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Position Paper

AISF-SIMIT practice guidance on treatment of hepatitis d virus (HDV): A 2025 update

Associazione Italiana per lo Studio del Fegato (AISF) and Società Italiana di Malattie Infettive e Tropicali (SIMIT)

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ABSTRACT

Chronic hepatitis Delta virus (HDV) infection represents the most severe form of viral hepatitis, characterized by accelerated progression to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. For decades, Pegylated Interferon (PegIFNα) has been the only therapeutic option, with limited efficacy and poor tolerability. The approval of the HBV/HDV entry inhibitor Bulevirtide marked a turning point, by providing the first anti-HDV specific antiviral drug. This position paper, developed jointly by the Italian Association for the Study of the Liver (AISF) and the Italian Society of Infectious and Tropical Diseases (SIMIT), updates prior national guidance by providing practical recommendations for diagnosis, staging, and treatment of chronic HDV infection.

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1. Introduction

Chronic infection with hepatitis Delta virus (HDV) is considered the most severe viral hepatitis, leading to accelerated fibrosis progression to cirrhosis and its complications (end-stage liver disease and hepatocellular carcinoma) compared to hepatitis B virus (HBV) monoinfected patients [1]. Until now, treatment with Interferon (IFN) has represented the mainstay of HDV treatment, resulting in suboptimal virological response rates and limited tolerability due to IFN side effects. Recently, the HBV-HDV entry inhibitor Bulevirtide (BLV) 2 mg/day has been conditionally (2020) and fully (2023) approved by European Medicines Agency (EMA) for treatment of compensated hepatitis Delta (CHD); in Italy, it was approved by the Italian Medicines Agency (AIFA) in January 2023. Treatment recommendations with BLV have been incorporated in the HBV and HDV European Clinical Practice Guidelines [1,2]. In 2023, the Italian association for the Study of the liver (Associazione Italiana Studio del Fegato - AISF) and the Italian society of tropical and infectious diseases (Società Italiana Malattie Infettive e Tropicali – SIMIT) have released a joint guidance for the diagnosis and management of patients with chronic HDV infection [3]. This paper serves as an update of the previous document, with the aim of focusing in detail about treatment options, including therapy for special patient populations and practical issues about treatment management. The writing board (nominated by the AISF-SIMIT governing board) assimilated data from EASL HDV and HBV practice guidelines, published clinical trials and real-world data about IFN and BLV, expert opinions and selected unpublished data. The document has been reviewed by a review board of renowned experts in the field from both AISF-SIMIT societies. Additional clinical trial and real-world data will result in future revisions of this paper.

2.1. Epidemiology of hdv infection: current updates

According to most recent estimates, approximately 10-20 million people worldwide are positive for hepatitis Delta virus (HDV) antibodies, corresponding to 3-5 % of hepatitis B surface antigen (HBsAg) carriers [4–7]. Among total anti-HDV positive individuals, the estimated prevalence of viremic HDV infection ranges from 60 to 70 %. Eastern Europe, Mongolia, Western and Middle Africa represent hotspots of HDV infection, while prevalence is also higher among people who inject drugs, men who have sex with men, commercial sex workers, hemodialysis recipients, and people with hepatitis C virus (HCV) or HIV co-infection [5–7]. In Italy, the Polaris study estimated an adjusted anti-HDV prevalence of 3.4 % among HBsAg carriers and 60 % HDV RNA positivity among anti-HDV positive subjects, resulting in 6,800 HDV RNA positive cases [7]. More recently, an Italian study based on national data about exemptions codes and a dedicated survey across 30 centers, estimated 9,360 HDV patients, corresponding to 7.7 % of HBsAg positive subjects [8].

Precise estimates of HDV epidemiology, however, suffer from lack of universal anti-HDV screening of HBsAg carriers, due to heterogeneous recommendations across scientific societies, along with low awareness and implementation of HDV testing in clinical practice, and lack of confirmatory HDV RNA testing in all anti-HDV positive subjects. Therefore, many studies in recent years have underlined the importance of automatic reflex testing of HBsAg carriers (anti-HDV antibodies ± HDV RNA), in order to increase HDV diagnosis [9–11].

2.2. Pre-treatment evaluation: liver disease staging

Although liver biopsy still represents the gold standard for fibrosis staging, non-invasive tests (NITs) can be applied as useful tools also in patients with HDV infection. Performance of liver stiffness measurement (LSM) has been recently evaluated by two papers in large European cohorts: LSM>10.0 kPa was proposed as cut-off for advanced fibrosis (F3), while LSM >12.0 kPa or 15.2 kPa were the suggested cut-offs for cirrhosis (F4), respectively [12,13]. However, LSM showed higher negative predictive values, that is better accuracy in ruling out than ruling in significant fibrosis. Therefore, a possible algorithm was proposed, where LSM <6 kPa almost totally exclude significant fibrosis, advanced fibrosis is highly probable for LSM values ≥10 kPa, and liver biopsy should be discussed in the "grey zone" between 6-10 kPa [13]. In addition, liver biopsy remains the preferred tool in case of conflicting results from NITs, imaging and blood tests, when the definition of liver staging is expected to change patient management, and to assess co-factors of liver disease (i.e. metabolic liver disease, autoimmune hepatitis) [1]. Several serological NITs for fibrosis staging have been evaluated in HDV patients, such as APRI (Aspartate Aminotransferase to Platelet Ratio Index), FIB-4 (Fibrosis-4 score), D4FS (Delta-4 Fibrosis score), AAR (Aspartate Aminotransferase-to-Alanine Aminotransferase Ratio): however, serological NITs showed lower accuracy than LSM [12,13], mainly because they are highly influenced by transaminases values.

2.3. Therapeutic and clinical endpoints

HDV RNA replication has been identified as one of the strongest drivers of disease progression in chronic hepatitis Delta [14–16], and a ≥ 2 $LogIU_{10}$/mL HDV RNA reduction upon anti-HDV treatment has been associated with improved long-term outcomes and survival. This concept was first suggested by Farci et al., who reported an association between early HDV RNA decline upon Interferon (IFN)-based treatment and improved long-term outcomes and survival in a small cohort [17]. Subsequently, this observation was refined by an expert consensus panel as an initial efficacy endpoint for clinical trials in CHD [18], by aiming to provide a pragmatic surrogate for disease control in the absence of validated long-term endpoints. More recently, international societies and regulatory agencies have established as desired treatment endpoints the combined response, defined as undetectable HDV RNA or at least ≥ 2 $LogIU_{10}$/mL HDV RNA reduction (virological response) plus aminotransferases normalization (biochemical response) after 48 weeks of anti-HDV therapy when considering long-term (> 48 weeks) treatment strategies, while HBsAg loss + undetectable HDV RNA or at least undetectable HDV RNA 24 weeks off-therapy should be the desirable endpoints in short-term treatment strategies (≤48 weeks) [19]. Recent follow-up data at 1 year after discontinuation of BLV monotherapy for 96 or 144 weeks in the MYR-301 trial [20,21] and preliminary data in the real-world setting [22], underline the importance of prolonged and maintained on-treatment HDV RNA undetectability, as well as reaching a deep HDV RNA suppression defined as target not detected (TND) with highly sensitive HDV RNA assays to avoid false negative HDV RNA results (see below paragraph *On-treatment and off-treatment monitoring*).

2.4. Treatment of hepatitis delta

2.4.1. Currently available treatment options

2.4.1.1. NUCs. HDV is a defective RNA virus needing HBsAg envelope for efficient infection and propagation. Treatment with nucleos(t)ide analogues (NUCs) for hepatitis B virus (HBV) does not affect HDV replication. However, NUC treatment in HDV infected patients is recommended by European Guidelines [1,2] in all patients with advanced fibrosis or cirrhosis and detectable HBV DNA, in patients with decompensated cirrhosis irrespective of HBV DNA

Table 1
Efficacy of IFNα or PegIFNα in Randomized-controlled trials.

Study	Patients Number	Cirrhosis	Treatment	Weeks	Off-treatment FUP Weeks	ALT normalization at EOT	HDV RNA undetectable at EOT	HDV RNA undetectable Off-treatment	HBsAg loss Off-treatment
Niro et al. [25]	**38**	**74 %**							
	16		PegIFNα2b*	72	24	37 %	19 %	25 %	0 %
	22		PegIFNα2b* + RBV	72	24	41 %	9 %	18 %	0 %
Ormeci et al. [26]	**18**	**na**							
	11		PegIFNα2b*	96	24	na	na	na	27 %
	7		PegIFNα2b*	48					0 %
HIDIT-1 [27]	**90**	**18 %**							
	30		PegIFNα2a° + ADV	48	24	32 %	23 %	26 %	7 %
	29		PegIFNα2a°	48	24	28 %	24 %	31 %	0 %
	31		ADV	48	24	7 %	0 %	0 %	0 %
Abbas et al. [28]	**40**	**20 %**							
	21		PegIFNα2a° + ETV	72	24	19 %	38 %	33 %	5 %
	19		PegIFNα2a°	72	24	37 %	53 %	42 %	0 %
HIDIT-2 [29]	**120**	**40 %**							
	59		PegIFNα2a° + TDF	96	24	44 %	48 %	31 %	5 %
	61		PegIFNα2a°	96	24	38 %	33 %	23 %	5 %
LIMIT-2 [30]	**33**	**9 %**							
	14		PegIFNλ 180 µg+	48	24	14 %	36 %	36 %	0 %
	19		PegIFNλ 120 µg+	48	24	11 %	16 %	16 %	0 %
Anastasiou et al. [31]	**120**	**40 %**							
	59		PegIFNα2a° + TDF	96	356	44 %	48 %	75 %	18 %
	61		PegIFNα2a°	96	356	38 %	33 %	48 %	15 %

* 1.5 µg/kg/week;
° 180 mcg/week;
+ weekly administrationIFN: Interferon; PegIFN: Pegylated Interferon; RBV: Ribavirin; FUP: Follow-up; EOT: End of Treatment; HDV: Hepatitis Delta Virus; HBsAg: Hepatitis B Surface Antigen; ADV: Adefovir dipivoxil; ETV: Entecavir; TDF: Tenofovir Disoproxil Fumarate; na: not available

values, and in patients with milder fibrosis and active HBV replication (HBV DNA > 2,000 IU/mL). Finally, given the strong viral interference between HBV and HDV, NUC treatment should be administered in patients receiving anti-HDV agents, in order to prevent HBV reactivation upon HDV suppression [23].

2.4.1.2. PegInterferon (PegIFN). For more than 30 years, the only available therapeutic option for patients with chronic hepatitis Delta (CHD) has been Interferon alpha (IFNα), initially in its standard form and, subsequently, almost exclusively as pegylated form (PegIFNα). Besides a suppressive effect on HDV replication, recent findings showed that IFN prevents the intracellular spreading of HDV during hepatocyte cell division [24]. Efficacy and safety of IFNα or PegIFNα in CHD patients, alone or in combination with NUCs, have been extensively investigated in clinical trials and real-world studies, whose key results are summarized in Tables 1 **and** 2. Overall, PegIFNα resulted in sustained off-treatment HDV RNA undetectability ranging between 15-48 %, aminotransferase normalization was reported in 11-50 % of patients, and rates of HBsAg clearance ranged from 0-27 % [25–45]. Long-term follow-up studies showed reactivation of HDV replication in 50 % of patients with negative HDV-RNA 6 months after stopping treatment [46]. Most common IFN-related side effects include flu-like symptoms, fatigue, weight loss, hematological toxicity (neutropenia, anemia, thrombocytopenia) and neuropsychiatric disorders, that resulted in discontinuation rates due to adverse events ranging from 5-24 %. Moreover, IFN treatment is contraindicated in patients with decompensated cirrhosis, psychiatric comorbidities, autoimmune disorders or solid organ transplant recipients. The phase 3 LIMT-2 trial with PegIFN Lambda, which targets a receptor with highly specific hepatocyte expression granting for reduced myelosuppressive and neurological side effects, was prematurely discontinued due to some cases of hepatobiliary toxicity resulting in liver decompensation [47].

2.4.1.3. Bulevirtide (BLV). Efficacy of BLV monotherapy has been investigated in Phase 2 and 3 clinical trials and real-world setting: key results are summarized in Tables 3 **and** 4 [48–68]. Overall, after 48-96 weeks of BLV treatment, rates of virological response ranged from 60-80 % across studies, biochemical response 60-70 %, combined response 40-60 % and HDV RNA undetectability 15-40 % (with differences related to HDV RNA quantification assays used). Treatment with BLV monotherapy did not significantly reduce HBsAg levels or induce HBsAg loss. BLV administration results in elevation of bile acids due to blockage of NTCP (Na taurocholate co-transporting polypeptide) receptor, which is also the bile acid transporter. Nevertheless, pruritus is uncommon (10-12 %) and independent of bile acids levels. Other common side effects related to BLV include transient injection site reactions (5-20 %), while no discontinuation for adverse events occurred during clinical trials.

2.4.2. Antiviral strategies according to liver disease severity

2.4.2.1. Patients with chronic hepatitis [F0-F3]. According to EASL guidelines, anti-HDV treatment should be considered in all CHD patients, irrespectively of liver fibrosis stage, given the potential liver disease progression [1]. A 48-week treatment course with Peg-IFNα can be considered a treatment option in patients with compensated liver disease, especially in patients with mild to bridging fibrosis.

BLV monotherapy is a feasible option in all patients with compensated liver disease, based on efficacy and safety data from clinical trials (Table 3) and real-world studies (Table 4). Discussion about treatment options should take into account finite *vs.* long-term treatment strategies, drug availability, patient comorbidities and possible contraindications to PegIFNα, side effects and adherence (especially in long-term treatment strategies), as well as patient preferences and availability of alternative options (i.e. clinical trials).

De novo combination of BLV (2, 5 or 10 mg) + PegIFNα2a for 48 weeks has been explored in the MYR-203 and MYR-204 trials [50,51] and few real-world studies [60,61] (Tables 3-4). The combination of BLV 10 mg + PegIFNα2a was superior to BLV monotherapy in terms of undetectable HDV RNA 24 weeks after the end of treatment, however BLV 10 mg is currently unavailable in clinical

Table 2
Effectiveness of IFNα of PegIFNα in real-world studies.

Study	Study Design	Patients Number	Cirrhosis	Treatment	Weeks	Off-treatment FUP Weeks	ALT normalization at EOT	HDV RNA undetectable at EOT	HDV RNA undetectable Off-treatment	HBsAg loss Off-treatment
Castelnau et al. [32]	Prospective	**14**	na	PegIFNα2b*	48	24-168	36 %	57 %	43 %	7 %
Erhardt et al. [33]	Prospective	**12**	na	PegIFNα2b*	48	24	25 %	17 %	17 %	na
Gheorghe et al. [34]	Prospective	**48**	na	PegIFNα2b*	52	104	50 %	33 %	25 %	na
Gulsun et al. [35]	Retrospective	**46**	na							
		25		PegIFNα2a°	48	48	36 %	52 %	41 %	0 %
		21		PegIFNα2a°	96	48	33 %	66 %	48 %	0 %
Karaca et al. [36]	Retrospective	**32**	22 %	PegIFNα2a° or PegIFNα2b*	96	24-240	na	50 %	47 %	0 %
Abbas et al. [37]	Retrospective	**104**	39 %	PegIFNα2a° or PegIFNα2b*	48	24	35 %	42 %	23 %	0 %
Heller et al. [38]	Prospective	**13**	15 %	PegIFNα2a§	140 (6-260)	144	50 %	38 %	33 %	25 %
Keshvari et al. [39]	Retrospective	**20**	10 %	IFN standard α2b OD or OW	144	24	na	na	15 %	5 %
Bahcecioglu et al. [40]	Retrospective	**56**	39 %	PegIFNα2a° or PegIFNα2b*	48	24	32 %	32 %	30 %	na
Soyer et al. [41]	Retrospective	**65**	na	Standard or PegIFNα	<48 or >48 (max 96)	24	na	21 % 45 %	7 % 41 %	na
Borzacov et al. [42]	Prospective	**22**	5 %	PegIFNα2a° + ETV	48	24	68 %	95 %	95 %	na
Wranke et al. [43]	Retrospective	**52**	46 %	Standard or PegIFNα ± NUCs	48 (24-144)	240 (24-864)	na	na	44 %	15 %
Boglione et al. [44]	Retrospective	**46**	20 %	PegIFNα2a°	48	144	na	24 %	17 %	17 %
Gherlan et al. [45]	Retrospective	**76**	21 %	PegIFNα2a°	Up to 96	24	24 %	28 % (week 72)	22 %	0 %

* 1.5 µg/kg/week;
° 180 µg/week;
§ 180 µg/week titrated at maximum tolerated doseIFN: Interferon; PegIFN: Pegylated Interferon; FUP: Follow-up; ALT: Alanine Aminotransferase; EOT: End of Treatment; HDV: Hepatitis Delta Virus; HBsAg: Hepatitis B Surface Antigen; NUCs: Nucleos(t)ide analogues; na: not available; OD: once daily; OW: once weekly

practice. Combination of PegIFNα2a + BLV 2 mg showed higher on-treatment virological response and HDV RNA undetectability rates, however off-treatment data with PegIFNα + BLV 2 mg currently do not seem to support additional efficacy of PegIFNα + BLV 2 mg combination compared to PegIFNα or BLV monotherapy.

2.4.2.2. Patients with compensated cirrhosis (F4). According to the EASL 2023 guidelines, a PegIFNα course could be considered in all patients with compensated CHD, including those with cirrhosis [1]. Treatment decisions in patients with compensated cirrhosis should be individualized, balancing anticipated antiviral benefit with the risk of hepatic decompensation: in patients with clinically significant portal hypertension (CSPH), this risk-benefit assessment favors IFN-free options due to increased side effects in this advanced liver disease population.

BLV monotherapy is a valuable treatment option for patients with compensated cirrhosis, including those with CSPH. Safety and effectiveness of BLV in these patients have been extensively reported in clinical trials (Table 3) and real-world studies (Table 4) [48–67]: response rates did not differ in real-world compared to clinical trials, as well as in patients with cirrhosis compared to milder disease [63]. Besides virological and biochemical responses, patients receiving BLV showed significant improvement of transient elastography on-therapy, as well as non-invasive tests of fibrosis [57,64]. Currently available data up to 3 years follow-up with BLV monotherapy reported low rates of incident liver decompensation on-therapy [68].

2.4.2.3. Patients with decompensated cirrhosis. All patients with decompensated cirrhosis should be primarily evaluated for liver transplantation. IFN administration is contraindicated due to the risk of serious adverse events, including infections, further decompensation and cytopenia. Pharmacokinetic data reported comparable exposure to BLV 2 mg in patients with moderate hepatic impairment (Child B) compared to matched controls with preserved liver function. Elevation in total bile acids were higher in patients with hepatic impairment; however, no safety signals were detected [69]. Off-label treatment with BLV in 19 Child B patients has been reported in a real-world study [70], showing response rates comparable to patients with compensated disease. Moreover, no serious BLV-related adverse events were reported during therapy.

Outcomes of patients receiving BLV monotherapy while on the liver transplant waiting list were reported in 7 French and 3 Italian patients with decompensated cirrhosis: most patients showed liver function improvement and 6 patients were delisted [71,72]. The impact of BLV treatment in patients with advanced decompensated disease (Child C) remains still uncertain, so that no clear recommendations can be provided.

2.4.3. Antiviral treatment in special populations

2.4.3.1. Acute hepatitis. No data is available about PegIFNα or BLV monotherapy in patients with acute HDV infection, either in case of co-infection or super-infection. However, due to the risk of severe acute hepatitis resulting in acute liver failure, administration of PegIFNα is not recommended.

Table 3
Efficacy of BLV in clinical trials.

Study	Phase	Patients Number	Cirrhosis	Treatment	Weeks	Virological Response On-treatment	ALT Normalization On-treatment	Combined Response On-treatment	HDV RNA undetectable On-treatment	HDV RNA undetectable Off-treatment
MYR-201	**1b/2a**	**24**	**13 %**							
[48]		8		BLV 2 mg	24	86 %*	75 %	-	29 %	-
		8		BLV 2 mg + PegIFNα2a°	24	100 %*	13 %	-	71 %	-
		8		PegIFNα2a°	24	86 %*	13 %	-	29 %	-
MYR-202	**2**	**118**	**50 %**							
[49]		28		BLV 2 mg + TDF	24	54 %	43 %	21 %	4 %	4 %#
		32		BLV 5 mg + TDF	24	50 %	50 %	28 %	6 %	3 %#
		30		BLV 10 mg + TDF	24	77 %	40 %	37 %	3 %	0 %#
		28		TDF	24	4 %	7 %	0 %	0 %	0 %#
MYR-203	**2**	**90**	**17 %**							
[50]		15		PegIFNα2a°	48	40 %	27 %	7 %	13 %	0 %#
		15		BLV 2 mg + PegIFNα2a°	48	100 %	27 %	20 %	80 %	53 %#
		15		BLV 5 mg + PegIFNα2a°	48	93 %	47 %	33 %	87 %	27 %#
		15		BLV 2 mg	48	60 %	73 %	13 %	13 %	7 %#
		15		BLV 10 mg + PegIFNα2a°	48	93 %	27 %	20 %	80 %	7 %#
		15		BLV 5 mg BID + TDF	48	87 %	40 %	13 %	47 %	33 %#
MYR-204	**2**	**175**	**35 %**							
[51]		25		PegIFN α2a°	48	-	21 %	13 %§	21 %	25 %+
		50		BLV 2 mg-PegIFN α2a° + BLV	48 + 48	-	64 %	34 %§	44 %	26 %+
		50		BLV 10 mg-PegIFN α2a° + BLV	48 + 48	-	76 %	60 %§	70 %	46 %+
		50		BLV 10 mg	96	-	60 %	12 %§	22 %	12 %+
MYR-301	**3**	**150**	**47 %**							
[52-54]		50		BLV 2 mg	144	74 %	59 %	57 %	29 %	14 %@
		50		BLV 10 mg	144	76 %	60 %	54 %	50 %	20 %@
		50		BLV 10 mg	96	92 %	58 %	56 %	52 %	12 %@

° 180 mcg/weekVirological Response: Undetectable HDV RNA or ≥2 log decline from baseline; ALT: Alanine Aminotransferase; Combined response: Undetectable HDV RNA or ≥2 log decline from baseline + ALT normalization;
* Virological response defined as ≥1 Log HDV RNA decline;
# 24 weeks after EOT
+ 48 weeks after EOT
@ 96 weeks after EOT
§ combined endpoint defined as undetectable HDV RNA plus ALT normalizationEOT: End of Treatment; ALT: Alanine aminotransferase; BLV: Bulevirtide; PegIFN: Pegylated Interferon; TDF: Tenofovir Disoproxil Fumarate; BID: Bis in Die

Table 4
Effectiveness of BLV in real-world studies.

Author	Study Design	Country	Patients Number	Cirrhosis	Treatment	Weeks	Virological Response On-treatment	ALT normalization On-treatment	Combined Response On-treatment	HDV RNA undetectable On-treatment
Rinaldi et al. [55]	Prospective	Italy	108	90 %	BLV 2 mg	24	55 %	-	-	-
Herta et al. [56]	Prospective	Germany	7	57 %	BLV 2 mg	24	71 %	50 %	50 %	0 %
Dietz-Fricke et al. [57]	Retrospective	Germany	114	52 %	BLV 2 mg	48	76 %	62 %	33 %	22 %
Zöllner et al. [58]	Prospective	Germany	8	38 %	BLV 2 mg	48	75 %	63 %	38 %	37 %
Degasperi et al. [59]	Retrospective	Italy	18	100 %	BLV 2 mg	48	78 %	56 %	50 %	23 %
Zoulim et al. [60]	Prospective	France	55	55 %	BLV 2 mg	48	69 %	61 %	31 %	17 %
			55	55 %	BLV 2 mg +PegIFNα2a°	48	85 %	39 %	35 %	na
De Ledinghen et al. [61]	Prospective	France	41	63 %	BLV 2 mg	48	68 %	64 %	39 %	32 %
			70	63 %	BLV 2 mg	96	68 %	56 %	52 %	44 %
			69	63 %	BLV 2 mg + PegIFNα2a°	48	71 %	31 %	21 %	63 %
			17	na	BLV 2 mg + PegIFNα2a°	96	71 %	58 %	41 %	47 %
Jachs et al. [62]	Prospective	Austria	20	74 %	BLV 2 mg	48	65 %	90 %	60 %	25 %
Anolli et al. [63]	Prospective	Italy	445	74 %	BLV 2 mg	72	54 %	74 %	45 %	27 %
Degasperi et al. [64]	Retrospective	Europe	244	100 %	BLV 2 mg	96	79 %	64 %	54 %	48 %
Sapuk et al. [65]	Retrospective	Germany	14	86 %	BLV 2 mg	120	100 %	50 %	50 %	0 %
Loglio et al. [66]	Retrospective	Italy + Austria	3	100 %	BLV 2 mg	144*	67 %	67 %	67 %	67 %
Degasperi et al. [67]	Retrospective	Europe	48	100 %	BLV 2 mg	144	75 %	67 %	56 %	35 %

° 180 mcg/weekVirological Response: Undetectable HDV RNA or ≥2 log decline from baseline; Biochemical response: ALT normalization; Combined response: virological and biochemical;
* treatment stopped after 48 weeks in 1 patientALT: Alanine aminotransferase; BLV: Bulevirtide; PegIFN: Pegylated Interferon

2.4.3.2. Co-infection (HCV, HIV). Few data are available about efficacy and tolerability of PegIFNα treatment in HDV patients with hepatitis C (HCV) or human immunodeficiency virus (HIV) co-infection: efficacy and toxicity of IFN treatment seem not to significantly differ compared to HIV- or HCV-uninfected CHD patients [73–75], while IFN treatment could be considered only in well-controlled HIV infection (CD4>200, suppressed HIV viral load) (expert opinion).

No HCV-coinfected patients were enrolled in BLV Phase 2 or 3 clinical trials; conversely, real-world studies with BLV monotherapy included a total of 27 HDV patients with HCV coinfection [55,64], all HCV RNA undetectable following successful treatment with direct-acting antivirals (DAAs). No data is available about concomitant DAAs and BLV treatment in viremic HCV-HDV patients, however, based on limited drug-drug interactions (DDIs) between BLV and second-generation DAAs, no major issues are expected. Treatment with BLV monotherapy in people living with HIV (PLWH) has been published in a total of 50 patients from the multicenter real-world French study and a single-center Italian study [76,77]: no major DDIs between BLV and anti-retroviral treatment were observed, as well as no impact on rates of HIV RNA suppression, while increase in CD4/CD8 count was also reported. Detailed DDIs data about BLV are discussed in a dedicated paragraph (*see below*). Due to the low-level evidence, careful monitoring is advisable during anti-HDV treatment in HCV-HIV co-infected patients (expert opinion).

2.4.3.3. Immunosuppressed patients. Cases of increased HDV replication under immunosuppressive treatment have been reported, however data are limited [78]. IFN is contraindicated in immunosuppressed patients; data about BLV treatment in PLWH have been previously discussed (*see above*). Based on expected DDIs, co-administration of BLV and cyclosporin is not recommended (*see below*), while no other major DDIs are expected with other immunosuppressants. BLV treatment in a kidney transplanted patient resulted in HDV RNA undetectability and biochemical response; pharmacological evaluation indicated potential DDIs with tacrolimus, which led to increased serum levels of tacrolimus, whereas everolimus levels remained stable [79]. Given the limited data available, no definite recommendations can be provided concerning immunosuppressed patients. BLV-treated patients undergoing immunosuppressive treatment should be carefully monitored and managed at expert centers (expert opinion). All HDV patients undergoing immunosuppressive treatment should receive concomitant NUC treatment to avoid HBV reactivation.

2.4.3.4. Chronic kidney disease. Use of PegIFNα in patients with chronic kidney disease (CKD) has not been extensively studied in the context of HDV. Given the lack of data and potential for toxicity due to renal clearance of IFN, its use should be avoided or limited to highly selected patients under close monitoring by expert centers. Evaluation of pharmacokinetics and safety of BLV in 10 patients with impaired severe renal function (eGFR 15-29 ml/min; CKD-4) reported no significant differences in BLV exposure compared to matched controls with normal eGFR, suggesting that dose adjustment is not needed in patients with severe renal impairment treated with BLV 2 mg/day [80]. However, due to the scarcity of data available, treatment with BLV in patients with renal impairment should be managed in expert centers under close clinical monitoring (expert opinion).

2.4.3.5. Pregnancy. IFN administration is contraindicated in pregnancy. According to BLV package insert, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However, as no data are available about BLV use in pregnant women, it is preferable to avoid BLV during pregnancy and breastfeeding, and in women of child-bearing potential not using contraception.

2.4.3.6. HCC. While HCC treatment should not be deferred because of antiviral treatment, treatment of the underlying liver disease etiology could result in preserving liver function and facilitate oncologic treatments. No data is available on IFN treatment in patients with active HCC. A limited number of patients (n=31) with active HCC have been included in BLV real-world studies [55,64]: overall, there were no significant differences in term of effectiveness and safety of BLV monotherapy. In the French study by Meszaros et al, biochemical response and improved liver function improvement resulting from BLV treatment have provided access to HCC treatment options, allowing for successful downstaging in patients waiting for LT [71]. Despite few unpublished cases of patients receiving concomitant BLV treatment and immune checkpoint inhibitors for HCC are documented in the real-world setting, no extensive data are available: therefore, management of these patients should be reserved only to expert centers under close clinical monitoring (expert opinion).

2.4.3.7. Post-liver transplant. Due to successful prophylaxis with NUC ± hepatitis B immunoglobulins (HBIg) administration post-liver transplantation (LT), HBV (±HDV) graft reinfection is currently rare. IFN-based therapy is generally contraindicated after LT due to the high risk of immune-mediated graft rejection and poor tolerability. Despite historical use in selected LT recipients with HCV graft reinfection, no data are available in the setting of HDV and its use is not recommended in this setting.

One case of BLV monotherapy in a liver transplant recipient with hepatocellular carcinoma (HCC) and post-transplant HBV-HDV recurrence in the post-transplant has been reported: the patient achieved biochemical and virological response to BLV, without no major DDIs with immunosuppressive treatment and safety issues [81]. Due to the lack of data, no recommendations can be provided, so far.

2.4.4. Management of anti-HDV treatment

2.4.4.1. Identification of non-responders and treatment discontinuation. In patients receiving IFN-based treatment, many studies tried to assess predictors of response or futility rules to identify patients not responding to antiviral therapy: on-treatment (week 24) undetectable HDV RNA levels was the strongest predictors of post-treatment response, while the predictive value of $\leq$ 1 Log_{10}IU/mL HDV RNA decline at week 24 to identify non-responder patients was modest [82]. The combination of HDV RNA and HBsAg serum levels <1,000 IU/mL was reported to efficiently differentiate patients with the likelihood of achieving both HBsAg and HDV RNA undetectable at the end of follow-up [83].

There are no current recommendations about BLV treatment discontinuation, while EMA and BLV package insert state that treatment should be continued until clinical benefit. However, a precise definition of clinical benefit has not been established: indeed, clinical benefit should rely on improvement of liver-related outcomes and prevention of liver disease progression and its complications, such as cirrhosis, liver decompensation, hepatocellular carcinoma and liver-related mortality. However, these clinical endpoints cannot be assessed in the short-term, so that “surrogate” endpoints of clinical benefit should rely on effectiveness of treatment: virological response, ALT normalization, improvement of fibrosis and histological parameters, as well as surrogate markers of liver fibrosis (NITs). In everyday practice, evaluation of clinical benefit has to be performed at the single patient level by treatment physicians.

Clinical trials and real-world studies have reported that prolonged BLV treatment in patients with a suboptimal virological re-

Table 5
Summary of recommended treatment options in CHD patients.

CHD Patients	PegIFNα 48 weeks	BLV 2 mg/day long-term	PegIFNα-BLV 2 mg/day48 weeks + BLV 2 mg/day 48 weeks
Chronic hepatitis (F0-F3)	YES*	YES	YES**
Cirrhosis (F4) without CSPH	YES*	YES	YES**
Cirrhosis (F4) with CSPH	NO	YES	NO
Decompensated cirrhosis	NO	YES°	NO
HCV/HIV Co-infection	NO+	YES	NO+
CKD stages 4-5§	No data	YES	No data
Acute hepatitis	No data	No data	No data
Post liver transplantation	NO	Limited data#	NO
Immunosuppression	NO	Limited data#	NO
Pregnancy	NO	NO	NO
Active HCC	No data	YES	No data

CHD: Chronic hepatitis Delta; PegIFN: Pegylated Interferon; BLV: Bulevirtide; CSPH: Clinically Significant Portal Hypertension; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; CKD: Chronic Kidney Disease; HCC: Hepatocellular carcinoma

* Selected patients

** Current data show increased on-treatment virological response rates, but no significant advantage in off-treatment response rates compared to BLV monotherapy

° Off-label treatment with real-world safety and effectiveness data in Child B patients; unclear benefit in Child C patients

+ IFN treatment possible only in selected patients with well-controlled HIV infection

§ eGFR <30 ml/min (including dialysis)

Patients should be managed in expert centers

sponse (<2 LogIU/mL HDV RNA decline) can indeed achieve virological response in the long-term [53,64]. Moreover, despite suboptimal virological response, most patients achieve ALT normalization, so that management of these patients should be individualized, and continuing treatment seems reasonable, in absence of alternative treatment options. Clinical trials in BLV-experienced patients (including virological failures) with new anti-HDV compounds (anti-HBs monoclonal antibodies ± small interfering RNAs) are currently in progress.

Off-treatment data from the MYR-301 phase 3 trial showed sustained (at week 48 and 96) HDV RNA undetectability in 7/49 (14 %) patients treated with BLV 2 mg *vs.* 10/50 (20 %) treated with BLV 10 mg for 144 weeks *vs.* 6/50 (12 %) treated with BLV for 96 weeks [20]. Most relapses occurred within the first 24 weeks off-treatment, and no relapses were reported after week 48. Post-treatment hepatic serious adverse events (SAEs) were reported in 20/142 (14 %) patients: 15 experienced virological rebounds (ALT >10 x ULN in 7), 4 had liver-related hospitalizations, 1 additional patient experienced non serious ascites. The hepatic SAEs resolved in 85 % of patients. Longer duration of on-treatment HDV RNA undetectability predicted off-treatment HDV RNA undetectability, which was achieved by 3/32 (9 %) patients with on-treatment undetectable HDV RNA for <48 weeks *vs.* 11/22 (50 %) for 48-96 weeks *vs.* 9/10 (90 %) for >96 weeks [21]. Five cases of BLV monotherapy discontinuation after different durations (12-60 weeks) of HDV RNA undetectability have been reported by an Austrian study, resulting in three virological relapses [84], while one case of HDV RNA sustained off-treatment undetectability without HBsAg loss has been published in a patient with cirrhosis and clinically significant portal hypertension: after 96 weeks of persistent on-treatment HDV RNA undetectability, the patient maintained undetectable HDV RNA 48 weeks after treatment discontinuation with negative HDAg staining and fibrosis regression at liver biopsy [85]. Given the limited amount of data available, currently BLV monotherapy discontinuation cannot be recommended in clinical practice.

2.4.4.2. Management of DDI. Assessment of potential DDIs is recommended before BLV start: dedicated tools (i.e. Liverpool Drug-drug interaction) could provide useful information. BLV shows non-linear pharmacokinetics, due to target-mediated drug disposition, so it is expected to be influenced by interactions of other drugs with NTCP, while it is not substrate of CYPs and ABC transporters. Basing on *in-vitro* data, BLV package insert does not recommend co-administration of BLV with NTCP inhibitors (sulfasalazin, irbesartan, ezetimibe, ritonavir, atazanavir, cobicistat, efavirenz, and ciclosporin A), while clinical monitoring is recommended when co-administering NTCP substrates (estrone-3-sulfate, fluvastatin, atorvastatin, pitavastatin, pravastatin, rosuvastatin, and thyroid 5 hormones). In addition, a weak inhibitory effect on OATP transporters was observed, but at much higher concentrations than ones expected in vivo. *In-vivo*, investigated DDIs showed no clinically relevant interactions, but a weak inhibitory effect was suggested on CYP3A4 when used at high doses (10 mg) [86].

2.4.4.3. On-treatment and off-treatment monitoring. On-treatment monitoring has the goal of assessing virological and biochemical response, as well as checking for safety and compliance. Complete liver biochemistry and virological (quantitative HBsAg, HBV DNA and HDV RNA) tests are recommended on a 3 to 6-month basis during BLV monotherapy, while bile acids levels can be monitored on BLV but do not show direct correlation with treatment adherence. IFN treatment requires more intense monitoring of complete blood count (1-3 month-basis), in order to check for cytopenia, and TSH (at least on 3-month basis) in order to check for thyroid dysfunction. Assessment of adherence should be part of on-treatment monitoring, especially with BLV where long-term treatment is expected. Clinicians should reinforce adherence by providing continued information about treatment results and expected goals, strategies to cope with daily injections and drug storage in everyday working life, along with active involvement of caregivers. Closer biochemical and virological monitoring (1 to 3 month-basis) is recommended off-treatment, especially in the first 24-48 weeks, where most virological relapses can occur. Prompt detection of virological relapse is needed especially in patients with cirrhosis, where ALT flares should be avoided.

Accurate HDV-RNA quantification is essential for monitoring treatment response and guiding clinical decisions; however, current assays face significant limitations. Inter-laboratory variability has been documented in multicenter evaluations, highlighting differences in extraction methods, calibration, and reporting units [87]. Moreover, the lack of full standardization and the use of heterogeneous commercial assays can lead to differences of up to 1–1.5 log IU/mL in viral load estimation, potentially impacting response definitions and therapeutic strategies [88,89]. Finally, WHO international standards exist only for HDV genotype 1, fur-

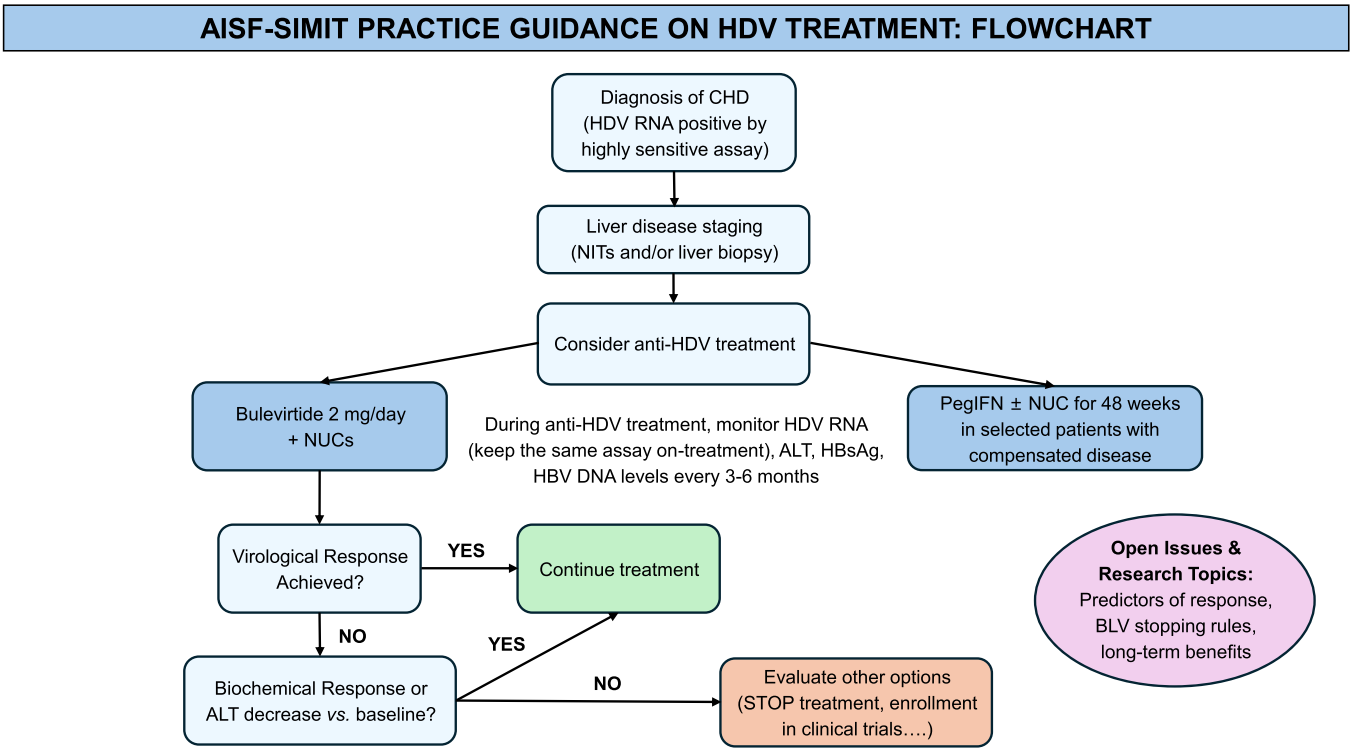

Fig. 1. The AISF-SIMIT algorithm for management of HDV patients' treatment.

ther complicating harmonization across diverse genotypes [87,90]. These limitations underscore the need for assay-specific consistency within clinical trials and routine practice, and the need for keeping the same assay for on-treatment monitoring, in order to correctly assess virological endpoints. In this line, as BLV clinical trials have underlined the importance of achieving a prolonged undetectable HDV-RNA as a predictor of treatment response, the use of commercial assays with high sensitivity is advisable in order to avoid false negative HDV RNA results. Indeed, HDV RNA undetectability can be referred as below the lower limit of quantification (LLOQ), that means that HDV RNA is undetectable or not quantifiable in the sample, whereas target not detected (TND) indicates that no viral RNA was detected at all, even below the LLOQ, which represents a stricter analytical threshold [89].

2.4.4.4. New biomarkers. Beyond HDV-RNA, several biomarkers are under investigation for their potential utility in CHD management. Hepatitis B core-related antigen (HBcrAg) and serum HBV RNA have shown promising results as surrogate markers of intrahepatic covalently closed circular (ccc)DNA activity: in HBV monoinfection, they correlate with viral replication and disease progression, and have been shown to predict treatment response and relapse after treatment cessation [91,92]. In HDV co-infection, a divergent pattern (HBcrAg positive/HBV RNA negative) is mainly observed, at variance with HBV monoinfection [93]. Currently, the role of HBcrAg and HBV RNA during HDV natural course of infection is under investigation [94], whereas HBcrAg was associated with virological response to IFN treatment, but not to BLV [95,96]. Growing research is also focused on other new HBV biomarkers, such as large, medium, and small HBsAg isoforms, that may reflect distinct phases of HBV activity and influence HDV particle formation. Lower baseline concentrations of specific isoforms, particularly L-HBsAg and M-HBsAg, have been associated with HDV-RNA undetectability during therapy [97]. While these biomarkers are not yet validated for routine use in HDV infection, they represent promising tools for future approaches.

2.4.5. Practice recommendations

Fig. 1 reports an algorithm summarizing practical aspects of HDV patients' management.

In addition, a summary of recommended treatment options is provided in Table 5**.**

2.4.6. Unmet medical needs in HDV treatment

Currently, optimal duration of BLV monotherapy remains undefined, due to the lack of strong predictors of response (both on- and off-treatment). Moreover, data about efficacy and safety of BLV monotherapy beyond year 3 are still limited, as well as long-term off-treatment responses after BLV discontinuation. Despite preliminary reports about clinical benefit of BLV treatment on liver decompensation risk, the impact of BLV on long-term liver-related outcomes and mortality needs to be defined. More efforts are also needed to provide treatment options in patients with suboptimal response to BLV monotherapy: while combination with PegIFNα has a strong biological rationale, the optimal strategy (de-novo combination *vs.* add-on) is not currently defined, as well as the possibility to offer these patients IFN-free treatment options (i.e. investigational anti-HDV drugs). Finally, new pharmacological compounds to increase HBsAg loss rates are awaited. Unmet needs in HDV treatment are summarized in Table 6

Table 6
Unmet needs in HDV treatment.

Unmet needs	Current status
Predictors of response to BLV monotherapy	Limited data
Optimal duration of BLV monotherapy	Limited data
Treatment options in non-responders to BLV monotherapy	Limited data
Efficacy and safety of BLV monotherapy after year 3	No data
Impact of BLV treatment on long-term outcomes	Limited data
Treatment of decompensated cirrhosis	Limited data
Strategies for combined PegIFN-BLV treatment (de-novo; add-on)	Limited data
Long-term off-treatment responses after BLV discontinuation	Limited data
Strategies to increase HBsAg loss rates	Limited data
Efficacy and safety of investigational anti-HDV drugs	Limited data

BLV: Bulevirtide; PegIFN: Pegylated Interferon

3. Conclusions

After more than 40 years from HDV discovery, the drug development process triggered renewed interest in HDV research. Many efforts are still required to implement efficient universal screening of HBsAg carriers and increase HDV testing and care cascade. Widespread commercially available HDV RNA assays with high sensitivity are also needed in order to allow precise HDV RNA quantification and confirm chronic infection or guide treatment decisions. PegIFNα remains indicated in selected patients with CHD and compensated liver disease for a preferred treatment schedule of 48 weeks. The approval of the HBV/HDV entry inhibitor Bulevirtide provided the first anti-HDV specific drug. Long-term administration of BLV monotherapy was effective in clinical trials and real-world studies, also in patients with advanced fibrosis and cirrhosis. However, as relapse rates after a finite course of BLV are not negligible, there is an unmet need for treatment stopping rules at the single patient level. Combination of PegIFNα2a + BLV showed higher on-treatment virological response, however it remains uncertain whether a higher dosage of BLV (10 mg) might warrant a significantly lower rates of post-treatment relapse as compared to monotherapy. Identification of host or viral factors predicting treatment response could better refine treatment duration and allow for individualized schedules. Finally, research in investigational compounds to increase viral response and HBsAg loss rates could provide more efficient curative strategies for HDV treatment.

Declaration of competing interest

ED: speaking and/or advisory board for Gilead, Ipsen, Roche, Mirum. AA: speaking and/or advisory board for Gilead, Ipsen, BMS, Novo Nordisk, Madrigal, Abbvie. VC: speaking and/or advisory board for Advanz, Alfa-sigma, Echosens, Ipsen, Gilead, GSK, Mirum, Roche. NC: advisory board and travel grants for AbbVie, Gilead. RD: speaking, teaching and advisory board for Gilead Science and AbbVie; consultant and advisory board for Madrigal. GAN: Speaking and teaching for Gilead. GDO: speaking and teaching for AbbVie, Gilead, GSK, Viatris. MP: speaking and teaching for AbbVie and Gilead; advisory board for AbbVie. FPR: speaking, travel grant and advisory board for Gilead Sciences, Biotest, Grifols, AbbVie, GSK, Novonordisk. PT: speaking for AbbVie, Gilead, AstraZeneca, Roche; advisory board for Gilead, Ipsen. MV: speaking and teaching for Gilead Sciences, AbbVie, Advanz Pharma, IPSEN, Kedrion.

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