HEPATOLOGY

A clinical textbook

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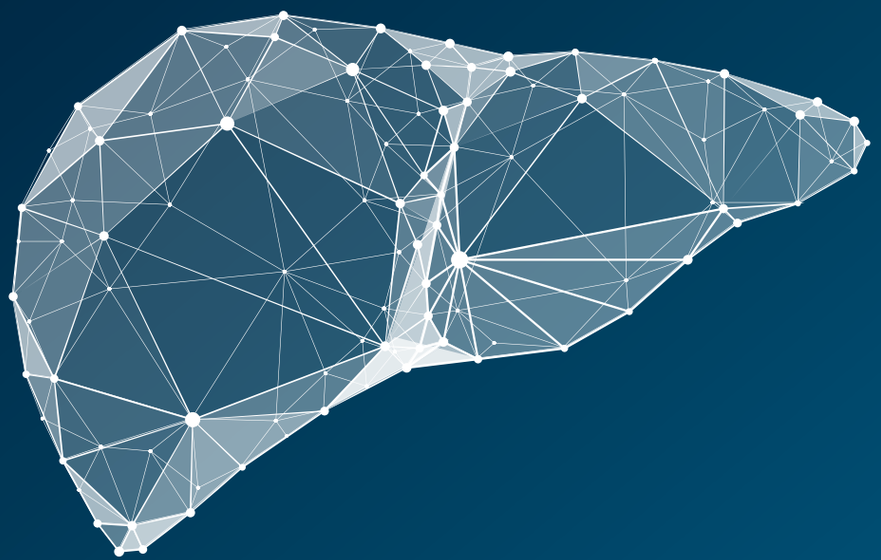

4. Hepatitis D – diagnosis and treatment

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Introduction

The hepatitis delta virus (HDV) is a defective RNA virus which requires the hepatitis B virus (HBV) surface antigen (HBsAg) for generation of infectious virus particles and transmission, while the full extent of the HBV helper function is unexplored (Rizzetto 1983, Taylor 2012). Hence, HDV occurs only in HBsAg positive individuals either as acute coinfection or as superinfection in patients with chronic HBV (Wedemeyer 2010b) (Figure 1). Several studies have shown that chronic HDV infection leads to more severe liver disease than chronic HBV monoinfection, with an accelerated course of fibrosis progression, an increased risk of hepatocellular carcinoma and early decompensation in the setting of established cirrhosis (Beguelin 2017b, Hughes 2011, Manesis 2013). Currently, two treatment options are available and recommended by guidelines (EASL 2023, Sandmann 2023a). The entry-inhibitor bulevirtide has been approved by EMA. Results from phase 2 and 3 studies were published (Wedemeyer 2023a, Wedemeyer 2023c) and confirmed in real-world cohort analyses (Degasperi 2022a, Dietz-Fricke 2023) In the phase 3 study, on-treatment rates of combined response were 45% and 55% at 48 or 96 weeks of treatment, respectively (Wedemeyer 2024, Wedemeyer 2023a). Currently, treatment is recommended indefinitely for as long as the patient is benefitting (EMA 2024a). This is in contrast to treatment with pegylated interferon alfa (PEG-IFN) in which a defined treatment duration of 48 weeks is recommended (EASL 2023, Sandmann 2023a). About one quarter of patients showed prolonged virological off-treatment response but long-term HDV RNA relapses may occur (Heidrich 2014). HBsAg clearance should be the preferred endpoint of interferon-based therapies of HDV, but this is rarely achieved. Yet, suppression of HDV RNA in the presence of HBsAg has been associated with improved clinical outcomes (Farci 2004, Wranke 2017, Yurdaydin 2018a). Additional treatment options are currently in clinical development.

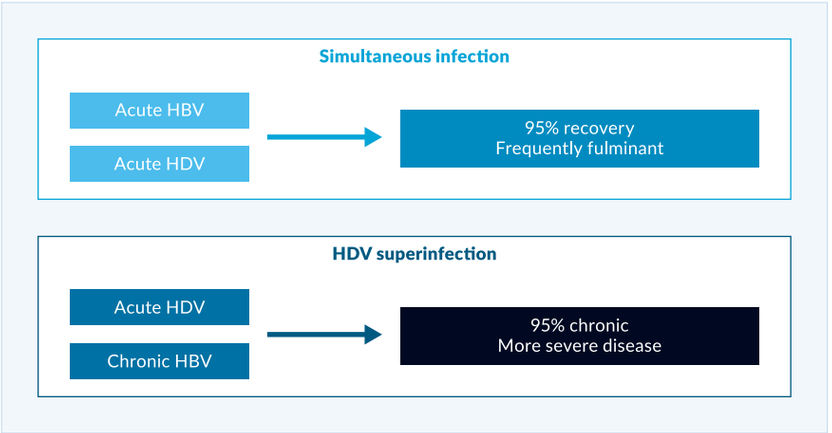

Figure 1. Courses of hepatitis delta

Virology of HDV

The hepatitis D virion is approximately 36 nm in size, containing HDV RNA and delta antigen. HDV RNA is single-stranded, highly base-paired, circular and by far the smallest known genome of any animal virus, containing close to 1700 nucleotides (Sureau 2016, Taylor 2012). It is coated with the envelope protein derived from the pre-S and S antigens of HBV. Other enveloped viruses including HCV and VSV can also propagate HDV infection, both *in vitro* as well in humanized mice (Perez-Vargas 2019). Still, it is currently unclear if viruses distinct from HBV induce dissemination of HDV also in patients. The HDV RNA has six open reading frames (ORFs), three on the genomic and three on the antigenomic strand. One ORF codes for the hepatitis delta antigen (HDAg), while the other ORFs do not appear to be actively transcribed. Two HDAgs exist: the small HDAg (24 kD) is 155 amino acids long and the large HDAg (27 kD) is 214 amino acids long. A single nucleotide change (A-G) in the small HDAg sequence leads to the synthesis of the large HDAg. The small HDAg accelerates genome synthesis, while the large HDAg that inhibits HDV RNA synthesis is necessary for virion morphogenesis (Taylor 2012). Replication of HDV RNA occurs through a 'double rolling circle' model in which the genomic strand is replicated by a host RNA polymerase to yield a multimeric linear structure that is then autocatalytically cleaved to linear monomers and ligated into the circular HDV RNA viral progeny (Sureau 2016). Recent work showed that the host RNA polymerase II-is coactivated by S-HDAg using a histone mimicry strategy (Abeywickrama-Samarakoon 2020).

Genetic analysis has revealed the presence of at least eight HDV genotypes (Le Gal 2017) (Figure 2). Genotype 1 is the most frequently seen and is distributed throughout the world, especially in Europe, the Middle East, North America and North Africa. Genotype 2 is seen in East Asia and the Yakutia region of Russia, and genotype 3 is present exclusively in the northern part of South America, especially in the Amazon basin. Genotype 4 is seen in Taiwan and Japan, while genotypes 5-8 are found in Africa (Deny 2006). HDV genotype 1 is associated with both severe and mild disease whereas genotype 2 causes a milder disease over a long-term course (Su 2006). HDV genotype 5 may also take a milder course and a better response to PEG-IFN treatment compared to genotype 1 (Spaan 2020).

HDV quasispecies evolution declines over time during HDV infection even though a continuous adaptation of HDV occurs indicating ongoing immune pressure in chronic HDV (Homs 2016).

HBV genotypes may also contribute to distinct clinical courses of HDV. There is no evidence that specific HDV genotypes may infect patients with one specific HBV genotype exclusively. However, data indicate that distinct HDV mutations may facilitate association of certain HDV genotypes with different HBV genotypes (Kay 2014). The global distribution of HBV and HDV genotypes is shown in Table 1.

Table 1. HBV and HDV genotypes

Region	HDV genotype	HBV genotype
Europe	1	D/A
Brazil	1/3	F/A/D
China, Taiwan, Japan	1/2/4	B/C
Turkey, Iran, Pakistan, India	1	D
Western Pacific	1/2	B/C/D
Africa	1, 5–8	D/A/E

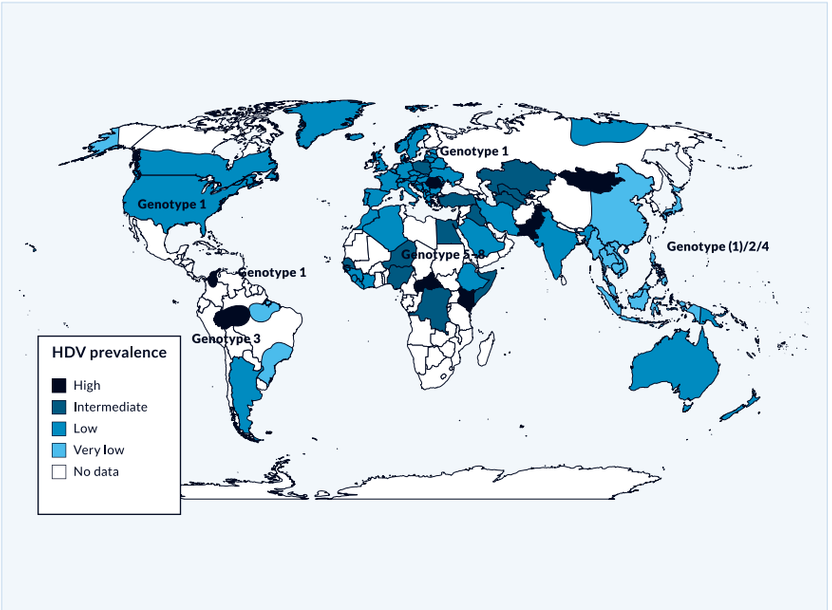

Figure 2. HDV prevalence

Epidemiology of HDV

Being linked to HBV, HDV is spread in the same way as HBV, mainly through parenteral exposure (Niro 1999). Worldwide, 217 to 316 million people are chronically infected with HBV (Polaris Observatory 2023) and 9–19 million of those are estimated to be anti-HDV positive (Stockdale 2020). However, conflicting data on the prevalence of HDV exists (Wedemeyer 2020) which might be partially due to different testing strategies that are currently present. Risk-based testing is recommended by the AASLD guideline (Terrault 2018) while anti-HDV testing for all HBsAg positive samples is recommended by EASL (EASL 2023). In high-income countries, high anti-HDV prevalence is found in people who inject drugs (PWID) who are HBsAg positive, both in Europe (Erhardt 2010, Gaeta 2000, Heidrich 2009) and North America (Kucirka 2010). Historically, HDV was endemic in Southern Europe. Several studies performed in the 1980s and 1990s showed a prevalence of anti-HDV of more than 20% among HBsAg positive individuals. As a result of the implementation of HBV vaccination programs, the incidence of HDV infections significantly decreased in Southern Europe in the 1990s (Degertekin 2008, Gaeta 2000). Countries with a particularly high prevalence of HDV are Mongolia with up to one third of chronic hepatitis cases being caused by HDV (Tsatsralt-Od 2005), Romania (Gheorghe 2015), some Central Asian countries like Uzbekistan (Khodjaeva 2019) and Pakistan (Abbas 2012), northwestern states of Brazil (Braga 2014, Kay 2014), distinct regions in Africa (Andernach 2014), and some Polynesian islands (Han 2014) (Figure 2). Of note, prevalence rates of HBV and HDV are not linked - for example, HDV infections have been considered to be rare in most parts of mainland China despite very high frequencies of HBV. However, some studies revealed an HDV prevalence of up to 6.5%, suggesting that HDV may be more frequent in China than previously thought (Liao 2014). In Taiwan, a country with a well-established national HBV vaccination program, the epidemiology of HDV changed over the last 20 years with PWID and HIV positive persons being particular risk groups and representing a main reservoir for HDV infection (Hung 2014, Lee 2015, Lin 2015). Thus, even though HDV is a major problem in distinct regions and specific cohorts, HDV is overall a rare disease and has therefore been granted orphan designation both by the FDA and by the European Commission.

One problem is that many HBsAg positive patients are not tested for HDV. The HDV testing rate was low in four hospitals in London where people with HDV frequently had severe disease and patients were of very diverse ethnicity (El Bouzidi 2015). In the United States Veterans Affairs medical system, only 8.5% of more than 25,000 HBsAg positive patients were tested for HDV. Of those, 3.4% had evidence for HDV and HDV was associated with a 2.9-fold higher HCC incidence and a higher risk of all-cause mortality (Kushner 2015). Recent studies evaluated the effects of reflex testing in HBsAg positive individuals (Palom 2022). In doing so, the absolute number of HDV diagnoses quintrupled compared to the era without reflex testing. A current modelling analysis from the Polaris Observatory recommends double reflex testing (anti-HDV testing for all HBsAg positive individuals followed by HDV RNA testing in anti-HDV positive samples) for the correct estimation of the worldwide HDV prevalence (Razavi 2023).

Pathogenesis of HDV

Knowledge about the pathogenesis of HDV infection is limited. Clinical observations have provided examples of mostly an immune-mediated process in HDV (Grabowski 2010). However, patterns suggesting a cytopathic viral disease have occasionally been observed. A typical example of this were outbreaks of severe hepatitis in the northern part of South America (Nakano 2001). These mostly fulminant hepatitis cases were induced by genotype 3 HDV. In HDV, liver histology is not different from a patient with HBV or HCV with accompanying necroinflammatory lesions. Importantly, HDV viremia is not directly associated with the stage of liver disease in HDV genotype 1 infection (Zachou 2010) while in HDV genotype 3 infection

higher viral loads were observed in patients with cirrhosis (Braga 2014). In both humanized chimeric mice as well as mice expressing the human HBV receptor (sodium taurocholate co-transporting polypeptide (NTCP)) HDV infection provoked a marked and broad induction of interferon stimulated genes and cytokines which was more pronounced than in HBV monoinfection (Giersch 2015, He 2015) which may directly contribute to the more severe inflammation in patients with HDV. Another study showed that modification of three amino acids in mouse NTCP (H84R, T86K, and S87N) rendered mice susceptible to HDV (He 2016). In this respect it is important to note that distinct polymorphisms in the IL28B gene may be associated with HBsAg persistence also in HDV coinfected patients (Karatayli 2015).

Cellular immune responses against the HDV have been described (Hoblos 2023, Huang 2004, Nisini 1997) suggesting that the quantity and quality of T cell responses may be associated with some control of the infection. HDV-specific IFN gamma and IL-2 responses are more frequent in patients with low HDV viraemia (Grabowski 2011). However, HDV-specific T cell responses are very weak and exhausted in chronic infection. *In vitro,* the third signal cytokine IL-12 was able to restore the function of HDV-specific CD4+ and CD8+ T cells (Schirdewahn 2017). In addition to immune exhaustion, T cell failure may also be caused by T cell escape variants (Karimzadeh 2018, Karimzadeh 2019, Kefalakes 2019). However, T cell responses in the liver may also lead to immune pathogenesis. One study investigated innate and adaptive immune responses localized in the liver and showed that also liver-resident CD8+ T cells, and in particular antigen-nonspecific T cells, contribute to liver disease pathogenesis (Kefalakes 2021). NK cells from patients with HDV have recently been investigated in more detail (Lunemann 2014). Overall, NK cell frequencies increased but the cells were less activated and functionally impaired. HDV infection also did not alter NK cell differentiation, and the activity of liver disease reflected alterations in NK cell surface receptor expression. NK cell frequency may also be associated with early virological response to PEG-IFN therapy although NK cells are severely functionally impaired during antiviral therapy (Lunemann 2015). Finally, mucosa-associated invariant T (MAIT) cells, which are innate-like T cells highly enriched in the human liver, are activated, functionally impaired and severely depleted in patients with chronic hepatitis D (Dias 2019). This loss of MAIT cells was associated with severity of liver disease. Collectively, this information suggests that HDV is mainly an immune-mediated disease, at least in HDV genotype 1 infection. Ideally, antiviral therapies should therefore also aim to enhance anti-HDV immunity to confer long-term control of the infection.

Coinfections with multiple hepatitis viruses are associated with diverse patterns of reciprocal inhibition of viral replication (Raimondo 2006, Wedemeyer 2010a). HDV has frequently been shown to suppress HBV replication (Calle Serrano 2012). Between 70% and 90% of HDV patients are HBeAg negative with low levels of HBV DNA. Humanized HBsAg positive mice that become superinfected with HDV also show a decrease in HBV replication (Lutgehetmann 2012). A molecular explanation for the suppression of HBV replication by HDV has been suggested via the HDV proteins p24 and p27 repressing HBV enhancers (Williams 2009). In addition, induction of a type-I interferon response by HDV may contribute to HBV repression. This hypothesis is supported by the induction of interferon stimulated genes in HBV cells which were superinfected with HDV which led to a decrease of HBV replication markers (Alfaiate 2016). Viral dominance may change over time and about half of the hepatitis delta patients showed significant HBV replication in one study (Schaper 2010).

HDV may also play a direct role in the development of hepatocellular carcinoma by altering DNA methylation events (Benegiamo 2013). Recent systematic reviews and meta-analyses noted a significantly higher risk of HCC development in HDV compared to HBV monoinfection (Alfaiate 2020, Kamal 2021). If this higher risk is due to earlier development of liver cirrhosis or a consequence of direct oncogenic effects of HDV is a matter of debate.

Clinical course of HDV

Acute HBV/HDV coinfection

Acute HBV/HDV coinfection in adults leads to recovery in more than 90% of cases but frequently causes severe acute hepatitis with a high risk for developing a fulminant course (Rizzetto 2009). In contrast, HDV is cleared spontaneously only in a minority of patients with HDV superinfection of chronic HBsAg carriers (Figure 1). The observation that the histopathology of simultaneous HBV and HDV infection is more severe than in infection with HBV alone has also been documented in experiments with chimpanzees (Dienes 1990). Several outbreaks of very severe courses of acute HDV have been described in different regions of the world (Casey 1996, Flodgren 2000, Tsatsralt-Od 2006). Fortunately, acute HDV has become infrequent over the last two decades in high-income countries due to the introduction of vaccination programs.

Chronic HDV infection

Several early studies showed that chronic HDV leads to more severe liver disease compared to chronic HBV monoinfection, with an accelerated

course of fibrosis progression, and early decompensation in the presence of cirrhosis (Asselah 2023, Wranke 2023, Wranke 2024). Long- term follow-up data from Italy, Spain, Greece and Germany confirmed the particularly severe course of HDV (Buti 2011, Calle Serrano 2014, Manesis 2013, Niro 2010, Romeo 2009). Characteristics of patients with HDV genotype 3 infection were reported in more detail confirming the severity of liver disease also for this specific HDV genotype (Braga 2014). HDV infection has been associated with a particular high risk of developing liver cirrhosis in people who are living with HIV (Calle Serrano 2012, Fernandez-Montero 2014). In one cross-sectional study from Spain, 66% of people coinfected with HIV/HBV/HCV/HDV presented with liver cirrhosis compared to only 6% of people coinfected with only HBV/HCV/HIV (Castellares 2008) and this translated to higher rates of liver decompensation and death (Fernandez-Montero 2014). Similarly, HDV was associated with poorer survival in HIV positive people in Taiwan (Lee 2015, Sheng 2007) and in the Swiss HIV cohort study (Beguelin 2017b). The Swiss study showed a prevalence of HDV of 15.4% and showed a 2.3- fold increased risk of overall death for those coinfected with HIV/HDV. Furthermore, a six-fold increased risk of HCC was calculated for HIV/HBV/HDV triple infected patients (Kamal 2021). Recent data from Sweden showed that HDV infection was associated with a 3.8-fold higher risk for liver related outcomes (Kamal 2020).

An easy-to-apply clinical score, the baseline-event anticipation (BEA) score, has been suggested to predict the risk of developing liver-related morbidity and mortality (Calle Serrano 2014). Factors associated with a poor long-term outcome included age above 40, male sex, low platelet counts, high bilirubin and INR values and southeast Mediterranean origin. The BEA score was validated in two independent European cohorts. However, the cohort size was limited (n=77 and 62, respectively), so the use of the score has not yet become widespread.

Diagnosis of HDV

Current EASL guidelines recommend that everyone who is HBsAg positive should be tested for anti-HDV antibodies at least once (Figure 3). Testing should be repeated whenever clinically indicated, e.g. in case of elevated liver enzymes or decompensation of chronic liver disease (EASL 2023, Sandmann 2023a).

In case of positive anti-HDV, HDV RNA testing should be performed with a standardized and sensitive nucleic acid test. It is important to note that the sensitivity of available HDV RNA assays varies (Le Gal 2016) and also the extraction method has an influence on the viral load quantification (Bremer 2019). This has to be taken into account when comparing results from different laboratories (Sandmann 2024a, Wedemeyer 2023b). In case of detectable HDV RNA subsequent evaluation of grading and staging of liver disease, surveillance for hepatocellular carcinoma and consideration of antiviral treatment is indicated (EASL 2023, Sandmann 2023a). So far, there is no consistent evidence that HDV RNA levels are strongly correlated with histological markers of liver disease (Zachou 2010) even though high HDV RNA levels may be predictive of developing cirrhosis and HCC in the long term (Romeo 2014). HDV genotyping may help to stratify patients, e.g. identify patients with a higher or lower risk of developing end-stage liver disease (Su 2006). In high-income countries, almost all patients are infected with HDV genotype 1, thus genotyping may be considered mainly in immigrants or populations with mixed genotype prevalence. However, genotyping is no prerequisite for antiviral treatment and can be omitted based on current treatment guidelines (Sandmann 2023a). As HDV occurs only in the context of HBV coinfection, a work-up of HBV infection including HBV DNA quantification and HBeAg/anti-HBe determination is warranted. Between 10% and 20% of HDV patients are HBeAg positive. Of note, HBV DNA can be suppressed even in HBeAg positive hepatitis (Heidrich 2012) suggesting that the inhibitory effect of HDV on HBV is independent from the phase of HBV infection. The long-term clinical outcome of anti-HDV positive patients did not differ between HBeAg positive and HBeAg negative individuals in one study from Germany (Heidrich 2012). Most HDV patients in Europe are infected with HBV genotype D but infection with genotype A can also occur (Soriano 2011). Because of the similar risk profiles of the patients, tests for HIV and HCV are also mandatory.

Quantitative HBsAg levels may be helpful for therapeutic management in certain situations (Sandmann 2023a). During treatment with PEG-IFN, a strong HBsAg decline may be a reason to extend the treatment duration from 48 to 96 weeks. During bulevirtide (BLV) monotherapy no effect on HBsAg has been observed so far. Therefore, quantitative determination is not mandatory during BLV treatment. Staging of liver disease is of particular importance in HDV as treatment options are still limited. Various non-invasive serum markers have been developed to predict liver fibrosis and cirrhosis in HCV, HBV and MASLD. However, scores such as APRI, FIB-4 or AST/ALT ratio have to be used with caution in HDV infection (Da 2020, Lutterkort 2017, Sandmann 2024b, Takyar 2017). Novel scores specifically developed for HDV have been proposed. One score is based on serum cholinesterase, gamma glutamyl transferase, albumin and age and has been validated in European patients (Lutterkort 2017). Transient elastography has been shown to be useful to exclude liver cirrhosis (<15 kPa) and advanced fibrosis (<10 kPa) in HDV patients (Sandmann 2024b).

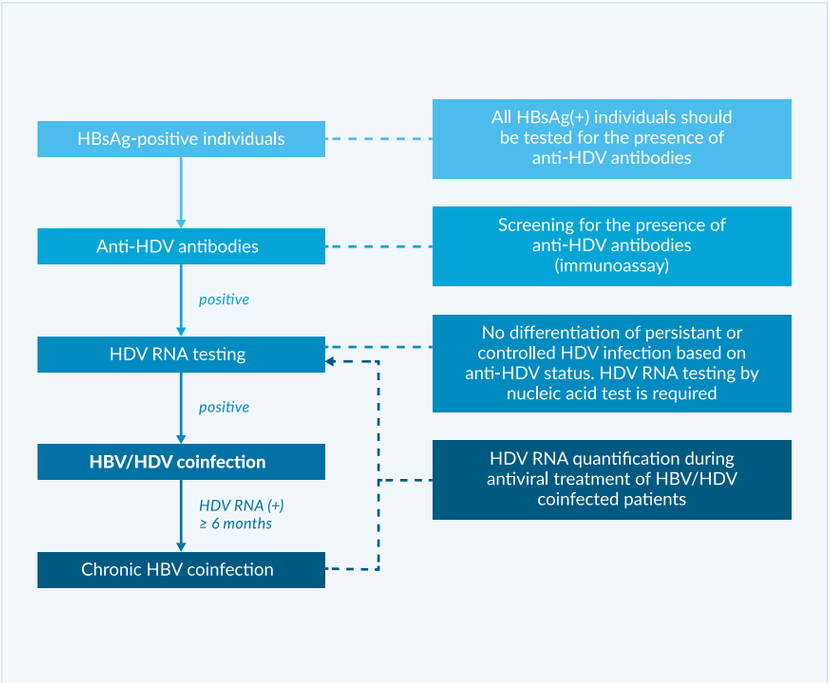

Figure 3. Diagnostic algorithm in HBsAg positive individuals

Treatment of HDV

With bulevirtide (BLV) and pegylated interferon alfa (PEG-IFN) two treatment options are currently available. Antiviral efficacy against HDV has been demonstrated in randomized trials for both compounds. Therefore, treatment options should be evaluated in all patients with chronic HDV infection and detectable HDV RNA. Patients with high levels of liver inflammation advanced liver fibrosis or liver cirrhosis should be prioritized for antiviral therapy (Sandmann 2023a). Due to the rarity of the disease, treatment in a hepatology center is recommended. This is especially true for patients with advanced liver disease as liver transplantation should also be considered for these patients (Sandmann 2023a). In general, BLV and PEG-IFN show different treatment modalities, side effect profile and response rates. For the choice of treatment, advantages and disadvantages of available treatment options should be weighed up and discussed with the patient (Table 2 and Table 3). A summary of treatment options is depicted in figure 4.

Table 2. Advantage and disadvantages of bulevirtide and pegylated interferon treatment (adapted from (8))

	Advantages	Disadvantages
Bulevirtide	• Approval by the European Medicines Agency (EMA 2024a) • Good tolerability (Lampertico 2022, Wedemeyer 2023a, Wedemeyer 2023c) • Approximately 50% virologic and biochemical response after 48 weeks of therapy (Lampertico 2022, Wedemeyer 2023a, Wedemeyer 2023c) • Use in advanced liver disease appears to be safe (Dietz-Fricke 2023)	• Long-term data not yet available due to new availability • Effect on clinical endpoints not yet investigated • No effect on HBsAg (Lampertico 2022, Wedemeyer 2023a, Wedemeyer 2023c) • Duration of therapy not defined (currently continuous therapy) (EMA 2024a) • Daily subcutaneous administration (EMA 2024a)
Pegylated interferon alfa	• Limited treatment duration (Wedemeyer 2011, Wedemeyer 2019b) • Long-term data available and effect on clinical endpoints have been studied (Farci 2004, Wranke 2020, Wranke 2017) • Weekly administration (EMA 2024b) • Substance with much experience in clinical use (Sandmann 2023b) • HBsAg loss rare but possible (Wedemeyer 2019b)	• Approximately 25% virologic response 24 weeks after end of therapy (Heidrich 2014, Sandmann 2023b) • Subcutaneous administration (EMA 2024b) • Side effect profile • Dose adjustments required for thrombocytopenia or not recommended (EMA 2024b) • Contraindicated in autoimmune diseases (EMA 2024b) • Contraindicated in decompensated liver cirrhosis (EMA 2024b) • Restricted approval indication* (EMA 2024b)
Pegylated interferon alfa plus bulevirtide	• Synergistic effect possible (Zhang 2022) • HBsAg loss possible (Wedemeyer 2019a) • Limited treatment duration possible (Lampertico 2022, Wedemeyer 2019a)	• No additional effect of combination with bulevirtide 2 mg compared to interferon monotherapy (Asselah 2024) • Treatment regimen and combination strategy unclear (De Ledinghen 2022, de Lédinghen 2022, Fontaine 2022, Lampertico 2022, Wedemeyer 2019a)

* PEG-IFN-2a is indicated for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in adult patients with compensated liver disease, evidence of viral replication, elevated alanine aminotransferase (ALT) levels, and histologically verified liver inflammation and/or fibrosis (EMA 2024b).

Table 3. Virological and biochemical response rates from major clinical studies investigating PEG-IFN or BLV (adapted from (Sandmann 2023a)).

Study	Cohorts	**Combined response** (≥2 log HDV RNA decline or negativity + ALT normalization) **at EOT**	**Virological response** (≥2 log HDV RNA decline or negativity) **at EOT**	**HDV RNA negativity at EOT**	**Biochemical response** (ALT normalization) **at EOT**	**HDV RNA negativity at FU24**
MYR202 N=118 (Wedemeyer 2023c)	a) 2mg BLV plus TDF 24W (n=28) b) 5mg BLV plus TDF 24W (n=32) c) 10mg plus TDF 24W (n=30) d) TDF 24W (n=28)	a) 21% b) 28% c) 37% d) 0%	a) 54% b) 50% c) 77% d) 4%	a) 4% b) 6% c) 3% d) 0%	a) 43% b) 50% c) 40% d) 7%	a) 4% b) 3% c) 0% d) 0%
MYR301, n=150 (Wedemeyer 2023a)	a) No therapy 48W1 (n=51) b) 2mg BLV 48W1 (n=49) c) 10mg BLV 48W1 (n=50) All groups with or without TDF	a) 2% b) 45% c) 48%	a) 4% b) 71% c) 76%	a) 0% b) 12% c) 20%	a) 12% b) 51% c) 56%	n.a.
HIDIT-I, n=90 (Wedemeyer 2011)	a) PEG-IFN plus ADF 48W (31) b) PEG-IFN 48W (n=29) c) ADV 48W (n=30)	n.a.	a) 26%[2] b) 31%[2] c) 0%2	a) 23% b) 24% c) 0%	a) 32% b) 28% c) 7%	a) 26% b) 31% c) 0%
HIDIT-II, n=120 (Wedemeyer 2019b)	a) PEG-IFN plus TDF 96W (n=59) b) PEG-IFN 96W (n=61)	n.a.	n.a.	a) 48% b) 33%	a) 44% b) 38%	a) 31% b) 23%

[1] total treatment duration of 96 (a) or 144 (b and c) weeks, primary endpoint analyses after 48 weeks of treatment. 2 from baseline to week 72

ADF, adefovir; BLV, bulevirtide; EOT, end of treatment; FU24, follow-up 24 weeks (24 weeks after end of treatment); PEG-IFN, pegylated interferon alfa; TDF, tenofovir; W, weeks

Bulevirtide

Bulevirtide is the first drug for the treatment of chronic HDV infection that received approval by the European Medicines Agency (EMA 2024a). BLV is approved for the treatment of patients with chronic HDV infection, detectable HDV RNA and compensated liver disease (EMA 2024a). Treatment is administered subcutaneously once daily at a dose of 2 mg with or without concomitant nucleos(t)ide analog (NA) treatment. Currently, the optimal treatment duration is not known and treatment should be administered as long as there is a benefit for the patient.

BLV blocks the entry of HBV and HDV into hepatocytes by binding to and blocking NTCP, a bile salt transporter of the liver (Li 2016). Analyses of biopsy data from clinical trials have shown that BLV leads to a reduction in necroinflammation (Wedemeyer 2023c) and a reduction in HDV-infected hepatocytes, which correlates with a reduction in intrahepatic HDV RNA (Allweiss 2024). Due to the mechanism of action, patients treated with BLV show elevated bile acid levels, which has not been shown to be of clinical relevance (i.e. patients do not experience pruritus) (Wedemeyer 2023a).

BLV was approved on the basis of two phase 2 studies in which either BLV in combination with tenofovir (MYR202) or BLV monotherapy (MYR203) was carried out. The duration of therapy was 24 and 48 weeks, respectively. BLV therapy resulted in a decrease in HDV RNA, which, however, was reversible after the end of therapy. Recently, results of the ongoing phase 3 study, MYR301 have been published (Wedemeyer 2023a). The primary endpoint, combined response (HDV RNA decline or undetectability and ALT normalization) after 48 weeks of treatment, was significantly more frequent in patients receiving BLV 2 mg compared to patients without BLV treatment (45% vs. 2%, p<0.001). After 48 weeks of treatment, 12% of patients receiving BLV 2 mg showed HDV RNA undetectability and 51% of patients had normalized their ALT values (Table 3) (Wedemeyer 2023a). BLV treatment was overall well tolerated and no treatment interruptions due to side effects were registered. Furthermore, health related quality of life measured by Hepatitis Quality of Life Questionnaire improved significantly for patients receiving treatment (Buti 2022).

Results of the interim analysis after 96 weeks of treatment were recently published. With ongoing treatment duration, virological, biochemical and combined response rates further increased (Wedemeyer 2024) . Due to the conditional approval in 2020, case reports and case series from Europe have been published that show the use of bulevirtide in clinical practice. Treatment response rates were overall comparable to the ones from clinical trials. In July 2023, BLV received full approval by EMA.

Importantly, the proportion of patients with cirrhosis, even portal hypertension, was high in these real-world cohorts, emphasizing that

bulevirtide can be safely used in (compensated) advanced cirrhosis (Degasperi 2022b, Dietz-Fricke 2023, Herta 2022, Jachs 2022, Zollner 2022). As of 4/2024, BLV is not approved in patients with decompensated liver disease. However, in the German real-world cohort, a total of 5 patient with decompensated liver cirrhosis (Child-Pugh B n=4, Child-Pugh C: n=1) were treated with BLV. ALT levels decreased and platelet counts increased in 4 patients and one patient with refractory ascites experienced transient improvement. One patient developed decompensation (ascites) during therapy, BLV was safely continued, and the cause of decompensation was attributed to another precipitating cause (Dietz-Fricke 2023). This is of particular importance as discontinuation of BLV therapy can lead to a rebound in HDV RNA and in patients with decompensated liver function there is concern that the rebound in HDV RNA could lead to a further deterioration of liver function. Therefore, if possible, treatment with BLV should be continued if decompensation occurs during therapy, especially if the HDV RNA is suppressed by the therapy.

In general, the treatment duration of BLV therapy is still unclear. Current guidelines recommend to continue treatment for as long as there is a benefit for the patient (EASL 2023). The phase 3 study (MYR301) is investigating the course after discontinuation of bulevirtide after a previous treatment duration of 96 to 144 weeks (Wedemeyer 2023a). These results are not yet available and must be awaited in order to assess whether a maintained response can be achieved after discontinuation of bulevirtide therapy for more than 96 weeks. Current real-world data show a rebound in HDV RNA after stopping bulevirtide, even after a treatment duration of more than 48 weeks (Jachs 2022). Re-treatment with BLV was successful in all cases and no resistances were detected (Jachs 2023). Nevertheless, some patients remained HDV RNA suppressed after treatment cessation even without achieving HBsAg loss (Anolli 2023, Jachs 2023). However, so far there are no stopping rules and due to the above-mentioned risk of deteriorating liver function, BLV should not be stopped in patients with decompensated liver disease. Maintained virological control has so far been shown in particular with the combination therapy PEG-IFN plus bulevirtide and HBsAg loss (Lampertico 2022).

The addition of PEG-IFN to bulevirtide therapy may in principle increase response rates, as the combination therapy may have synergistic effects. It has been shown *in vitro,* that interferon treatment inhibits cell-to-cell spread of HDV (Zhang 2022) thereby reducing the number of HDV-infected hepatocytes. The combination of PEG-IFN and BLV has been and is being investigated in clinical trials (Bogomolov 2016, Lampertico 2022). Data from the phase 2 study MYR204 has recently been published. The combination of PEG-IFN and BLV 2 mg showed similar off-treatment results compared to PEG-IFN monotherapy while the combination of PEG-IFN and BLV 10 mg achieved the highest rate of HDV RNA undetectability at 48 weeks after end of treatment (Asselah 2024). Data from the MYR203 study has only been presented as a congress paper (Wedemeyer 2019a) and further information is summarized in a review (Lampertico 2022). In addition, real-world data on the use of PEG-IFN plus BLV have been presented at congresses (De Ledinghen 2022, de Lédinghen 2022, Fontaine 2022) and published in small case series (Jachs 2022). With the limitation of heterogeneous treatment regimens, the overall data confirm the virological response rates and safety of PEG-IFN/BLV therapy reported in clinical trials (Lampertico 2022). Preliminary data from the French early access cohort show comparable data to BLV monotherapy in terms of combined response (HDV RNA decline ≥ 2 log plus ALT normalization) after 2 years of PEG-IFN/BLV therapy (De Ledinghen 2022). In an Austrian case series, combination therapy with PEG-IFN was initiated in patients who plateaued HDV RNA HDV RNA after 24-48 weeks of BLV therapy, regardless of initial response classification (Jachs 2022). It is currently unclear which patients will benefit from combination therapy. In addition, timing and duration of combination therapy are not known. It is unclear whether combination therapy should be given from the start or whether it should be started during the course of BLV monotherapy after certain criteria have been met. However, based on many years of experience with PEG-IFN therapy and the first real-world data, combination therapy with BLV plus PEG-IFN may be an option for experienced physicians treating hepatitis D in individual cases (EASL 2023, Sandmann 2023a).

Pegylated interferon alfa

Pegylated interferon alfa-2a (PEG-IFN) has antiviral activity against HDV, however, it is only approved for the treatment of hepatitis B (EMA 2024b). The specific mechanism of action of interferon alfa on HDV is still not fully understood. One effect of PEG-IFN treatment is the activation of the JAK-STAT pathway, which leads to transcription of interferon-stimulated genes, resulting in an "antiviral state." Importantly, in HDV infection, interferon alfa also suppresses cell division-mediated HDV spread by destabilizing HDV RNA during cell division (Zhang 2022). Interferon alfa therapy (standard or PEG-IFN) achieves up to 47% HDV RNA suppression, with the highest response rates documented in smaller cohort studies (Farci 1994, Sandmann 2023b). In the two large prospective randomized controlled HIDIT trials, the response rate in the PEG-IFN monotherapy groups was 23-33% at the end of treatment. At 24 weeks after end of treatment, 23-31% of patients had undetectable HDV RNA (Wedemeyer 2011, Wedemeyer 2019b) (Table 3). However, during long-term follow-up, late HDV RNA relapses

were detected in 55% of the patients from the HIDIT-I study (Heidrich 2014, Wranke 2020). Therefore, unlike in hepatitis C, the term "sustained virlogical response" (SVR) should not be used and long-term follow-up is needed even after antiviral treatment has ended. Based on these studies, the long-term effects on clinical endpoints after PEG-IFN based treatment have been investigated, providing a solid data base for therapy with PEG-IFN.

Current treatment guidelines recommend a treatment duration of 48 weeks (EASL 2023, Sandmann 2023a). During treatment, regularly blood tests are warranted as a decrease in leukocytes and platelets is a common side-effect and dose adjustments might be necessary. Interferon treatment can induce autoimmune thyreopathy (Andrade 2011). Therefore, also TSH should be monitored before and during therapy.

Extension of treatment duration to 96 weeks was investigated in the HIDIT-II study (Wedemeyer 2019b). Longer treatment duration did not significantly increase the number of patients with maintained treatment response. Therefore, an extension of therapy beyond 48 weeks is not generally recommended. However, if a decrease in HBsAg levels is observed during treatment, continuation of treatment beyond 48 weeks may be reasonable as the goal of HBsAg loss may be achieved in some patients (Heller 2014, Hercun 2021). HBsAg loss defines functional cure of the underlying HBV infection and is associated with improved long-term clinical outcome (Cornberg 2020, Wranke 2017).

Predictors of response or nonresponse to PEG-IFN have only been studied retrospectively. Based on data from the HIDIT-I trial (Wedemeyer 2011) HDV RNA and HBsAg were analyzed as predictors of treatment response to PEG-IFN (with or without adefovir). Patients with ≥ 2 log HDV RNA decrease at treatment week 24 were at low risk for nonresponse at the end of therapy and negative HDV RNA at treatment week 24 or 48 proved to be an important prerequisite for treatment response 24 weeks after end of therapy. The best parameter for predicting nonresponse at the end of therapy was an HDV RNA decline < 1 log combined with no decline of HBsAg at treatment week 24 (positive predictive value of 83%) (Keskin 2015). Post-hoc analyses also exist for the HIDIT-II study (Wedemeyer 2019b). Here, low levels of hepatitis B core related antigen (HBcrAg) before treatment initiation and at week 24 of therapy were associated with treatment response 24 weeks after the end of therapy (Sandmann 2022). However, the data are not yet robust enough to define clear stopping rules for PEG-IFN-based therapies. It is important to be aware that that PEG-IFN-related side effects (flu-like symptoms, myelosuppression, psychiatric effects) limit PEG IFN-based treatment in some patient groups, and the therapy is contraindicated in advanced liver disease and decompensated liver cirrhosis. Nevertheless, synergistic effects of PEG-IFN with other drugs under development are conceivable because of its particular mechanism of action.

Nucleoside and nucleotide analogues

Nucleoside and nucleotide analogues (NA) used for the treatment of HBV infection have no direct antiviral effects against HDV as HDV uses host polymerases for replication. Several studies have shown the lack of efficacy of NA against HDV (Famciclovir (Yurdaydin 2002), lamivudine (Niro 2005), entecavir (Kabacam 2012) and adefovir (Wedemeyer 2011)). However, data from HIV/HBV/HDV-coinfected patients from Spain and Switzerland showed a decline of HDV RNA during treatment with tenofovir (TDF) (Beguelin 2017a, Soriano 2014). In the Spanish cohort, HDV RNA suppression to undetectable levels occurred in 10/19 patients after a median use of TDF of 58 months (Soriano 2014). It is interesting to note that HDV RNA declines were not associated with HBsAg declines In the SWISS HIV cohort, TDF-containing ART was associated with relevant HDV RNA declines in 29% of patients and 14% had undetectable HDV RNA after 5 years (Beguelin 2017a). One hypothesis is that TDF may induce interferon lambda (Murata 2020) which has been shown to exert also direct antiviral effects against HDV (Giersch 2017). However, TDF in combination PEG-IFN showed no additional effect compared with PEG-IFN alone in the treatment of HBV/HDV coinfected patients (Wedemeyer 2019b). Another hypothesis is the improvement of host immunity that has been compromised by HIV through the effective treatment of antiretroviral therapy, which includes TDF.

Additionally, retrospective studies investigated the clinical course of patients receiving NA treatment. In these studies, outcomes were worse with NA alone compared to PEG-IFN treatment. However, selection bias should be considered here since NA monotherapy was usually used in patients with contraindication against PEG-IFN, e.g. decompensated liver disease (Kamal 2020, Wranke 2017).

To what extend liver disease progression due to hepatitis B viremia can be reduced by suppression of HBV DNA in HDV coinfected patients is elusive. Still, it can be assumed that the therapeutic principles that have been established in HBV monoinfection can also be applied in coinfection with HDV (EASL 2023). Therefore, in daily practice, the same treatment indications apply to HBV viremia in chronic HDV infection as to HBV monoinfection (EASL 2017). Importantly, patients with liver cirrhosis and detectable HBV DNA should receive NA treatment with entecavir or tenofovir (EASL 2023, Sandmann 2023a).

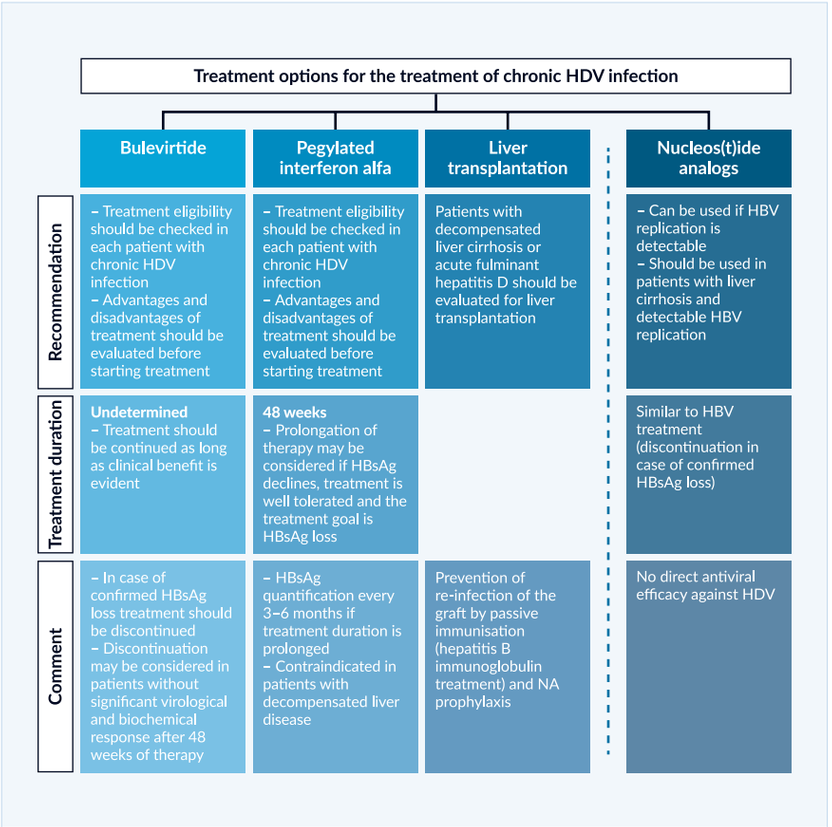

Figure 4. Treatment options for the treatment of chronic HDV infection (EASL 2017, 2023, Sandmann 2023a)

New drugs against HDV in clinical development

The prenylation of the large delta antigen is essential for virus particle formation. The prenylation inhibitor lonafarnib (LNF) showed a dose-dependent reduction of HDV RNA levels of up to 2 log IU/mL after 28 days of therapy (Yurdaydin 2018b). Importantly, HDV RNA declines were associated with LNF serum concentrations. While there was no evidence for viral resistance, higher doses of LFN caused nausea and diarrhea in most patients. Therefore, boostering with ritonavir was introduced in later clinical trials (Eiger 2023a). The phase 3 study is currently investigating the combination of LNF plus ritonavir (LFN/r) with or without PEG-IFN in chronic HDV patients receiving NA maintenance therapy. After 48 weeks of treatment, LNF/r and LFN/r plus PEG-IFN achieved the primary endpoint of virological and biochemical response in 12.6% and 24.2% of patients, respectively. Moreover, the combination arm showed statistically significant histological improvement (Etzion 2023a). Recently, follow-up 72-week data presented at the EASL 2023 meeting revealed that the combination still showed consistent endpoint response and that the treatment was well tolerated in both arms.

Nucleic acid polymers are being developed to treat patients with HDV (Bazinet 2017). Rep 2139-Ca is believed to block the release of subviral HBsAg particles from hepatocytes. The compound was injected once weekly and induced a marked decline of HBsAg in some but not all patients with HDV treated in a center in Moldova. Of note, all patients treated (n=12) showed an HDV RNA decline after 15 weeks of monotherapy when PEG-IFN was added. Responses were maintained in seven patients one year after completing treatment. A transient ALT increase was observed in patients with low HBsAg levels after REP 2139 monotherapy when PEG-IFN was introduced. In addition, several case reports from a Compassionate Use program have been presented at meetings confirming responses (HDV RNA decline and also HBsAg loss in some patients) observed in the trial from Moldavia (Stern 2023). Future studies will need to determine the efficacy and safety of REP 2139 in a larger group of patients with HDV infection.

Interferon lambda was also explored in patients with HDV infection, both as a monotherapy or in combination with LNF (Etzion 2023b, Sandmann 2021). *In vitro* and in humanized mice, an antiviral effect comparable to interferon alpha has been observed (Giersch 2017). The potential advantage of interferon lambda is the lower frequency of systemic side effects as compared to interferon alfa. However, the further development was recently stopped due to ALT flares in some patients that resulted in liver decompensation (Eiger 2023b).

Last but not least, monoclonal antibodies against HBsAg with neutralizing activity, as well as RNA interfering drugs (ASO, siRNA), have entered clinical evaluation. However, additional research is needed to validate their use in larger trials and real-world clinical settings (Sandmann 2021).

Liver transplantation for HDV

Liver transplantation remains the ultimate treatment option for many patients with chronic hepatitis D with end-stage liver disease. If prophylaxis by passive immunization with anti-HBs antibodies (hepatitis B immunoglobulins, HBIG) and administration of NA prophylaxis is applied, HBV/HDV reinfection can be prevented in all individuals (Rosenau 2007) leading to an excellent long-term outcome after transplantation. HDV RNA levels rapidly decline during the first days after transplantation (Mederacke 2012) but HDVAg may persist in the transplanted liver for several years

(Mederacke 2012, Smedile 1998). The possibility of reactivation of latent HDV infection by HBV superinfection has also been confirmed experimentally in a mouse model with transplanted human hepatocytes (Giersch 2014). Mice infected with HDV lacking HBV could be rescued by HBV superinfection after 2-6 weeks leading to a productive coinfection. Long-term prophylaxis to prevent HBV reinfection is therefore generally recommended in patients transplanted for HDV as reinfection may lead to HDV reactivation for which treatment options are very limited. Still, two recent reports challenge the current practice of dual prophylaxis as only 2 out of 34 and 1 out of 17 patients had HBV/HDV recurrence when administration of HBV immunoglobulins was stopped after transplantation (Cholongitas 2016, Ossami Saidy 2021). Furthermore, HDV recurrence was not observed after HBIG discontinuation in 64 cases that were separately reported from different groups (Caccamo 2017, Fernandez 2015, Lenci 2023, Manini 2018, Ocal 2015). However, due to the small risk of HBV/HBV recurrence and the present limited treatment options, HBIG discontinuation is not recommended by current guidelines (EASL 2023, Sandmann 2023a). Since evidence on HBIG discontinuation after one to two years after liver transplantation is accumulating, there is the need to address the safety of this approach as part of future clinical trials.

Summary and outlook

Chronic infection with the hepatitis D virus (HDV) is rare, but represents a severe form of chronic liver disease. Immunopathogenesis plays an essential role in the control or progression of the infection. As treatment options are available with bulevirtide and pegylated interferon alfa, early identification of infected patients is important. Therefore, all HBsAg-positive patients should be tested for HDV and risk groups, i.e. intravenous drug use, migration from countries with high HDV prevalence, should be tested repeatedly. Antiviral treatment should be evaluated in all individuals with chronic HDV infection, with priority given to patients with high inflammatory activity and advanced fibrosis and cirrhosis. For treatment decision, the advantages and disadvantages of current treatment options should be weighed against each other. Treatment with PEG-IFN is finite, may result in HBsAg loss in some patients, but is associated with side effects and cannot be used in the presence of advanced liver disease or autoimmune disease. Bulevirtide is well tolerated, leads to HDV RNA suppression and ALT normalization in a large proportion of patients, but the duration of treatment is not yet defined. Liver transplantation is a remaining option when antiviral treatment is no longer possible or in the setting of hepatic decompensation or hepatocellular carcinoma. Further promising therapy concepts are currently being developed with the aim of achieving HDV cure. These ongoing developments hold the promise of providing more effective and comprehensive care for individuals affected by HDV in the near future.

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