Hepatitis B virus is a major health problem, and the main cause of liver-related morbidity and mortality in Turkey. The morbidity and mortality are linked to the persistence of the hepatitis B virus replication and evolution to end-stage liver disease. Viral suppression with antiviral therapy has achieved clinical benefits, such as preventing the disease progression and reducing the hepatic decompensation in chronic hepatitis B patients. The current optimal management of hepatitis B virus infection is summarized here in a brief report based on European Association for the Study of the Liver 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. The prevalence of HBV infection has been decreasing in several endemic countries as a result of universal vaccination programs, improvements in the socioeconomic status, and effective antiviral treatment approaches. However, the migrations of populations from outside Europe has been changing the incidence and prevalence of HBV infection in several low endemic rate countries (1,2).

In 2012, the European Association for the Study of the Liver (EASL) published Clinical Practice Guidelines (CPG) on the management of HBV infection, which were recently modified. The aim of the present paper was to summarize the EASL 2017 CPGs updating the recommendations for the optimal management of an HBV infection. The phases of a chronic HBV infection can be classified into five phases based on biochemical, serological, and histological evaluations (Table 1); • Hepatitis B e-antigen (HBeAg)-positive chronic infection, • HBeAg-positive chronic hepatitis, • HBeAg-negative chronic infection, • HBeAg-negative chronic hepatitis and • HBsAg-negative phase.

Natural Course of Disease
Chronic HBV infection is a dynamic process and not all patients with chronic HBV infection have chronic hepatitis B (CHB). The natural course of a chronic HBV infection can be classified into five phases based on biochemical, serological, and histological evaluations (Table 1);

1. **Hepatitis B e-antigen (HBeAg)-positive chronic infection,**
2. **HBeAg-positive chronic hepatitis,**
3. **HBeAg-negative chronic infection,**
4. **HBeAg-negative chronic hepatitis and**
5. **HBsAg-negative phase,**

The phases of a chronic HBV infection are not necessary sequential; therefore, serial monitoring of the biochemical and serological tests is required. Some individuals fall into an indeterminate area, and each treatment needs to be individualized (2).
The risk of progression to cirrhosis and HCC is variable. The 5-year cumulative incidence of cirrhosis ranges from 8% to 20% of untreated CHB patients, and the annual risk of HCC in cirrhotic patients ranges from 2% to 5% (1,2,7).

A careful assessment of an individual with a chronic HBV infection is necessary. The initial evaluation should include a complete history, a physical examination, biochemical and serological evaluations and an assessment of the liver disease activity and severity. All first-degree relatives should be advised to be tested for the HBV serological markers. Any co-infections with other hepatic viruses and co-morbidities (other causes of chronic liver disease) should be identified. In addition, testing for antibodies (anti-HAV IgM and IgG) against the hepatitis A virus should be performed. An HAV vaccination is recommended for those patients that are anti-HAV negative.

**Aims of Antiviral Therapy**

Hepatitis B virus -related morbidity and mortality are linked to the persistence of viral replication. The purposes of antiviral treatments for those patients with chronic HBV infection include;

- Suppressing HBV replication to prevent disease progression and HCC development and improve survival and the quality of life,
- Preventing mother to child transmission in HBV-infected pregnant women with high viremia,
- Preventing HBV reactivation in HBV-infected patients or HBV-experienced patients requiring chemo/immunosuppressive therapy and
- Preventing and treating HBV-associated extrahepatic manifestations such as vasculitis, polyarteritis nodosa, glomerulonephritis, skin manifestations, and peripheral neuropathy.

Since the level of HBV replication represents the strongest predictive marker associated with HBV-induced disease progression and long-term outcomes, the inhibition of HBV replication represents the cornerstone endpoint of all current therapeutic approaches (1,2,8). The suppression of the HBV viral load is generally associated with the normalization of the serum aminotransferases levels. The ultimate goal of effective antiviral treatment is HBsAg loss and seroconversion to anti-HBs, which is described as a functional cure. HBsAg seroclearance can be achieved after interferon (IFN)-based antiviral treatment, but it is rarely achieved with the current oral antiviral agents.

**Indications for Antiviral Therapy**

The indications for treatment are basically the same for both HBeAg-positive and -negative CHB patients. They are based mainly on the combination of following criteria:

- Serum HBV DNA levels,
- Serum alanine aminotransferase (ALT) levels and
- Severity of liver disease

A liver biopsy may provide additional useful information, but it does not usually change the treatment decision. The patient’s age, health status, risk of HBV transmission, family history of cirrhosis or HCC, and extrahepatic manifestations may also be considered in the choice of antiviral treatment. Those patients with chronic HBV infection who are not candidates for treatment should be monitored with periodic assessments of biochemical (ALT), serological (HBV DNA), and liver fibrosis severity assessments.

**Recommendations (Reference 2)**

- All CHB patients, as defined by an HBV DNA >2,000 IU/mL, serum ALT > upper limit of normal (ULN), and/or at least moderate liver necroinflammation or fibrosis, should be treated (evidence level I, grade of recommendation 1).
- All cirrhotic patients with any detectable serum HBV DNA level need treatment (evidence level I, grade of recommendation 1).
- Patients with HBV DNA >20,000 IU/mL and ALT >2xULN should start treatment (evidence level II-2, grade of recommendation 1).
- Chronic HBV infected patients with a family history of HCC or cirrhosis and extrahepatic manifestations can be treated (evidence level III, grade of recommendation 2).
Treatment Approaches
Currently, two different types of antiviral agents can be used in the treatment of CHB: pegylated IFN alpha (PegIFNa) and nucleoside (lamivudine [LMV], telbivudine, emtricitabine and entecavir [ETV]) and nucleotide analogs (adefovir dipivoxil [ADV], tenofovir disoproxil fumarate [TDF] and tenofovir alafenamide [TAF]). The main advantage of treating patients with potent nucleoside or nucleotide analogs (NAs) (ETV, TDF, and TAF) is the predictable with long-term antiviral efficacy leading to HBV suppression in the vast majority of CHB patients (1,2,9).

The PegIFNa-based treatment approach is used to induce long-term immunological control with a finite duration of treatment. PegIFNa can be considered as an initial treatment approach for HBeAg-positive or negative CHB patients with mild to moderate disease. However, the high variability of the treatment response and its unfavourable safety profile are the main disadvantages of such therapy. Baseline treatment predictors, including the low serum HBV DNA level, high serum ALT levels (>2-5 times ULN), the presence of HBeAg, HBV genotype (A and B), and stage of disease (high activity scores on liver biopsy), and on-treatment predictors (i.e., declining of the HBsAg and HBV DNA levels at 12 weeks of treatment) can be helpful indicators to predict the treatment response (1,2,9).

The combination therapy with two NAs with high barrier to resistance is not recommended in the treatment of CHB. In addition, a NA and PegIFNa combination treatment is currently not recommended.

Treatment Responses
Treatment responses can be divided into virological, biochemical, serological and histological responses. The definitions of a virological response varies according to the timing and type of therapy. It is generally defined as an undetectable serum HBV DNA using a sensitive polymerase chain reaction (PCR, <10 IU/mL) assay during NA therapy, while it is defined as serum HBV DNA levels <2,000 IU/mL at 6 months and at the end of the PegIFNa therapy. A biochemical response is defined as the normalization of the serum ALT levels based on the traditional ULN (approximately 40 IU/L). A serological response is defined as an HBeAg loss and HBeAg seroconversion to anti-HBe in HBeAg-positive patients, and an HBsAg loss and HBsAg seroconversion to anti-HBs in all CHB patients. Finally, a histological response is defined as a decrease in the necroinflammatory activity by ≥ 2 points without a worsening in the fibrosis, when compared to the baseline liver biopsy findings.

NA Treatment for CHB Patients
ETV, TDF, and TAF are currently recommended as monotherapy in the treatment of CHB infection. These drugs are potent inhibitors of HBV polymerase and reverse transcriptase with minimal or no resistance. They have led to an undetectable serum HBV DNA in the vast majority of CHB patients within months or a few years of therapy. The efficacy and long-term safety profiles of all NAs are identical, and they can be given in both non-cirrhotic and compensated cirrhotic CHB patients (1,2).

Long-term ETV or TDF therapy has been demonstrated to prevent disease progression, and can also result in a significant histological improvement (1,2,10). Moreover, the complications of cirrhosis can improve or even disappear and the necessity of a LT is dramatically decreasing (1,2,10). Unfortunately, HCC may still develop. Previous studies have shown that long-term ETV or TDF monotherapy appears to favorably affect the incidence of HCC (8,10,11), especially in those patients, who have received more than 5 years of antiviral therapy (11). Since HCC seems to be the only predictive factor affecting long-term survival in-treated patients, the main clinical challenge is to identify the patients at risk of HCC who require close surveillance. The PAGE-B score (low, medium, and high risk of HCC) can accurately predict the risk of HCC in Caucasian CHB patients treated with NAs (12). A long-term, effective NAs treatment can also improve the patient’s overall survival (1,2,9,10).

All CHB patients treated with a NAs should undergo periodical monitoring. At the baseline, a complete blood count, serum liver injury and function tests, renal function tests (serum creatinine, phosphate levels and creatinine clearance [eGFR]), and an HBV DNA levels by PCR assay should be performed. The baseline renal risk includes an eGFR < 60 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerular disease, concomitant nephrotoxic drugs, solid organ transplantation, and decompensated cirrhosis, which should also be assessed for all patients.

During treatment, liver injury tests should be performed every 3-4 months during the first year of treatment, and every six months thereafter. The serum HBV DNA should be assayed every 3-4 months in the first year and every 6-12 months thereafter. The HBsAg should be checked at 12-month intervals if the HBV DNA is negative. The anti-HBs should be tested when HBsAg is lost.

Nucleotide analogs treatment can be used safely in all CHB patients, and minimal renal function declines have been reported during long-term ETV and TDF therapy. The nephrotoxic potential of TDF is higher than that of ETV; therefore, renal function tests (eGFR and serum phosphate levels) should be monitored in CHB patients at high renal risk receiving any NA therapy every 3-4 months during the first year and every 6 months thereafter. Previous studies have demonstrated that TAF is superior to TDF in its effects on several biomarkers of renal function and bone turnover (1,13).

NA Discontinuation
Nucleotide analog therapy does not usually achieve HBV eradication. The ultimate goal of effective NA therapy is an HBsAg loss and seroconversion to anti-HBs. The loss of HBsAg may occur in a minority of CHB patients; it is approximately 10-12% after 5-8
years of NA therapy in HBeAg-positive patients, but it is less than 2% in HBeAg-negative patients (1,14). Moreover, long-term antiviral treatments are given in the majority of CHB patients. Nucleotide analogs can be discontinued in HBeAg-positive CHB patients if they achieve HBeAg seroconversion to anti-HBe and reach HBV DNA undetectability and have completed at least 12 months of consolidation therapy. Unfortunately, virological remission will be maintained in only 50% of those patients during the 3 years after NA cessation (9). Long-term NA therapy is usually given in HBeAg-negative patients. However, NA therapy should be discontinued if such patients achieve an HBsAg loss with or without anti-HBs seroconversion. The duration of on-NA therapy HBV DNA undetectability is an important factor for predicting the probability of off-therapy virological remission (15). Unfortunately, the optimal duration of on-NAs remission before discontinuation remains unclear. NAs may be discontinued only in those patients who can be followed very closely with biochemical and serological tests. The retreatment criteria may be also applied based on the treatment indications for naïve CHB patients.

Treatment discontinuation is currently discouraged in patients with cirrhosis.

Management of Patients with NA Failure

The combination of NAs with low barriers to resistance include LAM or TBV with ADV may lead to inappropriate HBV suppression and the emergence of multidrug resistant strains. Currently, these drugs are not any more recommended for CHB treatment as monotherapy. Treatment failure can be defined as a primary non-response, partial virological response, and virological breakthrough. Since ETV and TDF are fully reimbursed for CHB patients in Turkey, managing NA failures is now not a crucial issue anymore.

Poor compliance is the main cause of NA treatment failure. A primary non-response is defined as a less than 1 log_{10} IU/mL decrease in the serum HBV DNA level at 3 months of therapy when compared to the baseline. However, a primary non-response to ETV or TDF is rarely seen. A partial virological response is defined as a decrease in the HBV DNA of more than 1 log_{10} IU/mL, but detectable HBV DNA at 12 months of therapy. A partial virological response may be encountered with any of the available antiviral agents. If the patients receive an NA with a low barrier to resistance, it is recommended to change it to a more potent drug without cross-resistance. A partial virological response is usually seen under ETV or TDF treatment, which is associated with a very high pretreatment viral load. The HBV DNA levels at week 48 and the kinetics of the HBV DNA decline are important factors in the treatment decision. The same NA should be continued in patients with declining HBV DNA levels. However, a switch to the other drug or a combination of ETV and TDF can be recommended in patients with advanced liver disease. A virological breakthrough is defined as an increase in the HBV DNA level of more than 1 log_{10} IU/mL when compared to the nadir HBV DNA level on therapy. A virological breakthrough is mainly related to the development of HBV drug resistance. Preventing the emergence of drug resistance is based on the use of NAs with high barriers to resistance, including ETV and TDF. When a virological breakthrough is identified, it should be confirmed one month later to prevent subsequent hepatic flare-ups and disease progression (1,2,9).

The risk of antiviral drug resistance is associated with high baseline serum HBV DNA levels, a slow decline in the serum HBV DNA levels, and previous suboptimal treatment. During the emergence of resistance, an appropriate rescue therapy should be started with a potent NA agent that does not share cross-resistance. The ETV and TDF combination therapy appears to be a safe option as a rescue therapy.

Management of Decompensated Cirrhotic Patients

Decompensated cirrhotic patients should be treated immediately with ETV or TDF and referred for LT. ETV and TDF have been shown to be effective, safe, and tolerable in such patients (1,2,9,16-18). Those patients with an earlier treatment initiation had better clinical outcomes than those with delayed treatment. Treatment with ETV or TDF treatment in decompensated cirrhotic patients has achieved clinical benefits as a result of the prevention of disease progression, reduction in hepatic decompensation and HCC development, and avoidance of LT. ETV or TDF modifies the natural course of the disease and increases survival (1,2,9,16-18).

Both drugs must be adjusted to the patient’s renal function. Lactic acidosis may be develop in the decompensated patients, especially in patients with a Model for End-Stage Liver Disease (MELD) score > 22 and impaired renal function (1,2). Lifelong antiviral therapy is recommended in such patients. Since HCC may still develop, although at a lower rate, HCC surveillance is mandatory, even under effective therapy.

The main conclusions of the EASL 2017 CPGs on the management of HBV infection are as follows;

- HBV infection is still a major cause of liver-related morbidity and mortality in endemic areas.
- A chronic HBV infection is a dynamic process, and not all patients with chronic HBV infection have CHB.
- CHB patients are at an increased risk for disease progression to end-stage liver disease and its complications, depending on the host, viral and environmental factors.
- Antiviral therapy against an HBV infection prevents disease progression and, consequently, HCC development, while improving survival and the quality of life.
- Induction of the long-term suppression of the HBV DNA levels represents the main endpoint of all current treatment strategies.
- The optimal endpoint is an HBsAg loss and, ultimately, HBsAg seroconversion to anti-HBs.
The main indications to start antiviral treatment are a high serum HBV DNA level with a more than 2,000 IU/mL, an elevated and/or normal serum ALT level, and/or at least moderate liver necroinflammation or presence of the fibrosis.

All cirrhotic patients with any detectable level of serum HBV DNA level need antiviral treatment.

ETV, TDF, or TAF with a high barrier to resistance are recommended in the treatment of CHB.

PegIFNa treatment can also be considered in mild to moderate CHB infection, especially in young, HBeAg-infected patients.

Combination therapies are not currently recommended.

All treated patients should be monitored for antiviral therapy adherence and response.

All CHB patients under effective long-term NA therapy should be monitored for the risk of disease progression and HCC. HCC surveillance is mandatory for all cirrhotic patients.

Patients with chronic HBV infection who do not fulfill any treatment indications should be followed regularly.

Future treatment strategies are coming.

REFERENCES
2. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67: 370-98. [CrossRef]