HBV cure therapies: How do we measure success?

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Disclosure

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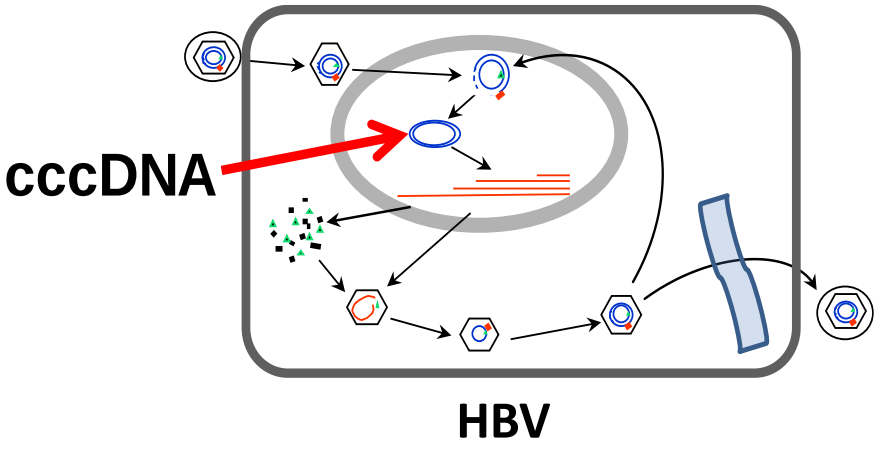
Key similarities between HBV and HIV

- 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

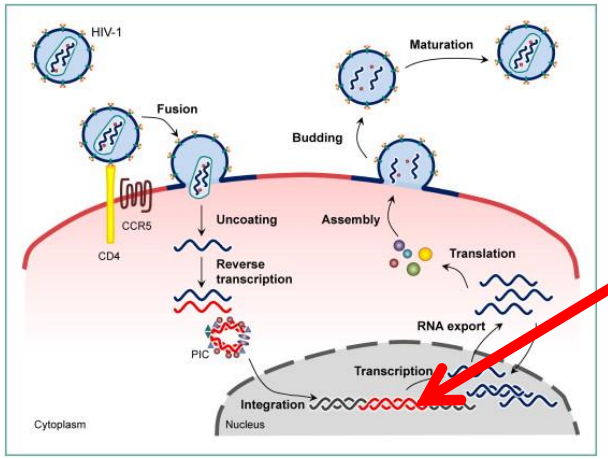
Key differences between HBV and HIV

- 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

HBV cccDNA vs. HIV provirus



HBV



HIV

Provirus

Annales Pharmaceutiques Françaises 73:87-99 2015

- 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!*

Functional cure for HBV

- The goal for new HBV therapies is a **Functional Cure**
- This is a stable state after therapy with:
  - 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*

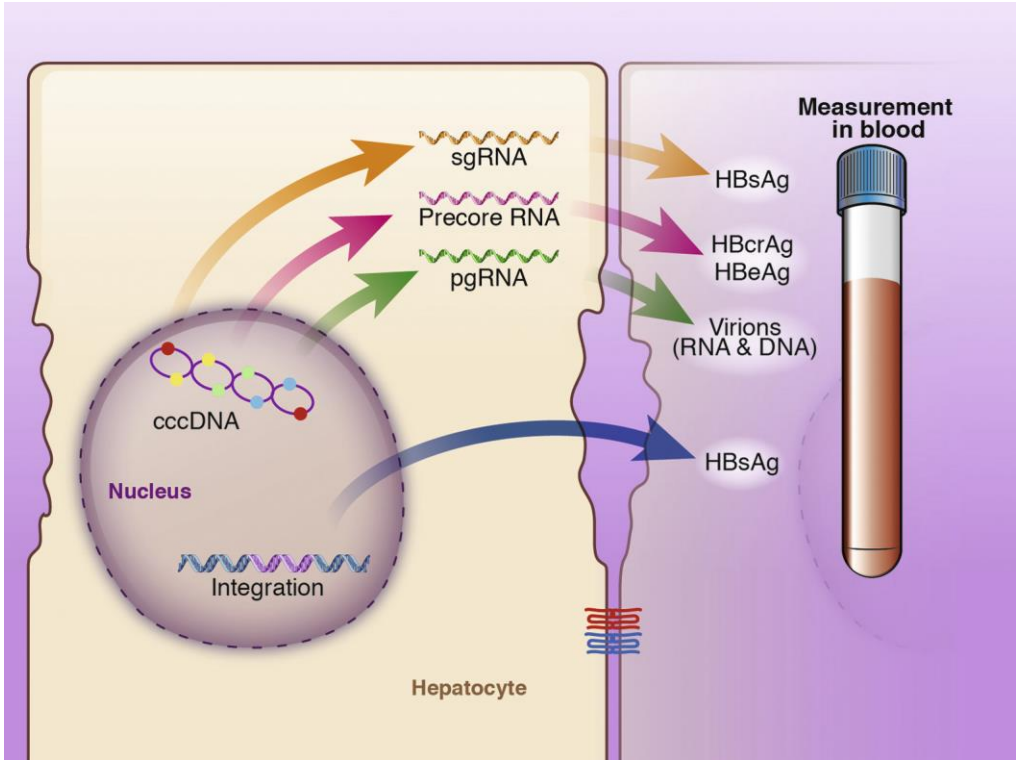
Current biomarkers for HBV

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

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

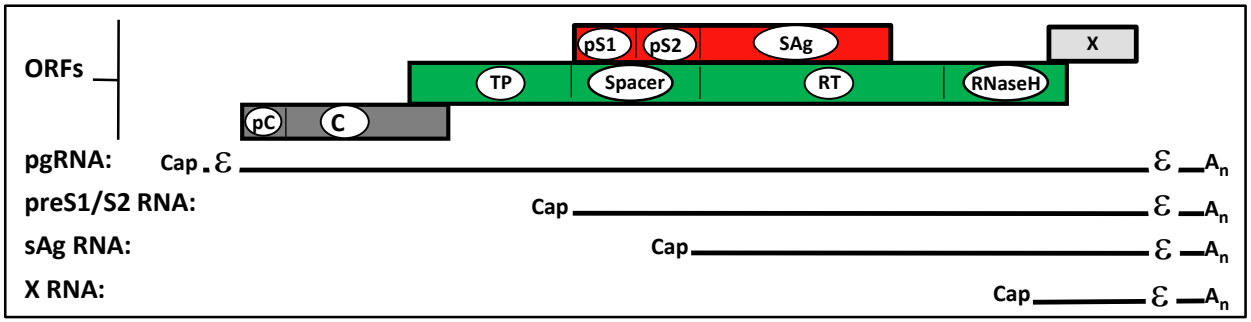
- HBsAg loss is currently the best indicator of cccDNA loss or inactivation
- *Problems*:
  - HBsAg can be made from integrated HBV DNA, so patients can eliminate cccDNA yet still be $HBsAg^{+}$
  - HBsAg tests are not sensitive enough to detect expression from trace levels of cccDNA in patients
  - 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

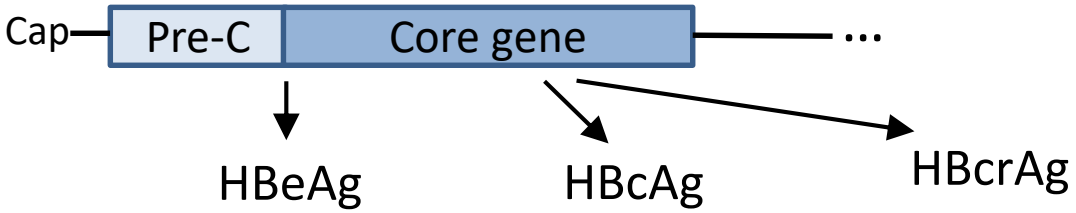
What about the other viral products?



HBV RNA and gene map (linear format)

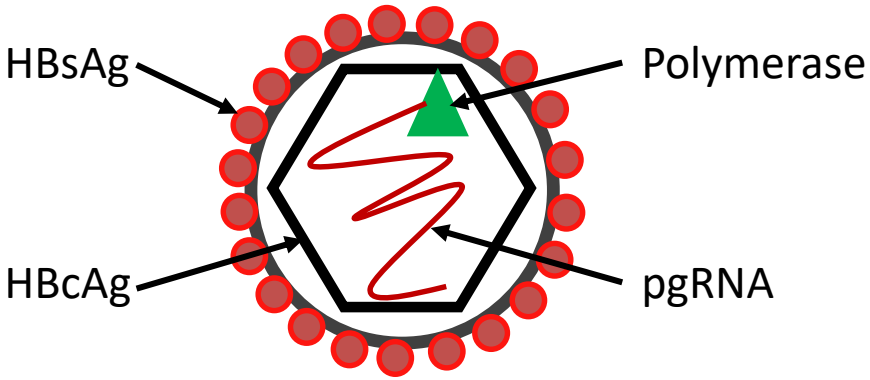
- HBeAg: Can be lost due to mechanisms other than cccDNA clearance
- HBcAg: Low level, masked in the HBV virion
- Other HBV proteins: The polymerase and X proteins are intracellular and of low abundance
- HBV DNA: cccDNA can persist without viremia

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:
  - New and Old Biomarkers for Diagnosis and Management of Chronic Hepatitis B Virus Infection. Coffin et al. *Gastroenterology*. 2019 56:355-368
  - Use of Current and New Endpoints in the Evaluation of Experimental Hepatitis B Therapeutics. Block et al. *Clin Infect Dis*. 2017 64:1283-1288
- Biological basis of HBV cure
  - Virological Basis for the Cure of Chronic Hepatitis B. Hu et al. *ACS Infect. Dis*. 2019 5:659−674
- 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