

HEPATITIS B

Hepatitis B is a major global health problem. The WHO reports that there are 350 million carriers worldwide. This disease is the leading cause of liver cancer in the world and frequently leads to cirrhosis and liver failure. Universal vaccination of children and young adults is not yet widespread in every country. The registered drugs currently available for treatment are divided into two main groups: immunomodulators, which include IFN- α and pegylated interferon, and nucleos(t)ide analogs, such as lamivudine, adefovir, entecavir, tenofovir and telbivudine. However, the currently available antiviral drugs are unable to eradicate hepatitis B virus (HBV) infection because of both the defective immune response against infected hepatocytes and the persistence of viral covalently closed circular DNA (cccDNA) in the liver of infected patients. Goals of treatment are to suppress viral replication to the lowest possible level, and thereby to halt the progression of liver disease and prevent the onset of complications.

Natural History

The natural course of chronic HBV infection can be divided into four, which are not always continuous.

Immune Tolerance Phase In the immune tolerance phase, the specific immune response against HBV is impaired. It is characterized by high levels of serum HBV DNA (>10 IU/ml) and HBeAg positivity. Alanine transaminase (ALT) is below the upper limit of normal (ULN). However, there is a lack of international standardization of ALT levels, which differ from one laboratory to another, and some studies have reported the existence of liver damage in patients with normal ALT levels.

This first phase is more frequent and more prolonged in subjects infected during the first years of life or perinatally, as in countries of high prevalence. Liver biopsy – if performed – shows normal liver or only minimal histological activity. These patients are highly contagious.

Immune Active Phase During the immune active phase, immune tolerance to the virus is lost and infected hepatocytes are killed by the immune system, leading to moderate or severe liver necroinflammation. As a consequence, liver fibrosis progression is observed. ALT levels are elevated, sometimes intermittently, and associated with markers of viral replication – that is, HBeAg positivity and lower levels of serum HBV DNA compared with the previous phase, because of infected hepatocyte lysis. This phase is more frequent in subjects infected during adulthood, but can also be frequently observed among perinatally infected young adults.

Inactive Phase The inactive phase is characterized by immune control of viral replication, with seroconversion from HBeAg to anti-HBe, which is associated with lower or undetectable levels of serum HBV DNA (<2000 IU/ml). This phase is called the

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'inactive HBV carrier state' because liver histology studies have shown a decrease in the necroinflammatory scores and a remission of the liver disease. However, other factors, such as age, ethnicity, HBV genotype and duration of infection, may alter outcome in these patients.

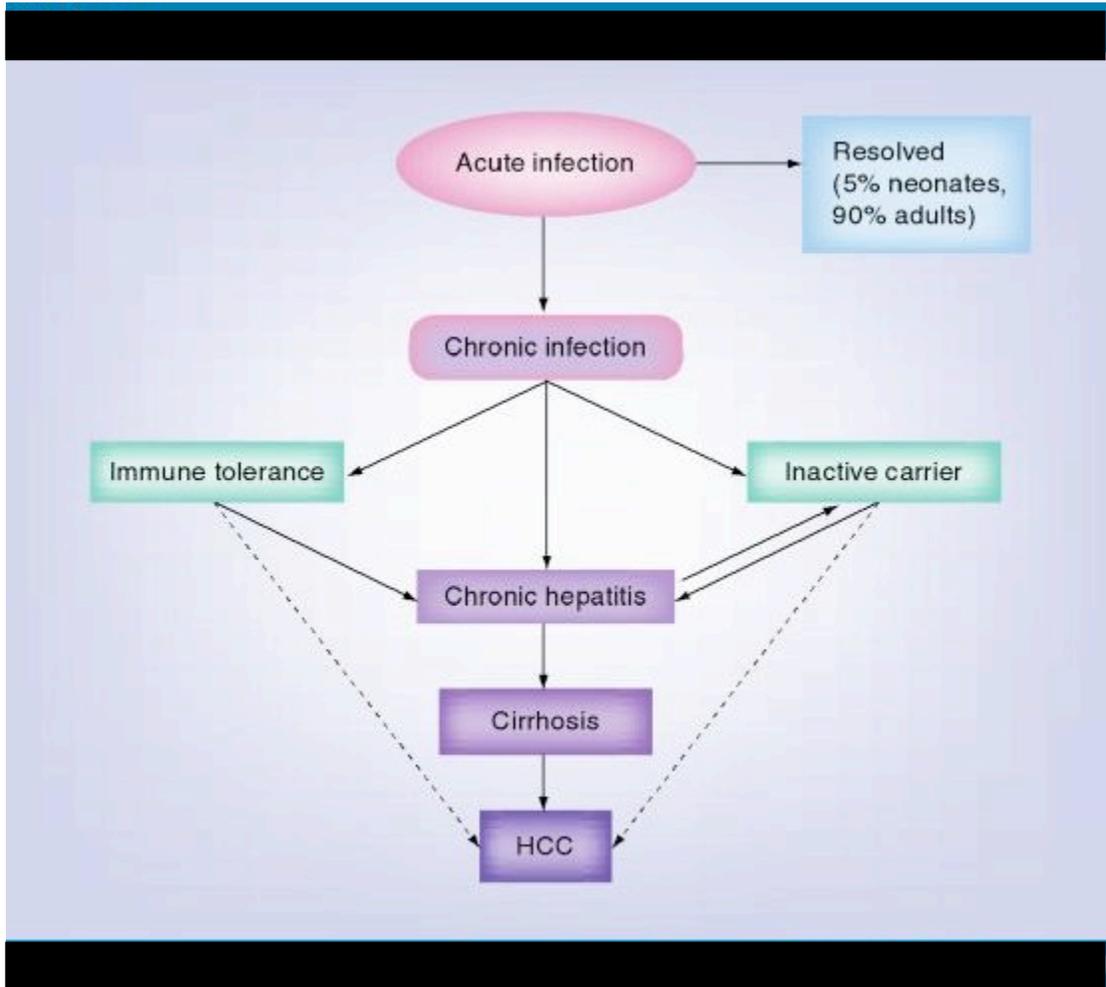
Reactivation Phase Reactivation of viral replication may occur either as a seroreversion to HBeAg with a dominant wild-type virus or as the consequence of the selection of pre-core or basal core-promoter mutants unable to express or expressing low levels of HBeAg. It is associated with an increase in ALT levels, which may be fluctuating. These episodes of viral reactivation and acute exacerbation of the disease may lead to liver deterioration and progression to cirrhosis.

Thus, the distinction between the inactive HBV carrier state and HBeAg-negative chronic hepatitis requires serial testing of ALT and HBV DNA levels. Longitudinal follow-up is mandatory at least every 3 months for a minimum of 1 year to diagnose the inactive carrier state, and long-term follow-up is required to detect phases of viral reactivation.

There may be another phase in the natural history of chronic hepatitis B named 'resolved infection', which overlaps in part with occult infection. The resolved infection phase is defined by the clearance of HBsAg; it is associated with the persistence of viral genome in the liver as a cccDNA form that may explain the cases of viral reactivation observed in cases of severe immune suppression as a result of the loss of immune control of infection. The occult infection is defined by the detection of low levels of HBV DNA (<200 IU/ml) in serum and/or in the liver in the absence of detectable serum HBsAg. The clinical relevance of this phase is still unclear; it may occur at a late stage of the disease or it may also be a course of its own without HBsAg at any time. The recognition of occult HBV infection has been improved by the development of very sensitive assays that allow the detection of low-level HBV DNA of less than 10 IU/ml in the serum and/or in the liver of patients who lost HBsAg. Patients may present with a serological status of anti-HBc with or without anti-HBs, or even without anti-HBc. This status should be considered, especially in cases with an immunosuppressant condition (e.g., anticancer chemotherapy, immunomodulators for autoimmune diseases and HIV-induced immunosuppression), which may lead to reactivation.

Complications of Chronic Hepatitis B

The complications of chronic HBV diseases include progression to cirrhosis, episodes of decompensation resulting in variceal hemorrhage, ascites, encephalopathy, liver failure and the development of hepatocellular carcinoma (HCC). These complications result in liver-related death. Although the most frequent pathway for HCC development occurs via the development of inflammatory and fibrotic lesions, it may also occur in rare conditions in noncirrhotic livers in immunotolerant patient's, or in inactive carriers as a consequence of the integration of viral genome in the host genome and dysregulation of cellular genes involved in the control of the cell cycle



Influence of HBeAg & HBsAg Seroconversion on the Outcome of Disease

Shortly after the discovery of HBV, the striking epidemiologic association between HBV infection and HCC was noted.

A more recent study underscores the importance of this association. In this prospective study, 11,893 men without evidence of HCC were enrolled in seven townships in Taiwan and followed for the development of HCC from 1991 to 2000. Approximately 20% were HBsAg-positive, and they were also tested for HBeAg at the start of the study to determine the role of this serologic marker in the occurrence of HCC. The risk of HCC was increased by a factor of ten among the men who were HBsAg-positive alone compared with the reference group who were negative; however, the risk was increased by a factor of 60 among those who were positive for both HBsAg and HBeAg, most likely because the viral load is higher in HBeAg-positive patients than in HBeAg-

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negative patients. This produced strong evidence that active replication is associated with an increased risk of HCC.

Owing to the rarity of HBsAg seroclearance, several issues concerning its clinical and virological impacts are still unknown. A large-scale longitudinal study conducted in Hong Kong (China) analyzed virologic, histologic and clinical outcome in 298 chronic hepatitis B patients with HBsAg seroclearance. HBsAg seroclearance was assessed by repeated testing for a period of at least 6 months. Results showed that the median age of HBsAg seroclearance was 49.6 years. Seven patients (2.4%) developed HCC and the cumulative risk for HCC was higher in patients with HBsAg seroclearance at ages over 50 years compared with those with HBsAg seroclearance at ages less than 50 years ($p = 0.004$). This study also showed that HBV persisted at low replicative and transcriptional levels after HBsAg seroclearance.

Role of Viral Replication in the Development of Cirrhosis & HCC

Cirrhosis develops as a result of hepatic inflammation and subsequent fibrosis in chronic hepatitis B. There is strong clinical evidence to support the association of HBV replication with the risk of development of cirrhosis and HCC.

Several studies have been performed to evaluate the relationship between serum HBV DNA level and risk of cirrhosis and HCC. The largest study with a long follow-up has been performed by the Risk Evaluation of Viral load Elevation and Associated Liver disease/cancer in HBV Study Group (REVEAL-HBV).

Risk of Cirrhosis

A total of 3852 untreated hepatitis B-infected patients established in Taiwan from 1991 to 1992 have been enrolled in this prospective study. During a mean follow-up time of 11 years 365 patients were newly diagnosed with cirrhosis using an ultrasound quantitative scoring system derived from the appearance of liver surface, liver texture, intrahepatic blood vessel size and splenic size. Ultrasound examinations have been performed every 6–12 months and results were interpreted blinded to the HBV DNA level.

The cumulative incidence of cirrhosis increased with baseline HBV DNA levels and ranged from 4.5 to 36.2% for patients with a viral load lower than 300 copies/ml or more than 10^6 copies/ml, respectively ($p < 0.001$). The risk of cirrhosis increased significantly with increasing HBV DNA level and was independent of HBeAg status and ALT level at entry.

Risk of HCC

In total, 3653 participants aged 30–65 years were recruited in a community-based cancer screening program in Taiwan between 1991 and 1992. During the follow-up period of 11 years, 164 incident HCC cases occurred. Risk of HCC increased across a biological

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gradient of serum HBV DNA level. The serum level of HBV DNA measured at entry to the study was the major risk for HCC independent of HBeAg status, ALT level and cirrhosis after adjustment for gender, cigarette smoking and alcohol consumption. Persistently high HBV DNA levels were associated with an increased risk of HCC by comparison with patients who showed a spontaneous decrease in serum viral DNA.

In patients with chronic hepatitis B infection the risk of HCC appears to vary depending upon geographic area and the underlying stage of liver disease. The presence of cirrhosis increases this risk, especially in studies performed in Europe where there is a low or intermediate rate of HBV endemicity and where HBV infection is acquired at an older age.

A recent study aimed to address the connection between a positive family history of liver cancer and HCC development in the USA. This case–control study enrolled 347 cases of pathologically confirmed HCC and 1075 controls, of which 190 cases and 1039 controls had no virus markers. Independently of HBV and hepatitis C virus, a history of liver cancer in first-degree relatives was significantly associated with HCC development (adjusted odds ratio = 4.1 [95% CI: 1.3–12.9]). This increased risk remained at fourfold after adjusting for numerous factors including age, gender, tobacco, alcohol and diabetes, even in patients without virus infection. Regarding the methodology, it was difficult to assess the part of familial or environmental factors. Thus, prospective studies are still needed to estimate the respective role of these factors.

Treatment Objectives

The American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Asian–Pacific Association for the Study of the Liver (APASL) have each published clinical practice guidelines for the management of hepatitis B and have discussed goals of treatment and end points in detail.

The major goal is to improve the quality of life and survival. This can be achieved if patients remain stable, and by preventing progression of disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. A favorable outcome can be achieved if HBV replication is suppressed. Therefore, viral suppression has become the primary objective of antiviral therapy.

However, HBV infection cannot be completely eradicated owing to the persistence of cccDNA in the nucleus of infected hepatocytes. cccDNA acts as a transcriptional template for HBV DNA production that is responsible for reinitiating viral replication after treatment cessation or in case of immune suppression.

Maintenance of the viral load as low as possible allows prevention not only of disease progression but also of antiviral drug resistance, which is a clinical challenge with respect to the long duration of antiviral therapy. Despite significant progress made with the use of more potent drugs with a high genetic barrier to resistance, cautious virologic

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monitoring with sensitive tools is needed during therapy, since treatment cannot achieve a complete cure of infection.

Another goal of antiviral therapy is to decrease the risk of virus transmission, as a complement to mass vaccination programs. In this setting, antiviral therapy using NUC may reduce vertical transmission when infected mothers are treated during the last trimester of pregnancy and neonates are vaccinated. The question of which drug to use during pregnancy is still debated. Studies have shown that lamivudine administration during the last trimester of pregnancy was safe and efficacious in decreasing the transmission rate to vaccinated neonates. However, the rate of resistance to lamivudine is a significant obstacle for its widespread implementation. The role of tenofovir or telbivudine in this situation needs to be clarified. For instance, a recent study reported that the use of tenofovir during pregnancy is not associated with an increased risk.

Results of Therapy According to the Approved End Points

The EASL clinical practice guidelines have recommended surrogate end points to evaluate the efficacy of antiviral therapy to prevent disease progression and death:

- Sustained HBsAg loss with or without anti-HBs acquisition, as most studies have shown it is associated with an improved long-term outcome;
- Durable HBeAg seroconversion in patients who are HBeAg positive at baseline, as it has been shown to be associated with improved prognosis;
- For the other patients (HBeAg-positive patients who do not achieve HBe seroconversion) and HBeAg-negative patients, the next most desirable end point was a maintained undetectable HBV DNA level (by real-time PCR assay) on treatment with NUC or a sustained undetectable HBV DNA level after interferon therapy.

Viral suppression has become the main treatment objective as this is now a clinical end point that can be reached in most patients with the currently available drugs. Treatment failure defined as the persistence of detectable HBV DNA (partial response or primary nonresponse) or the rebound in viral load by at least 1 log₁₀ IU/ml, is associated with progression of liver disease and should be managed according to the cross-resistance profile of the antiviral drugs as described in detail in recently published reviews. Should these end points be considered as surrogate criteria? This question has been debated for the treatment of chronic hepatitis B.

Is HBsAg loss a valid surrogate for clinical outcome?

- Sustained HBsAg loss is associated with decreased HBV replication and liver injury, as shown by several studies. Improved clinical outcome was illustrated by one study enrolling 309 patients with compensated cirrhosis followed for a

median of 68 months (range: 6–153) in which 32 patients with HBsAg clearance had less liver-related death compared with patients without HBsAg clearance (3 vs 20%; $p = 0.0006$);

- These results may advocate an early treatment intervention to achieve HBsAg clearance at an early stage of the disease and before the age of 50 years to prevent the development of HCC.

Is HBeAg seroconversion a valid surrogate end point for clinical outcome?

- Persistence of HBeAg is associated with significantly higher risk of progression to cirrhosis, as shown by several studies;
- HBeAg loss following interferon treatment results in increased survival, as shown by a study comparing 53 patients with HBeAg loss versus 50 patients without HBeAg loss in terms of survival ($p = 0.004$) or survival free of hepatic complications ($p = 0.018$)
- However, HBeAg remains a weak end point compared with viral suppression. This is mainly due to the fact that drugs belonging to the new generation exhibit a stronger antiviral potency, and that HBV DNA assays have an improved sensitivity, allowing more accurate measurement of the antiviral effect of the drugs.

Is maintained or sustained HBV DNA suppression a valid surrogate marker for clinical outcome?

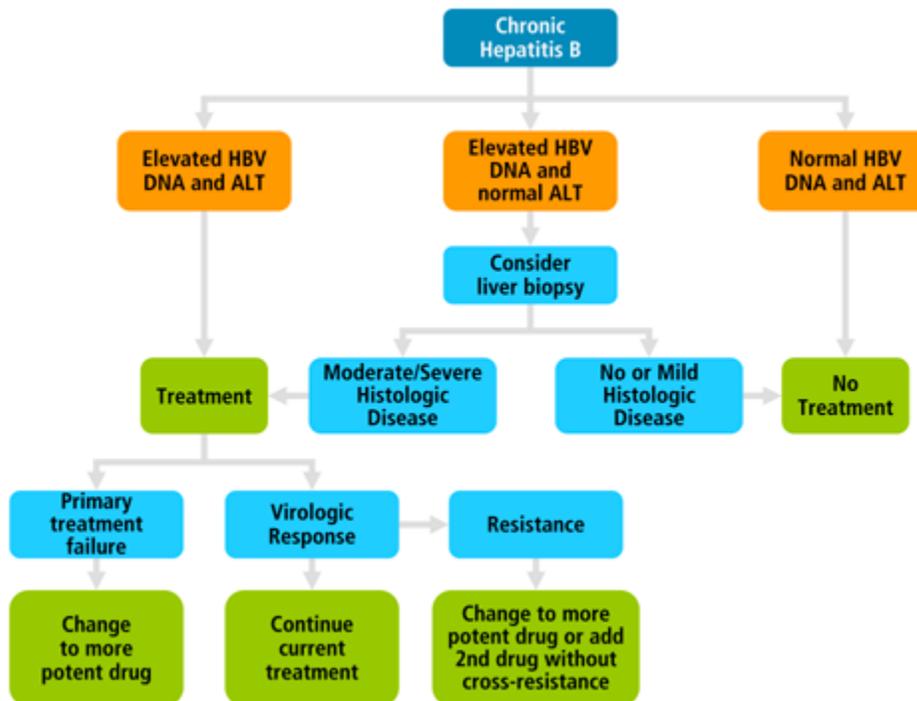
- The REVEAL study demonstrated that persistently high serum HBV DNA is associated with increased risk of HCC, and that spontaneous decline in HBV DNA levels is associated with a decreased risk of HCC compared with patients who maintained high levels of viral replication;
- Most studies have shown that viral suppression induced by antiviral therapy is associated with an increased rate of ALT normalization, a decrease in the necroinflammatory score and decreased liver fibrosis progression on liver histology analysis. A large study gave a proof-of-concept that maintained that viral suppression prevents disease progression. By following 651 patients with significant fibrosis, it was shown that 221 patients with lamivudine-induced HBV DNA suppression have less liver-related clinical deterioration than those with lamivudine resistance (209 patients with higher viremia level). Nonetheless, patients with lamivudine resistance had less disease progression than 215 placebo-treated patients;
- Furthermore, all studies demonstrated that antiviral drug resistance blunts the beneficial effect of antiviral therapy in terms of liver histology, ALT levels and exacerbation, and disease progression.

Guidelines for Treatment

Various guidelines have been published regarding when to initiate, stop, and alter therapy for hepatitis B. These include those published by the American Association for the Study of Liver Diseases (AASLD) in 2007 and 2010 [on-line], the Asian Pacific Association for the Study of the Liver (APASL) in 2008, a panel of Swedish experts in 2008, a panel of US hepatologists led by Emmet Keeffe (the "US guidelines") in 2009, the National Institutes of Health in 2009, and the European Association for the Study of the Liver (EASL) in 2009.

In general, physicians should consider treatment for patients who are at high risk for liver-related morbidity and mortality in the near future (5-10 years) or foreseeable future (10-20 years) and who have a high likelihood of maintaining viral suppression.

Candidates for therapy typically have increased liver enzyme levels, detectable HBV DNA, and/or histologic liver damage. However, thresholds for initiating therapy may vary according to severity of liver disease (ie, cirrhosis) and HBeAg status.



In patients with HBeAg-positive chronic hepatitis B, treatment is clearly indicated when serum HBV DNA is $\geq 20,000$ IU/mL (10^5 copies/mL) and ALT level is persistently elevated after 3-6 months of monitoring. The AASLD and APASL guidelines state that ALT should be at least 2 x the upper limit of normal (ULN), while the US guidelines simply require ALT to be above a threshold level of 30 IU/L in men and 19 IU/L in women.

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In patients who have HBV DNA levels = 20,000 IU/mL but a serum ALT that is normal or < 2 x ULN, all 3 groups recommend that a liver biopsy be considered, particularly in patients over 35-40 years of age. Treatment should then be started in those with moderate inflammation or fibrosis.

The AASLD and APASL guidelines recommend no therapy for individuals with HBV DNA levels < 20,000 IU/mL, whereas the US guidelines suggest that physicians consider liver biopsy on a case-by-case basis and initiate therapy when significant histologic disease is found.

The EASL guidelines differ from the other 3 groups' by requiring that all patients with HBV DNA levels > 2000 IU/mL or a serum ALT above the ULN undergo liver biopsy. They then recommend treatment for those with moderate-to-severe necroinflammation or moderate-to-severe fibrosis.

All of the guidelines aim to distinguish HBeAg-positive patients in the immune-clearance phase from those in the immune-tolerance phase, in whom treatment is not indicated.

Treatment duration varies by guideline and the antiviral agent that is used; this will be discussed in more detail later. Generally, treatment should be administered until HBV DNA levels are undetectable or HBeAg seroconversion is achieved.

HBeAg-Negative Chronic Hepatitis B

HBeAg-negative patients tend to have lower levels of serum HBV DNA than their HBeAg-positive counterparts but still may have active disease. As a result, the APASL and US guidelines recommend a lower HBV DNA threshold of 2000 IU/mL (10^4 copies/mL) for initiation of treatment. As with HBeAg-positive patients, this must be coupled with a persistently elevated serum ALT after 3-6 months of monitoring, defined as > 2 x ULN by the APASL and = 30 IU/mL in men and = 19 IU/mL in women by the US guidelines. The AASLD guidelines recommend treatment in patients with an HBV DNA level > 20,000 IU/mL and an ALT > 2 x ULN.

In those patients with HBV DNA levels > 2000 IU/mL and an ALT level between 1 and 2 x ULN, the APASL and AASLD guidelines recommend that a liver biopsy be performed, with treatment reserved only for those with moderate inflammation or fibrosis.

As with HBeAg-positive patients, the EASL guidelines recommend a liver biopsy in all patients with HBV DNA > 2000 IU/mL or an elevated serum ALT. Again, treatment is indicated only for those with moderate-to-severe inflammation or fibrosis.

Because HBeAg seroconversion is not an endpoint in these patients, treatment is typically administered indefinitely. However, variations do occur according to guideline or particular antiviral agent. This will be addressed further in another section.

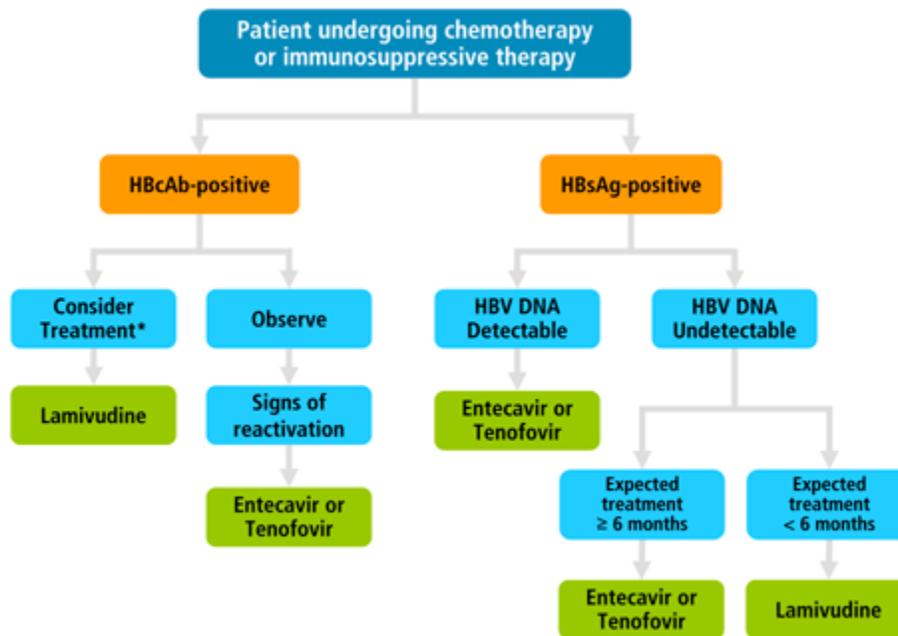
Cirrhosis

In HBV-infected patients with compensated cirrhosis, treatment is indicated regardless of ALT level when HBV DNA = 2000 IU/mL. In individuals with HBV DNA levels < 2000 IU/mL, the AASLD guidelines suggest treatment if serum ALT is elevated, whereas the EASL guidelines recommend treatment in any patient with a detectable level of HBV DNA. The US guidelines assert that both treatment and observation are acceptable, as existing data are insufficient to make a recommendation. Regardless of whether they are observed or treated, all patients with cirrhosis should undergo regular screening for HCC and other complications (eg, esophageal varices).

Treatment is universally indicated for patients with decompensated cirrhosis, regardless of HBV DNA level. However, therapy must be coupled with referral for liver transplantation.

Special Populations

Treatment for hepatitis B is also indicated in all HBsAg-positive patients undergoing potent immunosuppressive therapy or chemotherapy, regardless of their phase of infection. Reactivation of HBV replication has been reported in approximately 20% to 50% of HBsAg carriers in this setting. Although most flares are asymptomatic, hepatic decompensation and even death have been observed. Most guidelines recommend that prophylactic antiviral therapy be started at the onset of chemotherapy or immunosuppressive therapy and be continued for at least 3-6 months after treatment is complete. The EASL guidelines argue for a longer duration of therapy, up to 12 months after cessation of treatment. In patients with high pretreatment HBV DNA levels (= 2000 IU/mL), antiviral therapy should be continued until the same treatment endpoints are achieved as in immunocompetent patients.



A controversial indication for antiviral prophylaxis prior to chemotherapy is the presence of an isolated positive hepatitis B core antibody (HBcAb). Although such patients are considered to have resolved infection, recent studies have suggested that up to 25% are at risk for flare when exposed to chemotherapy regimens containing rituximab. Although other chemotherapeutic agents potentially pose the same risk, the majority of cases of reactivation have occurred in patients receiving rituximab-containing regimens. Therefore, it is recommended that patients with isolated HBcAb positivity be monitored closely during and after the administration of chemotherapy for signs of HBV reactivation. Those patients who develop reactivation or who are HBeAg positive should receive antiviral therapy according to the same indications as for HBsAg-positive patients undergoing chemotherapy or immunosuppressive therapy. Alternatively, given the nucleoside analog lamivudine's low cost and few associated adverse effects, another reasonable option in this high-risk group is to administer lamivudine prophylaxis without waiting for signs of reactivation, particularly in patients being treated with rituximab-containing regimens.

Antiviral therapy is also recommended for individuals coinfecting with HBV and HIV, using the same criteria as for treating patients with HBV mono-infection. In the United States, up to 10% of patients with HIV are coinfecting with HBV. As in patients undergoing chemotherapy or immunosuppressive therapy, screening must take into account those patients with an isolated positive HBcAb. In HIV-coinfecting patients, this can be associated with low levels of viral replication, resulting in detectable levels of HBV DNA. HIV-coinfecting patients in general tend to have higher levels of HBV DNA than do HBV-mono-infecting patients, as well as lower rates of spontaneous HBeAg

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seroconversion and more severe liver disease. The approach to hepatitis B therapy in these patients depends on the management and status of their HIV.

HBV-infected patients can also be coinfecting with hepatitis C virus (HCV) or hepatitis delta virus (HDV). The worldwide prevalence of HBV-HCV coinfection is unknown, although small studies have demonstrated anti-HCV antibodies in 5% to 20% of individuals with chronic hepatitis B, and HBsAg in 2% to 10% of individuals with chronic hepatitis C. HBV-HDV coinfection is much less common. In both cases, the risk of developing cirrhosis, hepatic decompensation, and HCC is significantly higher than in HBV monoinfection. Furthermore, in almost all cases of HCV and HDV coinfection, HBV is the nondominant virus (ie, nonreplicating). Given that treatment should be directed against the dominant virus, patients with HCV-dominant coinfection should be given pegylated interferon and ribavirin according to standard protocol for HCV infection, and patients with HDV-dominant coinfection should receive high-dose interferon (9 MU 3 times a week) or pegylated interferon.

A final group meriting special consideration is HBV-infected patients who have undergone liver transplantation. Therapy is important in these individuals because recurrence of HBV infection is seen in approximately 67% of patients when prophylactic antiviral therapy is not administered. This rate increases to as high as 83% in patients who have detectable levels of HBV DNA prior to transplant. When prophylactic antiviral therapy is administered, HBV recurrence decreases to as low as 0% to 15%.

Treatment Options

Options for the treatment of hepatitis B have expanded significantly since the introduction of interferon alfa over 2 decades ago. FDA-approved treatment options can be divided into interferon agents (interferon alfa-2b and pegylated interferon alfa-2a) and nucleos(t)ide analogs (lamivudine, adefovir, entecavir, tenofovir, and telbivudine). Newer agents such as emtricitabine and clevudine also demonstrate promise in treating hepatitis B, but have not yet received FDA approval.

Interferon Agents

The interferons have both antiviral and immunomodulatory effects they can be administered for finite courses with durable responses and virtually no risk for resistance. These agents confer the highest rates of HBsAg clearance, with a rate of approximately 3% at 72 weeks in patients receiving pegylated interferon. Although standard interferon is still available, it has largely been replaced by pegylated interferon in routine clinical practice due to the latter's improved efficacy and less demanding injection schedule.

Pegylated interferon is given at a dose of 180 µg weekly for 24-48 weeks in HBeAg-positive patients and for 48 weeks in HBeAg-negative patients. A large phase 3 randomized trial conducted in HBeAg-positive patients in 2005 demonstrated that

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pegylated interferon (both alone and in combination with lamivudine) resulted in significantly higher rates of HBeAg seroconversion, HBV DNA undetectability, and ALT normalization than lamivudine alone. A similar trial in HBeAg-negative patients also demonstrated higher rates of HBV DNA undetectability and ALT normalization in pegylated interferon-treated patients. No significant difference in efficacy has been demonstrated thus far between pegylated interferon monotherapy and the combination of pegylated interferon and lamivudine.

High pretreatment levels of ALT ($= 2 \times \text{ULN}$) and low levels of serum HBV DNA are the most important predictors of a response to interferon therapy. If HBV DNA has not decreased by at least 1 log unit in HBeAg-positive patients or by at least 2 log units in HBeAg-negative patients by week 24 of therapy, it is likely that pegylated interferon treatment will fail. Patients with HBV genotypes A and B also respond better to pegylated interferon than do those with genotypes C and D.

The major drawback of interferon-based therapy is its subcutaneous mode of administration and extensive side-effect profile, which most commonly includes influenza-like symptoms and mood changes. Interferon agents are also contraindicated in patients with decompensated liver disease, as they can precipitate worsening hepatic function.

Pegylated interferon is a reasonable choice for first-line therapy in patients infected with HBV genotypes A or B who are young, lack significant comorbidities, and have HBV DNA levels $< 10^9$ copies/mL and ALT levels $= 2-3 \times \text{ULN}$.

Nucleos(t)ide Analogs

The use of nucleos(t)ide analogs has gained "popularity" over the use of the interferons as a result of their oral route of administration, less frequent side effects, and increased potency in reducing HBV DNA and ALT levels. They must be administered for longer periods of time, however, and are associated with a risk for resistance.

For HBeAg-positive patients, the APASL, EASL, and US guidelines recommend that treatment be continued until HBV DNA levels are undetectable by a high-sensitivity real-time polymerase chain reaction assay for 12 months after HBeAg seroconversion or on 2 separate tests performed 6 months apart. In patients who achieve HBeAg seroconversion but in whom HBV DNA levels remain at a stable detectable level, the US guidelines recommend continuing therapy for 6 months after seroconversion.

In HBeAg-negative patients, treatment must be administered indefinitely, due to high rates of relapse despite prolonged HBV DNA undetectability. According to the AASLD guidelines, discontinuation of treatment can only be considered if HBsAg clearance is achieved. The APASL guidelines, however, state that discontinuation of therapy can also be considered if HBV DNA levels are undetectable on 3 occasions at least 6 months apart.

In patients with cirrhosis, treatment is usually administered lifelong, although the US guidelines suggest that treatment cessation can be considered in patients who achieve

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HBsAg clearance with an undetectable HBV DNA. The AASLD guidelines also allow for cessation of therapy in patients with compensated cirrhosis after HBsAg clearance (HBeAg-negative patients) or 6 months post-HBeAg seroconversion (HBeAg-positive patients).^[1] However, the potential for icteric flare, given the uncertain durability of seroconversion, must be carefully considered.

In any case, initiating therapy with a nucleos(t)ide analog requires consideration not only of the potency of each agent but also its resistance profile and rapidity of onset of action.

Lamivudine: The first oral anti-HBV therapy, lamivudine, received FDA approval in 1998. An enantiomer of 2'-3' dideoxy-3'-thiacytidine, lamivudine inhibits HBV DNA synthesis by incorporating into growing DNA chains and causing premature termination. It is administered at a dose of 100 mg daily and has been shown in trials to be safe and well tolerated. Although lamivudine is effective in reducing HBV DNA levels (undetectable levels have been achieved in 44% of HBeAg-positive patients at 48 weeks and 63% of HBeAg-negative patients at 24 weeks) and bringing about HBeAg seroconversion (16% to 17% at 48 weeks), durable response is seen in only 50% to 80% of HBeAg-positive patients and 20% to 25% of HBeAg-negative patients.

Furthermore, the use of lamivudine is hindered by its high rate of resistance, associated with a known mutation in the reverse transcriptase region of the HBV polymerase, designated YMDD. Lamivudine leads to resistance in approximately 20% of patients per year, with a rate as high as 70% after 5 years of therapy in HBeAg-positive patients or after 4 years in HBeAg-negative patients. As a result, lamivudine is not currently considered first-line therapy for the treatment of hepatitis B.

Adefovir: Adefovir is an acyclic nucleotide analog of adenosine monophosphate. It was approved by the FDA in 2002 for the treatment of chronic hepatitis B. Like lamivudine, it is incorporated into HBV DNA, causing chain termination and inhibition of both reverse transcriptase and DNA polymerase activity. Adefovir is administered at a dose of 10 mg daily and has been demonstrated to reduce serum HBV DNA in 21% of HBeAg-positive individuals and 71% of HBeAg-negative individuals. HBeAg seroconversion occurs in 12% of HBeAg-positive patients, with 91% exhibiting a durable response. Response to adefovir is similar across all HBV genotypes, although approximately 10% to 20% of treatment-naïve patients demonstrate primary nonresponse, perhaps as a result of suboptimal dosing.

Resistance to adefovir develops at a slower rate than with lamivudine, but several mutations have been described, typically developing after 1 year of treatment. Cumulative resistance rates of 0%, 3%, 11%, 18%, and 29% were reported in HBeAg-negative patients after 1, 2, 3, 4, and 5 years, respectively, of therapy. Although adefovir resistance occurred in 0% of HBeAg-positive patients after 1 year of treatment, there are no long-term data on resistance in this group. Adefovir resistance is most likely to occur in patients with a history of lamivudine resistance who are switched to adefovir monotherapy; it develops at a lower rate in those who have had adefovir added to lamivudine. Resistance is also more likely to develop when HBV DNA levels remain > 200 IU/mL (10^3 copies/mL) after 48 weeks of treatment.

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The most notable side effect associated with adefovir is nephrotoxicity, which has been reported in 3% of patients with compensated liver disease after 4-5 years and in 6% of transplant recipients and 28% of patients with decompensated cirrhosis during the first year of therapy. The drug is otherwise well tolerated, with a side-effect profile similar to that of placebo.^[1]

Recent studies, however, have shown the superiority of the most recently approved nucleotide analog, tenofovir, over adefovir. In both HBeAg-positive and HBeAg-negative patients, tenofovir was associated with a greater mean reduction in serum HBV DNA level than adefovir, as well as higher rates of HBeAg seroconversion, ALT normalization, and improvement in liver histology. As a result, the US and EASL guidelines, the only guidelines to be updated after FDA approval of tenofovir for the treatment of chronic hepatitis B, state that tenofovir should replace adefovir as a first-line drug in treatment-naïve patients.

Entecavir: Entecavir, an analog of cyclopentyl guanosine that results in potent inhibition of the priming and elongation functions of HBV polymerase, is considered by all guidelines to be a first-line therapeutic agent for the treatment of chronic hepatitis B.

In treatment-naïve patients with HBeAg-positive hepatitis, 0.5 mg daily of entecavir resulted in a greater mean reduction in viral load and a higher rate of HBV DNA undetectability than either lamivudine or adefovir. The HBeAg seroconversion rate was similar at 21%, with durable response seen in 69%. In HBeAg-negative patients, entecavir was associated with HBV DNA loss in 90%, ALT normalization in 78%, and histologic improvement in 70% to 72%. Entecavir has similar activity across all HBV genotypes and races, although HBeAg seroconversion rates are lower in patients with normal ALT.

Resistance to entecavir is relatively rare, as it requires 2 "hits": selection of an rtM204V/I or rtL180M mutation, followed by an amino acid substitution at rtI169, rtT184, rtS202, or rtM250, or a combination of these substitutions with or without an rtI169 substitution. Long-term data indicate a resistance rate of 1.2% in both HBeAg-positive and HBeAg-negative nucleoside-naïve patients treated for up to 5 years. Entecavir is well tolerated and safe, with a safety profile similar to that of lamivudine in clinical trials.

Telbivudine: Telbivudine is an L-nucleoside analog of thymidine that inhibits second-strand DNA synthesis by the HBV polymerase. It is administered at a dose of 600 mg daily and, like other nucleoside analogs, has been found to have an excellent safety and adverse-event profile.

A phase 3 clinical trial conducted in HBeAg-positive patients demonstrated superior rates of HBV DNA suppression (60% vs 40.4%) and ALT normalization (77% vs 74.9%) with 1 year of telbivudine therapy compared with lamivudine. The HBeAg seroconversion rate was similar, at approximately 22%. A higher rate of HBV DNA loss was also seen in HBeAg-negative patients for telbivudine vs lamivudine, although normalization of serum ALT levels was not significantly different. Trials comparing telbivudine with adefovir in

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HBeAg-positive patients likewise demonstrated a higher rate of HBV DNA loss and a greater mean reduction in HBV DNA level with telbivudine.

Telbivudine is limited by its high rate of resistance, second only to lamivudine. Data from HBeAg-positive patients demonstrate resistance rates of 5% and 25% at 1 and 2 years, respectively. Rates of 2.3% and 11% at 1 and 2 years are seen in HBeAg-negative patients. Like lamivudine, telbivudine selects for mutations in the YMDD motif of the HBV polymerase. Resistance is less likely to develop in patients who achieve early, rapid suppression of viral replication, as indicated by undetectable HBV DNA levels (< 300 copies/mL) at 24 weeks. These same patients were also more likely to achieve HBeAg seroconversion and ALT normalization. Nevertheless, the role of telbivudine in clinical practice is unclear at this time.

Tenofovir: Tenofovir is a nucleotide analog that is structurally related to adefovir but has more potent antiviral activity. Previously approved for the treatment of HIV, tenofovir gained FDA approval for the treatment of chronic hepatitis B in the third quarter of 2008.

Findings from 2 double-blind, phase 3 studies demonstrated that tenofovir 300 mg daily was more effective than adefovir 10 mg daily in the treatment of chronic HBV infection. In HBeAg-positive patients, tenofovir resulted in HBV DNA suppression (< 400 copies/mL [< 69 IU/mL]) in 72% at 3 years. Tenofovir also resulted in HBsAg loss in 8% of patients [after 3 years], the highest rate seen among oral nucleos(t)ide agents.

Trials in HBeAg-negative patients show a similar superiority of tenofovir over adefovir, with viral suppression occurring in 88% of patients at 3 years. Furthermore, no patients in either trial experienced renal toxicity, and no resistance has been reported thus far for tenofovir in data for up to 3 years.

On the basis of its greater potency and superior resistance profile, tenofovir has replaced adefovir as a first-line therapeutic agent for treatment-naïve patients with HBeAg-positive and HBeAg-negative hepatitis B.

Emerging Antiviral Agents

Currently approved for the treatment of HIV infection, emtricitabine, a nucleoside analog with structural similarity to lamivudine, is undergoing evaluation for the treatment of HBV infection. Data from trials showed that a 48-week course of emtricitabine resulted in HBV DNA loss (< 400 copies/mL) in 54% of patients and improved histology in 62%. Like lamivudine, however, emtricitabine is associated with an YMDD mutation conferring resistance, with a resistance rate of 9% after 1 year and 13% after 48 weeks. The role of emtricitabine is likely best restricted to combination therapy with tenofovir.

Another agent on the horizon is the pyrimidine nucleoside analog clevudine. Trials evaluating the efficacy of 30 mg of clevudine given once daily for 24 weeks demonstrated HBV DNA loss (< 300 copies/mL) in 59% and ALT normalization in 68.2% of HBeAg-positive patients. Among HBeAg-negative patients, HBV DNA loss occurred in 92% and ALT normalization in approximately 75%. The HBeAg seroconversion rate was not significantly different from that of placebo.

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Both emtricitabine and clevudine are well tolerated, with no significant difference in adverse effects when compared with placebo.

Combination Therapy

Due to the success of combination therapy in the setting of HIV and HCV infection, there is a substantial degree of interest in the potential utility of combination therapy for the treatment of hepatitis B. Theoretically, such therapy would improve treatment efficacy via additive or synergistic antiviral effects. This has yet to be demonstrated in clinical trials, however, and the primary role of combination therapy thus far is to decrease the risk of developing resistance when using therapies associated with low resistance barriers.^[99] This potential benefit, however, must be weighed against increased cost, risk for toxicity, and the potential for drug-drug interactions.

Various combination-therapy strategies pairing nucleoside agents with nucleotide agents have been evaluated for the initial treatment of HBV infection, but none have yet proven to be superior to monotherapy. Trials evaluating the use of lamivudine and adefovir in combination demonstrated decreased lamivudine resistance as compared with lamivudine monotherapy but no difference in HBV DNA levels or rates of HBeAg seroconversion. A study to determine the efficacy of adefovir monotherapy vs combination therapy with adefovir plus emtricitabine revealed similar findings, with improved rates of HBV DNA loss (HBV DNA suppression) but no difference in the rates of HBeAg seroconversion. Trials evaluating the combination of tenofovir and emtricitabine are currently ongoing in patients with adefovir resistance. Although the combination of tenofovir and emtricitabine leads to higher rates of HBV DNA loss compared with adefovir monotherapy, it is not yet clear, on the basis of data up to 1 year, whether the combination strategy is more effective than tenofovir monotherapy.

Combination regimens employing nucleos(t)ide agents plus pegylated interferon have also been studied. In a phase 3 randomized trial, combination therapy with lamivudine plus pegylated interferon was associated with a more profound decrease in viral load than pegylated interferon alone but no significant difference in viral suppression, HBeAg seroconversion, or HBsAg clearance. Preliminary data from trials of pegylated interferon used in combination with adefovir, however, do show promise. Data have demonstrated more profound HBV DNA suppression, a greater mean reduction in viral load at 24 weeks, and a marked decrease in intrahepatic cccDNA level. Further data regarding this combination therapy strategy are forthcoming.

Initial Choice of Therapy

The preferred agents for initial therapy in treatment-naïve patients vary from guideline to guideline. This is likely due in large part to the US and EASL guidelines being the only sets to have been updated *after* tenofovir gained FDA approval in late 2008.

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HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B

Due to their higher potency and low rates of resistance, the US and EASL guidelines recommend tenofovir, entecavir, or pegylated interferon for initial therapy in HBeAg-positive and HBeAg-negative patients. Although the AASLD guidelines suggest that any of the approved antiviral agents may be used, they recommend tenofovir, entecavir, or pegylated interferon. The APASL guidelines do not make specific recommendations except in cases in which serum ALT is $> 5 \times \text{ULN}$. Due to the risk for rapid decompensation in this patient group, they recommend an agent with fast onset of action, such as entecavir, telbivudine, or lamivudine.

Cirrhosis

In patients with compensated cirrhosis, the US and EASL guidelines recommend initial therapy with entecavir, tenofovir, or pegylated interferon, whereas the AASLD guidelines recommend entecavir or tenofovir. The use of pegylated interferon in patients with compensated cirrhosis is somewhat controversial, as interferon agents carry a risk of precipitating hepatic decompensation.

All of the guidelines agree that interferon agents are contraindicated in patients with decompensated cirrhosis. For this patient group, the US guidelines recommend initial treatment with entecavir, tenofovir, or the combination of lamivudine and tenofovir. The AASLD guidelines recommend the combination of lamivudine and adefovir, and the EASL guidelines recommend entecavir or tenofovir.

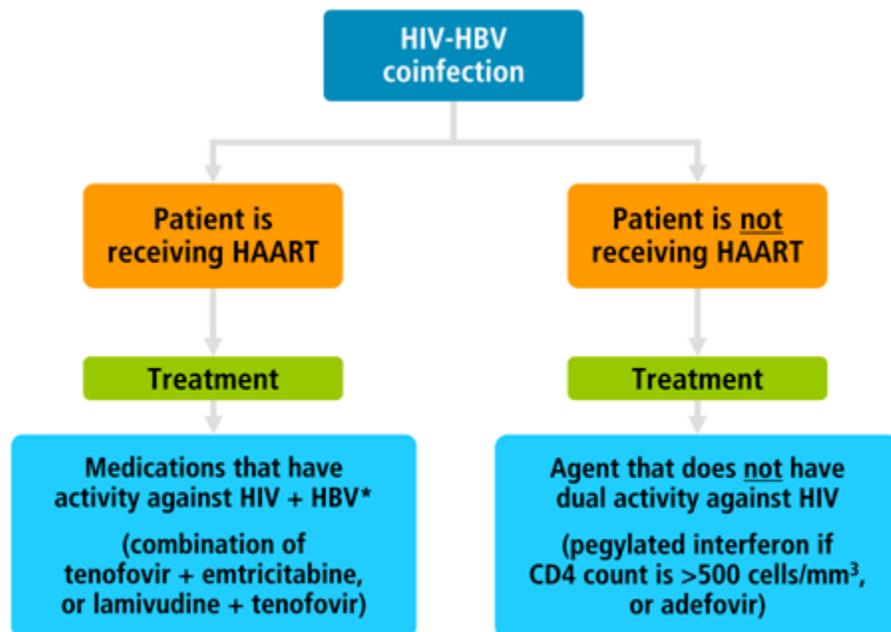
Special Populations

Patients undergoing immunosuppressive therapy or chemotherapy. Although lamivudine is the most extensively studied medication in patients undergoing immunosuppressive therapy, entecavir and tenofovir are recommended by many experts because of their lower risk for resistance and more potent viral suppression. This is particularly true in cases in which immunosuppressive therapy is to be administered for more than 6 months and in patients who have a detectable viral load. In patients with no detectable viral load by a sensitive assay, lamivudine may be a reasonable choice for therapy .

HIV-HBV coinfection. In HIV-HBV coinfecting patients, treatment regimens should be designed to avoid the potential development of drug-resistant HIV or HBV and cross-resistance among antiviral agents. Therefore, patients not on highly active antiretroviral therapy (HAART) should undergo hepatitis B treatment with medications that do not have dual activity against HIV, such as pegylated interferon (if CD4 count is > 500 cells/ μL) or adefovir. Although telbivudine does not have activity against HIV, its use is discouraged because of its high rate of cross-resistance with lamivudine. Entecavir is also not recommended due to a recent study in which HIV mutants with resistance to both lamivudine and entecavir were selected when entecavir was administered without simultaneous HAART. Patients being treated for HIV alone, or who need treatment for both HIV and HBV infection, should be treated with medications that have activity against both viruses. This regimen must include at least 2 agents with activity against

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HBV. The combination of tenofovir plus emtricitabine [Truvada] is preferred in this setting, although lamivudine plus tenofovir can also be used. In coinfecting patients with low CD4 counts and active liver disease, HBV infection should be treated first in order to avoid immune reconstitution syndrome.



Liver transplant patients: In patients who have undergone liver transplantation for HBV infection, the standard of care for prophylactic therapy is currently lamivudine in combination with HBIG. The recurrence rate decreases substantially on this regimen, with rates as low as 0% to 11% reported in studies. However, the use of HBIG is hampered by its high cost and need for recurrent clinic visits. The results of several studies suggest that oral combination therapy is associated with complete viral suppression and lack of resistance and thus might be a preferable option in patients receiving transplants for HBV infection.¹ Moreover, a recent pharmaco-economic study suggested that oral combination therapy may be a cost-effective alternative to HBIG and lamivudine in transplant recipients.

On-treatment Monitoring of Nucleos(t)ide Analog Therapy

HBV DNA levels must be monitored routinely during nucleos(t)ide analog therapy in order to detect treatment failures and avoid the development of resistance.

Primary treatment failure is assessed at week 12 and is defined as a $<1 \log_{10}$ IU/mL drop in HBV DNA level from baseline. If patient non-adherence to prescribed therapy has been ruled out, this finding warrants a change in therapy to a more potent drug. Primary treatment failure most commonly occurs with adefovir; a rapid switch to tenofovir or entecavir is recommended in these cases.

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At week 24, virologic response should be categorized as complete virologic response (HBV DNA level undetectable), partial virologic response (HBV DNA = 60 to < 2000 IU/mL), or inadequate virologic response (HBV DNA = 2000 IU/mL). If partial or inadequate response is encountered, non-adherence must be ruled out and therapy modified by changing to a more potent drug in the same class or adding a second drug that does not share cross-resistance. If the patient is receiving lamivudine or telbivudine, 1 of 2 strategies may be used: either add tenofovir or switch to tenofovir or entecavir. The use of lamivudine or telbivudine as initial therapy is discouraged, however, because of their high risk for cross-resistance, resulting in the limited utility of other drugs in the same therapeutic class. In patients with partial or inadequate response being treated with adefovir, the strategy involves either adding entecavir or switching to tenofovir or entecavir. If entecavir or tenofovir is being used, addition of the other agent is indicated.

Monitoring of HBV DNA and serum ALT levels should ensue every 3-6 months. In HBeAg-positive patients, HBeAg should also be monitored every 6-12 months in order to detect HBeAg seroconversion.

Antiviral Resistance

Once therapy is initiated, patients should be monitored closely for the development of antiviral drug resistance. Genotypic antiviral resistance specifically refers to the presence of known mutations in the HBV polymerase gene that may result in treatment failure. The development of resistance is associated with an increased risk of progressive liver disease, HCC, clinical decompensation and the potential for selection and transmission of multidrug-resistant HBV. The incidence of resistance varies depending on the specific antiviral agent used and may increase with duration of therapy. The rate of resistance associated with a particular agent is influenced by its genetic barrier, defined by the probability of viral mutation in response to the selective pressure exerted by the agent, resulting in genotypic and phenotypic resistance. Lamivudine therapy is associated with a significant rate of antiviral resistance, reaching up to 71% at 4 years. The genotypic resistance that occurs during lamivudine therapy is associated with two primary mutations that alter the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase, resulting in viral resistance to lamivudine. Adefovir has also demonstrated a potential for development of resistance, with an overall rate of 29% after 5 years of therapy in patients with HBeAg-negative chronic hepatitis B. Although long-term data are limited, telbivudine and emtricitabine are also associated with significant resistance within a short period following the initiation of therapy, with rates up to 25% at 2 years and 13% at 1 year. By contrast, entecavir has a high genetic barrier with minimal resistance (1.2%) after 5 years of therapy in nucleoside-naïve patients. However, cross-resistance to entecavir may develop in those who have pre-existing lamivudine resistance, occurring in as many as 50% of patients at 5 years. Tenofovir also appears to have a high genetic barrier as no antiviral resistance mutations have been identified after 3 years of therapy.

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How should the pregnant HBeAg-positive woman and newborn be managed before, during, and after delivery?

The hepatitis B virus (HBV) can be transmitted from an infected mother to her infant. In fact, the risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of hepatitis B e antigen (HBeAg)-positive mothers to approximately 25% in infants and children under 5 years of age, to less than 5% in adults. According to the recently revised guidelines approved by the American Association for the Study of Liver Diseases and endorsed by the Infectious Diseases Society of America, screening is recommended for all pregnant women. Newborns of HBV-infected mothers should receive both hepatitis B immune globulin (HBIG) and the HBV vaccine at the time of delivery and should complete the recommended vaccination series. The guidelines further state that hepatitis B surface antigen (HBsAg)-positive women who are pregnant should be counseled to make sure that they inform their providers of their hepatitis B status so that HBIG and the HBV vaccine can be administered to their newborns immediately after delivery. This has become an established and highly effective practice. Concurrent administration of HBIG and the HBV vaccine to the newborn is 95% effective in the prevention of perinatal transmission of HBV. However, efficacy is lower for maternal carriers with very high serum HBV DNA levels ($> 8 \log_{10}$ IU/mL). Because infants of HBsAg-positive mothers remain at risk for HBV infection, they should be tested for response to vaccination. Post-vaccination testing should be performed at 9-15 months of age in infants of carrier mothers.

Conclusion

HBV infection is an important public health concern responsible for over 1 million deaths per year worldwide. Morbidity and mortality from its known complications of cirrhosis, hepatic decompensation, and HCC can be reduced by recognizing when and how to start antiviral therapy, when to stop therapy, and when to alter therapy in the setting of resistance or inadequate treatment response.