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SHORT COMMUNICATION

"Real world" efficacy of bulevirtide in HBV/HDV-related cirrhosis including people living with HIV: Results from the compassionate use programme at INMI Spallanzani in Rome, Italy

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Abstract

Objectives: We describe the preliminary results of bulevirtide compassionate use in patients with hepatitis B and delta virus (HBV/HDV)-related cirrhosis and clinically significant portal hypertension, including those living with HIV.

Methods: We conducted a prospective observational study of consecutive patients. Clinical evaluation, liver function tests, bile acid levels, HDV-RNA, HBV-DNA, hepatitis B surface antigen, and liver and spleen stiffness were assessed at baseline and after treatment months 1, 2, 3, 4, 6, 9, and 12. HIV-RNA and CD4+/CD8+ count were assessed in people living with HIV. The first drug injection was administered under nurse supervision, and counselling was provided and adherence reviewed at each visit.

Results: In total, 13 patients (61.5% migrants) were enrolled. The median treatment duration was 11 months. At month 6, mean alanine aminotransferase (ALT) levels fell by 64.5% and mean liver and spleen stiffness decreased by 8.6 and 0.9 kPa, respectively. The mean baseline HDV-RNA was 3.34 log IU/mL and 5.10 log IU/mL in people without and with HIV ($n = 5$) ($p = 0.28$), respectively. A similar mean decline was observed in both groups: −2.06 log IU/mL and −1.93 log IU/mL, respectively ($p = 0.87$). A combined response (undetectable HDV RNA or ≥ −2 log IU/mL decline vs. baseline, with ALT normalization) was achieved in 66% of subjects without and in 60% of patients with HIV. Patients with HIV showed persistently undetectable HIV-RNA and a progressive increase in CD4+/CD8+ cells during treatment. No patient discontinued bulevirtide because of adverse effects.

Conclusions: Preliminary results suggest that bulevirtide is feasible and well-tolerated in populations with difficult-to-treat conditions, such as those with HIV/HBV/HDV co-infection and migrants, when special attention is given to patient education. HDV-RNA decline during treatment was similar in people living with and without HIV.

KEYWORDS

bile acids, bulevirtide, HDV-hepatitis, HIV infection, liver cirrhosis, viral load

INTRODUCTION

Hepatitis delta virus (HDV) infection is widespread globally, with an estimated 10 to 20 million individuals currently infected [1]. Until recently, interferon-alpha was the only therapy available to treat HDV. However, treatment success rates and tolerability were poor [2].

Bulevirtide is the first entry inhibitor with specific antiviral activity in subjects infected with both hepatitis B virus (HBV) and HDV [3]. Bulevirtide specifically inhibits the sodium taurocholate co-transporting polypeptide, used by HDV to infect hepatocytes.

Bulevirtide was approved in Europe by the European Medicines Agency in late 2020 based on phase II randomized controlled trials (RCTs) [4]. Successive "real-world" studies from France [5] and Italy [6] confirmed relevant antiviral activity, a significant reduction in liver enzyme levels, and minor side effects limited to the injection site and increased serum biliary salts due to the expected inhibitory effect on its transporter on the hepatocyte wall [7]. The registrative phase III trial MYR 301 is currently ongoing [8]. People living with HIV have been excluded from RCTs, and only the French Early Access Program [5] included people living with HIV. However, data focusing on people living with HIV have not yet been published.

In early 2022, Gilead Sciences allowed the use of bulevirtide in Italy for named-patient compassionate use in HBV/HDV compensated cirrhosis with clinically significant portal hypertension (CSPH). Drug delivery started at the end of March 2022, and access to the programme terminated in July 2022.

INMI Spallanzani is a public tertiary clinical care and research centre to which most patients in the Rome area with chronic viral hepatitis and/or HIV are referred.

The current HDV-infected population presenting to our institution mainly comprises people living with HIV aged 55–65 years [9] and younger uninfected immigrants, mainly from Eastern Europe. So far, no preliminary reports have been published reporting HDV viral loads and efficacy of bulevirtide in people living with HIV, although treatment prioritization has been suggested in this setting [10]. Concerns may arise regarding feasibility and adherence to bulevirtide in fragile patients such as migrants.

The aim of this study is to report the preliminary feasibility and efficacy results for bulevirtide in a small group of patients with difficult-to-treat conditions, consecutively enrolled in the compassionate programme at our centre, with a specific focus on people living with HIV.

METHODS

Between March and June 2022, we petitioned Gilead Sciences for compassionate use of bulevirtide in patients with HBV/HDV-related cirrhosis and CSPH, defined as the presence of oesophageal varices, a platelet count <100.000/mmc or enlarged portal vein diameter. After approval, the INMI Spallanzani Ethical Committee confirmed treatment for each patient. Thus, we enrolled 13 consecutive subjects in an observational, prospective single-centre study. Bulevirtide monotherapy was prescribed as a self-administered subcutaneous injection at a dosage of 2 mg/day.

HDV-RNA level was assessed using the EuroBioplex HDV-RNA real-time reverse transcriptase polymerase chain reaction quantification kit, with a quantification limit of 30 IU/mL and detection limit of 6 IU/mL.

Patients underwent clinical evaluation, blood testing, and liver and spleen stiffness assessment using Fibroscan© (Echosens, France) at baseline and after months 1, 2, 3, 4, 6, 9, and 12 of treatment. Blood tests included liver function, HDV-RNA, HBV-DNA, hepatitis B surface antigen (HBsAg) quantification, HIV-RNA, and CD3+/CD4+/CD8+ counts in people living with HIV, and serum bile acid levels, to assess adherence. A combined response was defined as undetectable HDV RNA or ≥2 log IU/mL decline vs. baseline and alanine aminotransferase (ALT) normalization, as previously published [10, 11]. Data analysis was performed on 10 May 2023 using R statistical software.

TABLE 1 (a) Individual baseline clinical features and (b) on-treatment HDV-RNA (IU/mL) and bile acid (μmol/L) levels in patients with HBV/HDV and cirrhosis with clinically significant portal hypertension included in the compassionate use bulevirtide treatment programme.

(a)

Pt ID	Origin	Age	Sex	HIV CDC	Antiviral regimen	CD4/mmc	Concomitant cancer	HBsAg (IU/ml)	MELD-Na	ALT (IU/ml)	Bilirubin (mg/dl)	PLT (10^3/mmc)	Oesophageal varices	Liver stiffness
1	Italy	65	M	-	ETV		No	13 678	10	73	0.84	87	F1	54
3	Russia	46	F	-	TDF		No	16 070	9	136	0.44	260	F0	11.4
6	Romania	72	F	-	ETV		No	30	11	55	1.3	72	F1 after EVB	6.8
7	Moldova	56	F	-	ETV		No	13 144	11	144	2.1	47	F1 after EVB	27.3
9	Romania	48	M	-	ETV		No	143	11	80	1.65	138	F0	18
10	Romania	40	M	-	ETV		No	11 571	11	220	1.29	129	F1	20.7
11	Romania	33	F	-	ETV		No	11 646	10	58	1.01	37	F0	19
12	Romania	47	M	-	ETV		No	2208	8	101	1.01	79	F2	32.1
2 (HIV+)	Italy	68	F	C3	TAF/FTC + DLT	387	No	4809	11	222	2.53	90	F0	14.7
4 (HIV+)	Italy	57	M	B3	TAF/FTC/BCT	235	Yes	22 598	8	289	0.83	101	F0	14.8
5 (HIV+)	Italy	63	M	B3	TDF/3TC/DOR	241	Yes	3694	8	111	1.12	116	F0	33.7
8 (HIV+)	Italy	45	M	B1	TAF/FTC/DRV/c	417	No	9742	11	74	1.46	152	F1	33.3
13 (HIV+)	Romania	32	F	C2	TDF/FTC + RAL	383	No	22 172	11	53	1.64	72	F0 after TIPS	9.5

(b)

	T0 (baseline)		T1		T2		T3		T4		T6		T9		T12
Pt ID	HDV-RNA (BA)		HDV-RNA (BA)		HDV-RNA (BA)		HDV-RNA (BA)		HDV-RNA (BA)		HDV-RNA (BA)		HDV-RNA (BA)		HDV-RNA (BA)
1	1169	(8)	326	(52)	277	(50)	<LOQ	(119)	<LOQ	(80)	<LOD	(31)	<LOD	(48)	
3	1 859 178	(4)	428 236	(19)	42 463	(45)	1752	(51)	675	(26)	99	(44)	70	(30)	
6	603	(3)	1802	na	1017	na	579	na							
7	698	(15)	45	(28)	<LOQ	(48)	<LOD	(82)	<LOD	(55)	<LOD	(66)	<LOD	(70)	
9	2252	(9)	398	(25)	289	(19)	<LOQ	(27)	<LOQ	(18)	<LOD	(37)	<LOD	(17)	
10	2132	(7)	1680	(16)	1417	(11)	116	(19)	245	(14)	2550	(7)	10 802	(3)	
11	36 070	(6)	17 906	(30)	5525	(37)	81 149	(27)	13 912	(25)	7595	(31)	57 826	(33)	
12	3756	(22)	447	(51)	604	(19)									

(Continues)

TABLE 1 (Continued)

(b)

Pt ID	T0 (baseline)		T1		T2		T3		T4		T6		T9		T12	
	HDV-RNA	(BA)	HDV-RNA	(BA)	HDV-RNA	(BA)	HDV-RNA	(BA)	HDV-RNA	(BA)	HDV-RNA	(BA)	HDV-RNA	(BA)	HDV-RNA	(BA)
2 (HIV+)	125 132	(4)	98 636	(30)	30 640	(41)	1466	(58)	339	(46)	<LOD	(50)	<LOD	(34)	<LOD	(48)
4 (HIV+)	368 756	(6)	77 752	(36)	58 843	(55)	24 988	na	24 988	(36)	2868	(21)	3897	(34)	16 426	(36)
5 (HIV+)	684 500	(4)	290 682	(25)	26 744	(13)	6930	(20)	47 025	(12)	27 041	(32)	13 707	(9)	950	(15)
8 (HIV+)	88 475	(11)	46 070	(166)	41 873	(169)	4099	(161)	1901	(141)	818	(108)	3913	(72)		
13 (HIV+)	82	(20)	1017	(112)	772	(133)	612	(147)	606	(160)	215	(181)				

Note: Numbers in parentheses represent Bile Acid (BA) levels as expressed in the legend.

Abbreviations: 3TC, lamivudine; ALT, alanine aminotransferase; BA, bile acid (normal range 3–10 μmol/L); BCT, bictegravir; DLT, dolutegravir; DOR, doravirine; DRV/c, darunavir/cobicistat; ETV, entecavir; EVB, endoscopic variceal banding; HBsAg, hepatitis B surface antigen; HIV+, people living with HIV infection; Liver stiffness, kPa values measured by Fibroscan©; LOD, limit of detection (6 IU/mL); LOQ, limit of quantification (30 IU/mL); MELD, Model for End-stage Liver Disease; na, result not available; PLT, platelet level; Pt, patient; RAL, raltegravir; T1–T12, on-treatment months 1–12; TAF/FTC, tenofovir alafenamide/emtricitabine; TDF, tenofovir difumarate; TIPS, transjugular intrahepatic portosystemic shunt.

RESULTS

All 13 patients were receiving long-term anti-HBV treatment with nucleos(t)ide analogues, as per international guidelines. The median age was 42 years (interquartile range [IQR 48–62]), 38% ($N = 5$) were people living with HIV, and 61.5% were migrants from Eastern Europe. The median treatment duration was 11 months (IQR 8.8–11.8). At baseline, the median CD4+ count for people living with HIV was 383/mmc (IQR 241–387). Two people living with HIV had concomitant cancer (no. 4, small-cell lung adenocarcinoma; no. 5, hepatocellular carcinoma; Table 1a). Language was not a barrier. No patients had obesity, diabetes, or current alcoholic intake as comorbidities.

Bulevirtide injections and treatment adherence

The first drug injection was performed at our outpatient clinic, under nurse supervision and after a brief oral presentation on the injection instruction manual. Bulevirtide was then self-injected subcutaneously at home. The nurse assessed self-reported adherence at all time points by asking specific questions at drug delivery, and missing doses were recorded in the chart. Serum bile acid increases >2× baseline during treatment was indirect confirmation of treatment adherence.

Patient no. 5 reported complete bulevirtide withdrawal between months 3 and 4 and 50% adherence until month 6. Thereafter, he reported full adherence.

Two migrant patients (no. 6 and no. 12) returned to their homeland between months 3 and 4 and were lost to follow-up. Reported adherence was otherwise complete.

Viroimmunological and biochemical outcomes

All 13 patients were anti-hepatitis B e-antigen positive at baseline. Mean HBsAg levels did not change while receiving treatment: 9867 IU/mL (IQR 2.951–14.919) at baseline and 9868 IU/mL (IQR 2.150–15.302) at 9 months. HBV-DNA remained undetectable (<10 IU/mL) at baseline and at all time points, with the exception of a single blip (139 IU/mL) in subject no. 13 at month 3.

In all people living with HIV, plasma HIV-RNA levels were <30 copies/mL at baseline and during the bulevirtide treatment period. Absolute CD3+, CD4+, and CD8+ cells progressively increased from baseline in all people living with HIV (mean CD4+: +18/mmc at month 3, +53/mmc at month 6, and + 131/mmc at month 12).

The mean baseline HDV-RNA was 3.34 log IU/mL in subjects without HIV and 5.10 log IU/mL in people living with HIV ($p = 0.28$, Mann–Whitney test) Overall, the mean HDV-RNA decline from baseline was −1.32, −2.00, and − 2.05 log IU/mL at 3, 6, and 9 months, respectively. Mean and individual HDV-RNA levels are depicted in Figure 1a,b. The decline in people both with and without HIV was similar at 6 months: mean −2.06

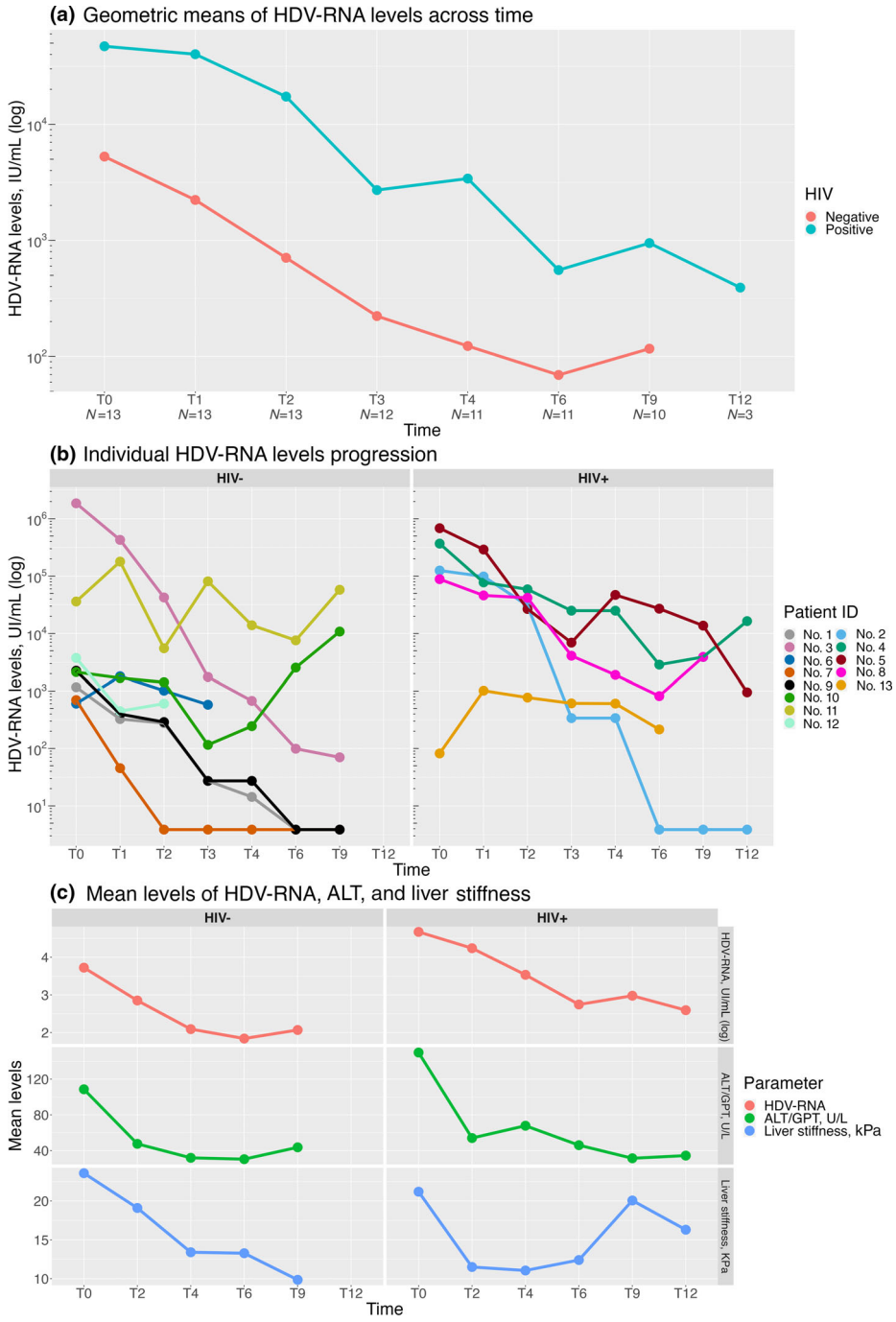

FIGURE 1 Clinical and virological parameters in 13 patients with hepatitis B virus (HBV)/hepatitis delta virus (HDV) cirrhosis and portal hypertension ($n = 8$ without HIV, $n = 5$ with HIV) while receiving bulevirtide treatment during the "real-world" bulevirtide compassionate use programme at INMI Spallanzani in Rome, Italy. (a) Mean serum HDV RNA levels in subjects without versus with HIV (analysis of variance, $p = 0.87$). (b) Individual serum HDV RNA levels of all patients. (c) HDV-RNA, alanine aminotransferase (ALT) and liver stiffness among the two groups. HDV-RNA values are expressed as IU/mL in the logarithmic scale; ALT is expressed in IU/mL; liver stiffness values are expressed in kPa. Stiffness values were missing in patients no. 10 and 11. T0, baseline; T1–T12, treatment months 1 to 12; GPT, glutamic-pyruvic transaminase

vs −1.93 log IU/mL, respectively ($p = 0.87$, analysis of variance test). Four patients (no. 10, 11, 4, and 8) experienced a rebound in HDV-RNA between months 6 and 9. In patient no. 10, viral rebound was concomitant to complete bile acid normalization (Table 1b).

Mean aspartate aminotransferase (AST) levels were reduced by 39.4%, 55.3%, and 63.4% at 3, 6, and 9 months compared with baseline, respectively; mean ALT levels were reduced by 53.2%, 70.0%, and 68.5% (Figure 1c).

At month 6, a combined response was achieved in 66% of subjects without HIV and 60% of people living with HIV. Undetectable HDV-RNA (<6 IU/mL) was achieved in 4 of 11 subjects (36.4%) at 6 months and in 4 of 10 subjects (40%) at 9 months of treatment.

Elastometry

At baseline, mean stiffness was 22.7 kPa (IQR 13.1–32.7) for liver and 34.1 kPa (IQR 21.6–43.7) for spleen, as expected for patients with CSPH.

Mean liver stiffness at 6 months (Figure 1c) was available in nine patients and had decreased by 8.6 kPa from baseline (−37.9%), whereas spleen stiffness remained unchanged (−3%).

Clinical features

No substantial changes in Child–Pugh class or Model for End-stage Liver Disease (MELD)-Na scores were observed during bulevirtide treatment. In patient no. 1, progression of a dysplastic nodule (Liver Imaging Reporting and Data System [LI-RADS] score of 3) to overt hepatocarcinoma (LI-RADS score of 4) was observed at month 3; this patient was liver transplanted at month 9 with undetectable HDV-RNA; bulevirtide was discontinued after transplant, and no HDV-RNA rebound was observed until month 4 of follow-up.

Safety

Patient no. 13 (with HIV) with severe portal hypertension (previously treated with transjugular intrahepatic portosystemic shunt), had an increase of HDV-RNA at month 1 (from 82 IU/mL to 1016 IU/mL). After 2 months, the patient experienced transient elevation of AST/ALT (252/250 IU/mL) with stable HDV-RNA, normal gamma-glutamyl transferase/bilirubin, and high bile acid levels. MELD-Na and Child–Pugh scores remained unchanged.

In patient no. 4, lung cancer reactivation was observed at month 7. The programmed cell death ligand-1 inhibitor nivolumab was started with a concomitant viral rebound despite full adherence to bulevirtide.

None of the patients experienced systemic itching, liver decompensation, major complications, or drug-related serious adverse events. Two patients reported pruritus at the injection site.

DISCUSSION

Adherence and treatment retention are important issues in long-term pharmacotherapy. Migrants and mobile populations, as well as people living with HIV receiving injective antivirals, are at risk of low adherence and treatment discontinuation [11, 12]. However, specific patient education programmes can reduce this risk [13]. In this study including people living with HIV and migrants, we implemented a brief training to avoid mistakes during drug administration and wasted doses. Using serum bile acid levels and nurse review of missed doses at each visit helped discriminate between drug failure and lack of adherence in individual cases (i.e., no. 10).

In a recent study of bulevirtide, 50% of subjects with liver cirrhosis had increased serum bile acid levels at baseline. Such high levels were associated with higher transient elastography values, evidence of portal hypertension, and a more pronounced HDV-RNA decline until treatment week 24 [7]. In our study, 30% of patients already had bile acid levels above the normal range (>10 μmol/L) at baseline, but only two showed a combined response to bulevirtide.

Our data confirm the efficacy of bulevirtide in reducing HDV-RNA and liver enzymes. ALT decline was evident at month 2 and occurred even in patients with poor virological response, as previously reported [7]. The mean HDV-RNA decline observed in our study (−1.32 log at 3 months and −2.00 log at 6 months) was similar to that reported in the bulevirtide 2 mg monotherapy arm in the French study [5]. Similarly, the ALT decline resembled that reported in previous French, Italian, and German cohorts [5, 7, 14].

A single patient (no. 13) had an unexpected significant AST/ALT flare between months 2 and 3. We speculate that an immune mechanism may be implicated, as previously described during treatment with interferon-alpha or with the prenylation inhibitor lonafarnib [15]. An alternative explanation is the potential cytotoxic effect of high bile acid levels in this particular subject.

In the Italian study, no significant difference in liver stiffness was reported after 24 weeks of treatment [6]. Conversely, in our series, a reduction in liver stiffness was observed in 11 of 13 patients, probably reflecting the decrease in liver inflammation rather than a real fibrosis regression. The same phenomenon was described with

oral anti-hepatitis C virus (HCV) therapy in subjects with cirrhosis for both liver and spleen stiffness [16]. In our study, bulevirtide treatment produced only a minimal effect on spleen stiffness reduction.

Bulevirtide is not expected to inhibit or induce the major cytochromes or efflux transporter [17]. The Liverpool HIV drug-interaction database indicates "green or yellow light" for the co-administration of bulevirtide with almost all antiretroviral drugs, except ritonavir, cobicistat, efavirenz, and etravirine [18]. No HIV-RNA failure or viral blips were observed among the five people living with HIV in this study, confirming the absence of clinically relevant effects of bulevirtide on antiretroviral activity. However, we could not exclude an effect of cobicistat on bulevirtide elimination in patient no. 8, which would have explained the very high serum bile acid levels; therefore, we decided to switch from darunavir/cobicistat to bictegravir.

Unexpectedly, all five people living with HIV showed a progressive increase in their CD3+, CD4+, and CD8+ cell counts during bulevirtide treatment. An increase in CD4+ cells after direct-acting antiviral-induced sustained virological response in people with HIV, HCV, and cirrhosis was initially hypothesized but not confirmed in cohort studies [19, 20]. We speculate that the reduction in liver inflammation and stiffness during bulevirtide treatment may induce a decrease in portal pressure and spleen size, leading to an increase in total number of circulating lymphocytes.

We are aware of the major limitations of our study: the limited sample size and the short treatment duration do not allow generalizations or comparisons with statistical significance. However, this small single-centre bulevirtide compassionate use programme did show that most patients with difficult-to-treat conditions, with HBV/HDV cirrhosis and CSPH, had good adherence and improved clinical parameters, extending the safety and efficacy noticed in RCTs to a "real-life" setting.

In conclusion, among 13 enrolled patients (five of whom were living with HIV), adherence to bulevirtide during the first 12 months was acceptable. Bulevirtide treatment resulted in a progressive decrease in HDV-RNA, liver enzymes, and liver stiffness, with no major differences based on HIV status. Bulevirtide treatment did not influence HIV suppression; thus, from a clinical point of view, no relevant drug–drug interactions were identified. Bulevirtide was generally well tolerated, and no treatment discontinuations due to drug toxicity were observed.

AUTHOR CONTRIBUTIONS

Ubaldo Visco Comandini planned and coordinated the study, performed elastometry measurements and patient clinical management, analysed data, and wrote the manuscript. Emanuela De Santis and Francesco De Maria collected patient data and managed the database. Raffaella Lionetti, Chiara Taibi, and Marzia Montalbano performed clinical management of the patients. Paola Piccolo revised the article and contributed to data presentation. Chiara De Ponte and Stefania Mazzotta organized bulevirtide storage and controlled distribution and patient adherence assessment. Alessandro Caioli performed statistical analysis and prepared the figures. Anna Rosa Garbuglia and Fabrizio Maggi performed virology/laboratory assays and contributed to clinical evaluation of the results. Gianpiero D'Offizi planned and contributed to the study coordination. All the authors approved the final manuscript.

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DISCLOSURES

None of the authors declare any conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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