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CLINICAL AND SYSTEMATIC REVIEWS

Treatment of Hepatitis B: A Concise Review

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INTRODUCTION

Chronic infection with hepatitis B virus (HBV) affects 400 million people worldwide, including at least 1.25 million in the United States. Those who develop chronic hepatitis B die, on average, 22 years earlier compared with those without HBV[1] owing to complications of cirrhosis, hepatocellular carcinoma, and liver failure. The burden of HBV is expected to grow in the face of immigration patterns into the United States from highly endemic countries.

Despite the approval of several anti-viral agents, very few patients are actually on treatment.[2–5] There are many possible reasons for this, including the need for lifelong treatment, lack of education and awareness of the disease in largely immigrant, non-English-speaking groups, under screening for the condition in primary care settings, and concerns regarding the requirement for liver biopsies to determine the need for treatment in many cases. Guidelines for hepatitis B treatment have also issued variable recommendations for the treatment of some phases of the disease,[6–9] which can lead to confusion for practitioners. In this review, we provide practical recommendations for both primary care doctors and subspecialists on who should be treated for hepatitis B and how.

The viral life cycle. Hepatitis B virus (HBV), a hepadnavirus, is a partially double-stranded DNA virus, composed of a nucleocapsid core (HBcAg), surrounded by an outer envelope containing the surface antigen (HBsAg) (Figure 1). The viral DNA contains four major open reading frames:

1. The precore/core gene, coding for the nucleocapsid protein and the precore protein (hepatitis B e antigen (HBeAg)).
2. The polymerase gene, coding for the reverse transcriptase/HBV polymerase.
3. The PreS1/L, PreS2/M, and Surface/S genes, coding for the three envelope proteins.
4. The X gene, coding for the regulatory X protein.[10]

The life cycle of HBV is complex. The virus enters the hepatocyte by binding to a receptor on the cell surface—the sodium taurocholate cotransporting polypeptide, a bile acid transporter.[11–13] After uncoating of the viral nucleic acid, the viral genomic DNA is transferred to the cell nucleus and the partially double-stranded viral DNA is then transformed into covalently closed circular DNA (cccDNA), a highly stable intermediate that serves as a template for transcription of viral mRNAs, including the pregenomic RNA. The pregenomic RNA serves as template for translation of viral proteins, including the surface antigen, nucleocapsid, and polymerase proteins. Taken together with the nucleocapsid and polymerase proteins, the HBV pregenomic RNA is encapsidated in the virus core particle. The first step is reverse transcription and first-strand cDNA synthesis, catalyzed by the HBV polymerase—the site of action of oral anti-HBV nucleoside/nucleotide analog (NA) agents. The next step is second-strand DNA synthesis to generate a partially double-stranded viral DNA genome. The HBV polymerase lacks proofreading activity; thus, mutations of the viral genome are frequent and result in the coexistence of genetically distinct viral species in infected individuals (quasispecies). Nucleocapsids associated with the partially double-stranded HBV DNA can then either re-enter the hepatocyte nucleus to replenish the pool of cccDNA or be enveloped for secretion as complete virions via the endoplasmic reticulum. After budding into the ER lumen, the envelope proteins are secreted from the cell either as non-infectious subviral particles (HBsAg) or incorporated into infectious virions known as Dane particles.

The persistence of the highly stable cccDNA accounts for the challenge in eradicating chronic HBV. In addition, error-prone replication of the HBV genome and generation of mutants in the precore region (precore mutants) are additional contributors to persistence of hepatitis B infection.

HBV proteins can also target key immune cells to circumvent host anti-viral immunity. Adaptive immune responses to HBV are blunted in CHB subjects when compared with those who have resolved acute infection. Studies have demonstrated that T cells responding to HBV antigens from these subjects have an exhausted phenotype and are less responsive to HBV antigens.[14]

Chronic hepatitis B has a complicated natural history with three identified phases. The immune-tolerant phase is characterized by high HBV DNA (usually >1 million IU/ml)

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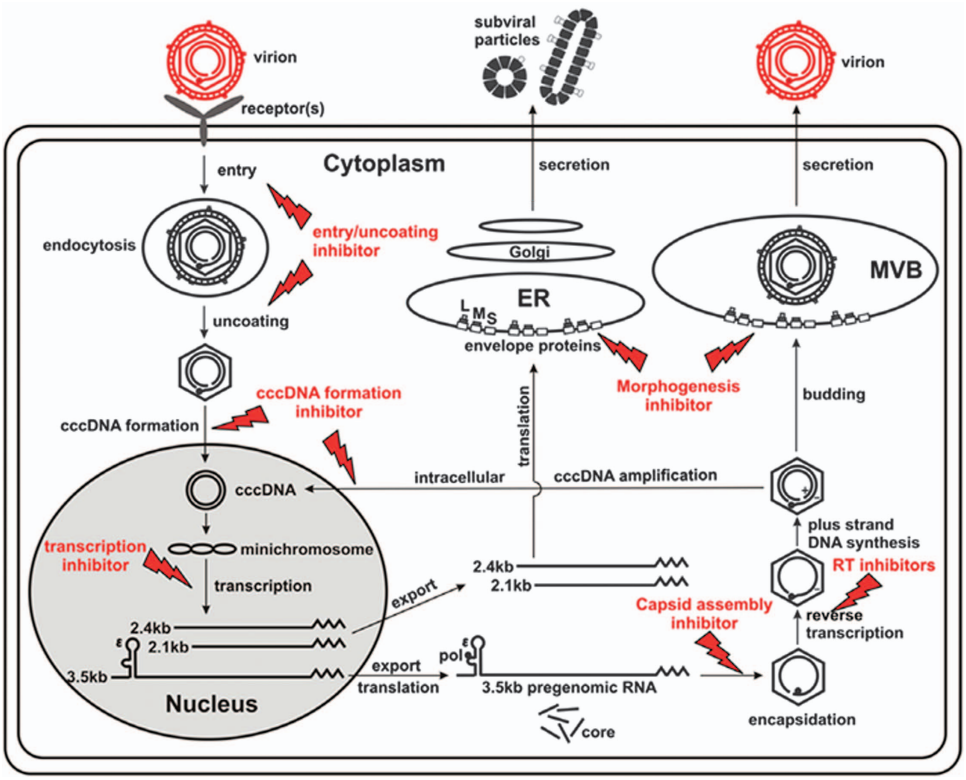

Figure 1 Hepatitis B virus (HBV) life cycle showing novel approaches for viral targets.[94] The HBV life cycle can be grouped into six different targetable steps: (1) entry/uncoating, (2) covalently closed circular DNA (cccDNA) formation, (3) POL/RT inhibitors, (4) capsid assembly, (5) cccDNA transcript and (6) morphogenesis. CsA, cyclosporine A; DSS, disubstituted sulfonamide; ER, endoplasmic reticulum; MVB, multivesicular body; POL, HBV DNA polymerase; RT, reverse transcription.

and normal alanine aminotransferase (ALT) with minimal liver disease. This phase is thought to occur most frequently in persons who are infected perinatally. The immune-active phase is marked by high HBV DNA and elevated ALT levels with active liver inflammation. Finally, the inactive phase is associated with low HBV DNA levels (<2,000 IU/ml) and normal ALT with minimal liver inflammation and fibrosis.

Initial management of hepatitis B infection. In most immunocompetent adults, acute HBV infection is self-limiting and management is supportive. For those with chronic infection, initial management should include a complete history and physical examination to assess for signs of cirrhosis, alcohol and metabolic risk factors, and family history of hepatocellular carcinoma. Routine laboratory tests should include assessment of liver disease activity and function (complete blood count, aspartate aminotransferase, ALT, total bili, alkaline phosphatase, albumin, international normalized ratio), markers of HBV replication (HBeAg/anti-HBe, HBV DNA quantitation), tests for coinfection with HCV, HDV, and HIV, and assessment of HAV immunity to determine need for vaccination. Patients should be educated on measures to prevent transmission and prevention of further liver damage (e.g., limiting alcohol intake and medications or supplements that could be hepatotoxic) and the importance of long-term monitoring, particularly with regard to the risk for hepatocellular carcinoma. Patients older than 40 years, with cirrhosis, or with a family history of hepatocellular carcinoma should undergo ultrasonography and α-fetoprotein testing every 6 months.[6]

The main aim of the anti-viral therapy are to decrease morbidity and mortality by suppressing HBV replication and hepatic inflammation and preventing progression to cirrhosis and hepatocellular carcinoma. Anti-viral treatment results in normalization of ALT, suppression of HBV DNA, possible loss of HBeAg and seroconversion to anti-HBe, possible loss of HBsAg and seroconversion to anti-HBs, and histological improvements with decreased inflammation and fibrosis.

The Food and Drug Administration has approved seven anti-viral drugs for the treatment of chronic HBV: interferon-a2b, pegylated interferon-a2α (peg-IFN), lamivudine (LAM), adefovir, entecavir (ETV), telbivudine, and tenofovir (TDF). Of these, the most commonly used first-line agents are peg-IFN, TDF, and ETV.

Who should be treated?

Immune-active, HBeAg+, chronic hepatitis B. Patients with hepatitis B e antigen-positive (HBeAg+) chronic hepatitis B, who have ALT levels >2 times normal with HBV DNA >20,000 IU/ml, should be considered for treatment (Table 1 and Figure 2). These recommendations are based on AASLD (American Association for the Study of Liver Diseases) and APASL (Asian Pacific Association for the Study of the Liver) guidelines. The EASL guidelines recommend considering therapy if HBV DNA is >2,000 IU/ml, ALT is greater than upper limit of normal, and there is moderate to severe active

necroinflammation and/or at least moderate fibrosis on liver biopsy. Initiation of treatment should be delayed for up to 6 months in persons with compensated liver disease to determine whether spontaneous HBeAg seroconversion occurs. Treatment initiation with TDF, ETV, or peg-IFN are preferred.[6]

Immune-active, HBeAg– chronic hepatitis B. Patients with hepatitis B e antigen-negative (HBeAg –) chronic hepatitis B (serum HBV DNA >2,000 IU/ml and elevated ALT >2 times normal) should be considered for treatment (Figure 3). For HBeAg – patients with lower HBV DNA levels (2,000–20,000 IU/ml) and borderline normal or minimally elevated ALT levels, liver biopsy should be considered and treatment initiated if there is moderate/severe inflammation or significant fibrosis on biopsy. Several studies have shown that patients with normal ALT can have substantial liver fibrosis, when ALT concentrations are at the high end of the normal range, HBV DNA concentrations are high (>10,000 IU), or when they are older than 40 years.[15] Treatment with TDF, ETV, or peg-IFN are preferred.[6]

Compensated cirrhosis. Treatment should be considered for any patient with cirrhosis and detectable HBV DNA regardless of ALT levels. Patients with compensated cirrhosis are best treated with NAs because of the risk of hepatic decompensation

Table 1 Who should be treated for hepatitis B?

Indication for treatment	Treatment strategy	Treatment end points/duration
Immune active, e Ag+, ALT>2× normal, HBV DNA>20,000 IU/ml	Peg-IFN, TDF or ETV	Peg-IFN usually 48–52 weeks, NAs variable. Continue until HBeAg seroconversion and undetectable serum HBV DNA and at least 6 months of additional treatment after appearance of anti-HBe.
Immune active, e Ag – , ALT>2x normal, HBV DNA >2,000 IU/ml	Peg-IFN, TDF or ETV	Peg-IFN usually 48–52 weeks, NAs variable. Continue until HBsAg clearance.
Compensated cirrhosis	TDF or ETV	Lifelong therapy.
Decompensated cirrhosis	TDF or ETV	Lifelong therapy.
Acute/symptomatic hepatitis B or fulminant hepatitis B	ETV is preferred	Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation.
Prevention of reactivation (in HBV carriers who require immunosuppressive or cytotoxic therapy)	TDF or ETV before the start of chemotherapy or immunosuppressive therapy	If baseline HBV DNA <2,000 IU/ml, continue treatment for 6 months after completion of chemo/immunosuppression. If high baseline DNA >2,000 U/ml, continue treatment until treatment end points reached as in immunocompetent patients.
Pregnant mothers with high viral load	TDF preferred (telbivudine or LAM also effective)	Initiate therapy at 28–30 weeks gestation and monitor for flares if stopping therapy after delivery.
HBV/HIV coinfection	TDF+(emtricitabine or LAM) or ETV+fully suppressive ARV regimen	Lifelong unless the patient has achieved HBeAg seroconversion and has completed an adequate course of consolidation treatment.

ALT, alanine aminotransferase; ARV, antiretroviral; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAM, lamivudine; NA, nucleotide analog; peg-IFN, pegylated interferon-a2α; TDF, tenofovir.

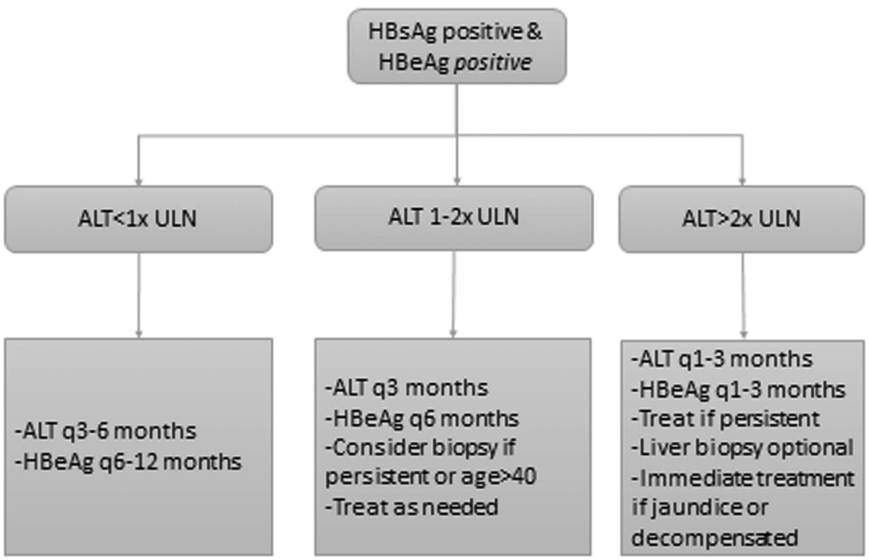

Figure 2 Treatment algorithm for patient with chronic hepatitis B and positive HBeAg. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; ULN, upper limit of normal. Figure Adapted from Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; 45: 507–539.

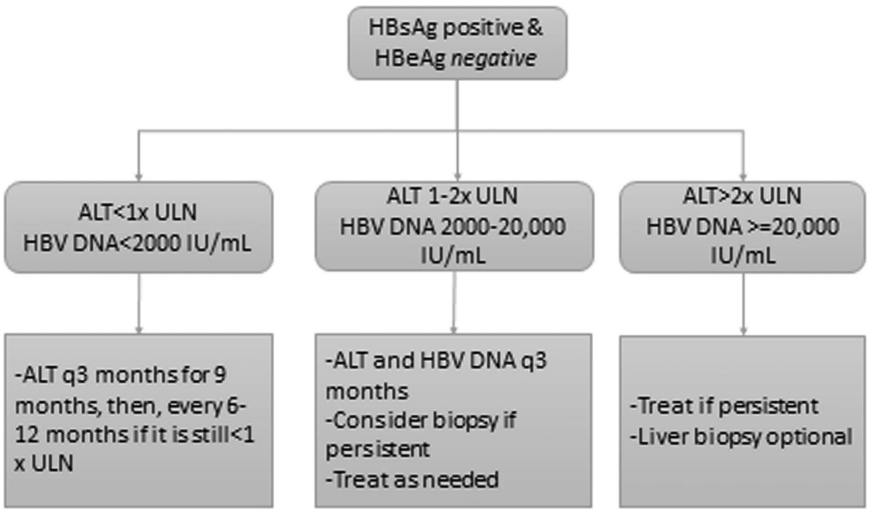

Figure 3 Treatment algorithm for patient with chronic hepatitis B and negative HBeAg. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen HBV, hepatitis B virus; ULN, upper limit of normal. Figure adapted from Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007; 45: 507–539.

associated with IFN-related flares of hepatitis. In view of the need for long-term therapy, TDF or ETV is preferred.

Decompensated cirrhosis. Treatment should be promptly initiated with an NA that can produce rapid viral suppression with low risk of drug resistance. At the time of drafting of the last AASLD guidelines in 2009, clinical data documenting the safety and efficacy of TDF and ETV in patients with decompensated cirrhosis was lacking. Since then, multiple studies have confirmed safety and efficacy of these agents in this subgroup.[16–19] Thus, TDF and ETV are the treatments of choice in decompensated cirrhotics with HBV. Treatment should be coordinated with a transplant center. IFN/peg-IFN should not be used in patients with decompensated cirrhosis.

Acute/symptomatic hepatitis B or fulminant hepatitis B. Since over 95% of immunocompetent adults with acute hepatitis B recover spontaneously, treatment is not recommended in most cases. Treatment is indicated only for patients with fulminant hepatitis (defined by the rapid development of acute liver injury with severe impairment of synthetic function and hepatic encephalopathy) and those with protracted, acute severe hepatitis persisting for >4 weeks.

In severe acute HBV with prolonged prothrombin time and increased bilirubin, interferon failed to be effective,[20–23] but NAs have been shown to be effective. A randomized controlled trial of 80 patients found that early treatment with LAM leads to a greater decrease in HBV DNA levels, better clinical improvement, and mortality improvement but with a lower HBsAg and HBeAg seroconversion rate.[24] Multiple randomized studies have produced results consistent with this randomized controlled trial.[25–28] Furthermore, most patients who died or required transplantation despite LAM therapy were started on LAM at advanced stages compared with those who survived. These findings suggest that prompt and timely anti-viral therapy is crucial.

Multicenter double-blind randomized trials to compare the efficacy between LAM and ETV or even TDF in acute severe HBV cases are lacking because of the difficulty of accruing cases. However, given the safety and efficacy of these agents in other cases of acute hepatitis B (e.g., reactivation in patients receiving chemotherapy),[29–37] the AASLD recommends treatment with an NA for fulminant and acute/symptomatic hepatitis B. In one prospective randomized trial of TDF vs. placebo in 27 patients with spontaneous reactivation of chronic hepatitis B who presented with acute on chronic liver failure, the 3-month probability of survival was higher in the TDF group compared with that in the placebo group (57% vs. 15%, $P=0.03$).[33] Because of their anti-viral potency, ETV or TDF are the preferred agents for the treatment of acute or fulminant hepatitis B. Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. IFN is contraindicated and has not been shown to be effective in fulminant hepatitis B.

Prevention of reactivation (hepatitis B carriers who require immunosuppressive or cytotoxic therapy). HBV persists in the body of all patients with infection, even those with evidence of serological recovery. Thus, individuals with a history of HBV infection who receive immunosuppressive therapy are at risk for HBV reactivation and a flare of their HBV disease with resultant increased serum aminotransferase levels, fulminant hepatic failure, and possible death.[38] For example, in an analysis of HBV reactivation in over 450 B-cell lymphoma patients treated with rituximab from the Asia Lymphoma Study Group, HBV reactivation was found in 27.8% of HBsAg+ patients. The frequency of reactivation was much lower in those receiving anti-viral prophylaxis compared with those who did not (22.9% vs. 59.1%; $P<0.001$).[39] Another randomized controlled trial showed that anti-viral prophylaxis can potentially prevent rituximab-associated HBV reactivation in patients with lymphoma and resolved hepatitis B (i.e., anti-HBc+, HBsAg $-$).[40]

Thus, to prevent reactivation of HBV replication, which can lead to hepatitis and liver failure, prophylactic anti-viral therapy with ETV or TDF is recommended in HBsAg+ patients who will be receiving anti-CD20 therapy (e.g., rituximab), hematopoietic cell transplantation, high-dose glucocorticoids (e.g., ≥ 20 mg per day for at least 4 weeks), the anti-CD52 agent alemtuzumab, cytotoxic chemotherapy without glucocorticoids, anti-TNF therapy, and antirejection therapy for solid

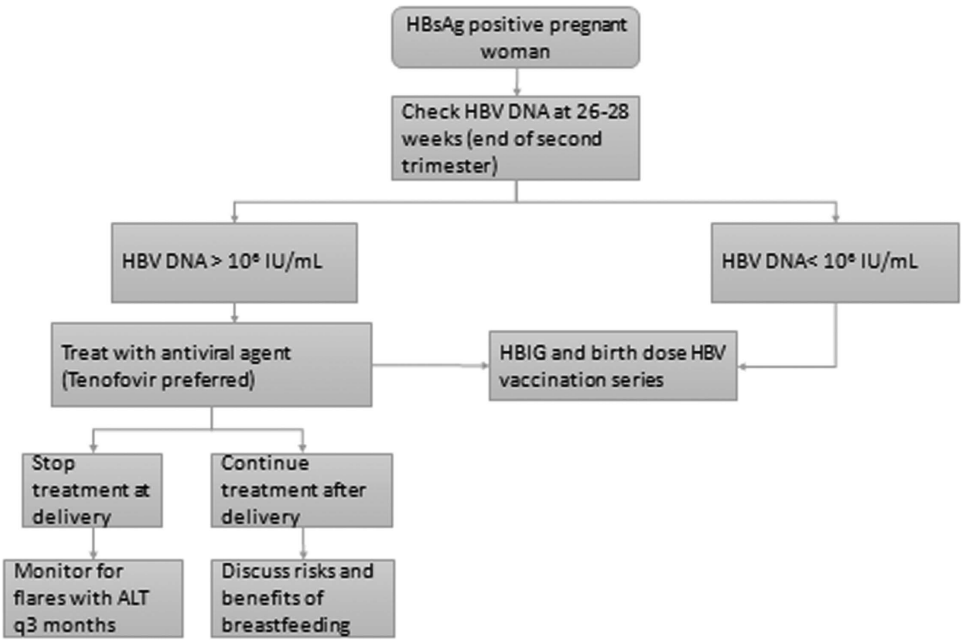

Figure 4 Algorithm for management of pregnant mothers with high HBV viral load in pregnancy. ALT, alanine aminotransferase; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus DNA level.

organ transplants. Prophylactic anti-viral therapy is also recommended for patients who are HBsAg – and anti-HBc+ and who will be receiving potent immunosuppressive therapies such as rituximab or myeloablation before hematopoietic stem cell transplantation, to prevent reappearance of HBsAg. HBsAg+ individuals are at low risk of reactivation if they receive methotrexate or azathioprine and thus in these low-risk patients prophylactic therapy is not indicated but they should be monitored for possible reactivation and treated with an anti-viral should this occur.[41]

Pregnant mothers with high viral load in the third trimester. Infants born to mothers who are HBeAg+ with concomitant high HBV DNA levels have a substantial risk of infection despite passive–active immunoprophylaxis. In one retrospective study of over 4,000 infants born to HBsAg+ mothers in the United States, the rates of infection were 3.37 per 100 births in HBeAg+ mothers and 0.04 for HBeAg – mothers.[42] The rates of failure of immunoprophylaxis have been shown to correlate with the levels of viral load.[43] Telbivudine or LAM use in late pregnancy from 28 weeks gestation to 4 weeks postpartum has been shown to safely reduce perinatal transmission of hepatitis B from highly viremic HBeAg+ mothers (HBV DNA >6 log 10 copies per ml) to their infants.[37,44–47] ALT flares were observed in 17.1% of treated mothers vs. 6.3% of untreated mothers ($P<0.001$).[37] In another retrospective study, TDF during the second and third trimester in HBeAg+ women with HBV DNA $>10^7$ copies per ml reduced perinatal transmission of HBV, with no adverse events reported in mothers or infants.[48]

Given these findings, the AASLD recommends the consideration of NAs with favorable resistance and safety profiles, such as TDF, during pregnancy to reduce the risk of mother-to-infant transmission. However, there is no consensus on the cutoff HBV DNA concentration for recommending anti-viral therapy and when anti-viral therapy should be started. At our institution, we have used the algorithm shown in Figure 4.

HBV/HIV coinfection. It is estimated that up to 5 million of the 33 million HIV-infected persons worldwide in 2009 have concomitant HBV infection. Recent discoveries in the pathophysiology of HIV in the liver has found that it may contribute to a more rapid progression of liver fibrosis, especially when there is underlying chronic hepatitis infection.[49] Furthermore, because of impaired immune control attributed to HIV infection, the rate of acute infections evolving into chronic HBV is five times higher in HIV compared with that in non-HIV-infected adults.[50] Coinfected patients have an excess risk of all-cause mortality as high as 36% compared with HIV-monoinfected patients[51] and 10 times higher risk of dying from liver-related causes compared with HIV- or HBV-monoinfected patients.[52] HIV thus accelerates HBV liver disease and administration of successful antiretroviral therapy has been demonstrated to slow fibrosis progression and to decrease liver disease-associated mortality.[53–55] Given recent changes designed to initiate antiretroviral therapy earlier regardless of HIV DNA or CD4 levels,[56] those with coinfection should be treated with agents active against both HBV and HIV. The recommended agents include TDF with either emtricitabine or LAM.[56]

If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is ETV in addition to a fully suppressive antiretroviral regimen (to prevent selection of the M184V mutation that confers HIV resistance to LAM and emtricitabine), or peg-IFNα monotherapy for 48 weeks, particularly in patients with HBV genotype A, high ALT, and low HBV DNA level.[56] When HAART (highly active antiretroviral therapy) regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV, unless

the patient has achieved HBeAg seroconversion and has completed an adequate course of consolidation treatment. Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV.

Who should NOT be treated?. Patients in the immune-tolerant state in whom HBV DNA levels are very high ($>10^8$ IU/ml), HBeAg is positive, and ALT levels are normal should not be treated. Liver biopsy may be considered in patients with fluctuating or minimally elevated ALT levels, especially in those above 40 years of age. Treatment should be initiated if there is moderate or severe necroinflammation or significant fibrosis on liver biopsy. However, it should be acknowledged that there may be theoretical benefits to treating patients in the immune-tolerant stage such as decreasing accumulation of cccDNA and abrogating infection early. Clinical trials are needed in this population to help address this question.

In addition, patients in the inactive carrier state (HBsAg+, HBeAg – , HBeAb+) in whom both HBV DNA levels are very low ($<$2,000 IU/ml) or undetectable and ALT levels are normal should not be treated but rather monitored on a biannual basis with ALT and HBV DNA levels, as well as with hepatocellular carcinoma screening in high-risk patients.

Finally, those who are HBeAg – with an intermediate viral load (between 2,000 and 20,000 IU/ml) and borderline normal or minimally elevated liver function tests should not be treated but should be considered for liver biopsy and treated if there is moderate or severe necroinflammation or significant fibrosis.

Selection of anti-viral agents. Peg-IFN, ETV, or TDF are recommended as first-line monotherapy by all major guidelines in patients with CHB or compensated cirrhosis (Table 2).[6,7,57] The choice of first-line monotherapy should be based on several factors including host, virus, and drug-related factors. Consideration should be given to the safety and efficacy of the treatment, risks of drug resistance, costs of the treatment (medication, lab tests, and clinic visits), as well as patient and provider preferences, and for women—when and whether they plan to start a family. The pros and cons of the approved first-line treatments are summarized in Table 2.

IFN monotherapy. Peg-IFN has dual immunomodulatory and anti-viral activity. Although the efficacy is not substantially different, peg-IFN is superior to standard IFN – because of its more convenient dosing schedule with once weekly subcutaneous injections. The most favorable candidates for peg-IFN are those with low HBV DNA levels, high ALT and HBV genotype A or B rather than C or D, and those without advanced disease. Advantages of peg-IFN include finite duration of therapy, higher rates of anti-HBe and anti-HBs seroconversion with 12 months of therapy, and the absence of resistance.[58–60] Disadvantages include inferior tolerability with many side effects (including flu-like symptoms, fatigue, anorexia and nausea, weight loss, hair loss, emotional lability and depression, bone marrow suppression, worsening of autoimmune disease, and hypothyroidism), need for weekly subcutaneous injections, and only moderate anti-viral effect. Contraindications to peg-IFN include a history of suicidal tendency, uncontrolled psychiatric or autoimmune conditions, severe leukopenia or thrombocytopenia, concurrent severe systemic disorders, decompensated cirrhosis, and pregnancy.

NA monotherapy. TDF and ETV are both NAs that inhibit the dual function HBV DNA polymerase. TDF is administered orally at a dose of 300 mg daily, whereas ETV is administered orally at a dose of 0.5 mg daily in those with no prior LAM treatment and 1.0 mg daily in those who are refractory/resistant to LAM. The other second-line agents, LAM, adefovir, and telbivudine are not recommended because of their limited potency and lower barrier to resistance.

Overall, all NAs have an excellent safety profile across a wide spectrum of persons with chronic hepatitis B and any side effects are infrequent.[61] Adverse events associated with TDF are rare and include renal insufficiency, Fanconi's syndrome, proximal tubular acidosis, and decreased bone density, particularly in children, in whom the drug is contraindicated.[61–65] If TDF is used in patients with renal insufficiency, the dose must be adjusted for creatinine clearance. Adverse events with ETV are mild to moderate and include headache, upper respiratory tract infection, cough, nasopharyngitis, fatigue, and upper abdominal

Table 2 Comparison of approved first-line treatments for chronic hepatitis B

	Peg-IFN	ETV	TDF
Indications			
HBeAg+, normal ALT	Not indicated	Not indicated	Not indicated
HBeAg+ chronic hepatitis	Indicated	Indicated	Indicated
HBeAg – chronic hepatitis	Indicated	Indicated	Indicated
Duration of treatment			
HBeAg+ chronic hepatitis	12 months	$\geq$1 year until e Ag seroconversion	$\geq$1 year until e Ag seroconversion
HBeAg – chronic hepatitis	1 year	$>$1 year, likely lifelong until HBsAg clearance	$>$1 year, likely lifelong until HBsAg clearance
Route	Subcutaneous	Oral	Oral
Side effects	Many	Negligible	Negligible
Drug resistance	Not applicable	1.2% up to year 5	0% up to year 5
Cost	Moderate as limited duration of therapy	High especially with lifelong therapy	High especially with lifelong therapy

ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; peg-IFN, pegylated interferon-a2α; TDF, tenofovir.

pain.[66] Severe lactic acidosis has been reported in a case series of patients with advanced cirrhosis (MELD score ≥ 20) and thus ETV should be used with caution in patients with decompensated liver disease. ETV should also be adjusted for creatinine clearance.[67]

TDF or ETV are the only therapeutic options in patients with decompensated liver disease, in patients undergoing immunosuppressive treatment, and in patients with other contraindications to or unwilling to receive peg-IFN. In HBeAg + patients, treatment can be discontinued after a 12-month consolidation period following documented HBeAg seroconversion with undetectable HBV DNA. Close monitoring for relapse is nonetheless required following therapy discontinuation. In HBeAg – patients, long-term therapy is required until HBsAg loss is documented. Advantages of NAs include potent anti-viral effect (viral suppression in $>95\%$ of patients over 5 years with fibrosis regression and prevention of cirrhosis),[68–70] good tolerability with minimal side effects, and oral administration. Disadvantages include indefinite duration of therapy, particularly in HBeAg – patients, and risk of resistance along with unknown long-term safety. Fortunately, the risk of drug resistance has thus far been minimal (1.2% with ETV after 6 years and 0% with TDF after 5 years).[70–72]

Combination therapy. There is no added benefit from *de novo* combination therapy with two NAs. In addition, the combination of peg-IFN and NAs has not yielded higher rates of off-treatment serological or virological responses and is not currently recommended by AASLD.[73,74] However, a recent randomized controlled trial has shown that a significantly greater proportion of patients receiving TDF plus peg-IFN for 48 weeks had HBsAg loss (9.1%) compared with those receiving TDF (0%) or peg-IFN alone (2.8%) or a shorter course of peg-IFN (16 weeks) with 48 weeks of TDF (2.8%).[75] Although further study is required, consideration may be given to a combination approach to enhance HBsAg loss rates (Table 3).

Duration of therapy. In HBeAg+ chronic hepatitis B, treatment should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV DNA and completed at least 12 months of additional consolidation treatment after appearance of anti-HBe.[73,76] The optimal duration of consolidation therapy after HBV seroconversion is not known, but studies show better outcomes with longer duration of consolidation.[77] In HBeAg – chronic hepatitis B, treatment should be continued until the patient has achieved HBsAg clearance.

Lifelong treatment is recommended for all patients with recurrent hepatitis B after liver transplantation and in all cirrhotics, both compensated and decompensated, due to concerns for potential reactivation and death when treatment is stopped.[73,76,78]

In addition, there appears to be an association between quantitative level of HBsAg and relapse after anti-viral therapy for chronic HBV infection.[79]

All guidelines recommend peg-IFN for 48–52 weeks in both HBeAg+ and HBeAg – patients. Irrespective of the underlying liver disease and the treatment used, patients need to be closely monitored for viral relapse and ALT flares when treatment is stopped, so that treatment can be reinitiated promptly.[80]

Prevention of HBV. Prevention is far simpler than treatment, particularly in the case of HBV, which requires lifelong treatment in most cases. Besides avoiding transmission from infected people via blood supply screening and universal precautions, vaccination is the most important means of reducing the global burden of disease. Vaccination in adults is recommended in high-risk groups at risk for infection by sexual exposure (e.g., men who have sex with men, people with multiple sexual partners, those seeking evaluation and treatment for sexually transmitted disease), or in persons at risk for infection by percutaneous or mucosal exposure to blood (e.g., injection drug users, household contacts of HBsAg+ patients, patients on hemodialysis, institutionalized patients, health-care workers, and public safety workers). Vaccination is also recommended in international travelers to regions with high or intermediate endemicity for HBV infection, persons with chronic liver disease, and with HIV infection.[81] Postexposure prophylaxis with the hepatitis B vaccine and/or hepatitis B immune globulin is also recommended for health-care workers not immune to HBV virus. Vaccination in children is recommended as part of the regular schedule of childhood immunizations. Thirty-five years after the availability of a safe and effective vaccine, universal vaccination of all children is finally available now in 184 of 196 countries in the world. Global vaccine coverage with all three doses of vaccine is estimated at 82%.[82]

How do we cure HBV?. A functional cure for HBV poses unique challenges given the stability and latency of cccDNA, along with the fact that replication of HBV DNA is uncoupled from protein (HBsAg) synthesis. In this regard, polymerase inhibitors can bring about DNA suppression without the loss of HBsAg. Because HBsAg can subvert the host immune response secretion, a successful functional cure for HBV (HBsAg loss, sAb seroconversion) will likely require a multipronged, multimechanism approach, including potential approaches to target both the virus and the host.[83] An examination of all of the novel approaches for viral targets is beyond the scope of this review, but we will briefly consider the major approaches below.

Direct virologic approaches include HBV capsid inhibitors, small interfering RNA targeted to viral mRNA, and cccDNA targeting strategies. The HBV capsid is polyfunctional, as it is essential for HBV genome packaging, reverse transcription, intracellular trafficking, maintenance of cccDNA, and inhibition of host innate immune responses. Thus, it is an attractive target for HBV therapies. Several capsid inhibitors being evaluated include NVR 3-778, GLS-4, and phenylpropenamide derivatives.[84] Small interfering RNAs directed against conserved HBV RNA sequences could knock down HBV RNA, proteins, and DNA levels. To this end, the HBV small interfering RNA ARC-520 is currently being evaluated in a phase 2 trial. cccDNA targeting strategies include prevention of cccDNA formation (e.g., disubstituted sulfonamide DSS), elimination of cccDNA by inhibition of viral or cellular factors contributing to cccDNA stability/formation (e.g., APOBEC3A, B agonists) or physical elimination of cccDNA (e.g., zinc-finger, transcription activator-

Table 3 Rates of seroconversion across different types of therapy[73,75]

	Peg-IFN (%)	ETV (%)	TDF (%)	Combination therapy (TDF+peg-INF for 48 weeks) (%)
HBeAg positive				
HBeAg seroconversion	29–36	21–22	21	23.1% (at 48 weeks) 25.0% (at 72 weeks)
HBsAg loss	2–7 (at 6 months) 11 (at 3 years)	2–3 (at 1 year) 4–5 (at 2 years)	3 (at 1 year) 8 (at 3 years)	6.5 (at 48 weeks) 9.3 (at 72 weeks)
HBeAg negative				
HBsAg loss	4 (at 6 months) 6 (at 3 years)	0–1 (at 1 year)	0 (at 1 year)	5.1 (at 48 weeks) 5.1 (at 72 weeks)

ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; peg-IFN, pegylated interferon-a2α; TDF, tenofovir.

like effector nucleases or TALEN, CRISPR/Cas9 nucleases), and silencing of cccDNA transcription.[84–87]

Indirect acting host target inhibitors include entry inhibitors, epigenetic modifiers (sirtuin inhibitors such as sirtinol), morphogenesis inhibitors (glucosidase inhibitors), and secretion inhibitors (Rep 9AC). A promising target is the inhibition of the sodium taurocholate cotransporting polypeptide receptor by which HBV/HDV enters hepatocytes (e.g., agents include myrcludex B, cyclosporine A, and ezetimibe),[12] although there may be limitations in terms of the clinical implications of inhibiting bile salt transport.

Immunomodulatory approaches include targeting innate and adaptive immune responses. Innate targets include IFN-α, TLR7 agonists, and STING agonists.[88,89] Adaptive immune agents include therapeutic T-cell vaccines and PD-1/PD-L1 antagonists. Targeting the T-cell response to HBV is important because, in contrast to HCV, there is a robust T cell (CTL) that spontaneously clears natural HBV infection with high frequency in adults. Chronic HBV is associated with attenuated CTL responses (high PD-1/PD-L1 expression) and thus inhibitors of PD-1/PD-L1 could reawaken these vigorous responses. A combination of these inhibitors with directly acting anti-virals against HBV could have merit, although caution will need to be exercised regarding the risk of triggering autoimmunity and hepatic flares.[90–93]

Conclusion

Chronic infection with HBV remains a major public health problem. Treatment of hepatitis B is indicated in immune-active patients, in those with cirrhosis or fulminant hepatitis B, in prevention of reactivation in HBV carriers who require immunosuppressive or cytotoxic therapies, in pregnant mothers with high viral load, and in HIV/HBV coinfection. Most of the effective anti-viral agents that are available require indefinite treatment; thus, efforts are being devoted to approaches to enhance functional cure rates and permit cessation of therapy. A true virologic cure for HBV is much more elusive, in contrast to HCV, because of its highly stable latent form (HBV cccDNA). However, a rich array of viral and host targets is being explored for manipulation. It is highly likely that a multimodality approach will be essential for the achievement of a functional and virologic cure.

CONFLICT OF INTEREST

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