Hepatitis B: How to manage in 2018

Seyed Moayed Alavian M.D.
Professor of Gastroenterology and Hepatology
Editor-in-chief of Hepatitis Monthly
E mail: editor@hepmon.com
HBV is a life long, dynamic disease

- Changes over time
- Risk of end stage liver disease and HCC increases with ongoing inflammation and viremia in adults
- Fibrosis can be reversible
- Drugs can decrease fibrosis progression
- HBV can be controlled but not cured
- Reactivation can occur even in those who have lost HBsAg
Barriers for Therapy in CHB

• Despite the approval of several anti-viral agents, very few patients are actually on treatment. There are many possible reasons for this, including the need for lifelong treatment, lack of education and awareness of the disease in the community, under screening for the condition in primary care settings,
Goals of treatment in chronic viral hepatitis B

• **Prevention of long-term negative clinical outcomes** (eg, cirrhosis, HCC, death) by durable suppression of HBV DNA

• **Remission of liver disease**

• **Primary treatment endpoint:** Sustained decrease in serum HBV DNA level to **low or undetectable**

• **Secondary treatment endpoints**
  • Decrease or normalize serum ALT
  • Induce HBeAg loss or seroconversion
  • Induce HBsAg loss or seroconversion
  • Improve liver histology
### Natural History of HBV - Revised Nomenclature

**EASL CPG on HBV**

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Liver disease</th>
<th>Old terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Positive</td>
<td>&gt;10E7 IU/mL</td>
<td>Normal</td>
<td>None/minimal</td>
<td>Immune tolerant</td>
</tr>
<tr>
<td>Low</td>
<td>Negative</td>
<td>&lt;2,000 IU/mL</td>
<td>Normal</td>
<td>None</td>
<td>Inactive carrier</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Negative</td>
<td>&gt;2,000 IU/mL</td>
<td>Elevated*</td>
<td>Moderate/severe</td>
<td>HBeAg negative Chronic hepatitis</td>
</tr>
</tbody>
</table>

**HBsAg Loss/Occult Hepatitis B**
- Serum HBV DNA phases, alternating undetectable and very low but detectable
- Detectable HBV DNA in the liver
- Intrahepatic replication-competent HBV genomes such as HBV cccDNA
- Integrated HBV DNA

*Persistently or intermittently

°° HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

**EASL 2017 Clinical Practice Guidelines on HBV, J Hepatol 2017**
6 Endpoints in HBV Treatment

Milestone 1: Start of decline of HBV infection

Milestone 2: HBeAg/anti-HBe seroconversion if there is wild type HBV infection

Milestone 3: HBV DNA decreased to undetectable

Milestone 4: Clearance of HBsAg

Milestone 5: Clearance of cccDNA

Milestone 6: Clearance of cells with integrated HBV DNA sequences

This is where we would like our patients to be

HBV DNA level

>10⁹ copies/mL

HBeAg/anti-HBe status

Undetectable level of HBV DNA

HBsAg status

normal ALT level

Immune low active

Immune high active/clearance

Inactive carrier state

Functional cure

Absolute cure

Imune control
Clinical Practice Guidelines Endpoints of Antiviral Therapy

1. The induction of **long-term suppression of HBV DNA** levels represents the **main endpoint** of all current treatment strategies.
   
   (Evidence level I, grade of recommendation 1)

2. **HBeAg loss**, with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a **valuable endpoint**, as it often represents a partial immune control of the chronic HBV infection.
   
   (Evidence level II-1, grade of recommendation 1)

3. A biochemical response defined as **ALT normalization** should be considered as an **additional endpoint**, which is achieved in most patients with long-term suppression of HBV replication.
   
   (Evidence level II-1, grade of recommendation 1)

4. **HBsAg loss**, with or without anti-HBs seroconversion, is an **optimal endpoint**, as it indicates profound suppression of HBV replication and viral protein expression.
   
   (Evidence level II-1, grade of recommendation 1)
**Clinical Practice Guidelines General Indications for Treatment**

1. **Patients with HBeAg-pos. or –neg. chronic hepatitis B**, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis.
   
   (Evidence level I, grade of recommendation 1)

2. Patients with compensated or decompensated **cirrhosis**, with any detectable HBV DNA level and regardless of ALT levels.
   
   (Evidence level I, grade of recommendation 1)

3. **HBV DNA >20,000 IU/ml and ALT >2xULN** regardless of the degree of fibrosis.
   
   (Evidence level II-2, grade of recommendation 1)

4. **HBeAg-pos. chronic HBV infection** (persistently normal ALT and high HBV DNA levels) > 30 yr regardless of histology
   
   (Evidence level III, grade of recommendation 2)

5. HBeAg-pos./ HBeAg-neg. **chronic HBV infection** + family history of HCC or cirrhosis and extrahepatic manifestations
   
   (Evidence level III, grade of recommendation 2)
When Antiviral Treatment Should Be Initiated?

APASL, AASLD & EASL recommend

Start treatment ASAP in life-threatening disease regardless of HBV-DNA and ALT levels

- Acute liver failure
- Decompensated cirrhosis
- Severe exacerbation of chronic hepatitis B

Drugs for HBV

• Seven drugs are now available for the treatment of chronic hepatitis B: they include
  • Conventional interferon alpha, and Pegylated interferon alpha
  • NUCs for HBV therapy belong to three classes:
    • **L-nucleosides** (lamivudine, telbivudine, emtricitabine)
    • **deoxyguanosine analogues** (entecavir)
    • **acyclic nucleoside phosphonates** (adefovir and tenofovir).
• **Entecavir and tenofovir** are potent HBV inhibitors and they have a high barrier to resistance.
• Thus they can be confidently used as **first-line mono-therapies**.
Nucleos(t)ide Analogue (NAs) for Treatment-Naive Chronic HBV patients

1. The **long-term administration of a potent NA** with high barrier to resistance **is the treatment of choice** regardless of the severity of liver disease

   (Evidence level I, grade of recommendation 1)

2. The **preferred regimens** are **Entecavir, Tenofovir Disoproxil Fumarate (TDF) and TAF** as monotherapies

   (Evidence level I, grade of recommendation 1)

3. Lamivudine, Adefovir and Telbivudine **are no longer recommended** in the treatment of chronic hepatitis B

   (Evidence level I, grade of recommendation 1)
Tenofovir Alafenamide (TAF) Prodrug of TFV Reduces Circulating TFV

- TAF is more stable in plasma compared with TDF
- TAF 25 mg has 92% lower circulating plasma TFV levels compared to TDF 300mg

Smaller Decline in Hip and Spine Bone Mineral Density with TAF vs TDF. Studies 108 & 110

Smaller Declines in eGFR and Lower Rates of CKD Stage Worsening with TAF vs TDF at wk 48

Improving Renal Safety. Tenofovir Alafenamide (TAF) Study 108 at wk 48 in HBeAg neg

**Indications for Selecting Entecavir or Tenofovir Alafenamide (TAF) over Tenofovir Disoproxil Fumarate**

<table>
<thead>
<tr>
<th>1. Age &gt;60 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Bone disease</td>
</tr>
<tr>
<td>Chronic steroid use or use of other medications that worsen bone density</td>
</tr>
<tr>
<td>History of fragility fracture</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>3. Renal alteration**</td>
</tr>
<tr>
<td>eGFR &lt;60 min/ml/1.73 m²</td>
</tr>
<tr>
<td>Albuminuria &gt;30 mg or moderate dipstick proteinuria</td>
</tr>
<tr>
<td>Low phosphate (&lt;2.5 mg/dl)</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
</tbody>
</table>

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) 15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.
# Naive Virological and Biochemical Response Rates Following 48/52 weeks of NA Therapy

## HBeAg pos.

<table>
<thead>
<tr>
<th></th>
<th>Nucleoside analogues</th>
<th>Nucleotide analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAM</td>
<td>TBV</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Anti-HBe-seroconversion</td>
<td>16–18%</td>
<td>22%</td>
</tr>
<tr>
<td>HBV DNA &lt;60–80 IU/ml</td>
<td>36–44%</td>
<td>60%</td>
</tr>
<tr>
<td>ALT normalisation*</td>
<td>41–72%</td>
<td>77%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0–1%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

## HBeAg neg.

<table>
<thead>
<tr>
<th></th>
<th>Nucleoside analogues</th>
<th>Nucleotide analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAM</td>
<td>TBV</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>HBV DNA &lt;60–80 IU/ml</td>
<td>72–73%</td>
<td>88%</td>
</tr>
<tr>
<td>ALT normalisation*</td>
<td>71–79%</td>
<td>74%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

CPG on HBV Therapy J Hepatol 2017
Cumulative Incidence of Selection of HBV Strains Resistant to Nucleos(t)ide analogues

Currently available data from pivotal trials (not head-to-head) in nucleos(t)ide-naïve patients with chronic hepatitis B

No evidence of resistance has been shown after 8 years of TDF treatment

EASL 2017 Clinical Practice Guidelines on HBV, J Hepatol 2017
## Extended NA in Naive. HBV Replication Is Successfully Controlled with Little/No Resistance

<table>
<thead>
<tr>
<th>Response</th>
<th>Entecavir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBeAg + (yr 5)</td>
<td>HBeAg - (yr 5)</td>
</tr>
<tr>
<td>HBV DNA suppression</td>
<td>99%</td>
<td>98%</td>
</tr>
<tr>
<td>Resistance</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>HBsAg loss (seroconversion)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*CPG on HBV Therapy J Hepatol 2017*
Tenofovir + PEG-IFN Increases HBsAg Loss Benefit Mainly in Geno A

HBsAg loss in 6/17 HBV geno A

Marcellin P et al. Gastroenterol 2016; 150: 134

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Recommended rescue strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM resistance</td>
<td>Switch to TDF or TAF</td>
</tr>
<tr>
<td>TBV resistance</td>
<td>Switch to TDF or TAF</td>
</tr>
<tr>
<td>ETV resistance</td>
<td>Switch to TDF or TAF</td>
</tr>
<tr>
<td>ADV resistance</td>
<td>If LAM-naïve: switch to ETV or TDF or TAF&lt;br&gt;If LAM-resistance: switch to TDF or TAF&lt;br&gt;If HBV DNA plateaus: add ETV*** or switch to ETV</td>
</tr>
<tr>
<td>TDF or TAF resistance</td>
<td>If LAM-naïve: switch to ETV&lt;br&gt;If LAM-R: add ETV*</td>
</tr>
<tr>
<td>Multidrug resistance</td>
<td>Switch to ETV plus TDF or TAF combination</td>
</tr>
</tbody>
</table>

* The long-term safety of these combinations is unknown.
** Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile.
*** Especially in patients with ADV resistant mutations (rA181T/V and/or rN236T) and high viral load, the response to TDF (TAF) can be protracted.
Outcome Following HBe Ag Seroconversion

- HBe Ag Loss
- HBeAg seroconversion
- Disease remission
- HBsAg loss/seroconversion
- Prevention of HCC
- Increased Survival

Lamivudine Reduces Risk of HBV Progression Including Decompensation. A RCT in AP

- 651 with HBV cirrhosis followed until HBeAg seroconversion or disease progression

![Graph showing the comparison between Lamivudine and Placebo in terms of progression of liver disease.](image)

<table>
<thead>
<tr>
<th>Pts With Disease Progression (%)</th>
<th>Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>30</td>
<td>36</td>
</tr>
</tbody>
</table>

- Lamivudine: n = 417, n = 198, n = 43
- Placebo: n = 385, n = 173, n = 122

P = .001

*Hepatic decompensation, HCC, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

The pattern of liver transplantation waiting list registration among patients with hepatitis B suggests that the widespread application of oral antiviral therapy for HBV contributed to the decreased incidence of decompensated liver disease.
Survival Benefits of NUC Therapy in HBV Patients with Decompensated Cirrhosis

Survival of treated vs untreated

Survival by treatment response

34% of treated patients delisted for LT

Jang et al, Hepatology 2015;61:1809-20
HBsAg Clearance Improves Survival

Survival in patients with and without HBsAg seroconversion:

retrospective study of 309 patients over a mean follow-up of 5.7 years

HBsAg Loss Decreases Subsequent Risk of HCC

REVEAL 2964 HBsAg, no cirrhosis

- Hazard ratio for HCC after sero clearance
  - HBeAg: 0.63
  - HBV DNA: 0.24
  - HBsAg: 0.18

- Among HBeAg (-) lifetime cumulative incidence of HCC for those clearing
  - Both HBV DNA and HBsAg: 4.0%
  - HBV DNA only: 6.6%
  - Neither: 14.2%

Liu J, Gut 2014; 63: 1648-57
Barriers to Curing Chronic Hepatitis B

Barriers

- Reservoir of cccDNA
- Dysfunctional T-cell response/exhaustion
- Insufficient or inadequate B-cell response

Strategic to overcome these barriers

- Deplete or silence cccDNA
- Improve potency of Polymerase inhibitors
- Broaden viral targets
- Activate antiviral immunity
The Clinical Benefits of Current NA Monotherapy
Take Home Message

- Current NAs improve disease outcome
  - Viral suppression and normalization of transaminases
  - Prevention of progression/regression of liver disease
  - Risk reduction of HCC
  - Reduced liver related mortality
  - Finite therapy possible following HBsAg loss/seroconversion

- No cure for HBV due to persistence of cccDNA
Duration of NUCs therapies

- Finite-duration treatment with NUCs is achievable for HBeAg-positive patients who develop HBe seroconversion on treatment.

- Long-term treatment with NUCs is necessary for patients who cannot achieve a sustained virological response off-treatment and require extended therapy, i.e. for HBeAg-positive patients who do not develop HBe seroconversion and in HBeAg-negative patients.
AASLD Guideline Recommendations for Duration of NA Treatment

**HBeAg-positive chronic hepatitis B:**
Treatment should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV DNA and completed at least 6 months of additional treatment after appearance of anti-HBe.

- Close monitoring for relapse is needed after withdrawal of treatment.

**HBeAg-negative chronic hepatitis B:**
Treatment should be continued until the patient has achieved HBsAg clearance.

EASL Clinical Practice Guidelines 2017
Can NAs Be Discontinued?

NAs should be discontinued

1. **After confirmed HBsAg loss**, with or without anti-HBs seroconversion

   (Evidence level II-2, grade of recommendation 1)

Nas can be discontinued

2. **In non-cirrhotic HBeAg pos.** patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and after completing ≥12 months of consolidation therapy. Close post-treatment monitoring is warranted

   (Evidence level II-2, grade of recommendation 2)

3. **In selected non-cirrhotic HBeAg-neg.** patients who have achieved long-term (3 years) virological suppression under NA(s) if close post-NA monitoring can be guaranteed

   (Evidence level II-2, grade of recommendation 2)
## Stopping Rules for NA Therapy in Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Patient hepatitis status</th>
<th>APASL 2016</th>
<th>EASL 2017</th>
<th>AASLD 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>without liver cirrhosis</td>
<td>therapy, but preferably after 3 years of additional therapy after HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels</td>
<td>NA therapy after HBeAg seroconversion, or treat until HBsAg loss</td>
<td>of NA therapy after HBeAg seroconversion with undetectable HBV and persistently normal ALT levels, or treat until HBsAg loss</td>
</tr>
<tr>
<td>HBeAg (-)</td>
<td>i ) HBsAg loss, following either anti- HBs seroconversion, or at least 12 months of post-HBsAg clearance consolidation period, or ii ) after treatment of at least 2 years with undetectable HBV DNA documented on 3 separate occasions, 6 months apart</td>
<td>i ) HBsAg loss, ii ) selected patients who have achieved long-term (&gt;3 years) virological suppression under NA</td>
<td>Long term treatment with NA until HBsAg loss.</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>Indefinite treatment with NA regardless of HBV DNA levels and HBeAg status</td>
<td>Indefinite treatment with NA regardless of HBeAg status or HBeAg seroconversion</td>
<td>Indefinite treatment with NA regardless of HBeAg status or HBeAg seroconversion</td>
</tr>
</tbody>
</table>

Kho-Herman SGR & Chan HLY, Liver Res. 2017
## Clinical Questions Evaluated

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Immune-active CHB</td>
<td>Antiviral therapy</td>
<td>No treatment</td>
<td>Cirrhosis, decompensation, HCC, death, loss of HBsAg</td>
</tr>
<tr>
<td>2</td>
<td>Immune-tolerant CHB, adults</td>
<td>Antiviral therapy</td>
<td>No treatment</td>
<td>Cirrhosis, decompensation, HCC, death, loss of HBsAg</td>
</tr>
<tr>
<td>3</td>
<td>HBeAg-positive immune-active chronic hepatitis, with HBeAg seroconversion on therapy</td>
<td>Continued antiviral therapy</td>
<td>Stopping antiviral therapy</td>
<td>Cirrhosis, HCC, reactivation, seroreversion, decompensation, loss of HBsAg</td>
</tr>
<tr>
<td>4</td>
<td>HBeAg-negative immune-active chronic hepatitis, with viral suppression on antiviral therapy</td>
<td>Continued antiviral therapy</td>
<td>Stopping antiviral therapy</td>
<td>Reactivation, decompensation, loss of HBsAg</td>
</tr>
<tr>
<td>5</td>
<td>CHB on treatment with oral therapy</td>
<td>Tenofovir</td>
<td>Entecavir</td>
<td>Renal function, hypophosphatemia, bone health</td>
</tr>
<tr>
<td>6</td>
<td>CHB on treatment with oral therapy with persistent viremia</td>
<td>Continue therapy</td>
<td>Change or switch therapy</td>
<td>HBV resistance, clinical flare, decompensation, loss of HBeAg</td>
</tr>
<tr>
<td>7</td>
<td>CHB with cirrhosis, with HBV DNA &lt;2,000 IU/mL</td>
<td>Antiviral therapy</td>
<td>No treatment</td>
<td>Decompensation, HCC, death</td>
</tr>
<tr>
<td>8</td>
<td>Pregnant women with CHB</td>
<td>Antiviral therapy in third trimester</td>
<td>No treatment</td>
<td>CHB in the infant, maternal safety, fetal/infant safety</td>
</tr>
<tr>
<td>9</td>
<td>HBeAg-positive CHB, children/adolescents</td>
<td>Antiviral therapy</td>
<td>No treatment</td>
<td>Cirrhosis, decompensation, HCC, death, HBeAg seroconversion, loss of HBsAg</td>
</tr>
</tbody>
</table>

TDF Reduces Perinatal Transmission of Hepatitis B Virus in Highly Viremic Mothers: A Multi-Center, Prospective, RCT

- Birth defect rates: 2.11% with TDF exposure vs. 1.14% without exposure (P = 1.00)

- The HBV serologic outcome did not differ between groups

Clinical Practice Guidelines
NA + NA and NA + Peg-IFNa Combinations

NOT RECOMMENDED:

1. **De novo combination** of NA and Peg-IFNa.
   - Evidence level I, grade of recommendation 1

2. In **treatment naïve HBeAg-pos** patients, short-term NA treatment before Peg-IFNa.
   - Evidence level II, grade of recommendation 1

3. In **long-term NA suppressed** CHB patients, adding Peg-IFNa or switching to Peg-IFNa.
   - Evidence level II, grade of recommendation 1

4. **De novo combination therapy with two NAs** with high barrier to resistance
   - Evidence level I, grade of recommendation 1