



St. Paul's Hospital Millennium Medical College

Graduate Study Program

Department of Internal Medicine

The prevalence and associated factors for liver enzyme abnormalities among patients with Human Immunodeficiency Virus at St. Paul's Hospital Millennium Medical College (SPHMMC)

Principal investigator: Dr. Abraham Tesfaye (M.D)

A Research Thesis to be Submitted to the Department of Internal Medicine and Department of Public Health St. Paul's Hospital Millennium Medical College in Partial Fulfillment of the Requirements for the Specialization Degree in Internal Medicine.

February, 2024

Addis Ababa, Ethiopia

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Advisor: Dr. Henok Fisseha (M.D, consultant Internist,
Gastroenterologist and Hepatologist)

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biostatics, MPH)

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Abstract

Introduction: Recent trends have shown that liver impairment in Human immune-deficiency virus (HIV)-infected individuals is a frequent and major contributor to non-Acquired Immunodeficiency Syndrome(AIDS)-related morbidity and mortality. Liver disease is often reflected by abnormalities in one of the liver biochemical tests. There are limited studies conducted to identify the magnitude of liver enzyme abnormalities and its contributing factors in our country.

Objectives: This study aims to assess the prevalence and associated factors for liver enzyme abnormalities among patients with HIV infection on follow-up at St. Paul's Hospital millennium medical college.

Methods: A hospital-based cross-sectional study from April 1 to September 30, 2023 G.C. at St. Paul's Hospital Millennium Medical College's Anti-Retro viral Therapy (ART) follow-up clinic employed medical record reviews and structured interviews. Descriptive and inferential analyses, including multivariable logistic regression for liver disease determinants, were conducted, with significance set at $p < 0.05$.

Results: A total of 386 participants living with HIV infection in this study. We found that the overall prevalence of elevated liver enzymes: either, Alanine Transaminase (ALT) or Aspartate Transaminase (AST) or Alkaline phosphatase (ALP) elevation was 26.9% (114/386). Out of the specific liver enzymes, elevated ALT levels, AST levels, and ALP levels was detected among 11.9%, 7.8%, and 17.6% of participants, respectively. Based on multivariable logistic regression analysis, after adjusting for other co-variables, younger age < 44 years, significant alcohol intake, and being on anti-hypertensive medications, were found to have statistically significant association with elevated liver enzymes with a p-value and AOR (95% CI) of ($p = 0.046$, $1.7(1.01,2.8)$), ($p = 0.039$, $1.8(1.03,3.1)$), ($P = 0.04$, $2.6(1.01,6.3)$), respectively.

Conclusion: Our study shows that the magnitude of liver enzyme abnormalities among people living with HIV infection is high. Routine assessment and monitoring of liver enzyme abnormalities among people living with HIV infection should be implemented.

Key words: HIV, Acquired immunodeficiency virus, Liver disease, Liver cirrhosis, chemical and drug induced liver injury

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List of Acronyms and Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
CLD	Chronic liver disease
D; A; D	Data collection on Adverse Effects of Antiretroviral Drugs
DILI	Drug induced liver injury
FMOH	Federal Ministry of Health
HAART	Highly active anti-retroviral therapy
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
MAFLD/NAFLD	Metabolism associated/Non-alcoholic fatty liver disease
PLWH/PLHIV	People living with HIV infection
SPSS	Statistical Package for Social Sciences
SPHMMC	St. Paul's Hospital Millennium Medical College

1. Introduction

1.1. Background

Chronic liver disease (CLD) is a progressive decline in liver function, including its metabolic, excretory, and synthetic functions that lasts longer than six months. CLD and its effects have impacted an estimated 1.5 billion people worldwide(1).

Particularly in underdeveloped countries, CLD is one of the most common causes of mortality. 53,000 to 103,000 fatalities per year in Africa are attributed to liver cirrhosis and CLD owing to viral hepatitis is a major source of morbidity and mortality in the African and Asia-Pacific regions. CLD is a common source of morbidity and mortality in many general medical wards of the tertiary hospitals of different countries including Ethiopia(2,3).

In spite of the global paradigm shift on the causes of CLD due to the development and implementation of a hepatitis B vaccination program, enhanced screening, and the early introduction of relatively safer antiviral for hepatitis B and C, novel factors in the incidence of CLD are playing a crucial role. The most frequent factor contributing to CLD is now non-alcoholic fatty liver disease (NAFLD). Moreover, Human immune-deficiency virus (HIV)-associated liver disease is a growing contributor to non-AIDS-related causes of mortality in HIV-positive individuals(3–5).

A significant decline in AIDS-related mortality has occurred with the introduction of effective antiretroviral therapy (ART) for human immunodeficiency virus (HIV)). Nonetheless, in the ART era, liver disease is currently the most prevalent non-AIDS related cause of death among HIV-infected patients, accounting for 14–18% of all deaths in this population and over half of mortality among HIV-infected patients hospitalized(6).

Liver disease is often reflected by abnormalities in one of the liver biochemical tests. Elevation of one of the three liver enzymes which include alanine aminotransferase [ALT], aspartate aminotransferase [AST]), and alkaline phosphatase (ALP) is a very important marker for liver injury due to a variety of causes (7). The kinds of liver disease the clinician is likely to meet among these patients have evolved also, just as the burden of non-AIDS morbidity and mortality has changed in the ART period. The most frequent causes of liver dysfunction in HIV-infected individuals before the advent of ART were opportunistic infections, such as cytomegalovirus (CMV) and mycobacterial infections, as well as AIDS-related neoplasm's including lymphoma and Kaposi's sarcoma(6,8,9).

However, since the advent of ART, nonalcoholic fatty liver disease (NAFLD), alcohol abuse, drug induced hepatotoxicity, chronic hepatitis C virus (HCV), and chronic hepatitis B virus (HBV) co-infection have become more common among HIV-infected people (10–12).

1.2. Statement of the problem

Recent trends have shown that liver impairment in HIV-infected individuals is a frequent and major contributor to non-AIDS-related morbidity and mortality. With the advent of ART, the spectrum of causes of liver impairment in HIV-positive patients has drastically shifted, moving from opportunistic infections to chronic infection sequelae, drug toxicity, alcohol use, and fatty liver. Recognition of the magnitude of liver enzyme abnormalities as well as contributing factors will be important to plan our prevention, diagnosis and treatment approaches in the future (6).

Liver enzyme abnormalities which include elevation of either of the three liver enzymes is an important markers of liver injury which caused by a variety of etiologies of liver disease. Early detection of liver injury and the possible underlying contributing factors to direct treatment is the primary component of the effective treatment of liver disease. Studies from different countries showed that the spectrum of causes of liver dysfunction is variable in different countries (13–18). In addition, in some people with HIV and liver dysfunction, the etiology is not entirely obvious exemplified by studies from Nigeria and India(15).From this perspective, the clinical spectrum appears broad and inconsistent between nations.

There are limited studies conducted to identify the magnitude of liver enzyme abnormalities and it's contributing factors in our country. These previous studies were conducted mainly focusing

on HAART associated hepatotoxicity and also in single institutions where the source population is different from our hospital (19–23).

1.3 Significance of the study

In this study, we will analyze and sort out the prevalence and associated factors for liver enzyme abnormalities among patients with HIV infection observed at one of Ethiopia's main hospitals, where a sizable number of patients access clinical services. This is one of the few studies to be conducted, in this topic, in our country. Two key information will be acquired from our study. The first one is knowing the overall burden of liver enzyme abnormalities among HIV patients which is important to give due emphasis. The second one is identifying the major associated factors and causes, which helps for targeting our prevention, detection and treatment strategy.

Collectively the information from our study will be very crucial to our health system from an individual or clinician level to the hospital and FMOH administration level. It will remind the clinicians to give due vigilance to look for liver dysfunction among HIV patients, as well as aid them in approaching and managing such patients in their routine practice. For hospital administrations and FMOH, it will be a base to give the due emphasis and to develop guidelines on how to prevent, monitor, and manage PLWH with hepatic impairment.

Lastly, it will be a foundation for future studies by sorting out areas of focus in terms of cause or treatment.

Given that non-AIDS related diseases, such as hepatic dysfunction, have emerged as major causes of morbidity and mortality among this population in the era of effective HAART, we believe that such information is crucial. This is especially important in developing nations like Ethiopia where the prevalence of CLD is quite high and liver transplantation facilities are not readily available. Hence, in order to lessen the condition, early detection and prevention strategies are crucial. Our research will lay the groundwork for dealing with these concerns.

2. LITERATURE REVIEW

2.1. Global and local perspectives on liver enzyme abnormalities among patients with HIV infection

2.1.1. Prevalence of liver disease among patients with HIV infection

In the ART era, liver disease is currently the most prevalent non-AIDS related cause of death among HIV-infected patients, accounting for 14–18% of all deaths in this population and over half of mortality among HIV-infected patients hospitalized(6). Studies conducted in different countries have demonstrated increased prevalence of liver enzyme abnormalities and liver cirrhosis among patients with HIV infection. A study from Spain, in which 2168 patients with HIV infection were included, liver cirrhosis was recognized in 181 (overall prevalence, 8.3%) (24).A cross-sectional study from Nepal on 144 recruited HIV patients found that 82 (56.7%) had liver enzyme damage. The majority of these cases 61 (42.4%) had hepatocellular pattern of liver injury (13).

Studies done in Africa have also suggested similar perspective. A study from Uganda among 2030 patients with HIV infection found the prevalence of liver fibrosis was higher among participants in the rural clinic (15% vs 11%; $P = .017$). (25)In a study done in Debre tabor, Ethiopia, the prevalence of liver enzyme abnormalities in a total of 164 HAART-experienced and 164 HAART-naïve individuals was 20.1% and 22.0%, respectively (19).

2.1.2. Associated factors for liver enzyme abnormalities among patients with HIV infection

In the era of effective ART, drug induced liver injury mainly from ART and anti-tuberculosis, Viral Hepatitis due to hepatitis B& C virus, Alcohol-related liver disease, and Non-alcoholic fatty liver disease account as a major of cause of liver enzyme abnormalities. Other less common factors include opportunistic infections, AIDS cholangiopathy, older age, male sex, and longer duration of HIV infection.

This was demonstrated from different studies. In a study from Athens, Greece, to determine the causes of hepatic fibrosis, 187 HIV patients were included, 92.5% (173/187) of the patients had little or mild fibrosis, while 7.4% (14/187) had substantial fibrosis. According to multivariate logistic regression analysis, Alcohol abuse, older age, HCV/HIV co-infection, and the CD4/CD8 ratio appear to be associated with hepatic fibrogenesis in HIV-infected people (14,26).

A prospective cohort study done in a Mumbai tertiary care facility, 98 HIV patients with abnormal LFTs, 98 HIV patients with normal LFTs, and 98 non-HIV patients were compared. LFTs were abnormal in 63 (64.3%) of the individuals on ART and normal in 59 (60.2%). In decreasing order, DILI due to anti-tubercular (ATT) or ART (29%), chronic hepatitis B (18%), alcohol-related liver disease (11%), and NASH (7%) were the most frequent causes of liver dysfunction. A longer duration of HIV-positivity and low CD4 count was significantly associated with deranged liver function ($P < 0.05$). No statistically significant difference existed between the various ART regimens and duration of ART (16).

In addition, a study from Nepal, cases of opportunistic infections were documented in 18 patients, including 9 (6.2%) TB cases and 8 (5.6%) HCV cases. There was no association found with coinfection, CD4 cells, ART therapy, or alcohol use by the test for significance of liver injury ($P > 0.05$). Nonetheless, there was a significant ($P < 0.05$) connection between gender and both the pattern and severity of liver injury (13).

A study from Uganda, in which 77 consecutive patients were included, hepatotoxicity from nevirapine (NVP) and/or isoniazid (INH) was the source of elevated transaminases in 23 (30%) of the patients. Only 2 (3% of patients) had anti-hepatitis C antibody reactivity, while 11 (15%) of the patients tested positive for hepatitis B surface antigen. Seven (9%) patients had a diagnosis of probable tuberculous granulomatous hepatitis. Other causes identified include alcoholic liver disease, AIDS cholangiopathy, hepatocellular carcinoma, schistosomiasis, haemangioma, and hepatic adenoma. Overall, 60 (78%) had drug histories, liver enzyme tests, ultrasounds, and hepatitis B and C investigations that determined the likely etiology (18).

In a study done in Debreabor, Ethiopia, Elevated ALT and/or AST were linked with viral hepatitis (AOR = 6.02; 95% CI = 1.87-19.39), opportunistic infections (AOR = 2.91; 95% CI = 1.04-8.19), a current CD4 count 200 cells/mm³ (AOR = 2.16; 95% CI = 1.06-4.39), and male sex (AOR = 1.83; 95% CI = 1.001–3.33). Both HAART-experienced and HAART-naïve HIV-1-infected patients had elevated levels of liver enzyme abnormalities. Therefore, in our setting, it is crucial to monitor and treat patients with abnormal liver enzymes (19).

In some patients with HIV infection, the cause of liver dysfunction is unexplained. This was shown in a cross-sectional, prospective study conducted in an Indian tertiary care hospital, the causes of liver dysfunction were discovered in 45 patients (90%), whereas 5 patients (10%) are still unexplained. Hepatitis B (10%), drug-induced 13 (26%), and alcoholic liver disease (9%) were the most frequent diagnoses (27). Similarly, a retrospectively analyzed case-control study in Nigeria, revealed that CLD is common in HIV patients without viral hepatitis B and C, found in 63 of 170 HIV-seropositive (37.1%). The most significant determinants of CLD were long-term use of drugs, particularly highly active antiretroviral therapy (5.1 ± 1.6 years, $P = 0.000$) and herbal preparations ($n = 20$, 11.8%, $P = 0.000$). Early risk factor detection and appropriate clinical assessment can help to mitigate it (15).

2.1.3. Overview of specific causes of liver disease among HIV patients

Viral Hepatitis

The majority of liver disease in HIV-infected people results from HCV and/or HBV co-infection because of overlapping risk factors. Reported rates of co-infection with HCV range from 10% to 90%. About 30% of those with HIV in the US and Europe also have HCV infection. The prevalence of HIV-HBV co-infection varies by region, about 10% of HIV-infected people globally also have chronic HBV infection(28–31).

Several studies conducted in Africa revealed a high rate of co-infection with HIV and HBV. In a study from Nigeria, for instance, 6.3% of the 176 HIV patients had co-infection with HBV, while in a study from Eastern Ethiopia, 11.7% of the 901 HIV patients had positive HBsAg, indicating a significant burden of co-infection with HBV among those using ART (20,32).

In a study conducted at the Dessie Referral Hospital in Northeastern Ethiopia, 13 (5.2%) of the 249 HIV-positive study participants had anti-HCV antibodies. According to a study conducted in Ethiopia on patients with CLD, including 128 patients with HCC and 217 non-HCC patients, the overall prevalence of HIV was 4.3% (15/345), with a 2% (7/345) and a 0.3% (1/345) co-infection rate for HIV/HBV and HIV/HCV, respectively (21,22).

Drug induced liver injury

The most frequent major adverse event linked to ART is liver damage which might range from asymptomatic transaminase elevations to overt liver failure. Life-threatening incidents occur at a rate of 2.6 per 100 person years, and the incidence of ART-related severe hepatotoxicity is about 10%. Several non-ART drugs also have potential adverse liver consequences (33–35).

The pooled prevalence of hepatotoxicity among HIV patients in Ethiopia, according to a systematic review and meta-analysis conducted, was 25.45% (95% CI = 20.06- 30.84%). A subgroup analysis by HAART status revealed that HAART-using HIV patients had a higher pooled prevalence of hepatotoxicity (23.63%) than did HAART-naïve patients (7.29%). In subgroup analysis, patients with HIV/Tb co-infection and HIV mono-infection had a pooled prevalence of hepatotoxicity of 26.3% and 17.94%, respectively, indicating that HIV-infected people have a significant rate of hepatotoxicity (23).

Alcohol related live disease

Alcoholic liver disease is the cause of approximately half of all mortality from chronic liver disease in the US. In a US study of 2864 HIV-positive persons, 15% of current drinkers and 8% of the overall cohort were categorized as heavy drinkers, which is nearly twice as common as in the general population (36).

Metabolism associated (Non-alcoholic) fatty liver disease

NAFLD affects between 17 and 33% of US citizens. Hepatic steatosis in HIV-infected patients is thought to occur often, especially in those with chronic HCV or those on NRTIs. The prevalence of steatosis rates among HIV-HCV co-infected range from 40 to 69%. However, 31%

of 216 HIV-infected individuals without viral hepatitis co-infection, in a recent study, had Non-alcoholic fatty liver disease detected based on ultrasound diagnoses (37–45).

Particularly metabolic abnormalities are very prevalent among patients on NRTI-PI combinations. By inhibiting mitochondrial DNA replication, NRTIs can also cause hepatic steatosis. The separate associations between HIV infection and metabolic abnormalities may be mediated by cytokines like IFN- α . In HIV-infected patients, the emergence of NASH has been linked to these metabolic abnormalities(37–45).

The presence of steatosis and hepatic fibrosis is a major health concern for PLWH mono-infection. This was shown from a cross-sectional study conducted in Iran with 100 HIV-positive patients receiving antiretroviral therapy (ART) found that majority of patients (F1:77%) had mild fibrosis, while 10% of patients (F2:6% and F3:4%) had substantial fibrosis, according to the TE results. HIV infection duration and fibrosis were found to have a substantial, direct link, particularly in cases where the illness had been present for longer than five years (17).

Opportunistic infections and malignancies

Hepatic involvement in advanced AIDS has been linked to a number of opportunistic infections. The most prevalent of them is *Mycobacterium avium* complex (MAC), and *Mycobacterium tuberculosis* found in about 8% of individuals with hepatic involvement. Other opportunistic infections include extrapulmonary *Pneumocystis jirovecii* in the case of inhaled pentamidine for the prophylaxis, disseminated HSV, HHV 6, VZV, EBV, adenovirus, *Candida albicans*, *Aspergillus fumigatus*, *Toxoplasma gondii*, and *Strongyloides stercoralis*, *Bacillary peliosis hepatis*. In individuals with advanced AIDS, CMV, fungal infections, such as *Cryptococcus neoformans*, were detected during autopsies, but seldom cause a clinical hepatitis (46–52).

The liver is involved in 33% and 9% of instances of the AIDS-defining malignancies, non-Hodgkin lymphoma (NHL) and Kaposi's sarcoma (KS), respectively. Hepatic involvement is commonly asymptomatic abnormalities on a liver function test (53,54).

AIDS cholangiopathy, which occurs at low CD4 counts (less than 100/mm³) suggested to be direct viral infection-related strictures in the biliary tract, is significantly rare in the ART era. Only 13 of 94 patients with AIDS cholangiopathy were diagnosed after 1996 in an urban hospital between 1983 and 2001 in a recent retrospective study. *Cryptosporidium parvum*, followed by CMV, are also the most frequent infections connected to AIDS cholangiopathy (55,56).

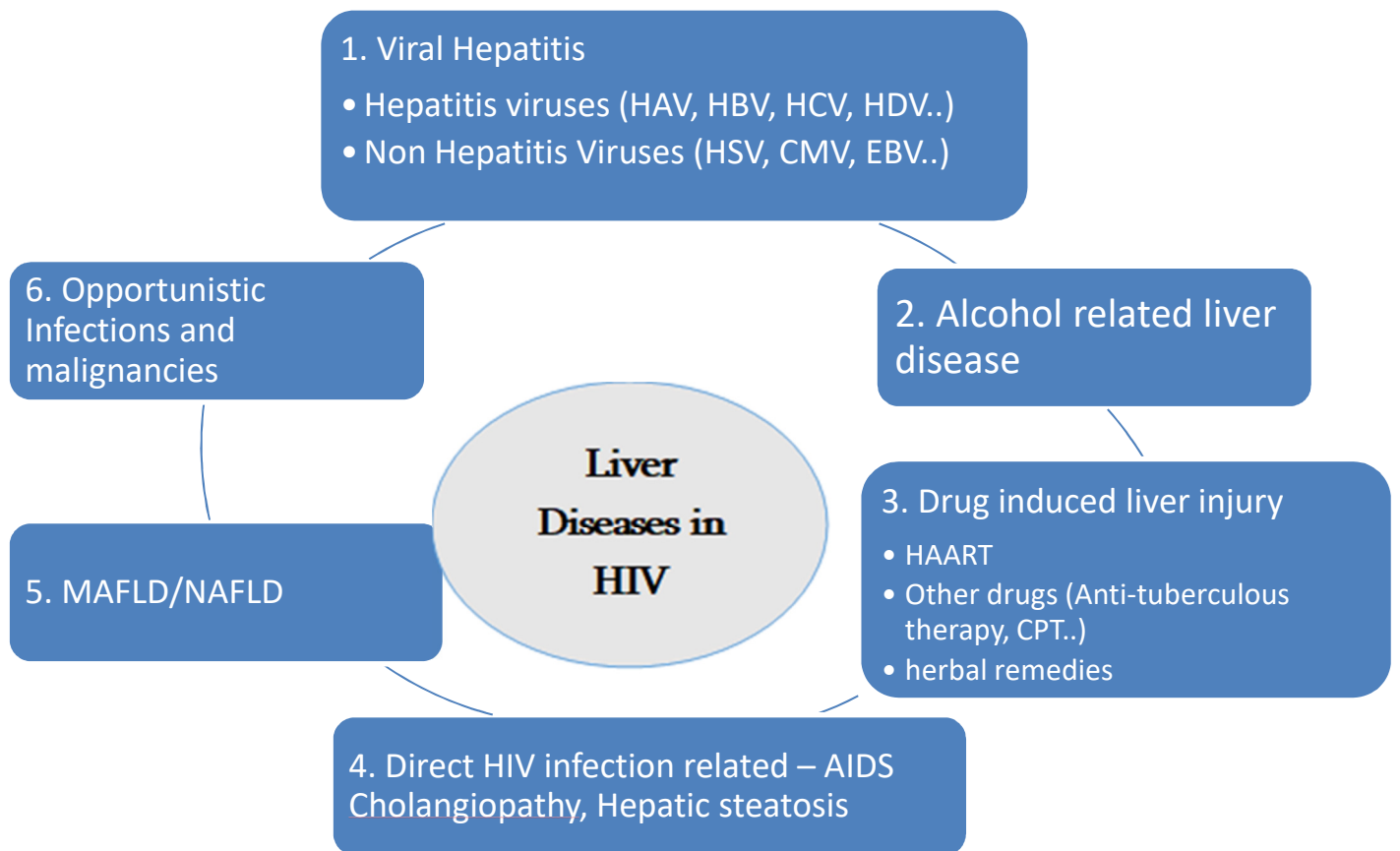


Figure 1: Figure: Conceptual Framework

7. Miscellaneous Causes – Schistosomiasis, metastatic tumors,

3. OBJECTIVES

3.1 General objective

- To Assess the prevalence and associated factors for liver enzyme abnormalities among patients with HIV infection from April 1, 2023 to September 30, 2023 G.C on follow-up at St. Paul's Hospital millennium medical college.

3.2 Specific objectives

- To assess pattern of liver enzyme abnormalities among HIV patients on follow-up at St. Paul's Hospital millennium medical college.
- To assess the prevalence of liver enzyme abnormalities among HIV patients on follow-up at St. Paul's Hospital millennium medical college.
- To determine associated factors for liver enzyme abnormalities among patients with HIV infection on follow-up at St. Paul's Hospital millennium medical college.

4. Methods and materials

4.1 Study area:

The study took place at the Anti-retroviral therapy (ART) follow-up clinic of St. Paul's Hospital Millennium Medical College, one of Ethiopia's largest referral hospitals, located in Addis Ababa, the country's capital. Emperor Haile SelassieI built the hospital in 1969. The Ethiopian Ministry of Health established the school in 2007. Since then, it became a key teaching hospital for both undergraduate and graduate medical schools. It served a catchment population of more than 5 million people and served as the primary center for the delivery of specialist healthcare services through its numerous (over 13) departments.

Patient care was provided in the hospital by the many departments, faculties, and residents undergoing specialty training in the School of Medicine. Among these divisions, the ART follow-up clinic provided service to PLWH daily on the whole days, including weekends. The ART follow-up clinic had a total of 4694 patients undergoing follow-up.

4.2 Study period:

The data collection was conducted over 6 months, from April 1/2023 G.C to September 30/2023.

4.3 Study Design:

A hospital-based cross-sectional observational study was conducted using both descriptive and inferential analysis.

4.4 Population

4.4.1 Sources population

- All PLWH who have follow-up at the ART follow-up clinic of St. Paul's Hospital Millennium Medical College

4.4.2 Study population

- All HIV patients who fulfill the eligibility criteria

4.5 Eligibility criteria

4.5.1 Inclusion criteria

- All patients with HIV infection on follow-up during the study period with available liver transaminase level tests done within 1 year
- Age ≥ 18 years old

4.5.2 Exclusion criteria

- Patients with HIV infection with no liver biochemical tests

4.6 Sample size;

The sample size was determined by using the formula for single population proportion. In a study done in Debre-Tabor, Ethiopia, the prevalence of liver enzyme abnormalities in a total of 164 HAART-experienced and 164 HAART-naïve individuals was 20.1% and 22.0%, respectively. (19) So, an overall proportion of 42.1% was taken.

The sample was calculated by assuming a Confidence interval of 95%, 5% margin of error, & 10% non-response rate.

$$n = (Z\alpha/2)^2 \times P(1-p) / d^2$$

Where: n = Sample size; P = proportion; d= margin of error; $Z (\alpha/2)^2$ = confidence interval and significance level

$$n = (1.96)^2 \times 0.42 (1-0.42) / 0.05^2 = 374$$

Since the population size is less than 10,000, we need additional correction with

$$n = \frac{n_0}{1 + \frac{n_0}{N}}$$

n= Final sample size, n_0 = Initial sample size (374), N= Source population size (4694 as recorded on ART clinic follow-up Registry over 6 months from April to September 2023) Using

correction for finite population (N=4694) and 10% non-response rate, final sample size =383 patients.

The sample size for alcohol intake as associated factors for liver enzyme abnormalities was calculated using a population proportion of (P= 41.2%) from a study done at Felegehiwot Hospital ,Amhara Region ,at Bhirdar Northwest Ethiopia A total of 269 HIV infected patients receiving antiretroviral therapy during the study period were included and the overall prevalence of hepatotoxicity (alanine aminotransferase elevation) in HIV-infected patients receiving ART was 32%.The proportion of ALT elevation among heavy alcohol user was 7(41.2%). and sample size was calculated as follows:

The sample was calculated by assuming a Confidence interval of 95%,5% margin of error, and P=41.2%

$$n = (Z\alpha/2)^2 \times P(1-p) / d^2$$

Where: n = Sample size for associated factors; P = proportion; d= margin of error; Z ($\alpha/2$)²= confidence interval and significance level

$$n = (1.96)^2 \times 0.412(1-0.412) / 0.05^2 = 372$$

Since the population size is less than 10,000, we need additional correction with

$$n = \frac{n_0}{1 + \frac{n_0}{N}}$$

n= Final sample size for alcohol intake association n₀= Initial sample size (372), N= Source population size (4694 as recorded on ART clinic follow-up Registry over 6 months from April to September 2023) Using correction for finite population (N=4694) and , sample size for alcohol intake associated liver enzyme abnormalities =344 patient and with 10 % non-response rate

The sample size for alcohol intake association=**381**

So our final sample size was =**383**, so we took it because higher value for our study than **381**.

4.7 Sampling procedures

The systematic random sampling method was used

Monthly on average 500 patients were seen during the study period

Where our sample (k)=500x6/383=7, every 7th patient and patients with HIV infection on follow-up at the ART clinic who had liver biochemical tests done within 1 year were included.

4.8 Study Variables

4.8.1 Dependent variable

- Liver enzyme abnormalities

4.8.2 Independent variables

- Age
- Sex
- Address
- Marital status
- Education
- Occupation
- BMI
- LFTs – ALT, AST, ALP, Bilirubin, INR, Albumin
- Imaging studies – Liver ultrasound, TE, abdominal CT/MRI
- HIV Viral Load, baseline CD4 count (if available)
- ART regimen & duration
- Opportunistic infections
- HCV antibody, HBsAg
- Alcohol history - Herbal medications
- Other hepatotoxic medications – anti-tuberculosis drugs, cotrimoxazole, fluconazole.
- Comorbidities – diabetes, non-AIDS malignancies

4.9 Operational Definitions

Significant Alcohol consumption: For female >14gm and for male >28gm per day is considered as significant alcohol consumption.

Cirrhosis: represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. The diagnosis of cirrhosis is based on stigmata of chronic liver disease discovered on physical examination, laboratory or radiologic testing, or presence of complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or hepatic encephalopathy.(57)

Significant Liver biochemical tests - Unexplained, persistent liver biochemical test elevations (≥ 1.25 times the upper limit of normal for aminotransferases or 1.25 times the upper limit of normal for alkaline phosphatase) or any elevation **with symptoms of liver disease**.(7,58)

4.10 Data collection and procedures

Data collection was conducted using patient's medical chart reviews as well as a structured questionnaire, which was written in English and translated into local languages by interviewers. The questionnaire included socio-demographic characteristics (Age, Gender, Religion, Marital Status, Address, Educational Level, Occupation), clinical characteristics (symptoms of liver disease, medication history including herbal remedies, alcohol consumption, known comorbidities, family history of liver disease).

The rest of the variables were extrapolated from patients' charts, which included liver biochemical tests, imaging results, HIV-associated variables (Viral Load (VL), CD4 Count, Time Since ART Initiated, The WHO Staging, ART Medication Regimen). The data collection took place from April 1 to September 30, 2023 G.C, and it was accomplished by health professionals (nurses, residents) working at the ART clinic.

4.11 Data Quality Control Data

Data quality was assured by training the staff and conducting a pre-test on 2.5% of samples (10 patients). The data collection was supervised regularly by the principal investigator. The collected data was checked for completeness each day. The data was collected using standard electronic data collection tools like Kobo Toolbox.

4.12 Data processing and analysis

All the data was checked for completeness and internal consistency on a regular basis. Once verified, it was exported from KoboToolbox for further analysis, using IBM/Statistical Package for Social Science (SPSS) version 26 software. Standard clinical classifications were used to recode variables. Descriptive analysis was done with measures of central tendency and frequency distribution. In specific variables, multivariable logistic regression analysis was used to identify associated factors of independent variables and dependent variables using odds ratio and Variables with P-value <0.25 in the bivariable logistic regression were included in the multivariable logistic regression model. All variables with a p-value of <0.05 in were considered statistically significant.

The results were presented in the form of tables, statements, and categorical data were summarized using frequencies and percentages.

4.13 Ethical consideration

The study proposal was submitted for approval to Institution Review Board (IRB) ethical review committees of the St. Paul's Hospital Millennium Medical College. Written informed consent was taken from all the participants. It was ensured that adequate explanations were given to participants about the study project and their right not to be involved in the study if they didn't wish, along with their ability to withdraw from the study.

4.14 Dissemination of the results

The results of the study will be presented to St. Paul's Hospital Millennium Medical College, Departments of Internal medicine & Public health. The results of the study will also be sent to reputable journals for publication.

5. Results

5.1 Socio-Demographic Characteristics

The study population consisted of 386 participants with a mean age of 43.25 years (SD=10.52). The majority of participants were below 44 years of age (52.8%), with 47.2% aged 44 years or older. Notably, the study included 247 females (64.0%) and 139 males (36.0%). In terms of educational background, the predominant categories were participants with a primary school education (34.5%) and those with a secondary school education (35.8%). A smaller percentage had no formal education (14.5%), while 15.3% had completed college and above. Geographically, the majority of participants were from Addis Ababa (67.6%), followed by Oromia (28.2%), Amhara (2.8%), and Southern Nation Nationality People Region (SNNPR) 1.3%. Regarding marital status, the participants were distributed among the following categories: never married (21.5%), currently married (54.1%), divorced (15.0%), and widowed (9.3%). In terms of job status, the distribution was diverse. The most prevalent categories included Non-Governmental Organizations(NGO) employees 24.9%, self-employed individuals (22.8%), and government employees (18.1%). Other categories included unemployed individuals able to work (10.6%), students (3.1%), retired individuals (4.1%), and homemakers (16.3%). **Table 1**

Table 1: Socio – Demographic characteristics of patients with HIV infection on follow-up at the ART clinic at St Pulis Hoptal Millenium Medical College over 6 months duration(from April 1 to September 30,2023)

		Frequency n	Percent %
Age (years)	<44 years	204	52.8
	>=44 years	182	47.2
	Mean age	Min=18 max=76	meanSD=43.25±10.516
Sex	Female	247	64.0
	Male	139	36.0
Educational level	No Formal Education	56	14.5

Region	Primary school	133	34.5
	Secondary school	138	35.8
	College and above	59	15.3
	Addis Ababa	261	67.6
Marital Status	Oromia	109	28.2
	Amhara	11	2.8
	SNNPR	5	1.3
	Never married	83	21.5
Job status	Currently married	209	54.1
	Divorced	58	15.0
	Widowed	36	9.3
	NGO employee	96	24.9
	Government employee	70	18.1
	Self-employee	88	22.8
	Unemployed (able to work)	41	10.6
	Student	12	3.1
	Retired	16	4.1
	Homemaker	63	16.3

Abbreviations: Southern Nation Nationality People Region (SNNPR)

Non-Governmental Organizations (NGOs)

5.2 Behavioral and Clinical Characteristics

In examining the behavioral and clinical characteristics of the study participants, 30.6% reported significant alcohol consumption. The majority (69.4%) did not engage in significant alcohol consumption. Among those reporting significant alcohol consumption, 82.1% had a total duration of significant alcohol use of ten or more years. Additionally, 54.7% of participants were taking current non-antiretroviral therapy (ART) medications. Among overall study participant; 37.8% were taking anti-tuberculosis (TB) medications within the last one year, 13.0% were on statins and 11.1% on anti-hypertensive medications. Furthermore, only a small percentage (6.2%) were taking co-trimoxazole preventive therapy (CPT), and 4.7% on anti-diabetic medications.

The duration of HIV infection was predominantly distributed among those with ten or more years (59.1%). Most participants were in WHO Stage 1 (97.4%) and were receiving the 1st line ART regimen (90.7%). The BMI categories indicated that 52.6% were classified as normal, 30.8% were overweight, 8.5% were class I obesity, 2.1% were class II obesity, and 6.0% were underweight according to WHO standards. **Table 2**

Table 2: Behavioral & Clinical Characteristics Assessments patients with HIV infection on follow-up at the ART clinic

		Frequency n	Percent %
Significant Alcohol consumption (F>14gm and M>28gm per day)	Yes	118	30.6
	No	268	69.4
Total Duration of Sig. Alcohol (years) N=123	>=10	101	82.1
	<10	22	17.9
Current non- ART Medications	Yes	211	54.7
	No	175	45.3
Taking Anti-TB	Yes	146	37.8
	No	240	62.2
Taking CPT	Yes	24	6.2
	No	362	93.8
Taking statins	Yes	50	13.0
	No	336	87.0
Taking Anti-diabetics	Yes	18	4.7
	No	368	95.3
Taking Anti-HTN	Yes	43	11.1
	No	343	88.9
Duration of HIV infection	>=10 years	228	59.1
	<10 years	158	40.9
WHO stage	Stage 1	376	97.4
	Stage 2	5	1.3
	Stage 4	5	1.3
ART regimen	1st Line	350	90.7
	2nd Line	33	8.5
	3rd Line	3	.8
BMI category (WHO)	Under	23	6.0
	Normal	203	52.6
	Over	119	30.8
	Class I	33	8.5
	Class II	8	2.1

5.3 Risk Factors and Comorbidities

The assessment of risk factors and comorbidities revealed that a small proportion of participants reported a history of liver disease, with drug-induced liver injury (DILI) being the most common (1.3%). Other liver conditions included fatty liver disease (0.8%), cholelithiasis (1.6%), liver hemangioma (1.0%), and acute hepatitis (0.3%). Notably, the majority of participants had missing data regarding their history of liver disease (95.1%).

A family history of liver diseases was reported by 7.3% of participants, while 92.7% had no such family history. Additionally, only a limited number of participants had a history of radiotherapy (1.0%). Comorbidities were present in 28.5% of participants, with hypertension (HTN) being the most prevalent (37.3 %), followed by dyslipidemia (26.4%), diabetes mellitus (DM) (16.4%), peripheral neuropathy (16.4%), and thyroid disease (8.2%) in those with comorbidities. **Table 3**

Table 3: Distribution of Risk factors and comorbidities among patients with HIV infection on follow-up at the ART clinic

		Frequency n	Percent %
History of liver disease	DILI	5	1.3
	Fatty liver disease	3	.8
	Cholelithiasis	6	1.6
	Liver Hemangioma	4	1.0
	Acute Hepatitis	1	.3
	Missing	367	95.1
Family history of liver diseases	Yes	28	7.3
	No	358	92.7
History of Radiotherapy	Yes	4	1.0
	No	382	99.0
Comorbidity	Yes	110	28.5
	No	276	71.5
HTN, n=110	Yes	41	37.3
	No	69	62.7
DM, n=110	Yes	18	16.4
	No	92	83.6
Dyslipidemia, n=110	Yes	29	26.4
	No	81	73.6
Peripheral Neuropathy, n=110	Yes	18	16.4
	No	92	83.6
Thyroid disease, n=110	Yes	9	8.2
	No	101	91.8

5.4 Biochemical Measurements and Abdominal Ultrasound finding

The biochemical measurements of the study participants provided crucial insights into their health status. Platelet levels were categorized as equal to or greater than 150k (95.1%) or below 150k (4.9%). HIV viral load status revealed that 87.3% had an undetectable viral load, 5.4% had a detectable viral load, and 7.3% had unknown status. CD4 count distributions were as follows: 66.8% had a CD4 count of 200 or more, 6.2% had a CD4 count below 200, and 26.9% had unavailable CD4 count data. Hepatitis C virus (HCV) antibody/RNA test results indicated that 13.0% tested negative, 0.8% tested positive, 2.3% had the test not done, and 83.9% had an unknown status.

For the HBsAg/HBV DNA test, 24.6% tested negative, 0.5% tested positive, 1.8% had the test not done, and 73.1% had an unknown status. Abdominal ultrasound findings included 6.0% with fatty liver, 1.0% with hepatic hemangioma, 1.6% with cholelithiasis, 0.5% with hepatosplenomegaly, and the majority (90.9%) with unremarkable results. **Table 4**

Table 4: Biochemical Measurements and abdominal ultrasound of patients with HIV infection on follow-up at the ART clinic

		Frequency n	Percent %
Platelet	>=150k	367	95.1
	<150k	19	4.9
HIV viral load	Detectable	21	5.4
	Undetectable	337	87.3
	Unknow	28	7.3
CD4 count	>=200	258	66.8
	<200	24	6.2
	Not available	104	26.9
HCV Ab/RNA test	Positive	3	.8
	Negative	50	13.0
	Not done	9	2.3
	Unknown	324	83.9
HBsAg/HBV DNA test	Positive	2	.5
	Negative	95	24.6
	Not done	7	1.8
	Unknown	282	73.1
Abdominal Ultrasound	Fatty liver	23	6.0
	Hepatosplenomegaly	2	.5
	Hepatic Hemangioma	4	1.0
	Cholelithiasis	6	1.6
	Unremarkable	351	90.9

5.5 Liver Biochemical Test Results

The analysis of liver biochemical tests yielded valuable information on the hepatic status of the study participants. Alanine transaminase (ALT) levels were elevated in 11.9% of participants, while 88.1% had normal ALT levels. As for aspartate transaminase (AST), 7.8% exhibited elevated levels, with 92.2% having normal values. Considering either ALT or AST abnormalities, 14.2% had elevated levels, and 85.8% had normal levels. Alkaline phosphatase (ALP) levels were elevated in 17.6% of participants, while 82.4% had normal ALP levels. Total bilirubin results showed that 2.3% had elevated levels (≥ 1), 8.5% had levels below 1, and 89.1% lacked documented bilirubin values. Serum albumin levels were less than 3g/dl in 0.8% of participants, while 4.4% had levels equal to or greater than 3g/dl, and 94.8% had undocumented values.

International normalized ratio (INR) values were elevated (≥ 1.5) in 0.3% of participants, 2.8% had INR values below 1.5, and 96.9% lacked documented INR values. Overall, 26.9% of participants exhibited liver enzyme test abnormalities, and 14.2 % of the study participant showed liver enzyme abnormalities (ALT and/AST elevation) providing critical data for the evaluation of hepatic function within the study cohort. **Table 5**

Table 5: Liver biochemical test distribution of patients with HIV infection on follow-up at the ART clinic

		Frequency n	Percent %
ALT	Elevated	46	11.9
	Normal	340	88.1
AST	Elevated	30	7.8
	Normal	356	92.2
Either ALT or AST	Elevated	55	14.2
	Normal	331	85.8
ALP	Elevated	68	17.6
	Normal	318	82.4
Total bilirubin	Elevated ≥ 1	9	2.3
	<1	33	8.5
	Not-documented	344	89.1
Serum albumin	$\geq 3\text{g/dl}$	17	4.4
	<3g/dl	3	.8
	Not-documented	366	94.8
INR	≥ 1.5	1	.3
	<1.5	11	2.8
	Not-documented	374	96.9
Liver biochemical test abnormality	Yes	104	26.9
	No	282	73.1

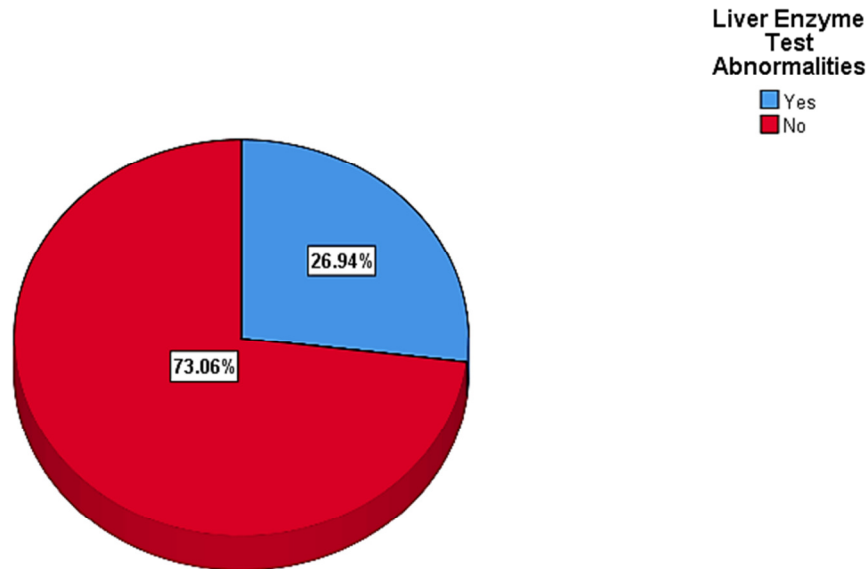


Figure 2: Prevalence of Liver enzyme test abnormality among patients with HIV infection on follow-up at the ART clinic

5.6 Associated factors for elevated liver enzymes

The bivariate/univariate binary logistic regression analysis was performed on each independent Variable to assess for significant association with liver enzyme elevation. After adjusting for other co-varieties, younger age < 44 years, significant alcohol intake, and being on anti-hypertensive medications, were found to have statistically significant association with elevated liver enzymes with a p-value and AOR (95% CI) of (p= 0.046, 1.7(1.01,2.8)), (p= 0.039, 1.8(1.03,3.1)), (P= 0.04, 2.6(1.01,6.3)), respectively.

Table 6: Multivariable Logistic Regression analysis of factors associated with liver enzyme test abnormalities among patients with HIV infection on follow-up at the ART clinic at SPHMMC (from April 1 to September 2023)

Variables		Hepatotoxicity		COR 95% CI	P value	AOR 95% CI	P Value
		Yes	No				
Age	<44	48	156	1.4(0.9,2.3)	0.11	1.7(1.01,2.8)	0.046
	>=44	56	126	1			
Sex	Female	68	179	0.9(0.6,1.5)	0.7		
	Male	36	103	1			
Address	AA	76	185	0.7(0.4,1.2)	0.16	0.63(0.4,1.1)	0.09
	Outside AA	28	97	1			
Marital status	Never married	19	64	1.03(0.5,2.1)	0.9	0.9(0.5,2.12)	0.9
	Currently married	63	146	0.7(0.4,1.2)	0.23	0.7(0.4,1.3)	0.3
	Divorced/Widowed	22	72	1			
Sig. Alcohol intake	Yes	23	95	1.8(1.1,3.02)	0.03	1.8(1.03,3.1)	0.039
	No	81	187	1			
Anti-TB	Yes	39	107	1.02(0.6,1.6)	0.94		
	No	65	175	1			
CPT	Yes	8	16	0.7(0.23,1.74)	0.45		
	No	96	266	1			
Anti-lipids	Yes	9	41	1.8(0.8,3.8)	0.3		
	No	95	241	1			
Anti-diabetics	Yes	7	11	0.6(0.2,1.5)	0.24	0.72(0.2,2.2)	0.6
	No	97	271	1			
Anti-HTN	Yes	7	36	2.03(0.9,4.7)	0.1	2.6(1.01,6.3)	0.04
	No	97	246	1			

<i>Duration of HIV infection</i>	<i>>=10 yrs.</i>	64	164	<i>0.9(0.5,1.4)</i>	0.6		
	<i><10 yrs.</i>	40	118	<i>1</i>			
<i>WHO stage</i>	<i>Stage I</i>	99	277	<i>2.8(0.8,9.9)</i>	0.11	2.7(0.7,9.8)	0.14
	<i>Stage II & IV</i>	5	5	<i>1</i>			
<i>ART regimen</i>	<i>1st line</i>	95	255	<i>0.9(0.4,1.9)</i>	0.8		
	<i>2nd and 3rd line</i>	9	27	<i>1</i>			
<i>BMI category</i>	<i>Under</i>	9	14	<i>0.5(0.2,1.5)</i>	0.22	0.5(0.2,1.6)	0.24
	<i>Normal</i>	46	157	<i>1.1(0.5,2.4)</i>	0.81	1.1(0.5,2.4)	0.9
	<i>Over</i>	39	80	<i>0.7(0.3,1.5)</i>	0.32	0.64(0.3,1.5)	0.3
	<i>Class I & II</i>	10	31	<i>1</i>			
<i>Personal hx of liver disease</i>	<i>Yes</i>	6	13	<i>0.8(0.3,2.2)</i>	0.64		
	<i>No</i>	98	269	<i>1</i>			
<i>Comorbidity</i>	<i>Yes</i>	29	81	<i>1.04(0.6,1.7)</i>	0.87		
	<i>No</i>	75	201	<i>1</i>			
<i>Fatty liver on Abdominal US</i>	<i>Yes</i>	9	14	<i>0.6(0.23,1.3)</i>	0.2	0.6(0.2,1.4)	0.23
	<i>No</i>	95	268	<i>1</i>			

6. Discussion

In the ART era, liver disease is currently the most prevalent non-AIDS related cause of death among HIV-infected patients, accounting for 14–18% of all deaths in this population and over half of mortality among HIV-infected patients hospitalized. Studies conducted in different countries have demonstrated increased prevalence of liver enzyme abnormalities and liver cirrhosis among patients with HIV infection(6).

In this study, we included a total of 386 participants living with HIV infection to assess the prevalence and associated factors for liver enzyme elevations among patients living with HIV infection. The majority of participants in our study were below 44 years of age (52.8%) with a mean age of 43.25 years (SD=10.52), and predominantly included female study participants (247, 64.0%). These results are comparable to previous studies(59,60).

The overall prevalence of elevated liver enzymes (i.e. either ALT, or AST, or ALP elevation) in our study is 26.9%(114/386). This result is comparable to previous studies done in Debre Berhan, Ethiopia (25%) and Eritrea (26.7%). However, it's higher than what is reported from studies in Debre Tabor, Ethiopia (20.1%) and Brazil (19.7%). This difference is partly explained by the higher percentage of patients taking concomitant anti-tuberculosis medication (37.8% of participants) and having also significant alcohol intake (30.6%) in our study population(19,61–65).

Out of the specific liver enzymes, elevated alanine transaminase (ALT) levels, aspartate transaminase (AST) levels, and Alkaline phosphatase (ALP) levels were detected among 11.9%, 7.8%, and 17.6% of participants, respectively. Our results are comparable to the study from Brazil which showed elevated ALT in 9.2 %, & AST in 13% of study participants. But when compared to reports from previous studies in Debre Tabor, Ethiopia (elevated ALT in 13.4% & AST in 15.2%), Eritrea (elevated ALT in 10.6%, AST in 25.5%, and ALP in 9.4%), Cameroon (elevated ALT in 22.67%, and AST in 54.0 %), our findings have remarkable difference with a lower prevalence of elevated AST level and predominantly elevated level of ALP seen in our study. This can be explained by the fact that a higher percentage of patients in our study are taking anti-tuberculosis medications (37.8%) which are associated with cholestatic pattern, as well as most of these studies were done before 2017 and patients were taking

nevirapine based regimens unlike our study population in which 1 j regimen (TDF, 3TC, and DTG) are commonly used which has a different hepatotoxicity profile(19,61–63,65).

Moreover,most of our studied HIV patient unlike other HIV patient studied in other comparable done studies in Ethiopia ,we have inadequate data on (HBV and HCV laboratory test),which are an important cause of elevated liver enzyme abnormalities from studies done at Debretabor ,Dessi Referral hospital and at North West part of Ethiopia as we previously mentioned from literature review.Those limitation make our studies to have a relatively lower prevalence of ALT and /AST(which in our study 14.2%) compared to Debretabor studies(the prevalence among HIV patient for ALT&AST elevation was 20.1%).

Based on Multivariable Logistic Regression logistic regression analysis, after adjusting for other co-varieties, younger age < 44 years, significant alcohol intake, and being on anti-hypertensive medications, were found to have statistically significant association with elevated liver enzymes with a significant a p-value and AOR (95% CI). In our study young patients with age < 44 years have 1.7x higher odds of having elevated liver enzymes compared to those $\geq$ 44 years old. This was reported from previous study done in Cameroon[66]. The possible explanation for this association is their lifestyle with higher risk of hepatitis B, alcohol intake, and concomitant intake of non-HAART medications. However, this association needs further studies in the future to clarify it better.

The other significantly associated factor for liver enzyme abnormalities is significant alcohol intake which increases the odds of having liver injury by 1.8x compared to patients with no significant alcohol intake(67–69). The odds of having liver enzyme abnormality is also 2.6x higher in those taking antihypertensive medications for hypertension. This could be partly explained by the association of hypertension with metabolic associated fatty liver disease, and the possible hepatotoxicity from this anti-hypertensive and other medications like statins which are more likely to be prescribed among this population. The specific type of anti-hypertensive drugs was not sorted out in our study which is one limitation that should be investigated in the future. The association of hypertension with liver enzyme elevation has been reported in previous studies(70,71).

Considering HIV-related clinical characteristics, the duration of HIV infection in majority of patients was ten or more years (59.1%). Most participants were in WHO Stage 1 (97.4%) and were receiving the 1st line ART regimen (90.7%). HIV viral load status revealed in 87.3% of patients is undetectable (suppressed), whereas most of the participants have a CD4 count of above 200 cells/cm². These reports are comparable to prior studies done in our country as well as other parts of the world. Even though, some of the HIV-related characteristics has been reported to have association with liver enzyme abnormalities, our study didn't find significant association (19,61,77).

7. Conclusion

Our study shows that the magnitude of liver enzyme abnormalities among people living with HIV infection is high. Routine assessment and monitoring of liver enzyme abnormalities among people living with HIV infection should be implemented.

Strength of our study

Our studies is among few studies done in our countries and first studies in St Paul's Hospital Millennium Medical College regarding liver enzyme abnormalities among HART taking HIV patient and specifically assessing the pattern of liver enzyme abnormalities and its determinant factor for abnormal liver enzyme tests ,and only done among HART taking HIV patient. All the data that we use in our study are more reliable because few data were collected per days ,over relatively adequate duration and was from patient structured questioner and card reviews .Moreover ,we use ample sample size relative to large source of HAART taking HIV patients who have regular follow up at ART clinic,SPHMMC.

Moreover ,the data was collected five trained General Practitioner who are working at ART clinic that indicate the data collectors know proper chart finding skills and experienced with HIV patient regarding important information to guide on history taking ,documentation and accurate physical measurement.

Our study results shows over all prevalence of 30% significant alcohol consumption, and also shows significant association for liver enzyme abnormalities in HAART taking HIV patient. It provide aground bases for further related studies and will be Incorporated to MOH ,AIDS related Organizations ,Hospital administrator and to individual care giver for HIV patients. This helps in implementing policies, strategies and intervention for reducing significant alcohol consumption and liver enzyme abnormalities in HIV patient. Finally ,it will brought, a tremendous change in reducing mortality and morbidity related to liver dysfunction in HIV patient at hospital to country level.

Our study also give us a new result which shows Ant-HTN medication are also one of a significant cause of liver enzyme abnormalities among HART taking HIV patients. Hence, it will lay down aground for further research and study, which will help us to answer, why and which Ant HTN medication caused such liver enzyme abnormalities. At the end, further study will brought solution for reducing liver related morbidity, and morality among HIV patients.

Limitation:

Limitations of this study include: the single-center and the use of Cross sectional study design at St. Paul's Hospital Millennium Medical College may limit the generalizability of findings to broader populations.

The selection of the study place at ART clinic only, inadequate HBV and HCV lab test limits viral hepatitis as cause of abnormal liver enzyme-test in HIV patients.

Also absence of other important imaging test (e.g TEL proper focused liver US, Abdominal CT or MRI) to detect liver damage and fibrosis also limit for further inquiring the cause liver enzyme abnormalities in our studied participant.

Additionally, the reliance on medical records and self-reported data introduces potential information bias.

The ART clinic in our hospital use the old chart keeping system than the newer computer based patient data at follow-up unlike the other sub specialty follow-up clinic(e.g GI patient follow-up clinic.) which use computer based patient data. This become one of the barrier to collect important investigation and old data that provided more source of the participant information for predicting more common determinant of liver enzyme abnormalities among HAART taking HIV patients at ART clinic in St. Paul's Hospital Millennium Medical College .

Recommendations

Recommendations for future research involve expanding the study's scope to include diverse health care settings and a larger participant pool. Prospective studies could enhance understanding of temporal relationships between HIV infection, liver enzyme abnormalities, and associated factors.

Additionally, incorporating more objective measures and advanced diagnostic tools could enhance the accuracy of liver disease assessment in HIV-infected individuals.

Efforts to explore interventions and preventive strategies for mitigating liver enzyme abnormalities in this population should be a focus for future investigations.

9. REFERENCES

1. Xu JH, Yu YY, Xu XY. Management of chronic liver diseases and cirrhosis: current status and future directions. *Chin Med J (Engl)* [Internet]. 2020 Nov 11 [cited 2023 Feb 20];133(22):2647. <https://doi.org/10.1097/CM9.0000000000001084> PMID: 32925282
2. Marchesini G, Day CP, Dufour JF, Canbay A, Nobili V, Ratziu V, et al. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* [Internet]. 2016 Jun 1 [cited 2023 Feb 20];64(6):1388–402. <https://doi.org/10.1016/J.JHEP.2015.11.004> PMID: 27062661
3. Abere ST, Oyan B, Azukoye-Amadi B, Amachree EE. Chronic liver disease in HIV patients: Determinants and clinical manifestations. *NIGERIAN JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY* [Internet]. 2022 [cited 2023 Feb 20];14(2):55. https://doi.org/10.4103/NJGH.NJGH_16_22
4. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Nouredin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. *Hepatology* [Internet]. 2016 Dec 1 [cited 2023 Feb 20];64(6):1969–77. <https://doi.org/10.1002/HEP.28677> PMID: 27301913
5. Murillas J, Rimola A, Laguno M, De Lazzari E, Rascón J, Agüero F, et al. The model for end-stage liver disease score is the best prognostic factor in human immunodeficiency virus 1-infected patients with end-stage liver disease: A prospective cohort study. *Liver Transplantation*. 2009;15(9):1133–41. <https://doi.org/10.1002/lt.21735> PMID: 19718643
6. Price JC, Thio CL. Liver Disease in the HIV-Infected Individual. *Clin Gastroenterol Hepatol* [Internet]. 2010 Dec [cited 2023 Feb 20];8(12):1002. <https://doi.org/10.1016/J.CGH.2010.08.024> PMID: 20851211
7. Approach to the patient with abnormal liver biochemical and function tests - UpToDate [Internet]. [cited 2023 Mar 3]. <https://www.uptodate.com/contents/approach-to-the-patient-with-abnormal-liver-biochemical-and-function->

tests?search=liver%20biochemical&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 (accessed 2023 Mar 3)

8. Keaveny AP, Karasik MS. Hepatobiliary and pancreatic infections in AIDS: Part one. *AIDS Patient Care STDS*. 1998;12(5):347–57. <https://doi.org/10.1089/apc.1998.12.347> PMID: 11361970
9. Lefkowitz JH. Pathology of AIDS-related liver disease. *Dig Dis* [Internet]. 1994 [cited 2023 Feb 20];12(6):321–30. <https://doi.org/10.1159/000171468> PMID: 7712615
10. Pol S, Lebray P, Vallet-Pichard A. HIV infection and hepatic enzyme abnormalities: intricacies of the pathogenic mechanisms. *Clin Infect Dis* [Internet]. 2004 Mar 1 [cited 2023 Feb 20];38 Suppl 2(SUPPL. 2). <https://doi.org/10.1086/381499> PMID: 14986277
11. Sulkowski MS. Management of hepatic complications in HIV-infected persons. *J Infect Dis* [Internet]. 2008 May 15 [cited 2023 Feb 20];197 Suppl 3(SUPPL. 3). <https://doi.org/10.1086/533414> PMID: 18447614
12. Crum-Cianflone N, Collins G, Medina S, Asher D, Campin R, Bavaro M, et al. Prevalence and factors associated with liver test abnormalities among human immunodeficiency virus-infected persons. *Clin Gastroenterol Hepatol* [Internet]. 2010 Feb [cited 2023 Feb 20];8(2):183–91. <https://doi.org/10.1016/J.CGH.2009.09.025> PMID: 19800985
13. Jha RK, Sah SK. Prevalence and Clinical Spectrum of Liver Disease in Nepalese HIV-Sero-Positive Patients Undergoing Antiretroviral Therapy: A Cross-Sectional Hospital Based Study. *AIDS Res Treat* [Internet]. 2017 [cited 2023 Mar 3];2017. <https://doi.org/10.1155/2017/3134790> PMID: 28695009
14. Androutsakos T, Schina M, Pouliakis A, Kontos A, Sipsas N, Hatzis G. Causative factors of liver fibrosis in HIV-infected patients. A single center study. *BMC Gastroenterol* [Internet]. 2020 Apr 6 [cited 2023 Mar 3];20(1):1–7. <https://doi.org/10.1186/S12876-020-01230-1/TABLES/5> PMID: 32252653
15. Abere ST, Oyan B, Azukoye-Amadi B, Amachree EE. Chronic liver disease in HIV patients: Determinants and clinical manifestations. *NIGERIAN JOURNAL OF GASTROENTEROLOGY*

AND HEPATOLOGY [Internet]. 2022 [cited 2023 Mar 3];14(2):55. https://doi.org/10.4103/NJGH.NJGH_16_22

16. Mohite AR, Gambhire PA, Pawar S V., Jain SS, Contractor QQ, Rathi PM. Changing clinical profile and factors associated with liver enzyme abnormalities among HIV-infected persons. *Trop Doct* [Internet]. 2017 Jul 1 [cited 2023 Mar 3];47(3):205–11. <https://doi.org/10.1177/0049475516655068> PMID: 27342920
17. Rasoulinejad M, Seyed Alinaghi SA, Sohrabi MR, Badie BM, Manshadi SAD, Nezhad MH, et al. Prevalence and Factors Associated with Hepatic Steatosis and Fibrosis Using Fibroscan in HIV-positive Patients Treated with Anti-retroviral (ARV) Medicines Referred to the Biggest Hospital in Tehran, 2018 to 2019. *Open AIDS J*. 2020 Dec 16;14(1):108–13. <https://doi.org/10.2174/1874613602014010108>
18. Ocama P, Katwere M, Piloya T, Feld J, Opio KC, Kambugu A, et al. The spectrum of liver diseases in HIV infected individuals at an HIV treatment clinic in Kampala, Uganda. *Afr Health Sci* [Internet]. 2008 Mar [cited 2023 Mar 3];8(1):8. PMID: 19357726
19. Shiferaw MB, Tulu KT, Zegeye AM, Wubante AA. Liver Enzymes Abnormalities among Highly Active Antiretroviral Therapy Experienced and HAART Naïve HIV-1 Infected Patients at Debre Tabor Hospital, North West Ethiopia: A Comparative Cross-Sectional Study. *AIDS Res Treat* [Internet]. 2016 [cited 2023 Mar 3];2016. <https://doi.org/10.1155/2016/1985452> PMID: 27493798
20. Ayana DA, Mulu A, Mihret A, Seyoum B, Aseffa A, Howe R. Hepatitis B virus seromarkers among HIV infected adults on ART: An unmet need for HBV screening in eastern Ethiopia. *PLoS One* [Internet]. 2019 Dec 1 [cited 2023 Mar 3];14(12):e0226922. <https://doi.org/10.1371/JOURNAL.PONE.0226922> PMID: 31887187
21. Gedefie A, Adamu A, Alemayehu E, Kassa Y, Belete MA. Hepatitis C Virus Infection among HIV-Infected Patients Attending Dessie Referral Hospital, Northeastern Ethiopia. *Int J Microbiol* [Internet]. 2021 [cited 2023 Mar 3];2021. <https://doi.org/10.1155/2021/6675851> PMID: 33552160

22. Tassachew Y, Abebe T, Belyhun Y, Teffera T, Shewaye AB, Desalegn H, et al. Prevalence of HIV and Its Co-Infection with Hepatitis B/C Virus Among Chronic Liver Disease Patients in Ethiopia. *Hepat Med* [Internet]. 2022 May [cited 2023 Mar 3];14:67–77. <https://doi.org/10.2147/HMER.S365443> PMID: 35591850
23. Mohammed O, Alemayehu E, Bisetegn H, Tilahun M, Gedefie A, Ebrahim E, et al. Prevalence of hepatotoxicity among HIV-infected patients in Ethiopia: a systematic review and meta-analysis. *BMC Infect Dis* [Internet]. 2022 Dec 1 [cited 2023 Mar 3];22(1). <https://doi.org/10.1186/S12879-022-07838-W> PMID: 36352398
24. Castellares C, Barreiro P, Martín-Carbonero L, Labarga P, Vispo ME, Casado R, et al. Liver cirrhosis in HIV-infected patients: prevalence, aetiology and clinical outcome. *J Viral Hepat* [Internet]. 2008 Mar [cited 2023 Mar 3];15(3):165–72. <https://doi.org/10.1111/J.1365-2893.2007.00903.X> PMID: 18233989
25. Wekesa C, Kirk GD, Aizire J, Benson EM, Karabarinde A, Parkes-Ratanshi R, et al. Prevalence and Factors Associated With Liver Fibrosis Among Adult HIV-Infected Patients Attending Urban and Rural Care Clinics in Uganda. *Open Forum Infect Dis* [Internet]. 2020 Nov 1 [cited 2023 Mar 3];7(11). <https://doi.org/10.1093/OFID/OFAA483> PMID: 33241065
26. Androutsakos T, Schina M, Pouliakis A, Kontos A, Sipsas N, Hatzis G. Causative factors of liver fibrosis in HIV-infected patients. A single center study. *BMC Gastroenterol* [Internet]. 2020 Apr 6 [cited 2023 Feb 20];20(1). <https://doi.org/10.1186/S12876-020-01230-1> PMID: 32252653
27. Mohite A, Gambhire P, Shah D, Somani P, Contractor Q, Rathi P. Clinical Profile and Factors Associated with Liver Enzyme Abnormalities among HIV-Infected Persons. *J Clin Exp Hepatol* [Internet]. 2014 Mar 1 [cited 2023 Mar 3];4:S69. <https://doi.org/10.1016/j.jceh.2014.02.134>
28. Collins S, Mertenskoetter T, Loeliger E, Tressler R, Weller I, Friis-Møller N, et al. Liver-Related Deaths in Persons Infected With the Human Immunodeficiency Virus: The D:A:D Study. *Arch Intern Med* [Internet]. 2006 Aug 14 [cited 2023 Mar 3];166(15):1632–41. <https://doi.org/10.1001/ARCHINTE.166.15.1632> PMID: 16908797
29. Sulkowski MS. Viral hepatitis and HIV coinfection. *J Hepatol* [Internet]. 2008 Feb [cited 2023 Mar 3];48(2):353–67. <https://doi.org/10.1016/J.JHEP.2007.11.009> PMID: 18155314

30. Staples CT, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. *Clin Infect Dis* [Internet]. 1999 [cited 2023 Mar 3];29(1):150–4. <https://doi.org/10.1086/520144> PMID: 10433578
31. Puoti M, Airoidi M, Bruno R, Zanini B, Spinetti A, Pezzoli C, et al. Hepatitis B virus co-infection in human immunodeficiency virus-infected subjects. *AIDS Rev*. 2002;
32. Innocent-Adiele HC, Michael BBT, Okonko I, Ogbu O. SEROPREVALENCE OF HEPATITIS B VIRUS INFECTION AMONG HIV INFECTED INDIVIDUALS IN UYO, AKWA IBOM STATE, NIGERIA. *medRxiv*. 2021; <https://doi.org/10.1101/2021.03.06.21253060>
33. Reisler RB, Han C, Burman WJ, Tedaldi EM, Neaton JD. Grade 4 Events Are as Important as AIDS Events in the Era of HAART. *J Acquir Immune Defic Syndr* (1988) [Internet]. 2003 Dec 1 [cited 2023 Mar 3];34(4):379–86. <https://doi.org/10.1097/00126334-200312010-00004> PMID: 14615655
34. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA* [Internet]. 2000 Jan 5 [cited 2023 Mar 3];283(1):74–80. <https://doi.org/10.1001/JAMA.283.1.74> PMID: 10632283
35. Puoti M, Nasta P, Gatti F, Matti A, Prestini K, Biasi L, et al. HIV-related liver disease: ARV drugs, coinfection, and other risk factors. *J Int Assoc Physicians AIDS Care (Chic)* [Internet]. 2009 Jan [cited 2023 Mar 3];8(1):30–42. <https://doi.org/10.1177/1545109708330906> PMID: 19211929
36. Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, et al. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. *J Stud Alcohol* [Internet]. 2002 [cited 2023 Mar 3];63(2):179–86. <https://doi.org/10.15288/JSA.2002.63.179> PMID: 12033694
37. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* [Internet]. 2006 Feb [cited 2023 Mar 3];43(2 Suppl 1). <https://doi.org/10.1002/HEP.20973> PMID: 16447287

38. Soriano V, Puoti M, Garcia-Gascó P, Rockstroh JK, Benhamou Y, Barreiro P, et al. Antiretroviral drugs and liver injury. *AIDS* [Internet]. 2008 Jan 1 [cited 2023 Mar 3];22(1):1–13. <https://doi.org/10.1097/QAD.0B013E3282F0E2FD> PMID: 18090386
39. McGovern BH, Ditelberg JS, Taylor LE, Gandhi RT, Christopoulos KA, Chapman S, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. *Clinical Infectious Diseases* [Internet]. 2006 Aug 1 [cited 2023 Mar 3];43(3):365–72. <https://doi.org/10.1086/505495> PMID: 16804853
40. Sulkowski MS, Mehta SH, Torbenson M, Afdhal NH, Mirel L, Moore RD, et al. Hepatic steatosis and antiretroviral drug use among adults coinfecting with HIV and hepatitis C virus. *AIDS* [Internet]. 2005 Mar 24 [cited 2023 Mar 3];19(6):585–92. <https://doi.org/10.1097/01.AIDS.0000163935.99401.25> PMID: 15802977
41. Crum-Cianflone N, Dilay A, Collins G, Asher D, Campin R, Medina S, et al. Nonalcoholic fatty liver disease among HIV-infected persons. *J Acquir Immune Defic Syndr* [Internet]. 2009 Apr [cited 2023 Mar 3];50(5):464–73. <https://doi.org/10.1097/QAI.0B013E318198A88A> PMID: 19225402
42. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* [Internet]. 2005 Jan 6 [cited 2023 Mar 3];352(1):48–62. <https://doi.org/10.1056/NEJMRA041811> PMID: 15635112
43. Ogedegbe AEO, Thomas DL, Diehl AM. Hyperlactataemia syndromes associated with HIV therapy. *Lancet Infectious Diseases* [Internet]. 2003 Jun 1 [cited 2023 Mar 3];3(6):329–37. [https://doi.org/10.1016/S1473-3099\(03\)00654-6](https://doi.org/10.1016/S1473-3099(03)00654-6) PMID: 12781504
44. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* [Internet]. 1992 [cited 2023 Mar 3];74(5):1045–52. <https://doi.org/10.1210/JCEM.74.5.1373735> PMID: 1373735
45. Lemoine M, Barbu V, Girard PM, Kim M, Bastard JP, Wendum D, et al. Altered hepatic expression of SREBP-1 and PPARgamma is associated with liver injury in insulin-resistant

- lipodystrophic HIV-infected patients. *AIDS* [Internet]. 2006 Feb [cited 2023 Mar 3];20(3):387–95. <https://doi.org/10.1097/01.AIDS.0000206503.01536.11> PMID: 16439872
46. Poles MA, Lew EA, Dieterich DT. Diagnosis and treatment of hepatic disease in patients with HIV. *Gastroenterol Clin North Am* [Internet]. 1997 [cited 2023 Mar 3];26(2):291–321. [https://doi.org/10.1016/S0889-8553\(05\)70296-X](https://doi.org/10.1016/S0889-8553(05)70296-X) PMID: 9187926
47. Keaveny AP, Karasik MS. Hepatobiliary and pancreatic infections in AIDS: Part one. *AIDS Patient Care STDS* [Internet]. 1998 [cited 2023 Mar 3];12(5):347–57. <https://doi.org/10.1089/APC.1998.12.347> PMID: 11361970
48. Bonacini M. Hepatobiliary complications in patients with human immunodeficiency virus infection. *Am J Med* [Internet]. 1992 [cited 2023 Mar 3];92(4):404–11. [https://doi.org/10.1016/0002-9343\(92\)90271-C](https://doi.org/10.1016/0002-9343(92)90271-C) PMID: 1558086
49. Barr DA, Ramdial PK. Clinicopathological correlates in HIV seropositive tuberculosis cases presenting with jaundice after initiating antiretroviral therapy with a structured review of the literature. *BMC Infect Dis*. 2012 Oct 14;12. <https://doi.org/10.1186/1471-2334-12-257> PMID: 23061403
50. Huang CT, McGarry T, Cooper S, Saunders R, Andavolu R. Disseminated Histoplasmosis in the Acquired Immunodeficiency Syndrome: Report of Five Cases From a Nonendemic Area. *Arch Intern Med* [Internet]. 1987 Jun 1 [cited 2023 Mar 3];147(6):1181–4. <https://doi.org/10.1001/ARCHINTE.1987.00370060177030> PMID: 3592886
51. Ng VL, Yajko DM, Hadley WK. Extrapulmonary pneumocystosis. *Clin Microbiol Rev* [Internet]. 1997 Jul [cited 2023 Mar 3];10(3):401–18. <https://doi.org/10.1128/CMR.10.3.401> PMID: 9227859
52. Perkocha LA, Geaghan SM, Yen TSB, Nishimura SL, Chan SP, Garcia-Kennedy R, et al. Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection. *N Engl J Med* [Internet]. 1990 Dec 6 [cited 2023 Mar 3];323(23):1581–6. <https://doi.org/10.1056/NEJM199012063232302> PMID: 2233946

53. Bonacini M. Hepatobiliary complications in patients with human immunodeficiency virus infection. *Am J Med* [Internet]. 1992 [cited 2023 Mar 3];92(4):404–11. [https://doi.org/10.1016/0002-9343\(92\)90271-C](https://doi.org/10.1016/0002-9343(92)90271-C) PMID: 1558086
54. Klatt E, Nichols L, Noguchi T. Evolving trends revealed by autopsies of patients with the acquired immunodeficiency syndrome. 565 autopsies in adults with the acquired immunodeficiency syndrome, Los Angeles, Calif, 1982-1993 [corrected]. *Arch Pathol Lab Med*. 1994;
55. Ko WF, Cello JP, Rogers SJ, Lecours A. Prognostic factors for the survival of patients with AIDS cholangiopathy. *Am J Gastroenterol* [Internet]. 2003 [cited 2023 Mar 3];98(10):2176–81. <https://doi.org/10.1111/J.1572-0241.2003.07718.X> PMID: 14572564
56. Yusuf TE, Baron TH. AIDS Cholangiopathy. *Curr Treat Options Gastroenterol* [Internet]. 2004 [cited 2023 Mar 3];7(2):111–7. <https://doi.org/10.1007/S11938-004-0032-2> PMID: 15010025
57. Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis - UpToDate [Internet]. [cited 2023 Mar 3]. https://www.uptodate.com/contents/cirrhosis-in-adults-etiological-clinical-manifestations-and-diagnosis?search=cirrhosis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 (accessed 2023 Mar 3)
58. National consolidated guidelines for comprehensive HIV prevention, care and treatment | WHO | Regional Office for Africa [Internet]. [cited 2024 Feb 16]. <https://www.afro.who.int/publications/national-consolidated-guidelines-comprehensive-hiv-prevention-care-and-treatment> (accessed 2024 Feb 16)
59. Osakunor DNM, Obirikorang C, Fianu V, Asare I, Dakorah M. Hepatic Enzyme Alterations in HIV Patients on Antiretroviral Therapy: A Case-Control Study in a Hospital Setting in Ghana. *PLoS One* [Internet]. 2015 Aug 6 [cited 2024 Feb 16];10(8). <https://doi.org/10.1371/JOURNAL.PONE.0134449> PMID: 26247879
60. Kimpiatu JPM, Mbendi CN lombi, Tshimpi AWY, Nkodila AN, Lepira FB, Mbendi SN, et al. Factors Associated with Liver Enzyme Abnormalities in HIV-HBV and/or HCV Co-infected Patients in Kinshasa, Democratic Republic of the Congo: Multicenter Cross-sectional Study.

Rambam Maimonides Med J [Internet]. 2022 Jul 1 [cited 2024 Feb 16];13(3). <https://doi.org/10.5041/RMMJ.10474> PMID: 35701157

61. Tesfa E, Siefu D, Belayneh Y, Mekonnen Z. Liver enzyme elevation in patients taking HAART compared with treatment naïve controls at Debre Berhan Referral Hospital: a comparative cross-sectional study, Northeast Ethiopia. *BMC Res Notes* [Internet]. 2019 Oct 30 [cited 2024 Feb 16];12(1). <https://doi.org/10.1186/S13104-019-4748-4> PMID: 31666123
62. Achila O, Kesete Y, Abrhaley F, et al. Assessment of Liver Enzyme Abnormality Among HIV-Infected Patients on Antiretroviral Therapy in Asmara, Eritrea [Internet]. [cited 2024 Feb 16]. https://www.researchgate.net/publication/359776550_Assessment_of_Liver_Enzyme_Abnormality_Among_HIV-Infected_Patients_on_Antiretroviral_Therapy_in_Asmara_Eritrea (accessed 2024 Feb 16)
63. Gil ACM, Lorenzetti R, Mendes GB, Morcillo AM, Toro AADC, da Silva MTN, et al. Hepatotoxicity in HIV-infected children and adolescents on antiretroviral therapy. *Sao Paulo Med J* [Internet]. 2007 [cited 2024 Feb 16];125(4):205–9. <https://doi.org/10.1590/S1516-31802007000400002> PMID: 17992389
64. Hoffmann CJ, Charalambous S, Thio CL, Martin DJ, Pemba L, Fielding KL, et al. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *AIDS* [Internet]. 2007 Jun [cited 2024 Feb 16];21(10):1301–8. <https://doi.org/10.1097/QAD.0B013E32814E6B08> PMID: 17545706
65. Lucien K, Clement A, Fon N, Weledji P, Ndikvu C. The effects of antiretroviral treatment on liver function enzymes among HIV-infected out patients attending the Central Hospital of Yaounde, Cameroon. *African Journal of Clinical and Experimental Microbiology* [Internet]. 2010 Aug 11 [cited 2024 Feb 16];11(3):174–8. <https://doi.org/10.4314/AJCEM.V11I3.57777>
66. Abongwa LE, Nyamache AK, Charles F, Torimiro J, Emmanuel N, Domkam I, et al. Risk factors of severe hepatotoxicity among HIV-1 infected individuals initiated on highly active antiretroviral therapy in the Northwest Region of Cameroon. *BMC Gastroenterol* [Internet]. 2022 Dec 1 [cited 2024 Feb 16];22(1). <https://doi.org/10.1186/S12876-022-02305-X> PMID: 35658835

67. Mugusi SF, Sando D, Mugusi FM, Hawkins C, Aboud S, Fawzi WW, et al. Risk Factors for Alanine Aminotransferase Elevations in a Prospective Cohort of HIV-Infected Tanzanian Adults Initiating Antiretroviral Therapy. *J Int Assoc Provid AIDS Care* [Internet]. 2019 [cited 2024 Feb 16];18. <https://doi.org/10.1177/2325958219884939> PMID: 31665968
68. Liu S, Zhou Y, Wang Y, Li CB, Wang W, Lu X, et al. The Correlated Risk Factors for Severe Liver Damage Among HIV-Positive Inpatients With Abnormal Liver Tests. *Front Med (Lausanne)* [Internet]. 2022 Feb 22 [cited 2024 Feb 16];9. <https://doi.org/10.3389/FMED.2022.817370> PMID: 35273978
69. Mulu W, Gidey B, Chernet A, Alem G, Abera B. Hepatotoxicity and Associated Risk Factors in HIV-Infected Patients Receiving Antiretroviral Therapy at Felege Hiwot Referral Hospital, Bahirdar, Ethiopia. *Ethiop J Health Sci* [Internet]. 2013 Nov 1 [cited 2024 Feb 17];23(3):217. <https://doi.org/10.4314/EJHS.V23I3.4> PMID: 24307821
70. Sato S, Kawai H, Sato S, Iwasaki H, Omori M, Kita Y, et al. Hypertension and diabetes mellitus are associated with high FIB-4 index in a health checkup examination cohort without known liver disease. *BMC Gastroenterol* [Internet]. 2022;22(1):478. <https://doi.org/10.1186/s12876-022-02575-5>
71. Sterling RK, Chiu S, Snider K, Nixon D. The prevalence and risk factors for abnormal liver enzymes in HIV-positive patients without hepatitis B or C coinfections. *Dig Dis Sci* [Internet]. 2008 May [cited 2024 Feb 17];53(5):1375–82. <https://doi.org/10.1007/S10620-007-9999-6> PMID: 17939038
72. Ejilemele AA, Nwauche CA, Ejele OA. Pattern of abnormal liver enzymes in HIV patients presenting at a Nigerian Tertiary Hospital. *Niger Postgrad Med J* [Internet]. 2007 [cited 2024 Feb 16];14(4):306–9. <https://doi.org/10.4103/1117-1936.180369> PMID: 18163139
73. Anyanwu CF, JohnBull TO, Usman IM, Aigbogun EO, Ochai J, Qasem AH, et al. Substance Use, Highly Active Antiretroviral Therapy, and Liver Enzymes: Evidence From a Cross-Sectional Study of HIV-Infected Adult Patients Without Comorbidities on HAART in the University of Port Harcourt Teaching Hospital. *Frontiers in Reproductive Health* [Internet]. 2021 [cited 2024 Feb 16];3:664080. <https://doi.org/10.3389/FRPH.2021.664080/FULL>

74. Pourcher V, Gourmelen J, Bureau I, Bouee S. Comorbidities in people living with HIV: An epidemiologic and economic analysis using a claims database in France. *PLoS One* [Internet]. 2020 Dec 1 [cited 2024 Feb 16];15(12). <https://doi.org/10.1371/JOURNAL.PONE.0243529> PMID: 33332394
75. Kendall CE, Wong J, Taljaard M, Glazier RH, Hogg W, Younger J, et al. A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. *BMC Public Health* [Internet]. 2014 Feb 13 [cited 2024 Feb 16];14(1). <https://doi.org/10.1186/1471-2458-14-161> PMID: 24524286
76. Gizamba JM, Davies J, Africa C, Choo-Kang C, Goedecke JH, Madlala H, et al. Prevalence of obesity, hypertension and diabetes among people living with HIV in South Africa: a systematic review and meta-analysis. *BMC Infect Dis* [Internet]. 2023 Dec 1 [cited 2024 Feb 16];23(1). <https://doi.org/10.1186/S12879-023-08736-5> PMID: 38062372
77. Iddi S, Minja CA, Silago V, Benjamin A, Mpesha J, Henerico S, et al. High Human Immunodeficiency Virus (HIV) Viral Load and Coinfection with Viral Hepatitis Are Associated with Liver Enzyme Abnormalities among HIV Seropositive Patients on Antiretroviral Therapy in the Lake Victoria Zone, Tanzania. *AIDS Res Treat* [Internet]. 2019 [cited 2024 Feb 16];2019. <https://doi.org/10.1155/2019/6375714> PMID: 31275646

10. Structured Questionnaire

Annex I : Participant information sheet and informed consent

Good morning/afternoon dear participant! My name is _____. I am working as a data collector for the study being conducted to assess about prevalence and clinical spectrum of liver diseases among HIV patients done by Dr. Abraham Tesfaye (Final year internal medicine resident). I kindly request you to give me your attention to explain you about the study and being selected as the study participant.

The study title: The prevalence and associated factors for spectrum of liver disease among patients with HIV infection at St. Paul hospital millennium medical college

Purpose of the study: to assess the prevalence and associated factors for spectrum of liver disease among patients with HIV infection at St. Paul hospital millennium medical college

Procedure and duration: the data collection will be conducted by reviewing patient medical chart and interview of patients using a structured questionnaire, which is translated to local language by interviewers

Risks and benefits: the study will be beneficial to give due emphasis for future follow up and guide clinicians, administrations to develop an approach and guidelines on prevention, detection, monitoring and management of patients with HIV infection. There are no specific major or minor risks associated with the procedure of our study.

Confidentiality: participants data confidentiality will be guaranteed by primary investigator as well as data collectors or any members involved in the study. The data collection will only go forward after informed consent is confirmed.

Rights: patients have the right not to give or withdraw consent at any time during the study.

Contact address: abrahamtesfaye09@gmail.com, phone number - 0909704351

Declaration of informed voluntary consent:

I have read/ was read to me the participant information sheet. I have clearly understood the purpose of the research, the procedures, the risks and benefits, issues of confidentiality, the rights of participating and the contact address for any queries. I have been given the opportunity to ask questions for things that may have been unclear. I was informed that I have the right to withdraw from the study at any time or not to answer any question that I do not want. Therefore; I declare my voluntary consent to participate in this study with my initials (signature) as indicated below.

Name of participant: _____ Signature of participant: _____.

Name of Data collector _____ Signature of Data collector_____.

Eligibility Assessment		Response	
		Yes	No
Inclusion criteria			
Age above 18 years			
Patients with HIV infection with available liver biochemical tests with in 1 year			
Consented to participate in the study			
Exclusion criteria			
Patients with HIV infection with no available (incomplete) liver biochemical tests			
Stop the interview if one answer to inclusion criteria is “No” or the answer to exclusion criteria is ”Yes”			
Interview Language and Name	Response		
Interview Language <i>[Insert Language]</i>			
Patient Name			
MRN/ I - care number			
Contact phone number			

Socio - Demographic Information			
Question	Response		
Sex	Male 1	Female 2	
Age	Years _____		
Level of education	No formal schooling 1	High school completed 5	
	Less than primary school 2	College/University completed 6	
	Primary school completed 3	Post graduate degree 7	
	Secondary school completed 4		
Region	Tigray 1	Somali 5	Gambella 9
	Afar 2	Benishangul-Gumuz 6	Addis Ababa 10
	Amhara 3	SNNPR 7	Dire-Dawa 11
	Oromia 4	Harari 8	
Marital status	Never married 1		Divorced 3
	Currently married 2		Widowed 4
Current Job	Government employee 1	Non-paid 4	Retired 7
	Non-government employee 2	Student 5	Unemployed (able to work) 8
	Self-employed 3	Homemaker 6	Unemployed (unable to work) 9

Behavioral & Clinical Assessments			
Question	Response		
Alcohol intake history	Yes 1 No 2		
If yes, to Alcohol intake	Amount (in local measurements) _____ Frequency per week _____, Total duration of intake _____		
Herbal medication	Type (ingested, tattoo..) _____, Amount _____		
Other habits (smoking, Khat intake, recent paracetamol intake)	_____		
Medications other than ART	Anti-tuberculosis ☐ CPT ☐ Other _____		
Documented symptoms related to liver disease (please tick available symptoms)	Hematemesis/melena/hematochezia ☐ anorexia ☐ fatigue ☐ Pruritus ☐ Sleep disturbance ☐ confusion ☐ abdominal swelling ☐		
Duration of HIV infection			
Current WHO stage			
ART initiation year			
ART Regimen	1 d – AZT, 3TC, EVF	2 e – AZT, 3TC, LPV/r	3a- DRV/r, DTG, AZT, 3TC

	1 e- TDF, 3TC, EFV	2 f – AZT, 3TC, ATV/r	3b- DRV/r, DTG, TDF, 3TC
	1 g – ABC, 3TC, EFV	2 g – TDF, 3TC, LPV/r	3c- DRV/r, TDF, 3TC, EFV
	1 j – TDF, 3TC, DTG	2 h – TDF, 3TC, ATV/r	3e- DRV/r, TDF, 3TC, EFV
	Other 1 st line _____	Other 2 nd line _____	Other 3 rd line_____
ART switches			

Physical Measurements	
Question	Response
Any signs/complications of chronic liver disease (please tick available signs)	Jaundice ☐ Splenomegally ☐ Ascites ☐ UGIB ☐ Encephalopathy ☐
Height in Centimetres (cm) _____ Weight in Kilograms (kg)_____	
Calculated BMI In kg/m ² _____	
Waist circumference in Centimetres (cm)_____	

Biochemical Measurements		
Question		Response
Thrombocytopenia		_____
Liver biochemical tests	AST	_____
	ALT	_____

	ALP	_____
	Total bilirubin/direct bilirubin	_____
	Serum Albumin	_____
	INR	_____
HIV RNA Viral load		_____
CD4 ⁺ count		_____
HCV anti body test/HCV RNA		_____
HBsAg/HBV DNA viral load		_____
Imaging Studies		
Question	Response	
Abdominal ultrasound report		
Transient Elastography report		
Cross sectional studies (CT or MRI)		

ASSURANCE OF PRINCIPAL INVESTIGATORS

We the undersigned agree to accept all responsibilities for the scientific and ethical conduct of the research project. We will provide timely progress report to my advisor and seek the necessary advice and approval from my primary advisors in the course of the research. We will communicate timely to my advisors all stakeholders involved in the study including any source of funding for this research.

Name of the student: _____

Signature: _____

Date: _____

Approval of the Advisor

Name of the advisors: _____ Signature_____

: _____ Signature__ _____

Date: _____