RISK FACTORS, MANAGEMENT AND OUTCOMES OF DRUG INDUCED HEPATIC INJURY AMONG ADULT PATIENTS WITH LIVER DISEASE AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This dissertation is my original work and to the best of my knowledge has not been presented for a degree in any other University and where other people's work or my own work has been used, this has properly been acknowledged and referenced in accordance with the University of Nairobi's requirements.

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DEDICATION

To my father Mr.Cosmas Asin and my mother Mrs. Jane Asin who instilled the value of education as well as the fundamental skills of life in me from childhood.

To my loving husband Lawrence Ofula who has tirelessly stood by my side with constant support and prayers during this study period and always.

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LIST OF ABBREVIATIONS

ADRs: Adverse Drug Reactions

AIDS: Acquired Immune Deficiency Syndrome

ALT: Alanine transaminase

ART: Antiretroviral Therapy

AST: Aspartate transaminase

CYP450: Cytochrome P450 enzyme system

DILD: Drug-induced Liver Disease

DILI: Drug-induced Liver Injury

HIV: Human Immunodeficiency Virus

KNH: Kenyatta National Hospital

LFTs: Liver Function Tests

NSAIDS: Non-steroidal Anti-inflammatory Drugs

OTC: Over the Counter Medications

SNP: Single Nucleotide Polymorphism

STD: Sexually Transmitted Disease

TB: Tuberculosis

UoN/KNH-ERC: University of Nairobi/Kenyatta National Hospital Ethics and Research Committee

USA: United States of America

WHO: World Health Organization

TABLE OF CONTENTS

Title **Page**

LIST OF TABLES

LIST OF FIGURES

DEFINITION OF TERMS

Adverse drug reactions – These are responses to medicinal products which are injurious, noxious and unintended.

Drug-drug interactions – These are the reactions that occur when a drug interacts or interferes with another drug in such a way as to alter the way one or both of the drugs act in the body or cause unexpected side effects.

Drug-induced Liver Disease – It is a type of liver disease that is caused or worsened by physician-prescribed medications, over-the-counter medications, vitamins, hormones, herbs, illicit ("recreational") drugs and environmental toxins.

Fulminant hepatitis – It is the severe impairment of hepatic functions or severe necrosis of hepatocytes in the absence of pre-existing liver disease.

Genetic polymorphism – Defines the natural variations in a gene, DNA sequence, or chromosome that have no adverse effects on the individual and occur with fairly high frequency in the general population. Polymorphism involves one of two or more variants of a particular DNA sequence.

Haptens – These are small molecules which when combined with a larger carrier such as a protein, can elicit the production of antibodies that bind specifically to them (in the free or combined state) and thereby causing an immune response.

Herbs - These are any plants with leaves, seeds or flowers that are used for flavoring, food, medicine or perfumes.

Mallory bodies – These are damaged intermediate filaments within the hepatocytes which occur as inclusions found in the cytoplasm of liver cells. They are also known as Mallory-Denk bodies or Mallory's hyaline.

Neoantigens – These are antigenic proteins formed by metabolic pathways like drug metabolism.

Over-the-counter medications – These are medicines sold directly to a consumer without a prescription from a healthcare professional.

Prescription drugs – These are pharmaceutical drugs that legally require a medical prescription to be dispensed. They are also known as prescription medications or prescription medicines.

Refractory to therapy – Refers to a situation in which there is resistance to treatment during provision of therapy.

Single Nucleotide Polymorphism – Refers to a variation in a single base pair in a DNA sequence.

Xenobiotics – These are foreign chemical substances found within organisms that are not normally naturally produced by or expected to be present within these organisms.

ABSTRACT

Background: Globally, liver injury due to medicines is a growing medical, scientific and public health problem. Over the past two decades, reports from World Health Organization have shown that there has been a rising number of patients with drug induced liver disease. Published literature on the local prevalence of possible drug-induced liver disease cases, associated risk factors as well as management of these conditions remains scanty.

Study Objectives: To assess drug induced liver disease in adult patients with liver disease with respect to the prevalence, risk factors, management and outcomes.

Study Design: A cross-sectional survey of adult patients with liver disease.

Study Area: Kenyatta National Hospital Liver Clinic and Medical Wards.

Study Population: Four hundred and eighty five patients (485) aged 18 years and above, with diagnosed liver disease who met the study inclusion criteria.

Methods: Patients attending the liver clinic were recruited consecutively as they came for their appointments. Those in the medical wards were selected consecutively using the admission list and then followed into the wards using their names and patient numbers.

Results: There were slightly more males, at 257(53.1%), than females. The mean age of the study participants was 41.4 years (± 14.1). Majority of patients (59.8%) had hepatocellular injury and presented with elevated liver enzymes (97 %) and jaundice (78.4 %). The most frequently used and suspected drug causing liver disease among patients was alcohol at 37.7 %. However, the use of antiretrovirals (OR=0.31; 95 % CI: 0.17-0.57; p=0.05) and alcohol (OR=0.56; 95 % CI: 0.35-0.89; p=0.05) increased the likelihood of having an admission, relapse or death among patients by 31% and 56% respectively.

Most of the management strategies (90.9%) was by withdrawal of the offending agent. Other strategies included use of steroids(OR=2.30;95% CI:1.46-3.64;p<0.00001), antihistamines(OR=4.52; 95% CI: 1.85-11.02;p<0.00001) and vitamin K(OR=3.09; 95% CI:1.82-5.22;p<0.00001) and these were found to increase the likelihood of having a desirable outcome by two times, five times and three times respectively. More than half (55.5 %) of the patients were admitted for more than 10 days during management and mortality was at 7%.

Conclusion and Recommendations: Clinicians should be encouraged to be vigilant in monitoring and counseling liver disease patients who are on antiretrovirals or using alcohol. In addition use of steroids, antihistamines and vitamin K should be encouraged where possible in the management of liver disease patients. Other similar studies should also be carried out in other hospitals so as to improve on the management of liver disease patients. Case control studies should be carried out as well with the aim of determining the cause-effect relationships of the various risk factors associated with liver injury in the country. This may help mitigate the risk factors identified.

1.0 INTRODUCTION

1.1 Background to the Study

Drug-induced liver disease is a disease of the liver that is caused or worsened by prescribed medications, over-the-counter-medications (OTCs), vitamins, hormones, herbs, illicit drugs as well as environmental toxins [1].Globally, liver injury due to prescription and non-prescription medications is a growing medical, scientific and public health problem [2]. The estimated annual incidence rate of drug-induced liver injury (DILI) globally is 13.9-24.0 per 100,000 inhabitants [2]. In the USA, drug induced liver injury accounts for 52% of all liver failure cases and is the leading single cause of withdrawal of approved drugs from the market [3].

There is a marked geographic variation in causative agents of drug induced liver disease. Antibiotics, anticonvulsants and psychotropic drugs have been described as being the most common offending agents in the western countries whereas in Asia, herbs and dietary supplements are the leading causes of drug induced liver disease [2].

1.2 Burden of Drug-induced Liver Disease Locally and Regionally

Due to lack of accurate data as well as many cases going unreported in Africa and other developing countries, DILD was previously believed to be a disease of the developed world [3].However, the various studies which have been done on different types of drugs believed to cause liver injury in many parts of Africa and indeed Kenya over the past years, have focused mainly on antiretrovirals and anti-TB drugs [4, 5, 6]. No studies have been done however on other prescription medicines, OTCs, dietary supplements as well as herbal medications [4, 6]. The aim of this study therefore was to assess drug induced liver disease cases among the adult patients with liver disease at the Kenyatta National Hospital Liver Clinic. Assessment was done with respect to prevalence, risk factors management and outcome of these diseases.

1.3 Problem Statement

As the population around the world continues to rise and with changes in technological advancement, people continue taking more and more drugs including prescription drugs, OTCs, herbal remedies, dietary supplements and alcohol. The liver is the principal organ for metabolizing, inactivating and disposing of these drugs and other chemical substances. The metabolites of these drugs may result to the development of liver disease and complex drug-drug interactions may further complicate the situation. For instance in countries like USA, DILD has become the leading cause of acute liver failure [3].

It has been found that while DILD is slowly becoming a global problem, most clinicians and patients are unaware of this potential disaster and are also unprepared to deal with this condition. The fact that DILD is in most cases not diagnosed and managed early has resulted in increased morbidity and mortality over the years [3].Due to the increased costs and burden that come with having to manage this condition, there are negative economic consequences [3]. Even with this information, very few studies have been conducted on the risk factors, management and outcome of drug-induced liver disease especially in Africa and indeed Kenya.

Studies that have been done in Kenya, for instance, have focused mainly on prevalence of drug induced liver injury caused by antiretrovirals and antituberculosis drugs [4, 6]. In addition, there are few published studies available on drug-induced liver disease in Kenyatta National Hospital.

1.4 Justification of the study

So far prevalence of drug induced liver disease has been reported in the Western countries [3] but few published literature is available in developing countries, especially Kenya. Information on drugs that cause drug-induced liver disease should be available especially in a big referral hospital like Kenyatta National Hospital so as to educate healthcare workers and patients on hepatotoxicity and the ways of curbing it. This will go a long way in ensuring continued patient monitoring and safety. In addition, other risk factors that may predispose patients to drug induced liver disease or exacerbate pre-existing liver disease conditions require to be explored with an aim of their minimization.

More importantly, patterns of drug-induced liver disease, the management interventions applied and outcomes of management should be investigated and evaluated .On evaluation, management strategies which give better outcome can be used to improve the knowledge of the health care providers regarding drug-induced liver disease. Pharmacists may also use the information obtained from this study to improve on their pharmacovigilance, in watching out for those drugs that may predispose a patient to drug-induced liver injury. This information may also be used in patients' monitoring and counseling. Various strategies for risk communication and management on hepatotoxicity can then be developed, implemented and evaluated to enhance patient safety. In addition the information collected will form a database on studies done on DILD at Kenyatta National Hospital, in particular and in Kenya as whole.

1.5 Objectives

1.5.1 Broad objective

To assess risk factors, management and outcome of Drug-induced Liver Disease among adult patients with liver disease at Kenyatta National Hospital (KNH) Liver clinic.

1.5.2 Specific objectives

1. To determine the prevalence of Drug induced Liver Disease among adult patients with liver disease at Kenyatta National Hospital Liver clinic.
2. To describe the pattern of drug induced liver injury amongst adult patients with liver disease at KNH liver clinic.
3. To find out the risk factors associated with Drug-induced liver Disease in the adult patients with liver disease at KNH liver clinic.
4. To evaluate the management strategies and outcomes of Drug-induced Liver Disease among patients with liver disease at KNH liver clinic.

1.6 Research questions

1. What is the prevalence of drug induced liver disease among adult patients with liver disease at KNH liver clinic?

2. What are the drugs that predispose patients to drug induced liver disease?

3. What is the pattern of the liver injury caused by the drugs in patients with liver disease at KNH liver clinic?

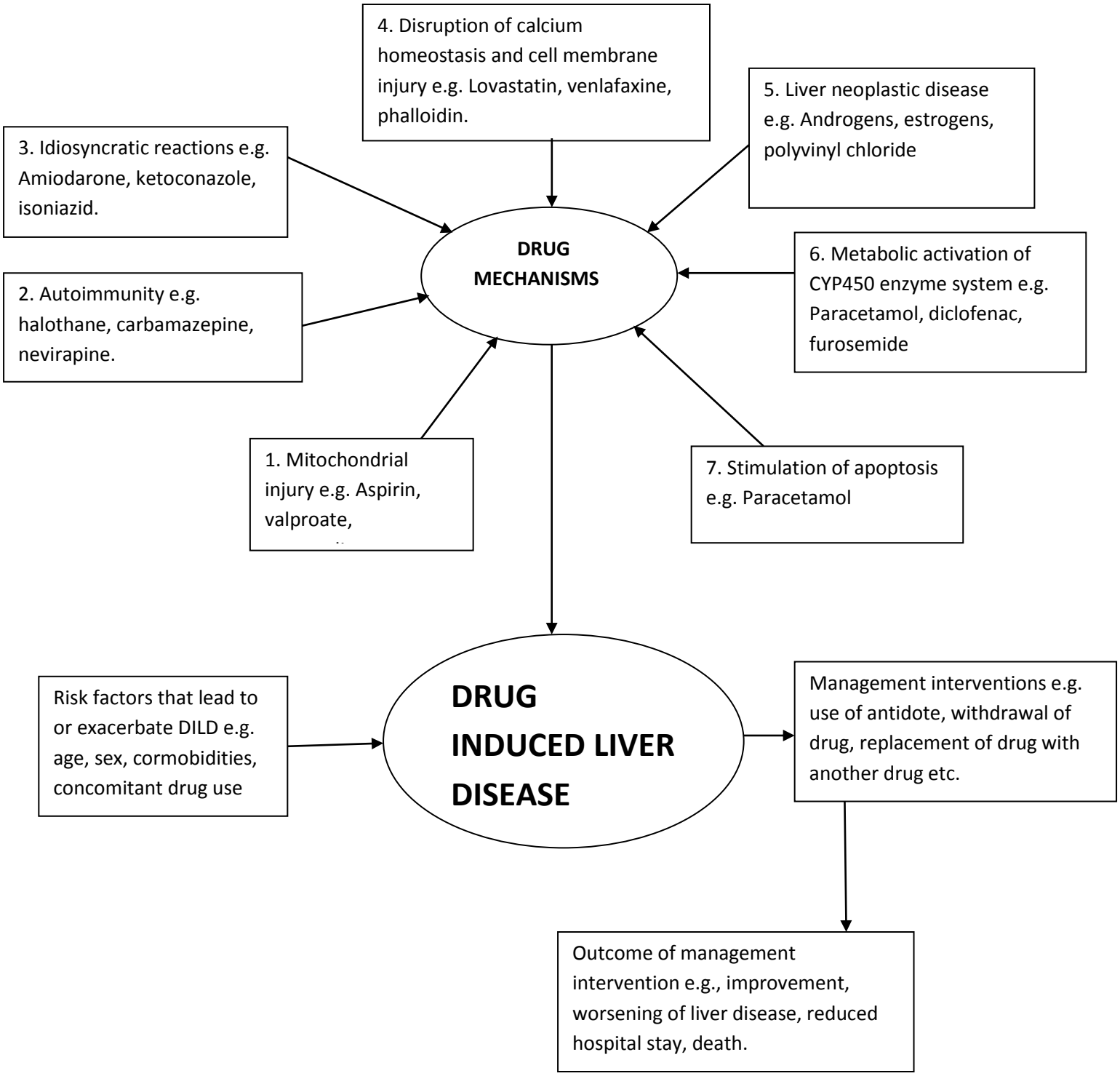
4. What are the risk factors associated with drug-induced liver disease in patients with liver disease at KNH?

5. What is the management pattern and outcome of drug induced liver injury among the patients?

1.7 Benefits from the Study

The findings obtained from this study will help the health care professionals to improve on their knowledge and management strategies of drug-induced liver disease. Patients attending the liver clinic and those who might be admitted to the medical wards after the release of these findings in the future will also benefit from improved service and patient care as well.

1.9 Conceptual Framework



2.0 LITERATURE REVIEW

2.1 Drugs Associated with Drug-induced Liver Disease

The number of drugs associated with adverse reactions involving the liver is extensive [7]. Drug-induced liver disease clinically presents in several ways: idiosyncncratic reactions, allergic hepatitis, toxic hepatitis, chronic active toxic hepatitis, toxic cirrhosis and liver vascular disorders. The mechanisms of DILD are diverse, representing many phases of biotransformation and are susceptible to genetic polymorphism [8].A study in 2010 to investigate nevirapine associated hepatotoxicity among women in Kenya, Zambia and Thailand showed that out of the 820 women who participated in the study, 41 of them developed severe hepatotoxicity while 3 of them died with symptoms suggestive of hepatotoxicity [6].

Similarly, a study in UK by Bjornsson *et al* found out that the drugs that were most commonly associated with liver disease were amoxicillin- clavulanate, diclofenac, azathioprine, infliximab and nitrofurantoin [9].Marzuki *et al*, in a study on prevalence and risk factors of anti-TB drug induced hepatitis concluded that 9.7% of the total number of patients studied developed signs of hepatotoxicity after using these drugs [10].Alcohol-induced liver disease has also been cited as the most common type of DILD. It has been found that all the other drugs together account for less than 10% of patients hospitalized for elevated liver enzymes. In approximately 75% of these cases, liver transplantation is ultimately required for patient survival [11]. The liver's function affects almost every other organ system in the body, but there are no specific diagnostic tests for DILD or a means to single out an implicated drug. It is therefore important to know the patterns of drug-related pathology in order to assess adverse reactions when they occur [8].

2.1.1 Patterns of Drug-induced Liver Disease

Hepatocellular Injury

Hepatocellular injury is characterized by significant elevations in the aminotransferases in serum which usually precede elevations in total bilirubin levels and alkaline phosphatase levels [12]. Most injuries occur within one year of initiating the offending agent. It can lead to fulminant hepatitis with a corresponding 20% survival rate with supportive care [13]. For those patients who present with the combination of hepatocellular injury and jaundice, there is a 10% mortality

rate [14]. Drugs that have been implicated in causing hepatocellular injury include acarbose, allopurinol, fluoxetine and losartan [8].A study in a Spanish population by Lucena *et al* found out that out of the 461 cases, hepatocellular pattern was the most common at 58% and also had the worst outcomes. Patients with drug-induced hepatocellular jaundice had an 11.7% chance of progressing to death or transplantation [15]

A similar study by Andrade *et al* in Spain concluded that the hepatocellular injury pattern was the most common and most severe [16].Paul Watkins in a report on the biomarkers for the diagnosis and management of DILD stated that hepatocellular injury is generally the most common liver injury pattern. It is also the pattern of greatest concern to patients and physicians because it can evolve quickly and be life threatening even before the development of signs and symptoms [17].Hepatocellular injuries can be further subdivided by specific histological patterns and clinical presentations as described below.

Centrilobular Necrosis

Centrilobular necrosis is often a dose-related, predictable reaction secondary to drugs such as paracetamol. However it can also be associated with idiosyncratic reactions such as those caused by the anaesthetic halothane. Also called direct or metabolite-related hepatotoxicity, centrilobular necrosis is usually the result of the production of a toxic metabolite. The damage spreads outward from the middle of a lobe of the liver [8].A study in a South African population in 1997 on hepatitis caused by halothane concluded that halothane hepatitis remains a major cause of morbidity and mortality in South Africa [18]. Similarly, a study in 2004 on liver transplantation for acute liver failure from DILD in the USA showed that the use of paracetamol alone or in combination with other drugs accounted for 49% of all the cases studied [19].

Patients suffering from centrilobular necrosis tend to present in one of two ways depending on the extent of necrosis. Mild drug reactions, involving only small amounts of parenchymal liver tissue, may be detected as asymptomatic elevations in the serum aminotransferases. If the reaction is diagnosed at this stage, most of these patients will recover with minimal cirrhosis and thus experience minimal chronic liver impairment. More severe forms of centrilobular necrosis are accompanied by nausea, vomiting, upper abdominal pain and jaundice [20, 21]. These reactions are predictable, often dose –related effects in the liver caused by specific agents. When taken in overdose, paracetamol becomes bioactivated to a toxic intermediate known as N-Acetyl-

p-benzoquinone imine (NAPQI).NAPQI is very reactive and with a high affinity for sulhydryl groups [8].

The amino acid glutathione provides a ready source of available sulfhydryl groups within the hepatocyte. When the liver's glutathione stores are depleted and there are no longer sulfhydryl groups available to detoxify this metabolite, it begins to react directly with the hepatocyte. Replenishing the liver's sulfhydryl capacity through the administration of N-acetylcysteine early after ingestion of the overdose normally halts this process [22, 23]. During the first hours of ingestion, some patients report mild symptoms of nausea and vomiting but no elevations of the commonly measured liver enzymes are seen. Elevations in the liver enzymes begin after about 40-50 hours after ingestion [8].

Valproate can also present in this pattern. In the same study in 2004 on liver transplantation for acute liver failure from drug induced liver injury in the U.S.A, valproate was shown to cause 10% of the cases studied [19].Another aggressive form of toxic hepatitis often associated with aspirin use in children is Reyes syndrome. Early in the process of mitochondrial dysfunction, Reyes syndrome leads to the depletion of acyl-coenzyme A and carnitine. Fatty acids then accumulate and gluconeogenesis is impaired resulting in hypoglycemia. A concurrent disruption of the urea cycle occurs subsequently, leading to a decrease in the removal of ammonia and a slowing of protein use. The common findings in this case are usually a threefold rise in the blood ammonia level and an increase in the prothrombin time. In the advanced stages of Reye's syndrome, many patients develop intercranial hypertension that can be life-threatening and refractory to therapy [24, 25].

Steatohepatitis

Also known as steatonecrosis, steatohepatitis is a specialized type of acute necrosis resulting from the accumulation of fatty acids in the hepatocyte. The drugs or their metabolites that cause steatonecrosis do so by affecting fatty-acid oxidation within the mitochondria of the hepatocyte. Hepatic vesicles become engorged with fatty acids, eventually disrupting the homeostasis of the hepatocyte. The liver biopsy is marked by a massive infiltration by polymorphonuclear leukocytes, degeneration of the hepatocytes and the prescence of Mallory bodies [26].

Alcohol is the drug that most commonly produces steatonecrotic changes in the liver. Upon conversion of alcohol into acetaldehyde, the synthesis of fatty acids is increased [27, 28] .When the hepatocyte becomes completely engorged with microvascular fat, it often breaks open and spills into the blood. When enough of the hepatocytes have broken open, an inflammatory response begins. If the offending agent is withdrawn before significant numbers of hepatocytes become necrotic, the process is completely reversible without long-term sequelae. In non-alcoholic steatohepatitis however, the same end point is often achieved through oxidation of lipid peroxidases [29].

A study in 2013 by Opiyo *et al* on the diagnosis of alcohol misuse and alcoholic liver disease in Uganda concluded that both alcohol misuse and alcoholic liver disease was significantly associated with male gender, region of origin, number of lifetime sexual partners and serum albumin below 3.5 mg/dl [30].Tetracycline has also been implicated in causing steatohepatitis and steatosis [31]. The lesions are characterized by large vesicles of fat found throughout the liver. The development of this reaction is related to the high concentrations achieved when tetracycline is given intravenously and in doses greater than 1.5g/day. The mortality of tetracycline steatohepatitis is high (70-80%) and those who survive often develop cirrhosis.

Sodium valproate can also produce steatonecrosis through the process of bioactivation in which cytochrome P450 converts valproate to delta-4-valproic acid, a potent inducer of microvascular fat accumulation [32].Patients experiencing steatohepatitis may present with abdominal fullness or pain as their only complaint. Patients with more severe steatonecrosis will present with all the symptoms characteristic of alcoholic hepatitis such as nausea, vomiting, steatorrhoea, abdominal pain, pruritus and fatigue [8].

Phospholipidosis

This pattern describes the accumulation of phospholipids instead of fatty acids. The accumulated phospholipids usually engorge the lysosomal bodies of the hepatocyte [33].An example of a drug that follows this pattern is amiodarone. Patients treated with amiodarone who develop overt hepatic disease tend to have received higher doses of the drug. These patients also have higher amiodarone-to-N-desethyl-amiodarone ratios, thereby indicating a greater accumulation of the parent compound. A study done in 1990 by Lewis *et al* on the histopathological analysis of

amiodarone hepatotoxicity showed that some of the liver specimens studied developed characteristic lamellar lysosomal inclusion bodies representing phospholipidosis[34] . Amiodarone and its major metabolite N-desethyl-amiodarone remain in the liver of all patients for several months after therapy is stopped. Usually, the phospholipidosis develops in patients treated for more than 1 year. The patient can present with either elevated aminotransferases or hepatomegaly. Jaundice is rare in this case [26, 35].

Generalized Hepatocellular Necrosis

This pattern mimics the changes associated with the common viral hepatitis. The onset of symptoms is usually delayed as much as a week or more after exposure to toxin. Bioactivation is often important for toxic hepatitis to develop but may not be the immediate cause of damage. Many drugs that are associated with toxic hepatitis produce metabolites that are not inherently toxic to the liver. Instead, they act as haptens, binding to specific cell proteins and producing an autoimmune reaction [36]. The rate of bioactivation can vary between males and females and between individuals of the same sex [35, 36]. The cytochrome P450 (CYP450) system tends to metabolize lipophilic substrates that are actively pumped into the hepatocyte by an organic anion (or cation) transporting protein [8].

The CYP450 subspecies 2C, 2D, 3A and 4A are regulated by the highly inducible xenobiotic receptor on complementary DNA. The receptor is found in the liver and to a lesser extent in the cells lining the intestinal tract and is normally responsible for cholesterol catabolism and bile acid homeostasis. The activity of this receptor is subject to genetic polymorphism as well. This result in a wide variation in the sensitivity of the population to generalized hepatocellular necrosis and other forms of hepatic damage [29, 33].The long-term administration of isoniazid can lead to hepatic dysfunction in 10-20% of those receiving the drug. Yet severe toxic hepatitis develops in only 1% or less of a particular population [37]. The N-acetyltransferase (NAT2) genotype appears to play a role in determining a patient's relative risk. In one study, patients with the slow-type NAT2 genotype had a 28-fold greater risk of developing serum aminotransferases elevations than did patients with the fast type NAT2 genotype [38].

Isoniazid is normally metabolized by several pathways, acetylation being the major pathway. It is acetylated to acetylisoniazid, which in turn is hydrolyzed to acetylhydrazine [39]. The

acetylhydrazine and to a lesser extent the acetylisoniazid are directly toxic to the cellular proteins in the hepatocyte, but rapid acetylators also detoxify acetylhydrazine very rapidly converting it to diacetylhydrazine(a non-toxic metabolite).Isoniazid simultaneously is an example of the potential predictability of drug-induced liver disease based on single nucleotide polymorphism. There are definite links to NAT2 genotype and toxicity [40]. The risk for this reaction is also influenced heavily by the age of the patient, with the older patients having a much higher risk than the younger patients. Infact age plays a more influential role than genotype [39, 40, 41].

A study to determine the incidences of hepatotoxicity due to isoniazid and rifampicin in TB patients in 1990 in the USA showed that 8 out of the 70 participants developed hepatotoxicity as a result of using these drugs and concluded that those patients with AIDS were significantly more likely to develop hepatotoxicity than those with any other risk factors[5].Ketoconazole has also been found to produce generalized hepatocellular necrosis or milder forms of hepatic dysfunction in 1-2% of patients treated for fungal infections. This reaction is fatal in high numbers of patients who are infected with the human immunodeficiency virus. The onset is usually early in therapy, although it can be delayed until several months into therapy. In the immune-compromised patients in whom ketoconazole is used for long periods of time, special care should be taken so as to watch for any changes in the liver function [43].

Toxic Cirrhosis

The scarring effect of hepatitis in the liver is what leads to the development of cirrhosis. Some drugs tend to cause such a mild case of hepatitis that it may not be detected. Sometimes, mild hepatitis can be easily mistaken for a more routine generalized viral infection. The damage continues to progress if the offending drug or agent is not discontinued. The patient will therefore present with cirrhosis and not hepatitis. An example of a drug in this case is methotrexate which causes periportal fibrosis in most patients who experience hepatotoxicity. The lesion results from the action of bioactivated metabolite produced by CYP450.This process occurs most commonly in patients treated for psoriasis and arthritis [44].

A report given in 2014 on methotrexate and liver fibrosis in people with psoriasis concluded that methotrexate increases the risk of liver fibrosis but not in everyone and also not on its own in certain cases. It also reported that there was a lack of clear dose-dependent relationship which

therefore indicated that other factors may influence the pathological development of the liver fibrosis [45].Vitamin A has also been known to cause liver fibrosis. It is normally stored in liver cells and causes significant hypertrophy and fibrosis when taken for long periods in high doses. Hepatomegaly is a common finding, along with ascites and portal hypertension. In patients with vitamin A toxicity, gingivitis and dry skin are also very common. This reaction is also usually accelerated by ethanol which competes with retinol for aldehyde dehydrogenase [27].

Cholestatic injury

This pattern of injury primarily involves the bile canalicular system. In cholestatic disease, disturbance of the subcellular actin filament around the canaliculi prevents the movement of bile through the canalicular system [45]. The inability of the liver to remove bile causes intrahepatic accumulation of toxic bile acids and excretion products [46]. Although this type of hepatic damage is rare, some patients develop progressive destruction of the cholangiocytes leading to the vanishing bile duct syndrome. Drug-induced cholestasis can occur as an acute disorder (like cholestasis with or without hepatitis and cholestasis with bile duct injury) or as a chronic disorder (like vanishing bile duct syndrome, sclerosing cholangitis and cholelithiasis) [47].However, the most common form of drug-induced cholestasis is cholestasis with hepatitis.

Most patients with this acute disorder present with nausea, malaise, jaundice and pruritus [10]. Elevations in serum alkaline phosphatase levels are more prominent and usually precede the elevations of other liver enzymes in serum [10]. On histologic examination, portal inflammation and hepatocyte necrosis are noted[48].The antipsychotic drug chlorpromazine has been singled out as the prototype drug for this disorder although other medications like erythromycin estolate, amoxicillin- clavulanic acid and carbamazepine have been found to be associated with other forms of cholestatic injury[11].In a study in 2002 on antimicrobial associated acute hepatitis, Nicholson *et al* showed that amoxicillin-clavulanate has hepatotoxic potential and that on taking this medication, typical symptoms of jaundice and pruritus occurred in certain patients after 2-4 weeks of starting oral or intravenous doses. This study therefore concluded that the administration of amoxicillin-clavulanate for more than 10 days should not be recommended [49].

Cholestatic injury also known as cholestatic jaundice is further classified by the area of the bile canalicular or ductal system that is impaired. For example, canalicular cholestasis is often associated with long-term high dose estrogen therapy. Clinically, these patients are often asymptomatic and present with mild to moderate elevations of serum bilirubin [50].The quinolone gatifloxacin has also been found to raise bilirubin levels in certain cases. In the same study on antimicrobial associated acute hepatitis in 2002 by Nicholson *et al*, it was seen that the patients who were on gatifloxacin were hospitalized 3 days after the last dose with ultrasonographic evidence of mild cholethiasis and elevated levels of total bilirubin, ALT,AST and Alkaline phosphatase. Other quinolones in this study that were found to have hepatotoxic effects were levofloxacin, trovafloxacin, moxifloxacin, ciprofloxacin, levofloxacin and norfloxacin [49].

Another drug that has been implicated in this case is the intravenous form of vitamin E (tocopherol acetate) which causes cholestatic jaundice, primarily involving the canalicular duct in premature infants. The incidence of this reaction in those receiving this formulation was high (>10%) and the mortality even higher (>50%) [51].In some patients, administration of total parenteral nutrition for periods greater than one week has been found to induce cholestatic changes and non-specific enzyme elevations in some patients. Those patients who have low serum albumin concentrations may be at a greater risk than patients with normal serum albumin concentrations[26].This reaction has been reported to occur rarely with drugs like sulfonamides, sulfonylureas, erythromycin estolate, captopril, lisinopril and other phenothiazines[52].

Sgro *et al*, in a study in France in 2002 on the incidence of drug induced hepatic injuries showed that the main drugs that led to hepatotoxicity were the anti-infectious drugs, the psychotropic and hypolipidemic agents as well as the NSAIDS. This study suggested that the number of hepatic ADRs in the French population would be 16 times greater than the number of hepatic ADRs reported to the French authorities and concluded that the incidence and seriousness of drug induced hepatitis was largely underestimated in the general population [53].

Mixed Hepatocellular and Cholestatic Injury

This pattern can be the result of three different processes. In some patients, an injury may begin as hepatocellular (or cholestatic) and simply spread so rapidly that by the time the patient

presents for diagnosis and treatment, all areas of the liver are affected. In other patients, the underlying mechanism of damage is such that cells are injured regardless of their anatomical location or metabolic role [8].

Liver Vascular Disorders

There are various drugs that cause occurrence of focal lesions in hepatic venules, sinusoids and portal veins. The most commonly associated drugs are the cytotoxic agents used to treat cancer, the pyrrolizidine alkaloids and the sex hormones. A centralized necrosis often follows and can result in cirrhosis. Azathioprine and herbal teas that contain comfrey (a source of pyrrolizidine alkaloids) are associated with the development of veno-occlusive disease. However, the exact incidence is rare and may be dose related [26].A study in 2000 by Chitturi *et al* on herbal hepatotoxicity showed that there were potential interactions between herbal medicines and conventional drugs and that this normally leads to interference with patient management. The study also showed that the concurrent use of such products was often not disclosed unless specifically sought after and this could therefore lead to perpetuation of liver injury. The conclusion made from this study was that there was need for continued public education, physician awareness and more stringent licensing so as to tackle this growing problem [54].

Another rare type of hepatic vascular lesion that can be seen as both an acute and a chronic disease is known as peliosis hepatitis [55]. In this case, the liver develops large, blood filled lacunae (space or cavity) within the parenchyma. Rupture of the lacunae can lead to severe peritoneal hemorrhage. Peliosis hepatitis is associated with exposure of the liver to androgens, estrogens, tamoxifen, azathioprine and danazol [55]. Those androgens with a methyl alkylation at the 17-carbon position of the testosterone structure are the most frequently reported agents that cause peliosis hepatitis, which occurs usually after atleast 6 months of therapy [55].

2.1.2. Mechanisms of Drug-induced Liver Disease

Stimulation of Autoimmunity

Autoimmune injuries usually involve antibody mediated cytotoxicity or direct cellular toxicity [48, 56]. This type of injury occurs when enzyme drug addicts migrate to the cell surface and

form neoantigens. The neoantigens serve as targets for cytolytic attack by T cells. The injury may then be exacerbated by the recruitment of inflammatory cells. Examples of drugs that are associated with autoimmune injuries are halothane, sulfamethoxazole, carbamazepine and nevirapine [46].Chu *et al*, in a study on nevirapine and efavirenz associated hepatotoxicity in Kenya and Mozambique in 2012, showed that 124 of the 5832 HIV-infected individuals who had initiated nevirapine or efavirenz based ART developed hepatotoxicity [6].

Stimulation of autoimmunity is often associated with some stage of all fulminant presentations. It is the primary cause of injury in idiosyncratic reactions. Dantrolene, isoniazid, phenytoin, nitrofurantoin and trazodone are associated with a type of autoimmune-mediated disease in the liver called 'chronic active hepatitis' [20, 57]. Patients experience periods of symptomatic hepatitis followed by periods of convalescence only to repeat the experience months later. It is a progressive disease with a high mortality rate and is more common in females than in males. Antinuclear antibodies appear in most patients. These drugs appear to form anti-organelle antibodies [37]. Identification of the exact causative agent is sometimes difficult as diagnosis requires multiple episodes occurring long after exposure to the offending drug [8].A study on anti-tuberculosis drug-induced hepatitis in India in 2003 concluded that patients receiving anti-tubercular drugs frequently developed acute or chronic hepatitis and that the time required for the metabolites to reach hepatotoxicity levels was much earlier with isoniazid plus rifampicin treatment than isoniazid alone. This reaction was reported to be synergistic rather than additive [58].

Idiosyncratic Reactions

Idiosyncratic drug-related hepatotoxicity is rare and usually occurs in a small proportion of individuals. These adverse reactions are often categorized into allergic and non-allergic reactions [59]. The allergic reactions are characterized by fever, rash and eosinophilia. They are usually dose related and have a short latency period (<1 month) [59].When the patient is exposed to the offending agent, the patient will experience rapid recurrence of hepatotoxicity. Studies show that minocycline, nitrofurantoin and phenytoin can cause allergic reactions [59]. Unlike the allergic reactions, the non-allergic idiosyncratic reactions are devoid of the hypersensitivity features and usually have a long latency period (several months).These patient often have normal liver function tests for 6 months or longer and then suddenly develop hepatotoxicity. Depending on

the medication, the incident can be independent of dose or dose-related. Drugs that are associated with this type of reaction include amiodarone, isoniazid and ketoconazole [59].

Disruption of Calcium Homeostasis and Cell membrane Injury

Drug-induced damage to the cellular proteins that are involved with calcium homeostasis can lead to an influx of intracellular calcium leading to a decline in adenosine triphospate levels and disruption of the actin fibril assembly. The resulting impact on the cell is blebbing of the cell membrane, rupture and cell lysis [46]. Drugs that impair calcium homeostasis include lovastatin, venlafaxine and phalloidin, which is the active component of mushrooms [46, 56].Hypolipidemic agents like lovastatin have been shown to cause hepatotoxicity in a study in France in 2002 on incidence of drug induced hepatic injuries [53].

Metabolic Activation of the Cytochrome P450 Enzymes

Most hepatocellular injuries involve the production of high-energy reactive metabolites by the CYP450 system. These reactive metabolites are capable of forming covalent bonds with cellular proteins (enzymes) and nucleic acids that lead to adduct formation. In the case of acute toxicity, the enzyme-drug addict can cause cell injury or cell lysis. Adducts that form with DNA can cause long term consequences such as neoplasia. Acetaminophen, furosemide and diclofenac are examples of this mechanism of liver injury [60]. Individual genetic differences can play a role in the significance of this process. Patients with a single nucleotide polymorphism (SNP) that codes for slow reacting variants of CYP450 will react differently from those with a SNP that code for very –fast-reacting variants.

Stimulation of Apoptosis

Apoptosis represents a distinct pattern of cell lysis that is characterized by cell shrinkage and fragmentation of nuclear chromatin. The apoptotic pathways are triggered by interactions between death ligand (tumor necrosis factor and Fas ligand) and death receptors (tumor necrosis factorreceptor-1 and Fas).These interactions activate caspases which cleave cellular proteins and eventually lead to cell death [61]. Cumulative doses of acetaminophen cause apoptosis [57].A study by Alistair *et al* on acetaminophen induced hepatotoxicity which involved following 560 patients over a 7 year period showed that the number of admissions due to paracetamol induced

toxicity increased considerably through the years and that the number of patients who underwent liver transplantation as well as those who survived after being managed medically also increased. The conclusion made from this study was that although severe acetaminophen induced hepatotoxicity remains a serious condition, the increased use of N-acetylcysteine, advances in medical management and the increased availability of liver transplantation have resulted in a significant improvement in survival rates [62].

Mitochondrial Injury

Drugs that impair mitochondrial structure function or DNA synthesis can disrupt oxidation of lipids and oxidative energy production within the hepatocyte [52]. In acute disease, prolonged interruption of oxidation leads to microvesicular steatosis, whereas in chronic disease, macrovesicular disease is present [11]. Severe damage to the mitochondria eventually leads to hepatic failure and death. Drugs that cause mitochondrial liver injuries by inhibiting oxidation include aspirin, valproic acid and tetracycline. Amiodarone causes mitochondrial injury through disruption of oxidative phosphorylation[46].Lewis *et al*, in a study on the histopathological analysis of suspected amiodarone hepatotoxicity involving 17 patients in 1990,showed that the liver specimens studied had changes similar to alcoholic liver injury with steatosis both macrovesicular and microvesicular being the most frequent histopathological feature. Some of the liver specimens studied also showed ballooning of hepatocytes as well as Mallory bodies [34].

Liver Neoplastic Disease

Hepatic tumors associated with drug therapy are usually benign and remit when drug therapy is discontinued. Except in rare instances, these lesions are associated with long-term exposure to the offending agent [63]. Androgens, estrogens and other hormonal related agents are the most frequently associated causes of neoplastic disease. The model for drug –induced hepatic cancer is polyvinyl chloride exposure which is used in the production of many types of plastic products. It induces angiosarcoma in exposed workers after as few as 3 years of exposure [64].

2.2 Risk Factors associated with Drug-induced Liver Disease.

Various risk factors have been found to be associated with drug-induced liver disease. A study on the risk factors for idiosyncratic drug-induced liver disease in USA by Chalasani *et al* found out that alcohol use was a major risk factor for DILD.Other risk factors implicated were age,sex,chronic liver disease,HIV and TB co-infection as well as genetics[65].Similarly, in a study by Gaude *et al* in India on drug-induced hepatitis in TB patients, it was found out that advanced age,hypoalbuminaemia,regular alcohol intake and advanced nature of liver disease were independent risk factors for the development of DILD.This study concluded that the risk of development of DILD is increased in the presence of these factors [66].

2.3 Assessment and Management of DILD.

The best and most important technique for assessing DILD is the patient's history. Questions addressing the patient's drug use along with a thorough review of systems are essential. Early recognition of drug-induced liver reactions is essential in minimizing injury [67]. Monitoring hepatic enzyme levels is appropriate and necessary with a number of agents especially those that lead to overt injury [1]. For drugs that produce liver injury unpredictably, biochemical monitoring is less useful.ALT values are more specific than AST values.ALT values that are within the reference range at baseline and rise 2-3 fold should lead to enhanced vigilance in terms of more frequent monitoring [1]. It is recommended that ALT values that are 4-5 times higher than the reference range should lead to prompt discontinuation of the drug [1].

There is no specific treatment for drug-induced hepatic disease. Treatment is largely supportive and based on symptomatology [1]. The first step is normally to discontinue the suspected drug. Specific therapy against DILD is limited to the use of N-acetylcysteine in the early phases of acetaminophen toxicity. L-carnitine is potentially valuable in cases of valproate toxicity [1]. It is recommended that the management of drug-induced cholestasis should be similar to that for primary biliary cirrhosis. Cholestyramine may be used for alleviation of pruritus. Ursodeoxycholic acid may be used as well [1].]In certain cases, after careful monitoring, re-introduction of drugs at tapering doses is recommended. A study in India in 2005 by Shakya *et al* on the management of anti-tubercular drug-induced hepatotoxicity and therapy re-introduction strategy showed that retreatment of therapy has to be done based on the severity of hepatitis. In

mild cases, all the drugs that were previously used were re-introduced at once in tapering doses and if the patient's condition worsened, then isoniazid and ethambutol were re-introduced in lower doses first and then the dose increment was done later followed by an increase in the number of drugs [68]. The study showed that all the patients tolerated the anti-TB drugs well after the re-introduction. There was no incidence of recurrence and all the patients completed their 8 months treatment regimen and all are currently cured. The study therefore concluded that the timely detection and temporary withdrawal of the offending agent can completely cure anti-TB drug induced hepatotoxicity and that the recurrence of hepatotoxicity is rare if the re-introduction is done in a well planned manner [68].

Various outcomes have been observed upon management of DILD.A study done on features and outcomes of 899 patients with DILI by Chalasani *et al* found out that among the 1,257 enrolled subjects with suspected DILI, 10% of the patients died or underwent liver transplantation [69].The use of drugs for recreational purposes must also not be overlooked. Cocaine has been directly linked to liver disease[70].A study in 1992 on cocaine toxicity by Roth *et al* showed that cocaine toxicity has the potential to cause an apparent shift in the intra-acinar site of necrosis under circumstances known to alter cocaine metabolism and hence lead to hepatotoxicity[71].

Ecstasy, which is the street name for methylenedioxymethamphetamine has also been found to induce fulminant hepatitis which has led to death in some cases [72]. It has been suggested that it is also very important to determine non-drug hepatic risk. Arsenic, for example, is known to induce both acute and chronic hepatic reactions. Arsenic in low concentrations is found in insect resistant lumber [72].

Following Occupational Safety and Health Administration, guidelines should decrease the danger of using these products but usually does not eliminate it. Even if the exposure to an environmental toxin in itself does not produce a hepatic reaction, it may predispose a patient to a hepatic reaction when a drug is added. Some of the more common hepatic toxins found in occupational or environmental exposures that can add to a patient's risk for developing a hepatic lesion include carbon tetrachloride, copper,dimethylformamide,2, 4-dichlorophenoxyacetic acid, fluorine, toluene, trichloroethylene and vinyl chloride[73].

A person's use of alternative medicine must be solicited. Many herbal remedies have been abandoned because of their common adverse reactions. Comfrey tea is a common cause of hepatocellular damage. Other herbs like pennyroyal oil, margosa oil and clove-oil have been found to cause dose-related hepatotoxicity [74]. A study in 2000 on herbal hepatoxicity by Chitturi et al showed that herbal remedies were popular in the patients with liver disease and concluded that the increased concern about these adverse effects have now led to a closer scrutiny of these herbal products [54].The nutritional status of a patient can be as important to the development of a drug-induced liver disease as the hepatotoxic itself [72]. Patients who are malnourished because of illness or long-term alcohol abuse make up the most troublesome group [75]. Low serum levels of vitamins E and C along with lutein and carotenes have been associated with asymptomatic elevations in transaminases [76].

All potential drug reactions should be judged as to the timing of the reaction versus drug administration, pharmacokinetic considerations, the information in the literature records about previous reactions, the inclusion of alternative non-drug causes as well as close clinical observation when the drug in question is stopped. It is also important to keep in mind that most elevations in liver enzymes will not be associated with a drug. In a study of all patients admitted to a hospital in the United Kingdom with elevated liver aminotransferases, only 9% of the cases involved a drug other than alcohol as the possible cause [59]. It has been found that even in cases in which the drug is absolutely targeted as the cause, viral hepatitis may be a complication. In all cases, levels of serum antibodies to hepatitis A, B and C should be investigated. No specific antidotes are available for the vast majority of hepatotoxic agents. Emergency liver transplantation has found increased utility in those settings where drug-induced fulminant hepatic injury has been diagnosed. However, if liver transplantation is an option, then it must be considered early enough [1].

3.0 METHODOLOGY

3.1 Study Design

This study was a cross-sectional survey involving consenting adult patients diagnosed with liver disease. Patients with liver disease who were attending the clinic and who were admitted in the medical wards during the study period were included in the study. Information on presence of confirmed liver disease was obtained from the patient's file as indicated by the clinician upon diagnosis.

3.2 Study Area

This study was carried out at KNH, the largest teaching and referral hospital in Kenya which also serves as a primary healthcare facility for the communities around it. The KNH liver clinic (clinic number 21) as well as the KNH medical wards were specifically used for this study. This is because most of the patients with liver disease are usually reviewed in the liver clinic and then some of the serious cases are admitted in the medical wards. Moreover, referrals for liver diseased patients from other hospitals all over the country are usually to this liver clinic. The monthly average outpatient attendance is about 100 patients. In the year 2013 alone, there were 1,115 outpatients in this clinic. Already over 800 outpatients were treated at the liver clinic between January and August 2014 [77]. Therefore, this liver clinic together with the medical wards formed ideal sites for this study.

3.3 Study Population

Adult patients aged 18 years and above with confirmed liver disease who were attending the liver clinic and those admitted in the medical wards during the study period. Diagnosis of the liver disease was done by the attending clinician. The study involved patients who met the inclusion criteria and had also consented to participate.

3.3.1 Inclusion criteria

Adult patients aged 18 years and over who have been diagnosed with liver disease who were attending the liver clinic and those admitted into the medical wards during the study period were eligible to participate in the study. Information on the presence of confirmed liver disease was obtained from the patient's file, as diagnosed by the attending clinician.

3.3.2 Exclusion criteria

Pregnant women, children and psychotic (agitated, hostile or violent) patients by their nature of vulnerability. Adult patients without diagnosed liver disease who were attending the liver clinic or admitted into the medical wards during the study period were not allowed to participate in the study.

3.4 Sample size and Sampling Procedure

The sample size for the patients was selected from those with liver disease who were attending the liver clinic and those admitted into the medical wards during the study period. Sample size was calculated using the Fischer's formula [78].

$n= \{Z^2 \times P (1-P)\}/d^2$

n=sample size

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

p=52%=estimated prevalence of drug-induced liver disease in the USA since no such studies had been done in Kenya and Africa as a whole [3]

d=level of desired precision of the study=5%

Therefore,

n = (1.96 X 1.96 X 0.52 X 0.48)/ (0.05 X 0.05)

= 384

From the calculation, the sample size was added a 10% to cater for data losses and non-responders

n = 423

The minimum sample size was **423** patients who were sampled for this study and so we collected data from **485** patients.

3.5 Sampling Method

The patients who were attending the liver clinic during the study period were recruited into the study consecutively as they came to the clinic during the appointments. Upon review by the clinician, the patient was requested to pass through the lead investigator's office for consenting and assessment using the eligibility criteria checklist. Those patients who satisfied the inclusion criteria were eligible for participation in the study. The lead investigator then carried on with interviewing the patient. For those patients who were admitted in the wards, the admission list was used to consecutively select patients starting from the first patient on the list, using their names and patient numbers and then they were followed into the wards for their eligibility criteria assessment, consent and interviews.

3.6 Recruitment and Consenting Process

Consent from patients who meet the inclusion criteria was sought and the consent forms signed by the patients. (See Appendix 1 and 2)

3.7 Data Collection

3.7.1 Research Assistants

The principal investigator was assisted by two trained and experienced research assistants in data collection. Both research assistants were trained and experienced holders of diploma in community health nursing. They were trained on data collection procedure by the principal investigator, before the actual study. Each assistant was required to collect data from at least three patients per day. The principal investigator was the overall co-coordinator of the project.

3.7.2 Data to be collected

Both primary and secondary data was abstracted into data collection tool (Appendix 4 and 5). The primary data was collected by interviewing patients directly and this included information such as the patient's age, gender, residence, marital status and duration of illness. Family history of liver disease was also be inquired from the patient. Information on social history of the patient to help in determining the risk factors that predispose patients to developing drug-induced liver

injury was also be sought. Patients were asked about workplace, education level, diet, as well as alcohol and tobacco use. Information that the patient was not able to report appropriately was cross-checked from the patient's file. Such information included any prior hospitalizations, surgeries and presence of cormobidities such as TB, heart problems, diabetes and HIV. Any drugs the patient had been using at the time of diagnosis and after diagnosis, reason for their prescription, their dosages and duration of use was recorded as well. Information on levels of ALT, AST, Alkaline phosphatase, bilirubin and other important serum biomarkers at the time of diagnosis of liver disease and atleast two consecutive LFT results taken within a 2 year period (with their corresponding signs and symptoms of the patient at the time of taking these tests) following exposure to a suspected offending agent after diagnosis was also obtained from the patient's file. The likely offending agent was also documented. Management strategies including use of antidotes, withdrawal of offending agent, replacement of offending drug, supportive therapy as well as the outcomes of the management intervention was checked in the patient's file. Outcomes of management include: complete recovery, improvement in LFTs, improvement in signs and symptoms, reduced hospital visits, admission, relapse, as well as death of the patient.

3.8 Study Variables

Independent variables: Participant's gender, age, height, weight, marital status, socioeconomic status, drug doses.

Dependent variables: Presence of confirmed liver disease

3.9 Data Management and Statistical Analysis Plan

Data was collected using standardized tools and entered into a password protected Microsoft Access Database 2014 developed by the statistician. Once entry was complete, the principal investigator compared the hard copy data with the entered data to ensure correctness and identify any inconsistencies. Exploratory data analysis was carried out to summarize all data variables and frequencies. Categorical data such as gender was summarized using frequency tables.

Continuous variables such as age, income, drug dosages was summarized using measures of central tendency and dispersion such as means, medians, minimum, maximum, standard deviation percentiles and interquartile ranges.

In order to determine the proportion of liver disease that was associated with drugs, 2x2 tables were generated for each drug that was assessed and statistical significance determined. A similar approach was used when determining risk factors that may have associated with Drug-induced Liver Disease. In order to determine independence of drugs as contributing to liver disease, a stepwise backward binary logistic regression model was developed.

3.10 Data Quality Control

Every data collection form for each patient was allocated a unique serial study number to avoid confusion and duplication of the data. The serial numbers were only revealed for matching of data during data analysis. Rectification of any errors identified during data clean-up was done before analysis.

3.11 Ethical Considerations

During this study, several ethical issues were considered as discussed below.

3.11.1 Approval to carry out the Study

The permission to carry out the study was obtained from the University of Nairobi/Kenyatta

National Hospital Ethics and Research Committee (KNH/UoN-ERC)

3.11.2 Informed consent

Consent from patients who met the inclusion criteria was sought and the consent forms signed by the patients.

3.11.3 Confidentiality

All the information obtained from this study was treated with confidentiality and serial numbers were used instead of the patient names to protect their identity. Only the information that was relevant to the study was obtained from the files and then they were returned after the

information had been obtained. The materials used to collect the data needed were locked up in a cabinet in the investigator's office during the entire study .The study numbers of the patients were also used during data analysis only so that the patients' identity was concealed.

3.12 Risks involved

There were no risks to the patients since the study only involved talking to the patients to get their patient history as well as looking through their files for any other important information.

4.0 RESULTS

This chapter describes the results obtained after data collection and analysis. The section starts with the description of the study participants and then results as per the set study objectives. The results present an analysis of a total of four hundred and eighty five study participants.

4.1 Characteristics of the study Population

Table 1 below shows the socio-demographic characteristics of the study population.

Table 1: Socio-demographic Characteristics of the Study Population

Characteristic	Category	n	%
Gender	Male	257	**53.1%**
	Female	228	46.9%
Age Category (Years)	18-25 years	36	7.4%
	26-30 years	78	16.1%
	31-40 years	163	**33.6%**
	41-50 years	98	20.2%
	>50 years	110	22.7%
Marital status	Divorced	42	8.7%
	Married	236	**48.7%**
	Single	129	26.6%
	Widowed	78	15.7%
Occupation	Employed	14	2.5%
	Salaried	116	23.5%
	Student	50	9.9%
	Unemployed	305	**62.5%**
Education level	College/University	132	26.6%
	Non-formal	45	8.9%
	Primary	128	25.8%
	Secondary	180	**36.5%**
Smoking Status	Smokers	170	35.1%
	Non Smokers	315	**64.9%**

As seen in table 1 above, our study population had a male predominance at 257(53.1%). The mean age of the study participants was 41.36 years (SD 14.09), with majority of the participants aged 31-40 years (33.6%). The median duration of liver disease was 86 days (range 7-7240days).Almost half of the patients were married (48.7%). Slightly more than sixty percent of the population was unemployed while about a third (36.5%) had reached secondary as the highest level of education. Thirty-five percent of the patients were smokers (Table 1).

4.2 Prevalence of use of agents known to cause liver disease in the study population

Figure 1 below shows the prevalence of use of agents known to cause liver disease in the study population.

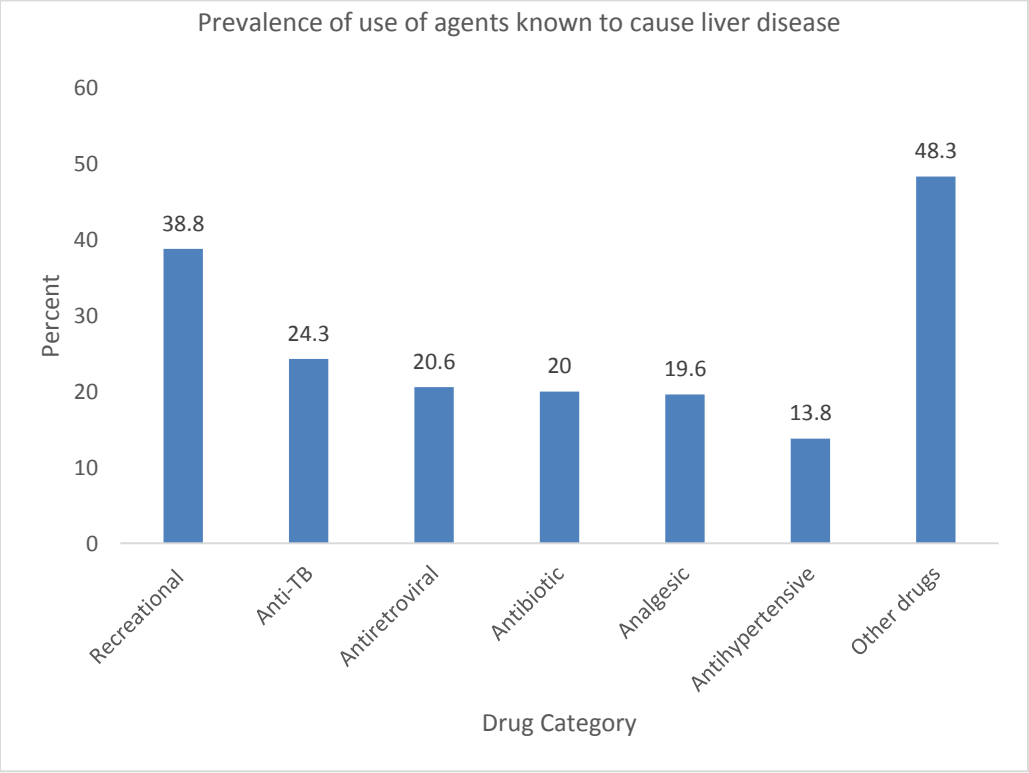


Figure 1: Prevalence of use of agents known to cause liver disease in the study population.

As seen in figure 1 above, recreational drugs were used by almost two-fifths of the patients (38.8%) while the proportion of use of anti-TB drugs, antiretroviral drugs and antibiotics was

almost the same (20.0 %). Almost the same proportion of patients in the study population that used the antibiotics also used the analgesics (20.0 % vs 19.6%) while slightly over 10% used the antihypertensives. Other drugs were also used by a majority of the patients in almost half of the study population (Figure 1)

4.2.1 Proportion of other drugs that were used by the patients

Table 2 below shows the proportion of the other drugs that were used by the patients.

Table 2: Proportion of other drugs used by the patients

Drug	Percentage
Herbal drugs	13.8%
Antidiabetic drugs	6.2%
Antifungal drugs	4.3%
Vitamin supplements	3.5%
Central Nervous System drugs	3.3%
Hypolipidemic drugs	3.2%
Hormones	2.9%
Cardiovascular drugs	2.3%
Anticancer drugs	1.0%

As seen in table 2 above, the prevalence of use of herbal drugs in the study population was at 13.8%.All the other drugs in the table were used by less than 10% of the study population (Table 2).

4.2.2 Proportion of use of specific drugs under each class of drugs known to cause liver disease in the study population.

Figure 2 below shows the proportion of use of specific drugs under each class of drugs known to cause liver disease in the study population.

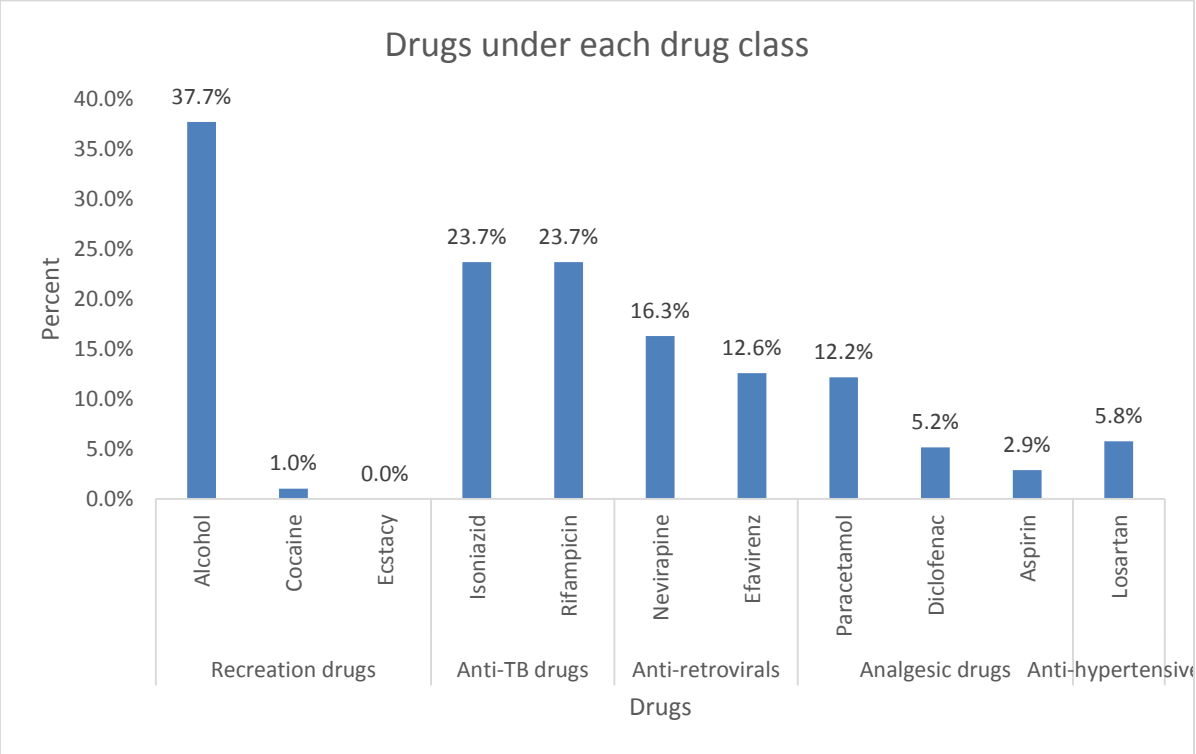


Figure 2: Proportion of specific drugs known to cause liver disease in the study population.

As seen in figure 2 above, alcohol was the most common recreational drug used by almost half of the patients while isoniazid and rifampicin were the major anti-TB drugs used by the patients. Amongst the antiretroviral drugs used by the patients, nevirapine and efavirenz were the most predominantly used at 16.3% and 12.6% respectively. As for the analgesics, patients reported to have used paracetamol more than other analgesics. This was at 12.2%, followed by diclofenac and aspirin at 5.2% and 2.9%, respectively. Losartan was the main antihypertensive used by the study population (Figure 2).

4.2.3 Proportion of specific antibiotics used by the study population.

Figure 3 below shows the proportion of specific antibiotics used by the study population.

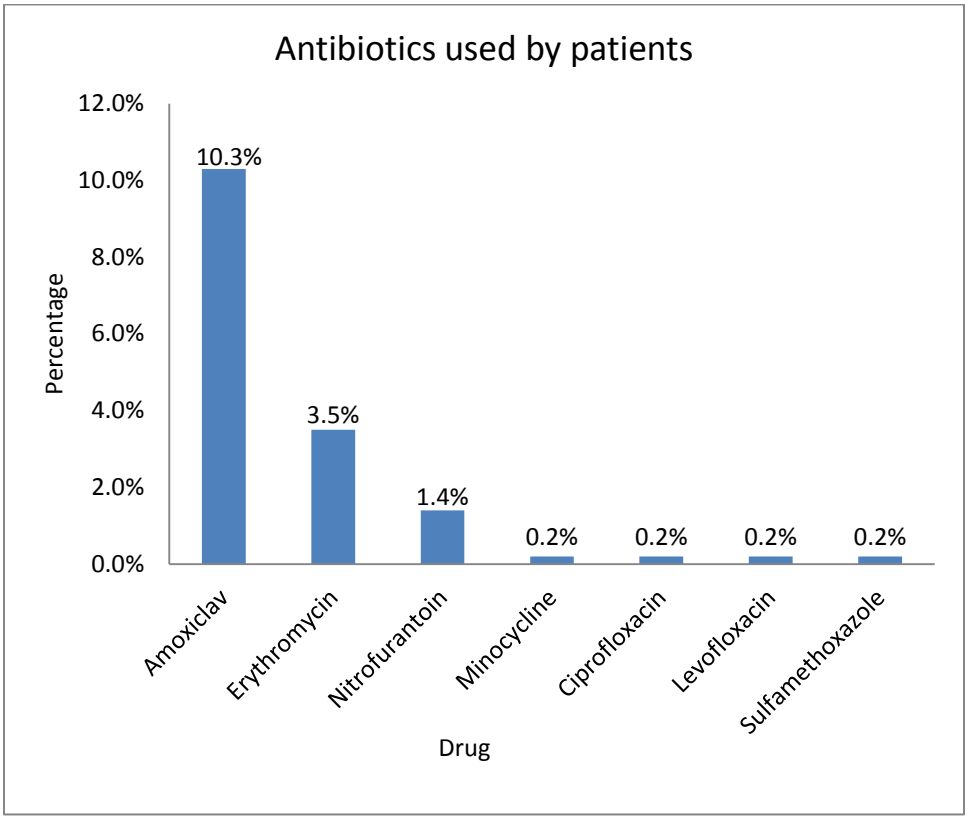


Figure 3: Proportion of specific antibiotics used by the study population.

As seen in Figure 3 above, amoxicillin-clavulanic acid was the main antibiotic used forming 10.3% of all the antibiotics used by the study population, followed by erythromycin and then nitrofurantoin. Other antibiotics that were also used, however, by a smaller proportion of the study population were ciprofloxacin, levofloxacin, sulfamethoxazole and minocycline (Figure 3).

4.3 Pattern of Liver Injury in the study population.

4.3.1 Hematological pattern of liver disease in the study population.

Figure 4 below shows the hematological pattern of liver disease in the study population.

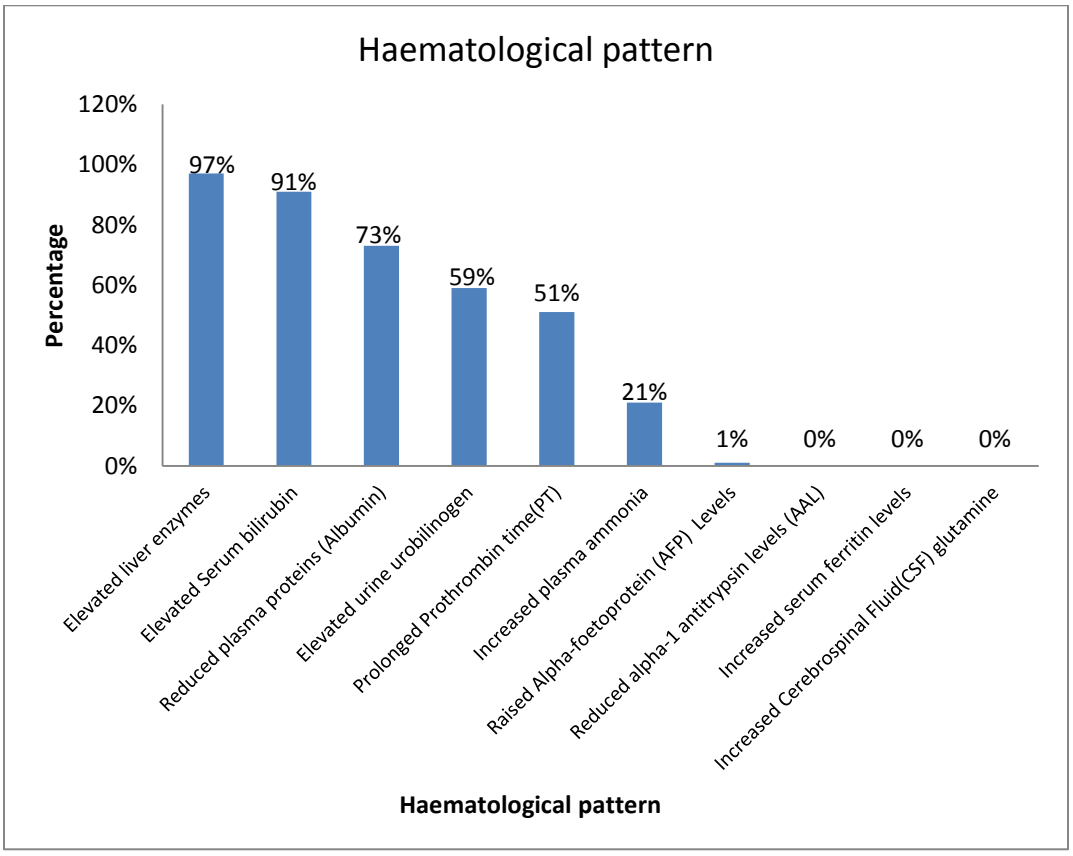


Figure 4: Hematological pattern of liver disease in the study population.

As shown in the Figure 4 above, almost all of the patients in the study population presented with elevated liver enzymes and elevated serum bilirubin while three-quarters of the patients presented with reduced plasma proteins (albumin). Those who presented with prolonged prothrombin time were slightly over half of the study population while 102 (21%) patients presented with elevated plasma ammonia. Only 5(1 %) patients presented with raised alfa fetoprotein levels (Figure 4).

4.3.2 Physical presentation pattern of liver disease in the study population.

Figure 5 below shows the pattern of the physical presentation of the signs and symptoms of liver disease in the study population.

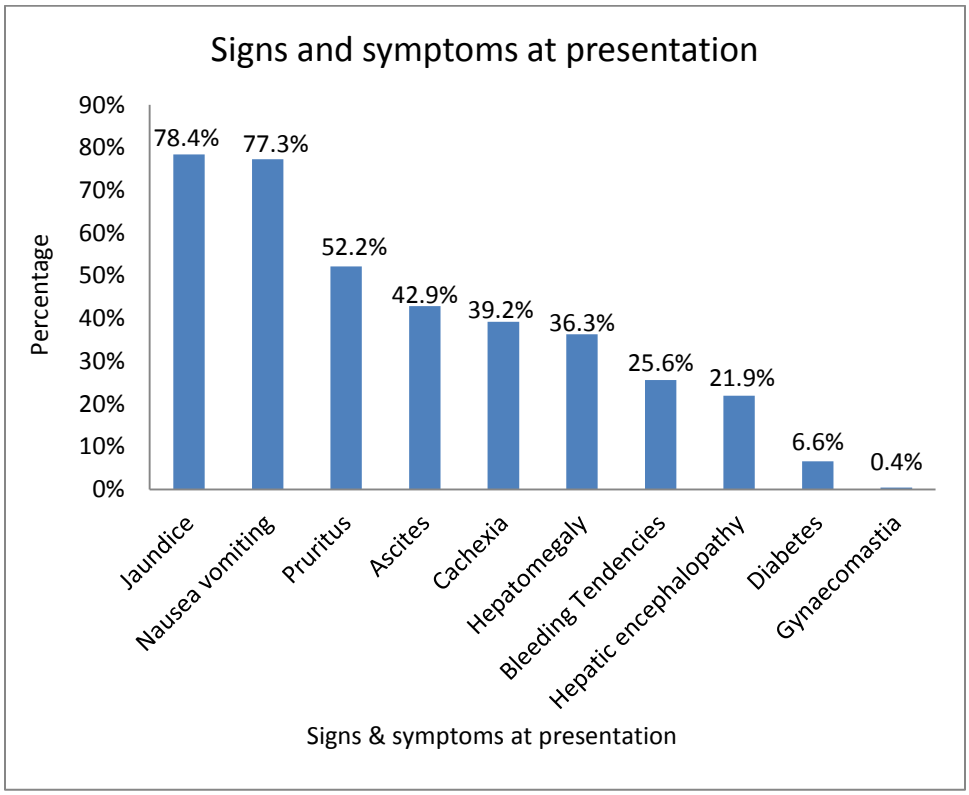


Figure 5: Physical presentation of the signs and symptoms of liver disease in the study population.

The commonest signs of liver disease were jaundice, at 78.4% and nausea and vomiting, at 77.3 % of the patients. Slightly over half of the patients presented with pruritus while almost half of all the patients studied presented with ascites and cachexia. Hepatomegaly was seen in almost 40% of the patients while bleeding tendencies and hepatic encephalopathy were seen in slightly over 20% of the patients. Only 0.4% patients presented with mild gynaecomastia (Figure 5).

4.3.3 Pathological pattern of liver disease in the study population

Figure 6 below shows the distribution of the pathological patterns of liver disease in the study population

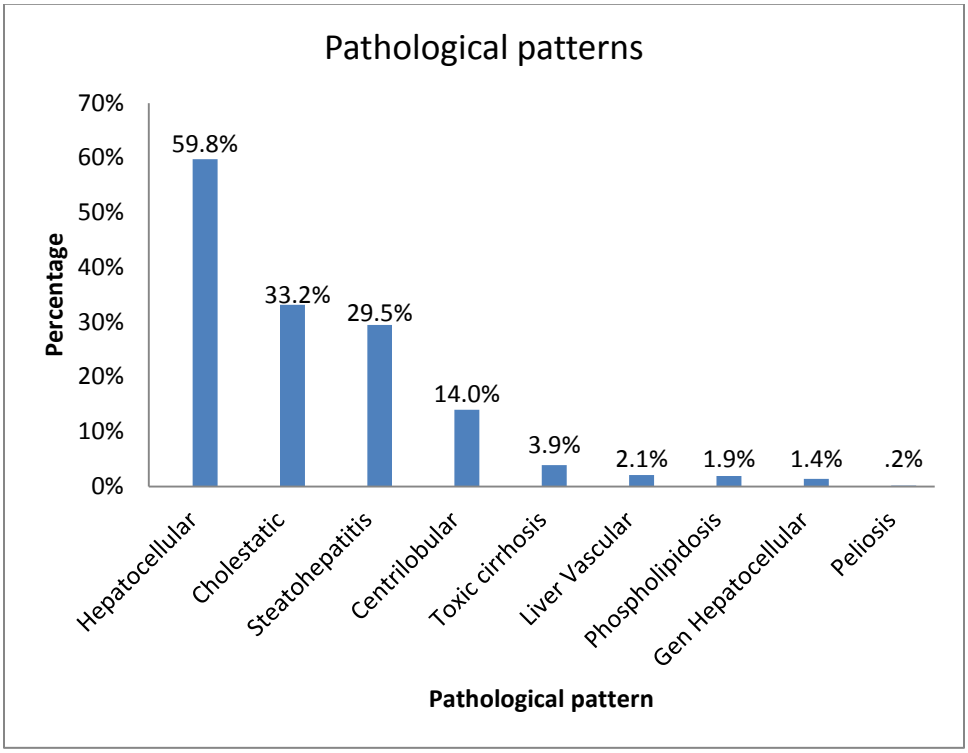


Figure 6: Distribution of the pathological patterns of liver disease in the study population.

As seen in the figure 6 above, the hepatocellular injury pattern was the most common and was seen in over half of in the study population followed by the cholestatic injury which was seen in almost half of the study population. The steatohepatitis pattern was seen in almost 30% of the patients while the centrilobular necrosis occurred in 14% of the total patients studied. The toxic cirrhosis pattern as well as the other patterns were seen in only a small minority of the patients studied (Figure 6).

4.4 Prevalence of risk factors for liver disease in the study population.

Figure 7 below shows the prevalence of risk factors for liver disease in the study population.

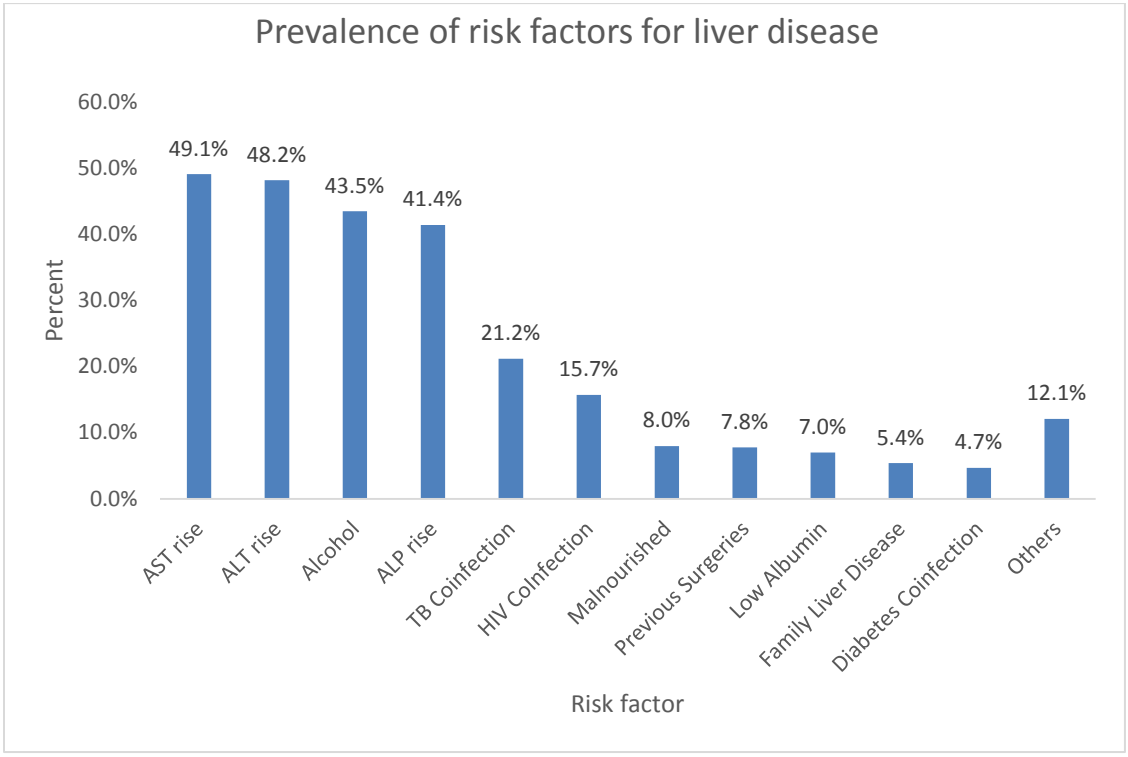


Figure 7: Prevalence of risk factors in the study population.
Key: AST- Aspartate aminotransferase**;** ALT- Alanine aminotransferase**;** HIV-Human immunodeficiency virus**;** TB: Tuberculosis

As seen in figure 7 above, elevated AST enzymes was the most common risk factor present for liver disease in the study population and was found in almost half of the patients.This risk factor was followed by elevated ALT and ALP as well as alcohol which were also found in almost half of the total patients studied.TB co-infection and HIV coinfection were seen in slightly over 15% of the patients. Those risk factors that were seen in less than 10% of the study population were malnourishment among patients, previous surgeries, low albumin levels, family history of liver disease and diabetes co morbidity. Other risk factors associated with liver disease in the study population were seen in 12% of the study population (Figure 7).

4.5 Strategies employed in the management of liver disease in the study population.

Figure 8 below represents the strategies employed in the management of liver disease in the study population.

Figure 8: Strategies employed in the management of liver disease in the study population.

From figure 8 above, drug withdrawal was the major management strategy employed in managing liver disease in almost all the patients. This was followed by the use of antibiotics in slightly over half of the total patients studied. Analgesic use was also was seen in around 40% of the patients. The proportion of use of diuretics, steroids and vitamins was almost the same and this was in about 30% of the study population. Cholestyramine use was seen in slightly above 15% of the patients while in other few cases, drugs that were suspected to induce liver injury were replaced with other drugs. Other management strategies such as use of antihistamines,

antidotes, beta blockers as well as surgical measures were employed in less than 10% of the study population. The only antidote that was used was N-acetylcysteine which was used to manage suspected paracetamol poisoning cases. (Figure 8).

4.5.1 Proportion of drugs in each class that was used to manage the patients with liver disease in the study population.

Figure 9 below shows the proportion of drugs in each class that was used to manage the patients with liver disease in the study population.

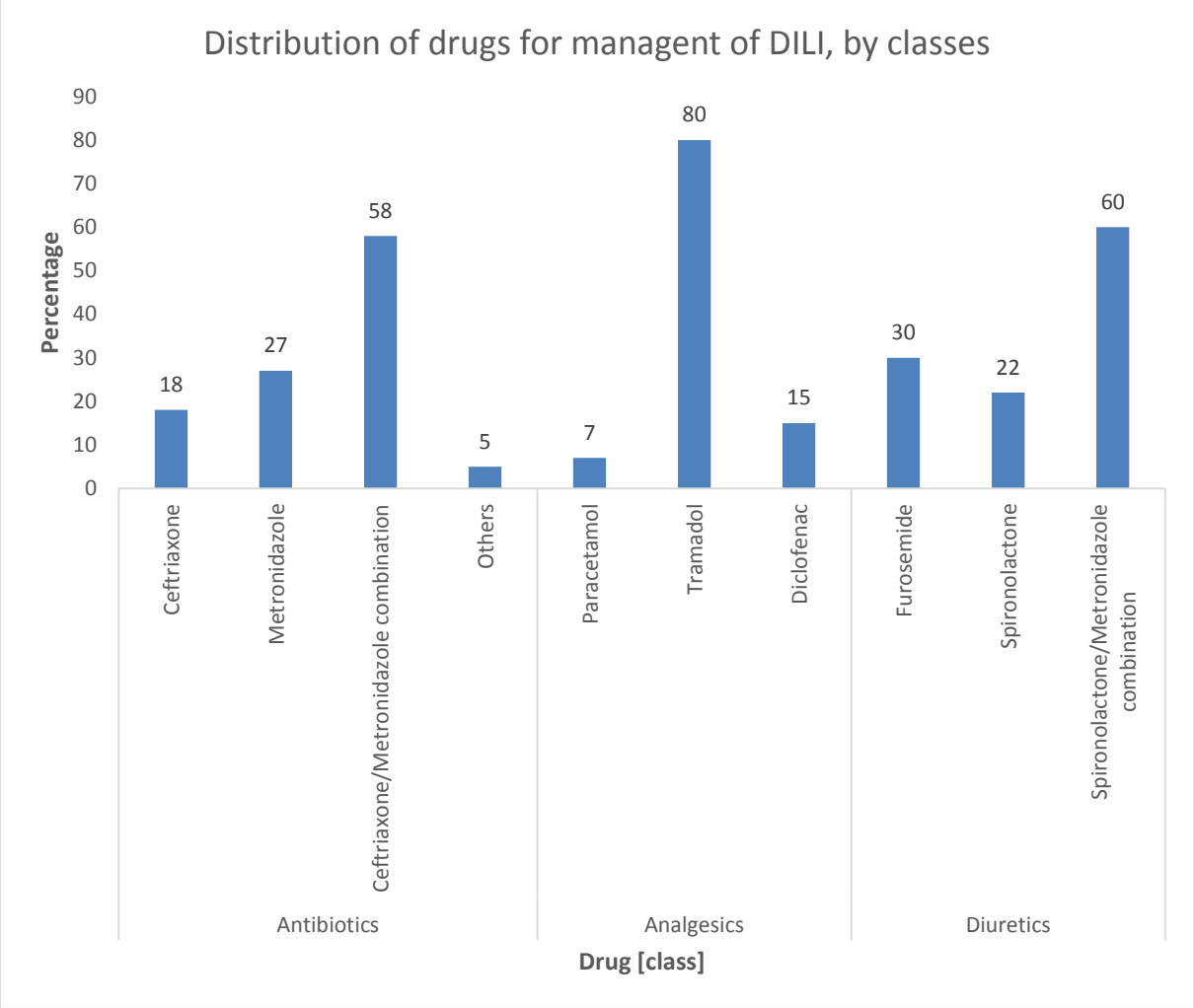


Figure 9: Proportion of drugs in each class that was used to manage the patients with liver disease in the study population.

As shown in the Figure 9, among the antibiotics used to manage the patients, the use of the combination of ceftriaxone/metronidazole was quite common in over half of the patients using antibiotics. This was followed by the use of metronidazole alone in slightly over 25% of the patients as well as use of ceftriaxone alone in almost 20% of those patients using antibiotics. Regarding the analgesics, tramadol was the main analgesic used in 80% of the patients, diclofenac in 15% of the patients and paracetamol in 7% of the patients.

As for the diuretics used to manage liver disease patients, the combination of spironolactone/furosemide was the most commonly used in over half of the patients , followed by furosemide alone which was used in almost half of the patients. The use of spironolactone alone was seen in about 20% of the patients using the diuretics (Figure 9)

4.5.2 Trend of follow up on the levels of serum biomarkers associated with liver disease in some patients during management.

Figure 10 below shows the trend of follow up on the levels of serum biomarkers associated with liver disease in some patients during management.

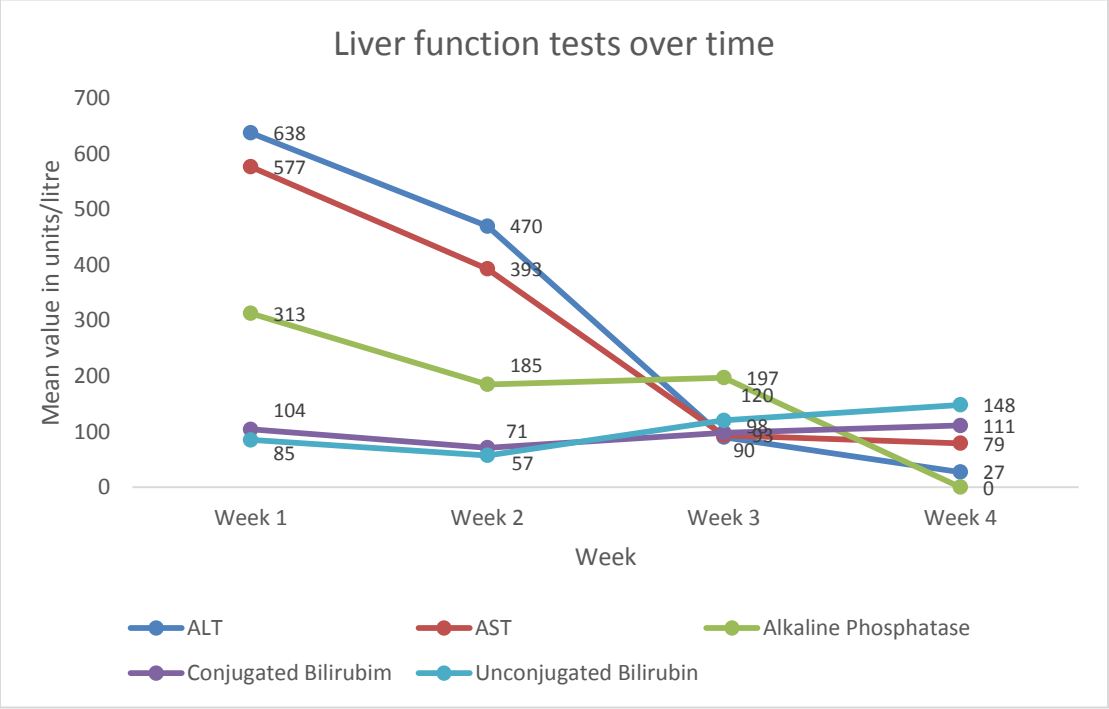


Figure 10: Trend on the levels of serum biomarkers.

Key: ALT:-Alanine aminotransferase**;** AST: Aspartate aminotransferase**;** ALP- Alkaline phosphatase

Mean values for ALT, AST and ALP-Units/litre**;** Mean values for Bilirubin-umol/litre

As seen in figure 10, over the 4 week follow up period, the mean levels of the three serum biomarkers ALT, AST and ALP for liver disease decreased progressively. In contrast, the mean levels of the two biomarkers, conjugated and unconjugated bilirubin increased slightly (Figure 10).

4.6 Outcomes of treatment of liver disease in the study population

Figure 11 below shows the outcomes of treatment of liver disease in the study population.

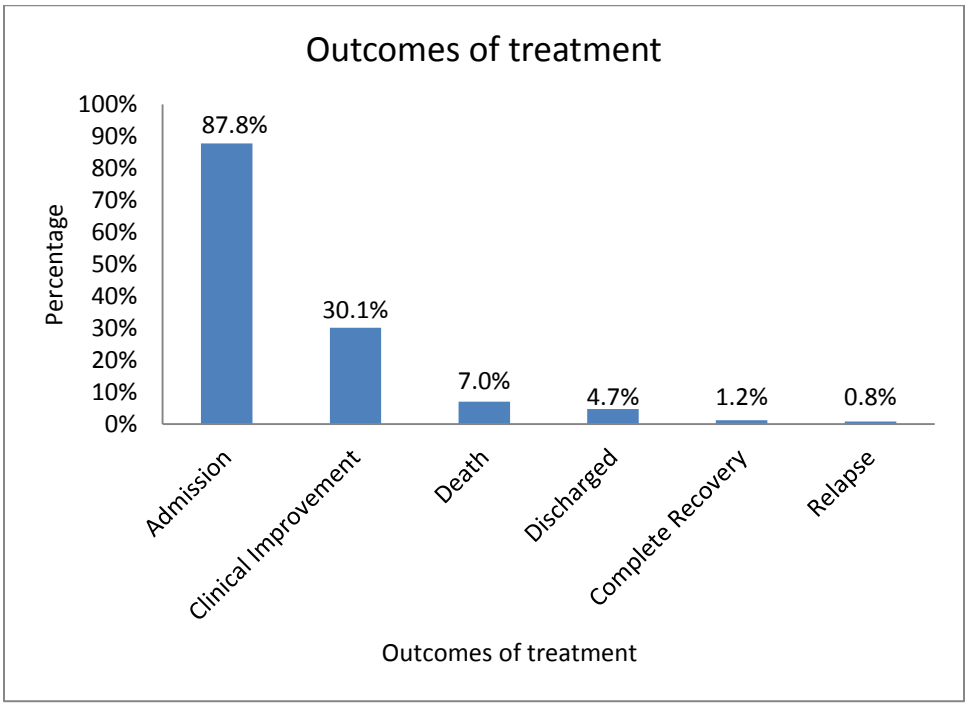


Figure 11: Outcomes of treatment of liver disease in the study population.

Figure 11 above shows that as the management strategies for liver disease were being applied, almost 90% of the patients studied were admitted at some point during management. Majority were still in the ward during the study period. Clinical improvement was seen in 150 patients

(30.1%) while about 7.0% of the total patients studied died while less than 10% of the patients were discharged. Complete recovery and relapse were seen in a small minority of the study population (Figure 11).

4.6.1 Length of Hospital Stay (days) by the admitted patients

Figure 12 below shows the proportion of patients and their number of days spent in the wards during management.

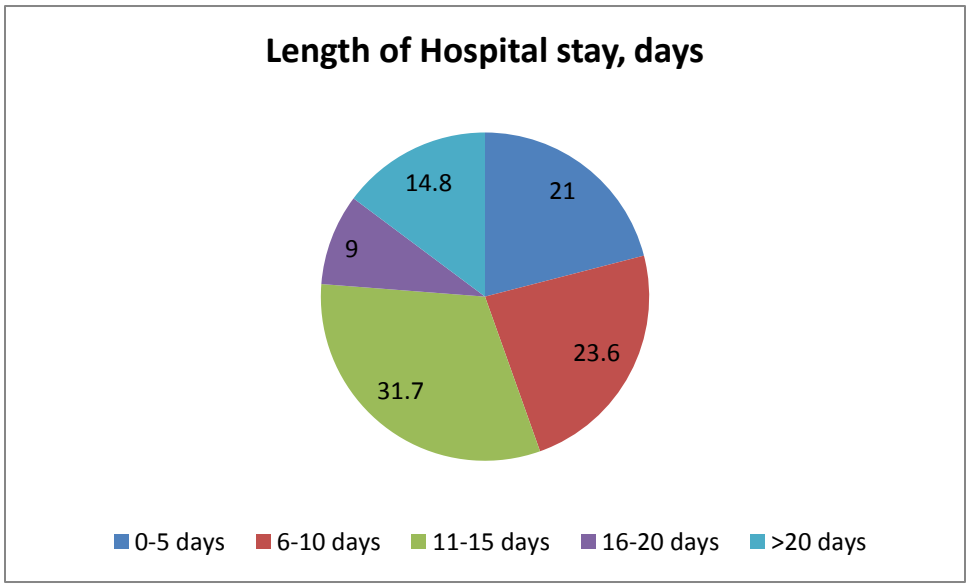


Figure 12: Length of hospital stay (days) by the admitted patients during management.

As represented in the figure 12 above, of all the patients admitted, the majority stayed in hospital for a period between 11-15 days .This was followed by those who stayed for between 6-10 days. Slightly above 20% of the admitted patients spent between 0-5 days while about 15% spent more than 20 days in the wards. Less than 10% of the patients admitted spent between 16-20 days in the wards. The median duration of hospital stay was 12.9 days (Range of 1-180 days) (Figure 12).

5.1 Bivariate Analysis of demographic characteristics and the outcomes of treatment.

A bivariate analysis was done to establish the relationship between demographic characteristics of the study population and the outcome of treatment and the following results in table 3 were obtained.

Table 3: Bivariate analysis of demographics characteristics and outcomes of treatment.

Sociodemographics		Outcome				
		Desirable		Undesirable		
		n	%	n	%	P value
Age group	18-25 years	3	8.8	31	91.2	0.435
	26-30 years	7	9.1	70	90.9	
	31-40 years	8	5.0	152	95.0	
	41-50 years	8	8.3	88	91.7	
	>50 years	4	3.7	105	96.3	
Gender	Male	15	5.9	238	94.1	0.711
	Female	15	6.8	207	93.2	
Marital status	Single	12	9.5	114	90.5	0.118
	Married	14	6.1	217	93.9	
	Divorced	0	.0	42	100.0	
	Widowed	3	4.0	72	96.0	
Occupation	Unemployed	21	7.1	276	92.9	0.354
	Salaried	3	2.7	109	97.3	
	Self-employed	1	8.3	11	91.7	
	Student	4	8.3	44	91.7	
Education level	College/University	6	4.7	121	95.3	0.278
	Secondary	15	8.7	158	91.3	
	Primary	6	4.8	119	95.2	
	Non-formal	1	2.4	41	97.6	

Desirable outcome: Complete recovery, Clinical improvement or Discharge
Undesirable Outcome: Admission, Relapse or Death

From the results in the table 3 above, it was found that none of the demographic characteristics of the study population had any statistically significant influence on the outcome of treatment of liver disease ($p>0.05$) (Table 3).

5.2 Bivariate analysis of drugs used by the study population and outcomes of treatment.

A bivariate analysis was done to establish if the particular drugs that were used by the study population had an effect on the outcome of treatment and the following results in table 4 below were obtained.

Table 4: Bivariate analysis of drugs used by the patients and outcomes of treatment.

		Outcome				
Drug		**Desirable**		**Undesirable -**		
		n	**%**	**n**	**%**	**P value**
Antiretroviral drugs	**No**	**28**	**7.4**	**351**	**92.6**	**0.050**
	Yes	2	2.1	95	97.9	
Antidiabetic drugs	No	29	6.5	417	93.5	0.489
	Yes	1	3.3	29	96.7	
CNS drugs	No	28	6.1	432	93.9	0.299
	Yes	2	12.5	14	87.5	
Antidiabetic drugs	No	28	6.8	382	93.2	0.239
	Yes	2	3.0	64	97.0	
Analgesic drugs	No	24	6.3	360	93.8	0.923
	Yes	6	6.5	86	93.5	
Antibiotic drugs	No	25	6.5	357	93.5	0.661
	Yes	5	5.3	89	94.7	
Anti-TB drugs	No	23	6.4	338	93.6	0.913
	Yes	7	6.1	108	93.9	
CVS drugs	No	29	6.2	436	93.8	0.700
	Yes	1	9.1	10	90.9	
Antifungal drugs	No	29	6.4	426	93.6	0.766
	Yes	1	4.8	20	95.2	
Anticancer drugs	No	30	6.4	442	93.6	0.602
	Yes	0	.0	4	100.0	
Hormones	No	30	6.5	432	93.5	0.325
	Yes	0	.0	14	100.0	
Vitamins	No	29	6.3	431	93.7	0.993
	Yes	1	6.3	15	93.8	
Recreational drugs	No	25	8.6	267	91.4	**0.011**
	Yes	5	2.7	179	97.3	
Herbal drugs	No	27	6.2	408	93.8	0.780
	Yes	3	7.3	38	92.7	
Other drugs	No	27	6.2	412	93.8	0.638
	Yes	3	8.1	34	91.9	
	Yes	5	5.0	96	95.0	

Desirable outcome: Complete recovery, Clinical improvement or Discharge

Undesirable Outcome: Admission, Relapse or Death

KEY: TB-Tuberculosis; CVS-Cardiovascular

From the results in the table 4, it was found that the use of recreational drugs (p=0.011) and antiretrovirals (p=0.05) were statistically significantly associated with increased chances of the patient experiencing an undesirable outcome such as admission, relapse or death (Table 4).

5.3 Bivariate analysis of levels of serum biomarkers and outcomes of treatment.

A bivariate analysis was done to establish if the levels of serum biomarkers had an effect on the outcome of treatment and the following results in table 5 were obtained.

Table 5: Bivariate analysis of serum biomarkers and outcomes of treatment.

		Outcome				
		Desirable		**Undesirable**		
		n	**%**	**n**	**%**	**P value**
Elevated Serum bilirubin	No	1	2.3	42	97.7	0.261
	Yes	29	6.7	404	93.3	
Elevated urine urobilinogen	No	16	8.0	183	92.0	0.186
	Yes	14	5.1	263	94.9	
Elevated liver enzymes	No	0	.0	14	100.0	0.325
	Yes	30	6.5	432	93.5	
Reduced plasma proteins (Albumin)	No	11	8.5	118	91.5	0.223
	Yes	19	5.5	328	94.5	
Prolonged Prothrombin time(PT)	No	22	9.5	209	90.5	**0.005**
	Yes	8	3.3	237	96.7	
Raised Alpha-foetoprotein (AFP) Levels	No	30	6.3	443	93.7	0.652
	Yes	0	.0	3	100.0	
Reduced alpha-1 antitrypsin levels (AAL)	No	30	6.3	446	93.7	-
Increased serum ferritin levels	No	30	6.3	445	93.7	0.795
	Yes	0	.0	1	100.0	

Desirable outcome: Complete recovery, Clinical improvement or Discharge
Undesirable Outcome: Admission, Relapse or Death

From the results in the table 5 above, it was found that prolonged prothrombin time (p=0.05) was statistically significantly associated with higher chances of experiencing an undesirable outcome such as admission, relapse or death (Table 5).

5.4 Bivariate analysis of risk factors known to be associated with drug induced liver disease and the outcomes of treatment

A bivariate analysis was done to establish if the presence of risk factors known to be associated with liver disease had an effect on the outcomes of treatment of suspected drug induced liver disease. The results in table 6 below were obtained.

Table 6: Bivariate analysis of risk factors and outcomes of treatment of liver disease

		Outcome				
		Desirable		Undesirable		
		n	%	n	%	P value
Risk factor						
Alcohol	No	22	8.2	247	91.8	**0.050**
	Yes	8	3.9	199	96.1	
TB Coinfection	No	25	6.6	352	93.4	0.565
	Yes	5	5.1	94	94.9	
HIV CoInfection	No	28	7.0	374	93.0	0.166
	Yes	2	2.7	72	97.3	
Diabetes Coinfection	No	29	6.4	424	93.6	0.693
	Yes	1	4.3	22	95.7	
Previous Cancer	No	30	6.3	443	93.7	0.652
	Yes	0	0.0	3	100.0	
Previous Hepatitis	No	28	6.0	436	94.0	0.135
	Yes	2	16.7	10	83.3	
Family Liver Disease	No	27	6.0	423	94.0	0.258
	Yes	3	11.5	23	88.5	
Previous Surgeries	No	26	5.9	413	94.1	0.240
	Yes	4	10.8	33	89.2	
Malnourished	No	29	6.6	408	93.4	0.316
	Yes	1	2.6	38	97.4	
Low Albumin	No	30	6.8	412	93.2	0.117
	Yes	0	0.0	34	100.0	
ALT rise	No	16	6.6	228	93.4	0.814
	Yes	14	6.0	218	94.0	
AST rise	No	16	6.7	224	93.3	0.742
	Yes	14	5.9	222	94.1	
ALP rise	No	18	6.5	258	93.5	0.817
	Yes	12	6.0	188	94.0	

Desirable outcome: Complete recovery, Clinical improvement or Discharge; Undesirable Outcome: Admission, Relapse or Death

Key: TB-Tuberculosis**;** HIV-Human immunodeficiency virus**;** AST-Aspartate aminotransferase**;** ALT-Alanine aminotransferase**;** ALP-Alkaline phosphatase;

From the results in table 6 above, it was found that alcohol use (p=0.05) as a risk factor was statistically significantly associated with increased chances of the patient experiencing an undesirable outcome such as admission, relapse or death (Table 6).

5.5 Bivariate analysis of management strategies employed to manage liver disease and the outcomes of treatment.

A bivariate analysis was done to establish if the management strategies employed to manage liver disease had an effect on the outcomes of treatment of suspected drug induced liver disease.

Table 7: Bivariate analysis of management strategies and outcomes of treatment

		Outcome				
		Desirable		Undesirable		
		n	%	n	%	P value
Management strategy						
Antidote	No	166	35.3	304	64.7	0.709
	Yes	6	40.0	9	60.0	
Drug Withdrawal	No	19	43.2	25	56.8	0.262
	Yes	153	34.7	288	65.3	
Replacement Drug	No	147	34.3	282	65.7	0.127
	Yes	25	44.6	31	55.4	
Other Drugs	No	151	35.5	274	64.5	0.936
	Yes	21	35.0	39	65.0	
Surgical Measures	No	169	35.7	305	64.3	0.566
	Yes	3	27.3	8	72.7	
Analgesics	No	91	31.1	202	68.9	**0.012**
	Yes	81	42.2	111	57.8	
Diuretics	No	106	30.9	237	69.1	**0.001**
	Yes	66	46.5	76	53.5	
Antibiotics	No	77	34.8	144	65.2	0.793
	Yes	95	36.0	169	64.0	
Beta Blockers	No	166	35.1	307	64.9	0.287
	Yes	6	50.0	6	50.0	
Steroids	No	100	28.2	254	71.8	**<0.0001**
	Yes	72	55.0	59	45.0	
Cholestyramine	No	130	32.1	275	67.9	**<0.0001**
	Yes	42	52.5	38	47.5	
Antihistamines	No	143	31.9	305	68.1	**<0.0001**
	Yes	29	78.4	8	21.6	
Vitamins	No	101	27.4	267	72.6	**<0.0001**
	Yes	71	60.7	46	39.3	

Desirable outcome: Complete recovery, Clinical improvement or Discharge
Undesirable Outcome: Admission, Relapse or Death

From the results in table 7 above, it was found that the use of analgesics (p=0.012), diuretics (p=0.001), steroids (p=<0.0001), cholestyramine (p=<0.0001), antihistamines (p=<0.0001) and vitamin K (p=<0.0001) were statistically significantly associated with increased chances of improvement and survival of the patients (Table 7).

5.6 Multivariate analysis - Logistic regression

Multivariate analysis was conducted using backward stepwise binary logistic regression with desirable/undesirable effects of treatment as the outcome variables and the factors that were significant at bivariate analysis as predictors and table 1.9 below shows the results of analysis.

Table 8: Independent Predictors of Outcome of Therapy in patients with DILI

	Coefficient	**S.E. of coefficient**	**P -value**	**OR**	**95% C.I. for OR**	
					Lower	**Upper**
ARVs	-1.178	.312	**.000**	**.308**	**.167**	**.568**
Recreational	-.581	.239	**.015**	**.559**	**.350**	**.893**
Steroids	.834	.234	**.000**	**2.302**	**1.455**	**3.640**
Antihistamines	1.508	.455	**.001**	**4.517**	**1.851**	**11.020**
Vitamin K	1.127	.268	**.000**	**3.086**	**1.824**	**5.220**
Analgesics	.299	.526	.570	1.348	.480	3.784
Diuretics	2.608	1.119	0.020	13.573	1.515	121.567

KEY:

ARVs-Antiretrovirals; S.E. -Standard error of the coefficient; OR-Odds Ratio; C.I.-Confidence interval.

From the table 8 above, the use of antiretrovirals (OR=0.31; 95 % CI: 0.17-0.57; p<0.00001) and recreational drugs (OR=0.56; 95 % CI: 0.35-0.89; p<0.00001) increased the likelihood of having an undesirable outcome by 31% and 56% respectively (Table 8).

The use of steroids(OR=2.30;95% CI:1.46-3.64;p<0.00001), antihistamines(OR=4.52; 95% CI: 1.85-11.02;p<0.00001) and vitamin K(OR=3.09; 95% CI:1.82-5.22;p<0.00001) as management strategies for patients with liver disease in this study population, increased the likelihood of having a desirable outcome by two times, five times and three times respectively (Table 8).

5.0 DISCUSSION

5.1 Introduction

This chapter is a discussion of the results obtained after data collection and analysis. The section starts with the description of the study participants and a subsequent comparison or contrast of these characteristics with other similar studies. This is then followed by the other results as per the set study objectives and in the same way these are compared or contrasted with other similar studies. The results being discussed below were obtained from an analysis of a total of four hundred and eighty five study participants.

5.2. Characteristics of the Study population.

Our study revealed male predominance at 257(53.1%) probably because during this study, majority of the patients who presented with liver disease, either in the liver clinic or in the medical wards were males. This was in contrast to a similar study done in the UK by Bjornsson *et al* in which there was a female predominance at 56.3% [9].This difference in proportions could have been brought about by the methodologies used for the two studies. While the study in our setting was a cross sectional survey, the UK study was a population based cohort involving data from patients already diagnosed with DILD. Out of our total study population of 485 patients with liver disease, almost half of the patients were married (48.7%).This could be explained by the fact that in our setting, most people get married above 25 years of age and most participants in this study were above this age.

Slightly more than sixty percent of the population was unemployed while about a third (36.5%) had reached secondary as the highest level of education. In our setting, most jobs require attainment of atleast a university degree. Majority of the study participants had reached only the secondary level of education. This could explain why most of them were not employed.

5.3 Prevalence of use of agents known to cause liver disease in the study population.

The prevalence of use of recreational drugs in the study population was highest at 38.8%, with, alcohol (37.7%) being the main drug used in these patients. These results were almost similar to

those of a study done in Uganda in which the prevalence of alcohol use was the highest at 46.8% [30].However, there was an almost 10% difference in the prevalence obtained from the two studies in which the prevalence in our setting was lower as seen when the number of study participants are compared. While the Ugandan study involved 371 patients, our study involved 485 patients. This difference in prevalence could also have been brought about by the different methodologies use.

The study in Uganda was a prospective study that involved causality assessment using defined scores and liver biochemistry results. Their alcohol-associated cases were clearly isolated and this therefore increased the chances of classifying a liver disease case that was caused by alcohol accurately thereby increasing its prevalence. This contrasts to our study which was a cross-sectional survey of suspected cases in which most patients were using more than one drug at a time. Since there was no definitive diagnostic criterion, there may have been cases where other drugs were associated with liver injury and yet alcohol was the main cause of the liver disease. This therefore increased the probability of getting a lower prevalence in the study in our setting. Another reason could be that the prevalence of use of alcohol in Uganda is higher than it is in our setting.

The prevalence of use of anti-TB drugs was at 24.3% with the main anti-TB drugs being isoniazid (23.7%) and rifampicin (23.7%) used together. This is because most patients who presented with suspected drug induced liver disease also had TB as a co-morbid condition. These patients were also on fixed dose combination medication and all of them were using isoniazid and rifampicin together at the same time. The results obtained in our study were in contrast to those of a study done in Malaysia on prevalence and risk factors for antituberculosis drug-induced hepatitis. In the Malaysian study involving 473 patients, the prevalence of anti-TB use among the patients was found to be at 9.7% but the main drugs were isoniazid and rifampicin [10].

One of the reasons for the difference in the values of the prevalence in the two settings could be attributed to the different methodologies used in the studies. The Malaysian study involved a comparison of the suspected cases with case controls selected by random sampling. This could have helped to eliminate any cases that were not ideally related to anti-TB drugs. Secondly,

Malaysia, unlike Kenya, had put in place adequate and effective systems of handling any suspected cases of drug-induced liver disease thereby reducing morbidity.

Antiretroviral use in the study population was the third most common at 20.6% with nevirapine (23.3 %) being the most common antiretroviral drug used followed by efavirenz. Most patients in this study who presented with liver disease were also on antiretroviral medication, mainly nevirapine and efavirenz .Similarly, in 2010, a similar study done by Chu *et al* reported that 14% of the patients were using nevirapine and that this drug was associated with hepatotoxicity. This difference in the proportions of nevirapine users could have been attributed to differences in the study population and geographical areas. Whereas our study involved both males and females and was localized, Chu et al study involved women in Kenya, Zambia and Thailand [4].In addition, the large number of study participants (820 women) in the latter study could have contributed to the difference.

The study done in Kenya, Zambia and Thailand was a prospective cohort where patients who were on nevirapine had their ALT and AST levels measured every 2,4,8,16 and 24 weeks followed by clinical evaluation for rash and hepatitis. This could mean that the results for nevirapine associated hepatoxicity were confirmed and other possible causes for the hepatotoxicity eliminated. This could have reduced the proportion of the number of cases that were actually nevirapine related as compared to our study which was a cross-sectional survey.

Another study by Chu et al in 2012 on nevirapine and efavirenz associated hepatotoxicity in Kenya and Mozambique also showed that 124 (2.13%) of the 5,832 HIV-infected individuals were using nevirapine and efavirenz based antiretroviral therapy. [6]. This proportion was much lower than those of nevirapine and efavirenz in our setting. The methodology in this study that involved follow up of patient liver biochemistry tests as well as causality assessment could have played a role in isolating the hepatotoxicity cases that were nevirapine and efavirenz associated. This could have reduced the number of cases that would otherwise have been inaccurately associated with nevirapine and efavirenz.

The use of antibiotics in the patients with liver disease in the study population was at 20% with amoxicillin-clavulanate use being the most common at 10.3%. A Spanish population based study involving 461 patients found out that the antibiotics were the most commonly used drugs among

DILI and amoxicillin-clavulanate was the most common at 12.8 % [15]. Probably, the use of amoxicillin –clavulanate was highly prevalent because of its broad spectrum of activity and affordability. Other antibiotics that were also used, however by a smaller proportion of the study population were ciprofloxacin, levofloxacin, sulfamethoxazole and minocycline.

The prevalence of analgesic use among the DILI patients was 19.6%, with paracetamol use being the most common. The reason for this could be that paracetamol is a drug that is available and affordable as an over the counter drug in our setting. A similar study in the USA found that the use of paracetamol alone or in combination with other drugs was quite common and accounted for 49% of all the cases studied [19].These proportions could have differed due to the difference in methodologies. The USA study involved 1000 patients and was a prospective cohort that was looking at the association between paracetamol and hepatic failure. There is also the probability that paracetamol use in the USA was much more common than in our setting.

5.4 Patterns of Drug-Induced Liver Disease

5.4.1 Hematological Pattern

Almost all of the patients in the study population presented with elevated liver enzymes and total bilirubin. A report by Watkins after a study in the USA stated that those biomarkers commonly implicated with liver disease were elevated ALT, AST and bilirubin levels [17].This finding was in tandem with the findings in our setting probably because the first presentation of any patient with liver disease is normally elevation of bilirubin and liver enzymes.

5.4.2 Physical presentation pattern

Almost 80% of the total patients studied presented with jaundice probably because this is a common sign of patients with liver disease. The results of the proportion of patients with jaundice were in contrast to those of a study done in UK by Bjornsson *et al*.In this study, the proportion of patients who presented with jaundice were 27% [9].This difference in proportion could have been due to the number of study participants. The study in UK involved only 96 patients while that done in our setting involved 485 patients.UK unlike Kenya is also a developed country that has established systems of diagnosis and management hence reducing

morbidity. Other signs and symptoms that were seen quite frequently in our study population were nausea, vomiting and pruritus.

5.4.3 Pathological pattern

Majority of our participants (60%) presented with hepatocellular injury pattern. The high proportion of the hepatocellular injury pattern in our setting could have meant that most of the agents might have induced liver injury following this pattern. This tallies with a study by Andrade *et al* in Spain which found out that that the hepatocellular injury pattern was the most common at 59% [15].This similarity in prevalence means that the agents associated with liver disease in both settings, followed this pattern. In about 30% of the patients in our study population, steatohepatitis pattern of liver injury was also seen. Alcohol is the drug that has been found to most commonly produce steatonecrotic changes in the liver [24, 25]. This could therefore have been true because the prevalence of alcohol use in our study population was also above 30%.

5.5 Prevalence of risk factors for Liver Disease in the study population.

Alcohol use (37.7%), TB coinfection (21.2%), HIV coinfection (15.7%) and low albumin (7%) were the major risk factors for liver disease found in our study population. This could have been because the prevalence of use of alcohol, anti-TB drugs and antiretrovirals were also of almost similar proportions. Most of the patients in our setting had used alcohol and also had TB and HIV co- morbidities. Low albumin levels were also seen in quite a number of patients. These results were in tandem with those of a study by Gaude *et al* in India in which it was found that regular alcohol intake, multiple co-morbid conditions and hypoalbuminaemia were independent risk factors for the development of DILD[66].This similarity in results could have been because these risk factors affect both the liver disease patients in our setting as well as those patients in India.Similarly,Marzuki *et al* in a study in Malaysia also found out that HIV infection, extra pulmonary TB and low albumin were major significant risk factors[10] .

In another study in the USA, Chalasani *et al* found out that alcohol use, HIV co-infection and TB co-infection were major risk factors for drug-induced liver disease [65].This similarity with our

study results could mean that these three risk factors for drug-induced liver disease were common in both our setting and the American setting.

5.6. Strategies employed in the management of Liver Disease in the study population

Among the management strategies employed, drug withdrawal was the major management strategy. Most patients showed some degree of recovery after the drugs had been withdrawn. A similar study in India by Shakya *et al* concluded that timely detection and withdrawal of the suspected offending agent can completely cure anti-TB drug associated hepatotoxicity [6].

The drug withdrawal strategy was followed by the use of antibiotics in over half of the study population. Metronidazole and ceftriaxone were the main antibiotics used and in some cases as a combination. This is due to their broad spectrum activities, availability and affordability in the hospital.

Antibiotic use was followed by analgesic use which was mainly tramadol. It is commonly used for epigastric pain in patients with liver disease in our setting due its availability and affordability in the hospital, and also less gastrointestinal side effects. There are some few patients who were put on diclofenac and paracetamol regardless of their hepatotoxic effect. This may have been due to lack of adequate knowledge on the hepatotoxicity effects of these two drugs on the part of some clinicians .Diuretics were also used in about 30% of the study population in which the combination of spironolactone/furosemide was most commonly used to manage ascites. The reason for their common use could be because they are effective, available in the hospital and affordable as well.

5.7. Outcomes of treatment of Liver Disease.

Out of the 485 patients studied, almost 90% of them were admitted at some point during management. Majority were still in the ward during the study period. These results were in contrast to those of the study done in the United Kingdom by Bjornsson *et al* in which 23% of the patients studied were admitted [9]. This difference in proportions could have been brought

about by the difference in the number of study participants. The study in UK involved 96 patients only while the one in our setting involved 485 patients.

The patients who were admitted in the UK study, were hospitalized for only 5 days[71].In the study in our setting,21%of the study population were hospitalized for between 0-5 days while majority(31.7%) of the patients in our study population were hospitalized for between 11-15 days. There was a delayed stay in hospital for our patients from these results as compared to the UK study. This could have been attributed to the fact that Kenyatta National Hospital is a referral hospital where patients with progressed liver disease are referred. These cases would have therefore required prolonged hospitalization.

The proportion of patients that died in our setting during management was 7%.Probable causes include late diagnosis, presence of chronic liver disease or even poor response to treatment on the part of the patient. Another similar study done by Chalasani *et al* in USA found out that among the 1,257 enrolled subjects with suspected DILI, 10% of the patients died. The larger number of patients who died in the USA study as compared to the one in our setting could be attributed to the fact that the USA unlike Kenya is a developed country that has advanced methods of capturing all mortality cases.

A bivariate analysis which was done to establish if there was an association between the participants social demographics and the outcome of treatment of liver disease found none of the characteristics to be statistically significant and therefore to have no effect on the outcome of treatment. .However, this finding contrasts with that of a study done in a Spain by Lucena *et al* which was found that being female was greatly associated with development of fulminant hepatic failure due to suspected drug induced liver injury [15].This could be attributed to a difference in the races of the two study populations. Perhaps the women in the Spanish population were more predisposed to developing drug induced hepatic failure compared to the women in the African population in our setting.

A multivariate analysis and logistic regression done to establish if there was a relationship between the drugs used by the patients with liver disease and the outcome showed that the use of antiretrovirals and recreational drugs increased the likelihood of having an undesirable outcome by 30% and 56% respectively even after a management strategy had been employed. Alcohol use

has been found to be one of the major causes of liver disease. Antiretroviral drugs have also been associated with hepatotoxicity and worse outcomes on chronic use as well [4, 6].These reasons could help explain why undesirable outcomes in our study population were quite common with patients who had used these drugs.

Similarly, a bivariate analysis of these liver function tests done on the study population and the outcomes of treatment established that patients who presented with prolonged prothrombin time were more likely to end up with an undesirable outcome like admission, relapse or death. This finding contrasted with that of the study by Lucena et al in Spain which concluded that those patients who presented with jaundice had an 11.7% chance of progressing to death or liver transplantation [72].This difference could have been because of the different management strategies employed in the two settings.

Another bivariate analysis done to establish an association between the risk factors and the outcomes of treatment of liver disease found alcohol use to be statistically significant and that the presence of this increased the chances of the patients experiencing an undesirable outcome such as admission, death or relapse. This finding was in tandem with the studies done in India and USA where it was found that alcohol played a major role in the development and worsening of drug-induced liver disease [66, 65].

In the same way, multivariate analysis and logistic regression was done to establish if there was an association between the particular management strategies and the outcome of treatment of the suspected drug induced liver disease cases. This analysis found out that the use of steroids, antihistamines and vitamin K as management strategies increased the likelihood of having a desirable outcome by two times, three times and five times respectively. Prolonged prothrombin time has been associated with undesirable outcomes in this study population and this can be greatly reduced by using vitamin K.

5.8 Limitations of the Study.

The study involved face to face interviews with patients and some patients declined to participate in the study due to their own reasons or other unexplained reasons. Addition of 10% to the sample size calculation helped to minimize this limitation. Secondly, some patients may have

underreported over reported their experiences. This was minimized by counterchecking some information in patients' files. However, as common with review of files, some data was missing but the researcher tried as much as possible to take files with as rich information as possible.

There were cases where patients were on more than one a drug at a particular time making it a bit challenging to associate a particular drug with the liver injury. This was minimized by using the bivariate and multivariate analysis which helped to identify those drugs that were statistically significantly associated with the liver injury cases.

This study involved a large sample size and was time consuming as well as costly.

CONCLUSION

Majority of patients (59.8%) had hepatocellular injury and presented with elevated liver enzymes (97 %) and jaundice (78.4 %). The most frequently used and suspected drug causing liver disease among patients was alcohol at 37.7 %.

Our study has demonstrated that use of antiretrovirals (OR=0.31; 95 % CI: 0.17-0.57; p=0.05) and alcohol (OR=0.56; 95 % CI: 0.35-0.89; p=0.05) increased the likelihood of having an admission, relapse or death among patients by 31% and 56% respectively.

Most of the management strategies (90.9%) involved the withdrawal of the offending agent. Other strategies included use of steroids(OR=2.30;95% CI:1.46-3.64;p<0.00001), antihistamines(OR=4.52; 95% CI: 1.85-11.02;p<0.00001) and vitamin K(OR=3.09; 95% CI:1.82-5.22;p<0.00001) and these were found to increase the likelihood of having a desirable outcome by two times, five times and three times respectively. More than half (55.5 %) of the patients were admitted for more than 10 days during management and mortality was at 7%.

RECOMMENDATIONS

For Change of Practice

Clinicians should be encouraged to be frequently monitoring and counselling liver disease patients who are using ARVs. Liver diseased patients who still use alcohol should be advised to stop as this has been shown to have undesirable outcomes. Clinicians should also be advised on those management strategies of DILD that have been found to increase the chances of desirable outcomes such as the use of vitamin K, steroids and antihistamines.

Other similar studies should also be carried out in other hospitals so as to improve on the management of liver disease patients. Case control studies should be carried out as well with the aim of determining the cause-effect relationships of the various risk factors associated with liver injury in the country. This may help mitigate the risk factors identified.

For Change of Policy

1. Liver diseased HIV positive patients on ARVs should be monitored more regularly compared to the HIV negative counterparts.

2. Steroids should be a cornerstone for the management of liver disease.

3. The management of DILI varied across the study participants. We suggest formulation of treatment guidelines to harmonize the management since there are no standard treatment guidelines for the management of DILI in the hospital.

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7.0 APPENDICES

7.1 APPENDIX 1: Informed Consent

Title of the Study: Risk factors, Management and Outcomes of Drug-induced Liver Disease in adult patients with liver disease attending the Kenyatta National Hospital.

Investigator: Dr.Caroline Asin.

Institution: Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, P.O.Box 30197-00400, Nairobi.TEL:0202119317

Ethical Approval: This study will be done only after approval from the University of Nairobi/Kenyatta National Hospital Ethics and Research Committee.

Permission is requested from you to enroll in this medical research study. Before you participate, it is important that you understand the following principles that apply to all participants.

i. Your agreement to participate in this study is voluntary.

ii. You may withdraw from the study at any time without necessarily giving a reason for your withdrawal.

iii. After you read the explanation above, please feel free to ask any questions that will enable you to understand the nature of this study clearly.

Introduction: In this study, I will be investigating the drugs and risk factors that may have caused you to develop liver disease or worsened your liver disease. I will also be looking at how these cases have been managed and the outcome of management.

Procedure: With your permission, I will interview you by asking you various questions about your condition and also obtain some information from your file. The information that I will obtain from your file will be on the various drugs that you have been using at the time of diagnosis of liver disease and after diagnosis, their doses and their duration of use. I will also collect information on the serum biomarkers in the blood that are used to confirm and monitor liver disease as well as any other risk factors that may have contributed to you developing liver disease or worsened it. Information on how your case was managed and the outcome of the management procedures will also be obtained from your file. All information will be handled with strict confidentiality. This information will then be used to analyze the drugs and other risk factors that lead to development or worsening of your condition as well as to analyze the management strategies so as to establish if these strategies are effective and the outcome of applying them in management. This will help in improving the way patients with liver disease

are managed in this hospital. On completion of this study, all the data collected (hard copies) will be kept under lock and key in a cabinet in the lead investigator's office for confidentiality for a period of 5 years and then shredded after this period. Data available on soft copy will be kept in a password protected database for confidentiality and deleted after the same period.

Risks: There will be no risks involved in this study to you.

Benefits: There will be no direct benefits to you but the results obtained from this study will help to improve patient care and safety in this hospital.

In case of any questions or concerns please feel free to contact me, my supervisors, my academic department or the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee using the contacts provided below.

I now request you to sign this consent form below.

CONSENT FORM

I …….. give consent to the investigator to use my patient information as well as my medical records in her study. The nature of the study has been explained to me by Dr. Caroline Asin.

Signature…… Date…….....

I confirm that I have explained the nature and effect of the study.

Signature…… Date……..

CONTACTS:

1. Principal Investigator: **Dr.Caroline Asin,** Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, P.O.Box 19676-00400, Nairobi. Mobile Number: 0716587342

2. Lead Supervisor: **Dr.D.G.Nyamu,** Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi, P.O.Box 19676-00400, Nairobi, Tel: 0202119217

3. Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee, P.O Box 20723-00100 Nairobi, Tel: 2726300/2726450 Ext: 44102.

7.2 APPENDIX 2: Hati ya Ridhaa (Kiwahili version of Informed Consent)

Hati hii itasomewa washiriki wa utafiti huu kwa umakini.

Jina la Utafiti: Madawa na sababu zinginezo za hatari zinazosababisha ugonjwa wa ini kati ya waliyo na ugonjwa wa ini, matibabu mbalimbali ya hali hizi na matokeo ya matibabu haya katika hospitali ya kitaifa ya Kenyatta.

Mtafiti Mkuu: Daktari Caroline Asin.

Taasisi: Idara ya Masomo ya Madawa katika Chuo Kikuu cha Nairobi.

Maadili idhini: Utafiti huu utatekelezwa baada ya kuidhinishwa na kamati la utafiti la Chuo Kikuu cha Nairobi/ Hospitali ya Kitaifa ya Kenyatta.

Hati hii ni ya kukuomba ruhusa ya kujiandikisha katika utafiti huu.Kabla ya kujiandikisha, ni muhimu kwanza uweze kuelewa kanuni zifuatazo zinazowahusu wale wote watakaojiandikisha kushiriki katika utafiti huu.

i. Kukubali kwako kushiriki katika utafiti huu si wa lazima.

ii.Unaweza kujiondoa kwenye utafiti huu hata baada ya kujiandikisha bila kutoa sababu zozote za kujiondoa.

iii.Baada ya kusoma hati hii, usiogope kuuliza maswali yoyote ambayo yatakuwezesha kuelewa kiini cha utafiti huu vizuri.

Kianzilio: Katika utafiti huu, nitakuwa nikichunguza maadawa na sababu zinginezo za hatarizinasobabisha ugonjwa huu wa ini uliyo nayo au hata kuuzidisha.Pia nitakuwa nikichunguzamatibabu uliyoyapata kuhusu ugonjwa huu na matokeo ya matibabu hayo.

Utaratibu: Kwa ruhusa yako, nitakuuliza maswali mbalimbali kuhusu ugonjwa huu wako wa inina pia nitatoa habari zingine kuhusu huu ugonjwa kwenye faili yako ya hospitali.Habarinitakazotoa kwenye faili yako zinahusu madawa mbalimbali ambazo umetumia kabla na baada ya kupatikana na ugonjwa wa ini, kiasi na dozi zao na muda ambayo ulizitumia.Pia nitatafutahabari kuhusu ngazi ya vipengele mbalimbali zilizo kwenye damu yako zinazosaidia kutambua ugonjwa wa ini.Habari kuhusu sababu zinginezo zinazosababisha madawa kuendeleza ugonjwa wa ini pia zitarekodiwa.Matibabu uliyoyapata pamoja na matokeo

ya matibabu haya yatarekodiwa pia.Habari hizi zote zitawekwa kwa siri na kufichwa ili watu wengine ambao siwatafiti wasiweze kuziangalia.Baadaye, habari hizi zote zitachambuliwa kwa ana na matokeo yake yatatumiwa kuboresha vile ambavyo wagonjwa wote wenye ugonjwa wa ini wanavyotunzwa na kutibiwa katika hospitali hii kuu ya Kenyatta.Baada ya kuchambuliwa,habari hizi zote ambazo zitakuwa zimekusanywa, zitawekwa vizuri kwenye kabati liyofungwa na kifuli iliyoko kwenye ofisi ya mtafiti mkuu kwa muda wa miaka mitano na kuharibiwa baadaye.Habari zitakazokuwa zimewekewa kwenye mtandao wa komputa pia zitawekwa kwa siri na kufutwa baadaye .Hakuna mtu mwingine atakayeweza kufungua kabati hili au kuangalia habari zilizoko kwenye komputa ila mtafiti mkuu peke yake.

Hatari: Hakutakuwa na hatari yoyote kwako utakaotokea kwasababu ya kuhusika katika utafiti huu.

Faida: Hakutakuwa na faida za moja kwa moja kwako kwasababu ya kuhusika katika utafiti huu lakini matokeo ya utafiti huu, yatatumiwa kusaidia kuboresha vile wagonjwa wenye ugonjwa wa ini watakavyotunzwa na kutibiwa katika hospitali hii.

Kama utakuwa na maswali yoyote hata baada ya kujiandikisha ili uweze kuhusika katika utafiti huu, usiogope kuwasiliana nami, msimamizi wangu, idara yangu ya masomo ya madawa au kamiti la utafiti la Chuo Kikuu cha Nairobi/Hospitali ya kitaifa ya Kenyatta kwa kutumia anwani au nambari za simu ambazo zimeandikwa hapo chini kwenye fomu la kutiwa ishara ya makubaliano.

Sasa ningependa kukuomba utie saini yako kwenye fomu hili hapa chini kama ishara ya kukubali kuhusika katika utafiti huu.

HATI YA RIDHAA YA MAKUBALIANO.

Mimi …….. nampa ruhusa huyu mtafiti mkuu kutumia habari kuhusu hali yangu na habari zozote atakazohitaji kutoka faili yangu ya matibabu kwenye utafiti huu.Asili na kiini cha utafiti huu vimeelezwa vizuri kwangu na Daktari Caroline Asin.

Saini…… Tarehe…….....

Nathibitisha ya kwamba asili na kiini cha utafiti huu vimeelezwa vizuri.

Saini…… Tarehe……..

MAWASILIANO

1. Mtafiti Mkuu: **Daktari Caroline Asin,** Idara ya Masomo ya Madawa katika Chuo Kikuu Cha Nairobi, P.O.Box 19676-00400, Nairobi. Nambari ya simu: 0716587342
2. Msimamizi Mkuu: **Daktari D.G.Nyamu,** Idara ya Masomo ya Madawa katika Chuo Kikuu Cha Nairobi, P.O.Box 19676-00400, Nairobi, Nambari ya Simu: 0202119217
3. Kamiti la Utafiti la Chuo Kikuu cha Nairobi/Hospitali ya Kitaifa ya Kenyatta P.O Box 20723-00100 Nairobi, Nambari ya Simu: 2726300/2726450 Ext: 44102.

7.3 APPENDIX 3: Eligibility Criteria Checklist

(Tick where appropriate).

Inclusion criteria:

1. ≥18 years ☐
2. Presence of diagnosed Liver Disease ☐

Exclusion Criteria:

1. < 18 years ☐
2. Pregnant ☐
3. Psychotic ☐
4. Absence of diagnosed liver disease ☐

7.4 APPENDIX 4: Data Collection Tool (English Version)

Section A: Participants' Social demographics

1. Age (Years) ----------
2. Gender: Male [ ] Female [ ]
3. Residence (County)…
4. Marital status: (Tick where appropriate): 1.Single------- [ ] 2.Married----- [ ] 3.Divorced---- [ ] 4.Widowed--- [ ]
5. Occupation: (Tick where appropriate): 1.Unemployed --[ ] 2.Salaried ----[ ] 3.Self employed-- [ ] 4.Student -------- [ ]
6. Highest academic level (Tick where appropriate): 1.College /University…. [ ] 2. Secondary… [ ] 3.Primary…. [ ] 4.Non –formal….. [ ]
7. Date of admission… ……(if admitted)
8. Duration of illness.....
9. History of smoking Yes[ ] No[ ]

Section B

To Determine the Prevalence of Drug Induced Liver Disease among Adult Patients.

Indicate in the table below if the patient has ever used/is using any of the mentioned drugs that may cause drug-induced liver disease.

CLASS OF DRUG	DRUG	Tick if used/using	DAILY DOSE	DURATION (days)
1.Antiretrovirals	Nevirapine			
	Efavirenz			
	Others(specify)			

2.Xanthine oxidase Inhibitors	Allopurinol			
	Others(specify)			
3.Antidiabetics	Acarbose			
	Others(specify)			
4.Antidepressants	Fluoxetine			
	Trazodone			
	Venlafaxine			
	Others(specify)			
5.Antihypertensives	Losartan			
	Others(specify)			
6.Anaesthetics	Halothane			
	Others(specify)			
7.Analgesics	Paracetamol			
	Diclofenac			
	Aspirin			
	Others(specify)			
8.Anticonvulsants	Valproate			
	Carbamazepine			
	Phenytoin			
	Others(specify)			
9.Antibiotics	Tetracycline			
	Minocycline			
	Erythromycin			
	Amoxicillin – Clavulanic acid			
	Quinolones e.g Ciprofloxacin, Levofloxacin.			
	Sulfamethoxazole			

	Nitrofurantoin			
	Others(specify)			
10.Anti-TB drugs	Isoniazid			
	Rifampicin			
	Others(specify)			
11.Antiarrhythmics	Amiodarone			
	Others(specify)			
12.Antifungal agents	Ketoconazole			
	Others(specify)			
13.Anticancer drugs	Methotrexate		(Indicate cumulative dose)	
	Azathioprine			
	Others(specify)			
14.Antipsychotics	Chlorpromazine			
	Others(specify)			
15.Diuretics	Furosemide			
	Others(specify)			
16.Hypolipidemics	Lovastatin			
	Others(specify)			
17.Muscle relaxants	Dantrolene			
	Others(specify)			
18.Hormones	Androgens			
	Estrogens			
	Tamoxifen			
	Danazol			
	Others(specify)			
19.Supplements	Vitamin A			
	Vitamin E			
	Others(specify)			
20.Recreational drugs	Alcohol			

	Cocaine			
	Ecstasy			
	Others(specify)			
21.Herbs	Comfrey oil			
	Pennyroyal oil			
	Margosa oil			
	Clove oil			
	Others(specify)			
22.Others classes	Others(specify)			

Section C

To Describe the Pattern of Liver Injury Caused by the Drugs

Part 1: Hematological pattern

Did the patient present with the following features at the time of diagnosis of liver disease?

1. Elevated Serum bilirubin Yes [ ] No[ ]
    a. conjugated bilirubin –indicate levels----------
    b. unconjugated bilirubin-indicate levels----------
2. Elevated urine urobilinogen Yes [ ] No[ ]
3. Elevated liver enzymes Yes [ ] No[ ]
    a. transaminases:
        i. Aspartate Transaminase (AST) Indicate Levels----------
        ii. Alanine Transaminase (ALT) Indicate Levels----------

b. Lactate Dehydrogenase (LD / LDH) Indicate Levels----------

c. alkaline phosphatase (alp)----------

d. Gamma Glutamyl Transpeptidase (GGT/γGT) ----------

4. Reduced plasma proteins (Albumin) Yes [ ] No[ ] Indicate levels ----------

5. Prolonged Prothrombin time(PT) Yes [ ] No[ ] Indicate Time----------seconds

6. Elevated immunoglobulins (Igs) Yes [ ] No[ ]

   Specify

   a) IgG Levels----------

   b) IgA Levels----------

   c) IgM Levels----------

   d) IgD Levels----------

   e) IgE Levels----------

7. Raised Alpha-foetoprotein (AFP) Levels----------

8. Reduced alpha-1 antitrypsin levels Yes [ ] No[ ] Levels----------

9. Increased serum ferritin levels Yes [ ] No[ ] Levels----------

10. Increased plasma ammonia Yes [ ] No[ ] levels----------

11. Increased Cerebrospinal Fluid(CSF) glutamine Yes [ ] No[ ] levels----------

Part 2: Physical Presentation/pattern

1. Pruritus Yes [ ] No[ ]
2. Nausea/Vomiting Yes [ ] No[ ]
3. Cachexia Yes [ ] No[ ]
4. Gynaecomastia in Males Yes [ ] No[ ]
5. Bleeding tendencies Yes [ ] No[ ]
6. Diabetes Mellitus Yes [ ] No[ ]
7. Hepatomegaly Yes [ ] No[ ]
8. Jaundice Yes [ ] No[ ]
9. Ascites Yes [ ] No[ ]

10. Hepatic Encephalopathy Yes [ ] No[ ]
11. Other(specify)----------

Part 3: For those patients with liver disease whose condition may have been worsened by a drug or by the specified risk factors after diagnosis, record atleast 2 separate LFT readings with their corresponding signs and symptoms at the time of performing these tests. These tests should have been taken within a 2 year period of taking a suspected offending drug or association with a specified risk factor.)

LFT READINGS	**DATE**	**LEVELS OF SERUM BIOMARKERS**	**SIGNS AND SYMPTOMS**
Reading 1		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	
Reading 2		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	
Reading 3		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	
Reading 4		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	

Part 4: Pathological pattern

(Tick in the column adjacent to the defined pattern)

PATTERN	FEATURES	TICK HERE
1. Hepatocellular injury	-Elevations in aminotransferases usually preceding elevations in total bilirubin levels and alkaline phosphatase levels.	
	-Most injuries occur within one year of initiating the offending agent.	
2. Centrilobular necrosis	-Often dose-related and predictable reaction secondary to drugs like paracetamol.	
	-Can also be associated with idiosyncratic reactions such as those caused by halothane.	
	-Patients present with elevations in the serum aminotransferases.	
	Severe forms are accompanied by nausea, vomiting, upper abdominal pain and jaundice.	
3. Steatohepatitis	-Patients may present with abdominal fullness or pain as their only complaint.	
	In more severe cases, patients will present with symptoms characteristic of alcoholic hepatitis such as nausea, vomiting, pruritus, steatorrhoea, abdominal pain and fatigue.	
4. Phospholipidosis	-Commonly seen in patients who have received higher doses of amiodarone.	
	-Usually develops in patients who have been treated for more than one year.	
	-Patients may present with either elevated aminotransferases or hepatomegaly	
	-Jaundice is rare in this case	
5. Generalized Hepatocellular Necrosis	-Onset of symptoms is usually delayed as much as one week after exposure to the toxin.	
	-Present as autoimmune reactions.	
6. Toxic cirrhosis	-Patients present with cirrhosis and not hepatitis.	
	-Commonly occurs in patients treated for psoriasis and arthritis using methotrexate.	
	-There is a lack of clear dose-dependent relationship.	
	-In patients with Vitamin A toxicity, gingivitis and dry skin are very common.	
	-The above reaction is worsened by use of	

	ethanol.	
7. Cholestatic injury	-Most patients present with nausea, malaise, jaundice and pruritus.	
	-Elevations in serum alkaline phosphatase levels are more prominent and usually precede the elevations of other liver enzymes in the serum.	
	-Clinically these patients are often asymptomatic and present with mild to moderate elevations of serum bilirubin.	
	-ALT, AST and levels are also elevated later on.	
	-The intravenous form of Vitamin E (Tocopherol acetate) which causes cholestatic jaundice commonly causes liver injury through this pattern.	
8. Liver Vascular Disorders	-May present as liver cirrhosis	
	-Incidences are rare and may be dose related.	
9. Peliosis hepatitis	-Androgens are the most frequently reported agents which cause peliosis hepatitis often after 6 months of therapy.	

Section D

To find out the Risk Factors Associated with Drug-Induced Liver Disease.

Indicate in the adjacent columns the duration of illness or duration of exposure to the environmental hepatotoxins in the event that the patient has been associated with the mentionedrisk factor. As for the serum biomarkers, indicate by ticking on the adjacent column.

Risk Factor	**Tick**	**Duration**	**Other**
1. Alcohol consumption			Indicate specific brand/number of bottles per day
2. Previous infection/Co-infection with TB			
3. Co-infection with HIV			

4. Co-infection with Diabetes Mellitus			
5. Previous illness with cancer			
6. Previous/Co-infection with Hepatitis B/C			
7. Family history of liver disease			(Indicate gender of the family members with liver disease)
8. Any previous surgeries			Specify
9. Malnourished patient because of illness or long-term alcohol abuse			
Environmental hepatotoxins:		**Duration of Exposure/Work**	
10. Arsenic chemical plants (insecticide factories), construction or agricultural workers.			
11. Carbon tetrachloride chemical plants workers (cement, soap, nylon and insecticide industries) and laboratory technicians.			
12. Copper plumbers and outdoor sculpture artists			
13. Dimethylformamide chemical plant workers and laboratory technicians			
14. 2,4-Dichlorophenoxycetic acid Horticulturists			
15. Fluorine chemical plant workers (Toothpaste industries) and laboratory technicians			
16. Toluene chemical plant workers (Paint, Glue, Nail polish remover and leather tanning industries) and laboratory technicians			
17. Vinyl chloride plastic plant workers.			

Serum biomarkers:			
18. Albumin below 3.5 mg/dl			
19. 2-4 fold rise in ALT value			
20. 2-4 fold rise in AST value			
21. 2-4 fold rise in Alkaline phosphatase value			
22. High serum iron and transferrin levels			

Section E

To Evaluate the Management Strategies Applied

(Fill in the adjacent column depending on the management strategy applied)

Management Strategy	**Tick**	**Other parameters to evaluate**
1. Use of antidote		Indicate specific antidote used and the dose
2. Drug withdrawal/Discontinuation		
3. Replacement/Substitution of drug with another drug		Specify drug used for substitution and daily dose
4. Others drugs used for management		
5. Surgical Measures		Specify:
Supportive Therapy		**For each specify type used and daily dose**
6. Analgesics		

7. Diuretics		
8. Antibiotics		
9. Beta-blockers		
10. Steroids		
11. Cholestyramine		
12. Antihistamines		
13. Vitamin supplementation		

Section F

To Evaluate the Outcomes of the Management Strategies Applied

(Indicate by ticking in the adjacent column the outcome of the management strategies applied above)

OUTCOME	**TICK**
1. Clinical Improvement	
Specify: eg Improvement in LFTs Improvement in signs and symptoms Reduced hospital visits	
2. Complete recovery	
3. Treated and discharged same day	
4. Relapse	
5. Admission/Length of hospital stay (days)	
6. Death	

7.5 APPENDIX 5: Fomu la kurekodi habari kuhusu wagonjwa

Sehemu ya A: Habari kuhusu ubinafsi wa mgonjwa

1. Umri (Miaka) ----------

2. Jinsia: Mume [ ] Mke [ ] (weka alama ya 'tick' kwenye jibu sahihi)

3. Makao (Kaunti)…….

4. Hali ya ndoa: (Weka alama ya 'tick' kwenye jibu sahihi): 1.Bado kuoa/kuolewa------- [ ] Amekwishaoa/Amekwishaolewa. ----- [ ] 3.Kupewa talaka---- [ ] 4.Mjane--- [ ]

5. Kazi: (Weka alama ya 'tick'kwenye jibu sahihi): 1.Kukosa ajira -- [ ] 2.Kuwa na ajira - [ ] Kujiajiri kibinafsi---- [ ] 4.Mwanafunzi -------- [ ]

6. Kiwango cha elimu (Weka alama ya 'tick' kwenye jibu sahihi): 1.Chuo kikuu…. [ ] 2.Shule ya upili [ ] 3.Shule ya msingi…. [ ] 4.Mafunzo yasiyo ya rasmi….. [ ]

7. Siku ya kulazwa hospitalini… ……. (kama mgonjwa amelazwa)

8. Muda wa ugonjwa.....

9. Historia ya kuvuta sigara Yes [ ] No [ ]

Sehemu ya B

Kuamua idadi ya maambukizi ya ugonjwa wa ini uliosababishwa na madawa kati ya wagonjwa wenye ugonjwa wa ini .

(Onyesha kwenye masafu hapa chini kama mgonjwa ashawahi kutumia haya madawa yaliyotajwa yanayoweza kusababisha ugonjwa wa ini.)

Kundi la dawa	**Dawa yenyewe**	**Weka alama ya "tick' hapa kama imetumiwa**	**Dozi ya kila siku**	**Muda wa kutumia dawa**
1.Madawa ya ugonjwa wa ukimwi	Nevirapine			
	Efavirenz			
	Zinginezo (Taja)			
2. Madawa aina ya "Xanthine oxidase inhibitors"	Allopurinol			
	Zinginezo (Taja)			
3.Madawa ya ugonjwa wa sukari	Acarbose			
	Zinginezo (Taja)			
4.Madawa yanayotibu kujiskia kuhuzunishwa	Fluoxetine			
	Trazodone			
	Venlafaxine			
	Zinginezo (Taja)			
5.Madawa ya presha juu ya damu	Losartan			
	Zinginezo (Taja)			
6.Madawa ya kupoteza hisa	Halothane			

	Zinginezo (Taja)			
7.Madawa ya kutuliza uchungu	Paracetamol			
	Diclofenac			
	Aspirin			
	Zinginezo (Taja)			
8.Madawa ya kutuliza degedege kwenye mwili	Valproate			
	Carbamazepine			
	Phenytoin			
	Zinginezo (Taja)			
9.Viuavijisumu(Mada-wa ya " antibiotics")	Tetracycline			
	Minocycline			
	Erythromycin			
	Amoxicillin – Clavulanic acid			
	Quinolones e.g Ciprofloxacin, Levofloxacin.			
	Sulfamethoxazole			
	Nitrofurantoin			
	Zinginezo (Taja)			
10.Madawa ya kifua kikuu	Isoniazid			
	Rifampicin			

	Zinginezo (Taja)			
11.Madawa ya ugonjwa wa moyo kupiga bila utaratibu (“anti-arrhythmics”)	Amiodarone			
	Zinginezo (Taja)			
12.Madawa ya magonjwa ya ngozi (“antifungals”)	Ketoconazole			
	Zinginezo (Taja)			
13.Madawa ya ugonjwa wa saratani	Methotrexate		(Rekodi dozi ya jumla)	
	Azathioprine			
	Zinginezo (Taja)			
14.Madawa ya kutuliza hali ya uazimu.	Chlorpromazine			
	Zinginezo (Taja)			
15.Madawa ya kupunguza maji mwilini kwa kuongeza mkojo	Furosemide			
	Zinginezo (Taja)			
16.Madawa ya kupunguza mafuta mwilini	Lovastatin			
	Zinginezo (Taja)			
17.Madawa ya kutuliza misuli	Dantrolene			
	Zinginezo (Taja)			

18.Madawa ya homoni za mwili	Androgens			
	Estrogens			
	Tamoxifen			
	Danazol			
	Zinginezo (Taja)			
19.Virutubisho (Madawa ya kuongezea afya mwilini)	Vitamin A			
	Vitamin E			
	Zinginezo (Taja)			
20.Madawa ya kulevya	Pombe			
	Cocaine			
	Ecstasy			
	Zinginezo (Taja)			
21.Madawa ya miti shamba	Comfrey oil			
	Pennyroyal oil			
	Margosa oil			
	Clove oil			
	Zinginezo (Taja)			
22.Kundi zinginezo za dawa	Taja madawa hayo moja kwa moja			

Sehemu ya C

Kuelezea mifano madawa yaliyotajwa yanapitia ili kusababisha ugonjwa wa ini

Sehemu ya 1: Mifano ya vipengele vya damu

Je, damu ya mgonjwa ilionyesha kuwa na vipengele hivi wakati wa kupatikana na ugonjwa wa ini?

1. Kuongezeka kwa serum bilirubin Ndio [ ] Hapana [ ]
    a. conjugated bilirubin –(onyesha ngazi)----------
    b. unconjugated bilirubin-(onyesha ngazi)----------
2. Kuongezeka kwa urobilinogen kwenye mkojo Ndio [ ] Hapana [ ]
3. Kuongezeka kwa enzymes zilizomo kwenye ini Ndio [ ] Hapana [ ]
    a. Transaminases:
        i. Aspartate Transaminase (AST) (Onyesha ngazi)----------
        ii. Alanine Transaminase (ALT) (Onyesha ngazi)----------
    b. Lactate Dehydrogenase (LD / LDH) (Onyesha ngazi) ----------
    c. alkaline phosphatase (alp) (Onyesha ngazi)----------
    d. Gamma Glutamyl Transpeptidase (GGT/γGT) (Onyesha ngazi) ----------
12. Kuongezeka kwa plasma ammonia Ndio [ ] Hapana[ ] (Ngazi)----------
13. Kuongezeka kwa glutamine iliyoko kwenye Cerebrospinal Fluid(CSF) Ndio [ ] Hapana[ ] (Ngazi)----------

Sehemu ya 2: Ishara na dalili ya kimwili

12. Kujikuna Ndio[ ] Hapana[ ]
13. Kichefuchefu/Kutapika Ndio [ ] Hapana[ ]
14. Kuzorota kwa mwili Ndio [ ] Hapana[ ]
15. Mwanaume kuwa na matiti Ndio[ ] Hapana[ ]
16. Kutokwa na damu mara kwa mara kwenye viungo Ndio [ ] Hapana[ ]

17. Ugonjwa wa sukari Ndio [ ] Hapana[ ]
18. Kufura kwa ini (Hepatomegaly) Ndio [ ] Hapana[ ]
19. Jaundice Ndio [ ] Hapana[ ]
20. Ascites Ndio [ ] Hapana[ ]
21. Hepatic Encephalopathy Ndio [ ] Hapana[ ]
22. Zinginezo (taja moja kwa moja)----------

Sehemu ya 3: Kwa wale wagonjwa ambao ugonjwa wao wa ini waweza kuwa ulizidishwa kwa kutumia dawa fulani au mazingira yake baada ya kupatikana na ugonjwa wa ini, rekodi angalau aina mbili za matokeo ya ngazi za vipengele vya damu pamoja na ishara na dalili za mgonjwa wakati ngazi hizi zilikuwa zikirekodiwa kwenye faili ya mgonjwa.Ngazi za vipengele hivi zapaswa kuwa zimerekodiwa kwa muda wa miaka miwili ya kutumia dawa hii au kuhusika na mazingira fulani ya hatari.

MATOKEO YA LFTs	**TAREHE**	**NGAZI ZA VIPENGELE VYA DAMU**	**ISHARA NA DALILI ZA MGONJWA**
Matokeo ya 1		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	
Matokeo ya 2		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	
Matokeo ya 3		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	
Matokeo ya 4		a.ALT- b.AST- c.Alkaline Phosphatase- d.Bilirubin i. Conjugated- ii.Unconjugated-	

Sehemu 4: Mfano wa patholojia

(Onyesha kwa kuweka alama ya 'tick' kwenye safu iliyoonyeshwa

MFANO	MAKALA	WEKA 'TICK' HAPA KAMA MAKALA YANAAMBATANA NA MGONJWA
1.Hepatocellular injury	-Kuongezeka kwa ngazi za aminotransferases sana sana baada ya kuongezeka kwa ngazi za total bilirubin na alkaline phosphatase	
	-Mfano huu waonekana sana baada ya mwaka moja wa kuanzishwa dawa.	
2.Centrilobular necrosis	-Yategemea sana dozi ya dawa na matokeo ni ya kutarajiwa.Dawa ya paracetamol ni mojawapo ya madawa hizi.	
	-Yaweza kuhusishwa na 'idiosyncratic reactions' yanayosababishwa na dawa ya halothane.	
	-Wagonjwa huonyesha ishara na dalili ya kuongezeka kwa serum aminotransferases.	
	-Kesi za kuhatarisha zinaandama na ishara kama kichefuchefu, kutapika, uchungu wa sehemu ya juu ya tumbo na jaundice.	
3.Steatohepatitis	-Wagonjwa huskia kujaa kwa tumbo ama uchungu pekee yake.	
	Kwenye kesi za kuhatarisha, wagonjwa huwa na ishara na dalili za ugonjwa wa ini unaosababishwa na pombe kama kichefuchefu, kutapika, kujikuna, kuhara mafuta kwenye haja kubwa, uchungu wa tumbo na uchovu.	
4.Phospholipidosis	-Yaonekana sana kwa wagonjwa waliotumia dozi ya juu sana ya dawa ya amiodarone.	
	-Pia yaonekana sana kwa wagonjwa waliotumia dawa kwa muda iliyozidi mwaka mmoja.	
	-Wagonjwa huonyesha kuongezeka kwa ngazi za aminotransferases au kufura kwa ini.	
	-Jaundice huwa haionekani sana kwenye kesi hizi.	
5.Generalized Hepatocellular	-Dalili huwa zinaonekana kama baada ya wiki moja ya kutumia dawa	

Necrosis		
	-Kesi hizi huwa zinaoekana kama ‘autoimmune reactions.’	
6.Toxic cirrhosis	-Wagonjwa huonyesha kuwa na cirrhosis wala si hepatitis.	
	-Yaonekana sana kwa wagonjwa waliyo ugua psoriasis na arthritis halafu wakatibiwa na dawa ya methotrexate.	
	-Ishara zinazoonekana hazitegemei dozi ya dawa iliyotumika.	
	-Kwa wagonjwa waliyotumia Vitamin A, kufura kwa gamu ya meno na ngozi iliyokauka ndizo ishara zinazoonekana sana.	
	-Ishara hizi huzidishwa kwa kutumia ethanol.	
7.Cholestatic injury	-Wagonjwa wengi huonyesha ishara za kichefuchefu, uchovu wa mwili, jaundice na kujikuna.	
	-Kuongezeka kwa ngazi za serum alkaline phosphatase ndio huonekana sana na huwa zinafuata kuongezeka kwa ngazi za liver enzymes zinginezo kwenye damu.	
	-Wakati mwingine wagonjwa huonyesha kuongezeka kidogo kwa ngazi ya serum bilirubin.	
	-Kuongezeka kwa ngazi za ALT na AST huonekana baadaye.	
	-Dawa ya kudungwa ya Vitamin E (Tocopherol acetate) inayosababisha ‘cholestatic jaundice’ ndio hufuata mfano huu sana.	
10. Liver Vascular Disorders	-Yaweza kuonekana kama liver cirrhosis	
	-Kesi hizi ni chache sana na yaweza kutegemea dozi ya dawa iliyotumika.	
11. Peliosis hepatitis	-Androgens ndizo dawa ambazo husababisha sana peliosis hepatitis sanasana baada ya kutumika kwa muda wa miezi sita.	

Sehemu ya D

Kuchunguza sababu za hatari zinazohusishwa na ugonjwa wa ini unayosababishwa na madawa.

Onyesha/Rekodi kwenye masafu yafuatayo, habari kuhusu muda wa ugonjwa uliotajwa pamoja na muda wa kujihusisha kwa mgonjwa na sababu za hatari zilizotajwa. Kuhusu vipengele vya damu, onyesha kwa kutia alama ya tick' katika safu inayofuata.

Sababu za hatari	**Alama ya Tick**	**Muda**	**Habari zinginezo**
1.Kunywa pombe			Rekodi aina na nambari za chupa za pombe zilizotumika.
2.Ugonjwa wa kifua kikuu			
3.Ugonjwa wa ukimwi			
4.Ugonjwa wa sukari			
5.Ugonjwa wa saratani			
6.Ugonjwa wa Hepatitis B/C			
7.Ugonjwa wa ini kwenye familia ya mgonjwa			(Rekodi jinsia ya waliyokuwa au waliyo na ugonjwa wa ini kwenye familia)
8.Kufanyiwa upasuaji wa aina yeyote			(Taja aina ya upasuaji)
9. Kuzorota kwa hali ya mgonjwa kwasababu ya ugonjwa au kutumia pombe sana.			
Sababu za hatari zilizoko kwenye mazingira		**Muda wa kufanya kazi/kuishi karibu na mazingira haya.**	
10. Kampuni zinazotumia kemikali ya 'arsenic' kutengeneza madawa ya kuua wadudu au wanaofanya kazi ya ujenzi na kilimo.			

11. Kampuni zinazotumia kemikali ya ‘carbon tetrachloride’ kutengeneza saruji, sabuni, nylon, madawa ya kuua wadudu au wanaofanya kazi kwenye maabara ambayo huwa na kemikali hii.			
12. Mafundi walio/wanaotumia shaba na wasanii walio/ wanaofanya kazi ya uchongaji wa shaba.			
13. Walio/Wanaofanya kazi kwenye maabara iliyo na kemikali ya ‘Dimethylformamide’.			
14.Walio/Wanaofanya kazi ya kupalilia maua kwa kutumia dawa iliyo na kemikali ya ‘2,4-Dichlorophenoxyacetic acid’			
15. Walio/ Wanaofanya kazi kwenye kampuni inayotumia ‘fluorine’ kutengeneza dawa ya meno au maabara iliyo na kemikali hii.			
16. Walio/Wanaofanya kazi kwenye kampuni zinazotumia kemikali ya ‘toluene’ kutengeneza rangi ya ukuta, gundi, rangi ya kupaka kwenye makucha, kampuni za kulainisha ngozi (leather) au maabara iliyo na kemikali hii.			
17. Walio/Wanaofanya kazi kwenye kampuni zinazotumia ‘vinyl chloride’ kutengeneza vyombo vya plastiki.			
Vipengele vya damu			
23. Albumin iliyopungua 3.5 mg/dl			
24. Kuongezeka kwa ngazi ya ALT mara mbili au mpaka mara nne			
25. Kuongezeka kwa ngazi ya AST mara mbili au mpaka mara nne			

26. Kuongezeka kwa ngazi ya Alkaline phosphatase mara mbili au mpaka mara nne			
27. Ngazi za serum iron na transferrin zilizo za juu sana.			

Sehemu ya E

Kutathmini matibabu yaliyotolewa kwenye kesi hizi.

(Jaza masafu vilivyo kulingana na matibabu yaliyotolewa.)

Matibabu	**Weka alama ya'tick' kama ilitolewa**	**Vigezo vingine vya kutathminiwa**
1.Kutumia antidote		(Taja antidote iliyotumiwa pamoja na dozi yake.)
2.Mgonjwa kuachishwa dawa		
3.Mgonjwa kupewa dawa ingine badala ya ile aliokuwa akitumia mbeleni		(Taja dawa hiyo na dozi yake ya kila siku.)
4.Kutumia dawa zinginezo		(Taja dawa hizi na dozi zao.)
5.Mgonjwa kufanyiwa upasuaji		(Taja aina ya upasuaji.)
Aina ya matibabu ya madawa mengine yaliyotolewa ili kutibu ishara na dalili mbalimbali.		**Taja jina maalum ya dawa iliyotumiwa na dozi yake.**
1.Madawa ya kutuliza uchungu mwilini.("Analgesics")		
2.Madawa ya kupunguza maji mwilini kwa kuongeza mkojo ("Diuretics")		

3.Viuavijisumu (“Antibiotics”)		
4.Madawa aina ya “Beta-blockers”		
5.Madawa aina ya “Steroids”		
6.Dawa ya “Cholestyramine”		
7.Madawa ya aina ya “Antihistamines”		
8.Aina ya vitamini		
9.Dawa zinginezo (Taja moja kwa moja)		

Sehemu ya F

Kutathmini matokeo ya matibabu yaliyotolewa

(Onyesha kwa kutumia alama ya ‘tick’ kama matokeo ya matibabu yaliyotajwa kwenye masafu yafuatayo yaliambatana/yanaambatana na hali ya mgonjwa.Kama inavyotarajiwa kwinginepo,toa maelezo kamili.)

MATOKEO YA MATIBABU	**WEKA ALAMA YA ‘TICK’**
1. Mgonjwa kupata nafuu Taja moja kwa moja kwa mfano: Kuboreka kwa LFTs Kuboreka kwa ishara na dalili za ugonjwa Mgonjwa kupunguza kukuja hospitalini.	
2. Mgonjwa kupata nafuu kabisa.	
3. Mgonjwa kutibiwa na kukubaliwa kuenda nyumbani siku hiyo bila kulazwa.	
4. Mgonjwa kutibiwa halafu baada ya muda kuanza kuonyesha ishara na dalili ya ugonjwa tena	
5. Mgonjwa kulazwa hospitalini (Taja idadi ya masiku ya kulazwa)	
6. Kifo cha mgonjwa.	

8.0 STUDY BUDGET

S/No		No. of Items	Cost Per Item (Kshs)	Total Cost (Kshs)
1.	Data analysis	1	40,000	40,000
2.	Research assistants	2	15,000	30,000
3.	Stationery	-	-	5000
4.	Monthly internet	10	1500	15000
5.	Report writing & binding	1	3000	3000
6.	Copies of Dissertation	6	600	3,600
7.	Transport to KNH	4	3000	12,000
8	Miscellaneous	-	-	10,000
	TOTAL			**118,600**

Source of funding: **Principal Investigator**

9.0 ETHICS APPROVAL FORM

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
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(254-020) 2726300 Ext 44355

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KENYATTA NATIONAL HOSPITAL APPROVED 17 MAR 2015 KNH/UoN-ERC P.O.BOX 20723-00202 NBI.

Ref: KNH-ERC/A/117

17th March, 2015

Caroline Achieng Asin
U56/69086/2013
School of Pharmacy
University of Nairobi

Dear Caroline

Research Proposal: Risk factors, Management and outcomes of drug induced Liver Disease Among Adult Patients at Kenyatta National Hospital (P25/01/2015)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and approved your above proposal. The approval periods are 17th March 2015 to 16th March 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c)
d) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
e) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
f) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
h) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website www.erc.uonbi.ac.ke

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chair, KNH/UoN-ERC
The Dean, School of Pharmacy, UoN
The Chair, Department of Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. Dr. G. Nyamu, Dr. S.A. Opanga