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Antiviral Therapy of Chronic Hepatitis D Virus Infection – Addendum to the S3 Guideline "Prophylaxis, Diagnosis and Therapy of Hepatitis B Virus Infection" of the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS)[1]

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1 We would like to dedicate this Addendum to Mr. Egbert Trowe, a patient representative with heart and soul, who unfortunately left us much too early.

LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
anti-HDV	HDV antibody
AWMF	Association of the Scientific Medical Societies e. V.
BEA	Baseline Event Anticipation
EoFU	end of follow up
EoT	end of treatment
GGT	Gamma-glutamyltransferase
HBcrAg	Hepatitis B core related antigen
HBV	Hepatitis B virus
HBIG	hepatitis B immune globulin
HCC	hepatocellular carcinoma
HDV	Hepatitis D virus
HDAg	Hepatitis D antigen
EMA	European Medicines Agency
NA	Nucleos(t)id analogs
NTCP	Sodium taurocholate cotransport polypeptide
PEG-IFN	pegylated interferon alfa
s. c.	subcutaneous
SVR	sustained virlogical response
TDF	Tenofovir disoproxil fumarate

List of tables

1 Guideline information

1.1 Publisher

1.2 Leading professional society

German Society for Gastroenterology, Digestive and Metabolic Diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, DGVS)

1.3 Scope and purpose

With the approval of the viral entry inhibitor Bulevirtide by the European Medicines Agency, an approved antiviral therapy for the treatment of chronic hepatitis D virus (HDV) infection is available for the first time. This development has made it necessary to update the recommendations of the chapter on chronic HDV infection from the recently published S3 guideline Prophylaxis, Diagnosis and Therapy of Hepatitis B Virus Infection [1].

Therefore, the present Addendum contains updates on the antiviral therapy of chronic HDV infection and considers study results as well as initial experience with the newly available substance bulevirtide. In addition, the last chapter contains important open questions from which research objectives can be derived. Chronic infection with HDV is always a coinfection with hepatitis B virus (HBV), i. e., it occurs only in HBsAg-positive individuals and is considered a rare disease in Germany. Nevertheless, it plays an important role in everyday hepatological practice due to migration, the increasing use of screening and, last but not least, new therapeutic options. Chronic HDV infection is associated with a higher risk of developing liver cirrhosis compared to HBV

monoinfection. This was shown in cohort analyses from the 1980 s and 1990 s and recently confirmed in several systematic reviews [2–6]. For example, a meta-analysis showed that the relative risk of developing liver cirrhosis was almost four times higher in anti-HDV-positive patients than in HBV-monoinfected patients [4]. In this context, patients with detectable hepatitis D viral load (HDV RNA) have a higher risk of liver-associated complications [7]. In addition, HDV infection is an independent risk factor for the development of hepatocellular carcinoma (HCC) [8, 9].

Due to the natural history of the disease described above and the treatment options available today, early detection of HDV infection is important. The recommendations of the published S3 hepatitis B guideline [1] on screening indications and diagnostic procedures therefore remain unchanged. All HBsAg-positive individuals should be tested at least once for HDV antibodies (anti-HDV) using a validated test. Re-screening for anti-HDV should be performed in HBsAg-positive individuals whenever clinically indicated (e. g., increase in aminotransferases or acute decompensation of chronic liver disease) and may be repeated annually in individuals who remain at risk for infection. Because antibody detection cannot distinguish between persistent and resolved hepatitis D, HDV RNA testing should be performed with a standardized and sensitive nucleic acid test if the patient is positive for anti-HDV. It should be noted that the sensitivity of available HDV RNA assays varies [10] and also the extraction method has an influence on the viral load quantification [11].

1.4 Representativeness of the guideline group: Participating professional societies

The participating professional societies that took part in the consensus conference and the Delphi survey correspond to the participating professional societies of the S3 guideline "Prophylaxis, diagnosis and therapy of hepatitis B virus infection":

- Deutsche Arbeitsgemeinschaft niedergelassener Ärzte in der Versorgung HIV-Infizierter e. V. (dagnä)
  Stefan Christensen
- Deutsche Gesellschaft für Infektiologie e. V. (DGI)
  Hartwig Klinker
- Deutsche Gesellschaft für Pathologie e.V / Bundesverband deutscher Pathologen e. V. (DGP/ BDP)
  Peter Schirmacher, Andrea Tannapfel
- Deutsche Gesellschaft für Innere Medizin e. V. (DGIM)
  Markus Cornberg, Michael P. Manns
- Deutsche Gesellschaft für Transplantationsmedizin e. V. (DTG)
  Christian P. Strassburg
- Gesellschaft für Virologie e. V. (GfV)
  Sandra Ciesek, Wolfram Gerlich, Dieter Glebe, Ulrike Protzer, Jörg Timm
- Gesellschaft für Pädiatrische Gastroenterologie & Ernährung e. V. (GPGE) & Deutsche Gesellschaft für Kinder- und Jugendmedizin e. V. (DGKJ)
  Jan de Laffolie, Gunter Flemming, Patrick Gerner, Thomas Lang, Michael Melter, Stefan Wirth
- Nationales Referenzzentrum HBV/HDV
  Christian Schüttler

▶ **Table 1** Steering group.

Name	Location	Responsibility
Thomas Berg	Leipzig	DGVS
Markus Cornberg	Hannover	DGVS, DGIM, Dt. Leberstiftung
Katja Deterding	Hannover	DGVS
Holger Hinrichsen	Kiel	DGVS
Jörg Petersen	Hamburg	DGVS
Lisa Sandmann	Hannover	DGVS, DGIM
Frank Tacke	Berlin	DGVS

- Ständige Impfkommission (STIKO)
  Wolfgang Jilg, Sabine Wicker

1.5 Representativeness of the guideline group: Participation of patients

- Deutsche Leberhilfe e. V.
  Claus Niederau, Ingo van Thiel
- Lebertransplantierte Deutschland e. V.
  Egbert Trowe

1.6 Representativeness of the guideline group: Other institutions

- Deutsche Leberstiftung (DLS)
  Markus Cornberg, Christoph Höner zu Siederdissen, Michael P. Manns, Heiner Wedemeyer

In addition to the steering group (▶ **Table 1**), experts from various disciplines (gastroenterology, internal medicine, pediatrics, pathology, hepatology, virology, infectious diseases, transplantation medicine) as well as from different fields of activity (private practice and inpatient care) – including patient representatives – collaborated on the Addendum.

The participants of the consensus conference is shown in the ▶ **Table 2**.

2 Methodological approach

The steering group (▶ **Table 1**) held a kick-off meeting in the form of a video conference on December 20, 2022, to discuss the contents of the addendum and formulate questions. The steering group presented an initial proposal for the formulation of the recommendations, but without specifying the level of recommendation. Subsequently, a literature search was conducted by Dr. Lisa Sandmann to evaluate the evidence and to write explanatory texts. Based on the literature search and evidence assessment, the recommendations were adjusted. On January 31, 2023, the structured consensus conference was held as a video-conference under neutral moderation by Dr. Monika Nothacker (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (AWMF)), which was attended by the

▶ **Table 2** Participants of the consensus conference on January 31, 2023.

Participating	Location	Professional society/organization
Steering group		
Thomas Berg	Leipzig	DGVS
Markus Cornberg (Koordination)	Hannover	DGVS, Deutsche Leberstiftung
Katja Deterding	Hannover	DGVS, Deutsche Leberstiftung
Holger Hinrichsen	Kiel	DGVS, BNG
Jörg Petersen	Hamburg	DGVS
Frank Tacke	Berlin	DGVS
Lisa Sandmann	Hannover	DGVS, DGIM
Guideline expert		
Christoph Berg	Tübingen	DGVS
Peter Buggisch	Hamburg	DGVS
Stefan Christensen	Münster	DAGNÄ
Sandra Ciesek	Frankfurt am Main	DGVS, GfV
Nektarios Dikopoulos	Dornstadt	DGVS
Dieter Glebe	Gießen	GfV, NRZ HBV/HDV
Christoph Höner zu Siederdissen	Hannover	Deutsche Leberstiftung
Patrick Ingiliz	Berlin	DGVS
Christoph Jochum	Berlin	DGVS
Hartwig Klinker	Würzburg	DGI
Benjamin Maasoumy	Hannover	DGVS
Claus Niederau	Oberhausen	DGVS
Kai-Henrik Peiffer	Münster	DGVS
Ulrike Protzer	München	GfV
Christoph Sarrazin	Wiesbaden	DGVS
Eckart Schott	Berlin	DGVS
Juilan Schulze zur Wiesch	Hamburg	DGVS
Jörg Timm	Düsseldorf	GfV
Egbert Trowe	Burgwedel	Lebertransplantierte Deutschland e. V.
Florian van Bömmel	Leipzig	DGVS
Ingo van Thiel	Köln	Deutsche Leberhilfe
Johannes Vermehren	Wiesbaden	DGVS
Heiner Wedemeyer	Hannover	DGVS, Deutsche Leberstiftung
Stefan Wirth	Wuppertal	GPGE, DGKJ
Karsten Wursthorn	Schwerin	DGVS
Methodology & Organization		
Monika Nothacker (moderator)	Berlin	AWMF
Torsten Karge	Berlin	CGS
Nadine Fischer	Berlin	DGVS

experts listed in ▶ **Table 2**. Two representatives of patient organizations also participated in the consensus conference. Subsequently, the agreed changes were implemented and *recommendations 2.3.1* and *2.5.2 were* voted on a second time in a Delphi process. Mr. Ingo van Thiel (Deutsche Leberhilfe) reviewed the final manuscript from the perspective of patient organizations, and his comments were included.

For further information, please refer to the Guideline Report of this Addendum.

2.1 Editorial note

2.1.1 Participatory decision making

All recommendations of the guideline are to be understood as recommendations that are made and implemented in the sense of a participatory decision-making process between physicians and patients and, if applicable, their relatives.

2.1.2 Special note

Medicine is subject to a continuous development process, so that all information, in particular on diagnostic and therapeutic procedures, can only correspond to the state of knowledge at the time of printing of the guideline. The greatest possible care has been taken with regard to the recommendations given for therapy and the selection and dosage of medications. Nevertheless, users are urged to consult the manufacturers' package inserts and expert information for verification and, in case of doubt, to consult a specialist. In the general interest, any discrepancies should be reported to the DGVS. The user himself remains responsible for any diagnostic and therapeutic application, medication and dosage. In this guideline, registered trademarks (protected trade names) are not specially marked. It can therefore not be concluded from the absence of a corresponding reference that it is a free trade name.

2.1.3 Gender neutral wording

For the sole purpose of better readability, gender-specific spelling is not used in the guideline text. All personal terms in this Addendum are therefore to be understood as gender-neutral.

1 Guideline – Indication for antiviral therapy

1.1 Which patients with HDV infection should be treated?

Recommendation 1.1.1	new 2023
All patients with chronic HDV infection and detectable HDV RNA should be evaluated for the possibility of antiviral therapy. [Evidence level 2, recommendation grade A, strong consensus].	
Patients with high inflammatory activity, advanced fibrosis and/or compensated cirrhosis should be treated with antiviral therapy with priority.	
[Expert consensus, recommendation, strong consensus.]	

Comment

Chronic hepatitis D virus (HDV) infection is associated with an increased risk of developing liver cirrhosis and hepatic complications, including the development of hepatocellular carcinoma (HCC) [2–9]. In the initial studies of the natural history of chronic hepatitis D, the majority of patients rapidly (within 5–10 years) developed advanced liver disease [2, 12, 13], and in a subset of patients, cirrhosis and decompensation developed even in less than a year [14]. High disease severity with rapid progression with a median time to decompensation of less than 2 years and poor survival was confirmed in a study from Romania [15]. Most studies have shown that detectable and persistent viremia (HDV RNA) is associated with the worst course and the most severe long-term sequelae [7, 15–18]. Whether the level of viremia (HDV RNA level) plays a prognostic role has not been conclusively determined. However, available data show that higher viral load seems to be associated with higher transaminases and worse clinical outcome [19, 20].

The risk of developing clinical complications of cirrhosis was lower in patients treated with interferon alfa or pegylated interferon alfa (PEG-IFN) in cohorts from Ankara [21], Hanover [22], France [16], Greece [23] and Sweden [7], and a negative test result for HDV RNA was associated with a more favorable clinical course.

When HBsAg loss could be achieved in addition to negative HDV RNA, an even better long-term outcome was documented [22, 24]. However, loss of HBsAg by antiviral therapy is rare [25, 26], so currently HDV suppression is the first treatment goal [27]. Ideally, suppression of HDV RNA occurs below the detection limit of sensitive assays. In a long-term observational study following therapy with interferon alfa (48 weeks of therapy with 9 million units or 3 million units), the high dose was associated with better survival compared with the low dose or no treatment. Interestingly, later measurements with the more sensitive *nested* PCR assay showed that HDV RNA was detectable in all patients. In the high-dose group, a mean 100-fold (2 log) reduction in HDV RNA from baseline until the end of treatment was documented and associated with the reported survival benefit [28]. Based on these data, an expert panel suggested using a 2 log or greater decrease in HDV RNA at the end of treatment as a surrogate marker of initial antiviral therapy efficacy [29].

Markers that predict the risk of hepatic complications have not yet been established. Using the Baseline Event Anticipation (BEA) score, European patients can be classified into three risk categories based on age, sex, country of origin, bilirubin, platelet count, and INR, with the highest risk group associated with a 25-fold increased risk of liver-related complications compared with the lowest risk group [30]. The BEA score was validated in two independent European cohorts. However, again, the cohort size was limited (n = 77 and 62, respectively), so use of the score has not yet become widespread. The region of origin may play a role partly due to local environmental factors, but also due to regional differences in the prevalence of viral variants (HDV genotypes) [16]. For example, African patients from sub-Saharan countries had a lower risk of cirrhosis compared with European patients. In turn, detection of HDV infection with HDV genotype 5 was associated with a higher risk of cirrhosis in this patient population compared with African patients infected with other HDV genotypes [16]. Similarly, there is evidence of differential disease progression in pa-

tients from the Amazon, where infection with HDV genotype 3 was associated with advanced liver disease [31].

In addition to aminotransferases, which are surrogate markers of disease activity, gamma-glutamyltransferase (GGT) was independently associated with cirrhosis in a cohort of 80 patients from Germany, Turkey, and Greece [32]. Interestingly, only GGT was independently associated with the development of endpoints in the long-term follow-up of the HIDIT-I trial in multivariate logistic regression [33]. However, no predictive cut-off values have been defined that are used in practice. Other factors that may be considered in identifying patients at higher risk for liver disease progression and HCC risk include HBV genotype (e. g., HBV-C [34]), coinfections (HIV [9]) and cofactors of chronic liver injury such as harmful alcohol consumption [18], obesity [35] and diabetes mellitus [36].

Due to the rarity of the disease, we recommend the presentation of patients with HDV infection to an experienced hepatology center for evaluation of therapeutic options. Here, the indication for antiviral treatment with bulevirtide or PEG-IFN or enrollment in clinical trials should be evaluated and discussed with the patients.

Studies on antiviral therapy in patients with HCC have not yet been performed. However, the focus in this patient population is certainly on HCC-specific therapy or on transplantation as a curative therapeutic approach to HCC. It is conceivable that antiviral therapy, e. g., with bulevirtide, may contribute to stabilization of liver disease so that HCC therapy is and remains feasible and therefore may be a reason to perform antiviral therapy in individual cases. However, data on this are lacking to date. Therefore, treatment options should be discussed in an interdisciplinary tumor conference.

2 Guideline – Therapy

2.1 Currently available treatment options

Statement 2.1.1	new 2023
Currently, two treatment options are available that have demonstrated antiviral efficacy against HDV in randomized-controlled clinical trials: 1. Bulevirtide 2. Pegylated interferon alfa (PEG-IFN).	
[Evidence level 2, strong consensus.]	

Comment

Bulevirtide is a synthetic myristoylated lipopeptide composed of 47 amino acids of the preS1 domain of the large HBV surface protein that inhibits the binding of HBsAg to the cell entry receptor, sodium taurocholate cotransport polypeptide (NTCP) [37, 38]. Since July 2020, conditional approval has been granted by the European Medicines Agency (EMA) for the dose of 2 mg once daily [39]. This conditional approval was based on data from phase 2 studies, only a portion of which have been published fully and *peer-reviewed* to date [40]. Bulevirtide received full approval from the EMA in July 2023.

In phase 2 and phase 3 clinical trials, bulevirtide has been studied both as monotherapy and in combination with PEG-IFN at different doses (2 mg vs. 5 mg vs. 10 mg) and treatment durations (24, 48, 96, 144 weeks) [40–46]. A decrease in HDV RNA was observed with bulevirtide monotherapy or combination therapy with PEG-IFN. Combination therapy showed a greater decline in HDV RNA, but data from the phase 2 trials have only been presented at congresses and have not yet been fully published [41–43]. No significant changes in HBsAg levels were observed with monotherapy, whereas a decrease in HBsAg levels and a stronger response after treatment were observed with the combination with PEG-IFN [41]. The phase 3 clinical trial is currently still ongoing. This study is evaluating the safety and efficacy of bulevirtide monotherapy 2 mg vs. 10 mg for 144 weeks vs. 10 mg for 96 weeks (initial 48-week delayed treatment initiation). The results of the primary endpoint (combined virologic and biochemical response, defined as HDV RNA negativity or HDV RNA decline ≥ 2 log plus ALT normalization after 48 weeks of therapy) were presented [45] and have been published [46] (▶ **Table 3**). The combined response rates after 48 weeks of therapy were 45 % (2 mg) vs. 48 % (10 mg) vs. 2 % (delayed treatment). Virologic response rates were 71 % and 76 % and 4 %, respectively, while ALT normalization occurred in 51 % and 56 % of patients receiving the 2 mg or 10 mg dose, respectively [45, 46]. Compared to PEG-IFN, therapy with bulevirtide is very well tolerated (for details on side effects and interactions, *see 2.4.1)*.

Due to the conditional approval in 2020, case reports and case series from Europe are already available showing the use of bulevirtide in clinical practice. Based on published real-world data, response rates are comparable to available clinical trial data. The proportion of patients with cirrhosis was high in the real-world cohorts, underscoring that bulevirtide is safe to use in (compensated) cirrhosis [47–51].

Pegylated interferon alfa-2a (PEG-IFN) is approved for the treatment of hepatitis B [52] and also has antiviral activity against HDV. The specific mechanism of action of interferon alfa on HDV is not fully understood. It is discussed that the antiviral effect results, among others, from activation of the JAK-STAT pathway, which leads to transcription of interferon-stimulated genes in the nucleus, resulting in an “antiviral state.” In HDV infection, interferon alfa also suppresses cell division-mediated HDV spread by destabilizing HDV RNA during cell division [53].

Interferon alfa therapy (standard or PEG-IFN) achieves up to 47 % HDV RNA suppression, with the highest response rates documented in smaller cohort studies [54, 55]. In the two large prospective randomized controlled HIDIT trials, the response rate in the PEG-IFN monotherapy groups was 24–33 % at the end of therapy, and at the time point 24 weeks after end of therapy, 23–31 % of patients had negative HDV RNA [25, 26] (▶ **Table 3**). However, late HDV relapses occurred in approximately 55 % of HIDIT-I patients during long-term follow-up of 4.5 (0.5–5.5) years [56], and an even later HDV relapse was reported up to 9 years after therapy [33]. Therefore, unlike in hepatitis C, the term “sustained virlogical response” (SVR) should not be used and long-term follow-up should be conducted even after antiviral treatment has ended.

▶ **Table 3** Virologic* and biochemical response in major studies with PEG-IFN or bulevirtide.

Study	Cohorts	≥ 2 log decrease in HDV RNA or negative EOT.	HDV RNA negative EOT	HDV RNA negative FU24	ALT normal EOT, FU[1]	≥ 2 log decrease HDV RNA or negative plus ALT normal EOT.
HIDIT-I, n = 90 [25]	a) PEG-IFN plus ADV 48 W (31) b) PEG-IFN 48 W (n = 29) c) ADV 48 W (n = 30)	a) 26 %[2] b) 31 %[2] c) 0 %[2]	a) 23 % b) 24 % c) 0 %	a) 26 % b) 31 % c) 0 %	a) 32 %, 35 %[1] b) 28 %, 45 %[1] c) 7 %, 10 %[1]	n.a.
HIDIT-II, n = 120 [26]	a) PEG-IFN plus TDF 96 W (n = 59) b) PEG-IFN 96 W (n = 61)	n.a.	a) 48 % b) 33 %	a) 31 % b) 23 %	a) 44 %, 46 %[1] b) 38 %, 26 %[1]	n.a.
MYR202, n = 118 [40]	a) 2 mg BLV plus TDF 24 W (n = 28) b) 5 mg BLV plus TDF 24 W (n = 32) c) 10 mg plus TDF 24 W (n = 30) d) TDF 24 W (n = 28)	a) 54 % b) 50 % c) 77 % d) 4 %	a) 4 % b) 6 % c) 3 % d) 0 %	a) 4 % b) 3 % c) 0 % d) 0 %	a) 43 % b) 50 % c) 40 % d) 7 %	a) 21 % b) 28 % c) 37 % d) 0 %
MYR301, n = 150 [45, 46]	a) No therapy 48 W (n = 51) b) 2 mg BLV 48 W (n = 49) c) 10 mg BLV 48 W (n = 50) *All groups with or without TDF*	a) 4 % b) 71 % c) 76 %	a) 0 % b) 12 % c) 20 %	n.a.	a) 12 % b) 51 % c) 56 %	a) 2 % b) 45 % c) 48 %

PEG-IFN – pegylated interferon alfa, BLV – bulevirtide, TDF – tenofovir disoproxil fumarate, W – week, EOT – end of treatment, FU – follow-up.
* sensitivity of tests may differ between studies.
[1] 24 weeks after end of treatment.
[2] from baseline to week 72.

Based on these studies, the long-term effects on clinical endpoints have been investigated (see above), providing a solid data base for PEG-IFN therapy.

Predictors of response or nonresponse to PEG-IFN have not been studied prospectively. In a retrospective analysis of data from the HIDIT-I trial. [25] HDV RNA and HBsAg were analyzed as predictors of treatment response to PEG-IFN (with or without adefovir). Patients who had a greater than 2 log decrease in serum HDV RNA at week 24 were at low risk for nonresponse at the end of therapy. A negative HDV RNA at treatment week 24 or 48 proved to be an important prerequisite for response to therapy at week 72 (24 weeks after end of therapy). For example, the best parameter for predicting nonresponse at the end of therapy was a decrease in HDV RNA of less than 1 log combined with no decrease in HBsAg levels at treatment week 24 (positive predictive value of 83 %). A drawback of this analysis was that serum samples were not available for all time points [57]. Post-hoc analyses also exist for the HIDIT-II study [26]. Here, low hepatitis B core related antigen (HBcrAg) before treatment initiation and at week 24 of therapy was associated with treatment response 24 weeks after the end of therapy. [58]. However, the data are not yet robust enough to define clear stopping rules for PEG-IFN-based therapies.

It should be taken into account that PEG-IFN-related side effects (flu-like symptoms, myelosuppression, psychiatric effects) limit PEG-IFN-based treatment in some patient groups, and treatment is contraindicated in advanced cirrhosis (stage Child-Pugh B or higher) and hepatic decompensation. Nevertheless, synergistic effects of PEG-IFN with other drugs under development are conceivable due to its particular mechanism of action.

Recommendation 2.1.2	new 2023
Nucleos(t)ide analogues (NA) have no direct antiviral efficacy against HDV. However, if HBV replication is detectable, nucleos(t)ide analogues can be used against HBV.	
[Expert consensus, recommendation open, strong consensus.]	
NA should be used in patients with liver cirrhosis and detectable HBV DNA (*see also S3 Guideline Hepatitis B, Recommendation 3.9.1*).	
[Recommendation grade A, strong consensus.]	

Comment

Unlike most RNA viruses, HDV does not encode its own replicase or RNA-dependent RNA polymerase, so direct antiviral agents such as NAs should not have a direct antiviral effect. Accordingly, numerous studies have shown that NAs have no efficacy against HDV. Data are available for famciclovir [59], lamivudine [60], entecavir [61] and adefovir [25].

However, in a Spanish cohort of HBV/HDV/HIV-coinfected patients, a decrease in HDV RNA was observed in 10 of 19 patients during long-term therapy with tenofovir disoproxil fumarate (TDF) [62]. In a cohort of HBV/HDV/HIV-coinfected patients from Switzerland receiving TDF-containing antiretroviral therapy, 28.6 % had a 2-log decrease in HDV RNA, and 14.3 % showed HDV RNA within 5 years of treatment, while no decrease of HBsAg

was documented [63]. It is not clear whether the decline of HDV RNA in some HBV/HDV/HIV-coinfected patients was directly induced by TDF or caused by immune phenomena (e. g., immune reconstitution in HIV). However, it has been shown that TDF can induce interferon lambda, which may have antiviral activity against HDV [64]. However, TDF in combination with PEG-IFN showed no additional effect compared with PEG-IFN alone [26]. Although in the HIDIT-I trial, the combination of PEG-IFN plus adefovir was associated with a greater HBsAg decline and with a higher rate of HBsAg loss compared with PEG-IFN monotherapy (6.5 % (2 of 31 patients) vs. 0 % in the other treatment groups) [25].

The clinical course of patients receiving NA was investigated in retrospective studies. It was found that outcomes were even worse with NA therapy alone compared to PEG-IFN-based therapies. However, bias should be considered here because NA therapy alone was usually used in patients in whom PEG-IFN was contraindicated, for example, because of already advanced liver cirrhosis [7, 22].

To date, there is little evidence for NA treatment in patients with chronic hepatitis D and positive HBV DNA with the aim of reducing liver disease progression by suppressing HBV DNA. Nevertheless, it can be assumed that the therapeutic principles that have been established in HBV monoinfection [1], also have a clinical benefit in terms of reducing complications of liver disease in coinfection with HDV. Therefore, in daily practice, the same treatment indications apply to chronic HDV infection with respect to HBV viremia as to HBV monoinfection. In the majority of cases, patients with hepatitis D have low HBV DNA levels regardless of HBeAg status [65, 66].

2.2 What diagnostics should be performed before starting antiviral therapy in patients with chronic HDV infection?

Recommendation 2.2.1	new 2023
Before initiating antiviral therapy, the severity of liver disease and potential contraindications to therapy should be evaluated.	
[Expert consensus, strong recommendation, strong consensus.]	

Comment

To assess the extent of inflammatory changes as well as possible impairment of liver function, various clinical-biochemical laboratory tests (e. g., liver inflammation and liver synthesis parameters, total bilirubin), blood count, and coagulation status are required. If advanced liver disease is suspected, additional tests (e. g., INR/Quick value, albumin) should be performed to determine the synthesis capacity of the liver. These tests are also used to determine possible contraindications to antiviral therapy (e. g., thrombocytopenia and decompensated liver disease as contraindications to treatment with PEG-IFN). An ultrasound of the abdomen should be performed to screen for hepatocellular carcinoma and concomitant liver diseases (e. g., fatty liver) [67].

Noninvasive methods to assess liver fibrosis may be used, but these have not been well evaluated in the context of HBV/HDV coinfection, and cutoff values to include or exclude liver cirrhosis are not available. Existing data on the use of noninvasive methods are based on small, retrospective cohort studies in which correlation with histologic findings was not always present [67–69]. Therefore, liver biopsy initially remains the gold standard for assessing the stage of liver fibrosis in patients with chronic HDV infection without clear clinical, laboratory, or imaging evidence of cirrhosis. In addition, assessment of liver histology may be important to exclude signs of autoimmune hepatitis prior to PEG-IFN therapy, which can occur in hepatitis D [71] and is a contraindication to PEG-IFN therapy [52].

In addition to laboratory chemistry and imaging diagnostics, the feasibility of the planned therapy must be assessed (e. g., performance of subcutaneous administration, adherence to therapy) before antiviral therapy is initiated.

Recommendation 2.2.2	new 2023
HDV RNA should be quantified before initiation of therapy.	
[Evidence level 2, recommendation grade B, strong consensus].	

Comment

If HDV RNA is detectable, there is an indication for antiviral treatment. In addition to suppression of HDV RNA to undetectable levels, a currently used virologic endpoint of therapy is a decrease in viral load by ≥ 2 log [27, 29] (*see 1.1*). To assess this endpoint, quantitative measurement of HDV RNA is required. Currently, there are various quantification assays from different manufacturers available that are combined with different extraction methods. In addition, there are in-house assays that have been established and continue to be used by local laboratories. The WHO international standard for HDV RNA is obtained from HDV genotype 1 positive plasma and international standards for non-genotype-1 are currently lacking. The first international quality control study of HDV RNA quantification involving 28 laboratories showed great heterogeneity in terms of test results, with only 46 % of laboratories correctly quantifying all 18 positive samples, while 57 % of laboratories were falsely negative on one to ten samples [10]. Possible causes of these differences included the amount of sample volume, extraction method (manual or automated extraction), different internal controls and quantification standards, equipment used for amplification, and different primer sequences [72]. Even when using the same commercially available kit, different extraction methods in the same assay can result in significant differences in HDV RNA quantification [11]. Therefore, when using commercial HDV RNA quantification methods, the extraction method recommended by the manufacturer should be used. Furthermore, to reliably assess the evolution of HDV RNA during the natural history or during therapy, the same assay should be used whenever possible. It is important to note that the lower detection limit differs from test method to test method.

Recommendation 2.2.3	new 2023
Quantitative determination of HBV DNA should be performed.	
[Evidence level 2, recommendation grade A, strong consensus].	

Comment

The determination of HBV DNA is used to evaluate the indication for HBV-specific antiviral therapy [1]. In patients with chronic HDV infection, HBV DNA is often suppressed. If HBV DNA is positive, treatment with NA can be conducted in accordance with the HBV guideline (*see 2.1.2*). Patients with detectable HBV DNA and liver cirrhosis should receive NA (*analogous to the S3 hepatitis B guideline*). [1].

Recommendation 2.2.4	new 2023
Quantitative determination of HBsAg can be performed.	
[Evidence level 2, recommendation grade 0, strong consensus].	

Comment

Quantitative determination of HBsAg may be helpful for therapeutic management in certain situations. If patients on treatment with PEG-IFN show a decline in HBsAg, this may be a reason to extend the duration of therapy to more than 48 weeks in order to increase the chances of HBsAg loss [73, 74]. However, there are no clear predictive HBsAg levels, so the decision to extend treatment with PEG-IFN remains an individual decision. A retrospective analysis of the HIDIT-I trial showed that a lack of HBsAg decline in combination with a decrease in HDV RNA levels of less than 1 log after 24 weeks of therapy identified future null responders at the end of therapy with a positive predictive value of 83 % [57]. Similar results were also seen in a post-hoc analysis of the HIDIT-II trial, in which high HBsAg levels before therapy initiation and at therapy week 24 were associated with a high risk of treatment failure (positive HDV RNA 24 weeks after end of therapy) [58]. Nevertheless, no clear rules for treatment discontinuation can currently be defined for PEG-IFN therapy (*see 2.1.1*).

Bulevirtide monotherapy showed no effect on HBsAg levels in the data published to date. [40]. Therefore, quantitative HBsAg monitoring is not required during bulevirtide monotherapy.

Recommendation 2.2.5	new 2023
Routine HDV genotyping can be omitted.	
[Evidence level 3, recommendation grade 0, strong consensus].	

Comment

Eight HDV genotypes have been described, of which HDV genotype 1, which is predominant in Germany, seems to be associated with a poor course of chronic infection [34]. Additionally, there are other cohort studies that have shown an association between HDV genotype and severity or progression of liver disease [16, 31]. Patients with chronic hepatitis D from West Africa are often infected with HDV genotype 5, which appears to be associated with a better response to PEG-IFN treatment [75]. Another study showed that African patients generally responded better to interferon therapy than non-African patients [16], so region of origin or genotype may play a causative role. Currently, no direct consequences for general treatment indication or contraindication or therapy management with PEG-IFN can be derived from these data. *In vitro* data show that bulevirtide has antiviral activity against HDV genotypes 1–8. [76]. Therefore, genotyping is currently not a prerequisite for initiation of antiviral therapy.

2.3 How should antiviral therapy for chronic HDV infection be administered?

Recommendation 2.3.1	new 2023
The advantages and disadvantages of the available therapy concepts with bulevirtide or PEG-IFN should be weighed against each other and discussed with the patients.	
[Expert consensus, strong recommendation, consensus.]	

Comment

Currently, two substances with different mechanisms of action, Bulevirtide (*see 2.4*) and PEG-IFN (*see 2.6*), can be used for the treatment of chronic HDV infection. There are different advantages and disadvantages depending on the substance, which should be discussed with the patient when deciding on therapy (▶ **Table 4**). An important aspect is the side effect profile, which is very positive for bulevirtide in the observation period of about three years so far (*see 2.4*). In contrast, therapy with PEG-IFN has side effects that can significantly impair quality of life during treatment or lead to treatment discontinuation (*see 2.6*). An advantage of PEG-IFN therapy is the limited duration of therapy of 48 weeks. Data on bulevirtide suggest that treatment response is not affected by the presence of cirrhosis at baseline [26, 41] and patients with advanced cirrhosis can also be treated [51] (*see 2.7.3*). There are also no limitations in the presence of comorbidities such as autoimmune diseases. PEG-IFN, on the other hand, is contraindicated in patients with severe extrahepatic comorbidities, autoimmune diseases, or advanced cirrhosis [52] (*see 2.6*). The choice of therapeutic option should be carefully considered, also taking into account new therapeutic approaches that are currently being developed (such as combination therapy or new agents) and may significantly increase the response rate in the near future.

Combination therapy with bulevirtide and PEG-IFN may be reasonable due to the combination of different mechanisms of action [53]. Combination therapy of bulevirtide and PEG-IFN is currently being investigated in phase 2 trials (MYR203, MYR204), the results of which, however, have not yet been fully published [42, 43]. To date, only a few data have been published, such as a case series from Austria [47] (*see 2.4.3*). Significantly larger patient groups are currently being treated with bulevirtide in combination with PEG-IFN in France as part of the early access program.

▶ **Table 4** Advantages and disadvantages of the available treatment concepts with bulevirtide or PEG-IFN (consensus).

	Advantages	Disadvantages
Bulevirtide	▪ Marketing authorization by the European Medicines Agency [39] ▪ Good tolerability [40, 41, 45, 46] ▪ Approximately 50 % virologic and biochemical response after 48 weeks of therapy [40, 41, 45, 46] ▪ Use in advanced liver cirrhosis appears to be safe [51]	▪ Long-term data not yet available due to new availability ▪ Effect on clinical endpoints not yet investigated ▪ No effect on HBsAg [40, 41, 45, 46] ▪ Duration of therapy not defined (currently continuous therapy). [39] ▪ Daily subcutaneous administration [39]
Pegylated interferon alfa	▪ Limited duration of therapy [25, 26] ▪ Long-term data available and effect on clinical endpoints have been studied [22, 28, 33] ▪ Weekly administration [52] ▪ Known substance with much experience in clinical use [55] ▪ HBsAg loss rare but possible [26]	▪ Only about 25 % virologic response 24 weeks after end of therapy [55] (Late HDV RNA relapse possible. [56]). ▪ Subcutaneous administration [52] ▪ Side effect profile ▪ Dose adjustments required for thrombocytopenia [52] or not recommended [1] ▪ Contraindicated in autoimmune diseases [52] ▪ Contraindicated in cirrhosis of Child-Pugh B stage or greater or decompensated liver cirrhosis [52] ▪ Restricted approval indication* [52]
Pegylated interferon alfa plus bulevirtide	▪ Synergistic effect possible [53] ▪ HBsAg loss possible [42] ▪ Limited duration of therapy conceivable [41, 42]	▪ No published results of randomized controlled trials are available yet, only congress data and published case series from observational studies [41–43, 46, 77–80]

* PEG-IFN-2a is approved 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. [52].

However, only interim results are currently available and have been presented at congresses [41, 77–79]. Therefore, no general recommendation for combination therapy can be made based on the available data. In the absence of contraindications to PEG-IFN, the addition of PEG-IFN may appear reasonable in individual cases and should be discussed with the patient (*see 2.4.3*).

2.4 How should therapy with bulevirtide be administered?

Recommendation 2.4.1	**new 2023**
Bulevirtide should be used at a dose of 2 mg 1x daily subcutaneously.	
[Evidence level 1, recommendation grade A, strong consensus].	

Comment

Bulevirtide inhibits the binding of HBsAg to the bile acid transporter NTCP expressed on hepatocytes, the cellular entry factor for HBV and HDV [37, 81]. This prevents reinfection of previously uninfected cells and continuous administration results in a reduction in the proportion of infected cells [82]. Bulevirtide has no direct effect on intrahepatic HDV spread mediated by cell division [83]. Various doses (2, 5, and 10 mg) have been studied to date either as monotherapy or in combination with PEG-IFN in phase 2 and phase 3 studies [40–46].

In the first phase 1b/2a study in chronic HDV infection, daily subcutaneous (s. c.) injections of 2 mg bulevirtide achieved a significant decrease in HDV RNA after 24 weeks of treatment, and the combination with PEG-IFN showed a greater HDV RNA decrease [44]. The primary endpoint of this pilot study, a 0.5 log decline in HBsAg levels at any time point, was not reached in any patient. In the subsequent phase 2 study (MYR202), the viral load decline induced by bulevirtide monotherapy was confirmed. After 24 weeks of therapy with 2, 5, and 10 mg of bulevirtide, HDV RNA decreased by 2.140 log IU/mL, 2.021 log IU/mL, and 2.702 log IU/mL, respectively. An HDV RNA decrease of ≥ 2 log IU/mL was achieved in 54 %, 50 %, and 77 % of patients, with undetectable HDV RNA in 4 %, 6 %, and 3 % of patients, respectively [40]. Paired liver biopsies were available in 22 patients, which also showed a significant decrease in intra-hepatic HDV RNA and a reduction in HDV-infected cells. After the end of therapy, 89 % (49/55) of patients with virologic response showed a relapse of HDV RNA, which was accompanied by an increase in transaminases in 22 % of cases [40]. Combined response (decrease in viral load ≥ 2 log and normal ALT) was achieved in 21 %, 28 %, and 37 % of patients treated with 2, 5, and 10 mg of bulevirtide, respectively [40] (▶ **Table 3**). No dose-dependent effect was observed in this study, so further studies used the lower 2 mg dose of bulevirtide. There was no effect on serum HBsAg levels during 6 months of bulevirtide monotherapy. The overall results of the Phase 2 study were confirmed by an interim analysis at week 48 of the ongoing Phase 3 study (MYR301). Again, there was no significant efficacy benefit in the group receiving 10 mg versus 2 mg of bulevirtide [45, 46]. After 48 weeks of therapy, 71 % and 76 % of patients treated with 2 mg and 10 mg of bulevirtide, respectively, showed a ≥ 2 log decrease in HDV RNA. Undetectable HDV RNA was detected in 12 % and 20 % of patients treated with 2 mg and 10 mg of bulevirtide, respectively, and the combined virologic and biochemical response was 45 % and 48 %, respectively [45, 46]. (▶ **Table 3**). Over-

all response rates increased from treatment week 24 to treatment week 48. Because the optimal duration of bulevirtide therapy to achieve a durable virologic response is not known yet, extending bulevirtide treatment to at least 1 year currently appears to be the most appropriate strategy to further increase or maintain virologic response. However, the duration of therapy has not yet been defined (*see 2.5.1*). There is one case report documenting sustained HDV RNA suppression 72 weeks after the end of three years of bulevirtide therapy. Intrahepatic HDV RNA and hepatitis D antigen (HDAg) were undetectable in the liver biopsy after the end of treatment; however, < 1 % of hepatocytes were still positive for HBsAg [84].

Bulevirtide therapy has been well tolerated and no serious adverse effects have occurred to date that have led to treatment discontinuation [40, 46]. A minority of patients complained of mild symptoms such as fatigue, nausea, headache, or dizziness; injection site side effects were mild [40, 46]. However, rare cases of severe skin effects, have been reported. One case report describes the late onset of a local T-cell-mediated allergic skin reaction after bulevirtide injection, the symptoms of which regressed despite continued treatment [85]. A similar case (hypersensitivity reaction to bulevirtide and continuation of therapy after successful desensitization) was reported [86].

Bulvirtide may pose a risk for drug interactions. In vitro data suggest possible inhibition of the uptake transporters OATP1B1 and OATP1B3 and possible inhibition of CYP3A (indirect pathways, e. g., through increased bile acids). However, the results of *in vitro studies* suggest that this interaction potential is not very high. Thus, *in vitro* inhibition of OATP1B1/3 transporters by bulevirtide was observed only at a concentration that is reached *in vivo* only after administration of high doses of bulevirtide (10 mg s. c.) [87]. Nevertheless, these potential interactions should be considered when concomitantly taking drugs that are metabolized via this pathway (e. g., statins, HIV or HCV protease inhibitors) [39]. Similarly, it has been shown *in vitro* that other drugs can also inhibit NTCP [88–90], so concomitant use (e. g., sulfasalazine, irbesartan, ezetimibe, ritonavir, and ciclosporin A) is not recommended [39]. No relevant effects on tenofovir pharmacokinetics were shown with concomitant use of tenofovir and bulevirtide. However, concomitant administration of tenofovir and bulevirtide in healthy volunteers resulted in decreased clearance of the CYP3A substrate midazolam [91]. In future studies, the interaction potential of bulevirtide should be carefully investigated.

Due to the mechanism of action of bulevirtide, at NTCP-saturating concentrations there is an inhibition of bile salt transport into hepatocytes, which leads to a dose-dependent increase in bile acids in the blood [40, 46]. In the phase 2 study, elevated bile acid concentrations (> 10 µmol/L) were observed at week 24 in 64 % of the 2-mg bulevirtide group, 75 % of the 5-mg bulevirtide group, and 87 % of the 10-mg bulevirtide group [40]. The elevation of bile acid concentrations was asymptomatic and not associated with pruritus in previous studies [40].

In July 2020, bulevirtide 2 mg received conditional approval from the European Medicines Agency (EMA) for the treatment of chronic HDV infection, with a recommendation to maintain treatment as long as clinical benefit is observed [39] (*see 2.5.2*).

Recommendation 2.4.2	**new 2023**
Bulevirtide may be combined with a nucleos(t)ide analogue.	
[Evidence level 2, recommendation grade 0, strong consensus].	

Comment

In the phase 2 study (MYR202), bulevirtide was used in combination with the NA tenofovir (TDF) [40]. The background included concerns that suppression of HDV RNA could possibly lead to an increase in HBV replication [27, 92, 93], which in turn could cause deterioration of liver function.

In the phase 3 study (MYR301), not all patients were treated with an NA (e. g., TDF), and even in the group without NA treatment, a decrease in HBV DNA was documented during bulevirtide therapy [45, 46]. There was no evidence of a different virologic response or without TDF. Also, in previous studies with PEG-IFN, the addition of NA did not improve virologic response (HDV RNA) [25, 26]. Regardless of these considerations, there are indications for treatment of HBV infection in HBV/HDV coinfection: reasons would include significant HBV DNA replication (HBV DNA > 2000 IU/ml), liver cirrhosis with detectable HBV DNA, or prevention of HBV reactivation [1]. The combination of NA (evidence for TDF) and bulevirtide was safe and without drug interactions in clinical trials [40, 46] and can therefore be used without hesitation [39].

Recommendation 2.4.3	**new 2023**
In individual cases, combination therapy with PEG-IFN can be performed.	
[Evidence level 4, recommendation grade 0, strong consensus].	

Comment

The addition of PEG-IFN to bulevirtide therapy may, in principle, increase response rates due to potential synergistic effects [53]. The combination of PEG-IFN and bulevirtide has been and is being investigated in clinical trials [41, 44]. Data from the relevant phase 2 trials MYR203 and MYR204 have only been presented in the form of congress papers [42, 43] and summarized in a review to date [41]. In the MYR203 trial, 48 weeks of combination therapy of PEG-IFN with 2, 5, or 10 mg of bulevirtide resulted in HDV RNA suppression below the limit of detection in 53 %, 27 %, and 7 % of the respective patient groups. A ≥ 1 log decrease of HBsAg occurred in 40 %, 13 %, and 13 % of patients treated with bulevirtide 2 mg, 5 mg, and 10 mg plus PEG-IFN, respectively. HBsAg loss was observed in 4/15 (27 %) and 1/15 (7 %) of patients receiving 2 mg and 10 mg bulevirtide, respectively. Only patients with HBsAg loss showed undetectable HDV RNA even after the 24-week follow-up period. In all other cases, there was a rebound of HDV RNA [42].

The MYR204 trial (bulevirtide 2 mg or 10 mg plus PEG-IFN for 48 weeks followed by 48 weeks of monotherapy with bulevirtide 2 mg or 10 mg versus PEG-IFN for 48 weeks or bulevirtide 10 mg

for 96 weeks) also showed that only patients in the combination arms had a HBsAg decline of ≥ 1 log [43].

In addition, real-world data on the use of combination therapy have already been presented at congresses [77–79], published in small case series [47] and commented in a review [41]. With the limitation of heterogeneous treatment regimens, the overall data confirm the improved virologic response rates (decline of HDV RNA) and safety of PEG-IFN/bulevirtide therapy reported in clinical trials [41]. However, preliminary data from the French early access cohort show comparable data to bulevirtide monotherapy in terms of combined response (HDV RNA drop ≥ 2 log plus ALT normalization) after 2 years of PEG-IFN/bulevirtide treatment [78]. In a case series from Austria, combination therapy with PEG-IFN was initiated in patients who showed no further decline of HDV RNA after 24–48 weeks of bulevirtide therapy, regardless of initial response classification. The addition of PEG-IFN resulted in a further decline in HDV RNA in all eight patients (1.29 ± 0.19 [SD] log within 12 weeks) [47]. The authors proposed a response-guided algorithm for PEG-IFN addition in suboptimal response to bulevirtide [47]. However, limitations of this study include the lack of a predefined treatment protocol and the lack of long-term data. Therefore, it is currently unclear which patients will benefit from combination therapy. In addition, it is not known whether combination therapy should be administered from the beginning or started during the course after certain criteria have been met during bulevirtide monotherapy. Here, the results of further clinical studies have to be awaited. However, based on many years of experience in therapy with PEG-IFN and the availability of first real-world data, combination therapy of bulevirtide plus PEG-IFN by experienced physicians in the treatment of hepatitis D may be an option in individual cases.

Recommendation 2.4.4	new 2023
Regular clinical, laboratory, and virologic monitoring should be performed during therapy with bulevirtide.	
[Expert consensus, strong recommendation, strong consensus.]	
The determination of bile acids can be used to check therapy adherence.	
[Evidence level 3, recommendation grade 0, strong consensus].	

Comment

During antiviral therapy with bulevirtide, established clinical practice follow-up parameters should be monitored. These include laboratory parameters including liver function parameters as well as virological parameters. The endpoint of the current phase 3 study is defined as a combined virologic (≥ 2 log HDV RNA decline or suppression below detection limit) and biochemical (ALT normalization) endpoint after 48 weeks of therapy [45, 46]. To assess virologic response to bulevirtide therapy, quantitative determination of HDV RNA should be performed at least every 3 months. Quantitative determination of HBV DNA is also recommended to assess the therapeutic indication for NA therapy or the therapeutic response during NA therapy. Although no effect on HBsAg was observed during bulevirtide monotherapy [40], HBsAg should be determined at least once a year. This may include a quantitative determination. Although HBsAg loss is rare, immunologic events during and also independent of therapy are conceivable that can lead to HBsAg loss. Since stable HBsAg loss is associated with sustained immunological control of HDV and HBV, termination of antiviral therapy is recommended in this case (*see 2.4.6*).

Bulevirtide specifically binds NTCP, whose natural function in the enterohepatic circulation is the hepatic reuptake of conjugated bile salts into hepatocytes. This results in inhibition of bile salt transport at saturating concentrations and an asymptomatic increase in blood bile acids that is dose-dependent [40] (*see 2.4.1*). Determination of bile acids may therefore help to monitor adherence to therapy, although even with adherence, blood bile acid concentrations may be normal. However, a correlation between bile acid levels during therapy and response to therapy has not yet been demonstrated [94].

2.5 When can therapy with bulevirtide be stopped?

Recommendation 2.5.1	new 2023
A general recommendation for the timing of discontinuation of therapy with bulevirtide cannot be given at this time.	
[Expert consensus, recommendation open, strong consensus.]	
In case of confirmed HBsAg loss, therapy should be discontinued.	
[Expert consensus, recommendation, strong consensus.]	

Comment

The phase 3 study (MYR301) is investigating the course after discontinuation of bulevirtide after a prior therapy duration of 96 to 144 weeks [45, 46]. These results are not yet available and must be awaited to assess whether a sustained response can be achieved after discontinuation of bulevirtide therapy after 96 weeks or longer. Recent real-world data show a rebound in HDV RNA after discontinuation of bulevirtide even after more than 48 weeks of therapy [47]. A single case report from Milan documented a maintained virologic response 72 weeks after the end of three years of bulevirtide treatment, even in the absence of HBsAg loss [84]. Maintained virologic control was previously shown particularly with combination therapy of PEG-IFN plus bulevirtide and HBsAg loss [41]. In the PEG-IFN trials, HBsAg loss was associated with durable HDV RNA suppression. The patients with late HDV RNA relapse were all still HBsAg positive [56]. Therefore, analogous to the treatment of chronic HBV infection [1], we recommend to discontinue antiviral therapy upon confirmed HBsAg loss. Confirmed HBsAg loss is defined as two or more consecutive negative HBsAg results at least 6 months apart without the need for anti-HBs seroconversion [27, 95]. However, long-term data after HBsAg loss in the setting of chronic HDV infection are insufficient, so follow-up should be continued after HBsAg loss.

Recommendation 2.5.2	new 2023
Bulevirtide therapy should be continued as long as clinical benefit is evident.	
[Expert consensus, recommendation, strong consensus.]	

Comment

Because HBsAg loss is rarely achieved with bulevirtide therapy and the duration of therapy has not yet been defined (*see 2.5.1*), the current regulatory text for bulevirtide recommends continuation of therapy as long as it is associated with clinical benefit [39]. This wording is reasonable because non-response to bulevirtide therapy has not previously been defined. Not all patients achieve the combined response defined in the phase 3 trial (HDV RNA decline ≥ 2 log or negative plus ALT normalization), but patients may still achieve a virologic or biochemical response, show clinical improvement, or stabilize liver disease. Early discontinuation of bulevirtide therapy without achieving HBsAg loss can potentially lead to a rebound in HDV RNA (*see 2.5.1*), which in turn can lead to immunologic responses. An ALT increase may increase the risk of hepatic decompensation in patients with cirrhosis but may theoretically be associated with beneficial effects (e. g., viral control). In a patient with compensated cirrhosis who discontinued bulevirtide after achieving virologic and biochemical response after 48 weeks of therapy, the initial virologic and biochemical relapse was followed by normalization of ALT in association with low HDV RNA and HBsAg levels [96]. However, systematic data on the discontinuation of bulevirtide therapy are not yet available. Real-world data indicate that a treatment duration of 48 weeks or longer is safe. [78]. In two patients from Milan treated continuously with bulevirtide for three years, virologic and biochemical responses were maintained throughout the treatment period. In one patient with advanced compensated cirrhosis, liver function tests improved markedly after three years of bulevirtide therapy, esophageal varices regressed, and histologic and laboratory features of HDV-associated autoimmune hepatitis improved [96]. In this single case report, HDV RNA remained negative 72 weeks after cessation of three years of bulevirtide therapy, and intrahepatic HDV markers (HDV RNA, HDAg) were also undetectable, although HBsAg was still positive [84].

Although nonresponse to bulevirtide therapy has not yet been defined, discontinuation of therapy may be considered in patients who do not have a significant virologic and biochemical response (HDV RNA decline < 1 log and no improvement in ALT levels) after 48 weeks of bulevirtide therapy despite treatment adherence.

2.6 How should pegylated interferon alfa therapy be administered?

Recommendation 2.6.1	new 2023
PEG-IFN therapy should be administered for 48 weeks.	
[Evidence level 2, recommendation grade B, strong consensus].	
Prolongation of therapy may be considered if HBsAg declines, treatment is well tolerated, and the treatment goal is HBsAg loss.	
[Evidence level 3, recommendation grade 0, strong consensus].	

Comment

The majority of previous studies of chronic hepatitis D therapy with PEG-IFN have examined a treatment duration of 48 weeks [55]. In the HIDIT-I trial, suppression of HDV RNA below the limit of detection at the end of therapy was achieved in 23% and 24% of patients treated with PEG-IFN with or without adefovir for 48 weeks. The proportion of patients with negative HDV RNA at 24 weeks after the end of treatment was 26 % and 31 %, respectively [25]. Another randomized study by the German Hepatitis Competence Network investigated prolonged PEG-IFN therapy of 96 weeks in 120 patients, with half of the patients receiving additional tenofovir (TDF). At the end of therapy, 48 patients (40 %) were HDV RNA negative, whereas 46 patients already became HDV RNA negative during the first 48 weeks of therapy. Thus, few patients achieved this goal during the therapy extension to week 96. Importantly, 40 % of patients (19/48) who were HDV RNA negative at the end of therapy experienced viral relapse during follow-up (24 weeks after the end of treatment) despite the extended treatment duration. All in all, only 26.7 % of patients showed negative HDV RNA 24 weeks after the end of therapy [26]. Thus, a treatment duration of 96 weeks did not significantly increase the number of patients with durable HDV RNA suppression. An extension of therapy beyond 48 weeks is not generally justified. If HBsAg levels decline during treatment with PEG-IFN, continuation of treatment beyond 48 weeks may be reasonable. In these cases, the goal of HBsAg loss may be achieved in some patients [73, 74]. HBsAg loss is defined as functional cure of the underlying HBV infection [27], which also cures HDV infection in principle. HBsAg loss is associated with improved long-term clinical outcome [22, 27]. In case of treatment extension with PEG-IFN, the duration of therapy should be individually adjusted to the HBsAg decline and HBsAg levels should be quantified every 3–6 months. Case series from Italy and Germany [97], Turkey [21] and the USA [73, 74] have described HBsAg losses after a treatment duration of up to 6 years. In the case of prolonged therapy, however the tolerability of the treatment and the risk of serious side effects should be taken into account.

Prospective clinical trials investigating PEG-IFN treatment shorter than 48 weeks are not available. Currently, there is no evidence for the benefit of shortening therapy in terms of response-guided therapy based on HDV RNA kinetics during treatment (no analogy to the now obsolete hepatitis C therapy with PEG-IFN) (*see 2.1.1 and 2.2.4*).

Data on the effects of stage of liver disease are somewhat conflicting, although most studies suggest that PEG-IFN is equally effective in patients with or without compensated cirrhosis [26, 98]. Importantly, PEG-IFN is contraindicated in cirrhosis of Child-Pugh B stage or higher or decompensated cirrhosis [52].

Recommendation 2.6.2	**new 2023**
During and after therapy with PEG-IFN, regular safety-related blood tests should be performed and interferon-typical side effects should be elicited.	
[Expert consensus, strong recommendation, strong consensus.]	

Comment

A decrease in leukocytes and platelets is common during IFN-based therapy. Therefore, blood counts should be checked (initially after 2–4 weeks, thereafter every 4–12 weeks) and, depending on the findings, dose adjustments should be performed according to the prescribing information. IFN-based therapy can induce autoimmune thyreopathy [99]. Therefore, TSH should be monitored every 8–12 weeks before and during therapy. ALT should be determined every 4–12 weeks due to possible ALT flares. Patients with advanced liver fibrosis should be monitored closely (every 4 weeks).

2.7 How should patients with HBV/HDV coinfection and decompensated liver disease be treated?

Recommendation 2.7.1	**new 2023**
Patients with decompensated cirrhosis or acute fulminant hepatitis D should be evaluated for liver transplantation.	
[Expert consensus, strong recommendation, strong consensus.]	

Comment

When antiviral therapy with bulevirtide or PEG-IFN is not possible due to advanced liver cirrhosis and its associated complications, liver transplantation is a potential therapeutic option. Patients undergoing liver transplantation for hepatitis D have a very good prognosis after liver transplantation compared with other indications [100]. Reinfection with HBV and HDV can be prevented by passive immunization against HBV (HBIG) and concurrent administration of NA against HBV. In contrast to HBV monoinfection, HBIG should not be discontinued in this case, as data on this are lacking to date and HBV reactivation may also be accompanied by HDV reactivation (*see chapter 4.3 of the S3 hepatitis B guideline*) [1].

In line with the hepatitis B guideline, we also recommend the initiation of antiviral therapy to treat HBV infection in HBV/HDV-coinfected patients with liver cirrhosis and detectable HBV DNA [1] (*see 2.1.2*). HBV-monoinfected patients with advanced liver disease are also at risk from mild episodes of chronic hepatitis ("flares"), and even low HBV DNA levels are associated with an increased risk of HCC in this patient group [1, 101–103]. In contrast, sustained HBV DNA suppression by antiviral therapy prevents hepatic decompensation, HCC, liver transplantation, and death [1, 104]. Whether this can be analogously applied to HBV/HDV-coinfected patients, in whom HBV DNA is often detectable at low positive levels, has not been systematically investigated. Given the good tolerability of NA and the proven benefit in HBV-monoinfected patients, we recommend its use also in HBV/HDV-coinfected patients with liver cirrhosis and detectable HBV DNA.

Recommendation 2.7.2	**new 2023**
Therapy with PEG-IFN should not be performed in the presence of decompensated liver disease.	
[Expert consensus, strong recommendation, strong consensus.]	

Comment

The use of PEG-IFN is contraindicated in patients with cirrhosis of Child-Pugh B stage or higher or decompensated cirrhosis [52]. Therefore, PEG-IFN should not be used in this patient population [1].

Recommendation 2.7.3	**new 2023**
Bulevirtide therapy may be administered to patients with decompensated liver disease after weighing the risks and benefits on a case-by-case basis.	
[Expert consensus, recommendation open, strong consensus.]	
If decompensation occurs during therapy with bulevirtide, therapy should be continued.	
[Evidence level 4, recommendation grade B, strong consensus].	

Comment

Currently, no data from randomized clinical trials are available for the use of bulevirtide in decompensated liver cirrhosis. Due to the limited data available to date, the general use of bulevirtide in patients with decompensated liver cirrhosis cannot be recommended at present. However, due to the mechanism of action of the substance, deterioration of liver function during therapy seems unlikely. Individual case reports published to date show no worsening of liver function with bulevirtide therapy in patients with liver cirrhosis and portal hypertension. In some patients with advanced but not decompensated cirrhosis, improvement in liver function has even been reported, and the increase in bile acids was asymptomatic in these patients as well [48]. In the German Real-World Cohort, a total of 5 patients with decompensated

cirrhosis (Child-Pugh B: n = 4; Child-Pugh C: n = 1) were treated with bulevirtide. ALT levels decreased and platelet counts increased in 4 patients. One patient with refractory ascites experienced transient improvement. In another patient who was compensated at baseline and developed decompensation (ascites) during therapy, bulevirtide was safely continued and the cause of decompensation was attributed to another precipitating cause [51]. Discontinuation of therapy with bulevirtide may result in a rebound of HDV RNA. Therefore, there is concern, particularly in patients with decompensated liver function, that a rebound in HDV RNA after discontinuation of bulevirtide therapy could lead to further deterioration of liver function. Patients with advanced or decompensated liver cirrhosis should generally be managed in specialized centers in order to evaluate the indication for liver transplantation appropriately in time (*see 2.7.1*).

3 Open questions

To improve the treatment of patients with HBV/HDV co-infection, further research activities are needed. In the following, we have phrased important open questions, that should be addressed in future research.

- What measures are needed to standardize the quantification of HDV RNA?
- How reliable are noninvasive techniques such as elastography in assessing liver fibrosis in patients with HBV/HDV coinfection?
- What markers can better predict treatment response or non-response to enable response-guided therapy with both PEG-IFN and bulevirtide or combination therapy?
- What long-term effects (side effects, drug interactions, and effectiveness) may be observed in patients during or after therapy with bulevirtide?
- How can patients be treated antivirally during pregnancy?
- Will bulevirtide therapy achieve HDV cure in the long term ?
- How long should patients be treated with bulevirtide to achieve complete virologic control without risk of relapse?
- Can antiviral therapy with bulevirtide be safely discontinued after HBsAg loss?
- Can therapy with bulevirtide be stopped before HBsAg loss?
- Is bulevirtide safe and effective to use in patients with decompensated liver disease, and how does dosing in these patients differ from dosing in patients with preserved liver function?
- What strategies should be used for combination therapy with bulevirtide and other antiviral agents, and which patients benefit most?

Conflicts of Interest

The overview of the authors' conflicts of interest is published in the appendix of the guideline report.

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