Bergamo, 26 Ottobre 2023

Nuovi orizzonti terapeutici per il trattamento delle epatiti: focus su epatite B e Delta

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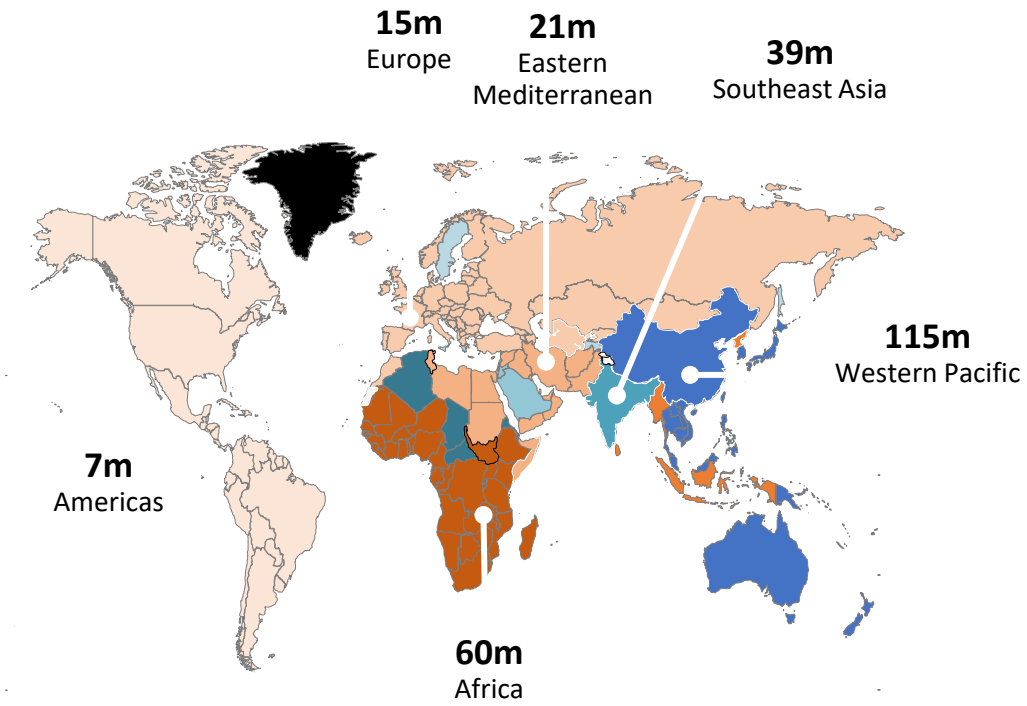
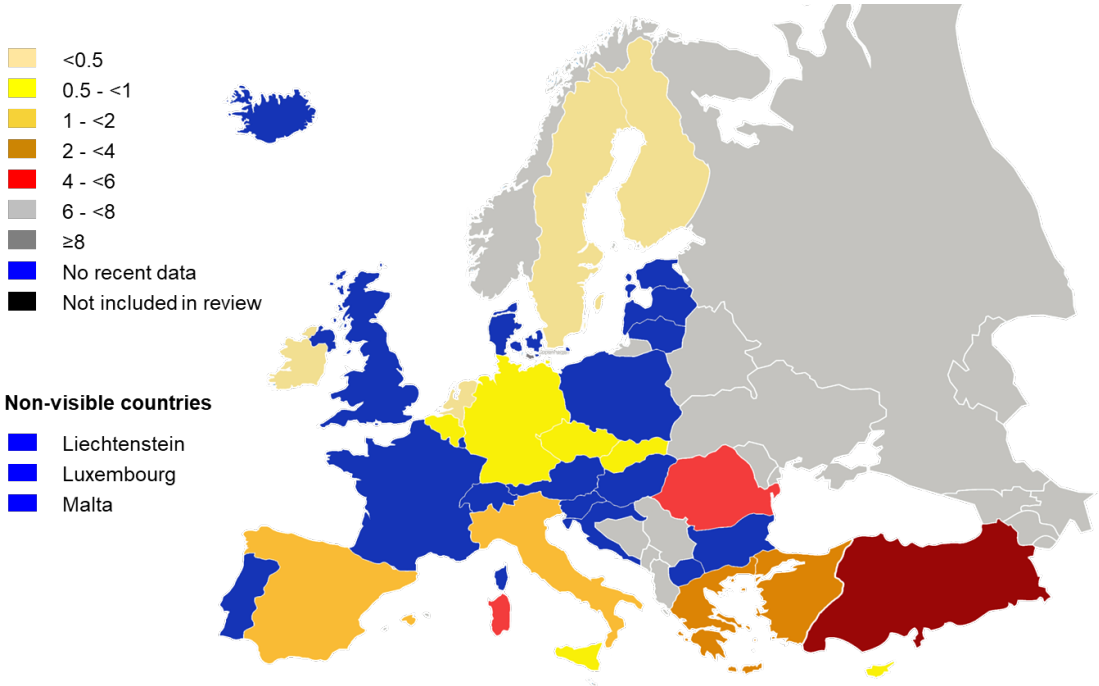
HBsAg prevalence in the general population of Europe





WHO, Global Hepatitis Report 2017

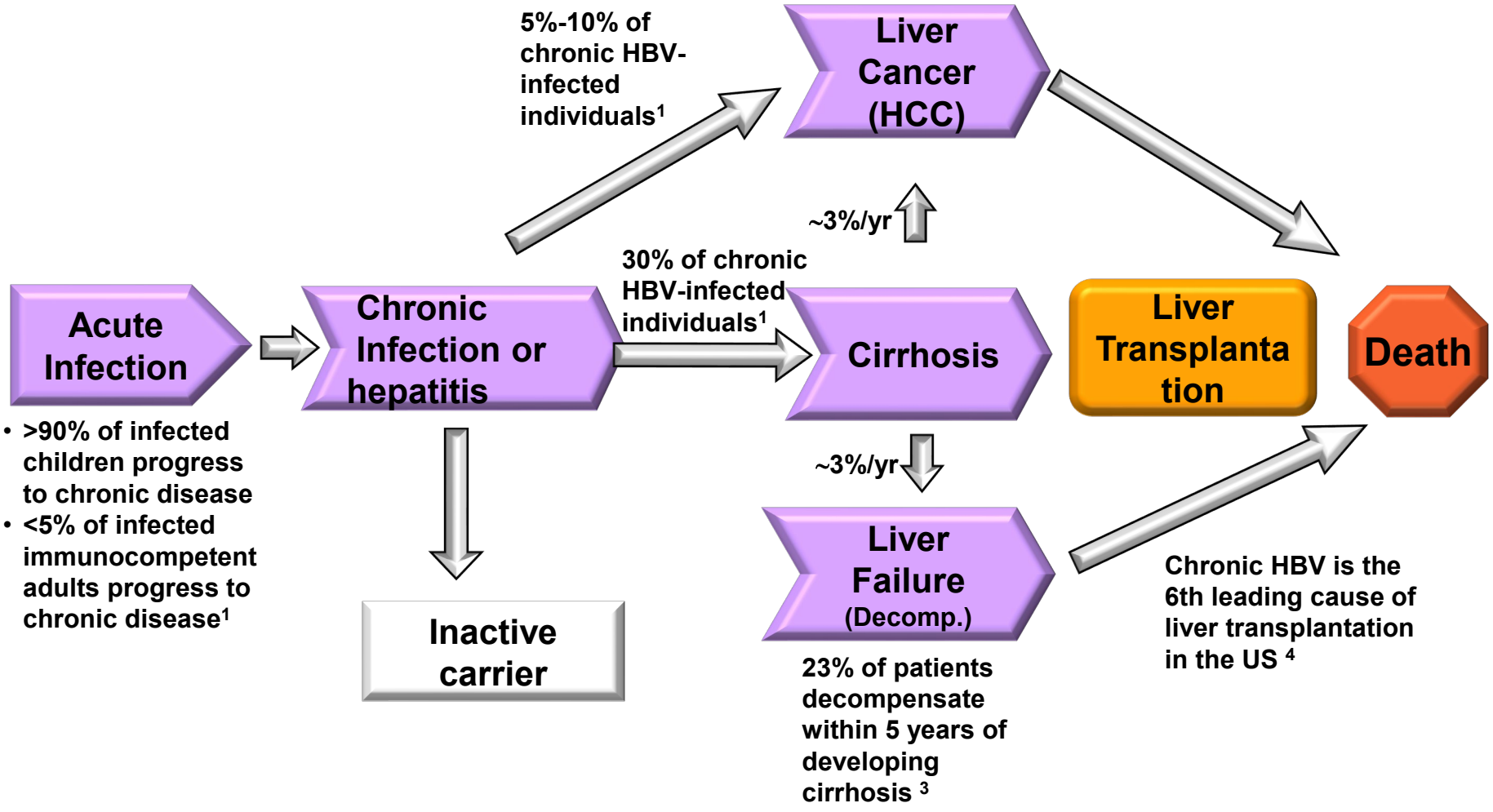
ECDC Technical Report, September 2010

HBV prevalence in Italy

	Population size estimates	Rationale and comments	Source	Strength of source
Prevalence of chronic hep B	457 384	• **Prevalence of 0.6% HBV infections among the total population.** • The modelled prevalence was used from the Lancet Study.	• Lancet 2018 Study, World Bank Data	
Diagnosed Hep B	133 771	• **The diagnostic rate of HBV infections is 29%.**	• According to the Lancet 2018 Study, and Polaris observatory (CDA foundation) modelling.	
Actively treated	50 833	• **38% of diagnosed Hep B patients**	• Stoffolini, et. Al	

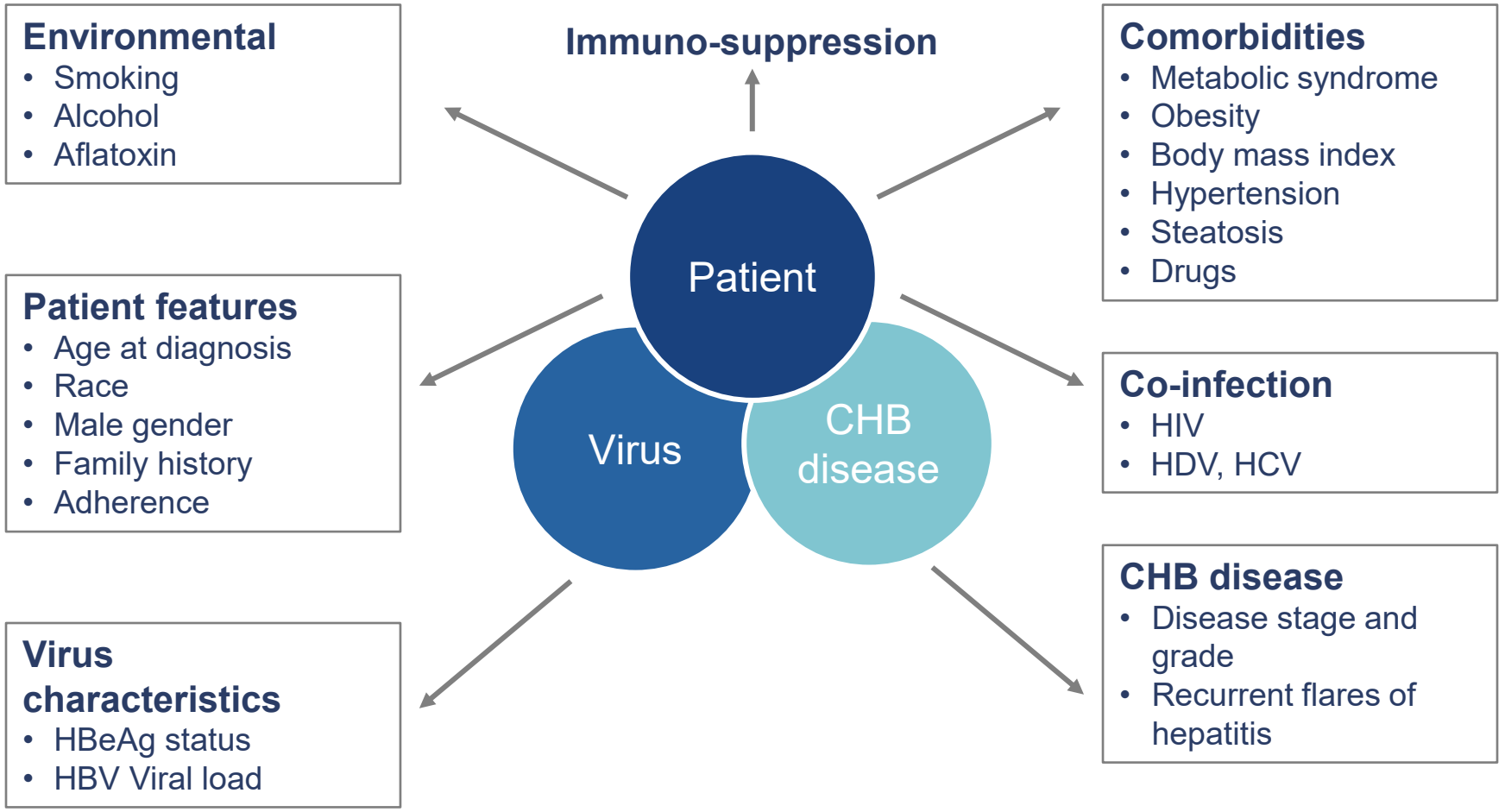
HepB Lancet modelling (2018), Polaris Group modelling (2018)

Natural History of Hepatitis B Virus Infection



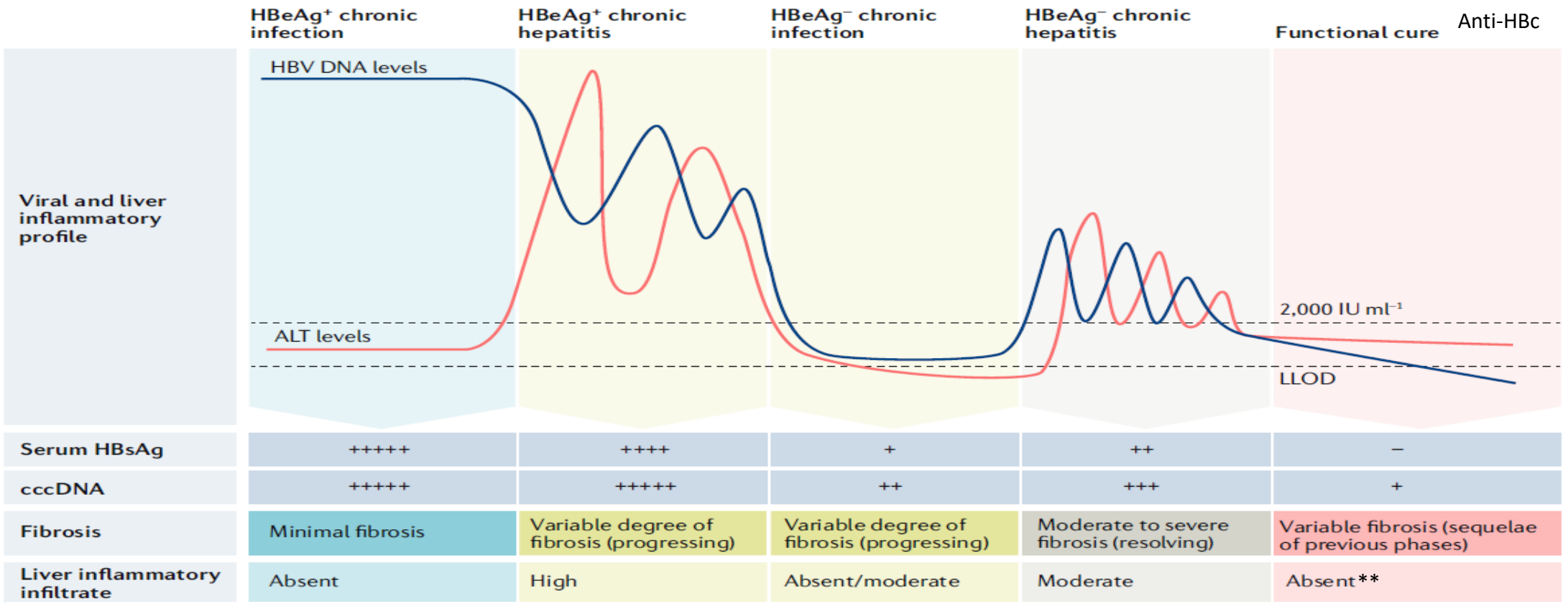
1. Torresi, J, Locarnini, S. Gastroenterology. 2000. 2. Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995.
3. Moyer, LA, Mast, EE. Am J Prev Med. 1994. 4. Perrillo, R, et al. Hepatology. 2001.

Many factors affect CHB disease progression



Fattovich G Semin Liver Dis 2003;23:47–58; Fattovich G et al. J Hepatol 2008;48:335–52.

Natural History of Hepatitis B and treatment indication



TREATMENT

Modified from Fanning, G.C., Zoulim, F., Hou, J. *et al. Nat Rev Drug Discov* 18, 827–844 (2019)

* HBV DNA levels can be between 2000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
** HCC risk only if cirrhosis has developed before HBsAg loss

Current treatment strategies of CHB

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)[1]
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment adverse events (psychiatric, neurological, endocrinological)	Probably not (uncertainties regarding kidney function, bone diseases for some NA)
Contraindications	Many (*i.e.*, decompensated disease, co-morbidities etc.)	None (dose adjustment according to eGFR[2])
Strategy	Induction of a long-term immune control by finite treatment	Stopping hepatitis and disease progression by inhibiting viral replication
Level of viral suppression	Moderate (variable response pattern)	Universally high
Effect on HBeAg loss	Moderate, depending on baseline characteristics	Low in the first year, increases to moderate during long-term treatment
Effect on HBsAg levels	Variable, depending on baseline characteristics (overall higher as compared to NA)	Low: slowly increases with treatment time in HBeAg-positive patients[3]; usually very low in HBeAg-negative patients
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance development	No	Minimal to none[4]

Long-term administration of a potent NA with a **high barrier to resistance** is the treatment of choice, regardless of severity of liver disease:

- Entecavir, ETV
- Tenofovir Disoproxil Fumarate, TDF
- Tenofovir Alafenamide, TAF (II line)

Lamivudine only for anti-HBc prophylaxis

EASL CPG HBV, J Hepatol 2017

Treatment with ETV or TDF in CHB

Achievements

- Excellent virological and biochemical responses (>95%)
- Histological progressi
  prevented
- Histological improver
  regression?)
- Decompensation prevented; portal
  hypertension improved
- HCC risk decreased but not abolished
- Improved survival

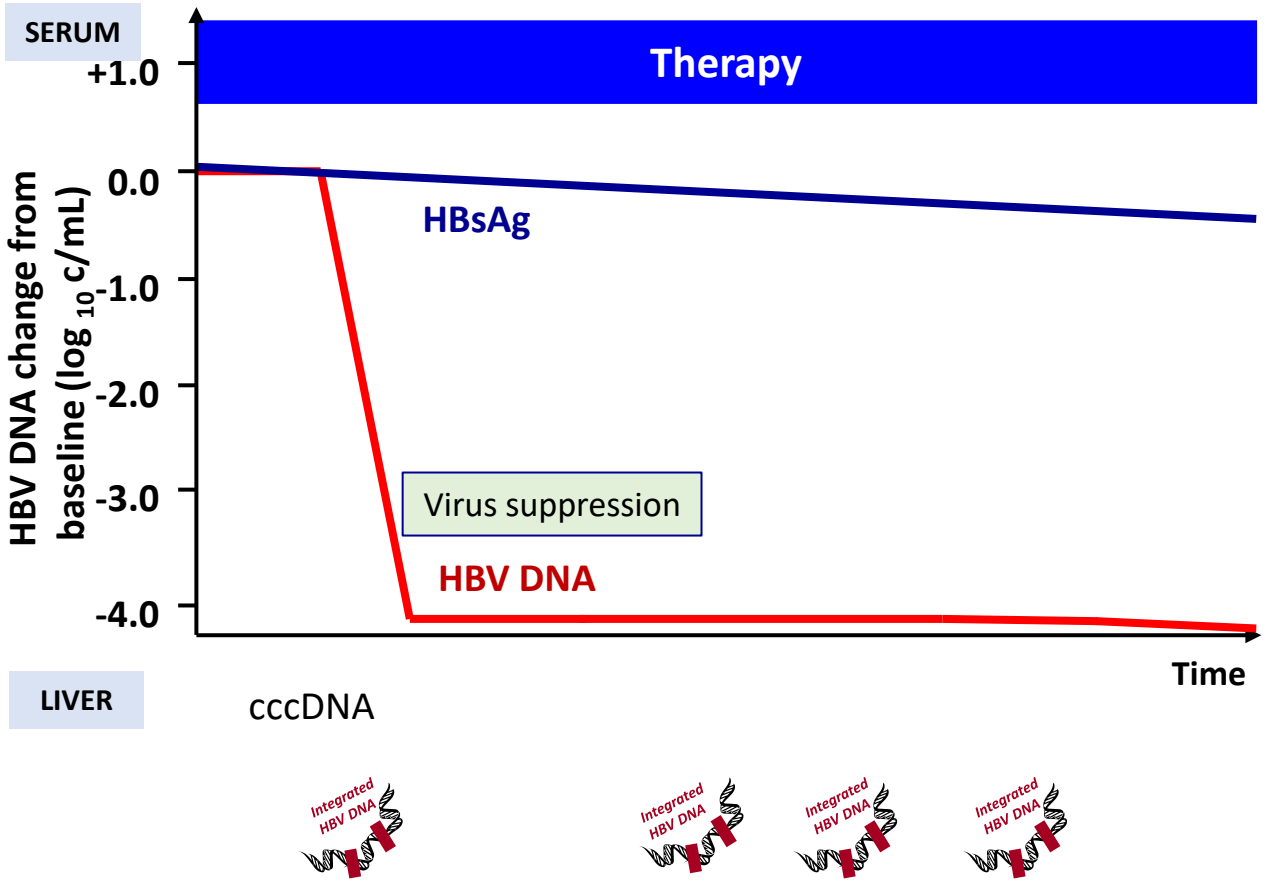
Unsolved issues

- Partial virological response in highly viremic patients (HBeAg pos)
- TDF treated patients
- term NUC therapy
- Low HBsAg loss rates

"The main goal of therapy for patients with chronic HBV infection is to improve survival and quality of life by preventing disease progression, and consequently HCC development"

EASL CPG HBV. J Hepatol 2017;67:370–98

Definition of HBV cure



- **Partial cure***:

Detectable HBsAg but persistently undetectable serum HBV DNA

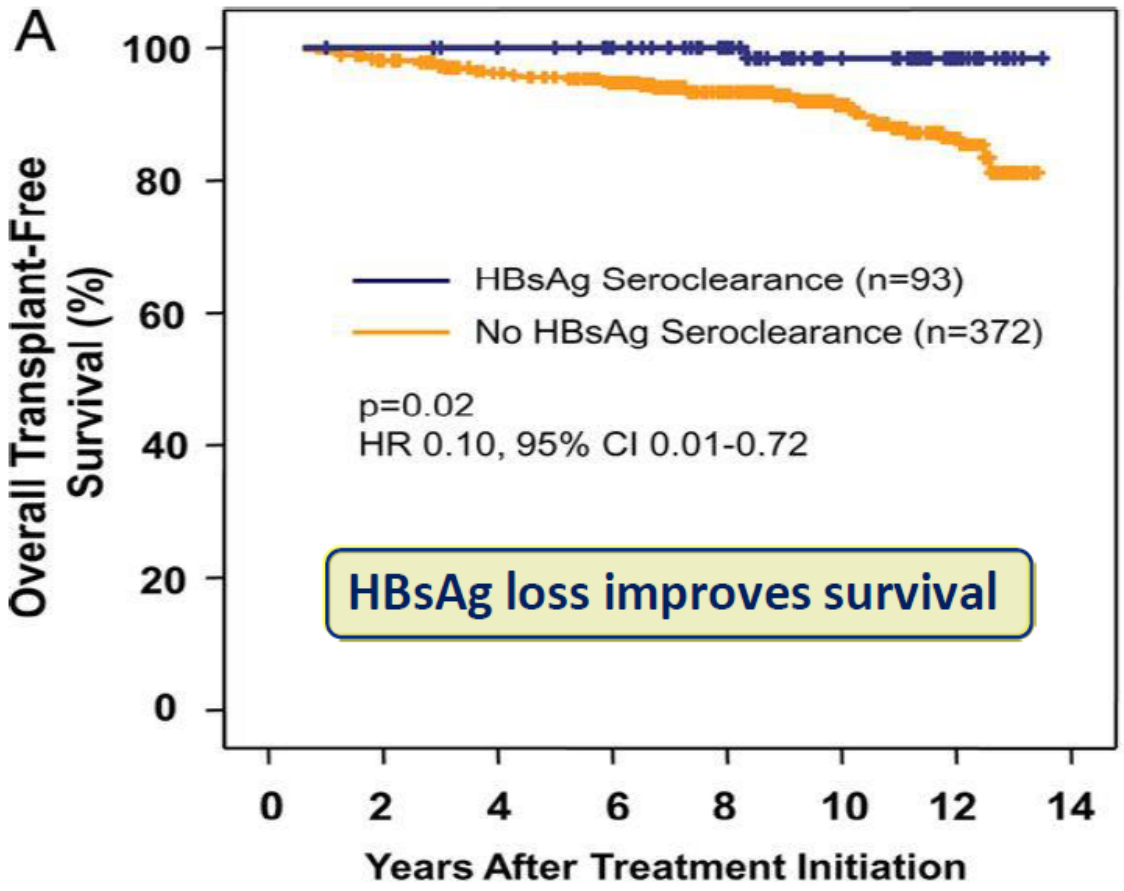
* Inactive carriers with undetectable HBV DNA

Adapted from: Testoni B, et al. Semin Liver Dis 2017;37:231–24

Lok AS, et al. J Hepatol 2017;67:847–61

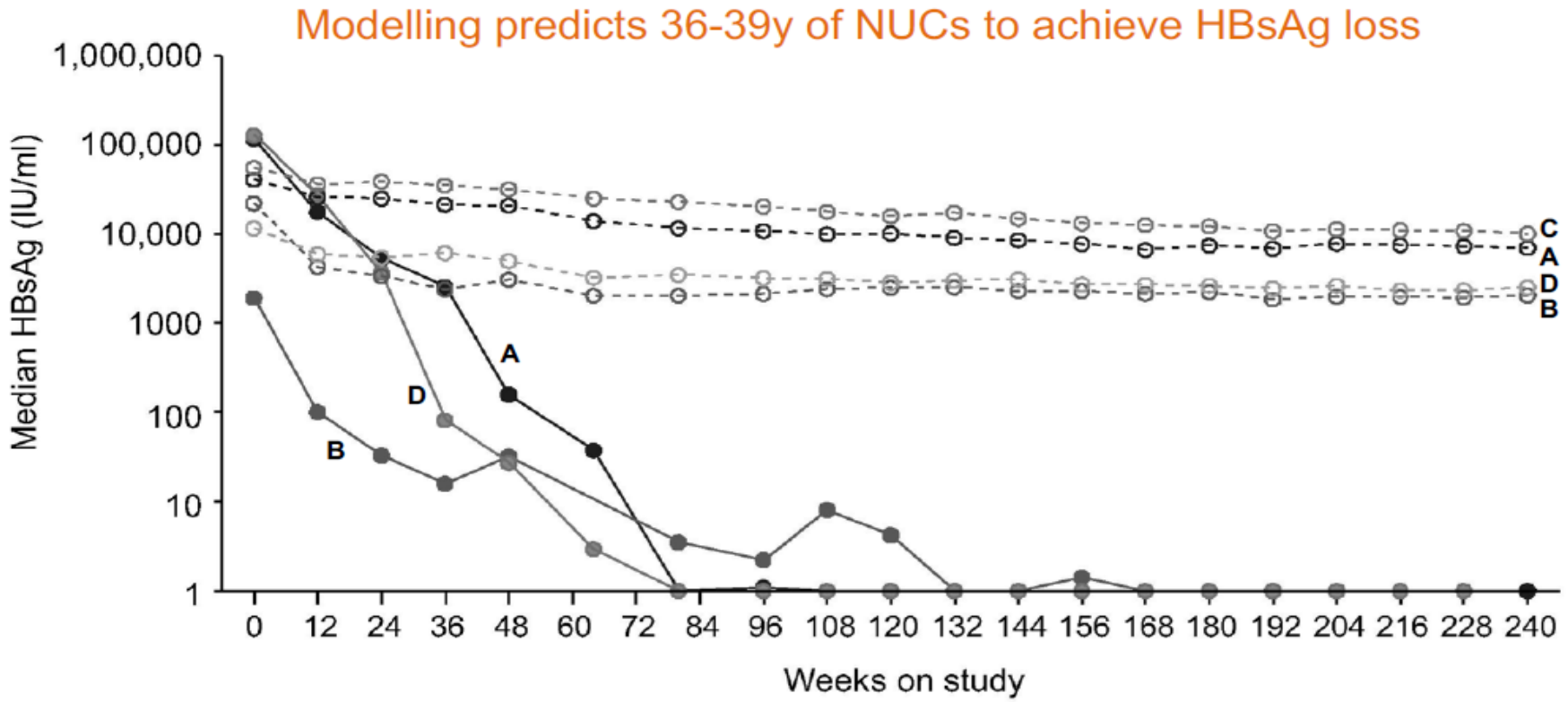
Is HBV DNA Undectability the Best End Point?

- 5409 CHB patients on long-term Entecavir



Kim GA et al. *Gut* 2014;63:1325-1332

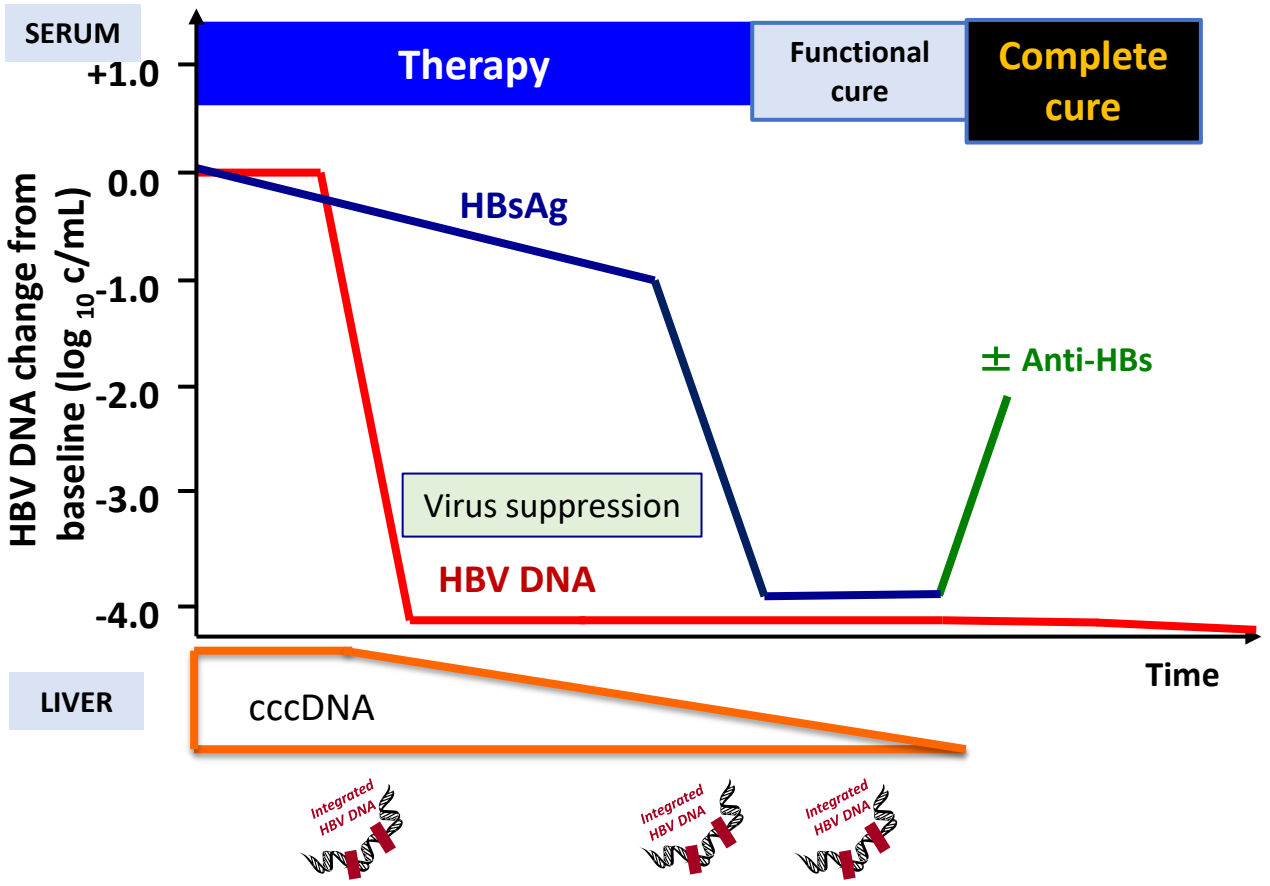
HBsAg Kinetics in Patients Receiving NUCs



HBsAg loss - Genotype A	N = 14	14	14	13	13	13	13	12	12	11	10	11	10	10	9	8	8	8	7	7
HBsAg loss - Genotype B	N = 1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1		
HBsAg loss - Genotype D	N = 7	7	7	7	7	6	6	6	6	6	4	4	3	2	2	3	2	2	2	
No HBsAg loss - Genotype A	N = 45	44	43	43	42	40	40	40	40	39	39	35	38	37	36	37	35	32	32	33
No HBsAg loss - Genotype B	N = 34	33	33	31	30	26	24	24	22	23	22	22	22	22	22	21	22	22	21	21
No HBsAg loss - Genotype C	N = 68	68	66	65	65	60	59	57	57	58	58	57	56	53	53	52	51	47	49	46
No HBsAg loss - Genotype D	N = 77	76	77	73	73	72	68	67	66	65	62	62	59	58	58	57	55	58	57	53

Marcellin, J Hepatol 2014;61(6):1228–1237; Zoutendijk R, et al. J Infect Dis 2012;206:974–80

Definition of HBV cure: what do we want to achieve?



- **Functional cure****:

Sustained undetectable HBsAg and HBV DNA in serum ± anti-HBs (**stop treatment, less monitoring in non cirrhotic, more safety, less money, no adherence issue, lower HCC, expand treatment criteria**).

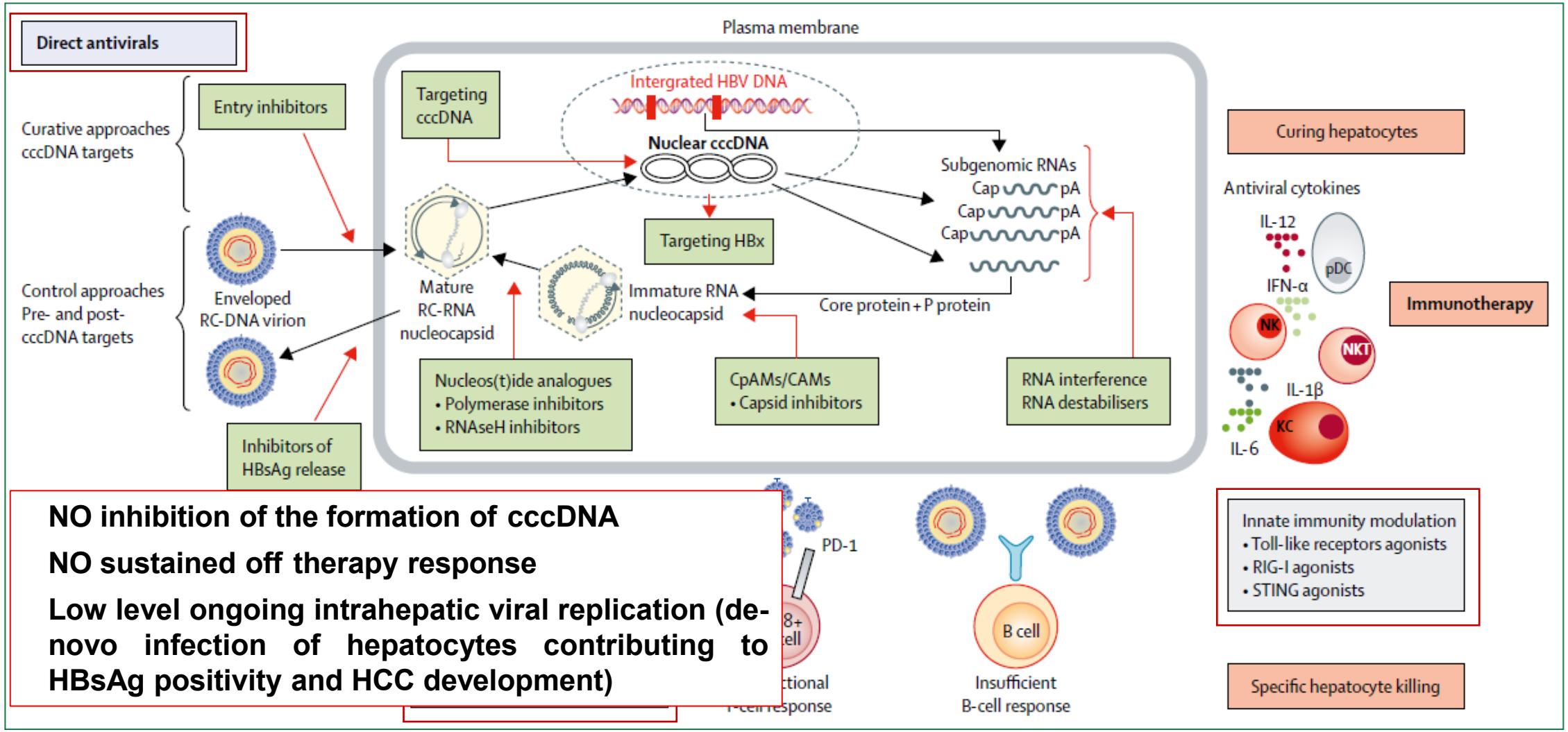
- **Complete Cure:**

Absence of cccDNA and Integrated HBV DNA

Adapted from: Testoni B, et al. Semin Liver Dis 2017;37:231–24

Lok AS, et al. J Hepatol 2017;67:847–61

Current and future HBV virological and immunological targets that will be necessary for treatment and cure of CHB



Revill P et al, Lancet GH 2019

Ideal future HBV Treatment Strategy

Inhibitors of viral replication

To suppress viral replication and cccDNA re-amplification (NA, CAMs)

+

Viral antigen inhibitors

To suppress antigen production or egress and to inhibit HBV life-cycle (entry inhibitors, RNA interference, ASO, NAPs)

Under advanced development

+

Immune modulators

To activate or restore immune responses to HBV (TLR-agonist, check point inibitors, therapeutic vaccines)

=

FUNCTIONAL CURE

+

cccDNA inhibitors

To silence or eliminate cccDNA (new liver-targeted delivery systems should overcome the potential off-target toxicities associated with ASO)

Future prospects

=

STERILIZING CURE

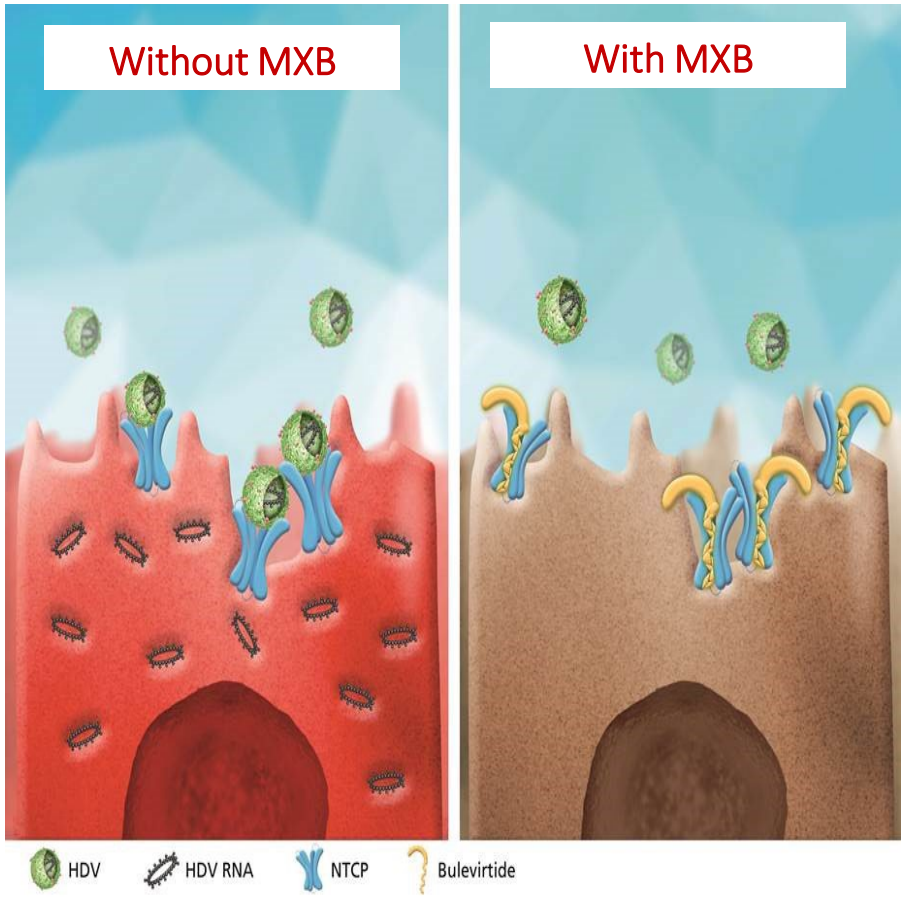
Loglio A, Viganò M, Lampertico P. CLD 2021

Novel anti-HBV drugs under clinical development

Antiviral Group	Main Mechanism	Subtype	Drug	Phase	Delivery	Clinical Trial Number
Inhibitors of viral replication	Inhibition of Capsid formation (CpAM)	Class 1	GLS-4 (Morphothiadin)/ritonavir	2	Oral	NTC04147208
		Class 2	JNJ-6379	2		NCT03361956
		Class 2	ABI-HB0731 (Vebicorvir)	2		NCT03780543
		Class 2	ABI-H2158	2		NCT04398134
		Class 2	EDP-514	1		NCT04470388
		NA	QL-007	1		NCT03244085
		Class 2	ZM-H1505R	1		NCT04220801
		Class 2	ABI-H3733	1		NCT04271592
		Class 2	ALG-000184	1		NCT04536337
		Class 1	RO7049389 (RG7907)	1		NCT02952924
Viral Antigen Inhibitors	Entry-inhibitor	NTCP binding	Bulevirtide	3	SC	NCT03852719
		Cyclophilin Inhibitor	CRV-431	1	Oral	NCT03596697
	RNA Interference	siRNA	JNJ 3989	2	SC	NCT04129554
			AB-729	2		NCT04820686
			VIR-2218	2		NCT03672188
			RG 6346	1 / 2		NCT03772249
		ASO	GSK-836-nonGaINAc	2	SC	NCT04449029
			GSK-404-GaiNAc	2		NCT03020745
			RO7062931-GaiNAc	1		NCT03038113
	Inhibition of HBsAg release	Nucleic acid polymer (NAP)	REP 2139	2	IV	NCT02565719
		STOPS	ALG-010133	1	SC	NCT04485663
	Interaction with host nuclear receptors	FXR agonist	EYP001	2	Oral	NCT04465916
Immune modulation	Enhancement of innate immunity	TLR-7 agonist	Vesatolimod (GS-9620)	2	Oral	NCT02166047
			RO7020531 (RG-7854)	1		NCT02956850
		TLR-8 agonist	Selgantolimod (GS-9688)	2	Oral	NCT03491553
	Enhancement of adaptative immunity	Checkpoint inhibitor	ASC22 (Anti-PDL1)	2	SC	NCT04465890
			APG-1387 (apoptosis inducer)	2	IV	NCT04568265
			Cemiplimab (Anti-PD1)	1 / 2		NCT04046107
			IMC-I109V (soluble T-cell receptor, ImmTAV molecule)	1 / 2		NCT03973333
			Nivolumab (Anti-PD1)	1		ACTRN126150011 33527 (Aaustralian-NZ registry)
		Therapeutic vaccine	HeberNasvac (ABX-203)	3	Intranasal	NCT02249988
			GS-4774	2	SC	NCT01943799
			HepTcell	2	IM	NCT04684914
			TG-1050	1	SC	NCT02428400
			AIC649	1	IV	NA
		Monoclonal antibody	GC1102	2	IV	NCT03801798
			VIR-3434	1	SC/IV	NCT04423393

Loglio A, Viganò M , Lampertico P. Clin Liv Dis 2021

Myrcludex B (MXB) or Bulevirtide (BLV) is the first-in-class entry inhibitor



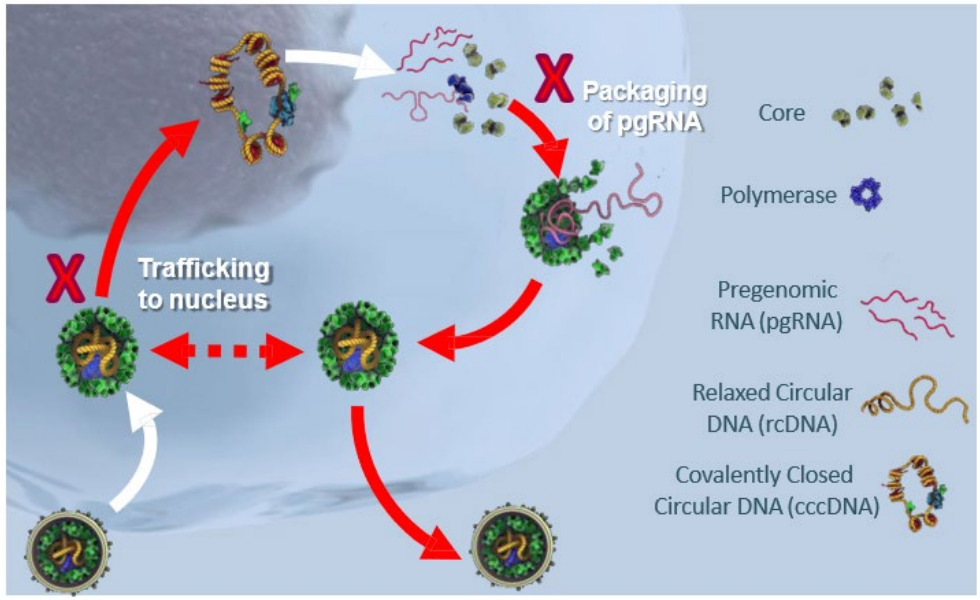
- BLV blocks the interaction between sodium/taurocholate cotransporting polypeptide (NTCP) and large-HBsAg, is the **first** entry receptor for HBV/HDV.
- Hence, new infections are prevented.
- Infected hepatocytes are replaced by naive cells, which will be protected from infection.
- Consequently, viral spread in the liver is prevented.

A phase 1b/2a clinical trial evaluated daily BLV vs ETV in 48 naïve HBeAg-negative CHB patients (0.5 mg, 1 mg, 2 mg, 5 mg daily doses for 12 weeks, 10 mg/day for 24 weeks and ETV 0.5 mg for 24 weeks).
No one showed HBsAg >0.5 Log decline during 24 weeks of BLV 10 mg vs ETV.
At week 12, HBV DNA was negative in 25%, 0%, 25%, 12%, 75% under increasing dose of BLV, while 100% under ETV, while ALT normalized in 43%, 57%, 50%, 50%, 67% and 57%, respectively.

Urban S, Gastroenterology. 2014;147:48–64

CAM (capsid assembly modulators)

Core Protein Inhibitors (CIs)



- Bind to dimer-dimer interface of Core protein (a unique viral protein that is essential for the HBV nucleocapsid assembly).
- Trigger formation of aberrant capsids, preventing packaging of pgRNA and production of virus
- Disrupt trafficking of nucleocapsids to nucleus, blocking the generation of **cccDNA**
- A CAM-based strategy would have the advantage of being administered **orally** but the disadvantage of requiring a **combination therapy with NUC** to minimize the risk of resistance. **Serum antigen were not affected and rebound was observed after withdrawal**.

Colonno R. et al, EASL 2019

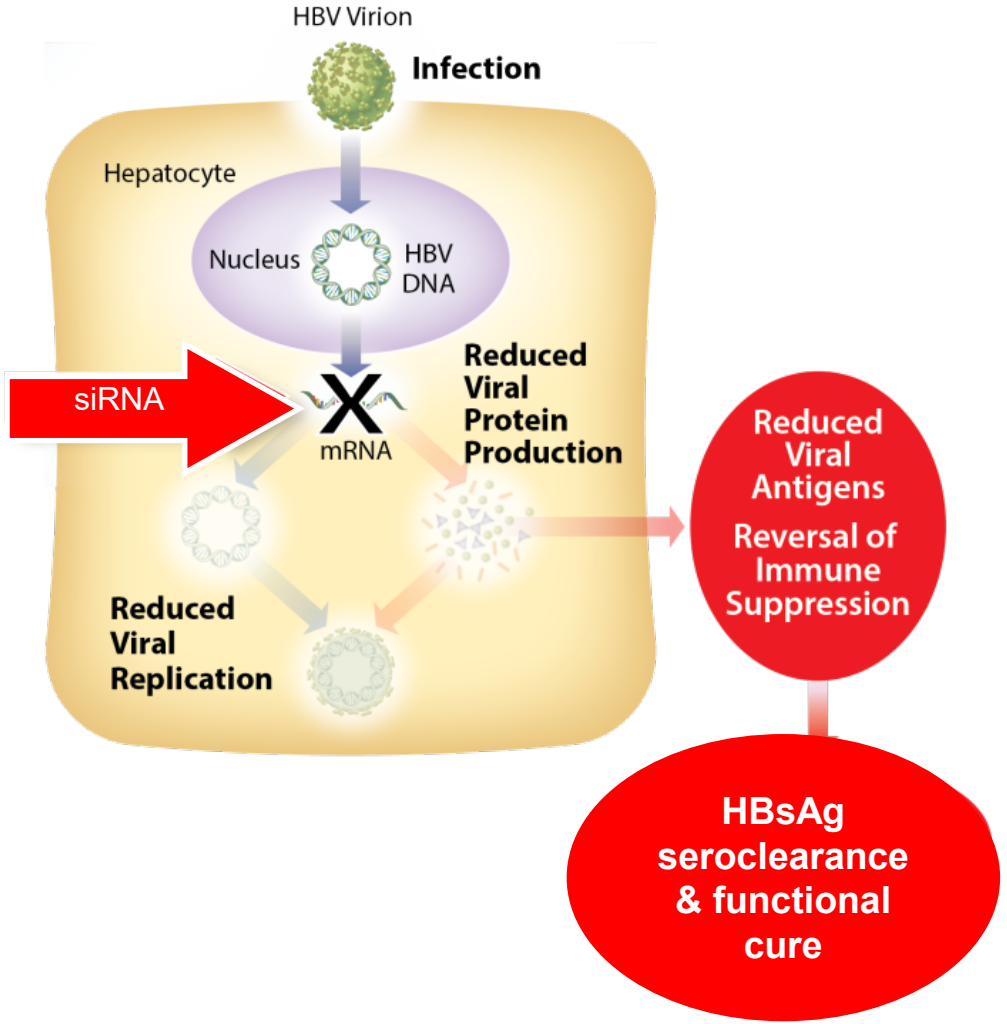
CAM (capsid assembly modulators)

Drug in phase-I/II development	Pharma	Strategy	Control Group	Interesting results
GLS-4	Sunshine Lake Pharma	CAM+ritonavir+ETV	ETV	At week 24 HBsAg decline: 0.43 vs 0.21 Log IU/mL, pgRNA suppression: 2.63 vs 0.27 Log IU/mL
		CAM+ritonavir+ETV	ETV	At week 24 HBsAg decline: 0.11 vs 0 Log IU/mL, pgRNA suppression: 1.59 vs 0.15 Log IU/mL
JNJ-6379	Janssen	CAM 75 mg+NA	NA	At week 24 HBV RNA decline: 2.8 vs 1.4 Log cp/mL
		CAM 250 mg+NA	NA	At week 24 HBV RNA decline: 3.1 vs 1.4 Log cp/mL
		CAM+NA	NA	At week 24 HBsAg decline: 0.4 vs 0 Log IU/mL
ABI-H0731 (Vebicorvir)	Assembly Biosciences	All patients experienced a virological relapse and none achieved HBsAg clearance following drug discontinuation to achieve a finite HBV treatment, the clinical development of this compound was halted by the company in February 2021. (Vebicorvir is now being considered as a chronic rather than curative treatment).		
ABI-H2158	Assembly Biosciences	The biotech stop work on the experimental treatment due to increased liver toxicity.		

Zhang M, J Hepatol 2020;73:S878–S879; Janssen H, J Hepatol 2020;73:S129-S130; Huang Q, Antimicrob Agents Chemother. 2020;64:e01463-20; Xiaoli MA, J Hepatol 2019;70:e130; Gane E, J Hepatol 2021;75:S736

RNAi therapeutics for HBV

- Subcutaneously at monthly doses
- A single siRNA can silence multiple transcripts, potentially blocking the production of the core, X-, polymerase, surface proteins, and directly inhibit HBV replication and indirectly restore HBV-specific immunity.
- While first developed siRNA targets cccDNA-derived pgRNA a second-generation (i.e. ARC521) which targets both integrated and cccDNA have been developed.



Chen Y, Pharm Res 2008;25:72–86; Flisiak R, Expert Opin Biol Ther 2018;18:609–17; Yuen M, J Hepatol. 2016;64:S390

Short-term RNAi therapy with JNJ-3989 in NUC naïve and NUC suppressed CHB

- GAL-NAC conjugation ⇨ SC administration
- X and S triggers → silence all mRNA from both cccDNA and host integrated viral DNA

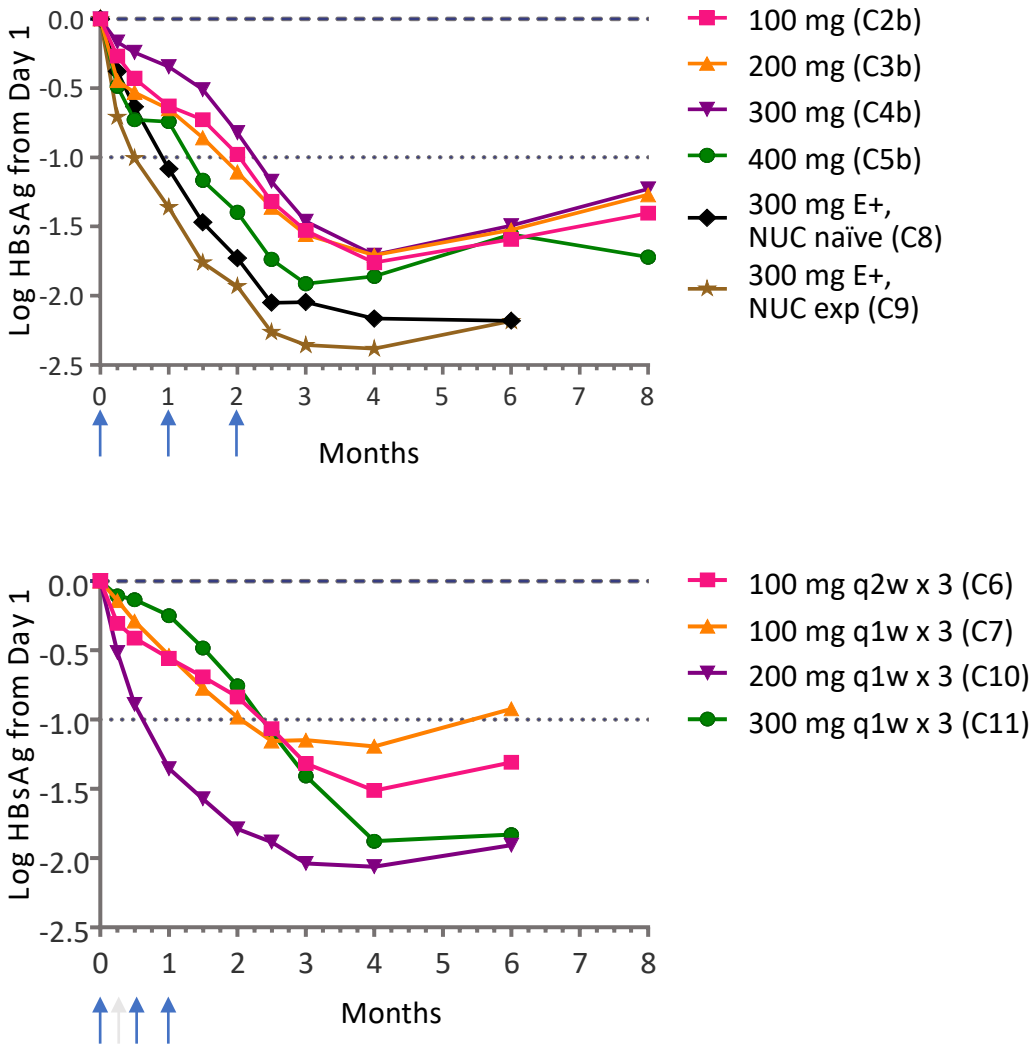
Safety (56 CHB patients received 168 doses)

- No Grade 3 or 4 AEs, or treatment withdrawal
- No clinically significant laboratory abnormalities
- No dose relationship with AEs or lab abnormalities
- Injection site AEs in 10% (rash, erythema, bruising, etc)

Efficacy

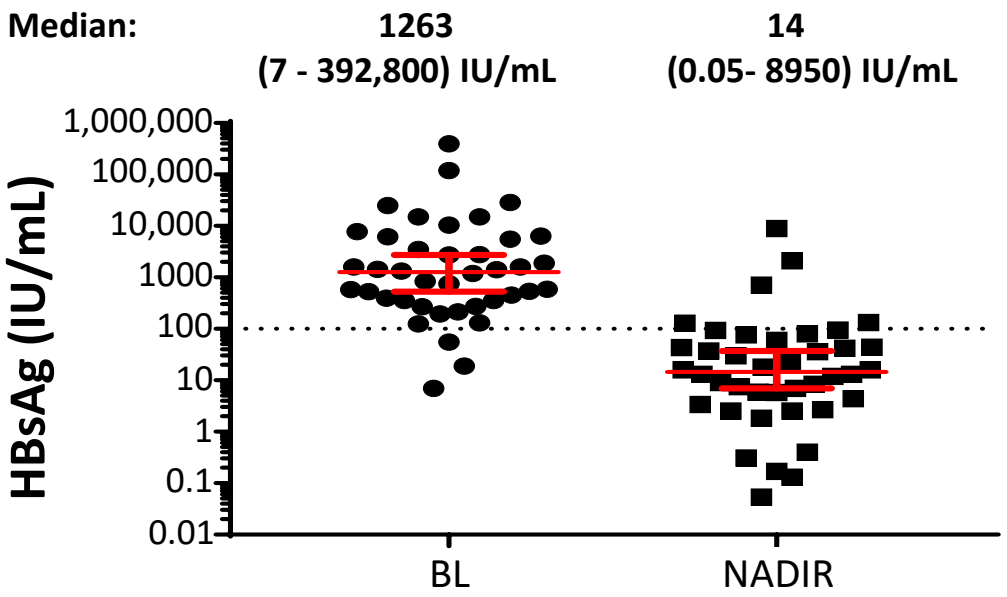
- Nadir in HBsAg is reached at around 4 months post start of therapy and persisted for >4 months after last dose
- Nadir is same with shorter dosing intervals

Mean HBsAg reductions



Short-term RNAi therapy with JNJ-3989 in NUC naïve and NUC suppressed CHB

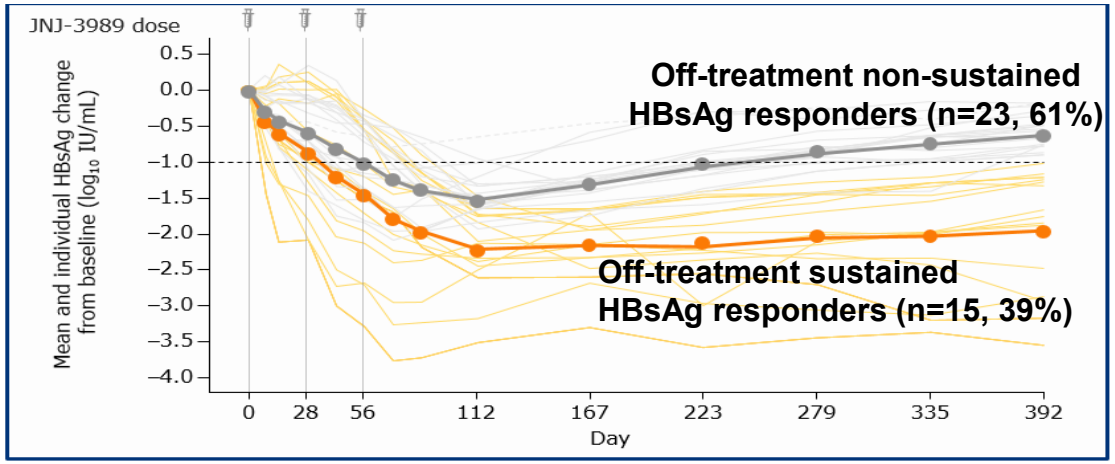
HBsAg <100 IU/mL in most patients



Baseline HBsAg	
>1000 IU/mL	51%
>100 IU/mL	93%

NADIR HBsAg	
≤100 IU/mL	88%
≤10 IU/mL	43%
≤1 IU/mL	13%

Sustained response (≥1 Log IU/mL reduction in HBsAg)



Reductions in HBV RNA, HBcrAg and HBeAg levels were generally more pronounced in HBsAg sustained responders than in non-responders.

Further studies will determine whether repeated dosing achieves sustained HBsAg loss.

Safety and antiviral activity of the siRNA VIR-2218 with the neutralizing, vaccinal monoclonal antibody VIR-3434: post-treatment follow-up from the MARCH trial

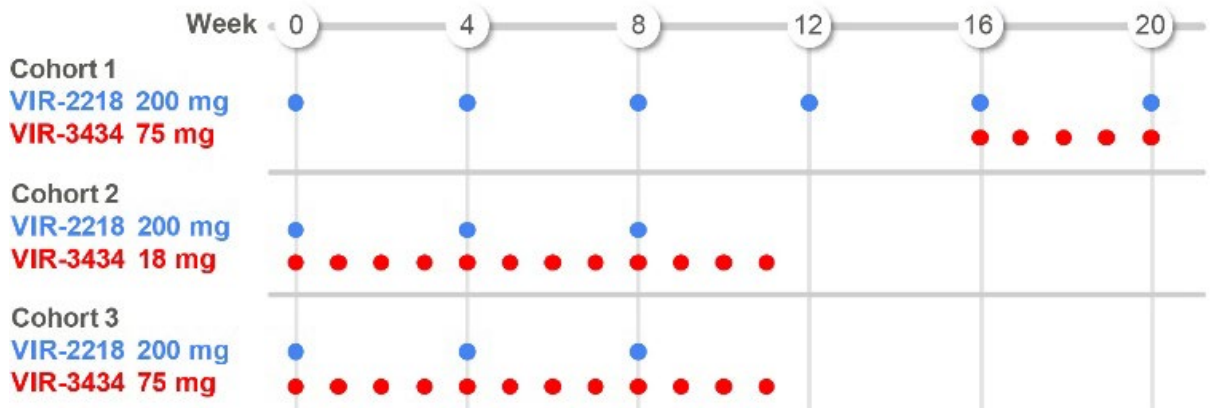
BACKGROUND & AIMS

- There is an unmet need for a finite, curative, and well-tolerated treatment regimen for chronic HBV infection
- VIR-2218 is an investigational siRNA targeting the HBx region of the HBV genome
- VIR-3434 is an investigational Fc-engineered human monoclonal antibody targeting the conserved antigenic loop of HBsAg
- The phase 2, open-label MARCH trial is evaluating the safety, tolerability, and antiviral activity of combination regimens containing VIR-2218 and VIR-3434 for the treatment of chronic HBV infection
- **AIM:** To report post-treatment follow-up from part 1 of the MARCH study, evaluating low-dose, short-duration regimens in patients with chronic HBV infection

METHOD

Eligibility for Cohort 1:
Aged ≥18 years
Chronic HBV infection
Received continuous NRTI therapy for ≥2 months

Eligibility for Cohorts 2 and 3:
Aged ≥18 years
Chronic HBV infection
Received continuous NRTI therapy for ≥2 months
HBsAg <3,000 IU/mL at screening



Primary endpoints:
Proportion of participants with TEAEs
Proportion of participants with serious AEs
HBsAg loss at EOT and at 24 weeks post-EOT

Gane EJ, et al. EASL 2023; OS-031

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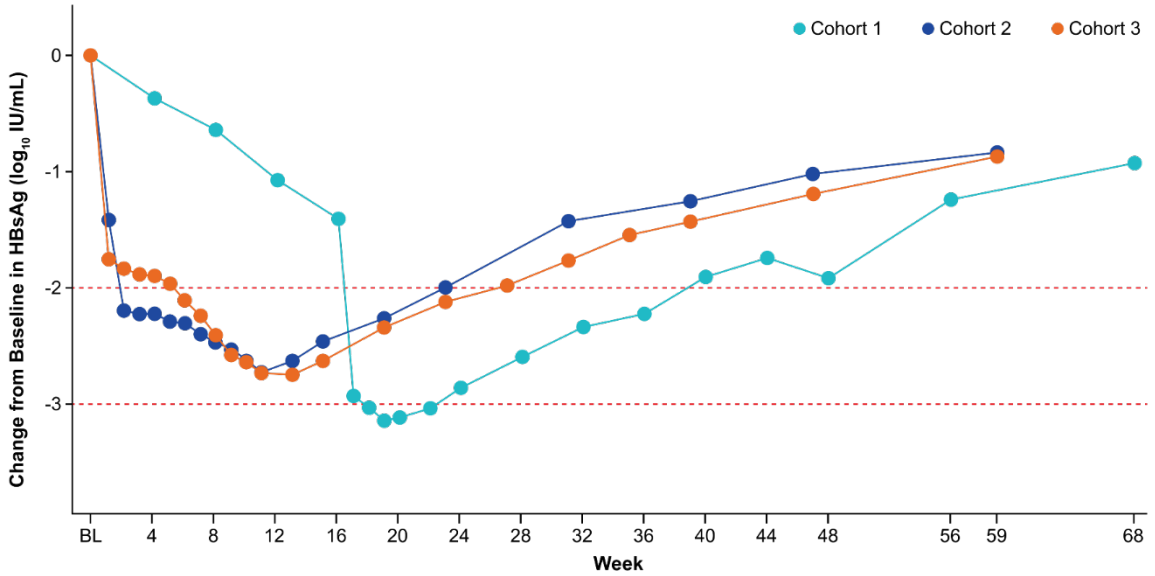
Safety and antiviral activity of the siRNA VIR-2218 with the neutralizing, vaccinal monoclonal antibody VIR-3434: post-treatment follow-up from the MARCH trial

RESULTS

- 40 participants were enrolled across Cohort 1 (n=17), Cohort 2 (n=4), and Cohort 3 (n=19)
- At EOT, mean HBsAg reductions were 2.7-3.1 log_{10} IU/mL; 90% of participants achieved HBsAg < 10 IU/mL
- HBsAg gradually rebounded after EOT but remained almost 1 log_{10} IU/mL below baseline on average in all cohorts at 48 weeks post-EOT
- No participants achieved HBsAg loss or functional cure
- TEAEs were generally mild or moderate
  - Treatment-related TEAEs were uncommon, and no TEAEs led to treatment discontinuation

Mean HBsAg change from baseline by cohort (log_{10} IU/mL)



CONCLUSIONS

- The on-treatment data from Part 1 of the MARCH study established initial proof-of-concept that combination treatment with VIR-2218 plus VIR-3434 is well tolerated and results in additive antiviral activity
- As expected, given the low dose of VIR-3434 administered and short duration of combination treatment, participants experienced an increase in HBsAg off treatment
- These data, together with VIR-2218 plus interferon data showing 31% HBsAg loss at EOT, support the evaluation of longer durations of treatment with VIR-2218 plus VIR-3434 with and without interferon in part 2 of the MARCH study

Gane EJ, et al. EASL 2023; OS-031

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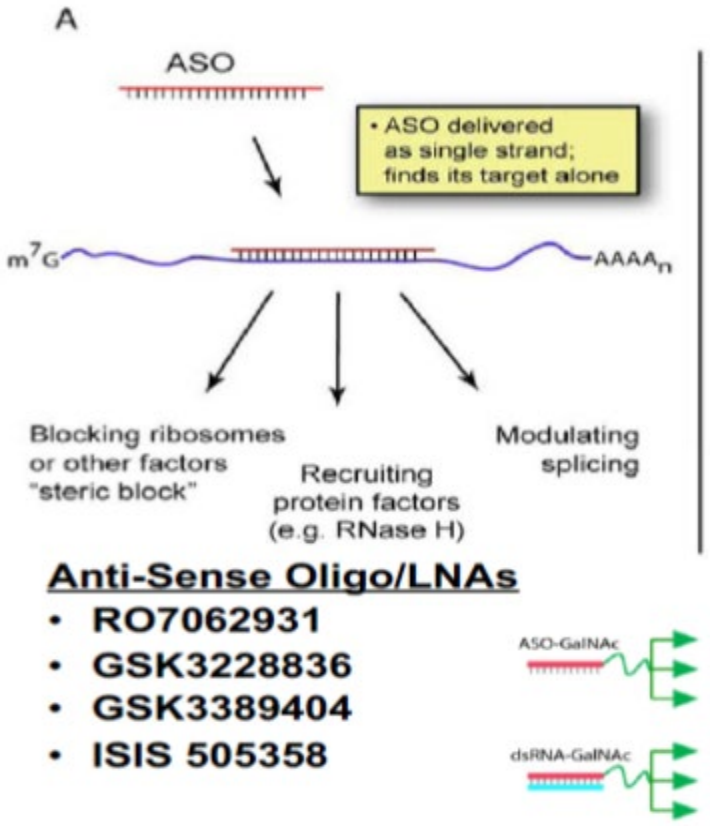
Antisense oligonucleotide (ASO) IONIS-HBVRx (GSK3228836)

Drug in phase-II development	CHB population	Strategy	Interesting results
GSK3228836	NA-naive	ASO followed by NA	HBsAg decline: >3 Log IU/mL in 3 out of 12 patients
	NA-treated	ASO + NA	HBsAg decline: >3 Log IU/mL in 3 out of 4 patients



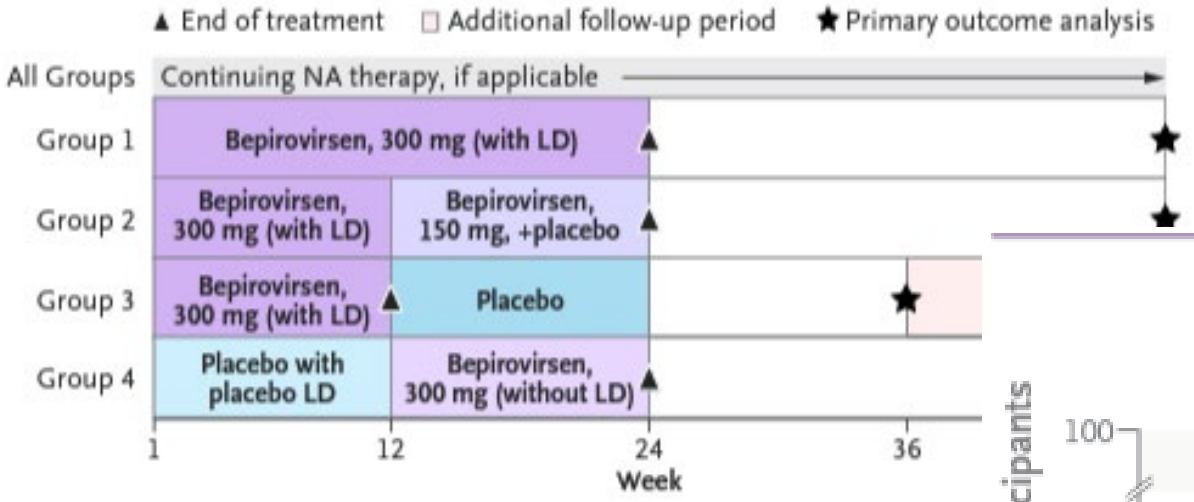
Subcutaneus administration
Recognize all HBV RNAs and reduce the production of viral proteins, by inducing cleavage of HBV RNAs in the nucleus and cytoplasm via RNase H1.

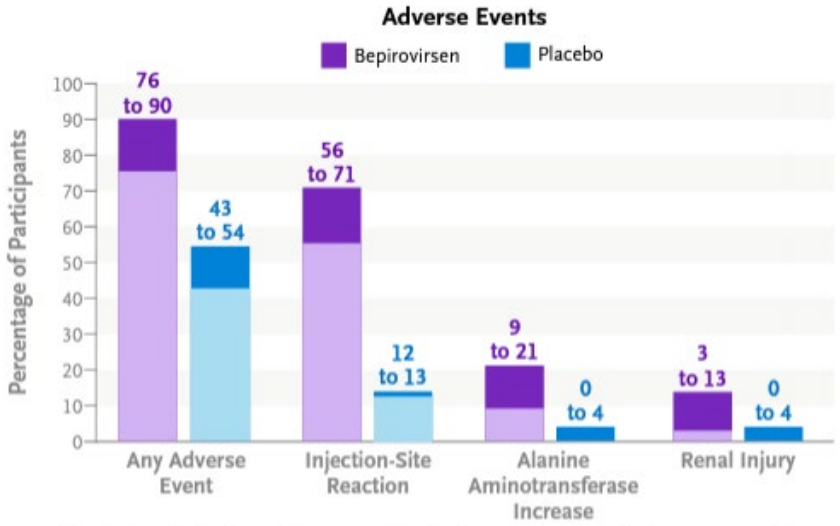
Prolonged HBsAg loss was observed in one NA-treated and one NA-naive patient. However, post-ASO, **ALT flare** (up to 15xUNL) occurred in both naive than NA-treated group, likely indicative of infected hepatocyte clearance.

Longer administration of GSK3228836 in under evaluation.

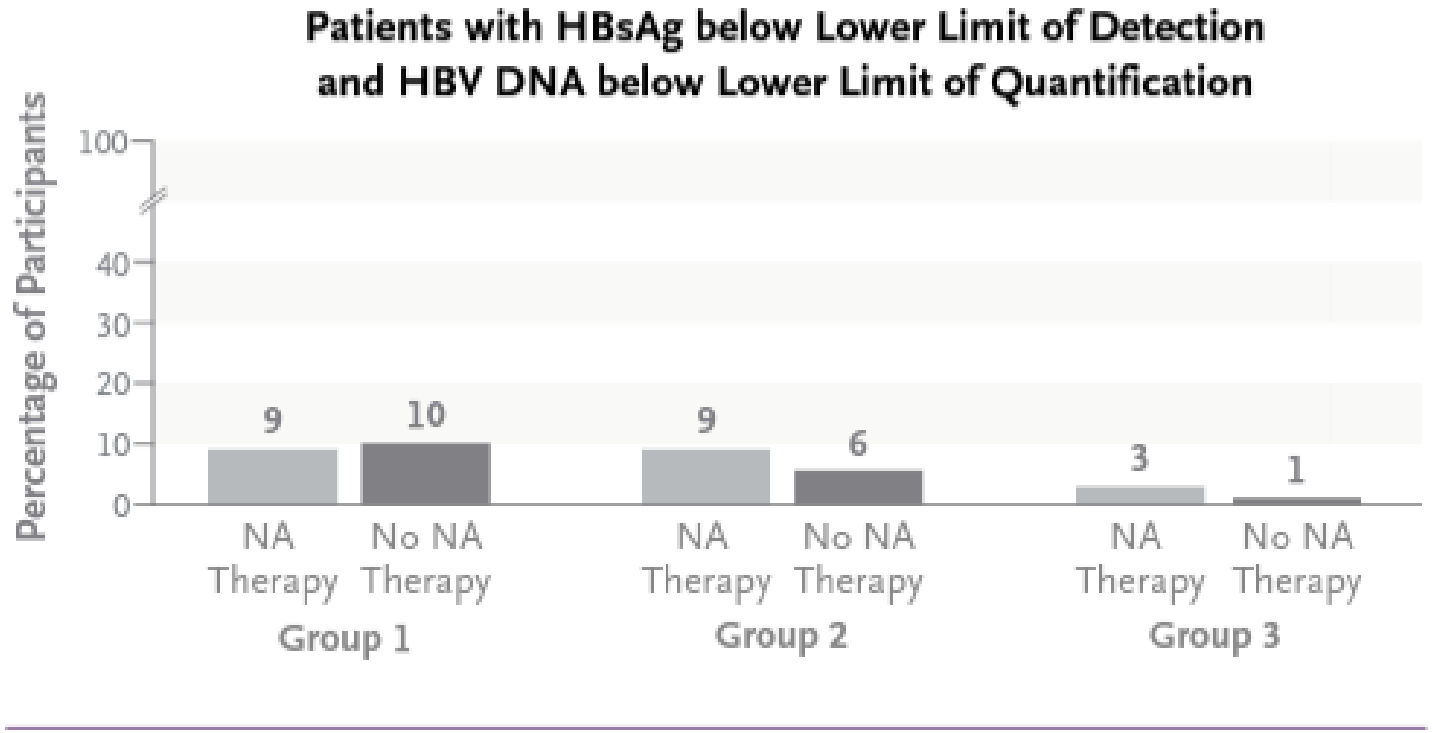
Yuen MF, J Hepatol 2020;73:S49

Bepirovirsen





The lighter shade in each bar extends to the lower percentage in the range, and the darker shade to the higher percentage.



Yuen MF, NEJM 2022; 387(21):1957-1968

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

RESULTS

Baseline characteristics and demographics

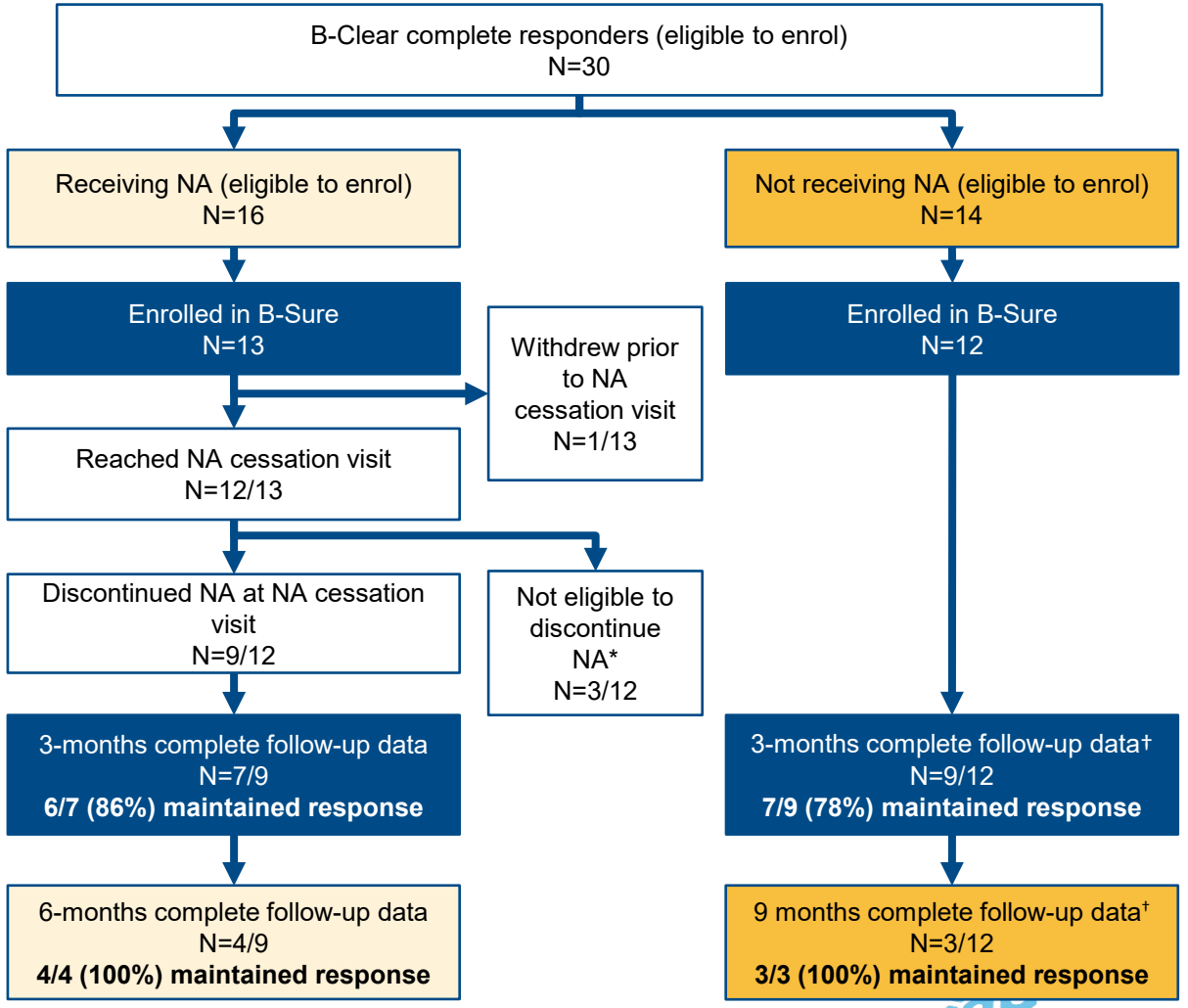
Characteristic	NA N=13	No NA N=12
Age, mean, years	53.2	43.8
Sex, male, n (%)	12 (92)	7 (58)
Chronic HBV infection ≥20 years, n (%)	6 (46)	3 (25)
$HBeAg^-$, n (%)	10 (77)	12 (100)
HBsAg ≤1000 IU/mL at baseline in B-Clear study	9 (69)	7 (58)

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

CONCLUSION

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

Participant flow diagram and treatment response



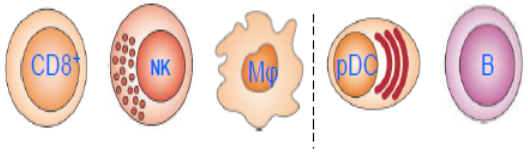
*Investigator discretion: evidence of prior or current cirrhosis, or participant preference leading to contraindication. †Duration of response does not include the time between end of bepirovirsen treatment and B-Sure enrolment (≥6 months).

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

EASL™ The Home of Hepatology

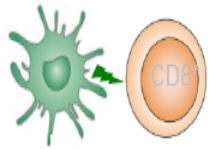
How can we activate Antiviral Immune Responses?

1. Stimulate Antiviral Effector Cells



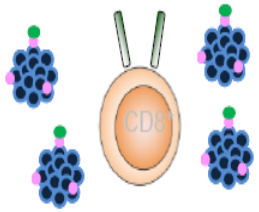
- TLR-7, TLR-8, RLRs, CLRs, NLRs
- DNA sensors

2. Generate New T cells



- Therapeutic vaccines

3. "Rescue" Exhausted T cells



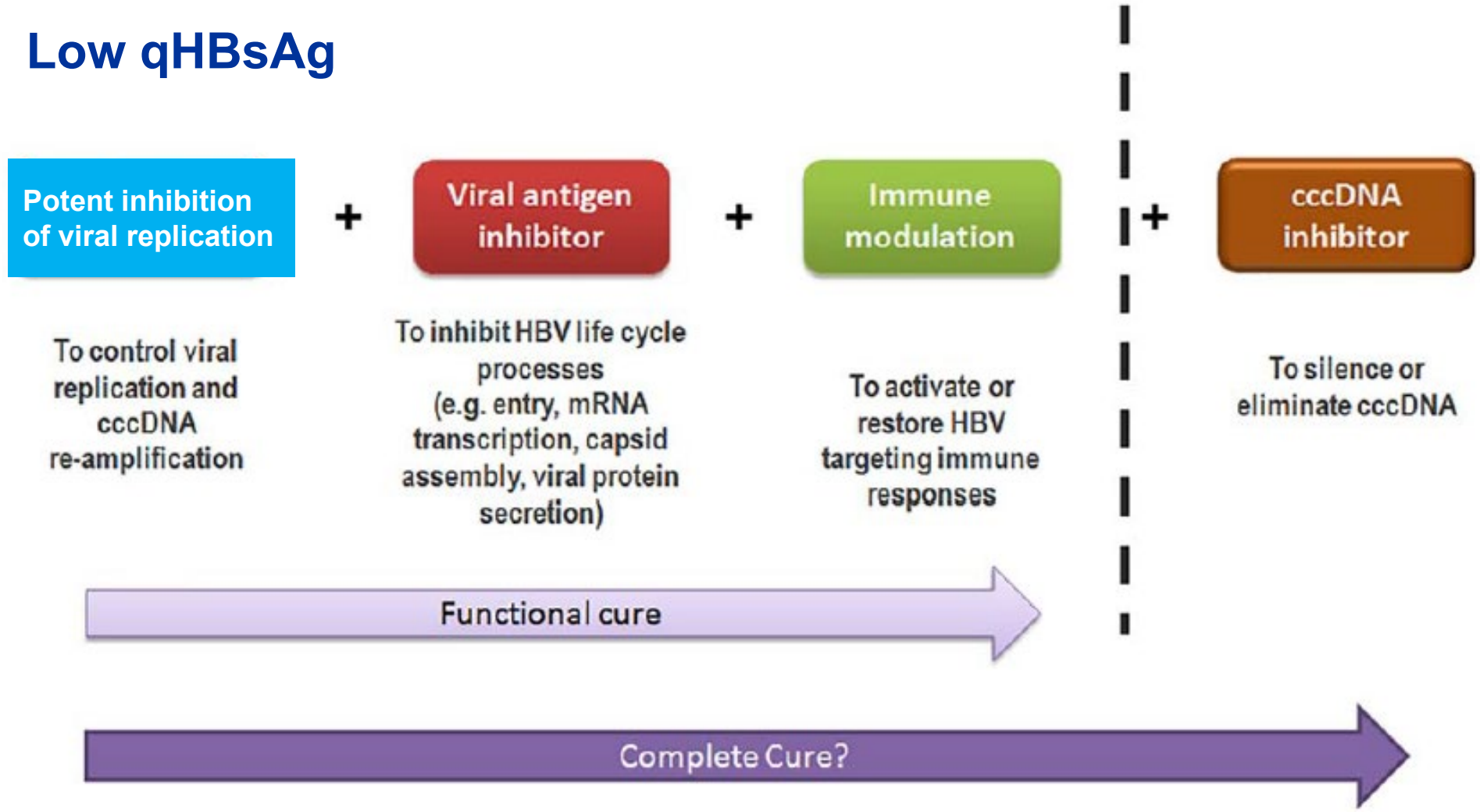
- Reduce viral antigens
- Modulate immune receptors (PD-1)
- Relieve suppression of T cells
- Inhibit T regs

Since a vigorous and multispecific host immune response, mainly CD8+ T-cell mediated, against HBV is the major determinant of spontaneous clearance following an acute infection, several approaches were evaluated that were thought **to activate antiviral immunity against HBV**, through the:

- stimulation of antiviral effector cells (T, B cells and dendritic cells)
- generation of "new" T cells (therapeutic vaccines)
- recovery of exhausted T-cells (typical of chronic HBV infection).

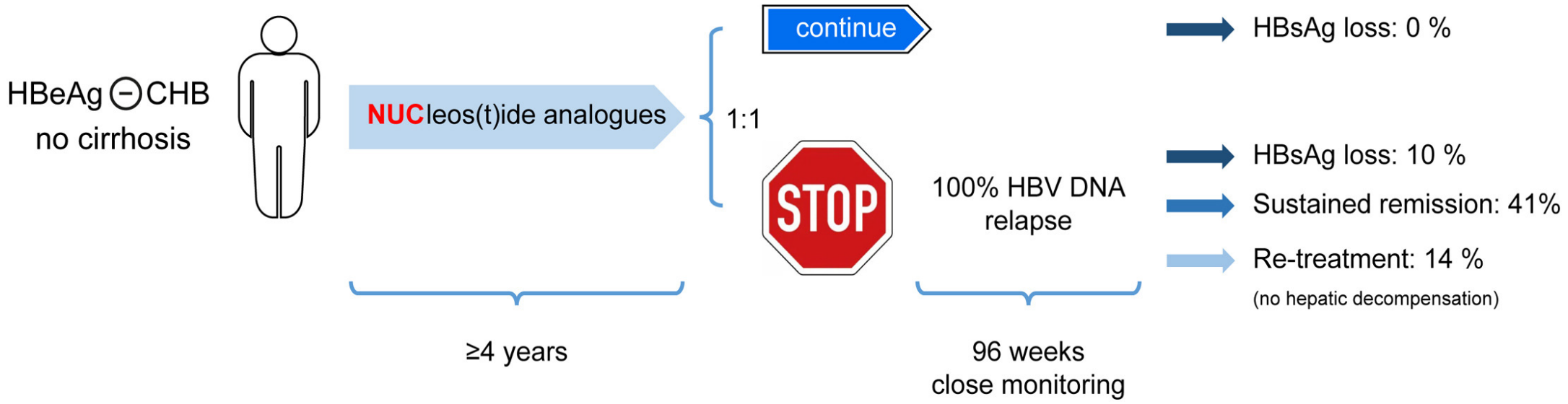
Combination of drugs - The possible future curative regimen for HBV

Low qHBsAg



modified from Seto WK And Yuen MF. Clinical Liver Disease 2016;8,4, 83-88

Stop NUC for HBsAg seroclearance?



Non cirrhotic patients

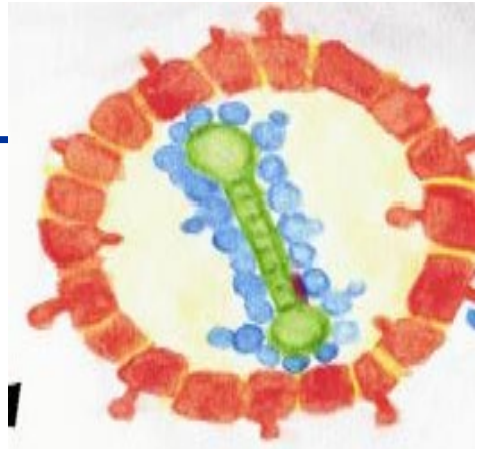
<65 years old

qHBsAg <1,000 or <100 IU/mL according to Caucasian or Asian ethnicity

Prospective and multicenter studies required, with close EOT monitoring

Van Bommel F, J Hep 2023; Cheng Hepatology 2018; Loglio, Viganò DLD 2023

Hepatitis D (delta) Virus

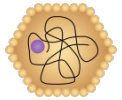
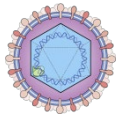
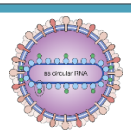
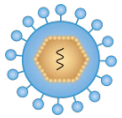


Calle Serrano et al, Semin Liver Dis. 2012
Lempp et al, Nat Rev. 2016

- Defective RNA virus that needs HBsAg for its propagation
- Causes the most severe form of chronic viral hepatitis

  More rapid progression to liver cirrhosis and liver cancer; 5-7x more likely to develop cirrhosis and HCC vs HBV
- No effective therapy (NUC not effective, IFN for selected patients with only 20% VR)
- New therapies under development (LNF, Peg-Lamda) and one approved (Bulevirtide)

HDV is the most severe form of viral hepatitis

	Risk of progression to chronic infection?		Risk of cirrhosis/HCC?	
 Hepatitis A[1]	✗	No, but can cause fatal fulminant hepatitis in a very small proportion	✗	No as infection is generally short-lived
 Hepatitis B[2,3]	✓	Acquired in Adulthood: <5% Acquired as an infant/child: ~95%	✓	Cirrhosis: 8–20% (5 years)* HCC: 2–5% (annually)†
 Hepatitis C[4,5]	✓	55–85%	✓	Cirrhosis: 10–30% (20 years)
 Hepatitis D[6]	✓	Coinfection: 10%[6] Superinfection: 77%‡[6]	✓	Cirrhosis: 70% (5–10 years)[7] HCC: within 10 years[6]
 Hepatitis E[8]	✓	Can occur rarely in immunosuppressed individuals	✗	No, as virus does not result in chronic infection

*In untreated CHB patients. †In patients with cirrhosis. ‡Superinfection refers HDV infection in an individual who already has established HBV infection or HBsAg+.

1. WHO. Hepatitis A. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-a; 2. WHO. Hepatitis B. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b; 3. EASL. J Hepatol 2017;67:370–98; 4. Chen SL, et al. Int J Med Sci 2006;3:47–52; 5. WHO. Hepatitis C. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c; 6. Miao Z, et al. J Infect Dis 2020;221:1677–87; 7. Noureddin M, et al. Curr Gastroenterol Rep 2013;16:365; 8. WHO. Hepatitis E. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-e (all WHO fact sheets).

HDV vs HBV: disease progression

Clinical Outcome	RR increase compared with HBV
Cirrhosis	2- to 3-fold
HCC	3- to 6-fold
Liver transplantation	2-fold
Hepatic decompensation	2-fold
Mortality	2-fold

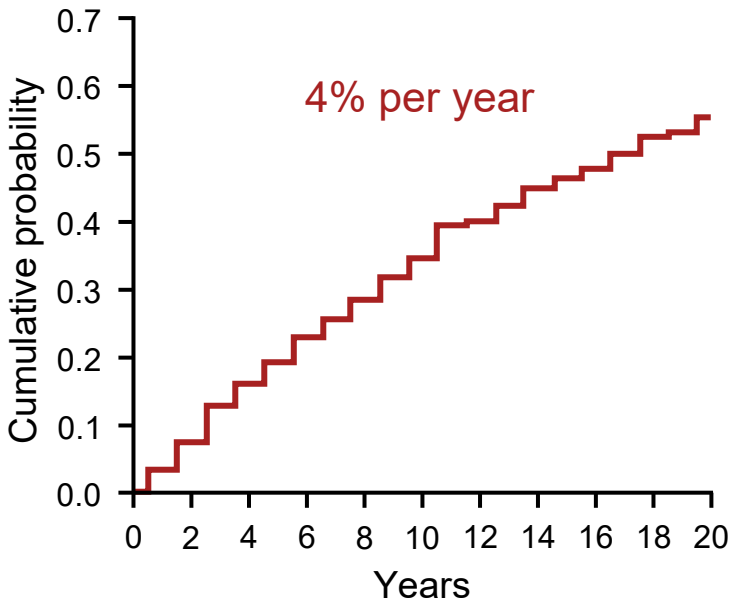
HIV/HBV/HDV triple-infected had **6-fold** increased risk of HCC compared to HIV/HBV patients

Papatheodoridis G, Lampertico P et al. Hepatology 2017

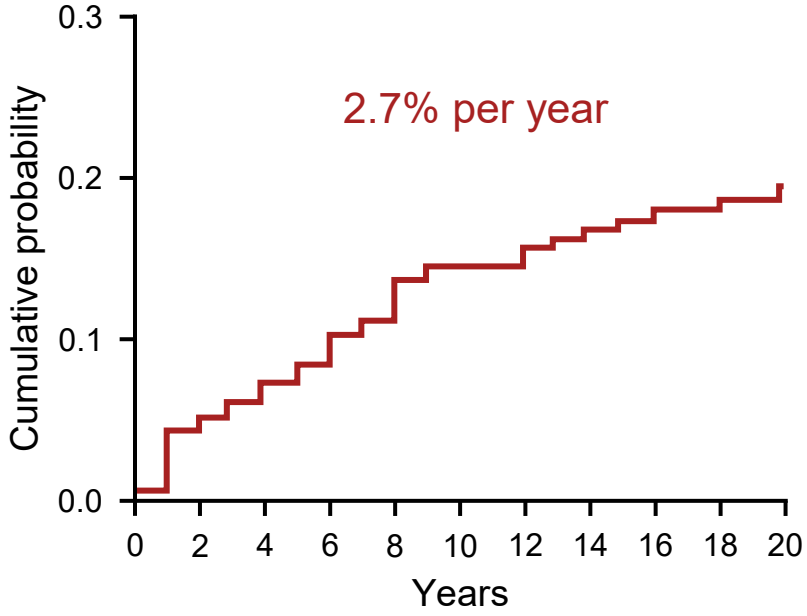
HDV RNA levels and liver disease progression

Retrospective study of a cohort from Milan, Italy (n=299, mean follow-up: 233 months)

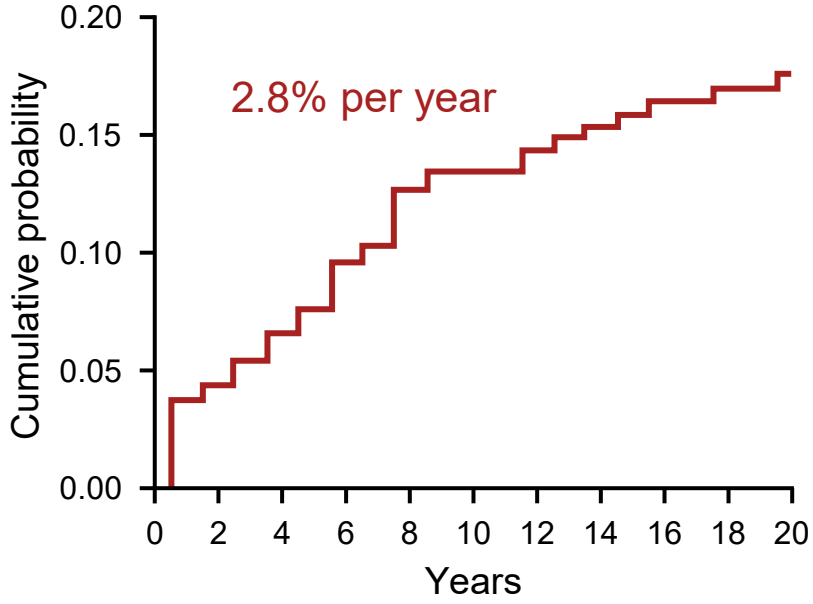
Cirrhosis development
(n=299 non-cirrhotics, mean FU 233 months)



Clinical decompensation
(n=186 cirrhotics, mean FU 125 months)



HCC development
(n=299 non-cirrhotics, mean FU 233 months)



HDV RNA was independently associated with all liver-related outcomes and was the only predictor of mortality

Romeo R et al. Gastroenterology 2009; 136:1629–1638

HDV in Italy

	Population size estimates	Rationale and comments	Source	Strength of source
Prevalence of chronic hep B	**457 384**	• **Prevalence of 0.6% HBV infections among the total population** • The modelled prevalence was used from the Lancet Study	• Lancet 2018 Study, World Bank Data	
Diagnosed Hep B	**133 771**	• **The diagnostic rate of HBV infections is 29%**	• According to the Lancet 2018 Study, and Polaris observatory (CDA foundation) modelling.	
HDV co-infected	**13 000**	• Study done by Stroffolini T et al. in 2020 found a prevalence of **9,9%** among HBsAg-positive people (6.4% in Italian natives and 26.4% in non-natives) • Higher co-infection rates from previously used study of Brancaccio et al 2019, which had a HDV prevalence of 8,2% among HBsAg+ patients	• Cited in the journal Viral Hepatitis. • Study performed in 9 tertiary centers during a six-month period from January 2019 to June 2019.	

Outcomes		• **Anti-HDV antibodies were more frequently detected in patients with cirrhosis (17.5% vs 5.4%)**
		• In another study from HDV referral centres,
		  • Majority (80.3%) of HDV co-infected them was >50y years or older
		  • Presence of liver cirrhosis was diagnosed in 52.4% of cases
		• **Non-natives are six-fold more likely anti–HDV-positive with an increasing trend.**
		• A decrease of HDV co-infection was previously shown among Italian patients
				

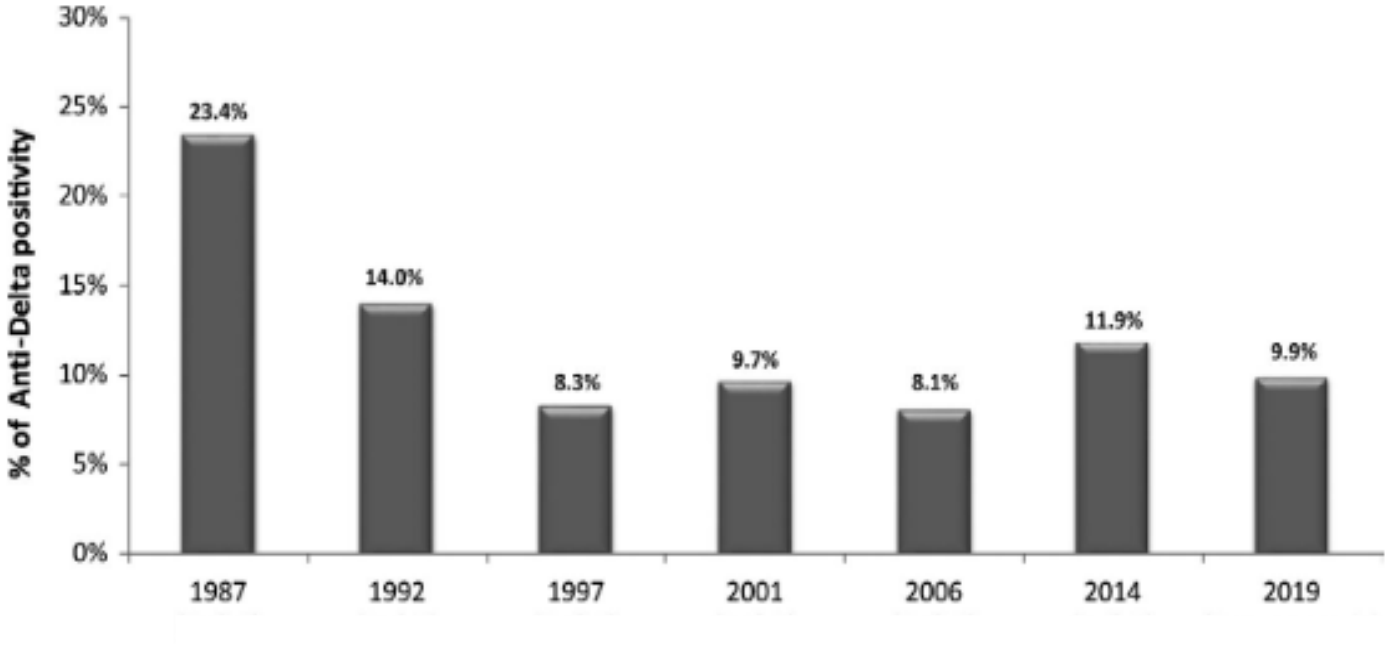
HepB, Lancet modelling (2018), Polaris Group modelling (2018)
HepD, Alexander J. Stockdale et al., The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis

HDV prevalence in HBsAg positive populations: Differences in general and Hepatology clinics

Region	General HBsAg+ Populations		HBsAg+ in Hepatology Clinics	
	% HDV-Ab (HDV RNA pos)	95% CI	%	95% CI
African region	5.9 (41)	4.98-7.24	12.2	10.13-14.70
Region of the Americas	5.9 (64)	3.02-9.71	3.3	2.58-4.21
Eastern Mediterranean region	3.5 (49)	2.10-6.28	17.4	11.15-26.34
European region	3.0 (64)	2.09-4.21	19.5	17.31-21.76
South-East Asian region	3.2 (50)	0.36-12.4	4.0	3.09-5.15
Western Pacific region	4.0 (73)	3.47-4.77	8.0	7.50-8.64
Global	4.5 (58)	3.57-5.68	16.4	14.58-18.56

Stockdale. J Hepatol. 2020;73:523.

Changing Epidemiology of HDV in Italy



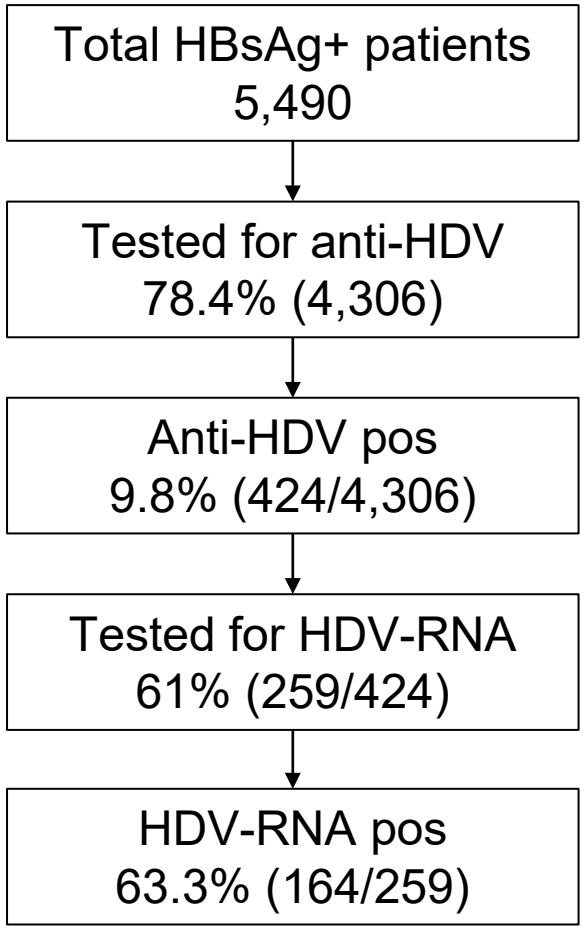
- Improvements in public health
- Modifications in sexual behaviors due to HIV
- Introduction of universal HBV vaccination
- HDV infection is vanishing in the domestic populations
- Young migrants

Inadequate HDV Testing Rates in Italy – PITER HDV

A cross-sectional, consecutive study of HBsAg-pos patients over 2019-2/2022 from 59 tertiary Centers in Italy

22% migrants

60% of non-Italian have cirrhosis



21.6% patients never tested for HDV
(22.3% Italian *vs* 18.4% non-Italian)

39% never tested for HDV-RNA

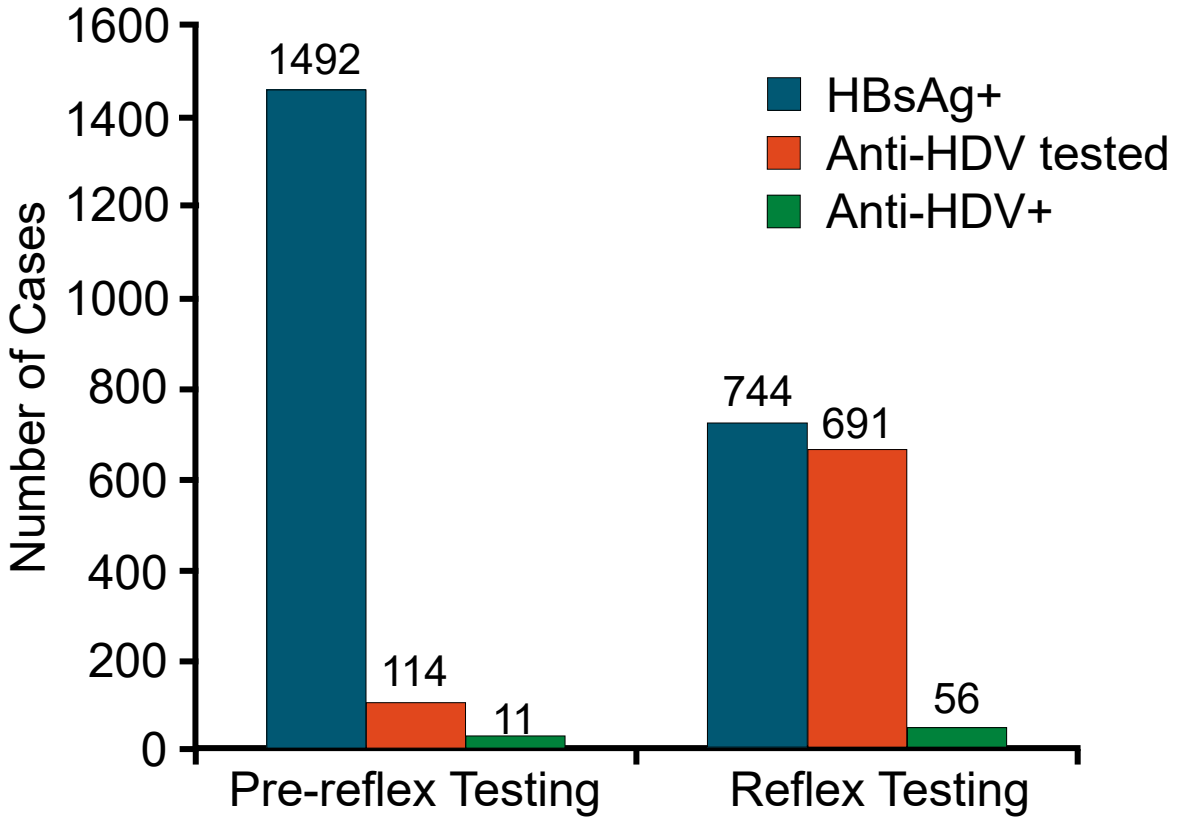
Importance of HDV RNA quantification test

Kondili L. AISF 2023 meeting. Brancaccio G., et al. Int J Infect Dis 2023; 129: 266-273.

Anti-HDV reflex testing increases the number of cases diagnosed

- Anti-HDV reflex testing in all HBsAg+ patients led to a 5-fold increase in absolute chronic HDV diagnoses
- anti-HDV testing with reflex: from 7.6% (23% in academic vs 2% in primary care centers) to 93% (91% vs 100%)
- 65% HDV-RNA positive, 64% HBV-DNA undetectable, 48% normal ALT
- 60% of patients had unknown risk factors

Number of Anti-HDV+ Cases Prior To and After Reflex Testing



Palom. JHEP Rep. 2022;4:100547

HDV REFERRAL

Vista la rapida progressione della malattia da HDV verso forme avanzate di cirrosi, si ritiene che i pazienti con epatite cronica Delta (CHD) debbano essere seguiti presso centri epatologici con documentata esperienza nella gestione dei pazienti con epatite virale e accesso alla diagnostica di secondo livello (ie. centri con esperienza nella gestione dei pazienti con epatite da HBV e accesso ai test di laboratorio per HDV). È fondamentale, inoltre, che questi centri abbiano uno stretto collegamento con i centri trapianto di fegato di riferimento a livello regionale per il *referral* dei pazienti con malattia HDV scompensata o con HCC. Tutti i centri autorizzati a livello regionale a prescrivere antivirali diretti contro HCV (DAA) che presentano queste caratteristiche possono essere considerati come il *setting* ideale per il *referral* e la gestione di pazienti con CHD.

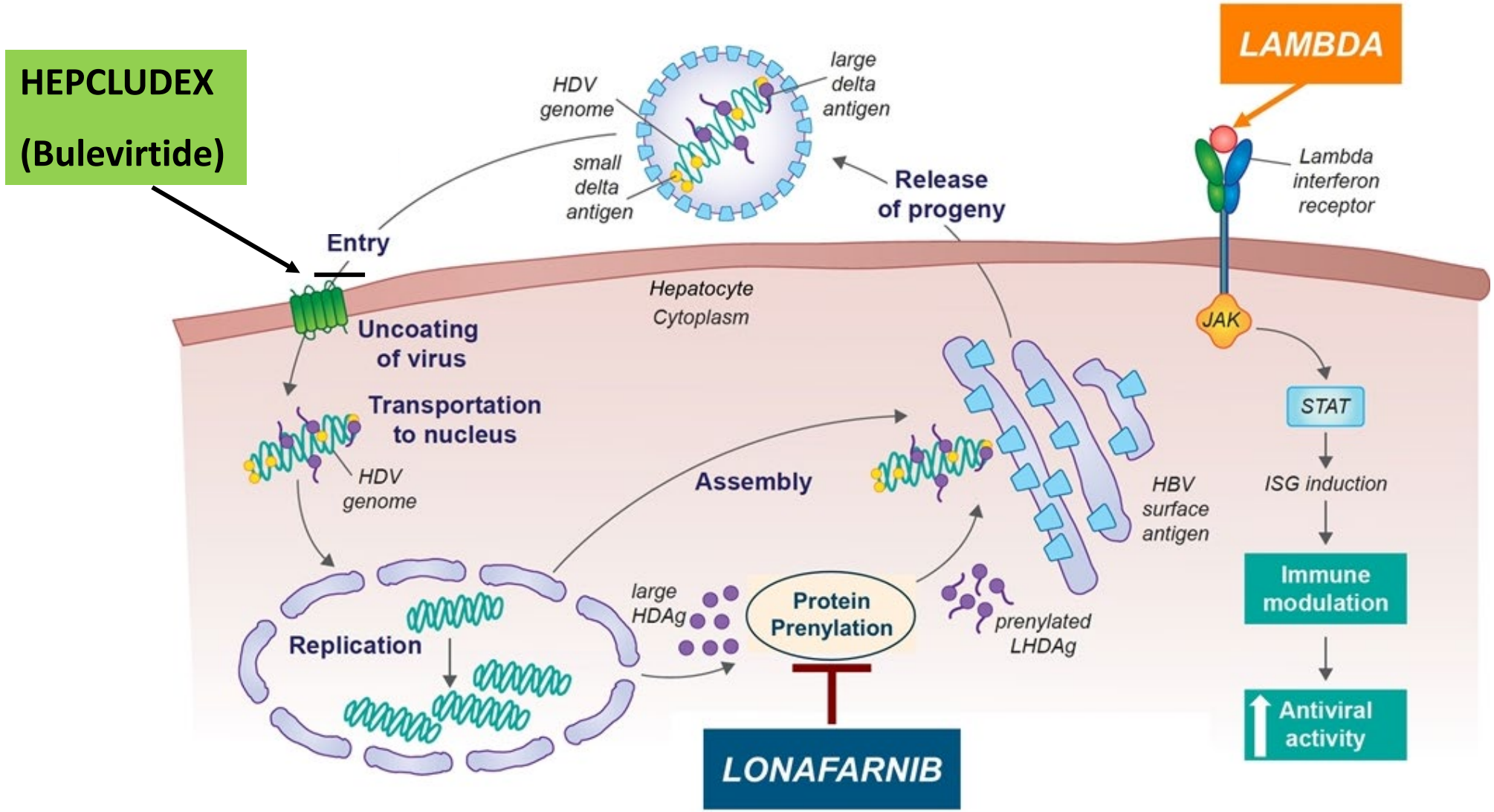
HPG23 experience

*… Spesso i pazienti **non manifestano alcun sintomo** se non quando il fegato è ormai seriamente compromesso: per questo motivo **la diagnosi precoce è fondamentale**.*
Tutti i soggetti che hanno avuto un test positivo per l'epatite B devono sottoporsi anche al test per l'epatite Delta, che avviene tramite ricerca degli anticorpi negli esami del sangue.

*… Da gennaio 2023 è attivo al Papa Giovanni XXIII un **ambulatorio dedicato al trattamento dell'epatite Delta**. Per accedere all'ambulatorio è sufficiente **richiedere una prima visita epatologica**, con una prescrizione del medico di medicina generale che contenga il **quesito diagnostico "epatite Delta".** Il paziente viene sottoposto a un test specifico per la quantificazione dell'HDV RNA sierico con un sistema di ultima generazione, estremamente sensibile. Viene in seguito valutato lo stadio della malattia epatica e definita la strategia terapeutica più appropriata per ciascun singolo caso.*

>25 pazienti trattati con bulevirtide, off-label nello scompensato, Biobanca, studi clinici

HDV treatment



Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for CHD: results from an interim analysis of a phase 3 randomized study

RESULTS

Baseline characteristics	
Age, years, mean (SD)	41.8 (8.4)
Sex, male, %	57
Ethnicity, White, %	83
Compensated cirrhosis, %	47
HDV RNA, log_{10} IU/mL, mean (SD)	5.05 (1.34)
ALT, U/L, mean (SD)	110.9 (69.0)
LS, kPa, mean (SD)	15 (8.9)
Concomitant NA therapy, %	61

- Baseline characteristics were similar between groups
- 143 (95%) patients completed 96 weeks of treatment
- Week 96 efficacy responses improved compared with Week 48
  - Arms B and C had similar combined, viral, and biochemical responses
- BLV was safe and well-tolerated
- There were no drug discontinuations, SAEs, or deaths attributed to BLV
- Bile acid increases, without a correlation to pruritus or other symptoms, were noted with BLV
- Injection site reactions occurred in a higher proportion of patients who received 10 mg QD BLV

Efficacy and safety results for BLV at Weeks 48 and 96.

	Arm A Delayed Treatment/BLV 10mg (N = 51)		Arm B BLV 2 mg (N = 49)		Arm C BLV 10 mg (N = 50)	
	Week 48	Week 96 (48 week BLV 10 mg)	Week 48	Week 96	Week 48	Week 96
Combined Response: Responder n (%)	1 (2)	20 (39)	22 (45)	27 (55)	24 (48)	28 (56)
95% CI (%)	(0, 10)	(26, 54)	(31, 60)	(40, 69)	(34, 63)	(41, 70)
Viral Response: Responder n (%)	2 (4)	46 (90)	36 (73)	37 (76)	38 (76)	41 (82)
95% CI (%)	(0, 13)	(79, 97)	(59, 85)	(61, 87)	(62, 87)	(69, 91)
Undetectable HDV RNA: Responder n (%)	0	12 (24)	6 (12)	10 (20)	10 (20)	18 (36)
95% CI (%)	(0, 7)	(13, 38)	(5, 25)	(10, 34)	(10, 34)	(23, 51)
ALT normalization: Responder n (%)	6 (12)	22 (43)	25 (51)	31 (63)	28 (56)	32 (64)
95% CI (%)	(4, 24)	(29, 58)	(36, 66)	(48, 77)	(41, 70)	(49, 77)
Change from BL in HDV RNA levels (log_{10} IU/mL): least square means (95% CI)	0.0 (-0.4, 0.3)	-3.6 (-4.0, 3.3)	-2.6 (-3.0, -2.3)	-3.2 (-3.6, 2.8)	-3.0 (-3.4, -2.7)	-3.6 (-4, 3.2)
Change from BL in HBsAg levels (log_{10} IU/mL): least square means (95% CI)	0.0 (-0.1, 0.1)	-0.2 (-0.3, 0.0)	0.1 (-0.0, 0.2)	-0.2 (-0.4, -0.1)	0.1 (0.0, 0.2)	-0.1 (-0.3, 0.0)
Change from BL in liver stiffness (kPa): least square means (95% CI)	0.9 (-0.8, 2.6)	-3.0 (-4.6, -1.5)	-3.1 (-4.7, -1.5)	-4.0 (-5.6, -2.5)	-3.2 (-4.9, -1.5)	-4.7 (-6.3, -3.2)
Adverse Events at Week 96 Number (%) of patients with:						
Any AE	39 (77)	47 (96)	41 (84)	47 (96)	44 (88)	48 (96)
Any Grade ≥3-4 AE	4 (8)	7 (14)	5 (10)	9 (18)	4 (8)	8 (16)
Any AE related to BLV	0	22 (43)	24 (49)	25 (51)	36 (72)	36 (72)
Any SAE	1 (2)	3 (6)[1]	2 (4)	2 (4)	1 (2)	4 (8)

BL, baseline, CI, confidence interval.
Undetectable HDV RNA defined as below lower limit of quantification (target not detected). ALT normalization defined as: ≤31 U/L for females and ≤41 U/L for males (Russian sites); or ≤34 U/L for females and ≤49 U/L for males (all other sites). Confidence intervals were calculated using Clopper-Pearson (exact) for proportions.
[1]Includes 1 death due to plasma cell myeloma not related to study treatment.

CONCLUSION

- BLV monotherapy continues to be safe and well-tolerated for CHD through Week 96
- Virological and biochemical responses increased with longer term therapy

Wedemeyer H, et al. EASL 2023; OS-068

HEP4Di – real-life study – BLV 2 mg/die

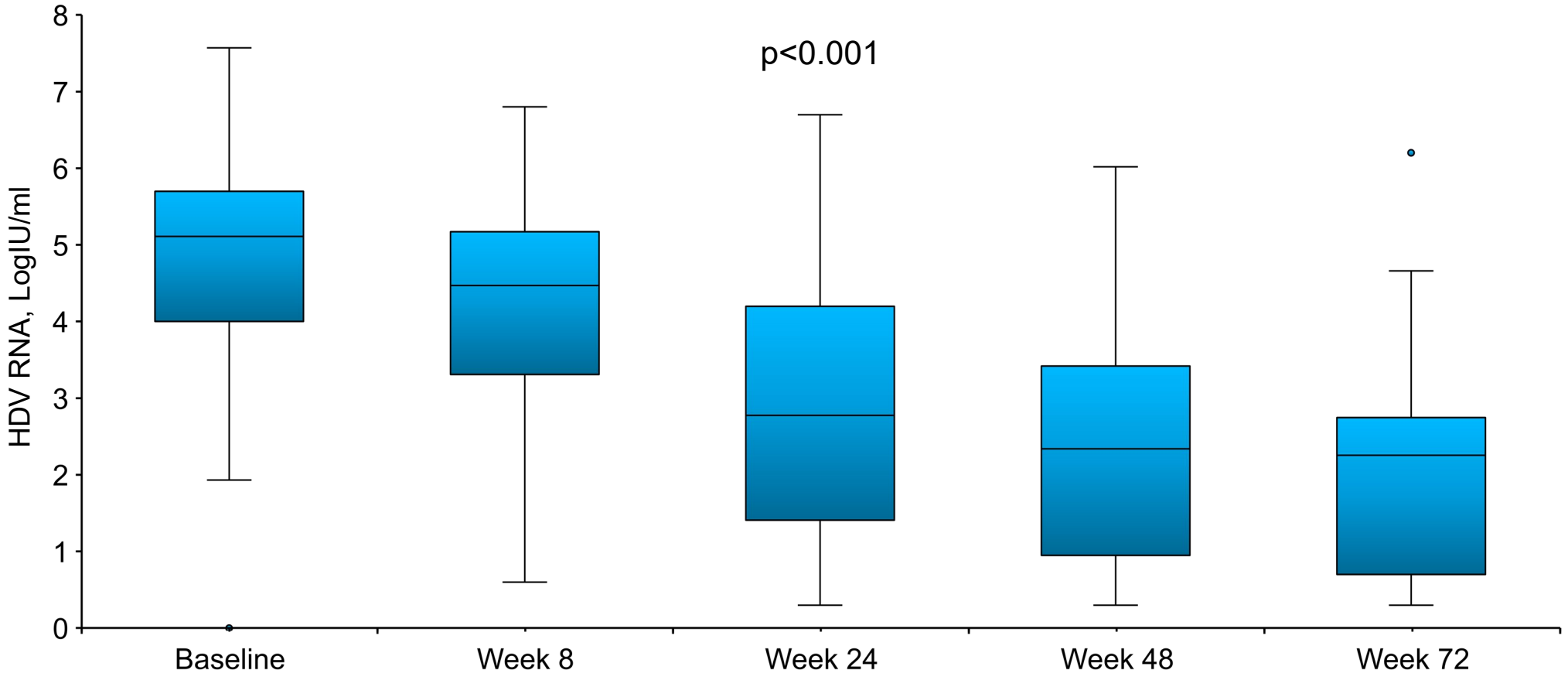
Baseline Variables	Overall (n=95)
Age, years	52 (29-77)
Males	49 (52%)
European origin	90 (95%)
HDV genotype 1*	32 (97%)
HIV coinfection°	8 (8%)
BMI, Kg/m^2	25 (18-37)
CPT score A§	95 (100%)
Spleen diameter, cm	15 (9-31)
Esophageal varices@	49 (51%)
Previous ascites	19 (20%)
History of HCC#	13 (14%)
Previous IFN treatment	51 (52%)
NUC treatment	92 (97%)

Baseline Variables	Overall (n=95)
LSM, kPa	17.2 (4.7-68.1)
Bilirubin, mg/dl	1.0 (0.4-4.4)
AST, U/l	86 (7-738)
ALT, U/l	80 (26-1,074)
GGT, U/l	61 (13-362)
Albumin, g/dl	3.9 (2.9-4.7)
Creatinine, mg/dl	0.8 (0.4-1.2)
PLT, 10^3/mm^3	82 (17-330)
Bile acids, µmol/l	18 (3-306)
qHBsAg, Log IU/ml	3.7 (0.7-4.5)
HBeAg negative	92 (97%)
HBV DNA detectable	14 (15%)
HDV RNA, Log IU/ml	5.1 (1.9-7.6)

***** available in 33 patients; ° all patients HIV RNA undetectable; §CPT A6 in 32 (34%); @34 (36%) on prophylaxis (33% primary; 3% secondary) #active HCC in 11 (12%)

Values are expressed as number (percentage) or median (range)
BLV: Bulevirtde; BMI: body mass index; CPT: Child Pugh Turcotte; HCC: hepatocellular carcinoma; IFN: Interferon; NUC: nucleos(t)ide; LSM: Liver Stiffness Measurement; PLT: platelets

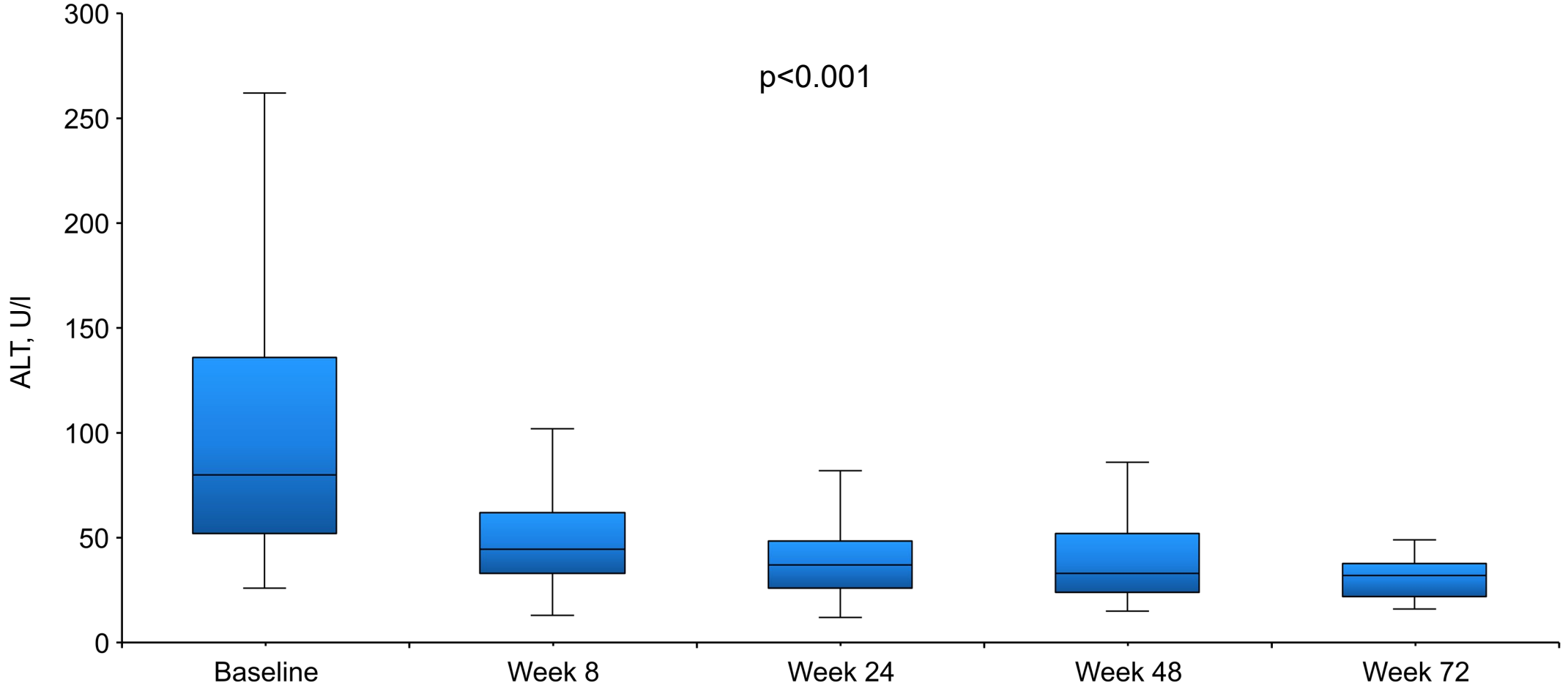
HDV RNA Levels During BLV Treatment



	Baseline	Week 8	Week 24	Week 48	Week 72
Median	5.1	4.5	2.8	2.3	2.3
Range	(1.9-7.6)	(0.6-6.8)	(0.3-6.6)	(0.3-6.0)	(0.3-6.2)
HDV RNA Decline (Log)			**2.1 (0.4-4.9)**	**2.5 (0.2-4.3)**	**2.8 (0.1-5.3)**

Degasperi E, et al. AISF 2023 meeting

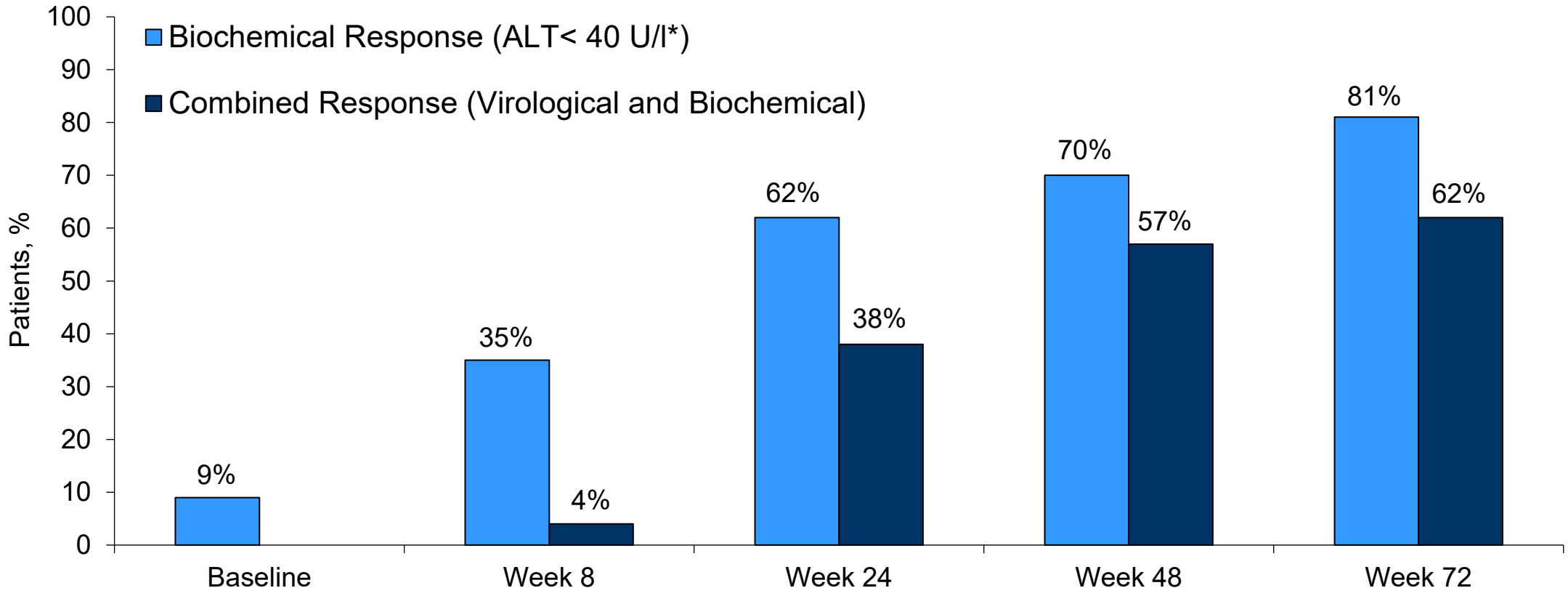
ALT Levels During BLV Treatment



	Baseline	Week 8	Week 24	Week 48	Week 72
Median	79	44	32	35	32
Range	(26-383)	(13-195)	(12-124)	(15-86)	(16-82)

Degasperi E, et al. AISF 2023 meeting

Biochemical & Combined Response During BLV Treatment



ALT <ULN and HDV RNA <1000 IU/mL	11%	35%	52%	69%
ALT<1.5 ULN and HDV RNA <1000 IU/mL	16%	51%	70%	75%

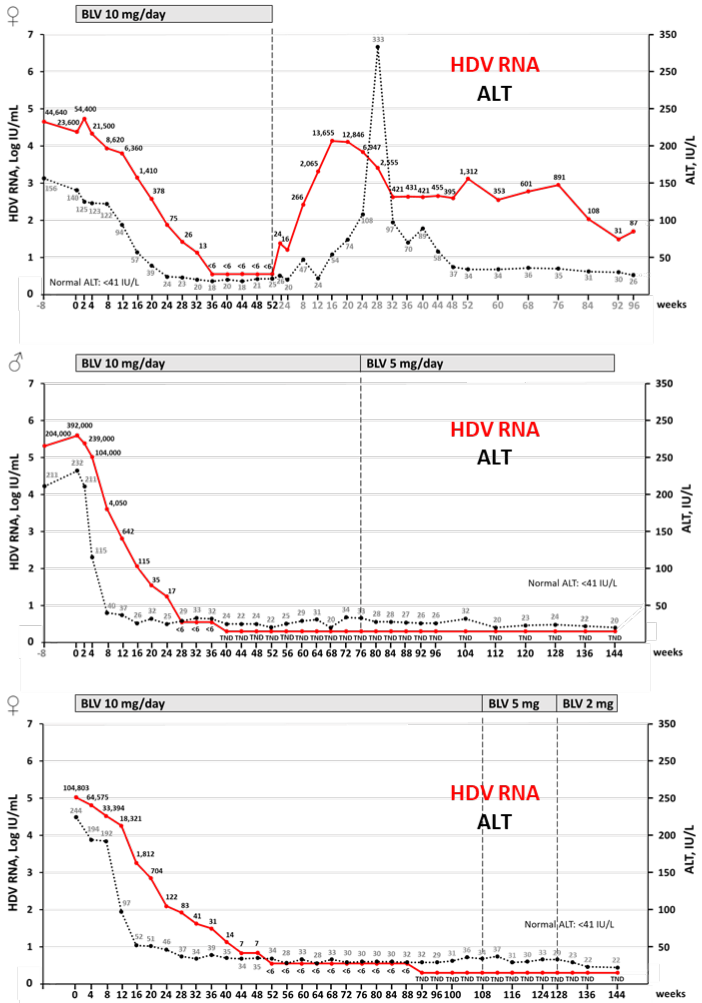
Degasperi E, et al. AISF 2023 meeting

Efficacy and safety of Bulevirtide 10 mg/day up to 3 years

3 patients with HDV compensated cirrhosis
+
contraindications to Interferon treatment

started entry-inhibitor Bulevirtide (BLV) at 10 mg/day *as per* compassionate use

All patients were on TDF treatment



HDV RNA undetectable in all patients

Virological and biochemical response maintained over 3 years of BLV even after dose reduction

Regression of small esophageal varices

Recovery of HDV-related autoimmune features

No adverse events

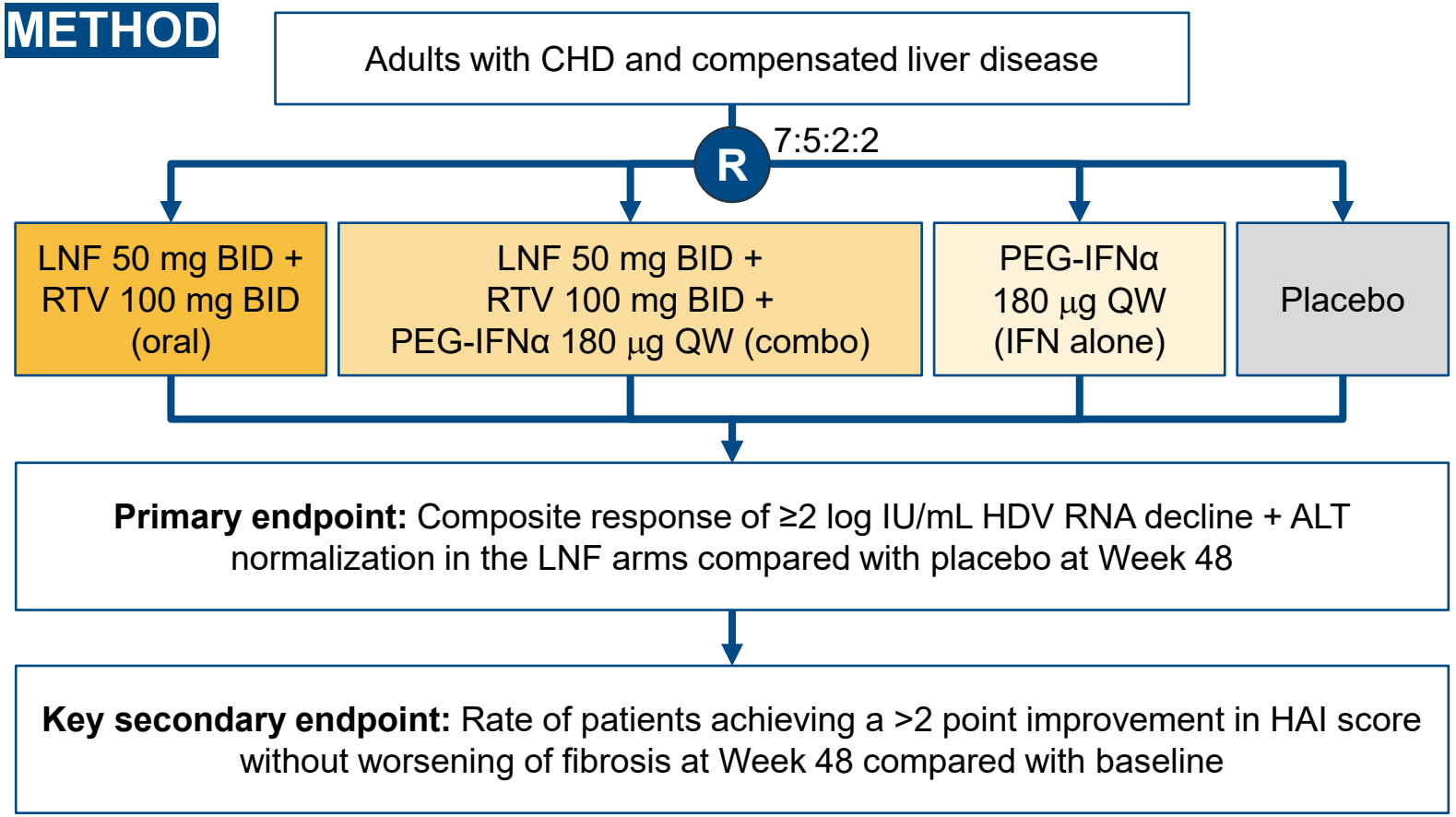
Loglio A, et al. J Hepatol 2022

Week 48 results of the phase 3 D-LIVR study evaluating the safety and efficacy of lonafarnib boosted with ritonavir with or without PEG-IFNα in patients with CHD

BACKGROUND & AIMS

- CHD is the most severe form of human viral hepatitis
  - There is no FDA approved therapy
- LNF is a farnesyl transferase inhibitor that interferes with HDV virion assembly through inhibition of the interaction of the large delta antigen with HBsAg
- D-LIVR (NCT03719313) is an ongoing, randomized, double-blind, placebo-controlled, parallel-group clinical trial in adults with CHD and compensated liver disease
- **AIM:** To evaluate the safety and efficacy of LNF boosted with RTV with or without PEG-IFNα-2a for the treatment of CHD

METHOD



- All patients were on a background of entecavir or tenofovir throughout
- Paired liver biopsies were obtained at baseline and at Week 48
- Follow-up continued for 24 weeks beyond the primary endpoint

EASL The Home of Hepatology

Etzion O, et al. EASL 2023; GS-012

Week 48 results of the phase 3 D-LIVR study evaluating the safety and efficacy of lonafarnib boosted with ritonavir with or without PEG-IFNα in patients with CHD

RESULTS

- A total of 407 patients (mean age: 42.7 years; 69% male; 73% White) were enrolled; N=405 were randomized and treated
  - Mean ALT, total bilirubin, albumin, platelets and HDV RNA levels were comparable across the four arms at baseline
  - 27% of patients had evidence of cirrhosis as per investigator assessment
- Composite response rates for both LNF-based arms were statistically significant vs. placebo
- Of the N=229 evaluable paired liver biopsies, a statistically significant improvement in the secondary endpoint was seen between the combo and placebo arms, but not between the oral or IFN alone and the placebo arms
- Both LNF-based regimens were well-tolerated, with comparable rates of treatment discontinuations across all arms

Primary endpoints*	Oral (n=178)	Combo (n=125)	IFN alone (n=52)	Placebo (n=52)
Composite primary (ITT population)	10.1% (p=0.0044)	19.2% (p<0.0001)	9.6%	1.9%
≥2 log decline in HDV RNA	14.6% (p=0.0026)	32% (p<0.0001)	36.5%	3.8%
ALT normalization	24.7% (p=0.003)	34.4% (p<0.001)	11.5%	7.7%
Secondary endpoint*	**Oral (n=107)**	**Combo (n=66)**	**IFN alone (n=26)**	**Placebo (n=30)**
>2 point improvement in HAI without worsening of fibrosis	33% (p=0.61)	53% (p=0.0139)	38% (p=0.46)	27%

CONCLUSION

- The Phase 3 D-LIVR trial achieved the primary efficacy endpoint for both LNF-based regimens compared with placebo, with the oral arm matching and the combo arm doubling the IFN alone response rate
- A statistically significant histologic improvement was observed in the combo arm

*All reported p values are compared with placebo.

Etzion O, et al. EASL 2023; GS-012

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Possible antiviral strategies in HDV patients

STRATEGIES	DURATION	TYPE OF RESPONSE	DEFINITION OF RESPONSE	TIMING
Finite therapy	≤48 weeks	Virological	HDV RNA undetectable	Off-therapy (24 weeks)
Long-term therapy	>48 weeks	Combined	HDV RNA >2 log decline + ALT normalization	On-therapy (48 weeks)

Disease severity	Contraindications to PegIFN	Treatment strategy
Moderate-severe chronic hepatitis or compensated cirrhosis without CSPH	No	BLV 2 mg + PegIFNα for 48 weeks or PegIFNα monotherapy for 48 weeks
Moderate-severe chronic hepatitis or compensated cirrhosis without CSPH	Yes	BLV 2 mg monotherapy
Compensated cirrhosis with CSPH	Yes	BLV 2 mg monotherapy
Decompensated cirrhosis	Yes	No approved therapy

Lampertico P, AASLD 2022

TAKE HOME MESSAGES

- NUC are safe; combination treatment for HBV functional cure
- **Screening patients and family for HBV** (HBsAg, antiHBs e antiHBc IgG) and vaccination
- Prevalence estimates for HDV are inaccurate due to insufficient data
- HDV is the most severe form of viral hepatits
- **Test anti-HDV in all HBsAg positive patients** (Recalling HBsAg+ patients who were not initially screened for anti-HDV; retest in risk factors ongoing; increase HDV awareness and education for healthcare professionals)
- **Referral HDV** to tertiary centers

HBV and HDV Referral: **aloglio@asst-pg23.it**

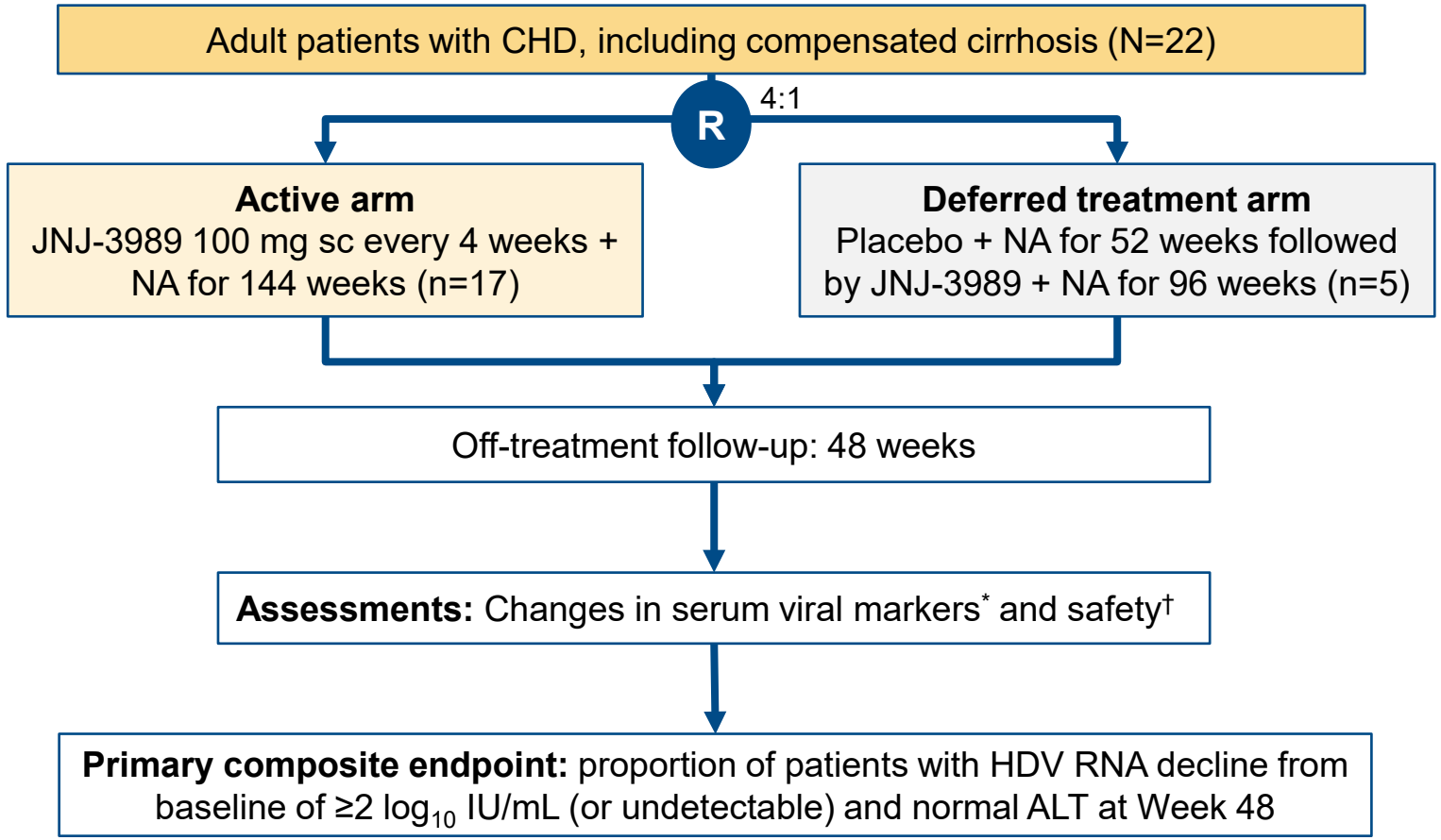
Treatment with siRNA JNJ-73763989 plus NA decreases HBsAg and HDV RNA levels in patients with CHD: part 1 of the REEF-D study

BACKGROUND & AIMS

- HDV requires HBsAg to form infectious viral particles
- siRNA JNJ-3989 has been shown to reduce HBsAg in chronic HBV
- **AIM:** To evaluate the effect of JNJ-3989 in patients with CHD to investigate whether reduction of HBsAg will lead to a reduction in HDV replication

METHOD

- REEF-D is a 2-part, phase 2, multicenter, randomized, double-blind, placebo-controlled study
- Antiviral activity in Part 1 was used to expand this study (Part 2)



Data from Part 1, Week 48 interim analysis are reported here

*HBsAg and HDV RNA; †ALT levels

Wedemeyer H et al. EASL 2023; OS-030

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Treatment with siRNA JNJ-73763989 plus NA decreases HBsAg and HDV RNA levels in patients with CHD: part 1 of the REEF-D study

RESULTS

	Active arm (n=17)	Deferred treatment arm (n=5)
Achieved primary composite endpoint, n (%)	4 (23.5)	0
HBsAg change from baseline, mean (SE), log_{10} IU/mL*	-1.75 (0.29)	0.07 (0.04)
HDV RNA change from baseline, mean (SE), log_{10} IU/mL*	-1.52 (0.38)	-0.23 (0.15)

- 12 (70.6%) patients in the active arm experienced treatment-emergent ALT elevations† (Week 8–20), which were associated with HDV RNA rebound, limited transient HBV DNA increase in most patients, but no clear impact on HBsAg decline
  - Grade 3/4 ALT elevations were observed, with no cases of decompensation
  - Treatment was discontinued early in 8 patients
  - In general, ALT levels returned to baseline values after treatment discontinuation
- 5 patients did not experience ALT elevations
  - 4 (80.0%) achieved the primary composite endpoint
  - 2 (40.0%) had HDV RNA below the LLOQ of the assay
- Aside from ALT elevations, safety outcomes were unremarkable
- Predefined criterial to initiate Part 2 of the study were met
- ALT flares, predominantly in patients with high HBsAg and HDV RNA levels at baseline, led to exclusion of patients with cirrhosis or HBsAg >10,000 IU/mL and HDV RNA >100,000 IU/mL

CONCLUSION

- JNJ-3989 leads to a simultaneous reduction of HBsAg and HDV RNA in patients with CHD (first proof-of-concept)
- ALT elevations were frequent, associated with HDV RNA increases and treatment discontinuation
- Patients without ALT elevations generally had a continuous reduction in HDV RNA (80% met the primary endpoint)

*Out of 9 atients still on treatment at Week 48; †(≥3× upper limit of normal [ULN] and ≥2× nadir.

Wedemeyer H et al. EASL 2023; OS-030

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