OCTOBER 11-12, 2024 MILAN, ITALY

DeltaCure 3rd International Meeting

What can we learn from HBV trials for HDV cure?

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Disclosures

I am not

Disclosures

I am not

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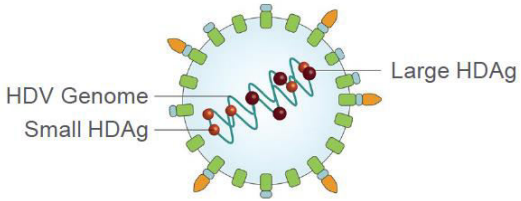
Relations that could be relevant for the meeting	Company names
Sponsorship or refund funds	Gilead, MSD, Roche, Abbvie, Bayer, Ipsen, Bayer,
Payment or other financial remuneration (Research Projects)	Ipsen
Shareholder rights	NA
Other relations (Speaking and Teaching) (Advisory Committees or Review Panels)	Gilead, Roche, Abbvie, Ipsen Evotec/Sanofi

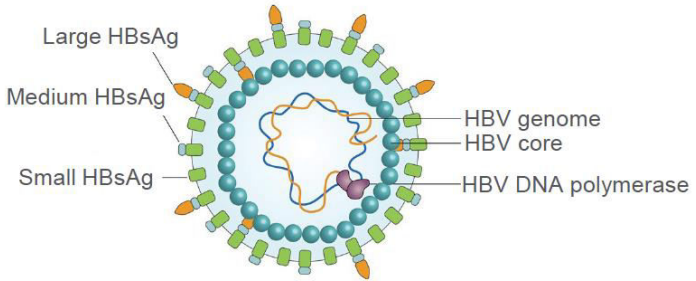
- compare the 2 viruses
- review the HBV cure concept
- focus on DAA (strategies of antiviral intensification and viral antigen load reduction)
- (try to) answer the question from the co-organizers

HDV



- (-) RNA virus (1.7kb) (satellite virus of HBV)
- one viral protein (HDAg), two ribozymes
- HDV RNP as an RNA mini-chromosome
- abundant RNP in HDV replicating cells
- Bulevirtide (BLV) approved in the EU, UK & CH
- PEG-IFN-α used off label but poorly tolerated
- low rate of durable undetectable HDV RNA off-treatment

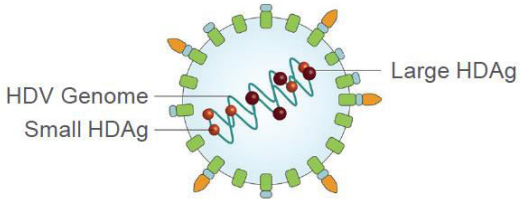
HBV



- dsDNA virus (3.2 kb) (helper virus of HDV)
- 7 viral proteins, one enzyme (pol)
- cccDNA as a viral mini-chromosome
- 1 to few cccDNA molecules per infected cell
- multiple pol/RT inhibitors (“NUCs”) approved
- IFN-α and PEG-IFN-α also approved
- current therapies improve patient outcomes, but “cure” is rare

mofified ftom S Fletcher (DZIF Eibsee 2024)

HDV



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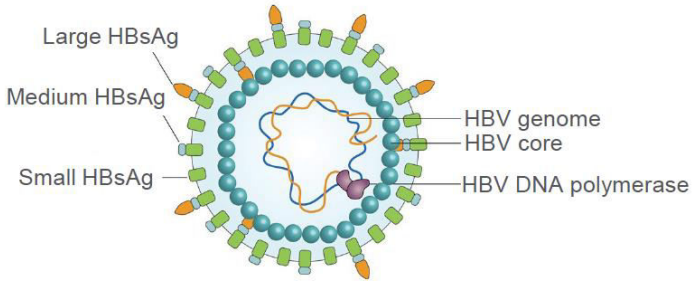

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the 2 viruses share the entry and the exit doors

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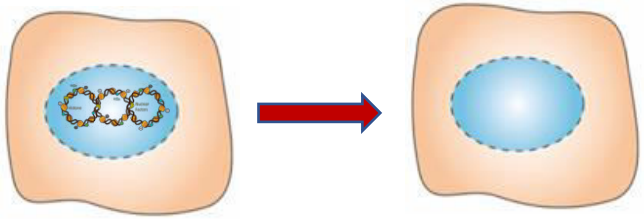
Key Concepts to Cure HBV Infection

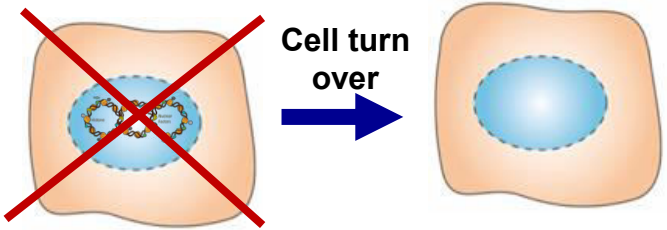
Curing infected hepatocytes



- **Viral targets**
- Antiviral state

➢ **Targeting cccDNA**

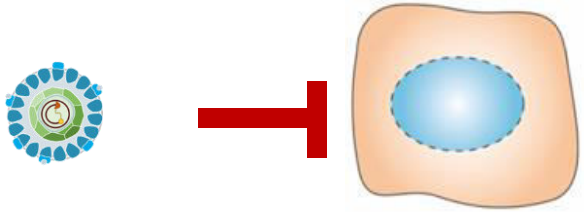
Specific killing of infected cells



- **HBV specific T cells**
- Inducing specific cell death

➢ **Restoring & stimulation of adaptive immunity**

Protecting non infected cells



- **Virus neutralization**
- Antiviral state

The HBV drug pipeline and the potential for combination therapy to cure HBV

Replication inhibition ± **Antigen reduction** ± **Immune stimulation**

hNTCP
Entry inhibitors: bulevirtide, other small molecules & MAb
HBV polymerase
NUC: ETV, TDF, TAF, novel NUCs & RNAseH inhibitors
Nucleocapsids
CAM: ALG 000184, ZM-H1505R, ABI-H4334, EDP-514, JNJ-56136379

Transcription
FXR agonist: EYP001
Viral RNAs
siRNA: JNJ-3989, VIR-2218 (Elebsiran), AB-729 (Imdurisan), ALG-125755
ASO: Bepirovirsen, AHB-137
LNA: RO7062931
RNA destabilizers: GSK 3965193, BJT-628
HBsAg release
NAPs: REP 2139

Invigorate immune responses
Innate immunity
TLR7: GS9620, RG7854 (Ruzotolimod)
TLR8: Selgantolimod, CB06, GSK 5251738
Immune check points
Anti-PD1: nivolumab
Anti-PDL1: envafolimab (ASC22)
PDL1 LNA: RG6084
Oral PDL1 sm: AB-101

Stimulate HBV specific B/T cells
Therapeutic Vaccines
HepTcell
VTP-300
GSK3528869A
VVX001
HB-400 (GS2829/GS6779)
TherVacB
AVX70371
BRII-179

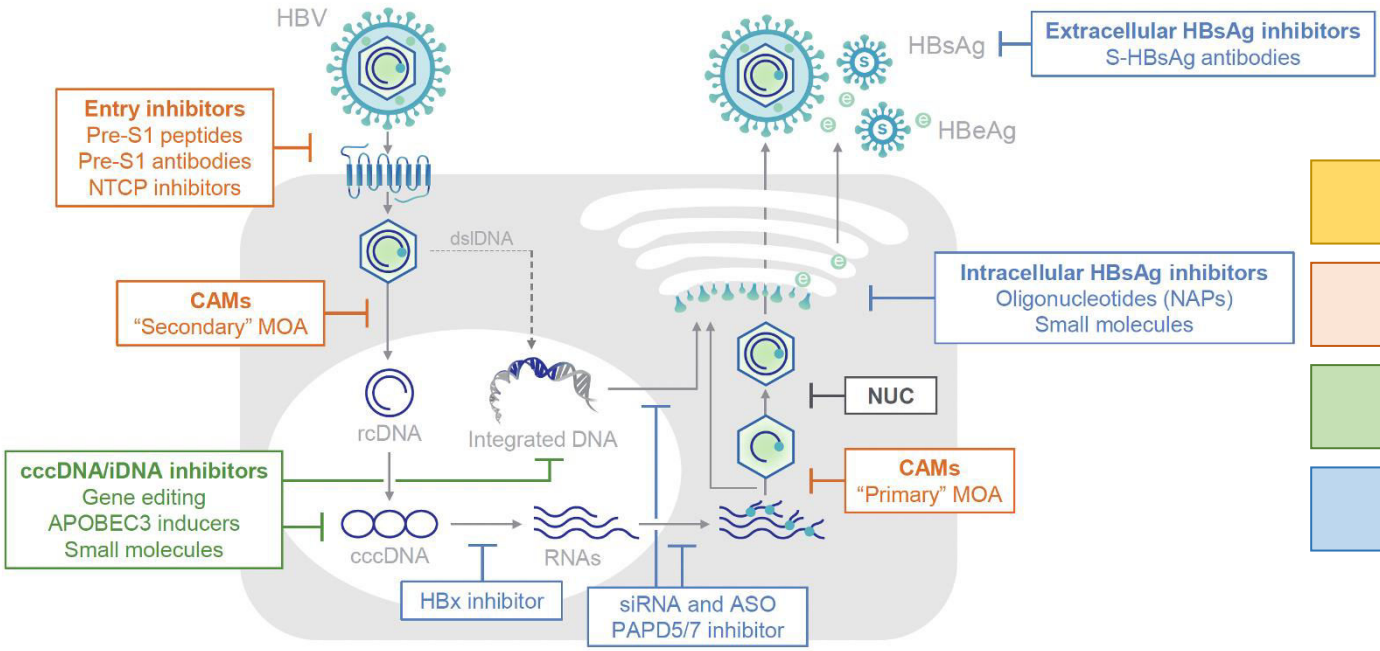
Exogenous HBs Mab
VIR-3434
BJT-778
RG6449

T Cell Engineering

Gene and epigenome editing

Revill et al, Lancet Gastroenterol Hepatol 2019; Lim et al Nat Rev Gastroenterol Hepatol. 2023; Feld et al, Clin Gastroenterol Hepatol 2023; https://www.hepb.org/treatment-and-management/drug-watch;

DAA strategies for HBV Cure



Entry inhibitors

Antiviral intensification (+ NUC)

Direct targeting cccDNA and iDNA

Reduce HBV antigen load

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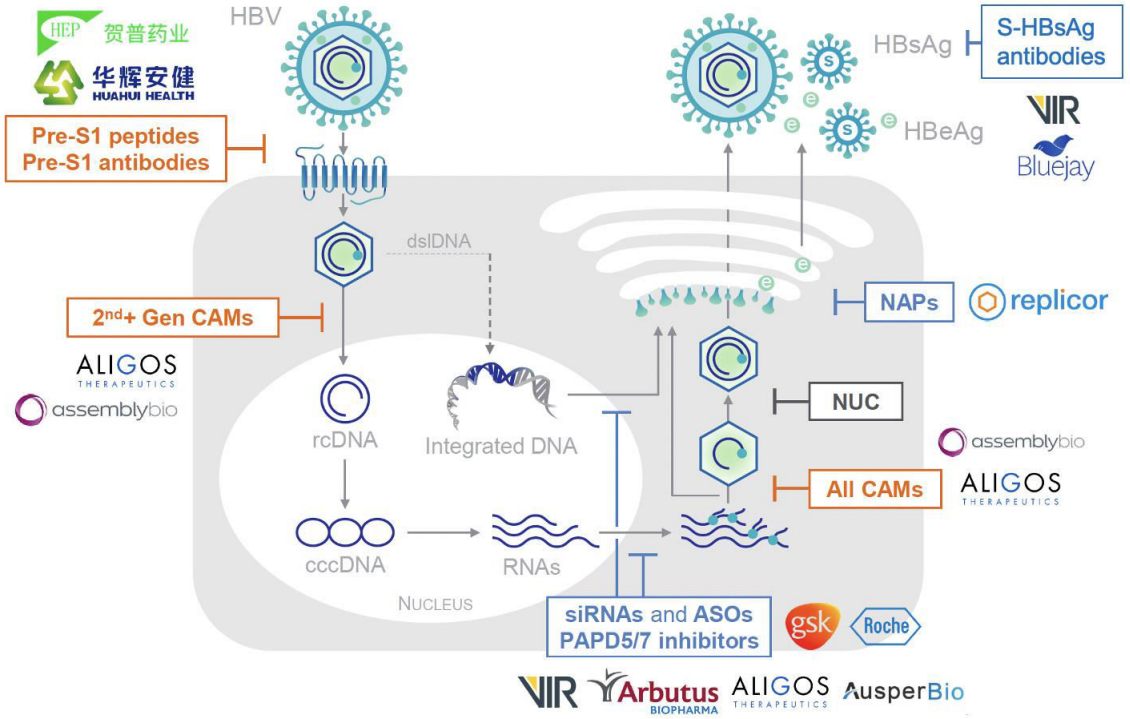
DAA strategies for HBV cure in clinical development



Antiviral intensification (+ NUC)

Attractive concept and the "simplest" approach to HBV Cure
Multiple agents with clinical POC are currently in development, the majority being CAMs

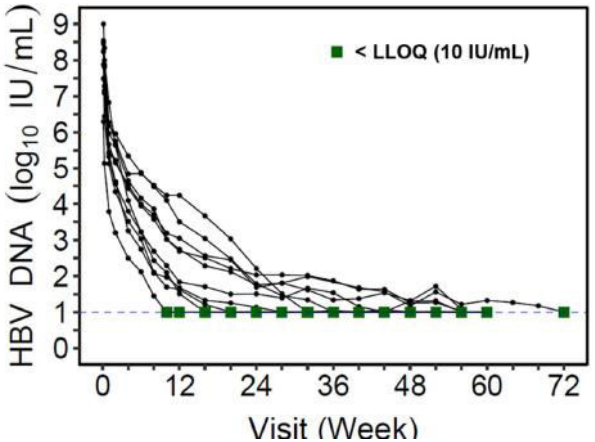
NUC + 1st generation CAM ± siRNA clinical studies have globally not been successful
Can more potent CAMs achieve the goal via secondary mechanism (inhibiting cccDNA formation)?

ALG-000184 ± ETV for 60 weeks:
mean ~1 log10 HBsAg ↓ in treatment-naïve HBeAg+ patients No HBsAg loss, HBsAg levels appear to plateau towards the end of treatment. Awaiting data in HBeAg-negative and NUC-suppressed patients

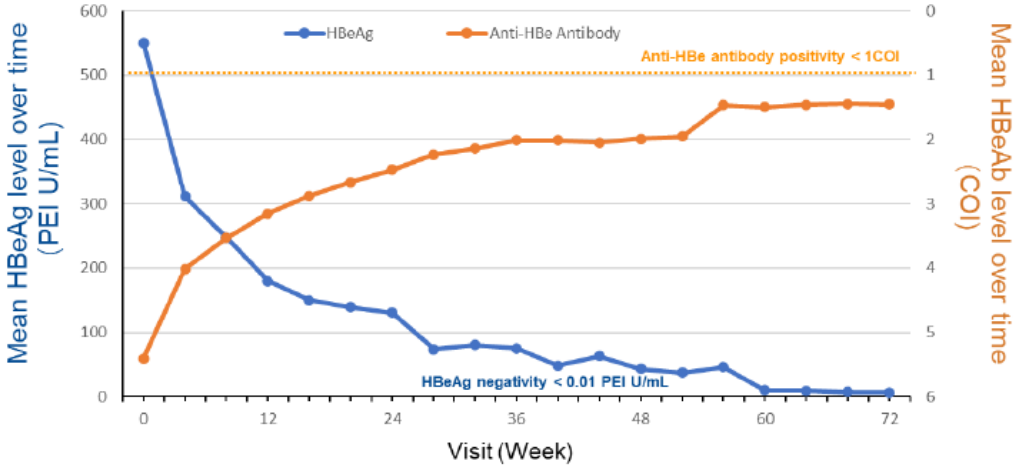
mofified ftom S Fletcher (DZIF Eibsee 2024)

Extended Treatment of HBeAg+ CHB Subjects with the Capsid Assembly Modulator (CAM) ALG-000184 with or without Entecavir is Associated with reductions in Viral Markers and Favorable Anti-HBeAg trends.

300 mg ALG-000184 Mono
HBV DNA Change



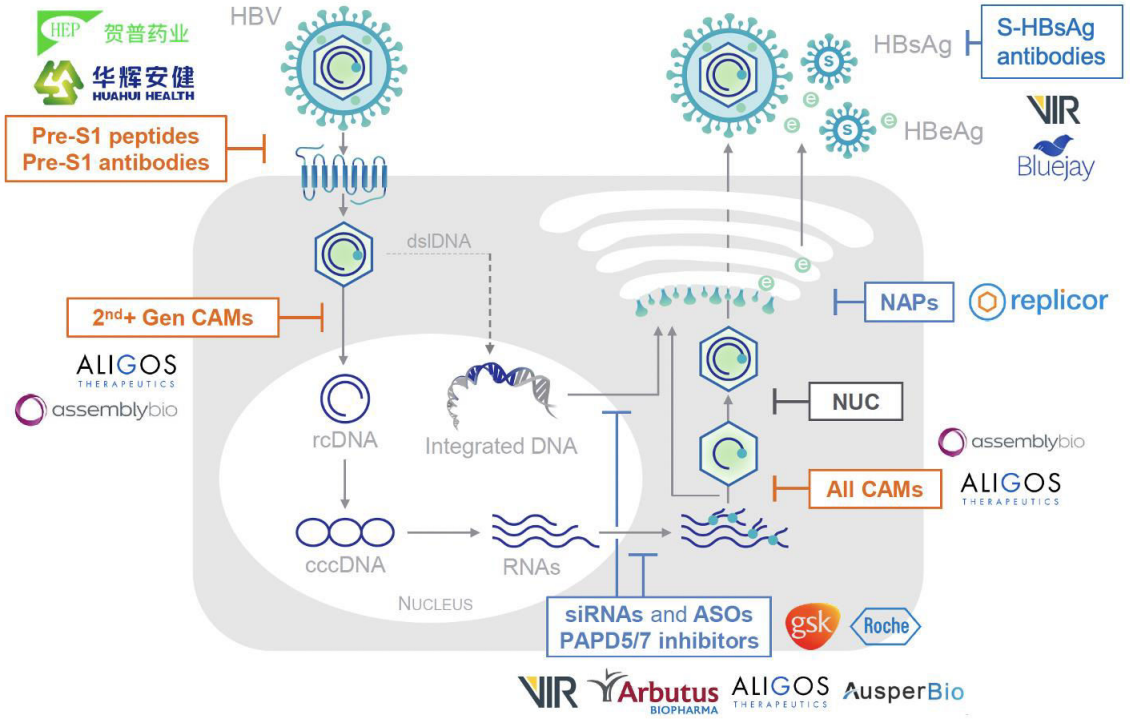
300 mg ALG-000184 Mono
HBeAg/Ab Change



6/10 (60%) achieved sustained DNA suppression of <10 IU/mL by W48; 9/10 (90%) by W72
Time to achieve HBV DNA <10 IU/mL depends on baseline HBV DNA levels

MF Yuen et al, EASL 2024

DAA strategies for HBV cure in clinical development



Antiviral intensification (+ NUC)

Feasibility of cure with reasonable DAA treatment duration likely depends on several factors

- the potential to reduce HBV spread *and* new HBV integrations to (close to) zero
- relatively rapid turnover of cccDNA+ cells and cells with transcriptionally active integrated HBV

Unless sterilizing cure is achieved, will still need restoration/development of effective HBV-specific immune response (neutralizing antibody response at the least)

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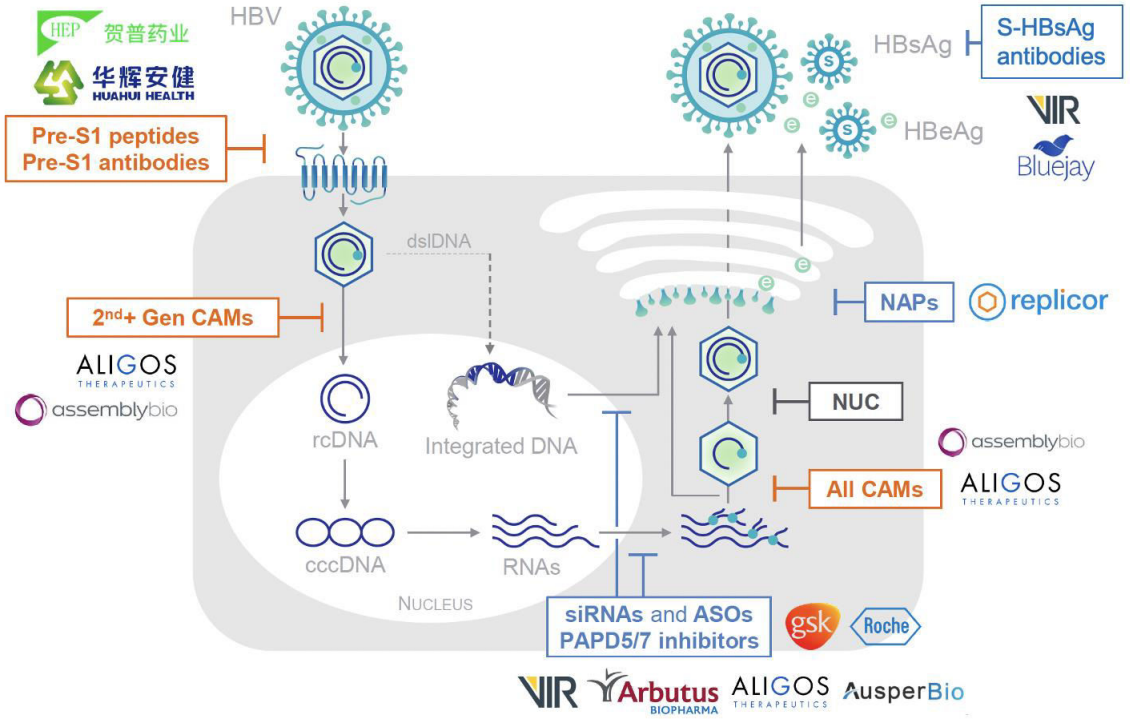
DAA strategies for HBV cure in clinical development



Reduce HBV antigen load

siRNAs
e.g. VIR-2218

- GalNAc-conjugated for hepatocyte targeting; very prolonged PD effect
- generally, well tolerated in mono-infected patients
- disappointing clinical efficacy to-date
- potential for combination with therapeutic vaccine

αRNAs
e.g. VIR-3434

- Rapid, dose-dependent HBsAg reduction in patients with low baseline HBsAg levels
- PK “sink” with HBsAg; need for combination to address broad patient population
- Combination studies with HBV siRNA and PEG-IFN-α ongoing

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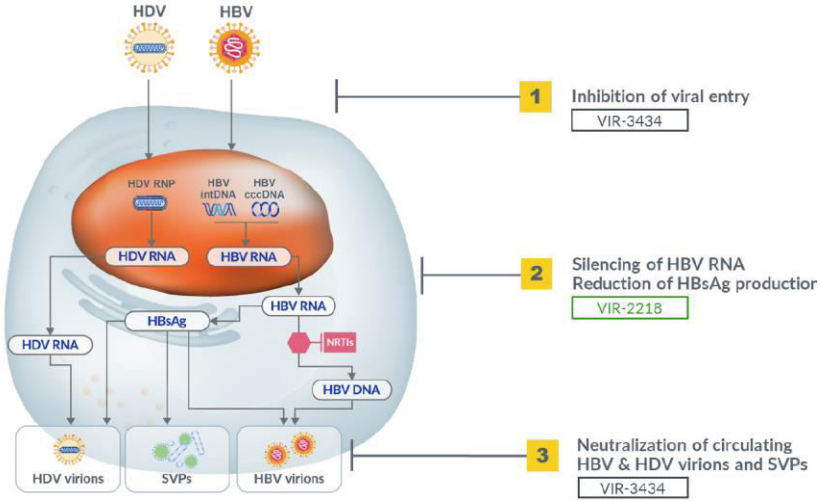
Investigational combination therapies

VIR-2218 and VIR-3434 target different steps in the HBV and HDV replication cycles



Combination therapy with VIR-2218/VIR-3434 in clinical trials

VIR-2218-1001 Part F	VIR-2218 + PEG-IFNα	Virally suppressed
MARCH	VIR-2218 + VIR-3434 (+ PEG-IFNα)	
PREVAIL	VIR-2218 + VIR-3434 (+ PEG-IFNα)	Immune active/inactive

HBsAg seroclearance observed after combination treatment

	VIR-2218-1001 TRIAL	MARCH TRIAL	
	elebsiran + PEG-IFN-α	tobevibart + elebsiran	tobevibart + elebsiran + PEG-IFN-α
EOT after 24w Tx	5.6% (N=1 of 18) HBsAg seroclearance	15.0% (N=3 of 20) HBsAg seroclearance	14.3% (N=3 of 21) HBsAg seroclearance
EOT after 48w Tx	25.8% (N=8 of 31) HBsAg seroclearance	Data Expected in Q4 2024	
24w Off Tx (Post-48w Tx)	16.1% (N=5 of 31) Sustained HBsAg loss	Data Expected in Q2 2025	

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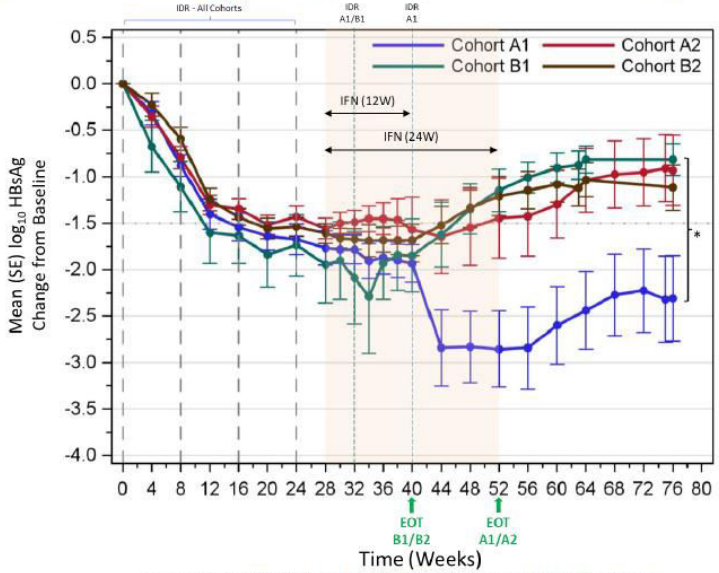
Imdusiran (AB-729) administered every 8 weeks in combination with 24 weeks of pegylated interferon alfa-2a in virally suppressed, HBeAg-negative subjects with chronic HBV infection leads to HBsAg loss in some subjects at end of IFN treatment

Figure 1: Mean Log_{10} HBsAg Change from Baseline by Cohort



* p < 0.001 (by ANCOVA) for A1 vs all other cohorts at Week 52 and Week 76

Table 3: Number of Subjects with Undetectable HBsAg at Key Timepoints

Achieved HBsAg ≤ LLOQ (0.05 IU/mL)	Cohort A1: IDR x 6 + NA + IFN x 24W (N = 12)	Cohort A2: IDR x 4 + NA + IFN x 24W (N = 13)	Cohort B1: IDR x 5 + NA + IFN x 12W (N = 8)	Cohort B2: IDR x 4 + NA + IFN x 12W (N = 10)
Any time during treatment	6/12 (50%)	3/13 (23%)	2/8 (25%)	0/10
EOT	4/12 (33.3%)	3/13 (23%)	0/8	0/10
	7/25 (28%)		0/18	
Next Assay negative	4/4	2/3	N/A	N/A
24 weeks post-EOT (NA therapy only)	4/12 (33.3%)	2/13 (15.4%)	0/8	0/10
	6/25 (24%)		0/18	
Next Assay negative	2*/4 (*1 subject pending)	2/2	N/A	N/A
Discontinued NA therapy	9/12 (75%)	3/13 (23%)	4/8 (50%)	5/10 (50%)

NA: nucleos(t)ide analogue; IFN: pegylated interferon alfa-2a; W: weeks; EOT: end of treatment (Week 52 [A1/A2] or Week 40 [B1/B2]); Next Assay LLOD=0.005 IU/mL

MF Yuen et al, EASL 2024

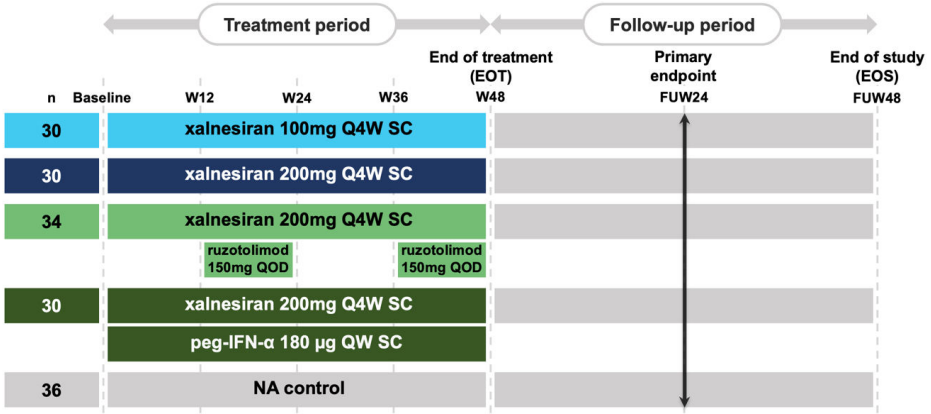
Efficacy and safety of xalnesiran with and without an immunomodulator in virologically suppressed participants with chronic hepatitis B: End of study results from the phase 2, randomized, controlled, adaptive, open-label platform study (Piranga).

Piranga (NCT04225715) is a **phase 2 platform study** designed to evaluate the efficacy and safety of **new finite duration therapies to achieve functional cure in CHB**

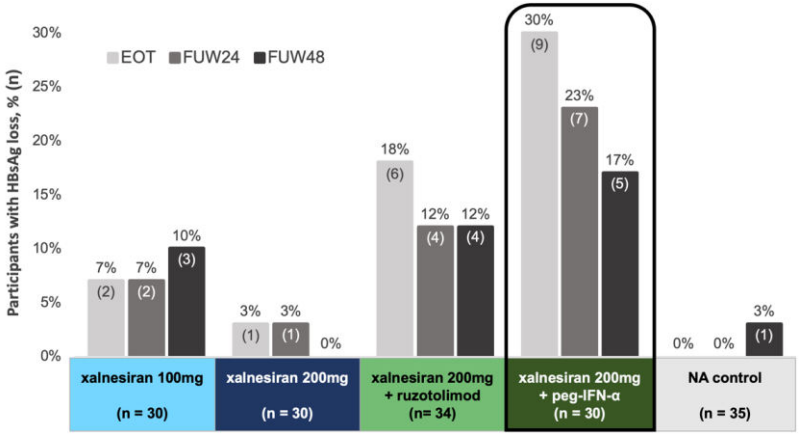
Here, we report **end of study results** of **xalnesiran** (RO7445482), a GalNAc-conjugated siRNA targeting HBsAg transcripts **with or without an immunomodulator**: **ruzotolimod (toll-like receptor 7 agonist, RO7020531)** or **pegylated interferon alfa-2a** (Peg-IFN-α).

Study design and endpoints

- **Virologically suppressed CHB participants (**26 sites in 8 countries and regions)
- HBsAg loss (HBsAg < 0.05 IU/mL) and seroconversion (HBsAg loss and anti-HBsAb ≥ 10 IU/L) rates were measured throughout the study.



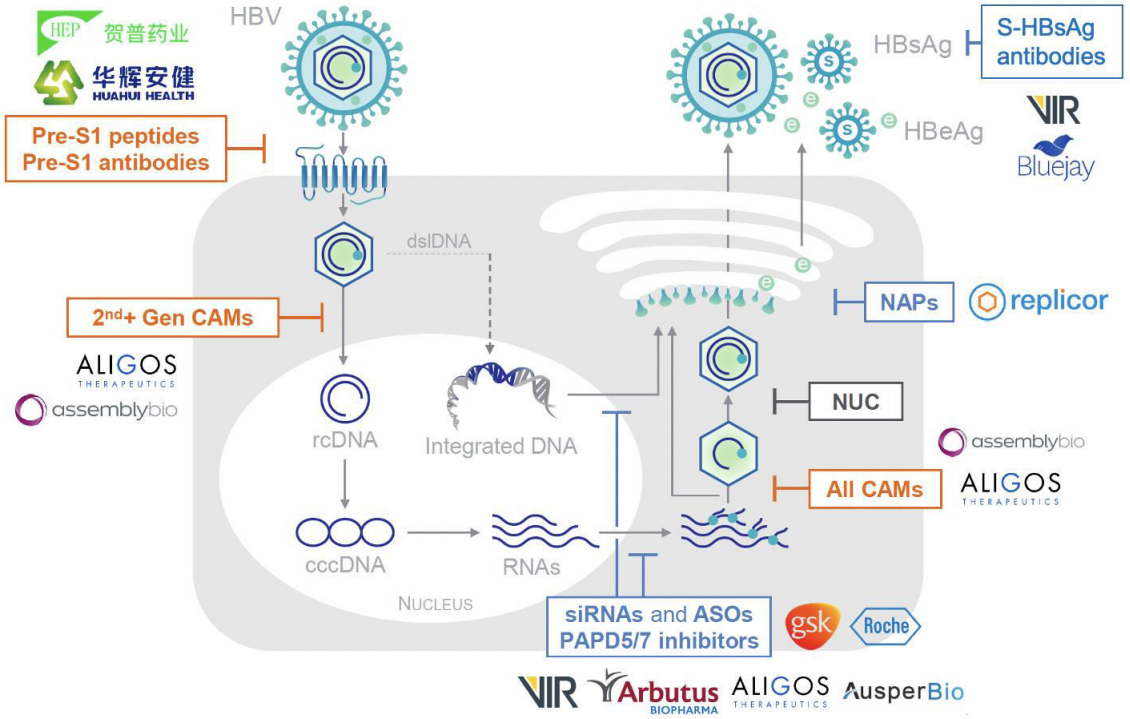
Key takeaways



- **HBsAg seroconversion was highest for xalnesiran combined with peg-IFN-α**
- HBsAg loss and seroconversion were observed only in participants with **screening HBsAg < 1000 IU/mL**
- **Durability of HBsAg loss between at FUW48 was observed in 56%-67% of participants**,
- Xalnesiran with or without an immunomodulator for 48 weeks was generally **safe and well tolerated**
- Ongoing arms of this platform study will evaluate the safety and efficacy of combination of other novel agents in participants with CHB

Hou J et al. EASL 2024 OS-030

DAA strategies for HBV cure in clinical development



Reduce HBV antigen load

NAPs
e.g. REP-2139

- MOA : HBsAg secretion inhibitor
- clinical efficacy –typically accompanied by substantial ALT elevation6
- sustained response requires combination with immune modulator, e.g., PEG-IFN-α

ASOs
e.g. Bepivirosen

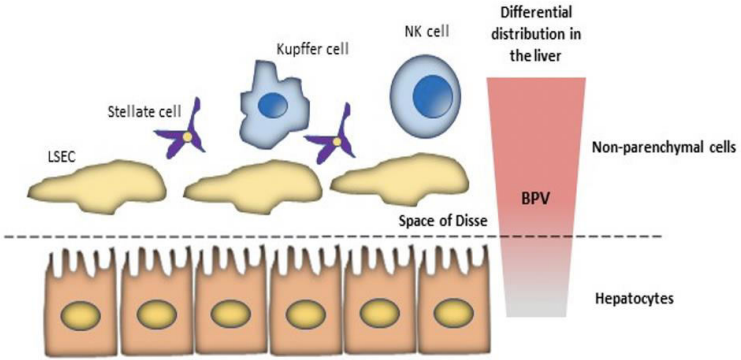
- rapid, dose-dependent HBsAg reduction in patients with low baseline HBsAg levels
- combination studies with HBV siRNA and PEG-IFN-α ongoing

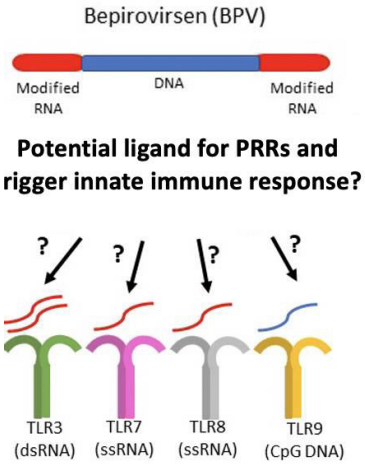
mofified ftom S Fletcher (DZIF Eibsee 2024)

Bepirovirsen is an antisense oligonucleotide targeting all HBV RNAs, including pregenomic RNA, thereby reducing viral proteins (including HBsAg) and stimulating the immune system via mechanisms such as activation of the TLR8 pathway[1,2]

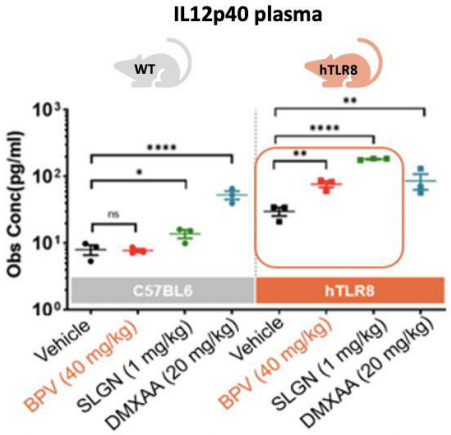
Differential distribution of unconjugated ASO in the liver[3]

Nonparenchymal cells >>> hepatocytes



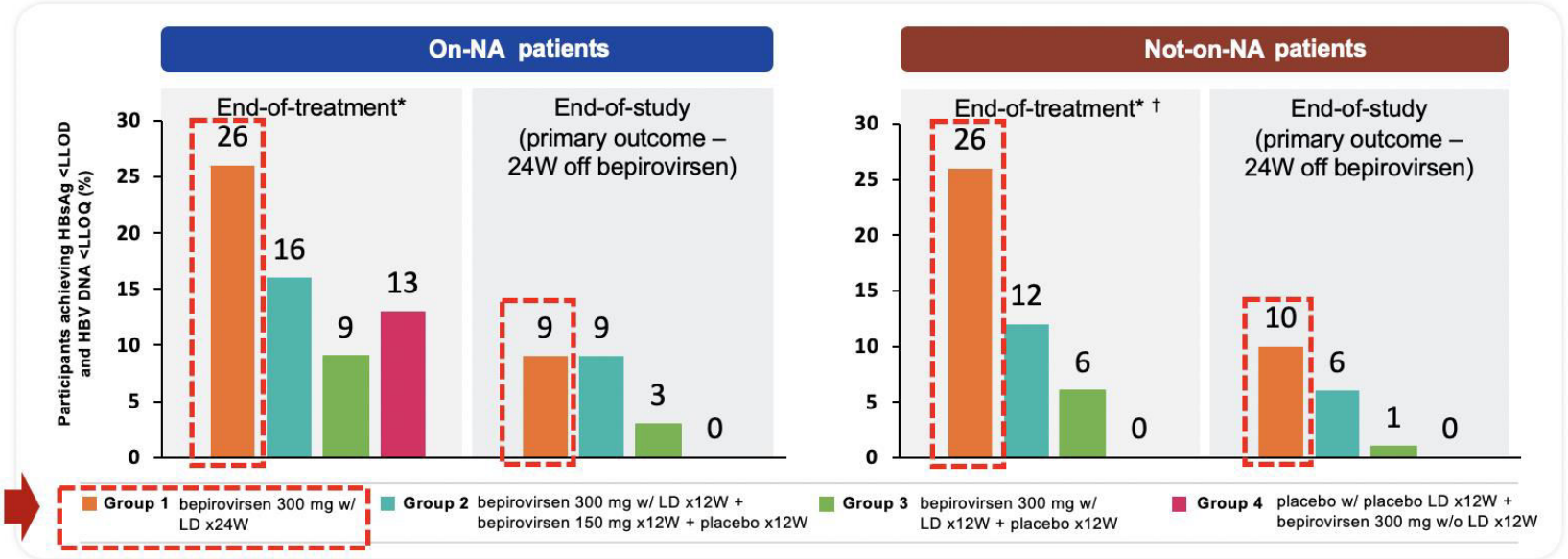


Cytokine response by bepirovirsen in hTLR8 mice, but not in WT[2,3]



1. Yuen MF, et al. *N Engl J Med* 2022;387:1957–1968; 2. You S, et al. Presented at EASL 2022 (Poster No. SAT439); 3. Ermler ME, et al. Presented at AASLD 2023 (Poster No. 1460-C).

B-Clear study
HBsAg loss/HBV DNA undetectable levels during/after Bepirovirsen (BEPI, GSK836) in NUC-naive and NUC-suppressed patients



*End of treatment was 24 weeks in Group 1, 2 and 4. and 12 weeks in Group 3, †34 (14.5%) participants received NA during the study, Graphs were recreated independently from data provided in Yuen MF, et al. N Engl J Med 2022;387(21):1957-1968. Figures represent total populations without staritfications by HBsAg.

In Group 1 (bepi 300 mg for 24 weeks) 9% of participants On-NA and 10% of participants Not-on-NA achieved sustained HBsAg and HBV DNA loss for 24 weeks off-treatment

Yuen MF, et al. N Engl J Med 2022;387(21):1957-1968

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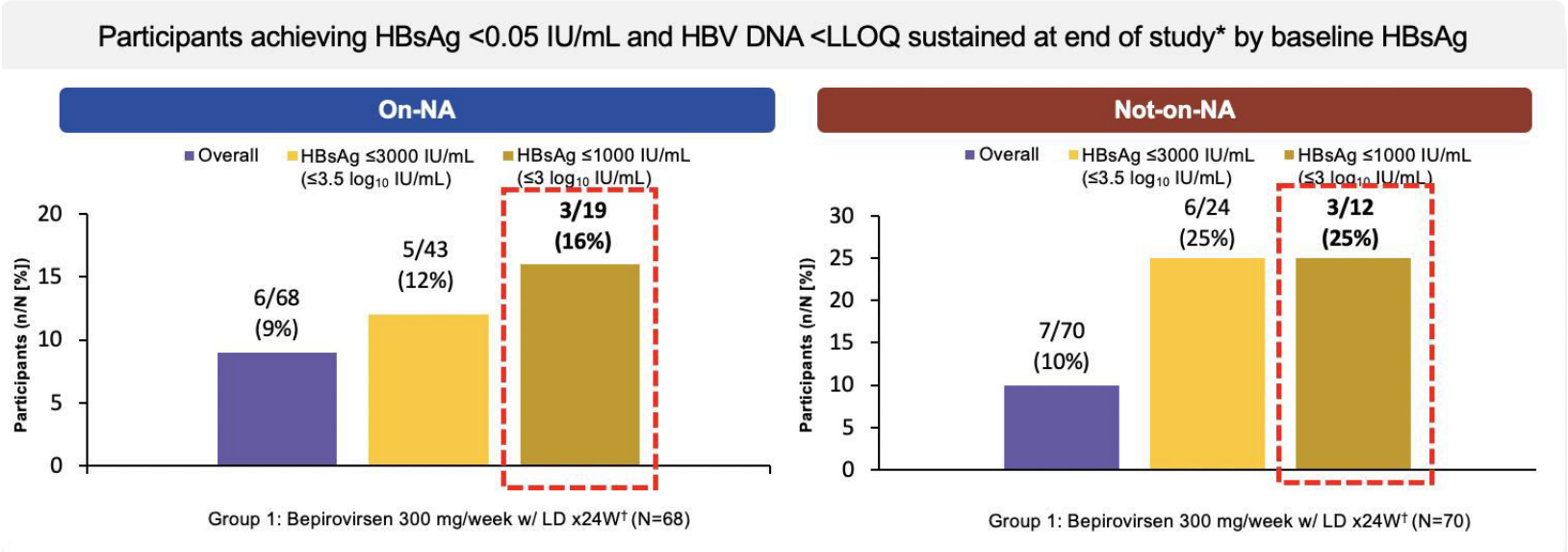
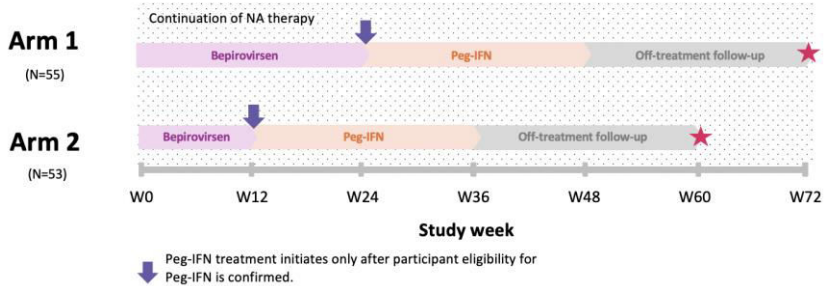


Baseline HBsAg levels are strong predictors of BEPI response

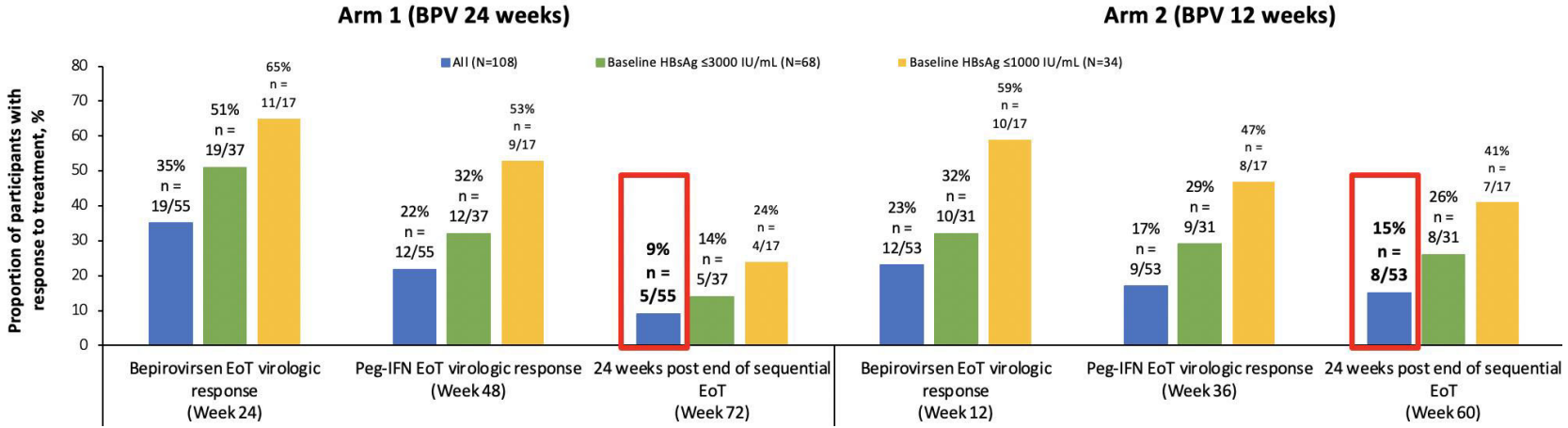
Figure independently created by GSK using data from Yuen MF, et al. *N Engl J Med* 2022;387(21):1957–68 (article and supplement) and data on file.*End of study is defined as 24 weeks post end of treatment. Additional efficacy data for investigational Groups 2, 3 and 4 are available in the appendix. 1. Yuen MF, et al. *N Engl J Med* 2022;387(21):1957–68 (article and supplement); 2. GSK. Data on file REF-214341. 2023: 3. GSK. Data on file REF-214339. 2023, HBsAg, hepatitis B surface antigen; LD, loading dose; NA, nucleos(t)ide analog; W, week.

The aim of the **B-Together** trial was to examine whether **sequential treatment with bepirovirsen (12 or 24 weeks) followed by Peg-IFN (24 weeks)** could reduce relapse rates and improve responses observed in the B-Clear trial[2]

B-Together Study Design



Primary outcome: HBsAg and HBV DNA <LLOQ* sustained at every visit for 24 weeks from planned end of Peg-IFN treatment in the absence of newly initiated antiviral treatment

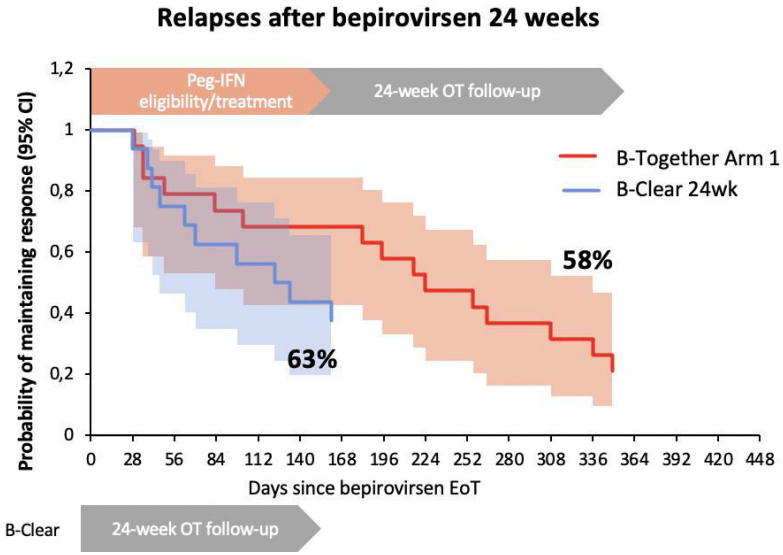


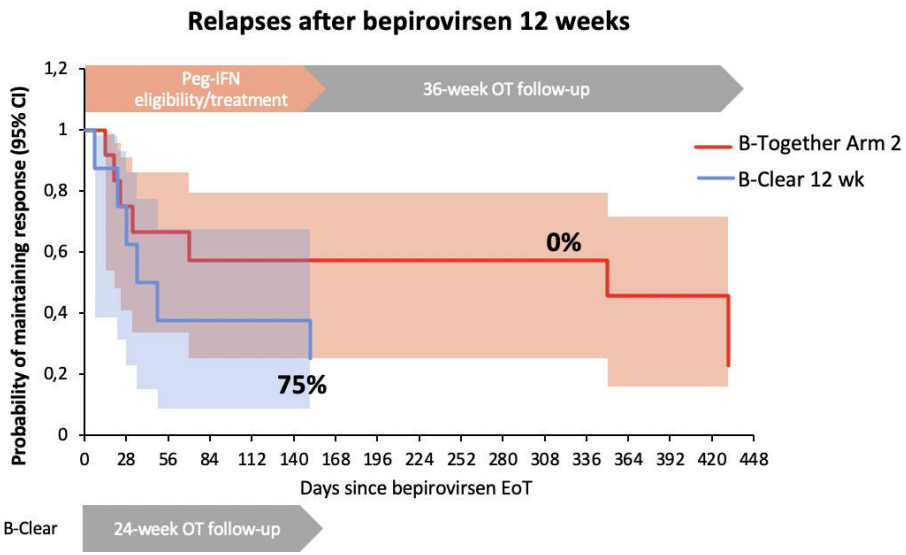
Buti M, et al. *J Hepatol* 2024 Aug 28:S0168-8278(24)02488-7. doi: 10.1016/j.jhep.2024.08.010 [Online ahead of print].

B-Together
Sequential treatment with bepirovirsen followed by Peg-IFN reduced relapse rates compared with B-Clear

ITT population

- In, most participants (58% in each arm) who were responders at bepirovirsen EoT did not relapse on Peg-IFN treatment
- Only two participants (both in Arm 2) with a partial response at bepirovirsen EoT were responders at Peg-IFN EoT
- Of the participants who achieved response at Peg-IFN EoT, 58% (Arm 1) and 0% (Arm 2) of participants relapsed off-treatment





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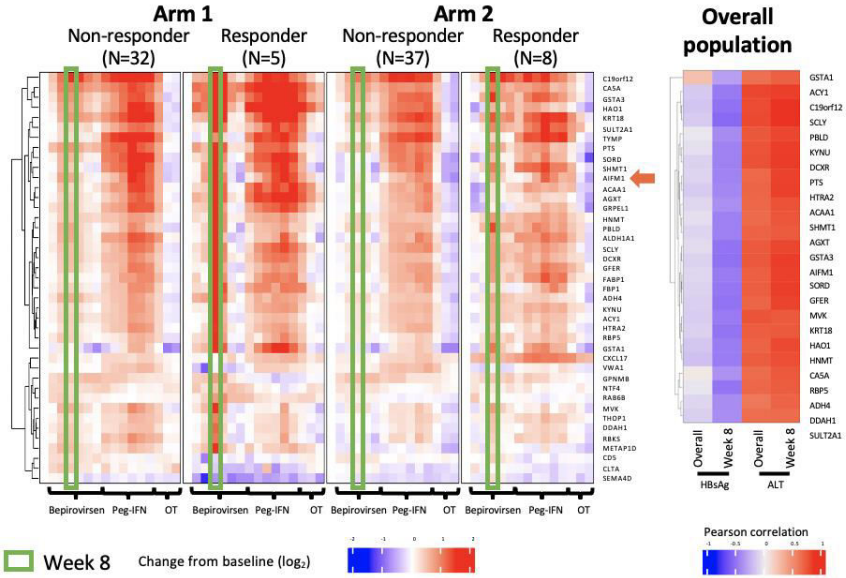
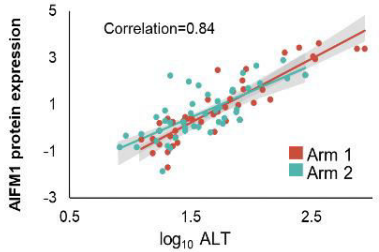
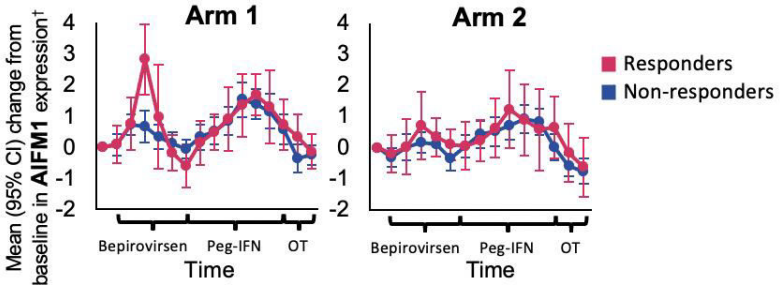
B-Together
Bepirovirsen may mediate hepatocyte cell death associated with response by Week 8



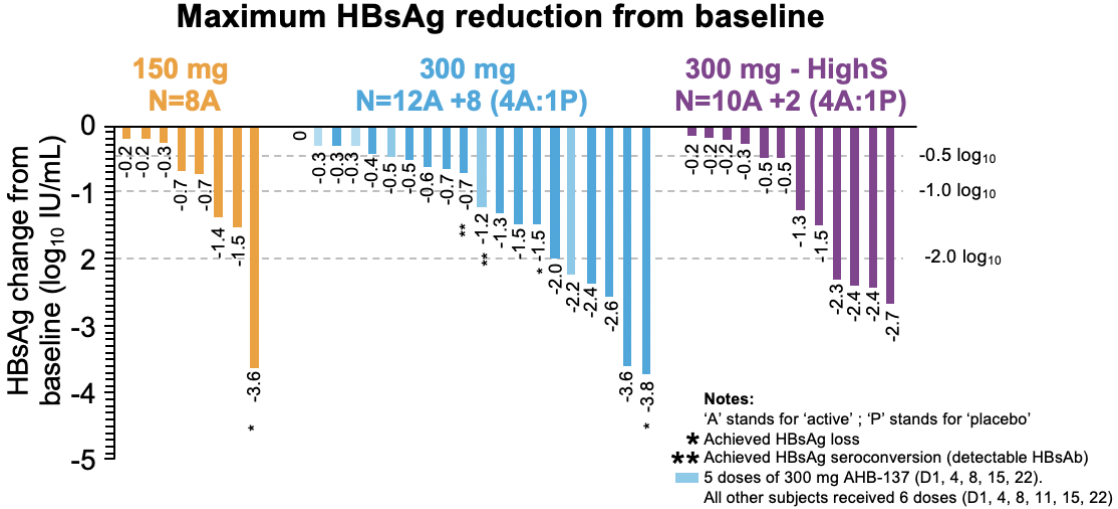


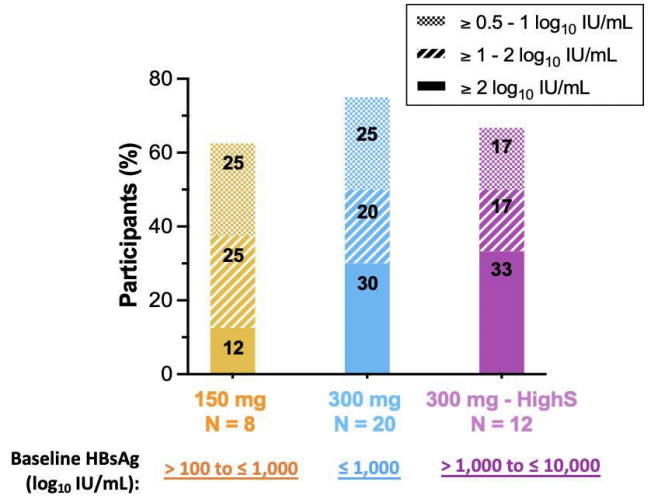


- The top 25 of these proteins showed high association with ALT and a trend of inverse correlation with HBsAg
- Significant direct association between expression of the apoptosis marker AIFM1 and ALT levels was observed

Joshi S, et al. Presented at GIHEP 2024

Preliminary efficacy of AHB-137, a novel antisense oligonucleotide, among healthy volunteers and patients with CHB



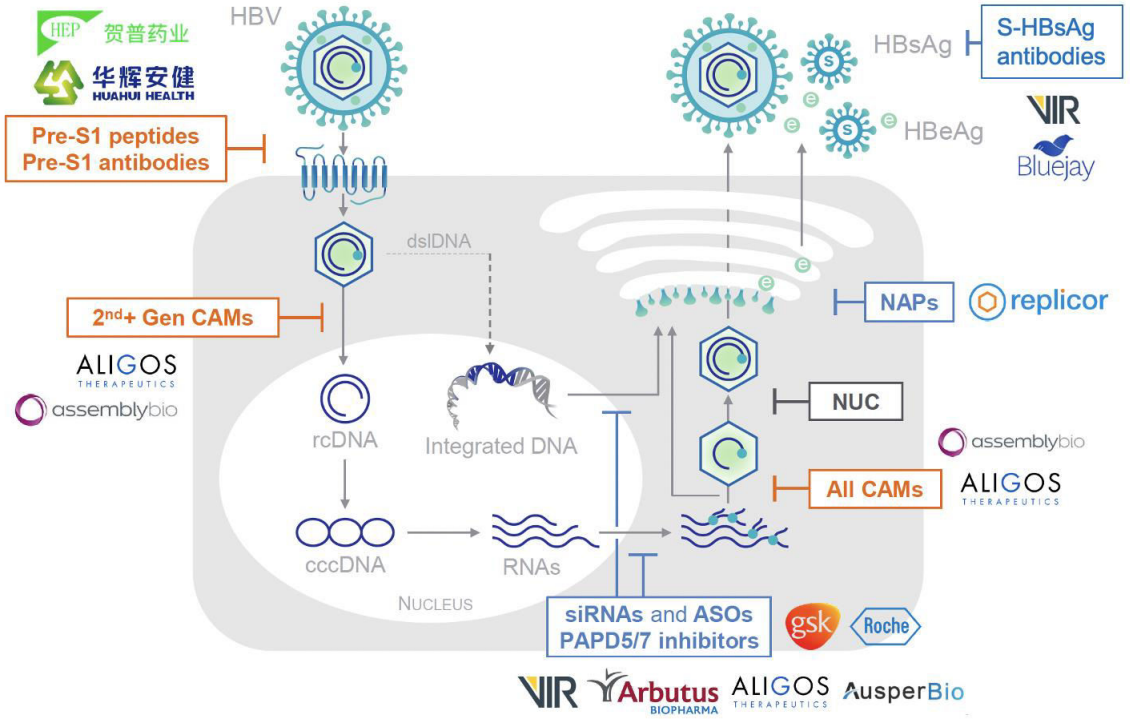


With 4-week dosing of AHB-137 at 300 mg per dose:

- **50% CHB patients showed > 1-log HBsAg reduction; 30% showed > 2-log reduction**
- **Comparable antiviral efficacy between 100 - 1,000 and 1,000 - 3,000 IU/ml HBsAg levels**
- **Five of 40 patients (12%) achieved HBsAg loss, including 2 with seroconversion**

Gane EJ, et al. EASL ILC 2024. LBP-019. Sponsored by Ausper Biopharma

DAA strategies for HBV cure in clinical development



DIFFERENT APPROACHES ADDRESS DIFFERENT POTENTIAL BARRIERS TO HBV CURE

- **antiviral intensification (+ nuc)**
  - studies with 2nd generation CAMs ongoing; some promising initial data

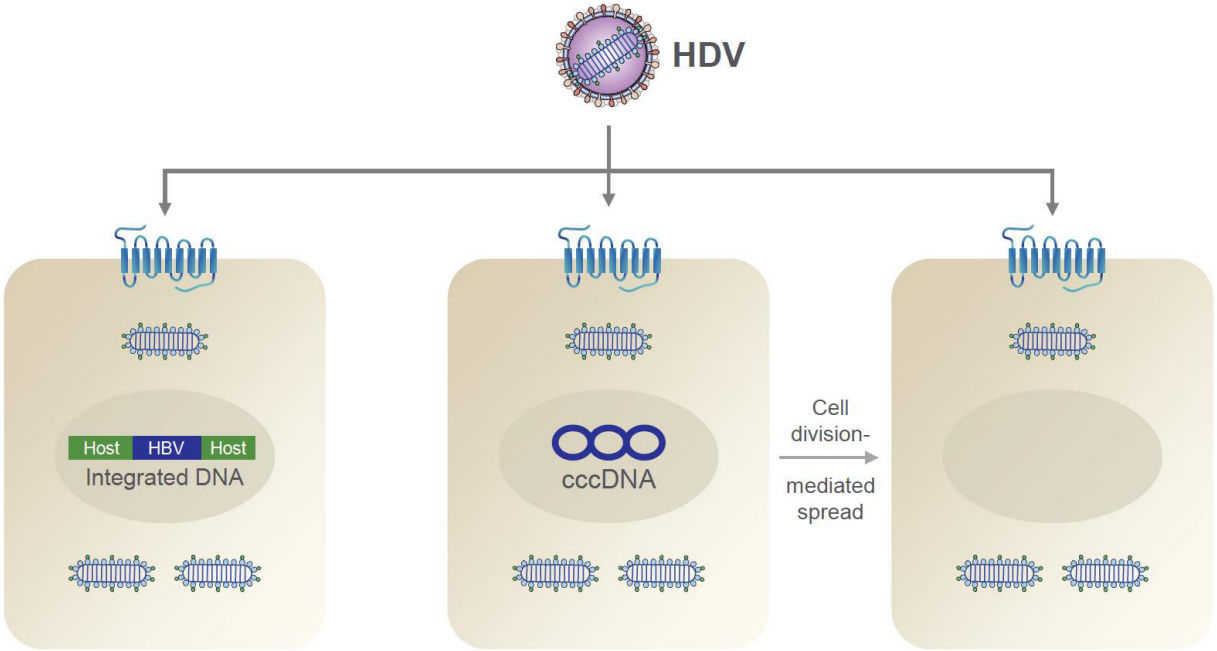
- **targeting cccDNA and/or integrated HBV**
  - agent that destabilizes pre-existing cccDNA previously viewed as the holy grail for HBV cure
  - recent studies suggest also necessary to reduce levels of transcriptionally active integrated hbv
  - no agents in clinical development

- **antigen reduction**
  - multiple agents clinically validated, but still few HBsAg loss
  - bepirovirsen & NAPs have profound HBsAg reducing activity
  - combination of antigen reducing agents with various agents being evaluated in the clinic

mofified ftom S Fletcher (DZIF Eibsee 2024)

- **Impact of HBV functional (or partial cure) on HDV. Are they enough to achieve HDV cure ?**
- **Role of residual HBV reservoir**
- **Role of HBV iDNA**
- **What are the minimal levels of HBV envelope proteins required to support HDV persistance and spread ?**

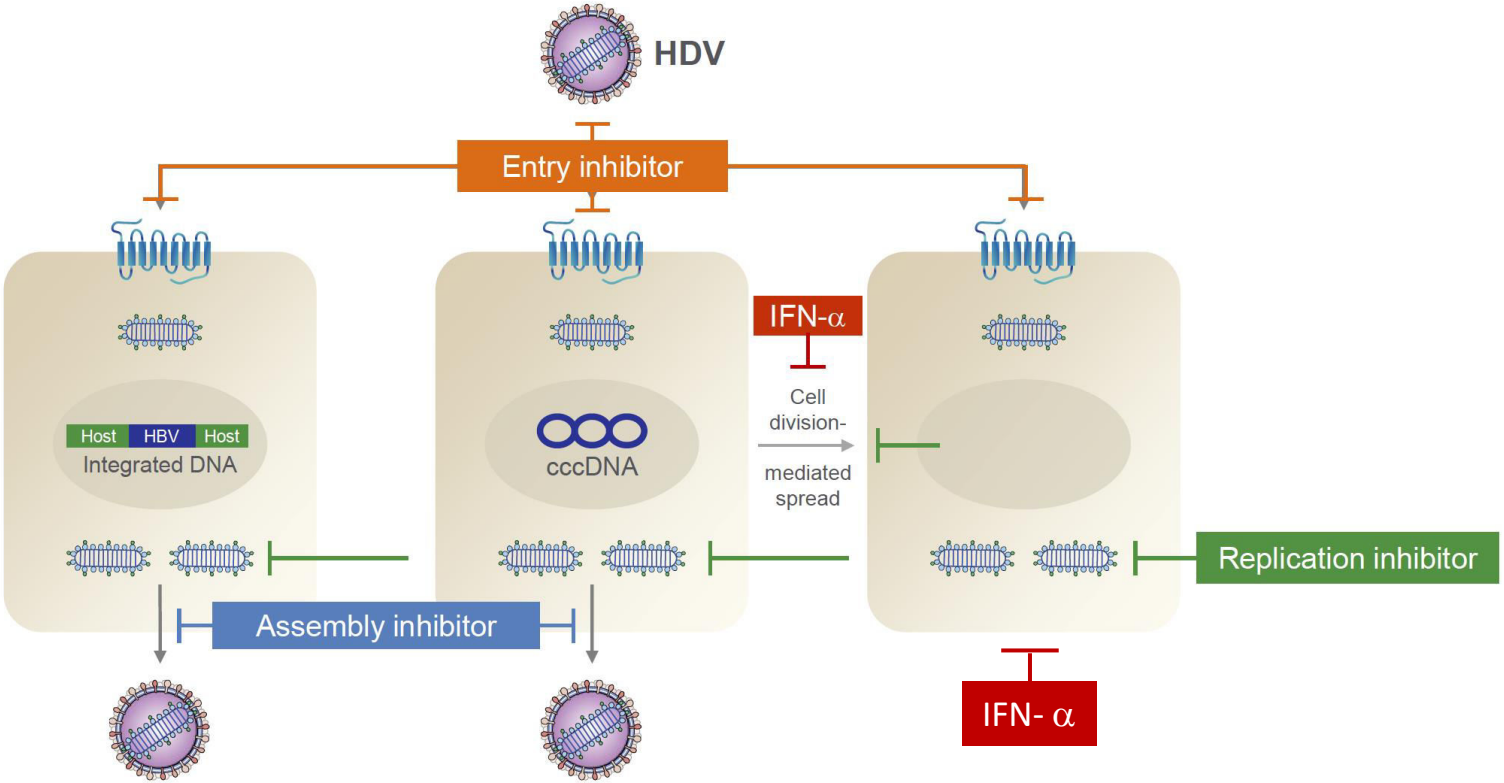
Landscape of HDV and HBV infected cells

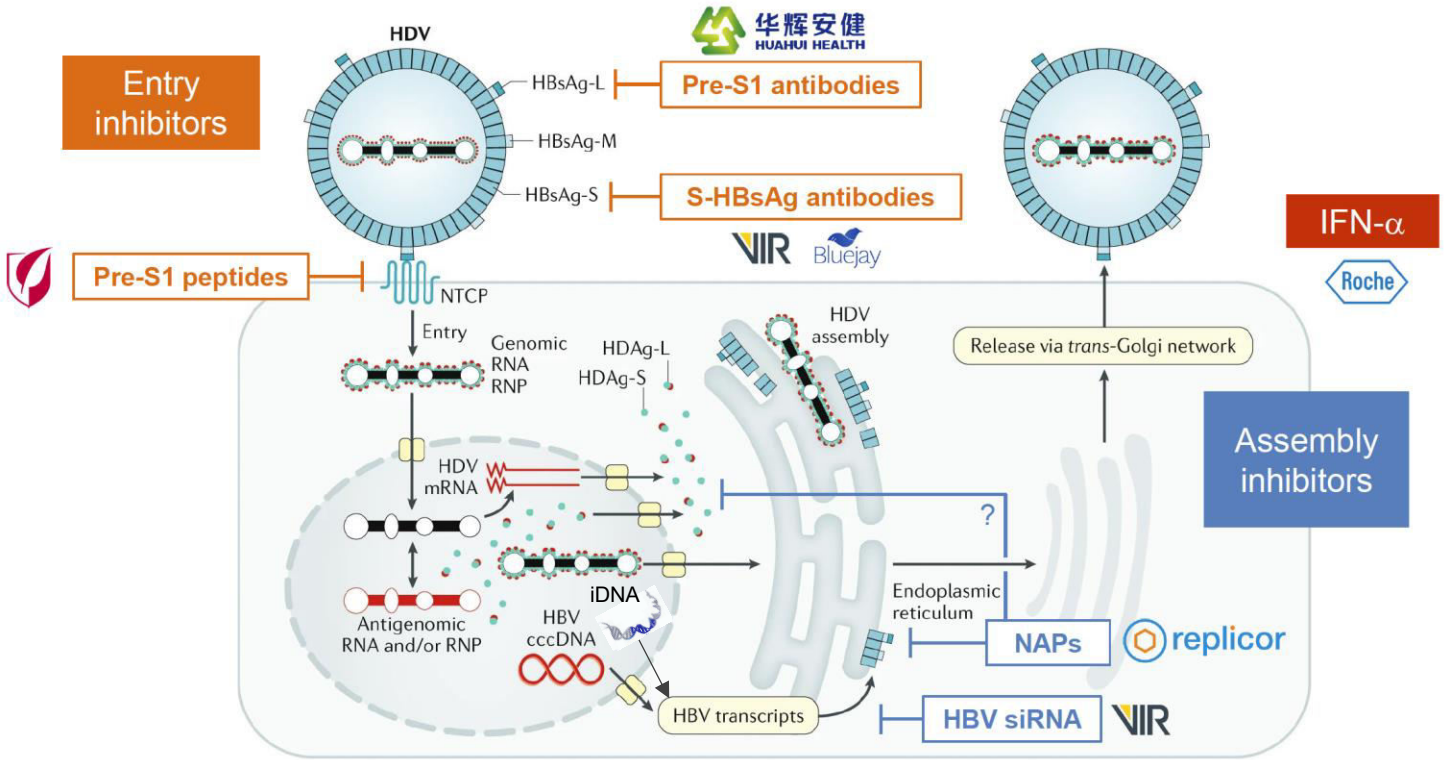


HBV integrated
- *cells produce infectious HDV*
- *iDNA and HDV survive cell division*

HBV-infected
- *cells produce infectious HDV*
- *only HDV survives cell division*

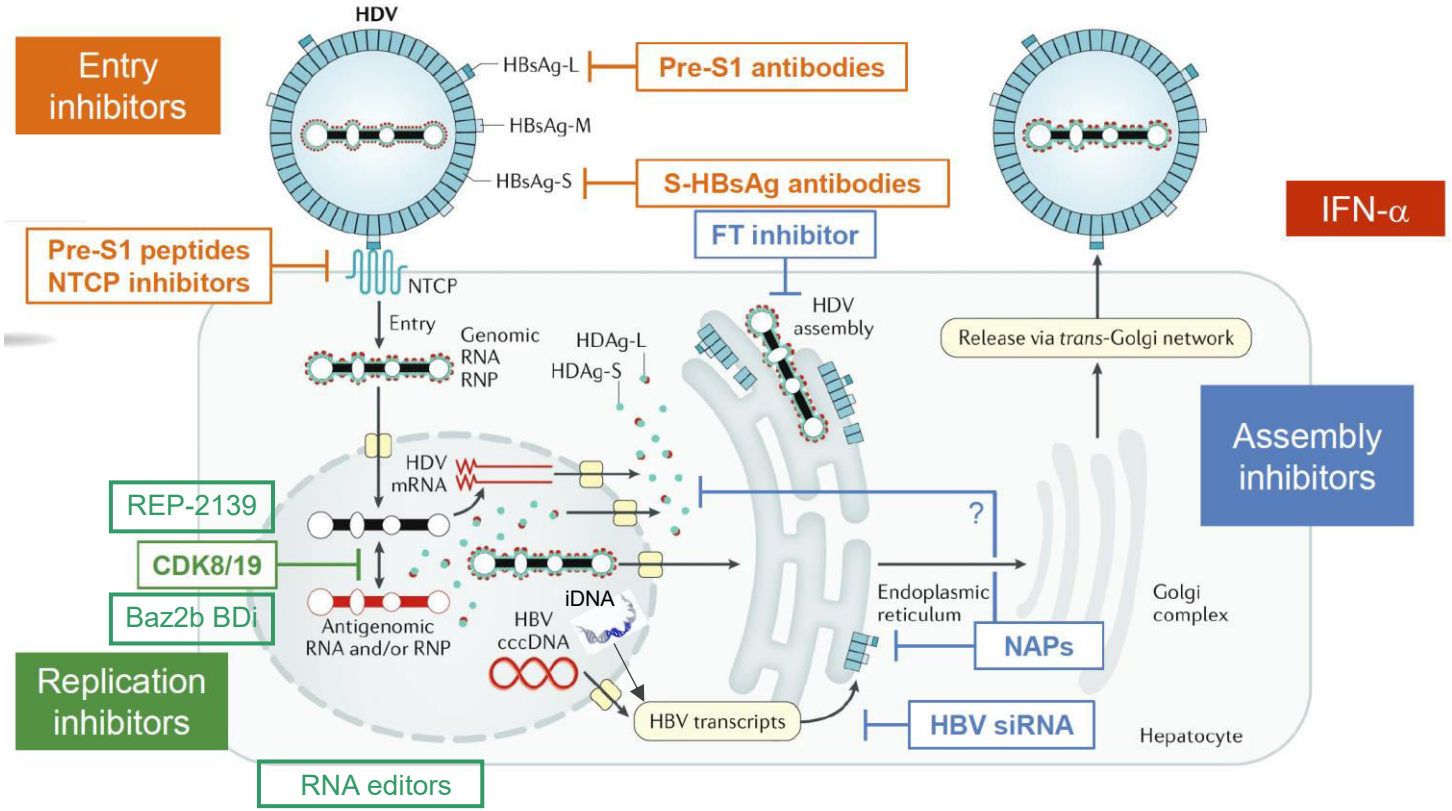
No HBV
- *cells do not produce infectious HDV*
- *can be super-infected with HBV*


HDV
Entry inhibitor
IFN-α
Cell division-mediated spread
Host HBV Host
Integrated DNA
cccDNA
Replication inhibitor
Assembly inhibitor
IFN- α



mofified ftom S Fletcher (DZIF Eibsee 2024)

DAA strategies for HDV cure in clinical development



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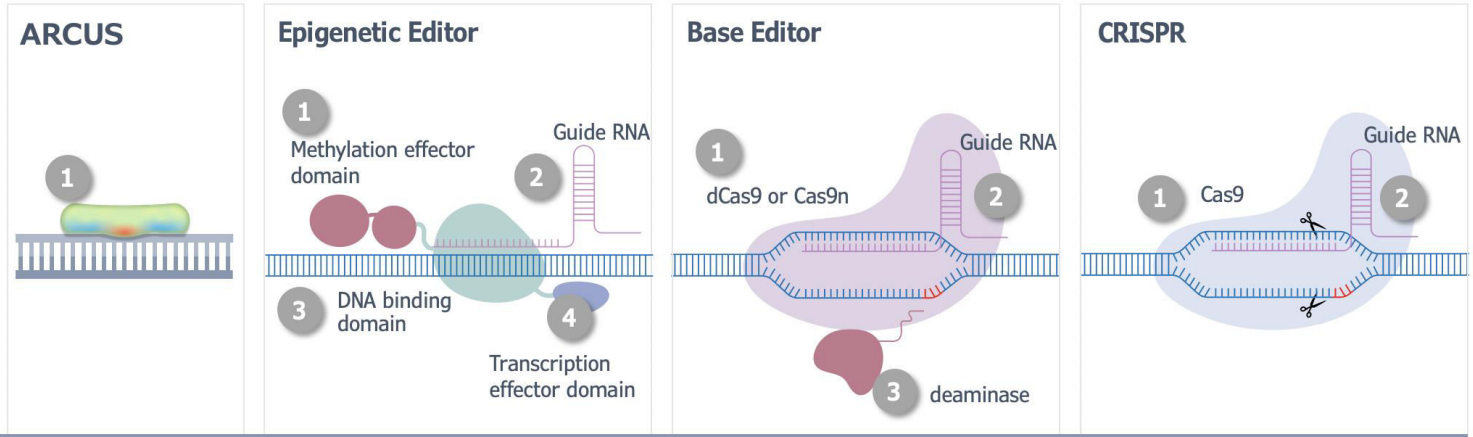
Gene Editors Include Components to Identify the Target Site and Make a Cut
Epigenome Editors Include a Methylation Effector



	ARCUS	Epigenetic Editor[1]	Base Editor[2]	CRISPR Editor[3]
Intended Edit Result	Eliminate cccDNA, inactivate integrated DNA	Silences cccDNA and integrated DNA via methylation	Mutates and inactivates cccDNA and integrated DNA	Creates cccDNA indels or excises portion of DNA with multiple guides
Cut type	Cut resulting in double stranded break with 3′ overhangs	Methylation (No Cut)	Single Stranded Nick	Cut resulting in double stranded break with blunt ends
Kilobases (kb)	~1 kilobase	~7 kilobases	4.8-5.4 kilobases	3.2-4.1 kilobases
# of Components	1 component	≥3 components (based on number of gRNAs)	≥3 components (based on number of gRNAs)	≥2 components (based on number of gRNAs)

No head-to-head studies of these approaches have been conducted and therefore no conclusions concerning safety or efficacy can be drawn

[1.] Epigenetic Editor data to date presented by Chroma Medicine [2.] Base editor data to date presented by Beam Therapeutics [3.] Seeger, et al. 2014, 2016; https://pubmed.ncbi.nlm.nih.gov/25514649/; https://pubmed.ncbi.nlm.nih.gov/27203444/

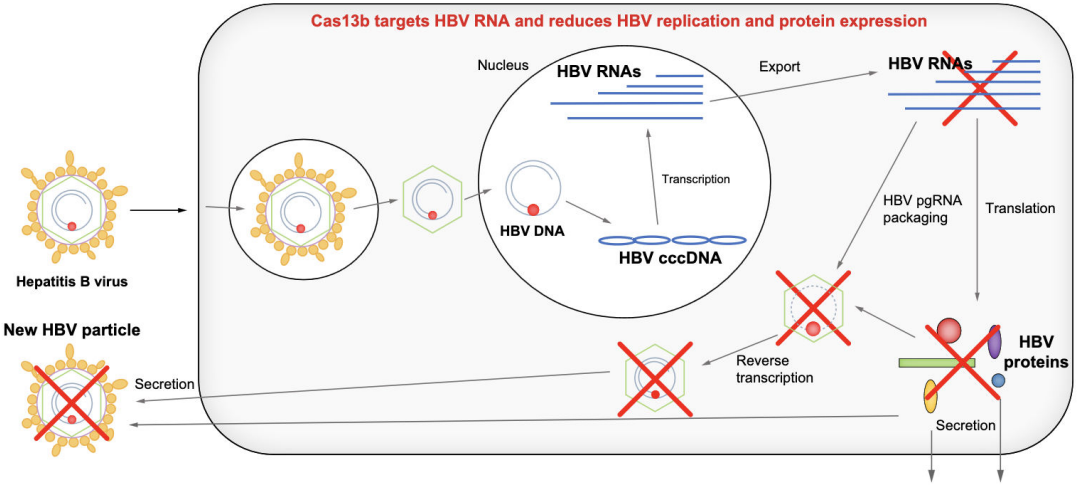
see Kumar et al. P50 HDV cure 2025

Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

CRISPR-Cas13b-mediated suppression of HBV replication and protein expression

Laura C. McCoullough[1,2], Mohamed Fareh[3,4], Wenxin Hu[3,4], Vitina Sozzi[1], Christina Makhlouf[1], Yianni Droungas[1,2], Chee Leng Lee[1,5], Mina Takawy[1,6], Stewart A. Fabb[5], Thomas J. Payne[5], Colin W. Pouton[5], Hans J. Netter[1], Sharon R. Lewin[6,7,8], Damian FJ. Purcell[2], Jacinta A. Holmes[9], Joseph A. Trapani[3,4], **Margaret Littlejohn**[1,6,†], **Peter A. Revill**[1,6,*,†]



Crispr-Cas 13 is currently used for innovative HDV diagnostics

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- Liver Transplantation

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