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Prospective Study

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

Hepatitis D in Romania

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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 monoinfection, 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 monoinfection ($P = 0.03$). 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 ($P = 0.0003$) and 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

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Core Tip: In this study, we investigated the epidemiology, natural history, risk factors and clinical management of HBV and 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.

INTRODUCTION

² 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]. ² Chronic HDV infection causes the most severe form of viral hepatitis, ³ 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. ¹ 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]. ¹ 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]. ¹ 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 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].

3 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 ICD-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 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% confidence interval (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 [COVID-19] 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/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 standard deviation [SD], 53.5 ± 11.7 years *vs* 51.6 ± 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%).

[insert Table 1 and Figure 1]

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 ± 11.4 years *vs* 51.2 ± 13.4 years, $P = 0.002$). In contrast, ages were similar between men with HBV monoinfection and HBV/HDV coinfection ($P = 0.67$).

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 monoinfection 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 monoinfection (mean \pm 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 monoinfection ($P < 0.0001$).

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/hepatitis C virus (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 ($P < 0.0001$).

[insert Table 2]

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 ($P = 0.01$) 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 mono-infection 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 mono-infection 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 published¹ 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 ²entry 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 World Health Organization'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.

ARTICLE HIGHLIGHTS

Research background

²Chronic hepatitis D virus (HDV) infection is associated with the most severe form of viral hepatitis. Certain regions, particularly Eastern European countries such as Romania, are characterized as 'endemic pockets' with hyperendemic levels of HDV infection. Given the emergence of dedicated antiviral therapeutics for HDV, an updated

understanding of HDV epidemiology and clinical management is imperative. Although epidemiological data on hepatitis B virus (HBV) and HDV coinfection in Romania exist from previous studies, updated research is needed to accurately target high-risk populations for diagnosis and treatment.

Research motivation

Accurate data on HDV prevalence and health burden are sparse, hindering effective public health interventions. Additionally, the availability of novel antiviral therapies for HDV underscores the importance of revisiting the clinical management landscape. Despite recent advancements, treatment access issues persist, particularly in regions heavily affected by HDV. Addressing these gaps in knowledge is essential for developing targeted strategies to combat HDV infection effectively.

Research objectives

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

Research methods

This prospective cohort study was conducted in six tertiary gastroenterology and hepatology referral centres in Romania. Eligible participants were adults (≥ 18 years) who tested positive for HBV. Data regarding patient demographics, disease stage, previous therapy use and risk factors for HBV and HDV infection were collected *via* patient questionnaires and medical charts.

Research results

The hospital-based prevalence of HBV infection was 3.8% (95% confidence interval [CI]: 1.8-5.8). Overall, 963 individuals were HBV-positive and were enrolled in the study; the prevalence of HBV/HDV coinfection was 33.1% (95%CI: 31.2-35.1). Over 90% of patients with HBV/HDV coinfection were treated, with 42.5% receiving pegylated

interferon- α therapy, 36.4% receiving nucleos(t)ide analogues and 49.6% receiving combination therapy. Multivariate multiple regression analysis identified several independent risk factors for HDV infection: female gender ($P = 0.0006$), current or previous imprisonment ($P < 0.0001$), older age at diagnosis ($P = 0.01$) and sexual contact with a partner positive for HBV/HCV/HDV (monoinfection or coinfection, $P = 0.0003$).

Research conclusions

The present 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.

Research perspectives

Further investigation into the geographic variability of HBV and HDV epidemiology, including prevalence, distribution patterns and emerging trends worldwide would provide valuable insights into regional disparities and the effectiveness of public health interventions. Evaluating the effectiveness and cost-effectiveness of novel screening strategies, including universal screening, double reflex testing and point-of-care testing will allow us to optimize early detection of HBV and HDV infection, particularly in resource-limited settings and high-risk populations. Continued research into novel therapeutic agents may improve clinical outcomes for affected individuals.

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