INCIDENCE AND PATTERNS OF ADVERSE DRUG REACTIONS IN HIV POSITIVE PATIENTS ON ISONIAZID TUBERCULOSIS PREVENTIVE THERAPY AT KENYATTA NATIONAL HOSPITAL

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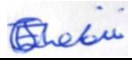
Signature: 

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LIST OF ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AST	Aspartate transaminase
ALT	Alanine transaminase
CDC	Centres for Disease Control and prevention
DLTLD	Division of Leprosy, TB and Lung Disease
eGFR	Estimated Glomerular Filtration Rate
ENT	Ear nose throat
GABA	Gamma aminobutyric acid
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
ICF	Intensified case finding
INH	Isoniazid
IPT	Isoniazid preventive therapy
KNH-CCC	Kenyatta National Hospital comprehensive care centre
LBTI	Latent tuberculosis infection
MDRD	Modification of Diet in Renal Disease
NASCOP	National AIDs and STIs Control Programme
NAT2	N-acetyltransferase2
PLHIV	People living with Human immunodeficiency virus
PUD	Peptic ulcer disease
RHZE	Rifampicin, isoniazid, pyrazinamide and ethambutol
RH	Rifampicin and pyrazinamide
TB	Tuberculosis
ULN	Upper limit of the normal
URTI	Upper respiratory tract infections

UTI	Urinary tract infections
UNAIDS	Joint United Nations Programme on HIV/AIDS
UoN	University of Nairobi
WHO	World Health Organization

DEFINITION OF TERMS

Adverse drug reaction- It is a response to a drug that is harmful and unintended, and occurs at therapeutic doses normally used for prophylaxis, diagnosis or treatment of disease.

Isoniazid preventive therapy- It is use of isoniazid at a dose of 5mg/kg/day (maximum 300mg) for at least six months to reduce risk of TB reactivation in persons with latent TB infection.

Latent tuberculosis infection- Is a condition in which a person is infected with *Mycobacterium tuberculosis*, but does not currently have active TB. Therefore despite constant immune stimulation in response to *M. tuberculosis* antigens, the person does not show any signs and symptoms of active TB disease.

Highly active antiretroviral therapy- Is the standard treatment of HIV using a combination of at least three active antiretroviral drugs to prevent HIV replication and emergence of drug resistance.

Estimated glomerular filtration rate- Is a measure of the function of the kidneys and to determine stages of kidney disease. Its calculated based on creatinine levels in blood.

ABSTRACT

BACKGROUND: Isoniazid tuberculosis preventive therapy (IPT) is use of isoniazid at a dose of 5mg/kg/day (max 300mg) in adults for a period of 6 to 9 months to prevent reactivation of active tuberculosis (TB). Isoniazid tuberculosis preventive therapy has been recommended by World Health Organization (WHO) since 1998 and by the end of 2016; over 300,000 patients had been enrolled on IPT in Kenya which represents 33% of all the People Living with HIV. At the time of the study, isoniazid was the only available treatment for latent tuberculosis infection although clinical trials on rifapentine and isoniazid combination were being conducted.

Adverse drug reactions can occur during IPT which can lead to increased morbidity and mortality, reduced adherence and treatment failure. Several risk factors increase toxicity to IPT.

OBJECTIVES: The main objective of this study is to measure the incidence and identify risk factors for adverse drug reactions in HIV positive patients on isoniazid preventive therapy.

METHODS: Two study methods were used; comparative cross sectional study and longitudinal cohort study. The study was carried out at Kenyatta National Hospital Comprehensive Care Centre from April to September 2018. Data collection was divided into three parts; patients interview using a structured questionnaire, abstraction of information from the patient files and database review. Data analysis was done using STATA software version 13.

RESULTS: Longitudinal cohort study was conducted for 592 patients who had completed IPT. Mean age was 45.1 years and majority were females (66%). ALT measurements were recorded for 436 patients at baseline and during IPT. Incidence of liver disease during IPT was 4.4%. The prevalence of abnormal ALT levels increased from 11.7% at baseline to 15.6% during IPT (p=0.056). Majority of the patients had mild hepatotoxicity (13.8%), those with moderate were 1.4% and 0.5% had a life threatening hepatotoxicity. The prevalence of all levels of liver severity increased during IPT.

There was a significant improvement of renal function during IPT as compared to the baseline by 4.8% (p=0.036).

Creatinine measurements were also obtained for 562 patients at baseline and during IPT. There was an increase in eGFR from a median of 76.3 ml/min/1.73m^2 at baseline to 80.5 ml/min/1.73m^2 during IPT ($p<0.001$).

Male patients had significantly higher prevalence of liver failure (27.5%) compared to females (9.9%), $p< 0.001$. Patients with renal failure were significantly older (mean 47.2 years) compared to those with normal eGFR (mean 40.3 years), $p<0.001$. Females had a higher prevalence of renal failure (81.8%) compared to males (44.8%), $p<0.001$.

In the comparative cross sectional study, 264 patients were interviewed and their mean age was 41.3 years while majority were females (56.8%). Patients who had used IPT were more likely to report any ADR sign (36.9%) compared to those who had never used IPT (25.2%), OR 1.7 (95% CI 1.2-3.0), $p=0.043$.

Main ADRs experienced during IPT were; numbness, tingling feet/burning sensation (8.7%), skin rash (6.7%), gastrointestinal (5.3%) and hepatotoxicity (4.7%). For the majority (73.9%) no action was taken for the ADRs while IPT was withdrawn in 24.6%.

Conclusion: Adverse drug reactions are likely to occur during IPT. Incidence of liver disease was 4.4% in patients on IPT and the prevalence was significantly higher in males compared to females ($p< 0.001$). There was a significant improvement in renal functions in 4.8% of the patients on IPT with females and older patients experiencing higher prevalence of renal disease.

Close monitoring of high risk groups such as the elderly, diabetic and hypertensive patients is therefore necessary to ensure their safety during IPT.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Tuberculosis (TB) is an infectious disease caused by the bacillus, *Mycobacterium tuberculosis* and is usually transmitted from one person to another by inhalation of aerosolized droplet nuclei. After exposure to a droplet containing nuclei, 10% of the people develop active TB while approximately 90% of the bacteria remains dormant in the body producing an asymptomatic latent TB infection [1].

Active TB refers to pulmonary or extra-pulmonary clinical manifestations of the disease and it usually presents with chronic persistent cough, unintentional weight loss, fever and coughing of blood. Those at high risk of contracting active TB are People Living with HIV (PLHIV), healthcare workers, contacts of TB patients, prisoners, miners and persons with a history of TB infection [2].

Latent tuberculosis infection (LBTI) is a persistent immune response to stimulation by *M. tuberculosis* antigens without clinical active TB. However, a latent TB infection may be reactivated to active TB [3]. It is estimated that 5-10% of healthy persons with a positive test will progress from latent to active TB disease in their lifetime [4].

Tuberculosis is a leading cause of morbidity and mortality among PLHIV. As a result of immune suppression, HIV infection increases the likelihood of TB reactivation. The risk of developing tuberculosis is 20 to 37 times greater in PLHIV than in HIV negative individuals [3].

Antiretroviral therapy (ART) is treatment of people infected with HIV using drugs that slow the rate at which HIV multiplies in the body. It is an effective way of reducing TB incidence in PLHIV especially when initiated on time. By end of 2015, 826,097 adults and 71,547 children living with HIV were on ART in Kenya. Although all HIV positive patients on HAART were eligible for IPT, most of them had not been started on IPT treatment as a result of insufficient drug supplies, patients refusing treatment and low uptake by clinicians as a result of inadequate information on safety and efficacy of IPT [5].

Currently available treatments for LBTI have an efficacy ranging from 60-90% [6, 7]. They include ; 6 to 9 months of isoniazid 10mg/kg/daily, combination of isoniazid and rifapentine 15-30mg/kg given weekly for three months or rifampicin 10mg/kg/day for patients who are resistant to isoniazid. In Kenya, isoniazid therapy was the only available treatment for latent tuberculosis at the time of the study. Phase III clinical trials on use of rifapentine and isoniazid combinations were being conducted by Kenya Medical Research Institute (KEMRI) in Kisumu since May 2012. Other eligible patients were not on IPT as a result of drug stock outs or patient refusing treatment [1, 4, 6].

Isoniazid preventive therapy (IPT) is the daily use of isoniazid for at least six months to prevent infection with latent tuberculosis. The recommended dose is 5mg/kg/day for adults and 10-15mg/kg/day for children. Isoniazid preventive therapy reduces the risk of TB by 65% alone and up to 80% when combined with ART [8].

Adverse drug reactions (ADRs) can occur during IPT which can lead to treatment interruption. According to World Health Organization (WHO), an ADR is a response to a drug that is harmful and unintended, and it usually occurs at therapeutic doses [9].

To decrease TB infection in PLHIV, WHO issued a policy in 1998 to implement the “three I’s strategies” which include; control of TB infection, intensified finding of TB cases and IPT. This policy was modified in 2011 to include use of IPT in people at high risk of contracting TB; for example those living in resource constrained settings [7, 10].

Isoniazid preventive therapy was first introduced in Kenya in 2011, although its implementation has been relatively slow. The IPT policy was issued in March, 2015 through the Operational Guidelines for Provision of IPT in PLHIV by the Ministry of Health. The guidelines clearly state the eligibility criteria for IPT, ordering mechanisms for isoniazid, pyridoxine supplementation to prevent peripheral neuropathy and reporting to the IPT registry at the facility level [11]. Studies have shown that IPT can cause various ADRs which need to be identified and managed accordingly.

1.2 PROBLEM STATEMENT

The prevalence of HIV in Kenya was 5.9% in 2015. This consists of 826,097 adults and 71,547 children who are HIV positive already on ART. In the same year, 77,647 new HIV infections and 35,821 HIV/AIDS related deaths were reported [5].

HIV is the strongest risk factor for developing TB which is one of major causes of illnesses and death amongst PLHIV, even those taking ART. There were 81,518 TB case notifications in the country, of which 26,288 (32%) were TB patients with a positive HIV status [12]. Isoniazid preventive therapy is a key public health intervention among PLHIV that has been recommended by WHO.

In Kenya, IPT policy was issued in March 2015 and the Ministry of Health recommends IPT for PLHIV who are eligible [11]. In a report by Centres for Disease Prevention and Control (CDC); over 300,000 patients had been started on IPT in Kenya by end of 2016 [8, 12].

Drug specific ADRs can occur with IPT and they include; peripheral neuropathy, hepatotoxicity, nephrotoxicity, hypersensitivity and neuropsychiatric symptoms [13, 14]. Other rare but reported ADRs are acute pancreatitis, encephalopathy, pyrexia and pure red blood cell aplasia [15]. Studies have shown that isoniazid therapy increases levels of serum aminotransferase in10 to 20% of patients, and levels may rise above 5 times the upper limit of the normal (ULN) in 3 to 5% of the patients [4].

These ADRs can result in patients interrupting treatment, increase in morbidity and mortality, drug resistance, treatment failure, increased costs of managing ADRs and reduced quality of life [9]. Several risk factors increase the incidence of ADRs during IPT. Examples of such risk factors include; older age, female gender, alcohol consumption, co-administration with other hepatotoxic drugs, hepatitis B and C infections, slow acetylator status and pregnancy [13, 16,17].

In 2017, the Pharmacy and Poisons Board Pharmacovigilance section had received up to 17 cases of fatalities in HIV positive women who had been adequately managed with ART. These women presented with acute liver and renal failure, both of which are possible side effects of IPT (unpublished data). This further raises concerns about the risk of liver and kidney dysfunctions and other side effects in patients on IPT in Kenya. This study is therefore necessary in identifying whether isoniazid therapy is safe on HIV positive patients and prevent further mortalities.

1.3 STUDY QUESTIONS

1. What is the incidence of adverse drug reactions in HIV positive patients on isoniazid preventive therapy?
2. Which are the risk factors for adverse drug reactions during IPT in patients who are HIV positive?

1.4 STUDY OBJECTIVES

1.4.1 Broad Objectives

The main objective of this study was to measure and compare incidence and risk factors for adverse drug reactions in HIV positive patients on IPT and those not on IPT.

1.4.2 Specific Objectives

The specific objectives of the study were to;

1. Measure incidence of adverse drug reactions in HIV positive patients on IPT and those not on IPT.
2. Identify the risk factors for adverse drug reactions in HIV positive patients on IPT and those not on IPT.

1.4 STUDY JUSTIFICATION

Despite IPT being implemented in Kenya, there is no information on its safety profile in large numbers of HIV positive patients.

The findings of this study will provide evidence as to whether IPT is causing excess morbidity and mortality which would make a case for interventions such as dose reduction and prior pharmacogenetic testing.

By identifying the risk factors for ADRs, this study would contribute to identification of patients for whom IPT should be contraindicated or closely monitored, thereby reducing further deaths and complications.

National AIDs and STIs Control Programme (NASCOP) and other stakeholders in TB control requires evidence on the incidence of ADRs in patients on IPT in order to inform IPT policy and make appropriate recommendations.

CHAPTER 2: LITERATURE REVIEW

2.1 TUBERCULOSIS DISEASE

2.1.1 Pathogenesis of Tuberculosis

Transmission of *M. tuberculosis* is dependent on the immune status of the exposed person and ability to infect others [18]. Environmental factors such as air pollution, poor ventilation, smoking and occupational risks also affect transmission of *M. tuberculosis* organisms. After inhalation, the bacilli droplet is carried down the bronchial tree before being implanted in the alveolus [24].

When the tubercle bacilli enters the body, three outcomes are possible: clearance of the organism; onset of active disease (primary TB); or latent infection without signs and symptoms of disease [20]. The tubercle bacilli may also enter the other parts of the body such as the; lymph node, brain, spine, bone and kidney [2,19].

Latent TB infection (LBTI) occurs when immune cells keep infection under control by ingesting and surrounding the bacilli to form a granuloma. This usually occurs within two to eight weeks after transmission. Positive tuberculin skin test may be the only indication that infection had occurred. Consequently, active TB will eventually develop if the immune system is inadequate and cannot prevent infection with tubercle bacilli [4, 18].

About 5% of persons infected with tubercle bacilli will rapidly progress to TB within the first two years. Reactivation of latent TB is higher in PLHIV by up to 10% per year because of reduced immunity. Persons with reduced immunity have higher frequency of extrapulmonary TB (30%) compared to those with normal immunity (15%). Presenting symptoms are usually non- specific and are mainly systemic such as fever, unintended weight loss, anorexia night sweats and fatigue [18, 21].

Other risk factors for reactivation are; diabetes, malnutrition, smoking, alcohol intake, use of immunosuppressive drugs and renal disease (Table 2.1).

Table 2.1: Risk factors for tuberculosis activation

Source: Risk factors for latent tuberculosis reactivation by Ai et al, 2014 [3]

Risk factor	TB Risk %	Reference
High risk factors		
HIV/AIDS	10-100	Landry and WHO, 2014
Close contacts with active TB	15	Sutherland, 2008
Organ transplantation	20-70	Lopez, 2016
Chronic renal failure requiring dialysis	6.9-52.5	Menzies, 2009
TNF-alpha blockers	1.6-25.1	Soloril, 2010
Silicosis	2.8	Cowie, 2008
Moderate risk factors		
Healthcare workers	2-5.5	Chu, 2014
Diabetes mellitus	1.6-7.8	Harries, 2011
Smoking	2-3.4	Shang, 2011
Use of corticosteroids	2.8-7.7	Jick, 2006
Underweight	2-3	McDonald, 2010

2.1.2 Epidemiology of Tuberculosis

Tuberculosis is one of the top 10 causes of death worldwide. In 2015, 10.4 million TB infections and 1.8 million deaths were reported including 0.4 million PLHIV [12, 26]. The highest burden of TB occurs in low and middle-income countries such as India, China, South Africa, Nigeria and Pakistan which accounted for 60% of TB deaths [26].

The African continent has the highest burden of HIV/TB co-infections whereby 81% of notified TB patients were HIV positive. The proportion of known HIV-positive TB patients on ART and IPT has significantly improved in countries such as South Africa, Kenya, Malawi and Mozambique. In 2015, South Africa had achieved 45% coverage of PLHIV on IPT [27, 29].

The global TB incidence has fallen by 1.5% per year which is in line with the WHO's "End TB Strategy" that advocates for a 90% reduction in TB deaths and an 80% reduction in incidence rate by 2030 [26].

Kenya is ranked 15th among the 22 high TB burden countries that account for 80% of the global TB burden, and 5th in Africa [19]. The country reported 81,518 TB case notifications in 2015 (Table 2.2).

Table 2.2: Tuberculosis profile in Kenya 2015

Source: Estimates of TB burden in Kenya by Word Health Organization, 2016 [12].

Estimates of tuberculosis burden	**Number (1000's)**	**Incidence (per 100,000 population)**
Mortality (excludes HIV & TB)	9 (6.1-12)	20 (13-27)
Mortality (HIV & TB only)	7.2 (0.71-21)	16 (1.5-45)
Incidence (all cases)	107 (87-129)	233 (189-281)
Incidence (HIV & TB only)	36 (29-43)	78 (63-94)
Incidence (MDR-TB)	2 (1.3-2.8)	4.3 (2.8-6.1)

2.1.3 Diagnosis of Tuberculosis

The recommended diagnostic tests for detecting TB are nucleic acid amplification tests, sputum smear microscopy, radiography and bacteria culture methods [30, 31]. The biological specimens which can be used are; sputum, cerebrospinal fluid, urine, pleural fluid and biopsy specimens [21].

Xpert MTB/RIF^{R} is one of the nucleic acid amplification tests (rapid molecular tests) used as an diagnostic test for TB. Since 2013, it is recommended for diagnosis in both adults and children and it works by amplifying DNA and RNA segments of the mycobacterium. Xpert MTB/RIF ^{R} has better accuracy compared to microscopy and culture methods. When used as an initial test to detect *M. tuberculosis,* Xpert MTB/RIF^{R} achieved a pooled sensitivity of 88% and a pooled specificity of 98% compared to smear microscopy [30].

Smear microscopy is where the bacilli are stained and examined under microscope to provide the bacteriological evidence of *M. tuberculosis* in a specimen. There are two procedures for smear microscopy; Ziehl-Neelsen (direct microscopy) and fluorescent microscopy [31].

A chest radiograph may aid in diagnosis of pulmonary TB but it should not be used primarily to establish diagnosis of TB. Radiographic features that are usually suggestive of TB include; pleural and pericardial effusion, patchy shadows in upper zone of the lung and lymph nodes enlargement in HIV infected persons [21]. Persons with nodular or fibrotic lesions as a result of previous TB infection should be considered for LTBI treatment after active TB is excluded [31].

Culture is still the standard test for diagnosis of TB, drug-susceptibility testing and genotyping. Positive cultures confirm diagnosis of TB. However, diagnosis may still be done clinically based on symptoms of disease in absence of positive culture [30].

Mantoux tuberculin skin test and interferon gamma release assays are other diagnostic tests for LBTI [2]. After infection with *M. tuberculosis,* there is usually a delayed-type hypersensitivity reaction response to certain antigenic components of the organism [21].

2.1.4 Treatment of Tuberculosis

The approved first line treatment for TB should be given to all patients who have not received treatment in the past and do not have drug resistance. The initial phase consists of rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE) given for two months. Rifampicin and isoniazid (RH) are used in the continuation phase for a period of 4 months [30, 32].

The initial phase of treatment is important in preventing drug resistance and determining treatment outcomes. It is crucial to include all the four drugs in the initial treatment because each of the drugs plays an important role. For example; rifampicin and isoniazid allow for short duration of treatment and increased efficacy [32]. Since pyrazinamide has potent sterilizing activity, it allows shortening of continuation phase from 9 to 6 months. Ethambutol helps to prevent the emergence of drug resistance [19].

The continuation phase of treatment is usually given for either four or seven months. Patients whose sputum culture has turned negative within the first two months receive 4-months course of treatment. The 7-month continuation phase is recommended only for patients with extensive pulmonary TB and those whose sputum culture is still positive after 2 months of treatment [32].

Treatment of TB may require modifications of dose, regimen and frequency of drug administration in some conditions such as presence of liver and renal disease, pregnancy and HIV infection [16]. The dosing interval of TB drugs should be increased to three times a week in patients with end-stage renal disease on hemodialysis and is based on creatinine clearance [32].

2.2 METABOLISM OF ISONIAZID

Isoniazid was first used against *M. tuberculosis* in the 1950s. It works by inhibition of mycolic acid synthesis required for development of bacterial cell wall. Isoniazid is a pro-drug which is metabolized by intracellular catalase reductase enzyme to its active form (INH-NAD). This active form irreversibly inhibits catalase peroxidase enzyme required for the synthesis of mycolic acids [33].

After oral administration, isoniazid is rapidly absorbed through the gastrointestinal tract. It has a half -life of 1–2 hours. After absorption, it distributes to all body tissues such as the cerebrospinal fluid, placenta and breast milk. The degree of protein binding is between 10-15% [16].

The predominant metabolic pathway of isoniazid is acetylation by N-acetyltransferase 2 (NAT2) enzyme to acetylisoniazid. A small part of isoniazid is directly hydrolysed into isonicotinic acid and hydrazine (Figure 2.1).

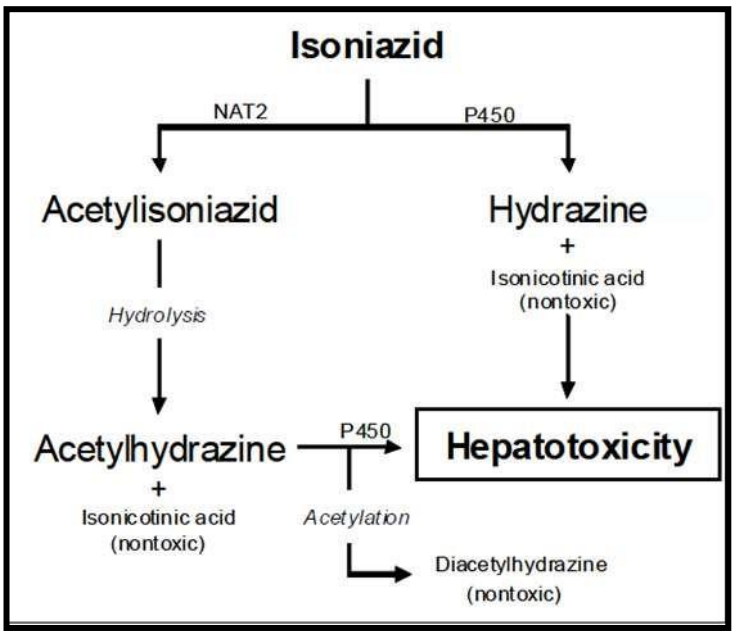

Figure 2.1: Metabolic Pathway of Isoniazid

Source: INH-Associated hepatotoxicity by Story & Nelson [33].

Polymorphisms of N-acetyltransferase 2 have been identified in the population and this results in grouping of humans as either slow or rapid acetylators. In fast acetylators, more than 90% of the drug is excreted as acetylisoniazid compared to 67% in slow acetylators [34]. The elimination half-life for fast acetylators is usually 30-100 min while slow acetylators have a longer time of 2-5 hours [33].

Secondary metabolic pathway of oxidation via cytochrome P450 usually occurs in slow acetylators producing hydrazine and isonicotinic acid [34, 35]. Hydrazine may induce cytochrome P450 2E1 which increases production of additional toxic metabolites. Patients carrying the homozygous cytochrome P450 2E1 c1/c1 host gene polymorphism have an increased risk of developing hepatotoxicity especially if they are slow acetylators [35].

2.3 ISONIAZID PREVENTIVE THERAPY

The protective benefit of IPT ranges from 6 months to 5 years although this may reduce significantly in presence of high prevalence of TB in the community and re-infection following close contact with persons having active TB [6]. In spite of WHO recommendations for the use of IPT in 1998, its uptake has been very slow because of concerns of drug resistance if active TB has not been excluded [7, 10].

Isoniazid preventive therapy reduces the risk of developing active TB by 33% (relative risk 0.67; 95% CI 0.51-0.87) in PLHIV [36]. A meta-analysis of eleven clinical trials carried out in 2000 found out that among 73,375 HIV negative persons who were given IPT for six months, the risk of progression to active TB was reduced with a relative risk of 0.44 (95% CI 0.27-0.73) [2].

2.3.1 Indications for Isoniazid Preventive Therapy

Isoniazid preventive therapy should be provided to those patients who meet eligibility criteria and active TB has been excluded using the Intensified Case Finding (ICF) tool. The ICF tool inquires on the presence of persistent cough, fever, sweating at night and excessive weight loss [10, 37].

Those eligible for IPT include HIV positive children less than 12 months of age who have had recent close contact with persons having active TB, all PLHIV above 12 months of age who do not have active TB and prisoners [11, 37].

Contraindications for IPT include; active TB, hepatitis B or C co-infection, alcohol intake, substance abuse and symptoms of peripheral neuropathy. Other contraindications are patients who have poor adherence to ART and infants less than 1 year who do not have direct exposure to TB patients [11, 37].

2.4 ADVERSE DRUG REACTIONS ASSOCIATED WITH ISONIAZID PREVENTIVE THERAPY

2.4.1 Hepatotoxicity

Isoniazid is thought to induce hepatic necrosis, macrovesicular degeneration and steatosis mainly through hydrazine which is a toxic metabolite. It also inhibits mitochondrial complex II and affects the function of electron transport chain and ATP production in mice hepatocytes. Recent studies also show INH can bind to liver proteins and cause immune-mediated hepatotoxicity [34, 38].

Isoniazid therapy is associated with elevated serum aminotransferase enzymes in 10 to 20% of patients which are usually asymptomatic and often resolves without dose adjustment [36, 39]. Acute liver injury with apparent jaundice has been observed in 0.5 to 1% of patients treated with IPT [16].

The incidence of hepatotoxicity varies with older studies showing a low incidence of between 0.5-1% while more recent studies demonstrate a higher incidence of 5-10% [1, 34]. In one of the studies carried out in the USA in 1972 among 13,838 patients on IPT, the risk of hepatitis was approximately 1%. There were eight deaths, associated with older age above 35 years and daily alcohol consumption [1].

A clinical trial study was carried out by Centres for Disease Prevention and Control (CDC) in Botswana among PLHIV. Patients who developed severe hepatitis after receiving IPT for 36 months were 1.9% (19 of 1,006) while another 3.1% (31 of 1,006) experienced moderate hepatitis [36].

In another retrospective study done in Malaysia between 2011 and 2014 involving 242 HIV patients, 8.5% developed adverse drug reactions including hepatotoxicity, while 5.4% developed rash. The risk factors for hepatotoxicity were Hepatitis B/C co-infection and elevated alanine transaminase levels at baseline [6].

In a case series study that described patients on IPT in Uganda between December 2013 and March 2014, the prevalence of INH related toxicity was 1.5% among children 4 to 10 years old. All the cases of hepatotoxicity had elevated serum aminotransferase enzymes above 10 times the upper limit of the normal [40].

A longitudinal cohort study was done in Kenya between December 2011 and July 2013 by Okwara on the effectiveness of IPT in children who are at close contact with adults infected with TB. It included 428 children aged below five years, living in low income residential estates of Nairobi. Side effects associated with IPT were reported in 82 (22%) of the subjects; transient skin rash was observed in 46 (12.5%), gastro-intestinal symptoms in 35 (9.5%), neurological symptoms in 20 (5.4%) and yellow discolouration of eyes and urine in 6 (1.6%) of the patients [41].

2.4.2 Isoniazid induced Peripheral Neuropathy

Peripheral neuropathies develop as result to damage to the nerves which transmit information from all parts of the body to the spinal cord and the brain. Neuropathy is classified into sensory, motor or autonomic. Motor nerve damage is associated with muscle weakness, painful cramps, decreased muscle reflexes and muscle atrophy. Sensory nerve damage can lead to loss of pain, touch and heat sensations as well as inability to maintain body balance [13].

Peripheral neuropathies can either be hereditary or acquired. HIV infection causes several different types of peripheral nerve diseases. In addition, toxic neuropathy has been associated with the use of stavudine, didanosine and zidovudine during HIV treatment [42].

Peripheral neuropathy is a common adverse effect associated with prolonged use of isoniazid. Isoniazid binds with the active form of pyridoxine called pyridoxal-5-phosphate to form isoniazid–pyridoxal hydrazine which is excreted in urine causing pyridoxine deficiency. It is usually observed in 10-20% of patients, even though it can be reversed by administration of pyridoxine. High doses of pyridoxine (>50mg per day) also causes peripheral neuropathy. Peripheral neuropathy can manifest 2 weeks after starting treatment with isoniazid [13, 43].

Signs and symptoms of isoniazid induced peripheral neuropathy include; numbness or tingling feet, muscle weakness, a burning sensation and pricking pain [42]. Some of the risk factors for INH induced neuropathy are old age, alcohol intake, diabetes, chronic renal and liver failure, HIV infection and pregnancy [13, 16, 43].

2.4.3 Neuropsychiatric Disorders in patients on isoniazid

Isoniazid toxicity occurs through its metabolites which inhibit pyridoxine phosphokinase enzyme. This enzyme is required for the synthesis of gamma aminobutyric acid (GABA) by converting pyridoxine (vitamin B-6) to its active form, pyridoxal-5'-phosphate.

Gamma aminobutyric acid is an inhibitory neurotransmitter in the central nervous system producing a relaxation effect. When there is GABA deficiency, excessive excitatory activity occurs in the brain and disorders such as anxiety, seizures, psychosis, restlessness and Parkinson's disease can develop. The duration of onset of psychotic symptoms varies between 7 to 120 days [14, 16, 44].

Central nervous system toxicity typically occurs when isoniazid is given as an overdose, but it may also develop with therapeutic doses if co-administered with CYP-450 inducers such as rifampicin, phenytoin and ethanol. Susceptibility to isoniazid induced psychosis increases with old age, personal and family history of psychiatric disorders, malnutrition and alcohol intake [17].

2.4.4 Acute Pancreatitis

Acute pancreatitis is rare during IPT, with most studies reporting a prevalence of between 0.2-2% [45]. According to eleven case reports, acute pancreatitis related to isoniazid developed within a median onset of 16 days after starting isoniazid initiation and recurred earlier after re-challenge [15, 46].

Symptoms of INH induced acute pancreatitis include loss of weight and appetite, anorexia, afebrile seizures and epigastric tenderness. Isoniazid induced hepatitis and pancreatitis is reversible if the drug is withdrawn early and is the key to preventing hazardous consequences [45].

2.5 RISK FACTORS FOR ADVERSE DRUG REACTIONS

Several factors may contribute to isoniazid toxicity. These include; old age, alcohol consumption, female gender, acetylator status, pregnancy, hepatitis B and C co-infection and intravenous drug use. The risk of developing ADRs is higher in females, slow acetylators, patients aged above 35 years, heavy alcohol consumption, concomitant use of other hepatotoxic and intravenous drugs [17, 34, 38, 47].

Isoniazid inhibits the activity of several liver enzymes especially P450 2C and 2E [33]. Concomitant co-administration of drugs such as acetaminophen, phenobarbital, carbamazepine, methotrexate and rifampicin increases the risk of hepatotoxicity. Drugs such as para-aminosalicylic acid may increase toxicity of isoniazid by interfering with its acetylation [16].

A prospective study was conducted in Canada and USA from March 2007 to 2008 involving 1,306 adults initiated on IPT for treatment of LBTI. The relative risk of isoniazid discontinuation as a result of ADRs was 15% (95% CI 13.1-17.1%) while those who completed treatment were 47.2% (95% CI 44.5-50.0%). The independent risk factors for INH discontinuation were alcohol use (RR 1.41 (95% CI 1.13-1.77)) and female sex(RR 1.67 (95% CI 1.32-2.10%)).

Pregnancy increases the risk of isoniazid induced hepatotoxicity by up to 3.8 times especially in HIV positive women. It is thought that pregnancy increases activity of P450 enzymes which may be the cause of liver injury. In addition, ART during pregnancy has been associated with percentage increase of ALT levels between 0.5- 25.9% [17].

CHAPTER 3: METHODS

3.1 STUDY DESIGNS

Two study designs were used; longitudinal cohort study which entailed database review of patient's medical records and comparative cross sectional study which was conducted through active recruitment of the patients and interviews. One study arm was HIV positive patients on IPT and HAART while the comparative arm were HIV positive patients on HAART alone.

3.2 STUDY AREA

The study was carried out at the Kenyatta National Hospital Comprehensive Care Centre (KNH-CCC). Kenyatta National Hospital is the largest teaching and national referral hospital in Kenya. It provides both outpatient and inpatient services to diverse groups of patients from all over the country as well as primary healthcare services to neighbouring communities. KNH-CCC provides outpatient care to HIV/AIDS patients. These services include HAART and IPT among others. The facility has enrolled more than 10,000 HIV positive patients of whom approximately 5,000 are aged 18 years and above had completed IPT by October 2017.

3.3 STUDY POPULATION

The target population were adult HIV positive patients on IPT and HAART. The study population were HIV positive patients of either sex, aged 18 years and above on HAART and IPT who were attending KNH-CCC from April to September 2018.

3.4 ELIGIBILITY CRITERIA

3.4.1: Longitudinal cohort study

Patients were eligible for inclusion if they were;

1. HIV positive patients
2. Aged 18 years and above
3. Had been on HAART and IPT
4. They had liver and/or renal function tests done at baseline and at any point of time after IPT initiation.

3.4.2: Comparative cross sectional study

Patients were eligible if they were;

1. HIV positive patients.
2. Aged 18 years and above.
3. Had been on HAART for at least six months.
4. Had been on IPT for at least one month before recruitment for the treatment group and not on IPT for the comparative arm.
5. Had given a written informed consent.

Patients were excluded from the study if they;

1. Declined to participate
2. Had missing or incomplete records on IPT and key socio-demographic characteristics.
3. Had abnormal elevation of ALT and creatinine at the time of IPT initiation.
4. Had history /signs of peripheral neuropathy and neuropsychiatric disturbances before IPT initiation.

3.5 SAMPLE SIZE

Given that the study was comparative design, the formula for computation of sample size calculation in comparative studies that entail a categorical variable was used. (Equation 1).

Equation 1: Formula for sample size calculation [49]

$$n = \frac{[(a+b)^2 (p_1 q_1 + p_2 q_2)]}{x^2}$$

n= sample size in each of the groups

p_1= proportion of patients with hepatotoxicity in patients on IPT

q_1= proportion of patients without hepatotoxicity in patients on IPT

p_2=proportion of patients with hepatotoxicity in patients not on IPT

q_2= proportion of patients without hepatotoxicity in patients not on IPT

x=the difference the investigator wishes to detect

a= critical value for 95% confidence interval of the estimate=1.96

b= power of the study set at 0.85

To estimate the various proportions required for the computation of sample size, studies on the prevalence of ADRs in IPT patients were used. From a large multisite study conducted in Canada, the estimated incidence of any ADRs that led to treatment discontinuation of patients on IPT was 15% [17].

From a smaller study conducted in an African setting, the incidence of liver toxicity in patients not on IPT by was 5% [48]. Therefore the estimated difference in incidence of ADRs in patients on IPT and those not on IPT was about 10%. Using the formula and the estimated proportions, the calculated sample size for each of the study arms was 138. This figure was inflated by 10% to cater for non-response or missing data. Therefore the minimal sample size was **152** for each of the study arms.

3.6 SAMPLING METHOD AND PARTICIPANT RECRUITMENT

3.6.1 Longitudinal cohort study

For database review, all patients with liver and/or renal function tests done at baseline and after IPT initiation were included in the study. This was done through a database query on all HIV positive patients who had been enrolled at KNH CCC from January 2011 to June 2018. The query was done on 25th June 2018. It was generated from IQ Care Electronic Medical Record system. The system runs on Microsoft SQL Server version 2008 R2 database server. The data was generated using a SQL query.

3.6.2 Comparative cross sectional study

Given that there were only 174 participants who were on IPT at KNH-CCC at the time of the study, universal sampling was therefore conducted. The two groups of patients; on IPT and those not on IPT were recruited by convenience sampling during their routine visit to the facility. They were recruited by the investigator as they collected their medications from pharmacy. Informed consent was obtained from the participants before they were recruited using the Informed Consent Form in appendix A.

3.7 DATA COLLECTION

3.7.1 Participants interview and abstraction of participant files

The purpose of participant interview was to obtain information on socio-demographic characteristics, as well as signs, symptoms and outcomes of ADRs experienced by the patients. This was done using a structured questionnaire in appendix B.

The interviews were conducted in a side room next to pharmacy. The interviews of patients who gave informed consent to participate were conducted in a side room next to pharmacy. Additional information was obtained from their medical files which were retrieved from the records department. Information that was collected included; date of initiation of IPT, HAART regimens, co-morbidities, co-medications, laboratory results and clinical information that are indicative of ADRs

3.7.2 Database review

The head of Information and Communications Technology at the CCC created a database of patients on IPT through a query of the main database containing information of all HIV positive patients enrolled in the clinic. The main variables collected from database were results of liver and renal function tests done before and after a minimum of one month following IPT initiation. Although most of the patients develop symptoms after one month of initiating treatment, some cases could have been missed out especially those who experienced ADRs before one month [13, 43].

Other variables obtained were; HAART regimens, co-medications, co-morbidities and socio-demographic characteristics. The database was subjected to cleaning before being used for subsequent data analysis. The information from the database was collected using data collection tool in appendix C.

3.8 CASE DEFINITIONS

Hepatotoxicity was defined using AIDS Clinical Trials Group criteria and clinical evaluation of signs and symptoms of hepatotoxicity. Liver disease was defined as ALT levels above 40 µ/l. This criteria is presented in Table 3.1.

Table 3.1: Definition of Hepatotoxicity by AIDS Clinical Trials Group

Source: Anti-tuberculosis drug-induced hepatotoxicity by Alma et al, 2007 [38].

Grade	Criteria
1 Mild	1.25-2.5 times ULN (ALT 51-125 µ/l)
2 Moderate	>2.5-5 times ULN (ALT 126-250 µ/l)
3 Severe	> 5-10 times ULN (ALT 251-500 µ/l)
4 Life threatening	>10 times ULN (ALT >500 µ/l)

Clinical evaluation of hepatotoxicity included signs and symptoms of lethargy, weight loss, loss of appetite, hepatic encephalopathy, yellow discolouration of eyes and urine, painful tense and distended abdomen.

Nephrotoxicity was estimated using Modification of Diet in Renal Disease (MDRD) formula. Renal disease was defined as eGFR less than 50ml/min/1.73m^2. The MDRD formula is presented in equation 2.

Equation 2: MDRD formula for computation of eGFR [50]

$$\text{eGFR} = 175 \times [\text{serum creatinine } (\mu\text{mol/L}) / 88.4]^{-1.154} \times \text{age (years)}^{-0.203} \times 0.742 \text{ if female and } \times 1.21 \text{ if African}$$

eGFR units= ml/min/1.73m^2

The severity of renal failure was graded based on eGFR as presented in Table 3.2.

Table 3.2: Classification of renal disease using the MDRD formula [51]

Stage	Criteria (GFR in ml /min/1.73m^2)
Normal	>90
Mild impairment	60-89
Moderate impairment	30-59
Severe impairment	15-29
Established renal failure	< 15 or patient dialysis

Peripheral neuropathy was defined as the presence of any one of the following signs/symptoms; numbness and pain in the feet, muscle weakness, tingling of the feet and burning sensations. Neuropsychiatric symptoms were defined as a written diagnosis of any of the following; upon presence of psychosis, mental depression, suicidal tendencies, restlessness, hallucinations, irritability and agitation. The diagnosis of the above symptoms was done by medical officers who assess the patients on every visit to the clinic.

3.9 DATA MANAGEMENT AND QUALITY ASSURANCE

Data was coded and single-entered into Epi Info software version 7.2.0.1. A pre-test of the questionnaire and data collection form in appendix B was done on 10 patients on IPT who were attending KNH-CCC before initiating data collection. The findings from the pre-test were used to improve the design of the data collection tools.

All data entries were double checked against source document by the lead investigator. Data generated during the study was subjected to a quality audit to ensure they conformed to the protocols by the investigator.

3.10 STUDY VARIABLES

The primary outcomes of interest were hepatotoxicity and nephrotoxicity. The secondary outcomes of interest were peripheral neuropathy, gastrointestinal disturbances, neuropsychiatric and hypersensitivity reactions. For regression analysis, the only outcome variables that were considered were hepatotoxicity and nephrotoxicity.

The key independent variable was isoniazid preventive treatment. Other independent variables included patient demographic characteristics such as age, gender, education, occupation, marital status and body mass index (BMI).

Data on possible confounding variables such as alcohol consumption, smoking, co-medications (including HAART regimen) and co-morbidities were collected. Laboratory parameters such as ALT levels and creatinine were also recorded both at baseline and after IPT initiation.

3.11 DATA ANALYSIS

Data analysis was done using STATA software version 13 (StataCorp USA). It was divided into three phases; descriptive, exploratory and regression analysis.

In descriptive analysis, all continuous variables were tested for normal distribution by Shapiro Wilk test and visual inspection of histograms before summarizing data into percentages and averages. Variables that were normally distributed were summarized as mean and standard deviation of the mean.

Variables that were not normally distributed were presented as median and interquartile range. Categorical variables were summarized as frequencies and percentages. Baseline socio-demographic characteristics of participants on IPT and those not on IPT were summarized and compared across arms.

Exploratory analysis was done through correlation testing and comparative analysis of variables in patients on IPT and those not on IPT. Comparative analysis was done by inferential testing using Paired t test and Signed Rank test.

Regression analysis was done for the following dependent variables; hepatotoxicity and nephrotoxicity. The continuous measures for liver and renal toxicity were converted to binary variables. Logistic regression analysis was done to identify risk factors for ADRs. Model building using a forward stepwise building approach starting with bi-variable analysis. The primary independent variable was use of IPT. The level of significance was set at 0.05.

3.12 ETHICAL CONSIDERATIONS

Ethical approval was sought from KNH/ UoN Ethics and Research Committee (Ref No; P43/01/2018) in appendix C.

Informed consent was obtained from the participants before they were recruited in the study. Potential participants were informed about the purpose of the study, procedures to be carried out, potential benefits and harms and their rights during the study period using the Informed Consent Form in appendix A.

All the information that was obtained from the patients was treated with confidentiality. Serial numbers were used instead of participant names to protect patient's identity. Only relevant information was obtained from the participant's records and materials used to collect data were locked up in a secure cabinet only accessible to the lead investigator.

CHAPTER 4: RESULTS

The results are presented in two different sections; the first part (section 4.1) describes findings of longitudinal cohort study. Database review was done for HIV positive patients on IPT to collect information on ALT and creatinine in order to establish incidence of hepatotoxicity and nephrotoxicity respectively.

The second part (section 4.2) presents findings of comparative cross sectional study of HIV patients on IPT and those not on IPT. This involves interview of these patients and use of their medical records to obtain information on incidence of ADRs based on sign and symptoms reported by the patients.

4.1 : LONGITUDINAL COHORT STUDY

4.1.1 : Patient characteristics on Isoniazid Preventive Therapy

This was a cohort of 592 ART patients who were started on IPT in Kenyatta National Hospital from January 2011 to June 2018. Their mean age was 45.1 years (SD 10.5 years) and majority of the patients (66%) were females. This cohort of patients had been on ART for a median of 55.4 months while mean duration of IPT was 5.6 months. Majority (94.3%) were on cotrimoxazole during IPT (Table 4.1).

Majority (91.9%) of the patients were still taking HAART and regularly attending the clinic at the time of analysis. For those who were no longer attending the clinic, 1.4% had died while 4.6% were lost to follow-up and 2.2% had been transferred to other facilities. Patients who were lost to follow-up could have been as a result of death, ADRs or non-compliance.

Table 4.1: Socio-demographic characteristics of patients on Isoniazid Preventive Therapy

Variable	Frequency (%)
Mean age (SD)	45.1 (10.5)
Gender	
Female	391 (66.0)
Male	201 (34.0)
Education level	
None	4 (0.7)
Primary	81 (13.7)
Secondary	121 (20.4)
College/University	82 (13.9)
Missing	304 (51.4)
Duration of ART in months, median (IQR)	55.4 (16.8-89.9)
Mean duration of IPT in months (SD)	5.6 (0.2)
Weight in Kg	
During IPT	67.6 (17.7)
Baseline	70.0 (17.1)
On Cotrimoxazole	
Yes	558 (94.3)

4.1.2 : HAART regimens of patients on Isoniazid Preventive Therapy

As shown in Table 4.2, most of the patients (75.7%) were on TDF based regimens followed by AZT (19.6%) and ABC based regimens (4.7%). Majority of the patients (85.5%) were on first line HAART regimens; while those on second and third therapy were 14.3% and 0.2% respectively.

Table 4.2: HAART regimens of patients on Isoniazid Preventive Therapy

Variable	Frequency (%)
TDF based regimens	**448 (75.7%)**
TDF/3TC/EFV	336 (56.8)
TDF/3TC/NVP	30 (5.0)
TDF/3TC/LPVr	38 (6.4)
TDF/3TC/DTG	31 (5.2)
TDF/3TC/ATVr	12 (2.0)
TDF/3TC/RAL/DRV	1 (0.2)
AZT based regimens	**116 (19.6%)**
AZT/3TC/NVP	41 (6.9)
AZT/3TC/EFV	49 (8.3)
AZT/3TC/LPVr	15 (2.5)
AZT/3TC/ATVr	10 (1.7)
AZT/3TC/DTG	1 (0.2)
ABC based regimens	**28 (4.7%)**
ABC/3TC/EFV	11 (1.9)
ABC/3TC/NVP	6 (1.0)
ABC/3TC/LPVr	7 (1.2)
ABC/3TC/ATVr	3 (0.5)
ABC/3TC/DTG	1 (0.2)

Abbreviations: TDF- Tenofovir; 3TC- Lamivudine; EFV- Efavirens; NVP- Nevirarapine; LPVr-Lopinavir; DTG- Dolutegravir; ATVr- Atazanavir; RAL- Raltegravir; DRV-Darunavir; AZT-Zidovudine; ABC-Abacavir.

4.1.3 : LIVER AND RENAL INJURY DURING ISONIAZID PREVENTIVE THERAPY

There was an increase in incidence of hepatotoxicity during IPT by 4.4%. Out of 385 patients who had normal liver functions at baseline, 17 developed hepatotoxicity during IPT.

Patients with abnormal ALT levels (ALT $\geq$ 40 µ/l) increased from 11.7% at baseline to 15.6% during IPT (p=0.056). ALT was significantly higher during IPT (median 27 µ/l) compared to baseline (22 µ/l), (p<0.001).

There was a significant reduction of patients with renal impairment by 4.8% during IPT among 562 patients whose creatinine were taken at baseline and during IPT. Patients with normal kidney functions increased from 31.5% at baseline to 36.3% during IPT (p=0.036).

Creatinine levels decreased from a median of 83.7 µmol/L at baseline to 79 µmol/L during IPT (p=0.001). This translated to an increase in eGFR from a median of 76.3 ml/min/1.73m^2 to 80.5 ml/min/1.73m^2 (p<0.001) (Table 4.3).

Table 4.3: ALT and creatinine levels at baseline and during IPT

Variable	**Baseline**	**During IPT**	**P value**
ALT	n=436	n=436	
Median (IQR)	22.0 (15.0-31.0)	27.0 (19.0-38.0)	**<0.001**
Category, n (%)			
Normal	385 (88.3)	368 (84.4)	**0.056**
Mild	46 (10.6)	60 (13.8)	
Moderate	5 (1.1)	6 (1.4)	
Life threatening	0	2 (0.5)	
Creatinine	n=562	n=562	
Median (IQR)	83.7 (69.5-99.0)	79.0 (64.9-96.0)	**0.001**
eGFR	n=562	n=562	
Median (IQR)	76.3 (61.5-96.6)	80.5 (63.4-102.9)	**<0.001**
Category, n (%)			
Normal	177 (31.5)	204 (36.3)	**0.036**
Mild impairment	262 (46.6)	245 (43.6)	
Moderate impairment	110 (19.6)	105 (18.7)	
Severe impairment	8 (1.4)	5 (0.9)	
Established renal failure	5 (0.9)	3 (0.5)	

4.1.4 : Assessment of severity of hepatotoxicity and nephrotoxicity

During IPT, majority of the patients had mild hepatotoxicity (13.8%), those with moderate were 1.4% and 0.5% had a life threatening hepatotoxicity. The prevalence of all levels of liver severity increased during IPT (Figure 4.1).

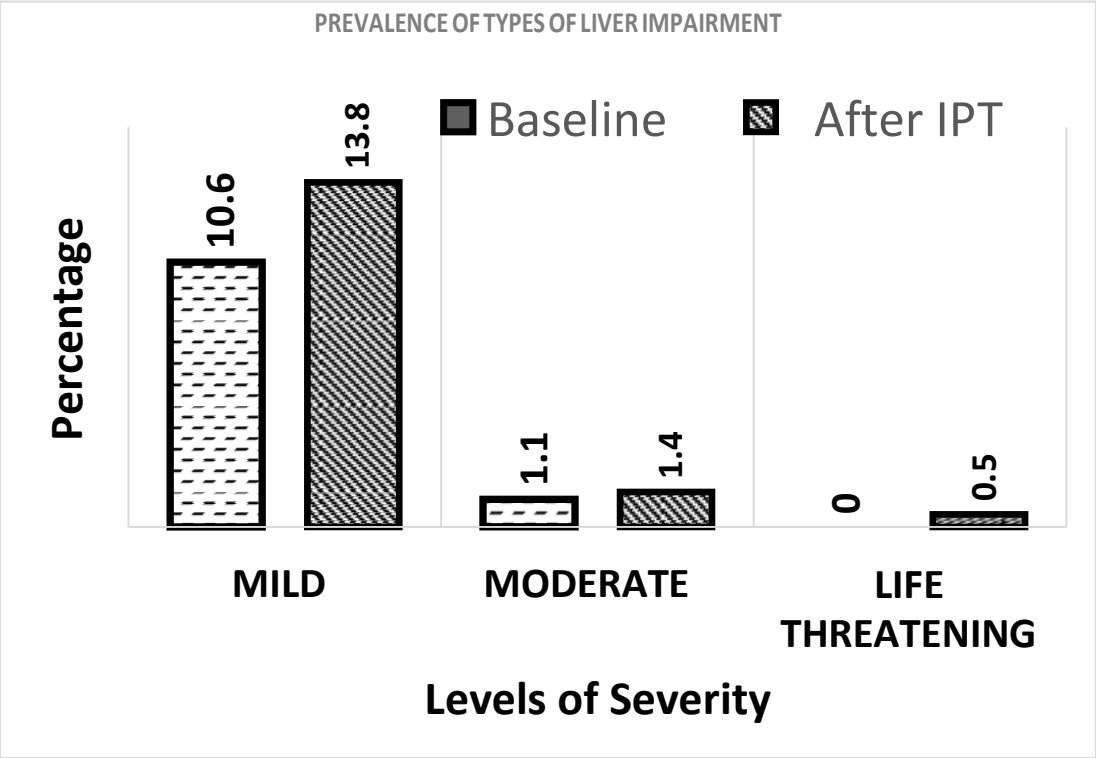

Figure 4.1: Changes in the prevalence of the various categories of hepatotoxicity after IPT initiation

Majority of the patients with nephrotoxicity during IPT had mild nephrotoxicity (43.6%), followed by moderate (18.7%) and 0.9% had severe nephrotoxicity. The proportion of the patients in each of these three categories decreased during IPT (Figure 4.2).

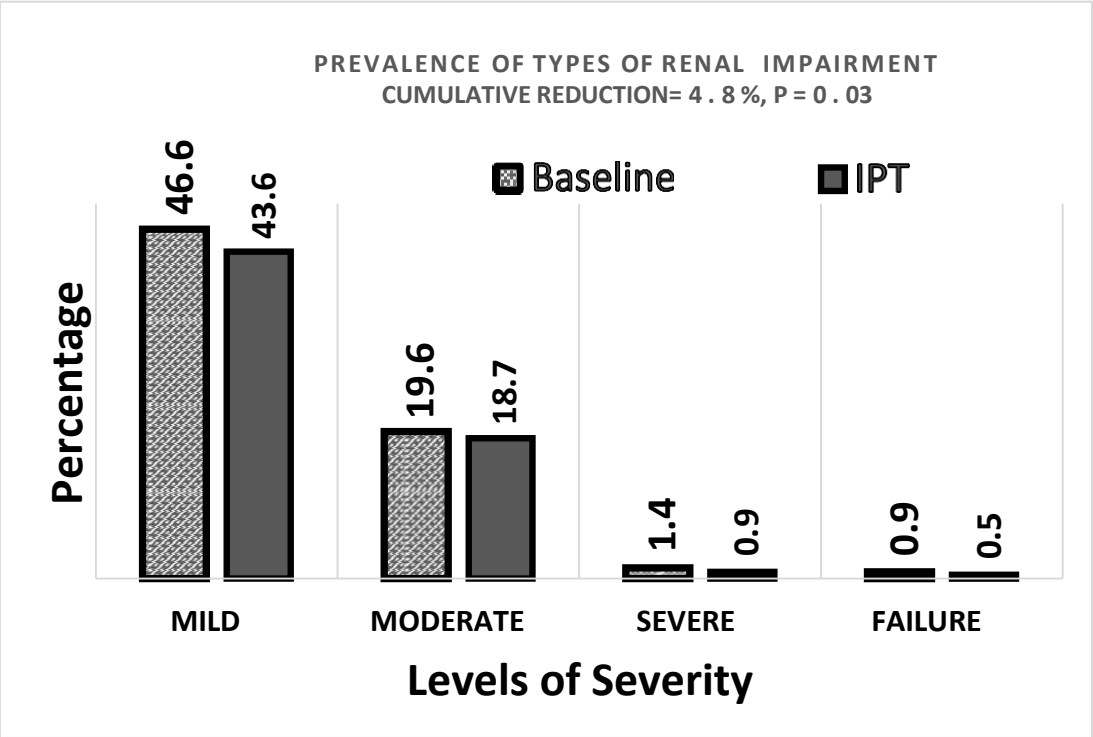

Figure 4.2: Changes in prevalence of the various categories of nephrotoxicity after IPT initiation

4.1.5 : Risk factors for hepatotoxicity and nephrotoxicity during Isoniazid Preventive Therapy

Male patients had a significantly higher prevalence of liver disease (27.5%) compared with females (9.9%), p<0.001. Age, duration of IPT and ART regimens were not significantly associated with liver disease.

Patients with renal failure were significantly older (mean 47.2 $\pm$ SD) compared to those with normal eGFR (mean 40.3 $\pm$ SD), p<0.001.

Females had significantly higher prevalence of renal disease (81.8%) compared to males (44.8%), p<0.001. Similarly, patients on ABC based regimens had significantly higher prevalence of renal disease compared to other regimens, (p 0.040). Duration on ART and IPT were not significantly associated with renal failure (Table 4.4).

Table 4.4: Risk factors for hepatotoxicity and nephrotoxicity

	Hepatotoxicity		
Variable	**High ALT (Above 40 µ/l) n (%)**	**Normal ALT (Below 40 µ/l) n (%)**	**P value**
Mean age (SD)	45.5 (8.6)	44.4 (11.1)	0.451
Sex			
Female	29 (9.9)	265 (90.1)	**<0.001**
Male	39 (27.5)	103 (72.5)	
Median duration on ART in months (IQR)	42.9 (12.4-89.6)	54.1 (15.0-88.8)	0.505
Mean duration of IPT in months	5.6 (0.1)	5.6 (0.1)	0.292
ART regimens			
TDF- based	51 (15.3)	282 (84.7)	0.517
AZT- based	13 (14.9)	74 (85.1)	
ABC-based	4 (25)	12 (15)	
	Nephrotoxicity		
Variable	**High eGFR (above 50 ml /min/1.73m^2)**	**Normal e GFR**	**P value**
Mean age (SD)	47.2 (9.8)	40.3 (10.7)	**<0.001**
Sex			
Female	320 (81.8)	71 (18.2)	**<0.001**
Male	90 (44.8)	111 (55.2)	
Median duration of ART in months (IQR)	56.6 (17.8-89.9)	51.8 (14.4-89.6)	0.344
ART regimen			
TDF-based	310 (69.2)	138 (30.8)	**0.040**
AZT-based	75 (6.7)	41 (35.3)	
ABC-based	25 (89.3)	3 (10.7)	

4.5.1: Prevalence of opportunistic infections in patients on Isoniazid Preventive Therapy

The prevalence of opportunistic infections increased from 1.4% to 4.1 % during IPT. There was 0.4% increase in incidence of pulmonary TB after IPT. Most of the 24 reported OIs were infections of the respiratory tract (58%), including upper respiratory tract infections (URTIs), pneumonia and pulmonary TB (Table 4.5).

Table 4.5: Opportunistic infections during IPT

Variable	**Before IPT n (%)**	**After IPT n (%)**	**P value**
OIs diagnosed			
Yes	8 (1.4)	24 (4.1)	< **0.001**
URTI	1 (0.2)	6 (1.0)	0.184
Pneumonia	0	6 (1.0)	0.580
Skin condition	2 (0.3)	4 (0.7)	0.583
HIV-associated nephropathy	0	3 (0.5)	0.105
TB	1 (0.2)	2 (0.4)	0.352
Other OIs	4 (0.7)	3 (0.6)	0.096

Abbreviations: URTI-Upper respiratory tract infections

4.2 : COMPARATIVE CROSS SECTIONAL STUDY ON HIV POSITIVE PATIENTS ON IPT

A comparative cross sectional study was done through patient's interview and review of patient's medical records. The aim of this study was to determine if there is significant difference in incidence if ADRs in patient on IPT and those not on IPT. Some of the data that was obtained included presence of ADRs through evaluation of signs and symptoms, the outcome of ADRs and other co-morbidities. Presence of other risk factors for INH induced ADRs such as alcohol intake, smoking and pregnancy were also evaluated.

Among the 264 patients who were recruited, majority were on IPT 149 (56.4%) while 115 (43.6%) were on IPT. The mean duration of IPT use was 107.9 days. Mean age of patients on IPT 41.6 years ($\pm$ SD). More females (63.1%) were on IPT compared to those not on IPT (48.7%), p= 0.019. There were no other significant differences in patients on IPT and those not on IPT regarding age, alcohol intake, smoking and pregnancy status.

Most of the patients were on TDF-based regimens 181 (70.6), followed by AZT 66 (25.9) and ABC 9 (3.5). There were no significant differences in ART regimens in patients on IPT and those not on IPT (Table 4.6).

Table 4.6: Characteristics of participants on IPT and those not on IPT recruited in April 2018

Variable	On IPT (n %)	Not on IPT (n %)	P value
Mean age (SD)	41.6 (13.4)	41.0 (12.4)	0.728
Gender			
Female	94 (63.1)	56 (48.7)	**0.019**
Male	55 (36.9)	59 (51.3)	
Marital status			
Married	64 (43.2)	53 (47.7)	0.731
Single	57 (38.5)	42 (37.8)	
Divorced	14 (9.5)	10 (9.0)	
Widowed	13 (8.8)	6 (5.4)	
Education			
None	5 (3.4)	3 (2.7)	0.865
Primary	50 (34.0)	36 (31.9)	
Secondary	56 (38.1)	41 (36.3)	
Tertiary	36 (24.5)	33 (29.2)	
Alcohol use			
Never	127 (85.1)	89 (77.4)	0.187
Occasionally	19 (12.8)	20 (17.4)	
Regularly	3 (2.0)	6 (5.2)	
Smoking status			
Current smoker	5 (3.4)	5 (4.3)	0.743
Never smoked	132 (88.6)	101 (87.8)	
Previously smoked	12 (8.1)	9 (7.8)	
Pregnant			
Yes	8 (8.5)	4 (7.1)	1.000
No	86 (91.5)	52 (92.9)	
Mean BMI (SD)	25.7 (5.4)	25.0 (4.6)	0.278
ART regimens			
TDF	110 (74.8)	70 (64.8)	0.193
AZT	32 (21.8)	34 (31.5)	
ABC	5 (3.4)	4 (3.7)	

4.2.2 : Prevalence of comorbidities in patients on IPT

As shown in table 4.7, the most prevalent comorbidity was hypertension (6%), followed by TB (5.7%), peptic ulcer disease (4.2%), diabetes (2.7%) and renal disease (2.7%).

Table 4.7: Comorbidities in patients on IPT

Variable	Frequency (%)
Hypertension	16 (6.0)
TB	15 (5.7)
PUD	11 (4.2)
Diabetes	7 (2.7)
Renal disease	7 (2.7)
Asthma	4 (1.5)
URTI	3 (1.1)
History of renal disease	2 (0.8)
History of surgery	2 (0.8)
Stroke	2 (0.8)
UTI	2 (0.8)
Others	9 (3.6)

Abbreviations: PUD-Peptic ulcer disease, URTI- Upper respiratory tract infections, UTI- Urinary tract infections, ENT- Ear nose and throat infections

4.2.3 : Prevalence of adverse drug reactions in patients using Isoniazid Preventive Therapy

Among patients who used IPT, 36.9% reported to have experienced ADRs. The most prevalent ADRs were peripheral neuropathy 8.7%, skin rashes 6.7%, hepatotoxicity 4.7% and gastrointestinal symptoms 5.3%. One patient developed erectile dysfunction which is usually rare ADR associated with IPT and the symptoms resolved after withdrawal of the drug. The prevalence of hepatotoxicity in both prospective and retrospective studies were almost similar; 4.7 and 4.4% respectively. Other non- specific symptoms were headache, weight loss and fatigue (Table 4.8).

Table 4.8: Prevalence of adverse drug reactions in patients on IPT

Variable	Frequency (%)
Presence of any ADRs	55 (36.9)
Peripheral neuropathy	13 (8.7)
Skin rashes	10 (6.7)
Gastrointestinal	8 (5.3)
Hepatotoxicity	7 (4.7)
Blurred vision	3 (2.0)
Reproductive	2 (1.3)
Psychiatric	2 (1.3)
Cardiovascular	2 (1.3)

4.2.4 : Adverse drug reactions by Isoniazid Preventive Therapy use status

Patients who had used IPT were more likely to report any ADR sign (36.9%) compared to those who had never used IPT (25.2%); OR 1.7 (95% CI 1.2-3.0). The prevalence of peripheral neuropathy was higher in patients on IPT compared to those not on IPT though this difference was not statistically significant (p=0.086). Patients with peripheral neuropathy presented with numbness and painful feet, muscle weakness, tingling and burning sensations. Similarly hepatotoxicity was 5 times more common in those on IPT though it was not statistically significant (p=0.143). Presenting symptoms for hepatotoxicity were yellow discoloration of eyes and urine, loss of appetite, lethargy and pale stool (Table 4.9).

Table 4.9: Adverse drug reactions by IPT use status

Variable	IPT use		OR (95% CI)	P value
	Yes (n %)	**No (n %)**		
Any ADR sign	55 (36.9)	29 (25.2)	1.7 (1.2-3.0)	**0.043**
Peripheral neuropathy	13 (7.4)	3 (2.6)	3.0 (0.8-10.9)	**0.086**
Skin rash	10 (6.7)	3 (2.6)	2.7 (0.7-10.0)	0.127
Hepatotoxicity	7 (4.7)	1 (0.9)	5.6 (0.7-46.3)	0.143
Gastrointestinal	8 (5.3)	5 (3.3)	0.4 (0.1-1.3)	0.098

4.2.5 : Risk factors for adverse drug reactions

Older patients (mean 47 ±SD) reported more ADRs 14.3% compared to 11% in those of younger age (mean 39 ±SD), (p =0.002). The prevalence of ADRs was also higher in patients with hypertension than those without hypertension, (p =0.068). Similarly, patients with diabetes also had higher prevalence of ADRs (75%) than those without diabetes (25%), (p =0.049). Apart from IPT and HAART, patients with diabetes and hypertension were also receiving other co-medications. Gender, smoking, alcohol intake, pregnancy and ART regimens were not significantly associated with prevalence of ADRs in patients on IPT (Table 4.10).

In management of ADRs, no action was taken for majority of the cases (73.9%), while IPT was withdrawn in 24.6% and additional drugs were required in 1.4%.

Table 4.10: Risk factors for adverse drug reactions

Variable	On IPT			Not on IPT		
	ADRs n (%)	No ADRs n (%)	P value	ADRs n (%)	No ADRs n (%)	P value
Mean age (SD)	43.3 (12.7)	40.6 (13.8)	0.224	47.0 (14.3)	39.0 (11.0)	**0.002**
Gender						
Female	31 (33.0)	63 (67.0)	0.193	14 (25.0)	42 (75.0)	0.958
Male	24 (43.6)	31 (56.4)		24 (43.6)	44 (74.6)	
Hypertension	12 (57.1)	9 (42.8)	**0.068**	1 (16.7)	5 (83.3)	1.000
History of TB	4 (36.4)	7 (63.6)	1.000	0	4 (100.0)	0.571
Diabetes	2 (66.7)	1 (33.3)	0.555	3 (75.0)	1 (25.0)	**0.049**
Renal disease	0	5 (100.0)	0.158	1 (25.0)	3 (75.0)	1.000
TDF-based	1 (33.3)	2 (66.7)	1.000	2 (28.6)	5 (71.4)	1.000
AZT-based	3 (37.5)	5 (62.5)	1.000	0	5 (100.0)	0.328
ABC-based	5 (31.3)	11 (68.8)	0.786	2 (16.7)	10 (83.3)	0.726
Alcohol use						
Never	46 (83.6)	80 (86.0)	0.645	21 (72.4)	68 (79.1)	0.652
Occasionally	7 (12.7)	12 (12.9)		6 (20.7)	14 (16.3)	
Regularly	2 (3.6)	1 (1.1)		2 (6.9)	4 (4.7)	
Smoking						
Current	0	4 (4.3)	0.407	0	5 (6.3)	0.147
Previous	5 (9.6)	7 (7.6)		4 (13.8)	4 (5.1)	
Never	47 (90.4)	81 (88.0)		25 (86.2)	70 (88.6)	
Pregnancy	3 (9.7)	5 (7.9)	0.753	1 (7.1)	3 (7.1)	1.000

CHAPTER 5: DISCUSSION

5.1 : Incidence of adverse drug reactions

Isoniazid preventive therapy has been recommended for use in HIV positive patients since it reduces the risk of developing latent TB by 33%. Despite its use; IPT is claimed to cause asymptomatic elevations of serum transaminase liver enzymes in 10-20% of the patients and other ADRs such as peripheral neuropathy [7].

In this study, 36.9% of the patients on IPT were more likely to report any ADR sign compared to those who had never used IPT (25.2%), OR 1.7 (95% CI 1.2-3.0), p=0.043. This is higher prevalence compared to a longitudinal study that was conducted in Kenya in 2015 among children using IPT in which 22% of them experienced ADRs related to IPT [41].

Prevalence of hepatotoxicity in both prospective and retrospective studies were almost similar; 4.7 and 4.4% respectively. Majority of the patients had mild hepatotoxicity (13.8%), followed by moderate (1.4%) and severe liver injury (0.5%).

The severity of liver injury increased in all the three categories of patients. Incidence of severe liver injury was lower compared to that of a clinical trial carried out in Botswana among 1762 HIV positive patients on IPT which reported incidence of severe hepatitis of 1.9% [36].

There was a significant reduction of patients with renal impairment by 4.8% among 562 HIV positive patients on IPT. This is a unique finding as no other studies have shown similar results. Other confounding variables such as co-treatments and severity of HIV illness may have had impact on the kidney functions in addition to IPT.

5.2 Risk factors and outcomes for adverse drug reactions

Older age was also significantly associated with renal failure in which older patients above 47 years had high risk compared to young patients below 40 years, p<0.001. Australian study indicated that among 6% of patients on IPT experienced WHO grade 3-4 ADRs; older age was significantly associated with risk of ADRs [17].

Similarly, females had a higher prevalence of renal failure (81.8%) compared to males (44.8%), p<0.001. Duration on ART and IPT were not significantly associated with renal failure.

Other risk factors associated with isoniazid toxicity that were not analyzed in this study were slow acetylator status, hepatitis B and C co-infection and use of other hepatotoxic drugs. Study done in Tunisia found that high serum concentrations of isoniazid above 3.6 mg 1^{-1} and a combined genotype CYP 2E1 (C/D) /slow acetylator are major risk factors for isoniazid toxicity [39].

Most of the patients (73.9%) continued with treatment without any interruption, 24.6% had treatment withdrawn as a result of ADRs, while 1.4% needed additional drugs to manage ADRs. This was almost comparable to Australian study in which 85% of the patients completed treatment while 10% stopped treatment as a result of side effects [41].

According to Malaysia study, 81.1% of the patients completed IPT while the remaining discontinued due to ADRs and loss to follow up. Another retrospective study conducted in San Diego, USA among 3,788 patients on IPT reported that 1.4% stopped treatment due to side effects [1, 52].

Study limitations

This study had some limitations which include selection bias since the ALT and creatinine tests were initiated by clinicians depending on clinical assessment and may have fallen short of an objective assessment. Other study limitation is sample size determination whereby the two studies on which sample size calculation was done varied grossly in setting. One study was conducted in Kenya while the comparative study was done in Canada whereby the two study populations may have different genetic predispositions which influence prevalence of ADRs.

Other study limitation include failure to collect information on other co-medications that patients where using apart from IPT which may have contributed to the ADRs. Information from database review of patients on IPT was incomplete in that such critical information like co-medications was missing. Severity of HIV disease was not controlled and this may have introduced possible confounding variable.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 : Conclusion

Patients on IPT were more likely to report ADRs than those not on IPT. Prevalence of hepatotoxicity was 4.4% with majority of cases being mild. Risk factors for hepatotoxicity were male gender and older age. One in two hundred patients developed life threatening liver injury. Other main ADRs were peripheral neuropathy, skin rashes and gastrointestinal. Unexpectedly, there was improvement of renal functions in patients on IPT by 4.8%. Older, diabetic and hypertensive patients had higher overall incidence of ADRs.

6.2 : RECOMMENDATIONS

6.2.1 Recommendations for practice

1. Given the low incidence of severe ADRs associated with IPT, the current policy recommendation on use of IPT may be safe on HIV positive patients.

2. Routine monitoring of patients on IPT is recommended especially for at-risk patients such as the elderly, diabetic and hypertensive.

3. Rare ADRs such as erectile dysfunction and blurred vision require more pharmacovigilance monitoring.

4. Any mortalities and loss to follow up should be carefully investigated to establish causality given that there were eight cases of mortalities of HIV positive patients on IPT.

6.2.2: Recommendation for future research

Further research is needed to definitely establish if IPT improves renal functions given that, in this study, eGFR was observed to improve during IPT. More studies are required to confirm rare ADRs such as erectile dysfunction and blurred vision in patients on IPT. Large sample size is needed to establish some of the risk factors associated with use of IPT such as alcohol intake, female gender, pregnancy and slow acetylator status. The efficacy of IPT need to be consistently monitored given that one patient developed TB while on IPT.

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