Hep D: HDV 2022 Update

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Disclosures

- Advisory Board Membership: Gilead
- Principal Investigator for a Drug Study: Durect Corporation, Salix Pharmaceutical

Disclosures

- I will be discussing unapproved or “off-label” uses of the following medications:
  - Pegylated interferon alpha (Peg-IFN-α)
  - Pegylated interferon lambda (Peg-IFN-λ)
  - Lonafarnib (LNF)
  - REP 2139 (NAPs)

Introduction

- Hepatitis D is a rare form of viral hepatitis first described in 1977 in HBV carriers[1]
- Estimates[2]
  - Old estimates: 15–20 million people worldwide
  - New estimates: 62–72 million people worldwide
- Incomplete RNA virus that requires the assistance of HBsAg to be infectious[3]
- Once chronicity is established, HDV is the most severe form of viral hepatitis
  - Progression to cirrhosis in 10–15% within 2 years[4], 70–80% within 5–10 years[5]

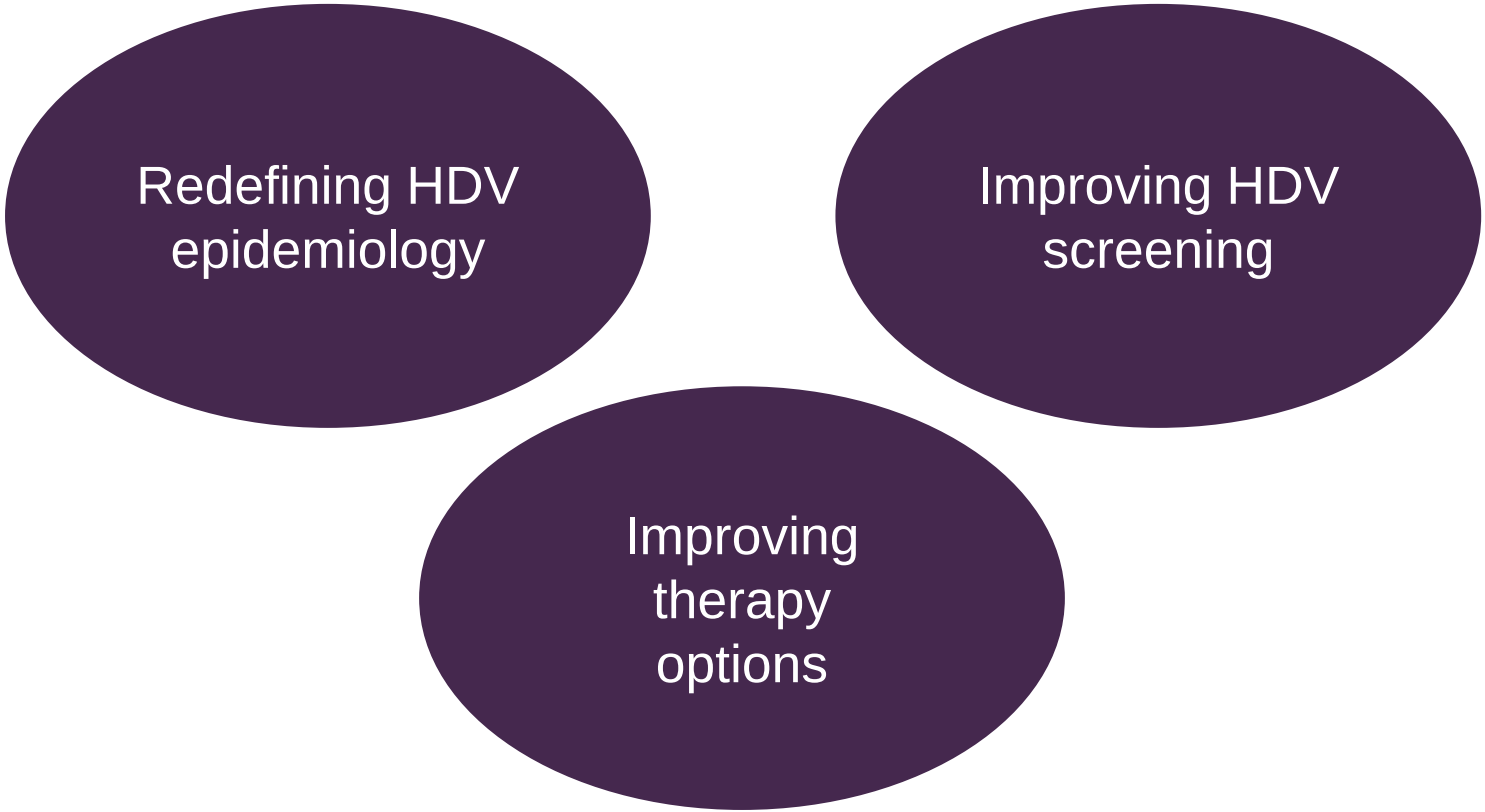
[1]Rizzetto M et al. *Gut*. 1977; [2]Chen HY et al. *Gut*. 2018; [3]Taylor JM. *Curr Top Microbiol Immunol*. 2006; [4]Rizzetto M et al. *Ann Intern Med*. 1983; [5]Yurdaydin C et al. *J Viral Hepat*. 2010.

Introduction

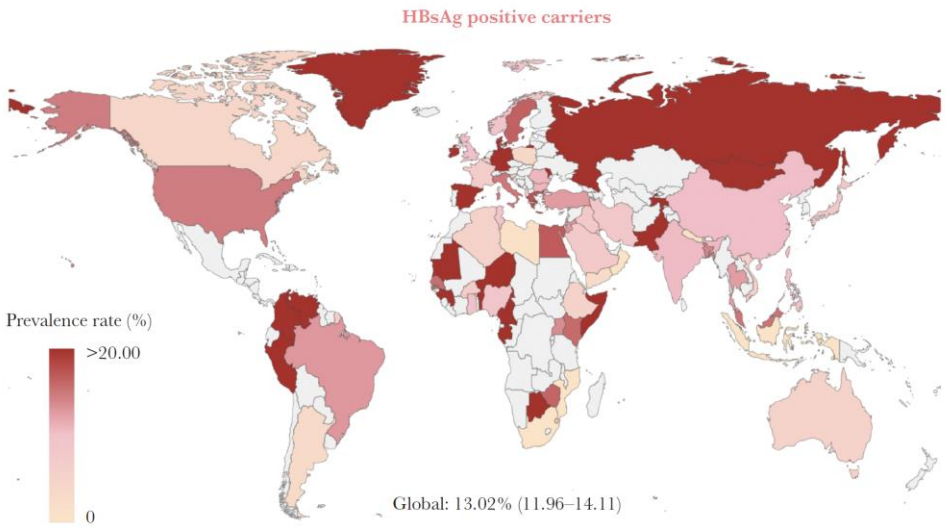
- Anti-HDV screening is recommended in high-risk HBV patients by the AASLD[1] and in all HBV patients by EASL[2]
- Despite the lack of an FDA-approved therapy, AASLD/EASL recommends the use of peg-interferon alpha (peg-IFN-α) for 12 months[1,2]
- Therapies under investigation for HDV includes:
  - Prenylation inhibitor (Lonafarnib)
  - Nucleic acid polymer (REP-2139-Ca or REP-2139-Mg)
  - Lambda interferon (Peg-IFN-λ)
  - Bulevertide (HEPCLUDEX®)
- Bulevertide was conditionally approved in the EU (July 2020)

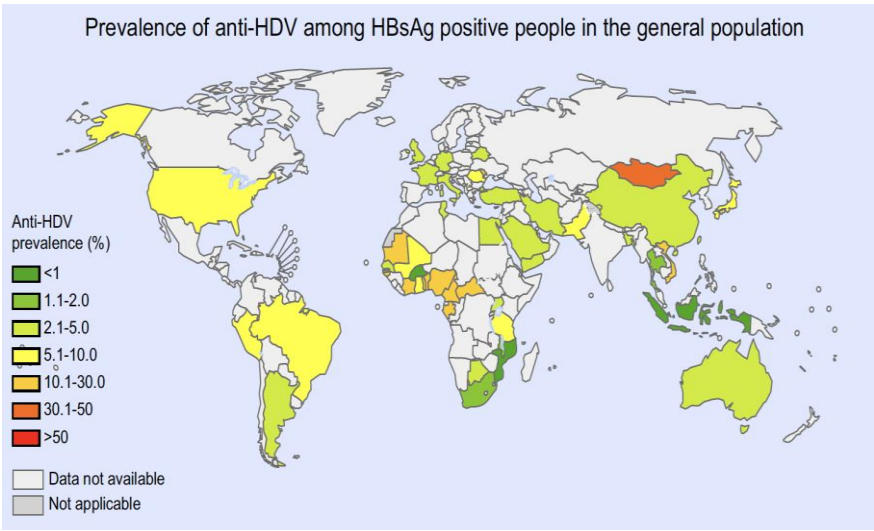
[1]Terrault NA et al. *Hepatol.* 2018; 67: 1560–1599; [2]EASL. *J Hepatol.* 2018; 67: 370: 398.

Active Areas of Research



Prevalence of HDV Remains Poorly Defined



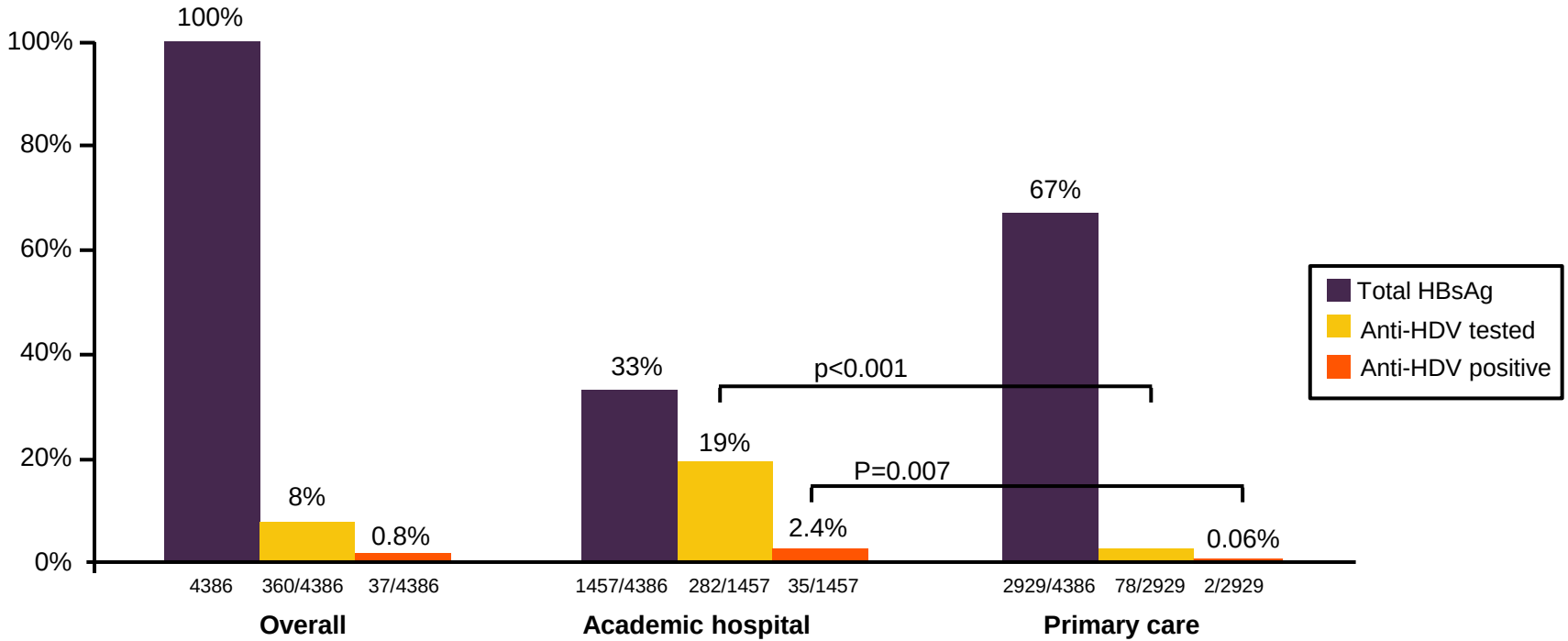


13.02% of HBsAg+
Estimate = 48-60 million HDV Ab+ cases

4.5% of HBsAg+
Estimate = 12 million HDV Ab+ cases

[1]Miao Z et al. *J of Infect Disease*. 2020; 221: 1677–1687; [2]Stockdale AJ et al. *J of Hepatol*. 2020; 73: 523–532.

Low Adherence to Guideline Recommendations for HDV Screening



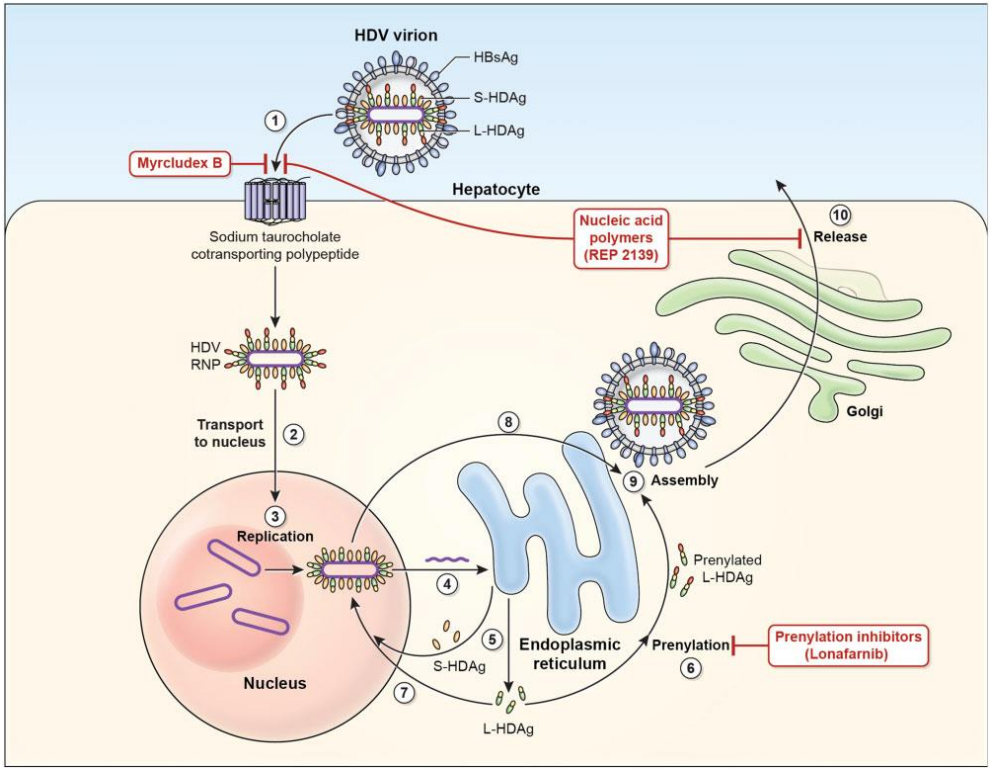
Palom A et al. *AASLD*. 2021.

HDV Hospitalizations in the United States

- Hepatitis D-associated Hospitalizations in the United States: 2010–2018*
  - 3,825 HDV associated hospitalizations identified based on ICD-9/ICD-10 codes compared to 413,355 (HBV only)
  - HDV cohort – more males (66%) + hispanics (14.5%), and more often located in the Northeast region (41%)
  - HDV cohort – higher frequencies of liver failure, portal hypertension, ascites, and thrombocytopenia

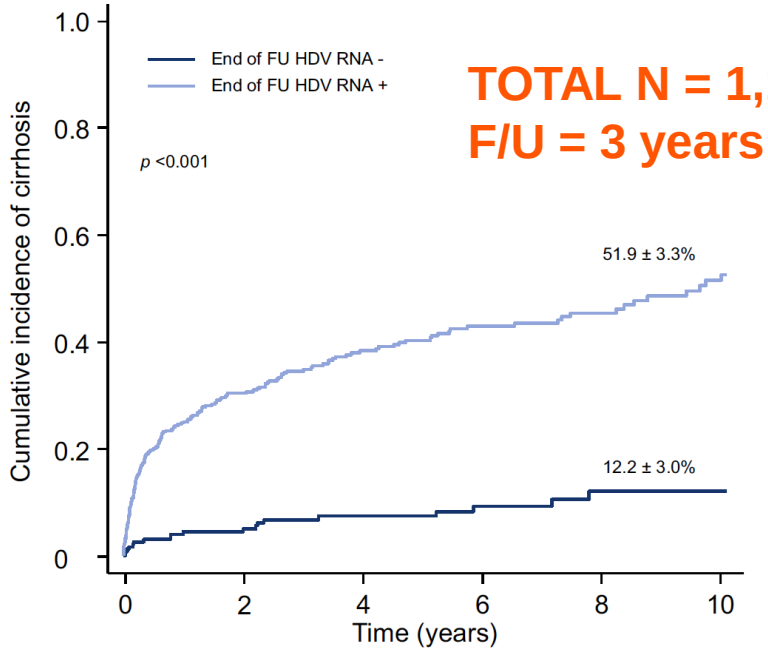
*National Inpatient Sample from the Healthcare Cost and Utilization Project
Wasuwanich P et al. *AASLD*. 2021.

New HDV Treatments

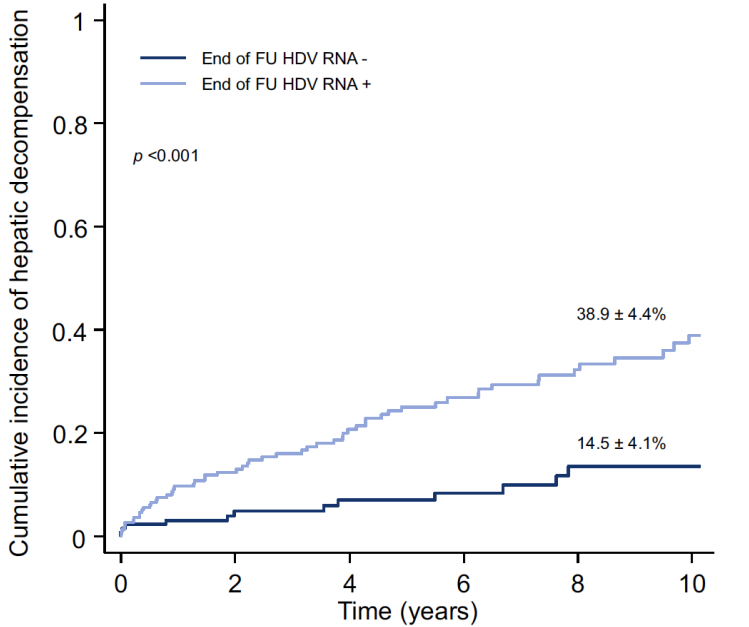


Da BL et al. *Gastroenterol Rep*. 2019; 7: 231–245.

Persistent HDV Viremia Is Associated With Long-Term Clinical Outcomes



N° at risk (events)						
HDV RNA -	242 (10)	169 (5)	126 (2)	91 (2)	50 (0)	33
HDV RNA +	506 (138)	250 (25)	163 (11)	115 (4)	74 (7)	41



N° at risk (events)						
HDV RNA -	122 (6)	101 (2)	76 (1)	61 (3)	39 (0)	31
HDV RNA +	216 (25)	136 (13)	107 (8)	79 (7)	55 (4)	36

Roulot D et al. *J of Hepatol.* 2020; 73: 1046–1062.

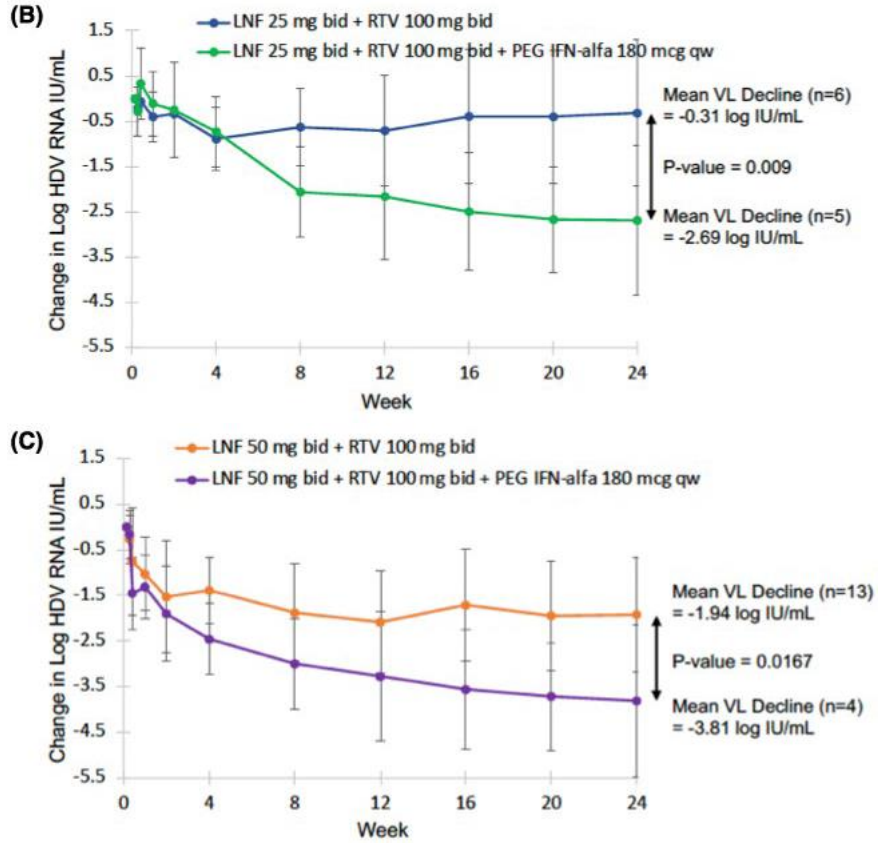
Lonafanib (LOWR-2)

Study design: Phase 2, single center, open-label, non-controlled, dose-finding of LNF + RTV +/- PEG-IFNα

- 55 patients into 3 main treatment groups
- Primary outcome: ≥ 2 log decline or < LLOQ

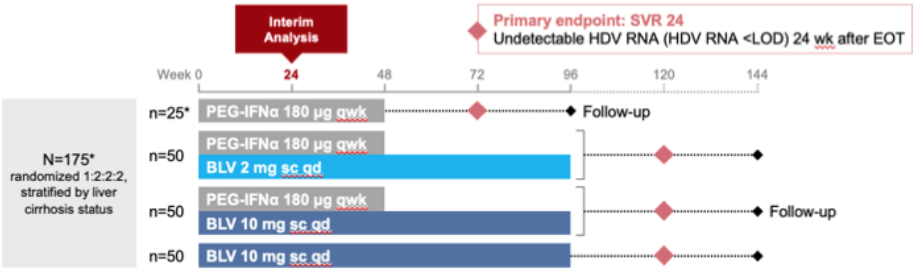
Results:

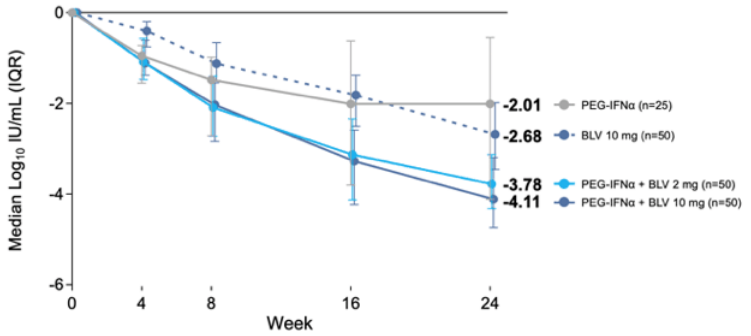
- Low-dose LNF (≤ 50 mg bid) + RTV = high dose
- LNF 50 mg bid + RTV was best, 46% reached primary outcome
- Efficacy further boosted by PEG-IFNα
- GI adverse events was common (mostly grade 1)



Yurdaydin C et al. *Hepatol.* 2021 (Online ahead of print).

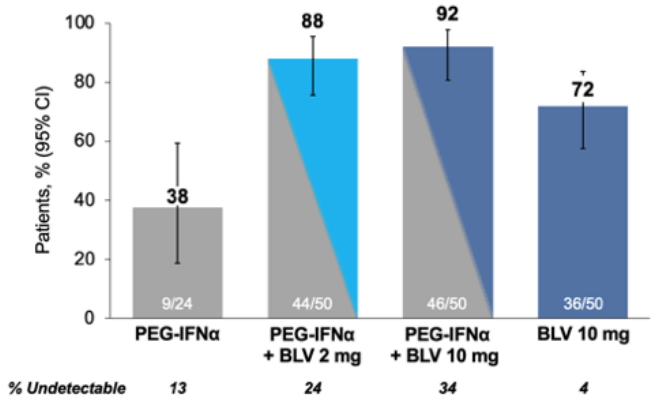
Bulevirtide – 24-Week Interim Combination Data – MYR 204





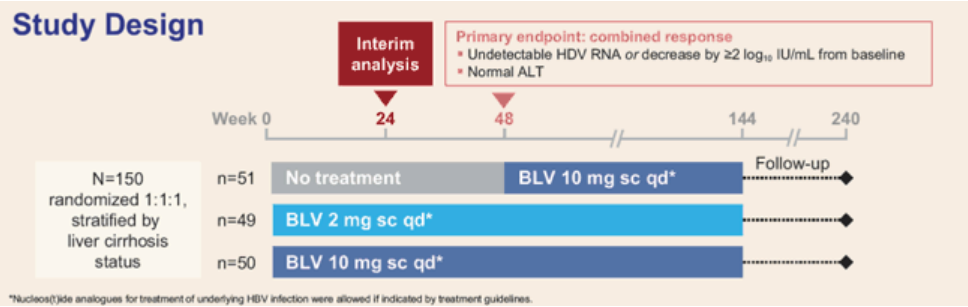
Results:

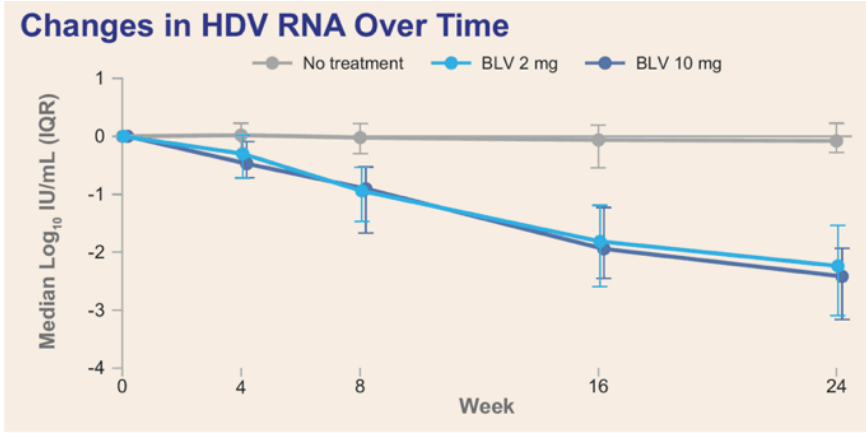
- Combination arms achieved better virologic response
- Monotherapy arm (10 mg) achieved better rates of ALT normalization and combined response
- Combined virologic/chemical endpoints may not be a great marker in patients treated with combination therapy



Asselah T et al. *EASL*. 2021.

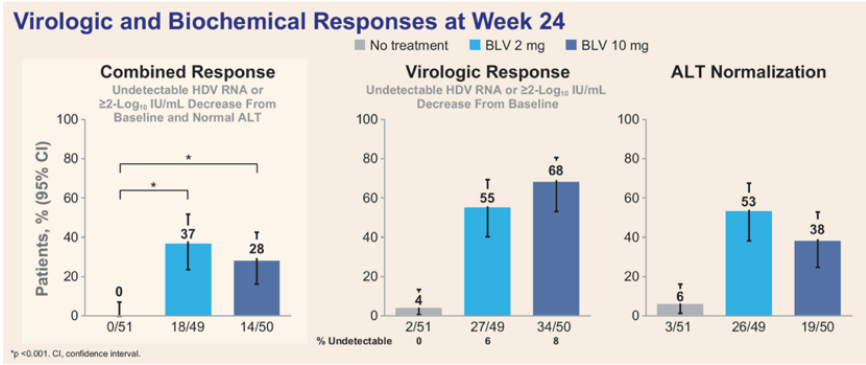
Bulevirtide – 24-Week Interim Monotherapy Data – MYR 301





Results:

- BLV 2 mg and 10 mg had comparable median HDV decline
- BLV 2 mg had higher rates of combined response defined as undetectable HDV RNA or ≥ 2 log decline PLUS normalization of ALT
- Results supported the use of BLV 2 mg



Wedemeyer H et al. *EASL*. 2021.

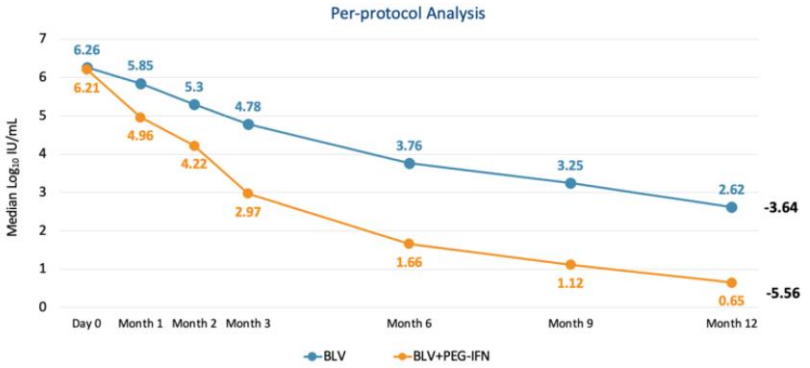
Bulevirtide – Real World Experience

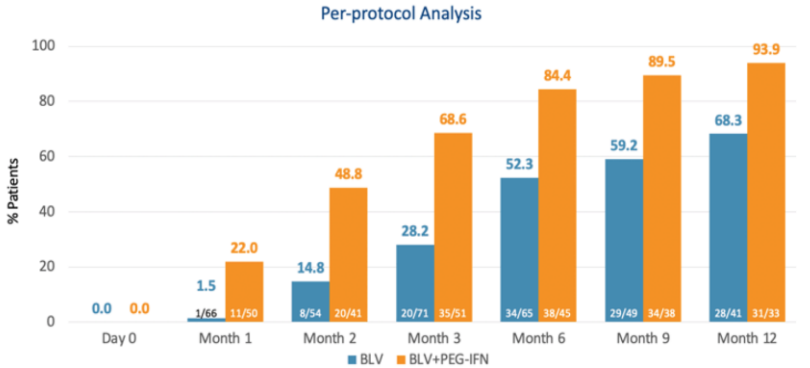
Study design: Multi-center, observational study without randomization of BLV 2 mg vs BLV 2 mg + PEG-IFNα

- 145 patients, at least 12 months of treatment
- Virologic efficacy: ≥ 2 log decline or undetectable
- Biochemical efficacy: ALT < 40 IU/L

Results:

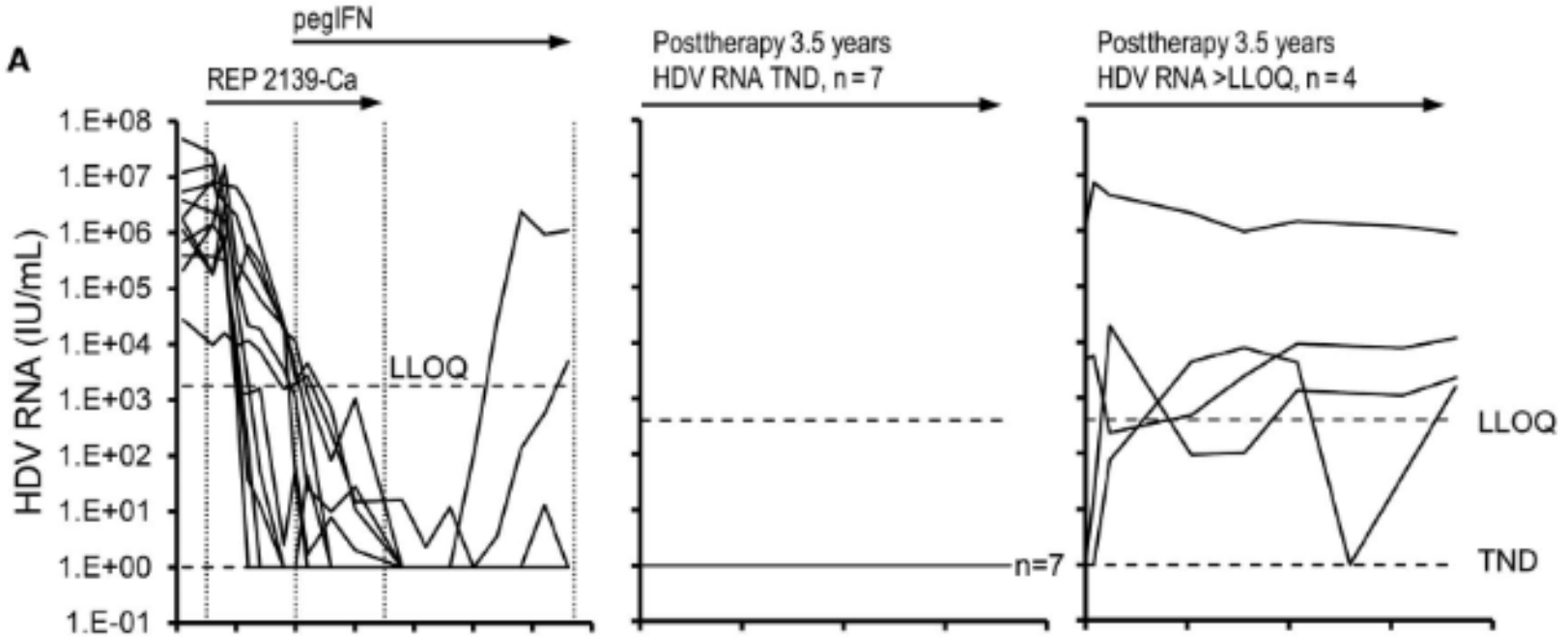
- Better virologic response (93.9% vs 68.3%) was seen in the combination group but with poorer chemical response (48.8% vs 36.4%)
- Asymptomatic elevated total bile acids seen





de Ledinghen V et al. *AASLD*. 2021.

REP 2139-Ca
Long-term Follow-up (REP 301-LTF)



Bazinet M et al. *Hepatol Commun.* 2020; 5: 189–202.

Active Late-stage Trials

Drug	Name/Phase	Mechanism	Duration	#	Estimated Completion
BLV +/- PEG-IFNα	MYR 204 Phase 2	Inactivates NTCP, prevents entry	Up to 96 weeks OT	175	September 2022
LNF/RTV +/- PEG-IFNα	D-LIVR Phase 3	Prenylation Inhibitor	48 weeks OT, 24 weeks f/u	400	April 2023
BLV	MYR 301 Phase 3	Inactivates NTCP, prevents entry	144 weeks OT, 96 weeks f/u	150	July 2024
PEG-IFNλ-1a	LIMT-2 Phase 3	IFN type 3	48 weeks OT, 24 weeks f/u	150	January 2025
REP 2139-Mg + PEG-IFNα	Planning in progress				

In Summary

- HDV is under recognized and under screened
- Real prevalence of HDV remains a mystery
- Persistent HDV viremia is a harbinger of clinical outcomes
- Several promising therapies are in development

Thank You!

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