ARSI UNIVERSITY COLLEGE OF HEALTH SCIENCES DEPARTMENT OF INTERNAL MEDICINE

THE EVOLVING BURDEN OF LIVER DISEASE IN THE ART ERA: MAGNITUDE AND DETERMINANTS AMONG HIV SERO-POSITIVE PATIENTS AT ASELLA REFERRAL AND TEACHING HOSPITAL, ETHIOPIA, 2026

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A THESIS REPORT TO BE SUBMITTED TO DEPARTMENT OF INTERNAL MEDICINE, COLLEGE OF HEALTH SCIENCES, ARSI UNIVERSITY, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE SPECIALITY CERTIFICATE IN INTERNAL MEDICINE.

JANUARY, 2026,

ASELA, ETHIOPIA

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ACRONYM / ABBREVIATIONS

3TC	Lamivudine
AHR	Adjusted hazard ratio
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AOR	Adjusted odds ratio
ART	Anti-retro viral therapy
ARTH	Asella Referral and Teaching Hospital
AST	Aspartate amino transferase
ATV/r	Atazanavir boosted with Ritonavir
AU	Arsi University
AUDIT	Alcohol Use Disorders Identification Test
AZT	Zidovudune
CD4	Cluster of differentiation
CFAR	Center for AIDS Research
CoHS	College of health sciences
DRV/r	Darunavir boosted with Ritonavir
DTG	Dolutegravir

ETB	Ethiopian Birr
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
NASH	Nonalcoholic Steato hepatitis
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OR	Odds Ratio
PLHIV	People living with HIV
SD	Standard deviation
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TDF	Tenofovir

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ABSTRACT

Background: *Liver disease remains a significant cause of morbidity and mortality among people living with human immunodeficiency virus, even in the era of widespread antiretroviral therapy. Multiple factors, including demography, clinical status, and treatment related effects, may contribute to liver disease in this population. However, data from resource limited settings like Ethiopia remains limited.*

Objective; *To determine the magnitude of liver disease and associated factors among human immunodeficiency virus sero-positive patients on follow up at Asella referral and teaching hospital, Arsi Zone, Ethiopia.*

Methods: *An institution-based cross-sectional study was conducted from October to December, 2025. Data on socio-demographic, behavioral, and clinical characteristics were gathered using a structured questionnaire and a thorough review of medical records. Liver disease was defined based on biochemical criteria. Data were entered and analyzed using SPSS version 27. Variables with a P-value < 0.25 in the bivariate analysis were entered into the multivariate model, and statistical significance was declared at a p-value < 0.05.*

Results: *A total of 288 participants were included in the final analysis, with a mean age of 45.6 years. Females represented 61.1% (n=176) of the cohort. The overall prevalence of liver disease was 27.4% (95% CI: 0.222 – 0.326). In multivariable logistic regression analysis, male sex was significantly associated with higher odds of liver disease (AOR = 2.698; 95% CI: 1.340 - 5.431). Participants with a history of tuberculosis had nearly four-fold increased odds of liver disease (AOR = 3.944; 95% CI: 2.044 - 7.611), while under nutrition was the strongest predictor of hepatic injury (AOR = 4.996; 95% CI: 2.373 - 10.518). Other factors, including age, viral load, CD4 count, and ART regimen, were not significantly associated with liver disease.*

Conclusion: *This study identified a high prevalence of liver disease (27.4%) among adults living with HIV in Asella. Male sex, under nutrition, and a history of tuberculosis were identified as the key determinants of hepatic complications. These findings suggest that liver health monitoring and nutritional support should be prioritized for these specific high-risk subgroups to improve long-term clinical outcomes.*

Key Words; *Liver disease, HIV patients, Hepatotoxicity, ART, Viral hepatitis, Ethiopia*

1. INTRODUCTION

1.1. Background

Globally, chronic liver disease and its consequence has affected an estimated 1.5 billion persons (1). Human Immunodeficiency Virus (HIV) constitutes a significant global public health challenge of the twenty-first century. Untreated, HIV infection progressively weakens the immune system, rendering individuals highly susceptible to developing fatal opportunistic infections within a decade (2). This cytopathic retrovirus destroys the immune system that leads to opportunistic infections and tumors. Various organs of the body, including liver, may be affected, leading to a variety of clinical presentations (3).

HIV is known to accelerate the natural history of liver disease, with co-infected individuals demonstrating accelerated progression to hepatic fibrosis, cirrhosis, and increased risk for hepatocellular carcinoma. More recently, data from the Center for acquired immunodeficiency syndrome (AIDS) Research (CFAR) Network of Integrated Clinical Systems (CNICS) study cohort demonstrates that poorly controlled HIV mono-infection is an independent risk factor for liver fibrosis (4,5).

Liver enzyme elevations are common in HIV infected patients. The cause is multifactorial and often clinically silent until advanced stages. Diagnosis or management may be difficult because of the intricacies of the pathogenic mechanisms involved. Some of the factors involved in this pathologic mechanism are hepatotoxicity related to anti-retro viral therapy (ART0, hepatitis B and C virus co-infections, alcohol use, metabolic dysfunction associated steatotic liver disease, and opportunistic infections which all contribute to progressive hepatic injury (6–9). HIV itself

also accelerates liver fibrosis through persistent immune activation and inflammation, even in the absence of viral hepatitis co-infection, making liver disease a direct and indirect complication of HIV infection (7,10). As a result, liver enzyme abnormalities and subclinical fibrosis are frequently encountered in HIV care, yet remain under recognized and under investigated.

1.2. Statement of the problem

With the widespread availability of ART, HIV infection has transitioned into a chronic manageable condition. As AIDS-related morbidity and mortality decline, non-AIDS comorbidities particularly liver disease have emerged as major determinants of long-term outcomes among people living with HIV (PLHIV). Globally, liver disease is now one of the leading non-AIDS–related causes of death in the ART era, accounting for approximately 14–18% of mortality among PLHIV (3).

Sub-Saharan Africa bears a disproportionate burden of this dual epidemic. The region is home to nearly 70% of the global PLHIV population and has high prevalence of hepatitis B and C virus infections, with reported HIV/HBV or HIV/HCV co-infection rates ranging from 8% to 15% (11,12). Behavioral and structural factors including alcohol use, food insecurity, limited access to diagnostic services, and fragmented healthcare systems further amplify the risk of liver disease and liver related mortality (11).

In Ethiopia, where an estimated 630,000 people are living with HIV, liver disease represents a growing but inadequately characterized clinical challenge. Studies report HIV/HBV co-infection rates ranging from 4.3% to 13.5%, with particularly high prevalence among patients with advanced liver disease and hepatocellular carcinoma (4,13). A national systematic review and

meta-analysis conducted in 2022 estimated the prevalence of hepatotoxicity among HIV-infected patients to be 25.45%, with substantially higher rates observed among patients receiving ART compared to ART-naïve individuals (14). Tuberculosis co-infection further increases the risk, with recent Ethiopian data demonstrating nearly threefold higher odds of severe hepatotoxicity among HIV/TB co-infected patients (15).

Although Ethiopia has transitioned to dolutegravir (DTG) based ART regimens, which are generally associated with improved safety profiles, hepatotoxicity remains a concern due to residual use of older drugs such as zidovudine (AZT), inconsistent laboratory monitoring, and drug–drug interactions related to TB treatment (11). In addition, food insecurity and under nutrition which are both common among PLHIV exacerbate hepatic vulnerability by contributing to hypoalbuminemia, impaired drug metabolism, and increased susceptibility to hepatic decompensation (16). Limited hepatitis B vaccination coverage, estimated at approximately 48%, further compounds the risk of preventable liver disease (17).

These challenges are particularly pronounced in rural and semi-urban settings such as ARTH, where ART clinics serve large catchment populations with constrained diagnostic capacity. Routine screening for hepatitis B and C virus infection and structured assessment of chronic liver disease are not consistently available, and liver enzyme abnormalities are often managed empirically without comprehensive evaluation (18). As a result, liver disease may remain undetected until advanced stages, leading to avoidable morbidity, ART interruptions, hospitalization, and premature mortality.

Despite several institution based studies conducted at Asella Referral and Teaching Hospital that examine long-term metabolic and treatment outcomes among people living with HIV (18,19), there is no published evidence within this setting on liver disease burden or its determinants. As ART programs mature, chronic complications extend beyond viral suppression and contribute substantially to morbidity. This absence of localized data limits clinicians' ability to identify high risk patients, tailor screening protocols, optimize ART regimens in the presence of hepatotoxicity risk factors, and allocate limited diagnostic resources effectively, potentially leading to delayed diagnosis and preventable progression to advanced liver disease. Therefore, understanding the magnitude and determinants of liver disease in the ART care population at ARTH is both an urgent clinical and public health priority in this semi urban referral setting.

In Ethiopia, several institution based studies conducted within ART clinics have demonstrated that locally generated clinical evidence can lead to meaningful improvements in HIV care delivery and patient outcomes. Research identifying the prevalence and predictors of ART related adverse effects including hepatotoxicity and other metabolic complications—has informed revisions in patient monitoring practices, earlier detection of drug toxicity, and safer ART regimen selection at facility and program levels (8,11,16,20,21). Similarly, Ethiopian studies documenting high rates of treatment-related complications among patients on long-term ART have supported the transition toward improved regimen selection, closer laboratory follow-up, and integration of comorbidity screening into routine HIV care, contributing to improved treatment continuity and survival (11,14). These experiences illustrate that when ART clinics generate evidence based on their own patient populations, the findings are directly applicable and actionable within the same clinical setting. Without such evidence, clinicians are unable to

stratify risk, prioritize screening, or intervene early, allowing preventable liver injury to progress to advanced disease. Conducting this study at ARTH therefore has the potential to directly inform ART clinic practices, strengthen liver disease monitoring, optimize treatment decisions, and ultimately improve survival and quality of life among HIV infected patients in this setting.

Taken together, the growing burden of liver disease among people living with HIV, the demonstrated impact of institution based research on improving ART care in Ethiopia (6,11,13,14), and the absence of local evidence from Asella Referral and Teaching Hospital highlight a critical and actionable knowledge gap. In the absence of facility specific data, clinicians at ARTH are unable to systematically identify high-risk patients, implement targeted liver disease screening, or optimize ART regimens in the presence of hepatotoxicity risk factors, allowing preventable liver injury to progress unchecked. Determining the magnitude of liver disease and its associated demographic, clinical, behavioral, and environmental factors among HIV sero positive patients on follow-up at ARTH is therefore essential to inform evidence-based clinical decision-making, strengthen integrated HIV care, and improve patient survival and long term outcomes in this setting..

1.3. Significance of the study

This study is expected to have important clinical, programmatic, and public health relevance for HIV care at ARTH and similar settings in Ethiopia. By determining the magnitude of liver disease and identifying its associated factors among people living with HIV on antiretroviral therapy, the study will generate locally relevant evidence that directly reflects the patient population, treatment practices, and resource constraints of the ARTH ART clinic. Such facility

specific data are essential for bridging the gap between generalized national recommendations and day to day clinical decision making.

At the clinical level, the findings will support healthcare providers in identifying patients at higher risk of liver disease, informing targeted screening strategies, closer laboratory monitoring, and timely modification of ART regimens in the presence of hepatotoxicity risk factors. Improved recognition and early detection of liver disease may help reduce avoidable ART interruptions, prevent progression to advanced liver disease, and decrease liver-related morbidity and mortality among patients receiving long-term HIV care.

From a programmatic perspective, the results of this study can inform ART clinic management and hospital administrators by highlighting priority areas for resource allocation, such as laboratory monitoring, hepatitis screening, and integrated management of comorbid conditions. The evidence generated may also contribute to strengthening routine HIV care by supporting the incorporation of liver disease assessment into existing ART follow-up protocols at ARTH.

At a broader level, this study will contribute to the limited body of Ethiopian data on liver disease among people living with HIV, particularly from rural referral settings. The findings may serve as a baseline for future research, quality improvement initiatives, and policy relevant discussions aimed at improving long-term outcomes for people living with HIV in the ART era. Ultimately, by linking locally generated evidence to clinical practice, this study has the potential to enhance the quality of HIV care and improve patient survival in this setting.

Furthermore, the recent introduction of hepatitis C treatment services at ARTH underscores the timeliness of this study and the need for locally generated evidence to guide the integration of liver disease assessment and management into routine ART care.

2. LITERATURE REVIEW

2.1. Burden of liver disease among people living with HIV

A 2021 multinational cohort study (22) found that 35% of HIV patients exhibit hepatic abnormalities, driven by ART toxicity, viral co-infections (HBV/HCV), and metabolic syndromes. This aligns with earlier findings from India, where 82% of HIV patients showed deranged liver function tests (LFTs), predominantly elevated SGOT/SGPT, alongside pathologies like fatty liver and granulomas (12). Recent data from sub-Saharan Africa further emphasize this burden. A 2022 study in South Africa (4) reported that 28% of ART-naïve patients developed hepatotoxicity within six months of treatment initiation, with efavirenz-based regimens posing higher risks. In East Africa, tuberculosis-associated liver disease remains prevalent. A 2023 Ugandan study (21) found that 22% of HIV/TB co-infected patients had advanced liver fibrosis (FIB-4 >3.25), linked to prolonged ART use and isoniazid toxicity.

In Ethiopia, recent evidence highlights evolving trends. A 2023 study in Addis Ababa (9) revealed a 6.2% HIV/HBV co-infection rate, with 40% of co-infected patients progressing to cirrhosis within five years. Another 2022 Ethiopian study on liver Enzyme Abnormalities among HIV Patients on Dolutegravir-Based Regimens (23) found that 18% of patients developed grade 1–2 ALT elevations, though severe hepatotoxicity was rare (<2%).

2.2. Factors associated with liver disease among PLHIV

2.2.1. Demographic Factors

Aging significantly exacerbates hepatic vulnerability. A 2021 U.S. study (24) demonstrated that PLHIV aged >50 years had a 3-fold higher risk of progressive liver fibrosis compared to younger cohorts, attributed to mitochondrial dysfunction and chronic inflammation. Sex disparities persist: a 2023 Nigerian study (25) found that men had higher rates of metabolic dysfunction-associated steatotic liver disease (MASLD) (27% vs. 18% in women), driven by insulin resistance and visceral adiposity.

2.2.2. Clinical Factors

Low CD4+ counts (<200 cells/mm³) and high HIV viral loads (>10,000 copies/mL) independently predict liver injury. A 2022 meta-analysis (26) confirmed that each 100-cell/mm³ decline in CD4+ count increased cirrhosis risk by 15%. In another study, subjects with cirrhosis had statistically significantly lower CD4+ T cell counts than did HIV-negative subjects (27). There is also correlation between HIV viral load and aminotransferases as liver damage markers in HIV infected patients. A concordance cross-sectional study, There was a significant positive correlation between HIV viral load and AST/ALT level(28). HBV co-infection remains a key driver: a 2023 Ethiopian study (17) reported that only 48% of HIV patients completed HBV vaccination, with 12% acquiring HBV post-ART initiation. Newer ART regimens, like DTG, show mixed impacts; while safer than older drugs, a 2023 Kenyan trial (29) linked it to grade 1–2 bilirubin elevations in 14% of patients. Other important factor is tuberculosis. Both active and previous TB exposure has shown significant increment in liver disease among HIV patients. Based on study done in referral hospitals of Ethiopia in 2020, the prevalence of drug-induced hepatotoxicity high in TB?HIV co infection and even higher if the TB is extra pulmonary (8).

2.2.3. Behavioral Factors

Alcohol consumption is prevalent in the HIV infected population and is not only associated with decreased HAART adherence and decreased HIV suppression but also increased risk of HAART induced hepatotoxicity (30). Alcohol use synergizes with ART to accelerate liver damage. A 2021 South African cohort study (20) found that heavy drinkers had 4.5-fold higher odds of severe hepatotoxicity (OR=4.5, 95% CI: 2.1–9.8). Smoking amplifies risks: a 2023 global analysis (31)(32) associated smoking with a 30% increase in liver-related deaths, mediated by oxidative stress and immune activation. khat use is also associated with serum enzyme elevations or alterations in liver function. (33)

2.2.4. Environmental and Institutional Factors

Food insecurity exacerbates liver disease in low-income settings. A 2022 Ethiopian study (34) revealed that undernourished HIV patients had 2.3-fold higher rates of hypoalbuminemia and hepatic encephalopathy. Several researches have also proved that Both under and over nutrition may occur among HIV infected individuals and impact on the course of liver disease (16), Limited access to HBV/HCV diagnostics further compounds risks; a 2023 Tanzanian report (35) found that only 32% of ART clinics offered routine HBV/HCV testing.

2.2.5. Conceptual framework

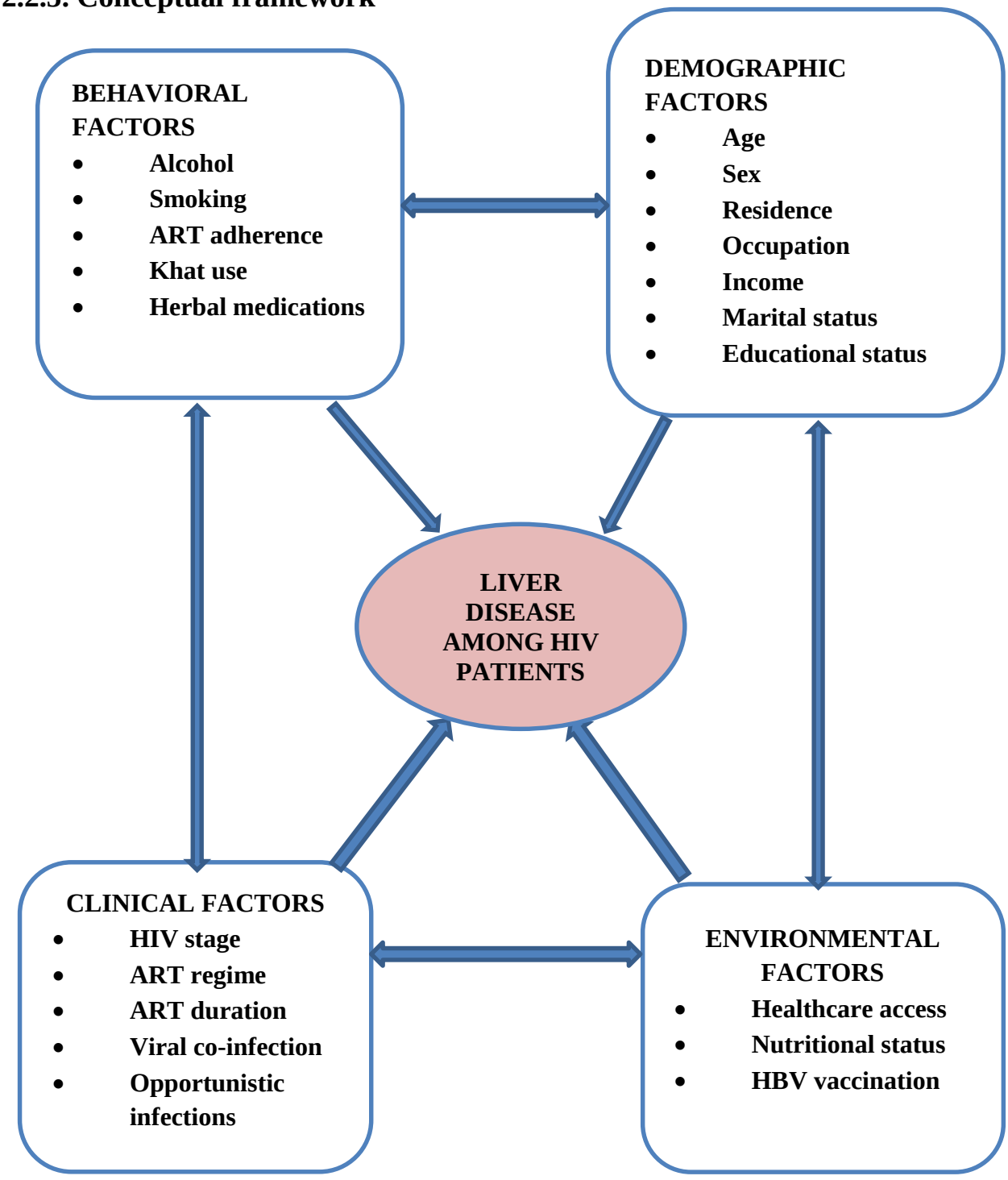

FIGURE 1 Conceptual framework, Asella, 2026

The variables selected for this conceptual framework are based on evidence from previous studies highlighting the role of ART-related toxicity (4,15, 22), the impact of tuberculosis co-infection (8), behavioral risks (19,29), and the critical influence of nutritional status (16,33) on hepatic health among PLHIV.

3. OBJECTIVE

3.1. General objective

- To determine the magnitude of liver disease and associated factors among HIV sero-positive patients on follow up at ARTH, 2025.

3.2. Specific objectives

- To determine the magnitude of liver disease among HIV sero-positive patients on follow up at ARTH, 2025.
- To assess factors associated with liver disease among HIV sero-positive patients on follow up at ARTH, 2025.

4. METHOD AND MATERIALS

4.1. Study area

The study was conducted at Arsi University, Asella referral and teaching hospital found in the town of Asella. Asella town is center of Arsi Zone in Oromia Region about 175 kilometers from Addis Ababa, the capital city of the country. Arsi University is one of the young universities in Ethiopia established in 2014. Since 1964 Asella teaching and referral hospital has been serving 3.8 million populations in Arsi and the nearby zones. The hospital has 321 beds with more than 6 departments (Internal Medicine, Surgery, Pediatrics, Gynecology and Obstetrics, Orthopedics and Oncology). The hospital is involved in training undergraduate and postgraduates in different specialties in 04 major departments (Internal Medicine, Surgery, Pediatrics and Child Health and Gynecology and Obstetrics). The hospital has been improving its health service delivery, currently has modern investigation modalities like digital X-rays, portable X-ray, different types of Ultrasound, Echocardiography, Computerized tomography scan and culture service. The Department of internal medicine has a separate ART follow up clinic which is functional 5 days per week. There are 3911 patients on regular follow up at the clinic as taken from HMIS logbook of the clinic. Among those 3799 are adult patients. The monthly patient flow at ART clinic for adult patients on the month of December and January were 930 and 1114 patients respectively. Based on the schedule, 1,743 patients have follow-up every three months while 2056 patients have follow-up scheduled every six months.

4.2. Study design and period

4.2.1. Study design

Institution based cross-sectional prospective study design was employed.

4.2.2. Study period

This study was conducted from October 1, 2025 - December 30, 2025 to determine the magnitude of liver disease and associated factors among HIV sero-positive patients on follow-up at ARTH ART clinic.

4.3. Source and Study population

4.3.1 Source population

All patients who are living with HIV and who have follow-up at ARTH ART clinic

4.3.2 Study population

All adult patients who are living with HIV, on follow up at ARTH ART clinic during the study period, and were selected at random.

4.4. Eligibility Criteria

4.4.1 Inclusion criteria

All patients who participate in this study have fulfilled all of the following criteria.

- Age should be greater than 18 years
- Has at least one CD4 count result
- Has at least two LFT result

4.4.2 Exclusion Criteria

- Patients with known liver disease which is not related with HIV or ART
- Patients with known stage 3 or 4 cancer which is not related to HIV
- Patients who has hepatobilary surgery at any time in the past

4.5 Sample size and sampling procedures

4.5.1 Sample size determination

The sample size for the study was determined using single population formula considering the following assumption. In Ethiopia, based on a systemic review and meta-analysis done in 2022(4), the prevalence of hepatotoxicity among HIV patients was 25.45%. We used P value 0.25.

$$n = \frac{Z_{\frac{a}{2}}^{2} P(1-P)}{d^2}$$

Where

n = Sample size

a = The level of significance which can be obtained as 1-confidence level

$Z\frac{a}{2}$ = The value under standard normal table for the given value of confidence level

P = Best estimate of population proportion

d = Maximum difference level

$= (1.96)^2 * 0.25(1-0.25) / (0.05)^2 = 288$

Since study population is <10,000

$$n = \frac{no}{\left(1 + \frac{no}{N}\right)}$$

Where

n = Final sample size

no = Sample size from the above calculation

N = Total population

= 288/[1+(288/3799)} = 267

Adding the 10% non-respondent rate

Final sample size is 294

4.5.2. Sampling procedure

Systematic random sampling technique is employed to select participants from ART clinic registry book who fulfill inclusion criteria. Each month 98 patients (one third of the sample size) are accessed. The first participant is selected using lottery method from the first early arrivers and every K^{th} of the participants is taken, K value being K= N/n. i.e. in one month around 1114 patients visited the ART clinic (based on January report), so k=1114/98 = 11, hence every eleventh patient is taken every month. If the Kth participant does not meet the inclusion criteria or meet exclusion criteria, sequential sampling method for replacement is employed which is to continue recruiting and screening participants until the desired sample size is met and replace exclusions incrementally.

4.6. Study variables

4.6.1, Outcome variable

- Magnitude of liver disease among HIV patients

4.6.2. Independent variables

1. Demographic factors
    - Age
    - Sex
    - Residence
    - Occupation
    - Income
    - Marital status
    - Educational status
2. Clinical factors
    - Duration HIV
    - CD4 level
    - Viral load
    - ART regimen
    - ART duration
    - Viral co-infection
    - Opportunistic infections
3. Behavioral factors
    - Alcohol use

- Smoking
- ART adherence
- Khat use

4. Environmental/ Institutional factors
    - Healthcare access
    - Nutritional status
    - HBV vaccination

4.7. Operational definitions

Alcohol-associated liver disease - AUDIT score ≥ 4 + imaging/histology). Categorized as low-risk (0–3), moderate (4–5), high-risk (≥6).

ART Adherence - Categorized using the ACTG Adherence Questionnaire; "Good" adherence is defined as missing 0 doses in the past month (100%).

Food Insecurity - An affirmative response to experiencing insufficient meals (≤1 meal/day) or as categorized by the Household Food Insecurity Access Scale.

HIV Disease Stage: WHO clinical stage

Liver disease diagnosis: Defined by the presence of one or more of the following

- Biochemical markers: Elevated ALT/AST (>1.5× upper limit of normal for ≥6 months), bilirubin >2.5× ULN, INR > 1.5 (36)
- Imaging: Ultrasound, CT, or MRI showing steatosis, fibrosis, cirrhosis, or hepatocellular carcinoma

Monthly Income - Ethiopian Birr (ETB): <1,000 (below poverty line), 1,000–3,000 (low income), >3,000 (middle/high). | World Bank (2022) Ethiopia Poverty Assessment

Over weight – A BMI >24.9 kg/m² (16)

Undernutrition - A Body Mass Index (BMI) <18.5 kg/m² (16)

Viral Load Suppression: A plasma HIV RNA level < 1000 copies/mL (28)

4.8. Data collection tools and procedures

Pre-tested and structured questionnaire was utilized to collect data on socio-demographic, behavioral, clinical and environmental characteristics. The questionnaires are prepared in English language, translated to Afaan Oromo and Amharic. And finally was translated back to English language by other person who has good command of English, Afaan Oromo and Amharic to check for its consistency.

An interviewer-administered questioner was used to collect demographic, socioeconomic and behavioral factors related to the objectives of the study from HIV patients at ART clinic. Laboratory results and imaging, antiretroviral therapy history, previous history and physical examination findings were taken from medical record. Prospective data was collected from October 1 to December 30, 2025.

Four data collectors (two medical interns and two nurses) and one supervisor (general practitioner) participate in data collection process. Two days of training was given for data collectors and supervisor.

4.9. Data quality control

To assure the quality of the data, two days of training were given to data collectors and supervisor on the aim of the study, content of the questionnaire, how to conduct the interview and how to take laboratory results from patient chart. Data was collected using Kobo toolbox.

Pre-test was done on the 5% of HIV patients before the actual data collection and sequence of some questions was changed based on pre-test result. Additionally, FIB-4 and APRI scores were excluded from diagnostic modalities due to incomplete availability of complete blood count required for their calculation in the data collection tool. Data collected during pretest were not included in the final analysis. Progress report was taken from data collectors following the data collection, the collected data are kept in the form of file in secured place.

4.10. Data processing and analysis

Data was exported from Kobo toolbox to SPSS version 27.0 for analysis. Anthropometric measurements are calculated using WHO Anthro software version 3.2.2 and then transferred to SPSS version 27.0 for analysis. Missing values were checked and also data cleaning was done by using simple frequency analysis and by sorting. All descriptive statistics are reported. A binary logistic regression analysis was used to assess the association between the dependent variables with each independent variable. Finally variables which showed association in binary logistic regression at P-value less than 0.25 were entered in to multivariable analysis to control the possible effect of confounders. Interaction between variables was assessed. Model fit was tested with Hosmer-Lemeshow Goodness of Fit test. An odds ratio together with the 95% CI was used to report associations between liver disease and HIV disease. P-value <0.05 was considered for statistical significance. Results are presented in tabulation, charts and percentage.

4.11. Ethical considerations

Ethical clearance letter was obtained from Asella College of Health Sciences ethical review committee with project protocol number CoHS/R/180/2025. Then, official letter was delivered to

data manager and ARTH ART clinic coordinator. Patient permission was obtained through a mandatory question, *"Are you willing to participate?"* on Kobo toolbox before starting question and reading patient's chart, after the adequate information was given about the research. After getting permission, patient's charts that fulfill the criteria were selected. Data security and confidentiality were maintained at all levels of data collection and storage. Names of the patients were not included during data collection and information gained was not exposed to third party.

4.12. Results Dissemination plan

The final result of this study will be presented for a research defense at Arsi University, Asella Referral and Teaching hospital. The results will be disseminated to Internal medicine department, hospital administration, policy makers, regional health bureau and federal health bureau for service improvements. The research will also be sent for publication.

5. RESULT

5.1. Socio-demographic characteristics of study participants

A total of 288 participants were included in the study. The study population was predominantly middle-aged, with a mean age of 45.6 years (± 12.7 SD) and a range of 18 to 92 years. Over half of the participants (61.1%, n=176) were female. Regarding residency, the majority lived in urban settings. In terms of economic status, participant income was categorized based on the World Bank Ethiopia Poverty Assessment (2025). A significant portion of the cohort 71.9 % fell into the middle-income bracket, earning greater than or equal to 3,000 ETB per month, while 15.6 % were living below the poverty line with a monthly income of less than 3,000 ETB. The educational profile showed that primary education 37.8% was the most frequent attainment among the study participants TABLE 1.

TABLE 1 Socio-demographic characteristics of study participants, ARTH, Ethiopia (n = 288)

Variable	Category	Frequency	Percentage
Sex	Male	112	38.9
	Female	176	61.1
Age	Mean ± Std. Deviation	45.6 ± 12.7	
	Median (Range)	45.0 (74)	
Residence	Urban	218	75.7
	Rural	70	24.3
Age category	≤50 years	193	67.0
	>50 years	95	33.0
Marital status	Married	142	49.3

	Single	32	11.1
	Divorced	52	18.1
	Widowed	61	21.2
	Missing value	1	0.3
Education	No formal education	67	23.3
	Grade 1–8	109	37.8
	Grade 9–12	83	28.8
	College and above	28	9.7
	Missing value	1	0.3
Monthly income	≥3000 birr	207	71.9
	<3000 birr	45	15.6
	Missing value	36	12.5

5.2. Behavioral and clinical characteristics

Less than five percent of participants were smokers, less than ten percent use khat, and most (83.3%) did not drink alcohol. Poor ART adherence was reported in 9.7%. Nearly one-third (31.3%) had a history of tuberculosis. DTG-containing regimens were used by 81.2% of participants. Table 2

TABLE 2 Behavioral and clinical characteristics of study participants, ARTH, Ethiopia (N = 288)

Variable	Category	Frequency	Percentage
Khat use	No	263	91.3
	Yes	25	8.7

Alcohol use	No	240	83.3
	Yes	48	16.7
Smoking	No	276	95.8
	Yes	10	3.5
	Missing value	2	0.7
Herbal medication use	No	282	97.9
	Yes	5	1.8
	Missing value	1	0.3
ART adherence	Excellent	14	4.9
	Good	246	85.4
	Poor	28	9.7
TB history	No	194	67.4
	Yes	90	31.3
Viral load	Detectable	27	9.4
	Undetectable	253	87.8
CD4 count	<200	22	7.6
	≥200	264	91.7
Nutritional status	Under nutrition	53	18.4
	Normal	183	63.5
	Excess nutrition	52	18.1
ART regimen	DTG-containing	234	81.2
	Non DTG-containing	54	18.8
HBV	Negative	95	33.0

	Positive	4	1.4
	Not done	188	65.3
HCV	Negative	55	19
	Positive	7	2.4
	Not done	226	78
Opportunistic infections	PCP	5	1.7
	Cryptococcus	6	2.1
	Toxoplasmosis	4	1.4
	CMV	4	1.4
HIV duration	<5 Years	84	29.2
	≥5 Years	159	55.2
ART duration	<3 Years	74	25.7
	≥3 Years	170	59

TABLE 3 ART regimen proportion of study participants, ARTH, Ethiopia (N = 288)

Regimen	**Drug combination**	**Frequency**	**Percentage**
1J	TDF + 3TC + DTG	228	79.2%
1F	TDF + 3TC + NVP	1	0.3%
2F	AZT + 3TC + ATV/r	15	5.2%
2H	TDF + 3TC + ATV/r	37	12.8%
3A	DRV/r + DTG + AZT + 3TC	3	1.0%
3B	DRV/r + DTG + TDF + 3TC	2	0.7%
1K	AZT + 3TC + DTG	1	0.3%

5.3. Prevalence of liver disease

From 288 participants included in the final analysis, 79 participants had liver disease. The prevalence of liver disease was 27.4% (95% CI: 0.222 – 0.326).

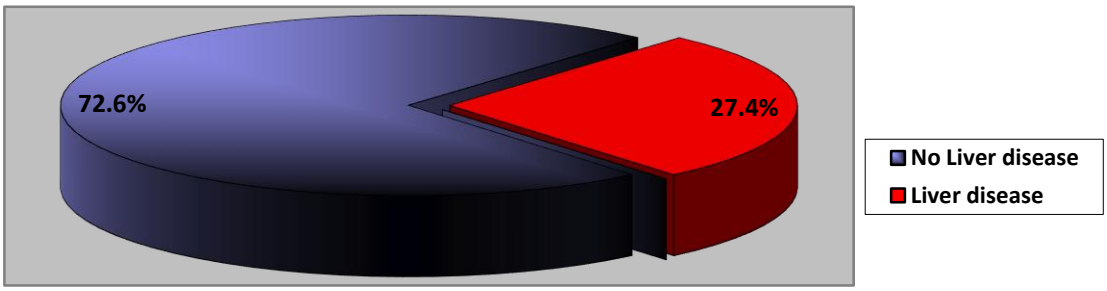

FIGURE 2 OVERALL MAGNITUDE OF LIVER DISEASE OF STUDY PARTICIPANTS, ARTH, ETHIOPIA (N = 288)

5.4. Factors associated with liver disease

A bivariate and multivariable logistic regression analysis was performed to identify factors associated with liver disease among HIV patients. In the multivariable analysis, sex, history of tuberculosis (TB), and nutritional status remained significantly associated with liver disease ($p<0.05$).

Males were nearly 2.7 times more likely to develop liver disease compared to females (AOR = 2.69; 95% CI: 1.34–5.43, p=0.005). Patients with a history of TB infection had a 3.9-fold increased risk of liver disease compared to those without (AOR = 3.94; 95% CI: 2.04–7.61, $p<0.001$). Additionally, under-nutrition was the strongest predictor identified, with under-nourished patients being approximately five times more likely to have liver disease than those with a normal nutritional status (AOR = 4.99; 95% CI: 2.37–10.51, $p<0.001$). While age, Khat

use, and viral load showed significant associations in the crude analysis, they did not maintain statistical significance after adjusting for potential confounders (p>0.05).**Table 4.**

TABLE 4 : BIVARIATE AND MULTIVARIABLE LOGISTIC REGRESSION OF FACTORS ASSOCIATED WITH LIVER DISEASE AMONG HIV PATIENTS AT ARTH, ASSELA, 2025(N = 288)

Variable	**Category**	**Liver disease**		**COR (95% CI)**	**P-value**	**AOR (95% CI)**	**P-value**
		No (%)	**Yes (%)**				
Sex	Female	142 (80.7)	34 (19.3)	1		1	
	Male	67 (59.8)	45 (40.2)	2.805	<0.001	2.698	**.005 ****
				(1.648 - 4.774)		(1.340 - 5.431)	
Age	≤50 years	148 (76.7)	45 (23.3)	1		1	
	>50 years	61 (64.2)	34 (35.8)	1.833	.027	1.450	.264
				(1.073 - 3.133)		(.756 - 2.780)	
Smoking history	No	203 (73.6)	73 (26.4)	1		1	
	Yes	5 (50.0)	5 (50.0)	2.780	.114	2.195	.455
				(.782 - 9.884)		(.280 - 17.236)	
TB history	No	160 (82.5)	34 (17.5)	1		1	
	Yes	46 (51.1)	44 (48.9)	4.500	<0.001	3.944	**<0.001*****
				(2.585 - 7.839)		(2.044-7.611)	
Khat use	No	197 (74.9)	5 (50.0)	1		1	
	Yes	12 (48.0)	13 (52.0)	3.230	.006	2.793	.087
				(1.406 - 7.435)		(.862 - 9.046)	
Alcohol use	No	179 (74.6)	61 (25.4)	1		1	
	Yes	30 (62.5)	18 (37.5)	1.760	.089	1.039	.931
				(.917 - 3.381)		(.438 - 2.483)	

Herbal medication use	No	206 (73.0)	76 (27.0)	1		1	
	Yes	2 (40.0)	3 (60.0)	4.066 (.666 - 24.805)	.128	1.041 (.087 - 12.924)	.975
Viral load	Non detectable	189 (74.7)	64 (25.3)	1		1	
	Detectable	13 (48.1)	14 (51.9)	3.180 (1.420 - 7.123)	.005	1.162 (.385 - 3.511)	.790
CD4 count	≥200	195 (73.9)	69 (26.1)	1		1	
	<200	12 (54.5)	10 (45.5)	2.355 (.974 - 5.695)	.057	1.374 (.424 - 4.454)	.596
Nutritional status	Normal	146 (79.8)	37 (20.2)	1		1	
	Under nutrition	25 (47.2)	28 (52.8)	4.260 (2.202 - 7.901)	<0.001	4.996 (2.373 - 10.518)	<0.001 ***
ART regimen	DTG containing	174 (74.7)	59 (25.3)	1		1	
	Non DTG containing	35 (63.6)	20 (36.4)	1.685 (.903 - 3.144)	.101	1.799 (.830 - 3.902)	.137

Note: * Significant at p<0.05; ** Significant at p<0.01; *** Significant at p≤0.001. Abbreviations: AOR, Adjusted Odds Ratio; ART, Antiretroviral Therapy; CI, Confidence Interval; COR, Crude Odds Ratio; DTG, Dolutegravir; TB, Tuberculosis.

6. DISCUSSION

The magnitude of liver disease in this study was 27.4%, which is notably high and aligns with the 2022 Ethiopian national meta-analysis that estimated hepatotoxicity at 25.45% (14). This finding confirms that despite the transition to safer, Dolutegravir (DTG)-based regimens, liver injury remains significant non-AIDS comorbidity among PLHIV in Ethiopia. This prevalence is higher than reports from Addis Ababa (22) likely due to the unique socio-demographic and nutritional challenges faced by patients in the Arsi Zone.

The Role of Nutritional Status – Under nutrition emerged as the strongest predictor of liver disease in this study (AOR=5.00). This is a critical finding. Malnutrition leads to hypoalbuminemia and depleted glutathione levels, which are essential for the liver to detoxify ART metabolites. In resource-limited settings like Asella, food insecurity may be exacerbating the hepatotoxic potential of even modern ART regimens (16,34).

Economic Context and Nutritional Vulnerability - The strong association between under nutrition and liver disease found in this study must be interpreted within the current socioeconomic landscape of Ethiopia. As of 2025/2026, the country has faced significant inflationary pressures, particularly in food prices, which the World Bank and WHO have identified as a major driver of "health-related poverty" (34).

For PLHIV at ARTH, the rising cost of a basic food basket means that even those in the "low-income" bracket (1,000–3,000 ETB) are likely facing severe food insecurity. This economic strain directly leads to the high rates of under nutrition observed in this cohort. From a clinical

perspective, under nutrition is not merely a lack of calories; it represents a state of micronutrient deficiency (such as zinc and selenium) and hypoalbuminemia. These deficiencies impair the liver's ability to metabolize ART and neutralize oxidative stress, thereby accelerating hepatic injury.

Tuberculosis Co-infection - Participants with a history of TB were nearly four times more likely to exhibit liver disease (AOR=3.94). This likely reflects the "double hit" theory: the liver suffers initial insult from hepatotoxic anti-TB drugs (like Isoniazid and Rifampicin) and subsequent stress from long-term ART (8). This suggests that the hepatic impact of TB treatment persists long after the TB itself is cured.

Gender Disparities - Male sex was significantly associated with higher odds of liver disease (AOR=2.69). This aligns with previous literature suggesting that men may have higher rates of metabolic dysfunction-associated steatotic liver disease (MASLD) and potentially higher (though often underreported) rates of alcohol consumption or late presentation to care compared to women (24)

Unexpected Non-Associations - Interestingly, age, viral load, and specific ART regimens were not significantly associated with liver injury in this cohort. This suggests that in the current treatment era, "host factors" (nutrition and co-morbidities) may be more influential in causing liver damage than the "viral factors" or the ART drugs themselves."

6.1. Conclusion

This study assessed the prevalence of liver disease and its associated factors among adults living with HIV receiving antiretroviral therapy. The findings demonstrated that liver disease remains a

common clinical problem in this population, with more than one-quarter of participants affected. This indicates that hepatic complications continue to pose a significant burden despite the widespread availability of ART.

Male sex was identified as an independent factor associated with liver disease. In addition, under nutrition and a history of tuberculosis were independently associated with increased odds of liver disease after controlling for potential confounders. These findings highlight the multifactorial nature of liver disease in people living with HIV and emphasize avoiding a narrow focus on antiretroviral therapy alone.

6.2. Recommendation

For ARTH ART Clinics

- Integrated Nutritional Support: Given that undernutrition was the strongest predictor of liver disease (AOR=5.00), the ART clinic should prioritize routine BMI screening and provide therapeutic nutritional supplementation for those below 18.5 kg/m².
- Targeted Screening for TB Patients: Patients with a current or past history of tuberculosis should undergo more frequent liver function monitoring (ALT/AST and Bilirubin) due to their significantly higher risk (AOR=3.94) of hepatic injury.
- Male-Friendly Health Services: Since men were 2.7 times more likely to have liver disease, the hospital should design outreach or "male-only" clinic hours to improve health-seeking behavior and early detection in this high-risk group.

For the Oromia Health Bureau and Federal Ministry of Health

- Review of Food Insecurity Programs: Policy-makers should link HIV care programs with social safety nets. Ensuring food security for PLHIV is not just a social issue but a clinical necessity to prevent non-AIDS comorbidities like liver disease.
- Standardized Liver Monitoring Guidelines: National HIV guidelines should be updated to include mandatory baseline and annual ultrasound or biochemical liver

For Future Researchers

- Longitudinal Studies: A prospective cohort study should be conducted to establish the temporal relationship between the start of DTG-based ART, nutritional recovery, and the progression of liver fibrosis.
- Genetic and Lifestyle Focus: Further research is needed to investigate why males are at higher risk—specifically looking at the interaction between traditional practices (like Khat use) and genetic predispositions in the Ethiopian population.

6.3. Strengths and Limitations

Strengths of the Study

- Clinical Relevance: This study addresses a critical gap in HIV care in the Arsi Zone, focusing on non-AIDS comorbidities (liver disease) during a transition period in ART regimens (DTG-based therapy).
- Rigorous Outcome Definition: Unlike studies that rely solely on ALT levels, this study used a comprehensive definition of liver disease, including biochemical markers (INR, Bilirubin, and Enzymes) and imaging (Ultrasound/CT), increasing the diagnostic accuracy.

- Timeliness: By incorporating the most recent 2025/2026 World Bank poverty benchmarks, the study provides a contemporary view of how the current economic climate in Ethiopia impacts the health of PLHIV.
- Multivariable Approach: The use of logistic regression allowed for the adjustment of confounders, isolating Undernutrition, Male Sex, and TB History as the true independent predictors.

Limitations of the Study

- Cross-sectional Design: Due to the nature of the study design, we cannot establish a definitive "cause-and-effect" relationship. For example, we cannot prove whether undernutrition caused liver disease or if advanced liver disease led to wasting (undernutrition).
- Recall Bias: Behavioral data, such as alcohol consumption (AUDIT-C) and ART adherence, were self-reported. Participants may have under-reported alcohol use or over-reported adherence due to social desirability bias.
- Income Measurement: In the context of the high inflation observed in Ethiopia in 2025/2026, self-reported monthly income may not perfectly reflect a household's true purchasing power or "real" food security status.
- Hepatitis Screening: Due to resource constraints, the study may not have captured all cases of viral hepatitis (HBV/HCV) if previous laboratory

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Annexes

Annex 1: Subject information sheet

INTRODUCTION: how are you?

My name is …….. I am here on behalf of Dr. Yohanes Zebenu, from AUARTH. He is conducting a research on "The Evolving Burden of Liver Disease in the ART Era: Magnitude and Determinants among HIV Sero-Positive Patients at Asella Referral and Teaching Hospital, Ethiopia" for the partial fulfillment of specialty program in Arsi University. He received permission from Arsi University. The aim of this study is to assess magnitude and associated factors for liver disease among HIV patients. The study will help in providing a base line data for policy makers and other researchers on issues. You are selected randomly to participate in this study because you are eligible for this study. Your participation is purely based on your willingness. You have full right either to participate or decline to be a participant in this study. If you choose to take part in the study you may respond to all the questions or you may not answer questions you don't want to, and have the right to stop the interview at any time. You also have the right to choose not to take part in this study. Participating in this study will not have any risk or harm. Whether you are willing to participate, refuse or decide to withdraw later, you will not be subjected to any ill treatment. If you agree to participate in the study, you will be asked to answer some questions about yourself, and the interview lasts with you will take about 20-30 minutes. We will also review your chart and results will be used in the research. Any information that you provide will be kept confidential, names will not be written or specified and all the questionnaires will be coded for anonymity. No one will have access to the non-coded data except the principal investigator. Only the principal investigator will know the details and He will discard it after completing analysis. The data will not be used for purposes other than the study. Your willingness and active participation is very important for the success of this study.

Annex II: Informed consent

The above information regarding my participation in the study is clear to me. I have been given a chance to ask questions and my questions have been answered to my satisfaction. My participation in this study is entirely voluntary. I understand that my records will be kept private and that I can leave the study at any time.

Respondent agree to participate?

Yes **No**

1. If yes, continue the interview

2. If no, skip to the next participant by writing reasons for his refusal. _____

Informed consent Certified by:

Respondent's signature/thumb print_____ Date _____

Interviewer: Name _____ Signature _____

Questionnaire ID number _____

Date of interview _____ Time started _____ Time completed_____

Result of interview:

1. Completed 2.Partially completed 3.Refused 4.Other (specify)

Checked by: Supervisor: Name _____ Signature_____

Annex III: Questionnaire

TABLE 5 Table showing questionnaire to determine the evolving burden of liver disease in the ART era: magnitude and determinants among HIV sero-positive patients at ARTH, Ethiopia, 2025

Section	Sn.	Variable	Question/Item	Response option
1. Demographic factors	1	Age	How old are you?	___Years
	2	Sex	Sex?	Male / Female
	3	Residence	Where do you live?	Urban / Rural
	4	Occupation	What is your Occupation?	A. Self-employed B. Govt C. Other
	5	Income	What is your approximate monthly income?	
	6	Marital status	What is your marital status?	Single / Married / Divorced/ Widowed
	7	Educational status	What is your educational status?	No formal education / Grade 1-8 / Grade 9-12, college / Other __
2. Clinical factors	8	Liver disease	Have you been diagnosed with liver disease?	Yes / No
	9	Duration of HIV	When were you diagnosed with HIV?	
	10	CD4 level	What is your most recent CD4 count?	
	11	Viral load	What is your most	

			recent Viral load?	
	12	ART regime	What ART regime are you currently taking?	Regime
	13	ART duration	How long have you been on ART?	
	14	Opportunistic infections	Have you ever had TB?	Yes / No
3. Behavioral factors	15	Alcohol use	Do you drink alcohol?	Yes / No
			If yes, how often do you drink alcohol?	Occasionally, Weekly, Daily
			If yes, which beverage do you often drink? Amount?	_____ Name of the drink _____ ounce / bottle
	16	Smoking	Do you smoke?	Yes / No
			If yes, the amount in pack year	_ Pack year
	17	ART adherence	How often do you miss ART doses?	Excellent <5% Good 5-20% Poor >20%
	18	Khat use	Do you use khat?	Yes / No
			If yes, how often do you use khat?	Occasionally, Weekly, Daily
	19	Traditional medicines	Do you take herbal or traditional medicines?	Yes / No

4. Environmental factors	20	Healthcare access	How far is nearest ART clinic?	
	21	Food security	How secure is your household food supply?	_____ meals / day
	22	HBV vaccination	Are you vaccinated against HBV?	Fully vaccinated, Partially vaccinated, Unvaccinated

TABLE 6.Table showing questionnaire for laboratory results and history and physical examination findings to determine the evolving burden of liver disease in the ART era: magnitude and determinants among HIV sero-positive patients at ARTH, Ethiopia, 2025 (from chart)

Sn.	Laboratory parameter	Result	
1	LFT	LFT 1	LFT 2
		ALT_____IU/L AST____IU/L ALP_____IU/L BIL D_____ BIL T_____ Albumin_____ PT/INR_____	ALT_____IU/L AST____IU/L ALP_____IU/L BIL D_____ BIL T_____ Albumin_____ PT/INR_____
2	CD4 count (most recent)		
3	Viral load	Detectable / Undetectable	
4	Abdominal ultrasound	Impression	

5	HBV	+ / =, Not done
6	HBC	+ / =, Not done
Sn	History and physical examination	Result
1	Opportunistic infections documented on chart	TB PCP Cryptococcus Toxoplasmosis CMV infection
2	Nutritional status	BMI….. kg/m^2 MUAC …..cm

Annex IV: Declaration of Investigator

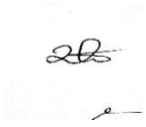
I, the undersigned Internal Medicine Resident, declare that this thesis entitled "The evolving burden of liver disease in the ART era: magnitude and determinants among HIV sero-positive patients at ARTH, Ethiopia, 2026" submitted in partial fulfilment of the requirement for the specialty degree in internal medicine to Arsi university, is my original work. I also declare that a complete list of references is provided indicating all sources of information quoted or cited.

Name of investigator: Dr Yohanes Zebenu (MD)

Signature: _____ Date_____

Declaration of Advisors

We, the undersigned advisors, declare that this research thesis is our original work in partial fulfilment of the requirement for speciality certificate in internal medicine for DR Yohanes Zebenu in our best knowledge. We confirmed that this thesis is ready for submission with our approval as the university advisor(s).

NAME OF MEDICAL ADVISOR	SIGNATURE	DATE
• **Dr. Tamiru Adugna (MD, Asst prof.)**		**27/01/2026**

NAME OF PUBLIC HEALTH ADVISOR	SIGNATURE	DATE
• **Dr. Ayalneh Demissie (PHD)**		**27/01/26**

NAME OF DEPARTMENT HEAD	SIGNATURE	DATE
•	_____	_____