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HBV-RNAs and HBcrAg in patients with CHD

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Disclosures

Advisory Board/Speaker Bureau for:

- ROCHE PHARMA/DIAGNOSTICS, GILEAD SCIENCES, GSK, ABBVIE, JANSSEN, MYR, EIGER, ANTIOS, ALIGOS, VIR, GRIFOLS, ALTONA, ROBOSCREEN

Outline of the presentation

- Background and rationale for HBV RNA and HBcrAg
- New HBV biomarkers in untreated CHD patients
- New HBV biomarkers in pegIFN-treated CHD
- New HBV biomarkers in BLV-treated patients
- Summary and conclusions

HBcrAg levels in untreated CHD patients

Quantification of serum HBV and HDV markers in untreated CHD patients
A crossectional collaborative study (Italy and Romania)

122 untread CHD patients included in the study (100% GT 1 and D)

HBV and HDV markers according to disease stage

		Cirrhosis			Multivariate		
		Absent	Present				
		n = 20	n = 89	P	OR	95% CI	P
HBeAg Status	HBeAg+	0 (0.0)	8 (9.0)	.347			
	HBeAg−	20 (100.0)	81 (91.0)				
HBV-DNA (log_{10} IU/mL)	Median	1.41	1.03	.302			
	Range	0.70-4.66	0.70-5.34				
HBsAg (log_{10} IU/mL)	Median	4.02	3.87	.211			
	Range	−1.00-4.48	−1.00-4.46				
Total anti-HBc (IU/mL)	Median	1267.49	557.02	.097			
	Range	58.52-9978.66	14.60-20 564.87				
HBcrAg (log_{10} U/mL)	Median	3.84	3.90	.742			
	Range	2.00-6.29	2.00-6.21				
HDV-RNA (log_{10} cp/mL)	Median	3.79	4.32	.071			
	Range	2.70-6.29	2.70-6.82				
IgM anti-HDV (AU/mL)	Median	22	40	.050			
	Range	10-107	10-200				
Total anti-HDV	≤1:100	3 (15.0)	6 (6.7)	.433			
	≤1:5000	9 (45.0)	49 (55.1)				
	≤1:50 000	8 (40.0)	34 (38.2)				
Total anti-HBc/ IgM anti-HDV	Median	28.35	10.86	.042	0.990	0.981-0.999	
	Range	0.87-997.87	0.10-425.96				

HBV and HDV markers according to disease activity

		ALT > ULN			Multivariate		
		No	Yes				
		n = 26	n = 83	P	OR	95% CI	P
HBeAg Status	HBeAg+	0 (0.0)	8 (9.6)	.194			
	HBeAg−	26 (100)	75 (90.4)				
HBV-DNA (log_{10} IU/mL)	Median	0.70	1.15	.301			
	Range	0.70-4.03	0.70-5.34				
HBsAg (log_{10} IU/mL)	Median	3.45	3.92	.113			
	Range	−1.00-4.41	1.72-4.48				
Total anti-HBc (IU/mL)	Median	742.66	649.12	.001			
	Range	41.62-8790.81	14.60-20564.87				
HBcrAg (log_{10} U/mL)	Median	3.69	3.95	.001			ns
	Range	2.00-6.29	2.30-6.21				
HDV-RNA (log_{10} cp/mL)	Median	2.70	4.40	<.001	2.366	1.456-3.844	.001
	Range	2.70-5.46	2.70-6.82				
IgM anti-HDV (AU/mL)	Median	12.5	47	<.001			ns
	Range	10-100	10-200				
Total anti-HDV	≤1:100	6 (23.1)	3 (3.6)	.002	10.105	1.671-61.107	.012
	≤1:5000	15 (57.7)	43 (51.8)				
	≤1:50 000	5 (19.2)	37 (44.6)				
Total anti-HBc/ IgM anti-HDV	Median	19.44	9.43	.009			ns
	Range	2.31-699.88	0.10-997.87				

Correlation between HBV and HDV markers

	HBsAg	Total anti-HBc	HBcrAg	HDV-RNA	IgM anti-HDV	Total anti-HDV
HBV-DNA (log_{10} IU/mL)						
ρ Spearman	0.185	0.269	0.324	0.276	0.000	−0.199
P	.067	.007	.001	.005	.998	.047
no of cases	99	100	100	100	100	100
HBsAg (log_{10} IU/mL)						
ρ Spearman		−0.227	0.395	0.404	0.059	0.037
P	-	.018	<.001	<.001	.543	.706
no of cases		108	108	108	108	108
Total anti-HBc (IU/mL)						
ρ Spearman			0.078	−0.105	−0.033	−0.076
P	-	-	.420	.276	.735	.432
no of cases			109	109	109	109
HBcrAg (log_{10} U/mL)						
ρ Spearman				0.332	0.148	0.066
P	-	-	-	<.001	.124	.495
no of cases				109	109	109
HDV-RNA (log_{10} cp/mL)						
ρ Spearman					0.416	0.094
P	-	-	-	-	<.001	.329
no of cases					109	109
IgM anti-HDV (AU/mL)						
ρ Spearman						0.605
P	-	-	-	-	-	<.001
						109

In 122 untreated CHD patients, HBcrAg levels positively correlate with HBsAg, HBV DNA and HDV RNA levels but did not independently predict disease activity (ALT) or severity (cirrhosis)

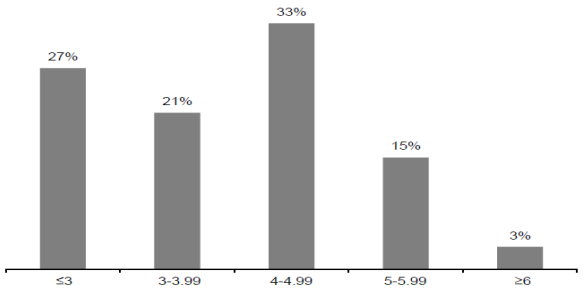
Ricco G. et al, JVH 2018

HBcrAg levels in untreated CHD patients – HIDIT-II subanalysis

Baseline features of 99 patients

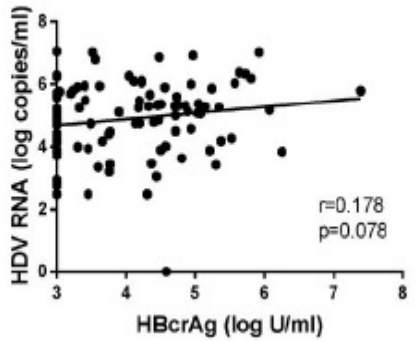
Sex	
Male	66 (66.7%)
Female	35 (33.3%)
Age	
Median (IQR)	47 (42-60)
HDV RNA	
<300 copies/mL	5 (5.1%)
Median log10 copies/mL (IQR)	5.17 (4.27-5.76)
>10^5 copies/mL	53 (53.5%)
HBV DNA	
Negative	8 (8.1%)
Median log10 IU/mL (IQR)	1.93 (1.3-3.22)
<100 IU/mL	38 (38.4%)
>2,000 U/mL	20 (20.2%)
HBsAg	
Median log10 IU/mL (IQR)	3.92 (3.51-4.2)
<1,000 IU/mL	10 (10.1%)
HBeAg	
Positive	18 (18.2%)
Missing	10 (10.1%)
HBcrAg	
Median log U/mL (IQR)	4.11 (3-4.76)
≤3 log U/mL	27 (27.3%)
3-4.5 log U/mL	39 (39.4%)
>4.5 log U/mL	33 (33.3%)
ALT	
Median IU/L (IQR)	85 (58-149)
AST	
Median IU/L (IQR)	58 (44-99)

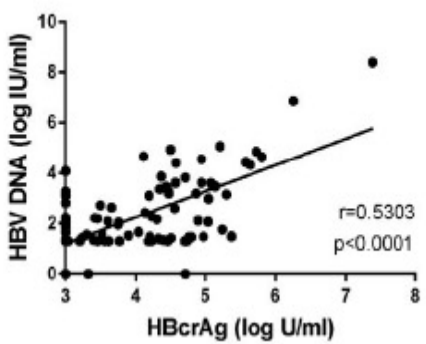
Distribution of patients for HBcrAg

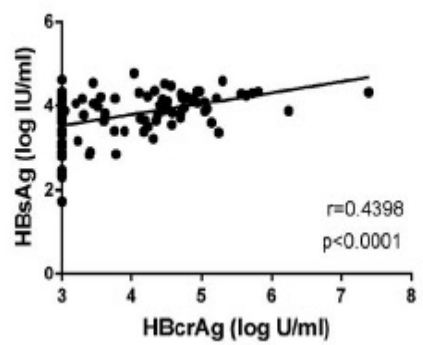


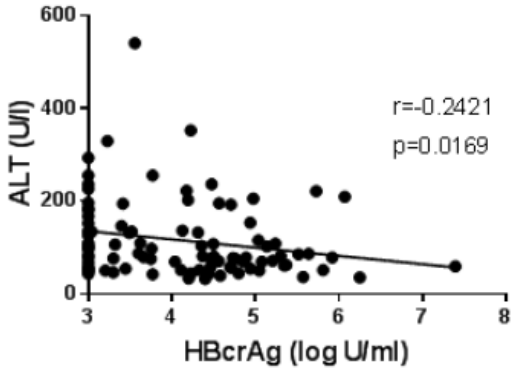
HBcrAg levels [log U/ml] at baseline

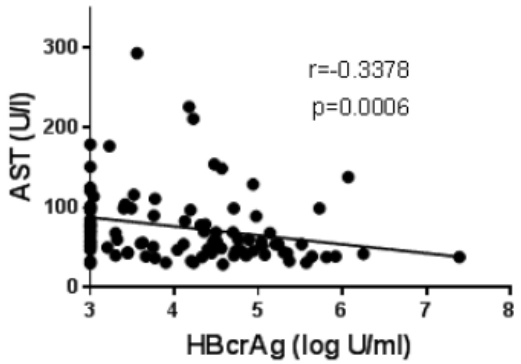
Baseline

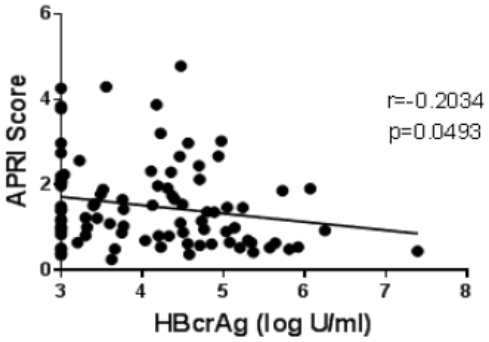












In 99 untreated CHD patients, HBcrAg levels positively correlate with HBsAg and HBV DNA levels and negatively correlated wit ALT/AST levels

Sandmann L. et al, Hepatology Communications 2022

HBcrAg and HBV RNA levels in untreated CHD

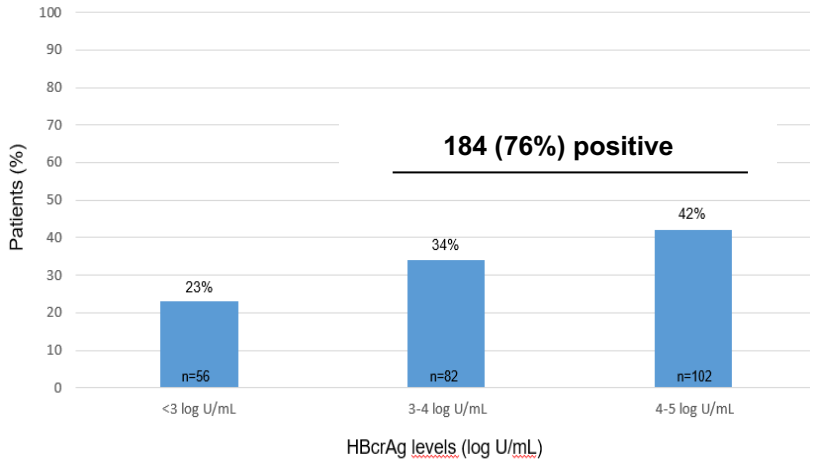
Serum pgHBV-RNA and HBcrAg levels in 240 untreated CHD patients: A multicenter cross-sectional study

Baseline features of the patients

Age, years	46 (20-78)
Males	144 (62%)
European origin	170 (71%)
BMI, Kg/m^2	24 (17-44)
Cirrhosis	126 (53%)
CPT- A	101 (80%)
Esophageal varices°	46 (47%)
Active HCC	16 (7%)°
LSM, kPa§	10.4 (3.4-74.6) §
ALT, U/L	70 (15-889)
ALT>ULN	193 (80%)
AST, U/L	63 (17-380)
GGT, U/L	49 (8-491)
PLT, 10^3/mm^3	140 (29-369)
On NUC treatment	137 (57%)
HBsAg, Log IU/ml	3.8 (0.3-4.6)
HBeAg positive	45 (19%)
HBV DNA detectable	74 (31%)
HBV DNA log IU/ml*	1.8 (1.0-8.1)
HDV genotype 1@	84 (95%)@
HDV RNA, Log IU/mL	4.9 (0.8-9.6)

(Milan, Lyon and Barcelona)

Distribution of patients according to HBcrAg levels (log IU/ml)



In 184 HBcrAg positive patients, median levels were high: 4.2 log IU/ml (range 3-8)

Variables associated with positive HBcrAg (76%)

Variables	Variables Category	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Age	Continuous	0.99 (0.97-1.02)	0.99	-	-
Male sex	Yes vs. No	1.28 (0.70-2.35)	0.42	-	-
European origin	Yes vs. No	1.34 (0.71-2.54)	0.37	-	-
Cirrhosis	Yes vs. No	0.86 (0.47-1.57)	0.62	-	-
LSM, kPa	Continuous	0.98 (0.96-1.01)	0.24	-	-
ALT, U/L	Continuous	1.00 (0.99-1.00)	0.54	-	-
GGT, U/L	Continuous	0.99 (0.99-1.00)	0.07	-	-
PLT, 10^3/mm3	Continuous	1.00 (0.99-1.00)	0.92	-	-
NUC treatment	Yes vs. No	1.09 (0.60-2.00)	0.77	-	-
HBsAg, LogIU/mL	Continuous	3.07 (1.86-5.07)	**<0.0001**	2.80 (1.62-4.81)	**0.0002**
HBeAg positive	Yes vs. No	17.3 (2.32-128.56)	**0.005**	13.76 (1.79-105.41)	**0.01**
HBV DNA detectable	Yes vs. No	1.45 (0.74-2.86)	0.28	-	-
HDV RNA, LogIU/mL	Continuous	1.33 (1.10-1.61)	**0.003**	1.10 (0.89-1.38)	0.35

- **HBV RNA levels**: quantified by real-time PCR-based investigation assay (Roche Diagnostics, Pleasanton, Ca, USA, lower limit of quantification [LOQ] 10 cp/ml).
- **HBcrAg levels** quantified by LUMIPULSE® G HBcrAg assay (Fujirebio Europe, LOD 2 log10 U/ml).

Degasperi E et al, EASL 2022, manuscript in preparation

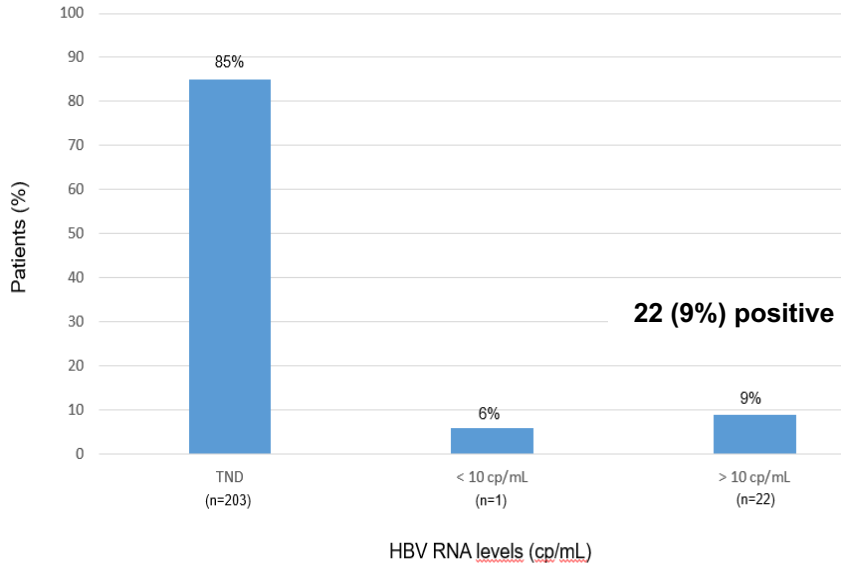
Serum pgHBV-RNA and HBcrAg levels in 240 untreated CHD patients
A multicenter cross-sectional study

Baseline features of the patients

Age, years	46 (20-78)
Males	144 (62%)
European origin	170 (71%)
BMI, Kg/m^2	24 (17-44)
Cirrhosis	126 (53%)
CPT- A	101 (80%)
Esophageal varices°	46 (47%)
Active HCC	16 (7%)°
LSM, kPa§	10.4 (3.4-74.6) §
ALT, U/L	70 (15-889)
ALT>ULN	193 (80%)
AST, U/L	63 (17-380)
GGT, U/L	49 (8-491)
PLT, 10^3/mm^3	140 (29-369)
On NUC treatment	137 (57%)
HBsAg, Log IU/ml	3.8 (0.3-4.6)
HBeAg positive	45 (19%)
HBV DNA detectable	74 (31%)
HBV DNA log IU/ml*	1.8 (1.0-8.1)
HDV genotype 1@	84 (95%)@
HDV RNA, Log IU/mL	4.9 (0.8-9.6)

Milan, Lyon and Barcelona

Distribution of patients according to HBV RNA levels (cp/ml)



In 22 HBV RNA positive patients, median levels were low: 40 cp/ml (range 13-82,000)

Variables associated with positive HBV RNA (9%, 22 pts)

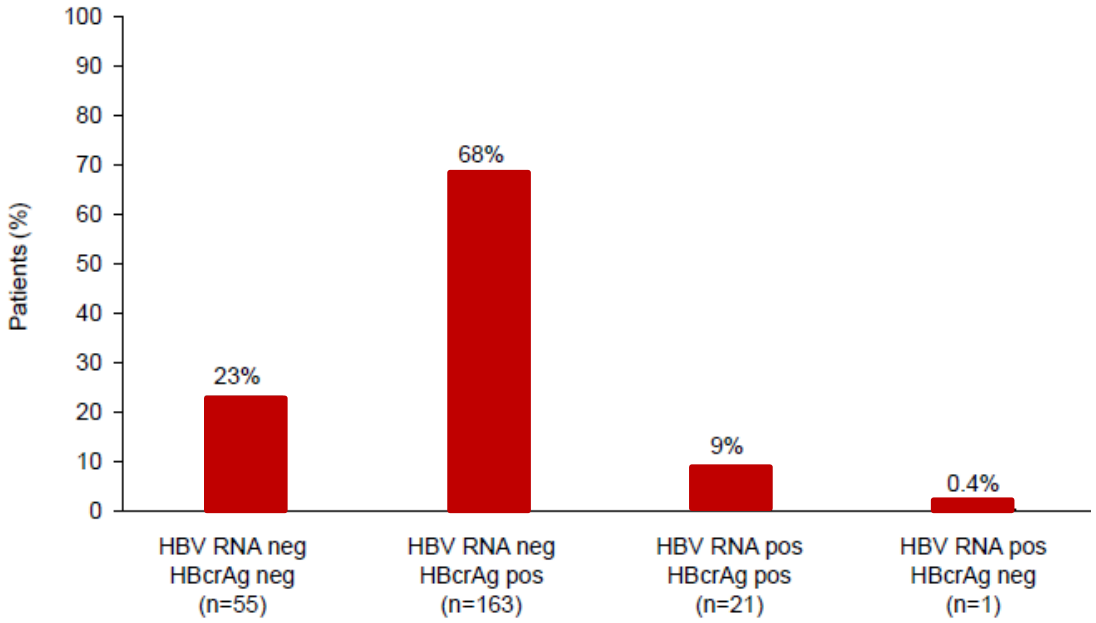
Variables	Variables Category	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Age	Continuous	0.94 (0.90-0.98)	**0.001**	0.94 (0.89-0.98)	**0.01**
Male sex	Yes vs. No	3.29 (1.07-10.03)	**0.04**	5.11 (1.36-19.16)	**0.02**
European origin	Yes vs. No	0.19 (0.08-0.50)	**0.001**	-	-
Cirrhosis	Yes vs. No	0.48 (0.20-1.20)	0.11	-	-
LSM, kPa	Continuous	1.01 (0.97-1.04)	0.68	-	-
ALT, U/L	Continuous	0.99 (0.98-1.00)	0.25	-	-
GGT, U/L	Continuous	1.00 (0.99-1.01)	0.26	-	-
PLT, 10^3/mm3	Continuous	1.00 (0.99-1.01)	0.19	-	-
NUC treatment	Yes vs. No	0.39 (0.16-0.97)	**0.04**	-	-
HBsAg, LogIU/mL	Continuous	1.71 (0.69-4.22)	0.24	-	-
HBeAg positive	Yes vs. No	10.56 (4.09-27.25)	**<0.001**	12.99 (4.24-39.82)	**<0.0001**
HBV DNA detectable	Yes vs. No	7.36 (2.75-19.70)	**<0.001**	4.93 (1.57-15.48)	**<0.01**
HDV RNA, LogIU/mL	Continuous	1.54 (1.19-2.01)	**0.001**	-	-

- **HBV RNA levels**: quantified by real-time PCR-based investigation assay (Roche Diagnostics, Pleasanton, Ca, USA, lower limit of quantification [LOQ] 10 cp/ml).
- **HBcrAg levels** quantified by LUMIPULSE® G HBcrAg assay (Fujirebio Europe, LOD 2 log10 U/ml).

Degasperi E et al, EASL 2022, manuscript in preparation

Serum pgHBV-RNA and HBcrAg levels in 240 untreated CHD patients
A multicenter cross-sectional study

Distribution of patients according to HBV RNA and HBcrAg levels



In CHD untreated patients, HBV RNA and HBcrAg show a divergent pattern: while HBV RNA was undetectable in most patients, most of them had quantifiable HBcrAg but negative HBeAg

Variables associated with different HBV RNA/HBcrAg patterns

Variables	HBV RNA neg HBcrAg neg (n=55)	HBV RNA neg HBcrAg pos (n=163)	HBV RNA pos HBcrAg pos (n=21)	p value
Age, years	48 (23-64)	47 (20-78)	36 (20-56)	**0.005**
Males	30 (55%)	96 (59%)	17 (81%)	0.10
European origin	36 (66%)	126 (77%)	7 (33%)	**0.0001**
BMI, Kg/m^2	25 (19-37)	24 (17-44)	25 (18-31)	0.12
Cirrhosis	30 (55%)	88 (54%)	7 (33%)	0.19
Active HCC	8 (15%)	7 (4%)	1 (5%)	0.08
LSM, kPa[§]	8.4 (4.1-66.0)	10.9 (3.4-57.4)	8.5 (5.0-35.0)	0.39
AST, IU/L	64 (23-380)	64 (17-374)	53 (32-186)	0.36
ALT, U/L	51 (17-743)	78 (15-889)	62 (26-171)	0.10
ALT>ULN	37 (67%)	135 (83%)	19 (91%)	**0.02**
GGT, IU/L	57 (13-491)	49 (8-362)	42 (16-469)	0.70
PLT, 10^3 x mm^3	131 (41-369)	145 (29-316)	140 (84-307)	0.36
On NUC therapy	30 (55%)	99 (61%)	7 (33%)	0.05
HBsAg, Log IU/mL	3.4 (0.3-4.4)	3.8 (2.0-4.6)	3.9 (2.8-4.3)	**0.001**
HBeAg positive	0	16 (10%)	11 (52%)	**<0.0001**
HBV DNA detectable	13 (24%)	45 (28%)	15 (71%)	**0.0001**
HDV genotype 1[@]	20 (100%)	55 (97%)	9 (82%)	0.17
HDV RNA, Log IU/mL	3.9 (1.1-8.2)	4.9 (0.8-9.0)	6.4 (1.0-9.6)	**<0.001**

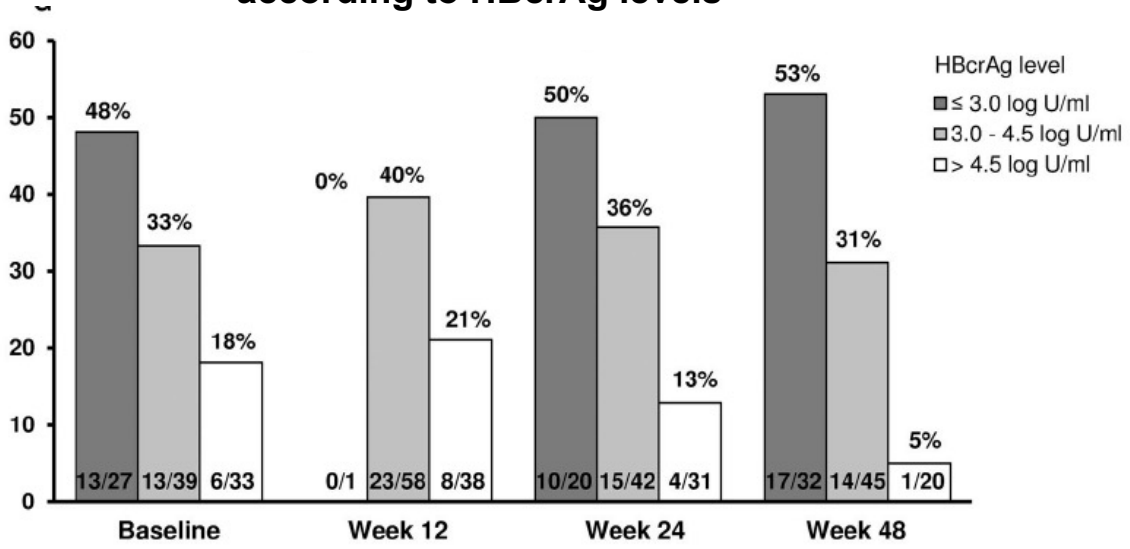
Degasperi E et al, EASL 2022, manuscript in preparation

PegIFN-treated CHD patients

HBcrAg Levels Are Associated With Virological Response to Treatment With IFN in CHD patients (HIDIT-II)

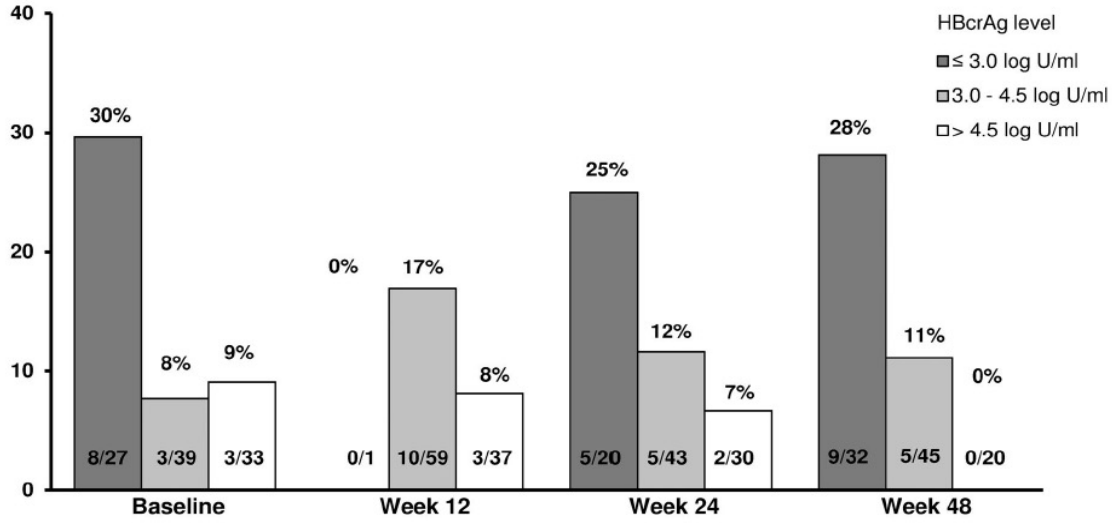
Overall, 99 CHD patients included: 48 treated with pegIFN+TDF and 48 treated with pegIFN monotherapy for 96 weeks; 24 weeks post Tx fup

Proportion of HDV RNA responders* according to HBcrAg levels



*Undetectable HDV RNA at FU24 (n=32)

Proportion of HBsAg responders* according to HBcrAg levels



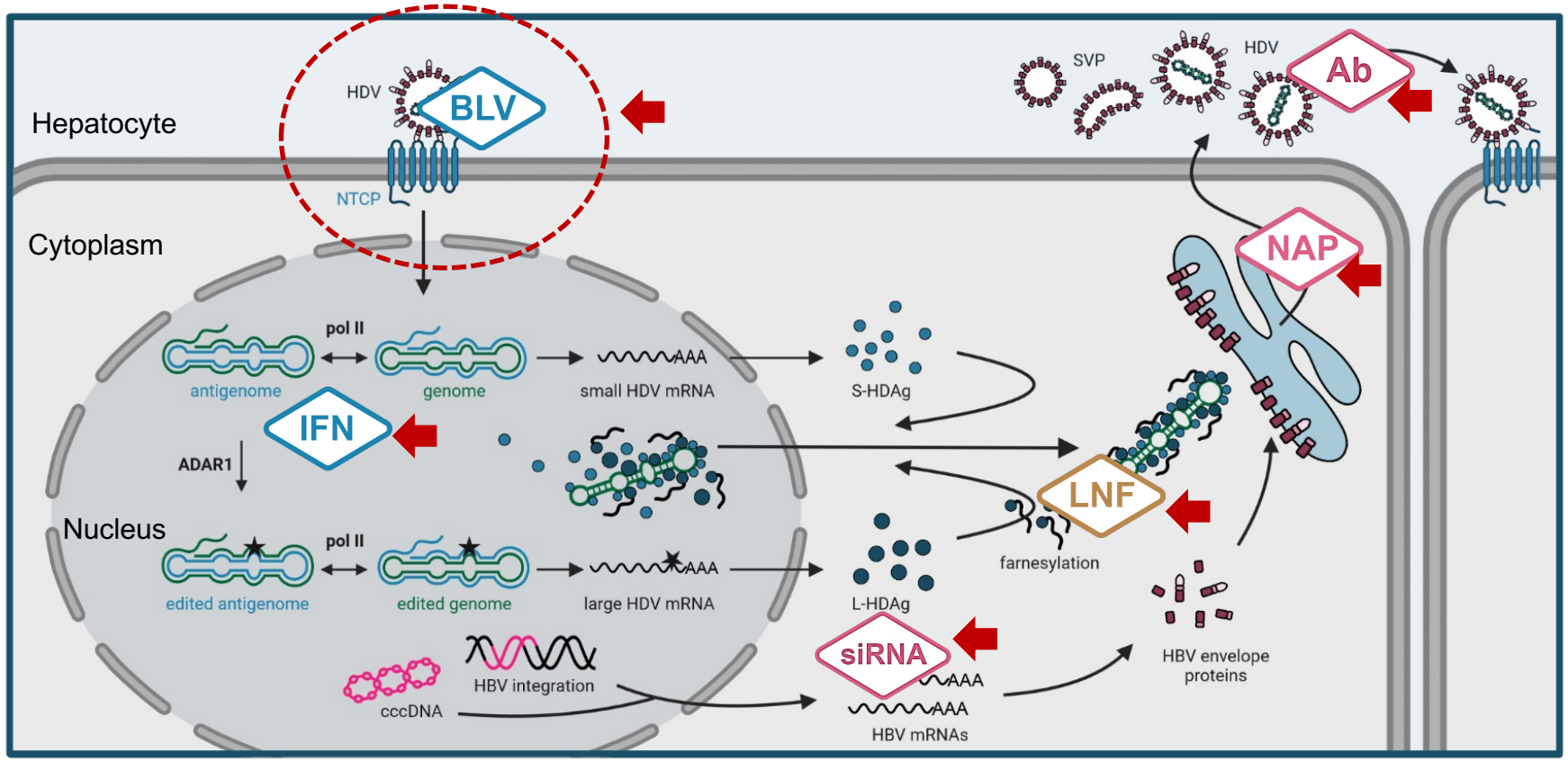
*HBsAg response=HBsAg <100 IU/mL at FU24 (n=14)

HBcrAg could be a promising baseline and on-treatment marker to predict pegIFN response in CHD patients. It could be a promising marker to determine treatment futility

Sandmann L. et al, Hepatology Communications 2022

BLV-treated CHD patients

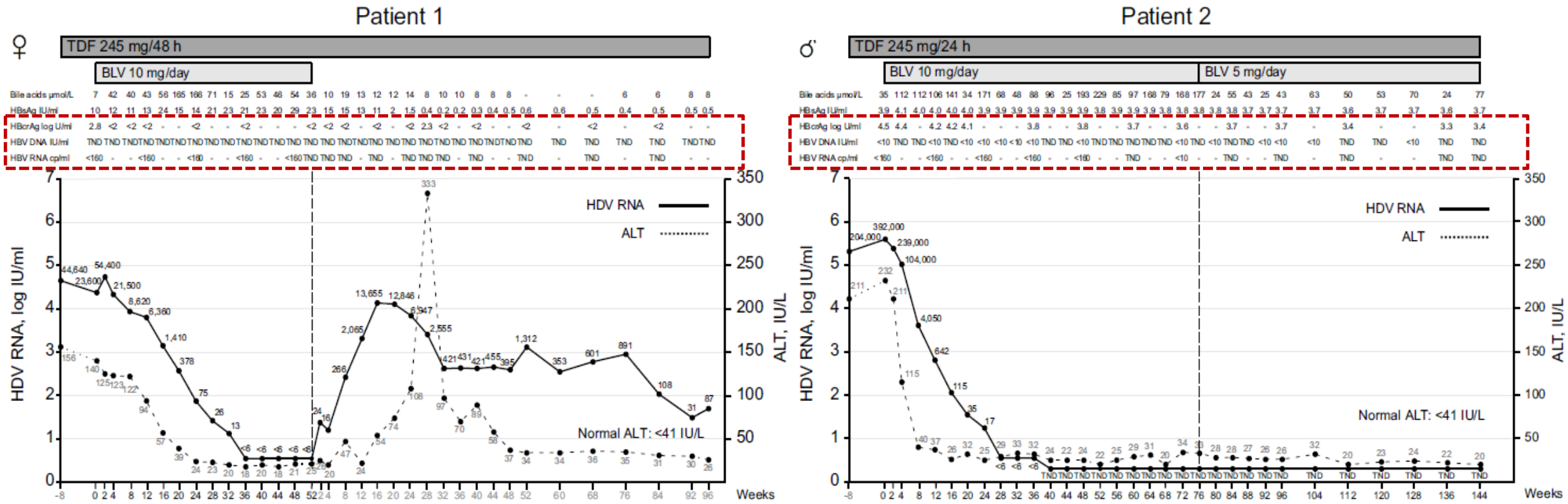
Therapeutic targets for HDV infection



NUC therapy for HBV does not directly interfere with HDV replication

Courtesy of L. Allweiss/A. Volmari, adapted from Dandri et al J. Hepatol 2022

Serum HBcrAg and HBV RNA levels in CHD patients treated with BLV monotherapy for up to 3 years



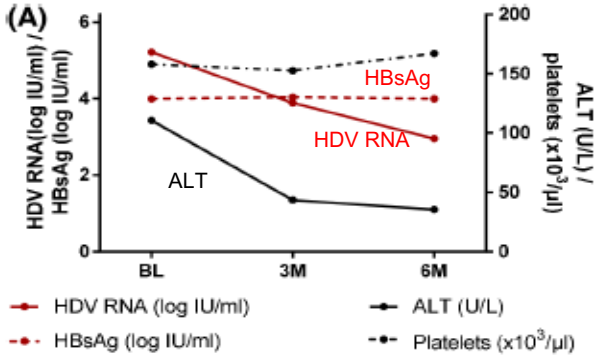
- HBV RNA levels were quantified by an inhouse real-time PCR technique (Leipzig, LOD 160 cp/ml) in the first year, and by a real-time PCR-based investigation assay (Roche Diagnostics, Pleasanton, Ca, USA, lower limit of quantification [LOQ] 10 cp/ml) in the following 2 years.
- HBcrAg levels were measured using LUMIPULSE® G HBcrAg assay (Fujirebio Europe, LOD 2 log10 U/ml).

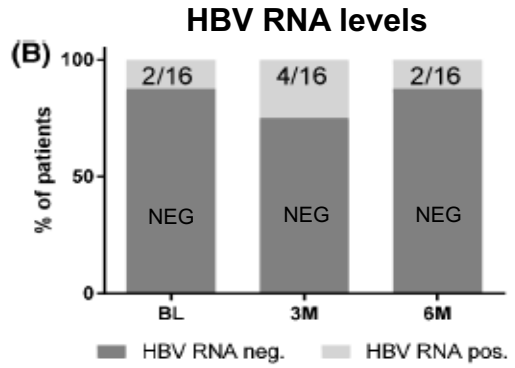
Loglio A et al, J Hepatol 2021

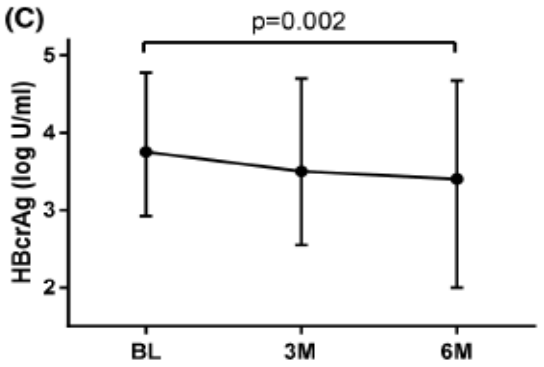
HBcrAg and HBV RNA levels during BLV treatment of CHD patients
A single center study from Germany

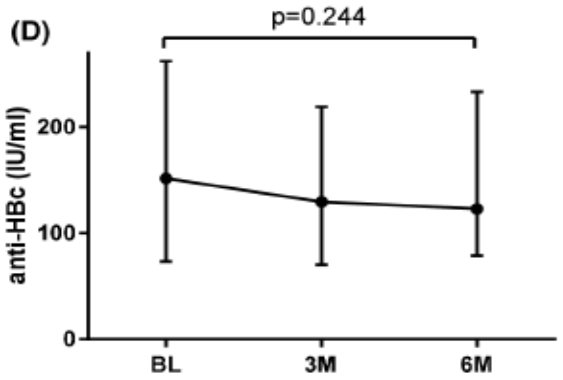
Study outline

- Retrospective single center study (Germany)
- 16 patients CHD treated with BLV 2 mg/day
- Duration of therapy: 6 months
- 15/16 patients on NUC
- HBV RNA by Robogene 2.0 (LLOG 82 IU/ml)
- HBV RNA by Roche Cobas 6800 (LLQ 10 cp/ml, HBcrAg by Lumupulse Fujirebio
- At baseline, 10 patients (63%) showed an HBcrAg level >3 log IU/mL, with median levels of HBcrAg were 3.75 log U/mL (IQR 2.93–4.78 log U/mL).
- At baseline, HBV RNA was detectable in only two (12%) patients .









After 6 months of BLV treatment, levels of HBcrAg showed a significant decline, while HBV RNA and anti-HBc levels did not change. Reduction of HBV cccDNA transcriptional activity and immunological effects of antiviral treatment might explain these changes.

Sandman L. et al, JVH 2023

BLV monotherapy for 48 weeks in compensated cirrhotics with CSPH - Time course of virological variables

Variables	Baseline n = 18	Week 8 n = 18	Week 16 n = 18	Week 24 n = 18	Week 32 n = 18	Week 40 n = 18	Week 48 n = 18	p value
HDV RNA, Log IU/ml	4.9 (3.3-6.6)	3.5 (1.2-5.9)	2.7 (0.9-5.9)	2.3 (0.7-5.8)	2.0 (0.7-5.8)	1.8 (0.3-6.0)	2.2 (0.3-6.0)	**<0.001**
HDV RNA decline, Log IU/ml	-	1.4 (0.4-3.1)	2.2 (0.4-3.6)	2.7 (0.6-3.9)	2.8 (0.4-3.9)	3.1 (0.3-4.6)	3.1 (0.2-4.3)	**<0.001**
HDV RNA decline ≥2 Log IU/ml	-	2 (11%)	7 (39%)	15 (83%)	15 (83%)	14 (78%)	14 (78%)	**<0.001**
HDV RNA decline <1 Log/ml	-	2 (11%)	2 (11%)	2 (11%)	2 (11%)	2 (11%)	2 (11%)	0.97
HDV RNA <1,000 IU/ml	0	8 (44%)	10 (56%)	13 (72%)	14 (78%)	14 (78%)	14 (78%)	**<0.001**
HDV RNA <100 IU/ml	0	2 (11%)	7 (39%)	9 (50%)	10 (56%)	10 (56%)	7 (39%)	**<0.001**
HDV RNA <6 IU/ml	0	0	0	2 (11%)	5 (23%)	6 (33%)	5 (23%)	**0.003**
Virologic response°	-	**2 (11%)**	**7 (39%)**	**15 (83%)**	**15 (83%)**	**14 (78%)**	**14 (78%)**	**<0.001**
HBsAg, Log IU/ml	3.7 (2.5-4.3)	3.8 (2.6-4.3)	3.8 (2.6-4.3)	3.8 (2.5-4.3)	3.7 (2.5-4.2)	3.7 (2.5-4.3)	3.7 (2.4-4.2)	0.31
HBV DNA detectable**	4 (28%)	0	0	0	2 (11%)	2 (11%)	1 (5%)	0.08
HBV RNA detectable***	1 (6%)	n.a.	n.a.	0	n.a.	n.a.	0	n.a.
HBcrAg, Log U/ml	3.8 (3.0-5.0)	3.7 (3.0-5.1)	3.8 (3.0-5.0)	3.7 (3.0-5.0)	3.7 (3.0-4.9)	3.7 (3.0-4.9)	3.7 (3.0-4.9)	**0.03**
HBcrAg >3 log U/ml	17 (94%)	16 (89%)	16 (89%)	16 (89%)	16 (89%)	16 (89%)	16 (89%)	0.99

Values are expressed as n (%) or median (range). Bold enhances the concept that virologic response represents the primary study endpoint.
Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests (level of significance p <0.05); repeated analysis of variance was used to compare continuous variables assessed at different timepoints (level of significance p <0.05). Bonferroni correction was applied in order to counteract the multiple testing problem.
BLV, bulevirtide; HBcrAg, hepatitis B core-related antigen.
°Virological response: HDV RNA undetectable or ≥2 log IU/ml decline *vs.* baseline.
**HBV DNA >10 IU/ml.
***HBV RNA >10 cp/ml.(quantified by a real-time PCR-based investigation assay, Roche Diagnostics, Pleasanton, Ca, USA, LLOQ 10 cp/ml.

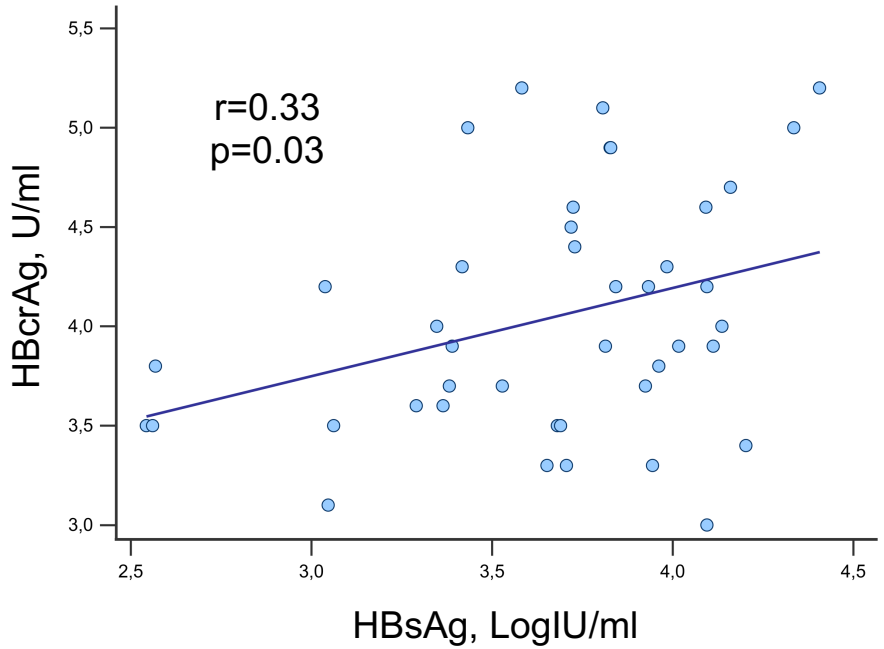
At baseline, 94% of the patients had positive HBcrAg (>3 logs) and 99% had negative HBV RNA (<10 cp/ml)
During BLV monotherapy, this pattern did not change

Degasperi E. et al, J Hepatol 2023

Kinetics of Hepatitis B Core related Antigen in Patients with Compensated HDV Cirrhosis Treated with Bulevirtide Monotherapy

Single-Center, longitudinal, real-life study
49 patients with HDV-related cirrhosis and CSPH treated with BLV 2 mg monotherapy up to 72 weeks

Variables	Overall (n=49)
Age, years	52 (29-77)
Males	29 (59%)
Caucasians	45 (92%)
HDV genotype 1	48 (99%)
CPT score A	49 (100%)
Esophageal varices	28 (57%)
Spleen diameter, cm	15 (9-25)
LSM, kPa	17.3 (6.4-68.1)
AST, U/l	89 (33-738)
ALT, U/l	97 (30-1,074)
Bilirubin, mg/dl	1.0 (0.4-4.4)
Albumin, mg/dL	3.9 (2.9-4.6)
qHBsAg, LogIU/ml	3.7 (0.8-4.4)
HDV RNA, LogIU/ml	5.2 (2.4-6.9)
HBcrAg, U/ml	**4.1 (3.0-5.2)**
HBcrAg detectable	**42 (86%)**



Variables	Baseline	Week 24	Week 48	Week 72	p value
HBcrAg detectable	86%	81%	88%	71%	0.21
HBcrAg, U/ml	**4.1 (3.0-5.2)**	**3.9 (3.1-5.4)**	**3.9 (3.1-4.9)**	**3.9 (3.1-4.7)**	**0.03**
HBsAg, LogIU/ml	3.7 (0.8-4.4)	3.8 (0.4-4.4)	3.7 (2.5-4.3)	3.6 (2.5-4.3)	0.77

Degasperi E, et al. EASL 2023 SAT-199 poster

HBV RNAs and HBcrAg in HDV - Summary

- Overall, limited data on new HBV markers (HBcrAg and HBV RNA) in CHD patients
- Most untreated CHD patients are HBcrAg positive but HBV RNA negative. This is a unique and very specific pattern for HDV (vs HBV). The underlying molecular mechanisms are not fully clarified.
- In pegIFN-treated pts, high HBcrAg levels at baseline/on-therapy may serve as a futility rule. No data on HBV RNA
- In BLV-treated patients, HBcrAg levels decline slowly overtime (relevant ?). Few HBV RNA data (but 90% patients are already negative at baseline)
- These new HBV biomarkers may play a role in the diagnosis, prognosis and monitoring of CHD patients, but new studies are needed

Thank You for Your Attention!

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