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HBV/HDV: una nuova sfida all'orizzonte

SCHOOL OF MEDICINE AND SURGERY

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HBV/HDV una nuova sfida all'orizzonte

- Virology
- Natural History
- Epidemiology
- Treatment:
  - Endpoints
  - Peg-IFN
  - Bulevirtide monotherapy
  - Bulevirtide + PEG IFN
  - New drugs

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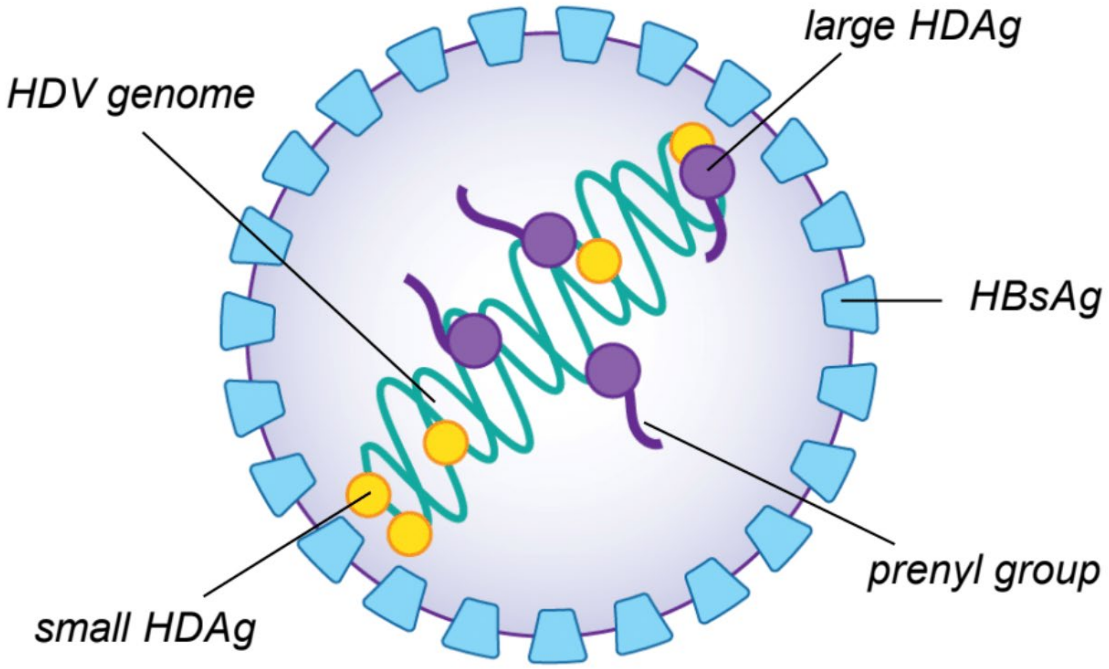
Hepatitis Delta Virus

Discovered in 1977 by Prof. Mario Rizzetto (Turin)



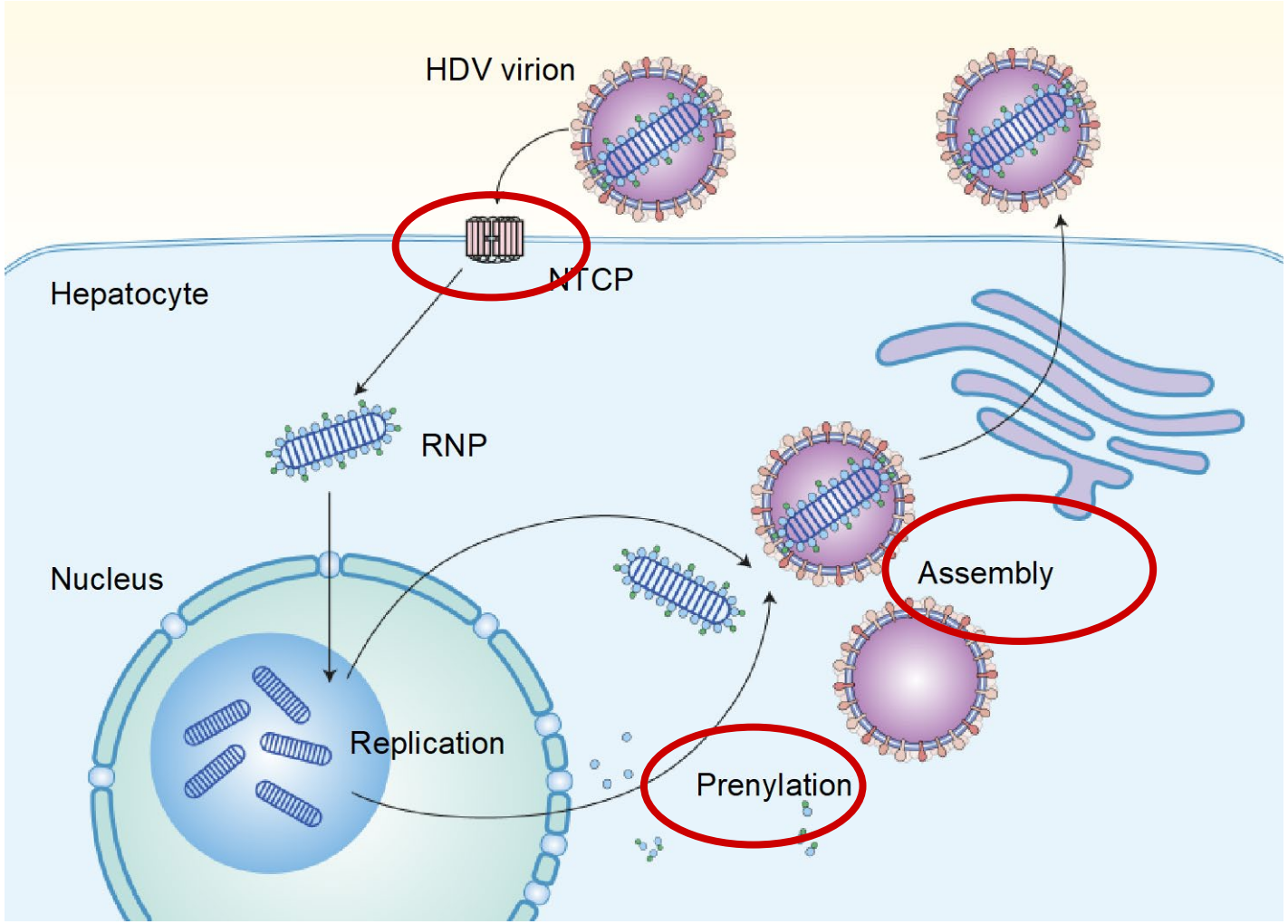
Characteristic	HDV
Family	Kolmioviridae
Genus	Deltavirus
Genome	Single-stranded (-) RNA 1.7 kbp
Virus-encoded Proteins	L-/S-HDAg
Cellular Receptors	HSPG, NTCP

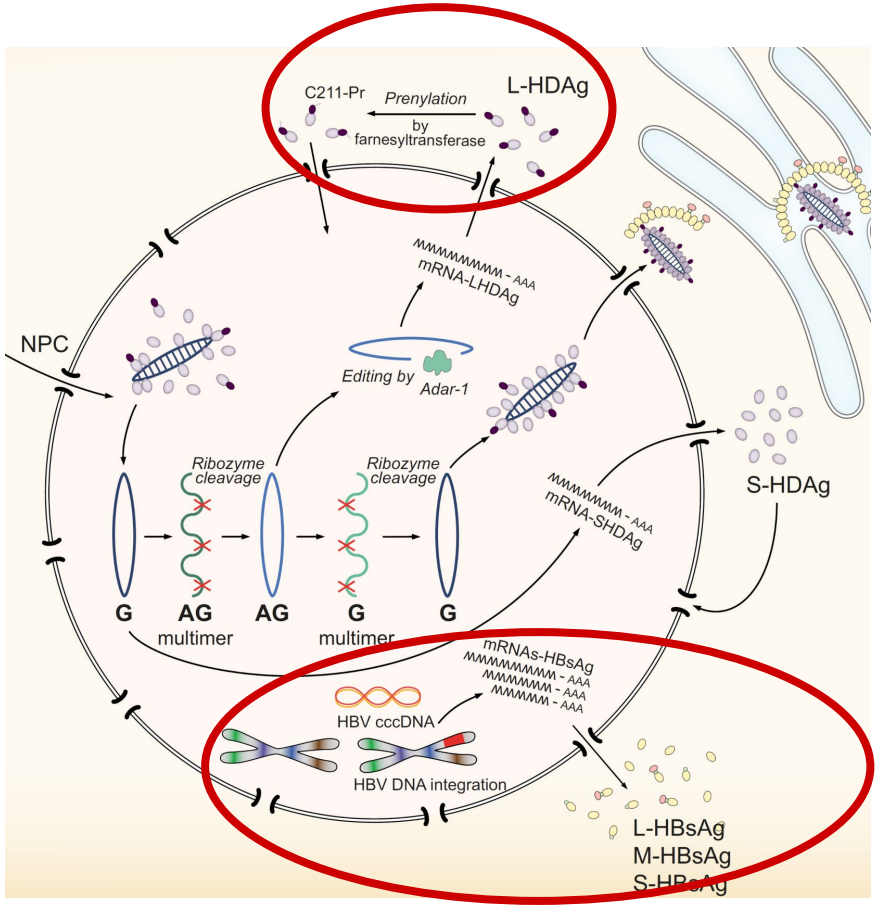
Defective virus that needs HBsAg for its propagation

HDAg = hepatitis D antigen = HSPG: heparan sulfate proteoglycans; L- = large; M- = middle; NTCP = sodium taurocholate cotransporting polypeptide; pol = polymerase; S- = small

Lempp FA. Urban S. Viruses. 2017;9:172; Netter HJ et al. Front Microbiol. 2021;12: 652962; Stockdale AJ et al. J Hepatol. 2020; 73:523–532; Miao Z et al. J Infect Dis. 2020; 221:1677–1687

HDV Life Cycle and potential therapeutic targets

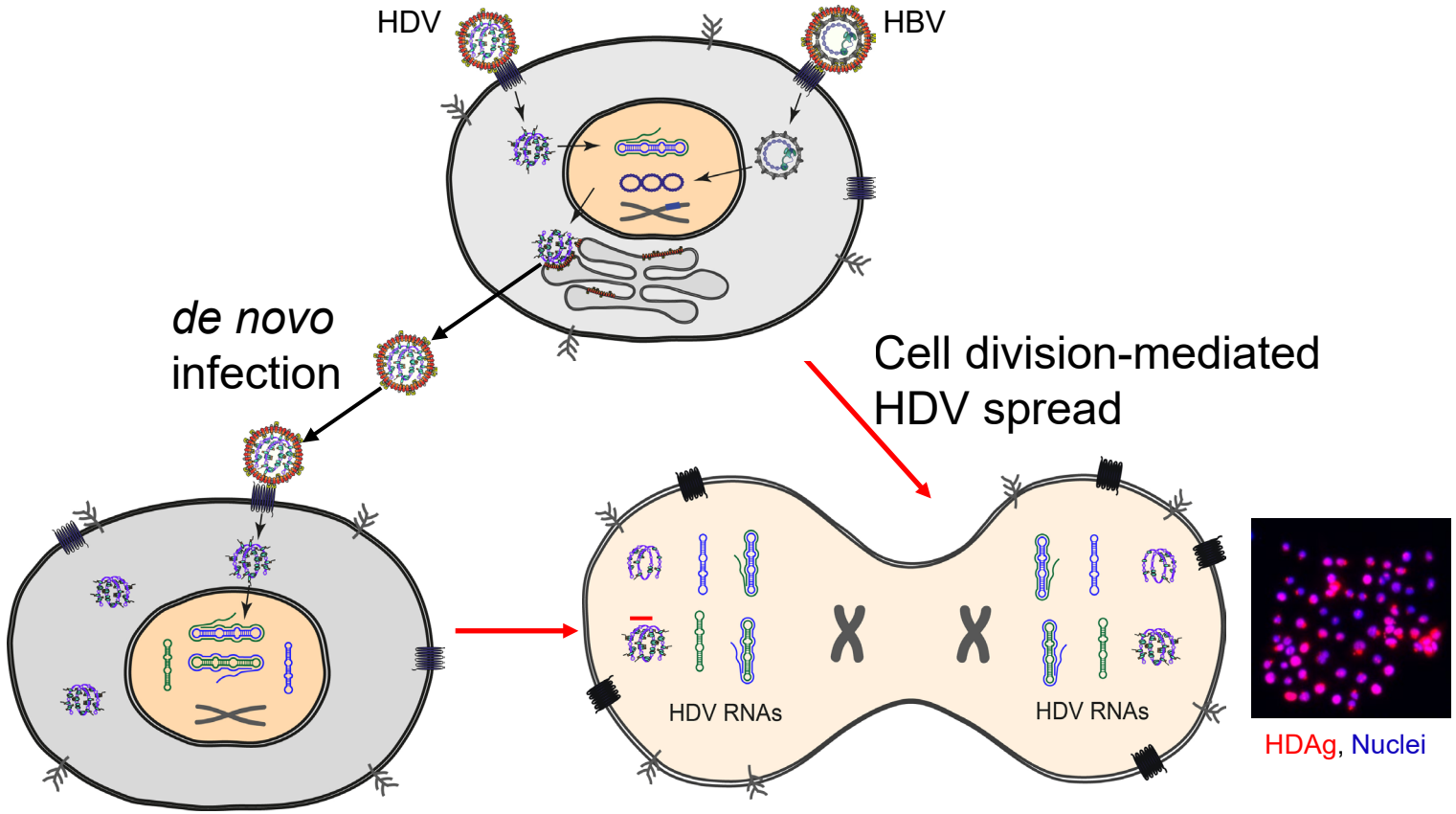




NTCP = Sodium taurocholate cotransporting polypeptide; RNA= ribonucleic acid; RNP = ribonucleoprotein

Adapted from Gilman C et al. World J Gastroenterol. 2019; 25: 4580–4597; EASL CPG on HDV, J Hepatol 2023: 79:433-460

HDV intra-hepatic propagation



- Extracellular HDV spread (HBV envelope dependent de novo infection)
- Cell division-mediated HDV spread

Bogomolov et al. J Hepatol. 2016; Yurdaydin et al. Hepatology 2018; Giersch et al. Gut. 2019; Zhang et al. J Hepatol. 2022

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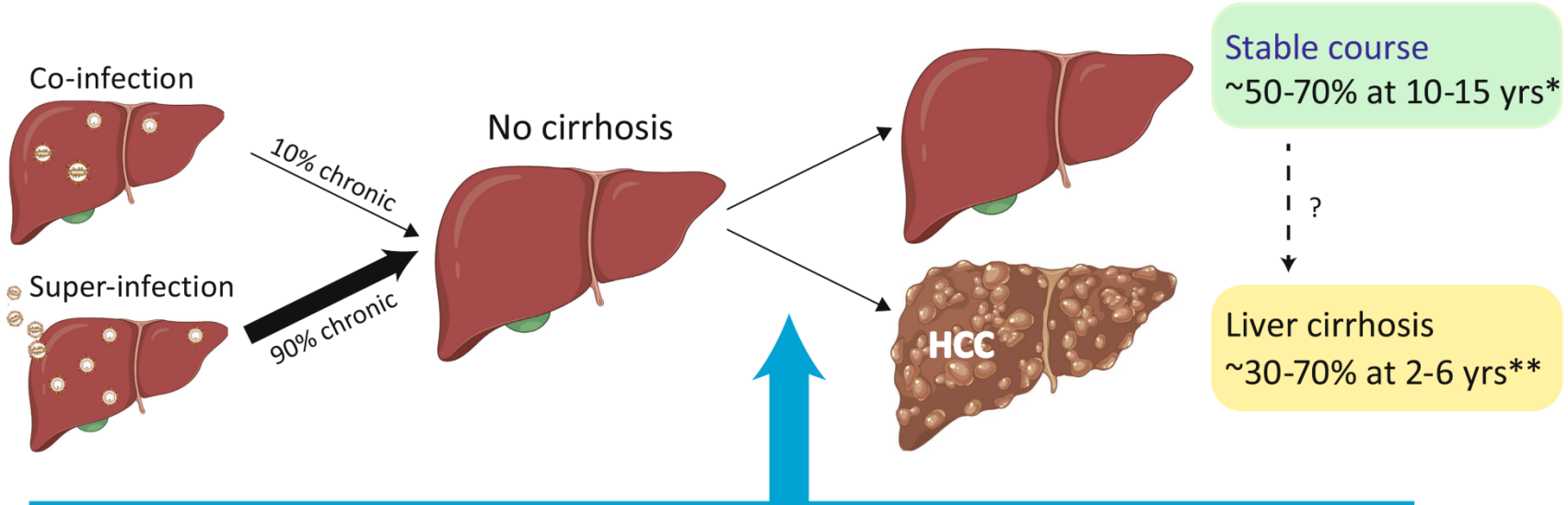
HDV Natural History



PROGNOSTIC FACTORS FOR DISEASE PROGRESSION

Viral:
- HDV RNA positivity
- HDV RNA level?
- HDV genotype 1 or 3↑, genotype 5↓
- HIV or HCV co-infection
- HBV genotype C or B?
- HBV DNA level?
- **HDV subtypes ?**

Clinical and host:
- Older age
- Male sex (HCC)
- Origin – Eastern European↑ African ↓ Asian↑?
- Alcohol or metabolic factors?
- HDV anti-IgM level?
- Serum cholinesterase? GGT?
- Immunological perturbations?

Antiviral therapy?
- Interferon
- Upcoming agents?

New HBV markers ?
- HBcrAg
- HBVRNA
- qHBsAg

**Roulot D, J Hepatol. 2020; Kamal H, Hepatology 2020; Spaan M, J Hepatol 2020; Niro GA, J Hepatol. 2010*
***Hernandez-Evole H, World J Hepatol 2020; Wranke A, Hepatology 2017; Miao Z, J Infect Dis. 2020; Fattovich G, Gut. 2000; Rizzetto M, Ann Intern Med. 1983*

Determinants of worse liver-related outcome according to HDV infection among HBsAg positive Persons Living with HIV (PLWH): data from the ICONA cohort

	N PLWH	SLRE	Prevalence (95%CI)	IR x1000 PYFU (95%CI)
HDV Ab neg	612	15	2.4% (1.4-4.0)	3.6 (2.0-6.0)
HDV Ab pos / HDV-RNA neg	29	4	13.8% (3.9-31.7)	13.7 (3.8-35.1)
HDV Ab pos / HDV-RNA pos	59	12	20.3% (11.0- 32.8)	23.7 (12.2-41.4)
HDV-RNA>1.000 IU/ml	43	8	18.6% (8.4-33.4)	23.7 (10.2-46.7)
HDV-RNA≤1.000 IU/ml	14	3	21.4% (4.6-50.8)	21.4 (4.4-62.8)

	SHR	95%CI	p	ASHR*	95%CI	p
HDV Ab neg	1			1		
HDV Ab pos / HDVRNA neg	4.16	1.36-12.67	0.012	3.14	1.00-9.91	0.050
HDV Ab pos / HDVRNA pos	6.61	3.17-13.79	<.001	4.61	2.02-10.5	<.001
* Adjusted for baseline CD4, age, alcool use, metabolic syndrome and HCV status						

ASHR of SLRE was similar in the two groups of low and high HDV viremia:
4.8 (95% CI 1.3-18.3) in HDV-RNA <1,000 IU/mL 4.3 (95% CI 1.7-10.6) for HDV-RNA >1,000 IU/mL.

	N PLWH	SLRE	Prevalence (95%CI)	IR x1000PYFU (95%CI)
HDVAb+ HCVAb+	101	20	19.8% (12.5-28.9)	23.6 (14.4-36.4)
HDVAb+ HCVAb-	37	2	5.4% (0.6-18.2)	6.7 (0.8-24.3)
HDVAb- HCVAb+	133	9	6.7% (31.5-12.4)	8.6 (3.9-16.3)
HDVAb- HCVAb-	455	6	13.2% (4.8-28.5)	2.1 (0.7-4.4)

	SHR	95%CI	p	AHSR*	95%CI	p
HDVAb- HCVAb-	1			1		
HDVAb+ HCVAb+	11.72	4.74-28.96	<.001	11.93	4.60-30.93	<.001
HDVAb+ HCVAb-	3.65	0.76-17.62	0.107	3.76	0.73-19.27	0.113
HDVAb- HCVAb+	4.23	1.52-11.82	0.006	4.07	1.45-11.45	0.008
*Adjusted for baseline CD4, age, metabolic syndrome alcohol use						

Role of nadir CD4 HDV Ab pos PLWH with nadir CD4 <=200/mmc showed a marginally significantly higher independent risk of SLRE 3.9 3.1 times higher (95%CI: 0.9-10.8) as compared to patients with CD4>200/mmc at nadir

Impact of HCV-RNA negativisation on clinical outcome of HDV positive individuals: HCV-RNA positivity showed a not significant independent double risk of SLRE as compared to those eradicating HCV (ASHR: 2.0- 95%CI 0.54-7.4).

A. D'Arminio Monforte et al Liver International in press

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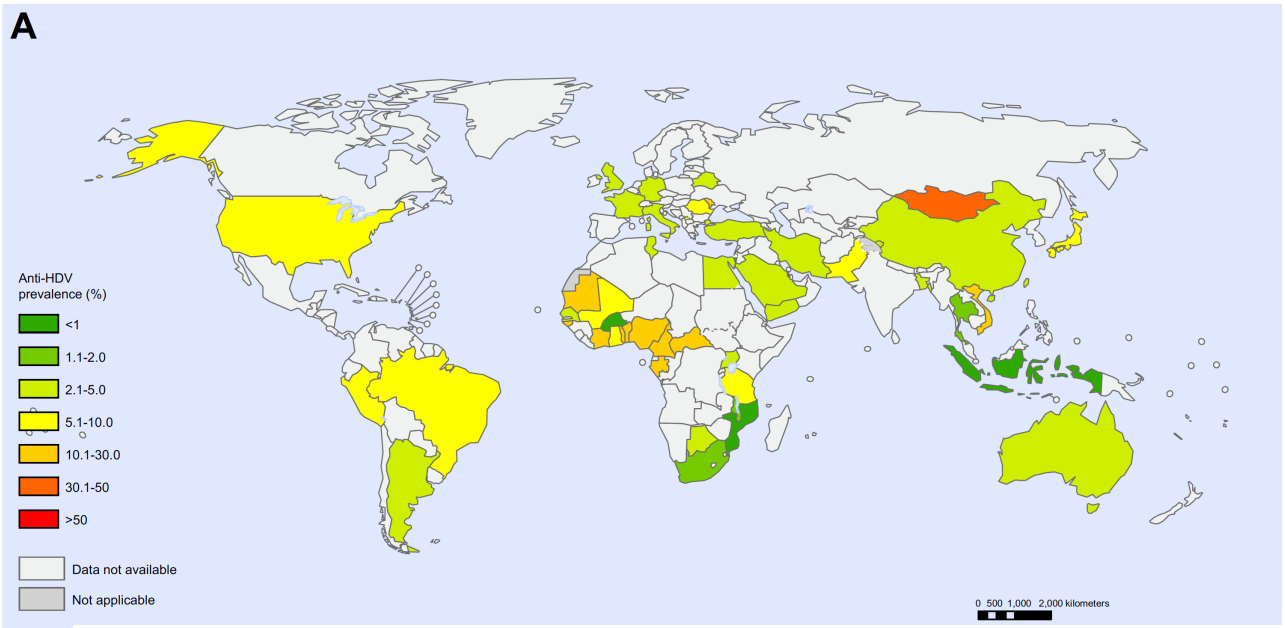
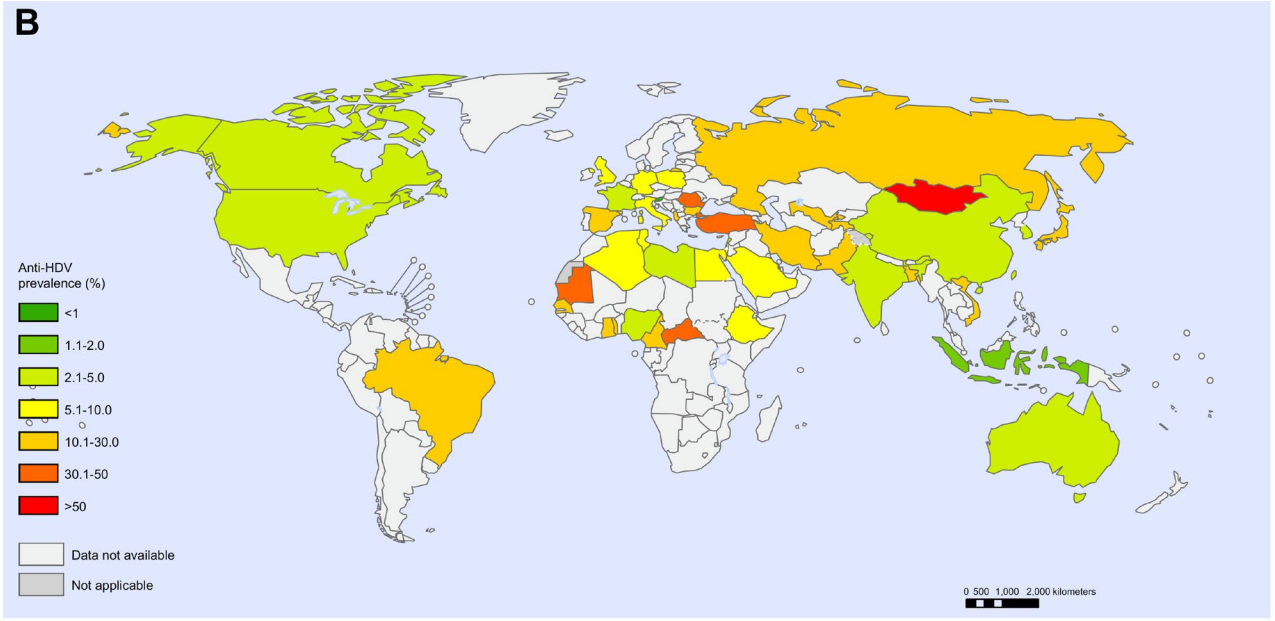
Country level estimates of anti-HDVAb prevalence among HBsAg positive people

General population (A), Hepatology clinic population (B)



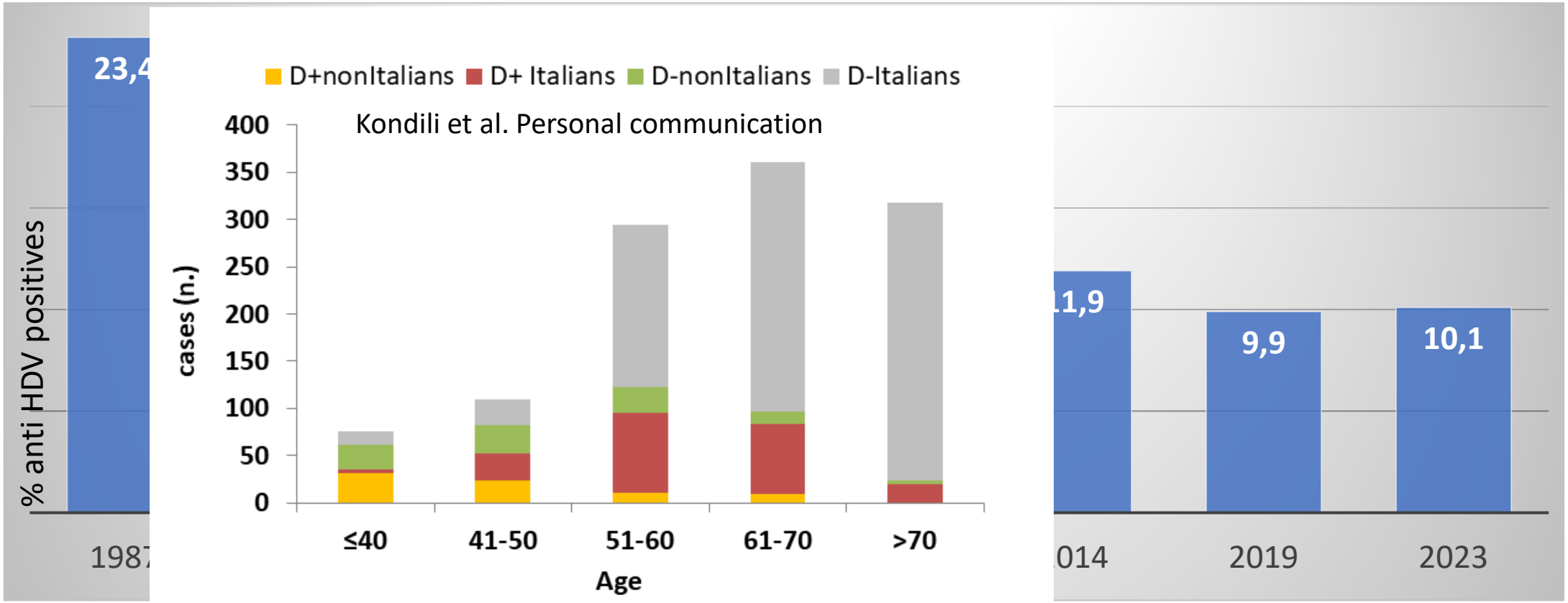


	AFR	AMR	EMR	EUR	SEAR	WPR	Global
Population (thousands)	1,052,766	1,006,458	715,425	928,490	1,982,239	1,945,717	7,631,091
HBsAg prevalence, % (95% CI)	6.1 (4.6–8.5)	0.7 (0.4–1.6)	3.3 (2.6–4.3)	1.6 (1.2–2.6)	2.0 (1.5–4.0)	6.2 (5.1–7.6)	3.5 (2.7–5.0)
Anti-HDV prevalence among people with HBsAg, % (95% CI)	6.0 (5.0–7.2)	5.9 (3.0–9.7)	3.5 (2.1–6.3)	3.0 (2.1–4.2)	3.2 (0.4–12.4)	4.1 (3.5–4.8)	4.5 (3.6–5.7)
Anti-HDV prevalence among the general population, % (95% CI)	0.36 (0.26–0.54)	0.04 (0.02–0.11)	0.12 (0.07–0.23)	0.05 (0.03–0.09)	0.06 (0.01–0.35)	0.25 (0.20–0.33)	0.16 (0.11–0.25)
HDV RNA prevalence among people with anti-HDV, % (95% CI)	41.3 (31.8–51.1)	64.2 (21.5–98.0)	49.4 (30.1–68.7)	64.1 (54.3–73.3)	50.1 (31.4–70.3)	73.3 (57.8–68.7)	58.5 (52.4–64.5)
HDV RNA prevalence among the general population, % (95% CI)	0.15 (0.10–0.24)	0.03 (0.01–0.09)	0.06 (0.03–0.12)	0.03 (0.02–0.06)	0.03 (0.00–0.18)	0.19 (0.13–0.26)	0.09 (0.07–0.15)
Number of people with anti-HDV, thousands, % (95% CI)	3,835 (2,779–5,706)	416 (185–1,135)	836 (482–1,610)	445 (293–833)	1,267 (172–6,841)	4,935 (3,836–6,391)	11,992 (8,662–18,743)
Number of people with HDV RNA, thousands, (95% CI)	1,584 (1,059–2,506)	267 (78–881)	413 (203–877)	285 (184–544)	635 (83–3,622)	3,617 (2,583–4,971)	7,015 (4,994–11,109)

AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asian Region;; WPR, Western Pacific Region.

Stockdale AJ J of Hepatol 2020; 73: 523–532

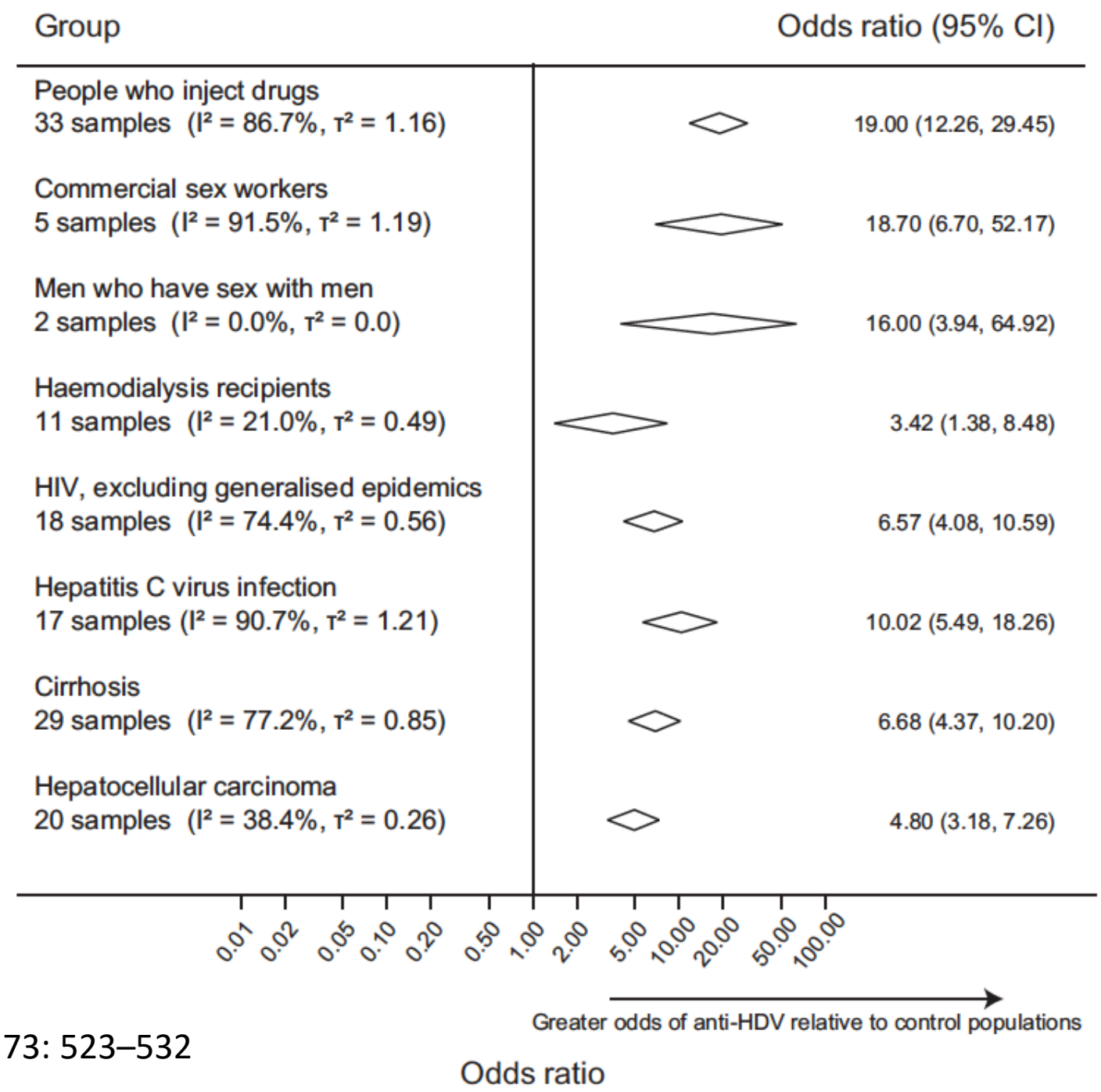
Prevalence of anti-delta positivity among chronic HBsAg carriers in liver units in Italy over more than three decades (1987-2023)



Author	Sagnelli E	Sagnelli E	Gaeta GB	Sagnelli E	Gaeta GB	Stroffolini T	Stroffolini T	Kondili
N of HBsAg+ pts	1556	996	834	1336	1179	513	786	4152
N of centers	35	31	14	79	21	16	9	59

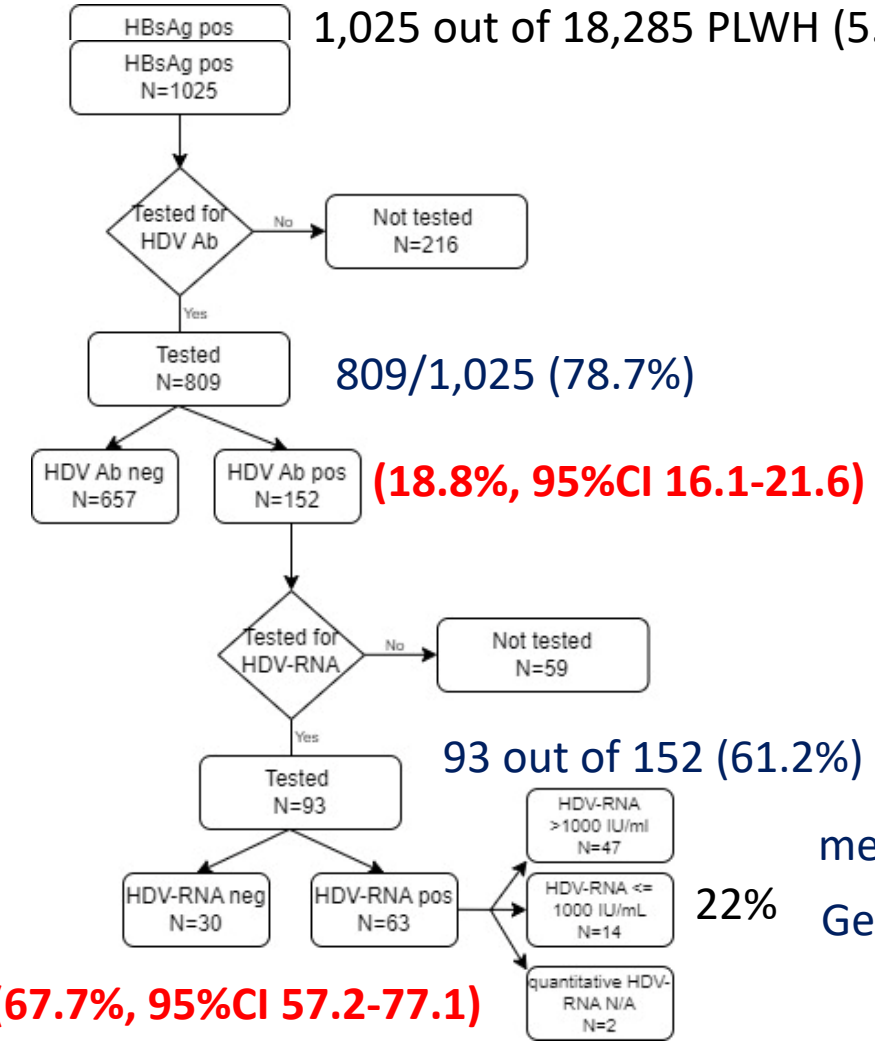
Sagnelli E, et al J Hepatol. 1992;15:211-215; Sagnelli E, et al . J Hepatol. 1997;26:20-24. Gaeta GB,et al Hepatology. 2000; 32:824-827; Sagnelli E, et al Clin Infect Dis. 2008;46:110-113. Gaeta GB et al. Hepatology. 2007;46:1312-1313. Stroffolini T, et al. Infection. 2017;45:277-281. Stroffolini T et al. J Viral Hepat. 2020;27:941–947. Kondili L et al personal communication

HDV seroprevalence among selected population groups relative to general populations or asymptomatic HBsAg-positive people from the same geographic region.



Stockdale AJ et al Journal of Hepatology 2020 vol. 73: 523–532

HDV infection in HBsAg positive Persons Living with HIV in Italy data from the ICONA cohort



1,025 out of 18,285 PLWH (5.6%)

809/1,025 (78.7%)

(18.8%, 95%CI 16.1-21.6)

93 out of 152 (61.2%)

22%

63 (67.7%, 95%CI 57.2-77.1)

Last available follow up in 2020-21:

HDVAb- 275/657 (42%)

HDVAb+ 35/152 (23%)

ICONA: HDVAb+ among HBsAg+ PLWH in 2020-21: 35/310: 11% (8,8-12,1%)

Piter HDVAb+ among HBsAg+ HIV- 405/3695: 11% (10,9-11,1%)

median plasma HDV-RNA of 5.75 (3.67-7.15) log IU/ml.

Genotype 1 was detected in 100%

D'Arminio Monforte et al Liver International in press; Kondili L et al personal communication

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Endpoints of anti-HDV treatment

- HBsAg loss/seroconversion
- Virological response (HDV RNA undetectable; ≥ 2log decline ?)
- Biochemical response (ALT normalization)
- Combined response (≥ 2log decline of HDV RNA and ALT normalization)
- Histological response
- Clinical response (stop disease progression, improve survival)

At different time points: during therapy, EOT, EOF (≥24 weeks off therapy)

modified from Yurdaydin C et al J Hepatol 2019;70:1008-15; Cornberg M et al, J Hepatol 2020;72:539-57, Urban et al, Gut 2021

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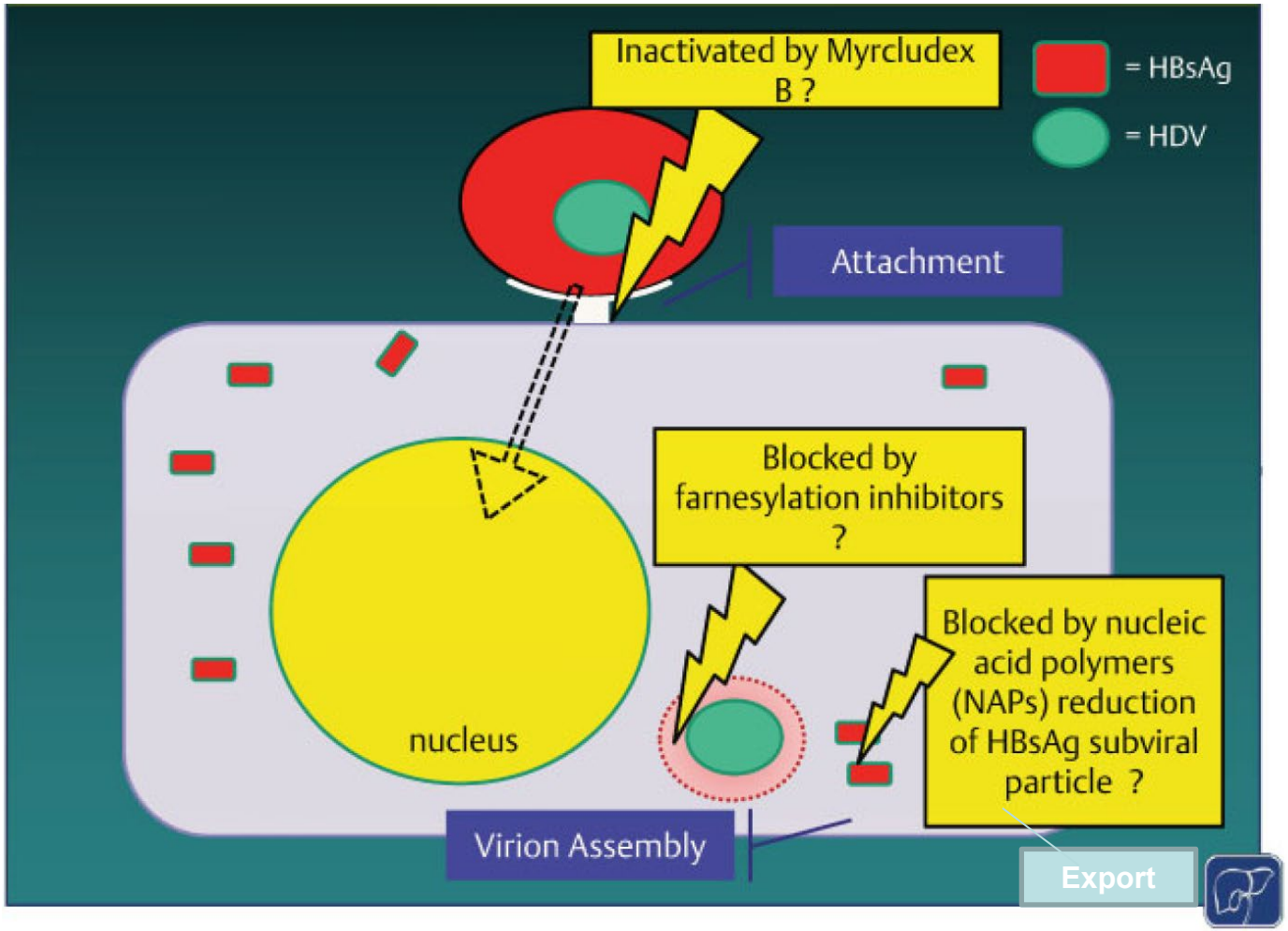
Treatment	Schedule	N of persons	HDVRNA – 24 w after Tx withdrawal	Author/yr
IFN-alfa: 3–18 MUI 3x/settimana	**3–12 months**	201	17%	Abbas Z /2011 (Cochrane Metanalysis)
Peg IFN-alfa 2b: 1.5 mg/kg settimana	18 months	16	25%	Niro GA 2006
	18 months + Ribavirin (1–1.2 g qd Per 12 months)	22	18%	
	12 months	14	43%	Castelnau 2006
	12 months	12	17%	Erhartdt 2006
	12 months	48	25%	Gheorghe 2011
Peg IFN-alfa 2a: 180 mcg/kg qw	12 Months	29	26% (12.5% at 8 years)	Wedemeyer 2011
	12 months + adefovir (10 mg qd per 12 months)	31	31% (12.5% at 8 years)	
Pegy IFN-alfa 2b: 1.5 mcg/kg qw o Peg IFN-alfa 2a: 180 mcg/kg qw	12 months + TDF	104	23%	Abbas Z 2014
Peg IFNalpha 12 – 18 months		**276**	**25% (12.5% at 8 years)**	
Peg- IFN alfa 180 mcg qw	**6 years**	**12**	**58% (33% HBsAg-)**	**Harcun J 2021**

HDV: new therapeutic targets



- Myrcludex-B, entry inhibitor, sc injections, with or without IFN
- Lonarfarnib, prenilation inhibitor, oral, with or without IFN
- Any therapy aimed to HBV functional cure (HBsAg loss) (??)

Rizzetto Semin Liver Dis 2018;38:66–72.

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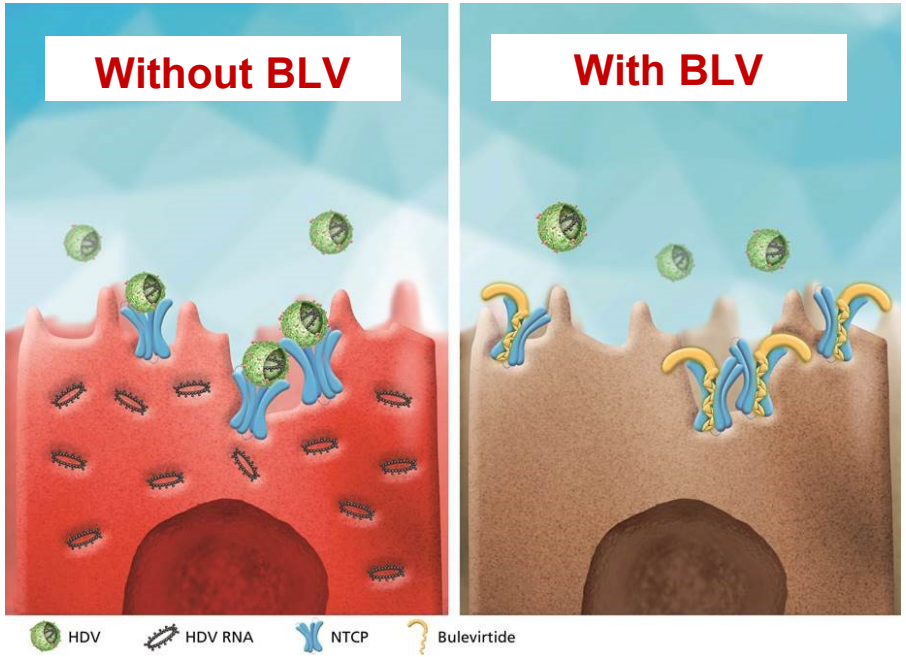
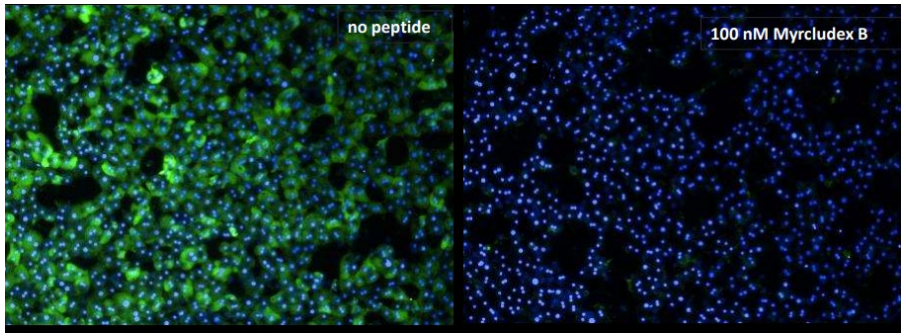
Bulevirtide (BLV) (Myrcludex B) is the first-in-class entry inhibitor HEPCLUDEX® for Europe



with permission of MYR Pharmaceuticals



Immunofluorescence of HBsAg (green) and DAPI (blue) in HBV-infected PHHs at day 15 p.i.[1]

Mode of action:

- Synthetic lipopeptide (47 amino acids) derived from the preS1 domain of the HBV large surface protein
- Mechanism of action: entry inhibitor
- Cellular target (NTCP)
- BLV blocks NTCP, the 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

Modified from Urban S, Neumann-Haefelin C, Lampertico P. GUT 2021

HEPCLUDEX (Bulevirtide) EMA Indication

Indication	• Treatment of chronic hepatitis delta virus (HDV) infection in HDV RNA-positive adult patients with compensated liver disease
Administration	• Administered at 2 mg once daily (every 24 hours ± 4 hours) by subcutaneous injection • Monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying HBV infection
Instructions for Use	• Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection • Optimal treatment duration is unknown. Treatment should be continued as long as associated with clinical benefit

Reference: Summary of Product Characteristics, available at www.eua.europa.eu

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*

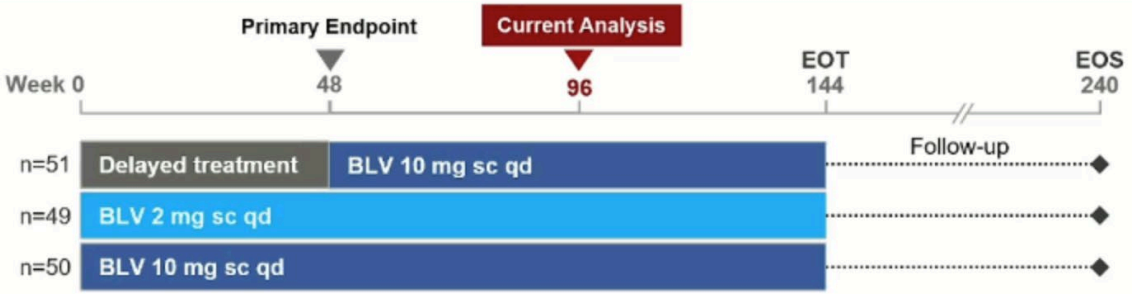
Efficacy and safety at 96 weeks of bulevirtide 2 mg or 10 mg monotherapy for chronic hepatitis D (CHD): results from an interim analysis of a phase 3 randomized study

Heiner Wedemeyer[1], Soo Aleman[2], Maurizia Brunetto[3,4], Antje Blank[5], Pietro Andreone[6], Pavel Bogomolov[7], Vladimir Chulanov[8], Nina Mamonova[8], Natalia Geyvandova[9], Morozov Viacheslav[10], Olga Sagalova[11], Tatyana Stepanova[12], Dmitry Manuilov[13], Renee-Claude Mercier[13], Qi An[13], John F. Flaherty[13], Anu Osinusi[13], Audrey Lau[13], Julian Schulze zur Wiesch[14], Markus Cornberg[1], Stefan Zeuzem[15], Pietro Lampertico[16,17]

[1]Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Hannover, Germany, [2]Karolinska University Hospital/Karolinska Institutet, Department of Infectious Diseases, Stockholm, Sweden, [3]University Hospital of Pisa , Hepatology Unit, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, Pisa, Italy, [4]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy, [5]Heidelberg University Hospital, Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany, [6]University of Modena and Reggio Emilia, Internal Medicine, Baggiovara Hospital, Modena, Italy, [7]State budgetary institution of health care of Moscow region "Moscow regional research clinical institute after M.F. Vladimirsky", Moscow, Russian Federation, [8]FSBI National Research Medical Center for Phthisiopulmonology and Infectious Diseases of the Ministry of Health of the Russian Federation, Moscow, Russian Federation, [9]Stavropol Regional Hospital, Stavropol, Russian Federation, [10]LLC Medical Company "Hepatolog", Samara, Russian Federation, [11]Federal state-funded institution of higher education "Southern Ural State Madical University of Ministry of Health of the Russian Federation", Chelyabinsk, Russian Federation, [12]Limited liability company "Clinic of Modern Medicine", Moscow, Russian Federation, [13]Gilead Sciences, Foster City, United States, [14]Universitätsklinikum Hamburg-Eppendorf , Medizinische Klinik Studienambulanz Hepatologie, Hamburg, Germany, [15]University Hospital Frankfurt, Department of Medicine, Frankfurt am Main, Germany, [16]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy, [17]CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy

International Liver Congress, 21–24 June 2023: Oral OS-068.

Study Design



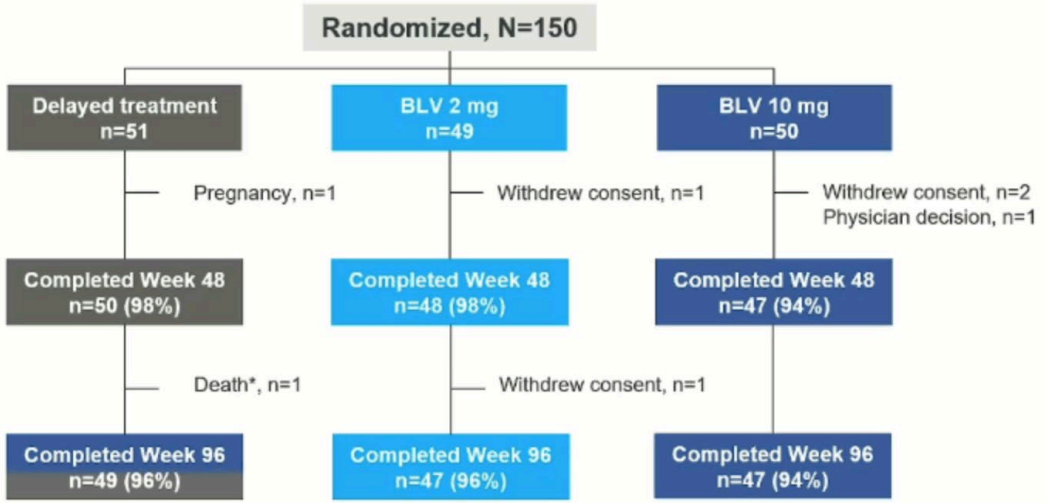
- Multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in 16 sites across 4 countries (Germany, Italy, Russian Federation, and Sweden)
- **Key Inclusion Criteria:**
  - CHD without or with cirrhosis and CPT ≤7
  - ALT >1X to <10X ULN
  - Platelets ≥60,000 cells/mm^3
  - Controlled HIV coinfection allowed

Demographic and Disease Characteristics

		Delayed Treatment/ BLV 10 mg n=51	BLV 2 mg n=49	BLV 10 mg n=50
Mean age, years (SD)		41 (8)	44 (9)	41 (9)
Male sex, n (%)		26 (51)	30 (61)	30 (60)
Race#, n (%)	White	40 (78)	41 (84)	43 (86)
	Asian	11 (22)	8 (16)	6 (12)
Cirrhosis, n (%)		24 (47)	23 (47)	24 (48)
Mean platelets, X10^3 cells/mm^3 (SD)		158 (57)	153 (53)	160 (53)
Mean liver stiffness, kPa (SD)		15.3 (9.0)	14.0 (8.2)	14.8 (9.3)
Mean ALT, U/L (SD)		102 (62)	108 (63)	123 (81)
Mean HDV RNA, $\log_{10}$ IU/mL (SD)		5.08 (1.36)	5.10 (1.20)	4.96 (1.46)
HDV genotype 1, n (%)*		51 (100)	49 (100)	48 (96)
Mean HBsAg, $\log_{10}$ IU/mL (SD)		3.68 (0.47)	3.67 (0.52)	3.61 (0.59)
HBV DNA >10 IU/mL, positive, n (%)		13 (26)	14 (29)	11 (22)
Mean HBV DNA, $\log_{10}$ IU/mL (SD)		0.89 (0.99)	1.30 (1.29)	1.08 (1.26)
HBeAg positive, n (%)		4 (8)	4 (8)	7 (14)
HBV genotype, n (%)	A	4 (8)	2 (4)	3 (6)
	D	39 (77)	44 (90)	43 (86)
	Other^/Missing	8 (16)	3 (6)	4 (8)
Previous IFN therapy, n (%)		29 (57)	26 (53)	29 (58)
Concomitant HBV NUC treatment, n (%)		32 (63)	32 (65)	27 (54)

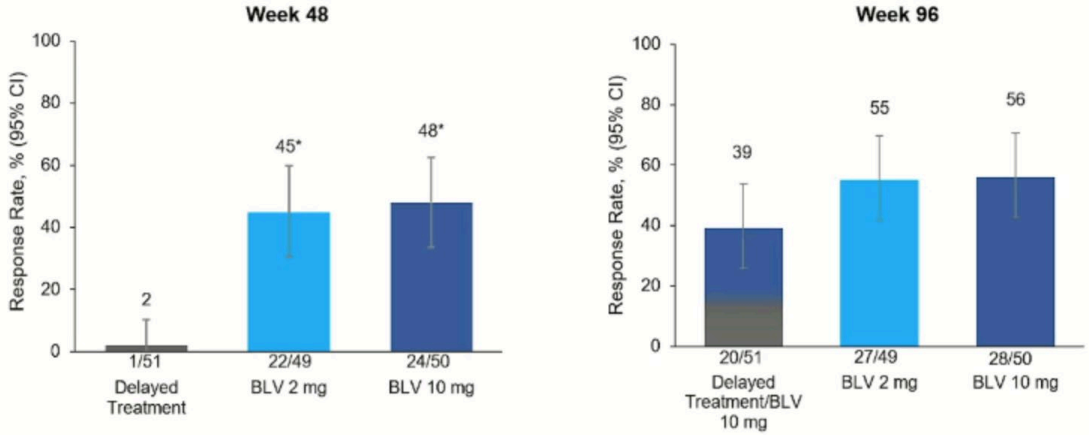
#BLV 10-mg group: n=1 Black; *BLV 10-mg group: n=1 HDV GT 5, n=1 missing HDV GT; ^BLV 10-mg group: n=1 HBV GT E. HBeAg, hepatitis B e antigen; IFN, interferon; IQR, interquartile range; NUC, nucleos(t)ide; GT: genotype.

Patient Disposition



- 2 patients did not complete week 96, none related to study treatment

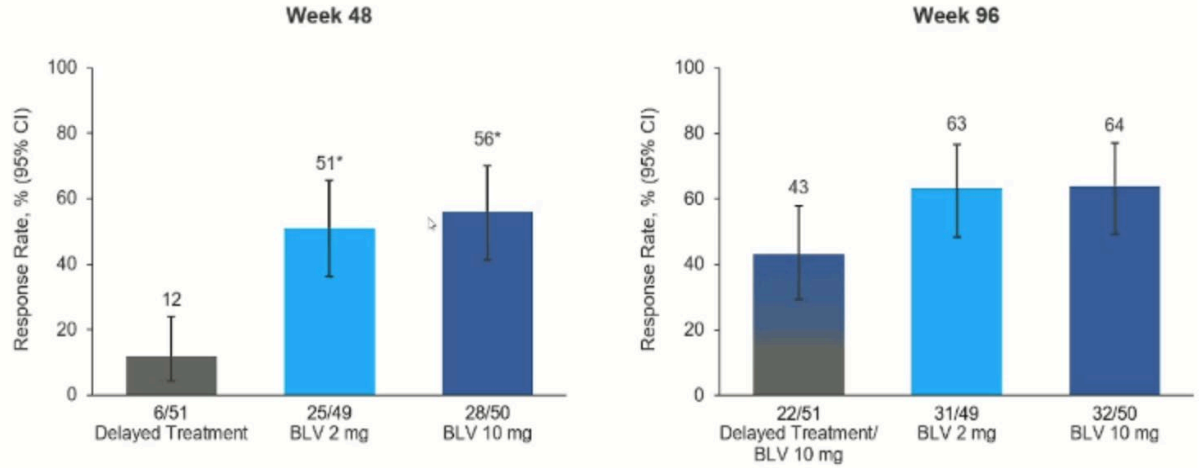
Results: Combined Response



- Combined response rates were increased at Week 96 in all arms; similar response between BLV 2-mg and 10-mg doses

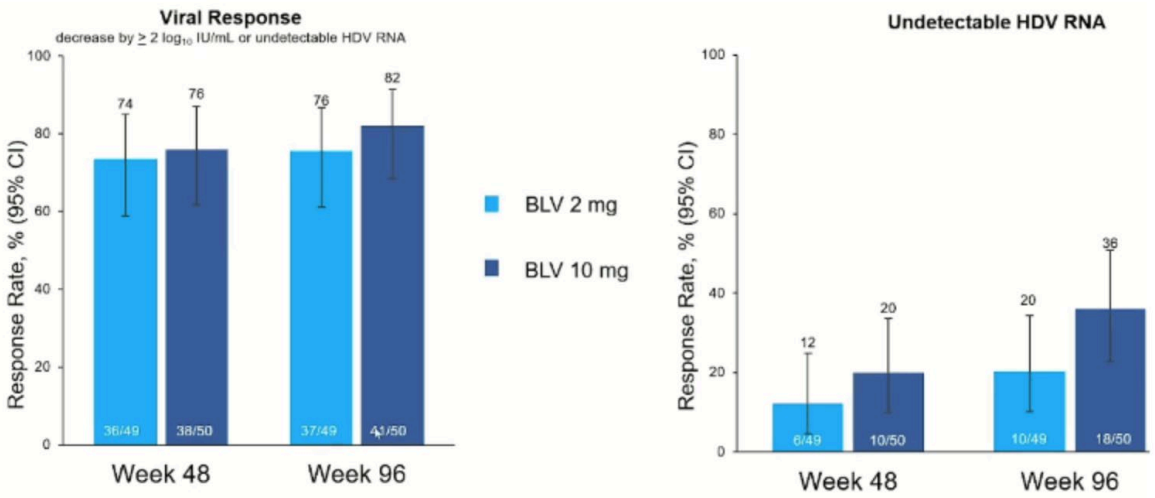
*p<0.0001 vs Delayed treatment arm. Combined response defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from BL and ALT Normalization; Undetectable HDV RNA defined as <LLOQ (50 IU/mL) (target not detected). ALT ULN: <31 U/L for females and <41 U/L for males (Russia sites); <34 U/L for females and <49 U/L for males (all other sites). BLV, bulevirtide.

Results: ALT Normalization



- Rates of biochemical response improved over time and were similar between doses

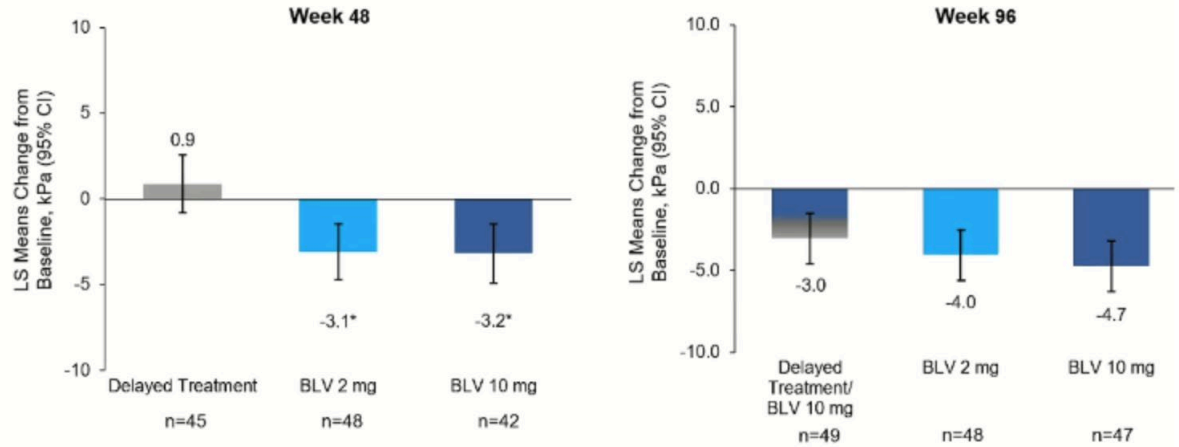
Results: Virologic Endpoints



- Rates of virological response in BLV arms increased over time

Viral response defined as HDV RNA decrease by ≥ 2 log10 IU/mL or undetectable HDV RNA; Undetectable HDV RNA defined as <LLOQ (50 IU/mL) (target not detected). BLV: bulevirtide; HDV, hepatitis delta virus.

Results: Change in Liver Stiffness at Weeks 48 and 96

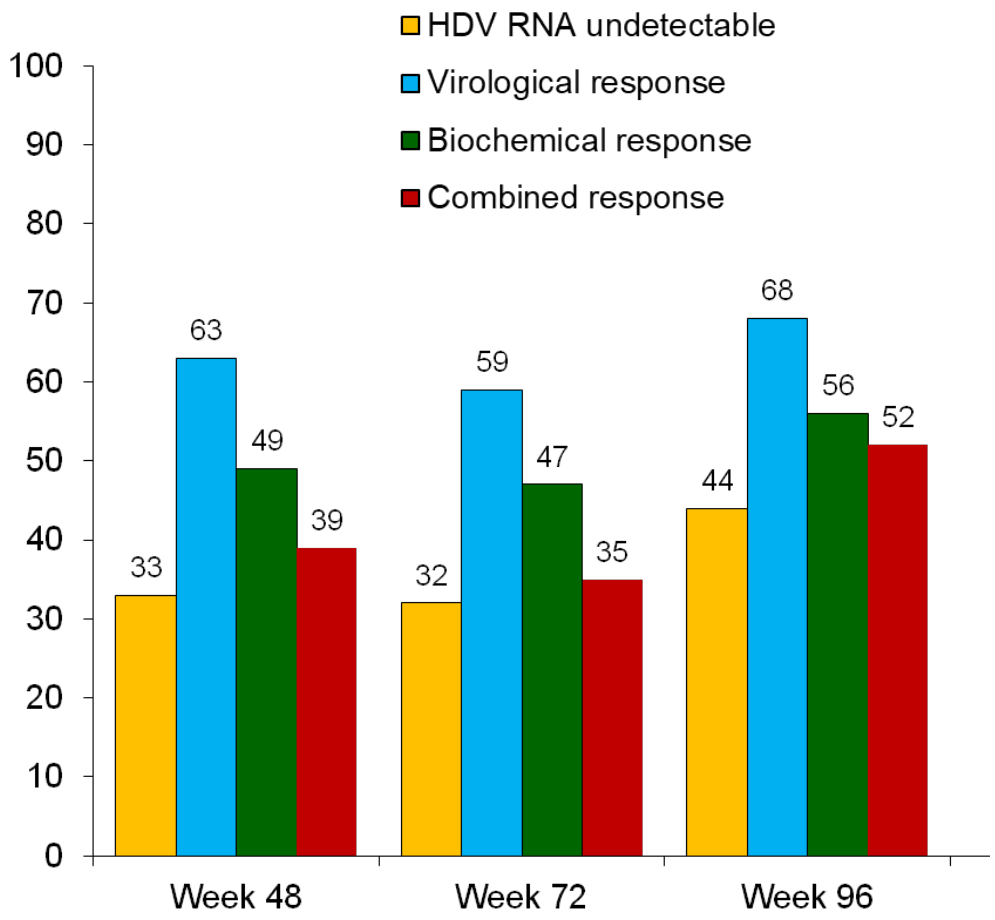


- BLV was associated with continued reductions in liver stiffness by transient elastography

*p=0.0010 vs Delayed treatment arm. BLV, bulevirtide; LS, least-squares.

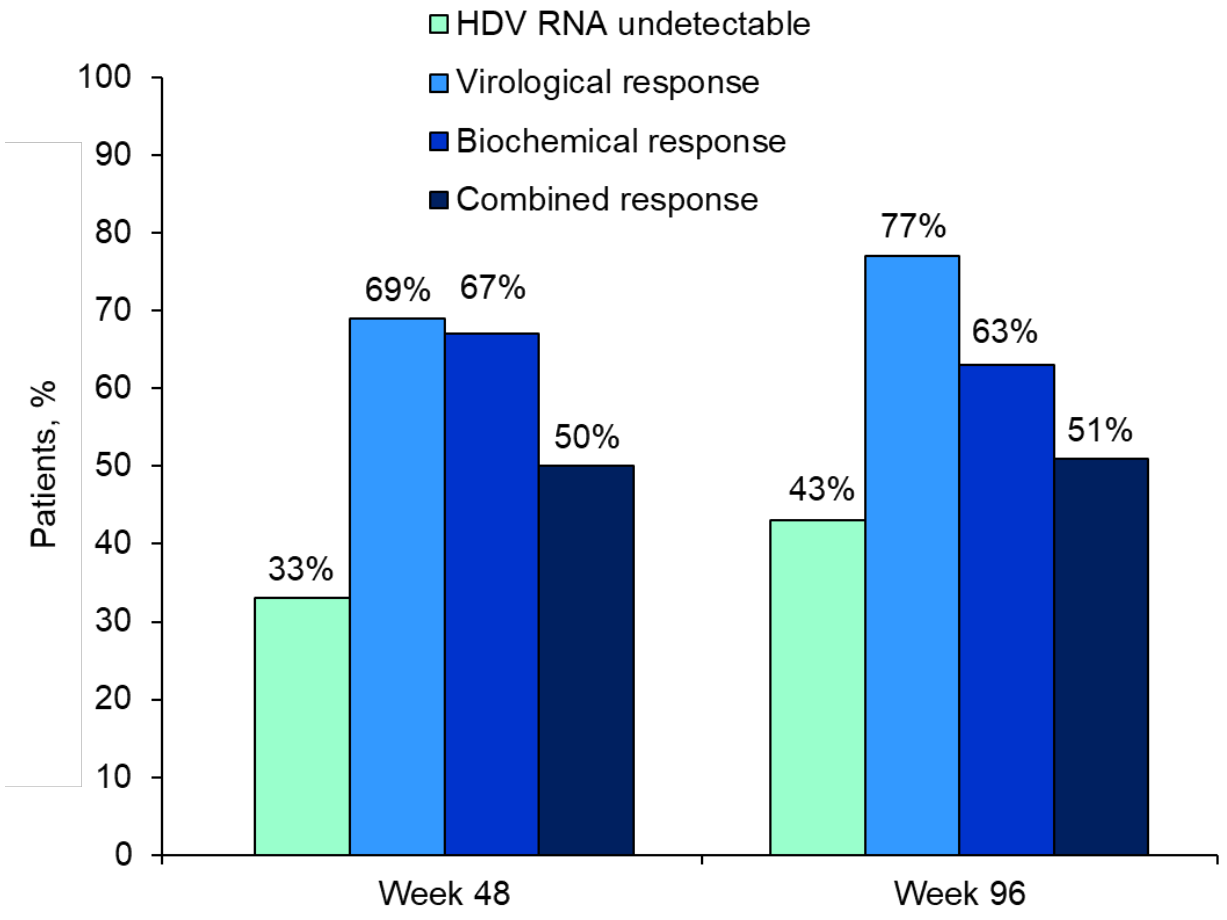
BLV 2 mg Monotherapy Beyond Week 48 in Real-life Studies

French ATU Program
n=70 patients (63% cirrhosis)



De Ledinghen V, et al, Abstract AASLD 2022 #28

SAVE-D Study; European, retrospective study
n=176 patients with cirrhosis (55% with CSPH)



Degasperi E et al, Poster EASL 2023 LBP-11

Extension of BLV 2 mg monotherapy up to 72 weeks in patients with compensated CHD-related cirrhosis (HEP4Di)

Variables	Baseline	Week 8	Week 24	Week 48	Week 72	p-value (A)*	p-value (B)*
Bilirubin, mg/dl	1.3 (0.5-1.8)	1.0 (0.4-2.9)	1.0 (0.3-2.5)	1.2 (0.5-4.6)	0.8 (0.4-1.7)	0.27	0.07
AST, U/L	92 (52-214)	52 (26-123)	38 (24-134)	39 (21-92)	32 (18-82)	**<0.001**	**<0.001**
ALT, U/L	106 (32-222)	44 (21-114)	34 (18-82)	35 (15-86)	32 (16-82)	**<0.001**	**<0.001**
GGT, U/L	52 (13-262)	43 (11-270)	30 (6-237)	23 (6-158)	21 (7-157)	**0.01**	**<0.001**
Albumin, g/dL	3.9 (2.9-4.4)	4.0 (3.1-4.8)	3.9 (3.5-4.6)	4.0 (3.6-4.7)	4.1 (3.3-4.6)	**0.03**	**0.02**
CHE, U/L	4,471 (1,807-8,378)	4,459 (2,337-8,861)	4,982 (2,854-6,849)	5,396 (2,229-8,826)	5,924 (2,068-8,971)	**0.01**	**0.02**
PLT, $10^3/mm^3$	70 (37-227)	68 (40-210)	70 (33-219)	73 (24-221)	71 (37-206)	0.73	0.71
Creatinine, mg/dL	0.8 (0.7-1.0)	0.9 (0.6-1.1)	0.9 (0.7-1.1)	0.9 (0.6-1.1)	0.9 (0.7-1.1)	0.09	0.59
AFP, µg/L	9 (3-596)	9 (3-846)	6 (3-14)	5 (2-15)	4 (2-40)	0.21	0.33
IgG, mg/dL	2,168 (1,047-4,059)	2,126 (1,009-3,208)	1,666 (980-2,286)	1,643 (901-2,200)	1,561 (444-2,055)	**<0.001**	**<0.001**
HBsAg, Log IU/mL	3.7 (2.5-4.3)	3.9 (2.6-4.3)	3.8 (2.5-4.3)	3.7 (2.4-4.2)	3.6 (2.7-4.0)	0.10	0.07
HBV DNA detectable	4 (22%)	1 (6%)	0	1 (6%)	1 (6%)	0.52	0.23

(A) Subanalysis of 30 patients with complete paired data (BSL-week 24)
(B) Subanalysis of 18 patients with complete paired data (BSL-week 72)

Anolli MP, Degasperi E et al, AASLD 2022

Off-label Bulevirtide monotherapy for chronic hepatitis D virus infection in patients with decompensated liver disease

Baseline characteristics	
Child-Pugh stage	A, n=1 B, n=14
Ascites at treatment initiation	n=10
History of variceal bleeding	n=2
Oesophageal varices present	n=13
Bilirubin (mean ± SD) - Hyperbilirubinemia (>34.2 µmol/l)	36.1 ± 24.6 µmol/l n=6
Albumin (mean ± SD) - Hypoalbuminemia (<35 g/dl)	33 ± 4.6 g/dl n=9

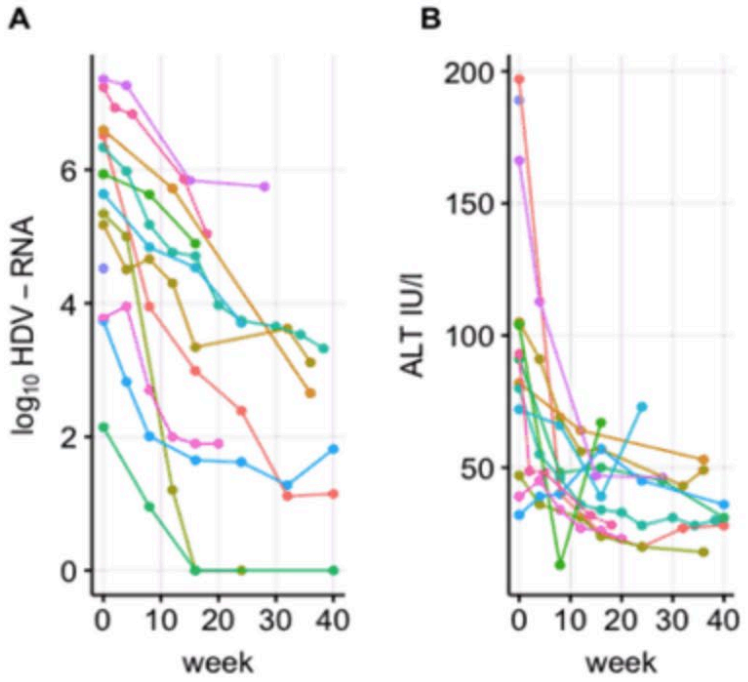


Figure 1. Decline in HDV-RNA (A) and ALT (B) in patients with decompensated liver disease under BLV treatment

Shown are individual data points from patients with complete data sets (n=13). Viral response was achieved in 10 cases.

Efficacy

- Virologic response after a mean of 23 weeks in n=10 (66%) patients
- Virologic non-response did not occur
- Decrease of ALT levels under BLV therapy, normalization in n=7 patients (47%), see figure 1
- Improvement of liver function under BLV treatment from Child-Pugh B to Child-Pugh A in n=4 cases
- Improvement of ascites in n=4 patients.

Safety

- Worsening of liver function to Child-Pugh C after add-on pegylated interferon in n=1 patient (data censored after start of interferon)
- Further decompensation after TIPS insertion and incarceration of a hernia in n=1 patient
- In both cases decompensation was not attributed to BLV therapy
- In n=3 cases BLV was terminated at liver transplantation

Fricke Dietz C et al EASL ILC 2023

Bulevirtide: DDI with Antiretrovirals

Viral hepatitis drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
HDV	Bulevirtide	↑	↑	↑	↑	↑	E	↑	↑	↔	E	↔	E	↔	↔	E	↔	↑	↔	↔	↔

- https://www.hep-druginteractions.org

Bulevirtide in PLWH

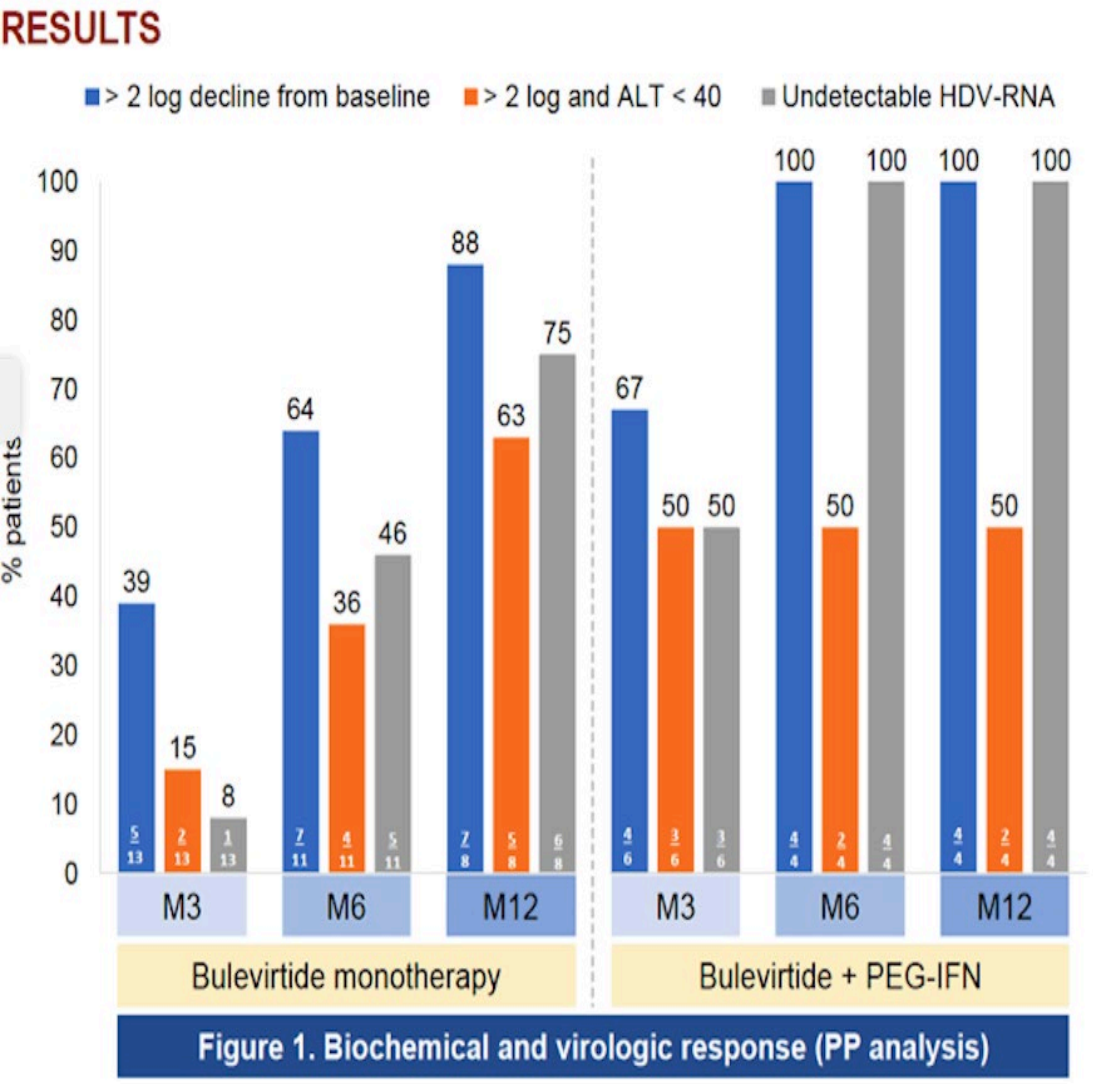
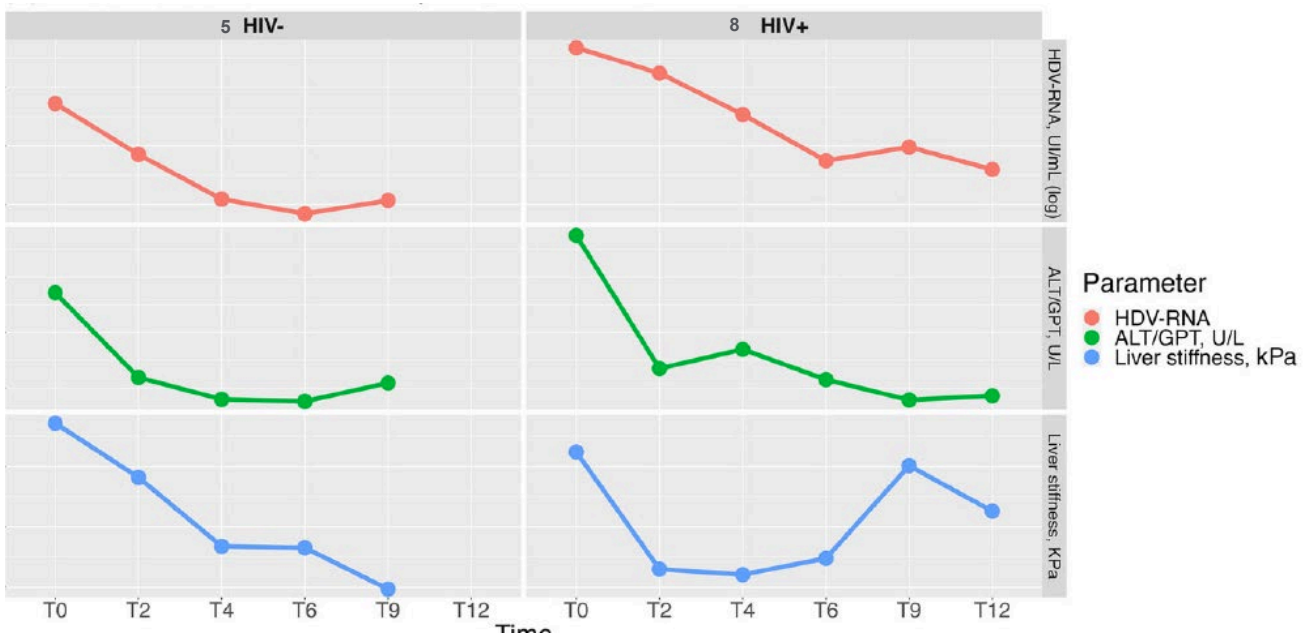


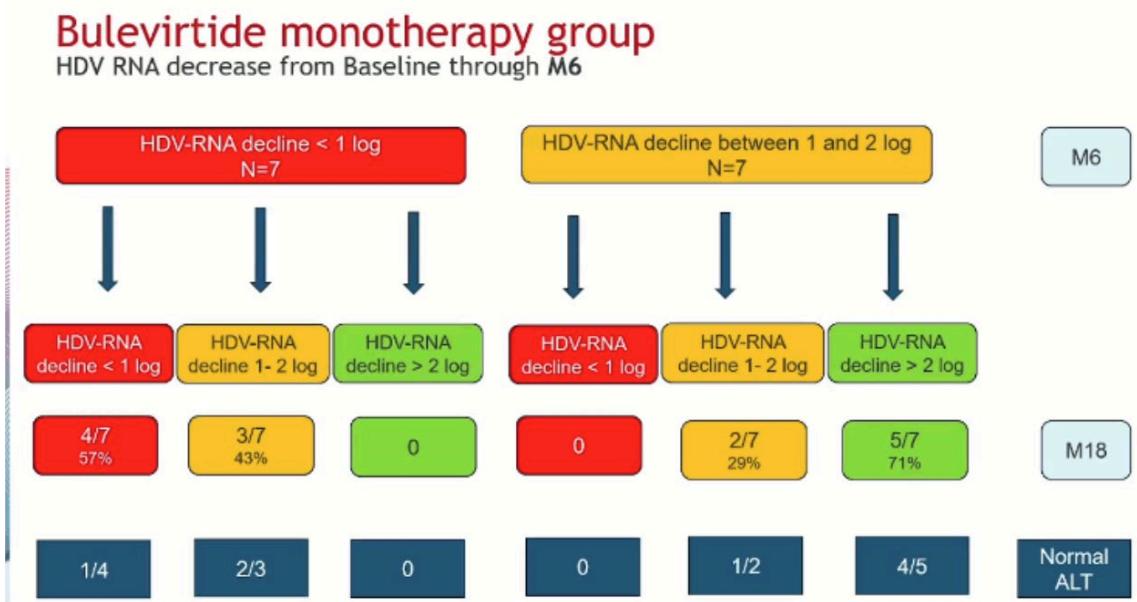
Figure 1. Biochemical and virologic response (PP analysis)

De Ledinghen et al CROI 2023



Visco- Comandini U et al HIV Med. 2023;1–8.

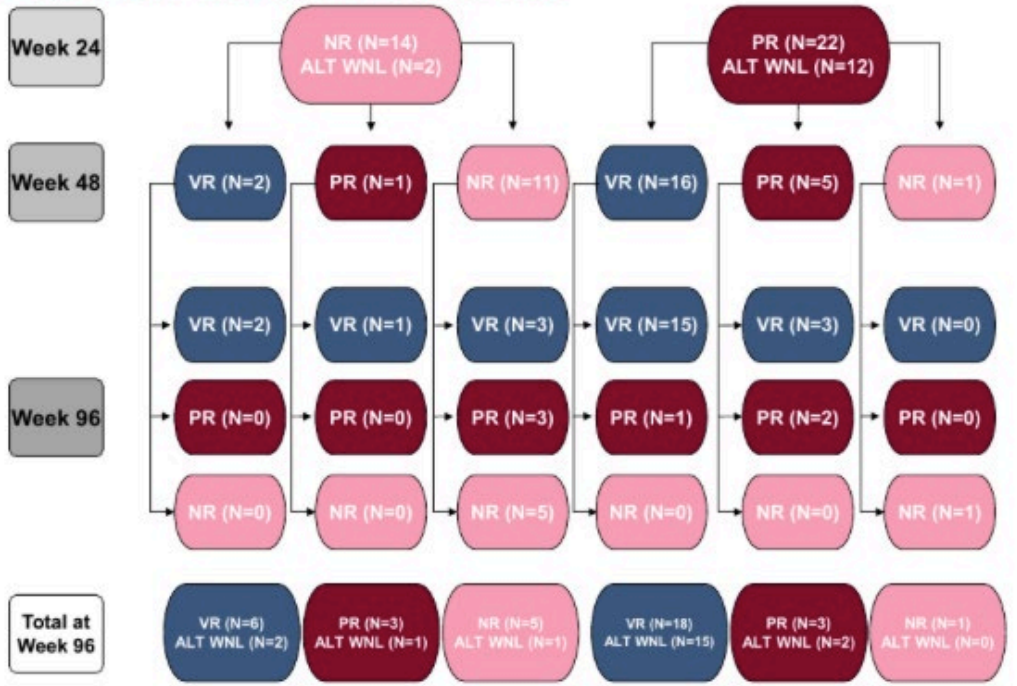
HDV-RNA decline less than 1 log after 6 months of BLV 2 mg monotherapy could define poor-response and lead to therapeutic decision. Data from real-life cohort



deLedinghen V et al EASL ILC 2023

The majority of patients of MYR-301 with early suboptimal viral response at week 24 became viral responders at week 96

Figure 2. Progression of Suboptimal Responders (NR and PR) at W24 Through W48 and W96



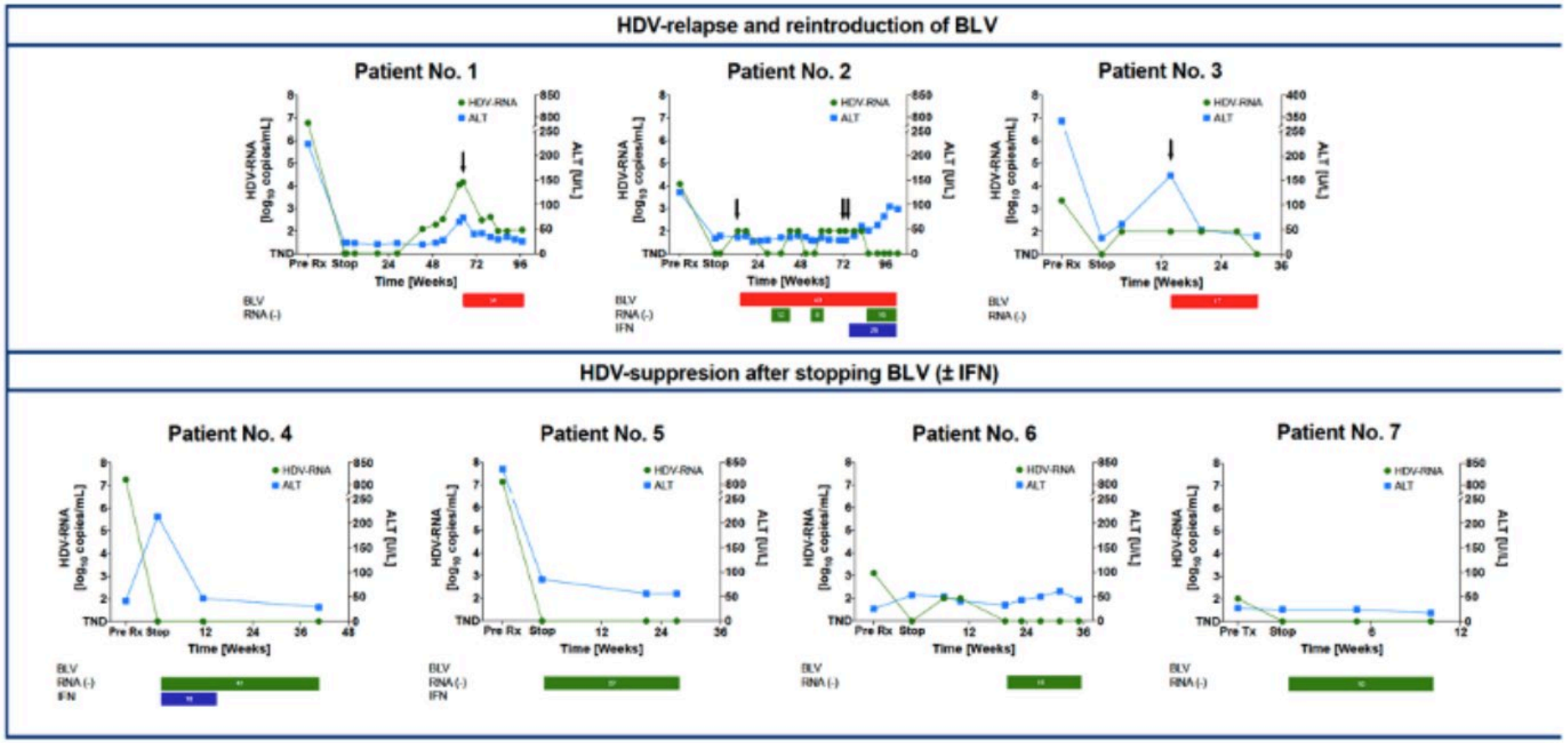
ALT, alanine aminotransferase; NR, nonresponder; PR, partial responder; VR, virologic responder; W, week; WNL, within normal limits.

- 43% (6 of 14) of NR at W24 and 82% (18 of 22) of PR at W24 progressed to VR at W96
- 35% (5 of 14) of NR at W24 and 5% (1 of 22) of PR at W24 were NR at W96
- 29% (4 of 14) of NR at W24 and 77% (17 of 22) of PR at W24 achieved ALT WNL at W96

Lampertico P et al EASL ILC 2023

Confidential - Internal Use Only

Stopping Bulevirtide After Long-Term HDV Control Appears Safe With Close Monitoring



Jachs M et al EASL ILC 202333

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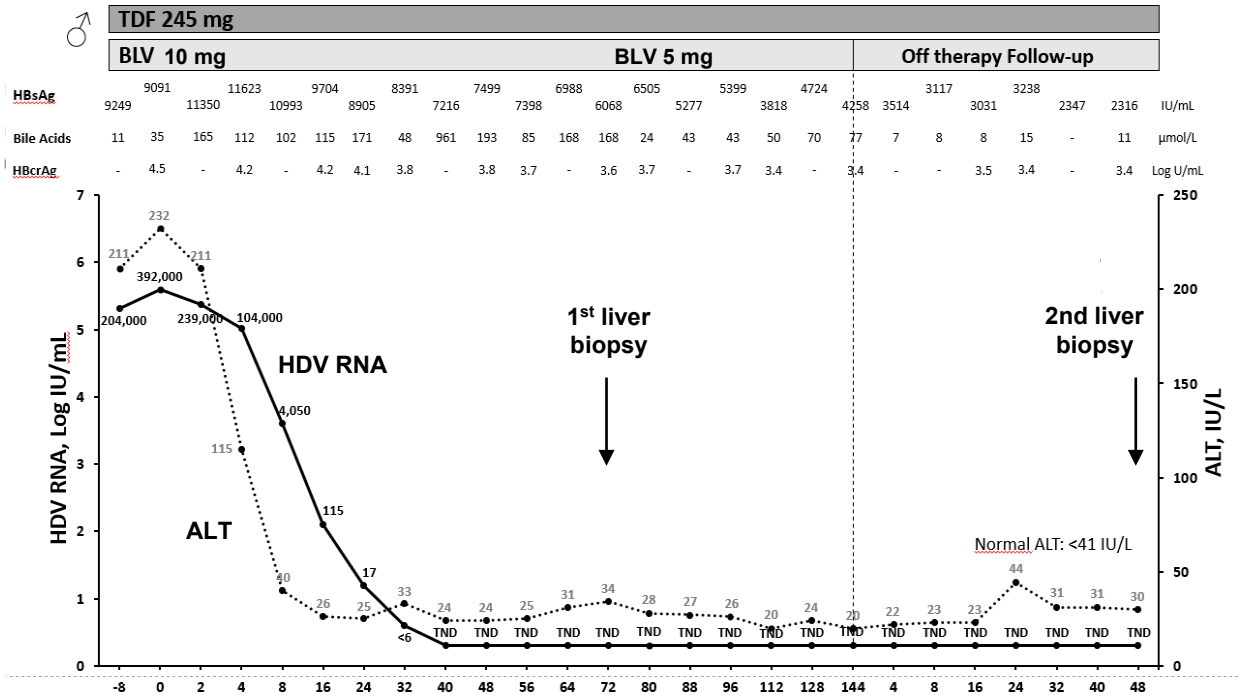
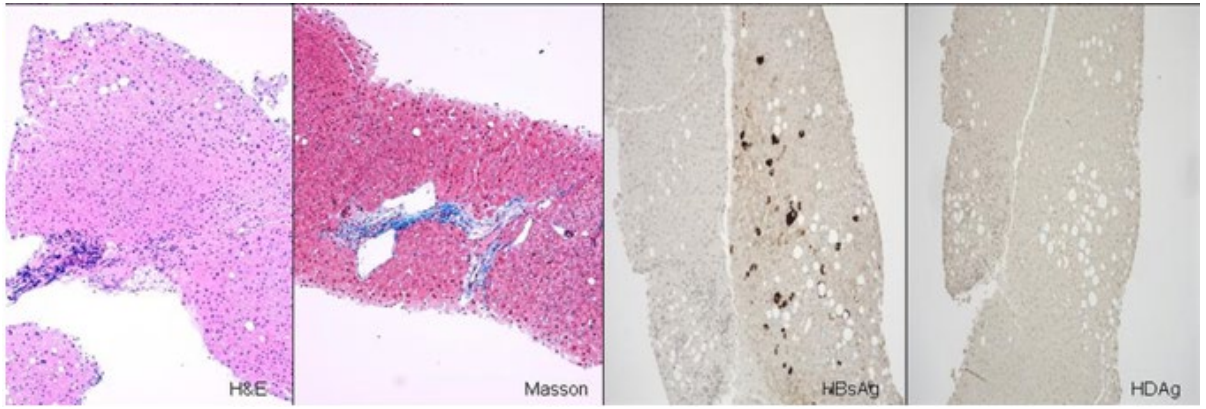
A 3-year course of BLV monotherapy may cure HDV - The "Milan patient"

A 55 year-old patient with HDV-related compensated cirrhosis with F1 esophageal varices and contraindications to pegIFNα

Virological and biochemical response during and off BLV therapy



2nd liver biopsy performed at week 48 off-therapy



H&E staining | Masson staining | HBsAg staining | HDAg staining

- Minimal features of inflammation, improvement of fibrosis (Ishak G1 S4) and resolution of autoimmunity features compared to baseline biopsy (Ishak G9 S6)
- HBsAg staining positive (<1%), HBcAg negative.
- **HDAg, HDV RNA and cccDNA undetectable (Dandri's lab)**
- **HDAg and intrahepatic HDV RNA were already undetectable** in the liver biopsy performed on-therapy at week 72 (Dandri's lab)

Clinical outcomes

- HDV suppression/cure resulted in a significant improvement in biochemistry, liver function parameters, AFP, LSM, and in regression of esophageal varices.
- No specific safety issues, BA normalized after BLV discontinuation

Conclusions

- **A 3-year course of BLV monotherapy may cure HDV infection even in difficult-to-treat patients with advanced compensated cirrhosis**
- **HDV eradication occurred without HBsAg loss**

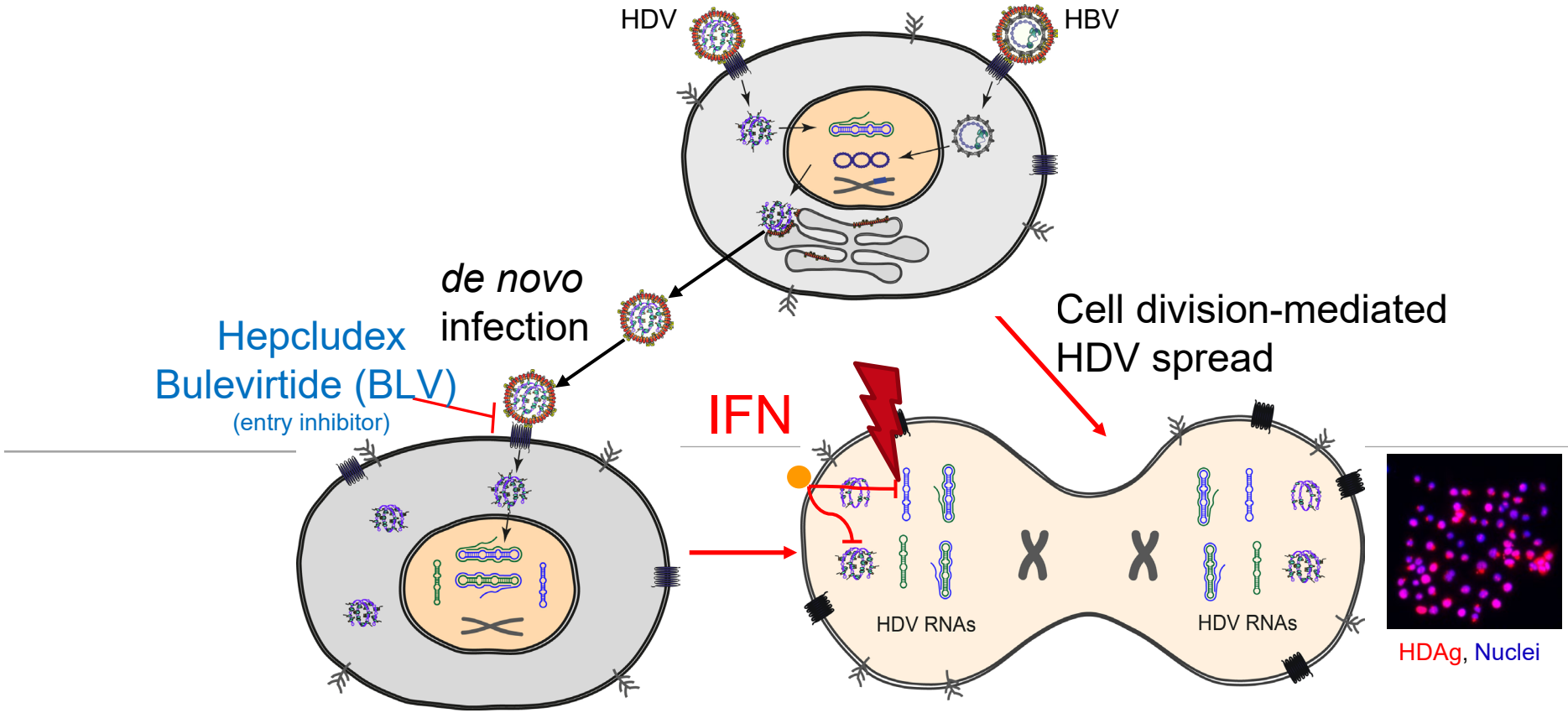
Loglio A et al, J Hepatol 2019, Loglio A et al, J Hepatol 2022

Anolli MP et al, EASL 2022 and J Hepatol 2022

HBV/HDV una nuova sfida all'orizzonte

- Virology
- Natural History
- Epidemiology
- Treatment:
  - Endpoints
  - Peg-IFN
  - Bulevirtide monotherapy
  - Bulevirtide + PEG IFN
  - New drugs

Synergism of Bulevirtide and Interferon

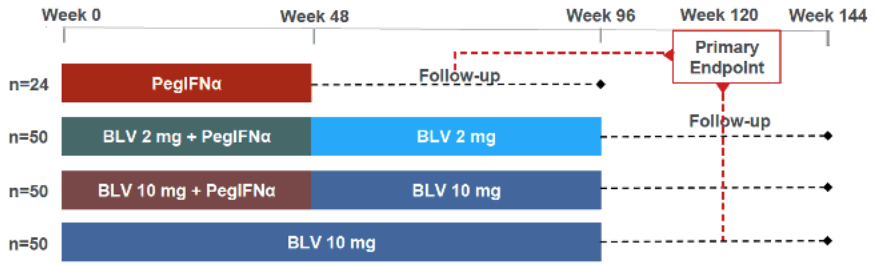


- Extracellular HDV spread (HBV envelope dependent de novo infection) **is inhibited by Bulevirtide**
- Cell division-mediated HDV spread **is inhibited by IFN**

Bogomolov et al. J Hepatol. 2016; Yurdaydin et al. Hepatology 2018; Giersch et al. Gut. 2019; Zhang et al. J Hepatol. 2022

Efficacy and Safety of Bulevirtide in Combination with Pegylated Interferon alfa-2a in Patients with Chronic Hepatitis Delta: Primary Endpoint Results from a Phase 2b Open-Label, Randomized, Multicenter Study MYR204

Study Design

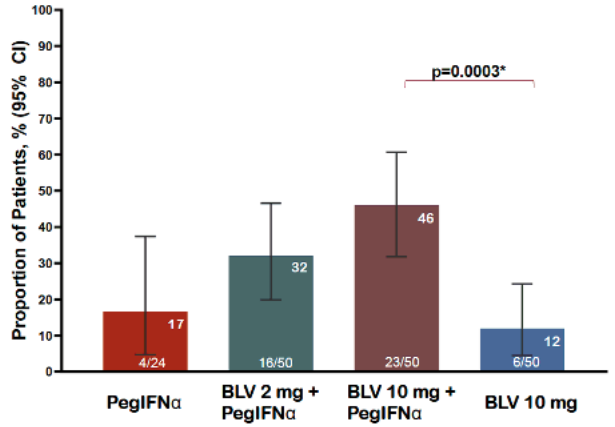


- Open-label, randomized, multicenter, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Key Inclusion Criteria

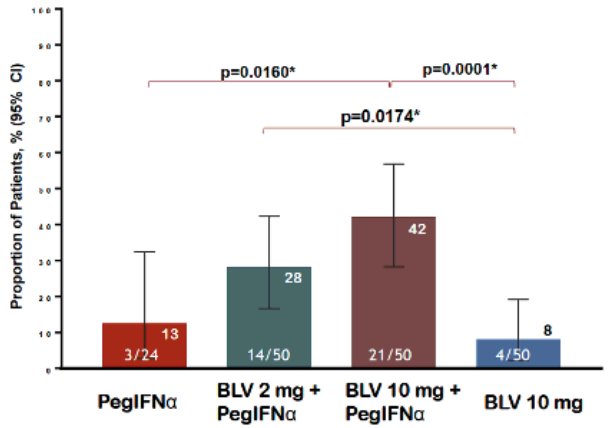
- CHD with detectable serum HDV RNA
- With or without cirrhosis; Child-Turcotte-Pugh (CTP) ≤6
- ALT >1× - <10× ULN; Platelets ≥90,000 cells/mm^3
- No IFN within 6 months before enrollment

Primary Endpoint: HDV RNA Undetectable at Week 24 after EOT



- Significantly higher rate with BLV 10 mg + PegIFNα vs. BLV 10 mg monotherapy

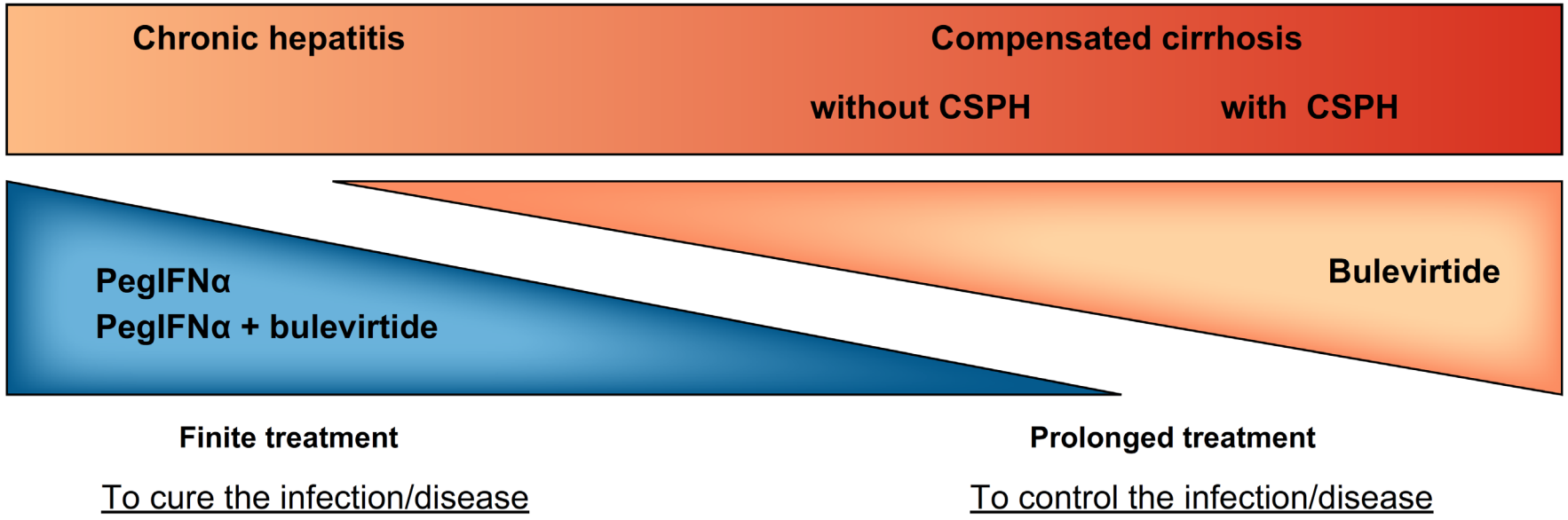
Composite Response (HDV RNA Undetectable + ALT Normalization) at Week 24 after EOT



- Significantly higher rate with BLV 10 mg + PegIFNα vs. BLV 10 mg or PegIFNα monotherapy
- Significantly higher rate with BLV 2 mg + PegIFNα vs. BLV 10 mg monotherapy

Asselah T et al AASLD The Liver Meeting 10-14 nov 2023

Treatment with Bulevirtide in HDV patients: Possible Strategies



Additional factors influencing the treatment schedule

- Phase of HBV infection (HBeAg/anti-HBe status; HBV DNA and HBsAg levels)
- IFNα contraindication, tolerability
- Patient's will and compliance to treatment

EASL CPG on HDV, J Hepatol 2023: 79:433-460

HBV/HDV una nuova sfida all'orizzonte

- Virology
- Natural History
- Epidemiology
- Treatment:
  - Endpoints
  - Peg-IFN
  - Bulevirtide monotherapy
  - Bulevirtide + PEG IFN
  - New drugs

Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of Lonafarnib-boosted with Ritonavir with or without Peginterferon Alfa in patients with chronic hepatitis delta

D-LIVR Phase 3 Clinical trial

Objective

To evaluate the safety, tolerability, and efficacy of LNF boosted with RTV with or without pegIFN Alfa for treatment of chronic HDV infection compared to placebo

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

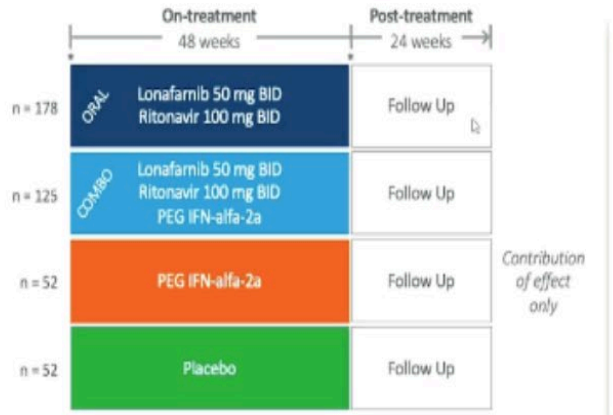
Key Inclusion criteria

CHD with compensated liver disease

HDV RNA > 500 IU/mL

ALT > 1.3X < 10X ULN

HBV DNA < 20 IU/mL



D-LIVR: Baseline Patient Characteristics

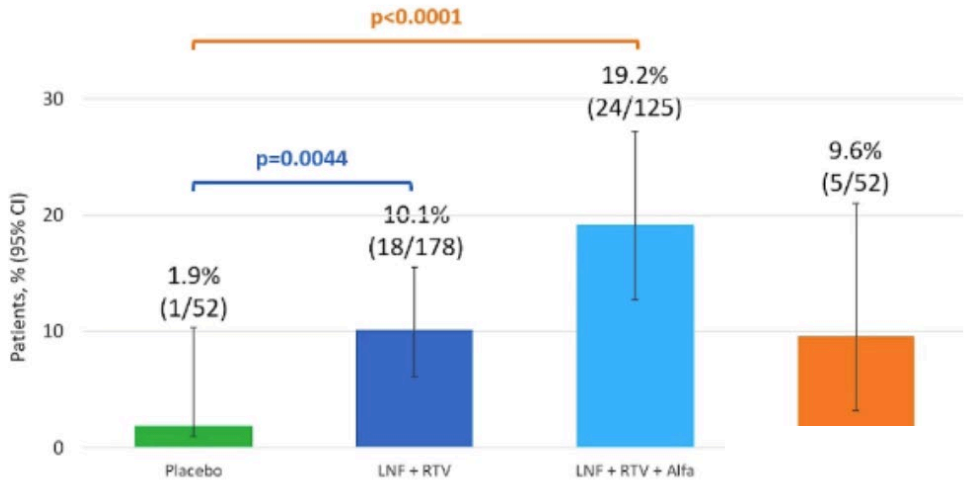
		Placebo (n=52)	LNF + RTV (n=178)	LNF + RTV + Alfa (n=125)	Alfa (n=52)	Total (N=407)
Mean age, y (SD)		45.7 (10.9)	42.9 (10.8)	41.4 (11.5)	42.3 (11.0)	42.7
Men, n (%)		39 (75)	126 (71)	84 (67)	33 (64)	282 (69)
Race, n (%)	White	42 (81)	130 (73)	85 (68)	41 (79)	298 (73)
	Asian	10 (19)	40 (23)	35 (28)	10 (19)	95 (23)
	Black	0	3 (2)	3 (2)	0	6 (2)
	Other/no reported	0	5 (3)	1 (1)	1 (2)	7 (2)
Region	Asia	6 (12)	25 (14)	21 (17)	7 (14)	59 (15)
	Europe	43 (83)	127 (71)	92 (74)	41 (79)	303 (74)
	North America	1 (2)	14 (8)	9 (7)	2 (4)	26 (6)
	Other	2 (4)	12 (7)	3 (2)	2 (4)	19 (5)
Mean ALT, U/L (SD)		122 (83)	100 (69)	99 (73)	82 (47)	100 (70)
Mean HDV RNA, log IU/mL (SD)		4.97 (1.12)	4.94 (1.13)	5.14 (1.17)	4.88 (1.19)	5.00 (1.15)
HDV genotype, n (%)	1	47 (90)	174 (98)	118 (94)	52 (100)	391 (96)
	4 / 5 / 8 / not reported	1 (2) / 0 / 0 / 4 (8)	0 / 1 (0.6) / 0 / 3 (2)	0 / 0 / 1 (1) / 6 (5)	0 / 0 / 0 / 0	16 (4)
Median HBsAg, log IU/mL (range)		3.92 (2.18, 4.75)	3.83 (2.11, 4.75)	3.91 (1.16, 4.75)	3.92 (2.22, 4.63)	4.00 (1.16, 4.75)
Cirrhosis, n (%)		15 (29)	47 (26)	32 (26)	14 (27)	108 (27)

Etzion O et al EASL ILC 2023

Week 48 results of the phase 3 D-LIVR study, a randomized double-blind, placebo-controlled trial evaluating the safety and efficacy of Lonafarnib-boosted with Ritonavir with or without Peginterferon Alfa in patients with chronic hepatitis delta

Primary Endpoint: Composite Response at Week 48

INTENT TO TREAT (ITT) POPULATION (N=405)



EVALUABLE PAIRED LIVER BIOPSIES (N=229)

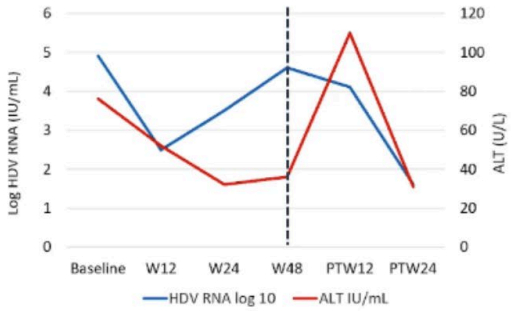
Response	% (n)			
	LNF + RTV n=107	LNF + RTV + Alfa n=66	Alfa n=26	Placebo n=30
Histologic Composite Endpoint* In Patients with Evaluable Paired Biopsies (n=229)	33% (35) (p=0.61)	53% (35) (p=0.0139)	38% (10) (p=0.46)	27% (8)

*≥ 2-point improvement in histology activity index (HAI) score + no worsening in Ishak fibrosis score

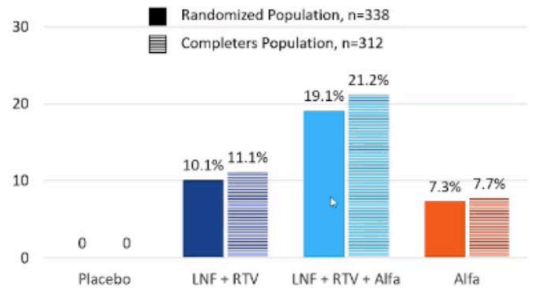
Beneficial Post-treatment Flares

- WELL-TOLERATED, WITHOUT SIGNS OF DECOMPENSATION
- TRANSIENT ALT ELEVATIONS ASSOCIATED WITH HDV RNA DECLINE

HDV RNA & ALT Kinetics

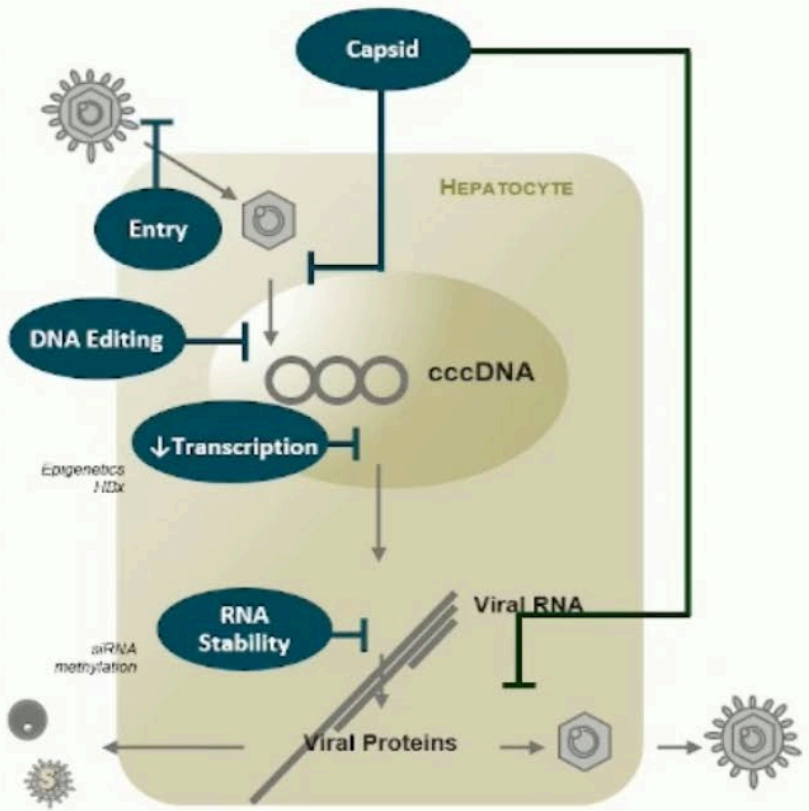


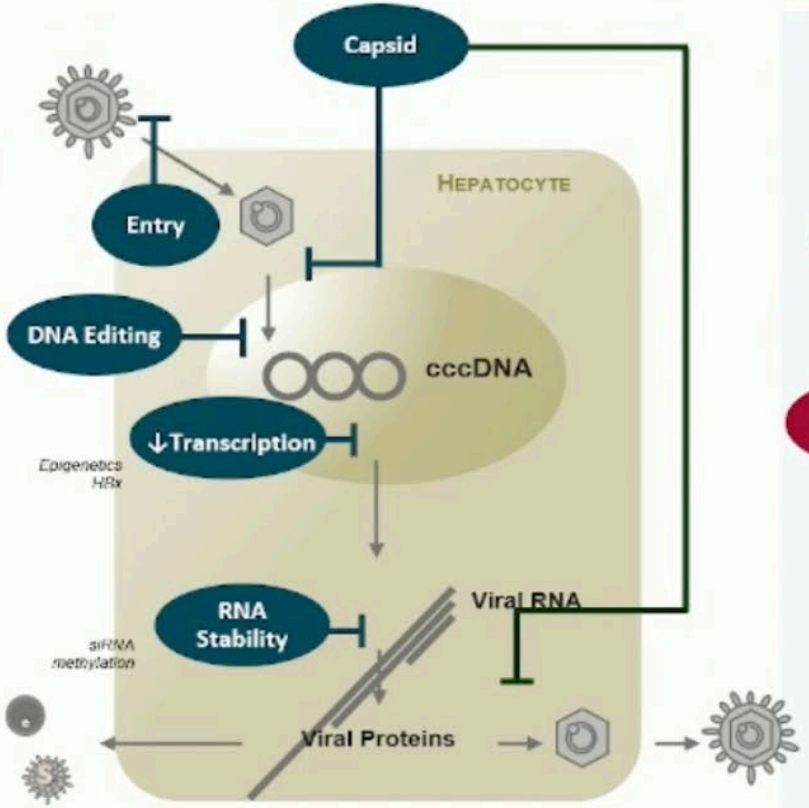
Beneficial Post-Treatment Flares

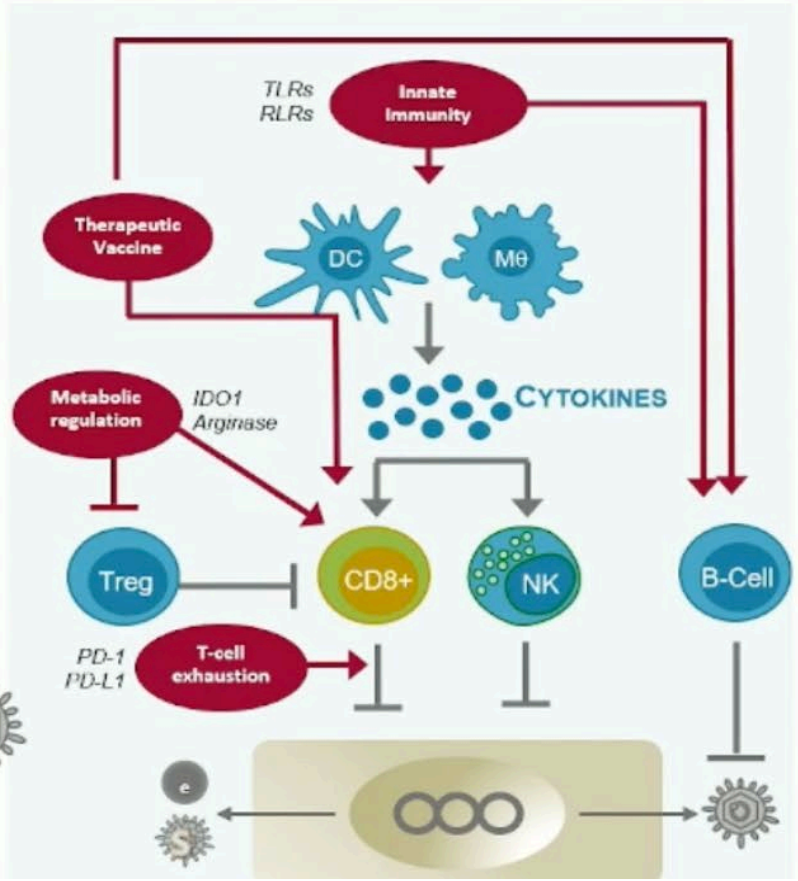


Therapeutic Approaches to HBV Cure

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







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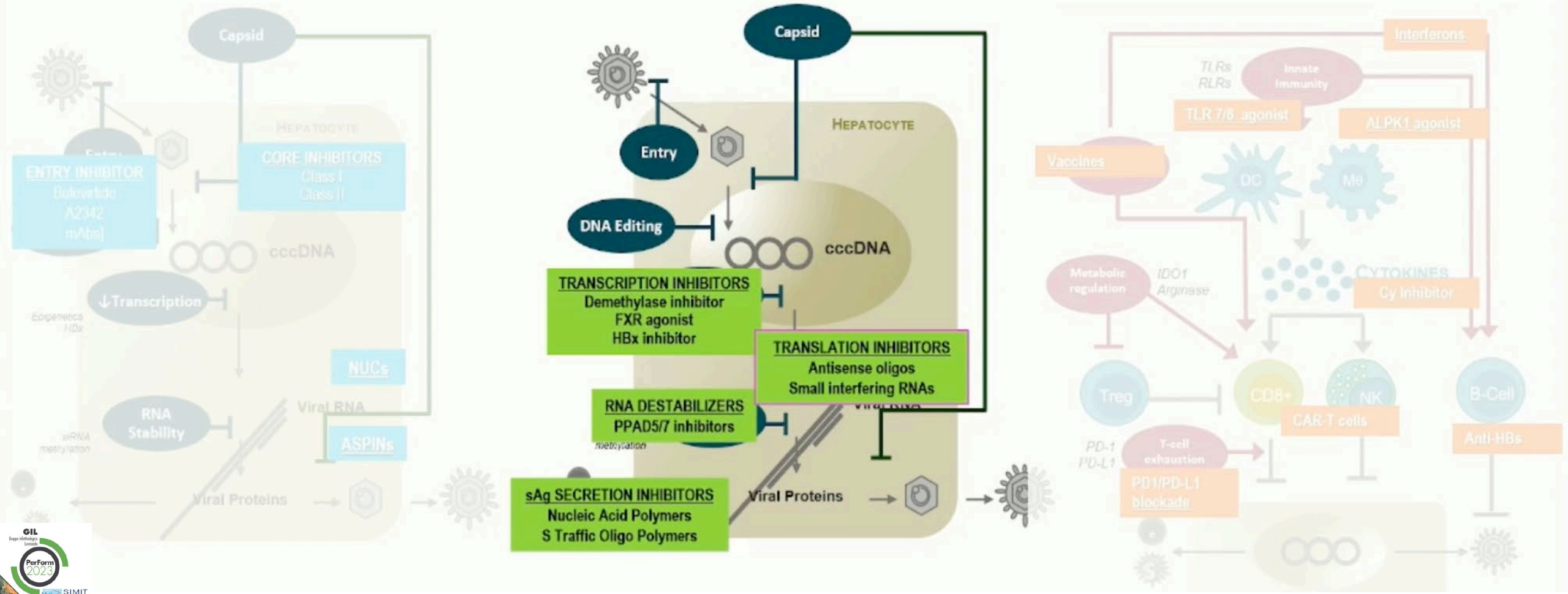
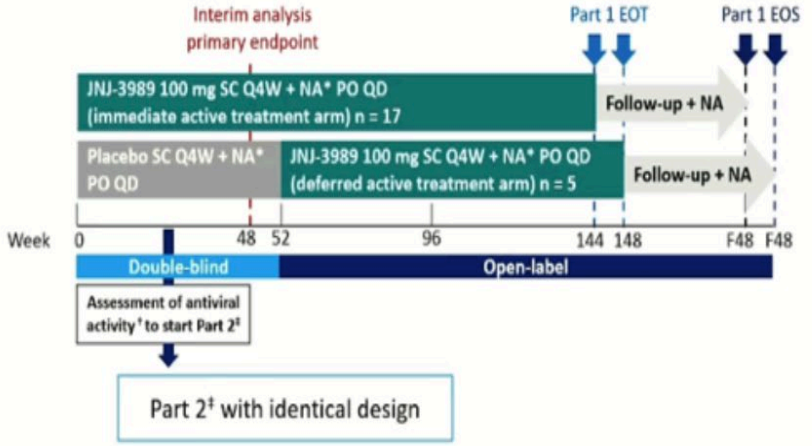


Treatment with siRNA JNJ-73763989 plus nucleos (t)ide analogue (NA) decreases HBsAg and HDV RNA levels in patients with chronic hepatitis D (CHD): part 1 of the REEF-D study

REEF-D (NCT04535544): Study Design

Phase 2, multicenter, randomized (4:1), 2-part, double-blind, placebo-controlled, parallel

- Patients aged 18 to 65 years
- Chronic hepatitis D: HDV RNA >1,000 IU/mL
- ALT >ULN and <10 × ULN
- Patients with compensated cirrhosis were eligible for Part 1 (platelets >100/nL)



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. ‡Part 2 of the study will be presented at a later date.

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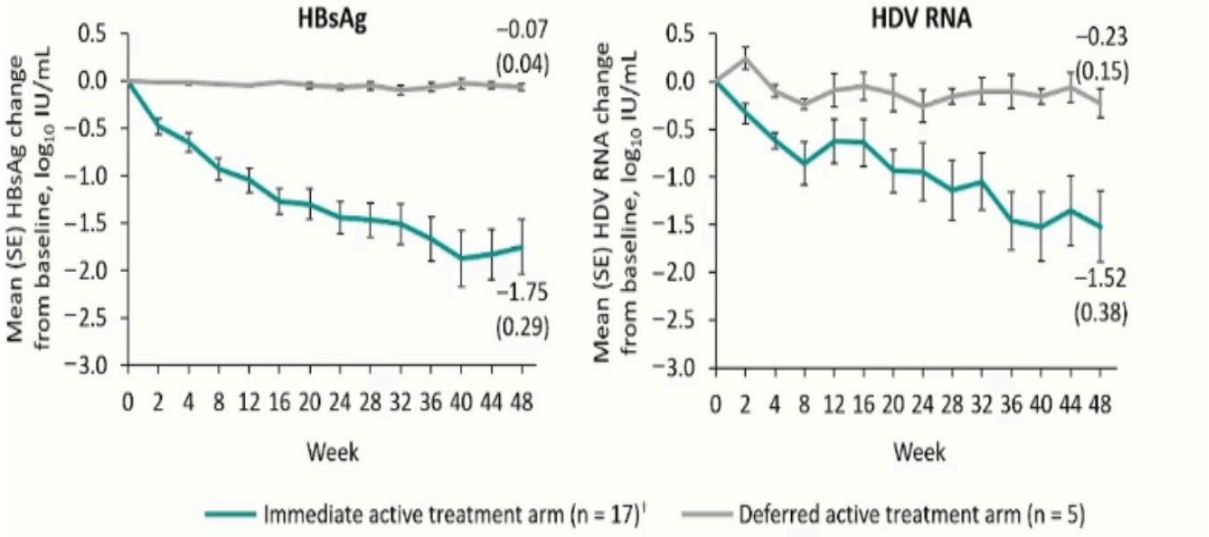
janssen Infectious Diseases & Vaccines

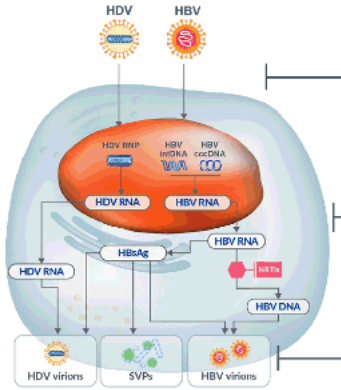
REEF-D: Change in HBsAg and HDV RNA Over Time



Wedemeyer H et al EASL ILC 2023

The monoclonal antibody VIR-3434 and siRNA VIR-2218 for the treatment of chronic Hepatitis D Virus: preliminary results from the Phase 2 SOLSTICE trial

Complementary MOA of VIR-3434 (mAb) and VIR-2218 (siRNA) in the Treatment of HDV

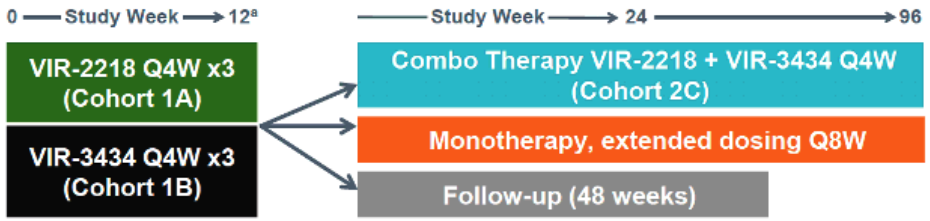


VIR-3434 — Inhibition of viral entry (neutralization)

VIR-2218 — Reduction of HBsAg production (silencing HBV RNA)

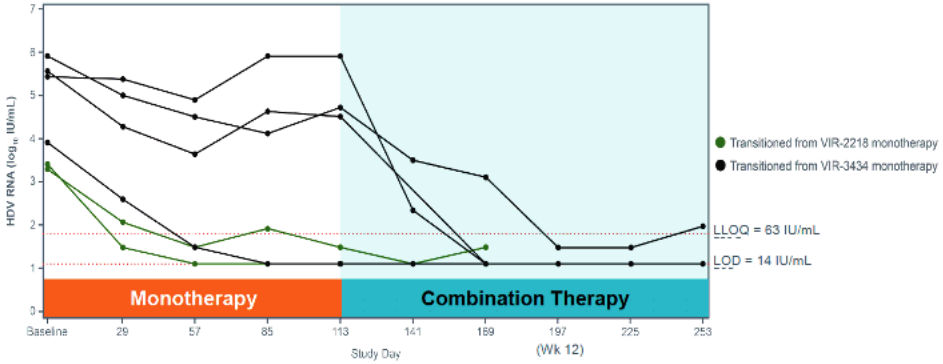
VIR-3434 — Clearance of free virions (opsonization)

SOLSTICE Trial Design – First Cohorts



- Participants achieving combined endpoint at Week 12 transition to extended dosing (Q8W) monotherapy.
- Participants not achieving ALT normalization and virologic response at Week 12 can transition to combination therapy or follow up.

Antiviral Activity of Combination VIR-2218 and VIR-3434 Therapy



Baseline is the most recent non-missing measurement before the initial study intervention.
Participants not achieving ALT normalization and virologic response at Week 12 of monotherapy can transition to combination therapy or follow-up.
From the 5 participants who have reached at least Week 16, 4 participants achieved HDV RNA < LOD at Week 16. One of six participants has not reached Week 12 in the Combination therapy.
LLOQ, lower limit of quantification; values below LLOQ but above LOD are shown as 31 IU/mL.
LOD, limit of detection; values below LOD are reported as 13 IU/mL.

ALT, alanine aminotransferase; HDV, hepatitis D virus; RNA, ribonucleic acid; Wk, week.

Week 12 Preliminary Results

	VIR-2218 Q4W (Cohort 1A) N = 5	VIR-3434 Q4W (Cohort 1B) N = 6	VIR-2218+3434 Q4W (Cohort 2C) N = 6[a]
HDV Virologic Response[b], n (%)	1 (20)	3 (50)	5 (100)
Reduction from Baseline in HDV RNA (log_{10} IU/mL), Median (IQR)	-1.39 (-1.51, -1.04)	-1.98 (-2.82, -0.94)	-4.29 (-5.47, -3.93)
HDV RNA < LLOQ[c], n (%)	1 (20)	2 (33)	5 (100)
HDV RNA < LOD[d], n (%)	1 (20)	1 (17)	4 (80)
Reduction from Baseline in HBsAg (log_{10} IU/mL), Median (IQR)	-1.35 (-1.52, -1.27)	-0.18 (-0.35, -0.09)	-3.88 (-4.03, -3.88)
ALT normalization[e], n (%)	2 (40)	2 (33)	1 (20)
ALT (U/L), Mean (SD)	118.8 (145.5)	44.0 (19.5)	42.6 (7.5)
Combined Endpoint[f], n (%)	0	1 (17%)	1 (20)

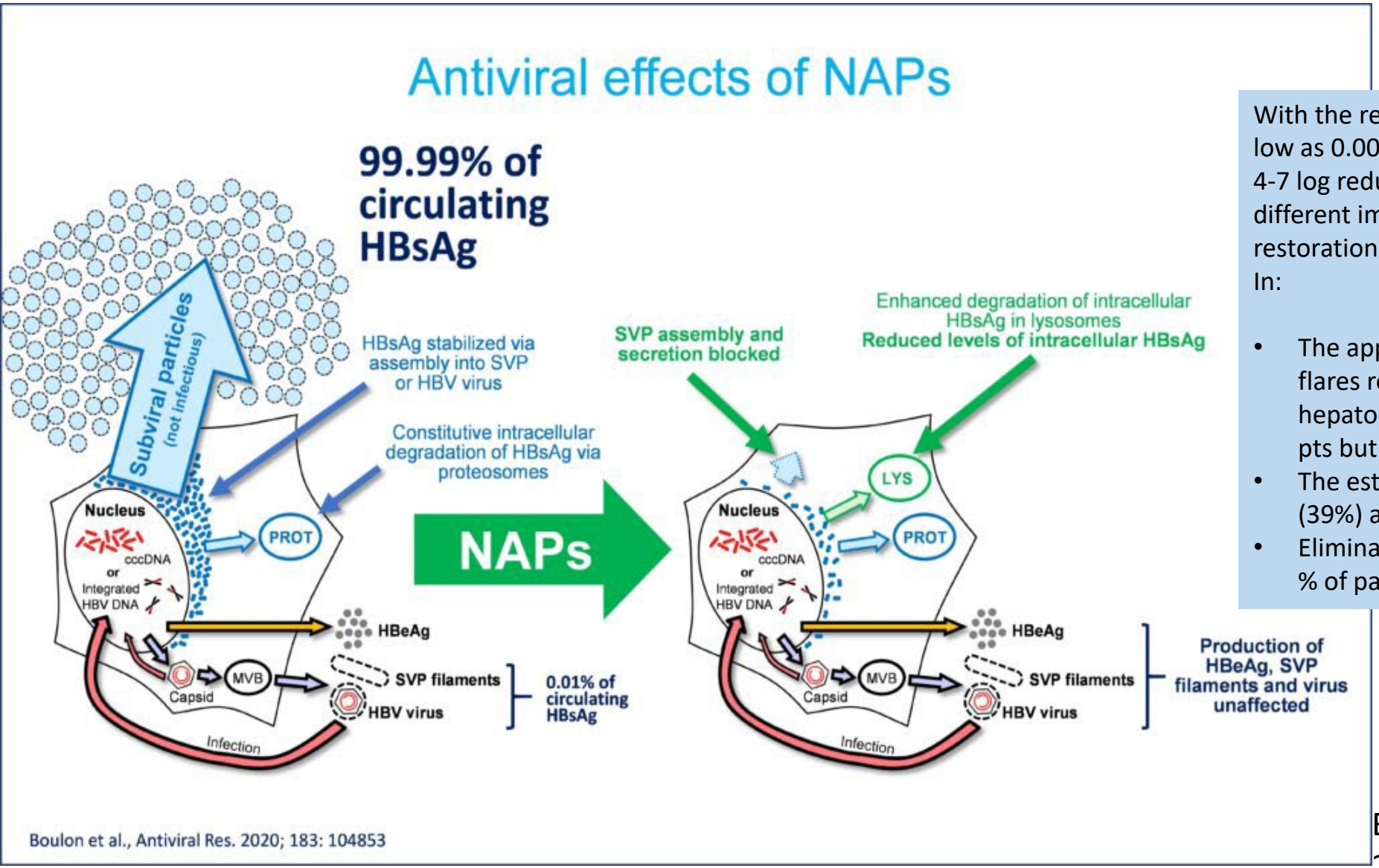
[a] Cohort 2C has 6 total participants enrolled with 5 participants reaching at least 12 weeks.
[b] Undetectable or ≥ 2 log_{10} decrease in HDV RNA.
[c] LLOQ <63 IU/mL, supplied by Robogene® 2.0 Assay was used to assess HDV RNA, supplied and analyzed by Viroclinics-DDL™.
[d] LOD <14 IU/mL, supplied by Robogene® 2.0 Assay was used to assess HDV RNA, supplied and analyzed by Viroclinics-DDL™.
[e] ALT ≤ ULN: Female = 33 U/L; Male ULN = 40 U/L.
[f] Combined Endpoint = undetectable *or* ≥ 2 log_{10} decrease in HDV RNA + ALT normalization.

ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; IQR, interquartile range; LLOQ, lower limit of quantification; LOD, limit of detection; Q4W, once every 4 weeks; RNA, ribonucleic acid; SD, standard deviation; ULN, upper limit of normal

Asselah T et al AASLD The Liver Congress Boston November 10-14 2023

Inhibitors of HBsAg release

Nucleic acid polymers (NAPs) block the release of subviral particles



With the removal of HBsAg to levels below 1 IU/mL (as low as 0.005 IU/mL) occurring in most patients (typically 4-7 log reduction from baseline), the addition of different immunotherapies is accompanied by restoration of immune control in humans which results In:

- The appearance of host mediated transaminase flares resulting from immune clearance of infected hepatocytes from the liver (greater in NAP treated pts but w/o symptoms)
- The establishment of high rates of functional cure (39%) and virologic control (39%)
- Elimination of the need for further treatment in 78 % of patients.

Bazinet M, et al Gastroenterology. 2020 Jun;158(8):2180-2194.

REP 2139 and Peg-IFN in CHD patients - A phase 2 trial

Patients: 12 naive HBV/HDV coinfected patients without cirrhosis (HBeAg negative, HBsAg > 1000 IU/ml, HDV RNA positive)

Study design:

REP 2139-Ca
500 mg qW IV 15 weeks

REP 2139-Ca
250 mg qW IV 15 weeks

Pegylated interferon α-2a
180µg qW SC 48 weeks

Efficacy:

	EOT	1 year FU	3.5 years FU
HBsAg <0.05IU/ml	4/12	5/12	4/11
HDV RNA negative	9/12	7/12	7/11

Safety:
Combined REP 2139 and Peg-IFN was safe, side effects attributed to Peg-IFN toxicity

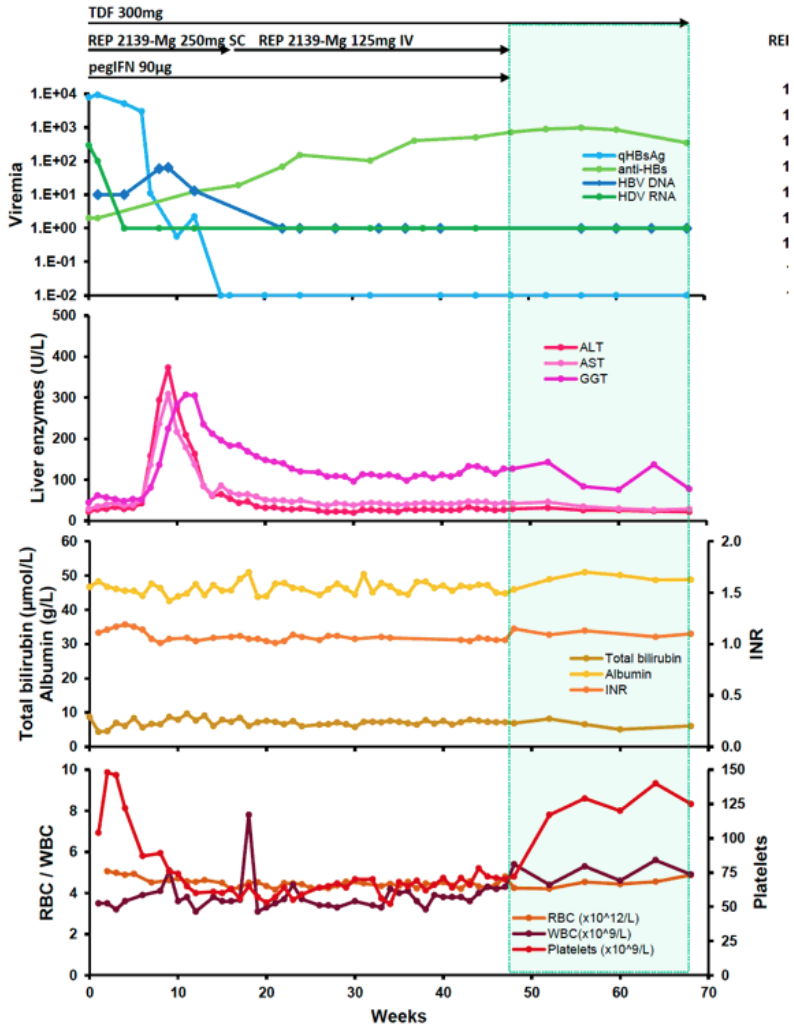
Asymptomatic grade 1-2 ALT elevations occurred in 2 participants accompanying viral rebound;

***Bazinet et al . Lancet Gastroenterol Hepatol* 2017, and Hepatology communications 2021**

Compassionate use REP-2139 in cirrhotic HBV-HDV coinfected

Patient 1: Senegalese male, 51
Chronic HBV/HDV (GT5)
Compensated cirrhosis

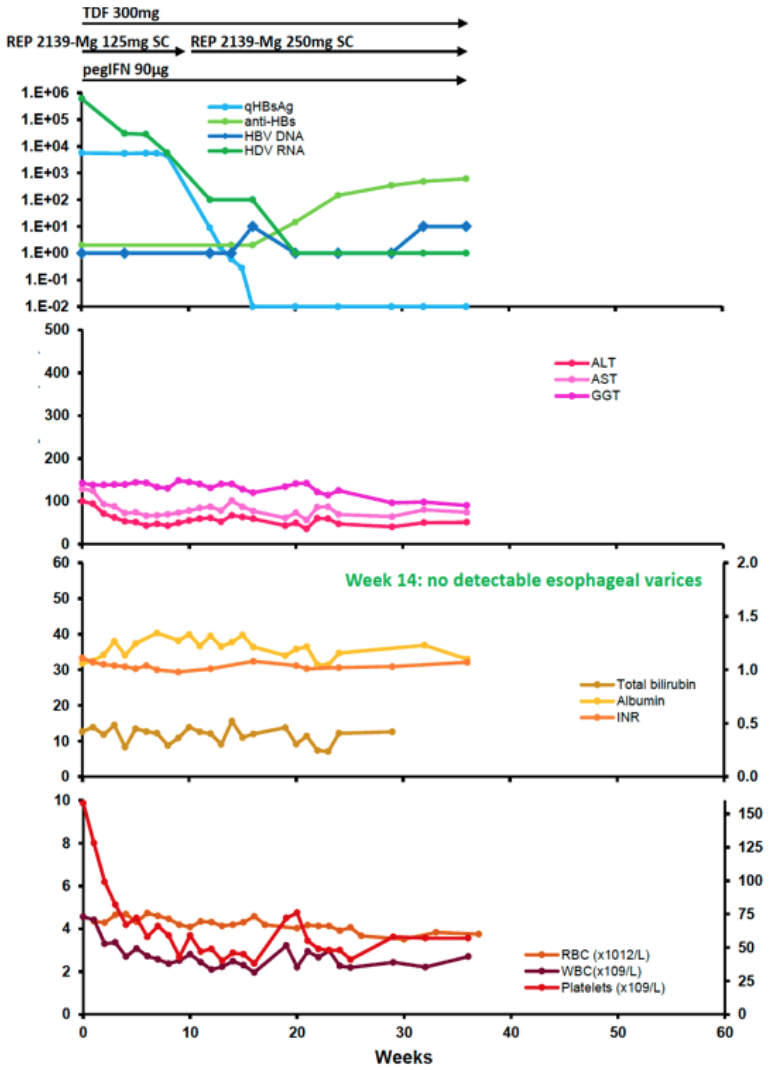
Previous treatment failure:
TDF + pegIFN
TDF + pegIFN + 2mg BLV



Sustained HBsAg loss, seroconversion, with undetectable HDV RNA and normal ALT for 20 weeks in the absence of REP 2139-Mg and pegIFN

Patient 2: Caucasian male, 47
Chronic HBV/HDV (GT1)
Compensated cirrhosis
Child A5, stage 1 esophageal varices

Previous treatment failure:
TDF + pegIFN
TDF + pegIFN + 2mg BLV

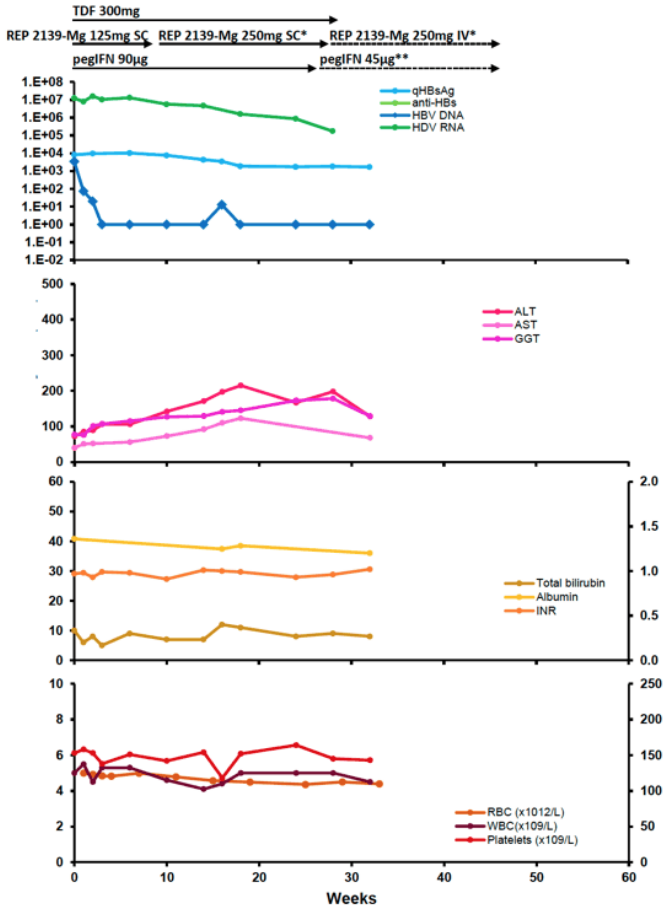


Bourliere M et al AASLD 2022

Compassionate use REP-2139 in cirrhotic HBV-HDV coinfected

Patient 3: Asian male, 54
Chronic HBV/HDV (GT1)
Compensated cirrhosis, central obesity

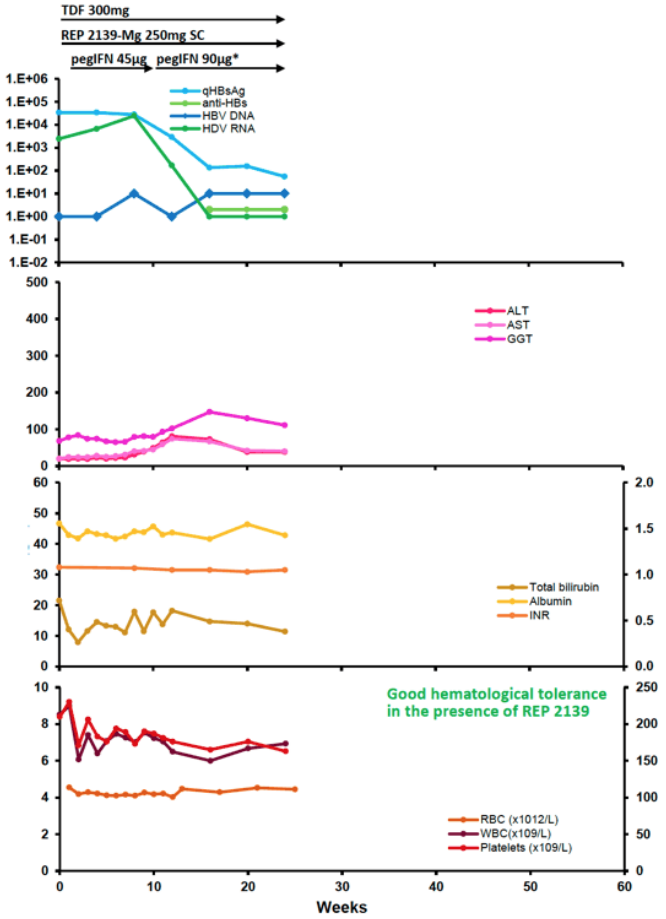
Previous treatment failure:
TDF + pegIFN
TDF + pegIFN + 2mg BLV
TDF + pegIFN + 10mg BLV



*High BMI likely compromising liver targeting via SC administration
** Transition to 45µg pegIFN due to lip lesions.

Patient 4: Caucasian female, 59
Chronic HBV/HDV (GT1)
Compensated cirrhosis

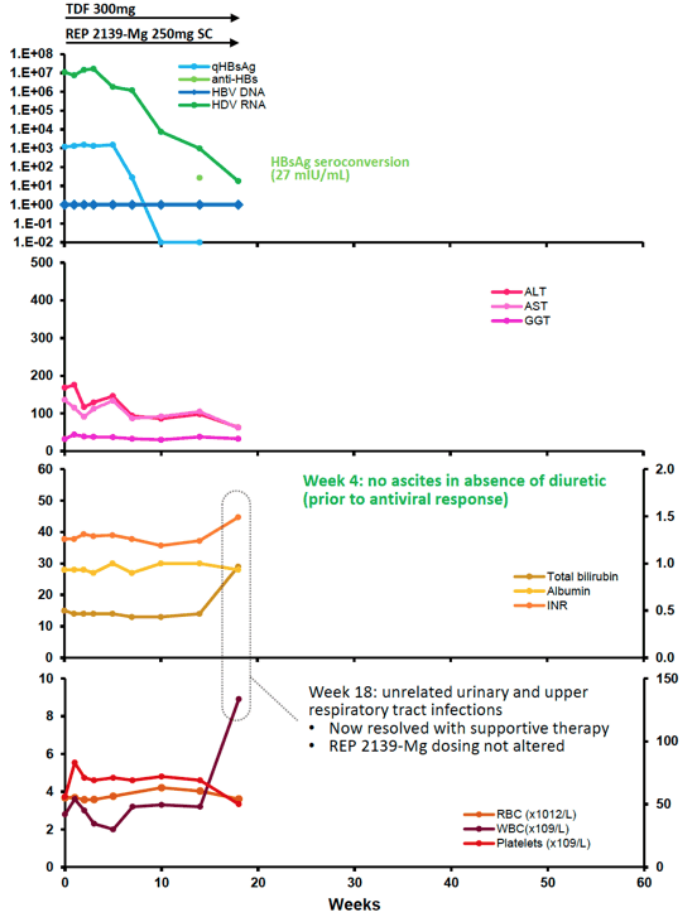
Previous treatment failure:
TDF + pegIFN (hematological intolerance)
TDF + 2mg BLV
TDF + 10mg BLV



*PegIFN tolerability significantly improved in the presence of REP 2139

Patient 5: Caucasian female, 54
Chronic HBV/HDV (GT1)
Decompensated cirrhosis with significant ascites

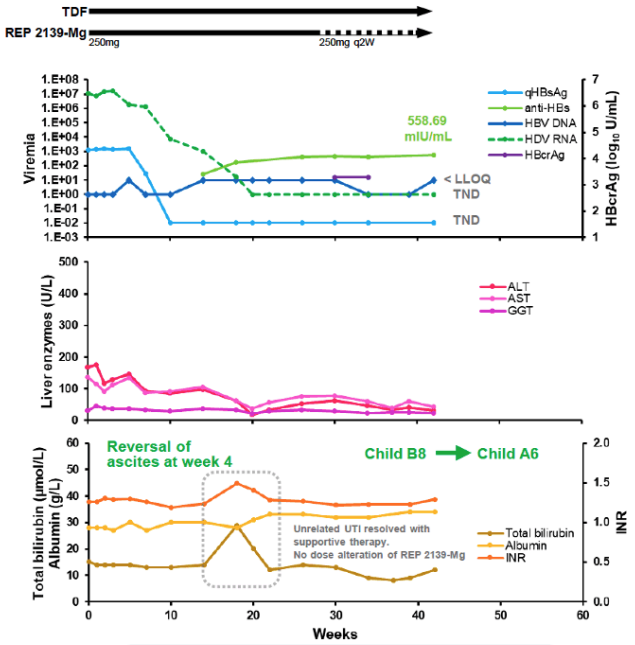
PegIFN and BLV therapy contraindicated in this patient



Fast Response to REP 2139-Mg in 3 With HDV/HBV and Decompensated Cirrhosis

Patient 1
(RCAP 5)

Caucasian female, 56, HDV GT-1
Decompensated cirrhosis Child B8 with ascites

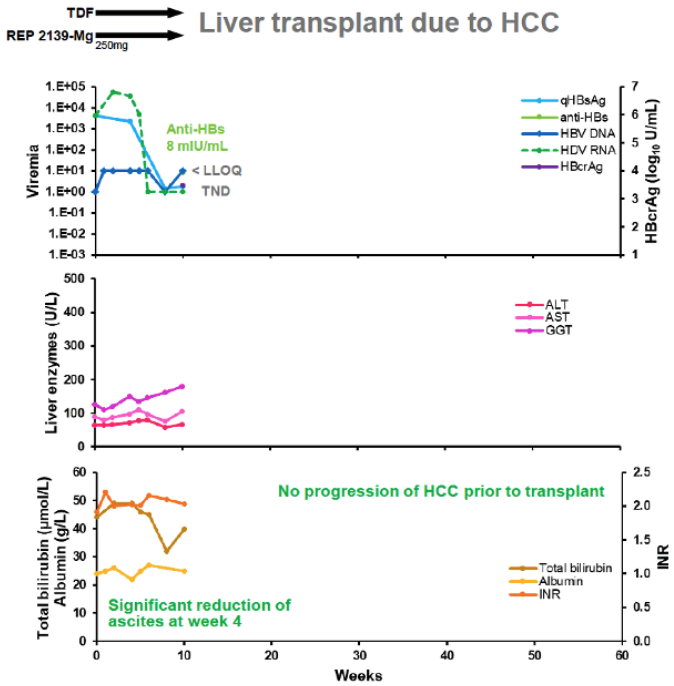


- HBsAg undetectable since W10 (> 4.37 log_{10} IU/mL decline from baseline)
- Anti-HBs seroconversion since W14
- HDV RNA undetectable since W20

- ALT normalisation at W20

Patient 2
(RCAP 8)

African female, 56, HDV GT-5
Decompensated cirrhosis Child C12 with ascites
Arterial hypertension, diabetes, HCC

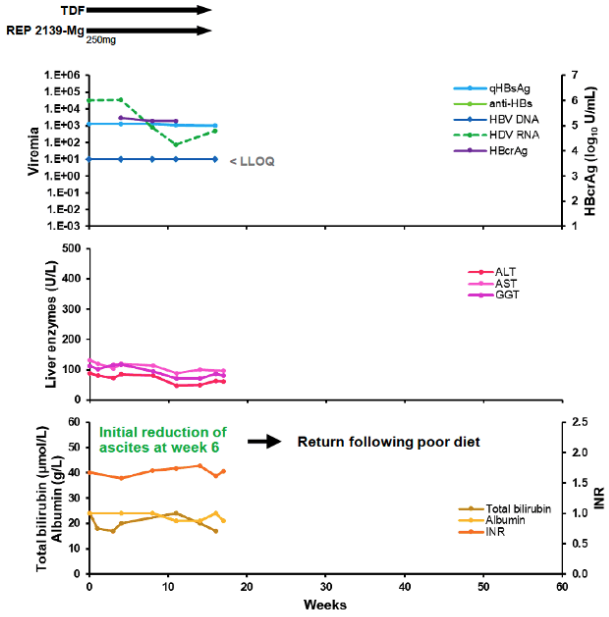


- HDV RNA undetectable at W6
- 3.4 log_{10} IU/mL HBsAg reduction at week 8

- Ascites reversal since W4
- Child-Pugh from C12 to C10 at W8

Patient 3
(RCAP 11)

African male, 47, HDV GT-5
Decompensated cirrhosis child C10 with ascites
Arterial hypertension, diabetes



HDV-RNA 2.7 log IU/mL decline at W11

- Albumin perfusion after paracentesis due to relapse of chylous ascites may be sequestering REP 2139
- Albumin is a known interactor for all phosphorothioate oligonucleotides including REP 2139

Gaus et al, Nuc Acids Res 2019
Shamur et al, Hepatology 2017

Stern C et al EASL ILC 2023

HBV/HDV una nuova sfida all'orizzonte

- HDV is the «*worst*» hepatitis agent (viroid) ;
- Replication dependent from host and HBV proteins
- Determinants of natural history still to be clarified
- 7 million HBV-HDV coinfected worldwide
- 11% HBsAg+ are HDVAb+ in Italy (younger: foreigners with less cirrhosis; older: italian native with more cirrhosis)
- Treatment
  - Peg IFN 25% response at 24 weeks from EOT but 50% relapse in the following years
  - Bulevirtide 2 mg/d monotherapy
    - the first and only EMA approved drug for HDV infection
    - 56% ALT normalization and HDVRNA suppression at 96 weeks confirmed by real world evidence in pts with advanced liver disease
    - Duration of treatment unknown and no stopping rules
    - Improvement of liver function in cirrhotics with portal hypertension
    - **HDV cure is possible with Bulevirtide monotherapy for more than 2 years**
  - Bulevirtide + PEG IFN synergy and significantly better response than PREGIFN or Bulevirtide monotherapies (42%) but at 10 mg/d
  - Lonafarnib (prenylation inhibitor) better than placebo, but not than PEGIFN
  - HBsAg synthesis and release inhibitors: good results in phase II studies, but caution with ALT flares