Consensus AASLD-EASL HBV Treatment Endpoint and HBV Cure Definition

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Why is there a cure for hepatitis C but not for hepatitis B?
Efficacy and Limitations of Current HBV Treatment

**Efficacy**
- Potent virus suppression
- Reverses hepatic inflammation and fibrosis
- Prevents progression to cirrhosis and liver failure
- Decreases risk of HCC
- Excellent safety profile for NAs

**Limitations**
- Does not eradicate cccDNA or integrated HBV DNA
- Low rate of HBsAg loss
- Long duration of treatment required
- Risk of HCC persists albeit at lower rate

NA = nucleos/tide analogue, HCC = hepatocellular carcinoma
Barriers to Eradicating HBV

- Covalently closed circular (ccc) DNA
  - Long t1/2
  - Not affected by NAs
  - Partially impacted by IFN
  - Replenished from cytoplasmic core
- Integrated HBV DNA
- Impaired immune response
- Existing therapies act only on a few steps in HBV lifecycle

NA = nucleos(t)ide analogue, IFN = interferon
Can treatment accomplish what nature can’t?
HBV persists in persons who have recovered from acute hepatitis B with HBsAg to anti-HBs seroconversion
• Reactivation of HBV replication can occur during potent immunosuppressive therapy
• Transmission of HBV is possible when these livers are transplanted
• Long-lasting rigorous immune response to HBV possibly from continued stimulation by residual virus
AASLD/EASL HBV Treatment Endpoints Workshop
In collaboration with FDA and EMA
From Discovery to Regulatory Approval

September 8-9, 2016
Alexandria, VA

Program Chairs
Anna S. Lok, MD, FAASLD
Marc G. Ghany, MD, FAASLD
Fabien Zoulim, MD
Geoffrey M. Dusheiko, MD
How should a virologic cure for HBV be defined in clinical trials? (choose one)

<table>
<thead>
<tr>
<th>Type of Cure</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete cure</strong> with outcome similar to persons never exposed to HBV</td>
<td>5 (7.6)</td>
</tr>
<tr>
<td><strong>Functional cure</strong> with outcomes similar to persons with chronic HBV infection with spontaneous or antiviral induced clearance of HBsAg</td>
<td>58 (87.9%)</td>
</tr>
<tr>
<td><strong>Partial cure</strong> with outcomes similar to persons with inactive chronic HBV</td>
<td>4 (4.5%)</td>
</tr>
</tbody>
</table>
What criteria do you believe should be used for defining functional cure? (choose all that apply)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum HBV DNA undetectable</td>
<td>62 (93.9)</td>
</tr>
<tr>
<td>HBsAg negative</td>
<td>62 (93.9)</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>54 (81.8)</td>
</tr>
<tr>
<td>Anti-HBs positive</td>
<td>37 (56.1)</td>
</tr>
<tr>
<td>Anti-HBe positive</td>
<td>34 (51.5)</td>
</tr>
<tr>
<td>cccDNA transcriptionally inactive</td>
<td>31 (47.0)</td>
</tr>
<tr>
<td>cccDNA eliminated</td>
<td>4 (6.1)</td>
</tr>
<tr>
<td>Integrated HBV DNA eliminated</td>
<td>2 (3.0)</td>
</tr>
</tbody>
</table>
Which should be the primary efficacy endpoints for phase 2/3 clinical trials of novel ANTIVIRAL therapies aimed at HBV virologic cure? (rank)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Phase 2 Rank</th>
<th>Phase 3 Rank</th>
</tr>
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<tbody>
<tr>
<td>Serum HBV DNA undetectable</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sustained decrease in HBsAg level by &gt;1 log10 IU/mL off treatment</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>HBsAg negative</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Maintained decrease in HBsAg level by &gt;1 log10 IU/mL on treatment</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Anti-HBs positive</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

When should endpoint be assessed
- Month 6 on Rx
- Month 6 off Rx
Which should be the primary efficacy endpoints for phase 2/3 clinical trials of novel IMMUNOMODULATORY therapies aimed at HBV virologic cure? (rank)

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<th>Endpoint</th>
<th>Phase 2 Rank</th>
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<tr>
<td>Serum HBV DNA undetectable</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Restoration of T cell response to HBV antigens</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Sustained decrease in HBsAg level by &gt;1 log10 IU/mL off treatment</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Maintained decrease in HBsAg level by &gt;1 log10 IU/mL on treatment</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>HBsAg negative</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Anti-HBs positive</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

When should endpoint be assessed: Month 6 off treatment
For each of the following prerequisites, do they need to be satisfied before a new therapy can be tested in combination with other therapies? (yes/no)

<table>
<thead>
<tr>
<th>Prerequisite</th>
<th>With existing therapies</th>
<th>With other novel therapy</th>
</tr>
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<tbody>
<tr>
<td>Antiviral activity as monotherapy</td>
<td>32 (48.5%)</td>
<td>26 (39.4%)</td>
</tr>
<tr>
<td>Safety as monotherapy</td>
<td>55 (83.3%)</td>
<td>59 (89.4%)</td>
</tr>
<tr>
<td>Infrequent/insignificant drug-drug interactions</td>
<td>47 (71.2%)</td>
<td>53 (80.3%)</td>
</tr>
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# Definitions of HBV Cure

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Complete/Sterilizing cure</th>
<th>Idealistic functional cure</th>
<th>Realistic functional cure</th>
<th>Partial “cure”</th>
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<td>Clinical scenario</td>
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<td>Recovery after acute HBV</td>
<td>Chronic HBV with HBsAg loss</td>
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<td>HBsAg</td>
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<td>Negative</td>
<td>Positive</td>
<td>Positive/negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Serum HBV DNA</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Low level or not detected</td>
</tr>
<tr>
<td>Hepatic cccDNA, transcription</td>
<td>Not detected</td>
<td>Detected</td>
<td>Detected</td>
<td>Detected Low level</td>
</tr>
<tr>
<td>Integrated HBV DNA</td>
<td>Not detected</td>
<td>Detected?</td>
<td>Detected</td>
<td>Detected</td>
</tr>
<tr>
<td>Liver disease</td>
<td>None</td>
<td>None</td>
<td>Inactive, fibrosis regress over time</td>
<td>Inactive</td>
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<tr>
<td>Risk of HCC</td>
<td>Not increased</td>
<td>Not increased</td>
<td>Declines with time</td>
<td>Risk lower vs. active hepatitis</td>
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Virologic Cure vs. Liver (Clinical) Cure

**Partial Cure**
- HBsAg+, HBV DNA UD
- cccDNA+, integrated HBV DNA+

**Decreased necroinflammation**
- Fibrosis persists
- HCC risk persists

**Functional Cure**
- HBsAg-, HBV DNA UD
- cccDNA+, integrated HBV DNA+

**Regression of fibrosis**
- HCC risk decreases

**Sterilizing Cure**
- HBsAg-, anti-HBs+, HBV DNA UD
- cccDNA & integrated HBV DNA eliminated

**Restoration of liver to normal**
- HCC risk eliminated

UD = undetectable
Reversal of Fibrosis and Cirrhosis
Tenofovir Phase III trial: biopsies at Year 0, 1 & 5

- 348/641 (54%) had liver biopsy at baseline and Year 5
- 71/96 (74%) with cirrhosis (Ishak Score ≥5) at baseline no longer had cirrhosis at Year 5

*Marcellin, P, Lancet 2013; 381: 468*
Risk of HCC remains after 5 years of Entecavir or Tenfovir therapy in Caucasian CHB patients

794 adult Caucasian CHB patients

HCC risk seems to be decreasing after first 5 years of ETV/TDF therapy especially in those with compensated cirrhosis at baseline. Older age (≥55 yrs) main risk factor associated with late HCC development

Papatheodoridas G, Hepatology 2017 (in press)
HBsAg Loss Decreases Subsequent Risk of HCC

REVEAL study 2964 HBsAg+, no cirrhosis

Hazard ratio for HCC after seroclearance during follow up
- HBeAg 0.63
- HBV DNA 0.24
- **HBsAg** 0.18
after adjustment for age, gender ALT

Among HBeAg- lifetime cumulative incidence of HCC for those with clearance of
- **Both HBV DNA and HBsAg** 4.0%
- HBV DNA only 6.6%
- Neither 14.2%

Liu J, Gut 2014; 63: 1648
Durability of HBsAg Loss in Patients Treated with NUC ± PEG-IFN

74 patients with HBsAg loss during NUC +/- PEG-IFN treatment

>95% durable if HBsAg loss confirmed ≥24 weeks apart, seroconversion to anti-HBs not important

Chan H, EASL 2017
**Definition of HBV Cure**

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**Functional virologic cure but residual liver damage and risk of HCC that decreases with time**

Akin to HCV cirrhosis with SVR

*Lok A, AASLD-EASL HBV Treatment Endpoint Workshop, Hepatology & J Hepatol 2017 (in press)*
Virologic Efficacy Endpoints

- HBsAg-, HBV DNA not detected
  - Are current assays for HBsAg sufficiently sensitive?
  - How to detect residual HBsAg in immune complex with anti-HBs?
  - Is seroconversion to anti-HBs required?
  - Can kinetics of HBsAg decline predict HBsAg clearance?
  - How to differentiate HBsAg translated from cccDNA vs integrated HBV DNA?

- Timing of assessment
  - On treatment response for phase 2 and off treatment response for phase 3 trials
  - Timing of assessment may depend on mechanism of action of drug
  - Longer follow-up post-treatment needed to confirm durability of response and impact on clinical outcomes
Liver (Clinical) Efficacy Endpoints

• Symptoms, patient reported outcomes
  – Many patients do not have symptoms until advanced disease

• Biochemical: ALT normalization
  – Need standardized definition of upper limit of normal
  – Failure to normalize ALT maybe due to other causes, notably fatty liver

• Histology: decrease necroinflammation, reverse fibrosis
  – Paired biopsies costly, risky, impractical and unnecessary
  – May be required in proof-of-concept studies to confirm a novel mode of action and/or to validate noninvasive surrogate markers of antiviral activity, e.g. to demonstrate decrease in cccDNA
  – Non-invasive assessment of liver fibrosis, elastography measures inflammation & fibrosis, treatment decreases inflammation before fibrosis

• Clinical outcomes: decrease cirrhosis, liver failure, HCC, death
  – Longer follow-up needed, also to confirm durability of response
Standardized Assays for New Markers to Determine Therapeutic Efficacy

• To provide mechanistic insights into effects of novel antiviral or immune modulatory agents and to have surrogate markers to assess cure

• Virologic assays
  – Serum
    • HBsAg (ultrasensitive, epitope mapping, immune complex)
    • HBV RNA – circulating pgRNA, more direct measure of cccDNA?
    • HBcrAg (core related antigen)
  – Liver: cccDNA quantification and transcriptional activity

• Immunologic assays
  – T and B cell response, innate immunity
  – Which epitope/peptide, pangenotype?
  – Cutoffs for meaningful response
Assessment of Safety and Stopping Rules

• Remarkable safety profile of current NAs imposes a stringent requirement for safety of new HBV therapies

• Unique concern for HBV drug development is risk of hepatitis flares
  – Transient flares not always harmful, may reflect immune clearance of infected hepatocytes
  – Severe flares with increase bilirubin or prothrombin time can result in liver failure and death, particularly in cirrhotics

• Any death, liver transplantation, hepatic decompensation or irreversible autoimmunity, or incidence of severe hepatitis flare in >5% of patients could prompt a halt
Collaborations Needed to Overcome Obstacles to HBV Cure