New Treatments for Chronic Hepatitis B

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EASL Clinical Practice Guidelines on the management of HBV infection

Choice of therapy: Potent NA with high barrier to resistance regardless of the severity of liver disease

- TAF, TDF and ETV as monotherapies are preferred
- LAM, ADV and LdT are not recommended

<table>
<thead>
<tr>
<th>Indications for selecting TAF or ETV over TDF</th>
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<tr>
<td>Age &gt;60 years</td>
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<tr>
<td>Bone disease</td>
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<tr>
<td>Chronic steroid use or use of other medications that worsen bone density, history of fragility fracture, osteoporosis</td>
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<tr>
<td>Renal aberration (eGFR &lt;60 min/mL/1.73 m²; albuminuria; low phosphate; haemodialysis)</td>
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<tr>
<td>• ETV dose adjusted if eGFR &lt;50 mL/min</td>
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<tr>
<td>• No dose adjustment of TAF is required in adults or adolescents* with estimated CrCl ≥15 mL/min or in patients with CrCl &lt;15 mL/min who are receiving haemodialysis</td>
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<td>TAF preferred to ETV in patients with previous NA exposure</td>
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*Aged at least 12 years and of at least 35 kg body weight

EASL. J Hepatol 2017; 67:370-98
Why are new agents needed for CHB?

• Most patients need long-term NA therapy; relapse rate high after stopping treatment

• Ultimate aim would be to ‘cure’ CHB
  – Functional cure
    • Off-therapy persistent HBV suppression
  – HBsAg loss and seroconversion
  – cccDNA eradication
  – Prevention of negative outcomes (HCC)


cccDNA: covalently closed circular DNA
HBV therapies: new targets, new drugs, new aims

Immunomodulation
- Toll-like receptors agonists: **GS-9620**
- Anti-PD-1 mAb: **BMS-936559, CYT107**
- **SB9200**
- Therapeutic vaccines: **GS4774,ABX203**

Entry inhibitors (HBV/HDV)
- Lipopeptides: **Myrcludex B**

RNA interference, (siRNA): **ARC-520, ARC-521, ARB-1740**

Inhibition of HBsAg release: **REP 9AC, REP2139-CA**

Polymerase inhibitors
- Nucleos(t)ide analogues: **TAF, amdoxovir, MIV-210, besifovir**
- Non-nucleoside: **LB80380**

Inhibition of nucleocapsid assembly: **Bay 41-4109, NVR 3-778, AB-423, JNJ 56136379NVR 3-778**

Targeting cccDNA:
- HAPs
- Chromatin-modifying enzymes

HBV ENTRY INHIBITOR
Identification of NTCP as an HBV receptor

NTCP = sodium taurocholate cotransporting polypeptide

HBV infectivity domains

N-terminal myristoylation of L protein for plasma membrane association

Pre-S1 aa 2-48 specifically interacts with NTCP

Antigenic loop (AGL) of the S domain for HSPG binding and membrane fusion

Myrcludex B = myristoylated peptide encompassing aa 2-48 of the Pre-S1 region

Urban S, et al Gastroenterology 2014;147:48-64
Phase 1 study on health volunteers for Myrcludex B

• Non-linear PK up to dose of 20mg, receptor saturation at 10mg to 20mg doses

• Readily SC bioavailable

• Very well tolerated, no serious adverse events

• Adverse events or lab abnormalities transient and not related to the drug

• No anti-drug antibodies detected

Interim results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection

- 120 HBV/HDV co-infected patients randomized into 4 treatment arms in a ratio of 1:1:1:1 – 30 patients per arm
- Patients pretreated with tenofovir for ≥12 weeks
- Myrcludex B was self administered by patients once daily SC
- All patients received tenofovir (oral QD) during entire study period

Drop in HDV RNA but no change in HBsAg levels in all arms

RNA INTERFERENCE
The RNA therapeutic aims to reverse immune suppression.

**HBV virion**

Infection → Hepatocyte → HBV DNA → mRNA → Viral protein production → Viral antigens (HBsAg, HBeAg)

- Reduced viral replication
- Immune suppression unchanged
- Reduction/elimination of reinfection, contagion

**HBV virion**

Infection → Hepatocyte → HBV DNA → mRNA → siRNA → Reduced viral protein production → Reduced viral replication

- HBsAg loss and functional cure
- Reduced viral antigen

mRNA: messenger RNA
A phase 2a study evaluating the multi-dose activity of ARB-1467 in HBeAg-positive and negative virally suppressed patients with HBV

**ARB-1467**: 3 synthetic, double-stranded, siRNAs directed against HBV mRNAs

Adult CHB patients on ETV or TDF

**Efficacy**

- HBeAg-negative ARB-1467 0.2 mg/kg
- HBeAg-negative ARB-1467 0.4 mg/kg
- HBeAg-positive ARB-1467 0.4 mg/kg
- Placebo

Stepwise, additive reductions with multiple doses (>1 log10 IU/mL in 5/11 patients with 0.4 mg/kg)

No significant differences in serum HBsAg between HBeAg-negative and HBeAg-positive

Streinu-Cercel A, et al. EASL 2017, Amsterdam. #SAT-155
Multi-dose activity of ARB-1467 in HBeAg-negative virally suppressed subjects with HBV

Week 0  8  12  24  48  72

Cohort 1  
N=8  
HBeAg-  
0.2 mg/kg QM

Cohort 2  
N=8  
HBeAg-  
0.4 mg/kg QM

Cohort 3  
N=8  
HBeAg +  
0.4 mg/kg QM  
Cohort 3 were HBeAg+, data not presented

Cohort 4  
N=12  
HBeAg-  
0.4 mg/kg BIW  
Responders only

Randomized 3:1 active:PBO

*Responder criteria: HBsAg ≤1000 IU/mL with ≥1 log_{10} decline during the first 10 wks of treatment

Overall HBsAg and HBV RNA declines by cohort (HBeAg−)

Mean change from BL HBsAg

7/11 had HBsAg reductions >1 log_{10} reduction

Mean change from BL HBV RNA

No correlation between HBsAg and HBV-RNA declines

Cohort 2
Cohort 4 (all)
Cohort 4 (responders)

Agarwal K, et al. AASLD 2017, Washington DC. #40
CAPSID INHIBITOR
HBV Core Protein

- HBV Core plays multiple essential roles – high efficacy potential for inhibitors
- Core proteins highly conserved – potential broad-spectrum activity across genotypes
- Core functions can be allosterically modulated by binding of small-molecule inhibitors

![Diagram of HBV nucleocapsid and functions]

1. Capsid Assembly
2. cccDNA replenishment
3. Nuclear Function

- Suppression of Viral replication
- Suppression of Innate immune responses (ISGs)
- cccDNA maintenance & transcription
Maximum HBV DNA reduction with peginterferon and NVR 3-778 combination

- Optimal trough level and maximum effect on HBV DNA reduction at 600 mg bd dose (1.72 log IU/ml)
- Additive effect of NVR 3-778 with PegIFN on HBV DNA (1.97 log IU/ml) and RNA (1.51 log copies/mL)
- 1 SAE of grade 3 papulovesicular hand-foot rash
**JNJ-56136379: Capsid assembly modulator (CAM)**

- Potent in vitro inhibitor of HBV replication
  - Interferes with capsid assembly, resulting in formation of non-functional capsids w/out RNA, DNA
  - Prevents cccDNA formation during de novo infection, probably by interfering w/capsid disassembly
- 1st report of multiple doses in humans with CHB x 28 days
- 24 non-cirrhotic, treatment naive patients

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**HBV DNA change from baseline (Log10 IU/mL)**

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Pooled PBO (n=8)</th>
<th>JNJ-379 25 mg QD (n=8)</th>
<th>JNJ-379 75 mg QD (n=8)</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
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<tr>
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<tr>
<td>4</td>
<td>-3</td>
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* and *** refer, respectively, to one and three patients with HBV DNA <LLOQ of the HBV DNA assay

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IMMUNE MODULATORS
TLR-7 agonists

- TLR-7 activation leads to secretion of type I IFN, T-cell co-stimulation and B-cell differentiation
- GS-9620 is an oral TLR-7 agonist with nanomolar potency
- Preclinical studies show GS-9620 reduces HBsAg and HBV DNA in woodchucks and chimpanzees
- Phase 1a single ascending dose study complete: favourable safety profile shown in healthy volunteers (N=75)

GS-9620 is an investigational agent and not licensed for use in CHB; IRF: interferon regulatory transcription factor; NFκB: nuclear factor kappa B; ISG: interferon stimulating genes

Gane E, et al. AASLD 2013; Abstract 9896
TLR-7 agonist (GS-9620): significant dose dependent ISG15 mRNA induction but no change in HBsAg decline.

GS-9620 treatment was seen to have a favourable safety profile and was well tolerated; Longer treatment durations required to assess safety and efficacy in CHB patients.

MAD: multiple ascending dose; SAD: single ascending dose.

Phase 2, double-blind, randomized, PBO-controlled study in patients with chronic HBV infection who were not being treated (GS-US-283-1062)

- Vesatolimod (GS-9620) was safe and well tolerated in patients with chronic HBV infection
- Dose-dependent pharmacodynamic induction of cytokines and ISGs was demonstrated, although this did not result in significant HBsAg declines

Therapeutic vaccination with GS-4774

- GS-4774 is a yeast-based vaccine expressing recombinant X, large S and core HBV antigens

<table>
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<tr>
<th>GS-4774 structure</th>
<th>GS-4774 recombinant antigen</th>
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<tr>
<td>M</td>
<td>X</td>
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</table>

- X = 60 amino acids
- Large S = 399 amino acids
- Core = 182 amino acids
- M = MADEAP metabolic stability tag
- His$_6$ = 6 histidine-tag

- Detectable HBV-specific immune responses in healthy individuals for HBsAg, HBcAg and HBx

Gaggar A, et al. AASLD 2013; Abstract 9952; Clinicaltrials.gov NCT01779505

GS-4774 is an investigational agent and not licensed for use in CHB; env: envelope
No significant decline in HBsAg with therapeutic vaccine GS-4774 among patients on long-term antiviral drugs

- GS-4774 is a yeast-based vaccine expressing recombinant X, large S and core HBV antigens
- Randomized controlled trial in CHB patients on oral antiviral (OAV) for >1 year; on GS-4774 every 4 weekly until week 20 and OAV till week 48


No HBsAg loss in all patients
A phase 1 study evaluating anti-PD-1 treatment with or without GS-4774 in HBeAg-negative chronic hepatitis B patients

Blockade of programmed cell death protein (PD-1) or its ligand (PD-L1) to rescue HBV-specific T-cell responses

Sentinel A (n=2)
- Nivolumab 0.1 mg/kg

Sentinel B (n=2)
- Nivolumab 0.3 mg/kg

Cohort A (n=10)
- Nivolumab 0.3 mg/kg

Cohort B (n=10)
- Nivolumab 0.3 mg/kg
- GS-4774 40 YU

Primary endpoint HBsAg

Gane E, et al. EASL 2017, Amsterdam. #PS-044
Retinoic acid-inducible protein I (RIG-I) agonist - ACHIEVE trial

SB 9200 = RIG-I activator

RIG-I

HBV pgRNA

HBV P protein

Reverse transcription
Viral replication

Type III IFNs

Dual antiviral effect against HBV

12 weeks (SB 9200 monotherapy QD)

12 weeks

Viread® (TDF) 300 mg

SB 9200 25 mg

SB 9200 50 mg

SB 9200 100 mg

SB 9200 200 mg

Placebo

- 20 non-cirrhotic HBV subjects per cohort
- Randomized 4:1 between SB 9200 and PBO

Cohort 1: HBeAg(−) (n=7); HBeAg(+) (n=9); PBO (n=4)

Mean HBV DNA \((\log_{10})\) SB 9200 vs PBO alone + TDF switch

TDF 300 mg

SB9200 arm

Placebo

Day 1 Week 2 WK 4 WK 8 WK 12 WK 14 EOS WK 24

Combination therapy approach will be required to achieve cure of HBV

Ag: antigen; TLR: toll-like receptor; Tx: therapeutic