

SASLT Practice Guidelines for the Management of Hepatitis B Virus

Faisal Abaalkhail, Hussien Elsiey¹, Ahmed AlOmair², Mohammed Y. Alghamdi³,
Abduljaleel Alalwan⁴, Nasser AlMasri⁵, Waleed Al-Hamoudi^{1,6}

Department of Liver and Small Bowel Transplantation, ¹Adult Transplant Hepatology, Organ Transplant Center, King Faisal Specialist Hospital and Research Center, ²Department of Medicine, Gastroenterology Unit, King Fahad Medical City, Riyadh, ³Department of Gastroenterology, King Fahad Military Medical Complex, Dhahran, ⁴Hepatobiliary Sciences and Liver Transplantation, King Abdulaziz Medical City, National Guard Health Affairs, ⁵Department of Gastroenterology, Prince Sultan Medical Military City, ⁶Gastroenterology Unit, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Address for correspondence: Dr. Waleed Al-Hamoudi, Gastroenterology and Hepatology Unit (59), Department of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. E-mail: walhamoudi@gmail.com

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The Saudi Association for the Study of Liver diseases and Transplantation (SASLT) has formed a working group to develop hepatitis B virus (HBV) practice guidelines in the Kingdom of Saudi Arabia. This working group was organized and then started during the second quarter of 2012. The methodology used to develop these guidelines was based on reviewing the available evidence, local data, and major international practice guidelines on the management of HBV. These practice guidelines have been developed to assist healthcare providers in the management of HBV in Saudi Arabia. Additionally, the guidelines summarize the major studies performed on HBV epidemiology in Saudi Arabia to emphasize the major change in the prevalence of this virus in the region. The grading of our summary of recommendations was based on the best available evidence that is applicable to Saudi patients, and this system was adopted from major international practice guidelines on the management of HBV^[1-4] [Table 1].

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that approximately 2 billion people worldwide have been infected

with HBV and approximately 350 million live with chronic infection.^[5,6] HBV was considered hyperendemic in Saudi Arabia according to the WHO classification. In the 1980s, various studies on the seroprevalence of hepatitis B surface antigen (HBsAg) were conducted in blood donors, pregnant women, and various outpatient populations. Pooling these data together revealed the prevalence of HBV infection to be 5.5%, 8.9%, and 9.6% in the central, southwestern, and eastern provinces of the Kingdom of Saudi Arabia, respectively. The overall average prevalence in the Kingdom was estimated to be 8.3%, making Saudi Arabia one of the most highly endemic areas of HBV infection in the world.^[7-20] These studies also revealed significant information on the prevalence of other HBV markers. The HBV exposure rate was very high, ranging between 20 and 80% in different regions of the Kingdom.^[11,13,14,20-23] The highest exposure rate of 80% was registered in the city of Khaiber in the western province.^[21] However, the prevalence of hepatitis B e antigen (HBeAg) positivity ranged from 8 to 26%.^[7,13,14,24,25] These rates are much lower than the rates reported in different Asian countries, where the prevalence was found to range from 70 to 80%.^[7] Horizontal transmission of the virus is the main route of transmission in Saudi Arabia. This finding is supported by the fact that infection acquired through close personal contact is far more common than that acquired through needle pricks or blood transfusions.^[26] Furthermore, prevalence studies in Saudi Arabia revealed a higher infection rate in children aged 1-12 years compared with infants less than 1 year of age.^[8-18] A study assessing the prevalence of infection in preschool children born to HBsAg-positive mothers showed that the infection rate increased rapidly between the ages of 10 weeks

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Table 1: Grading of recommendations

Grade	Recommendations
A	Recommendation based on high-quality evidence: At least one high-quality randomized controlled trial or at least one high-quality meta-analysis
B	Recommendation based on moderate-quality evidence: High-quality cohort study, case-control study, or systematic review
C	Recommendation based on weak evidence: Case series or case report
D	Weak recommendation based on expert opinion only

and 5 years from 3.6 to 14.6%.^[18] These studies demonstrate the strong horizontal transmission of HBV infection. The low HBeAg positivity of HBsAg-positive mothers in Saudi Arabia makes vertical transmission a less important route compared with the relevant routes in other Asian populations.^[27] These accumulating data on the prevalence of HBV and the availability of a safe and efficacious vaccine triggered the governmental launching of a mass vaccination program in Saudi Arabia.

In 1989, the HBV vaccine was integrated into the expanded program of immunization (EPI), through which all newborn children were vaccinated throughout the country.^[28] The vaccination schedule consisted of three pediatric doses of 10 µg SKF or 5 µg MSD recombinant HB vaccine administered intramuscularly at specified intervals (0, 1, and 5 months). Details of the vaccinations were recorded in the registries of the primary healthcare centers and on the children's EPI cards. One year later, a catch-up program was also initiated with the aim of vaccinating all children at school entry, expatriates, healthcare workers, and hemodialysis patients. As a result of these programs, all Saudi individuals aged 28 years or younger would potentially be vaccinated. To evaluate the efficacy of the vaccination program, three large post-vaccine follow-up studies were conducted. The first study was conducted 2 years after starting the program. In this study, none of the vaccinated children were positive for HBsAg.^[29] The second study was performed in 1997, eight years after initiation of the program. Saudi children aged 1-12 years were included. The prevalence of HBsAg positivity was 0.16% in children vaccinated at birth, compared with 0.7% in those vaccinated at school entry.^[30] The third study was conducted 18 years after starting the program. School students between the ages of 16 and 18 years from different regions of the Kingdom were included. In this study, no cases of HBsAg or anti-hepatitis B core antibody (anti-HBc) positivity were detected among the study population. Additionally, this study showed that 38% of the study population had protective anti-hepatitis B surface (anti-HBs) titers (≥ 10 ml U/ml).^[31] These post-vaccination follow-up studies confirm the efficacy of the vaccination program. The decreasing prevalence of HBV infection in the country has also been shown in various

other studies. For example, prevalence data from pregnant Saudi women showed a significantly lower infection rate in younger (<20 years) pregnant women, ranging from 0 to 0.5%, compared with older, non-vaccinated pregnant women (4%).^[32-34] Similar findings were also observed in various studies from different blood banks across the country.^[35-37] In January 2008, the Saudi Arabian health authority included mandatory testing for human immunodeficiency virus (HIV), HBV, and hepatitis C virus (HCV) in the premarital screening program. A cross-sectional descriptive study originating from this program, with the aim of studying the prevalence of viral hepatitis among this population ($N = 74,662$ individuals), was conducted. This study revealed a prevalence of 0.33% and 1.3% for HCV and HBV infections, respectively. They also showed that the infection prevalence was higher in older participants.^[38] Despite the significant decline in the prevalence of HBV infection in Saudi Arabia, HBV infection remains a significant cause of morbidity and mortality. Disease prevalence in older patients remains high, placing an extra burden on the healthcare system for the next few decades. Furthermore, recent genotype studies showed that genotype D is the most common genotype among infected Saudi patients; further studies on the natural history and treatment response of patients with this genotype are required.^[39]

NATURAL HISTORY OF HBV

An understanding of the natural history of chronic hepatitis B (CHB) is fundamental to the evaluation and management of CHB and plays a critical role in the assessment of patient status and in guiding decisions regarding candidacy for treatment and treatment endpoints. In Mediterranean countries, transmission of HBV usually occurs from person to person during childhood, as previously mentioned. In these populations, most children who are HBeAg positive have elevated alanine aminotransferase (ALT) levels, and seroconversion to anti-hepatitis B e (anti-HBe) is common near, or shortly after, the onset of puberty.^[40-42] The natural history of CHB can be schematically divided into five phases, which are not necessarily sequential.

The "immune tolerant phase" is characterized by HBeAg positivity, high levels of HBV replication [reflected by high levels of serum hepatitis B virus deoxyribonucleic acid (HBV DNA)], normal or low levels of aminotransferases, mild or no liver necroinflammation, and no or slow progression of fibrosis.^[42,43] During this phase, the rate of spontaneous HBeAg loss is very low. This first phase is more frequent and more prolonged in subjects infected prenatally or in the first years of life. These patients are highly contagious.

The "immune reactive phase" is characterized by HBeAg positivity, lower levels of replication (as reflected by lower serum HBV DNA levels), increased or fluctuating levels of

aminotransferases, moderate or severe liver necroinflammation, and more rapid progression of fibrosis.^[42-44] This phase may last for several weeks to several years. In addition, the rate of spontaneous HBeAg loss is enhanced. This phase may occur after several years of immune tolerance and is more frequently reached in subjects infected during adulthood.

The “*inactive HBV carrier state*” is characterized by very low or undetectable serum HBV DNA levels and normal levels of aminotransferases. As the infection is controlled, this state confers a favorable long-term outcome with a very low risk of cirrhosis or hepatocellular carcinoma (HCC) in the majority of patients. HBsAg loss and seroconversion to anti-HBs antibodies may occur spontaneously in 1-3% of cases per year, usually after several years of persistently undetectable HBV DNA.^[40,44]

The “*HBeAg-negative CHB phase*” may follow seroconversion from HBeAg to anti-HBe antibodies during the immune reactive phase and represents a later phase in the natural history of CHB. It is characterized by periodic reactivation with a pattern of fluctuating levels of HBV DNA and aminotransferases and active hepatitis. These patients are HBsAg negative and harbor HBV variants with nucleotide substitutions in the pre-core and/or basal core promoter regions unable to express or expressing low levels of HBeAg. HBeAg-negative CHB is associated with low rates of prolonged spontaneous disease remission. It is important and sometimes difficult to distinguish true inactive HBV carriers from patients with active HBeAg-negative CHB in whom phases of spontaneous remission may occur. The former patients have a good prognosis with a very low risk of complications, whereas the latter patients have active liver disease with a high risk of progression to advanced hepatic fibrosis, cirrhosis, and subsequent complications such as decompensated cirrhosis and HCC.^[45,46]

“*HBsAg-negative phase:*” After HBsAg loss, low-level HBV replication may persist with detectable HBV DNA in the liver.^[47] Generally, HBV DNA is not detectable in the serum, whereas anti-HBc antibodies with or without anti-HBs are detectable. HBsAg loss is associated with improvement of the outcome with a reduced risk of cirrhosis, decompensation, and HCC. The clinical relevance of occult HBV infection [detectable HBV DNA in the liver with low level (<200 IU/ml) of HBV DNA in the blood] is unclear.^[40] Immunosuppression may lead to reactivation in these patients.^[48,49]

HBV DIAGNOSIS

The diagnosis of chronic HBV infection is based on the evaluation of serological and virological markers of HBV infection in serum and the evaluation of biochemical and histological markers of liver disease.

HBsAg is the first serological marker to appear after infection. Its persistence for more than 6 months indicates chronic HBV infection. The presence of antibodies to HBsAg (anti-HBs), which are detectable following immunity conferred by hepatitis B vaccination, implies recovery and/or immunity to HBV. The presence of HBeAg indicates active replication of HBV. However, its absence cannot be assumed to imply the absence of viral replication because HBeAg is undetectable in patients with HBeAg-negative (pre-core or core promoter mutant) HBV infection. The presence of anti-HBe generally indicates HBeAg seroconversion, although it is also found in patients with pre-core or core promoter mutant HBV infection. HBeAg seroconversion has generally been considered the endpoint for HBV therapy in HBeAg-positive patients because it has been shown to be associated with a lower risk for disease progression.^[42]

However, this is not a true reflection of inflammation and should be used in conjunction with other markers, such as HBV polymerase chain reaction (PCR). Histological evaluation of liver biopsy specimens is a more sensitive and accurate indicator of liver disease assessment than ALT levels, and is useful for establishing the baseline status of liver histology at the initial evaluation before the initiation of therapy and to exclude other causes of liver disease. However, liver biopsy examination is not always used as a method of diagnosis and is resisted by some patients because of its invasive nature.^[41,48]

Recently, the upper limit of normal for serum ALT concentrations was redefined as 30 U/l for males and 19 U/l for females.^[50,51]

We assessed these new standards in our population by evaluating 175 consecutive healthy Saudi potential living liver donors with biopsy-proven normal liver histology who underwent a liver biopsy as part of a pre-liver donation workup. We concluded that the upper limit of normal should be lowered (33 IU/l for males and 22 IU/l for females).^[52] These new ALT standards should be utilized when assessing disease activity and when deciding whether to perform liver biopsies in infected patients.

Although the universal vaccination program in Saudi Arabia is strictly enforced, high-risk populations should be screened for hepatitis B [Table 2].

Recommendations

1. All Saudi healthcare facilities should adhere to the hepatitis B vaccination policy through the implementation of universal neonatal or infant vaccination (Grade B)
2. A routine booster dose of HBV vaccination is not indicated in immunocompetent individuals. (Grade A)
3. Repeating the vaccination is indicated if the first series of vaccination fails (Grade A)

4. High risk individuals whose screening tests are negative for HBsAg and anti-HBs should receive hepatitis B vaccines (Grade A)
5. Hepatitis A vaccine should be administered to all individuals with chronic liver disease (Grade C).
6. A liver biopsy should be considered if the disease severity is unclear or if there is a possibility of coexisting liver disease (Grade B).
7. All pregnant women should be screened for HBsAg and, if positive, tested for HBV DNA, HBeAg, and ALT (Grade A)
8. All infants born to HBsAg-positive women should receive both anti-HBs immunoglobulin (HBIG) and HBV vaccines within 12 hours of birth, in adherence with the ministry of health regulations (Grade A).

HBV MANAGEMENT

The current aims of treating CHB with antiviral agents are to achieve sustained suppression of HBV replication and remission of the ongoing liver disease, with the ultimate goal of preventing cirrhosis and HCC. However, the current treatment options are far from ideal. The limitations of current treatments for chronic HBV are related to the unique abilities of HBV to chronically persist in host hepatocytes [due to the unique existence of covalently closed circular DNA (cccDNA) HBV] despite immune and therapeutic pressure. Based on this limitation, we need to be careful in interpreting the inconsistent definitions of responders to antiviral therapy (whether on-therapy or sustained off-therapy), primary non-responders, and on-therapy breakthroughs. Indicators of responses to antiviral treatment include biochemical normalization, viral suppression, HBeAg seroconversion, and histological improvement. Recently, some investigators have used HBsAg titers as another indicator of response; however, the value of this indicator is

currently inconsistent and, accordingly, will not be included in these guidelines.^[53]

Pretreatment assessment

Obtaining a complete history is essential before considering antiviral therapy initiation [Table 3]. Specific information, such as family history of hepatitis B and HCC and history of jaundice and previous treatment, is important. Histories of high-risk behavior, such as intravenous drug use, are important, as individuals exhibiting such behavior may transmit the infection to the community. Vaccination history, especially for hepatitis A, should be addressed, as hepatitis A infection in CHB-infected patients could be fatal. Providing certain advice to patients during history-taking, such as advice regarding diet, alcohol intake, and avoidance of herbal medicine during antiviral therapy, is important. A detailed discussion about the risks and benefits of therapy, cost of treatment, and goal of therapy should be carried out before starting any antiviral therapy. All patients with CHB infection should be carefully assessed with a complete examination to look for the signs and stigmata of chronic liver disease and hepatosplenomegaly. A complete blood workup is essential in assessing the relationship between HBV and the severity of liver disease. Complete liver function tests (LFTs), including total bilirubin, prothrombin time (PT), and albumin; complete blood counts, including platelets; and assessment of biochemical markers, including aspartate aminotransferase (AST), ALT, gamma-glutamyltransferase (GGT), and alkaline phosphatase, should be performed.^[54]

Hepatitis serology, including hepatitis e antigen and e antibody, is important for determining the immunological response to hepatitis B and for differentiating the hepatitis B wild-type from the pre-core mutant type. Hepatitis B DNA level measurement became a major cornerstone in deciding when to initiate therapy and plays an important role in patient follow-up during or following treatment. The standard tests are real-time PCR tests that should be standardized using international units (IU/ml). The same assay should be used consistently to assess the effectiveness of therapy. The HBV DNA level is very important for determining therapy indications and for assessing responses to therapy.^[55-58] Different values have been associated with significant disease based on HBeAg status. A cut-off value of 20,000 IU/ml (>100,000 copies/ml) is considered to be significant in patients who are HBeAg positive, and a value of 2000 IU/ml is considered to be significant in patients who are HBeAg negative. The presence of other viruses should be assessed in patients with hepatitis B, including HIV, hepatitis D virus/hepatitis delta virus (HDV), and HCV. Screening for other liver diseases, such as autoimmune liver disease and steatosis, should be performed, especially before starting the antiviral treatment.

Table 2: High-risk individuals who should be screened for chronic hepatitis B virus infection

High-risk individuals who should be screened for chronic HBV infection

Expatriated individuals as part of their routine pre-employment healthcare evaluation
 Household contacts of HBV carriers
 Sexual contacts of HBV carriers
 Individuals who have used recreational or intravenous drugs
 Inmates
 Patients with chronic renal failure needing dialysis
 Patients with abnormal alanine aminotransferase/aspartate aminotransferase levels
 All pregnant women
 Patients needing immunomodulation therapy
 Immunosuppressed individuals, such as those undergoing cancer chemotherapy

HBV: Hepatitis B virus

Table 3: Pretreatment assessment

History	Physical examination	Laboratory tests	Radiological tests	Liver biopsy	FibroScan
Symptom of liver disease (e.g. jaundice, itching, fever)	Signs of chronic liver disease	CBC, renal function, liver enzymes and function (AST, ALT, ALP, GGT, PT, bilirubin, albumin)	Ultrasound	In special circumstances	In special circumstances
Family history of viral hepatitis or HCC		Hepatitis B serology (HBeAg, HBe antibody, HBsAg and antibody)	CT, MRI in special circumstances		
Drug history		Hepatitis B DNA PCR, genotyping			
High-risk behavior (IV drug)		Alpha fetoprotein			
Vaccination history (especially Hep A and Hep B)		FibroScan test (in special circumstances)			
Diet, herbal medicine, alcohol					

AST: Aspartate aminotransferase, GGT: Gamma-glutamyltransferase, ALP: Alkaline phosphatase, PT: Prothrombin time, HCC: Hepatocellular carcinoma

Ultrasound of the liver is mandatory to assess the signs of portal hypertension and to exclude any focal lesions before starting antiviral therapy. Liver biopsy is very helpful in determining the degree of inflammation and the degree of fibrosis. It is also very helpful in excluding other co-existing liver diseases such as steatosis, steatohepatitis, and autoimmune liver disease. Furthermore, liver biopsy can be very helpful in patients who do not clearly meet the treatment criteria.

Hepatitis B patients, especially those older than 40 years, with mildly elevated ALT levels may have significant histological abnormalities and increased mortality from liver disease. Thus, the decision of whether to perform liver biopsy in specific patient groups should take into consideration age, the new upper-limit level of ALT, HBeAg status, and HBV DNA level. New noninvasive markers and FibroScan have become widely used for the assessment of patients with hepatitis B, but have not yet replaced the standard liver biopsy.^[59-63]

Goal of treatment

The goal of treatment is to suppress hepatitis B replication and achieve sustained suppression of the virus to decrease the effect of the virus on the liver and reduce histological activity. There is substantial evidence that suppression of the virus will decrease the progression of liver disease and development of HCC and, thus, improve the quality of life and survival.^[64] The main parameters used to assess response to treatment are HBV DNA, ALT, and disappearance of the HBeAg, with or without development of the hepatitis B e antibody. Different types of responses to antiviral therapy have been proposed, namely, biochemical, virological, and histological responses. The response to therapy can be classified as a response while on therapy or a sustained response while off therapy.

Endpoint of treatment

A high level of HBV DNA has been associated with a worse outcome.^[65-67] An effective antiviral treatment must reduce HBV DNA to the lowest level possible and ideally below the

lower limit of detection (10-15 IU/ml). Reducing HBV DNA to a lower level should result in reducing the probability of viral resistance and in biochemical remission, histological improvement, and the reduction of complications such as cirrhosis, decompensation, and HCC.^[68,69] In general, sustained HBsAg loss with or without hepatitis B surface antibody is ideally the best outcome, as this scenario has been associated with improved long-term outcomes. The other alternative and acceptable endpoint is hepatitis e antibody seroconversion in HBeAg patients, as this has also been associated with improved outcomes.

Treatment indications

All patients with hepatitis B should be monitored and followed closely. The majority of patients are chronically inactive, have normal liver enzymes, and respond poorly to currently available antivirals. In general, elevated ALT is important in initiating antiviral treatment in HBeAg-positive or -negative patients, depending on the variable cut-off levels of HBV DNA. A careful assessment of liver injury indicators, including liver enzymes and hepatitis B DNA, with and without histological assessment of the liver tissue to assess the grade of inflammation and degree of fibrosis on certain occasions, is important for deciding which group of patients will benefit from treatment. Consideration of treatment with antiviral therapy is variable depending on HBeAg status and the presence or absence of cirrhosis [Figures 1 and 2]. For example, patients with cirrhosis should be treated regardless of ALT level, HBeAg status, and HBV DNA level. Additionally, if patients have signs or symptoms of decompensation, antiviral therapy must be initiated immediately, along with early referral to a liver transplant center.^[70-72] Immunotolerant patients (normal ALT and a high HBV DNA level of more than 10^7 copies/ml) without evidence of advanced liver disease or a family history of HCC or cirrhosis should not be treated, as the risk of drug resistance is very high in this group of patients.

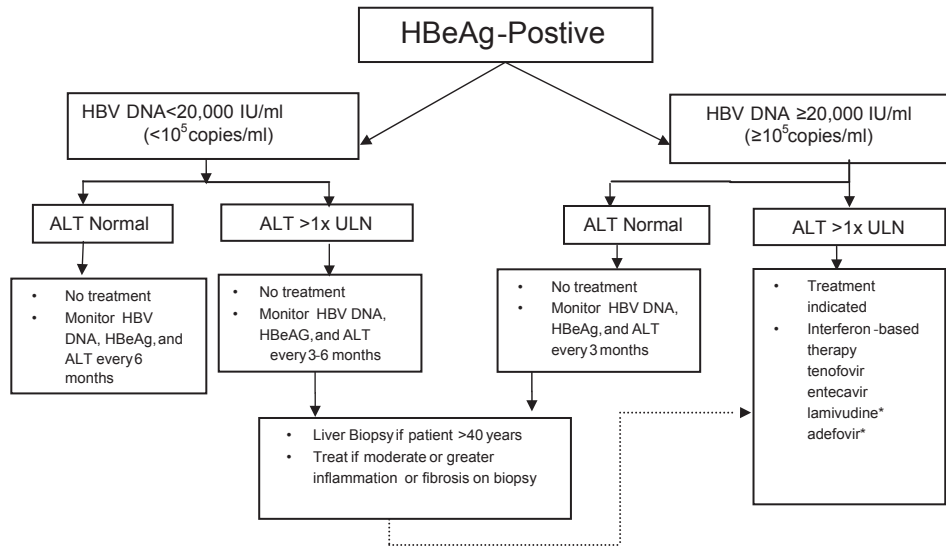


Figure 1: Algorithm for the management of hepatitis B e antigen (HBeAg)-positive patients with chronic hepatitis B infection. ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal. *Not considered as first-line therapy due to a high rate of resistance

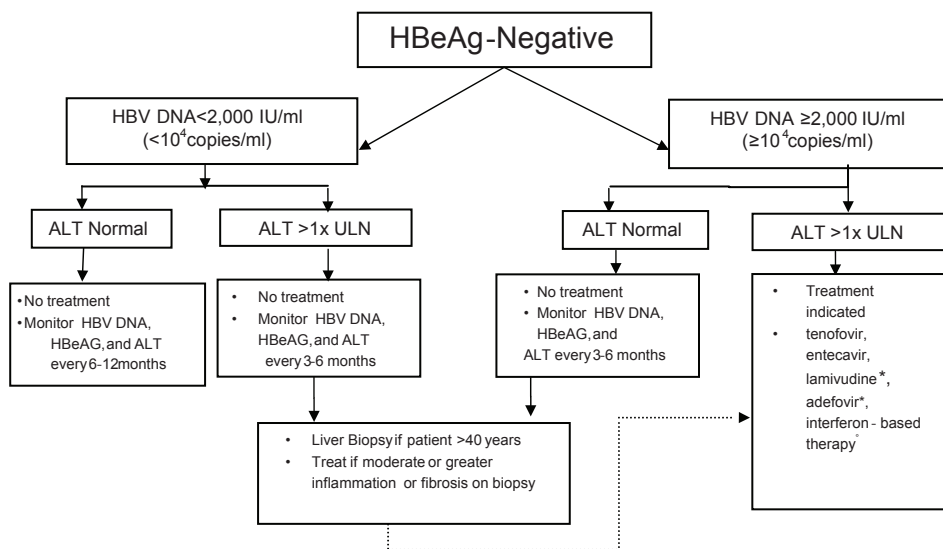


Figure 2: Algorithm for the management of hepatitis B e antigen (HBeAg)-negative patients with chronic hepatitis B infection. ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal. *Not considered as first-line therapy due to high rates of resistance; °not recommended in this subgroup of patients

Monitoring of therapy

It is very crucial to carefully monitor patients with hepatitis B after starting antiviral treatment. Periodic testing of liver enzymes, AST, ALT, HBeAg, HBV DNA, and liver function should be performed every 3 months. Patients on interferon (IFN) should have their complete blood count, electrolytes, thyroid function, and kidney function checked monthly. Patients on adefovir should also have their renal function and phosphate levels checked every 3 months.

At the end of therapy, ALT and HBV DNA should be monitored monthly for the first 3 months and then every 3-6 months to detect early relapse.

Response to therapy and treatment failure

The response to therapy can be divided into biochemical, histological, serological, and virological responses.

All clinical trials using antiviral agents address these responses individually or in combination. Different types of

responses resulting from IFN or oral antiviral therapy have been identified, namely, complete response, partial response, non-response, and virological breakthrough.

In IFN-based regimens, the quantitative HBsAg titer has been shown to predict response and could aid in deciding whether to continue or stop therapy.^[73-75]

In HBeAg-positive patients treated with nucleoside or nucleotide agents, therapy can be stopped following the development of hepatitis e antibody and negative HBV DNA based on three consecutive measurements at two occasions 6 months apart. In HBeAg-negative patients, the optimal duration of therapy is unknown, and the decision to stop therapy should be individualized based on HBV DNA response and liver disease severity.^[76-78]

The response to therapy may be variable in patients with hepatitis B treated with IFN, nucleos(t)ide, and nucleotide analogs.

Virological response to IFN therapy is defined by a decrease in HBV DNA to less than 2000 IU/ml at week 24 of treatment, whereas virological response to nucleos(t)ide analogs (NAs) is defined as undetectable HBV DNA by the real-time PCR assay within 48 weeks.^[79-81]

For patients treated with IFN, the other important parameter associated with serological response is the development of hepatitis B e antibody in patients with HBeAg positivity.^[80]

Primary non-response is the failure to obtain a decrease in HBV DNA of less than 1 log from baseline to 12 weeks of therapy following both IFN and oral antiviral therapy. Two other responses should be identified during oral antiviral therapy, namely, virological breakthrough and partial virological response. *Partial virological response* is defined as a decrease in HBV DNA of less than 1 log, but detectable DNA by real-time PCR. It is important to recognize partial response at week 24 of therapy to modify treatment according to the agents being used.

Virological breakthrough is defined as an increase in the HBV DNA level of more than 1 log compared with the lowest level reached while undergoing therapy. It is usually preceded by biochemical breakthrough with an increase in ALT. The most common causes of virological breakthrough are non-adherence and drug resistance. Primary non-response can occur with adefovir, but rarely occurs with tenofovir, entecavir, telbivudine, or lamivudine. The appropriate action in cases of adefovir virological non-response is to switch to entecavir (preferably) or tenofovir.

Identification of HBV-resistant mutations can be performed to plan rescue strategies and to aid in choosing appropriate antiviral agents.

Partial non-response can occur with all nucleoside agents. It can occur with the use of lamivudine, adefovir, or telbivudine, and can be diagnosed with the assessment of HBV DNA at week 24.^[82,83]

Switching to more potent antivirals (tenofovir or entecavir) or adding another drug that does not share cross-resistance is another strategy (add tenofovir to lamivudine in cases of telbivudine resistance or add entecavir in cases of adefovir resistance).

In cases of partial virological response to tenofovir or entecavir, many experts recommend adding another agent to prevent long-term resistance.

Virological breakthrough should be diagnosed early and is mainly related to viral resistance. Viral resistance is increased in patients with high baseline DNA levels and patients previously treated with antiviral agents. Virological breakthrough should be expected in patients with a slow decline in DNA after therapy initiation. Early suspicion of virological breakthrough and appropriate detection of genetic mutations will aid in deciding which type of rescue therapy to utilize. When drug resistance develops, the most effective measure is to add a second antiviral agent without cross-resistance to the first agent to avoid multi-drug resistance [Tables 4 and 5].^[84-86]

In cases of lamivudine resistance, adding adefovir or switching to tenofovir is recommended. In cases of adefovir resistance, it is recommended to switch to entecavir or tenofovir or add lamivudine in the absence of previous lamivudine resistance. In N236 T mutation cases, adding lamivudine, entecavir, or telbivudine is an option. In A181 T/V mutation cases, adding entecavir is the best choice. In cases of entecavir and telbivudine resistance, the best choice is to switch to or add tenofovir.^[87-89]

Recommendations

9. HBeAg-positive patients with HBV DNA levels

Table 4: Management of drug resistance

Lamivudine resistance	Adefovir resistance	Entecavir resistance
Switch to tenofovir	Switch to tenofovir	Switch to tenofovir
Add adefovir	Switch to or add entecavir	
	Add lamivudine in the absence of previous lamivudine resistance	

Table 5: Response categories

Response categories	
Biochemical (BR)	Decrease in serum ALT to within the normal range
Virological (VR)	Decrease in serum HBV DNA to undetectable levels based on PCR assays and loss of HBeAg in patients who were initially HBeAg positive
Primary non-response (not applicable in cases of interferon therapy)	Decrease in serum HBV DNA by <2 log _{10 IU} /ml after at least 24 weeks of therapy
Virological relapse	Increase in serum HBV DNA of 1 log _{10 IU} /ml after discontinuation of treatment in at least two assays performed more than 4 weeks apart
Histological (HR)	Decrease in the histological activity index by at least 2 points and no worsening of fibrosis score
Complete (CR)	Fulfillment of biochemical and virological response criteria and loss of HBeAg
Time of assessment	
On-therapy	During therapy
Maintained	Persists throughout the course of treatment
End-of-treatment	At the end of a defined course of therapy
Off-therapy	After discontinuation of therapy
Sustained (SR-6)	6 months after discontinuation of therapy
Sustained (SR-12)	12 months after discontinuation of therapy

BR: Biochemical response, VR: Virological response, HR: Histological response, CR: Complete response, SR: Sustained response, ALT: Alanine aminotransferase, HBV: Hepatitis B virus

>20,000 IU/ml and elevated ALT for 3-6 months should be considered for treatment (Grade B)

10. HBeAg-negative patients with HBV DNA levels >2000 IU/ml and elevated ALT levels for 3-6 months should be considered for treatment (Grade B)
11. Patients with significant inflammation and fibrosis based on liver biopsy or other noninvasive modalities should also be treated irrespective of the ALT level, even if the viral load is below 20,000 IU/ml in HBeAg-positive patients or below 2000 IU/ml in HBeAg-negative patients (Grade B)
12. Tenofovir and entecavir are considered first-line therapies for treatment-naïve HBV patients because they are the most potent agents available with no (tenofovir) or very low (entecavir) rates of antiviral resistance (Grade A)
13. Tenofovir is the first-line therapy for lamivudine-resistant HBV. Entecavir should not be used in this setting due to the risk of entecavir resistance development (Grade A)
14. In HBeAg-positive patients, nucleos(t)ide analog therapy should be continued until 12 months after

HBeAg seroconversion with close monitoring of HBV DNA and ALT levels following treatment withdrawal (Grade B)

15. In HBeAg-negative patients, nucleos(t)ide analog therapy should be continued indefinitely or until HBeAg loss (Grade B)
16. HBV DNA should initially be monitored every 3 months to enable early detection of antiviral resistance and every 6 months once aviremia is achieved (Grade B).

TREATMENT OF CHB

The promoter of liver disease in chronic HBV is continuous HBV replication; thus, effective sustained viral suppression is of paramount importance.^[90] However, there are limitations to the current therapy for chronic HBV that are related to the unique abilities of HBV to chronically persist in host-infected hepatocytes (due to the unique existence of cccDNA HBV) despite immune and therapeutic pressures.^[91,92] Indicators of antiviral treatment response include biochemical normalization, viral suppression, HBeAg seroconversion, and histological improvement [Table 5].^[93] To date, seven antiviral agents have been approved for the treatment of chronic HBV, and each of them will be discussed briefly [Table 6].

Antiviral agents can be categorized into two main groups: IFN-based agents and nucleos(t)ide analogs (NAs). The first type of agent is given for a definite period of time and is associated with well-recognized side effects, whereas the second type of agent is given for an indefinite duration. There are currently no reliable endpoints with which to determine the duration of NA treatment. With the long-duration use of NAs, a major concern of HBV antiviral-resistant mutations arises, which can make long-term HBV treatment challenging.^[94] Thus, chronic HBV patients with minimal disease (especially immune-tolerant HBeAg and inactive carriers) should not be treated with NAs, particularly if they are young (<30 years). Moreover, whenever possible, treatment should start with the most potent NA with the highest resistance barrier.

Interferon

IFNs are unique because they have antiviral, anti-proliferative, and immune-modulatory effects. However, their HBV suppression efficacy is limited to a small percentage after 1 year of treatment for various categories of HBV patients.^[95]

Efficacy in various disease categories

HBeAg-positive chronic HBV: This needs to be subcategorized into the following.

- Normal ALT: This is the most common pattern of chronic HBV in Saudi Arabia among children and young adults based on the prevalent vertical transmission of HBV.

Table 6: Results of the main studies for the treatment of HBeAg-negative chronic hepatitis B at 6 months following 12 months (48 weeks) of pegylated interferon alpha therapy and at 12 months (48 weeks) following nucleos (t) ide analog therapy

	PEG-IFN		Nucleoside analogs			Nucleotide analogs	
	PEG-IFN- α 2a	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir	
Dose*	180 μ g	100 mg	600 mg	0.5 mg	10 mg	245 mg	
Ref	(91)	(68, 90-92)	(68)	(92)	(70, 93)	(70)	
HBV DNA <60-80 IU/ml (%)	19	72-73	88	90	51-63	93	
ALT normalization# (%)	59	71-79	74	78	72-77	76	
HBsAg loss (%)	4	0	0	0	0	0	

*PEG-IFN-2a was administered as a percutaneous injection once weekly, and nucleos (t) ide analogs were administered as oral tablets once daily. #The definition of ALT normalization varied among different trials (e.g. decrease in ALT to <1.25 \times the upper limit of normal (ULN) in the entecavir trial and <1.3 \times the ULN in the telbivudine trial). HBV: Hepatitis B virus, PEG-IFN: Pegylated interferon

Despite high viral replication in this category of chronic HBV, no antiviral treatment is indicated. This unique situation is related to the immune-tolerant phase of the natural course of the virus; thus, IFNs are not expected to work effectively as antiviral agents due to a lack of immune recognition of the virus.^[96]

- Persistently or intermittently elevated ALT: At different stages of the immune-tolerant phase, some patients may have elevated ALT, indicating the beginning of the immune system recognition of the virus. This is usually manifested by successive and variable-intensity immune system attacks on hepatocytes harboring HBV, leading to variable degrees of elevated enzymes and histological necroinflammatory activity. Because of this immune recognition of the virus, antiviral trials with IFN were found to be effective. Meta-analyses of randomized controlled trials revealed that a higher percentage of IFN-treated patients had a virological response, compared with untreated controls. High pretreatment ALT levels (greater than twice the upper limit of normal) and low levels of serum HBV DNA are the most important predictors of IFN therapy response.^[97] The virological response is usually identified by suppression of the HBV viral load, seroconversion of HBeAg to HBe antibodies, and some degree of histological improvement. Although long-term studies indicate that IFN-induced HBeAg seroconversion is durable, it does not result in definite changes in chronic HBV disease, as only 5% of responders achieve HBsAg loss over the next 5 years. However, some studies have suggested favorable results in terms of reducing cirrhosis and HCC incidence over the following years in responding patients.
- Children: The efficacy of IFN in children is similar to that in adults. However, most children have normal ALT levels, and less than 10% of children with intermittently elevated ALT levels who received IFN had achieved HBeAg seroconversion.^[98]
- HBeAg-negative CHB: Most Saudi adults with chronic HBV reach this stage of the natural HBV course in their third or fourth decade of life, and can either be inactive carriers (if associated with a low viral load and normal ALT levels and histology) who require no treatment or progress to a pre-core mutant HBV state (due to immune pressure escape). The latter group of patients generally exhibits a broad spectrum of progressive disease and requires antiviral treatment.
- Results of four randomized controlled trials of IFN- α showed virological response ranging from 38% to 90% occurring after 1 year of treatment, compared with only 0-37% response in controls.^[99] The wide range of response rates is related to the different HBV genotypes that were found to affect the response rate; specifically, patients with genotypes A and B were found to respond better than those with genotypes C and D. Al Ashgar *et al.* conducted a study to determine the safety and efficacy of pegylated (PEG)-IFN α -2a in HBeAg-negative, genotype D-naive patients and to analyze the predictors of response. They concluded that HBeAg-negative genotype D-naive patients treated with PEG-IFN α -2a achieved sustained virological response (SVR) with rates of 23% (HBV < 400 copies/ml) and 57% (HBV < 20,000 copies/ml), which is a better response than previously reported and may be related to the absence of drug resistance in these naive patients. Pretreatment predictors of SVR were low body weight, high ALT levels, low HBV DNA levels, and low triglyceride levels.^[100] However, approximately 70% of the responders relapse when therapies are discontinued, and relapses can occur up to 5 years post-therapy. Retreatment of patients who undergo such relapses or of non-responders was found to be of no benefit, but a longer treatment duration may increase the rate of sustained response
- Decompensated or compensated cirrhosis: Approximately 20-40% of patients with HBeAg-positive CHB develop a spike in their ALT levels during IFN- α treatment. In patients with cirrhosis, the spike may precipitate hepatic decompensation. Two studies on IFN- α in patients with Child's class B or C cirrhosis reported minimal benefit. Similar outcomes have been observed in HBeAg-negative patients with established cirrhosis when they are treated with IFN- α .^[101]

Type of IFN, dose, treatment duration, and long-term outcome

- Conventional IFN- α is given as subcutaneous injections at a dose of 5 MU daily or 10 MU thrice weekly (30-35 MU weekly) for adults and approximately 6 MU/m² thrice weekly for children, with a maximum of 10 MU weekly. The recommended duration of treatment for patients with HBeAg-positive chronic HBV is 16-24 weeks. Current data suggest that patients with HBeAg-negative chronic HBV should be treated for at least 48 weeks, and one study suggested that 96 weeks of treatment may increase the rate of sustained response. The frequent injection of conventional IFN makes this treatment unpopular among patients, especially due to the frequent side effects.^[102]
- PEG-IFN- α has the advantages of a more convenient, once-weekly injection and more uniform viral suppression during the treatment weeks, with marginally fewer side effects. PEG-IFN- α 2a is administered subcutaneously at a dose of 180 mcg weekly, whereas PEG-IFN- α 2b is administered at a dose of 1.5 mcg/kg for 48 weeks in HBeAg-positive or -negative chronic HBV patients. Variable results for on-treatment viral suppression and HBeAg seroconversion have been reported in different clinical trials; however, results are comparable 24 weeks after the end of treatment, with rates ranging from 16 to 24% and from 24 to 32%, respectively.^[103] However, neither of these two viral response indicators is considered reliable. In fact, low levels of HBV DNA persist and are detectable (due to the persistence of cccDNA in hepatocytes) even following HBeAg seroconversion or viral suppression (400 copies/ml); thus, loss of HBsAg was considered to be a more reliable indicator. The long-term benefits of IFN treatment, as manifested by HBsAg loss, were variable between studies from North America and Europe (12-65%) compared with Asian studies (5-12%). This variability was attributed to the geographic variation of HBV; specifically, patients with genotypes A and B (common in North America and Western Europe) respond better to IFN compared with patients with genotypes C and D (common in Asia and the Middle East).

In HBeAg-negative patients, relapse after the end of IFN treatment is frequent, with a sustained virological response rate of only 15-30%.

Lamivudine (3TC)

Lamivudine is an NA that acts by incorporating an active triphosphate into the growing HBV DNA chains, resulting in the premature termination of synthesis.

Efficacy

The initial enthusiasm that was present regarding the value

of lamivudine in treating chronic HBV (in view of its low cost and minimal side effects) declined over time based on the high number of lamivudine-resistant HBV mutations that steadily increased with longer durations of drug exposure. The most common mutation involves substitution of methionine in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV DNA polymerase for valine or isoleucine rtM204V/I.

Genotypic resistance can be detected in 14-32% of cases after 1 year of lamivudine treatment and increases with the duration of treatment to 60-70% after 5 years of treatment. In addition to a long treatment duration, a high pretreatment viral load and high HBV residual after 1 year of treatment are also associated with higher rates of lamivudine resistance. Different HBV genotypes were found to contribute very little to the slow suppression rate or resistance.^[104,105]

Dose regimen, duration of treatment, and durability of response

The recommended dose of lamivudine for adults with normal renal function (creatinine clearance > 50 ml/min) and no HIV coinfection is 100 mg orally daily. The recommended dose for children is 3 mg/kg/d, with a maximum dose of 100 mg/d. Dose reduction is necessary for patients with renal insufficiency. The endpoint of treatment for HBeAg-positive patients is HBeAg seroconversion. Liver enzymes should be monitored every 3 months and HBV DNA levels every 6 months while on therapy, and HBeAg and anti-HBe status should be tested at the end of 1 year of treatment and every 6 months thereafter. Treatment may be discontinued in patients who have confirmed HBeAg seroconversion (HBeAg loss and HbeAb detection), followed by approximately 1 year of consolidation treatment. Treatment may be continued in patients who do not achieve seroconversion, although the benefits of continued treatment should be balanced with the risk of developing resistance. HBV viral suppression after cessation of therapy is not maintained in up to 60% of patients, and major virological and clinical relapse can occur even after 1 year following lamivudine cessation; thus, patients should be carefully monitored every 3 months. The durability of HBeAg seroconversion is not more than that of IFN, and it can be as low as 30% within the first year and may continue to decrease thereafter.^[106]

For HBeAg-negative patients, the endpoint of lamivudine treatment is not known, and post-treatment relapse (up to >90% in some trials) occurs even in patients with persistently undetectable HBV DNA throughout therapy.

With the availability of newer therapies with a lower risk of drug resistance, lamivudine is not considered a first-line therapy. Furthermore, in patients previously treated with lamivudine, a switch to an alternative, more potent

treatment with a high genetic barrier must be considered, particularly in patients who have received lamivudine for more than 2 years.

Long-term outcome

Despite maintained virological and biochemical responses in lamivudine patients who do not develop resistance, histological and long-term fibrosis resolution benefits are hampered by YMDD mutation development and viral breakthrough, potentially causing major clinical and histological relapse. Accordingly, the long-term benefits of lamivudine are questionable.^[107]

Adefovir

Adefovir is a nucleotide analog that can inhibit both reverse transcriptase and DNA polymerase, causing chain termination and preventing HBV replication. It was found in clinical studies to suppress both wild-type and YMDD mutant viruses because of its different resistance pattern than that of lamivudine.

Efficacy

The HBeAg seroconversion rate after 1 year of treatment with 10 mg adefovir was reported as 12%, and the average HBV DNA reduction was reported to be 3.5 logs. In the same study, a 30-mg dose of adefovir yielded better results; however, this dose was associated with higher nephrotoxicity (defined as an increase in serum creatinine by > 0.5 mg/dl above baseline in two consecutive readings), and the only approved dose is 10 mg. Nephrotoxicity has also been reported in 3% of patients with compensated liver disease after 4-5 years of continued adefovir therapy, and in 12% of transplant recipients and 28% of patients with decompensated cirrhosis during the first year of therapy. Most patients with decompensated cirrhosis have some degree of renal insufficiency; thus, the use of alternative treatment is more appropriate in these patients.^[108]

Some studies have reported that 20-50% of patients receiving the 10-mg dose of adefovir exhibit primary non-response, indicating that the approved dose of adefovir may be suboptimal.

In the HBeAg-negative group of patients, clinical trials have reported a higher rate of viral suppression, with a 51% undetectable level at 1 year that increases up to 71% at 2 years.

Adefovir was found to be of particularly great value in controlling lamivudine-resistant HBV that manifests as degrees of clinical and histological worsening. The “add-on policy” of adefovir on top of lamivudine was associated with a 3-4 log reduction in viral load, which was sustained throughout treatment and led to clinical improvements.

This method is particularly valuable in post-liver transplant patients who need to be on long-term lamivudine for HBV suppression. Recent data showed that switching to adefovir in patients with lamivudine-resistant HBV was associated with a higher risk of adefovir resistance, compared with adding adefovir.^[109]

Dose regimen, duration of treatment, and durability of response

The recommended dose of adefovir for adults with normal renal function (creatinine clearance > 50 ml/min) is 10 mg orally daily. The dosing interval should be increased in patients with renal insufficiency. Adefovir has not been approved for use in children.

In HBeAg-positive patients, adefovir can be stopped after approximately 1 year of consolidation treatment after HBeAg seroconversion. HBeAg seroconversion usually occurs after a long duration of adefovir therapy (more than 2 years) due to its associated low viral suppression potency. In patients who do not reach seroconversion, adefovir may be continued as long as HBV DNA remains suppressed.

For HBeAg-negative patients, continued treatment is needed, but treatment duration is not clear. More importantly, viral relapse occurs in 92% of patients after 1 year of cessation of adefovir treatment. However, the majority of patients on long-term adefovir (up to 5 years) maintained their response, but with little increase compared with the response during the first year. Thus, adefovir is considered to have low viral suppression potency and is valuable primarily in suppressing lamivudine- or entecavir-resistant HBV. For this reason, for most patients with lamivudine-resistant HBV (especially patients with decompensated cirrhosis or recurrent HBV post-liver transplant), long-term use of adefovir is required indefinitely in combination with lamivudine.^[110]

Resistance occurs at a slower rate with adefovir compared with lamivudine and can reach 29% at 5 years. However, resistance was observed more frequently in patients taking lamivudine who were shifted to adefovir monotherapy.^[111]

Entecavir

Entecavir inhibits HBV replication in three different steps; thus, it is considered more potent than lamivudine and adefovir. This statement is true in the setting of wild-type HBV infection, whereas entecavir is less potent in lamivudine-resistant HBV.

Efficacy

In HBeAg-positive patients, 48 weeks of 0.5 mg entecavir resulted in higher biochemical, virological, and histological responses compared with those associated with lamivudine. However, HBeAg seroconversion

was similar between the two groups (21% vs. 18%), although this rate continued to increase with continued treatment.^[112]

Comparable results were also noted in HBeAg-negative patients.^[113]

Of particular importance is the finding that entecavir was highly efficacious in decompensated cirrhotic patients and in patients with recurrent HBV post-liver transplant.

While patients with lamivudine-resistant HBV require higher doses of entecavir (1 mg), the ability of entecavir to suppress HBV replication is lower than its suppression ability in wild-type HBV. This finding is related to a similar resistance pattern between the two NAs and, accordingly, entecavir was found to be effective in suppressing resistance to adefovir only.^[114]

Dose regimen, duration of treatment, and durability of response

The dose of entecavir is 0.5 mg p.o. once daily, and it needs to be increased to 1 mg once daily only in cases of resistant HBV. The dose needs to be adjusted in patients with a creatinine clearance of less than 50 ml/min.

The duration of treatment is still controversial. HBeAg seroconversion is not maintained in more than 30% of patients, even after 1 year of consolidation therapy following seroconversion. Similarly, in HBeAg-negative patients, it seems that indefinite entecavir use is warranted to keep HBV under continuous suppression.^[115]

Entecavir resistance is rare in nucleoside-naive patients, reaching only 5% after 5 years of therapy. However, resistance reaches 16% within 2 years in cases of lamivudine-resistant HBV. The susceptibility of HBV to entecavir decreases with the increase in the number of resistant mutations for both lamivudine and entecavir. Accordingly, it is advisable to stop lamivudine and switch to entecavir if the decision is to treat these patients with entecavir.

Safety

Entecavir had a similar safety profile to that of other nucleosides.

Tenofovir

Tenofovir is a nucleotide reverse transcriptase inhibitor that is more potent than adefovir and is administered at a dose of 300 mg once daily. It was also found to be more potent in suppressing lamivudine-resistant HBV compared with adefovir. However, this potency is decreased 3- to 4-fold when treating adefovir-resistant HBV because of the partial cross-resistance between tenofovir and adefovir.

Tenofovir has been repeatedly reported to achieve much higher biochemical, virological, and histological responses in both HBeAg-positive and -negative patients, compared with adefovir and lamivudine.

The 7-year safety and efficacy data were presented at American Association for the Study of Liver Diseases (AASLD) 2013 as an abstract. Specifically, HBV DNA suppression to less than 400 copies/ml in 99% of HBeAg-positive and -negative patients undergoing treatment, HBeAg loss/seroconversion rates of 55%/40%, and a confirmed HBsAg loss of 12% (10% seroconversion) were reported. No resistance was detected throughout the 7-year study.

Although tenofovir has been reported to cause renal insufficiency, Fanconi syndrome, and osteomalacia, no bone disease was detected at the 3-year follow-up. The 7-year data demonstrated renal side effects in 2% of patients who were manageable, although dose adjustment was required in patients with renal impairment.

Tenofovir demonstrated safety and efficacy in patients with liver cirrhosis, and regression of cirrhosis during treatment with tenofovir was observed in 71 (74%) of 96 patients treated for 5 years.^[116] Tenofovir was also found to be safe during pregnancy (category B).

Telbivudine

Telbivudine is an NA with antiviral activity against HBV. It is more potent than lamivudine; however, it is associated with a high rate of resistance that increases with time and is not notably different from lamivudine resistance. Therefore, it has a limited role in the treatment of HBV as a monotherapy.

The approved dose of telbivudine is 600 mg once daily, although the dose must be adjusted in patients with renal insufficiency. Cases of myopathy and peripheral neuropathy have been reported.

Combination therapies

Although combination therapies have been proven to be of significant value in treating HIV and HCV based on their synergistic antiviral effects, such therapies have not been proven to be of clear benefit in treating HBV. Several combinations have been tested to date for HBV (PEG-IFN with NA or a different NA), and none of them were found to be superior to monotherapy. This limited value of combination therapy in HBV is likely related to our limited knowledge of the most effective combination.

To date, the only proven benefit of using combinations of different NAs is the reduction of resistance in cases of drugs that have high resistance patterns when used alone.

The other disadvantages of combination therapies are increased cost, increased toxicity, and potential drug interactions.

TREATMENT OF HBV IN SPECIAL POPULATIONS

HBV–HCV coinfection

Infection with HBV and HCV may occur, as the two viruses share similar risk factors and modes of transmission, especially in regions of the world where both viruses are endemic and among injection drug users. Usually, one virus (generally HCV) dominates over the other. These infections are usually associated with more severe liver disease. Combination therapy with PEG-IFN and ribavirin is equally effective in patients with HCV mono-infection and in those with HBV/HCV coinfection with similar SVR.^[117] Because HCV is the dominating virus in most cases, patients should receive treatment for HCV.^[118]

HBV may be reactivated after HCV clearance and after achieving SVR;^[119] thus, patients should be closely monitored and treated with NAs if needed.

HBV–HDV coinfection

HDV is a defective virus, as it requires HBsAg to envelop its delta antigen. Thus, the virus simultaneously coinfects patients with HBV or causes a superinfection in patients already chronically infected with HBV. Active HDV infection is defined by the presence of HDV IgM and RNA in patients with an unexplained elevation of LFTs. The primary endpoint of treatment is the suppression of HDV replication. Based on available data, PEG-IFN for 1 year appears to have long-term beneficial effects in patients, although most patients had viral relapse after stopping therapy that was usually accompanied by normalization of ALT level and a decrease in necroinflammatory activity based on liver biopsy, which were maintained over the long term.^[120,121] NA monotherapy does not appear to affect HDV replication and related disease.^[122]

HBV–HIV coinfection

The prevalence of CHB infection among HIV-infected individuals may be ten times or more than that in the background population because they share the same mode of transmission with an accelerated course to cirrhosis and HCC. The indications for therapy are the same as those in HIV-negative patients and are based on HBV DNA levels, serum ALT levels, and histological stages. Treatment regimens depend on the clinical status of both HIV and HBV, but monotherapy with an agent that is effective against both HIV and HBV should be avoided; otherwise, resistance to both HIV and HBV will rapidly occur. Because anti-retroviral regimens may include drugs with activity against HBV (lamivudine, emtricitabine, and tenofovir are NAs with activity against both HIV and HBV),^[123,124] it is reasonable to base HBV treatment decisions on whether HIV treatment is ongoing or

Table 7: Management of patients with HIV coinfection

Not on or Anticipating Antiretroviral Therapy*	Planning Antiretroviral Therapy*	Already Receiving Antiretroviral Therapy*
*Treat with antiviral therapy that is not active vs. HIV, such as pegIFN or ADV 10 mg *Although Ldt does not target HIV, it should not be used in this circumstance	*Treat with therapies that are effective against both viruses: TDF + (FTC or LAM) preferred (plus ≥1 other anti-HIV agent)	*If regimen does not include drug active against HBV, May add pegIFN or ADV *If LAM resistance, add TDF

planned. Patients who are not on highly active anti-retroviral therapy (HAART) and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as PEG-IFN- α or adefovir.^[125] Although telbivudine does not target HIV, it should not be used in this circumstance due to high resistance in the long term. Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses; lamivudine plus tenofovir or emtricitabine plus tenofovir is preferred. Patients who are already on effective HAART that does not include a drug active against HBV may be treated with PEG-IFN or adefovir (in patients with lamivudine resistance, tenofovir should be added). When HAART regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV, unless the patient has achieved HBeAg seroconversion and has completed an adequate course of consolidation treatment [Table 7].

Immunosuppressed patients

Hepatitis B inactive carriers and patients undergoing immunosuppressive or cancer chemotherapy (especially regimens that include corticosteroids or rituximab) are at a 20-50% greater risk of HBV reactivation. These individuals are usually asymptomatic, but immunosuppression may lead to hepatic decompensation and death.^[126] All patients undergoing immunosuppressive treatment or chemotherapy, even short-term courses, should be screened for HBsAg, anti-HBc, and anti-HBs (and HBV DNA if HBsAg is already positive). Prophylactic antiviral therapy is recommended for HBV-inactive carriers at the onset of cancer chemotherapy or after a finite course of immunosuppressive therapy, and if baseline HBV DNA is <2000 IU/ml, this prophylactic therapy should be continued for 6 months after the completion of chemotherapy or immunosuppressive therapy. Tenofovir or entecavir is preferred if a longer duration of treatment is anticipated, as lamivudine and telbivudine result in resistance with prolonged use. IFN should be avoided due to its bone marrow suppression effect, which may lead to a hepatitis flare.

Active HBV-immunosuppressed patients should be treated in the same manner as immunocompetent individuals.

In patients with isolated core antibodies, prophylactic antivirals should be considered, particularly in patients receiving a regimen containing high-dose steroids or rituximab.

Recommendations

17. All patients undergoing chemotherapy or treatment with other immunosuppressive therapies should be screened for HBsAg and anti-HBc antibodies (Grade A)
18. Patients testing positive for HBsAg should receive antiviral prophylaxis starting as soon as possible before treatment and continuing for at least 6 months after the last dose of immunosuppressive drug with close monitoring during and after therapy (Grade B)
19. Patients with isolated anti-HBc who are immunosuppressed should have close HBV DNA monitoring, and should be considered for antiviral therapy (Grade C).

Symptomatic acute hepatitis B

Although more than 95-99% of adults with acute HBV infection recover spontaneously and exhibit anti-HBs antibody seroconversion without antiviral therapy, a small subset of patients may develop acute liver failure and, accordingly, may benefit from NA treatment. Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. IFN is contraindicated because of the risks of worsening hepatitis and the frequent side effects.

Pregnant women

Most women with chronic HBV infection have mild disease during pregnancy; however, hepatitis may flare up after delivery, so close monitoring is warranted.

Based on the risk of teratogenicity as assessed during preclinical evaluation, the nucleos(t)ides are listed by the US Food and Drug Administration (FDA) as pregnancy category C drugs (lamivudine, adefovir, and entecavir) and category B drugs (telbivudine and tenofovir). There is a considerable amount of safety data on pregnant HIV-positive women who have received tenofovir, lamivudine, and/or emtricitabine.^[127] In these women, tenofovir is preferred because it has a better resistance profile and more extensive safety data when used during pregnancy.^[128] Pregnant women should be treated with NAs in the third trimester after organogenesis. However, if patients discover they are pregnant while on antivirals, treatment should be continued if they are on tenofovir, lamivudine, or telbivudine, especially after the first trimester and in cases of advanced fibrosis. However, if patients are on adefovir, entecavir, or PEG-IFN, treatment should be stopped and switched to tenofovir. IFN-based therapy is contraindicated in pregnancy because of its anti-proliferative

effect. Breastfeeding is generally not recommended while receiving antivirals because nucleos(t)ide analogs are present in breast milk. However, based on the existing data, tenofovir is safe because it is a pro-drug with low oral bioavailability.

Recommendations

20. HBV treatment should be considered in high-risk mothers to reduce the risk of vertical transmission in cases of high viral loads (Grade B)
21. Initiation of therapy should be in the third trimester (Grade B)
22. Patients should be monitored during pregnancy and postpartum for withdrawal flare-ups after nucleos(t)ide analog treatment is stopped (Grade A)
23. The recommended first-line treatment during pregnancy is tenofovir (FDA category B) (Grade B).

Children

The majority of children present with CHB in an immune-tolerant phase, causing benign disease. In these cases, children should not be treated. However, in patients with elevated ALT levels for >6 months and those with ensuing hepatic decompensation, conventional IFN- α , lamivudine, and adefovir, which have been shown to have a similar safety and efficacy to that found in adults, should be administered.^[129-131]

Chronic renal failure and renal transplant patients

Patients with chronic renal failure who are undergoing dialysis can be treated with NA, but the dosage needs to be adjusted based on renal function. Nucleosides (lamivudine and entecavir)^[132] are a safer choice in these patients than nucleotide (adefovir and tenofovir) analogs because they yield better renal outcomes [Table 8].

Prevention of recurrent hepatitis B after liver transplantation

Patients with CHB and end-stage liver disease who are awaiting liver transplant should be treated with NAs, regardless of ALT and HBV DNA levels, to maintain an undetectable viral load at the time of transplantation.

In addition, viral suppression rescues some patients with decompensated cirrhosis, thereby avoiding the need for a future transplant.^[133] Therapy with a potent NA with a high barrier to resistance and/or a combination of nucleos(t)ides should be administered to avoid resistance that may lead to disease flare-ups, which may lead to acute liver failure.^[134,135] After transplantation, long-term combination treatment with NAs and HBIG reduces the risk of HBV re-infection of the graft. Recent evidence suggests the safety of early cessation of HBIG post-liver transplant in the era of new potent antiviral agents.

Table 8: Dosage adjustments of nucleos (t) ide analogs according to creatinine clearance

Lamivudine		CrCL (ml/min)
100 mg daily		>50
100 mg loading dose- 50 mg daily		30-49
100 mg loading dose- 25 mg daily		15-29
35 mg loading dose- 15 mg daily		5-14
<35 mg loading dose- 10 mg daily		5
Adefovir		CrCL (ml/min)
10 mg daily		>50
10 mg every 2 nd day		20-49
10 mg every 3 rd day		10-19
-		<10, no HD
10 mg once weekly after HD		HD
Entecavir		CrCL (ml/min)
NA-naïve patients		
With lamivudine resistance +		
0.5 mg daily	1.0 mg daily	>50
0.25 mg daily or 0.5 mg every 2 nd day	0.5 mg daily	30-49
0.15 mg daily or 0.5 mg every 3 rd day	0.3 mg daily or 0.5 mg every 2 nd day	10-29
0.05 mg daily or 0.5 mg every 5 th -7 th day	0.1 mg daily or 0.5 mg every 3 rd day	<10 or HD+
Telbivudine		CrCL (ml/min)
600 mg daily		>50
400 mg daily or 600 mg every 2 nd day		30-49
200 mg daily or 600 every 3 rd day		<30, no HD
200 mg/24 hours or 600 mg/96 hours		HD+
Tenofovir TDF		CrCL (ml/min)
300 mg daily		>50
300 mg every 2 nd day		30-49
300 mg every 3 rd - 4 th day		10-29
-		<10, no HD
300 mg once weekly after HD		HD+

CrCL: Creatinine clearance

Compensated cirrhosis

Treatment of patients with cirrhosis should not be based on ALT levels, as these may be normal in advanced disease.^[136,137] The use of potent NAs with a very low risk of resistance (tenofovir or entecavir) and close monitoring of HBV DNA levels are important, and resistance must be prevented by adding a second drug without cross-resistance if HBV DNA is still detectable at week 48 of therapy. Patients with cirrhosis require long-term therapy with careful monitoring

for resistance and flare-ups, as prolonged and adequate suppression of HBV DNA may stabilize patients and delay or even obviate the need for transplantation.^[138] PEG-IFN- α 2a should be used with caution for the treatment of well-compensated cirrhosis because it places patients at increased risk of sepsis and decompensation.^[139]

Decompensated cirrhosis

Patients with decompensated cirrhosis should be treated in a specialized liver unit because many of these patients may have progressed significantly and may not benefit from treatment, thus requiring transplantation.^[140] Treatment is indicated even if the HBV DNA level is low, to prevent recurrent reactivation. Potent NAs with good resistance profiles (entecavir or tenofovir) should be used to avoid hepatic decompensation due to hepatic flare-ups when a resistant strain is selected. Although PEG-IFN- α 2a can be used for the treatment of compensated cirrhosis, albeit with some caution, it is definitely contraindicated in cases of decompensated cirrhosis.

OCCUPATIONAL ASPECTS OF HBV IN THE KSA

Provider-to-patient transmission of HBV has been well documented in the literature. The Centers for Disease Control and Prevention (CDC) reported 42 instances of provider-to-patient transmission of HBV involving 375 patients.^[141] Other studies reported 19 and 4 patients who acquired HBV from cardiothoracic and orthopedic surgeons, respectively,^[142,143] and several other reports from the UK and USA confirmed these findings.^[144,145]

HBV transmission is either parenteral or across mucus membranes, making the risk for transmission negligible during routine medical care. The risk is still very small even with invasive procedures, but it is clearly elevated compared with the risk associated with other routine medical care, necessitating a balance between patient safety and unnecessary exclusion of healthcare providers.

HBV INTERNATIONAL REGULATIONS

Regulations related to HBV-infected healthcare workers vary. The US guidelines, published in 1991, recommend that "healthcare providers who perform exposure-prone procedures and who have HBV (and HBeAg positive) should not perform exposure-prone procedures unless they have sought counsel from an Expert Review Panel and been advised that they may continue to perform these procedures after informing their patients."^[146] In 2010, the Society for Healthcare Epidemiology of America (SHEA) used the HBV DNA level to stratify HBV-infected healthcare providers. According to this stratification, there are no restrictions imposed on healthcare providers if HBV is $<10^4$ genome equivalents (GE)/ml, whereas

providers with HBV >10⁴ GE/ml are allowed to perform category 1 and 2 procedures but not category 3 procedures.^[147]

In the UK, HBV-infected providers who are HBeAg positive may not perform exposure-prone invasive procedures; HBV-infected providers who are HBeAg negative but have HBV DNA levels greater than 10³ GE/ml may not conduct exposure-prone invasive procedures; and HBV-infected providers who are HBeAg negative and have HBV DNA levels less than 10³ GE/ml may conduct exposure-prone invasive procedures but must be retested at least every 12 months to ensure that the level of viremia remains below 10³ GE/ml.^[148] More recently, authorities in the UK have allowed healthcare providers to perform such procedures if their viral loads decrease to below 10³ GE/ml following treatment.^[149] In 2012, the CDC issued an update with a cut-off point of 1000 IU/ml (5000 GE/ml), regardless of HBeAg status.^[150]

A European consortium used a cut-off level of 10⁴ GE/ml,^[151] whereas scientists from the Netherlands used a cut-off level of 10⁵ GE/ml.^[152]

In a comprehensive analysis, van der Eijk *et al.*^[153] listed the challenges of standardizing recommendations for practice restrictions for HBV-infected providers, emphasizing that guidelines have to strike a balance between unnecessarily excluding providers and patient safety.

THE CURRENT NATIONAL REGULATION

In March 2006, the Ministry of Health Preventive Medicine Department within Saudi Arabia issued an updated regulation for HBV consisting of the following three main categories:

1. Visitors, tourists, and Hajj and Omra visitors are not required to be tested for HBV or HCV before obtaining a visa or after landing, except if they apply to change their visa status to a resident visa
2. New resident visa for work:
 - New expatriates, regardless of job title, are required to be tested for HBsAg in their country of origin, with repeated testing required after arriving in the Kingdom and before beginning work. Only HBsAg-negative individuals are allowed to work, with the exception of university professors in rare cases
 - Indeterminate results should be confirmed by PCR
 - Individuals who test negative should receive the vaccines.
3. Individuals currently working in Saudi Arabia are further divided into healthcare workers and non-healthcare workers.

Healthcare workers

- All healthcare workers who were not previously tested for HBsAg should be tested

- HBsAg testing should be repeated every 2 years upon residency visa renewal for non-Saudi physicians and healthcare workers in surgery department, operating rooms, Ob/GYN clinic, intensive care unit, emergency department, neonatal intensive care unit, burn unit, dental clinic, HD unit, phlebotomy laboratory, or wound management clinics
- Physicians and healthcare workers performing exposure-prone procedures, who test positive for HBsAg, should undergo HBV PCR. If the titer is >10⁵ copies/ml, they should stop performing these procedures, but can work in other departments
- Individuals who are HBsAg positive with HBV DNA < 10⁵ copies/ml in two consecutive tests can continue performing their exposure-prone procedures due to a lack of transmission risk, but annual testing is required.
- Physicians and healthcare workers not performing exposure-prone procedures and who have HBsAg with HBV DNA <10⁵ copies/ml can continue working, as they do not pose a risk to patients
- Physicians and healthcare workers not performing exposure-prone procedures and who have HBsAg with HBV DNA >10⁵ copies/ml can continue working, as they do not pose a risk to patients, but they must strictly follow the universal precautions for infectious control.

Non-healthcare workers

- HBsAg testing should be repeated every 2 years upon residency visa renewal for housemaids, drivers, babysitters, and barbers; those who test positive will not be allowed to work in these jobs, and their residency visa will not be renewed
- Individuals with jobs not listed above and who test positive can continue to work.^[154]

We have chosen a cut-off value of 1000 IU/ml to separate providers who can and cannot perform invasive procedures. This level was chosen in the absence of data associating a given level with either a clear risk for transmission or, more importantly, an absence of risk; nevertheless, this is the lowest HBV DNA level at which transmission from a healthcare worker to a patient occurred.

Recommendations

24. All providers should follow the standard precautions (Grade A)
25. HBV-infected healthcare providers should not be prohibited from participating in patient care activities solely on the basis of their HBV infection status (Grade C)
26. Providers infected with HBV who have circulating viral burdens ≥ 1000 IU/ml should refrain from performing exposure-prone invasive procedures (Grade D)
27. Healthcare providers who have circulating HBV burdens

of less than 1000 IU/ml should be allowed to perform invasive procedures with monitoring of the viral load every 6 months (Grade D).

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