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Chronic Hepatitis B: Treatment Criteria Expansion and Demystifying the "Grey Zone"

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This summary reviews Ghany MG, Pan CQ, Lok AS, et al. AASLD/IDSA Practice Guideline on treatment of chronic hepatitis B. Hepatology. 2025 Nov 4. doi: 10.1097/HEP.0000000000001549.

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Keywords: Chronic hepatitis B, Guideline, surveillance, infectious diseases

STRUCTURED ABSTRACT

Question: What are the evidence-based strategies for the prevention, surveillance, and treatment of chronic hepatitis B (CHB), including antiviral initiation thresholds, antiviral discontinuation criteria, and HCC surveillance protocols across multiple populations and clinical scenarios?

Design: This clinical practice guideline was developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). The methodology employed 6 structured PICO (Population, Intervention, Comparison, Outcomes) questions and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Four de novo systematic reviews were conducted alongside the utilization of 2 existing systematic reviews. Multiple clinical trials were considered. Certainty of evidence was rated as high, moderate, low, or very low, with adjustments for risk of bias, imprecision, inconsistency, indirectness, and publication bias. Recommendations were classified as strong or conditional based on the balance of benefits and harms, evidence

certainty, patient values, and equity considerations.

Patients: The guideline applies to adults and children with chronic hepatitis B infection, including: HBsAg-positive pregnant individuals with high viremia (HBV DNA >200,000 IU/mL); persons in the immune-tolerant phase (HBeAg-positive, HBV DNA >10,000,000 IU/mL, normal ALT); individuals in the indeterminate or "grey zone" phase (HBeAg-positive or negative with ALT and HBV DNA levels outside of the defined immune-active or inactive thresholds); patients on long-term nucleos(t)ide analogue therapy with sustained HBV DNA suppression; individuals who have achieved HBsAg loss; and persons coinfected with hepatitis C virus (HCV), hepatitis D virus (HDV), and/or human immunodeficiency virus (HIV).

Interventions: Interventions evaluated include: maternal antiviral prophylaxis with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) initiated at gestational week 28 (or week 16 when hepatitis B immune globulin is unavailable) to prevent mother-to-child transmission; antiviral therapy to reduce horizontal transmission in high-risk scenarios through shared decision-making; treatment initiation in immune-tolerant CHB for individuals over 40 years of age or with significant fibrosis (F2 or greater) or inflammation (grade 2 or higher); treatment initiation in patients who are HBeAg-negative and in the indeterminate phase using individualized risk assessment; continuation versus cessation of nucleos(t)ide analogue therapy in virally suppressed HBeAg-negative individuals without cirrhosis; and semiannual HCC surveillance with ultrasound and alpha-fetoprotein for at-risk populations including those with viral coinfections or older age at the time of HBsAg loss.

Outcomes: The guideline aims to optimize: reduction of vertical (mother-to-child) and horizontal HBV transmission; prevention of progression to cirrhosis, hepatic decompensation, and HCC; achievement of virologic suppression (undetectable HBV DNA), biochemical response (ALT normalization), and HBsAg loss (functional cure); reduction in liver-related mortality and need for liver transplantation.

Data Analysis: Data informing these recommendations were derived from randomized controlled trials, prospective and retrospective cohort studies, and observational analyses with systematic reviews. Meta-analyses quantified pooled incidence rates and, where appropriate, treatment effects. When high-quality direct evidence was

lacking, biological plausibility and indirect evidence informed recommendations. Strong recommendations indicate that most informed patients would choose the recommended intervention, while conditional recommendations suggest substantial variability in patient preferences necessitating shared decision-making.

Funding and Disclosures: This guideline was funded by AASLD and IDSA without external commercial support. Development adhered to National Academy of Medicine standards for transparency and methodological rigor.

Results: Chronic hepatitis B (CHB) remains an important global public health concern affecting approximately 296 million individuals worldwide.1 This updated 2025 guideline addresses critical topics including prevention of mother-to-child transmission and horizontal transmission, treatment in immune-tolerant and indeterminate phases ("grey zone"), treatment discontinuation, and hepatocellular carcinoma (HCC) surveillance.

Prevention of Mother-to-Child Transmission. A strong recommendation is provided for initiating TDF or TAF at gestational week 28 for pregnant individuals with HBV DNA >200,000 IU/mL, regardless of e-antigen status. If hepatitis B immune globulin is unavailable, TDF can be considered at gestational week 16, based on a recent randomized clinical trial demonstrating noninferiority in preventing transmission.3 TDF has a more extensive safety record in pregnancy than TAF. The choice of antiviral therapy should account for each medication's side-effect profile. Antiviral therapy can be discontinued at delivery, with monitoring for withdrawal flares every 1-3 months for up to 6 months post-partum.

Horizontal Transmission Prevention. AASLD addresses antiviral therapy to reduce horizontal transmission in high-risk scenarios (conditional recommendation, very low certainty). A shared decision-making approach is suggested for viremic individuals in high-risk settings, including those engaging in unprotected sex, injecting drugs with inconsistent harm reduction practices, living with susceptible household members, or healthcare workers performing exposure-prone procedures.

Immune-Tolerant Phase. Antiviral therapy is now conditionally recommended for persons in the immune-tolerant phase who are over the age of 40, or who have significant liver inflammation (grade 2 or higher) or fibrosis (F2 or greater), reflecting

subgroups. The most accurate non-invasive liver disease assessment is vibration-controlled transient elastography (VCTE). A cutoff threshold of ≥7kPa can identify patients with F2 fibrosis or higher. For individuals under 40 without significant fibrosis, treatment initiation should be based on shared decision-making. Providers should consider a family history of HCC. Close monitoring with HBV DNA and ALT testing at least every 6 months is suggested if treatment is not initiated.

HBeAg-negative Indeterminate Phase. There has been a paradigm shift from prior recommendations favoring monitoring alone to this guideline which now suggests antiviral therapy using a shared decision-making approach for HBeAg-negative adults without cirrhosis in the indeterminate phase (conditional recommendation, very low certainty). A meta-analysis demonstrated that antiviral treatment was associated with a 64% reduction in HCC incidence (adjusted incidence rate ratio 0.36, 95% CI 0.16-0.81). [2,4]

Nucleos(t)ide Analogue Discontinuation. The guideline conditionally recommends against discontinuing nucleos(t)ide analogue therapy until HBsAg loss is achieved. This recommendation reflects results from systematic reviews demonstrating modest rates of HBsAg loss (10.6% at 2 years) offset by substantial risks, including ALT flares (26.9% at 2 years), need for re-treatment (42% at 5 years).[5–10] Patients that can be considered to stop therapy should have no cirrhosis or hepatic decompensation, no HCC or extrahepatic HBV disease, no HIV or HDV coinfection, have ≥2 years of undetectable HBV DNA (after HBeAg seroconversion if initially HBeAg-positive), HBsAg <100 IU/mL, and be reliable for close monitoring.

HCC Surveillance Expansion. Following HBsAg loss, continued surveillance is suggested for patients with cirrhosis, a family history of HCC, men with loss of HBsAg after age 40, and women with loss of HBsAg after age 50. For HDV coinfection, surveillance is suggested for all adults regardless of cirrhosis status, given that the annual rates of incident HCC are 1.87% even without cirrhosis. For HIV coinfection, surveillance is suggested for men ≥18 years and women ≥40 years. For HCV coinfection, DAA therapy is recommended with subsequent surveillance following HBV mono-infection criteria.

The presented information is summarized in **Table 1**.

Clinical Question	Key Recommendation	Strength	Certainty
Prevention of Mother-to-Child Transmission	Initiate TDF or TAF at gestational week 28 for pregnant individuals with HBV DNA >200,000 IU/mL; TDF has a more extensive safety record	Strong	Moderate
Horizontal Transmission Prevention	Shared decision-making for antiviral therapy in high-risk viremic individuals not meeting standard treatment indications	Conditional	Very Low
Immune-Tolerant Phase Treatment	Antiviral therapy suggested for persons >40 years or with significant inflammation (grade ≥2) or fibrosis (≥F2); shared decision-making for those <40 years	Conditional	Very Low
HBeAg-Negative Indeterminate Phase	Antiviral therapy suggested using shared decision-making approach; factors favoring treatment include age >40, male sex, platelet count <180k/mm3	Conditional	Very Low
NA Therapy Discontinuation	Suggests not withdrawing NA therapy until HBsAg loss; strict criteria for those desiring discontinuation including qHBsAg <100 IU/mL	Conditional	Very Low
HCC Surveillance After HBsAg Loss	Continue surveillance for those with cirrhosis, family history of HCC, men with HBsAg loss after age 40, women after age 50	Conditional	Very Low
HCC Surveillance in HBV-HDV Coinfection	Surveillance suggested for all adults independent of cirrhosis status; individualize decision for children	Conditional	Very Low
HCC Surveillance in HBV-HIV Coinfection	Surveillance suggested for men ≥18 years and women ≥40 years of age	Conditional	Very Low
HCC Surveillance in HBV-HCV Coinfection	Recommend DAA therapy for HCV; HCC surveillance per HBV mono-infection criteria	Conditional	Very Low

Table 1. Overview of AASLD/IDSA 2025 chronic hepatitis B guideline recommendations.

AASLD, American Association for the Study of Liver Diseases; DAA, direct acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinom; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

COMMENTARY

Why Is This Important?

CHB leads to an estimated 1.1 million deaths annually from cirrhosis and HCC. In the United States alone, the disease burden may reach 1.8 million persons, with approximately 50% unaware of their diagnosis. This guideline is important because it addresses several key clinical scenarios. AASLD now provides recommendations on antiviral therapy for prevention of horizontal transmission and a change in the management of patients in the indeterminate or "grey zone" phase (a population comprising up to 40% of CHB patients). Additionally, it adopts a more conservative stance on nucleos(t)ide analogue discontinuation. It also recommends the expansion of HCC surveillance to include viral coinfections and post-HBsAg clearance populations.

Key Study Findings

For mother-to-child transmission prevention, a systematic review of 31 studies demonstrated that TDF and TAF are equally effective (risk ratio 1.09, 95% CI 0.15-7.65) and safe when initiated at gestational week 28 for pregnant individuals with HBV DNA >200,000 IU/mL.[11] A recent randomized clinical trial further showed that TDF initiation at week 16 with infant vaccination was noninferior to week 28 initiation with HBIG (0.76% vs 0% transmission).[3] For the indeterminate phase, a meta-analysis of 37 cohorts involving 14,691 individuals found that antiviral treatment was associated with a 64% reduction in HCC incidence (adjusted aIRR 0.36, 95% CI 0.16-0.81) after adjusting for age, sex, HBeAg status, and platelet count.[4] Regarding nucleos(t)ide analogue discontinuation, evidence from four RCTs showed that while HBsAg loss rates were 10.6% at 2 years among those stopping therapy (versus 0% in those continuing), this benefit was offset by ALT flares in 26.9% and retreatment requirements in 42% at 5 years.[5,12–14] Studies demonstrated annual incidence rates of 1.87% for HCC in HBV/HDV coinfected patients regardless of cirrhosis status, supporting surveillance for all adults with this cohort.

Caution

Several limitations warrant consideration when applying these recommendations. First, most recommendations carry low or very low certainty of evidence, highlighting the need for individualized clinical judgment. The evidence supporting treatment in the immune-tolerant phase comes largely from comparisons between antiviral strategies rather than treatment versus placebo, with a focus on virological response rather than clinical outcomes.[15,16] For horizontal transmission prevention, recommendations are based on biological plausibility rather than direct studies.[17] There are no clinical trials

supporting continuing nucleos(t)ide analogue therapy until HBsAg loss, instead, recommendation is derived from moderate risks of stopping therapy (ALT flares, 27% at 2 years; need for retreatment 42% at 5 years).[5,12]

My Practice

Not too FAST! – a simple mnemonic for providers considering factors that determine treatment for patients that fall in the "grey zone." **F**ibrosis, **A**ge, and **S**ex determine **T**reatment.

In practice, patients infrequently meet the immune active treatment thresholds. We often encounter situations that are nuanced, and until now, providers have lacked clear guidance. Given the safety profile of the "NUCs," the key decision comes down to explaining the benefits of treatment vs. monitoring, particularly for patients in the grey zone. Though guidelines provide recommendations, ultimately, there is an art as well as a science to CHB treatment.

Above all else, we do not know if we do not ask or test. For every patient that I evaluate, I ensure they have been screened for CHB at least once in their lifetime and I highly encourage vaccination for all adults even those over 60 without risk factors. This is particularly important in our pre-transplant population. Similarly, I am hesitant to discontinue therapy once started, though now with new guidance, I will be more likely to continue therapy until HBsAg loss is achieved or updated data identifies candidates in whom this strategy is appropriate. In addition, novel therapies, including bepirovirsen, are in late-stage trials to determine whether HBsAg clearance rates can be improved.

I continue to utilize resources like Transient Elastography for upfront risk stratification, and I ensure that patients have consistent 6-month follow-up visits, even when visits may be brief, to prevent gaps in care, including missed laboratory monitoring or HCC surveillance.

A final word on the CDC's Advisory Committee on Immunization Practices recent vote to end universal infant hepatitis B vaccination. This shift to individualized decision-making will undoubtedly change the landscape of CHB in the United States. However, as healthcare providers, we are still obliged to inform, advocate, and safeguard evidence-based prevention strategies to ensure our progress is not reversed.

For Future Research

Several research priorities emerge from this guideline. High-quality randomized controlled trials are needed to evaluate major liver-related outcomes (cirrhosis, HCC, mortality) with antiviral treatment in the immune-tolerant and indeterminate phases, as current evidence relies heavily on observational data with surrogate

virological endpoints. Studies examining the effectiveness of antiviral therapy in preventing horizontal transmission would strengthen recommendations currently based on indirect evidence. It would be worth examining patients specifically listed for liver transplantation as they have a heightened risk of developing HCC.[18–20] Research is needed to identify optimal biomarkers for predicting outcomes after nucleoside analogue or any other novel therapy that is discontinued beyond quantitative HBsAg, including HBV RNA and HBcrAg. Validation of HCC risk prediction models following HBsAg clearance would refine surveillance recommendations.[21] As novel therapeutic agents targeting functional cure advance through clinical development, updated guidelines incorporating these new treatment paradigms will be essential.

Reducing the burden of chronic hepatitis B will require systematic identification of infected individuals, sustained commitment to vaccination, timely antiviral treatment, and deliberate efforts to close persistent gaps in HCC surveillance and care.[22]

Social Media

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Conflict of Interest

The authors do not have conflicts of interest to disclose.

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