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**HBV/HDV-ACT Connect**  
**(ADVANCING CURATIVE TREATMENTS)**



# HDV Update: Review of the Last 3 Years

EPI, Testing & Linkage to Care

Dr. Robert Gish

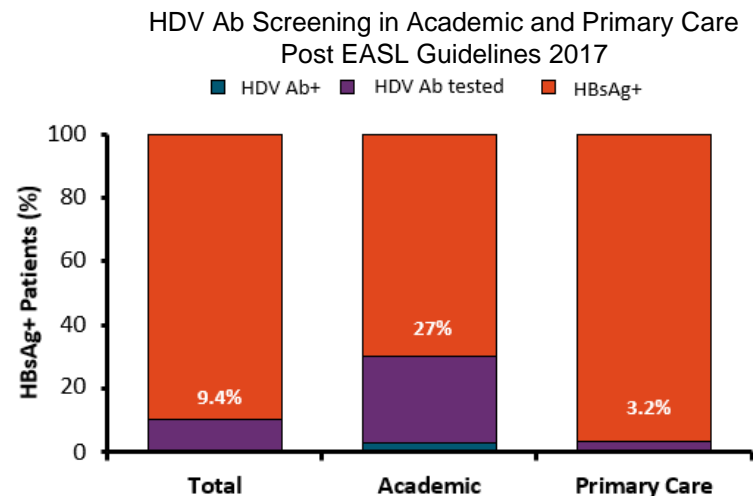
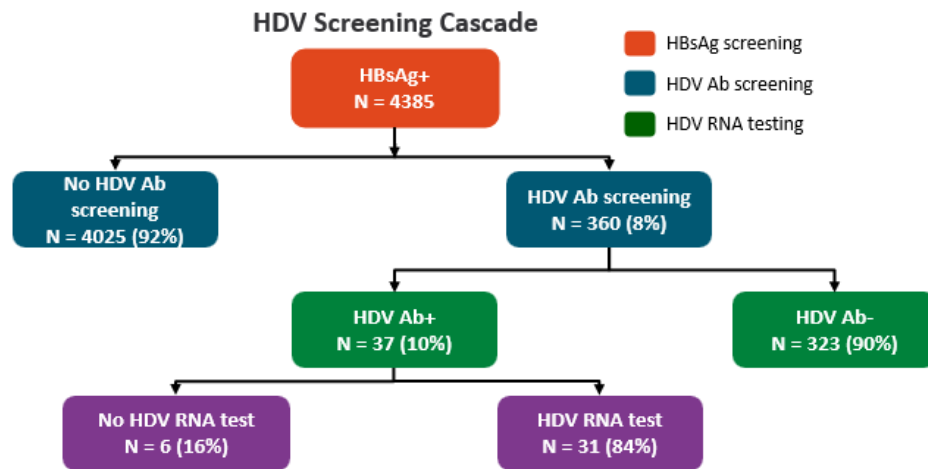
# Disclosures

A decorative graphic at the top of the slide features a network of interconnected nodes and lines. The nodes are represented by circles of varying sizes and colors, including shades of orange, red, and grey. The lines are thin and light-colored, creating a complex web-like structure that spans across the top of the page.

- See [robertgish.com](http://robertgish.com)

# Screening of HDV in HBsAg+ Patients in Barcelona: Are EASL Guidelines Implemented?

- Retrospective analysis of HBsAg+ serum samples from central laboratory in Barcelona from January 2015 - May 2021
  - 1457 (33%) and 2929 (67%) of HBsAg+ samples came from academic hospitals and primary care centers, respectively
  - 282 (78%) and 78 (22%) of anti-HDV requests came from academic hospitals and primary care centers, respectively

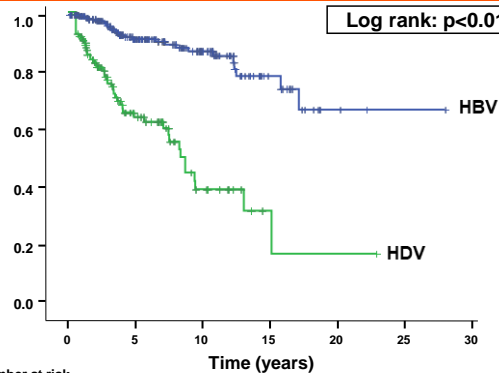


# Long-Term Clinical Outcome of HDV



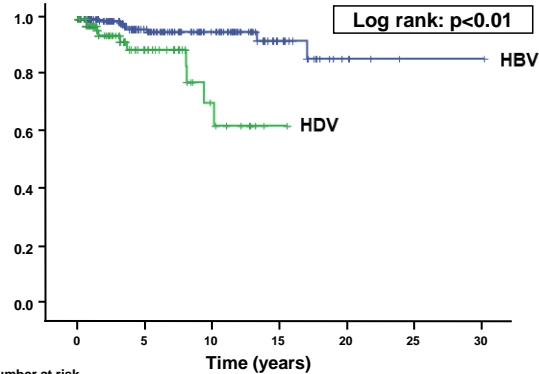
Single-center retrospective observational study to compare long-term outcomes\* in 175 individuals with HDV/HBV against 175 individuals with HBV mono-infection\*\*

Cumulative event-free survival



Number at risk	0	5	10	15	20	25	30
HBV:	175	125	67	18	3	1	
HDV:	175	42	12	2	1		

Cumulative event-free survival in individuals without cirrhosis



Number at risk	0	5	10	15	20	25	30
HBV:	144	110	58	16	3	1	
HDV:	96	28	7				

Factors Associated with Long-Term Outcome

Parameter	Univariate Analysis	Multivariate Analysis
<b>HDV+</b>	<b><math>p &lt; 0.01</math>; HR=3.6</b>	<b><math>p &lt; 0.01</math>; HR=3.0</b>
Age (linear)	$p < 0.01$ ; HR=1.1	$p < 0.01$ ; HR=1.1
Male Gender	$p = 0.04$ ; HR=1.7	$p = 0.05$ ; HR=2.1
Cirrhosis	$p < 0.01$ ; HR=11.6	Not Significant
PLT (linear)	$p < 0.01$ ; HR=0.98	$p < 0.01$ ; HR=0.9
INR	$p < 0.01$ ; HR=55.5	$p < 0.01$ ; HR=9.9
HBeAg-	$p < 0.01$ ; HR=3.5	Not Significant
NA Therapy	$p < 0.01$ ; HR=1.9	Not Significant
IFN Therapy	$p < 0.01$ ; HR=0.5	Not Significant

Individuals with HDV had a higher risk to develop liver-related events compared to HBV mono-infected individuals even after accounting for relevant baseline characteristics

\*Outcomes of interest were defined as hepatic decompensation (ascites, encephalopathy, variceal bleeding), liver transplantation, HCC, or liver-related death; \*\*HDV and HBV

mono-infected cohorts were matched for gender, age, region of origin, HBeAg status, and bilirubin.

PLT, platelets; INR, international normalized ratio; NA, nucleos(t)ide analog; IFN, interferon.; HR, hazard ratio

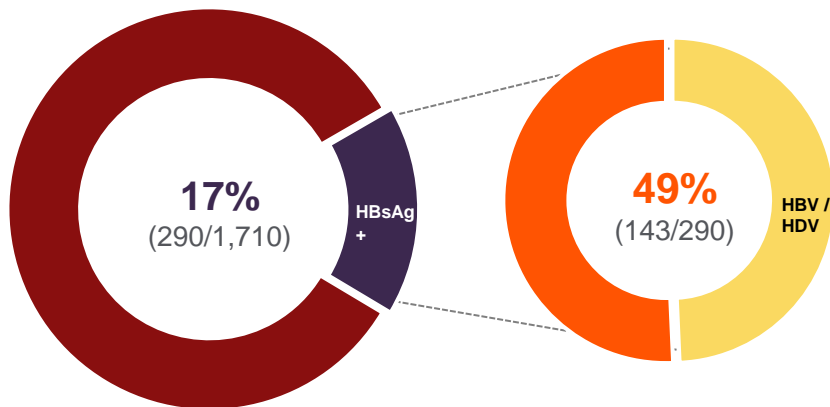
Wranke A. *DeltaCure*. 2022. Poster #6.

# Characteristics of Liver Transplant Patients With HDV



Retrospective single center study of 290 HBsAg+ patients that underwent liver transplantation (2010–2021)

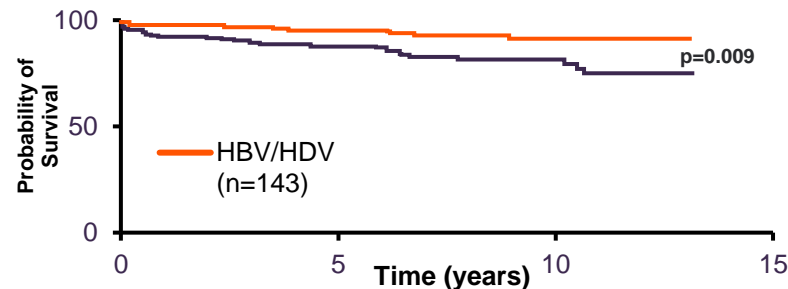
## Proportion of Patients Undergoing LT



290 HBsAg+ patients underwent LT

143 HBsAg+ patients receiving LT were coinfectd with HDV

## Probability of Survival Following LT



Demographic and Clinical Characteristics	Overall (n=290)	HBV (n=147)	HBV/HDV (n=143)	p value
Age, median years (IQR)	57 (51–61)	59 (55–63)	55 (49–60)	p<0.001
HCC*, n (%)	187 (65)	109 (74)	78 (55)	p<0.001
MELD, median (IQR)	14 (9–18)	11 (8–16)	15 (11–20)	p<0.001

HBsAg+ patients undergoing LT were disproportionately coinfectd with HDV. Following LT, the 5-year probability of survival for patients with HDV was ~95%

University of Turin

\*Main indication for LT. HCC, hepatocellular carcinoma; IQR, interquartile range; LT, liver transplant; MELD, model for end-stage liver disease.

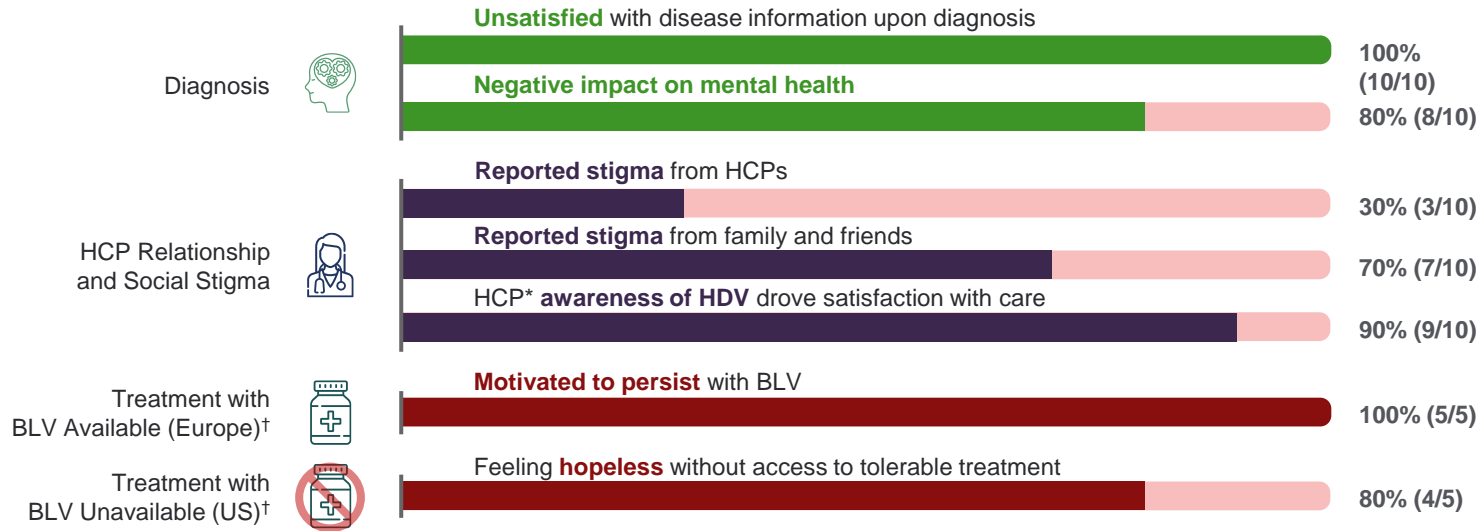
Manuli C. AASLD. 2022. Poster #1508.

# Patient Perspective on HDV Disease Burden



Insights from 10 patients with HDV included in advisory meetings and surveys

## Key Learnings from Austrian, French, UK, and US CHD Patients



The median time to diagnosis for HDV was **10 years** post-HBV or HIV diagnosis

Improvement of HCP and patient knowledge around HDV, reducing delays in diagnosis, and combatting stigma are required

\*HCPs include providers who specialize in primary care, infectious disease, gastroenterology, and hepatology; <sup>†</sup>BLV only available in European countries following conditional EMA approval, it was not available in the US at the time of this study; <sup>‡</sup>Unmet needs and actionable opportunities also assessed (systematic tools enabling earlier diagnosis, increased HDV awareness among HCPs, accessible and realistic lifestyle information for diagnosed patients, reduce associated stigma among HCPs, mental health support, patient and community engagement, access to tolerable HDV-specific treatments). BLV, bulevirtide; HCP, healthcare provider; SC, subcutaneous.



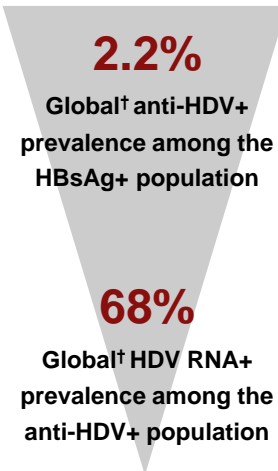
# Population Adjusted Prevalence of HDV



Literature review & expert validation\* of HDV prevalence in 16 countries & territories

## Global Prevalence of HDV among HBsAg+ Populations

Region	Country/Territory	2020 HBsAg+ (n)	Unadjusted		Adjusted <sup>†</sup>		
			anti-HDV+ <sup>**§</sup> (%)	HDV RNA+ <sup>‡</sup> (%)	anti-HDV+ <sup>**</sup> (%)	RNA+ in anti-HDV+ (%)	HDV RNA+ <sup>**§§</sup> (n)
South America	Brazil	1,057,700	3.2	75	1.7	76	13,600
	Colombia	329,000	5.2	70	1.0	70	2,300
Europe	England	361,900	2.9	50	1.0	50	1,800
	France	308,400	1.8	75	3.5	74	8,100
	Germany	226,900	5.5	60	3.0	60	4,100
	Spain	249,400	5.2	73	1.2	75	2,200
	Italy	315,100	8.3	61	6.0	60	11,400
	Sweden	30,000	3.8	75	2.0	85	500
	Romania	622,100	23.1	80	2.9	79	14,400
Asia	Japan	562,000	8.5	41	0.5	40	1,100
	South Korea	1,409,400	0.3	54	0.3	67	2,300
	Taiwan	963,400	3.3	60	0.9	56	5,200
Middle East	Saudi Arabia	560,500	8.6	60	4.0	60	13,400
North America	Turkey	2,001,100	2.8	68	2.8	68	38,100
North America	USA	1,834,600	6.0	66	3.0	67	36,300
	Canada	223,200	1.6	65	4.8	65	6,900
	<b>Total</b>	<b>11,054,700</b>	<b>5.2</b>	<b>67</b>	<b>2.2</b>	<b>68</b>	<b>161,700</b>



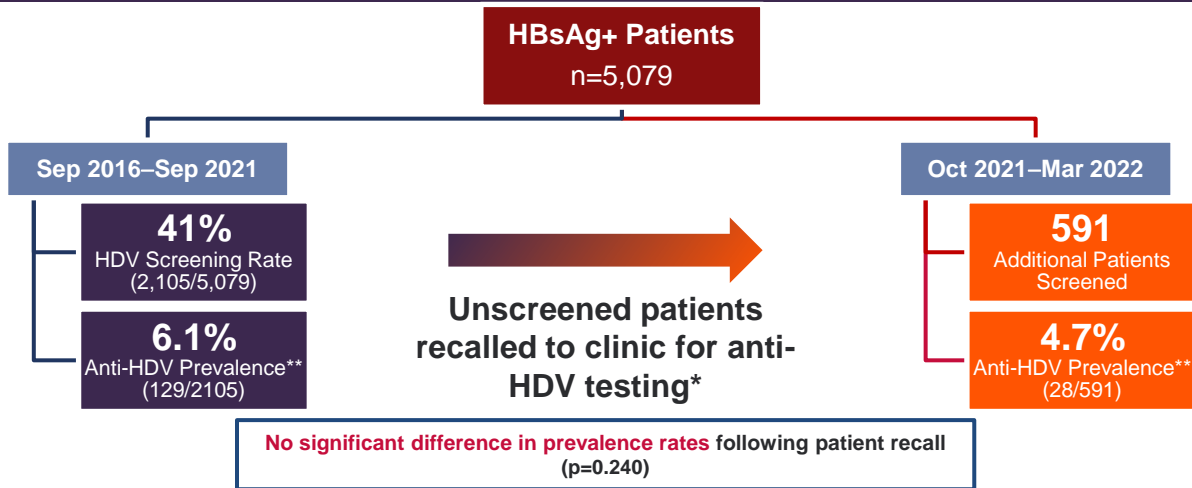
Adjusted prevalence figures provide an updated picture of HDV burden in these 16 countries; authors conclude that reflex testing would improve the knowledge base of HDV prevalence

\*Virtual meetings were held with experts from each setting to discuss the literature search findings, collect unpublished data, and weigh data for patient segments and regional heterogeneity to estimate the overall prevalence in the HBV-infected population; \*\*Among the HBsAg+ population; <sup>†</sup>Adjusted for geographical distribution, disease stage, and special populations; <sup>‡</sup>Among the anti-HDV+ population; <sup>§</sup>Unadjusted anti-HDV based on literature; <sup>§§</sup>Adjusted for HDV RNA positivity. HBsAg, hepatitis B surface antigen.

# Impact of Patient Recall for HDV Testing in Greece



Assessment of HDV screening & prevalence rates of 5,079 HBsAg+ patients from 14 liver centers



Recalling patients previously unscreened for HDV was successful and resulted in comparable prevalence rates

## HERACLIS-HDV

\*Patients without anti-HDV screening who visited the liver centers in the study or could be recalled to visit the centers were tested for anti-HDV; \*\*Positive results for anti-HDV were independently associated with younger age (OR/year: 0.97 [95% CI: 0.96–0.99]; p<0.001), risk group (PWID: 46% vs other/none: 5.3%; OR: 13.9 [95% CI: 5.9–32.4]; p<0.001), place of birth (outside of Greece: 12.8% vs Greece: 3.3%; OR: 2.8 [95% CI: 1.8–4.4]; p<0.001), disease progression (cirrhosis/liver transplant: 25% vs none: 4%; OR: 11.5 [95% CI: 7.3–18.1], p<0.001), and clinic location (Athens/Southern Greece: 8.6% vs Northern Greece: 2.9%; OR: 2.0 [95% CI: 1.3–3.1], p=0.003). CI, confidence interval; HBsAg, hepatitis B surface antigen; PWID, person who inject drugs.

Papatheodoridis G. AASLD. 2022. Poster #1176.

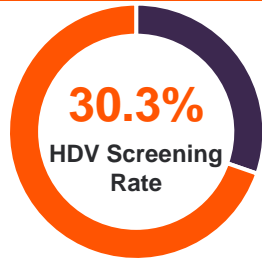
# HDV Screening for Special Populations in the US



Retrospective analysis of HDV screening among CHB cohorts within safety-net\* and VA health systems

Safety-Net CHB Cohort (n=884)\*\*

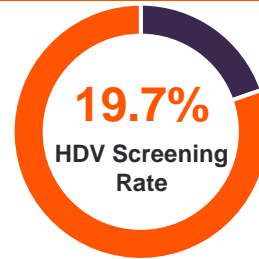
VA CHB Cohort (n=12,002)†



9.0%  
HDV Prevalence  
Among CHB Patients

Lower odds of HDV testing in non-Hispanic whites (OR: 0.47) and African Americans (OR: 0.45), compared to Asians

Greater odds of HDV testing in patients with cirrhosis compared to patients without cirrhosis (OR: 2.10)



3.1%  
HDV Prevalence  
Among CHB Patients

Greater odds of HDV testing in Asians (OR: 1.23), compared to non-Hispanic whites

Greater odds of HDV testing in patients aged 18–39 (OR: 1.53), compared to patients aged 60 and over

Screening rates are low in the US, including among health systems serving at-risk communities

\*Safety-net health systems serve predominantly under-served vulnerable populations and include many ethnic minority and immigrant populations. \*\*Compared to Asians, there was a lower odds of HDV testing in non-Hispanic whites (OR 0.47, 95% CI 0.31—0.72) and African Americans (OR 0.45, 95% CI 0.30—0.66). †Compared to non-Hispanic whites, Asians had a higher odds of receiving HDV testing (OR 1.23, 95% CI 1.05—1.45) and younger patients were more likely to be tested (OR for Age <40 vs. Age 60 and Over; OR 1.53, 95% CI 1.31—1.78). CHB, chronic hepatitis B; OR, odds ratio; VA, Veterans Affairs.

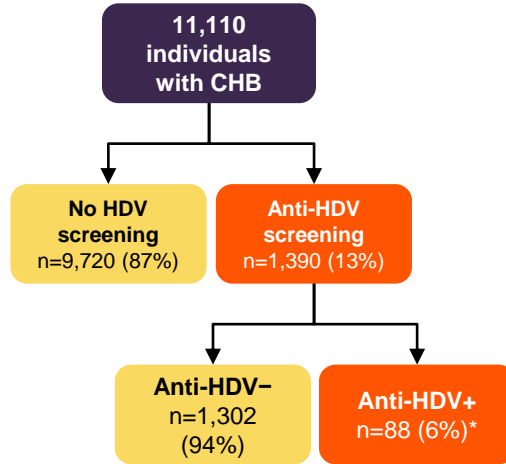
Wong R. AASLD. 2022. Oral #20.

# Gaps in Risk Factor-Based HDV Screening

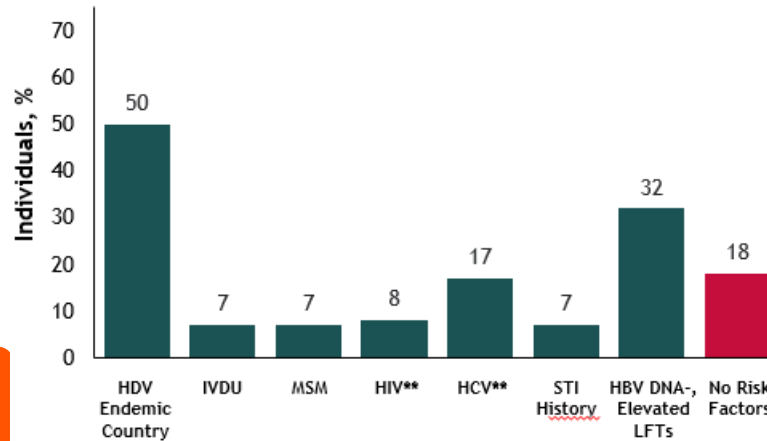


Retrospective single center study evaluating HDV screening in 11,110 CHB patients (2016–2021)<sup>1,2</sup>

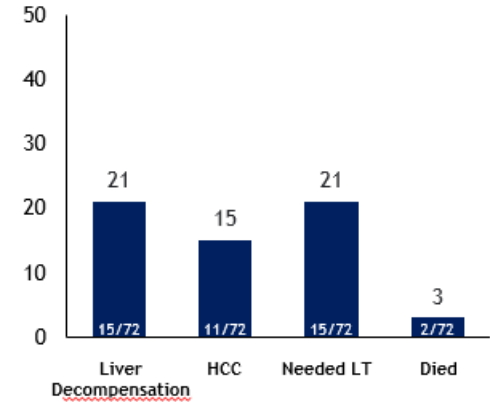
## HDV Screening Patterns<sup>1,2</sup>



## HDV Risk Factors Among Patients with HDV\* (n=72)<sup>2</sup>



## Liver-Related Events (2016-2021)<sup>1</sup>



Current screening practices in the US are inadequate, supporting the need for universal screening of HDV in CHB patients

Mount Sinai Health System

\*72 patients had complete information on chart review and were included in the analyses; \*\*Patients with coinfection. IVDU, intravenous drug user; LFT, liver function test; MSM, men who have sex with men; STI, sexually transmitted infection.

1. Nathani R. *EASL*. 2022. Poster #THU392; 2. Nathani. *AASLD*. 2022. Poster #1006.

# Prevalence of HDV in Patients With HIV/HBV Coinfection



Cross-sectional study of 597 HIV/HBV+ patients from 8 sites\* tested for anti-HDV (1996–2019)

597 Patients with HIV/HBV

Anti-HDV-  
n=573 (96%)

Anti-HDV+  
n=24 (4%)

HDV RNA-  
n=14 (58%)

HDV RNA+  
n=10 (42%)

Patient samples collected from 1996-2019

HDV test performed on samples meeting qualifying HBV test (HBsAg+, HBeAg+, or HBV DNA+)

Prevalence of anti-HDV was 4% among patients with HIV/HBV coinfection; authors' conclusion support HDV testing in this patient population

CNICS

\*Birmingham, Seattle, San Diego, San Francisco, Cleveland, Baltimore, Boston, Chapel Hill. CNICS, Center for AIDS Research Network of Integrated Clinical Systems.

Ferrante N. AASLD. 2022. Poster #1002.

# Deficits in HDV Care Cascade (The “Delta Delta”)

## Background

- Current AASLD guidelines recommend risk-factor based screening for HDV among patients with CHB → real-world practice patterns for HDV testing poorly described

## Methods

- Retrospective cohort study of CHB cohort in New York City 2016-2021
- Examined screening, baseline characteristics, and clinical outcomes for HDV → comparison of HDV positive cases with HDV negative matched controls

## Main Findings

- N=11,190 patients with CHB → 1356 (12.1%) screened for HDV, primarily by GI/hepatology specialists (90.2%) rather than IM specialists (2.7%)
- HDV seropositivity was 88/1356 (6.4%) → high risk sexual behavior and endemic country of origin were most commonly identified risk factors → 18% of cases did not meet any risk-based criteria for screening
- HDV patients more likely to have baseline cirrhosis at diagnosis (55.5% vs. 16.4%,  $p < 0.01$ ) → numerically more decompensation (20.8 vs 0%), HCC (15.2 vs. 5.9%) and liver transplant (20.8 vs. 0%) at follow-up but not statistically significant

## Conclusions

- HDV may be underscreened in patients with CHB → not all patients with HDV had identifiable risk factors → HDV associated with higher risk of liver vents

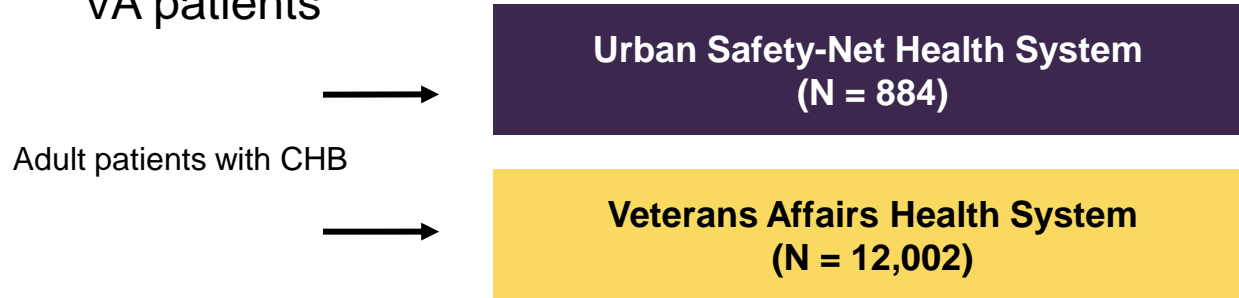
**Table 1. Baseline demographics and Outcomes Cases vs Controls**

	HDV Positive n=72	HDV negative n=67	P value
Mean Age at diagnosis	48	48	(matched)
Male (%)	45 (62.5)	45 (67.2)	(matched)
Mean BMI at diagnosis (SD)	27.2 (5.2)	26.8 (4.5)	(matched)
E antigen positive (%)	7 (9.7)	6 (8.9)	(matched)
Comorbidities (%)	HCV (11.1) HIV (8.3) HLD (13.9) HTN (13.9) DM (9.7) NAFLD (6.9)	HCV (1.5) HIV (11.9) HLD (7.4) HTN (14.9) DM (16.4) NAFLD (7)	
Cirrhosis (%) at the time of HDV diagnosis	40 (55.5)	11 (16.4)	<0.01
HBV (%) suppressed	49 (68.05)	26 (38.8)	<0.01
on HBV treatment	53 (73.6)	14 (20.9)	<0.01
Significant fibrosis by FIB-4 score calculation	68%	40%	0.001
Liver decompensation- Ascites, EV, HE (%)	15 (20.8)	0	NA
Developed HCC	11 (15.2)	4 (5.9)	0.07
Needed LT	15 (20.8)	0	NA
Death	2	2	0.94

Abbreviations: HDV= hepatitis D virus; BMI= body mass index; SD= standard deviation; HCV= hepatitis C virus; HIV= human immunodeficiency virus; HLD= hyperlipidemia; HTN= hypertension; DM= diabetes mellitus; NAFLD= non-alcoholic fatty liver disease; HBV= hepatitis B virus; FIB 4= fibrosis index; EV= Esophageal varices; HE= Hepatic encephalopathy, HCC= Hepatocellular carcinoma, LT= Liver transplantation

# HDV Prevalence Among Ethnically Diverse, Urban, Safety-Net Populations: Study Design

- Retrospective review of adult patients (age >18 yr) with CHB from 2010-2021 among a large urban safety-net health system and a national cohort of VA patients



*Cohorts stratified by age, sex, race/ethnicity, presence of cirrhosis, and other relevant risk factors*

- Primary outcome:** proportion of patients tested for HDV by any available testing method



# HDV Prevalence Among Ethnically Diverse, Urban, Safety-Net Populations: Patient Characteristics

- Higher HDV positivity in safety-net cohort may be due to higher prevalence of immigrant population and high-risk behaviors associated with HDV acquisition

Population, %	Urban Safety-Net Health System (N = 884)	Veterans Affairs Health System (N = 12,002)
Male	54	94
Black	35	42
Asian	29	10
Non-Hispanic White	28	40
HIV coinfectd	8.7	2.3
Cirrhosis	18.2	29.4
Tested for HDV	30	19.7
HDV positive	7.8 (95% CI 4.9-11.7)	3.1 (95% CI 2.4-3.8)



Slide credit: [clinicaloptions.com](http://clinicaloptions.com)

Wong. AASLD. 2022. Oral 20.



# Take-Home Points: Hepatitis Delta

- HDV testing rates in safety-net and VA cohorts with CHB were 20%-30% and varied by race and ethnicity, presence of liver disease, and age
  - Double reflex testing must be promoted and should become standard
  - Risk-based screening was underutilized; different screening strategies needed
- Bulevirtide monotherapy demonstrated similar efficacy to bulevirtide combined with pegIFN $\alpha$ -2a
- In patients with compensated cirrhosis, bulevirtide was associated with increasing virologic and biochemical responses over time out to Wk 72
- Potential on-treatment and long-term off-treatment benefit of lonafarnib
  - A large (N = 400) phase III study of lonafarnib was recently completed and data will be available in the next 4-8 wk



**Thank You!**

**Acknowledgements:**

**HDIN**

**Delta Patients and Their Families**

**Delta Cure Annual Meeting**