HBV TREATMENT GUIDELINES AND GUIDANCE

ABDURAKHMANOV D.T.
Department of internal, occupational diseases and rheumatology
Who needs to be treated and why?
How to treat and when to stop?
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Non-cirrhotic patients

* Elevated ALT levels
  - [EASL, APASL]: >40 IU/ml;
  - [AASLD]: >35 IU/ml (male) and >25 IU/ml (female);
Who needs to be treated and why?

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  - [AASLD]: >35 IU/ml (male) and >25 IU/ml (female);

**AASLD ALT value**
* For healthy persons:*
  * <31 IU/ml (for male)*
  * <19 IU (for female)*
* For treatment decisions:*
  * >35 IU/ml (for male)*
  * >25 (for female)*

**APASL ALT value definition**
* ULN is 40 IU/ml*
  * Low normal (≤0.5 ULN)*
  * High normal (>0.5 and <1 ULN)*
  * Minimally raised (>1 and <2 ULN)*
  * Raised (≥2 ULN)*

**EASL ALT value definition**
* ULN is 40 IU/ml*
Who needs to be treated and why?

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  * [AASLD-2018]: >35 IU/ml (male) and >25 IU/ml (female);

* HBV DNA levels
  * [EASL]: >2000 IU/ml;
  * [AASLD, APASL]:
    * >20000 IU/ml (for HBeAg-pos)
    * >2000 IU/ml (for HBeAg-neg);
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  - [AASLD, APASL]: >20000 IU/ml (for HBeAg-pos) and >2000 IU/ml (for HBeAg-neg);

* Severe inflammation (A2 or A3) or significant fibrosis (≥F2) [Liver biopsy by METAVIR]
  - [EASL]: Liver stiffness >9 kPa (for normal ALT) or >12 kPa (for elevated ALT but below 5x ULN);
  - [APASL]: Liver stiffness ≥8 kPa or APRI≥1.5;
  - [AASLD]: Liver stiffness cut-off value not indicated (F≥2)
Who needs to be treated and why?

* Elevated ALT levels
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Patients with cirrhosis should be treated if any detectable HBV DNA, regardless of ALT level
## Indications for treatment

Primarily based on the combination of 3 criteria

* HBV DNA, serum ALT and severity of liver disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Should be treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients with HBeAg-positive or -negative chronic hepatitis B*</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>• Patients with HBV DNA &gt;20,000 IU/mL and ALT &gt;2x ULN, regardless of severity of histological lesions</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td><strong>May be treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients with HBeAg-positive chronic HBV infection†</td>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td>&gt;30 years old, regardless of severity of liver histological lesions</td>
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<tr>
<td><strong>Can be treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations‡</td>
<td>III</td>
<td>2</td>
</tr>
</tbody>
</table>

*Defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis;
†Defined by persistently normal ALT and high HBV DNA levels;
‡ Even if typical treatment indications are not fulfilled
HBV GUIDELINES AND GUIDANCE

- Who needs to be treated and why?
- How to treat and when to stop?
HBV life cycle and therapeutic targets

Janssen H., Reijnders J., Sonneveld M. In Zakim and Boyer ‘s Hepatology, 2017
HBV life cycle and therapeutic targets

Janssen H., Reijnders J., Sonneveld M. In Zakim and Boyer ‘s Hepatology, 2017
# First-Line Antiviral Therapies in Adults with Chronic Hepatitis B (Not Head-to-Head Comparisons)

<table>
<thead>
<tr>
<th></th>
<th>Peg-IFN*</th>
<th>Entecavir†</th>
<th>Tenofovir Disoproxil Fumarate†</th>
<th>Tenofovir Alafenamide†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg Positive</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>% HBV-DNA suppression (cutoff to define HBV-DNA suppression)</td>
<td>30-42 (&lt;2,000-40,000 IU/mL)</td>
<td>61 (&lt;50-60 IU/mL)</td>
<td>76 (&lt;60 IU/mL)</td>
<td>73 (&lt;29 IU/mL)</td>
</tr>
<tr>
<td>% HBeAg loss</td>
<td>32-36</td>
<td>22-25</td>
<td>—</td>
<td>22</td>
</tr>
<tr>
<td>% HBeAg seroconversion</td>
<td>29-36</td>
<td>21-22</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>% Normalization ALT</td>
<td>34-52</td>
<td>68-81</td>
<td>68</td>
<td>—</td>
</tr>
<tr>
<td>% HBsAg loss</td>
<td>2-7</td>
<td>4-5</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>(at 3 years posttreatment)</td>
<td>11</td>
<td></td>
<td></td>
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<tr>
<td><strong>HBeAg Negative</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>% HBV-DNA suppression (cutoff to define HBV-DNA suppression)</td>
<td>43 (&lt;4,000 IU/mL)</td>
<td>90-91 (&lt;50-60 IU/mL)</td>
<td>93 (&lt;60 IU/mL)</td>
<td>90 (&lt;29 IU/mL)</td>
</tr>
<tr>
<td>% Normalization ALT</td>
<td>59</td>
<td>78-88</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>% HBsAg loss</td>
<td>4</td>
<td>0-1</td>
<td>0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>(at 3 years posttreatment)</td>
<td>6</td>
<td></td>
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</tbody>
</table>

References: (6-16).

*Assessed 6 months after completion of 12 months of therapy.
†Assessed after 3 years of continuous therapy.
‡Assessed after 2 years of continuous therapy.
§HBV DNA <2,000-40,000 IU/mL for peg-IFN; <60 IU/mL for entecavir and tenofovir disoproxil fumarate; <29 IU/mL for tenofovir alafenamide.
¶HBV DNA <20,000 IU/mL for peg-IFN; <60 IU/mL for entecavir and tenofovir disoproxil fumarate; <29 IU/mL for tenofovir alafenamide.
¶ALT normalization defined by laboratory normal rather than ≤35 and ≤25 U/L for males and females.
Baseline Predictors of Response to Treatment With Peg-IFN-α

<table>
<thead>
<tr>
<th>HBeAg-Positive Patients</th>
<th>HBeAg-Negative Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype A/B</td>
<td>Higher ALT</td>
</tr>
<tr>
<td>Higher ALT</td>
<td>Lower HBV DNA</td>
</tr>
<tr>
<td>Lower HBV DNA</td>
<td>Younger age</td>
</tr>
<tr>
<td>Older age</td>
<td>Female sex</td>
</tr>
<tr>
<td>Female sex</td>
<td>Lower HBsAg</td>
</tr>
<tr>
<td>Lower HBsAg</td>
<td></td>
</tr>
<tr>
<td>Lower HBeAg</td>
<td></td>
</tr>
</tbody>
</table>

Baseline parameters associated with higher response rates to 1 year of pegylated interferon-α therapy. Variables associated with response on a continuous scale are designated higher or lower if cutoff levels were not reported.

Janssen H., Reijnders J., Sonneveld M. In Zakim and Boyer ‘s Hepatology, 2017
Predictors of Peg-IFNα response and stopping rules

HBeAg-positive chronic hepatitis B*

- Genotype
  - A
    - Week 12: Stop if HBsAg
    - Week 24: No decline
  - B
    - Week 12: No decline
    - Week 24: >20,000 IU/ml
  - C
    - Week 12: >20,000 IU/ml
    - Week 24: >20,000 IU/ml
  - D
    - Week 12: No decline
    - Week 24: >20,000 IU/ml

HBeAg-negative chronic hepatitis B (genotype D)†

- HBsAg levels
  - Week 12
  - Any decline: Continue
  - No decline
    - >2 log_{10} decline: Continue
    - <2 log_{10} decline: Stop

*Evidence level II-2, grade of recommendation 2; †Evidence level II-2, grade of recommendation 1
**Indications for selecting ETV or TAF over TDF**

*In some circumstances ETV or TAF may be a more appropriate treatment choice than TDF*

<table>
<thead>
<tr>
<th>Age</th>
<th>• &gt;60 years</th>
</tr>
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</table>
| Bone disease | • Chronic steroid use or use of other medications that worsen bone density  
• History of fragility fracture  
• Osteoporosis |
| Renal alteration† | • eGFR <60 ml/min/1.73 m²  
• Albuminuria >30 mg/24 h or moderate dipstick proteinuria  
• Low phosphate (<2.5 mg/dl)  
• Haemodialysis |

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

EASL CPG HBV. J Hepatol 2017;67:370–98
EASL Recommendations for NAs cessation

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)
Novel biomarkers to predict off-treatment response

* **Viral markers to predict outcome after NAs cessation**
  
  • End of treatment qHBsAg level (cut-off have not yet been defined)
  
  • HBsAg kinetics during treatment
  
  • Quantification of serum Hepatitis B core-related antigen (HBcrAg) and/or of circulating viral RNAs appearing promising
  
  • Need for assay standardization and evaluation in clinical trials
Outcome after long-term NAs treatment cessation

End of treatment qHBsAg level as a guide for safe NAs cessation?

36 patients treated with NAs (mean duration - 77.4±23.5 mo)

Before NAs therapy
- HBeAg-positive, n (%) - 5 (13.9%)
- HBV genotype D, n (%) - 21 (91.3%)

Type of NAs therapy, n (%)
- ETV - 26 (72.2%)
- TDF - 4 (11.1%)
- TBV - 6 (16.7%)

Off-treatment follow-up – 24 mo

Abdurakhmanov D.T. et al. personal observation, 2018
CURRENT OPTIONS:

• Peg-IFN-alfa (for 1 year) ± NAs (if HBV-DNA > 2000 IU/ml);

FUTURE OPTIONS:

• Peg-IFN-λ
• Nuclear Acid Polymers
• Lonafarnib
• Myrcludex-B
HDV treatment with Peg-IFN-alfa

Peg-IFN-alfa once a week during 1 year

**COMPLETE RESPONSE**
HDV-RNA-neg, ALT-N

**PARTIAL RESPONSE**
↓HDV-RNA>2 log

**NO RESPONSE**
PHK-HDV+, ALT>N

**HDV-RNA and ALT every 3 mo**

**CONTINUE TREATMENT**

**HDV-RNA+*, ALT>N**

**RELAPSE**

**RETREATMENT**

**HDV-RNA+, ALT-N**

**FOLLOW-UP**

**CLINICAL TRIALS?**

**HDV-RNA-neg, ALT-N**

**REMISSION**

**FOLLOW-UP**

Yurdaydin C., 2008
CURRENT OPTIONS:

- Peg-IFN-alfa (for 1 year) ± NAs (if HBV-DNA > 2000 IU/ml);

FUTURE OPTIONS:

- Peg-IFN-λ
- Nuclear Acid Polymers
- Lonafarnib
- Myrcludex-B
Peg-IFN-lambda in HDV

Potential Impact of Lambda Receptor Distribution

IFN alfa receptors **widely** distributed throughout body.

Lambda receptors **NOT widely** distributed throughout body.

Potential for **MORE** IFN-associated abnormalities:

- Neutropenia
- Thrombocytopenia
- Flu-like Symptoms
- Musculoskeletal Symptoms

Potential for **LESS** IFN-associated abnormalities:

- Neutropenia
- Thrombocytopenia
- Flu-like Symptoms
- Musculoskeletal Symptoms

HDV life cycle and treatment targets

The HDV Life Cycle

ENTRY BLOCKING (Myrcludex-B)

Uncoating of Virus

Release of Progeny

HBsAg SECRETION BLOCKING
Nuclear Acid Polymers (REP-2139)

Cytoplasm

Transport to Nucleus

Assembly

Replication

Prenylation

PRENYLATION INGIBITORS (LONAFARNIB)

HDV genome
- small HDAg
- large HDAg
- prenylated LHDAg
- prenyl moiety
- HBsAg

Taylor JM. Virology 2006;344:71-76
<table>
<thead>
<tr>
<th>HDV Registration Options</th>
<th>Clinical Description</th>
<th>Treatment Option</th>
<th>Treatment Option</th>
<th>Treatment Option</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All Oral</td>
<td>Triple Combo</td>
<td>Mono</td>
</tr>
<tr>
<td><strong>Cure</strong></td>
<td>HDV RNA Negativity + ALT Normalization</td>
<td>Lonafarnib + Ritonavir</td>
<td>Lonafarnib + Ritonavir + Lambda</td>
<td>Lambda</td>
</tr>
<tr>
<td><strong>Chronic Treatment</strong></td>
<td>HDV RNA Reduction + ALT Normalization</td>
<td>Lonafarnib + Ritonavir</td>
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</table>
**REP-2139+Peg-IFN-alfa in HDV**

(12 non-cirrhotic pts)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>End of treatment</th>
<th>1 year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg&lt;0.05 IU/ml</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>anti-HBs&gt;10 IU/ml</td>
<td>42%</td>
<td>50%</td>
</tr>
<tr>
<td>HBV-DNA&lt;15 IU/ml</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>HDV-RNA&lt;15 IU/ml</td>
<td>75%</td>
<td>58%</td>
</tr>
<tr>
<td>normal ALT</td>
<td>75%</td>
<td>75%</td>
</tr>
</tbody>
</table>

HBV life cycle and main classes of antivirals in development
Schematical representation of various types of “cure”

- No treatment
- Nucleos(t)ide analogue induced virus suppression (HBe seroconversion ≈ 20%)
- Decreased viral RNA and protein synthesis; HBsAg loss and seroconversion
- Elimination of cccDNA but persistence of integrated viral DNA

Virus suppression → Functional cure → Complete cure

**Legend:**
- Infectious particles
- HBsAg
- Mature nucleocapsid
- Integrated DNA
- cccDNA
- HBeAg
- Anti-HBe
- Anti-HBs

Durantel D, Zoulim F. J Hepatol 2016;64:S117–31
Unresolved issues and unmet needs

- When to start antiviral therapy in patients with HBeAg-positive chronic HBV infection
- Stopping rules for HBeAg-negative patients treated with an NA
- Retreatment criteria after NA discontinuation
- How to accelerate HBsAg decline in long-term NA-treated patients
- Better baseline or on-treatment predictors of sustained response in patients treated with PegIFNα
- Definition of the residual risk of HCC in patients on long-term NA therapy and impact on surveillance
- Requirement for new treatments with finite duration and high cure rates
- Novel endpoints to define a cure of HBV infection