

The Ethiopian Public Health Institute



Epidemiology of Viral Hepatitis (B and C) among HIV Infected People in Ethiopia: a Systematic Review

Technical Report

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Abbreviations

AIDS: acquired immunodeficiency syndrome

ANC: Antenatal care

ART: antiretroviral therapy

CHB: chronic hepatitis B infection

DAA: directly acting antiviral therapy

DNA: deoxyribonucleic acid

HBsAg: Hepatitis B surface antigen

HBV: Hepatitis B virus

HCC: Hepatocellular carcinoma

HCV: Hepatitis C Virus

HIV: human immunodeficiency virus

MeSH: Medical subject heading

PLHIV: people living with HIV

PRISMA: preferred reporting items for systematic reviews and meta-analyses

RCT: randomized controlled trial

RNA: Ribonucleic acid

WHO: World Health Organization

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Summary

Background: People living with HIV (PLHIV) are at higher risk of acquiring viral hepatitis (hepatitis B & C virus) owing to shared transmission routes and risk factors. Since HIV decreases the spontaneous clearance rate of acute hepatitis infections, PLHIV are at increased risk of hepatitis related end-stage liver disease. In Ethiopia, there is a paucity of epidemiological data on hepatitis B and C infection among HIV infected patients.

Objectives: This systematic review aimed to assess and synthesize all available data published on the prevalence of hepatitis B and C infection among HIV infected population in Ethiopia. The review also sought to assess risk factors associated with HBV and/ or HCV infections in HIV infected patients.

Methods: Primary studies reporting prevalence of HBV and/or HCV infection among HIV patients in Ethiopia were retrieved through searches conducted in PubMed, Medline, Science Direct, and Google scholar databases. Online searches were conducted in May 2020. Further, searches were conducted through reference screening of retrieved papers.

Results: Out of 116 retrieved records through electronic search, 16 studies conducted across different geographic regions (North, Northwest, southern, central and eastern) of Ethiopia were included in this review. These studies included a total of 6545 HIV infected population. The reported HBV prevalence ranged from 2.0 to 11.7 %. In this review, the estimated prevalence of HBV was determined as 6.5%. On the other hand, the prevalence of HCV was ranged from 3.1%-10.5% and the estimated prevalence rate among the study population was 4.9%. While risk factors for HCV infection in these studies remain elusive, having multiple sexual partner, CD4 count <200 cells, family history of HBV, and genital discharges were significantly associated with HBV co-infection.

Conclusions: the findings of this review demonstrate a high prevalence of HBV and HCV infection among HIV infected people in Ethiopia. Thus, there is a strong need to scale up hepatitis preventive interventions, and control efforts across HIV services.

Keywords: HIV, Hepatitis B virus, Hepatitis C virus, Co-infection, Prevalence, Ethiopia

1. Background

Viral hepatitis B and C are global public health challenges that posed a heavy toll on lives people which is comparable to HIV, tuberculosis and malaria. Annually, an estimated 1.4 million people die from acute infection and hepatitis-related liver cancer and cirrhosis. Of those deaths, approximately 47% are attributable to hepatitis B virus (HBV), 48% to hepatitis C virus (HCV) and the remainder to hepatitis A virus and hepatitis E virus [1, 2]. An estimated 2 billion persons worldwide have been infected with HBV, and more than 350 million persons have chronic infections. Furthermore, about 130–150 million people are chronically infected with HCV [1-5]. Despite the significant burden it places on communities across the globe, hepatitis has been largely ignored as a health and development priority until recently [1, 2]. Viral hepatitis B and C are blood-borne infections, with significant transmission occurring in early life and through unsafe injections and medical procedures, and less commonly through sexual contact.

Hepatitis B virus and HCV infections are more common in people living with HIV (PLWHIV) than in the general population owing to shared route of transmission and risk factors for viral acquisition [6-12]. Of 37.9 million HIV-infected people, approximately 4 million have chronic hepatitis B infection and 2.3 million have HCV co-infection in 2016 [2, 11]. HIV increases the transmission efficiency of HCV and decreases spontaneous clearance of HBV as well as HCV infections [13-15]. HIV infection results in an accelerated course of chronic hepatitis and rapid progression of liver disease to terminal stages of cirrhosis and hepatocellular carcinoma (HCC). Furthermore, co-infection with these viruses was indicted to associate with increased cardiovascular morbidity, renal dysfunction and various types of cancer other than HCC [1-6]. The estimated liver-related mortality rate in HBV/HIV co-infected patients was 14.2 per 1000 persons-years, while the rate in HBV or HIV mono-infected ones were only 0.8 and 1.7 per 1000 persons-years respectively [11]. The basis for such outcomes could be related to the poor immune response due to HIV infection,

facilitation of HBV/HCV replication, and hepatic fibrogenesis [16-18]. Furthermore, viral hepatitis B and C co-infection associated with an increased risk of antiretroviral-related hepatotoxicity, drug-induced liver injury, and poor treatment outcomes.

The burden of HBV and HCV is particularly high in low and middle-income countries, such as Sub-Saharan Africa, Southeast Asia, and the Middle East [1–3]. However, most people infected with these viruses remain unaware of their status [1-8] and are at an increased risk of liver-related morbidity and mortality. The recent advent of directly acting antiviral (DAA) therapy for hepatitis C with >95% cure rate even in HIV/HCV co-infected individuals has significantly reduced HCV-related morbidity and mortality in many Western Countries [19]. Similarly, treatment of chronic hepatitis B is highly effective and leads to viral suppression in 90% of cases [20]. However, since onset of disease and initial development of liver damage are often asymptomatic [21-23], HBV and HCV infection may go undetected for many years [23]. Recent estimates indicate that the majority of the chronically infected population remains undiagnosed [24, 25].

The introduction of combined antiretroviral treatment (cART) has dramatically improved mortality from opportunistic diseases and AIDS in HIV positive patients. Thus, morbidity and mortality from viral hepatitis co-infection has gained increased importance, and liver-related mortality remains a critical problem in co-infected patients. The existence of effective treatment options for HBV and HCV infection, and effective vaccination against HBV prompt World Health Organization (WHO) to step up their responses to these diseases. In 2016, the WHO adopted a global hepatitis strategy with the goal of eliminating viral hepatitis as a public health threat by 2030. The targets to be achieved by 2030 are a 90% reduction in new cases of chronic HBV and HCV, and a 65% reduction in mortality due to these infection, both of which rely on 80% of treatment-eligible individuals with chronic HBV and HCV infections being treated globally [26]. This necessitates scale-up of testing programme to fast track elimination efforts, particularly among the most

affected populations like PLHIV [26]. Recent estimates show that without an accelerated response, the number of people living with hepatitis virus is projected to remain at the current high levels for the next 40–50 years, with a cumulative 20 million deaths occurring between 2015 and 2030 [27].

Ethiopia is an endemic country for HIV and it is likely that there is a high burden of viral hepatitis infection among these patients owing to shared risk factors and transmission modes [28-32]. However, HBV and HCV infections are not routinely screened in HIV patients and the level of morbidity and mortality from these infections is unclear. Understanding the burden of HBV and HCV infection in the HIV-infected population could substantially contribute to effective management of both infections and to reduce subsequent morbidity and mortality related to these infections. In particular, identifying the risk factors for HBV and HCV infection in HIV infected persons can provide an insight to foster the development of targeted intervention strategies. Therefore, the aim of this systematic review was to assess and synthesize all available data published on the prevalence of hepatitis B and C infection in Ethiopia among HIV infected population. This would help to provide reliable data on prevalence estimates of HBV and HCV infection in PLHIV to inform the development of effective local strategies that target this population groups.

2. Methods

2.1. Search strategy

This review was conducted in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines [33]. Original research articles were retrieved from PubMed, Medline, Google Scholar and Science Direct databases in May 2020. Further, references of selected articles were searched manually to identify relevant articles for inclusion. Search strategies combined controlled (MeSH terms) and natural vocabulary on terms for disease (HBV, HCV), terms for occurrence (prevalence or incidence), population subgroups (people living with HIV) and geographic terms (Ethiopia) (see Table 1). The employed search strategy covered a range of populations with viral hepatitis. However, this systematic review is restricted to PLHIV who co-infected with Hepatitis B virus and/or Hepatitis C virus.

Table 1. Search strategy for hepatitis B and hepatic C virus infection among HIV infected people in Ethiopia, 2020

1.1. Search strategy for HBV infection		
Steps	Key words	Results
1	Human immunodeficiency virus OR HIV OR AIDS OR acquired immune deficiency syndrome	#1
2	Hepatitis B virus OR HBV OR HBsAg OR HBV-DNA OR hepatitis B surface antigen	#2
3	Prevalence OR Seroprevalence OR Sero-prevalence	#3
4	Ethiopia	#4
5	#1 AND #2 AND #3 AND #4	Search results
1.2. Search strategy for HCV infection		
I	Hepatitis C virus OR HCV OR anti-HCV antibodies OR hepatitis C antibody	#5
II	Human immunodeficiency virus OR HIV OR AIDS OR acquired immune deficiency syndrome	#6
III	Prevalence OR Seroprevalence OR Sero-prevalence	#7
IV	Ethiopia	#8
V	#5 AND #6 AND #7 AND #8	Search results

2.2. Inclusion and exclusion criteria

Studies were included only if they reported HBV and HCV infection prevalence rate among HIV-infected persons in Ethiopia. Generally, laboratory diagnosis of chronic HBV infection is based on the detection of hepatitis B surface antigen (HBsAg) and that of HCV is depending on anti-HCV antibody. Hence, only studies reporting prevalence of HBV in HIV persons based on HBsAg and/or anti-HCV sero-positivity were included. Studies reporting HBV prevalence in general populations were excluded as these were out of the scope of this review. Only articles published in English language with data on prevalence of HBV and/or HCV among HIV infected population were included.

Table 2. Inclusion and exclusion criteria for a systematic review of HBV and HCV prevalence in HIV infected population in Ethiopia, 2020

Categories	Inclusion criteria	Exclusion criteria
Study design	<ul style="list-style-type: none"> ✓ Surveillance studies ✓ Cross-sectional studies ✓ Prospective observational studies ✓ Retrospective studies ✓ Systematic reviews ✓ RCT or non-randomized clinical trials 	<ul style="list-style-type: none"> ➤ Case reports, outbreak investigations ➤ Article without patient data (Expert opinions, editor comments). ➤ Laboratory studies (e.g. molecular, biochemistry or Animal studies) ➤ Projections or mathematical modelling studies
Country/ study area	Ethiopia	Other countries
Study subjects	Hepatitis B or C infection	Other or unspecified hepatitis
Study population	PLWHIV in representative studies	Other populations
Outcomes	Prevalence/proportion/ incidence based on HBsAg, anti-HCV measurement in study population	Outcomes based on measurement of other criteria

Key: RCT: randomized controlled trial; HbsAg: hepatitis B surface antigen, anti-HCV: anti-hepatitis C antibody; PLHIV: People living with HIV

2.3. Data extraction and Quality assessment

Publications of interest were first reviewed based on their title and abstract to select potentially relevant papers. The full text of all publications selected during the title and abstract screening was then assessed for relevance. This was followed by extracting the relevant data from the final selected publications. Data from each study were extracted using a predefined set of variables covering study characteristics, study population details, prevalence of HBV and HCV markers (HBsAg and anti-HCV antibodies), including the type of sample that was collected and the type of laboratory test that was used. Finally, the risk of bias was assessed for each study and used to categorize the included studies according to quality indicators defined in the study design.

2.4. Quality assessment and data extraction

Studies' qualities were assessed using a 12-point scoring system based on the Downs and Black checklist as adopted in similar reviews [34-36]. These were: if objective of the study clearly described, study design clearly stated, participants representative of the population from which they were recruited, modest sample size, management of missing data, age, gender and other characteristics explored/reported, e.g. were confounders reported, was detection method of HBV and/or HCV reported, were potential biases reported, was outcome clearly described. Each study was issued with a unique number for identification purposes and the following descriptive information collected; author details, year of publication, region of Ethiopia, type of study population, mean/median age of subjects, number of subjects involved (sample size), gender of study participants and the HIV/HBV co-infection prevalence rate.

3. Results

3.1. Study selection and study characteristics

The electronic search yielded a total of 116 citations. Out of these, 28 duplicates were removed and the remaining 88 records were screened for eligibility on the basis of titles and abstracts. After the title and abstract review, an additional 65 studies were eliminated. Then, full text articles were reviewed (23) for eligibility. Of those, 7 articles were excluded for various reasons including lack of report on viral hepatitis co-infections with HIV (4), and laboratory based molecular/immunological studies (3). The remaining 16 studies were included in this systematic review (Fig.1).

Out of the total 16 studies included, six studies presented data on HBV prevalence and six studies described both HBV and HCV infections including a total population of 5524 HIV-infected study population. Ten studies provided HCV prevalence data (of which four studies presented data only on HCV) for 3457 HIV-positive patients (Table 3 and 4).

Geographically, the selected studies included study subjects from Northwest Ethiopia (4 studies), Southern Ethiopia (5 studies), Tigray (2 studies), Addis Ababa (3 studies) and others (2 studies) (Table 3 and 4). Except for one study that was conducted among children below the age of 15 year [44], all the remaining studies included to this systematic review were conducted among adult populations. The large proportion of the study participants were female among the adult study subjects (51-73.4% of the study participants).

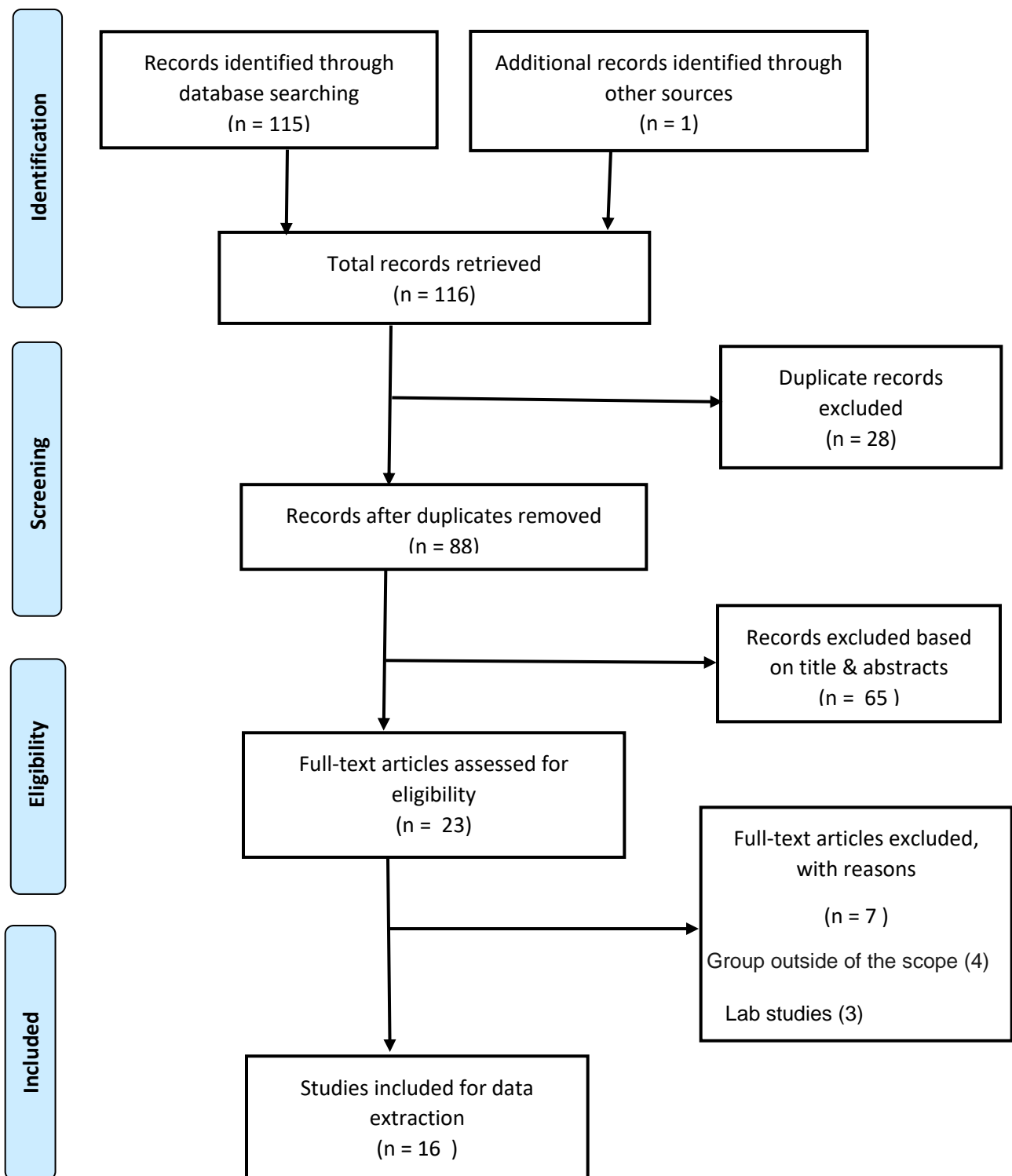


Fig 1. PRISMA flow diagram for the systematic review of hepatitis B and C virus prevalence among PLHIV in Ethiopia, 2020.

3.2. Prevalence estimates of HBV infection among HIV infected persons

The included articles into this systematic review yielded a total of 22 prevalence estimates on HBV and HCV infection among PLHIV from different parts of the country. Out of the 16 studies included for the systematic review, 12 studies reported prevalence estimates of HBV among HIV infected population. Mean age of the study participants range from 11-40 years with majorities of the study participants being female. The prevalence estimate of HBV among children infected with HIV was 2.0% [44]. Among the adult population, HBV prevalence was ranging from 3.0-11.7% [37-43, 48-51]. In this review, the overall prevalence of HBV was calculated to be 6.5% (Table 3).

Table 3. Prevalence of HBV among HIV infected persons in Ethiopia with characteristics of the included studies in the systematic review 2020.

Authors	Year	design	Study area	Sample size	Mean age (Yrs)	Female, %	Prevalence (n, %)
[37]	2017	CS	S. Ethiopia	477	33.4	61	30(6.3)
[38]	2014	CS	Addis Ababa	500		51.2	15(3.0)
[39]	2013	CS	NW Ethiopia	400	32*	69.9	20(5.6)
[40]	2019	CS	East Ethiopia	901	40(IQR32, 45)	69	105(11.7)
[41]	2016	CS	Tigray	508	37.8 + 9.6	60	30(5.9)
[42]	2019	CS	S. Ethiopia	442	36.79 ±9.97	57.7	37(8.4)
[43]	2017	CS	NW Ethiopia	308	38(IQR27, 49)	62.7	17(5.6)
[44]	2014	CS	NW Ethiopia	253	11	47.5	5(2.0)
[48]	2011	CS	C. Ethiopia	760		61.6	30(3.9)
[49]	2016	CS	S. Ethiopia	411	28.8+11.2	65.5	33(8.0)
[50]	2017	CS	Addis Ababa	169	39.9+9.9	66	12(7.3)
[51]	2014	CS	NW Ethiopia	395	36.3+9.9	59.2	24(6.1)
Total study population				5524			358 (6.5)

HBV, hepatitis B virus; HIV, human immunodeficiency virus; n, number of patients; NW, Northwest; CS, cross-sectional study; * Median age; IQR, Interquartile range; Empty rows denote missing value from the original article

3.3. Prevalence of HCV in HIV infected population

As presented in table 4, ten HCV prevalence estimates were retrieved among 3457 HIV infected population. Out of these, one study presented data on HCV among children infected with HIV with a prevalence estimate of 5.5% [44]. Majorities of the study subjects were female (Range, 48-73.4% of the study population). The prevalence of HCV among adult HIV infected population was ranging from 3.1% to 10.5% [37-39, 45-47]. Overall, the prevalence of HCV infection among all the subjects was 4.9%.

Table 4. Prevalence of HCV among HIV infected persons in Ethiopia with characteristics of the included studies in the systematic review, 2020.

Author	Year	Study design	Study Area	Sample size	Mean age (Yr)	Female, %	Prevalence (n, %)
[37]	2017	CS	Southern Ethiopia	477	33.4	61	15(3.1)
[38]	2014	CS	Addis Ababa	500		51.2	18(3.6)
[39]	2013	CS	NW Ethiopia	400	32*	69.9	18(5.0)
[45]	2002	CS	Addis Ababa	165			8.0(4.5)
[46]	2013	CS	Tigray	174			16(9.2)
[47]	2011	CS	Southern Ethiopia	400	31.7+8.4	62.2	42(10.5)
[44]	2014	CS	NW Ethiopia	253	11	47.5	14(5.5)
[52]	2014	CS	Addis Ababa	282		73.4	15(5.3)
[49]	2016	CS	Southern Ethiopia	411	28.8+11.2	65.5	20(4.9)
[51]	2014	CS	NW Ethiopia	395	36.3+9.9	59.2	5(1.3)
Total study population				3457			171(4.9)

HCV, hepatitis C virus; HIV, human immunodeficiency virus; n, number of patients; NW, Northwest; CS, cross-sectional study; Empty rows denote missing value from the original article; * Median age.

3.4. Risk factors for HBV and/or HCV infection among HIV patients

In this systematic review, the risk factors reported for acquisition of HBV and/or HCV infection among the included studies were assessed qualitatively. Of multiple variables fitted to regression models, the following factors were reported to associate with HBV infection among HIV patients: Family history of HBV, AOR 8.8 (95% CI, 2.6-3.5) [42], having multiple sexual partners, AOR 2.5 [43], 4.2 [41], 7.01 [40]) and 8.1 [51], and CD4 count<200 cells, (AOR 3.5 [41] and 2.4 [37]). Furthermore, sharing sharp objects, having genital discharge, being male, single, and older age above the age of 40 years were also mentioned as risk factors for HBV infection [37, 40, 43, 50]. On the other hand, being female sex worker, AOR 3.9 and receiving transfusion blood, AOR 5.6 were reported to associate with HCV infection among the study subjects [45, 51].

4. Discussion

People living with HIV (PLHIV) are at higher risk of acquiring viral Hepatitis (hepatitis B & C virus) owing to shared transmission routes and risk factors. In the era of increased access to HAART, liver disease is a major cause of non-AIDS-related mortality in PLHIV [13, 53], although HCV infection can be cured by treatment, and HBV can be treated or prevented by vaccine [54]. Moreover, as several antiretroviral drugs (ARVs) have dual anti-HIV and anti-HBV activity, there is high possibilities of selecting for resistance mutations in HBV and then, confer cross-resistance in HIV [3]. Thus, there is a need for reliable epidemiological data on the burden of viral hepatitis in this vulnerable population group to guide policy makers for prevention, treatment, and control of these infections.

In this systematic review, epidemiological evidences on HBV/HCV in PLHIV in Ethiopia was synthesized in order to determine the extent of viral hepatitis burden. The overall prevalence of HBV and HCV infection among PLHIV was found to be 6.5% and 4.9% respectively. This data suggesting that HIV positive patients in Ethiopia are concurrently suffering from dual burden of HIV and viral hepatitis infections. When compared with other studies, the prevalence rate of HBV found in this review was slightly higher (6.5% vs 5.2%) than the finding of previous systematic review [55]. The reason for such disparity between the two studies could be due to the fact that the estimate by the previous review included data from various study population including blood donors, antenatal care (ANC) attendants, and community based studies, unlike the current review that included data only from studies on PLHIV as the study population. Nevertheless, both reviews clearly indicated that HBV is a significant co-morbidity among PLHIV and underscore the needs for a concerted effort to improve the quality of life of this group of population. The prevalence of HBV found in this study is lower when compared with the 9.7% HBV-HIV co-infection rate in South

Africa, 16.7% in Ghana, and 20.4% in Malawi [56-58]. These could be due to differences in the study population and prevailing risk factors.

The WHO recommends screening of all PLHIV for viral hepatitis, vaccination against HBV in non-immune individuals and providing anti-HBV and/or HCV therapy in co-infected patients [1, 2]. However, since screening HIV-positive patients for viral hepatitis co-infection is not a standard practice in Ethiopia, PLHIV in the country are not benefiting from such guidance currently. The finding high prevalence of HBV and HCV in HIV patients as determined in this review necessitates the need for a national policy to offer HBV as well as HCV screening as part of the comprehensive care for all HIV positive persons.

The prevalence of HCV in PLHIV was determined to be 4.9%. This prevalence rate was higher when compared with HCV prevalence in the general population from the Northwest Ethiopia (0.7%-5.0%), Central Ethiopia (0.32%), and Eastern Ethiopia (0.7%) [59-62]. It was also higher than the prevalence estimate of anti-HCV by a similar study (3.1%, 95%CI: 2.2-4.4) [55]. The high prevalence of anti-HCV antibody among HIV infected population could be related to immune dysfunction in HCV/HIV co-infected patients. An impaired lymphocytes function in HIV infection allowing hepatitis virus to escape immune response and establish a persistent infection, which is a relevant factor for the high prevalence of HCV in this population [17, 63, 64]. Further, it has been shown that there is more HCV RNA in the semen of HCV/HIV co-infected patients than in those with HCV mono-infection, and thus, this might facilitate HCV transmission through mucosal route in the HIV positive population [66, 66]. Moreover, prevalent risk factors among HIV patients, which associate with an increased risk of HCV acquisition and transmission, such as unprotected sex, and history of infection with other sexually transmitted infections might explain the high frequency of HCV infection in this population group [67, 68].

The prevalence of HBV in the reviewed studies ranged from 3.0% to 11.7% among adult PLHIV and that of HCV was ranged from 3.1% to 10.5% [37-47]. The WHO testing guidance for HBV and HCV proposes a 2% threshold for HBV/HCV infection prevalence, above which testing scale-up is recommended [69]. All reported HBV and HCV infection prevalence estimates for PLHIV, in the included studies to this review were above this threshold. Therefore, our data presents a strong case to warrant fast-tracked testing coverage in these populations.

5. Conclusions and Recommendation

The findings of this review demonstrate that a high prevalence of HBV and HCV infection exists among PLHIV in Ethiopia. This indicating that there is a strong need to scale up preventive efforts and strategic policy directions including screening of all newly diagnosed PLHIV for coinfection with viral hepatitis in order to identify and link positive cases to care and treatment.

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