

# When to Initiate HBV Treatment

This is a PDF version of the following document:

Section 2: [Treatment of HBV](#)

Topic 1: [When to Initiate HBV Treatment](#)

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<https://www.hepatitisB.uw.edu/go/hbv/initial-treatment/core-concept/all>.

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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, such as cirrhosis, decompensated liver disease, or hepatocellular carcinoma, become manifest.[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 results in the abnormal formation of collagenous scar or fibrosis that progresses over time.[2] The vast majority of individuals with HBV infection remain without symptoms or clinical manifestations unless cirrhosis-related complications develop and cirrhosis, in its asymptomatic form, is often unrecognized.[2] A clinician's ability to detect cirrhosis is also limited by the absence of a readily accessible, sufficiently sensitive and well-validated biomarker or test to detect cirrhosis.[3] In the following discussion, we will review the goals for HBV treatment and the 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.[4]

## 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 achieve virologic suppression, as indicated by plasma HBV DNA levels below the limit of detection.
- **Intermediate Goal:** With sustained virologic suppression, additional intermediate goals should include improvement in serologic and histologic markers. For hepatitis e antigen (HBeAg)-positive persons, 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.[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: cirrhosis, hepatocellular carcinoma, and liver-related mortality.
- **Prevention of HBV Transmission:** When treating pregnant mothers with HBV DNA levels greater than 20,000 IU/mL, the primary goal is to prevent HBV transmission to the infant.[6] 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, but this is not usually considered a primary prevention strategy since HBV vaccination is a more reliable and proven means of protecting persons at risk of acquiring HBV.
- **Control Rather than Eradication of HBV:** The eradication of HBV is not currently feasible with existing antiviral therapy and thus HBV treatment is not considered curative but rather disease-modifying.[1] This viral persistence is thought to be due in part to the stability of the HBV genome and its incorporation into the hepatocyte nucleus in the form of covalently closed circular (ccc) DNA.[1,5,7] Notably, loss of hepatitis B surface antigen (spontaneously or with antiviral therapy) does not necessarily indicate complete HBV eradication.[1] For example, HBV reactivation can still occur in some individuals with isolated hepatitis B core antibody (anti-HBc) who are treated with immunosuppressive, cytotoxic, or disease-modifying antirheumatic drugs.[8,9,10]

## Factors Used to Determine Whether to Initiate Treatment

Because of 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, but rather reserved for those who are thought most likely to benefit from the standpoint of disease modification. Conceptually, the clearest indications for treatment are when extensive liver fibrosis has occurred and/or when there is active HBV DNA replication causing ongoing significant hepatic inflammation. The decision to treat persons with chronic HBV therefore typically incorporates the following three factors: (1) cirrhosis status, (2) evidence of hepatic inflammation, as measured by alanine aminotransferase (ALT) levels or 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 in deciding whether to initiate HBV treatment.

Prior to making a decision on treatment, it is therefore important to have evaluated cirrhosis status, ALT levels, serum HBV DNA levels, and HBeAg status. The following will also include a discussion of the concepts related to the immune phases of chronic HBV, since the categories immune active and immune tolerant have been used as categories in the treatment-decision process. In addition to the laboratory-based 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 cirrhosis and/or hepatic inflammation; these conditions will be discussed briefly as well.

### Cirrhosis Status

Individuals with chronic hepatitis B 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.[11] The evidence base for the beneficial impact of antiviral therapy on reducing the risk of adverse clinical outcomes, such as hepatic decompensation or hepatocellular carcinoma (HCC), is particularly compelling for patients with cirrhosis.[12] The presence of cirrhosis is generally considered a strong indicator that favors initiating HBV treatment.

### Evaluation of Cirrhosis Status

Since cirrhosis is a strong indicator for HBV treatment, it is important to evaluate persons with chronic HBV for the presence of 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 hepatitis B. 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 persons 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 angiomas, splenomegaly, or encephalopathy, are important to evaluate and can increase the likelihood of a cirrhosis diagnosis.
- **Liver Biopsy:** A liver biopsy remains the gold standard for determining disease severity in chronic hepatitis B 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 results in the distortion of hepatic architecture. Liver biopsy can have limitations, including undersampling and misclassification.[13] 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.[13]

- **Transient Elastography:** Transient elastography 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.[14] For persons with chronic hepatitis B, an optimal transient elastography cutoff for distinguishing cirrhosis in the context of significant hepatic inflammation has not been established.[14]
- **Hepatic Ultrasound:** Ultrasonography is often used in clinical practice for staging chronic viral hepatitis. While it can have high specificity for detecting cirrhosis if a small nodular liver and signs of portal hypertension are present, its sensitivity for detecting advanced fibrosis can be suboptimal.[15,16]
- **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. Gradual decline in serum albumin in conjunction with gradual increase in alkaline phosphatase or prothrombin time without 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; the actual Fib-4 score can be determined with a [Fib-4 Calculator](#) and this score has been shown to have reasonable performance in differentiating mild (stage 0-1) from more advanced (stage 3-4) fibrosis in chronic hepatitis B.[17,18]

## 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 or total bilirubin). Decompensated cirrhosis is formally defined as a Child 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.[19,20] 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) ([Figure 1](#)).[21] This landmark study provided the early proof of concept for serum HBV DNA levels as a surrogate endpoint and the possibility of HBV suppression as a key intervention in mitigating disease progression.[21] 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 with those with a HBV DNA level less than 300 copies/mL (less than approximately 60 IU/mL) ([Figure 2](#)).[22]

## Alanine Aminotransferase (ALT) Levels

Serum ALT levels provide a rapid and noninvasive measure that can indicate hepatic inflammation. In 2002, investigators suggested using upper limits of normal for ALT levels of greater than 19 U/L in women and 30 U/L in men as the recommended cutoffs to accurately identify those with underlying hepatitis C viremia. Subsequently, the American Association for the Study of Liver Diseases (AASLD) hepatitis B guidelines suggested using these same threshold values as the upper limit of normal for ALT levels.[23,24,25] More

recently, however, the 2018 AASLD Hepatitis B Guidance has changed the upper limit of normal for treatment purposes to 25 U/L for women and 35 U/L for men.[4] These cutoffs are lower than the upper limit of normal defined by many commercial laboratories, which generally derive their range from the general population and more specifically from blood donors without evidence of hepatitis B or hepatitis C infection. Due to the high prevalence of fatty liver in "healthy" donors (who may have elevated ALT levels), use of the upper limit of normal obtained from such healthy donor pools may not maximize detection of individuals with underlying liver disease due to viral hepatitis.[26] Therefore, even though a patient may have a "normal" ALT result as defined by a local or referral laboratory, the more stringent cutoffs would reduce the likelihood of missing underlying liver disease caused by hepatitis B. It is also important to note that a treatment decision should not be made on the basis of a single serum ALT measurement. These values often vary and the phase of HBV infection will need to be confirmed with multiple measurements of serum ALT over time, typically drawn every 3 to 4 months, particularly given the dynamic nature of HBV infection.

## Immune Phases of Chronic HBV Infection

From a conceptual standpoint, chronic hepatitis B virus (HBV) infection has been characterized by four phases (or types of immune responses): immune tolerant, immune active, inactive carrier, and reactivation.[27,28,29,30] 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 is 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 3).[4,28]

### Immune-Tolerant Chronic HBV

The AASLD characterizes the immune-tolerant phase as one with a positive HBeAg, very high HBV DNA levels (typically greater than 1 million IU/mL), normal or minimally elevated ALT and/or AST levels, and liver biopsy (if done) showing no fibrosis and minimal inflammation.[4] Despite having very high HBV DNA levels, there is little immune reaction to the virus-infected hepatocytes and minimal liver inflammation. Also, these individuals do not tend to respond well to oral antiviral therapy or peginterferon.[31] Thus, persons in the immune-tolerant phase are not generally considered candidates for therapy unless they meet specific age and/or histologic criteria. These individuals should have their ALT monitored every 6 months to assess for transition to immune-active infection.[4] In contrast, studies have shown that up to one-third of persons 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); normal ALT can be a less reliable predictor of quiescent or minimal disease in these patients.[32,33]

### Immune-Active Chronic HBV or Reactivation of Chronic HBV

The AASLD 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.[4] If this occurs in HBeAg-negative patients after a period in the inactive carrier phase, this is called 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 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.[12] 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.[12] 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.[12]

## **Inactive Chronic Hepatitis B**

The AASLD characterizes inactive chronic HBV as HBeAg negative (and anti-HBe positive), serum HBV DNA levels less than 2,000 IU/mL, persistently normal ALT and/or AST levels, and liver biopsy that confirms absence of significant necroinflammation, and variable levels of fibrosis observed on liver biopsy or noninvasive testing.[4] These individuals are not usually considered candidates for therapy, but 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.[32,34] Therefore, guidelines recommend these patients undergo HCC screening, despite evidence of immune control of infection, are as per guidelines.

## Hepatitis B Treatment Guidance Recommendations

Several leading organizations have addressed guidance for treatment of chronic HBV, including when to initiate treatment.[4,35,36] The following summary is intended to provide a succinct description of the indications for initiating HBV treatment in persons with chronic HBV, as outlined by the different organizational guidelines. The reader is encouraged to access these documents for additional details, descriptions, and discussion. The following summaries do not include guidance for the treatment of HBV in special situations or circumstances, such as reactivation of HBV, pre- or post-liver transplantation, treatment of HBV in persons who have coinfection (hepatitis D, HIV, or hepatitis C), or treatment of HBV reactivation in persons undergoing immunosuppressive or cytotoxic therapy. These issues are addressed later in this topic review.

### American Association for the Study of Liver Diseases (AASLD)

The American Association for the Study of Liver Disease (AASLD) hepatitis B guidance has served as the dominant HBV treatment guidance in the United States and it includes comprehensive recommendations. The most recent guidance—Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance—was developed by consensus of an expert panel (gastroenterology and hepatology) and was published in 2018.[4] The 2018 AASLD Hepatitis B Guidance recommends initiating HBV treatment in the following situations in persons with chronic HBV.

- **Decompensated Cirrhosis:** Initiation of oral antiviral treatment is recommended in conjunction with referral for consideration of liver transplantation.
- **Cirrhosis:** Treatment is recommended for persons with cirrhosis if HBV DNA levels are greater than 2,000 IU/mL, regardless of HBeAg status or ALT levels.
- **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.
- **Selected Older Patients:** Treatment is recommended in the select group of adults older than 40 years of age who have normal ALT levels, elevated HBV DNA (1,000,000 IU/mL) levels, and a liver biopsy specimen that shows significant necroinflammation or fibrosis.

### Asian Pacific Association for the Study of the Liver (APASL)

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 guidance was published in 2015.[36] The 2015 APASL Hepatitis B Guidelines recommend initiating HBV treatment in the following situations for persons with chronic HBV.[36]

- **Decompensated Cirrhosis:** Treatment is recommended with any detectable HBV DNA level, regardless of ALT levels or HBeAg status.
- **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 elevated, regardless of HBeAg status.
- **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.

## European Association for the Study of the Liver (EASL)

The European Association for the Study of the Liver (EASL) hepatitis B clinical practice guidelines is the major hepatitis B guidance for Europe and this document was primarily written by gastroenterology and hepatology specialists.[35] The 2017 EASL Hepatitis B Guidelines recommend initiating HBV treatment in the following situations.[35]

- **Decompensated Cirrhosis:** Treatment is recommended with any detectable HBV DNA level, regardless of ALT levels or HBeAg status.
- **Compensated Cirrhosis:** Treatment is recommended with any detectable HBV DNA level, regardless of ALT levels or HBeAg status.
- **Without Cirrhosis**
  - Treatment is recommended regardless of HBeAg status if (1) the HBV DNA level is greater than 2,000 IU/mL, (2) the ALT is greater than the upper limit of normal (approximately 40 IU/L for males and females), and (3) there is liver biopsy evidence of at least moderate liver necroinflammation and/or at least moderate fibrosis.
  - Treatment is recommended regardless of ALT levels or HBeAg status if (1) the HBV DNA level is greater than 2,000 IU/mL and (2) there is liver biopsy evidence of at least moderate fibrosis (based on liver biopsy or noninvasive markers of fibrosis).
  - Treatment is recommended regardless of HBeAg status if (1) the HBV DNA level is greater than 20,000 IU/mL and (2) the ALT is greater than 2 times the upper limit of normal (approximately 40 IU/L for males and females), regardless of the degree of fibrosis.
- **Selected Indications:** These guidelines also note that treatment can be offered, even in the absence of preceding indications for:
  - HBeAg-positive persons older than 30 years of age with persistently normal ALT and high HBV DNA levels, regardless of the severity of liver histological lesions.
  - Persons with a family history of hepatocellular carcinoma, cirrhosis, or extrahepatic manifestations.

## HBV Primary Care Workgroup

The HBV Primary Care Workgroup includes members in the United States from hepatology, infectious diseases, pharmacy, primary care, and public health.[37] The 2020 HBV Primary Care Workgroup Guidance was first released in early 2020 and is accessible on this web site (Hepatitis B Online), with the aim to have regular updated versions posted online.[37] The goal of this document is to provide simplified, up-to-date, and readily accessible HBV management guidance for primary care medical providers. Note, this guidance does not incorporate HBeAg status in the initial decision-making process, but persons positive for HBeAg are recommended to undergo monitoring of HBeAg for evidence of HBeAg seroconversion. The 2020 HBV Primary Care Workgroup Guidance recommends initiating HBV treatment in the following situations.[37]

- **Decompensated Cirrhosis:** Treatment is recommended but persons should be promptly referred to a hepatologist.
- **Cirrhosis:** Treatment is recommended for all persons with cirrhosis, regardless of HBV DNA level, ALT level, or HBeAg status.
- **Without Cirrhosis:** For persons without cirrhosis, treatment is recommended if the HBV DNA level is greater than 2,000 IU/mL and the ALT level is elevated, regardless of HBeAg status. For this purpose, elevated ALT is defined as greater than 25 U/L in females and greater than 35 U/L in males that is persistent for at least 3 to 6 months.



## Special Indications for Initiating Treatment

There are a variety of special clinical situations in patients with hepatitis B where antiviral therapy may be warranted regardless of cirrhosis status, hepatic aminotransferase levels, or HBV DNA levels.[\[4\]](#) The most common of these specific circumstances are listed below.

- **Pregnant Women with an HBV DNA level Greater than 20,000 IU/mL:** Treatment of HBV is indicated for all pregnant women with an HBV DNA level greater than 20,000 IU/mL in the third trimester of pregnancy.[\[6\]](#) The purpose of HBV treatment of a pregnant mother 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.[\[38\]](#)
- **Persons with HIV and HBV Coinfection:** Fully suppressive antiretroviral therapy to treat HIV is recommended for all persons with HIV.[\[39\]](#) 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.[\[40\]](#) 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 persons who have HBV mono-infection or HIV mono-infection).[\[41,42\]](#) 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.[\[40\]](#)
- **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 disease-modifying antirheumatic drugs.[\[9,10,43\]](#) 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.[\[9,10\]](#) Reactivation of HBV can also occur in persons receiving HCV therapy with direct-acting antiviral agents (DAAs).[\[44,45\]](#) 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.[\[9,10\]](#)
- **Persons with Chronic HBV Receiving HIV Preexposure Prophylaxis:** In the United States, two regimens are FDA-approved for HIV preexposure prophylaxis (PrEP): tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine.[\[46,47\]](#) The use of HIV PrEP may be indicated in a person who also has chronic HBV infection. Since both of the medication combinations used for HIV PrEP are highly active against HBV, any person with chronic HBV who is receiving HIV PrEP is also receiving treatment for HBV. It is important to understand that any person who intermittently takes the currently recommended HIV PrEP or goes on and off HIV PrEP could create unintended negative consequences related to the HBV infection, such as generation of HBV drug resistance or developing HBV-related hepatic flares. When HIV PrEP is used in persons with chronic HBV infection, it should include appropriate counseling related to interruption of HIV PrEP, as well as clinical and laboratory monitoring if HIV PrEP is stopped.

## 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 have issued guidance that address treatment indications for persons with chronic HBV. In the United States, two main groups—the AASLD and Hepatitis B Primary Care Workgroup—have issued hepatitis B treatment guidance.
- According to these groups, antiviral therapy is indicated in patients with chronic HBV and cirrhosis, regardless of ALT level.
- Antiviral therapy is indicated in patients with chronic HBV without cirrhosis who meet 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 and Primary Care Workgroup guidance recommend using an upper range of normal ALT of 25 IU/L in women and 35 IU/L in men.
- Antiviral therapy 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, and comorbidities (i.e. extrahepatic manifestations) should be considered in the decision to treat or perform a biopsy in an individual with chronic hepatitis B.
- In general, young immune-tolerant patients without cirrhosis who have HBeAg-positive status and persistently normal ALT levels do not need to start treatment, even if they have very high HBV DNA levels. They should have their ALT monitored every 6 months.
- Inactive HBV carriers without cirrhosis who have persistently normal ALT, HBeAg-negative status, and low HBV DNA level are not recommended to start treatment, but should have their ALT monitored every 6 months.

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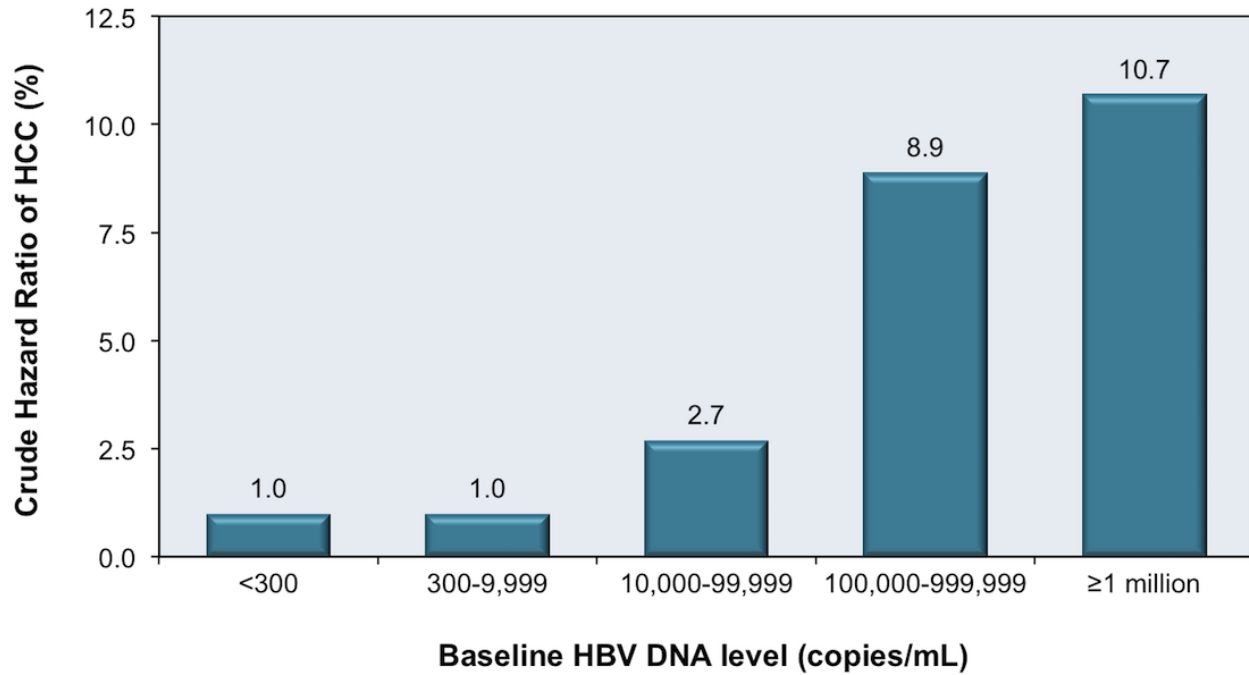
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## Figures

**Figure 1 Baseline HBV DNA Levels and Risk of Developing Hepatocellular Carcinoma**

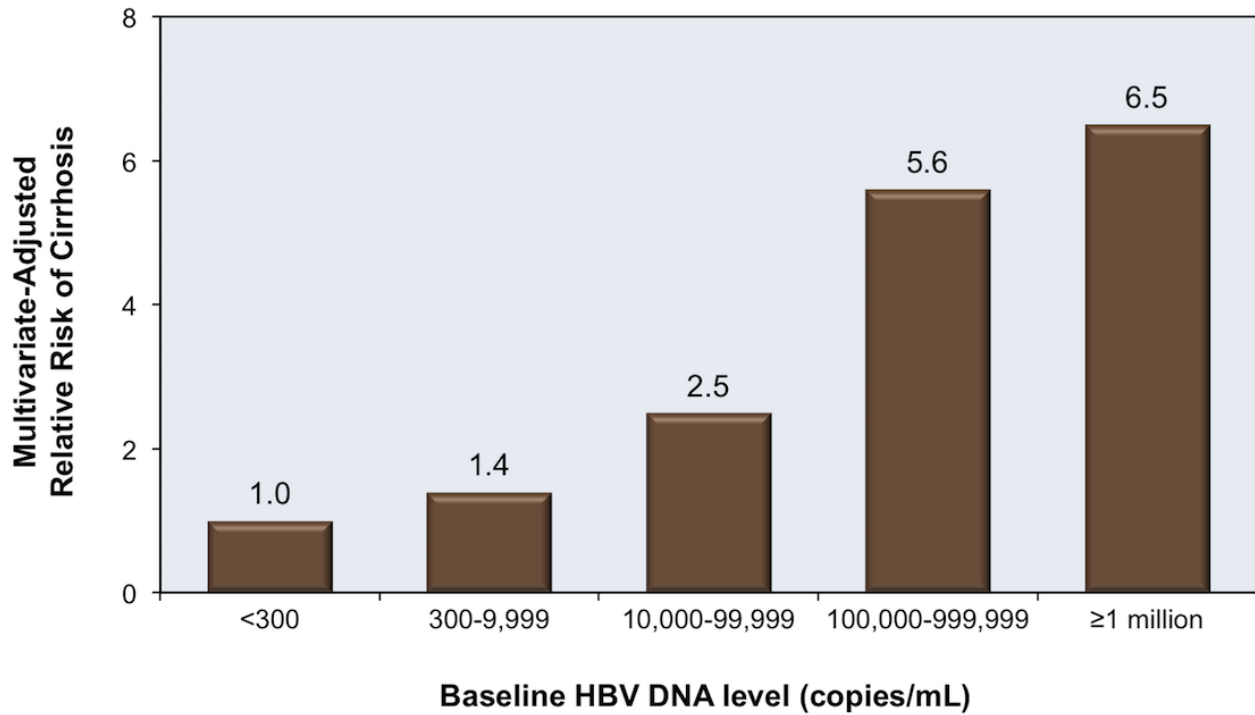
Source: Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295:65-73.



**Figure 2 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 3 Hepatitis B Disease Phases

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

Illustration: David H. Spach, MD

