

World Journal of *Virology*

World J Virol 2020 December 15; 9(5): 54-90



MINIREVIEWS

- 54 Chronic hepatitis B-associated liver disease in the context of human immunodeficiency virus co-infection and underlying metabolic syndrome
Amponsah-Dacosta E, Tamandjou Tchuem C, Anderson M
- 67 Thymosin alpha 1: A comprehensive review of the literature
Dominari A, Hathaway III D, Pandav K, Matos W, Biswas S, Reddy G, Thevuthasan S, Khan MA, Mathew A, Makkar SS, Zaidi M, Maher M, Beas R, Castaneda V, Paul T, Halpern J, Baralt D

SYSTEMATIC REVIEWS

- 79 Reinfection risk of novel coronavirus (CoVID-19): A systematic review of current evidence
SeyedAlinaghi S, Oliaei S, Kianzad S, Afsahi AM, MohsseniPour M, Barzegary A, Mirzapour P, Behnezhad F, Noori T, Mehraeen E, Dadras O, Voltarelli F, Sabatier JM

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Production Editor: Yan-Xia Xing **Production Department Director:** Yun-Xiaojuan Wu, **Editorial Office Director:** Dong-Mei Wang.

NAME OF JOURNAL

World Journal of Virology

ISSN

ISSN 2220-3249 (online)

LAUNCH DATE

February 12, 2012

FREQUENCY

Continuous Publication

EDITORS-IN-CHIEF

Mahmoud El-Bendary, En-Qiang Chen

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3249/editorialboard.htm>

PUBLICATION DATE

December 15, 2020

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INSTRUCTIONS TO AUTHORS

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<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Chronic hepatitis B-associated liver disease in the context of human immunodeficiency virus co-infection and underlying metabolic syndrome

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Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

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Abstract

Globally, a shift in the epidemiology of chronic liver disease has been observed. This has been mainly driven by a marked decline in the prevalence of chronic hepatitis B virus infection (CHB), with the greatest burden restricted to the Western Pacific and sub-Saharan African regions. Amidst this is a growing burden of metabolic syndrome (MetS) worldwide. A disproportionate co-burden of human immunodeficiency virus (HIV) infection is also reported in sub-Saharan Africa, which poses a further risk of liver-related morbidity and mortality in the region. We reviewed the existing evidence base to improve current understanding of the effect of underlying MetS on the development and progression of chronic liver disease during CHB and HIV co-infection. While the mechanistic association between CHB and MetS remains poorly resolved, the evidence suggests that MetS may have an additive effect on the liver damage caused by CHB. Among HIV infected individuals, MetS-associated liver disease is emerging as an important cause of non-AIDS related morbidity and mortality despite antiretroviral therapy (ART). It is plausible that underlying MetS may lead to adverse outcomes among those with concomitant CHB and HIV co-infection. However, this remains to be explored through rigorous longitudinal studies, especially in sub-Saharan Africa. Ultimately, there is a need for a comprehensive package of care that integrates ART programs with routine screening for MetS and promotion of lifestyle modification to ensure an improved quality of life among CHB and HIV co-infected individuals.

Manuscript source: Invited manuscript

Specialty type: Virology

Country/Territory of origin: South Africa

Peer-review report's scientific quality classification

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: June 26, 2020

Peer-review started: June 26, 2020

First decision: September 21, 2020

Revised: September 24, 2020

Accepted: October 12, 2020

Article in press: October 12, 2020

Published online: December 15, 2020

P-Reviewer: Tugizov SM

S-Editor: Huang P

L-Editor: Filipodia

P-Editor: Xing YX



Key Words: Hepatitis B virus; Human immunodeficiency virus; Metabolic syndrome; Fatty liver disease; Chronic liver disease; Sub-Saharan Africa

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Core Tip: Independently, chronic hepatitis B virus (HBV) infection, human immunodeficiency virus (HIV) infection and metabolic syndrome (MetS) are known risk factors of chronic liver disease. The presence of MetS components, including type 2 diabetes mellitus, central obesity and lipid abnormalities, are associated with adverse outcomes and altered treatment response among HBV and HIV infected individuals. While underlying MetS may have an additive effect on the development and progression of chronic liver disease among HBV-HIV co-infected individuals, the evidence from endemic regions like sub-Saharan Africa is limited and deserves further attention in the research agenda.

Citation: Amponsah-Dacosta E, Tamandjou Tchuem C, Anderson M. Chronic hepatitis B-associated liver disease in the context of human immunodeficiency virus co-infection and underlying metabolic syndrome. *World J Virol* 2020; 9(5): 54-66

URL: <https://www.wjgnet.com/2220-3249/full/v9/i5/54.htm>

DOI: <https://dx.doi.org/10.5501/wjv.v9.i5.54>

INTRODUCTION

Chronic liver disease is a frequent clinical condition accounting for an estimated 2 million deaths each year worldwide^[1]. It is characterized by a progressive deterioration of liver function, involving a continuous process of inflammation, destruction and regeneration of the cells of the liver. This often leads to complications such as liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). A broad spectrum of etiologies is associated with chronic liver disease and typically includes alcohol use disorder, chronic exposure to toxins, viral hepatitis including chronic hepatitis B virus (HBV) infection and immune and metabolic disorders^[1]. Globally, an epidemiological shift in the burden of chronic liver disease has been observed, mainly driven by diabolical factors. On the one hand are the global efforts that have led to the increased elimination of aflatoxins from food, improved safety of transfusions and transplantations, the establishment of viral hepatitis treatment programs and universal childhood hepatitis B vaccination programs; and on the other hand is the increasing burden of metabolic disorders worldwide and the persisting endemicity of chronic HBV infection (CHB) in regions such as the Western Pacific and sub-Saharan Africa^[1-3].

It is well established that CHB is a leading cause of liver disease and death worldwide. The World Health Organization estimates that currently 257 million persons or 3.5% of the world's population are chronic carriers of HBV, 68.0% of whom live in the Western Pacific (115 million) and sub-Saharan African (60 million) regions alone^[4]. The greater proportion of chronic carriers are persons who were born prior to the establishment of universal childhood hepatitis B vaccination programs. What further compounds the situation in a region like sub-Saharan Africa is the fact that it is also home to 71.0% of the global population (35 million) of people living with human immunodeficiency virus (PLHIV)^[5,6]. Due to similar routes of transmission, co-infection with HBV and HIV are not uncommon. Of the 2.7 million HBV-HIV co-infected persons worldwide, 69.0% or 1.9 million live in sub-Saharan Africa^[7]. With rapid expansion of antiretroviral treatment (ART) programs, there has been a dramatic decline in AIDS-related deaths and consequently an increase in the life expectancy of PLHIV, including those co-infected with HBV^[5,6]. However, as PLHIV are living longer, an increased risk of chronic liver disease has been observed and is emerging as an important cause of non-AIDS-related mortality within this population^[8,9]. Among PLHIV, liver-related mortality has been found to be up to 10 times of that occurring within the general population^[10]. Development of chronic liver disease among PLHIV has been associated with underlying viral hepatitis (including CHB) and non-viral hepatitis risk factors such as lifelong exposure to components of ART regimens with hepatotoxic effects and the development of metabolic syndrome (MetS)^[8].

MetS is a common yet complex condition characterized by a clustering of various metabolic disorders (Table 1) that are known to increase the risk of developing chronic liver disease or to worsen the prognosis among individuals with other underlying risk factors of chronic liver disease^[11-14]. Chronic liver disease among individuals with MetS is often preceded by the accumulation of fats or triglycerides in the cells of the liver due to MetS components like insulin resistance, abnormal lipid metabolism and dysregulation of cytokines and adipokines, leading to a spectrum of fatty liver disorders known as non-alcoholic fatty liver disease (NAFLD). With significant liver inflammation and injury over time, a severe form of NAFLD develops, referred to as non-alcoholic steatohepatitis (NASH). NASH is associated with liver damage and progression to advanced liver cirrhosis and fibrosis^[15]. The evidence on the association between MetS and other common risk factors of chronic liver disease, such as CHB, is oftentimes conflicting. In addition, the role of MetS in the development and prognosis of chronic liver disease among HBV-HIV co-infected individuals is unclear. With the concomitant high burden of CHB and HIV infection, and the growing prevalence of MetS and its associated complications, sub-Saharan Africa presents a unique case for continuously examining key risk factors of chronic liver disease in order to inform ongoing public health interventions^[16].

We review evidence emerging over the last decade (2010-2020) to improve current understanding of the pathogenesis of chronic liver disease among CHB and HIV co-infected individuals with underlying MetS. We identify gaps in the evidence base and propose recommendations for future research, as well as current policy and practice. This review takes a special focus on sub-Saharan Africa where the burden of CHB and HIV co-infection is high, the prevalence of MetS is growing and the need for intervention is often the greatest.

CONFLICTING EVIDENCE ON THE ASSOCIATION BETWEEN METS AND CHB

With 6.1% of the population living with CHB, the burden of liver cirrhosis, fibrosis and HCC in sub-Saharan Africa is significant^[4]. The association between MetS and the increased risk of chronic liver disease presents an added burden and calls for greater attention within this population. Despite this, our review of primary studies published within the last decade reveal a profound lack of data on CHB and MetS from sub-Saharan Africa.

Drawing on data from elsewhere, the combined prevalence of MetS among those with CHB varies from 5.0% to 30.1%^[17,18]. In Europe, studies conducted in Slovakia report MetS prevalence rates of 27.8% among Roma^[19] and 24.6% among both Caucasian and Roma^[20] populations with CHB. This is comparable to findings from a study conducted in Spain that found that 24.0% of individuals with CHB had underlying MetS^[21]. In both Slovakian studies, however, no significant association between MetS and HBV infection was found, as the prevalence of the condition was comparable between those with or without CHB (27.8% in CHB patients *vs* 29.6% in controls, $P = 0.785$ ^[19]; and 24.6% in CHB patients *vs* 24.7% in controls, $P = 0.561$ ^[20]), irrespective of age and sex. Instead, the studies did show that CHB patients with MetS presented with significantly higher HBV-DNA viral load and elevated liver enzymes, including alanine aminotransferase (ALT) and gamma-glutamyl transferase, compared to those without MetS, suggesting an additive effect of MetS on the liver damage caused by CHB^[19,20]. Contrary to these findings, a large population-based study conducted in the United States (the NHANES III study) described a significantly lower prevalence of MetS in CHB patients compared to controls (10.4% *vs* 25.6%, $P = 0.019$). Stratified by sex, this inverse correlation between MetS and CHB was found to persist in males but not in females^[22]. Unlike the Slovakian observations, CHB patients with high levels of ALT in the NHANES III study had a significantly lower rate of MetS compared with controls (2.1% *vs* 49.8%, $P < 0.001$). Given these findings, the authors hypothesized that chronic liver inflammation, instead of HBV itself, may be responsible for metabolic derangements in CHB patients^[22]. It is worth noting that participants in the NHANES III study were relatively older than those in the Slovakian studies, and this may have influenced the conflicting findings. Evidence emerging from Asia on the association between CHB and MetS is no less conflicting than that discussed previously. For example, a case-series conducted in Taiwan found no correlation between CHB and MetS^[23], while two other cross-sectional studies from Taiwan reported an inverse correlation between CHB and MetS^[24,25]. Contrary to this, a positive association between latent HBV infection and MetS [hazard ratio (HR) = 2.27,

Table 1 Metabolic syndrome—definition, diagnostic criteria and association with chronic liver disease**Definition of MetS**

A clustering of metabolic disorders that include hypertension, central obesity, impaired glucose metabolism including insulin resistance and abnormal cholesterol or triglyceride levels. MetS increases the risk of morbidity and mortality from cardiovascular disease, stroke, type 2 diabetes, chronic kidney disease and chronic liver disease

Diagnostic criteria¹

NCEP/ATP III^[27]	AHA/NHLBI^[28]	IDF^[29]	JIS^[30]	WHO^[31]
Presence of ≥ 3 of the following:	Presence of ≥ 3 of the following:	Central obesity; ethnicity-specific waist circumference values ² or BMI > 30 kg/m ² plus any 2 of the following:	Presence of ≥ 3 of the following:	Glucose intolerance, impaired glucose tolerance or diabetes mellitus and/or insulin resistance and any 2 of the following:
Abdominal obesity; > 102 cm in males and > 88 cm in females	Elevated waist circumference; ≥ 102 cm in males and ≥ 88 cm in females	Raised triglycerides; ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality	Elevated waist circumference; population- and country-specific definitions ²	Raised arterial pressure; ≥ 160/90 mmHg
Elevated triglycerides; ≥ 150 mg/dL or treatment for elevated triglycerides	Elevated triglycerides; ≥ 150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides	Reduced HDL cholesterol; < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality	Elevated triglycerides; ≥ 150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides	Raised plasma triglyceride; ≥ 150 mg/dL, and/or low HDL cholesterol; < 35 mg/dL in males and < 39 mg/dL in females
Reduced HDL cholesterol; < 40 mg/dL in males and < 50 mg/dL in females	Reduced HDL cholesterol; < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females or treatment for reduced HDL cholesterol	Raised blood pressure; ≥ 130/≥ 85 mmHg, or treatment of previously diagnosed hypertension	Reduced HDL cholesterol; < 40 mg/dL (1.0 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females, or treatment for reduced HDL cholesterol	Central obesity; waist/hip ratio > 0.90 in males and > 0.85 in females and/or BMI > 30 kg/m ²
Elevated blood pressure; ≥ 130/≥ 85 mmHg or treatment for elevated blood pressure	Elevated blood pressure; ≥ 130/≥ 85 mmHg or antihypertensive treatment	Raised fasting plasma glucose; ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes	Elevated blood pressure; ≥ 130/≥ 85 mmHg or anti-hypertensive treatment	Microalbuminuria; urinary albumin excretion rate ≥ 20 µg/min or albumin/creatinine ratio ≥ 20 µg/mg
Elevated fasting glucose; ≥ 110 mg/dL or treatment for elevated glucose	Elevated fasting glucose; ≥ 100 mg/dL or treatment for elevated glucose		Elevated fasting glucose; ≥ 100 mg/dL, or treatment of elevated glucose	

MetS and chronic liver disease

The association between MetS and chronic liver disease involves a complexity of risk factors which are yet to be fully understood. NAFLD which covers a spectrum of fatty liver disorders including NASH, is the most common cause of abnormal liver function among individuals with MetS. MetS components like insulin resistance may increase fatty acids in the liver, leading to fat or triglyceride accumulation in hepatocytes. NASH, which is an advanced form of NAFLD, is associated with liver inflammation and liver damage, leading to the development of liver cirrhosis and progression to advanced liver fibrosis. In addition, type 2 diabetes and obesity may increase the risk of HCC. The presence of MetS may have worse outcomes in individuals with other causes of chronic liver disease, such as viral hepatitis.

¹NCEP/ATP III: National Cholesterol Education Program/Adult Treatment Panel III; AHA/NHLBI: American Heart Association/National Heart, Lung and Blood Institute; IDF: International Diabetes Federation; JIS: Joint Interim Statement; WHO: World Health Organization.

²Currently, ethnicity-specific waist circumference values have not been defined for populations from sub-Saharan Africa. BMI: Body mass index; HCC: Hepatocellular carcinoma; HDL: High-density lipoprotein; MetS: Metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis.

95%CI: 1.52-3.38] was demonstrated in a retrospective cohort study conducted in China, suggesting that latent HBV infection may be a risk factor for the development of MetS^[26].

Evidently, the mechanistic association between CHB and MetS remains poorly

resolved. Reasons for the conflicting findings may include variations in the MetS diagnostic criteria used in the various studies (Table 1)^[27-31]. The geographic heterogeneity of the published data also means that a comparison between studies may not always be feasible. Also, worth noting is the fact that a majority of the published studies are cross-sectional in nature, which often draws the weakest evidence for the establishment of causal associations between CHB and MetS, as opposed to robust longitudinal studies. Despite the disparities in the prevalence of MetS reported among those with CHB, the evidence base strongly suggests that older age^[24] and female sex^[18,25,32,33] may be predictors of MetS within this population.

Several studies have shown that underlying MetS increases the risk and progression of liver fibrosis, cirrhosis and HCC in patients with CHB^[17,34-36]. A longitudinal population-based study involving 2979 participants aged 40-65 years, of whom 1690 had CHB, revealed that the presence of three or more metabolic risk factors, compared with no factors, significantly increased the risk of HCC by two- to three-fold among CHB patients^[36]. This relationship persisted after controlling for viral factors such as high HBV-DNA viremia (≥ 10000 copies/mL) and other known risk factors of HCC^[36]. These findings are consistent with observations made elsewhere^[34]. Among these metabolic risk factors, insulin resistance and central obesity are independently associated with the development of liver damage and HCC. In a longitudinal cohort study conducted by Huang *et al.*^[37], a significantly higher cumulative incidence of cirrhosis [log-rank test, $P < 0.001$, with a relative risk (RR) of 3.43, 95% confidence interval (CI): 2.62-4.49] and decompensated cirrhosis (log-rank test, $P < 0.001$, with an RR of 4.11, 95%CI: 2.95-5.70) was noted among CHB patients with newly diagnosed diabetes as compared to those without diabetes. Adjusting for age, sex, CHB treatment, HCC and comorbidity index, type 2 diabetes mellitus (T2DM) remained an independent predictor for cirrhosis (HR = 2.015; 95%CI: 1.393-2.915; $P < 0.001$) and decompensated cirrhosis (HR = 1.792; 95%CI: 1.192-2.695; $P = 0.005$)^[37]. Another study showed that pre-existing T2DM for > 5 years before cirrhosis diagnosis, insulin and/or sulphonylurea use and poor diabetic control (defined as glycated hemoglobin A1c $\geq 7.0\%$) were predictors of cirrhosis complications and HCC development^[38]. These findings were confirmed by a longitudinal study that reported a significantly higher incidence of HCC (13.3% *vs* 10.0%; $P < 0.001$) and HCC-related mortality (7.5% *vs* 4.7%; $P < 0.001$) among 2966 CHB patients with T2DM compared to 2966 CHB patients without T2DM, after a median follow-up of 11.4 years^[39]. Elevated serum adiponectin levels may also play a role in the increased risk of liver fibrosis, cirrhosis and HCC^[40,41].

When investigating dyslipidemia, including hypercholesterolemia or hypertriglyceridemia, among CHB patients *vs* controls, several studies have reported significantly lower levels of total cholesterol and triglycerides among those with CHB^[19,20,42,43]. Among CHB patients, significant disparities have been observed in the levels of triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) detected among males *vs* females and those aged ≤ 45 years *vs* > 45 years^[18,23,32]. While the heterogeneity in the lipid profiles detected among CHB patients is not fully understood, some virus-specific risk factors have been linked with the lipid abnormalities observed within this population. For example, HBV infection is known to cause liver injury, which may lead to impaired liver function, thereby altering total cholesterol and triglyceride levels^[42]. Moreover, it has been shown that the viral HBx protein inhibits the secretion of apolipoprotein B, which is an essential component for the formation of very-LDL and LDL, thereby lowering serum triglyceride levels and causing the accumulation of hepatic triglycerides^[43,44]. This is particularly concerning as excessive accumulation of triglycerides in the liver leads to NAFLD.

Both CHB and NAFLD are recognized as significant causes of liver cirrhosis and fibrosis. Thus, it is only reasonable to examine the relationship between these conditions. Several studies have reported a positive association between hepatic steatosis and MetS components such as high body mass index or central obesity, elevated serum triglyceride and total cholesterol levels and insulin resistance, among those with CHB^[45-47], although an inverse relationship with HBV replication and hepatitis B surface antigen positivity has also been reported^[46,48-50]. These observations suggest host factors, and not HBV itself, as predictors of hepatic steatosis in those with CHB. Interestingly, Joo *et al.*^[51] found that HBV infection was significantly associated with a lower risk of incident NAFLD. By investigating the lipid profiles in these patients, the authors reported a significant decrease in total cholesterol levels over time among CHB patients compared with controls, suggesting that HBV infection could protect against the development of NAFLD, possibly through its effect on lipid metabolism.

SUBSTANTIAL BURDEN OF METS AND NAFLD AMONG PLHIV

Sub-Saharan Africa has a disproportionate burden of HIV infection, and there is evidence to suggest that a significant proportion of PLHIV within this region are at increased risk of developing MetS and its associated complications, including chronic liver disease^[43,52]. It is worth noting however, that the true burden of MetS among PLHIV in sub-Saharan Africa is often difficult to ascertain, given the heterogeneity of the condition itself, the lack of ethnicity-specific diagnostic criteria for sub-Saharan African populations and the disparities in the associated risk factors (HIV-related *vs* host and environmental-related risk factors). Table 2 shows the variable prevalence rates of MetS among PLHIV from selected studies conducted in sub-Saharan African countries within the last decade^[53–67]. These variations in the prevalence of MetS among PLHIV are not exclusive to sub-Saharan African countries but have been reported in similar population groups in Latin America^[68] and Europe^[69–72]. The commonly reported independent risk factors associated with MetS among PLHIV in sub-Saharan Africa include female sex, age > 40 years and central obesity^[56,59,62]. The potential influence of host genetics in the development of MetS within this population has also been suggested previously^[66].

A persistent matter of debate in the evidence-base has been the impact of lifelong exposure to ART on the burden of MetS among PLHIV. In a recent cross-sectional study conducted among PLHIV in Ghana, Obirikorang *et al*^[65] found a higher prevalence of MetS among participants on ART compared to their ART-naïve counterparts, irrespective of the diagnostic criteria used. Consistent with this finding, a study conducted in Cameroon reported prevalence rates of 36.0% and 23.4% among those on ART compared to ART-naïve individuals, respectively^[57]. Mbunkah *et al*^[60] further reported statistically significant ($P = 0.02$) variations in MetS prevalence among those on first-line ART (24.2%) and second-line or protease inhibitor-based ART (10.0%), compared to ART-naïve (11.5%) Cameroonian PLHIV. Contrary to these findings, Ngatchou *et al*^[63] found that ART-naïve individuals rather experience a two-fold increase in the prevalence of MetS, suggesting a possible influence of uncontrolled HIV replication, while Tesfaye *et al*^[67] noted that the prevalence of MetS among PLHIV in Ethiopia was not influenced by whether or not they had initiated ART. To date, the findings from sub-Saharan Africa have been limited by the cross-sectional design adopted by most studies. Findings from a previous longitudinal study conducted in Italy show that after 3 years of follow-up, there was no significant difference in the incidence of MetS among those on ART and ART-naïve individuals. Instead, the authors posit that there may be different metabolic pathways underlying the development of MetS in ART-naïve individuals compared to those on ART^[72]. While the findings on MetS among PLHIV in sub-Saharan Africa remain inconclusive, they do suggest a possible multi-factorial mechanism—involving viral, host and environmental factors—underlying the pathogenesis of MetS among PLHIV, which underscores the importance of the condition within this population.

Historically, the development of chronic liver disease among PLHIV has been associated with concomitant viral hepatitis, ART-associated hepatotoxicity and alcoholic liver disease^[8]. Emerging evidence now shows that NAFLD is increasingly becoming an important cause of significant liver morbidity among PLHIV^[73–75]. Unfortunately, evidence emerging from sub-Saharan Africa on the burden of NAFLD among PLHIV is limited, and this has been raised previously as a regional public health concern^[76]. Our search for relevant sub-Saharan African studies published within the last decade on this topic returned only one output from South Africa that reported a hepatic steatosis prevalence rate of 28.0% among PLHIV^[77]. This is considerably lower than prevalence rates reported for Asian populations (31.0%)^[78] as well as from studies conducted in Canada (54.0%)^[79] and Greece (55.0%)^[80]. These studies also provide strong evidence suggesting that PLHIV are at high risk for developing NASH, fibrosis and HCC, spurred by a high burden of traditional MetS components such as insulin resistance, central obesity and dyslipidemia^[78–81]. Several reports from sub-Saharan Africa do indicate that these traditional MetS components (insulin resistance, T2DM, central obesity and dyslipidemia) are in fact prevalent among PLHIV, which could suggest a significant risk for the development of NASH and other chronic liver complications, although this association is less well researched within the region^[82–85]. The scarcity of evidence from sub-Saharan Africa means that the true burden and natural history of NAFLD among PLHIV may be underappreciated. This could have negative implications for the development of evidence-based public health interventions tailored to the sub-Saharan African context.

Table 2 Prevalence of metabolic syndrome among people living with human immunodeficiency virus in sub-Saharan Africa from selected studies

Ref.	Country	Study design	Sample size, n	MetS diagnostic criteria	Prevalence of MetS	Independent risk factors ¹
Adébayo <i>et al</i> ^[53]	Benin	Cross-sectional	244	IDF	18.4%	-
Ayodele <i>et al</i> ^[54]	Nigeria	Cross-sectional	291	NCEP/ATP III; IDF; JIS	12.7%; 17.2%; 21.0%	-
Berhane <i>et al</i> ^[55]	Ethiopia	Cross-sectional	313	NCEP/ATP III	21.1%	HAART > 12 mo, female sex
Bosho <i>et al</i> ^[56]	Ethiopia	Cross-sectional	286	NCEP/ATP III; IDF; JIS	23.5%; 20.5%; 27.6%	BMI ≥ 25 kg/m ² , formal education
Dimodi <i>et al</i> ^[57]	Cameroon	Cross-sectional	463	IDF; NCEP/ATP III	32.8%; 30.7%	-
Guira <i>et al</i> ^[58]	Burkina Faso	Cross-sectional	300	IDF	18.0%	-
Hirigo <i>et al</i> ^[59]	Ethiopia	Cross-sectional	185	IDF; NCEP/ATP III	24.3%; 17.8%	BMI ≥ 25 kg/m ² , female sex, age > 40 yr
Mbunkah <i>et al</i> ^[60]	Cameroon	Cross-sectional	173	NCEP/ATP III	15.6%	-
Muhammad <i>et al</i> ^[61]	Nigeria	Cross-sectional	200	NCEP/ATP III	15.0%	-
Muyanja <i>et al</i> ^[62]	Uganda	Cross-sectional	250	AHA/NHLBI	58.0%	Female sex, age > 40 yr
Ngatchou <i>et al</i> ^[63]	Cameroon	Cross-sectional	108	AHA/NHLBI	47.0%	-
Nguyen <i>et al</i> ^[64]	South Africa	Cross-sectional	748	JIS; IDF; NCEP/ATP III	28.2%; 26.5%; 24.1%	-
Obirikorang <i>et al</i> ^[65]	Ghana	Cross-sectional	433	NCEP/ATP III; WHO; IDF	48.3%; 24.5%; 42.3%	-
Sobieszczyk <i>et al</i> ^[66]	South Africa	Longitudinal	160	NCEP/ATP III	19.2%	Older age, time post HIV infection, family history of diabetes, human leukocyte antigen B 81:01 allele
Tesfaye <i>et al</i> ^[67]	Ethiopia	Cross-sectional	374	IDF; NCEP/ATP III	25.0%; 16.8%	Female sex, older age, BMI ≥ 25 kg/m ² , total cholesterol ≥ 200 mg/dL

¹Based on multivariate analysis in the individual studies. AHA/NHLBI: American Heart Association/National Heart, Lung and Blood Institute; BMI: Body mass index; HAART: Highly active antiretroviral therapy; IDF: International Diabetes Federation; JIS: Joint Interim Statement; MetS: Metabolic syndrome; NCEP/ATP III: National Cholesterol Education Program/Adult Treatment Panel III; WHO: World Health Organization.

LIMITED EVIDENCE ON PLAUSIBLE SYNERGISTIC EFFECT BETWEEN METS AND HBV-HIV CO-INFECTION

Given the substantial risk of MetS and NAFLD among those with CHB and PLHIV, it is important to understand if there is a synergistic effect between MetS and HBV-HIV co-infection in the pathogenesis of chronic liver disease. It is well established that HBV-HIV co-infected individuals are at increased risk of chronic liver disease^[86,87]. In addition to the widely recognized mechanisms underlying chronic liver disease in HBV-HIV co-infected individuals, it has now been shown that interactions between HIV gp120 and tat proteins with epithelial cells may induce epithelial-mesenchymal transition, leading to the development of fibrosis^[88]. Thus, among those with HBV-HIV co-infection, HIV interactions with liver cells may synergize the development of fibrosis and cirrhosis. In comparison, very little is known of the effect of underlying MetS on the progression of chronic liver disease among HBV-HIV co-infected individuals. While a synergistic effect may be plausible, there is insufficient evidence to confirm this as very few studies report on the burden of MetS among HBV-HIV co-infected individuals. In fact, only three studies met the criteria for this review, one of which involved a sub-Saharan African population^[89-91]. In this study involving 41891 ART-naïve HIV-infected individuals from Tanzania, Nagu *et al*^[89] sought to identify independent risk factors of elevated ALT titers (> 40 IU/L) as a less sensitive but non-invasive predictor of liver injury and increased risk of mortality from liver disease. Multivariate analysis showed that MetS components including hypertriglyceridemia, hyperglycemia and central obesity, as well as immunosuppression due to uncontrolled

HIV infection and HBV co-infection, were significantly associated with higher risk of elevated ALT^[88]. However, the cumulative effect of these risk factors on liver function was not investigated as part of this study.

In a study using the more sensitive transient elastography to assess liver fibrosis and determine associated risk factors among German PLHIV on ART, T2DM and central obesity were found to be associated with the presence of significant fibrosis with ($n = 23$, 18%) or without ($n = 343$, 10%) HBV co-infection^[90]. Finally, when investigating the etiology of liver-related hospital admissions among PLHIV and CHB patients in the United States, Rajbhandari *et al*^[91] found a high prevalence of NASH among HIV mono-infected patients (43.6%) and HBV-HIV co-infected patients (26.9%). In addition to this, a three-fold surge in in-hospital mortality was reported among PLHIV with concomitant HBV co-infection and cirrhosis or portal hypertension compared to those without these comorbidities (odds ratio: 3.00, 95%CI: 1.80-5.02)^[91]. Taken together, these findings suggest high risk of adverse outcomes among HBV-HIV co-infected individuals with liver disease and some form of metabolic disorder. It will be important to explore these findings in sub-Saharan Africa where the burden of HBV-HIV co-infection is significantly higher.

While there is an obvious need for further research to improve our understanding of the association between HBV-HIV co-infection and MetS, it is still possible to draw some implications for the clinical management of this population. Comprehensive programs targeted at HBV-HIV co-infected individuals that integrate ART programs with routine screening for MetS components and promotion of lifestyle modifications could be low-hanging fruits for effectively reducing the risk of adverse outcomes including chronic liver disease. Where underlying MetS is left undetected and uncontrolled there may be negative implications for ART outcomes. For example, the presence of central obesity and T2DM has been associated with lower rates of fibrosis regression among patients with CHB undergoing long-term treatment with nucleotide/ nucleoside analogues^[92]. The effect of nucleotide/ nucleoside analogues on MetS components such as lipid abnormalities has also been investigated. A retrospective cohort study that compared tenofovir disoproxil fumarate (or TDF, which forms part of some ART regimens) and entecavir (ETV) therapy among CHB patients found that serum lipoprotein lipid levels significantly differed pre- and post-treatment for median total cholesterol (3.92 *vs* 4.42 mmol/L, $P < 0.01$), LDL-C (2.25 *vs* 2.51 mmol/L, $P < 0.01$) and HDL-C (1.14 *vs* 1.34 mmol/L, $P < 0.01$) in the TDF arm whereas no significant differences were observed in the ETV group^[93]. In fact, TDF was shown to be an independent predictor of changes in lipid profiles, with TDF-treated patients being 14.0%, 13.0% and 20.0% more likely to attain a reduction in levels of total cholesterol, LDL-C and HDL-C, respectively, compared to those on ETV. However, triglycerides levels did not change over the follow-up period (median of 56 mo) in the TDF group^[93]. Similarly, while a recent phase IV randomized control trial demonstrated the superiority (by 8.0%-10.0%) of pitavastatin over pravastatin in reducing LDL-C among PLHIV with dyslipidemia, there was no difference between either cholesterol-lowering drug in altering triglyceride levels^[94].

CONCLUSION

As HBV-HIV co-infected individuals are living longer due to the benefits of ART, there is a need to ensure optimal quality of life, and this can be achieved by reducing the risk of comorbidities like MetS and chronic liver disease. There is a need to expand the research agenda in sub-Saharan Africa in order to improve our understanding of the role of MetS in the progression of chronic liver disease among the substantial population of CHB and HBV-HIV co-infected individuals within the region. Future research should include rigorous longitudinal studies to allow for the determination of the temporal sequence of the development and progression of chronic liver disease among CHB and HBV-HIV co-infected individuals with underlying MetS. In addition, a consensus on ethnicity-specific diagnostic criteria for sub-Saharan African populations is required in order to improve the assessment of MetS within the region.

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