Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Le nuove terapie per l'HDV

Ciocco, 15 Aprile 2023

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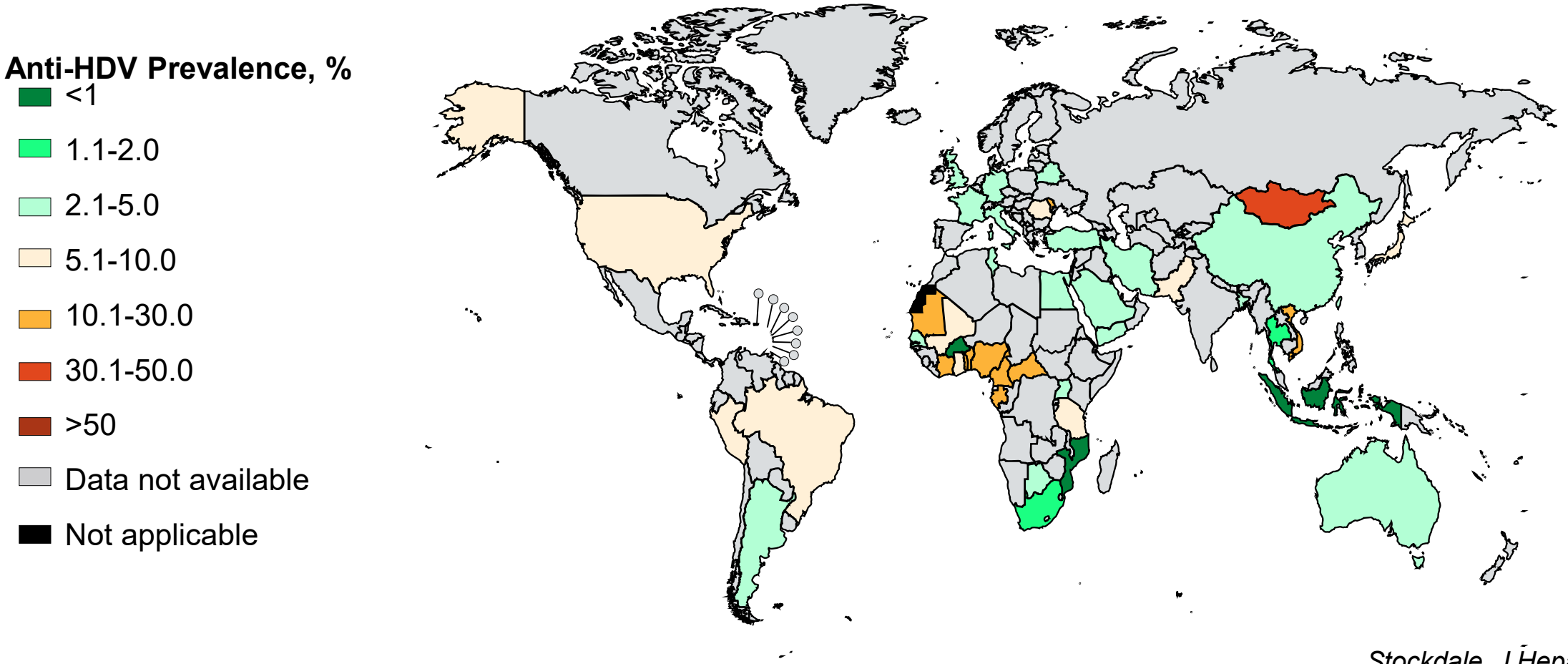
Proportion of people with HBV who have HDV

Among HBsAg-positive people the estimated prevalence of HDV is 4.5% (95% CI: 3.6-5.7)



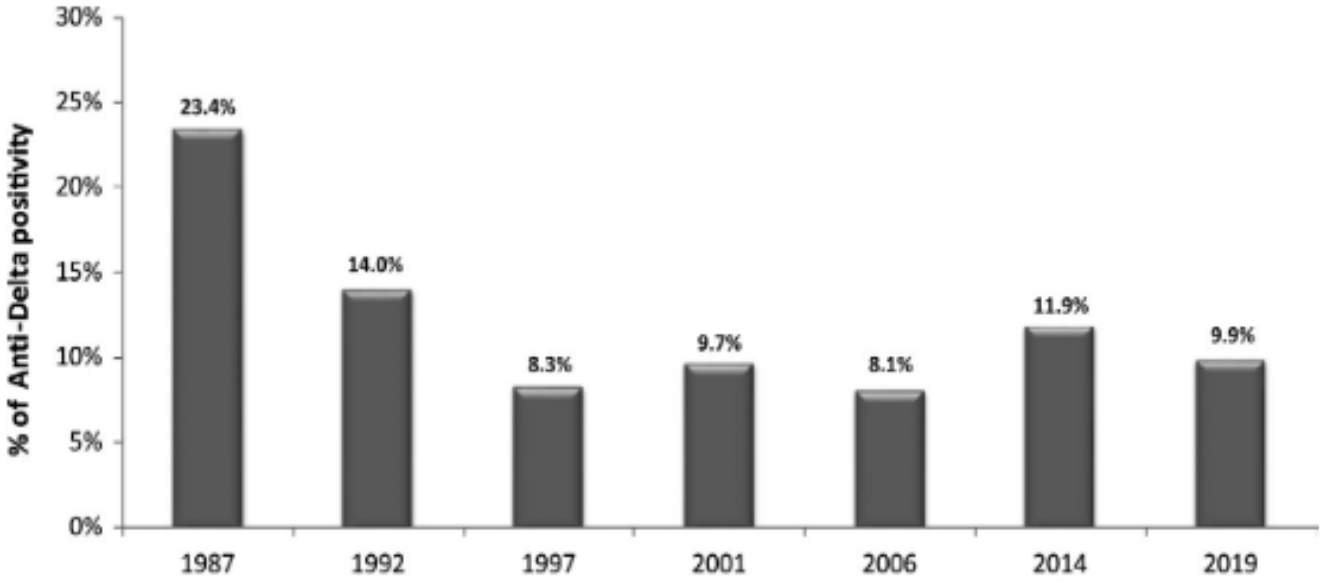
Stockdale. J Hepatol. 2020;73:523.

HDV prevalence in HBsAg positive populations 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

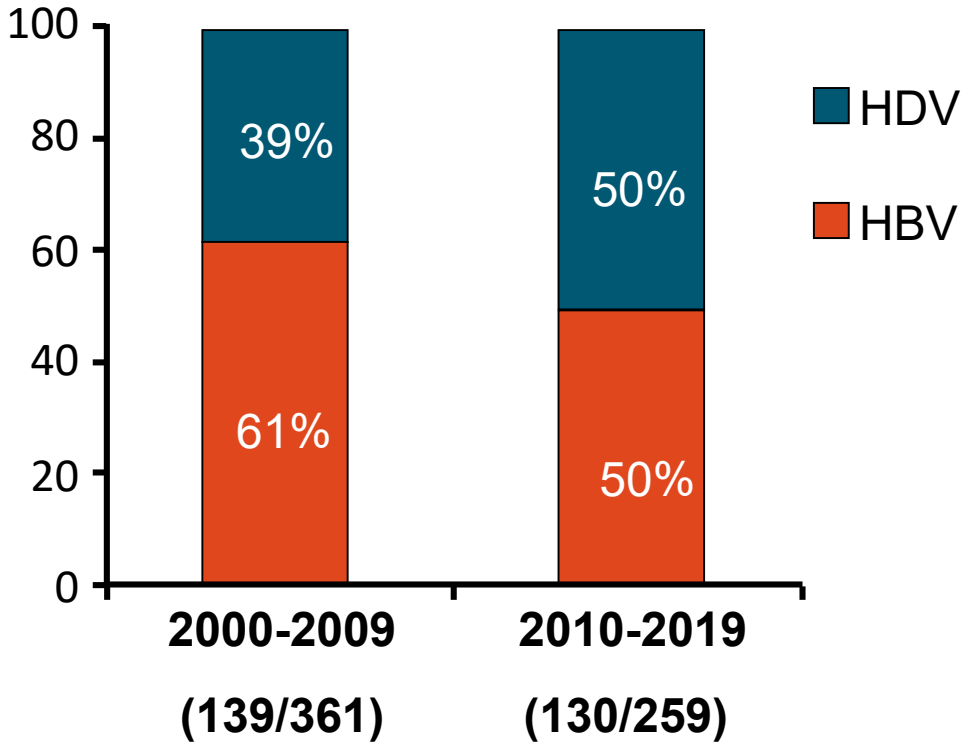
HDV vs HBV: disease progression

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

CHD: the most severe form of chronic viral hepatitis

Da. Gastroenterol Rep (Oxf). 2019;7:231. Kamal H et al. J Viral Hep 2021;28:1431–1442.

Disproportionate role of HDV in LT compared to the prevalence of HDV infections in Italy



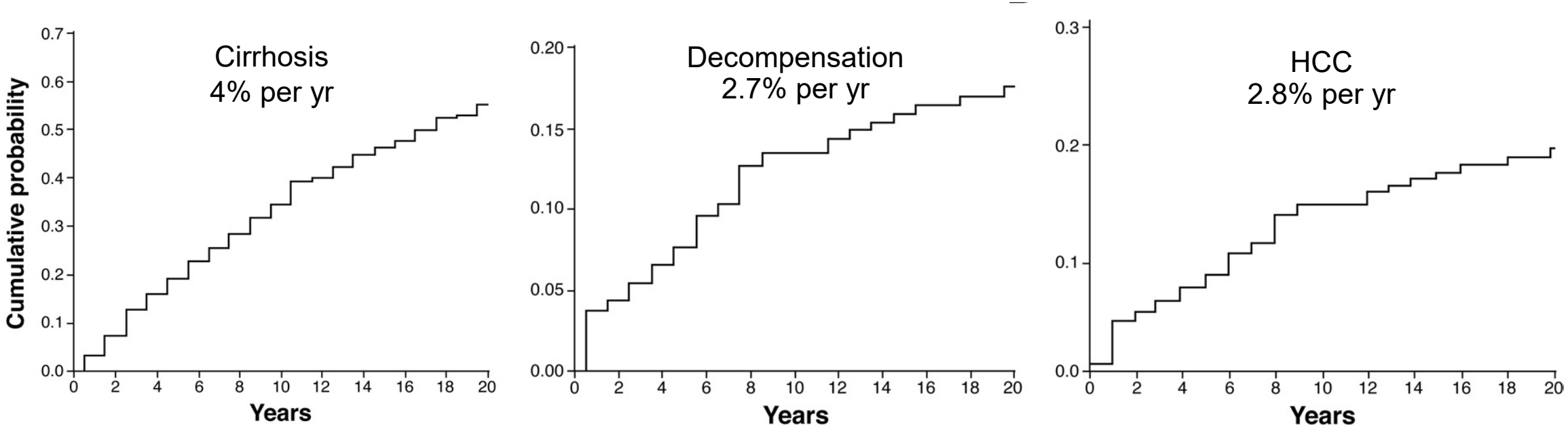
	2000 – 2009		2010 – 2019	
	HDV n = 139	HBV n = 222	HDV n = 130	HBV n = 129
HCC	29 (20.9%)	121 (54.5%)	49 (37.7%)	91 (70.5%)
Liver failure	110 (79.1%)	101 (45.5%)	81 (62.3%)	38 (29.5%)

Though HDV is vanishing in Italy, a legacy of ageing native-Italian patients with advanced HDV liver disease still represents an important medical issue and maintains an impact on LT

Caviglia et al. J Adv Res. 2021;33:183

HDV RNA is a surrogate marker of disease progression

299 HDV patients in a Tertiary Center between 1978-2006 (34% cirrhosis, 30% IFN) f-up 233 months

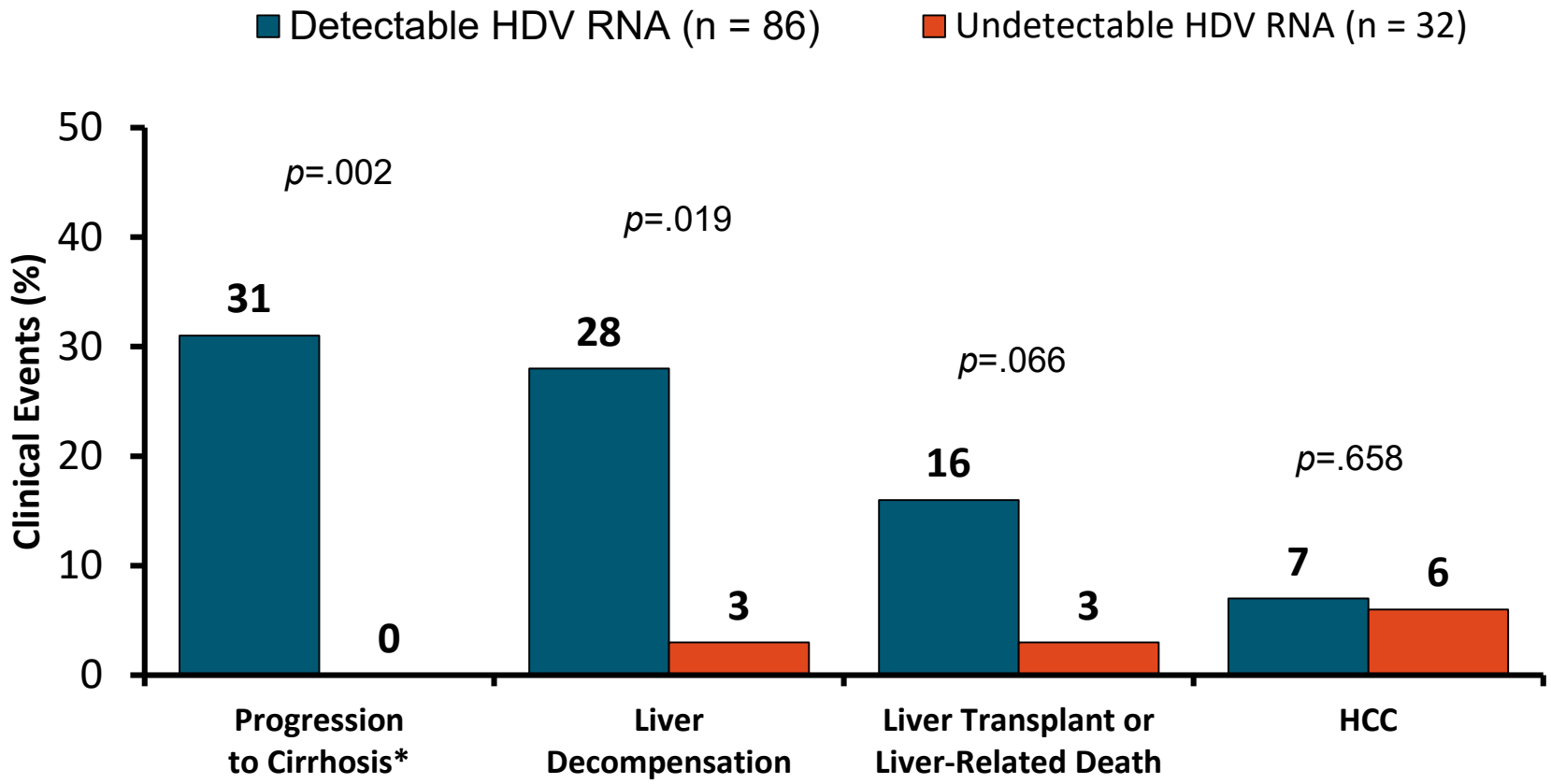


HDV RNA was independently associated with all liver-related outcomes and was the only predictor of mortality

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

Long-term outcomes in HDV: role of persistent viremia

Retrospective, multicenter study of 118 HBV/HDV patients in Spain followed for 8 yrs



Patients with persistently positive HDV RNA had worse prognosis

Palom at al. Aliment Pharmacol Ther. 2020;51:158

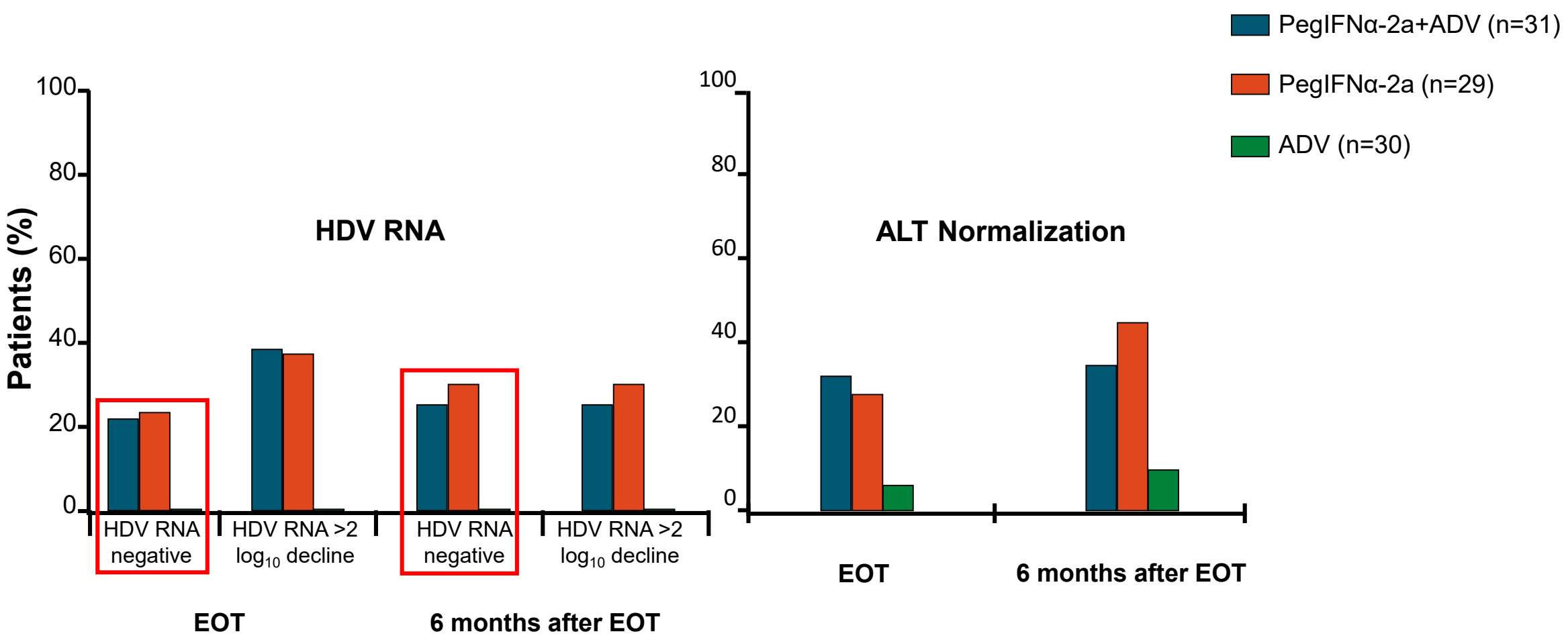
EASL and AASLD guidelines

- There were no EMA or FDA approved drugs
- In compensated liver disease: PegIFN for at least 48 weeks for patients with elevated HDV RNA levels and elevated ALT (if well tolerated)
- Treatment success: undetectable HDV RNA 24 weeks after EOT (~20%)
- Virologic response typically associated with ALT normalization
- In those with ongoing HBV DNA replication (persistently >2.000 IU/mL) and in those with advanced liver disease with any HBV DNA levels: NUCs (not active against HDV)

EASL. J Hepatol. 2017;67:370. Terrault. Hepatology. 2018;67:1560

PegIFNα-2a ± ADV for chronic HDV infection

Multicenter, RCT of treatment in patients with chronic HDV for 48 weeks



Wedermeyer. NEJM. 2011;364:322

Endpoints of anti-HDV treatment

- Improve survival
- Reduce liver related complications (ESLD, HCC)
- HBsAg loss/seroconversion
- HDV RNA undetectable
- ALT normalization
- Combined response (HDV RNA decline ≥2 log + ALT normalization)

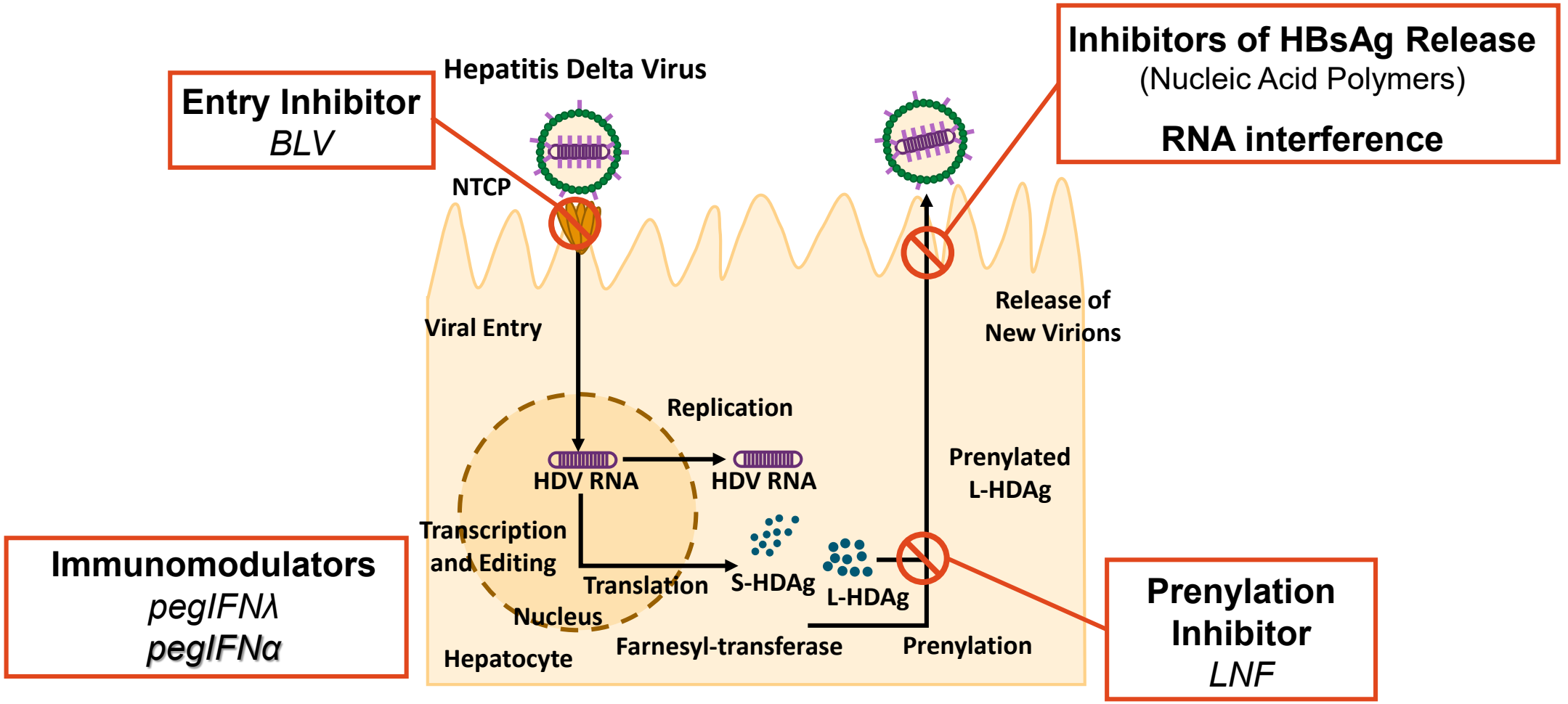
Endpoints of anti-HDV treatment: FDA and EASL-AASLD Guidance

	Long-term treatment	Short-term treatment
FDA	≥2 Log HDV RNA reduction + ALT normalization	Undetectable HDV RNA + ALT normalization
EASL-AASLD	HDV RNA suppression (≥2 Log HDV RNA reduction) + ALT normalization	Undetectable HDV RNA 6 months after EOT, ALT normalization and ideally HBsAg loss

For drugs that are intended to be used as chronic suppressive therapy a ≥2 log decline in HDV RNA + ALT normalization on-treatment could be considered an acceptable surrogate endpoint reasonably likely to predict clinical benefit

https://www.fda.gov/media/132137/download; Cornberg M, et al. Hepatology. 2019; Farci et al. 2004; Yurdaydin et al. 2019

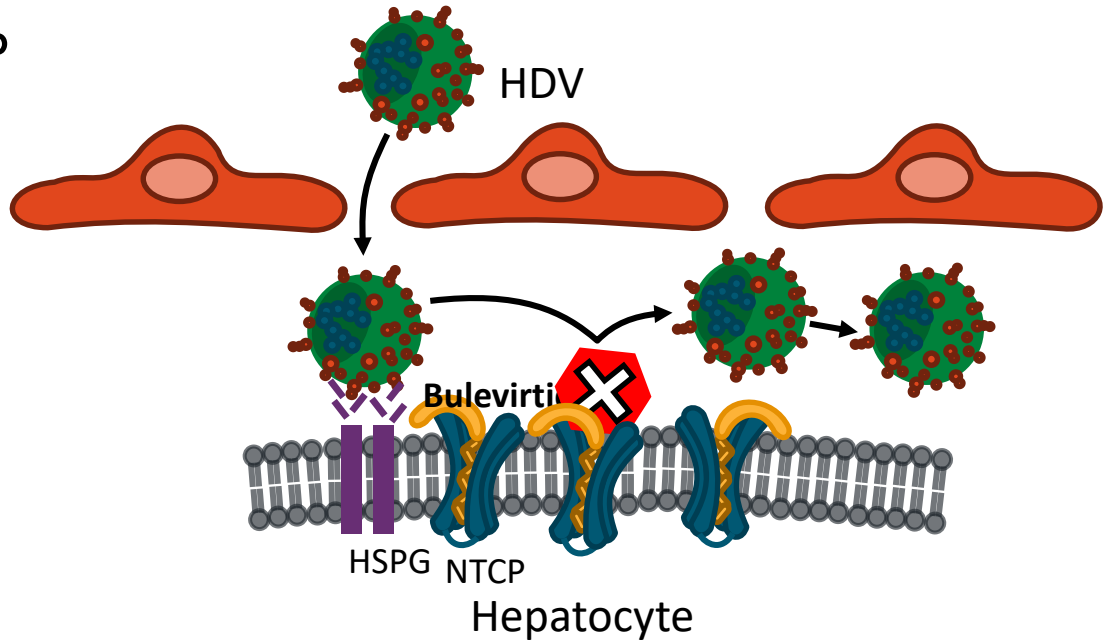
Therapeutic targets for HDV infection



Loureiro. Liver Int. 2021;41:30

Bulevirtide

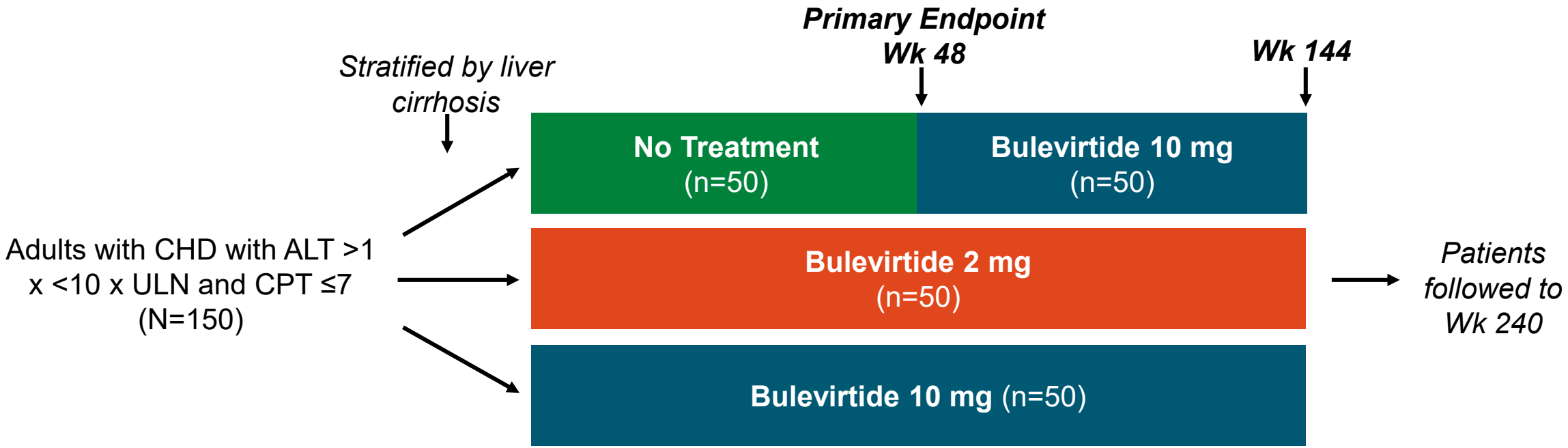
- HBV and HDV entry inhibitor (synthetic lipopeptide)
- Binds and blocks the hepatocyte surface protein NTCP
- **No viral replication inhibition**
- Infected hepatocytes are replaced by naive cells which will be protected from infection
- **Bile acids increase**
- Every day self administered (sc injections)
- Conditional approval for 2 mg by EMA for adults with compensated CHD



Yardeni. Drugs Today (Barc). 2021;57:433. Gilead press release. November 19, 2021

MYR301: Week 48 interim analysis of high- vs low-dose BLV in patients with CHD

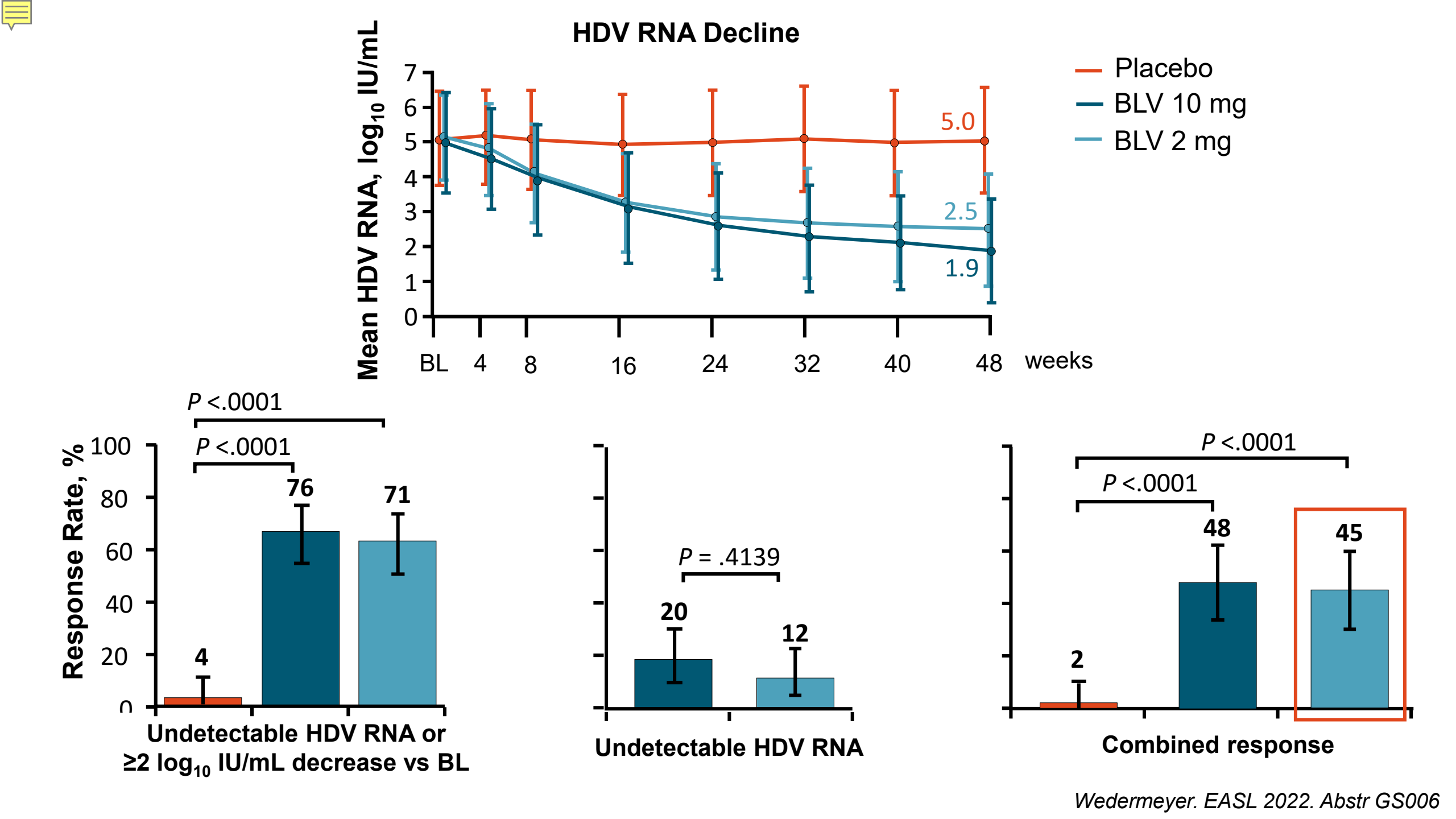
Multicenter, open-label, randomized phase III trial of BLV 2 mg or 10 mg for 48 weeks vs delayed BLV treatment in patients with CHD (n=150)



Primary endpoint: combined response at week 48

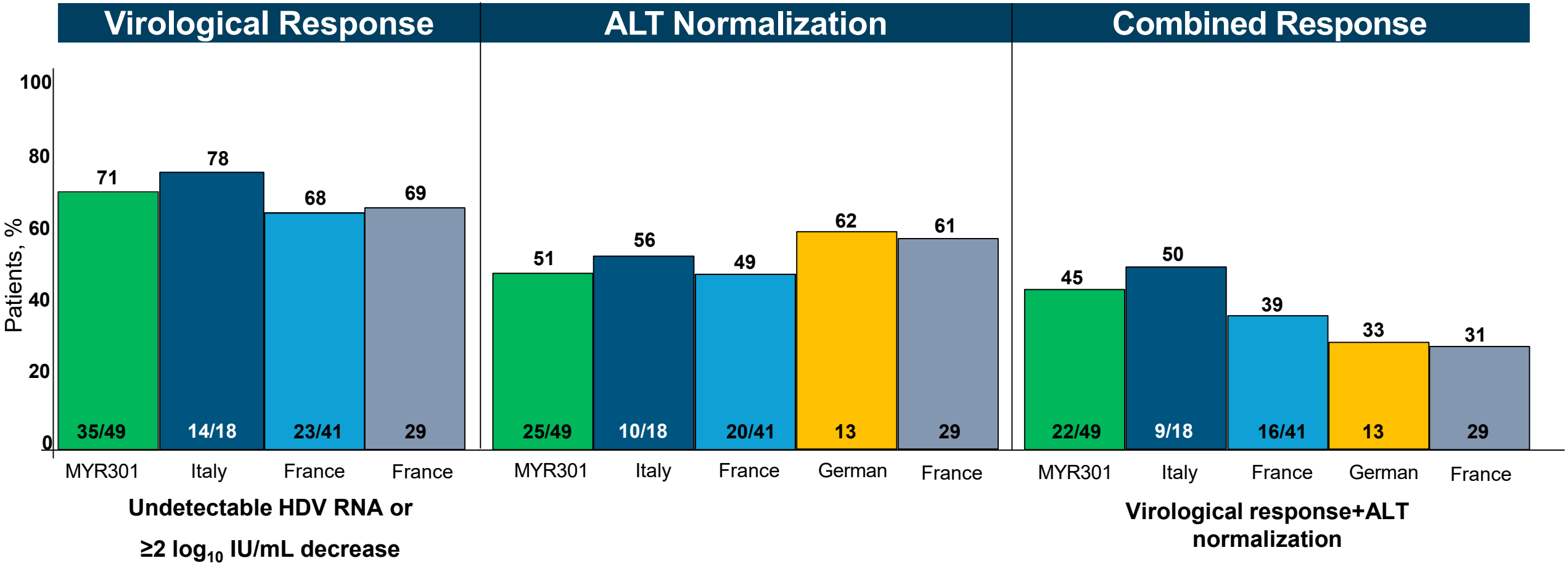
(HDV RNA undetectable or ≥2 $\log_{10}$ decrease + ALT normalization)

Allweiss. AASLD 2021. Abstr 223



Wedermeyer. EASL 2022. Abstr GS006

BLV 2 mg monotherapy in CHD: efficacy at week 48

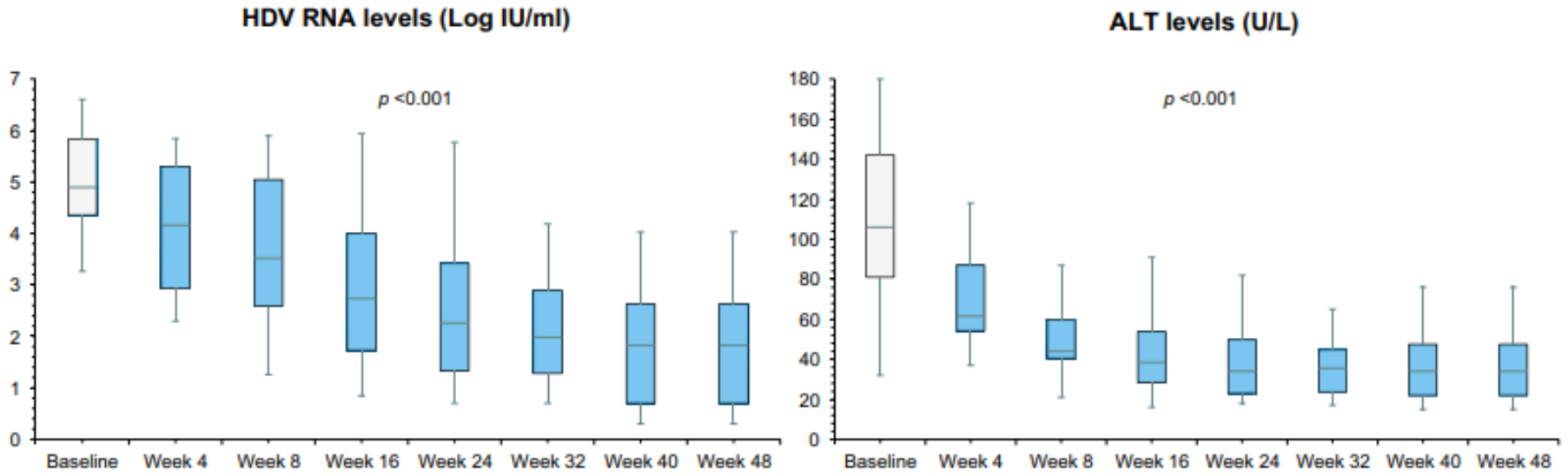


Week 48 RWD support the efficacy of BLV 2 mg observed in MYR301

Wedermeyer et al. EASL 2022, De Gasperi et al. EASL 2022, de Ledinghen et al. AASLD 2021, Fontaine et al. EASL 2022,Killer et al. EASL 2022

BLV for patients with HDV, cirrhosis, and portal hypertension

18 patients with HDV-related cirrhosis and clinically significant portal hypertension treated with bulevirtide monotherapy 2 mg/day for 48 weeks



- 78% Virological response (≥2 log decline)
- 23% HDV RNA undetectable (<6 IU/ml)
- 11% Virological non-responders (<1 log decline at wk 24)
- 83% Biochemical response (ALT cut-off 41 U/L ♀; 59 U/L ♂)
- 67% Combined response

Degasperi. et al. J Hep 2022

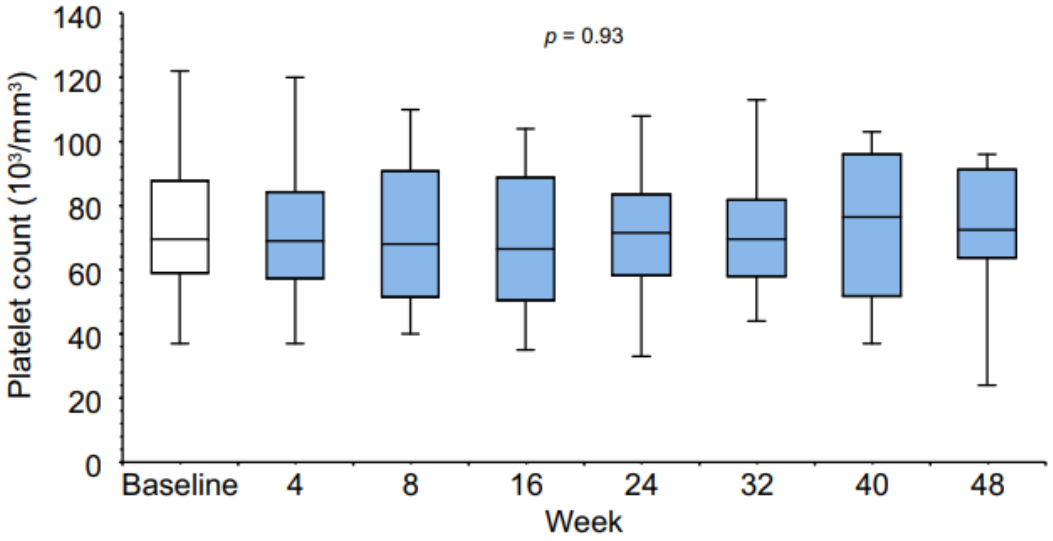
BLV for patients with HDV, cirrhosis, and portal hypertension

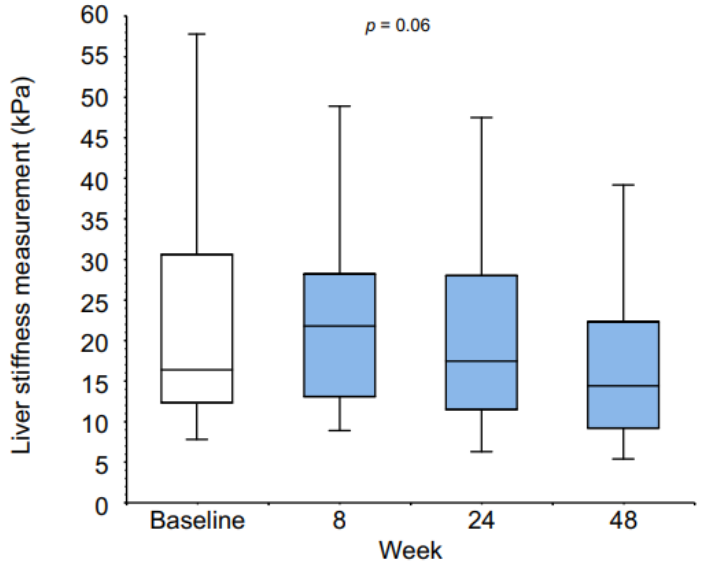
Variables	Baseline	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	*p* value
Bilirubin, mg/dl	1.3 (0.5-1.8)	1.0 (0.4-2.9)	0.9 (0.5-2.4)	1.0 (0.3-2.5)	1.0 (0.5-2.5)	0.9 (0.4-4.1)	1.2 (0.5-4.6)	0.51
AST, U/L	92 (52-214)	52 (26-123)	42 (26-141)	38 (24-134)	39 (25-97)	36 (23-86)	39 (21-92)	**<0.001**
ALT, U/L	106 (32-222)	44 (21-114)	39 (16-91)	34 (18-82)	36 (17-80)	34 (15-76)	35 (15-86)	**<0.001**
GGT, U/L	52 (13-262)	43 (11-270)	35 (6-229)	30 (6-237)	29 (7-199)	27 (7-179)	23 (6-158)	**0.01**
Albumin, g/dl	3.9 (2.9-4.4)	3.9 (3.1-4.8)	3.9 (3.0-4.4)	3.9 (3.5-4.6)	4.0 (3.5-4.5)	4.1 (3.5-4.7)	4.0 (3.6-4.7)	**0.03**
Platelet count, $10^3/\mu l$	70 (37-227)	68 (40-210)	67 (35-228)	70 (33-219)	70 (44-192)	77 (37-211)	73 (24-221)	0.93
Bile acids, µmol/L[a]	23 (8-306)	60 (11-490)	48 (11-710)	37 (7-748)	49 (10-748)	61 (7-416)	63 (10-416)	**0.04**
Creatinine, mg/dl	0.8 (0.7-1.0)	0.9 (0.6-1.1)	0.9 (0.7-1.2)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.6-1.1)	0.9 (0.6-1.1)	0.66
AFP, µg/L°°	9 (3-596)	9 (3-846)	8 (2-495)	6 (3-14)	5 (2-17)	5 (2-15)	5 (2-15)	0.29
IgG, mg/dl	2,168 (1,047-4,059)	2,056 (1,009-3,208)	1,570 (988-2,329)	1,666 (980-2,286)	1,604 (953-2256)	1,611 (996-2312)	1,643 (901-2200)	**<0.001**
Gamma globulins, g/dl	2.0 (1.0-3.4)	2.0 (0.9-2.8)	1.7 (1.0-2.6)	1.6 (1.0-2.1)	1.5 (1.0-2.2)	1.5 (0.9-2.2)	1.5 (0.9-2.1)	**<0.001**
CHE, U/L	4,471 (1,807-8,378)	4,599 (2,337-8,861)	4,949 (2,715-8.759)	4,982 (2,854-6.849)	4,997 (2,837-7,793)	5,550 (2,465-8,826)	5,396 (2,229-8,826)	**0.04**
LSM, kPa	16.4 (8-58)	21.8 (9-49)	-	17.4 (6-48)	-	-	13.7 (5-30)	0.06
Biochemical response*	1 (6%)	9 (50%)	14 (78%)	13 (72%)	14 (78%)	16 (89%)	15 (83%)	**<0.001**
Combined response°	-	0	5 (28%)	12 (67%)	11 (61%)	13 (72%)	12 (67%)	**<0.001**

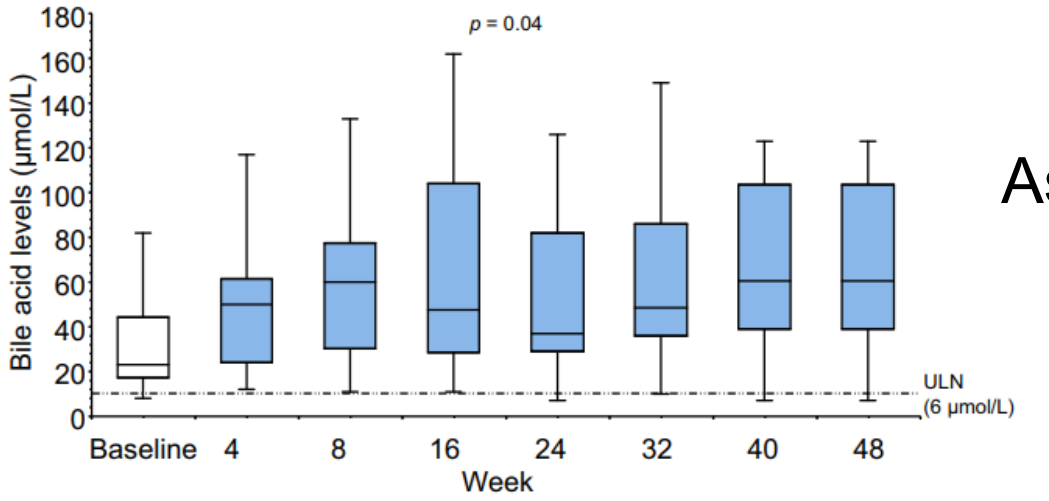
No symptomatic adverse effects

Degasperi. et al. J Hep 2022

BLV for patients with HDV, cirrhosis, and portal hypertension







Asymptomatic increase in bile acids

Degasperi. et al. J Hep 2022

Extension of BLV to 72 weeks in HDV patients with compensated cirrhosis: efficacy and safety from the Italian Multicenter Study HEP4Di

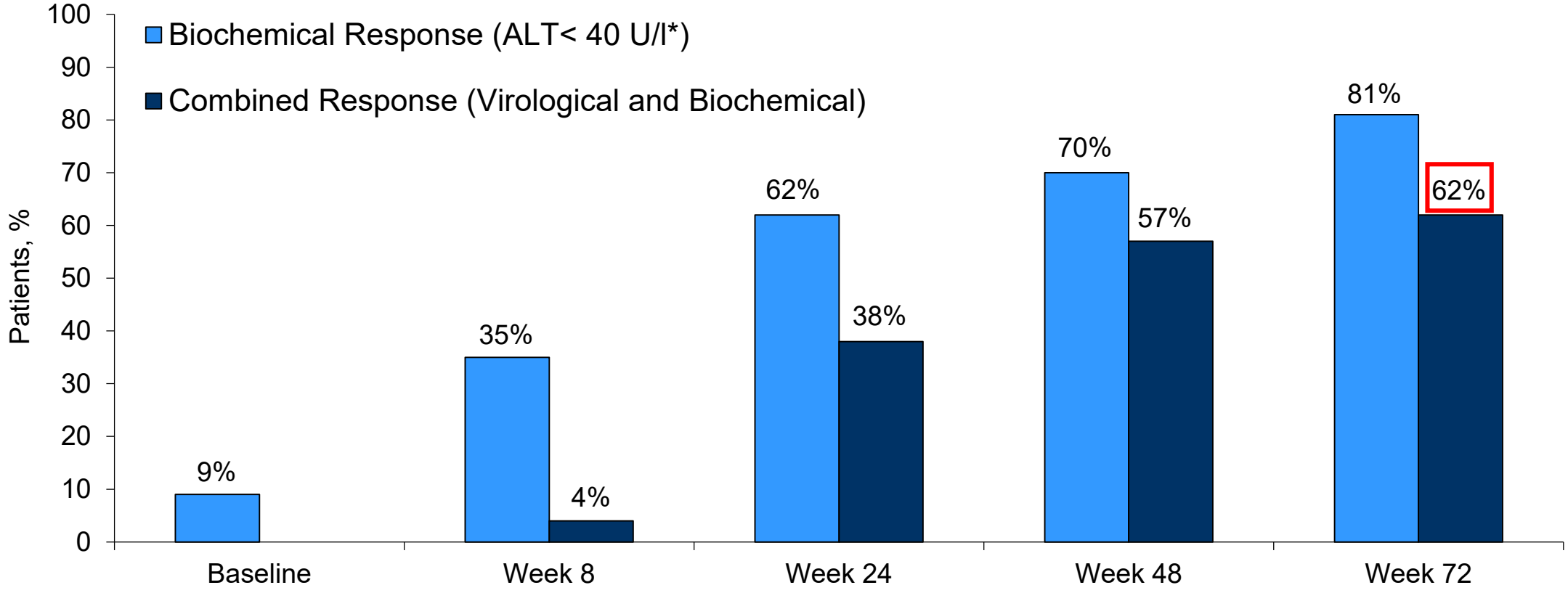
	Overall (n=95)
Age, years	52 (29-77)
Males	49 (52%)
European origin	90 (95%)
HIV coinfection°	8 (8%)
BMI, Kg/m^2	25 (18-37)
Spleen diameter, cm	15 (9-31)
Esophageal varices@	49 (51%)
Previous ascites	19 (20%)
History of HCC#	13 (14%)
Previous IFN treatment	51 (52%)
NUC treatment	92 (97%)

	Overall (n=95)
LSM, kPa	17 (4.7-68.1)
Bilirubin, mg/dl	1.0 (0.4-4.4)
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)

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

Anolli et al. AISF 2023

Extension of BLV to 72 weeks in HDV patients with compensated cirrhosis: Combined Response



	Week 8	Week 24	Week 48	Week 72
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%

Anolli et al. AISF 2023

Extension of BLV to 72 weeks in HDV patients with compensated cirrhosis: biochemical and virological variables

Variables	Baseline	Week 8	Week 24	Week 48	Week 72	p value (A)*	p value (B)*
Bilirubin, mg/dl	1.0 (0.4-4.4)	0.9 (0.2-3.1)	0.8 (0.3-2.5)	0.9 (0.5-4.6)	0.8 (0.4-1.7)	0.44	0.07
AST, U/L	86 (7-738)	49 (26-159)	43 (11-134)	40 (21-92)	32 (18-82)	**<0.001**	**<0.001**
ALT, U/L	80 (26-1,074)	45 (13-195)	37 (12-164)	33 (15-86)	32 (16-82)	**<0.001**	**<0.001**
GGT, U/L	61 (13-362)	51 (11-270)	42 (6-237)	32 (6-158)	21 (7-157)	**<0.001**	**<0.001**
Albumin, g/dL	3.9 (2.9-4.7)	3.9 (2.9-4.9)	3.9 (2.8-5.3)	4.0 (3.2-4.7)	4.1 (3.6-4.6)	**0.003**	**0.02**
CHE, U/L	5,034 (1,558-9,109)	5,128 (1,434-9,576)	5,034 (1,201-9.298)	5,436 (2,117-8,826)	5,924 (2,068-8,971)	**0.01**	**0.02**
PLT, $10^3/mm^3$	82 (17-330)	87 (14-383)	82 (24-335)	77 (24-221)	71 (37-206)	0.07	0.79
Creatinine, mg/dL	0.8 (0.4-1.2)	0.8 (0.5-1.3)	0.8 (0.4-1.3)	0.9 (0.5-1.3)	0.9 (0.7-1.1)	0.10	0.57
AFP, µg/L	7 (1-596)	7 (1-846)	5 (1-17)	4 (2-15)	4 (2-40)	0.15	0.37
IgG, mg/dL	2,125 (1,047-4,059)	1,958 (1,009-3,332)	1,790 (980-3,033)	1,715 (901-3,636)	1,561 (444-2,055)	**<0.001**	**<0.001**
HBsAg, Log IU/mL	3.7 (0.8-4.5)	3.7 (0.8-4.5)	3.9 (0.5-4.6)	3.7 (2.5-4.3)	3.6 (2.5-4.3)	0.81	0.66

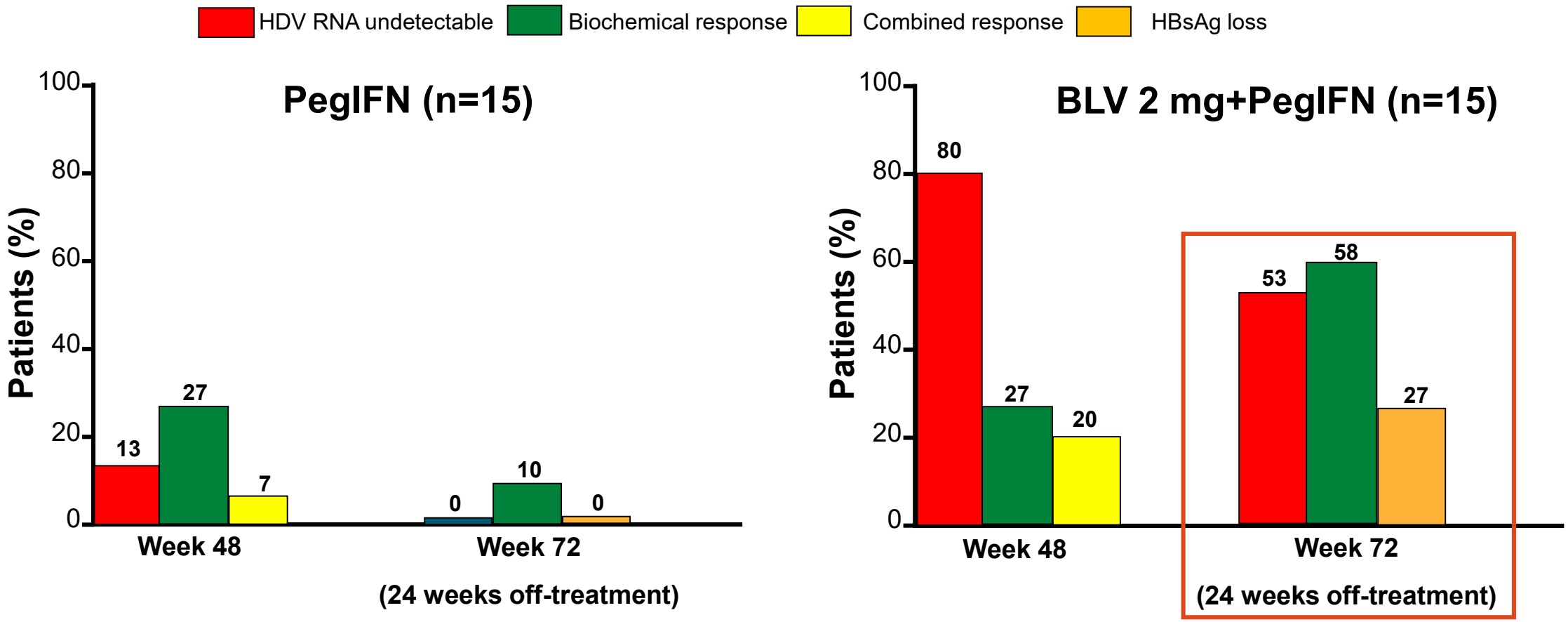
- Significant bile acids elevation
- Mild, transient pruritus in 12 (13%) patients
- No discontinuations due to AEs

BLV is safe and effective

Anolli et al. AISF 2023

BLV 2 mg ± PegIFN vs PegIFN in patients with CHD

Phase 2 MYR203 study in CHD patients treated with PegIFN ± BLV for 48 weeks

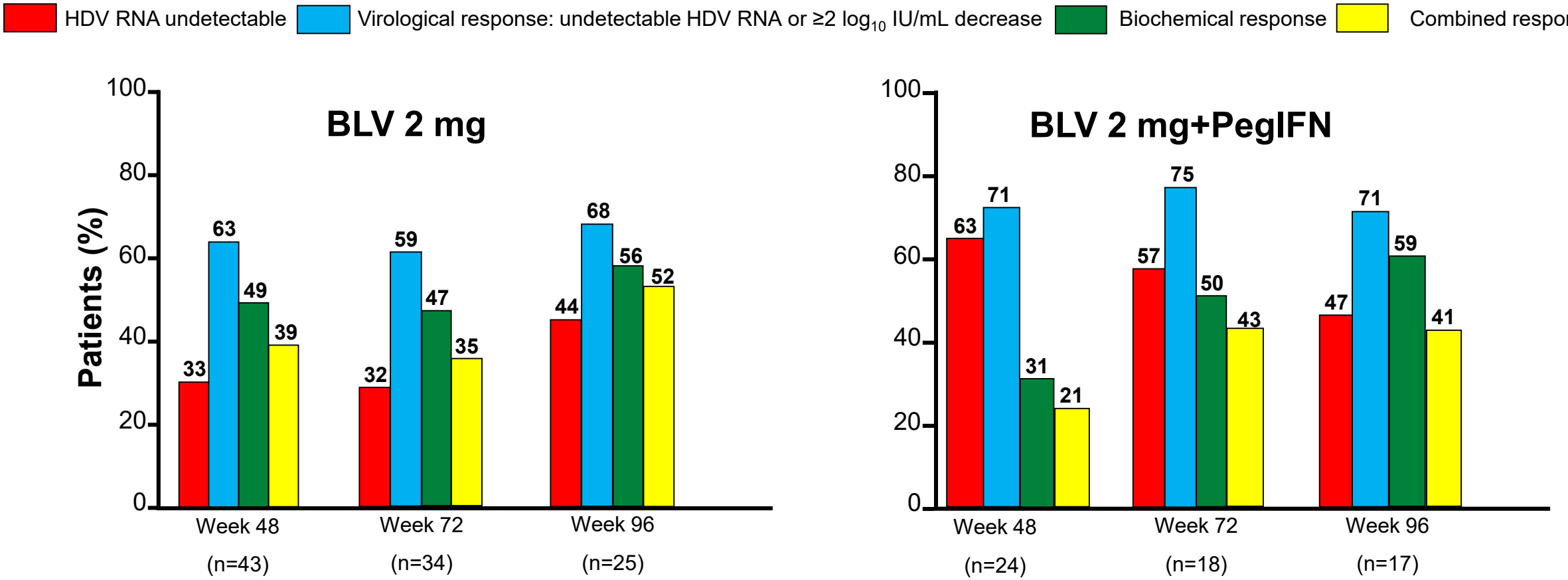


BLV 2 mg+PegIFN showed strong synergism. Off-treatment HDV RNA responses were only observed in patients achieving an HBsAg response

Wedemeyer et al. EASL 2020

BLV 2 mg ± PegIFN in patients with CHD

Multicenter, prospective, retrospective, observational study in CHD patients from French cATU program



BLV monotherapy demonstrated similar efficacy to BLV+PegIFN

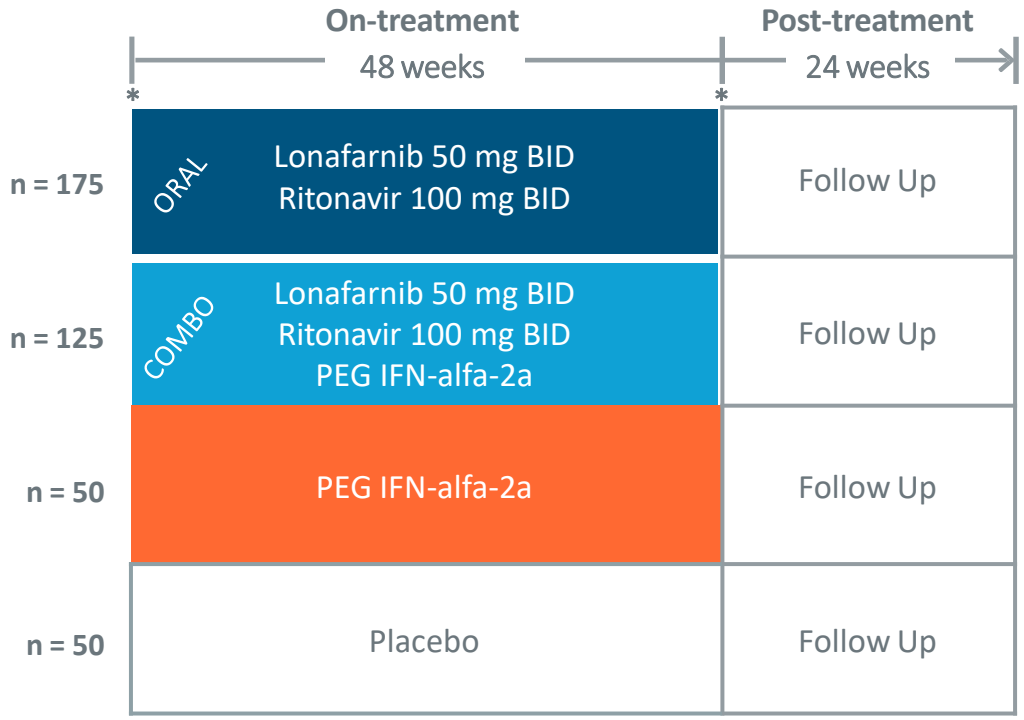
De Ledinghen et al. AASLD 2022

BLV for CHD: current challenges

In patients with HDV and compensated cirrhosis (+ CSPH) BLV is safe and effective and bile acids increase is expected and asymptomatic

- Adherence
- Optimal duration of suppressive treatment is currently unknown
- No qHBsAg decline and/or HBsAg seroclearance (no HBV/HDV functional cure!)
- BLV monotherapy vs BLV+PegIFN combo
- 10-20% of primary virological NR
- Safety data beyond week 48/96 (what about bile acids increase)?
- No data for hard clinical end-points
- Cost

Lonafarnib phase 3 global study in CHD



Primary Endpoint at week 48

≥ 2 log decline in HDV RNA
+
Normalization of ALT

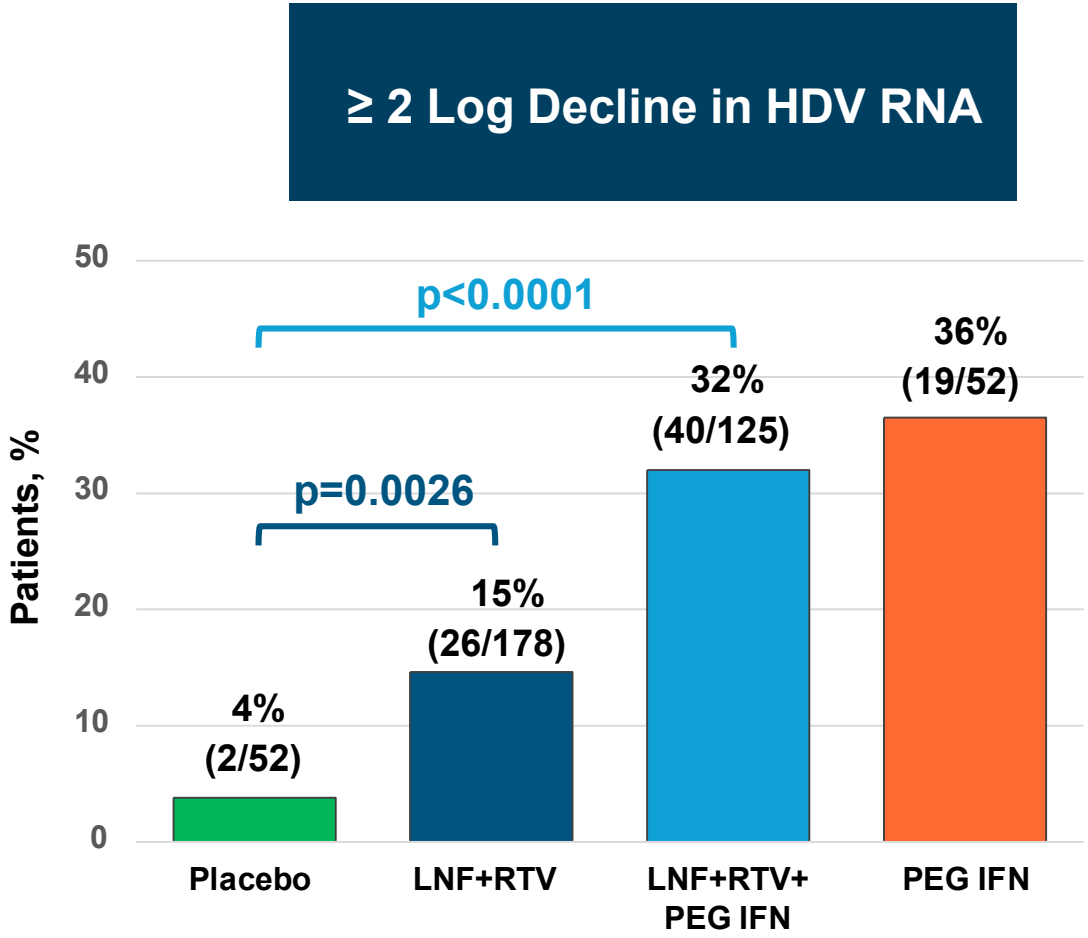
Secondary Endpoint at week 48

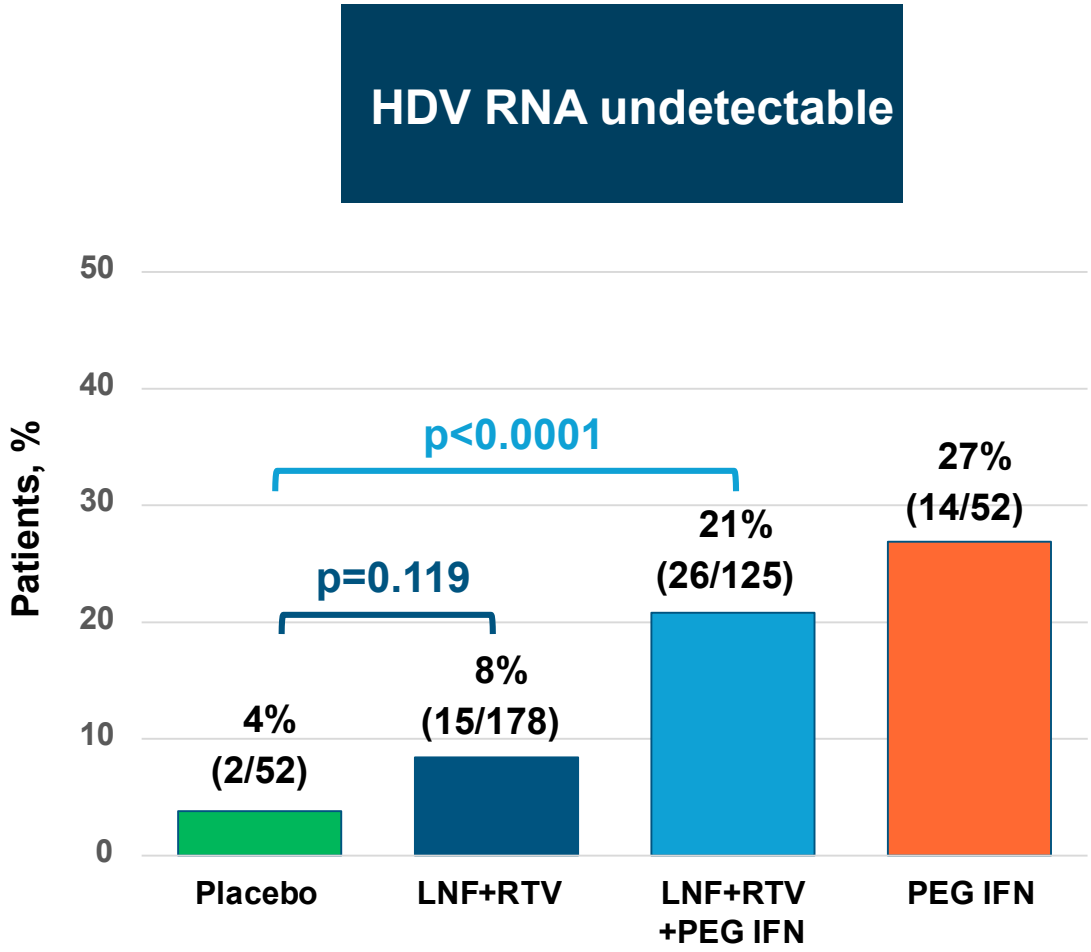
No worsening in fibrosis
+
≥ 2-point in Ishak HAI Score

* Liver biopsy
All patients will be maintained on background HBV nucleoside therapy.

Eiger press release 2023

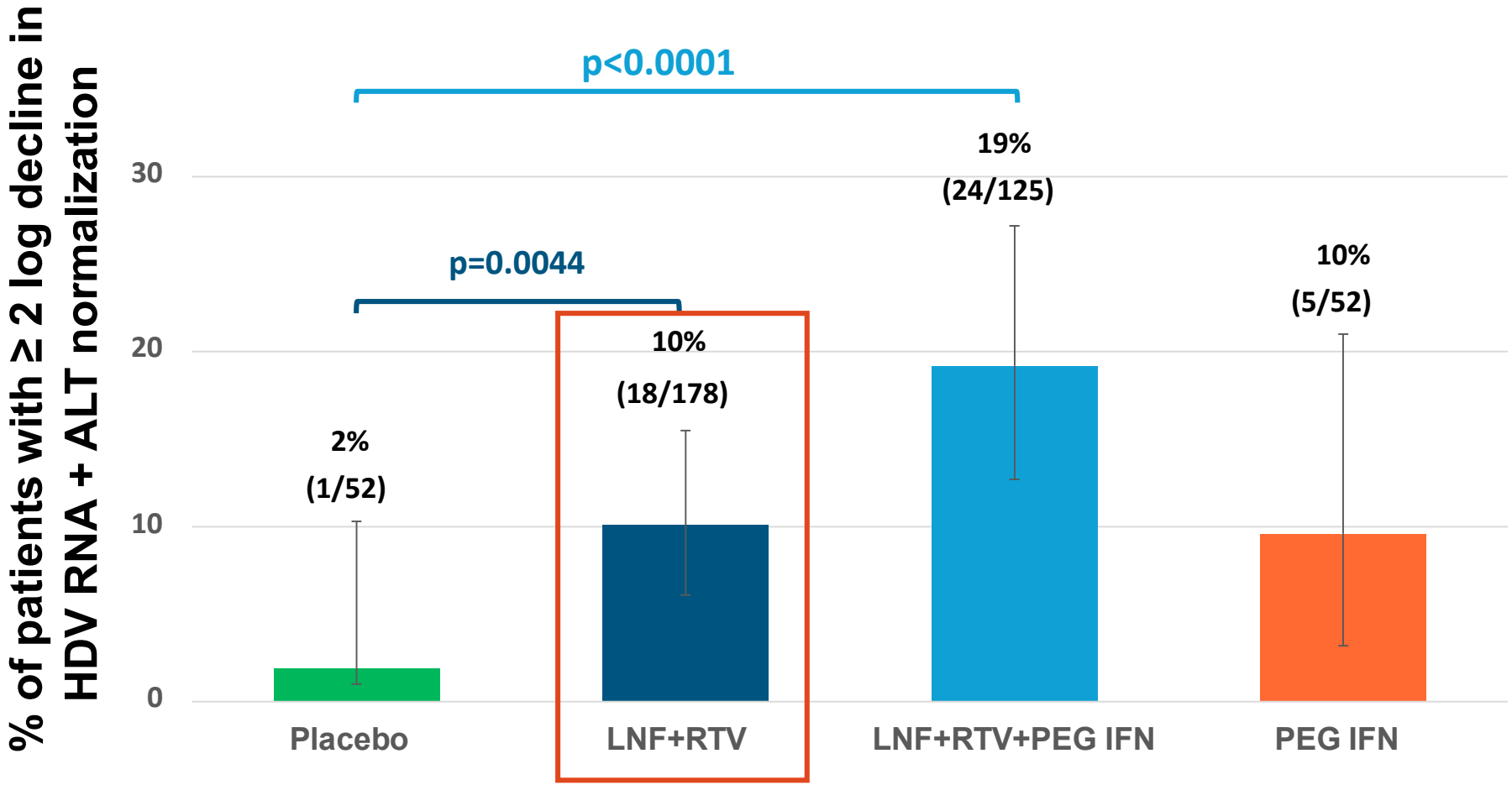
Lonafarnib phase 3 global study in CHD: virologic response at EOT





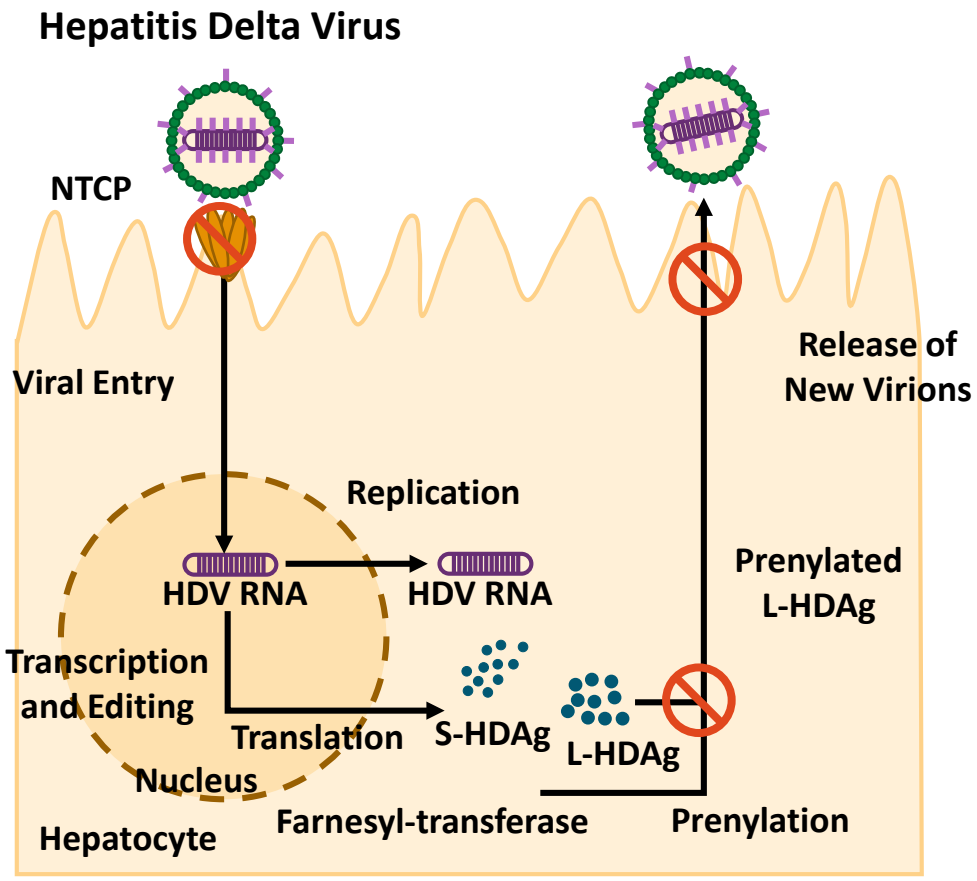
Eiger press release 2023

Lonafarnib phase 3 global study in CHD: Combined Response



Eiger press release 2023

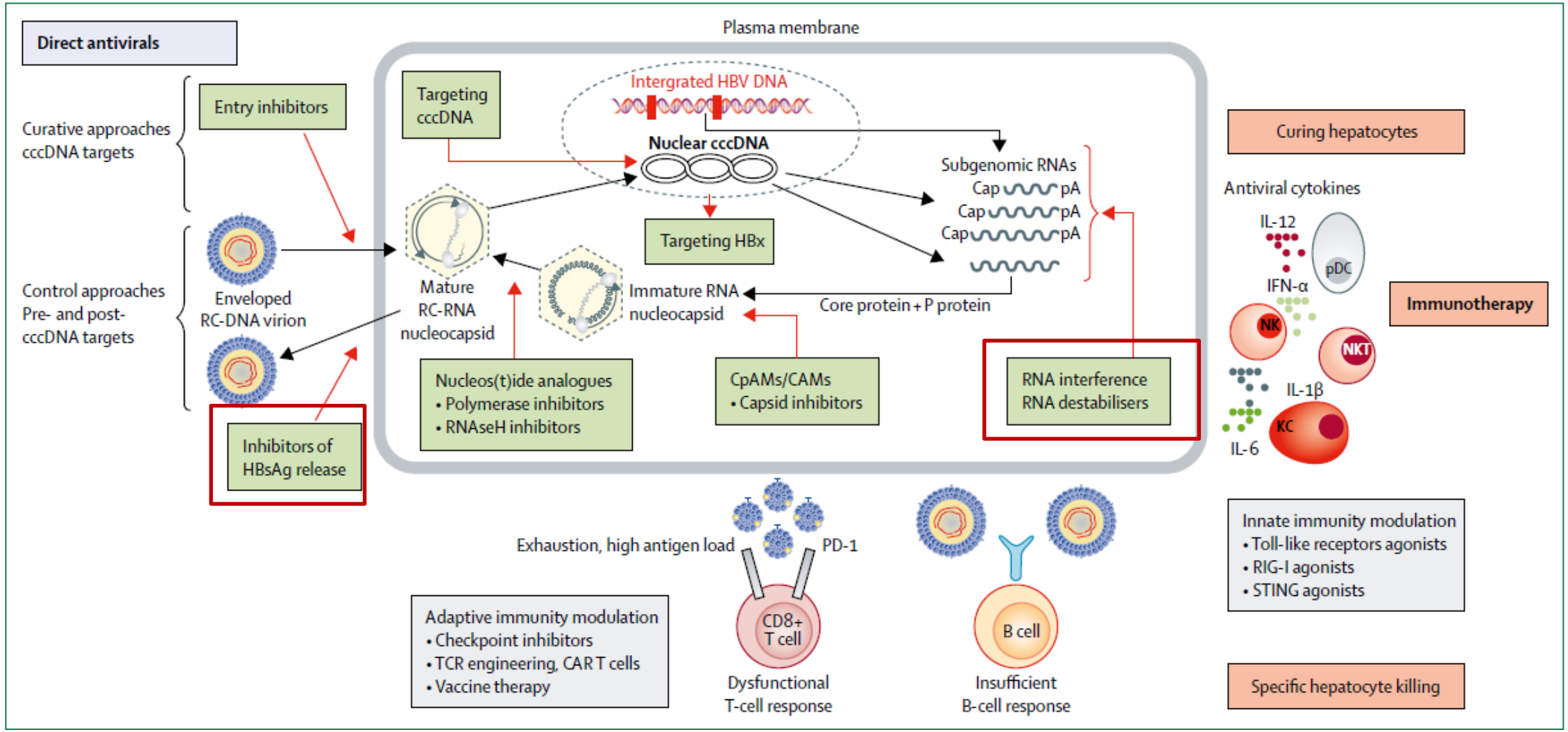
Therapeutic targets for HDV infection



Immunomodulators
pegIFNλ

Loureiro. Liver Int. 2021;41:30

Current and future HBV targets that will be necessary for CHD treatment



Revill P et al, Lancet GH 2019

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		ACTRN12615001133527 (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

Summary and Conclusion

- An approved anti-HDV drug is now available for the treatment of CHD patients.
- Referral (HDV RNA test, uniformity of management, HCC, LT).
- BLV monotherapy should be started in all patients with compensated liver cirrhosis and in all patients with advanced fibrosis. Long-term suppressive treatment with BLV+NUCs is recommended.
- In patients with F≤2 the decision to start BLV should be individualized considering the alternative use of PegIFN+BLV or the new trials.
- Other studies with different therapeutics are under way.
- A combination of different compounds tackling different steps of the HBV/HDV life cycle could be required to achieve a functional cure.