Gianpiero D'Offizi

UOC Malattie Infettive Epatologia

Dipartimento Trapianti

INMI Lazzaro Spallanzani I.R.C.C.S

UniCamillus University

BULEVIRTIDE IN HIV COINFECTED PATIENTS

SISTEMA SANITARIO REGIONALE
IRCCS
LAZZARO SPALLANZANI

REGIONE
LAZIO

COI

SPEAKER IN OWN EVENTS OR MEMBER OF TEMPORARY ADVISORY BOARDS OR RECIPIENT OF TRAVEL GRANTS IN THE LAST TWO YEARS

GILEAD

ABBVIE

MSD

BRISTOL

JANSSEN

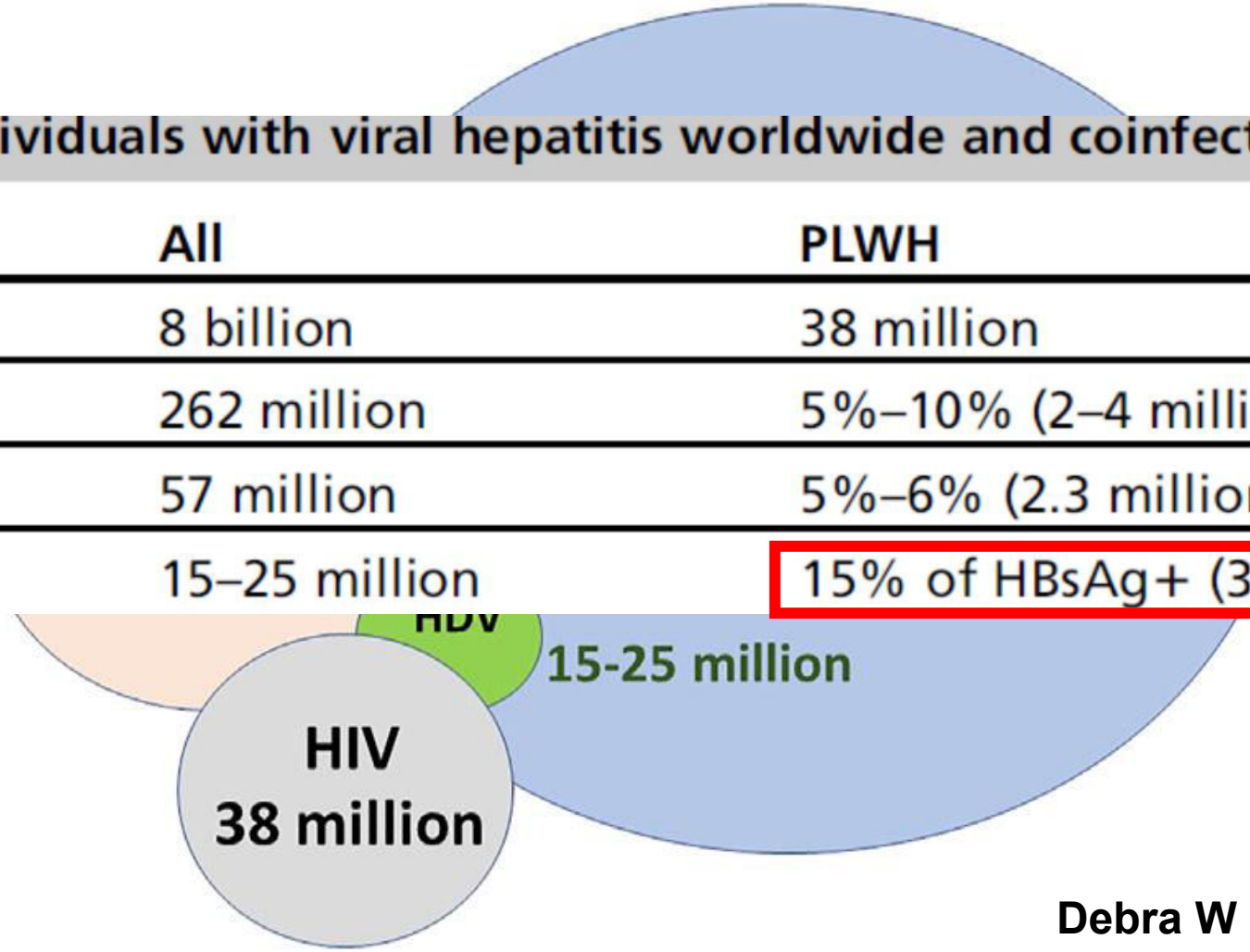
Road Map

- HEPATITIS DELTA VIRUS EPIDEMIOLOGY IN PEOPLE LIVING WITH HIV
- GENERAL THERAPY CONSIDERATIONS
- BULIVERTIDE IN HIV/HBV/HDV

Global viral hepatitis and HIV

Estimated number of individuals with viral hepatitis worldwide and coinfection with HIV

	All	PLWH
Total	8 billion	38 million
Hepatitis B[31]	262 million	5%–10% (2–4 million)
Hepatitis C[32,43]	57 million	5%–6% (2.3 million)
Hepatitis delta[36,41]	15–25 million	15% of HBsAg+ (350,000–700,000)



Debra W Clin Liv Dis 2023

HDV seroprevalence in people living with HIV in Italy

		HBsAg positive (%)	Screened for anti-HDV (%)	Anti-HDV+ prevalence (%)
ICONA Cohort[1,2]	• Multicentre, prospective study (1997–2015)[1] • People living with HIV with data (or stored samples for testing) for viral hepatitis serology • 52 infectious disease centres[1] • N=18,285[2]	5.6	78.7	18.8
CISAI Cohort[3]	• Cross-sectional survey • People living with HIV with CHB • 10 centres • N=316	100	86.1	15.2

Seroprevalence taken from reference 2.

Prevalence estimates of hepatitis Delta in Italian cohorts of HIV-infected individuals (15.2–18.8%)[2,3] are higher than in non-HIV cohorts (8.3–9.8%)*[4,5]

1. Brancaccio G, et al. Pathog Glob Health 2023;117:181–9; 2. Puoti M, et al. EASL 2023; WED-174;
3. Nicolini L, et al. Front Med 2023;10.3389; 4. Brancaccio G, et al. Int J Infect Dis 2023;129:266–273; 5. Kondili L, et al. EASL 2023; WED-146.

*Not a head-to-head comparison
HBsAg: hepatitis B surface antigen.

Treatment considerations

- Spanish study: Long-term exposure to tenofovir significantly reduces serum HDV-RNA (apart from lowering HBV-DNA) in people with HIV/HDV. This virological benefit is coupled with significant improvements in liver fibrosis (Soriano V AIDS 2014)

- French and Swiss studies: patients with HIV/HBV/HDV on TDF followed up over 3 to 5 years did not experience a significant reduction in HDV viral load or change in clinical outcomes such as liver fibrosis (Boyd A AIDS Res Hum Retrovir 2023; Beguelin C CID 2017)

IFN-α has been used for treatment of HIV/HBV/HDV, but it is poorly tolerated and has low rates of long term effectiveness. Only 20% to 25% of patients achieved sustained virological response at 24 weeks after a 48-week treatment course, and out of all responders, half experienced late virological relapse (Abbas Z Antivir Ther 2014; Heidrich B Hepatology 2014)

Novel Therapies in HBV/HDV

- Lonafarnib (an oral farnesyl transferase inhibitor that interfere with HDV virion assembly and release)
- REP-2139 (a nuclear acid polymer that blocks the release of HBV suviral particles and clears circulating HBsAg)
- PEG-IFNλ (a secreted cytokine that is genetically and structurally close to members of the IL-10 family of cytokines)
  the
- Bulivertide

BULEVIRTIDE +/- PEG-IFN IN HIV/HBV/HDV CO-INFECTED PATIENTS IN REAL-LIFE SETTINGS (#589)

RESULTS

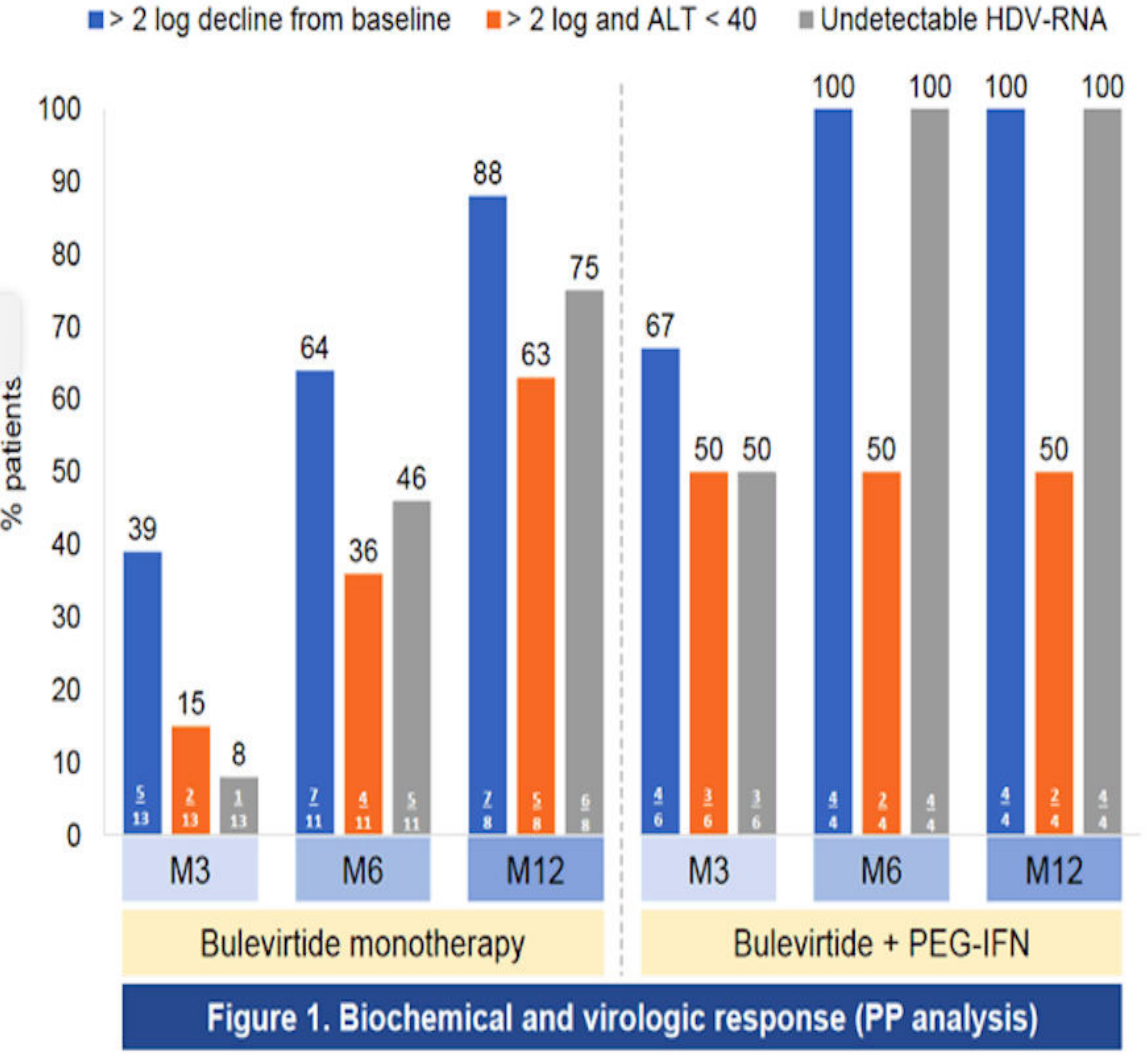


Figure 1. Biochemical and virologic response (PP analysis)

- Strong HDV antiviral and biochemical responses were observed in real-life independently of the BLV regimen administered
- In this first real-world cohort of HIV/HBV/HDV patients, daily administration of BLV 2 mg for 12 months was safe and well tolerated with no impact on CD4, HIV viral suppression or HIV treatment regimen

De Ledinghen et al CROI 2023

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

Ubaldo Visco Comandini[1] | Emanuela De Santis[2] | Francesco De Maria[1] | Raffaella Lionetti[1] | Chiara Taibi[1] | Marzia Montalbano[1] | Alessia Rianda[1] | Paola Piccolo[3] | Chiara De Ponte[4] | Stefania Mazzotta[4] | Alessandro Caioli[1] | Anna Rosa Garbuglia[5] | Fabrizio Maggi[5] | Gianpiero D'Offizi[1]

Prospective observational study

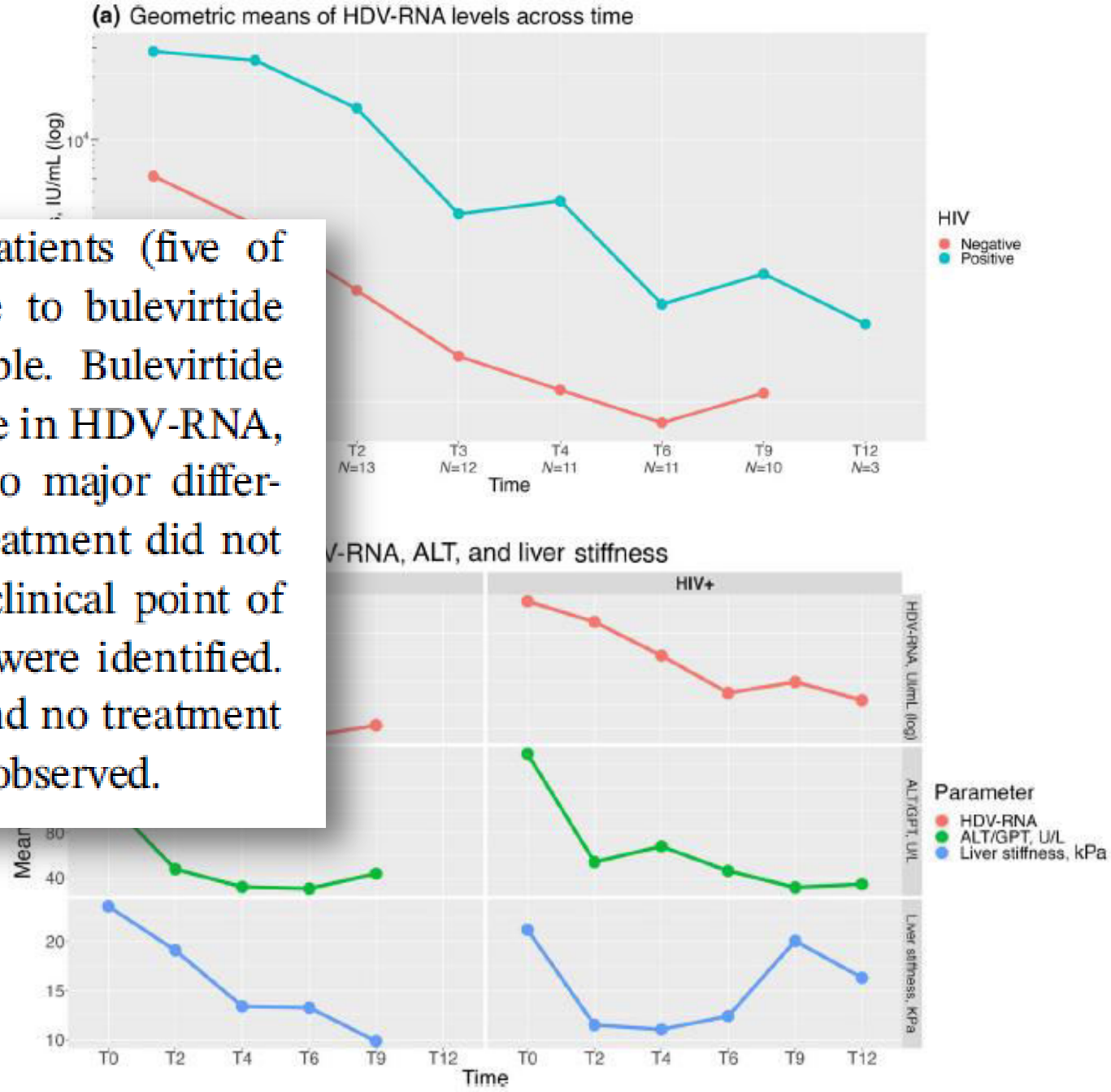
Clinical evaluation, liver function tests, bile acid levels, HDV-RNA, HBV-DNA, hepatitis B surface antigen, and liver and spleen stiffness were assessed at baseline and after treatment months 1, 2, 3, 4, 6, 9, and 12. HIVRNA and CD4+/CD8+ count were assessed in people living with HIV.

The first drug injection was administered under nurse supervision, and counselling was provided and adherence reviewed at each visit.

Baseline Clinical Features

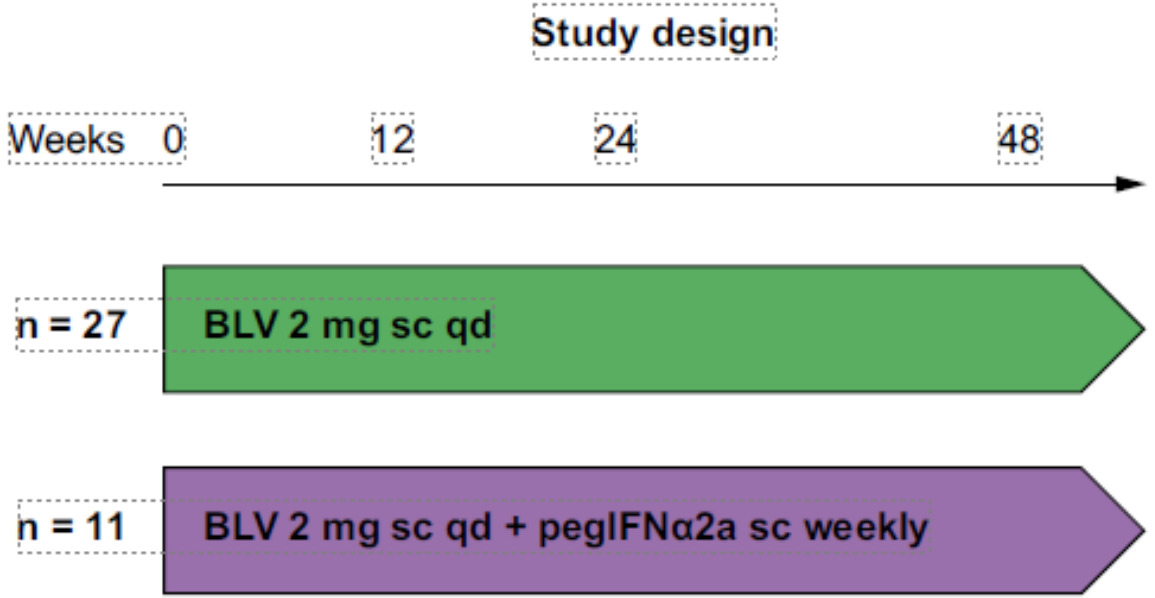
Pt ID	Origin	Age	Sex	HIV CDC	Antiviral regimen	CD4/ mmc	Concomitant cancer	HBsAg (IU/ml)	MELD-Na	ALT (IU/ml)	Bilirubin (mg/dl)	PLT (10^3/ mmc)	Oesophageal varices	Liver stiffness
1	Italy	65	M	-	ETV		No	13 678	10	73	0.84	87	F1	54
3	Russia	46	F	-	TDF		No	16 070	9	136	0.44	260	F0	11.4
6	Romania	72	F	-	ETV		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

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.



Treatment with bulevirtide in HIV-infected patients with chronic hepatitis D: ANRS HD EP01 BuleDelta and compassionate cohort (Victor de Lédinghen JHEP Reports 2024)

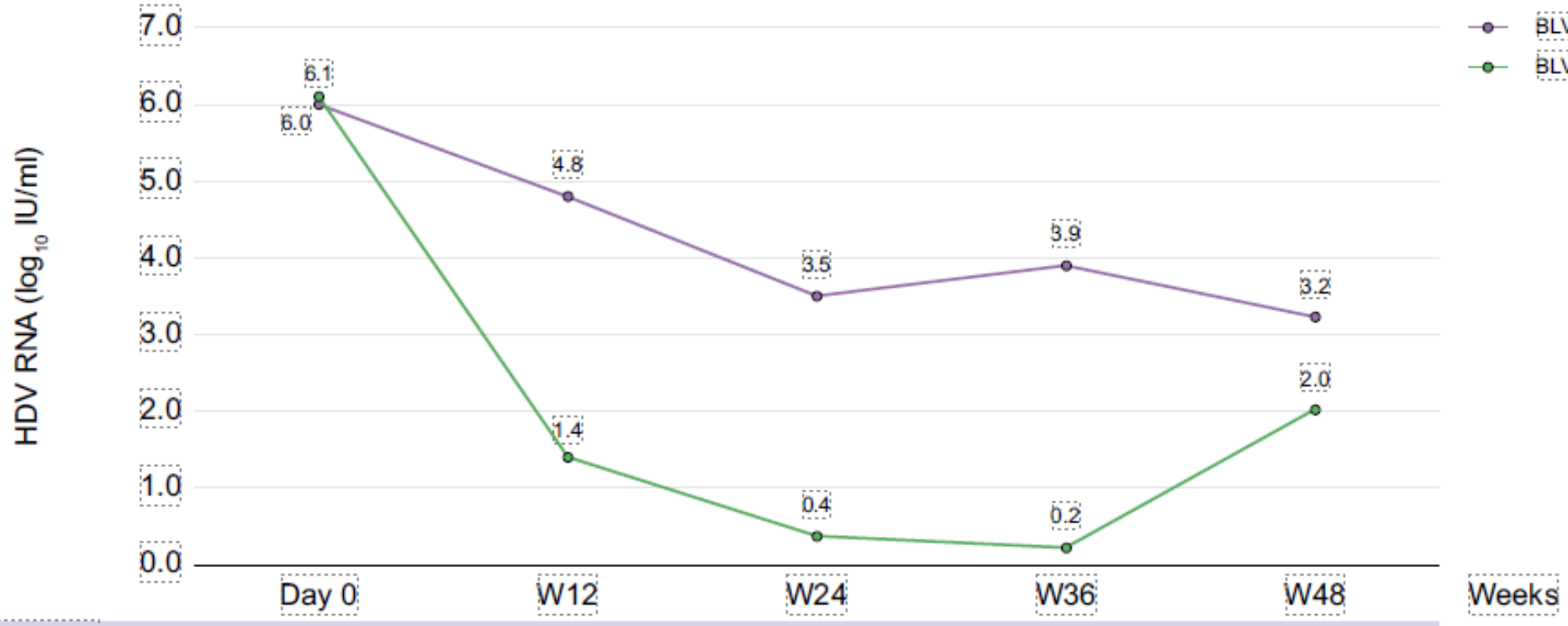
- ✓ Multicenter prospective and retrospective observational study
- ✓ Not a randomized study
- ✓ Therapy, duration and modifications were at the discretion of the physician



Baseline Clinical Features

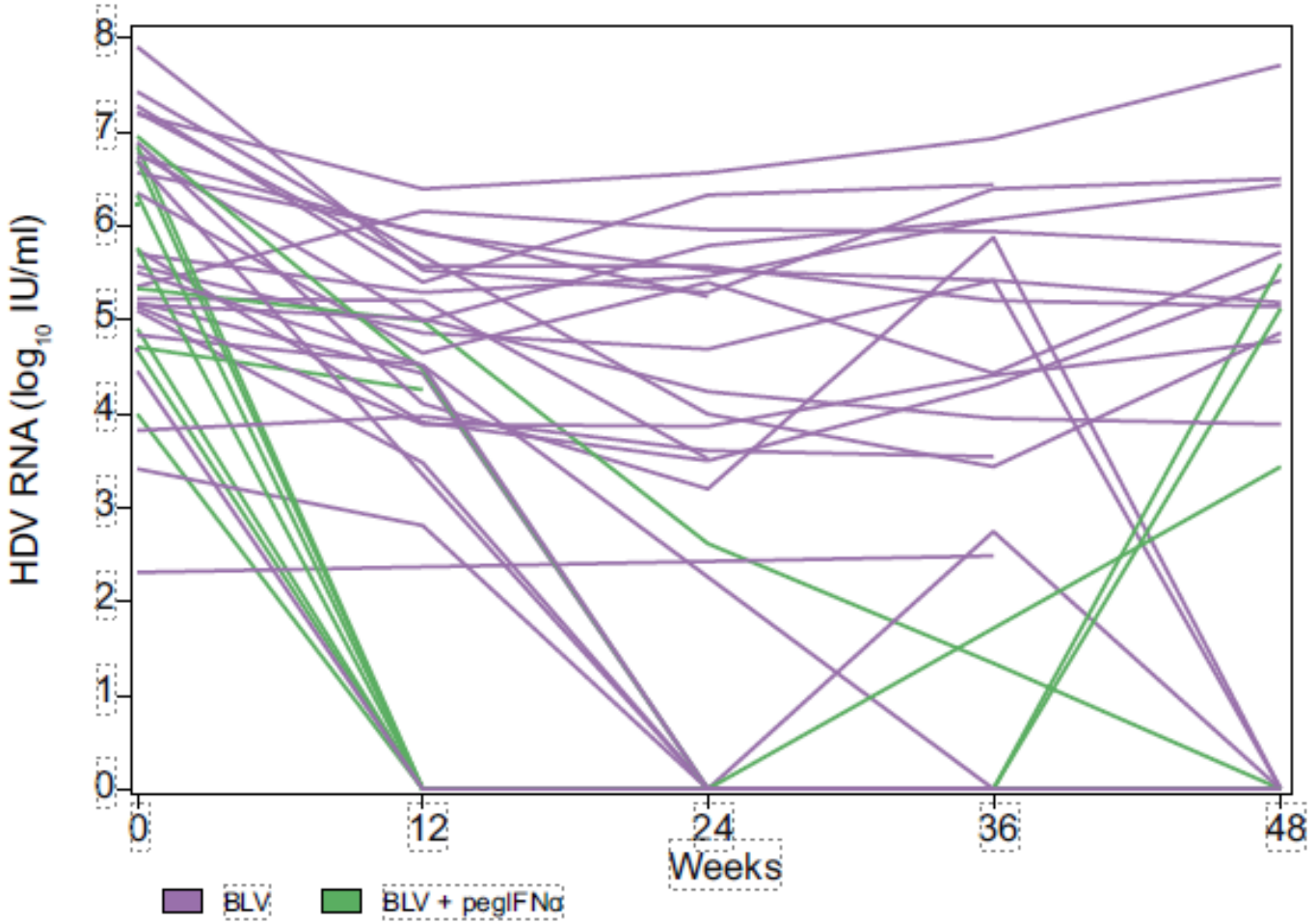
	All patients (N = 38)	BLV monotherapy (n = 27)	BLV + pegIFNα (N = 11)	*p* value
Age (years), mean ± SD	47.7 ± 8.6	47.7 ± 9.8	47.8 ± 5.1	0.9627
Male, n (%)	28 (73.7)	21 (77.8)	7 (63.6)	0.4318
BMI (kg/m^2), mean ± SD	26.1 ± 6.3	24.6 ± 3.9	29.2 ± 9.1	0.0589
CD4 count (cells/mm^3), mean ± SD	566.2 ± 306.6	583.4 ± 331.0	524.2 ± 249.0	0.6340
HIV RNA (copies/ml), median (IQR)	32 (30–65)	50 (30–123)	30 (21–31)	0.2086
Patients with quantifiable HIV RNA, n (%)	10 (26.3)	7 (25.9)	3 (30)	1.0000
Time since HDV diagnosis (years), mean ± SD	11.3 ± 9.0 *11	10.8 ± 9.0 *6	13.3 ± 9.3 *5	0.5533
Past history of hepatocellular carcinoma, n (%)	1 (2.6)	1 (3.7)	0 (0)	1.0000
Liver stiffness measurement (kPa), median (IQR)	10.1 (7.9–15) *9	9.3 (6.3–15) *8	13.2 (9.5–22) *1	0.1832
FIB-4, mean ± SD	3.3 ± 2.7 *1	3.5 ± 3.1	2.6 ± 1.4 *1	0.3778
Cirrhosis, n (%)	26 (68.4)	18 (66.7)	8 (72.7)	1.0000
Previous use of pegIFNα, n (%)	22 (59.5) *1	15 (55.6)	7 (70) *1	0.4806
Platelets (G/L), mean ± SD	152.9 ± 54.0	152.8 ± 58.3	153.3 ± 44.1	0.9815
AST (IU/L), mean ± SD	80.0 ± 40.1 *1	86.1 ± 41.6	63.7 ± 31.7 *1	0.1329
ALT (IU/L), mean ± SD	101.7 ± 65.6	113.4 ± 70.8	73.0 ± 40.2	0.0852
Normal ALT, n (%)	5 (13.2)	2 (7.4)	3 (27.3)	0.1341
GGT (IU/L), mean ± SD	100.7 ± 97.0 *5	99.5 ± 101.0 *3	103.9 ± 91.0 *2	0.9091
Total bilirubin (µmol/L), mean ± SD	11.7 ± 7.4 *2	11.8 ± 7.6 *1	11.3 ± 7.1 *1	0.8499
Albumin (g/L), mean ± SD	37.8 ± 3.6 *9	37.7 ± 3.5 *7	38.1 ± 3.8 *2	0.7653
Negative HBeAg, n (%)	28 (87.5)	17 (81.0)	11 (100)	0.2720
Undetectable HBV DNA, n (%)	23 (62.2) *1	16 (59.3)	7 (70.0) *1	0.8007
NUC treatment, n (%)	37 (97.4)	26 (96.3)	11 (100)	1.0000
qHBsAg (IU/ml), mean ± SD	6,117.8 ± 10,208 *9	5,935.1 ± 10,643 *8	6,465.0 ± 9,869 *1	0.8971
HDV RNA (log_{10} IU/ml), mean ± SD	5.7 ± 1.2	5.7 ± 1.3	5.7 ± 1.0	0.9311
HDV genotype, n (%)	*19	*11	*8	0.0103
1	14 (73.7)	14 (87.5)	0 (0)	
5	4 (21.1)	2 (12.5)	2 (66.7)	
7	1 (5.3)	0 (0)	1 (33.3)	
HIV treatment, n (%)				
3TC	3 (8.1)	3 (11.5)	0 (0)	
TAF/FTC	22 (59.5)	15 (57.7)	7 (63.6)	
TDF/FTC	12 (32.4)	8 (30.8)	4 (36.4)	
INSTI	23 (62.1)	16 (61.5)	7 (63.6)	
NNRTI	12 (32.4)	9 (34.6)	3 (27.3)	

Evolution of HDV RNA through Week 48

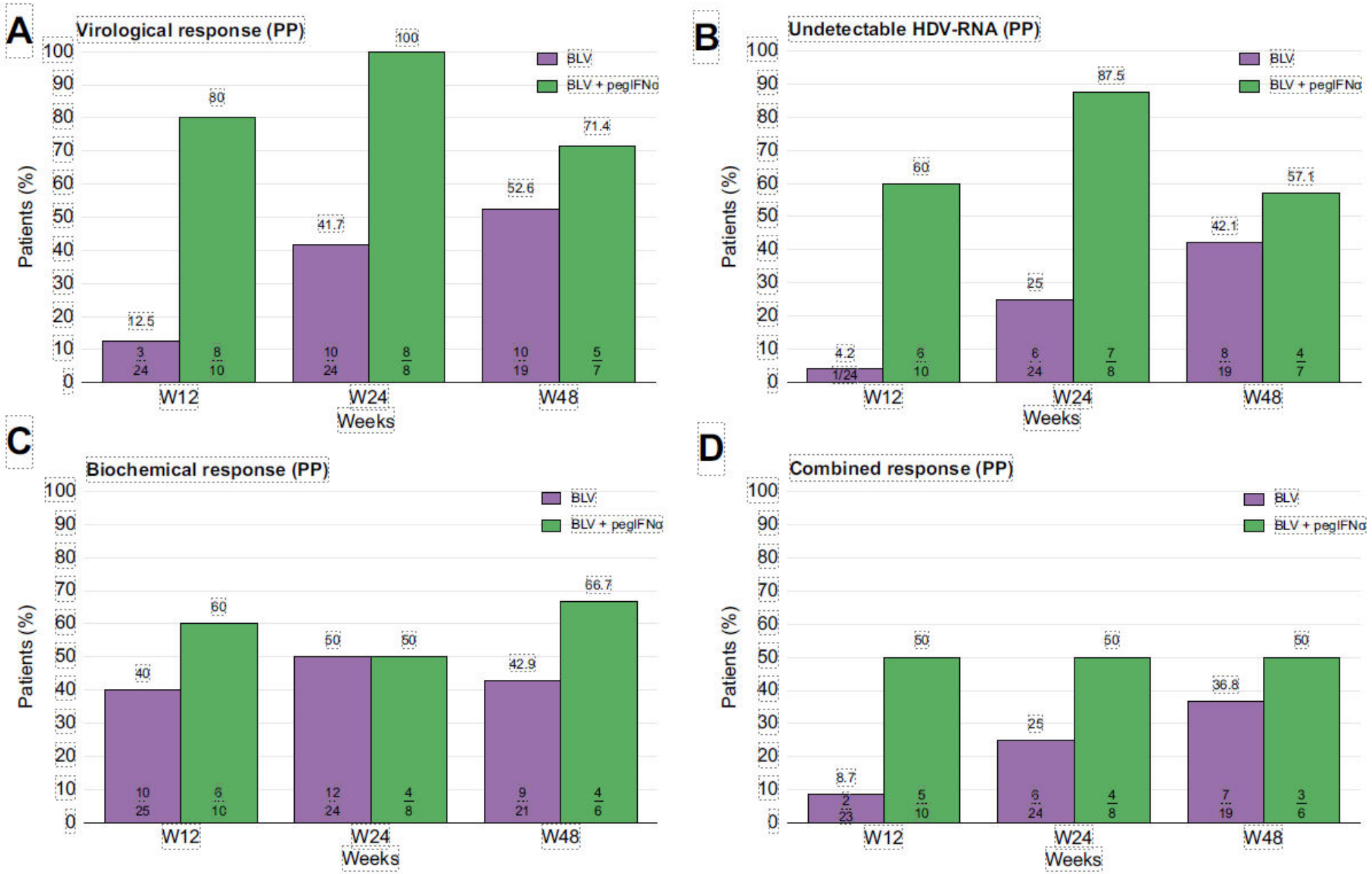


N° at risk					
BLV	19	18	18	18	19
BLV + pegIFNα	7	7	7	6	7
Missing	0	1	1	2	0

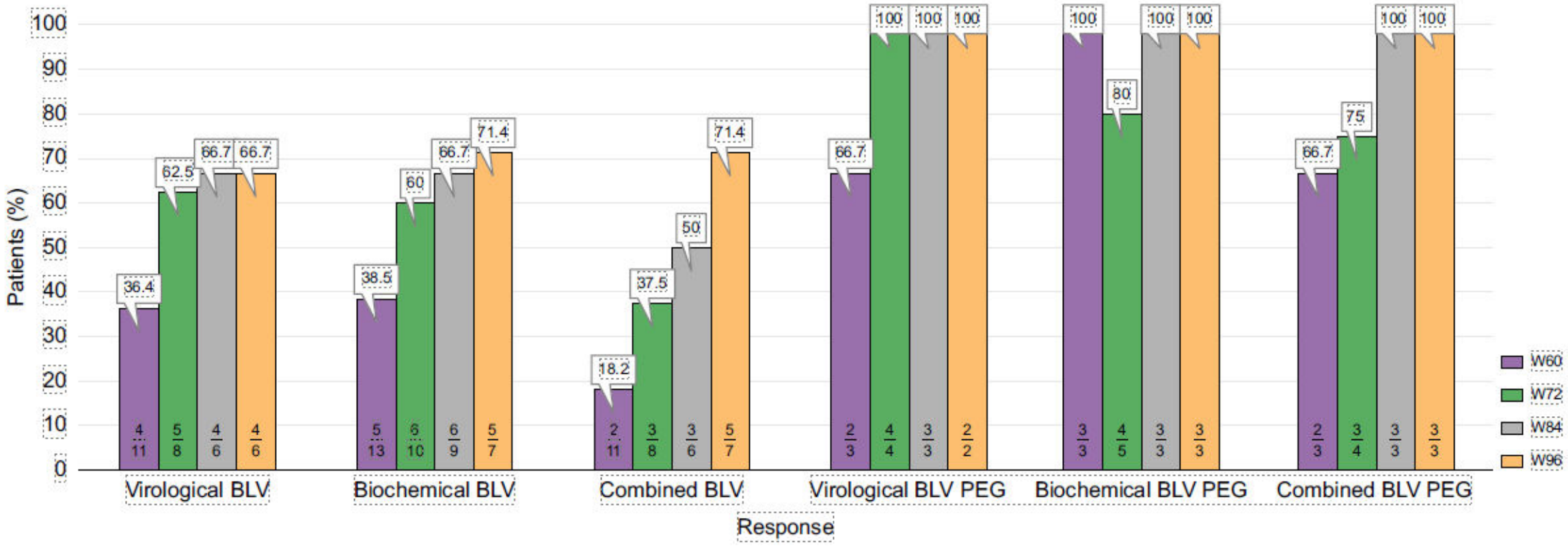
Individual evolution of HDV RNA through Week 48



Per-protocol analysis results at Weeks 12, 24, and 48



Virological, biochemical, and combined response at Weeks 60, 72, 84, and 96 in patients who continued treatment after Week 48.



Treatment discontinuation and main adverse events

	BLV monotherapy (n = 27)	BLV + pegIFNα (n = 11)	*p* value
Discontinuation before Week 48, n (%)	4 (14.8)	4 (36.4)	0.1950
Duration of treatment before discontinuation (weeks), mean ± SD	31.1 ± 6.4	14.1 ± 8.5	0.0304
Causes of discontinuation before Week 48, n (%)			
Severe adverse events*	0 (0)	2 (50)	
Lost to follow-up	1 (25)	1 (25)	
Poor response or compliance	3 (75)	1 (25)	
All grade 3 and 4 adverse events*, n (%)	9 (42.9)	6 (100)	0.0200
Serious adverse events	9 (42.9)	4 (66.7)	0.3845
Increased bile acids (>15 N)	1 (4.8)	0	
Thrombocytopenia	1 (4.8)	2 (33.3)	
Neutropenia	1 (4.8)	5 (83.3)	
Gamma-glutamyl transferase increase	1 (4.8)	2 (33.3)	
Pruritus	3 (14.3)	1 (16.7)	

Drug-drug Interactions between Viral Hepatitis Drugs and ARVs

EACS Guidelines 12.0

Viral hepatitis drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
HCV DAAs	elbasvir/ grazoprevir	↑	↑376% ↑958%	↑	↑66% ↑650%	↑271% ↑1186%	↓4% ↑7%	↓54% ↓83%	↓	↓	↑7% ↓2%	↔ ↑	↔	↔	↔	↔	↓2% ↓19%	↑118% ↑436%	↓19% ↓11%	↔	↓7% ↓14%
	glecaprevir/ pibrentasvir	↑	↑553% ↑64%	↑	↑397%	↑338% ↑146%	↔	↓	↓	↓	E 84%	↑	E	↔	E	↔	↔	↑205% ↑57% E47%	E47%	↔	E29%
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↓6%	↔	↔	↑9%	↑	↔	↔	↔	↔	↔	↔	↓5% D27%	↔	↓6%
	sofosbuvir/ ledipasvir	↑a	↑8% ↑113%a	↑a	↑34% ↑39%a	↔a	↑4% ↓8%	↓6% ↓34%a	↔	↔	↑10% ↑8%a	↑	E	↔	↑7% ↓13%	↔	↔	↑36% ↑78%a	↓5% ↓9% D~20%	E32%	E a
	sofosbuvir/ velpatasvir	↔a	↑22% ↑142%a	↔a	↓28% ↓16%a	↓29% ↑2%a	↔	↓3% ↓53%	↓	↓	↑16% ↓1%	↑	E	↔	↔	↔	↓8% ↓9%	↑a	↑24% ↓2%	↔	E a
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40% ↑93% ↑331%	↑a	↓28% ↓5% ↑143%b	↑	↔	↓	↓	↓	↔	↑	E	↔	↑9% ↓4% ↓9%	↔	↔	↑22% ↑16% ↑171%a	↔	E	E a
HDV	Bulevirtide	↑	↑	↑	↑	↑	E	↑	↑	↔	E	↔	E	↔	↔	E	↔	↑	↔	↔	↔

No clinically significant interaction expected
These drugs should not be co-administered
Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
Potential interaction likely to be of weak intensity. Additional action/ monitoring or dosage adjustment is unlikely to be required

EACS European AIDS Clinical Society

Last results from SAVE-D study

SAVE-D study
Efficacy and safety of BLV monotherapy in HIV positive patients

24 HIV positivevs 220 HIV negative CHDpatients

	Week 24			Week 48			Week 72			Week 96		
	HIV+	HIV-	p value	HIV+	HIV-	p value	HIV+	HIV-	p value	HIV+	HIV-	p value
Virological Response	36%	54%	0.10	59%	65%	0.60	73%	67%	0.69	80%	79%	0.94
Biochemical Response	45%	54%	0.47	65%	59%	0.63	69%	58%	0.42	100%	56%	**0.03**
Combined Response	18%	35%	0.11	41%	45%	0.78	45%	47%	0.97	80%	52%	0.22

Virological response: ≥2 log decline from baseline or HDV RNA TND/<LOD; **Biochemical response**: ALT <40 U/L; **Combined response**: virological and biochemical response; comparisons were performed by Fischer exact tests

BLV monotherapy is effective and safe also in HIV coinfected patients

Degasperi E et al, EASL 2024

Conclusions

- Bulevirtide induces an on-treatment virological response in more than 50% of patients with HIV/HBV/HDV, suggesting that it should be considered as a first-line therapy in this population
- Treatment of hepatitis delta with bulevirtide in patients with HIV is safe, with no relevant drug–drug interactions
- Bulevirtide in combination with pegIFNα could be used in patients without pegIFNα contraindication
- The ideal duration of treatment and whether treatment may be curative in this population remains unknown

HDV seroprevalence

Globally

~5% in people with chronic HBV infection

~16% in people with HBV attending liver clinics

Global burden 9-19 million

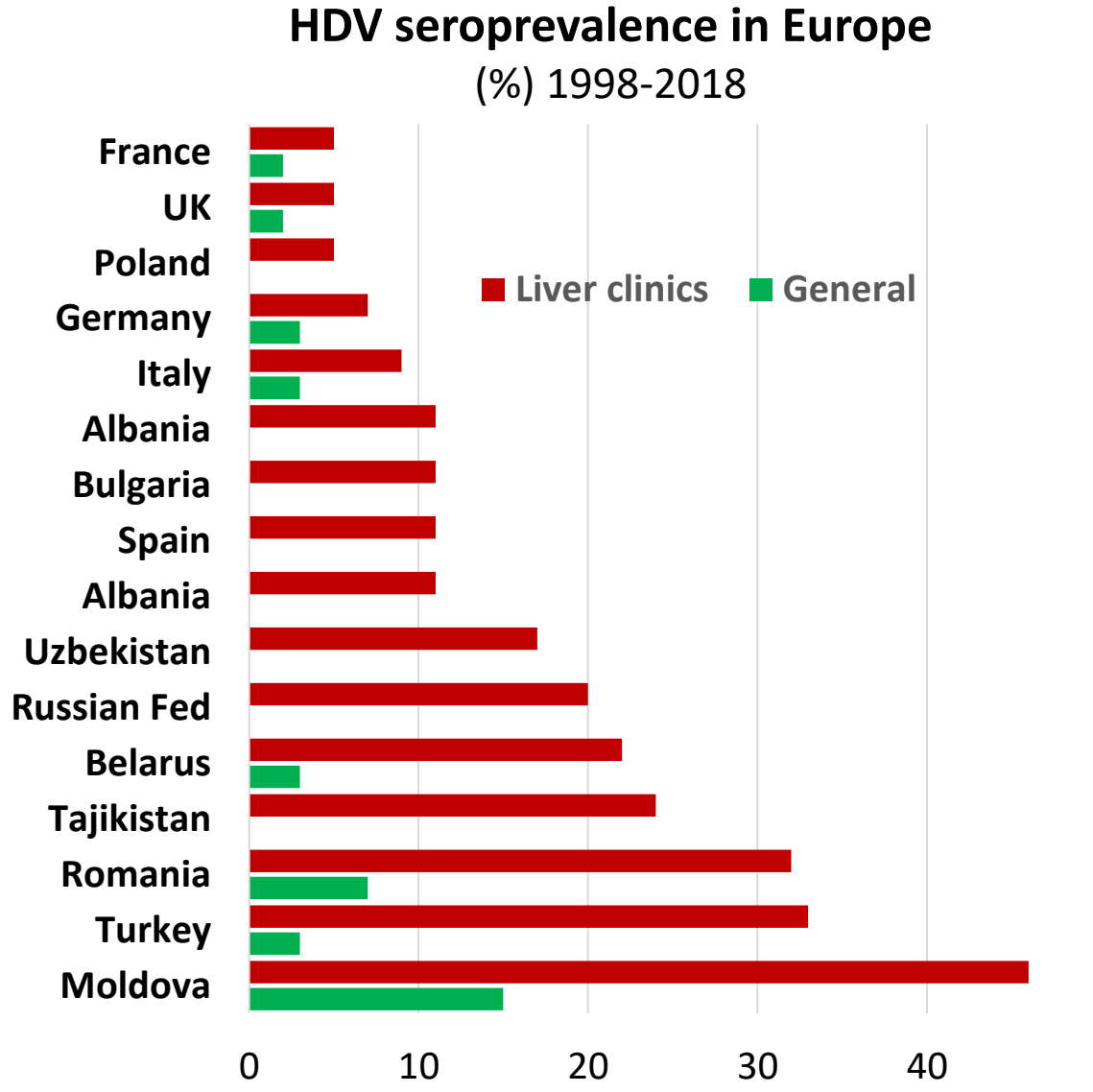
Highest prevalence in Mongolia, Moldova, Western and Middle Africa

Factors associated with ↑ HDV seroprevalence

IDU | Sex work | MSM | Hep C | HIV | Cirrhosis | Haemodialysis | HCC

HIV associated with ↑ HDV seroprevalence* (pooled OR 6.6; 95% CI 4.2, 10.6)

*excluding settings with generalised HIV epidemics



Stockdale et al. J Hepatol 2020