

REVIEW ARTICLE

WHO 2024 Hepatitis B Guidelines: No more gray zone for low- and middle-income countries? An evaluation

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Points to Note

• Synthesis of Current Evidence:

The WHO 2024 guidelines expand HBV treatment eligibility to 50% by lowering ALT/APRI thresholds and removing HBV DNA test dependency, significantly benefiting “gray zone” patients in LMICs.

• **Major Controversies:** The HIV-like “treat-all” strategy sparks debates regarding over-treatment risks due to lower test specificity, long-term drug toxicity, and financial sustainability in resource-limited settings.

• **Future Directions:** Refining simplified algorithms, validating non-invasive biomarkers, and integrating decentralized point-of-care models are required.

ABSTRACT

The World Health Organization (WHO) has established targets to reduce the incidence rates of viral hepatitis by 90% and the death rate by 65% by 2030. However, despite global efforts, a substantial treatment gap persists, with merely 3% of eligible patients worldwide receiving antiviral therapy as of 2022. With more than 254 million people living with chronic HBV infection and approximately 1.1 million related deaths annually, the updated 2024 WHO guidelines significantly expand treatment eligibility to help achieve this objective. This review discusses how the new changes would benefit gray zone patients, particularly those in low- and middle-income countries (LMICs) who were historically excluded from therapy. By introducing age-based thresholds, incorporating non-invasive grading methods, and persistent ALT elevation to the treatment network, the 2024 guidelines promise broader inclusion. This review highlights the significance of these changes and evaluates the potential impact on the gray zone patients in resource-limited settings.

Keywords: Chronic HBV, hepatitis B virus, HBV gray zone.

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How to cite this article: Saravanan S, Vignesh R, Shankar EM, Sivadoss R, Sivamalar S, Velu V, et al. WHO 2024 Hepatitis B Guidelines: No more gray zone for low- and middle-income countries? An evaluation. *Hepatology Forum* 2026; 7(3):236–240.

Received: June 16, 2025; **Revised:** November 12, 2025; **Accepted:** January 16, 2026; **Available Online:** July 27, 2026

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Introduction

According to WHO estimates, 254 million people worldwide are afflicted by chronic hepatitis B (CHB) virus (HBV) infection, with a disproportionately high burden in low- and middle-income countries (LMICs). Chronic HBV infection is responsible for about 1.1 million deaths annually, primarily due to cirrhosis and hepatocellular carcinoma (HCC).^[1] Between 2016 and 2040, there will likely be a more than twofold increase in HBV-related HCC deaths.^[2,3] CHB is characterized by dynamic fluctuations in viral replication and host immune responses, which can lead to the risk of disease development over time. These interactions define four recognized phases of chronic HBV infection: immune tolerant (IT), immune active (IA), immune control (IC), and immune reactivation (IR) phases (Fig. 1). The term 'gray zone' is frequently used to describe the indeterminate cases that do not fall into any of these four classical phases, often with fluctuating alanine aminotransferase (ALT) levels around the upper limit of normal (ULN).

According to the revised WHO CHB guidelines 2024, HBV treatment eligibility is determined based on the evidence of significant fibrosis, HBV DNA level > 2000 IU/mL, and elevated ALT level, and the presence of coinfections and comorbidities. The expanded treatment eligibility aims to capture a higher proportion of HBsAg-positive individuals. However, in resource-limited settings (RLS) without access to HBV DNA testing, persistently elevated ALT

levels alone justify treatment initiation, irrespective of APRI scores. Hence, there remains a possibility that a proportion of gray zone CHB patients from LMICs with fluctuating ALT levels may remain untreated under the current guidelines. This is in contrast to the management of HIV or HCV, where early treatment is prioritized for all infected individuals regardless of disease stage. Despite evidence that antiviral therapy reduces the risk of HCC and liver-related mortality, only about 3% of CHB patients were receiving treatment as of 2022.^[4] Consequently, gray zone patients from LMICs, many of whom are experiencing ongoing inflammation and fibrosis, might face an increased risk of progression to cirrhosis and hepatocellular carcinoma.^[5,6] Given that a substantial liver inflammation is a key indication for initiating antiviral treatment, the absence of HBV DNA testing precludes several gray zone patients from treatment under current practice guidelines. This review advocates updating RLS treatment criteria by incorporating affordable alternatives to identify gray zone patients who require therapy.

Epidemiology of Gray Zone Patients

The current staging criteria of chronic HBV infection are insufficient for classifying about 30%-40% of patients in the gray zone.^[6] Discussing therapy and prognosis for these patients, often referred to as being in the gray zone, presents challenges. Recent studies suggest that many patients in this category exhibit benign outcomes without

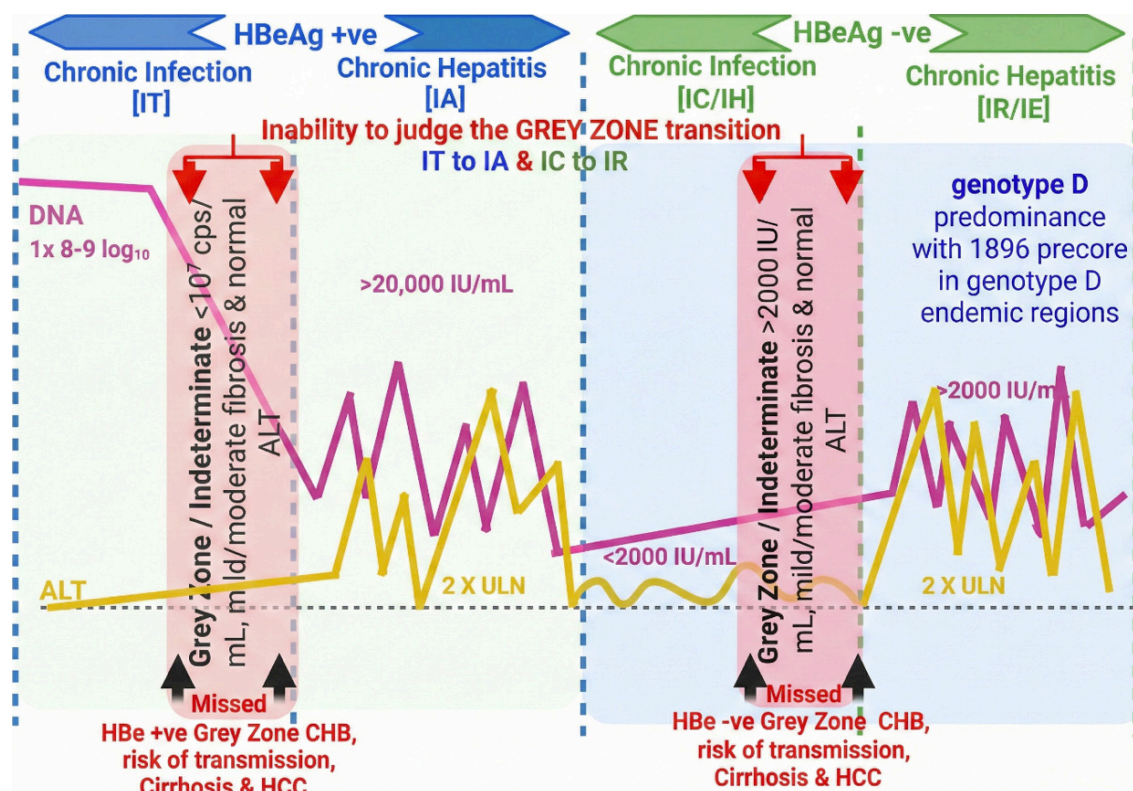


Figure 1. Defined clinical phases of chronic HBV infection and an emerging indeterminate/gray zone chronic HBV (author-created figure).

IT: Immune tolerance; IA: Immune active; IC: Immune control; IR: Immune reactivation; IE: Immune escape; OBI: Occult HBV infection; SN: Surface antigen negative; FC: Functional cure.

treatment, leading to proposals to delay antiviral therapy, especially for those in the HBeAg-negative gray zone.^[5] However, prior studies suggest that patients in this gray area who do not receive treatment are more likely than those in other phases to experience bad clinical outcomes, including liver cirrhosis and hepatocellular carcinoma (HCC).^[7,8] Existing studies primarily rely on serum ALT and HBV DNA levels for classification. Still, liver histology could provide more accurate insights, as levels of serum markers and HBV DNA may fluctuate. A study conducted on 3366 treatment-naïve CHB patients without cirrhosis found that 38.7% of them were characterized as being in an ‘indeterminate’ phase at the beginning. Out of these patients, 52.7% remained in the indeterminate phase after ten years.^[7] In patients who remained in the indeterminate category, the 10-year cumulative incidence of HCC was found to be higher than in those who remained in the inactive category (HR: 14.1). Moreover, a study of 2,150 treatment-naïve, HBeAg-negative, non-cirrhotic patients with CHB found that patients classified in the indeterminate or gray-zone groups had an increased risk of HCC.^[9] An additional study reported an HCC incidence of 0.41 cases per 100 patient-years (95% CI, 0.35–0.48) among untreated patients in the inactive phase.^[10] In patients with HBV DNA levels between 2000 and 20,000 IU/mL, this rate is comparable to that observed in the REVEAL-HBV study (0.30 per 100 patient-years).

Preventing cirrhosis and HCC is still the primary goal of HBV therapy in the absence of curative treatments. Antiviral suppressive therapy is considered for a broader range of HBV-infected patients due to the significant positive link between HBV DNA levels and HCC risk found in the REVEAL-HBV cohort study, regardless of ALT and fibrosis stage. It is encouraged to use caution when comparing these studies because higher initial levels of HBV DNA (up to 10⁶ IU/mL) are linked to an increased risk of HCC among individuals with CHB who have tested negative for HBeAg. Moreover, the beginning of the investigations revealed that the patients involved in these studies had different baseline levels of HBV DNA.^[11]

Hsu et al.^[12] found that 36.6% of 198 untreated patients fell into the gray zone when ALT >40 IU/L was used as the threshold. Like the previous research, 28.0% of the patients were categorized as being in the gray zone according to the AASLD standards. This classification was based on their serum ALT levels and HBV DNA. Histological analysis increased the gray zone classification to 49%, reinforcing its utility in staging. Considerable variability exists between international guidelines, underscoring the need for globally harmonized criteria.^[6] According to the Global hepatitis report 2024, less than 30% of low and middle-income countries (LMICs) have access to performing HBV DNA assays, highlighting the significant challenge in diagnosis.

WHO 2024 Treatment Guidelines: Key Changes for Gray Zone Patients?

The updated 2024 WHO HBV guidelines offer four options for meeting treatment eligibility that will capture a much higher proportion (about 50%) of all HBsAg-positive people versus about 8–15%. While the aspartate aminotransferase-to-platelet ratio index

(APRI) continues to be recommended as the preferred non-invasive test to assess for the presence of significant fibrosis or cirrhosis among adults in resource-limited settings, new recommendations have brought down the thresholds for establishing the presence of significant fibrosis or cirrhosis.

Considering that only a low proportion of LMICs have capacity and access to HBV DNA assays, the updated guidelines recommend treatment initiation in case of persistently abnormal ALT levels (defined as two ALT values >ULN at unspecified intervals during a 6-to-12-month period), regardless of APRI score, in the absence of HBV DNA assay.

Since pre-2024 guidelines excluded about 30 to 40% of patients in the gray zone due to the strict reliance on HBV DNA and ALT thresholds, these updated recommendations could increase the treatment coverage significantly in LMICs. A recent cross-sectional study compared the rates of HBV treatment eligibility among 10,042 treatment-naïve patients according to the 2024 guidelines with eligibility rates across other international guidelines, which displayed significantly higher treatment-eligible rates.^[13] A recent study from China that retrospectively analyzed 1454 CHB patients found that about 47.5% belonged to the gray zone category. Of these, about 46.7% had significant liver histological changes based on liver biopsy, and antiviral therapy was indicated in them.^[14]

Hence, there is no doubt that the updated guidelines would help broaden the antiviral treatment coverage, thereby aiming to improve access to therapy and patient outcomes. Earlier initiation of antiviral treatment in chronic HBV patients, especially the gray zone patients, would benefit from the reduction in the risk of fibrosis progression and development of HCC.^[15]

Impact of the WHO 2024 HBV Guidelines on LMICs

According to modelling studies, to meet the WHO 2030 HBV elimination targets, the treatment coverage needs to be increased to 80% among people eligible for antiviral treatment. While less than 20% of people living with HBV infection (PLWHB) were eligible for antiviral treatment as per the WHO 2015 treatment criteria, the WHO 2024 guidelines aim to increase this to 50% of PLWHB. A study found that about 67% of treatment-naïve patients with CHB will meet treatment eligibility based on the 2024 guidelines.^[16] The newer guidelines are expected to have a positive impact on the nations representing about two-thirds of the global disease burden.^[11] The diagnosis and monitoring recommendations have been curated based on the clinical setting and the availability of resources, keeping the LMICs with high disease burden in mind. Significant fibrosis/cirrhosis based on APRI score is sufficient to initiate therapy. In regions with access, point-of-care HBsAg and HBV DNA testing are recommended as primary care options based on their excellent diagnostic accuracy. However, considering the limited access to HBV DNA PCR in LMICs, HBV viral load is no longer a barrier to treatment initiation.

To enable more straightforward implementation with accessible diagnostic tools, the treatment criteria have been simplified in the revised guidelines. With Hepatitis B, the leading cause of death in LMICs, treating advanced fibrosis and cirrhosis irrespective of HBV DNA or ALT levels broadens the treatment eligibility. These updated guidelines also serve to avoid the gray zones associated with different ranges of ALT and HBV DNA levels.

Lowering the APRI threshold for diagnosis of advanced fibrosis and cirrhosis as per the revised guidelines is particularly important and relevant to resource-limited settings like African regions. When the APRI cut-off was >2 for cirrhosis, about 50% of individuals eligible for treatment were missed in Ethiopia.^[17] A recent study that compared the treatment coverage between the WHO 2024 hepatitis B guidelines and the WHO 2015 hepatitis B guidelines, included 6925 treatment-naïve CHB patients, found that only 36.2% of patients met the treatment criteria as per the previous guidelines, while the treatment eligibility rate rose to 63.8% in the case of the 2024 guidelines. Interestingly, if HBV DNA testing was not accessible, the treatment coverage remained as high as 61.6%, which is relevant to the LMIC settings.^[4]

Gray Zone and the Persistent Gaps in LMICs

It is understood that using the 2024 WHO treatment criteria would increase the treatment coverage to about 80%, as opposed to 20% being eligible for treatment as per 2015 guidelines, and considered a solution for eliminating HBV globally by 2030. Following the HIV test-and-treat model of care, a treat-all strategy is put forward to curb the HBV load worldwide. However, this sparks a lot of debate on the possible benefits of expanded treatment indications, because in contrast to HIV infection, a small percentage of HBV-infected patients could achieve a functional cure spontaneously over time. Also, compared to HIV, there is an effective HBV vaccine available, and several CHB patients belong to the HBeAg-negative chronic infection phase, associated with a very low risk of hepatic complications. Furthermore, expanded treatment eligibility and antiviral treatment raise concerns about toxicity and the need for monitoring treatment toxicity. Since there is no clear indication on when the antiviral therapy should be stopped, the potential for long-term treatment-related toxicity must be balanced against the possible risk of hepatitis flare following the discontinuation of treatment. It is important that no study has ever been conducted to evaluate the pros and cons of this strategy in sub-Saharan Africa. Further studies and more data are required on the toxicity of nucleoside analogues in HBV-infected individuals, especially from LMICs, where there would be limited access to laboratory monitoring. In addition, in resource-limited settings like LMICs, broadened treatment eligibility leading to an increase in the proportion of those initiating treatment also brings up the need for additional long-term cost implications and sustainability. Although several LMICs are in the process of improving their access to generic drugs, the costs of HBV treatment remain too high for many countries.^[18]

Lowering of cut-offs of non-invasive tests for liver fibrosis was one of the strategies of the WHO 2024 guidelines aimed at identifying a maximum number of individuals with significant liver fibrosis, including cirrhosis. However, this raises the concern of prioritizing the sensitivity of the testing method over specificity, which could lead to overtreatment of patients. Likewise, the revised cut-offs of APRI and FibroScan are found to be associated with reduced performance characteristics (sensitivities and specificities) for the detection of significant liver fibrosis or cirrhosis.^[16]

Conclusion

In summary, the revised WHO hepatitis B guidelines represent a progressive step toward expanding CHB treatment and reducing missed opportunities, particularly in LMICs. By eliminating HBV DNA dependency and embracing age, APRI and ALT as treatment criteria, more gray zone patients are likely to be covered than ever before. While these changes are expected to significantly expand diagnosis and treatment access, ultimately improving individual outcomes and advancing global HBV elimination goals, there still remain several barriers to the management and treatment of hepatitis B in resource-limited settings. The current research gaps, particularly regarding the LMICs, need to be focused further on refining simplified algorithms, validating additional non-invasive biomarkers, and ensuring equitable access to diagnostics and treatment in high-burden regions. Thus, in LMICs, successful implementation will require the integration of fragmented healthcare services and targeted allocation of limited domestic resources to ensure sustained delivery of HBV care.

Ethics Committee Approval: This article is a review study and does not contain any original studies with human participants or animals performed by any of the authors. Therefore, ethical approval was not required for this study. The authors declare that they have complied with all academic and publishing ethical standards.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: No specific financial support was received for the preparation of this manuscript. VV is supported by the Emory National Primate Research Center through NIH Grant No. ORIP/OD P51OD011132.

Use of AI for Writing Assistance: The authors declare that tools such as Grammarly and Quillbot were used for language assistance.

Author Contributions: Concept: SSa, RV, PB; Design: SSa, RV, PB; Supervision: SSa, PB, EM, RS; Literature Search: RV, SSa, SSi; Writing: RV, SSa, SSi; Critical Reviews: SSa, PB, VV, ARV.

Peer-review: Externally peer-reviewed.

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