Hepatitis B virus: Overview of management

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INTRODUCTION

Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the family of hepadnaviruses. HBV infection is a global public health problem. It is estimated that there are more than 250 million HBV carriers in the world, of whom approximately 600,000 die annually from HBV-related liver disease.

The following topic review will summarize issues related to the management of HBV infection. The recommendations below are generally consistent with guidelines from the European Association for the Study of the Liver (EASL) guidelines, Asian-Pacific Association for the Study of the Liver guidelines, and American Association for the Study of Liver Diseases (AASLD) Practice Guidelines [1-3]. Clinical decisions regarding individual patients should be based upon patient-specific clinical information and test results.

Topic reviews that discuss the management of pregnant women and children with HBV infection, as well as the data supporting this section, are presented separately.

- (See "Hepatitis B and pregnancy".)
- (See "Clinical manifestations and diagnosis of hepatitis B virus infection in children and adolescents" and "Management of hepatitis B virus infection in children and adolescents".)
- (See "Hepatitis B virus: Case studies".)
- (See "Pegylated interferon for treatment of chronic hepatitis B virus infection".)
- (See "Entecavir in the treatment of chronic hepatitis B virus infection".)
- (See "Tenofovir and adefovir for the treatment of chronic HBV infection".)

ACUTE INFECTION

The diagnosis of acute HBV infection is based upon the detection of hepatitis B surface antigen (HBsAg) and immunoglobulin M (IgM) antibody to hepatitis B core antigen (anti-HBc) (table 1A-B and figure 1). Treatment of acute HBV depends upon the clinical setting. However, appropriate measures should be taken to prevent infection in all exposed contacts, and hepatitis B immune globulin and hepatitis B vaccine should be administered to all household and sexual contacts who are not known to be immune. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection", section on 'Prevention'.)

For most patients, treatment is mainly supportive. The likelihood of liver failure from acute HBV is less than 1 percent, and in immunocompetent adults, the likelihood of progression to chronic HBV infection is less than 5 percent [4]. There are known subgroups of patients whose prognosis is relatively worse (eg, patients who are immunocompromised, have concomitant infection with hepatitis C or human immunodeficiency virus [HCV or HIV], have preexisting liver disease, or are older adults), but the role of antiviral therapy for such patients remains unsettled since few studies have addressed its benefits during acute infection.

As a general rule, we treat patients with a severe or a protracted course (eg, those who develop a coagulopathy [international normalized ratio (INR) >1.5], those with persistent symptoms or marked jaundice [bilirubin >3 mg/dL] for more than four weeks after presentation) [3]. We also treat patients with acute liver failure due to HBV to reduce the likelihood of reinfection post-liver transplant, should a liver transplant become necessary.

For those who require treatment, tenofovir or entecavir are acceptable options given as monotherapy. Treatment can be stopped after confirmation that the patient has cleared HBsAg (two consecutive tests four weeks apart). Lamivudine or telbivudine can also be used, as the duration of treatment is generally short. However, since severe exacerbations of chronic HBV in previously undiagnosed patients can be difficult to differentiate from acute HBV, tenofovir or entecavir are preferred. Adefovir is not typically used because of its weak antiviral activity, and interferon should be avoided because of the risk of bacterial infections and a further increase in hepatic necroinflammation in patients with severe hepatitis or acute liver failure.

CHRONIC HEPATITIS B

The diagnosis of chronic HBV infection is based upon the persistence of hepatitis B surface antigen (HBsAg) for greater than six months. A number of risk factors for HBV infection have been identified, providing a rationale for screening (table 2 and table 3) [3,5-7]. A more

detailed discussion of screening and diagnosis of HBV is found elsewhere. (See "Hepatitis B virus: Screening and diagnosis in adults" and "Hepatitis B virus immunization in adults".)

The management of chronic HBV infection is complex and depends upon multiple factors including clinical variables (eg, the presence or absence of liver inflammation and/or cirrhosis), the patient's immunologic response to infection (eg, hepatitis B e antigen [HBeAg] status), virologic factors (eg, the HBV viral load and genotype), and risk factors for disease progression (eg, age >40 and family history of hepatocellular carcinoma).

Initial evaluation

General approach — The initial evaluation of patients with chronic HBV infection should include (table 4):

- A history and physical examination, emphasizing: risk factors for coinfection with hepatitis C virus (HCV), hepatitis delta virus (HDV), and/or HIV; use of alcohol; family history of HBV infection and hepatocellular carcinoma (HCC); and signs and symptoms of cirrhosis.
- Laboratory tests, including: a complete blood count with platelets, liver chemistry tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, alkaline phosphatase, albumin), international normalized ratio (INR), and tests for HBV replication (HBeAg, antibody to HBeAg [anti-HBe], HBV DNA). Testing for immunity to hepatitis A virus (HAV) with HAV immunoglobulin G (IgG) antibody should be performed in patients who are not known to be immune.
- Evaluation for other causes of liver disease (eg, hemochromatosis, HCV, HDV) by testing for iron, total iron binding capacity, ferritin, and HCV antibody in all patients. For HDV, we screen patients with a history of injection drug use and those who migrated from countries where HDV is prevalent (eg, Southern or Eastern European countries); however, other experts suggest one-time screening for HDV in all patients with chronic hepatitis B. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection".)
- Screening for HIV infection in those who have not undergone routine screening, and in those persons with ongoing risk factors for HIV (eg, injection drug use, multiple sexual exposures, men who have sex with men). (See "Screening and diagnostic testing for HIV infection".)
- Screening for HCC if indicated. (See "Surveillance for hepatocellular carcinoma in adults".)
- Screening for fibrosis using noninvasive tests (eg, vibration-controlled transient elastography, serum fibrosis panel) or liver biopsy. Noninvasive assessments of liver

fibrosis, notably measurements of liver stiffness, are increasingly used instead of liver biopsies; however, liver stiffness can be influenced by inflammation as well as fibrosis, and therefore, liver stiffness measurements may overestimate liver fibrosis in patients with a high ALT (more than 100 units/L) [8]. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations" and "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography" and 'Role of liver biopsy' below.)

Role of liver biopsy — Most patients will not need a liver biopsy. However, a liver biopsy may be useful in the following scenarios:

- Patients who have persistently elevated ALT but persistently low HBV DNA to exclude other causes of liver disease.

- Patients who do not meet criteria for treatment but are at risk for having histologically active or advanced liver disease that would benefit from treatment. These include patients who have ALT levels that are normal or mildly elevated (<2 x the upper limit of normal [ULN]), an HBV viral load that is persistently elevated (eg, >6 months), and one of the following risk factors:

  - Age >40 years.
  - A family history of HCC.

  An elevated HBV DNA is considered >2000 international units/mL (10^4 copies/mL) for HBeAg-negative patients or >20,000 international units/mL (>10^5 copies/mL) for HBeAg-positive patients.

  A normal serum ALT level alone in patients with active viral replication does not predict mild or normal histologic findings [9,10]. As an example, one report found that up to 37 percent of patients with persistently normal ALT and HBV DNA levels >10,000 copies/mL (approximately >2000 international units/mL) had significant fibrosis and inflammation on liver biopsy. On subgroup analysis, most such patients had an ALT in the high range of normal and were older than 40 years of age. By contrast, two studies in patients in the immune tolerant phase of chronic HBV infection found that despite high HBV DNA levels, most patients had no or minimal fibrosis [11,12].

  The decision to obtain a liver biopsy should be made on a case-by-case basis in consultation with a specialist in liver diseases. More detailed information on the approach to liver biopsy is presented elsewhere. (See "Approach to liver biopsy".)

Indications for antiviral therapy — The decision to initiate treatment is primarily based upon the presence or absence of cirrhosis, the ALT level, and the HBV DNA level (table 5). However, there are additional indications for patients with certain concurrent conditions, such as malignancy and pregnancy. (See 'Patients receiving immunosuppressive therapy' below and 'Pregnant women' below and 'Patients with hepatocellular carcinoma' below.)

Patients who are deemed **not** to be treatment candidates at presentation, and those who decide to defer treatment, should undergo monitoring of liver biochemical tests, HBV DNA, and HBeAg status since liver disease and/or HBV replication may become active later. The frequency of monitoring is described in the table (table 4). These patients should also undergo HCC surveillance if indicated. (See 'Screening for hepatocellular carcinoma' below.)

Our approach is consistent with recommendations from the American Association for the Study of Liver Diseases (AASLD) [3]. The AASLD, European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver (APASL) guideline recommendations are very similar. However, there are minor differences related to the year of publication, the prevalence of HBV infection within the population, and the availability of resources [13].

Acute liver failure or decompensated cirrhosis — Patients with life-threatening liver disease secondary to HBV should initiate antiviral therapy. This includes patients with acute liver failure (eg, fulminant acute HBV, severe exacerbation of chronic HBV), as well as those with decompensated cirrhosis and a detectable HBV DNA by polymerase chain reaction (PCR) assay (regardless of the ALT level) [14]. Such patients should also be evaluated for liver transplant. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

Nucleos(t)ide analog treatment has been shown to stabilize liver disease, and in some cases reverse liver failure [15,16]. Antiviral treatment also reduces the risk of recurrent HBV should these patients require liver transplantation. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

Compensated cirrhosis — Patients with compensated cirrhosis and an HBV DNA >2000 international units/mL (>10^4 copies/mL) should be treated with antiviral therapy regardless of the HBeAg status or the serum ALT level (table 5). Treatment should be considered even if HBV DNA levels are lower than 2000 international units/mL, since there are data showing that patients with cirrhosis and low HBV DNA levels have a higher risk of hepatocellular carcinoma than those with undetectable HBV DNA levels [17].

Patients without cirrhosis

HBeAg-positive (immune active phase) — For HBeAg-positive patients without cirrhosis, treatment should be initiated when the HBV DNA is >20,000 international units/mL (>10^5 copies/mL) and the ALT is >2 x ULN (table 5) [3]. The ULN should be considered 35 U/L for males and 25 U/L for females; these levels should be used rather than individual laboratory cut-off levels. Treatment should be delayed for three to six months in newly diagnosed HBeAg-positive patients with compensated liver disease to determine whether spontaneous HBeAg seroconversion will occur. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Phases of chronic HBV infection'.)

Patients with chronic hepatitis whose serum ALT is persistently below 2 x ULN can be observed, considering treatment if and when the serum ALT becomes higher (table 4). Exceptions to this rule include: those who have recurrent hepatitis flares that fail to clear HBeAg, patients with icteric flares, those with active or advanced histologic findings (such as moderate/severe inflammation or bridging fibrosis/cirrhosis) or advanced fibrosis on noninvasive tests such as elastography, patients with extrahepatic manifestations (eg, HBV-related polyarteritis nodosa), patients above the age of 40 who remain HBeAg-positive with persistently high HBV DNA levels, those with a family history of HCC (there is a lower threshold for HBV DNA and ALT in these patients), and health care providers performing exposure-prone procedures (as required by local guidelines). (See "Epidemiology, transmission, and prevention of hepatitis B virus infection", section on 'Health care providers'.)

Although treatment can lead to virus suppression in HBeAg-positive patients with normal ALT (immune tolerant phase), the likelihood of HBeAg seroconversion on treatment is low, and HBV DNA rebounds to baseline levels when treatment is stopped. The poor results are true for monotherapy as well as combination therapy with two nucleos(t)ide analogs or a nucleos(t)ide analog and pegylated interferon (PegIFN) [18-20]. In addition, despite high HBV DNA levels, the risk of HCC during follow-up to 10 years is low [21]. Thus, the benefits of long-term treatment in such patients, most of whom are young and Asian with perinatally acquired HBV infection, must be balanced against the risks of drug resistance, side effects, and costs, particularly since some of these individuals will undergo spontaneous HBeAg seroconversion and remain in remission for many years afterwards.

HBeAg-negative chronic hepatitis — Treatment may be initiated immediately once a diagnosis of HBeAg-negative chronic hepatitis (ALT >2 x ULN and HBV DNA >2000 international units/mL) is established because sustained remission is rare in the absence of treatment. However, delaying treatment for two to three months to allow patients to understand the disease, the need for long-term (and often lifelong) treatment, and the importance of adherence is reasonable in patients with no evidence of cirrhosis. We follow the AASLD

recommendations that define the ULN for ALT as 35 U/L for males and 25 U/L for females, rather than using individual laboratory cut-off levels [3].

For those with an ALT <2 x ULN, serial follow-up is needed to differentiate an inactive carrier state from HBeAg-negative chronic hepatitis because of the fluctuating course of HBeAg-negative chronic hepatitis. Liver biopsy should be considered in HBeAg-negative patients who have serum HBV DNA levels >2000 international units/mL and normal or mildly elevated ALT to determine if treatment is warranted. Alternately, noninvasive tests such as elastography may be used to assess fibrosis stage. Patients with low HBsAg levels (<1000 international units/mL) are more likely to be in the inactive phase than those with higher HBsAg levels.

Patients receiving immunosuppressive therapy — Antiviral therapy should be administered to most patients with chronic HBV prior to initiating immunosuppressive therapy, regardless of the HBV DNA or aminotransferase levels. Such patients are at risk for HBV reactivation if they receive immunosuppressive therapy. The level of risk is influenced by the type of immunosuppressive agent that is used. Prophylactic antiviral therapy may also be indicated in HBsAg-negative, anti-HBc-positive patients receiving potent immunosuppressive therapy such as anti-CD20. A detailed discussion of prophylactic antiviral therapy is presented elsewhere. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Pregnant women — For pregnant women, the indications for antiviral therapy are generally the same as those for patients who are not pregnant. However, women with high viral loads (>2 x 10^5 international units/mL) should initiate therapy in the late second or early third trimester, even if the aminotransferase levels are normal, to prevent transmission to their child. The management of HBV in pregnancy is presented in a separate topic review. (See "Hepatitis B and pregnancy".)

Patients with hepatocellular carcinoma — All patients with hepatocellular carcinoma (HCC) should be treated with a nucleos(t)ide analog (eg, tenofovir or entecavir). Treatment with nucleos(t)ide analogs can reduce the risk of HCC recurrence, particularly late recurrence (>2 years after initial diagnosis), and improve the prognosis of HBV-related HCC after curative therapy. This approach was supported in a meta-analysis that included 15 studies with 8060 patients where the recurrence rate was significantly decreased among those who received treatment (one-year recurrence: risk ratio [RR] 0.41, 95% CI 0.28-0.61; three-year recurrence: RR 0.63, 95% CI 0.43-0.94) [22].

Patients with hepatitis C coinfection — Patients who have coinfection with HBV and HCV are at risk for HBV reactivation if they are being treated for HCV with direct-acting antiviral therapy and are not receiving treatment for HBV [23].

- For HBsAg-positive patients who meet criteria for antiviral treatment of HBV (table 5), HBV treatment should be initiated prior to or at the same time as HCV therapy. For those who do not meet criteria for HBV therapy, the HBV DNA levels should be monitored at regular intervals (eg, every four weeks) during and for up to 12 weeks after HCV therapy. HBV therapy should be initiated if HBV DNA levels meet criteria for treatment.

- For HBsAg-negative, hepatitis B core antibody-positive patients, the risk of HBV reactivation during HCV direct-acting therapy is low. Monitoring of ALT is recommended, and if the ALT increases during treatment, HBV markers (HBsAg and HBV DNA) should be tested.

More detailed discussions of the management of HCV infection are found elsewhere. (See "Overview of the management of chronic hepatitis C virus infection", section on 'Monitoring during antiviral therapy'.)

Antiviral therapy — The goals of antiviral therapy are suppression of HBV DNA, loss of HBeAg (in patients who were initially HBeAg-positive), and loss of HBsAg. A sustained viral response, particularly in those who clear both HBeAg and HBsAg, is almost invariably accompanied by normalization of serum ALT, a decrease in necroinflammatory activity, and over time, a decrease in fibrosis as well. Antiviral treatment can also reduce the risk of long-term complications from chronic HBV (eg, liver failure and hepatocellular carcinoma) as well as the transmission of HBV to others. For some patients, immediate antiviral therapy is indicated, whereas for others, treatment may be deferred with careful monitoring. (See 'Indications for antiviral therapy' above.)

Overview of antiviral agents — Treatment strategies for chronic HBV typically include PegIFN or nucleos(t)ide analogs (eg, entecavir and tenofovir) (table 5) [24]. Investigational treatments can be considered in selected patients where such protocols are available. In addition, new strategies for the treatment of HBV continue to be developed.

The following discussion provides an overview of the different agents in nonpregnant adults. More detailed discussions of how to select a regimen and the use of these agents for the treatment of children and pregnant women are found elsewhere. (See 'Choice of initial agent' below and 'Persistent viremia/breakthrough infection' below and "Hepatitis B and pregnancy" and "Management of hepatitis B virus infection in children and adolescents", section on 'Choice of treatment'.)

Interferon — The main role of interferon is primarily treatment of young patients with well compensated liver disease who do not wish to be on long-term treatment. Among HBeAg-

positive patients, HBV genotype A (and to a less extent, genotype B), as well as low HBV DNA and high ALT levels are predictive of response to interferon therapy.

The advantages of interferon compared to nucleos(t)ide analogs are its finite duration of treatment, the absence of selection of resistant variants, and a higher rate of HBeAg loss and HBsAg loss compared to the same duration of nucleos(t)ide analog therapy. On the other hand, side effects from interferon are troubling for many patients, and (less commonly) can be severe. Furthermore, interferon should not be used in pregnant women and patients with decompensated disease or compensated cirrhosis and portal hypertension. (See "Pegylated interferon for treatment of chronic hepatitis B virus infection", section on 'Whom to treat'.)

Interferon alfa is administered by subcutaneous injection. The preferred formulation is peginterferon alfa-2a, which should be administered as 180 mcg once weekly for 48 weeks for HBeAg-positive or HBeAg-negative chronic HBV [25]. A more detailed discussion of interferon for the treatment of chronic HBV is found elsewhere. (See "Pegylated interferon for treatment of chronic hepatitis B virus infection".)

Nucleos(t)ide analogs — Several nucleos(t)ide analog agents are available. The predictors of response depend in part upon the HBeAg-status of the patient:

- For HBeAg-positive patients, the likelihood of a virologic response (HBV DNA suppression) to nucleos(t)ide analogs is independent of ALT levels and HBV genotype; however, the serologic response (HBeAg clearance), like interferon, is higher in those with elevated serum aminotransferases [26,27]. As a general rule, treatment with any of these drugs does not result in higher rates of HBeAg seroconversion compared with no treatment in those who have a serum ALT ≤2 x ULN. (See 'HBeAg-positive (immune active phase)' above.)

  In patients with high HBV DNA levels, it takes more time for HBV DNA to become undetectable after initiating nucleos(t)ide analogs. For such patients, the HBV DNA often remains detectable after one and sometimes two years of treatment; however, treatment with the same nucleos(t)ide analog as monotherapy is appropriate as long as HBV DNA levels continue to decline and the nucleos(t)ide analog has a high barrier to resistance. The management of persistent viremia is discussed below. (See 'Persistent viremia/breakthrough infection' below.)

- For HBeAg-negative patients, prediction of response (eg, HBsAg loss or sustained virologic response after discontinuation of treatment) is less precise. Because of the need for long-term treatment, therapy is recommended only for those with persistent or intermittent elevation in ALT and/or substantial histologic abnormalities (moderate/severe

inflammation or bridging fibrosis/cirrhosis) or advanced fibrosis based on elastography. (See 'HBeAg-negative chronic hepatitis' above.)

The available agents include:

- Entecavir – The main advantages of entecavir are its potent antiviral activity and low rate of drug resistance in patients who are nucleos(t)ide-naïve (approximately 1 percent with up to five years of treatment). However, entecavir should **not** be used for patients with lamivudine-resistant HBV, since resistance has been observed in up to 50 percent of lamivudine-refractory patients after five years of treatment. (See "Entecavir in the treatment of chronic hepatitis B virus infection".)

  Entecavir is administered orally. The dose should be adjusted for patients with reduced kidney function (table 6).

  - For nucleoside-naïve adults and adolescents older than 16, the recommended dose is 0.5 mg once daily.
  - The dose should be increased to 1 mg daily for those with decompensated liver disease.

  The dose should also be increased to 1 mg daily if it is used for patients who have been treated with lamivudine in the past; however, for such patients, tenofovir is preferred. (See 'Persistent viremia/breakthrough infection' below.)

- **Tenofovir** – Tenofovir can be used as first-line therapy in treatment-naïve patients and also in those who have had prior exposure, or developed drug resistance, to other nucleos(t)ide analogs (eg, lamivudine). In clinical trials of patients receiving tenofovir disoproxil fumarate (TDF), no signature mutation for tenofovir resistance has been identified, even among those who have been treated for up to eight years. (See "Tenofovir and adefovir for the treatment of chronic HBV infection", section on 'Risk of resistance'.)

  There are two formulations of tenofovir, TDF and tenofovir alafenamide. For most patients, we recommend tenofovir alafenamide (25 mg daily) rather than TDF (300 mg daily), if available. For those who were originally started on TDF, we generally suggest switching to tenofovir alafenamide, particularly in older patients and those with risk factors for renal impairment or osteoporosis. Although there is more experience with TDF compared with tenofovir alafenamide, tenofovir alafenamide appears to be equally effective and is associated with less renal and bone toxicity [28-31]. (See "Tenofovir and adefovir for the treatment of chronic HBV infection", section on 'Safety'.)

The use of tenofovir and the choice of tenofovir formulation in patients with reduced kidney function and in patients with decompensated cirrhosis are discussed below. In addition, until more data are available, tenofovir alafenamide should be avoided in pregnant women. (See 'Choice of initial agent' below.)

- Lamivudine – The main advantages of lamivudine are its lower cost compared with the other oral agents and the many years of experience confirming its safety. However, lamivudine should not be used, given the high rate of drug resistance, unless entecavir or tenofovir is not available. (See "Entecavir in the treatment of chronic hepatitis B virus infection" and "Tenofovir and adefovir for the treatment of chronic HBV infection".)

  Lamivudine (or the closely related agent emtricitabine) may still have a role in patients coinfected with HIV when used as part of an antiretroviral regimen that contains a second drug with anti-HBV activity, such as tenofovir. A detailed discussion of the treatment of HBV in HIV-infected patients is found elsewhere. (See "Treatment of chronic hepatitis B in patients with HIV".)

  The recommended dose of lamivudine for adults with normal renal function without concomitant HIV infection is 100 mg daily. Dose adjustment is required in those with decreased renal function (table 6). For patients with HIV, a higher dose (lamivudine 300 mg once daily) is used as part of an HIV antiretroviral regimen. (See "Treatment of chronic hepatitis B in patients with HIV", section on 'Preferred regimens'.)

- Adefovir – The most important role of adefovir is in the treatment of patients with lamivudine-resistant HBV, preferably in combination with other agents. However, this role has been replaced by tenofovir, which is more potent and effective when used as monotherapy. If used, adefovir is administered orally, and the dose is 10 mg daily. Patients with impaired renal function should have the dosing interval adjusted (table 6).

  Virus suppression is slow at the approved dose, and up to 25 percent of patients experience minimal or no viral suppression. Adefovir at high doses has been associated with nephrotoxicity. At the approved dose of 10 mg daily, a reversible increase in serum creatinine has been reported in 3 to 9 percent of patients after four to five years of treatment. Adefovir resistance was not detected after one year of treatment, but the rate of drug resistance has been reported to be as high as 29 percent after five years of treatment. (See "Tenofovir and adefovir for the treatment of chronic HBV infection", section on 'Adefovir'.)

- Telbivudine – Telbivudine is administered orally. The recommended dose is 600 mg once daily. Dose should be adjusted in patients with impaired renal function. This agent is no

longer manufactured in the United States.

Telbivudine appears to have slightly more potent antiviral effects compared with lamivudine and adefovir. In addition, telbivudine has been reported to produce mild improvements in renal function due to an unidentified mechanism [32]. Despite these potential benefits, we generally do not recommend this agent given the increased risk of drug resistance and other adverse events (eg, myopathy and peripheral neuropathy) compared with alternative antiviral agents.

Cost-effectiveness — The cost-effectiveness of various treatment strategies for chronic HBV is incompletely understood as many cost-effectiveness analyses were conducted before approval of peginterferon, entecavir, TDF, and tenofovir alafenamide. Furthermore, the cost of generic nucleos(t)ide analogs is markedly reduced and highly variable in different countries. However, a cost-effectiveness analysis using data from Hong Kong suggests that PegIFN may be the most cost-effective treatment for HBeAg-positive patients, especially if a 12-week stop rule is used, whereas entecavir is more cost-effective for HBeAg-negative patients [33].

Choice of initial agent

Approach for most patients — For most treatment-naïve patients, either tenofovir or entecavir is preferred because they both are well tolerated, have potent antiviral activity, and have a low risk of selecting for drug-resistant virus. We avoid monotherapy with lamivudine, adefovir, or telbivudine given the high risk of developing resistance with long-term use and, in the case of adefovir, its weak antiviral activity. (See 'Overview of antiviral agents' above.)

PegIFN is also an option for select immunocompetent patients without cirrhosis. However, given the increased risk of adverse events with this agent compared with nucleos(t)ide analogs, it is typically reserved for those who desire a finite duration of treatment (eg, young adults and women planning to conceive in the future), particularly if they are HBeAg positive, are infected with HBV genotype A, and if a week 12 stop rule will be applied. A detailed discussion of interferon therapy for treatment of hepatitis B is presented separately. (See "Pegylated interferon for treatment of chronic hepatitis B virus infection".)

Considerations for select patients

- **Patients with cirrhosis** – Tenofovir or entecavir can be used for patients with cirrhosis. We generally prefer entecavir for patients with decompensated cirrhosis who are treatment-naïve. Such patients are at risk for acute kidney injury secondary to the hepatorenal syndrome, and entecavir has not been shown to be nephrotoxic, whereas TDF has been associated with reduced kidney function. Tenofovir alafenamide is an alternative

agent, but efficacy and safety data in patients with decompensated liver disease are lacking. Lactic acidosis has been reported in patients with severe liver dysfunction receiving entecavir [34]; however, this is likely a class effect of nucleos(t)ide analogs. Several larger studies did not observe any clinical cases of lactic acidosis, but lactate levels were not monitored in those studies. Treatment of such patients should be coordinated with a transplant center. (See "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients".)

In general, there is no evidence that initiating combination therapy with two nucleos(t)ide analogs (eg, entecavir and TDF) is superior to monotherapy. Although combination therapy results in more rapid viral suppression in patients with high baseline HBV DNA, it has not been determined whether accelerating viral suppression improves clinical outcomes.

For patients with decompensated cirrhosis, interferon is **contraindicated** [35]. Interferon may be used with caution in patients with compensated cirrhosis, normal hepatic synthetic function, and minimal or no evidence of portal hypertension, but nucleos(t)ide analogs are safer. (See 'Nucleos(t)ide analogs' above and 'Interferon' above.)

- **Pregnancy** – For pregnant women who require treatment, we prefer TDF rather than other antiviral agents. Interferon is contraindicated in such patients, and we do not use tenofovir alafenamide or entecavir given the lack of sufficient safety data. A detailed discussion of the management of HBV and pregnancy is presented separately. (See "Hepatitis B and pregnancy".)

- **Patients with reduced kidney function** – For patients with chronic HBV and reduced kidney function, the choice of agent depends in part upon the creatinine clearance and if the patient is on dialysis (table 6). As examples:

  - For patients with a creatinine clearance (CrCl) <60 mL/min, TDF should be avoided, if possible.

  - For patients with a CrCl >15 mL/min, either entecavir or tenofovir alafenamide can be used. An advantage of tenofovir alafenamide over entecavir is that the dose does not need to be adjusted for renal function.

  - For patients with a CrCl <15 mL/min, tenofovir alafenamide should be avoided in patients who are **not** on dialysis given the lack of pharmacokinetic data in this population; for such patients, entecavir (with the dose modified for the degree of renal insufficiency) can be used.

- Entecavir, tenofovir alafenamide, and TDF can all be administered to patients on hemodialysis with appropriate dose adjustments.

Information on the dosing of antiviral agents in patients with reduced kidney function can be found in the table (table 6) and in the drug information topics within UpToDate. More detailed discussions of the renal toxicity associated with tenofovir are presented in separate topic reviews. (See "Tenofovir and adefovir for the treatment of chronic HBV infection", section on 'Renal insufficiency and renal tubular dysfunction' and "Overview of antiretroviral agents used to treat HIV", section on 'Tenofovir'.)

- **Other considerations** – Treatment considerations for patients with breakthrough infection and those who require preemptive antiviral therapy to prevent HBV reactivation are discussed in detail elsewhere. (See 'Persistent viremia/breakthrough infection' below and "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Monitoring on therapy — To monitor the response to nucleos(t)ide therapy we measure:

- HBV DNA every three months until undetectable for at least two consecutive visits. We then decrease the frequency to every six months.
- Aminotransferases every three months. The frequency can be decreased to every six months in patients with an undetectable HBV DNA or normalized ALT.
- HBeAg and anti-HBe every 12 months in patients who are HBeAg positive to determine if seroconversion has occurred. If HBeAg seroconversion has occurred, we repeat the HBeAg and anti-HBe to confirm the result.
- HBsAg should be tested yearly in patients with undetectable HBV DNA.

In addition, we monitor for adverse reactions to the antiviral medications. If TDF or adefovir are used, creatinine and phosphate should be monitored every three to six months. For those with decompensated cirrhosis, the creatinine should be monitored more frequently (eg, every one to three months). The frequency of monitoring can be reduced (but not eliminated) if tenofovir alafenamide is used, although there are no clear guidelines. Monitoring creatinine every 12 months is reasonable for patients at low risk of renal impairment.

For patients who receive interferon, monitoring the response to therapy and adverse events is discussed elsewhere and is summarized in the table (table 7). (See "Pegylated interferon for treatment of chronic hepatitis B virus infection", section on 'Monitoring'.)

Duration and treatment endpoints — Patients receiving interferon therapy receive a finite duration of therapy of 48 weeks. (See 'Interferon' above and "Pegylated interferon for treatment of chronic hepatitis B virus infection".)

The optimal duration of therapy for the oral drugs is not well established. Most patients receiving nucleos(t)ide analog therapy will require at least four to five years of treatment, and some may require indefinite treatment (table 5). In a systematic review that included 1716 patients with chronic HBV who discontinued oral therapy (of whom 18 percent had cirrhosis), virologic remission, defined as HBV DNA <20,000 international units/mL, was maintained in 50 percent of patients after 12 months, 39 percent after 24 months, and 38 percent after 36 months [36]. Remission rates were lower using more stringent definitions, but were higher in HBeAg-positive patients who discontinued treatment after HBeAg seroconversion and additional consolidation therapy. The presence of HBV RNA in serum at the end of treatment may be a predictor of viral rebound when treatment is discontinued [37]; however, this test is not yet clinically available, and this finding needs to be validated.

Long-term treatment is particularly important for patients with cirrhosis. This was illustrated in a retrospective cohort study of 263 patients with chronic HBV (94 with cirrhosis) who discontinued lamivudine after being treated for a hepatitis flare [38]. Patients were treated for a median duration of 12 months, and over half required retreatment after lamivudine was discontinued. When compared with those without cirrhosis, patients with cirrhosis were significantly more likely to require retreatment (64 versus 47 percent) and/or experience a clinical relapse (76 versus 60 percent).

Patients without cirrhosis

- **HBeAg-positive chronic hepatitis** – The endpoint of treatment for HBeAg-positive patients is HBeAg seroconversion (ie, HBeAg undetectable and the development of hepatitis B e antibodies confirmed by testing on two occasions at least two months apart). For patients being treated with nucleos(t)ide analogs, a prolonged duration of therapy is often required since HBeAg seroconversion only occurs in about 40 percent of patients after five years of treatment (table 5) [39-41].

  Treatment should be continued for at least 12 more months to reduce the rate of relapse after HBeAg seroconversion has been confirmed [3]. Patients who discontinue treatment should be closely monitored as viral relapse may lead to hepatitis flares and hepatic decompensation. For patients without cirrhosis, the ALT, HBV DNA, and HBeAg should be monitored every one to three months for at least one year.

Because relapse can occur even after completion of 12 months consolidation treatment following HBeAg seroconversion, an alternative is to continue treatment until HBsAg loss, but this would mean most patients will have to be on lifelong treatment.

- **HBeAg-negative chronic hepatitis** – We discontinue treatment in patients with HBeAg-negative hepatitis without cirrhosis if they have confirmed loss of HBsAg on two occasions at least six months apart (table 5). The APASL guidelines suggest 12 months of consolidation therapy after HBsAg loss unless anti-HBs seroconversion has occurred [1]. However, only a small minority of patients (approximately 5 percent) lose HBsAg after five years of continued therapy.

  Our approach for those who remain HBsAg positive is as follows:

  - **Preferred approach** – For most patients who remain HBsAg positive, we continue treatment indefinitely, since almost all patients will experience a virologic relapse after therapy is stopped. In a systematic review that evaluated the duration of HBV DNA suppression after treatment discontinuation in 17 studies of HBeAg-negative patients who achieved virologic remission while on therapy, the probability of having virologic remission 12 months after discontinuing treatment was 51 percent when remission was defined as HBV DNA <20,000 international units/mL [36]. When more stringent criteria were used (eg, HBV DNA <200 international units/mL), the probability of being in remission 12 months after stopping treatment was only 29 percent. In one study, virologic relapse rates (HBV DNA >200 international units/mL) were reported to be as high as 90 percent 24 months after therapy was discontinued [42]. Although those receiving tenofovir appear to have virologic relapse sooner than those receiving entecavir, the risk of relapse is the same at 12 months [43]. (See "Entecavir in the treatment of chronic hepatitis B virus infection", section on 'Risk of relapse after discontinuing entecavir'.)

  - **Patients who are unable/do not want to continue life-long therapy** – For patients without cirrhosis or advanced fibrosis who are unable to or do not want to continue life-long therapy because of its associated risk of adverse events or cost, a trial of treatment discontinuation may be reasonable for those who:

    - Have had HBV DNA suppression to undetectable levels by PCR assays for >3 years;

      and

    - Agree to close monitoring for at least one year (a monthly liver panel and testing for HBV DNA every three months for the first six months; a liver panel and HBV

DNA testing every three months for the next six months). Monitoring can be decreased to every 6 to 12 months thereafter for patients who remain in an inactive carrier state. This approach is consistent with guideline recommendations from the EASL [2] and the APASL [1].

For such patients, we review the risks and benefits of stopping treatment. We explain that several studies have evaluated the risk of virologic and clinical relapse in HBeAg-negative patients who have achieved virologic suppression for several years but continue to have detectable HBsAg [42-47]. While studies indicate that viral relapse (detection of HBV DNA by PCR assay) is nearly universal when the nucleos(t)ide analog is stopped prior to HBsAg clearance, regardless of specific patient characteristics [42], not all patients will experience clinical relapse (HBV DNA >2000 international units/mL and ALT >2 x ULN). In one study that evaluated 21 patients who stopped nucleos(t)ide analog therapy, 63 percent did not reinitiate therapy after almost three years of follow-up because they had an HBV DNA <2000 international units/mL or HBsAg loss [44]. Patients who have received a longer duration of therapy (eg, >24 versus <24 months) are less likely to develop a flare [13,36].

Withdrawal of therapy may even result in higher rates of HBsAg clearance than continuation of treatment, although some patients may experience a flare of their HBV [44,45,48]. In a randomized trial in Europe that included 178 HBeAg-negative patients without cirrhosis who had HBV DNA suppression for ≥4 years on nucleos(t)ide analog therapy, HBsAg loss was observed at 96 weeks after randomization in 8 of the 79 patients (10 percent) who discontinued treatment and 0 of 79 who continued treatment; however, 35 percent of those who discontinued therapy experienced ALT flares, and 14 percent resumed treatment [49]. Similarly, in a retrospective study of 1541 HBeAg-negative patients from North America, Europe, and Asia who discontinued nucleos(t)ide analog therapy (23 percent of whom were HBeAg positive at the start of treatment), the cumulative HBsAg loss was 14 percent after four years, with 50 percent having resumed treatment by year 4 [48]. White individuals were six times more likely to lose HBsAg, while patients ≥50 years of age were more likely to resume treatment. In this study, 15 (1 percent) of patients experienced hepatic decompensation and 12 died; of these 12, 9 were liver related. These data indicate that, in select patients (HBeAg-negative and no cirrhosis), discontinuation of nucleos(t)ide analog therapy after ≥4 years of therapy may be associated with a higher rate of HBsAg loss, more so in White than in Asian patients, but over time, many will develop clinical relapse necessitating resumption of treatment.

Several new HBV markers including quantitative HBsAg level, HBV RNA level, and hepatitis B core related antigen (HBcrAg) level have been shown to be predictive of sustained clinical remission or HBsAg clearance after withdrawal of nucleos(t)ide analogs [37,45,50]. If a quantitative HBsAg level is obtained, a low level (<100 international units/mL) at the time of treatment withdrawal is the best marker of HBsAg clearance. Assays for HBV RNA and HBcrAg are not standardized and are not available clinically.

Patients with cirrhosis — For patients with cirrhosis, lifelong therapy with oral agents is typically administered to reduce the risk of clinical decompensation if a relapse occurs. Therapy should be continued even with those who are HBeAg-positive and have seroconverted to anti-HBe on nucleos(t)ide therapy, as well as those with decompensated cirrhosis who have resolution of cirrhosis complications on treatment.

Although it is possible that treatment may be discontinued in those with compensated cirrhosis who have lost HBsAg, or those who have documentation of cirrhosis regression by histology or noninvasive assessment of liver fibrosis, there is insufficient evidence to guide treatment decisions for this group of patients.

Persistent viremia/breakthrough infection — The management of patients with persistent viremia depends upon the viral load and the initial antiviral agent that was used. As examples:

After interferon therapy — Patients who failed to respond to interferon therapy (ie, failure to achieve HBeAg seroconversion six months posttreatment for HBeAg-positive patients or failure to achieve HBV DNA <2000 international units/mL six months posttreatment for HBeAg-negative patients) can be treated with any of the nucleos(t)ide analogs with the expectation of a similar response as treatment-naïve patients. Because most patients require a long duration of treatment, entecavir or tenofovir is preferred. (See 'Nucleos(t)ide analogs' above.)

While receiving tenofovir or entecavir — For patients receiving tenofovir or entecavir, the AASLD considers an initial virologic response as an undetectable HBV DNA after 96 weeks of treatment. Although most HBeAg-negative patients have undetectable HBV DNA after 48 weeks of treatment, some HBeAg-positive patients with high baseline HBV DNA may remain viremic at week 96.

For patients who remain viremic after 96 weeks, or have breakthrough infection (an increase in serum HBV DNA by >1 $\log_{10}$ [10-fold] from nadir or after HBV has been undetectable), we verify medication adherence since tenofovir- or entecavir-resistant virus rarely occurs in treatment-naïve patients. This is in contrast to patients receiving therapy with nucleos(t)ide analogs with a

low barrier to resistance, such as lamivudine, adefovir, and telbivudine. (See 'While receiving other nucleos(t)ide analogs' below.)

In patients who are adherent, we do not modify our therapy if there is persistent viremia as long as the HBV DNA levels are low (ie, <200 international units/mL) and continue to decrease [13]. However, we obtain resistance testing if the HBV DNA has plateaued after 96 weeks of treatment or if there is virologic breakthrough.

For those failing entecavir, we add tenofovir until the HBV DNA becomes undetectable; at that point, we discontinue entecavir and treat with tenofovir alone. Some providers increase the dose of entecavir from 0.5 to 1.0 mg daily, but there are very little data to support whether this accelerates HBV DNA suppression. Other providers switch to tenofovir without an overlap period since data suggest that monotherapy with TDF has similar efficacy compared with combination therapy (ie, TDF plus entecavir) [51]. For those failing tenofovir, we add entecavir until the HBV DNA becomes undetectable; at that point, we discontinue tenofovir. Information on the individual agents is found above. (See 'Nucleos(t)ide analogs' above.)

While receiving other nucleos(t)ide analogs — Although nucleos(t)ide analogs with a low barrier to resistance (eg, lamivudine, adefovir, or telbivudine) are not generally recommended for initial therapy, these agents are sometimes used in settings where cost is a consideration. Patients receiving these agents should be switched to tenofovir if possible, particularly if the HBV DNA remains >4 $\log_{10}$ international units/mL after 12 months or the patients develop confirmed breakthrough infection (an increase in serum HBV DNA by >1 $\log_{10}$ [10-fold] from nadir or >2 $\log_{10}$ international units/mL after HBV had been undetectable). Tenofovir monotherapy is effective in suppressing HBV replication in patients who have lamivudine-, telbivudine-, or adefovir-resistant virus. By contrast, there is a high risk of entecavir resistance developing in patients with pre-existing drug-resistant virus after lamivudine or telbivudine treatment. An overview of the different nucleos(t)ide agents is found above. (See 'Nucleos(t)ide analogs' above.)

Therapy should be changed promptly once virologic breakthrough is confirmed to prevent a biochemical breakthrough. This is particularly important in those with worsening liver disease, decompensated cirrhosis, recurrent HBV after transplantation, or immunosuppression.

Testing for antiviral drug-resistant variants is desirable but not essential for most patients. However, resistance mutation testing should be obtained to guide selection of salvage therapy if the patient received sequential nucleos(t)ide analog therapy. As an example, for patients with adefovir-resistant virus, we add entecavir to tenofovir if viral suppression is slow (eg, HBV DNA

>10,000 international units/mL after three months). Although TDF has been found to be effective in suppressing adefovir-resistant HBV, the efficacy is lower in patients with double mutations (A181T/V and N236T). (See "Tenofovir and adefovir for the treatment of chronic HBV infection", section on 'Adefovir resistance'.)

Counseling and prevention

- Alcohol use – Heavy use of alcohol (>40 g/day for men and >20 g/day for women) has been associated with worsening liver disease and an increased risk of hepatocellular carcinoma. Although the exact amount of alcohol that can be safely consumed is unclear, advising patients to be completely abstinent is reasonable in those who have cirrhosis. (See "Hepatitis B virus: Clinical manifestations and natural history".)

- Immunizations – Patients with chronic HBV should receive appropriate immunizations, particularly hepatitis A vaccination. (See "Immunizations for adults with chronic liver disease".)

- Preventing transmission to others – Carriers of HBV should be counseled regarding the risk of transmission to others (table 8A-B). Patients should be advised regarding prevention of sexual transmission (ie, vaccination of spouses and steady sex partners in individuals with monogamous partners, and safe sex practice including use of condoms in subjects with multiple partners), perinatal transmission, and risk of environmental exposure from blood. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

Screening for hepatocellular carcinoma — Periodic screening for hepatocellular carcinoma (HCC) should be performed in select patients with chronic HBV. Screening should be performed regardless of antiviral therapy.

Several different guidelines provide recommendations for HCC screening [1-3,52]. We perform ultrasound screening (with or without screening for alpha-fetoprotein) every six months for:

- All HBsAg-positive patients with cirrhosis

- HBsAg-positive adults at high risk for HCC

  - Asian men over 40 years of age
  - Asian women over 50 years of age
  - Persons with a first-degree family member with a history of HCC
  - Persons with HDV
  - African Americans

A more detailed discussion of screening for HCC is presented in a separate topic review. (See "Surveillance for hepatocellular carcinoma in adults".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Management of hepatitis B" and "Society guideline links: Diagnosis of hepatitis B".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hepatitis B (The Basics)")
- Beyond the Basics topic (see "Patient education: Hepatitis B (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the family of hepadnaviruses. It is estimated that there are more than 250 million HBV carriers in the world, of whom approximately 600,000 die annually from HBV-related liver disease. (See 'Introduction' above.)
- **Acute HBV infection** – The diagnosis of acute HBV infection is based upon the detection of hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core antigen (anti-HBc). For most patients, treatment is mainly supportive. The likelihood of liver failure from

acute HBV is less than 1 percent, and in immunocompetent adults, the likelihood of progression to chronic HBV infection is less than 5 percent. However, preventive measures (eg, hepatitis B immune globulin and hepatitis B vaccine) should be administered to all household and sexual contacts who are not known to be immune. (See 'Acute infection' above.)

- **Chronic HBV infection** – The diagnosis of chronic HBV infection is based upon the persistence of HBsAg for more than six months. The management of chronic HBV infection is complex and depends upon multiple factors including clinical variables (eg, the presence or absence of liver inflammation and/or cirrhosis), the patient's immunologic response to infection (eg, hepatitis B e antigen [HBeAg]), virologic factors (eg, HBV viral load and genotype), and risk factors for disease progression (eg, age >40, family history of hepatocellular carcinoma) (table 4). (See 'Initial evaluation' above.)

- **Antiviral therapy for chronic HBV** – Antiviral agents for chronic HBV include pegylated interferon (PegIFN) or nucleos(t)ide analogs (eg, entecavir and tenofovir). The goals of antiviral therapy are suppression of HBV DNA, loss of HBeAg (in patients who were initially HBeAg-positive), and loss of HBsAg. (See 'Overview of antiviral agents' above.)

  - **When to initiate treatment** – The decision to initiate treatment is primarily based upon the presence or absence of cirrhosis, the alanine aminotransferase (ALT) level, and the HBV DNA level (table 5). There are additional indications for patients with certain concurrent conditions, such as malignancy and pregnancy. Patients who are not deemed to be treatment candidates at presentation, and those who decide to defer treatment, should undergo monitoring of liver biochemical tests, HBV DNA, and HBeAg status since liver disease and/or HBV replication may become active later (table 4). (See 'Indications for antiviral therapy' above.)

  - **Choice of agent** – For treatment-naïve patients who initiate therapy, we generally administer a nucleos(t)ide analog. We recommend tenofovir or entecavir rather than other nucleos(t)ide analogs (**Grade 1B**). Tenofovir and entecavir have potent antiviral activity and are at low risk of selecting for drug-resistant virus. PegIFN may also be reasonable as an initial agent for certain treatment-naïve patients without cirrhosis, particularly if they have genotype A infection and/or they do not wish to be on long-term treatment. However, PegIFN is typically associated with more side effects compared with nucleos(t)ide analogs. (See 'Choice of initial agent' above.)

    For most patients who are initiating therapy with tenofovir, we recommend tenofovir alafenamide (25 mg daily), if available, rather than tenofovir disoproxil fumarate (TDF)

(300 mg daily) (**Grade 1B**). Although there is more experience with TDF, tenofovir alafenamide appears to be equally effective and is associated with less renal and bone toxicity. In addition, for most patients who were originally started on TDF, we suggest switching to tenofovir alafenamide (**Grade 2B**). (See 'Nucleos(t)ide analogs' above and 'Choice of initial agent' above.)

There are special treatment considerations when choosing an antiviral agent for patients with decompensated cirrhosis or reduced kidney function and for women who are pregnant. (See 'Choice of initial agent' above and "Hepatitis B and pregnancy".)

- **Patient monitoring** – Patients should be monitored while on therapy to assess for virologic response and medication toxicity. Most patients receiving nucleos(t)ide analog therapy will require at least four to five years of treatment, and some may require indefinite treatment (table 5). (See 'Monitoring on therapy' above and 'Duration and treatment endpoints' above.)

- **Patients with persistent viremia** – The management of patients with persistent viremia or breakthrough infection on therapy depends upon the viral load and the antiviral agent that was used.

  - Tenofovir- or entecavir-resistant virus is unlikely to emerge in treatment-naïve patients, and most cases of treatment failure are due to poor adherence. However, on rare occasion, a patient may need to be transitioned to an alternative agent. (See 'While receiving tenofovir or entecavir' above.)

  - By contrast, drug-resistant virus is likely to develop in patients failing therapy with nucleos(t)ide analogs, such as lamivudine, adefovir, or telbivudine. For patients with persistent viremia or breakthrough infection on one of these agents, we recommend tenofovir rather than entecavir (**Grade 1B**). Tenofovir is effective in suppressing HBV replication in this setting, whereas entecavir should generally be avoided since there is a high risk of entecavir resistance developing in patients with pre-existing drug-resistant virus after lamivudine or telbivudine treatment. (See 'While receiving other nucleos(t)ide analogs' above.)

- **Patient counseling** – Patients with chronic HBV should receive counseling on ways to prevent worsening liver disease (eg, avoid alcohol use, hepatitis A vaccination) and to reduce transmission to others. In addition, screening for hepatocellular carcinoma is indicated for certain high-risk patients. (See 'Counseling and prevention' above and 'Screening for hepatocellular carcinoma' above.)

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GRAPHICS

Diagnostic tests to determine phase of acute or chronic hepatitis B virus infection[1]

HBsAg	HBeAg	IgM anti-HBc	Total anti-HBc*	Anti-HBs	Anti-HBe	HBV DNA	ALT¶	Interpretati
Acute HBV infection								
+	+	+	±			+++	Elevated	Early phase
		+	±			+	Elevated	Window phase
			+	+	+	±	Normal	Recovery phas
Chronic HBV infection (HBsAg-positive for >6 months)								
+	+		+	-	-	+++ (Serum HBV typically >1 million international units/mL)	Normal or mildly elevated	Immune-tolera phase[Δ]
+	+		+	-	-	+++ (Serum HBV >20,000 international units/mL)	Persistently elevated	Immune-active HBeAg-positive
+	-		+	-	+	++ (Serum HBV >2000 international units/mL)	Elevated	Immune-active HBeAg-negativ
+	-		+		+	- to ++ (Serum HBV ≤2000 international units/mL)	Normal or mildly elevated	Inactive chroni HBV[§]
-	-		± (generally	±	±	+ in liver; - to + in serum	Normal	Occult HBV

			+)					

ALT: alanine aminotransferase; anti-HBc: antibody to hepatitis B core antigen; anti-HBe: antibody to hepatitis B e antigen; anti-HBs: antibody to hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

* This test is typically ordered as total anti-HBc, which includes IgM and IgG.

¶ The upper limits of normal for ALT in healthy adults are reported to be 29 to 33 units/L for males and 19 to 25 units/L for females. For healthy children after infancy, the upper limits of normal are 25 to 38 units/L and 22 to 31 units/L for boys and girls, respectively.

Δ For patients with immune-tolerant chronic hepatitis B, liver biopsy or noninvasive tests show no fibrosis and minimal inflammation. This is the initial phase seen in patients with perinatally acquired HBV infection.

◇ For patients with immune active chronic hepatitis B, liver biopsy or noninvasive tests show chronic hepatitis with moderate or severe necroinflammation with or without fibrosis. For patients who are HBeAg positive, immune-active chronic hepatitis B (also known as the clearance phase) can last for 10 to 20 years, and may be associated with the loss of HBeAg. For patients who are HBeAg negative, immune-active chronic hepatitis B is associated with immune reactivation and is also referred to as HBeAg-negative chronic hepatitis B or HBeAg-negative replicative phase.

§ Patients with inactive chronic hepatitis B are HBeAg negative. In such patients, liver biopsy confirms the absence of significant necroinflammation, but biopsy or noninvasive testing show variable levels of fibrosis. This stage has also been referred to as the nonreplicative or carrier phase.

References:

1. *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.*

Graphic 60627 Version 8.0

Interpretation of the hepatitis B serologic panel

Tests	Results	Interpretation
HBsAg	Negative	Susceptible
anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Prior infection (inactive)
anti-HBc	Positive	
anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination*
anti-HBc	Negative	
anti-HBs	Positive	
HBsAg	Positive	Acutely infected
anti-HBc	Positive	
IgM anti-HBc	Positive	
anti-HBs	Negative	
HBsAg	Positive	Chronically infected
anti-HBc	Positive	
IgM anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Four interpretations possible¶
anti-HBc	Positive	
anti-HBs	Negative	

HBsAg: hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; anti-HBs: hepatitis B surface antibody; IgM: immunoglobulin M; HBV: hepatitis B virus.

* Antibody response (anti-HBs) can be measured quantitatively or qualitatively. A protective antibody response is reported quantitatively as 10 or more milli-international units (≥10 mIU/mL) or qualitatively as positive. Postvaccination testing should be completed one to two months after the third vaccine dose for results to be meaningful.

¶ Four interpretations:

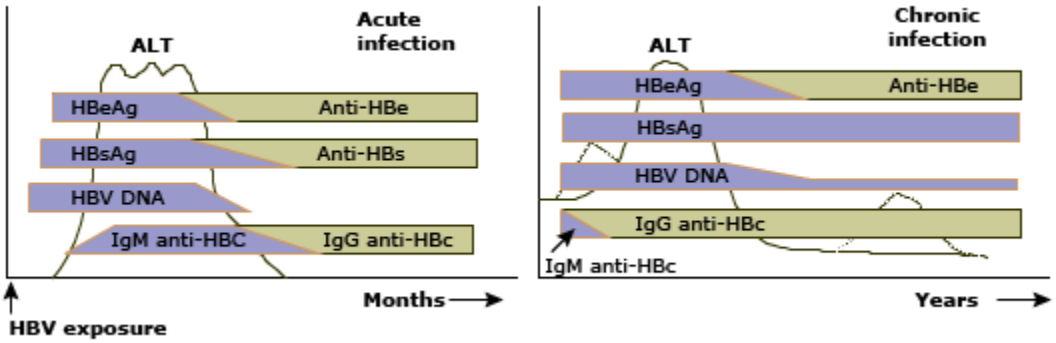
1. Might be recovering from acute HBV infection.
2. Might have had prior infection and test not sensitive enough to detect very low level of anti-HBs in serum.
3. Might be susceptible with a false positive anti-HBc.

4. Might be undetectable level of HBsAg present in the serum, and the person is actually chronically infected.

Centers for Disease Control and Prevention, Hepatitis B information for health professionals: Interpretation of hepatitis B serologic test results. Available from the CDC website.

Graphic 60827 Version 7.0

Serologic responses to hepatitis B virus infection



Schematic representation of the serologic responses to acute and chronic HBV infection in relation to the serum ALT concentration.

(Left panel) Acute infection is characterized initially by the presence of HBeAg, HBsAg, and HBV DNA beginning in the preclinical phase. IgM anti-HBc appears early in the clinical phase; the combination of this antibody and HBsAg makes the diagnosis of acute infection. Recovery is accompanied by normalization of the serum ALT, disappearance of HBV DNA, HBeAg to anti-HBe seroconversion, and subsequently HBsAg to anti-HBs seroconversion and switch from IgM to IgG anti-HBc. Thus, previous HBV infection is characterized by anti-HBs and IgG anti-HBc.

(Right panel) Chronic infection is characterized by persistence of HBeAg (for a variable period), HBsAg, and HBV DNA in the circulation; anti-HBs is not seen (in approximately 20% of patients, a non-neutralizing form of anti-HBs can be detected). Persistence of HBsAg for more than 6 months after acute infection is considered indicative of chronic infection.

HBV: hepatitis B virus; ALT: alanine aminotransferase; HBeAg: hepatitis B e-antigen; anti-HBe: antibody to hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; anti-HBs: antibody to hepatitis B surface antigen; IgM: immunoglobulin M; anti-HBc: antibody to hepatitis B core antigen; IgG: immunoglobulin G.

Graphic 69344 Version 5.0

Groups at increased risk for hepatitis B virus

Individuals at risk for HBV due to vertical transmission (ie, mother to child transmission)
▪ Individuals born in regions with high (≥8%) or intermediate (≥2%) prevalence rates for HBV, including immigrants and adopted children* ▪ Infants born to pregnant persons who are HBsAg-positive¶ ▪ US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥8%)*
Individuals at risk due to horizontal transmission (ie, percutaneous or mucosal exposure to blood or body fluids contaminated with blood)Δ
▪ Household contacts of HBsAg-positive persons ▪ Needle sharing or sexual contacts of HBsAg-positive persons ▪ Individuals who have ever injected drugs ▪ Individuals with multiple sexual partners and/or history of sexually transmitted infections ▪ Men who have sex with men ▪ Inmates of correctional facilities or other detention settings ▪ Individuals with HIV infection◇ ▪ Individuals with current or past HCV infection§ ▪ Individuals with end-stage kidney disease on maintenance renal dialysis
Other individuals
▪ Individuals with elevated alanine aminotransferase or aspartate aminotransferase levels of unknown origin ▪ Individuals who request HBV testing

In the United States, screening for HBV includes[4]:

- **Risk-based screening** – For all individuals (including children and adolescents), screen those who have any of the risk factors listed in the table if they might have been susceptible during the period of increased risk¥. For those with ongoing risk factors (ie, for horizontal transmission) who remain susceptible, continue to test periodically.Δ
- **Universal screening** – For individuals ≥18 years of age, screen at least once in a lifetime. However, for those without risk factors for HBV, screening is generally not needed if there is documentation of completing a hepatitis B vaccine series and evidence of immunity (anti-HBs ≥10 milli-international units/mL) after vaccination.‡
- **Pregnancy screening** – Screen all pregnant people during each pregnancy, regardless of vaccination status of history of prior testing.

Refer to UpToDate content on screening and diagnosis of HBV, HBV immunization, and HBV and pregnancy for more detailed information on screening and vaccination.

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; US: United States; HIV: human immunodeficiency virus; HCV: hepatitis C virus; anti-HBs: hepatitis B surface antibody; anti-HBc: hepatitis B core antibodies; HBIG: hepatitis B immune globulin.

* If HBsAg-positive persons are found in first-generation immigrants of a family, subsequent generations should be tested.

¶ To reduce the risk of perinatal transmission, infants born to HBsAg-positive mothers should receive HBIG and hepatitis B vaccine as soon as possible and within 12 hours of birth and then complete the hepatitis B series. Post-vaccination serology should be obtained at 9 to 12 months. Refer to the UpToDate topic that discusses HBV immunization in infants.

Δ In unvaccinated individuals with ongoing HBV risk through percutaneous or mucosal exposure, hepatitis B vaccine should be initiated at the time of screening; the need for subsequent doses will depend upon the results. Post-vaccination serology should be performed to ensure immunity. For at-risk persons who do not complete the vaccine series, repeat testing should be performed periodically (eg, every 1 to 2 years).

◇ The presence of HBV coinfection informs the choice of antiretroviral regimen. In addition, patients with HIV who are not immune should be vaccinated regardless of age or risk factors, since HBV infection has an accelerated course in coinfected patients.

§ Patients with chronic HBV are at risk for HBV reactivation with direct-acting antiviral therapy for hepatitis C. Refer to the UpToDate topic that provides an overview of the management of hepatitis C infection.

¥ Susceptible persons include those who have never been infected with HBV (ie, HBsAg-negative, total anti-HBc-negative, and anti-HBs-negative) and either did not complete a HepB vaccine series per the Advisory Committee on Immunization Practices recommendations or who are known to be vaccine nonresponders.

‡ For most patients who remain without risk factors for acquiring HBV, repeat screening is not warranted. However, screening prior to blood, plasma, organ, tissue, or semen donation is routinely performed, regardless of the person's prior history. In addition, screening is warranted prior to initiating immunosuppressive therapy (eg, corticosteroids, biologics, cancer chemotherapy, anti-rejection therapies) since persons with HBV are at risk for HBV reactivation. Refer to the UpToDate topic on HBV reactivation.

References:

1. *Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008; 57:1.*
2. *Abara WE, Qaseem A, Schillie S, et al. Hepatitis B vaccination, screening, and linkage to care: Best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017; 167:794.*
3. *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.*
4. *Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations – United States, 2023. MMWR Recomm Rep 2023; 72:1.*

Graphic 55052 Version 18.0

Epidemiology and modes of transmission of hepatitis B virus infection

	High	Intermediate	Low
Carrier rate	≥8%	2 to 7%	<2%
Geographic distribution	Parts of sub-Saharan Africa (eg, Western Africa, South Sudan)	Mediterranean basin; Eastern Europe; Central Asia; Southeast Asia; China; Japan; parts of Latin and South America (eg, Peru, Colombia); Middle East	United States; Canada; Western Europe; Mexico; Australia; New Zealand
Predominant age at infection	Perinatal and early childhood	Early childhood	Adult
Predominant mode of infection	Mother to child; percutaneous	Percutaneous; sexual	Percutaneous; sexual

For updated information on the prevalence of chronic hepatitis B virus infection, refer to the United States Centers for Disease Control and Prevention and the World Health Organization websites.

References:

1. *Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012; 30:2212.*
2. *Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. Lancet 2015; 386:1546.*
3. *HIV, viral hepatitis and sexually transmissible infections in Australia: Annual Surveillance Report 2013. Sydney: The Kirby Institute, The University of New South Wales; 2013.*
4. *New Zealand Society of Gastroenterology. www.nzsg.org.nz/cms2/research/hepatitis/hepatitis b/ (accessed 12/31/2015).*

Graphic 51820 Version 9.0

Evaluation of patients with chronic HBV infection

Initial evaluation
1. History and physical examination*
2. Family history of HBV infection, liver disease, HCC
3. Laboratory tests to assess liver disease – complete blood counts with platelets, aminotransferase levels, total bilirubin, alkaline phosphatase, albumin, and INR
4. Tests for HBV replication – HBeAg, anti-HBe, HBV DNA
5. Tests to rule out viral coinfections – anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV[¶]
6. Tests to screen for HCC[Δ] – (eg, ultrasound)
7. Tests to screen for fibrosis[◇] – vibration-controlled transient elastography, serum fibrosis panel, or liver biopsy[§]
Suggested follow-up for patients not considered for treatment: HBeAg+, HBV DNA >20,000 international units/mL, and normal ALT without cirrhosis[¥]
ALT every 3 to 6 months and HBeAg every 6 to 12 months.
If ALT levels increase between 1 to 2 × ULN:[‡] ▪ Recheck ALT every 1 to 3 months and HBeAg every 6 months. ▪ Consider liver biopsy or noninvasive assessment of fibrosis if ALT levels remain persistently elevated, age >40 years, and/or family history of HCC. Recommend treatment if biopsy shows moderate/severe inflammation or significant fibrosis (eg, METAVIR score ≥F2).
If ALT increases to >2 × ULN[‡] for 3 to 6 months and HBeAg+, HBV DNA >20,000 international units/mL, recommend treatment.
Screen for HCC in relevant population.[Δ]
Suggested follow-up for patients not considered for treatment: HBeAg-, HBV DNA <2000 international units/mL, and normal ALT without cirrhosis[¥]
ALT and HBV DNA every 3 months for 1 year, if persistently normal, ALT and HBV DNA every 6 to 12 months.[†]
If ALT increases between 1 to 2 × ULN:[‡] ▪ Check serum HBV DNA level and exclude other causes of liver disease. ▪ Monitor ALT and HBV DNA every 3 months. ▪ Consider liver biopsy or noninvasive assessment of fibrosis if ALT remains elevated on serial tests or if HBV DNA persistently ≥2000 international units/mL. Recommend treatment for patients with moderate/severe inflammation or significant fibrosis.

If ALT increases to >2 × ULN, recommend treatment if HBV DNA >2000 international units/mL.
If HBV DNA increases to >2000 international units/mL, recommend treatment if ALT > 2 × ULN. If ALT <2 × ULN, assess liver fibrosis by biopsy or noninvasive tests. Recommend treatment if moderate/severe inflammation or significant fibrosis is present.[§]
Screen for HCC in relevant population.

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; INR: international normalized ratio; HBeAg: hepatitis B e antigen; anti-HBe: antibody to HBeAg; HCV: hepatitis C virus; HDV: hepatitis delta virus; ALT: alanine aminotransferase; ULN: upper limit of normal.

* Patient should be evaluated for signs and symptoms of cirrhosis, risk factors for coinfections, alcohol use, and information on vaccination status.

¶ In patients who have not undergone one-time screening and those with ongoing risk factors for HIV-infection.

Δ Refer to the topic that discusses screening of hepatocellular carcinoma.

◇ Refer to the topics in UpToDate that discuss noninvasive assessment of hepatic fibrosis.

§ Liver biopsy can also assess severity of inflammation and help rule out other causes of liver disease, information that will not be provided by noninvasive assessment of liver fibrosis. Refer to the UpToDate topic on management of hepatitis B virus for additional information on the role of liver biopsy.

¥ Cirrhosis is based upon findings from the initial evaluation. Patients with advanced fibrosis determined by noninvasive methods should be evaluated using a second method, and if results are concordant, consider managing the same way as patients with cirrhosis.

‡ The AASLD recommends using an ALT >35 U/L for men and >25 U/L for women as the upper limit of normal rather than local laboratory values.

† If cost is a concern, ALT alone can be monitored.

References:

1. *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.*

Graphic 62875 Version 13.0

Recommendations for initial treatment of chronic hepatitis B in nonpregnant adults

HBeAg	HBV DNA (PCR)	ALT	Treatment strategy
Patients without cirrhosis*			
+	>20,000 international units/mL	≤2 x ULN[¶]	Treatment is not recommended, because current treatment has low efficacy in inducing HBeAg seroconversion. Treatment may be considered in older patients (>40 years) and in those with family history of HCC.
			Patients should be monitored[Δ] and treatment considered if ALT becomes elevated >2 x ULN, liver biopsy shows moderate/severe inflammation or fibrosis[◇] (eg, METAVIR score ≥F2), and/or noninvasive testing suggests moderate/severe fibrosis.
+	>20,000 international units/mL	>2 x ULN[¶]	Observe for 3 to 6 months if compensated and treat if no spontaneous HBeAg loss.
			Immediate treatment if severe hepatitis flare (eg, icteric or clinical decompensation).
			ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – Seroconversion from HBeAg to anti-HBe.[‡]
			Duration of therapy:
			▪ PegIFN alfa: 48 weeks.
			▪ ETV, TAF, or TDF: Continue for at least 12 months after HBeAg seroconversion.
–	>2000 international units/mL	>2 x ULN[¶] OR 1 to 2 x ULN[¶] if liver biopsy shows moderate/severe necroinflammation or significant fibrosis[◇] (eg, METAVIR score	ETV, TAF, TDF, or PegIFN alfa are preferred for initial therapy.[§ ¥]
			End-point of treatment – HBsAg loss.
			Duration of therapy:
			▪ PegIFN alfa: One year.

		≥F2) or non-invasive testing shows significant fibrosis	
			▪ ETV, TAF, or TDF: Several years or indefinite.†
–	≤2000 international units/mL	≤ULN¶	Monitor and treat if HBV DNA and ALT increase as described above.
Patients with cirrhosis*			
+/–	Detectable	Any ALT	Compensated:
			▪ HBV DNA >2000 international units/mL – Treat with ETV, TAF, or TDF.§¥ Treatment should be continued indefinitely.**
			▪ HBV DNA <2000 international units/mL – Consider treatment particularly if ALT elevated; close monitoring if treatment is not initiated.
			Decompensated:
			▪ Treat immediately, regardless of ALT or HBV DNA levels. ETV preferred.§¥ TDF may be used with close monitoring of renal function. Refer for liver transplant.
+/–	Undetectable	Any ALT	Compensated: Observe, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis if HBV DNA remains undetectable.
			Decompensated: Refer for liver transplant, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis.

ALT: alanine aminotransferase; anti-HBe: antibody to hepatitis B e antigen; ETV: entecavir; HBeAg: Hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; PegIFN alfa: pegylated interferon alfa; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; ULN: upper limit of normal.

* Based upon findings on noninvasive testing or liver biopsy performed during the initial evaluation. Patients with advanced fibrosis determined by noninvasive methods should be evaluated using a second method, and if results are concordant, consider managing the same way as patients with cirrhosis.

¶ The American Association for the Study of Liver Diseases (AASLD) recommends using an ALT >35 U/L for men and >25 U/L for women as the upper limit of normal (ULN) rather than local laboratory values.

Δ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of monitoring.

◇ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of indications for biopsy.

§ Adefovir, lamivudine, and telbivudine are not recommended due to a high rate of resistance after the first year and/or weak antiviral activity.

¥ Refer to UpToDate topic on "Hepatitis B virus: Overview of management" for a discussion of which agent to use.

‡ Up to 50% of patients who achieve HBeAg seroconversion can experience a virologic relapse after discontinuing treatment with oral agents. Thus, some providers prefer to treat until HBsAg-loss.

† For most patients, antiviral therapy should be continued indefinitely. However, treatment discontinuation may be considered in persons without cirrhosis who have demonstrated loss of HBsAg and in selected patients who have had undetectable serum HBV DNA for >3 years and agree to close monitoring after stopping treatment. Persons who stop antiviral therapy should be monitored every month for the first six months. Refer to the UpToDate topic on management of hepatitis B virus infection for a detailed discussion of the risks and benefits of stopping antiviral therapy in this setting.

** This includes HBeAg-positive adults with cirrhosis who seroconvert to anti-HBe on therapy.

References:

1. *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.*

Graphic 58520 Version 22.0

Adjustment of adult dose of nucleos(t)ide analogues for treatment of chronic hepatitis B in accordance with creatinine clearance

Creatinine clearance (mL/min)*	Recommended oral dose
Entecavir[¶] (nucleoside)	
NA treatment naïve	
≥50	0.5 mg daily
30 to 49	0.25 mg daily or 0.5 mg every 48 hours
10 to 29	0.15 mg daily or 0.5 mg every 72 hours
<10 or hemodialysis[Δ] or continuous ambulatory peritoneal dialysis	0.05 mg daily or 0.5 mg every 7 days
Lamivudine refractory/resistant	
≥50	1 mg daily
30 to 49	0.5 mg daily or 1 mg every 48 hours
10 to 29	0.3 mg daily or 1 mg every 72 hours
<10 or hemodialysis[Δ] or continuous ambulatory peritoneal dialysis	0.1 mg daily or 1 mg every 7 days
Tenofovir disoproxil fumarate (TDF, nucleotide)	
≥50	300 mg daily
30 to 49	300 mg every 48 hours
10 to 29	300 mg every 72 to 96 hours
<10 with hemodialysis[Δ]	300 mg once a week or after a total of approximately 12 hours of dialysis
<10 without hemodialysis	Insufficient data; no recommendation[◇]
Continuous ambulatory peritoneal dialysis	Insufficient data; no recommendation[◇]
Tenofovir alafenamide (TAF, nucleotide)	
≥15	25 mg daily
<15 with hemodialysis	25 mg on hemodialysis days; dose after dialysis
<15 without hemodialysis	Insufficient data; no recommendation[◇]
Lamivudine (3TC, nucleoside)	
≥50	100 mg daily
30 to 49	100 mg first dose, then 50 mg daily

15 to 29	100 mg first dose, then 25 mg daily
5 to 14	35 mg first dose, then 15 mg daily
<5 or hemodialysis[Δ] or continuous ambulatory peritoneal dialysis	35 mg first dose, then 10 mg daily
Adefovir dipivoxil (nucleotide)	
≥50	10 mg daily
30 to 49	10 mg every 48 hours
10 to 29	10 mg every 72 hours
<10 (not receiving hemodialysis)	Insufficient data; no recommendation[◇]
Hemodialysis	10 mg every seven days following dialysis
Continuous ambulatory peritoneal dialysis	Insufficient data; no recommendation[◇]
Telbivudine (LdT, nucleoside)[§]	
≥50	600 mg daily
30 to 49	600 hours mg every 48 hours
10 to 29 (not receiving hemodialysis)	600 mg every 72 hours
Hemodialysis	600 mg every 96 hours following dialysis[Δ]
Continuous ambulatory peritoneal dialysis	Insufficient data; no recommendation[◇]

Doses are for patients without HIV coinfection.

NA: nucleoside or nucleotide analogue.

* Can be estimated by using the Cockroft-Gault equation. Separate calculators for creatinine clearance using conventional and SI units are available in UpToDate.

¶ For doses <0.5 mg, entecavir oral solution is recommended.

Δ Administer after intermittent hemodialysis.

◇ Data establishing the safety, efficacy, and optimal dosing in end-stage kidney disease (with or without dialysis) are not available.

§ Discontinued in the United States; may be available in other countries.

Data from:

1. *Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan; 63:261.*
2. *Lexicomp Online. Copyright 1978-2023 Lexicomp, Inc. All Rights Reserved.*

Graphic 71024 Version 28.0

Monitoring of patients receiving interferon therapy for the treatment of HBV

Assessment point	Laboratory tests
Baseline	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ HBeAg and anti-HBe¶ ▪ HBsAg ▪ Quantitative HBsAgΔ ▪ INR ▪ TSH ▪ Creatinine ▪ Triglycerides ▪ Glucose ▪ Pregnancy test◇
Week 4	▪ CBC with differential ▪ Hepatic panel*
Week 12	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ Quantitative HBsAgΔ ▪ TSH ▪ Pregnancy test◇
Week 24	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ HBeAg and anti-HBe¶ ▪ TSH ▪ Pregnancy test◇
Week 48	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ HBeAg and anti-HBe¶ ▪ HBsAg§ ▪ TSH ▪ Pregnancy test◇

Week 12 post-treatment	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ HBeAg and anti-HBe¶ ▪ TSH
Week 24 post-treatment	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ HBeAg and anti-HBe¶ ▪ HBsAg§
Week 36 post-treatment	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ HBeAg and anti-HBe¶ ▪ HBsAg§
Week 48 post-treatment	▪ CBC with differential ▪ Hepatic panel* ▪ HBV DNA ▪ HBeAg and anti-HBe¶ ▪ HBsAg§

ALT: alanine aminotransferase; AST: aspartate aminotransferase; anti-HBe: hepatitis B e antibody; CBC: complete blood count; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; INR: international normalized ratio; TSH: thyroid stimulating hormone.

* Hepatic panel includes: ALT, AST, albumin, bilirubin, and alkaline phosphatase.

¶ Only for patients who are HBeAg-positive at baseline.

Δ If available to assess utility of continued therapy.

◇ Only for women of childbearing age.

§ Only for HBeAg-negative patients if HBV DNA is undetectable and for HBeAg-positive patients who have undergone HBeAg seroconversion.

Adapted from: Konerman MA, Lok AS. Interferon treatment for hepatitis B. Clin Liver Dis 2016 (in press).

Graphic 109129 Version 2.0

Recommendations for infected persons regarding prevention of transmission of HBV to others

Persons who are HBsAg positive should:
Have sexual and household contacts vaccinated
Use barrier protection during sexual intercourse if partner not vaccinated or naturally immune
Not share toothbrushes or razors
Cover open cuts and scratches
Clean blood spills with detergent or bleach
Not donate blood, organs or sperms
Children and adults who are HBsAg positive:
Can participate in all activities including contact sports
Should not be excluded from daycare or school participation and should not be isolated from other children
Can share food, utensils, or kiss others

HBV: hepatitis B virus; HBsAg: hepatitis B virus surface antigen.

Reproduced with permission from: Lok ASF, McMahon BJ. Chronic hepatitis B: Update 2009. Hepatology 2009; 50:661. Available online at http://publish.aasld.org/Pages/Default.aspx. Accessed September 8th 2009. Copyright © 2009 American Association for the Study of Liver Diseases.

Graphic 82151 Version 10.0

Recommendations for counseling and prevention of transmission of hepatitis B from individuals with chronic hepatitis B virus (HBV) infection:

HBsAg-positive persons should be counseled regarding prevention of transmission of HBV
Sexual and household contacts of HBsAg-positive persons who are negative for HBV seromarkers should receive hepatitis B vaccination
Newborns of HBsAg-positive mothers should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series. In addition, antiviral therapy should be offered to mothers with a high HBV DNA level.*
Persons who remain at risk for HBV infection such as infants of HBsAg-positive mothers, healthcare workers, dialysis patients, and sexual partners of HBsAg-positive persons should be tested for response to vaccination
• Postvaccination testing should be performed at 1 to 2 months after the last dose, except for infants born to HBsAg-positive mothers in whom testing should be performed at age 9 to 12 months or 1 to 2 months after the last dose of hepatitis B vaccine if immunization is delayed
• Follow-up testing of vaccine responders is recommended annually for chronic hemodialysis patients
Abstinence or only limited use of alcohol is recommended in HBsAg-positive persons
Persons who are positive only for anti-HBc (HBsAg-negative) and who are from a low endemic area with no risk factors for HBV should be given the full series of hepatitis B vaccine

Anti-HBc: hepatitis B core antibody; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

* Refer to the topic that discusses hepatitis B and pregnancy.

References:

1. *Lok, ASF, McMahon, BJ. Chronic hepatitis B: Update 2009. Hepatology 2009; 50:661. Available online at http://publish.aasld.org/Pages/Default.aspx. Accessed September 8, 2009.*
2. *Schillie S, Murphy TV, Fenlon N, et al. Update: Shortened Interval for Postvaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers. MMWR Morb Mortal Wkly Rep 2015; 64:1118.*
3. *Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan;63(1):261-83.*

Graphic 55845 Version 2.0

Contributor Disclosures

Anna SF Lok, MD Grant/Research/Clinical Trial Support: Target Pharma [NAFL, hepatitis B virus, PBC]. Consultant/Advisory Boards: Arbutus [Hepatitis B virus]; Chroma [Hepatitis B virus]; CLEAR-B [Hepatitis B virus]; GlaxoSmithKline [Hepatitis B virus]; Novo Nordisk [NAFLD]; Target [Hepatitis B virus, PBC, and NAFLD treatment]; Virion [Hepatitis B virus]. All of the relevant financial relationships listed have been mitigated. **Rafael Esteban, MD** Grant/Research/Clinical Trial Support: Gilead [Hepatitis B]. Consultant/Advisory Boards: Abbvie [Hepatitis C]; Gilead [Hepatitis C]. Speaker's Bureau: Gilead [Hepatitis C]. All of the relevant financial relationships listed have been mitigated. **Jennifer Mitty, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

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