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Review Article

"Treat-all" Strategy for Patients with Chronic Hepatitis B Virus Infection in China: Are We There Yet?

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Abstract

Chronic hepatitis B remains the primary cause of liver-related events in China. The World Health Organization set a goal to eliminate viral hepatitis as a public health threat by 2030. However, achieving this goal appears challenging due to the current low rates of diagnosis and treatment. The "Treat-all" strategy, which proposes treating all patients with detectable hepatitis B virus (HBV) DNA or even all patients with positive HBsAg, has been suggested to simplify anti-HBV treatment. In 2022, the Chinese Society of Hepatology and the Chinese Society of Infectious Diseases updated the guidelines for the prevention and treatment of chronic hepatitis B in China, expanding antiviral indications and simplifying the treatment algorithm. According to this latest guideline, nearly 95% of patients with detectable HBV DNA are eligible for antiviral treatment. This review aimed to provide a detailed interpretation of the treatment indications outlined in the Chinese *Guidelines for the Prevention and Treatment of Chronic Hepatitis B* (version 2022) and to identify gaps in achieving the "Treat-all" strategy in China.

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Introduction

The burden of hepatitis B virus (HBV) infection remains high despite advances in vaccination and antiviral therapy. It is estimated that HBV infection results in 1.16 million annual deaths globally and 453 thousand deaths in China in 2022.[1] The World Health Organization (WHO) set a goal in 2016 to eliminate viral hepatitis as a threat to public health by 2030. To achieve this goal, WHO proposed specific targets, such as identifying 90% of chronic HBV infections, treating 80% of eligible individuals, and reducing viral hepatitis-related mortality by 65%.[2] However, the targets are out of reach due to low diagnosis and treatment rates. According to a modeling study from the Polaris Observatory Collaborators, in 2022, the diagnosed rates were 13% globally and 22% in China. The corresponding treatment rates were 36% and 43%. The number of HBV-related deaths, incident cases of hepatocellular carcinoma (HCC), and incident cases of decompensated cirrhosis are projected to increase by 2030 if current levels of HBV diagnosis and treatment remain constant.[3]

The "treat-all" strategy was proposed for patients with chronic HBV infection based on several key considerations: Early treatment can reduce the disease burden of hepatitis B, accelerate HBV elimination, prevent disease progression, eliminate stigma and discrimination, improve quality of life, and decrease infectivity via blood. Additionally, emerging comorbidity factors for patients with HBV infection, such as metabolic dysfunction-associated fatty liver disease and alcohol intake, increase the risk of developing liver-related events. The increasing use of immunosuppressive therapy may also lead to hepatitis due to HBV reactivation.[4] This strategy has two possible scenarios: Treating all patients with detectable HBV DNA or even treating all patients with positive HBsAg. The latter has higher treatment coverage and is more proactive.

In 2022, the Chinese Society of Hepatology and the Chinese Society of Infectious Diseases updated the guidelines for the prevention and treatment of chronic hepatitis B (CHB) in China (hereinafter referred to as the Chinese CHB guideline (version 2022)).[5] This latest Chinese CHB guideline (version 2022) expands treatment indications and simplifies treatment algorithms, which are more proactive compared to the major international guidelines for preventing and treating CHB.[6–8] This article provides a detailed interpretation of the treatment indications in this guideline and identifies the gap in achieving the "treat-all" strategy.

How far are we from treating all patients with detectable HBV DNA?

Current major international and national guidelines have gradually expanded antiviral treatment indications. The Chinese CHB guideline (version 2022) reduced the thresholds of HBV DNA and alanine transaminase (ALT) for initiating treatment to increase the eligible population. The new guidelines also recommend actively managing patients at high risk for

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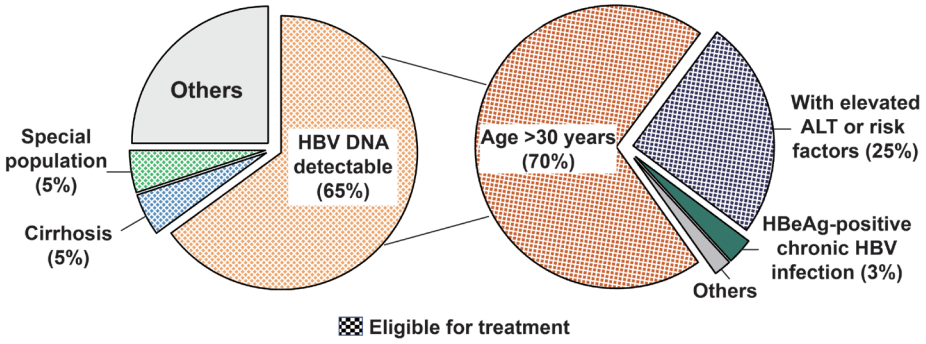

Fig. 1. The treatment coverage of adult patients with positive HBsAg and positive HBV DNA according to the Chinese CHB guideline (2022 version). HBV, hepatitis B virus; CHB, chronic hepatitis B; ALT, alanine transaminase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e-antigen.

disease progression, including those older than 30 years, with family histories of HBV-related cirrhosis or HCC, with significant fibrosis or inflammation by liver biopsy or non-invasive assessments, and those with HBV-related extrahepatic manifestations. Based on the China Registry of Hepatitis B (CR-HepB), a hospital-based registry involving more than 400,000 CHB patients from 55 centers in China, up to 95% of patients with detectable HBV DNA are eligible for antiviral treatment according to the latest Chinese CHB guideline (version 2022) (Fig. 1).

Antiviral treatment is recommended for HBV DNA-positive patients over 30 years old

According to the Chinese CHB guideline (version 2022), patients who are over 30 years old with detectable HBV DNA are recommended to receive antiviral treatment. The potential risk of liver disease progression is an essential reason for this recommendation. A Chinese cross-sectional study involving 4,759 untreated patients with chronic HBV infection found that the proportion of patients with HBeAg-positive chronic HBV infection (formerly known as the immune tolerance phase) decreased from 10–15% to 5% after age 30.[9] A study on long-term trends of HCC incidence and mortality in China suggested that patients aged over 30 years had a higher risk of HCC and HCC-related death.[10] As shown in Figure 1, approximately 70% of CHB patients with detectable HBV DNA are covered when treating patients over 30 years old.[11] Considering the average age of patients with chronic HBV infection rises due to a decline in new cases, which results from effective prevention efforts, the proportion of individuals over 30 years who need treatment will keep increasing.

Antiviral treatment is recommended for HBV DNA-positive patients under 7 years old

Pediatric patients are recommended to undergo active treatment due to their considerably high functional cure rate.[12] It was reported that a certain proportion of children clinically diagnosed with HBeAg-positive chronic HBV infection presented significant pathological liver injury.[13] A pilot open-label randomized controlled study from China indicated that antiviral treatment resulted in a high rate of virological response, HBeAg seroconversion rate, and HBsAg clearance in children aged 1–16 years, with positive HBeAg, HBV DNA over 10^7 IU/mL, and ALT lower than 60 U/L at baseline.[14] Another study from China that treated with sequential combined interferon and lamivudine therapy in children diagnosed as the HBeAg-positive chronic HBV infection phase showed that HBsAg clearance rates were 36.4% for ages 1–7 versus 8.3% for ages 7–16 years.[15] It was recently reported that younger age is a favorable factor in achieving a high functional cure rate after antiviral treatment.[10] Based on these findings, the Chinese CHB guideline (version 2022) recommends that children aged 1–7 years receive active antiviral treatment after comprehensive counseling with their guardians, regardless of whether liver biopsies are performed.

Antiviral treatment is recommended for at-risk HBV DNA-positive adult patients

For patients with evidence of liver injury or at a high risk of disease progression, early antiviral treatment should be considered. These patients are defined as those with elevated ALT [≥upper limits of normal (ULN)], cirrhosis, significant fibrosis (F≥2), HBV-related extrahepatic manifestations, or family histories of HCC or cirrhosis. Non-invasive examinations for liver fibrosis are recommended to detect significant fibrosis and identify at-risk patients in a timely manner. According to the CR-HepB, approximately 85% of adult patients under 30 years with detectable HBV DNA are eligible for antiviral treatment.

The estimated annual spontaneous HBeAg seroconversion rate was lower than 2–15% in treatment-naive CHB patients younger than 30 years.[16] Therefore, the current antiviral treatment indications cover most HBeAg-negative patients with detectable HBV DNA, including those in the HBeAg-negative CHB and HBeAg-negative "indeterminate phase." The HBeAg-negative "indeterminate phase" is characterized as having negative HBeAg, normal ALT levels (≤upper limits of normal), and detectable HBV DNA. Studies from China based on liver biopsies have shown that about 41–48% of these patients had histological evidence of significant necroinflammation.[17,18] In a recent Chinese study, continuous antiviral treatment with good adherence was satisfactory in lowering the risk of liver cirrhosis in HBeAg-negative CHB patients with normal ALT.[19] However, the benefit to these patients from early initiation of antiviral therapy still needs more evidence.

Early initiating treatment of patients with HBeAg-positive chronic HBV infection remains controversial

The patient with HBeAg-positive chronic HBV infection is an essential part of those ineligible for antiviral treatment. Based on the CR-HepB, approximately 24% of patients under 30 are in the clinically diagnosed HBeAg-positive chronic HBV infection phase, defined as positive HBeAg, normal ALT, and a high HBV DNA load (>2×10^7 IU/mL). Recently, there has been a heated debate regarding whether patients with HBeAg-positive chronic HBV infection should receive treatment. Reasons supporting the initiation of antiviral treatment are as follows:

Firstly, adult patients with clinical features of the HBeAg-positive chronic HBV infection phase may exhibit significant histological damage. A recent meta-analysis showed that the estimated prevalence of significant fibrosis and advanced fibrosis was 16.9% and 5.4%, respectively, although none had cirrhosis.[20] The risk of significant histological necroinflammation or fibrosis was reported to increase in patients with older age and high-normal ALT levels.[21–23]

Secondly, there is still a risk of developing HCC in the phase of HBeAg-positive chronic HBV infection. HBV integration and clonal hepatocyte expansion may contribute to carcinogenesis.[24,25] The REVEAL cohort found a biological gradient in HCC development based on HBV DNA levels in clinical studies. The risk of developing HCC increases with a higher level of HBV DNA.[26] A Korean study reported significantly higher HCC incidence and accumulated mortality rates in patients with HBeAg-positive chronic HBV infection than in those treated patients with HBeAg-positive CHB.[27] However, a cut-off value of HBV DNA>20,000 IU/mL was used for diagnosing the HBeAg-positive chronic HBV infection phase, which was relatively low. Furthermore, the patients in this study were much older than previously reported, with a mean age of 38. Both of these factors raise concern about the appropriateness of diagnosing the HBeAg-positive chronic HBV infection phase. In another systematic analysis, the pooled 5-year and 10-year incidence rates of HCC in HBeAg-positive chronic HBV infection patients were 1.1% and 2.7%, comparable with those in treated HBeAg-positive CHB patients.[28] This result indicates that although the occurrence of HCC in HBeAg-positive chronic HBV infection patients might have been overestimated previously, a certain number of these patients still develop HCC.

Thirdly, it has been reported that initiating treatment during the HBeAg-positive chronic HBV infection phase is more cost-effective than delaying treatment until the active hepatitis phase, based on the Markov model.[29] Lastly, although the HBeAg-positive chronic HBV infection phase was formerly called the "immune tolerance" phase, it is not a non-response state to HBV. A study proposed that adolescent patients with chronic HBV infection showed quantitatively and functionally superior HBV-specific T cells compared to adult patients in the "immune active" phase.[30–32] HBV-specific T cells were the key to the HBV-specific immune response in chronic HBV infection. Therefore, the term "immune tolerance" phase was challenged and updated to "HBeAg-positive chronic HBV infection" phase in guidelines published by the European Association for the Study of the Liver in 2017 and in the Chinese CHB guideline (version 2022).

The benefits of early treatment initiation for adult patients in the HBeAg-positive chronic HBV infection phase remain unclear. A meta-analysis supports antiviral therapy for patients in the HBeAg-positive chronic HBV infection phase, as it promotes HBsAg loss and HBV DNA clearance and reduces the risk for HCC and cirrhosis.[33] However, some studies mostly included children, so their findings may not be generalizable to adults. More multi-center prospective studies with larger sample sizes and excellent conduction quality are needed to confirm this conclusion. Patients in the HBeAg-positive chronic HBV infection phase with a high risk of disease progression can be selected for treatment by lowering the threshold of ALT for initiating antiviral treatment. A retrospective study showed that the prevalence of significant fibrosis was significantly higher in the high normal ALT (26–40 IU/L) group.[23] Therefore, reducing the threshold of ALT for initiating treatment can help identify the "true" HBeAg-positive chronic HBV infection patients, which has been recommended in a consensus published in 2022.[34] Based on the data extracted from the CR-HepB, it was evaluated that lowering the ALT threshold for initiating treatment to 30 IU/L for males and 19 IU/L for females can increase the treatment rate by 8%.[35]

How far are we from treating all patients with positive HBsAg

Treating individuals with positive HBsAg has been recommended for special populations

The current strategy of treating all individuals with positive HBsAg, regardless of the HBV DNA level, is only implemented in highly selected patients. Typically, these populations include patients with liver failure, HBV-related HCC, or cirrhosis (either compensated or decompensated), patients co-infected with hepatitis C virus infection and requiring treatment of direct-acting agents, or patients undergoing chemotherapy, targeted therapy, or immunosuppressant therapy.[5]

Antiviral therapy is recommended for patients with compensated cirrhosis regardless of HBV DNA levels

The Chinese CHB guideline (version 2022) recommends treating all positive HBsAg patients with cirrhosis regardless of the HBV DNA. Several studies suggest that even with undetectable HBV DNA, patients with compensated cirrhosis have a remarkable risk of developing HCC. A Korean retrospective study found that the 5-year cumulative incidences of HCC were approximately 8% and 2.2% in compensated cirrhotic patients with low-level viremia (HBV DNA ranging from 12 to 2,000 IU/mL) and undetectable HBV DNA (HBV DNA<12 IU/mL).[36] In another retrospective study of HBeAg-negative patients, the 7-year cumulative incidence of HCC reached 15.2% in patients with cirrhosis.[37] It has been reported that antiviral therapy can decrease the likelihood of developing HCC. In a single-center American retrospective study of CHB patients with compensated cirrhosis, those untreated with undetectable HBV DNA had higher rates of HCC than those with suppressed HBV DNA by antiviral therapy.[38] However, the lower limit of the linear range of HBV DNA quantification varied from 10 to 200 IU/mL, which may cause an overestimation of HCC incidence in patients with low HBV DNA levels.

The strategy of treating all HBsAg-positive patients has been gradually expanded to include patients with compensated cirrhosis. The indications for treating HBV-related cirrhosis according to the published international guidelines are concluded in Table 1. The 2015 Asian Pacific Association for the Study of the Liver guidelines suggest initiating antiviral therapy in compensated cirrhosis patients with an HBV DNA level greater than 2,000 IU/mL.[8] The American Association for the Study of Liver Disease 2018 Guidelines for the Treatment of Hepatocellular Carcinoma and European Association for the Study of the Liver 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection only require HBV DNA to be detectable.[6,7] The Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection released by WHO in 2015 recommends treatment initiation regardless of HBV DNA level, considering the infeasibility of the test in some regions and the high risk of developing life-threatening complications of liver disease.[39] Meanwhile, expert algorithms in America provided a fresh overview of treatment goals and indications for CHB in 2022. They proposed treating all patients with cirrhosis, regardless of the level of HBV DNA or ALT.[40]

Treating all HBsAg-positive patients helped reduce HBV-related mortality and showed good cost-effectiveness

Treating all HBsAg-positive patients could help decrease liv-

Table 1. Comparison of indications for treating HBV-related cirrhosis

	Compensated cirrhosis	Decompensated cirrhosis
2015 WHO	HBsAg+	HBsAg+
2015 APASL	HBVDNA>2000 IU/mL	HBVDNA+
2017 EASL	HBVDNA+	HBsAg+
2018 AASLD	HBVDNA+	HBsAg+
2022 CSH/CMID	HBsAg+	HBsAg+

WHO, World Health Organization; APASL, Asian Pacific Association for Study of the Liver; EASL, European Association for Study of the Liver; AASLD, American Association for the Study of Liver Disease; CSH/CMID, the Chinese Society of Hepatology and Chinese Society of Infectious Diseases. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

er-related events, the costs of diagnosis, and expenditure on future consequences of disease progression from untreated CHB. A Chinese study developed a decision-tree Markov state-transition model to analyze the health outcomes and cost-effectiveness of expanding anti-HBV treatment by simulating different ALT treatment initiation thresholds, population age groups, and treatment coverages. Treating all HBsAg-positive patients with 80% coverage for ages 18–80 is deemed optimal. Expanded antiviral treatment with the ALT threshold of 30 IU/L for males and 19 IU/L for females can also contribute to achieving the global target of a 65% reduction in HBV-related mortality and save costs.[41] A recent review conducted by the Asian Pacific Association for the Study of the Liver Viral Elimination Task Force recommends that all HBsAg-positive patients with ALT≥30 IU/L for males and ALT≥19 IU/L for females should receive antiviral treatment, regardless of detectable HBV DNA.[42]

The "Treat-all" strategy is still widely debated

Currently, antiviral treatment indications encompass most HBV DNA-positive patients. For those with negative HBV DNA, antiviral treatment was considered only in specific populations. Despite the global expansion of antiviral therapy, the "Treat-all" strategy remains controversial. The considerations are as follows: Firstly, the therapeutic benefit has not been confirmed in patients without evidence of liver injury, potentially leading to overtreatment. Secondly, considering that oral antiviral therapy is virtually lifelong in most instances, ensuring long-term adherence in asymptomatic individuals is particularly challenging. Indeed, the estimated 5-year adherence to oral antiviral therapy is around 75%.[43] The withdrawal of antiviral therapy carries risks of viral or clinical relapses, which may progress to decompensation and liver failure.[44] Thirdly, while side effects of long-term use of oral antiviral agents are rare, they can be challenging, particularly in patients with comorbidities such as metabolic disorders.[45]

Conclusion

In conclusion, expanding treatment criteria and simplifying the treatment algorithm can help prevent further disease progression and reduce HBV-related liver events. The "Treat-all" strategy might be critical to eliminating hepatitis B by 2030. According to the latest Chinese CHB guideline (version 2022), it is speculated that 95% of patients with detectable HBV DNA are eligible for antiviral therapy. This may prevent patients with HBV infection from progressing to HCC or cirrhosis. It is still debated whether antiviral therapy benefits patients in the HBeAg-positive chronic HBV infection phase, which could represent the final step in treating all patients with detectable HBV DNA. Antiviral therapy is recommended for patients with positive HBsAg and undetectable HBV DNA in some specific conditions. However, the expansion of treatment still requires more evidence.

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Conflict of interest

JJ has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013, HY has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Writing the manuscript (MZ), developing the idea and revising (HY, YS, JJ), and material support (YK, XX). The authors approved the final version of the manuscript.

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