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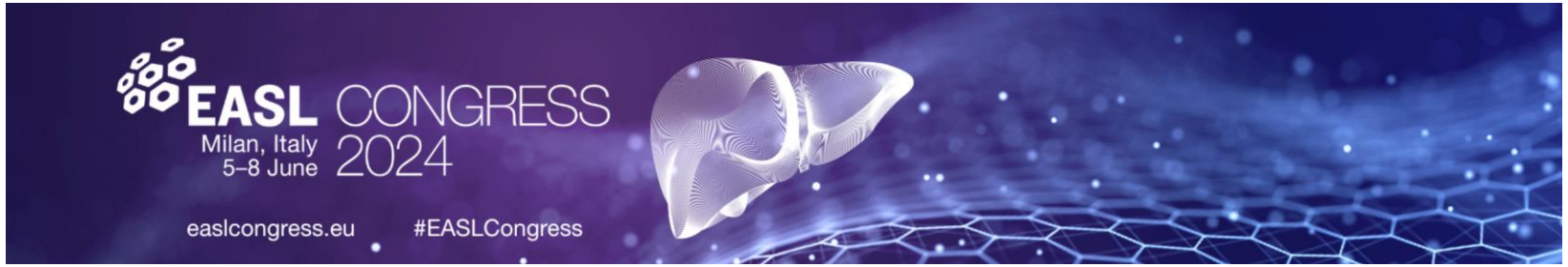
WHAT IS NEW IN INFECTIOUS DISEASES? DATA FROM 2024 CONGRESSES

EASL: novità in tema di HBV e HDV



EASL Congress 2024 in numbers

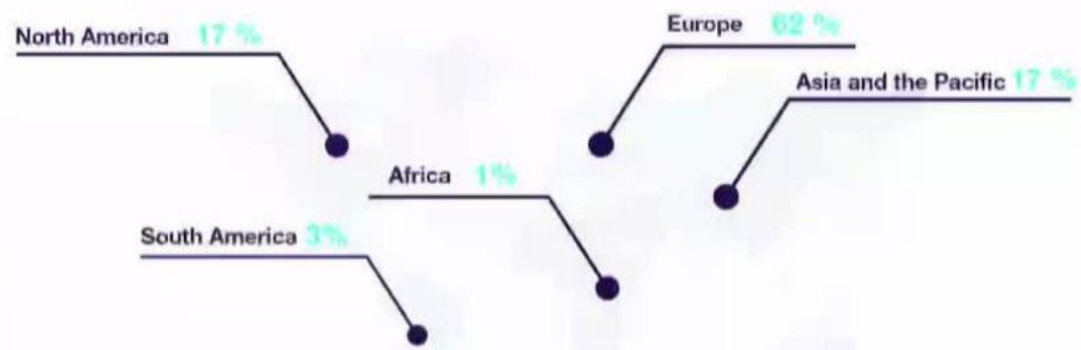
7,578 Delegates

117 Countries

6,922 in Milan
656 online

1,887 accepted abstracts

188 scientific sessions



Viral Hepatitis: The Yellow track

- 13 sessions on viral hepatitis
- 4 abstract sessions (1 HCV + 3 HBV/HDV) with 20 oral presentations
- 6 poster tours -> 42 posters

- HCV 84 abstracts
- HBV 146 abstracts
- HDV 48 abstracts

HBV

Functional cure

How to achieve functional cure

- Functional cure: why we need it
- How to achieve functional cure
  - Current treatments: NUC withdrawal
  - New treatments

How to achieve functional cure

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HBV: Goals and endpoint of therapy

Goals

- Improve survival and quality of life by preventing disease progression and HCC
- Prevent mother-to-child transmission, hepatitis B reactivation, and prevent and treat HBV-associated extrahepatic manifestations

Recommendations
Main endpoint • Induction of long-term suppression of HBV DNA
Valuable endpoint • Induction of HBeAg loss (± anti-HBe seroconversion) in HBeAg-positive patients with chronic hepatitis B*
Additional endpoint • ALT normalization (biochemical response)†
Optimal endpoint • HBsAg loss (± anti-HBs seroconversion)‡

*Often represents a partial immune control of the chronic HBV infection;
†Achieved in most patients with long-term suppression of HBV replication;
‡Indicates profound suppression of HBV replication and viral protein expression
EASL CPG HBV. J Hepatol 2017;67:370–88

Antiviral therapy decreases liver outcomes in HBV

- retrospective cohort study on all patients with CHB who had received entecavir and/or tenofovir disoproxil fumarate (TDF) for at least 6 months between 2005 and 2016 from Hospital Authority, Hong Kong.
- 11% cirrhosis; 17488 complete viral suppression (< 20 IU/mL) 376 HBsAg loss
- Viral suppression decreased all outcomes HBsAg further reduced incidence of HCC but not of liver related mortality

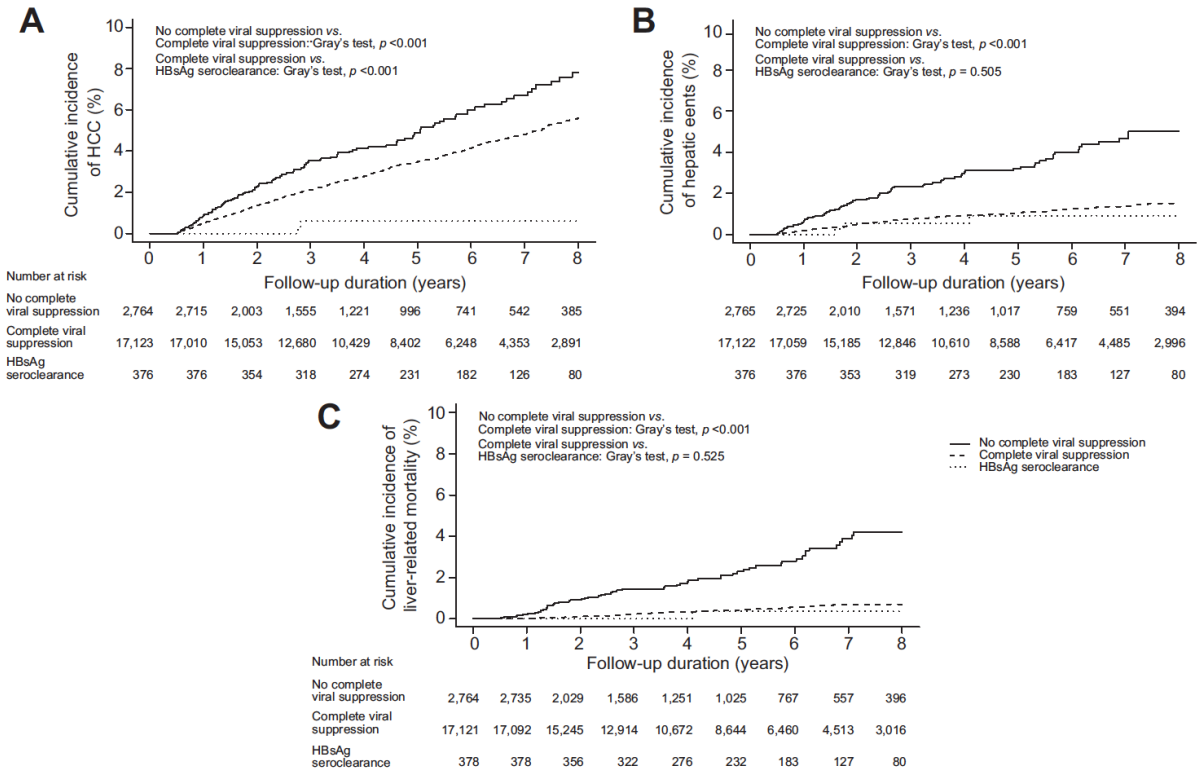
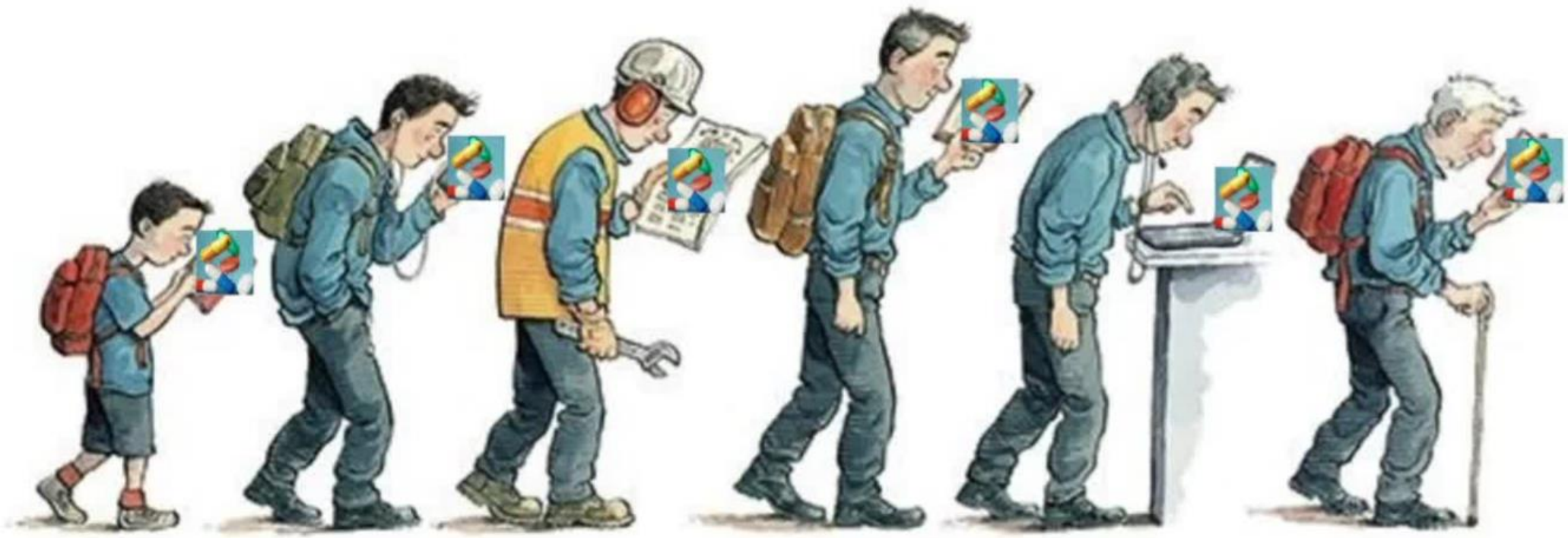


Table 3. Univariate and multivariable analysis with proportional subdistribution hazards regression model on factors associated with HCC.

	Univariate analysis		Multivariable analysis (n = 17,462)*	
Parameters	**HR (95% CI)**	***p* value**	**aHR (95% CI)**	***p* value**
Viral suppression				
Complete viral suppression	Referent		Referent	
Lack of complete viral suppression	1.47 (1.21–1.79)	<0.001	1.69 (1.36–2.09)	<0.001
HBsAg seroclearance	0.13 (0.03–0.53)	0.004	0.24 (0.06–0.97)	0.045
Age	1.06 (1.06–1.07)	<0.001	1.05 (1.04–1.06)	<0.001
Male gender	1.70 (1.43–2.03)	<0.001	1.90 (1.57–2.31)	0.004
Cirrhosis	4.50 (3.87–5.22)	<0.001	2.15 (1.79–2.59)	<0.001
Diabetes mellitus	1.89 (1.63–2.19)	<0.001		
Platelet (log-transformed)	0.36 (0.30–0.43)	<0.001	0.54 (0.46–0.65)	<0.001
Albumin	0.93 (0.92–0.94)	<0.001		
Total bilirubin (log-transformed)	1.19 (1.09–1.29)	<0.001	0.80 (0.68–0.94)	0.006
Alanine aminotransferase (log-transformed)	0.84 (0.80–0.89)	<0.001	0.86 (0.79–0.94)	<0.001
Alpha-fetoprotein (log-transformed)	1.45 (1.39–1.51)	<0.001	1.41 (1.33–1.49)	<0.001
Positive HBeAg	0.67 (0.56–0.79)	<0.001		
Other NAs prior baseline#	0.84 (0.68–1.03)	0.090		

Yip T –C et al J Hepatol 2018; 70: 361-70

Is my NUC treatment lifelong?



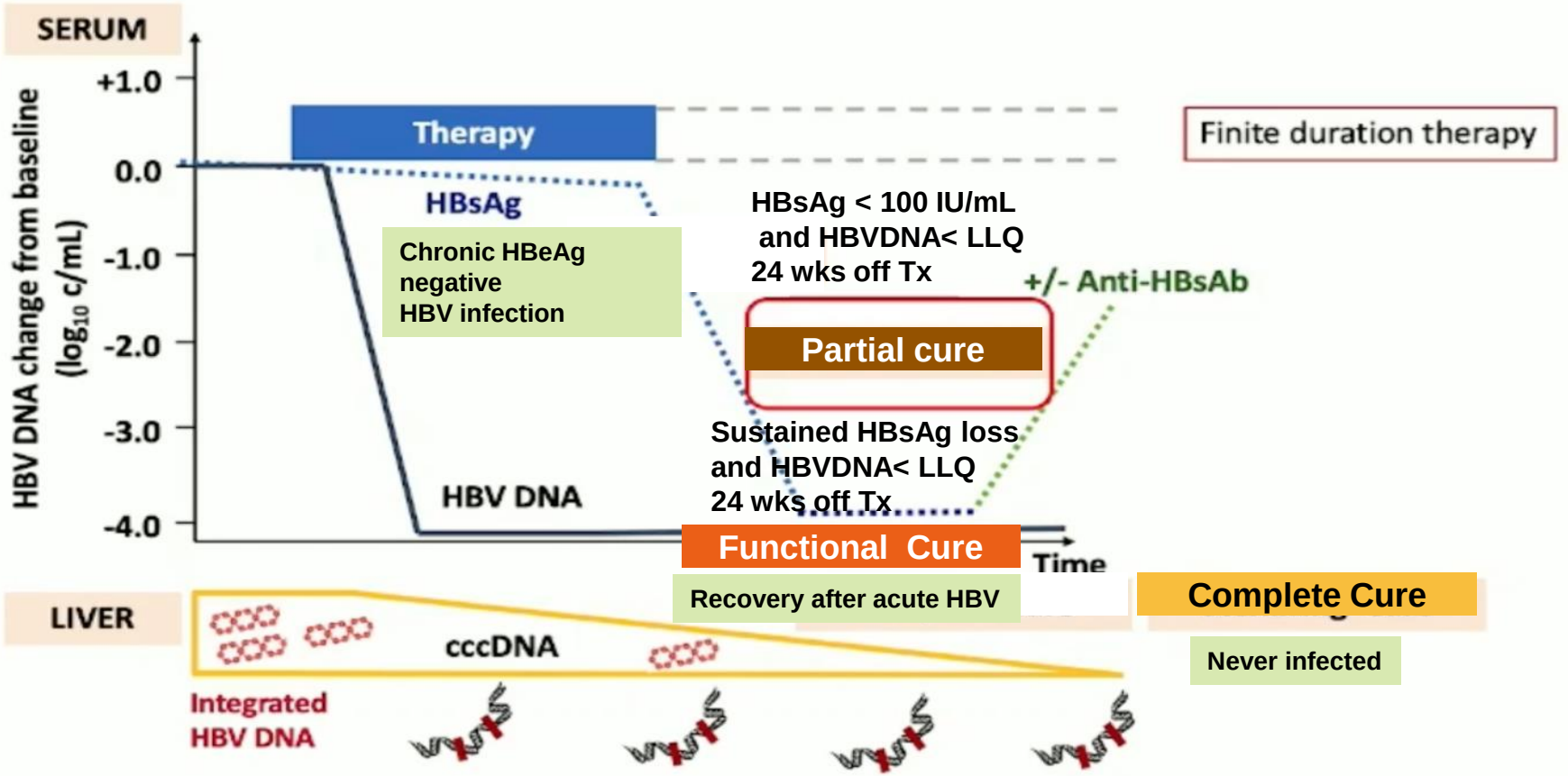
…NOW

Functional HBV cure

durable hepatitis B surface antigen (HBsAg) loss (based on assays with lower limit of detection [LLOD] 0.05 IU/ml) with or without HBsAg seroconversion and undetectable serum HBV DNA after completing a course of treatment

EASL. Journal of Hepatology 2020

Major goals of current strategies towards « HBV cure »



Finite duration therapy

- Favorable clinical outcome after treatment withdrawal
- Further reduction in HCC risk

Functional Cure

- Sustained loss of serum HBV DNA and HBsAg (+/- anti-HBs)
- Finite course of treatment

- Indication of marked suppression of HBV replication and cccDNA transcription, but HBV still present in the liver!

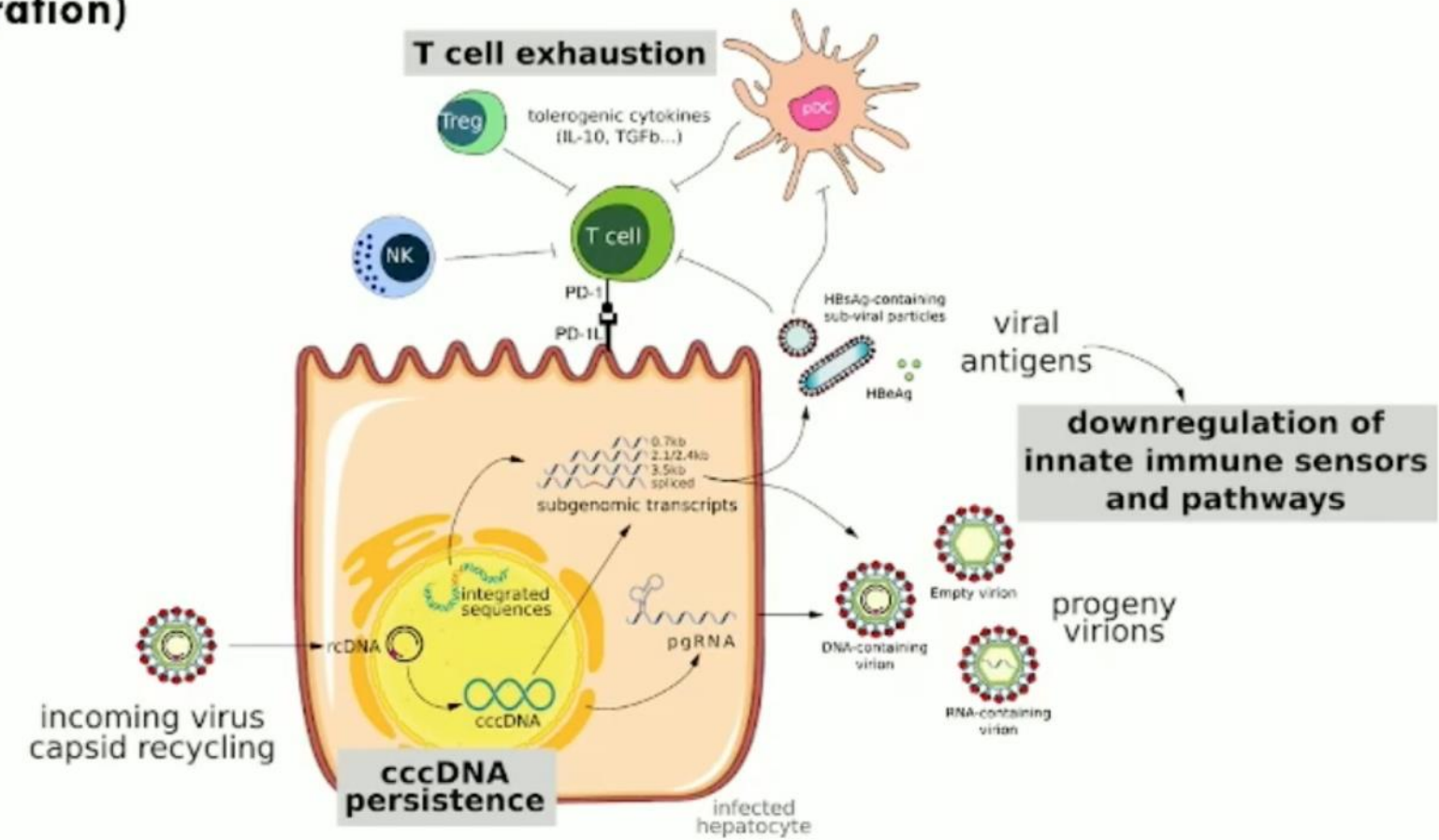
Testoni, 2017; Fanning, 2019; Cornberg, 2020; Martinez, 2021 ...

Obstacles to HBV functional cure

Intrahepatic viral reservoir: long-lived cccDNA (+integration)

High viral antigen load

Defective innate and adaptive immune responses



Adapted from Testoni, 2017

How to achieve functional cure

- Functional cure: why we need it
- How to achieve functional cure
  - Current treatments: NUC withdrawal
  - New treatments

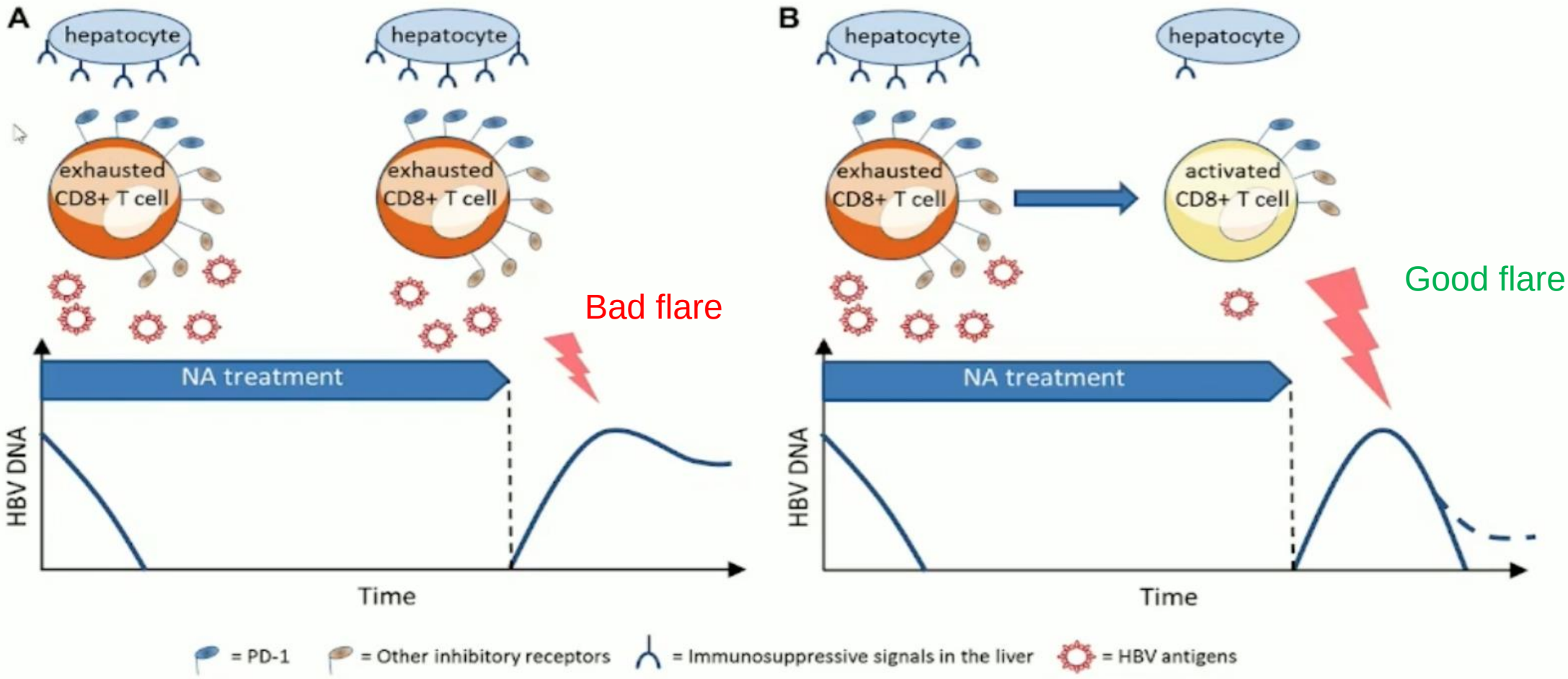
Summary of studies reporting HBsAg loss in patients with chronic hepatitis B who had stopped nucleos(t)ide analogues

Table 2. Summary of studies reporting HBsAg loss in patients with chronic hepatitis B who had stopped nucleos(t)ide analogues (modified from Kao *et al.*).[35]

Author/study design	N	NUC	Cirrhosis (%)	Tx (years)	Consolidation Tx (months)	FU (months)	HBsAg loss
HBeAg-positive							
Liem/RCT	18	ETV/TDF	0	7.9	41	18	0% (*vs.* 0% in control)
Cao/Pros	60	Mixed	0	4	25	24	10%[#]
Liu/Pros	138	Mixed	0	2.4	21	120	0%
Su/Pros	28	ETV/TDF	0	3.1	26	48	0%
Chi/Pros	71	Mixed	0	3.9	26	31	4%
He/Retro	97	Mixed	n.a.	2.8	48	12	0%
Chen/Retro	148	LAM/ETV	0	2.7	-	96	19.6%
Kuo/Retro-Pros	154	ETV/TDF	0	3.1	>12	24	4.7% (ETV) 0% (TDF)
Song/Retro	262	Mixed	20.6	2.9	17.5	73.3	9.5% (median FU 6.1 yr)
HBeAg-negative							
Hadziyannis/Pros	33	ADV	0	4–5	45	69	39.4%
Berg /RCT	21	TDF	0	>4	>42	36	19% (*vs.* 0% in control)
Liem/RCT	27	ETV/TDF	0	7.4	85	18	4% (*vs.* 5% in control)
Van Bommel/RCT	79	Mixed	0	>4	n.a.	24	10.3% at 96 weeks (*vs.* 0% in control)
Cao/Pros	22	Mixed	0	4	35	48	10%[#]
Papatheodoridis/Pros	57	ETV/TDF	0	>4	64	18	25%
Liu/Pros	85	Mixed	0	2.4	21	120	14%
Su/Pros	72	ETV/TDF	0	3.1	26	48	0%
Chi/Pros	29	Mixed	0	3.9	106	31	10%
Jeng/Retro-Pros	691	ETV/TDF	45	2.9	25	36	13% by 6 years
Chen/Retro	263	LAM/ETV	0	2.9	–	96	33.1%
Kuo/Retro-Pros	353	ETV/TDF	0	3.1	>12	36	10% (ETV) 15.4% (TDF)
Chen/Retro-Pros	250	ETV	0	3.2	>12	58	20.8%
Song/Retro	226	Mixed	36.4	2.7	25	73.3	14.6% (median FU 6.1 yr)
Hirode/Retro	1,183	Mixed	5	3	–	17	15% by 4 years

Wong G et al J hepatol 2022; 76: 1248-62

THE CONCEPT OF NUC TREATMENT DISCONTINUATION



T cell activity measurement: “HBVferon ?????”

Modified from van Bömmel F, Bergt T. Hepatol Comm 2021

Serious adverse events after cessation of nucleos(t)ide analogues in individuals with chronic hepatitis B: A systematic review and meta-analysis

Total 50 studies

- Mentioning safety outcomes
- 1/3 without clear definitions
- 1/4 sample size <100
- Great heterogeneity in:
  - Retreatment criteria
  - Definitions of decompensation
  - Patient characteristics

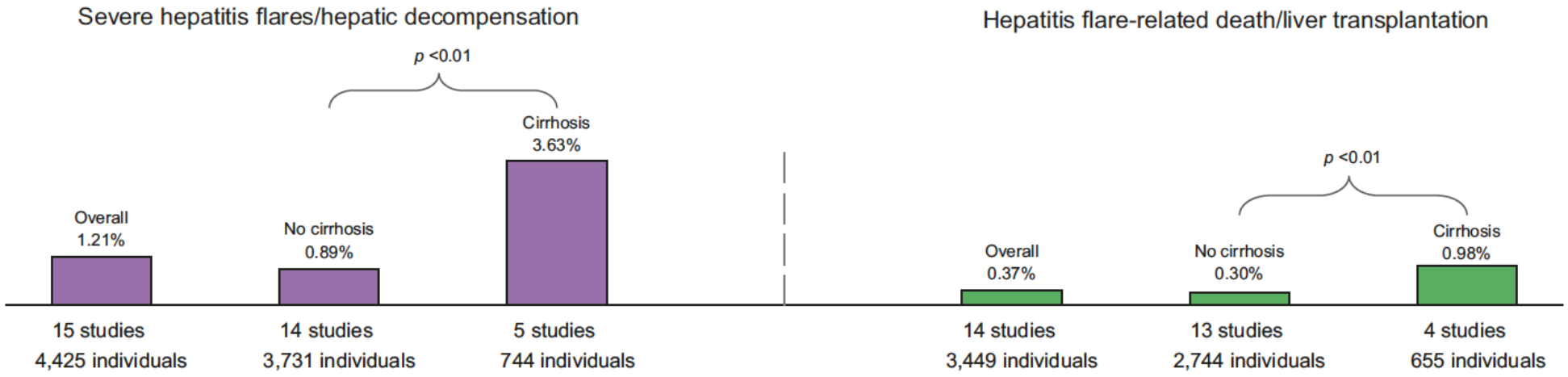
10 studies

- Prespecified safety events as the study outcome

4 studies

- Prespecified safety events including decompensation
- Follow-up >12 months
- Sample size >100

Pooled proportions of serious adverse events



Tseng CH et al JHEP Reports 2023. https://doi.org/10.1016/j.jhepr.2022.100617

Hepatic flares after nucleos(t)ide analogue cessation in HBeAg-negative hepatitis B: results from the Nuc-Stop study

- 127 HBeAg-negative patients, virally suppressed for at least 24 months on NA treatment, were included from 11 centers in Norway, Sweden, Denmark and Ethiopia.
- All patients stopped NA treatment and were followed up for 36 months.
- Flares were defined as ALT increase above 2x upper limit of normal (ULN) or above 2x baseline and divided into three groups:
  - Mild (ALT 2 - 5x ULN or 2 – 5x baseline),
  - Moderate (ALT 5 - 20x ULN or 5 – 20x baseline)
  - Severe (ALT > 20x ULN or > 20x baseline).
- Kruskal Wallis tests were used to compare groups. Logistic regression was used to identify predictors of flares.

Figure 1. Distribution of flares

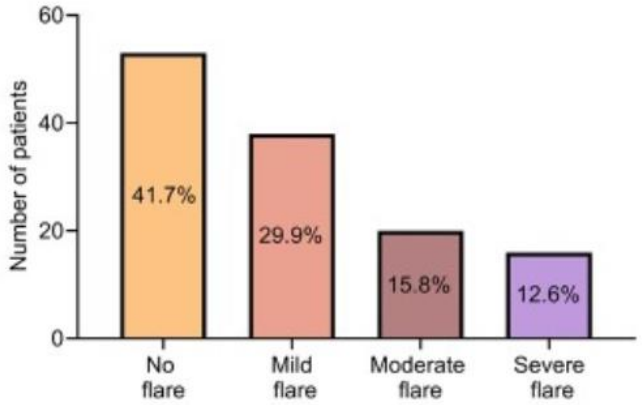
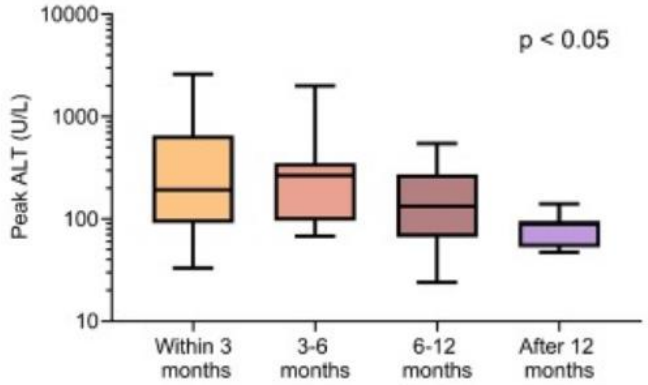


Figure 2. Severity and timing of flares



Flares moderate –severe in 27,6%
More severe flares occurr during the 1° year
Earlier after TDF withdrawal
Predictors: Older age and Higher HBsAg

Figure 3. Time to flare by tenofovir/entecavir

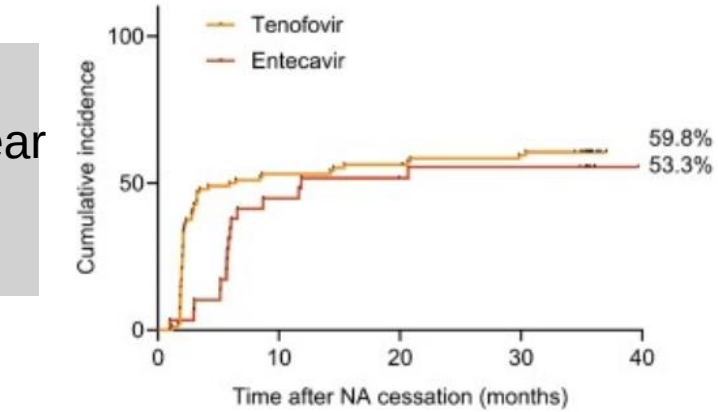


Table 3. Predictors of hepatic flares

	Unadjusted			Adjusted		
Variable	OR	95% CI	p-value	OR	95%CI	p-value
Age (years)	1.05	1.01-1.09	0.02	1.07	1.02-1.12	0.01
Sex (male vs. female)	0.98	0.46-2.09	0.97			
Ethnicity (Asian vs. Non-Asian)	1.40	0.68-2.88	0.36			
Genotype (B/C vs. other)	2.36	0.98-5.68	0.05	2.29	0.87-6.02	0.09
BMI (kg/m²)	0.97	0.89-1.06	0.47			
Tenofovir vs. entecavir	0.77	0.34-1.75	0.53			
Treatment duration (months)	1.00	0.99-1.01	0.70			
qHBsAg (IU/mL)	1.61	1.07-2.42	0.02	2.09	1.20-3.62	0.01

Holmberg M et al EASL-ILC June 5°-8th° 2024 poster iD WED 384

Association between post-treatment ALT elevation and subsequent hepatitis B surface antigen seroclearance in chronic hepatitis B patients stopping nucleos(t)ide analogue therapy

- A total of 850 patients (74.5% male, with a median age of 53.2 years) were enrolled and summarized in Table 1.
- During median 3.7-year follow-up, 47 patients cleared HBsAg with a 10-year cumulative incidence of 13.2% (Figure 1).

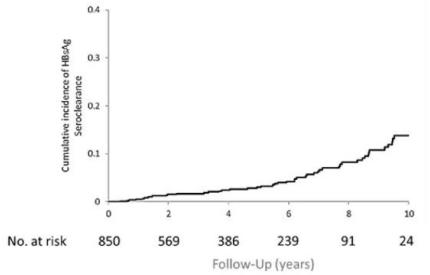


Figure 1. Cumulative incidence of HBsAg loss

Table 1. Characteristics of the study cohort

Characteristics	All (N = 850)
Female sex, n (%)	217 (25.5)
Age, years	53.2 (44.2, 61.7)
Diabetes mellitus, n (%)	179 (21.0)
AST, U/L	28 (23, 38)
ALT, U/L	26 (19, 38)
Bilirubin, mg/dL	1.05 (0.74, 1.46)
Creatinine, mg/dL	1.1 (0.9, 1.2)
Prothrombin time, second	10.7 (10.3, 11.4)
Thrombocytopenia†, n (%)	42 (4.9)
Entecavir user, n (%)	541 (63.7)
Tenofovir user, n (%)	309 (36.3)
Duration on therapy, months	34.7 (30.9, 38.4)
Pretreatment cirrhosis#, n (%)	149 (17.5)
Pretreatment positive HBeAg, n (%)	133 (17.2)
Pretreatment HBV DNA, log IU/ml	5.3 (3.6, 6.8)
Pretreatment AST, U/L	76.5 (49.0, 148.0)
Pretreatment ALT, U/L	107.0 (54.0, 226.0)

Table 3. Subgroup analysis with end-of-treatment HBsAg levels

Variables		Adjusted SHR	95% CI	P value
Time-varying ALT flare*		0.83	0.25--2.70	0.75
HBsAg levels at end of treatment	>100 IU/ml	1.00	-	-
	10 IU/ml – 100 IU/ml	4.85	1.44--16.35	0.011
	< 10 IU/ml	32.06	11.83--86.92	<0.001

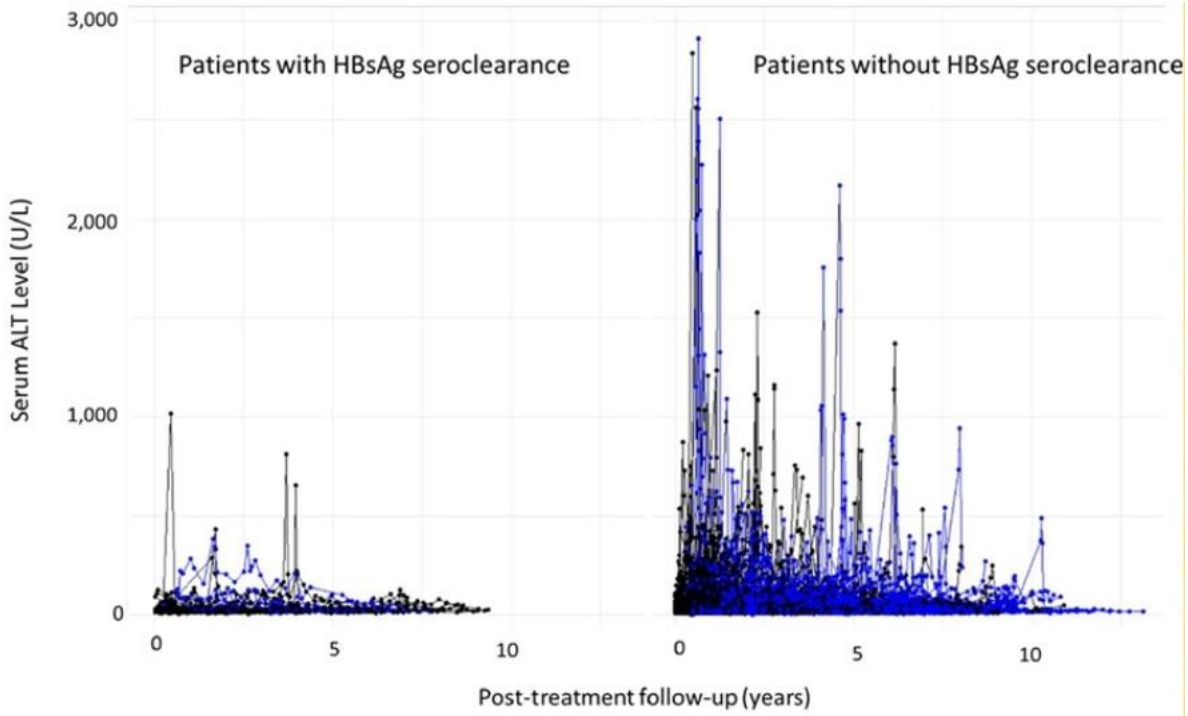


Figure 2. Peak serum ALT levels in patients with and without HBsAg loss (patients who resumed NUCs were indicated in blue).

Good minor flares in pts with HBsAg seroclearance (13,2%) predicted by lower HBsAg at NUC withdraw

DARING-B study: 5-year outcomes after nucleos(t)ide analogue (NA) cessation in Caucasian non-cirrhotic patients with HBeAg-negative chronic hepatitis B (CHBe-)

DARING-B study prospectively enrolled 57 patients (M/F: 37/20, mean age: 58±10 years) from 2 tertiary liver centers in Greece from 12/2015 to 03/2016. Inclusion and exclusion criteria are presented below. Patient and treatment characteristics before and at discontinuation of NAs were recorded.

INCLUSION CRITERIA

- CHBe- diagnosis before NA treatment
- Absence of cirrhosis at NA treatment (Ishaak score ≤4 or liver stiffness ≤10 kPa)
- NA treatment duration ≥4 years
- Duration of undetectable HBV DNA ≥ 3years
- Written informed consent

EXCLUSION CRITERIA

- Coinfection with hepatitis C, D or Human-immunodeficiency virus
- History of cirrhosis
- Liver cancer
- Liver transplantation

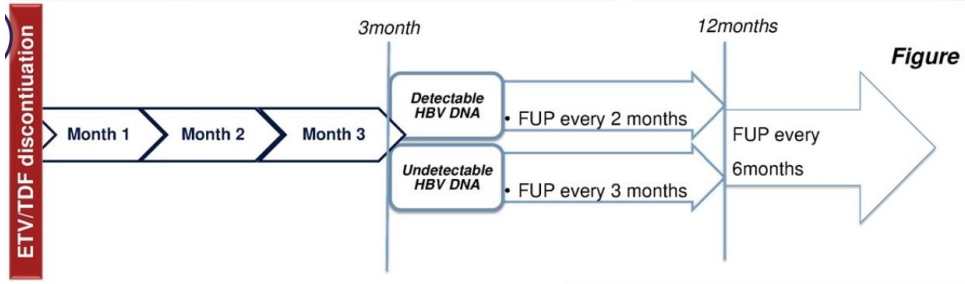


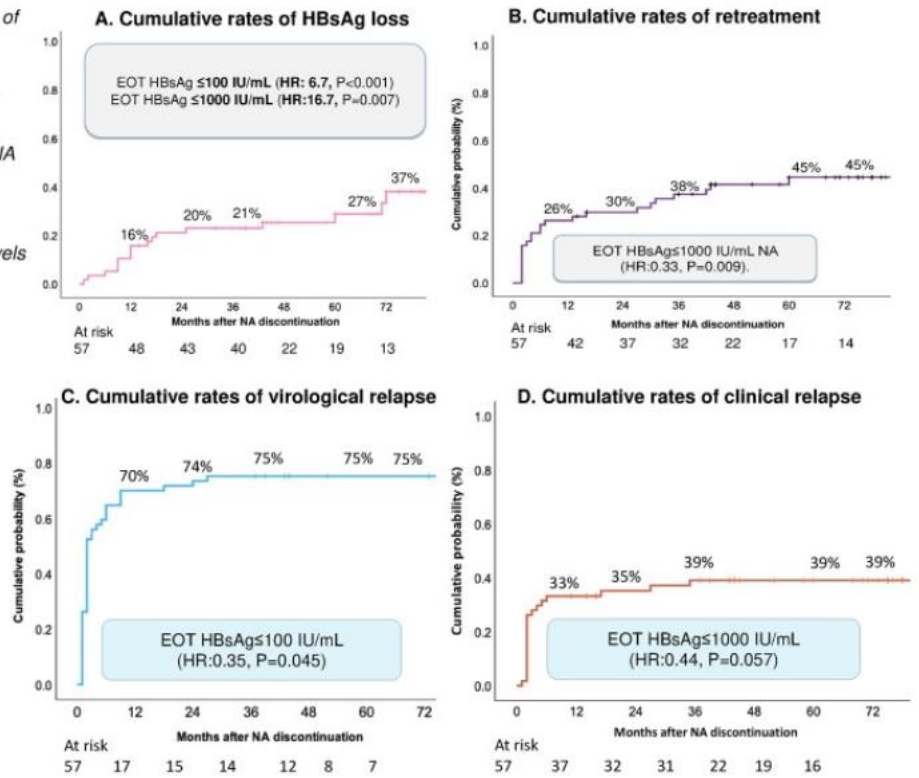
Figure 1. *Patients' follow-up (FUP) protocol*

Main study outcomes were liver transplantation, liver decompensation, hepatocellular carcinoma, HBsAg loss and retreatment and relapse according to various definitions.

STUDY OUTCOMES

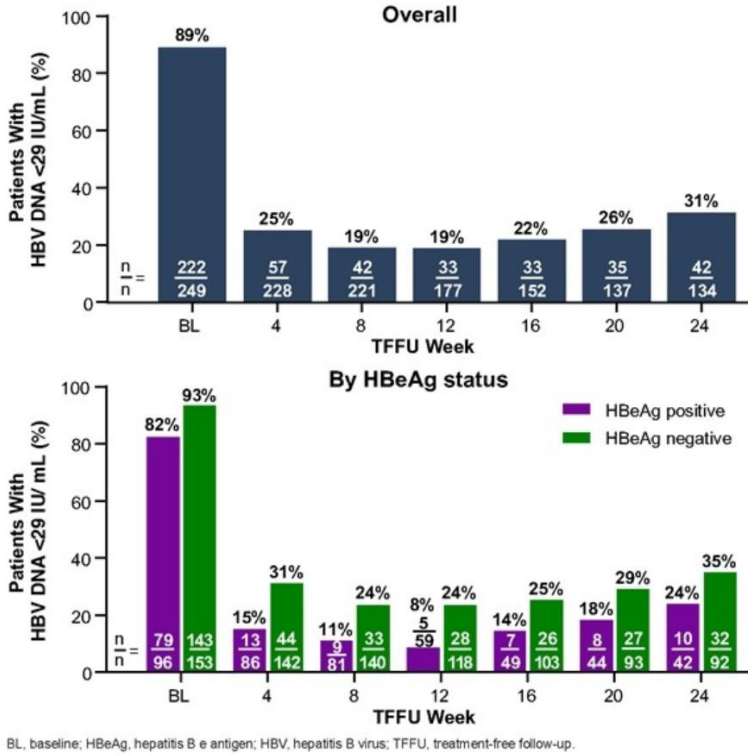
- **Virological relapse** (HBV DNA>2,000 IU/mL)
- **Clinical relapse** (HBV DNA>2,000 IU/mL & ALT>2xULN)

Figure 2. *Cumulative rates of A. HBsAg loss, B. retreatment, C. virological relapse (HBV DNA>2,000) D. clinical relapse (HBV DNA >2,000 and ALT >2xULN) in study patients and their association with end of treatment (EOT) HBsAg levels*



Off-treatment outcomes after discontinuing tenofovir-based treatment in hepatitis B e antigen-positive and hepatitis B e antigen-negative patients with chronic hepatitis B virus

Percentages of Patients With HBV DNA <29 IU/mL During the TFFU Period

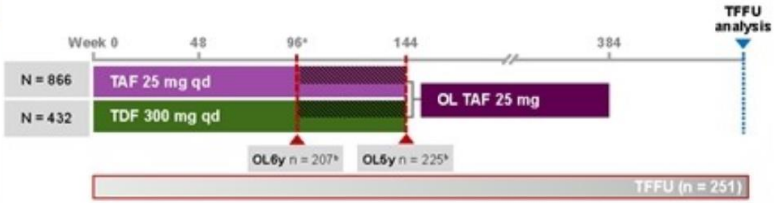


BL, baseline; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TFFU, treatment-free follow-up.

Study Design

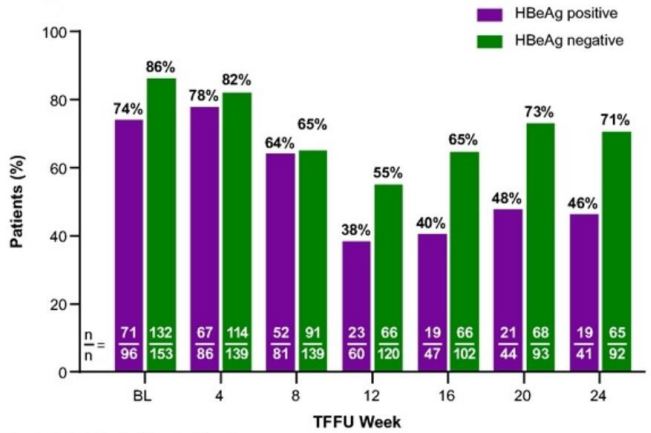
Key inclusion criteria

- HBV DNA ≥20,000 IU/mL
- ALT >60 U/L (males) and >38 U/L (females)
- With/without compensated cirrhosis
- $eGFR_{CG}$ ≥50 mL/min
- Treatment-naïve or treatment-experienced



[a]Amendment 3 enacted to extend DB to week 144 and OL to week 384 (year 8). Shaded areas represent patients who rolled over to OL TAF at week 96 (OL6y) or week 144 (OL5y) based on the timing of the amendment. [b]Patients who received DB TDF and switched to TAF.
ALT, alanine aminotransferase; DB, double blind; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBV, hepatitis B virus; OL, open label; qd, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFFU, treatment-free follow-up; y, year.

Proportion With Normal ALT Over 24 Weeks[a]



[a]Normal ALT as determined by central laboratory.
ALT, alanine aminotransferase; BL, baseline; HBeAg, hepatitis B e antigen; TFFU, treatment-free follow-up.

12 24
TFFU Week

	Patients, n/n (%)	HBeAg Positive (n = 96)	HBeAg Negative (n = 143)
HBeAg loss and seroconversion[a]	Week 12	2/59 (3)	NA
	Week 24	8/41 (20)	NA
HBsAg loss	Week 12	0/63	1/111 (1)
	Week 24	0/43	2/85 (2)[b]

Hepatitis B surface antigen (HBsAg) seroclearance following discontinuation of nucleos(t)ide analogues (NA) treatment has comparable durability to HBsAg seroclearance achieved during NA therapy

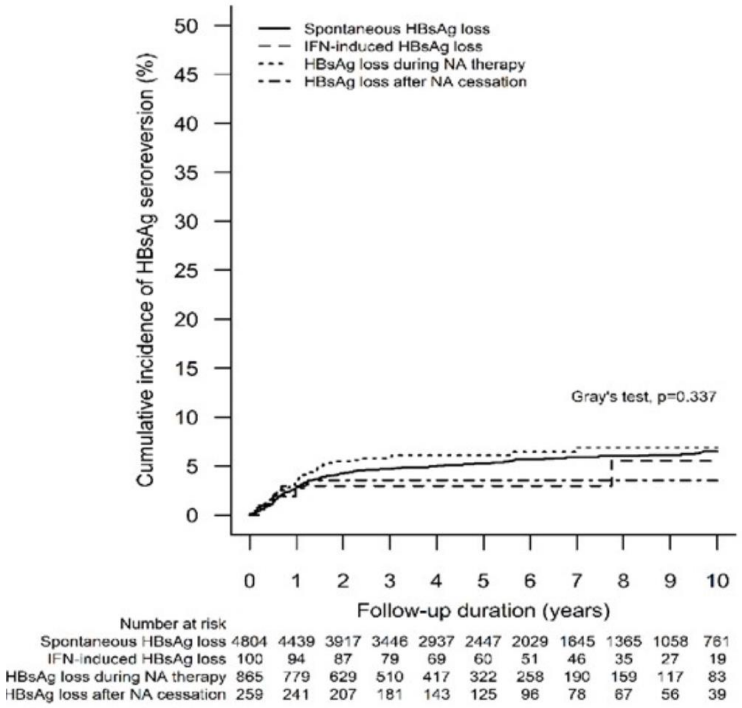


Fig. 2. Cumulative incidence of HBsAg seroreversion in patients who achieved HBsAg loss spontaneously, after IFN therapy, during NA therapy, or after NA cessation.

The 10-year overall cumulative risk (95% CI) of HBsAg seroreversion was 9.6% (7.8%-11.6%)

Factors associated with HBsAg seroreversion (N=6,028)				
Parameters	Univariate analysis		Multivariable analysis	
	CSHR (95% CI)	P	aCSHR (95% CI)	p
HBsAg loss type				
- During NA therapy	Reference		Reference	
- After NA cessation	0.56 (0.27 - 1.13)	0.11	**0.58 (0.29 - 1.19)**	**0.14**
- IFN-induced	0.60 (0.22 - 1.68)	0.33	**0.65 (0.23 - 1.81)**	**0.41**
- Spontaneous	0.86 (0.64 - 1.16)	0.33	**0.81 (0.59 - 1.10)**	**0.18**
Positive anti-HBs during follow-up*	0.45 (0.31 - 0.65)	<0.001	**0.44 (0.30 - 0.64)**	**<0.001**
Immunosuppressants during follow-up*	2.57 (1.78 - 3.70)	<0.001	**1.79 (1.17 - 2.74)**	**0.007**
Cancer during follow-up*	4.07 (2.73 - 6.06)	<0.001	**3.03 (1.89 - 4.84)**	**<0.001**
Age (years)	1.00 (0.99 - 1.01)	0.75	1.00 (0.99 - 1.00)	0.33
Male gender	0.81 (0.65 - 1.01)	0.059	**0.76 (0.61 - 0.95)**	**0.018**
Liver cirrhosis	1.28 (0.74 - 2.18)	0.37	1.20 (0.69 - 2.08)	0.53

Hepatitis B surface antigen (HBsAg) seroclearance following discontinuation of nucleos(t)ide analogues (NA) treatment has comparable durability to HBsAg seroclearance achieved during NA therapy

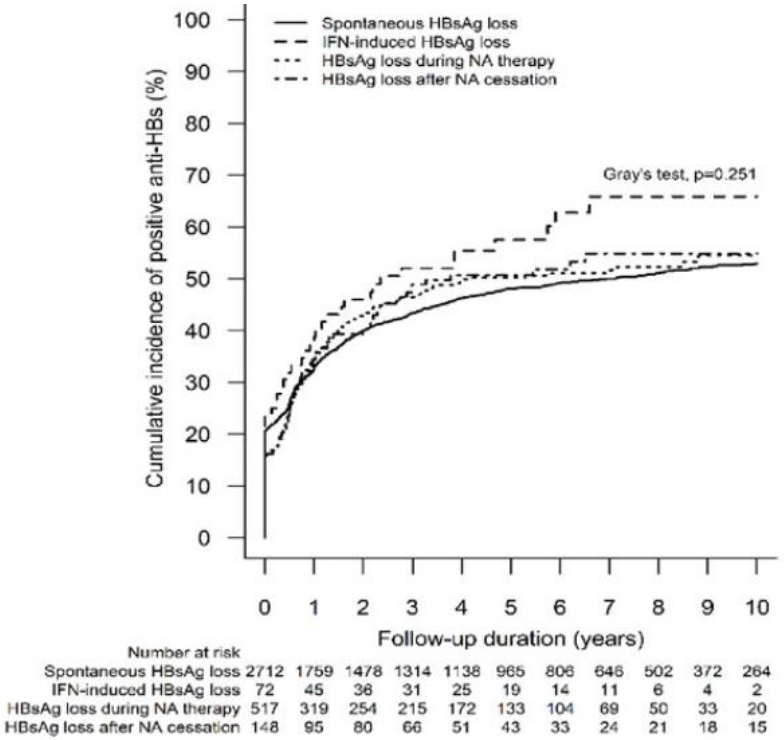


Fig. 3. Cumulative incidence of positive anti-HBs in patients who achieved HBsAg loss spontaneously, after IFN therapy, during NA therapy, or after NA cessation.

Among 3,449 patients with antibody to HBsAg (anti-HBs) measurement, the 10-year cumulative incidence (95% CI) of positive anti-HBs was 53.6% (51.7%-55.5%) (Fig. 3)

Factors associated with positive anti-HBs development (N=3,449)				
Parameters	Univariate analysis		Multivariable analysis	
	CSHR (95% CI)	P	aCSHR (95% CI)	p
HBsAg loss type				
- **During NA therapy**	Reference		Reference	
- **After NA cessation**	1.02 (0.79 - 1.32)	0.87	**1.00 (0.77 - 1.29)**	**0.99**
- **IFN-induced**	1.27 (0.92 - 1.75)	0.15	**1.19 (0.86 - 1.65)**	**0.28**
- **Spontaneous**	0.97 (0.85 - 1.12)	0.71	**0.98 (0.86 - 1.13)**	**0.83**
Immunosuppressants during follow-up*	0.97 (0.74 - 1.26)	0.80	1.05 (0.79 - 1.39)	0.73
Cancer during follow-up*	0.77 (0.49 - 1.19)	0.24	0.83 (0.52 - 1.33)	0.45
Age (years)	0.99 (0.98 - 0.99)	<0.001	**0.99 (0.99 - 0.99)**	**<0.001**
Male gender	0.87 (0.79 - 0.96)	0.006	**0.88 (0.80 - 0.97)**	**0.013**
Liver cirrhosis	1.02 (0.80 - 1.30)	0.88	1.10 (0.86 - 1.41)	0.44

** Modelled as time-dependent covariate; aCSHR = adjusted cause-specific hazard ratio*

Tabella 1

EASL 2024: studi sulla sospensione dei NUC in persone HBsAg positive

Autore	Setting	N pazienti	Durata follow-up	% Clearance HBsAg	% Flare moderati-gravi	Note
Holmberg[5]	Pazienti HBeAg- virosoppressi da almeno 24 mesi in Scandinavia e Eritrea	127	36 mesi	NR	27,6%	Flare più gravi si sono verificati durante il 1° anno Subito dopo la sospensione di TDF Predittori di flare: età più avanzata e livelli più elevati di HBsAg
Hsu[6]	Pazienti HBsAg+ (17% HBeAg+ al basale) trattati per 36 mesi in Asia	850	10 anni	13,2% a 10 anni	NR	La clearance di HBsAg è predetta da "flare minori" e livelli inferiori di HBsAg alla sospensione del NUC
Papatheodoridis[8]	Pazienti HBeAg- trattati per > 4 anni virosoppressi da > 3 anni in Grecia	57	72 mesi	37% a 72 mesi	39%	La clearance di HBsAg è predetta da livelli inferiori di HBsAg alla sospensione del NUC
Buti[4]	Pazienti HBsAg+ dello studio registrativo TDF vs TAF che interrompono il trattamento per qualsiasi motivo, 40% HBeAg +	240	24 settimane	1,6%	29% in HBeAg- 54% In HBeAg+	

NR, Non Riportato

Discontinuation of NA treatment

- Long-term therapy with NAs is usually required
  - HBV eradication is not usually achieved

Recommendations	Grade of evidence	Grade of recommendation
NAs <u>should</u> be discontinued • After confirmed HBsAg loss (± anti-HBs seroconversion)	II-2	1
NAs <u>can</u> be discontinued • In HBeAg-positive patients, without cirrhosis, who achieve stable HBeAg seroconversion and undetectable HBV DNA and complete ≥12 months of consolidation therapy **Close post-NA monitoring is warranted**	II-2	2
NAs <u>may</u> be discontinued • In selected HBeAg-negative patients, without cirrhosis, who achieve long-term (≥3 years) virological suppression, **if close post-NA monitoring can be guaranteed**	II-2	2

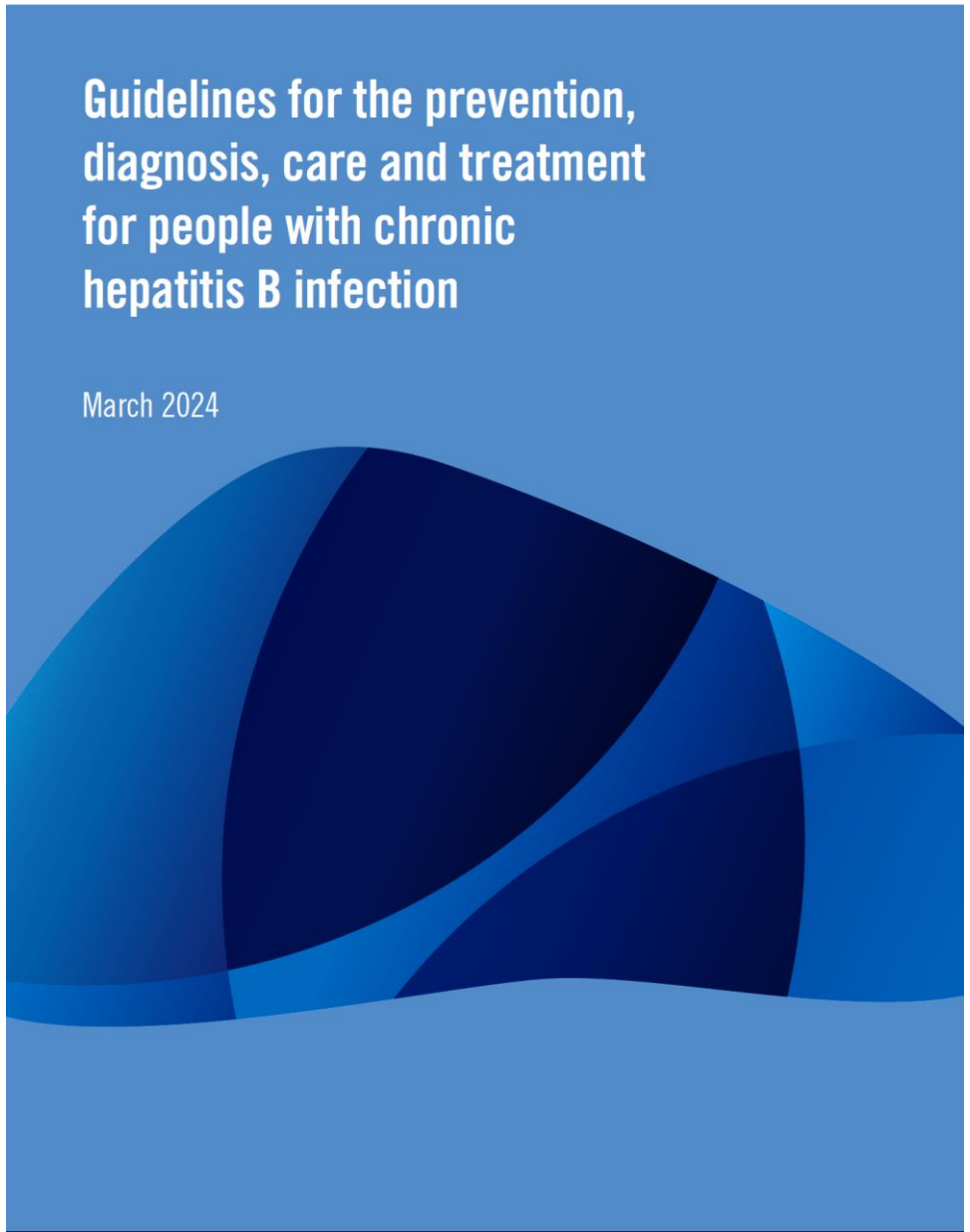
EASL CPG HBV. J Hepatol 2017;67:370–88

Recommendations on stopping NAs EASL VS AASLD vs APASL guidelines

Recommendations on stopping NAs by the European, American and Asian Pacific Guidelines for Chronic Hepatitis B, stratified by HBeAg status and cirrhosis.

Guideline	EASL (2017)	AASLD (2018)	APASL (2015)
HBeAg positive	-HBsAg seroclearance -HBeAg seroconversion and HBV DNA undetectable with at least 12 months of consolidation therapy	-HBsAg seroclearance -HBeAg seroconversion with at least 12 months of persistently normal ALT levels and undetectable HBV DNA levels (close monitoring every 3 months for at least 1 year)	HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels with 1–3 years of consolidation therapy
HBeAg negative	-HBsAg seroclearance	HBsAg seroclearance (close monitoring every 3 months for at least 1 year for recurrent viremia, ALT flares, and clinical decompensation).	-HBsAg seroclearance with anti-HBs seroconversion
	-May be considered before HBsAg loss in selected patients with undetectable HBV DNA for at least 3 years if guaranteed close post-treatment monitoring for at least 1 year	- May be considered if there is a compelling rationale and under careful monitoring every 3 months for at least 1 year.	-HBsAg loss with at least 12 months of a post-HBsAg loss consolidation period
			-After treatment for at least 2 years with undetectable HBV DNA on three separate occasions, 6 months apart
Cirrhosis	Not recommended before HBsAg loss	Not recommended before HBsAg loss	May be considered before HBsAg loss in compensated cirrhosis with careful monitoring plan

AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.



Discontinuation

Antiviral therapy is lifelong. Discontinuing nucleos(t)ide analogue therapy may be considered exceptionally for:

- people without clinical evidence of cirrhosis (or based on a non-invasive test score – APRI or transient elastography;

and

- who can be followed carefully after discontinuation and long term for reactivation;

and

- if there is evidence of HBeAg loss and seroconversion to anti-HBe (for people initially HBeAg-positive) and after completion of at least one additional year of treatment;

and

- in association with persistently normal ALT levels[b] and persistently undetectable HBV DNA levels (if HBV DNA testing is available).

If HBV DNA testing is not available: discontinuing nucleos(t)ide analogue therapy may be considered for people who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of previous HBeAg status.

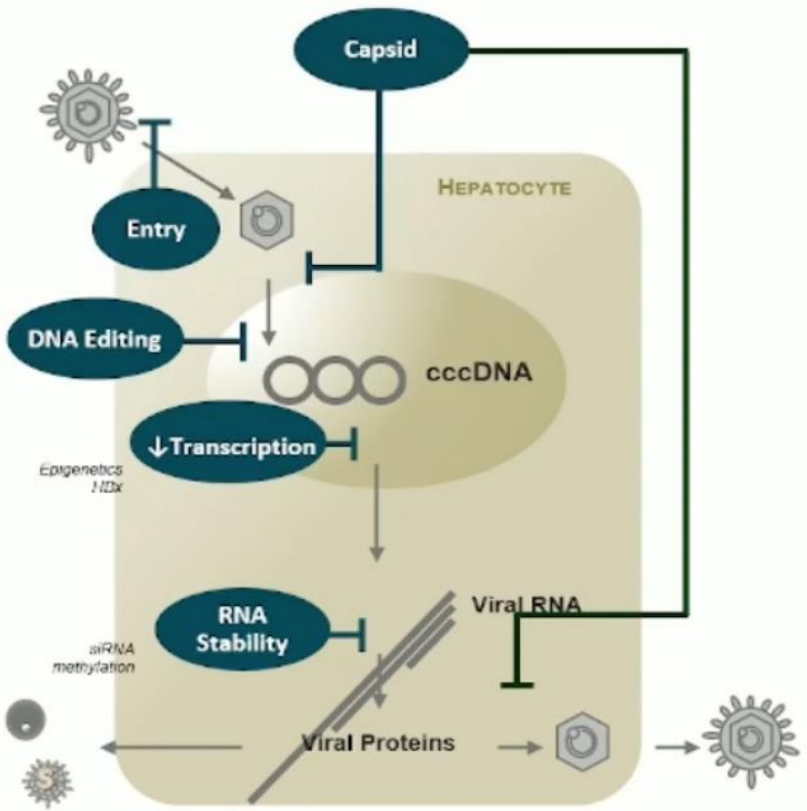
(conditional recommendation, low-certainty evidence)

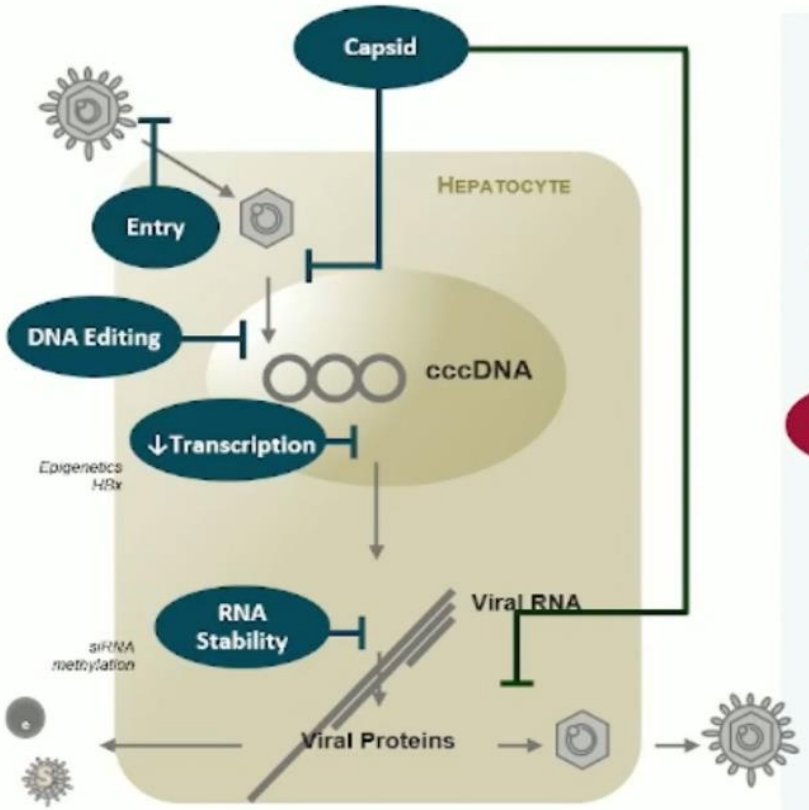
How to achieve functional cure

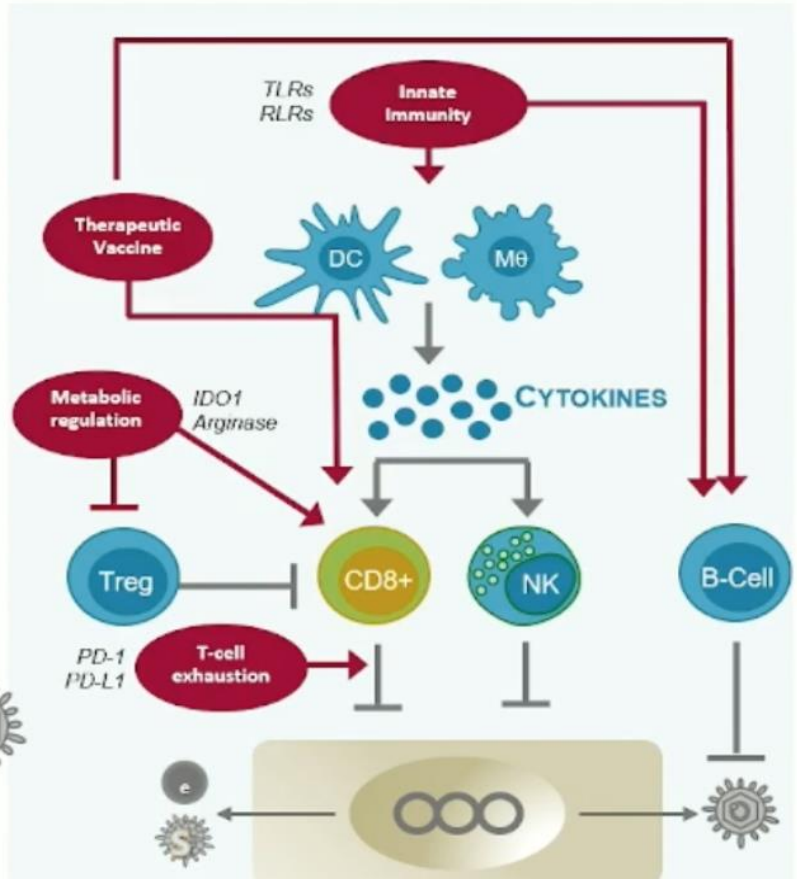
- Functional cure: why we need it
- How to achieve functional cure
  - Current treatments: NUC withdrawal
  - New treatments

Therapeutic Approaches to HBV Cure

Inhibit Viral Replication | **Lower Viral Antigen Burden** | **Boost Immune Response**

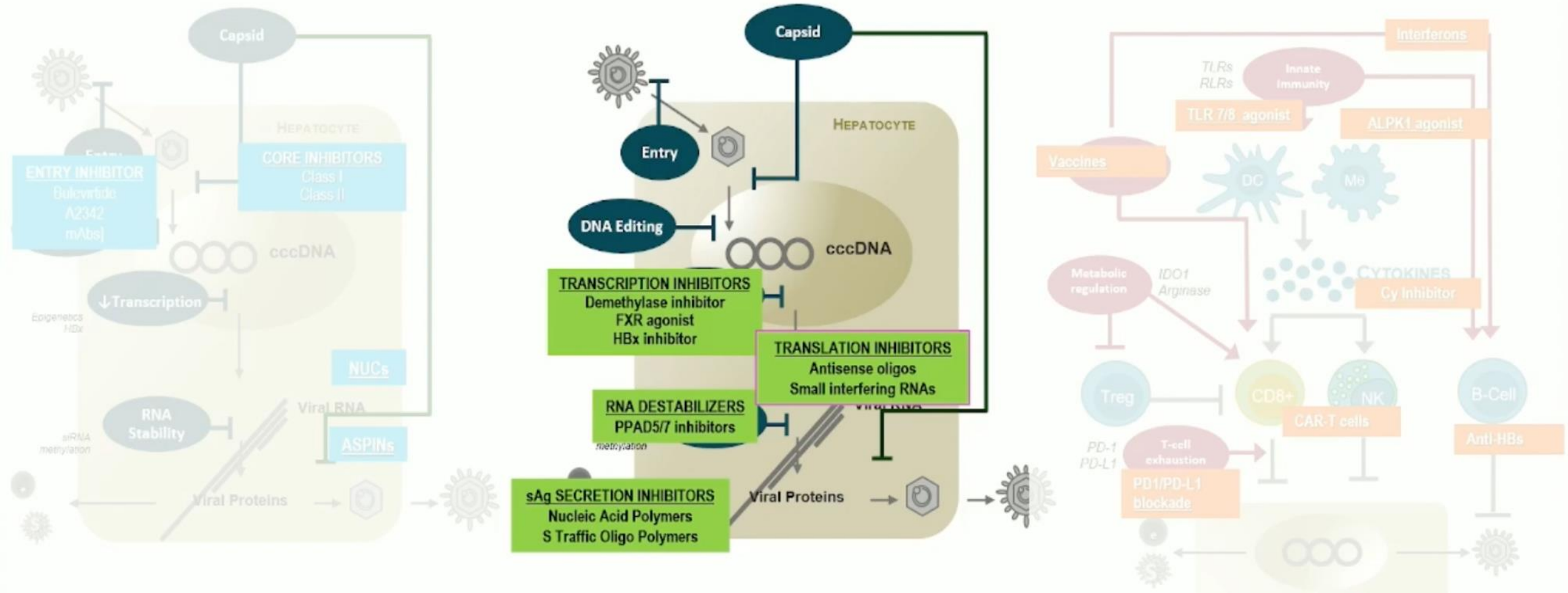






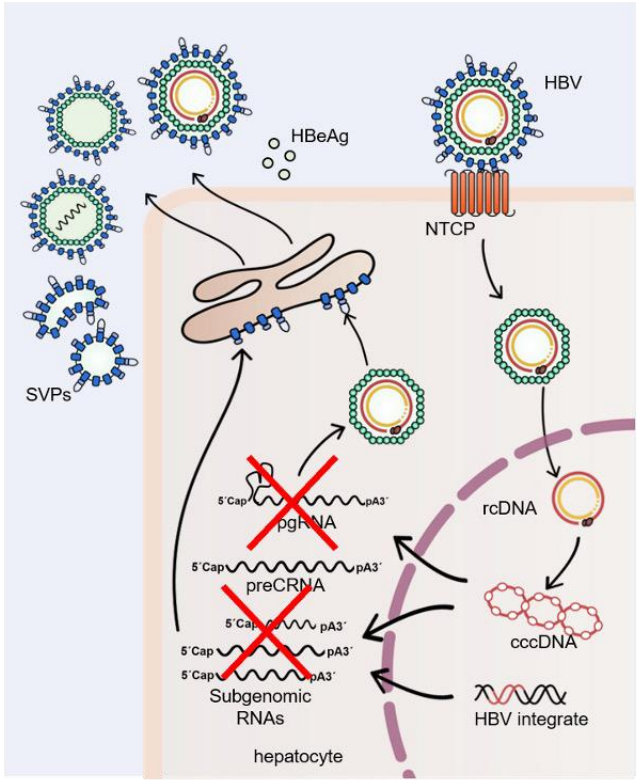
Therapeutic Approaches to HBV Cure

Inhibit Viral Replication	Lower Viral Antigen Burden	Boost Immune Response



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

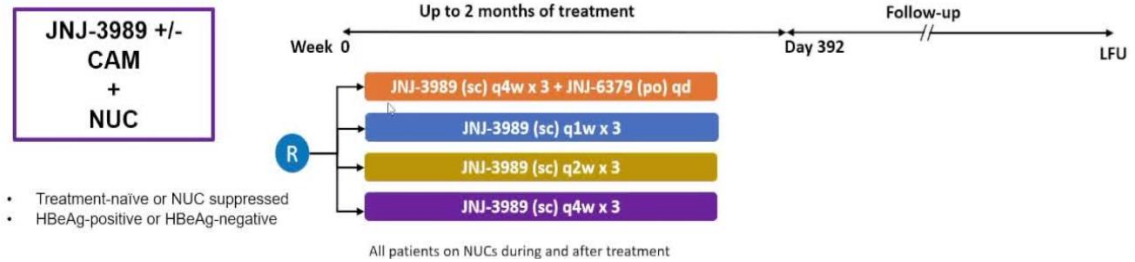
↕

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

Long-term hepatitis B surface antigen response after finite treatment with siRNAs ARC-520 or JNJ-3888



HBsAg outcomes at nadir and at last follow-up

	siRNA (n=53)	ARC-520 (n=15)	JNJ-3989 (n=38)	Placebo (n=5)
HBsAg seroclearance at LFU	1 (1.9%)	1 (6.6%)	0 (0%)	0 (0%)
HBsAg log reduction at nadir^	1.58 (SD 0.84)	0.77 (SD 0.49)	1.89 (SD 0.74)	0.53 (SD 0.29)
>1 log reduction at nadir (%)	71.7%	20%	92.1%	0%
HBsAg log reduction at LFU	0.85 (SD 0.77)	0.78 (SD 0.75)	0.87 (SD 0.78)	0.52 (SD 0.35)
>1 log reduction at LFU (%)	18.9%	13.3%	21.1%	20%*
<100 IU/mL at LFU (%)	31.2%	20%	36.8%	0%
Annual HBsAg decline (log IU/mL per year)	0.21 (SD 0.22)	0.13 (SD 0.12)	0.24 (SD 0.24)	0.08 (SD 0.05)

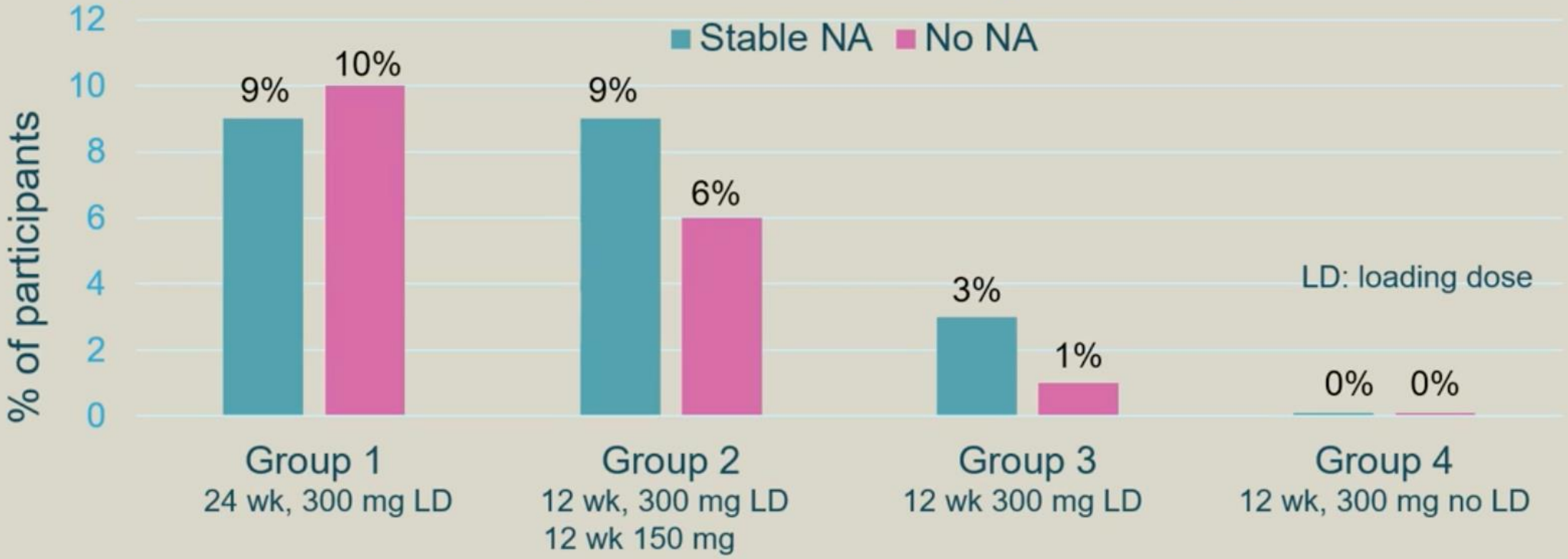
Characteristics at baseline (i.e. at start of initial study)

	Received ARC-520 (n=15)	Received JNJ-3989 (n=38)	Received placebo (n=5)
Age	46.6 (SD 10.4)	46.9 (SD 9.4)	48.6 (SD 7.5)
Gender (M:F)	11: 4	21: 17	4: 1
Chinese ethnicity	100%	100%	100%
Body mass index (kg/m^2)	24.1 (SD 4.1)	24.5 (SD 3.7)	24.6 (SD 3.4)
ALT (U/L)	28 (SD 9)	29 (SD 12)	30 (SD 7)
Baseline HBsAg			
• expressed in IU/mL	1878 (SD 2875)	7303 (SD 18119)	2130 (SD 2532)
• Expressed in $\log_{10}$IU/mL	2.92 (SD 0.61)	3.14 (SD 0.82)	3.05 (SD 0.58)
• <100 IU/mL	2 (13.3%)	2 (5.3%)	0 (0%)
On NUC at start of original study	15 (100%)	29 (76.3%)	5 (100%)
HBeAg-positive	7 (46.7%)	11 (28.9%)	2 (40%)
Follow-up duration from the start of dosing (months)	68 (SD 9.8)	43.8 (SD 7.7)	72 (SD 0)

Conclusion

- HBsAg levels were reduced by up to 3 months of siRNA treatment with ARC-520 x 4 injections or JNJ-3989 x 3 injections
- In some patients there was a prolonged effect on HBsAg levels for up to 6 years after initial dosing
- At ~6 years from initial dosing with siRNA, 1.9% achieved HBsAg seroclearance and 31.2% achieved HBsAg <100 IU/mL, compared to 0% for both parameters for placebo
- Compared to placebo, siRNA led to faster annual decline rate of HBsAg (0.08 vs 0.21 log, p=0.003)
- Age, baseline HBsAg level and lower nadir appear to influence HBsAg reduction or absolute level at long-term FU
- No safety signals arose after prolonged FU

B-CLEAR Trial: Phase 2 Bepirovirsen (Naked ASO) Proportion of Participants Achieving Primary Outcomes

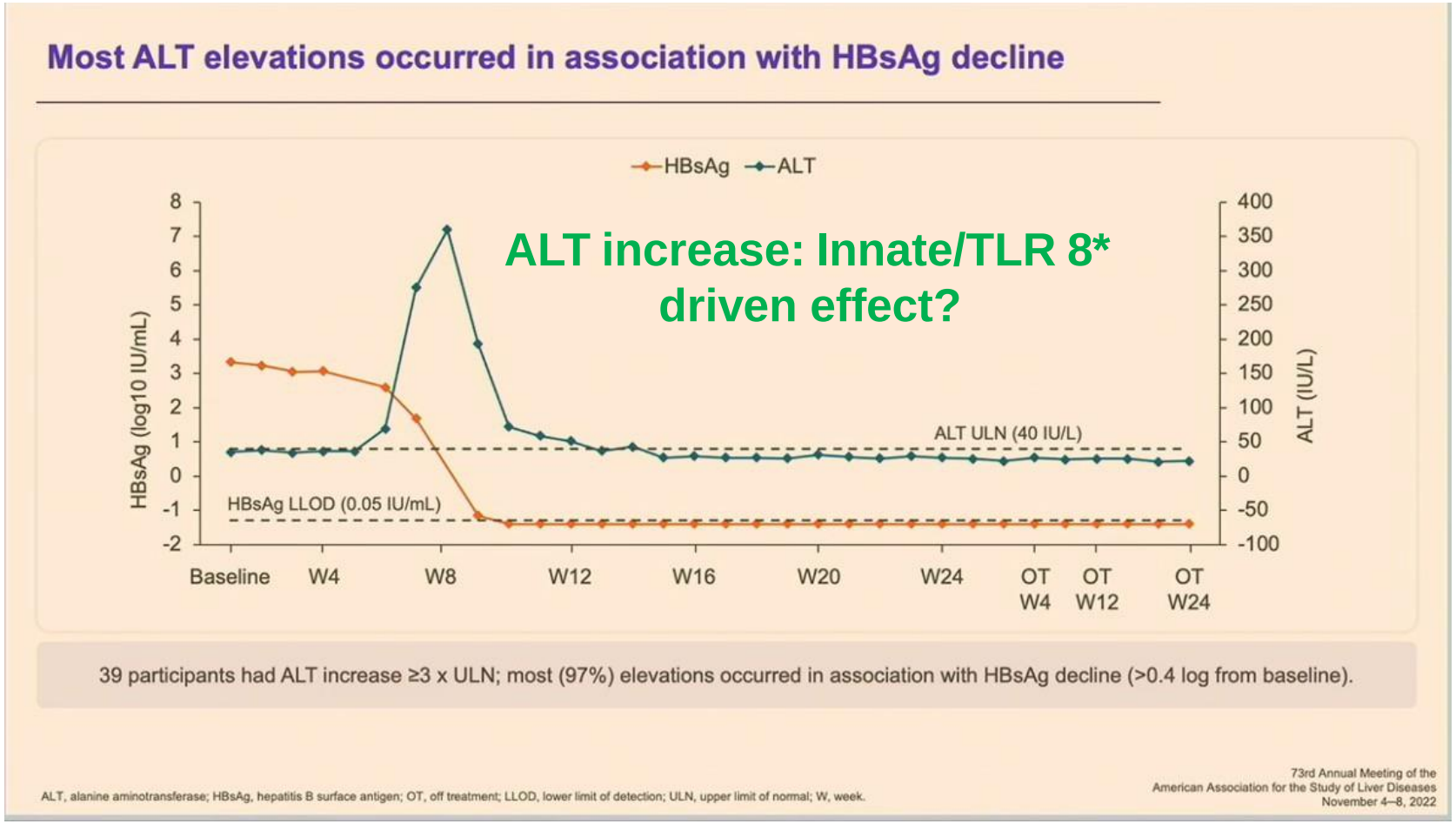


- 2 identical trials: stable NA and no NA
- Primary outcome: HBsAg <LLOD and HBV DNA <LLOQ 24 weeks after end of treatment
- Higher rate of response in HBeAg- participants and those with baseline HBsAg ≤3 log10 IU/mL
- NO HBeAg+ participant not receiving NA achieved primary outcome
- Does Bepirovirsen act as antiviral or immune modulatory agent?

NA: nucleos(t)ide analogue, LLOD: lower limit of detection, LLOQ: lower limit of quantification

Yuen MF, NEJM 2022; 387: 1957

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.

Evidence of durable response to bepirovirsen in B-Clear responders: B-Sure first annual report

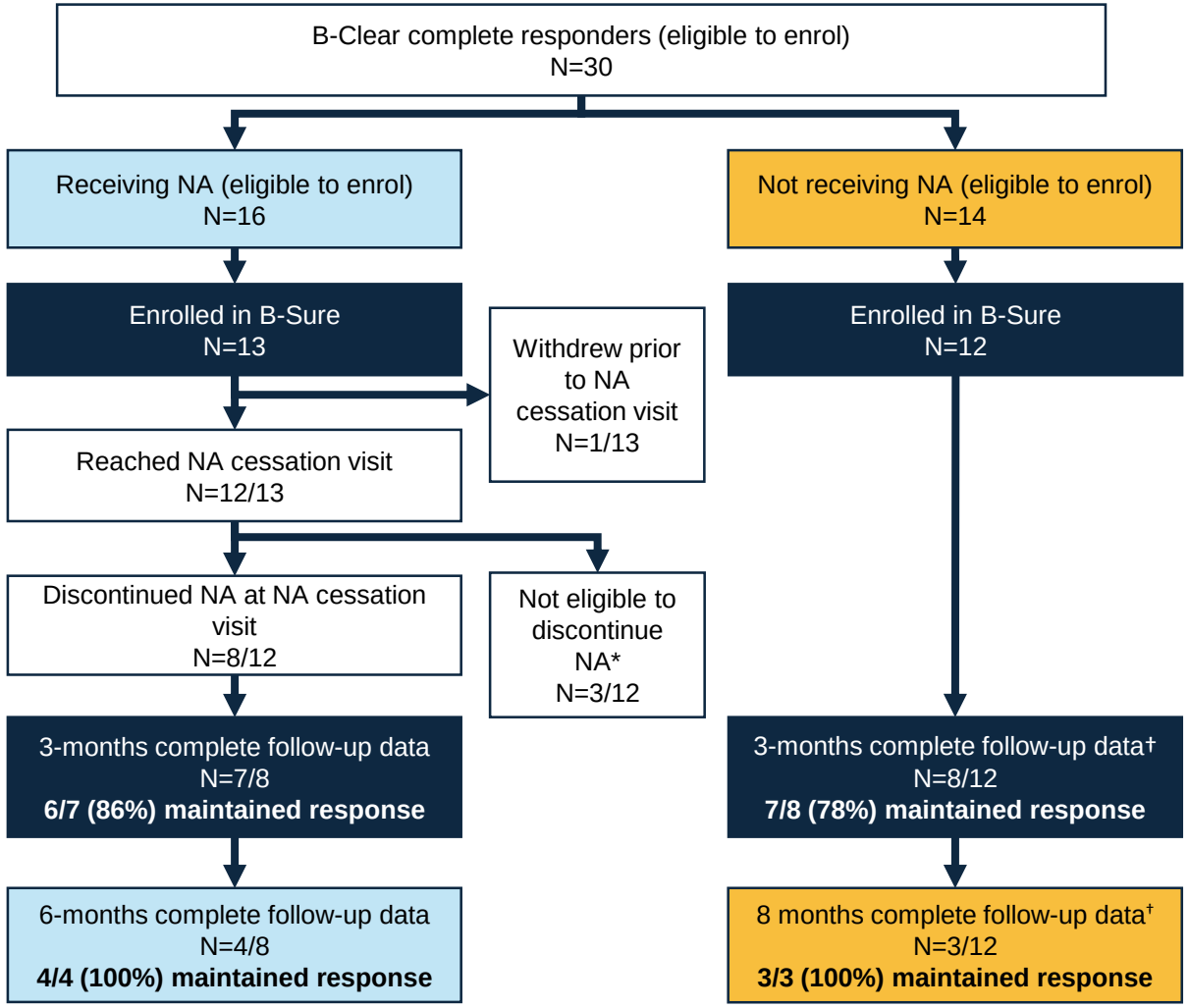
RESULTS

Baseline characteristics and demographics

Characteristic	NA N=13	No NA N=12
Age, mean, years	53.2	43.8
Sex, male, n (%)	12 (82)	7 (58)
Chronic HBV infection ≥20 years, n (%)	6 (46)	3 (25)
$HBeAg^-$, n (%)	10 (77)	12 (100)
HBsAg ≤1000 IU/mL at baseline in B-Clear study	8 (68)	7 (58)

- There were no new safety signals that suggested a latent adverse drug effect following use of bepirovirsen

Participant flow diagram and treatment response



CONCLUSION

- These data provide early evidence on the durability of response to bepirovirsen

*Investigator discretion: evidence of prior or current cirrhosis, or participant preference leading to contraindication. †Duration of response does not include the time between end of bepirovirsen treatment and B-Sure enrolment (≥6 months).

Elston R, et al. EASL 2023; LBP-15

Bepirovirsen immune mechanism of action may potentiate infected hepatocyte killing: Indirect evidence from B-Together peripheral longitudinal biomarker analysis

Shilpy Joshi[1], Johannes Freudenberg[1], Jennifer M. Singh[1], Leigh Felton[2], Susan Dixon[2], Melanie Paff[1], Dickens Theodore[3], Jill Walker[4]

[1]GSK, Collegeville, PA, USA; [2]GSK, London, UK; [3]GSK, Research Triangle Park, NC, USA; [4]GSK, San Francisco, CA, USA

Conclusions

Two key findings support the hypothesis that bepirovirsen treatment leads to the modulation of the immune response and subsequent killing of infected hepatocytes in chronic HBV infection:

- Bepirovirsen appears to induce immune responses, as evidenced by increased cytokines and activation/proliferation of immune cells
- ALT increases on bepirovirsen appear to be the outcome of infected hepatocyte cell death, as evidenced by concurrent transient increase in HBV DNA, and several liver and apoptosis-related proteins in serum

Background

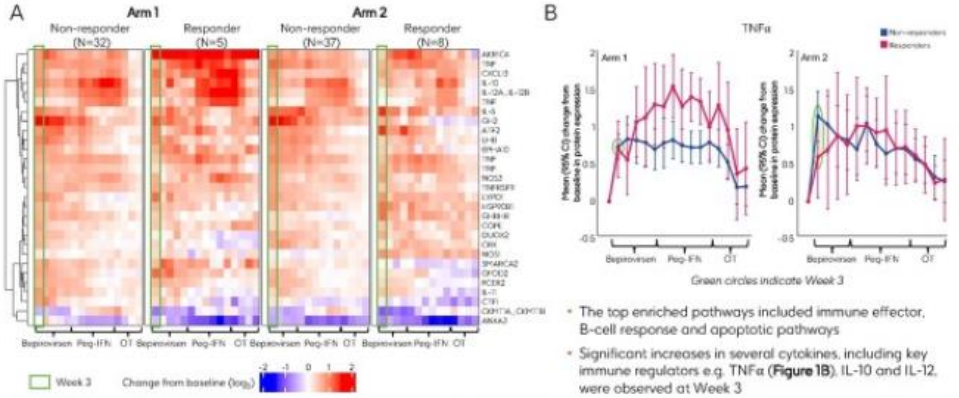
- Transient ALT increases, which were associated with concurrent HBsAg decline,[1,2] have been observed in some participants treated with bepirovirsen, an HBV-targeting unconjugated antisense oligonucleotide[3]
- Using data from the B-Together study (NCT04676724), we investigated bepirovirsen's immune mechanism of action, its role with respect to virological response, surrogate markers associated with hepatocyte cell death and ALT increases

Methods

- B-Together was a Phase 2b trial; 108 participants with chronic HBV infection on stable NA received bepirovirsen for 24 (Arm 1) or 12 (Arm 2) weeks, then up to 24 weeks of Peg-IFN[4]
  - Responders: achieved the primary endpoint: HBsAg <0.05 IU/mL and HBV DNA <20 IU/mL sustained for 24 weeks after the end of sequential bepirovirsen + Peg-IFN treatment (OT period) in the absence of rescue medication
  - Non-responders: did not meet the primary endpoint or had missing data in the OT period
- In this longitudinal peripheral biomarker exploratory analysis, which was performed post hoc on 82 participants (excluding China), flow cytometry of peripheral blood mononuclear cells, serum proteomics and whole blood transcriptomics were performed
- Relative expression of biomarkers was measured at baseline and post-baseline at multiple timepoints during the bepirovirsen, Peg-IFN and OT periods
- To determine differential expression, multivariate models were fit that included treatment arms and response subgroups

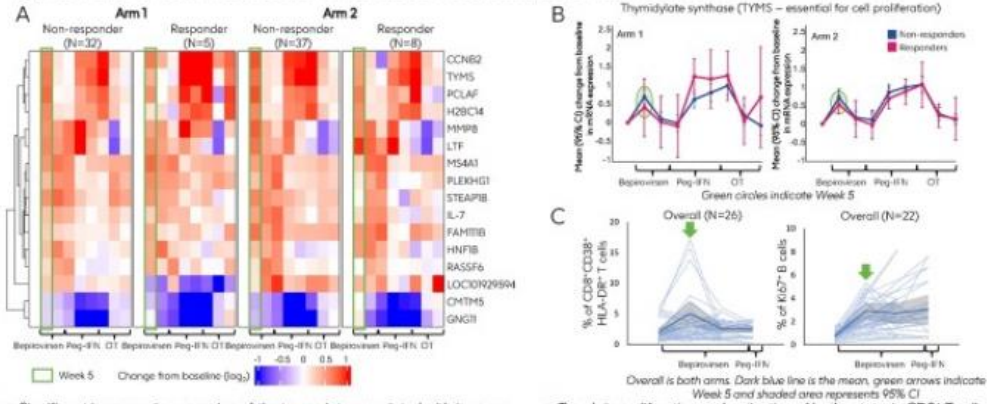
Results

Figure 1: **Bepirovirsen induces key immune response regulators at Week 3**



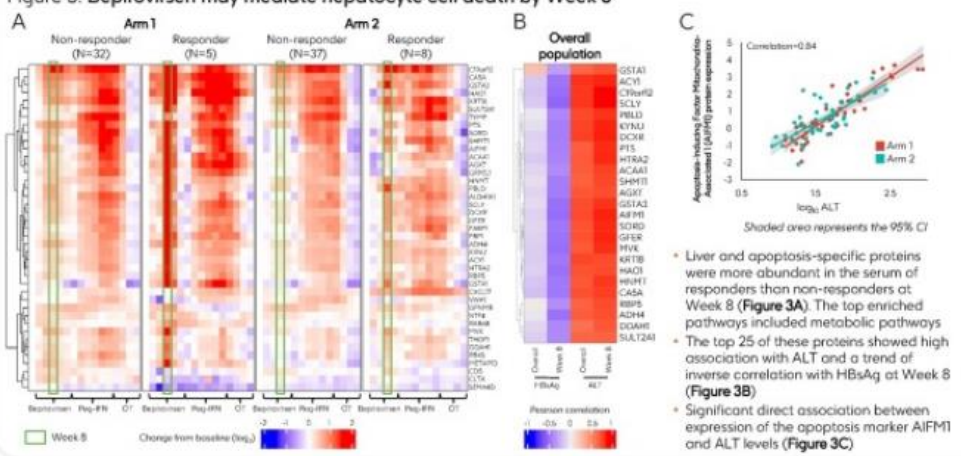
- The top enriched pathways included immune effector, B-cell response and apoptotic pathways
- Significant increases in several cytokines, including key immune regulators e.g. TNFα (**Figure 1B**), IL-10 and IL-12, were observed at Week 3

Figure 2: **Bepirovirsen increases immune cell activation and proliferation at Week 5**



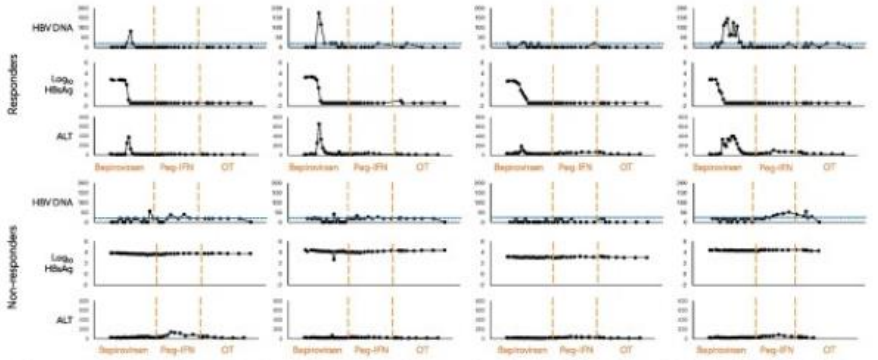
- Significant increases in expression of the transcripts associated with immune cell activation and proliferation e.g. TYMS (**Figure 2B**) was observed by Week 5
- Trends in proliferation and activation of both cytotoxic CD8+ T cells (CD38+; HLA-DR+) and B cells (Ki67+) were also observed (**Figure 2C**)

Figure 3: **Bepirovirsen may mediate hepatocyte cell death by Week 8**



- Liver and apoptosis-specific proteins were more abundant in the serum of responders than non-responders at Week 8 (**Figure 3A**). The top enriched pathways included metabolic pathways
- The top 25 of these proteins showed high association with ALT and a trend of inverse correlation with HBsAg at Week 8 (**Figure 3B**)
- Significant direct association between expression of the apoptosis marker AIFM1 and ALT levels (**Figure 3C**)

Figure 4: **Bepirovirsen potentiates killing of infected hepatocytes**



Figures show representative individual participant-level profiles for responders and non-responders in Arm 1. The blue line indicates the LLOQ for HBV DNA (20 IU/mL)

- During the bepirovirsen treatment period, concurrent transient increases in HBV DNA alongside ALT elevations, indicative of infected hepatocyte death and release of HBV DNA into the periphery, appeared to be more prominent in responders than non-responders (**Figure 4**)

High-dimensional analysis of flow cytometry data reveals differences in post-treatment frequencies of naïve B cells, CD56^{dim} natural killer cells, and terminally differentiated effector memory CD8^{+} T cells in responders versus non-responders to bepirovirsen

Thea Hogan,[1] Eduardo Gomez Castaneda,[1] Esther Perez Garcia,[1] Ruth Barnard,[1] Avijit Ray,[2] Melanie Paff,[2] Dickens Theodore,[3] Jennifer M. Singh[2]

[1]GSK, Stevenage, Hertfordshire, UK; [2]GSK, Collegeville, PA, USA; [3]GSK, Durham, NC, USA

Conclusions

- These analyses provide a first glance into the immunological landscape in participants treated with bepirovirsen
- In B-Clear, bepirovirsen had a longer lasting impact on some immune cell populations in responders compared with non-responders
- These data will shape subsequent analyses in future clinical trials to further elucidate the immune response in bepirovirsen-treated participants

Background and aims

- Bepirovirsen is an unconjugated antisense oligonucleotide in development for the treatment of chronic HBV infection[1, 2, 3]
- In the Phase 2b B-Clear study (NCT04449029), 9–10% of participants who received bepirovirsen 300 mg for 24 weeks achieved the primary endpoint (HBsAg and HBV DNA <LLOQ sustained for 24 weeks after planned end of treatment)[2]
- This post hoc analysis investigated the impact of bepirovirsen on immune cell frequencies and phenotypes using high-dimensional analysis of flow cytometry data from participants in the B-Clear study
- Understanding differences between responders and non-responders may lend insights into therapeutic approaches to achieve functional cure

Methods and data visualisation

- Peripheral blood mononuclear cell samples from B-Clear participants with available samples (114 samples from 47 participants) were analysed by spectral flow cytometry using a 30-colour deep immunophenotyping panel
- Participant off-treatment responses were defined as:
  - **PE responder**: HBsAg and HBV DNA <LLOQ maintained for 24 weeks after planned end of treatment in the absence of any rescue medication[2]
  - **Relapse**: HBsAg and HBV DNA <LLOQ and had ≥2 consecutive visits with HBsAg or HBV DNA ≥LLOQ during follow-up
  - **Intermittent responder**: HBsAg and HBV DNA <LLOQ, with a single visit of HBsAg or HBV DNA >LLOQ
  - **Moderate responder:** HBsAg and HBV DNA >LLOQ but had >0.4 $\log_{10}$ reduction in HBsAg at ≥2 consecutive visits
  - **Null responder:** HBsAg and HBV DNA >LLOQ and not had >0.4 $\log_{10}$ reduction in HBsAg at ≥2 consecutive visits
- Cells were visualised in UMAP and metaclustered using FlowSOM
- Metaclusters were analysed descriptively for:
  - Abundance according to the participants off-treatment response
  - Change in abundance relative to baseline at OTD1, 78 and 162
  - Phenotypic annotation
- Metaclusters of interest were selected based on their differential behaviour in participant responses

Select results

Figure 1: **UMAP plots revealed unique cell clusters between PE responders and null responders (red arrow)**

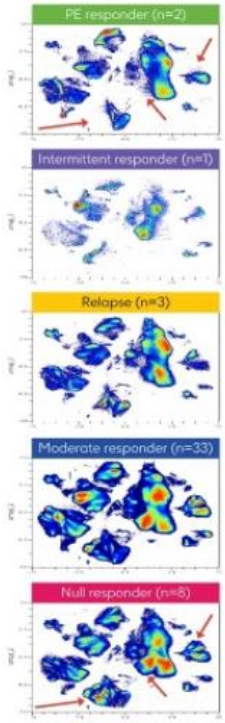
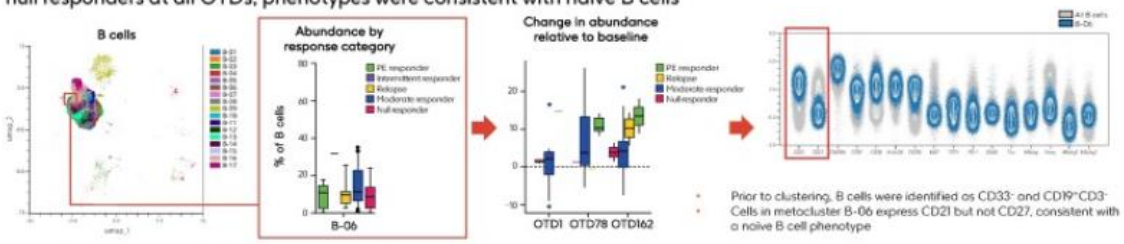
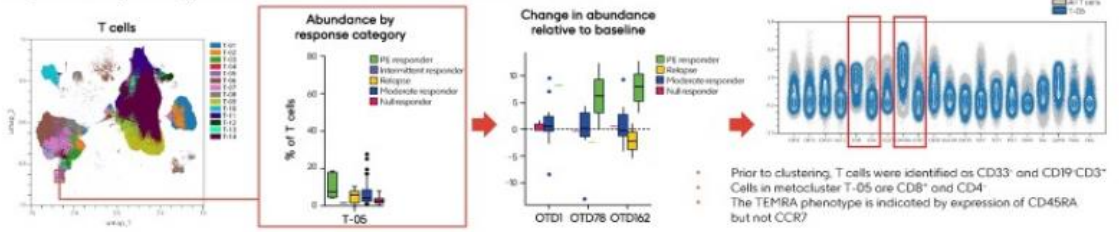


Figure 2: **B cell metacluster B-06 showed increased abundance relative to baseline in PE responders versus null responders at all OTDs; phenotypes were consistent with naïve B cells**



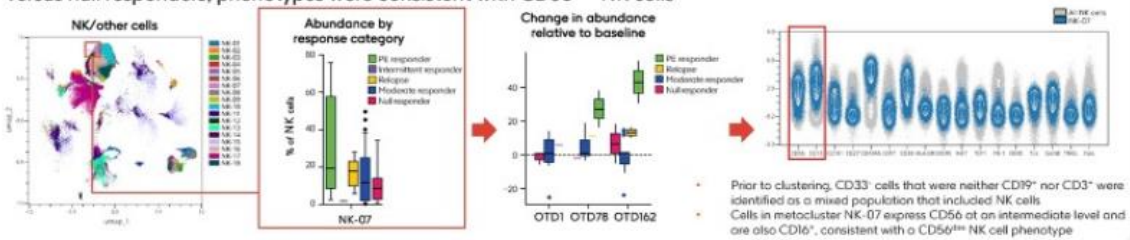
- Prior to clustering, B cells were identified as CD33^{-} and CD19^{+}CD3^{-}
- Cells in metacluster B-06 express CD21 but not CD27, consistent with a naïve B cell phenotype

Figure 3: **Metacluster T-05 had increased abundance relative to baseline at all OTDs in PE responders versus null responders; phenotypes were consistent with TEMRA CD8^{+} T cells**



- Prior to clustering, T cells were identified as CD33^{-} and CD19^{-}CD3^{+}
- Cells in metacluster T-05 are CD8^{+} and CD4^{-}
- The TEMRA phenotype is indicated by expression of CD45RA but not CCR7

Figure 4: **NK cell metacluster NK-07 had increased abundance relative to baseline at OTD78 and 162 in PE responders versus null responders; phenotypes were consistent with CD56^{dim} NK cells**



- Prior to clustering, CD33^{-} cells that were neither CD19^{+} nor CD3^{+} were identified as a mixed population that included NK cells
- Cells in metacluster NK-07 express CD56 at an intermediate level and are also CD16^{+}, consistent with a CD56^{dim} NK cell phenotype

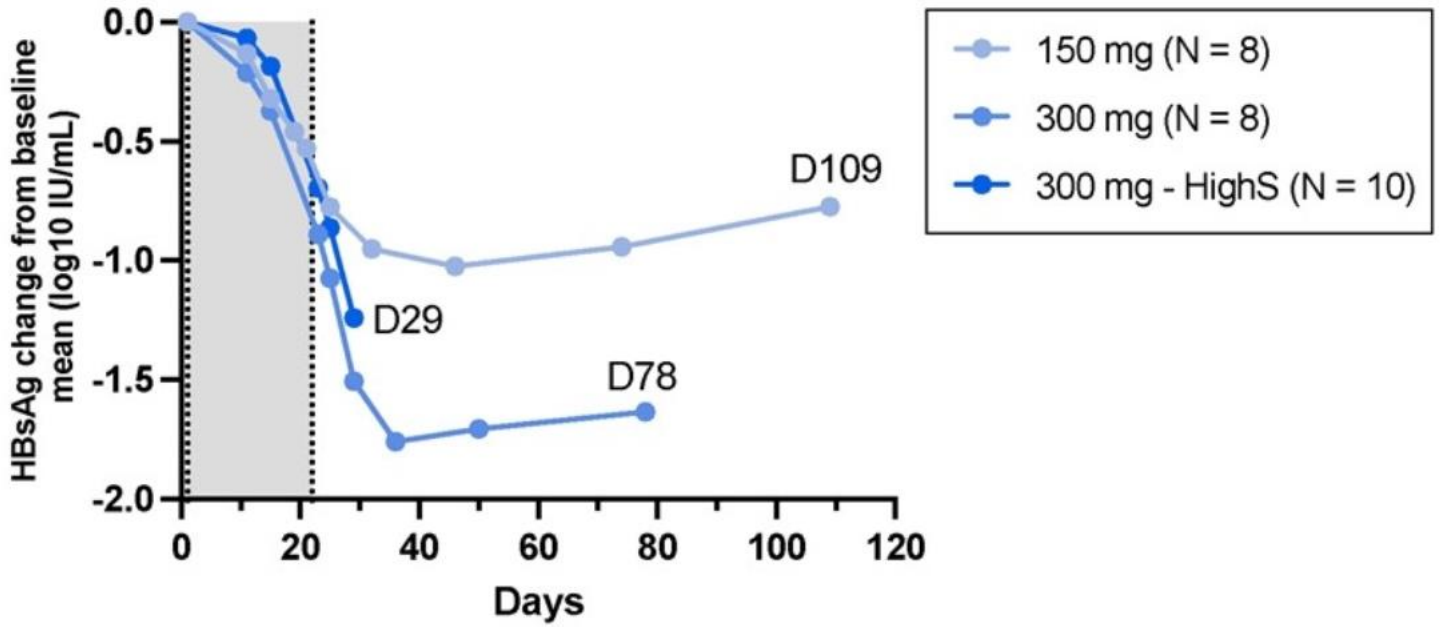
New OAS AHB-137

RESULTS

- AHB-137 exhibited more potent inhibition of HBsAg production in

ASO	EC_{50} (nM)	Selectivity index
AHB-137	0.13	>768-fold
Bepirovirsen	1.50	>67-fold

- AHB-137 reduced HBsAg by 10-fold and 6-fold vs. bepirovirsen in HepAD38 and HBV-infected PHH, respectively
- AHB-137 showed potent, dose-dependent reductions in serum HBsAg, HBeAg, HBV DNA, and intrahepatic HBV RNA in all *in*



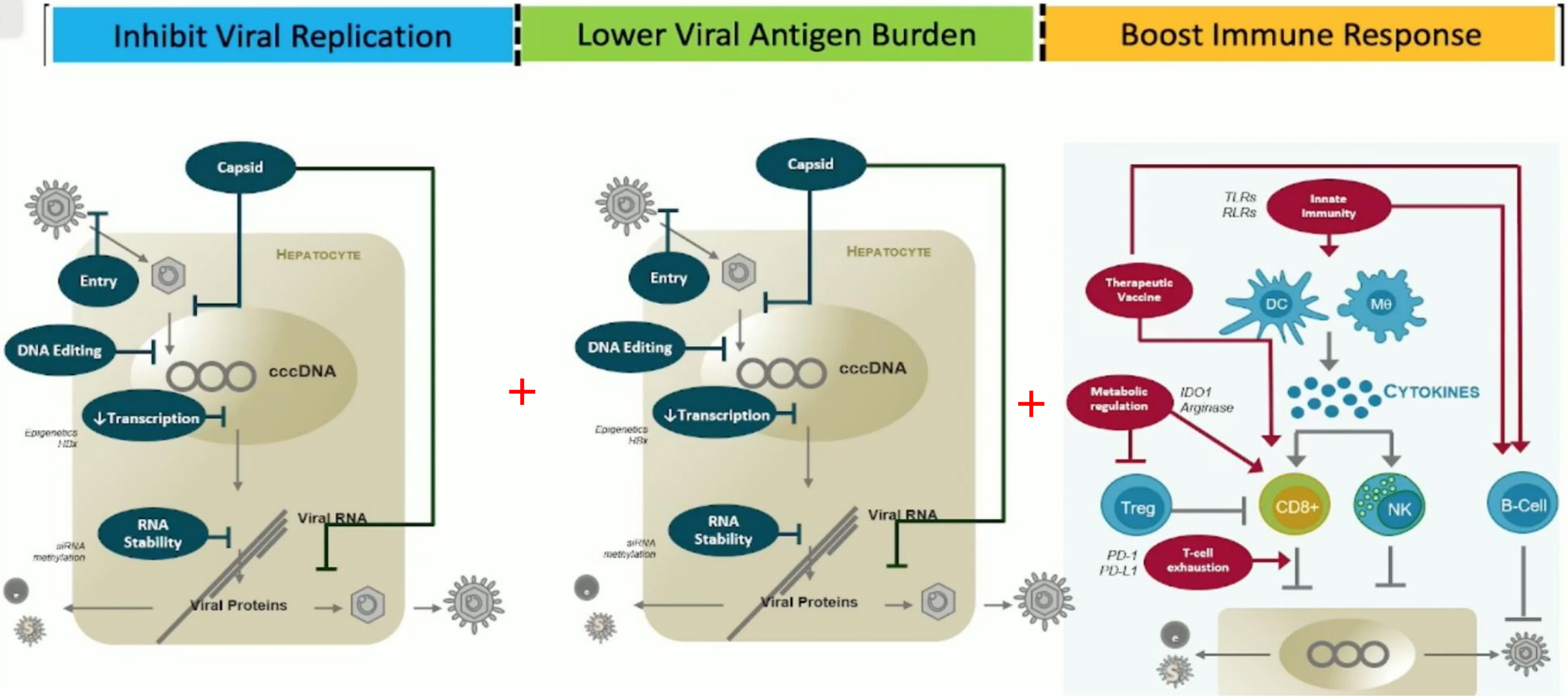
CONCLUSIONS

- AHB-137 demonstrated strong antiviral activity against HBV mRNA, both from cccDNA and integrated genomes
- AHB-137 was more potent in reducing serum HBsAg than bepirovirsen across *in vitro* and *in vivo* models
- The favorable PK and safety profile of AHB-137 supports further clinical development

- Four-week treatment with AHB-137 could result in rapid dose-dependent reduction in HBsAg levels. Significant HBsAg reduction was observed in 300 mg treated CHB subjects with baseline HBsAg in both 100 - 1,000 IU/mL and 1,000 - 3,000 IU/mL levels.

Wu X, et al. EASL 2023; SAT-173; Wag W et al EASL 2024 LBP-043

Combining novel and old therapies for functional cure



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)

Therapeutic approach to achieve functional cure

Combination of a **direct acting antiviral** plus an **immunomodulator**

Direct acting antiviral

xalnesiran (HBV siRNA)
- Liver-targeted oligonucleotide
- Degrades HBV transcripts coding for the HBsAg

Immunomodulator

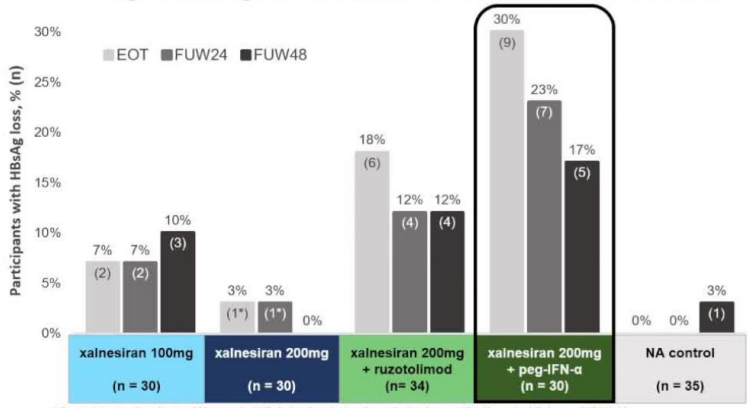
ruzotolimod (TLR7 agonist)
- Double pro-drug selectively activated in the liver
- Stimulates cytokine production and dendritic cell activation

OR

peg-IFN-α
- Induces the innate antiviral immune response

HBsAg loss at EOT, and at follow-up weeks 24, and 48

Highest HBsAg loss rates in xalnesiran with an immunomodulator (peg-IFN-α or ruzotolimod)



Durability of HBsAg loss rate in xalnesiran with peg-IFN-α:
- **At FUW24: 7/9 (78%)** participants maintained HBsAg loss
- **AT FUW48: 5/9 (56%)** participants maintained HBsAg loss

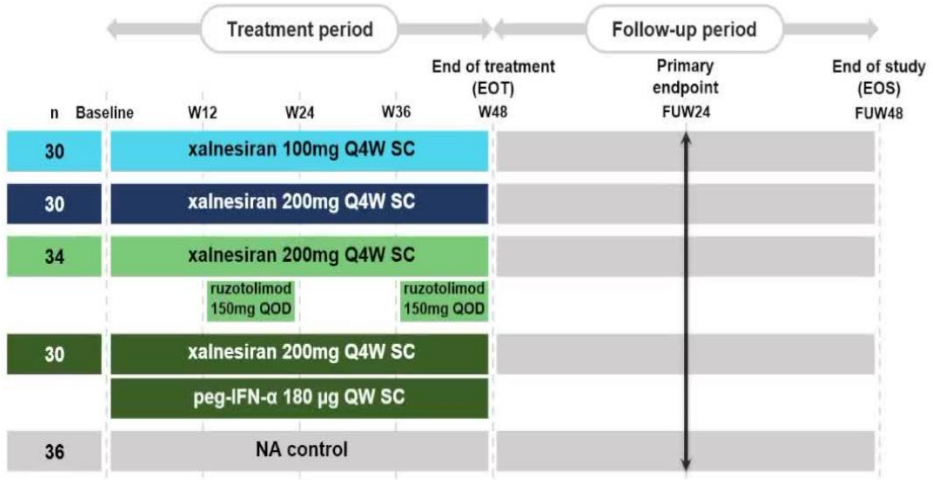
Across all arms, HBsAg loss was observed in participants with:
- **HBsAg < 1000 IU/mL** at screening
- **HBV RNA < LLOQ** at these 3 timepoints

* One participant in the xalnesiran 200mg arm had HBsAg loss from the baseline visit with infrequent blips (Screening HBsAg was 3.05 IU/mL)
HBsAg loss is defined as HBsAg <0.05 IU/mL
Abbreviations: %, percent; EOS, end of study; EOT, end of treatment; FUW, follow-up week; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogues (entecavir or tenofovir disoproxil fumarate or tenofovir alafenamide); peg-IFN-α,

Piranga study design (NCT04225715)

Primary endpoint is the percentage of participants with HBsAg loss at 24 weeks of follow-up

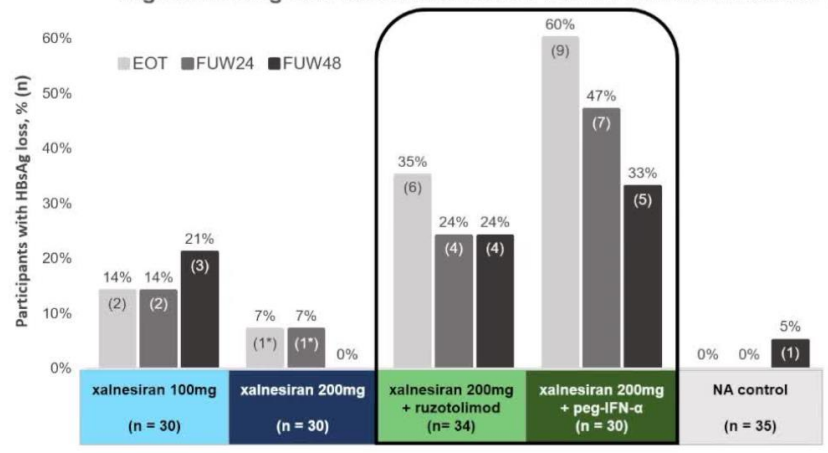
Participants
- Chronic HBV infection ≥ 6 months
- NA monotherapy ≥ 12 months
- HBV DNA < LLOQ
- ALT < 1.5 x ULN
- Non-cirrhotic
- Recruitment across 26 sites in 8 countries and regions



NA was administered daily in all arms of the study until NA stopping criteria were met

HBsAg loss among participants with screening HBsAg < 1000 IU/mL

Highest HBsAg loss rates in xalnesiran with an immunomodulator (peg-IFN-α or ruzotolimod)



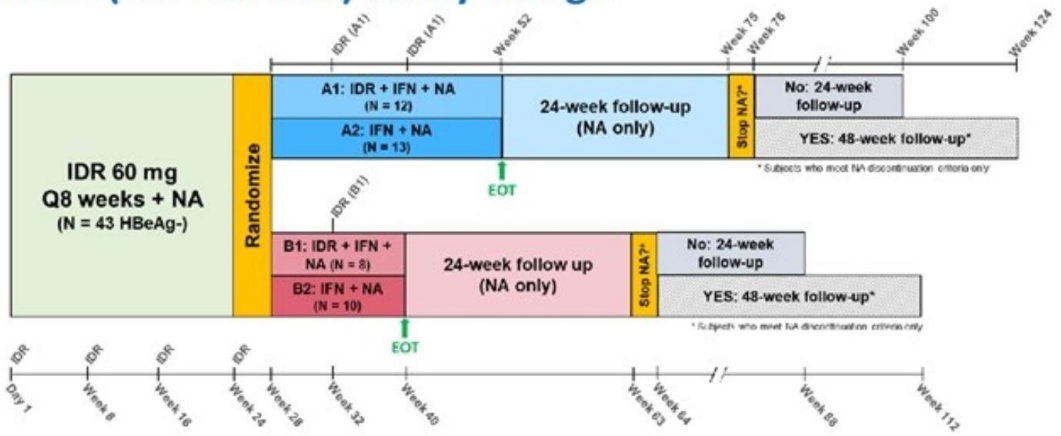
Range of screening HBsAg titers of participants with HBsAg loss at FUW24 (primary endpoint):
- **0.39 to 179.4 IU/mL** for xalnesiran with **ruzotolimod**
- **5.66 to 892 IU/mL** for xalnesiran with **peg-IFN-α** arm

* One participant in the xalnesiran 200mg arm had HBsAg loss from the baseline visit with infrequent low HBsAg titer relapses (Screening HBsAg was 3.05 IU/mL)
HBsAg loss is defined as HBsAg <0.05 IU/mL
Abbreviations: %, percent; EOS, end of study; EOT, end of treatment; FUW, follow-up week; NA, nucleos(t)ide analogues (entecavir or tenofovir disoproxil fumarate or tenofovir alafenamide); peg-IFN-α, pegylated interferon α

AsselahT et al

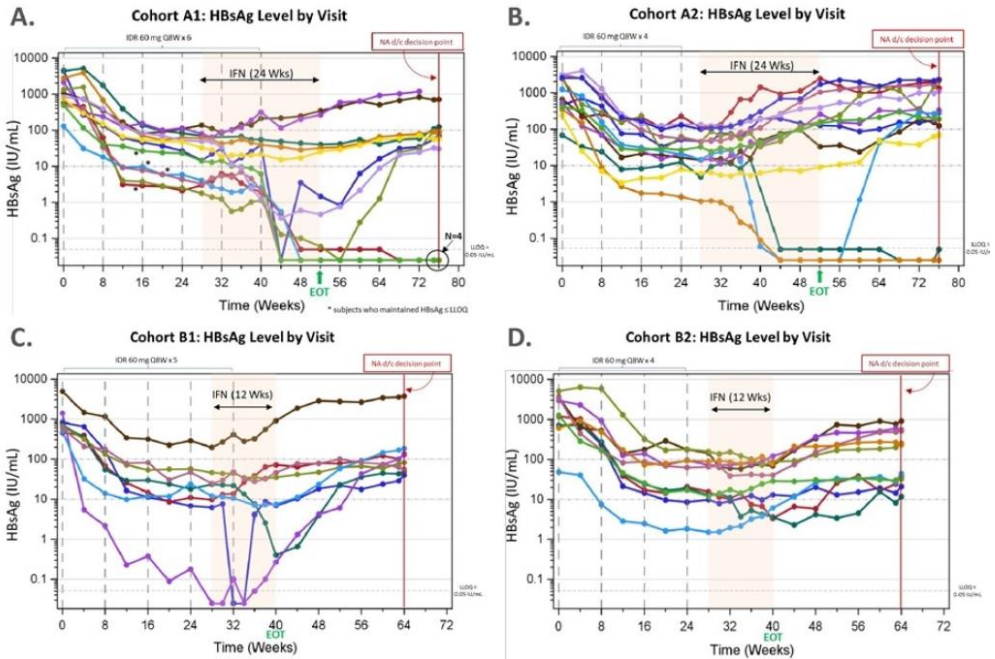
Imdusiran (AB-728) administered every 8 weeks in combination with 24 weeks of pegylated interferon alfa-2a in virally suppressed, HBeAg-negative subjects with chronic HBV infection leads to HBsAg loss in some subjects at end of IFN treatment

IM-PROVE I (AB-729-201) Study Design



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



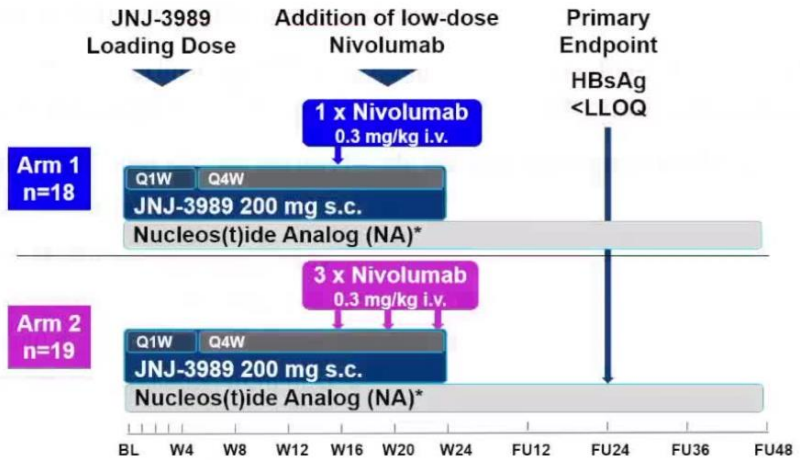
A phase 2 open-label study to evaluate safety, tolerability, efficacy, and pharmacodynamics of JNJ-73763888, nucleos(t)ide analogs, and a low-dose PD-1 inhibitor in patients with chronic hepatitis B – Interim results of the OCTOPUS-1 study

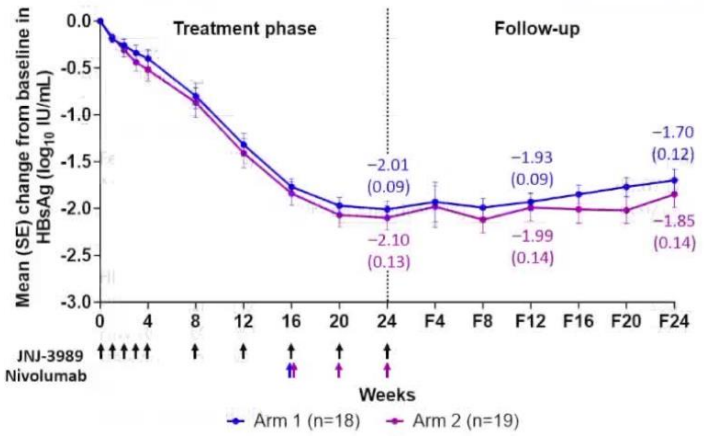
- Efficacy and safety of **low-dose PD-1 inhibitor** added to JNJ-3989
- Impact of a **JNJ-3989 loading dose** (LD) on HBsAg kinetics

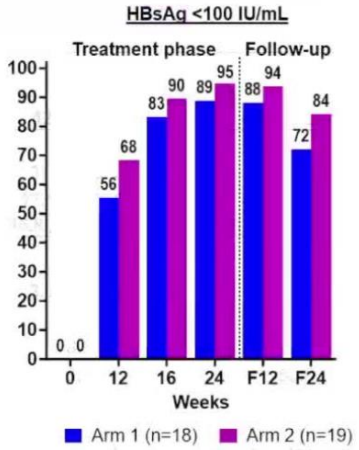
- Adults with CHB (18-55 y)
- HBeAg negative
- Virologically suppressd with NA
- HBV DNA <60 IU/mL
- HBsAg ≥5 and ≤10,000 IU/ml
- LSM ≤ 9kPa or Metavir F0-2

- Randomization: 1:1
- Stratification by HBsAg level at screening
  - <100 IU/mL
  - 100 to <1,000 IU/mL
  - ≥1,000 IU/mL

10 Countries in Europe, Asia, North America







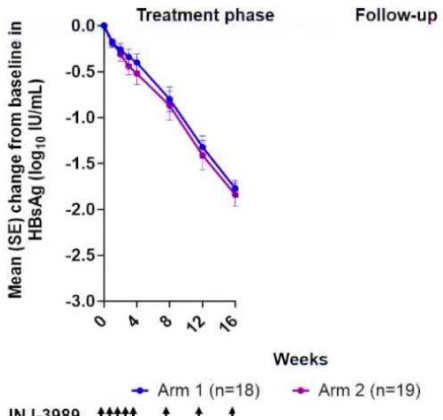
Octopus-1: Baseline Demographic and Disease Characteristics

Percentages or Mean Value (SD)	JNJ-3989 + NA + Nivolumab (1 infusion)	JNJ-3989 + NA + Nivolumab (3 infusions)	Total
N	18	19	37
Stratification Factor			
HBsAg level: <100 IU/mL	0	0	0
100 to <1,000 IU/mL, and ≥1,000 IU/mL (%)	38.9 / 61.1	42.1 / 57.9	40.5 / 59.5
Demographics			
Female v. Male (%)	16.7 / 83.3	21.1 / 78.9	18.9 / 81.1
Age, years	40.67 (7.746)	47.89 (5.054)	44.38 (7.384)
Asian / White/ Black or African American (%)	38.9/ 61.1 / 0	36.8 / 57.9 / 5.3	37.8 / 59.5 / 2.7
Hepatitis B Viral Markers			
HBsAg, log_{10} IU/mL	3.25 (0.47)	3.13 (0.54)	3.19 (0.50)
HBV DNA <LLOQ (%)[a]	100.0	100.0	100.0
HBV RNA <LOD (%)[b]	72.2	78.9	75.7
HBcrAg <LLOQ (%)[c]	38.9	73.7	56.8
HBcrAg, log_{10} U/mL[c]	3.37 (0.820)	2.94 (0.444)	3.15 (0.680)
Disease Characteristics			
ALT, U/L	26.9 (12.87)	19.6 (7.90)	23.1 (11.10)
Fibroscan - LSM, kPa	5.64 (1.247)	4.68 (0.951)	5.15 (1.191)

Octopus-1

JNJ-3989 200 mg Q4W with Q1W LD for first 4 weeks

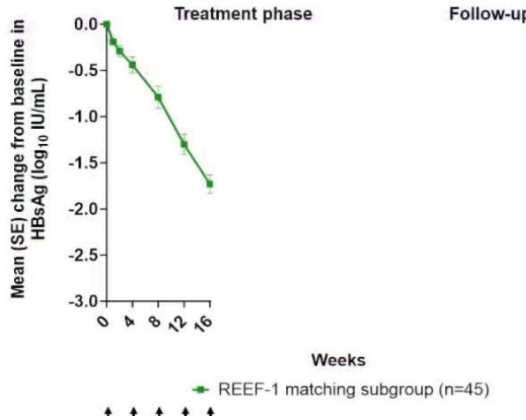
Population: Virologically suppressed, HBeAg negative



REEF-1

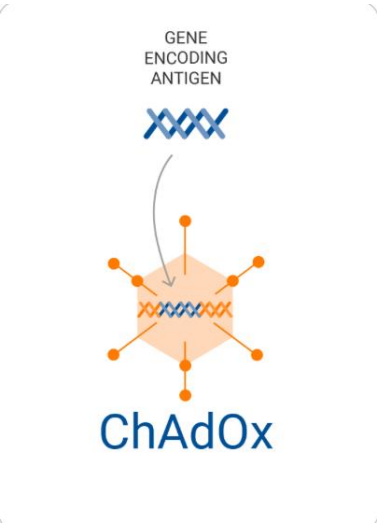
JNJ-3989 200 mg Q4W without loading dose (LD) or nivo

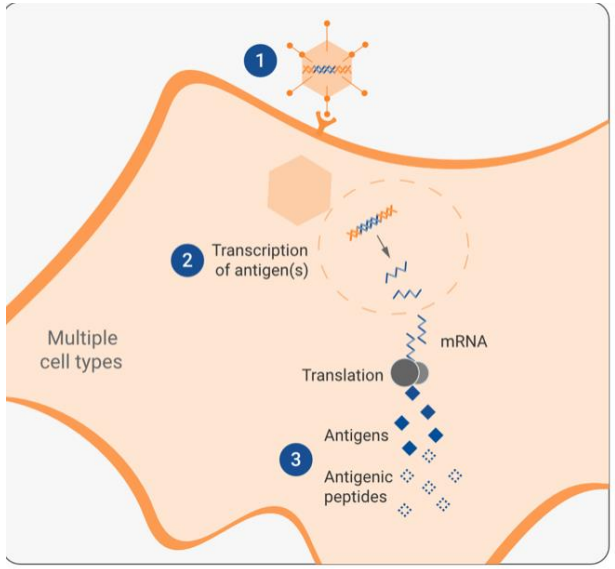
Sub-population: Virologically suppressed, HBeAg negative

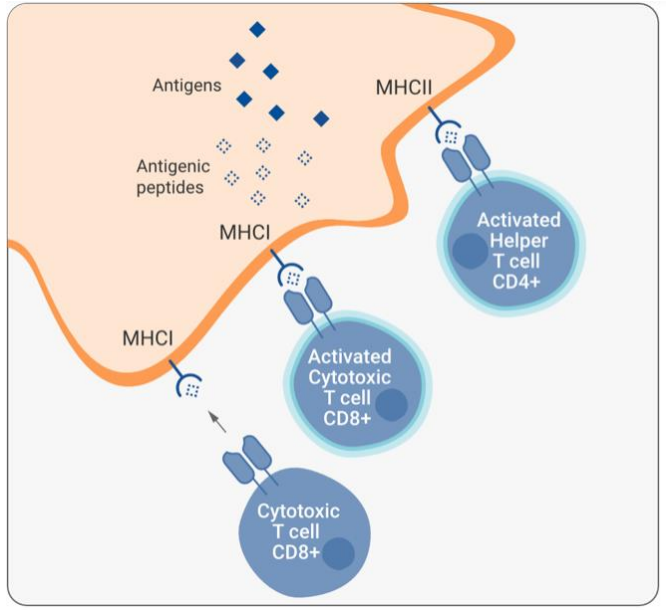


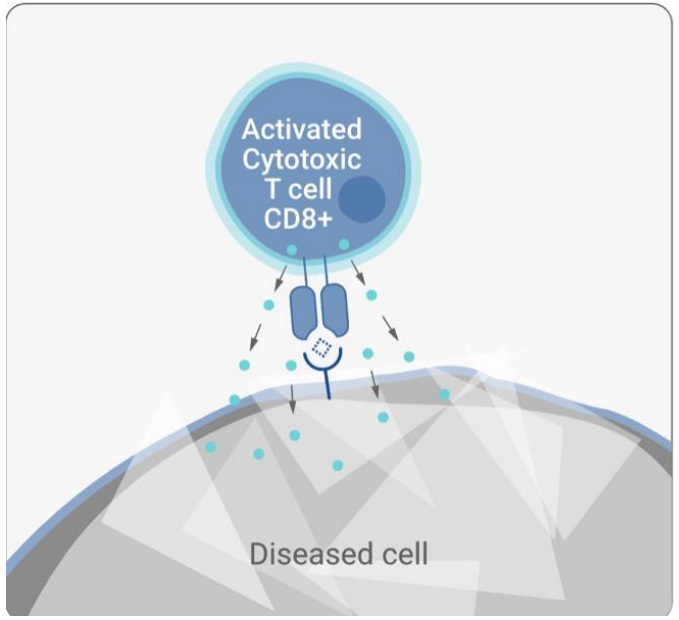
VTP-300

- Vector initial dose using the ChAdOx vector and a secondary dose(s) using the MVA (Modified Virus Ankara) vector, both encoding multiple HBsAg, including full-length surface, modified polymerase, and core antigens.





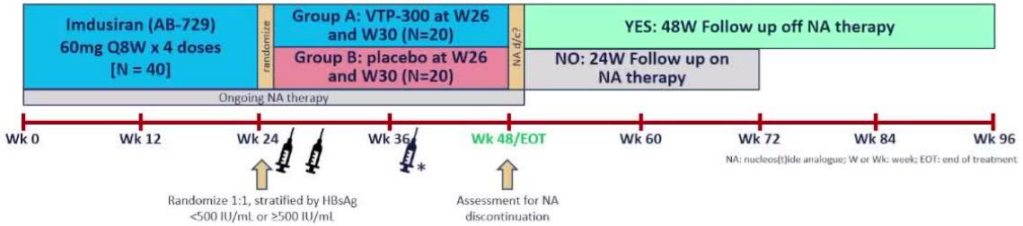




Imdusiran (AB-728) administered every 8 weeks for 24 weeks followed by the immunotherapeutic VTP-300 maintains lower HBV surface antigen levels in NA-suppressed CHB subjects than 24 weeks of imdusiran alone

Study overview: IM-PROVE II (AB-729-202)

- IM-PROVE II is a randomized, placebo-controlled, multicenter Phase 2a proof-of-concept study (ACTRN12622000317796)
- Primary Objective: To evaluate the safety and reactogenicity of the combination of imdusiran followed by VTP-300 or placebo injection
- Week 48/EOT data is reported for 38/40 subjects who reached timepoint, data to Week 72 and beyond reported as available*



Study population:

- NA-suppressed for at least 12 months with HBV DNA < 20 IU/mL
- HBeAg-positive or -negative
- HBsAg ≥100 IU/mL and < 5000 IU/mL
- ALT ≤ 2 × ULN
- Non-cirrhotic

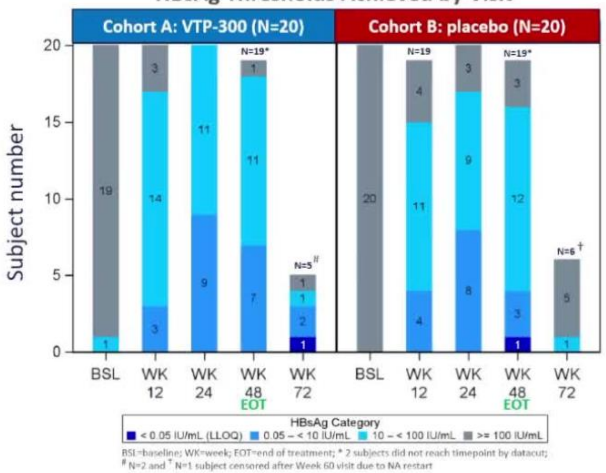
Protocol decision rules:

- Optional 2nd MVA-HBV boost/placebo dose at Week 38:
  - Additional ≥0.5 $\log_{10}$ HBsAg decline between Weeks 26 and 34
- **NA discontinuation occurred after Week 48/EOT visit if all criteria were met:**
  - HBV DNA < LLOQ
  - HBeAg negative
  - HBsAg < 100 IU/mL
  - ALT <2 × ULN

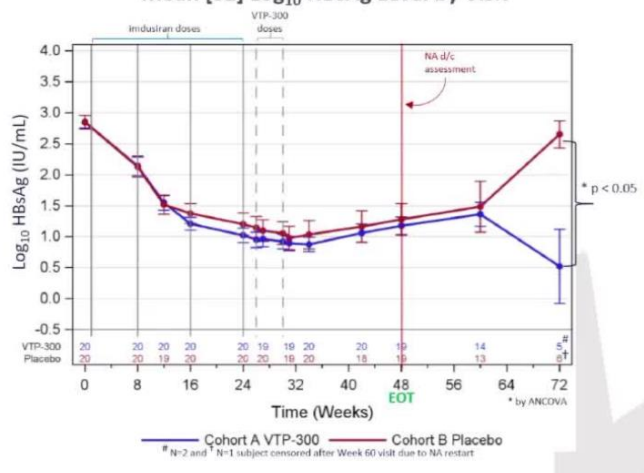
*Data cut date April 12, 2024

Results: Lower HBsAg levels maintained over time in VTP-300 group

HBsAg Thresholds Achieved by Visit



Mean [SE] $\log_{10}$ HBsAg Level by Visit

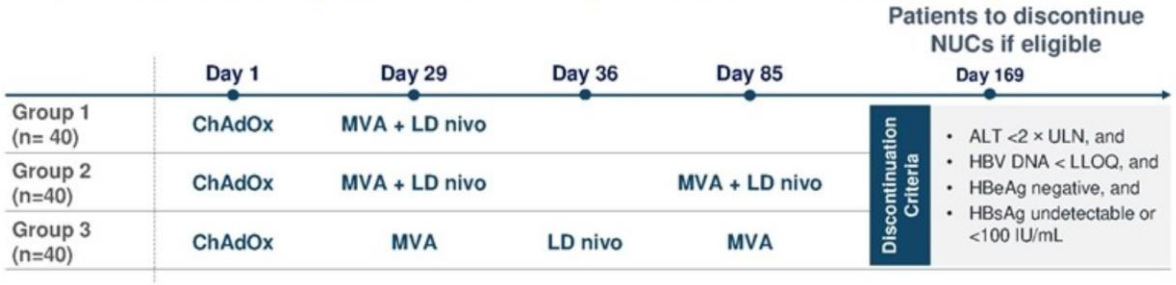


- Imdusiran led to declines of -1.8 $\log_{10}$ by Week 26, 95% of subjects had HBsAg <100 at time of VTP-300 or placebo dosing
- More subjects maintained HBsAg thresholds of <100 IU/mL and <10 IU/mL when administered VTP-300 vs placebo
- At 24 weeks post-EOT (Week 72, N=11), there was a significant difference in HBsAg levels between groups, which may reflect the delayed effect of VTP-300 on HBsAg levels observed in other trials

VTP-300 immunotherapeutic, plus low dose PD-1 inhibitor, nivolumab, continues to show meaningful, sustained reductions in HBsAg levels

VTP-300 + Low-Dose (LD) nivolumab (N=120) - Initiated in Q4 2022

Objective: Evaluating Additional Dosing and PD-1 Inhibition Timing



Inclusion Criteria

- HBV DNA ≤1,000 IU/mL.
- HBsAg ≤200 IU/mL.
- On NUCs for ≥6 months.

Primary Endpoint

- % participants with a greater than 1 log HBsAg reduction 6 months after initiation of therapy.

Secondary Endpoints

- Safety and reactogenicity.
- Immunogenicity.
- Eligibility for, and efficacy, of NUC discontinuation

Table 3: HBsAg reductions (participants with screening HBsAg ≤200 IU/mL & Day 169 follow-up)

	Group 1 (N=7)	Group 2 (N=7)	Group 3 (N=7)	Total (N=21)
≥0.5 log reduction at Day 169	2 (29%)	5 (71%)	6 (86%)	13 (62%)
≥1 log reduction at Day 169	0	5 (71%)	1 (14%)	6 (29%)
Undetectable at Day 169	0	2 (29%)	0	2 (10%)
Discontinued NUCs	1 (14%)	3 (43%)	3 (43%)	7 (33%)
Undetectable at any time	0	3 (43%)	1 (14%)	4 (19%)
<10 IU/mL at Day 169 or later	4 (57%)	5 (71%)	5 (71%)	14 (67%)

- HBsAg declines were observed in all treatment groups; 62% achieved a ≥0.5 log HBsAg reduction, 29% achieved a ≥1 log HBsAg reduction.
- 76% (16 of 21) of participants became eligible for NUC discontinuation; 7 participants discontinued NUCs (across all groups).

- VTP-300 and LD nivolumab treatment was generally well tolerated in all three study regimens with no treatment related SAEs.
- 19% of participants across groups with HBsAg baseline <200 IU/mL and Day 169 visit reached undetectable HBsAg.
- 62% of participants across groups with HBsAg baseline <200 IU/mL and Day 169 visit experienced a ≥0.5 log HBsAg reduction.
- HBsAg reductions were greatest following the administration of study drug on Day 29.
- Robust T cell responses were observed to all encoded antigens.
- These preliminary data support the administration of additional doses of VTP-300 to potentially sustain strong T cell responses to enhance rates of HBsAg loss.
- VTP-300 and LD nivolumab regimen is also being studied after a 24-week lead-in of the siRNA, imdusiran, which reduces HBsAg levels prior to administration of VTP-300 with or without nivolumab (AASLD 2023 Poster LB#5036-C).

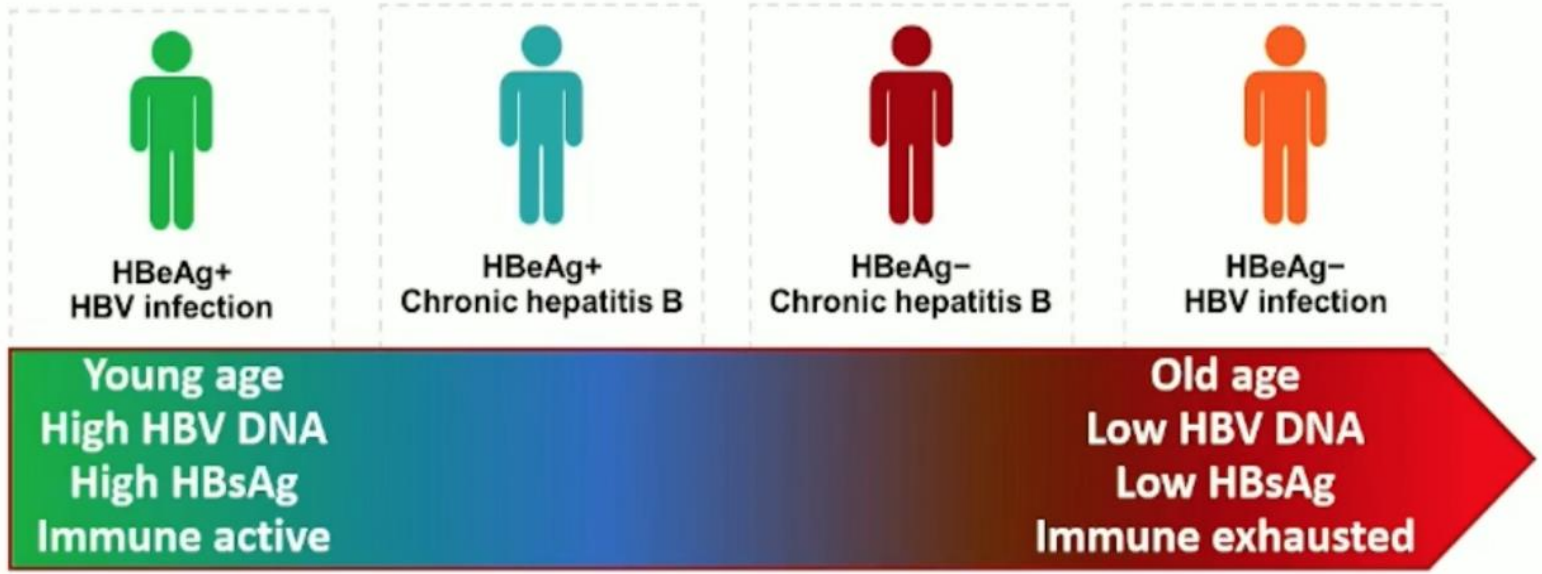
Tait D et al EASL-ILC June 5°-8° 2024 WED-375

Tabella 2 EASL 2024: studi sull'efficacia di HBV siRNA e/o immunostimolatni specifici ed aspecifici

Autore/Studio	Trattamenti	Durata (settimane)	N pazienti	Clearance HBsAg a fine trattamento	Clearance HBsAg al follow-up post-trattamento	Clearance HBsAg post-trattamento HBsAg < 100 UI/mL al basale	Durata follow-up post-trattamento (settimane)	Risposta funzionale parziale post-trattamento (HBsAg < 100 UI/mL)
Tait D[16]	VTP 300 giorno 1 → MVA + bassa dose Nivolumab giorno 29	4	40	NR	0/7	NR	1	4/7 (57%)
	VTP 300 giorno 1 → MVA + bassa dose Nivolumab giorno 29 → MVA + bassa dose Nivolumab giorno 85	12	40	NR	2/7 (29%)	NR	2	5/7 (71%)
	VTP 300 giorno 1 → MVA giorno 29 → bassa dose Nivolumab giorno 36 → MVA giorno 85	12	40	NR	0/7	NR		5/7 (71%)
Agarwal K[14] IM-PROVE II	Imdusiran 60 mg Q8W x 24 sett. → placebo + NUC	48	16	1%	0	NR	24	1
	Imdusiran 60 mg Q8W x 24 sett. → VTP-300 & MVA at w26 e w30 No NUC		20	0	5%	NR		4
Yuen MF[15] IM-PROVE I	Imdusiran 60 mg SC x 6 + NUC + pegIFN 24 sett.	8+24	12	33%	33,3%	NR	24	NR
	Imdusiran 60 mg SC x 4 + NUC + pegIFN 24 sett.		13	23%	15,4%	NR		
	Imdusiran 60 mg SC x 5+ NUC + pegIFN 12 sett.	8+12	8	0	0	NR		
	Imdusiran 60 mg SC x 4 + NUC + pegIFN 12 sett.		10	0	0	NR		
Asselah T[17] OCTOPUS I	NUC + JNJ73763888 200 mg SC Q1w → Q4W + Nivolumab 0,3 mcg/kg ev una volta	24	18	NR	NR	NR	24	72%
	NUC + JNJ73763888 200 mg SC Q1w → Q4W + Nivolumab 0,3 mcg/kg ev una volta		19	NR	NR	NR		84%
Asselah T[13] PIRANGA	Xalnesitran 100 mg SC Q4w	48	30	2/30 (7%)	3/30 (10%) HBsAg < 1000	3 (21%)	48	NR
	Xalnesiran 200 mg SC Q4w		30	1 (3%)	0	0		
	Xalnesiran 200 mg SC Q4w + Ruzotolimod 150 mg QOD sett. 12-24 & 36-48		34	6 (18%)	4 (12%)	4 (24%)		
	Xalnesiran 200 mg SC Q4W + pegIFN alfa 180 mcg QW		30	9 (30%)	5 (17%)	5 (33%)		
	Monoterapia NUC		36	0	1 (3%)	1 (5%)		

NR, non riportato QOD ogni 48 ore; QW e Q1W: una volta la settimana Q4W: una volta ogni 4 settimane Q8W una volta ogni 8 settimane

Combining Novel Therapies: Final Thoughts



- Should we be trying to cure EVERY patient who is **HBsAg positive** regardless of his/her disease phase?

Agent and Mode of Action	Drug(s)	Delivery
Entry inhibitor	Hepcludex (Bulevirtide)	s.c. injection
CAM	Vebicorvir (H0731)[a], JNJ-6379[a], EDP-514, RG7907, ABI-H3733, ALG-000184, AB-836	Oral
Translation inhibitor: siRNA	JNJ-3989 (ARO-HBV), VIR-2218, AB-729, RG6346	s.c. injection
Translation inhibitor: ASO	GSK 3228836, GSK 3389404	s.c. injection
Inhibitor of HBsAg release and subviral particle assembly: NAP	REP-2139[b], REP-2165[b], ALG-10133	i.v. infusion or s.c. injection

Real benefit of functional cure: patients' view

1 pill a day
2 visits / year

pills +/- sc/iv
Weekly-monthly visits for 12 months
Blood tests /Biopsies/FNAs..

HBV

Other than functional cure

Progression and risk factors after treatment with tenofovir or entecavir for chronic hepatitis B based on a multistate modeling approach

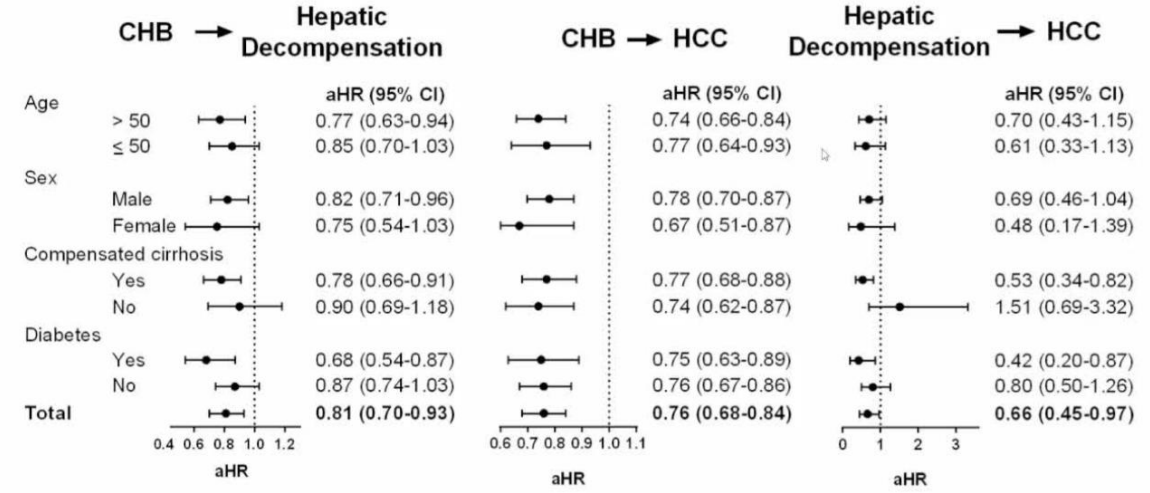
- Study design: Retrospective cohort study
- Study population: Taiwan's National Health Insurance Research Database
  - Administrative claims database covering 99% of Taiwan's population
    - National death certification
    - Cancer registry
    - Registry for catastrophic illness patient
    - Outpatient and in-patient care, prescription drugs and diagnostic codes
- Reimbursement time in Taiwan
  - ETV: 2008, TDF: 2011, TAF: 2019

Baseline Characteristics

	No matching		PSM		IPTW*		
	Tenofovir N=14353	ETV N=33125	Tenofovir N=14353	ETV N=28162	Tenofovir	ETV	Standardized mean difference
Sex, male, N(%)	10290 (71.7)	24549 (74.1)	10290 (71.7)	20548 (73.0)	73.6	73.4	0.00364
Age, y, median(IQR)	46 (38-55)	48 (40-56)	46 (38-55)	47 (39-55)	48.4	48.3	0.00426
Drug duration, y, median(IQR)	2.9 (2.3-4.7)	2.9 (2.5-5.2)	2.9 (2.3-4.7)	2.9 (2.5-5.1)	3.7	4.0	-0.13426
Compensated cirrhosis, N(%)	3086 (21.5)	7989 (24.1)	3086 (21.5)	6218 (22.1)	23.4	23.3	0.00084
Diabetes, N(%)	2893 (20.2)	7755 (23.4)	2893 (20.2)	5803 (20.6)	22.5	22.4	0.00194
Hyperlipidemia, N(%)	4306 (30.0)	11029 (33.3)	4306 (30.0)	8697 (30.9)	32.1	32.5	-0.00782
Hypertension, N(%)	5047 (35.2)	12874 (38.9)	5047 (35.2)	10201 (36.2)	37.8	37.8	0.00057
CVD, N(%)	2294 (16.0)	6080 (18.4)	2294 (16.0)	4609 (16.4)	17.7	17.6	0.00048
COPD, N(%)	3531 (24.6)	8454 (25.5)	3531 (24.6)	6909 (24.5)	25.2	25.2	-0.00019
Metformin, N(%)	1790 (12.5)	4709 (14.2)	1790 (12.5)	3620 (12.9)	13.7	13.7	0.00141
Statins, N(%)	2463 (17.2)	5789 (17.5)	2463 (17.2)	4884 (17.3)	17.5	17.4	0.00238
Aspirin, N(%)	9642 (67.2)	21905 (66.1)	9642 (67.2)	18908 (67.1)	66.4	66.4	-0.00035
NSAIDs, N(%)	12494 (87.1)	28162 (85.0)	12494 (87.1)	24444 (86.8)	85.6	85.6	0.00033
Hepatoprotective, N(%)	11034 (76.9)	25446 (76.8)	11034 (76.9)	21744 (77.2)	76.9	76.9	0.00159
IFN, N(%)	478 (3.3)	674 (2.0)	478 (3.3)	673 (2.4)	2.4	2.4	-0.00037
Excess alcohol use, N(%)	911 (6.4)	2476 (7.5)	911 (6.4)	2015 (7.2)	6.6	7.4	-0.02871

*mean or % in IPTW

Adjusted hazard ratios of tenofovir vs ETV by subgroup analysis



Improvement of liver stiffness during nucleo(s)tide analogue treatment in patients with chronic hepatitis B and advanced fibrosis is not associated with a reduction in hepatocellular carcinoma risk

At on-treatment LSM (n=512)	
Median time between baseline and on-treatment LSM, years	4.5 (3.5 – 7.0)
ALT, U/L	29 (22 – 42)
Undetectable HBV DNA, n (%)	434 (84.7)
LSM, n (%)	
- <6 kPa	196 (38.3)
- 6-9 kPa	156 (30.5)
- >9 kPa	160 (31.3)

Results

- In univariable and multivariable analysis on-treatment LSM was not associated with HCC development (HR 1.01, *p=0.607* and aHR 1.027, *p=0.833*)
- 5-year cumulative HCC incidence comparable across on-treatment LSM strata; 4,7% for <6 kPa, 6.2% for 6-9 kPa and 4.3% for >9 kPa (*p=0.454*, figure 1)

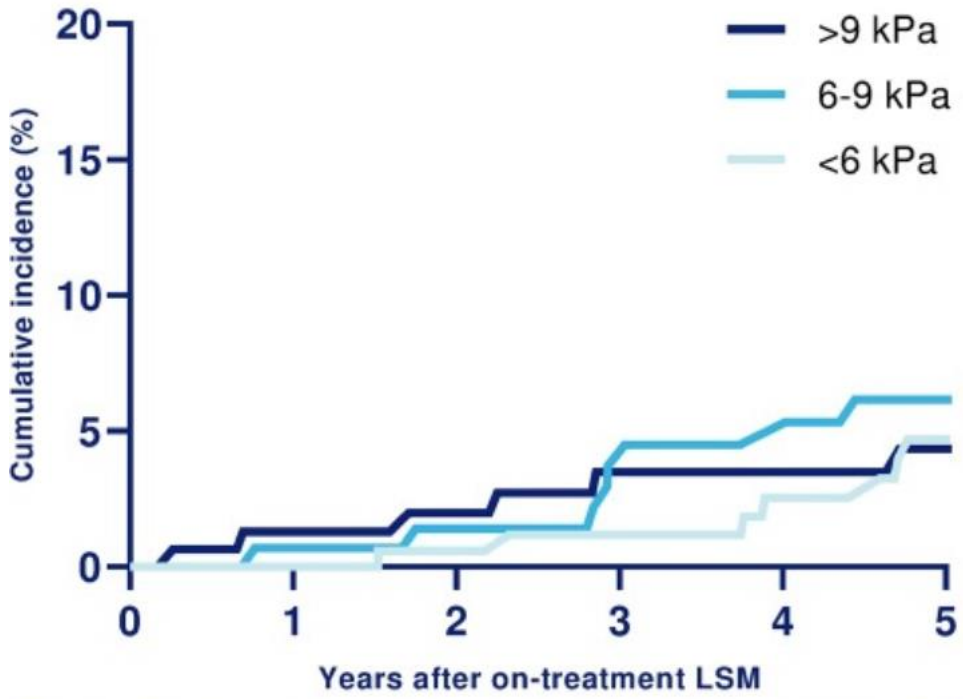


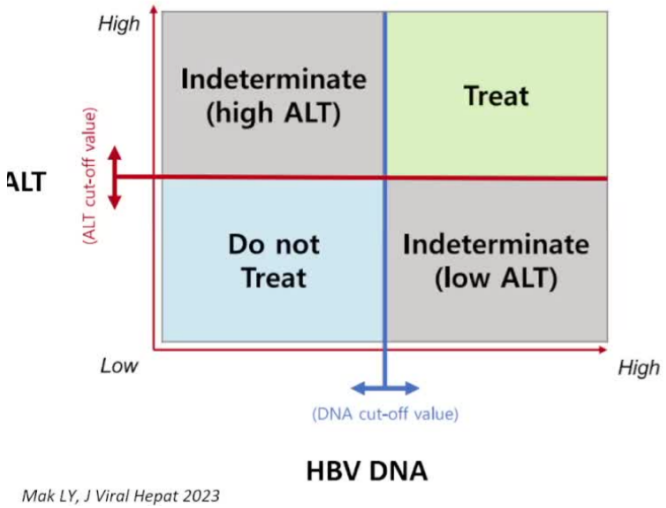
Figure 1. Cumulative HCC incidence across different on-treatment LSM strata

Multinational randomized trial to investigate the efficacy of tenofovir alafenamide in reducing adverse clinical events in chronic hepatitis B patients who are beyond treatment indications by current guidelines (ATTENTION trial): first interim analysis

Societal Guidelines – Defining "Active" CHB

	AASLD	APASL	EASL	WHO
HBeAg+	HBV DNA >20,000 + ALT >2 ULN or Age 40 + ≥F2/A2	HBV DNA >20,000 + ALT >2 ULN or Age 30 + ≥F2/A2 or FH HCC	HBV DNA >20,000 + ALT> ULN or Age 30 or HBV DNA >2000 + ALT >ULN + ≥A2	HBV DNA >2000 + ALT >ULN or ± F2 or greater
HBeAg -	HBV DNA >2000 + ALT >2ULN	HBV DNA >2000 + ALT >2ULN	HBV DNA >2000 + ALT >ULN	
ALT ULN	25 F, 35 M	40 M/F	40 M/F	19 F, 25 M

Grey Zone Issues



Mak LY, J Viral Hepat 2023

ALT

- Related to ULN vs 2XULN
- Concurrent liver diseases not infrequent
- Different definitions for ULN

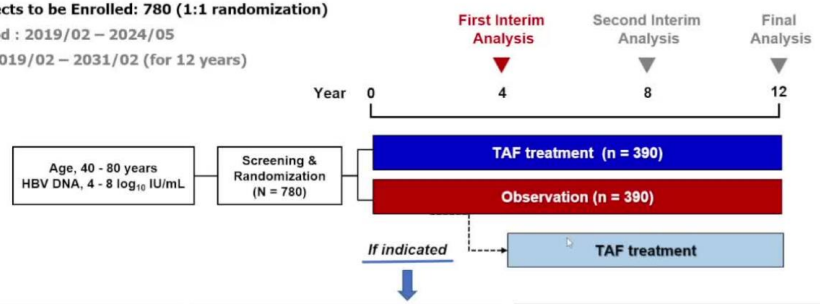
HBV DNA

- >2000 IU/mL and >20,000 IU/mL thresholds are historic (conversion from older non-PCR based assays)

Multinational randomized trial to investigate the efficacy of tenofovir alafenamide in reducing adverse clinical events in chronic hepatitis B patients who are beyond treatment indications by current guidelines (ATTENTION trial): first interim analysis

Study Design

- Randomized controlled open-label trial
- Interactive Web-based response system
- Number of Subjects to be Enrolled: 780 (1:1 randomization)
- Enrollment Period : 2019/02 – 2024/05
- Study period : 2019/02 – 2031/02 (for 12 years)



Key Inclusion criteria
- CHB
- No cirrhosis
- Age, ≥40 and ≤80 years
- HBV DNA, ≥4 and <8 log_{10} IU/mL
- ALT, <70 U/L (males); <50 U/L (females)

Transition to TAF treatment
- ALT, ≥70 U/L (males); ≥50 U/L (females)
- Development of cirrhosis (Fibroscan ≥12 kPa or biopsy)

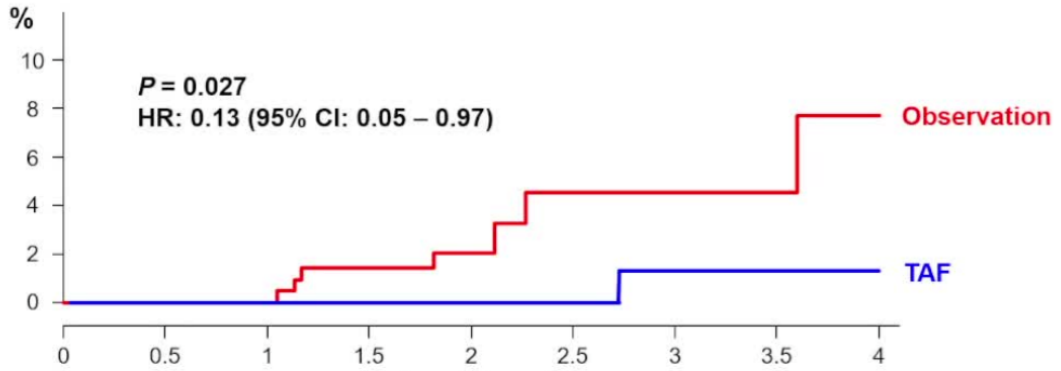
Primary Endpoint
: **Composite clinical events**
HCC, Death, Transplant, Decompensation (Child-Pugh score ≥7, ascites, varices)

Baseline Characteristics

Characteristics	TAF (N = 369)	Observation (N = 365)
Age, years	52 (46 – 60)	54 (47 – 60)
Male, n	169 (45.8%)	172 (47.1)
Family history of HCC	81 (22.0%)	88 (24.1%)
Platelets, × 10^3/μL	208 (177 – 243)	211 (178 – 246)
Albumin, g/dL	4.4 (4.1 – 4.6)	4.3 (4.1 – 4.5)
Total bilirubin, mg/dL	0.7 (0.5 – 0.9)	0.7 (0.5 – 0.9)
ALT, U/L	31 (22 – 40)	31 (23 – 40)
HBeAg-negative, n	305 (82.7%)	302 (82.7%)
HBV DNA, log_{10} IU/mL	4.8 (4.3 – 5.4)	5.0 (4.4 – 5.7)
eGFR, mL/min	93.0 (85.0 – 104.0)	92.5 (84.0 – 102.0)
LSM* by Fibroscan, kPa	5.5 (4.5 – 6.8)	5.2 (4.3 – 6.4)
Alpha-fetoprotein, ng/mL	2.8 (2.0 – 4.0)	2.9 (2.0 – 4.1)
Follow-up period, months	17.7 (11.5 – 24.4)	17.7 (11.4 – 24.4)

Data are presented with median (interquartile range) or number (proportion)
*Normal ALT was defined as ≤25 IU/L for females and ≤35 IU/L for males
LSM, liver stiffness measurement; TAF, tenofovir alafenamide.

Cumulative Incidence of Serious Adverse Events
Excluding the Events Occurred in <1-Year of F/U



Number at Risk									
Observation	250	250	227	173	105	69	52	41	18
TAF	277	277	249	176	106	76	53	35	16

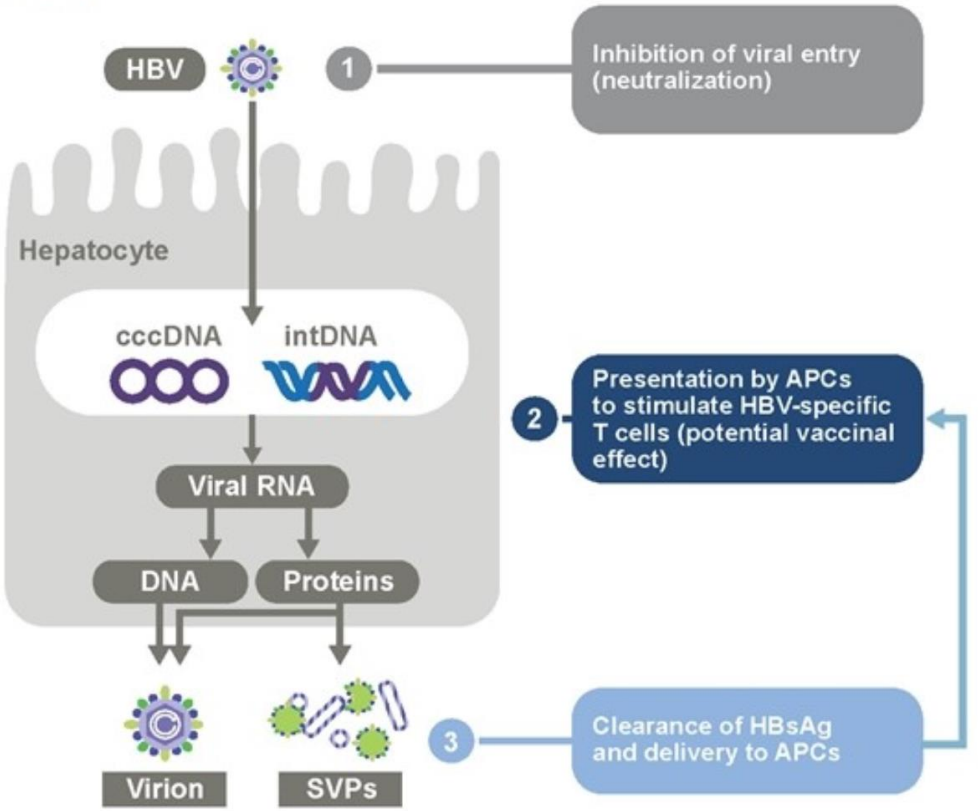
	Event (n)	Follow-Up (PY)	Incidence (per 1,000 PYs)	95% CI
Observation	7	536	13.1	3.4 – 22.7
TAF	1	580	1.7	0 – 5.1
Total	8	1,116	7.2	2.2 – 12.1

-years

Kim LS et al EASL ILC June 5°-8°2024 Id –OS 121

Tobevirbart (VIR-3434), a monoclonal antibody, resistance analysis in participants with chronic HBV: Results from a Phase 1 single dose study

Figure 1. Tobevibart Has Multiple Potential Mechanisms of Action



- All viremic participants from VIR-3434-1002 were successfully sequenced at baseline and at least 1 postbaseline visit
- In Part D, participants were infected with HBV genotypes A, B, C, and D
  - All participants treated with tobevibart experienced HBsAg decline, regardless of genotype[9]
- No treatment-emergent substitutions were identified in the epitope of tobevibart
- All treatment-emergent or -enriched substitutions were unique and were not identified in >1 participant
- In participants treated with tobevibart, 3 binding-site polymorphisms were identified (R122K, K122R, and T118A). Substitutions at position 122 were previously determined to retain susceptibility to tobevibart *in vitro*[10]
- The G145E and C147Y substitutions identified in the tobevibart binding site at AF ~50% in 1 participant in the placebo group resulted in reduced susceptibility to tobevibart *in vitro*
- The G145A substitution identified in 1 participant in the placebo group could not be evaluated due to a reduced infectious titer of pseudotyped virus
- Overall, in this study from a limited number of participants, no emergent resistance was detected in viremic participants treated with a single dose of tobevibart monotherapy

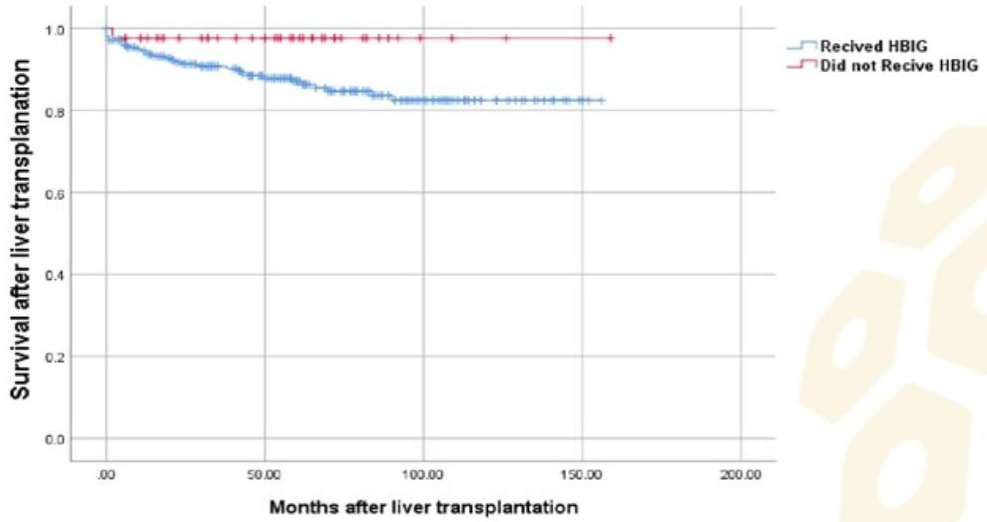
The UK experience of liver transplantation for HBV: excellent clinical outcomes despite a significant burden of HBV/Delta disease and wide variation in hepatitis B immunoglobulin prophylaxis practices – time for a consistent approach?

Table 1 : Patient characteristics of all subjects included in analysis

Characteristics (n=273)	(%)	Median	Range
Age Distribution (Years)			
		51	18-72
Gender Distribution			
Male	79.1% (n=216)		
Female	20.9% (n=57)		
Ethnic Distribution			
White/Other White/ Caucasians	44.7% (n=122)		
Black African/ Caribbean/ Other black	17.6% (n= 48)		
Asian	23.4% (n= 64)		
South Asian	11.7% (n=32)		
Middle Eastren	1.1% (n=3)		
Others	1.5% (n=5)		
Type of Infection			
HBV Monoinfection	68.5% (n=187)		
HBV/HDV Coinfection	23.8% (n= 65)		
HBV/HCV Coinfection	3.7% (n= 10)		
HBV/HIV Coinfection	2.6% (n= 7)		
HBV/HDV/HCV Coinfection	0.7% (n=2)		
HBV/HDV/HIV Coinfection	0.7% (n=2)		
Indications for liver transplant			
Fulminant HBV infection	10.1% (n=28)		
Cirrhosis with HCC	43.6% (n=119)		
Decompensated Cirrhosis	44.7% (n=122)		
Other	1.6% (n=4)		
HBV DNA Pre-transplant (IU/mL)			
Detected	32.2% (n=88)	749	21- 3.2E8
Not Detceted	67.8% (n=185)		
HDV RNA pre-transplant (IU/mL)			
Detected	63.7% (n=44)	5.72E+05	4.70E3-1.25E8
Not Detected	36.3% (n=25)		
UKELD score pre-transplant			
		52	41-77
NUCs post-transplant			
Tenofovir Disoproxil Fumarate (TDF)	49.5% (n=135)		
Entecavir (ETV)	42.8% (n=117)		
Tenofovir Alafenamide (TAF)	1.1% (n=3)		
Lamuvidine +/- Adefovir	6.6% (n=18)		

- All patients with available data (96.3%) had NUCs post-LT and 81% received HBIG post-LT regardless of HBV DNA at the time of LT. However, there was heterogeneity in HBIG doses in the first week (range 0 to 10 HBIG doses) and maintenance dosing following LT (51.8% had maintenance HBIG doses, range 1 week to > 10 years).

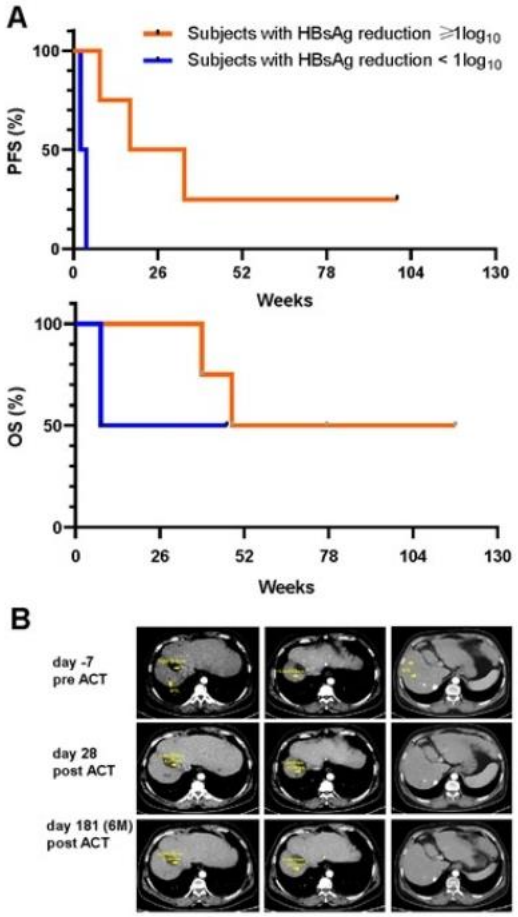
- During a median follow up of 5 years, only 15 patients (5%) had HBV recurrence. Of them, 86.7% (n=13) had high-risk of recurrence pre-LT; 4 had HBV/HDV coinfection, 5 had HCC, and 4 had fulminant HBV. Out of 43 patients (14.4%) who did not receive HBIG post-LT; only 1 patient had HBV recurrence (HBsAg positive at 6 months), and 1 patient died due to non-HBV related graft failure.



Kaplan Meire survival for HBV patients post liver transplantation

First-in-human clinical result of a novel HBV-specific TCR T cell therapy (SCG101) in patients with HBV-related hepatocellular carcinoma (HCC)

8. TUMOR RESPONSE AND SURVIVAL



- The overall response rate for the 6 subjects was 33%.
- Tumor control was observed in all 4 antiviral responders (serum HBsAg reduction ≥ 1 log_{10}), with 2 partial responses (PR) and 2 stable diseases (SD) as per mRECIST.
- Both patients with PR maintained in remission for over 6 months. One had complete remission of the extrahepatic target lesion and remained progression-free for 27 months. The other achieved a durable remission with a target lesion reduction by 74.5% per mRECIST.
- Antiviral responders showed a longer PFS and OS than subjects with a weaker antiviral response (mPFS: 5.9 vs 0.7 months, mOS:19.0 vs 6.3 months).

- Subject ST1206's tumor burden via multiphasic CT scan at days -7 prior to ACT and on days 28, 181 after ACT showed a 74.5% reduction of the size of the target lesions no.1 and no.2 per mRECIST (indicated in yellow).

HBV key messages (other than functional cure)

- Tenofovir/TAF is associated with better long term results than entecavir
- Improvement of liver stiffness during NA is not associated with a decreased risk of HCC
- HBV patients in the guidelines' grey zone should be strongly considered for NUC lifelong treatment
- Anti-HBs Monoclonal antibodies may act as entry inhibitors: beware of genetic viriants (at baseline opr selected during treatment)
- Liver transplant in HBV: good outcome but stndardization on Ig use is required
- TCR T cell therapy vs HBVantigen may be effective in HBsAg+ HCC

HDV

- Virology and natural history
- Bulevirtide monotherapy
- Bulevirtide + PEGIFN
- New treatments

HDV

- Virology and natural history
- Bulevirtide monotherapy
- Bulevirtide + PEGIFN
- New treatments

The concentration of HDV-RNA correlates with the probability of developing clinical events in patients with chronic hepatitis D

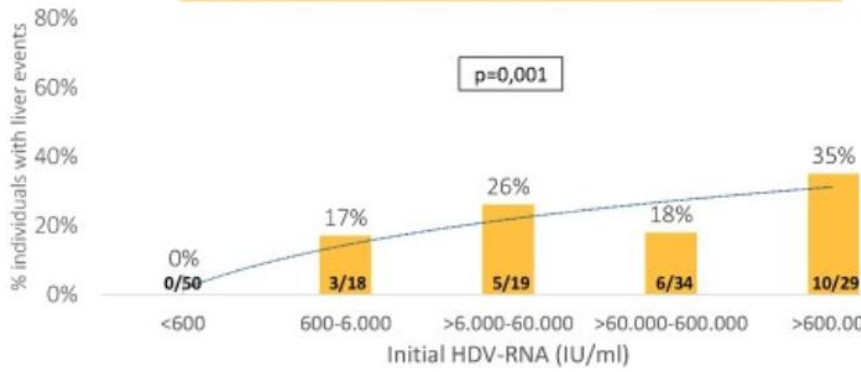
A total of 150 individuals with HBsAg+ and anti-HDV+ were included and monitorized during a median follow-up of 5,5 (2,2-7,3) years. Twenty-four (16%) subjects developed a clinical event during the follow-up.

Baseline characteristics

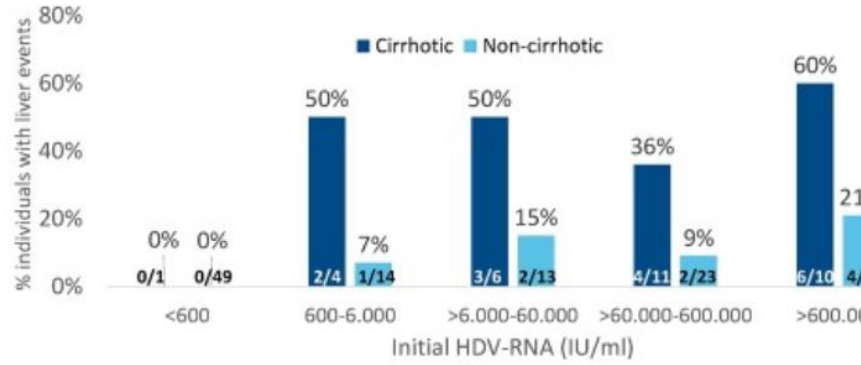
	Total = 150
Age	44 (36-52)
Male	91 (61%)
Caucasian	101 (67%)
ALT (UI/L)	53 (31-96)
Normal ALT (<50 UI/L)	71 (47%)
Anti-HCV+	19 (13%)
Anti-HIV+	7 (5%)
Liver cirrhosis	32 (21%)
HDV-RNA (IU/ml)	
<600*	50 (33%)
600-6.000	18 (12%)
>6.000-60.000	19 (13%)
>60.000-600.000	34 (23%)
>600.000	29 (19%)

Quantitative variables are expressed as md(IQR), and qualitative variables are expressed as n(%)

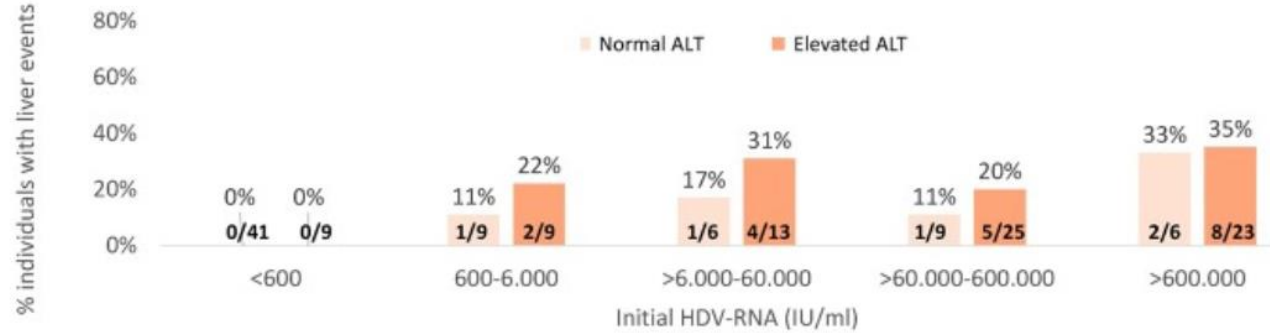
Impact of HDV-RNA levels in liver-related outcomes



Impact of HDV-RNA levels according to presence/absence of cirrho



Liver-related outcomes according to ALT and HDV-RNA levels



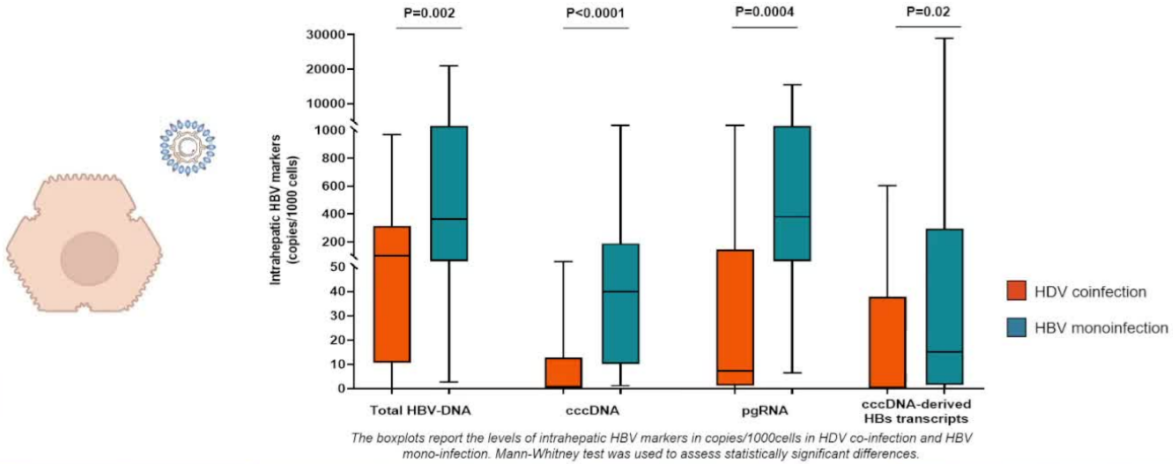
Palom A et al EASL-ILC June 5°-8°2024 FRI-432

Chronic HDV infection is sustained by an intense HBsAg production from integrated HBV-DNA in the setting of a limited or even absent HBV reservoir

By comparing **intrahepatic HBV markers between the two groups…**

➢ **HDV co-infection** was associated with a **significantly lower size of HBV reservoir…**

…and with a more limited transcriptional activity of HBV reservoir



The boxplots report the levels of intrahepatic HBV markers in copies/1000cells in HDV co-infection and HBV mono-infection. Mann-Whitney test was used to assess statistically significant differences.

By analysing **intrahepatic HBV markers in these two subgroups of HDV-coinfected individuals:**

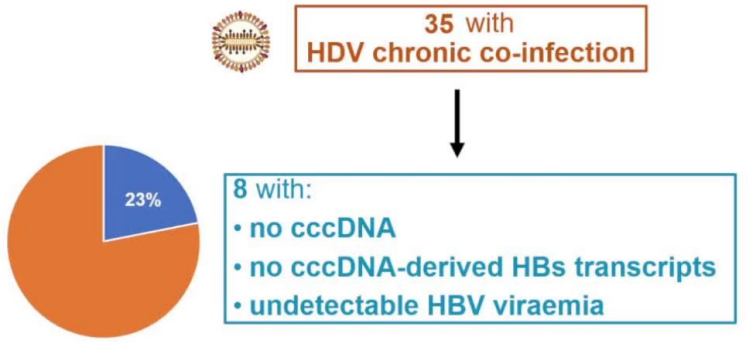
➢ A lower cccDNA pool correlated with **lower levels of all intrahepatic HBV markers**

➢ Conversely, **HDV-RNA** levels were **comparable** independently from cccDNA size…

Intrahepatic markers, median (IQR) copies/1000cells	cccDNA <1 copy/1000cells N=19	cccDNA >1 copy/1000cells N=16	P-value
Total HBV-DNA	30 (1 – 73)	247 (158 – 406)	<0.001
HBV pgRNA	1.4 (0.4 – 25)	89 (6 – 238)	0.005
cccDNA	0.02 (0 – 0.1)	15 (5 – 32)	<0.0001
cccDNA-derived HBs transcripts	0.3 (0.1 – 0.9)	41 (7 – 179)	0.001
Integrated-derived HBs transcripts	432 (3 – 7748)	19,312 (5476 – 42,448)	0.003
HDV-RNA	782 (1 – 5,559)	1026 (40 – 6,984)	0.5

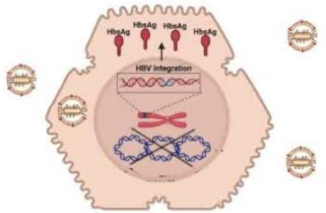
Even more, it is interesting to note that…

among individuals with HDV chronic coinfection, **8 (23%) had undetectable levels of cccDNA, cccDNA-derived HBs transcripts and serum HBV-DNA**



Remarkably, despite no evidence of HBV reservoir, an **intensive HDV activity** was revealed **at both serum and intrahepatic levels** in these individuals, coupled to the presence of **integrated HBV DNA-derived HBs transcripts**

Variables	N=8
Serum HDV-RNA, median (IQR) log IU/ml	6.0 (5.9 – 7.3)
Intrahepatic HDV-RNA, median (IQR) copies/1000cells	5,495 (976 – 14,946)
Integrated HBV DNA-derived HBs transcripts, median (IQR) copies/1000cellls	3 (1 – 497)



…supporting that **HDV replication can persist independently of HBV reservoir**, sustained by **HBV integration**

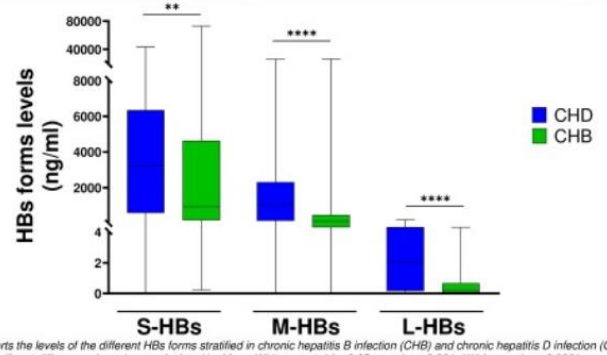
Chronic HDV coinfection (CHD) is characterized by a more elevated production of Middle and Large HBsAg than HBV mono-infection, that parallels HDV replicative and cytolytic activity

No differences are observed between CHD and CHB patients in demographic with the exception for HBV-DNA, total HBsAg and ALT levels

	Chronic Hepatitis D (N=145)	Chronic Hepatitis B (N=130)	P-value
Male, *N (%)*	92 (63.4)	85 (65.4)	0.801
Age, *median years (IQR)*	53 (43-60)	50 (49-63)	0.299
NUC treatment naïve, *N (%)*	50 (37.6)	40 (34.8)	0.523
HDV RNA, *median log IU/mL (IQR)*	5.1 (3.4-6.1)	-	-
HBV DNA, *median log IU/mL (IQR)*	1.3 (0.0-2.3)	2.5 (1.3-3.5)	<0.0001
Total HBsAg, *median IU/mL (IQR)*	5181 (817-8544)	1145 (206-5269)	<0.0001
ALT, *median U/l (IQR)*	79 (50-114)	30 (20-53)	<0.0001

The table reports the characteristics of the study population stratified according to the HDV coinfection status. Statistically significant differences have been assessed by Mann-Whitney or Chi-squared test according to the king of data.

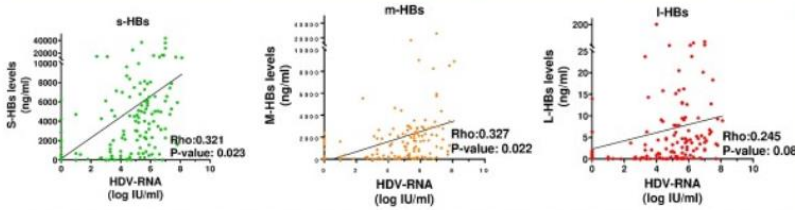
HBs forms composition varies between CHD and CHB with remarkably higher M-HBs and L-HBs in CHD despite similar S-HBs levels in the two groups



*The graph reports the levels of the different HBs forms stratified in chronic hepatitis B infection (CHB) and chronic hepatitis D infection (CHD). Statistically significant differences have been calculated by Mann-Whitney test. * for 0.05> p-value >0.001, **** for p-value >0.0001.*

Multivariable analysis confirms CHD as an independent factor associated with higher levels of M-HBs and L-HBs (OR [95%CI]: 4.7 [1.7-12-4] and 6.2 [2.2-17.9], P<0.002 for both)

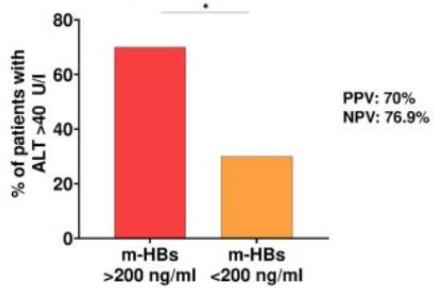
Among CHD, the HBs forms positively correlate with HDV-RNA levels while, in CHB, milder correlation with HBV DNA levels is observed only for L-HBs



The graphs report the correlations of the different HBs forms with HDV-RNA viral load. The correlations have been evaluated by the Pearson correlation coefficient calculation.

Furthermore, patients with highly-replicating HDV (HDV-RNA >3 logIU/ml) show significantly higher levels of all HBs forms than lowly-replicating HDV (median [IQR] ng/ml: 4431 [1251-6950] vs 274 [25-2640] for S-HBs; 1404 [191-2484] vs 127 [4-1242] for M-HBs; 3.3 [0.2-7.8] vs 0.3 [0.04-1.1] for L-HBs, P<0.001 for all)

Focusing on lowly-replicating HDV patients (HDV-RNA <3 logIU/ml), 43.5% have altered ALT (median [IQR]: 75 [55-93] U/L). Notably, in this set of patients, M-HBs >200 ng/ml is the best cut-off predicting altered ALT supporting the role of M-HBs in reflecting cytolytic activity in the setting of low HDV replication.



*The graph reports the percentage of patients with ALT >40 U/l in the two subsets of patients stratified according the levels of m-HBs higher or lower than 200ng/ml. Statistically significance have been calculated by Chi-squared test. * for 0.05> p-value >0.001. PPV: positive predictive value; NPV: negative predictive value.*

Conclusions

- The composition of HBs forms varies in CHD and CHB patients, with CHD characterized by more elevated M-HBs and L-HBs production paralleling HDV replicative activity.
- This could reflect a variation in the proportion of circulating viral and subviral particles between CHD and CHB.
- Overall, HBs forms can play a role in identifying patients more prone to liver disease progression, in whom treatment could be prioritized.

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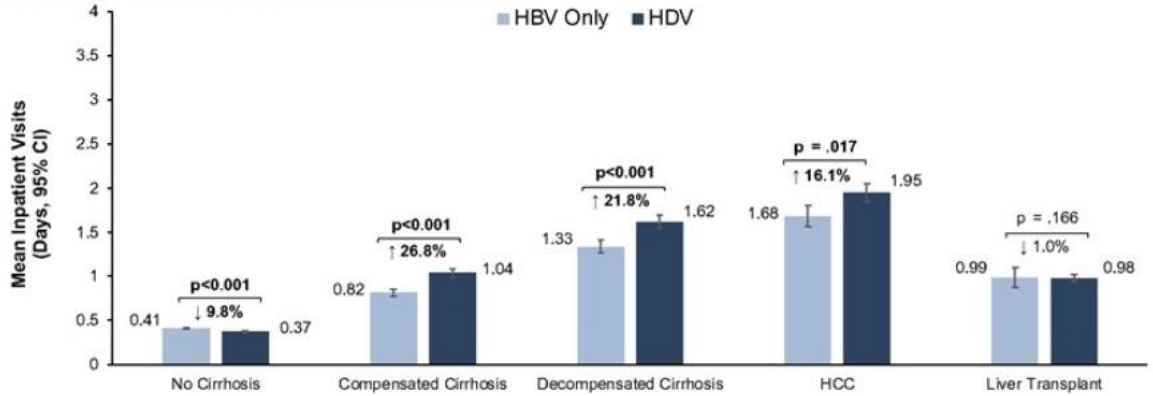
Healthcare resource utilisation and costs of hepatitis delta virus infection vs hepatitis B virus monoinfection across disease states among hospitalised adults in Italy

Table 2. Mean Time Spent in Disease State

	HBV Only	HDV	p value
No cirrhosis	66.0 (65.1–66.9)	70.7 (69.7–71.7)	0.062
Compensated cirrhosis	43.9 (41.8–46.0)	39.2 (37.4–40.9)	0.530
Decompensated cirrhosis	31.5 (29.6–33.4)	25.5 (23.9–27.0)	0.317
HCC	24.7 (22.2–27.3)	19.7 (18.2–21.3)	0.537
Liver transplant	62.8 (56.3–69.2)	61.8 (59.4–64.1)	0.996

Data are reported as mean (95% CI) number of months.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus.

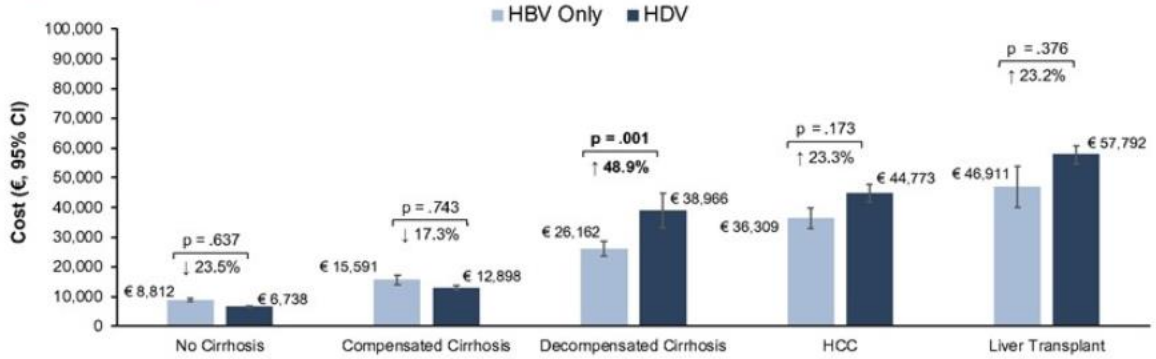
Figure 4. Mean IPTW Inpatient Visits PPPY



Bold p values indicate statistical significance.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; IPTW, inverse probability of treatment weighting; PPPY, per-patient-per-year.

- The mean number of inpatient visits PPPY was significantly greater for inpatients with HDV vs HBV among those with compensated cirrhosis, decompensated cirrhosis, and HCC

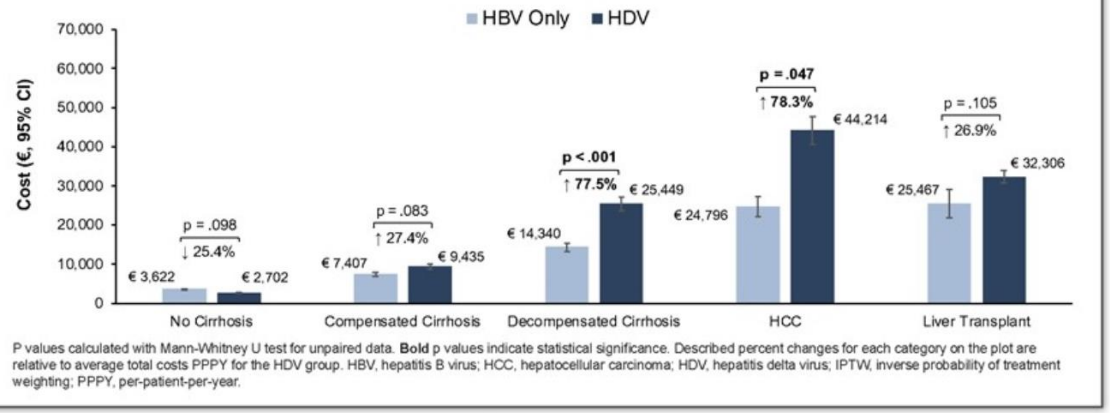
Figure 5. Average IPTW All-Cause Total Costs PPPY



P values calculated with Mann-Whitney U test for unpaired data. **Bold** p values indicate statistical significance. Described percent changes for each category on the plot are relative to average total costs PPPY for the HDV group. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; IPTW, inverse probability of treatment weighting; PPPY, per-patient-per-year.

- Total costs PPPY were significantly higher in patients with decompensated cirrhosis in patients with HDV vs HBV only
- The largest difference in all-cause total healthcare costs was in the HDV vs HBV-only group with decompensated cirrhosis, for which a difference of 48.9% in total cost was observed (p = .001)

Figure 6. Average IPTW Inpatient Costs PPPY



P values calculated with Mann-Whitney U test for unpaired data. **Bold** p values indicate statistical significance. Described percent changes for each category on the plot are relative to average total costs PPPY for the HDV group. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; IPTW, inverse probability of treatment weighting; PPPY, per-patient-per-year.

- Inpatient costs PPPY in patients with HDV were significantly higher compared to patients with HBV only when stratified by decompensated cirrhosis and HCC
- The largest numerical difference in average inpatient costs between the HDV and HBV-only groups was within HCC, with an average increase of inpatients costs of € 19,418

Lampertico P et al EASL ILC June 5°-8°2024 FRI-393

Unique characteristics and risk of liver-related events among individuals with hepatitis D virus infection with and without concurrent hepatitis C virus infection: a United States administrative claims analysis

Table 1. Demographics and Baseline Liver and Medication Characteristics

	Full HBV/HDV Cohort	
HBV/HDV Cohort	HBV/HDV n = 6,747	HBV/HDV/HCV n = 2,885
Patient sex		
Male	2,988 (44.3)	1,772 (61.4)
Female	3,759 (55.7)	1,113 (38.6)
Age at index date		
18 to <35	1,064 (15.8)	238 (8.2)
35 to <45	1,189 (17.6)	416 (14.4)
45 to <55	1,497 (22.2)	660 (22.9)
55 to <65	1,732 (25.7)	970 (33.6)
≥65	1,263 (18.7)	601 (20.8)
Missing	2 (<0.01)	0 (0.0)
Baseline liver status		
CC	481 (7.1)	1,112 (38.5)
DC	364 (5.4)	755 (26.2)
HCC	117 (1.7)	221 (7.7)
LTx	47 (0.7)	107 (3.7)
Portal hypertension	162 (2.4)	463 (16.0)
End-stage liver disease	159 (2.4)	427 (14.8)
Baseline medications		
Interferon	1 (<0.01)	16 (0.6)
NAs	1,341 (19.9)	943 (32.7)
HCV DAA treatment ever	n/a	726 (25.2)
Follow-up time, days		
Median (Q1, Q3)	820 (406, 1,382)	691 (316, 1,236)
Min, max	1, 2,544	1, 2,546
Mean (SD)	933.7 (626.5)	836.4 (632.5)

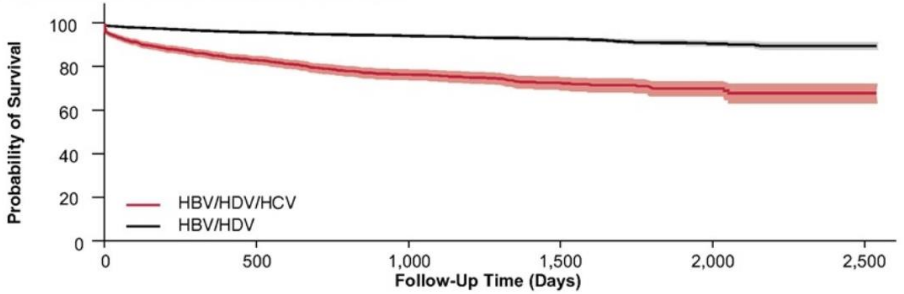
Values in table reflect n (%) unless otherwise noted. All differences between "HBV/HDV" and "HBV/HDV/HCV" were significant at p <0.05 except for age 45 to <55 (p = 0.47) and age missing (p = 0.88). Unless otherwise indicated, liver conditions and medication use were identified through diagnosis and dispensing claims at any point prior to index date. The conditions listed in Table 1 are not mutually exclusive.
CC, compensated cirrhosis; DAA, direct-acting antiviral; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; LTx, liver transplant; n/a, not applicable; NA, nucleos(t)ide analogue; Q, quartile.

Table 3. Risk of Developing LREs in Patients With HBV/HDV/HCV vs HBV/HDV

Analysis	Cohort	Persons, n	Events, n	Person-Years	PS-Weighted HR (95% CI)
Risk of cirrhosis among individuals with no evidence of CC, DC, HCC, or LTx at baseline	HBV/HDV	5,370	168	13,650	1.00[a]
	HBV/HDV/HCV	1,512	239	3,202	4.03 (3.19–5.09)
Risk of any LRE[b] among individuals with no evidence of CC, DC, HCC, or LTx at baseline	HBV/HDV	5,737	314	14,359	1.00[a]
	HBV/HDV/HCV	1,587	327	3,227	3.22 (2.68–3.86)
Risk of DC, HCC, or LTx among individuals with CC at baseline	HBV/HDV	156	23	385	1.00[a]
	HBV/HDV/HCV	288	92	565	2.39 (1.29–4.43)

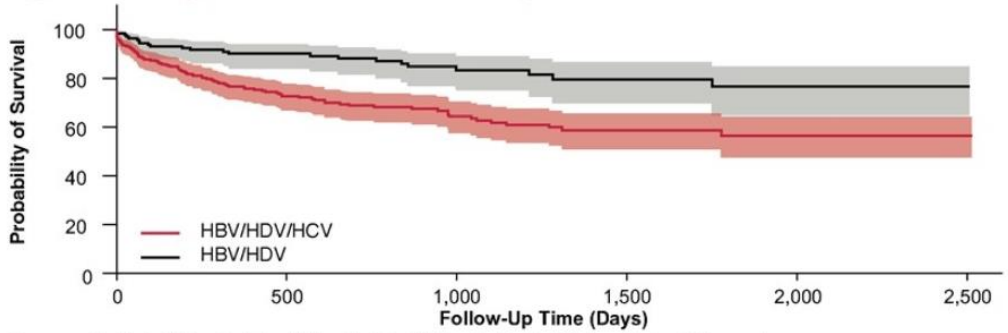
[a]No HCV. [b]Any LRE includes CC, DC, HCC, and LTx.
CC, compensated cirrhosis; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; HR, hazard ratio; LRE, liver-related event; LTx, liver transplant; PS, propensity score.

Figure 3. PS-Weighted LRE-Free Survival



HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; LRE, liver-related event; PS, propensity score.

Figure 4. PS-Weighted LRE-Free Survival Among Individuals With CC at Baseline



CC, compensated cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; LRE, liver-related event; PS, propensity score.

HDV

- Virology and natural history
- Bulevirtide monotherapy
- Bulevirtide + PEGIFN
- New treatments

The NEW ENGLAND JOURNAL of MEDICINE

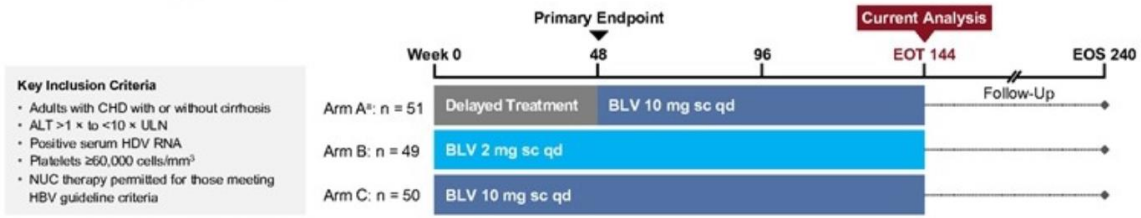
ORIGINAL ARTICLE

A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

H. Wedemeyer, S. Aleman, M.R. Brunetto, A. Blank, P. Andreone, P. Bogomolov, V. Chulanov, N. Mamonova, N. Geyvandova, V. Morozov, O. Sagalova, T. Stepanova, A. Berger, D. Manuilov, V. Suri, Q. An, B. Da, J. Flaherty, A. Osinusi, Y. Liu, U. Merle, J.S.. Wiesch, S. Zeuzem, S. Ciesek, M. Cornberg, and P. Lampertico, for the MYR 301 Study Group*

Efficacy and safety of 144 weeks of bulevirtide 2 mg or 10 mg monotherapy from the ongoing Phase 3 study, MYR301

MYR301 Study Design



[a]One patient discontinued the study prior to receiving BLV; therefore, n = 50 was used for all arm A efficacy results, with baseline reset at the week 48 visit, and efficacy presented by BLV duration (not including the delayed treatment period).
BLV, bulevirtide; EOS, end of study; EOT, end of treatment; NUC, nucleos(t)ide analogue; qd, once daily; sc, subcutaneous.

Baseline Demographics and Disease Characteristics

	BLV 2 mg (n = 49)	BLV 10 mg (n = 50)	Delayed Treatment to BLV 10 mg (n = 51)
Age, years, mean (SD)	44 (9)	41 (9)	41 (8)
Male sex, n (%)	30 (61)	30 (60)	26 (51)
Race,[a] n (%)			
White	41 (84)	43 (86)	40 (78)
Asian	8 (16)	6 (12)	11 (22)
Cirrhosis present, n (%)	23 (47)	24 (48)	24 (47)
Liver stiffness, kPa, mean (SD)	14.0 (8.2)	14.8 (9.3)	15.3 (9.0)
ALT, U/L, mean (SD)	108 (63)	123 (81)	102 (62)
HDV RNA, log_{10} IU/mL, mean (SD)	5.10 (1.20)	4.96 (1.46)	5.08 (1.36)
Genotype HDV-1,[b] n (%)	49 (100)	48 (96)	51 (100)
HBsAg, log_{10} IU/mL, mean (SD)	3.67 (0.52)	3.61 (0.59)	3.68 (0.47)
HBV DNA, log_{10} IU/mL, mean (SD)	1.30 (1.29)	1.08 (1.26)	0.89 (0.99)
HBV genotype, n (%)			
A	2 (4)	2 (4)	2 (4)
D	47 (96)	44 (88)	44 (86)
Other[c]/missing	0	4 (8)	5 (10)
Previous IFN therapy, n (%)	26 (53)	29 (58)	29 (57)
Concomitant HBV NUC treatment,[d] n (%)	32 (65)	27 (54)	32 (63)

[a]BLV 10 mg arm: Black, n = 1. [b]BLV 10 mg arm: HDV GT 5, n = 1; missing HDV GT, n = 1. [c]BLV 10 mg arm: HBV GT E, n = 1; delayed treatment to BLV 10 mg arm: unclassified HBV GT, n = 2. [d]All patients who started NUC therapy at or post BL, except 1, started at BL or within 2 days of BL.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; GT, genotype; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NUC, nucleos(t)ide analogue; W, week.

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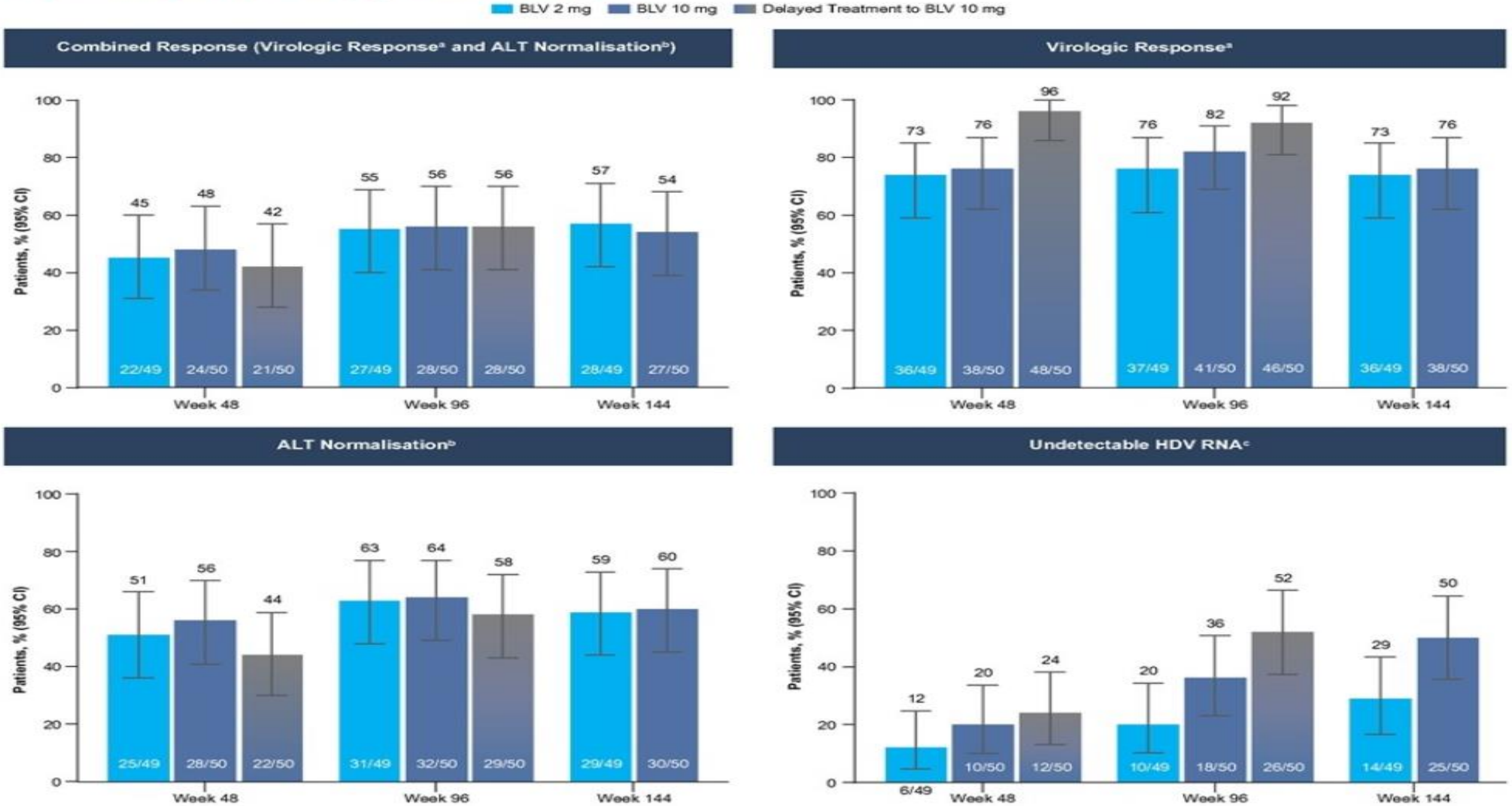
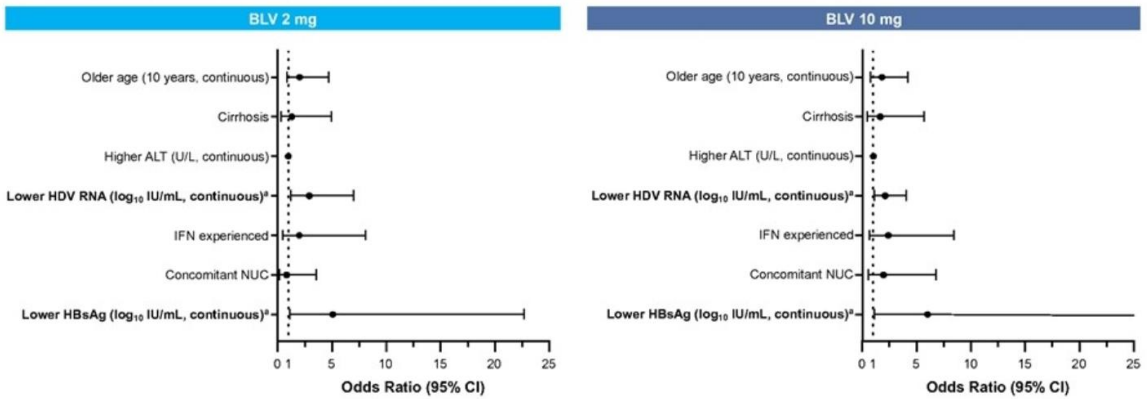
Key Efficacy Over Time (by BLV Duration)



Patients with missing values were considered nonresponders. [a]Undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from BL. [b]ALT normalisation was defined at Russian sites as ≤31 U/L for females and ≤41 U/L for males, and at all other sites as ≤34 U/L for females and ≤49 U/L for males. [c]Undetectable HDV RNA was defined as <LLOQ (50 IU/mL; target not detected).

Baseline Predictors of Undetectable HDV RNA at W144



[a]p <0.05. The upper CI boundary for lower HBsAg with BLV 10 mg (32) is not shown due to the figure scale. The analysis population included patients who completed W144 with BL HDV RNA ≥250 IU/mL.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; IFN, interferon; NUC, nucleos(t)ide analogue; W, week.

- Lower HDV RNA and hepatitis B surface antigen (HBsAg) levels at BL were identified as potential predictors of undetectable HDV RNA at W144

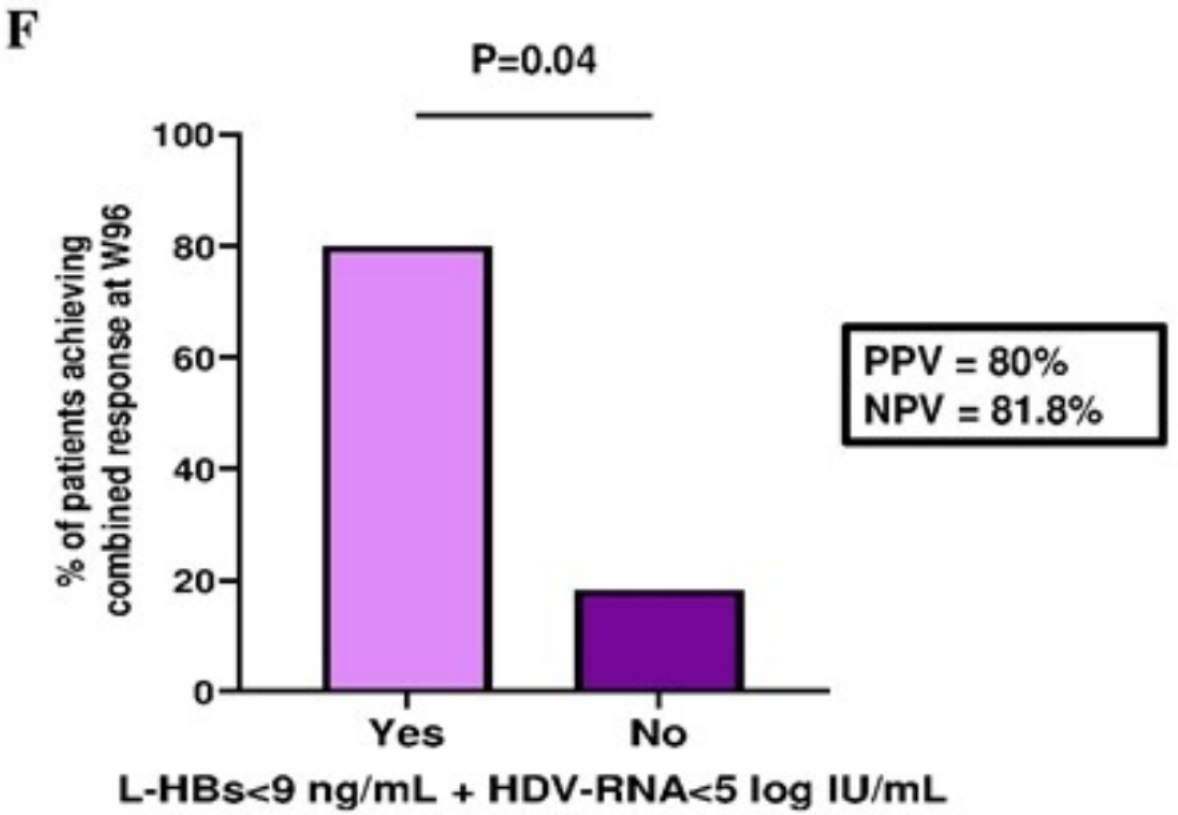
Platelet Count, Liver Chemistries, and Other Efficacy Markers Over Time

	BLV 2 mg (n = 49)			BLV 10 mg (n = 50)		
	BL	Week 96	Week 144	BL	Week 96	Week 144
Platelets, × 10^9/L, mean (SD)	153 (52.5)	169 (69.1)	162 (62.5)	160 (53.1)	174 (70.7)	163 (63.5)
Platelets <90 × 10^9/L, %	14	13	14	12	11	14
Total bilirubin, µmol/L, median (Q1, Q3)	10.4 (6.7, 14.7)	12.7 (7.5, 15.9)	13.6 (8.6, 19.0)	10.5 (7.6, 13.6)	10.2 (7.5, 14.5)	11.8 (7.2, 15.0)
Albumin, g/L, mean (SD)	44 (3.1)	45 (2.6)	47 (2.9)	44 (3.2)	45 (3.2)	46 (3.3)
Albumin <35 g/L, %	0	0	0	2	2	0
GGT, U/L, median (Q1, Q3)	57 (27, 73)	27 (18, 37)	25 (18, 37)	42 (27, 73)	24 (17, 36)	23 (19, 39)
INR, mean (SD)	1.12 (0.111)	1.10 (0.116)	1.12 (0.145)	1.14 (0.112)	1.10 (0.129)	1.14 (0.222)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.67 (0.515)	3.47 (0.578)	3.29 (0.866)	3.61 (0.593)	3.47 (0.638)	3.41 (0.583)
Liver Stiffness, kPa, mean (SD)	13.99 (8.190)	10.2 (6.434)	9.43 (5.281)	14.81 (9.265)	10.04 (6.754)	11.28 (9.836)
Liver stiffness >15 kPa, %	31	15	11	30	15	19

Values are based on available data.
BL, baseline; BLV, bulevirtide; GGT, gamma-glutamyl transferase; HBsAg, hepatitis B surface antigen; INR, international normalised ratio; LS, least square; n/a, not applicable; Q, quartile.

The composition of HBsAg along with HDV-RNA predicts virological response in chronic hepatitis delta patients treated with bulevirtide for 48 weeks

- 36 consecutive patients with HDV-related compensated cirrhosis starting BLV monotherapy 2mg/day were enrolled in this single centre retrospective/longitudinal study.
- All patients were under effective NUC treatment at study entry.
- L-HBs, M-HBs and S-HBs were quantified by ad hoc ELISAs (Beacle Inc.) at baseline and at week 48 (W48) for all patients and at week 96 (W96) for a subset of 16 patients.
- Virological response to BLV was defined as HDV-RNA undetectable or >2log decline compared to baseline, biochemical response as ALT normalization, while combined response as the achievement of both virological and biochemical responses.



Bulevirtide monotherapy prevents liver decompensation and reduces mortality in patients with HDV-related cirrhosis: a case control study with propensity score weighted analysis

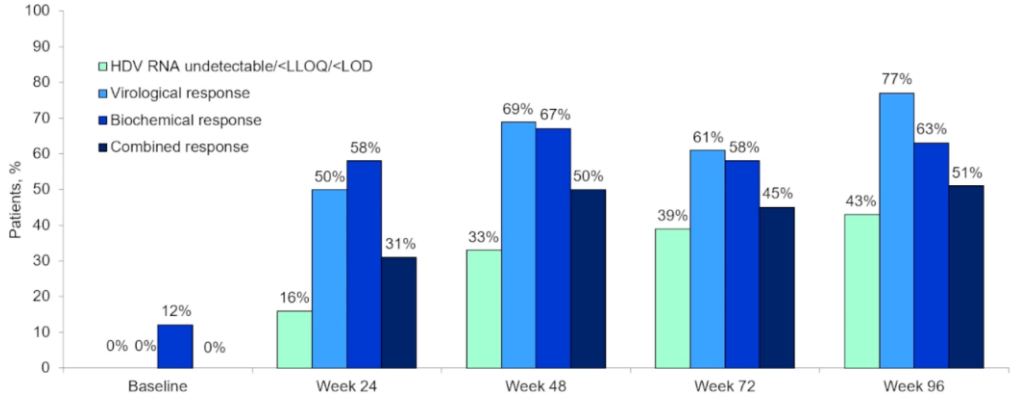
Baseline Features of the Study Cohorts

Variables	Untreated (n=140)	BLV-Treated (n=176)	p value
Age, years	40 (34-49)	49 (39-59)	**<0.0001**
Males	109 (78%)	104 (59%)	**0.0004**
Caucasians	136 (97%)	161 (91%)	**0.04**
CPT score A	140 (100%)	176 (100%)	1.00
- A6	22 (16%)	54 (31%)	**<0.0001**
Previous LRE	5 (4%)	35 (20%)	**<0.0001**
- HCC	-	12 (7%)	
- Decompensation	5 (4%)	23 (13%)	
Esophageal varices*	64 (46%)	65 (55%)	0.13
IFN-experienced	56 (40%)	103 (59%)	**0.001**
ALT, U/L	102 (57-176)	77 (53-127)	**0.03**
Bilirubin, mg/dL	0.9 (0.7-1.4)	1.0 (0.7-1.4)	0.40
Albumin, g/dL	3.9 (3.6-4.3)	4.0 (3.7-4.4)	0.08
HBsAg, LogIU/mL	pos	3.7 (3.3-4.1)	na
HBeAg negative	132 (94%)	164 (93%)	0.82
HBV DNA undetectable/low**	109 (78%)	143 (81%)	0.48
HDV RNA, LogIU/mL	pos	5.4 (4.1-6.4)	na

Values are expressed as number (percentage) or median (IQR); *available in 118/176 patients in the BLV-treated cohort; **<2000 copies/mL
BLV-Treated Cohort: PLT 89 (66-133)x10^3/mm^3, Liver Stiffness Measurement 18.4 (13.0-26.3) kPa; 92% NUC-treated

BLV: Bulevirtide; CPT: Child-Pugh Turcotte; LRE: Liver-related Event; HCC: Hepatocellular Carcinoma; IFN: Interferon; ALT: Alanine Aminotransferase; PLT: Platelets; NUC: Nucleos(t)id analogue; HBV: Hepatitis B Virus; HDV: Hepatitis Delta Virus

Effectiveness of BLV Treatment Up to 96 Weeks (Treated Cohort)



BLV Treatment Effect on Liver-related Events IPTW-Adjusted Analysis

Outcomes	Category	Unadjusted Cox Regression Analysis		IPTW-Adjusted Cox Regression Analysis		IPTW-Adjusted Competing Risks Regression Model	
		HR (95% CI)	p value	HR (95% CI)	p value	SHR (95% CI)	p value
Liver-related Events	Treated vs. Untreated	0.52 (0.25-1.05)	0.07	0.38 (0.23-0.62)	**<0.0001**	0.38 (0.23-0.61)	**<0.0001**
Decompensation	Treated vs. Untreated	0.48 (0.18-1.28)	0.14	0.32 (0.16-0.63)	**0.001**	0.32 (0.17-0.61)	**0.001**
De-novo HCC	Treated vs. Untreated	0.57 (0.20-1.62)	0.29	0.50 (0.24-1.06)	0.07	0.50 (0.24-1.04)	0.06

Total Events: Untreated n=21; BLV-Treated: n=12

IPTW-Adjusted Cox Regression Analysis results confirmed in the CPT-A subclasses
IPTW analysis covariates: age, gender, varices, ALT, albumin

BLV: Bulevirtide; IPTW: Inverse Probability of Treatment Weighting; HR: Hazard Ratio; SHR: Sub-distribution Hazard Ratio; CI: Confidence Interval; HCC: Hepatocellular Carcinoma; ALT: alanine aminotransferase

Bulevirtide efficacy and safety in chronic hepatitis delta patients on liver transplant waiting list

Table 1: Baseline characteristics of included patients (n=20)

Characteristics	Total (n=20)
Age, mean (range), years	52.8 (9.98)
Sex	
Male No. (%)	15 (75)
Liver disease (No. %)	
Refractory ascites	1 (5%)
Active Hepatocellular Carcinoma (HCC)	8 (40%)
BCLC stage O	4 (50%)
BCLC stage A	1 (12.5%)
BCLC stage B	3 (37.5%)
LSM KPa «	24.16 (10-58)
Large esophageal varices (grade II-III)	11 (57,89)
CHILD-PUGH score	
A(5-6 points)	14 (70%)
B(7 points)	1 (5%)
C(10-15 points)	5(25%)
MELD score median(min-max)	9 (6-32)
ETV or TDF treatment	18 (90%)
Laboratory tests on baseline	
Albumin, g/L	34.3 (29-39.8)
Platelet count 10^3/mmolL	94 (50.2-285.5)
Creatinin mmol/L	69.01 (51.5-84.5)
AST, U/L	78 (65.5-125)
ALT, U/L	91 (60-135.5)
Bilirubin ,mmol/l	24.7 (10-444)
Protrombin time %	78 (26-100)
HBsAg, IU/ml	4171 (1620-4908.5)
HBeAg negative	18 (90%)
HBV DNA detectable (range 12-4620 UI/ml)	5 (25%)
HDV RNA, Log IU/ml	5.98 (2.23-10)

Table 2: Progression of viral parameters for included patients

	Baseline N=20	Week 24 N=17	Weak 48 N=15	At LT N=12
HDV RNA, Log IU/ml	5.98 (2.23-10)	4.53(0.15-10)	2 (0.1-7.5)	3.11 (0,1-6.37)
HDV RNA decline >−2 Log IU/ml	-	7 (41,18%)	11 (73,33%)	4 (33,33%)
HDV RNA undetectable	0	3 (18,7%)	8 (53,33%)	3 (37,5%)
HDV RNA decline <1 log/ml	-	4 (23.53%)	3 (6,25%)	4 (33,33%)
HBV DNA undetectable	15 (75%)	14 (82,35%)	14 (93,3%)	11 (91,6%)
HBs Ag UI/ml	4171 (1620-4908.5)	4700 (2519-8580)	2629 (111-12854.81)	2186 (200-5976)
Virological response		**7 (41,18%)**	**11 (73,33%)**	**4 (33,33%)**

Table 3: Progression of clinical and biochemical parameters for included patients

	Baseline N=20	Week 24 N=17	Weak 48 N=15	At LT N=12
CHILD-PUGH score				
A(5-6 points)	14(70%)	11(64,7%)	12 (80%)	6 (50%)
B(7 points)	1 (5%)	3 (17,6%)	2 (13,33%)	2 (16.66%)
C(10-15 points)	5 (25%)	3(17,6%)	1 (0,67%)	4 (33.34%)
MELD score	9 (6-32)	8 (6-18)	9 (6-16)	12 (6-31)
Active Hepatocellular Carcinoma (HCC)	8 (40%)	10 (58,8%)	8 (53,33)	8 (66,6%)
BCLC stage O	4 (50%)	2 (20%)	2 (25%)	0
BCLC stage A	1 (12,5%)	6 (60%)	4 (50%)	8 (100%)
BCLC stage B	3 (37.5%)	2 (20%)	1 (12,5%)	0
BCLC stage C	0	0	1 (12,5%)	0
Platelet count 10^3/mmolL	94 (50.2-285.5)	92 (23-153)	104 (25-138)	70 (28-246)
AST, U/L	78 (65.5-125)	60 (25-477)	52 (20-70)	79.5 (26-322)
ALT, U/L	91 (60-135.5)	42(14-512)	33.5 (8-93)	62 (21-335)
Bilirubin ,mmol/l	20.7 (10-444)	18(6-182)	13.5 (9-29)	18,5 (7-525)
Protrombin time %	78 (26-100)	75 (39-100)	72(39-100)	59.5 (27-100)
Biochemical response (ALT normalization)	-	**6 (35,29%)**	**10 (66,6%)**	**3 (25%)**

Conclusions

BLV demonstrates safety and efficacy in patients on LT waiting list for decompensated liver disease or HCC.

A 48-week course of BLV therapy leads to significant virological and biochemical responses, with 73% of patients achieving a virological response and 66% a biochemical response providing valuable insights for the management of chronic hepatitis Delta in the LT setting.

6 de-listed (no HCC)
12 transplanted (8 HCC) 3/12 with normal ALT
2 on the waiting list

Metzaros M et al EASL-ILC June 5°-8°2024 FRI -370

HDV

- Virology and natural history
- Bulevirtide monotherapy
- Bulevirtide + PEGIFN
- New treatments

The NEW ENGLAND JOURNAL of MEDICINE

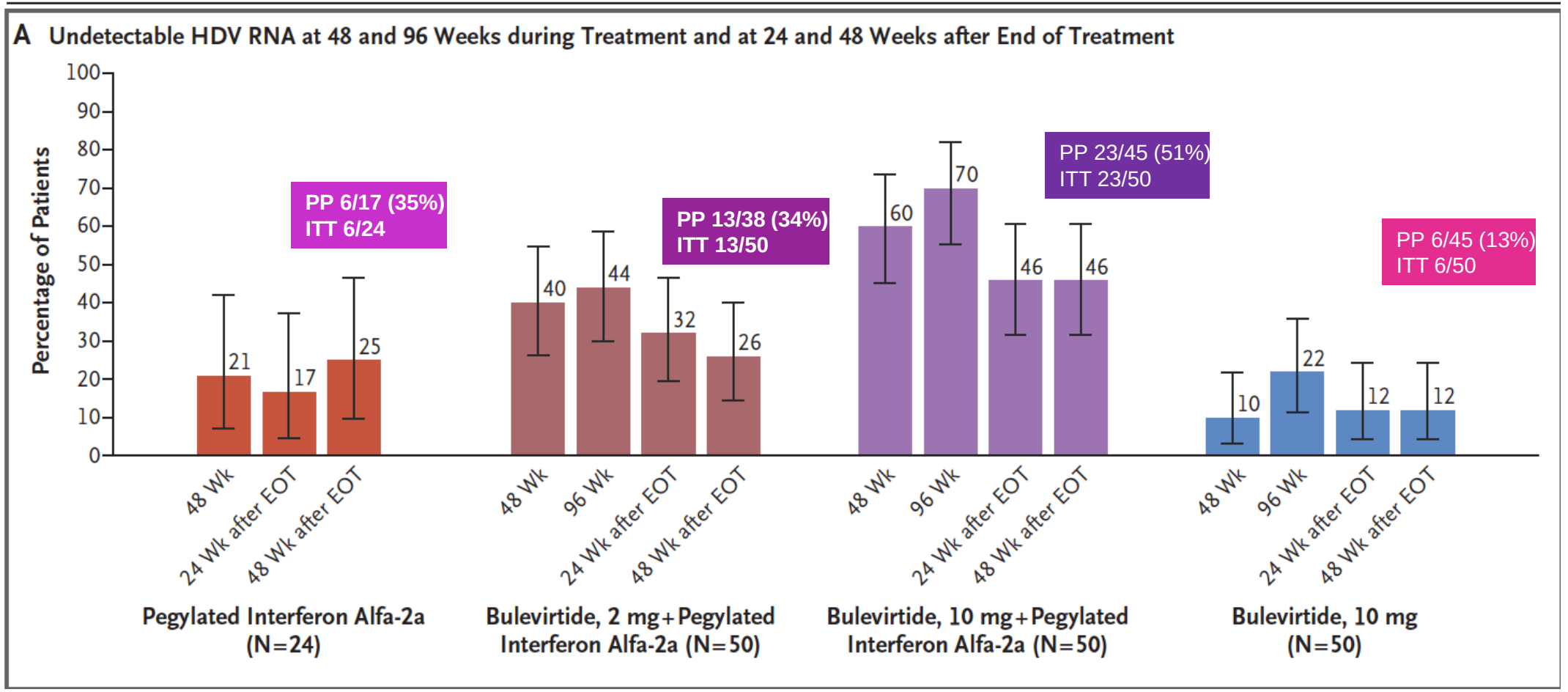
ORIGINAL ARTICLE

Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D

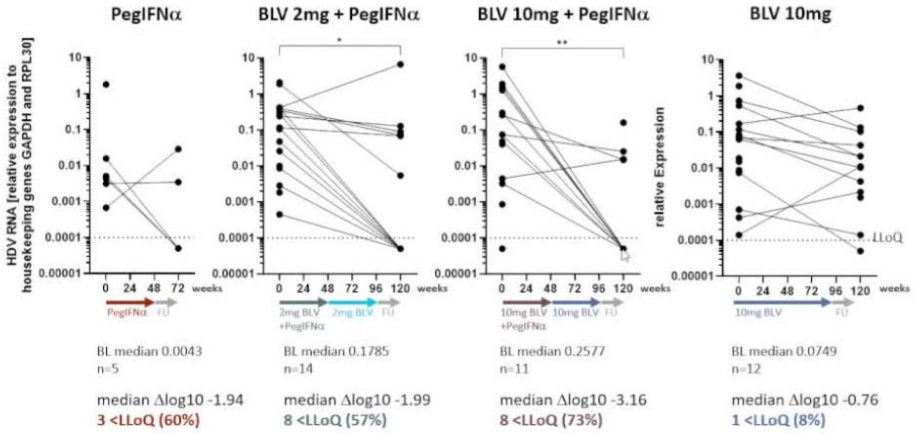
T. Asselah, V. Chulanov, P. Lampertico, H. Wedemeyer, A. Streinu-Cercel, V. Pântea, S. Lazar, G. Placinta, G.S. Gherlan, P. Bogomolov, T. Stepanova, V. Morozov, V. Syutkin, O. Sagalova, D. Manuilov, R.-C. Mercier, L. Ye, B.L. Da, G. Chee, A.H. Lau, A. Osinusi, M. Bourliere, V. Ratziu, S. Pol, M.-N. Hilleret, and F. Zoulim

Study 301
Bulevirtide 10 mg 96 week : 18/50 36%

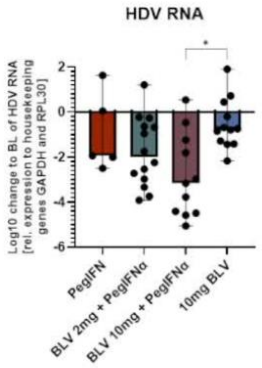
Present study :
Bulevirtide 10 mg 96 week 11/50 (22%) → sum 301 + present 29/100
Bulevirtide 10 mg 96 w + PEGIFN 48 w 35/50 (70%)
P < 0.00001

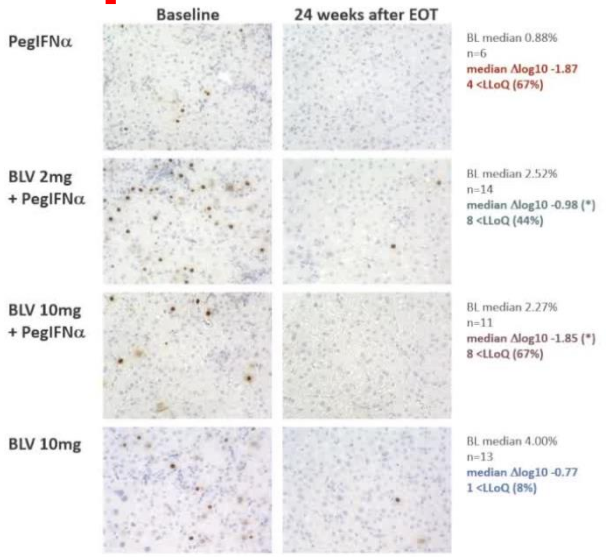


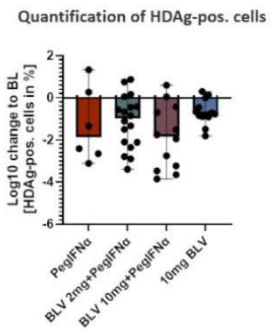
Bulevirtide in combination with pegylated interferon alfa-2a shows a sustained off-treatment response in the liver



HDV RNA levels in the liver were reduced at 24w after EOT compared to baseline levels. The highest off-treatment decline in HDV RNA was observed in the BLV 10mg + PegIFNα combination arm.

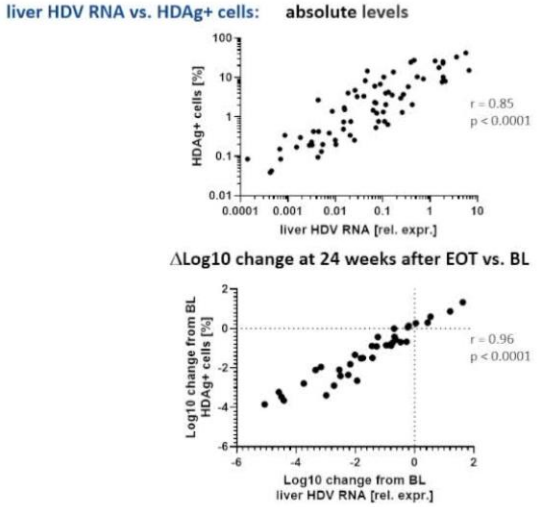




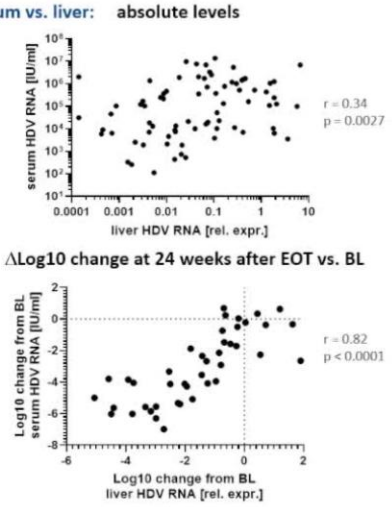


24 weeks after EOT:

- HDAg-positive cell numbers were lower compared to baseline.
- The lowest levels of infected cells was observed in the BLV 10mg + PegIFNα combination and PegIFNα monotherapy arm.



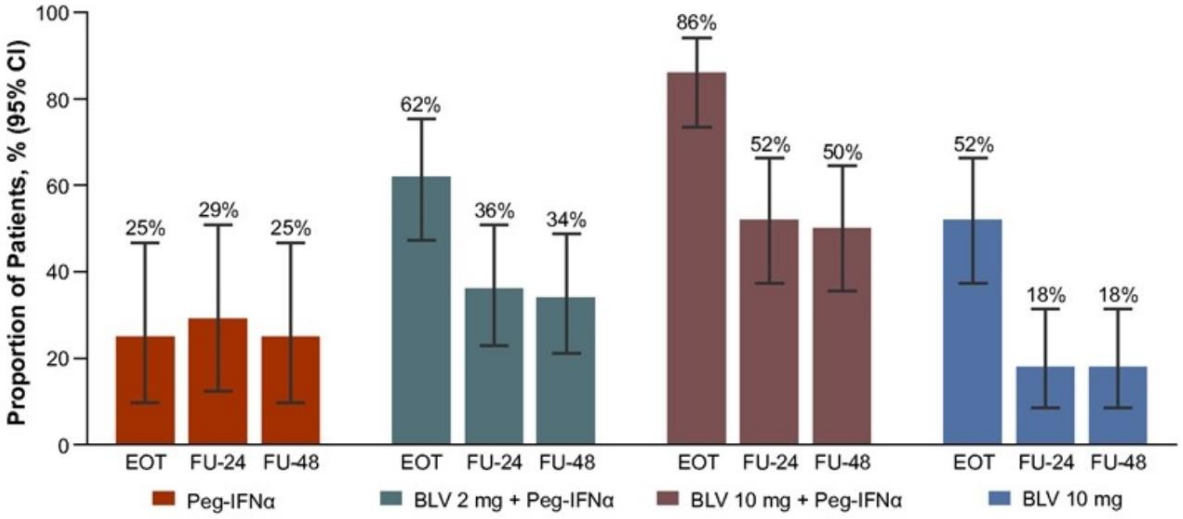
Intrahepatic HDV RNA levels strongly correlated with the number of HDAg positive cells suggesting that BLV treatment reduced the number of infected cells.



Serum HDV RNA levels correlate with liver HDV RNA levels. Intrahepatic changes of HDV RNA mirror the changes observed in the serum.

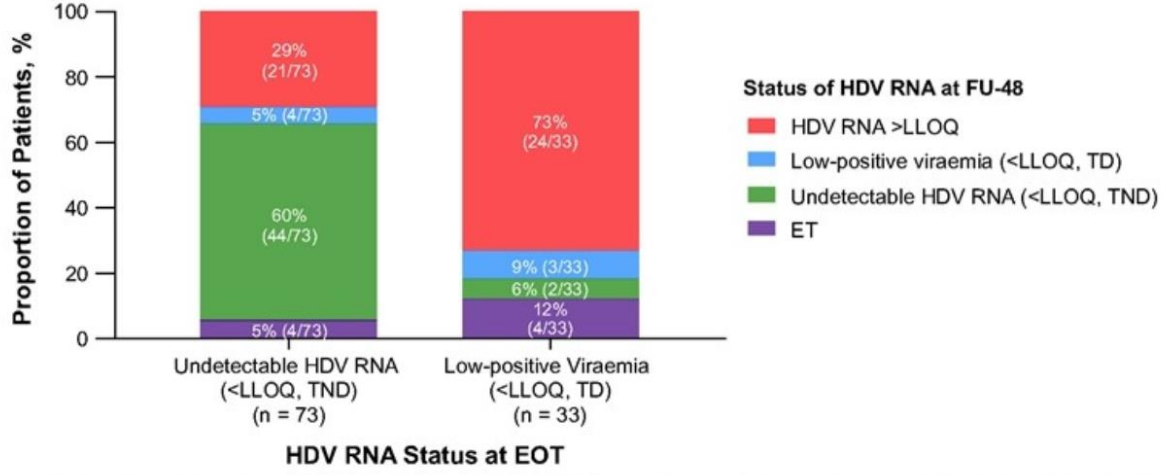
Undetectable hepatitis delta virus RNA at the end of treatment with bulevirtide and pegylated interferon alpha-2a is an important predictor of 48 weeks sustained virologic response in chronic hepatitis delta

Proportion of Patients With HDV RNA <LLOQ (TD or TND) at EOT and Post-EOT



BLV, bulevirtide; EOT, end of treatment; FU-24, follow-up at 24 weeks after EOT; FU-48, follow-up at 48 weeks after EOT; HDV, hepatitis delta virus; LLOQ, lower limit of quantification; Peg-IFNα, pegylated interferon alpha-2a; TD, target detected; TND, target not detected.

HDV RNA Status at FU-48 Based on HDV RNA Status at EOT



EOT, end of treatment; ET, early termination; FU-48, follow-up at 48 weeks after EOT; HDV, hepatitis delta virus; LLOQ, lower limit of quantification; TD, target detected; TND, target not detected.

Sustained virological response after treatment with Bulevirtide in HDV patients. Data from the french multicenter real-life cohort

At 96 weeks FU, 16 patients (47.1 %) had a **SVR** (Figure 1).

During the first 96 weeks FU, 18 patients (52.9%) experienced a **relapse** (quantifiable HDV RNA) (**Table II**)
Relapse was observed in:

- 10/18 patients (55.6%) within the first 12 weeks FU;
- 6/18 patients (33.3%) between week 13 and week 24 FU;
- 2/18 patients (11.1%) between week 25 and week 36 FU;
- 0/18 patients between week 37 and week 48 FU.

No additional relapse was observed between week 49 and week 96 FU.

Factors associated with a virological relapse at W48 after stopping BLV (univariate analysis)

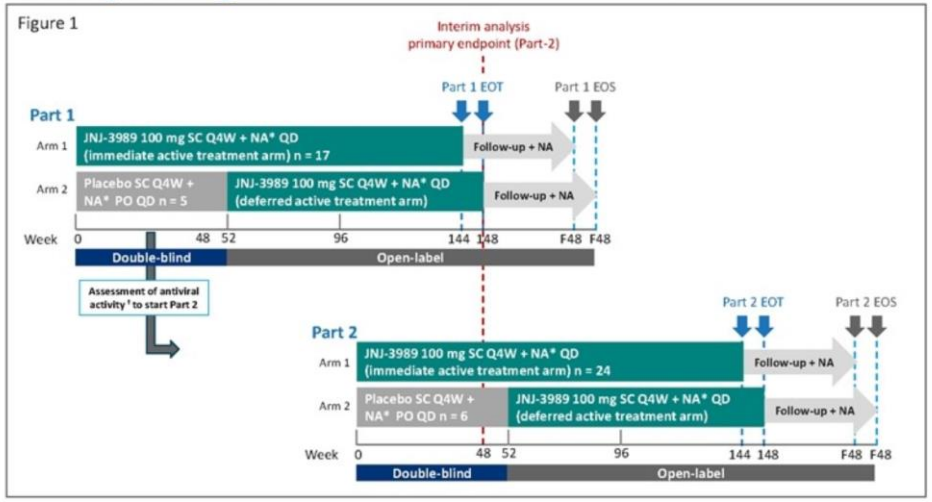
Variables	N of patients	Virological relapse	OR [IC95%]	P
Gender	34	18		
M	17	7	1	p = 0.1735
F	17	11	2.62 [0.65 ; 10.48]	
BLV duration (months)	34	18	1.00 [0.98 ; 1.02]	p = 0.7699
IFN treatment	34	18		
yes	12	7	1	p = 0.6423
no	22	11	0.71 [0.17 ; 2.95]	
HDV RNA log IU/mL, D1	32	16	1.21 [0.70 ; 2.08]	p = 0.4996
Cirrhosis	34	18		
yes	8	3	1	p = 0.3233
no	26	15	2.27 [0.45 ; 11.59]	
ALT < ULN at EOT	32	17		
YES	11	6	1	p = 0.9073
NO	21	11	0.92 [0.21 ; 3.96]	
HBsAg (UI/ml) at D1	22	14	0.97 [0.95 ; 1.00]	p = 0.0706
HBsAg (UI/ml) at EOT	26	15	0.97 [0.94 ; 1.00]	p = 0.0747
Time to stopping BLV after first PCR HDV < LoQ	33	18	0.99 [0.97 ; 1.01]	p = 0.4825
Time to first PCR HDV < LoQ after BLV start	33	18	1.08 [1.01 ; 1.15]	p = 0.0161 *
* = not significant at the multivariate analysis				

HDV

- Virology and natural history
- Bulevirtide monotherapy
- Bulevirtide + PEGIFN
- New treatments

Treatment with siRNA JNJ-73763989 plus nucleos (t)ide analogue (NA) decreases HBsAg and HDV RNA levels in patients with chronic hepatitis D)

Study Design



ALT, alanine transaminase; EOS, end of study; EOT, end of treatment; ETV, entecavir; F, follow-up; LLOQ, lower limit of quantification; PO, oral; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TND, <LLOQ target not detected. *ETV/TDF/TAF according to label. †≥8 JNJ-3989–treated patients with ≥0.5 $\log_{10}$ reduction from baseline in HBsAg and HDV RNA and 4 of those with ≥1 $\log_{10}$ reduction in HDV RNA.

Key efficacy endpoints: Part 1 and 2 combined

- Among all patients who completed 48 weeks of JNJ-3989+NA treatment 41% achieved the primary endpoint (HDV RNA decline ≥ 2log10 IU/mL and ALT normal).
  - Among patients with HBsAg <10 000 IU/mL at screening this was 9/20 (45%).

Table 2

		Normal ALT	HDV RNA ≥2 $\log_{10}$ IU/mL from BL or TND	Combination of both = primary EP	HDV RNA <LLOQ (63 IU/mL)
JNJ-3989 +NA	All patients (ITT)	14/45 (31%)	14/45 (31%)	11/45 (25%)	9/45 (20%)
	Patients with W48 data*	14/27 (52%)	14/27 (52%)	11/27 (41%)	9/27 (33%)
	Patients with W48 data* and HBsAg <10,000 IU/mL†	11/20 (55%)	13/20 (65 %)	9/20 (45%)	7/20 (35%)
Placebo +NA		3/11 (28%)	0/11 (0%)	0/11 (0%)	0/11 (0%)

*Four Part-1 placebo patients who rolled over at w52 were counted once for placebo (W0-48) and again for JNJ-3989 (W52-100); † assessed at screening.

AEs reported during double blind phase – Part-2

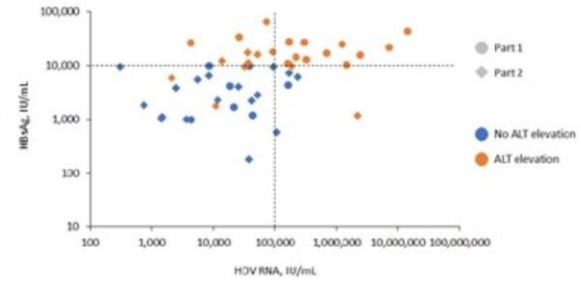
	JNJ-3989 + NA 48 weeks (n = 24)	Placebo + NA 48 weeks (n = 6)
Patients with ≥1 AEs, n (%)	20 (83.3)	5 (83.3)
Related AEs	12 (50.0)	3 (50.0)
Related to JNJ-3989/placebo	12 (50.0)	3 (50.0)
Related to NA	2 (8.3)	0
AEs leading to death	0	0
SAEs, n (%)	3 (12.5)	0
Related SAEs*	0	0
AEs leading to discontinuation of any study treatment, n (%)†	1 (4.2)	0
Grade 3 or 4 AEs, n (%)‡	8 (33.3)	0
Related Grade 3 or 4 AEs	7 (29.2)	0
AEs of special interest, n (%)		
ALT§/AST elevations	9 (37.5)	2 (33.3)
Injection-site reactions	1 (4.2)	0
Renal complications	0	0
Cholesterol increases	1 (4.2)	0
Hematologic abnormalities	0	0

AE, adverse event; AST, aspartate transaminase; SAE, serious adverse event. *Transaminases increased and ALT/AST flare occurred in 1 patient each. †Not all ALT/AST elevations leading to discontinuation prior to Week 48 (n = 8) were reported as AEs. Not all AEs reported as ALT/ AST elevation met criteria for flare definition and/or stopping criteria for JNJ-3989 . ‡No cases of decompensation. §Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir

- Among 24 patients with HBsAg <10,000 IU/mL at screening 24 (82.8%) had no ALT elevation while all 19 (100%) with HBsAg ≥ 10,000 IU/mL had ALT elevation

Table 3 / Figure 5

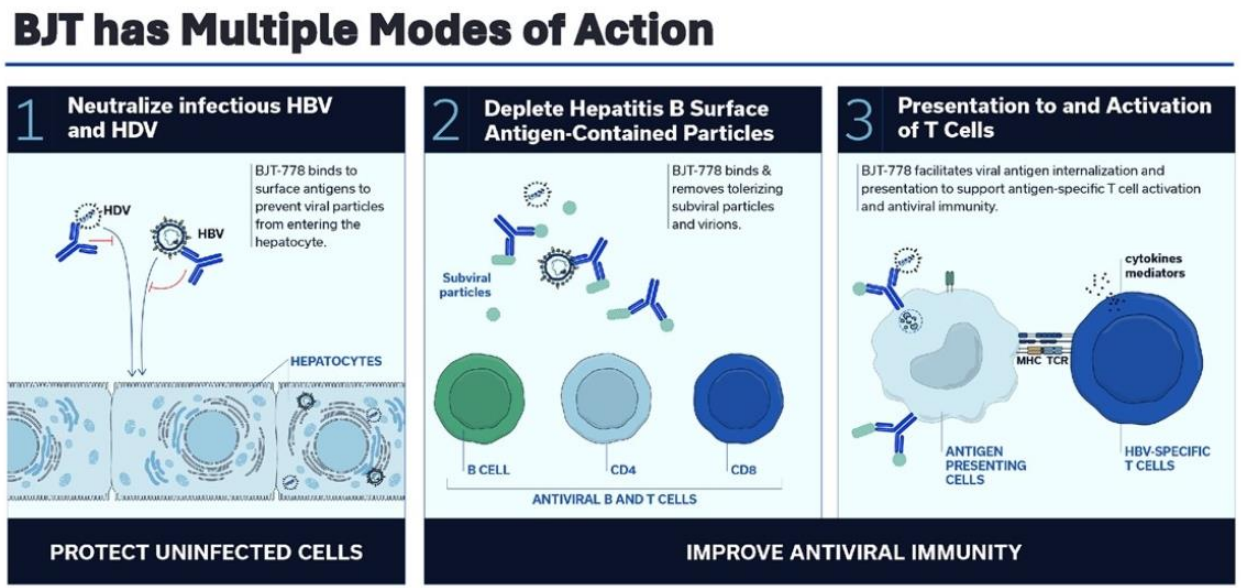
	n*	At Scr/BL	n	ALT elevation	No ALT elevation
HBsAg IU/mL	48	<10,000	29	5 (17.2%)	24 (82.8%)
		≥10,000	19	19 (100%)	0
HDV RNA IU/mL	48	<100,000	31	11 (35.5%)	20 (64.5%)
		≥100,000	17	13 (76.5%)	4 (23.5%)
HBcrAg log U/mL	47†	<4	24	6 (25%)	18 (75%)
		≥4	23	17 (74%)	6 (26%)

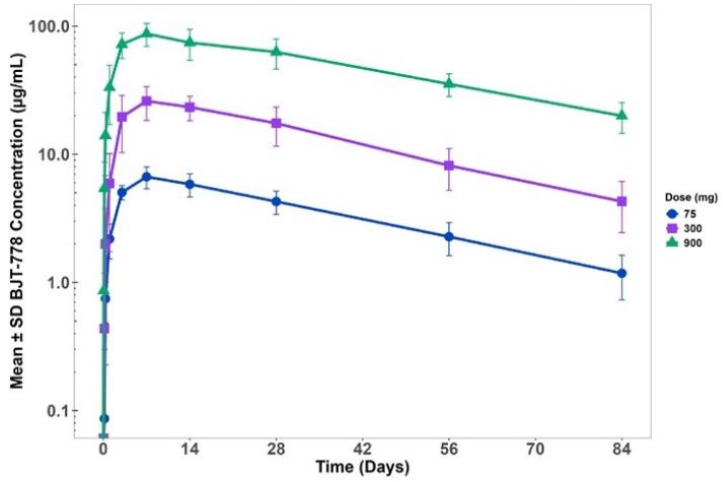


*Includes 48 participants who received >4 weeks of JNJ-3989 in either arm. *HBcrAg baseline value is missing in one participant.

Wedemeyer H et al EASL ILC 2024 LBP-

Rapid reductions of HDV RNA and ALT with the monoclonal antibody, BJT-778: results from a phase 2 study



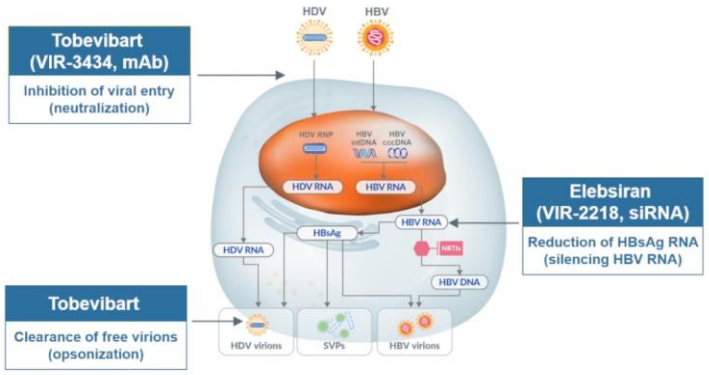


- BJT-778 is a fully human anti-HBsAg monoclonal antibody that exhibits potent antiviral activity against HBV and HDV in vitro.
- BJT-778 administered subcutaneously (SC) for a duration of up to 48 weeks in subjects with CHD.
- 10 subjects per arm were to be enrolled into:
  - Arm 1: BJT-778 300 mg SC once weekly (QW); → 10 subjects enrolled all completed 16 week of treatment
  - Arm 2: BJT-778 600 mg SC QW for 12 weeks followed by Q2W; → 11 subjects enrolled
  - Arm 3: BJT-778 900 mg SC Q2W for 4 weeks followed by Q4W. → enrollment is ongoing
- In arm 1 90% of the subjects (9 out of 10) achieved a virologic response,
- With:
  - 40% (4 out of 10) falling below the limit of quantification (BLQ) and
  - 30% (3 out of 10) BLD.

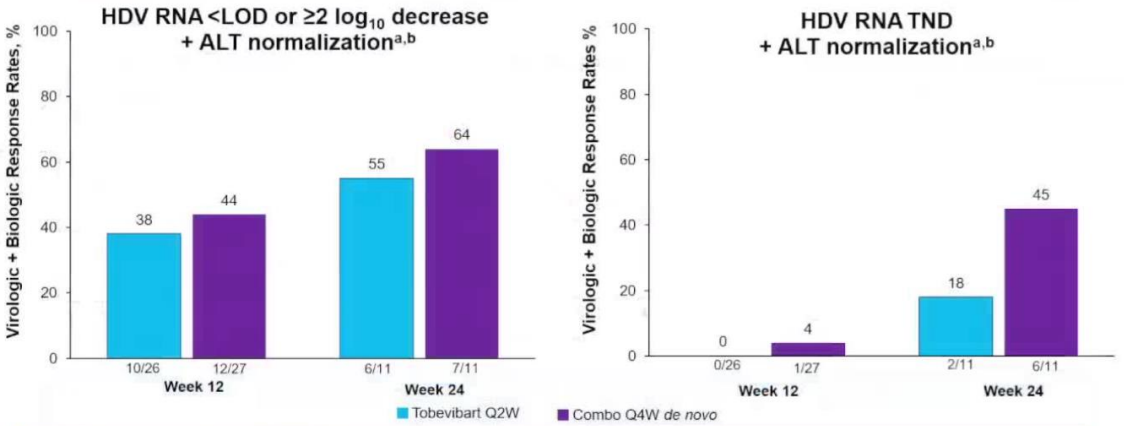
Agarwal K et al EASL ILC June 5-8°2024 LBP-001

Efficacy and safety of tobevibart (VIR-3434) alone or in combination with elebsiran (VIR-2218) in participants with chronic hepatitis delta virus infection: preliminary results from the phase 2 SOLSTICE trial in non-cirrhotic and compensated cirrhotic participants

Tobevibart and Elebsiran Mechanisms of Action

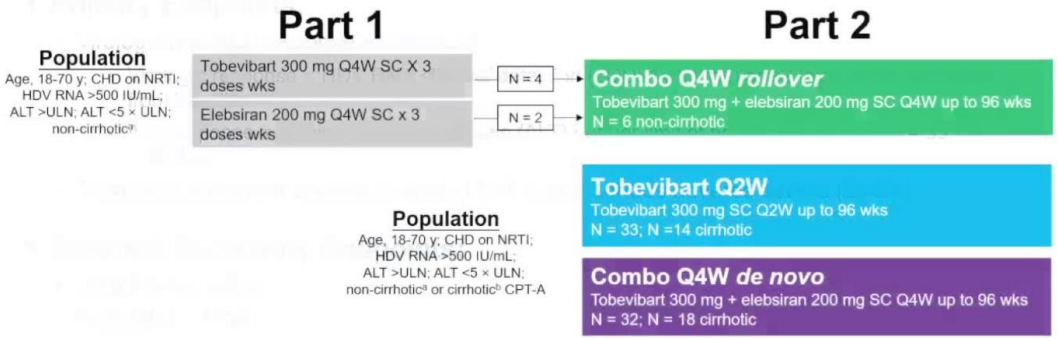


Tobevibart Q2W and Tobevibart + Elebsiran (Combo *de novo*): Combined Response Rates (Preliminary Data)

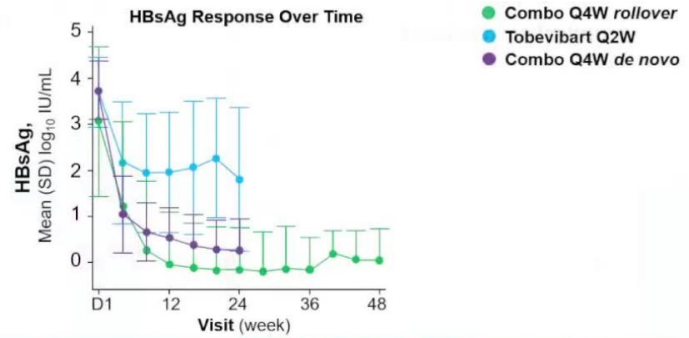


Tobevibart: 26/33 (79%) and 11/33 (33%) of participants reached Weeks 12 and 24, respectively
Tobevibart + elebsiran: 27/32 (84%) and 11/33 (33%) of participants reached Weeks 12 and 24, respectively

SOLSTICE Study Design



Tobevibart Q2W and Tobevibart + Elebsiran (Combo) Cohorts: HBsAg Responses



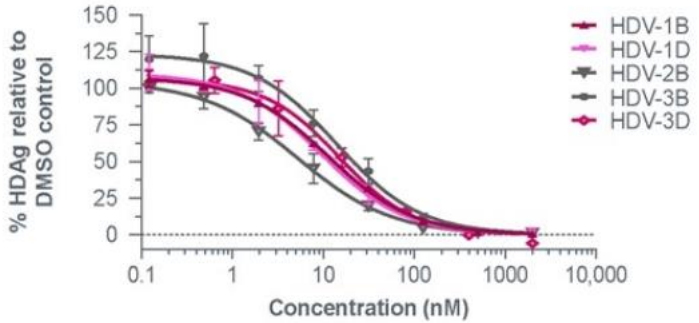
	Combo Q4W *rollover*			Tobevibart Q2W		Combo Q4W *de novo*	
	Week 12 N = 6[a]	Week 24 N = 6[a]	Week 48 N = 5[a]	Week 12 N = 25[a]	Week 24 N = 9[a]	Week 12 N = 29[a]	Week 24 N = 14[a]
Δ HBsAg relative to Day 1 (mean ± SD),[b] log_{10} IU/mL	–3.1 ± 1.0	–3.2 ± 0.9	–3.5 ± 0.8	–1.7 ± 0.8	–1.8 ± 0.9	–3.2 ± 0.5	–3.3 ± 0.5

Preclinical profiling of ABI-6250, a novel orally bioavailable small-molecule therapeutic candidate for the treatment of chronic hepatitis D

ABI-6250 orally bioavailable small molecule entry inhibitor

Figure 1. ABI-6250 Efficiently Inhibited HDV Infection of the Most Prevalent Genotypes

A. Anti-HDV Activity in HepG2-NTCP Cells



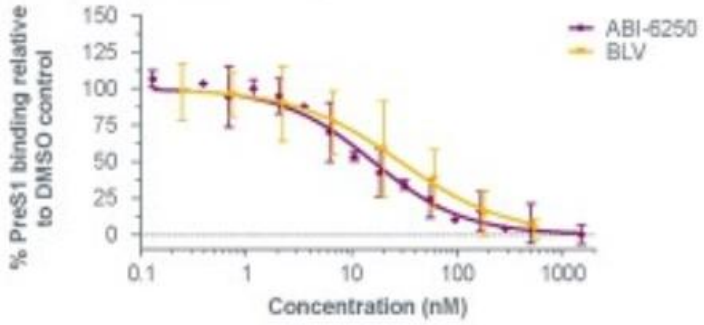
B. ABI-6250 EC_{50} Values in HepG2-NTCP Cells

HDV/HBV genotype	EC_{50} (nM)
1B	11.4
1D	9.6
2B	5.2
3B	14.2
3D	14.9

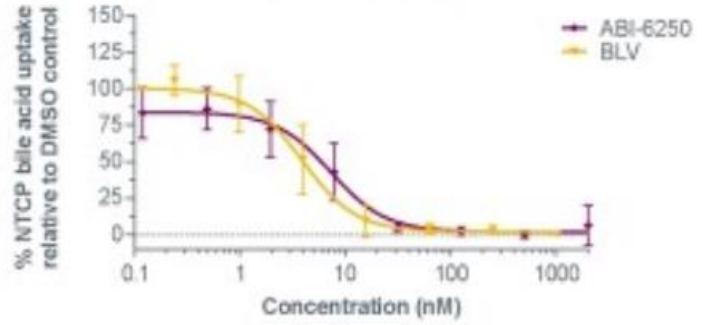
DMSO, dimethyl sulfoxide; EC_{50}, half-maximal effective concentration; HBV, hepatitis B virus; HDAg, hepatitis D antigen; HDV, hepatitis D virus; NTCP, sodium taurocholate cotransporting polypeptide.

Figure 2. ABI-6250 Inhibited PreS1-NTCP Binding and NTCP-Mediated Bile Acid Uptake

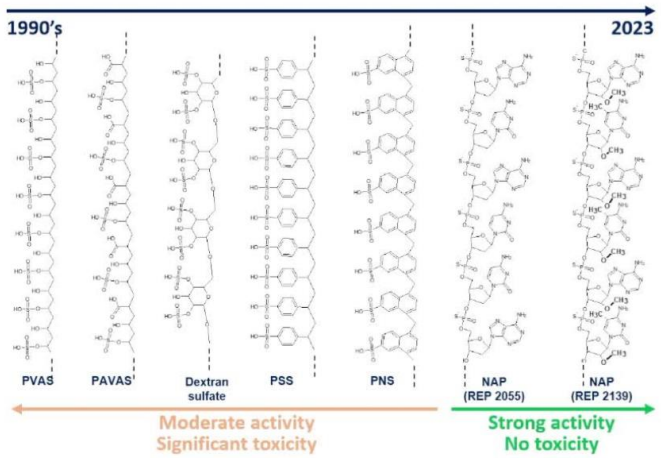
A. PreS1-NTCP Binding Inhibition



B. NTCP-Mediated Bile Acid Uptake Inhibition



Safety and efficacy of REP 2139-Mg in hepatitis D patients with advanced liver disease: an international compassionate use program



PK: pharmacokinetics

NAPs = **broad-spectrum antiviral** compounds active against diverse enveloped viruses and other agents

Interact with the exposed hydrophobic surfaces of **amphipathic α-helix proteins**

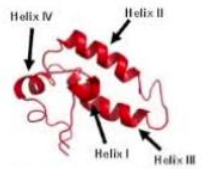
Primary accumulation in the liver = 250-500 mg repeated dosing required for effective Cmax (PK IV ~ SC)

40mer oligonucleotide polymer of alternating adenosine and cytidine = **strong activity, prevents host genome interactions and immunostimulation**

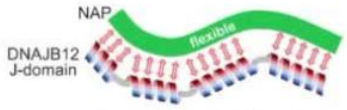
Mechanism of action

Passage through secretory pathway (transient)

- Target the host HSP40 chaperone DNAJB12
- Inhibition of HBV SVP assembly
- Blocks envelopment of HDV RNP



J-domain crystal structure of DNAJB12 at neutral pH (4 linked alpha helices)



Flexible nature of NAPs adapts to minor alterations in α-helical confirmation, maintaining high affinity interactions

Accumulation in nucleus

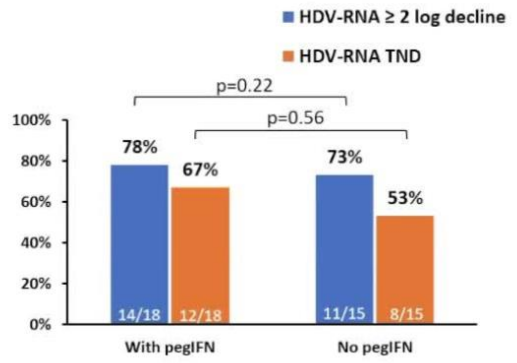
- Targets S-HDAg and L-HDAg
- Inhibits HDV RNA replication
- Blocks HDV RNA interaction with HDAg during HDV RNP morphogenesis
- **Nuclear accumulation is more efficient**
- Anti-HDV effects are easier to achieve

HDAg crystal structure

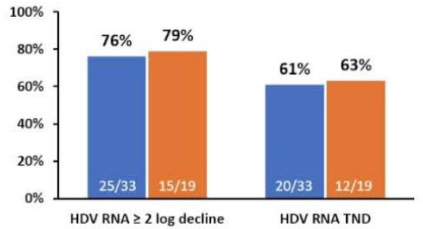
Safety and efficacy of REP 2139-Mg in hepatitis D patients with advanced liver disease: an international compassionate use program

	N = 33
Age (years)#	47 (21 – 69)
Male Sex (n, %)	21 (64 %)
Ethnicity	24 Caucasian, 5 African, 2 Middle Eastern, 1 Asian, 1 Central Asian
Previous failure to pegIFN (n, %)	24 (73 %)
Previous BLV treatment (n, %) *	20 (61 %)
Liver fibrosis (n) Advanced fibrosis F3 Compensated cirrhosis Decompensated cirrhosis	 5 22 6
Positive HBeAg at baseline (n)	6
HDV genotype (n) GT1 / GT5 / GT7 / Unknown	 19 / 4 / 1 / 9
HIV co-infection (n)	2
HDV RNA (IU/mL) #	1.96 x10^6 (295-1.68x10^7)
HBsAg (IU/mL) #	8307 (626-33559)
HBV DNA (IU/mL) #	1234 (TND-3440)
ALT (U/L) #	88 (19-266)
Bilirubin (µmol/L) #	17 (3.4-34)

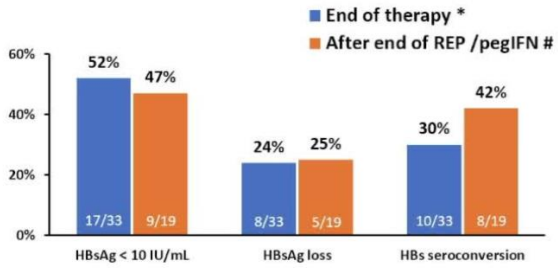
Virological response according to pegIFN therapy



HDV RNA response



HBsAg response



ALT normalized in 47% (9/19) after end of REP / pegIFN

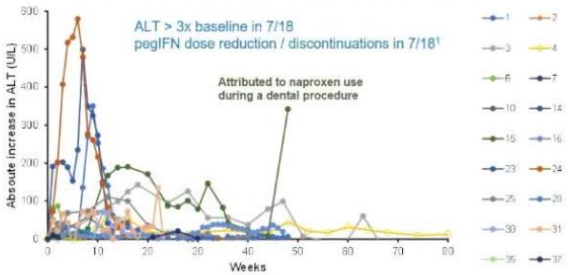
Removal of all therapy in three patients:
all with HDV RNA TND and HBsAg loss (24 weeks of follow-up)

* 3 patients still on therapy: 1 has < 16 weeks, 2 on extension therapy > 48 weeks. 7 patients halted therapy prior to 48 wks; 2 due to LT, 2 due to poor IV access, 1 due to unrelated burst varices, 1 for futility and 1 due to lost contact.
# With available follow-up (4-48 weeks) after completion of at least 48 weeks of therapy. Four patients completed extension therapy totalling 60-80 weeks.

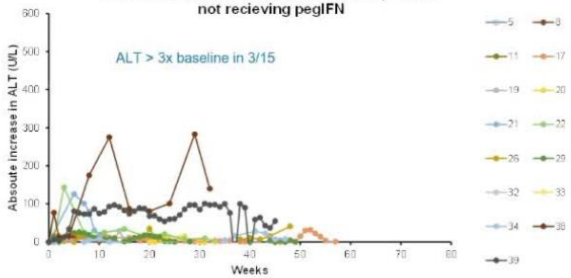
Suboptimal virological response can be improved with REP 2139 dose modification and/or therapy extension

- No SAE related to REP 2139-Mg
- Reported REP 2139-Mg AE: 1. transient mild injection site reactions (55%)
  2. grade 1-2 thrombocytopenia (18%) self resolving after removal of REP 2139-Mg
- ALT flares are asymptomatic and self resolving (mainly with pegIFN)
  - Appear to be lower in intensity and prevalence than observed in prior clinical trials with HDV non-cirrhotic patients

Absoute ALT increase from baseline in patients recieving pegIFN



Absoute ALT increase from baseline in patients not recieving pegIFN



HDV key messages

- HDVRNA levels and HCV coinfection are related to worse prognosis in chronic delta hepatitis
- HBsAg on delta virions comes from integrated HBVDNA and is more frequently composed by Middle and Large HBsAg
- In chronic delta hepatitis patients healthcare resources utilization is higher only in pts with decompensated cirrhosis
- Bulevirtide monotherapy maintains 96 weeks response at 144 weeks
- Early HDVRNA negativisation and L-HBsAg concentrationsat baseline predict virological response
- Bulevirtide in cirrhosis reduces mortality and decompensation in comparison with old historical data
- Bulevirtide could be an option in HDV patients on the transplant waiting list
- Finite combo Tx with PEGIFN increases the response rate in comparison with Bulevirtide monotherapy at 10 mg/d and shows a sustained off ttrreatment response in the liver
- Negative HDVRNA and earlier negativisation of HDVRNA predict sustained response after bulevirtide + PEGIFN
- Promising results with anti HBs monoclonal antibodies used alone or in combo with siRNA inhibitors
- An oral HDV entry inhibitor is on the block
- NAP may work well even in decompensated cirrhosis