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ORIGINAL ARTICLE

The Management of Chronic Hepatitis B in Asian Americans

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Abstract Hepatitis B virus (HBV) infection is common with major clinical consequences worldwide. In Asian Americans, the HBsAg carrier rate ranges from 7 to 16%; HBV is the most important cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Patients are first diagnosed at different stages of clinical disease, which is categorized by biochemical and virologic tests. Patients at risk for liver complications should be identified and offered antiviral therapy. The two antiviral agents recommended for first-line treatment of chronic hepatitis B (CHB) are entecavir and tenofovir. The primary goal of therapy is sustained suppression of viral replication to achieve clinical remission, reverse fibrosis, and prevent and reduce progression to end-stage liver disease and HCC. Asian patients with chronic hepatitis, either HBeAg-positive or -negative, with HBV DNA levels $>10^4$ copies/mL (>2,000 IU/mL) and alanine aminotransferase (ALT) values above normal are candidates for antiviral therapy. HBeAg-negative patients with HBV DNA $>10^4$ copies/mL (>2,000 IU/mL) and normal ALT levels but who have either serum albumin $\leq$3.5 g/dL or platelet count $\leq$130,000 mm^3, basal core promoter mutations, or who have first-degree relatives with HCC should be offered treatment. Patients with cirrhosis and detectable HBV DNA must receive antiviral therapy. Considerations for treatment include pregnant women with high viremia, coinfected patients, and those requiring immunosuppressive therapy. In HBsAg-positive patients with risk factors, lifelong surveillance for HCC with alpha-fetoprotein testing and abdominal ultrasound examination at 6-month intervals is required. These recommendations are based on a review of relevant literature and the opinion of a panel of Asian American physicians with expertise in hepatitis B treatment.

Keywords Hepatitis B · Clinical features · Antiviral therapy

Abbreviations

HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
Anti-HBe	Antibody to HBeAg
Anti-HBs	Antibody to HBsAg
Anti-HBc	Antibody to hepatitis B core antigen
PC	Precore
BCP	Basal core promoter

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HBV DNA	Hepatitis B virus DNA
CHB	Chronic hepatitis B
ALT	Alanine aminotransferase
HAI	Histology activity index
HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus

Introduction

Asians are the ethnic group with the highest prevalence of hepatitis B in the United States. In this report, the epidemiology and clinical outcomes of chronic hepatitis B infection were derived from reports from Asian countries where Hepatitis B virus (HBV) is endemic. The recommendations for treatment were based on a natural history study in a predominantly Asian population in the USA in which patients who progressed to liver related complications were identified by biochemical and virologic tests early in the course of their disease. It is anticipated that the information provided in this manuscript will assist physicians involved in the day to day management of Asian Americans with hepatitis B.

Epidemiology, Natural History, Clinical Stages, and Progression of Disease in Asians

Prevalence of HBsAg

Hepatitis B virus (HBV) infection is common and clinically consequential worldwide. Up to 400 million people are chronic carriers; three-quarters of these individuals are Asian [1, 2]. In endemic countries, an estimated 50 million new cases are diagnosed annually. In the Asian continent, HBV is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) [2, 3].

The HBV carrier rates in Asia have been reported to be as high as 20% in the male population of Guangxi Province, China [4]. HBV carrier rates ranging from 10 to 15% have been reported in Hong Kong, Shanghai, Taipei, Taiwan, and in southeast Asia (Table 1) [2]. A recent study, conducted in China, showed that HBV carrier rates have fallen to 7.2% in regions where hepatitis B vaccination programs had been implemented [5]. In Korea, the HBV carrier rates ranged from 5.0 to 8.6% in the 1970s and 1980s and have subsequently declined to 3.7–5.7% as a result of national vaccination programs [6, 7].

In other parts of Asia, the hepatitis B surface antigen (HBsAg) carrier rates remain high, particularly in countries in which vaccine programs have not yet been implemented. In Japan, the hepatitis B carrier rate is 1.0%—the lowest among all Asian countries. In China, Vietnam, and Korea, up to 80% of patients with chronic hepatitis, 92% with cirrhosis, and 80% with hepatocellular carcinoma, are HBsAg-positive [3, 6, 8–11]. Notably, the HBsAg rates among Asians residing in the USA are similar to rates reported in their countries of origin, especially in first-generation immigrants to the USA (Table 1) [5, 11–13]. The HBsAg prevalence rates in these older Asian American immigrants may actually be higher than the rates in their origin countries where HBV vaccination programs have been implemented [5, 6]. Thus, the disease burden from HBV, including mortality from liver disease progression and development of HCC, is a major health problem among Asian Americans with chronic hepatitis B (CHB) and represents an important challenge to physicians who provide their medical care [14].

Table 1 The prevalence of HBsAg in Asian Americans and in their respective native countries [5, 6, 13]

Ethnicity	Country of origin (%)	USA (%)
Cambodia	7.7–10.8	8–13
China*	7.2	10–17
Hmong	13.8	17
India	1.4–3	1–6
Indonesia	2.5–5	7–10
Japan	0.8	0.6–1.1
Korea*	3.7–5.7	5–11
Laos	NS	10–13
Malaysia	3–5	7–10
Philippines	5–16	4.2–9
Thailand	>8	1.5–10
Vietnam	10–16	6–18

NS not studied or unpublished

* Hepatitis B vaccination programs implemented

Routes of Infection

In Asian countries, perinatal transmission of HBV from mother to newborn infant is the most common route of infection. Without passive-active immunoprophylaxis, up to 90% of infants born to hepatitis B e antigen (HBeAg)-positive mothers, and 10–40% of infants born to HBeAg-negative mothers may become infected [15, 16]. Horizontal transmission in infants and children may occur via HBsAg-positive fathers and from other HBsAg-positive family members. In Asian adults, sexual contact may account for up to 10% of HBV carriers [17]. HBV transmission also occurs at high rates among injection drug users in Asia [17].

The Phases of Chronic Hepatitis B

In Asian patients, the course of CHB infection can be divided into five distinct phases (Fig. 1).

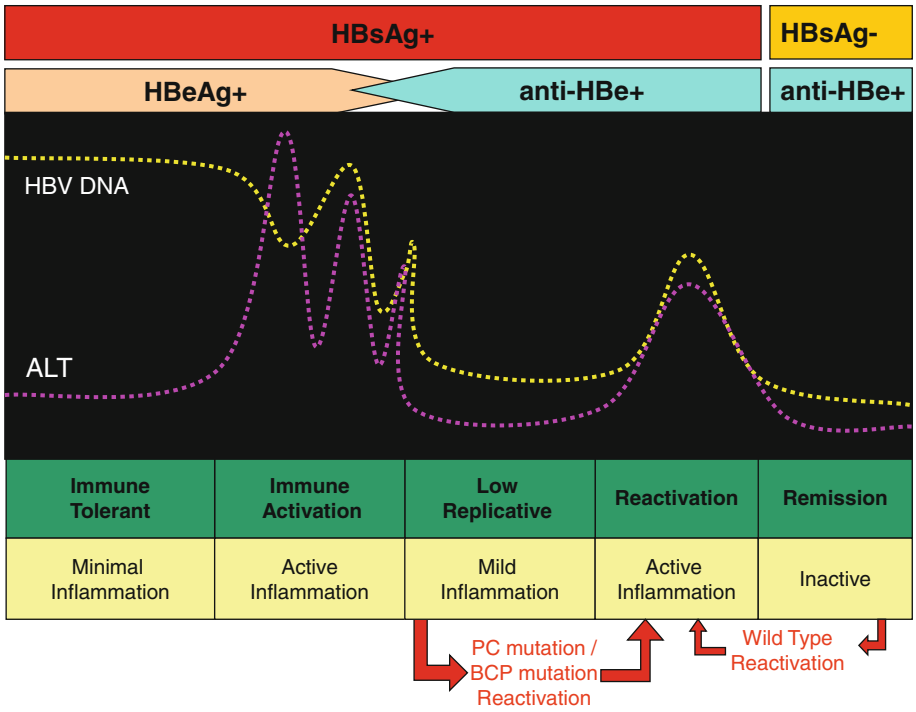


Fig. 1 The five phases of chronic hepatitis B infection. *ALT* alanine aminotransferase, *HBsAg* hepatitis B s antigen, *anti-HBs* hepatitis B s antibody, *HBeAg* hepatitis B e antigen, *Anti-HBe* hepatitis B e antibody, *PC/BCP* precore/basal core promoter

Phase 1: Immune Tolerant

After mother-to-infant transmission during birth (or soon thereafter), patients may enter a phase of immune-tolerant chronic infection characterized by HBeAg positivity, high viremia, and normal serum alanine aminotransferase (ALT) values. This clinically asymptomatic phase may last into the second or third decade of life [18]. Notably, this differs from the pattern seen in Western countries, in which the immune-tolerant phase is rare in adult patients with acute hepatitis B who develop chronic hepatitis [17, 19].

Phase 2: Immune Activation

Patients may subsequently enter into the immune activation phase, which is marked by loss of tolerance to HBV by the host immune system. This HBeAg-positive phase is characterized by elevated ALT values and necroinflammatory changes in the liver. This phase may last months to years with fluctuating ALT and HBV DNA levels and may be accompanied by episodes of clinical exacerbation and remission [20, 21]. Following immune activation, patients may remain HBeAg-positive, enter into the low replicative phase, or progress to HBeAg-negative hepatitis.

Phase 3: Low-Replicative Phase

The immune activation phase may be followed by seroconversion to HBeAg-negativity and appearance of antibody to HBeAg (anti-HBe), which is associated with low levels of serum HBV DNA and normalization of ALT. After a period of time, patients will follow one of two clinical courses. Some patients may become inactive carriers and continue to have persistently normal ALT values and low or undetectable HBV DNA, whereas others may have reactivation of chronic hepatitis [22, 23].

Phase 4: Reactivation

Following the low-replicative phase, patients may experience reactivation of liver disease, referred to as HBeAg-negative chronic hepatitis. This phase is associated with mutations in the precore (PC)/basal core promoter (BCP) regions of the HBV genome, elevation of both serum ALT and HBV DNA levels and recurrent necroinflammation in the liver. In some instances, reversion to HBeAg-positive chronic hepatitis may even occur [23].

Phase 5: Remission

After a number of years, some patients may enter into a remission phase. During this time, there is seroclearance of HBsAg with or without seroconversion to anti-HBs, and low or undetectable levels of HBV DNA in the serum. The remission stage is not considered a "cure" since intracellular covalently closed circular (CCC) DNA is still present. Moreover, reactivation to clinical disease, i.e., HBeAg-positive chronic hepatitis still may occur, especially in patients who require cancer chemotherapy or immunomodulatory agents such as corticosteroids or rituximab, and

in patients receiving bone marrow transplantation. Such reactivation may also occur in antibody to hepatitis B core antigen (anti-HBc)-positive patients who experienced seroclearance of HBsAg. Spontaneous HBsAg clearance in Asian patients occurs at an annual rate of 1–2%, [24] but may range from 5 to 12% in HBV patients who experience virologic and biochemical responses to antiviral therapy [25–28]. However, patients who have HBsAg seroclearance are still at risk for HCC, especially if cirrhosis is present at the time of HBsAg loss [29].

The Clinical Stages of Chronic Hepatitis B

Based on the HBeAg status, ALT and HBV DNA levels at presentation, patients may be classified into one of several clinical stages of HBV infection (Fig. 2) [30]. During subsequent visits, changes in the patient's virologic and biochemical parameters may clarify the patient's clinical status, especially regarding the evaluation of disease progression and assessment of the need for antiviral therapy.

Patients usually present in the HBeAg-positive immune tolerant stage during the first or second decade of life. At this stage, there are no symptoms or signs of liver disease, ALT values are normal, and HBV DNA levels may range from 10^7 to 10^{12} copies/mL (2,000,000–200,000,000,000 IU/mL). These patients have liver biopsy findings of minimal or no fibrosis [1].

By the third or fourth decade of life, patients may present with either HBeAg-positive or HBeAg-negative chronic hepatitis with or without symptoms of liver disease and elevated ALT values and HBV DNA levels in the range of 10^5–10^8 copies/mL (20,000–20,000,000 IU/mL). Liver biopsy findings show active necroinflammation and moderate to advanced fibrosis.

Patients may also have established cirrhosis at the time of initial presentation, often without previous knowledge of their CHB. These patients may be in their fourth or fifth decade of life, be either HBeAg-positive or -negative, have elevated ALT values and HBV DNA levels of 10^5–10^7 copies/mL (20,000–2,000,000 IU/mL). Other laboratory findings that suggest cirrhosis, such as decreased albumin levels and low platelet counts, also may be present.

Finally, HBsAg-positive patients may present in the inactive carrier stage. These patients are HBeAg-negative, have normal ALT values and HBV DNA levels that range from undetectable to $\leq 10^4$ copies/mL ($\leq$2,000 IU/mL). The prognosis in this stage is usually good. However, reversion to active liver disease may occur at any stage of HBV, even in inactive carriers. Although it is more common in patients with cirrhosis, HCC may develop at any stage of disease [31, 32].

Progression of Liver Disease and Mortality Rates in Hepatitis B

The annual rate of progression from the immune tolerant stage to chronic hepatitis ranges from 0.84 to 2.7% (Fig. 3) [33]. The rate of progression from chronic hepatitis to cirrhosis is 1–4% in China and Taiwan [34]. In Korea, the 5, 10, 15, and 20-year progression rates from chronic hepatitis to cirrhosis are 9, 23, 36, and 48% respectively [35]. Thereafter, progression of compensated to decompensated cirrhosis occurs at an annual rate of 3.2–4.6% [33]. In a Taiwanese study, the mean age at decompensation in cirrhotic patients was 57.2 years [36]. Progression to HCC occurs at any stage of clinical disease. The annual rate of progression from the inactive carrier stage to HCC is 0.27–0.4%, from chronic hepatitis to HCC is 0.27–10%,

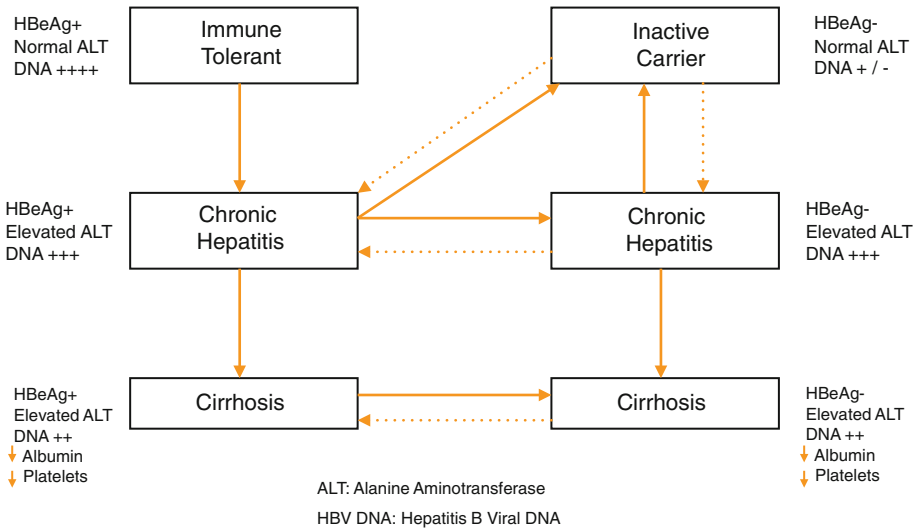


Fig. 2 The clinical stages of hepatitis B [30]

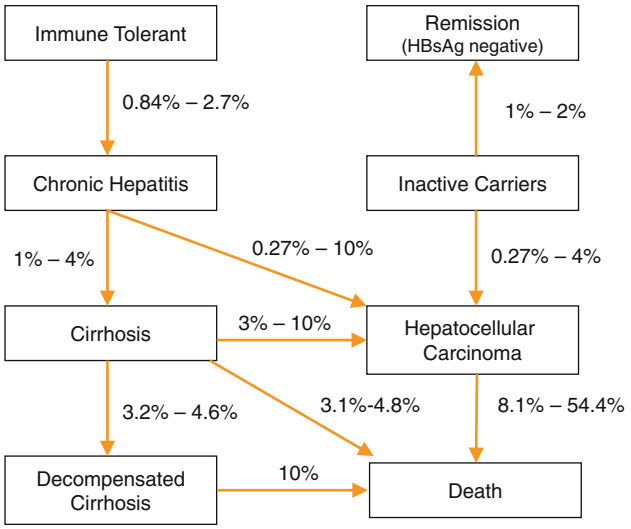


Fig. 3 The annual rates of disease progression in Asian patients with hepatitis B [11, 33–37]

and from cirrhosis to HCC is 3–10% [33, 37, 38]. In Korea, the 5, 10, and 15-year rates of progression from chronic hepatitis to HCC is 2.7, 11, and 25% respectively, and the rate of progression from cirrhosis to HCC is 13, 27, and 42%, respectively [11].

Many studies have examined the mortality rates among patients with CHB. In one report of Chinese HBV carriers, between 25 and 40% eventually died from either cirrhosis-related complications or from HCC [35]. In another report of CHB patients, 11% of cirrhosis patients died during a 12-year follow-up [39]. Mortality varied according to the severity of liver disease. In China and Taiwan, the annual mortality rates in inactive carriers range from 0.38 to. 0.93%. Annual mortality rates of 3.1–4.8% were reported in cirrhosis patients and increased to 10% in patients with decompensated cirrhosis [36]. The annual mortality rates for patients with HCC range from 8.1 to 54.4% and from 34 to 98% after 5 years of follow-up [36].

Laboratory Predictors of Disease Progression

HBeAg

HBeAg is used as a surrogate marker for high levels of serum HBV DNA. HBeAg positivity is a risk factor for chronic hepatitis, cirrhosis, and HCC [22, 40, 41].

HBV Genotype

Genotype C is predictive of poor clinical outcomes and the development of HCC, particularly in patients with BCP mutations [42–45]. Genotype B was associated with HCC in younger Taiwanese patients, but in older HCC patients in Japan.

HBV DNA

A linear relationship between HBV DNA levels and progression to cirrhosis and the development of HCC was reported in a large cohort of HBsAg-positive patients in Taiwan. In over 3,600 Chinese patients, the rate of progression to cirrhosis increased with increasing levels of HBV DNA starting from 10^4 copies/mL (2,000 IU/mL) [46]. In the same patient population, the incidence of HCC increased from 1.3% for HBV DNA <300 copies/mL (<60 IU/mL) to 14.9% for HBV DNA levels $\geq 10^6$ copies/mL (≥200,000 IU/mL) [47].

Basal Core Promoter Mutants

BCP mutants were more frequently detected in HCC patients, particularly in patients with higher HBV DNA levels and genotype C [43, 48, 49]. The presence of BCP mutants is associated with an increased risk for disease progression and for development of HCC in both HBV genotype B and C patients [43, 44, 50, 51].

Precore Mutants

PC mutants are most often detected in HBeAg-negative CHB patients [41, 52]. PC mutations are associated with ALT elevations, increased HBV DNA levels and persistent hepatic necroinflammatory activity in patients with CHB.

Surveillance for HCC in Asian Patients with Chronic Hepatitis B

Patients with CHB have a >100-fold increased risk for the development of HCC compared with those without HBV infection [47, 53]. The annual incidence of HCC in inactive carriers is estimated to be 0.5%, increasing to 3–10% in patients with cirrhosis [54]. According to the REVEAL study, there is a strong correlation between HBV DNA levels $>10^4$ copies/mL (>2,000 IU/mL) and the risk for HCC [41, 47]. Additional studies have evaluated risk factors for HCC in Asian patients. A report on 820 patients with CHB from Hong Kong showed that male gender, increasing age, higher HBV DNA levels, presence of BCP mutations, and cirrhosis were independent risk factors for HCC [55]. A second study, conducted in 188 patients in Korea, showed that age and persistent ALT elevations were independent risk factors for progression to cirrhosis, decompensation, and HCC [56]. In a predominantly Asian American population, risk factors for HCC included older

age, cirrhosis, PC mutations, BCP mutations, and high serum alpha-fetoprotein levels [45, 57].

A recent randomized controlled trial for HCC screening in >18,000 subjects in Shanghai, China, reported a 37% reduction in HCC-related mortality among patients detected by surveillance [58]. Another Hong Kong study in 579 patients reported an increase in survival with surveillance [59]. A recent study in Asian Americans with HBV showed that surveillance identified patients with smaller tumor burdens and better-preserved liver function who were more likely to receive curative therapies which prolonged survival [60].

Our recommendations for HCC surveillance are shown in Table 2. All HBsAg-positive patients should be regularly followed for HCC. HCC surveillance should include alpha-fetoprotein testing and abdominal ultrasound examination at 6-month intervals. HBsAg-positive patients at highest risk for HCC development include those with more advanced stage of liver disease, i.e., chronic hepatitis or cirrhosis, and those with blood relatives with HCC [61]. Patients with low-moderate risk include inactive carriers and immune tolerant patients. Also, patients who clear HBsAg may still develop HCC; thus surveillance should be continued, especially if cirrhosis is present at the time of HBsAg loss [62].

Although debate remains regarding the optimal age to begin HCC surveillance, it is probably not warranted among pediatric patients because of the low risk of HCC. The benefit of surveillance in HBsAg-positive males aged <40 years and females aged <50 years has not been determined. However, up to 20% of HCC cases in Asians may be in this younger age range, and if clinically active chronic hepatitis, cirrhosis, or other risk factors for HCC are present in these patients, then surveillance for HCC should be instituted [60, 63, 64]. Liver lesions detected by surveillance require confirmation of HCC by computed tomography scan, magnetic resonance imaging or liver biopsy. For confirmed cases of HCC, referral to a multidisciplinary liver cancer center consisting of hepatologists, surgeons, interventional radiologists, and oncologists who specialize in the treatment of this malignancy should be considered [65].

Table 2 Surveillance for hepatocellular carcinoma in Asian Americans with hepatitis B

1. Surveillance tests	1. Alfa-fetoprotein
	2. Abdominal Ultrasound
2. Surveillance interval	Every 6 months
3. Surveillance candidates	a. High-risk patients
	Cirrhosis
	HCC in blood relatives
	b. Low–moderate risk patients
	Inactive carriers
	Immune-tolerant patients
	HBsAg-positive males <40 years
	HBsAg-positive females <50 years
	Patients with HBsAg loss (especially cirrhosis patients)

Treatment of Chronic Hepatitis B in Asian Americans

Proposed Candidates for Treatment Based on Clinical Stage

The goal of antiviral therapy in patients with hepatitis B is to prevent progression from chronic hepatitis to cirrhosis. Moreover, in patients with already advanced fibrosis or cirrhosis, the goal of treatment is to prevent or delay progression to end-stage liver disease and development of HCC. There are three recently published guidelines and one expert consensus algorithm pertaining to the treatment of chronic hepatitis B [54, 66–68]. The eligibility for antiviral therapy in these publications is based on HBeAg status, levels of HBV DNA and ALT values in the setting of either chronic hepatitis or cirrhosis. The reported recommended levels of ALT and HBV DNA may exclude some hepatitis B patients who have the potential to develop HCC or die from liver-related complications. Based on a natural history study in a predominantly Asian population in the USA, the treatment criteria described in the above four publications were matched to the database of 369 hepatitis B patients, in whom 30 developed HCC and 37 died of non-HCC liver related deaths during a mean follow-up of 84 months [69]. Using the recommended ALT and HBV DNA values as stated in the four publications, 23–50% of patients who developed HCC and 19–30% who died from non-HCC-related liver complications would have been excluded for antiviral therapy [70]. Nevertheless, if the serum albumin and platelet counts were added to the treatment criteria, up to 94% of patients who went on to serious liver-related complications would have been recommended for antiviral therapy. Therefore, these routine liver tests should be included into hepatitis B treatment strategies, especially in patients who do not fulfill the recommended ALT and DNA criteria. Moreover, the decision to initiate therapy may also include liver histology in patients whose treatment candidacy is unclear.

The serum ALT has been used as a marker of necroinflammation in the liver. The "upper limit of normal" of ALT values varies in clinical laboratories. Furthermore, the upper limit of normal for ALT in clinical trials for hepatitis B treatment were not consistent. A recent report from Korea indicated that individuals with ALT levels within the normal range have a risk for liver-related mortalities, and

based on receiver operating characteristics for prediction of liver disease, the best cut-off level for ALT in men was 31 IU/L and was 30 U/L in women [66]. Another report from Hong Kong showed that using the upper limit of normal for ALT of 53 IU/L for males and 31 IU/L for females, patients with ALT levels of 0.5–1 times upper limit of normal have a risk for development of cirrhotic complications and HCC [36].

Subsequently, a treatment algorithm from the USA suggested that serum ALT values of 30 U/L for men and 19 IU/L for women be used as the upper limit of normal when making decisions for starting antiviral treatment for hepatitis B [66]. Nonetheless, this latter approach may not be practical, principally due to the lack of standardization among clinical laboratories. Moreover, candidate selection for nucleos(t)ide antiviral therapy in phase 3 clinical trials was based on ALT levels above the baseline range of the clinical laboratories. While evaluating elevated serum ALT in patients, other factors that may increase ALT such as steatosis, dyslipidemia, obesity, and medications causing liver injury should be kept in mind. At present, the panel recommends that the upper limit of normal for ALT be the value stated by the clinical laboratory that is used by the physician. If there is an issue concerning the ALT level when considering antiviral treatment, the patient may be assessed by the "risk impact score" which is described in the following section.

The most important risk factor for liver disease progression is the serum HBV DNA level. The highest risk for liver complications were in patients with baseline HBV DNA levels of $>10^6$ copies/mL (>200,000 IU/mL). For this reason, suppression of serum HBV DNA is the major goal in the treatment of hepatitis B patients.

Treatment did not reduce the incidence of liver complications, development of HCC, or liver-related mortality in a report of 436 Chinese HbsAg-positive patients followed long-term after receiving standard interferon alfa therapy [72]. Yet recent publications report that successful nucleoside/nucleotide therapy reduces necroinflammation, reverses fibrosis and prevents or reverses clinical decompensation in chronic hepatitis and cirrhosis patients [73, 74].

The benefit of reducing liver complications was demonstrated in a prospective trial of lamivudine in Asian patients with compensated cirrhosis [75]. This study enrolled both HBeAg-positive and HBeAg-negative patients with detectable HBV DNA who had Ishak Fibrosis Scores of 4–6. The primary endpoint was time to disease progression, defined as hepatic decompensation, spontaneous bacterial peritonitis, bleeding esophageal varices, HCC, and death related to liver disease. After a median follow-up of 32 months, 7.8% of patients who received lamivudine versus 17.7% of controls reached the primary endpoint. Benefit was primarily observed in patients with sustained viral suppression; however, less significant benefit was noted in patients who developed lamivudine resistance. Treatment with antiviral agents with low resistance profiles significantly improved clinical outcomes in patients with decompensated cirrhosis [73, 76]. Based on these findings, patients with cirrhosis with any level of detectable HBV DNA are recommended for lifelong antiviral therapy.

Recommendations for Treatment

Our recommendations for treatment are summarized in Table 3 and Fig. 4.

Antiviral treatment is not recommended for patients who are in the immune-tolerant stage of infection or in inactive carriers.

Patients with either HBeAg-positive or -negative chronic hepatitis with HBV DNA $>10^4$ copies (>2,000 IU/mL) and ALT levels above the upper limit of normal should be

Table 3 Treatment candidate selection based on clinical stage HBeAg, HBV DNA, and serum ALT

Clinical stage	HBe Ag	HBV DNA	ALT[a]	Recommendation
Immune tolerant	+	>2,000 IU/mL[c]	≤ULN	Monitor
Chronic hepatitis[b,a]	+	>2,000 IU/mL	>ULN	Treat
Chronic hepatitis[b,a]	−	>2,000 IU/mL	>ULN	Treat
Chronic hepatitis[a]	−	>2,000 IU/mL	≤ULN	Assess gray zone considerations
Chronic hepatitis[a]	±	≤2,000 IU/mL	>ULN	Assess gray zone considerations
Cirrhosis	±	Detectable	NA	Treat
Cirrhosis	±	Undetectable	NA	Monitor
Decompensated cirrhosis	±	NA	NA	Treat
Inactive carrier	−	≤2,000 IU/mL	≤ULN	Monitor

ULN upper limit of normal, *NA* not applicable

[a] ALT normal range is based on local laboratory reference range

[b] Liver biopsy grade 1–3 and/or stage 1–3

[c] HBV DNA usually 10^7–10^{12} copies/mL

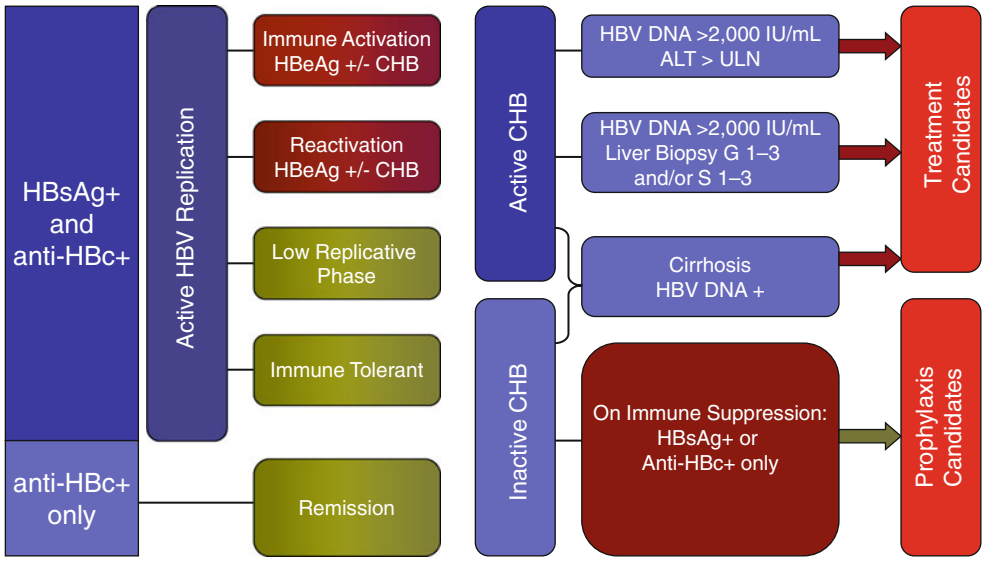


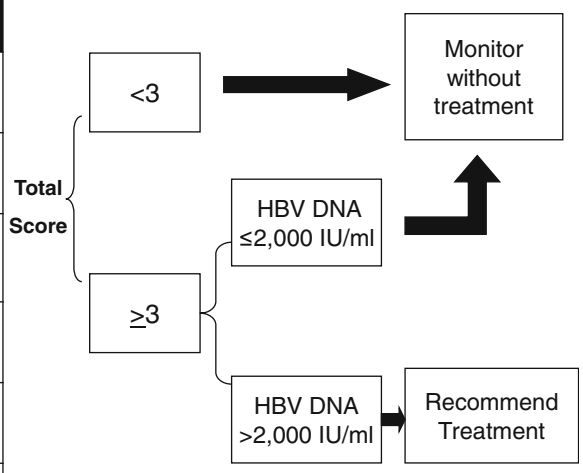
Fig. 4 Candidates for antiviral treatment or prophylaxis

offered antiviral therapy. Treatment may also be beneficial in patients with normal ALT values who have histologic evidence of necroinflammation (histology activity index [HAI] ≥ 4, Metavir $\geq$ G2) and fibrosis (stage 2 portal fibrosis, Metavir $\geq$ S2).

Patients in the 'gray zone' for treatment are those who do not meet the above criteria but refuse liver biopsy (Table 4). These include chronic hepatitis patients who are (1) HBeAg-negative with HBV DNA levels $>10^4$ copies/mL (>2,000 IU/mL) but have "normal" ALT values and (2) HBeAg-positive or -negative patients who have HBV DNA $\leq 10^4$ copies/mL ($\leq$2,000 IU/mL) but who have elevated ALT values. In these individuals, a liver biopsy may be useful to assess the degree of inflammation and fibrosis. Alternatively, we recommend a "risk impact" scoring system that includes age, gender, BCP mutations, HCC in first-degree relatives and those with low albumin or decreased platelet values [77]. Moreover, males with ALT $\geq$30 U/L and females with $\geq$19 U/L are assigned a numerical score in order to take into account the higher

Table 4 Evaluation of hepatitis B patients in the gray zone for antiviral treatment using a risk impact score

Risk Factors	Impact Score
Age ≥40 years	1
Male Gender	1
Male ALT >30 U/L Female ALT >19 U/L	1
Basal Core Promoter (BCP) Mutation	2
HCC in First Degree Relative	3
Albumin ≤3.5 g/dl or Platelet Count ≤130,000 mm^3	3



upper limit of normal for ALT in clinical laboratories. Each of the factors included in this scoring system has been identified as independent risk factors for liver disease progression [36, 43, 44, 48, 57, 69, 78–81]. In this system, a numerical score has been assigned for each risk factor. Thus, if the score is ≥3 and the HBV DNA is $>10^4$ copies/mL (>2,000 IU/mL), antiviral treatment is considered. If the score is ≥3 and the HBV DNA is $\leq 10^4$ (≤2,000 IU/mL), continue monitoring without treatment. If the score is <3, monitor without treatment. This scoring system is based on expert opinion and warrants further clinical experience and validation.

Patients with cirrhosis who have any detectable level of HBV DNA should receive antiviral therapy regardless of HBeAg status or ALT level. Patients with compensated cirrhosis with undetectable HBV DNA should have tests for ALT and HBV DNA every 3 months. Patients with decompensated cirrhosis should be started on antiviral therapy and immediately referred to a liver transplant center.

Antiviral Therapy, Monitoring Treatment and Resistance

Current Treatments for CHB

At present, seven drugs are approved by the FDA for the treatment of hepatitis B. These include standard interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, telbivudine, entecavir, and tenofovir. Three of these—entecavir, tenofovir and peginterferon alfa-2a—are the most commonly recommended first-line drugs for the treatment of hepatitis B. A summary of their virologic, biochemical, and histologic responses in Asian patients are shown in Table 5. Lamivudine, adefovir, and telbivudine are considered second-line agents. Since the availability of more potent drugs, standard interferon alfa-2b is seldom used for HBV treatment. This section reviews the relevant clinical data for the six other drugs.

Lamivudine

Lamivudine, the first oral agent for CHB, was approved in the USA in 1998. In HBeAg-positive patients, lamivudine at a dose of 100 mg/day was effective in suppressing viral replication, and HBeAg seroconversion rates of up to 20% per year were observed [81]. After 5 years of therapy, HBeAg seroconversion rates approached 70% but were offset by increasing rates of lamivudine resistance, which was as high as 65% [81–83]. In a 2-year treatment trial of lamivudine in HBeAg-negative patients, up to 56% of Chinese patients achieved HBV DNA levels of <10,000 copies/mL (<2,000 IU/mL) and normal ALT values [84]. Following cessation of lamivudine, relapse was common and resistance developed in >30% of treated patients. Thus, the major limitation of lamivudine has been development of drug resistance. Although not considered a first-line agent for the treatment of hepatitis B, lamivudine may be useful for short-term treatment, such as in HBsAg-positive patients requiring cancer chemotherapy.

Adefovir

Adefovir, the second oral agent for CHB, was approved in the USA in 2002. Although less potent than lamivudine, this agent was effective in patients with lamivudine resistance [85]. A recent study compared the responses to adefovir at a dose of 10 mg/day among Asian and non-Asian patients enrolled in two pivotal trials for HBeAg-positive and HBeAg-negative patients, respectively [86]. After 48 weeks of treatment, there were no significant differences in serum HBV DNA reduction or the proportion of patients achieving undetectable HBV DNA levels between the groups. The rates of resistance, biochemical response, and HBeAg seroconversion were also similar. However, the emergence of drug-resistance rates of up to 29% after 5 years of treatment, as well as the possibility of renal function impairment, has limited its use for long-term antiviral therapy [87]. At present, adefovir is not considered a first-line agent for patients with CHB.

Telbivudine

Telbivudine was approved in 2006 for the treatment of CHB. In the GLOBE trial, approximately half of the patients enrolled in the HBsAg-positive and HBsAg-negative arms were from China [88]. In Asian patients treated with telbivudine at a dose of 600 mg/day for 1 year, HBV DNA suppression and HBeAg loss were noted in 67 and 31% of patients, respectively [89]. In HBeAg-negative patients, telbivudine was associated with HBV DNA suppression rates of up to 78%. Resistance to telbivudine was lower than with lamivudine but resistance rates increased to 22% after 2 years of therapy [88]. At present, telbivudine is not considered a first-line agent for the treatment of hepatitis B especially in lamivudine-experienced patients. However, this drug may be considered for use in patients requiring short-term therapy.

Peginterferon Alfa-2a

Two phase 3 international trials examined the efficacy of 1 year of treatment with peginterferon alfa-2a at a dose of 180 μg/day in patients with CHB [90, 91]. The results from a subset of Asian patients have been

Table 5 Virologic, biochemical, and histological responses to antiviral agents in treatment-naive Asian patients with CHB

	Trial endpoints		First-line agents		
			Peginterferon alfa-2a [25, 92]	Entecavir [26, 74, 96, 97] (up to 240 weeks)	Tenofovir [101, 102, 152–154] (up to 192 weeks)
HBeAg(+)	HBV DNA	Year 1 undetectable HBV DNA	14% @ 24 weeks post Rx	69% (<300 c/mL)	85% (ITT) (<400 copies/mL)
		Long-term undetectable HBV DNA	N/A	95%	97%
	ALT	Year 1 ALT normalization	41% @ 24 weeks post Rx	63%	72%
		Long-term ALT normalization	N/A	76%	86%
	HBeAg loss/ seroconversion	Year 1 HBeAg loss/ seroconversion	31% @ 24 weeks post Rx	16/16%	17/17%
		Long-term HBeAg Loss/seroconversion	41% @ 48 weeks post Rx	40/18%	35/26%
	HBsAg loss/ seroconversion	Year 1 HBsAg seroconversion	2% @ 24 weeks post Rx	0.5%	0/0%
		Long-term HBsAg loss/seroconversion	N/A	2.9% in Genotype B 0.9% in Genotype C	2.3%
	Histological improvement	Year 1 histological improvement	38%	71%	77%
		Long-term histological improvement	N/A	100%	N/A
HBeAg(−)	HBV DNA	Year 1 undetectable DNA	19%	93%	82% (ITT)
		Long-term undetectable HBV DNA	N/A	98.3%	97%
	ALT	Year 1 ALT normalization	59%	76%	72%
		Long-term ALT normalization	N/A	85.7%	86% (combined with HBeAg(+) patients) @ 192 weeks
	HBsAg loss/ seroconversion	Year 1 HBsAg seroconversion		0/0%	0/0%
		Long-term HBsAg loss/seroconversion		0/0%	0/0%
	Histological improvement	Year 1 histological improvement	N/A	68%	77%
		Long-term histological improvement	N/A	100%	N/A

published [92]. At 20 weeks after discontinuing peginterferon alfa-2a monotherapy in HBeAg-positive patients, 14% had undetectable HBV DNA, 31% had HBeAg loss, 41% had normalization of serum ALT values and 38% had histologic improvement. During long-term follow-up, 41% of Asian patients eventually became HBeAg-negative.

Peginterferon alfa-2a has been evaluated in HBeAg-negative chronic hepatitis. At 20 weeks after cessation of therapy, 19% of patients had undetectable HBV DNA, and 59% had normalized serum ALT [90]. Overall, genotypes B and C patients had similar response rates to peginterferon alfa-2a treatment. Patients with baseline ALT >5× ULN prior to therapy had higher response rates.

Treatment with peginterferon alfa-2a monotherapy for a finite period has associated HBeAg seroconversion rates of up to 31% 12-months post-treatment. In HBeAg-positive and HBeAg-negative patients, less than 20% remain HBV DNA undetectable during follow-up, with virologic and biochemical relapse rates unknown. Therefore, the use of

peginterferon alfa-2a for the treatment of HBsAg-positive Asian patients may be considered if a finite period of treatment is desired. Such circumstances include young female patients who are planning on pregnancy in the near future, patients who are unwilling to commit to long-term antiviral therapy and HBeAg-positive, genotype A, Asian patients with chronic hepatitis B. Nonetheless, interferon is not recommended for patients with decompensated cirrhosis since hepatic failure may occur.

Entecavir

Entecavir was approved in 2005 for the treatment of CHB. In a subset of HBeAg-positive Asian patients from pivotal trials, 69% achieved undetectable HBV DNA levels, 63% normalized ALT, 16% had HBeAg loss, and 68% had histologic improvement after 48 weeks of treatment with entecavir 0.5 mg/day [93]. For HBeAg-negative Asian patients, 93% had undetectable HBV DNA, 76% had normal serum ALT, and 68% had histologic improvement [94]. Chinese patients treated with entecavir showed that the overall rate of subjects achieving undetectable HBV DNA levels was up to 90% in HBeAg-positive and HBeAg-negative patients [95].

Entecavir treatment for up to 6 years was well tolerated and was associated with HBV DNA suppression in up to 95% of patients with excellent histological improvement [96, 97]. The resistance rates for entecavir were only 1.2% during the first 3 years of therapy with no new cases emerging for up to 6 years [98, 99]. Suboptimal responses to entecavir are rare [100]. Because of cross-resistance issues, entecavir is not recommended in patients with lamivudine resistance [98]. Entecavir is an effective therapy for CHB and is recommended as a first-line agent for Asian patients.

Tenofovir

Tenofovir disoproxil fumarate was approved in 2008 for the treatment of CHB. In a subset of Asian patients treated in pivotal trials, 85% had undetectable HBV DNA levels, 17% had HBeAg loss, 72% had ALT normalization, and 77% had histologic improvement after 1 year of treatment [101]. At week 192 of tenofovir treatment, 97% had undetectable HBV DNA, 35% had HBeAg loss, and 86% had normal ALT values [102]. In HBeAg-negative Asian patients treated for 48 weeks, 82% had undetectable HBV DNA, 72% had normal ALT values, and 77% had histologic improvement [101, 103]. At week 192 of tenofovir treatment, 84% of patients had undetectable HBV DNA and up to 86% normalized serum ALT. No resistance mutations for tenofovir have been identified up to 4 years of therapy [102]. Tenofovir is considered a first-line agent for treatment in Asian patients with CHB.

Treatment for Decompensated Cirrhosis

The efficacy and safety of lamivudine, adefovir, tenofovir, and entecavir have been evaluated in patients with decompensated cirrhosis [75]. As a result of high potency and low resistance rates, either entecavir or tenofovir are preferred agents for use in these patients [73, 76]. Since long-term antiviral therapy can improve the stage of liver fibrosis, indefinite treatment is recommended for patients with cirrhosis [97]. Interferon is contraindicated in patients with decompensated cirrhosis [104].

Treatment Monitoring and Diagnosis of Antiviral Resistance

Monitoring Treatment

After initiation of antiviral treatment, close follow-up is required to evaluate treatment response and adverse events. Serum HBV DNA should be measured every 3 months until undetectable levels are obtained and then every 3–6 months thereafter. Patients receiving oral antiviral agents should be tested every 3 months until the serum ALT levels are within the normal limit and thereafter at 3 to 6-month intervals. Monitoring of renal function may be necessary in patients receiving adefovir treatment [105–107]. Moreover, complete blood cell counts with absolute neutrophil and platelet counts should be performed every 2–4 weeks in patients receiving pegylated interferon therapy. Thyroid function tests are required in patients treated with interferon [104].

HBeAg-positive patients on antiviral therapy should have tests for HBeAg every 6 months until seronegative; then initiate testing for anti-HBe. HBsAg should be tested every 12 months after seroconversion from HBeAg to anti-HBe-positive. In HBeAg-negative patients, test for HBsAg every 12 months after sustained suppression of HBV DNA.

As HBV DNA suppression is the primary goal, assessment of treatment response is based on reduction in viremia after starting therapy. "Non-response" to an oral antiviral agent is defined at <1 $\log_{10}$ drop from baseline after 12 weeks of treatment. The definition of a "suboptimal response" varies between antiviral agents. For patients receiving telbivudine, adefovir, or lamivudine, the criterion is a viral load >1,000 copies/mL (>200 IU/mL) after 24 weeks of therapy [108]. For patients on tenofovir or entecavir, the criterion for suboptimal response is a viral load >1,000 copies/mL (>200 IU/mL) after 48 weeks of treatment [108, 109]. Switching antiviral agents should be

considered if patients have been fully compliant with their treatment regimen.

When to Stop Treatment

HBeAg-positive CHB patients should be treated until seroconversion to anti-HBe positivity, and then continued with consolidation therapy for at least an additional 1–2 years before stopping therapy. After cessation of treatment, patients should be closely monitored for relapse, which may be manifested by seroreversion to HBeAg positivity, reappearance of HBV DNA, and ALT elevation. In a retrospective study of 124 Chinese patients treated with lamivudine who achieved HBeAg seroconversion with HBV DNA <200 copies/mL (<40 IU/mL), the relapse rates (HBeAg seroreversion) at 1 and 2 years post treatment were 54 and 68%, respectively [110]. In another study, serologic and virologic recurrence was present in 67% of the patients who continued lamivudine after HBeAg seroconversion, preceded by development of lamivudine resistance in the majority [111, 112]. In a recent cohort of HBeAg-positive Chinese patients who continued lamivudine after HBeAg seroconversion, 78% of patients remained HBV DNA undetectable, 16% had ALT flares, and only 10% developed lamivudine resistance after a median treatment period of 79 months [112]. In those patients who stopped lamivudine after HBeAg seroconversion, all had reappearance of HBV DNA with 44% of patients having ALT flares. Further studies using the more potent antiviral agents with lower resistance profiles (i.e., entecavir or tenofovir) for consolidation therapy after HBeAg seroreversion are required to clarify the issue. Prolonged consolidation treatment may be necessary in some HBeAg-positive patients but risk factors associated with HBeAg seroreversion remains to be identified.

For HBeAg-negative chronic hepatitis, the rate of relapse after stopping therapy is high. In patients who received 5 years of treatment with adefovir, up to 60% had virologic relapse with elevated ALT levels after stopping treatment [113]. To maintain HBV DNA suppression, it is recommended that treatment be continued indefinitely in HBeAg-negative patients. Nevertheless, if HBsAg becomes undetectable, then antiviral therapy may be stopped. If therapy is discontinued, close follow-up is mandatory, and prompt retreatment is necessary if elevations of HBV DNA and ALT levels are observed. Additional studies are needed to determine the optimal length of treatment with antiviral agents in HBeAg-negative chronic hepatitis patients.

Patients with cirrhosis should continue oral antiviral treatment indefinitely.

In CHB patients in whom long-term antiviral therapy is deemed necessary, achievement of continued HBV DNA negativity with monotherapy does not require switching to an alternative drug. Thus, patients receiving either lamivudine or adefovir alone who have undetectable HBV DNA levels may remain on their respective medications unless a virological breakthrough occurs. If the latter circumstance is encountered and antiviral drug resistance is present, then switching to another drug to which HBV is susceptible will be necessary.

Antiviral Drug Resistance

Persistent viremia may lead to drug resistance defined as any substitutions in the HBV genome that reduce susceptibility to a drug to which it was previously susceptible. Antiviral resistance is divided into two categories; (1) genotypic resistance, which refers to substitutions at conserved sites within the polymerase gene targeted by the drug, and (2) phenotypic resistance, which refers to reduction in in vitro susceptibility to antiviral agents associated with genotypic resistance. The clinical consequences of drug resistance include a reduced rate of HBeAg seroconversion, reversal of virologic and histologic improvement, an increased rate of disease progression, and severe exacerbations, especially in patients with cirrhosis [114, 115]. The potential exists for transmission of drug-resistant HBV, and for appearance of HBsAg mutations that may lead to vaccine failure [116, 117]. It is recommended that any patient with a virological breakthrough (defined with as an increase in serum HBV DNA by >1 $\log_{10}$ from nadir or reappearance of HBV DNA ≥tenfold the lower limit of detection of the HBV DNA assay after having undetectable HBV DNA) undergo drug-resistance analysis. In a recent report, up to 40% of virological breakthroughs in CHB patients receiving nucleos(t)ide analogs were related to medication non-adherence, not antiviral genotypic resistance [118]. Thus, close counseling of patients regarding adherence to their antiviral medications, confirmation of virological breakthrough, and drug resistance testing are recommended in order to avoid unnecessary changes in antiviral mediations.

Management of Pre-Existing Mutations, Suboptimal Response, and Antiviral Resistance

Preexisting mutations are detected in 7.5–28% of presumed treatment-naive patients (Table 6). The majority of mutations identified in clinical studies were lamivudine, telbivudine, or adefovir signature mutations, suggesting that mutations occur spontaneously or the patients' histories were not reliable. However, pre-existing mutations in treatment-naive patients or in those with prior lamivudine or adefovir experience with no documented genotypic resistance may not have a significant impact on clinical

Table 6 Antiviral resistance, cross-resistance, and recommended therapy [66, 119–123]

	Mutation analysis and diagnosis			Management approach	
	Genotypic mutations	Cross-resistance in vitro	Susceptible to the drug in vitro	First-line treatment options	Second-line treatment options
Lamivudine resistance	M204V/I ± L180M	Entecavir	Adefovir	Switch to tenofovir, or to	Add adefovir
		Telbivudine	Tenofovir	Tenofovir + entecavir	
	A181T	Telbivudine	Tenofovir	Switch to tenofovir, or to	Peginterferon alfa-2a
		Adefovir	Entecavir	Tenofovir + entecavir	
Adefovir resistance	N236T	Tenofovir	Lamivudine	Switch to tenofovir or entecavir, or to	Add lamivudine or telbivudine
			Telbivudine	Tenofovir + entecavir	
			Entecavir		
	A181V/T	Telbivudine	Entecavir	Switch to tenofovir or entecavir, or to	Peginterferon alfa-2a
		Lamivudine	Tenofovir	Tenofovir + entecavir	
Telbivudine resistance	A181T	Lamivudine	Entecavir	Switch to tenofovir, or to	Add adefovir
		Adefovir	Tenofovir	Tenofovir + entecavir	
	M204V/I ± L180M	Lamivudine	Adefovir	Switch to tenofovir, or to	Peginterferon alfa-2a
		Entecavir	Tenofovir	Tenofovir + entecavir	
Entecavir resistance	M204V/I + L180M + T184G or 202I or M250V	Lamivudine	Adefovir	Switch to tenofovir, or to	Add adefovir
		Telbivudine	Tenofovir	Tenofovir + entecavir	Peginterferon alfa-2a

outcomes when using highly potent antiviral agents with low resistance profiles such as tenofovir or entecavir [119, 120]. However, resistance analysis should be performed when second-line antiviral agents are considered for use, especially in treatment-experienced patients.

The management of resistance to oral antiviral agents includes obtaining a detailed treatment history and accurately interpreting drug-mutation analysis before choosing a new antiviral regimen. "Virologic breakthrough" is seen in patients with genotypic resistance and viral rebound but in whom serum ALT levels remain normal. "Clinical breakthrough" is defined as virologic breakthrough associated with elevation of serum ALT above baseline levels. When single-drug genotypic resistance is confirmed, the preferred approach in patients with either lamivudine, telbivudine, or entecavir resistance is to switch to tenofovir or tenofovir plus entecavir [119]. Patients with adefovir resistance should be switched to tenofovir or entecavir or both tenofovir plus entecavir [66]. Nevertheless, switching to tenofovir is not recommended in patients who developed renal dysfunction during adefovir treatment.

If multidrug resistance is identified, the combination of entecavir and tenofovir is preferred [121]. Another option is to treat with pegylated interferon. In patients with suboptimal responses, therapy should be chosen to avoid potential cross-resistance. Patients with suboptimal response to adefovir may be switched to entecavir or tenofovir [66, 119, 122]; those with suboptimal response to telbivudine or lamivudine may be switched to tenofovir [66, 119]; and patients with suboptimal response to entecavir may be switched to tenofovir [123].

Special Populations

Hepatitis B and Pregnancy

There are two issues that must be addressed when considering treatment for hepatitis B during pregnancy. One is prevention of maternal-to-child transmission of HBV from carrier mothers to their newborn infants. In the USA, all women are screened for HBsAg during pregnancy; if positive, their infants receive hepatitis B immune globulin and the first dose of hepatitis B vaccine within 12 h of birth. The subsequent two doses of vaccines are usually administered within 6–12 months of age [124]. Nevertheless, even with passive-active immunoprophylaxis, from 7 to 32% of infants born to carrier mothers with high viral loads still become HBsAg-positive [125, 126]. Recently, a study conducted in China showed that immunoprophylaxis failures mainly occurred in HBeAg-positive mothers with HBV DNA levels ≥ 6 $\log_{10}$ copies/mL ($\geq$200,000 IU/mL) [127]. Failure rates continued to rise when maternal HBV DNA levels reached 10^7 to $>10^8$ copies/mL (2,000,000 to >20,000,000 IU/mL). Thus, antiviral therapy should be considered in pregnant women with high levels of viremia, especially for mothers with infants who had previously failed immunoprophylaxis.

The use of lamivudine and telbivudine during the latter stages of pregnancy appears to be well tolerated, and both agents have comparable efficacy and safety in mothers and their infants during short-term observation (up to 12 months post-partum) [125, 128]. The rate of maternal-to-child transmission was reduced when lamivudine or telbivudine was given to HBeAg-positive mothers with high viral loads during the third trimester of pregnancy [125, 129]. At present, the use of oral antiviral agents during the first or second trimester of pregnancy is not recommended since data regarding their safety and efficacy during those time periods are not available. Interferon use is contraindicated in pregnancy [104]. Elective caesarean section in high-risk HBsAg-positive mothers also reduced the maternal-to-child transmission rate of hepatitis B [130]. Further studies are warranted to confirm these findings.

The second issue is maternal/viral reactivation during pregnancy. Hepatitis B flares during pregnancy are uncommon but if encountered, antiviral therapy should be considered, especially if the reactivation is clinically severe [128, 131].

Telbivudine and tenofovir are classified as Pregnancy Category B drugs, whereas lamivudine, adefovir, and entecavir are in Category C. Among the oral antiviral agents, lamivudine and tenofovir have been extensively used in the human immunodeficiency virus (HIV)-infected population and showed no higher incidence of teratogenicity than the untreated general population. In the event of pregnancy while receiving antiviral agents, therapy should either be stopped or switched to a pregnancy category B agent. In mothers who prefer breast-feeding, antiviral therapy should be discontinued, since the safety of these agents secreted in breast milk is unknown. Stopping antiviral treatment in mothers after delivery for the purpose of lactation appears to be safe since significant hepatitis flares have not been reported [125, 128].

HBV Coinfection with HCV or HDV

Since HBV and hepatitis C virus (HCV) share similar routes of transmission, coinfection with both viruses is detected in 7–22% of chronic HBV patients. Coinfection with HCV is found predominantly among individuals at high risk for parenteral infection, including injection drug users. Coinfection with hepatitis D virus (HDV) is particularly seen in those residing in areas where HBV infection is highly endemic (such as Southeast Asia, China, and Africa) [132]. HBV patients coinfected with HCV or HDV

are at higher risk for rapid progression to decompensated liver disease and HCC [133, 134].

HBV replication is suppressed by HCV infection, with genotype 1b having the most pronounced effect [135, 136]. Acute HCV superinfection in patients with chronic HBV results in a higher cumulative incidence of cirrhosis and HCC, whereas acute HBV superinfection in patients with chronic HCV infection may decompensate with higher incidence. The treatment strategy should be directed toward the dominant replicating virus.

Coinfected HBV/HCV patients treated with peginterferon alfa-2a and ribavirin may clear HCV RNA and achieve sustained virologic response rates comparable to that of monoinfected HCV patients. A small proportion (11%) of patients also may become HBsAg-negative [137]. Nonetheless, HBV DNA levels may rebound in some patients who achieve a sustained virologic response to HCV treatment, so continuous monitoring for HBV reactivation should be continued. Response to HBV treatment with oral antiviral agents does not appear to be affected by concurrent HCV infection.

Treatment for HBV patients coinfected with HDV remains a challenge for clinicians. Most Asian patients with CHB who are super-infected with HDV may present with lower levels of HBV DNA. The treatment of choice in HBV and HDV coinfection is pegylated interferon, which may lead to 30–50% clearance rates for HDV infection. Thereafter, unresolved HBV monoinfection may require oral antiviral treatment.

HBV and HIV Coinfection

Chronic hepatitis B affects nearly 15% of HIV-infected individuals. HIV accelerates the course of HBV infection to end-stage liver disease with more rapid progression of fibrosis [138, 139]. Because of complex interactions between HIV, HBV, the immune system, and antiretroviral agents, the treatment of HBV in HBV/HIV coinfected patients should take into account both viruses. Treatment for HBV improves clinical outcomes [140]. In patients not requiring highly active antiretroviral therapy (HAART), drugs with dual activity against HBV and HIV such as lamivudine, entecavir, emtricitabine, or tenofovir should not be used as monotherapy since these drugs may lead to mutation selection and development of antiretroviral resistance [141, 142]. Pegylated interferon monotherapy or adefovir in combination with telbivudine may be useful in these patients [139, 143]. In contrast, in coinfected patients with low CD4 counts who require HAART, HBV treatment should include a regimen that includes tenofovir combined with either lamivudine or emtricitabine [142]. For lifelong therapy in HIV coinfected patients, the goal is sustained suppression of HBV DNA. Reactivation of HBV has been observed in patients on HAART after immune reconstitution [144].

Hepatitis B Reactivation During Cancer or Immunosuppressive Therapy

Treatment with cancer chemotherapy or immunomodulatory agents may induce potentially fatal hepatic flares in HBsAg-positive patients. The acute flare or "reactivation" results from immune reconstitution directed toward the rise in HBV DNA following use of immunosuppressive or immunomodulating agents [145]. Hepatitis flares, which range from subclinical to severe or even fatal hepatitis, are characterized by increased HBV DNA levels, with or without seroreversion to HBeAg positivity and ALT elevations [146]. A recent meta-analysis of 14 clinical trials suggested that treatment with lamivudine may prevent HBV reactivation during chemotherapy [147]. It is recommended that Asian patients be screened for HBsAg prior to initiation of chemotherapy or immunosuppressive therapy, since many of the HBV carriers have clinically silent disease and are unaware of their chronic HBV infection [148]. Patients who are HBsAg-negative but anti-HBc-positive should be tested for HBV DNA.

All HBsAg-positive patients who require chemotherapy, immunomodulatory agents such as corticosteroids or rituximab, or those receiving bone marrow transplantation should be treated with antiviral prophylaxis [148]. Furthermore, anti-HBc-positive patients who had HBsAg seroclearance and patients positive for both anti-HBc and anti-HBs who require such therapies should be considered as candidates for antiviral treatment [146, 149–151]. Patients who are HBV DNA-negative and anti-HBs-positive only may not require antiviral therapy.

Recommendations

Based on the evidence above, the authors have agreed to the following recommendations regarding the management of CHB in Asian Americans.

1. For HBeAg-positive or -negative chronic hepatitis patients with HBV DNA $>10^4$ copies/mL (>2,000 IU/mL) and ALT > ULN: treat with a first-line agent (entecavir, tenofovir).
2. For cirrhotic patients with detectable HBV DNA, treat with entecavir or tenofovir.
3. In HBeAg-negative patients with HBV DNA $>10^4$ copies/mL (>2,000 IU/mL) and normal ALT, a liver biopsy is recommended. If not available, further stratification for risk factors including measurement of albumin and platelets should be conducted prior to treatment.

4. Monitoring treatment: test for serum ALT every 3 months. Measure HBV DNA every 3 months until negative, then every 3–6 months. Measure HBeAg every 6 months until negative, then test for anti-HBe.
5. After seroconversion from HBeAg-positive to anti-HBe, test for HBsAg every 12 months. In HBeAg-negative patients, test for HBsAg every 12 months after sustained suppression of HBV DNA.
6. Monitoring of resistance: viral breakthrough with confirmation of single drug resistance requires switching to another first-line oral antiviral agent.
7. Surveillance for HCC with alpha-fetoprotein and abdominal ultrasound should be performed every 6 months in HBsAg-positive patients with chronic hepatitis, cirrhosis, and for patients with a family history of HCC.
8. Pregnancy: HBsAg-positive mothers should be tested for HBV DNA. If HBV DNA is $\geq 10^6$ copies/mL, consider using oral antiviral agents during the third trimester of pregnancy. Avoid breast-feeding if the mother is receiving antiviral therapy.
9. HBsAg-positive patients requiring cancer chemotherapy or immunomodulatory agents should receive antiviral treatment.

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References

1. Hui CK, Leung N, Yuen ST, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. *Hepatology*. 2007;46:395–401.
2. Merican I, Guan R, Amarapuka D, et al. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol*. 2000;15:1356–1361.
3. Lau GK, Lai CL, Wu PC. The natural history of chronic hepatitis B infection. *Hong Kong Med J*. 1997;3:283–288.
4. Yeh FS, Yu MC, Mo CC, Luo S, Tong MJ, Henderson BE. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. *Cancer Res*. 1989;49:2506–2509.
5. Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in China–declining HBV prevalence due to hepatitis B vaccination. *Vaccine*. 2009;27:6550–6557.
6. Chae HB, Kim JH, Kim JK, Yim HJ. Current status of liver diseases in Korea: hepatitis B. *Korean J Hepatol*. 2009;15:S13–S24.
7. Park NH, Chung YH, Lee HS. Impacts of vaccination on hepatitis B viral infections in Korea over a 25-year period. *Intervirology*. 2010;53:20–28.
8. Lin CL, Kao JH. Hepatitis B viral factors and clinical outcomes of chronic hepatitis B. *J Biomed Sci*. 2008;15:137–145.
9. Iino S. Natural history of hepatitis B and C virus infections. *Oncology*. 2002;62:18–23.
10. Hann HW, Kim CY, London WT, Whitford P, Blumberg BS. Hepatitis B virus and primary hepatocellular carcinoma: family studies in Korea. *Int J Cancer*. 1982;30:47–51.
11. Yuen MF, Hou JL, Chutaputti A. Hepatocellular carcinoma in the Asia-Pacific region. *J Gastroenterol Hepatol*. 2009;24:346–353.
12. Tong MJ, Hwang SJ. Hepatitis B virus infection in Asian Americans. *Gastroenterol Clin North Am*. 1994;23:523–536.
13. Welch S, Chiang B, Shadday P, Brosgart CL. *Estimated prevalence of chronic hepatitis B (CHB) in foreign born (FB) persons living in the United States (U.S.) by country/region of origin*. Presented at 59th Annual Meeting of the American Association for the Study of Liver Diseases; October 31–November 4, 2008. San Francisco, CA; 2008: Poster number 853.
14. Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep*. 2008;57:1–20.
15. Beasley RP, Hwang LY. Hepatocellular carcinoma and hepatitis B virus. *Semin Liver Dis*. 1984;4:113–121.
16. Burk RD, Hwang LY, Ho GY, Shafritz DA, Beasley RP. Outcome of perinatal hepatitis B virus exposure is dependent on maternal virus load. *J Infect Dis*. 1994;170:1418–1423.
17. World Health Organization. *Hepatitis B*. Department of Communicable Diseases Surveillance and Response. www.who.int/csr/disease/hepatitis/HepatitisB/_whocdscsrlyo2002_2.pdf; Accessed April 13, 2011.
18. World Health Organization. Hepatitis fact sheet WHO/204, revised August, 2008. www.who.int/mediacentre/factsheets/fs204/en; Accessed June 4, 2008.
19. Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev*. 2006;28:112–125.
20. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127:S35–S50.
21. Han KH, Ahn SH. How to predict HCC development in patients with chronic B viral liver disease? *Intervirology*. 2005;48:23–28.
22. Lin CL, Liao LY, Liu CJ, et al. Hepatitis B viral factors in HBeAg-negative carriers with persistently normal serum alanine aminotransferase levels. *Hepatology*. 2007;45:1193–1198.
23. Sharma SK, Saini N, Chwla Y. Hepatitis B virus: inactive carriers. *Virol J*. 2005;2:82.
24. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology*. 2007;45:1056–1075.
25. Marcellin P, Piratvisuth T, Brunetto M, et al. *Increasing rates of HBsAG clearance and seroconversion in patients with HBeAG-negative disease treated with peginterferon Alfa-2A ± lamivudine: results of 5-year post-treatment follow up*. Presented at the 44th Annual Meeting of the European Association for the Study of the Liver, April 22–26 2009. Abstract no. 805; 2009.
26. Gish RG, Chang TT, Lai CL, et al. Loss of HBsAg antigen during treatment with entecavir or lamivudine in nucleoside-naive HBeAg-positive patients with chronic hepatitis B. *J Viral Hepat*. 2010;17:16–22.
27. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology*. 2011;140:132–143.
28. Heathcote EJ, Gane E, de Man R, et al. *Long-term (4 year) efficacy and safety of tenofovir disoproxil fumarate (TDF)*

treatment in HBeAg-positive patients (HBeAg+) with chronic hepatitis B (study 103): preliminary analysis. Presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases, Boston, MA; 2010. Abstract number 477.
29. Huo TI, Wu JC, Lee PC, et al. Sero-clearance of hepatitis B surface antigen in chronic carriers does not necessarily imply a good prognosis. *Hepatology*. 1998;28:231–236.
30. Tong MJ, Hsu L, Hsien C, et al. A comparison of hepatitis B viral markers of patients in different clinical stages of chronic infection. *Hepatol Int*. 2010;4:516–522.
31. Moyer LA, Mast EE. Hepatitis B: virology, epidemiology, disease, and prevention, and an overview of viral hepatitis. *Am J Prev Med*. 1994;10:45–55.
32. Perrillo RP, Wright T, Rakela J, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology*. 2001;33:424–432.
33. Lin X, Robinson NJ, Thursz M, et al. Chronic hepatitis B virus infection in the Asia-Pacific region and Africa: review of disease progression. *J Gastroenterol Hepatol*. 2005;20:833–843.
34. Chu CM. Natural history of chronic hepatitis B virus infection in adults with emphasis on the occurrence of cirrhosis and hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2000;15:E25–E30.
35. Kim CY, Kim JO, Lee HS, Yoon YB, Song IS. Natural course and survival of chronic hepatitis B and liver cirrhosis in Korea: observation of 20 years. *Korean J Med*. 1994;46:217–229.
36. Yuen MF, Yuan HJ, Wong DK, et al. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut*. 2005;54:1610–1614.
37. Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. *Semin Liver Dis*. 2006;26:142–152.
38. Tong MJ, Hsien C, Song JJ, et al. Factors associated with progression to hepatocellular carcinoma and to death from liver complications in patients with HBsAg-positive cirrhosis. *Dig Dis Sci*. 2009;54:1337–1346.
39. Wu GC, Zhou WP, Zhao YR, et al. The natural history of chronic hepatitis B: a retrospective study. *Hepatobiliary Pancreat Dis Int*. 2003;2:566–570.
40. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med*. 2002;347:168–174.
41. Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. *J Gastroenterol Hepatol*. 2011;26:628–638.
42. Chan HL, Hui AY, Wong ML, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. *Gut*. 2004;53:1494–1498.
43. Liu CJ, Chen BF, Chen PJ, et al. Role of hepatitis B viral load and basal core promoter mutation in hepatocellular carcinoma in hepatitis B carriers. *J Infect Dis*. 2006;193:1258–1265.
44. Kao JH, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology*. 2003;124:327–334.
45. Tong MJ, Blatt LM, Kao JH, Cheng JT, Corey WG. Basal core promoter T1762/A1764 and precore A1896 gene mutations in hepatitis B surface antigen-positive hepatocellular carcinoma: a comparison with chronic carriers. *Liver Int*. 2007;27:1356–1363.
46. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology*. 2006;130:678–686.
47. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295:65–73.
48. Yuen MF, Tanaka Y, Shinkai N, et al. Risk for hepatocellular carcinoma with respect to hepatitis B virus genotypes B/C, specific mutations of enhancer II/core promoter/precore regions and HBV DNA levels. *Gut*. 2008;57:98–102.
49. Chan HL, Jia J. Chronic hepatitis B in Asia-new insights from the past decade. *J Gastroenterol Hepatol*. 2011;26:131–137.
50. Fang ZL, Yang J, Ge X, et al. Core promoter mutations (A(1762)T and G(1764)A) and viral genotype in chronic hepatitis B and hepatocellular carcinoma in Guangxi, China. *J Med Virol*. 2002;68:33–40.
51. Yuen MF, Tanaka Y, Mizokami M, et al. Role of hepatitis B virus genotypes Ba and C, core promoter and precore mutations on hepatocellular carcinoma: a case control study. *Carcinogenesis*. 2004;25:1593–1598.
52. McMahon BJ. The natural history of chronic hepatitis B virus infection. *Hepatology*. 2009;49:S45–S55.
53. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. *Lancet*. 1981;2:1129–1133.
54. Liaw YF, Leung N, Kao JH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int*. 2008;2:263–283.
55. Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol*. 2009;50:80–88.
56. Park BK, Park YN, Ahn SH, et al. Long-term outcome of chronic hepatitis B based on histological grade and stage. *J Gastroenterol Hepatol*. 2007;22:383–388.
57. Tong MJ, Blatt LM, Kao JH, Cheng JT, Corey WG. Precore/basal core promoter mutants and hepatitis B viral DNA levels as predictors for liver deaths and hepatocellular carcinoma. *World J Gastroenterol*. 2006;12:6620–6626.
58. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2004;130:417–422.
59. Wong GL, Wong VW, Tan GM, et al. Surveillance programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. *Liver Int Official J Int Assoc Study Liver*. 2008;28:79–87.
60. Tong MJ, Sun HE, Hsien C, Lu DS. Surveillance for hepatocellular carcinoma improves survival in Asian American patients with hepatitis B: results from a community-based clinic. *Dig Dis Sci*. 2010;55:826–835.
61. McClune AC, Tong MJ. Chronic hepatitis B and hepatocellular carcinoma. *Clin Liver Dis*. 2010;14:461–476.
62. Tong MJ, Nguyen MO, Tong LT, Blatt LM. Development of hepatocellular carcinoma after seroclearance of hepatitis B surface antigen. *Clin Gastroenterol Hepatol*. 2009;7:889–893.
63. Chen MF, Tsai HP, Jeng LB, et al. Prognostic factors after resection for hepatocellular carcinoma in noncirrhotic livers: univariate and multivariate analysis. *World J Surg*. 2003;27:443–447.
64. Chang CH, Chau GY, Lui WY, Tsay SH, King KL, Wu CW. Long-term results of hepatic resection for hepatocellular carcinoma originating from the noncirrhotic liver. *Arch Surg*. 2004;139:320–325; discussion 326.
65. Tong MJ, Chavalitdhamrong D, Lu DS, et al. Survival in Asian Americans after treatments for hepatocellular carcinoma: a seven-year experience at UCLA. *J Clin Gastroenterol*. 2010;44:e63–e70.
66. Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol*. 2008;6:1315–1341; quiz 1286.
67. Marcellin P, Dusheiko G, Zoulim F, et al. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol*. 2009;50:227–242.

68. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50:661–662.
69. Tong MJ, Hsien C, Hsu L, Sun HE, Blatt LM. Treatment recommendations for chronic hepatitis B: an evaluation of current guidelines based on a natural history study in the United States. *Hepatology*. 2008;48:1070–1078.
70. Tong MJ, Hsu L, Chang PW, Blatt LM. Evaluation of current treatment recommendations for chronic hepatitis B: a 2011 update. *J Gastroenterol Hepatol*. 2011;26:829–835.
71. Yuen MF. Revisiting the natural history of chronic hepatitis B: impact of new concepts on clinical management. *J Gastroenterol Hepatol*. 2007;22:973–976.
72. Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. *Hepatology*. 2001;34:139–145.
73. Liaw YF, Sheen IS, Lee CM, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. *Hepatology*. 2011;53:62–72.
74. Gish R, Tsai N, Pan C, et al. *Efficacy and safety of entecavir in nucleos(t)ide Naïve Asians with HBeAg-positive and -negative chronic hepatitis B: results from studies ETV-022/027*. Presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA. October 30–November 3; 2010: Abstract No. 485.
75. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351:1521–1531.
76. Shim JH, Lee HC, Kim KM, et al. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol*. 2010;52:176–182.
77. Han SH, Durazo FA, Saab S, Tong MJ. A proposed, evidence-based approach to the treatment of chronic Hepatitis B. *J Clin Gastroenterol*. 2011;45:259–266.
78. Fattovich G. Natural history and prognosis of hepatitis B. *Semin Liver Dis*. 2003;23:47–58.
79. Liu CJ, Chen BF, Chen PJ, et al. Role of hepatitis B virus precore/core promoter mutations and serum viral load on non-cirrhotic hepatocellular carcinoma: a case-control study. *J Infect Dis*. 2006;194:594–599.
80. Liaw YF. Natural history of chronic hepatitis B virus infection and long-term outcome under treatment. *Liver Int*. 2009;29:100–107.
81. Leung N. Recent data on treatment of chronic hepatitis B with nucleos(t)ide analogues. *Hepatol Int*. 2008;2:163–178.
82. Chang TT, Lai CL, Chien RN, et al. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol*. 2004;19:1276–1282.
83. Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology*. 2003;125:1714–1722.
84. Chan HL, Wang H, Niu J, Chim AM, Sung JJ. Two-year lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B: a double-blind, placebo-controlled trial. *Antivir Ther*. 2007;12:345–353.
85. Peters MG, Hann Hw H, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology*. 2004;126:91–101.
86. Lim SG, Marcellin P, Tassopoulos N, et al. Clinical trial: effects of adefovir dipivoxil therapy in Asian and Caucasian patients with chronic hepatitis B. *Aliment Pharmacol Ther*. 2007;26:1419–1428.
87. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology*. 2006;131:1743–1751.
88. Liaw YF, Gane E, Leung N, et al. 2-year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology*. 2009;136:486–495.
89. Hou J, Yin YK, Xu D, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: results at 1 year of a randomized, double-blind trial. *Hepatology*. 2008;47:447–454.
90. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2004;351:1206–1217.
91. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352:2682–2695.
92. Piratvisuth T, Lau G, Chao YC, et al. Sustained response to peginterferon alfa-2a (40 kD) with or without lamivudine in Asian patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. *Hepatol Int*. 2008;2:102–110.
93. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2006;354:1001–1010.
94. Seto WK, Lai C-L, Fung J, et al. *Three-year study on viral suppression and resistance profile for treatment-naive CHB patients receiving continuous entecavir treatment*. Presented at the 20th Conference of the Asian Pacific Association for the Study of the Liver, Beijing, China; March 25–28 2010. FP-095.
95. Yao G. Entecavir is a potent anti-HBV drug superior to lamivudine: experience from clinical trials in China. *J Antimicrob Chemother*. 2007;60:201–205.
96. Pan C, Tong MJ, Kowdley K, et al. *Long-term Entecavir treatment for up to 5 years in Asians with HBeAg-positive nucleos(t)ide-naive chronic hepatitis B: results from ETV-022 and -901*. Presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston MA; November 2010: Abstract no. 478.
97. Tong MJ, Chang TT, Wu SS, et al. *Histologic improvement in Asian patients with HBeAg(+) and HBeAg(-) chronic hepatitis B after long-term treatment with entecavir: results from ETV-022, -027 and -901 studies*. Presented at Digestive Disease Week 2010. New Orleans, LA; May 2010: Abstract no. 433.
98. Tenney DJ, Pokornowski KA, Rose RE, et al. *Entecavir maintains a high genetic barrier to HBV resistance through 6 years in naive patients*. Presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, CA; November 2009: Abstract no. 20.
99. Yuen MF, Seto WK, Fung J, Wong DK, Yuen JC, Lai CL. Three years of continuous entecavir therapy in treatment-naive chronic hepatitis B patients: VIRAL suppression, viral resistance, and clinical safety. *Am J Gastroenterol.* 2011.
100. Pan C, Hu KQ. *Excellent treatment response to tenofovir (TDF) monotherapy in chronic hepatitis B (CHB) patients with prior suboptimal response to entecavir (ETV) monotherapy*. Presented at the 59th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA; November 2008: Abstract no. 932.
101. Lee S, Heathcote EJ, Sievert W, et al. *Tenofovir disoproxil fumarate (TDF) versus adefovir dipivoxil (ADV) in Asians with HBeAg-positive and HBeAg-negative chronic hepatitis B participating in studies 102 and 103*. Presented at the 59th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA; November 2008: Abstract no. 980.
102. Gane E, Lee S, Heathcote EJ, et al. *Four years efficacy and safety of tenofovir disoproxil fumarate (TDF) in Asians with HBeAg-positive and HBeAg-negative chronic hepatitis B (CHB), preliminary analysis*. Presented at the 61st Annual

Meeting of the American Association for the Study of Liver Diseases. Boston, MA; November, 2010: Abstract number 481.
103. Pan C, Chan S, Trinh H, et al. *Tenofovir disoproxil fumarate (TDF) shows similar virologic suppression and safety between Asians and Non-Asians with chronic hepatitis B (CHB)*. Presented at the 21st Conference of the Asian Pacific Association for the Study of the Liver, Bangkok, Thailand; February 18, 2011: Abstract no. PP05-99.
104. Genentech, Inc. *PEGASYS (peginterferon alfa-2a) full prescribing information*; 2011. http://www.gene.com/gene/products/information/pegasys/pdf/pi.pdf. Accessed April 16, 2011.
105. Gilead Sciences Inc. *HEPSERA® (adefovir dipivoxil) tablets full prescribing information*; 2009. http://www.hepsera.com/. Accessed April 16, 2011.
106. Gilead Sciences Inc. *VIREAD® (tenofovir disoproxil fumarate) tablets Full Prescribing Information*. 2010; http://www.viread.com/global_pdfs/Viread_FPI.pdf. Accessed April 16, 2011.
107. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. *Hepatology*. 2009;49:S185–S195.
108. Keeffe EB, Zeuzem S, Koff RS, et al. Report of an international workshop: roadmap for management of patients receiving oral therapy for chronic hepatitis B. *Clin Gastroenterol Hepatol*. 2007;5:890–897.
109. Pan C, Hu KQ, Yu A, Chen W, Bunchorntavakul C, Reddy R. Response to tenofovir monotherapy in chronic hepatitis B patients with prior suboptimal response to entecavir. *J Viral Hepat.* 2011 (in press).
110. Kuo YH, Chen CH, Wang JH, et al. Extended lamivudine consolidation therapy in hepatitis B e antigen-positive chronic hepatitis B patients improves sustained hepatitis B e antigen seroconversion. *Scand J Gastroenterol*. 2010;45:75–81.
111. Reijnders JG, Perquin MJ, Zhang N, Hansen BE, Janssen HL. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. *Gastroenterology*. 2010;139:491–498.
112. Fung J, Lai CL, Tanaka Y, et al. The duration of lamivudine therapy for chronic hepatitis B: cessation vs. continuation of treatment after HBeAg seroconversion. *Am J Gastroenterol.* 2009;104:1940–1946; quiz 1947.
113. Hadziyannis SJ, Sevastianos V, Rapti IN, Tassopoulos N. Sustained biochemical and virological remission after discontinuation of 4 to 5 years of adefovir dipivoxil (ADV) treatment in HBeAg-negative chronic hepatitis B. *Hepatology*. 2006;44:231A.
114. Yuen MF, Kato T, Mizokami M, et al. Clinical outcome and virologic profiles of severe hepatitis B exacerbation due to YMDD mutations. *J Hepatol*. 2003;39:850–855.
115. Nafa S, Ahmed S, Tavan D, et al. Early detection of viral resistance by determination of hepatitis B virus polymerase mutations in patients treated by lamivudine for chronic hepatitis B. *Hepatology*. 2000;32:1078–1088.
116. Mutimer D, Pillay D, Shields P, et al. Outcome of lamivudine-resistant hepatitis B virus infection in the liver transplant recipient. *Gut*. 2000;46:107–113.
117. Thibault V, Aubron-Olivier C, Agut H, Katlama C. Primary infection with a lamivudine-resistant hepatitis B virus. *AIDS*. 2002;16:131–133.
118. Hongthanakorn C, Chotiyaputta W, Oberhelman K, et al. Virological breakthrough and resistance in patients with chronic hepatitis B receiving nucleos(t)ide analogues in clinical practice. *Hepatology*. 2011;53:1854–1863.
119. Patterson SJ, George J, Strasser SI, et al. Tenofovir disoproxil fumarate rescue therapy following failure of both lamivudine and adefovir dipivoxil in chronic hepatitis B. *Gut*. 2011;60:247–254.
120. Reijnders JG, Deterding K, Petersen J, et al. Antiviral effect of entecavir in chronic hepatitis B: influence of prior exposure to nucleos(t)ide analogues. *J Hepatol*. 2010;52:493–500.
121. Choe WH, Hong SP, Kim BK, et al. Evolution of hepatitis B virus mutation during entecavir rescue therapy in patients with antiviral resistance to lamivudine and adefovir. *Antivir Ther*. 2009;14:985–993.
122. Nguyen MH, Trinh HN, Do ST, et al. Response to entecavir (ETV) in patients with chronic hepatitis B (CHB) and prior suboptimal response to adefovir (ADV): interim report of a multicenter study. *Gastroenterology*. 2009;136:A-798.
123. Pan CQ, Hu KQ. Excellent treatment response to tenofovir monotherapy in chronic hepatitis B (CHB) patients with prior suboptimal response to entecavir monotherapy. *Hepatology*. 2008;8:725A.
124. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep.* 2006;55(RR-16):1–33; quiz CE31-34.
125. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat*. 2009;16:94–103.
126. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust*. 2009;190:489–492.
127. Zou H, Chen Y, Duan Z, Zhang H, Pan CQ. Virologic factors associated with failure to passive active immunoprophylaxis in infants born to HBsAg-positive mothers. *J Viral Hepat.* (in press).
128. Pan CQ, Han GR, Zhao W, Jiang HX, Cao MK. A prospective open-label study to evaluate the efficacy, safety and tolerability of telbivudine in HbeAg+ chronic hepatitis B pregnant women. *Hepatology*. 2010;52:500A.
129. Han GR, Zhao W, Jiang HX, Cao MK, Jiang HX, Pan CQ. A prospective open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus to the infant. *Hepatology*. 2010;52:427A.
130. Zhou H, Chen Y, Duan Z, Zhang H, Pan CQ. A prospective study for clinical outcomes of caesarean section on perinatal transmission of hepatitis B virus in infants born to HBeAg-positive mothers with chronic hepatitis B. *Hepatology*. 2010;52:441A.
131. Hung JH, Chu CJ, Sung PL, et al. Lamivudine therapy in the treatment of chronic hepatitis B with acute exacerbation during pregnancy. *J Chin Med Assoc*. 2008;71:155–158.
132. Abbas Z, Jafri W, Raza S. Hepatitis D: scenario in the Asia-Pacific region. *World J Gastroenterol*. 2010;16:554–562.
133. Liu CJ, Liou JM, Chen DS, Chen PJ. Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. *J Formos Med Assoc*. 2005;104:783–791.
134. Wedemeyer H. Hepatitis D revival. *Liver Int Official J Int Assoc Study Liver*. 2011;31:140–144.
135. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. *J Gastroenterol Hepatol*. 2008;23:512–520.
136. Yu JW, Sun LJ, Zhao YH, Kang P, Gao J, Li SC. Analysis of the efficacy of treatment with peginterferon alpha-2a and ribavirin in patients coinfected with hepatitis B virus and hepatitis C virus. *Liver Int Official J Int Assoc Study Liver*. 2009;29:1485–1493.
137. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology*. 2009;136:496–504 e493.
138. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. Impact of hepatitis B virus infection on the progression of AIDS and

mortality in HIV-infected individuals: a cohort study and meta-analysis. *Clin Infect Dis*. 2009;48:1763–1771.
139. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology*. 2009;49:S138–S145.
140. Martin-Carbonero L, Teixeira T, Poveda E, et al. Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. *AIDS*. 2011; 25:73–79.
141. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med*. 2007;356:2614–2621.
142. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. 2011; 1–166. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed April 17, 2011.
143. Soriano V, Puoti M, Sulkowski M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS*. 2007;21:1073–1089.
144. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis*. 2001;32:144–148.
145. Hoofnagle JH, Dusheiko GM, Schafer DF, et al. Reactivation of chronic hepatitis B virus infection by cancer chemotherapy. *Ann Intern Med*. 1982;96:447–449.
146. Lubel JS, Angus PW. Hepatitis B reactivation in patients receiving cytotoxic chemotherapy: diagnosis and management. *J Gastroenterol Hepatol*. 2010;25:864–871.
147. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med*. 2008;148:519–528.
148. Centers for Disease Control. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR*. 2008;57:1–20.
149. Yamagata M, Murohisa T, Tsuchida K, et al. Fulminant B hepatitis in a surface antigen and hepatitis B DNA-negative patient with diffuse large B-cell lymphoma after CHOP chemotherapy plus rituximab. *Leuk Lymphoma*. 2007;48:431–433.
150. Onozawa M, Hashino S, Izumiyama K, et al. Progressive disappearance of anti-hepatitis B surface antigen antibody and reverse seroconversion after allogeneic hematopoietic stem cell transplantation in patients with previous hepatitis B virus infection. *Transplantation*. 2005;79:616–619.
151. Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol*. 2011;22:1170–1180.
152. Lee SS, Heathcote EJ, Sievert W, et al. *Three years efficacy and safety of tenofovir disoproxil fumarate (TDF) in Asians with HBeAg-positive and HBeAg-negative chronic hepatitis B*. Presented at 60th Annual Meeting of the American Association for the Study of Liver Diseases; October 30–November 3 2009. Boston, MA: Poster no. 490.
153. Chan S, Pan C, Bae H, et al. *A phase 4 study to evaluate the efficacy, safety, and tolerability of tenofovir disoproxil fumarate (TDF) in Asian American adults with chronic hepatitis B (CHB) infection*. Presented at the 21st Conference of the Asian Pacific for the Study of the Liver. Bangkok, Thailand; February 17–20 2011: Abstract no. 608.
154. Berg T, Marcellin P, Zoulim F, et al. Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. *Gastroenterology*. 2010;139:1207–1217.