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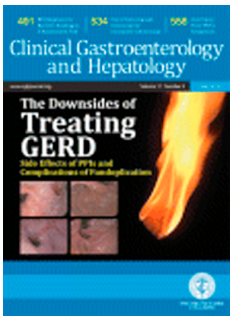

Treatment Algorithm for Managing Chronic Hepatitis B Virus Infection in the United States: 2021 Update

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Treatment Algorithm for Managing Chronic Hepatitis B Virus Infection in the United States: 2021 Update

Short title: Chronic Hepatitis B Treatment Algorithm

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Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; AST, aspartate aminotransferase; CHB, chronic hepatitis B; eGFR, estimated glomerlular filtration rate; ETV, entecavir; HAART, highly active antiretroviral therapy; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; HIV, human immunodeficiency virus; IU, international units; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; pegIFN, peginterferon alfa; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal

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Abstract

Background and Aims. Chronic hepatitis B (CHB) infection remains the most frequent etiology of hepatocellular carcinoma globally as well as a major cause of cirrhosis. Despite vaccination, substantial numbers of persons have already been infected with hepatitis B virus and remain at risk of progressive liver disease.

Methods. In 2004, a CHB management algorithm was developed by a panel of North American hepatologists which was subsequently updated in 2006, 2008, and 2015. Since the most recent version, several developments have altered the management of CHB. Tenofovir alafenamide, with a more favorable safety profile than tenofovir disoproxil fumarate, has been introduced as an initial antiviral choice as well as an alternative for long-term therapy. Quantitation of hepatitis B surface antigen (HBsAg) is becoming more widely available in clinical practice, with implications for monitoring response to treatment. Additionally, there has been a shift in how the natural history of CHB is perceived as newer evidence has challenged the concept that during the immunotolerant phase of infection disease progression is not a concern. Finally, recent analyses indicate that in the United States, the average age of CHB patients has increased implying that the presence of comorbidities including metabolic liver disease increasing use of biologics associated with aging will increasingly affect disease management.

Results. This updated algorithm is intended to serve as a guide to manage CHB while new antiviral strategies are developed.

Conclusions. Recommendations have been based on evidence from the scientific literature, when possible, as well as clinical experience and consensus expert opinion. Points of continued debate and areas of research need are also described.

Keywords: peginterferon alfa, tenofovir, entecavir, coinfection

Introduction

Chronic hepatitis B (CHB) remains a substantial public health problem and the leading cause of hepatocellular carcinoma (HCC) worldwide.[1] In the United States, an estimated 840,000 to 1.59 million individuals, representing 0.3% of the population, are chronically infected with hepatitis B virus (HBV).[2, 3] Universal vaccination of infants has led to significant decreases in the prevalence of HBV infection in persons younger than 20 years; however, its prevalence of 0.3% in the general population has been constant between 1999 and 2016, largely because of continued immigration of persons of areas endemic for CHB infection.[4] Cohort study data have indicated the mean age of persons with CHB has increased from approximately 43 years in the period from 2000-2005 to 49 years from 2011 to 2015.[5] With this increase in age has come increases in liver-related comorbidities such as fatty liver as well as non-liver-related comorbidities (hypertension, hyperlipidemia, diabetes mellitus, osteoporosis, and chronic kidney disease).[5]

CHB infection is a dynamic process that does not always progress linearly. In addition, not all patients with CHB infection have histological evidence of hepatitis. Traditionally, the natural history of HBV infection was thought of as being divided into 4 phases (immune tolerance, immune clearance, low viral replication, and reactivation). More recently, updated terminology places a focus on describing the 2 main characteristics of chronicity, infection alone and infection with evidence of ongoing hepatic inflammation, i.e. hepatitis (Figure 1).

Antiviral therapy for CHB can lead to regression of liver fibrosis and even cirrhosis[6-8] as well as decrease the risk of HCC, cirrhosis, decompensated liver disease, and death.[9] Recent evidence suggests antiviral therapy may reduce the risk of HCC in patients without cirrhosis and with normal serum alanine aminotransferase (ALT) levels, groups previously considered as

having a relatively low risk of developing HCC.[10, 11] Unfortunately, a substantial proportion of infected individuals who meet criteria for treatment based on recommendations from the American Association for the Study of Liver Diseases are not undergoing treatment including those who already have HCC.[12, 13] In fact, only 10% of the world CHB and 18% of the United States CHB burden have been diagnosed, and less than 20% of people with CHB in the United States are aware of having a liver disease.[1, 4, 14] Patient barriers to seeking evaluation and treatment vary but can be related to income level, health insurance coverage or lack of, and linguistic isolation or cultural or spiritual beliefs.[15-18]

To help guide clinicians managing patients with CHB, a panel of North American hepatologists developed a practical treatment algorithm in 2004.[19] The algorithm was subsequently revised in 2006,[20] 2008,[21] and 2015.[22] Since the 2015 version of the algorithm was published, several developments have altered the management of CHB. The oral agent tenofovir alafenamide was licensed, affecting decisions regarding treatment choices in patients initiating as well as already undergoing therapy. Additionally, quantitative evaluation of hepatitis B surface antigen (HBsAg) levels has become more widely adopted in clinical practice, with implications for monitoring response to treatment. There is also evidence that during the immune tolerant phase virological events occur such as integration of viral DNA into the host genome which may help set the stage for the subsequent development of HCC.[23] A recent report evaluating the current linkage to care for CHB by the World Health Organization also called for more "simplified management algorithms" in their proposed action plan.[24]

In light of these development, a panel of 7 hepatologists (6 from the United States and 1 from Canada) met to reassess and revise the 2015 recommendations. The following algorithm is meant to serve as practical guidance for managing CHB. Recommendations have been based on

evidence from the scientific literature, when possible, as well as clinical experience and consensus expert opinion.

Candidates for Antiviral Therapy

Approaches for managing patients with CHB are listed in Table 1. The consensus opinion of the panel is that all patients (HBeAg-positive or -negative) who have HBV DNA ≥2,000 IU/mL and elevated ALT (above 35 IU/mL for men and 25 IU/mL for women[25]) should receive treatment for CHB. If patients with HBV DNA ≥2,000 IU/mL and elevated ALT without fibrosis do not undergo treatment, their HBV DNA and ALT levels should be monitored every 3-6 months.

Whether to initiate treatment in "immune tolerant" (IT) patients, meaning those that are HBeAg-positive and have HBV DNA ≥2,000 IU/mL but persistently normal ALT, is an area of continued discussion. Typically IT patients have not been recommended to receive antiviral therapy as the perception had been they were not at risk of progressive liver disease during this phase of CHB infection and furthermore response to antiviral therapy in IT patients has been disappointing with a low likelihood of HBeAg seroconversion rates (<5% at 4 years).[26] However, in recent years the concept of a generic immune tolerant phase has been challenged, and there is now question whether it should be a premise for withholding treatment. It has been shown that HBeAg-positive patients considered immune tolerant have similar levels of HBV DNA integration into host chromosomes and of clonal hepatocyte expansion as those considered immune active.[23] This evidence indicates that patients with high viral replication and normal ALT levels are subject to events that may contribute significantly to progression to cirrhosis and/or development of HCC.[27] Because of this, some members of the panel believe all adults, including those <30 years old, are candidates for treatment if they have viremia in the absence of

elevated ALT. While other members of the panel did not disagree with this view, they raised concerns about patients potentially being on therapy for decades and the risk of hepatitis flares or development of resistance if therapy is initiated and then stopped. For these reasons, all of the panelists agree that decisions about initiating treatment in HBeAg-positive patients with HBV DNA ≥2,000 IU/mL and normal ALT should be made on an individual basis taking into account the patient's age, circumstances, and preference for initiating treatment as well as risk factors for disease progression, such as family history of HCC, infection with genotype C HBV,[28-31] and presence of basal core promoter mutations.[31] A single-center study from Korea suggested that IT patients were at risk of major complications at rates comparable to patients with immune reactive disease on antiviral therapy; however, the IT patients included in this report were older than in most other series and more importantly, the definition of IT in this study was based only on the baseline ALT level, so some may not have been truly IT patients since ALT levels frequently fluctuate.[32] Lastly, not all patients can be classified into one of the established immune phases (immune inactive, immune tolerant, and immune active) as defined by current practice guidelines based on routine clinical and laboratory assessment. A recent multicenter study inclusive of 3,366 treatment-naïve CHB patients without cirrhosis from the United States and Taiwan found that 39% of patients could not be classified into any of the clinical phases as defined by the American Association for the Study of Liver Diseases; and of these 1,300 "indeterminate" phase patients, 53% remained "indeterminate" over a median study follow-up of 12.5 years.[33] Yet, compared to inactive patients and after adjustment for relevant confounders, those who remained indeterminate had nearly 40% higher risk of development HCC, further highlighting the importance of individualizing patient management and consider treatment in patients with HBV DNA >2000 IU/mL who are older than 45 years.

Treating Chronic Hepatitis B

The goal of therapy for CHB is to eliminate or significantly suppress HBV replication and thus prevent progression of liver disease to cirrhosis, liver failure, or HCC.[9] In patients who are HBeAg-positive before therapy, an additional goal of treatment is loss of HBeAg with seroconversion to anti-HBe, although the usefulness of this endpoint for determining long-term outcomes with oral antiviral therapies is unclear. Loss of HBsAg, although highly desirable, occurs in only a minority of patients including those who receive antiviral therapy.[34]

Currently, there are 2 key treatment strategies for either HBeAg-positive or HBeAg-negative CHB: finite therapy for one year with peginterferon-alfa or longer term therapy with nucleoside/nucleotide analogues. Finite treatment with peginterferon-alfa has the advantage of higher rates of HBeAg seroconversion and loss of HBsAg compared to nucleoside or nucleotide analogues administered for an equivalent duration. However, peginterferon-alfa is administered by injection and has significant toxicity.[6, 35-37]

The 4 first-line therapies available for managing CHB infection in the United States are peginterferon alfa-2a, ETV, TDF, and tenofovir alafenamide (TAF). The nucleosides/nucleotides lamivudine, adefovir, and telbivudine are also indicated for CHB, but they have inferior efficacy to ETV, TDF or TAF and higher risk of resistance and are therefore no longer recommended as first-line agents.

Peginterferon alfa-2a is a reasonable choice particularly in genotype A or B patients who are young, lack significant comorbidities, have no detectable precore or basal core promoter viral mutants, and have HBV DNA levels $\leq 2 \times 10^8$ IU/mL and ALT >2 x ULN. ETV should not be administered to patients with any history of lamivudine use because there may be amino acid substitutions in the HBV cccDNA (covalently closed circular DNA) that could serve as a

foundation for ETV resistance. Table 2 summarizes current data for the preferred first-line agents.

In 2016, TAF, a prodrug of tenofovir, was approved by the U.S. Food and Drug Administration for the treatment of CHB. TAF has greater stability in plasma than TDF, and this enables more efficient delivery of the active metabolite to target cells at a substantially lower dose.[38-41] In two randomized, double-blind, multinational, Phase 3, non-inferiority trials for HBeAg-positive and -negative patients, TAF 25 mg orally once-daily was not inferior to TDF 300 mg in achieving an HBV DNA <29 IU/mL at week 48.[42, 43] No resistance to TAF or amino-acid substitutions associated with viral breakthrough were found through week 96. Compared with TDF, TAF was associated with a significantly higher ALT normalization rate at 48 weeks. At week 48, TAF resulted in a significantly lower decrease in median estimated glomerular filtration rate (eGFR) than TDF in both HBeAg-positive (TAF -0.6 vs TDF -5.4 mL/min, P,0.0001)[43] and HBeAg-negative (TAF -1.8 vs TDF -4.8 mL/min, *P*=0.004)[42] patients. Similarly, the declines of hip and spine bone mineral density were significantly less among TAF-treated patients (HBeAg-positive: hip -0.10% and spine -0.42%, HBeAg-negative: hip -0.29% and spine -0.88%).[42, 43] These trends of renal and bone safety continued through week 96. Moreover, patients switched from TDF to TAF have significant improvement in hip and spine bone mineral density, as well as improvement in creatinine clearance, 48 weeks after switch compared to those continuing on TDF.[44] Real-world data also found continued increase in viral suppression, ALT normalization, and stable renal function in patients switched from TDF to TAF.[45] Observational data have also indicated that in patients switched to TAF after an average of 6 years on ETV, viral suppression rate increased from 91.9% at switch to 97.2% at 96 weeks later, while renal function remained stable.[46]

It is the opinion of most—but not all—members of the panel that when antiviral therapy is contemplated TAF is preferred over TDF because of the lower risks of renal or bone side effects and higher likelihood of ALT normalization through 48 weeks.[42, 43] Renal and bone safety are important in an aging CHB population with increased likelihood for comorbidities. For patients undergoing TDF treatment, there is substantial evidence to date indicating that switching from TDF to TAF is not associated with risk for viral rebound.[44] Members of the panel were divided in whether they recommend patients stay on TDF or switch to TAF. Some members of the panel favor transitioning patients from TDF to TAF because of the potential benefits for renal and bone safety and potentially greater chance of achieving ALT normalization if it has not already occurred. Others believe maintaining patients on TDF is supported by its demonstrated efficacy and safety during its 10-year history in treating CHB, and that most decreases in bone density occur in the first 1-2 years of TDF treatment, potentially negating any bone safety benefits of TAF in patients who have been taking TDF long-term. Members of the panel did agree that particularly compelling candidates for switching from TDF to TAF are patients with borderline renal function (eGFR <90 mL/min/1.73m^2) or increased risk for osteopenia/osteoporosis, hypertension, diabetes, or age greater than 50 years.

Combination Therapy

ETV, TDF, and TAF have potent antiviral activity and high barriers to resistance. Therefore, monotherapy with ETV, TDF, TAF, or peginterferon alfa-2a is recommended for nearly all CHB patients. There is some evidence that combining TDF with peginterferon alfa-2a increases the likelihood of loss of HBsAg compared to TDF or peginterferon alfa-2a monotherapy.[47]

Duration of Therapy

The optimal duration of therapy with peginterferon alfa remains unclear, although treatment for 48 weeks appears to induce higher rates of HBeAg seroconversion than 24 weeks.[48] Evidence from a small study has indicated that extension of peginterferon therapy to 96 weeks improves rates of sustainable HBeAg and HBsAg seroconversion.[49] In a study of HBeAg-negative patients with HBV genotype D infection, extending peginterferon therapy to 96 weeks improved rates of virologic suppression and ALT normalization.[50] For individual patients, the benefits of extending interferon-based therapy should be weighed against issues of tolerability. With peginterferon-alfa therapy, HBeAg-positive patients with no decline in HBsAg or an HBsAg level >20,000 IU/mL at week 12 are justified in stopping treatment,[51, 52] as are HBeAg-negative patients without HBsAg decline and a <2-log IU/mL decline in HBV DNA at week 12.[53, 54]

For nucleoside/nucleotide analogues, the panel recommends long-term treatment for all patients with decompensated cirrhosis at the start of therapy and for the majority of patients who have significant fibrosis (F3) or compensated cirrhosis (F4) at the start of therapy. Patients with compensated liver disease at the start of therapy may be discontinued from therapy if they experience HBsAg loss for 6-12 months or HBsAg seroconversion. However, patients must undergo lifelong screening for HCC even if they no longer have cirrhosis.

HBeAg-positive patients. HBeAg-positive patients with evidence of less extensive fibrosis (< F3) should be treated long-term, even after HBeAg seroconversion and virologic suppression because of the risks of virologic relapse[55] and ALT flares, except when treatment is initiated solely for the purpose of prevention of vertical transmission.[56] If patients prefer to stop treatment despite advice to the contrary, they should undergo liver biopsy or transient elastography prior to stopping therapy to ensure they have only mild histologic fibrosis (F0-F1). Patients who stop

therapy should be monitored for HBV DNA and ALT levels. Those who relapse can be re-treated.

HBeAg-negative patients. For HBeAg-negative patients without HBsAg seroconversion, the panel does not recommend stopping treatment. However, if patients prefer to stop treatment, physicians can have a dialogue with patients who have mild histologic fibrosis (F0-F1) and inflammation based on liver biopsy or by non-invasive evalution about the pros and cons of stopping after 5 years. Discontinuation of nucleos(t)ide therapy in HBeAg-negative patients is almost invariably followed by virologic relapse to at least low viral levels.[57] However, many maintain persistently normal ALT, and some who stop therapy after long-term viral suppression appear to have an immunologic response that can accelerate the loss of HBsAg.[58-60] This process occurs more frequently in patients with low HBsAg levels (<100 IU/ml) at the time of stopping treatment. Still, it should be emphasized that relapse rates are substantial, and even patients without cirrhosis can experience ALT flares.[57, 61] Therefore, patients who stop therapy should be monitored for HBV DNA and ALT levels. Those who relapse can be re-treated with the same agent.

Monitoring for Renal Toxicity

The dosage of all nucleoside/nucleotide analogs needs adjustment in patients with progressive degrees of renal impairment, except for TAF which can be administered at 25 mg/day unless GFR is less than 15 mL/min, in which case its use is not advised.[62] Some nucleotide analogs (adefovir, TDF) have been associated with diminished renal function.[63] Before starting therapy with a nucleoside/nucleotide analogue, patients should be evaluated with serum creatinine levels and estimated creatinine clearance. Risk factors for renal events include decompensated cirrhosis, pretreatment creatinine clearance <60 mL/min, poorly controlled hypertension,

proteinuria, uncontrolled diabetes, active glomerulonephritis and concomitant nephrotoxic drugs. Furthermore, following the fourth decade of life, physiologic renal function decline is expected at about 8 mL/min/1.73m per decade [64], which is very relevant as the CHB population continues to age, with 42% already 55 years or older in 2015 in the United States as as high as 60% being 65 years or older in 2016 elsewhere such as Japan[65-69]. Notably, observational data from population-based studies from both the United States and Asia have also found CHB to associate with higher prevalence and incidence of chronic kidney disease[65, 70-72]. For patients at risk of nephrotoxicity or for those taking TDF,[73] creatinine clearance (eGFR) and serum phosphorus should be monitored every 3 months during the first year of therapy. If renal function is unchanged, monitoring can be extended to every 6 months thereafter. Dose adjustments can be made either prior to treatment for high-risk patients or during therapy based on assessments of renal functioning.

Bone Density Measurements

Patients with chronic liver disease including CHB have increased risk for osteopenia and often underdiagnosed.[65, 74] In addition, since the majority of the CHB population are male and pathologic fracture has been reported to associate with higher one-year mortality among males, the issue of bone health is a particularly relevant in the management of CHB.[75, 76] In two 48 week pivotal trials of TDF versus TAF in HBeAg-positive and HBeAg-negative patients, TDF was associated with a reduction in hip density of 1.72 – 2.16% and in spine density of 2.29 – 2.51%, compared with reductions of 0.10 - 0.29% and 0.42 - 0.88% with TAF for hip and spine density, respectively. In the HBeAg-negative study, over 3% reduction in hip and spine density at 48 weeks were noted in 33 - 39% with TDF versus 10 - 22% with TAF.[42, 43] Some members of the panel perform a bone mineral density scan in patients prior to starting oral antiviral therapy,

particularly in patients at risk for osteopenia or osteoporosis. Additionally, some members monitor levels of 25-hydroxy vitamin D during therapy and provide oral supplementation for deficiency.

On-Treatment Monitoring

Serum HBV DNA levels should be monitored at 12 weeks to assess initial treatment reponse (HBV DNA decline of <1 $\log_{10}$ IU/mL) and at 24 weeks to confirm continued virologic suppression by antiviral therapy. Monitoring of HBV DNA levels should occur every 3 to 6 months during the first year to confirm adequate viral suppression and detect viral breakthrough.

Primary treatment failure. Primary nonresponse to ETV, TDF, or TAF is rare; therefore, any patients who are not responsive to these agents after 12-24 weeks should be evaluated for compliance. In patients who have been compliant, resistance analyses (see below) should be performed after 24 weeks to determine an optimal rescue strategy in case drug-resistant variants are present.

Partial or inadequate virological response. Patients with HBV DNA ≥2,000 IU/mL at 24 weeks or HBV DNA positive at 48 weeks of treatment with a nucleoside or nucleotide analogue should also be evaluated for compliance. The optimal management of patients who have detectable HBV DNA after 48 weeks of ETV, TDF, or TAF therapy is unclear. Patients with declining serum HBV DNA levels may continue with ETV or tenofovir given the rise in rates of virological response over time and the very low risk of resistance to either antiviral.[77, 78] Patients with partial response to ETV but HBV DNA <1,000 IU/mL after 1 year of therapy often achieve viral suppression by continuing ETV through at least 2 years.[79] Another strategy described has been in patients with partial response to ETV after 1 year of therapy is a switch to TDF or TAF monotherapy or TDF or TAF plus ETV combination therapy.[80] For patients with partial response

to ETV 0.5 mg daily, increasing the dose to 1.0 mg daily does not appear to increase the likelihood of achieving complete viral suppression.[81]

Virological resistance. Clinically, antiviral resistance manifests as virologic breakthrough, defined as a ≥1 $\log_{10}$ IU/mL increase in serum HBV DNA levels from nadir in 2 consecutive samples taken 1 month apart in patients who have responded and have been adherent to therapy with antiviral medications.[82] With ETV the rate of resistance is 1% after ≥ 5 years except in HIV-infected patients treated with ETV monotherapy and HBV resistance remains unreported with TDF and TAF. The vast majority of cases of virologic breakthrough in clinical practice are due to nonadherence.[83, 84] Yamada et al[85] however detected ETV resistant variants in 2 patients with viral breakthrough in the absence of other NUC therapy and who experienced viral breakthrough on ETV therapy. However, this appears to be a rare event.

Recommendations for managing resistance vary[86-88] but generally involve either adding or switching to a drug in a separate class. In clinical practice, we recommend using either TDF or TAF monotherapy in patients with established or suspected resistance.A combination option approved for HIV infection is available for TAF/emtricibatine (Descovy, 25 mg/200 mg, also not approved for CHB). No cases of TDF or TAF resistance have been recognized.

The most commonly used methods in clinical practice include standard population-based direct sequencing and line probe assays. Direct sequencing–based assays such as population-based sequencing is the gold standard for genotypic HBV resistance testing because they detect the full variety of mutations that confer resistance, including those not previously identified, but this technique can only identify mutations that comprise >20% of the total viral population. Line probe assays can detect resistance mutation that comprises 5% of the total HBV population.[89]

Conclusions

Although a variety of agents are in clinical development,[90] for the next few years the panel anticipates that currently licensed agents will continue to be the only options available to treat HBV infection. The panel feels that efforts to identify HBV infected patients as well as continuing to reevaluate the need for antiviral therapy in each patient are important goals.

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Table 1. Chronic Hepatitis B Recommendations for Treatment

	Treatment Strategy
Cirrhosis absent	
HBV DNA <2,000 IU/mL, normal ALT[a]	● No treatment ● Assess ALT levels every 6−12 months[b] ● If ALT becomes increased, check serum HBV DNA and exclude other causes of disease ● Consider therapy if significant histologic disease
HBV DNA ≥2,000 IU/mL, normal ALT[a]	
HBeAg-positive	● Consider treatment based on risk factors for developing HCC as well as patient's age, lifestyle, and desire to undergo treatment ● If treated, entecavir, TAF, or peginterferon alfa-2a are preferred ● Long-term treatment may be needed for oral agents
HBeAg-negative	● Treat if fibrosis is present. In the absence of histologic data, observe for rise in serum ALT ● If treated, entecavir, TAF, or peginterferon alfa-2a are preferred
HBeAg-positive and negative	● If not treated– ○ Assess ALT every 3−6 months ○ Consider assessing for fibrosis ● Consider initiating treatment when ALT level increases or fibrosis is present
HBV DNA ≥2,000 IU/mL, elevated ALT[a]	● Treat ● Entecavir, TAF, TDF, or peginterferon alfa-2a are preferred ● Long-term treatment may be needed for oral agents
Cirrhosis present	
Compensated	● Treat ● Entecavir (0.5 mg), TAF (25 mg), or TDF (300 mg) ● Peginterferon alfa can be used in patients with well-compensated cirrhosis ● For oral antivirals, long-term treatment is required
Decompensated	● Treat ● Entecavir (1 mg) or TDF (300 mg) ● TAF is not recommended

	● Peginterferon alfa is contraindicated ● Long-term treatment is required ● Wait list for liver transplantation
HIV coinfection	
All patients with HBV and HIV	● Treat ● Avoid single-therapy HBV agent ● Long-term treatment required ● Pretreatment, assess fibrosis and screen for HCC ● Patients with platelets <120,000/μL or severe fibrosis should undergo endoscopy to detect varices
HBV treatment-naïve	● Preferred: (TDF or TAF) plus (emtricitabine or lamivudine) ● Entecavir plus HAART is also an option
Lamivudine-resistant HBV	● Preferred: Truvada[c] or tenofovir plus entecavir

[a]The upper limits of normal for serum ALT concentrations are 30 IU/L for men and 19 IU/L for women.
[b]Upon initial diagnosis, monitor every 3 months for 1 year to ensure stability.
[c]Truvada is the trade name for emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg.
ALT, alanine aminotransferase; HAART, highly active antiretroviral therapy; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 2. Results of Main Studies for First-Line Therapies for Chronic Hepatitis B

	PegIFN alfa-2a	Entecavir	Tenofovir Disoproxil Fumarate	Tenofovir Alafenamide
48 or 52 weeks[42, 43, 87, 91]				
HBeAg-positive				
Dose[a]	108 µg	0.5 mg	245 mg	25 mg
Anti-HBe seroconversion	32%	21%	21%	10%
HBV DNA <60-80 IU/mL	14%	67%	76%	64%
ALT normalization[b]	41%	68%	68%	72%
HBsAg loss	3%	2%	3%	1%
HBeAg-negative				
Dose[a]	108 µg	0.5 mg	245 mg	25 mg
HBV DNA <60-80 IU/mL	19%	90%	93%	94%
ALT normalization[b]	59%	78%	76%	83%
HBsAg loss	4%	0%	0%	0%
≥5 years[6, 35, 36, 92]				
HBeAg-positive and -negative				
HBV DNA undetectable[c]		97% to 100%		93%
ALT normalization[b]		86% to 100%		85%
HBsAg loss		<1%		1%
7 years[37]				
HBeAg-positive and -negative				
HBV DNA undetectable[c]			99%	
ALT normalization[b]			80%	
HBsAg loss			4%	

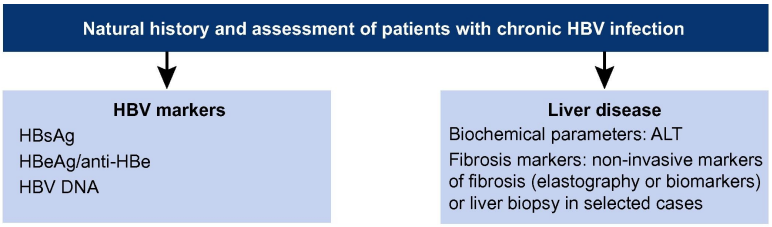
ALT, alanine aminotransferase; HBV, hepatitis B virus; PegIFN, peginteferon

[a]Peginteferon alfa-2a was given as percutaneous injections once weekly. Nucleoside/nucleotide analogues were given as oral tablets once daily.

[b]The definition of ALT normalization varied between trials.

[c]The lower limit of HBV DNA assays was different across studies.

Figure 1. Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers. *Persistently or intermittently. °°HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis. Reproduced from EASL 2017.[91]



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

What you need to know to accompany Manuscript # CGH-D-21-00985

Backgound: The management of chronic hepatitis B infection is complex due to its natural history, which includes fluctuating viral replication and associated hepatic dysfunction. This complicates decisions about antiviral therapy.

Findings: A group of North American hepatologists met to provide guidance on the management of chronic hepatitis B infection based on the available literature and expert opinion.

Implications for patient care: Treatment decisions in chronic hepatitis B are based on a number of considerations including level of viral replication, hepatocellular dysfunction, and histological severity of disease.