JAMA | Review

Chronic Hepatitis B Infection
A Review

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IMPORTANCE More than 240 million individuals worldwide are infected with chronic hepatitis B virus (HBV). Among individuals with chronic HBV infection who are untreated, 15% to 40% progress to cirrhosis, which may lead to liver failure and liver cancer.

OBSERVATIONS Pegylated interferon and nucleos(t)ide analogues (lamivudine, adefovir, entecavir, tenofovir disoproxil, and tenofovir alafenamide) suppress HBV DNA replication and improve liver inflammation and fibrosis. Long-term viral suppression is associated with regression of liver fibrosis and reduced risk of hepatocellular carcinoma in cohort studies. The cure (defined as hepatitis B surface antigen loss with undetectable HBV DNA) rates after treatment remain low (3%-7% with pegylated interferon and 1%-12% with nucleos[t]ide analogue therapy). Pegylated interferon therapy can be completed in 48 weeks and is not associated with the development of resistance; however, its use is limited by poor tolerability and adverse effects such as bone marrow suppression and exacerbation of existing neuropsychiatric symptoms such as depression. Newer agents (entecavir, tenofovir disoproxil, and tenofovir alafenamide) may be associated with a significantly reduced risk of drug resistance compared with older agents (lamivudine and adefovir) and should be considered as the first-line treatment.

CONCLUSIONS AND RELEVANCE Antiviral treatment with either pegylated interferon or a nucleos(t)ide analogue (lamivudine, adefovir, entecavir, tenofovir disoproxil, or tenofovir alafenamide) should be offered to patients with chronic HBV infection and liver inflammation in an effort to reduce progression of liver disease. Nucleos(t)ide analogues should be considered as first-line therapy. Because cure rates are low, most patients will require therapy indefinitely.

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More than 240 million individuals worldwide are infected with chronic hepatitis B virus (HBV).[1] Chronic HBV infection progresses to cirrhosis in up to 40% of untreated patients, and there is an associated risk of decompensated cirrhosis (defined as developing symptomatic complications of liver fibrosis such as jaundice, ascites, variceal hemorrhage, and hepatic encephalopathy) and hepatocellular carcinoma.[2-5] Research is ongoing regarding the relative efficacy of HBV treatments, their association with long-term outcomes, their relative safety and tolerability, and management strategies in special patient populations.

This review provides a summary of the current evidence regarding the treatment of patients with chronic HBV infection and summarizes clinical trial evidence regarding the efficacy of available antiviral treatments to improve outcomes, including preventing progression of liver fibrosis and hepatocellular carcinoma.

Methods

We conducted a literature search of the PubMed, EMBASE, and the Cochrane databases for articles published from 1997 through October 31, 2017. Results were limited to clinical trials of human adults with chronic HBV infection. Bibliographies of the retrieved studies and reviews were searched for other relevant studies. We also reviewed the reference articles that had been cited in the guidelines from the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver.[2,6,7]

Epidemiology

Central and east Asia, sub-Saharan Africa, and the Pacific regions have the highest prevalence of HBV (range, 5%->8% of adults[8]), which is predominantly acquired during infancy or at a young age. Approximately 565 000 to 1 130 000 individuals in the United States (0.3%) have chronic HBV infection (**Table 1**).[9-11] However, higher levels of prevalence are observed in communities with large immigrant populations from countries with high levels of prevalence (**Box 1**),[1] and in communities with a large prevalence of individuals at high risk, including those who inject drugs, are incarcerated, and men who have sex with men (**Table 2**).[12,13]

There are 8 major HBV genotypes (A-H) in humans. In North America and Africa, the infections are primarily HBV genotype A

Table 1. Major Epidemiological Characteristics of Patients With Chronic Hepatitis B Virus (HBV) Infection in the United States

	Chronic HBV Infection From 1988-2012 (N = 565 000-1 130 000),[9] %
HBV genotype[10]	
A	35.0
B	22.0
C	31.0
D	10.0
Other	2.0
Race/ethnicity[11,a]	
Asian or Pacific Islander	27.9
White	13.3
Black	10.5
Hispanic	4.1
Non-Hispanic	3.4
Unknown	40.7
Sex[11,a]	
Male	54.7
Female	45.1
Age group, y[11,a]	
<25	6.7
25-39	33.7
40-54	32.4
≥55	27.3

[a] Category does not sum to 100% due to rounding.

(HBV genotype C is almost as common in the United States; Table 1), whereas infections in East Asia are most commonly HBV genotypes B and C and infections in Southern Europe and India are HBV genotype D. The HBV genotype A responds most favorably to interferon-based therapy relative to other genotypes,[14] and the HBV genotype C is associated with more advanced liver fibrosis and an increased risk of hepatocellular carcinoma.[15,16] Commercial testing for HBV genotype is not required for clinical care except when interferon-based therapy is considered, or when knowledge of the HBV genotype may aid risk stratification of disease progression.

Life Cycle and Natural History of Chronic HBV Infection

The HBV virion and life cycle are illustrated in **Figure 1**. The HBV life cycle includes a phase that occurs within the hepatocyte nucleus in which HBV DNA is converted to a highly stable double-stranded circular DNA structure called covalently closed circular DNA. Hepatitis B virus DNA is also integrated into host DNA. Covalently closed circular DNA serves as a template for transcription of viral RNA, can persist indefinitely within the long-lived hepatocyte nucleus, and serves as a reservoir of viral replication.

The natural history of chronic HBV infection (which results from failure to clear acute infection) varies widely and is affected by host and viral factors. After acute HBV infection, infants are more susceptible to developing chronic HBV infection (90% of infants with acute infection develop chronic infection vs 5%-10% of adults).[16] Chronic HBV infection progresses to liver cirrhosis in up to 40% of untreated patients.[2-4] In an observational study[4] of 673 patients, 30% of patients with cirrhosis developed hepatocellular carcinoma during 10 years of follow-up.

Box 1. Who Should be Screened for Chronic Hepatitis B Virus (HBV) Infection?[a]

- Individuals born in a country with at least moderate prevalence (ie, ≥2% of population is positive for HBV surface antigen [HBsAg])[b]
- Individuals with ≥1 parent from a country with high prevalence (ie, ≥8% of population is positive for HBsAg)[b]
- All pregnant women
- Household members and sexual partners of anyone infected with chronic HBV
- Individuals within the following groups are at an increased risk (≥2%) of HBV infection: those who are incarcerated, those who inject illicit drugs, men who have sex with men, those who have HIV, and those who have chronic hepatitis C virus infection (Table 2)
- Health care workers
- Patients undergoing immunosuppressive therapy (eg, chemotherapy, biological immunomodulators, after a transplant)
- Patients undergoing hemodialysis

Individuals meeting any of these criteria should be screened with serological tests for HBsAg, HBV surface antibody (anti-HBs), and HBV core antibody (anti-HBc). Such individuals also should have access to routine testing and care. If both HBsAg and anti-HBs are negative, then the HBV vaccine should be offered. Nonimmune pregnant women who are at risk of HBV infection (women who inject illicit drugs or who have sexual partners with HBV infection) should be vaccinated. Patients with chronic HBV infection are at risk of HBV reactivation and potentially life-threatening sequelae.

[a] Commercially available HBsAg screening tests have a sensitivity and specificity greater than 98%.

[b] All of Africa (>8% in most sub-Saharan and Western African countries), most of Asia except Japan (>8% in Mongolia, Vietnam, and Laos; >5% in China), Pacific Islands (>8%), New Zealand (>4%), Eastern Europe, Russia, Italy, Middle East (except Israel, Iran, Iraq, Lebanon), Ecuador and Peru, and the Caribbean (Haiti >8%).[1]

Chronic HBV infection accounts for at least 50% of hepatocellular carcinoma cases,[17] and primary liver cancer (approximately 75%-90% of cases are hepatocellular carcinoma) is the second most common cause of death from cancer in the world.[18] Among patients with HBV infection, hepatocellular carcinoma can develop in the absence of cirrhosis (approximately 10% of cases in a large Veteran's Affairs cohort of 8539 patients)[19]; however, hepatocellular carcinoma is typically preceded by cirrhosis (70%-90% of patients).[5]

Diagnosis

Serological markers can be used to diagnose and distinguish between acute and chronic infections. Commercially available serological tests detect HBV surface antigen (HBsAg), HBV envelope antigen (HBeAg), HBV surface antibody (anti-HBs), HBV core antibody (anti-HBc), HBV envelope antibody (anti-HBe), and HBV DNA (**Table 3**).[20] Chronic HBV infection is defined as detection of HBsAg on 2 occasions measured at least 6 months apart.

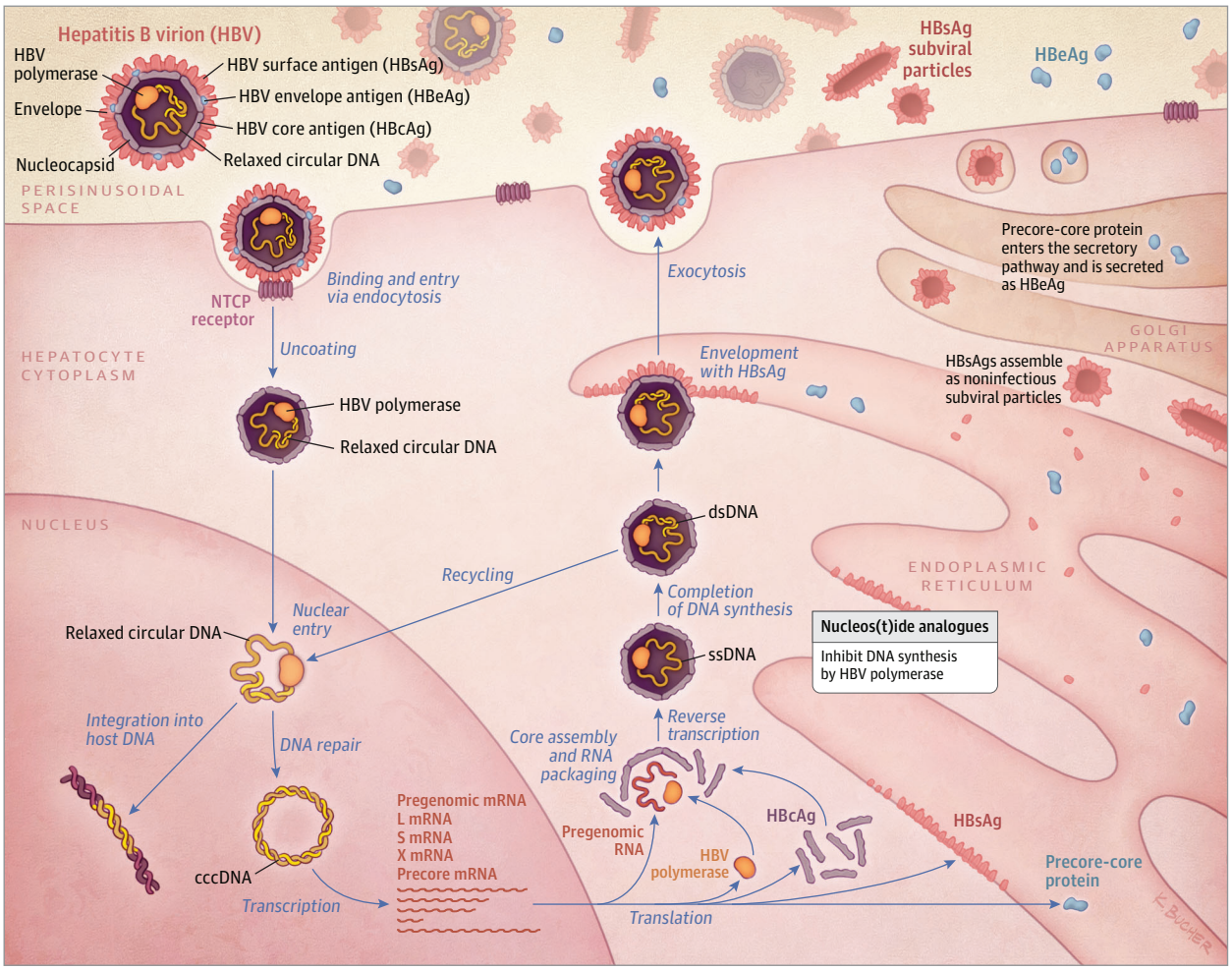
Individuals at risk for HBV infection (populations with ≥2% prevalence of HBV infection) should be screened with serological tests for the presence of HBsAg, anti-HBs, and anti-HBc, and offered a vaccine if not immune (Box 1). Among individuals who recover from HBV infection, 80% will develop anti-HBs and all will develop anti-HBc.[20] Therefore, testing for anti-HBc is important for

Table 2. Patient Groups at Risk for Hepatitis B Virus (HBV) Infection[12]

Group Description	Prevalence Range for HBV Infection, %
A household contact of an individual with chronic HBV	3.0-20.0
A sexual contact of an individual with chronic HBV	3.5-9.0
Individuals born outside the United States[a]	1.0-2.6
Individuals infected with HIV	4.0-17.0
Individuals who inject illicit drugs	2.7-11.0
Men who have sex with men	1.0-3.0
Individuals who are incarcerated[13]	0.3-3.1

[a] Additional information appears in Box 1.

Figure 1. The Hepatitis B Virion and Replication Cycle



The hepatitis B virion is a small enveloped DNA virus consisting of an outer lipoprotein envelope and an inner nucleocapsid core that houses the viral genome. The viral genome codes for all of the viral proteins required for replication: hepatitis B virus (HBV) surface antigen (HBsAg; 3 different sizes: small, medium, large), HBV core antigen (HBcAg), HBV envelope antigen (HBeAg), X protein, and HBV polymerase. The virus binds to the sodium taurocholate co-transporting polypeptide (NTCP) receptor on the surface of hepatocytes and is endocytosed, releasing its DNA-containing nucleocapsid into the cytoplasm where it is transported to the nucleus. In the nucleus, viral DNA in its relaxed circular form is repaired and converted to closed covalent circular DNA (cccDNA). Integration of HBV DNA into the host genome also takes place. The cccDNA functions as a minichromosome and template for transcription of viral RNA. Due to the long half-life of hepatocytes, cccDNA will persist indefinitely within the host hepatocyte nucleus, thereby serving as a reservoir for reactivation of viral replication. Nucleos(t)ide analogues inhibit reverse transcription by HBV polymerase. mRNA indicates messenger RNA; L mRNA, large surface antigen mRNA; S mRNA, small and medium surface antigen mRNA; X mRNA, X protein mRNA.

identifying individuals who may have been previously infected (further described in Table 3). Individuals younger than 19 years should be vaccinated. Individuals in high-risk groups who were vaccinated as infants or schoolchildren should still be screened to determine immunity (or lack of) to HBV. Individuals with anti-HBs levels of less than 10 IU/L are considered not immune.

Table 3. Diagnosis of Acute and Chronic Hepatitis B Virus (HBV) Infection

Interpretation	HBsAg	Anti-HBs	Anti-HBc	HBV DNA Detected	Interpretation Details
HBV infection	Positive	Negative	Positive	Positive	• Presence of HBsAg for >6 mo defines chronic infection • In acute infection, anti-HBc is in the form of IgM
Resolved infection	Negative	Positive	Positive	Negative	• Adults infected with HBV will resolve infection within 6 mo • HBsAg is no longer detected (termed *HBsAg loss*) • 80% of adults will develop anti-HBs (termed *anti-HBs seroconversion*)[20] • Anti-HBc is present in the form of IgG
Immunity	Negative	Positive	Negative	Negative	• Immunity gained through vaccination
Isolated core	Negative	Negative	Positive	Negative or positive	• Undetectable HBV DNA: previous infection without anti-HBs or level of anti-HBs is below the level of detection by serological test[a] • Detectable HBV DNA: occult HBV infection[a] • Period during acute infection either immediately after infection and before the appearance of HBsAg or during resolution of infection after HBsAg loss and before appearance of anti-HBs • False-positive test result

Abbreviations: anti-HBc, HBV core antibody; anti-HBs, HBV surface antibody; HBsAg, HBV surface antigen.

[a] Individuals at risk for disease reactivation and should be identified prior to immunosuppressive therapy.

Presentation

Individuals with chronic HBV infection are typically asymptomatic and are diagnosed during routine health maintenance or screening (eg, blood donation or an evaluation for an elevated level of liver enzymes). Among adults with acute HBV infection, only 5% to 10% will progress to chronic HBV infection. Only one-third of adults develop symptoms (eg, fever, fatigue, malaise, abdominal pain, jaundice) during an acute HBV infection. The remainder have subclinical or asymptomatic illness that may be undetected.[21]

Phases of Chronic HBV Infection

Hepatitis B virus does not kill cells directly. Recognition of the virus as a foreign antigen activates the host immunity to target and destroy infected liver cells, resulting in inflammation and necrosis of liver tissue. However, this process occurs intermittently throughout the course of chronic HBV infection. A patient with chronic HBV infection can transition between periods (or phases) of immunologic activity and inactivity, possibly several times during a lifetime. Repeated periods of immunologic activity with associated liver injury leads to liver fibrosis and hepatocellular carcinoma (**Figure 2**).

Chronic HBV infection is divided into 4 phases: immunotolerance, HBeAg-positive immunoactive disease, HBeAg-negative inactive disease (inactive chronic HBV or low replicative), and HBeAg-negative immunoreactive disease. These phases do not have unique clinical presentations. Individuals in the immunotolerance and HBeAg-negative inactive disease phases are asymptomatic and individuals in the HBeAg-positive immunoactive and HBeAg-negative immunoreactive disease phases can range from asymptomatic to having liver failure. Therefore, serological markers are needed to determine disease phase.

The biomarkers used to determine the phase of chronic HBV infection consist of the presence or absence of HBeAg and anti-HBe, the quantity of HBV DNA (known as HBV DNA level), level of alanine aminotransferase (ALT; a sensitive marker of liver inflammation), and the presence or absence of intrahepatic necroinflammation and fibrosis. Combining these markers provides information about the presence of intrahepatic immunologic activity, which is a measure of damage to liver cells and is clinically important in determining the need for treatment initiation.

Figure 2 summarizes the serological and histological criteria in each phase of chronic HBV.[6,7,16,18,22-26] There are 2 immunologically active phases (the HBeAg-positive immunoactive phase and the HBeAg-negative immunoreactive phase) and 2 immunologically inactive phases (the HBeAg-negative immunotolerance phase and the HBeAg-negative inactive phase).

Patients with acute HBV infection (infected perinatally or later in life) are positive for HBeAg. If chronic HBV infection develops over time, patients can become negative for HBeAg (which is termed *HBeAg loss*). This usually represents partial host immune control of the infection (ie, host mitigation of liver inflammation), and the patient transitions from HBeAg-positive to HBeAg-negative serostatus in most cases (67%-80%), which is associated with a decrease in HBV DNA level (<2000 IU/mL) and cessation of liver inflammation and injury (the HBeAg-negative inactive disease phase). The duration of each phase is not well described; however, by the fourth decade of life, most individuals with chronic HBV who were infected perinatally have undergone HBeAg loss and only 6% to 10% of adults aged 40 years or older remain positive for HBeAg.[26]

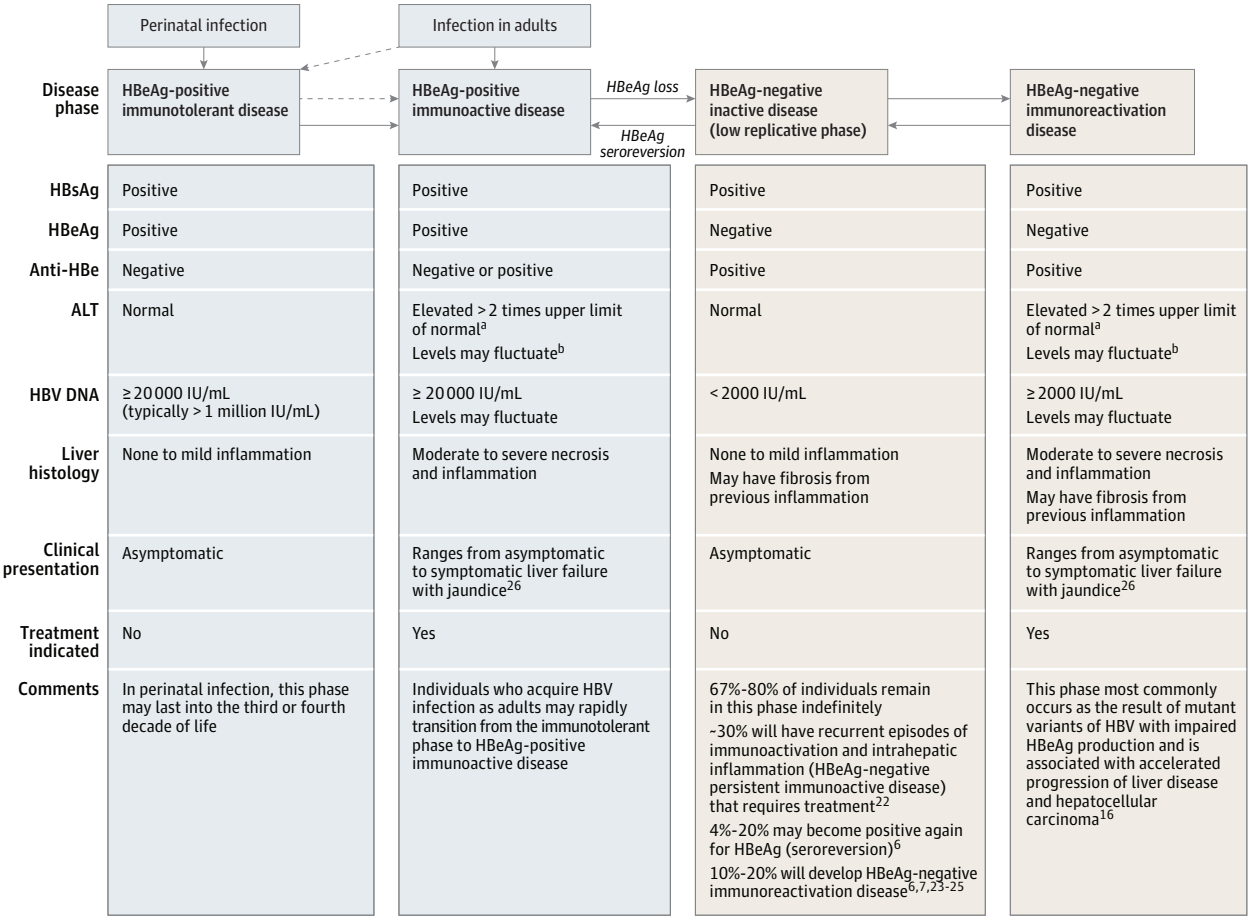
At any time during the course of chronic HBV infection, spontaneous, immunologic clearance of chronic HBV infection (defined as HBsAg loss with or without seroconversion to anti-HBs combined with an undetectable HBV DNA level in the peripheral blood) may occur. Immunologic clearance is associated with improved survival and reduced risk of liver failure and hepatocellular carcinoma[27] and occurs at an annual rate of 0.5% to 2% in the absence of treatment.[16,28]

Key Concepts for HBV Cure

Three categories of cure have been defined: virological, functional (also referred to as immunologic cure), and partial. Virological cure is defined as eradication of HBV DNA from the blood and liver (with continued positive serological test results for anti-HBc with or without anti-HBs). Once hepatocytes are infected with HBV, a reservoir of covalently closed circular DNA is established in the nucleus of hepatocytes, contributing to the persistence of HBV infection (Figure 1).

Covalently closed circular DNA cannot be eradicated from liver cells; therefore, virological cure is unattainable and theoretical.

Figure 2. Phases of Chronic Hepatitis B Virus (HBV) Infection



Disease phase	HBeAg-positive immunotolerant disease	HBeAg-positive immunoactive disease	HBeAg-negative inactive disease (low replicative phase)	HBeAg-negative immunoreactivation disease
HBsAg	Positive	Positive	Positive	Positive
HBeAg	Positive	Positive	Negative	Negative
Anti-HBe	Negative	Negative or positive	Positive	Positive
ALT	Normal	Elevated > 2 times upper limit of normal[a] Levels may fluctuate[b]	Normal	Elevated > 2 times upper limit of normal[a] Levels may fluctuate[b]
HBV DNA	≥ 20 000 IU/mL (typically > 1 million IU/mL)	≥ 20 000 IU/mL Levels may fluctuate	< 2000 IU/mL	≥ 2000 IU/mL Levels may fluctuate
Liver histology	None to mild inflammation	Moderate to severe necrosis and inflammation	None to mild inflammation May have fibrosis from previous inflammation	Moderate to severe necrosis and inflammation May have fibrosis from previous inflammation
Clinical presentation	Asymptomatic	Ranges from asymptomatic to symptomatic liver failure with jaundice[26]	Asymptomatic	Ranges from asymptomatic to symptomatic liver failure with jaundice[26]
Treatment indicated	No	Yes	No	Yes
Comments	In perinatal infection, this phase may last into the third or fourth decade of life	Individuals who acquire HBV infection as adults may rapidly transition from the immunotolerant phase to HBeAg-positive immunoactive disease	67%-80% of individuals remain in this phase indefinitely ~30% will have recurrent episodes of immunoactivation and intrahepatic inflammation (HBeAg-negative persistent immunoactive disease) that requires treatment[22] 4%-20% may become positive again for HBeAg (seroreversion)[6] 10%-20% will develop HBeAg-negative immunoreactivation disease[6,7,23-25]	This phase most commonly occurs as the result of mutant variants of HBV with impaired HBeAg production and is associated with accelerated progression of liver disease and hepatocellular carcinoma[16]

Chronic HBV infection is divided into 4 phases. Patients transition between phases (ie, better and then worse or worse and then better). Not all patients will go through all of these phases. Some patients may transition through the phases rapidly such that distinct phases may not be discerned in clinical practice. Alternative nomenclature refers to phases of chronic HBV infection without intrahepatic inflammation and fibrosis as chronic infection, and those phases with intrahepatic inflammation and fibrosis as chronic hepatitis. Only 6% to 10% of adults older than 40 years who acquired chronic HBV infection perinatally remain positive for HBeAg.[26] Anti-HBe indicates HBV envelope antibody; ALT, alanine aminotransferase.

[a] The upper limit of normal for ALT level was defined by the American Association for the Study of Liver Diseases as 19 IU/mL for women and 30 IU/mL for men.[6]

[b] The immunoactive and immunoreactive phases may occur with ALT levels within 2 times the upper limit of normal.[23]

Functional cure is defined as HBsAg loss combined with undetectable levels of HBV DNA in the peripheral blood that is sustained indefinitely after a finite course of therapy. Partial cure is characterized by a low (<2000 IU/mL) to undetectable level of HBV DNA maintained indefinitely after treatment is stopped, but with detectable HBsAg.[29] Unlike virological cure, functional cure is attainable but occurs in only 3% to 11% of patients treated with interferon therapy.[6,14,30-32] HBeAg loss is associated with a decreased level of HBV DNA (termed *HBV DNA suppression*) and normalization of ALT level (indicative of reduced hepatic inflammation); therefore, partial cure is defined by HBeAg loss combined with a sustained low to undetectable level of HBV DNA and a normal ALT level.

The persistence of covalently closed circular DNA allows HBV infection to reactivate in individuals with previous functional cure (reversion to a detectable level of HBV DNA or HBsAg in a person who was previously negative for both) who are undergoing immunosuppressive therapy (eg, treatment with the B-cell-depleting chemotherapy agent rituximab). The incidence of reactivation among patients who have immunologically cleared HBV (negative for HBsAg and positive for anti-HBc) ranges from 1.5% to 23.8%.[33]

The US Food and Drug Administration issued a warning regarding HBV reactivation in association with direct-acting antiviral agents during treatment for chronic hepatitis C virus that was based on 29 reported cases between November 2013 and October 2016.[34] However, a recent study[35] conducted from January 2014 through September 2016 of 62 290 veterans treated for chronic hepatitis C virus infection with direct-acting antiviral agents reported only 1 case of reactivation of resolved HBV infection.

Evaluation of a Patient With Chronic HBV Infection

Phase Assessment

Individuals with chronic HBV infection should be evaluated to determine the phase of infection and for the presence of liver inflammation and fibrosis (Figure 2). In addition to a comprehensive

Box 2. Evaluation of a Patient With Chronic Hepatitis B Virus (HBV) Infection[a]

Laboratory Tests

Quantitative HBV DNA

HBV envelope antigen (HBeAg) and HBV envelope antibody (anti-HBe)

Screening for HIV, hepatitis C virus, hepatitis A virus immunity

Complete blood cell count

Complete metabolic panel (glucose, electrolytes, assessment of renal and liver function, including measurement of liver enzyme level)

Liver Fibrosis Evaluation

Liver biopsy

Transient elastography

If either of the above is not available, a blood test should be used (types of blood tests include: FibroSure, FIB-4 [a score based on levels of aspartate aminotransferase {AST} and alanine aminotransferase and age], and APRI [AST-to-platelet ratio index])[b]

Health Maintenance

Hepatocellular carcinoma screening with ultrasonography, computed tomography, or magnetic resonance imaging

Hepatitis A vaccine

[a] Defined as 2 positive test results for HBV surface antigen measured at least 6 months apart.

[b] Cutoffs for advanced fibrosis (including cirrhosis based on FIB-4 and APRI scores) were originally validated among patients with chronic hepatitis C virus and HIV co-infection. The validity of the same cutoffs for patients with chronic HBV infection are unclear. In a study of 575 patients with chronic HBV infection who underwent a liver biopsy, increases in APRI and FIB-4 scores correlated with Ishak grade ($P < .001$). However, the scores overlapped and an APRI score greater than 2.0 and an FIB-4 score greater than 3.25 missed advanced fibrosis or cirrhosis in 113 of 139 patients and 179 of 195 patients, respectively.[36] In a meta-analysis of FibroTest (name of the test in Europe; called FibroSure in the United States), there was a correlation with fibrosis diagnosis by METAVIR grade in 2494 patients, sensitivity for cirrhosis was 62% (95% CI, 47%-75%), and specificity was 91% (95% CI, 88%-93%).[37]

history and physical, the following blood tests should be obtained: HBV DNA level by quantitative polymerase chain reaction assay, complete metabolic panel, complete blood cell count, and serological testing for HBeAg and anti-HBe.

Because levels of ALT and HBV DNA fluctuate during the immunoactive phases, differentiating between these phases and the inactive chronic HBV phase requires serial measurements (at least every 3 months for ≥1 year). Additional items for consideration when evaluating a patient with chronic HBV infection appear in **Box 2**.[36,37]

Liver Fibrosis Staging

Liver biopsy remains the gold standard for establishing the presence of liver inflammation and fibrosis; however, a biopsy is associated with significant risks, including bleeding (0.60%)[38] and injury to other organs (0.08%),[39] and is subject to sampling error that can underestimate disease presence.[40] In 1 study,[41] 51 participants underwent 2 liver biopsies on the same day. Discordance (severe fibrosis in one sample but not the other) occurred in 12% of the participants.

Transient elastography, which is an imaging technique that uses vibration pressure waves to measure liver stiffness, can be used as a noninvasive alternative to liver biopsy.[42] If liver biopsy or transient elastography are not available or clinically feasible, proprietary composite biomarker scoring systems (FibroSure, aspartate aminotransferase [AST]-to-platelet ratio index [APRI], and FIB-4 [a score based on levels of AST and ALT and age]), which use biochemical markers to determine the likelihood of cirrhosis, can be used; however, the data regarding these scores and their correlation with Ishak and METAVIR liver pathology scores in chronic HBV infection are variable (Box 2).[36,37,43]

Initiating Antiviral Treatment

The therapeutic goals are to reduce the risk of liver failure and hepatocellular carcinoma. Treatment is indicated during the immunoactive phase of chronic HBV infection when liver injury and fibrosis occur. The immunoactive phase is when a patient has an ALT level greater than the upper limit of normal in combination with a high HBV DNA level (>2000 IU/mL if negative for HBeAg or >20 000 IU/mL if positive for HBeAg), or if a patient has evidence of at least moderate liver inflammation or fibrosis. Patients with cirrhosis should be treated regardless of ALT level and at any detectable level of HBV DNA.

Furthermore, because a high level of HBV DNA is strongly associated with liver disease progression, treatment should also be offered to patients with HBV DNA levels greater than 20 000 IU/mL and elevated ALT levels regardless of fibrosis stage. Clinical response to treatment is based on serological, biochemical, and virological responses (**Box 3**).

Overview of the Available Therapies for the Treatment of Chronic HBV Infection

There are 7 antiviral treatments for chronic HBV infection available in the United States, and the mechanisms of action and adverse effects appear in **Table 4**.[2,7,14,31,32,44-62] These antiviral treatments can be categorized into 2 groups: interferons and nucleos(t)ide analogues.

Interferons

Mechanisms of Action and Adverse Effects | Interferons (alfa, beta, and gamma) are cytokines that are endogenously produced by immune system cells in response to viral infections. All have antiviral and immunomodulatory effects; however, alfa and beta interferons have more potent antiviral actions. Injectable formulations of pegylated interferon alfa (pegylated interferon alfa-2a and alfa-2b) are available for HBV therapy.

The exact mechanism through which interferons have an antiviral effect is not understood, but it is believed to have both direct antiviral (degradation of covalently closed circular DNA and viral messenger RNA and inhibition of viral DNA) and host immunomodulation effects (boosting host immune response against infected hepatocytes, facilitating viral clearance).[63,64]

Pegylated interferon therapy is administered once weekly as a subcutaneous injection for 48 weeks. Its use is limited by adverse effects, which include cytopenia, exacerbations of neuropsychiatric symptoms such as depression and insomnia,[14,32] and induction of thyroid autoantibodies.[65] The frequency of adverse effects is summarized in Table 4.

Box 3. Treatment Outcome Measures for Chronic Hepatitis B Virus (HBV) Infection[a]

Serological Response to Treatment

HBV surface antigen (HBsAg) loss

The presence of HBsAg is a marker of persistent chronic infection. The HBsAg loss (undetectable HBsAg by commercially available assays) can be followed by the presence of HBV surface antibody (anti-HBs; known as anti-HBs seroconversion) and is associated with sustained undetectable levels of HBV DNA and improved prognosis. This is considered functional cure, but occurs at very low rates both on and off treatment.

HBV envelope antigen (HBeAg) loss

The role of HBeAg is not fully understood. However, detection of HBeAg (HBeAg-positive disease) is associated with increased replicative activity (HBV DNA levels can be >1 million IU/mL) and infectivity. Serological transition from HBeAg positive to negative is associated with reductions in liver inflammation and HBV DNA level. The HBeAg loss may be associated with detection of HBV envelope antibody (anti-HBe). It is not known whether production of anti-HBe is associated with improved prognosis.

Virological Response to Treatment

HBV DNA suppression

Inhibition of HBV DNA replication results in a reduction of HBV DNA level measured in blood. A reduction of HBV DNA level to below the level of local assay detection is the cornerstone of available antiviral treatment, especially the nucleos(t)ide analogues.

Biochemical Response to Treatment

Alanine aminotransferase normalization

Level of alanine aminotransferase is a surrogate marker of hepatic inflammation. Reduction to a normal level (termed *normalization*) is used to monitor response to treatment and is associated with improvement in liver inflammation and damage.

Histological Response to Treatment

Liver biopsy

Monitoring response to treatment via a liver biopsy is not routinely recommended in clinical practice.

[a] For patients symptomatic with liver failure, improvement in symptoms such as ascites and hepatic encephalopathy can be a measure of clinical response.

Efficacy of Pegylated Interferon | In randomized clinical trials, pegylated interferon achieved higher rates of HBeAg loss (30% vs 21% with lamivudine, $P < .001$).[31] Long-term follow-up of patients treated with interferon has demonstrated an association between therapeutic response (with HBeAg loss and sustained HBV DNA suppression) and higher incidence of HBsAg loss,[66] improved liver histology,[67] and a reduction in cirrhosis and hepatocellular carcinoma compared with untreated controls.[68] However, overall responses remain suboptimal in that only approximately one-third of patients achieve HBeAg loss and fewer achieve HBsAg loss.

Nucleos(t)ide Analogues

Adverse Effects | The following 5 nucleos(t)ide analogues are available in the United States: lamivudine, adefovir, entecavir, tenofovir disoproxil, and tenofovir alafenamide. The nucleos(t)ide analogues inhibit the RNA-dependent DNA polymerase reverse transcriptase.

Nucleos(t)ide analogues are oral medications taken once daily. These drugs have been well tolerated and adverse effects were generally mild to moderate in clinical trials. All nucleos(t)ide analogues carry a warning on their package inserts for lactic acidosis and severe hepatomegaly[69-72]; however, these adverse events were observed among patients taking the older nucleoside analogues such as stavudine and didanosine for HIV infection and these types of adverse events have not occurred in clinical trials for chronic HBV infection.

The most common adverse effects were fatigue (3.3%-10.4%), dizziness (5.0%-6.6%), headache (4.9%-15.5%), and nausea (3.0%-10.0%).[51,58,61,73-75] In trials of maternal-fetal transmission, there were no differences in fetal development and infant growth associated with nucleos(t)ide analogue therapy compared with no therapy.[76,77]

Tenofovir disoproxil is renally excreted. Due to its structural similarities with adefovir and cidofovir (both are known to cause clinically significant proximal tubule toxicity), there have been concerns for renal toxicity with its use (eg, Fanconi syndrome, diabetes insipidus, and bone demineralization). However, in phase 3 clinical trials[78-80] including 444 patients, Fanconi syndrome and diabetes insipidus were not reported after 144 to 240 weeks of treatment. One study of 280 patients[78] reported a mean decline in bone mineral density of 0.98% and 2.54% at the spine and hip after 240 weeks of treatment with tenofovir disoproxil. However, the fracture incidence was low (10 fractures among 7 patients) and was related to trauma, not use of the study drug.

The clinical significance of these bone density changes among patients taking tenofovir disoproxil is unclear and this drug has not been compared with placebo. Closer monitoring of renal function is warranted while patients are taking tenofovir disoproxil; however, there are no recommendations to increase bone density screening beyond age-appropriate preventive health recommendations. Similar to tenofovir disoproxil, tenofovir alafenamide is a prodrug of tenofovir, but has greater stability within plasma, resulting in higher levels of the active drug within liver cells, less systemic exposure, and less renal- and bone-related adverse effects compared with tenofovir disoproxil. This is consistent with short-term phase 3 studies, but long-term follow-up data are needed.

Efficacy | Lamivudine,[46-50] adefovir,[53-55] entecavir,[81] and tenofovir disoproxil[82] show histological improvement and reduce the level of HBV DNA in the blood in randomized trials of patients with HBeAg-positive and HBeAg-negative immunoactive disease compared with placebo. After 1 year of treatment with lamivudine or adefovir, histological improvement was observed in 53% to 64% of patients compared with 23% to 33% of patients who received placebo ($P < .001$ in all studies); and 60% of patients treated with adefovir for 1 year had HBV DNA levels below detection (compared with 0% in the placebo group).[46,50,54,55]

In a study by Liaw et al,[48] 651 patients were randomized to receive lamivudine or placebo. Treatment with lamivudine (median, 32 months) reduced the rate of overall liver disease progression among patients with advanced liver disease from 17.8% to 7.8% ($P = .001$); furthermore, the incidence of hepatocellular carcinoma was less frequent with lamivudine compared with placebo (3.95%

Table 4. Mechanism of Action and Adverse Effects of Major Therapies Available for Chronic Hepatitis B Virus (HBV) Infection

Drug	Mode of Delivery and Dose	Mechanism of Action	Development of Resistance	Considerations for Use	Adverse Effects	Monitoring During Treatment	
						Safety	Efficacy
Interferons							
Pegylated alfa-2a Pegylated alfa-2b	Subcutaneous injection: 180 µg/wk for 48 wks	• Antiviral treatment that targets host • Binds to type 1 interferon receptors, activating immunomodulatory and antiviral proteins	No resistance reported	• Finite duration of therapy may be advantageous for women positive for HBeAg with high HBV DNA levels planning on getting pregnant • Best treatment response seen among patients with HBV genotype A infection	• Flu-like symptoms: fatigue or asthenia, pyrexia, myalgia, headache (30%-62%)[14,31,32] • Thyroid dysfunction (6%)[44,45,a] • Gastrointestinal symptoms: nausea, diarrhea, decreased appetite (9%-18%)[14,31,32] • Psychiatric disorders: depression (3%-21%),[14,31,32] insomnia (8%-15%)[14,32] • Dermatologic disorders: alopecia (14%-27%), pruritus (5%-14%)[14,31,32] • Neutropenia (17%-21%)[14,32] • Thrombocytopenia (13%-19%)[14,32]	• Liver function test and complete blood cell count at wks 2 and 4 and then monthly • Measure thyroid stimulating hormone level every 12 wk	HBV DNA and serological tests every 3 mo
Nucleos(t)ide Analogues[b]							
Lamivudine	Oral: 100 mg/d	• Antiviral treatment that directly targets the virus • Inhibits reverse transcriptase activity of HBV polymerase	Resistance among 24%-30% after 1 y[46,47] and 70% after 5 y[2,7]		• Malaise or fatigue (15%-19%)[46,48,49] • Nausea, vomiting (9%)[46,48,49] • Headache (15%-17%)[48-50] • Upper respiratory tract infections (8%-35%)[48-50] • Abdominal pain (13%-15%)[48-50] • Diarrhea (14%)[48,50]	• Measure renal and liver function every 3-6 mo • Assess lactic acid level[c]	HBV DNA and serological tests every 3-6 mo
Adefovir	Oral: 10 mg/d	• Antiviral treatment that directly targets the virus • Inhibits reverse transcriptase activity of HBV polymerase	Resistance among 20%-29% after 5 y[51,52]		• Headache (15%-24%)[53,54] • Abdominal pain (18%-24%)[49,55] • Nausea (10%) • Asthenia (10%-25%)[53-55]	• Measure renal and liver function every 3-6 mo • Assess lactic acid level[c]	HBV DNA and serological tests every 3-6 mo
Entecavir	Oral: 0.5-1.0 mg/d	• Antiviral treatment that directly targets the virus • Inhibits reverse transcriptase activity of HBV polymerase	• Resistance among 1.2% after 5 y in nucleos(t)ide-naive patients • Resistance increased to >50% among patients with resistance to lamivudine[56,57]	Recommended as first-line therapy	• Headache (10%) • Fatigue (6%) • Elevated alanine aminotransferase level (4%-10%)[58,59]	• Measure renal and liver function every 3-6 mo • Assess lactic acid level[c]	HBV DNA and serological tests every 3-6 mo
Tenofovir disoproxil	Oral: 300 mg/d	• Antiviral treatment that directly targets the virus • Inhibits reverse transcriptase activity of HBV polymerase	No resistance reported for up to 7 y[60]	Recommended as first-line therapy	• Headache (10%)[61] • Nasopharyngitis (10%)[61,62] • Nausea (9%)[62] • Fatigue (8%)[62] • Upper respiratory tract infection (7%)[61]	• Measure renal and liver function every 3-6 mo • Assess lactic acid level[c] • Measure creatinine kinase level • Category B drug for pregnancy	HBV DNA and serological tests every 3-6 mo
Tenofovir alafenamide	Oral: 25 mg/d	• Antiviral treatment that directly targets the virus • Inhibits reverse transcriptase activity of HBV polymerase	No long-term follow-up data available	Recommended as first-line therapy	• Headache (14%)[61] • Nasopharyngitis (11%)[61] • Upper respiratory tract infection (7%)[61] • Fatigue (6%)[61]	• Measure renal and liver function every 3-6 mo • Assess lactic acid level[c] • Category B drug for pregnancy	HBV DNA and serological tests every 3-6 mo

Abbreviation: HBeAg, hepatitis B virus envelope antigen.

[a] Reported in observational studies but not in any randomized clinical trials.

[b] Known as reverse transcriptase inhibitors. Most adverse events were graded as mild or moderate and not related to the drug; the frequency was similar in both intervention and comparison groups.

[c] Lactic acidosis and severe hepatomegaly reported during postmarketing; all nucleos(t)ide analogues carry a black box warning.

vs 7.40%, respectively; $P = .047$).[48] Treatment of patients with acute liver failure secondary to reactivation of chronic HBV infection with tenofovir disoproxil for up to 3 months was associated with an improvement in the probability of survival from 17% to 57% ($P < .01$).[82] However, serological responses (HBeAg and HBsAg loss with or without detection of corresponding antibodies) were low (11%-32% and 0%-2%, respectively).[47,49,53]

Use of lamivudine and tenofovir disoproxil during pregnancy was associated with lower rates of HBV fetal transmission. In a study of 200 pregnant women who took tenofovir disoproxil during the third trimester, the rate of HBV transmission was reduced from 18% to 5% ($P = .007$).[76]

Drug Selection | Lamivudine and adefovir were the first nucleos(t)ide analogues developed, and their use is limited by the development of resistant variants of HBV. In randomized clinical trials of lamivudine compared with placebo, mutant variants associated with reduced sensitivity to lamivudine were detected in approximately 30% of patients after just 1 year of treatment.[46,47] Mutations causing resistance to adefovir are detected in up to 20% to 29% of patients after 5 years of therapy.[51,52]

In contrast, more recently developed nucleos(t)ide analogues (entecavir and tenofovir disoproxil) have markedly lower rates of resistance with a 1.2% probability of developing a resistant strain after 5 years of entecavir therapy among patients not previously treated with nucleos(t)ide analogues[56] and no clinically significant resistant variants identified during up to 7 years of follow-up with tenofovir.[60] Cross-resistance occurs between lamivudine- and entecavir-resistant HBV strains, and the cumulative probability of developing entecavir-resistant variants is more than 50% among patients with disease refractory to lamivudine.[56]

Randomized clinical trials comparing entecavir or tenofovir disoproxil with either lamivudine or adefovir have demonstrated that entecavir and tenofovir disoproxil show histological improvement (including among patients with lamivudine-resistant HBV)[59,83,84] and HBV DNA suppression[58,62,85] more than the comparator. After 96 weeks of treatment with either entecavir or lamivudine, HBV DNA was suppressed in 80% of patients treated with entecavir compared with 39% treated with lamivudine ($P < .001$).[58] The rate of HBV DNA suppression after 48 weeks of treatment with tenofovir disoproxil was 93% vs 63% with adefovir among patients positive for HBeAg ($P < .001$) and was 76% vs 13%, respectively, among patients negative for HBeAg ($P < .001$). However, the incidence of histological improvement was not different (approximately 70% for all).[62]

In randomized clinical trials comparing entecavir, tenofovir disoproxil, and tenofovir alafenamide, there was no difference in HBV DNA suppression and no therapy was associated with higher rates of HBeAg nor HBsAg loss (14%-30% and <1%, respectively).[61,79,80,86] Two randomized clinical trials compared tenofovir disoproxil and tenofovir alafenamide.[61,80] More than 90% of patients treated with either form of tenofovir achieved HBV DNA suppression; however, treatment with tenofovir alafenamide resulted in ALT level normalization more commonly than tenofovir disoproxil (50% vs 32%, respectively; between-group difference, 17.9% [95% CI, 8.0%-27.7%; $P < .001$]) and the declines in the mean percentage for bone mineral density and renal function were lower with tenofovir alafenamide.

Role of Combination Therapy

The combination of a pegylated interferon and a nucleos(t)ide analogue as initial therapy among untreated patients with viremia was evaluated in a randomized clinical trial of 740 patients.[75] Patients received pegylated interferon or tenofovir disoproxil either in combination or alone. The overall rates of HBsAg loss at 72 weeks (24 weeks after completion of interferon therapy) were low but significantly higher when pegylated interferon was combined with tenofovir compared with tenofovir alone (9.1% vs 0%, respectively; $P < .001$) or pegylated interferon alone (2.8%; $P < .005$).

However, when pegylated interferon was added to treatment for HBeAg-negative patients (total of 183 patients) already receiving nucleos(t)ide analogue therapy with an undetectable HBV DNA level, rates of HBsAg loss at 48 weeks of follow-up did not differ between individuals who received pegylated interferon and those who did not (7 of 93 patients [8%] with pegylated interferon combined with nucleos[t]ide analogue vs 3 of 90 patients [3%] with nucleos[t]ide analogue alone; $P = .15$).[75]

The combination of entecavir and tenofovir disoproxil has been studied among patients who were not previously treated and among patients with HBV disease resistant to adefovir or entecavir. Antiviral efficacy of dual therapy did not differ from monotherapy and there was no meaningful between-group difference in HBsAg loss (0%-3%).[87-89]

Selection of Antiviral Therapy

Selecting an antiviral regimen requires consideration of both host and viral factors. For most patients, treatment with a nucleos(t)ide analogue is optimal due to its excellent adverse effect profile and ease of administration.

The newer nucleos(t)ide analogues of entecavir, tenofovir disoproxil, and tenofovir alafenamide are considered first-line regimens because of their high efficacy and low rates of resistance. Treatment with an interferon is not associated with the development of mutant viruses with resistance to therapy; however, interferon therapy is not well tolerated.

Treatment with an interferon is contraindicated in patients with uncontrolled psychiatric disorders such as depression, autoimmune disease, severe cardiac disease, and cytopenia.[65] Treatment with an interferon should be reserved for patients with HBV genotype A and who are positive for HBeAg. Treatment with an interferon can also be considered in patients for whom a short-term treatment course is beneficial such as women planning to become pregnant.

Long-Term Monitoring

All individuals with chronic HBV infection should be evaluated at least every 6 months for a history and physical, a complete metabolic panel with renal and liver function tests, complete blood cell counts, HBV DNA level, and serological tests for HBeAg and HBsAg. Patients with increasing HBV DNA and ALT levels should be evaluated more frequently.

Screening for Hepatocellular Carcinoma

Hepatocellular carcinoma tumors double in volume every 4 to 6 months.[90] Therefore, ultrasonography of the liver should be performed every 6 months to screen for hepatocellular carcinoma in an adult patient even if ALT level is normal. In a randomized clinical

trial[91] of 18 816 patients, screening with ultrasonography of the liver and an alpha-fetoprotein test every 6 months was associated with earlier detection and improved hepatocellular carcinoma survival (5-year survival rate of 46.4% vs 0% among unscreened patients). There have been no randomized clinical trials comparing screening every 6 months with annual screening. An abnormal ultrasound of the liver should be followed up by either dynamic computed tomography or magnetic resonance imaging of the liver.[92,93]

Controversies and Challenges

Cessation of Nucleos(t)ide Analogue Therapy

The presence of HBsAg loss is associated with HBV DNA suppression and is an ideal outcome of antiviral therapy; however, this occurs in only 3% to 11% of patients treated with an interferon,[6,14,30-32] and in only 1% to 12% of patients treated with a nucleos(t)ide analogue for 5 to 7 years.[60,94,95] Therefore, most individuals initiated on nucleos(t)ide analogues remain on therapy indefinitely.

Recent observational studies have reported that the HBsAg loss and HBV DNA suppression that occur during antiviral therapy are durable even after treatment is stopped.[96,97] Therefore, stopping treatment can be considered after extending antiviral therapy 6 to 12 months after HBsAg and HBV DNA become undetectable. However, this approach has not been evaluated in a randomized clinical trial.

For patients without HBsAg loss, discontinuing therapy may be desirable due to potential long-term toxic effects, the cost of medication, and the development of resistance. Current recommendations allow consideration of therapy cessation 1 year after HBeAg becomes unmeasurable.[2,6,7] For patients who are negative for HBeAg at the time of antiviral initiation, cessation can be considered after 3 years of therapy.[2,7]

High rates of virological relapse (91.4%) have been reported within 48 weeks of therapy cessation among patients with HBeAg-negative disease.[57] Patients with cirrhosis should remain on therapy at least until HBsAg loss regardless of HBeAg status; however, this recommendation is based on expert opinion, with few supporting data.

Screening for Hepatocellular Carcinoma After HBsAg Loss

Even after HBsAg loss, hepatocellular carcinoma can occur, possibly related to persistent covalently closed circular DNA and integration of HBV into host DNA. In an observational prospective study[98] of 158 cases with HBsAg loss not receiving treatment (mean follow-up, 19.6 years), the annual incidence of hepatocellular carcinoma was 3.8%. There are few data to inform screening recommendations for patients without cirrhosis who undergo HBsAg loss (spontaneous or with antiviral therapy).

Conclusions

Antiviral treatment with either pegylated interferon or a nucleos(t)ide analogue (lamivudine, adefovir, entecavir, tenofovir disoproxil, or tenofovir alafenamide) should be offered to patients with chronic HBV infection and liver inflammation in an effort to reduce progression of liver disease. Nucleos(t)ide analogues should be considered as first-line therapy. Because cure rates are low, most patients will require therapy indefinitely.

ARTICLE INFORMATION

Author Contributions: Dr Kottilil had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tang, Kottilil.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Tang, Covert, Kottilil.
Critical revision of the manuscript for important intellectual content: Tang, Wilson, Kottilil.
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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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