





An expert consensus for the management of chronic hepatitis B in Asian Americans

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Funding information

Independent grants to the Gi Health Foundation from Bristol Myers Squibb and Gilead Sciences, Inc. were used to help support the development of these recommendations

Summary

Background: Hepatitis B virus (HBV) infection is common with major clinical consequences. In Asian Americans, the HBsAg carrier rate ranges from 2% to 16% which approximates the rates from their countries of origin. Similarly, HBV is the most important cause of cirrhosis, hepatocellular carcinoma (HCC) and liver related deaths in HBsAg positive Asians worldwide.

Aim: To generate recommendations for the management of Asian Americans infected with HBV.

Methods: These guidelines are based on relevant data derived from medical reports on HBV from Asian countries as well as from studies in the HBsAg positive Asian Americans. The guidelines herein differ from other recommendations in the treatment of both HBeAg positive and negative chronic hepatitis B (CHB), in the approach to HCC surveillance, and in the management of HBV in pregnant women.

Results: Asian American patients, HBeAg positive or negative, with HBV DNA levels >2000 IU/mL (>10⁴ copies/mL) and ALT values above normal are candidates for anti-viral therapy. HBeAg negative patients with HBV DNA >2000 IU/mL and normal ALT levels but who have either serum albumin <3.5 g/dL or platelet count <130 000 mm³, basal core promoter (BCP) mutations, or who have first-degree relatives with HCC should be offered treatment. Patients with cirrhosis and detectable HBV DNA must receive life-long anti-viral therapy. Indications for treatment include pregnant women with high viraemia, coinfecting patients, and those requiring immunosuppressive therapy. In HBsAg positive patients with risk factors, life-long surveillance for HCC with alpha-fetoprotein (AFP) testing and abdominal ultrasound examination at 6-month intervals is required. In CHB patients receiving HCC treatments, repeat imaging with contrast CT scan or MRI at 3-month intervals is strongly recommended. These guidelines have been assigned to a Class (reflecting benefit vs. risk) and a Level (assessing strength or certainty) of evidence.

Conclusions: Application of the recommendations made based on a review of the relevant literature and the opinion of a panel of Asian American physicians with expertise in HBV treatment will inform physicians and improve patient outcomes.

The Handling Editor for this article was Professor Grace Wong, and it was accepted for publication after full peer-review.

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1 | INTRODUCTION

Hepatitis B virus infection is common and clinically consequential worldwide. The prevalence of HBV carriers globally ranges from 240 million to 300 million persons.^{1,2} An estimated 75% of these infected individuals reside in the Asia-Pacific region wherein HBV is responsible for up to one-third of all cases of cirrhosis and over 50% of HCC cases. HBV infection is a major public health problem in the USA, especially among ethnic minorities. The prevalence of HBsAg positive persons in the USA is estimated to be 2.2 million persons. Of these, 1.32 million are foreign born with 58% immigrating from high or intermediate endemic areas of Asia.³ At present, immigrants account for 95% of newly diagnosed HBV infections in the USA.⁴ As a result, Asian Americans are the ethnic group with the highest prevalence of HBV, and have the highest rates of HCC incidence and mortality in this country. A recent study in 400 HBsAg positive Asian American patients showed that during a mean 84-month follow-up, 67 of 71 (94%) deaths were from either liver-related complications or HCC.⁵ Recent reports indicate that both screening for HBV in the Asian American population and linkage to health care have been suboptimal.^{6,7} Despite the availability of potent anti-viral medications, improving the morbidity and mortality rates associated with HBV in Asian Americans require greater emphasis on HBV education among health care providers.

2 | METHODS

In April 2016, a panel of Asian American physicians with expertise in the management of HBV convened in Pasadena, CA. Each member was pre-assigned a section and instructed to review the relevant medical literature specifically aimed at Asian and Asian Americans with hepatitis B infection. During the meeting, each topic was presented and subsequently, the manuscript was compiled and edited (MJT). The manuscript was reviewed by the authors and a consensus on management of Hepatitis B in Asian Americans was finalised.

Unique for Asians and Asian Americans with CHB include maternal to child transmission (MTCT), the long period of chronicity beginning in the immune tolerant stage with high viraemia, presence of genotypes B or C, and the high rate of progression to liver related complications and HCC. More recently, disparities in HCC survival was reported in a subgroup of first generation Asian immigrants to the USA, specifically due to paucity of medical care, lack of hepatitis B screening and treatments, and late stage of HCC presentation.⁸ Thus, the aim of this manuscript is to review the natural history, virology and clinical characteristics as it pertains to the approach, management and treatment of Asian Americans with chronic hepatitis B. It is anticipated that the information herein will assist physicians in the day to day management of CHB in the Asian American population.

3 | QUALITY OF EVIDENCE

This document was intended to provide recommendations regarding the management of CHB infection in adult Asian Americans. Recommendations set forth herein have been assigned to a Class (reflecting benefit vs risk) and a Level (assessing strength or certainty) of evidence according to the grading system set forth in the 2015 update of the American College of Cardiology/American Heart Association Clinical Practice Guideline Recommendation Classification System (Data S1).⁹

4 | EPIDEMIOLOGY, NATURAL HISTORY, CLINICAL STAGES AND PROGRESSION OF DISEASE IN ASIANS

4.1 | Prevalence of HBsAg

Hepatitis B virus carrier rates in Asia have been reported to be as high as 20% in the male population of Guang Xi Province and up to 27.5% in the Fujian Province of China.¹⁰ HBV carrier rates ranging from 10% to 15% have been reported in Hong Kong, Shanghai, Taiwan and Southeast Asia.¹¹ According to the results of a recent study from China, HBV carrier rates have fallen to 7.2% in regions where HBV vaccination programmes have been implemented.¹² The report also indicated that the carrier rate in children <5 years of age had decreased from 9.7% in 1992 to 1% in 2006, thus preventing an estimated 16-20 million HBV carriers through HBV vaccination of infants and young children. A similar study in Taiwan showed a decrease in the HBV carrier rate in children from 10% in 1984 to 0.5% in 2009 as well as in the childhood HCC rate after implementation of HBV vaccination of infants at birth.¹³ However, in other parts of Asia, the HBsAg carrier rates remain high, particularly in countries in which HBV vaccine programmes have not yet been implemented. In these endemic areas, 80% of patients with chronic hepatitis, 92% with cirrhosis, and 80% with HCC are HBsAg positive.¹⁴⁻¹⁹

Notably, the HBsAg carrier rates among Asian Americans are similar to rates reported in their countries of origin, especially in first generation immigrants to the USA^{3,12,19,20} Table 1 shows a comparison of HBsAg prevalence rates derived from screening programmes in various cities in the USA, to a study which derived the HBsAg carrier rates by estimating the number of foreign born persons in the USA and the prevalence of HBsAg carriers reported from their native countries.³

4.2 | Routes of infection

In high and intermediate HBV endemic areas (HBsAg prevalence rates of $\geq 8\%$ and 2%-7% respectively) in Asia, HBV infection takes place from mother to child during birth. Up to 90% of infants born to HBsAg positive mothers with high viraemia become chronically infected if immunoprophylaxis is not administered at

TABLE 1 The prevalence of HBsAg in Asian Americans

Country of origin	Screening in the USA	Derived from prevalence in country of origin
China	5.6%-12.3%	12.3%
Vietnam	3.2%-13.6%	12.8%
Philippines	5.5%-7.4%	7.4%
South Korea	5.3%	5.3%
Laos	2.3%-16.4%	11.6%
Burma	9.4%-12.4%	11.6%
Cambodian	10.3%	13.6%
Thailand	3.9%-6.1%	12.5%
Malaysia	8.8%	5.6%
India	1.5%	3.2%

birth. In low endemic areas (HBsAg prevalence rates <2%), exposure to HBV occurs primarily among adolescents and adults, in whom the carrier rate following acute infection is <5%. In Asian adults, sexual contact may account for up to 10% of all HBV carriers. HBV transmission also occurs at high rates among injection drug users in Asia.²¹

4.3 | The phases of CHB infection

In Asian patients, the natural course of CHB infection can be divided into five distinct phases which include the immune tolerant, immune activation, low replication phase, reactivation and the clinical resolution phase (Figure 1). A description of the five phases is provided in Data S2.

4.4 | The clinical stages of CHB infection

Based on HBeAg status, as well as ALT and HBV DNA levels at presentation, patients may be classified into one of several clinical stages of HBV infection (Figure 2).²² During subsequent visits, changes in the patient's virological and biochemical parameters may clarify the patient's clinical status, especially regarding the evaluation of disease progression and assessment of the need for anti-viral therapy. The six clinical stages include: HBeAg positive immune tolerant, chronic hepatitis and cirrhosis patients, and the HBeAg negative low replication carrier, chronic hepatitis and cirrhosis patients. These clinical stages are further characterised in Table S1.

4.5 | Predictors of disease progression

The annual rates of progression from chronic hepatitis to cirrhosis, decompensated cirrhosis, HCC and death are shown on Figure S1 and described in Data S3. Serologic predictors of disease progression in CHB patients include HBeAg, HBV genotype, HBV DNA titres, BCP mutants and PC mutants. A description of each of these factors are shown in Table S2. Tests for HBV genotype, BCP mutants and PC mutants are readily available at commercial laboratories in the

USA. In addition, serum AFP levels are elevated in patients with acute and chronic liver diseases in the absence of HCC, especially in the presence of ongoing necroinflammation.^{23,24} Elevation of AFP levels during ALT flares was detected in CHB-infected patients who eventually developed cirrhosis, and thus is another parameter to use when evaluating patients for anti-viral therapy.²⁵

4.6 | Family history of HCC

In a recent study, of 413 Asian American HBsAg positive patients, 173 with HCC and 240 without HCC were sub grouped into those with or without a family history of HCC and analysed for risk factors associated with HCC development.²⁵ Forty-four of 173 (25.4%) HCC patients had 82 other blood relatives with HCC. Of these, 69 (84.1%) were first degree relatives. In a multivariate logistic regression model, a family history of HCC was an independent factor associated with HCC development (OR = 2.58, $P = 0.048$). In addition, in a large population-based cohort study of 22 472 participants from Taiwan, 374 cases of incident HCC were identified during 362 268 person-years of follow-up.²⁶ The multivariate-adjusted hazard ratio for HCC for HBsAg positive individuals with family history of HCC was 32.33 ($P < 0.001$), confirming a synergistic effect of family history and HBV on incidence of HCC.

5 | SURVEILLANCE FOR HCC IN ASIAN PATIENTS WITH CHB INFECTION

Patients with CHB infection have a > 100-fold increased risk for the development of HCC compared with those without HBV infection.^{27,28} The annual incidence of HCC in low replication carriers is estimated to be 0.5% and increases to 3%-10% in patients with cirrhosis.²⁹ The REVEAL study from Taiwan by Chen et al demonstrated a strong correlation between increasing HBV DNA levels beginning at >2000 IU/mL (>10⁴ copies/mL) and risk for HCC.^{27,30} Another report on 820 patients with CHB infection 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.³¹ In a predominantly Asian American population, risk factors for HCC included older age, cirrhosis, PC mutations, BCP mutations, and high serum AFP levels.³²⁻³⁴

A randomised controlled trial for HCC screening in >18 000 subjects in Shanghai, China showed a 37% reduction in HCC-related mortality among patients detected by surveillance.³⁵ Another recent study in Asian Americans with HBV showed that surveillance identified HCC patients with smaller tumour burdens and better preserved liver function who were more likely to receive curative therapies which prolonged survival.³⁶

Surveillance for HCC in all HBsAg positive patients should include both AFP testing and abdominal ultrasound examination (Figure 3). However, lesion detection rates by ultrasound may be compromised by body habitus, fatty liver and cirrhosis.³⁷ Therefore, cross sectional imaging with contrast enhanced computed

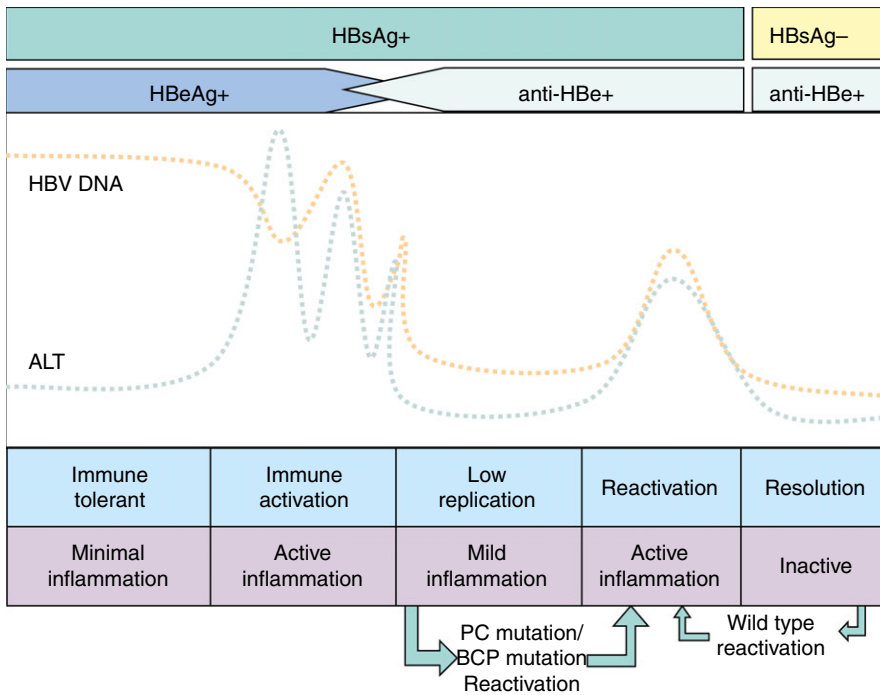


FIGURE 1 The five phases of chronic hepatitis B infection

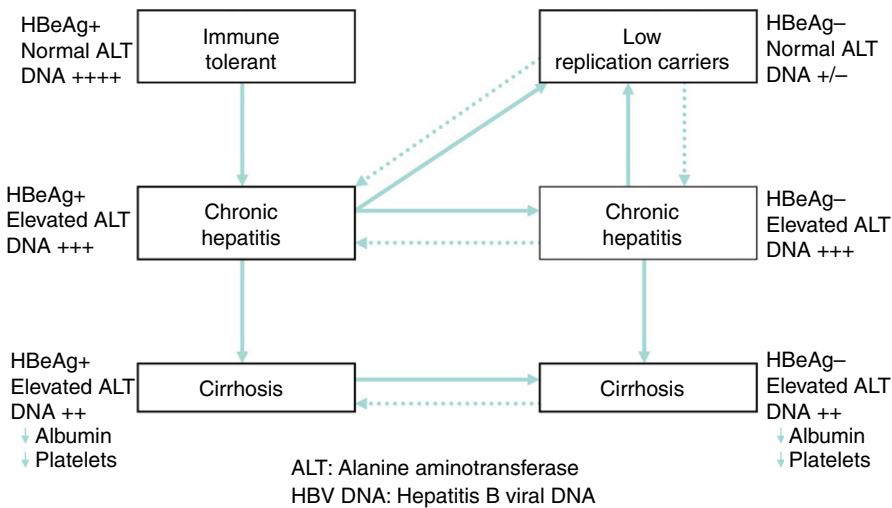


FIGURE 2 The clinical stages of hepatitis B

tomography (CT) or magnetic resonance imaging (MRI) should be considered in a surveillance programme whenever the image quality of an ultrasound is suboptimal (Figure S2). HBsAg positive patients at high risk for HCC development include those with more advanced stage of liver disease, ie, chronic hepatitis, cirrhosis and those with blood relatives with HCC.^{25,38} Patients with low-to-moderate risk include low replication carriers and immune tolerant patients. In addition, since patients who clear HBsAg may still develop HCC, surveillance should be continued, especially if cirrhosis is present at the time of HBsAg loss.³⁹ The current recommendation for HCC surveillance is every 6-12 months in immune tolerant and low replication carriers, and every 6 months in chronic hepatitis and cirrhosis patients (Figure 4). In patients with persistently elevated AFP levels with undetectable lesions by ultrasound examination and in patients receiving HCC treatment, surveillance should include contrast CT

scan or MRI at 3-month intervals, which is based on the average HCC doubling time of 4.3 months.⁴⁰

Although debate remains regarding the optimal age to begin HCC surveillance, it is probably not warranted among paediatric 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. If clinically active chronic hepatitis infection, cirrhosis or other risk factors for HCC are present, then surveillance for HCC should be instituted.^{36,41,42}

Further management guidelines for liver lesions detected by surveillance are presented in Data S4. Confirmed cases of HCC must be referred to a multidisciplinary centre consisting of hepatologists, surgeons, interventional radiologists and oncologists who specialise in the treatments of this malignancy (Table S3).⁴³ We recommend

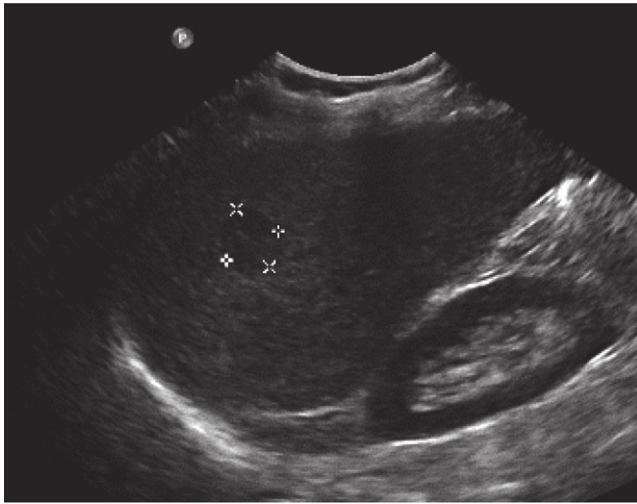


FIGURE 3 Ultrasound detection of a 3 cm HCC

that during the initial workup of a new HBsAg positive patient, a baseline abdominal ultrasound and AFP measurement should be obtained. Thereafter, routine HCC surveillance with the above tests must be performed at the recommended intervals.

6 | TREATMENT OF CHB INFECTION IN ASIAN AMERICANS: PROPOSED CANDIDATES FOR TREATMENT BASED ON CLINICAL STAGE

The goal of anti-viral therapy in patients infected with HBV is to prevent progression from chronic hepatitis to cirrhosis, end-stage liver disease, and development of HCC. The eligibility for anti-viral therapy in recently published guidelines is based on HBeAg status, ALT values, and levels of HBV DNA in the setting of either chronic hepatitis or cirrhosis.⁴⁴⁻⁴⁷

6.1 | The significance of ALT

Elevated serum ALT levels are indicators of hepatic necroinflammatory activity. Because studies have shown that an elevated pre-treatment ALT level was a significant predictor of HBeAg loss or seroconversion to treatments with interferon,^{48,49} pegylated-interferon alfa-2a,⁵⁰ lamivudine (LAM),^{51,52} and adefovir (ADV),⁵³ all of the published guidelines recommend anti-viral therapy for patients with CHB infection who have elevated ALT levels. However, a significant proportion of CHB-infected patients with normal to minimally increased ALT levels may have significant inflammation and fibrosis on liver biopsy.⁵⁴⁻⁵⁷ Also, a meta-analysis demonstrated that approximately one in five patients with persistently normal ALT had fibrosis scores of F2 or higher.⁵⁸ Finally, a study from Hong Kong which included 3,233 CHB patients followed up for over 180 months were stratified by ALT level at presentation and during follow-up ($<0.5 \times \text{ULN}$, $0.5-1 \times \text{ULN}$, $1-2 \times \text{ULN}$, $2-6 \times \text{ULN}$ and $>6 \times \text{ULN}$) and observed for development of decompensated cirrhosis or HCC.⁵⁹ The highest risk of complications was associated with ALT

levels $1-2 \times \text{ULN}$, followed by lesser risks in patients with ALT levels $2-6 \times \text{ULN}$, and $0.5-1 \times \text{ULN}$.

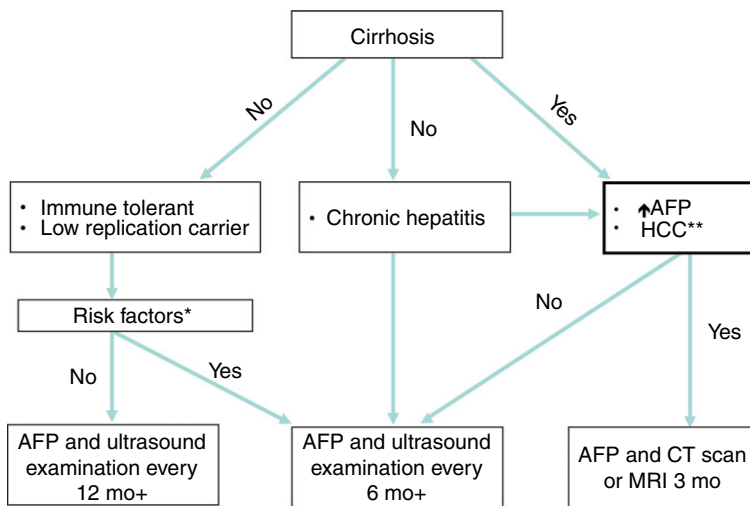
6.2 | The significance of HBV DNA

The advent of PCR-based assays with improved sensitivity heralded the era of serum HBV DNA as a marker of disease progression. HBeAg positive patients and many HBeAg negative patients have HBV DNA levels below 10^5 copies/mL.⁶⁰ From 2001 through 2006, several studies noted the development of HCC in cirrhotic and non-cirrhotic patients with CHB infection with HBV DNA levels as low as $3.7 \log_{10}$ copies/mL.^{5,61-63} In 2006, Chen et al published a study of 3653 HBsAg positive patients followed up for a mean of 11.4 years which showed that the incidence of HCC increased with serum HBV DNA levels at study entry in a dose-related fashion.²⁷ In a parallel publication, Iloeje and colleagues demonstrated a similar relationship between serum HBV DNA and the development of cirrhosis.⁶⁴ In both studies, there was an increased risk of progression to cirrhosis and development of HCC at HBV DNA levels above 10^4 copies/mL. Since then, additional studies have confirmed a serum HBV DNA level $>4 \log_{10}$ copies/mL as predictive of an increased risk for HCC development.^{65,66}

6.3 | Criteria from current guidelines and new era for a more comprehensive treatment strategy

Several recently published guidelines and an expert consensus algorithm focusing on the treatment of CHB infection are summarised in Table S4. The difference in selection of HBV patients for anti-viral therapy in these published guidelines are discussed in Data S5. In a long term, natural history study of predominantly Asian CHB-infected patients in the USA by Tong et al, the treatment criteria designated in the established treatment guidelines were applied to a cohort of 369 HBsAg positive patients followed up for a mean of 84 months (7 years).⁶⁷ Using the threshold, HBV DNA and ALT values stated in the published documents, only 20%-60% of patients who developed HCC and 27%-70% who died from or were transplanted for non-HCC-related liver complications would have been identified initially as anti-viral treatment candidates. Previously, Tong et al reported on a cohort of 400 CHB-infected patients in the USA followed up for a mean of 83.6 months.⁵ The results of a multivariate analysis showed that older age (OR = 26.51, $P = 0.007$), PC mutants (OR = 4.23, $P = 0.02$), and BCP mutants (OR = 2.93, $P = 0.02$) were independent predictors for HCC. Additional studies on PC and BCP mutants are discussed in Data S6.

Recently, Chen et al showed that lower serum albumin levels was an independent risk factor for HCC development.²⁷ In the aforementioned study by Tong et al,⁶⁷ the addition of a platelet count $<130\,000 \text{ mm}^3$ and serum albumin value $<3.5 \text{ g/dL}$ to the criteria established by the published treatment guidelines increased the detection rate of patients eligible for treatment to 89%-100% of patients who died of non-HCC liver-related causes and 96%-100% of patients who developed HCC.



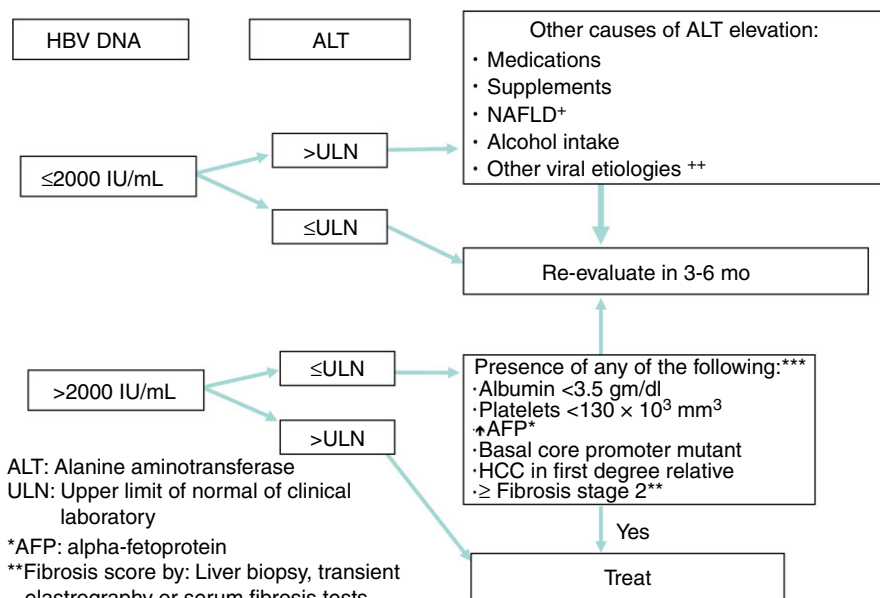
*Risk factors; Family history of HCC, Basal core promoter mutant, diabetes, NASH, HCV or HIV coinfection

**Ongoing HCC treatment

+ If ultrasound examination suboptimal, proceed with contrast CT scan or MRI

AFP: alpha-fetoprotein
HCC: Hepatocellular carcinoma
CT: Computerized tomography
MRI: Magnetic resonance imaging

FIGURE 4 HCC surveillance intervals in Asian patients with hepatitis B



ALT: Alanine aminotransferase
ULN: Upper limit of normal of clinical laboratory

*AFP: alpha-fetoprotein

**Fibrosis score by: Liver biopsy, transient elastography or serum fibrosis tests

*NAFLD: nonalcoholic fatty liver disease

**Viral etiologies: HAV, HCV, HDV, HIV, EBV, CMV

***Based on data from Asian patients

FIGURE 5 Treatment algorithm for HBsAg positive patients with HBsAg positive/negative chronic hepatitis B

6.4 | Recommendations for treatment in Asian American patients with chronic hepatitis B

At present, anti-viral treatment is not recommended for patients who are in the immune tolerant stage or in low replication carriers. Our guidelines are illustrated in a new algorithm, which includes additional laboratory parameters to better identify candidates for treatment to prevent disease progression (Table 2 and Figure 5). The algorithm specifies a quantitative HBV DNA threshold of 2000 IU/mL as the initial determination to consider treatment in both HBeAg positive

and HBeAg negative patients, primarily based on data from the REVEAL-HBV study from Taiwan indicating 10^4 copies/mL (2000 IU/mL) as the threshold HBV DNA level predictive of future cirrhosis and HCC development.²⁷ In patients with an HBV DNA quantitation above this threshold level, determination of serum ALT is the next decision point for treatment. Patients with an ALT value > ULN in the physician's local laboratory in conjunction with an elevated serum HBV DNA would be eligible for consideration of anti-viral therapy.

ALT values of 30 U/L for men and 19 U/L for women were established as the ULN in healthy patients with the lowest risk for

subclinical liver disease⁶⁸ and are used as the ULN determination in the AASLD guidelines and US algorithm. However, in real-world practice, ALT values often exceed these “healthy” values due to underlying factors including steatosis, dyslipidemia, obesity and medications unrelated to CHB infection; therefore, these ALT values cannot be reliably interpreted to reflect inflammation due solely to HBV infection. Moreover, since “normal” ranges in clinical laboratories are determined by the patient population served by that laboratory in addition to nonstandardised assays for ALT measurement, these values will inherently vary between laboratories. The inclusion criteria used for patients treated with nucleoside/nucleotide analog anti-viral therapy in several phase 3 clinical trials were based on > ULN ALT values derived from different clinical laboratories. Thus, the panel recommends ALT > ULN as the threshold value for treatment based on data from Hong Kong showing that significant inflammation and fibrosis were noted in patients with ALT 1-1.5 × ULN.⁶⁹

In patients with an elevated serum HBV DNA above threshold level but serum ALT ≤ ULN, further determination is necessary before initiating anti-viral therapy. The next step is to assess the patient's serum albumin and platelet count. If the serum albumin is <3.5 g/dL or the platelet count is <130 000 mm³, anti-viral therapy can be initiated. However, if serum albumin and platelet counts are persistently above threshold values, then testing to determine the presence of the BCP mutation is recommended. Testing for this mutation should be considered even in patients who are HBeAg positive, since these mutations may exist at baseline and if present, then anti-viral therapy can be initiated. If laboratory testing is unremarkable for hypoalbuminemia, thrombocytopenia, or BCP mutations, then we recommend grading and staging of liver disease with liver biopsy or assessment by noninvasive methods such as transient elastography or serum markers for fibrosis. The presence of F2 fibrosis

or higher in conjunction with inflammation would be an indication to start anti-viral therapy. In the absence of active liver inflammation and advanced fibrosis, anti-viral therapy can be deferred; however, the patient should be monitored at least twice annually or more frequently if indicated. Other risk factors for disease progression include first-degree relatives with HCC.⁷⁰ In addition, patients with elevated AFP levels during flares of hepatitis B (without HCC) may be more prone to have liver disease progression.²⁵ The presence of any of these risk factors indicate that anti-viral therapy should be initiated.

For patients with HBV DNA levels <2000 IU/mL and ALT >ULN, search for other causes of ALT elevation (ie, medications, NASH, excessive alcohol consumption, other viral infections, etc.). In patients with HBV DNA levels <2000 IU/mL and normal ALT values, continual evaluation should be repeated at 3-6 month intervals.

Recent publications report that successful NA therapies reduces necroinflammation, reverses fibrosis and prevents or reverses clinical decompensation in chronic hepatitis and cirrhosis patients.^{71,72} The benefit of reducing liver complications was demonstrated in a prospective trial of LAM in Asian patients with compensated cirrhosis.⁷³ Benefit was primarily observed in patients with sustained viral suppression; however, less significant benefit was noted in patients who developed LAM resistance. Other studies showed that treatment with anti-viral agents with low resistance profiles significantly improved clinical outcomes in patients with decompensated cirrhosis.^{71,74} Furthermore, a recent report indicated that the risk of HCC is significantly increased in patients with HBV-related cirrhosis with low viral loads.⁷⁵ Based on these findings, patients with cirrhosis who have any detectable level of HBV DNA should receive lifelong anti-viral therapy regardless of HBeAg status or ALT values. 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 anti-viral therapy and immediately referred to a liver transplant centre.

TABLE 2 Recommendations for anti-viral therapy in HBeAg positive and HBeAg negative chronic hepatitis B patients

Clinical stage	HBeAg	HBV DNA	Comments	Quality of evidence
Immune tolerant	+	>2000 IU/mL	Insufficient evidence to warrant treatment	IIb C-EO
Low replication carrier	-	<2000 IU/mL	Insufficient evidence to warrant treatment	IIb C-EO
Chronic hepatitis ^a	+/-	>2000 IU/mL	See algorithm	IA
Cirrhosis	+/-	Detectable ^b	Treat	IA
Decompensated cirrhosis	+/-	Detectable ^b	Treat	I B-NR
Hepatocellular carcinoma	+/-	Detectable ^b	Treat	IIb C-EO

EO, expert opinion; NR, Non randomised studies.

^aDiffers from APASL and AASLD guidelines.

^bOption to treat if HBV DNA undetectable.

7 | ANTI-VIRAL THERAPY

7.1 | Current treatments for HBV infection

There are currently seven drugs licensed by the FDA for the treatment of CHB infection, including standard interferon alfa-2b, LAM, ADV, pegylated interferon alfa-2a, telbivudine, entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF), which represents a prodrug of the currently approved formulation of tenofovir. Interferon alfa-2b is no longer used in the USA for the treatment of HBV infection. LAM, ADV, and telbivudine are considered second line agents and a summary of their effectiveness in HBV treatment is described in Data S7. The preferred or first-line agents for the treatment of CHB infection include entecavir, TDF, and pegylated interferon alfa-2a,⁴⁶ although the latter is uncommonly used in the USA. TAF was recently approved for use in the USA in 2016 and also may be considered as a first line treatment for CHB. In this section, we review key data governing the efficacy of

approved agents with regard to clinical endpoints including normalisation of ALT, suppression of HBV DNA to undetectable levels, HBeAg seroconversion, and HBsAg seroconversion. A summary of the four current agents for anti-viral treatment in Asian CHB patients is shown in Table 3.

7.1.1 | Pegylated interferon Alfa-2a

Pegylated interferon alfa-2a (Pegasys) was licensed by the FDA for the treatment of HBV infection in 2005. Two phase 3 clinical trials provided the evidence base supporting approval. In the first, Lau et al⁵⁰ reported the findings in 814 HBeAg positive patients which showed that after 48 weeks of treatment, pegylated interferon alfa-2a alone and pegylated interferon alfa-2b plus LAM were superior to LAM alone in achieving HBeAg seroconversion (32% vs 27% vs 19%, $P = 0.02$) and suppression of HBV DNA to <100 000 copies/mL (32% vs 34% vs. 22%, $P = 0.003$). Eight patients in each of the pegylated interferon groups achieved HBsAg seroconversion, whereas no patients treated with LAM alone achieved this endpoint (3% vs. 3% vs. 0%, $P = 0.004$). In the second, Marcellin et al⁷⁶ reported the findings in 537 HBeAg negative patients which showed that after 48 weeks of treatment, pegylated interferon alfa-2b alone and pegylated interferon alfa-2b plus LAM were superior to LAM alone in achieving normalisation of serum ALT (59% vs 60% vs 44%, $P = 0.004$), and suppression of HBV DNA to <400 copies/mL (19% vs 20% vs 7%, $P < 0.001$). Seven patients in the pegylated interferon alone group and five patients in the pegylated interferon plus LAM group achieved HBsAg seroconversion, whereas no patients treated with LAM achieved this endpoint (4% vs 2.8% vs 0%, $P = 0.029$). Additional studies combined pegylated interferon alfa-2a with NAs such as LAM,⁷⁷ ADV,⁷⁸ telbivudine,⁷⁹ entecavir,⁸⁰ and TDF,⁸¹ but due to limited evidence, these regimens have not been incorporated into practice guidelines.

7.1.2 | Entecavir

Entecavir is an oral NA which was licensed by the FDA for the treatment of HBV infection in 2005. Two phase 3 clinical trials provided the evidence base supporting FDA approval. In the first, Chang et al⁸² reported the findings in 715 treatment-naïve HBeAg positive patients which showed that after 52 weeks of treatment, entecavir was superior to LAM in achieving the primary efficacy endpoint of histological improvement (72% vs 62%, $P = 0.009$), as well as in achieving secondary endpoints including undetectable HBV DNA (67% vs 36%, $P < 0.001$), normalisation of serum ALT (68% vs 60%, $P = 0.02$), and mean log reduction in serum HBV DNA between baseline and week 48 (6.9 vs 5.4 log copies/mL, $P < 0.001$).⁸² No statistical difference was observed in HBeAg seroconversion rates (21% vs 18%, $P = 0.33$). In the second, Lai et al⁸³ reported the findings in 648 HBeAg negative patients which showed that after 52 weeks of treatment, entecavir was superior to LAM in achieving the primary efficacy endpoint of histological improvement (70% vs 61%, $P = 0.01$), as well as in

achieving secondary endpoints including undetectable HBV DNA (90% vs 72%, $P < 0.001$), normalisation of serum ALT (78% vs 71%, $P = 0.045$), and mean log reduction in serum HBV DNA (5.0 vs 4.5 log copies/mL, $P < 0.001$).⁸³ Multiple studies have confirmed the long-term safety and efficacy of entecavir in USA cohorts with sustained virological suppression to undetectable levels and histological improvement.^{84,85}

7.1.3 | Tenofovir disoproxil fumarate (TDF)

Tenofovir disoproxil fumarate is an oral nucleotide analogue, which was licensed by the FDA for the treatment of HBV infection in 2008. Two phase 3 clinical trials provided the evidence base supporting FDA approval. Marcellin et al⁸⁶ reported the findings of both phase 3 clinical trials in which 276 treatment-naïve HBeAg positive patients and 375 treatment-naïve HBeAg negative patients were randomised to receive 48 weeks of treatment with either TDF 300 mg daily or ADV 10 mg daily. TDF was superior to ADV in achieving the primary efficacy endpoint of suppression of HBV DNA to <400 copies/mL (69 IU/mL) and histological improvement in both HBeAg positive (66% vs 12%, $P < 0.001$) and HBeAg negative patients (71% vs 49%, $P < 0.001$). TDF was also superior to ADV for other secondary endpoints including undetectable HBV DNA (76% vs 13%, $P < 0.001$ in HBeAg positive patients and 93% vs 63%, $P < 0.001$ in HBeAg negative patients). TDF was associated with higher rates of normalisation of serum ALT (68% vs 54%, $P = 0.03$) in HBeAg positive patients, but not in HBeAg negative patients (76% vs 77%, $P = 0.86$). Rates of HBeAg seroconversion were not statistically different between TDF and ADV (21% vs 18%, $P = 0.36$), although TDF was associated with a higher rate of HBsAg loss (3.2% vs 0%, $P = 0.02$). Long-term studies have further confirmed the sustained safety and efficacy of TDF including virological suppression and histological regression at 5 years of therapy.⁸⁷⁻⁸⁹

7.1.4 | Tenofovir alafenamide (TAF)

Tenofovir alafenamide represents a prodrug which enhances delivery of active tenofovir to hepatocytes and reduces circulating levels of tenofovir relative to TDF, and thereby decreases the risk of renal dysfunction and bone mineral density (BMD) decline. Two phase 3 clinical trials provided the evidence base supporting FDA approval. Chan et al⁹⁰ reported the results in 873 HBeAg positive patients randomised 2:1 to TAF 25 mg daily ($n = 581$) or TDF 300 mg daily ($n = 292$) for a period of 96 weeks. Based on a non-inferiority study design, no difference was observed between groups in the primary therapeutic endpoint of suppression of HBV DNA to <29 IU/mL (64% TAF vs 67% TDF, $P = 0.25$), or secondary endpoints such as normalisation of serum ALT (72% TAF vs 67% TDF, $P = 0.18$), HBeAg loss (14% TAF vs TDF 12%, $P = 0.47$), HBeAg seroconversion (10% TAF vs 8% TDF, $P = 0.32$) or HBsAg loss (<1% TAF vs <1% TDF, $P = 0.52$). Although total AEs, SAEs, and discontinuations due to AEs were similar between groups, fewer patients on TAF experienced a > 3% decrease in bone

TABLE 3 Virological, biochemical and histological responses to anti-viral agents in treatment naive patients with CHB

Asian patients	Trial endpoints	First line agents					
		Pegylated interferon alfa 2a (up to 45 weeks)	Entecavir (up to 240 weeks)	Tenofovir (up to 192 weeks)	Tenofovir alafenamide (up to 48 weeks)		
HBeAg(-)	HBV DNA	Year 1 undetectable HBV DNA	19%	93%	82% (ITT)	94%	
		Long-term undetectable DNA	N/A	98.3%	97%		
	ALT	Year 1 ALT normalisation	59%	76%	72%	83%	
		Long-term ALT normalisation	N/A	85.7%	86% (combined with e-pos patients) @ 192 weeks		
	HBsAg loss / sero-conversion	Year 1 HBsAg sero-conversion		0/0%	0/0%	0%/0%	
		Long-term HBsAg loss/sero-conversion		0/0%	0/0%		
	Histological Improvement	Year 1 histological improvement	N/A	68%	77%		
		Long-term histological improvement	N/A	100%	N/A		
	HBeAg(+)	HBV DNA	Year 1 undetectable HBV DNA	14% @ 24 wk post Rx	69% (<300 c/mL)	85% (ITT) (<400 copies/mL)	64% (<29 IU/mL)
			Long-term undetectable HBV DNA	N/A	95%	97%	
ALT		Year 1 ALT normalisation	41% @ 24 wk post Rx	63%	72%	72%	
		Long-term ALT normalisation	N/A	76%	86%		
HBeAg loss/ seroconversion		Year 1 HBeAg loss/ seroconversion	31%@24 wk post Rx	16/16%	17/17%	14/10%	
		Long-term HBeAg loss/ sero-conversion	41% @ 48 wk post Rx	40/18%	35/26%		
HBsAg loss/ seroconversion		Year 1 HBsAg seroconversion	2% @ 24 wk post Rx	0.5%	0/0%	<1%/0%	
		Long-term HBsAg loss / sero-conversion	N/A	2.9% in genotype B 0.9% in genotype C	2.28%		
Histological Improvement		Year 1 histological improvement	38%	71%	77%		
		Long-term histological improvement	N/A	100%	N/A		

mineral density at week 48 in the spine (18% TAF vs 38% TDF, $P < 0.001$) and hip (8% TAF vs 24% TDF, $P < 0.001$), and fewer changes were observed in bone turnover markers. In addition, TAF was associated with less change in serum creatinine (0.009 vs 0.026, $P = 0.02$) and fewer patients with decline in the estimated glomerular filtration rate (eGFR) to <50 mL/min (0 vs 2%, $P = 0.004$). Buti et al⁹¹ reported the results in 425 HBeAg negative patients randomised 2:1 to TAF 25 mg daily ($n = 285$) or TDF 300 mg daily ($n = 140$) for a period of 96 weeks. Based on a non-inferiority study design, no difference was observed between groups in the primary therapeutic endpoint of suppression of HBV DNA to <29 IU/mL (94% TAF vs 93% TDF, $P = 0.47$), or secondary

endpoints such as normalisation of serum ALT (83% TAF vs 75% TDF, $P = 0.076$). Although total AEs, SAEs, and discontinuations due to AEs were similar between groups, fewer patients on TAF experienced a $> 3\%$ decrease in bone mineral density at week 48 in the spine (22% TAF vs 39% TDF, $P < 0.001$) and hip (10% TAF vs 33% TDF, $P < 0.001$), and fewer changes were observed in bone turnover markers. The mean change in serum creatinine at week 48 was minimal in both groups (TAF 0.01 mg/dL vs TDF 0.02 mg/dL, $P = 0.32$), but patients receiving TAF, had a smaller reduction in creatinine clearance (median change in eGFR -1.8 mL/min vs -4.8 mL/min, $P = 0.04$), with minimal changes in markers of proximal renal tubular function. Based on a superior

safety profile and non-inferiority of efficacy endpoints, TAF represents an attractive alternative to TDF in the treatment of CHB.

7.1.5 | Treatment for decompensated cirrhosis

The efficacy and safety of oral NAs has been studied in patients with decompensated cirrhosis, although the evidence base is limited with historical anti-viral agents.⁹² Interferon alfa-2b and pegylated interferon alfa-2a are contraindicated in this population. Due to superior potency and low rates of virological resistance, and more robust evidence in prospective trials,^{71,74,93} either entecavir or TDF are preferred agents for use in patients with decompensated cirrhosis. Long-term studies documenting the impact of anti-viral therapy in this population on both pre-transplant and post-transplant clinical outcomes (eg, hepatic decompensation, hospitalisations, HCC, liver-related and all-cause mortality) remain limited and would be helpful in clarifying the role and timing of treatment in this population.

8 | MONITORING HBV TREATMENT

Prior to initiating anti-viral treatment, patients should be informed that therapy is long-term and adherence and regular follow-up visits are essential. Anti-viral medications for hepatitis B are usually well tolerated with minimal side effects.^{11, 93-97} Timely prescription refills and appropriate patient support will improve patient compliance and treatment outcomes.

8.1 | Laboratory monitoring

After initiating anti-viral therapy, liver tests should be performed every 3 months until serum ALT levels are within normal limits and thereafter at 3-6 month intervals. ALT flares may occur after initiation of treatment, but usually do not require discontinuation of medication. Renal impairment including cases of acute renal failure and Fanconi syndrome (renal tubular injury) with hypophosphatemia have been reported in a few cases treated with TDF.⁹³ If clinically indicated, serum creatinine, estimated creatinine clearance, phosphorus and urine glucose and protein should be measured.^{11,93,94} Similar assessment of renal function also is recommended for patients treated with TAF.⁹⁸ In patients receiving pegylated interferon therapy, complete blood cell counts including absolute neutrophil and platelet counts, and thyroid function tests are required. Serum HBV DNA should be measured using a sensitive PCR test with preferred detection limit of 20-50 IU/mL every 3 months until undetectable, and then every 3-6 months thereafter. HBeAg positive patients on anti-viral treatment should have tests for HBeAg every 6 months until seronegative before initiating anti-HBe testing. HBsAg should be tested every 12 months after seroconversion from HBeAg to anti-HBe positive.^{11,93} Although on-treatment HBsAg clearance is rare in Asian patients, it is recommended that testing for HBsAg be performed every 12 months after sustained suppression of HBV DNA in HBeAg negative patients.⁹⁴ Recent reports have indicated HBsAg

quantification may be useful in predicting HBV treatment responses, but such tests are not widely available at present.⁹⁹

8.2 | Treatment duration and endpoints

Hepatitis B virus treatment duration with anti-viral regimens is dependent on the clinical stage of disease and HBeAg status.¹⁰⁰ The decision to discontinue anti-viral therapy should be made only after careful assessment of patients' compliance for continued monitoring since only 38% of patients will maintain their clinical endpoints within 36 months of follow-up, as described in a recent meta-analysis of 25 studies for NA cessation.¹⁰¹

The optimal duration of anti-viral therapy for HBeAg positive and HBeAg negative chronic hepatitis patients without cirrhosis is unknown. Also, risk factors associated with relapse after stopping anti-viral therapy have not yet been identified. However, based on current information, our recommendations for duration of treatment and the importance of close post-treatment monitoring are described below.

8.2.1 | HBeAg positive CHB Infection

For HBeAg positive CHB infection without histological or imaging evidence of advanced CHB infection, it had been recommended that anti-viral treatment may be discontinued with at least 12-24 months of consolidation treatment after HBeAg seroconversion.¹⁰² However, studies have indicated that HBV progression may continue after HBeAg seroconversion, and a substantial number of patients who discontinue therapy after completing consolidation therapy can experience recurrent viraemia, biochemical flares, and clinical relapse.¹⁰³ In a retrospective study of 124 Chinese patients treated with LAM who achieved HBeAg seroconversion with HBV DNA <200 copies/mL, the relapse rates (HBeAg seroconversion) at 1 and 2 years post-treatment were 54% and 68% respectively.¹⁰⁴ In a recent report in HBeAg positive Asian American patients who discontinued anti-viral therapy after loss of HBeAg and development of anti-HBe, 90% developed recurrent viraemia, 38% had elevated ALT levels and 8% had seroreversion to HBeAg positivity.¹⁰⁵ Another study of HBeAg positive Chinese patients who discontinued LAM after HBeAg seroconversion showed that all patients experienced reappearance of HBV DNA and 44% of patients had ALT flares.¹⁰⁶ Due to the risk of recurrent viraemia and biochemical flares after discontinuing therapy, a long-term anti-viral treatment is now recommended until 6-12 months after HBsAg clearance or HBsAg seroconversion.¹⁰³⁻¹⁰⁵ However, if treatment discontinuation is being considered after HBeAg seroconversion and a period of consolidated treatment but before HBsAg clearance, we recommend that the patient meet the following criteria:

1. Histological or elastography evidence of hepatic fibrosis stage <2
2. Close post-treatment monitoring at monthly intervals for the first 3 months, and then 3-6 months thereafter. Close attention for recurrent viraemia, with or without HBeAg seroreversion, ALT elevations and clinical relapse will determine if anti-viral therapy needs to be reinstated. Recently, in patients treated with

entecavir, HBsAg titres of ≤ 2 to $\leq 2.5 \log_{10}$ IU/mL at the time of HBeAg seroconversion were predictive of a low virological relapse rate in Asian patients.^{107,108} Further studies quantifying HBsAg levels will be useful in confirming these findings.

8.2.2 | HBeAg negative CHB infection

Although NA treatment is highly effective in suppressing HBV replication, it does not eliminate HBV infection. The recurrent viraemia rate is high even after a long-term treatment-induced suppression of HBV replication, and may result in biochemical flare or even hepatic decompensation. A recent systematic review study on 1732 HBeAg negative CHB-infected patients who received anti-viral treatment reported that 1-year off-therapy virological relapse and clinical relapse occurred in <70% and <50% of the patients, respectively, and <40% of the patients received re-treatment.¹⁰⁰ In patients who received 5 years of treatment with ADV, up to 60% had virological relapse with elevated ALT levels after stopping treatment.¹⁰⁹ Recently, two Asian studies also showed high relapse rates after ETV therapy. One reported a virological relapse rate of 57.8%, a clinical relapse rate of 45.2%, and a re-treatment rate of 35.8% after 2 years of ETV therapy.¹¹⁰ Another study reported a virological relapse rate of 91.4%, and a retreatment rate of 88.5% after 3 years of ETV therapy.¹¹¹ Therefore, for HBeAg negative CHB patients with histological or imaging evidence of advanced CHB infection, indefinite NA treatment is recommended to maintain HBV DNA suppression. However, if stopping anti-viral therapy is being considered, then close follow-up with frequent laboratory testing to detect relapse and reinstitution of anti-viral treatment is strongly recommended. Although HBsAg loss or HBsAg seroconversion is desired, it is rarely achievable in Asian patients. If HBsAg clearance does occur, NA treatment discontinuation with close follow-up may be considered.

8.2.3 | Cirrhosis

Discontinuation of anti-viral treatment in patients with cirrhosis carries a risk of hepatic decompensation or even liver failure.^{11,93} Furthermore, a large retrospective study indicated that even among patients already on anti-viral therapy, a low-level viraemia, defined as persistent or intermittent episodes of HBV DNA > than the lower detection limit of 12 IU/mL but, <2000 IU/mL was associated with a higher risk of developing HCC, particularly in patients with cirrhosis, when compared to those who maintained virological response with persistently undetectable HBV DNA levels.¹¹² It is recommended that all patients with baseline clinical evidence of compensated or decompensated HBV cirrhosis, regardless of HBeAg and HBV DNA status, remain on a life-long course of anti-viral therapy.

8.2.4 | Monitoring and managing anti-viral treatment nonresponse or suboptimal response

As summarised in Table S5, primary virological non-response to anti-viral treatment is defined as a $< 1 \log_{10}$ drop from baseline after 3 months of therapy, whereas a suboptimal response is defined as a

$> 1 \log_{10}$ decline, but detectable HBV DNA after 3-6 months of treatment. Primary nonresponse or suboptimal response may occur if:

1. The patient is noncompliant to the treatment regimen, or is having difficulty with prescription refills.
2. The anti-viral agent had limited potency, or
3. There is pre-existing anti-viral resistance.

These potential scenarios must be determined during clinic visits.

8.2.5 | Virological breakthrough or rebound and anti-viral resistance

Virological breakthrough is defined as a $> 1 \log_{10}$ increase from the nadir HBV DNA (IU/mL) level while on therapy in compliant patients. Virological rebound is defined as an increase in serum HBV DNA to $> 20\,000$ IU/mL or above the pre-treatment baseline level during continued therapy. Both virological breakthrough and rebound may occur after achieving an initial virological response. Once noncompliance is excluded, virological breakthrough and rebound usually denotes anti-viral resistance.

Hepatitis B virus anti-viral resistance can be 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 a reduction in the in vitro susceptibility to anti-viral agents associated with genotypic resistance.¹¹³ Anti-viral resistance can be single, multiple, or cross-resistant. Cross-resistance is defined as decreased susceptibility to more than one HBV anti-viral drug conferred by the same amino acid substitution or combination of amino acid substitutions. The clinical consequences of drug resistance include a reduced rate of HBeAg seroconversion, reversal of virological and histological 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 the appearance of HBsAg mutations that may lead to vaccine failure.^{116,117}

It is recommended that any patient with a virological breakthrough or rebound undergo drug resistance analysis. Currently, there are two types of genotypic HBV resistance tests; direct sequencing allowing the identification of mutations that comprise $> 20\%$ of the total HBV population, and a line probe assay that identifies resistance mutations using real-time PCR analysis with specific probes and polymorphism analysis that allows for the identification of mutations that comprise 5% of the total HBV population. In a recent report, up to 40% of virological breakthroughs in CHB-infected patients receiving NA were related to medication non-adherence and not anti-viral genotypic resistance.¹¹⁸ Thus, close counselling of patients on adherence to their anti-viral medications as well as confirmation of virological breakthrough and drug resistance testing are recommended to avoid unnecessary changes in anti-viral medications.

Table 4 summarises recommended therapy for anti-viral resistance and cross-resistance. When a single-drug genotypic resistance is confirmed, the preferred approach in patients with either LAM, telbivudine, ADV or ETV resistance is to switch to TDF therapy.¹¹⁹

Patients with ADV resistance may also be switched to ETV.^{11,93} However, switching to ADV is not recommended in patients who developed renal dysfunction during ADV treatment. If multidrug resistance is identified, the combination of ETV and TDF is preferred.¹²⁰ Recently, TDF genetic resistance was reported in a few treatment experienced Korean patients.¹²¹ However, identification of a triple mutation that confers tenofovir resistance in HBV patients has not yet been established.

Patients with a suboptimal response to ADV may be switched to ETV or TDF,^{11,93,103,122} those with suboptimal response to telbivudine or LAM may be switched to TDF,^{11,93,119} and patients with suboptimal response to ETV may be switched to TDF.¹²³

9 | SPECIAL POPULATIONS

9.1 | Chronic hepatitis B infection during childhood and adolescence

Chronic HBV infection in children is a major health problem not only in high endemic regions, but also in Western countries with large proportions of immigrants from endemic areas, as well as in cases of international adoption from regions where HBV is prevalent.¹²⁴ HBV exposure leading to chronicity occurs either via perinatal transmission from infected mothers or during early childhood. If immunoprophylaxis is not administered at birth, 90% of infants born to HBeAg positive highly viremic mothers, and 5% born to HBeAg negative mothers will become chronic carriers.¹²⁵ In addition, 25%-50% of children exposed to HBV before 5 years of age via horizontal transmission from non-maternal sources, ie, HBsAg positive family members, also will become chronic carriers. When infected beyond 5 years of age or during adolescence, 2.5%-10% become HBV carriers. HBV infection during infancy and childhood is usually clinically asymptomatic with minimal or normal liver histological changes. However, although rare, acute and fulminant hepatitis have been reported in Asian infants born to HBeAg negative carrier mothers.¹²⁶⁻¹²⁸

Similar to adults, chronic HBV infection in children is classified into four phases: the HBeAg positive immune tolerant and immune active phases, and the HBeAg negative low replication and reactivation phases.¹²⁹ HBsAg positive children who acquired HBV by vertical transmission or during early childhood begin in the immune tolerant

phase. In Asian HBsAg positive children, HBeAg seroconversion is uncommon and only occurs at an annual rate of less than 2% per year in infants less than 3 years of age, and at 4%-5% per year in children over the age of 3 years.¹²⁹ Progression to the HBeAg positive immune active phase may occur at any age in children and is accompanied by ALT elevation and inflammatory activity in the liver.¹³⁰ In a recent report, up to 40% of children in the HBeAg positive immune active phase experienced seroconversion to HBeAg negative and entered into the low replication phase.¹³¹ In the study, approximately 50% of the children remained in the HBeAg positive immune tolerant phase during the course of follow-up. Also, other reports showed that by 17 years of age, 25% of Asian American children and 40% of Japanese children had experienced spontaneous HBeAg seroconversion.^{131,132}

Progression to cirrhosis and development of HCC in HBsAg positive Asian children is rare. In a report from Taiwan, only three of 426 (0.7%) of chronic carrier children progressed to cirrhosis.¹³³ Two reports from Asia showed low rates of 0.5% to 1.5% for HCC development.^{129,133} In one report, early HBeAg seroconversion and presence of cirrhosis were risk factors for HCC in HBsAg positive children. The youngest reported Asian American child to develop HCC was a 6-year-old male born to an HBeAg positive carrier mother.¹²⁷ By the age of 3 years, a liver biopsy showed cirrhosis and seroconversion to anti-HBe positivity had already occurred.

Anti-viral treatment is recommended for children and adolescents who are in the HBeAg positive immune active phase of CHB, with elevated serum ALT values and HBV DNA levels >2000 IU/mL.^{124,129} The primary endpoint of therapy in HBeAg positive children is HBeAg seroconversion. Children with HBeAg negative hepatitis (reactivation phase) with elevated ALT levels and HBV DNA levels >2000 IU/mL to >20 000 IU/mL also are recommended for anti-viral treatment.¹²⁴ In HBeAg negative children, the primary endpoints are reduction in HBV DNA and normalisation of ALT levels. Children with compensated cirrhosis with any detectable HBV DNA value should receive immediate anti-viral treatment regardless of ALT levels or HBeAg status. The primary endpoint of treatment in children with compensated cirrhosis is undetectable HBV DNA. Children with decompensated cirrhosis should be immediately referred to liver transplant centres.

At present, children in the HBeAg positive immunotolerant phase are not recommended for treatment since anti-viral therapies have

TABLE 4 Anti-viral resistance, cross resistance and recommended therapy

NA-based resistance	Common mutation sites	Resistance rates	Recommended therapy
LAM	M204V/I/S, L180M/I, M204V/I/S, A181T/V	74% at 5 years	Switch to TDF
ADV	A181T/V, N236T, I233V	29% at 3 years	Switch to TDF
LdT	M204I/V, rtA81T/V, rtL229W/V	21.6% at 2 years	Switch to TDF
ETV	M204V/I, L180M, M250V, I169T	1.2% at 6 years	Switch to TDF
TDF	No known mutation	0% at 8 years	Continue TDF
LAM+ADV	A181V and N236T	Variable	Switch to TDF
Multiple resistance	Variable combination	Variable	Switch to TDF + ETV

LAM, lamivudine; ADV, adefovir; LdT, telbivudine; ETV, entecavir; TDF, tenofovir.

not been proven to be effective.¹²⁴ Also, anti-viral therapy is not recommended in children with HBeAg negative low replication (HBV DNA <2000 IU/mL) "inactive carrier" phase.^{124,134} More detailed information for the treatment of HBV in children and adolescents are summarised in recent reports.^{124,129}

Currently, there are five drugs that are approved for treatment of children with CHB.¹²⁴ Standard interferon is approved for use in children ages 1-17 years. Entecavir is approved for use in children 2 to <18 years and tenofovir is recommended for use in children ≥ 12 to 18 years of age. Entecavir and tenofovir have low cumulative rates of resistant variants of 2.6% and 0% respectively, and both drugs are well tolerated with minimal side effects. Lamivudine and adefovir are seldom used in the USA. Only nucleos(t)ide analogs should be used in children with cirrhosis.

9.2 | HBV infection and pregnancy

Pregnant mothers with CHB infection can vertically transmit HBV to their infants,¹²⁵ and if untreated, CHB infection will develop in up to 90% of infants born to HBeAg positive mothers. The combination of postnatal passive and active immunisation reduces the rate of MTCT from 90% to 10%.¹³⁵⁻¹³⁷ However, even with passive-active immunoprophylaxis, 7%-32% of infants born to carrier mothers with HBV DNA levels $\geq 200\ 000$ IU/mL ($\geq 10^6$ copies/mL) will still become HBsAg positive.¹³⁸⁻¹⁴⁰ To reduce immunoprophylaxis failure rates among infants born to mothers with high viral loads, anti-viral therapy with TDF, LAM or telbivudine is indicated during the third trimester of pregnancy.¹⁴¹⁻¹⁴⁴ Another indication for anti-viral treatment during pregnancy is maternal liver disease progression or reactivation, especially if clinically severe.¹⁴⁵ Candidates for anti-viral therapy during pregnancy are as follows:

1. Women with HBV DNA levels $\geq 200\ 000$ IU/mL ($\geq 10^6$ copies/mL) at the third trimester of pregnancy.
2. Mothers with exacerbation of ALT ($>5 \times$ ULN of laboratory reference value), or severe fibrosis (ie, stage IV at Metavir scale; I).^{146,147} Anti-viral treatment can be initiated at any time point during pregnancy as indicated.

The use of LAM and telbivudine to reduce the transmission of HBV from mothers with high viral loads during the third trimester appears to be effective and well tolerated.^{139,141-143} However, high-quality data are lacking. Recently, a prospective randomised control study with TDF demonstrated that the rate of MTCT was significantly reduced from 7% to 0% when TDF was given during the third trimester to HBeAg positive mothers with high viral loads. The safety profiles were comparable between the TDF-treated group and the control group at 28 weeks of postpartum follow-up.¹⁴⁴

Although few studies investigated the safety of using LAM or telbivudine during the first or second trimester to control active CHB disease, the treatment appears to be effective at normalising ALT or reducing viraemia with a comparable safety profile.^{146,147} Anti-viral resistance has been reported in mothers who received LAM therapy, although this could be managed by switching to

telbivudine or TDF during pregnancy. Therefore, the authors recommend the following treatment selection for mothers, and an algorithm for anti-viral therapy during pregnancy is presented in Figure 6. These recommendations are based on studies in HBsAg positive pregnant Asian women.

1. TDF should be considered as the first line treatment option for mothers with high viraemia and started at gestational week 30, or earlier if maternal liver disease required treatment.
2. As the second line treatment, telbivudine may be used during pregnancy. LAM should be limited to late second trimester or third trimester treatment for patients with HBV DNA between 6 and 9 \log_{10} copies/mL due to the potential for resistance and lower potency.^{139,148}

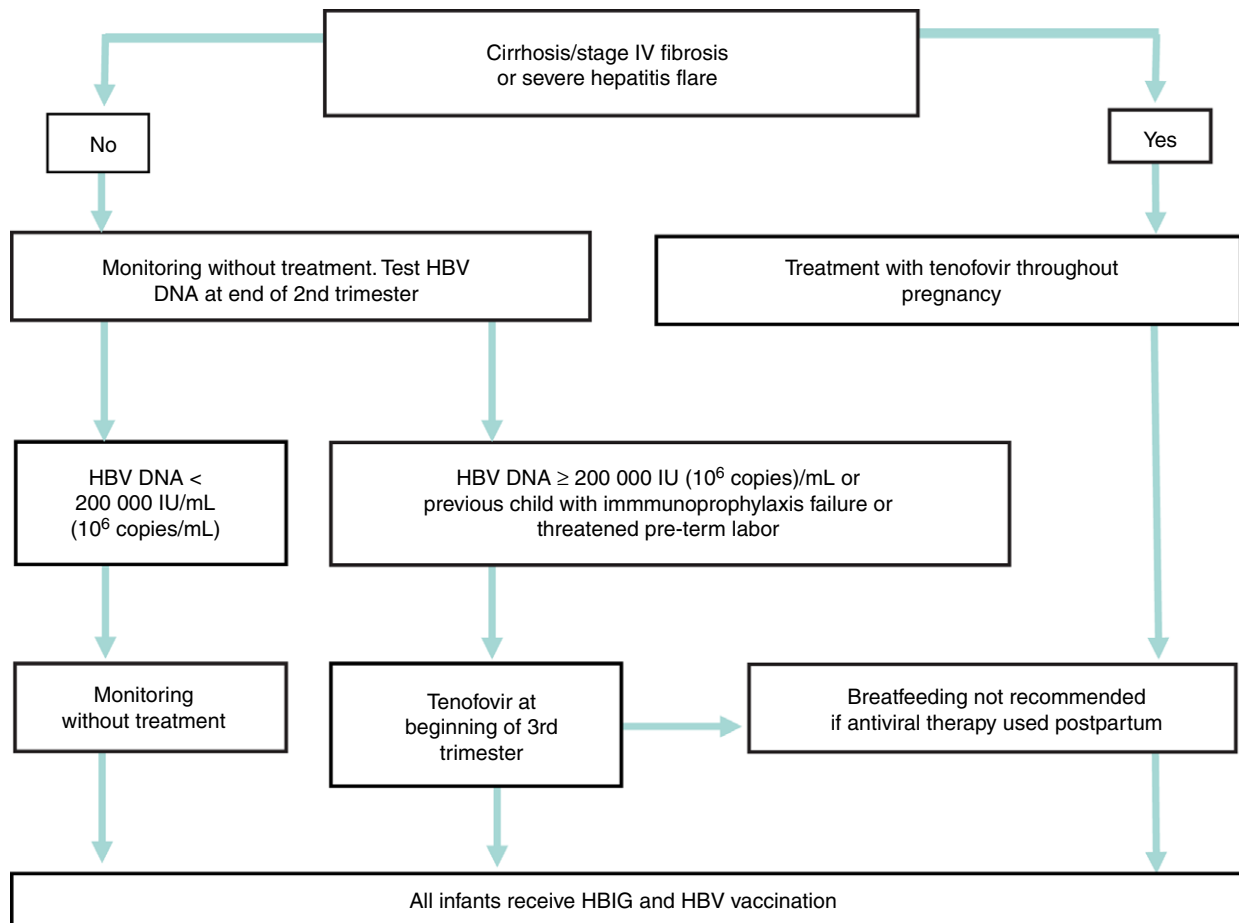
In a retrospective study by Pan et al, a significant reduction in the MTCT rate of HBV was observed in HBeAg positive mothers with high viral loads when elective caesarean section was performed.¹⁴⁹ However, further studies are warranted to confirm these findings. Mothers with high viral loads who missed the opportunity for third trimester anti-viral treatment may consider this option and careful assessment of the risk-benefit ratio with the participation of patient's obstetrician is recommended.

For consultation on pre-conception, antepartum, or postpartum care, and infant outcomes, the discussion may include the following:

1. Treatment naïve patients with a treatment indication may consider interferon therapy to seroconvert HBeAg prior to becoming pregnant if the pregnancy is planned more than 1 year in advance.
2. For patients who are receiving oral anti-viral treatment and found to be pregnant, therapy should either be stopped or switched to TDF if the patient was receiving non-TDF-based treatment.^{146,147,150}
3. Amniocentesis may increase the risk of HBV transmission in mothers with viral loads $>10^7$ copies/mL. The decision to perform this procedure should be made with careful assessment on the risk-benefit ratio for these mothers.¹⁵¹
4. As gestational diabetes, antepartum haemorrhage, and threatened preterm labor frequently occur among HBV-infected mothers, close monitoring with at least one HBV DNA quantitative testing at gestational week 28 is highly recommend for assessing the risk of HBV transmission.¹⁵²
5. In mothers who prefer breast-feeding, anti-viral therapy should be discontinued since these agents may be secreted in breast milk, and long-term data on the safety of exposing infants to anti-viral agents are not currently available. Stopping anti-viral treatment in mothers after delivery for lactation appears to be safe, as significant hepatitis flares have not been observed.¹⁵³⁻¹⁵⁵ Postpartum monitoring on ALT should be performed on weeks 4 and 12.^{144,156,157}

9.3 | HBV coinfection with HCV or HDV

Since HBV and HCV share similar routes of transmission, coinfection with either virus is detected in 7%-22% of CHB-infected



*Recommendations based on studies in Asian HBsAg positive women.

†Pan CQ, et al. *Semin Liver Dis* 2013;33:138–146

FIGURE 6 Anti-viral therapy for mothers during pregnancy*[†]

patients. Coinfection with HCV is found predominantly among individuals at high risk for parenteral infection, including injection drug use.¹⁵⁸ Coinfection with HDV is often seen in those residing in areas where HBV infection is highly endemic.¹⁵⁹ HBV patients co-infected with HCV or HDV are at higher risk for rapid progression to decompensated liver disease and HCC.^{160,161} In dual HBV/HCV infection, the treatment strategy should be directed towards the dominant replicating virus, though HCV eradication should be considered if appropriate treatment is accessible.^{158,162,163} When receiving direct acting anti-viral therapy for HCV infection, dual HBV/HCV-infected patients may experience an acute exacerbation of HBV unless anti-viral treatment for HBV is also provided.¹⁶⁴ The response to HBV treatment with oral anti-viral agents does not appear to be effected by concurrent HCV infection. In addition, it has been reported that there is a risk for HBV reactivation in patients with HCV/HBV co-infection whose HCV has been cleared by direct acting anti-viral therapy (DAA).¹⁶⁵ The FDA recently issued a warning on the risk of HBV reactivation and recommend that HCV patients should begin treatment for HBV prior to initiating DAA therapies (<https://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf>).

Among CHB-infected Asian patients with HDV super-infection, lower levels of HBV DNA are common. HDV antigen or antibody tests are often used for screening. Weekly injection of pegylated interferon is currently used for 12–18 months to treat co-infected patients.¹⁶⁶ The HDV RNA PCR qualitative test is available for monitoring the treatment response. Sustained viral response at 6 months post-treatment, which correlates better with long-term cure in the absence of advanced fibrosis, is only seen in 17% of patients. However, late HDV RNA relapse may occur.¹⁶⁶

9.4 | HBV and HIV coinfection

CHB infection 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.^{167,168} The treatment of HBV in HBV/HIV co-infected patients should take into account both viruses. Initiation of treatment for HBV infection is based on the presence of significant fibrosis or meeting the HBV treatment criteria.¹⁶⁹

Treatment for HBV has been shown to improve clinical outcomes.¹⁷⁰ In patients not requiring highly active antiretroviral therapy (HAART), drugs with dual activity against HBV and HIV such as

LAM, entecavir, emtricitabine, or TDF should not be used as monotherapy since these drugs may lead to mutation selection and development of antiretroviral resistance.^{171,172} Pegylated interferon monotherapy or ADV in combination with telbivudine may have a role in treating these patients.^{168,173} In contrast, TDF and emtricitabine or other TDF based regimens should be initiated in co-infected patients with low CD4 counts who require HAART.^{169, 172} Reactivation of HBV has been observed in patients on HAART therapy after immune reconstitution.¹⁷⁴

9.5 | HBV reactivation during chemotherapy or immunosuppressive therapy

Treatment with cancer chemotherapy or immunomodulatory agents may induce potentially fatal hepatic flares in HBsAg positive patients or those who are HBsAg negative but maintain a detectable level of HBV DNA. The acute flare or "reactivation" results from immune reconstitution directed towards the rise in HBV DNA following the use of immunosuppressive or immunomodulating agents.¹⁷⁵ A recent meta-analysis of clinical trials suggested that treatment with LAM or entecavir may prevent HBV reactivation during chemotherapy.^{176,177} It is recommended that Asian patients be screened for HBsAg prior to initiation of chemotherapy or immunosuppressive therapy. Patients who are HBsAg negative but anti-HBc positive should be tested for HBV DNA. When the level of HBV DNA level is undetectable in these patients, they may have the option of being monitored closely without anti-viral therapy if a moderate or low level of immunosuppressant therapy is used. In addition, CHB patients who will require long-term corticosteroid therapy alone or in combination with other immunosuppressive or anti-neoplastic medications, should receive concomitant oral anti-viral HBV drugs.^{178,179} An algorithm for selecting patients for anti-viral therapy is shown in Figure S3.

1. It is recommended that all HBsAg positive patients who require chemotherapy or immunomodulatory agents should receive anti-viral therapy.¹⁷⁷
2. Among HBsAg negative but anti-HBc positive patients, anti-viral prophylaxis is recommended when the HBV DNA level is detectable and the patient is to receive immunosuppressant agents such as rituximab, or will be receiving bone marrow transplantation.¹⁸⁰
3. For better efficacy of viral suppression and preventing ALT flares, entecavir is preferred over LAM in patients with B cell lymphoma,¹⁷⁸ or other solid tumours.¹⁸¹

10 | RECOMMENDATIONS

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

1. For HBeAg positive or negative chronic hepatitis patients with HBV DNA >2000 IU/mL (>10⁴ copies/mL) and ALT > ULN, treat with a first-line agent (entecavir, TDF, TAF) (I,A).
2. For compensated cirrhosis patients with detectable HBV DNA, treat with entecavir, TDF or TAF. For decompensated cirrhotic patients, entecavir or TDF are currently the agents of choice (I,A).
3. In HBeAg negative patients with HBV DNA >2000 IU/mL (>10⁴ copies/mL) and normal ALT, a liver biopsy, transient elastography or serum marker for fibrosis is recommended. If not available, further stratification for risk factors including measurement of serum albumin values and platelet counts should be conducted prior to treatment (IIa, C-LD).
4. To monitor 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 (I, C-LD).
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 (I, C-EO).
6. Regarding monitoring for resistance, viral breakthrough with confirmation of single drug resistance requires switching to another first-line oral anti-viral agent (IIa, B-NR).
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 (I, B-R).
8. HBsAg positive pregnant women should be tested for HBV DNA. If the HBV DNA level is $\geq 200\ 000$ IU/mL ($\geq 10^6$ copies/mL at gestational week 28, TDF treatment is preferred and should be initiated at gestational week 30 (I, B-R).
9. HBsAg positive patients or patients with any detectable levels of HBV DNA requiring chemotherapy or treatment with immunomodulatory agents should receive anti-viral treatment (I, B-NR).

ACKNOWLEDGEMENTS

Editorial services were provided by William Perlman, PhD, and Thomas Saenz.

Declaration of personal interests: Myron J. Tong has served on advisory boards for Gilead, and is a speaker for Gilead and Merck. Calvin Q. Pan has served on advisory boards for AbbVie and Gilead. He has served as a consultant for Gilead and has received research grants from Merck and Gilead. He has served as a speaker for AbbVie and Gilead. Steven-Huy B. Han has served as a speaker for Gilead and has received research grants from Gilead. David S-K Lu has served as a speaker, a consultant and an advisory board member for Neuwave, Amgen, Perseon, and has received research funding from Neuwave. Steven Raman has served as a consultant for Bayer, Johnson and Johnson and Amgen. Ke-Qin Hu has served as a speaker, a consultant and an advisory board member for Gilead, Merck, and Intercept. Joseph K. Lim has received research contracts (to institution) from Allergan, Conatus, Genfit, Gilead, Hologic, Intercept, and Prometheus, and has served as a consultant to AbbVie, Bristol-Myers Squibb, and Gilead. Hie-Won Hann has served on the advisory board for Gilead and has received clinical research grant support from Gilead. Albert D.

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Author contributions: The participation of the authors in the preparation of this manuscript were as follows. All of the authors were assigned a section of the paper so the data acquisition, analysis and interpretation had the participation of Drs. Myron Tong, Calvin Pan, Steven Han, David Lu, Steven Raman, Ke-Qin Hu, Joseph Lim, Hie-Won Hann and Albert Min. The impetus and research design for this paper included Drs. Myron Tong and Calvin Pan.

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

How to cite this article: Tong MJ, Pan CQ, Han S-HB, et al. An expert consensus for the management of chronic hepatitis B in Asian Americans. *Aliment Pharmacol Ther*. 2018;47:1181-1200. <https://doi.org/10.1111/apt.14577>