GLOBAL HEPATITIS SUMMIT 2023

PARIS FRANCE

April 25 - 28, 2023

HBV / HDV debrief

Markus Cornberg

CiiM
CENTRE FOR INDIVIDUALISED INFECTION MEDICINE

GHE
Gastroenterologie
Hepatologie
Infektiologie
Endokrinologie

Disclosures

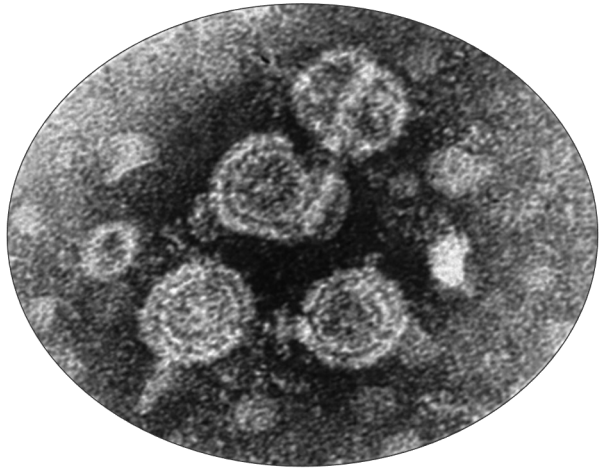
Fees for lectures and/or consulting from

- **AbbVie**
- **AiCuris**
- **Falk Foundation e.V.**
- **Gilead Sciences**
- **GlaxoSmithKline (GSK)**
- **MSD Sharp & Dohme**
- **F.Hoffmann-La Roche**

Disclaimer

"Please note that in the context of this scientific presentation, substances or indications of substances may be mentioned that have not yet been approved and are currently still in clinical development, or data may be shown that have not yet found their way into the expert information reviewed by the regulatory authority."

Picture: Wikipedia (DE)

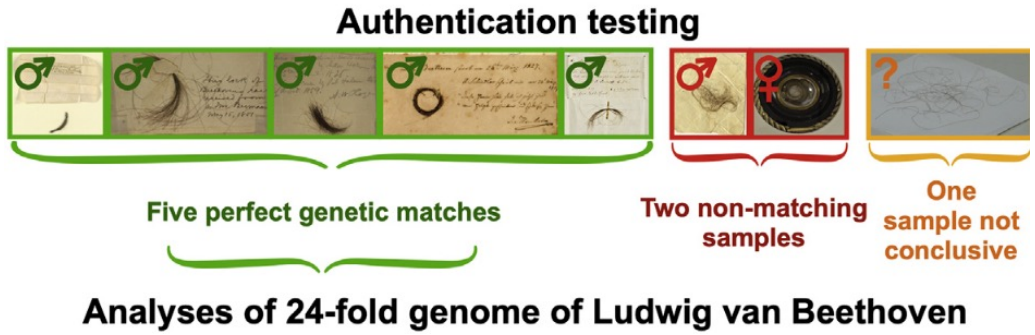


Hepatitis B

B = Back on the Agenda or Beethoven

Ludwig van Beethoven, 1770 - 1827

Picture: https://www.sueddeutsche.de/



Analyses of 24-fold genome of Ludwig van Beethoven

Current Biology

Genomic analyses of hair from Ludwig van Beethoven

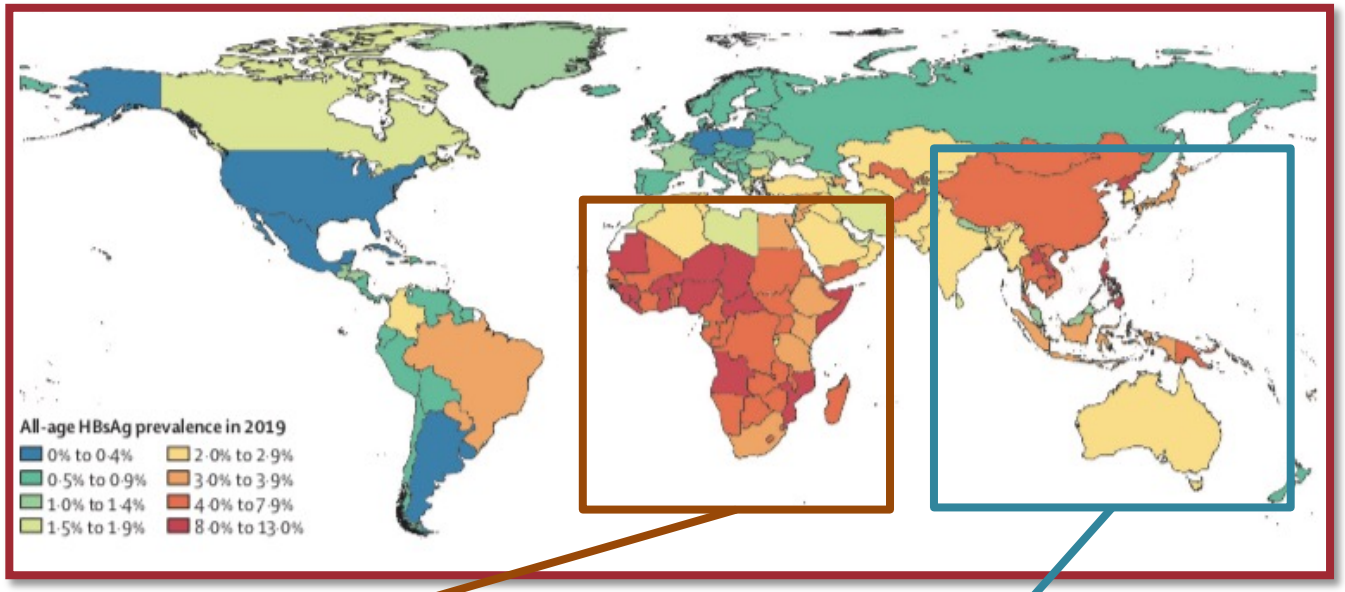
Highlights

- Eight locks of hair attributed to Ludwig van Beethoven underwent genomic analyses
- We deemed five of these authentic and sequenced Beethoven's genome to high coverage
- Beethoven had a predisposition for liver disease and became infected with hepatitis B
- We also discovered an extra-pair-paternity event in Beethoven's paternal line

Begg et al. ***Curr Biol.*** 2023 Mar 13;S0960-9822(23)00181-1. doi: 10.1016/j.cub.2023.02.041.

Epidemiology of HBV infection

316 million (284 to 351) chronic HBV infections
High prevalence in low middle income countries



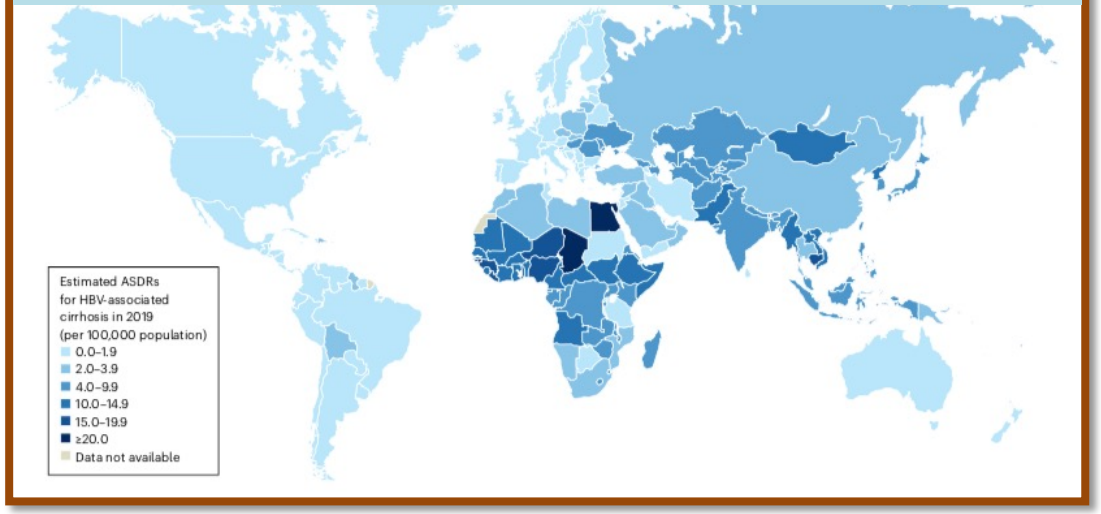
WHO African region
HBsAg prevalence: 7.53%
82.3 M

WHO West Pac Region
HBsAg prevalence 5.92%
115 M

GBD 2019, ***Lancet Gastroenterol Hepatol***. 2022;7(9):796-829.

Age-standardized death rate due to HBV-related cirrhosis

331,000 deaths due to HBV cirrhosis in 2019



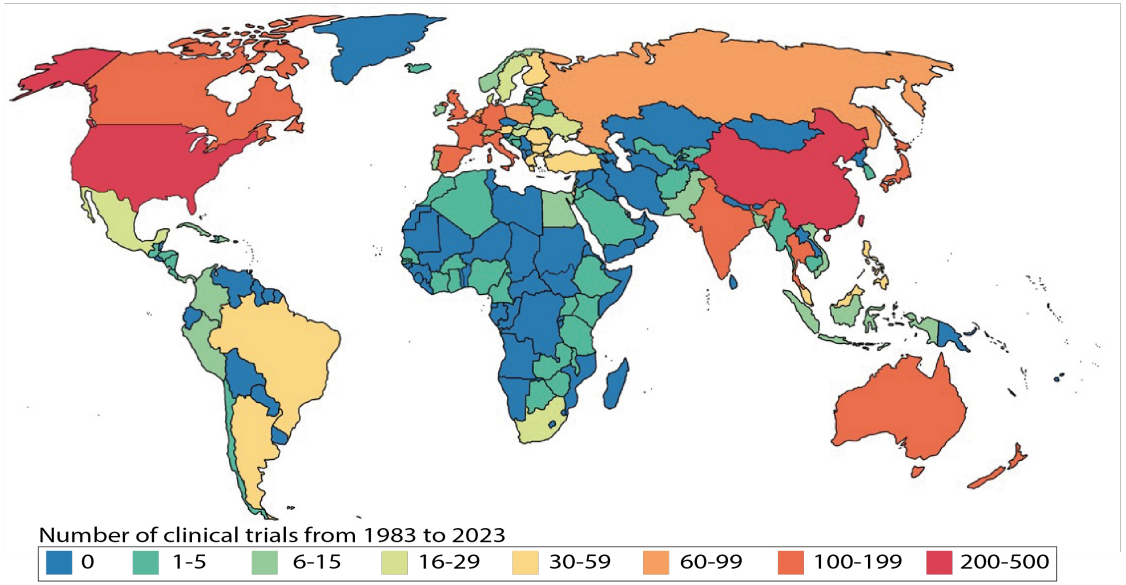
Adapted from GBD 2019, ***Lancet Gastroenterol Hepatol***. 2022;7(9):796-829
Hsu et al. ***Nat Rev Gastroenterol Hepatol***. 2023: 10.1038/s41575-023-00760-9.

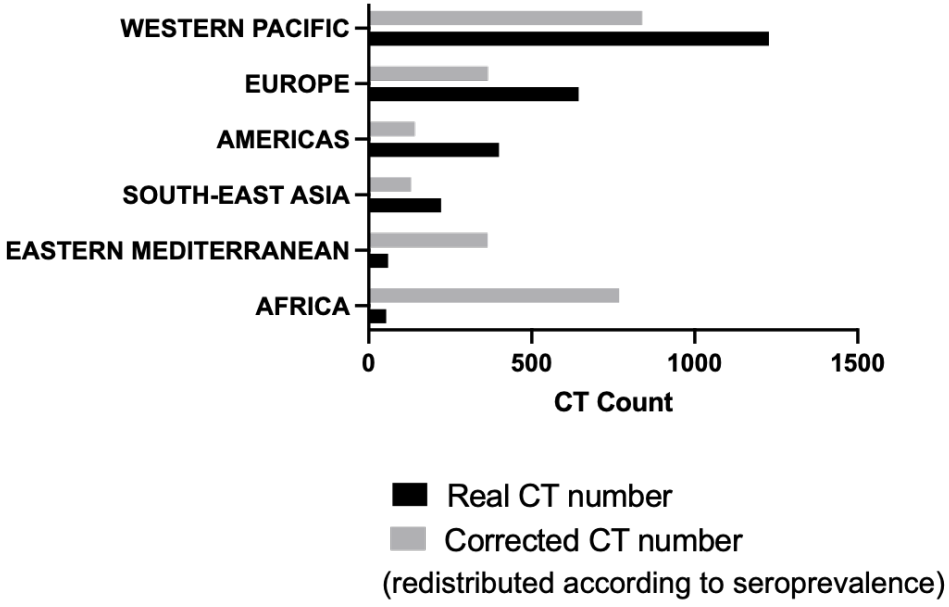
Ndow et al. ***GHS*** 2023 (O44): Gambia, West Africa
Median survival was 17.1, 11.3 and 1.5 months among patients with compensated cirrhosis, decompensated cirrhosis, and HCC, respectively (median age 42 years)

Under-Representation of WHO Africa Region In HBV Clinical Trials: The Field Advances, But In Which Direction?

Delphin et al screened the clinicaltrial.gov repository for 'Hepatitis B' related CT. They classified studies to investigate (1) location, (2) design (interventional/observational), (3) funding and (4) publication.

HBV related CT from 1983 to 2023

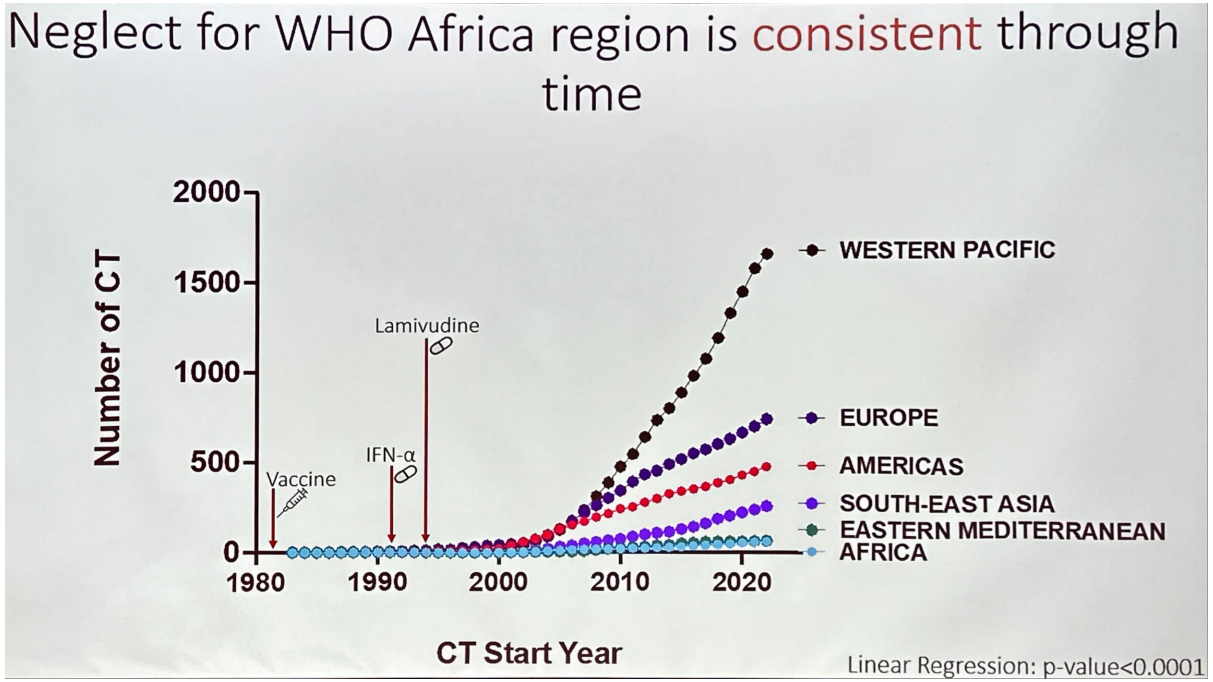


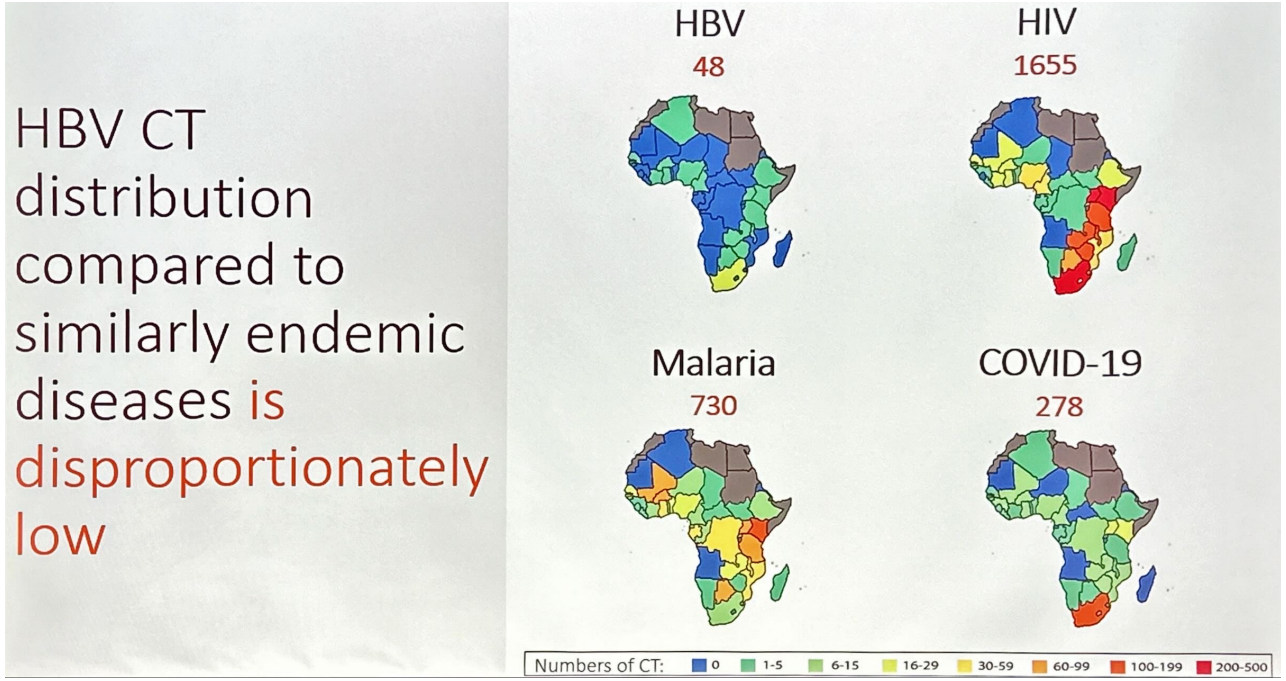


→ There is a clear neglect of investment in HBV-focused clinical trials in Africa, particularly for interventions, to reduce the morbidity and mortality of chronic HBV infection.

Delphin et al. ***GHS*** 2023 (LB/O110)

Under-Representation of WHO Africa Region In HBV Clinical Trials: The Field Advances, But In Which Direction?

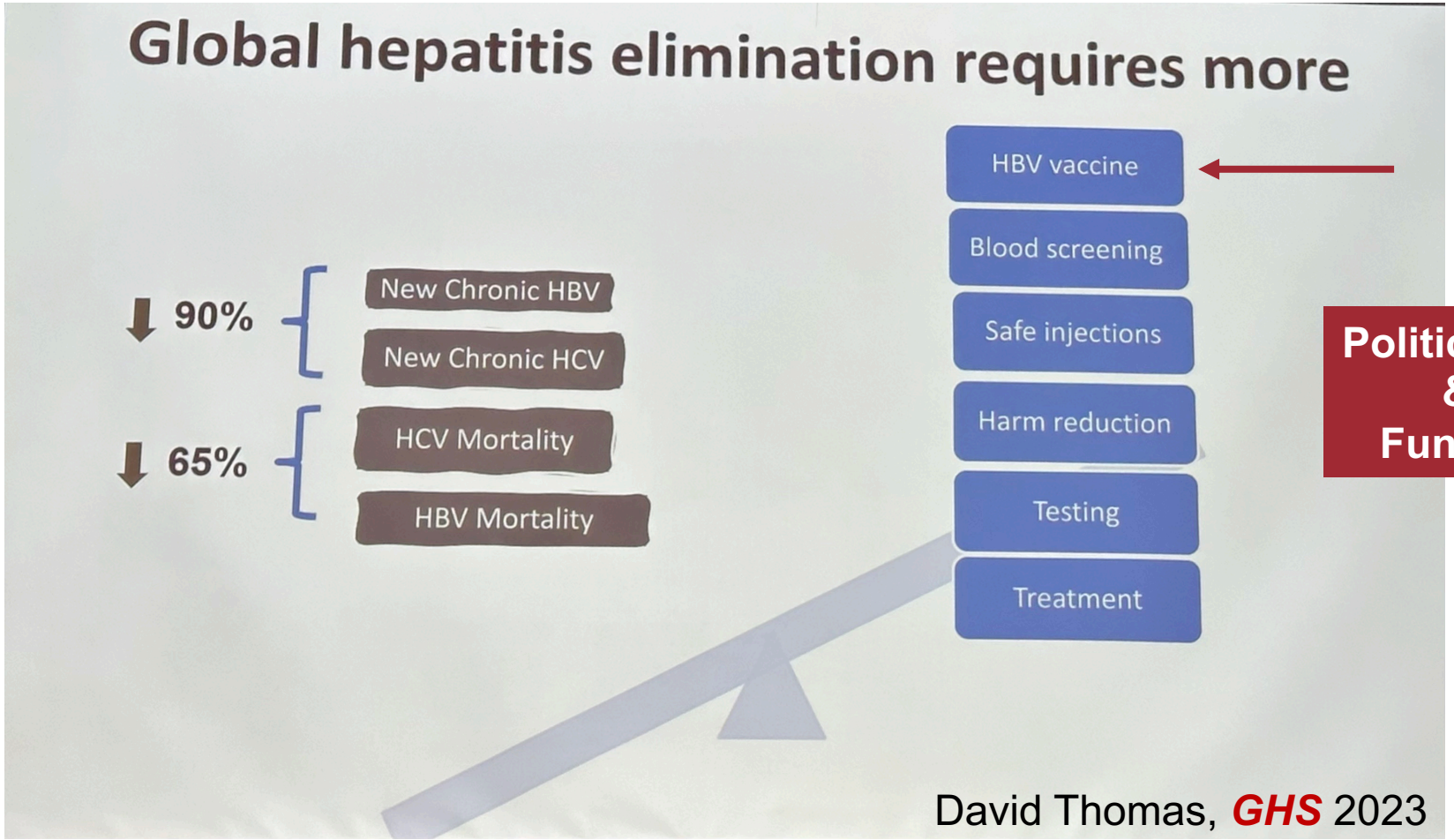




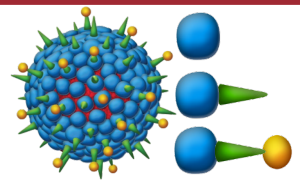
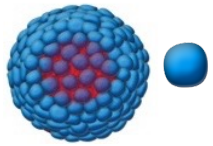
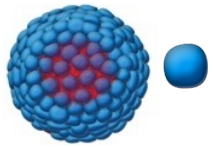
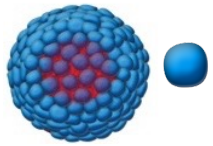
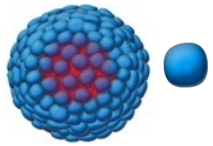
→ **There is a clear neglect of investment in HBV-focused clinical trials in Africa, particularly for interventions, to reduce the morbidity and mortality of chronic HBV infection.**

Delphin et al. ***GHS*** 2023 (LB/O110)

Toolbox for HBV elimination



Effective HBV Vaccines

Manufacturer	Non-Proprietary Name	Brand Name	Effective HBV-Vaccine Antigen		Approved Adult Populations	Administration	Antigen Dose + Adjuvant
VBI VACCINES	Hepatitis B Vaccine (Recombinant)	**PreHevbri®**		**S** **+ Pre-S2** **+ Pre-S1**	**3 antigens produced in mammalian cells**	• All, Age 18+	3 x 1ml	10µg + 500µg alum
GSK	Hepatitis B Vaccine (Recombinant)	**Engerix-B®** *(also included in Twinrix®)*		**S**	**1 antigen produced in yeast**	• All, Age 16+ • in CKD	3 x 1ml 4 x 2ml	20µg + 500µg alum 40µg + 1,000µg alum
MERCK	Hepatitis B Vaccine (Recombinant)	**HBVAXPRO®**		**S**	**1 antigen produced in yeast**	• All, Age 16+ • in CKD	3 x 1ml 3 x 1ml	10µg + 500µg alum 40µg + 500µg alum
DYNAVAX	Hepatitis B Vaccine (Recombinant) Adjuvanted	**Heplisav-B®**		**S**	**1 antigen produced in yeast**	• All, Age 18+	2 x 0.5ml	20µg + 3,000µg CpG 1018
GSK	Hepatitis B Vaccine (Recombinant) Adjuvanted	**FENDRIX®**		**S**	**1 antigen produced in yeast**	• CKD only, Age 15+	4 x 0.5 ml	20µg + ASO4C + 500µg alum

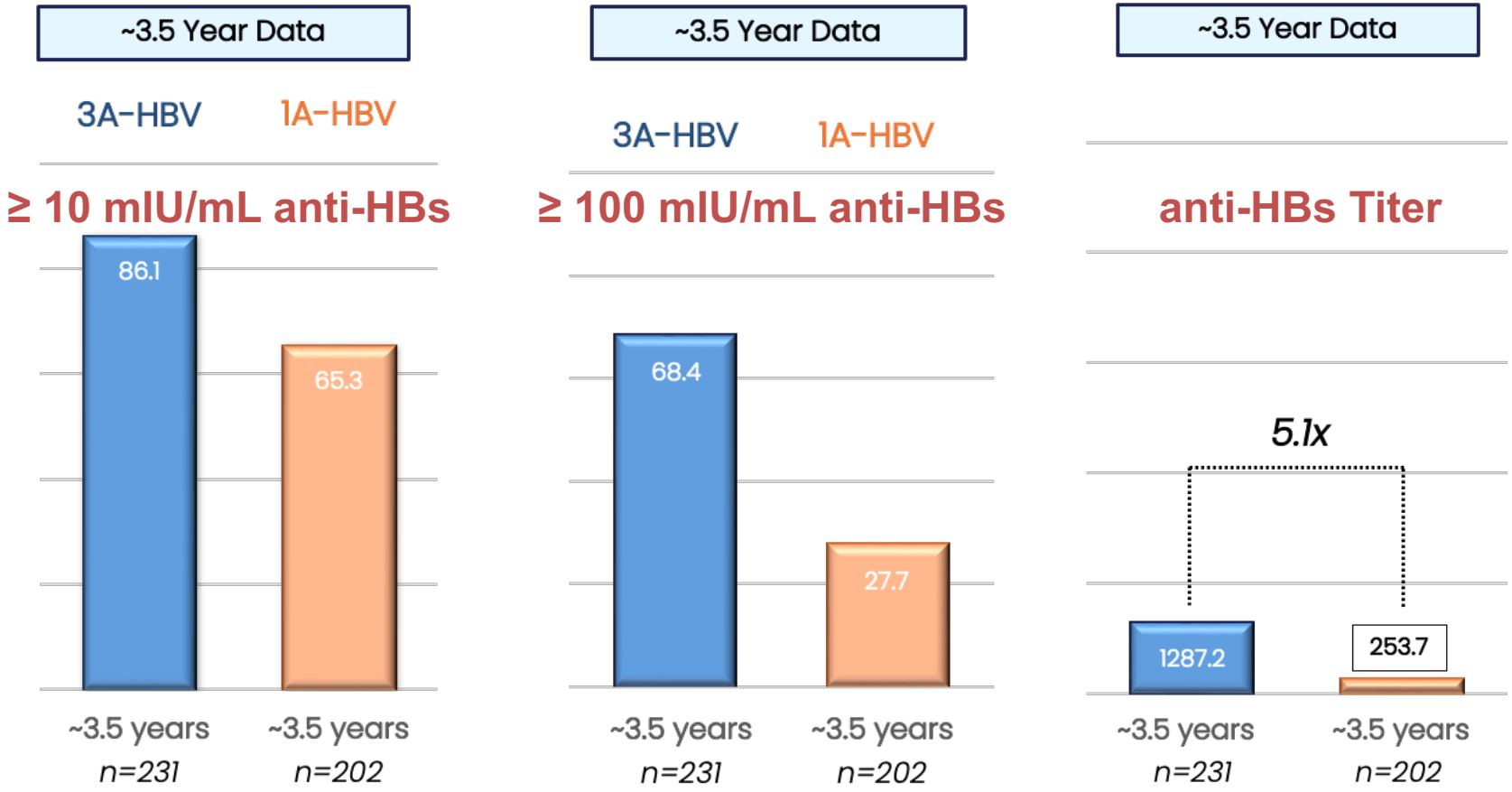
Slide from Vesikari, Maubach et al. ***GHS*** 2023 (LB/O106)

3-Antigen HBV vaccine, with Pre-S1, Pre-S2 and S antigens, induces a higher and more durable immune response compared to 1-antigen HBV vaccine

Phase 3 Studies
N=1,607 (PROTECT)
N=2,838 (CONSTANT)

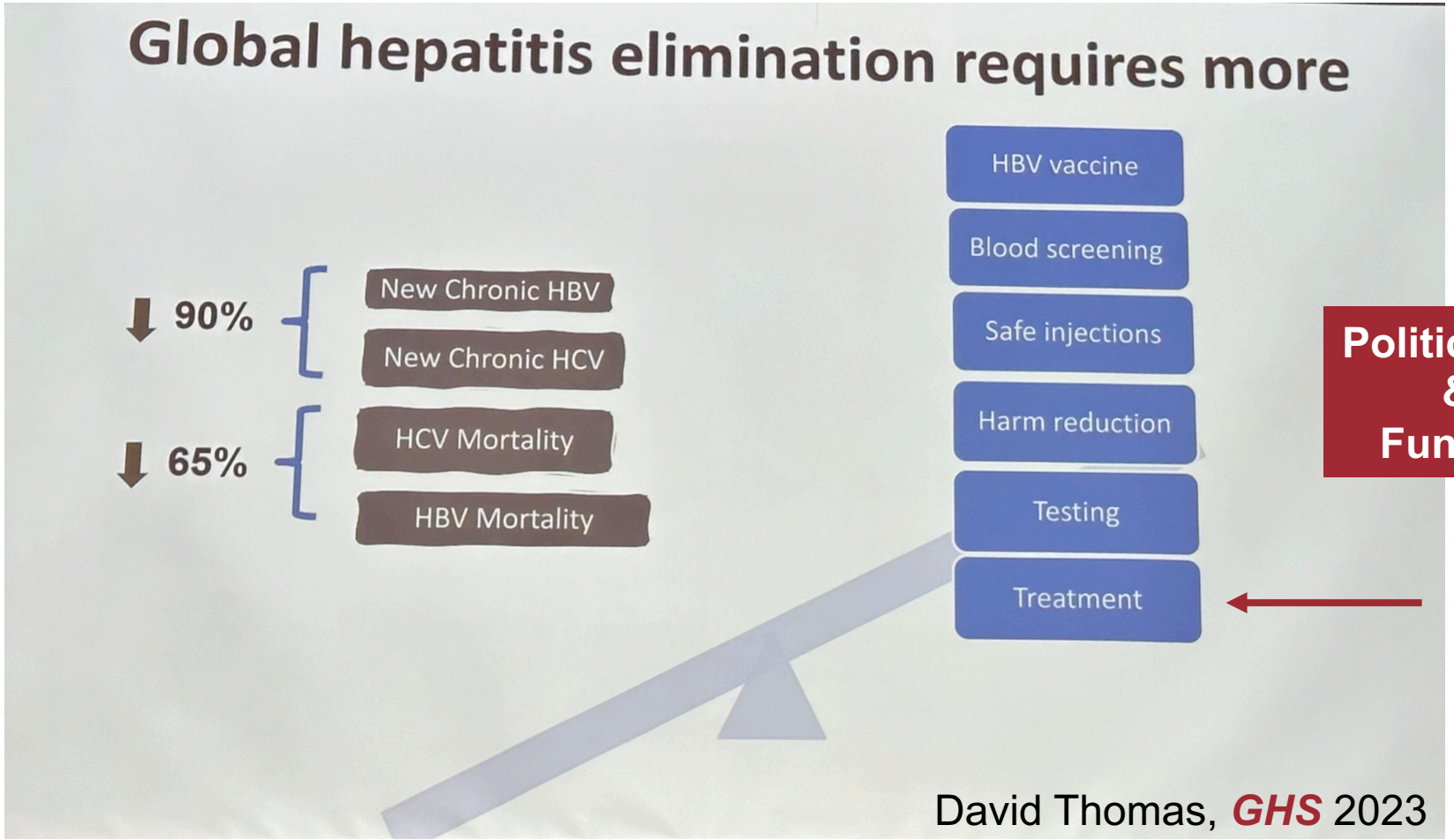
FU 3.5 years from PROTECT
N=433

Median Age 60-60.5 years
41.1-42.1% ≥65 years



Vesikari, Maubach et al. ***GHS*** 2023 (LB/O106)

Toolbox for HBV elimination



Debate: Should we treat all individuals (without cirrhosis) whose HBV DNA is ≥ 2,000 IU/mL)?

PRO

- NUCs prevent cirrhosis and HCC
- NUCs are safe
- NUCs are generic
- **That makes it simple**

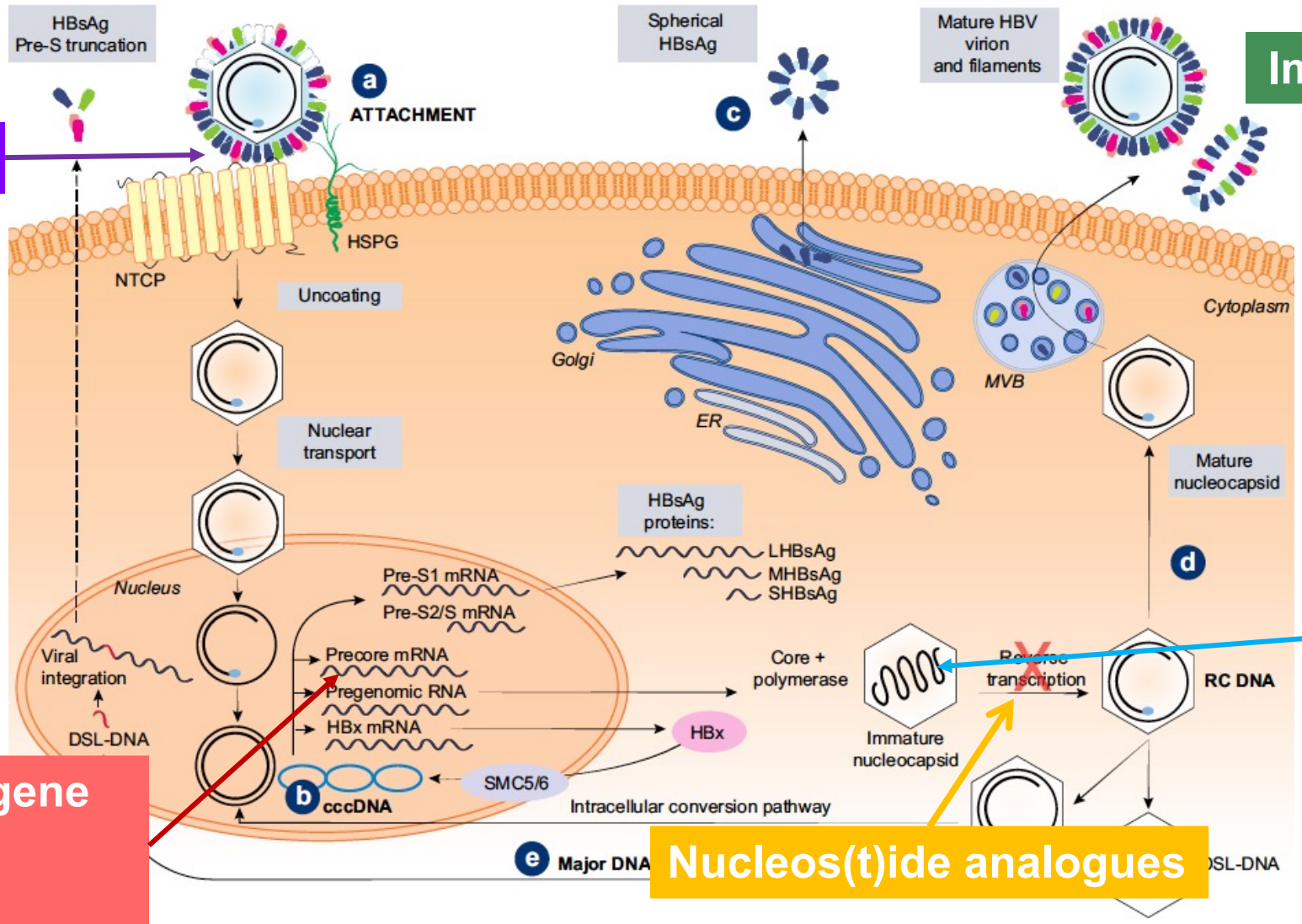
CONTRA

- Not cost effective for all patient cohorts?
- Adherence to treatment may be a challenge?

Novel therapies aimed at HBV cure

Entry inhibitors

Immunomodulators



Core or Capsid Inhibitors

Inhibition of HBV gene expression (ASO, siRNA).

Nucleos(t)ide analogues

Figure: Cornberg et al., ***J Hepatol***. 2017 Feb;66(2):398-411.

Core or Capsid Inhibitors (CAM)

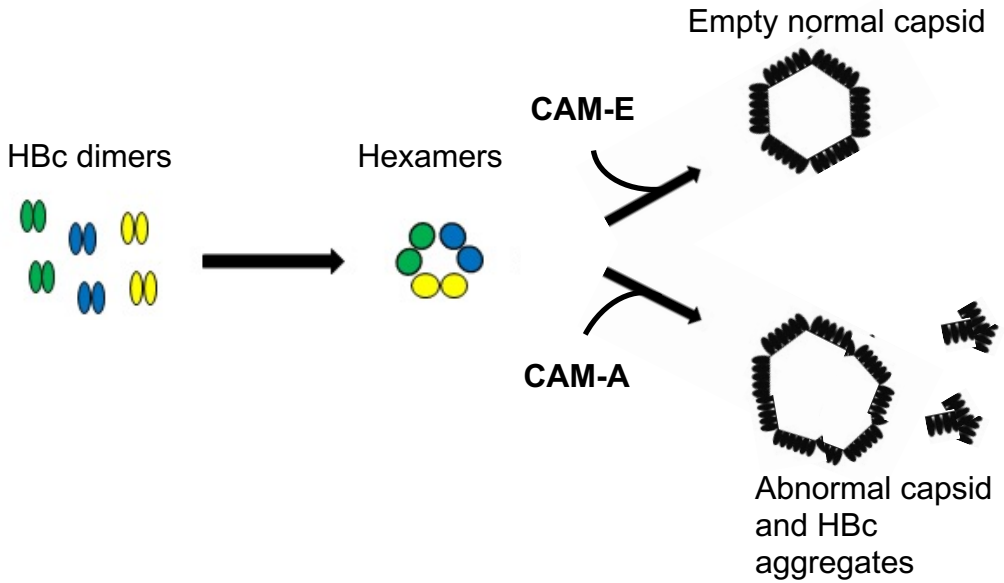
Slide from A Zlotnik

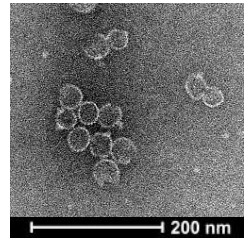
HBc is structural
assembly
disassembly

HBc is non-structural
regulatory
druggable

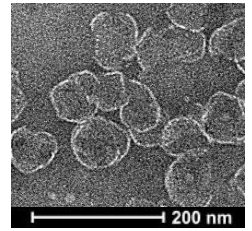
CAMs now
drive assembly and dis-assembly

CAMs in the future
apoptosis of infected cells
dysregulation of non-structural activity





CAM-E



CAM-A

Class-A capsid assembly modulators (RG7907) induce cell death through HBV core protein aggregation and potentially activate the innate immune response

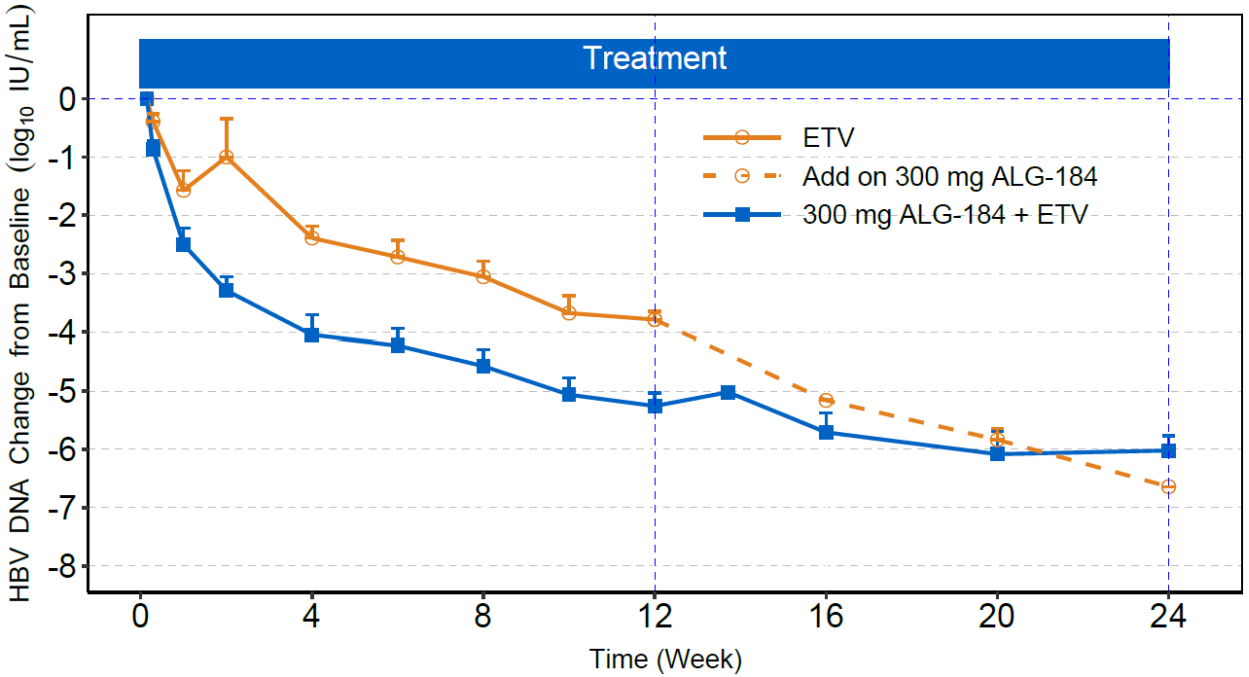
Taverniti et al. ***GHS*** 2023 (O20)

MF Yuen: „Additive effects to NUC therapy. More patients achieve HBV DNA supression to undetectable level. So far no convincing effect on HBsAg (with early generation CAM)“

CAM-E ALG-000184 (interim analysis)

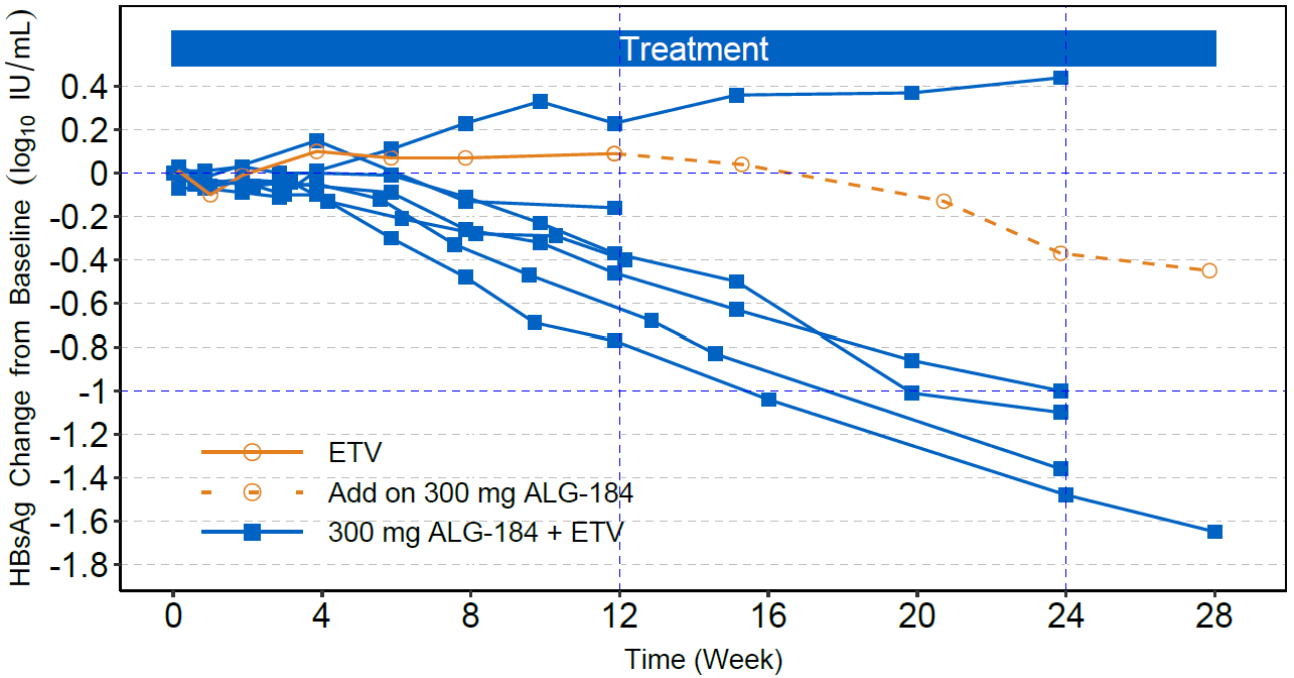
Part 4 Cohort 2 (n=15: 8.1 log HBV DNA, 100% HBeAg pos, Age 31.4 yrs) (300 mg ALG-00184 + ETV x 48 weeks)

HBV DNA with ALG-000184 x ≥12 Weeks



- At Week 24, all subjects had HBV DNA decline ≥6 $\log_{10}$ IU/mL, 1 subject was undetectable

HBsAg with ALG-000184 x ≥12 Weeks

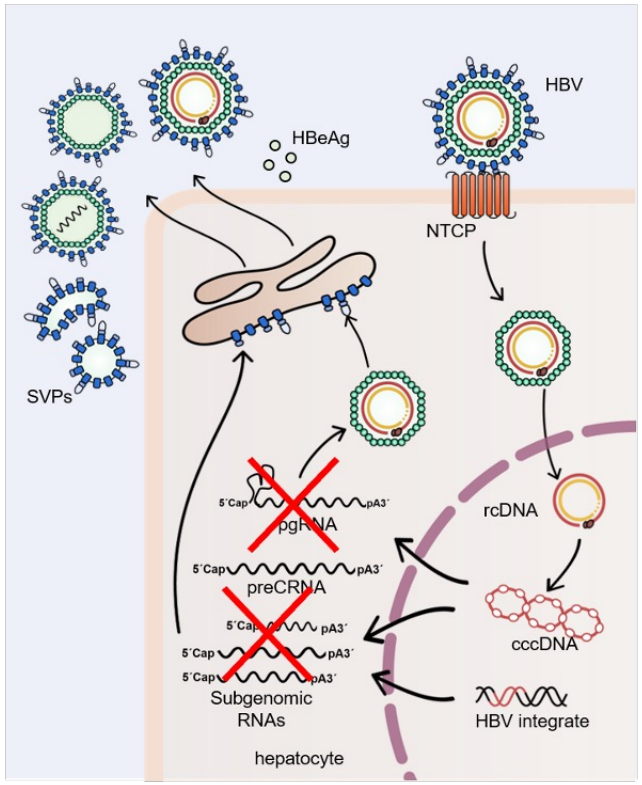


- HBsAg declines appear to be correlated to plasma ALG-001075 PK (both AUC and Ctrough)

McClure, …, Gane. ***GHS*** 2023 (LB/O103)

Inhibition of HBV RNAs (ASO, siRNA).

Potential advantages of targeting HBV RNAs



Adapted from Dandri et al. Seminars Immun. 2021

1) pgRNA degradation: inhibition of HBV replication

2) to degrade all HBV RNAs → hinder production of all HBV proteins

↓ circulating viral antigens (HBsAg)	chronic HBsAg exposure is linked to immune dysfunction / anergy / viral clearance inability
↓ regulatory HBx protein	Essential to maintain the cccDNA transcriptionally active

Overall goals:

Sustained loss of HBsAg: functional cure

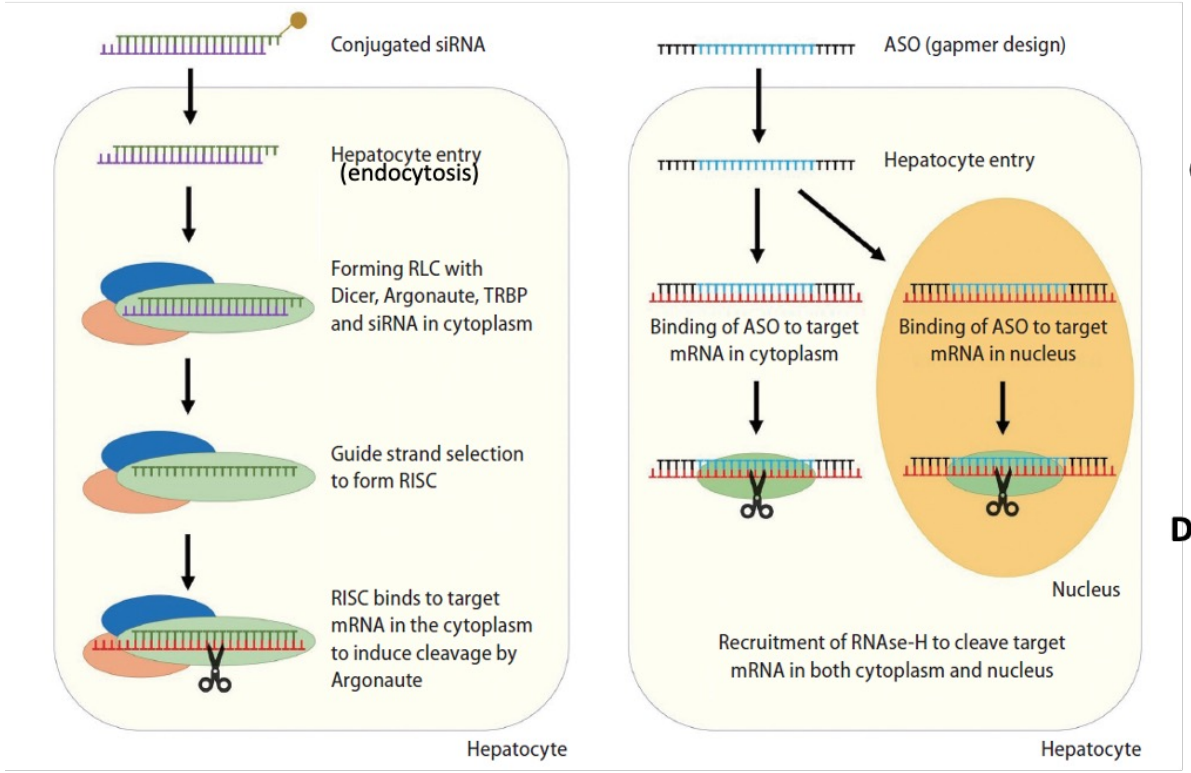
↕

to attain reconstitution of HBV-specific immune responses

Reduction of viral RNAs and HBx induces transcriptional cccDNA silencing through the come-back of SMC5/6

Allweiss, Giersch et al. Gut 2021

Inhibition of HBV RNAs (ASO, siRNA).



siRNA
small-interfering RNA

dsRNA (21nt)
Guide strand (target mRNA)
+Passenger strand

Delivery systems needed for uptake
(LNPs; GalNac-conjugation)

a) Formation of RISC Loading complex (RLC):
Dicer (Rnase III endonuclease)
Argonaute (RNase)

b) Formation RNA-induced silencing complex (RISC)

mRNAs are targeted in cytoplasm

ASO
antisense oligonucleotides

ssDNA (15-25nt)
flanked by gapmers
(RNA-like segments)

Conjugation not needed for uptake
(GalNac ↑ uptake)

RNAseH-mediated cleavage of targeted mRNA

mRNAs are targeted in cytoplasm and nucleus

1 ASO silences 1 targeted mRNA (more frequent dosing)

1 siRNA silences >> targeted mRNAs

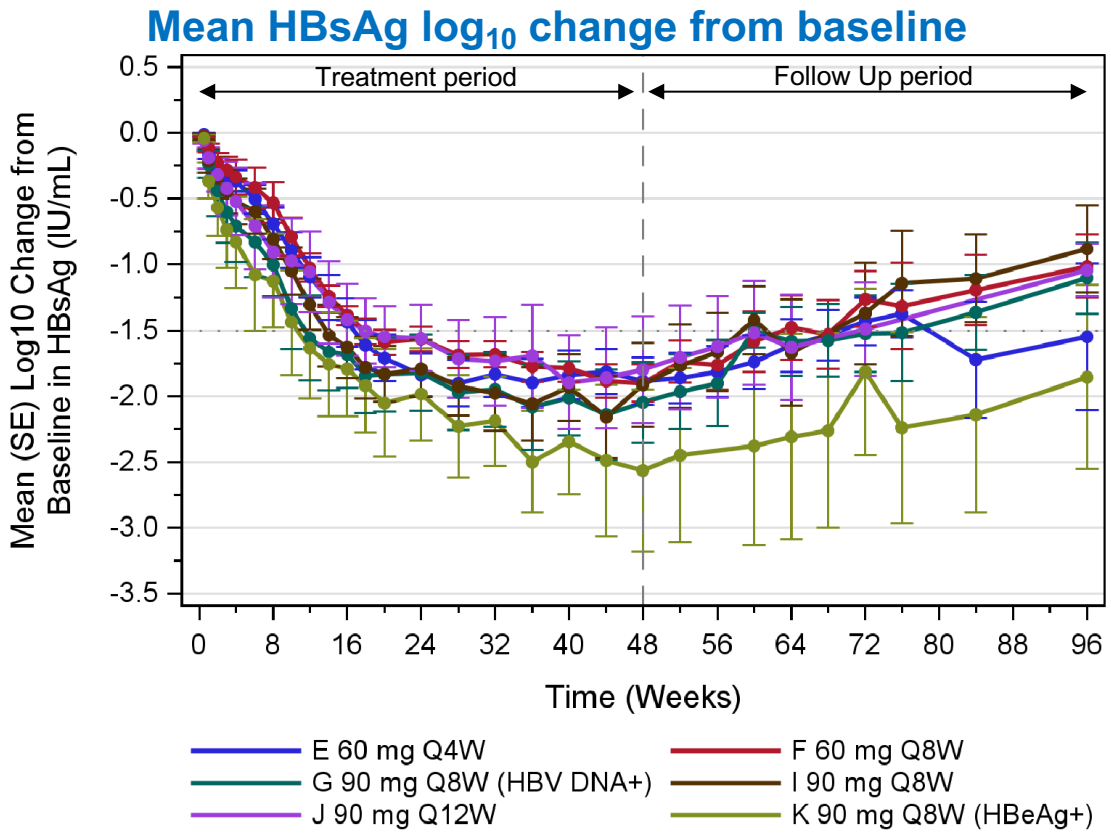
RNA interference as a novel treatment strategy for chronic hepatitis B infection

Rex Wan-Hin Hui[1], Lung-Yi Mak[1,2], Wai-Kay Seto[1,2], and Man-Fung Yuen[1,2]

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2022.0812
Clinical and Molecular Hepatology 2022;28:408-424

AB-729 is a GalNAc-conjugated siRNA therapeutic that targets all HBV RNA transcripts



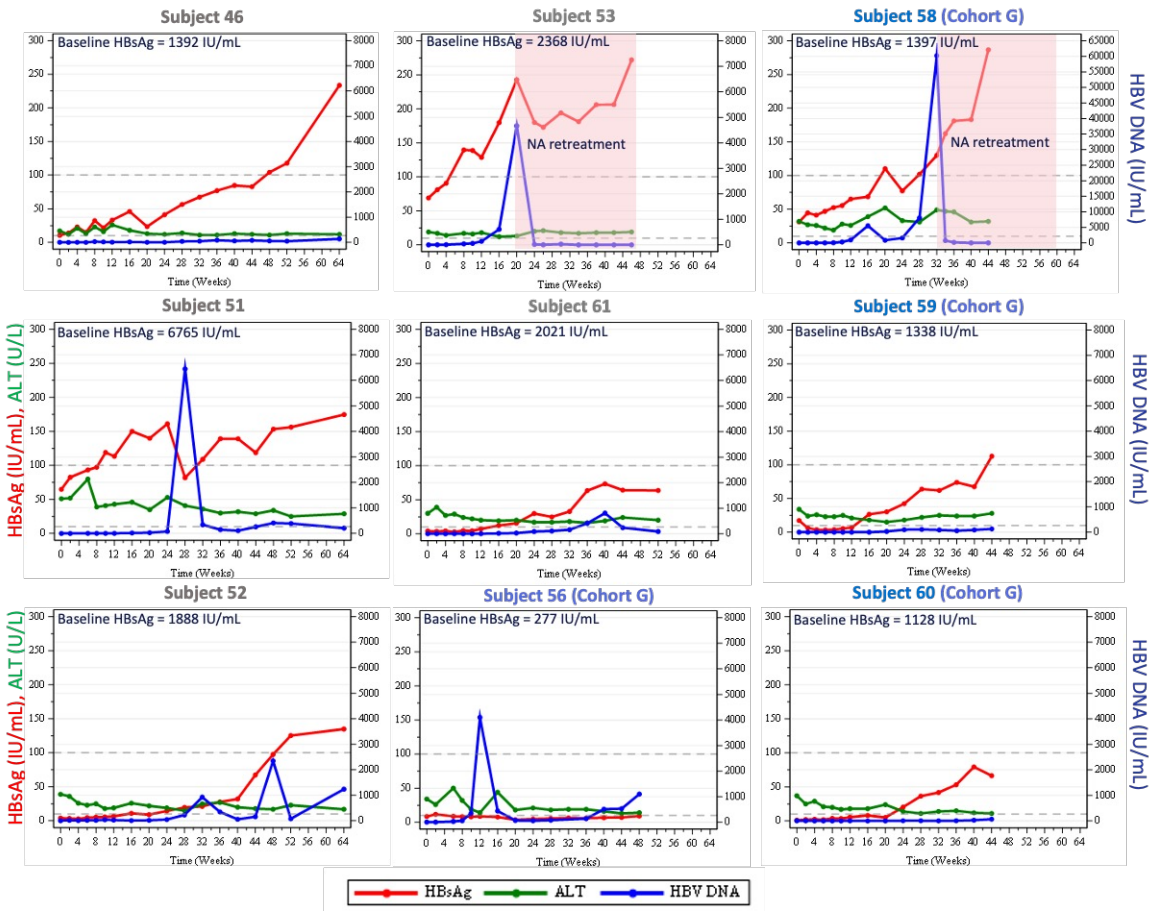
- All Cohorts achieved at least a -1.8 log_{10} decline in mean HBsAg at the end of the treatment period (Week 48)
- Mean HBsAg levels remained below baseline values at Follow Up Week 48
- There were no significant differences in mean HBsAg declines between the 60 mg and 90 mg doses or between different dosing intervals
- AB-729 was well-tolerated at all dose levels and intervals, with no treatment discontinuations due to AEs or treatment-related Grade 3 or 4 AEs

Yuen et al. ***GHS*** 2023 (LB/O99)

AB-729 is a GalNAc-conjugated siRNA therapeutic that targets all HBV RNA transcripts

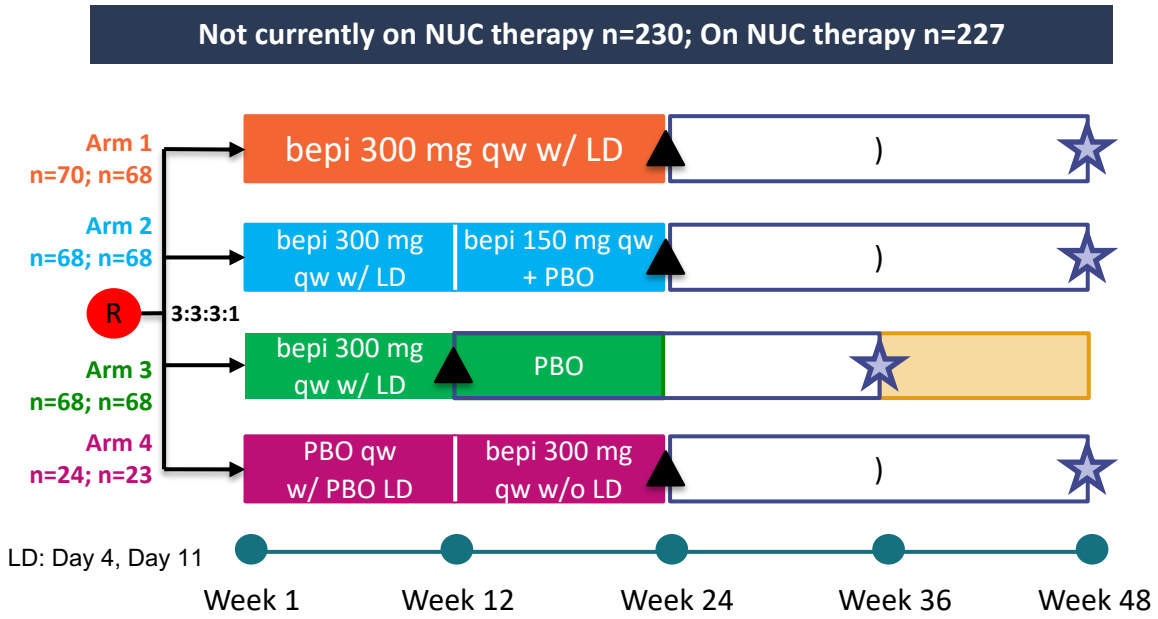
Part 3 subjects who completed 48 weeks of AB-729 treatment and met protocol-defined NA stopping criteria (assessed at least 24 weeks after the last dose of AB-729) were permitted to stop NA therapy

- ALT <2 × ULN,
- Undetectable (target not detected, TND) HBV DNA,
- HBeAg negative, and
- HBsAg <100 IU/mL at two consecutive visits



Yuen et al. ***GHS*** 2023 (LB/O99)

Bepirovirsen (bepi) in patients with chronic hepatitis B virus (HBV) infection: Efficacy and Safety 6 months after end of treatment (B-Clear Study)



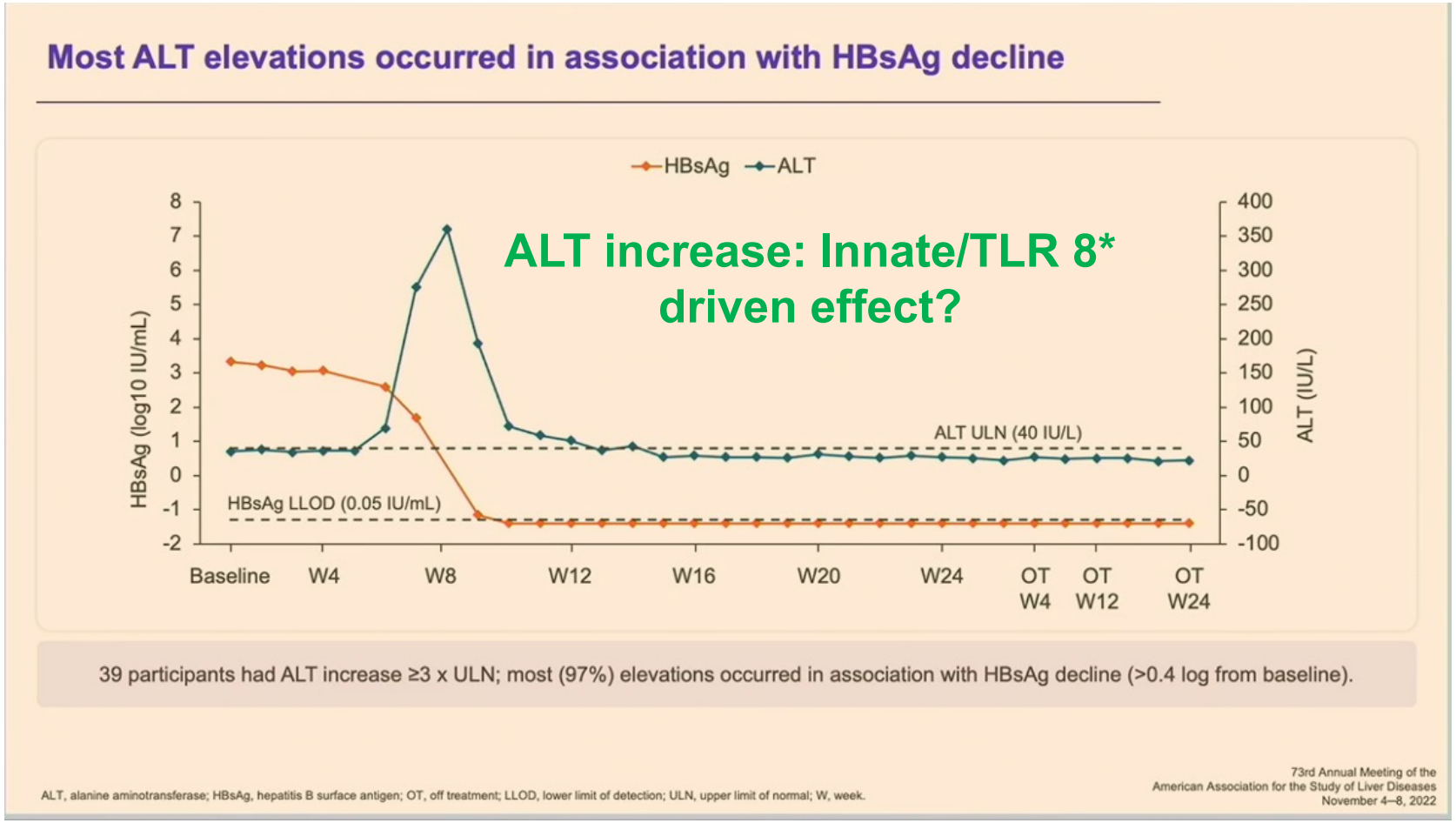
Primary outcome (HBsAg loss)

or modified primary outcome (permitted blips)

	No NUC (n=230)		NUC (n=227)	
bepi 300 mg qw w/ LD	10%	14%	9%	10%
bepi 300 mg qw w/ LD + bepi 150 mg qw + PBO	6%	6%	9%	9%
bepi 300 mg qw w/ LD + PBO	1%	1%	3%	4%
PBO qw w/ PBO LD + bepi 300 mg qw w/o LD	0%	4%	0%	0%

Lim S-G et al. **AASLD** 2022 (LB poster #5022)
Yuen et al. **AASLD** 2022 (LB session III #4)
Yuen al et al. ***N Engl J Med***. 2022 Nov 8. doi:10.1056/NEJMoa2210027

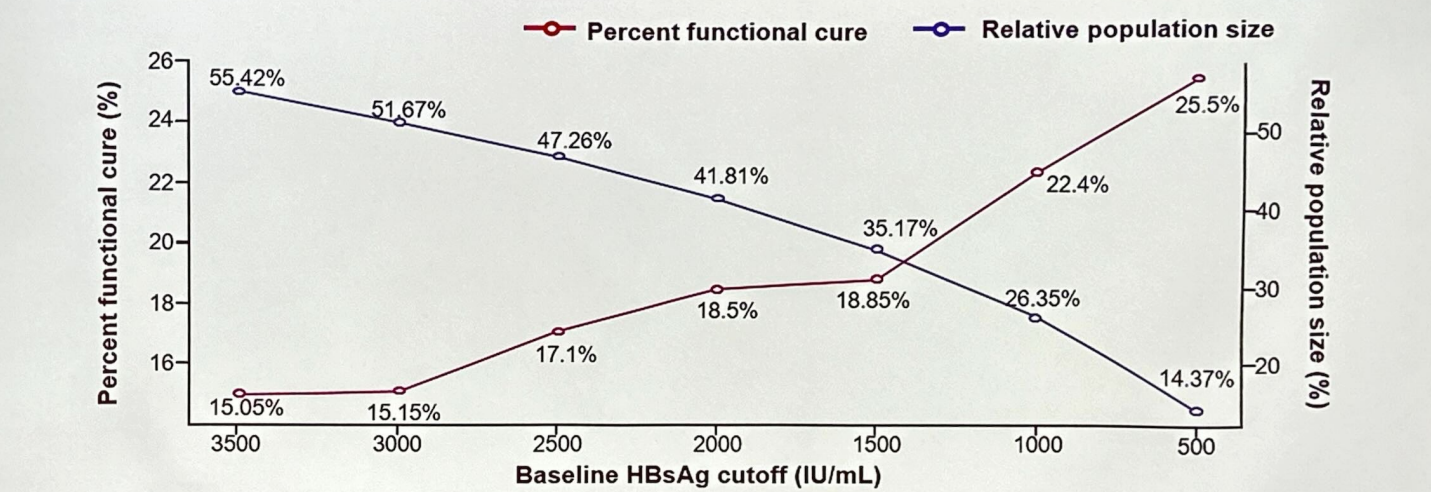
Explanation for HBsAg loss in patients treated with Bepirovirsen (bepi) ?



Lim S-G et al. **AASLD** 2022 (LB poster #5022)
Yuen et al. **AASLD** 2022 (LB session III #4)
Yuen al et al. ***N Engl J Med***. 2022 Nov 8. doi:10.1056/NEJMoa2210027

*J Hepatol 2022;77:Suppl 1:S873-S874.

Mechanistic PK/PD modeling and simulation of bepirovirsen PK, HBsAg and ALT changes from phase 2b study to inform phase 3 study design and dose selection



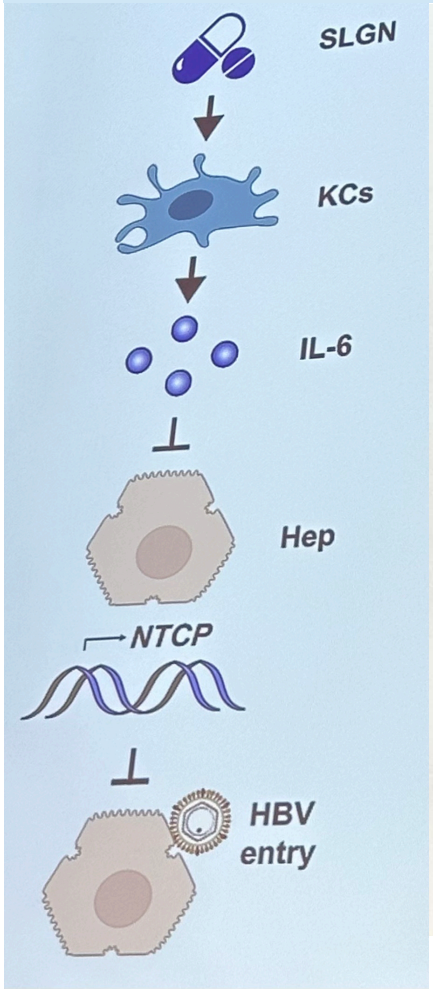
- Baseline HBsAg is a significant predictor of response to bepirovirsen treatment.
- Enrolment of a higher percentage of participants with lower baseline HBsAg increases the estimated percentage of a response to treatment

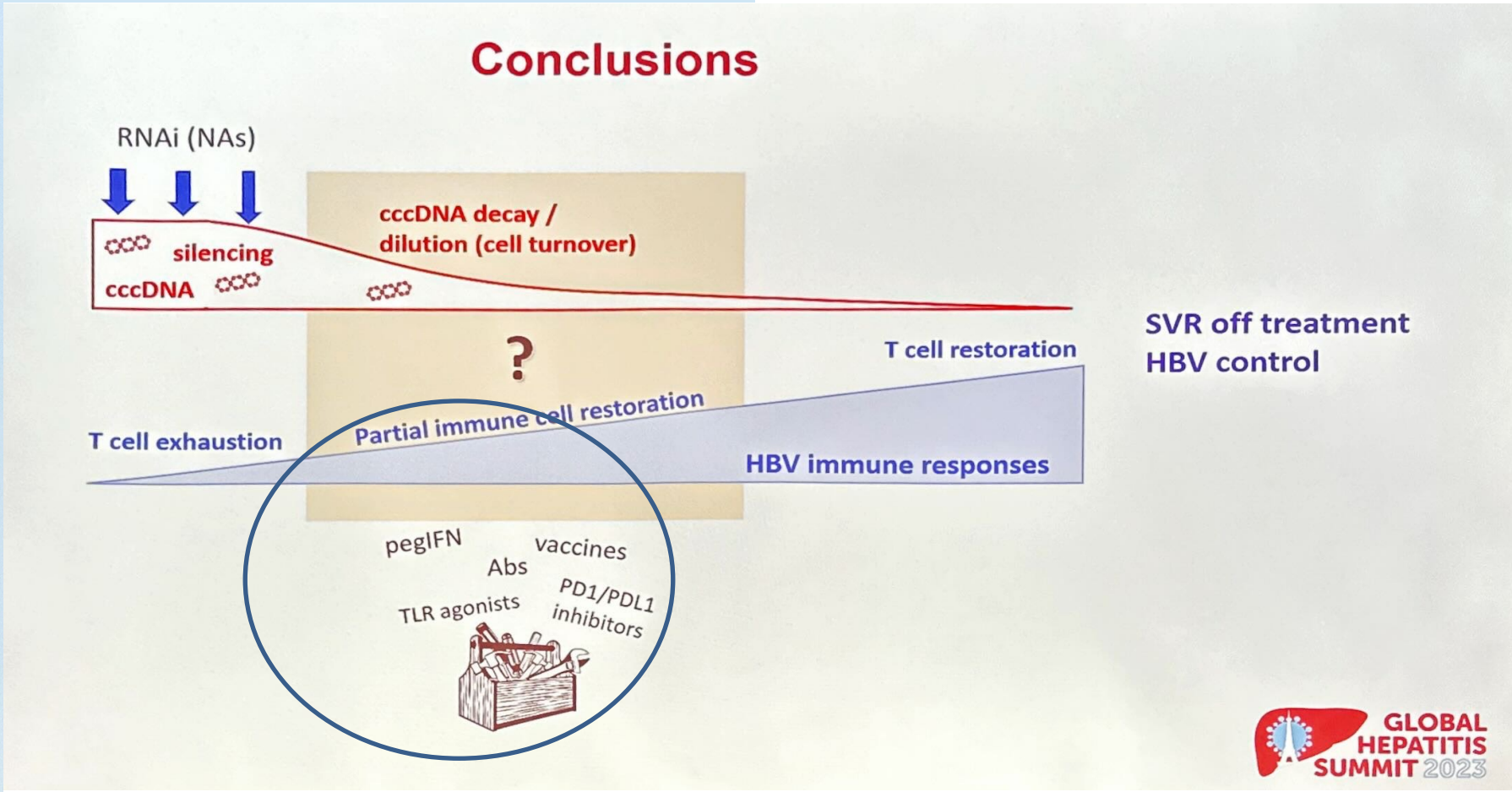
These modeling and simulation results support enrollment of pts with low baseline HBsAg in Phase 3 studies to maximize the benefit of BPV treatment. Simulation results will also be used to support BPV dose selection for the Phase 3 studies.

Youssef et al. ***GHS*** 2023 (LB/O94)

THE **TLR8 AGONIST** SELGANTOLIMOD MODULATES KUPFFER CELL DIFFERENTIATION STATUS AND INDIRECTLY IMPAIRS HBV ENTRY INTO HEPATOCYTES VIA AN IL-6-DEPENDENT MECHANISM

Roca Suarez et al. ***GHS*** 2023 (O24)

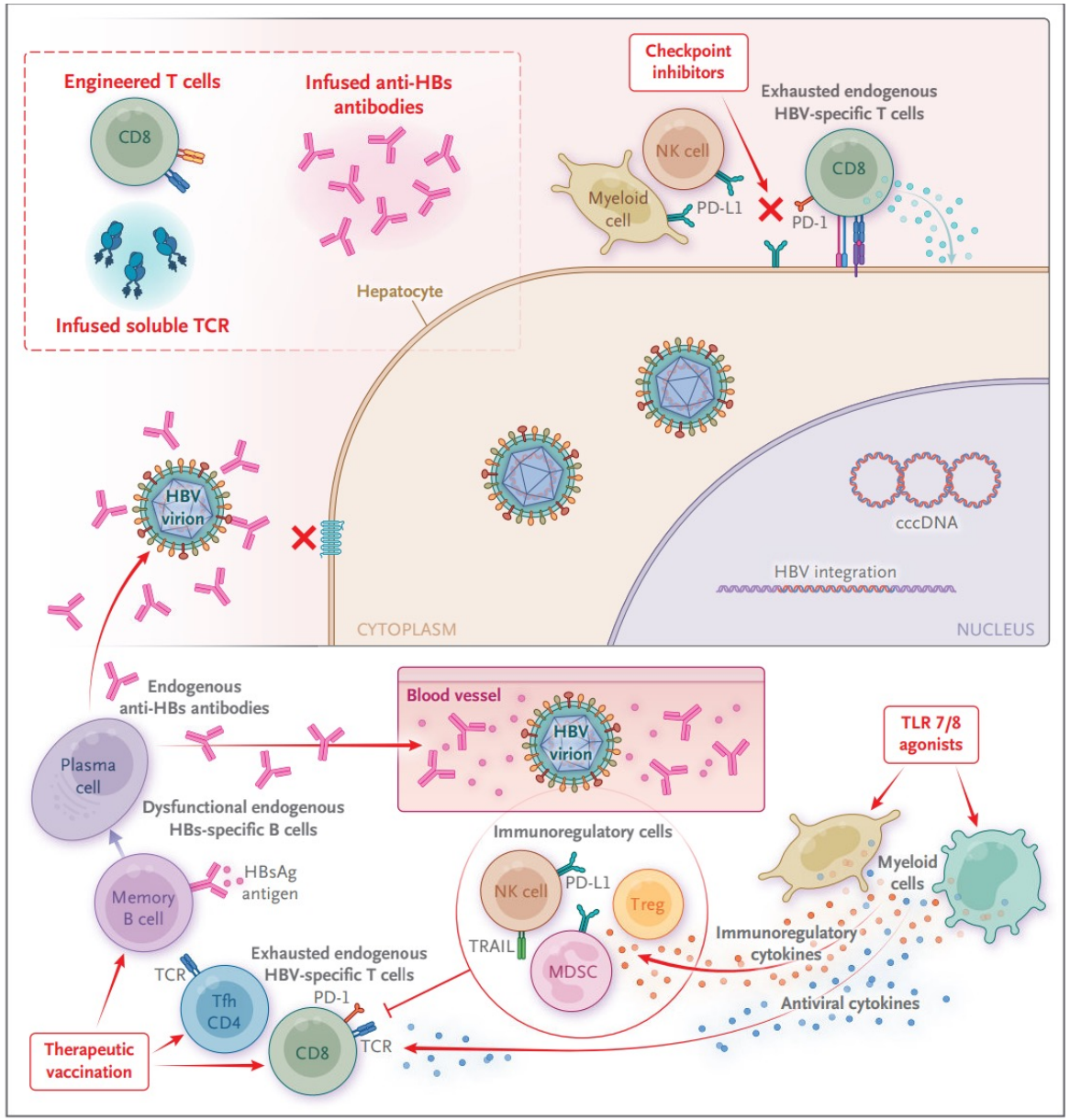




Slide from M Dandri

Redirect HBV-specific T cells

Recovery of the exhausted immune response



Generate adaptive immune responses

Stimulation of innate immunity

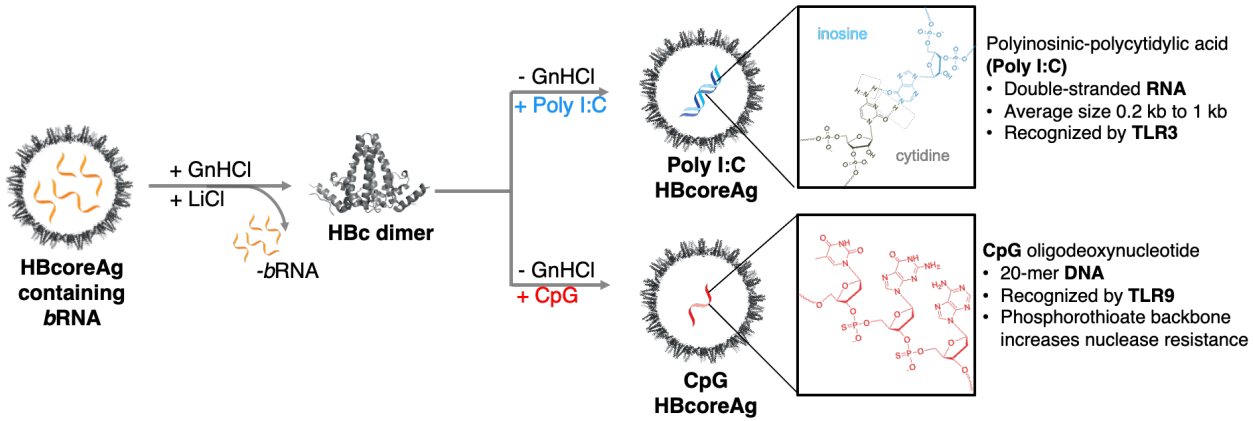
Figure from Dusheiko, Agarwal, Maini.
N Engl J Med. 2023 Jan 5;388(1):55-69.

Therapeutic Vaccines

E. Gane: „Graveyard of therapeutic vaccines“
U. Protzer: „HBV is a perfect use case. Why did therapeutic vaccines fail so far?“

- Preexsiting Antigen level (i.e. HBsAg) and level of immune exhaustion
- Antigens (e.g. HBs, HBc, Peptides) – B and/or T cell responses
- Vectors (DNA, AdV, MVA, mRNA)
- Prime-Boost strategies
- **Adjuvants (Alum, TH1 Adj, …)**

THERAPEUTIC VACCINATION FOR CHRONIC HEPATITIS B USING ADJUVANT-LOADED PARTICULATE HEPATITIS B CORE ANTIGEN



Adjuvant-loaded HBcoreAg retains capsid integrity *in vitro* and demonstrates strong immunogenicity *in vivo*, representing a novel promising platform for vaccine development.

Su et al. ***GHS*** 2023 (O18)

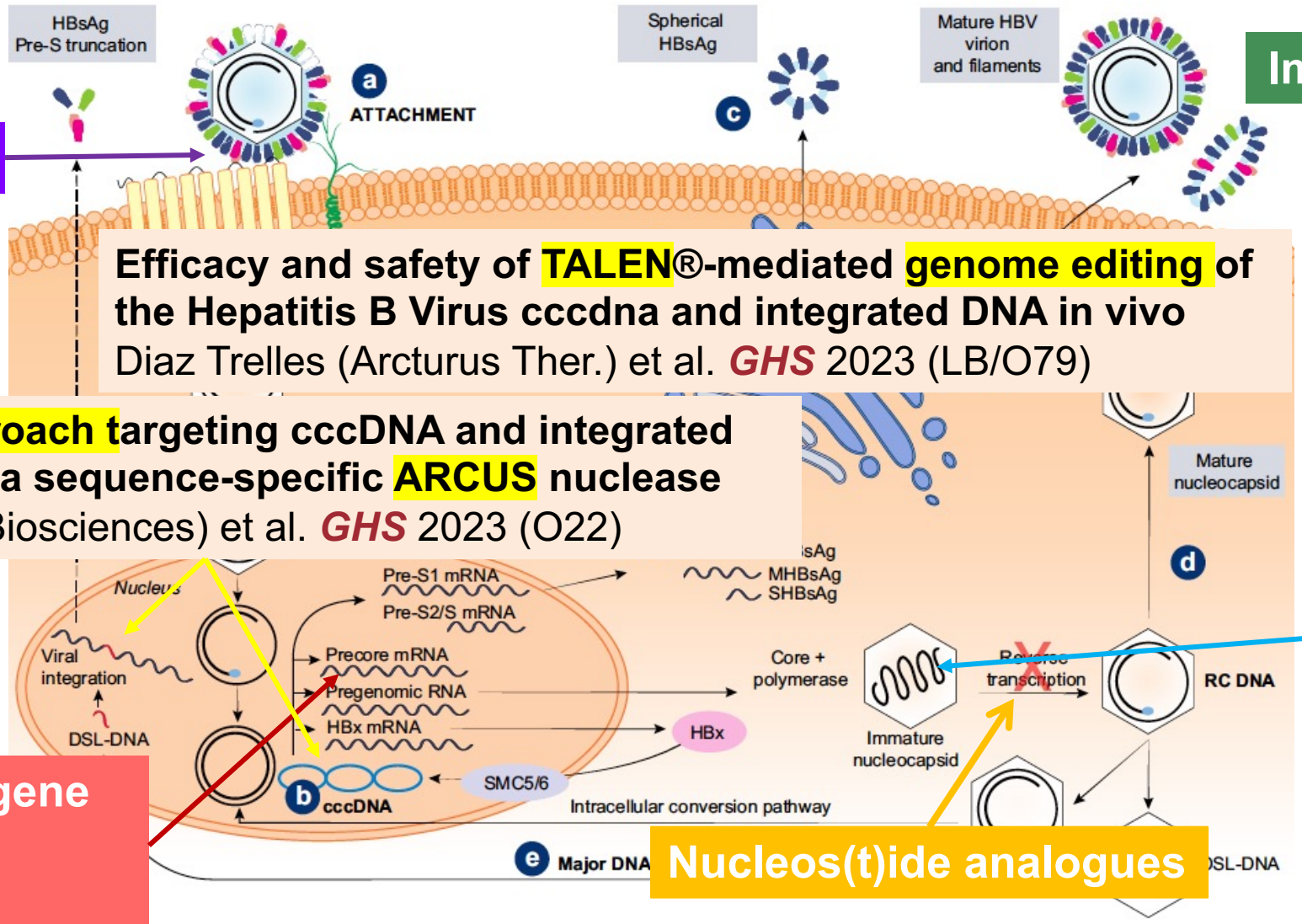
Novel therapies aimed at HBV cure

Entry inhibitors

Immunomodulators

Efficacy and safety of TALEN®-mediated genome editing of the Hepatitis B Virus cccdna and integrated DNA in vivo
Diaz Trelles (Arcturus Ther.) et al. *GHS* 2023 (LB/O79)

A gene editing approach targeting cccDNA and integrated viral genomes with a sequence-specific ARCUS nuclease
Gorusch (Precision Biosciences) et al. *GHS* 2023 (O22)



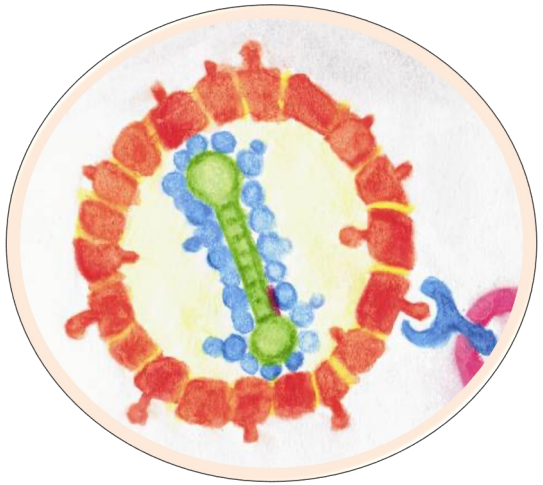
Core or Capsid Inhibitors

Inhibition of HBV gene expression (ASO, siRNA).

Nucleos(t)ide analogues

Figure: Cornberg et al., ***J Hepatol***. 2017 Feb;66(2):398-411.

Picture: Calle Serrano et al. ***Semin Liver Dis.*** 2012 May;32(2):120-9.



Hepatitis D

D = Devil

Treatments for HDV infection

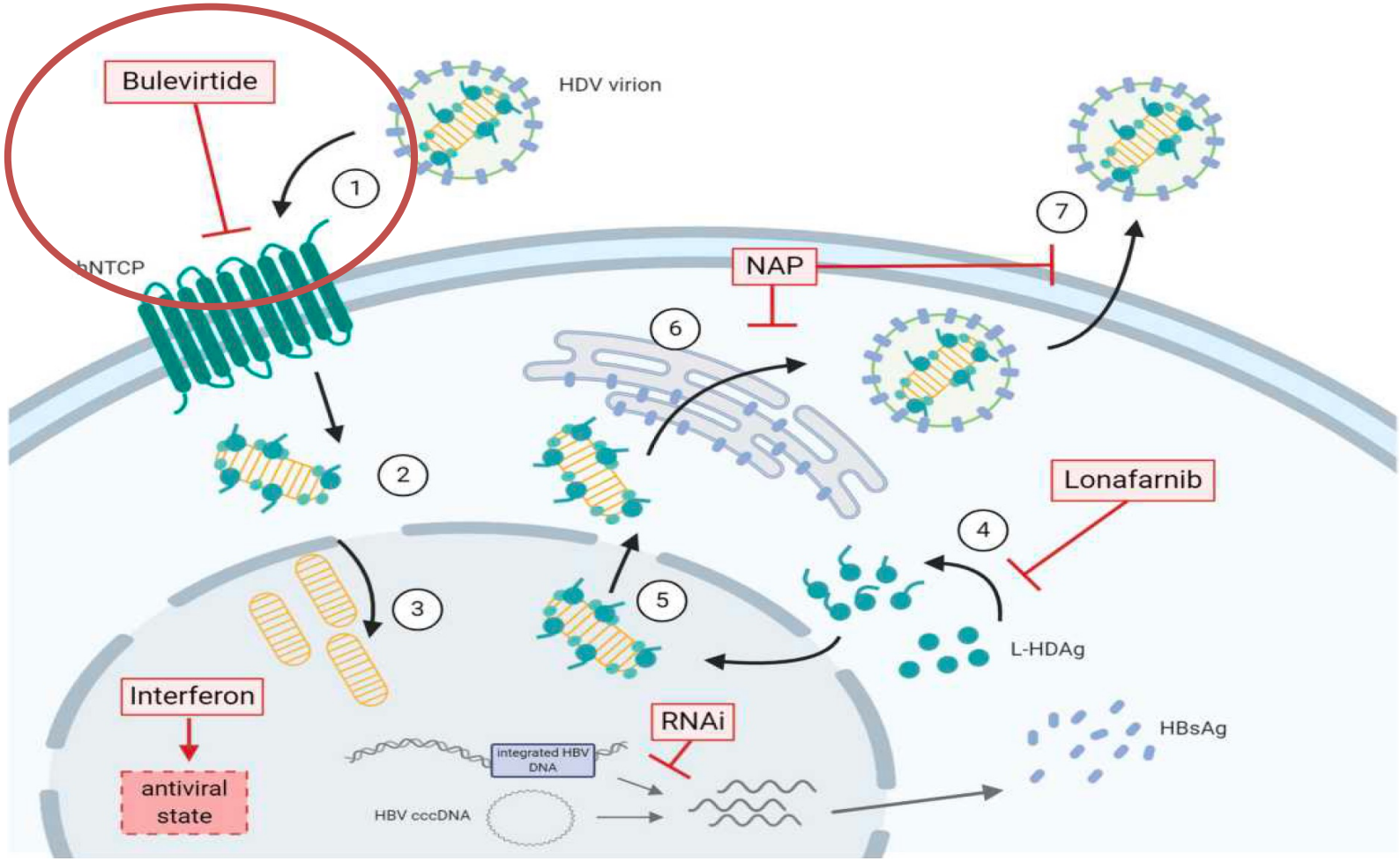


Figure: Sandmann & Cornberg. ***J Exp Pharmacol***. 2021 Apr 16;13:461-468.

Results of the phase 3 study (48 weeks of therapy with Bulevirtide)

Week 0 → 48

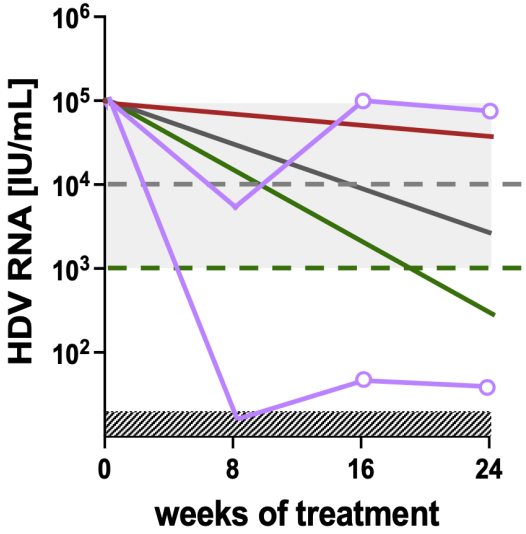
		HDV-RNA ≥2log decline and ALT normalization	HDV-RNA ≥2log decline or HDV-RNA negative	HDV-RNA negative	ALT normalization	Fibroscan
n=51	Delayed Tx	2 %	4 %	0 %	12 %	N=45 + 0.88
n=49	BLV 2 mg	45 %	71 %	12 %	51 %	N=48 - 3.08
n=50	BLV 10 mg	48 %	76 %	20 %	56 %	N=42 - 3.17

- Undetectable HDV RNA defined as below LOD (6 IU/mL); no data for undetectable RNA in the delayed treatment group at any visit.

Wedemeyer et al. ***EASL 2022***; GS006

No resistance detected to Bulevirtide monotherapy in participants with chronic hepatitis D through 24 weeks of treatment from Phase II and Phase III clinical trials

Virologic Response was defined by the HDV-RNA from baseline to week 24



Non-Responder (NR):
- decline <1 log_{10} IU/ml at Week 24

Δ ≥1 log_{10}: Partial Responder

Δ ≥2 log_{10}: Responder

N=21

Virologic breakthrough (VB):
Rebound of HDV-RNA at 2 consecutive visits after
- undetectable HDV RNA → detectable
- decline ≥1 log_{10} IU/ml → increase ≥1 log_{10} IU/ml

No amino acid substitutions in the HBV PreS1 BLV region or HDV HDAg associated with resistance to BLV, neither at BL nor at week 24.

Hollnberger et al. ***GHS*** 2023 (LB/O101)

Bulevirtide Treatment For Hepatitis D In Decompensated Liver Disease – Clinical Experience Based On Real-World Case Reports

Research article JHEP|Reports

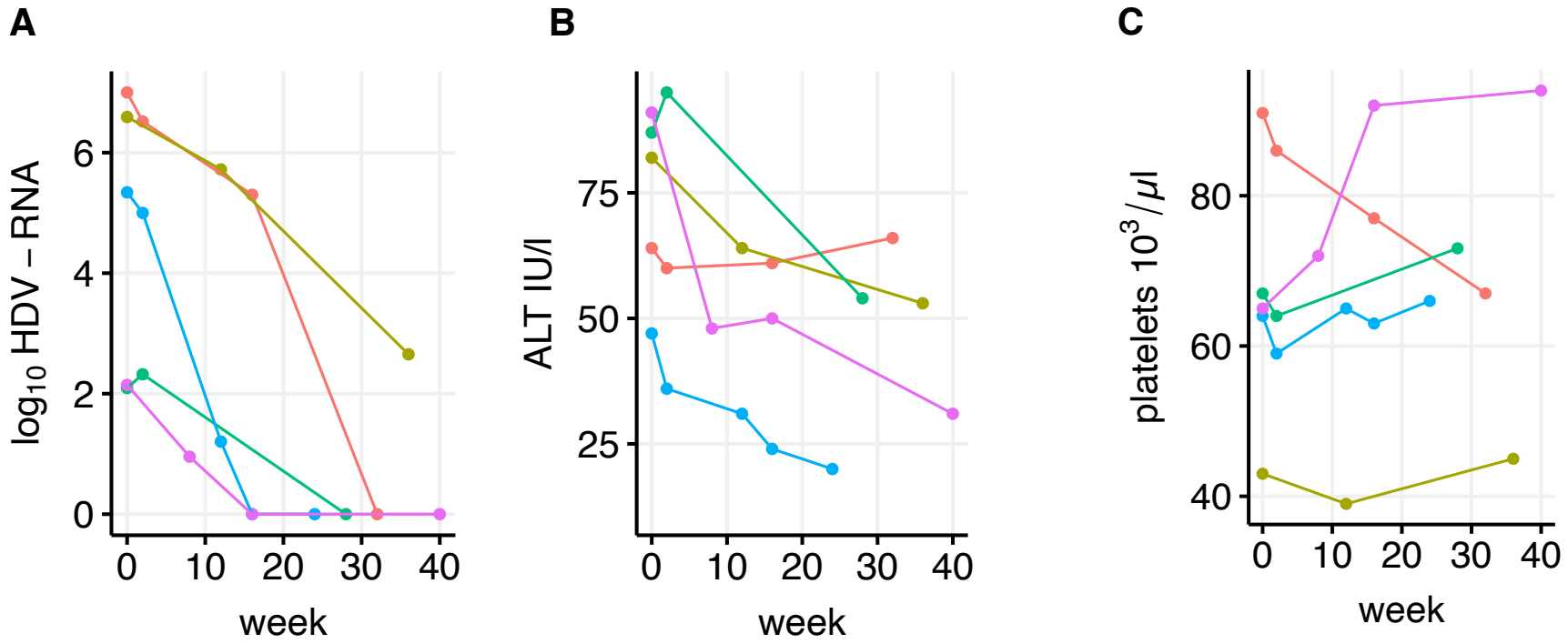
Treating hepatitis D with bulevirtide – Real-world experience from 114 patients

Dietz-Fricke et al. ***JHEP Rep***. 2023 Mar 15;5(4):100686.

Case	Child-Pugh	ALT (IU/l)	Platelets (10^3/µl)	Bilirubin (µmol/l)	INR	Albumin (g/l)
1	B	64	91	12	1,02	46
2	B	47	64	17	1,2	38
3	B	82	43	**43**	1,2	**31**
4	B	91	65	21	1,09	**29**
5	C	87	67	**72**	1,5	**23**

Dietz-Fricke et al. ***GHS*** 2023 (O89)

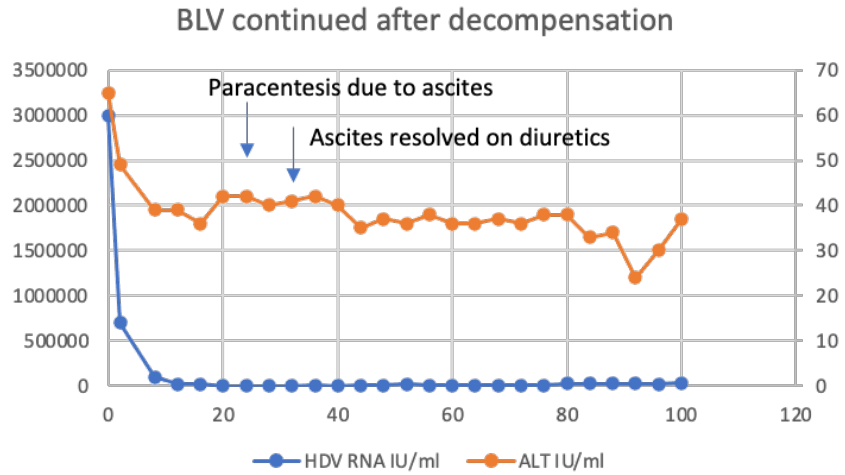
Bulevirtide Treatment For Hepatitis D In Decompensated Liver Disease – Clinical Experience Based On Real-World Case Reports



Dietz-Fricke et al. ***GHS*** 2023 (O89)

Bulevirtide Treatment For Hepatitis D In Decompensated Liver Disease – Clinical Experience Based On Real-World Case Reports

- Stopping an antiviral treatment might bear the risk of flares
- In order to avoid a second hit in dACLD treatment was continued in a case with decompensation due to ascites



Dietz-Fricke et al. ***GHS*** 2023 (O89)

Treatments for HDV infection

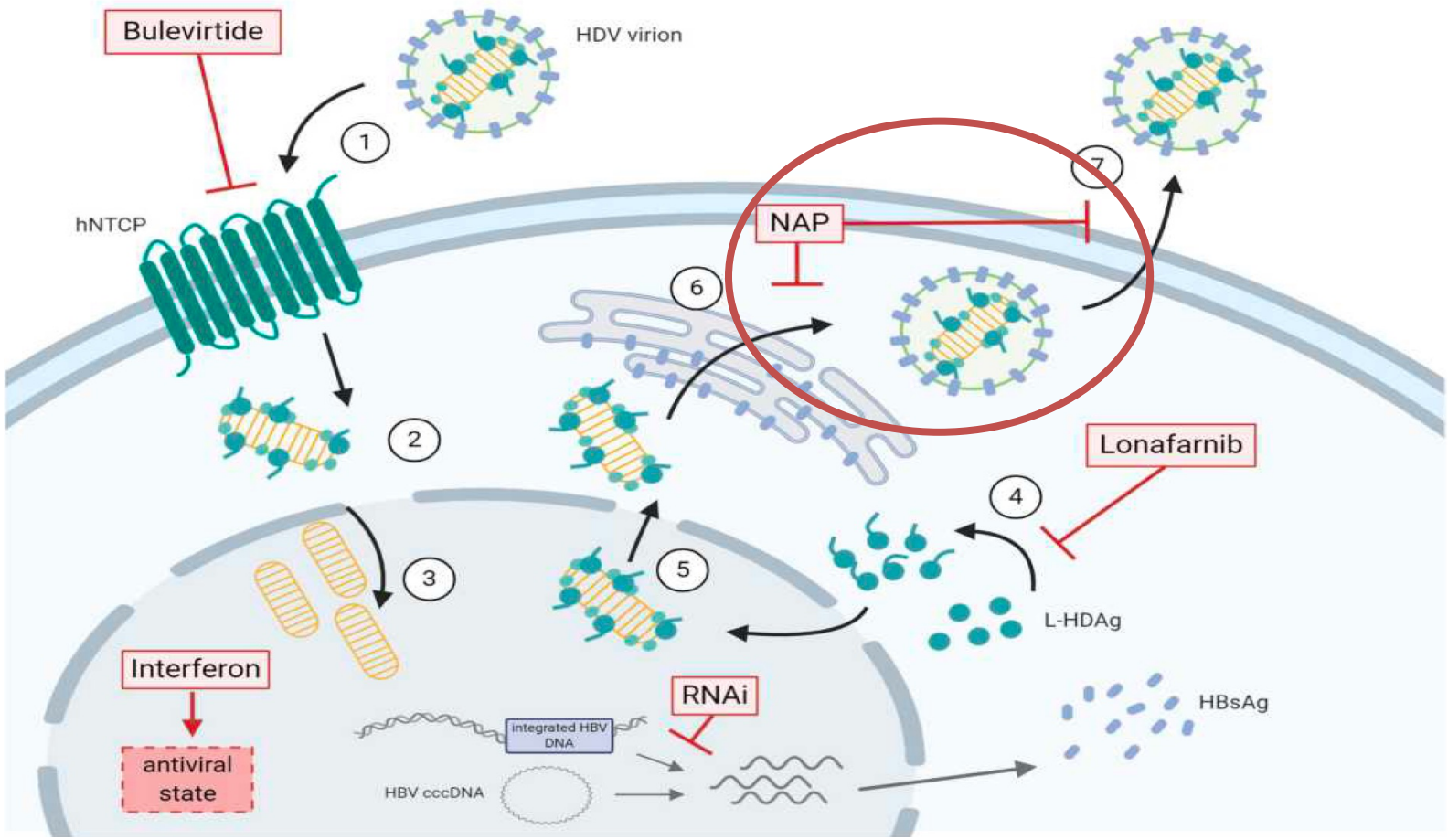


Figure: Sandmann & Cornberg. ***J Exp Pharmacol***. 2021 Apr 16;13:461-468.

Rescue of cirrhotic chronic HBV / HDV infection from Bulevirtide failure by subcutaneous Rep 2139-Mg

Replicor compassionate access program

Compassionate access to REP 2139-Mg (NCT05683548) in eligible patient populations worldwide

- HBV / HDV with previous failure to pegIFN, bulevirtide and lonafarnib
- HBV / HDV decompensated cirrhosis
- HBV with compensated or decompensated cirrhosis
- **TDF daily + Weekly 250mg REP 2139-Mg SC with 90µg pegIFN (only with compensated cirrhosis)**
- **Scheduled treatment duration of 48 weeks**

Current enrollment: 33 patients

- France (18 patients, 8 centers) – available data presented today
- Israel (1 patient, 1 center)
- Austria (3 patients, 1 center)
- Turkey (4 patients, 1 center)
- Italy (4 patients, 1 center)
- Germany (1 patient, 1 center)
- Australia (1 patient, 1 center)
- Canada (1 patient, 1 center)

Baseline characteristics (in patients with ≥ 4 weeks of therapy completed)

Parameter	Mean (range) where applicable
Number	**11**
Age	**44.7** (21-59)
Sex	**4 female, 7 male**
Ethnicity	**8 Caucasian** **1 African** **1 Asian** **1 Central Asian**
Liver status	**9 Compensated cirrhosis** (CP A5: 6, A6: 1, B7: 1, one unknown) **2 F3-F4 Fibrosis**
HBeAg status at baseline	**8 negative, 3 positive**
HDV genotype (Done centrally at Hôptial Avicenne)	**6 genotype 1** **1 genotype 5** 4 genotypes to be assessed
HDV RNA (IU/mL)	**3.59 x10^6** (295-1.68x10^7)
HBsAg (IU/mL)	**11759.58** (2200-33559)
HBV DNA (IU/mL)	**320.6** (TND-3440*)
ALT (U/L)	**93.4** (20-266)
Bilirubin (µmol/L)	**14.9** (8-34)

*TDF therapy started at baseline

Bourlière et al. ***GHS*** 2023 (O87)

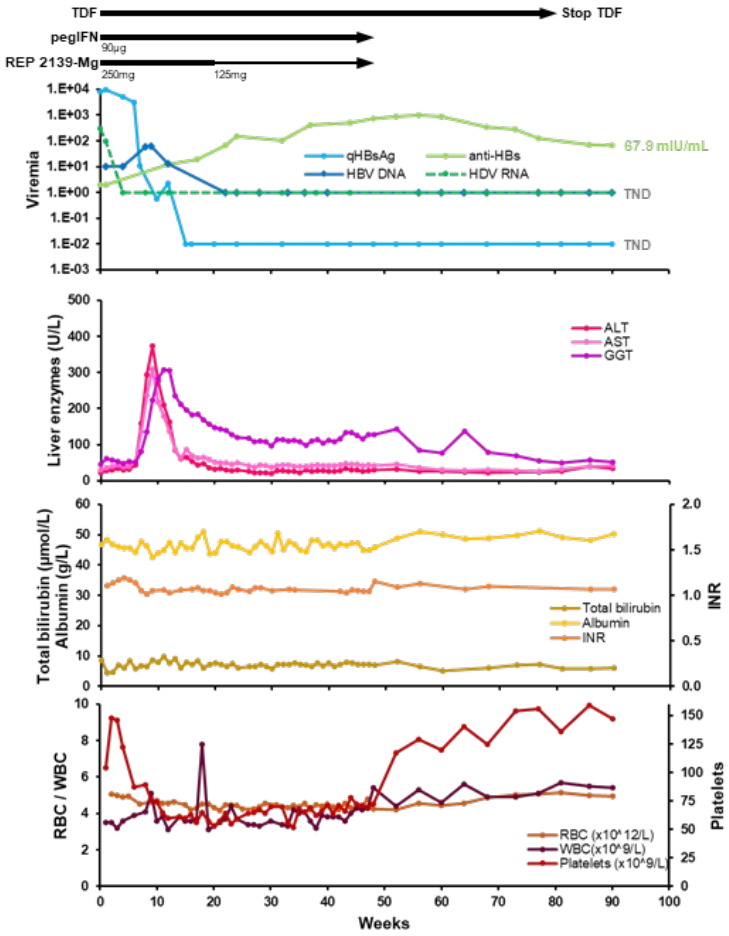
Rescue of cirrhotic chronic HBV / HDV infection from Bulevirtide failure by subcutaneous Rep 2139-Mg

Patient 1

Senegalese male, 51
HDV GT-5, cirrhosis
Previous failure on pegIFN + BLV

HBsAg, HDV RNA TND and HBsAg seroconversion maintained 10 months after withdrawal of REP 2139-Mg and pegIFN

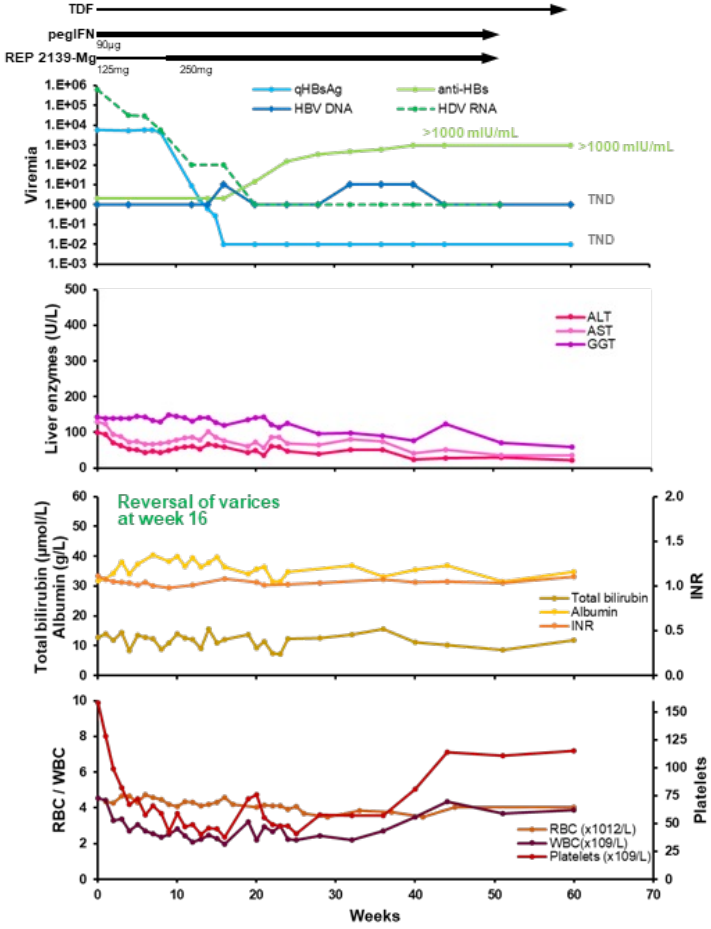
TDF now withdrawn for two months with HBV DNA TND



Patient 2

Caucasian male, 47
HDV GT-1, cirrhosis, stage 1 varices
Previous failure on pegIFN + BLV

HBsAg, HDV RNA TND and HBsAg seroconversion maintained 2 months after withdrawal of REP 2139-Mg and pegIFN



Bourlière et al. ***GHS*** 2023 (O87)

Safety and efficacy Of Rep 2139-Mg In association with TDF in patients with chronic hepatitis delta and decompensated cirrhosis

REP 2139-Mg in association with TDF is safe and well tolerated in patients with CHD and decompensated cirrhosis. Liver function improvement with significant ascites reversal was rapid, occurring after only 4 weeks of treatment.

HBV-HDV functional cure with HBsAg loss and HBs seroconversion appears achievable in this special population which could prevent the need for a future liver transplant.

de Frietas, Stern et al. ***GHS*** 2023 (O88)

GLOBAL HEPATITIS SUMMIT 2023

PARIS FRANCE

April 25 - 28, 2023

HBV / HDV debrief

Markus Cornberg

CiiM
CENTRE FOR INDIVIDUALISED INFECTION MEDICINE

GHE
Gastroenterologie
Hepatologie
Infektiologie
Endokrinologie