity [Y] [N] Date of ADR [if recorded] ----------.

Which of the following signs are recorded? (Tick where appropriate)

	Absent	Present	One eye affected	Both eyes affected	Date
Eye pain					
Red green colour blindness					
Blurred vision					

Any other ----------.

Action taken

Regimen change---------- -[ ]

Admission---------- [ ]

Stopping of medication------ -[ ]

None---------- [ ]

Addition of a non anti-TB drug [ ] specify ----------.

Patient outcomes

Continued taking anti-TB drugs [ ]

Cessation of anti-TB drugs [ ]

Significant disability [ ] specify----------.

Death [ ]

Time taken for ADR to resolve

Did the ADR resolve? [Y] [N]

If Yes, time taken to resolve (months) ----------.

If No, fate of the ADR: ----------

d. Gastrointestinal disturbances

Gastrointestinal disturbance [Y] [N] Date ADR was recorded ----------

Which of the following signs are recorded? (Tick where appropriate)

	Present	Date
Vomiting		
Nausea		
Stomach		
Diarrhoea		

Any other ----------.

Action taken

Regimen change---------- -[ ]

Admission---------- [ ]

Stopping of medication------ -[ ]

None---------- [ ]

Addition of a non anti-TB drug [ ] specify ----------.

Patient outcomes

Continued taking anti-TB drugs [ ]

Cessation of anti-TB drugs [ ]

Significant disability [ ] specify ----------.

Death [ ]

Time taken for ADR to resolve

Did the ADR resolve? [Y] [N]

If Yes, time taken to resolve (months) ----------.

If No, fate of the ADR: ----------

e. Cutaneous reactions

Cutaneous reactions [Y] [N] Date ADR was recorded----------

Which of the following signs was recorded? (Tick where appropriate)

	Present	Date
Skin rash		
Itchiness		
Wetness		
Dryness		

Any other ----------.

Action taken

Regimen change---------- -[ ]

Admission---------- [ ]

Stopping of medication------ -[ ]

None---------- [ ]

Addition of a non anti-TB drug [ ] specify ----------.

Patient outcomes

Continued taking anti-TB drugs [ ]

Cessation of anti-TB drugs [ ]

Significant disability [ ] specify ----------.

Death [ ]

Time taken for ADR to resolve

Was the ADR resolved? [Y] [N]

If Yes, time taken to resolve (months)

If No, fate of the ADR: ----------

f. Ototoxicity / Vestibular toxicity

Ototoxicity / vestibular toxicity [Y] [N] Date ADR was recorded----------

Which of the following signs was recorded? (Tick where appropriate)

	Present	Date
Hearing loss		
Ringing in the ears		
Nausea		
Vomiting		
Clumsiness/ dizziness		

Any other ----------.

Action taken

Regimen change---------- -[ ]

Admission---------- [ ]

Stopping of medication------ -[ ]

None---------- [ ]

Addition of a non anti-TB drug [ ] specify ----------.

Patient outcomes

Continued taking anti-TB drugs [ ]

Cessation of anti-TB drugs [ ]

Significant disability [ ] specify ----------.

Death [ ]

Time taken for ADR to resolve

Did the ADR resolve? [Y] [N]

If Yes, time taken to resolve (months) ----------.

If No, fate of the ADR: ----------

Appendix 3: TB treatment regimens used in 2006 – Kenya Regimens used [3]

In 2006 the following regimens were applied:

1. 2RHZE/6EH for new cases with smear-positive PTB (Category 1), smear negative PTB and extra-pulmonary TB
2. 2SRHZE/1RHZE/5RHE (re-treatment regimen) for smear positive relapse cases, recurrent negative PTB/EPTB cases, failures and defaulters
3. 2RHZ/4RH for new cases of smear positive or negative PTB or EPTB who are younger than 15 years.
4. 2SRHZE/4RHZE for nomadic patients admitted in the so-called TB manyattas for TB re-treatment (Category 2).

Appendix 4: Tuberculosis case notification by province, average annual increase: 2002-2006

Province	2002	2003	2004	2005	2006	Annual increase '05 – '06 (%)	Average annual increase (%)
Nairobi	15,979	18,360	19,871	19,486	19,472	0	7
Central	7,075	8,686	9,508	9,281	10,259	11	12
Coast	9,313	9,922	9,923	10,455	11,037	6	6
Eastern	11,937	13,756	16,270	16,910	16,863	0	10
North Eastern	2,736	2,959	3,088	3,412	3,355	-2	10
Nyanza	14,788	17,527	19,262	20,999	23,272	11	12
Rift Valley South	7,985	9,874	11,320	11,209	12,584	12	11
Rift Valley North	7,202	8,080	10,041	9,684	10,704	11	11
Western	5,099	6,146	6,500	6,965	7,688	10	10
Kenya	82,114	95,310	105,783	108,401	115234	6	9

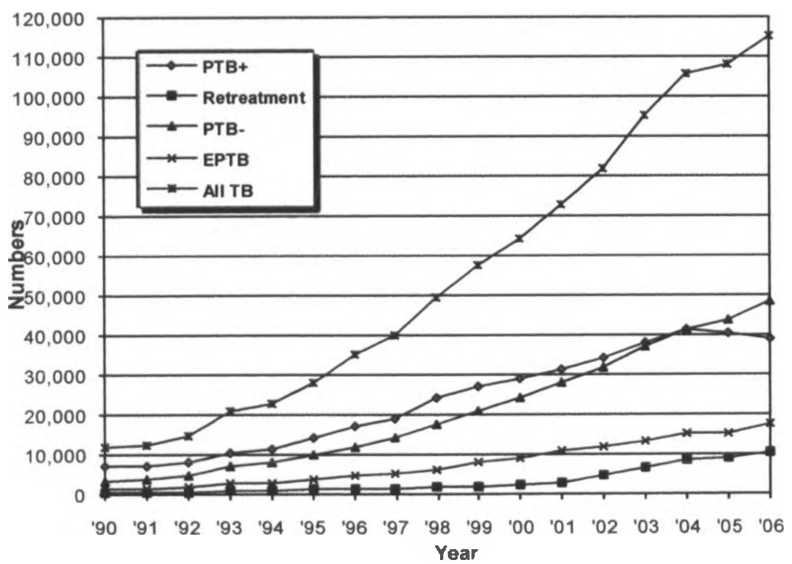
The table shows that over the last five years there was an average annual increase of 9% in the number of TB case notified in the country with a range of 6% in Coast Province to 12% in Nyanza and Central Provinces.

Appendix 5: Case Notification Rates different types of TB for provinces: Year 2006 [3]

(N/100,000 population)

Province	PTB+	PTB-	EPTB	Re-treatment	Total
Nairobi	232	211	133	79	654
Central	93	96	26	15	230
Coast	143	134	40	41	359
Eastern	92	164	32	27	315
North Eastern	56	77	36	17	185
Nyanza	149	193	72	38	452
South Rift Valley	102	111	35	15	264
North Rift Valley	74	120	46	21	261
Western	58	80	31	19	189

Appendix 6: TB case notification NLTP Kenya: 1990 – 2006 [3]



Appendix 7: Work plan

Schedule of the milestones of the study

	Activity planned	November 2007 - October 2008											
		N	D	J	F	M	A	M	J	J	A	S	O
1.	Proposal writing & submission of 1st draft	X											
2.	Supervisor corrections & feedback, Correction & submission of 2nd draft		X										
3.	Supervisor corrections & feedback. Corrections & submission of 3rd draft for supervisor approval.			X									
4.	Submission for approval by ethics committee.				X								
5.	Correction and resubmission to ethics committee.					X							
6.	Submission of a copy of approval letter from ethics committee to the KNH records department and request to begin data collection.						X						
7.	Data collection						X	X					
8.	Data analysis & supervisor guidance & corrections.								X	X			
9.	Report writing & supervisor corrections & guidance									X	X		
10.	Submission of finalized dissertation.											X	
11.	Defense of the study												X