*TTU Journal of Biomedical Sciences 2023, **02**:71-76*
(RESEARCH ARTICLE) DOI: 10.53901/tjbs.2023.08.art08

Research article

Situation of HDV Infection in Adult Hepatitis B Patients at The Outpatient Clinic of Pasteur Institute in Ho Chi Minh City

Thu Huong Thi Nguyen [1], Thoi Van Dinh [1], Minh Ngoc Nguyen [1], Phuong Lan Thi Nguyen [1], Thu Thuy Thi Nguyen [1], Tuong Giao Hoang [1], Hai Hoang Hanh Do [1], My Linh Lam [1], Hoai Thu Mong Nguyen [1], Duy Quang Pham [1], Duc Hoang Nguyen [2,3], Thach Nguyen [4,5], Nghi Viet Tran [2,6,*]

[1] *Pasteur Institute Ho Chi Minh City, Vietnam*
[2] *Cardiovascular laboratories, Methodist Hospital, Merrillville, Indiana, USA*
[3] *Hanoi Medical University, Hanoi, Vietnam*
[4] *Tan Tao University, School of Medicine, Long An Province, Vietnam*
[5] *Cardiovascular Research Department, Methodist Hospital, Merrillville, IN, USA*
[6] *Weiss Memorial Hospital, Chicago, Illinois, USA*

***Corresponding author**:
Nghi V Tran, MD.
Department of Medicine, Louis A. Weiss Memorial Hospital, Chicago, IL, USA
Email: tranvietnghi2007@gmail.com

Article history: Manuscript received May 10, 2023; revised manuscript received June 16, 2023; accepted June 19, 2023.

ABSTRACT

Hepatitis D virus (HDV) infection, also known as delta virus, has been identified as a crucial risk factor contributing to severe complications among hepatitis B patients. Such complications arise as HDV accelerates the progression towards cirrhosis, exacerbates the risk of decompensated cirrhosis, and increases mortality rates compared to non-HDV hepatitis B infections. Despite its clinical significance, data on HDV infection remains scarce, and exhibits marked regional disparities in Viet Nam. This study endeavors to explore HDV co-infection in adult hepatitis B patients.

A descriptive cross-sectional investigation was conducted, involving 539 hepatitis B subjects attending the Outpatient Clinic of the Pasteur Institute in Ho Chi Minh City between October 2021 and May 5, 2022. The study sample featured three hepatocellular carcinoma (HCC) patients, 148 patients with elevated alanine aminotransferase (ALT) levels, and nine patients whose ALT levels exceeded five times the upper limit of normal (ULN). Additionally, 11 patients reported a history of blood transfusion, while no participants had any history of intravenous drug use.

Remarkably, the study did not document any instances of HDV co-infection among the subjects. These findings suggest that HDV screening may not be a routine recommendation for patients diagnosed with moderate or mild hepatitis B, particularly when presenting with low-risk factors. Further research is warranted to better understand the prevalence of HDV co-infection in this population and to guide the development of evidence-based screening guidelines.

KEYWORDS Hepatitis D, HDV, Anti-HDV, hepatitis B virus, HBV, Co-infection, Pasteur Institute, Ho Chi Minh City, Screening guidelines, Alanine aminotransferase (ALT), Hepatocellular carcinoma (HCC), Cirrhosis.

INTRODUCTION

In patients with hepatitis B virus (HBV), co-infection with hepatitis delta virus (HDV), also known as delta virus, is considered a leading factor in the development of severe complications such as rapidly progressing liver fibrosis, decompensated cirrhosis and death, compared to HBV infection alone [1], [2]. HDV uses the surface antigen of HBV (HBsAg) to enter and escape from liver cells; therefore, HDV-induced hepatitis only occurs in HBsAg-positive patients and can occur in the form of either co-infection or super-

infection with HBV. Despite the fact that HDV exacerbates the disease and accelerates the progression of complications in HBV-infected patients, research on HDV is still limited in Vietnam. In contrast, Vietnam is located in a high endemic area for HBV infection (with an HBV infection rate >8%). According to the World Health Organization's report in 2022, an estimated 296 million people worldwide were living with chronic HBV infection in 2019, with 820,000 deaths, mostly due to complications such as liver cirrhosis and hepatocellular carcinoma (HCC) [3]. It is estimated that approximately 9.5 million people are infected with HBV in Vietnam, which will be a burden on society in the coming decades due to complications related to HBV infection, such as liver cirrhosis and cancer [4].

According to WHO, there is approximately 5% of patients with HBV are co-infected with HDV [3]. A study by Stockdale AJ (2020) indicates that Mongolia, Moldova, and countries in the West and Central Africa are hotspots for HDV infection rates [5]. Meanwhile, research in the United States shows that the proportion of Asian chronic hepatitis B virus patients with positive Anti-HDV is 42% [6].

In recent years, diagnostic techniques for HDV have become increasingly refined and accessible at healthcare facilities in Vietnam. Additionally, new HDV treatment medications have been developed that improve treatment efficacy and significantly reduce side effects compared to older interferon-based treatments [7]. Therefore, identifying HDV infection status in patients with chronic hepatitis B virus can help establish a reasonable HDV infection strategy to timely detect and control the disease, as well as reduce the economic burden on patients with chronic hepatitis B virus, thereby improving their quality of life. The information from this study can also serve as a reference for the development of appropriate HDV prevention strategies by the Public Health and Preventive Medicine Department.

Currently, research on HDV in Vietnam is still very limited. Recent studies in the north of Vietnam, including Hanoi and several large cities, have shown that the HDV/HBV ratio ranges from 10% to 25% [4], [8], [9]. In contrast, a report from more than 15 years ago in Ho Chi Minh City showed a very low HDV co-infection rate in HBV-infected patients. However, the sample size of this study was small [10]. This study aims to investigate the prevalence of HDV infection in adult patients with chronic hepatitis B virus.

PERSPECTIVES

Knowledge

The present study contributes valuable insights into the current situation of HDV co-infection among adult hepatitis B patients in HoChiMinh City, Vietnam. By examining a diverse group of patients with varying risk factors, this investigation helps to elucidate the prevalence of HDV co-infection within this specific population. Despite the study's findings indicating a lack of HDV co-infection among the participants, it is essential to consider the limitations of the sample size and the regional context of the research. The results, therefore, may not be generalizable to the broader hepatitis B patient population in Vietnam or other countries with distinct epidemiological patterns. Further research is necessary to comprehensively understand the HDV co-infection landscape and its implications for hepatitis B patients.

Translational Outlook

The absence of HDV co-infection in this study's patient cohort raises critical questions about the necessity of routine HDV screening for individuals with moderate or mild hepatitis B, particularly those with low-risk factors. In light of these findings, healthcare practitioners and policymakers should reevaluate current screening guidelines and consider the development of more targeted, evidence-based recommendations. By refining the screening criteria for HDV co-infection, healthcare systems could potentially allocate resources more efficiently, directing them towards patients with higher risks or more severe hepatitis B infections. Ultimately, a better understanding of the prevalence and distribution of HDV co-infection may lead to improved patient outcomes and more effective strategies for managing hepatitis B and its associated complications.

METHODS

Research subjects

Inclusion criteria: Adult patients aged 18 years or older infected with HBV (both acute and chronic infection).

Exclusion criteria: Foreign patients.

Study location and time

From October 2021 to May 2022 in the Outpatient Department, Pasteur Institute Ho Chi Minh City.

Study design

Cross-sectional descriptive study

Sample size

The sample size was calculated using the following formula to estimate the proportion of the population:

$$n = \frac{Z^2_{(1-\alpha/2)}p(1-p)}{d^2}$$

Whereas: n is the minimum sample size for the study; $Z_{1-\alpha/2}$: confidence level (1.96); α: significance level (0.05); p: 15.4% (based on a study by Bui Tien Sy [9]); d: desired absolute error or precision decided by the researcher is 3.5 (%). Substituting these values, the minimum sample size required was $\geq$ 490 individuals. In reality, the study recruited 539 eligible patients who agreed to participate.

Sampling method

Whole sampling method.

Study variables

The study variables included demographic and socioeconomic variables (age, ethnicity, place of residence, occupation), variables related to the risk of infection (history of blood transfusion, drug injection, hemodialysis or blood filtration), variables related to family history (family member with liver cirrhosis, hepatocellular carcinoma), personal history (alcoholism, jaundice or hospitalization for hepatitis

treatment, previously diagnosed with cirrhosis, prior diagnosis of HCC, co-infection with hepatitis C virus (HCV), history or prior or current treatment for HBV, reason for this visit), and laboratory results variables (HBeAg, Anti-HBe, quantification of HBV DNA, Anti-HDV, AST, ALT, GGT).

Data collection method

The researchers conducted interviews with eligible participants using a pre-designed questionnaire, performed necessary examinations and tests for patients infected with HBV following the guidelines of the Ministry of Health, and ordered Anti-HDV tests for all participants. They also read and recorded the results of the tests in the study's medical records.

The anti-HDV test was performed using Dia.Pro Anti-HDV Dia.Pro (Italy). The test was an ELISA test that detects Anti-HDV IgG, with sensitivity and specificity $> 98\%$. Positive Anti-HDV samples were further tested for HDV RNA to determine current infection status (however, no positive Anti-HDV cases were recorded in the study, so this test was not used).

The biological specimens used for HBV testing were Elecsys HBsAg II, Elecsys HBeAg II, Elecsys Anti-HBe II, Elecsys Anti-HBc IgM II, and Anti-HCV, which were performed using ELISA. Blood samples with HBsAg ≥ 1.0 were considered positive for HBV. The biological specimen used for HCV testing was Elecsys Anti-HCV II and samples with Anti-HCV ≥ 1.0 were considered positive for HCV. The viral load of HBV was measured using the Tapman system with a detection threshold of 116 copies/ml. Liver function tests included AST and ALT, where ALT levels $\geq$ 35U/L were considered elevated in males and $\geq$ 25U/L in females, according to the 2019 Ministry of Health guidelines. These tests were performed according to standard procedures in the biochemistry laboratory at the Outpatient Clinic of the Pasteur Institute Ho Chi Minh City.

Data analysis

Data were entered using Epidata 8.0 software and analyzed using Stata 14.0 software. Descriptive statistics were used to describe quantitative variables using median, interquartile range (IQR), and qualitative variables using frequency and proportion.

Ethics and consent to participate

Ethical considerations were addressed in this study. The research protocol was approved by the Institutional Review Board for Biomedical Research at the Pasteur Institute Ho Chi Minh City under protocol number 50/GCN-PAS dated November 10, 2020. Patients were provided with an explanation of the study procedures and the benefits as well as risks of participation. Anti-HDV testing was performed free of charge. Follow-up tests for disease progression and HBV treatment were conducted in accordance with the 2019 Ministry of Health guidelines and did not violate ethical principles.

RESULTS

Between October 2021 and May 2022, 539 patients who met the study criteria were recruited. Table 1 presents the sociodemographic characteristics of the study population (n=539).

TABLE 1. Sociodemographic characteristics of the study population (n=539)

Characteristics		Median (min-max)	IQR
Age (years)		38 (18-82)	30-48
		Number	**Proportion (%)'**
Gender	Male	276	51.2
	Female	263	48.8
Ethnicity	Kinh	526	97.6
	Others	13	2.4
Area of residence	Ho Chi Minh City	372	69.0
	Others	167	31.0
Occupation	White collar occupation	244	45.3
	Blue collar occupation	72	13.4
	Others	222	41.3

The median age of the participants was 38 years (IQR 30-48). The oldest participant was 82 years old. The proportion of male and female participants in the study was relatively evenly distributed, with 51.2% and 48.8%, respectively. The majority of patients in the study were of the Kinh ethnicity (97.6%) and resided in Ho Chi Minh City (69.0%). Among the patients, 45.3% were categorized as having a white-collar occupation, while 13.4% were categorized as having a blue-collar occupation and 41.3% were classified as having other types of occupations, such as self-employment, trade, and so on.

Characteristics of prior family history, risk of infection, and medical history among participants.

The study found that up to 44% of participants had at least one family member (spouse, child, parent, sibling) currently infected with HBV, and 13.5% reported that their family members had not been screened for HBV. Among the study population, 42.5% did not have any family members currently infected with HBV. Additionally, 12.6% participants reported having family members (spouse, child, parent, sibling, grandparent, aunt/uncle on both mother's and father's side) with cirrhosis. Furthermore, 13.9% of participants reported having family members (spouse, child, parent, sibling, grandparent, aunt/uncle on both mother's and father's side) with HCC. The majority (86.1%) of participants did not have any family members with HCC.

In the study, only 11 out of 539 patients had a history of blood transfusion, accounting for 2%. The study did not report any patients with a history of or current injection drug use, blood filtering, or artificial kidney treatment.

As many as 91.1% of patients in the study were aware of their chronic HBV infection status, with this visit being for regular follow-up or to monitor treatment response. The

TABLE 2. Characteristics of prior family history, risk of infection, and medical history among participants (n=539). (TDF: Tenofovir disoproxil fumagate; TAF: Tenofovir alafelamide; *: diagnosed within a year.)

Characteristics		Median (min-max)	IQR
Time since HBV diagnosis (years)		8 (0*-30)	3-14
		Number	**Proportion (%)'**
Family members with HBV infection	Yes	273	44.0
	No	229	42.5
	Not specified	73	13.5
Family members with liver cirrhosis	Yes	68	12.6
	No	471	87.4
Family members with HCC	Yes	75	13.9
	No	464	86.1
History of blood transfusion	Yes	11	2.0
	No	528	98.0
History of intravenous drug use	Yes	0	0.0
	No	539	100
History of hemodialysis	Yes	0	0.0
	No	539	100
Alcoholism	Yes	3	0.6
	No	536	99.4
History of acute hepatitis B infection	Yes	16	3.0
	No	523	97.0
Reason for HBV diagnosis	Chronic HBV infection	490	91.1
	Regular check-up	22	4.1
	HBV vaccination checkup	08	1.5
	Others (pregnancy, mandatory testing, blood donation, visa, surgical clearance)	18	3.3
Antiviral treatment	Previously treated	42	7.8
	Currently treated	126	23.4
	Never	371	68.8
Antiviral drugs	TDF or TAF	141	81.0
	Lamivudine	7	4.0
	Entecavir	6	3.5
	TDF/Emtricitabine	1	0.6
	Unknown	19	10.9

TABLE 3. Clinical and laboratory characteristics of the study subjects (n=539). (*: included 9 cases with acute hepatitis.)

Characteristics		Median (min-max)	IQR
ALT (U/L)		24 (8-589)	18-35
AST (U/L)		24 (10-729)	19-30
HBV DNA (log10cps/ml) (n=267)		3.5	0-5.4
		Number	**Proportion (%)'**
HBeAg and Anti-HBe (n=403)	$HBeAg^+$	114	28.3
	$Anti\text{-}HBe^+$	284	70.5
	Both positive	04	1.2
	Not Tested	136	
Severity of HBV infection	HCC	03	0.6
	Acute hepatitis	09	1.7
	HBV with elevated ALT*	148	27.5
	HBV without elevated ALT	388	71.9
Co-infected with HCV		04	0.7
Anti-HDV	Positive	0	0.0
	Negative	539	100

remaining 4.1% of patients were newly diagnosed with HBV infection, with 1.5% being detected during routine health check-ups and 3.3% detected during screening for prenatal care, preoperative evaluation, blood donation, military conscription examination, or medical examinations required for overseas labor migration. The study identified 16 out of 539 (3%) patients who reported jaundice and yellowing of the skin and had to receive outpatient or inpatient treatment for acute exacerbation of hepatitis.

The median duration of HBV infection among patients in the study was 8 years (IQR 3-14). Among them, 38 patients were newly diagnosed with HBV infection. The longest known duration of HBV infection in the study was 30 years. Of the patients, 7.8% had received antiviral treatment for HBV, 23.4% were currently undergoing treatment, and 68.8% had never received treatment. Of those who had received or were currently receiving treatment, 81.0% were being treated with TDF or TAF, 4% had received Lamivudine, and 3.5% and 0.6% were being treated with Entecavir and TDF/Emtricitabine, respectively. A total of 10.9% of patients had received specialized treatment, and it was unclear what medication they had received.

Clinical and laboratory characteristics of the study subjects.

The median levels of ALT and AST were 24U/L (IQR 18-35) and 24U/L (IQR 19-30), respectively. Among 403

individuals who underwent HBeAg testing, 28.3% were HBeAg positive and Anti-HBe negative, 70.5% were Anti-HBe positive and HBeAg negative, and four patients (0.2%) were positive for both HBeAg and Anti-HBe. Around 136 patients had unknown HBeAg status as the testing was not indicated due to the unavailability of testing reagents at the Pasteur Institute. Of the 267 patients who underwent viral load testing, the median viral load was 3.5 log10cps/ml (IQR 0-5.35). Four patients (0.7%) had positive Anti-HCV or had received HCV treatment.

Regarding disease severity, three patients (0.6%) had progressed to hepatocellular carcinoma, 27.4% of HBV-infected patients had elevated ALT levels, and 71.9% of HBV-infected patients had normal ALT levels. Among these, nine patients (1.7%) had ALT levels five times the upper limit of normal (ULN) and in the range (135-589U/L), which were classified as acute exacerbation of hepatitis B.

The characteristics of HDV coinfection among study subjects

All 539 study subjects in this investigation had negative Anti-HDV test results. Therefore, the prevalence of HDV infection in the study population was 0% (Table 3).

DISCUSSION

The positive rate of Anti-HDV in the study population was 0%. This finding is consistent with the results of previous studies conducted in Ho Chi Minh City in 2003 (78 patients) and Thai Binh province in 2007 (159 patients), which reported HDV infection rates of 0% and 1.3%, respectively [10], [11]. In comparison with studies conducted in the Central and Northern regions, as well as Linda Dunford's study, our study showed a significant difference. Specifically, Nguyen Hung Minh's study in the South Central provinces in 2017 reported that 25 out of 250 (10%) HBV-infected patients had positive HDV RNA, and most Delta viruses in this study were genotype 2. The study population mostly consisted of patients with mild chronic hepatitis B, which is similar to our study population [8]. Meanwhile, Bui Tien Sy's study in Hanoi in 2014, which included 266 hospitalized patients with acute or chronic hepatitis B, cirrhosis, or HCC, reported an HDV infection rate of 15.4%, with most Delta viruses being genotype 1 [9]. This study focused on a group of patients with severe liver disease or complications requiring inpatient treatment, which may explain why the HDV infection rate was higher than in our study. As many studies have shown, HDV-HBV coinfection, especially with genotype 1 HDV, is more likely to lead to severe chronic hepatitis B progression [1], [2]. Finally, Linda Dunford's study in 2012, which was conducted in five provinces (Hanoi, Hai Phong, Da Nang, Khanh Hoa, and Can Tho) and included 318 patients with chronic hepatitis B, showed a positive Anti-HDV rate of 10.7%. This study had a large number of patients with a previous history of intravenous drug use (78/318), and the positive Anti-HDV rate was 25.6%. When compared to our study population, this study had a much higher rate of intravenous drug use (78/318 vs. 0/539), and we already know that HDV is highly transmissible through contaminated needles [4].

Upon comparing our study with some research conducted in the region, such as in Taiwan and China, we observed the following: Wei et al. conducted a surveillance study on Anti-HDV among 346 patients with hepatitis B virus (HBV) infection in several districts in Taiwan in 2021, and found that the prevalence of Anti-HDV was 1.15% (4/346), and all four of these patients tested negative for HDV RNA, indicating a zero prevalence of HDV infection in the study, which is consistent with our findings [12]. In contrast, a study conducted in 2015 on patients with HBV-related complications in central hospitals of major cities found a prevalence of 4.4% [13]. Additionally, a study in China screened for Anti-HDV in 4103 HBV-infected patients and 1661 non-HBV-infected patients and found hotspots for HDV in Inner Mongolia (13.9%) and among intravenous drug users (9.3%-31.8%), whereas no Anti-HDV-positive cases were reported among 2634 HBV-infected patients in many large urban areas, and the study did not report any positive cases among the non-HBV-infected group [14]. Based on these research data, low-risk HBV-infected patients with mild to moderate clinical symptoms had a very low prevalence of Anti-HDV.

The comparisons above demonstrate that our study is the sixth study conducted in Vietnam and the second study in Ho Chi Minh City regarding HDV infection. This study had the largest number of participants to date, and the study participants represent the population of chronic HBV-infected individuals who are being monitored and treated on an outpatient basis. While the results of this study differ significantly from those of studies conducted in other regions of Vietnam, they are consistent with the results of a study conducted in Ho Chi Minh City in 2003. This suggests that the population of HBV-infected individuals in Ho Chi Minh City and the southern region, in general, have a very low rate of HDV infection.

Study limitations and recommendations

The study did not identify any positive Anti-HDV cases, which may be explained by the following limitations. First, the study only recruited outpatients with chronic HBV infection, who were in the early and mild stages of hepatitis B virus (HBV) infection and had a low risk of blood-borne infections, such as a 2% transmission rate of blood transfusions, with no cases of intravenous drug use. Second, the true prevalence of HDV infection among HBV-infected patients in the southern region may be very low, and thus the sample size of the study may not have been sufficient. Third, the sensitivity of the Anti-HDV test used in the study was not 100% (>98%).

Therefore, further studies with larger sample sizes and greater diversity in the recruitment of participants and the locations of recruitment are recommended to obtain more complete and accurate data on the prevalence of HDV infection in the southern region and throughout the country.

CONCLUSION

The prevalence of Anti-HDV in HBV-infected patients in this study was 0%. The majority of HBV-infected patients in this study were those with mild or moderate clinical symptoms and had a low risk of infection. The study identified 03/539 HCC patients, 148/539 patients with elevated ALT, and 9/539 patients with acute exacerbation of hepatitis B.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

REFERENCES

[1] Puigvehí M, Moctezuma-Velázquez C, Villanueva A et al."The oncogenic role of hepatitis delta virus in hepatocellular carcinoma." JHEP reports : innovation in hepatology, Aug. 2019, 1:120–130, DOI: 10.1016/j.jhepr.2019.05.001, PMID: 32039360.

[2] Romeo R, Petruzziello A, Pecheur EI et al."Hepatitis delta virus and hepatocellular carcinoma: an update." Epidemiology and infection, Oct. 2018, 146:1612–1618, DOI: 10.1017/S0950268818001942, PMID: 29991359.

[3] "Hepatitis B." [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

[4] Dunford L, Carr MJ, Dean J et al."A multicentre molecular analysis of hepatitis B and blood-borne virus coinfections in Viet Nam." PloS one, 2012, 7:e39 027, DOI: 10.1371/journal.pone.0039027, PMID: 22720022.

[5] Stockdale AJ, Kreuels B, Henrion MYR et al."The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis." Journal of hepatology, Sep. 2020, 73:523–532, DOI: 10.1016/j.jhep.2020.04.008, PMID: 32335166.

[6] Patel EU, Thio CL, Boon D et al."Prevalence of Hepatitis B and Hepatitis D Virus Infections in the United States, 2011-2016." Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, Aug. 2019, 69:709–712, DOI: 10.1093/cid/ciz001, PMID: 30605508.

[7] Mentha N, Clément S, Negro F et al."A review on hepatitis D: From virology to new therapies." Journal of advanced research, May. 2019, 17:3–15, DOI: 10.1016/j.jare.2019.03.009, PMID: 31193285.

[8] Nguyen HM, Sy BT, Trung NT et al."Prevalence and genotype distribution of hepatitis delta virus among chronic hepatitis B carriers in Central Vietnam." PloS one, 2017, 12:e0 175 304, DOI: 10.1371/journal.pone.0175304, PMID: 28403190.

[9] Sy BT, Ratsch BA, Toan NL et al."High prevalence and significance of hepatitis D virus infection among treatment-naïve HBsAg-positive patients in Northern Vietnam." PloS one, 2013, 8:e78 094, DOI: 10.1371/journal.pone.0078094, PMID: 24205106.

[10] Tran HTT, Ushijima H, Quang VX et al."Prevalence of hepatitis virus types B through E and genotypic distribution of HBV and HCV in Ho Chi Minh City, Vietnam." Hepatology research : the official journal of the Japan Society of Hepatology, Aug. 2003, 26:275–280, DOI: 10.1016/s1386-6346(03)00166-9, PMID: 12963426.

[11] Nguyen VTT, McLaws ML, Dore GJ"Highly endemic hepatitis B infection in rural Vietnam." Journal of gastroenterology and hepatology, Dec. 2007, 22:2093–2100, DOI: 10.1111/j.1440-1746.2007.05010.x, PMID: 17645465.

[12] Lee WC, Chen TK, Han HF et al."Investigating the prevalence and clinical effects of hepatitis delta viral infection in Taiwan." Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi, Oct. 2021, 54:901–908, DOI: 10.1016/j.jmii.2021.03.014, PMID: 34162528.

[13] Hsieh MH, Wang SC, Hsieh MY et al."Hepatitis D virus infections among injecting drug users with and without human immunodeficiency virus infection in Taiwan." The Kaohsiung journal of medical sciences, Oct. 2016, 32:526–530, DOI: 10.1016/j.kjms.2016.08.004, PMID: 27742037.

[14] Roggenbach I, Chi X, Lempp FA et al."HDV Seroprevalence in HBsAg-Positive Patients in China Occurs in Hotspots and Is Not Associated with HCV Mono-Infection." Viruses, Sep. 2021, 13, DOI: 10.3390/v13091799, PMID: 34578380.