

World Journal of *Hepatology*

World J Hepatol 2024 April 27; 16(4): 490-660



EDITORIAL

- 490 Erdafitinib and checkpoint inhibitors for first-line and second-line immunotherapy of hepatic, gastrointestinal, and urinary bladder carcinomas: Recent concept
Wishahi M
- 494 Progress of mitochondrial and endoplasmic reticulum-associated signaling and its regulation of chronic liver disease by Chinese medicine
Zheng Y, Zheng YH, Wang JH, Zhao TJ, Wang L, Liang TJ
- 506 Subclinical hepatitis E virus genotype 1 infection: The concept of “dynamic human reservoir”
Shrestha A, Basnet S, KC S
- 511 Metabolic dysfunction-associated steatotic liver disease: A silent pandemic
Samanta A, Sen Sarma M

REVIEW

- 517 Spectrum of COVID-19 induced liver injury: A review report
Singh L, Kumar A, Rai M, Basnet B, Rai N, Khanal P, Lai KS, Cheng WH, Asaad AM, Ansari S
- 537 Multifaceted roles of lymphatic and blood endothelial cells in the tumor microenvironment of hepatocellular carcinoma: A comprehensive review
Li JJ, Mao JX, Zhong HX, Zhao YY, Teng F, Lu XY, Zhu LY, Gao Y, Fu H, Guo WY
- 550 Quantitative hepatitis B core antibody and quantitative hepatitis B surface antigen: Novel viral biomarkers for chronic hepatitis B management
Leowattana W, Leowattana P, Leowattana T
- 566 Molecular mechanism of nanomaterials induced liver injury: A review
Das SK, Sen K, Ghosh B, Ghosh N, Sinha K, Sil PC

ORIGINAL ARTICLE

Case Control Study

- 601 Expression and clinical significance of short-chain fatty acids in patients with intrahepatic cholestasis of pregnancy
Ren SJ, Feng JT, Xiang T, Liao CL, Zhou YP, Xuan RR

Retrospective Cohort Study

- 612 *Klebsiella pneumoniae* infections after liver transplantation: Drug resistance and distribution of pathogens, risk factors, and influence on outcomes
Guo L, Peng P, Peng WT, Zhao J, Wan QQ

Retrospective Study

- 625** Development and validation of a nomogram for predicting in-hospital mortality of intensive care unit patients with liver cirrhosis

Tang XW, Ren WS, Huang S, Zou K, Xu H, Shi XM, Zhang W, Shi L, Lü MH

Prospective Study

- 640** Prospective study of hepatitis B and D epidemiology and risk factors in Romania: A 10-year update

Iacob S, Gheorghe L, Onica M, Huiban L, Pop CS, Brisc C, Sirli R, Ester C, Brisc CM, Diaconu S, Rogoveanu I, Sandulescu L, Vuletic D, Trifan A

SYSTEMATIC REVIEWS

- 650** Relative carcinogenicity of tacrolimus *vs* mycophenolate after solid organ transplantation and its implications for liver transplant care

Liu D, Youssef MM, Grace JA, Sinclair M

ABOUT COVER

Peer Reviewer of *World Journal of Hepatology*, Somchai Amornyotin, MD, Professor, Staff Physician, Department of Anesthesiology and Siriraj Gastrointestinal Endoscopy Center, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. somchai.amo@mahidol.ac.th

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJH* as 2.4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yi-Xuan Cai, Production Department Director: Xiang Li, Cover Editor: Xiang Li.

NAME OF JOURNAL

World Journal of Hepatology

ISSN

ISSN 1948-5182 (online)

LAUNCH DATE

October 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF

Shuang-Suo Dang

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5182/editorialboard.htm>

PUBLICATION DATE

April 27, 2024

COPYRIGHT

© 2024 Baishideng Publishing Group Inc

PUBLISHING PARTNER

Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

POLICY OF CO-AUTHORS

<https://www.wjgnet.com/bpg/GerInfo/310>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER's OFFICIAL WEBSITE

http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html



Prospective Study

Prospective study of hepatitis B and D epidemiology and risk factors in Romania: A 10-year update

Speranta Iacob, Liana Gheorghe, Mirela Onica, Laura Huiban, Corina Silvia Pop, Ciprian Brisc, Roxana Sirli, Carmen Ester, Cristina Mihaela Brisc, Sorina Diaconu, Ion Rogoveanu, Larisa Sandulescu, Deiana Vuletici, Anca Trifan

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sargsyants N, Armenia

Received: December 6, 2023

Peer-review started: December 6, 2023

First decision: January 19, 2024

Revised: February 19, 2024

Accepted: March 22, 2024

Article in press: March 22, 2024

Published online: April 27, 2024



Speranta Iacob, Liana Gheorghe, Mirela Onica, Corina Silvia Pop, Carmen Ester, Sorina Diaconu, Department of Gastroenterology, Carol Davila University of Medicine and Pharmacy, Bucharest 050474, Romania

Speranta Iacob, Liana Gheorghe, Mirela Onica, Carmen Ester, Department of Gastroenterology and Hepatology, Fundeni Clinical Institute, Bucharest 022328, Romania

Laura Huiban, Department of Gastroenterology, Grigore T Popa University of Medicine and Pharmacy, Iasi 700115, Romania

Laura Huiban, Anca Trifan, Institute of Gastroenterology and Hepatology, Saint Spiridon County Hospital, Iasi 700111, Romania

Corina Silvia Pop, Department of Gastroenterology and Medical Oncology, University Emergency Clinical Hospital, Bucharest 050098, Romania

Ciprian Brisc, Cristina Mihaela Brisc, Faculty of Medicine and Pharmacy, University of Oradea, Oradea 410087, Romania

Ciprian Brisc, Cristina Mihaela Brisc, Department of Gastroenterology, Emergency County Hospital, Oradea 410169, Romania

Roxana Sirli, Deiana Vuletici, Center for Advanced Research in Gastroenterology and Hepatology, Department of Gastroenterology and Hepatology, "Victor Babeș" University of Medicine and Pharmacy, Timisoara 300041, Romania

Roxana Sirli, Deiana Vuletici, Department of Gastroenterology and Hepatology, Timiș County Emergency Clinical Hospital "Pius Branzeu", Timisoara 300723, Romania

Sorina Diaconu, Department of Internal Medicine II and Gastroenterology, University Emergency Clinical Hospital, Bucharest 050098, Romania

Ion Rogoveanu, Department of Gastroenterology, University of Medicine and Pharmacy, Craiova 200349, Romania

Ion Rogoveanu, Department of Cardiology, Emergency County Hospital, Craiova 200642, Romania

Larisa Sandulescu, Department of Gastroenterology, Research Center of Gastroenterology and

Hepatology, University of Medicine and Pharmacy, Craiova 200349, Romania

Larisa Sandulescu, Department of Gastroenterology, Emergency County Hospital, Craiova 200642, Romania

Anca Trifan, Department of Gastroenterology, Faculty of Medicine, Grigore T Popa University of Medicine and Pharmacy, Iasi 700115, Romania

Corresponding author: Liana Gheorghe, MD, PhD, Doctor, Professor, Department of Gastroenterology, Carol Davila University of Medicine and Pharmacy, Dionisie Lupu Street 37, Bucharest 050474, Romania. drlgheorghe@gmail.com

Abstract

BACKGROUND

The global burden of hepatitis D virus (HDV) infection represents a major medical challenge and a public health crisis worldwide. However, there is a lack of accurate data on the epidemiology and risk factors for HDV. Hepatitis B virus (HBV) and HDV coinfection causes the most severe form of viral hepatitis, leading to a higher cumulative incidence of liver-related events compared with HBV mono-infection, including the need for liver transplantation and death.

AIM

To investigate the epidemiology, natural history, risk factors and clinical management of HBV and HDV coinfection in Romanian patients.

METHODS

This prospective study was conducted between January and July 2022 in six tertiary gastroenterology and hepatology referral centres in Romania. All consecutive adults admitted for any gastroenterology diagnosis who were HBV-positive were enrolled. Patients with acute hepatitis or incomplete data were excluded. Of the 25390 individuals who presented with any type of gastroenterology diagnosis during the study period, 963 met the inclusion criteria. Testing for anti-HDV antibodies and HDV RNA was performed for all participants. Demographic and risk factor data were collected by investigators using medical charts and patient questionnaires. All data were stored in an anonymized online database during the study.

RESULTS

The prevalence of HBV was 3.8%; among these patients, the prevalence of HBV/HDV coinfection was 33.1%. The median age of the study population was 54.0 years, and it consisted of 55.1% men. A higher prevalence of HBV/HDV coinfection was observed in patients 50–69 years old. Patients with HBV/HDV coinfection were significantly older than those with HBV mono-infection ($P = 0.03$). Multivariate multiple regression analysis identified female gender ($P = 0.0006$), imprisonment ($P < 0.0001$), older age at diagnosis ($P = 0.01$) and sexual contact with persons with known viral hepatitis ($P = 0.0003$) as significant risk factors for HDV.

CONCLUSION

This study shows that HDV infection among those with HBV remains endemic in Romania and updates our understanding of HDV epidemiology and associated risk factors. It emphasizes the need for systematic screening for HDV infection and collaborative initiatives for controlling and preventing HBV and HDV infection.

Key Words: Epidemiology; Hepatitis B; Hepatitis D; Natural history; Risk factors; Romania

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In this study, we investigated the epidemiology, natural history, risk factors and clinical management of hepatitis B virus (HBV) and hepatitis D virus (HDV) coinfection in Romanian patients. We found that HDV infection among those with HBV remains endemic and identified the following significant risk factors associated with HBV/HDV chronic hepatitis: female gender, older age at diagnosis, sexual contact with persons with known viral hepatitis and imprisonment. This study emphasizes the need for systematic screening for HDV infection, subsequent reflex testing of HDV RNA and collaborative initiatives for controlling, treating and preventing HBV and HDV infection.

Citation: Jacob S, Gheorghe L, Onica M, Huiban L, Pop CS, Brisc C, Sirli R, Ester C, Brisc CM, Diaconu S, Rogoveanu I, Sandulescu L, Vuletic D, Trifan A. Prospective study of hepatitis B and D epidemiology and risk factors in Romania: A 10-year update. *World J Hepatol* 2024; 16(4): 640-649

URL: <https://www.wjgnet.com/1948-5182/full/v16/i4/640.htm>

DOI: <https://dx.doi.org/10.4254/wjh.v16.i4.640>

INTRODUCTION

Hepatitis D virus (HDV) requires hepatitis B virus (HBV) to infect humans; it uses the envelope proteins of HBV, which acts as a helper virus for HDV entry and infection of hepatocytes[1]. Chronic HDV infection causes the most severe form of viral hepatitis, associated with accelerated progression to cirrhosis and a higher cumulative incidence of events including hepatic decompensation, liver failure, hepatocellular carcinoma, liver transplantation and liver-related death[1-5]. The global burden of HDV infection represents a major medical challenge and a public health crisis worldwide. Data on prevalence and health burden are patchy and heterogeneous owing to a lack of awareness, systematic population-based screening and accurate diagnostic assays[6]. Three large meta-analyses estimated the pooled global seroprevalence of HDV infection to be 0.2%-1.0% among the general population, 4.5%-14.6% among people who are hepatitis B surface antigen (HBsAg)-positive and 14.6%-18.6% among patients with chronic liver disease attending hepatology clinics[2,7,8]. These figures would correspond to an estimated burden of 12-72 million people living with serological evidence of HDV infection worldwide.

There is significant geographic variability in the prevalence of HDV infection, driven by various factors such as coverage of HBV vaccination, routes of transmission, hygiene, socio-economic conditions, migration and viral heterogeneity[1,9,10]. HDV infection is hyperendemic in certain geographic hotspots and populations called 'endemic pockets', including Eastern European countries such as Romania[1,9]. Mass migration from these HDV endemic areas in the early 2000s has prompted a rise in the HDV prevalence in some Western European countries[3,11-13]. Therefore, efforts to update our understanding of the HDV prevalence, particularly in endemic pockets, will guide strategies to decrease HDV infection Europe-wide.

The availability of efficacious and specific treatment options for HDV is limited. The World Health Organization (WHO) recommends pegylated interferon- α therapy for HDV infection; however, treatment efficacy is low and side effects are common[14,15]. Nucleos(t)ide analogues are recommended for control of HBV infection in patients with HBV/HDV coinfection if there is evidence of ongoing HBV replication[6]. The antiviral bulevirtide, which inhibits HBV and HDV entry into hepatocytes, received conditional European marketing authorization in 2020 for HDV infection in adults with compensated liver disease[16]. However, pegylated interferon- α remains the only HDV treatment recommended by the Romanian National Health Insurance House, suggesting that there may be issues with treatment access in endemic pockets[17].

With the development and emerging availability of dedicated antiviral therapeutics for HDV, an updated understanding of the epidemiology and clinical management of HDV infection is needed to allow more accurate targeting of high-risk populations for diagnosis and treatment. Epidemiological data on HBV/HDV coinfection in Romania have been published previously[18-20]. However, these data were collected more than 10 years ago and may no longer be accurate owing to healthcare policy changes, including the implementation of double reflex testing following an internal policy agreement between gastroenterology centre hepatologists and virologists. Double reflex testing refers to the testing of anti-HDV antibodies in patients with HBV, followed by HDV RNA testing in patients with a positive anti-HDV antibodies test result[21]. Therefore, this study aims to update our understanding of the epidemiology, natural history, risk factors and clinical management of HBV and HDV coinfection in patients in Romania.

MATERIALS AND METHODS

This short-term prospective study was conducted between January and July 2022 in six tertiary gastroenterology and hepatology referral centres in Romania, covering approximately 70%-80% of the population from all geographical regions of the country [Bucharest (two referral centres), Craiova, Iasi, Oradea, Timisoara]. All adults (≥ 18 years) admitted for any gastroenterology diagnosis who were HBV-positive were eligible, and the specific disease stage of each participant upon enrolment was classified using International Classification of Diseases-10 codes[22]. If a participant was hospitalized multiple times during the study period, data were collected only during their first admission. Patients with acute hepatitis or incomplete data were excluded. The number of admissions of any gastroenterology diagnosis during the study period was also recorded.

All HBV-positive participants were tested for anti-HDV immunoglobulin G antibodies by enzyme-linked immunosorbent assays (HDV antibody ELISA kit, Dia.Pro, Milan, Italy), following implementation of a policy agreement between hepatologists and virologists at our gastroenterology centres. If the test result for anti-HDV antibodies was positive, subsequent reflex testing of HDV RNA was also performed by single and nested polymerase chain reaction amplifications of a highly conserved region of the HDV genome, using primers selected from genotype 1 of HDV (RoboGene HDV RNA Quantification Kit 2.0, Roboscreen GmbH, Leipzig, Germany). Demographic data on gender, age, area of residence, education, and partner status were collected by the participating investigators using a patient

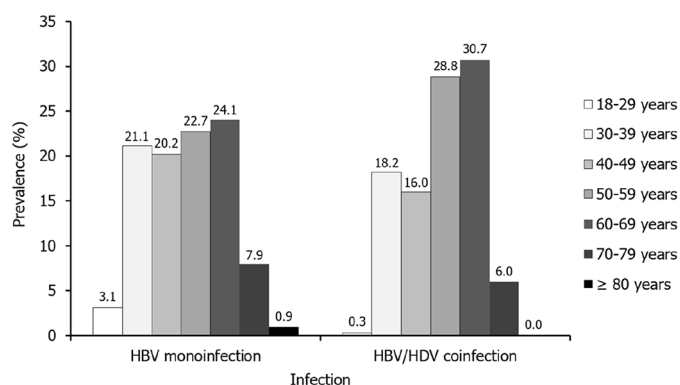


Figure 1 Prevalence of hepatitis B virus monoinfection and hepatitis B virus/hepatitis D virus coinfection across different age groups. A statistically significant difference in overall prevalence was identified between those with hepatitis B virus (HBV) monoinfection and HBV/hepatitis D virus coinfection ($P = 0.001$). HBV: Hepatitis B virus; HDV: Hepatitis D virus.

questionnaire. Data were collected on disease stage and therapeutic history from the admission medical charts. Risk factors for HBV and HDV infection were collected using both patient questionnaires and medical charts. All data were stored in an anonymized online database during the study.

The study was approved by the institutional ethics committees and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Fundeni Clinical Institute obtained the ethical approval to enrol patients across all hospitals included in this study. Written informed consent was obtained from each participant before enrolment.

The prevalence of HBV monoinfection and HBV/HDV coinfection was calculated with a 95% CI. Qualitative or quantitative variables were analysed using non-parametric Chi-square, Kruskal-Wallis or Mann-Whitney U tests, as appropriate. Using multivariate multiple regression analysis, variables identified as risk factors for HBV/HDV coinfection from the univariate multiple regression analysis were investigated. These variables included sociodemographic factors [participant age, gender, residence (urban or rural) and education level [no or elementary school, high school, college/university] and medical history (previous documented coronavirus disease 2019 or comorbid diabetes mellitus). The HBV vaccination status of participants and their life partners was also included, as were the existence of any known family members positive for HBV/hepatitis C virus (HCV)/HDV (monoinfection or coinfection) and sexual contact with a partner positive for HBV/HCV/HDV (monoinfection or coinfection). In addition, exposure to healthcare procedures was considered; variables included were an occupational risk of exposure to blood products, history of blood transfusion, haemodialysis in antecedents (long-term or incidental owing to complications in an intensive care unit), any surgery before diagnosis (excluding dental surgery), at least one hospitalization before diagnosis and any dental surgery before diagnosis. Other risk factors included as variables were any history of severe accidents (work, traffic, domestic), record of accidents with blood-contaminated objects, history of injections at home or at an outpatient unit, imprisonment (current or previous), tattoos or any body piercing, injecting drug use, multiple sexual partners in the past three years, previous sexually transmitted diseases and history of abortions in improper conditions. All statistical tests were two-sided, and a P value of less than 0.05 was used to indicate statistical significance.

RESULTS

During the study period, 25390 individuals with any gastroenterology disease were admitted to the six study centres, of whom 963 individuals were HBV-positive, were eligible, provided informed consent and were enrolled into the study. Therefore, the hospital-based prevalence of HBV infection was 3.8% (95% CI: 1.8-5.8). The relative per-centre distribution of patients with HBV enrolled in the study was as follows: Bucharest (40.3%), Iasi (29.3%), Oradea (19.0%), Timisoara (7.8%) and Craiova (3.6%). Among those 963 patients who were HBV-positive, the prevalence of HBV/HDV coinfection was 33.1% (95% CI: 31.2-35.1).

A comparison of patient characteristics between those with HBV monoinfection and those with HBV/HDV coinfection is shown in [Table 1](#). Overall, the median age of the study population was 54.0 years. Participants with HBV/HDV coinfection were significantly older than participants with HBV monoinfection (mean age \pm SD, 53.5 \pm 11.7 vs 51.6 \pm 13.6 years, $P = 0.03$; [Table 1](#)). Upon assessment of prevalence data within 10-year age brackets, a relatively equal distribution of HBV monoinfection was noted among patients aged between 30 years and 69 years (20.2%-24.1%, [Figure 1](#)). In contrast, there was an unequal distribution of HBV/HDV coinfection among the age groups, with the majority of those with HBV/HDV coinfection aged between 50 years and 69 years (59.5%).

The study population consisted of 531 men (55.1%) with a median age of 53.0 years, and 432 women (44.9%) with a median age of 54.0 years ($P = 0.16$). The proportion of men was lower in those with HBV/HDV coinfection than in those with HBV monoinfection (48.3% vs 58.5%, $P = 0.002$). Women with HBV/HDV coinfection were older than women with HBV monoinfection (mean \pm SD, 55.5 \pm 11.4 years vs 51.2 \pm 13.4 years, $P = 0.002$). In contrast, ages were similar between men with HBV monoinfection and HBV/HDV coinfection ($P = 0.67$).

Table 1 Demographic and clinical data for patients with hepatitis B virus mono-infection or hepatitis B virus/hepatitis D virus coinfection, %

Variable	HBV mono-infection (n = 644)	HBV/HDV coinfection (n = 319)	P value
Sex			
Female	41.5	51.7	0.002 ^a
Male	58.5	48.3	0.002 ^a
Age, mean ± SD, yr			
Total	51.6 ± 13.6	53.5 ± 11.7	0.03 ^a
Female	51.2 ± 13.4	55.5 ± 11.4	0.002 ^a
Male	51.8 ± 13.6	51.3 ± 11.7	0.67
Time since HBV diagnosis, mean ± SD, months	86.2 ± 3.4	112.8 ± 7.1	0.36
Stage of disease at diagnosis			< 0.0001 ^a
Chronic hepatitis	87.9	73.1	
Compensated liver cirrhosis	9.9	19.4	
Decompensated liver cirrhosis	2.2	7.5	
Hepatocellular carcinoma at diagnosis	2.6	4.1	0.22
HBeAg-positive	5.1	3.3	0.19
Liver stiffness measurement at therapy initiation, mean ± SD, kPa	8.7 ± 3.3	10.9 ± 5.7	0.003 ^a
HBV DNA serum level at diagnosis, mean ± SD, IU/mL	2994542.8 ± 3014.7	610025.3 ± 158.9	< 0.0001 ^a
Past or current pegylated interferon-α therapy	14.6	42.5	< 0.0001 ^a
Current nucleos(t)ide analogue therapy	70.3	36.4	< 0.0001 ^a
Previous documented COVID-19	40.8	34	0.0003 ^a
Associated diabetes mellitus	11.2	7.5	0.07

^a*P* < 0.05, statistically significant *P* values.

COVID-19: Coronavirus disease 2019; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; HDV: Hepatitis D virus.

Diagnosis of HBV/HDV coinfection was obtained by HDV antibody reflex testing in 75.7% of patients. In the remaining patients with coinfection, the HDV diagnosis was delayed by a mean time of 34.7 months. Regarding the serological profile of HBV infection, 59.2% of patients positive for HBsAg had anti-hepatitis B e antigen-positive antibodies. A positive HDV RNA viral load at diagnosis was observed in 86.5% of patients; the median HDV viral load was 16200 IU/mL (range: Undetectable to 3570742 IU/mL). HBV viremia was less than 20 IU/mL in 1.79% and 27.9% of patients with HBV mono-infection and HBV/HDV coinfection at diagnosis, respectively.

Liver stiffness at therapy initiation was higher in patients with HBV/HDV coinfection than in those with HBV mono-infection (mean ± SD, 10.9 ± 5.7 kPa *vs* 8.7 ± 3.3 kPa, *P* = 0.003). The distribution of fibrosis stages (F) according to the METAVIR score[23] in patients with HBV/HDV coinfection who had received antiviral therapy with pegylated interferon-α was as follows: F0 2.7%, F1 11.8%, F2 32.6%, F3 41.2% and F4 11.8%. There were statistically significant differences in disease stage at diagnosis, with patients with HBV/HDV coinfection having an increased likelihood of compensated and decompensated liver cirrhosis compared with patients with HBV mono-infection (*P* < 0.0001).

More than 90% of patients with HBV/HDV coinfection were treated, with 42.5% and 36.4% of patients receiving pegylated interferon-α therapy and nucleos(t)ide analogues, respectively (Table 1). Combination therapy of pegylated interferon-α and nucleos(t)ide analogues was received by 49.6% of patients with HBV/HDV coinfection.

Independent risk factors for HDV infection were identified from analysis of medical chart and patient questionnaire data. Female gender (*P* = 0.002) and older age at HBV/HDV diagnosis (*P* = 0.03) were identified from the medical chart data as risk factors for coinfection, while statistical analysis of the patient questionnaire data identified the following significant risk factors (Table 2): Education level (*P* = 0.0006), sexual contact with a partner positive for HBV/HCV/HDV (*P* = 0.0001), blood transfusion (*P* = 0.0004), haemodialysis in antecedents (*P* < 0.0001), at least one hospitalization before diagnosis (*P* < 0.0001), any dental surgery before diagnosis (*P* < 0.0001), serious accidents [work, traffic, domestic (*P* < 0.0001)], accidents with blood-contaminated objects (*P* < 0.0001), injections at home/outpatient unit (*P* < 0.0001), imprisonment [current or previous (*P* < 0.0001)], tattoos/any body piercing (*P* < 0.0001), injecting drug use (*P* < 0.0001), multiple sexual partners in the past 3 years (*P* = 0.001) and sexually transmitted diseases (*P* < 0.0001).

Multivariate regression analysis identified the following independent risk factors for HBV/HDV coinfection in Romanian patients: female gender (*P* = 0.0006), imprisonment (current or previous) (*P* < 0.0001), older age at diagnosis (*P*

Table 2 Risk factors for hepatitis D virus infection based on the patient questionnaire data

Variable, %	HBV monoinfection (n = 644)	HBV/HDV coinfection (n = 319)	P value
Urban area	59.0	51.5	0.06
Education level			0.0006 ^a
No or elementary school (0 to 8 yr)	17.6	24.3	
High school (12 yr)	48.7	55.7	
College/university	33.7	20	
Vaccination against HBV (any dose)	15.6	12.5	0.25
Life partner vaccinated against HBV (any dose)	26.5	30.3	0.41
Known family members positive for HBV/HCV/HDV (monoinfection or coinfection)	18.4	20.5	0.48
Sexual contact with a partner positive for HBV/HCV/HDV (monoinfection or coinfection)	4.6	12.5	0.0001 ^a
Occupation with risk of exposure to blood products	3.9	6.2	0.17
Blood transfusion	18.4	30	0.0004 ^a
Haemodialysis in antecedents (long-term or incidental owing to a complication in ICU)	2.5	15.9	< 0.0001 ^a
Any surgery before diagnosis (excluding dental surgery)	58.1	52.7	0.16
At least one hospitalization before diagnosis	82.3	65	< 0.0001 ^a
Any dental surgery before diagnosis	83	67	< 0.0001 ^a
Serious accidents (work, traffic, domestic)	8.4	21.3	< 0.0001 ^a
Accidents with blood-contaminated objects	5.5	19	< 0.0001 ^a
Injections at home/outpatient unit	4.8	16.7	< 0.0001 ^a
Imprisonment (current or previous)	0.2	15.5	< 0.0001 ^a
Tattoos/any body piercing	15	29.5	< 0.0001 ^a
Injecting drug use	0.5	10.5	< 0.0001 ^a
Multiple sexual partners in the past 3 years	15.9	25.6	0.001 ^a
Previous sexually transmitted diseases	2.3	8.9	< 0.0001 ^a
Abortions (improper conditions) ¹	3.3	5.9	0.14

^a*P* < 0.05, statistically significant *P* values.¹Abortion was restricted between 1966 and 1989 in Romania.

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Hepatitis D virus; ICU: Intensive care unit.

= 0.01) and sexual contact with a partner positive for either HBV/HCV/HDV (*P* = 0.0003).

DISCUSSION

This short-term, prospective study updates our understanding of the epidemiology, natural history, risk factors, diagnostic methodology and treatments for HBV/HDV coinfection in Romania. Our study data suggest that Romania is still an HDV endemic pocket as the prevalence of HBV/HDV coinfection was high, with 33.1% anti-HDV antibody positivity among patients with HBV. In comparison, a prospective study of nearly 900 participants conducted in 2019

reported that the prevalence of anti-HDV antibodies among patients with HBV in Italy was more than threefold lower than the Romanian data reported here, at 9.9%[24]. Interestingly, the prevalence of HBV infection varied widely between the different sites in this study (3.6%-40.3%), probably influenced by regional variations in the quality of healthcare services across the country, exposure to risk factors for HBV infection and per-centre addressability[25].

We observed a change in the demographic characteristics of those with HBV/HDV coinfection compared with our previous epidemiological study population from 2011[18]. In this study conducted in 2022, there were proportionally more female patients with HDV, and patients were older compared with the previous study, with the prevalence peaking among those aged 60-69 years, an increase of 10 years from the previous study. In the present study, there was a significant difference in prevalence between those with HBV monoinfection and HBV/HDV coinfection. A relatively equal distribution in the prevalence of HBV monoinfection was noted among participants aged between 30 years and 70 years, whereas the prevalence of HBV/HDV coinfection was markedly higher in those aged 50-69 years than in those younger than 50 years. This may reflect the different modalities of acquiring HBV compared with HDV infection. The observed age-related trends suggest a cumulative risk of HDV exposure over time, as well as a cohort phenomenon of HDV infection in Romania. These demographic data highlighting age as a risk factor are similar to studies from our group and others on HCV, HBV and HDV infection[25-27]. The profile of risk factors for HDV coinfection has changed from the previous epidemiological study and now includes both nosocomial and sexually transmitted infections, similar to several Western European countries[18,28-30].

A higher proportion of women had HBV/HDV coinfection than HBV monoinfection in the current study. Abortion was restricted between 1966 and 1989 in Romania[31]. Unsafe abortion practices, particularly in settings where access to safe reproductive healthcare services was limited, may have posed a significant risk of viral transmission. Historical practices, policies and societal conditions may have shaped patterns of infection transmission and healthcare practices, leading to disparities between genders.

HBV vaccination was noted in 15.6% and 12.5% of people with HBV monoinfection and HBV/HDV coinfection, respectively. The effectiveness of the HBV vaccine can be reduced in people with certain risk factors, including older age, obesity or other chronic illnesses[32]. Some study participants may not have received all doses of the vaccine required for full protection[33]. The difference in HBV vaccination rates between these groups probably reflects a combination of factors related to healthcare access, provider practices, patient characteristics and the complex interplay between HBV and HDV infections.

Although guideline recommendations for HDV screening vary, the recently published European Association for the Study of the Liver (EASL) clinical practice guidelines have highlighted the importance of universal screening and double reflex testing in patients who are HBsAg-positive[6,34,35]. Owing to the high prevalence of HBV/HDV in Romania, this strategy is now standard practice following a policy agreement between hepatologists and virology specialists from the tertiary gastroenterology centres where testing is performed. Reflecting this, in our study diagnosis of HDV coinfection was obtained by the above approach in 75.7% of participants. The virological profile of the helper virus was similar to other observational studies: predominantly hepatitis B e antigen-negative, with an undetectable or low HBV viral load and significant fibrosis (\geq F2 METAVIR) in most individuals[36-38]. Compared with our previous epidemiological study, HDV viral load was positive in a higher proportion of patients, probably due to the extensive use of double reflex testing and the improved sensitivity of the kits used for quantification of HDV viremia[6,18]. Our data, therefore, support the adoption of double reflex testing policies at a national level. If this is not possible, high-risk groups such as prisoners could be prioritized[39,40].

HDV infection is associated with various comorbidities. Our data confirm that chronic HDV infection is associated with advanced liver fibrosis, advanced liver disease, chronic progressive hepatitis, compensated and decompensated cirrhosis, and hepatocellular carcinoma, in line with the published literature in this area[4,19,41,42]. HBV monoinfection has a milder evolution and a decreased risk of liver transplantation for decompensated liver cirrhosis or hepatocellular carcinoma compared with HBV/HDV coinfection[19,43,44]. There are studies showing that HDV coinfection can constrain HBsAg evolution and modulate the emergence of drug-resistance profiles, thus highlighting the need to optimize the use of existing antiviral therapies and find new therapeutic targets against HDV infection[45,46].

Antiviral treatment of hepatitis D has been demonstrated to prevent cirrhosis, liver failure and hepatocarcinoma[47, 48]. Most patients were treated for HDV in our practice setting, with pegylated interferon- α therapy (42.5%) and nucleos(t)ide analogues (36.4%) being the most commonly used treatments, in line with the 2017 EASL clinical practice guidelines for HBV/HDV coinfection[49]. These data reflect both the severity of disease and the lack of available therapies. At present, approved treatment options for chronic HDV infection are limited to pegylated interferon- α in most countries, even though its efficacy has been demonstrated to be low and it is frequently associated with significant side effects[14,15]. The HBV/HDV entry inhibitor bulevirtide, approved by the European Medicines Agency for the treatment of adult patients with compensated liver disease when the presence of HDV RNA has been confirmed by blood tests, demonstrated its efficacy and safety as a monotherapy or combined with pegylated interferon- α in clinical trials and real-world studies[16,50,51]. Bulevirtide is the only anti-HDV therapeutic option approved within the past decade that may improve the long-term prognosis of these patients. Bulevirtide is also being investigated in patients with chronic HDV, with and without compensated cirrhosis[52,53]. However, there are still several issues to be addressed, such as the optimal duration of treatment, the rates of off-therapy responses, associated costs and the cost-benefit ratio in relation to the need for liver transplantation. Other promising investigational agents are in development, including the prenylation inhibitor lonafarnib, nucleic acid polymers and an interferon subtype distinct from interferon- α , interferon- λ [54].

This study has several limitations, which should be considered. A larger sample size would have increased the statistical power of the study for the detection of HDV infection risk factors. The use of patient questionnaires may have resulted in a bias in the reported data. Additionally, enrolling patients from a hospital-based cohort may have resulted in selection bias, and the HDV prevalence may be overestimated owing to the severity of chronic liver disease that requires

evaluation and admittance to hospital. However, the global HDV prevalence may be underestimated owing to the lack of universal HDV screening in the people who are HBsAg-positive or among selected high-risk populations. In contrast, the prevalence data presented in this study benefit from Romania's implementation in tertiary hepatology clinics of double reflex testing in patients who are HBsAg-positive. As this study was conducted in Romania, the findings may not be generalizable to other populations or settings. Cultural, socioeconomic, and healthcare system differences between Romania and other countries could affect the prevalence and risk factors for HBV/HDV coinfection. Extended efforts should be made to elucidate the true HDV disease burden across the globe to enable the development of public health strategies to achieve HDV elimination, one of the WHO's global health strategy targets[55]. The implementation of the recommendations regarding screening, characterization, therapy and monitoring of HDV infection in the latest EASL guidelines will facilitate this aim[6]. Continued implementation of preventive measures for HDV transmission, along with increasing coverage of HBV vaccination and further development of innovative, efficacious, targeted therapies for both HBV and HDV remain crucial for policy-makers and healthcare providers.

CONCLUSION

In conclusion, HBV/HDV coinfection remains endemic in Romania, with a heterogeneous distribution across the country. Demographic characteristics of patients with HBV/HDV coinfection have changed in comparison to a similar study conducted over 10 years ago, suggesting a cumulative risk of HDV exposure over time. Encouragingly, national policy decisions regarding double reflex testing have elevated HDV detection rates. Further rollout of preventive measures and development of treatments will aid efforts to eliminate HDV globally.

FOOTNOTES

Author contributions: Jacob S, Gheorghe L, Pop CS, and Trifan A were involved in the study design and concept; Onica M, Huiban L, Brisc C, Sirli R, Ester C, Brisc CM, Diaconu S, Rogoveanu I, Sandulescu L, and Vuleti D acquired the data; Jacob S performed the data analysis; Jacob S and Gheorghe L interpreted the data; all authors were involved in drafting the manuscript, provided critical revisions for important intellectual content, approved the final version submitted for publication and agreed to be accountable for all aspects of the work.

Supported by Gilead Sciences Europe Ltd.

Institutional review board statement: The study was approved by the institutional ethics committees and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Fundeni Clinical Institute obtained the ethical approval to enrol patients across all hospitals included in this study.

Informed consent statement: All study participants provided informed written consent before study enrolment.

Conflict-of-interest statement: Medical writing support was provided by Joe Jones, PhD, of PharmaGenesis London, London, United Kingdom, with funding provided by Gilead Sciences Europe Ltd.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Romania

ORCID number: Speranta Jacob 0000-0002-7805-5920; Liana Gheorghe 0000-0001-6244-1686; Mirela Onica 0000-0002-7489-1841; Laura Huiban 0000-0002-3044-0715; Corina Silvia Pop 0000-0001-8739-1961; Ciprian Brisc 0000-0003-4416-2848; Roxana Sirli 0000-0002-0179-1014; Carmen Ester 0009-0001-6779-9131; Cristina Mihaela Brisc 0000-0003-3603-8070; Sorina Diaconu 0000-0001-9882-9981; Ion Rogoveanu 0000-0002-3385-098X; Larisa Sandulescu 0000-0001-7696-3733; Deiana Vuleti 0009-0005-6629-5280; Anca Trifan 0000-0001-9144-5520.

S-Editor: Li L

L-Editor: A

P-Editor: Yu HG

REFERENCES

- 1 Koh C, Heller T, Glenn JS. Pathogenesis of and New Therapies for Hepatitis D. *Gastroenterology* 2019; **156**: 461-476.e1 [PMID: 30342879 DOI: 10.1053/j.gastro.2018.09.058]

- 2 **Chen HY**, Shen DT, Ji DZ, Han PC, Zhang WM, Ma JF, Chen WS, Goyal H, Pan S, Xu HG. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut* 2019; **68**: 512-521 [PMID: 30228220 DOI: 10.1136/gutjnl-2018-316601]
- 3 **Manesis EK**, Vourli G, Dalekos G, Vasiliadis T, Manolaki N, Hounta A, Koutsounas S, Vafiadis I, Nikolopoulou G, Giannoulis G, Germanidis G, Papatheodoridis G, Touloumi G. Prevalence and clinical course of hepatitis delta infection in Greece: a 13-year prospective study. *J Hepatol* 2013; **59**: 949-956 [PMID: 23850875 DOI: 10.1016/j.jhep.2013.07.005]
- 4 **Farci P**, Niro GA. Clinical features of hepatitis D. *Semin Liver Dis* 2012; **32**: 228-236 [PMID: 22932971 DOI: 10.1055/s-0032-1323628]
- 5 **Alfaite D**, Clément S, Gomes D, Goossens N, Negro F. Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies. *J Hepatol* 2020; **73**: 533-539 [PMID: 32151618 DOI: 10.1016/j.jhep.2020.02.030]
- 6 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines on hepatitis delta virus. *J Hepatol* 2023; **79**: 433-460 [PMID: 37364791 DOI: 10.1016/j.jhep.2023.05.001]
- 7 **Stockdale AJ**, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, Hutin Y, Geretti AM. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. *J Hepatol* 2020; **73**: 523-532 [PMID: 32335166 DOI: 10.1016/j.jhep.2020.04.008]
- 8 **Miao Z**, Zhang S, Ou X, Li S, Ma Z, Wang W, Peppelenbosch MP, Liu J, Pan Q. Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection. *J Infect Dis* 2020; **221**: 1677-1687 [PMID: 31778167 DOI: 10.1093/infdis/jiz633]
- 9 **Vlachogiannakos J**, Papatheodoridis GV. New epidemiology of hepatitis delta. *Liver Int* 2020; **40**: 48-53 [PMID: 32077599 DOI: 10.1111/liv.14357]
- 10 **Alexopoulou A**, Dourakis SP. Genetic heterogeneity of hepatitis viruses and its clinical significance. *Curr Drug Targets Inflamm Allergy* 2005; **4**: 47-55 [PMID: 15720236 DOI: 10.2174/1568010053622867]
- 11 **Cross TJ**, Rizzi P, Horner M, Jolly A, Hussain MJ, Smith HM, Vergani D, Harrison PM. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. *J Med Virol* 2008; **80**: 277-282 [PMID: 18098143 DOI: 10.1002/jmv.21078]
- 12 **Wedemeyer H**, Heidrich B, Manns MP. Hepatitis D virus infection—not a vanishing disease in Europe! *Hepatology* 2007; **45**: 1331-1332; author reply 1332 [PMID: 17464980 DOI: 10.1002/hep.21590]
- 13 **Ordieres C**, Navascués CA, González-Diéguez ML, Rodríguez M, Cadahía V, Varela M, Rodrigo L. Prevalence and epidemiology of hepatitis D among patients with chronic hepatitis B virus infection: a report from Northern Spain. *Eur J Gastroenterol Hepatol* 2017; **29**: 277-283 [PMID: 27902514 DOI: 10.1097/MEG.0000000000000795]
- 14 **World Health Organization**. Hepatitis D. Jul 20, 2023. [cited 2 November 2023]. Available from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-d>
- 15 **Wedemeyer H**, Yurdaydin C, Dalekos GN, Erhardt A, Çakaloğlu Y, Değertekin H, Gürel S, Zeuzem S, Zachou K, Bozkaya H, Koch A, Bock T, Dienes HP, Manns MP; HIDIT Study Group. Peginterferon plus adefovir versus either drug alone for hepatitis delta. *N Engl J Med* 2011; **364**: 322-331 [PMID: 21268724 DOI: 10.1056/NEJMoa0912696]
- 16 **European Medicines Agency**. Hepcludex. [cited 2 November 2023]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex>
- 17 **Casa Națională de Asigurări de Sănătate**. Protocoale terapeutice. [cited 2 November 2023]. Available from: <https://cnas.ro/protocoale-terapeutice/>
- 18 **Gheorghe L**, Csiki IE, Iacob S, Gheorghe C, Trifan A, Grigorescu M, Motoc A, Suceveanu A, Curescu M, Caruntu F, Sporea I, Brisc C, Rogoveanu I, Cerban R, Tugui L, Alexandrescu A. Hepatitis Delta Virus Infection in Romania: Prevalence and Risk Factors. *J Gastrointest Liver Dis* 2015; **24**: 413-421 [PMID: 26697566 DOI: 10.15403/jgld.2014.1121.244.dtv]
- 19 **Gheorghe L**, Iacob S, Simionov I, Vadan R, Gheorghe C, Iacob R, Parvulescu I, Constantinescu I. Natural history of compensated viral B and D cirrhosis. *Rom J Gastroenterol* 2005; **14**: 329-335 [PMID: 16400347]
- 20 **Grigorescu M**, Pascu O, Acalovschi M, Radu C. What is the real prevalence of the D virus infection in chronic hepatitis and liver cirrhosis in Romania? *Rom J Gastroenterol* 2003; **12**: 179-182 [PMID: 14502316]
- 21 **National Institute of Public Health Romania**. The National Framework Plan for the viral hepatitis control in Romania, 2019-2030, coordinated by the Ministry of Health Romania. [cited 2 November 2023]. Available from: <https://www.globalhep.org/about/partner-programs/national-framework-plan-viral-hepatitis-control-romania-2019-2030>
- 22 **World Health Organization**. ICD-10. 2019. [cited 2 November 2023]. Available from: <https://icd.who.int/browse10/2019/en>
- 23 **Bedossa P**, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; **24**: 289-293 [PMID: 8690394 DOI: 10.1002/hep.510240201]
- 24 **Stroffolini T**, Ciancio A, Furlan C, Vinci M, Fontana R, Russello M, Colloredo G, Morisco F, Coppola N, Babudieri S, Ferrigno L, Sagnelli C, Sagnelli E. Migratory flow and hepatitis delta infection in Italy: A new challenge at the beginning of the third millennium. *J Viral Hepat* 2020; **27**: 941-947 [PMID: 32338810 DOI: 10.1111/jvh.13310]
- 25 **Gheorghe L**, Csiki IE, Iacob S, Gheorghe C. The prevalence and risk factors of hepatitis B virus infection in an adult population in Romania: a nationwide survey. *Eur J Gastroenterol Hepatol* 2013; **25**: 56-64 [PMID: 22968488 DOI: 10.1097/MEG.0b013e328358b0bb]
- 26 **Gheorghe L**, Csiki IE, Iacob S, Gheorghe C, Smira G, Regep L. The prevalence and risk factors of hepatitis C virus infection in adult population in Romania: a nationwide survey 2006 - 2008. *J Gastrointest Liver Dis* 2010; **19**: 373-379 [PMID: 21188327]
- 27 **Tahaei SM**, Mohebbi SR, Azimzadeh P, Behelgard A, Sanati A, Mohammadi P, Khanyaghma M, Hosseini Razavi A, Sharifian A, Zali MR. Prevalence of hepatitis D virus in hepatitis B virus infected patients referred to Taleghani hospital, Tehran, Iran. *Gastroenterol Hepatol Bed Bench* 2014; **7**: 144-150 [PMID: 25120894]
- 28 **Manghisi OG**, Guglielmi V, Cozzolongo R, Buongiorno G, Cuppone R, Ragnini F, Pirrelli M, Rosina F. [The risk factors for hepatitis D viral infection in southern Italy]. *Minerva Gastroenterol Dietol* 1996; **42**: 11-16 [PMID: 8652736]
- 29 **Beudeker BJB**, Voermans JJC, GeurtsvanKessel CH, de Knecht RJ, Kuhlemann T, Boonstra A, van der Eijk AA. Prevalence of hepatitis delta virus among chronic hepatitis B carriers in a large tertiary center in the Netherlands. *J Clin Virol* 2021; **141**: 104870 [PMID: 34182298 DOI: 10.1016/j.jcv.2021.104870]
- 30 **Jackson C**, Gunson RN, Bradley-Stewart A, Bennett S, Black H, Kennedy N, Bell DJ. Epidemiology and patient characteristics of hepatitis D virus infection in the West of Scotland 2011-2016. *J Viral Hepat* 2018; **25**: 1395-1396 [PMID: 29851188 DOI: 10.1111/jvh.12939]
- 31 **Indaco Lege**. Decretul nr. 770/1966 pentru reglementarea intreruperii cursului sarcinii. [cited 2 November 2023]. Available from: <https://Lege5.ro/gratuit/g43dqmzt/decretul-nr-770-1966-pentru-reglementarea-intreruperii-cursului-sarcinii>
- 32 **Hepatitis B Foundation**. Vaccination: vaccine non-responders. [cited 16 February 2024]. Available from: <https://www.hepb.org/prevention->

- and-diagnosis/vaccination/vaccine-non-responders/
- 33 **Hepatitis B Foundation.** Vaccine for Hepatitis B. [cited 16 February 2024]. Available from: <https://www.hepb.org/prevention-and-diagnosis/vaccination/>
 - 34 **Sarin SK,** Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]
 - 35 **Terrault NA,** Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]
 - 36 **Bahcecioglu IH,** Aygun C, Gozel N, Poyrazoglu OK, Bulut Y, Yalniz M. Prevalence of hepatitis delta virus (HDV) infection in chronic hepatitis B patients in eastern Turkey: still a serious problem to consider. *J Viral Hepat* 2011; **18**: 518-524 [PMID: 20546500 DOI: 10.1111/j.1365-2893.2010.01329.x]
 - 37 **Da BL,** Rahman F, Lai WC, Kleiner DE, Heller T, Koh C. Risk Factors for Delta Hepatitis in a North American Cohort: Who Should Be Screened? *Am J Gastroenterol* 2021; **116**: 206-209 [PMID: 33027083 DOI: 10.14309/ajg.0000000000000954]
 - 38 **Bakhshipour A,** Mashhadi M, Mohammadi M, Nezam SK. Seroprevalence and risk factors of hepatitis delta virus in chronic hepatitis B virus infection in Zahedan. *Acta Med Iran* 2013; **51**: 260-264 [PMID: 23690107]
 - 39 **Pashangzadeh S,** SeyedAlinaghi S, Dadras O, Pashaei Z, Soleymanzadeh M, Barzegary A, Mirzapour P, Vahedi F, Fakhfour A, Noori T, Hossein Irani SM, Mehraeen E, Jahanfar S. Prevalence of Hepatitis in Prisoners: A Systematic Review of Current Evidence. *Infect Disord Drug Targets* 2022; **22**: 61-72 [PMID: 35726418 DOI: 10.2174/1871526522666220620115006]
 - 40 **Diaconu S,** Filip P, Tiuca N, Tomescu A, Dugan C. Preliminary data from the viral hepatitis microelimination project through HCV/HBV screening in prisoners in Romania [presentation]. Proceedings of the 41st National Congress of Gastroenterology, Hepatology and Digestive Endoscopy; 2023 Jun 7-10
 - 41 **Naoumov NV,** Gueorgiev A, Ognyanov M, Maleev A. Infection with hepatitis delta virus in patients with fulminant hepatitis B and chronic HBsAg carriers in Bulgaria. *Hepatogastroenterology* 1986; **33**: 49-51 [PMID: 3721387]
 - 42 **Wranke A,** Pinheiro Borzacov LM, Parana R, Lobato C, Hamid S, Ceausu E, Dalekos GN, Rizzetto M, Turcanu A, Niro GA, Lubna F, Abbas M, Ingiliz P, Buti M, Ferenci P, Vanwolleghem T, Hayden T, Dashdorj N, Motoc A, Cornberg M, Abbas Z, Yurdaydin C, Manns MP, Wedemeyer H, Hardtke S; Hepatitis Delta International Network. Clinical and virological heterogeneity of hepatitis delta in different regions world-wide: The Hepatitis Delta International Network (HDIN). *Liver Int* 2018; **38**: 842-850 [PMID: 28963781 DOI: 10.1111/liv.13604]
 - 43 **Kushner T,** Da BL, Chan A, Dieterich D, Sigel K, Saberi B. Liver Transplantation for Hepatitis D Virus in the United States: A UNOS Study on Outcomes in the MELD Era. *Transplant Direct* 2022; **8**: e1253 [PMID: 34957333 DOI: 10.1097/TXD.0000000000001253]
 - 44 **Ho E,** Deltenre P, Nkuize M, Delwaide J, Colle I, Michielsens P; Belgian Association for the Study of the Liver. Coinfection of hepatitis B and hepatitis delta virus in Belgium: a multicenter BASL study. Prospective epidemiology and comparison with HBV mono-infection. *J Med Virol* 2013; **85**: 1513-1517 [PMID: 23852675 DOI: 10.1002/jmv.23653]
 - 45 **Colagrossi L,** Salpini R, Scutari R, Carioti L, Battisti A, Piermatteo L, Bertoli A, Fabeni L, Minichini C, Trimoulet P, Fleury H, Nebuloso E, De Cristofaro M, Cappiello G, Spanò A, Malagnino V, Mari T, Barlattani A, Iapadre N, Lichtner M, Mastroianni C, Lenci I, Pasquazzi C, De Sanctis GM, Galeota Lanza A, Stanzione M, Stornaiuolo G, Marignani M, Sarmati L, Andreoni M, Angelico M, Ceccherini-Silberstein F, Perno CF, Coppola N, Svicher V. HDV Can Constrain HBV Genetic Evolution in HBsAg: Implications for the Identification of Innovative Pharmacological Targets. *Viruses* 2018; **10** [PMID: 29987240 DOI: 10.3390/v10070363]
 - 46 **Lucifora J,** Delphin M. Current knowledge on Hepatitis Delta Virus replication. *Antiviral Res* 2020; **179**: 104812 [PMID: 32360949 DOI: 10.1016/j.antiviral.2020.104812]
 - 47 **Yuen MF,** Chen DS, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, Peters MG, Lai CL. Hepatitis B virus infection. *Nat Rev Dis Primers* 2018; **4**: 18035 [PMID: 29877316 DOI: 10.1038/nrdp.2018.35]
 - 48 **Buti M,** Roade L, Riveiro-Barciela M, Esteban R. Optimal management of chronic hepatitis B patients receiving nucleos(t)ide analogues. *Liver Int* 2020; **40**: 15-21 [PMID: 32077604 DOI: 10.1111/liv.14367]
 - 49 **European Association for the Study of the Liver.** EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]
 - 50 **Asselah T,** Loureiro D, Le Gal F, Narguet S, Brichler S, Bouton V, Abazid M, Boyer N, Giuly N, Gerber A, Tout I, Maylin S, Bed CM, Marcellin P, Castelnau C, Gordien E, Mansouri A. Early virological response in six patients with hepatitis D virus infection and compensated cirrhosis treated with Bulevirtide in real-life. *Liver Int* 2021; **41**: 1509-1517 [PMID: 33999515 DOI: 10.1111/liv.14950]
 - 51 **De Ledinghen V,** Guyader D, Metivier S, Hilleret M-N, Fontaine H, Roche B, Carrie NG, Alteroche LD, Ratti VL, Gervais A. Safety and efficacy of 2mg bulevirtide in patients with chronic HBV/HDV co-infection: first real-world results French early access program. Proceedings of the AASLD: The Liver Meeting; 2021 Nov 13-16; Digital
 - 52 **Wedemeyer H,** Aleman S, Brunetto MR, Blank A, Andreone P, Bogomolov P, Chulanov V, Mamonova N, Geyvandova N, Morozov V, Sagalova O, Stepanova T, Berger A, Manuilov D, Suri V, An Q, Da B, Flaherty J, Osinusi A, Liu Y, Merle U, Schulze Zur Wiesch J, Zeuzem S, Ciesek S, Cornberg M, Lampertico P; MYR 301 Study Group. A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D. *N Engl J Med* 2023; **389**: 22-32 [PMID: 37345876 DOI: 10.1056/NEJMoa2213429]
 - 53 **Bogomolov P,** Alexandrov A, Voronkova N, Macievich M, Kokina K, Petrachenkova M, Lehr T, Lempp FA, Wedemeyer H, Haag M, Schwab M, Haefeli WE, Blank A, Urban S. Treatment of chronic hepatitis D with the entry inhibitor myrccludex B: First results of a phase Ib/IIa study. *J Hepatol* 2016; **65**: 490-498 [PMID: 27132170 DOI: 10.1016/j.jhep.2016.04.016]
 - 54 **Urban S,** Neumann-Haefelin C, Lampertico P. Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease. *Gut* 2021; **70**: 1782-1794 [PMID: 34103404 DOI: 10.1136/gutjnl-2020-323888]
 - 55 **World Health Organization.** Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. [cited 16 February 2024]. Available from: <https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies>



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

