Hot Topics in Hepatology

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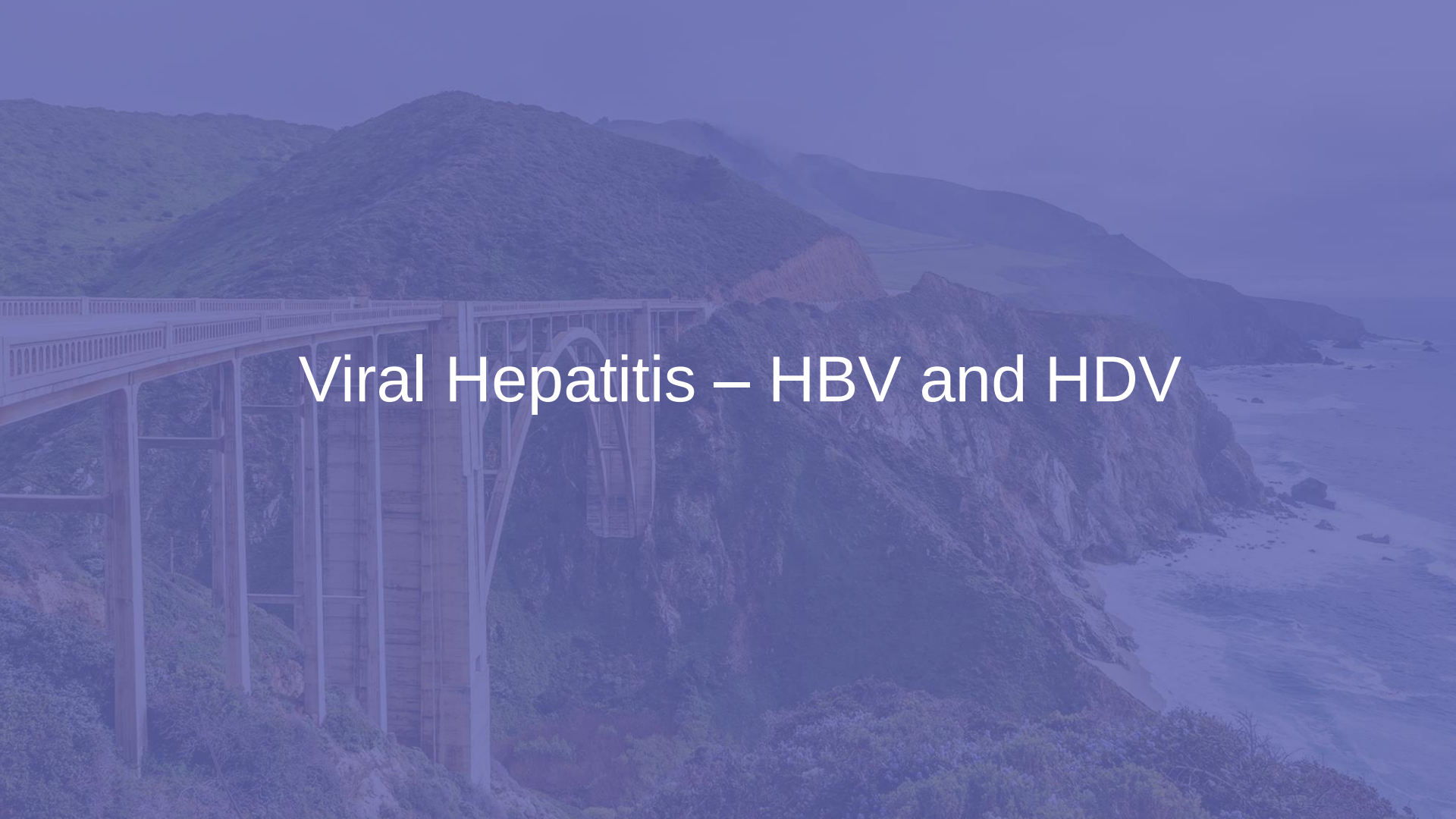
Disclosures

- No relevant disclosures

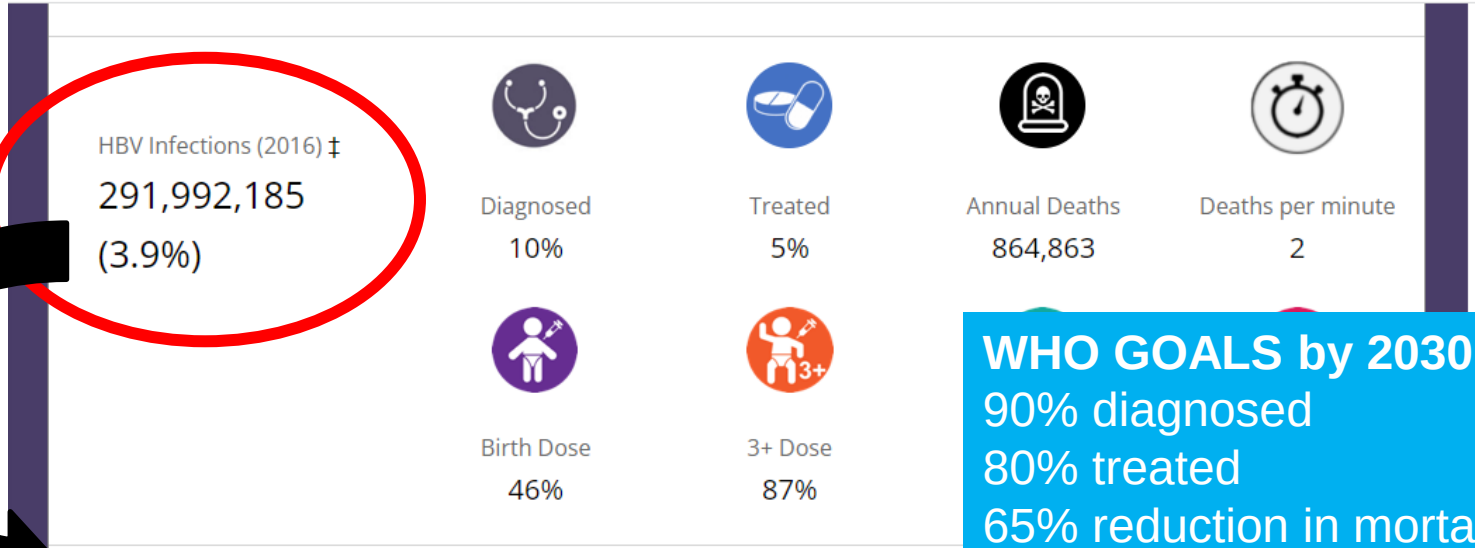
Objectives

- Review hot topics and recent updates in viral hepatitis
- Review recent updates in alcohol-associated liver disease (ALD)
- Summarize recent data on the impact of COVID-19 on patients with chronic liver diseases



Viral Hepatitis – HBV and HDV

Epidemiology and Disease Prevalence

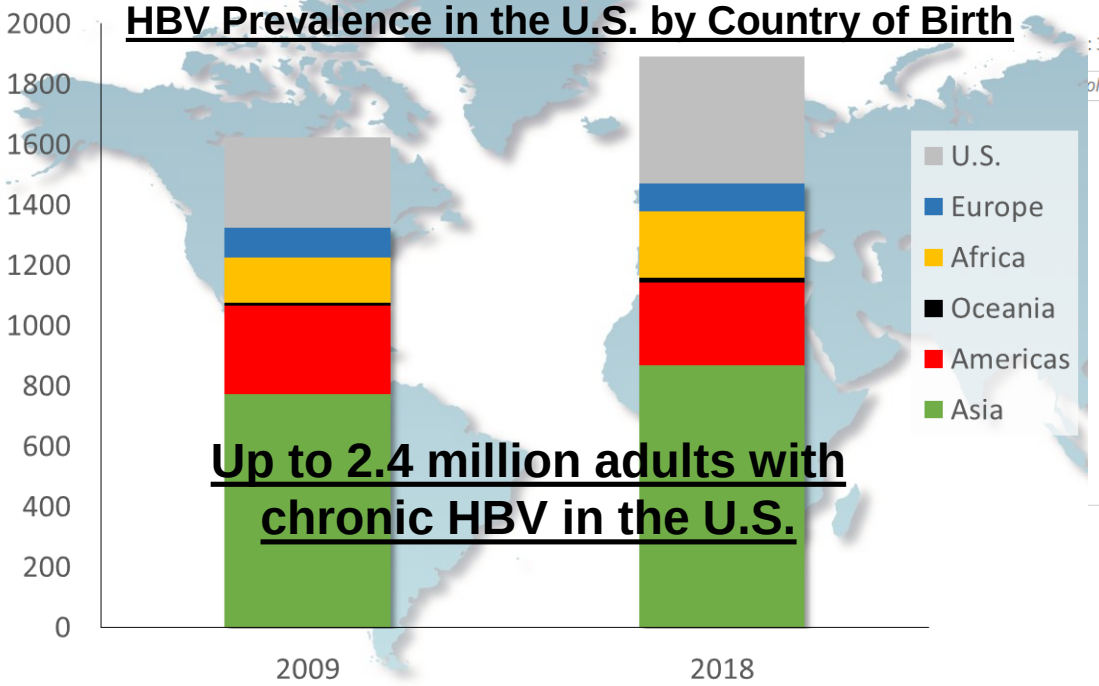


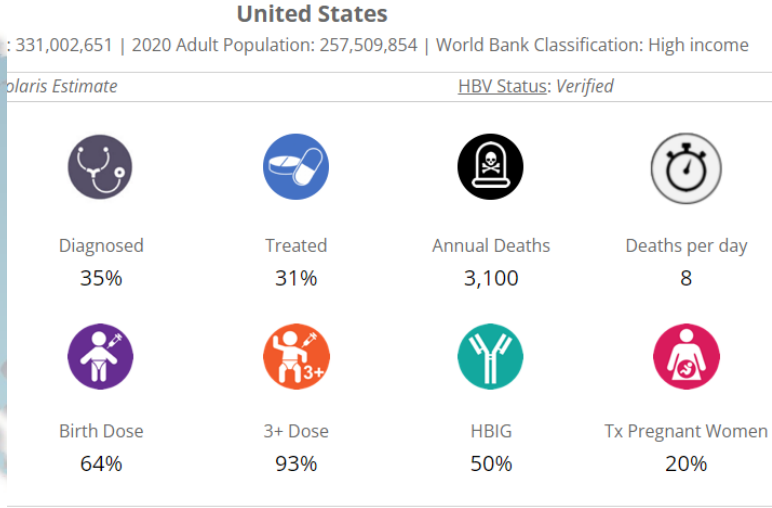
WHO GOALS by 2030
90% diagnosed
80% treated
65% reduction in mortality

~270 million (2020 estimates)
Less new infections – vaccination
Increased mortality of aging HBV population

CDA Foundation – POLARIS Observatory.

Epidemiology – United States





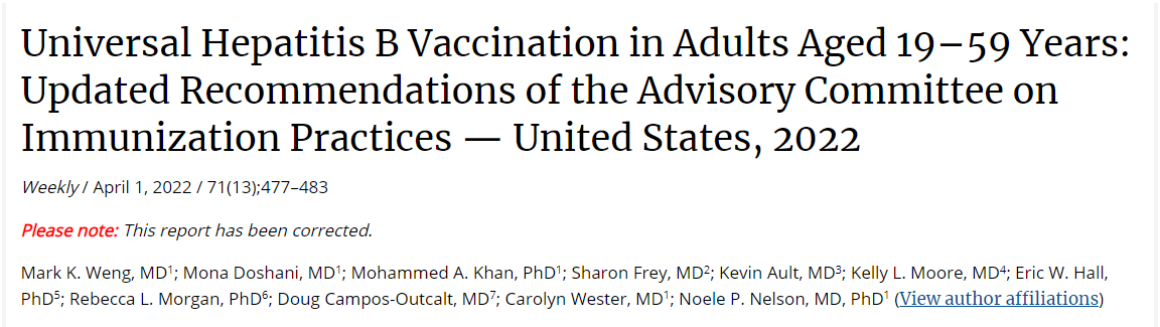
CDA Foundation – POLARIS Observatory; Wong, et al. *Hepatology* 2021.

Gaps and Disparities in HBV Care Cascade

- ***Persistent gaps*** in the HBV care cascade from effective HBV screening, timely HBV diagnosis, linkage to care, appropriate disease monitoring, and timely antiviral therapy
- ***Underserved populations***, including ethnic minorities and safety-net populations are disproportionately affected
- How are we going to reach viral hepatitis elimination targets?
  - Effective **screening**
  - Expanding **vaccination**
  - Reduce barriers to **treatment**

How Do We Achieve HBV Elimination

- Expand and improve HBV **screening** from risk-based to universal adult screening – only 1/3 of HBV patients in US are aware
  - Toy, et al. conducted a Markov simulation model, one-time universal HBV screening is cost-effective and cost-saving:
    - ↓ 7.4 compensated cirrhosis, ↓ 3.3 decompensated cirrhosis, ↓ 5.5 HCC, ↓ 1.9 liver transplants, ↓ 10.3 HBV–related deaths, cost savings of $263 000 per 100 000 adults screened
- Expand and improve HBV **vaccination**



Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022

Weekly / April 1, 2022 / 71(13);477–483

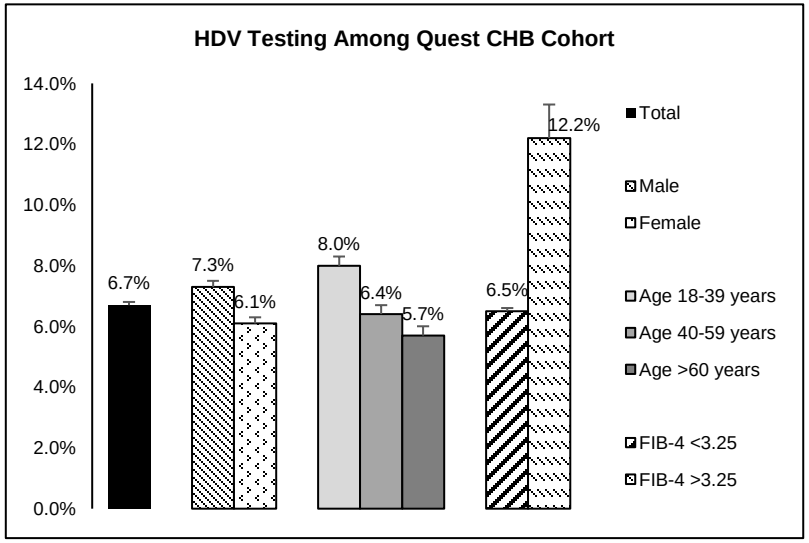
Please note: *This report has been corrected.*

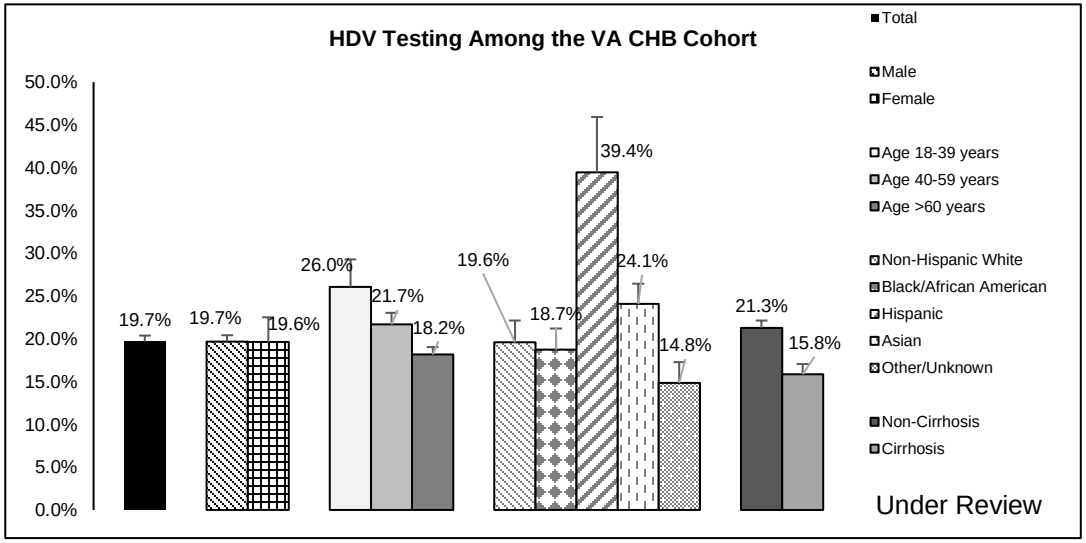
Mark K. Weng, MD[1]; Mona Doshani, MD[1]; Mohammed A. Khan, PhD[1]; Sharon Frey, MD[2]; Kevin Ault, MD[3]; Kelly L. Moore, MD[4]; Eric W. Hall, PhD[5]; Rebecca L. Morgan, PhD[6]; Doug Campos-Outcalt, MD[7]; Carolyn Wester, MD[1]; Noele P. Nelson, MD, PhD[1] (View author affiliations)

Toy et al. *Clinical Infectious Diseases*. 2022.

What's All the Buzz About Hepatitis Delta

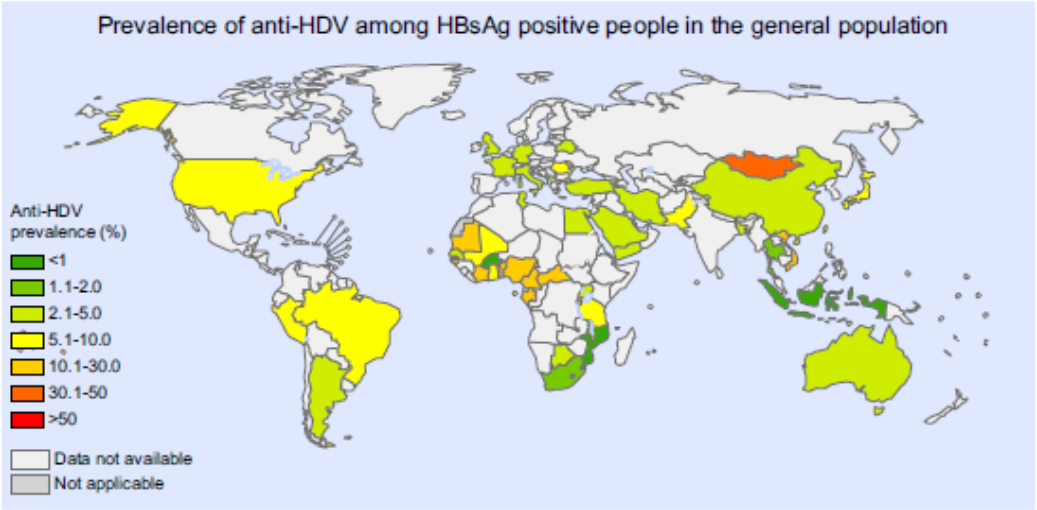
- HDV occurs in setting of chronic HBV and is associated with significantly more aggressive disease: 3 times higher risk of **cirrhosis**, 2 to 4 times higher risk of liver **decompensation**, 1.6 to 3 times higher risk of **HCC**, 2 to 5 times higher risk of liver related **mortality.**
- However, sub-optimal testing leads to delays in diagnosis and lack of clarity about the true disease burden of HDV.





HDV Prevalence

- Global HDV prevalence estimated at 4.5%, ~12 million adults.
- HDV prevalence in the US limited by sub-optimal data, estimated ~80-150k
- Quest HBV data: 2.2% prevalence
- VA HBV cohort: 3.1% prevalence
- However, data limited by testing bias, availability of diagnostic testing, lack of clarity on who to test, etc



Under Review; Stockdale et al. *J Hepatol*. 2020.

Drug	Mechanism	Route	Phase of Development	Efficacy	Approval Status
Bulevirtide	Virion entry inhibitor	s.c.	Phase 3 completed	Week 24 – 55-68% achieved ≥2log HDV RNA decline	EMA approval; FDA application in
Lonafarnib	Prenylation inhibitor	oral	Phase 3 recruiting	LOWR-4 study: mean HDV RNA decline was 1.58+/-1.38 log IU/mL	Approved for other indication; under evaluation for HDV
REP2139	Nucleic acid polymer	i.v.	Phase 2	83.3% achieved ≥2log HDV RNA decline	None
Pegylated Interferon Lambda	Immune modulator	s.c.	Phase 2	7(50%) and 4 (21%) patients from the high- and low-dose groups achieved a >2log IU/ml decline in HDV RNA	None

Alcohol-Associated Liver Disease

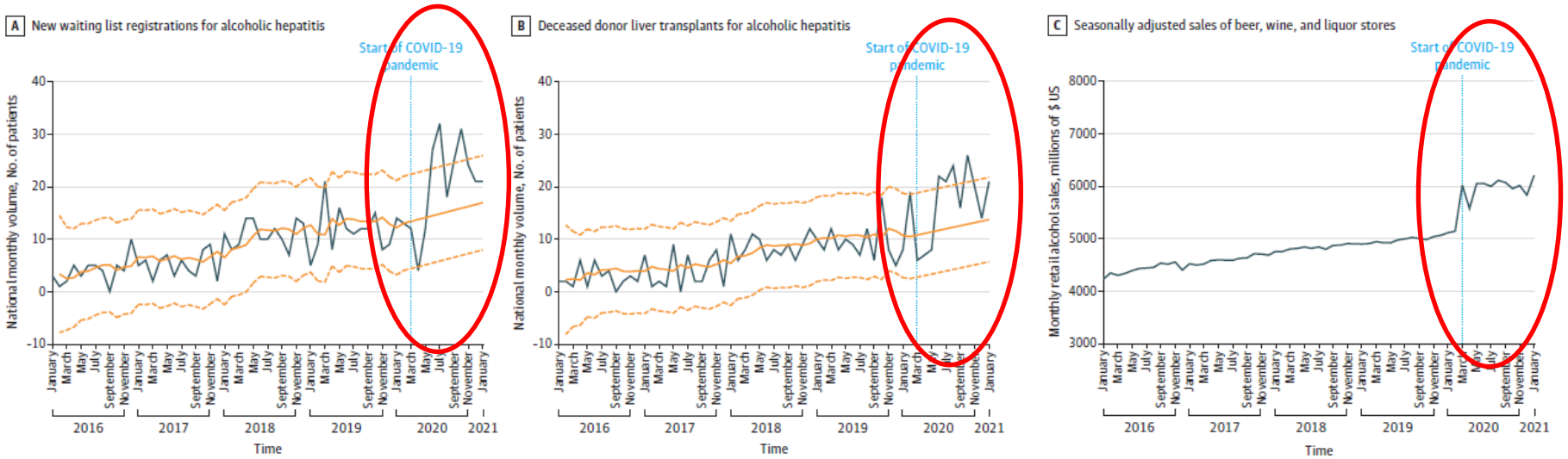
Epidemiology and Disease Prevalence

JAMA Network Open

Research Letter | Gastroenterology and Hepatology

Association of COVID-19 With New Waiting List Registrations and Liver Transplantation for Alcoholic Hepatitis in the United States

Maia S. Anderson, MD; Valeria S. M. Valbuena, MD; Craig S. Brown, MD, MSc; Seth A. Waits, MD; Christopher J. Sonnenday, MD, MHS; Michael Englesbe, MD; Jessica L. Mellinger, MD, MSc



Anderson et al. *JAMA Netw Open*. 2021.

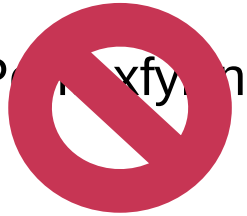
Effect of Increased Alcohol Consumption During COVID-19 Pandemic on Alcohol-Related Liver Disease: A Modeling Study

- Validated microsimulation model that estimated the short- and long-term effect of increased drinking during the COVID-19 pandemic compared with a counter-factual scenario wherein no COVID-19 occurs and drinking patterns do not change
- One-year increase in alcohol consumption during the COVID-19 pandemic is estimated to result:
  - 8,000 [95% UI 7,500-8,600] additional ALD-related deaths
  - 18,700 [95% UI 17,600-19,900] cases of decompensated cirrhosis
  - 1,000 [95% UI 1,000-1,100] cases of HCC
  - 8.9 million disability-adjusted life-years between 2020 and 2040
- ***A sustained increase in alcohol consumption for more than 1 year could result in additional morbidity and mortality***

Julien et al. *Hepatology*. 2021.

ALD Treatments

- Alcohol abstinence and multidisciplinary interventions are needed
- Lack of novel effective medical therapies, especially for severe acute alcoholic hepatitis
- Prednisolone . . . . .. .Pentoxifylline



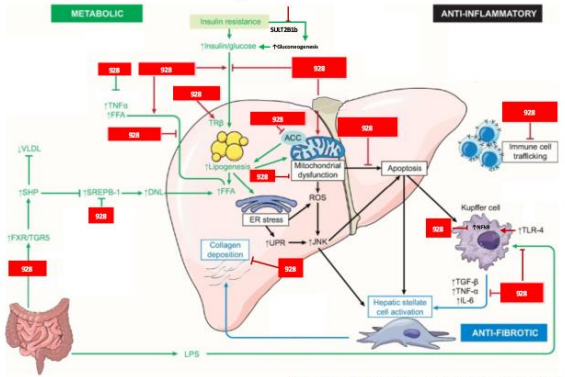
- There is an urgent need for effective therapies, particularly for those ALD patients with severe acute alcoholic hepatitis

DUR-928

- Natural occurring endogenous newly discovered regulatory Molecule
- Sulfated oxysterol, small molecule
  - Produced in the cytoplasm and acts intracellularly
  - Highly conserved across 7 mammalian species studied to date, including humans (*Important in the regulation of cell function*)
- Epigenetic regulator with broad activity
  - Modulates gene activities
  - Regulates metabolism, inflammation, cell survival, and tissue regeneration
- Well tolerated in multiple Phase 1 studies

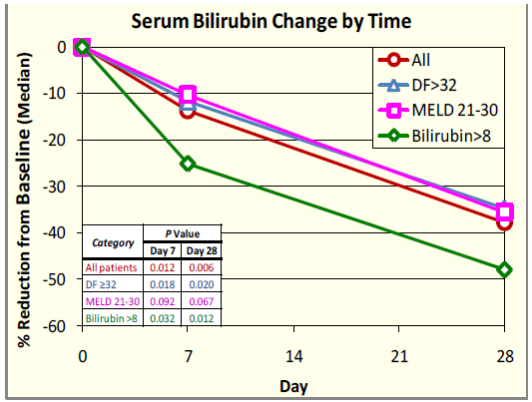
Biological Pathways Potentially Influenced by DUR-928

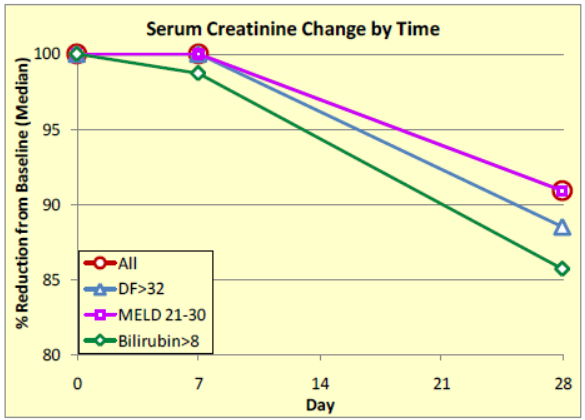
DUR-928 modulates multiple biological pathways involved in metabolic homeostasis, inflammatory response, cell survival and tissue regeneration

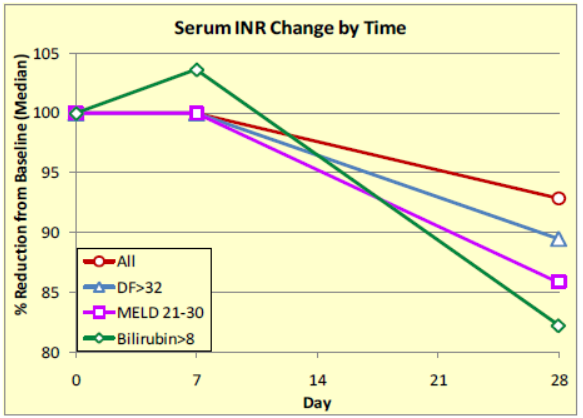


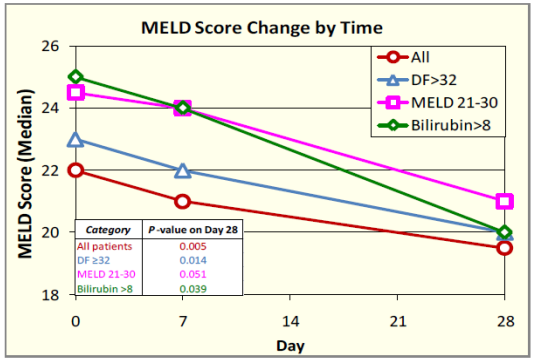
Source: modified from Konerman M et al., J. Hepatol 2018; 68:362-75

Courtesy of Hassanein, et al. AASLD Liver Meeting; Durect Corporation.







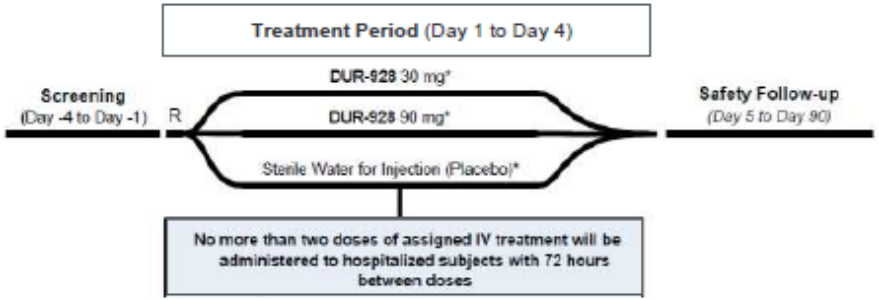


- Significant early reduction of bilirubin from baseline by Day 7
- Patients with higher baseline bilirubin (>8 mg/dL) had higher bilirubin reduction, 25% decrease by Day 7 and 48% decrease by Day 28
- 100% treatment response rate (Lille score <0.45) in patients receiving 30 or 90 mg doses; 89% response rate in all patients
- Significant reduction of MELD by Day 28

Courtesy of Hassanein, et al. AASLD Liver Meeting; Durect Corporation.

Advancing to Phase 2b

Study Objectives, Design & Endpoints: AFHIRM



NorCal Sites

UCSF – Courtney Sherman
Neil Mehta

Stanford: Aparna Goel

UC Davis: Vikrant Rachakonda

Trial Endpoints

Primary: Safety and efficacy (90-day mortality)

Secondary: 28-day mortality, TESAEs, Lille score at Day 7, MELD scores at Day 28, and ICU days at Day 28

Design

Randomized, double-blind, placebo-controlled, multi-arm, multi-center, parallel design

Severe AH patients with Maddrey's DF score ≥ 32 and MELD scores 21-30

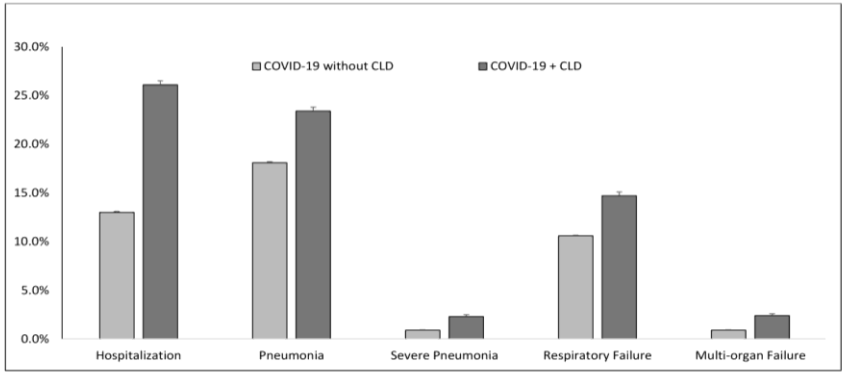
300 subjects in three dosing groups at a 1:1:1 ratio (30 mg, 90 mg, Placebo + SOC)

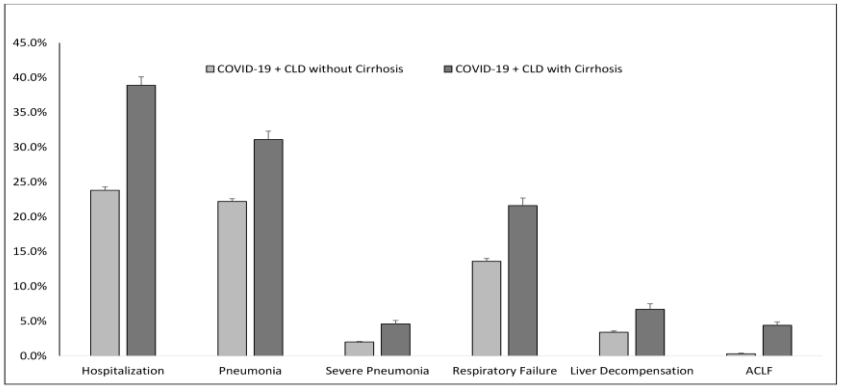
Courtesy of Durect Corporation.

COVID-19 and CLD

COVID-19 Database

- Data from the COVID-19 Research Database were evaluated from 4/1/2020-8/31/2021, to evaluate outcomes in CLD patients with COVID-19
- 1,208,905 unique patients with COVID-19 were identified; 44,008 (3.6%) had concurrent CLD, among which 6,515 (14.8%) had cirrhosis.
- Compared to COVID-19 patients without CLD, COVID-19+CLD patients had higher risk of:
  - Hospitalization (aOR 1.65, 95% CI 1.61-1.69)
  - Pneumonia (aOR 1.11, 95% CI 1.08-1.14)
  - Severe pneumonia (aOR 1.74, 95% CI 1.62-1.86)
  - Respiratory failure (aOR 1.14, 95% CI 1.10-1.17)
  - Multi-organ failure (aOR 1.84, 95% CI 1.72-1.97)





Wong, Zhang, Thamer. 2022. Under Review.

National COVID Cohort Collaborative

- Multi-center study of 220,727 adults with liver disease that underwent COVID-testing:
  - 128,864 (58%) were noncirrhosis/negative
  - 29,446 (13%) were noncirrhosis/positive
  - 53,476 (24%) were cirrhosis/negative
  - 8941 (4%) were cirrhosis/positive
- Thirty-day all-cause mortality rates were 3.9% in cirrhosis/negative and 8.9% in cirrhosis/positive patients

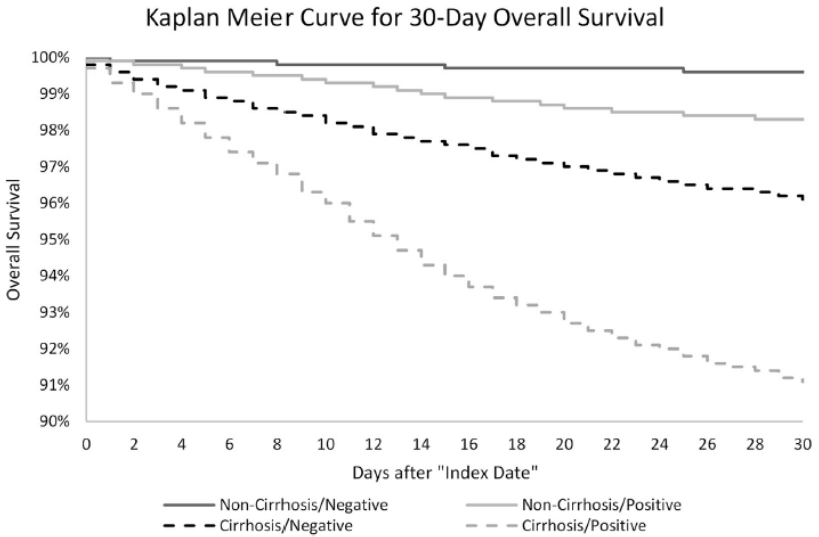


Figure 1. Kaplan-Meier curve for 30-day overall survival.

Ge et al. *Gastroenterology.* 2021;161:1487–1501.

Take Home Points

- HBV and HDV remains a major global burden and contributor to liver related morbidity and mortality
- Efforts to improve and expand HBV screening are needed. Universal adult HBV vaccination is now recommended
- HDV is one of the most severe forms of viral hepatitis – potential treatment is just on the horizon
- Rising burden of ALD has been exacerbated by COVID-19 pandemic
- Lack of effective medical therapies for severe ALD
- CLD-COVID-19 is associated with significantly greater risk of poor clinical outcomes
- Ensuring adequate vaccine-induced protection and close monitoring of CLD patients is needed following COVID-19

Thank you

- Northern California Society for Clinical Gastroenterology
- NCSCG GI Symposium Organizing Committee