



The changing context of hepatitis D

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Summary

The global epidemiology of hepatitis D is changing with the widespread implementation of vaccination against hepatitis B. In high-income countries that achieved optimal control of HBV, the epidemiology of hepatitis D is dual, consisting of an ageing cohort of domestic patients with advanced liver fibrosis who represent the end stage of the natural history of HDV, and of a younger generation of immigrants from endemic countries who account for the majority of new infections. As observed in Europe in the 1980s, the distinctive clinical characteristic of chronic hepatitis D in endemic countries is the accelerated progression to cirrhosis and hepatocellular carcinoma. Despite some recent progress, the therapeutic management of HDV remains unsatisfactory, as most patients are not cured of HDV with currently available medicines. This review article describes the current epidemiology and clinical features of chronic hepatitis D, based on the literature published in the last 10 years.

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Introduction

Originally thought to be localised to Italy and Southern Europe, HDV has been recognised as an infectious agent of worldwide medical importance.¹ However, despite 40 years of epidemiological surveys, the global number of infected patients remains undefined. Based on the literature published from the 1980s–1990s, 3 meta-analyses have attempted to estimate the total number of HDV-infected patients and their proportion in epidemiological categories. Two of them estimated the global number to be between 48–60 million and 62–72 million in 2018 and 2019, respectively,^{2,3} while the third scaled down the prevalence to 12 million people in 2020.⁴ These widely different figures emphasise the heterogeneity of reports on HDV over the last 40 years, owing to disparate recruitment methodology and a lack of sufficient quality data.

The quality and performance of diagnostics have improved over the years. The screening test for epidemiologic surveys involves measuring total antibody to HDV (anti-HD) with a validated enzyme immunoassay (several versions with sufficient specificity and sensitivity are commercially available).^{5,6} IgM antibodies are also detectable in primary infection and persist with progression to chronicity, although they may be absent in some patients from Africa.⁷ Active infection is confirmed by the detection of HDV RNA in serum by reverse transcription PCR.⁸ However, most available in-house or commercial assays suffer from suboptimal sensitivity, especially in patients infected with HDV genotypes 5 to 8.⁹ An optimised assay has been proposed based on the amplification of consensus sequences and the use of a World Health Organization reference standard.¹⁰

The lack of universal testing of HBsAg-positive individuals for anti-HD is certainly the single most important reason for underestimating the prevalence of HDV infections.¹¹ In Europe, as many as 37.1% of anti-HD-positive individuals do not exhibit active HDV replication,¹² but information on serum HDV RNA is often lacking in Asia and Africa; this is an important limitation when it comes to correctly determining the medical burden of HDV, since – as discussed below – HDV RNA is the main driver of hepatitis D progression. Thus, inadequate screening, technical limitations and lack of testing to confirm ongoing viral replication all affect studies on the epidemiology and clinical impact of HDV; these considerations must be kept in mind when assessing the available data.

The epidemiology of HDV has consistently changed in the last decade following the advent of vaccination against HBV. The critical variable determining the epidemiology of hepatitis D is the network of HBsAg-susceptible individuals.¹³ By depleting their number, HBV vaccination provides the most efficient means to control HDV infections. In this review, we attempted to determine the current impact of chronic hepatitis D (CHD) in the world based on the analysis of the pertinent literature published in the last 10 years.

HDV infection in Europe and the US

In high income countries, vaccination programmes against HBV started in the 1990s. At present, the younger generations are protected from HBV and by default from HDV.^{14,15} The decline in infection has been age-dependent and most marked in the youngest cohorts. As an example, of 513 Italian HBsAg carriers identified in 2014, 61 were positive



for anti-HD but only 3% were younger than 30, while 80% were 50 years or older.¹⁶

In Europe, HDV remains endemic in Romania¹⁷ and Moldova.¹⁸ Hot spots sustained by immigrants and intravenous drug users (IVDUs) have been reported in Russia.^{19,20}

IVDUs are the group at highest risk of hepatitis D.²¹ However, the HDV scenario is also changing in IVDUs in Europe, reflecting the impact of HBV vaccination and the success of harm reduction programmes. In Spain, the prevalence of anti-HD among active HBsAg-positive IVDUs declined from 30% in the 1990s to 4.2% in 2018.²² In a nationwide study from Italy in 2012, only 2.8% of 543 IVDUs with HCV infection were also HBsAg carriers susceptible to HDV infection.²³ Surprisingly, despite a successful HBV vaccination programme in Taiwan, as many as 43.9% of 164 HBsAg-positive IVDUs enrolled from 2001 to 2012 had anti-HD.²⁴ However, over half of them were over 40 years and presumably had been infected decades before. Nevertheless, the rate of HDV has remained consistent in HBsAg-positive IVDUs infected with HIV.^{12,25,26} On the other hand, although mercenary sex was considered an important risk factor for HDV transmission in the 1990s,²⁷ it has not been reported in the literature of the last decade, except in a recent study from Thailand that found no HDV marker in HBsAg-positive migrant sex workers.²⁸

In Europe, the demise of HDV in domestic populations has been offset by new infections introduced by immigrants from areas where HDV remains endemic.²⁹ The relative proportion of HDV-infected migrants is increasing compared to HDV-infected native populations³⁰; migratory flows have interrupted the decline in infections, whose prevalence in HBsAg carriers stabilised in the last decade at 8–10% in Germany, Italy, Spain and France.³¹ The pattern of decreasing domestic and increasing migrant HDV infections is being observed in all high-income countries.^{32–34}

In the US, HDV infection is not perceived to be of significant concern. In the 1999–2012 National Health and Nutrition Examination Survey (NHANES),³⁵ only 0.02% of 52,209 individuals with the HBsAg or with the anti-HBc antibody were positive for anti-HD. However, a more recent study from the same NHANES database for the years 2011 to 2016 has shown an estimated prevalence of HBsAg of 0.36% overall and of 3.4% in non-Hispanic Asians, with a prevalence of anti-HD among HBsAg-positive individuals as high as 42%.³⁶ As in Europe, the infection predominates in IVDUs and foreign-born individuals.^{37–40} Although the scarcity of HBsAg carriers in the US may affect perceptions on the impact of CHD, the recent NHANES

findings would support screening all HBsAg carriers.

HDV infection in the rest of the world

With the implementation of HBV vaccination programmes since the 1990s, the control of HBV has improved in many lower middle-income countries. The enforcement of the vaccine is also changing the epidemiology of hepatitis D in less affluent countries, as a function of the degree of protection afforded by vaccination; it can be assumed that where the prevalence of HBsAg is decreasing, HDV is coming under control and the younger generations are increasingly protected from the infection. For example, 8 years after the introduction of HBV vaccination, hepatitis D has been eliminated in children less than 11 years of age in indigenous populations of the Peruvian Amazon.⁴¹

A 2018 survey by the Polaris Observatory has considered the impact of HBV vaccination on the worldwide prevalence of HBsAg,⁴² providing a crude background to extrapolate the current risk of acquiring HDV. Of note, the HBsAg figures reported in this study are cumulative but for logistical and cultural reasons, vaccine coverage may vary in socially advanced urban vs. rural areas; thus, intra-country variations in HBsAg and HDV prevalence may be significant, in particular in large countries. The country-specific rate of anti-HD reported in the last 10 years is shown over the background of corresponding HBsAg prevalence in Africa (Fig. 1A) and Asia (Fig. 1B). To determine temporal changes with respect to previous decades, please refer to specific articles in the bibliography.^{29,43,44}

Hepatitis D is diminishing in countries with consolidated vaccination programmes. In Northern Africa,^{45–51} Saudi Arabia,⁵² Israel⁵³ and the Caucasus⁵⁴ (Fig. 1B) the rate of anti-HD in different HBsAg-positive populations varies between 0.8% and 11.9%. Pockets of the infection were reported in HBsAg carriers with liver disease in Central Tunisia⁵⁵ and in Upper Egypt,⁵⁶ with rates of anti-HD of 30.2% and 43%, respectively. The infection has diminished in Turkey and Iran, which historically were endemic areas.²⁹ In a nationwide survey conducted in 2015, anti-HD was found in only 2.8% of the general HBsAg-positive Turkish population.⁵⁷ However, there are still consistent regional differences: in Eastern Turkey, the rate of infection was 61.4% in 2011 in HBsAg-positive patients with cirrhosis in the Elazir Region⁵⁸ and 18.4% in 2016 in chronic HBsAg-positive patients in Van.⁵⁹ In Iran, seroprevalence has diminished to 2.1% and 1.7% in cohorts of unselected HBsAg carriers collected in the north-west in 2015–2016⁶⁰ and in Kermanshah, Western Iran, in 2004–2016,⁶¹ respectively. However, a 65.5% and a 21.8% rate of anti-HD was

Key point

HDV infection is vanishing in the domestic populations of high-income countries as a secondary effect of long-standing and successful HBV vaccination programmes, leaving behind an ageing cohort of patients with advanced liver fibrosis.

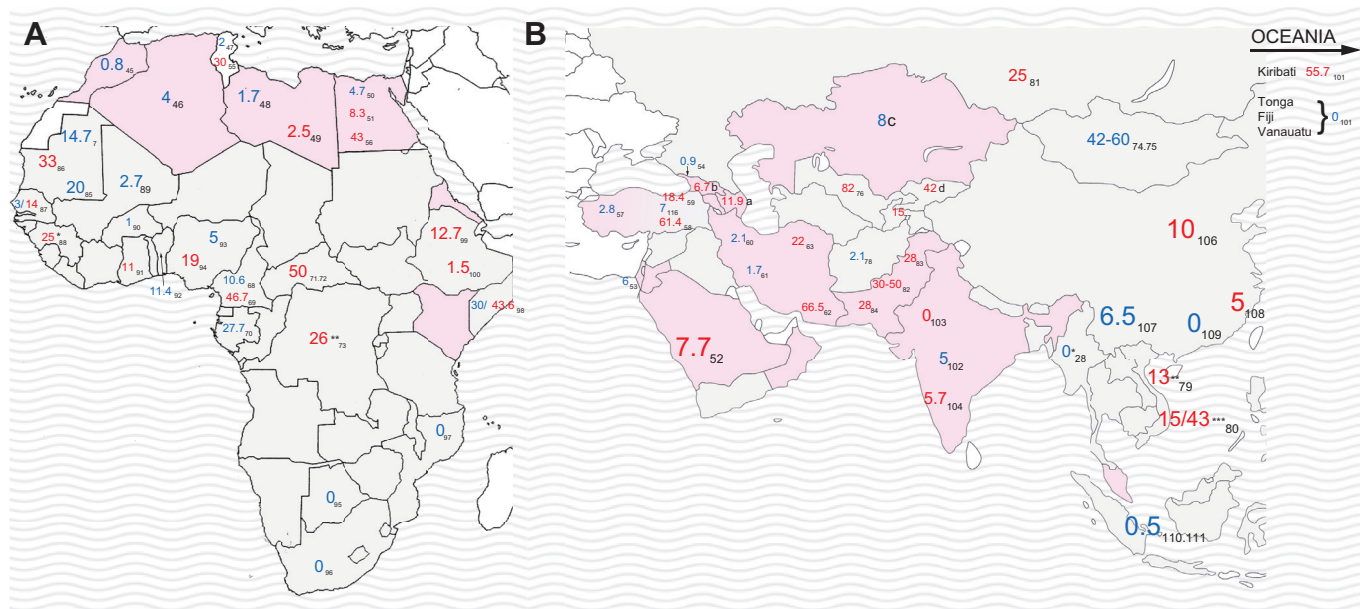


Fig. 1. Prevalence of antibody to HDV reported in the last decade in HBsAg carriers in Africa (1A) and Asia (1B). Blue: the rates of anti-HD when the prevalence were evaluated in patients at low risk of HDV infection (*i.e.* collected at blood banks, pregnancy clinics, in the general population, in general HBsAg populations, in outpatient clinics). Red: the rates of anti-HD when the prevalence were evaluated in patients with chronic HBsAg-positive liver disease. Pink background: countries where the prevalence of HBsAg carriers in the population is lower than 3%.⁴² White background: countries where the prevalence of HBsAg carriers in the population is higher than 3%.⁴² (A) *in HIV patients; ** in acute HBsAg hepatitis. (B) *in HBsAg-positive prostitutes; **HDV RNA testing; ***in chronic HBsAg infections/in acute HBsAg-positive hepatitis. Personal communications from: (a) Prof. Gulnara Aghayeva, Liver Diseases Department, EGE Hospital, Baku, Azerbaijan; (b) Prof Tengiz Tsertsvadze, Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi State University, Tbilisi, Georgia; (c) Prof. Alexander V. Nersesov, Dr. Almagul Jumabaeva, and Dr Gulsana Nuralieva, Department of Gastroenterology, Kazakh National Medical University, Almaty, Kazakhstan; (d) Dr Kalys Nogoibaeva, Dr Zuridin Nurmatov, Republican Centers for Viral Hepatitis Control and for the Control of Viral Infections, Ministry of Health of the Kyrgyz Republic, Bishkek, Kyrgyz Republic).

reported, respectively, in 2014 in HBsAg-positive patients with cirrhosis in Zahedan⁶² and in 2018 in those with chronic HBsAg-positive hepatitis in Mashhad.⁶³

The burden of HBsAg throughout Central and Latin America is generally less than 1%.⁴² Data on CHD are lacking but the low historical prevalence of HBsAg seems to dismiss HDV as an infectious protagonist. The exception is the western Amazon Basin spanning through Brazil, Venezuela, Colombia, Peru and Ecuador, where HBV and HDV remains endemic despite efforts to implement HBV vaccination and enforce the screening of blood.^{64,65}

The medical burden of HDV remains high in low- and low-to-middle-income countries of Africa, Asia and Oceania, where the prevalence of HBsAg carriers is often in excess of 5% in the population. The impact of HBV vaccination is still low: in Africa, only 11 countries had introduced HBV birth vaccine coverage by 2017.⁶⁶

Rates of HDV have not been reported for several countries and no longitudinal trend has been described. In Africa, a 2017 meta-analysis⁶⁷ determined that the pooled seroprevalence of HDV in general and in liver disease populations was, respectively, 25.6% and 37.7% in Central Africa and 7.33% and 9.5% in Western Africa. It was only 0.05% in the general population of Eastern and Southern Africa but information from these macro-areas is

scarce. Recent surveys have confirmed a hyperendemic pattern of HDV infection in poor countries of the equatorial belt (Fig. 1A). HDV seroprevalence in Cameroon was 10.6% in 1,621 unselected HBsAg-positive individuals in 2011⁶⁸ and 46.7% in 1,928 HBsAg-positive hospital patients in 2010 to 2016,⁶⁹ while it was 27.7% in 303 HBsAg carriers between 2005 and 2008 in Gabon.⁷⁰ In both countries there were large regional variations. In the Central African Republic, 50% of patients with chronic HBsAg-positive hepatitis and hepatocellular carcinoma (HCC) were anti-HD positive between 1998 and 2010^{71,72} and, in the Democratic Republic of Congo, 26.1% of HBsAg-positive patients with jaundice were seropositive in 2017.⁷³

In Asia, the rate of HDV is high in the central part of the continent (Fig. 1B). Recent reports have indicated a seroprevalence of 50–60% in the general HBsAg-positive population of Mongolia^{74,75} and of 82%, 15% and 42%, respectively, in HBsAg-positive patients with cirrhosis in Uzbekistan,⁷⁶ Tajikistan⁷⁷ and Kyrgyzstan (Fig. 1B). In Kazakhstan, the data of the National Registry updated to September 2020 indicated a 7.9% prevalence of HDV in 21,283 patients with chronic HBsAg-positive liver disease (Fig 1B). However, HDV was reported as the most common indication for liver transplantation.⁷⁸ Despite being encircled by hyperendemic countries, in 2019 the prevalence

of anti-HD in Afghanistan was only 2.1% in the general HBsAg-positive population.⁷⁹ Hot-spots have been reported in Vietnam⁸⁰ and Yakutia,⁸¹ and hepatitis D remains an important medical issue in Pakistan,⁸² where 30–50% of HBsAg-positive patients are seropositive in a large but well defined area in the middle of the country, so-called the “Delta belt”; countrywide, the HDV RNA positivity rate was 28% in 2011 in HBV viraemic patients⁸³ and anti-HD was found in 28.1% of HBsAg-positive patients in Karachi in 2007–2011.⁸⁴

The information on HDV from other countries in Africa comes from a single or few regional studies^{85–100} (Fig. 1A). These studies are limited by geographic distribution, as such, accurate country-specific prevalence estimates remain elusive, as slight variations in studies can significantly change national prevalence figures. The distribution of HDV reported in Oceania is also limited and irregular; anti-HD and serum HDV RNA were found in 55.7% and in 37%, respectively, of 54 HBsAg-positive patients in Kiribati, Western Pacific, but in no patients from Tonga, Fiji and Vanuatu¹⁰¹ (Fig. 1B).

Although India, China and Indonesia bear a large part of the global HBV burden, hepatitis D appears to play a minor role in the 3 macroareas. In India, the rate of HDV was 5% in a nationwide survey of HBsAg-positive patients in 2006.¹⁰² No case of infection was found in 262 HBsAg-positive patients with chronic hepatitis and cirrhosis in Northern India in 2012–2014,¹⁰³ but a 5.7% seroprevalence was reported in Chennai in 2014.¹⁰⁴ Although extensive data are available from Taiwan, where the prevalence of HDV was high before the introduction of HBV vaccination,¹⁰⁵ only fragmentary figures were reported from mainland China, despite an overall prevalence of HBsAg of 6.5%. In a 2016 report, 10% of 211 patients with chronic HBsAg-positive liver disease in Chongqing were superinfected with HDV¹⁰⁶; between 2005 and 2011, 6.5% of 6,604 HBsAg-positive patients in Guangdong had IgM anti-HD¹⁰⁷ and 5% such patients in Shanghai were recently reported to circulate HDV RNA of genotype 2.¹⁰⁸ Finally, no HDV cases were detected in Hong Kong in the general HBsAg-positive population in 2019.¹⁰⁹ While the prevalence of HDV appears to be declining in both India and China, the data are sparse, limited by regional distribution and by the small size of the groups that were tested in most reports, and are therefore difficult to translate into a national prevalence figure in such large countries. In Indonesia, HDV is considered virtually absent, based on 2 old studies involving 235 HBsAg-positive cases,^{110,111} 145 of whom were blood donors, pregnant women and haemodialysis cases at low risk of HDV.

Interpretation of the epidemiological data

The geographical discrepancies in HDV cannot be accounted for by genetic variability in the virus or by different susceptibilities of HBsAg carriers, as the infection occurs over the world in association with all viral genotypes. Thus, rather than being intrinsic to the virus and host, the reasons for the baffling geographical variations appear to be extrinsic. An important reason for discrepancies are differences in patient sampling (Fig. 1A,B). As mentioned, screening for HDV relies primarily on the finding of total anti-HD. A confirmatory HDV RNA test is out of reach for many countries in Asia and Africa. However, the antibody to HDV is a marker of exposure to the virus rather than of ongoing infection: it may also represent a serologic scar of resolved infections.¹³ Compared to HBV, which often does not elicit significant liver damage, HDV results in the development of cirrhosis within 5 to 10 years of infection in approximately 70% of cases,¹ corresponding to a 3-fold increase in risk in HBV/HDV-coinfected than in HBV-monoinfected patients.¹¹² It follows that the rate of anti-HD increases in parallel with the severity of liver disease – the probability of finding the antibody throughout the clinical spectrum of HBV infections is lowest in asymptomatic/minor forms and highest in patients with serious disease. This is confirmed by the 5- to 10-fold difference in the prevalence of anti-HD between asymptomatic blood donors and patients with cirrhosis,¹¹³ as seen in Italy,^{114,115} Turkey¹¹⁶ and Uzbekistan.¹¹³ Blood donors are largely non-viraemic: serum HDV RNA was detected in 22.9% of 61 donors in a French study from 1997 to 2011¹¹⁷ and in only 2 of 13 donors in a study from Turkey in 2014.¹¹⁶ The corollary is that the interpretation of the clinical meaning of anti-HD must consider the type of population recruited for testing. Surveys for anti-HD in asymptomatic HBsAg-positive carriers at small risk of HDV are bound to retrieve low prevalence rates of the infection, which do not reflect the true medical burden. In many studies, the determination of reliable prevalence figures is further hampered by low sample sizes and by regional differences, especially when this data is used to make generalised statements. Thus, the appraisal of the medical burden of HDV in a given country should preferentially be based on surveys for anti-HD among HBsAg-positive patients with cirrhosis.¹¹³

The current clinical patterns

In countries where hepatitis D remains endemic, transmission modes and the demographic and clinical features of CHD are not different from those described in the 1980s.¹ Non-invasive fibrosis scores have been proposed to help in staging the

Key point

A major factor behind the discrepancies in epidemiological data lies in the different populations sampled, *i.e.* surveys in asymptomatic HBsAg carriers at low risk of HDV do not reflect the true burden of the infection.

Key point

However, migratory fluxes from HDV endemic countries are reintroducing hepatitis D and pose new problems and constraints to national health services.

disease.^{118,119} Patients are on average younger by a decade than those with HBV monoinfection, the disease is usually accompanied by an HBeAg-negative HBV infection, and HDV replication is the major factor affecting disease severity. These features were confirmed in 1,576 HDV patients enrolled across Europe, Asia and the Americas¹²⁰ and in a recent study on HDV-related cirrhosis in Uzbekistan.⁷⁶

In Europe, the clinical features of current CHDs are different in the domestic ageing survivors of infection acquired decades ago and in the younger immigrants importing new disease.^{13,121} The mean age of native Italians with CHD identified between 2010 and 2019 was 58 years and all had extensive liver fibrosis or overt cirrhosis, demonstrated by a median liver stiffness of 12 kPa on Fibroscan®.¹²² This cohort still has an impact on liver transplantation programmes. Despite the much lower epidemiologic burden of HDV compared to HBV, the proportion of liver transplants in HDV-infected vs. total HBsAg-positive transplants has remained stable in the last 20 years in Italy (~45%) as well as in the European Liver Transplant Registry (~25%).¹²³ This can be explained by the effective control of hepatitis B afforded by antivirals in contrast with the poor efficacy of therapeutic options available for HDV, which cannot prevent progression to end-stage cirrhosis in most cases.¹²⁴

The clinical features of CHD in immigrants have been studied in 2 large series, one of 1,112 immigrants in France,¹²⁵ and the other of 337 immigrants in Sweden.¹²⁶ In the French series the mean age of patients was 36.5 years; 77% had active HDV infection, based on increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Sub-Saharan patients were younger, more frequently overweight and less often abused alcohol; their geographic origin was reflected by the diversity of HDV genotypes, with the scarcely characterised HDV-5 accounting for 32.7%, HDV-7 for 5.3%, HDV-6 for 3.2% and HDV-8 for 2.7% of infections in these patients. Cirrhosis was significantly less frequent in African than in European patients regardless of HDV genotype. The prevalence of cirrhosis increased from 28.1% at enrolment to 48.8% after 3 years of follow-up, although progression was less frequent among sub-Saharan patients. One-quarter of patients had ≥1 episode(s) of hepatic decompensation and 9.2% developed HCC. Persistent replication of HDV was associated with decompensation, HCC and death. In the Swedish study, the mean age of patients was 36.3 years; they were followed for a mean of 6.5 years. Asian origin, together with a high FIB-4 score, diabetes and liver cirrhosis at referral were independent predictors of liver-related outcomes. In this series, HDV viraemia was a major driver of hepatic decompensation and of liver-related death/transplantation, with a 3.8-fold increase in risk compared to patients without viraemia. Thirty

percent of viraemic patients had cirrhosis at their first presentation; this was not different between patients of Swedish origin vs. migrants. The overall outcome was nevertheless more benign than in other previously reported studies.

HDV with HIV or HCV infection

The antibody to HDV was found in 14.5% of 422 HIV/HBV-coinfected individuals in the EuroSIDA database¹²⁷ and in 15.4% of 771 such patients in the Swiss HIV Cohort Study; in the latter, serum HDV RNA was detectable in 62.9% of antibody-positive patients.¹² In the EuroSIDA cohort the major risk factor for HDV was drug addiction (in 72.1%). More recently, HIV/HDV coinfections were associated with immigration from highly endemic areas¹⁵ or promiscuous sexual activity.¹⁵ HIV-infected persons with anti-HD were also more often anti-HCV-positive than those without HDV markers (73.1% vs. 17.8%),¹² but triple infection did not affect survival, probably because HCV replication was suppressed in up to 90% of those who were anti-HCV-positive. A shift in the risk profile has also been reported in Taiwan where HDV superinfection of HBsAg carriers is now associated with male homosexuality, and frequently also with hepatitis flares and syphilis.¹²⁸ Although in the EuroSIDA cohort HDV did not increase progression to AIDS, the infection increased the risk of death; after a median follow-up of 90.2 months, the presence of anti-HD, together with lower CD4 count, higher HIV load and older age, were significantly correlated with death from any cause and with liver-related death.¹²⁷ Likewise, in the Swiss HIV cohort, HDV coinfection was associated with increased overall death and development of HCC.¹² In a retrospective analysis of 1,147 HIV-infected persons, followed on average for 81.2 months, only 17 were positive for anti-HD but in these patients HDV coinfection was associated with a higher rate of decompensation and liver-related death.¹²⁹

Triple infection with HDV, HBV and HCV has been reported in areas of the world where these infections are prevalent.¹³⁰ In most cases, HDV is the dominant virus via undefined mechanisms of interference, leading to suppression of both HBV and HCV replication.¹³¹ Occasionally, superinfection with HCV of an HBV/HDV-coinfected person may result in HCV dominance.¹³² Despite the mutual viral interference, triple infection has been consistently associated with a more aggressive histological picture.¹³² The issue may soon become irrelevant due to the availability of potent direct-acting antivirals against HCV.

HDV- and HBeAg-positive HBV infection

HDV infection usually suppresses HBV replication, leading to the typical anti-HBe-positive profile of CHD. It is however not infrequent to observe patients, usually IVDUs, who are HBeAg-positive.¹³³ Although more HBeAg-positive patients had

detectable HBV DNA in a study of HBeAg-positive and -negative CHD, on average HBV DNA levels were comparable to HBeAg-negative patients, and so were serum HDV RNA levels; likewise, the long-term clinical course was similar.¹³⁴

HDV and the risk of HCC

Some studies suggest that the major complication and cause of death in CHD is liver failure,^{135,136} while others suggest that HDV infection increases the risk of HCC compared to HBV mono-infection. In a European study on compensated cirrhosis,¹¹² the presence of anti-HD increased the risk of HCC by 3-fold, and of mortality by 2-fold, compared to HBV mono-infection. HDV replication emerged as a risk factor for HCC relative to HBV in studies in Italy^{14,137} and in the analysis of the Swiss HIV Cohort; in the latter, HBV replication was presumably suppressed by anti-retrovirals and HDV infection was independently associated with mortality and liver-related events, including HCC.¹² A recent systematic review and meta-analysis of CHD has also shown that the disease is associated with an increased risk of HCC compared to HBV mono-infection, with a pooled odds ratio (OR) of 1.28 (95% CI 1.05–1.57; $I^2 = 67.0\%$).¹³⁸ In a sensitivity analysis limited to prospective studies,⁴ the OR was 2.77 (95% CI 1.79–4.28; $I^2 = 0\%$), suggesting that the overall rating may have been underestimated by study heterogeneity. Furthermore, the risk was higher in HIV-coinfected populations (pooled OR 7.13; 95% CI 2.83–17.92; $p < 0.001$, $I^2 = 0\%$) and in studies from Asia, albeit with substantial heterogeneity (pooled OR 1.44; 95% CI 1.04–2.00; $p = 0.03$; $I^2 = 68.5\%$). Although an association between higher HCC risk and particular HDV genotypes was not reported, this cannot be ruled out based on the selective geographical distribution of some genotypes, in particular genotype 2 which is localised mostly in the Far East.

Therapeutic perspectives

The HDV challenge

Permanent long-term HDV RNA suppression is associated with improved clinical outcome, as recently confirmed by the prolonged follow-up of patients with CHD responding to pegylated interferon (Peg-IFN α) in the HIDIT-II Study.¹³⁹ However, following the hepatitis C paradigm, most IFN α -based trials of CHD have used sustained virologic response (SVR), *i.e.* undetectable serum HDV RNA 6 months after stopping therapy, as an endpoint and have thereafter dismissed patients without further follow-up. Unfortunately, late viral relapses occur frequently in patients with CHD who have achieved a SVR,¹⁴⁰ indicating that it may be an inadequate endpoint to identify patients who remain in permanent remission. End-titration experiments in susceptible chimpanzees have shown that HDV can be extremely contagious, as an HDV-containing serum could still transmit the infection after a

10^{-11} dilution;¹⁴¹ therefore, the persistence of circulating HBsAg in patients who obtained a SVR may enable the late rescue of HDV still present at low levels but undetectable with currently available HDV RNA assays.^{142,143} The number of genuine, post-treatment relapses will diminish with the development of more sensitive assays for serum HDV RNA. Using a new test with a lower limit of detection of 14 IU/ml, as many as one-third of samples previously classified as undetectable by an in-house assay at the end of Peg-IFN α therapy were actually HDV RNA positive.¹⁴⁴

Targeting HBV with antivirals, such as entecavir or tenofovir, in an effort to abolish its helper function is of no avail, since HDV only requires the HBsAg necessary to coat its virion and its replication proceeds independently of HBV replication. The HDV relies for its replication on the synthetic machinery of the infected hepatocyte and has no enzymatic activities to be targeted by conventional antivirals, with the exception of the autocatalytic activity of the ribozymes.¹⁴⁵ Some ribozyme inhibitors have been identified^{146,147} but their activity *in vivo* has not yet been proven.

New therapies against hepatitis D

Current therapeutic efforts are aimed at depriving HDV of functions critical to its life cycle. The 3 approaches currently being explored are:

- 1) Blocking HDV particles from entering hepatocytes. HDV uses the lipopeptide pre-S1 of the HBsAg coat to dock to liver cells via the sodium/bile acid cotransporter (NTCP) prior to cell entry.¹⁴⁸ Bulevirtide (formerly known as Myrcludex-B), a myristoylated synthetic lipopeptide corresponding to the preS1 sequence of HBsAg, can effectively dock to the NCTP inhibiting HDV binding.¹⁴⁹
- 2) Preventing the assembly of mature infectious HDV particles by inhibiting the prenylation of the large HDAG, a post-translational modification necessary for its interaction with HBsAg.¹⁵⁰ This activity is catalysed by a cellular farnesyl transferase; lonafarnib (LNF), a tricyclic derivative of carboxamide, has been developed as the prototype inhibitor of human farnesyl transferase and is being tested for the treatment of HDV.
- 3) Preventing the export of HDV particles: nucleic acid polymers (NAPs) appear to inhibit the secretion of the HBsAg from hepatocytes as well as to stop virion entry into the cell.¹⁵¹ The REP-2139 is the first NAP selected for human studies with the aim of preventing the export of HDV particles.

These approaches have all been supported by initial proof-of-concept studies.^{152–154} A subsequent bulevirtide phase IIb trial¹⁵⁵ enrolled 120 patients who had failed to respond to or were ineligible to receive IFN α ; they were randomised to bulevirtide at

Key point

HDV infection remains a significant medical burden in many less affluent parts of the world, but the epidemiological data is heterogeneous and largely incomplete.

Key point

The current therapeutic management of hepatitis remains unsatisfactory but new therapies are in evaluation: they appear to perform best in association with pegylated interferons, although bulevirtide – combined with nucleotide analogues – may control hepatitis D in a proportion of patients.

the doses of 2, 5 or 10 mg combined with tenofovir or to tenofovir alone for 24 weeks. The results, available in abstract form, showed a dose-dependent HDV RNA decline of at least 2 Log in up to 77% of patients receiving 10 mg of bulevirtide, followed by a relapse after treatment cessation in most patients. In view of the high number of relapses, a new trial of bulevirtide in combination with Peg-IFN α was launched (the Myr-203 study).¹⁵⁶ Four groups of 15 patients each were randomised to receive 180 μ g of Peg-IFN α alone or combined with 2 mg or 5 mg of bulevirtide, or to receive 2 mg of bulevirtide monotherapy for 48 weeks. While the response to either drug monotherapy was poor, HDV RNA became undetectable at end of treatment in 9 of 15 (60%) patients given Peg-IFN α combined with the 2 mg dose of bulevirtide. At the end of the 24-week post-treatment follow-up, the mean HDV RNA Log decline was 4.04 and 1.48 for the combination of 2 mg or 5 mg of bulevirtide + Peg-IFN α vs. 0.26 and 1.08 Log declines with Peg-IFN α or bulevirtide (2 mg) monotherapy, respectively. Interestingly, ALT remained normal not only in 12 of the 15 patients treated with the 2 combinations, but also in 3 patients given 2 mg of bulevirtide alone. HBsAg became undetectable in 4 of the 15 patients treated with the combination using 2 mg of bulevirtide. These encouraging results, presented at the 2019 EASL annual meeting, are not yet available in full. In a more recent report,¹⁵⁷ 30 patients with CHD were randomised to receive a high, single daily dose (10 mg) of bulevirtide combined with Peg-IFN α or divided into 2x 5 mg doses as monotherapy for 48 weeks. All patients received tenofovir. Strong HDV RNA Log declines were observed at the end of therapy in both groups (-6.09 and -4.58 Log, respectively), becoming undetectable in 86.7% and 40% of patients. Two patients treated with the combination cleared HBsAg 24 weeks after the end of therapy, and one of them was the only patient with persistently undetectable HDV RNA. However, the overall HBsAg response rate was lower than that reported using lower doses of bulevirtide in association with Peg-IFN α , showing that the synergistic effect afforded by the combination did not increase in parallel with the dose of bulevirtide. Bulevirtide received conditional marketing authorisation under the trade name Hepcludex[®] from the European Medicines Agency on July 31st, 2020, at the dose of 2 mg daily, alone or in combination with a nucleos(t)ide analogue for the treatment of the underlying hepatitis B¹⁵⁸; bulevirtide administration should continue “as long as the patient benefits from it” (*i.e.* in terms of clinical efficacy and safety), and until future clinical trial data may indicate different therapeutic actions.

To reduce the side effects of LNF observed in the original proof-of-concept study,¹⁵³ a subsequent trial (LOWR-1) combined smaller doses of LNF (100 mg twice a day) with ritonavir, a cytochrome P450 3A4 inhibitor, for 8 weeks.¹⁵⁹ The combination was better tolerated than LNF monotherapy (300 mg twice daily) and improved antiviral efficacy, leading to a

HDV RNA decline of about 3 Log after only 8 weeks of therapy. Comparable results were observed in patients treated with 100 mg of LNF twice daily in combination with Peg-IFN α . Additional studies (LOWR-2, -3 and -4), only available in abstract form,^{160–162} have refined the schedule, testing multiple and/or progressing doses of LNF in patients receiving nucleotide analogue therapy to prevent the recrudescence of the underlying hepatitis B.

Almost all patients treated with LNF regimens, however, have relapsed or remained viraemic after the end of therapy. Thus, more recently, Peg-IFN λ has been used. The interest in using this form of IFN lies in its better tolerability – in terms of cytopenia, flu-like and psychiatric symptoms – relative to Peg-IFN α . Preliminary results are only available in abstract form. In the LIMT HDV Study,¹⁶³ Peg-IFN λ was given as monotherapy at the dose of 120 or 180 μ g weekly for 48 weeks. All 33 patients were receiving nucleos(t)ide analogue therapy for HBV. Intent-to-treat response rates 24 weeks after the end of therapy were slightly superior to the historical rates of 28% obtained with Peg-IFN α .¹⁶⁴ Patients who previously received Peg-IFN α reported fewer side effects.

Despite encouraging results reported in the proof-of-concept study of REP-2139 in a small series of 12 patients,¹⁵⁴ we await further information on this therapy for CHD.

Current therapeutic perspectives

Although bulevirtide and LNF have activity against HDV, Peg-IFN α was still needed to optimise treatment. Even so, the virologic response after 48 weeks of combined therapy is mostly transient, suggesting that longer durations of therapy are required. The critical problem is the lack of a fully reliable virologic endpoint of therapy. As the clearance of the HBsAg is not realistic^{142–144} and SVR may not be dependable because of the risk of late relapses,¹⁴⁰ the only feasible virologic endpoint of therapy is undetectable HDV RNA that persists over time. The advent of more sensitive HDV RNA assays will reduce the rate of false relapses, improving the identification of long-term virologic responders.

The question, therefore, is whether prolonged therapy can achieve the cure of CHD within a reasonable timeframe compatible with tolerability and safety, or whether continuous therapy may be adjusted to maintain latent, clinically inactive HDV infection in patients who clear serum HDV RNA but remain HBsAg-positive. Recently a more pragmatic approach to HDV therapy has been suggested based on prioritising clinical factors (*e.g.* normalising ALT/AST and improving liver function). Based on the observation that bulevirtide and LNF induce a 2-log decrease of HDV RNA in a sizeable proportion of patients and that this was mostly associated with ALT normalisation, a decline of 2 or more Logs of serum HDV RNA has been proposed as

an acceptable endpoint of initial treatment efficacy in CHD.¹⁶⁵ This unorthodox approach is a compromise intended to justify long-term therapies aimed at maintaining clinical and biochemical remission over time. However, a prolonged, clinically uneventful surveillance is needed to confirm that therapy is controlling HDV, especially to rule out late hepatitis relapses. How long this therapy should last has not been established.

Prolonged treatments raise the problem of safety, in particular in association with the poorly tolerated Peg-IFN α . Peg-IFN λ might provide an alternative, as it is credited with fewer side effects than Peg-IFN α . Despite its lesser clinical efficacy, bulevirtide monotherapy is well tolerated and appears the only option for long-term, conservative therapy in patients with HDV-related cirrhosis who cannot tolerate Peg-IFN α . In summary, bulevirtide, LNF and REP-2019 provide interesting advances for the treatment of HDV, but the exact schedules and role of combination therapies warrant further studies. Additional therapeutic strategies targeting the background HBsAg *via* a ribonucleic acid interference approach, such as ARC-520¹⁶⁶ (MON-ARCH study, <https://clinicaltrials.gov/ct2/show/NCT02577029>) or JNJ-73763989 (REEF-D study, <https://clinicaltrials.gov/ct2/show/NCT04535544>), are currently being tested in clinical trials, but data are not available at the time of writing.

Conclusions and perspectives

In high-income countries, the success of vaccination campaigns against HBV has led to a dramatic reduction in HDV prevalence, to the point that this infection is vanishing in domestic populations of Europe. Middle income countries are also catching up with the control of HDV through more delayed vaccination programmes. However, migratory fluxes are reintroducing hepatitis D and posing new problems and constraints to national health services. The burden of hepatitis D remains unknown in many poor countries and is high in tropical and subtropical areas and in Central Asia where resources are limited against the HDV epidemic. It is urgent therefore that International Health Agencies raise awareness and pay more attention to the problem of CHD, promoting data collection and expanding screening efforts. National surveys for HDV should be centred on patients with advanced liver disease as they are most representative of the local burden of the infection.

Who should be tested for HDV in the US and Europe? AASLD Guidelines recommend testing only in risk groups¹⁶⁷ while EASL⁸ and APASL¹⁶⁸ recommend testing in all HBsAg-positive patients.

These strategies reflect a different perception of hepatitis D, *i.e.* a pretty rare disease in the US vs. a consistent medical burden in Asia and Europe. Of note, in common practice, physicians often restrict testing to patients with severe HBsAg-positive liver disease, in the belief that HDV is only associated with advanced hepatitis. However, HDV infection is not uncommon. Even in the most conservative global meta-analysis,⁴ the estimated prevalence of hepatitis D in HBsAg-positive patients attending hepatology clinics in the US and Europe was 2.6% and 19.5%, respectively. The recommendation of EASL/APASL to test for anti-HD in all HBsAg-positive patients with liver disease is preferred for 3 reasons: first, healthcare providers may not be experienced with HDV – reflex testing will prevent a diagnosis of hepatitis D being overlooked; second, general testing will improve our epidemiological understanding of HDV, providing a comprehensive view of the burden of the infection, in particular in the US; third, new promising therapies against hepatitis D may be in sight. Hopefully new treatments will not only control cirrhosis but also prevent progression of CHD, changing its ominous natural course. Therefore, identifying CHD early through universal testing of HBsAg carriers is crucial.

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHD, chronic hepatitis D; HCC, hepatocellular carcinoma; HDIN, hepatitis Delta International Network; IVDU, intravenous drug users; LNF, lonafarnib; NAP, nucleic acid polymers; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; Peg-IFN, pegylated interferon; SVR, sustained virologic response.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

All authors conceived, collected the pertinent literature and wrote the article.

Supplementary data

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Key point

It is urgent that international health agencies increase awareness and pay more attention to HDV infection in the world, promoting data collection and expanding screening efforts to determine the remaining impact of hepatitis D.

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