HBV: When Will it be a Curable Disease

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University of California, San Francisco
2016
Types of HBV cure

**Functional Cure - clinical resolution**
Sustained, off drug:
• No inflammation: ALT and liver biopsy
• HBsAg loss
• HBsAb gain

**Complete cure - virological cure**
• All of above plus
• Loss of cccDNA
HBeAg Seroconversion Rates 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 Limited Duration (1 Yr) Peginterferon Treatment

- Entecavir
- Tenofovir
- Peginterferon

*With sustained undetectable HBV DNA.

Long-term Entecavir Treatment Improves Liver Histology and Fibrosis


![Graph showing percentage of patients with histologic and fibrosis improvement over time.](image_url)
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

Undetectable HBV DNA (%) over time:
- Entecavir: 90, 96, 100
- Tenofovir: 93, 91, 87
- Peginterferon: 63, 15, 16

*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

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HBsAg Loss Over Time in HBeAg Negative Patients

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

*With sustained undetectable HBV DNA.

Viral Life Cycle- “latent or recovered” HBV: functional cure

Immune system considers this “recovered”
BUT cccDNA remains: template for viral replication

HBsAg neg
Anti-HBs
Anti-HBc
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
- TLR-7
- PD-1/ PDL-1
- IL-7
- Therapeutic vaccines
  - Immune complex vaccines
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HBV entry through NTCP receptor
HBV Targeting cell entry

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

- HBV pre-S1-derived lipopeptide Myrcludex-B competes with HBV/HDV for binding to NTCP
  - prevents HBV/HDV entry
  - Phase II in Russia (HBeAg -, naïve, ↑ALT, DNA >2k
    - nl ALT, ↓qHBsAg, myr preSAbs, HBV reactivation in 2.
  - Blocks entry at pM concentrations that do not inhibit bile salt transport
  - Decrease new cccDNA production

Urban ISVHLD 2015; Gastro 2014
Gonzalez 2015 Antimicrobe
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cccDNA

- Cannot replicate itself but is replenished from cytoplasmic nucleocapsid rcDNA
- Complexes with HBc, histones to form a minichromosome
  - Not static has inactive and active forms
  - Long half life
  - Stable in quiescent cells
  - Turnover with cell death
  - Diluted by cell proliferation but survives cell division
Potential Mechanisms to Target cccDNA

• preventing cccDNA formation
• eliminating cccDNA
• silencing cccDNA transcription
• Control of cccDNA
  – capsid disassembly
  – inhibition of rcDNA (relaxed circ cccDNA precursor) entry into the nucleus
  – inhibition of conversion of rcDNA to cccDNA
  – physical elimination of cccDNA
  – inhibition of cccDNA transcription (epigenetic control)
  – inhibition of viral or cellular factors contributing to cccDNA stability/formation.
  – HBx regulates cccDNA (Levrero AASLD 2015)
HBV targeting cccDNA formation/decay

disubstituted sulphonamide (DSS) compounds

- inhibitors of cccDNA in cell-based assays.
- inhibit de novo cccDNA formation by interfering with rcDNA conversion into cccDNA

DNA cleavage enzymes, specifically targeting the cccDNA are currently being engineered

- homing endonucleases or meganucleases
- zinc-finger nucleases introduce ds breaks and cleave HBV DNA targets
- TALEN effector nucleases HBeAg/sAg
- CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 as platform to mutate or inactivate viral genomes (Cullen)

Chen et al, Molecular Therapy 2014; Weber 2014; Zimmerman 2008 Ren 2014
APOBEC3A/3B and cccDNA modification by IFN-α/LTβR

- IFN-a, LTBR activation up-regulated APOBEC3A/B cytidine deaminases
- HBV core protein mediates interaction with nuclear cccDNA, resulting in cytidine deamination, apurinic/apyrimidinic site formation, and finally cccDNA degradation that prevents HBV reactivation
- No effect on inactive cccDNA
- New therapeutic target

Lucifora, Protzer; Science 2014
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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.
  - phase II clinical trial NCT02065336
- 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)
siRNA: ARC520

- Suppressing both viral load and HBsAg: Data from chimp model

Phase IIb iv q mo in HBV suppressed (Given-2015)

Lanford et al, AASLD 2013
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HBV capsid

• It is essential for
  – HBV genome packaging
  – reverse transcription
  – intracellular trafficking
  – maintenance of chronic infection as encapsidated HBV genomes are imported into the nucleus.

• NVR- 3-778- capsid inhibitor
  – Small molecule and direct acting antiviral through aberrant core protein assembly that inhibits capsid assembly and viral replication
  – Phase Ila Novira -HBsAg pos, ↑ALT
  – Endpoints normal ALT then HBsAg decrease/loss
1) Capsid Assembly

Inhibition of Viral replication

2) cccDNA Amplification

Inhibition of Viral replication

3) ISG Inhibition

Restoration of host innate immune response

4) Maintenance of cccDNA in Active State

cccDNA silencing inhibits viral replication & restores host immune response

Core Dimer

Core Inhibitor

Core dimer bound to host chromosome

CORE dimer bound to virus mini-chromosome (cccDNA)

Novira website 2015
HBV Nucleocapsid Inhibitors

Heteroaryldihydropyrimidinines (HAPs)

– bind to core particles to reduce both HBV DNA and HBcAg levels, the latter via degradation by the proteasome pathway.

– enhance viral assembly
  • favour assembly of aberrant particles, indicating that HAPs interfere with capsid formation/stability in a complex manner.

– Similar to phenylpropenamide derivatives, HAPs are able to efficiently inhibit NA resistant viral variants
Nucleocapsid inhibitors: GLS4 first member of HAP nucleocapsid compounds

Morphothiadine mesilate (GLS4)
• Triggers aberrant core particle assembly
• Hep AD38 cells

Phase I/II trials in China

Gonzalez 2015 Antimicrobe
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HBsAg Release Inhibitor-Nucleic Acid Polymer (NAP) REP 2139

- Taken up by hepatocytes, targets apolipoprotein, block entry and formation of subviral particles (not virion production)
- Phase Ib: iv q w x15 lead in then, 15w plus peg IFN, then PEGIFN for 48w in 12 HBV HDV pts
  - Led to HBsAg lo 6/12; ud 6/12; HDVAg <LLQ 9/12; 4 HBsAb
  - HBsAg and HDV RNA.
- Many patients had u/d serum HBsAg or HDV RNA at 15w
  - Does not decrease HBV DNA by itself ?need NA or IFN
- Phase II Canada +/- PEG-IFN
  - Combination of REP 2139 and immune stimulant and oral nucleos(t)ide being tested

Vaillant EASL 2015
HBV Inhibit Secretory Pathway

• Benzimidazole BM601
  – selectively inhibit intracellular relocatisation of the HBV surface protein to the Golgi apparatus
  – Thus decreases HBsAg and HBV release
  – without affecting HBeAg secretion
• iminosugar derivatives of butyldeoxynojirimycin and related glycolipids
• α-glucosidase inhibitors
• triazol-o-pyrimidine derivatives

• Will suppression of HBsAg in serum restore T cell responsiveness?
# Strategies to Eradicate HBV

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GS-9620, an orally available agonist

Selective for antiviral vs proinflammatory response

Preclinical studies: Reduces sAg, viral DNA in woodchucks & chimpanzees

Phase 1a (SAD) complete: Safety shown in healthy volunteers

Lopatin U et al. Antivir Ther 2013; 18:409-418
TLR-7 agonist Induces sAg Seroconversion in Chronically Infected Woodchucks

### Results

**Mean WHsAg Titer (ODU)**

- **Weeks -2, 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24**

**α-sAg Ab+ (#)**

- **5 mg/kg:** 0/7
- **5/2.5 mg/kg:** 1/7
- **5/2.5 mg/kg:** 3/7
- **Placebo:** 2/7

**Max Δ DNA (log_{10})**

- **5 mg/kg:** -0.6
- **5/2.5 mg/kg:** -1.0
- **5/2.5 mg/kg:** -3.9
- **Placebo:** -4.7

**GS-9620 Phase II in suppressed HBV patients**
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Effect of PD-1/L1 on Antiviral Immunity
Expansion of HBV-specific CD8 T Cell Response by Blocking PD-1/L1/2 Interaction *In Vitro* (mice)

In studies in HCC patients

Sherman AC et al. *AIDS Res Hum Retr* 2012
### Published Efficacy Data in HCC: Nivolumab, ASCO 2015

<table>
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<tr>
<th></th>
<th>Uninfected (n = 21)</th>
<th>HBV+ (n = 10)</th>
<th>HCV+ (n = 11)</th>
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<tr>
<td>Duration of response</td>
<td></td>
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<tr>
<td>(months, range)</td>
<td>7.2 – 12.5</td>
<td>11.9</td>
<td>1.4 – 8.3</td>
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<tr>
<td>Duration of stable</td>
<td></td>
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<td>disease (months, range)</td>
<td>1.1 – 17.3</td>
<td>2.9 – 14.0</td>
<td>2.7 – 6.9</td>
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<td>Overall survival at 9</td>
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<tr>
<td>months (%)</td>
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<td>70 (52 – 82)</td>
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<td>Overall survival at 12</td>
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<tr>
<td>months (%)</td>
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<td>62 (42 – 76)</td>
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<tr>
<td>Objective response*</td>
<td>3 (14%)</td>
<td>1 (10%)</td>
<td>4 (36%)</td>
<td>8 (19%)</td>
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<tr>
<td>(10 stable, 8 progressive)</td>
<td></td>
<td>(5 stable, 4 progressive)</td>
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<td>Complete responses*</td>
<td>2 (10%)</td>
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<td>2 (5%)</td>
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*Investigator-determined best overall response assessed by RECIST

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El-Khoueiry A, J Clin Oncol 33, 2015
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Tarmogens can induce HBV-specific T cell response in vitro

GS-4774 ± TDF Phase 2: qHBsAg

King T et al. PLOS ONE (2014), 9 (7): e101904
Emerging DAAs against HBV

Many currently in the pipe-line
- novel polymerase inhibitors
- capsid inhibitors
- cccDNA inhibition or eradication
- Packaging inhibitors - not very potent alone
- small interfering RNA (siRNA)-based strategies
- 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

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BUT  Selection of HBV patient will be critical
Optimization of HBV endpoints needed