EASL HBV guidelines 2017

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Disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN
Clinical Practice Guidelines

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

European Association for the Study of the Liver*

Chair: Pietro Lampertico

Panel members:
Kosh Agarwal, Thomas Berg, Maria Buti, Harry L.A. Janssen, George Papatheodoridis, Fabien Zoulim; EASL Governing Board representative: Frank Tacke

Reviewers:
EASL Governing Board, Maurizia Brunetto, Henry Chan, Markus Cornberg
HBV clinical practice guidelines - topics

1) Goals of therapy
2) Endpoints of therapy
3) Indications for treatment
4) Monitoring of patients currently not treated
5) Treatment strategies
6) Definition of response
7) NA monotherapy (efficacy, safety, long-term outcome……)
8) Peg-IFNalpha monotherapy (efficacy, safety, long-term outcome…)
9) Combination therapy (NA+NA, NA + PEG-IFN)
10) Patients with decompensated cirrhosis
11) Prevention of HBV recurrence after LT
12) Treatment of special populations (coinfection, acute hepatitis, children….)

EASL 2017 CPG HBV, J Hepatol 2017
# Natural history of HBV and treatment indications

<table>
<thead>
<tr>
<th>PHASE</th>
<th>1</th>
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* HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis
** Persistently or intermittently
*** Treatment is indicated in some patients

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** Persistently or intermittently: *** Treatment is indicated in some patients; \(^a\) in >95% of patients but HBV-DNA frequently detectable in the liver; \(^b\) residual HCC risk only if cirrhosis has developed before HBsAg loss

\(^*\) HBsAg negative/anti-HBcore positive

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* EASL 2017 CPG HBV, J Hepatol 2017
Indications for treatment

Recommendations:

1) All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated. (Evidence level I, grade of recommendation 1)

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

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

4) Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions. (Evidence level III, grade of recommendation 2)

5) Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled. (Evidence level III, grade of recommendation 2)
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** Persistently or intermittently

*** Treatment is indicated in some patients

EASL 2017 CPG HBV, J Hepatol 2017
Endpoints of therapy

Recommendations:

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) The induction of 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)
Main concepts and features of current treatment strategies for HBV

<table>
<thead>
<tr>
<th>Features</th>
<th>PegIFNα</th>
<th>ETV, TDF, TAF</th>
</tr>
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<tbody>
<tr>
<td>Route of administration</td>
<td>Subcutaneous injections</td>
<td>Oral</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>48 weeks</td>
<td>Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)¹</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Long-term safety concerns</td>
<td>Very rarely persistence of on-treatment adverse events (psychiatric, neurological, endocrinological)</td>
<td>Probably not (uncertainties regarding kidney function, bone diseases for some NA)</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Many (i.e., decompensated disease, co-morbidities etc.)</td>
<td>None (dose adjustment according to eGFR²)</td>
</tr>
<tr>
<td>Strategy</td>
<td>Induction of a long-term immune control by finite treatment</td>
<td>Stopping hepatitis and disease progression by inhibiting viral replication</td>
</tr>
<tr>
<td>Level of viral suppression</td>
<td>Moderate (variable response pattern)</td>
<td>Universally high</td>
</tr>
<tr>
<td>Effect on HBeAg loss</td>
<td>Moderate, depending on baseline characteristics</td>
<td>Low in the first year, increases to moderate during long-term treatment</td>
</tr>
<tr>
<td>Effect on HBsAg levels</td>
<td>Variable, depending on baseline characteristics (overall higher as compared to NA)</td>
<td>Low: slowly increases with treatment time in HBeAg-positive patients³; usually very low in HBeAg-negative patients</td>
</tr>
<tr>
<td>Risk of relapse after treatment cessation</td>
<td>Low for those with sustained response 6–12 months after therapy</td>
<td>Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease</td>
</tr>
<tr>
<td>Early stopping rules</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk of viral resistance development</td>
<td>No</td>
<td>Minimal to none⁴</td>
</tr>
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1. See section on ‘Treatment strategies’.
2. Dose adjustments in patients with eGFR <50 ml/min are required for all NA, except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis).
3. A plateau in serologic responses has been observed beyond treatment year 4.
4. So far no TDF or TAF resistance development has been detected.

Table 2  EASL 2017 CPG HBV, J Hepatol 2017
Cumulative incidence of HBV resistance for NA in pivotal trials in nucleos(t)ide-naïve patients with CHB

Collation of currently available data – not from head-to-head studies

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

Figure 3

EASL 2017 CPG HBV, J Hepatol 2017
Indications for selecting ETV or TAF over TDF*

<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.
NA discontinuation

Recommendations:

1) NAs **should be discontinued after confirmed HBsAg loss**, with or without anti-HBs seroconversion. (Evidence level II-2, grade of recommendation 1).

2) NAs **can be discontinued in non-cirrhotic HBeAg positive** CHB patients who achieve **stable HBeAg seroconversion** and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted. (Evidence level II-2, grade of recommendation 2)

3) **Discontinuation of NAs in selected non-cirrhotic HBeAg-negative** patients who have achieved long-term (3 years) virological suppression under NA(s) **may be considered** if close post-NA monitoring can be guaranteed. (Evidence level II-2, grade of recommendation 2)
NUC discontinuation in HBeAg negative CHB before HBsAg loss

Potential outcome predictors

- Age, time to undetectable HBV DNA, and duration of viral suppression under NA, HBsAg levels at NA baseline and NA cessation, type of NA (TDF vs. ETV), HBV DNA levels during reactivation phase, retreatment strategy, and HBV genotype

Treatment phase (> 3 years)  Lag-phase (<1-12 months)  Reactivation phase (~ 3 months)  Consolidation phase (~ 12 months)  Long-term outcome

A) HBsAg loss (~ 20% after 2-3 years of follow-up)
B) Sustained virologic response (true „healthy carrier“ state) ± HBsAg level decline ~ 20-30%
C) Indeterminate state not fulfilling immediate retreatment criteria (~ 10-20%)
D) Chronic hepatitis B requiring re-treatment (~ 40%)

Lampertico P and Berg T, Hepatology 2018 in press
Management of HDV co-infected patients

Recommendations:

1) **PegIFNa** for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease. (Evidence level I, grade of recommendation 1)

2) In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered. (Evidence level II-2, grade of recommendation 1)

3) PegIFNa treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated. (Evidence level II-2, grade of recommendation 2)
## Management of HCV coinfected patients

### Recommendations:

1) Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment. (Evidence level II, grade of recommendation 1)

2) HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely. (Evidence level II-2, grade of recommendation 2)

3) HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation. (Evidence level II, grade of recommendation 1)
Prevention of HBV recurrence after liver transplantation

**Recommendations:**

1) **All patients on the transplant waiting list** with HBV related liver disease **should be treated with NA.** (Evidence level II, grade of recommendation 1)

2) **Combination** of hepatitis B immunoglobulin (HBIG) and a potent NA is **recommended** after liver transplantation for the prevention of HBV recurrence. (Evidence level II-1, grade of recommendation 1)

3) Patients with a low risk of recurrence **can discontinue HBIG** but need continued monoprophylaxis with a potent NA. (Evidence level II-1, grade of recommendation 2)

4) HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA. (Evidence level II-2, grade of recommendation 1)

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Pregnancy and HBV

Recommendations:

1) **Screening** for HBsAg in the first trimester of pregnancy is strongly recommended. (Evidence level 1, grade of recommendation 1)

2) **In a woman of childbearing age** without advanced fibrosis who plans a pregnancy in the near future, it may be prudent to delay therapy until the child is born. (Evidence level II-2, grade of recommendation 2)

3) **Pregnant women with CHB and advanced fibrosis or cirrhosis**, therapy with TDF is recommended. (Evidence level II-2, grade of recommendation 1)

4) **In pregnant women already on NA therapy**, TDF should be continued while ETV or other NA should be switched to TDF. (Evidence level II-2, grade of recommendation 1)

5) **In all pregnant women with high HBV DNA levels** (>200,000 IU/ml) or HBsAg levels >4 log10 IU/ml, antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery. (Evidence level 1, grade of recommendation 1)

6) **Breast feeding is** not contraindicated in HBsAg positive untreated women or on TDF-based treatment or prophylaxis. (Evidence level III, grade of recommendation 2)
Patients undergoing immunosuppressive therapy or chemotherapy

Recommendations:

1) **All candidates** for chemotherapy and immunosuppressive therapy **should be tested** for HBV markers prior to immunosuppression. (Evidence level I, grade of recommendation 1)

2) **All HBsAg-positive patients** should receive ETV or TDF or TAF as treatment or prophylaxis. Evidence level II-2, grade of recommendation 1)

3) **HBsAg-negative, anti-HBc positive** subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation. (Evidence level II-2, grade of recommendation 1)
Algorithm for the management of HBV infection

Suspected HBV infection

HBsAg positive

Chronic HBV infection¹
(no signs of chronic hepatitis)

Monitor
(includes HBsAg HBeAg, HBV DNA, ALT, fibrosis assessment)

Consider
Risk of HCC, risk of HBV reactivation, extrahepatic manifestations, risk of HBV transmission

Chronic hepatitis B (CHB) ± cirrhosis¹

Start antiviral treatment

HBsAg negative, anti-HBc positive

No specialist follow-up but inform patient and general practitioner about the potential risk of HBV reactivation

In case of immunosuppression, start oral antiviral prophylaxis or monitor

Figure 2
Standard and New markers for HBV

Standard markers:
- qHBsAg
- HBeAg/anti-HBe
- HBV-DNA levels
- Anti-HBc

New markers:
- ultra sens qHBsAg
- HBcAg levels
- ultra sens HBV-DNA
- Anti-HBc levels
- HBcAg
- HBV-RNA levels
- Different HBsAg proteins

* No commercially available assays available
The "future" of HBV management

- New biomarkers (cccDNA, HBcrAg, HBV-RNA)
- Future treatment options for HBV
- Future treatment options for HDV
## Unresolved issues and unmet needs

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<td>1</td>
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<td>2</td>
<td>Stopping rules for HBeAg-negative patients treated with NA</td>
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<tr>
<td>3</td>
<td>Retreatment criteria after NA discontinuation</td>
</tr>
<tr>
<td>4</td>
<td>How to accelerate HBsAg decline in long-term NA treated patients?</td>
</tr>
<tr>
<td>5</td>
<td>Better baseline or on-treatment predictors of sustained treatment in patients treated with PegIFNa</td>
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<td>6</td>
<td>Definition of the residual risk of HCC in patients on long-term</td>
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<td>NA therapy and impact on surveillance</td>
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<td>8</td>
<td>Unmet need: new treatments with finite duration and high cure rates</td>
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<tr>
<td>9</td>
<td>How to define a cure of HBV infection? Definition of novel endpoints</td>
</tr>
<tr>
<td>10</td>
<td>Biomarkers for the cure of infection and for the cure of the liver disease</td>
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Back-up slides
Phase 5 – "resolved" HBV infection

- HBsAg neg, anti-HBc pos (anti-HBs pos/neg, anti-HBe pos/neg)
- Undetectable serum HBV-DNA in >90%, normal ALT
- Long-lasting persistence of HBV genomes in the liver with active HBV replication in few liver cells
- Different nomenclature partially overlapping (Occult HBV Infection, recovery phase, functional cure…….)
- Outcome of different clinical situations (acute HBV, spontaneous or drug-induced HBsAg loss, inactive cirrhosis…….)
- Residual HCC risk (age and gender)
- HBV may reactivate during immunosuppression

EASL HBV Guidelines, J Hepatol 2017