Virushepatitis – Update - 2023

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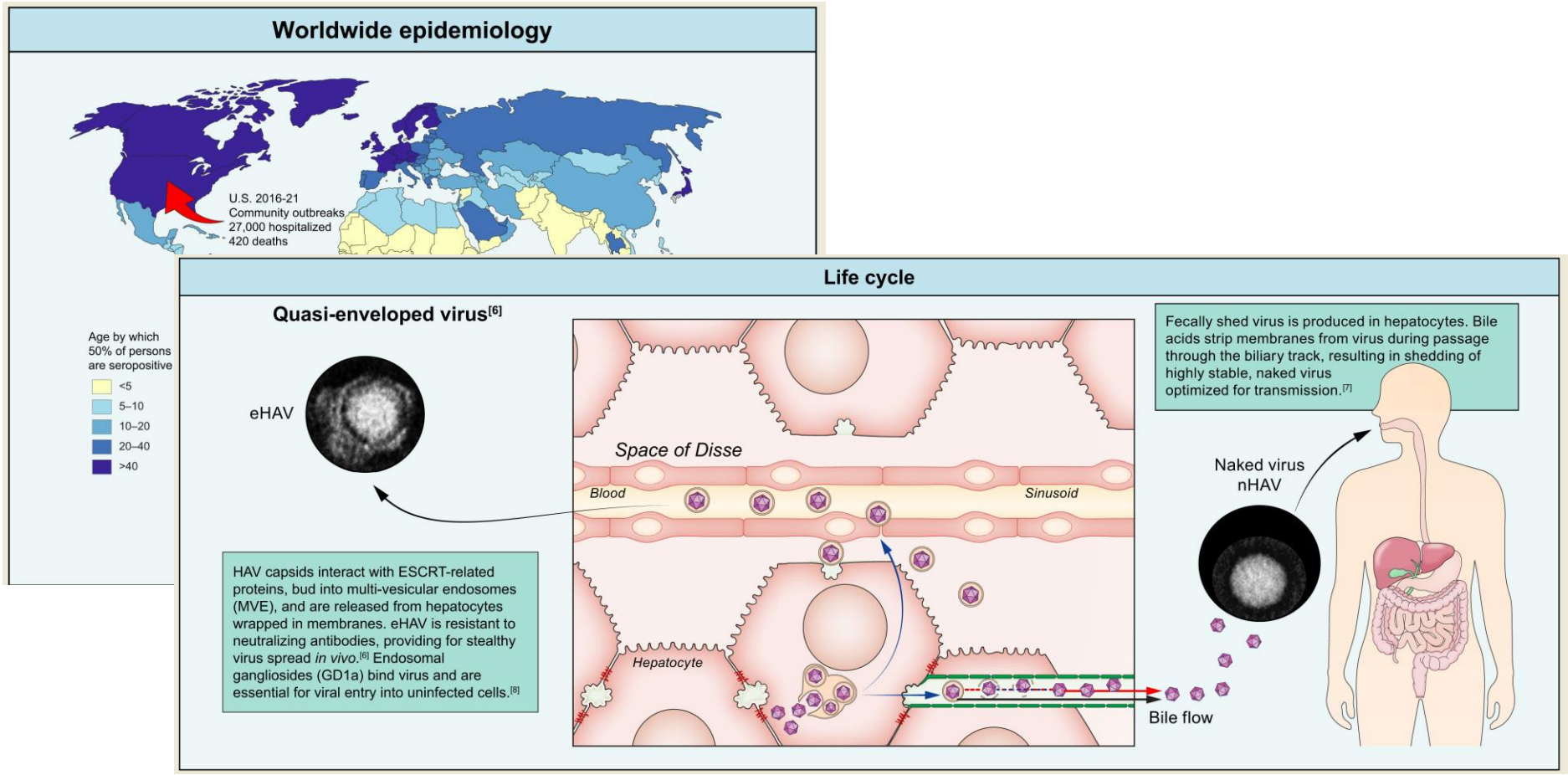
Virushepatitis A

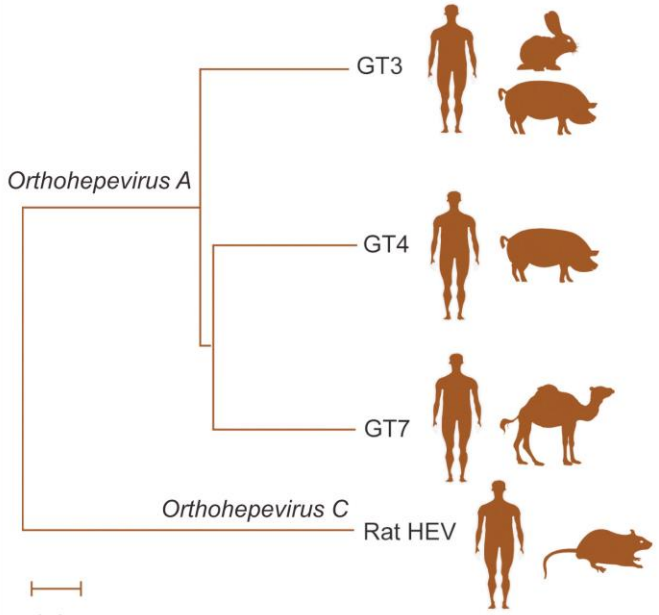


Journal of Hepatology 2022; 77: 243-244

Hepatitis A - Patientenfall

- 54 jähriger Mann (Informatiker)
- Grippale Beschwerden, Krankheitsgefühl, Durchfall, Abklärung erhöhter Leberwerte und **Ikterus**
- ALT 1.500 IU/l, AST 1.200 IU/l, Bilirubin 8 mg /dl, Quick-Wert 65%
- Anamnese: vor 2 Wochen Busreise mit Essen beim „Italiener“: **Meeresfrüchtesalat!!**
- Serologie: anti-HAV-IgG positiv und anti-HAV-IgM positiv
- **Diagnose: akute Hepatitis A**

Virushepatitis E



Genotype	Host	Country/region	Reverse genetics	*In vitro* model	Animal model
GT3		Mainly Europe	Yes	Cell lines Organoids Stem cell derived-HLCs	Humanized mice Monkeys + INS Pigs + INS Rabbits + INS
GT4		Mainly China	Yes	Not robust	Rabbits + INS
GT7		The Middle East	Yes	Not widely used	Not available
Rat HEV		Hong Kong, China	Yes	Not widely used	Athymic nude rats

Journal of Hepatology 2022 vol. - j 1–15

Hepatitis E – klinischer Verlauf

- meistens **asymptomatisch** oder als **leichte / milde selbstlimitierte Hepatitis** mit Ausheilung nach 3-6 Monaten
- Cave: **extrahepatische Manifestationen (GBS, GN, Arthralgien)**
- Bei **Immunsuppression - Z.n. Organ-Tx:** chronische Hepatitis (Leberzirrhose, HCC, usw..), Therapie mit Ribavirin wirksam
- Inzidenz bei **Blutspendern** in Europa bis zu 0,19% (Screening erforderlich!!!)

Journal of Hepatology 2016 vol. 65 j 200–212

Journal of Hepatology 2022 vol. - j 1–15

Hepatitis E – der seltene Fall

- 63 jährige Patientin, **Z.n. Nieren-Tx** wegen Zystennieren
- **Immunsuppression** (MMF, Tacrolimus, Prednisolon)

- Abklärung erhöhter Leberwerte
- Anti-HEV IgG positiv / IgM negativ

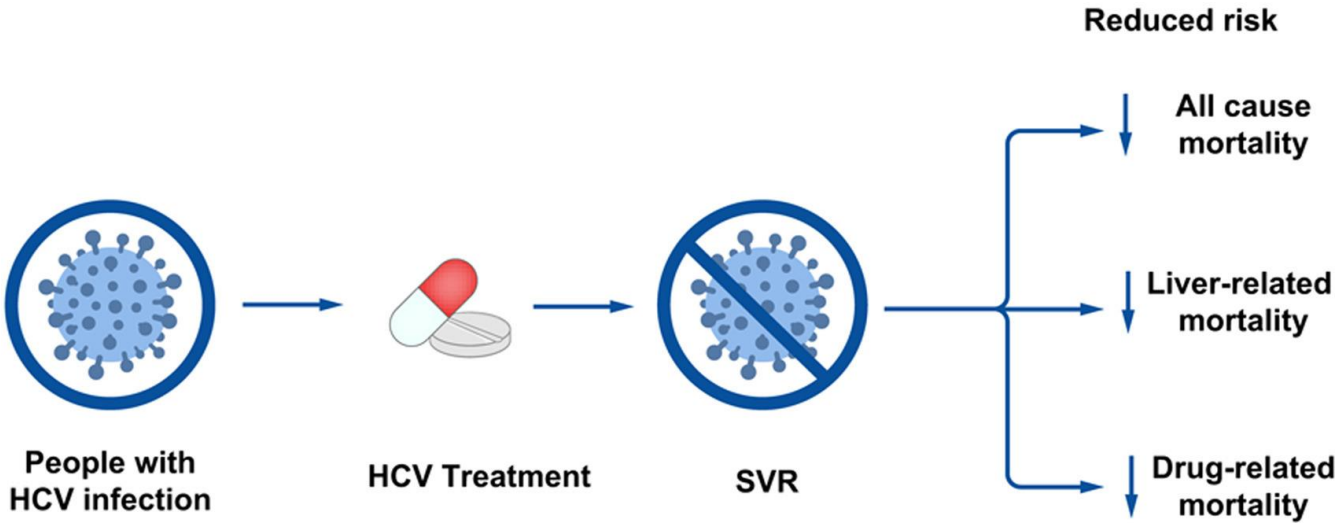
- **HEV-RNA im Serum** positiv über 6 Monate
- **Chronische Hepatitis E**

Chronische Hepatitis E – Therapie

- Reduktion der Immunsuppression so weit möglich
- **Ribavirin** für 6 Monate (Cave: GFR, Hb !!)
- 63 jährige Patientin: nach 6 Monaten Transaminasen normal, **HEV-RNA negativ**

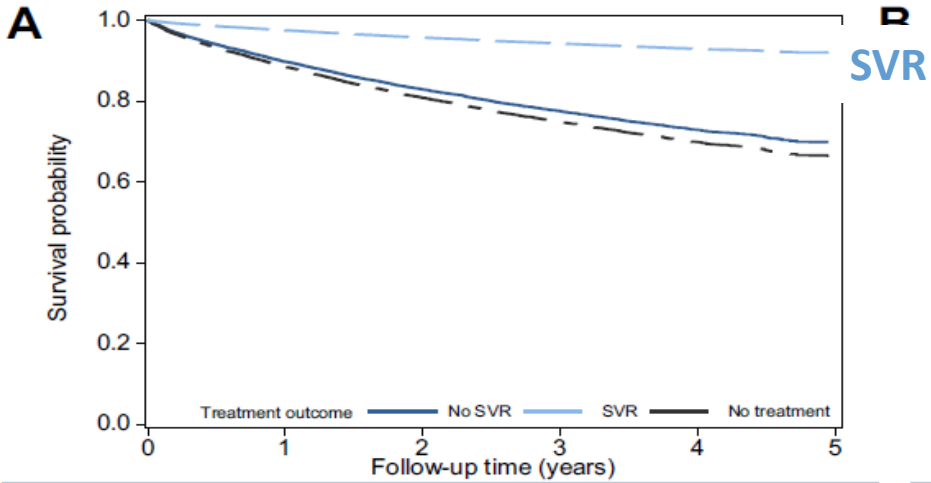
Virushepatitis C

The impact of direct acting antiviral therapies for treatment of HCV on mortality in a large population-based cohort study

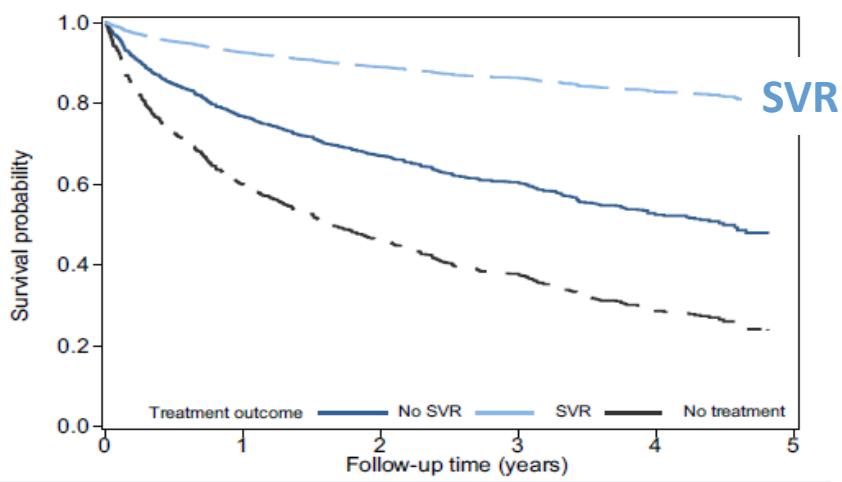


Journal of Hepatology 2021 751049-1057DOI: (10.1016/j.jhep.2021.05.028)

Höhere Überlebensraten nach SVR



N° at risk						
SVR	10,426	9,189	6,372	4,207	2,326	343
No SVR	425	322	198	117	66	12
No treatment	10,851	8,366	5,229	3,082	1,497	98

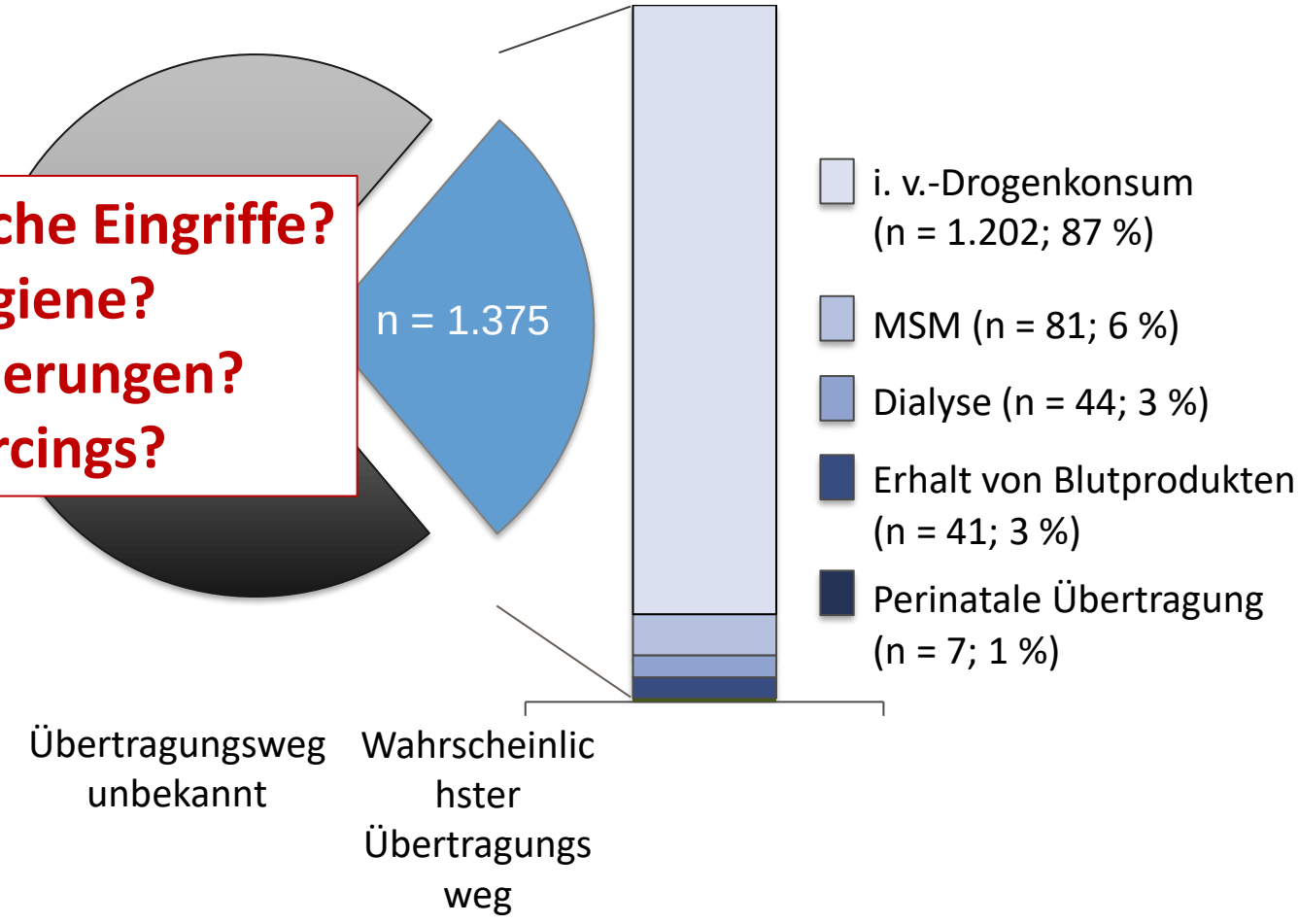


N° at risk						
SVR	888	846	715	587	403	65
No SVR	59	50	34	26	15	3
No treatment	579	290	172	98	45	4

Journal of Hepatology 2021 751049-1057DOI: (10.1016/j.jhep.2021.05.028)

HCV-Übertragungswege

Medizinische Eingriffe?
Hygiene?
Tätowierungen?
Piercings?



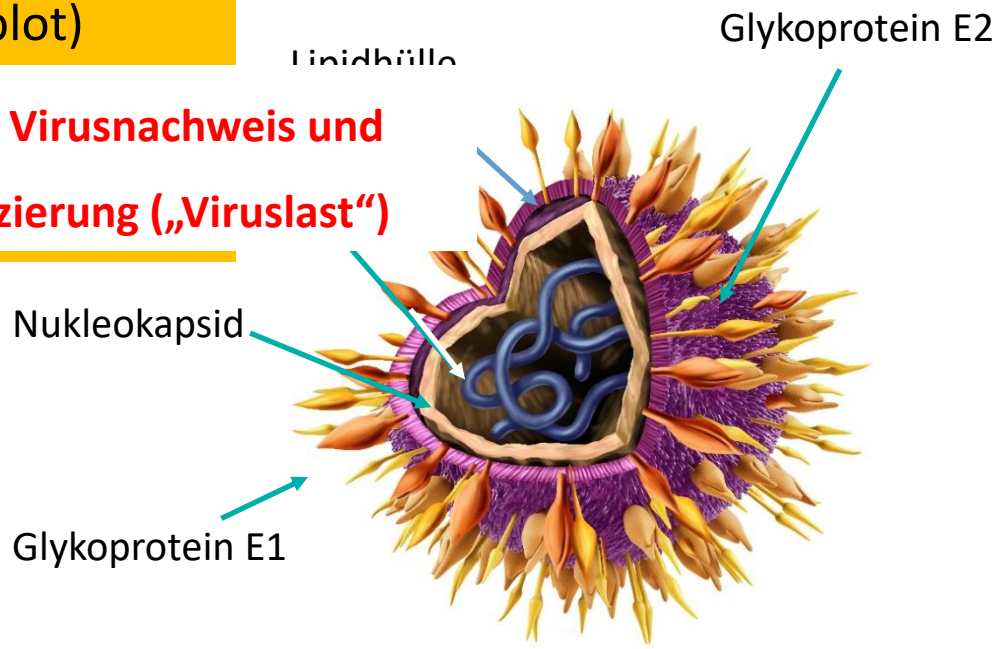
Robert Koch Institut (RKI). Epidemiologisches Bulletin, Nr. 30, Juli 2013.

HCV-Diagnostik

- Anti-HCV-AK Suchtest (ELISA) → **Neu in der Ü-35**
- Anti-HCV-AK Bestätigungstest (Immunoblot)

- HCVcore-Ag (ELISA oder Immunoblot)
- **HCV-RNA (PCR)**
- **HCV-Genotyp (PCR)**

Direkter Virusnachweis und Quantifizierung („Viruslast“)



62 jährige Patientin

„Ein erstaunlicher Fall!“

- Seit über 10 Jahren erhöhte Leberwerte: ALT 140 U/l, AST 85, gGT 90 U/l
- Sonographie: fortgeschrittene Fibrose/beginnende Leberzirrhose

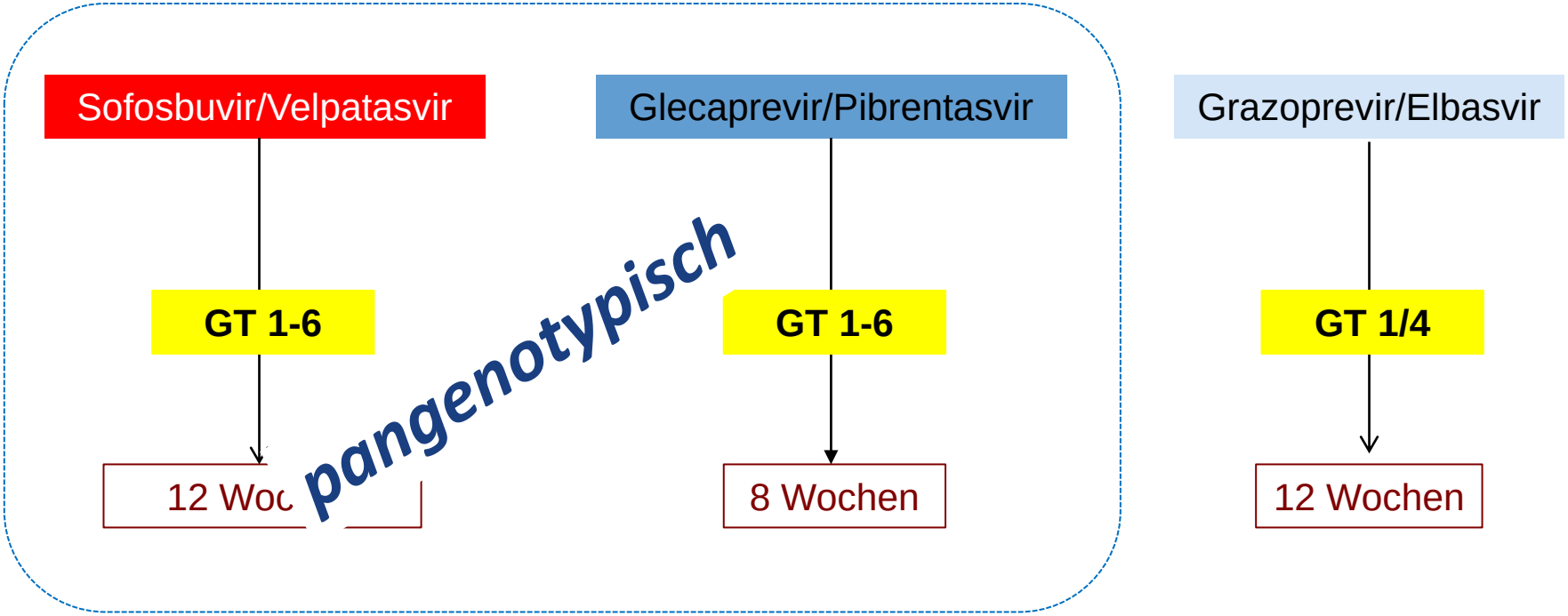
- Anamnese: Z.n. Sectio mit Blutverlust/Blutübertragung in Russland

- ED chronische Hepatitis C im Mai 2021
- Antivirale Therapie (DAA-Therapie für 3 Monate)

- Ausheilung der Virushepatitis C
- Leberwerte wieder normal

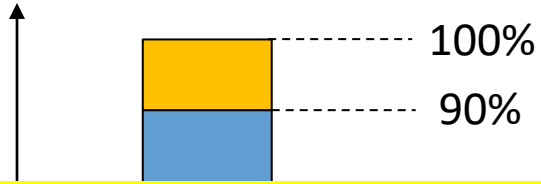
Wie behandeln wir aktuell die Hepatitis C?

Aktuelle DAA-Therapie



Sarrazin C et al. Z Gastroenterol 2020; 58: 1110–1131

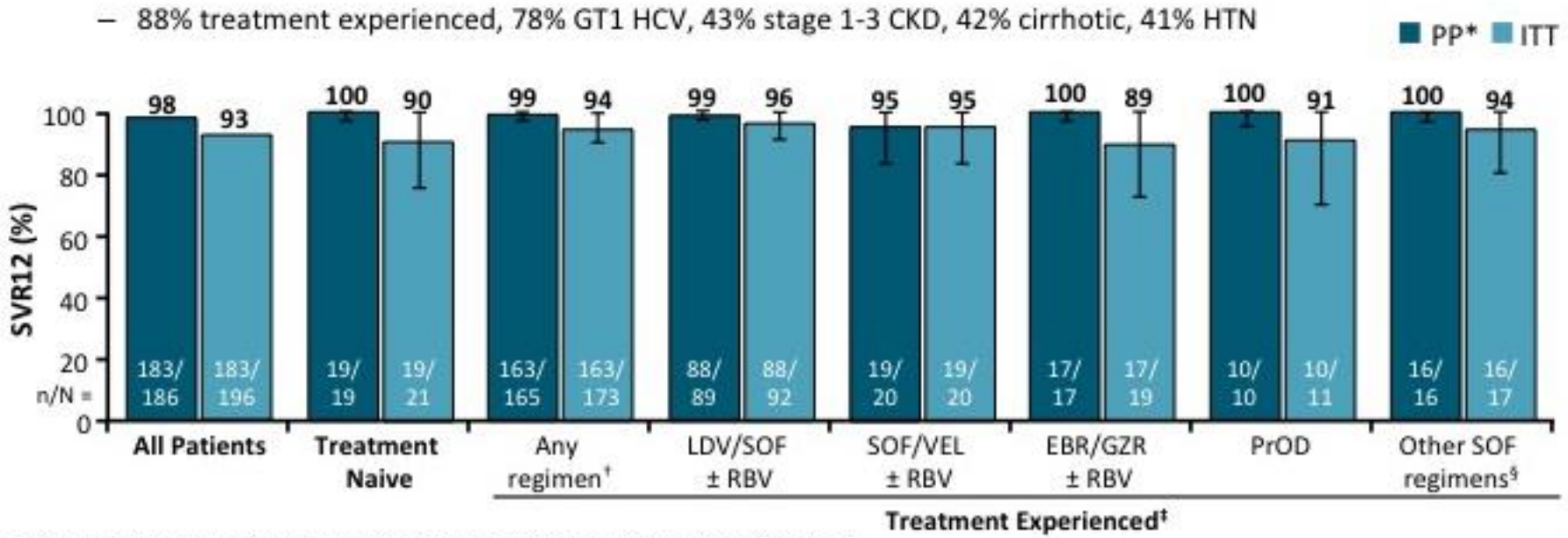
Ergebnisse der neuen HCV Therapie



- 90-100% Heilungsrate bei allen Genotypen
- 8 – 12 Wochen Therapie
- Sehr gute Verträglichkeit
- Auch bei schwierigen Patienten: Zirrhose, Ko-Infektionen, Dialysepatienten, LTx Patienten, usw….

“Registerdaten” verschiedener Zentren in den USA

- Real-world data from providers and specialty pharmacies in the TRIO Health disease management program on SOF/VEL/VOX for 12 wks initiated between July 2017 and April 2018 (N = 196)
  - 88% treatment experienced, 78% GT1 HCV, 43% stage 1-3 CKD, 42% cirrhotic, 41% HTN



*Primary endpoint. †One patient with prior GLE/PIB achieved SVR. ‡Regimens prior to SOF/VEL/VOX.
§Includes DCV + SOF (n = 10), SOF + RBV (n = 6), PegIFN + SOF + RBV (n = 1).
Bacon. EASL 2019. Abstr THU-116. Reproduced with permission.

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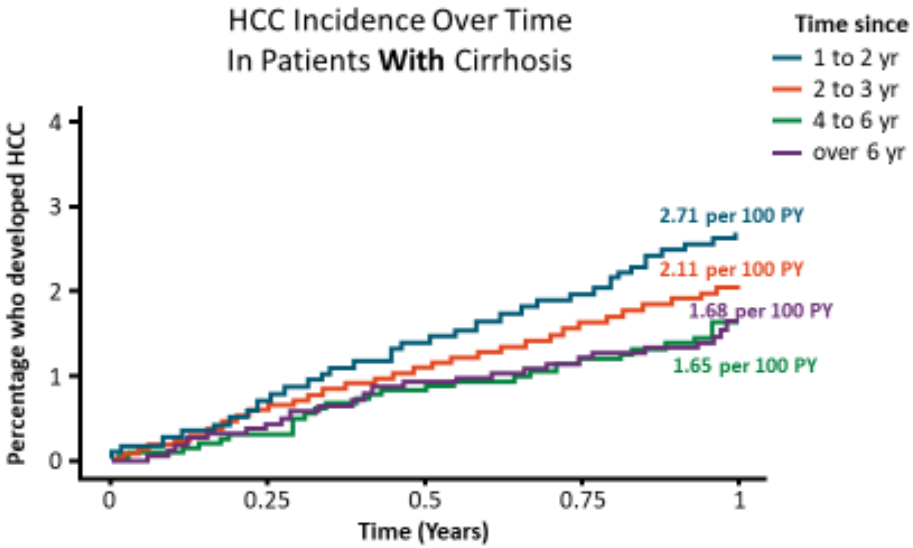
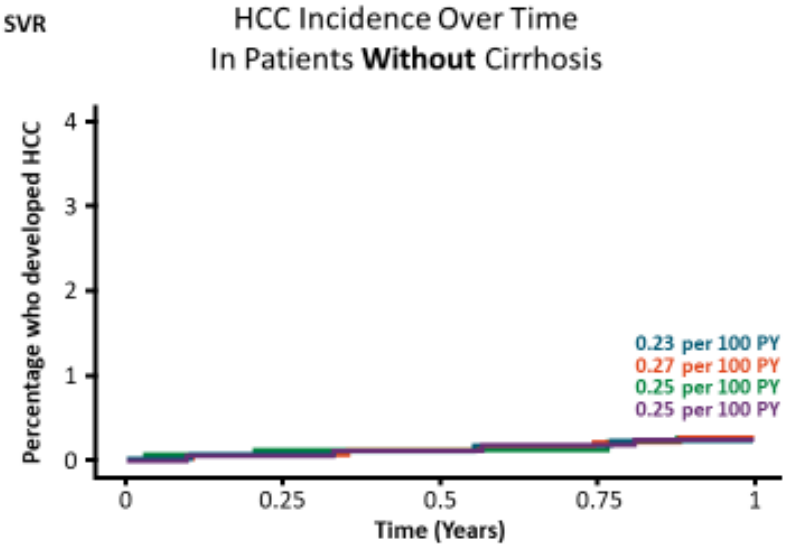
Annual HCC Risk in Patients With and Without Cirrhosis, Stratified by Time Since SVR



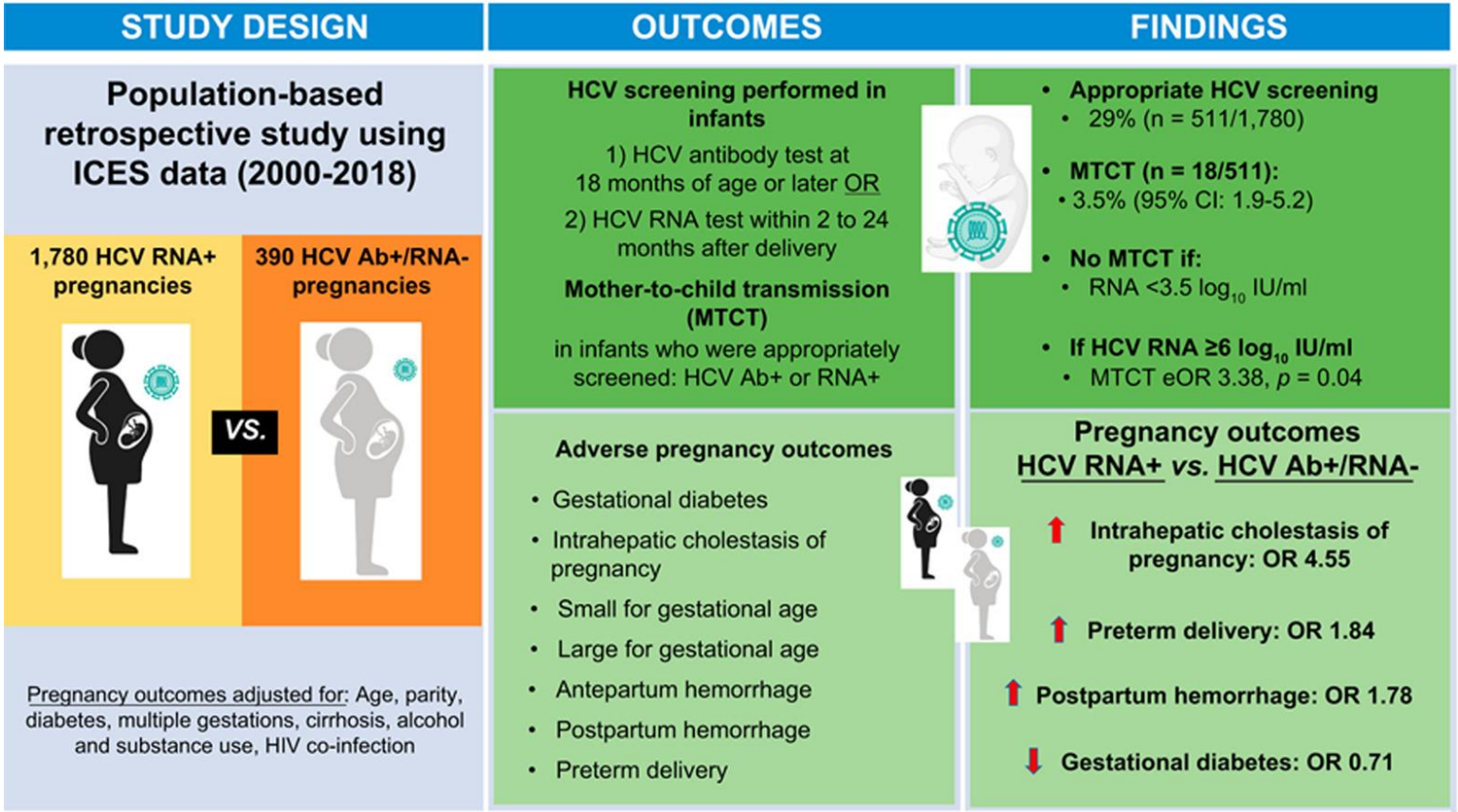


- In patients **with** cirrhosis, **HCC incidence decreased** from Yr 1 to Yr >6
- In patients **without** cirrhosis, HCC incidence was low across all time points and did not change with time

Vutien. AASLD 2022. Abstr 46.

Slide credit: clinicaloptions.com

HCV in der Schwangerschaft



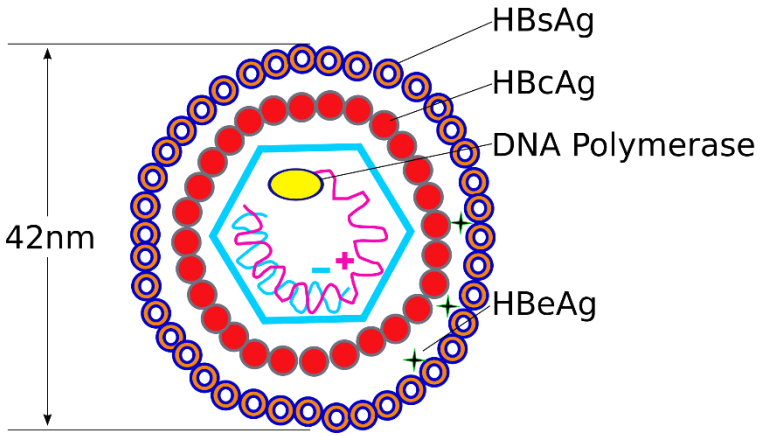
Journal of Hepatology 2022 vol. 77 j 1256–1264

Hepatitis C - Fazit

- HCV im Ü-35-Screening implementiert
- DAA-Therapie führt zu Heilungsraten > 90% („SVR12“)
- Therapiedauer 8-12 Wochen
- Bei allen HCV-Genotypen und allen HCV-Patientengruppen (Vorbehandlung, Niereninsuffizienz/Dialyse, HIV/HBV-Koinfektion, IVDU, Leberzirrhose, Immunsuppression, Chemotherapie, usw) sicher und effektiv
- Eindeutige Verbesserung der Langzeitprognose !!

Virushepatitis B und D

Ü35-Screening einer Hepatitis B



HBsAg im Serum

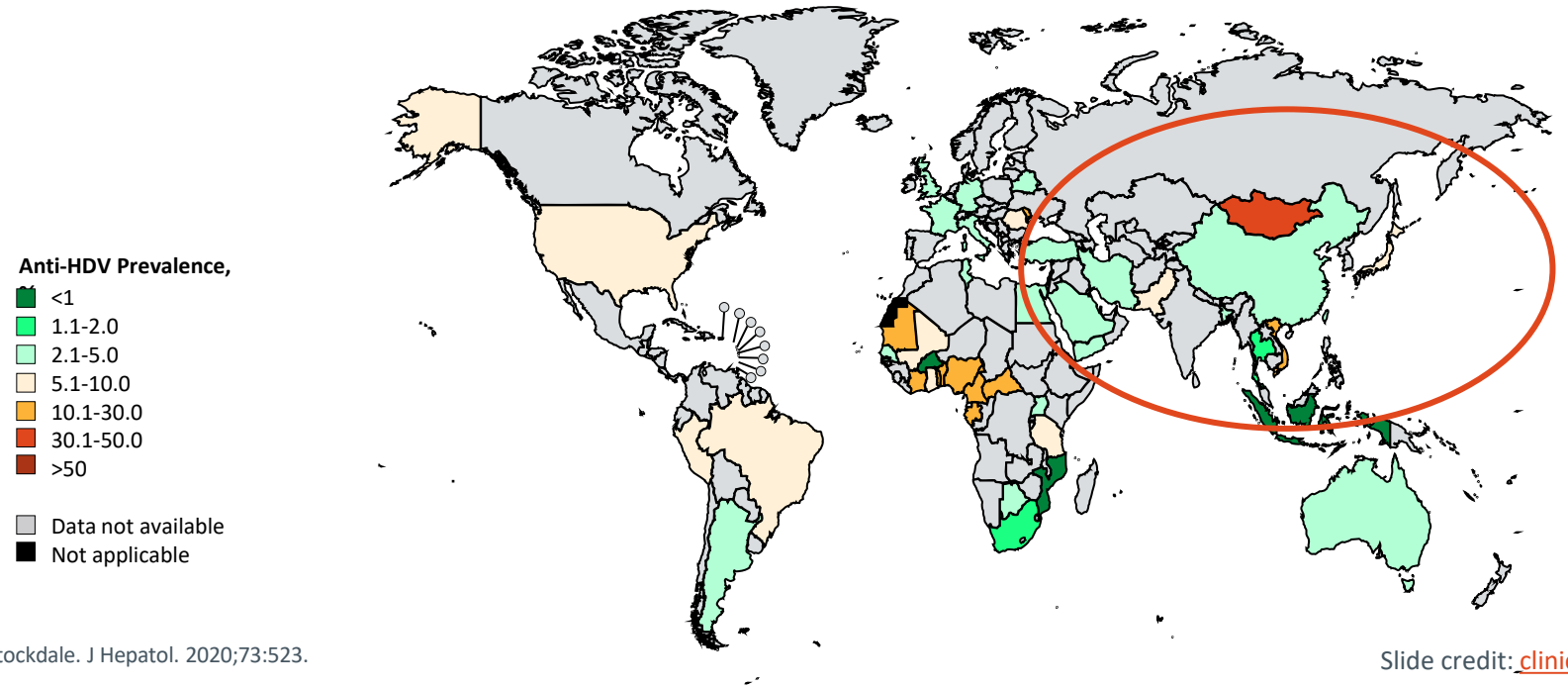
HBV-DNA im Serum

Spezialdiagnostik:

HBeAg/anti-HBe, HBsAg quantitativ, HBV-Genotyp, anti-HDV/HDV-RNA

Proportion of People With HBV Who Have HDV

- Among HBsAg-positive people with HBV, the estimated prevalence of HDV is 4.5% (95% CI: 3.6-5.7)



Stockdale. J Hepatol. 2020;73:523.

Slide credit: clinicaloptions.com

HDV Prevalence Among Selected Population Groups Across the Globe

- HDV seroprevalence among selected population groups relative to general populations or asymptomatic HBsAg-positive people from the same geographic region
- Population attributable fraction of HBsAg-positive patients suggested HDV accounted for:
  - 18% of cirrhosis
  - 20% of HCC

Stockdale. J Hepatol. 2020;73:523.

Slide credit: clinicaloptions.com

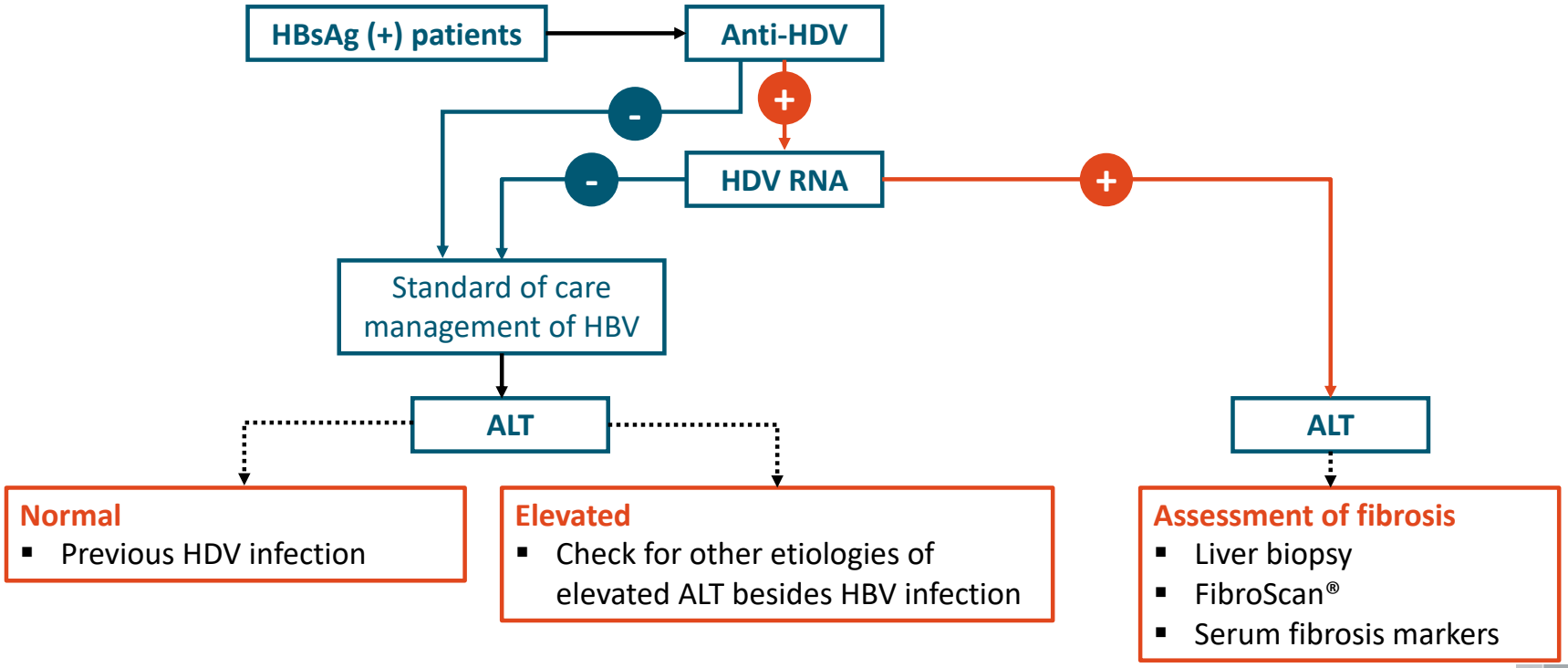
HDV Prevalence in HBsAg Positive Populations by WHO Region and in General and Hepatology Clinics

WHO Region	General HBsAg+ Populations		HBsAg+ Populations in Hepatology Clinics	
	%	95% CI	%	95% CI
African region	5.97	4.98-7.24	12.26	10.13-14.70
Region of the Americas	5.91	3.02-9.71	3.34	2.58-4.21
Eastern Mediterranean region	3.54	2.10-6.28	17.36	11.15-26.34
European region	3.00	2.09-4.21	19.48	17.31-21.76
South-East Asian region	3.20	0.36-12.4	4.00	3.09-5.15
Western Pacific region	4.09	3.47-4.77	8.07	7.50-8.64
Global	4.49	3.57-5.68	16.42	14.58-18.56

Stockdale. J Hepatol. 2020;73:523.

Slide credit: clinicaloptions.com

Algorithm for the Evaluation of HDV



Adapted from: Shah. Gastroenterol Rep (Oxf). 2019;7:396.

Slide credit: clinicaloptions.com

34 jährige Patientin mit HBV/HDV

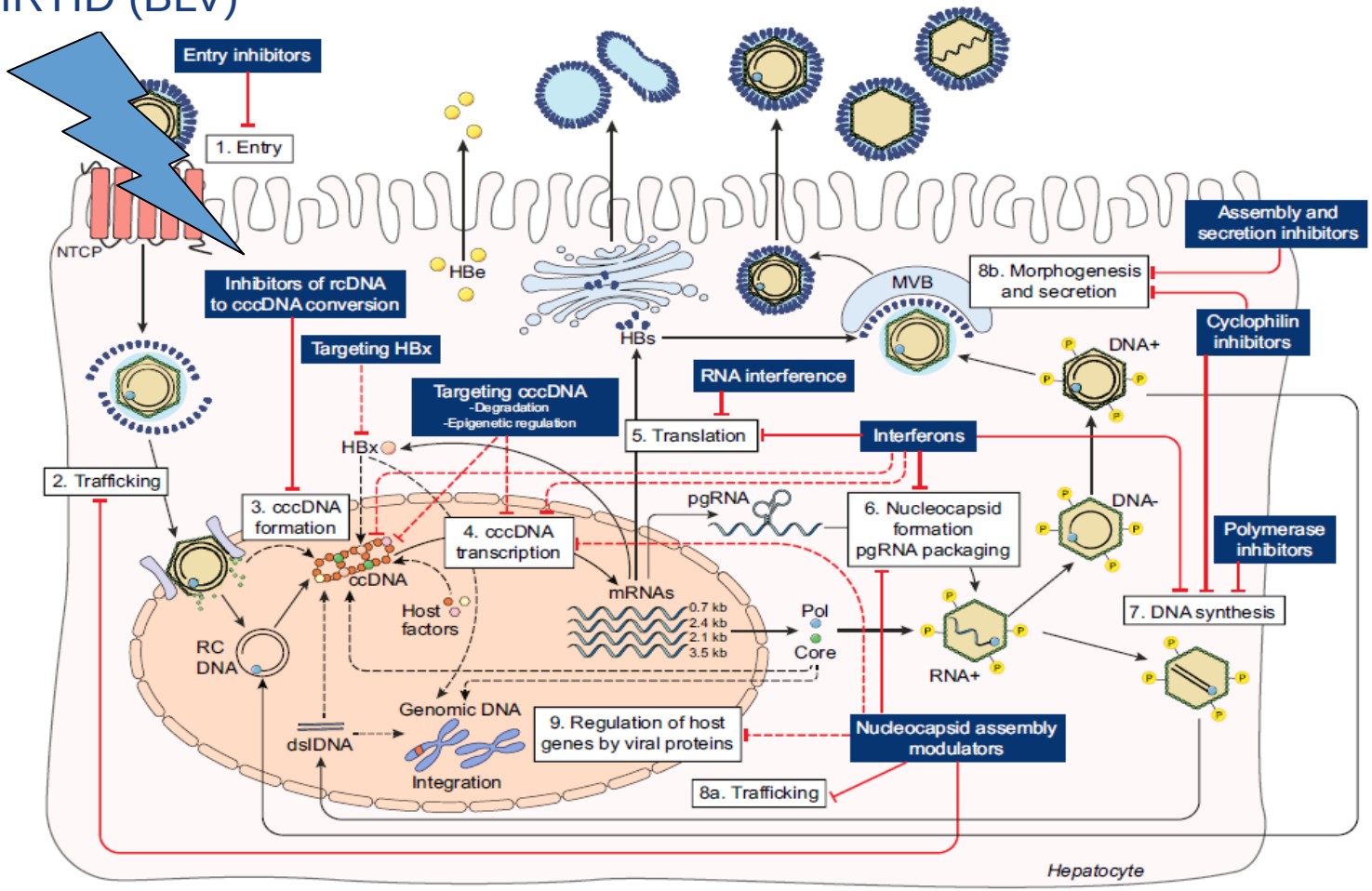
- Chronische Hepatitis B/D
- HBV-DNA negativ, HBsAg positiv, HDV-RNA 7 x 10^5 GÄ/ml
- AST 150 U/l, ALT 142 U/l, gGT 450 U/l, AP 180 U/l
- Bilirubin 4,5 mg/dl, Quick 63%, Thrombozyten 68.000 / µl

- **Leberzirrhose CHILD A, Z.n. Dekompensation mit Aszites**

- Wie würden Sie die Patientin behandeln ?

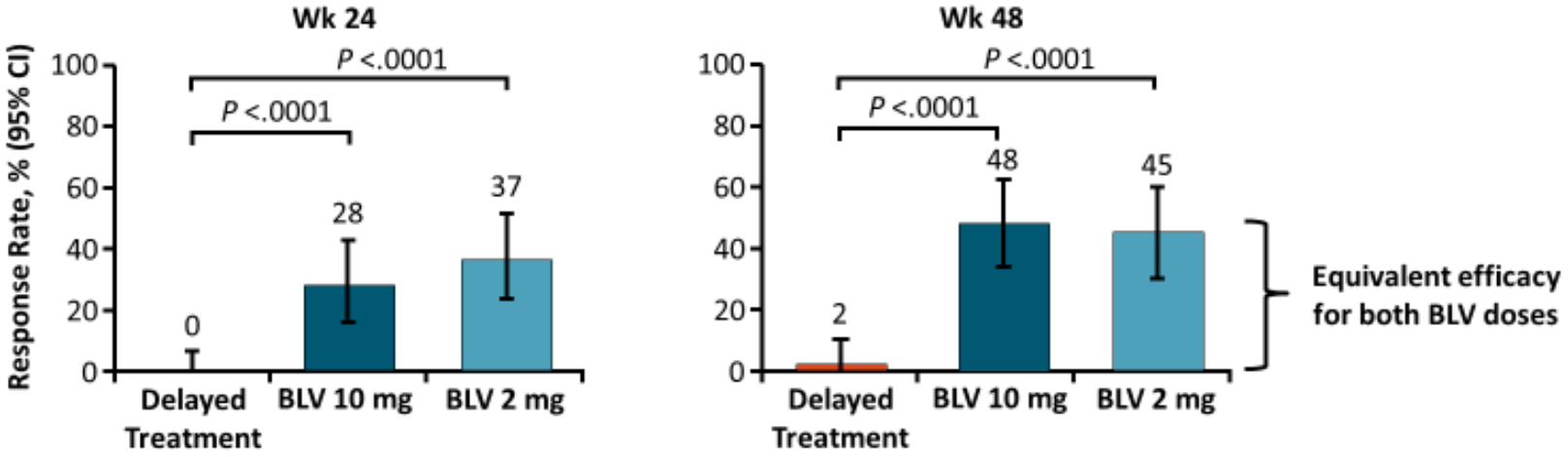
Erster „Entry-Inhibitor“: Bulevirtid

BULEVIRTID (BLV)



MYR301: Immediate vs Delayed Bulevirtide Monotherapy for Chronic HDV

- Multicenter, randomized, phase III trial of BLV 2 mg or 10 mg SC QD for 48 wk vs delayed BLV treatment (10 mg SC QD beginning Wk 48) in patients with chronic HDV (N = 150)
  - Primary endpoint: combined response at Wk 48 (HDV RNA undetectable or ≥2 $\log_{10}$ copies/mL decrease vs baseline with ALT normalization)



Wedermeyer. EASL 2022. Abstr GS006.

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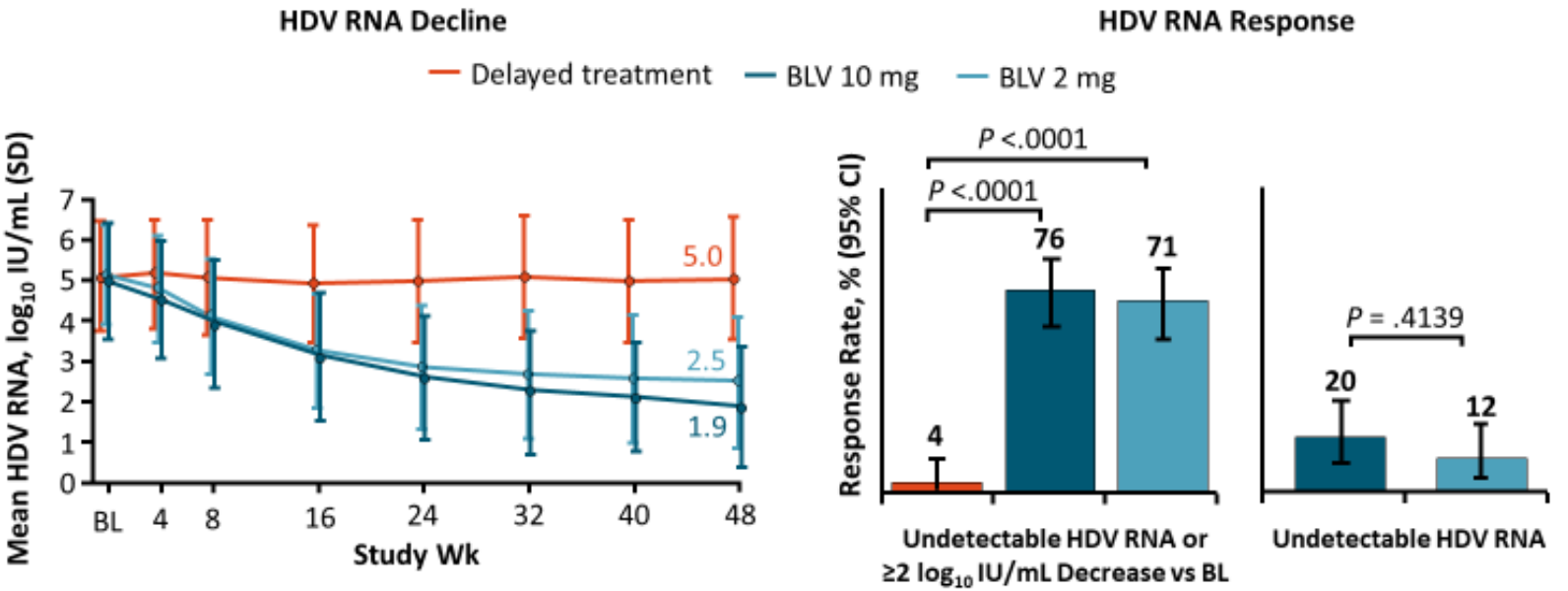
MYR301: HDV RNA Response at Wk 48



Wedermeyer. EASL 2022. Abstr GS006.

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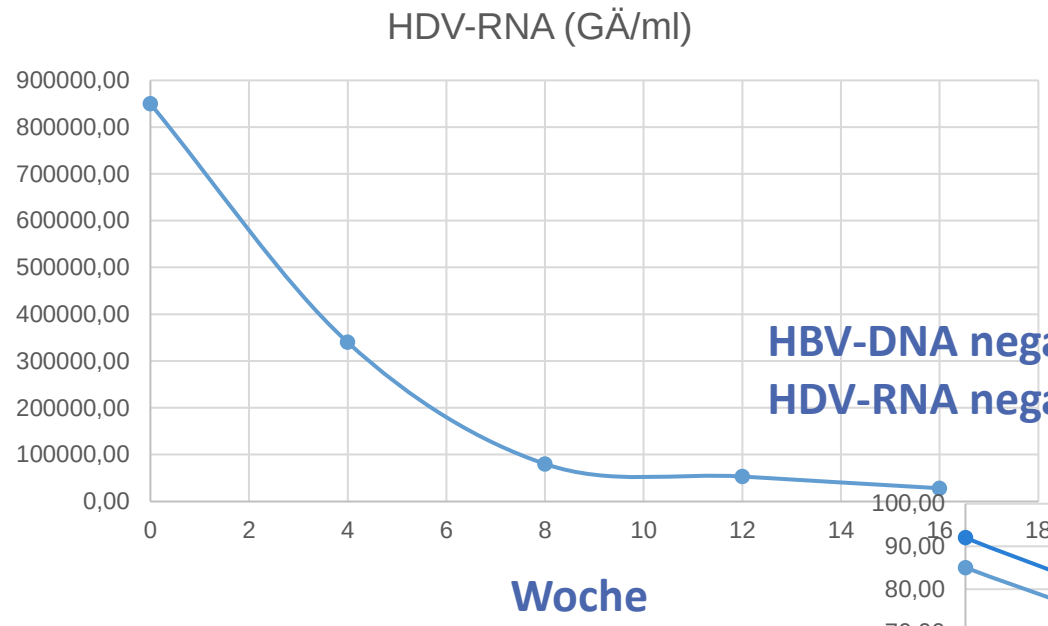
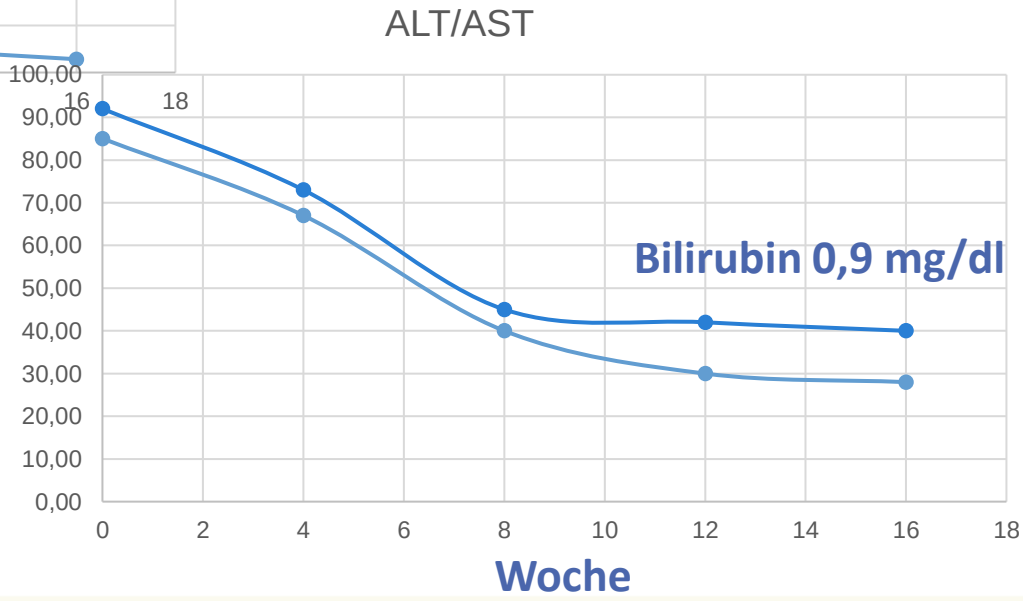
34 jährige Patientin mit HBV/HDV



HBV-DNA negativ
HDV-RNA negativ

Bulevirtid 2 mg tgl. s.c.



Bilirubin 0,9 mg/dl

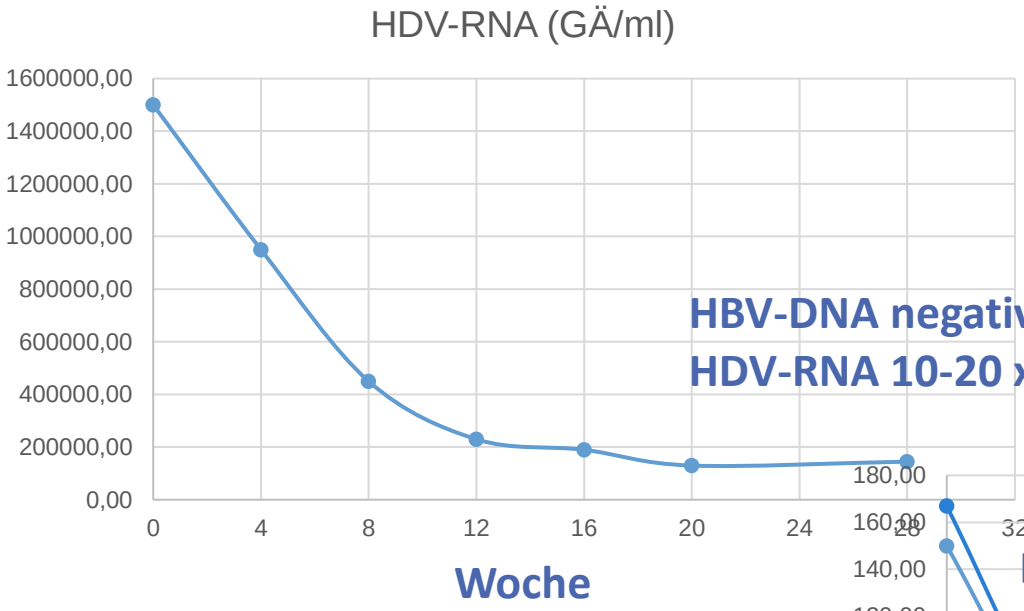
55 jähriger Patient mit HBV/HDV

- Chronische Hepatitis B/D-Infektion
- Bekannte Leberzirrhose CHILD A
- Z.n. Peg-Interferon für 36 Monate, Abbruch bei Non-Response

- HBV-DNA 2 x 106 IU/ml, HDV-RNA 6 x 105 GÄ/ml
- AST 150 U/l, ALT 180 U/l, Bilirubin 4,5 mg/dl, Quick 72%, Thrombozyten 95.000/µl

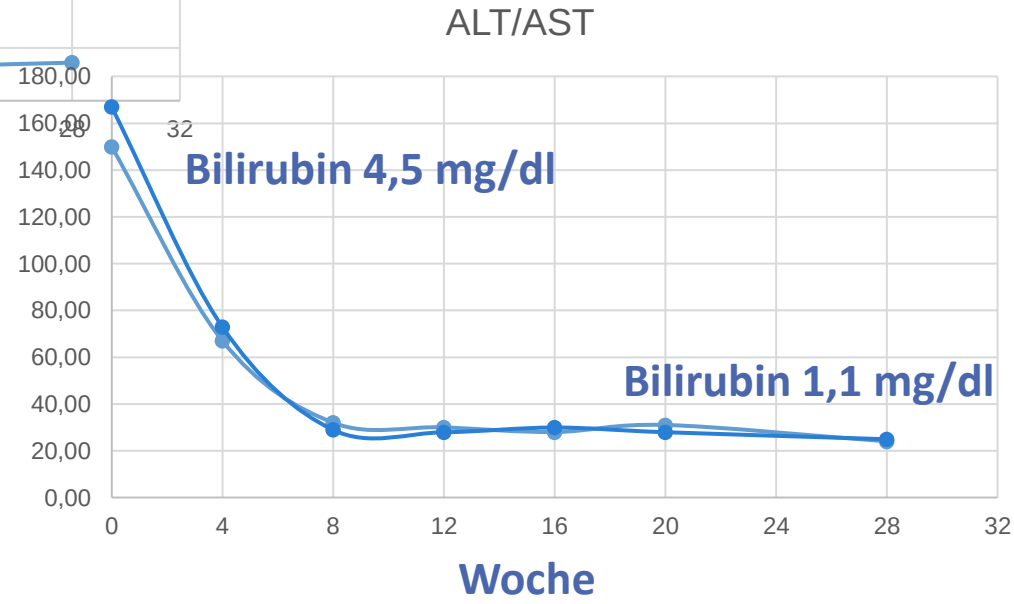
- Wie würden Sie den Patienten behandeln?

55 jähriger Patient mit HBV/HDV



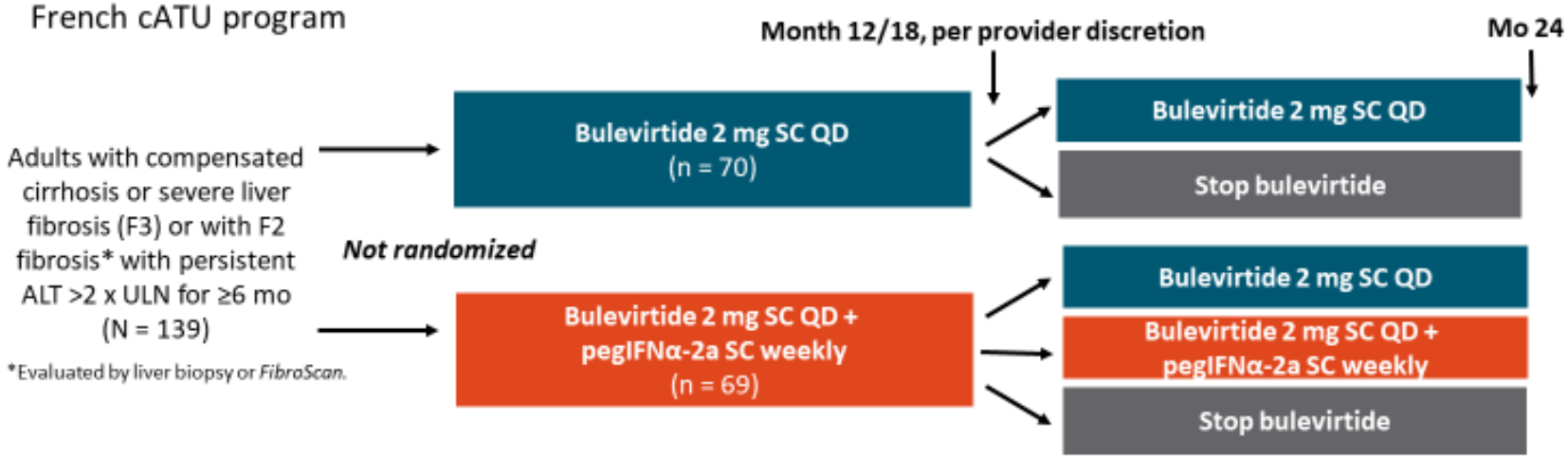
- **Bulevirtid 2 mg tgl. s.c.**
- **Tenofovir 245 mg**

HBV-DNA negativ
HDV-RNA 10-20 x 10^4



Bulevirtide ± PegIFNα-2a for Chronic HDV Infection: Study Design

- Multicenter, prospective, retrospective, observational study in patients with chronic HDV from French cATU program



- **Primary combined endpoint:** undetectable HDV RNA or decrease ≥2 $\log_{10}$ from baseline and normal ALT
- **Secondary endpoints:** HDV RNA undetectable from baseline to Mo 12, 18, 24; normalization of ALT (ALT <40 IU/L); factors associated with virologic response at Mo 18, 24

De Ledinghen. AASLD 2022. Abstr 28.

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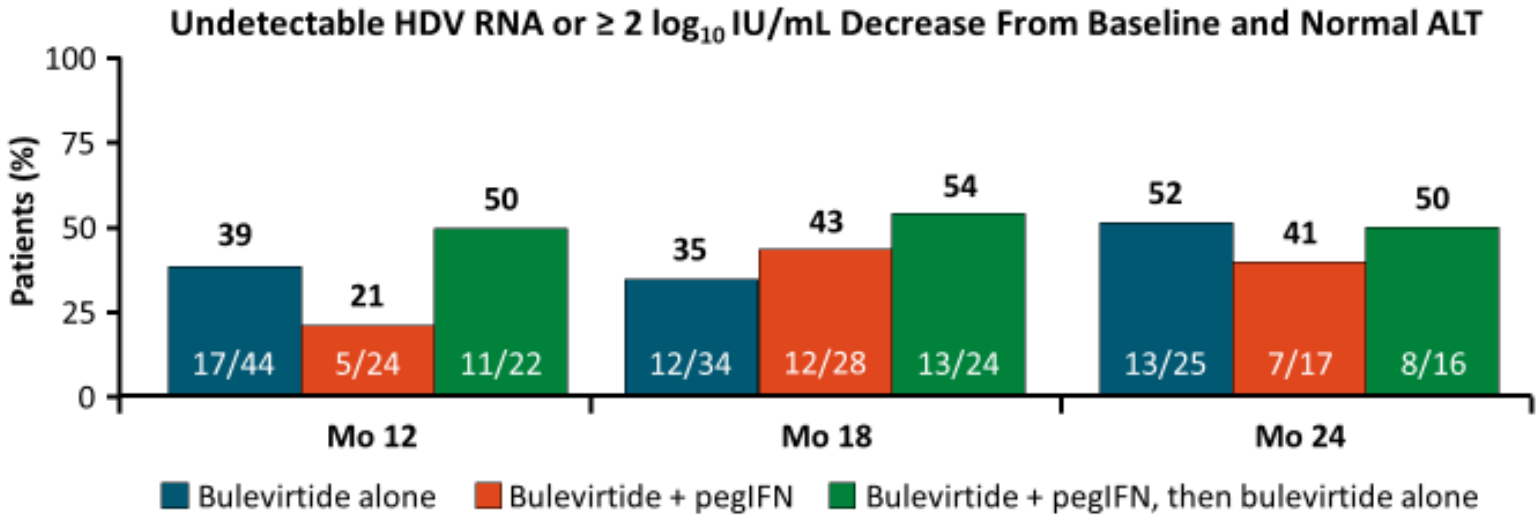
Bulevirtide ± PegIFNα-2a for Chronic HDV Infection: On-Treatment Primary Combined Endpoint



- 52% of patients receiving bulevirtide monotherapy achieved a combined response at Month 24
- Bulevirtide monotherapy did not perform differently than when combined with pegIFN

De Ledinghen. AASLD 2022. Abstr 28.

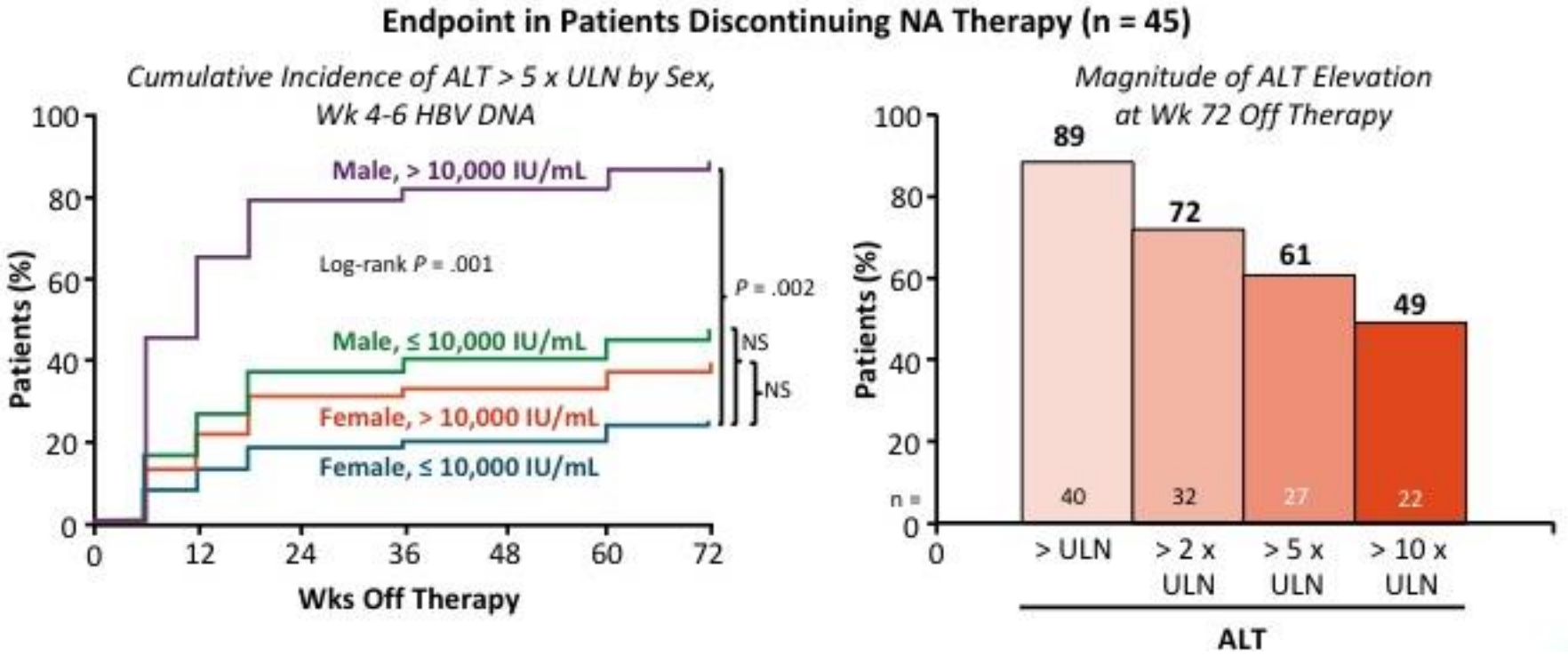
Slide credit: clinicaloptions.com

Hepatitis B/D - Fazit

- HBV im Ü-35-Screening implementiert
- HDV-Screening bei allen HBV-Patienten obligatorisch!
- HBV/HDV-Koinfektion mit schlechterer Prognose, aggressiverer Verlauf, höhere Raten an Leberzirrhose und HCC
- Therapie der HBV-Infektion mit NUCs und Therapie der HDV-Infektion mit Peg-IFN
- Bulevirtide (BLV) bei fortgeschrittener Lebererkrankung erwägen
- BLV + Peg-IFN als neue Therapieoption?

NUC-STOP „Erfahrungen“

STOP: Incidence, Magnitude of Off-Therapy ALT Flares

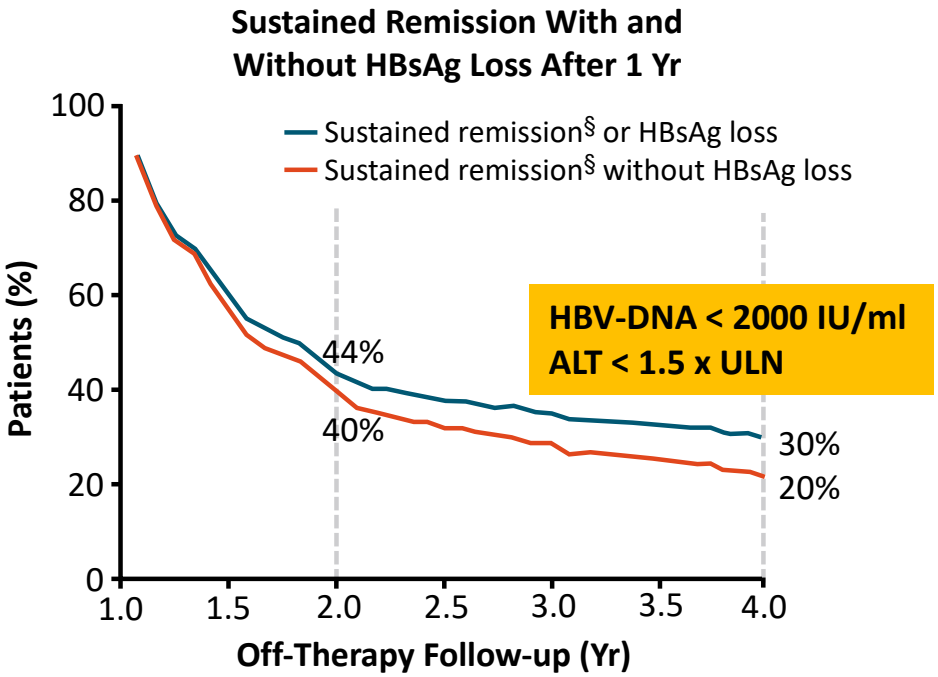


Liem. EASL 2019. Abstr FRI-190.

RETRACT-B: Outcomes After Therapy Cessation

Relapse Within 1 Yr of Therapy Cessation	Patients (N = 945)
Virologic relapse,* n (%)	542 (57)
▪ Median max HBV DNA, log_{10} IU/mL (IQR)	4.4 (3.9-5.2)
Biochemical relapse,† n (%)	340 (36)
▪ Median max ALT x ULN (IQR)	2.8 (1.9-5.4)
Clinical relapse,‡ n (%)	222 (24)
≥1 relapse, n (%)	621 (66)

*Virologic relapse: HBV DNA >2000 IU/mL.
†Biochemical relapse: ALT >1.5 x ULN.
‡Clinical relapse: HBV DNA >2000 IU/mL and ALT >1.5x ULN.
§Sustained remission: sustained HBV DNA ≤2000 IU/ml and ALT ≤1.5 x ULN.



- Only 30% had sustained remission or HBsAg loss at 4 yr
- 10% had HBsAg loss after 4 yr and only 20% had sustained remission without HBsAg loss at 4 yr

Hirode. AASLD 2021. Abstr OA22. Reproduced with permission.

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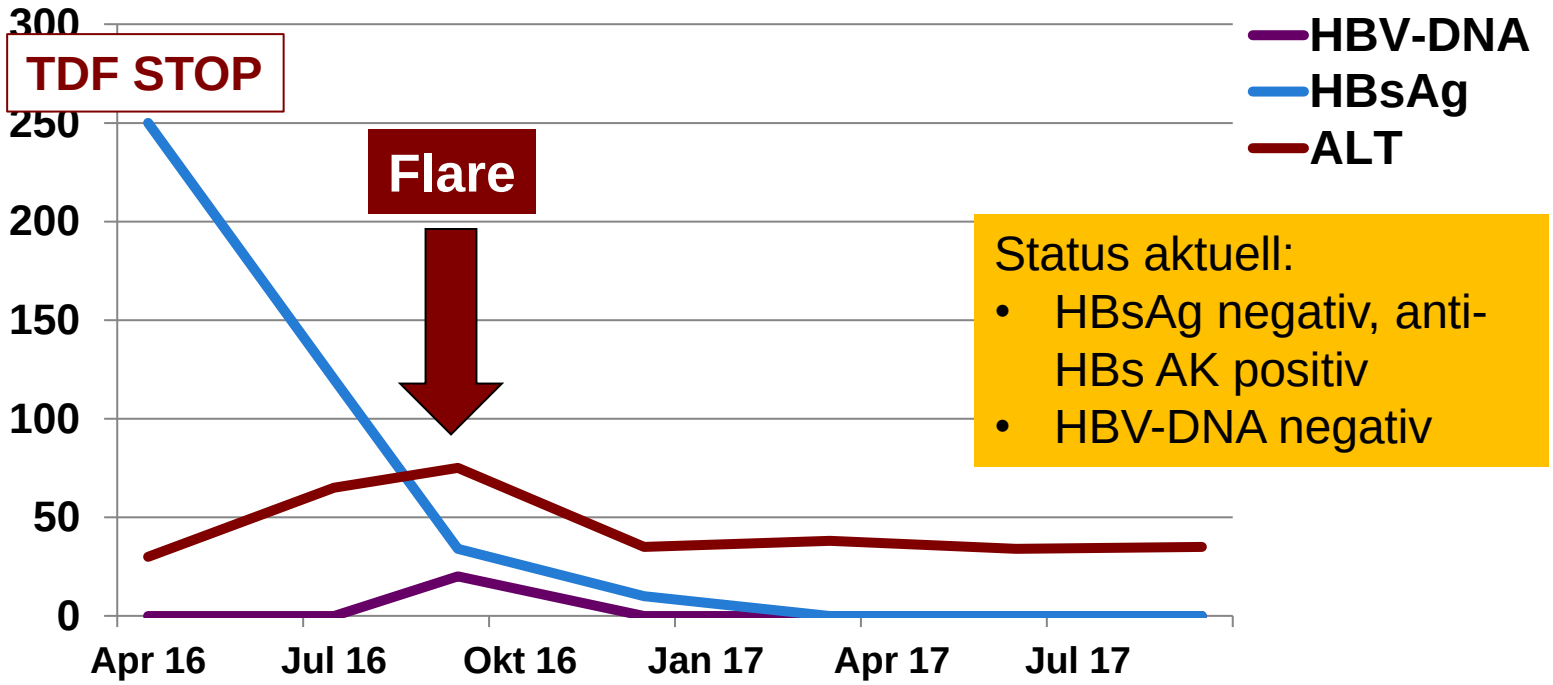
Klinischer Fall 1: NUC-STOP

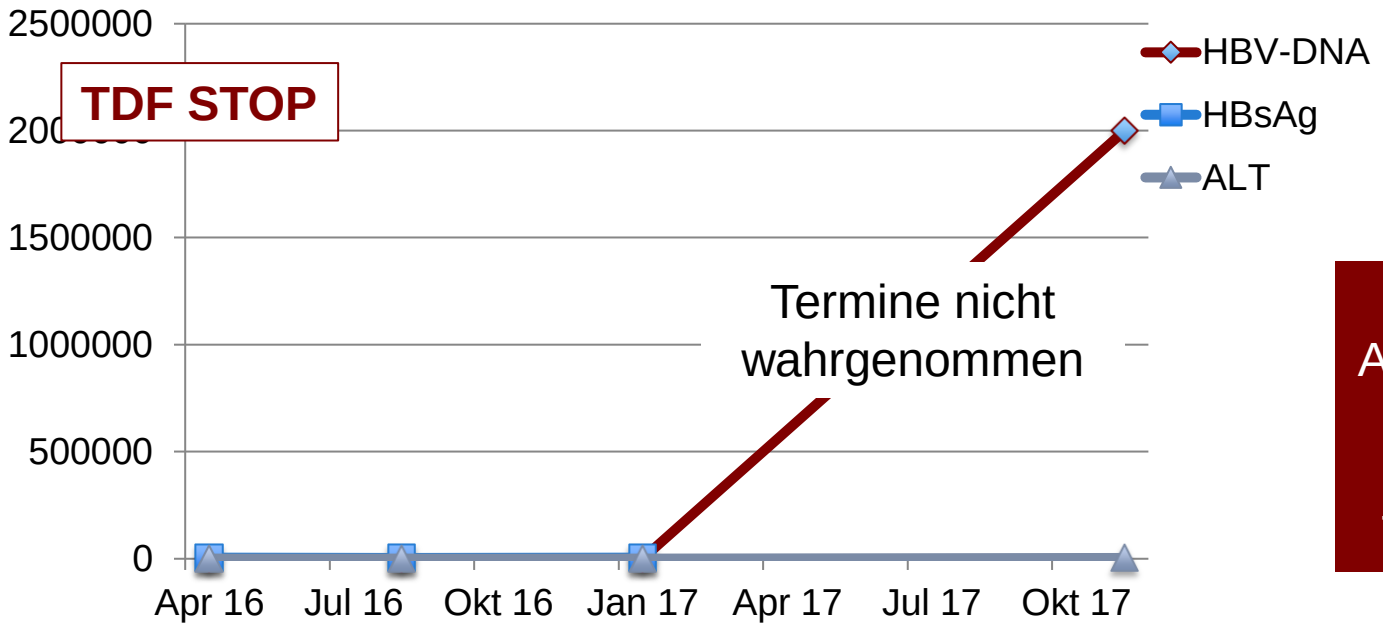
- 58 jähriger Mann unter TDF seit > 5 Jahren HBV-DNA negativ
- HBsAg niedrig: 250 IU/ml
- ALT normal
- Keine fortgeschrittene Fibrose/Zirrhose



Status aktuell:
- HBsAg negativ, anti-HBs AK positiv
- HBV-DNA negativ

Klinischer Fall 2: NUC-STOP

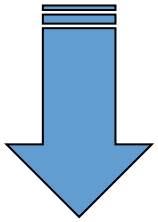
- 32 jähriger Mann unter TDF seit > 4 Jahren HBV-DNA negativ
- HBsAg mittelmäßig: 4.200 IU/ml
- ALT normal
- Keine fortgeschrittene Fibrose/Zirrhose
- Compliance „nicht ganz so wie gewünscht“



BWK Ulm:
ALT 3.500 U/l
Bili 9 mg/dl
Quick 65%
TDF + ETV

Klinischer Fall 3: NUC-STOP

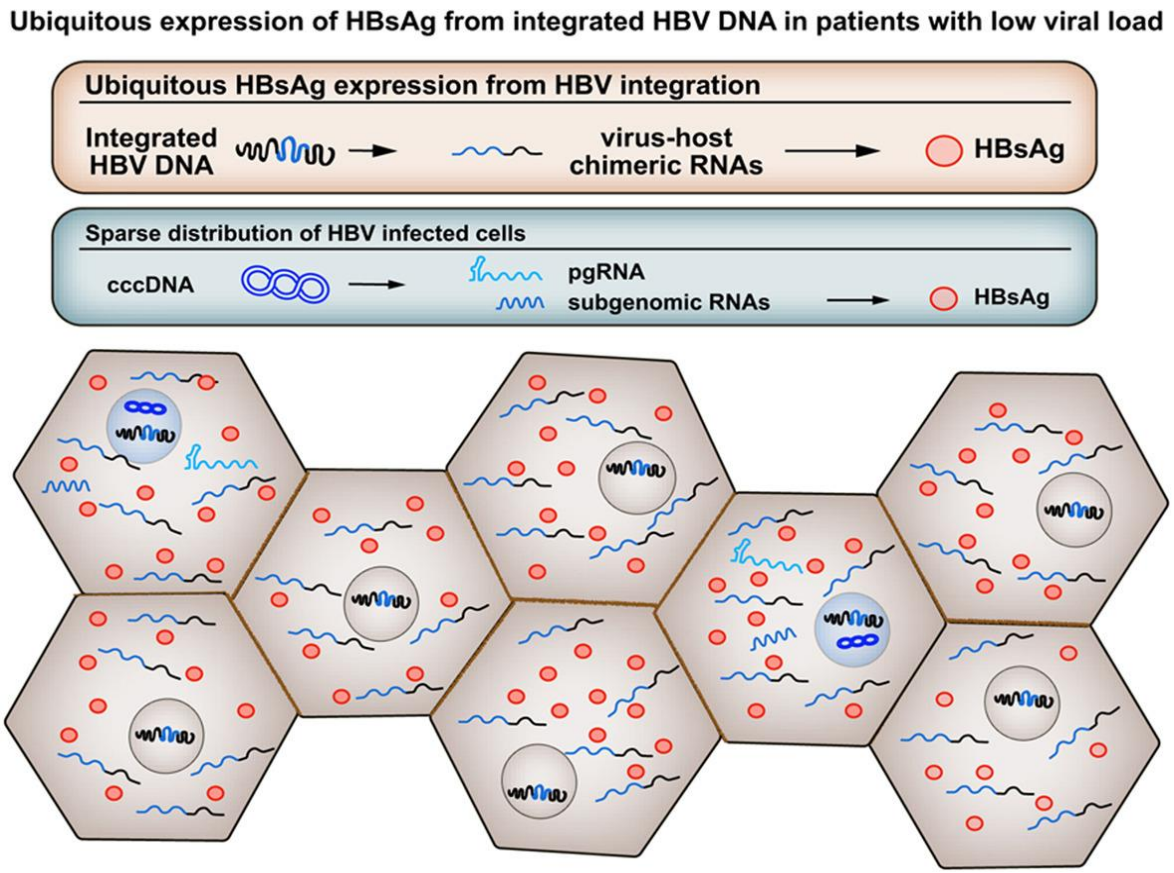
- 54 jähriger Mann unter TDF seit > 8 Jahren HBV-DNA negativ
- HBsAg mittelmäßig: 3.500 IU/ml
- ALT normal
- Keine fortgeschrittene Fibrose/Zirrhose
- Compliance „sehr gut“



In den letzten 3 Jahren:

- HBV-DNA 500 bis 1500 IU/ml
- HBsAg 2.000 bis 3.400 IU/ml
- AST/ALT normal
- Sono: o.B.
- Elastographie: keine relevante Fibrose

HBsAg-Verlust ist nicht immer erreichbar!



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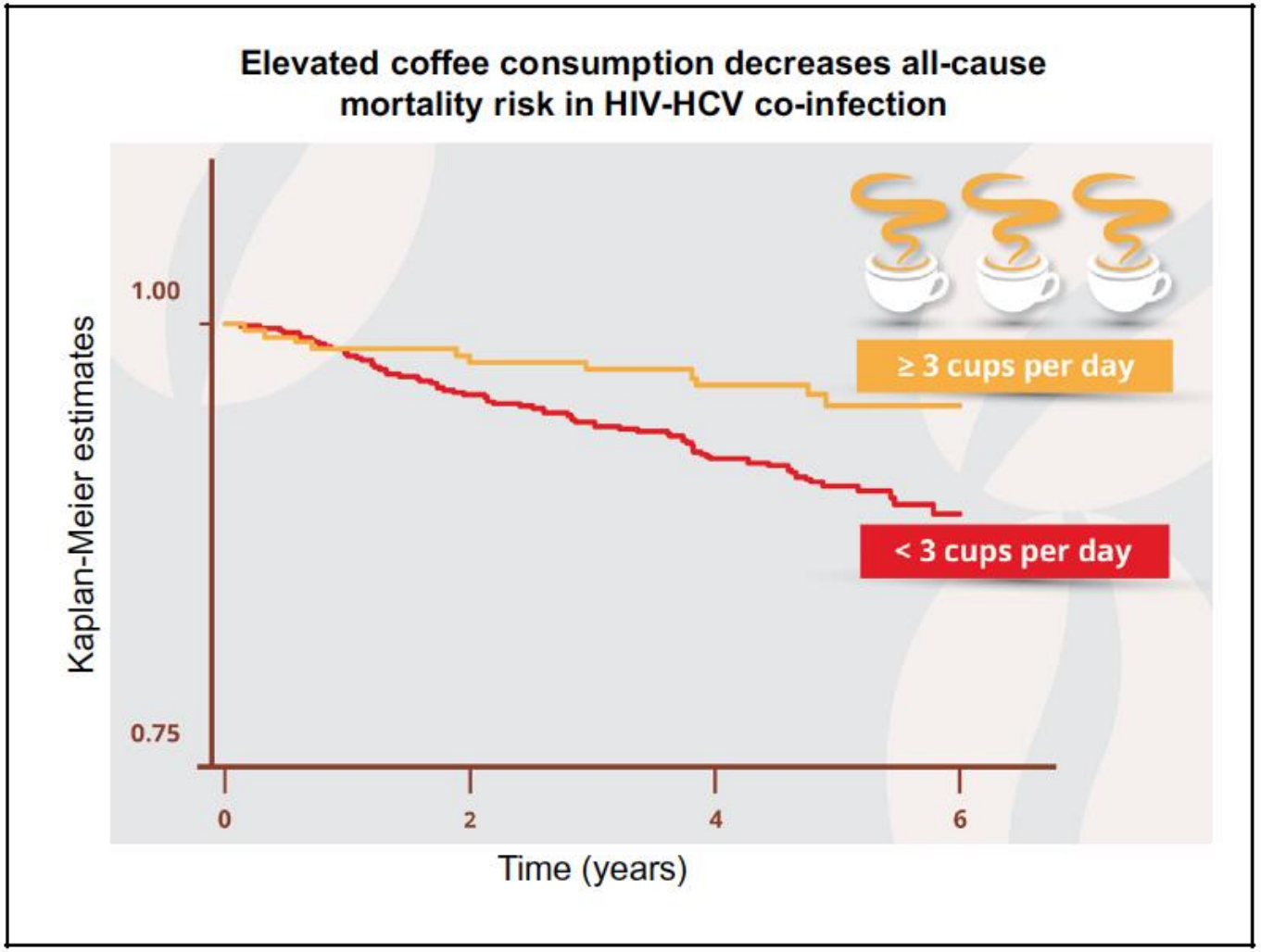
„NUC-STOP“ - FAZIT

- HBV-Reaktivierung nach DAA-Therapie möglich, aber auch HBsAg-Verlust
- NUC-STOP nur bei Patienten ohne fortgschrittene Fibrose/Zirrhose
- HBV-DNA sollte über mindestens 2-3 Jahre negativ sein
- Gute Prognose bei:
  - HBsAg < 1.000 IU/ml vor NUC-STOP
  - HBV-DNA < 10.000 IU/l 4-6 Wochen nach NUC-STOP



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