Hepatitis B (and D) Cure Strategies: How far are we?

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International Hepatitis E Symposium February 14-16, 2019
HBV is present in humans since >5,000 years (maybe 100,000 years)!
(isolation of HBV Genotype C2 from a korean mummy 15th century)
Bar-Gal et al., Hepatology 2012

Paraskevis, Hatzakis et al.: Hepatology 2013 Mar;57(3):908-916
HBV Diversity in comparison to human evolution:
HBV infection of humans longer than 33,000 years!

Ancient hepatitis B viruses from the Bronze Age to the Medieval period.
Hepatitis B Virus: Co-evolution over more than 400 Million years!

Lauber, Seitz, .... Bartenschlager; Cell Host Microbe 2017
The hepatitis B-associated disease burden is still increasing!

Mortality due to HBV 2013 ~ 650,000

GBD-Study: Lancet Jan 2015

Cowie et al.: EASL 2015

HBV-Cirrhosis Mortality Increase 36%

HBV-HCC Mortality Increase 51%
Hepatitis B ≠ Hepatitis B
Different phases of HBV infection

Lok, Zoulim et al., J Hepatology 2017
NA treatment of chronic hepatitis B

Suppression of HBV DNA in >95%

Improvement of fibrosis\(^1,2\)

Reduction of risks for HCC and decompensation\(^3\)

\(^1\)Chang et al., Hepatology 2010
\(^2\)Marcellin et al., Lancet. 2013
\(^3\)Hosaka et al., Hepatology 2013, Kwon and Lok, Antivir Ther 2011
Glebe & Bremer, Semin Liver Dis. 2013
HBV NA-treated patients have an excellent longterm outcome!

<table>
<thead>
<tr>
<th></th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N = 1,951)</td>
<td>0.82 (0.66–1.03)</td>
</tr>
<tr>
<td>Males (n = 1,379)</td>
<td>0.78 (0.62–1.01)</td>
</tr>
<tr>
<td>Females (n = 572)</td>
<td>1.00 (0.63–1.59)</td>
</tr>
<tr>
<td>CHB without cirrhosis (n = 1,379)</td>
<td>0.58 (0.41–0.82)</td>
</tr>
<tr>
<td>CHB with cirrhosis (n = 526)</td>
<td>1.22 (0.90–1.66)</td>
</tr>
<tr>
<td>Patients without HCC (n = 1,833)</td>
<td>0.58 (0.44–0.77)</td>
</tr>
<tr>
<td>Patients with HCC (n = 118)</td>
<td>3.09 (2.13–4.48)</td>
</tr>
</tbody>
</table>

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; SMR, standardized mortality ratio; TDF, tenofovir disoproxil fumarate.

*Papatheodoridis, GV et al., J. Hepatol. 2018; 68: 1129-1136*
Do we really need new therapies for hepatitis B?
Why would “curative” therapies for HBV be useful?

- HBsAg-positive patients have an increased risk to develop hepatocellular carcinoma
- Long-term treatment is associated with costs and may cause side-effects
- Immunosuppression may lead to severe HBV reactivation
- Very limited treatment options for HDV coinfection
Heterogeneity of hepatitis delta world-wide: the HDIN network

- The Hepatitis Delta International Network (HDIN)
- 1579 anti-HDV+ or HDV-RNA+ patients from 15 countries

Hepatic clinical complications

Wranke et al., Liver International 2018
HDV infection increases the risk for liver-related clinical events

Analysis by HDV serological status

- **Overall survival on ART**
- **Liver-related death**
- **HCC free survival**

**Anti-HDV+ vs. anti-HDV(-)**

Analysis by HDV-RNA status in anti-HDV seropositive patients

- **Overall survival on ART**
- **Liver-related death**
- **HCC free survival**

**HDV-RNA+ vs. HDV-RNA(-)**

Beguelin et al., J Hepatol 2017 (66:297-303)
PEG-IFNa leads to HDV RNA suppression in ~25% of cases

**Figure 1.** Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.

**A** HDV-RNA

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Week 48, End of Treatment</th>
<th>Week 72, End of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDV-RNA negative</td>
<td>Peginterferon alfa-2a + adebovir</td>
<td>Peginterferon alfa-2a + adebovir</td>
</tr>
<tr>
<td>HDV-RNA &gt;2 log_{10} decline, copies/ml</td>
<td>Peginterferon alfa-2a + adebovir</td>
<td>Adefovir + placebo</td>
</tr>
</tbody>
</table>

**B** Median HDV-RNA Levels over Time

- Peginterferon alfa-2a + adebovir
- Adefovir
- Peginterferon alfa-2a + placebo

Wedemeyer, Yurdaydin et al. NEJM 2011
New treatments aiming for HBV cure
<table>
<thead>
<tr>
<th>Targets</th>
<th>Compounds</th>
<th>Developer</th>
<th>Stage of development</th>
<th>ClinicalTrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAA</td>
<td>GBpol</td>
<td>GS-7340; Tenofovir Alafenamide (prodrug of tenofovir)</td>
<td>Gilead</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>GBpol</td>
<td>AGX-1009 (prodrug)</td>
<td>Agenix</td>
<td>Phase 3 (?)</td>
</tr>
<tr>
<td></td>
<td>GBpol</td>
<td>Besifovir</td>
<td>Ildong Pharmaceutical</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>GBpol</td>
<td>CMX-157 (lipid acyclic nucleoside phosphonate)</td>
<td>Contravir</td>
<td>Phase 1</td>
</tr>
<tr>
<td>HBc</td>
<td>GLS-4 (Morphothiadine mesilate)</td>
<td>HEC Pharm/SUnshine</td>
<td>Phase 2</td>
<td>China-CFDA</td>
</tr>
<tr>
<td>HBc</td>
<td>NVR 3-778</td>
<td>Novira Pharmaceuticals</td>
<td>Phase 1</td>
<td>NCT02112799 &amp; NCT02401737</td>
</tr>
<tr>
<td>HBs</td>
<td>REP-2139 (nucleic acid polymers)</td>
<td>Replicor</td>
<td>Phase 2 for both HBV and HDV</td>
<td>NCT02565719 and NCT02233075</td>
</tr>
<tr>
<td>Viral RNAs</td>
<td>siRNA: ARC-520/ARC-521</td>
<td>Arrowhead</td>
<td>Phase 2</td>
<td>NCT02604212 and NCT02604199</td>
</tr>
<tr>
<td>Viral RNAs</td>
<td>siRNA: ISIS-HBVRx</td>
<td>Ionis Pharmaceuticals</td>
<td>Phase 1 or 2 (?)</td>
<td>No identifier found</td>
</tr>
<tr>
<td>HTA</td>
<td>NTCP</td>
<td>Myrcludex</td>
<td>Hepatera and MYR GmbH</td>
<td>Phase 2 for both HBV and HDV</td>
</tr>
<tr>
<td></td>
<td>Promotion of apoptosis in infected cells</td>
<td>Birinapant</td>
<td>Tetralogic</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Prenylation/farnesylation</td>
<td>Lonafarnib</td>
<td>Eiger BioPharmaceuticals</td>
<td>Phase 2 for HDV</td>
</tr>
<tr>
<td></td>
<td>Immune stimulation</td>
<td>Thymosin alpha</td>
<td>Seoul National University Hospital</td>
<td>Phase 4</td>
</tr>
<tr>
<td></td>
<td>pDC stimulation</td>
<td>GS-9620 (TLR7 agonist)</td>
<td>Gilead</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Immune stimulation</td>
<td>INO-1800</td>
<td>Inovio Pharmaceuticals</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Immune stimulation</td>
<td>Cyt-107 (IL-7)</td>
<td>Cythesis</td>
<td>Phase 1/2 (discontinued)</td>
</tr>
<tr>
<td></td>
<td>Immune stimulation</td>
<td>IFN-lambda</td>
<td>BMS</td>
<td>Phase 2 (discontinued)</td>
</tr>
<tr>
<td></td>
<td>Adaptive responses</td>
<td>ABX-203</td>
<td>Abivax</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td></td>
<td>Adaptive responses</td>
<td>GS-4774 (therapeutic vaccine)</td>
<td>Gilead</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Adaptive responses</td>
<td>TG-1050 (therapeutic vaccine)</td>
<td>Transgene</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Adaptive responses</td>
<td>DV-601 (therapeutic vaccine)</td>
<td>Dynavac</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Adaptive response</td>
<td>HB-110</td>
<td>Genexine</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Adaptive responses</td>
<td>Nivolumab (Anti-PD1 mAb)</td>
<td>Ono Pharmaceuticals/ BMS</td>
<td>Phase 1/2 for HCC</td>
</tr>
</tbody>
</table>

HBV-specific T cells kill HBV infected cells

Kah, ..., Bertoletti, Dandri. Journal of Clinical Investigation 2017
HBsAg-Reduction by siRNAs

Wooddell et al., Sci. Transl. Med. 2017
Nucleic Acid Polymers to block HBV release

Bazinet et al. Lancet G&H 2017
Median HDV RNA levels

Wedemeyer et al., EASL 2018
Hepatitis B cure: From discovery to regulatory approval

Anna S. Lok\textsuperscript{1,*}, Fabien Zoulim\textsuperscript{2}, Geoffrey Dusheiko\textsuperscript{3}, Marc G. Ghany\textsuperscript{4}
The virological endpoint of novel therapies

HBsAg loss
Is HBsAg loss a reliable surrogate endpoint?
Loss of HBsAg during Nuc-Therapy can be predicted by HBsAg kinetics

Jaroszewicz et al., Antiviral Therapy 2011
Is HBsAg loss a reliable surrogate endpoint?

**Group II** (44% of pts)
HBeAg(+) 29%, median HBsAg (log10) decline: 0.21

**HCC**
2 years after HBsAg loss

HBsAg loss after 12 years of therapy

Jaroszewicz, Cornberg et al., AVT 2011

H. Wedemeyer 10-2018  HBV cure
HBsAg loss was **not** associated with a lower HCC incidence in Alaska!

Gounder et al., AP&T 2016
HBsAg loss was not associated with a lower HCC incidence in Alaska!

HCC rate / 100,000 person years:

HBsAg loss: 132
no HBsAG loss: 178

HR 0.7 (0.2-2.4); p=0.65

Gounder et al., AP&T 2016
Early loss of HBsAg is important

Risk of HCC After HBsAg Loss

Yuen et al., Gastroenterology 2008
### Potential Surrogate Markers for HBV: HBsAg

<table>
<thead>
<tr>
<th>HBV Marker</th>
<th>Purpose</th>
<th>Rationale/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg, ultrasensitive qualitative or quantitative assay</td>
<td>To detect minimal residual HBsAg, lower limit of detection of Lumipulse assay 0.004 IU/ml compared to current assays 0.05 IU/ml</td>
<td>HBsAg loss is considered the most reliable indicator for functional cure.</td>
</tr>
<tr>
<td>HBsAg fragments, epitope mapping</td>
<td>To determine whether residual HBsAg is translated from cccDNA transcripts or integrated HBV DNA transcripts. To detect antiviral-resistant/immune escape HBsAg variants</td>
<td>Persistent detection of HBsAg may be from integrated HBV DNA and not cccDNA. Integrated HBV DNA is often fragmented with deletions and rearrangements, while cccDNA translates into full-length HBsAg. HBsAg variants may give rise to false-negative results or inaccuracy in quantification in current assays.</td>
</tr>
<tr>
<td>Large (L) vs. middle (M) vs. small (S) surface protein</td>
<td>To differentiate complete virions from empty envelope particles</td>
<td>Complete virions are coated with L, M, &amp; S surface proteins; but empty envelope particles comprise mostly S surface proteins.</td>
</tr>
<tr>
<td>HBsAg–anti-HBs immune complex</td>
<td>To detect residual HBsAg masked by anti-HBs in immune complex</td>
<td>HBsAg loss is considered the most reliable indicator for functional cure.</td>
</tr>
<tr>
<td>Quantitative HBsAg level</td>
<td>To facilitate differentiation of inactive carriers from HBeAg-negative chronic hepatitis. To predict outcome in HBeAg-negative patients with low serum HBV DNA</td>
<td>Serves as an intermediary measure of HBsAg loss. HBsAg level declines before it becomes undetectable, but accuracy in predicting HBsAg loss is low.</td>
</tr>
</tbody>
</table>

*References*

Lok, Zoulim et al., *J Hepatology* 2017
Different sources of HBsAg
Cornberg et al., J Hepatol 2017; 66:398-411
• Integration randomly across chromosomes
• clonal hepatocyte-expansion high in high viremic infection

Similar data: Urban-lab (J Virol 2018)
Potential Surrogate Markers for HBV: HBV-RNA

To predict viral relapse when treatment is stopped

Serves as a surrogate for transcriptionally active cccDNA, particularly if assay is specific for pgRNA. Encapsidated pgRNA can be enveloped and secreted, levels higher in patients on NA because reverse transcription of pgRNA to HBV DNA is blocked. Shown in some studies to predict viral relapse after discontinuation of NA. Specificity of current assays for pgRNA vs. subgenomic RNAs is unknown.

Lok, Zoulim et al., J Hepatology 2017
Mean change from baseline (log_{10} copies/mL)

Cohort I (600 mg BD) - 0.82
Cohort J (peg-IFN alpha-2a + 600 mg BD) - 1.51
Cohort K (peg-IFN alpha-2a + placebo) - 0.73

Yuen et al., EASL 2016 (LB06)

HBV-RNA is induced by NVR 3-778
Potential Surrogate Markers for HBV: HBcrAg

To correlate levels with intrahepatic HBV DNA
To predict viral relapse when treatment is stopped

Translated from HBV precore/core gene, can assemble into defective particles that are secreted. Shown in some studies to correlate with intrahepatic HBV DNA and cccDNA transcriptional activity and to predict viral relapse after discontinuation of NA.
Limitation: lack of sensitivity, composite biomarker

Lok, Zoulim et al., J Hepatology 2017
HBcrAg in different phases of HBV infection

Maasoumy, Cornberg et al., CMI 2015

Higher Risk for reactivation?
To quantify cccDNA from treated and untreated patients
To assess transcriptional activity: pgRNA/cccDNA ratio

cccDNA serves as a template for transcription of HBV RNA and translation of HBV antigens. Most direct measure of HBV cure. Adequate sample of liver tissue and stringent protocol to ensure specificity are required.
New treatments for HBV

- Immunotherapies
  - Host targeting agents
  - Direct acting antivirals
New treatments for HBV

...or simply to stop NA therapy?
Stopping TDF-Treatment: The Gemran FINITE-Study

*Berg, T et al., J. Hepatol. 2017; 67: 918–924*

CHB patients
- HBsAg-negative
- ≥4 years TDF therapy

Randomised 1:1

- TDF-stop
  - n = 21

- TDF-continue
  - n = 21

Primary endpoint:
HBsAg loss by Week 144

HBsAg kinetics in patients
- Stopping TDF therapy (n = 21)

- Remained off therapy
- Restarted therapy
- Time of restarting therapy
- HBsAg loss

HBsAg kinetics in patients
- Continuing TDF therapy (n = 21)

- Continued TDF

H. Wedemeyer  10-2018   HBV cure
Induction of IP-10, IL12, TNFα, IL-10 and T-cell responses after cessation of therapy

Hoener zu Siederdissen, Rinker, et al. JID 2016
Stopping NA-Therapy leads to an immune induction „auto-vaccination“

Höner zu Siederdissen et al., J infect Dis 2016; 214: 1492-97
Zimmer et al., J Infect Dis 2018; epub
Rinker et al., J Hepatol 2018 epub
How to use a new drug against HBV?
Putative Target Profile
for a New Curative Therapy for Hepatitis B
“The musts”

➢ No major safety signal

➢ Finite therapy
  *ideally 12 weeks – 48 weeks (max)*

➢ Endpoint: HBsAg loss
  *> 30% of patients (HBsAg decline sufficient?)*
HBsAg kinetics have to be considered in the development of novel curative therapies.
HBsAg kinetics have to be considered in the development of novel curative therapies.

- **Antiviral Therapy**
  - eraBicate

- **Graph**
  - **HBsAg**
  - **HBV DNA**

- **Question**
  - Continue Therapy?
  - Is this clinically meaningful?
Novel curative therapies as first line treatment?

Continue Therapy?
Is this clinically meaningful?
Was kann der Patient noch tun?

Kaffee ist gut für die Leber.
**Is Aspirin good or bad?**

**Good:** Lower HCC Incidence!

**Original Investigation**
October 4, 2018
Association Between Aspirin Use and Risk of Hepatocellular Carcinoma
Tracey G. Simon, MD; Yanan Ma, PhD; Jonas F. Ludvigsson, MD, PhD; et al

JAMA Oncology

**Bad:** Aspirin may cause cancer!

NEJM Sept 16 2018
Effect of Aspirin on All-Cause Mortality in the Healthy Elderly
John J. McNeil, et al., for the ASPREE Investigator Group

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*Death Related to Cancer*

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Cumulative Incidence (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>6</td>
<td>6.7</td>
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</table>

Hazard ratio, 1.31 (95% CI, 1.10–1.56)

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Placebo</th>
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<tr>
<td>0</td>
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<td>9589</td>
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<td>1</td>
<td>9481</td>
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<td>6</td>
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