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LETTER TO THE EDITOR

Elimination of hepatitis B as a public health threat: Addressing the challenge and taking action

Lei Ma, Hui-Chun Xing

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Abstract

Despite the significant efforts made in recent years, the latest data from the World Health Organization indicates that there are substantial challenges in achieving the elimination of hepatitis B virus (HBV) infection by 2030. The article in the *World Journal of Hepatology* by Ismael *et al* highlighted the limited accessibility to screening and antiviral treatment for HBV infection in eastern Ethiopia. Therefore, the editorial comments on this article will focus on the current challenges and recent efforts in the prevention and treatment of chronic hepatitis B, particularly emphasizing the expansion of screening and antiviral therapy, as well as feasible strategies to improve accessibility for HBV testing, antiviral therapy, and adherence enhancement.

Key Words: Hepatitis B virus; Chronic hepatitis B; Cirrhosis; Treatment; Diagnosis

Core Tip: Currently, the rates of diagnosis and treatment are significantly low, particularly in resource-limited developing countries. Therefore, immediate action must be taken without any delay. In the expanding screening population, it is essential to prioritize hepatitis B surface antigen testing for all high-risk groups and utilize high sensitivity hepatitis B virus DNA testing to detect low-level viremia, which is associated with the prognosis of hepatitis B virus infection. Some patients in the indeterminate phase require immediate antiviral treatment. Reducing the cost and improving access to screening and treatment are also crucial, highlighting the need for collaboration between governments, healthcare organizations, and pharmaceutical companies. Integrating the delivery of care, prevention, and treatment for hepatitis B into existing health services can streamline testing, care, and treatment for hepatitis B.

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TO THE EDITOR

Chronic hepatitis B remains a significant public health threat. According to the most recent World Health Organization (WHO) report[1], an estimated 254 million individuals were affected by hepatitis B at the end of 2022. Although the number of new viral hepatitis infections declined from 3 million in 2019 to 2.2 million in 2022, the number of deaths increased from 1.1 million to 1.3 million, with 83% attributed to hepatitis B. This increase suggests a worsening clinical condition, including a rise in hepatitis-related cancer cases. Additionally, a major concern is the low rates of diagnosis and antiviral therapy. The WHO report[1] indicated that only 13% of individuals with chronic hepatitis B had been diagnosed, and nearly 3% had received treatment by the end of 2022, falling significantly short of the WHO targets of 90% for diagnosis and 80% for treatment by 2030. Even in developed countries, substantial gaps exist in the evaluation and treatment of hepatitis B patients[2]. A cohort study by Ye *et al*[2] found that about half of the patients (n = 6559; 52.3%) did not undergo a complete laboratory evaluation [defined as having Hepatitis B e Antigen (HBeAg), hepatitis B virus (HBV) DNA, and alanine transaminase (ALT) tests]. Among those with an adequate evaluation (at least HBV DNA and ALT), 11.2% met the treatment criteria set by the American Association for the Study of Liver Diseases (AASLD) and 13.9% met the European Association for the Study of the Liver (EASL) criteria set. Only 60.4% of AASLD-eligible patients and 54.3% of EASL-eligible patients received treatment within 12 months of becoming eligible. The low rates of diagnosis and treatment highlight a concerning gap in healthcare services for those affected by chronic hepatitis B, particularly in low- and middle-income countries such as those in the African region[3,4]. The article in the *World Journal of Hepatology* by Ismael *et al*[5] investigated the characteristics and antiviral treatment of 193 chronic hepatitis B patients in eastern Ethiopia. In this cohort, one-third of the patients had cirrhosis at enrollment, only 30.6% of participants received antiviral treatment, and 20.3% of treated patients died within 2 years. These findings indicate that access to HBV services in this region was limited and underscore the need for continued efforts to improve access to care and reduce the global burden of this disease. To address these challenges, the following actions must be taken without delay.

TAKING ACTION

Expanding screening population

Expanding screening is a crucial strategy for identifying potential HBV infection and enhancing the diagnostic rate of hepatitis B. The WHO[1] recommends testing for hepatitis B surface antigen (HBsAg) among high-risk groups, including household contacts, people who inject drugs, sex workers or sexual contacts of individuals with chronic hepatitis B, people living with human immunodeficiency virus or hepatitis C virus, and individuals who have received blood or organ transplants. Additionally, screening for HBsAg in patients undergoing invasive procedures or treatments in hospitals may help improve the detection rate of HBV infection. However, differences of regional economic and cultural backgrounds seriously may affect the effective scope of screening. In low-income countries, people may forgo screening because they cannot afford it, or they may not realize the importance of detection or for fear of discrimination. Therefore, regional strategies with focused screening should be developed according to local epidemic profiles. A comprehensive public advocacy strategy is imperative for raising awareness about hepatitis B and dispelling misconceptions, ultimately reducing stigma and increasing screening rates. Additionally, substantial financial investment, including government subsidies for diagnostic and treatment expenses, is essential in alleviating the financial burden of screening for patients. In addition, point-of-care or self-testing[1] may be useful models to facilitate HBV testing, particularly in resource-limited developing countries[6]. Serum HBV DNA levels are a critical indicator of viral replication activity and are significantly associated with HBV-related liver complications. They also serve as a valuable tool in treatment decision-making. If economic conditions permit, high-sensitivity HBV DNA testing should be prioritized. High-sensitivity HBV DNA testing can not only identify more infected individuals but also detect patients with poor responses to antiviral therapy. Research [7] has shown that low-level viremia is a significant predictor of poor prognosis compared to those who maintain a virological response. Therefore, highly sensitive HBV DNA testing is also a key index for evaluating the effectiveness of antiviral therapy. By increasing access to testing and raising awareness about HBV infection, healthcare providers can work towards reducing the burden of this disease in communities worldwide.

Important of anti-HBV treatment

Due to the suboptimal efficacy of current antiviral agents (which only inhibit HBV DNA replication), various guidelines over the past two decades have recommended antiviral therapy only for individuals who meet certain criteria, such as HBV DNA > 2000 IU/L and ALT > 2 upper limit of normal (ULN)[8] or ALT > ULN[9]. However, recent studies on the indeterminate phase (those who do not fit the criteria for the traditional four phases of chronic hepatitis B: HBeAg-positive chronic HBV infection, HBeAg-positive chronic hepatitis B, HBeAg-negative chronic HBV infection, and HBeAg-negative chronic hepatitis B) have found that 29.2% to 84.2% of these patients exhibited significant liver inflammation and

necrosis, 34% to 73.3% showed significant liver fibrosis, and 40.6% to 91.1% had significant liver histological lesions[10-12], even though they do not yet meet the treatment indications according to current guidelines[8,9]. Our study also demonstrated that 29.3% and 36.6% of patients with normal or slightly abnormal ALT levels (upper limit was 40 U/L) exhibited advanced liver fibrosis or significant liver inflammation and necrosis, or both, as confirmed by liver biopsy. Other studies have suggested similar findings. Jiang *et al*[10] found that among 634 patients with ALT levels less than 40 U/L, over 20% displayed severe liver histopathological injury (21.45% with ≥ A2 and 24.29% with ≥ F2). Liver fibrosis, inflammation, and necrosis are known to be strongly associated with poor prognosis in chronic hepatitis B[13]. Huang *et al*[14] demonstrated that 4.6% of patients (n = 1303) who remained in the indeterminate phase developed hepatocellular carcinoma (HCC), a rate 14 times higher than that of those (n = 1370) who remained inactive over a ten-year follow-up period. Therefore, timely antiviral therapy is crucial for improving the prognosis of patients. Research[13] has shown that antiviral therapy can reduce the risk of HCC, especially among patients aged 45 years or older. In this study, the cumulative incidence of HCC was significantly lower at 5, 10, and 15 years of follow-up in individuals receiving antiviral treatment (2.6%, 5.0%, and 14.7%, respectively) compared to those who were untreated (5.0%, 19.0%, and 24.0%, respectively; P = 0.04)[15]. These findings suggest that patients with indeterminate-phase chronic hepatitis B could benefit from antiviral treatment[13,15]. Consequently, the eligibility criteria for antiviral treatment were expanded in the 2022 guidelines for the prevention and treatment of chronic hepatitis B in China (updated by the Chinese Society of Hepatology and the Chinese Society of Infectious Diseases)[16]. Some indeterminate-phase chronic hepatitis B patients now meet the expanded criteria, including those over 30 years old with positive HBV DNA or with a family history of cirrhosis or HCC. Cirrhotic patients with positive HBsAg should also receive antiviral treatment irrespective of their HBV DNA levels. This expanded criteria largely aligns with the WHO's 2024 eligibility guidelines for antiviral therapy. According to the 2024 WHO criteria, patients meeting any of the following conditions should receive antiviral treatment: Significant fibrosis (*e.g.*, aspartate transaminase to platelet ratio index score > 0.5 or transient elastography > 7 kPa), HBV DNA > 2000 IU/mL with abnormal ALT, or persistently abnormal ALT levels alone (ALT ULN level was 30 U/L for men and boys, and 19 U/L for women and girls). This measure is expected to result in a 65% to 88% increase in the treatment rate[1]. However, this is only a professional effort; it also requires collaboration between governments, healthcare organizations, and pharmaceutical companies to ensure that affordable and effective treatments are accessible to those who need them. Such collaboration will be crucial for reducing the burden of this disease on individuals and communities worldwide. Therefore, advocating for the inclusion of some indeterminate-phase chronic hepatitis B patients in treatment may improve treatment rates, and utilizing high-sensitivity HBV DNA detection can help identify more cases of HBV infection.

Scaling up anti-HBV treatment

An important factor affecting the timely treatment of viral hepatitis B is the availability of antiviral medicines, especially in resource-limited developing countries. Recently, the use of generic medicines at very low prices has been increasing in many countries, which facilitates higher rates of antiviral therapy. China has implemented a "centralized drug procurement policy" that significantly reduces the cost of antiviral drugs and increases their accessibility. This approach has the potential to enhance availability of antiviral therapy, especially in settings with limited resources, and is anticipated to significantly improve the prevention and control of HBV. Besides. local authorities can develop comprehensive management and economic support plans based on local economic conditions, alleviating the financial burden of treatment costs for patients. At the same time, we should vigorously publicize the importance of antiviral treatment, so that more HBV infected people actively seek help from doctors and receive treatment. In addition, poor adherence to treatment remains a challenge for improving patient outcomes. Therefore, regular counseling should be provided to HBV-infected patients. Medication adherence training helps patients understand the detrimental effects of the disease and the benefits of antiviral treatment, thereby promoting active collaboration with healthcare providers throughout the treatment process. It is also crucial to monitor for poor response or rebound promptly, as this is important for effectively improving patient prognosis. The WHO[4] recommends integrating the delivery of care, prevention, and treatment for hepatitis B with other health services, such as human immunodeficiency virus prevention and control systems. This approach may facilitate simultaneous testing, care, and treatment of hepatitis B, saving time and resources. These measures will help improve patient outcomes and enhance the efficiency of disease prevention and control efforts.

CONCLUSION

In conclusion, expanding the screening population, scaling up antiviral therapy, and simplifying testing strategies can advance efforts to eliminate hepatitis B as a public health threat. However, unresolved issues remain, including the suboptimal response of patients with high viral loads, strategies for rescuing these patients, their long-term prognosis, and the safety of prolonged treatments. We also anticipate the imminent availability of innovative, broad-spectrum curative medications that will provide global benefits.

FOOTNOTES

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