

The changing context of hepatitis delta

28 and 29 October 2021

Online meeting

Objectives

The objectives of the two-day meeting were:

- to provide an overview of the current epidemiology of hepatitis D and discuss potential associated risk factors
- to review diagnostic tools and screening recommendations for hepatitis D
- to examine the prevention, treatment and control of hepatitis D
- to discuss the public health impact of hepatitis D and the arguments for its inclusion in the elimination goals of the World Health Organization (WHO).

Participants would also consider relevant hepatitis B-related issues.

The virus

Recognized in 1977, hepatitis D virus (HDV), a small circular single-stranded RNA virus (about 1.7 kb long), replicates in the nucleus of hepatocytes.¹ It is then packaged within the envelope of hepatitis B virus (HBV), which enables binding to the same receptor on liver cells (sodium taurocholate co-transporting polypeptide, NTCP) as HBV (Figure 1). Genomic sequences (both partial and complete) are being collected in a new comprehensive database which is regularly updated and publicly accessible.²

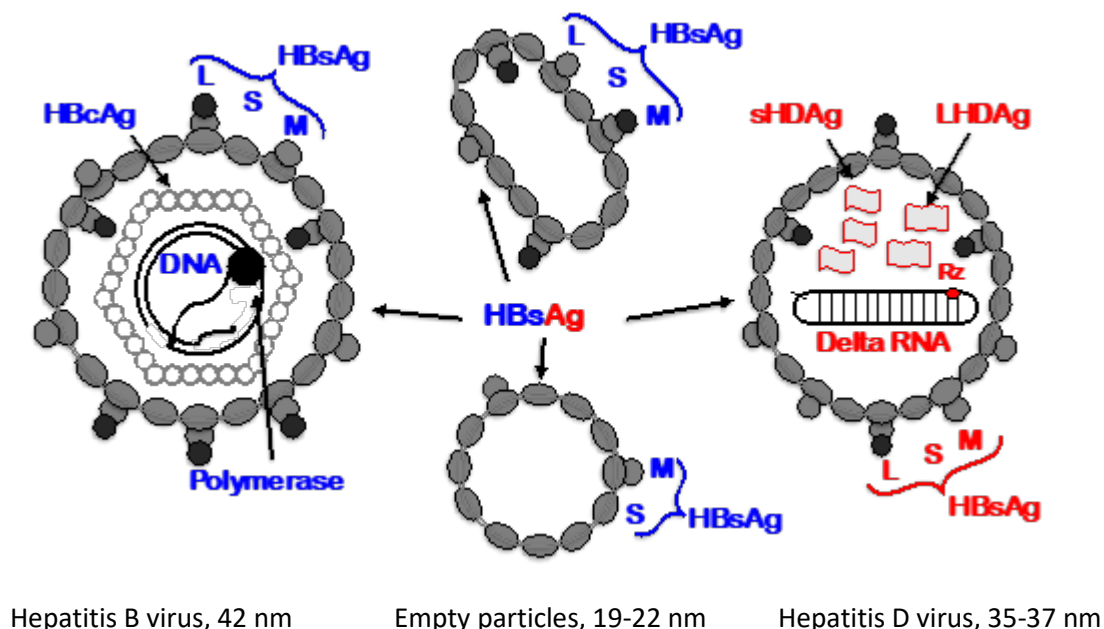


Figure 1. Viral particles of HBV and HDV: HBcAg, hepatitis B virus core antigen; L, S and M HBsAg, large, small and medium hepatitis B virus surface antigen; L and S HDsAg, large and small hepatitis D virus surface antigen; Rz, ribozyme. *From E. Gordien.*

The virus is highly heterogeneous, with eight genotypes broadly and discretely distributed globally (with five in Africa) (Figure 2).³ Genotypes 5-8 have recently been imported into Western countries from central Africa.⁴ Phylogenetic analyses of sequences of the large HDV antigen obtained from the database have enabled the identification of subtypes of various genotypes – five for genotype 1 and two for genotypes 2 and 4, with intersubtype differences of between 3% and 10%. Among the eight genotypes, the sequence difference is about 10%.⁵ Future work needs to focus on the whole genome rather than partial sequences and to look at not just amino acid changes but also conformational changes.

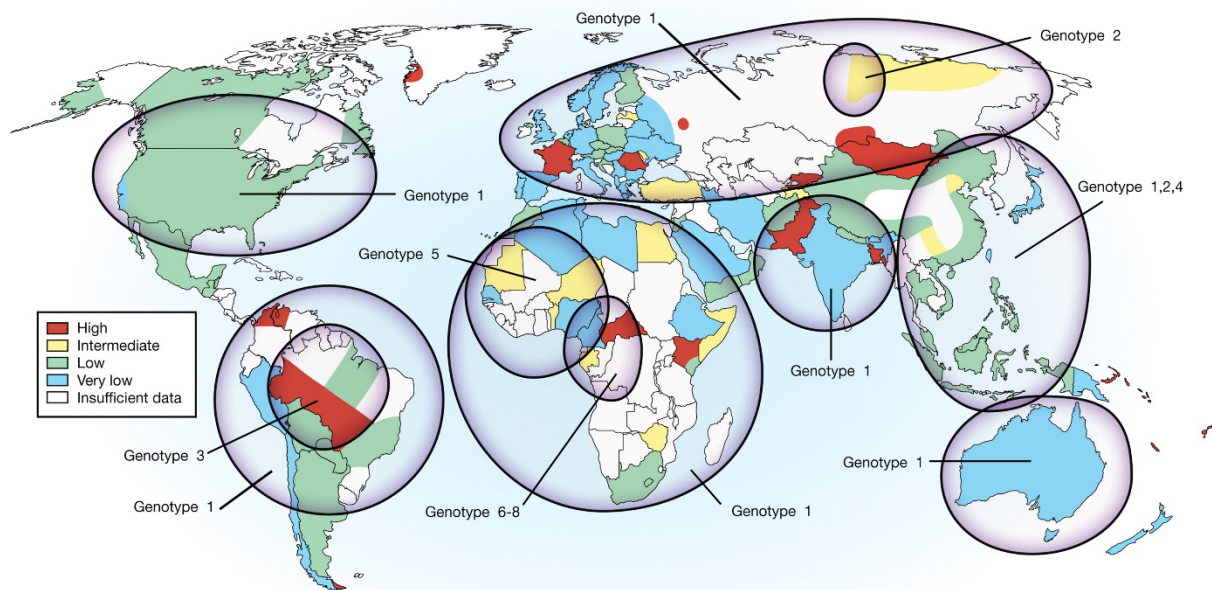


Figure 2: World map showing the estimated prevalence of HDV infection and genotype distribution. Source: Koh C, Heller T, Glenn JS: [Pathogenesis of and New Therapies for Hepatitis D - ScienceDirect. Gastroenterology \(2019\) 156\(2\): 461-476.e1](#)

Different genotypes have been associated with everything from asymptomatic infection and mild forms of acute and chronic disease to progressive and severe liver disease. Genotype 3 has been reported to be the most pathogenic,⁶ but more data are needed to link genotype with clinical outcome. In vitro they replicate with different efficacies.⁷

Simultaneous infection with HDV and HBV leads to *coinfection* and infection with HDV after HBV infection leads to *superinfection*. Coinfection can result in a fulminant hepatitis but rarely leads to chronic infection whereas superinfection does result in chronic infection and an accelerated progression to liver disease and hepatocellular carcinoma (HCC) compared with HBV mono-infection. HDV may thus be considered an oncogenic virus itself.⁸ Even though mild clinical forms of disease resulting from HDV infection are seen, as well asymptomatic carriage of HBV and HDV together, because of the rapid pathogenesis that can result the combination of HDV and HBV infection is considered the most severe form of chronic viral hepatitis.

Epidemiology and disease burden

Infection with HDV is underdiagnosed owing to limited access to diagnostics,⁹ and its burden and impact are thought to be largely underestimated and not well understood. As observed in Europe in

the 1980s, the distinctive feature of chronic hepatitis D in countries endemic for HDV is the accelerated progression to cirrhosis and HCC.¹⁰

Risk factors for HDV infection are similar to those for HBV infection, and include injecting drug use and unprotected sex, together with other infections (for example HIV and HCV), and living in or coming from countries endemic for HDV. Vertical transmission, however, is rare. Generally, men are at greater risk than women.

As global coverage rates of universal childhood hepatitis B vaccination progressively grow, reported incidence rates of hepatitis D in countries with testing and surveillance have declined in some regions; outbreaks of fulminant hepatitis D with high mortality are, however, still reported in many countries. Nevertheless, hepatitis B vaccination coverage is not optimal everywhere and WHO estimates that still some 257–296 million people are living with chronic HBV infection and thus may be either already infected with HDV or at risk of infection with HDV. For 2016, WHO's figures (based on an assumed global rate of 5% of HBsAg-positive carriers being infected with HDV) indicate that about 15 million people are likely to be infected with HDV¹¹ and a more recent systematic review and meta-analysis of reports from 95 countries puts the estimated figure at 12 million (range 8.8–18.7 million).¹² Other estimates put the current figure between 15 and 48 million people worldwide or even as high as 72 million, but good data are missing.

The prevalence of HDV infection and genotypes varies across the world, with highest rates seen in foci around the Mediterranean, central Africa, in the Middle East and in central, northern and eastern Asia.¹³ Reported figures range from 3% in Europe and Asia to 6% in Africa and the Americas (especially among Amerindian peoples), with global figures of 4.5% in HBsAg-positive people in the general population and 16.4% in those in hepatology clinics. People who inject drugs (PWID), commercial sex workers, men who have sex with men and people with HCV infection have higher odds ratios for being infected with HDV than those not reporting these risk factors.^{12, 14} Some of the highest reported rates have been observed in Mongolia and other countries in central Asia (including Uzbekistan and Kyrgyzstan), the Punjab region of India, Pakistan, Somalia and west and central Africa. Particularly high rates are seen in central Africa but there are only limited data for eastern and southern Africa. High rates of HBV and HDV coinfection are reported also in WHO's Western Pacific Region, in response to which WHO is establishing service delivery networks and coordinating prevention and control measures, although more needs to be done on hepatitis D. In South America, where genotype 3 predominates, the highest burden of HDV infection and disease is found in the Amazon Basin (covering areas of Bolivia, Brazil, Colombia, Peru (see below) and Venezuela). Data from the USA show that the reliability of reported prevalence rates depends on consistency of testing and the tests being used. In Europe, after an initial significant decline in disease burden in the 1990s there has been no further decrease over the past years, probably because of immigration of people from countries endemic for HDV.¹⁵ Few temporal data are available, making it difficult to identify trends.

Several reports described low prevalence of HDV infection in general populations (at about 1–2% of the figure for HBsAg positivity), but caution must be taken when interpreting these findings given the paucity of large-scale studies, the fact that many studies were not representative, and questions about the tests used. WHO's prequalified lists currently contain no HDV diagnostics; most tests in use are locally manufactured or based on in-house assays. Moreover, in lower- and middle-income countries testing for HDV is rare, especially outside tertiary care centres. Thus, treatment algorithms and policies based on the premise that prevalence was low may need to be reconsidered.

Two different patterns of patient distribution are being seen. In those low- and lower- and middle-income countries where the virus is endemic, there has been no substantial change in the epidemiological trends, although there have been reports of HDV associated with HBeAg-negative HBV infection. In high-income countries, in contrast, the pattern has shifted from an ageing cohort of domestic patients with advanced liver disease representing the end stage of HDV disease to a younger generation of immigrants from endemic countries who now account for most new infections (the population with the highest HBV burden in the USA, for instance). The epidemiological situation in Italy was described as “vanishing but not yet vanished” as HBV rates plummeted, leading to the perception that hepatitis D was no longer a medical problem in the domestic population. Nevertheless, cases of hepatitis D in immigrants rose, adding to the public health burden.¹⁶ In Switzerland, a 10-year retrospective study found that one third of the hepatitis D patient population was of African origin, confirming that population movements and migration from highly endemic regions to low-prevalence countries are changing the demographics of chronic hepatitis B and thus HDV, particularly in central Europe. The authors judged that the situation represents a public health challenge for host countries.¹⁷

Chronic hepatitis D poses a significant risk for development of HCC. An extreme example of this significant problem is seen in Mongolia but it is also seen in other central Asian countries.* Persistent HDV replication more than doubles the rate of progression to liver disease and the presence of HDV RNA is a major predictor of progression to cirrhosis and mortality.

The question was raised of how much disease that is thought to be caused by HBV is actually due to HDV? Are flares in chronic hepatitis B actually manifestations of hepatitis D? In Italy, cases of HBsAg positivity are being reanalysed in order to assess the real burden of hepatitis D. Asymptomatic carriers of both HBV and HDV may exist. Some instances of HBV-negative but HDV-positive patients with HCV infection have been seen, raising the possibility of transmission of HDV through viruses unrelated to HBV.¹⁸ Studies in humanized mice show that several viruses unrelated to HBV and including HCV can act as helper viruses by packaging HDV ribonucleoproteins, facilitating egress of HDV particles and entry into cells with relevant receptors. Furthermore, HCV also propagated HDV infection of the liver.¹⁹ Alternatively, HDV infection in the apparent absence of HBV could reflect occult HBV infection.

The finding of new HDV-like viruses in a diverse range of animals raises questions about the origin of HDV and its evolution.²⁰ It was observed that in Guadeloupe, where many people have their roots in Africa, there is no HDV, suggesting that HDV was not present in the African continent several centuries ago.

Epidemiology: country examples

France

There have been a few studies on HDV infection and its clinical sequelae. Academic interest in HDV and its disease burden is growing, as exemplified for instance by the establishment of specialist centres including a national reference centre for HDV. In separate studies, reported prevalence ranged from 2% in blood donors and 3.7% in new HBV-positive patients to 12.6% in coinfecting HIV-infected subjects.

A nationwide retrospective study of 1112 HDV-infected patients from 34 centres across France (the DeltaVir cohort of hospitalized patients in 2000-2013) found that most cases of HDV infection (86%)

* See Mentha et al (2019), reference 3.

were in immigrants, mainly from sub-Saharan Africa (49%) or Europe (16-17% from both western and eastern Europe); most cases were due to genotypes 1 and 5 (with those with genotype 5 having higher rates of liver fibrosis). Risk factors included injecting drug use, but place of birth, genotype and persistent viraemia constituted the main determinants of liver involvement and response to treatment in patients with chronic HDV infection.²¹

Germany

Notifications of HDV infection have been increasing in recent years, but this finding could be due to increasing awareness, more testing or both. A broad systematic literature review was undertaken to support the national strategy on meeting WHO's goals for eliminating viral hepatitis by 2030, but data on hepatitis D were scarce and often old.²² Prevalences of HDV infection of 1.2% for HBsAg-positive blood donors and 1.45% for general HBsAg-positive cohorts were reported; generally higher figures are recorded in at-risk populations. Most patients with hepatitis D (85%) were from other countries (including eastern Europe), with more men than women and average age of 37 years. The number of notified cases has increased over the past 20 years. The picture remains incomplete, with much research remaining to be done.

Georgia

Data on HDV in the country are poor (and those on trends are not very reliable). The burden of HBV in the country is intermediate to high (2.7%) – a 2013 study reported an HBsAg prevalence of 2.5% in pregnant women. HBV vaccination rates have risen since the introduction of the vaccine into the childhood immunization schedule in 2001 and as a universal birth dose in 2003, leaving fewer individuals susceptible to HBV and HDV. Georgia has an internationally-supported national hepatitis C elimination programme, which includes serosurveys for HBV and HCV infection in the general population. The prevalence of coinfection with HBV and HCV is among the highest in the world. The estimated prevalence of HDV coinfection (HDV RNA positive) is 0.9%; all cases (mostly men with compensated liver disease) have been due to genotype 1. Risk factors for HDV infection include a history of blood transfusion, incarceration and injecting drug use.²³ Infection control is insufficient.

Challenges include poor knowledge of viral hepatitis in the general population and of HBV and HDV among clinicians, lack of standardized international guidelines for management of HDV infection and disease, lack of access to HBV treatment, no access to clinical trials and no financial support from the State or private insurance companies.

Peru

A report from Peru highlighted the striking impact of hepatitis B vaccination as prevention of both hepatitis B and D.²⁴ Previously, Peru was a country with an intermediate endemicity level for HBV infection, with areas of high, medium and low endemicity in its different regions. The government introduced a pilot hepatitis B vaccination programme in children aged 5 years in hyperendemic regions in 1991, extending this to universal vaccination of all newborns in all areas in 2003. Among native communities in the jungle and in some locations in the highlands such as Abancay and Huanta, however, a prevalence of 14% of HDV infection had been reported in apparently healthy school-age children. After 20 years of the vaccination programme, the prevalence of HBsAg in children aged under 5 years in the Peruvian Amazon fell to zero in 2010,²⁵ and the prevalence of HBsAg in the general population of the highlands decreased from 9.8% to <2%. Nationally, hepatitis D has almost disappeared; a low prevalence of 0.4% has been reported and no case has been detected recently in people under 30 years of age.²⁶ Before the vaccination programme, HDV circulated in eight departments in the country; subsequently it has been reported in only two (Ayacucho and Loreto). Declines in infections and liver disease were also recorded. The health

ministry issued national guidelines for the prevention, diagnosis and treatment of viral hepatitis in 2018, and an elimination plan for viral hepatitis in Ayacucho will run until 2024.²⁷

Policy responses

Generally, policy responses to hepatitis D have been unremarkable; for instance, it is not covered by WHO’s global health-sector strategy for viral hepatitis for 2016–2021 and hepatitis D does not feature among the elimination targets for 2030. WHO is in the process of drafting a new high-level strategy for viral hepatitis for 2022–2030²⁸ (which will take into consideration the conclusions of the present meeting) for submission to its governing bodies in 2022.

Until recently, little research has been done, with the pharmaceutical industry showing little interest in developing antiviral agents for what has sometimes, erroneously, been described as an orphan disease. In recent years, academic institutions have stepped into the breach, and research is generating new tools, medicines and approaches, which are being tested.

The European Association for the Study of the Liver (EASL) includes coinfection with HBV and HDV in its latest HBV clinical practice guidelines and is currently drafting recommendations for the treatment of hepatitis D and for testing all HBsAg-positive people for anti-HDV antibodies. The American Association for the Study of Liver Disease (AASLD) recommends such testing only for HBsAg-positive people with risk factors, but complex criteria may have resulted in targeted testing. (Also, in the USA the Food and Drug Administration has not approved any HDV assay.) Despite EASL’s recommendations, a study in Spain found that a large proportion of HBsAg-positive individuals were not tested for anti-HDV antibodies, particularly in primary care settings, resulting in many hepatitis D patients remaining undiagnosed.²⁹ (See Table 1 for a summary of key elements regarding hepatitis D in guidelines addressing hepatitis B)

Funding remains an issue in every country.

Table 1

Key elements regarding hepatitis D in guidelines addressing hepatitis B (last updated February 2022)*

| | Epidemiology | Natural history | Screening, diagnosis | Treatment | Management | Prognosis |
|-------|---------------------|------------------------|--|--|---|------------------|
| AASLD | – | – | Anti-HDV screening is recommended in HIV positive persons, persons who inject drugs, men who have sex with men, those at risk for sexually transmitted diseases, | Pegylated IFN α (PegIFN α) for 12 months is the recommended therapy for those with elevated HDV-RNA levels and ALT elevation. If HBV-DNA levels are | Assessment of HDV-RNA is warranted if ALT elevation occurs following treatment because of the high rates of relapse. Reasonable to refer patients to specialized centres that | – |

| | Epidemiology | Natural history | Screening, diagnosis | Treatment | Management | Prognosis |
|-------|--|---|--|--|---|---|
| | | | migrants from areas of high HDV endemicity, patients with low HBV-DNA levels and elevated ALT levels. | elevated, concurrent therapy with NA is indicated. | offer access to experimental therapies. | |
| EASL | – | Severe or fulminant hepatitis is more frequently reported in HBV-HDV co-infection compared to HBV mono-infection. Chronic infection after acute HBV-HDV hepatitis is less common, while chronic delta hepatitis develops in 70–90% of patients with HDV superinfection. | Confirmed by detectable HDV RNA, immuno-histochemical staining for HDV antigen, or IgM anti-HDV. However, diagnosis of active HDV infection may be difficult, as HDV RNA assays are not standardised and HDV antigen and IgM anti-HDV assays are not widely available. | PegIFN α for at least 48 weeks is the current choice in HDV-HBV co-infected patients with compensated liver disease. It can be continued irrespective of on-treatment response pattern if well tolerated. Patients with ongoing HBV DNA replication, NA therapy should be considered. | Long-term follow-up HDV RNA monitoring is recommended for all treated patients as long as HBsAg is present. | Persistent HDV replication leads to cirrhosis and HCC at annual rates of 4% and 2.8%, leading to high fatality rate and justifying the need for antiviral therapy. |
| APASL | The prevalence of HDV has not declined. In the United States of America, Australia and some European countries, the prevalence of HDV infection is increasing. | Chronic infection after acute HBVHDV hepatitis is less common, while chronic hepatitis D develops in 70–90% of patients with HDV superinfection. | Confirmed by detectable HDV RNA, immuno-histochemical staining for HDV antigen, or IgM anti-HDV. But diagnosis of active HDV infection may be difficult, as HDV RNA assays are not | Pegylated interferon is effective against HDV. Weekly injection of pegylated interferon is currently used for 12–18 months. Nucleotide analogues treatment might be | Patients should be monitored for 6 months post treatment and beyond. | HDV can cause severe liver injury that may result in fulminant hepatic failure and rapid progression to cirrhosis and hepatic decompensation, as well as an increased risk of liver cancer. |

| | Epidemiology | Natural history | Screening, diagnosis | Treatment | Management | Prognosis |
|-----|---|--|---|--|-------------------|---|
| | | | standardized and HDV antigen and IgM anti-HDV assays are not widely available. | considered in some patients who have active HBV replication with persistent or fluctuating serum HBV DNA levels above 2000 IU/ml. | | |
| WGO | Up to 5% of the world's population is infected with HBV, and probably 5% of those chronically infected with HBV have HDV infection. Some endemic areas in the developing world may have much higher prevalence. | Coinfection evolves to chronicity in only 2% of cases, but is associated with a higher chance of fulminant acute infection, while superinfection leads to progressive disease and cirrhosis in more than 80% of cases. | Should be evaluated particularly if hepatitis is present in the face of little or no HBV viral replication, or if they come from an HDV-endemic region or have acquired HBV through injection drug use. Infection should be diagnosed by detection of HDV RNA in serum by polymerase chain reaction, or indirectly by detection of antibodies against hepatitis D antigen of the IgG and IgM classes. | Chronic hepatitis D should be treated with IFN (preferably pegIFN) for at least 12 months, but the treatment results are suboptimal. Patients with active HBV replication despite HDV coinfection may benefit from treatment with NA in combination with PegIFN. | — | Cirrhosis develops at a younger age than in patients with chronic HBV mono-infection. |

*AASLD, American Association for the Study of Liver disease; EASL, European Association for the Study of the Liver; APASL, Asian Pacific Association for the Study of the Liver; WGO, World Gastroenterology Organisation Global Guideline.

ALT, alanine aminotransferase; NA, nucleos(t)ide analogue; IFN, interferon; PegIFN, pegylated interferon

Source: Hayashi T, Takeshita Y, Hutin YJ, et al. The global hepatitis delta virus (HDV) epidemic: what gaps to address in order to mount a public health response? Archives of Public Health 2021 Oct;79(1):180. DOI: 10.1186/s13690-021-00693-2. PMID: 34663473; PMCID: PMC8525025.

Diagnostic tools and screening

Participants agreed that testing for HDV infection should be a reflex action for every new case of HBsAg-positivity that is detected, incorporated into management guidelines and policies. Diagnosis can identify exposure (antibodies – total or IgG) and infection (RNA). Although IgM antibodies persist in chronic HDV infection, they can be absent in African patients and were generally ruled to be not useful in clinical practice.

Diagnostic tests to detect anti-HDV antibodies are not widely available, and there has been limited standardization of HDV RNA assays (PCR). For the few that are available, quality assurance is not guaranteed. Existing sensitive assays include qualitative PCR tests, antibody ELISAs, and the quantitative microarray antibody capture (Q-MAC) assay (the latter is proposed as valuable for population screening following its use in detecting an HDV prevalence of about 60% in HBV-infected Mongolian subjects).³⁰ Nevertheless, more reliable tools for diagnosis or detection of markers of HDV infection are needed. Most available assays underestimate or fail to measure viral load (the variability of the viral genome is responsible), but some show promise. Quantification of viral load is important as the concentration of HDV RNA predicts the response to treatment and is a guide to deciding the duration of maintenance of treatment. The probability of detecting anti-HDV antibodies is not consistent across all stages of the clinical spectrum, from lowest in asymptomatic and mild disease to high in advanced disease and in high-risk settings. Point-of-care tests are being developed but are not yet on the market. Whole-blood tests for rapid diagnosis would be valuable.

The first international study on quality control for HDV RNA viral load quantification attracted 28 participating laboratories from 17 countries worldwide. Less than one half the participants correctly quantified all positive samples and several underestimated RNA from African genotypes (1 and 5-8).³¹ The results underline the urgent need to improve methods for monitoring HDV viraemia.

Non-invasive diagnostic methods for liver fibrosis, such as transient elastography, are considered useful tools for evaluating the stage of fibrosis, and are often preferable to liver biopsy, but specific cut-offs for degrees of fibrosis in hepatitis D have not been well defined. Newer promising methods include the delta-4 fibrosis score³² and the BEA (baseline event anticipation) score.

Not only should diagnostic tests be standardized but they should be optimized for genotypes and genotype subtypes. Strategies for their use and application should be developed, including diagnostic algorithms, starting from detection of a positive result for HBV infection. Once those tools are available and deemed reliable, they can be used for the screening of all HBsAg carriers. The Russian Federation has changed its clinical guidelines for HDV; testing for HDV is now mandatory in all cases of HBsAg-positive tests irrespective of clinical presentation.

Screening for HDV infection is insufficient and, in some countries (for instance, Greece) declining. Its practice is also limited; for example, few people with HCV or HIV infection are screened for HDV; higher but still low rates of screening are reported for different groups and races. How to ensure reporting of results from laboratories on a routine basis is an issue to be resolved, and it was noted that many laboratories are not prepared to invest in expensive tests that may be used only infrequently – HDV infection is not seen as a priority compared with the other workload.

As reported in France, most cases of HDV infection are being seen in immigrants. As with other marginalized groups, their management is difficult – they face poor access to healthcare systems in

the first place, they tend to attend for one visit and then are lost to follow-up. Rapid testing methods would be a great help.

Some argue that low prevalence rates argue against screening, but given limited information on burden and prevalence screening is needed to best characterize the true epidemiological picture before creating risk-based strategies. Testing in lower- and middle-income countries and outside tertiary centres is low. Elsewhere there may be a “diagnostic inertia” to test for HDV and questions arise about reimbursement of costs. Advent of new treatments will provide an additional reason for screening.

Treatment

WHO estimated that globally at least 26 million people and possibly 65 million with HBV infection are eligible for treatment.³³ For those with HDV, treatment options are limited and current recommended treatment does not have high success rates.

The only currently-recommended treatment, with **pegylated interferon-alpha**, is unsatisfactory with undetectable serum HDV RNA levels 24 weeks after end of treatment in only 20—33% of cases as well as side effects and poor tolerance. A recent meta-analysis confirmed its limited effectiveness, noting only rare clearance of HBsAg and seroconversion to anti-HBs in treated chronic HDV patients.³⁴ Re-examination with a new quantitative PCR assay of samples from one large clinical trial that had previously been classified as having undetectable levels of HDV RNA showed that one-third contained HDV RNA. Furthermore, detectable low-level HDV viraemia with the sensitive assay at 48—96 weeks after cessation of treatment was associated with a high risk of HDV RNA relapse.³⁵ Addition of nucleos(t)ide analogues added no benefit and doubling the duration of treatment to two years did not improve results. Some data indicate that long-term treatment, up to 10 years, may produce better virological results.

The main targets for novel antiviral approaches against HDV are viral entry, assembly and egress. Four new therapeutic agents or approaches were reviewed.

Bulevirtide, a polypeptide analogue (47 amino acids) of the hepatitis B large surface antigen, blocks the entry of the HBV and thereby also HDV into liver cells by competitive inhibition of binding to the HBV receptor, the sodium taurocholate co-transporting polypeptide. This results in a limitation of cell-to-cell spread of HBV and HDV in the liver. In 2020 it was given “conditional marketing authorization” by the European Medicines Agency, which regularly reviews further evidence on the effectiveness of the antiviral agent.³⁶ It is administered by daily subcutaneous injections.

Monotherapy with bulevirtide is safe and well tolerated through 24 weeks of treatment (and in some cases up to three years³⁷); it was associated with significant HDV RNA declines and improvements in biochemical parameters (alanine aminotransferase activity). Longer follow-up to confirm clinical benefit of this new treatment is underway in phase III trials.

Lonafarnib, a small non-peptide molecule, inhibits a host enzyme (farnesyl transferase) that is essential in the assembly of HDV particles, namely the prenylation of its major structural protein. It is an oral medication that has been approved by the US Food and Drug Administration for treatment of rare disorders, but is currently under investigation for the treatment of hepatitis D. It can be used as monotherapy for hepatitis D or boosted with ritonavir and pegylated interferon. Several phase II clinical trials in various countries have been completed with promising results; a phase III trial of the triple combination is underway, and although there have been no major safety concerns to date but tolerance is poor.³⁸

Interferon-lambda is a class III interferon, receptors for which are highly expressed on epithelial cells but otherwise not widely distributed in the body, and thus might be better tolerated than other interferons. Phase II trials have shown promising virological and biochemical responses. A phase III trial to evaluate the safety and efficacy of pegylated interferon lambda treatment for 48 weeks with 24 weeks follow-up compared to no treatment for 12 weeks in patients chronically infected with HDV is in preparation; the outcome sought will be the proportion of patients with undetectable HDV RNA.³⁹ The results of a Phase II trial show that the combination of lonafarnib, ritonavir and interferon lambda is safe and generates a good virological response on treatment, but there are gastrointestinal side effect due to inhibition of a host enzyme and off-treatment viral relapses occur in a considerable proportion of patients.⁴⁰

The end points in clinical trials of treatment of coinfection with HBV and HDV need definition. Undetectable serum HDV RNA six months after stopping treatment has been considered a primary end point with an intermediate goal of normalization of alanine aminotransferase activity, but RNA negativity is now not considered to be a good marker for treatment efficacy. A reliable early predictor of nonresponse has not yet been defined.⁴¹ Some experts have proposed a decline in HDV RNA from baseline of ≥ 2 log together with normalization of alanine aminotransferase activity as a reasonable surrogate for future treatments, but others do not endorse this endpoint.⁴²

Discussions also touched on the question of when to start treatment. Serological markers were deemed to be not suitable to guide the decision.

Treatment: group discussion

A group discussion focused on three questions: how to improve the outcome for patients with hepatitis D, is treatment optimal and, if not, what would constitute the best treatment, and can HDV be eliminated and, if not, why not?

Outcomes could be improved by starting with raising awareness of hepatitis D – from the general population through to clinicians and policy-makers. Advocacy campaigns and publication of data and results would help. Revised guidelines resulting in routine screening and better testing methods and programmes, including those for anti-HDV antibodies, could lead to earlier identification and treatment.

The optimal treatment does not yet exist. Current regimens are unsatisfactory. New treatments are in clinical trials, some at phase III, but it will be some time before they become approved, established and available at affordable prices. Combination therapies against HDV rather than monotherapy may be necessary to obtain firm clinical endpoints, especially when aiming at loss of HBsAg. Further work is needed to determine factors that predict those patients who need long-term treatment and the timing of cessation of treatment. Bulevirtide looks promising for maintenance therapy, but alternative formulations to daily injection would be preferable; an oral form would be valuable or even a version that could be self-injected.

Elimination of HDV depends on elimination of HBV, for which the answer lies in vaccination against hepatitis B with much broader coverage of vaccination programmes. In this way, elimination of hepatitis D as a public health problem is feasible and relatively cheap, but the goal will not be achieved before 2030. Elimination activities will need a better understanding of the epidemiology of HDV, standardized testing strategies and better treatment options. For individual patients, it is not yet possible to talk of cure of hepatitis D – such expectations of clinicians and patients need to be tempered; the immediate goal is functional remission through treatment.

Issues and needs

Poor awareness of hepatitis D and HDV exists in many countries at clinical, medical, scientific, political and general population levels. Physicians need to be educated about prevention, control and management. More information needs to be disseminated broadly about the essential role of hepatitis B vaccination in eliminating HDV, using examples such as the success of the hepatitis B vaccination programme in Peru in reducing the burden of HDV at the same time as HBV infection and disease. Also, the severity of the public health problem due to hepatitis D needs to be recognized, for example the situation among PWID in Ukraine where prevalences of HIV and HCV as well as HDV are also high. Publication of more abstracts and articles is one way to spread the message.

Several taxonomies exist for naming HDV genotypes. Consensus needs to be reached on one nomenclature and its application ensured (with notification of journal editors, for instance).

Poor or lacking data, often old and not updated and from unrepresentative groups, result in underestimation of prevalence. Many studies have been small and limited (geographically and in scope) and focus on patients with advanced liver disease or at high-risk; denominators are varied (general population or HBsAg-positive cases); temporal data (trends) are few; and not all antibody-positive subjects have active HDV-related liver damage. Necessary improvements include:

- different, broader and more representative groups for both screening and epidemiological studies;
- generation of more genotype-specific information;
- screening of marginal groups for both HBV and HDV;
- standardization or better definition of methods for determining prevalence;
- creation of algorithms for HDV testing of every new case of HBsAg-positivity.

It is clear that HDV is widespread but often has not been recognized or identified. The maxim “seek, and ye shall find” seems to apply to future epidemiological work.

Beside epidemiological studies, better data are needed on everything from hepatitis D virus itself (genetic features, phylogeny and correlation with clinical outcomes) to antiviral agents in the development pipeline. Areas for further work include:

- definition of markers of infection and their behaviour (for example, the probability of finding HDV antibodies at all stages of the clinical spectrum is low);
- descriptions of the natural history of hepatitis D;
- determination of the attributable fraction of HDV to cirrhosis and HCC (estimated at 20% in one study);
- standardization of sera and reference materials;
- development or refinement and standardization of diagnostic assays, including commercial, inhouse and new tests (for instance, PCR tests for genotypes) and their availability and affordability;
- staging of liver fibrosis: development of reliable non-invasive tests;
- conclusion of clinical trials of new therapies and investigation of new combination treatments, aiming for licensure and negotiations for availability and affordable pricing;
- identification of reproducible virological endpoints that predict long term clinical outcomes in clinical trials;
- indications of when to stop treatment and evaluation of benefits of long-term versus short-term treatment;

- developments of alternatives to daily subcutaneous injection of bulevirtide such as an oral formulation or possibly self-administered injections.

At the public health level, the practicality, benefits and costs of screening (as well as of new treatment regimens) need greater consideration. Building and maintaining networks such as those in WHO's Western Pacific Region must be given attention. Sources and mechanisms of sustainable funding must be found. High-level input into the drafting of WHO's global health sector strategy for viral hepatitis 2022–2030 should continue urgently for its consideration by WHO's governing bodies. At national levels, efforts should be made to intensify maximal implementation of universal coverage of hepatitis B vaccination; this would accelerate declines in the prevalence of hepatitis D even if not in a sufficiently timely manner to ensure elimination of HDV by 2030.

The final, strong message was that every new diagnosis of a case of HBV infection should be, as a reflex, tested for HDV. Liver associations such as EASL and AASLD should be encouraged to change their guidelines for screening to start with the detection of every new case of HBsAg-positivity, and these should be broadly disseminated and promoted. Meanwhile, more intensive educational activities and new strategies for anti-HDV testing particularly focused on migrant populations should be devised and implemented.

References

- ¹ Jacobson IM (2021) Hepatitis D virus (<https://www.hepb.org/assets/Uploads/HDV-program-MYR-Jan-26-2021-FINAL-2-3-1.pdf>, accessed 1 November 2021).
- ² Usman et al (2020) Welcome to Hepatitis Delta Virus Database (HDVdb) (hdvdb.bio.wzw.tum.de, accessed 2 November 2021)
- ³ Mentha N, Clément S, Negro F, Alfaiate D. A review on hepatitis D: From virology to new therapies. *Journal of Advanced Research*, 2019 May; 17:3-15. DOI: 10.1016/j.jare.2019.03.009. PMID: 31193285; PMCID: PMC6526199
- ⁴ Sagnelli C, Sagnelli E, Russo A, Pisaturo M, Occhiello L, Coppola N. HBV/HDV Co-Infection: Epidemiological and Clinical Changes, Recent Knowledge and Future Challenges. *Life (Basel)*. 2021 Feb 22;11(2):169. doi: 10.3390/life11020169. PMID: 33671730; PMCID: PMC7926847.
- ⁵ Karimzadeh, H, Usman, Z, Frishman, D, Roggendorf, M. Genetic diversity of hepatitis D virus genotype-1 in Europe allows classification into subtypes. *J Viral Hepat*, 2019; 26: 900– 910. <https://doi.org/10.1111/jvh.13086>
- ⁶ Barros LMF, Gomes-Gouvêa MS, Pinho JRR, Alvarado-Mora MV, Dos Santos A, Mendes-Corrêa MCJ et al. Hepatitis delta virus genotype 8 infection in Northeast Brazil: inheritance from African slaves? *Virus Res*. 2011; 160: 333-339
- ⁷ Wang W, Lempp FA, Schlund F, Walter L, Decker CC, Zhang Z, Ni Y, Urban S. Assembly and infection efficacy of hepatitis B virus surface protein exchanges in 8 hepatitis D virus genotype isolates. *J Hepatol*. 2021 Aug;75(2):311-323. doi: 10.1016/j.jhep.2021.03.025. Epub 2021 May 5. PMID: 33845061.
- ⁸ Farci P, Niro GA, Zamboni F, Diaz G. Hepatitis D virus and hepatocellular carcinoma. *Viruses*. 2021 May 4;13(5):830. doi: 10.3390/v13050830. PMID: 34064419; PMCID: PMC8147829.
- ⁹ Papatheodoridi, M, Papatheodoridis, GV. Is hepatitis delta underestimated? *Liver Int*. 2021; 41: 38– 44. <https://doi.org/10.1111/liv.14833>
- ¹⁰ Rizzetto, M., Hamid, S. S., Negro, F. (The changing context of hepatitis D. *J Hepatology*, 2021; 74(5):1200-1211. (<https://www.sciencedirect.com/journal/journal-of-hepatology/vol/74/issue/5>).
- ¹¹ WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015, p.22 (https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1)
- ¹² 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 Sep;73(3):523-532. doi: 10.1016/j.jhep.2020.04.008. Epub 2020 Apr 23. PMID: 32335166; PMCID: PMC7438974.

-
- ¹³ Hayashi T, Takeshita Y, Hutin YJ, Harmanci H, Easterbrook P, Hess S, van Holten J, Oru EO, Kaneko S, Yurdaydin C, Bulterys M. The global hepatitis delta virus (HDV) epidemic: what gaps to address in order to mount a public health response? *Arch Public Health*. 2021 Oct 19;79(1):180. doi: 10.1186/s13690-021-00693-2. PMID: 34663473; PMCID: PMC8525025.
- ¹⁴ 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 Apr 27;221(10):1677-1687. doi: 10.1093/infdis/jiz633. PMID: 31778167; PMCID: PMC7184909.
- ¹⁵ Vlachogiannakos J, Papatheodoridis GV (2020). New epidemiology of hepatitis delta. *Liver Int.*, 2021; Feb;40 Suppl 1:48-53. doi: 10.1111/liv.14357. PMID: 32077599.
- ¹⁶ Caviglia GP, Martini S, Ciancio A, Niro A, Olivero A, Fontana R, Tandoi F, Rosso C, Romagnoli R, Saracco GM, Rizzetto M. The hepatitis D in Italy. A vanishing infection, not yet a vanished disease. *Physician's Weekly* (<https://www.physiciansweekly.com/the-hepatitis-d-virus-in-italy-a-vanishing-infection-not-yet-a-vanished-disease>, accessed 3 November 2021).
- ¹⁷ Vieira Barbosa J, Sahli R, Aubert V, Chaouch A, Moradpour D, Fraga M. Demographics and outcomes of hepatitis B and D: a 10-year retrospective analysis in a Swiss tertiary referral center. *PLoS One*; 2021; April 27: <https://doi.org/10.1371/journal.pone.0250347>
- ¹⁸ Chemin I, Pujol FH, Scholtès C, Loureiro CL, Amirache F, Levrero M, Zoulim F, Pérez-Vargas J, Cosset FL. Preliminary Evidence for Hepatitis Delta Virus Exposure in Patients who are Apparently not infected with Hepatitis B Virus. *Hepatology*; 2021; Feb;73(2):861-864. doi: 10.1002/hep.31453. Epub 2021 Jan 27. PMID: 32628280; PMCID: PMC7898870.
- ¹⁹ Perez-Vargas J, Amirache F, Boson B, Mialon C, Freitas N, Sureau C, Fusil F, Cosset FL. Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo. *Nat Commun*. 2019; May 8;10(1):2098. doi: 10.1038/s41467-019-10117-z. PMID: 31068585; PMCID: PMC6506506.
- ²⁰ Peres-Vargas J, Pereira de Oliveira R, Jacquet S, Pontier D, Cosset F-L, Freitas N. HDV-like viruses. *Viruses*;2021: 13(7):1027 (<https://doi.org/10.3390/v13071207>, accessed 4 November 2021).
- ²¹ Roulot D, Brichtler S, Layese R, Ben Abdesselam Z, Zoulim F, Thibault V, Scholtes C, Roche B, Castelnau C, Poynard T, Chazouilleres O, Ganne N, Fontaine H, Gournay J, Guyader D, Le Gal F, Nahon P, Roudout-Thoraval F, Gordien E, Deltavir Study Group. Origin, HDV Genotype and persistent viraemia determine outcome and treatment response with chronic hepatitis delta. *J Hepatol*, 2020; 73(5):1046-1062
- ²² Steffen G, Sperle I, Leendertz SA, Sarma N, Beermann S, Thamm R, Zimmerman R, Dudareva S. The epidemiology of hepatitis B, C and D in Germany: a scoping review. *PLoS One*, 2020; 15(3): e0229166. <https://doi.org/10.1371/journal.pone.0229166>
- ²³ Kasradze A, Shadaker S, Kuchuloria T, Gamkrelidze A, Nasrullah M, Gvinjilia L, Baliashvili D, Chitadze N, Kodani M, Tejada-Strop A, Drobeniuc J, Hagan L, Morgan J, Imnadze P, Averhoff F. The burden and epidemiology of hepatitis B and hepatitis D in Georgia: findings from the national seroprevalence survey. *Public Health*, 2021; 185:341-347 doi:10.1016/j.puhe.2020.06.024.
- ²⁴ Cabezas C, Trujillo O, Gonzales-Vivanco Á, Benites Villafane CM, Balbuena J, Borda-Olivas AO, et al. Seroepidemiology of hepatitis A, B, C, D and E virus infections in the general population of Peru: A cross-sectional study. *PLoS One*, 2020; 15(6): e0234273. <https://doi.org/10.1371/journal.pone.0234273>
- ²⁵ Cabezas C, Trujillo O, Balbuena J, Peceros FdM, Terrazas M, Suarez M, et al. Decrease in the prevalence of hepatitis B and D virus infections in an endemic area in Peru 23 years after the introduction of the first pilot vaccination program against hepatitis B. *PLoS ONE*, 2020; 15(8): e0236993. <https://doi.org/10.1371>.
- ²⁶ Cabezas C, Trujillo O, Balbuena J, Peceros FdM, Terrazas M, Suárez M, et al. Decrease in the prevalence of hepatitis B and D virus infections in an endemic area in Peru 23 years after the introduction of the first pilot vaccination program against hepatitis B. *PLoS ONE*, 2020; 15(8): e0236993. <https://doi.org/10.1371/journal.pone.0236993>
- ²⁷ PAHO. Eliminating endemic hepatitis B and D in Ayacucho, Peru. Washington DC: Pan American health Organization (https://www3.paho.org/hq/index.php?option=com_content&view=article&id=15249:eliminating-endemic-hepatitis-b-and-d-in-ayacucho-peru&Itemid=40264&lang=en, accessed 1 November 2021).
- ²⁸ World Health Assembly decision WHA74(20), (2021). The global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections ([https://apps.who.int/gb/ebwha/pdf_files/WHA74/A74\(20\)-en.pdf](https://apps.who.int/gb/ebwha/pdf_files/WHA74/A74(20)-en.pdf), accessed 3 November 2021).
- ²⁹ Palom A (2021). Low adherence to guidelines recommendation for testing hepatitis S in HBsAg positive patients leads to a high rate of undiagnosis. Abstract, AASLD: The Liver Meeting, 12-15 November 2021

(Anaheim, California, USA and virtually) (<https://www.aasld.org/the-liver-meeting/low-adherence-guidelines-recommendation-testing-hepatitis-d-hbsag-positive>, accessed 3 November 2021).

³⁰ Chen X, Oidovsambuu O, Liu P, Grosely R, Elazar M, Winn VD, Fram B, Boa Z, Dai H, Dashtseren B, Yagaanbuyant D, Genden Z, Dashdorj N, Bungert A, Dashdorj N, Glenn JS. A novel quantitative microarray antibody capture assay identifies an extremely high hepatitis delta virus prevalence among hepatitis B virus-infected Mongolians. *Hepatology*, 2017;. Dec;66(6):1739-1749. doi: 10.1002/hep.28957. Epub 2017 Oct 30. PMID: 27880976; PMCID: PMC5441964.

³¹ Le Gal F, Brichler S, Sahli R, Chevret S, Gordien E. First international external quality assessment for hepatitis delta RNA quantification in plasma. *Hepatology*, 2016; 64(5):1483-1494 (<https://doi.org/10.1002/hep.28772>, accessed 4 November 2021).

³² Lutterkort GL, Wranke A, Yurdaydin C, Budde E, Westphal M, Lichtinghagen R, Stift J, Bremer B, Hardtke S, Keskin O, Idilman R, Koch A, Manns MP, Dienes HP, Wedemeyer H, Heidrich B. Non-invasive fibrosis score for hepatitis delta. *Liver Int.* 2017 Feb;37(2):196-204. doi: 10.1111/liv.13205. Epub 2016 Aug 10. PMID: 27428078; and Da BL, Suyrana P, Kleiner DE, Heller T, Koh C (2020). The Delta-4 fibrosis score (D4FS): a novel fibrosis score in chronic hepatitis D. *Antiviral Res* 174:104691. <https://doi.org/10.1016/j.antiviral.2019.104691> (accessed 3 November 2021).

³³ Tan M, Bhadoria AS, Cui F, Tan A, Van Holten J, Easterbrook P, Ford N, Han Q, Lu Y, Bulterys M, Hutin Y. Estimating the proportion of people with chronic hepatitis B virus infection eligible for hepatitis B antiviral treatment worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2021 Feb;6(2):106-119. doi: 10.1016/S2468-1253(20)30307-1. Epub 2020 Nov 14. Erratum in: *Lancet Gastroenterol Hepatol.* 2021 Feb;6(2):e1. PMID: 33197397; PMCID: PMC7801814.

³⁴ Abdрахman A, Ashimkhanova A, Almawi WY. (Effectiveness of pegylated interferon monotherapy in the treatment of chronic hepatitis D virus infection: a meta-analysis. *Antiviral Res*, 2021; 185(January):104995 (<https://doi.org/10.1016/j.antiviral.2020.104995>, accessed 1 November 2021).

³⁵ Bremer, B, Anastasiou, OE, Hardtke, S, Carfuntt FA, Curescu MG, Yalcon K, Akarca US, Gurel S, Zeuzem S, Erhardt A, Luth S, Papatheodoros GV, Radu M, Idilman R, Manns MP, Cornberg M, Yurdaydin C, Wedemeyer H. Residual low HDV viraemia is associated HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis delta: Results from the HIDIT-II study. *Liver Int.*, 2021 ; 41: 295– 299. <https://doi.org/10.1111/liv.14740>

³⁶ European Medicines Agency. Hepcludex (bulevirtide) (https://www.ema.europa.eu/en/documents/overview/hepcludex-epar-medicine-overview_en.pdf, accessed 1 November 2021).

³⁷ Loglio A, Ferenci P, Renteria SCU, Tham CYL, Scholtes C, Holzmann H, van Bämmel F, Birghi M, Perbellini R, Rimondi A, Farina E, Trombette E, Manunta M, Porretti L, Prati D, Ceriotti F, Zoulim F, Bertoletti A, Lampertico P (2021). Safety and effectiveness of up to 3 years' bulevirtide monotherapy in patients with HDV-related cirrhosis (https://www.natap.org/2021/HBV/102521_01.htm, accessed 4 November 2021).

³⁸ Dhillon S. Lonafarnib: first approval. *Drugs*, 2021; 81, 283–289 (<https://doi.org/10.1007/s40265-020-01464-z>, accessed 1 November 2021).

³⁹ US National Library of Medicine (2021). Phase 3 Study to Evaluate the Efficacy and Safety of Peginterferon Lambda for 48 Weeks in Patients with Chronic HDV (LIMT-2) (<https://clinicaltrials.gov/ct2/show/NCT05070364>, accessed 1 November 2021).

⁴⁰ Koh C, Hercun J, Rahman F, Huang A, Da B & Surana P et al. A phase 2 study of peginterferon lambda, lonafarnib and ritonavir for 24 weeks: end-of-treatment results from the LIFT HDV study. The Liver Meeting, October 30, 2020 (oral late breaker L08). https://assets.website-files.com/5f3d77cd56d46907a50fb8d9/5f9d9c2057efc43f55b78db7_2020%20TLMdX%20Late-breaking%20Abstracts-%20Oct%2030.pdf.

⁴¹ Niro GA, Smedile A, Fontana R, Olivero A, Ciancio A, Valvano MR, Pittaluga F, Coppola N, Wedemeyer H, Zachou K, Marrone A, Fasano M, Lotti G, Andreone P, Iacobellis A, Andriulli A, Rizzetto M. HBsAg kinetics in chronic hepatitis D during interferon therapy: on-treatment prediction of response. *Aliment Pharmacol Ther*, 2016;44: 620-628 (<https://doi.org/10.1111/apt.13734>, accessed 1 November 2021).

⁴² Lok AS, Negro F, Asselah T, Farci P, Rizzetto M. Endpoints and new options for treatment of chronic hepatitis D. *Hepatology*, 2021; 74:3479-3485 (<https://doi.org/10.1002/hep.32082>).