Hepatitis B virus: Overview of management

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INTRODUCTION

Hepatitis B virus (HBV) is a double-stranded deoxyribonucleic acid (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 800,000 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), Asian Pacific Association for the Study of the Liver (APASL), American Association for the Study of Liver Diseases (AASLD), and World Health Organization (WHO) [1-4]. Clinical decisions regarding individual patients should be based upon patient-specific clinical information and test results.

Topic reviews that discuss the management of pregnant patients 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 or infected. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection", section on 'Prevention'.)

For most patients, treatment is mainly supportive. The likelihood of acute 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 [5]. There are known subgroups of patients whose prognosis is relatively worse (eg, patients who are immunocompromised, have concomitant infection with hepatitis C virus [HCV] or human immunodeficiency virus [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, such as those who develop a coagulopathy (international normalized ratio [INR] >1.5) or 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 (coagulopathy and encephalopathy) 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 monotherapy is preferred. 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 (see 'Overview of antiviral agents' below). Treatment can be stopped after confirmation that the patient has cleared HBsAg (two consecutive tests four weeks apart).

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. 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 [HCC]).

Initial evaluation

General approach — The initial evaluation of patients with chronic HBV infection should include (table 2):

- 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 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 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 in adults".)

- 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 thus liver stiffness measurements may overestimate liver fibrosis in patients with a high ALT (more than 100 units/L) [6]. (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 histologic findings [7,8]. 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 of these patients had an ALT in the high range of normal and were older than 40 years of age. By contrast, two studies of patients in the immune tolerant phase of chronic HBV infection found that despite high HBV DNA levels, most patients had no or minimal fibrosis [9,10].

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 for HBV is primarily based upon the presence or absence of cirrhosis, the ALT level, and the HBV DNA level, as outlined in the table (table 3) and discussed in detail below. Therapy may also be indicated for those who have certain concurrent conditions (eg, pregnancy, those requiring immunosuppressive therapy) and risk factors for HCC (eg, age >40 or family history of HCC). (See 'Acute liver failure or decompensated cirrhosis' below and 'Compensated cirrhosis' below and 'Selected patients without cirrhosis' 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 [11].

The World Health Organization (WHO) has provided a simplified approach for countries with limited access to HBV DNA assays and tests to assess liver fibrosis [4]. (See 'Considerations in resource-limited settings' below.)

Acute liver failure or decompensated cirrhosis — Patients with life-threatening liver disease secondary to HBV should initiate antiviral therapy as soon as possible. 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) [12]. 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 [13,14]. 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 detectable HBV DNA should be treated with antiviral therapy regardless of the HBeAg status or the serum ALT level (table 3). (See 'Antiviral therapy' below.)

Selected patients without cirrhosis

HBeAg positive (immune active phase) — For hepatitis B e antigen (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 3) [3]. The AASLD recommends ULN should be 35 units/L for males and 25 units/L for females. 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; treatment should be considered if and when the serum ALT becomes higher (table 2). (See 'Monitoring those not on treatment' below.)

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, and patients with extrahepatic manifestations (eg, HBV-related polyarteritis nodosa). Treatment should also be considered for 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 persistently 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) [15-17]. In addition, despite high HBV DNA levels, the risk of HCC during follow-up to 10 years is low [18]. Thus, the benefits of long-term treatment in such patients, most of whom are young Asian patients with perinatally acquired HBV infection, must be balanced against the risks of side effects and costs, particularly since some of these individuals will undergo spontaneous HBeAg seroconversion and remain in remission for many years afterwards. Some studies

have found that the risk of HCC in untreated HBeAg-positive patients in the immune tolerance phase is higher than that in treated HBeAg-positive patients in the immune active phase; however, immune tolerance phase in several of these studies was based on a single timepoint assessment, and many patients met guideline criteria for treatment based on age and should have been treated [19,20].

HBeAg-negative chronic hepatitis — Treatment may be initiated immediately once a diagnosis of hepatitis B e antigen (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 units/L for males and 25 units/L for females, rather than 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 is also 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 patients — For pregnant individuals, the indications for antiviral therapy are generally the same as those for patients who are not pregnant. However, to prevent transmission to their child, pregnant patients 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. 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 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 by 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) [21].

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 [22].

- For HBsAg-positive patients who meet criteria for antiviral treatment of HBV (table 3), 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 discussion of the management of HCV infection is found elsewhere. (See "Overview of the management of chronic hepatitis C virus infection", section on 'Monitoring during antiviral therapy'.)

Considerations in resource-limited settings — The WHO has put forth recommendations for treatment of HBV [4]. These guidelines are primarily intended for countries and settings with no or limited access to HBV DNA assays and tests to assess liver fibrosis. The goal of the WHO recommendations is to increase access to HBV treatment.

Treatment is indicated for either of the following patient groups with chronic HBV,

regardless of HBV DNA or ALT levels:

- Those with evidence of cirrhosis (based on clinical criteria, an APRI score of >1, or transient elastography value of >12.5 kPa).
- Those with significant fibrosis (APRI score of >0.5 or transient elastography value of >7 kPa).

It should be noted that the cutoffs for APRI or transient elastography for cirrhosis or significant fibrosis are lower than those used in most studies.

The WHO also recommends treatment for those without evidence of fibrosis or significant fibrosis with any of the following:

- An HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal.
- The presence of coinfections with HIV, hepatitis D, or hepatitis C or comorbid conditions such as diabetes or metabolic dysfunction–associated steatotic liver disease.
- A family history of liver cancer or cirrhosis.
- Immune suppression (eg, long-term steroid use, solid organ or stem cell transplant) (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)
- Extrahepatic manifestations (eg, glomerulonephritis or vasculitis) (See "Kidney disease associated with hepatitis B virus infection".)

If HBV DNA testing is not available, treatment can be considered for those without cirrhosis or significant fibrosis who have persistently abnormal ALT levels (defined as two ALT values above the upper limit of normal during a 6- to 12-month period). However, the benefit of antiviral therapy is unclear if the increase in ALT is due to a non-viral cause (eg, the patient has metabolic dysfunction-associated steatotic liver disease and the HBV DNA is <2000 copies/mL).

More detailed information about management of patients in resource-limited settings can be found on the WHO website.

Monitoring those not on treatment

What to monitor — 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 2). Selected patients should also undergo HCC surveillance. (See 'Screening for hepatocellular carcinoma' below.)

Serial monitoring is important to identify those who would subsequently benefit from treatment. This includes those with HBeAg-positive chronic hepatitis and those with HBeAg-negative chronic hepatitis. (See 'HBeAg positive (immune active phase)' above and 'HBeAg-negative chronic hepatitis' above.)

Close follow-up also ensures that patients are initiated on treatment if they develop a concurrent condition that warrants treatment (eg, if the patient requires immunosuppressive therapy). (See 'Patients receiving immunosuppressive therapy' above.)

Patients with persistent discordant HBV DNA and ALT levels — Some patients with chronic HBV persist in the indeterminate phase (ie, they do not meet all criteria for treatment based on HBV DNA and ALT levels) (table 3). There are several reasons why this may happen. As an example, some HBeAg-positive patients with low HBV DNA (<5 $\log_{10}$ international units/mL) and elevated ALT levels may be in the process of clearing HBeAg. In HBeAg-negative patients, a persistently low HBV DNA with elevated ALT levels may indicate the presence of other concomitant causes of liver disease (eg, steatotic liver disease or concurrent infection with HCV or HDV). HBeAg-negative patients with high HBV DNA (>2000 international units/mL) but normal ALT levels may have HBeAg-negative chronic hepatitis with fluctuating HBV DNA.

Such patients should be monitored with HBV DNA and ALT levels every three to six months and assessed for liver fibrosis using biopsies or noninvasive tests. Patients who remain in these indeterminate phases after one to two years should be considered for antiviral therapy unless other causes are identified, particularly if they are above the age of 40, have evidence of advanced fibrosis, or have a family history of HCC [23-25].

Several studies have found a high rate of HCC during long-term follow-up of patients in the indeterminate phase [26,27]. Most of these patients were HBeAg negative with high HBV DNA (>2000 international units/mL) and normal ALT levels, or low HBV DNA (≤2000 international units/mL) and elevated ALT levels. In these studies, the frequency of HBV DNA and ALT monitoring in patients was often suboptimal, and transition to active disease may have been missed, contributing to their poor outcomes.

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 HCC) 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 3) [28]. 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 patients 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 lesser extent, genotype B), as well as low HBV DNA and high ALT levels, are predictive of a response to interferon therapy.

The advantages of interferon compared with nucleos(t)ide analogs are its finite duration of treatment, the absence of selection of resistant variants, and a higher rate of HBeAg and HBsAg loss compared with the same duration of nucleos(t)ide analog therapy. On the other hand, the side effects from interferon are troubling for many patients and (less commonly) can be severe. Furthermore, interferon should not be used in pregnant patients 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 [29]. 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 [30,31]. 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, substantial histologic abnormalities (moderate/severe inflammation or bridging fibrosis/cirrhosis), and/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".)

Considerations regarding the use of entecavir in persons with HIV is presented separately. (See "Treatment of chronic hepatitis B in patients with HIV", section on 'Approach to treatment'.)

Entecavir is administered orally. The dose should be adjusted for patients with reduced kidney function (table 4).

- For nucleos(t)ide-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 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) or tenofovir alafenamide (TAF), 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 TAF. For most patients, we recommend TAF (at 25 mg daily) rather than TDF (at 300 mg daily), if available. For those who were originally started on TDF, we generally suggest switching to TAF, particularly in older patients and those with risk factors for renal impairment or osteoporosis. TAF is equally effective and is associated with less renal and bone toxicity. More detailed information on the safety and efficacy of tenofovir is presented in a separate topic review. (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 pregnant patients, patients with reduced kidney function, and patients with decompensated cirrhosis are discussed below. (See 'Choice of initial agent' below.)

- **Lamivudine** – Lamivudine should not be used, given the high rate of drug resistance, unless entecavir or tenofovir are 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 patients infected with HIV 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 4). 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'.)

Cost-effectiveness — The cost-effectiveness of various treatment strategies for chronic HBV is incompletely understood. A cost-effectiveness analysis using data from Hong Kong suggested 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 [32]. However, this study and many other cost-effectiveness analyses were conducted before approval of peginterferon, entecavir, TDF, and TAF, and prior to availability of generic entecavir and TDF.

Choice of initial agent

Approach for most patients — For most treatment-naïve patients, either tenofovir or entecavir is preferred because both are well tolerated, have potent antiviral activity, and have a low risk of selecting for drug-resistant virus [33]. In addition, both agents reduce the risk of HCC. Although some studies have suggested that tenofovir may lead to a greater reduction in HCC than entecavir, many studies are confounded, and this finding, which was first reported in Asia, has not been confirmed in studies in Europe and the United States [34-40]. (See "Tenofovir and adefovir for the treatment of chronic HBV infection" and "Entecavir in the treatment of chronic hepatitis B virus infection".)

In some countries, it may be difficult to access tenofovir monotherapy [4]. In these settings, tenofovir may be more readily available when combined with emtricitabine

or lamivudine (tenofovir disoproxil fumarate-emtricitabine, tenofovir disoproxil fumarate-lamivudine; tenofovir alafenamide-emtricitabine) since these agents are used for treatment of HIV. Although dual therapy is generally not needed for treatment of chronic HBV; there is no harm in using these combination agents when tenofovir monotherapy is not available.

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 persons planning to get pregnant in the future), particularly if they are HBeAg positive, 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 hepatorenal syndrome, and entecavir has not been shown to be nephrotoxic, whereas TDF has been associated with reduced kidney function. TAF is an alternative agent, and available efficacy and safety data in patients with decompensated liver disease suggest comparable efficacy with TDF with less renal and bone adverse effects. Lactic acidosis has been reported in patients with severe liver dysfunction receiving entecavir [41]; 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** [42].

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 patients who require treatment, we prefer TDF, although there is increasing data showing TAF has similar efficacy and safety. Interferon is contraindicated in pregnant patients, and we do not use entecavir given the lack of 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 (CrCl) and if the patient is on dialysis (table 4). As examples:

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

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

  - For patients with a CrCl <15 mL/min, TAF 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, TAF, 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 4) 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 to six months until undetectable and every six months thereafter.
- Aminotransferases every three months until ALT is normal or near normal (<2 x ULN) and then 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 in six months to confirm the result. (See 'Duration and treatment endpoints' below.)

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 TAF 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 summarized in the table (table 5) and discussed elsewhere. (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 3). Long-term treatment is particularly important for patients with cirrhosis. Though cirrhosis has been reported to regress in patients with maintained virus suppression after many

years of nucleos(t)ide analogue therapy [43], these patients are at greater risk of relapse and/or hepatic decompensation after treatment is stopped [44,45].

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 [46]. 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.

Some studies have found higher HBsAg levels at the end of treatment and older age to be predictors of clinical relapse (HBV DNA >2000 IU/mL and ALT >2 x ULN) [47]. The presence of HBV ribonucleic acid (RNA) in serum at the end of treatment may be a predictor of viral rebound when treatment is discontinued [48]. Presence of hepatitis B core-related antigen (HBcrAg) has also been shown in some studies to be predictive of viral rebound [47]. However, tests for HBV RNA and HBcrAg are not yet clinically available, and the clinical utility of these tests need to be validated.

Patients without cirrhosis

- **HBeAg-positive chronic hepatitis** – The endpoint of treatment for HBeAg-positive patients is HBeAg seroconversion (ie, undetectable HBeAg 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 approximately 40 percent of patients after five years of treatment (table 3) [49-51].

  Treatment should be continued for at least 12 more months after HBeAg seroconversion has been confirmed to reduce the rate of relapse [3]. Patients who discontinue treatment should be closely monitored, as viral relapse may lead to hepatitis flares and hepatic decompensation. For patients without cirrhosis, 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 of consolidation treatment following HBeAg seroconversion, an alternative is to continue treatment until HBsAg loss, but this would mean most patients would 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 3). 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 [46]. 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 [52]. Although those receiving tenofovir appear to have virologic relapse sooner than those receiving entecavir, the risk of clinical relapse is the same at 12 months [53]. (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 [52-57]. 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 [52], not all patients will experience clinical relapse (HBV DNA >2000 international units/mL and ALT >2 x ULN).

Some clinical trial data suggest withdrawing therapy may actually result in higher rates of HBsAg clearance than continuing treatment in selected patients, but patients may experience a hepatitis flare [54,55,58,59]. As an example, in a randomized trial that included 166 HBeAg-negative patients without cirrhosis who had HBV DNA suppression for ≥4 years on nucleos(t)ide analog therapy, HBsAg loss was observed in 8 of the 79 patients (10 percent) who discontinued treatment and 0 of 79 who continued treatment 96 weeks after randomization [58]. However, 35 percent of those who discontinued therapy experienced ALT flares, and 14 percent resumed treatment. In addition, this benefit has not been observed in all populations. The two randomized controlled trials that showed a benefit of stopping antiviral therapy in patients without cirrhosis at the start of treatment included mostly White patients who were all HBeAg negative at the time of randomization [54,58]. No difference in HBsAg loss (4 versus 5 percent at 18 months) was seen in a third trial that included predominantly Asian patients, as well as a small percentage of patients who were HBeAg positive at the start of treatment [59]. 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), White individuals were six times more likely to lose HBsAg than Asian patients [60]. The low rate of HBsAg response in Asian patients may be a surrogate for a longer duration of infection or the presence of certain HBV genotypes (B and C versus D). (See "Clinical significance of hepatitis B virus genotypes".)

Although not routinely available, several new HBV markers (eg, quantitative

HBsAg level, HBV RNA level, and hepatitis B core-related antigen level) have been shown to be predictive of sustained clinical remission or HBsAg clearance after withdrawal of nucleos(t)ide analogs [48,55,61]. A low HBsAg level at the time of treatment withdrawal is highly predictive of HBsAg clearance, but a lower level must be achieved for Asian versus White patients (<100 versus <1000 international units/mL) to achieve a >30 percent chance of HBsAg loss. (See 'Monitoring on therapy' above.)

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 in 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 post-treatment for HBeAg-positive patients or failure to achieve HBV DNA <2000 international units/mL six months post-treatment for HBeAg-negative patients) can be treated with entecavir or tenofovir with the expectation of a similar response as treatment-naïve patients. (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 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 [11]. 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 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) [62]. 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) are not 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. 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 preexisting 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 males and >20 g/day for females) has been associated with worsening liver disease and an increased risk of HCC. 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 6A-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 individuals with multiple partners), perinatal transmission, and risk of environmental exposure from blood. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

- **Healthy lifestyle** – Patients should be counseled about the importance of a healthy diet and regular exercise to maintain normal weight and metabolism. With the increasing prevalence of obesity, many patients with chronic HBV infection have concomitant hepatic steatosis, which may accelerate progression to cirrhosis and increase risk of HCC. (See "Clinical features and diagnosis of metabolic dysfunction-associated steatotic liver disease (nonalcoholic fatty liver disease) in adults".)

Screening for hepatocellular carcinoma — Periodic screening for 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 [1-3,63]. 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 males over 40 years of age
  - Asian females over 50 years of age
  - Persons with a first-degree family member with a history of HCC
  - Persons with HDV
  - Persons who are from Africa and likely acquired HBV in Africa

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 800,000 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 or infected. (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), virologic factors (eg, hepatitis B e antigen [HBeAg] status, HBV viral load and genotype), and risk factors for disease progression (eg, age >40, family history of hepatocellular carcinoma [HCC]) (table 2). (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 3). There are additional indications for patients with certain concurrent conditions, such as pregnancy and medical conditions requiring immunosuppressive therapies. 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 2). (See 'Indications for antiviral therapy' above and 'Monitoring those not on treatment' above and 'Patients with persistent discordant HBV DNA and ALT levels' 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 (TAF; 25 mg daily), if available, rather than tenofovir disoproxil fumarate (TDF; 300 mg daily) (**Grade 1B**). Although there is more experience with TDF, TAF is 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 TAF if possible (**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 patients 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 3). (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 occasions, 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 early generations of nucleos(t)ide analogs that had a low barrier to resistance (eg, 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 preexisting 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, hepatitis A vaccination, avoid alcohol use) and to reduce transmission to others. In addition, screening for HCC is indicated for certain high-risk patients. (See 'Counseling and prevention' above and 'Screening for hepatocellular carcinoma' above.)

REFERENCES

1. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016; 10:1.
2. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67:370.
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. World Health Organization. Guidelines for the prevention, diagnosis, care and treat ment for people with chronic hepatitis B infection. Available at: https://www.who.in t/publications/i/item/9789240090903 (Accessed on August 26, 2024).

5. Kumar M, Satapathy S, Monga R, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. Hepatology 2007; 45:97.

6. Wong GL, Wong VW, Choi PC, et al. Evaluation of alanine transaminase and hepatitis B virus DNA to predict liver cirrhosis in hepatitis B e antigen-negative chronic hepatitis B using transient elastography. Am J Gastroenterol 2008; 103:3071.

7. Lai M, Hyatt BJ, Nasser I, et al. The clinical significance of persistently normal ALT in chronic hepatitis B infection. J Hepatol 2007; 47:760.

8. Kumar M, Sarin SK, Hissar S, et al. Virologic and histologic features of chronic hepatitis B virus-infected asymptomatic patients with persistently normal ALT. Gastroenterology 2008; 134:1376.

9. Andreani T, Serfaty L, Mohand D, et al. Chronic hepatitis B virus carriers in the immunotolerant phase of infection: histologic findings and outcome. Clin Gastroenterol Hepatol 2007; 5:636.

10. Hui CK, Leung N, Yuen ST, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. Hepatology 2007; 46:395.

11. Yapali S, Talaat N, Lok AS. Management of hepatitis B: our practice and how it relates to the guidelines. Clin Gastroenterol Hepatol 2014; 12:16.

12. Kwon H, Lok AS. Hepatitis B therapy. Nat Rev Gastroenterol Hepatol 2011; 8:275.

13. Fontana RJ, Hann HW, Perrillo RP, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. Gastroenterology 2002; 123:719.

14. Yao FY, Terrault NA, Freise C, et al. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. Hepatology 2001; 34:411.

15. Chan HL, Chan CK, Hui AJ, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. Gastroenterology 2014; 146:1240.

16. Rosenthal P, Ling SC, Belle SH, et al. Combination of Entecavir/Peginterferon Alfa-2a

in Children With Hepatitis B e Antigen-Positive Immune Tolerant Chronic Hepatitis B Virus Infection. Hepatology 2019; 69:2326.

17. Feld JJ, Terrault NA, Lin HS, et al. Entecavir and Peginterferon Alfa-2a in Adults With Hepatitis B e Antigen-Positive Immune-Tolerant Chronic Hepatitis B Virus Infection. Hepatology 2019; 69:2338.

18. Lee HA, Lee HW, Kim IH, et al. Extremely low risk of hepatocellular carcinoma development in patients with chronic hepatitis B in immune-tolerant phase. Aliment Pharmacol Ther 2020; 52:196.

19. Lee HA, Kim SU, Seo YS, et al. Comparable outcomes between immune-tolerant and active phases in noncirrhotic chronic hepatitis B: a meta-analysis. Hepatol Commun 2023; 7:e0011.

20. Kim GA, Lim YS, Han S, et al. High risk of hepatocellular carcinoma and death in patients with immune-tolerant-phase chronic hepatitis B. Gut 2018; 67:945.

21. Yuan P, Chen P, Qian Y. Evaluation of Antiviral Therapy Performed after Curative Therapy in Patients with HBV-Related Hepatocellular Carcinoma: An Updated Meta-Analysis. Can J Gastroenterol Hepatol 2016; 2016:5234969.

22. FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivati ng in some patients treated with direct-acting antivirals for hepatitis C. http://www.f da.gov/Drugs/DrugSafety/ucm522932.htm (Accessed on November 23, 2016).

23. Practice Guidelines. American Association for the Study of Liver Disease. Available a t: https://www.aasld.org/practice-guidelines (Accessed on August 11, 2023).

24. EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy . European Association for the Study of the Liver. Available at: https://easl.eu/public ation-category/clinical-practice-guidelines/ (Accessed on August 11, 2023).

25. Guidelines. Asian Pacific Association for the Study of the Liver. Available at: http://a pasl.info/subscription-of-journal/guidelines/ (Accessed on August 11, 2023).

26. Huang DQ, Li X, Le MH, et al. Natural History and Hepatocellular Carcinoma Risk in Untreated Chronic Hepatitis B Patients With Indeterminate Phase. Clin Gastroenterol Hepatol 2022; 20:1803.

27. Huang DQ, Tran A, Yeh ML, et al. Antiviral therapy substantially reduces HCC risk in

patients with chronic hepatitis B infection in the indeterminate phase. Hepatology 2023; 78:1558.

28. Lok AS, McMahon BJ, Brown RS Jr, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology 2016; 63:284.

29. Liaw YF, Leung N, Guan R, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. Liver Int 2005; 25:472.

30. Chien RN, Liaw YF, Atkins M. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Asian Hepatitis Lamivudine Trial Group. Hepatology 1999; 30:770.

31. Perrillo RP, Lai CL, Liaw YF, et al. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. Hepatology 2002; 36:186.

32. Lo AO, Wong VW, Wong GL, et al. Cost effectiveness of response-guided therapy with peginterferon in the treatment of chronic hepatitis B. Clin Gastroenterol Hepatol 2015; 13:377.

33. Lumley SF, Delphin M, Mokaya JF, et al. A systematic review and meta-analysis of the risk of hepatitis B virus (HBV) resistance in people treated with entecavir or tenofovir. J Clin Virol 2024; 174:105711.

34. Choi WM, Choi J, Lim YS. Effects of Tenofovir vs Entecavir on Risk of Hepatocellular Carcinoma in Patients With Chronic HBV Infection: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2021; 19:246.

35. Pol S, ANRS/AFEF study group. Similar 5-year HCC occurrence in Tenofovir- and Entecavir-treated HBV chronic infection in the French AFEF/ANRS CO22 Hepather cohort. Aliment Pharmacol Ther 2021; 53:616.

36. Tan DJH, Ng CH, Tay PWL, et al. Risk of Hepatocellular Carcinoma With Tenofovir vs Entecavir Treatment for Chronic Hepatitis B Virus: A Reconstructed Individual Patient Data Meta-analysis. JAMA Netw Open 2022; 5:e2219407.

37. Choi J, Kim HJ, Lee J, et al. Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B: A Korean Nationwide Cohort Study. JAMA Oncol 2019; 5:30.

38. Choi WM, Yip TC, Wong GL, et al. Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- vs. entecavir-based regimens: Individual patient data meta-analysis. J Hepatol 2023; 78:534.

39. Hsu YC, Wong GL, Chen CH, et al. Tenofovir Versus Entecavir for Hepatocellular Carcinoma Prevention in an International Consortium of Chronic Hepatitis B. Am J Gastroenterol 2020; 115:271.

40. Papatheodoridis GV, Dalekos GN, Idilman R, et al. Similar risk of hepatocellular carcinoma during long-term entecavir or tenofovir therapy in Caucasian patients with chronic hepatitis B. J Hepatol 2020; 73:1037.

41. Lampertico P, Chan HL, Janssen HL, et al. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. Aliment Pharmacol Ther 2016; 44:16.

42. Köklü S, Tuna Y, Gülşen MT, et al. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol 2013; 11:88.

43. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013; 381:468.

44. Hirode G, Hansen BE, Chen CH, et al. Incidence of Hepatic Decompensation After Nucleos(t)ide Analog Withdrawal: Results From a Large, International, Multiethnic Cohort of Patients With Chronic Hepatitis B (RETRACT-B Study). Am J Gastroenterol 2023; 118:1601.

45. Chang ML, Jeng WJ, Liaw YF. Clinical events after cessation of lamivudine therapy in patients recovered from hepatitis B flare with hepatic decompensation. Clin Gastroenterol Hepatol 2015; 13:979.

46. Papatheodoridis G, Vlachogiannakos I, Cholongitas E, et al. Discontinuation of oral antivirals in chronic hepatitis B: A systematic review. Hepatology 2016; 63:1481.

47. Brakenhoff SM, de Knegt RJ, van Campenhout MJH, et al. End-of-treatment HBsAg, HBcrAg and HBV RNA predict the risk of off-treatment ALT flares in chronic hepatitis B patients. J Microbiol Immunol Infect 2023; 56:31.

48. Wang J, Shen T, Huang X, et al. Serum hepatitis B virus RNA is encapsidated

pregenome RNA that may be associated with persistence of viral infection and rebound. J Hepatol 2016; 65:700.

49. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. Hepatology 2009; 49:1503.

50. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006; 354:1001.

51. Ahn J, Lee HM, Lim JK, et al. Entecavir safety and effectiveness in a national cohort of treatment-naïve chronic hepatitis B patients in the US - the ENUMERATE study. Aliment Pharmacol Ther 2016; 43:134.

52. Papatheodoridis GV, Manolakopoulos S, Su TH, et al. Significance of definitions of relapse after discontinuation of oral antivirals in HBeAg-negative chronic hepatitis B. Hepatology 2018; 68:415.

53. Su TH, Yang HC, Tseng TC, et al. Distinct Relapse Rates and Risk Predictors After Discontinuing Tenofovir and Entecavir Therapy. J Infect Dis 2018; 217:1193.

54. Berg T, Simon KG, Mauss S, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients - FINITE study. J Hepatol 2017; 67:918.

55. Jeng WJ, Chen YC, Chien RN, et al. Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen-negative chronic hepatitis B. Hepatology 2018; 68:425.

56. Seto WK, Hui AJ, Wong VW, et al. Treatment cessation of entecavir in Asian patients with hepatitis B e antigen negative chronic hepatitis B: a multicentre prospective study. Gut 2015; 64:667.

57. Jeng WJ, Sheen IS, Chen YC, et al. Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. Hepatology 2013; 58:1888.

58. van Bömmel F, Stein K, Heyne R, et al. A multicenter randomized-controlled trial of nucleos(t)ide analogue cessation in HBeAg-negative chronic hepatitis B. J Hepatol 2023; 78:926.

59. Liem KS, Fung S, Wong DK, et al. Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study). Gut 2019; 68:2206.

60. Oral Abstracts. Hepatology 2020; 72 Suppl 1:1.

61. Wang CC, Tseng KC, Hsieh TY, et al. Assessing the Durability of Entecavir-Treated Hepatitis B Using Quantitative HBsAg. Am J Gastroenterol 2016; 111:1286.

62. Lim YS, Byun KS, Yoo BC, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in patients with entecavir-resistant chronic hepatitis B with multiple drug failure: results of a randomised trial. Gut 2016; 65:852.

63. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68:723.

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