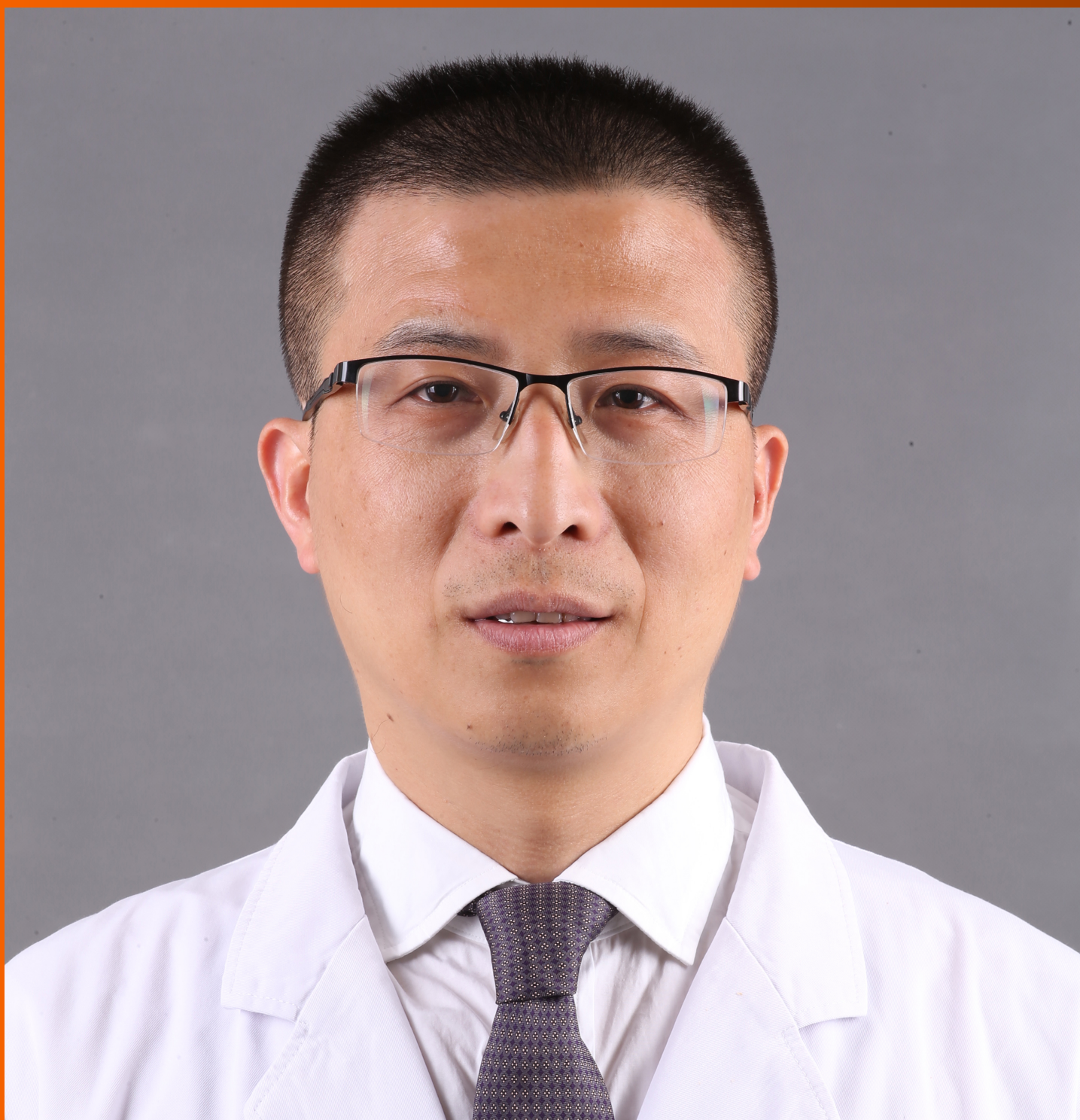


World Journal of *Hepatology*

World J Hepatol 2022 July 27; 14(7): 1269-1529



EDITORIAL

- 1269 Checkpoint inhibitor-induced hepatotoxicity: Role of liver biopsy and management approach
Bessone F, Bjornsson ES

REVIEW

- 1277 Gut microbiota contribution to hepatocellular carcinoma manifestation in non-alcoholic steatohepatitis
Liakina V, Strainiene S, Stundiene I, Maksimaityte V, Kazenaite E
- 1291 Hepatogenous diabetes: Knowledge, evidence, and skepticism
Kumar R, García-Compeán D, Maji T
- 1307 Small extracellular vesicles and liver diseases: From diagnosis to therapy
Tsuchiya A, Natsui K, Ishii Y, Koseki Y, Takeda N, Tomiyoshi K, Yamazaki F, Yoshida Y, Terai S
- 1319 Hepatocellular carcinoma and microbiota: Implications for clinical management and treatment
Spanu D, Pretta A, Lai E, Persano M, Donisi C, Mariani S, Dubois M, Migliari M, Saba G, Ziranu P, Pusceddu V, Puzzone M, Astara G, Scartozzi M

MINIREVIEWS

- 1333 Challenge of managing hepatitis B virus and hepatitis C virus infections in resource-limited settings
Said ZNA, El-Sayed MH
- 1344 Alfapump® implantable device in management of refractory ascites: An update
Weil-Verhoeven D, Di Martino V, Stirnimann G, Cervoni JP, Nguyen-Khac E, Thévenot T

ORIGINAL ARTICLE

Basic Study

- 1357 Tissue pad degradation of ultrasonic device may enhance thermal injury and impair its sealing performance in liver surgery
Kajiwara M, Fujikawa T, Hasegawa S
- 1365 Regulation of PPAR-γ activity in lipid-laden hepatocytes affects macrophage polarization and inflammation in nonalcoholic fatty liver disease
Li XY, Ji PX, Ni XX, Chen YX, Sheng L, Lian M, Guo CJ, Hua J

Clinical and Translational Research

- 1382 Transcriptome changes in stages of non-alcoholic fatty liver disease
Aljabban J, Rohr M, Syed S, Khorfan K, Borkowski V, Aljabban H, Segal M, Mukhtar M, Mohammed M, Panahiazar M, Hadley D, Spengler R, Spengler E

Retrospective Cohort Study

- 1398** Cardiac risk factors limiting survival to liver transplantation in patients with nonalcoholic fatty liver disease

Delicce M, Mauch J, Joseph A, Lyu R, Kren H, Bartow R, Ferchill D, Fares M, Wakim-Fleming J

Retrospective Study

- 1408** Differential distribution of gene polymorphisms associated with hypercholesterolemia, hypertriglyceridemia, and hypoalphalipoproteinemia among Native American and Mestizo Mexicans

Torres-Valadez R, Roman S, Ojeda-Granados C, Gonzalez-Aldaco K, Panduro A

- 1421** Effect of thrombocytopenia and platelet transfusion on outcomes of acute variceal bleeding in patients with chronic liver disease

Biswas S, Vaishnav M, Pathak P, Gunjan D, Mahapatra SJ, Kedia S, Rout G, Thakur B, Nayak B, Kumar R, Shalimar

Observational Study

- 1438** Polymorphism AGT2 (rs4762) is involved in the development of dermatologic events: Proof-of-concept in hepatocellular carcinoma patients treated with sorafenib

Sapena V, Iavarone M, Boix L, Facchetti F, Guarino M, Sanduzzi Zamparelli M, Granito A, Samper E, Scartozzi M, Corominas J, Marisi G, Diaz A, Casadei-Gardini A, Gramantieri L, Lampertico P, Morisco F, Torres F, Bruix J, Reig M

- 1459** Hepatobiliary phases in magnetic resonance imaging using liver-specific contrast for focal lesions in clinical practice

Fernandes DA, Dal Lago EA, Oliver FA, Loureiro BMC, Martins DL, Penachim TJ, Barros RHO, Araújo Filho JAB, Eloy da Costa LB, da Silva AMO, de Ataíde EC, Boin IFSF, Caserta NMG

- 1470** Efficacy and safety of COVID-19 vaccination in patients with cirrhosis

Ivashkin V, Ismailova A, Dmitrieva K, Maslennikov R, Zharkova M, Aliev S, Bakhitov V, Marcinkevich V

- 1480** Pre-sarcopenia and Mac-2 binding protein glycosylation isomer as predictors of recurrence and prognosis of early-stage hepatocellular carcinoma

Nakai M, Morikawa K, Hosoda S, Yoshida S, Kubo A, Tokuchi Y, Kitagataya T, Yamada R, Ohara M, Sho T, Suda G, Ogawa K, Sakamoto N

- 1495** Hepatitis C virus burden: Treating and educating people without prejudice

Merola E, Menotti E, Branz G, Michielan A, Seligmann S, Ratti A, Agugiaro F, Moser L, Vettori G, Franceschini A, Mantovani W, Pertile R, de Pretis G, Pravadelli C

Prospective Study

- 1504** Volumetric assessment of hepatic grafts using a light detection and ranging system for 3D scanning: Preliminary data

Katsanos G, Karakasi KE, Karolos IA, Kofinas A, Antoniadis N, Tsioukas V, Tsoulfas G

CASE REPORT

- 1512** Hepatitis B virus markers in hepatitis B surface antigen negative patients with pancreatic cancer: Two case reports

Batskikh S, Morozov S, Kostyushev D

- 1520** "Starry liver" - Von Meyenburg complex clinical case presentation and differential diagnosis discussion: A case report

Priadko K, Niosi M, Vitale LM, De Sio C, Romano M, De Sio I

RETRACTION NOTE

- 1528** Retraction Note: Screening and identification of bioactive compounds from citrus against non-structural protein 3 protease of hepatitis C virus genotype 3a by fluorescence resonance energy transfer assay and mass spectrometry

Khan M, Rauf W, Habib FE, Rahman M, Iqbal M

ABOUT COVER

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Challenge of managing hepatitis B virus and hepatitis C virus infections in resource-limited settings

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Abstract

The global burden of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and coinfection represents a major public health concern, particularly in resource-limited settings. Elimination of HCV by 2030 has become foreseeable, with effective direct-acting antiviral oral therapies and the availability of affordable generics in low-and-middle-income countries (LMICs). However, access to oral nucleos(t)ide therapy for HBV remains critical and is limited outside the existing global HIV program platforms despite affordable prices. Prevention of mother-to-child transmission of HBV through scaling up of birth dose implementation in LMICs is essential to achieve the 2030 elimination goal. Most individuals living with HBV and/or HCV in resource-limited settings are unaware of their infection, and with improved access to medications, the most significant barrier remains access to affordable diagnostics and preventive strategies. The coronavirus disease 2019 pandemic interrupted hepatitis elimination programs, albeit offered opportunities for improved diagnostic capacities and raised political awareness of the critical need for strengthening health care services and universal health coverage. This review underpins the HBV and HCV management challenges in resource-limited settings, highlighting the current status and suggested future elimination strategies in some of these countries. Global efforts should continue to improve awareness and political commitment. Financial resources should be secured to access and implement comprehensive strategies for diagnosis and linkage to care in resource-constrained settings to fulfill the 2030 elimination goal.

Key Words: Hepatitis B virus/hepatitis C virus; Chronic hepatitis; Resource-limited settings; HBV and HCV elimination

Core Tip: This minireview presents the data and challenges associated with hepatitis B virus (HBV) and hepatitis C virus (HCV)/coinfection in resource-limited settings. It also underlines the key gaps and strategies for elimination of HBV and HCV infections in the low and middle-income countries. Global efforts should continue to improve awareness and political commitment. Equally important is securing financial resources for access and implementation of comprehensive strategies for diagnosis and linkage to care in resource-constrained settings to fulfill the 2030 elimination goal.

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INTRODUCTION

Despite the coronavirus disease 2019 (COVID-19) pandemic, viral hepatitis B and C still claim thousands of lives daily. Both viruses are responsible for 96% of all hepatitis-related mortality worldwide because of the chronicity of these diseases. Globally, approximately 325 million people have viral hepatitis B and C, and most of them are undiagnosed or untreated[1].

Low-income countries (LICs) have a high implication of hepatitis B virus (HBV) infection, with limited availability of detection, prevention, and management[2,3]. The incidence and prevalence of HBV infection are 9.2 and 7.4 times higher, respectively, in LICs than in high-income countries. Anyhow, the proportion of diagnosed subjects decreases from 18% in high-income countries to 0.8% in LICs[2]. Moreover, among the diagnosed individuals the proportion of those accessing therapy, also decreases from 14% in high-income countries to 9% in LICs[2]. Different programs often lead to interventions to prevent viral hepatitis, *e.g.*, immunization, blood transfusion services, and infection control measures. As a result, the proportion of hepatitis C virus (HCV) infected individuals who are diagnosed is higher (46%) in high-income countries than in low- and middle-income countries (LMICs) (6%). Furthermore, annual rates of treatment initiation are higher in high-income countries (8%) than in LMICs (2%)[2]. In 2015, access to direct-acting antivirals (DAAs) was low in LMICs; therefore, the projected cure rates were lower in LMICs than in high-income countries. However, the access patterns are changing rapidly with the availability of affordable generics[2].

Coinfection with HBV and HCV is not uncommon, particularly in LMICs. Although the primary site for HBV and HCV replication is the hepatocyte, their life cycles are totally different. HCV is an RNA virus that replicates in the cytoplasm, while HBV is a DNA virus that replicates in the nucleus. But, both have RNA replicative intermediates and theoretically can interact in coinfecting cells, inducing different viral expression and serologic patterns[4]. There is a lack of sufficient data regarding the intracellular interplay between both viruses because of a proper *in vitro* cellular model. Superinfection is the dominant mechanism for developing coinfection, whereas HCV superinfection is more common[5]. In HBV and HCV coinfection and immune-related regulations, HCV is usually dominant and thus overt, whereas HBV presents either an overt or occult pattern[4,6,7]. However, the possibility that HCV and HBV can alternate their dominance during coinfection cannot be excluded[8]. Coinfection with HCV and HBV can result in the spontaneous viral clearance of either one or both viruses, chronic infection, or development of acute fulminant hepatitis[5]. Chronic coinfection is associated with adverse hepatic outcomes than HBV or HCV mono-infection[9], warranting effective treatment[10]. It is noted that disease progression is faster in HBV/HCV dual infection than in those with mono-infection[5]. Recently, an extensive study was conducted on 8513 chronic HCV patients, of whom 87 were positive for both hepatitis B core antibody (HBcAb) and HBV surface antigen (HBsAg), 1577 were only HBcAb positive, and 6849 were HBcAb negative. The results suggested that prior HBV infection adversely affects liver health despite apparent clearance[11]. The risk of developing hepatocellular carcinoma (HCC) was also reported to be higher in patients with dual chronic HCV/HBV infection than that with mono-infection[12]. It was also shown that dual/triple infection by HIV/HBV/HCV increases the risk of HBV/HCV-associated HCC[13]. Thus, it is important to recognize coinfection, where viral interaction has implications for disease severity, clinical picture, and management strategy[4]. The current success in treating HCV infection highlights the need for proper selection of antiviral regimens for long-term suppression of any concurrent viral coinfection[13].

The current review addresses the current challenges in managing HBV and HCV infections in resource-limited settings and suggested elimination strategies in some of these countries to achieve the 2030 goal.

WHO 2030 ELIMINATION GOAL FOR HBV AND HCV

In May 2016, the World Health Assembly adopted the Global Health Sector Strategy (GHSS) on Viral Hepatitis 2016-2021, targeting the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65% and expanding HCV diagnoses from < 20% to 90% and number of eligible individuals getting HCV treatment from < 10% to 80%). The GHSS also aims to decrease hepatitis incidence from 6-10 million cases to 0.9 million cases and decrease annual hepatitis mortality from 1.4 million to 0.5 million by 2030[14]. To achieve the above-mentioned goal, five core intervention areas are documented by the GHSS: (1) HBV vaccination; (2) prevention of mother-to-child transmission of HBV; (3) injection and blood safety; (4) harm reduction; and (5) testing and treatment of HBV and HCV[14]. Different countries have developed their strategies for elimination. By November 2017, 84 countries had developed hepatitis control programs[15]. In addition, 62% of HCV-infected persons live in countries that can buy generic DAAs (LMICs)[16]. According to the Polaris records, 18 countries are working toward elimination, and 12 countries, Australia, Egypt, France, Georgia, Iceland, Italy, Japan, Mongolia, the Netherlands, Spain, Switzerland, and the UK, are on track to meet hepatitis C elimination targets[16]. In contrast, only 20 countries will not meet the 2030 and 2020 targets for HBV prevalence, 12 of which are in sub-Saharan Africa (SSA)[17].

The global hepatitis prevention, testing, treatment, and immunisation programmes were disrupted as a result of the COVID-19 pandemic. Implementing and maintaining successful interventions across the full range of hepatitis-related critical services is key to meeting the 2030 viral hepatitis elimination targets and goal. This spurred the theme "Hepatitis Can't Wait" for World Hepatitis Day 2021, which aims to ensure the longterm viability of viral hepatitis services and to investigate opportunities presented by the COVID-19 pandemic[1].

HIGH PREVALENCE AREAS FOR HBV AND HCV IN RESOURCE-LIMITED SETTINGS

Globally, viral hepatitis B and C are the most common causes of liver cancer, leading to 1.100 million deaths every year[1], comparable to the number of deaths caused by tuberculosis and higher than that caused by HIV and malaria[2]. Viral hepatitis is now ranked as the seventh leading cause of mortality worldwide[18]. Despite the fact that LMICs have implemented universal HBV vaccination as part of their expanded immunisation program, a previous WHO Global Hepatitis Report showed that the number of HBsAg-positive persons was highest in the WHO Western Pacific Region (115 million, prevalence estimated as 6.2%; 95% uncertainty interval (UI) 5.1-7.6) and African Region (60 million, prevalence estimate 6.1%; 95% UI 4.6-8.5), which together accounted for 68% of the global burden. Approximately 2.7 million of the 36.7 million individuals living with HIV are also infected with HBV, with a 7.4% global HBV prevalence in HIV-infected persons[2]. In an Egyptian community-based cross-sectional study of 3600 children aged 9 months to 16 years who were fully vaccinated with HBV vaccine during infancy, seroprotection was detected in 57.2 percent, HBsAg was positive in 0.11 percent, and breakthrough infection was 0.36 percent and 0.39 percent, depending on anti-HBc and DNA detection positivity, respectively[19].

Remarkably, the burden of HCV is increasing over time and is affecting all regions as a mostly "silent pandemic"[20], with significant disparities between and within nations.

The WHO Eastern Mediterranean Region (2.3%), followed by the European Region (1.5%), has the highest reported prevalence of HCV[2]. However, reports from Egypt have suggested a decrease in incidence over time[21]. In most LMICs, the prevalence of HCV infection is 2%[22].

Worldwide, most of chronic hepatitis B patients acquire infection at birth or in early childhood, and perinatal or horizontal transmission dominates in SSA and Asia[23]. HCV infection is most typically linked to unsafe health and injection practices in healthcare institutions with insufficient infection control measures, particularly in resource-limited settings[24].

HBV/HCV coinfection prevalence is about 5%-20% in HBsAg-positive patients and 2%-10% in HCV-positive patients, with rather different geographical distributions[25]. A study conducted in Cameroon between January 2008 and December 2014 on 524 anti-HCV-positive patients found a low coinfection rate with HBV (3.6%)[26], notably, however, the prevalence of HBV/HCV coinfection is not known or underestimated in cases with occult HBV infection[27]. HCV superinfection in patients with chronic HBV has been reported as the most common clinical feature of coinfection in the Asia-Pacific Region[27]. A recent systematic review and meta-analysis from India revealed a prevalence of 1.89% for HBV/HCV coinfection[27]. The prevalence was 0.16% among 3750 patients at a tertiary care hospital in Barabanki, Uttar Pradesh[28]. An estimate of the global prevalence of HBV/HCV coinfection is critical for developing testing and care cascades, particularly in resource-limited settings.

DIAGNOSTIC CHALLENGES AND EXPENSES NEEDED TO ACCESS DIAGNOSTICS IN RESOURCE-LIMITED SETTINGS

The indicator for treatment is the proportion of infected persons diagnosed and thus underwent the treatment protocol. Early detection of chronic HBV/HCV infection is critical for initiating therapy and thus delaying the progression of liver damage.

However, a recent WHO report emphasized the limited access to affordable hepatitis testing, where; only 9% of HBV-infected persons (22 million) and 20% of HCV-infected persons (14 million) have been diagnosed. This report dictates the acceleration of the diagnosis rate of such infections by tracking those already infected and linking them to treatment[2]. In low- and middle-income settings, it is estimated that less than 1% of chronic HBV or HCV patients know their illness, because of lack of awareness, limited facilities or services, limited access to reliable and low-cost HBV and HCV diagnostics, poor hepatitis surveillance programs, and lack of political and financial commitment[3]. Meanwhile, those who have HBV and HCV co-infections are untreated and unaware of their infection[29].

A recent modeling study in 120 countries included a literature review of PubMed and Embase, followed by interviews with experts, to quantify the historical epidemiology of HBV infection found that in 2016, the global prevalence of HBsAg was 3.9% (95% UI 3.4-4.6). Of these infections, 10% were diagnosed; only 5% eligible for treatment received antiviral therapy, and less than 1% of mothers with high viral loads accessed antiviral treatment to decrease mother-to-child transmission[17]. Notably, the cost of diagnostics remains one of the most significant barriers in LMICs. A report released in 2017 showed increased demand for HCV diagnostics in 29 LMICs, representing 80% of absolute HCV viremic burden in LMICs, and in countries with high relative prevalence and active HCV programs. In middle-income countries, laboratory-based immunoassays are mainly used for HCV screening, while for cost and accessibility reasons, most LICs use rapid diagnostic tests (RDTs)[30]. WHO proposes using RDTs, viral load (VL) testing, and DAAs in a streamlined screening and treatment strategy[31].

It was found that 79% of the projected demand for VL assays was driven by four countries (China, Egypt, Pakistan, and India), with 36% of the total demand being driven by Egypt. The prices of HCV VL tests remain high in most countries (from \$15–30 per test in the public sector to \$60–200 per test in the private sector)[30].

IMPACT OF ANTIVIRAL THERAPY ON HBV/HCV REACTIVATION

Hepatitis B and hepatitis C dual infection have a negative impact on the prognosis of liver disease, but the data is insufficient, and no clear treatment guidelines are known. Because of the interaction between both viruses and the possibility for reactivation of either virus with antiviral therapy directed against only one of them, treatment decision is not a straightforward task[4]. Before implementing antiviral therapy, full serological and virological evaluations are required to verify the activity of each virus and choose the optimal antiviral regimen[8]. The general management approach is to treat the dominant virus as a mono-infection and then monitor for reactivation of the other one. HCV likes to be the priority target to be managed in HBV/HCV coinfected patients with active hepatitis C. Treatment of HCV showed that HBV breakthrough infection and reactivation have been recorded by many researchers[32, 33]. However, for coinfected patients with active hepatitis B or with established cirrhosis, more researches are needed to determine the optimal regimen to manage both viruses simultaneously[8]. Advanced fibrosis was reported to be common in HBV/HCV-coinfected patients (58%) than in HBV mono-infections (32%, $P < 0.0001$), but the frequency was similar to that in HCV-mono-infections (52%, $P = 0.3142$). Decompensated cirrhosis was found to be common in coinfections (11%) than in either HBV or HCV-mono-infections (2%, $P = 0.0002$) and (4%, $P = 0.0275$) respectively[34]. A recent Egyptian study reviewed data extracted from the National Network of Treatment Centers database for HCV viremic patients diagnosed during the national campaign for HCV elimination (October 2018–April 2019). Among 297965 patients who underwent HBsAg testing, 2347 patients (0.8%) were positive. HBsAg +ve patients showed less advanced fibrosis by FIB-4 ($P < 0.01$). Only 14% of HBsAg +ve patients showed liver cirrhosis by ultrasound and two patients had HCC[35].

The DAAs are more effective for HCV clearance than interferon (IFN)-based therapy, exhibiting better tolerability and cure rates $> 95\%$ [10,36]. A retrospective study including 40 HBV/HCV dually infected patients to assess their clinical profiles and treatment outcomes showed DAAs are efficient for HCV eradication and recommended screening for HBV and monitoring for reactivation[37]. A systematic review and meta-analysis evaluated the risk of HBV reactivation following treatment for HCV infection with DAAs in patients with active or resolved HBV infection. The study showed that HBV reactivation occurred earlier and was clinically significant in dually infected chronic hepatitis C patients with overt and occult HBV treated with pan-oral DAAs than in those treated with IFN-based therapy. HBV screening was, therefore, recommended for the management of patients during pan-oral DAA therapy[38]. An updated systematic review and meta-analysis documented frequent HBV reactivation in dually infected chronic HBV and HCV patients receiving DAA therapy, albeit a rare encounter among patients with resolved HBV infection. Therefore, use of antiviral prophylaxis might be

warranted in HBsAg positive patients, particularly those with quantifiable HBV DNA[39].

ACCESS TO MEDICINE/PREVENTIVE MEASURES FOR HBV AND HCV IN RESOURCE-LIMITED SETTINGS

Treatment of HBV infections has been possible since 1985 and has progressively improved, first with IFN-based therapy and subsequently with the development of new medicines[2]. In 2015[40], the WHO prepared a recommendation to include nucleos(t)ide analogs with high barriers to resistance (*i.e.*, Tenofovir and Entecavir). Both compounds are easy to be given (one pill a day), highly effective, have few side effects, and induce relatively little resistance, but rarely result in cure[2].

Although HBV treatment is available through the WHO HIV programs in LMICs, access to HBV-monoinfected individuals is quite limited. Nucleos(t)ide analogs that are active against HBV are currently used as part of antiretroviral combinations and are taken by most HIV patients[41]. In addition, Tenofovir is now recommended for use as part of first-line treatment for HIV and to treat chronic HBV infection[2]. Thus, extension of Tenofovir-based treatment for HIV will provide effective treatment for HBV infection for individuals dually infected with HIV and HBV and will prevent transmission of HBV from mother-to-child[42]. However, data are scarce on the actual coverage of Tenofovir-based treatment for patients infected with HIV and HBV[2]. The Polaris Observatory records showed that only 5% of patients eligible for HBV treatment were treated, and most of these patients were from high-income countries[17]. This shows that HBV/HCV mono- and co-infections are underdiagnosed and undertreated in resource-limited settings.

The São Paulo Declaration on Hepatitis from the World Hepatitis Summit in 2017 recommended that LMICs promote fair access to and availability of high-quality, effective, safe diagnostics, vaccines, services, and treatment and make them affordable at the country level[43]. However, it was recognized that the proportion treated with WHO-recommended antivirals of those individuals diagnosed with HBV infection did not more than 8% (1.7 million patients). Among patients diagnosed with chronic HCV infection, 7% began treatment in 2015 (1.1 million persons). As of 2015, a cumulative total of 5.5 million chronic HCV patients had ever received treatment, but most of these treatments were older, less effective IFN-based regimens[2]. The WHO report following the World Hepatitis Summit in Brazil in 2017 emphasized that 3 million people could get treatment for HCV within the last two years, and an additional 2.8 million people started lifelong treatment for HBV infection in 2016[43].

The WHO-recommended treatment of HBV infection is available in a generic form in most LMICs and costs as little as US\$30 for a year of treatment. The prices of WHO-recommended DAAs for HCV vary substantially (US\$200–45 000 for a curative course), but prices have been dropping, and most LMICs should be able to buy generic medicines at affordable prices[2,43]. Currently, HCV can be treated within 8–12 wk with highly effective DAAs and high cure rates[44,45]. Introducing locally produced pharmaceutical products paves the way for further lowering prices. Prices for a full treatment course have been reported to be as low as US\$45 in Egypt, which is considered an LMIC, yet many countries are not accessing these low prices[46]. Since October 2014, treatment in Egypt has been established on DAAs, and as of March 2017, at least a million individuals have obtained treatment in the public sector at the expense of the State (with more being treated in the private sector). Through the 100 Million Healthy Lives Initiative, the country has undertaken an ambitious model elimination program with a treatment scale-up. Egypt is also actively testing the general population (18–59y) to eliminate HCV[2]. A national population-screening program was initiated in October 2018[46]. Nearly 49.6 million individuals were screened, of whom approximately 2.2 million were seropositive for HCV and were referred for evaluation and treatment[47]. Uniquely, Egypt implemented a school screening program testing more than 9 million students above the age of 12 years, linking them to treatment, but COVID-19 disrupted school attendance and the program temporarily. With the support of the WHO, Egypt pledged to provide testing and treatment for one million persons in fourteen African countries that bear a high hepatitis burden[48]. Similarly, a collaborative simplified public health approach was used to support a hepatitis C elimination program in seven countries, including Cambodia, India, Indonesia, Myanmar, Nigeria, Rwanda, and Vietnam (with anti-HCV antibody prevalence ranging from 0.85 percent to 4 percent), with drug and diagnostic costs as low as US\$80 per patient (country dependent). By December 2019, over 5900 healthcare personnel had received hepatitis C training, over two million patients had been screened, and over 120000 patients had begun treatment, with cure rates above 90% [49].

Gaining access to preventive strategies in LMICs remains challenging. Safe injections reduce HCV transmission by 70%. Globally, 5% of health-care-related injections remain unsafe, with about 1.75 million new HCV infections occurring worldwide in 2015[2]. Access to safe injection programs and devices is limited and remains a major contributing factor to the continuous transmission of blood-borne infections in resource-limited settings.

Prevention of neonatal and early childhood infection with HBV is also crucial for preventing chronic infection and further complications[18]. Universal infant and birth dose HBV vaccines to reduce mother-to-child transmission remain key strategies for the prevention and control of the HBV epidemic[50]. In

1991, the WHO-recommended inclusion of HBV vaccines into the Expanded Program of Immunization in all countries[51], and in 2009, the WHO-recommended the use of the HBV birth dose vaccine in all countries[52], followed by two or three doses to complete the primary series[2]. In 2015, the worldwide coverage of the three doses of HBV vaccine in infancy reached 84% (90% is the global target), and the coverage was 39% for the initial birth dose vaccination (global target 50% by 2020 and 90% by 2030), with a consequent reduction of HBV among children to 1.3%[2]. The latest WHO reports estimate that the proportion of children under five years of age chronically infected with HBV dropped to just under 1% in 2019, from 5% in the pre-vaccine era between the 1980s and early 2000s[53]. However, access to hepatitis B immunoglobulin and the birth dose of the HBV vaccine remains limited in LICs and needs to be increased to achieve global elimination goals. Globally, it was estimated that only 42% of children have access to the birth dose of the HBV vaccine, where, low coverage of the vaccine in some regions, particularly in SSA, is documented[1]. All immunization programs should use delivery of hepatitis B birth dose vaccine as a performance indicator[22]. In SSA, however, where qualified birth attendants deliver barely 50% of newborns, WHO estimates that birth dose coverage is no more than 10%[54].

Expansion to include health care workers is also recommended[43]. HBsAg prevalence in the WHO African Region remains at 3%[2]. Innovative approaches to confirm timely administration of the HBV vaccine birth dose have been successful in Vietnam, Indonesia, and China[55-57]. A recent modeling study showed that percentage of infants who had received the three-dose HBV vaccination in the first year of life was 87%; that for infants who had received timely birth dose vaccination was 46%, and it was 13% for those who had received HBV immunoglobulin along with the full vaccination regimen[17]. In 2020, the WHO had new guidelines for preventing HBV mother-to-child transmission, demanding universal birth dose vaccination of infants. These guidelines also provide evidence-based advice on using peripartum antiviral prophylaxis, namely Tenofovir, in HBsAg-positive pregnant women to prevent mother-to-child transmission of HBV infection[58].

RECOMMENDATIONS FOR SCREENING AND TESTING

Worldwide, the rate of diagnosis of viral hepatitis is very low, and there remains an enormous burden of undiagnosed infection. It was estimated that 9 out of 10 people living with viral hepatitis are not aware of their status and thus do not benefit from clinical care, treatment, and interventions that lessen further transmission[18]. As a result, good integration with other disease program and approaching case discovery through high-risk subpopulations should be beneficial[1].

The World Hepatitis Alliance (WHA) surveyed in 2018 and outlined the five main causes for misdiagnosis of viral hepatitis: (1) Shortage of public knowledge of the disease; (2) Need of knowledge of the disease among healthcare professionals; (3) lack of easily accessible testing; (4) stigma and discrimination; and (5) out-of-pocket costs to patients. The WHA consequently started an initiative named “Find the Missing Millions” for massive scale-up of screening, diagnosis, and linkage to care to find the millions of undiagnosed people living with viral hepatitis[59]. Key challenges in hepatitis testing currently include a shortage of quality-assured serological and low-cost virological *in vitro* diagnostics, testing limited facilities, deficient data to guide country-specific hepatitis testing approaches, stigmatization of those with or at risk of viral hepatitis, and need of guidelines on hepatitis testing for resource-limited settings[3]. The availability of noninvasive feasible and cost effective serological and imaging modalities to measure hepatic fibrosis would also enable identifying patients with significant or advanced liver fibrosis[60,61]. Current costs for enzyme immunoassays range from 1 to US\$9 per test, and those for RDTs range from 0.5 to US\$7, while the costs of hepatitis nucleic acid test (NAT) assays currently range from 30 to US\$120, which seems unaffordable for a majority of patients in low-resource settings[3,62]. Additionally, FibroScan is not widely used in resource-limited settings because of its high cost, the need for trained personnel, and continuous maintenance[18]. Innovations in testing and sampling approach can increase access to testing and reduce the enormous burden of undiagnosed infection[62]. The 2017 WHO hepatitis testing guidelines for adults, adolescents, and children in LMICs outline the public health approach to strengthen and expand current testing practices for viral hepatitis. The guidelines also address testing approaches (who to test) and strategies (which serological and virological test to use) as well as interventions to promote linkage to prevention and care[3]; these guidelines recommended the use of the HCV core antigen with comparable clinical sensitivity to NAT assays as an affordable alternative[30,62]. The current availability of pan-genotypic HCV treatment using DAA terminates the need for expensive genotyping, unattainable in resource-limited setting[62]. In 2017, Peeling *et al*[61] examined a range of technological testing innovations to provide simplified affordable approaches for testing of HBV and HCV infection and monitoring of the treatment response to improve access to testing *via* alternative sampling methods (use of dried blood spots (DBS), oral fluids, and self-testing). Four systematic reviews and meta-analyses confirmed the high diagnostic accuracy of using DBS specimens for serological testing and NAT assays of HBV and HCV[63,64]. Combined rapid tests for the detection of HIV, HBV, and HCV infection and affordable confirmatory testing for the HBV and HCV viral genomes, such as point-of-care molecular assays, HCV core antigen testing, and multi-disease polyvalent molecular platforms, make use of existing centralized laboratory-

based or decentralized TB and HIV instrumentation for viral hepatitis testing[57]. Resources needed for implementing WHO-recommended hepatitis testing and treatment have been estimated across 67 low-income and middle-income countries, from 2016 to 2030 and it was found that access to affordable medicines in all countries will be key to reach hepatitis elimination and the feasibility of hepatitis elimination will be achieved in the context of universal health coverage[65]. This is confirmed by the last global progress report on accelerating access to hepatitis C diagnostics and treatment despite limited services caused by the current ongoing COVID-19 pandemic[66]. The report also emphasized that many LMIC increased access to testing and treatment by up to 20-fold increase in the number of individuals treated with safe and effective direct-acting antiviral drugs between 2015 and 2018[66]. However, access to HCV testing and treatment has not come to adequate levels of coverage to achieve the global goal of viral hepatitis elimination as a major public health problem by 2030[67]. It is recommended that point-of-care rapid diagnostic and viral load testing be used, as well as existing platforms and capabilities created for other diseases such as HIV and COVID-19.

CHOICE OF TREATMENT AND AVAILABILITY OF GENERICS

The WHO has developed guidelines for managing HBV infection that apply to resource-limited countries, but each should develop its guidelines according to its needs[40]. Only patients with HCV RNA-confirmed infection should start antiviral therapy[21].

Current HBV and HCV treatment rates are very low. According to the Global Hepatitis Report 2017, treatment has reached only a small fraction of diagnosed individuals[2]. In 2015, 8% of individuals diagnosed with HBV infection (1.7 million persons) were on treatment, while 7.4% of individuals diagnosed with HCV infection (1.1 million persons) had started treatment[1,2]. Tenofovir or Entecavir should be part of the treatment for patients with active HBV infection, those coinfecting with HIV, and those with cirrhosis[10]. HCV treatments based on IFN/ribavirin are poorly tolerated and are associated with marked side effects, and these treatments have resulted in cure rates between 40% and 65%, depending on different factors. In 2012, Hartl *et al*[68] reported a case study of a 38-year-old Caucasian male coinfecting with HCV (genotype 3a), HBsAg, and an antibody to the hepatitis B core antigen, which effectively responded to the pegylated-IFN plus ribavirin treatment regimen for HBV and HCV coinfection. A noticeable advance in HCV therapy followed the introduction of DAAs that directly inhibited the HCV replication cycle, which were better used in combination[2]. The WHO released its first guidelines on HCV treatment in 2014[69] and updated these guidelines in 2016[36] and 2018[70]. The Eastern Mediterranean Region accounted for the largest proportion of individuals that started treatment (12%), which was boosted by the large-scale elimination plans in Egypt[15]. In 2015, the HCV elimination program in Egypt was based on DAAs. Despite the development of generic antivirals that help reduce treatment costs, treatment remains unaffordable in some low-income settings where patients have to pay for their treatment.

CONCLUSION

In order to eliminate viral hepatitis in resource-constrained settings by 2030, a worldwide commitment to tackle this health burden with increased scale-up investment is essential. Political will, financial support, accessible pricing, integration with other current programs, community engagement, and multi-stakeholder collaboration are all critical. Active contribution of the private health sector in the management agenda together with an adequate strategic plan are required to solve problems regarding HBV/HCV screening, diagnosis, treatment and prevention in resource-limited settings. Monitoring liver enzymes and markers indicative of HBV/HCV replication before and during treatment are mandatory for early diagnosis and treatment of viral reactivation. HBV is a preventable infection with an available affordable vaccine, but the continuous assessment of the ongoing efficacy of HBV vaccination programs is crucial. Eliminating HCV is possible with DAAs, and implementing of preventive measures and the involvement of stakeholders.

Funding remains a major barrier and most LICs lack suitable financial resources for hepatitis services. The difficulties associated with the procurement of enough data from different low-income settings are also barriers to detection, testing, treatment, and thus for proper intervention. However, sharing experiences may pave the way for the successful implementation of elimination strategies. Transfer of successful stories like the Egyptian model to interested countries is of value. The development of sustainable and resource-appropriate mitigation strategies focusing on reducing transmission in resource-limited settings is needed. The strategies should fulfill preventive measures that include expanding HCV testing, safe injection, HCV treatment coverage, and birth dose HBV vaccination. Meanwhile, the impact of host and viral genomic factors on dual HBV & HCV infection must also be investigated.

FOOTNOTES

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