HBV Cure – Definition and New Drugs in Development

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HBV Cure Meeting
November 2016
Boston
Disclosures for HLA Janssen

GRANTS
AbbVie, Bristol Myers Squibb, Gilead, Innogenetics, Janssen, Medimmune, Merck, Novartis, Roche

CONSULTANT
AbbVie, Arbutus, Benitec, Bristol Myers Squibb, Eiger Bio, Spring Bank Pharma, Gilead, GSK, Fujirebio, Ionis Pharmaceuticals, Janssen, Medimmune, Merck, Novartis, Roche
HBV – A Global Health Problem

• One-third of the world's population has evidence of HBV infection
• Chronic hepatitis B affects 350-400 million people
  World population 6 billion
  2 billion people with evidence of HBV
  Approximately 350 million with Chronic HBV (75% in Asia)
  25–40% die of cirrhosis or liver cancer

First Line Treatment: Tenofovir, Entecavir and PEG-IFN

Majority of patients not diagnosed
Natural history of CHB

New drugs: Is risk/benefit different depending on therapy, age of patient or phase of disease? Do different phases need different therapies?

The decision to treat is historically based on phase of disease and risk of disease progression

<table>
<thead>
<tr>
<th>Phase</th>
<th>Immune tolerant</th>
<th>HBeAg-positive CHB</th>
<th>Inactive carrier</th>
<th>HBeAg-negative CHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg status</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Very high</td>
<td>&gt;2000 IU/mL</td>
<td>&lt;2000 IU/mL</td>
<td>&gt;2000 IU/mL (fluctuating)</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated (fluctuating)</td>
</tr>
<tr>
<td>Liver histology</td>
<td>Normal or mild inflammation and limited fibrosis</td>
<td>Inflammation and fibrosis: degree varies</td>
<td>Normal or mild inflammation</td>
<td>Inflammation and fibrosis: degree varies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease progression</th>
<th>Low</th>
<th>Moderate to high</th>
<th>No, very low</th>
<th>Moderate to high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Not indicated*</td>
<td>Indicated</td>
<td>Not indicated</td>
<td>Indicated</td>
</tr>
</tbody>
</table>

* Treatment indicated in some patients

Key Considerations for Current Treatment Options

- HBV nucleos(t)ides are highly effective and generally well tolerated, but with low rates of successful discontinuation.

- Long-term nucleos(t)ide-analogues reduce cirrhosis, liver failure and HCC; safety remains to be determined but appears very good.

- PEG-IFN monotherapy is finite but only effective in subgroup of patients and its use is limited due to toxicity.

- Thus, unlike in HCV drug development there is effective and safe therapy available which suppresses HBV.
Why is Finite Therapy a Goal for HBV Treatment?

Younger patients may find lifelong treatment hard to accept.

Women who want to become pregnant.

Patients reluctant to start treatment.

Working days lost to hospital visits.

Cost savings to healthcare system.

Long-term adherence issues.
Important Issues for HBV Drug Development

- Low vaccine uptake in adults
- Still many CHB undiagnosed
- Many countries cannot provide long term therapy to patients with CHB
- Unapproved Combination drugs have been studied for HCV, NAFLD and HBV
What can be considered as a defined cure?

• **Virological cure**
  – elimination of cccDNA
  – lowering or silencing cccDNA
  – Undetectable HBV DNA in serum
  – Off-therapy HBsAg loss

• **Disease cure**
  – No risk of progression to liver failure or HCC
  – Identifiable by clinical parameters, biomarkers or gene signatures
Is HBV Treatment Paradigm Changing?

**Current PARADIGM**
- Indefinite Treatment
- Poor off-Rx response
- Reduces overall mortality
- Reduce but does not eliminate the risk of HCC
- Potent NAs: suppresses viral replication but cannot cure the disease

**New PARADIGM**
- Finite treatment duration
- Sustained off-Rx response shift towards endpoint of true immune control & HBsAg seroconversion
- No increased risk of mortality and HCC
- New HBV treatments with increased chance of curing disease
Defining HBV Cure

**Functional cure**
- Associated with clinical benefit (disease progression and HCC)
- Off-therapy sustained HBV suppression and disease remission
- HBsAg seroconversion and cccDNA inactivation/reduction
- Risk under immunosuppression
- Feasible

**Complete cure**
- Associated with clinical benefit (disease progression and HCC)
- HBsAg seroconversion and cccDNA eradication
- Feasibility very uncertain

### Survey: Surrogate for HBV cure (true/false)

#### Best endpoint for HBV cure

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg seroconversion</td>
<td>61</td>
<td>92.4%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>43</td>
<td>65.2%</td>
</tr>
<tr>
<td>HBsAg decline</td>
<td>22</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents $n=66$ about 45% academic, 45% industry, 10% rest group
Approaches to Therapy

Viral targets - DAA
- Viral entry
- cccDNA formation/ transcription/degredation
- RNA intermediates
- Encapsidation
- DNA replication
- Assembly
- Release

Immunomodulators
- Innate immune response
  - IFN
  - TLR agonists
  - RIG-I agonists
- Adaptive immune response
  - Anti-antagonists (checkpoint inhibitors)
  - Vaccination
HBV cure – Compounds in Development

Entry inhibitors:
e.g., Mycudex, ezetimibe, cyclosporine derivatives...

Entry via NTCP

siRNA:
e.g., ALN-HBV, TKM-HBV, ARC-520/521, Lais HBV

CpAM:
e.g., NVR 3-778, AT-130, BAY41-419, GLS4...

NUC:
e.g., TAF (GS7340), AGX-1009, CMX-157, besifovir, ...

Translation

Encapsulation

Reverse transcription

(-) strand synthesis

(+) strand synthesis

HBx, HBe

HBs, HBe

Recycling of nucleocapsid

Virion assembly

Secretion of HBsAg

Assembly and secretion of HBsAg particles

Inhibitors of HBs release:
e.g., Rep2129

cccDNA:
e.g., CRISPR/Cas9, IFN-α, LT-β, sulfonamides, HDAC inhibitors...

Integration

Regulation of host-gene expression

Hepatocyte

B cells

CD8+ cells

CD4+ cells

Adaptive immune responses

Innate responses

Immune modulation:
- PRR agonist or immune-stimulator:
e.g., GS9620, TLR8-L, SB9200, CYT107, INO1800
- PD1/PDL1 or CTLA4 inhibitors:
e.g., Nivolumab, Pidilizumab, MEDI-4736, Lamlisolizumab, MPDL3280A, AMP-224
- Therapeutic vaccine:
e.g., TO-1050, GS4774, DV601, Altravax HBV, Chimigen

Testoni & Zoulim, Hepatology 2015; Durantel & Zoulim, J Hepatol 2016
Combination Approaches

- **Viral target A** + **Viral target A** → **NA + NA**
- **Viral target A** + **Viral target B** → **NA + RNAi**
- **Immune Target A** + **Immune Target B** → **TLR7 + Vaccine**
- **Viral target A** + **Immune Target A** → **NA + TLR7**
## Multiple Viral Targets

### Pros
- More profound suppression
- Higher barrier to resistance – not necessary with nucs
- Reduce immuno-suppressive effects of HBV → combo 4
- Safety – in context of nuc suppressive therapy

### Cons
- Same target – only as good as most potent
- May be hard to assess efficacy
- No synergy…or even antagonism?
- Safety
Viral + Immune Target

• Appears attractive option
• HBV impairs innate and adaptive immune function
  – Viral replication
  – Viral protein production
• Viral inhibition → improve immune function and responsiveness
• Immunotherapy – the knock-out punch!
Attractive Combinations

**HBV DNA suppression** + **Viral protein depletion (s, x, core)** + **Immuno-therapy**

- Nuc
- RNAi
- TLR/RIG-I agonist

- +/- cccDNAi
- +/- entry inhibitor
- +/- RNAi
- +/- CpAM

May not need all 3 ‘classes’…mix and match
Current endpoints in HBV treatments

Biochemical: ALT normalization
Virological: HBV DNA decline/undetectability
Serological: HBsAg/HBeAg loss/seroconversion
Histological: Reduction of necrosis, inflammation, fibrosis
Combined: Most often HBeAg, HBVDNA and ALT
Endpoints: Key considerations

- What surrogate markers of efficacy to monitor success: Immunologic, Virologic, Pathologic?
- Phase 2 or 3 studies
- Primary & secondary endpoints
- Antiviral vs. immunomodulatory drugs
- Treatment naive vs. virally suppressed patients
- Timing of endpoint assessment: on- or off-treatment
- Efficacy criteria for further development of drug
Clinical trial phases

**Phase 1**
Safety
- **Phase 1a**
  - Safety of single ascending dose
- **Phase 1b**
  - Safety of multiple ascending doses
- 20-100 volunteers

**Phase 2**
Efficacy & Safety
- **Phase 2a**
  - Optimal dose
- **Phase 2b**
  - Efficacy prescribed dose
- 100-200 patients

**Phase 3**
Efficacy & Safety
- Comparison to standard of care
- 500-2000 patients

**Phase 4**
Post-marketing
- Safety surveillance in ‘real-life’ patients
- 500-2000 patients

Pharmacokinetics & pharmacodynamics
## Experimental HBV treatment in naive vs virally suppressed patients

<table>
<thead>
<tr>
<th>Treatment Naive</th>
<th>Suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>Have safe and effective therapy with reduction of HCC and improved survival</td>
</tr>
<tr>
<td>Active Disease</td>
<td>Partial immune restoration may benefit immune modifying therapy</td>
</tr>
<tr>
<td>HBVDNA can be used as a biomarker</td>
<td>Potentially better protection against flares</td>
</tr>
<tr>
<td>No resistance</td>
<td>May have more objections to accept experimental therapy</td>
</tr>
<tr>
<td>May be more likely to accept finite therapy</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Naive vs Suppressed**
- Younger patients are more likely to benefit from experimental therapy due to their active disease and lack of resistance.
- Suppressed patients may have less objection to accepting experimental therapy due to the potential for improved survival and reduced HCC.
In principle, rather not:
• All HBV treatments aimed at common clinical goal
• Association with clinical endpoint is essential

But:
Different mechanism of action $\rightarrow$ different response durability
• HBsAg loss with immune modifying treatment vs. viral treatments such as RNA interference

Different validated endpoints could be used for different treatments in phase 2 studies (proof of concept) also because drugs with different MOA and endpoints could potentially be combined into one regimen.
HBeAg (+) patients: More HBsAg decline with PEG-IFN than ETV

**HBV DNA decline**

<table>
<thead>
<tr>
<th>Week</th>
<th>PEG-IFN (N=61)</th>
<th>ETV (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>-4.5</td>
<td>-2.2</td>
</tr>
<tr>
<td>24</td>
<td>-3</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>-1</td>
<td></td>
</tr>
</tbody>
</table>

**HBsAg decline**

<table>
<thead>
<tr>
<th>Week</th>
<th>PEG-IFN (N=61)</th>
<th>ETV (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>-0.94</td>
<td>-0.38</td>
</tr>
<tr>
<td>24</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>-2</td>
<td></td>
</tr>
</tbody>
</table>
Sustained Response: ETV Peg-IFN add-on vs. ETV ARES Study

ETV PEG-IFN add-on
- 81% Continue ETV therapy
- 19% Response: HBeAg loss, normal serum ALT and HBV DNA <2000 IU/mL
- 21% Stop Rx
- 79% Sustained Response

ETV monotherapy
- 90% Continue ETV therapy
- 10% Response: HBeAg loss, normal serum ALT and HBV DNA <2000 IU/mL
- 75% Sustained Response
- 25% Stop Rx

Response: HBeAg loss, normal serum ALT and HBV DNA <2000 IU/mL

Brouwer et al. Hepatology 2015
Endpoint differentiation based on clinical study phase?

**Phase 2a, b**
- Proof of concept
- Dose finding
- Safety very important
- On- and off-treatment efficacy

**Phase 3**
- Aim is functional cure
- Comparison to standard treatment
- Sustained response off-treatment
### Survey: Primary efficacy endpoints for phase 2/3 trials aimed at virologic cure

#### Antiviral therapy

<table>
<thead>
<tr>
<th>Endpoint Description</th>
<th>Phase 2 Rank</th>
<th>Phase 3 Rank</th>
<th>Phase 2 Rank</th>
<th>Phase 3 Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum HBV DNA undetectable</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sustained decrease in HBsAg level by $&gt;1 \log_{10}$ IU/mL off treatment</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HBsAg negative</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Maintained decrease in HBsAg level by $&gt;1 \log_{10}$ IU/mL on treatment</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Anti-HBs positive</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Restoration of T cell response to HBV antigens</td>
<td>N/A</td>
<td>N/A</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

#### Immunomodulatory therapy

<table>
<thead>
<tr>
<th>Endpoint Description</th>
<th>Phase 2 Rank</th>
<th>Phase 3 Rank</th>
<th>Phase 2 Rank</th>
<th>Phase 3 Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum HBV DNA undetectable</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sustained decrease in HBsAg level by $&gt;1 \log_{10}$ IU/mL off treatment</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>HBsAg negative</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Maintained decrease in HBsAg level by $&gt;1 \log_{10}$ IU/mL on treatment</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
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<td>5</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Restoration of T cell response to HBV antigens</td>
<td>N/A</td>
<td>N/A</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

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Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents $n=66$ about 45% academic, 45% industry, 10% rest group
Survey: Prediction of HBsAg loss

Assuming HBsAg loss is reliable surrogate for cure what is the desired response in phase 2 and 3 studies on antiviral and immune therapies to move to the next phase?

<table>
<thead>
<tr>
<th>Antiviral &amp; immunomodulatory therapies</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg level decrease by $&gt;1\log_{10}$ IU/mL in $&gt;50%$ participants</td>
<td>31 (47.0%)</td>
<td>12 (18.2%)</td>
</tr>
<tr>
<td>HBsAg loss in $&gt;10%$ participants</td>
<td>18 (27.3%)</td>
<td>21 (31.8%)</td>
</tr>
<tr>
<td>HBsAg loss in $&gt;30%$ participants</td>
<td>17 (25.8%)</td>
<td>33 (50.0%)</td>
</tr>
</tbody>
</table>

Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents n=66 about 45% academic, 45% industry, 10% rest group
HBeAg positive CHB: PEG-IFN α-2b
HBsAg decline in those who achieve HBsAg loss

Baseline Mean HBsAg 4.5 log

* At End-Of-Follow-Up or Long-Term Follow-Up

Sonneveld et al. Hepatology 2011
Survey: When should primary efficacy endpoints be assessed in phase 2/3 trials aimed at HBV virologic cure?

<table>
<thead>
<tr>
<th>Survey AASLD/EASL HBV Treatment Endpoints Workshop: respondents n=66 about 45% academic, 45% industry, 10% rest group</th>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Antiviral therapy</th>
<th>Immunomodulatory therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 2</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Month 6 off treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 (45.5%)</td>
<td>42 (63.6%)</td>
<td>33 (50.8%)</td>
</tr>
<tr>
<td>Month 6 on treatment</td>
<td>25 (37.9%)</td>
<td>4 (6.1%)</td>
</tr>
<tr>
<td>Month 12 off treatment</td>
<td>N/A</td>
<td>14 (21.2%)</td>
</tr>
<tr>
<td>Month 12 on treatment</td>
<td>11 (16.7%)</td>
<td>6 (9.1%)</td>
</tr>
</tbody>
</table>
New Virologic and Host Markers Endpoints?

Current

Virologic Markers
- HBV DNA (q, non q)
- HBsAg (non q)
- HBsAg (q)
- HBeAg

Host Markers
- Anti-HBs (q/non q)
- Anti-HBc (q/non q)
- IgM and IgG
- Standard liver tests
- Imaging

Experimental

Virologic Markers
- HBcrAg (q)
- cccDNA (q)
- Integrated DNA (q)
- HBV RNA

Host Markers
- PD1, Tim3, CTLA4 expression (q) on HBV-specific CD8 T cells by Flow cytometry
- CD127 on HBV-specific T cells by Flow cytometry/ functional assays
- Cytokines (q)
- HBsAg epitopes
New Kits on the Block

- Further standardization and validation of tests needed
- Association with clinical outcome is preferred or needed for further use
- Of interest to dissect mechanism of response in treatments targeting host and virus
HBV cure - Remaining challenges

Basic science
- cccDNA biology
- Regulation of HBV specific immune response

Translational issues
- Standardized assays for cccDNA quantification and epigenetics
- Clinical immunology assays
- Studying viral integration

Clinical trials, drug evaluation, new conceptsTx
- New regulatory path
- Re-defining patient populations, virus characteristics, etc.
- New endpoints linked to cure and treatment strategy
- Combination of investigational drugs
- Safety: major issue (NUCs are safe !)

Conclusions

- NA are effective, safe and not so easy to replace
- Shift towards endpoint of true immune control, functional cure and HBsAg seroconversion
- New Viral agents: HBV entry inhibitors, small interfering RNA, capsid inhibitors promising but early in development
- Direct ccc-DNA inhibition may be needed but is difficult to reach
- Immune modification: TLR/RIG-I agonist, therapeutic vaccination, PD1-PDL1 blocking in development
- Combination therapy most likely needed!
- The science is the ‘easy part’…getting these agents into people, doing the right trials and getting them approved is a whole other story…
Conclusions

• Quantitative HBsAg and HBVDNA will probably be the most important biomarkers used for endpoint in phase 2 and 3 studies

• Endpoints are different in naive vs suppressed patients

• Endpoints may not have the same meaning for different drugs

• For proof of concept (phase 2) studies different validated endpoints can be used for different compounds depending on their MOA, also to allow future combination therapy
SPARES
Other Questions for HBV Cure studies

- Which patients should and can we treat with new drugs?
  - Should patients be already suppressed on nucs?
  - Is risk/benefit different depending on therapy, age of patient or phase of disease?
  - Do different phases need different therapies?
Conclusions

Endpoint selection will differ between phase 2 and 3 studies:

**Phase 2**
- Response can be assessed on- and off-treatment
- HBsAg decline $>1$ log, HBsAg loss, HBVDNA decline $>1$ log or HBVDNA undetectable

**Phase 3**
- Response should be assessed at least 6 months off-treatment
- HBsAg loss/seroconversion and HBVDNA undetectable
- More definite endpoint reflecting functional cure of HBV infection
Viral Targeting Combos

- Targeting different steps in viral lifecycle may lead to greater/even complete suppression of replication
- May still require long-term therapy to clear existing infected hepatocytes...especially if a leak persists
- Given safety & potency of nucs...logical choice to combine with newer agents
- But could combine any 2 or more viral targeting agents – challenging studies (safety, monotherapy for each, different companies...)
- **Key issue:** need assays to detect low level replication below current LOD to determine efficacy
HBV Curative Regimen?

**Antiviral**
- Prevent viral spread, cccDNA re-amplification

**Immune activator**
- Activate antiviral immunity or relieve repression of the system

**HBV Functional Cure**

**HBV antigen inhibition**
- Inhibit other components in HBV life cycle [entry or cell-spread, capsid, HBX, HBsAg]

**cccDNA inhibitor**
- Deplete or perturb cccDNA
Summary

- Multiple promising therapeutic approaches
- Combining tools to:
  1. Improve viral suppression to ‘plug the leak’ and prevent replenishment of cccDNA
  2. Promote immune clearance
- Combination improved antiviral + immunotherapy +/- viral protein depletion
- The science is the ‘easy part’…getting these agents into people, doing the right trials and getting them approved is a whole other battle…
Chronic HBV: a Dynamic and Heterogeneous Disease

- Phases neither clear nor distinct
- Varying levels of HBsAg even in inactive
- Immunologic status between stages fluid
- A high level of HBV-DNA integration and clonal hepatocyte expansion in young patients even immune tolerant indicating that possible hepatocarcinogenesis even in patients with early stage CHB
<table>
<thead>
<tr>
<th>Virological Markers to Follow CHB Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV DNA</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Quantitative HBeAg</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Quantitative HBsAg</strong></td>
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</tbody>
</table>

Immune control: HBeAg neg and low HBVDNA
New HBV Treatments

**Virology**
- Entry inhibitors
- cccDNA Degradation/Silencing/Elimination
- RNA interference (RNAi)/Gene silencing
- Assembly (Nucleocapsid) inhibitors
- New Nucleos(t)ide Analogues

**Immunology**
- PEG-IFN Lambda
- TLR agonists
- Therapeutic vaccination
- PD-1, PDL-1 Blocking
Other Potential Viral and Immunologic Endpoints in Phase 2 and 3 Studies

**Viral**
- Hepatitis B core-related antigen (HBcrAg)
- HBV RNA in serum
- (Quantitative) cccDNA in liver/blood
- HBsAg epitope mapping

**Immunologic**
- HBV-specific T & B-cell response
- T-lymphocyte markers
- Expression of inhibitory molecules (PD-1, Tim-4, CTLA4)
- Quantitative anti-HBs
- Anti-HBc (IgM/total)
Advances in HBV treatment

1957 Discovery interferon

1990 Discovery PMEA

1991 Discovery lamivudine (3TC)

1991 Discovery interferon alfa-2b licensed

1998 Discovery entecavir

1999 Lamivudine (3TC) licensed

2001 Discovery telbivudine

2003 Adefovir dipivoxil (PMEA prodrug) licensed

2005 Peginterferon alfa-2a, Peginterferon alfa-2b* licensed

2007 Telbivudine licensed

2008 Tenofovir licensed

2006 Entecavir licensed

2007 Peginterferon licensed

2008 TAF licensed

Adapted from: ClinicalCareOptions.com

* Specific countries only
Current HBV treatments

- PEG-IFN for few patients, effective in some
- ETV/TDF for most CHB patients, very effective (>95%)
- IFN-NUC for selected patients, TAF available in 2017
- Prevention of clinical decompensation, improvement of portal hypertension, HCC the only complication
- Excellent 5-yr overall and liver-related survival
- New strategies/drugs needed to reduce HCC and to improve HBsAg loss rates
Primary endpoint catered to treatment modality and patient group?

- Antiviral Therapy
- Immunomodulatory Therapy
- Combination Therapy

- Treatment naive
- Virally suppressed