Is Hepatitis B Curable?

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Learning Objectives

After attending this presentation, learners will be able to:

- List the limitations of current therapies for HBV
- Describe types of HBV cure
- Describe HBV latency
- List mechanisms of action of putative new therapies for HBV

ARS 1: HBV status in 2019: which is true?

1. Acute HBV in adults leads to loss of HBsAg usually
2. HBV infection can be cured
3. Currently available drugs lead to loss of HBsAg usually
4. HBV is not a latent virus
ARS 2: New drugs in Phase I/II: which is false?

1. Target Hepatitis B core protein
2. Target HBV entry into hepatocyte
3. Target cccDNA in nucleus
4. Target HBV mRNA
5. Target HBV secretion

Prevalence of HBV/HCV Coinfection in People with HIV

- About 5% to 10% of anti-HCV antibody-positive patients are HBsAg-positive
- Hepatitis C superinfection of chronic HBsAg carriers is common in HBV-endemic regions, such as Southeast Asia

HBV is a life long, dynamic disease

- Changes over time
- Risk of end stage liver disease and cancer increases with ongoing inflammation and viremia in adults
- Fibrosis can be reversible
- Drugs can decrease fibrosis progression
- HBV can be controlled but not cured
- Reactivation can occur even in those who have lost HBsAg
- HBV infection in neonates and young children leads to chronicity >90-95%
- HBV infection in adults (HIV) leads to chronicity <5% (~20%)
HBV Control

- **Inflammatory**: normalize serum ALT, biopsy
- **Virologic**: decrease HBV DNA
- **Immune**: seroconversion
  - HBeAg to anti-HBe
  - HBsAg to anti-HBs
- HBV as of 2019 not “cured” but controlled

Approved HBV treatments 2019

- Interferon alfa-2b – 1991
- Lamivudine – 1998
- Adefovir – 2002
- Entecavir – 2005
- Peginterferon alfa-2a – 2005
- Telbivudine – 2006
- Tenofovir Disoproxil– 2008
- Tenofovir alafenamide- 2017

Long-term Entecavir Treatment Improves Liver Histology and Fibrosis

**Undetectable HBV DNA Over Time in HBeAg Negative Patients**

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues vs 1 Yr Peginterferon Treatment

![Graph showing undetectable HBV DNA percentages over time for different treatments.](image)

*Single center study.

**HBsAg Loss Over Time in HBeAg Positive Patients**

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues* vs 1 Yr Peginterferon Treatment

![Graph showing HBsAg loss percentages over time for different treatments.](image)

*With sustained undetectable HBV DNA.

**HBsAg Loss Over Time in HBeAg Negative Patients**

Not head-to-head trials; different patient populations and trial designs

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![Graph showing HBsAg loss percentages over time for different treatments.](image)

*HBV sustained undetectable DNA.
**Viral Life Cycle- latent or "recovered" HBV**

Immune system considers this "recovered" cccDNA is template for viral replication.

**Types of HBV cure**

- **Functional Cure - clinical resolution**
  - Sustained, off drug:
    - No inflammation: ALT and liver biopsy
    - HBsAg loss
    - +/- anti-HBs gain
  - **Complete cure - virological cure**
    - All of above plus
    - Loss of cccDNA in liver
  - **Inactive state - an interim goal**
    - No inflammation: ALT and liver biopsy
    - HBV DNA low or u/d
    - HBsAg positive

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Los Angeles, California, May 6, 2019
Strategies to Eradicate HBV

Virologic approaches
- Entry inhibitors
- Block cccDNA
- Transcription inhibitors
- RNA interference
- HBV capsid inhibitor
- Polymerase inhibitors
- Secretion inhibitors

Host immune approaches
- Interferons
- RIG-I agonists
- TLR-7
- PD-1/ PD-1
- IL-7
- Therapeutic vaccines
  - Immune complex vaccines
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HBV entry through NTCP receptor

- HBV pre-S1-derived lipopeptide Myrcludex-B competes with HBV/HDV for binding to NTCP
  - Prevents HBV/HDV entry
  - Blocks entry at pM concentrations increased serum bile acids
  - Stops new infection of hepatocytes

HBV Targeting cell entry

Small molecule compounds binding to Sodium taurocholate cotransporting polypeptide (NTCP)

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Multicentre, open-label Phase 2b clinical trial to assess safety and efficacy of Myrcludex B + TDF in chronic HBV/HDV coinfection

- 120 HBsAg-negative HDV patients in 4 arms were treated in the MIR 201 study for 24 weeks
- Excellent safety in 228 subjects dosed so far for 2, 5, 10 mg sq + TDF 24 w
- No persistent, drug related AEs/SAEs
- Primary endpoint was: HDV RNA >2 log decline or undetectable
- Strong on-treatment decrease in ALT, liver stiffness, intranhepatic HDV RNA
- Relapse in most patients in the follow-up: ?? longer treatment needed

HBV RNA decrease by >2 log in %

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 48</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg MyrB/TDF</td>
<td>-1.75</td>
<td>-0.35</td>
</tr>
<tr>
<td>5 mg MyrB/TDF</td>
<td>-1.60</td>
<td>-0.12</td>
</tr>
<tr>
<td>10 mg MyrB/TDF</td>
<td>-2.70</td>
<td>-0.39</td>
</tr>
<tr>
<td>TDF</td>
<td>-0.18</td>
<td>+0.07</td>
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</tbody>
</table>

Negligible effects on qHBsAg

*p<0.001
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cccDNA inhibitors

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Antiviral agent</th>
<th>Trials</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>cccDNA Blocking</td>
<td>Disubstituted sulphonamides</td>
<td>Preclinical</td>
<td></td>
</tr>
<tr>
<td>cccDNA Degradation</td>
<td>RNA guided nucleases (CRISPR/CAS9)</td>
<td>Preclinical</td>
<td>Excision Biotherapeutics</td>
</tr>
<tr>
<td></td>
<td>EBT106</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-HBV sgRNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silencing</td>
<td>histone acetyltransferase (HAT) inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HBx targeting drugs</td>
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<td></td>
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</tbody>
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RNA interference

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<tr>
<th>Antiviral agent</th>
<th>Trials</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALN-HBV (siRNA)</td>
<td>Phase I-II</td>
<td>Alnylam</td>
</tr>
<tr>
<td>ARB-1467 (siRNA)</td>
<td>Terminated</td>
<td>Arbutus Biopharma</td>
</tr>
<tr>
<td>ARB-1740 (siRNA)</td>
<td>Preclinical</td>
<td>Arbutus Biopharma</td>
</tr>
<tr>
<td>RO7020322 (RG7834) (small molecule mRNA inhibitors)</td>
<td>Phase I</td>
<td>Roche</td>
</tr>
<tr>
<td>IDNIS-HBVRx (GSK3228836) (antisense molecule)</td>
<td>Phase I</td>
<td>Isis Pharma/GSK</td>
</tr>
<tr>
<td>IDNIS-HBVRx (GSK3330404A) (antisense molecule)</td>
<td>Phase I</td>
<td>Isis Pharma/GSK</td>
</tr>
<tr>
<td>AB-452 (RNA destabilizer)</td>
<td>Preclinical</td>
<td>Arbutus Biopharma</td>
</tr>
</tbody>
</table>
Silencing HBV gene expression using RNAi-based therapy

- ARC-520 is a combination of siRNAs directed against conserved HBV RNA sequences and efficiently knocks down HBV RNA, proteins and DNA levels.
- 2 siRNAs (cover 99.6% of known HBV sequences) conjugated to cholesterol and hepatocyte-targeted ligands
- Taken up by endosomes in hepatocyte then released into cytoplasm after lysis of endosomal membrane
  - Given (Arrowhead Hepdart 2015)
  - Arbutus ARB-1740 decreases HBsAg, HBeAg, HDV RNA (AASLD 2016)
  - ARO-HBV EASL 2018
  - 1 month human data

RNA interference therapy with ARC-520 injection –
Case 1: HBeAg positive patient flared when ARC-520 stopped

![Graph showing HBsAg, HBeAg, and HBV RNA levels over time after ARC-520 injection.]

- 2.3 log, HBsAg reduction from baseline to 46 IU/mL
- 1.7 log, HBeAg reduction
- 2.4 log, HBV RNA reduction to 100U/mL
- HBeAg seroclearance post therapy coincides with HBV RNA drop to 100U/mL
- HBsAg flared with HBV RNA by 7.3 log, to 100U/mL
- ALT elevations coinciding with antigen, RNA and DNA reductions & rise after ARC-520 stopped

Bi-weekly Dosing of ARB-1467 LNP siRNA in HBeAg Negative, ViraS suppressed Patients with Chronic HBV Infection Leads to Deeper Declines in HBsAg and Potential Association with IL28b

![Graph showing changes in HBsAg and HBV RNA levels before and after bi-weekly dosing of ARB-1467 LNP siRNA.]

- ViraS suppression
- Dose escalation
- Case report: IL28b genotypes
- ALT reductions
- HBV RNA reductions
- HBsAg reductions
- AEs: mild to moderate

Los Angeles, California, May 6, 2019
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Core is essential for

- HBV genome packaging
- Reverse transcription
- Intracellular trafficking
- Maintenance of chronic infection as encapsidated HBV genomes are imported into the nucleus.
### Nucleocapsid assembly inhibitors/ modulators

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<tr>
<th>Antiviral</th>
<th>Trials</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS-4</td>
<td>Phase II</td>
<td>HEC Pharm, Sunshine</td>
</tr>
<tr>
<td>NVR 3-778</td>
<td>Phase Ia</td>
<td>Novira Pharmaceuticals/Janssen</td>
</tr>
<tr>
<td>BAY41-4109</td>
<td>Phase I</td>
<td></td>
</tr>
<tr>
<td>JNJ56136379</td>
<td>Phase II</td>
<td>Janssen</td>
</tr>
<tr>
<td>Core protein allostERIC modulators (CpAMs)</td>
<td>Phase I (ABI-H0731)</td>
<td>IND enabling (ABI-H2158)</td>
</tr>
<tr>
<td>AB-423</td>
<td>Phase I</td>
<td>Arbutus Biopharma</td>
</tr>
<tr>
<td>AB-506</td>
<td>IND enabling</td>
<td>Arbutus Biopharma</td>
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</table>

### Antiviral Activity of JNJ-56136379, a novel HBV Nucleocapsid Inhibitor

- **Session 8**: 100mg or placebo (Day 1)
- **Sessions 8 and 9**: 25mg (D2-28) or placebo (D2-28), QD
- **Session 9**: 75mg or placebo, QD
- **Session 10**: 150mg or placebo, QD

**Sessions 8 and 9**: n=12 per session (8 active/4 placebo)

- 28 days of treatment followed by 8 weeks of follow-up
- 56% with one AE, no SAEs, treatment d/c or deaths
- One patient with Grade III elevations in ALT and AST-TDF started

**HBV DNA**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>N</th>
<th>Mean (SD), log10IU/mL</th>
<th>Mean (SD) change from baseline log10IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>25mg QD</td>
<td>8</td>
<td>6.90 (1.91)</td>
<td>-2.16 (0.49)</td>
</tr>
<tr>
<td>75mg QD</td>
<td>8</td>
<td>5.26 (1.50)</td>
<td>-2.89 (0.48)</td>
</tr>
<tr>
<td>Pooled placebo</td>
<td>8</td>
<td>5.49 (1.77)</td>
<td>0</td>
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An oral dose regimen of 250 mg daily for 28 days is being evaluated

Phase 2a study is ongoing in treatment-naive and virologically suppressed CHB patients (NCT03361956)
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HBsAg inhibitors

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<tr>
<td>REP2139 &amp; REP2165</td>
<td>Phase II</td>
<td>Replicor</td>
</tr>
<tr>
<td>BM601 (benzimidazole derivative)</td>
<td>Preclinical</td>
<td></td>
</tr>
</tbody>
</table>

REP 2139-Mg and REP 2165-Mg Combination Therapy in CHB (REP 401 - NCT02565719)

Global summary of follow-up responses after removal of all therapy (2018)

<table>
<thead>
<tr>
<th>Participants entered into trial</th>
<th>N=40 (20 with NAPs following 24 weeks of pegIFN*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants currently completed treatment and ≥ 24 weeks of follow-up</td>
<td>34</td>
</tr>
<tr>
<td>Functional cure (HBsAg negative, HBV DNA TN)</td>
<td>14/34 (41%)</td>
</tr>
<tr>
<td>Inactive chronic HBV state (HBV DNA &lt; 2000 IU/mL, normal ALT)</td>
<td>15/34 (44%)</td>
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**qHBsAg change on anti-PD1 0.3mg/kg (Nivolumab)**

![Graph showing qHBsAg change on anti-PD1 0.3mg/kg (Nivolumab)](image)

**NB:** 240 mg IV Q2w for RCC, SC lung, Melanoma

**Emerging DAAs against HBV**

Many currently in the pipe-line
- Novel polymerase inhibitors
- Capsid inhibitors
- cccDNA inhibition or eradication
- Core protein packaging inhibitors
- Small interfering RNA (siRNA) based strategies
- Secretion inhibitors
- Immune activators

Combination therapy will likely be required for cure
- Inhibitors of polymerase, entry, core, cccDNA etc
- IFN, immune stimulant, TLR 7
- Checkpoint inhibitors PD-1/L1

**BUT**

Selection of HBV patient will be critical
Optimization of HBV endpoints needed
ARS 2: HBV status in 2019: which is true?

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Peters and Locarnini Gastro and Hep 2017
Question-and-Answer