Risk of Liver-Related Events in Individuals With Hepatitis B Virus/HIV Coinfection With and Without Hepatitis Delta Virus

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Plain-Language Summary

There is limited understanding of triple infection with HBV/HIV/HDV. We examined liver health, HDV prevalence, and the risk of liver-related events in individuals living with HBV/HIV with and without HDV in the US. Those included in this study were identified via medical and pharmacy claims, electronic medical records, and hospital data. Individuals with HBV/HIV/HDV triple infection experienced more liver- and non–liver-related comorbidities and had worse liver health than those infected with HBV and HIV. Additionally, compared to those with HBV, individuals with HBV/HIV were more likely to have HDV infection and to be injection drug users. Further studies may reveal additional medical implications of triple infection with HBV/HIV/HDV.

References: **1.** Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32.

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Introduction

- Approximately 10% of individuals with HIV are coinfected with hepatitis B virus (HBV)[1]
- Limited data are available describing the natural history of triple infection with HBV/HIV/hepatitis delta virus (HDV)
- This study examined HDV prevalence among persons with HBV/HIV and examined baseline liver health and risk of liver-related events from US administrative claims data among individuals living with HBV/HIV with or without HDV

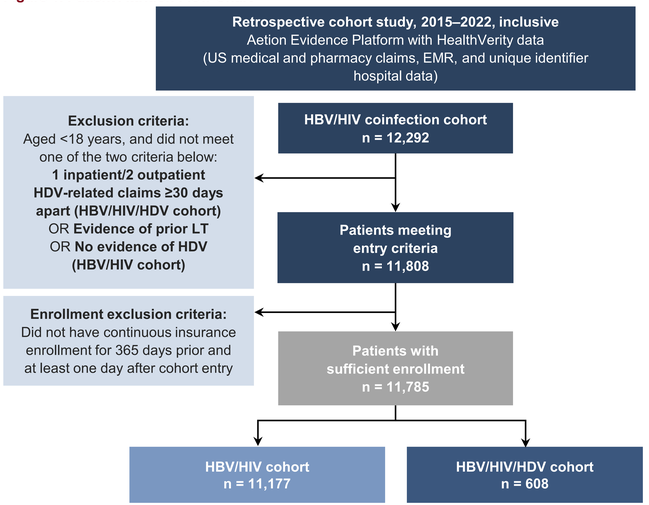
Methods

- A retrospective cohort study was conducted using a HealthVerity dataset, which included US medical and pharmacy claims, electronic medical records, and hospital data from years 2015 to 2022 for more than 100 million individuals
- Those included were ≥18 years of age at cohort entry with 1 inpatient or 2 outpatient *ICD-9/10-CM* codes at least 30 days apart for each type of viral infection
- Cohort entry was the date of the last infection among HBV, HIV, and HDV
- All included patients had 365 days of continuous insurance enrollment prior to and ≥1 day after cohort entry
- Cox proportional hazards methods were used to estimate the risk of liver-related events (cirrhosis, liver decompensation, hepatocellular carcinoma [HCC], and liver transplant [LT]) in individuals with vs without HDV
- Prevalence of HDV was assessed using any single HDV claim in any enrollment period from patients with HBV and HIV

Results

- Of the 12,292 patients with HBV/HIV coinfection, we identified 608 patients with HDV and 11,177 with no evidence of HDV (**Figure 1**)

Figure 1. Patient Attrition Flow Chart



EMR, electronic medical record; HBV, hepatitis B virus; HDV, hepatitis delta virus; LT, liver transplant.

Results

- Distributions of age and sex were similar between cohorts (**Table 1**)

Table 1. Cohort Demographics

		HBV/HIV (n = 11,177)	HBV/HIV/HDV (n = 608)
Sex[a]	Male	8561 (76.6)	462 (76.0)
	Female	2616 (23.4)	146 (24.0)
Age group[a]	18 to <35	921 (8.2)	47 (7.7)
	35 to <45	1951 (17.5)	103 (16.9)
	45 to <55	3762 (33.7)	185 (30.4)
	55 to <65	3619 (32.4)	213 (35.0)
	≥65	924 (8.3)	60 (9.9)

Data shown as n (%). [a]*P* >0.05; *P* ranges from 0.11–0.79
HBV, hepatitis B virus; HDV, hepatitis delta virus.

- Individuals with HDV were more likely to have liver-related and non–liver-related (renal, cardiac, and blood related) comorbidities at baseline (**Tables 2 and 3**)

Table 2. Liver-Related Baseline Comorbidities

	HBV/HIV (n = 11,177)	HBV/HIV/HDV (n = 608)	*P* value
Alcoholic hepatitis	76 (0.7)	8 (1.3)	0.12
Biliary cirrhosis	9 (0.1)	2 (0.3)	0.20
Chronic HCV	2748 (24.6)	180 (29.6)	<0.01
Elevated enzymes	1191 (10.7)	88 (14.5)	<0.01
Hyperbilirubinemia	6 (0.1)	0	1.00
MASLD, unspecific	928 (8.3)	64 (10.5)	0.06

Data shown as n (%).
HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; MASLD, metabolic dysfunction–associated steatotic liver disease.

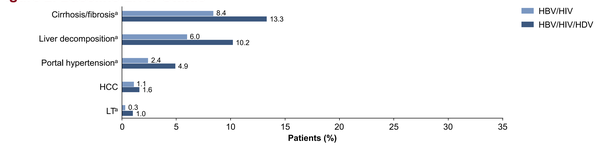
Table 3. Non–Liver-Related Baseline Comorbidities

Condition	HBV/HIV (n = 11,177)	HBV/HIV/HDV (n = 608)	*P* value
Anemia - nutrition related	1455 (13.1)	127 (20.9)	<0.01
Anemia - other causes	2931 (26.2)	223 (36.7)	<0.01
Angina	328 (3.4)	33 (5.4)	0.01
Arrhythmia	2529 (22.6)	165 (27.1)	0.01
Autoimmune disease	266 (2.4)	18 (3.0)	0.44
Cancer	1915 (17.1)	132 (21.7)	<0.01
Congestive heart failure	1155 (10.3)	72 (11.8)	0.26
COPD	3377 (30.2)	215 (25.4)	<0.01
Diabetes	2490 (22.3)	176 (28.9)	<0.01
Essential hypertension	5576 (49.9)	347 (57.1)	<0.01
Hyperlipidemia	4209 (37.7)	263 (43.3)	<0.01
Myocardial infarction	707 (6.3)	47 (7.7)	0.20
Renal insufficiency - acute	1634 (14.6)	133 (21.9)	<0.01
Renal insufficiency - chronic	2097 (18.8)	138 (22.7)	0.02
Stroke (ischemic)	637 (5.7)	46 (7.6)	0.07
Thrombocytopenia	1067 (9.5)	83 (13.7)	<0.01

Data shown as n (%).
COPD, chronic obstructive pulmonary disease; HBV, hepatitis B virus; HDV, hepatitis delta virus.

- Patients with HBV/HIV/HDV had significantly more liver-related comorbidities at baseline than those without HDV (**Figure 2**)

Figure 2. Baseline Liver Status



[a]*P* <0.01. Statistical comparisons are between HBV/HIV and HBV/HIV/HDV groups.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; LT, liver transplant.

- No notable differences were observed in the proportions of individuals treated with nucleos(t)ide analogues or antiretroviral therapy; in alcohol, tobacco, or drug use; or in the prevalence of obesity or mental health disorders at baseline (**Table 4**)

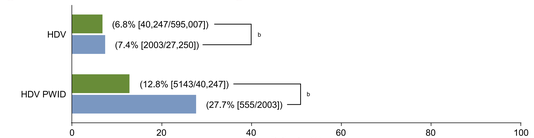
Table 4. Baseline Medications and Additional Conditions

	HBV/HIV (n = 11,177)	HBV/HIV/HDV (n = 608)	*P* value
Baseline medications, n (%)			
Interferon	3 (0.0)	2 (0.3)	0.01[a]
Nucleos(t)ide analogue	8128 (72.7)	460 (75.7)	0.12
Antidiabetics	1316 (11.8)	86 (14.1)	0.09
Antiretroviral therapy	8393 (75.1)	468 (77.0)	0.32
Additional conditions, n (%)			
Mental illness	7267 (65.0)	415 (68.3)	0.11
Substance abuse	5541 (49.6)	300 (49.3)	0.94
Use of alcohol	1594 (14.3)	92 (15.1)	0.59
Overweight/obese	1666 (14.9)	98 (16.1)	0.45
Smoking	5255 (47.0)	284 (46.7)	0.92
PWID	2714 (24.3)	169 (27.8)	0.06

[a]While significance was achieved, the comparison of 5 patients in the interferon group was underpowered.
HBV, hepatitis B virus; HDV, hepatitis delta virus; PWID, person who injects drugs.

- There was a higher prevalence of HDV coinfection among individuals with HBV/HIV compared to HBV (**Figure 3**)
- A higher proportion of patients with HBV/HIV/HDV coinfection had injection drug use compared to patients with HBV/HIV (**Figure 3**)

Figure 3. Prevalence[a] of HDV Among Patients With HBV and HBV/HIV Coinfection



[a]The prevalence of HDV was assessed using any single HDV claim in any enrollment period from patients with HBV and HIV. [b]*P* <0.01.
HBV, hepatitis B virus; HDV, hepatitis delta virus; PWID, person who injects drugs.

- The risk of cirrhosis was higher among patients with HBV/HIV and HDV coinfection compared to those without HDV coinfection though the confidence interval included 1
- Among individuals with HBV/HIV and evidence of cirrhosis at baseline, the risk of liver decompensation, HCC, or LT was higher in individuals with HDV coinfection than in those with no evidence of HDV (**Table 5**)

Table 5. Risk of Liver-Related Events in Individuals With and Without HDV Coinfection

Cohort	Individuals, n	Events, n	Person-Years	Hazard Ratio (95% CI)	Median FU Days (IQR)
Risk of cirrhosis among individuals with no baseline evidence of cirrhosis, hepatic decompensation, HCC, or LT					
HBV/HIV	9919	588	22,527	1.00	690 (316, 1241)
HBV/HIV/HDV	497	34	1087	1.20 (0.85–1.69)[a]	654 (313, 1157)
Risk of hepatic decompensation, HCC, and LT among individuals with compensated cirrhosis at baseline					
HBV/HIV	484	113	913	1.00	481 (316, 1241)
HBV/HIV/HDV	39	14	60	1.72 (0.99–3.00)[a]	363 (150, 872)

[a]Note that confidence intervals included 1.
FU, follow-up; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; IQR, interquartile range; LT, liver transplant.

Conclusions

- HDV infection was associated with worse liver health at baseline and increased risk of developing liver-related events in individuals with HBV/HIV coinfection
- In this dataset, the prevalence of HDV in general and in people who inject drugs was significantly higher among individuals with HBV/HIV coinfection vs the general HBV population