MANAGEMENT OF CHRONIC HBV INFECTION

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A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: 2015 Update

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- Chronic hepatitis B (CHB) is a substantial public health problem and the leading cause of hepatocellular carcinoma (HCC) worldwide.

- National Health and Nutrition Examination Survey data suggest an estimated 704,000 individuals, or 0.27% of the population, have chronic infection with hepatitis B virus (HBV).

- The number of chronically infected individuals has diminished since the early 1990s, when a strategy to eliminate HBV transmission, including universal vaccination of infants, was implemented.

- The incidence of HBVrelated HCC has remained undiminished as older generations with long-standing CHB develop long-term sequelae, which, in addition to HCC, include cirrhosis and hepatic decompensation.

- The goal of the revised algorithm :

- (1) which patients are candidates for antiviral therapy
- (2) what are the advantages and disadvantages of available treatment options
- (3) when should therapy be initiated
- (4) when can therapy be discontinued
- (5) what is the role of on treatment monitoring
- (6) which strategies should be used to decrease the risk of antiviral resistance?

Table 1. Phases of CHB Infection

Phase	ALT	Liver histology	HBV DNA	HBeAg	HBsAg
Immune tolerance phase	Normal or minimally elevated	Minimal activity; absent or scant fibrosis	High levels: serum HBV DNA >20,000 IU/mL	Positive; anti-HBe negative	Positive >6 months
Immune clearance phase (HBeAg-positive CHB)	Elevated, usually persistently or with intermittent elevations	Active; liver biopsy showing chronic hepatitis (necroinflammatory score ≥4)[a]	High levels: serum HBV DNA >20,000 IU/mL	Positive; anti-HBe negative	Positive >6 months
Low viral replication	Persistently normal	Inactive; liver biopsy showing variable, usually minimal fibrosis (necroinflammatory score <4)[a]	Low or undetectable levels: serum HBV DNA negative or <2000 IU/mL	Negative; anti-HBe positive	Positive >6 months
Reactivation phase (HBeAg-negative CHB[b])	Elevated, often fluctuating levels	Active; liver biopsy showing variable amounts of fibrosis (necroinflammatory score ≥4)[a]	Moderate, often fluctuating levels: serum HBV DNA >2000 IU/mL	Negative; anti-HBe positive	Positive >6 months
Resolution	Normal	Inactive; scant fibrosis	No detectable serum HBV DNA (low levels may be detectable in the liver)	Negative; anti-HBe positive	Negative

Table 2. Definitions of Clinical Terms Used in Course of HBV Infection

Acute exacerbation or flare of hepatitis B	
	Intermittent increase of aminotransferase activity to >10 × ULN and >2 × baseline value
Reactivation of hepatitis B	
	Reappearance of active necroinflammatory disease of the liver in a person known to be in the low viral replication state or to have resolved hepatitis B
HBeAg clearance	
	Loss of HBeAg in a person who was previously HBeAg-positive
HBeAg seroconversion	
	Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg-positive and anti-HBe–negative, associated with decrease in serum HBV DNA to <20,000 IU/mL
HBeAg reversion	
	Reappearance of HBeAg in a person who was previously HBeAg-negative, anti-HBe–positive
Occult hepatitis B	
	Having detectable HBV DNA while being negative for HBsAg
Resolution	
	Loss of HBsAg and no further virologic, biochemical, or histologic evidence of active virus infection or disease
Seroreversion	
	Reappearance of HBsAg in a person with previously resolved HBV and loss of HBsAg

Table 3. Pretreatment Evaluation for CHB

History and physical examination

- Risk factors for viral hepatitis
- Duration of infection
- Route of transmission
- Risk factors for HIV coinfection
- Alcohol history
- Presence of comorbid diseases
- Family history of liver cancer
- HBV testing of family members
- General counseling regarding transmission
- Vaccination of at-risk household and sexual contacts
- Family planning

Pretreatment tests

- Serial testing of ALT and HBV DNA level for 6 months
- Liver function tests
  - Complete blood count with platelets
  - Hepatic function panel
  - Prothrombin time
- HBeAg and anti-HBe
- HBV genotype
- Tests to rule out other causes of liver disease
  - Anti–hepatitis C virus
  - Anti–hepatitis D virus
- Hepatitis A immunity: anti–hepatitis A virus Ig G or total
- HIV: anti-HIV
- Screen for HCC in high-risk patients: MRI (preferred), computed tomography, AFP, or ultrasound
- Transient elastography to grade histologic fibrosis or liver biopsy examination to grade and stage liver disease[a]
- Urinalysis; if abnormal, do 24-hour urine for creatinine and protein

[a]Liver biopsy is optional for patients meeting treatment criteria but may be especially helpful in those with normal ALT levels and age older than 35–40 years of age.

- Viral Threshold for Treatment:

- In the panel's experience, patients can have advanced liver disease even if they have serum HBV DNA levels persistently <20,000 IU/mL

- The consensus opinion of the panel is that all patients (HBeAg-positive or -negative) who have HBV DNA >=2000 IU/mL and elevated ALT (> ULN) should be treated if they have any degree of fibrosis and can be considered for treatment even if they do not have fibrosis.

- If patients with HBV DNA >=2000 IU/mL and elevated ALT without fibrosis do not undergo treatment, their HBV DNA and ALT levels should be monitored every 3–6 months.

Table 5. Recommendations for Treatment: HBeAg-positive CHB

HBV DNA	ALT[a]	Treatment strategy
<2000 IU/mL	Normal	• No treatment • Monitor every 6–12 months[b] • Consider therapy in patients with known significant histologic disease, even if low-level viral replication
≥2000 IU/mL	Normal	• Low rate of HBeAg seroconversion for all current treatments • Younger patients often immune tolerant • Consider liver biopsy or transient elastography, particularly if older than 35–40 years; treat if disease. In absence of histologic data, observe for increase in ALT levels • If treated, entecavir, tenofovir, or peginterferon alfa-2a is preferred
≥2000 IU/mL	Elevated	• Entecavir, tenofovir, or peginterferon alfa-2a is preferred • Long-term treatment may be needed for oral agents

[a]ULNs for serum ALT concentrations are 30 IU/L for men and 19 IU/L for women.
[b]On initial diagnosis, monitor every 3 months for 1 year to ensure stability.

Table 6. Recommendations for Treatment: HBeAg-negative CHB

HBV DNA	ALT[a]	Treatment strategy
<2000 IU/mL	Normal	• No treatment; majority are in low viral replication state • Monitor every 6–12 months[b] • Consider therapy in patients with known significant histologic disease, even if low-level viral replication
≥2000 IU/mL	Normal	• Consider biopsy or transient elastography; treat if disease present. In absence of histologic data, observe for rise in serum ALT levels. • If treated, entecavir, tenofovir, or peginterferon alfa-2a is preferred
≥2000 IU/mL	Elevated	• Entecavir, tenofovir, or peginterferon alfa-2 is preferred • Long-term treatment required for oral agents

[a]ULNs for serum ALT concentrations are 30 IU/L for men and 19 IU/L for women.
[b]On initial diagnosis, monitor every 3 months for 1 year to ensure stability.

Table 4. Suggested Follow-up for Patients Not Initiating Treatment

- HBeAg-positive or -negative CHB with HBV DNA ≥2000 IU/mL and normal ALT
  - Assess ALT levels every 3–6 months
  - Consider liver biopsy or transient elastography to assess fibrosis
  - Consider initiating treatment when ALT levels increase or fibrosis is present
- HBV DNA <2000 IU/mL and normal ALT
  - Assess ALT levels every 6–12 months
  - If ALT levels become increased, check serum HBV DNA and exclude other causes of disease

- UpToDate:

- HBeAg-positive patients —
- Treatment is recommended for those with HBV DNA >20,000 int. unit/mL and ALT >2 x ULN in patients without cirrhosis.
- Patients with compensated cirrhosis and HBV DNA >2000 int. unit/mL and those with decompensated cirrhosis and detectable HBV DNA by PCR assay should be considered for antiviral therapy, regardless of the serum ALT level.

- Treatment should be delayed for three to six months in newly diagnosed HBeAg positive patients with compensated liver disease to determine whether spontaneous HBeAg seroconversion will occur.

- UpToDate:

- Patients with chronic hepatitis whose serum ALT is persistently below two times the upper limit of normal can be observed, considering treatment if and when the serum ALT becomes higher.
- Possible exceptions to this rule are:

✓ recurrent hepatitis flares that fail to clear HBeAg,

✓ patients with icteric flares,

✓ active or advanced histologic findings (such as moderate/severe inflammation or bridging fibrosis/cirrhosis),

✓ patients above the age of 40 who remain HBeAg positive with persistently high HBV DNA levels.

- UpToDate:

- HBeAg-negative patients —
- Treatment may be initiated immediately once a diagnosis of HBeAg negative chronic hepatitis (ALT >2 x ULN and HBV DNA >2000 int. unit/mL) is established because sustained remission is rare in the absence of treatment.
- Liver biopsy should be considered in HBeAg negative patients who have serum HBV DNA levels >2000 int. unit/mL and normal or mildly elevated ALT to determine if treatment is warranted.

- UpToDate:
- WHO SHOULD BE TREATED:
- We recommend that treatment be considered in patients with HBeAg positive or HBeAg negative chronic hepatitis.

- Patients with compensated cirrhosis and HBV DNA >2000 int. unit/mL

- Those with decompensated cirrhosis and detectable HBV DNA by PCR assay should be considered for therapy, regardless of the serum ALT level.

- UpToDate:

- ✓ Patients in whom therapy is indicated:
- ✓ Acute liver failure.
- ✓ Clinical complications of cirrhosis.
- ✓ Cirrhosis or advanced fibrosis with high serum HBV DNA .
- ✓ Prevention of reactivation of chronic HBV during chemotherapy or immunosuppression.

- UpToDate:

- Patients for whom therapy may be indicated:

- ✓ patients in the immune-active phase who do not have advanced fibrosis or cirrhosis (HBeAg-positive or HBeAg-negative chronic hepatitis).

- UpToDate:

- Patients for whom immediate therapy is not routinely indicated:

- ✓ (1) Patients with chronic HBV in the immune tolerant phase

- ✓ (2) Patients in the inactive carrier phase

- ✓ (3) Patients who have latent HBV infection (HBV DNA without HBsAg).

Goals of Therapy:

- Eliminate or significantly suppress HBV replication and thus prevent progression of liver disease to cirrhosis, liver failure, or HCC.

- In patients who are HBeAg-positive before therapy, an additional goal of treatment is:
- loss of HBeAg with seroconversion to antibody to hepatitis B e antigen (anti-HBe), although the usefulness of this end point for determining long-term outcomes with oral antiviral therapies is unclear.

- Loss of hepatitis B surface antigen (HBsAg), although highly desirable, occurs in only a minority of patients who receive antiviral therapy.

- Currently, there are 2 key treatment strategies for either HBeAg-positive or HBeAg-negative CHB:

✓ 1 year of therapy with peginterferon alfa

✓ long-term therapy with nucleoside/nucleotide analogues.

- Hepatitis B Therapies:

- Currently, 7 drugs are available for managing chronic HBV infection in the United States:

- ✓ interferon alfa-2b,
- ✓ peginterferon alfa-2a,
- ✓ lamivudine,
- ✓ adefovir,
- ✓ entecavir,
- ✓ telbivudine,
- ✓ tenofovir.

- The preferred first-line treatment choices among the oral nucleosides/nucleotides are entecavir and tenofovir because of their superior efficacy and favorable resistance profiles in HBeAgpositive and HBeAg-negative CHB over comparable drugs.

- Lamivudine is not a first-line choice because of its high rate of resistance and inferiority to entecavir and telbivudine.

- Adefovir is no longer a first-line drug because its efficacy and resistance profiles are inferior to those of tenofovir.

- Although telbivudine has superior efficacy to lamivudine and adefovir, it is associated with an intermediate rate of resistance compared with these agents.

- Telbivudine cannot be considered a first-line agent, although as a pregnancy category B drug it has a role in preventing vertical transmission of HBV in HBeAg-positive pregnant women.

- In routine practice, standard interferon alfa-2b has largely been replaced by peginterferon alfa-2a.

- Treatment-naive patients who are beginning therapy for the first time should be treated with peginterferon alfa, entecavir, or tenofovir on the basis of their superior potency and low rate or absence of antiviral drug resistance.

- Patients with any history of lamivudine use should not receive entecavir

- Peginterferon alfa-2a:
- 1) HBeAgpositive patients
- At the end of 48 w treatment, therapy with peginterferon alfa-2a, with or without lamivudine, resulted in significantly greater rates of HBeA seroconversion, HBV DNA undetectability, and ALT normalization, compared with treatment with lamivudine alone.

- Although the combination of peginterferon alfa-2a and lamivudine resulted in a greater degree of on-treatment viral load reduction, the rate of HBeAg seroconversion was not different from treatment with peginterferon alfa- 2a monotherapy.

- Higher rates of HBeAg seroconversion were observed in patients who had:
- HBV genotype A,
- Low baseline HBV DNA concentrations,
- increased baseline serum ALT levels.

- The licensed peginterferon alfa-2a treatment regimen (180 mg weekly for 48 weeks) appears to be more effective at inducing HBeAg seroconversion than regimens with shorter (24 weeks) or lower (90 mg/wk) dosing.

- The side effect profile of peginterferon alfa :

- ✓ influenza-like illness characterized by fever, chills, headache, malaise, and myalgia
- ✓ cytopenias
- ✓ and psychological side effects.

- Peginterferon alfa-2a is a reasonable choice as firstline therapy especially in:
- ✓ genotype A or B patients
- ✓ young patients
- ✓ lack significant comorbidities
- ✓ have no detectable precore or basal core promoter viral mutants
- ✓ HBV DNA levels <10 (9) copies/mL
- ✓ ALT levels at >2 ULN

- Data support response-guided therapy :

- ✓ genotypes A or D who have no decline in HBsAg at week 12
- ✓ genotype B or C patients with HBsAg >20,000 IU/mL at week 12

- ✓ all patients with HBsAg >20,000 IU/mL at 24 weeks

are justified in stopping peginterferon alfa therapy

- Hepatitis B e antigen-negative patients:

- In a 3-year post-treatment follow-up study:

patients who had been treated with peginterferon alfa-2a had higher rates of :

- ✓ ALT normalization,
- ✓ HBVDNA suppression,
- ✓ HBsAg loss,
- ✓ HBsAg seroconversion

than patients treated with lamivudine alone.

- HBeAg-negative patients treated with peginterferon alfa- 2a with or without lamivudine, pretreatment factors predicting response at 24 weeks after treatment included:

- ✓ Younger age
- ✓ Female gender
- ✓ High baseline ALT
- ✓ Low baseline HBV DNA
- ✓ HBV genotype B or C

- HBeAg-negative patients who have no decline in HBsAg and <2-log decline in HBV DNA at week 12 of treatment with peginterferon alfa therapy have a very low chance of achieving a sustained virologic response
- Stopping therapy is warranted for such patients.

- Entecavir:

Both in Hepatitis B e antigen–positive & Hbe -negative patients resulted in:

- Higher rates of histologic improvement
- Mean HBV DNA reduction
- HBV DNA undetectability (<300 copies/mL)
- ALT normalization (1 ULN)

- UpToDate:

- The main advantages of Entecavir are its potent antiviral activity and a low rate of drug resistance.

- Entecavir has a more important role in primary treatment of HBV than in patients with lamivudine-resistant HBV.
- Entecavir may also have an important role in patients with decompensated cirrhosis because of its potent antiviral activity and low rate of drug resistance.

- Resistance to Entecavir is rare among nucleoside-naïve patients (approximately 1 percent with up to five years of treatment).

- By contrast, resistance has been observed in up to 50 percent of lamivudine-refractory patients after five years of treatment.

- Tenofovir:
- Tenofovir is used as first-line therapy for treatment-naïve patients and for most patients with drug-resistant virus.
- Resistance to tenofovir is unlikely to develop, even among patients who have been treated for up to eight years .
- Tenofovir is effective in suppressing wild-type as well as lamivudine, telbivudine, or entecavirresistant HBV.
- It is also effective in suppressing adefovir-resistant HBV, although the efficacy is lower in patients with double mutations (A181T/V and N236T).

- Combination Therapy:
- For nearly all HBV patients, monotherapy with entecavir or tenofovir is the appropriate first-line treatment because both have potent antiviral activity and high barriers to resistance.

- Combination therapy with entecavir and tenofovir has been evaluated in a superiority study of 379 patients with HBeAg-positive or -negative CHB.

- After 96 weeks of treatment, the group receiving entecavir monotherapy had a similar percentage of patients with HBV DNA <50 IU/mL as the group receiving combination therapy with entecavir plus tenofovir (83% vs 76%)

- The combination of entecavir plus tenofovir did have incremental benefit in HBeAg-positive patients with baseline levels of HBV DNA 10 (8) IU/mL; 79% of those receiving combination therapy had HBV DNA <50 IU/mL versus 62% receiving entecavir alone, although the clinical relevance of this difference is unclear.

- Monotherapy with tenofovir appears to be sufficient for maintaining virologic suppression even in patients with high viral load at the start of treatment.

- In immune tolerant patients, there is evidence that combination therapy with tenofovir and emtricitabine provides better viral suppression than tenofovir alone.

- Combining lamivudine with peginterferon alfa can lead to increased rates of on-treatment virologic response relative to peginterferon alfa alone, but the combination does not appear to impact sustained virologic or serologic response off treatment.

- Adding telbivudine to peginterferon alfa has a potent antiviral effect but should be avoided because of the increased risk of severe polyneuropathy.

- Adding or Switching Therapies:

- The concept of add-on therapy stemmed from experience by using adefovir in the setting of lamivudine resistance.

- In patients with lamivudine resistance, switching to adefovir monotherapy results in a greater likelihood of developing resistance to adefovir than adding adefovir in combination with lamivudine.

- Unlike substituting adefovir, switching to tenofovir monotherapy in the setting of lamivudine resistance confers effective virologic suppression and does not appear to increase the risk of resistance to tenofovir.

- A randomized study of tenofovir versus tenofovir combined with emtricitabine convincingly demonstrated that tenofovir monotherapy is sufficient in lamivudine-resistant patients, attaining HBV DNA <400 copies/mL in 89% of patients at 96 weeks of monotherapy compared with86% in those receiving dual therapy, with no emergent resistance in either group.

- In the setting of adefovir resistance, tenofovir monotherapy is less effective.

- In a retrospective analysis of antiviral response to tenofovir therapy in 127 patients with prior nucleoside/nucleotide analogue experience with lamivudine, adefovir, or both, patients with genotypic adefovir resistance had a significantly slower decrease of HBV DNA levels at month 12 than did patients without adefovir resistance, an effect that persisted through a median treatment duration of 23 months.

- Despite findings indicating that tenofovir has antiviral efficacy in patients with genotypic adefovir resistance, the suppression of HBV DNA replication with tenofovir occurs at a slower rate, and complete suppression of HBV DNA replication occurs in only a minority of patients.

- Duration of Therapy:

1) Hepatitis B e Antigen–positive Patients:

- ✓ The optimal duration of therapy with peginterferon alfa remains unclear, although the standard duration of 48 weeks appears to induce higher rates of HBeAg seroconversion than 24 weeks.

- ✓ Evidence from a small study has indicated that the extension of peginterferon therapy to 96 weeks improves rates of sustainable HBeAg and HBsAg seroconversion.

- During peginterferon alfa therapy, levels of HBsAg at week 12 can guide decisions about continuing therapy.

- HBeAg positive patients with no decline in HBsAg or an HBsAg level >20,000 IU/mL at week 12 are justified in stopping peginterferon alfa therapy.

- For nucleoside/nucleotide analogues, the panel recommends lifelong treatment for all patients with decompensated cirrhosis at the start of therapy and for the majority of patients who had significant fibrosis (F3) or compensated cirrhosis (F4) at the start of therapy.

- Patients with compensated liver disease at the start of therapy may be discontinued from therapy if they experience HBsAg loss for 6–12 months or longer or HBsAg seroconversion.

- For HBeAg-positive patients with histology less than F3, the duration of therapy is less clear.

- HBeAg-positive patients who fail to lose HBeAg should be treated long-term because the chance of HBeAg seroconversion increases with time, and there is a high risk of recurring viremia if therapy is stopped in the absence of HBeAg seroconversion.

- Historically, HBeAg seroconversion was considered to portend a durable response, and discontinuation of antiviral therapy was recommended after a period of consolidation therapy of 6–12 months from the time of HBeAg seroconversion.

- However, a substantial number or even the majority of patients who discontinue therapy after completing such consolidation therapy can experience recurrent viremia.

- Thus, long-term therapy can be justified even after HBeAg seroconversion and virologic suppression.
- For patients without HBsAg loss or seroconversion, the panel does not recommend stopping treatment.
- However, if patients prefer to stop treatment, they should undergo liver biopsy or transient elastography before stopping therapy to ensure they have only mild histologic fibrosis (F0–F1).
- Patients who stop therapy should be monitored for HBV DNA and ALT levels. Those who relapse can be retreated.

2)Hepatitis B e Antigen–negative Patients:

- HBeAg-negative patients receiving therapy should be monitored every 3–6 months.
- The duration of therapy with peginterferon alfa is 12 months.
- During therapy with peginterferon alfa, the absence of HBsAg decline and a <2-log IU/mL decline in HBV DNA at week 12 are good predictors of non-response and are justification to stop therapy.

- For nucleoside/nucleotide analogues, the panel recommends lifelong treatment for all patients with decompensated cirrhosis at the start of therapy and for the majority of patients who had significant fibrosis (F3) or compensated cirrhosis (F4) at the start of therapy.
- Patients with compensated liver disease at the start of therapy may be discontinued from therapy if they experience HBsAg loss for 6–12 months or HBsAg seroconversion.
- However, they must undergo lifelong screening for HCC even if they no longer have cirrhosis

- For patients without HBsAg seroconversion, the panel does not recommend stopping treatment.

- However, if patients prefer to stop treatment, physicians can have a dialogue with patients who have only mild histologic fibrosis (F0–F1) and inflammation about the pros and cons of stopping after 5 years.

- This is based on observations indicating that even though most patients have virologic relapse, many have persistently normal ALT, and some may clear not only viremia but HBsAg without reinstitution of treatment during the next 5 years.

- Monitoring for Renal Toxicity:
- ✓ For all nucleos(t)ide analogues except telbivudine, a decline in renal function has been reported.
- ✓ Risk factors for renal events include:
- decompensated cirrhosis
- Pretreatment creatinine clearance <60 mL/min
- poorly controlled hypertension
- proteinuria
- uncontrolled diabetes
- active glomerulonephritis
- concomitant nephrotoxic
- Drugs
- solid organ transplantation.

- Before starting therapy with a nucleoside/nucleotide analogue, patients should have serum creatinine levels and estimated creatinine clearance obtained.

- For patients at risk of renal events or for those taking tenofovir or adefovir,creatinine clearance (eGFR) and serum phosphorus should be monitored every 3 months during the first year of therapy.

- If renal function is unchanged, monitoring can be extended to every 6 months thereafter.

- Bone Density Measurements:
- ✓ Patients with chronic liver disease have increased risk for osteopenia.
- ✓ During the first year of treatment with tenofovir, a minority of HIV and HBV patients experience bone density decreases of 4%–7%.
- ✓ Therefore, some members of the panel perform a bone mineral density scan in patients before starting oral antiviral therapy.

- ✓ In addition, some members monitor levels of 25-hydroxy vitamin D during therapy and provide oral supplementation for deficiency.

- Monitoring Virologic Response and Managing Resistance to Oral Antiviral Therapy:
- The rate of resistance depends on a number of factors including:
- pretreatment HBV DNA level
- potency of the antiviral agent
- prior exposure to oral nucleoside or nucleotide antiviral therapy,
- duration of treatment
- the degree of genetic barrier to resistance to the individual drug.

- The long-term rates of resistance are highest for lamivudine (65%–70% at 4–5 years)
- intermediate for telbivudine (25% in HBeAg-positive patients and 11% in HBeAg-negative patients at 2 years)
- lower for adefovir (29% at 5 years)
- lowest for entecavir in the absence of prior lamivudine resistance (1.2% after 5 years)and for tenofovir in treatment-naive patients(0% at years).

- The development of resistance is associated with:

- ✓ loss of initial response and HBV DNA rebound,
- ✓ may be followed by biochemical breakthrough
- ✓ eventual reversion of histologic improvement
- ✓ in some cases, resistance leads to severe exacerbations, which may be particularly problematic for patients with cirrhosis.

- Antiviral Resistance Testing:

- Clinically, antiviral resistance manifests as virologic breakthrough, defined as >1 log10 IU/mL increase in serum HBV DNA levels from nadir in 2 consecutive samples taken 1 month apart in patients who have responded and have been adherent to therapy with antiviral medications.

Table 7. Definitions of Terms Relating to Antiviral Resistance to Nucleoside and Nucloetide Analogue Treatment for CHB

Genotypic resistance	Detection of viral populations bearing amino acid substitutions in reverse transcriptase region of HBV genome that have been shown to confer resistance to an antiviral in phenotypic assays during antiviral therapy. These mutations are usually detected in patients with virologic breakthrough but can also be present in patients with persistent viremia and no virologic breakthrough.
Virologic breakthrough	Increase in serum HBV DNA level by >1 $\log_{10}$ IU/mL above nadir after achieving virologic response during continued therapy
Viral rebound	Increase in serum HBV DNA to $>20{,}000$ IU/mL or above pretreatment level after achieving virologic response during continued therapy
Biochemical breakthrough	Increase in ALT level above ULN after achieving normalization during continued therapy
Cross-resistance	Decreased susceptibility to more than 1 antiviral drug conferred by same amino acid substitution or combination of amino acid substitutions

- On-Treatment Monitoring:

- Serum HBV DNA levels should be monitored at 12 weeks to identify primary treatment failure (HBV DNA decline of <1 log10 IU/mL) and at 24 weeks to confirm continued virologic suppression by antiviral therapy.

- Monitoring of HBV DNA levels should occur every 3–6 months during the first year to confirm adequate viral suppression and detect viral breakthrough.

- Primary treatment failure.:
- Primary nonresponse to entecavir, tenofovir, telbivudine, or lamivudine is rare; therefore, any patients who are not responsive to a nucleoside or nucleotide analogue after 12–24 weeks should be evaluated for compliance.
- In patients who have been compliant, resistance analyses should be performedafter 24 weeks to determine an optimal rescue strategy in case drug-resistant variants are present.
- Nucleoside/ nucleotide-naive patients who have a primary or completem non-response to adefovir should be immediately switched to tenofovir or entecavir.

- Partial or inadequate virologic response.
- Patients with partial or inadequate virologic response (HBV DNA>2000 IU/mL at 24 weeks or HBV DNA positive at 48 weeks of therapy) to a nucleoside or nucleotide analogue should also be evaluated for compliance.
- If patients receiving lamivudine or telbivudine have a partial or inadequate virologic response at 24 weeks, they should be switched to entecavir or tenofovir.
- Published reports indicate patients who have an inadequate virologic response after 24 weeks of adefovir therapy can be switched to either entecavir or tenofovir.

- The optimal management of patients who have detectable HBV DNA after 48 weeks of entecavir or tenofovir therapy is unclear.
- Patients with declining serum HBV DNA levels may continue with entecavir or tenofovir because of the rise in rates of virologic response over time and the very low risk of resistance to either drug.
- Patients with partial response to entecavir but HBV DNA <1000 IU/mL after 1 year of therapy often achieve viral suppression by continuing entecavir through at least 2 years total.

- Patients with partial response to entecavir and higher residual HBV DNA level after 1 year of therapy can be switched to tenofovir monotherapy or tenofovir plus entecavir combination therapy.

- For patients with partial response to entecavir 0.5 mg daily, increasing the dose to 1.0 mg daily does not appear to benefit the likelihood of achieving complete viral suppression.

- Virologic resistance:

- In clinical practice, most members of the panel generally avoid monotherapy in patients with resistance and either use add-on therapy with tenofovir or entecavir or switch to tenofovir/emtricitabine (a combination drug containing tenofovir 300 mg and emtricitabine 200 mg that has not been approved for anti-HBV therapy)

Table 9. Antiviral Resistance and Salvage Therapy

	Salvage therapy for antiviral resistance
Lamivudine-R	Switch to tenofovir or Truvada[a]
Adefovir-R	Switch to Truvada or combination of entecavir plus tenofovir
Entecavir-R	Add tenofovir or switch to Truvada
Telbivudine-R	Add tenofovir or switch to Truvada

[a]Truvada is a combination drug containing tenofovir 300 mg and emtricitabine 200 mg and has not been approved for anti-HBV therapy.

- Conclusions:
- The primary goal of CHB treatment is to eliminate or significantly suppress replication of HBV, thereby preventing progression of liver disease to cirrhosis, liver failure, or HCC.

- For HBeAgpositive patients, an additional goal of treatment is loss of HBeAg with seroconversion to anti-HBe, although the importance of this end point for patients receiving oral antiviral therapy is unclear.

- Loss of HBsAg is a highly desirable outcome but happens only in a minority of patients who receive antiviral therapy.
- For patients with HBeAg-positive or –negative CHB and elevated ALT levels, an HBV DNA level of 2000 IU/mL or higher is a reasonable threshold for determining candidates for treatment.
- CHB patients with HBV DNA >=2000 IU/mL and normal ALT should undergo biopsy or transient elastography to assess liver histology.
- If histologic disease is detected, patients should initiate treatment. In the absence of histologic data, patients should be observed for rises in HBV DNA and ALT levels.

- All CHB patients with either compensated or decompensated cirrhosis who have detectable HBV DNA should initiate treatment, regardless of ALT level.
- The preferred first-line treatments for CHB are entecavir, tenofovir, and peginterferon alfa-2a.

- Currently the 2 main treatment strategies for both HBeAg-positive and HBeAg-negative CHB are either 1 year of treatment with peginterferon alfa or long-term therapy with a nucleoside or nucleotide analogue.

- Finite treatment with peginterferon alfa has the advantage of higher rates of HBeAg seroconversion and loss of HBsAg relative to nucleoside or nucleotide analogues.
- However, peginterferon alfa is administered via subcutaneous injection, can be difficult to tolerate, and is contraindicated in patients with decompensated cirrhosis.
- The nucleoside analogue entecavir and nucleotide analogue tenofovir are both highly potent antiviral agents, with rates of virologic remission of >90% in treatment-adherent patients after 3 years.

- Before initiating treatment for CHB, all patients should have a baseline assessment of liver fibrosis.
- A baseline assessment is necessary for evaluating histologic response to therapy and informs decisions regarding duration of therapy.

- The panel recommends lifelong therapy for all HBeAg-positive or -negative patients with decompensated cirrhosis at the start of therapy and for the majority of patients who had significant fibrosis (F3) or compensated cirrhosis (F4) at the start of therapy.

- Patients with compensated liver disease at the start of therapy may be discontinued from therapy if they experience HBsAg loss for 6–12 months or longer or HBsAg seroconversion.
- However, they must undergo lifelong screening for HCC even if they no longer have cirrhosis.
- For HBeAg-positive patients with histology <F3, the optimal duration of therapy is less clear.
- Historically, HBeAg seroconversion was considered a durable response, and discontinuation of antiviral therapy was recommended after a period of consolidation therapy of 6–12 months from the time of HBeAg seroconversion.

- However, patients who discontinue therapy after completing consolidation therapy can experience recurrent viremia and ALT flares. Thus, longterm therapy is justified even after HBeAg seroconversion and virologic suppression.

- HBeAg-positive patients who fail to lose HBeAg should be treated long-term because the chance of HBeAg seroconversion increases with time, and there is a high risk of recurring viremia if therapy is stopped in the absence of HBeAg seroconversion.

- For managing resistance to oral antiviral therapies, the members of the panel generally either use add-on therapy with tenofovir or entecavir or switch to combination tenofovir and emtricitabine. The exception is rescuing lamivudine resistance with tenofovir monotherapy.