

COMMENTARY

Comment on AASLD ISDA Practice Guideline on treatment of chronic hepatitis B (2025 Update)

Chronic HBV infection affects ~258 million people globally and is responsible for 1.1 million deaths per year, mainly due to cirrhosis and HCC.^[1] Although a very effective preventative vaccine has been available for decades, the estimated burden of disease in the United States is as high as 1.8 million people, reflecting immigration from endemic areas.^[2,3] Long-term antiviral treatment with nucleos(t)ide analogs (NAs) is well-tolerated, can reduce the risk of liver-related morbidity and mortality due to HBV, and can reduce the risk of onward transmission. While NAs started during the immune-active phase of CHB reduce the risk of HCC, they do not abolish it—this has led to interest in expanding criteria for treatment eligibility to include individuals at earlier stages of disease. This issue of *HEPATOLOGY* contains the 2025 update to the AASLD Practice Guideline on the Treatment of Chronic Hepatitis B.^[4] The update to the guideline was developed by an expert panel using the GRADE framework, PICO questions, and systematic literature reviews, ensuring a rigorous, evidence-based process aligned with National Academy of Medicine standards.

The update addresses 6 common and important clinical questions formulated through the PICO process, including questions concerning issues for which level one clinical evidence is lacking and expert guidance is necessary. For the first time, the Practice Guideline strongly endorses shared clinical decision-making and patient-centered care, particularly relevant to decisions about antiviral treatment guided by expert opinion. The 2025 update has an expanded focus on antiviral treatment for the main purpose of preventing onward transmission, both mother-to-child transmission (MTCT) and horizontal transmission, in partnership with vaccination, hepatitis B immunoglobulin, and harm reduction measures. The panel recognized the role of treatment to reduce the risk of liver-related outcomes, in particular HCC, and the update considers expanded treatment criteria beyond the immune-active phase disease. This guideline is important—effective HBV DNA suppression with NA will plausibly reduce long-term HCC risk due to the association between persistent HBV DNA replication, genomic integration, and HCC carcinogenesis,^[5] but to design long-term randomized controlled trials to prove this in patients in the immune-

tolerant or indeterminate phases of disease will be practically and ethically challenging. The favorable long-term safety profile of first-line NAs, the low risk of antiviral resistance, and the availability of generic versions of entecavir and tenofovir disoproxil fumarate that improve cost-effectiveness all support this approach. Recent updates to international guidelines on the management of hepatitis B have also recommended expanding eligibility criteria for antiviral treatment.^[6–8]

In contrast to these international documents, the AASLD Practice Guideline continues to endorse the use of HBeAg serostatus, different HBV DNA levels to indicate treatment eligibility in HBeAg-positive ($\geq 20,000$ IU/mL) versus HBeAg-negative (≥ 2000 IU/mL) CHB, and a multi-tiered approach to interpretation of ALT elevation (ALT < ULN vs. ALT 1–2 \times ULN vs. ALT > 2 \times ULN), acknowledging the ease of access to laboratory testing in the United States compared with low and middle-income countries. As a consequence, AASLD retains the definitions of immune-tolerant, immune-active, inactive, as well as indeterminate phase (also known as the “gray zone”) for CHB. In contrast, WHO and EASL promote a simplified nomenclature for clinical practice.^[6,7] At the same time, EASL has separately proposed a more detailed nomenclature for research purposes.^[6] Harmonization of terminology across guidelines would be desirable in the future to reduce confusion among clinicians and facilitate global alignment of treatment algorithms.^[9]

The AASLD Practice Guideline update is focused primarily on treatment, and therefore does not consider topics related to the screening and diagnosis of hepatitis B. However, in recognition of the importance of HCC surveillance for the early detection of HCC that can be treated with curative intent, there are updated recommendations for HCC surveillance in a number of subsets of patients, including people who have achieved functional cure as well as people with HCV, HDV, and HIV coinfection. The document is intended to be complementary to the previous AASLD 2018 Guidance^[10], and does not address topics that have previously been well covered and for which recommendations have not changed.

The Practice Guideline will be a living document for ease of update as drug development changes the

landscape of hepatitis B treatment in the coming years. Future updates should also consider the place of novel biomarkers, noninvasive tests, and point-of-care tests in clinical decision-making. Further consideration of the role of serum HBsAg levels in clinical practice will be important. Quantitative HBsAg level testing is becoming more widely available and was recently recognized by EASL as a recommended diagnostic test in the EASL clinical practice guideline (CPG).^[6] Serum HBsAg levels can be used to personalize the approach to stopping NA therapy—the EASL CPG recommends considering discontinuation of NAs in selected patients who were HBeAg-negative and who meet the following criteria: sustained undetectable HBV DNA for ≥ 3 years, no advanced liver fibrosis, low HBsAg level (HBsAg level < 1000 in Caucasians, HBsAg level < 100 in Asians), and able to comply with a close monitoring schedule.^[6] In contrast, AASLD suggests that patients should not stop NA therapy until they achieve HBsAg loss and does not yet endorse the role of low HBsAg levels to identify patients who are HBsAg-positive and who have a high likelihood of achieving functional cure after stopping NAs. HBsAg levels may also be used to guide HCC risk assessment.^[11] Finally, HBsAg levels are very likely to be used to select patients for novel therapies currently in development, including the antisense oligonucleotide bepirovirsen.^[12]



Future updates will also provide an opportunity to develop a roadmap for the United States to eliminate hepatitis B as a public health threat. The World Health Organization has set targets for elimination by 2030.^[7] Up to half the people living with hepatitis B in the United States are not aware of their diagnosis,^[13] and the Centers for Disease Control and Prevention has recommended universal screening for hepatitis B in all US adults > 18 years. Novel models of care will be required to scale up screening programs and linkage to care to achieve the WHO targets of 90% of people living with hepatitis B diagnosed and 80% actively linked to treatment. The specialist hepatology/infectious diseases communities do not have the workforce to manage this demand. There will need to be upskilling of primary care in partnership with specialist services and an engaged and motivated community. Further simplification of clinical algorithms may be required. Lessons can be learnt from the hepatitis C experience over the past decade, allowing specialist services to prioritize the management of more complicated patient populations (cirrhosis, decompensated liver disease, HCC, coinfection with HDV, HCV, HIV, or significant comorbidities). Importantly, specialist services will need to deliver the functional cure strategies currently in development.^[14,15]

In conclusion, the AASLD ISDA Practice Guideline on treatment of chronic hepatitis B is an important reference document for all clinicians managing people living with hepatitis B. Notably, AASLD has applied a particularly strict methodology, which may explain the more conservative and evidence-focused stance in certain areas

compared with other guidelines. This rigor ensures credibility and robustness, although it limits opportunities for simplification that have been adopted in recent EASL and WHO guidelines. The field is evolving with new therapies advancing down the development pipeline, and it is hoped that the next iteration of this living document will be able to make recommendations that lead to a functional cure.

CONFLICTS OF INTEREST

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