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Diagnosis, management and treatment of hepatitis B virus infection: Turkey 2017 Clinical Practice Guidelines

Panel Chairmen: Fehmi Tabak, Cihan Yurdaydın

Coordinators: Sabahattin Kaymakoğlu and Fehmi Tabak

Panel Members (alphabetically): Mesut Akarsu, Esra G. Akıncı, Hikmet Akkız, Canan Alkım, Ayhan H. Çekin, Nefise Ö. Çuvalcı, Kadir Demir, Bülent Değertekin, İlyas Dökmetaş, Galip Ersöz, Kenan Hizel, Fatma Ö. Kandemir, Yusuf Önlen, Abdullah Sonsuz, Ebubekir Şenateş, Selma Tosun, Nurdan Tözün, Ramazan Idilman, and Viral Hepatitis Guidelines Study Group

Turkish Association for the Study of the Liver, Istanbul, Turkey
Viral Hepatitis Society, Ankara, Turkey

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SUMMARY

Dear Colleagues,

Guidelines provide guidance to physicians in the diagnosis and management of diseases as well as to official authorities in the process of approval and reimbursement. The Turkish Association for the Study of the Liver (TASL) and Viral Hepatitis Society (VHS) have collaborated in the preparation of the first "Viral Hepatitis B, D and C: Diagnosis and Treatment Guideline" in 2015. Viral hepatitis are the most common risk factors posing a threat to liver health in our country while being one of the most dynamic topics in our scientific discipline. Therefore, there is definitely a need to update the guidelines based on the emerging information about diagnosis and treatment.

In December 2016, the members of two societies organized for the update of "Turkish Viral Hepatitis Diagnosis and Treatment Guideline 2017" all viral hepatitis experts came together to cover the topics of diagnosis-patient evaluation-treatment-follow-up during and after treatment in instances of viral hepatitis B, C and D and to identify the principles of the guideline in unison. To this end, three different study groups were formed with joint participation of the members. Group I: Chronic Hepatitis B and D; Group II: Chronic Hepatitis C-Pretreatment evaluation (screening, diagnosis of acute-chronic hepatitis C, treatment indications, preparation for treatment), Follow-up of patients during and after treatment; Group III: Chronic Hepatitis C-Treatment. They first came to a consensus among themselves; they then finalized the principles of the guideline with the approval of all the participants.

Under these principles, each group prepared a text that they had consensus on and presented this for the approval of all groups. The texts were finalized together with the feedback provided and the condition of 70% consensus was sought. Our guidelines in such an effort was the internationally accepted guidelines like European Association for the Study of Liver (EASL), American Association for the Study of Liver Disease (AASLD) and Asian Pacific Association for the Study of Liver (APASL). Drugs approved by Food and Drug Administration (FDA), European Medicines Agency (EMA), Japan, Canada and Australia were recommended as treatment regimens. This guideline is supported by the memberships of the TASL and VHS and not by pharmaceutical companies.

We hope that "Turkey Viral Hepatitis Diagnosis and Treatment Guideline 2017" will be a useful tool for all of us.

With my sincere regards,

Sabahattin Kaymakoğlu
President of TASL

Fehmi Tabak
President of VHSD

Address for Correspondence: Ramazan Idilman E-mail: idilman@medicine.ankara.edu.tr
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I- TESTING FOR HEPATITIS B VIRUS INFECTION

Hepatitis B virus (HBV) remains to be an important cause of liver-related morbidity and mortality in Turkey. Turkey is a moderately endemic country for chronic hepatitis B (CHB) infection. Hepatitis B surface antigen (HBsAg) positivity in the Turkish population was 4% based on the result of an epidemiological study. HBV infection is present in approximately 50% of the patients with hepatocellular carcinoma (HCC), most of whom have cirrhosis.

The following groups are considered as high-risk groups and therefore they should be given priority for screening:

- First degree relatives of HBsAg-positive individuals
- Individuals living in the same household with a HBsAg-positive person
- Drug-injection and substance users
- People with percutaneous/parenteral exposures in an unregulated setting (tattoos and piercings, group circumcisions, manicure or pedicure performed under unhygienic conditions, being blood brothers, cutting of the forehead, sublingual region, and the neck, cupping)
- People, who has lived or was born in the high HBV endemic areas of the country
- People having sexual contact with HBsAg-positive person
- People with multiple sexual partners and/or history of sexually transmitted diseases
- Men who have unprotected sex with men
- Sex workers
- People living or working at the correctional institutions
- Individuals with persistently high serum aminotransferases levels
- Patients infected with hepatitis C virus (HCV) or Human Immunodeficiency Virus (HIV)
- Hemodialysis patients
- All pregnant women
- People who have received blood and blood product transfusion
- People with a history of risky and/or surgical dental procedures (such as a root canal therapy)
- Occupational groups (physicians, nurses, healthcare, emergency medical, hairdressers, beauty salon workers, etc.)
- Members of professions who have frequent exposure to blood and blood products
- People living in nursing homes and care centers and people with cognitive disabilities and their caregivers
- Donors and recipients of blood and plasma products, sperm, organ and tissues
- Patients who will receive chemo/immunosuppressive therapy
- Patients who are candidate for surgical procedures (1,2)

II- TESTING AND MANAGEMENT OF THE HIGH-RISK PATIENTS

Patients with high-risk should initially be screened for HBsAg, antibody against HBsAg (anti-HBs) and antibody against hepatitis B core antigen (anti-HBc) immunoglobulin G (IgG). If HBsAg and/or anti-HBc IgG is found positive, the patient should be referred to a Gastroenterologist or Infectious Diseases specialists for further counseling.

III- MANAGEMENT OF THE HBsAg-POSITIVE INDIVIDUALS

- Detailed patient history and physical examination.
- Family history of liver disease and HCC should be investigated.
- Biochemical tests: Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total and direct bilirubin and albumin levels should be performed to identify the presence and severity of liver disease. Serum alpha fetoprotein (AFP) level should be recommended for diagnosis and surveillance of HCC.
- Hematological tests: Complete blood count (CBC), international normalized ratio (INR)
- Serum anti-HBc Immunoglobulin M (IgM), anti-HBc IgG, hepatitis B e antigen (HBeAg), antibody against HBeAg (Anti-HBe) antibodies should be recommended to distinguish acute or chronic HBV infection. Quantitative serum HBV DNA level should be recommended to determine the HBV replication status.
- Testing for antibodies against hepatitis delta virus (HDV), HCV and HIV should be performed to rule out any co-infection with other hepatotropic viruses.
- Testing for antibodies against hepatitis A virus (HAV) should be recommended to determine the immunity against HAV.
- Upper abdominal sonography should be performed to assess liver abnormality and spleen size and the presence of portal hypertension (1-3).

The diagnosis, management and treatment decisions of CHB is based on biochemical, virological and histological findings.

1. Biochemical tests
   Serum AST, ALT, GGT, ALP, bilirubin, albumin, CBC and INR
2. Markers for replication
   Serum HBeAg, Anti-HBe and sensitive HBV DNA level (IU/ml)
   - Co-infections (HDV, HCV and HIV) and co-morbid medical conditions (diabetes, non-alcoholic fatty liver disease, alcohol abuse) should be evaluated. Anti-HAV IgG should be performed. HAV vaccination is recommended for those patients that are anti-HAV negative.
3. Liver biopsy should be performed for the assessment of the severity of hepatic necroinflammation and fibrosis.
4. Non-invasive methods to estimate the degree of liver fibrosis
   - Transient elastography (TE) methods are magnetic resonance (MR) elastography and fibroscan.
5. Direct and indirect serum markers such as fibrotest, aminotransferase to platelet ratio index (APRI) and fibrosis 4 (FIB-4)

The most efficient approach for identification of the degree of fibrosis is to combine direct serum markers and TE.

6. Radiological interventions
   Abdominal sonography
   Transient elastography
   MR Elastography

IV- TREATMENT OF ACUTE HEPATITIS B INFECTION

- Most of the cases with acute HBV infection have an anicteric and/or asymptomatic course and thus cannot be diagnosed during the acute phase.
- Majority of the patients with acute HBV infection can be followed without being hospitalized (4). Supportive treatment is recommended in symptomatic cases.
- Dietary restriction is not necessary (4). Alcohol consumption and hepatotoxic medications should be restricted until there is clinical and biochemical improvements.
- The use of nucleos(t)ide analogues (NAs) should be decided on an individual basis. NAs treatment should be recommended in patients with a clinical presentation of severe acute hepatitis (persistent symptoms, marked long-term jaundice [4 weeks], INR ≥1.5 and/or prothrombin time (PT) time 4 seconds longer than the upper threshold), or signs of acute liver failure (5), and in patients without HBV DNA suppression even having the peak of serum ALT and AST levels (expert opinion) (5).
- A differential diagnosis should be determined differentiate the patients with acute HBV infection and patients with an exacerbation of CHB. Acute exacerbation can happen following immunosuppressive treatment during the course of chronic HBV infection (especially in patients with HBeAg-negative chronic HBV).

V- TREATMENT OF FULMINANT HEPATITIS B

- HBV-induced acute liver failure (ALF) is an uncommon condition in which rapid deterioration of liver function results in jaundice and coagulopathy, and alteration in the mental status (encephalopathy) of a previously healthy individual.
- ALF patients should be transferred to liver transplantation (LT) center and followed in an intensive care unit. The mortality rate of ALF is high if LT cannot be performed (6-8).

VI- MANAGEMENT OF INACTIVE HBsAg CARRIERS (HBeAg-negative chronic HBV infection)

A. Definition of Inactive HBsAg Carriers

1. HBsAg positive >6 months
2. HBeAg negative, anti-HBe positive
3. Serum HBV DNA level <2000 IU/mL
4. Persistently normal serum ALT/AST levels
5. A negative anti-HDV antibody
6. Absence of hepatic fibrosis by non-invasive techniques and/or the presence of minimal liver injury by liver biopsy (a low histological activity index [HAI] < 4 and no fibrosis or a low fibrosis [F1]).

B. Follow-Up and Management of Inactive HBsAg Carriers

- Unfortunately, we do not have large scaled population-based studies investigating the normal serum ALT levels of the Turkish population. Therefore, local laboratory cut-offs should be used to define the range of serum ALT levels.
- Serum ALT level should be monitored within 3-month intervals for the first year and for every 6-12 months intervals for the following years. Serum HBV DNA levels should be assessed at 6-12 months intervals (1,3,9-12).
- During serum ALT levels flares, serum HBV DNA should be assessed and the presence of other causes of liver diseases should be investigated (1,9,10).
- In high-risk individuals (a family history of cirrhosis or HCC, living in an endemic region, male gender and older age [>40 years]), serum AFP level and abdominal sonography should be performed every 6 months, whereas individuals with low-risk yearly evaluation is recommended.

VII- TREATMENT OF CHB INFECTION IN DIFFERENT PHASES OF DISEASE

Chronic HBV infection is a dynamic process and not all patients with chronic HBV infection have CHB. The natural course of a chronic HBV infection can be classified into five phases based on biochemical, serological, and histological evaluations. The phases of a chronic HBV infection are not sequential, and some patients fall into an indeterminate area, and each treatment needs to be individualized.

A. Patients Who Should Be Treated Immediately

- Patients with life-threatening liver diseases
  - Acute on chronic liver failure (ACLF)
  - Decompensated cirrhosis
- Patients who have a risk of develop liver failure/HCC in the short-term interval
  - Compensated cirrhosis with detectable serum HBV DNA level
- HBsAg and/or anti-HBc IgG-positive patients who will receive immunosuppressive therapies (*high-risk immunosuppressive therapy)
- Liver transplant recipients
- Patients, who have a risk for progressive liver disease

B. Antiviral Treatment Should Be Decided in an Individual Based

- Patients with immune reactive phase, who do not have advanced fibrosis or cirrhosis
- Patients with a persistently serum HBV DNA levels >20.000 IU/mL and serum ALT>2 times upper limit of normal (ULN), regardless of the level of fibrosis (11-13).

- Patients who are HBeAg positive, older than 30 years of age, with normal ALT and high HBV DNA levels,
- Patients with a family history of cirrhosis or HCC, and extrahepatic manifestations (13).

C. Patients Who Do Not Need to Receive Antiviral Treatment and Should Be Followed-Up

C1. Immunotolerant patients (HBeAg-positive chronic HBV infection)

- HBeAg-positive patients with younger age (<30 years), normal ALT levels, high HBV DNA levels, no significant liver damage, no family history of HCC or cirrhosis should be followed-up within 3-6-month intervals.

C2. Inactive HBV carriers

- Inactive HBV carriers with normal serum ALT levels should be followed up every three months during the first year, every 6-12 months in the following years. Those patients with a low or negative serum HBV DNA should be followed up every 6-12 months.

C3. Patients with isolated Anti-HBc IgG positivity

- Isolated anti-HBc IgG positivity is defined based on serological results (HBsAg negative, anti-HBs-negative and Anti-HBc-positive). It is more commonly seen in HIV or HCV co-infected patients, in immunocompromised patients, in pregnancy, in dialysis patients and in drug injection users.
- In such cases, a single dose of HBV vaccine should initially be applied. If the antibody response is not occurred (anti-HBs positivity), serum HBV DNA level should be ordered. If the HBV DNA is detectable, the management of those patients is as same as the management of CHB patients.

C4. Occult HBV Infection

- HBsAg-negative patients with low levels of HBV DNA (<200 IU/mL).
- The most of these patients have positive anti-HBc IgG antibody.
- Some patients have negative for all HBV serological markers
- Patients can disseminate the virus during donation.
- The gold standard diagnostic method is documented the presence of HBV DNA in the liver tissue. However, serum HBV DNA assay is recommended for the diagnosis.
- Patients with occult HBV infection should be evaluated as well as CHB patients.

VIII- INDICATIONS FOR TREATMENT OF CHB

The indications for treatment are the same for both HBeAg-positive and -negative CHB patients and are based on the following 3 criteria:

- Serum HBV DNA level
- Serum ALT level
- Severity of liver disease

A. Treatment of Patients without Cirrhosis

For patients with serum HBV DNA levels >2000 IU/mL and fulfilling the following criteria's, treatment should be decided based on liver biopsy and/or non-invasive methods.

1. Patients with elevated serum ALT levels
2. Patients with a persistently normal serum ALT level
   a. Older than 30-years age
   b. The presence of advanced liver disease

Patients with a high HAI score (≥6) and/or moderate and severe fibrosis (≥2) based on Ishak score should be treated. Transient elastography and serum markers can be used as an alternative to liver biopsy (13-16).

B. Treatment of Patients with Cirrhosis

Treatment should be started in patients who have compensated cirrhosis with a detectable serum HBV DNA level.

The diagnosis of cirrhosis can be made as clinical presentation, biochemical tests, non-invasive fibrosis tests and liver biopsy if available.

Decompensated cirrhotic patients should be immediately treated. Biopsy is not necessary.

IX- EXPECTED END-POINTS AFTER TREATMENT

The main objective of HBV treatment is to prevent disease progression to cirrhosis, the development of decompensation and HCC, to improve survival and the quality of life as a result of suppression of HBV replication.

The success of treatment is based on:

- Virological response
- Biochemical response
- Histological response
- Prevention of complications

- Ideal end-point
  - HBsAg loss and anti-HBs seroconversion
- Achievable end-point
  - Sustained virological and biochemical response after treatment
  - Anti-HBe seroconversion in HBeAg-positive patients
- Acceptable end-point
  - Sustained virological suppression (undetectable serum HBV DNA levels)

X- DRUGS USED FOR THE TREATMENT OF CHB INFECTION

Lamivudine (LMV), adefovir dipivoxil (ADV) telbivudine (TBV), entecavir (ETV), tenofovir disoproxil fumarate (TDF) and pegylated inferferon alpha (PegIFNα 2a and 2b) are approved in the treatment of CHB infection in Turkey (Table 1) (17-19). The

Table 1. The doses and durations of drugs used in the treatment of CHB

Drug	Dose	Duration
Peginterferon alpha-2a	135-180ug-once a week	48 weeks
Peginterferon alpha-2b	1.5 mg/kg once a week	48 weeks
Lamivudin	100 mg/day	*
Adefovir	10 mg/day	*
Entecavir	0.5-1 mg/day	*
Tenofovir	245 mg/day	*
Telbuvidin	600 mg/day	*

CHB: chronic hepatitis B
*Oral antivirals can be stopped upon confirmation of HBsAg loss (anti-HBs can be positive or negative). In HBeAg positive non-cirrhotic cases, the treatment can be stopped 12 months after the seroconversion of anti-HBe.

efficacies of these drugs have been evaluated with previous randomized controlled trials (1, 3, 9, 11, 13, 20). Baseline serum HBV DNA and serum ALT level, HBeAg status and the genotype of the virus are of utmost importance in the treatment success and the choice of antiviral agent to be used.

A. Use of Pegylated Interferons

- PegIFNα therapy can be considered as an initial treatment approach for HBeAg-positive CHB patients, with a low baseline HBV DNA level (<7 log IU/mL), for patients infected with genotypes A and B, for patients with a high HAI and for patients with a high baseline serum ALT level (three times more than the ULN). The success rate for Peg-IFNα treatment is highest in patients infected with genotype A and lowest in patients infected with genotype D (HBeAg seroconversion 46% and 24% respectively, HBsAg loss 13% and 2% respectively) (21,22). PegIFNα should not be given to patients who have normal ALT or HBV DNA of $>10^9$ IU/mL (22).

B. Use of Oral Antivirals

- Entecavir, TDF and tenofovir alafenamide (TAF) are currently recommended as first-line monotherapy in the treatment of CHB. TAF is an approved antiviral drug but it does not currently have a license in Turkey.
- Several factors including low baseline serum HBV DNA level, high serum ALT level and high necroinflammatory activity affect the success of the treatment response (23).

XI- TREATMENT CHOICE AND DURATION OF TREATMENT IN CHB INFECTION

A. CHB Patients without Cirrhosis

All CHB patients, as defined by an HBV DNA ≥2000 IU/mL, serum ALT levels>ULN or normal, and/or at least moderate liver necroinflammation (HAI≥6) or the presence of fibrosis (≥2), should be treated with either oral antiviral agents or PegIFNα.

B. Patients with Cirrhosis

B.1. Compensated cirrhosis

All cirrhotic patients with any detectable serum HBV DNA level should be treated with an oral antiviral agent with a high potency and high resistance barrier such as ETV or TDF.

B2. Decompensated cirrhosis

- Decompensated cirrhotic patients (presence of ascites, variceal bleeding, hepatic encephalopathy, jaundice [total bilirubin level ≥3mg/dL] should be treated with ETV or TDF. PegIFN treatment is contraindicated (24-26).

C. Treatment Selection

- Currently, two different types of antiviral agents can be used in the treatment of CHB:
  - PegIFN treatment
  - Oral antiviral agents (LMV, TBV, ADV, ETV, TDF and TAF).
- In treatment naive patients, the selection of antiviral treatment should be made based on patients' characteristics as well as patients' choice.
- ETV or TDF is recommended as a first line therapy in the treatment of CHB infection because of their predictable long-term efficacy. CHB patients treated with other NAs, who have undetectable HBV DNA level should be continued their treatment in the same manner as long as they do not have any side effects or antiviral resistance.
- PegIFNα can be considered as an initial treatment option for patients with mild to moderate HBeAg-positive or -negative CHB .

D. Treatment Doses

- Treatment doses should be adjusted based on the package insert information provided for each drug.

E. Treatment Duration

- Oral antiviral treatment should be continued indefinitely in compensated or decompensated cirrhotic patients.
- NAs therapy does not usually achieve HBV eradication. The ultimate goal of effective NA therapy is HBsAg loss followed by a seroconversion to anti-HBs.
- NAs treatment can be discontinued in HBeAg-positive CHB patients if they achieve HBeAg seroconversion to anti-HBe and reach undetectable HBV DNA level and have completed at least 12 months of consolidation therapy.
- Nucleos(t)ide analogues treatment should not be discontinued in HBeAg-negative CHB patients before HBsAg loss with/without anti-HBs seroconversion.
- Treatment duration for PegIFNα is 48 weeks. Treatment response in HBeAg-negative patients should be evaluated at 12^{th} weeks of treatment. Treatment should be discontinued if a combination of <2 log reduction in serum HBV DNA levels and no decrease in HBsAg titer compared to baseline, and switched to NAs treatment.

Table 2. Details of included studies

Response	Definition
Primary non-response	<1log10 IU/mL decrease in HBV DNA level at week 12 of NAs treatment
Partial virological response	>1log10 IU/mL decrease in HBV DNA level at week 24, but detectable HBV DNA at 12 months of NAs treatment.
Permanent response to Peg IFN	HBV DNA level of <2000 IU/mL 12 months after the completion of treatment
Serological response	HBeAg seroconversion in HBeAg-positive patients
Biological response	Serum ALT levels within normal
Histological response	Decrease in the necroinflammatory activity score by ≥2 points without a deterioration in the fibrosis score
Total response	HBsAg loss with biochemical and virological responses
End treatment response	Biochemical and virological responses at the end of treatment
Permanent response	Biochemical and virological responses 6-12 months after stopping treatment

HBV: hepatitis B virus; DNA: deoxyribonucleic acid; NAs: nucleos(t)ide analogues; PegIFN: pegylated interferon; HBeAg: hepatitis B e antigen; ALT: alanine aminotransferase; HBsAg: hepatitis B surface antigen

Table 3. Definition of resistance

Definition	Characteristic
Virological breakthrough	An increase in the HBV DNA level of more than >1log10 IU/mL when compared to the nadir HBV DNA level on therapy
Genotypic resistance	Identification of NAs resistance-related mutations.
Phenotypic resistance	*In vitro* demonstration of decrease sensitivity to NAs, with NAs resistance-related mutation.

HBV: hepatitis B virus; DNA: deoxyribonucleic acid; NAs: nucleos(t)ide analogues

XII- MONITORIZATION DURING TREATMENT AND FOLLOW-UP

A. Patients Using PegIFNα (1,21,22):

- A CBC and liver injury tests should be performed at the end of the first week of the treatment, first month, third month and every three months thereafter.
- Serum HBV DNA levels should be assayed every 3-6 months throughout the treatment, at the end of the treatment and every six months after the discontinuation of treatment.

B. Patients Using NAs (1,11,18):

- Serum ALT levels should be performed every 3-months during the treatment.
- Serum HBV DNA levels should be assayed every 3-6 months.
- After stopping the treatment, serum ALT levels should be performed once a month for three months and serum HBV DNA levels should be assayed at 3 months. After 3 months, serum ALT levels should be performed every 3-6 month intervals and serum HBV DNA levels should be assayed every 6 month intervals.

XIII- TREATMENT RESPONSES

Treatment response can be divided into biochemical, virological and histological responses (Table 2) (1,18).

XIV- DEFINITION AND MANAGEMENT OF ANTIVIRAL RESISTANCE DURING CHB TREATMENT

The definition of antiviral resistance is given in Table 3 (1,19,27,28). Patients should be tested for genotypic resistance when a virological breakthrough is detected. Antiviral resistance testing is not recommended for treatment naïve cases. (19).

A. Signs of Antiviral Resistance (1,27,28):

1. 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
2. An increase in the serum ALT level on therapy
3. Clinical deterioration and the development of progressive liver disease as a result of a serious hepatic exacerbation.
4. Demonstration of HBV DNA polymerase gene mutations

B. To Prevent Antiviral Resistance?

1. Refrain from unnecessary treatments
   - Antiviral therapy should not be recommended in immunotolerant patients
   - Do not treat inactive HBV carriers
   - Do not immediately treat HBeAg-positive patients with serum ALT levels of >5 XULN because of the possibility of a spontaneous HBeAg seroconversion. These patients should be followed up for at least 3-6 months.
2. Refrain from using consecutive antiviral therapies
3. Increase the treatment compliance
4. Drugs that have similar resistance profiles should not be co-administered.
5. Treatment should be initiated with the most potent antiviral drug or antiviral drug combination
6. NAs with a high genetic barrier to resistance should be started (29,30)

Poor compliance is the main cause of NAs treatment failure (1,18,28). Resistance mutation analysis testing should be performed to differentiate antiviral resistance from patient non-compliance (1,28). The treatment choice should be made im-

Table 4. Cross resistance for oral antivirals agents

	M204I	L180M +M204V	A181T/V	N236T	L180M+ M204 V/I ±I169T ±V173L ±M250V	L180M+ M204 V/I ±T184G ±S202I/G
LAM	R	R	I	S	R	R
TBV	R	R	S	S	R	R
ETV	I/R	I	S	S	R	R
ADV	S	S	R	R	S	S
TDF	S	S	S	I	S	S

R: Resistance, Intermediate, S: Sensitive
LAM: TBV: telbivudine; ETV: entecavir; ADV: adefovir dipivoxil; TDF: tenofovir disoproxil fumarate

Table 5. Treatment approach in the presence of antiviral resistance (13)*

Resistance	Approach
Lamivudine	Switch to tenofovir
Adefovir (lamivudine-naive)	Switch to entecavir and tenofovir
	Add lamivudine
Telbivudine	Switch to tenofovir or tenofovir+lamivudine
Adefovir (lamivudine-resistant)	Switch to tenofovir
Entecavir	Switch to tenofovir
Tenofovir* (lamivudine-naive)	Switch to entecavir
Tenofovir* (lamivudine-resistant)	Add entecavir

*No evidence of resistance has been shown

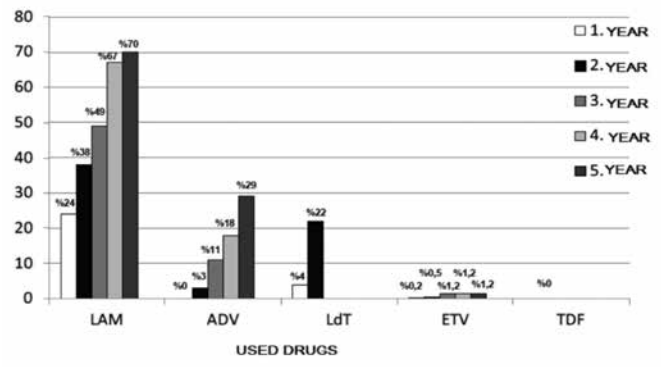

Figure 1. Resistance rates to oral antiviral treatments

mediately based on antiviral resistance testing (31). Cumulative incidence of HBV resistance for NAs are shown in Figure 1. ETV and TDF are fully reimbursed in the treatment of CHB patients in Turkey. Moreover, NA failures is not any more crucial issue in CHB treatment.

Cross resistance is an important issue in patients who are on NAs treatment. There are cross resistances between LMV, ETV and TBV. A181T/V is an ADV resistance mutation. However, in vitro studies have shown that the presence of this mutation also decreases the response to LMV. N236T is an ADV resistance mutation. It has been reported N236T mutation is caused in an ineffective viral suppression in patients, who treated with TDF (32).

During emergence of resistance mutation, treatment decisions should be made according to cross resistance data (Table 4). A different NA treatment that does not have to show cross resistance should be started or added to the existing treatment (Table 5) (1,16,18,19,33,34).

XV- MANAGEMENT OF NON-RESPONSIVE PATIENTS (WITHOUT RESISTANCE)

Treatment adherence should be investigated. If treatment adherence is not cause, a switch to a new drug should be considered (1,19).

A. Non-responders to PeGIFN:

- If there are less than 2 logs of a decrease in HBV DNA level and 1 log of a decrease in HBsAg in the 12th week of treatment, the treatment should be stopped. If HBsAg titers cannot be measured, the decision to stop the treatment should be based on HBV DNA titer.
- In such cases treatment should be continued with ETV or TDF.

B. Non-responders to NAs:

- The following recommendations are considered in primary non-responder patients (<1$\log_{10}$ IU/mL decrease in HBV DNA level at week 12 of NAs treatment)
  - If the drug is TBV or LMV, a switch to TDF or ETV
  - If the drug is ETV, a switch to TDF
  - If the drug is TDF, a switch to ETV
- If HBV DNA decrease is >1 $\log_{10}$ but at the same level in at least two consecutive measurements after 24 weeks, the resistance mutation testing should be performed. If the resistance mutation is not detected, a combination treatment or a switch to other potent oral antiviral drug is recommended.

XVI- MANAGEMENT OF PATIENTS WHOM DISCONTINUED ANTIVIRAL TREATMENT FOR SOME OTHER REASONS

Patients should be reevaluated. The treatment can be re-started with the same drug or started a different potent antiviral agent (35). Potent antiviral treatment should immediately be re-started in cirrhotic patients.

XVII- THE ROLE OF COMBINATION TREATMENT IN CHB INFECTION

Pegylated interferon and oral antiviral agent combination treatment or a combination therapy with two oral antiviral agents is not recommended for treatment-naïve CHB patients. (13,36-38).

XVIII- COST EFFECTIVENESS OF CHB TREATMENT

Chronic HBV infection may lead to end-stage liver disease, hepatic decompensation and HCC. Antiviral therapy has achieved

clinical benefits. It has been shown that antiviral treatment for HBV is cost effective. (39-41).

XIX- MANAGEMENT OF DIALYSIS AND RENAL TRANSPLANT PATIENTS

Entecavir is the preferred option for NA-naïve dialysis patients. TDF treatment may be considered in patients with LMV-resistant. PegIFN treatment is not recommended because of weak tolerance. Treatment dose should be adjusted according to GFR values (Table 6) (18, 42-47).

All HBsAg positive renal transplant recipients should receive antiviral prophylaxis or treatment. ETV is preferred for NA naïve patients. TDF may be considered only for patients with NA resistance. NA prophylaxis or treatment should be long-term continued. Treatment dose should be adjusted according to GFR values.

For patients who are only anti-HBc antibody positive, serum ALT and HBV DNA levels should be monitored at six-month intervals. NAs treatment should be started when serum HBV DNA is detectable, based on the above recommendations.

For transplant recipients, who have not received any antiviral treatment, antiviral treatment should be considered based on serum HBV DNA level and liver histology findings. PegIFN therapy is contraindicated in renal transplanted patients because of the risk of rejection (46-48).

XX- TREATMENT OF CHB PATIENTS WHO ARE LIVER TRANSPLANT CANDIDATE

The approach should be similar with those of decompensated cirrhotic patients. ETV and TDF treatment should be preferred.

XXI- HBV PROPHYLAXIS AND TREATMENT AFTER LIVER TRANSPLANTATION

Pre-transplant serum HBV DNA level is an independent risk factor for HBV reactivation after LT. Treatment with a combination of NAs, either ETV or TDF, and hepatitis B immunoglobulin (HBIG) has dramatically reduced HBV recurrence and improved the clinical outcome after LT.

Hepatitis B immunoglobulin treatment doses and combination treatment protocols may differ among LT centers. HBIG has usually been administered for the maintenance of anti-HBs levels between 50 IU/L and 100 IU/L. However, the optimal dose and duration of HBIG use and optimal anti-HBs titer is still unclear (47-55).

Nephrotoxicity should be closely monitored in transplant recipients receiving calcineurin inhibitors and NAs.

Treatment of HBV Reactivation: Previous prophylactic treatments and the presence of HBV mutants have an effect on treatment decision in recipients with HBV reactivation. ETV and TDF should be preferred. PegIFN treatment should not be used because of its low efficacy and its serious adverse effects (47-55).

Table 6. Dose adjustments of NAs in CHB patients with CRF

Creatinine clearance mL/min	Recommended dose
LMV	
≥50	100 mg/day
30-49	First dose 100 mg, then 50 mg/day
15-29	First dose 100 mg, then 25 mg/day
5-14	First dose 35 mg, then 15 mg/day
<5 or hemodialysis	First dose 35 mg, then 10 mg/day
ADV	
≥50	10 mg/day
20-49	10 mg every other day
10-19	10 mg once every three days
Hemodialysis patients	10 mg once a week after dialysis
ETV	
Treatment-naive	
≥ 50	0.5 mg/day
30-49	0.25 mg/day or 0.5 mg every 48 hours
10-19	0.15 mg/day or 0.5 mg every 72 hours
<10 or hemodialysis or CAPD patients	0.05 mg/day or 0.5 mg every 7 days
LMV-resistant	
≥50	1 mg/day
30-49	0.5 mg/day or 1 mg every 48 hours
10-19	0.3 mg/day or 1 mg every 72 hours
<10 or hemodialysis suitable patient or CAPD	0.1 mg/day or 1 mg every 7 days
TBV	
≥50	600 mg/day
30-49	600 mg every 48 hours
<30 (not requiring dialysis)	600 mg every 72 hours
End stage renal disease	600 mg every 96 hours
TDF	
≥50	245 mg/day
30-49	245 mg every 48 hours
10-19	245 mg every 72 to 96 hours
<10 or dialysis patient	245 mg once a week
<10 not undergoing dialysis	No recommendation

NAs: nucleos(t)ide analogues; CHB: chronic hepatitis B; CRF: ADV: adefovir dipivoxil; ETV: entecavir; LMV: lamivudine; CAPD: TDF: tenofovir disoproxil fumarate

Recipients who, did not have HBV experience had donation from anti-HBc positive donor, should be received antiviral prophylaxis with ETV or TDF.

XXII- MANAGEMENT OF HBV-INFECTED PATIENTS UNDERGOING CHEMO/IMMUNOSUPPRESSIVE THERAPY

All candidates for chemo/immunosuppressive therapy should be screened for HBV markers, HBsAg, anti-HBc IgG and anti-HBs prior to treatment. HBV vaccination should be recommended if patients have all negative for HBV. All HBsAg positive patients should be referred to a specialist for diagnosis of the phase of HBV infection.

Entecavir or TDF should be started as a treatment or as a prophylaxis. The prophylaxis with potent NAs should continue for at least 12-18 months after discontinuation of the chemo/immunosuppressive therapy. CHB patients should be treated with NAs similarly to the immunocompetent patients.

The risk of HBV reactivation in HBV-experienced patients varies widely. If these subjects are viremic, they should be treated similarly to HBsAg-positive patients. If these subjects need to be treated with rituximab or other monoclonal antibodies, or those undergoing allogeneic stem cell transplantation, antiviral prophylaxis is recommended. Pre-emptive therapy is generally recommended in patients with moderate or low risk of HBV reactivation, Serum HBVDNA levels should be screened every three months during and after chemo/immunosuppressive therapy. Potent NA treatment should be recommended when HBV DNA is detectable (13,56-58).

XXIII- TREATMENT OF HBV AND HCV CO-INFECTED PATIENTS

As a general principle, antiviral treatment should be directed at the virus, which is at the replicative phase (1,11).

There is a potential risk of HBV reactivation during or after direct-acting antivirals (DAAs) therapy. HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until 12-week after DAA treatment in order to prevent HBV reactivation. In HBsAg-negative and anti-HBc IgG-positive patients serum ALT and HBV DNA levels should be monitored for HBV reactivation during DAA therapy (13).

XXIV- TREATMENT OF HBV AND HIV CO-INFECTED PATIENTS

Serological markers for HBV should be evaluated before administering antiretroviral treatment for HIV infection. In HBsAg-positive patients, HBV DNA should be quantified.

In co-infected patients, both HIV and HBV should be treated. Emtricitabine, LMV, ETV and TDF are effective in the treatment of both HIV and HBV infections, therefore these agents should be preferred in the combination regimens. TDF+Emtricitabine as nucleoside reverse transcriptase inhibitors should be preferred. ETV can be added to the ART regimen if TDF is not used. LAM, Emtricitabine or TBV and ART combination treatment is an alternative treatment regimen. Discontinuation TDF-containing ART should be avoided in co-infected patients because of the high risk of severe hepatitis flares and decompensation due to HBV reactivation (11,18). PegIFN or TBV can be used in patients with a CD4 of >500/mm^3, but these two agents are not effective against HIV.

Drug toxicity should be closely monitored during treatment. Antiviral monotherapy for HBV can cause HIV resistance mutations.

XXV- TREATMENT OF CHB DURING PREGNANCY AND AFTER LABOR

If the mothers have high levels of HBV viremia and positive HBeAg status, perinatal transmission might be happened despite immunoprophylaxis against HBV. Administration of antiviral treatment in the 3rd trimester reduces the viral load of the mother and risk of transmission. The combination of HBIG and HBV vaccination reduces the rate of perinatal transmission.

In HBV-infected pregnant women, serum aminotransferases and HBV DNA levels should be monitored. If serum HBV DNA level is >200,000/IU/mL, antiviral treatment should be recommended during 24-28 weeks of pregnancy. If serum HBV DNA level is <200,000 IU/mL, antiviral treatment should be recommended in mothers, who had baby transmission in the first pregnancy. TDF prophylaxis is the preferred in this setting during the last trimester of pregnancy.

Patient who gets pregnant while receiving an antiviral treatment, a switching to TDF is recommended. (11,18,59-62).

The duration of TDF prophylaxis is not known very well. It can be stop at delivery or within the first three months after delivery. The mothers should be followed-up with serial serum ALT levels every 3-6 months.

Chronic hepatitis B pregnant women should be treat as well as non-pregnant CHB patients.

Caesarean delivery is not recommended in order to prevent mother to baby HBV transmission.

The safety of antiviral therapy during lactation is uncertain. Breast feeding may not be considered a contraindication in HBsAg-positive mothers, even HBsAg can be detected in breast milk. In fact, TDF concentrations in breast milk have been reported but its bioavailability is limited (13,63-65).

XXVI- PRIMARY PREVENTION OF HBV

All newborns should be vaccinated against HBV (66-68).

Hepatitis B virus markers testing should be recommended in adolescents and young adults. If HBV markers are all negative, HBV vaccination is recommended (2).

Individuals, who have risk for HBV transmission should be vaccinated (5).

After contamination, HBV vaccine and HBIG should be administered as soon as possible (2,5).

Individuals with isolated anti-HBc positivity, who live in low endemic regions have should be vaccinated with routine vaccination schemes (2). However, occult HBV infection should be investigated.

The society should be informed and awaked of the importance of HBV infection, HBV transmission routes and prevention of disease (2).

Screening for HBV markers in the first trimester of pregnancy is strongly recommended in all women of childbearing age (2).

XXVII- HBV VACCINATION

The HBV vaccine should be administered intramuscularly at 0, 1 and 6 or at 0, 1, 2 and 12 months. A vaccination program is started with one brand of vaccine, and continued with another brand.

Antibody response at the end of vaccination scheme should be controlled in individuals, who have a high HBV transmission risk. No rapel dose is necessary if patients have anti-HBs titer >10 IU/mL.

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