Hepatitis B: How to manage in 2021-2022

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Global Elimination Strategy 2015 Baseline Towards 2030 Targets

Prevention
- HBV- Vaccination
- HBV- PMTCT
- Blood safety
- Injection safety
- Harm reduction

Care and treatment
- HBV - Diagnosis
- HCV - Diagnosis
- HBV- Treatment
- HCV- Treatment

Coverage (%)
Goals of treatment in chronic viral hepatitis

Prevention of:

- Progression of disease
- Development of cirrhosis
- Development of HCC
- Death from liver disease
- Decreasing the chance of transmission
# Natural History of HBV - Revised Nomenclature

EASL CPG on HBV

<table>
<thead>
<tr>
<th></th>
<th>HBeAg positive Chronic infection</th>
<th>HBeAg positive Chronic hepatitis</th>
<th>HBeAg negative Chronic infection</th>
<th>HBeAg negative Chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>High</td>
<td>High/Intermediate</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>$&gt;10^7$ IU/mL</td>
<td>$10^4$-$10^5$ IU/mL</td>
<td>&lt;$2,000$ IU/mL</td>
<td>$&gt;2,000$ IU/mL</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated*</td>
</tr>
<tr>
<td>Liver disease</td>
<td>None/minimal</td>
<td>Moderate/severe</td>
<td>None</td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Old terminology</td>
<td>Immune tolerant</td>
<td>Immune reactive HBeAg positive</td>
<td>Inactive carrier</td>
<td>HBeAg negative Chronic hepatitis</td>
</tr>
</tbody>
</table>

*Persistently or intermittently

$^{\text{o}}$ HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis
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)
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

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

# 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.

EASL 2017 Clinical Practice Guidelines on HBV, J Hepatol 2017
Naive: Virological and Biochemical Response Rates Following 48/52 weeks of NA Therapy

<table>
<thead>
<tr>
<th></th>
<th>HBeAg pos.</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nucleoside analogues</td>
<td>Nucleotide analogues</td>
</tr>
<tr>
<td></td>
<td>LAM</td>
<td>TBV</td>
<td>ETV</td>
</tr>
<tr>
<td>Dose*</td>
<td>100 mg</td>
<td>600 mg</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Anti-HBe-seroconversion</td>
<td>16–18%</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>HBV DNA &lt;60–80 IU/ml</td>
<td>36–44%</td>
<td>60%</td>
<td><strong>67%</strong></td>
</tr>
<tr>
<td>ALT normalisation*</td>
<td>41–72%</td>
<td>77%</td>
<td>68%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0–1%</td>
<td>0.5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HBeAg neg.</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Nucleoside analogues</td>
<td>Nucleotide analogues</td>
</tr>
<tr>
<td></td>
<td>LAM</td>
<td>TBV</td>
<td>ETV</td>
</tr>
<tr>
<td>Dose*</td>
<td>100 mg</td>
<td>600 mg</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>HBV DNA &lt;60–80 IU/ml</td>
<td><strong>72–73%</strong></td>
<td>88%</td>
<td><strong>90%</strong></td>
</tr>
<tr>
<td>ALT normalisation*</td>
<td>71–79%</td>
<td>74%</td>
<td>78%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

CPG on HBV Therapy 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></th>
<th>Tenofovir</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBeAg + (yr 5)</td>
<td>HBeAg - (yr 5)</td>
<td>HBeAg + (yr 5)</td>
<td>HBeAg - (yr 8)</td>
</tr>
<tr>
<td>HBV DNA suppression</td>
<td>99%</td>
<td>98%</td>
<td>97%</td>
<td>99%</td>
</tr>
<tr>
<td>Resistance</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>HBsAg loss (seroconversion)</td>
<td>NR</td>
<td>NR</td>
<td>10% (8%)</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

CPG on HBV Therapy J Hepatol 2017
## 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)
EASL Clinical Practice Guidelines 2017
NA + NA and NA + Peg-IFNa Combinations

NOT RECOMMENDED:

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

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

3. In **long-term NA suppressed** CHB patients, adding Peg-IFN a or switching to Peg-IFN a
   
   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
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
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

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
Decompensated HCV. Reduction in Liver Transplant Wait-Listing in the Era of DAA Therapy

Individuals listed for liver transplant in SRTR
Jan 1, 2003 – Dec 31, 2015
n = 138,997

- 9,593: < 18 years at listing
- 8,101: previous LT
- 36,622: MELD <15 no HCC
- 37,090: other etiologies, status 1

Final Cohort: n = 47,591
- HCV: 33,947 (71.3%)
- HBV: 3,469 (7.3%)
- NASH: 10,195 (21.4%)

A HCV
B HBV
C NASH

Year of wait-list registration

- Decompensated Cirrhosis
- Hepatocellular Carcinoma
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
## The Importance of TDF/ETV Treatment Duration

<table>
<thead>
<tr>
<th>Cohort</th>
<th>1946 Caucasian, 794 treated for &gt; 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed HCC</td>
<td>90 (4.6%) within the first 5 yrs of therapy</td>
</tr>
<tr>
<td></td>
<td>7 (0.9%) beyond 5 yrs of therapy</td>
</tr>
<tr>
<td>HCC rate x year</td>
<td>1.22% (C.I. 0.99-1.50%) within 5 yrs</td>
</tr>
<tr>
<td></td>
<td>0.63% (C.I 0.30-1.32%) beyond 5 yrs</td>
</tr>
<tr>
<td>Decreased HCC</td>
<td>First 5 yr vs beyond 5 yrs: 3.27% vs 1.07% p = 0.046</td>
</tr>
</tbody>
</table>
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

Courtesy of Prof. S. Locarnini
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
Stop or not stop New experience in NA Therapy in Chronic Hepatitis B

In HBsAg negative cases: without relapse during the 96-week follow-up

In HBsAg-positive after cessation, four types of clinical outcomes during the 96-week follow-up:

21.8% no relapse
12.7% underwent virological relapses but spontaneously had a non-virological relapse
18.2% maintained virological relapse
47.3% turned to clinical relapse, received NA retreatment, and achieved ALT normalization and negative conversion of HBV DNA within 12 months

➢ In Conclusion:

➢ Independent factors associated with virological relapse were:

➢ Duration of negative HBV DNA, EOT (end of treatment) HBsAg, and original status of HBeAg.

➢ The EOT HBsAg was also an independent factor for clinical relapse.

➢ It is soon to decide to stop the drugs before HBs Ag negativity

N=37 studies met inclusion criteria. Cumulative incidence of virological relapse and clinical relapse after stopping ETV/TDF was 44% and 17% at 6 months and 63% and 35% at 12 months.

Among patients stopping ETV/TDF, TDF cessation was associated with increased CR rates at 6 months versus ETV.

Hepatic decompensation and hepatocellular carcinoma were rare but occurred more frequently in studies including cirrhotic individuals.

**Conclusion:** VR is common after NA discontinuation, however, CR was only seen in one-third of patients at 12 months. Stopping NA therapy can be followed by HBsAg clearance, and rates are higher with longer follow-up.
A total of 72 pregnant women, who met the inclusion criteria, were randomly divided into the TDF (300 mg/day, n = 36) and TAF (25 mg/day, n = 36) groups.

The serum HBV DNA viral load and HBeAg levels of the two groups were significantly decreased following treatment.

All drug concentrations were undetectable in umbilical cord blood (UCB) and breast milk samples of the TAF group, while the drug concentration of UCB and breast milk samples in the TDF group was 2.98 ± 1.44 and 19.16 ± 15.26 ng/ml, respectively.

All infants were tested negative for serum hepatitis B surface antigen, HBV DNA, and HBeAg.

**Conclusions:** Both TAF and TDF effectively block the mother-to-child transmission of hepatitis B. **TAF was superior to TDF with regard to renal safety and breastfeeding.**
Toward a complete cure for chronic hepatitis B: Novel therapeutic targets for hepatitis B virus

Hepatitis B virus (HBV) affects approximately 250 million patients worldwide, resulting in the progression to cirrhosis and hepatocellular carcinoma, which are serious public health problems. Although universal vaccination programs exist, they are only prophylactic and not curative. In the HBV life cycle, HBV forms covalently closed circular DNA (cccDNA), which is the viral minichromosome, in the nuclei of human hepatocytes and makes it difficult to achieve a complete cure with the current nucleos(t)ide analogs and interferon therapies. Current antiviral therapies rarely eliminate cccDNA; therefore, lifelong antiviral treatment is necessary. Recent trials for antiviral treatment of chronic hepatitis B have been focused on establishing a functional cure, defined by either the loss of hepatitis B surface antigen, undetectable serum HBV DNA
When myrcludex B was used in combination with Peg-IFNα over 48 weeks, HBsAg decline was achieved in 46.7% of the subjects, indicating a potential role for myrcludex B in future HBV curative regimens.

REP2139 and REP 2165 are Nucleic acid polymers (NAPs) that inhibit the assembly and secretion of HBV SVP. In a phase 2 clinical trial, 48-week combination treatment with TDF, Peg-IFNα, and NAP showed HBsAg loss in 60% of the participants; The functional cure persisted in 35% of the participants during 48 weeks of treatment-free follow up. ARC-521 was the first siRNA against HBV designed to reduce all mRNA transcripts derived from cccDNA to be investigated in clinical trials.

In a preclinical study, CRISPR/Cas9 system treatment showed encouraging results, showing that more than 90% of HBV DNA was cleaved by Cas9.

pradefovir, which are prodrugs of tenofovir and adefovir, respectively, showed comparable efficacy to TDF in a phase 2 clinical study and are in a phase 3 clinical infect study.
## 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 (-) without liver cirrhosis</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