Clinical Practice

Taiwan consensus statement on the management of chronic hepatitis B

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The experts of Taiwan Association for the Study of Liver (TASL) have actively participated and led the guidelines on hepatitis B virus (HBV) management by Asian Pacific Association for the Study of Liver (APASL) which is the first international association for the study of liver to publish the statement on HBV management before. However, there are more and more new data...
on the natural history and treatment of HBV infection in the past decade. These include new application of an old biomarker (quantitative HBsAg), clinical significance of HBV genotype and naturally occurring mutations, the role of non-invasive examination in evaluating severity of hepatic fibrosis, clinical significance of outcome calculators, new drug or new combination strategies towards more effective therapy and organ transplantation including liver and non-liver transplantation. It is time to publish the guidelines on HBV management of Taiwan. Hence, TASL have conducted an expert meeting to review, to discuss and to debate the relevant literatures, followed by draft the manuscript of HBV management guidelines and recommendations. The guidelines include general management, indications for fibrosis assessment, time to start or stop drug therapy, choice of drug to initiate therapy, when and how to monitor the patients during and after stopping drug therapy. Recommendations on the therapy of patients in special circumstances, including women in childbearing age, patients with antiviral drug resistance, concurrent viral infection, hepatic decompensation, patient receiving immune suppression or chemotherapy and patients in the setting of liver transplantation and hepatocellular carcinoma, are also included.

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Introduction

Chronic infection with hepatitis B virus (HBV) is a major global health problem, an important cause of morbidity and mortality from sequelae such as liver cirrhosis (LC) and hepatocellular carcinoma (HCC). It affects 257 million people worldwide, 75% of them reside in the Asia Pacific region, and approximately 2 billion people have been infected worldwide and about 1 million die annually. In the past decades, researches exploring the virus, host and other factors contributing to pathogenesis and outcomes of chronic hepatitis B have provided a better understanding of the natural history and immunopathogenesis of chronic HBV infection.

The hepatitis activity, as reflected in the elevation of serum alanine aminotransferase (ALT), is the result of endogenous antiviral immune response against HBV. The severity, extent, duration and frequency of hepatic lobular alterations during hepatitis flares tend to determine the disease outcome and clearance of HBV. Furthermore, in the REVEAL study, the risk of developing cirrhosis and HCC is directly proportional to serum HBV DNA levels. However chronic HBV infection is a dynamic process, it is not the HBV DNA level or ALT level at the first test but the subsequent HBV-related immune clearance events, such as hepatitis activity and flare or even decompensation, determine the outcomes in these patients.

Conceptual background

Natural history and treatment consideration

The natural history of chronic HBV infection has been studied extensively. Different phases have been identified: the immune tolerance phase [hepatitis B e antigen (HBeAg) positive, high levels of serum HBV DNA, normal ALT and minimal histological changes], the immune clearance phase [HBeAg positive, declining levels of serum HBV DNA, elevated ALT and increased histological activity], the residual phase [antibody against HBeAg (anti-HBe) positive, very low levels of serum HBV DNA, normal ALT and minimal histological changes] and a variant immune clearance phase [HBeAg-negative, elevated ALT with increased hepatitis activity and higher HBV DNA level]. In addition, treatment of patients with chronic hepatitis B (CHB) has been evolving rapidly with an increasing range of treatment options and the availability of multiple new antiviral agents.

Three international association for the study of liver groups have updated their treatment guideline for chronic HBV infection. Obviously, active HBV replication is the key driver resulting hepatic necroinflammation and disease progression. Hence, the treatment aim of chronic hepatitis B is to suppress HBV replication permanently. The short-term goal of treatment is to achieve HBeAg seroconversion in HBeAg-positive patients and profound HBV DNA suppression in both HBeAg-positive and negative patients, ALT normalization, and prevent hepatic decompensation. Hopefully, the long-term goal of therapy can prevent hepatic decompensation and progress to cirrhosis or HCC and prolong survival. The ultimate goal of antiviral therapy is HBsAg loss and seroconversion to hepatitis B surface antibody (anti-HBs). Nowadays, two major classes of antiviral agents, pegylated interferon (Peg-IFN) and oral nucleos(t)ides analogues (NUC), are the mainstays of therapy for CHB in many parts of the world. Peg-IFN has the benefit of antiviral, antiproliferative, and immunomodulatory effects after a finite duration of therapy both in HBeAg-positive and -negative CHB patients. It is considered as one of the first line treatments by the regional guidelines although it has been limited by its poor tolerability and significant side effect profile. On the other hand, NUCs are safe and effective for hepatitis B virus DNA suppression, ALT normalization, and histological improvement. However, the antiviral potency of NUCs do not result in an increase in HBeAg

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seroconversion and HBsAg seroconversion. Therefore, continuing long-term drug therapy is usually necessary to maintain a virological response but virological relapse is common after premature cessation of therapy. Treatment duration is dictated by the desired treatment goal. The recent data from Korea demonstrated an annular incidence of HBsAg loss of 0.33% after long-term NUCs therapy. Of note, the incidence of HBsAg seroconversion after stopping NUCs therapy was much higher than that during therapy with an estimated annular incidence of 1.78%. Moreover, patients with clinical relapse who remain untreated had a 7.34 times higher incidence of HBsAg loss than those received re-treatment. Therefore, it remains a challenge to determine when to stop oral antiviral agents and when to re-treat clinical relapses.

Co-infection with HCV, HDV or HIV

In areas where the HBV is endemic, a substantial proportion of the patients are co-infected with hepatitis C and B. If the prevalence of anti-HCV positivity worldwide is approximately 1%–4% in the general population, the number of individuals with HCV/HBV co-infection among the 257 million HBV carriers would be approximately 2.5–10.2 million. Moreover, HCV/HBV co-infection can also be found in people at risk of parenteral hepatotropic viral transmissions such as people who use intravenous drugs, patients with thalassemia, and patients with hemophilia. In patients with dual chronic hepatitis B and C, the disease outcomes, including the development of LC and HCC, are generally more severe than those in patients with either hepatitis B or hepatitis C. In addition to cross-sectional data, a long-term community-based study finding supported the effect of HCV/HBV co-infection on the cumulative incidences of HCC. Therefore, patients dually infected with hepatitis C and B need attention and require effective antiviral treatments.

Hepatitis D virus (HDV) is a satellite and defective RNA virus requiring HBV to complete its life cycle; thus HDV infection occurs exclusively in subjects with HBV infection. Overall, the prevalence of HDV infection is around 1%–2% among all HBV carriers worldwide and accounts for approximately 2.6–5.1 million HDV carriers. Highly endemic areas include Central America, Middle East, West Africa, Pacific Islands and Eastern Europe. HDV is transmitted parenterally. Intravenous drug use (IVDU) is the most common route of transmission in non-endemic areas, such as North America and northern Europe. The HDV prevalence had declined in several endemic countries such as Italy, Spain, Turkey and Taiwan, possibly attributed to the successful control of HBV by universal vaccination, using disposable needles and improved precautions in sexual behaviors. Nevertheless, in countries like United States, Australia and some European countries, the prevalence of HDV is still on the rise.

Approximately 15–25% of the human immunodeficiency virus (HIV) infected population in Asia and Africa has concurrent chronic HBV infection, which is more common in areas of high prevalence for both viruses. HIV coinfection may accelerate the progression of HBV-related liver diseases. First, compared to HIV-uninfected subjects, patients with pre-existing HIV infection have a higher risk of chronicity after acute HBV infection. Second, clinical observational studies have demonstrated that HIV/HBV-coinfected patients may have faster progression of hepatic fibrosis and a higher risk of cirrhosis, end-stage liver disease, and HCC than HBV monoinfected patients. VICE versa, HBV coinfection may enhance the immunologic and liver disease progression of HIV infection. Compared with HIV-monoinfected patients, those with HIV/ HBV coinfection had a higher risk of acute hepatitis, hepatic decompensation, and liver-related mortality. Early prospective cohort studies of HIV/HBV coinfected patients revealed a 4–7-fold relative risk of progression to AIDS compared to those without HBV coinfection. A prospective observational cohort of adult patients with primary recent HIV infection further clarified the influence of the duration of HIV infection. HBV coinfection (adjusted hazards ratio 3.5; 95% CI 1.2–10.3) was found to be an independent predictor of immunological progression. Another study consistently found that the hazards ratio for an AIDS or death event was significantly higher (adjusted hazards ratio 1.80; 95% CI 1.2–2.7) for those with HBV coinfection.

New application of an old biomarker: quantitative HBsAg (qHBsAg)

In addition to qualitative serum HBsAg determination, the implementation of commercial assays for qHBsAg has improved our understanding and management of chronic HBV infection.

Prediction of natural history

Serum HBsAg level varies depending on the balance between viral replication and host immunity. The profile of serum HBsAg level has been demonstrated during the natural course of chronic HBV infection: being highest in the immune tolerance phase, starting to decline during the immune clearance phase, decreasing slowly but progressively after HBeAg seroconversion, and being lowest in inactive carrier state. Serum HBsAg level may increase again in those who develop HBeAg-negative hepatitis. A combination of HBsAg <1000 IU/ml and HBV DNA <2000 IU/ml can help identify inactive carriers in genotype D and genotype B or C HBeAg-negative carriers with a negative predictive value (NPV) of 97% and 74% respectively. In Asian-Pacific region including Taiwan, where HBV genotypes B and C are prevalent, HBsAg level of ≤10–100 IU/ml instead predicts HBsAg seroclearance over time. As for the prediction of liver disease progression, carriers with serum HBV DNA <2000 IU/ml and HBsAg >1000 IU/ml have been shown to be at higher risks of HBeAg-negative hepatitis, LC, and HCC than those low-viremic carriers with HBsAg ≤1000 IU/ml.

Clinical significance of HBV genotype and naturally occurring mutations

On the basis of recent advances in molecular biology techniques, ample evidence reveals that HBV genotype
and naturally occurring mutations, including the HBV precore, basal core promoter (BCP) A1762T/G1764A mutations and pre-S deletion mutation, are associated with disease progression, risk of HCC development and responses to antiviral treatments.\textsuperscript{37,38} At least 10 HBV genotypes (A to J) have been identified.\textsuperscript{37} In general, the rate of persistence of HBV infection after acute genotype A and D infection were reported to be high compared with rate of persistence of HBV infection after acute genotype B and C.\textsuperscript{39}

In the natural history of chronic HBV infection, genotype C infection was associated with lower rates of spontaneous HBeAg seroconversion than genotype B during the follow-up. The estimated annual rates of HBeAg seroconversion in genotype B and C infections were 15.5\% and 7.9\%, respectively.\textsuperscript{40} In addition, compared to genotypes C and D patients, genotype A and B patients had a higher rate of spontaneous HBeAg seroconversion.\textsuperscript{37,39} The possible influence of other genotypes on the natural history of HBV infection remains limited.\textsuperscript{41}

Most retrospective or case-control studies indicated that patients with genotype C infection have more severe liver disease, including cirrhosis and HCC, than those with genotype B.\textsuperscript{42,43} Community-based prospective cohort studies on Taiwanese HBV carriers demonstrated that HBV genotype C was associated with an increased risk of HCC than genotype B.\textsuperscript{44} A hospital-based cohort study on 2688 Taiwanese HBsAg-positive non-cirrhotic patients for a mean time period of 14.7 years (Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers (ERADICATE-B) cohort) also showed genotype C patients has a higher annual incidence rate of HCC than genotype B patients by multivariate analysis.\textsuperscript{45} Regarding to the clinicopathological features of patients with resectable HCC, genotype B patients had a higher rate of solitary tumor but more satellite nodules than genotype C patients.\textsuperscript{46,47} In addition, liver inflammation activity was higher in HBV genotype C patients than in genotype B patients, and more genotype C patients tended to have a high viral load (\(>10^6\) copies/ml) than genotype B patients.\textsuperscript{48}

These characteristics may contribute to the recurrence patterns and prognosis of HBV-related HCC patients with genotype B or C infection. Although limited studies have examined the relationship between other HBV genotypes and the risk of HCC development, HCC is more frequent in patients with HBV genotype D and F infection than those with genotype A infection.\textsuperscript{49}

Of the various naturally occurring HBV variants, several cohort studies reported that patients with BCP A1762T/G1764A mutations were significantly associated with the development of HCC than those without.\textsuperscript{43,44} In addition, a meta-analysis produced a summary odds ratio (OR) of HCC for BCP A1762T/G1764A mutations that was 3.79 (95\% CI: 2.71 to 5.29) (49). Recently, quantitative analysis using pyrosequencing revealed that risk of cirrhosis was higher in patients with BCP A1762T/G1764A variants:45\% compared to <45\% (adjusted OR:2.81; 95\% CI:1.40 to 5.67; \(P = 0.004\)).\textsuperscript{50} Additionally, a recent meta-analysis reported that BCP mutations is significantly associated the risks of developing acute-on-chronic liver failure.\textsuperscript{51}

Previous reports also showed that the deletion mutations within the Pre-S gene correlate with the development of cirrhosis and HCC.\textsuperscript{52,53} A meta-analysis further confirmed that the OR of HCC for Pre-S deletion was 3.77 (95\% CI: 2.57 to 5.52). Of particular note, the summary OR for Pre-S deletion was higher in genotype C patients than genotype B patients.\textsuperscript{49}

The specific virological manifestations of HBV genotypes and variants may play an important role in HBV pathogenesis. Genotype C exhibits a higher frequency of BCP A1762T/G1764A mutations and pre-S deletion mutations than genotype B. Serum HBV viral load is higher in genotype C than genotype B. Similarly, genotype D-infected patients with severe liver disease had a higher prevalence of BCP A1762T/G1764A mutation than those with genotype A infection.\textsuperscript{37,39}

### Role of non-invasive evaluation in examining severity of hepatic fibrosis

Hepatic fibrosis evaluation is important in the management of patients with chronic HBV infection. Noninvasive methods using biological and physical approaches have been recommended to be useful for the diagnosis, decision making in treatment, and monitoring clinical outcome.\textsuperscript{50,51} Serum bio-markers including patented and non-patented tests are available for chronic hepatitis B patients in clinical practice.\textsuperscript{52-56} The patented tests were similar in diagnosing performance with areas under the receiving operating characteristic curve (AUROC) around 0.84 for significant fibrosis and 0.9 for cirrhosis.\textsuperscript{54} One meta-analysis showed limited value of aspartate aminotransferase to platelet ratio index (APRI) in diagnosing HBV-related significant fibrosis and cirrhosis.\textsuperscript{55} FIB-4 index was proved to be more reliable than APRI.\textsuperscript{54} Serum bio-markers have the advantages of good reproducibility, high applicability and widespread availability of non-patented tests. However, none of was liver-specific and results of each parameters were influenced by changes in clearance and excretion.\textsuperscript{57}

Physical approaches based on liver elasticity measurement including 1-dimensional transient elastography, point shear wave elastography, 2-dimensional shear wave elastography, strain elastography and magnetic resonance elastography were the developed methods for clinical use currently.\textsuperscript{54,55} The results of elastography were confounded by several factors including inflammation, liver congestion and biliary obstruction. Values with shear wave-based elastography and with strain techniques vary between manufacturers. Therefore, interpretation of elastography results should be based on the full clinical context of the patient, taking into account the method used to obtain the results.\textsuperscript{58} Among these physical methods, transient elastography (TE) is the mostly widely used and validated methods. With liver biopsy as the reference standard for staging fibrosis, TE performed well in assessing fibrosis extent with accuracy of 0.88 and 0.93 for significant fibrosis and cirrhosis in a recent meta-analysis.\textsuperscript{59} Combined serum marker and TE algorithm might further improve the diagnostic accuracy.\textsuperscript{60} For treatment-naïve patients with chronic HBV infection, an algorithm including TE results, alanine aminotransferase and HBV-DNA levels is proposed for decision makings.\textsuperscript{57} Acoustic radiation force impulse (ARFI) elastography might be similar to TE in diagnostic performance of staging liver fibrosis for patients with chronic HBV infection.\textsuperscript{61}
Management of chronic hepatitis B

Clinical significance of outcome calculators

Prediction of hepatocellular carcinoma

Risk calculators for treatment-naive patients

Several studies have been carried out to create risk calculators for the prediction of HCC in treatment-naive CHB patients. In order to perform sufficient external validation of a robust prediction model, these study groups collaborated to establish the REACH-B risk score, a 17-point scoring system incorporating gender, age, serum ALT concentration, HBeAg serostatus, and HBV DNA level as its predicting factors for projecting HCC risk. The REACH-B score was first developed in the Taiwan community-based REVEAL-HBV cohort, then externally validated in a composite hospital-based cohort with patients recruited from Hong Kong and Korea. This model was able to predict the 3-, 5-, and 10-year risk of developing HCC with AUROC of 0.811, 0.796, and 0.769, respectively. The REACH-B score can be widely used in clinical settings, especially in non-cirrhotic CHB patients. It was also used to examine the efficacy of anti-viral therapy in reducing liver cancer risk in CHB patients.

With the establishment of quantitative HBsAg levels as an important seromarker in the natural history of chronic hepatitis B, the REACH-B risk score was recently updated by adding data on level of HBsAg (REACH-B IIa). In addition, as testing serum HBV DNA levels for risk calculators is relatively costly, a risk score that further excluded measurement of HBV DNA (REACH-B IIb) was also developed to address the issue of cost-effectiveness of HCC prediction scores. These systems (REACH-B IIa and IIb) were externally validated using CHB patients in National Taiwan University Hospital and in Chinese University of Hong Kong. The validation results show these modified systems identified patients who developed HCC with similar levels of accuracy as the original REACH-B score. Of note, all these updated systems have excellent accuracy in predicting 3-year HCC risk, with the AUROC of 0.92 and 0.90 for REACH-B IIa and IIb in the ERADICATE-B study, respectively; and 0.85 and 0.84 in the Chinese University of Hong Kong study, respectively.

Risk calculators in treated patients

Treatment with the current first-line oral NUCs results in long-term suppression of HBV replication in patients with CHB, and subsequent improvement in short-term and long-term outcomes. However, HCC still develops in CHB patients treated with NUCs regardless of virological response.

The performance of REACH-B risk score has been tested in a cohort of Hong Kong patients who were treated with entecavir (ETV) 0.5 mg daily for a mean of 42 months. The AUROC for the prediction of HCC using baseline parameters was 0.71 with the sensitivity and the negative predictive value (NPV) of 95.2% and 99.5% at a cutoff score of 8, respectively. The time-dependent AUROC was 0.74–0.97 during the 4 years of ETV therapy. After 2 years of antiviral therapy, the REACH-B score had a sensitivity value of 100% and a NPV of 100% using the score 8 as the cutoff score value.

A HCC risk score (PAGE-B) in Caucasian CHB patients treated with ETV or tenofovir disoproxil fumarate (TDF) was developed, which includes age, gender, and platelet count as predictors to project 5-year HCC risk. In the validation analysis, the risk score offered a c-index of 0.82. The study suggested that all cirrhotic patients under ETV/TDF therapy may better remain under surveillance for HCC regardless of risk scores, as the number of patients with cirrhosis in the low risk group by the PAGE-B score (≤ 9) was limited, and the predictability of the PAGE-B score was suboptimal in the cirrhotic patients. It is not clear whether PAGE-B score may be useful in untreated and in treated Asian CHB patients and need to be validated in such patients.

Prediction of clinical milestones of chronic hepatitis B progression

In addition to HCC, several prediction models have also been established for important clinical milestones prior to HCC progression, such as HBeAg seroclearance, HBV DNA undetectability, and HBsAg seroclearance. For HBeAg seroclearance, predictors included gender, ALT level, precore mutation, HBV genotype, and HBV DNA level, with decreased HBV DNA levels being the strongest predictor of seroclearance. Previous studies had also shown HBV DNA levels to be the strongest predictor of HBV DNA undetectability, however, the establishment of a prediction model incorporating quantitative HBsAg levels showed that HBsAg levels, rather than HBV DNA levels, were the strongest predictor of viral load undetectability. Lastly, a prediction model was also established for HBsAg seroclearance (70). While previous studies emphasized HBV DNA levels as the greatest predictor, this new model showed that, although HBV DNA levels were still important, HBsAg levels were the most significant predictive factor for HBsAg seroclearance. The prediction score for HBsAg seroclearance was externally validated using the ERADICATE-B cohort, with the AUROC for the prediction of HBsAg seroclearance of 0.82 and 0.74, respectively.

Minimal risk HBV Carrier

Inactive HBV carrier state has been adopted to describe HBsAg carriers who have persistently normal ALT levels and HBV DNA levels that are persistently less than 2000 IU/mL. Patients with low viral loads (HBV DNA < 2000 IU/mL) are usually defined as low-risk HBV carriers in terms of HBeAg-negative hepatitis, liver cirrhosis and HCC development. However, Tseng et al. have reported a cohort study indicating that the prognosis of low-viremic patients is variable, and HBsAg level can serve as a marker to stratify HCC risk. Their study has shown that the HCC risk in low-viremic patients with HBsAg ≥ 1000 IU/mL is higher than those with HBsAg < 1000 IU/mL. The authors further conduct a large cohort study to explore whether a higher HBsAg level is associated with increased liver related events. The results have demonstrated that patients with HBV DNA < 2000 IU/mL and HBsAg level < 1000 IU/mL was associated with a lower risk of HBeAg-negative hepatitis, hepatitis flares, and cirrhosis development. Hence, “minimal-risk HBV carriers” was proposed to describe HBeAg-negative patients with HBV DNA levels < 2000 IU/mL plus ALT < 40 U/L and HBsAg < 1000 IU/mL. These patients have...
been documented to have a similar HCC risk to subjects negative for HBSAg and anti-HCV. In addition, they have a significantly lower risk for HBV-related hepatitis and cirrhosis. But, even patients meeting these criteria still develop HCC.\textsuperscript{45} It is generally believed that the missing piece in defining the patients with the lowest HCC risks should be a marker reflecting insignificant hepatic fibrosis. Tseng et al.\textsuperscript{75} further reported none of these clinical favorable patients with a low FIB-4 index (cutoff of 1.29) developed HCC. Importantly, FIB-4 index <1.29 plus favorable clinical profile help identify HBV carriers with the lowest HCC risk. In addition, the authors\textsuperscript{76} further reported that only 1 in 326 patients with low FIB-4 developed cirrhosis but no other complications or liver-related mortality. Obviously, FIB-4 of 1.29 also helps define the lowest risks of adverse liver events in patients with a favorable clinical profile (ALT<40 U/L, HBV DNA <2000 IU/mL and HBSAg <1000 IU/mL).

**Anti-HBV therapy**

Conventional interferon (IFN), pegylated interferon alfa (Peg-IFN-\(\alpha\)), lamivudine (LAM), adefovir dipivoxil (ADV), ETV, telbivudine (Ldt), TDF and tenofovir alafenamide (TAF) have been approved in Taiwan. However, current evidence and global guidelines suggest that Peg-IFN-\(\alpha\), ETV, TDF and TAF are the first-line therapy for CHB patients.\textsuperscript{10–12} Hence, recent updated data on Peg-IFN-\(\alpha\), ETV, TDF and TAF in the treatment of CHB will be discussed.

**Peg-IFN-\(\alpha\)**

**HBeAg-positive CHB**

A phase II study of Peg-IFN-\(\alpha\)-2a therapy for 24 weeks in HBeAg-positive Asian patients revealed that Peg-IFN-\(\alpha\)-2a of all doses combined achieved a higher combined response (HBeAg loss, HBV DNA <500,000 copies/mL, and ALT normalization) rate (24% vs 12%, \(P = 0.036\)) and a higher HBeAg seroconversion rate (32% vs 25%, \(P = 0.185\)) compared with conventional IFN-\(\alpha\)-2a therapy for 24 weeks.\textsuperscript{77} In a subsequent phase III study involving 814 patients (87% Asian), Peg-IFN-\(\alpha\)-2a monotherapy at 180 \(\mu\)g once weekly for 48 weeks achieved ALT normalization, HBeAg seroconversion, HBV DNA <10\(^5\) copies/mL, HBV DNA <400 copies/mL, and HBSAg seroconversion in 41%, 32%, 32%, 14%, and 3% of patients, respectively, at 24 weeks post-treatment.\textsuperscript{78} A sub-analysis of Asian patients in that phase III trial revealed that 81% of initial responders had sustained HBeAg loss and 27% of initial non-responders achieved delayed HBeAg loss.\textsuperscript{79} Another long-term study (mean duration of 6.1 years) in 85 HBeAg-positive Chinese patients treated with Peg-IFN-\(\alpha\)-2a at a dose of 1.5 \(\mu\)g/kg weekly for 32 weeks and LAM 100 mg daily for 52 or 104 weeks revealed that 37% achieved HBeAg seroconversion at the end of Peg-IFN-\(\alpha\)-2a therapy and 77% of the initial responders had sustained HBeAg seroconversion at 5 years post-treatment.\textsuperscript{80}

**HBeAg-negative CHB**

In a phase III study involving 537 patients (61% Asian), Peg-IFN-\(\alpha\)-2a monotherapy at 180 \(\mu\)g once weekly for 48 weeks achieved ALT normalization, HBV DNA <20,000 copies/mL, HBV DNA <400 copies/mL, and HBSAg seroconversion in 59%, 43%, 19%, and 3% of patients, respectively, at 6 months post-treatment.\textsuperscript{81} A sub-analysis of Asian patients in that phase III trial revealed that HBV DNA <10,000 copies/mL was achieved in 50% and 40% of patients at 6 and 12 months post-treatment, respectively.\textsuperscript{82} A long-term follow-up study of 230 patients treated with Peg-IFN-\(\alpha\)-2a ± LAM revealed that 31% and 23% of patients achieved HBV DNA <2000 IU/mL at 1 and 5 years post-treatment, respectively, and 5% and 12% of patients achieved HBSAg seroconversion at 1 and 5 years post-treatment, respectively.\textsuperscript{83} Extended treatment for 96 weeks with 180 \(\mu\)g weekly for 48 weeks followed by 135 \(\mu\)g weekly for additional 48 weeks in genotype D infected patients achieved a higher rate of HBV DNA <2000 IU/mL (28.8% vs 11.8%, \(P = 0.03\)) and HBSAg <10 IU/mL (9.6% vs 0%, \(P = 0.06\)) at 1 year post-treatment compared with 48 weeks of treatment. Extended treatment was well tolerated with discontinuation rates similar to those with 48 weeks of treatment.\textsuperscript{84}

**Liver cirrhosis**

A study investigated the efficacy and safety of Peg-IFN-\(\alpha\)-2a ± LAM for 52 weeks in 70 HBeAg-positive patients with advanced fibrosis (24 with cirrhosis).\textsuperscript{85} HBeAg seroconversion with HBV DNA <10,000 copies/mL at 26 weeks post-treatment occurred more frequently in patients with advanced fibrosis (25% vs 12%, \(P = 0.02\)) and in patients with cirrhosis (30% vs 14%, \(P = 0.02\)). In addition, improvement in liver fibrosis occurred more frequently in patients with advanced fibrosis (66% vs 26%, \(P < 0.001\)). Side effects, dose reduction and discontinuation of therapy were comparable for patients with and without advanced fibrosis. However, dose reduction and discontinuation of therapy were more frequent in patients with cirrhosis than in those without cirrhosis.\textsuperscript{86}
Baseline and on-treatment predictors of response to Peg-IFN therapy

Serum HBV DNA and ALT levels
In CHB patients undergoing IFN or Peg-IFN therapy, lower HBV DNA levels and higher ALT levels are baseline predictors for a better response. In a pooled analysis of 721 HBeAg-positive patients receiving Peg-IFN ± LAM therapy for 48–52 weeks, an ALT level >2 times upper limit of normal (ULN) and an HBV DNA level <2.0 x 10^4 IU/mL were predictors of a sustained response (HBeAg loss with HBV DNA <2000 IU/mL) at 6 months post-treatment.\(^9\) In a pooled analysis of 518 HBeAg-negative patients receiving Peg-IFN, Peg-IFN plus LAM or LAM therapy for 48 weeks, a higher ALT level and a lower HBV DNA level were associated with a sustained combined response (ALT normalization and HBV DNA <20,000 copies/mL) at 6 months post-treatment.\(^8\)

HBV genotype
In HBeAg-positive patients with IFN-based therapy, patients with genotypes A and B had a significantly higher rate of HBeAg seroconversion post-treatment, than those with genotypes C and D.\(^9\) In a pooled analysis of 721 HBeAg-positive patients receiving Peg-IFN ± LAM therapy for 48–52 weeks, patients with genotype A infection had the best treatment response, those with genotype B or C infection had similar response, whereas those with genotype D infection had the worst response.\(^8\) A meta-analysis further confirmed that HBV genotype A has a better response to IFN treatment than genotype D patients, regardless of HBeAg status. HBV genotype B has a higher rate to IFN treatment than genotype C in HBeAg-positive patients.\(^9\)

In genotype B or C infected Asian patients receiving Peg-IFN therapy for 6 months, genotype B infection exhibited a better response compared with genotype C infection.\(^9\) However, both genotypes exhibited a similar response to 12 months of treatment.\(^6\) In a pooled analysis of 518 HBeAg-negative patients receiving Peg-IFN, Peg-IFN plus LAM or LAM therapy for 48 weeks, genotype B or C infection was associated with a better sustained response at 6 months post-treatment.\(^8\) In a subsequent long-term observational study on 315 patients derived from the initial cohort, genotype was not identified as a predictor of sustained response at 3 years post-treatment.\(^9\) Thus, genotype appears to play a minimal role in the treatment response to Peg-IFN in HBeAg-negative patients. Further study is required to clarify the role of genotype in relation to the discrepant findings among these studies.

HBeAg level, precore (PC) and BCP mutations
A retrospective analysis of 271 HBeAg-positive patients receiving Peg-IFN therapy for 48 weeks revealed that quantitative HBeAg levels decreased consistently during treatment and post-treatment follow-up in patients who achieved HBeAg seroconversion and were correlated with HBeAg seroconversion.\(^9\) Quantitative measurement of HBeAg was proposed as a tool for predicting HBeAg seroconversion. However, the quantitative HBeAg assay is not commercially available, thus limiting its role in routine clinical practice. In addition, the impact of HBV naturally occurring mutations on HBV treatment remains largely unknown. Mutations in the PC region or BCP abolish or downregulate the expression of HBeAg, and may play a role in the response to Peg-IFN therapy. BCP mutations were associated with HBeAg seroconversion and HBV DNA suppression at 6 or 12 months post-treatment.\(^9\)\(^9\)\(^9\) A study quantified the proportions of PC and BCP mutants at baseline and during treatment in 203 HBeAg-positive patients receiving IFN ± ribavirin or Peg-IFN-α2a therapy.\(^9\) The proportions of PC and BCP mutants at baseline were independent predictors of HBeAg seroconversion. The proportion of PC mutants at baseline was a predictor of HBeAg seroclearance with HBV DNA <2000 IU/mL at 6 months post-treatment. The proportion of PC mutants increased significantly during treatment in patients who achieved HBeAg seroclearance with HBV DNA <20,000 IU/mL at 6 months post-treatment.\(^9\) In summary, these studies suggest that PC and BCP mutations are associated with a higher response rate to IFN or Peg-IFN therapy in HBeAg-positive Asian patients. By contrast, another study measured the proportions of PC and BCP mutants with a line-probe assay (detection threshold: 5%) in 214 HBeAg-positive European patients (75% genotype A or D) receiving Peg-IFN-α2b ± LAM for 52 weeks and demonstrated that the presence of wild-type virus at baseline was an independent predictor for achieving HBeAg loss with HBV DNA <2000 IU/mL at 6 months post-treatment (34% vs 11%, P < 0.001).\(^9\) Confirmatory data are limited and therefore further large-scale studies are required to explore the association of common HBV variants with treatment response to currently available antiviral agents.

Quantitative serum HBsAg level
qHBsAg partially reflects host immune status against HBV infection. Thus HBsAg may serve as a biomarker to predict responses to Peg-IFN therapy. A French study first reported that a decline in serum HBsAg level of 0.5 log_{10} IU/ml at week 12 could differentiate sustained responders from relapsers in HBeAg-negative patients receiving Peg-IFN therapy.\(^9\) Thereafter, several retrospective studies supported the role of serum HBsAg level at week 12 of Peg-IFN treatment as a potential “stopping rule” in both HBeAg-positive and HBeAg-negative patients. It was further revealed that the value of qHBsAg was related to the definition of treatment response, HBV genotype and HBeAg status.

For example, of 202 HBeAg-positive Caucasian patients with genotype A or D infection,\(^9\) only 3% of patients without decline in serum HBsAg level at week 12 could achieve sustained response (NPV of 97%). However, of 399 HBeAg-positive Asian patients with genotype B or C infection, the NPV was only 82%.\(^9\) Instead, the Asian study proposed an alternate stopping rule, HBsAg >20,000 IU/mL at week 12.\(^10\) To investigate the value of qHBsAg across HBV genotypes, data from three large-scale clinical trials were pooled. It was found that the 12-week stopping rule can be defined as no decline in HBsAg level for genotype A or D, but an HBsAg level >20,000 IU/mL for genotype B and C patients; whereas an HBsAg level >20,000 IU/mL at 24 weeks could be applied to all patients as the 24 week stopping rule, irrespective of HBV genotype.\(^10\) As for patients with
HBeAg-negative chronic hepatitis B receiving Peg-IFN therapy, most data was obtained from patients with HBV genotype D infection. When adopting an HBV DNA level <2000 IU/mL combined with normal ALT level at 6 months post-therapy as the treatment endpoint, the stopping rule of no HBsAg decline plus <2 log serum HBV DNA decline at week 12 had a NPV of 100%. For patients with non-genotype D infections, an HBsAg decline of 10% has been shown to predict treatment response at 1-year post-therapy (47.2% for HBsAg decline ≥10% and 16.4% for HBsAg decline <10%). Another study on 61 HBeAg-negative patients exclusively with genotype B or C infection from Taiwan identified the HBsAg level at 12 weeks of treatment as a strong predictor of sustained response but failed to validate the stopping rule proposed by Rijckborst et al.

In summary, a stopping rule for Peg-IFN therapy at week 12 or 24 is clinically useful for HBeAg-positive patients. For HBeAg-negative patients with genotype D infection, a week 12 stopping rule is also clinically applicable. However, for HBeAg-negative patients with non-genotype D infections, more studies are warranted.

Quantitative serum anti-HBc level

Quantitative serum anti-HBc levels may reflect the strength of the adaptive immunity against HBV, and thus may have a predictive role for therapeutic response to anti-HBV therapy. A retrospective study investigated the role of quantitative serum anti-HBc levels in predicting HBeAg seroconversion in 231 and 560 patients treated with Peg-IFN and NA for up to 2 years, respectively. Baseline anti-HBc level of 4.4 log_{10} IU/mL was the optimal cut-off value to predict HBeAg seroconversion for both Peg-IFN and NA therapy. Patients with baseline anti-HBc ≥4.4 log_{10} IU/mL and HBV DNA <9 log_{10} copies/mL had HBeAg seroconversion rates of 65.8% and 37.1% in the Peg-IFN and NUC cohorts, respectively. In pooled analysis, baseline anti-HBc level was the best predictor for HBeAg seroconversion (odds ratio: 2.178; 95% CI: 1.487–3.156; P < 0.001) other than treatment strategy. Baseline anti-HBc titer is a potential useful marker for prediction of therapeutic efficacy to Peg-IFN and NUC treatment and further validation is warranted.

Interleukin-28B (IL-28B) genotype

Several IL-28B single nucleotide polymorphisms (SNPs), including rs12979860 CC genotype and rs8099917 TT genotype, are associated with a better response to IFN-based therapy for chronic hepatitis C. Its potential role in the response to IFN therapy for CHB has been investigated. Only one study on 182 HBeAg-positive patients (65% Asian) and one study on 101 HBeAg-negative Caucasian patients have demonstrated a positive association between rs12979860 CC genotype and treatment response. A recent meta-analysis of 8 studies failed to confirm an association between IL-28B SNPs and the response to IFN-based therapy for CHB.

HLA-DP SNPs

Recent genome-wide association study in Asian CHB patients revealed that SNPs in the human leukocyte antigen (HLA) region, HLA-DPA1 and HLA-DPB1, are associated with chronicity, and thus immune control of HBV infection. Two Asian studies investigated the association between HLA-DPA1 rs3077 GG genotype and HLA-DPB1 rs9277535 GG genotype and response to IFN therapy in HBeAg-positive patients. They revealed an association between rs3077 GG genotype and HBeAg seroconversion and response to IFN therapy in HBeAg-positive patients. They revealed an association between rs3077 GG genotype and HBeAg seroconversion and response to IFN therapy in HBeAg-positive patients. They revealed an association between rs3077 GG genotype and HBeAg seroconversion and response to IFN therapy in HBeAg-positive patients. They revealed an association between rs3077 GG genotype and HBeAg seroconversion and response to IFN therapy in HBeAg-positive patients. They revealed an association between rs3077 GG genotype and HBeAg seroconversion and response to IFN therapy in HBeAg-positive patients.

CXCL-9 and IP-10

CXCL-9 (monokine induced by IFN-γ, MIG) and IP-10 (IFN-γ-inducible protein 10, also called CXCL-10) are chemokines that can recruit T cells, natural killer (NK) cells and NKT cells and regulate hepatic inflammation and have been shown to be temporally associated with hepatitis flare in CHB patients. A study revealed an association between baseline IP-10 levels and on-treatment HBV DNA, HBeAg, and HBsAg decline from week 4 onwards in HBeAg-positive patients treated with Peg-IFN. Baseline IP-10 levels were associated with HBeAg loss (P = 0.001) and HBeAg loss with HBV DNA <2000 IU/mL at 6 months post-treatment (P = 0.052). Another study demonstrated that baseline CXCL-9 level is an independent predictor for achieving HBV DNA <2000 IU/mL at 12 months post-treatment mainly in HBeAg-negative patients. Therefore, the role of these chemokines in the response to IFN therapy in CHB patients warrants further study.

Side effects of IFN therapy

Many side effects are associated with IFN therapy, including flu-like symptoms, fatigue, headache, myalgia, alopecia, and local reaction at the injection site. In addition, IFN has myelosuppressive effects. However, neutropenia and thrombocytopenia induced by IFN do not significantly increase the risk of infection and bleeding, except in patients with cirrhosis or immunosuppression. IFN-associated side effects are mostly mild and well tolerated. IFN intolerance with premature discontinuation has been reported in 2%–8% of patients.

Therapy with Peg-IFN: overall conclusions

Current evidence suggests that Peg-IFN, ETV, TDF and TAF are the first-line therapy for CHB patients. Peg-IFN is contraindicated in patients with hepatic decompensation, immunosuppression, significant comorbid diseases, and pregnancy. Peg-IFN is preferred in young patients who wish to plan family in near future, those with good tolerance, and those who decline indefinite treatment. Peg-IFN is recommended as the treatment of choice for eligible and willing patients with favorable baseline host and viral profiles (higher ALT and lower HBV DNA levels). The recommended duration of therapy with Peg-IFN is 48 weeks for both HBeAg-positive and HBeAg-negative patients. During therapy, full blood counts and side effects should be
monitored monthly. Serum ALT, HBeAg/anti-HBe, and thyroid function should be monitored at least every 3 months and HBV DNA at least every 3–6 months. Serum HBsAg levels at 12 and 24 weeks of therapy should be monitored to assess the early response to Peg-IFN. Early discontinuation of therapy should be considered in patients who fulfill the early stopping rule but this decision should be thoroughly discussed with patients. Off-treatment efficacy should be assessed at both 6 and 12 months after the end of therapy. Baseline and on-treatment host and viral factors predictive of treatment outcomes warrant further exploration to optimize individualized IFN therapy for CHB.

### Nucleos(t)ide analogues (NUCs)

#### Acyclic nucleotide phosphonates

**Tenofovir disoproxil fumarate**

TDF is an acyclic adenine nucleotide analogue effective for both HBV and HIV. In a phase III randomized trial, TDF 300 mg daily has been shown to have superior HBV DNA suppression than ADV 10 mg daily in both HBeAg-positive and HBeAg-negative patients.**113** TDF treatment for 7 years was associated with 99.3% undetectable HBV DNA (<69 IU/mL) and 80.0% serum ALT normalization.**119** In HBeAg-positive patients, 84/154 (55.4%) and 25/154 (11.8%) achieved HBeAg and HBsAg loss, respectively. One of 375 (0.3%) HBeAg-positive patients were 66.6% and 59.1%, while they were 72.3% and 55.9%, respectively, in HBeAg-negative patients.**113** TDF treatment for 7 years achieved HBeAg and HBsAg loss, respectively. One of 375 (0.3%) HBeAg-positive patients had regression of liver cirrhosis.**115** A recent study showed that on a combination of TDF and emtricitabine achieved undetectable HBV DNA (<69 IU/mL) after 96 weeks of treatment.**124** In vitro studies showed that a single mutation of the ADV resistant mutations, A181 T/V or N236T, had little reduced susceptibility to TDF. However, the double mutant rtA181 V/T + rtN236T had reduced susceptibility to TDF.**125**

Previous studies showed that among patients who have A181 T/V and/or rtN236T substitution, viral suppression by TDF is reduced.**126** However, a randomized study showed that TDF monotherapy and the combination of TDF/emtricitabine had similar efficacy in patients with incomplete viral suppression after therapy with ADV; response was not influenced by the presence of baseline LAM- or ADV-associated mutations.**127** A European study showed that TDF monotherapy and TDF/FTC combination were equally effective in suppressing the HBV DNA to <400 copies in 168 weeks (82 and 84%, respectively) among ADV refractory patients, and there was no difference in the response with regard to the baseline LAM/ADV resistance profile.**128** A recent multicenter randomized study included patients who had ADV-resistant mutants (rtA181 V/T and/or rtN236T) could achieve HBV DNA <15 IU/mL in 62% vs 63.5% of TDF-TDF and TDF/ETV-TDF groups at weeks 48, respectively (P = 0.88) and 64% vs 63.5% of TDF-TDF and TDF/ETV-TDF groups at weeks 96, respectively; (P = 0.96).**129** In a case series of 57 patients with multi-drug resistant HBV, a combination of TDF and ETV could achieve undetectable HBV DNA (<80 IU/mL) in 90% of patients after treatment for a median of 21 months.**130** A recent multicenter randomized study included patients who had HBV with ETV resistance-associated mutations could achieve HBV DNA <15 IU/mL in 71% of TDF group and 73% of TDF + ETV group (P > 0.99) at week 48.**131** Thus, TDF monotherapy provided a virological response comparable to that of TDF and ETV combination therapy in patients infected with ETV-resistant HBV.

**Tenofovir alafenamide**

TAF, an oral prodrug of tenofovir, has been approved for the treatment of chronic HBV infection. TAF has higher intracellular concentration and more than 90% lower systemic tenofovir concentration after administration of a 25 mg dose of TAF than after a 300 mg dose of TDF.**132,133** The reduced systemic exposure of tenofovir offers the potential for the better safety profile of TAF compared with TDF, especially for renal and bone dysfunction, a benefit that has been demonstrated in a recent clinical trial in patients with HIV infection.**134** Two ongoing randomized, double-blind, phase 3, non-inferiority studies for hepatitis B e antigen (HBeAg)-positive and -negative patients showed that TAF was not inferior to TDF in achieving an HBV DNA level...
<29 IU/mL at week 48. However, TAF was associated with significantly higher rates of ALT normalization than TDF when assessed by AASLD criteria (male: ALT <30 U/L and female: ALT <19 U/L), but not central laboratory criteria. Furthermore, the analysis of renal safety showed that patients receiving TAF had a smaller reduction in the estimated glomerular filtration rate level than those receiving TDF. Similarly, patients receiving TAF had significantly smaller decreased in bone mineral density at the hip and spine than those receiving TDF in both HBeAg-positive and HBeAg-negative patients. However, longer term follow up will be required to determine the clinical impact of these changes. With its potential for improvement of safety profile, TAF is an important first-line option for the treatment of chronic HBV infection.

D-cyclopentanes

Entecavir

ETV is a cyclopentyl guanosine analogue with potent selective inhibition of the HBV polymerase. In the 5-year report of an international trial among HBeAg-positive patients, who switched from ETV 0.5 mg daily to 1 mg daily since year 3, the cumulative probability of HBV DNA<300 copies/mL was 94% in years 5. Among 222 treatment-naive patients treated with ETV in Hong Kong, 97.1% patients had undetectable HBV DNA, 66.9% had HBeAg seroconversion and only one patient achieved HBsAg seroclearance after 5 years. The other studies also showed that 83–90% patients having undetectable HBV DNA, and 24–44% patients having HBeAg seroconversion at year 3 of treatment. Continuous ETV treatment was associated with improvement of hepatic necroinflammation and fibrosis. The rate of HBsAg decline is approximately 0.125 log IU/mL/year, which explains the need for long-term therapy and low rate of HBsAg clearance in ETV-treated patients. Among HBeAg-positive patients with high viral load (>10^6 IU/mL), a combination of TDF and ETV could achieve a higher rate of undetectable HBV DNA than ETV monotherapy at week 96 (78.8 vs. 62.0%, respectively).

In a Korean study, approximately 14–16% of treatment-naive patients had primary nonresponse as defined by AASLD (<2 log reduction in HBV DNA at month 6) or EASL (<1 log reduction in HBV DNA at month 3), but all primary non-responders could achieve undetectable HBV DNA after 54 months of treatment. A previous study has suggested that patients receiving ETV with a partial virological response at week 48 with declining serum HBV DNA levels may continue treatment with the same agent given the rise in rates of virological response and the very low risk of resistance with long-term monotherapy. However, one study from Taiwan showed that among 23 patients with HBV DNA <2000 copies/mL at week 48, virological response was achieved in 18 (78.3%) patients (median: 36 months), compared with 3 of 11 patients (33%) with HBV DNA > 2000 copies/mL (median: 32 months) (p = 0.004).

Long-term cohort studies from Japan and Hong Kong have demonstrated that ETV-treated patients could reduce the incidence of mortality, liver related complication and HCC compared with historic untreated controls, especially among patients with liver cirrhosis. A multicenter cohort study from Taiwan also showed that four-year ETV therapy significantly reduces the risk of HCC, cirrhotic events and mortality in patients with CHB-related cirrhosis. However, the antiviral treatment with ETV did not completely eliminate the risk of developing HCC. Patients who achieved virological response during treatment are associated with a lower probability of disease progression. However, a previous study from Taiwan showed that virological response during ETV therapy was associated with a reduced risk of clinical liver disease progression and HCC only in NA-experienced patients who had prior LAM or ADV-resistant mutants, but not in NA-naive patients. A study including 306 patients with liver cirrhosis were treated with ETV for ≥12 months showed that virological response to ETV was associated with a low probability that the patients with decompensated cirrhosis (but not in those with compensated cirrhosis) would develop HCC.

Over 97% of treatment-naive patients could achieve undetectable HBV DNA level on ETV after 3 years. However, most patients who exposed to previous antiviral agents failed to achieve virological response. Among patients who failed to have complete HBV DNA suppression with ETV, switching or add-on TDF was associated with 97–100% undetectable HBV DNA after 12 months. A recent multicenter randomized study included patients who had HBV with ETV resistance-associated mutations could achieve HBV DNA <15 IU/mL in 71% of TDF group and 73% of TDF + ETV group (p > 0.99) at week 48.

In a retrospective Taiwanese study among 95 HBeAg-negative patients who discontinued ETV therapy who fulfilled the stopping rules of the Asian Pacific Association for the Study of the Liver (APASL) 2012, the cumulative clinical relapse rate was 45.3% in 1 year. Baseline lower HBV DNA levels were associated with predictive for clinical relapse. In another prospective study from Hong Kong, ETV was stopped in 184 HBeAg-negative patients who fulfilled the same stop treatment criteria. The cumulative rate of virological relapse (HBV DNA>2000 IU/mL) was 91.2% in 1 year and 25.8% of patients had elevated ALT level before ETV retreatment. No baseline or on-treatment factors were found to be predictive of post-treatment relapse after stopping ETV therapy. In a recent Taiwanese study showed that the 2-year post-treatment virological and clinical relapse rates were 42% and 37.6%, respectively in 83 HBeAg-positive patients, and the 3-year virological and clinical relapse rates were 64.3% and 51.6%, respectively in 169 HBeAg-negative patients. In HBeAg-positive patients, the HBV relapse risk increased with age ≥40 years. In HBeAg-negative patients, a combination of age (<55 years) and HBsAg level (<150 IU/mL) at the end of treatment could predict the lower HBV relapse rate (3 years: 4.5%). In a Taiwan study including 586 HBeAg-negative patients with compensated cirrhosis treated with ETV for at least 12 months, the clinical outcomes, including HCC, after cessation of a successful course of ETV therapy in patients with compensated cirrhosis were comparable to those who continued therapy.

A multicenter observational study including 600 NA-naive Taiwanese CHB patients showed that treatment-naive...
CHB patients with a 3-year ETV treatment have the lower likelihood of treatment modification and better rate of adherence compared with those with LdT or LAM treatment. In decompensated patients, a previous study showed that 5 of 16 patients with a model of end-stage liver disease (MELD) score >22 developed lactic acidosis and 1 died. A multicenter study with 93 patients with cirrhosis with Child’s class B or C showed that one patient with a MELD score of 21 developed lactic acidosis, which resolved spontaneously. However, no lactic acidosis was reported in Korean and Hong Kong studies of patients with severe acute exacerbation of CHB with decompensation or decompensated cirrhosis.

ETV has a high genetic barrier of resistance. Drug resistance requires at least 3 codon substitutions, including rtL180 M, rtM204 I/V, plus a substitution at one of the following amino acids: rtT184 S/G, rtS202 I/G, and/or rtM250 V. Among treatment-naïve patients, ETV resistance is very rare. An international trial on HBeAg-positive and HBeAg-negative patients showed that the cumulative incidence of ETV resistance was 1.2% after 5 years of ETV treatment. This is confirmed by studies in Japan, Hong Kong and Taiwan, where ETV resistance was detected in 0.8–3.3% of patients treated with ETV for 2–4 years.

Switching to ETV monotherapy (1 mg daily) in LAM-resistant patients is associated with high risk of ETV resistance. The presence of rtM204 I/V and rtL180 M resulted in a cumulative genotypic resistance and virological breakthrough of 51 and 43% at year 5, respectively. A real-world study showed that the 4-year cumulative incidence of ETV-resistant mutants in patients with LAM- and LAM/ADV-resistant at baseline was near 60%. Among LAM-resistant patients who had HBV DNA <2000 IU/mL on LAM and ADV combination therapy, a combination of ETV 1 mg daily and ADV could achieve undetectable HBV DNA (<60 IU/mL) in 29% in 1 year and 42% in 2 years.

**Quantitative serum HBsAg level**

The HBsAg decline is slow and does not correlate with HBV DNA levels during NUC therapy. NUC treatment typically induces a milder decline in HBsAg than IFN treatment; it has been estimated that 2-4 decades of continuous NUC therapy would be needed to achieve HBsAg clearance. However, a rapid HBsAg decline during NUC therapy may still occur in a minority and identify patients who will soon achieve seroclearance of HBsAg. Currently, there is no consensus on the clinical utility of serum HBsAg monitoring for evaluating responses to NUC therapy. Recent data from Taiwan revealed that a low baseline HBsAg level or a rapid reduction in HBsAg during NUC therapy may identify patients who will show HBsAg clearance, and predict virological response or HBsAg loss/seroconversion in HBsAg-positive patients. Viral breakthrough due to drug resistance can increase serum HBsAg titers. Among Asian patients, HBsAg levels of <100–200 IU/mL at the end of treatment may predict a lower risk of HBV relapse and cessation of treatment can be considered in HBeAg-negative patients who achieve these favorable end-points.

**HBV genotype**

The therapeutic responses to NUCs as well as the development of resistance were comparable among patients with different genotypes. Clearance of HBsAg has been reported in patients treated with NUCs. More specifically, most patients with NUCs-associated HBsAg loss had HBV genotype A or D infection, and the clearance of HBsAg by NUCs seem very rare in Asian patients with genotype B or C infection.

**Finite NUC therapy in HBeAg-negative patients**

The APASL guidelines have recommended to consider stopping NUC therapy in HBeAg-negative patients after treatment of at least 2 years with undetectable HBV DNA documented on three separate occasions 6 months apart. Haddiyannis SJ et al. reported ALT flares in 76% of the 33 patients after discontinuation of 4–5 year ADV therapy with subsequent HBsAg loss rate of 39% during a 5.5 years follow-up. A paradigm shift was then suggested that long-term NUC treatment and discontinuation strategy could be correctly applied to HBeAg-negative CHB patients in 2012. Together with subsequent studies, EASL and AASLD guidelines finally modified their strong recommendation of treating HBeAg-negative patients until HBsAg loss to accept finite therapy under certain conditions. More recently, Honer zu Siederdissen C et al. also demonstrated a 20% HBsAg loss during a median of 33 months follow-up after cessation of long-term NUC therapy in HBeAg-negative patients. A study involving 691 HBeAg-negative patients further demonstrated that off-NUC incidence of HBsAg loss was highest in patients with sustained response (6-year: 36%). Notably, those with clinical relapse but not retreated had a 7.34 times higher incidence of HBsAg loss (6-year: 19 vs 1%) than patients received retreatment. Recently, a randomized controlled trial by Berg et al. on this specific issue (FINITE study) showed a 19% HBsAg loss within 3-year after discontinuation of TDF therapy in contrast to 0% in those who continued TDF therapy. This small yet important study has provided data of well controlled head-to-head comparison, confirming and extending the pivotal observation of Hadziyannis et al. that stopping antiviral therapy in HBV DNA suppressed HBeAg-negative patient may increase subsequent HBsAg loss rate. Obviously, finite NUC therapy in HBeAg-negative patients provides cost saving and beneficial to the patients in term of increased close-to-cure outcomes of CHB. However, timely retreatment is required in some patients with hepatitis flare to prevent hepatic decompensation. Hence, off-therapy monitoring is of paramount importance. The difficulty of decision-making about when to retreatment puzzled many physicians. A recent proof-of-concept case study by Liaw et al. has suggested that retreatment is not necessary or can be held in hepatitis flares with successive HBsAg decline, whereas retreatment is required in flares with increasing HBsAg levels. Obviously, more studies are needed to validate that HBsAg kinetics is useful in decision-making concerning retreatment or not.

**Therapy with NUCs: overall conclusions**

Since most patients on NUCs treatment require long-term therapy, drug resistance is a great concern. ETV, TDF and TAF are potent HBV inhibitors with a high barrier to resistance. Thus, they can be confidently used as first-line monotherapies. Continuous viral suppression is associated with histologic improvement, regression of liver fibrosis
and cirrhosis. ETV-treated patients compared with historic untreated controls have demonstrated reduction in mortality, liver related complication and HCC, especially among patients with liver cirrhosis. Stopping treatment among HBsAg-positive patients can be considered if HBeAg seroconversion with undetectable HBV DNA by PCR persists for more than 12 months. Age ≥40 years at entry may be a significant risk factor for virological relapse after NUCs-induced HBeAg seroconversion with consolidation duration more than 12 months in Asian patients. Stopping treatment in HBeAg-negative patients after demonstration of undetectable HBV DNA ≥12 months result in a cumulative clinical relapse rate of 27.6%–45.3% in one year and 51.6% in 3 years. However, the virological relapse rate is still high. A combination of age and end-of-treatment quantitative HBsAg levels may be a potential marker to guide treatment cessation in HBeAg-negative patients. Despite the high rate of HBV relapse, recent studies showed that the incidence of HBsAg loss is relatively high in patients who achieved a sustained response after stopping NA therapy.18 In case of resistance, an appropriate rescue therapy should be administered with the most effective antiviral agent without cross-resistance to minimize the risk of multiple drug-resistant strains. Table 1 shows cross-resistance data for the most frequent HBV-resistant variants.

### NUCs and Peg-IFN combination therapy

Various types of combination therapies using NUCs and IFN with different pharmaceutical properties have been conducted. The therapeutic effects of combination of two different kinds of agents are recently tried to overcome the shortage of the monotherapy using NUCs or IFN alone. Theoretically, the immunomodulatory activity of IFN is considered to induce cytotoxic T-cell activity for immune clearance of infected cells, as well as to reduce the ccDNA level.189 A decreased viral load induced by NUCs treatment has been shown to result in the subsequent restoration of CD4 followed by CD8 cellular immune response against HBV.190 It is reasonable to combine IFN and NUCs on the concept that suppression of viral replication by NUCs can decrease viral loads, restore the immune response and optimize the immunomodulatory effects of IFN for clearing infected cells.182 However, the benefit of combinational therapy remains unclear. In general, combination therapies can be categorized into three manners: 1. Simultaneous combination with Peg-IFN and NUCs. 2. Sequential combination starting with NUCs and followed by Peg-IFN. 3. Sequential combination starting with Peg-IFN and followed by NUCs.

#### Simultaneous combination of NUCs and Peg-IFN

For HBeAg-positive patients, Janssen et al.183 found that more patients receiving the 52-week peg-IFN-α and LAM combination showed higher serum HBeAg loss than patients receiving 52-week peg-IFN-α monotherapy at the end of treatment (44 vs. 29%; P = 0.01), but the difference was not sustained; 35% of the combination therapy group and 36% of the monotherapy at the end of follow-up (P = 0.91). Other randomized controlled trials75,76 also did not show that 1-year combination therapy with LAM and peg-IFN-α was superior to monotherapy with peg-IFN-α in rate of sustained response. In contrast, most studies found that the combination therapy had greater on-treatment viral suppression and higher rates of sustained post-treatment response than therapy with LAM or Ldt alone.75,76,184 For HBsAg-negative patients, the results were similar to HBeAg-positive patients. A randomized study81 compared the efficacy and safety of peg-IFN-α2a (180 μg once weekly) plus placebo, peg-IFN-α2a plus LAM, and LAM alone for 48 weeks and revealed that higher rates of sustained response (suppression of HBV DNA) was found in patients with peg-IFN-α2a than with LAM. However, the addition of LAM or ADV to peg-IFN-α2a did not improve off-treatment response rate in this81 or other studies.76,81,185

#### Sequential combination starting with NUCs and followed by Peg-IFN

A pilot study by Serfaty et al.186 using sequential treatment with LAM and IFN-α can induce a sustained virological response, including HBsAg seroconversion, in patients with chronic hepatitis B not responding to IFN-α alone before, without the selection of drug-resistant mutants. Since then, many studies with similar protocols were conducted. The rationale is to lower the viral load before IFN therapy, thereby restoring treatment efficacy to IFN. A recent study from China (OSST trial)187 treated patients (who had received ETV for 9–36 months, with HBsAg <100 PEIU/ml and HBV DNA 61,000 copies/ml) and 1:1 randomized to receive peg-IFN-α2a or ETV for 48 weeks. They found patients who switched to peg-IFN-α2a achieved higher week 48 HBeAg serocconversion rates vs those who continued ETV (14.9% vs. 6.1%; p = 0.0467). Only patients receiving peg-IFN-α2a achieved HBsAg loss (8.5%). In a recent global multicenter, randomized trial (ARES study),188 CHB patients started on ETV monotherapy and were randomized in a 1:1 ratio to either peg-IFN-α2a add-on therapy from week 24–48 (n = 85) or to continue ETV monotherapy (n = 90). Peg-IFN-α2a add-on was significantly associated with response (odds ratio: 4.8; 95% confidence interval: 1.6–14.0; P = 0.004). Eleven (13%) of the add-on-treated

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**Table 1** Cross-resistance of the 3 nucleos(t)ide analogues.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Wild-type</th>
<th>TDF</th>
<th>ETV</th>
<th>TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double (ADV, TDF)</td>
<td>A181 T/V  + N236T</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>-cyclopentate (ETV)</td>
<td>L181M + M204V/I ± 169 ± T184 ± S202 ± M250</td>
<td>S</td>
<td>R</td>
<td>N</td>
</tr>
<tr>
<td>Multi-drug resistance</td>
<td>A181 T/V  + N236T + M204 I/V</td>
<td>R</td>
<td>R</td>
<td>N</td>
</tr>
</tbody>
</table>

I: intermediate/reduced sensitivity, R resistant, S: sensitive, N: not available.

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patients achieved disease remission after ETV cessation vs 2 of 90 (2%) of those treated with monotherapy \( (P = 0.007) \). At week 96, 22 (26%) patients assigned add-on vs 12 (13%) assigned monotherapy achieved HBeAg seroconversion \( (P = 0.036) \). However, another multicenter randomized trial (NEED study)\(^\text{189}\) from Taiwan revealed that adding a four week NUCs (ETV or ADV) before initiating peg-IFN-α2a therapy for 48 weeks did not provide additional benefit than Peg-IFN monotherapy at end of follow up. In summary, for HBeAg-positive patients, there was better outcome of NUCs initiating plus Peg-IFN than NUCs alone, but no significant difference can be found if the control group is Peg-IFN monotherapy.

For HBeAg-negative patients, a non-randomized study\(^\text{190}\) showed a higher rate of ALT normalization in sequential group, but no difference of HBV virological breakthrough at the end of follow up. Furthermore, there was also no additional benefit from sequential therapy if the control group is IFN monotherapy,\(^\text{191}\) which is consistent with the results from HBeAg-positive patients.

**Sequential combination starting with Peg-IFN and followed by NUCs**

For HBeAg-positive patients, a study from Hong Kong\(^\text{192}\) compare a staggered regimen of combination therapy with peg-IFN-α2b for 32 weeks plus LAM given for 52 weeks versus LAM monotherapy for 52 weeks. The rate of sustained virological response was 36% for the combination treatment group and 14% for the LAM monotherapy group.

End-of-treatment outcomes showed that, compared with monotherapy, patients receiving combination therapy more often had virological response (60% vs. 28% [absolute difference, 32 percentage points (CI, 14 to 50 percentage points)]); had more substantial reductions of HBV DNA (3.91 log\(_{10}\) copies/mL vs. 2.83 log\(_{10}\) copies/mL); and less often had LAM-resistant mutants (21% vs. 40%). Furthermore, Chan HL et al.\(^\text{193}\) tried to investigate whether simultaneous combination (group 1) of Peg-IFN-α2b (32 weeks) and LAM (104 weeks) has more potency than other staggered regimens (Peg-IFN initiated: group 2 or NUC initiated: group 3) in a small study. He found that HBV DNA reduction is more profound in group 1 than group 2 (\( p = 0.022 \)) or group 3 (\( p = 0.060 \)).

HBeAg seroconversion was 67% in group 1 than group 2 \( (p = 0.022) \) or group 3 \( (p = 0.037) \). However, there is a lack of comparison with Peg-IFN monotherapy in this study. The following Xie et al. study\(^\text{194}\) further elucidated that neither ETV add-on nor ETV pretreatment with Peg-IFN-α2a sequential therapy demonstrated superiority compared with 48 weeks of Peg-IFN-α2a monotherapy. For HBeAg-negative patients, there is very limited experience reported from this regimen.

**Overall comparison by meta-analysis**

In overall comparison, most studies indicated that IFN/Peg-IFN and NUCs combination or sequential therapies promised a better therapeutic outcome than NUCs monotherapy in both HBeAg-positive and HBeAg-negative patients. However, the duration of NUCs monotherapy in all studies were relatively short (mostly 1–2 years). Therefore, longer duration of NUCs therapy or follow up may be needed to elucidate the efficacy. But notably, in most studies using IFN/Peg-IFN as control of comparison, the additional benefit of combination therapy was obscured and insignificant. There were three recent meta-analyses to characterize these comparisons. Kim et al.\(^\text{195}\) performed a meta-analysis including 14 randomized controlled trials. It revealed that Peg-IFNα and LAM combination therapy produced better virological and biochemical, but not serological responses than PEG-IFNα monotherapy in both HBeAg-positive and HBeAg-negative patients at the end of treatment. However, the benefits of combination therapy all disappeared at the end of follow up. In the review of Wei et al.\(^\text{196}\) (17 studies, 11 in Chinese), HBeAg loss \( (RR = 1.73, 95\% CI = 1.32–2.26, p < 0.001) \), HBV-DNA undetectable rate \( (RR = 1.58, 95\% CI = 1.22–2.04, p < 0.001) \), HBeAg seroconversion \( (RR = 1.68, 95\% CI = 1.36–2.07, p < 0.001) \), and HBsAg loss \( (RR = 2.51, 95\% CI = 1.32–4.75, p < 0.001) \) in the combination therapy group were significantly higher than those in the NUCs monotherapy group. However, there were no significant differences in HBsAg seroconversion \( (RR = 4.25, 95\% CI = 0.62–29.13, p = 0.14) \), sustained virological response rates, and biochemical response rates observed between the two groups.

Xie et al.\(^\text{197}\) performed another meta-analysis including 11 trials (7 in Chinese) and 1010 participants for the efficacy and safety of ETV and IFN combination therapy in HBeAg-positive patients. It showed that at 12 and > 96 weeks of therapy, the combination of ETV and IFN was not better than ETV in improving the undetectable HBV DNA and HBeAg seroconversion rates. But at 48 weeks of therapy and approximately 2 years of follow up, combination therapy was superior to ETV in improving the undetectable HBV DNA and HBeAg seroconversion rates \( (48 \text{ weeks: } RR = 1.82, 95\% CI = 1.44–2.30; \text{ follow up: } RR = 1.92, 95\% CI = 1.19–3.11, \text{ respectively}) \). When compared to IFN group, at 24 and 48 weeks of therapy, combination group showed a greater undetectable HBV DNA. At 48 weeks of therapy, combination group achieved a greater HBeAg seroconversion rate than IFN \( (48 \text{ weeks: } RR = 1.58, 95\% CI = 1.24–2.00) \). Further qualified meta-analyses are needed to further elucidate the off-treatment efficacy of these studies.

**Special groups of patients**

**Pregnant women**

If a pregnant woman is indicated for treatment, we should consider the (1) drug safety and (2) the duration of treatment. Lamivudine or TDF is listed in category B and considered to be relatively safe in terms of the teratogenic effect. On the other hand, the recent studies had shown that these two NUCs are safe and cost-effective in preventing the mother-to-infant HBV transmission if administered to the pregnant women with HBV DNA > 10\(^6\) copies/mL in the third trimester.\(^\text{198,199}\) If there is no other indications, NUCs can be discontinued one month after delivery for those mothers who take NUCs for preventing mother-to-infant transmission.

**Pediatric patients**

The indications for treatment in children are similar to adults at present.\(^\text{200}\) HBV-infected children respond to IFN and LAM similarly to adults. Generally speaking, most CHB
children are only indicated for follow-up and rarely indicated for antiviral therapies. Long-term safety and drug resistance are more important concerns in children than in adults. A recent meta-analysis from the USA showed antivirals compared to no antiviral therapy improved HBV DNA suppression and frequency of ALT normalization and HBeAg seroconversion in children with chronic HBV infection, but inconclusive in terms of long-term outcome.201 Our studies showed either IFN or LAM therapy provided little long-term benefit in comparison with untreated children.202,203 Therefore, drug therapy is usually not recommended in pediatric patients because of the apparent lack of long-term benefits and the attending risks of starting drug therapy, unless in the setting of ensuing or overt hepatic decompensation,204 or in those who have evidence of severe liver disease or advanced fibrosis/cirrhosis. In all of these rare occasions, the pediatricians should carefully evaluate the treatment options and discuss with the patients themselves and their parents (guardians) the pros and cons of the treatment options. IFN is usually preferred to NUCs due to its finite treatment duration, while the side effects are notorious. IFN-alpha is approved for use in children as young as 12 months of age.205 Peg-IFN is now undergoing clinical trials and has not yet been marketed, but likely to be as effective in children as in adults with chronic HBV infection. LAM may be used starting at 3 years of age, ADV is approved for those aged 12 years and older, but these two are now seldom used because of their low genetic barriers and drug resistance. ETV is approved for age 2 years and older206 while TDF can be used for age 12 and older.207 The dilemma of NUCs administration is when and how to decide the appropriate timing to stop the medication. A clinical trial to utilize combination of IFN and NUC antiviral therapy is ongoing.207

**Co-infection with HBV and HCV**

The primary goal of the treatment of HCV and HBV co-infection is to eliminate or permanently suppress both viruses. Simultaneously, the long-term goal is to reduce or terminate hepatic necroinflammation, prevent progression to LC and the development of HCC, and ultimately prolong the survival of patients. We hope to achieve these goals by eradicating both viruses after providing an effective antiviral therapy for dually infected patients. In the next scenario, we may provide treatment to control the virus that is likely responsible for liver injury in most patients; or we may prioritize the treatment of the virus most responsive to antiviral therapy.

Accumulating data exist to reach firm conclusions on the management of patients with HCV co-infection. It is generally agreed that the dominant virus should be identified before designing therapeutic strategy. If HBV is dominant, treatment should be aimed toward this virus. If HCV is dominant, Peg-IFN therapy in combination with ribavirin can achieve a sustained HCV clearance rate comparable to that in HCV mono-infection.208 This has been demonstrated in an open-label, comparative, multicenter study involving 321 Taiwanese patients with active HCV infection, in which patients with HCV genotype 1 infection received Peg-IFN alfa 2a 180 ug weekly and ribavirin (1000–1200 mg) daily for 48 weeks. Patients with HCV genotypes 2 or 3 received Peg-IFN alfa 2a 180 ug weekly and ribavirin 800 mg daily for 24 weeks. The sustained virologic response in HCV genotype 1-infected patients was comparable between 161 HBV/HCV patients and 160 HCV mono-infection patients (72.2 vs. 77.3%). For patients with HCV genotype 2/3 infections, the sustained virologic response values were 82.8 and 84.0%, respectively.208 The HCV sustained virologic response (SVR) was durable in approximately 97% of the patients during a 5-year post-treatment follow up. Furthermore, approximately 30% of dually infected patients lost HBsAg within 5 years after the start of Peg-IFN-based therapy.209 The benefit of anti-HCV therapy in dually infected patients was further confirmed in another large population-based survey in Taiwan. Compared with the patients in an untreated dually infected cohort, the risk of developing HCC, all-cause mortality, and liver-related mortality decreased by 35%, 62%, and 59%, respectively, in patients who received active anti-HCV therapy.210

**Co-infection with HBV and HDV**

Currently, IFN-based therapy (3 MIU thrice weekly for 1 year) is the only effective regimen. However, the virus eradication rate is only about 20–36% at the end of treatment (EOT), and relapse rate is nearly 100% at the end of follow-up. Generally, a higher dosage (9 MIU) and longer duration of IFN is more effective than conventional regimen. The rate of ALT normalization and HDV RNA negativity at EOT was 71% versus 29–36% in the high-dose group compared with the low-dose group. Higher dose of IFN also significantly improves the long-term outcome, liver histology and survival. More than 1 year of IFN therapy may be beneficial;211 however, the optimal duration of IFN therapy is not well settled.212 Introduction of Peg-IFN may offer a better convenience then conventional IFN. However, the long-term effect of Peg-IFN remained undefined because of small case numbers and the lack of control groups in previous reports.

Adding ribavirin to IFN or Peg-IFN regimens did not improve HDV seroclearance. LAM, ADV and ETV have been found to be ineffective in the management of Hepatitis D alone or in combination with IFN. However, Wedemeyer et al. using combined Peg-IFN and ADV, showed significant decline in HBSAg titers.213 Case reports also demonstrated successful treatment of HBV and HDV using Peg-IFN and ETV,214 or Peg-IFN, TDF and emtricitabine ( FTC).215 Thus, NUC treatment might be considered in some patients who have active HBV replication indicated by persistent or fluctuating serum HBV DNA levels above 2000 IU/mL.

**Co-infection with HBV and HIV**

Co-existing HIV infection may accelerate the progression of HBV-related liver diseases. Treatment of HIV may lead to flares of hepatitis B due to immune reconstitution.216 Besides, progression of liver disease is faster in HIV–HBV coinfected patients as aforementioned. Facing these adverse interactions between HBV and HIV infections, there is a strong rationale to treat both HIV and HBV infections early, irrespective of immunological, virological or histological status.217

For most coinfected patients, the best option is triple combination of antiretrovirals against both HBV and HIV, including two reverse transcriptase inhibitors with anti-HBV activity. TDF combined with emtricitabine or LAM plus a
third agent active against HIV are indicated. However, among patients with CD4 count >500/ml who are unwilling to start HAART, HBV may be treated before the institution of anti-HIV therapy. In this situation, selection of anti-HBV agents will depend on whether HIV will be treated simultaneously or not. Peg-IFN, ADV and LdT, which are not proven to be active against HIV, should be preferred. Peg-IFN alpha could be considered as therapy for CHB in coininfected patients in specific situations, such as in patients unwilling to start HAART who have normal CD4 counts >500, HBsAg(+), low HBV DNA, elevated ALT, and lack of decompensated cirrhosis. Notably, if ADV or Ldt with a low barrier to resistance do not reach the goal of undetectable HBV DNA after 12 months of therapy, treatment of HIV infection should be envisaged. ETV displays weak activity against HIV and may select for resistance mutations; it should be administered only in the context of a fully suppressive HIV treatment. Oral anti-HBV drugs may select changes at the HBV polymerase gene, leading to loss of susceptibility to the corresponding drug and cross-resistance to other antivirals.

Changes in M204 I or V are usually responsible for LAM, FTC, and LdT resistance, whereas more changes (L180M plus M204V plus T250) are usually needed for ETV resistance. No mutations have been uniformly associated with significant loss of susceptibility to TDF in vivo. Resistance to LAM in HBV is more common and develops more quickly in HIV-HBV coinfected patients. Selection of LAM resistance in CHB is associated with poor outcomes, including the occurrence of liver enzyme flares, which occasionally may be life-threatening and prompt rescue antiviral interventions without cross-resistance should be provided. HIV-infected adults without protective anti-HBs titers should be vaccinated. The response rate and durability of the vaccine are poorer in HIV infected persons compared with HIV-negative persons, and they are influenced by both CD4 counts and plasma HIV RNA levels. Accordingly, in patients with low CD4 counts (<200 cells/ml) and uncontrolled HIV replication, the success of HBV immunization is low. In these individuals, previous antiretroviral therapy for at least 6 months may increase HBV vaccine response rates. Initially, conventional HBV vaccination schedule can be used. In the case of lack of achievement of protective anti-HBs titers (>10 mIU/ml), revaccination using double-dose and/or 3–4 injections (months 0, 1, 6, and 12) is recommended.

**Patients with hepatic decomposition**

Hepatic decomposition is a status of liver dysfunction, and can happen in CHB patients with or without underlying liver cirrhosis. In clinical setting, elevation of serum bilirubin level and prothrombin time (PT) prolongation are signs of hepatic decomposition. In general, a Child-Turcotte-Pugh score of ≥7 is considered as hepatic decomposition. Recently, APASL 2015 guideline defined hepatic decomposition as a serum bilirubin >2.5 times the ULN and PT by more than 3 s (or INR >1.5) or occurrence of complications related to decomposition, such as ascites or hepatic encephalopathy. In Taiwan, either a serum total bilirubin ≥2 mg/dl or a PT prolongation ≥3 s is suggested as hepatic decomposition according to the regulation of the National Health Insurance Administration, Taiwan and the definition from several clinical trials.

HBV-related hepatic decomposition can develop in patients with acute HBV infection, immune clearance phase of CHB, reactivation of HBV due to HBeAg-negative CHB, immunosuppressive or chemotherapy, or progression of liver cirrhosis. The risk of hepatic decomposition in patients with HBV-related compensated cirrhosis is around 3–5% annually. All patients with hepatic decomposition are candidates for liver transplantation and should be treated in specialized liver units. However, due to the shortage of liver donor, antiviral therapy with NUCs is the mainstay of treatment in CHB patients with this presentation. IFN-based treatment is contraindication in this stage of CHB. LAM has applied in patients with hepatic decomposition due to acute exacerbation of CHB. In that study, all patients with baseline bilirubin level <20 mg/dl survived, while the mortality rate was 25% in patients with high pretreatment serum total bilirubin level. ETV can also effectively suppress HBV viral load in CHB patients with hepatic decomposition. One study from Hong Kong to compare ETV treatment in 36 patients and LAM treatment in 117 patients with severe acute exacerbation of CHB showed that a short-term mortality was higher in ETV group than in LAM group (19% versus 4%). However, a recent study from Taiwan compared 215 cases treated with LAM and 107 cases treated with ETV due to severe acute exacerbation of CHB with hepatic decomposition; the findings showed that antiviral drug with either LAM or ETV was not the determinant associated with mortality. Therefore, LAM or ETV are equally effective in CHB patients with hepatic decomposition, but the long-term risk of resistance should be warranted in patients under LAM treatment. TDF has been proven to be effective in CHB patients with hepatic decomposition in a Phase 2 study to compare among TDF, FTC/TDF, and ETV (0.5 mg or 1 mg QD). The outcomes including virological, biochemical and clinical responses showed equivalent among the three groups.

Reversal or regression of liver cirrhosis has been proven after long-term treatment with LAM, ETV and TDF in patients with HBV-related cirrhosis. In the LAM study, 8 (73%) out of 11 cirrhotic patients improved their Histologic Activity Index (HAI) scores after three years of treatment. The ETV study evaluated 57 patients with paired baseline and follow-up liver biopsy samples to compare the histological improvement. The finding showed an improvement in the Ishak fibrosis score for 88% of patients during a median time of treatment for 6 years. The TDF study had 96 patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis after five years of TDF treatment. All these findings support that long-term NUCs treatment is required for cirrhotic CHB patients with hepatic decomposition to improve the inflammation and fibrosis in liver histology.

**Patients with drug resistance**

The definition of resistance is the presence of virological breakthrough, i.e. increasing in HBV viral load of more than 1 log10 IU/ml compared to the nadir (lowest value) HBV DNA level, on NUCs therapy in compliant patients. Resistance is associated with pretreatment HBV viral load and
the genetic barrier of the antiviral drugs used. In the presence of resistance during NUCs treatment, Peg-IFN remains a treatment option for CHB patients if no contraindications to Peg-IFN presented, as there is no cross-resistance issue between Peg-IFN and NUCs. Among the NUCs, LAM, Ldt and ADV are now rarely served as the first-line treatment for CHB due to their low genetic barrier and associating with high risk of resistance. Currently, there was no documented TDF resistance after 8 years of treatment in patients with CHB.

ETV potency

The cumulative incidence of resistance is 1.2% after 5 years of treatment in NUCs-naïve CHB. Multiple point mutations in HBV polymerase RT domain rtL180M + rtM204V/I ± rtT169T ± rtV173L ± rtM250V or rtL180M + rtM204V/I ± rtT184G ± rtS202I/G are required for the resistance. As there was no cross-resistance to nucleotide analogues in ETV resistance, add-on ADV or switch to TDF monotherapy is recommended in the presence of ETV resistance. In a randomized trial to compare TDF versus TDF/ETV combination therapy in CHB patients with ETV resistance showed that TDF monotherapy has similar virological response as that of combination therapy.

Multi-drugs resistance

In CHB patients with resistance to at least two NUCs, ETV and TDF combination therapy seems the last resort and should be feasible in such knotty circumstances except for PEG-IFN treatment. One study to apply ETV and TDF combination therapy in patients with resistance to either LAM/ETV, LAM/ADV, or LAM/ADV/ETV, the results showed that nearly 80% of the cases achieved complete virological suppression after a median of 4.5 months treatment.

Patients undergoing immunosuppressive or chemotherapy

HBV reactivation (HBVr) in patients with chronic HBV infection and undergoing chemotherapy is potentially life-threatening. Ten-fold increases in HBV viral load is the standard definition of HBVr in HBsAg-positive carriers. In an earlier study from Hong Kong to investigate the risk of HBVr in patients with cancers and undergoing chemotherapy, the overall HBVr rate was 26% in HBsAg-positive cases. Antiviral prophylaxis to prevent HBVr has been adopted since the development of NUCs. However, delayed HBVr can be observed even after discontinuing the NUCs prophylaxis. A high baseline HBV viral load (>10,000 cp/ml or 2000 IU/mL) is the risk factor of delayed HBVr. The duration of prophylactic antiviral therapy should be initiated one week before the start of chemotherapy and lasted till at least 6 months after completing the chemotherapy. Some associations recommend an additional 12 months of antiviral therapy after end of chemotherapy to prevent the delayed HBVr.

In addition to baseline viral load, the regimen of chemotherapy may have impact on the risk of delayed HBVr, such as anti-CD20 monoclonal antibody (e.g. rituximab) has prolonged suppressive effect on host immunity. Rituximab has higher risk to induce HBVr not only in HBsAg-positive cases but also in HBsAg-negative/anti-HBc-positive resolved hepatitis B patients. The risk of HBVr in resolved hepatitis B patients with lymphoma under rituximab-based chemotherapy is around 18% per person year. A randomized controlled trial from Taiwan to compare ETV prophylaxis in 80 CD20 positive lymphoma patients with resolved hepatitis B underwent rituximab-based therapy showed that the risk of delayed HBVr can persist till 7 months after stopping ETV prophylaxis. Another information from the study suggests that undetectable HBV viral load before chemotherapy in HBsAg-negative/anti-HBc-positive lymphoma patients does not confer reactivation-free status during or after chemotherapy. Recently, American Gastroenterology Association strongly recommends at least 12 months additional antiviral prophylaxis after discontinuation of immunosuppressive therapy is required for not only HBsAg-positive but also HBsAg-negative/anti-HBc-positive patients when receiving B cell depleting agents’ therapy.

Immunosuppressive agent other than chemotherapy can also induce HBVr. Biologic agents now are widely applied in patients with inflammatory bowel diseases, rheumatic diseases and psoriasis. The risk of HBVr related to biologic agents has been drawn the attention by clinicians. A retrospective study suggested that 5 out of 8 HBsAg-positive rheumatoid arthritis (RA) patients developed HBVr during anti-tumor necrotic factor (TNF) treatment; in addition, one in four RA patients with resolved hepatitis B had HBVr. One recent study from Taiwan showed that the risk of HBVr in HBsAg-positive patients with RA undergoing immunosuppressive treatment was around 24.4%. Glucocorticoid in combination with biologics and traditional disease-modifying antirheumatic drugs (DMARDs) had the highest risk of HBVr. HBVr is also reported to happen in a RA patient with occult HBV infection undergoing anti-CTLA4 (abatacept) treatment. However, the actual incidence of HBVr in rheumatic patients receiving biologics treatment is still waiting for future well-designed prospective studies with larger sample size to define.

It is also unclear regarding the risk of HBVr related to targeted therapy in cancer patients, because most of the Phase III studies excluded HBV carriers from clinical trials and the information is limited before marketing. Of them, inhibitors to mammalian target of rapamycin (mTOR) has documented immunosuppressive effect and the everolimus study for hepatocellular carcinoma patients demonstrated a high risk of HBVr in HBsAg-positive cases. Based on the safety concerns, antiviral prophylaxis is recommended in HBsAg-positive patients undertaken mTOR inhibitors treatment.

Whether low- or high-potency antiviral agents provide comparable preventive effect on HBVr is a controversial issue. Theoretically, antiviral drugs with low potency (such as LAM) should be enough for patients with low baseline HBV viral load. But a recent randomized study supports that ETV is superior to LAM resulting in a lower risk of HBVr and HBV-related hepatitis flare during chemotherapy in HBsAg-positive patients. Beside, ETV has been showed its effectiveness to prevent HBVr in a randomized trial for resolved hepatitis B patients. Therefore, high potency NUCs, including ETV and TDF are recommended for prophylaxis.
Liver transplantation

HBV infection is associated with liver-related complications that can lead to end stage liver disease (ESLD) and liver failure (1). Liver transplantation (LT) offers the ultimate cure for patients with CHB and is the only treatment available for patients with ESLD. However, HBV recurrence in LT recipient (LTR) can lead to rapid liver disease progression, graft failure, and death. By the year 1990s, HBV was considered as a contraindication for LT due to poor outcome, with a survival of only ~50% at 5 years. The landmark study by Samuel et al., in 1991 showed that passive immunization with Hepatitis B immunoglobulin (HBIG) reduced the HBV recurrence rate to around 30–40%. Since the approval and use of the first NUC LAM, combination of HBIG plus LAM has further reduced HBV recurrence and improved survival of HBV-related LT, and become the standard of care for prophylaxis against HBV recurrence after LT. The advent of more potent NUC with high genetic barrier to resistance, i.e. ETV and TDF, has further reduced long-term recurrence rates. Recent strategy has suggested the use of HBIG for only a period of time after LT, followed by long-term NUC alone. Till now, the consensus has not been documented.

Most studies have defined HBV recurrence in LT as the reappearance of HBsAg and/or HBV DNA post-transplant. Natural history studies from the era before the use of prophylactic therapies showed that the level of HBV DNA at the time of transplantation was the principal factor for HBV recurrence. Other potential factors included HBV variants with antiviral drug-resistant mutations and/or HBIG resistant mutations. Recurrence of HCC is another risk factor, possibly due to HBV replication in HCC cells.

Three recent meta-analyses have clearly demonstrated that combination of HBIG and LAM is superior to LAM alone. Subsequent reports of ETV plus low dose HBIG revealed that the recurrence rate of HBV was further reduced to 0–3.2%. A recent large cohort study in 145 patients using ETV plus low-dose, on-demand (when anti-HBs < 100 IU/L) IM HBIG prophylaxis showed a HBV recurrence rate of 1.37% during a median follow-up of 36 months, in contrast to a rate of 6.4% (P = 0.055) in 171 patients using LAM plus on-demand IM HBIG prophylaxis. A systematic review reported that antiviral prophylaxis with combination TDF/FTC plus HBIG is associated with negligible HBV recurrence post LT. For HBIG free NUC monotherapy, ETV monoprophylaxis pre and post-LT lead to HBsAg reappeared in 18/80 patients (22.5%) by 2 years post-LT. In a subsequent report including 362 patients, 176 (49%), 142 (39%), and 44 (12%) were treated with LAM, ETV, and combination therapy (predominantly LAM + ADV) respectively at the time of transplant. The rate of HBsAg seroclearance and HBV DNA suppression to undetectable levels at 8 years was 88% and 98%, respectively. Overall 8-year survival was not different among the three treatment groups. There are now increasing numbers of reports of HBIG-free antiviral prophylaxis in using ETV or TDF alone or in combination.

In overall comparison, a systematic review has shown that HBV recurrence was observed to be significantly higher in patients who received NUC monotherapy or HBIG monotherapy than that of HBIG plus NUC combination therapies, if the definition of HBV recurrence was based on HBsAg positivity (26% vs. 5.9%, P < 0.0001). However, if the definition of HBV recurrence was based on HBV DNA detectability, the HBV recurrence rate was similar between HBIG + NUC combination and potent NUC monotherapy (0.9% vs. 3.8%, P = 0.11), especially for monotherapy with ETV or TDF. Furthermore, LAM + HBIG developed HBV recurrence significantly more frequently when compared to patients under ETV/TDF + HBIG combination (6.1% vs. 1.0%, P < 0.001), and HBV-TDF had similar antiviral efficacy when they combined with HBIG (1.5% vs. 0%, respectively, P > 0.05). Therefore, the strategy of ETV/TDF + HBIG may still be recommended for patients who are HBV DNA positive at the time of LT.

A recent strategy has been to use HBIG for only a finite period of time after LT, followed by long-term NUC monotherapy. There were 4 randomized trials with both study group (HBIG discontinued with NUC maintained) and control group (HBIG continued with/without NUCs). A meta-analysis revealed that NUC with continued HBIG did not achieve a favorable outcome compared to NUC with HBIG discontinued though the HBV recurrence rate was relatively higher in the HBIG discontinued group (6/66, 9.09%) than that in HBIG continued group (2/58, 3.44%) (P > 0.05). In addition to randomized control studies, there are also prospective or retrospective studies without control group dealing with issues on the discontinuation of HBIG with NUC maintained. From data of randomized and non-randomized studies, the highest HBV recurrence 8.49% was observed in the LAM group followed by 4.42% in the TDF + FTC group, 3.87% in the LAM + ADV group, and 3.85% in the ETV group after HBIG discontinuation. There is no significant difference between four groups. Only LAM group exhibits a borderline significance of higher rates of HBV recurrence than that of other groups. Notably, ETV/TDF + FTC after HBIG discontinuation seems to be slightly inferior to ETV/TDF + FTC with maintained HBIG (4.42% vs. 0% in TDF/FTC regimen). But ETV/TDF + FTC after HBIG discontinuation is still superior to ETV/TDF + FTC monoprophylaxis in totally HBIG free regimen (P < 0.05). Nevertheless, HBIG discontinuation under LAM + ADV, ETV or TDF/FTC therapy may lead to a higher rate of HBsAg reappearance, although with low HBV DNA detectability, than when HBIG is continued long-term.

The availability and advances in the prophylactic therapies have changed such outcomes of LTRs. A large study in 5912 HBV-related LT in Europe over 20 years (1988–2010) showed that the patient and graft survival at 1 and 3 years before 1995 was significantly lower (73%, 65% and 69%, 60% respectively) when compared with year 1996–2000 (86%, 81% and 83%, 75% respectively; each p < 0.001), year 2001–2005 (88%, 83% and 84%, 79% respectively; each p < 0.001), and year 2006–2010 (86%, 81% and 83%, 77% respectively; each p < 0.001). This incremental improvement in survival over time reflects the availability of the newer NUC of ETV and TDF. Even with a totally HBIG-
free regimen, patient survival in LTRs could reach 95, 88 and 83% at 1, 5 and 8 years under potent NUC prophylaxis. The impact of HBV recurrence on the survival after LT is no longer a significant problem.

Given the shortage of donors, the use of HBV positive grafts in patients with HBV-unrelated diseases could expand the donor pool. A study reviewed the outcome of 92 LT using allografts from HBsAg-positive donors in the United States (1990–2009). Allograft and patient survival were comparable between the HBsAg-positive and HBsAg-negative (n = 82,108) allografts. However, there remains concern of the use of HBsAg-positive live donors, because of the risk of post-operative reactivation of HBV and possible liver failure in the donors. The use of anti-HBc-positive liver grafts is another solution to the current deceased door shortage. A systematic review including 13 studies showed a 2.7% incidence of de novo HBV infection during a median period of 25.4 months in patients receiving LAM monotherapy and 3.6% in patients receiving HBIG + LAM combination therapy during a median period of 31.1 months. Another systematic review including 39 studies showed recurrent HBV infection in 11% of HBsAg-positive LTRs who received anti-HBc-positive grafts, while survival was similar to HBsAg-positive recipients of anti-HBc-negative grafts. Furthermore, if LTRs did not receive any anti-HBV prophylaxis, de novo HBV infection developed in 47.8% of 186 HBV naive recipients which was significantly higher than 15.2% of 138 recipients with serological markers of past HBV infection (p < 0.001) or 9.7% (3/31) of recipients with successful pre-LT vaccination (p < 0.001). HBIG seems to be unnecessary either as monotherapy or in combination with LAM to prevent de novo HBV infection.

The active immunization of post-LT recipients with HBV vaccine has been tried. Earlier studies reported a successful response to HBV vaccination after LT. However, most studies of post-LT HBV vaccination were of low response rates. Patients who were not chronic HBV carrier used to have good response for vaccination. In contrast, the effect of vaccination was disappointing in patients with liver cirrhosis due to immune tolerance. A study has shown that a high anti-HBs titer (>1000 IU/L) in donors is essential for protective adoptive transfer. Notably, considering the extremely high rates of de novo HBV infection after LT in HBV naive recipients and the successful prevention of de novo HBV infection by pre-LT vaccination, HBV vaccination should be offered to all naive HBV patients pre-LT to minimize the need for post-transplant NUC prophylaxis. However, HBV vaccination alone (without any NUC) post-LT has been reported to be not effective to prevent de novo HBV infection.

Non-liver organ transplantation
HBV infection after non-liver organ transplantation was studied more in the setting of renal transplantation (RT). HBV infection is an established cause of morbidity and mortality in RT recipients (RTRs). Rates of HBV DNA reactivation of 50%–94% have been reported in the absence of prophylactic antiviral therapy, thereby leading to fatal liver complications. A longitudinal study in 51 HBsAg-positive RTRs showed that 13 (25.5%) developed cirrhosis during 57 months follow up after RT. HBV DNA levels at baseline could not predict LC development while persistent elevation of serum HBV DNA ≥ 10^5 copies/mL after RT was a significant risk factor for the development of LC. Mathurin and colleagues further showed that the 10 year survivals of HBV infected patients and HCV-infected patients were significantly lower than that of patients without HBV or HCV infection. The most important predictor of outcome following RT in HBsAg-positive RTR is the presence of cirrhosis prior to transplant. A meta-analysis including 6050 RTRs indicated clearly that serum HBsAg was an independent risk factor for death (relative risk: 2.49, P < 0.0001) and allograft loss (relative risk of 1.44, 95% CI of 1.02–2.04) after RT. The availability of LAM in 1998 marked the new era of oral therapy. A study showed that the survival of HBsAg-positive RTRs who received preemptive LAM treatment (transplanted after 1996) was similar to that of HBsAg-negative controls, whereas HBsAg-positive RTRs who did not receive LAM treatment (transplanted before 1996) had significantly increased liver related mortality (relative risk 68, 95% CI, 8.7 to 533.2) and lower survival (relative risk, 9.4, P < 0.001). A large study in RTRs in the United States from 2001 to 2007 also reported that HBV infection was no longer a risk factor for death or kidney failure, although 5 year cumulative incidence of hepatic failure was higher in 1346 HBV-RTRs (1.3% versus 0.2%; P < 0.001), compared with 74,355 HBV-negative RTRs. With the availability of NUC since 1998, HBV infection is no longer a risk factor for death or graft failure in organ transplant recipient.

About the selection of antiviral therapy, given the drug potency, safety and resistance issues during long-term therapy, LAM, ADV and LdT are no longer recommended for patients with organ transplantation. Instead, potent NUC with low resistance should be used for RTRs. Since long-term use of TDF in HIV patients has been associated with possible renal toxicity, as well as metabolic bone disease and osteomalacia, it has been suggested that ETV may be preferred over TDF in RT population because no nephrotoxicity has been reported in chronic hepatitis or cirrhotic populations. If renal allograft dysfunction is in progress, the inception of LdT, in theory, could potentially lead to renal function improvement. At present, the general consensus is that NUC therapy should be commenced pre RT in those with active CHB and start at time of transplant in those without CHB as the majority of patients will have increase in HBV DNA under immunosuppression. Preemptive LAM therapy has also been reported to improve the survival of HBV-infected RTRs but salvage treatment after hepatic dysfunction during HBV recurrence was less effective. The duration of anti-HBV therapy in RTR is another issue. A recent small study showed a high rate (75%, 9/12) of virological relapse (defined as HBV DNA > 2000 IU/mL) during a median follow-up of 65 weeks (range 8–194 weeks) in patients who had completed 2-year LAM treatment and discontinued therapy after demonstration of undetectable HBV DNA at 2 occasions 6-month apart. However, other studies reported successful NUC withdrawal after stable immunosuppression without liver related mortality. In high risk patients with high levels of HBV DNA at baseline, or those who are maintained with
a high dose of immunosuppressant, long term therapy may be needed.\textsuperscript{11,12}

It is acceptable for renal grafts from HBSAg-positive donors to HBSAg-positive or HBSAg-negative recipients with long-term NUC administration with or without HBIG.\textsuperscript{301,302} The benefit of renal graft absolutely outweighs the risk of HBV transmission. It was shown that the de novo HBV infection rate from anti-HBC-positive kidney and heart allografts was significantly lower than that from liver allografts. In a systemic review of 1385 anti-HBc seropositive renal donors, seroconversion of anti-HBc, anti-HBs or both occurs in 3\% of RTRs, and only 0.28\% of the recipients develop HBSAg seroconversion.\textsuperscript{303} NUC therapy initiation is indicated only when there is seroconversion of HBSAg or an increase in viral load.\textsuperscript{304} Pre-transplant immunization may be helpful to further reduce the risk of HBV transmission.\textsuperscript{301,302} Besides RT, there are less data available for other non-liver organ transplantation. It is also reasonable to consider recommendations similar to that for the RT setting.\textsuperscript{306–308} Among these, bone marrow transplantation (BMT) is the most serious one that should be addressed. Among patients with resolved hepatitis B before BMT, the anti-HBs titer may decline and serum HBV DNA may become detectable.\textsuperscript{305} Chemotherapy which was used before BMT may further reactivate HBV infection.\textsuperscript{237} Prophylactic antiviral therapy is recommended for all HBSAg-positive patients undergoing BMT regardless of HBV DNA status, and should be continued for at least 6 months or longer according to baseline serum HBV DNA levels.\textsuperscript{310} Finally, transplanting avascular organs such as cornea carries very low risk of HBV transmission, even from HBSAg-positive donors.\textsuperscript{311} Antiviral prophylaxis is not recommended for this transplant setting.

Issues and recommendations

According to the recommendation grade by Asian-Pacific consensus statement on the management of chronic hepatitis B: 2012 issue,\textsuperscript{13} the grade of recommendations were based on evidence as I (at least 1 well-designed, randomized control trial), II (well-designed cohort or case-control studies), III (case series, case reports, or flawed clinical trial), and IV (opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees). The strong recommendation was graded as A and weak recommendation was graded as B.

General management

Recommendation 1. Before considering antiviral therapy, counseling and complete evaluation are needed (IIA). Counseling of the patient includes information on the infectivity/transmission of HBV, preventive measure for family members, advice on lifestyle, need for careful follow-up and long-term monitoring and indications, the risks/benefits, advantages/disadvantages, cost, and problems of each therapies. Complete evaluation includes complete blood cell count, biochemical tests, HBV replication status, HBSAg level and liver fibrosis status.

Recommendation 2. HBV genotype and naturally occurring mutations

Recommendation 1. HBV genotyping is recommended for assessing the prognosis of CHB patients (IIA).

Recommendation 2. For patients intending to receive interferon-based therapy, pre-therapeutic HBV genotyping is strongly recommended since HBV genotype is associated with response to interferon-based therapy (IIA).

Recommendation 3. Detecting basal core promoter and pre-5 mutations in CHB patients is recommended to identify those who are at an increased risk of developing HCC (IIA).

Recommendation 4. Clinical evidence is insufficient to determine the correlation between HBV naturally occurring mutations and response of antiviral therapy, and further research is required (IIIA).

Recommendation 5. NUC therapy initiation is indicated only when there is seroconversion of HBSAg or an increase in viral load. NUC treatment is recommended when there is seroconversion of HBSAg (IIA).

Recommendation 6. Pre-transplant immunization may be helpful to further reduce the risk of HBV transmission (IIA).

Recommendation 7. Antiviral prophylaxis is not recommended for this transplant setting.

Recommendation 8. Antiviral prophylaxis is not recommended for this transplant setting.

Recommendation 9. Antiviral prophylaxis is not recommended for this transplant setting.

Recommendation 10. Antiviral prophylaxis is not recommended for this transplant setting.

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Recommendation 71. Antiviral prophylaxis is not recommended for this transplant setting.
assessed of liver fibrosis except for those with evidence of cirrhosis clinically (IIA).

**Time to start treatment**

**Recommendation.** HBeAg-positive patients with HBV DNA ≥20,000 IU/mL and HBeAg-negative patients with HBV DNA ≥2000 IU/mL and ALT ≥2 x ULN, as well as cirrhotic patients with HBV DNA ≥2000 IU/mL and any ALT level should be considered to treat (IA). Treatment should be started without delay if impending or overt hepatic decompensation (IA). On the contrary, observation for a period of 3–6 months is recommended to wait the spontaneous remission or the need of antiviral therapy (IIA).

**IFN-based therapy**

**Recommendation 1.** Peg-IFN can be considered as an initial treatment option for eligible and willing patients with favorable baseline predictors to treatment response (IA).

**Recommendation 2.** For Peg-IFN, the standard treatment is 180 μg weekly for 48 weeks for both HBeAg-positive and negative patients (IA).

**Recommendation 3.** During Peg-IFN therapy, full blood counts and serum ALT levels should be monitored monthly and TSH and free T4 should be monitored every 3 months. Side effects should be monitored throughout treatment (IA).

**Recommendation 4.** During Peg-IFN therapy, HBV DNA levels should be monitored every 3–6 months and quantitative HBsAg levels should be measured at 12 and 24 weeks of therapy. In HBeAg-positive patients, HBeAg/anti-HBe should be monitored every 3 months (IA).

**Recommendation 5.** In HBeAg-positive patients who fail to achieve serum HBsAg levels below 20,000 IU/mL (genotypes B and C infection) or any decline in serum HBsAg levels (genotypes A and D infection) at 12 weeks of Peg-IFN therapy and serum HBsAg levels below 20,000 IU/mL at 24 weeks of Peg-IFN therapy (genotypes A–D infection), Peg-IFN can be stopped (IIIA).

**Recommendation 6.** In HBeAg-negative patients with genotype D infection who fail to achieve any decline in serum HBsAg levels and a <2 log10 IU/mL decline in serum HBV DNA levels at 12 weeks of Peg-IFN therapy, Peg-IFN should be stopped (IIIA).

**Recommendation 7.** After completion of Peg-IFN therapy, liver biochemistry should be monitored every 1–3 months and HBV DNA and HBeAg/anti-HBe (for HBeAg-positive patients) should be measured at 6 and 12 months post-treatment to assess treatment response or detect relapse (IIIA).

**NUCs therapy**

**Recommendation 1.** Treatment-naïve patients can be treated with TDF 300 mg daily, TAF 25 mg daily, ETV 0.5 mg daily (IA).

**Recommendation 2.** During NUCs therapy, HBeAg, anti-HBe (in patients with HBeAg-positive) and ALT should be monitored every 3 months (IA) and the HBV DNA level should be monitored every 3–6 months (IA).

**Recommendation 3.** Renal function should be monitored at least every 3 months if TDF is used (IA).

**Recommendation 4.** In HBeAg-positive CHB patients, the NUCs therapy can be stopped after at least 1 year of consolidation therapy after HBeAg seroconversion with undetectable HBV DNA by PCR and persistently normal ALT levels (IIIA).

**Recommendation 5.** In HBeAg-negative CHB patients, the optimal duration of NUCs therapy is unknown. The cessation of treatment can be considered after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart (IIIA).

**Recommendation 6.** Finite NUC therapy in HBeAg-negative patients provides cost saving and beneficial to the patients in term of increased close-to-cure outcomes of CHB (IA).

**Recommendation 7.** After stopping of NUCs, liver biochemical tests (HBV DNA if necessary) should be monitored every 1–3 months for the initial 12 months and then every 3–6 months thereafter for relapse (IIIA).

**Recommendation 8.** The possibility of poor compliance or drug resistance should be considered in patients with viral breakthrough by more than 1 log IU/ml increase of HBV DNA from the nadir. Rescue therapy should be initiated as early as possible in case of drug resistance (IA).

**Combination therapy**

**Recommendation 1.** Combination or sequential combination of Peg-IFN and NUCs therapy yields a higher rates of on-treatment and off-treatment serological or virological responses than short term (1–2 years) NUCs therapy in both HBeAg-positive and HBeAg-negative patients (IA).

**Recommendation 2.** Combination or sequential combination of Peg-IFN and NUCs therapy has not yielded higher rates of off-treatment serological or virological responses than Peg-IFN monotherapy (IA).

**Recommendation 3.** The ideal manner of combination therapy has not been characterized (IIIA).
Pregnant women and pediatric patients

Recommendation 1. Pregnant women who need treatment can be treated with category B NUCs (IIA).

Recommendation 2. For the prevention of mother-to-infant transmission, pregnant women with high HBV DNA (>10^6 copies/mL) can be treated with TDF in the third trimester (IA). Ldt is an alternative (IIA). NUCs can be stopped one month after delivery without major side effects (IIA).

Recommendation 3. Pediatric patients need to be monitored at least every 6 months even without any symptoms (IB).

Recommendation 4. The management of children with CHB may observe the treatment guideline for adult patients. However, the pediatric patients', especially the adolescents and parents' values and preferences should be incorporated into shared decision-making. (IIA)

Concurrent infection with other virus(es)

Recommendation 1. It is important to determine which virus is dominant before designing the treatment strategy, and treat the patients accordingly (IIA).

Recommendation 2. In HBV—HCV coinfected patients who are HCV viremic, antiviral treatment may be selected using the same criteria as for those patients with HCV mono-infection (IA).

Recommendation 3. For any HBsAg carrier, anti-HDV should be examined (IA).

Recommendation 4. In patients with HBV and HDV coinfection, it is important to determine which virus is dominant and patients with active HDV infection may be treated with Peg-IFN alfa for 12–24 months (IA).

Recommendation 5. In HIV/HBV-coinfected patients, HBV coinfection accelerates immunological and clinical progression of HIV infection and increases the risk of hepatotoxicity when combined antiretroviral therapy is initiated; whereas HIV infection increases the progression rate of HBV-related liver diseases including cirrhosis, and end-stage liver disease (IA).

Recommendation 6. Given the faster progression of liver disease in HIV-HBV coinfected patients, early dual anti-HIV and anti-HBV therapy should be considered, irrespective of immunological, virological or histological status (IIA). TDF combined with FTC or LAM plus a third agent active against HIV should be used (IA).

Recommendation 7. Peg-IFN can be used in a highly selected group of coinfected patients (B1). ADV and Ldt can be considered in coinfected patients if HIV HAART therapy is delayed (IA).

Recommendation 8. LAM, ETV and TDF have activity against both HIV and HBV and are contraindicated as a single agent for the treatment of CHB in coinfected patients because of the risk of HIV resistance (IA).

Recommendation 9. HIV-infected adults without protective anti-HBs should be suggested to receive hepatitis B vaccination (IA).

Patients with hepatic decompensation

Recommendation 1. All CHB patients with hepatic decompensation should be treated promptly with antiviral agents to prevent further progression to liver failure (IA).

Recommendation 2. ETV (IA) or TDF (IA) is recommended in CHB patients with hepatic decompensation. LAM (IB), or Ldt (IIB) has comparable effect as that of ETV, but risk of resistance should be warranted. IFN is contraindication in patients with hepatic decompensation.

Recommendation 3. In patients with concomitant liver cirrhosis, long-term NUCs treatment is necessary (I).

Patients with NUC resistance

Recommendation 1. Peg-IFN is a treatment option for CHB patients with NUCs resistance, if there is no contraindication to IFN (IA)

Recommendation 2. LAM- or Ldt-resistance: TDF monotherapy (IA) or ADV add-on therapy (IA) is recommended in the presence of LAM-resistance. ETV 1 mg (IB) is an option, but cumulative risk of ETV-resistance will be high.

Recommendation 3. ADV-resistance: ETV (IIA), or TDF monotherapy (IA) is introduce in NUCs-naı¨ ve or experienced ADV-resistant CHB. Add-on therapy with LAM (IIB) or Ldt (IIB) is an option in NUCs-naı¨ ve CHB.

Recommendation 4. ETV-resistance: Add-on therapy with ADV (IIA) or TDF (IB), or TDF monotherapy (IA) is recommended in patients with ETV-resistance.

Recommendation 5. Multiple drugs resistance. ETV and TDF combination therapy (IIIA) is the treatment of option in patients with multi-drugs resistance.

Patients undergoing chemotherapy or immunosuppressive therapy

Recommendation 1. Antiviral prophylaxis with NUCs should be provided for all HBsAg-positive CHB patients.
when receiving cytotoxic chemotherapy (IA) or immunosuppressive therapy (IIA).

**Recommendation 2.** Antiviral prophylaxis with NUCs should be provided for HBsAg-negative/anti-HBc-positive resolved hepatitis B patients undergoing anti-CD20-based chemotherapy regardless baseline HBV viral load (IA).

**Recommendation 3.** ETV (IA) or TDF (IIA) is the preferred NUCs for antiviral prophylaxis. LAM (IB) or Ldt (IIB) can apply only in patients with low viremia (<2000 IU/mL) or shorter duration of prophylaxis (<12 months).

**Recommendation 4.** The duration of antiviral prophylaxis should start from one week prior to the chemotherapy till at least 6 months after completing the chemotherapy (IA).

**Recommendation 5.** An extending antiviral prophylaxis until 12 months after discontinuing chemotherapy is recommended when B cell-depleting agents (e.g. rituximab) are used in HBsAg-positive or HBsAg-negative/anti-HBc-positive resolved hepatitis B patients (IA).

**Recommendation 6.** Biologics treatment other than anti-CD20 agents can induce HBVr in HBsAg-positive patients. Whenever possible, antiviral prophylaxis is recommended, otherwise, regular HBV viral load monitoring is required.

**Recommendation 7.** Closely HBV viral load monitoring for resolved hepatitis B patients undergoing biologics treatment is recommended (IA). Antiviral therapy should be promptly initiated in the presence of HBV reactivation.

**Recommendation 8.** Targeted therapy with mTOR inhibitor has potential risk of HBVr, and antiviral prophylaxis should be provided for HBsAg-positive cases before the treatment (IA).

**Patients underwent organ transplantation**

**Recommendation 1.** For HBV related LT recipients, ETV or TDF plus HBIG is still the standard of care to prevent HBV recurrence post LT (IA)

**Recommendation 2.** HBIG discontinuation with potent NUC(s) maintained a 6–12 month after LT seems to be safe, but might lead to a higher HBsAg reappearance rate than HBIG contained regimens (IB)

**Recommendation 3.** HBIG free with potent NUC(s) prophylaxis could lead to a high rate of HBsAg reappearance. The long term outcome of HBsAg reappearance are unknown (IIA)

**Recommendation 4.** HBsAg-positive allograft can be used in HBV related or unrelated recipients with long term NUC prophylaxis. However, the use of HBsAg-positive live donors is not suggested (IIA).

**Recommendation 5.** HBV vaccination should be offered to all naive HBV patients before receiving a liver from an anti-HBc positive graft. Patients should receive long-term NUC prophylaxis (IIA).

**Recommendation 6.** NUC therapy should be commenced before RT in those with active CHB and start at time of transplant in those without CHB. Considering long-term treatment, antiviral agents such as ETV or TDF and lack of nephrotoxicity (e.g. ETV) are recommended (IA).

**Recommendation 7.** NUC withdrawal after stable immunosuppression can be considered. In high risk patients with high levels of HBV DNA at baseline, or those who are maintained with a high dose of immunosuppressant, long term therapy may be needed (IIA)

**Recommendation 8.** HBsAg-positive renal allografts can be safely used in HBsAg-positive or HBsAg-negative recipients with long-term NUC administration with or without HBIG (IA)

**Recommendation 9.** de novo HBV infection rate from anti-HBc-positive kidney allografts was significantly lower than that from liver allografts. Routine prophylaxis with NUC is not necessary (IIA)

**Recommendation 10.** Recommendations for other non-liver organ transplants are similar to that for the RT. Prophylactic antiviral therapy is recommended for all HBsAg-positive patients undergoing bone marrow transplantation regardless of HBV DNA status (IIA).

**Unresolved or unmet issues that needed further investigation**

Although recent advances in the relevant biomarkers and treatment of chronic HBV infection, the treatment efficacy and results are still unsatisfactory. Several unresolved or unmet issues remain, further research are needed.

1. Is the stopping rule routinely applied in patients with peg-IFN therapy?
2. What is the long-term outcome in patients with finite NUCs therapy?
3. Could a paradigm shift be suggested that long-term NUC treatment and discontinuation strategy are carefully applied to HBeAg-negative CHB patients.
4. Should patients with chronic HBV infection during the immune tolerance phase be treated?
5. How to improve the therapeutic efficacy of patients with chronic HDV infection?
6. How to improve the therapeutic efficacy using combination or sequential therapy of patients with chronic HBV infection?
7. When and how to apply qHBsAg in the treatment strategy, such as start to treat or early stopping rules?
8. Which is the ideal non-invasive assessment for hepatic fibrosis?
9. Should all cirrhotic patients be treated life-long?
10. What is the best treatment strategy in patients with advanced fibrosis under NUCs therapy and fibrosis regression?

The development of new drugs such as direct antiviral agents engaging entry inhibitor, targeting cccDNA, capsid inhibitor, or HBsAg excretion blockers or host targeting agents focusing on improving innate immunity like lymphotixin-B receptor agonist or Toll-like receptor agonist; and involving adaptive immunity like therapeutic vaccine or immune checkpoint inhibitor is the highest anticipated. Most of them are during preclinical or early phase study.

Conflicts of interest
The authors have no conflicts of interest relevant to this article.

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