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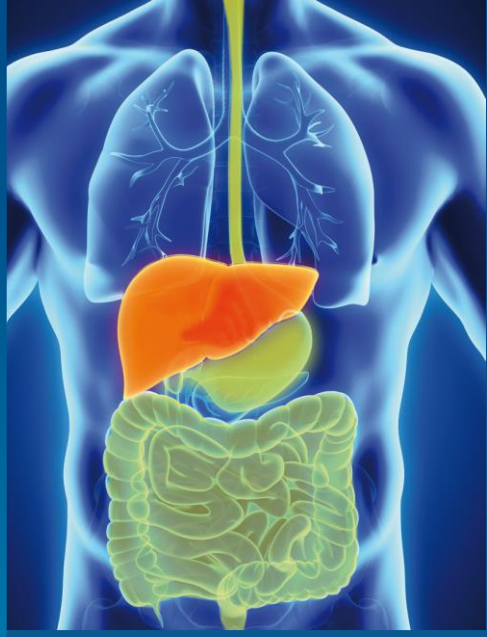


Hepatitis D Therapie

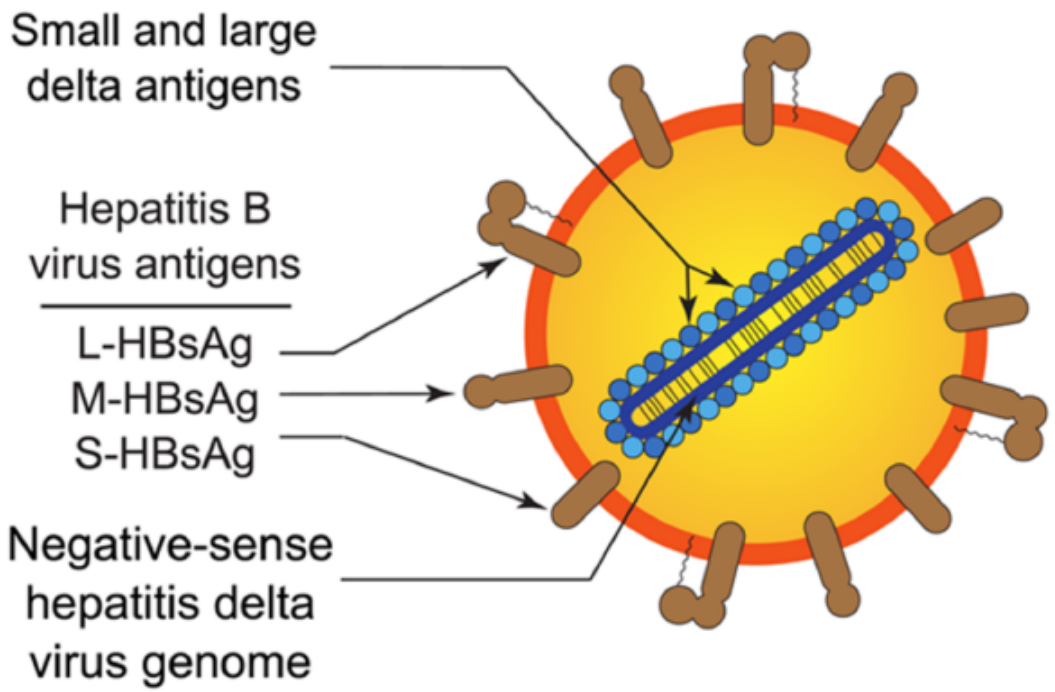
Andreas Kremer

Klinik für Gastroenterologie und Hepatologie

UniversitätsSpital Zürich

Wieterbildungsnetzwerk Gastroenterologie 2025, Zürich – 04. Juli 2025

Hepatitis D Virusinfektion (HDV)
- Klinische Aspekte -



- Envelope provided by the HBV (other pseudotypes are possible, and infectious, in the woodchuck, the woolly monkey and the bat)
- All three HBsAg isoforms are present
- The inner RNP contains ~70 molecules of two HDAg isoforms (Small and Large) and one RNA genome
- HDV RNA genome is (-) polarity, single-stranded, covalently closed circular, 1672-1697 nt, collapsed in a rod-like structure due to extensive internal base-pairing (*similar to Avsunviroids*)

Roughly 13 million people are estimated to have been exposed to HDV worldwide

Magnius L, et al. J Gen Virol 2018;99:1565-6; Sureau C and Negro F. J Hepatol 2016;64:S102-S116; Stockdale AJ, et al. J Hepatol 2020;73:523–32;

Hepatitis D Virusinfektion
- Leitlinien -

Clinical Practice Guidelin

EASL Clinic

European Association for the

Summary

Hepatitis D virus (HDV) is a c
humans. HDV is responsible
infection can cause acute li
associated with rapid and fr
patocellular carcinoma. Maj
specific Clinical Practice Gu
appropriate clinical and thera

1913 DGVS
Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten

Addendum „Antivirale Therapie der chronischen Hepatitis-D-Virusinfektion“ zur S3-Leitlinie „Prophylaxe, Diagnostik und Therapie der Hepatitis-B-Virusinfektion“ der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)[1]

Juli 2023 – AWMF-Registernummer: 021-11

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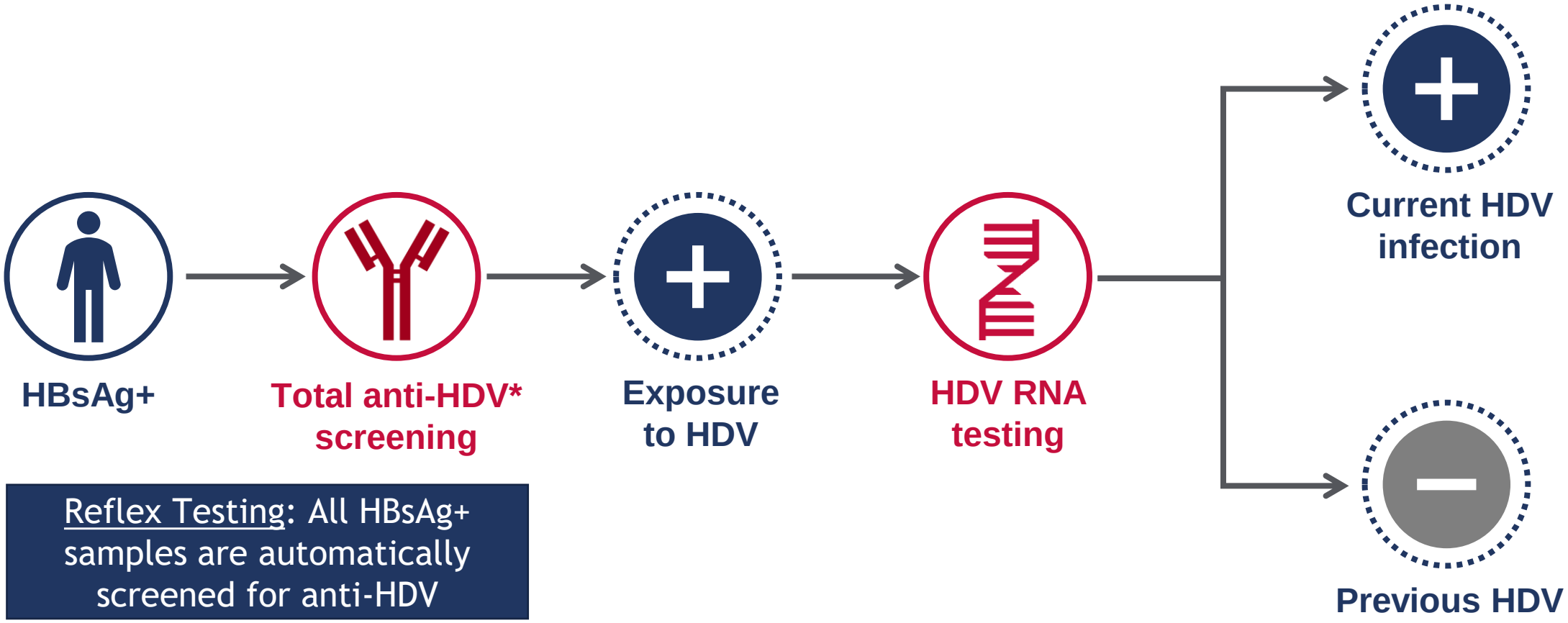
Lisa Sandmann[1,9], Thomas Berg[2], Katja Deterding[1], Nadine Fischer[3], Holger Hinrichsen[4], Jörg Petersen[5], Frank Tacke[6], Markus Cornberg[1,7,8,9]

Brunett MR et al., J Hepatol 2023; 79: 433-460 – EASL HDV Clinical Practice Guidelines; Sandann L et al., Z Gastroenterol 2023; 61: 1635-1653.

Diagnose der Hepatitis D Virusinfektion



*Total anti-HDV includes both IgM and IgG.
HBsAg: hepatitis B surface antigen

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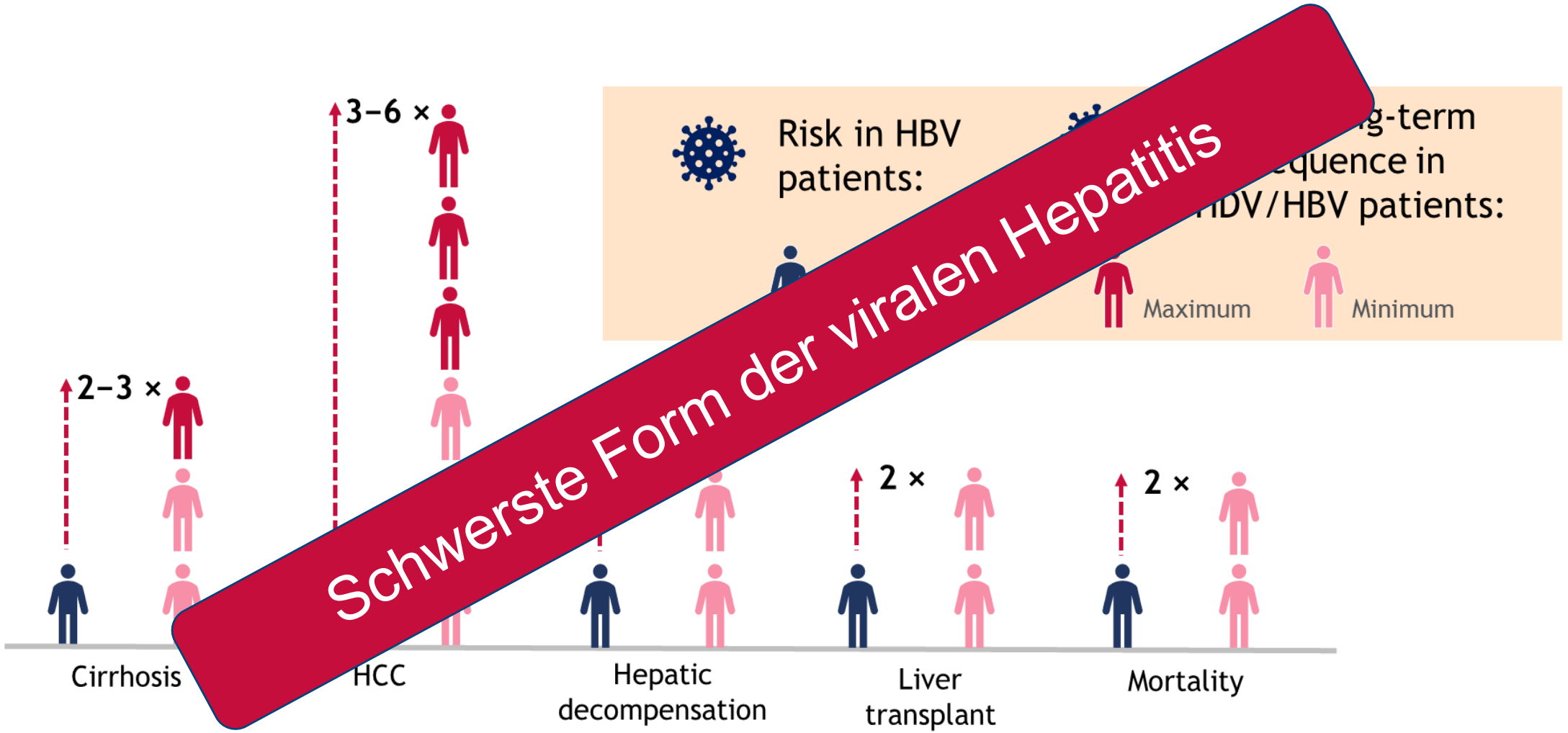
Rizzetto M, et al. J Hepatol 2021;74:1200–11; Terrault NA, Ghany MG. Dig Dis Sci 2021;66:2483–2485

Deutlich erhöhtes Risiko bei HBV-HDV-Coinfektion



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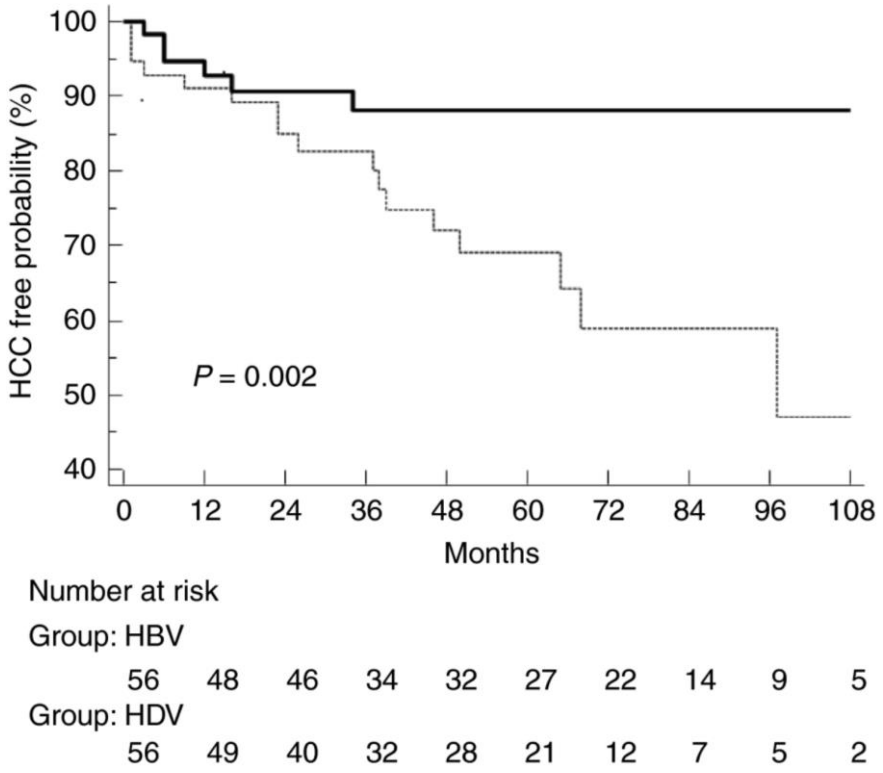
Da BL, et al. Gastroenterol Rep 2019;7:231; Chen VL, et al. Clin Gastroenterol Hepatol 2016;14:887.

Risk of liver-related events and mortality in HDV+ persons with advanced fibrosis ***persists*** despite NUC treatment

(N=112; median FU 50 months; matched 1:1 for age, gender, platelets, albumin, INR, bilirubin)

	Number of events	HDV cases/1000 patient-months	HBV cases/1000 patient-months	P-value*
Death/LT	19	2.92	0.38	0.001
- Death	8	1.06	0.10	0.03
- LT	11	3.44	0.78	0.016
Decompensation	13	1.53	0.13	0.015
HCC	23	3.12	1.12	0.02

*By log rank test



Annual HCC rate: 7.5% (HDV) vs. 2.5% (HBV) (P= 0.01)

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Brancaccio G. et al. Aliment Pharmacol Ther 2019; 49: 1071-6

NUC therapy in HDV Co-infected patients
- EASL GCP 2023 Recommendation -

Recommendations

- NAs should be given in patients with decompensated cirrhosis irrespective of the presence of detectable HBV DNA **(LoE 5, strong recommendation, strong consensus).**
- NAs should be given in patients with compensated cirrhosis and detectable HBV DNA **(LoE 5, strong recommendation, strong consensus).**
- NAs should be given in patients without cirrhosis if HBV DNA levels are higher than 2,000 IU/ml **(LoE 5, strong recommendation, strong consensus).**

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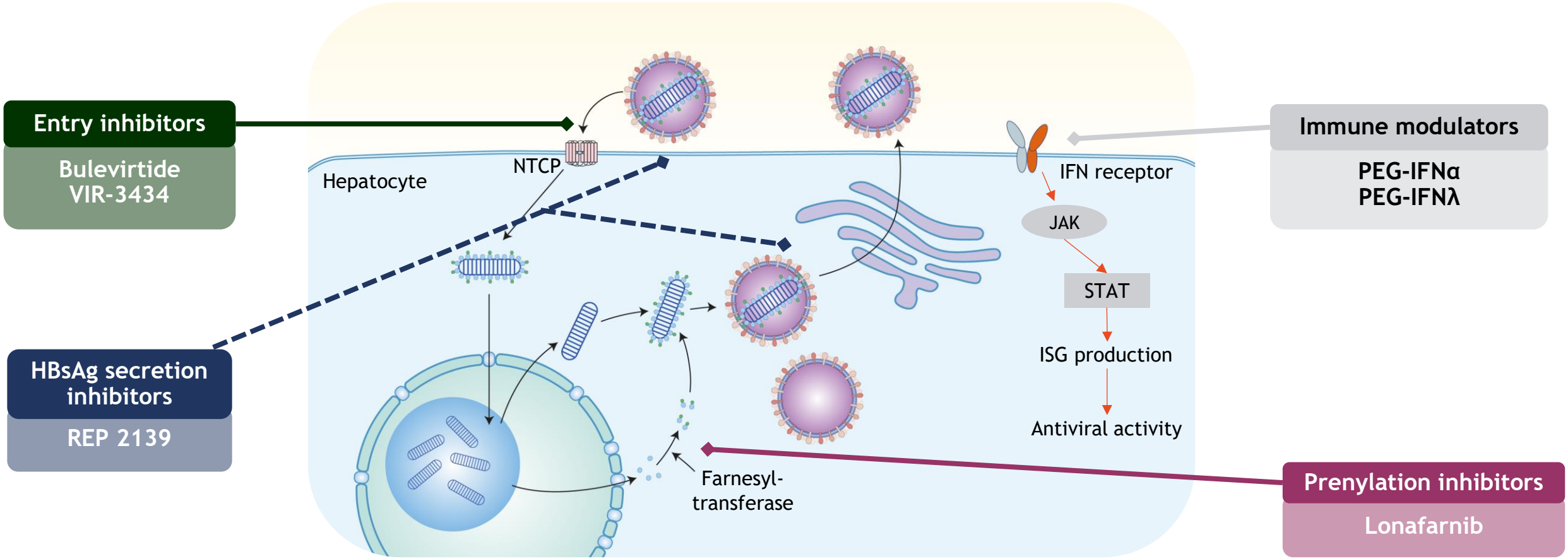
Brunetta RM et al., EASL GCP Hepatiits D, J Hep 2023; 79:433-460

Therapeutische Ziele im HDV Replikationszyklus



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Gilman C, et al. World J Gastroenterol 2019;25:4580; Bazinet M, et al. Lancet Gastroenterol Hepatol 2017;2:877; Park A, Iwasaki A. Cell Host Microbe 2020;27:870

Therapeutic Options in HDV Co-infected patients
- DGVS GCP 2023 Recommendation -

Statement 2.1.1. **neu 2023**

Aktuell sind zwei Therapieoptionen verfügbar, bei denen eine antivirale Wirksamkeit gegen HDV in randomisiert-kontrollierten klinischen Studien nachwiesen wurde:

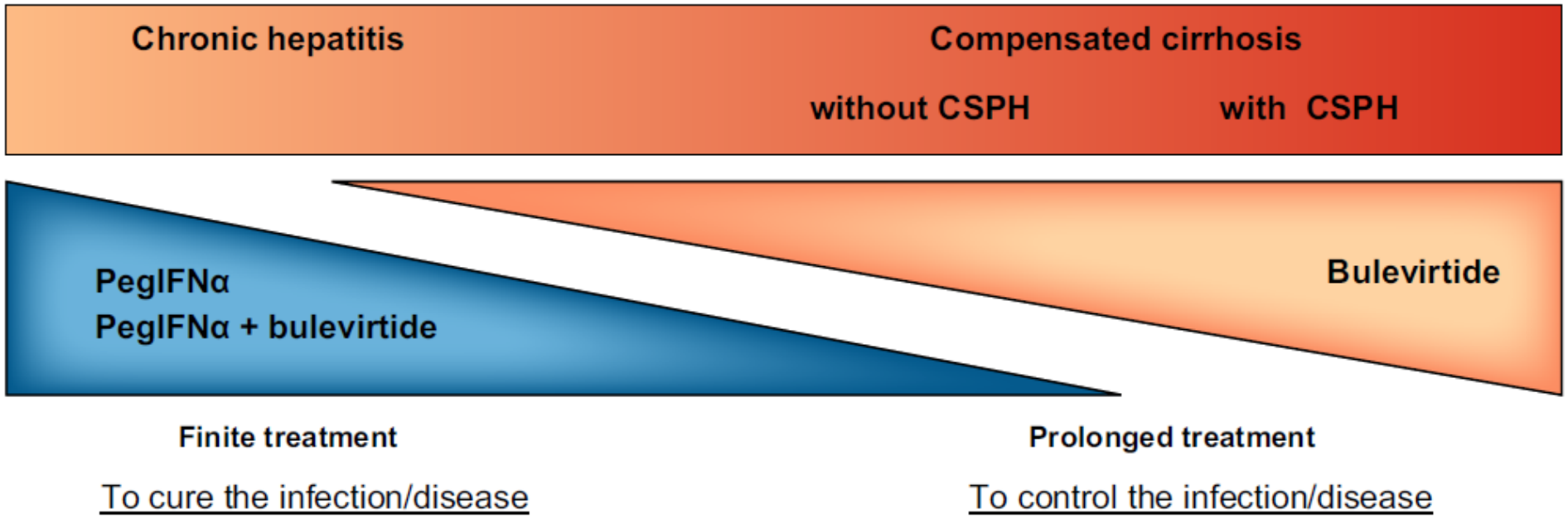
1. Bulevirtid
2. Pegyliertes Interferon alfa (PEG-IFN).

[Evidenzlevel 2, starker Konsens]

Literatur: Evidenztabelle 1, 4, 5

Brunetta RM et al., EASL GCP Hepatiits D, J Hep 2023; 79:433-460

Treatment of Hepatitis D: IFN-α and beyond



Additional factors influencing the treatment schedule

- Phase of HBV infection (HBeAg/anti-HBe status; HBV DNA and HBsAg levels)
- IFNα contraindication, tolerability
- Patient's will and compliance to treatment

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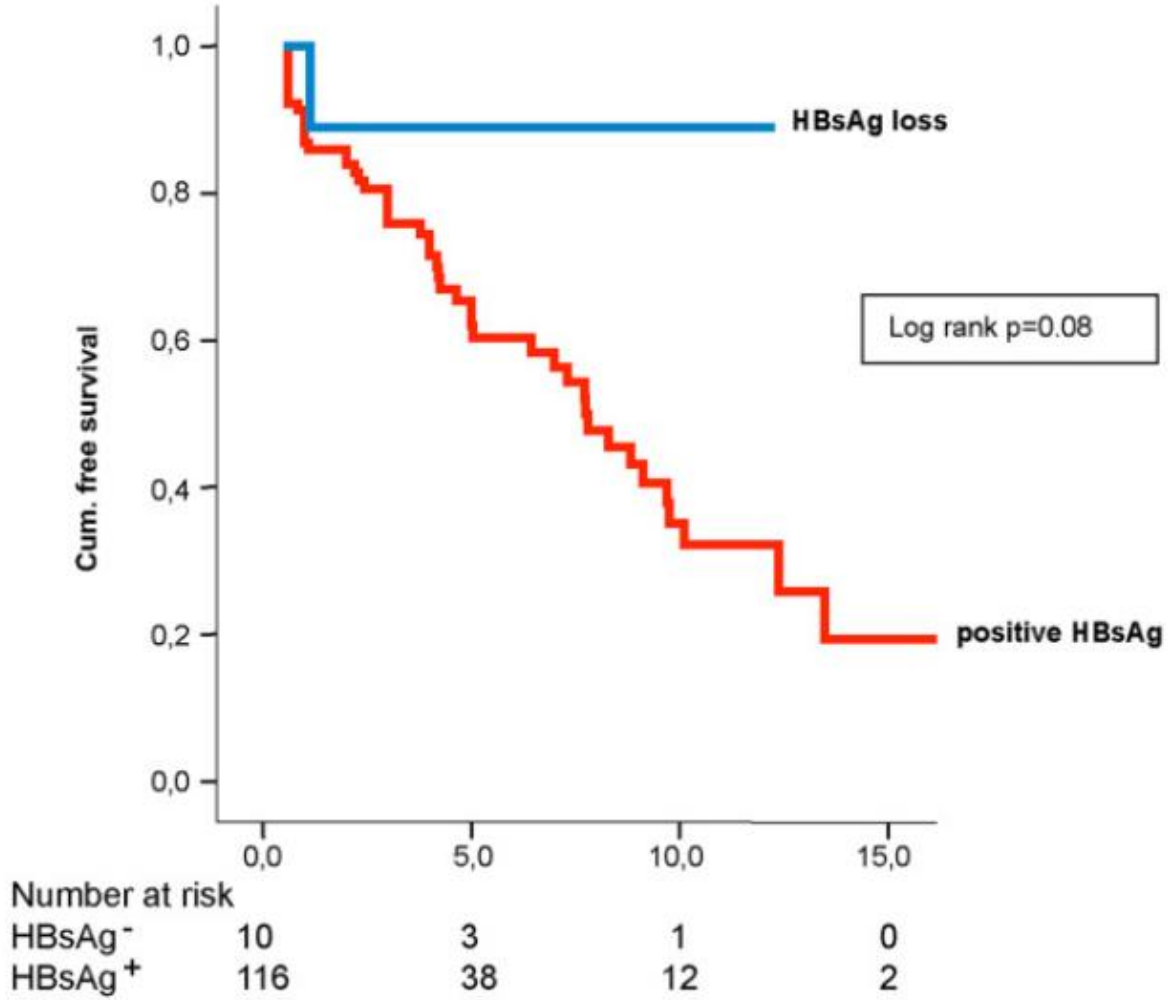
Wranke A, et al. Hepatology 2017; 65:414-425

Impact of HBsAg loss in chronic HDV treated with IFNα



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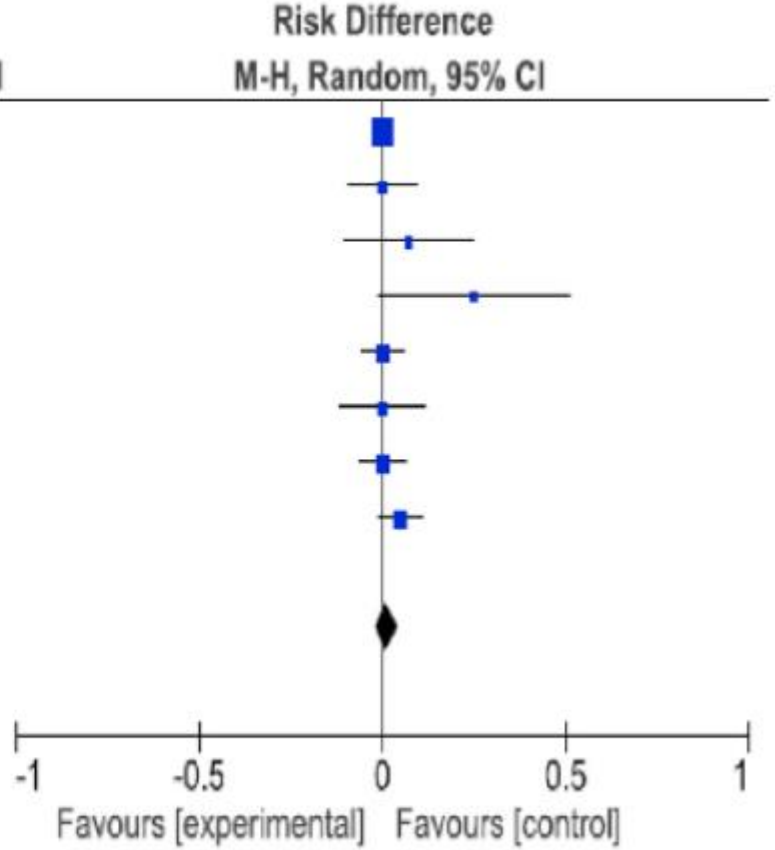
Wranke A, et al. Hepatology 2017; 65:414-425

HBsAg/anti-HBs seroconversion after PEG-IFNα of HDV
- Meta-Analysis (13 studies, N=475) -

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Abbas 2014	0	96	0	96	33.6%	0.00 [-0.02, 0.02]
Abbas 2016	0	19	0	19	8.4%	0.00 [-0.10, 0.10]
Castelnau 2006	1	14	0	14	3.0%	0.07 [-0.11, 0.25]
Heller 2014	3	12	0	12	1.4%	0.25 [-0.01, 0.51]
Karaca 2013	0	32	0	32	16.6%	0.00 [-0.06, 0.06]
Niro 2006	0	16	0	16	6.5%	0.00 [-0.11, 0.11]
Wedemeyer 2011	0	29	0	29	14.8%	0.00 [-0.06, 0.06]
Wedemeyer 2019	3	61	0	61	15.7%	0.05 [-0.01, 0.11]
Total (95% CI)		**279**		**279**	**100.0%**	**0.01 [-0.02, 0.05]**
Total events	7		0			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.34$, df = 7 (P = 0.12); $I^2 = 38\%$

Test for overall effect: Z = 0.83 (P = 0.41)



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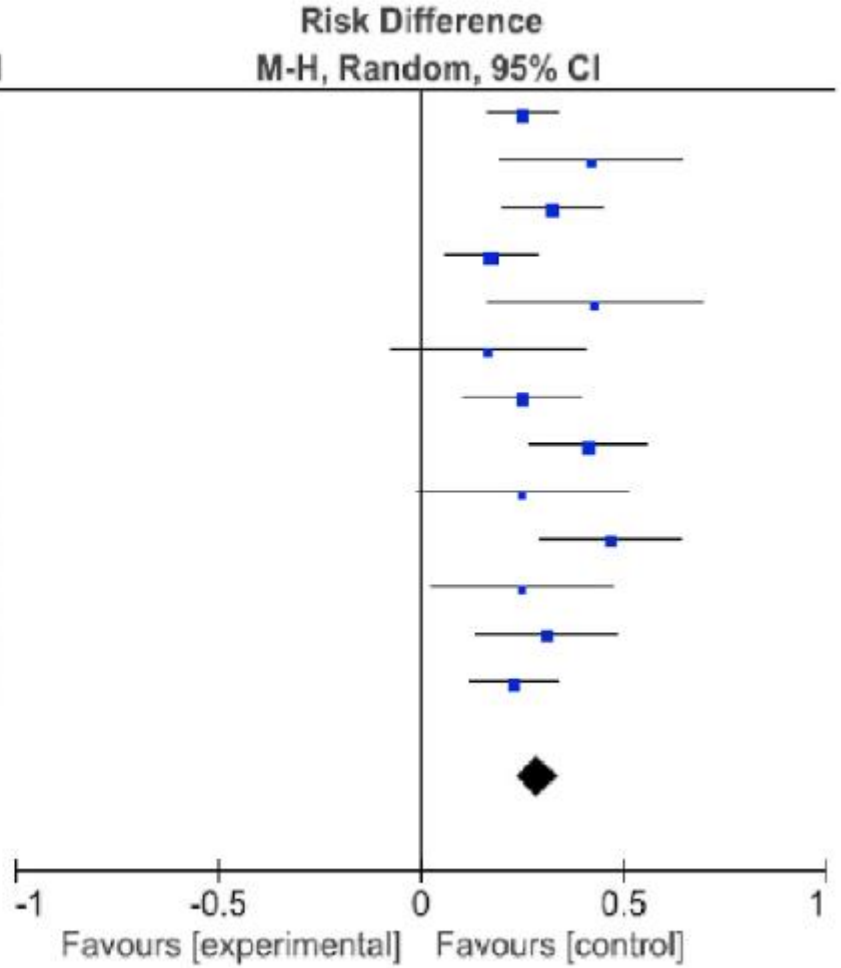
ABRADKHMAN A, et al. Antiviral Res 2021;185:104995

HDV clearance 6 months after stop of PEG-IFNα of HDV
- Meta-Analysis (13 studies, N=475) -

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Abbas 2014	24	96	0	96	15.3%	0.25 [0.16, 0.34]
Abbas 2016	8	19	0	19	4.3%	0.42 [0.19, 0.65]
Bahcecioglu 2015	18	56	0	56	10.6%	0.32 [0.20, 0.45]
Boglione 2019	8	46	0	46	11.7%	0.17 [0.06, 0.29]
Castelnau 2006	6	14	0	14	3.3%	0.43 [0.16, 0.70]
Erhardt 2006	2	12	0	12	4.0%	0.17 [-0.07, 0.41]
Gheorghe 2011	9	36	0	36	8.6%	0.25 [0.10, 0.40]
Gulsun 2011	19	46	0	46	8.7%	0.41 [0.27, 0.56]
Heller 2014	3	12	0	12	3.4%	0.25 [-0.01, 0.51]
Karaca 2013	15	32	0	32	6.5%	0.47 [0.29, 0.64]
Niro 2006	4	16	0	16	4.4%	0.25 [0.03, 0.47]
Wedemeyer 2011	9	29	0	29	6.7%	0.31 [0.14, 0.48]
Wedemeyer 2019	14	61	0	61	12.5%	0.23 [0.12, 0.34]
Total (95% CI)		**475**		**475**	**100.0%**	**0.29 [0.24, 0.34]**
Total events	139		0			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 17.09$, df = 12 (P = 0.15); $I^2 = 30\%$

Test for overall effect: Z = 11.02 (P < 0.00001)



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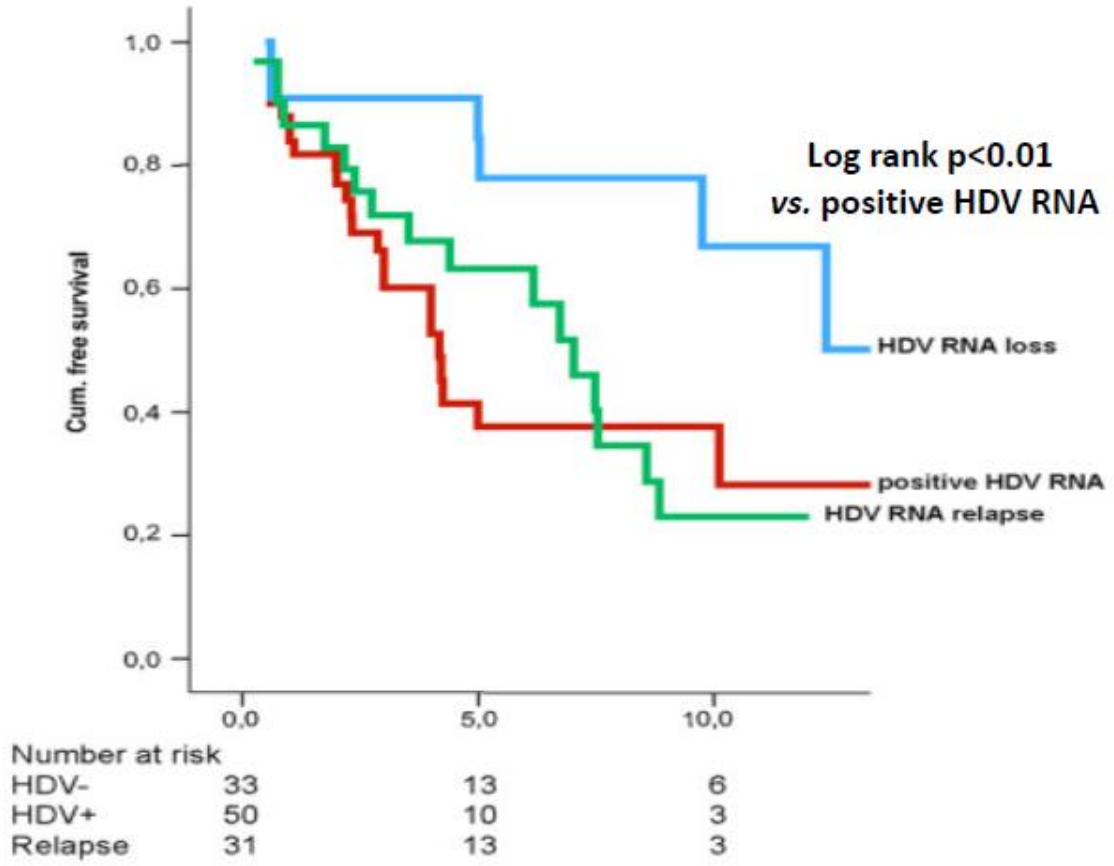
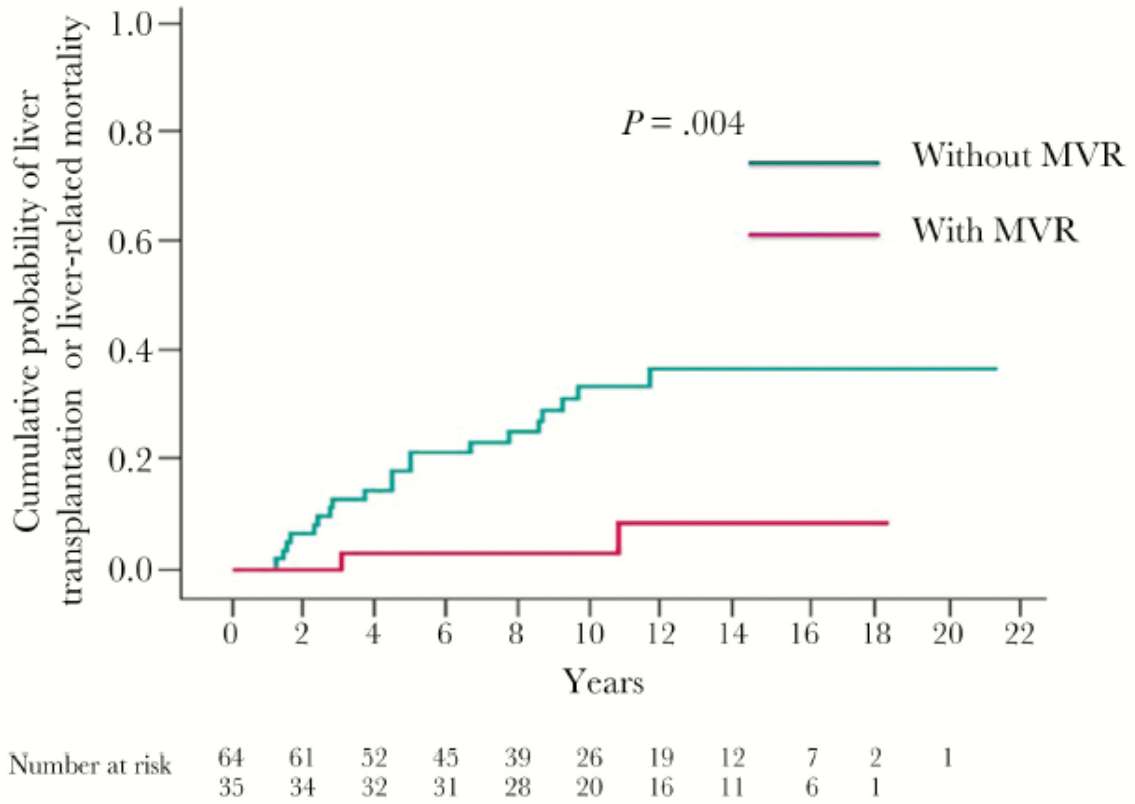
ABRADKHMAN A, et al. Antiviral Res 2021;185:104995

IFNα induced HDV clearance associated with improve survival





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Wranke A, et al. Hepatology 2017; 65:414-425

Yurdaydin C, et al. J Infect Dis 2018; 217:1184-1192

Therapy Strategies in HDV Co-infected patients
- EASL GCP 2023 Recommendation -

STRATEGIES	DURATION OF THERAPY	ENDPOINT	TIMING OF ENDPOINT
Short-term (finite) therapy	≤48 weeks	**Preferred:** HBsAg loss + HDV RNA <LLoQ **Alternate:** HDV RNA <LLoQ	Off-therapy (24 weeks)

1

1. There should be a commitment to long-term follow-up (minimum 5 y) to assess the durability of this endpoint

2. The optimal duration of maintenance therapy is currently unknown

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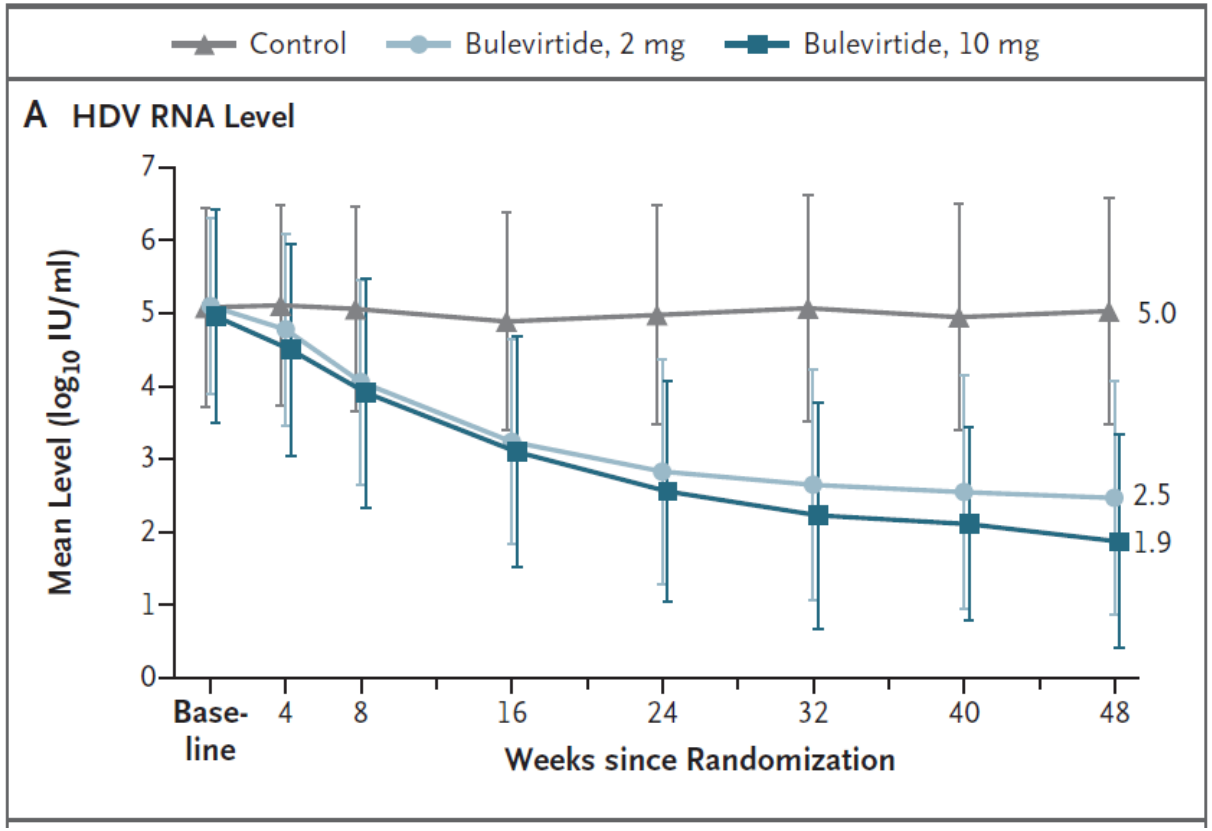
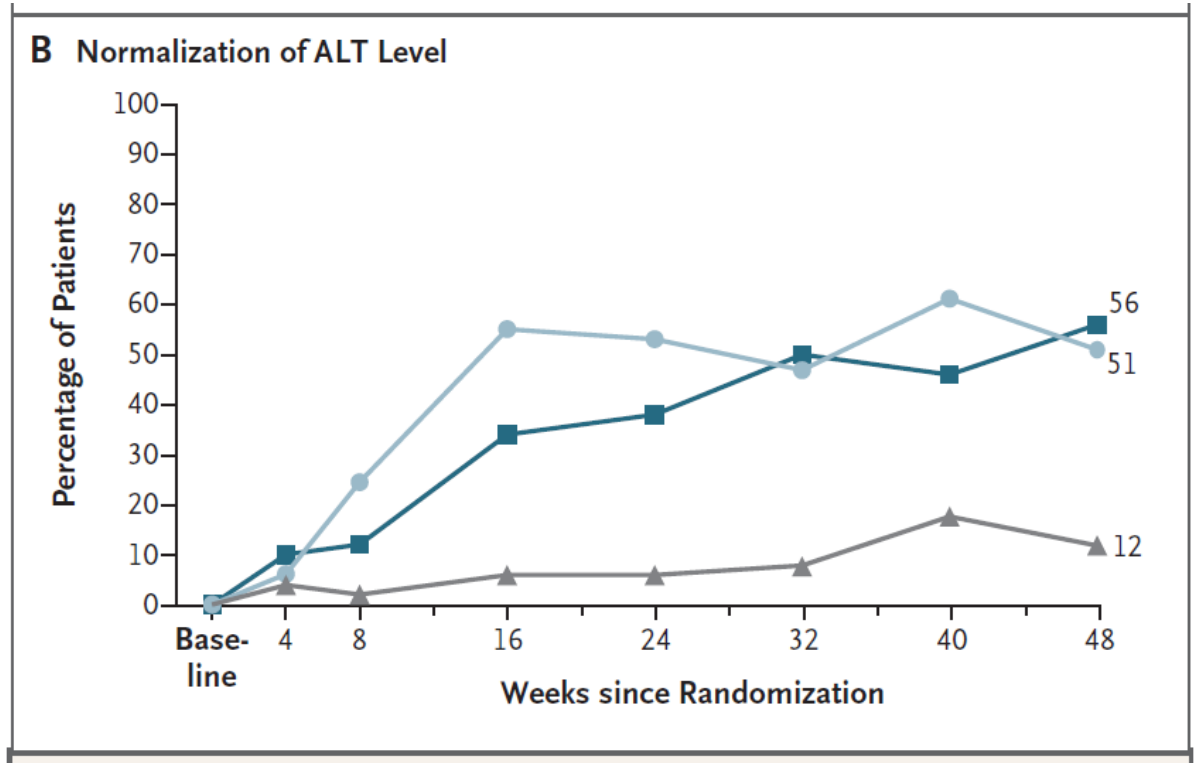
Brunetta RM et al., EASL GCP Hepatiits D, J Hep 2023; 79:433-460

Bulevirtid Monotherapie – Ansprechen nach 48 Wochen





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Wedemeyer H et al., NEJM 2023; 389: 22.

Bulevirtid (HEPCLUDEX) – Swiss Medic Approval

Indication

- Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in adults with compensated liver disease.

Dosage/Administration

- Therapy should be initiated by a physician experienced in the management of patients with HDV infection.
- The recommended dosage in adults is Hepcludex 2 mg once daily corresponding to a delivered dose of 1.7 mg administered by subcutaneous injection.
- In all patients, manage the underlying hepatitis B virus (HBV) infection simultaneously as clinically appropriate according to the official guidelines.

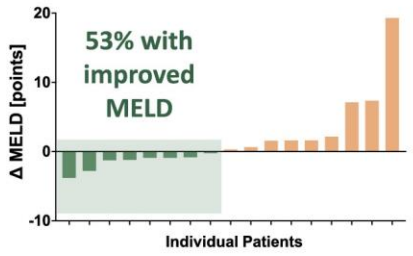
Duration

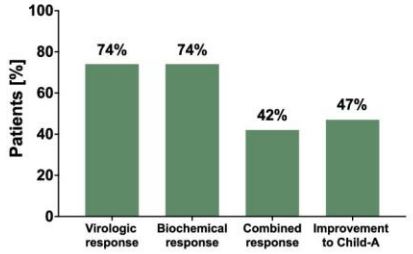
- Optimal treatment duration is unknown.
- Treatment should be continued as long as associated with clinical benefit

HDV Therapie bei Dekompensation

Safety and efficacy of off-label bulevirtide monotherapy in HDV patients with decompensated Child-B cirrhosis

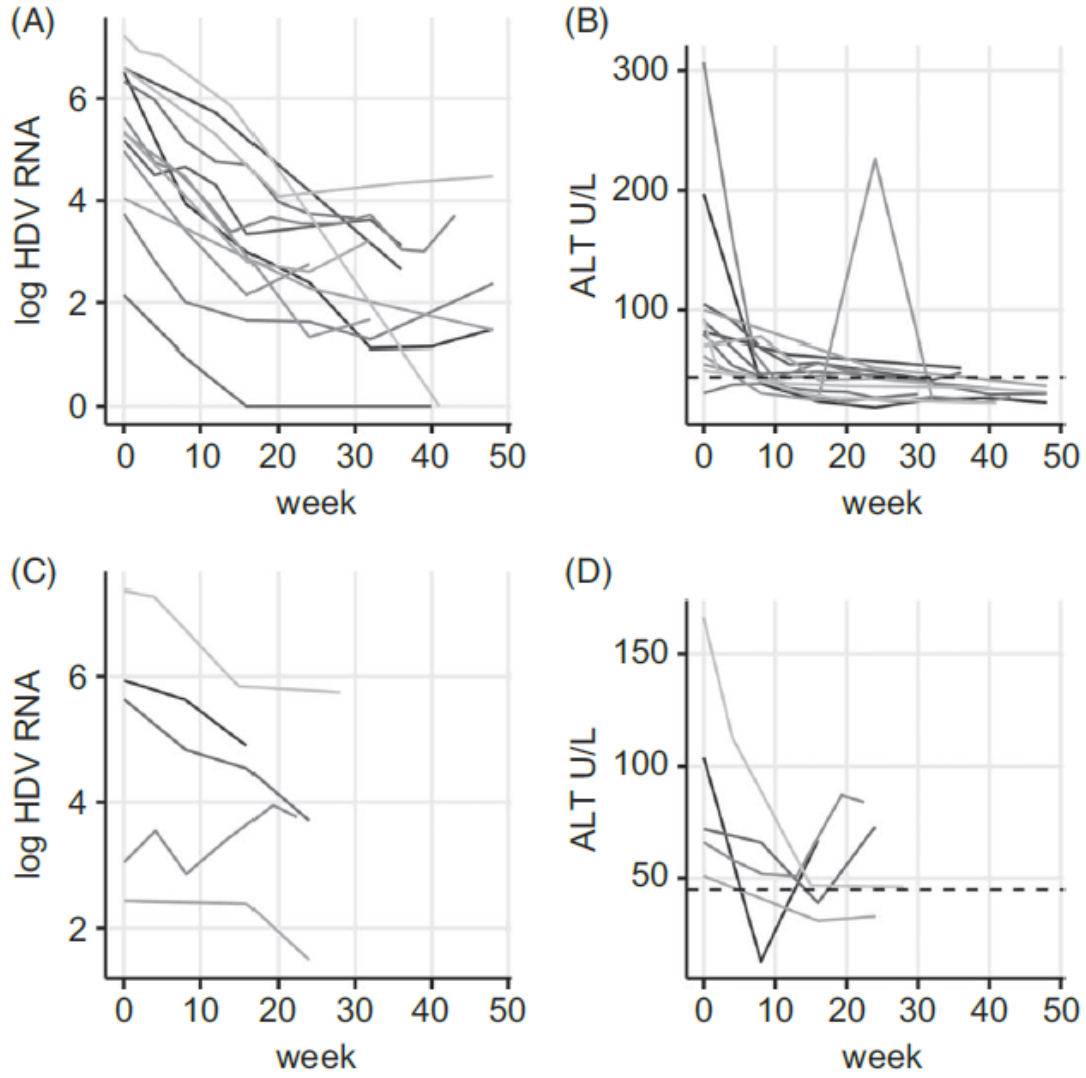
- Retrospective study including 19 European patients with decompensated HDV cirrhosis
- 41 (IQR: 26-75) weeks of bulevirtide treatment
- Response rates similar as reported for compensated HDV patients
- No serious bulevirtide-related AE
- Asymptomatic increases of serum bile acids
- Median MELD remained stable
- Prospective trial needed





Dietz-Fricke, et al. *Hepatology*.

HEPATOLOGY



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Dietz-Fricke C et al., Hepatology 2024; 80: 64

Take Home Message – Virushepatitis Delta

- **Jeder HBsAg+ Patient soll** einmalig auf **anti-HDV-AK getestet** werden.
- Falls **anti-HDV positiv,** soll eine **HDV-PCR** durchgeführt werden.
- **Alle Patienten** mit **HBV-HDV-Coinfektion sollten** mit einem **Nukleos(t)id-Analogon** behandelt werden.
- **PEG-IFNα kann** als **Off-Label-Therapie für 48 Wochen** vor allem in **frühen Therapiestadien und Inflammation** erwogen werden.
- **Bulevirtid (Hepcludex) 2 mg/Tag** ist für die Therapie der HDV-Infektion bei kompensierter Lebererkrankung zugelassen mit **unbegrenzter Therapiedauer. Compliance** kann über Bestimmung der **Serum-Gallensäuren** beurteilt werden.
- Diese Therapie ist **sicher,** wahrscheinlich auch in fortgeschrittenen Zirrhosestadien.
- **Neue Therapieansätze** werden aktuell in Phase II und Phase III Studien untersucht.

Vielen Dank!

Backup Slides