Seroprevalence of Hepatitis B Virus and Associated Factors among Human Immunodeficiency Virus Positive Adults Attending Antiretroviral Therapy at Bale Robe Hospital, Southeastern Ethiopia

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Abstract

Background: Hepatitis B virus is a major cause of morbidity and mortality among people living with the Human immunodeficiency virus (HIV), globally. However, there was a lack of data in the current study area. Therefore, this study aimed to determine the seroprevalence and associated factors of hepatitis B virus among Human immunodeficiency virus-positive adults attending antiretroviral therapy at Bale Robe Hospital, southeastern Ethiopia.

Methods: A hospital-based cross-sectional study was conducted among 300 HIV-positive adults between February 1 and 30, 2018. Data was collected by a face-to-face interview using a pretested structured questionnaire. A checklist was used to collect information from the patient's clinical records. A venous blood sample was collected and tested for Hepatitis B surface antigen using an Enzyme-Linked Immunosorbent Assay. Data was analyzed using Statistical Package for the Social Sciences version 22. A p-value <0.05 was considered to be statistically significant.

Results: The seroprevalence of hepatitis B was 9.7% (95% CI: 6.8, 13.5). Tattooing (AOR=4.34, 95% CI: 1.21 ,15.58), HIV viral load greater than 1000 copies/mL (AOR=5.53, 95% CI: 2.34, 13.1), and WHO clinical stages 3 and 4 (AOR=3.40, 95% CI: 1.38, 8.33) were factors associated with hepatitis B virus infection.

Conclusions: Infection with the hepatitis B virus was high in patients with HIV in the study area. Tattooing, unsuppressed viral load, and advanced WHO clinical stages were found to be independent predictors. Therefore, promotion of awareness about the role of tattooing in hepatitis B virus transmission, regular monitoring of viral load, and improving adherence support are all recommended for people with HIV.

***Keywords*:** *Hepatitis B virus, antiretroviral therapy, HIV, Bale Robe, Southeastern Ethiopia*

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Introduction

Hepatitis B virus (HBV) is a leading cause of chronic liver disease and death worldwide. In 2015, approximately 360 million individuals were chronically infected, and 1.34 million died globally (Chan, 2018, Stanaway *et al*., 2016). In Ethiopia, the average seroprevalence of HBV was 10.8 %(Shiferaw *et al*., 2016). Chronic hepatitis B (CHB) is associated with cirrhosis and hepatocellular carcinoma (HCC). It is common among patients suffering from congenital, acquired immunodeficiency and following immunosuppressive therapy (Askari *et al*., 2014; Kew, 2012). The hepatotoxicity of antiretroviral therapy in human immunodeficiency virus (HIV) infected patients might also worsen the problem in the liver (Hoffmann *et al.,* 2012). This condition is common in middle income countries where the highest number of HIV-HBV co-infections were reported (Milazzo and Antinori, 2014; Clumeck *et al*., 2008).HIV and HBV share similar transmission ways, resulting in a high magnitude of co-infection (Gatanaga *et al*., 2000; Thio *et al*., 2002). Around 10% of people with HIV are also co-infected with hepatitis B worldwide (Platt *et al*., 2020). In Sub-Saharan Africa, it is estimated that 10-15% of HIV-positive patients are also infected with HBV (Matthews *et al*., 2014; Stabinski *et al*., 2015). Nonetheless, Ethiopia appears to be less affected than other countries in Sub-Saharan Africa, with evidence indicating that 5.2% of HIV-positive individuals in Ethiopia also had HBV co-infection" (Belyhun *et al*., 2016).

The rate of progression and complications of viral hepatitis is accelerated in patients with HIV co-infection (Kew, 2012). Evidence suggests that HIV-positive people who contract HBV are six times more likely than HIV-negative people to develop chronic hepatitis

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B infection (Shiferaw *et al*., 2016). Liver-related mortality among HIV-infected men with chronic hepatitis B was 13.4 per 1000 person-years among individuals with acquired immunodeficiency syndrome (Stabinski *et al* 2015; Maponga *et al*., 2017).

The seroprevalence and factors associated with HBV and HIV co-infection vary from region to region (Askari *et al*., 2014; Kew, 2012; Puglia *et al*., 2016; Goa *et al*., 2019, Belayneh, 2015). Some of the studies reported multiple sexual exposures, a low immune CD4 count, and WHO clinical staging of 3 and 4 as the commonest factors (Chen *et al*., 2016; Yared *et al*., 2015)

In Southeastern Ethiopia, there is limited evidence regarding HBV and HIV co-infection. Therefore, this study determined the seroprevalence and associated factors of hepatitis B virus among HIV-positive adults attending antiretroviral therapy (ART) at Bale Robe Hospital, southeastern Ethiopia.

Materials and Methods

Study Setting, Design, and Period

A cross-sectional study was conducted among HIV-positive adults on ART at Bale Robe Hospital, southwestern Ethiopia from February 1–30, 2018. The hospital is found in Robe town, Bale Zone of the Oromia Region, which is located about 430 kilometers southeast of Addis Ababa, the capital city of Ethiopia. The hospital provides healthcare services for more than 600,000 people in the catchment area. It started providing ART services in 2008. During the study period, about 915 HIV-positive adult clients were attending ART clinics (Hospital Database, 2017).

Population, Inclusion/ Exclusion Criteria

All HIV-positive patients who visited Bale Robe Hospital for ART were the source population. Those who were mentally handicapped or significantly ill during the data collection period and had difficulty responding to questions were excluded.

Sample Size and Sampling Technique

The sample size was calculated by using Epi info version 7 software by considering the prevalence of HBV among HIV-positive individuals among the exposed (previous surgery=11%) and unexposed (no previous surgery-=2%) (Desalegn *et al*., 2016), the 95% confidence level, the power of 80%, and non-response rate (10%). The final sample size was 304. HIV-positive individuals who came to Bale Robe Hospital for ART during the study period were included until the sample size was fulfilled.

Data Collection Techniques

Data were collected by the following method;

Face-to-face interview: were conducted by three bachelor's degree nurses using a pretested questionnaire to gather information on socio-demographic data and other associated factors. The questionnaire contains socio-demographic information such as age, marital status, sex, residence, occupational status, educational status, monthly income, clinical, cultural, and behavioral factors such as multiple sexual partners, sexually transmitted infection (STI), history of abortion, ear piercing, nose piercing, tattooing on the body, alcohol drinking, hepatitis B vaccine, surgical procedure, cesarean section, dental extraction and history of hospital admission. A checklist was also used to collect information on the WHO clinical stage, opportunistic infections, CD4 findings, and HIV viral load from each study participant's clinical record (Govender *et al.,* 2014; WHO,2007)

Sample Collection and Laboratory Examination: About 3ml of venous blood was aseptically collected by trained laboratory professionals using a vacutainer needle connected to Ethylenediaminetetraacetic acid (EDTA) test tubes. The blood sample was centrifuged to separate plasma. Then, the plasma samples were transported using a cold box to the Goba Blood Bank laboratory and stored at -20°C until analyzed in the laboratory. The hepatitis B surface antigen (HBsAg) Enzyme-Linked Immunosorbent Assay (ELISA) Test Kit (WANTAI, Beijing Biological Pharmacy Enterprises Co.Ltd, China) was used to detect the presence of HBV surface antigen. The results of the test were reported as reactive and non-reactive following the manufacturer's instructions.

Data Quality Control

The English-language questionnaire was translated into Afan Oromo by a qualified translator fluent in the native tongue. The questions were then translated back into English to ensure consistency with the original format. The questionnaire was pretested on 5% of adults living with HIV at Gasera Health Center. Two days of training were given to the data collectors. The

completeness of the questionnaire and laboratory test results were checked daily. Sample collection, storage, transport, and testing processes were according to standard operating procedures (Chen *et al*., 2016). The ELISA test was done by trained and experienced laboratory personnel. Known positive and negative controls were used during running test samples to ensure the quality of the assay.

Data Processing and Analysis

Data were entered into Epi data version 3.1 and exported to SPSS 22 version software for further analysis. Descriptive statistics like frequency, mean, standard deviation, percentage, and range were performed to describe the data. The seroprevalence of HBsAg was determined as the proportion of reactive HBsAg to the total individuals tested. Bivariate and multivariable logistic regression was performed to identify factors associated with HBsAg. Variables with p-value <0.25 in bivariate analysis were a candidates for multivariable logistic regression. Variables with p values < 0.05 at a 95% confidence interval in multivariable analysis were considered as factors associated with HBV infection.

Ethical Consideration

Ethical clearance was obtained from the institutional Health Research Ethics Review Committee (IHRERC), College of Health and Medical Sciences of Haramaya University with Ref no(C/AC/R/D/01/895/18). Informed, voluntary, written, and signed consent was obtained from each study participant. Only the code number of patients was used to secure the confidentiality of information. Those study participants who received positive test results were sent to healthcare providers at the ART services for additional counseling, treatment options, and follow-up.

Results

Socio-Demographic Characteristics of Participants

A total of 300 study participants were included in this study, with a 98.7% response rate. Nearly two-thirds (71.7%) of the participants were female. The mean age of the participants was 36.7 (SD±11) years, with a range of (19-71) years. About 46.7%, 68.8%, 73.3%, and 39.8% of participants were married, attended elementary or secondary school, urban dwellers, and housewives, respectively. Over 86% of the participants earned less than $35(1,915 ETB) per month (Table 1).

Table 1:-Sociodemographic characteristics of HIV-positive patients attending at ART clinic at Bale Robe Hospital, Southeast Ethiopia, 2018. (n=300)

Variables	Category	Number (N %)
Sex	Female	215(71.7)
	Male	85(28.3)
Age (Years)	≤24	33(11)
	25-34	99(33)
	35-44	102(34)
	45-54	55(18.3)
	55-64	4(1.3)
	≥65	7(2.3)
Marital status	Single	27(9)
	Married	140(46.7)
	Divorced	73(24.3)
	Widowed	60(20)
Residence	Rural	80(26.7)
	Urban	220(73.3)
Occupation status (n=269)	Government employee	20(7.4)
	Self-employed	81(30.1)
	Student	4(1.5)
	Housewife	107(39.8)
	Farmer	57(21.2)
Educational status	Cannot read and write	79(26.3)
	Read and write	18((6)
	Elementary school (1-8grade)	107(35.7)
	Secondary school (9-12 grade)	78(26)
	University or college	18(6)
Estimated monthly income in (USD)	<35	260(86.7)
	≥35	40(13.3)

Clinical, cultural, and behavioral factors

One hundred fifty-two (50.7%) of the study participants had practiced ear piercing, 169 (56.3%) had a history of dental extraction, 207 (69%) of them had HIV viral load < 1000copies/mL, 208 (69.3%) of them had CD4 count <500 cells/mm3 and 210(74.2%) of them were on 1E (TDF/3TC/EFV) ART regimen (Table 2).

Table 2: Clinical, cultural, and behavioral factors of HBV among HIV-positive patients attending at ART clinic at Bale Robe Hospital, Southeast Ethiopia, 2018. (n=300)

Variables		Frequency (%)
Multiple sexual Partner	Yes	58(19.3)
	No	242(80.7)
Sexually transmitted infection (STI)	Yes	6(2.0)
	No	294(98)
History of abortion(n=215)	Yes	46(21.4)
	No	169(78.6)
Ear piercing	Yes	152(50.7)
	No	148(49.3)
Nose piercing	Yes	25(8.3)
	No	275(91.7)
Tattooing on the body	Yes	23(7.7)
	No	277(92.3)
Alcohol drinking	Yes	21(7.0)
	No	279(93)
Hepatitis B vaccine	Yes	4(1.3)
	No	296(98.7)
Surgical procedure	Yes	10(3.3)
	No	290(96.7)
Caesarean section(n=215)	Yes	6(2.8)
	No	209(97.2)
Dental extraction	Yes	169(56.3)
	No	131(43.7)
History of hospital admission	Yes	61(20.3)
	No	239(79.7)
HIV Viral load (copies/ml)	>1000	93(31)
	≤1000	207(69)
CD4(cell/mm^3)	0-200	105(35)
	200-500	103(34.3)
	≥500	92(30.7)
Presence of opportunistic infection (n=115)	Yes	53(31.6)
	No	115(68.5)
WHO stage (n=288)	3 and 4	47(16.3)
	1 and 2	241(83.7)
ART regimen (n=283)	1C	37(13.1)
	1E	210(74.2)
	1F	32(11.3)
	Pre ART	4(1.4)

1C:AZT/3TC/NVP,1D:AZT/3TC/EFV,1E:TDF/3TC/EFV,1F:TDF/3TC/NVP,2E:AZT/3TC/L V/r,2H:TDF/3TC/ATV/r(AZT: Zidovudine, 3TC: Lamivudine, NVP: Nevirapine, EFV: Efaverenze, TDF: Tenofovir, LPV/r;Lopinavir), ART: Antiretroviral therapy, HIV: human immunodeficiency virus, WHO: World Health Organization, mm3: cubic millimeter, CD:Cluster of Differentiation

Seroprevalence of Hepatitis B Virus Infection

The seroprevalence of HBsAg among adults with HIV was 9.7% (29/300) (95% CI= 6.8, 13.5). Hepatitis B Virus seropositivity was higher in the age group of >40 years (11.4%), urban dwellers (10.9%), high school and above educational status (16.6%), and widowed (16.6%). Higher HBV seropositivity was found among study participants with nose piercing (36%), tattooing on the body (26%), abortion history (17.4%), viral load of >1000copies/ml (21.5%), CD4 count between 200-500 cell/mm3(10.7%), WHO clinical stage 3 and 4 (23.4%), and presence of opportunistic infection (21%)(Table 3).

Factors associated with Hepatitis B Virus Infection

In the bivariate analysis, variables such as sex, residents, marital status, multiple sexual partners, nose piercing, tattooing on the body, history of abortion,

history of dental extraction, history of hospital admission, plasma HIV viral load, WHO clinical stage, and presence of opportunistic infection were candidate variables for multivariate analysis (Table 3).

In multivariate analysis, those who were HIV positive had tattoos on their bodies, had a plasma HIV viral load >1,000 copies/mL, and met WHO clinical stages 3 and 4 were identified as factors associated with HBV infection. The odds of being HBsAg positive were higher among those study participants with tattoos than without tattoos (AOR = 4.34; 95% CI: 1.21, 15.58). Likewise, HIV positives whose plasma HIV viral load ≥1,000 copies/mL were more than 5 times more likely to be HBsAg positive compared to those who had <1,000 copies/mL (AOR = 5.53; 95% CI: 2.34,13.1). HIV-positive patients in WHO clinical stages 3 and 4 were more than 3 times more likely to be HBsAg positive compared to WHO clinical stages 1 and 2 (AOR = 3.40, 95% CI, 1.38,8.33) (Table 3).

Table 3: Factors associated with HBV infection among HIV-positive patients attending at ART clinic at Bale Robe Hospital, Southeast Ethiopia, 2018 (n=300)

Variables		HBV Serostatus		COR (95% CI)	p-value	AOR (95% CI)
		Negative (n=271) N (%)	Positive (n=29) N (%)			
Age (Year)	≤29	72(90)	8(10)	1		
	30-39	98(92.5)	8(7.5)	0.74 (0.26,2.05)	0.56	
	≥40	101(88.6)	13(11.4)	1.16 (0.46,2.94)	0.76	
Sex	Female	197(91.6)	18(8.4)	1		1
	Male	74(87)	11(13)	0.61 (0.28,1.36)	0.23	1.87(0.76,4.64)
Residence	Urban	196(89.1)	24(10.9)	1		1
	Rural	75(93.7)	5(6.3)	0.54(0.20,1.48)	0.23	1.50(0.479,4.74)
Education status	Cannot read and write	87(89.7)	10(10.3)	0.58(0.2,1.6)	0.29	
	Elementary school	104(97.2)	3(2.8)	0.3(0.54,3.2)	0.56	
	High school and above	80(83.4)	16(16.6)	1		
Marital status	Married	131(93.6)	9(6.4)	2.91 (1.12,7.58)	0.029*	3.7(0.86,16.11)
	Widowed	50(83.4)	10(16.6)	1.62 (.63 ,4.14)	0.316	2.4 (0.54,10.6)
	Single	90(90)		1		1
Multiple sexual partners	Yes	50(86.2)	8(13.8)	2.36(0.82, 6.79)	0.11	1.90(0.61,5.96)
	No	221(91.3)	21(8.7)	1		1
Ear piercing	Yes	136(89.5)	16(10.5)	1.22 (0.57-,2.64)	0.610	
	No	135(91.5)	13(8.5)	1		
Nose piercing	Yes	16(64)	9(36)	7.17(2.82 ,18.27)	< 0.001	6.66(0.6-20.09)
	No	255(89.5)	20(10.5)	1		1
Tattooing on the body	Yes	17(74)	6(26)	3.9 (1.4, 10.85)	0.01	4.34(1.21 ,15.58)*
	No	254(91.7)	23(8.3)	1		1
History of Abortion	Yes	38(82.6)	8(17.4)	1.89 (0.76,4.73)	0.17	1.96(0.70,5.48)
	No	159(94.1)	10(5.9)	1		1
Dental extraction	Yes	149 (88)	20 (12)	1.82 (0.80, 4.14)	0.15	1.81(0.66 ,4.9)
	No	122(93.1)	9(6.9)	1		1
History of hospital admission	Yes	52 (85.2)	9(14.8)	1.89 (0.82,4.40)	0.14	2.21(0.69 ,7.05)
	No	219 (91.6)	20(8.4)	1		1
Viral load(copies/ml)	≥1000	73(78.5)	20(21.5)	6.03 (2 .62,13.84)	<0.001	5.53 (2.34,13.1)*
	<1000	198(95.6)	9(4.4)	1		1
CD4 count(cells/mm^3)	≤ 200	96(91.4)	9(8.6)	0.86(0.33,2.28)	0.779	
	200-500	92(89.3)	11(10.7)	1.10(0.43,2.79)	0.84	
	≥500	83(90.2)	9(9.8)	1		
WHO clinical stage	3 and 4	36 (76.6)	11(23.4)	3.78(1.65 ,8.67)	0.002	3.34(1.38,8.3)*
	1and 2	223(92.5)	18(7.5)	1		1
Presence of Opportunistic infection	Yes	42 (79.2)	11(20.8)	2.25(0.92 , 5.49)	0.08	2.24(0.78,6.5)
	No	103(89.6)	12(10.4)	1		1

AOR: Adjusted odd ratio, CI: crud odd ratio

Discussion

In this study, the seroprevalence of HBV among HIV-infected patients on ART was 9.7%. Having a tattoo, having an unsuppressed viral load, and being in an advanced clinical stage were factors associated with HBV.

In this study, the seroprevalence of HBV among HIV-infected patients was 9.7%. This indicates HBV is highly endemic in the study area according to WHO classification (≥8% of the population are HBsAg positive) (WHO, 2011). These findings are similar to the study conducted in Hawassa University Referral Hospital, Ethiopia (6.9%) (Belayneh *et al.,* 2015), Germany (9.5%) (Askari *et al*., 2014), and Asia-pacific region (10.4%) (Chen *et al*., 2016). However, the current finding was higher than previous studies conducted in different parts of Ethiopia; north Showa (3.9%) (Yared *et al*., 2015), Mekele (5.9%) (Weldemhret *et al*., 2016) and Addis Ababa (3.9% and 3%) (Shimelis *et al*., 2008; Manyazewal *et al*., 2014), and out of Ethiopia like South Africa (4.2%) (Hoffmann *et al*., 2012), Kenya (6%) (Muriuki *et al*., 2013), Brazil (3.8%) (Zago *et al*., 2007) and Japan (6%) (Yang *et al*., 2014). On the other hand, this study's finding is lower than the study conducted in Cameroon, Yaoundé (16%) (Djuidje *et al*., 2017), and Delta Nigeria (16.4%) (Avwioro *et al*.,2014).The difference in seroprevalence might be due to differences in geographical distribution, study design, method of laboratory analysis, associated factors, treatment options, or prophylaxis and vaccination (Liang *et al*., 2009).

In this study, participants who have had tattooing on any part of their body were more likely to be infected with HBV. This finding was consistent with previous studies from Addis Ababa, Ethiopia (Desalegn et al., 2016, Koli *et al*., 2016) and other rural parts of Africa (Kew, 2012). Tattooing with the unsterile instrument was practiced in rural Africa (Kang'ethe *et al*., 2017) which can increase the transmission of HBV in the community.

Human immunodeficiency virus results in the progressive deterioration of the immune system, which can increase viral replication (Okoye and Picker, 2013). HBV also affects immunity to infection and more rapid progression to liver fibrosis and hepatocellular carcinoma in HIV-positive patients (Askari *et al*., 2014; Milazzo and Antinori, 2014). In this study, HIV-positive individuals with unsuppressed viral load (≥1,000 copies/mL) were three times more likely to be infected with HBV. This is similar to studies conducted in China (Chen *et al*., 2016; Liu *et al*., 2018; Yang *et al*., 2014)

Hepatitis B infection can be contracted at an early stage of HIV infection, which may become dormant initially and become active at a later stage. This is due to the immunosuppression caused by the advanced stage of HIV/AIDS (Soriano *et al*., 2010). Participants with advanced clinical stages were more likely to be infected with HBV in this study, and similar findings have been reported in previous studies. (Shiferaw *et al*., 2016; Sarawavanan *et al*., 2007). Participants with advanced clinical stages were more likely to be infected with HBV in this study, and similar findings have been reported in previous studies. Unsuppressed HIV viral load, practicing tattooing on body parts, and advanced WHO clinical stage are factors independently associated with HBV infection. Thus, strengthening viral load measurement and ART adherence support is required to prevent HIV virologic failure and HBV co-infection Designing interventions, particularly for HIV patients, to aware them the role of tattooing in hepatitis B virus transmission, regular monitoring of viral load, and improving adherence support are all recommended. In addition, this study recommends further studies to be conducted in different parts of the country with a larger sample size and more HBV biomarkers to understand further the epidemiology of HBV infection.

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Competing Interests

The authors declare that they have no competing interests.

Funding Statement

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Authors' Contributions

H.D conceived the study, designed the study, performed data collection, and analysis. F.A., Z.T drafted the manuscript. D.A.A, Z.T, J.M, and F.A critically revised the design of the study, supported the analyses, interpretation of the findings, and revised the manuscript. All authors contributed significantly to the work reported, and gave final approval of the version to be published.

List of Abbreviations

AIDS; Acquired Immune Deficiency Syndrome, AOR; Adjusted Odd Ratio, ART; Anti-Retroviral Therapy, CD4; Cluster of Differentiation; CI Confidence Interval, COV; cut-off value, DNA; Deoxynucleic Acid, EDTA; Ethylene, Diamine Tetra acetic Acid, EIA; Enzyme Immuno Assay, ELISA; Enzyme-Linked ImmunoSorbent Assay, HAART; Highly Active Anti-Retro Viral Therapy, HBsAg, Hepatitis B Surface Antigen, HBV; Hepatitis B Virus, HIV; Human Immunodeficiency Virus, STI; Sexually Transmitted Infection, WHO; World Health Organization.

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