HBV cure therapies: How do we measure success?

John Tavis, PhD
Professor
Saint Louis University School of Medicine

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## Disclosure

<table>
<thead>
<tr>
<th>Relations that could be relevant for the meeting</th>
<th>Company names</th>
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<tbody>
<tr>
<td>Sponsorship or refund funds</td>
<td>• None</td>
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<tr>
<td>Payment or other financial remuneration</td>
<td>• Seventh Wave Laboratories</td>
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<td>Shareholder rights</td>
<td>• Casterbridge Pharmaceuticals</td>
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<td>Other relations</td>
<td>• Scientific advisor to Seventh Wave Laboratories and Casterbridge Pharmaceuticals</td>
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Key similarities between HBV and HIV

- Both establish chronic infections
- Both replicate by reverse transcription
- Both are transmitted by sex, blood contact, and vertical transmission from mother to child
- Therapy can control viremia for both viruses but cannot cure either infection
- Both kill about 1,000,000 people annually
Key differences between HBV and HIV

- HBV replicates in the liver, but HIV replicates in T-cells and macrophages
- Primary HBV infections are often cleared, but clearance of primary HIV infections is very rare
- HIV has a latent phase during replication, but HBV does not
- There is a great vaccine for HBV, but none for HIV
The template for HBV’s RNAs is the cccDNA episome.

HIV’s template is an integrated provirus.

Cure requires eradicating or permanently inactivating the cccDNA or provirus.

This will be easier with the cccDNA!
The goal for new HBV therapies is a **Functional Cure**

- No detectable cccDNA in cells or HBV DNA in the blood
- Immune control of any residual cccDNA in the body
- **No disease progression**

The clinical definition of a functional cure is still being debated

- *This is largely due to limitations to the HBV biomarkers*
Complications on the way to an HBV cure

• cccDNA clearance during acute infections is sometimes not complete
  – cccDNA can persist at undetectable levels after clearance of acute HBV infections
  – Residual cccDNA can relaunch HBV infection upon immune suppression

• HBV integration
  – HBV DNA can integrate into cellular DNA
  – Integrated HBV DNA cannot support viral replication
  – Some HBV proteins used as biomarkers can be made from integrated HBV DNA
## Current biomarkers for HBV

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>What is it?</th>
<th>What does it mean?</th>
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<tbody>
<tr>
<td>HBsAg</td>
<td>Viral surface protein</td>
<td>HBV infection or transcriptionally active HBV integration</td>
</tr>
<tr>
<td>Anti-HBsAg</td>
<td>Antibodies to HBsAg</td>
<td>Effective immune response or HBV vaccination</td>
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<tr>
<td>HBcAg</td>
<td>Viral capsid (core) protein</td>
<td>HBV infection</td>
</tr>
<tr>
<td>Anti-HBcAg</td>
<td>Antibodies to HBcAg</td>
<td>Past or present HBV infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Secreted variant of HBcAg</td>
<td>High HBV replication</td>
</tr>
<tr>
<td>Anti-HBeAg</td>
<td>Antibodies to HBeAg</td>
<td>Low HBV replication</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Viral genome in virions</td>
<td>Active viral replication</td>
</tr>
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</table>

**Missing:** A way to directly measure cccDNA!
Serum biomarkers for HBV Cure

- HBV cure biomarkers must:
  - Report on the cccDNA
  - Be non-invasive
  - Be amenable to point-of-care use
  - Be affordable

- This means sampling serum

Coffin et al. *Gastroenterology* 2019, 156:355-368
HBsAg loss as a marker for HBV cure

- HBsAg loss is currently the best indicator of cccDNA loss or inactivation

- **Problems:**
  - HBsAg can be made from integrated HBV DNA, so patients can eliminate cccDNA yet still be HBsAg$^+$
  - HBsAg tests are not sensitive enough to detect expression from trace levels of cccDNA in patients
  - HBV will resurge from residual cccDNA if immunity is not established
Stop rules for nucleoside analog treatment

- **HBsAg loss:**
  - EASL & AASLD: Treatment cessation can be considered
  - APASL: anti-HBsAg seroconversion and/or >1 year additional therapy

- **No HBsAg loss:**
  - HBeAg+ patients: Anti-HBeAg seroconversion and >1 year with undetectable HBV DNA (AASLD, EASL & APSL)
  - HBeAg- patients: Continue therapy (AASLD & EASL); Consider stopping after 2 years undetectable HBV DNA (APASL)

Rules for uncomplicated cases with no cirrhosis
What about the other viral products?

- **HBeAg**: Can be lost due to mechanisms other than cccDNA clearance
- **HBcAg**: Low level, masked in the HBV virion
- **Other HBV proteins**: The polymerase and X proteins are intracellular and of low abundance
- **HBV DNA**: cccDNA can persist without viremia
New biomarkers for HBV

- **HBcrAg**
  - HBV core-related antigen
  - Mixture of secreted core protein isomers in blood
  - Partial correlation with cccDNA function
  - Sensitivity issues exist
  - Validation studies are ongoing
  - Insufficient by itself to define a cure
New biomarkers for HBV

- HBV RNA
  - HBV RNAs in secreted virion-like particles
  - Potentially an excellent marker for functional cccDNA because 4 HBV products need to be made to be RNA⁺: pgRNA, HBcAg, polymerase, and HBsAg
  - Promising correlation with cccDNA in early studies
  - Validation studies are ongoing
  - Insufficient by itself to define a cure
Combinations of biomarkers

• Limitations to each biomarker alone imply that combinations of markers will be needed
• Work is just starting to define effective combinations
• These studies are hampered by the relatively low numbers of patients who achieve functional cure with current treatments
The immune system’s role in HBV cure

• Clearance of acute HBV infections does not always eliminate all cccDNA
• A single copy of active cccDNA could relaunch an infection without immune control
• Anti-HBsAg from natural clearance or vaccination is protective

Therefore, durability of an HBV cure will depend on establishing anti-HBV immunity
  – T-cells? anti-HBsAg? Innate control?
  – Can immune responses be a biomarker of cure?
HBV cure

Exciting prospects!

- HBV will be easier to cure than HIV
- Efforts are ongoing to develop curative therapies
- Current biomarkers cannot reliably identify a functional cure
- Novel biomarkers (or combinations) to reveal when a patient is cured are under development
Useful references

• ICE-HBV cure strategy:
  – A global scientific strategy to cure hepatitis B. Revill et al. *Lancet Gastroenterol Hepatol.* 2019 4:545-558

• Recent reviews of HBV biomarkers:

• Biological basis of HBV cure

• HBV perspective on the 50th anniversary of its discovery
  – Hepatitis B: 50 years after the discovery of Australia antigen. Lok. *J. Viral Hepat.* 2016 23:5–14