Terapie future HBV

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Why update HBV Therapy?

- **Long-term results** of therapy with NUCs are excellent but, we hope for a «functional therapy» for HBV.

- **Recent advances** in HBV biology/Immunology (cycle of replication, in vitro model, technology)

- **Hope to ameliorate** the burden of viral hepatitis
Why update HBV Therapy?

- **Long-term results** of therapy with NUCs are excellent but, we hope for a «functional therapy « for HBV.

Side effects
Entecavir

Marengo & Marzano
Antivir Ther 2013

TDF

100%

Marengo & Marzano
APT 2014
Clinical experience with III gen NUCs:

Entecavir  100 pts (55 compensated cirrhosis)

Marengo, & Marzano Antiviral Therapy 2013
Bone and kidney toxicity induced by nucleotide analogues in patients affected by HBV-related chronic hepatitis: a longitudinal study

Paolo Maggi¹*, Vincenzo Montinaro², Armando Leone¹, Massimo Fasano¹, Anna Volpe¹, Chiara Bellacosa¹, Vito Grattagliano³, Laura Coladonato³, Giovanni Lapadula³, Teresa Santantonio⁴ and Gioacchino Angaran³

60 pts LAM⇒LAM+ADV⇒TDF

Figure 1. Profile of eGFR variations during the study period. Data represent mean±SD. A comparison of the mean values at each timepoint versus T0, by paired t-test, yielded statistical significance at T3 and T4 (*P=0.003) and at T5 (**P=0.001).

Figure 2. The percentage of patients with normal, insufficient or deficient plasma levels of vitamin D at different timepoints. A statistical comparison between different timepoints of the prevalence of sufficient, insufficient or deficient levels of vitamin D generated a significant difference ($\chi^2=28.063$, $P=0.002$). *$P<0.004$ versus T0 (after implementation at baseline).

J Antimicrob Chemother 2015; 70: 1150–1154
Suppression vs. cure: viral biology is the basis

**HBV**

10 genotypes
(Latent Reservoir)

- Host cell
- cccDNA
- Host DNA
- Nucleus

Long-Term Reduction of Viral Replication to Lowest Possible Level

**HCV**

6 genotypes
(No Latent Reservoir)

- HCV RNA

Definitive Viral Clearance

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Suppression

Cure

cccDNA = covalently closed circular DNA.

Drug levels, Genetic barrier and the virus

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daily production of virions per day</td>
<td>$10^{12} - 10^{13}$</td>
<td>$10^{12}$</td>
</tr>
<tr>
<td>half-life of free virions (h)</td>
<td>3–24</td>
<td>2–3</td>
</tr>
<tr>
<td>half-life of intracellular virions</td>
<td>months (dependent on infected cells $t_{1/2}$)</td>
<td>hours (not dependent on infected cells $t_{1/2}$)</td>
</tr>
<tr>
<td>mutation rate</td>
<td>high</td>
<td>very high</td>
</tr>
<tr>
<td>constraints due to ORFs in targeted viral enzymes</td>
<td>high</td>
<td>none</td>
</tr>
<tr>
<td>immune-mediated escape mutants</td>
<td>infrequent</td>
<td>frequent</td>
</tr>
<tr>
<td>Target cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>half-life of infected cells</td>
<td>months</td>
<td>weeks</td>
</tr>
<tr>
<td>size of susceptible cells compartment</td>
<td>small</td>
<td>probably large</td>
</tr>
<tr>
<td>intracellular viral reservoir</td>
<td>yes (integrated cDNA)</td>
<td>yes (cccDNA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no</td>
</tr>
</tbody>
</table>
HBV

Immune responses against HBV

Adaptive immunity
- B cells
- Dendritic Cell
- CD4+ T cell
- CD8+ T cell
- Kupffer cells
- Antibodies
  - anti-HBs
  - anti-HBe
  - anti-HBc

Innate immunity
- Protection
- Long-term control
- Clearance
- Early Defense

Overt
Innate
Adaptive

HBV DNA

Figure 2. A model of occult hepatitis B highlighting the potential role of the immune system. Other factors such as HBV mutations and co-infection with HCV also appear to have a role.

The future

1. New anti-HBV drugs
Liver levels of TFV, TFV-MP, and TFV-DP following oral administration of 5 mg TFV equivalents/kg of TDF or TAF for 7 days to male beagle dogs

2. COMBO PEG+NUC
Studies in patients and humanized mice indicate that combination treatments suppressing both HBV replication (NUCs) and cccDNA transcription (IFNα) may trigger significant antigen decline (HBe and HBs) – combination needs to be done in a smart way

- should have additive or synergistic activity against HBV
- should have no added toxicity
- may induce cccDNA loss or control and higher rates of HBsAg loss

Adapted from Thimme & Dandri, J Hepatol 2012;58:205-9
Induction by NUC therapy
Active $\rightarrow$ Inactive carrier off -therapy
(Innate response recostitution)
HBsAg+, HBV DNA < 2000 IU/mL,
HBsAg < 1000 IU/mL

“Reset strategy”
NUC discontinuation in Long term responders

Virologic relapse

Clinical relapse

Figure 1. Cumulative rate of virologic relapse up to week 48. Virologic relapse defined as HBV DNA >2000 IU/mL. Relapse rate calculated using Kaplan-Meier method.

**Induction by NUC therapy** → Early PEG addition
Active → Inactive carrier off -therapy
(Innate response recostitution)
HBsAg+, HBV DNA < 2000 IU/mL, HBsAg < 1000 IU/mL

“Induction strategy”
++ HBeAg+
Pre-treatment with NAs

Partial restoration

CD8+ T cell  NK cell

Boni, 2001; Boni, 2013

PEG-IFN

HBV NAs
Sequential therapy with entecavir and PEG-INF in patients affected by chronic hepatitis B and high levels of HBV-DNA with non-D genotypes

Department of Infectious Diseases, Amedeo di Savoia Hospital, University of Turin, Turin, Italy

*Corresponding authors

Journal of Viral Hepatitis, 2013, 20, e11–e19

Induction
ETV 0.5 mg/day
12 weeks

Association
ETV 0.5 mg/day +
PEG-INF alfa-2a 180 µg/week
12 weeks

Maintenance
PEG-INF alfa-2a
180 µg/week
36 weeks

Stopping rule at 12 weeks of PEG-INF
>-0.5 Log <HbsAg
>-2 Log <HBV-DNA

Entecavir 24 weeks

PEG-INF 48 weeks
Adding Pegylated Interferon to Entecavir for Hepatitis B e Antigen–Positive Chronic Hepatitis B: A Multicenter Randomized Controlled Trial (ARES Study)

Willem Pieter Brouwer, Qing Xie, Milan J. Sonneveld, Ningping Zhang, Qin Zhang, Fehmi Tabak,

\* Response is defined as HBeAg loss with HBV DNA <200 IU/mL at week 48. Responders were to stop ETV at week 72.
** 14/16 and 8/9 responders for add-on and monotherapy discontinued ETV at week 72 according to protocol, respectively.
*** Disease remission is defined as: HBeAg negative, normal ALT and HBV DNA <2000 IU/mL.

(HEPATOLOGY 2015;61:1512-1522)
PEG vs PEG+TDF vs TDF - Study Design

- Randomized, controlled, open-label study (N=740)
  - Stratified by screening HBeAg status and HBV genotype
- Inclusion criteria
  - HBeAg+ and HBV DNA ≥20,000 IU/ml; HBeAg- and HBV DNA ≥2,000 IU/ml
  - ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
  - No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

Start TDF during follow-up if prespecified safety criteria met

Marcellin P et al, AASLD 2014
Efficacy: On-Treatment Changes in HBsAg Levels at Week 48

Results: Change in Serum HBsAg Levels

Study Week

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change (log_{10} IU/mL)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF 120 wk</td>
<td>-0.3 log</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TDF+PEG 16 wk → TDF 32 wk</td>
<td>-0.5 log</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PEG 48 wk</td>
<td>-0.8 log</td>
<td>.016</td>
</tr>
<tr>
<td>TDF + PEG 48 wk</td>
<td>-1.1 log</td>
<td>.001</td>
</tr>
</tbody>
</table>

3 patients who were re-treated at Week 48 were excluded from Week 48 calculations. Error bars represent 95% confidence intervals.

Marcellin P et al, AASLD 2014
Results: HBsAg Loss Over Time (Week 72)

- 7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk →TDF 32 wk])
  - 5/7 had ≤1 week of therapy after HBsAg loss
Induction by NUC therapy $\rightarrow$ LTRs

PEG addition

Active $\rightarrow$ Inactive carrier $\rightarrow$ OBI (HBsAg-)

off -therapy

(Innate and Adaprive response recostitution)

HBsAg+, HBV DNA < 2000 IU/mL, HBsAg < 1000 IU/mL $\rightarrow$ OBI (HBsAg-)

“Consolidation strategy”

++ antiHBe+
**Partial restoration**

Partial restoration

+ CD8+ T cell

+ NK cell

Boni, 2001; Boni, 2013

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**PEG-IFN ADD ON STRATEGY**

**ARES (HBe+, ETV)** (Brouver, Hepatology 2014); increased HBsAg decline

**PEGON (HBe+, NA)** (Chi, AASLD 2014); increased Hbe loss, and HBsAg decline

**PEGAN (HBe-, NA)** (Bourliere, AASLD 2014); Low HBsAg loss (6.6%), low BL HBs predictive

**HERMES (HBe-, NA)** (Lampertico, AASLD 2014): Increased HBsAg decline
Why update HBV Therapy?

- **Recent advances** in HBV biology/Immunology (cycle of replication, in vitro model, technology)

- **Hope to ameliorate** the burden of viral hepatitis
Immune therapy

Therapeutic vaccines

- Innate (Linf T)
- Adaptive (Linf B)
Innate and Adaptive HBV-specific immune response and immune-based therapeutic development

Liang J et al, Hepatology 2015
## Prospects for new treatment Approaches

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Target</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunotherapeutic</td>
<td>PegIFN-α1a (IL29)</td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>rIL-7</td>
<td>rIL-21</td>
</tr>
<tr>
<td>TLR agonists</td>
<td>TLR7 (GS-9620)</td>
<td></td>
</tr>
<tr>
<td>Therapeutic vaccines</td>
<td>Adeno-virus approaches (TG1050)</td>
<td>Tarmogen (GI-13020)</td>
</tr>
<tr>
<td>Blocking T cell inhibitory receptors</td>
<td>Anti-PD-1 moAB (BMS936558)</td>
<td>Anti-PD-L1 moAb (BMS936559)</td>
</tr>
<tr>
<td>Intrahepatic blocking of suppressive cytokines / regulatory T cells</td>
<td>TGF-β inhibitors</td>
<td>T reg depletion (e.g. α-CD25, daclizumab)</td>
</tr>
</tbody>
</table>

Courtesy S Locarnini
TLR-7 agonists - GS9620

- GS9620 orally available TLR-7 agonist with nano Molar potency
- Selective for antiviral vs pro-inflammatory response
- Induction of the innate immune response by GS-9620 has been characterized in monkeys, chimpanzees and humans.
- Preclinical studies: reduces HBsAg, HBV DNA in woodchucks and chimpanzee
- Phase Ia single ascending dose complete: favourable safety profile shown in healthy volunteers

Toll-like receptor 7 (TLR-7) is a pattern-recognition receptor located in the endolysosomal compartment of plasmacytoid dendritic cells (pDC) and B cells. TLR-7 activation results in innate and adaptive immune stimulation through:
- Secretion of type I interferon (IFN) by pDC
- Increased expression on pDC of molecules associated with antigen (Ag) presentation and T-cell costimulation
- B Lymphocytes differentiation in immunoglobulin producing plasma cells
Decline in WHsAg with GS9620 in WHV-infected Woodchucks

Adapted from Menne et al. EASL 2011; #170; Lanford et al. Gastroenterology 2013

<table>
<thead>
<tr>
<th>WHsAb</th>
<th>WHV DNA</th>
<th>HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/7</td>
<td>-0.6</td>
<td>5/7</td>
</tr>
<tr>
<td>2/7</td>
<td>-1.0</td>
<td>1/7</td>
</tr>
<tr>
<td>3/7</td>
<td>-3.9</td>
<td>2/7</td>
</tr>
<tr>
<td>3/7</td>
<td>-4.7</td>
<td>0/7</td>
</tr>
</tbody>
</table>

Groups 4, 5

Representative plots; HCC: hepatocellular carcinoma; TLR-7: Toll-like receptor 7; WHsAb: woodchuck hepatitis surface antibodies; WHV: woodchuck hepatitis virus.
GS-9620 – oral TLR7 agonist HBV Efficacy Study

- HBV infected chimpanzees were selected as the animal model for antiviral efficacy.
- Approx. 6-fold less potent in chimpanzees in comparison to man.

- 3 HBV chronically infected chimpanzees
- Oral dosing tiw

- Significant reductions in serum HBV DNA and hepatitis B surface antigen (HBsAg) levels
- Sustained serum viral DNA reduction >1 log10 in all 3 animals
- Sustained serum HBsAg level reduction in 2/3 animals
- Hepatic and peripheral induction of IFN-stimulated genes (ISGs) (OAS1, MX1, and ISG15) at 1-mg/kg dose, with little or no increase in serum IFN

Landorf et al. Gastroenterology
GS-9620 treatment was safe and well tolerated in 84 patients with chronic HBV treated with 1 or 2 doses

Significant dose-dependent ISG15 mRNA induction was observed in peripheral blood

No serum IFN was detected in most of the patients

Longer treatment duration is required to evaluate safety and efficacy in patients with chronic HBV
Gilead/GlobeImmune Tarmogen® platform

- From recombinant *S. cerevisiae*
- Selectively activates T cells
- Safe and well tolerated
  - >300 subjects treated for up to 4 years
- Scalable, efficient manufacturing
  - 250 liter commercial scale
GS-4774
- Was well-tolerated in healthy subjects
- Elicited an immune response with monthly administration at all doses evaluated
- Elicited an immune response to recombinant antigens and peptides
- Immunogenicity was independent of host HLA Alleles

Further evaluation of GS-4774 in virally suppressed chronic HBV patients is ongoing
Eradication of intra-hepatic HBV
## Prospects for new treatment Approaches

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</thead>
<tbody>
<tr>
<td>HBV life cycle</td>
<td>HBV Pol</td>
<td>TAF</td>
</tr>
<tr>
<td></td>
<td>Viral entry</td>
<td>Myrcludex-B</td>
</tr>
<tr>
<td></td>
<td>cccDNA</td>
<td>Zinc finger nucleases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cccDNA conversion inhibitors</td>
</tr>
<tr>
<td></td>
<td>mRNA transcription/ stability</td>
<td>Zinc finger proteins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epigenetic silencers</td>
</tr>
<tr>
<td></td>
<td>Viral assembly</td>
<td>HAPs</td>
</tr>
<tr>
<td></td>
<td>HBV antigen secretion</td>
<td>REP 9AC’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small molecule inhibitors of HBsAg secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>e.g. glucovirs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>e.g. triazolo-pyrimidines</td>
</tr>
</tbody>
</table>

*Courtesy S Locarnini*
Strategies to Inhibit Entry of HBV and HDV into Hepatocytes.

Urban et al. Gastroenterology 2014,

**Cellular receptor:**
Liver bile acid transporter (NTCP) (Yan, eLife 2012)
HBV lifecycle and entry inhibitors

- HSPG: Heparan sulfate proteoclicans
- NTCP, encoded by SLC10A1: Sodium-taurocholate co-transporting polypeptide

Humanized chimeric uPA mouse model for the study of hepatitis B and D virus interactions and preclinical drug evaluation (Myrcludex B)
Mycludex B: Targeting Entry of HBV into Hepatocytes

HBV Phase 2a Results

- 30 evaluable patients
- 7 patients >1log HBV DNA
- 6 patients
- 2

0.5mg, 1mg, 2mg, 5mg

- BL
- week 12
- week 24

- 23%

10mg

- BL
- 8 evaluable patients
- week 10-12

- 87%

7 patients: >1log HBV DNA

HDV Pilot Study

- 7 evaluable patients

Myr 2mg

- BL
- week 24

- 85%

6 patients >1log HDV RNA

Myr 2mg +PEG Inf 180 μg

- BL
- week 24

- 100%

7 patients: >1log HDV RNA

Urban S. et al. AASLD2014
Myrcludex B Phase 2a clinical trial in HBV infected individuals

Study Design

- **Population**
  - HBeAg-negative chronic hepatitis B patients
  - > 6 months without treatment
  - HBV DNA >10,000 copies/mL
  - Active hepatitis: ALT increase or biopsy

- **Randomization into 6 treatment arms (n = 48), 8 patients per arm**
  - Myrcludex B: 0.5, 1, 2, 5 mg/day s.c. for 12 weeks + 12 weeks follow up
  - Myrcludex B 10 mg/day s.c. for 24 weeks + 12 weeks follow up
  - Control arm: Entecavir 0.5 mg/day orally

- **Endpoints**
  - Safety and tolerability
  - Biochemical response (ALT)
  - Virological response (HBV DNA, HBsAg)
  - Immunogenicity
  - Bile salt elevations

S. Urban et al, AASLD 2014
(B) Design of a Myrcludex B Pilot study in HDV/HBV co-infected individuals

- **Population**
  - Chronic hepatitis delta infected patients
  - > 6 month without treatment
  - Positive for anti HDAg-specific antibodies
  - Active hepatitis: ALT increase or biopsy

- **Randomization into 3 treatment arms (n = 24), 8 patients per arm**
  - Myr B: 2 mg/day, s.c. for 24 weeks followed by PEG-IFNα for 48 weeks; 24 weeks follow up
  - (Myr B: 2 mg/day, s.c. + PEG-IFNα) for 24 weeks followed by PEG-IFNα for 24 weeks; 24 weeks follow up
  - PEG-IFNα for 48 weeks; 24 weeks follow up

- **Endpoints**
  - Safety and tolerability
  - Biochemical response (ALT)
  - Virological response (HDV-RNA, HBV-DNA, HBsAg)
  - Immunogenicity
  - Bile salt elevations
Summary and conclusions

- **Myrcludex B** was very well tolerated at all doses.
- ALT normalized in 55% of patients at week 12 (mean decline from 76 U/l to 36 U/l)
- HBV serum DNA decline > 1log10 in 75% of patients at 10 mg dosing at week 12.
- HBV serum DNA decline > 1log10 in 17% at 0.5, 1, 2 and 5 mg dosing at week 12.
- No effects on HBsAg levels during treatment and follow up.
- Dose dependent increase in bile acid levels at doses > 1mg. Saturation of NTCP at 5 mg.
- Induction of Myrcludex B specific preS-antibodies with HBV-neutralizing potential.
  - **Myrcludex B** (2 mg) in combination with IFNα was well tolerated; one discontinuation (psoriasis)
  - ALT normalization in 6/8 patients under Myrcludex B monotherapy.
  - HDV serum RNA decline > 1log10 in 6/7 patient under mono- and 7/7 under combination therapy.
  - Negativation of HDV serum RNA in 5 patients under Myrcludex B/IFNα combination therapy.
  - Pronounced effect on HBV-DNA decline in Myrcludex B/PEG-IFNα-combination group; No effect on HBsAg levels.
  - Moderate bile salt increase at 2 mg Myrcludex B dosing.
  - Induction of Myrcludex B specific preS-antibodies with HBV/HDV-neutralizing potential preferentially in the Myrcludex B/IFNα combination group.
Determinants of Infectivity and Domain Structure of HBV Surface Proteins

Urban et al, Gastroenterology 2014
Surface mutants and HCC

Pre-S1 or S2 mutants

Humans

Truncated mutants

Spontaneous

L (M+S)

M (+S)

S

181

POL

I-II gen NUC(s) (LAM, ADV,LdT)
Rescue ther.

‘a’ determinant

Virion interior

Virion surface

N

COOH

X

S

M(+S)

L (M+S)

172

Rescue ther.

Pre-S deletion mutant

Pre-S wild type

Time in months

Cumulative incidence of HCC (%)

rtA181T detectable (n = 10)
P < 0.001

rtA181T undetectable (n = 113)

Cumulative incidence of HCC

Follow-up (months)

0.0

0.2

0.4

0.6

0.8

1.0

0

20

40

60

80

100

120

140

Figure 4. Comparison of cumulative incidence of HCC between patients with and without pre-S deletion mutants.

Chen Gastroenterology 2007

Yeh, BMC Cancer 2011
Targeting HBc protein / HBV capsid

Core inhibitors / Core Protein Assembly Modulators (CpAM)

- Phenylpropenamide derivatives (AT61, AT130) [Gilead]
- Heteroaryldihydropyrimidines (HAP-1 and Bay 41-4109)
- Sulfamoylbenzamide derivatives (DVR-23, DVR-56 and Novira Therapeutics NVR 3-778)
- BCM-599 [2-amino-N-(2,6-dichloropyridin-3-yl) acetamide family]
- Isothiafludine (pg-RNA packaging)

Hap12 CpAM

Hap12 blocks new cccDNA formation
- reduces the cccDNA pool
- repress residual cccDNA transcription
- leads to an inappropriate assembly of viral capsids

virus specific mechanism
Effect of ARC-520 on HBV core antigen expression in livers of HBV transgenic mice

Anti-HBcAg immunostain

Isotonic glucose  siControl  ARC-520

Strong reduction of core antigen in all liver hepatocytes in animals receiving ARC-520

Wooddell et al, Mol Ther 2013 May; 21(5) 973-85
cccDNA status in HBV patients

Histones

PCAF  p300  CBP  PCAF  p300  CBP

Histones

High Replication

Low Replication

Occult HBV

spontaneously iatrogenic immunosuppression

Low-replicative to latent infection

Epigenetic control
Immune-modulators to combat hepatitis B virus infection: From IFN-α to novel investigational immunotherapeutic strategies

Nathalie Isorce, Julie Lucifora, Fabien Zoulim, David Durantel
IFN-α inhibits HBV transcription and replication in cell culture and in humanized mice by targeting the epigenetic regulation of the nuclear cccDNA minichromosome

Belloni et al., J Clin Invest 2012;122:2: 529-537

Histone acetylation/methylation affects the regulation of gene expression

Histone acetylation/methylation affects the regulation of gene expression

IFNα treatment is accompanied by a decrease in the acetylation of cccDNA bound H4 histones in vitro

Active IFN-α repression of HBV transcription associated with 60-70% reduction of 3.5 kb pgRNA, 2.4-2.1 mRNA (pres/s RNA), without affecting levels of cccDNA copies per cell
RNAi therapeutics vs. nucleotide/side treatment of chronic Hepatitis B

Reduction/Elimination of Reinfection, Contagion

Reduced Viral Replication

Immune Suppression Unchanged

Reduced Viral Antigens

HBsAg seroclearance & functional cure
“The future”
What May a HBV Curative Regimen Look Like?

- NUC ± Entry inhibitor
  - Agent to prevent viral spread, cccDNA re-amplification

- Immune activator
  - Agents to activate antiviral immunity or relieve repression of the system

- cccDNA inhibitor
  - Selective agent to deplete or perturb cccDNA

- HBV antigen inhibition
  - Agents to inhibit other components in the HBV life cycle [entry or cell-spread, capsid, HBX, HBsAg]

Adapted from S. Locarnini, 2014