**Name of Journal:** *World Journal of Virology*

**Manuscript NO:** 57835

**Manuscript Type:** MINIREVIEWS

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

Amponsah-Dacosta E *et al*. HBV-HIV co-infection with underlying metabolic syndrome

Edina Amponsah-Dacosta, Cynthia Tamandjou Tchuem, Motswedi Anderson

**Edina Amponsah-Dacosta,** Vaccines for Africa Initiative, School of Public Health and Family Medicine, University of Cape Town, Cape Town 7925, Western Cape, South Africa

**Cynthia Tamandjou Tchuem,** Health Economics Unit, School of Public Health and Family Medicine, University of Cape Town, Cape Town 7925, Western Cape, South Africa

**Motswedi Anderson,** Botswana Harvard AIDS Institute Partnership, Gaborone 999106, Botswana

**Author contributions:** Amponsah-Dacosta E defined the topic, performed the literature search and coordinated the writing of the manuscript; Amponsah-Dacosta E, Tamandjou Tchuem C and Anderson M screened and reviewed the literature and wrote the manuscript.

**Corresponding author: Edina Amponsah-Dacosta, PhD, MPH, Postdoctoral Fellow,** Vaccines for Africa Initiative, School of Public Health and Family Medicine, University of Cape Town, Anzio Road, Observatory, Cape Town 7925, Western Cape, South Africa. edina.amponsah-dacosta@uct.ac.za

**Received:** June 26, 2020

**Revised:** September 24, 2020

**Accepted:** October 12, 2020

**Published online:** December 15, 2020

**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.

**Key Words:** Hepatitis B virus; human immunodeficiency virus; Metabolic syndrome; Fatty liver disease; Chronic liver disease; sub-Sharan Africa

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

**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.

**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, 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 ≥ 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[13,52]. 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-naive 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-naive (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.

**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 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 theTDF 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.

**REFERENCES**

1 **Moon AM**, Singal AG, Tapper EB. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. *Clin Gastroenterol Hepatol* 2019; Online ahead of print [PMID: 31401364 DOI: 10.1016/j.cgh.2019.07.060]

2 **Magnussen A**, Parsi MA. Aflatoxins, hepatocellular carcinoma and public health. *World J Gastroenterol* 2013; **19**: 1508-1512 [PMID: 23539499 DOI: 10.3748/wjg.v19.i10.1508]

3 **GBD 2017 Cirrhosis Collaborators.** The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol* 2020; **5**: 245-266 [PMID: 31981519 DOI: 10.1016/S2468-1253(19)30349-8]

4 **World Health Organization.** Global hepatitis report, 2017. Geneva: World Health Organization, April, 2017. [cited 31 May 2020]. Available from: http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1

5 **Joint United Nations Programme on HIV/AIDS (UNAIDS).** The Gap Report. 2014. [cited 31 May 2020]. Available from: https://www.unaids.org/en/resources/documents/2014/20140716\_UNAIDS\_gap\_report

6 **Kharsany AB**, Karim QA. HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities. *Open AIDS J* 2016; **10**: 34-48 [PMID: 27347270 DOI: 10.2174/1874613601610010034]

7 **Platt L**, French CE, McGowan CR, Sabin K, Gower E, Trickey A, McDonald B, Ong J, Stone J, Easterbrook P, Vickerman P. Prevalence and burden of HBV co-infection among people living with HIV: A global systematic review and meta-analysis. *J Viral Hepat* 2020; **27**: 294-315 [PMID: 31603999 DOI: 10.1111/jvh.13217]

8 **Price JC**, Thio CL. Liver disease in the HIV-infected individual. *Clin Gastroenterol Hepatol* 2010; **8**: 1002-1012 [PMID: 20851211 DOI: 10.1016/j.cgh.2010.08.024]

9 **Farahani M**, Mulinder H, Farahani A, Marlink R. Prevalence and distribution of non-AIDS causes of death among HIV-infected individuals receiving antiretroviral therapy: a systematic review and meta-analysis. *Int J STD AIDS* 2017; **28**: 636-650 [PMID: 26868158 DOI: 10.1177/0956462416632428]

10 **Hernando V**, Perez-Cachafeiro S, Lewden C, Gonzalez J, Segura F, Oteo JA, Rubio R, Dalmau D, Moreno S, Amo JD; CoRIS. All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. *J Hepatol* 2012; **57**: 743-751 [PMID: 22709620 DOI: 10.1016/j.jhep.2012.06.010]

11 **Wang CC**, Tseng TC, Kao JH. Hepatitis B virus infection and metabolic syndrome: fact or fiction? *J Gastroenterol Hepatol* 2015; **30**: 14-20 [PMID: 25092429 DOI: 10.1111/jgh.12700]

12 **Ren H**, Wang J, Gao Y, Yang F, Huang W. Metabolic syndrome and liver-related events: a systematic review and meta-analysis. *BMC Endocr Disord* 2019; **19**: 40 [PMID: 31023282 DOI: 10.1186/s12902-019-0366-3]

13 **Todowede OO**, Mianda SZ, Sartorius B. Prevalence of metabolic syndrome among HIV-positive and HIV-negative populations in sub-Saharan Africa-a systematic review and meta-analysis. *Syst Rev* 2019; **8**: 4 [PMID: 30606249 DOI: 10.1186/s13643-018-0927-y]

14 **Wang CC**, Cheng PN, Kao JH. Systematic review: chronic viral hepatitis and metabolic derangement. *Aliment Pharmacol Ther* 2020; **51**: 216-230 [PMID: 31746482 DOI: 10.1111/apt.15575]

15 **Rosselli M**, Lotersztajn S, Vizzutti F, Arena U, Pinzani M, Marra F. The metabolic syndrome and chronic liver disease. *Curr Pharm Des* 2014; **20**: 5010-5024 [PMID: 24320032 DOI: 10.2174/1381612819666131206111352]

16 **Jaspers Faijer-Westerink H**, Kengne AP, Meeks KAC, Agyemang C. Prevalence of metabolic syndrome in sub-Saharan Africa: A systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis* 2020; **30**: 547-565 [PMID: 32143896 DOI: 10.1016/j.numecd.2019.12.012]

17 **Yoon H**, Lee JG, Yoo JH, Son MS, Kim DY, Hwang SG, Rim KS. Effects of metabolic syndrome on fibrosis in chronic viral hepatitis. *Gut Liver* 2013; **7**: 469-474 [PMID: 23898389 DOI: 10.5009/gnl.2013.7.4.469]

18 **Katoonizadeh A**, Ghoroghi S, Sharafkhah M, Khoshnia M, Mirzaei S, Shayanrad A, Poustchi H, Malekzadeh R. Chronic hepatitis B infection is not associated with increased risk of vascular mortality while having an association with metabolic syndrome. *J Med Virol* 2016; **88**: 1230-1237 [PMID: 26742819 DOI: 10.1002/jmv.24466]

19 **Janicko M**, Senajová G, Drazilová S, Veselíny E, Fedacko J, Siegfried L, Kristian P, Virág L, Pella D, Mareková M, Gecková AM, Kalanin P, Jarcuska P, Halánová M; HepaMeta Team. Association between metabolic syndrome and hepatitis B virus infection in the Roma population in eastern Slovakia: a population-based study. *Cent Eur J Public Health* 2014; **22** Suppl: S37-S42 [PMID: 24847613 DOI: 10.21101/cejph.a3900]

20 **Jarčuška P**, Janičko M, Kružliak P, Novák M, Veselíny E, Fedačko J, Senajová G, Dražilová S, Madarasová-Gecková A, Mareková M, Pella D, Siegfried L, Kristián P, Kolesárová E; HepaMeta Study Group. Hepatitis B virus infection in patients with metabolic syndrome: a complicated relationship. Results of a population based study. *Eur J Intern Med* 2014; **25**: 286-291 [PMID: 24445023 DOI: 10.1016/j.ejim.2014.01.006]

21 **Mena Á**, Pedreira JD, Castro Á, López S, Vázquez P, Poveda E. Metabolic syndrome association with fibrosis development in chronic hepatitis B virus inactive carriers. *J Gastroenterol Hepatol* 2014; **29**: 173-178 [PMID: 24219115 DOI: 10.1111/jgh.12432]

22 **Jinjuvadia R**, Liangpunsakul S. Association between metabolic syndrome and its individual components with viral hepatitis B. *Am J Med Sci* 2014; **347**: 23-27 [PMID: 23514672 DOI: 10.1097/MAJ.0b013e31828b25a5]

23 **Li WC**, Lee YY, Chen IC, Sun C, Chiu FH, Chuang CH. Association between the hepatitis B and C viruses and metabolic diseases in patients stratified by age. *Liver Int* 2013; **33**: 1194-1202 [PMID: 23782533 DOI: 10.1111/liv.12224]

24 **Kuo YH**, Tsai MC, Kee KM, Chang KC, Wang JH, Lin CY, Lin SC, Lu SN. Associated Factors for Metabolic Syndrome in the Older Adults with Chronic Virus Hepatitis in the Community. *PLoS One* 2016; **11**: e0155544 [PMID: 27177024 DOI: 10.1371/journal.pone.0155544]

25 **Kuo YH**, Kee KM, Wang JH, Hsu NT, Hsiao CC, Chen Y, Lu SN. Association between chronic viral hepatitis and metabolic syndrome in southern Taiwan: a large population-based study. *Aliment Pharmacol Ther* 2018; **48**: 993-1002 [PMID: 30277595 DOI: 10.1111/apt.14960]

26 **Zhou Y**, Cui Y, Deng H, Yu J. Association between hepatitis B virus infection and metabolic syndrome: a retrospective cohort study in Shanghai, China. *BMC Public Health* 2014; **14**: 516 [PMID: 24885963 DOI: 10.1186/1471-2458-14-516]

27 **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults**. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486-2497 [PMID: 11368702 DOI: 10.1001/jama.285.19.2486]

28 **Grundy SM**, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112**: 2735-2752 [PMID: 16157765 DOI: 10.1161/CIRCULATIONAHA.105.169404]

29 **International Diabetes Federation.** The IDF consensus worldwide definition of metabolic syndrome. 2006. [cited 05 June 2020]. Available from: https://www.idf.org/e-library/consensus-statements/60-idfconsensus-worldwide-definitionof-the-metabolic-syndrome

30 **Alberti KG**, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; **120**: 1640-1645 [PMID: 19805654 DOI: 10.1161/CIRCULATIONAHA.109.192644]

31 **Alberti KG**, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539-553 [PMID: 9686693 DOI: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S]

32 **Chung TH**, Kim MC, Kim CS. Association between Hepatitis B Surface Antigen Seropositivity and Metabolic Syndrome. *Korean J Fam Med* 2014; **35**: 81-89 [PMID: 24724003 DOI: 10.4082/kjfm.2014.35.2.81]

33 **Choi JS**, Han KJ, Lee S, Chun SW, Kim DJ, Kim HC, Kim HM. Serum HBV surface antigen positivity is associated with low prevalence of metabolic syndrome in Korean adult men. *J Epidemiol* 2015; **25**: 74-79 [PMID: 25283312 DOI: 10.2188/jea.JE20140053]

34 **Welzel TM**, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology* 2011; **54**: 463-471 [PMID: 21538440 DOI: 10.1002/hep.24397]

35 **Wong GL**, Chan HL, Yu Z, Chan AW, Choi PC, Chim AM, Chan HY, Tse CH, Wong VW. Coincidental metabolic syndrome increases the risk of liver fibrosis progression in patients with chronic hepatitis B--a prospective cohort study with paired transient elastography examinations. *Aliment Pharmacol Ther* 2014; **39**: 883-893 [PMID: 24612251 DOI: 10.1111/apt.12658]

36 **Yu MW**, Lin CL, Liu CJ, Yang SH, Tseng YL, Wu CF. Influence of Metabolic Risk Factors on Risk of Hepatocellular Carcinoma and Liver-Related Death in Men With Chronic Hepatitis B: A Large Cohort Study. *Gastroenterology* 2017; **153**: 1006-1017.e5 [PMID: 28711626 DOI: 10.1053/j.gastro.2017.07.001]

37 **Huang YW**, Wang TC, Lin SC, Chang HY, Chen DS, Hu JT, Yang SS, Kao JH. Increased risk of cirrhosis and its decompensation in chronic hepatitis B patients with newly diagnosed diabetes: a nationwide cohort study. *Clin Infect Dis* 2013; **57**: 1695-1702 [PMID: 24051864 DOI: 10.1093/cid/cit603]

38 **Hsiang JC**, Gane EJ, Bai WW, Gerred SJ. Type 2 diabetes: a risk factor for liver mortality and complications in hepatitis B cirrhosis patients. *J Gastroenterol Hepatol* 2015; **30**: 591-599 [PMID: 25250942 DOI: 10.1111/jgh.12790]

39 **Shyu YC**, Huang TS, Chien CH, Yeh CT, Lin CL, Chien RN. Diabetes poses a higher risk of hepatocellular carcinoma and mortality in patients with chronic hepatitis B: A population-based cohort study. *J Viral Hepat* 2019; **26**: 718-726 [PMID: 30739359 DOI: 10.1111/jvh.13077]

40 **Chen CL**, Yang WS, Yang HI, Chen CF, You SL, Wang LY, Lu SN, Liu CJ, Kao JH, Chen PJ, Chen DS, Chen CJ. Plasma adipokines and risk of hepatocellular carcinoma in chronic hepatitis B virus-infected carriers: A prospective study in Taiwan. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 1659-1671 [PMID: 24895413 DOI: 10.1158/1055-9965.EPI-14-0161]

41 **Hsu CS**, Liu WL, Chao YC, Lin HH, Tseng TC, Wang CC, Chen DS, Kao JH. Adipocytokines and liver fibrosis stages in patients with chronic hepatitis B virus infection. *Hepatol Int* 2015; **9**: 231-242 [PMID: 25788201 DOI: 10.1007/s12072-015-9616-2]

42 **Chen JY**, Wang JH, Lin CY, Chen PF, Tseng PL, Chen CH, Chang KC, Tsai LS, Chen SC, Lu SN. Lower prevalence of hypercholesterolemia and hyperglyceridemia found in subjects with seropositivity for both hepatitis B and C strains independently. *J Gastroenterol Hepatol* 2010; **25**: 1763-1768 [PMID: 21039839 DOI: 10.1111/j.1440-1746.2010.06300.x]

43 **Liu PT**, Hwang AC, Chen JD. Combined effects of hepatitis B virus infection and elevated alanine aminotransferase levels on dyslipidemia. *Metabolism* 2013; **62**: 220-225 [PMID: 22938729 DOI: 10.1016/j.metabol.2012.07.022]

44 **Chiang CH**, Yang HI, Jen CL, Lu SN, Wang LY, You SL, Su J, Iloeje UH, Chen CJ; REVEAL-HBV Study Group. Association between obesity, hypertriglyceridemia and low hepatitis B viral load. *Int J Obes (Lond)* 2013; **37**: 410-415 [PMID: 22531094 DOI: 10.1038/ijo.2012.63]

45 **Zheng RD**, Xu CR, Jiang L, Dou AX, Zhou K, Lu LG. Predictors of hepatic steatosis in HBeAg-negative chronic hepatitis B patients and their diagnostic values in hepatic fibrosis. *Int J Med Sci* 2010; **7**: 272-277 [PMID: 20714438 DOI: 10.7150/ijms.7.272]

46 **Rastogi A**, Sakhuja P, Kumar A, Hissar S, Jain A, Gondal R, Sarin SK. Steatosis in chronic hepatitis B: prevalence and correlation with biochemical, histologic, viral, and metabolic parameters. *Indian J Pathol Microbiol* 2011; **54**: 454-459 [PMID: 21934202 DOI: 10.4103/0377-4929.85074]

47 **Cai S**, Ou Z, Liu D, Liu L, Liu Y, Wu X, Yu T, Peng J. Risk factors associated with liver steatosis and fibrosis in chronic hepatitis B patient with component of metabolic syndrome. *United European Gastroenterol J* 2018; **6**: 558-566 [PMID: 29881611 DOI: 10.1177/2050640617751252]

48 **Wong VW**, Wong GL, Chu WC, Chim AM, Ong A, Yeung DK, Yiu KK, Chu SH, Chan HY, Woo J, Chan FK, Chan HL. Hepatitis B virus infection and fatty liver in the general population. *J Hepatol* 2012; **56**: 533-540 [PMID: 22027575 DOI: 10.1016/j.jhep.2011.09.013]

49 **Cheng YL**, Wang YJ, Kao WY, Chen PH, Huo TI, Huang YH, Lan KH, Su CW, Chan WL, Lin HC, Lee FY, Wu JC. Inverse association between hepatitis B virus infection and fatty liver disease: a large-scale study in populations seeking for check-up. *PLoS One* 2013; **8**: e72049 [PMID: 23991037 DOI: 10.1371/journal.pone.0072049]

50 **Hui RWH**, Seto WK, Cheung KS, Mak LY, Liu KSH, Fung J, Wong DK, Lai CL, Yuen MF. Inverse relationship between hepatic steatosis and hepatitis B viremia: Results of a large case-control study. *J Viral Hepat* 2018; **25**: 97-104 [PMID: 28772340 DOI: 10.1111/jvh.12766]

51 **Joo EJ**, Chang Y, Yeom JS, Ryu S. Hepatitis B virus infection and decreased risk of nonalcoholic fatty liver disease: A cohort study. *Hepatology* 2017; **65**: 828-835 [PMID: 28035771 DOI: 10.1002/hep.28917]

52 **Nguyen KA**, Peer N, Mills EJ, Kengne AP. A Meta-Analysis of the Metabolic Syndrome Prevalence in the Global HIV-Infected Population. *PLoS One* 2016; **11**: e0150970 [PMID: 27008536 DOI: 10.1371/journal.pone.0150970]

53 **Adébayo A**, Albert DC, Ericie S, Angelo AC, Jules G, Armand W, Séraphin A, Léopold C, Gabriel A. [Prevalence, associated and predisposing factors of metabolic syndrome among people living with HIV on antiretroviral treatment in Porto Novo in 2014]. *Pan Afr Med J* 2015; **22**: 296 [PMID: 26966492 DOI: 10.11604/pamj.2015.22.296.7923]

54 **Ayodele OE**, Akinboro AO, Akinyemi SO, Adepeju AA, Akinremi OA, Alao CA, Popoola AA. Prevalence and clinical correlates of metabolic syndrome in Nigerians living with human immunodeficiency virus/acquired immunodeficiency syndrome. *Metab Syndr Relat Disord* 2012; **10**: 373-379 [PMID: 22799758 DOI: 10.1089/met.2012.0050]

55 **Berhane T**, Yami A, Alemseged F, Yemane T, Hamza L, Kassim M, Deribe K. Prevalence of lipodystrophy and metabolic syndrome among HIV positive individuals on Highly Active Anti-Retroviral treatment in Jimma, South West Ethiopia. *Pan Afr Med J* 2012; **13**: 43 [PMID: 23330034]

56 **Bosho DD**, Dube L, Mega TA, Adare DA, Tesfaye MG, Eshetie TC. Prevalence and predictors of metabolic syndrome among people living with human immunodeficiency virus (PLWHIV). *Diabetol Metab Syndr* 2018; **10**: 10 [PMID: 29483948 DOI: 10.1186/s13098-018-0312-y]

57 **Dimodi H,** Etame L, Nguimkeng B, Mbappe F, Ndoe N, Tchinda J, Ebene J, Ntentié F, Kingue G, Angie M, Paka G, Kouanfack C, Ngondi J, Enyong J. Prevalence of metabolic syndrome in HIV-infected Cameroonian patients. *World J AIDS* 2014; **4**: 85-92 [DOI: 10.4236/wja.2014.41011]

58 **Guira O**, Tiéno H, Diendéré AE, Sagna Y, Diallo I, Yaméogo B, Zoungrana L, Yaméogo TM, Bognounou R, Drabo JY. Features of metabolic syndrome and its associated factors during Highly Active Antiretroviral Therapy in Ouagadougou (Burkina Faso). *J Int Assoc Provid AIDS Care* 2016; **15**: 159-163 [PMID: 26307211 DOI: 10.1177/2325957415601503]

59 **Hirigo AT**, Tesfaye DY. Influences of gender in metabolic syndrome and its components among people living with HIV virus using antiretroviral treatment in Hawassa, southern Ethiopia. *BMC Res Notes* 2016; **9**: 145 [PMID: 26945987 DOI: 10.1186/s13104-016-1953-2]

60 **Mbunkah HA**, Meriki HD, Kukwah AT, Nfor O, Nkuo-Akenji T. Prevalence of metabolic syndrome in human immunodeficiency virus - infected patients from the South-West region of Cameroon, using the adult treatment panel III criteria. *Diabetol Metab Syndr* 2014; **6**: 92 [PMID: 25197324 DOI: 10.1186/1758-5996-6-92]

61 **Muhammad S**, Sani MU, Okeahialam BN. Cardiovascular disease risk factors among HIV-infected Nigerians receiving highly active antiretroviral therapy. *Niger Med J* 2013; **54**: 185-190 [PMID: 23901181 DOI: 10.4103/0300-1652.114591]

62 **Muyanja D**, Muzoora C, Muyingo A, Muyindike W, Siedner MJ. High prevalence of metabolic syndrome and cardiovascular disease risk among people with HIV on stable ART in Southwestern Uganda. *AIDS Patient Care STDS* 2016; **30**: 4-10 [PMID: 26683587 DOI: 10.1089/apc.2015.0213]

63 **Ngatchou W**, Lemogoum D, Ndobo P, Yagnigni E, Tiogou E, Nga E, Kouanfack C, van de Borne P, Hermans MP. Increased burden and severity of metabolic syndrome and arterial stiffness in treatment-naïve HIV+ patients from Cameroon. *Vasc Health Risk Manag* 2013; **9**: 509-516 [PMID: 24043942 DOI: 10.2147/VHRM.S42350]

64 **Nguyen KA**, Peer N, de Villiers A, Mukasa B, Matsha TE, Mills EJ, Kengne AP. Metabolic syndrome in people living with Human Immunodeficiency Virus: An assessment of the prevalence and the agreement between diagnostic criteria. *Int J Endocrinol* 2017; **2017**: 1613657 [PMID: 28392801 DOI: 10.1155/2017/1613657]

65 **Obirikorang C**, Quaye L, Osei-Yeboah J, Odame EA, Asare I. Prevalence of metabolic syndrome among HIV-infected patients in Ghana: A cross-sectional study. *Niger Med J* 2016; **57**: 86-90 [PMID: 27226681 DOI: 10.4103/0300-1652.182082]

66 **Sobieszczyk ME**, Werner L, Mlisana K, Naicker N, Feinstein A, Gray CM, Masson L, Passmore JS, Williamson C, Abdool Karim Q, Abdool Karim SS, Garrett NJ. Metabolic syndrome After HIV acquisition in South African women. *J Acquir Immune Defic Syndr* 2016; **73**: 438-445 [PMID: 27391387 DOI: 10.1097/QAI.0000000000001123]

67 **Tesfaye DY**, Kinde S, Medhin G, Megerssa YC, Tadewos A, Tadesse E, Shimelis T. Burden of metabolic syndrome among HIV-infected patients in Southern Ethiopia. *Diabetes Metab Syndr* 2014; **8**: 102-107 [PMID: 24907175 DOI: 10.1016/j.dsx.2014.04.008]

68 **Alvarez C**, Salazar R, Galindez J, Rangel F, Castaãeda ML, Lopardo G, Cuhna CA, Roldan Y, Sussman O, Gutierrez G, Cure-Bolt N, Seas C, Carcamo C, Castrillo M. Metabolic syndrome in HIV-infected patients receiving antiretroviral therapy in Latin America. *Braz J Infect Dis* 2010; **14**: 256-263 [PMID: 20835509 DOI: 10.1016/S1413-8670(10)70053-2]

69 **Bonfanti P**, De Socio GL, Marconi P, Franzetti M, Martinelli C, Vichi F, Penco G, Madeddu G, Orofino G, Valsecchi L, Vitiello P, Menzaghi B, Magni C, Ricci E. Is metabolic syndrome associated to HIV infection per se? Results from the HERMES study. *Curr HIV Res* 2010; **8**: 165-171 [PMID: 20163341 DOI: 10.2174/157016210790442731]

70 **Calza L**, Masetti G, Piergentili B, Trapani F, Cascavilla A, Manfredi R, Colangeli V, Viale P. Prevalence of diabetes mellitus, hyperinsulinaemia and metabolic syndrome among 755 adult patients with HIV-1 infection. *Int J STD AIDS* 2011; **22**: 43-45 [PMID: 21364066 DOI: 10.1258/ijsa.2010.010256]

71 **Biron A**, Bobin-Dubigeon C, Volteau C, Piroth L, Perré P, Leport C, Prazuck T, Jovelin T, Billard M, Sébille V, Bard JM, Raffi F, Biron C. Metabolic syndrome in French HIV-infected patients: Prevalence and predictive factors after 3 years of antiretroviral therapy. *AIDS Res Hum Retroviruses* 2012; **28**: 1672-1678 [PMID: 22731114 DOI: 10.1089/AID.2012.0048]

72 **Bonfanti P**, De Socio GV, Ricci E, Antinori A, Martinelli C, Vichi F, Penco G, Madeddu G, Orofino G, Valsecchi L, Rusconi S, Menzaghi B, Pocaterra D, Quirino T. The feature of Metabolic Syndrome in HIV naive patients is not the same of those treated: Results from a prospective study. *Biomed Pharmacother* 2012; **66**: 348-353 [PMID: 22705335 DOI: 10.1016/j.biopha.2012.01.005]

73 **Rivero-Juárez A**, Camacho A, Merchante N, Pérez-Camacho I, Macias J, Ortiz-Garcia C, Cifuentes C, Torre-Cisneros J, Peña J, Pineda JA, Rivero A; Grupo para el estudio de las hepatitis vı´ricas (HEPAVIR) de la Sociedad Andaluza de Enfermedades Infecciosas (SAEI). Incidence of liver damage of uncertain origin in HIV patients not co-infected with HCV/HBV. *PLoS One* 2013; **8**: e68953 [PMID: 23874824 DOI: 10.1371/journal.pone.0068953]

74 **Maurice JB**, Patel A, Scott AJ, Patel K, Thursz M, Lemoine M. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. *AIDS* 2017; **31**: 1621-1632 [PMID: 28398960 DOI: 10.1097/QAD.0000000000001504]

75 **van Welzen BJ**, Mudrikova T, El Idrissi A, Hoepelman AIM, Arends JE. A review of Non-Alcoholic Fatty Liver Disease in HIV-infected patients: The next big thing? *Infect Dis Ther* 2019; **8**: 33-50 [PMID: 30607807 DOI: 10.1007/s40121-018-0229-7]

76 **Paruk IM**, Pirie FJ, Motala AA. Non-alcoholic fatty liver disease in Africa: A hidden danger. *Glob Health Epidemiol Genom* 2019; **4**: e3 [PMID: 31019719 DOI: 10.1017/gheg.2019.2]

77 **Hoffmann CJ**, Hoffmann JD, Kensler C, van der Watt M, Omar T, Chaisson RE, Martinson NA, Variava E. Tuberculosis and hepatic steatosis are prevalent liver pathology findings among HIV-infected patients in South Africa. *PLoS One* 2015; **10**: e0117813 [PMID: 25668620 DOI: 10.1371/journal.pone.0117813]

78 **Nishijima T**, Gatanaga H, Shimbo T, Komatsu H, Nozaki Y, Nagata N, Kikuchi Y, Yanase M, Oka S. Traditional but not HIV-related factors are associated with nonalcoholic fatty liver disease in Asian patients with HIV-1 infection. *PLoS One* 2014; **9**: e87596 [PMID: 24498148 DOI: 10.1371/journal.pone.0087596]

79 **Benmassaoud A**, Ghali P, Cox J, Wong P, Szabo J, Deschenes M, Osikowicz M, Lebouche B, Klein MB, Sebastiani G. Screening for nonalcoholic steatohepatitis by using cytokeratin 18 and transient elastography in HIV mono-infection. *PLoS One* 2018; **13**: e0191985 [PMID: 29381754 DOI: 10.1371/journal.pone.0191985]

80 **Lombardi R**, Sambatakou H, Mariolis I, Cokkinos D, Papatheodoridis GV, Tsochatzis EA. Prevalence and predictors of liver steatosis and fibrosis in unselected patients with HIV mono-infection. *Dig Liver Dis* 2016; **48**: 1471-1477 [PMID: 27623186 DOI: 10.1016/j.dld.2016.08.117]

81 **Morse CG**, McLaughlin M, Matthews L, Proschan M, Thomas F, Gharib AM, Abu-Asab M, Orenstein A, Engle RE, Hu X, Lempicki R, Hadigan C, Kleiner DE, Heller T, Kovacs JA. Nonalcoholic Steatohepatitis and Hepatic Fibrosis in HIV-1-Monoinfected Adults With Elevated Aminotransferase Levels on Antiretroviral Therapy. *Clin Infect Dis* 2015; **60**: 1569-1578 [PMID: 25681381 DOI: 10.1093/cid/civ101]

82 **Husain NE**, Noor SK, Elmadhoun WM, Almobarak AO, Awadalla H, Woodward CL, Mital D, Ahmed MH. Diabetes, metabolic syndrome and dyslipidemia in people living with HIV in Africa: Re-emerging challenges not to be forgotten. *HIV AIDS (Auckl)* 2017; **9**: 193-202 [PMID: 29184449 DOI: 10.2147/HIV.S137974]

83 **Prioreschi A**, Munthali RJ, Soepnel L, Goldstein JA, Micklesfield LK, Aronoff DM, Norris SA. Incidence and prevalence of type 2 diabetes mellitus with HIV infection in Africa: A systematic review and meta-analysis. *BMJ Open* 2017; **7**: e013953 [PMID: 28360243 DOI: 10.1136/bmjopen-2016-013953]

84 **Njuguna B**, Kiplagat J, Bloomfield GS, Pastakia SD, Vedanthan R, Koethe JR. Prevalence, Risk Factors, and Pathophysiology of Dysglycemia among People Living with HIV in Sub-Saharan Africa. *J Diabetes Res* 2018; **2018**: 6916497 [PMID: 30009182 DOI: 10.1155/2018/6916497]

85 **Tshikuka JG**, Magafu MGMD, Rankgoane-Pono G, Mwita JC, Masupe T, Hamda SG, Tapera R, Molefi M, Tshibangu J, Tlhakanelo JT. Overweight and Obesity among Recipients of Antiretroviral Therapy at HIV Clinics in Gaborone, Botswana: Factors Associated with Change in Body Mass Index. *AIDS Res Treat* 2020; **2020**: 8016791 [PMID: 32395339 DOI: 10.1155/2020/8016791]

86 **Lacombe K**, Bottero J, Lemoine M, Boyd A, Girard PM. HIV/hepatitis B virus co-infection: current challenges and new strategies. *J Antimicrob Chemother* 2010; **65**: 10-17 [PMID: 19900950 DOI: 10.1093/jac/dkp414]

87 **Singh KP**, Crane M, Audsley J, Avihingsanon A, Sasadeusz J, Lewin SR. HIV-hepatitis B virus coinfection: epidemiology, pathogenesis, and treatment. *AIDS* 2017; **31**: 2035-2052 [PMID: 28692539 DOI: 10.1097/QAD.0000000000001574]

88 **Lien K**, Mayer W, Herrera R, Rosbe K, Tugizov SM. HIV-1 proteins gp120 and tat induce the epithelial-mesenchymal transition in oral and genital mucosal epithelial cells. *PLoS One* 2019; **14**: e0226343 [PMID: 31869348 DOI: 10.1371/journal.pone.0226343]

89 **Nagu TJ**, Kanyangarara M, Hawkins C, Hertmark E, Chalamila G, Spiegelman D, Mugusi F, Fawzi W. Elevated alanine aminotransferase in antiretroviral-naïve HIV-infected African patients: magnitude and risk factors. *HIV Med* 2012; **13**: 541-548 [PMID: 22416813 DOI: 10.1111/j.1468-1293.2012.01006.x]

90 **Mohr R**, Schierwagen R, Schwarze-Zander C, Boesecke C, Wasmuth JC, Trebicka J, Rockstroh JK. Liver Fibrosis in HIV Patients Receiving a Modern cART: Which Factors Play a Role? *Medicine (Baltimore)* 2015; **94**: e2127 [PMID: 26683921 DOI: 10.1097/MD.0000000000002127]

91 **Rajbhandari R**, Jun T, Khalili H, Chung RT, Ananthakrishnan AN. HBV/HIV coinfection is associated with poorer outcomes in hospitalized patients with HBV or HIV. *J Viral Hepat* 2016; **23**: 820-829 [PMID: 27291562 DOI: 10.1111/jvh.12555]

92 **Seto WK**, Fung J, Cheung KS, Mak LY, Hui RW, Liu KS, Lai CL, Yuen MF. Body-mass index is associated with fibrosis regression during long-term nucleoside analogue therapy in chronic hepatitis B. *Aliment Pharmacol Ther* 2016; **44**: 1071-1079 [PMID: 27659292 DOI: 10.1111/apt.13804]

93 **Shaheen AA**, AlMattooq M, Yazdanfar S, Burak KW, Swain MG, Congly SE, Borman MA, Lee SS, Myers RP, Coffin CS. Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers. *Aliment Pharmacol Ther* 2017; **46**: 599-604 [PMID: 28707319 DOI: 10.1111/apt.14218]

94 **Aberg JA**, Sponseller CA, Ward DJ, Kryzhanovski VA, Campbell SE, Thompson MA. Pitavastatin *versus* pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial. *Lancet HIV* 2017; **4**: e284-e294 [PMID: 28416195 DOI: 10.1016/S2352-3018(17)30075-9]

**Footnotes**

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

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** June 26, 2020

**First decision:** September 21, 2020

**Article in press:** October 12, 2020

**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

**P-Reviewer:** Tugizov SM **S-Editor:** Huang P **L-Editor:** Filipodia **P-Editor:** Xing YX

**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 values2 or BMI > 30 kg/m2 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 definitions2 | 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/m2 |
| 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.

**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 factors1 |
| Adébayo *et al*[53] | Benin | Cross-sectional | 244 | IDF | 18.4% | - |
| Ayodele *et al*[54] | Nigeria | Cross-sectional | 291 | NCEP/ATP III; IDF; JIS | 12.7%; 17.2%; 21.0% | - |
| Berhane *et al*[55] | Ethiopia | Cross-sectional | 313 | NCEP/ATP III | 21.1% | HAART > 12 mo, female sex |
| Bosho *et al*[56] | Ethiopia | Cross-sectional | 286 | NCEP/ATP III; IDF; JIS | 23.5%; 20.5%; 27.6% | BMI ≥ 25 kg/m2, formal education |
| Dimodi *et al*[57] | Cameroon | Cross-sectional | 463 | IDF; NCEP/ATP III | 32.8%; 30.7% | - |
| Guira *et al*[58] | Burkina Faso | Cross-sectional | 300 | IDF | 18.0% | - |
| Hirigo *et al*[59] | Ethiopia | Cross-sectional | 185 | IDF; NCEP/ATP III | 24.3%; 17.8% | BMI ≥ 25 kg/m2, female sex, age > 40 yr |
| Mbunkah *et al*[60] | Cameroon | Cross-sectional | 173 | NCEP/ATP III | 15.6% | - |
| Muhammad *et al*[61] | Nigeria | Cross-sectional | 200 | NCEP/ATP III | 15.0% | - |
| Muyanja *et al*[62] | Uganda | Cross-sectional | 250 | AHA/NHLBI | 58.0% | Female sex, age > 40 yr |
| Ngatchou *et al*[63] | Cameroon | Cross-sectional | 108 | AHA/NHLBI | 47.0% | - |
| Nguyen *et al*[64] | South Africa | Cross-sectional | 748 | JIS; IDF; NCEP/ATP III | 28.2%; 26.5%; 24.1% | - |
| Obirikorang *et al*[65] | Ghana | Cross-sectional | 433 | NCEP/ATP III; WHO; IDF | 48.3%; 24.5%; 42.3% | - |
| Sobieszczyk *et al*[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 *et al*[67] | Ethiopia | Cross-sectional | 374 | IDF; NCEP/ATP III | 25.0%; 16.8% | Female sex, older age, BMI ≥ 25 kg/m2, 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.