When to Initiate HBV Treatment

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Module 1: HBO 3rd Edition
Lesson 5: When to Initiate HBV Treatment

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Background

Chronic hepatitis B is a clinically silent and indolent disease with a long period of latency before significant adverse outcomes manifest, such as cirrhosis, decompensated liver disease, or hepatocellular carcinoma (HCC).[1] The hepatitis B virus (HBV) is not directly cytopathic to hepatocytes; the disease occurs when recurrent cycles (flares) of immune-mediated inflammation and liver injury result in the abnormal formation of collagenous scar or fibrosis that progresses over time.[2] Most individuals with HBV infection remain without symptoms or clinical manifestations unless cirrhosis-related complications develop.[2] Because early stages of cirrhosis are typically asymptomatic, it often goes undetected. In the following discussion, we will review the goals for HBV treatment and clinical indications for initiating antiviral therapy for chronic HBV. For the purposes of initiating HBV treatment, most experts and guidelines define chronic HBV infection as the presence of hepatitis B surface antigen (HBsAg) for at least 6 months.[3]

Goals of Therapy with Treatment of Chronic HBV

When considering treatment for persons with chronic HBV, it is important to consider the following goals of therapy.

- **Immediate Goal**: The most immediate goal for the treatment of persons with chronic HBV is to reduce hepatic inflammation (as measured by alanine aminotransferase [ALT] and aspartate aminotransferase serum aminotransferases [AST] levels) and to achieve virologic suppression (as indicated by plasma HBV DNA levels below the limit of detection).
- **Intermediate Goal**: With sustained virologic suppression and normalization of ALT, additional intermediate goals should include improvement in serologic and histologic markers. For persons with a positive hepatitis e antigen (HBeAg), the loss of HBeAg and change of antibody to HBeAg (anti-HBe) from negative to positive is referred to as “HBeAg seroconversion” and indicates reduced intrahepatic HBV replication, and portends a more favorable prognosis. With sustained virologic suppression, it is expected that persons with chronic HBV will also have hepatic histologic improvement, manifested by histologic evidence of regression of inflammation and fibrosis on liver biopsy.[4,5]
- **Long-Term Goals**: The ultimate and most important goal for treating persons with chronic HBV is to prevent the clinical complications of this infection, which include cirrhosis, hepatocellular carcinoma, and liver-related mortality.[6,7,8]
- **Prevention of HBV Transmission**: When treating pregnant mothers with HBV DNA levels greater than 200,000 IU/mL, the primary goal is to prevent HBV transmission to the infant.[9] In addition, treatment of adults with chronic HBV may reduce sexual and injection-drug related transmission of HBV to another person who does not have HBV.[10]
- **Control Rather than Eradication of HBV**: The eradication of HBV is not currently feasible with existing antiviral therapy, which can be suppressive and potentially disease-modifying rather than curative.[1] The persistence of HBV is thought to be due in part to the stability of the HBV genome in the form of covalently closed circular (ccc) DNA and integrated HBV DNA.[1,4,11] These stable genetic templates make HBV eradication challenging. Notably, loss of hepatitis B surface antigen (spontaneously or with antiviral therapy) is a rare event with current therapy and does not necessarily indicate HBV eradication.[1] Reactivation of HBV can still occur in individuals with isolated hepatitis B core antibody (anti-HBc) who are treated with immunosuppressive, cytotoxic, or biologic disease-modifying antirheumatic drugs.[12,13,14]

Factors Used to Determine Whether to Initiate Treatment

Because of the dynamic nature of HBV infection, our inability to eradicate HBV, and the potentially long, if not indefinite, duration of therapy (as in the case of oral nucleoside or nucleotide analogues), treatment is not universally indicated for everyone with chronic HBV. Rather, treatment is recommended for those who are thought most likely to benefit from the standpoint of disease modification and/or reduction of onward transmission. Conceptually, the clearest indications for treatment are when significant liver fibrosis has occurred and/or when there is active HBV DNA replication along with sustained hepatic inflammation. Therefore, the decision to treat persons with chronic HBV typically incorporates the following three factors: (1) fibrosis status assessed by either noninvasive methods or biopsy, (2) evidence of hepatic inflammation, as measured by alanine aminotransferase (ALT) levels (or less commonly liver biopsy), and (3) ongoing HBV replication as indicated by serum HBV DNA levels. Some guidelines incorporate the HBeAg status as another parameter to consider when deciding whether to initiate HBV treatment. In addition to these criteria, there are special conditions for which treatment of chronic HBV would be advised, even if the patient does not have an indication based on the presence of significant fibrosis and/or hepatic inflammation; these conditions will be discussed briefly as well.

Presence of Moderate Disease or Significant Fibrosis

There is now consensus among the major hepatitis treatment guidelines (American Association for the Study of Liver Diseases [AASLD], European Association For The Study Of The Liver [EASL], Asian Pacific Association for the Study of the Liver [APASL], and the World Health Organization [WHO]) that the presence of at least moderate liver necroinflammation or fibrosis warrants initiation of HBV treatment.[3,15,16,17,18] Moderate or significant fibrosis has historically been defined by the gold standard of liver biopsy and the presence of METAVIR stage F2 fibrosis. However, given the risks and limited accessibility/acceptability of biopsy, noninvasive measures are considered reasonable alternatives when biopsy is not feasible.[3,16] Among these major HBV treatment guidelines, the 2024 WHO guidelines directly address the threshold of significant fibrosis by the AST-platelet ratio index (APRI) or transient elastography.[15]

Cirrhosis Status

Individuals with chronic HBV and cirrhosis are at much greater risk of liver-related morbidity and mortality than persons without cirrhosis. The 5-year cumulative risk of hepatocellular carcinoma, for example, is estimated to be 10- to 15-fold higher in patients with cirrhosis than those without.[19] The evidence base for the beneficial impact of HBV-active antiviral therapy on reducing the risk of adverse clinical outcomes, such as hepatic decompensation or HCC, is particularly compelling for patients with cirrhosis.[20] The presence of cirrhosis is generally considered a strong indicator that favors initiating HBV treatment.

Evaluation of Disease Severity

Since cirrhosis is a strong indication for HBV treatment, it is important to evaluate persons with chronic HBV for the presence of advanced fibrosis or cirrhosis. A detailed discussion of Evaluation and Staging of Liver Fibrosis can be found on the Hepatitis C Online site. Current guidelines do not directly address the best method for identifying cirrhosis in patients with chronic HBV. The following provides a brief summary regarding the evaluation of cirrhosis in a person with chronic HBV infection, including invasive testing that can establish a definitive diagnosis (liver biopsy) and noninvasive tests that make a presumptive diagnosis (transient elastography, hepatic ultrasound, and laboratory markers). Ultimately, as with many diagnoses, the determination of cirrhosis typically relies on an overall appraisal of multiple clinical parameters, as well as pre-test probability.

- **Clinical Features**: Since many people can develop cirrhosis without obvious clinical findings, the physical examination should not be used to rule out cirrhosis. Nevertheless, the presence of obvious manifestations of cirrhosis on physical examination, such as ascites, jaundice, spider angiomata,

splenomegaly, or encephalopathy, are important to evaluate and can increase the likelihood of a cirrhosis diagnosis.

- **Laboratory Markers**: Assessment of liver disease severity also includes laboratory evaluation of complete blood count with platelet count, serum aminotransferase levels (ALT and AST), alkaline phosphatase, bilirubin, serum albumin, and prothrombin time. A gradual decline in serum albumin, in conjunction with a gradual increase in alkaline phosphatase or prothrombin time without any other explanation, may signal cirrhosis. In viral hepatitis, ALT typically exceeds AST, but with advanced fibrosis, this ratio often reverses. The Fibrosis 4 (FIB-4) score is based on AST/ALT ratio, platelet count, and age (FIB-4 Calculator). This score has been shown to have reasonable performance in differentiating mild (stages 0–1) from more advanced (stages 3–4) fibrosis in chronic hepatitis B that is not being treated.[21,22] The aspartate aminotransferase to platelet ratio index (APRI) is also an acceptable alternative for identifying significant fibrosis in people with chronic HBV.[23] It was found in one meta-analysis to have moderate accuracy, with sensitivity and specificity varying by cutoff (e.g., APRI 0.5 has a sensitivity of 70% and a specificity of 60%) for significant fibrosis.[24]
- **Elastography**: Vibration-controlled transient elastography (VCTE) offers reasonably high diagnostic accuracy in detecting cirrhosis, but estimations of liver stiffness, the measurement of elastography, can be confounded by the presence of significant hepatic necroinflammation.[25,26] Magnetic resonance elastography (MRE) has also emerged as another highly accurate and noninvasive modality for assessing fibrosis in chronic HBV.[27,28]
- **Hepatic Ultrasound**: Ultrasonography is often used in clinical practice to stage chronic viral hepatitis. While it can have high specificity for detecting cirrhosis if a small nodular liver and signs of portal hypertension (e.g., splenomegaly) are present, its sensitivity for detecting advanced fibrosis can be suboptimal.[29,30] Hepatic ultrasound is not generally used for fibrosis staging or clinical decision-making with respect to treatment, unless findings of cirrhosis or portal hypertension are present.
- **Liver Biopsy**: A liver biopsy remains the gold standard for determining disease severity in chronic HBV and provides a direct assessment of inflammatory activity and degree of fibrosis. Cirrhosis is thus a histologic diagnosis, and refers to an advanced stage of fibrosis that has extended beyond the portal triad to form bridges of scar that eventually result in the distortion of hepatic architecture. Liver biopsy can have limitations, including undersampling and misclassification.[31] Liver biopsy is also invasive and although the risk of complications, such as intrahepatic bleeding or biliary injury, is very low, liver biopsy is recommended only for a subset of patients with chronic hepatitis B.[31]

Decompensated Cirrhosis

Persons with cirrhosis are considered to have decompensated cirrhosis if certain liver-related complications develop, including jaundice, ascites, esophageal variceal bleeding, hepatic encephalopathy, or impaired hepatic synthetic function (as reflected by elevated prothrombin time, elevated total bilirubin, and/or low serum albumin). Decompensated cirrhosis is often defined as a Child-Turcotte-Pugh score of 7 or greater (class B or C). Because antiviral therapy has been shown to improve transplant-free survival in patients with decompensated cirrhosis, they should also be started on oral antiviral therapy regardless of ALT or HBV DNA levels. Patients with more advanced disease should also be referred for liver transplantation, if eligible.

Serum HBV DNA Level

Because there can be a lack of correlation between ALT and disease activity when examined on its own, ALT must be considered in conjunction with the serum HBV DNA level.[32,33] The HBV DNA levels have been associated with the risk of developing hepatocellular carcinoma and cirrhosis (Figure 1).[34,35]

- In the large prospective REVEAL cohort study, investigators enrolled 3,653 persons 30 to 65 years of age in Taiwan, and followed them for a mean of 11.4 years. When compared with those with HBV DNA levels less than 10,000 copies/mL (approximately 2,000 IU/mL), the risk of liver cancer was shown to range from 2.7-fold higher in those with a serum HBV DNA level of 10,000 to 99,999 copies/mL (approximately 2,000 to 20,000 IU/mL) to 10.7-fold higher in those with a HBV DNA level greater than

or equal to 1 million copies/mL (greater than or equal to approximately 200,000 IU/mL).[34] This landmark study provided the early proof of concept for serum HBV DNA levels as a major driver of disease pathogenesis and the possibility of HBV suppression as a key intervention in mitigating disease progression.[34]

- In a separate but similar study, persons with chronic HBV were also found, in a dose-dependent gradient, to have an increased risk of cirrhosis with increasing serum HBV DNA levels, with a notable 6.5-fold higher risk in those with HBV DNA levels greater than 1 million copies/mL (approximately 200,000 IU/mL) compared to those with an HBV DNA level less than 300 copies/mL (less than approximately 60 IU/mL).[35]

Alanine Aminotransferase (ALT) Levels

Serum ALT levels provide a rapid and noninvasive measure that can indicate hepatic inflammation. The 2025 AASLD/IDSA HBV Treatment Guideline recommended using an upper limit of normal (ULN) for ALT (less than 25 U/L for women and less than 35 U/L for men) for HBV treatment decisions.[18] These ULN cutoffs are lower than the ULN defined by many commercial laboratories, which derive their range from the general population and more specifically from blood donors without evidence of HBV or hepatitis C virus (HCV) infection. Due to the high prevalence of steatotic liver disease among "healthy" donors, the ULN from these donor pools may be higher and therefore not optimized to detect individuals with underlying liver disease caused by viral hepatitis.[36] Ideally, a treatment decision should not be made on the basis of a single serum ALT value. These values often vary, and the phase of HBV infection generally needs to be confirmed with multiple assessments of serum ALT over time, typically every 3 to 6 months, given the dynamic nature of HBV infection.

Immune Phases of Chronic HBV Infection

From a conceptual standpoint, chronic HBV infection has been characterized by four phases (or types of immune responses): immune tolerant, immune active, inactive carrier, and indeterminate.[18,37,38,39] The liver damage that can occur with chronic HBV infection is primarily related to the host immune response to hepatocytes infected with HBV. The inflammation and liver cell death associated with this immune response are thought to occur predominantly in the immune-active phase of chronic HBV. The phases of chronic HBV infection are not considered static; individuals can undergo transitions in and out of these different stages throughout their lifetime (Figure 2).[3,38]

Immune-Tolerant Chronic HBV

The 2025 AASLD/IDSA HBV Treatment Guideline characterizes the immune-tolerant phase as one with a positive HBeAg, very high HBV DNA levels (typically greater than 10 million IU/mL), normal ALT and/or AST levels, and a liver biopsy (if done) showing no fibrosis and minimal inflammation.[18] Despite having very high HBV DNA levels, there is little immune reaction to the HBV-infected hepatocytes and minimal liver inflammation.& Although antiviral therapy was historically not recommended for persons in the immune-tolerant phase, the 2025 AASLD/IDSA HBV Treatment Guideline now recommends antiviral therapy for individuals in the immune-tolerant phase who (1) are older than 40 years of age and (2) have significant liver inflammation (grade 2 or higher) or fibrosis (F2 or higher) based on non-invasive testing or liver biopsy histologic findings.[18] For individuals in the immune-tolerant phase who do not meet these criteria, treatment can be started earlier based on shared decision-making.[18] Much of this shift in recommendations comes from studies that show a correlation between HBV DNA levels and HCC risk, as well as studies demonstrating that up to one-third of persons with chronic HBV who are older than 40 years of age with normal ALT can have significant inflammation (grade 2 or higher) and/or fibrosis (stage 2 or higher).[40] In these patients, normal ALT can be a less reliable predictor of quiescent or minimal disease.[40] Individuals in the immune-tolerant phase who are not on active antiretroviral therapy should have their ALT monitored every 6 months to assess for transition to immune-active infection.[18]

Immune-Active Chronic HBV or Reactivation of Chronic HBV

The 2025 AASLD/IDSA HBV Treatment Guideline defines immune-active chronic HBV as persistent elevation of ALT at least 2 times greater than the upper limit of normal (or evidence of significant histologic disease) plus elevated HBV DNA above 2,000 IU/mL if HBeAg negative or above 20,000 IU/mL if HBeAg positive.[18] If this occurs in persons who are HBeAg-negative after a period in the inactive carrier phase, this has also been referred to as reactivation. For persons who do not have cirrhosis or any special condition that warrants HBV treatment, the main indication for therapy would be evidence of immune activity, as reflected by persistent (at least 3 to 6 months) elevations in both ALT and plasma HBV DNA levels. The evidence to support the benefit of antiviral treatment in reducing the risk of clinical events (cirrhosis and HCC-related mortality) is found primarily in patients who have met criteria for immune-active disease.[20] These include observational studies as well as randomized controlled trials (RCTs) that compared a control group (no treatment or placebo) with either interferon-based therapy or an oral nucleoside or nucleotide analogue agent. Seven RCTs involving 3,463 patients followed for a mean of 28 months demonstrated that antiviral therapy significantly reduced the risk of decompensated liver disease and cirrhosis.[20] Further, in 35 observational studies of 59,201 patients followed for a mean of 60 months, antiviral therapy versus control was associated with a decreased risk of HCC, cirrhosis, and all-cause mortality in this population.[20]

Inactive Chronic Hepatitis B

The AASLD characterizes inactive chronic HBV as HBeAg-negative (and anti-HBe-positive), status with serum HBV DNA levels less than 2,000 IU/mL, persistently normal ALT and/or AST levels, a liver biopsy that confirms the absence of significant necroinflammation, and variable levels of fibrosis observed on liver biopsy or noninvasive testing.[3] Antiviral therapy is not typically recommended in these individuals, but they require ongoing monitoring for immune-active transition. In addition, these individuals can go on to HBV reactivation, either spontaneously or with immunosuppression. It is important to note that even inactive carriers with low HBV viral levels remain at risk for HCC.[41,42] Therefore, guidelines recommend these patients also undergo HCC screening when indicated.

Indeterminate or Gray-Zone Phase

Approximately 40–50% of persons with chronic hepatitis B fall into an indeterminate (or “gray zone”) phase of infection, meaning they do not fall into one of the defined HBV phases (immune tolerant, immune active, or immune inactive).[43] The most prevalent indeterminate profile is among those who are HBeAg-negative with normal ALT but elevated HBV DNA level greater than 2000 IU/mL.[43] More than 40% of these individuals may have significant hepatic inflammation or fibrosis on biopsy, even with normal ALT levels.[44,45] Studies have also shown that this group is at risk of adverse outcomes. Their 10-year cumulative risk of immune activity (ALT elevation) or HCC is not insubstantial and notably higher than in those with inactive disease.[46,47,48] Meta-analyses and cohort studies suggest that antiviral therapy can lower the risk of HCC and cirrhosis in patients in the indeterminate phase, particularly among subgroups at high risk.[48,49] The 2025 AASLD/IDSA HBV Treatment Guideline recommends antiviral therapy using a shared decision-making approach in individuals with chronic HBV in the indeterminate phase, taking into account risks and benefits of therapy, as well as patient specific factors (e.g., fibrosis stage, age, and sex).[18]

Hepatitis B Treatment Guidance Recommendations

Several leading professional organizations have provided guidance on when to initiate treatment for persons with chronic HBV.[3,16,17] The following summary is intended to provide a succinct description of their recommended indications for initiating HBV treatment. The reader is encouraged to access these original documents for additional details, discussion, and information about the level of evidence and strength of recommendations.Table 1.

HBV Treatment Recommendation Based on Major Organization Guidelines

Risk Group	AASLD/IDSA 2025	APASL 2015	EASL 2025	WHO 2024
Without cirrhosis	Treat if: – Immune-active disease defined as: • (1) elevation of ALT (≥2 x ULN) or evidence of significant histologic disease, and • (2) HBV DNA >2,000 IU/mL if HBeAg negative or >20,000 IU/mL if HBeAg positive. - Immune-tolerant if they are: >40 years of age or have significant liver inflammation (≥grade 2) or fibrosis (≥F2) on liver biopsy or non-invasive testing. - Indeterminant phase, HBeAg negative: shared decision-making - Higher risk for HBV transmission	Treat if: – ALT >2x ULN[3], *or* – Significant histologic disease[3] *and* – HBV DNA >2000 IU/mL if HBeAg-negative – HBV DNA >20,000 IU/mL if HBeAg-positive	Treat if: – HBV DNA >2,000 IU/mL and any of the following: • ALT >ULN, *or* • Fibrosis (equivalent of ISHAK ≥F3/Metavir ≥F2 [non-invasive assessment is preferred, liver stiffness measurement >7 kp]), *or* • Risk factors for HCC, *or* • Extrahepatic manifestations, *or* • Immunosuppression, or • Risk for HBV transmission	Treat if any: – Significant fibrosis[5] – HBV DNA >2,000 IU/ AND ALT level>ULN – Coinfection with HCV or HIV – Family history of live cancer or cirrhosis – Comorbidities – Immune suppressior – Extrahepatic – Persistent abnormal
Compensated cirrhosis	Treat all[4]	Treat if: - HBV DNA >2,000 IU/mL, *or* - ALT elevated[3]	Treat if: - HBV DNA is positive	Treat all[4]
Decompensated cirrhosis	Treat all[4] and refer for liver transplantation	Treat all[4]	Treat all[4]	Treat all[4]

Abbreviations: AASLD = American Association for the Study of Liver Diseases; APASL = Asian Pacific Association for Study of the Liver; EASL= European Association for the Study of the Liver; WHO = World Health Organization; ALT = alanine aminotransferase; ULN = upper limit of normal

[1]Regardless of HBV DNA, ALT, or HBeAg status

[2]Upper limit of normal, defined as ALT 35 IU/L for men, 25 IU/L for women

[3]Defined as ALT 40 IU/L for both men and women

[4]HBV DNA level is based on a sensitive NAT assay with a lower limit of detection <20 IU/mL

Risk Group	AASLD/IDSA 2025	APASL 2015	EASL 2025	WHO 2024

[5]The thresholds for significant fibrosis by APRI or transient elastography have not been fully validated in adolescent
[6]Defined as two ALT values greater than 19 IU/L for women and 39 IU/L for men at unspecified intervals during a 6-to-12-month period.

Source:

- European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2025:S0168-8278(25)00174-6. [PubMed Abstract]
- Ghany MG, Pan CQ, Lok AS, et al. AASLD/IDSA Practice Guideline on treatment of chronic hepatitis B. Hepatology. 2025 Nov 4. Online ahead of print. [PubMed Abstract]
- Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1-98. [PubMed Abstract]
- Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-99. [PubMed Abstract]
- World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. March 29, 2024. [WHO]

American Association for the Study of Liver Diseases

The American Association for the Study of Liver Disease (AASLD) hepatitis B guidance has served as the main HBV treatment guidance in the United States.[3,50] The most recommendations were developed by the AASLD in collaboration with the Infectious Diseases Society of America (IDSA).[18] The updated 2025 AASLD/IDSA HBV Treatment Guideline recommends initiating HBV treatment in the following situations in persons with chronic HBV.[18]

- **Immune-Active Disease**: Treatment is recommended for persons with immune-active disease. For treatment purposes, immune-active disease is defined as (1) elevation of ALT (at least 2 times the upper limit of normal) or evidence of significant histologic disease and (2) elevated HBV DNA above 2,000 IU/mL if HBeAg negative or above 20,000 IU/mL if HBeAg positive. The AASLD recommends using an ALT upper limit of normal of 35 U/L for males and 25 U/L for females to guide management decisions. Notably, neither the 2018 nor the 2025 guidance discusses the duration of ALT elevation to be counted as a persistent (rather than isolated) finding, but prior 2009 guidelines discuss using a period of 3 to 6 months. Significant histologic disease is defined as at least moderate necroinflammation and/or fibrosis.
- **Compensated Cirrhosis**: Treatment is recommended for all persons with cirrhosis, regardless of HBV DNA level, HBeAg status, or ALT levels.
- **Decompensated Cirrhosis**: Initiation of oral antiviral treatment is recommended in conjunction with referral for consideration of liver transplantation.
- **Select Patients in the Immune-Tolerant Phase**: Antiviral therapy is recommended for patients in the immune-tolerant phase who are older than 40 years of age or have significant liver inflammation (grade 2 or higher) or fibrosis (F2 or higher) on liver biopsy or non-invasive testing. Younger patients in the immune-tolerant phase can consider initiating antiviral therapy based on shared decision-making with their provider.
- **HBeAg-Negative Individuals in the Indeterminant Phase**: Treatment is recommended, using a shared-decision making approach. Individuals who are older (>40 years), male sex, have low normal platelets (1.45 or elastography ≥8 kPa) may be most likely to benefit.
- **Individuals in High-Risk Scenarios for Transmission**: For patients who are in high-risk scenarios for HBV transmission (e.g., multiple sex partners, injection drug use, health care workers engaged in exposure-prone procedures) but otherwise do not meet criteria for antiviral treatment, initiation of antiviral therapy can be considered based on shared decision-making.

Asian Pacific Association for the Study of the Liver

The Asian Pacific Association for the Study of the Liver (APASL) hepatitis B guidance was generated by a panel of experts in this region, predominantly from the specialties of hepatology and gastroenterology. The most recent APASL Hepatitis B Guidance was published in 2015.[17] The 2015 APASL Hepatitis B Guidelines recommend initiating HBV treatment in the following situations for persons with chronic HBV.[17]

- **Without Cirrhosis**: Treatment may be started in noncirrhotic patients who have (1) persistent elevation of ALT (greater than 2 times the upper limit of normal at least 1 month between tests) and (2) elevated HBV DNA above 2,000 IU/mL if HBeAg negative or above 20,000 IU/mL if HBeAg positive. The ALT upper limit of normal used to guide management decisions is 40 U/L for both males and females. In addition, patients who have evidence of at least moderate inflammation and/or significant fibrosis on biopsy should also be considered for therapy regardless of ALT or HBV DNA level. Moderate inflammation is defined as either an Ishak activity score greater than 3 (out of a possible 18 total) or a METAVIR activity score of A2 or A3; significant fibrosis means F2 or greater by METAVIR fibrosis score or Ishak fibrosis stage of 3 or greater.
- **Compensated Cirrhosis**: Treatment is recommended with (1) HBV DNA level greater than 2,000 IU/mL regardless of ALT level or HBeAg status, or (2) any detectable HBV DNA level if ALT is elevated, regardless of HBeAg status.
- **Decompensated Cirrhosis**: Treatment is recommended with any detectable HBV DNA level, regardless of ALT levels or HBeAg status.

European Association for the Study of the Liver

The European Association for the Study of the Liver (EASL) hepatitis B clinical practice guidelines are the major hepatitis B guidance for Europe and this document was primarily written by gastroenterology and hepatology specialists.[51] The EASL Hepatitis B Clinical Practice Guidelines state that, in principle, all individuals with HBsAg-positive status and detectable HBV DNA levels are candidates for antiviral therapy.[51] The indication for treatment is primarily based on HBV DNA and ALT levels, fibrosis stage, and risk of liver disease progression and HCC.[51] The following summarizes the EASL guidelines simplified treatment algorithm for persons with chronic HBV infection (HBsAg-positive), independent of HBeAg status.[51] More detailed and expert guidance on indications for hepatitis B treatment, including treatment decisions based on HBeAg status is provided in these guidelines, but will not be addressed here.[51]

With Cirrhosis or Advanced Fibrosis (equivalent of ISHAK ≥F4/Metavir ≥F3 [non-invasive assessment is preferred, liver stiffness measurement>8 kPa])

- Anti-HBV treatment is indicated if the HBV DNA is positive (HBV DNA measurement should be with a sensitive nucleic acid test (NAT) with a lower limit of detection ULN, *or*
- Fibrosis (equivalent of ISHAK ≥F3/Metavir ≥F2 [non-invasive assessment is preferred, liver stiffness measurement ;>7 kPa]) *or*
- Risk factors for HCC, *or*
- Extrahepatic manifestations, *or*
- Immunosuppression,*or*
- Risk for HBV transmission (threshold values for HBV DNA vary depending on the activity and risk of transmission. Tenofovir indicated in pregnant women with HBV DNA ≥200,000 IU/mL to prevent mother-to-child transmission.

Monitoring is recommended for persons without cirrhosis or advanced fibrosis and HBV DNA ≥2,000 IU/mL, but do not meet any of the above additional criteria.
Monitoring is recommended for persons who have an HBV DNA level less than 2,000 IU/mL, except if the ALT is greater than the ULN and other liver diseases have been excluded as the cause of the elevated ALT level.
For persons who do not meet criteria based on HBV DNA level and additional factors listed above, anti-HBV

treatment is indicated if any of the following are present or develop while monitoring:

- HCC
- HIV coinfection
- Extrahepatic manifestations
- Immunosuppression

orld Health Organization

2024, the World Health Organization (WHO) issued an update to its comprehensive guidance on HBV prevention, re and treatment. This update included expanded treatment eligibility for all adults, as well as for adolescents aged 2 or older. Among the four main criteria for treatment outlined below, only one requires access to HBV DNA uantitation, which has been a major barrier to accessing treatment in more resource-limited settings.

- **Without Cirrhosis**: Treat adults or adolescents ≥12 years if:
  - Significant fibrosis, as defined by:
    - APRI >0.5 or transient elastography >7.0 kPa, *or*
    - HBV DNA level >2000 IU/mL and ALT ≥30 U/L for males, ≥19 U/L for females
  - Presence of any of the following:
    - Coinfection (HDV, HIV, HCV), *or*
    - Family history of liver cancer or cirrhosis, *or*
    - Immune suppression, *or*
    - Comorbidities (e.g., diabetes, metabolic-associated steatotic liver disease [MASLD]), *or*
    - Extrahepatic manifestations (e.g., glomerulonephritis, vasculitis)
- **Persistently Abnormal ALT Levels**: Treatment is recommended for persistently abnormal ALT levels (defined as two ALT values of ≥19 for women or ≥30 I/U for men at unspecified intervals during a 6- to 12-month period).
- **Cirrhosis**: Treatment is recommended for all such individuals, regardless of HBV viral level.
- **Decompensated Cirrhosis**: Treatment is recommended for all such individuals, regardless of HBV viral level.

BV Primary Care Workgroup

he HBV Primary Care Workgroup includes members from primary care, hepatology, infectious diseases, pharmacy, nd community and public health.[52] The Hepatitis B Management: Guidance for the Primary Provider was first leased in early 2020 and was recently updated in 2025.[52,53] The guidance is accessible on this website lepatitis B Online).[52] The goal of this document is to provide simplified, up-to-date, and readily accessible HBV anagement guidance for health care professionals.[52] This guidance states that, in principle, all individuals who re HBsAg-positive with viremia are candidates for treatment. Factors to consider are fibrosis stage, HBV DNA level, LT level, risk of disease progression, HCC, and patient preference. The following summarizes the HBV Primary Care orkgroup 2025 Guidance on hepatitis B management for clinicians.[52]

1. Significant fibrosis or cirrhosis (≥F2; elastography >7 kPa or APRI >0.5) *and* detectable HBV DNA

   or

2. HBV DNA >2000 IU/mL and one of the following:

- Elevated ALT (male >35 U/L; female >25 U/L)
- Family history of HCC

or

3. Any of the following conditions:

- Immunosuppression
- Viral coinfections (e.g. HIV, HDV, HCV treatment)
- HBV transmission risk factors (e.g. pregnant with HBV DNA > 200,000 IU/mL)
- Extrahepatic manifestations of HBV (e.g., glomerulonephritis, polyarteritis nodosa)

or

4. Patient preference for treatment over monitoring-only

Special Indications for Initiating Treatment

There are a variety of special clinical situations in patients with HBV where antiviral therapy may be warranted regardless of cirrhosis status, hepatic aminotransferase levels, or HBV DNA levels.[3] The most common of these specific circumstances are listed below.

- **Pregnant Women with an HBV DNA Level Greater than 200,000 IU/mL**: Treatment of HBV, beginning at 28 weeks' gestation, is indicated for all pregnant women who have an HBV DNA level greater than 200,000 IU/mL at any time in the pregnancy.[9,18] The purpose of HBV treatment of a pregnant woman with a high HBV DNA level is to further reduce the risk of perinatal transmission beyond what is accomplished by passive and active HBV immunization given to the newborn.[54]
- **Persons with HIV and HBV Coinfection**: Fully suppressive antiretroviral therapy to treat HIV is recommended for all persons with HIV.[55] In addition, all persons with HIV and chronic HBV should receive concomitant treatment for HBV, regardless of the cirrhosis status, hepatic aminotransferase levels, or HBV DNA levels.[56] The goal of treating HBV in persons with HIV coinfection is to reduce the excess risk of liver-related morbidity and mortality that persons with HIV and HBV coinfection have (when compared to persons who have HBV monoinfection or HIV monoinfection).[57,58] Antiviral treatment should ensure concomitant fully active treatment for HIV and HBV, with a regimen that ideally includes three medications with activity against HIV and two medications with activity against HBV (typically tenofovir DF or tenofovir alafenamide with either emtricitabine or lamivudine).[56]
- **Persons at Risk for HBV Reactivation**: Individuals with untreated chronic HBV or past infection with HBV are at risk of HBV reactivation if they receive immunosuppressive, cytotoxic, or biologic disease-modifying antirheumatic drugs.[13,14,59] In this context, HBV reactivation is defined as either an increase in HBV DNA levels over baseline or seroreversion (from HBsAg negative to HBsAg positive). This reactivation results from loss of immune control of HBV, with potential high-level viral replication and resultant inflammatory activity or flare.[13,14] Reactivation of HBV can also occur in persons receiving HCV therapy with direct-acting antiviral agents (DAAs).[60,61] In any setting of increased risk of HBV reactivation, the primary goal of administering HBV antiviral therapy prior to immunosuppressive or HCV therapy is to reduce the risk of HBV reactivation and associated liver injury, which has the potential to be severe in this setting.[13,14] For more details on this topic, see the Lesson on HBV Reactivation in the Setting of Immunosuppression.
- **Persons with Chronic HBV Receiving HIV Preexposure Prophylaxis**: In the United States, there are two FDA-approved oral regimens for HIV preexposure prophylaxis (PrEP): tenofovir DF-emtricitabine (TDF-FTC) and tenofovir alafenamide-emtricitabine (TAF-FTC); both of these medications also have activity against HBV.[62] The use of HIV PrEP may be indicated in a person who also has chronic HBV infection. Since both of the oral medication combinations used for HIV PrEP are highly active against HBV, any person with chronic HBV who is receiving oral HIV PrEP is also receiving treatment for HBV. It is important to understand that intermittent use of oral HIV PrEP can create unintended negative consequences related to the HBV infection, such as generating HBV drug resistance or developing HBV-related hepatic flares. Thus, persons with chronic hepatitis B who are taking oral HIV PrEP should be counseled about the risks of intermittent use of oral HIV PrEP and discontinuation of oral HIV PrEP. If HIV PrEP is stopped and no additional treatment, such as entecavir, is used, then clinical and laboratory monitoring is needed after the HIV PrEP is stopped. In contrast to the oral PrEP options, the long-acting injectable medications approved for HIV PrEP—long-acting injectable cabotegravir (CAB-LA) and lenacapavir subcutaneous injection (LEN-SQ)—are not active against HBV.

Summary Points

- The goals of HBV treatment are to prevent the development of cirrhosis, hepatocellular carcinoma, and liver-related death.
- Antiviral therapy is not considered curative but can improve serologic, virologic, and histologic endpoints. It has also been shown to reduce the risk of liver-related outcomes such as cirrhosis and HCC in selected patients.
- Multiple organizations, including AASLD, EASL, APASL, and the WHO, have issued guidance that outlines treatment indications for persons with chronic HBV.
- According to these groups, antiviral therapy is indicated in all patients with chronic HBV and cirrhosis, regardless of ALT level.
- According to most guidelines, antiviral therapy is indicated in patients with chronic HBV without cirrhosis who meet the criteria for persistent immune-active disease, as defined by elevated HBV DNA level (greater than 2,000 IU/ML) and persistent elevated ALT levels.
- For the purpose of making treatment decisions in persons with chronic HBV infection, the AASLD guidance recommends using an upper range of normal ALT of 25 IU/L in women and 35 IU/L in men; the WHO ALT thresholds are 19 IU/L for women and 39 IU/L for men.
- Antiviral therapy for chronic HBV is indicated in patients who have evidence of at least moderate liver necroinflammation or fibrosis, determined traditionally by biopsy but now more often by noninvasive measures such as AST-platelet ratio index (APRI) or vibration-controlled transient elastography (VCTE).
- Antiviral therapy for chronic HBV may be indicated regardless of the phase of disease in those patients who have a variety of special conditions that include pregnancy, immune suppression, and HIV coinfection.
- Other clinical factors such as age, family history of HCC, risk of onward transmission, and comorbidities (i.e., extrahepatic manifestations) should be considered in the decision to treat or perform a biopsy on an individual with chronic HBV.

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Figures

Figure 1 (Image Series) - HBV DNA Levels and Liver Disease Outcomes (Image Series) - Figure 1 (Image Series) - HBV DNA Levels and Liver Disease Outcomes
Image 1A: Baseline HBV DNA Levels and Risk of Developing Hepatocellular Carcinoma

Source: Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65-73.

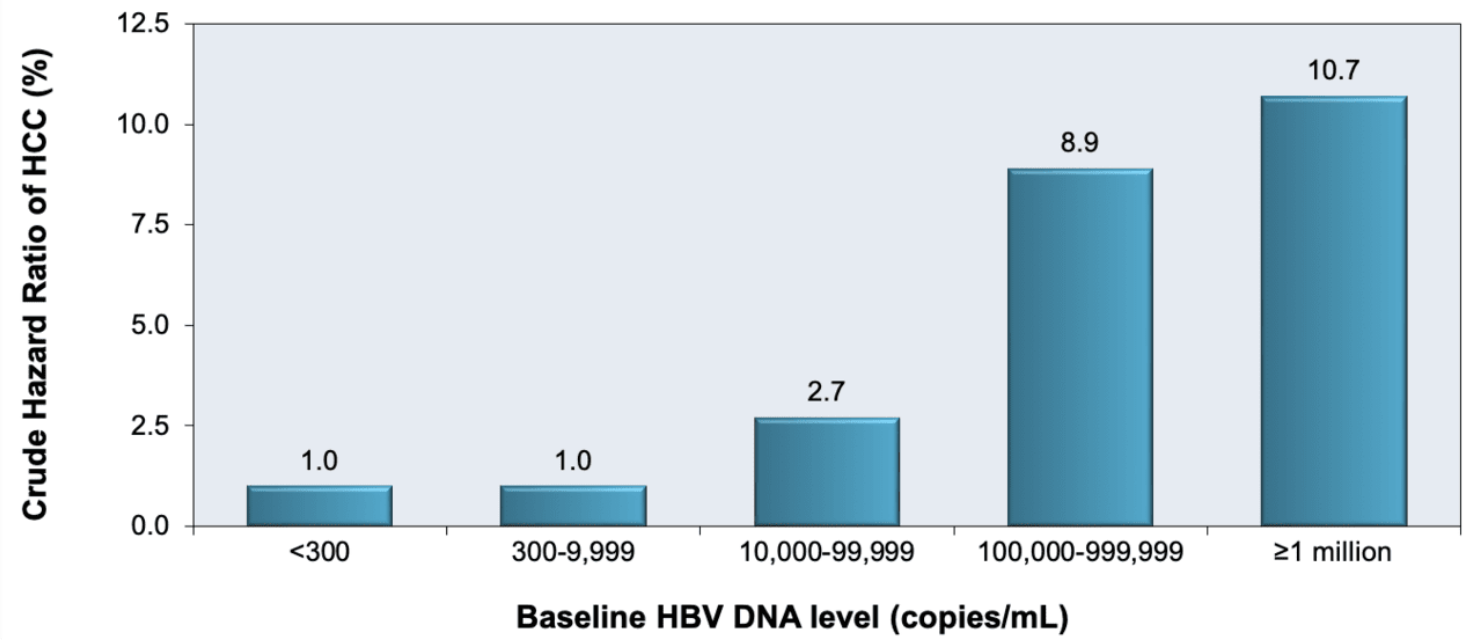

Figure 1 (Image Series) - HBV DNA Levels and Liver Disease Outcomes
Image 1B: Baseline HBV DNA Levels and Risk of Developing Cirrhosis

These data are from persons with chronic HBV infection who have a negative anti-hepatitis C virus antibody test. This graphic shows a clear correlation of HBV DNA levels and risk of developing cirrhosis.

Source: Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130:678-86.

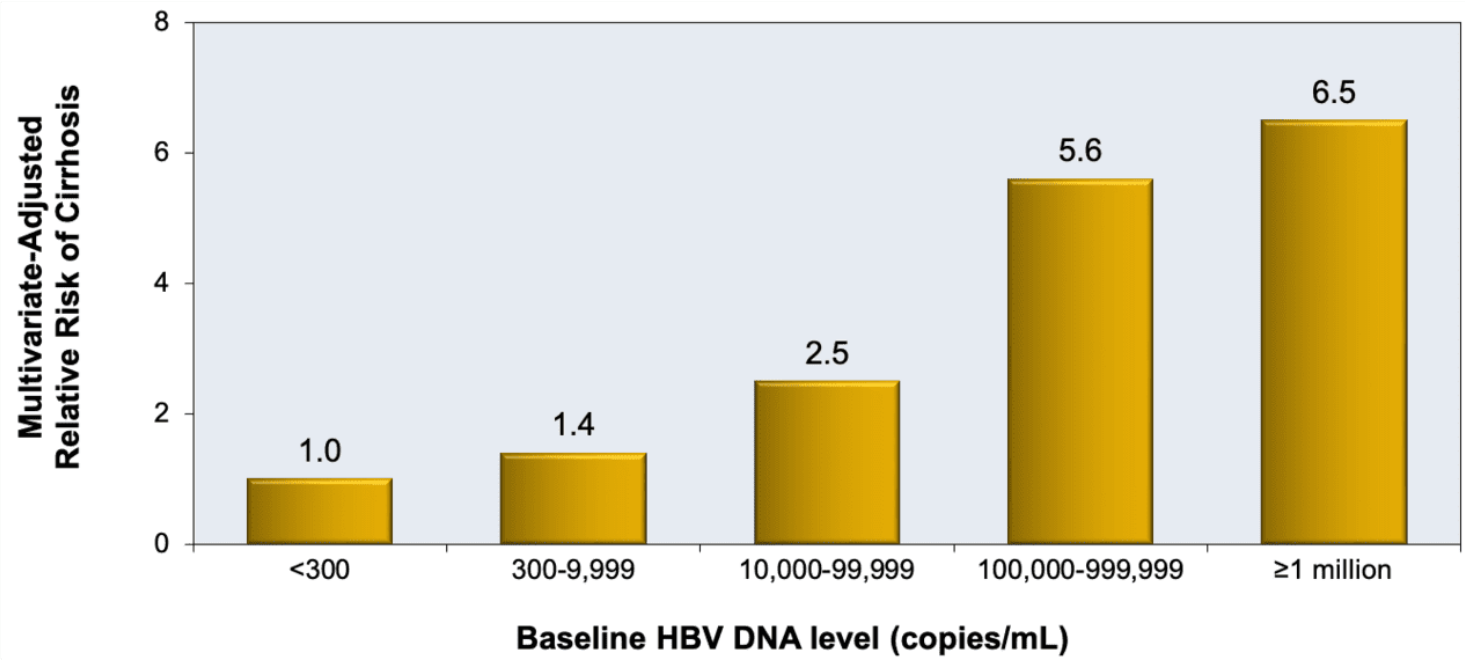

Figure 2 Hepatitis B Disease Phases

This illustration shows the relationship of different hepatitis B immune phases and fluctuations in HBV DNA and serum alanine aminotransferase (ALT) levels.

Illustration: David H. Spach, MD

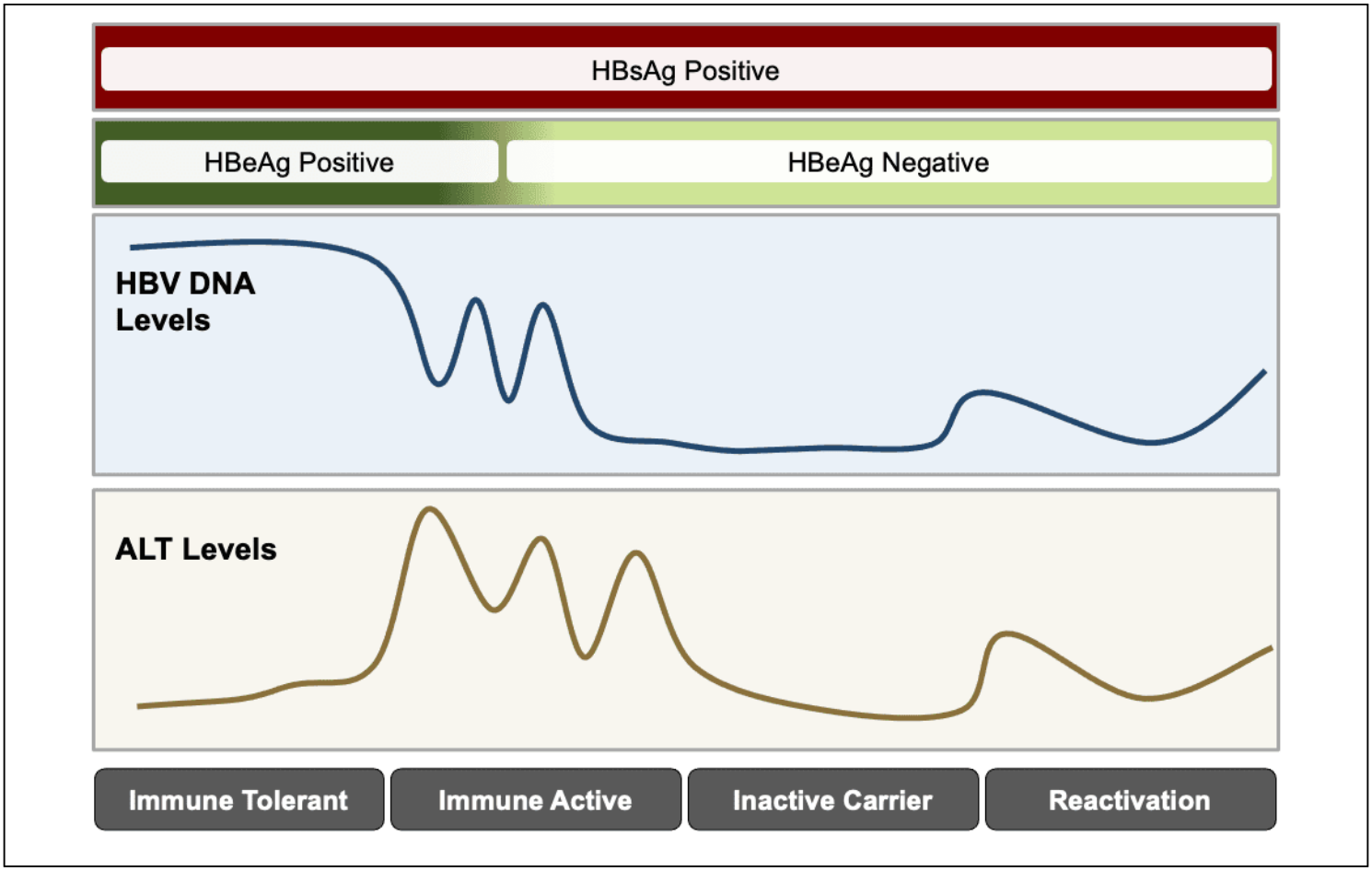

Table 1.

HBV Treatment Recommendation Based on Major Organization Guidelines

Risk Group	AASLD/IDSA 2025	APASL 2015	EASL 2025	WHO 2024
Without cirrhosis	Treat if: – Immune-active disease defined as: • (1) elevation of ALT (≥2 x ULN) or evidence of significant histologic disease, and • (2) HBV DNA >2,000 IU/mL if HBeAg negative or >20,000 IU/mL if HBeAg positive. - Immune-tolerant if they are: >40 years of age or have significant liver inflammation (≥grade 2) or fibrosis (≥F2) on liver biopsy or non-invasive testing. - Indeterminant phase, HBeAg negative: shared decision-making - Higher risk for HBV transmission	Treat if: – ALT >2x ULN[3], *or* – Significant histologic disease[3] *and* – HBV DNA >2000 IU/mL if HBeAg-negative – HBV DNA >20,000 IU/mL if HBeAg-positive	Treat if: – HBV DNA >2,000 IU/mL and any of the following: • ALT >ULN, *or* • Fibrosis (equivalent of ISHAK ≥F3/Metavir ≥F2 [non-invasive assessment is preferred, liver stiffness measurement >7 kp]), *or* • Risk factors for HCC, *or* • Extrahepatic manifestations, *or* • Immunosuppression, or • Risk for HBV transmission	Treat if any: – Significant fibrosis[5] – HBV DNA >2,000 IU/ AND ALT level>ULN – Coinfection with HCV or HIV – Family history of live cancer or cirrhosis – Comorbidities – Immune suppressior – Extrahepatic – Persistent abnormal
Compensated cirrhosis	Treat all[4]	Treat if: - HBV DNA >2,000 IU/mL, *or* - ALT elevated[3]	Treat if: - HBV DNA is positive	Treat all[4]
Decompensated cirrhosis	Treat all[4] and refer for liver transplantation	Treat all[4]	Treat all[4]	Treat all[4]

Abbreviations: AASLD = American Association for the Study of Liver Diseases; APASL = Asian Pacific Association for Study of the Liver; EASL= European Association for the Study of the Liver; WHO = World Health Organization; ALT = alanine aminotransferase; ULN = upper limit of normal

[1]Regardless of HBV DNA, ALT, or HBeAg status

[2]Upper limit of normal, defined as ALT 35 IU/L for men, 25 IU/L for women

[3]Defined as ALT 40 IU/L for both men and women

[4]HBV DNA level is based on a sensitive NAT assay with a lower limit of detection <20 IU/mL

[5]The thresholds for significant fibrosis by APRI or transient elastography have not been fully validated in adolescent

[6]Defined as two ALT values greater than 19 IU/L for women and 39 IU/L for men at unspecified intervals during a 6-to-12-month period.

Source:

- European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management

of hepatitis B virus infection. J Hepatol. 2025:S0168-8278(25)00174-6. [PubMed Abstract]
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