



Hepatitis D virus infection: Current management and novel treatment options

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Disclosures

Honoraria for consulting or speaking (last 5 years):

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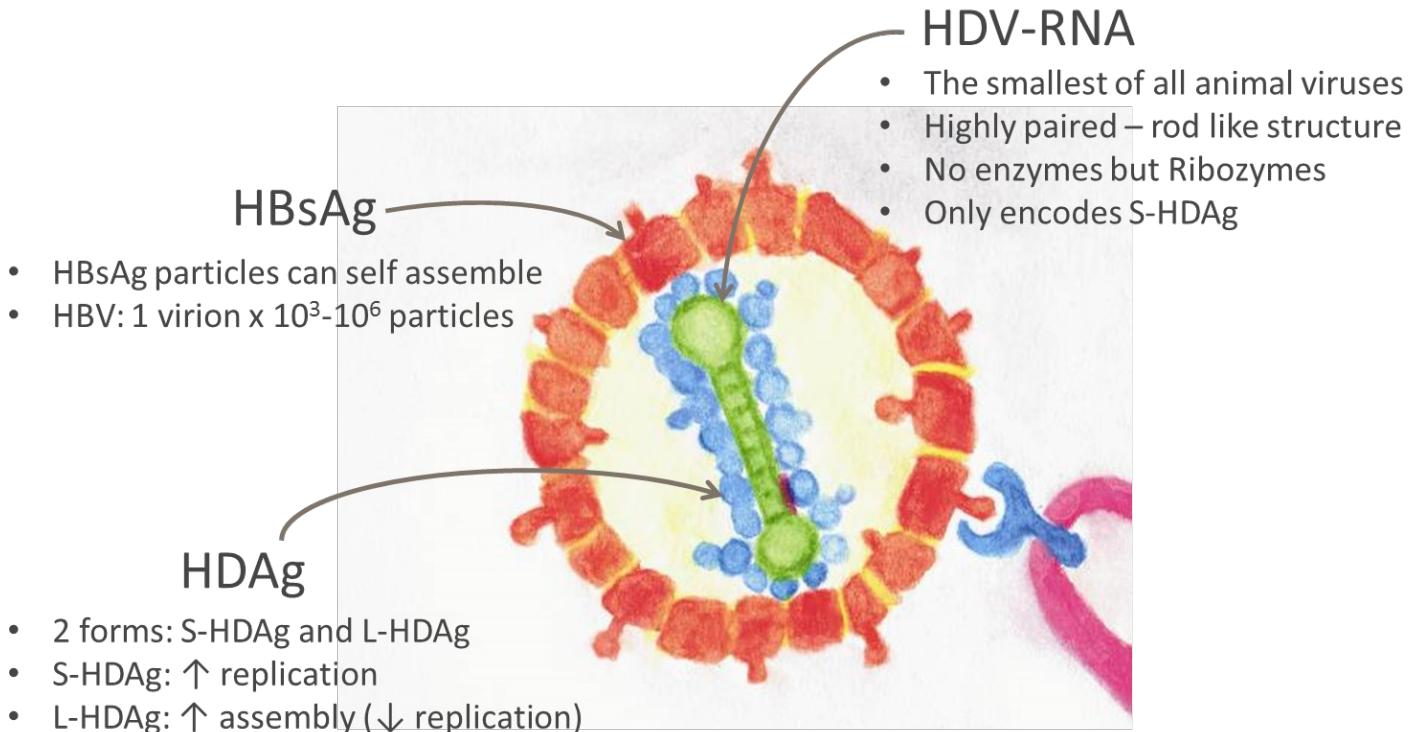
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Cihan Yurdaydin

Essen University Hospital / University of Duisburg-Essen

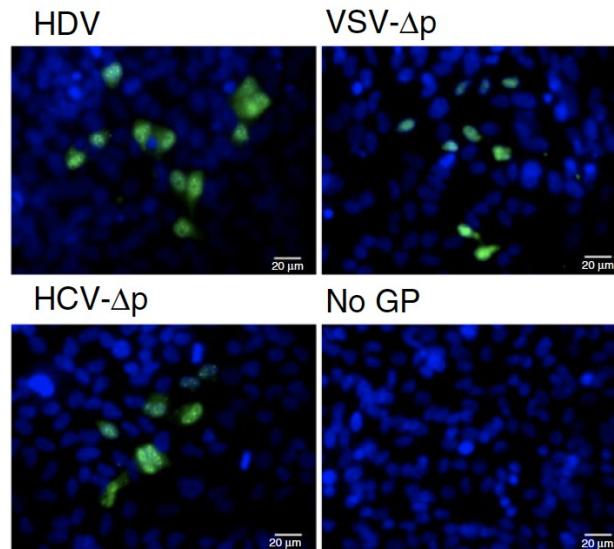
Katja Deterding, Martin Trippler, Sandra Ciesek, Matthias Hardtke-Wolenski
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Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus *in vivo*

Jimena Perez-Vargas¹, Fouzia Amirache¹, Bertrand Boson¹, Chloé Mialon¹, Natalia Freitas¹, Camille Sureau², Floriane Fusil¹ & François-Loïc Cosset¹



Nature Commun 2019; 10: 2098



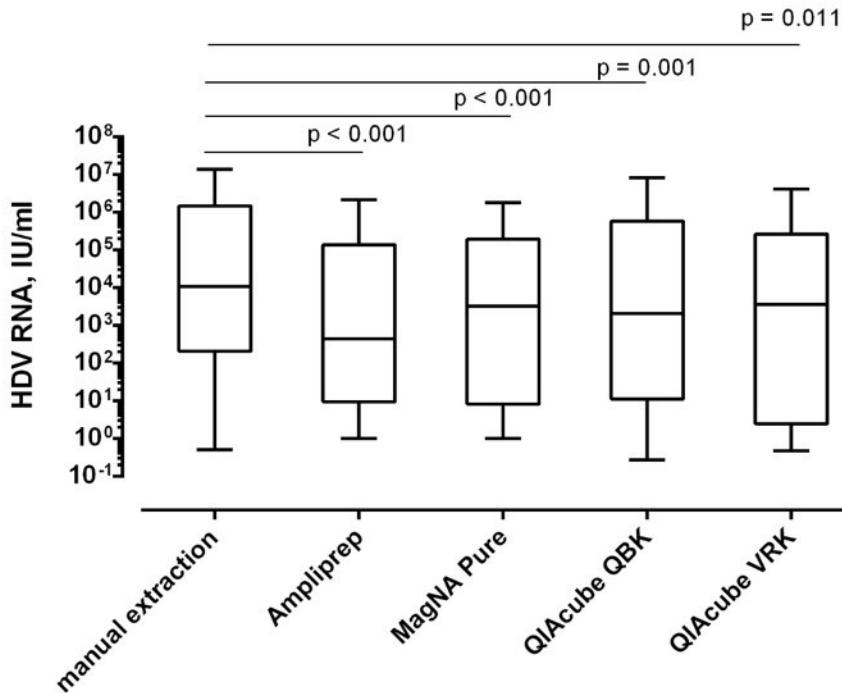
Diagnostics:

Virological assays

How to assess severity of liver disease?



Extraction methods influence HDV RNA quantification



Bremer, Anastasiou et al., Antiviral Therapy 2019 epub



Evaluation of non-invasive fibrosis scores and TE

Takyar V, Surana P, Kleiner DE, Wilkins K, Hoofnagle JH, Liang TJ, Heller T, Koh C.
Noninvasive markers for staging fibrosis in chronic delta hepatitis.
Aliment Pharmacol Ther. 2017 Jan;45(1):127-138.

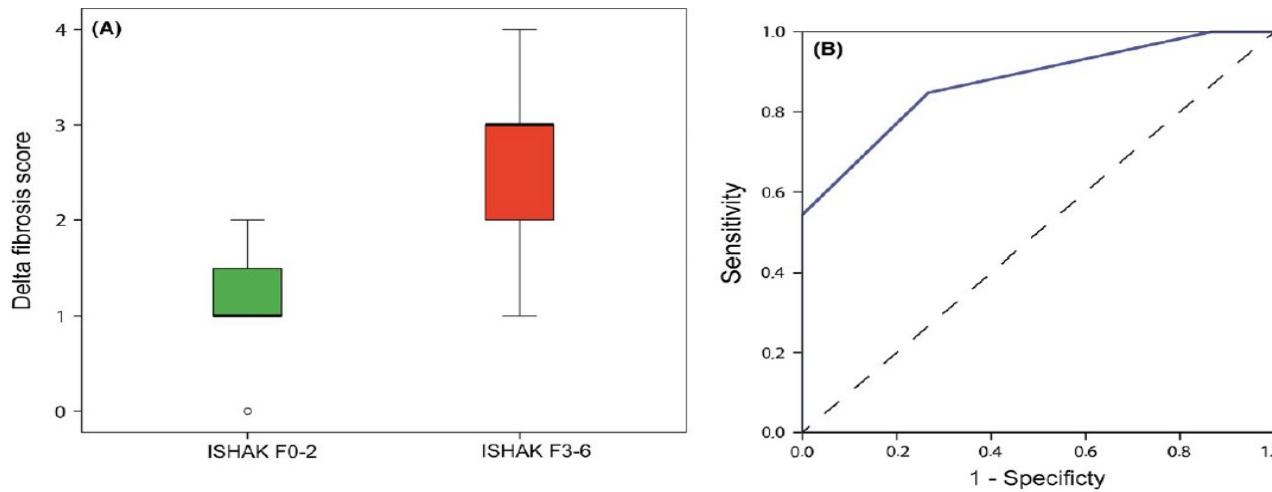
Da BL, Surana P, Takyar V, Kleiner DE, Heller T, Koh C
Vibration-controlled transient elastography for the detection of cirrhosis in chronic hepatitis D infection.
J Viral Hepat. 2019 Nov 19. doi: 10.1111/

Da BL, Surana P, Kleiner DE, Heller T, Koh C.
The Delta-4 fibrosis score (D4FS): A novel fibrosis score in chronic hepatitis D.
Antiviral Res. 2019 Dec 16;174:104691. doi: 10.1016



A non-invasive fibrosis score for hepatitis D (DFS): Albumin, gGT, CHE, Age

1 (if Alb < 1.19[*LLN]) + 1 (if gGT > 0.5[*ULN]) + 1 (if CHE < 1.46[*LLN]) + 1
(if age > 42)



Lutterkort et al., Liver International 2017

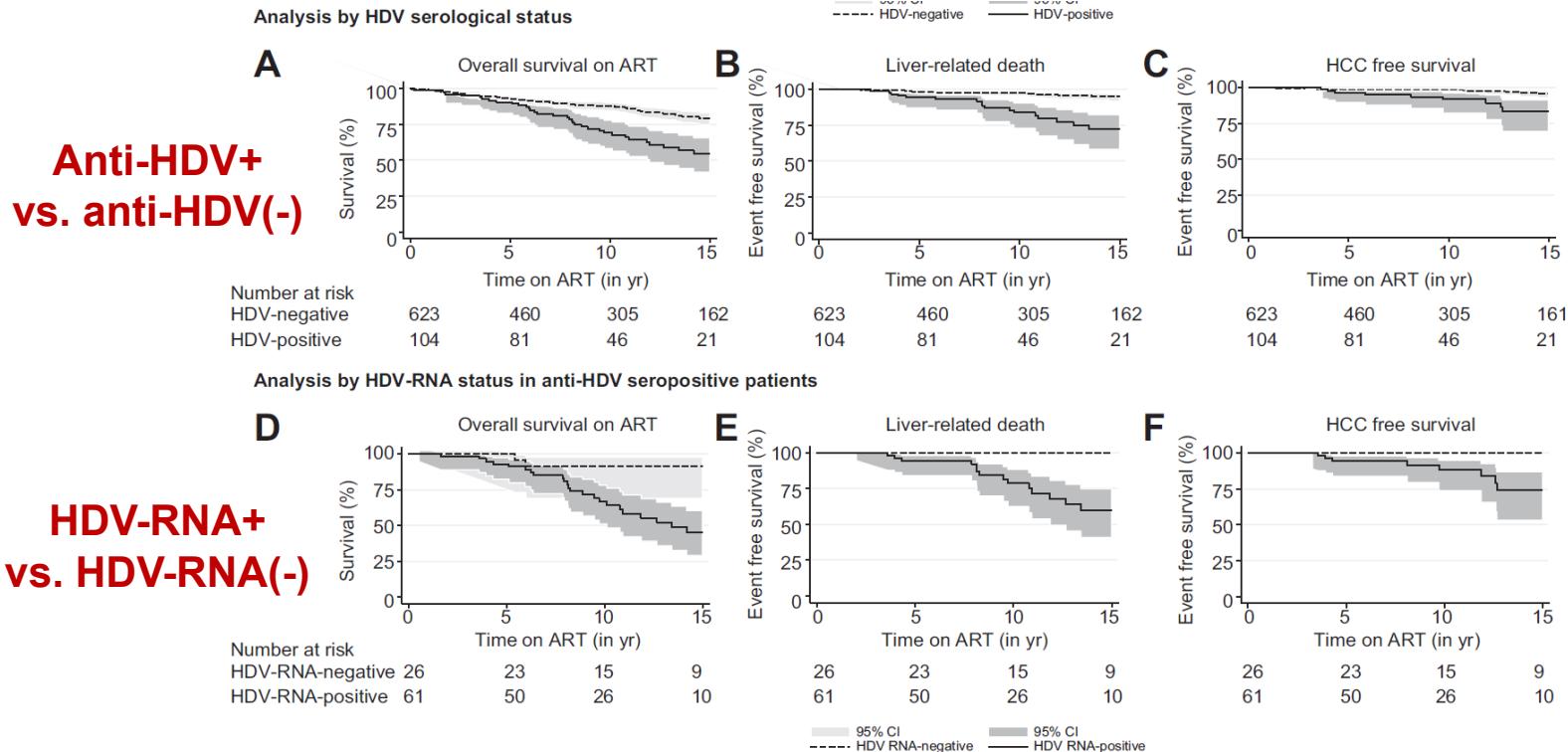


Natural History:

Always severe?



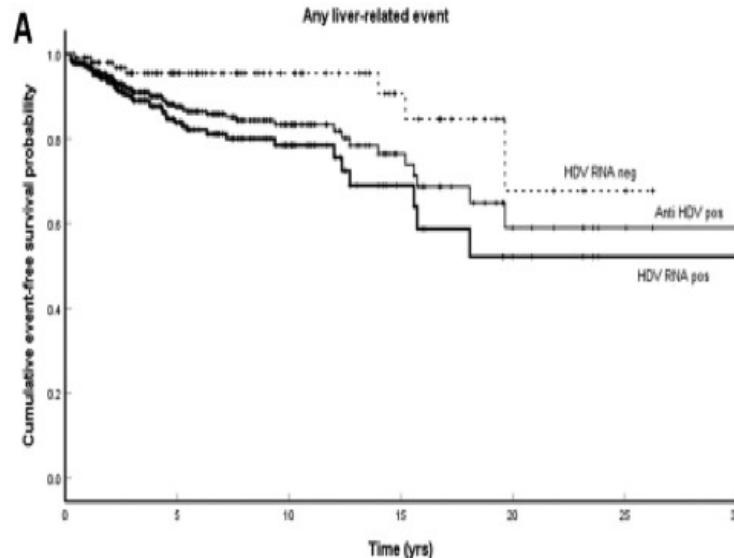
High frequency of clinical complications in HIV+ patients with hepatitis delta



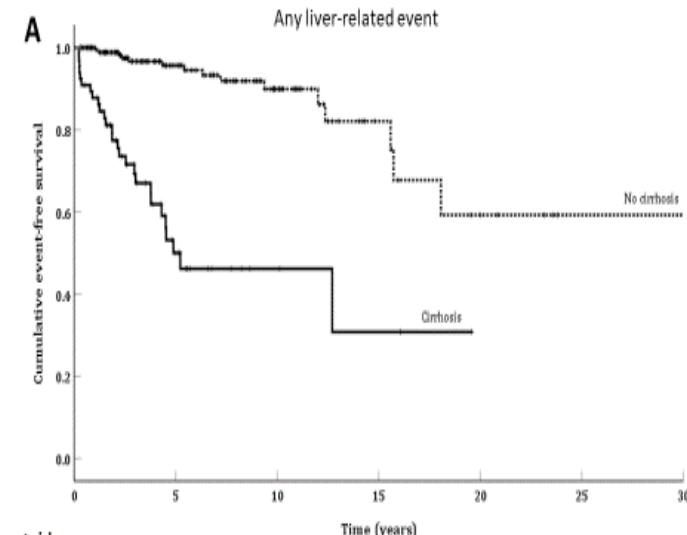
Beguelin et al., J Hepatol 2017 (66:297-303)



Swedish Data: High frequency of clinical complications in cirrhotic patients Association with HDV replication



Number at risk	1	2	3	4	5	6	7
Anti HDV pos	375	163	76	30	9	3	1
HDV RNA pos	260	103	42	14	5	1	1
HDV RNA neg	101	52	29	15	4	2	0



Number at risk	194	88	39	12	5	1	0
No cirrhosis	194	88	39	12	5	1	0
Cirrhosis	66	15	4	2	0		

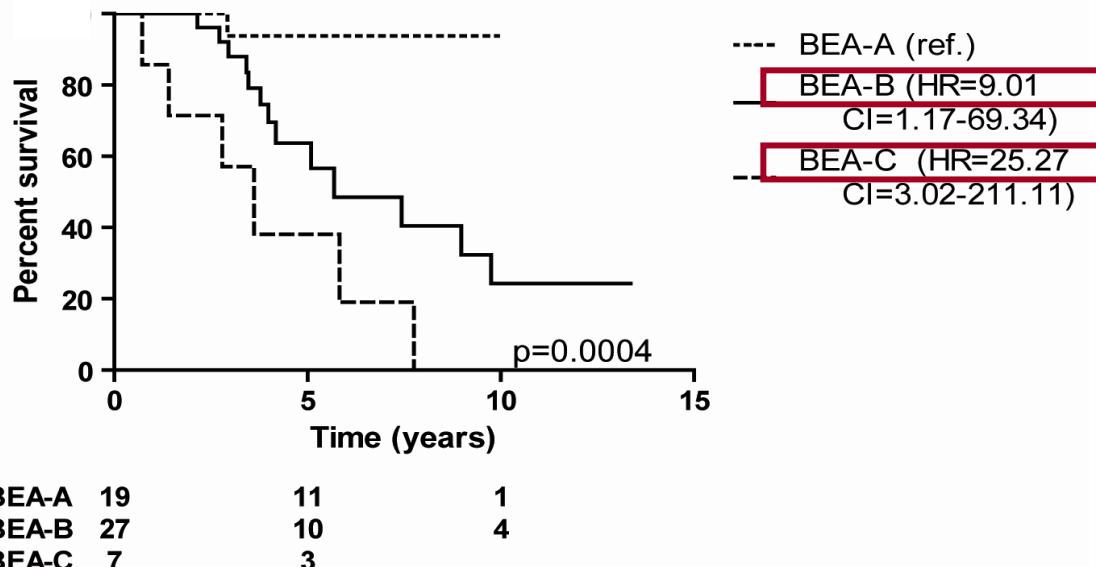
Kamal, ... Aleman et al., AASLD 2018



Survival according to the BEA-scoreC

A

Event free survival: Hannover



Calle Serrano et al. J Viral Hepatitis 2014



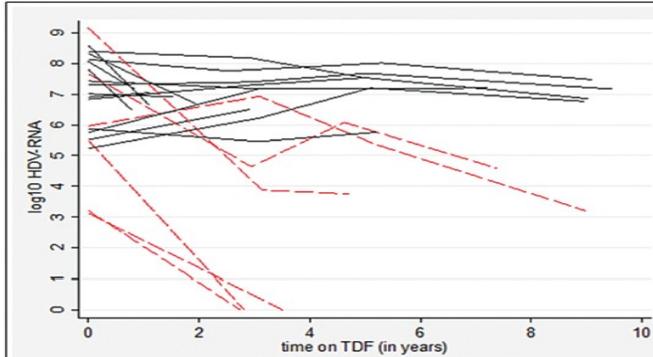
Treatment of Hepatitis Delta

Backbone NUC?

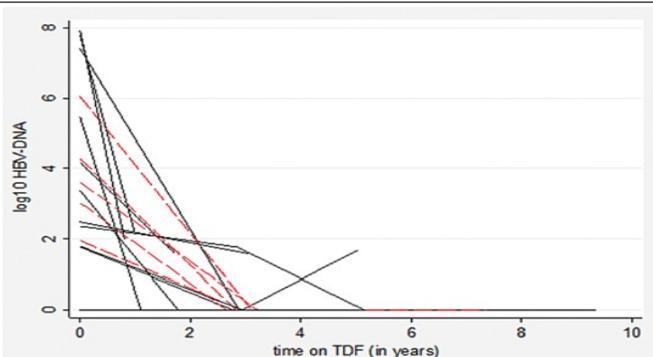


Longterm tenofovir therapy in HIV+/HBV+/HDV+ patients

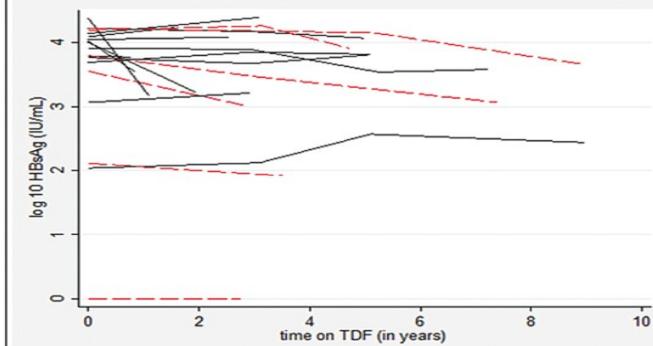
HDV-RNA



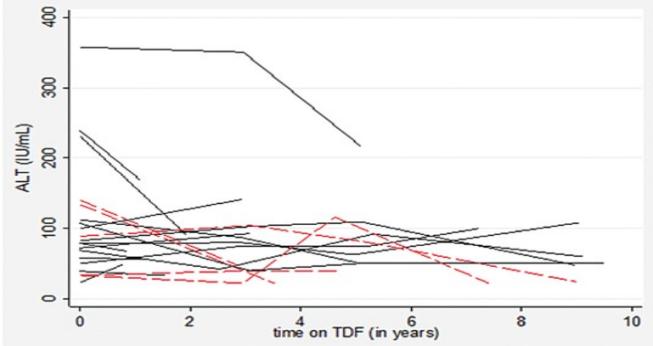
HBV-DNA



HBsAg



ALT



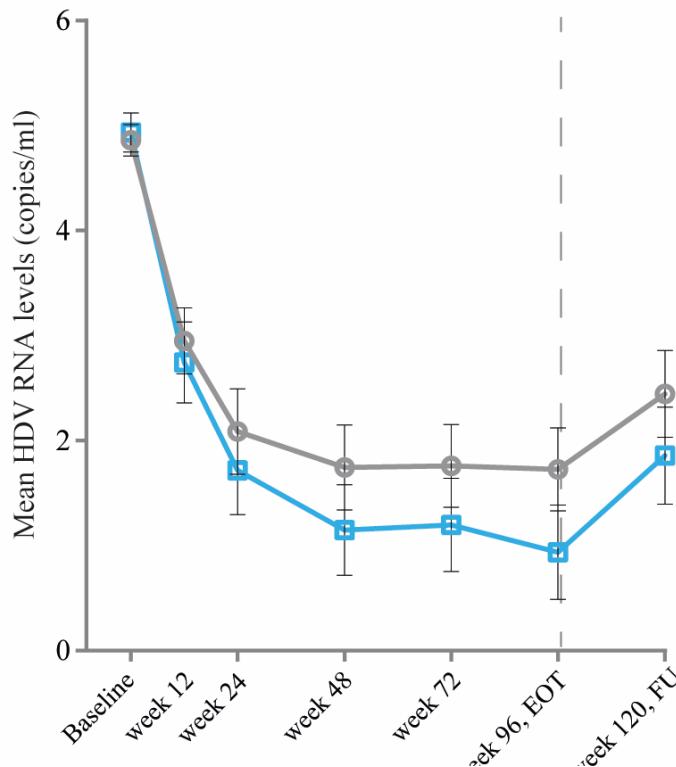
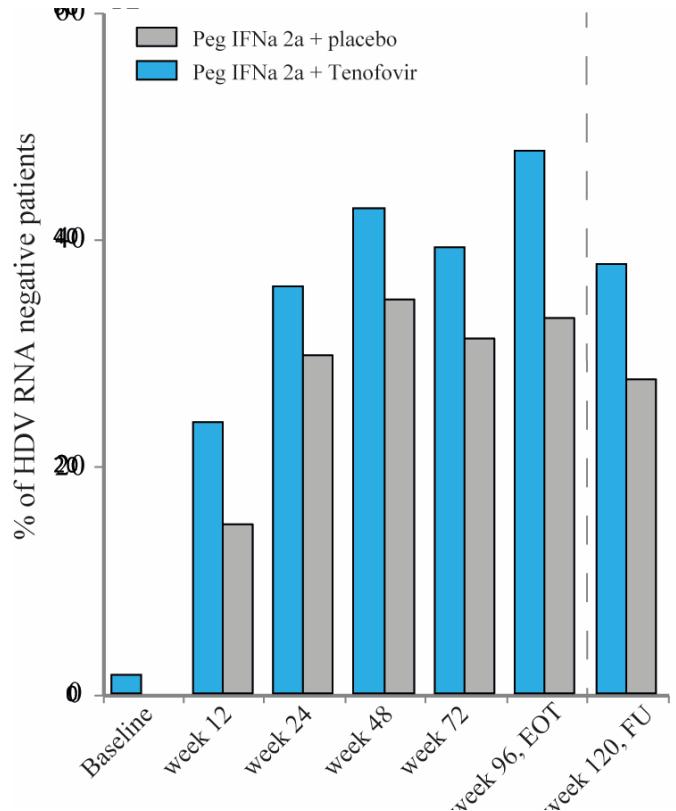
— <2log drop in HDV-RNA - - - >2log drop in HDV-RNA

Beguelin et al., Clin Infect Dis 2017



HDV-RNA relapses occur despite prolonged PEG-IFNa therapy

Numerically (but not significantly) higher response with TDF-combination



Wedemeyer, Yurdagin et al. Lancet ID 2019, 19(3):275-286



Treatment of Hepatitis Delta

PEG-IFNa:

always first line?

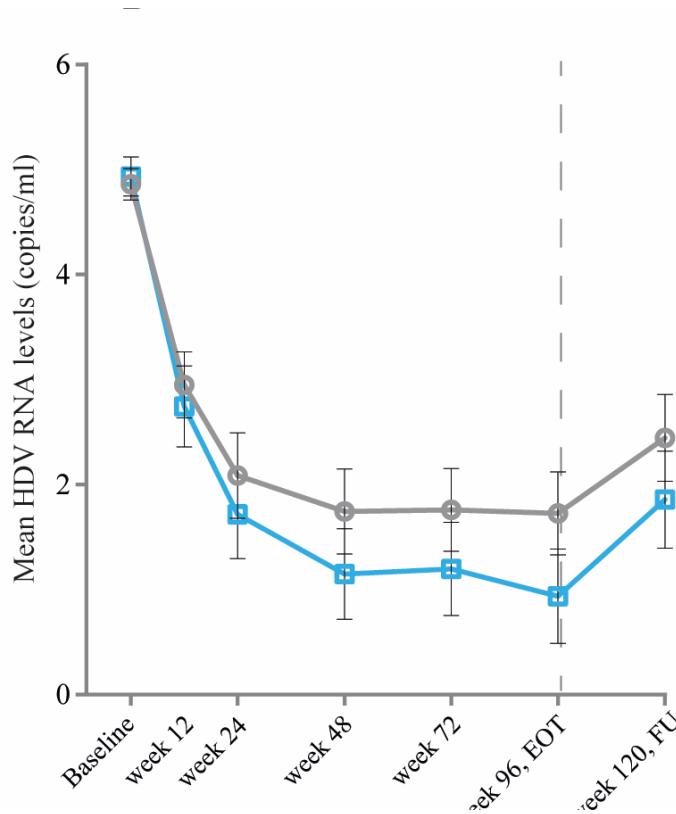
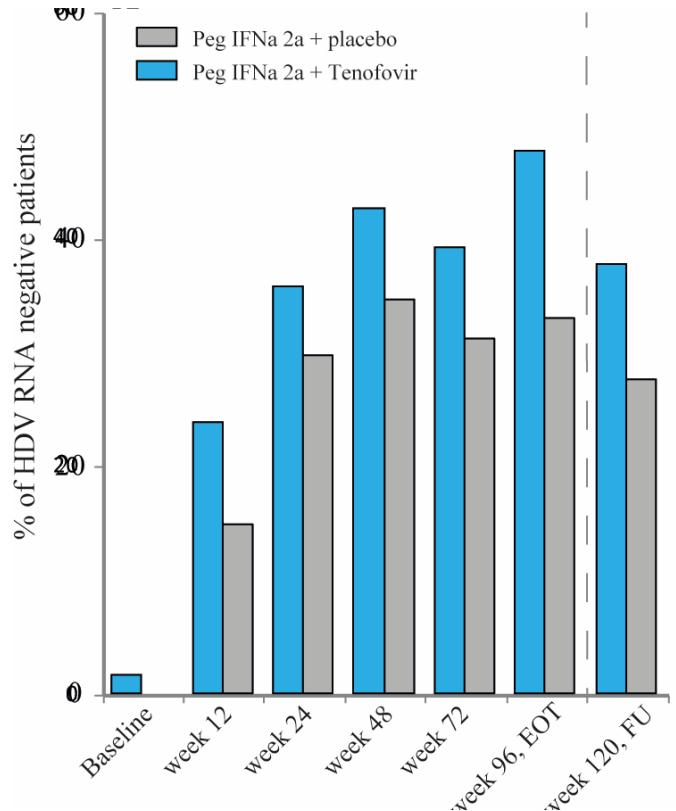
how long?

Stopping rules?



HDV-RNA relapses occur despite prolonged PEG-IFNa therapy

Numerically (but not significantly) higher response with TDF-combination



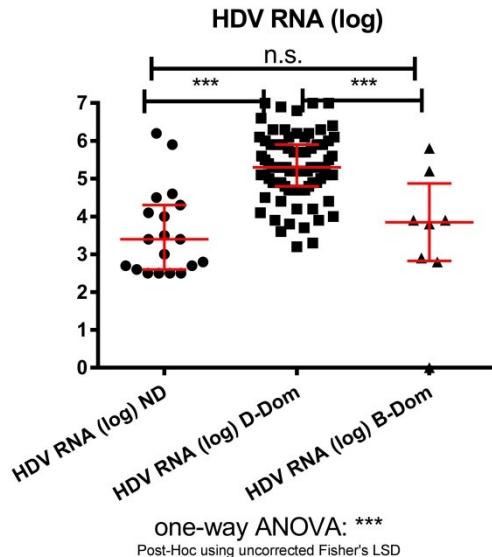
Wedemeyer, Yurdagin et al. Lancet ID 2019, 19(3):275-286



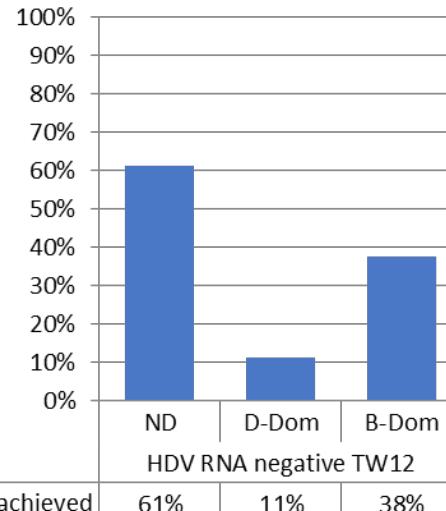
Peginterferon Treatment of Hepatitis Delta

HBV/HDV dominance patterns are associated with treatment response

HDV dominance over HBV



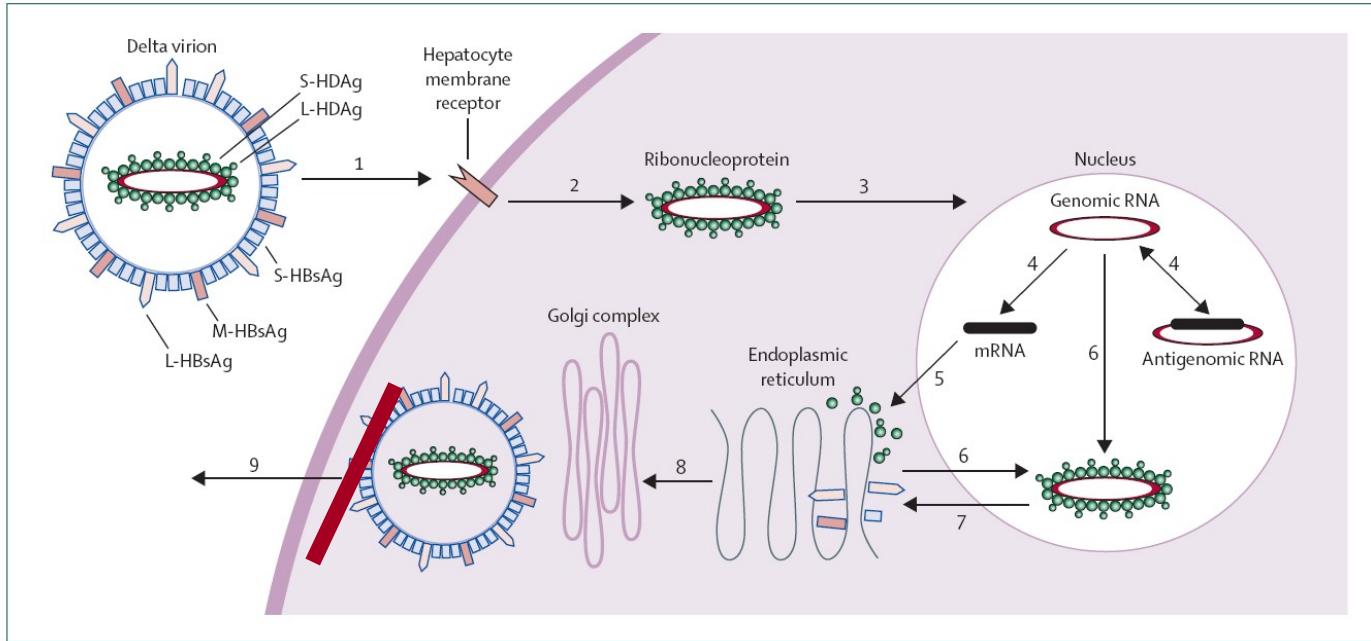
... is associated with reduced response to PEG-IFNa



Lutterkort et al., J Viral Hepatitis 2018



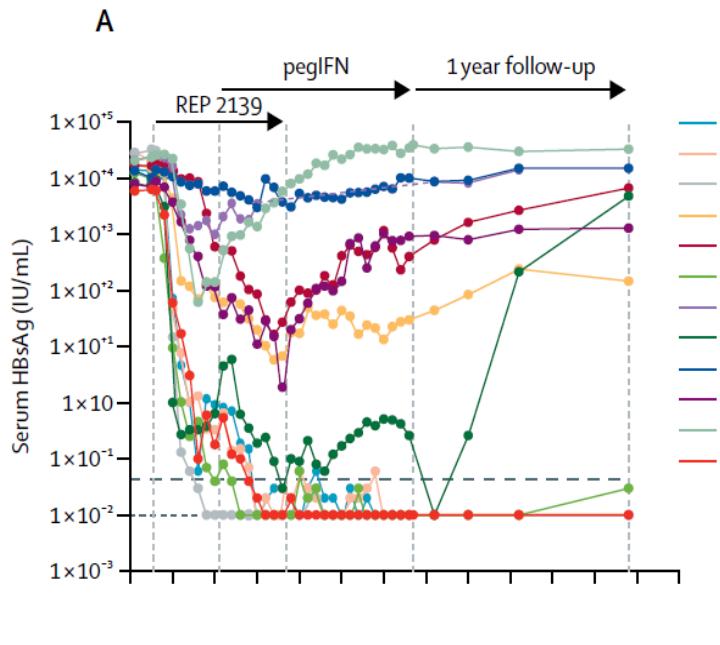
Blocking of subviral particle release



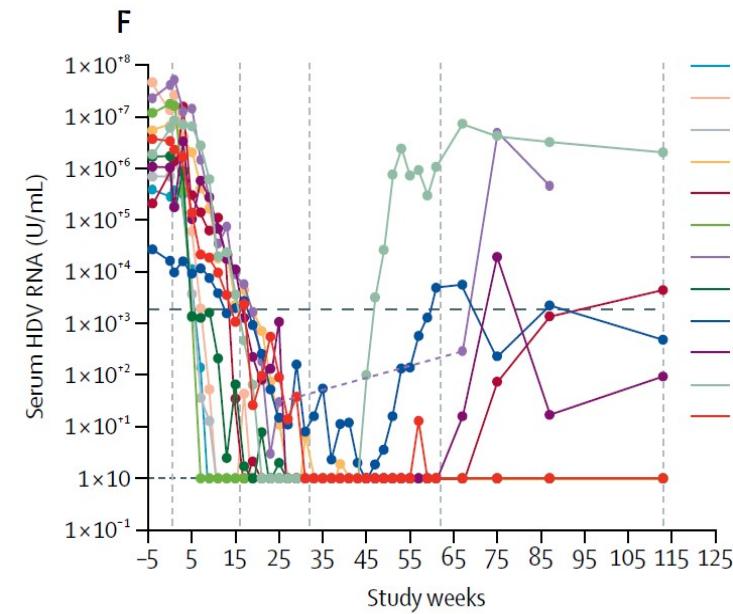
Nucleic Acid Polymers for HDV infection

Rep-3129 : blocking particle release

HBsAg



HDV RNA

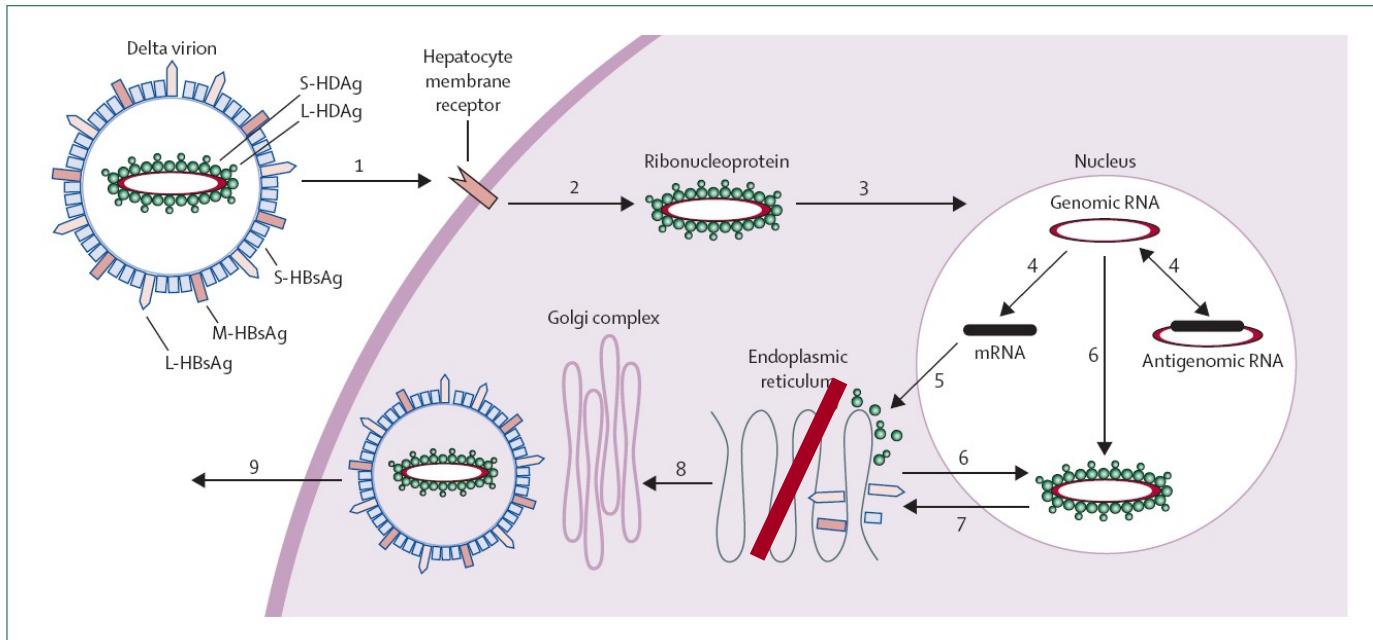


Bazinet et al., Lancet Gastroenterol & Hepatol 2017



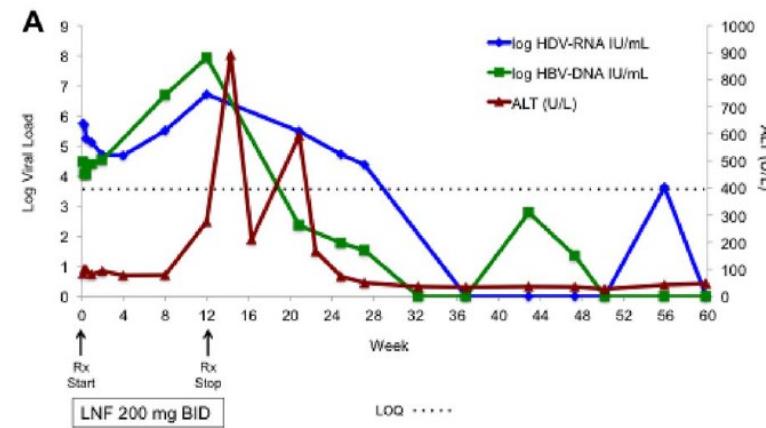
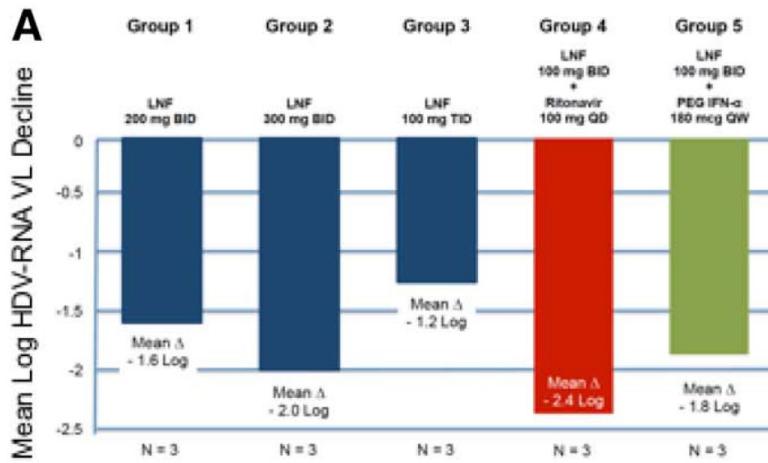
Prenylation inhibition

Blocks virion assembly and packing of viral particles



Lonafarnib for HDV infection

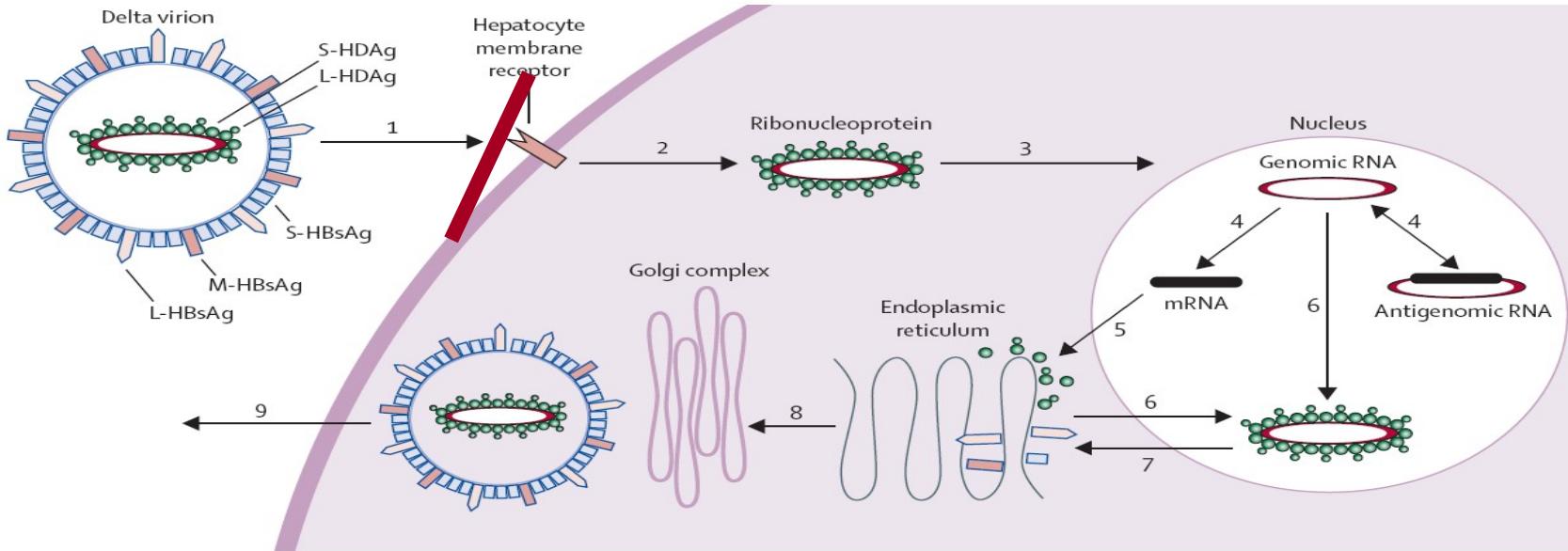
LOWR-HDV-1



Yurdaydin et al., Hepatology 2018

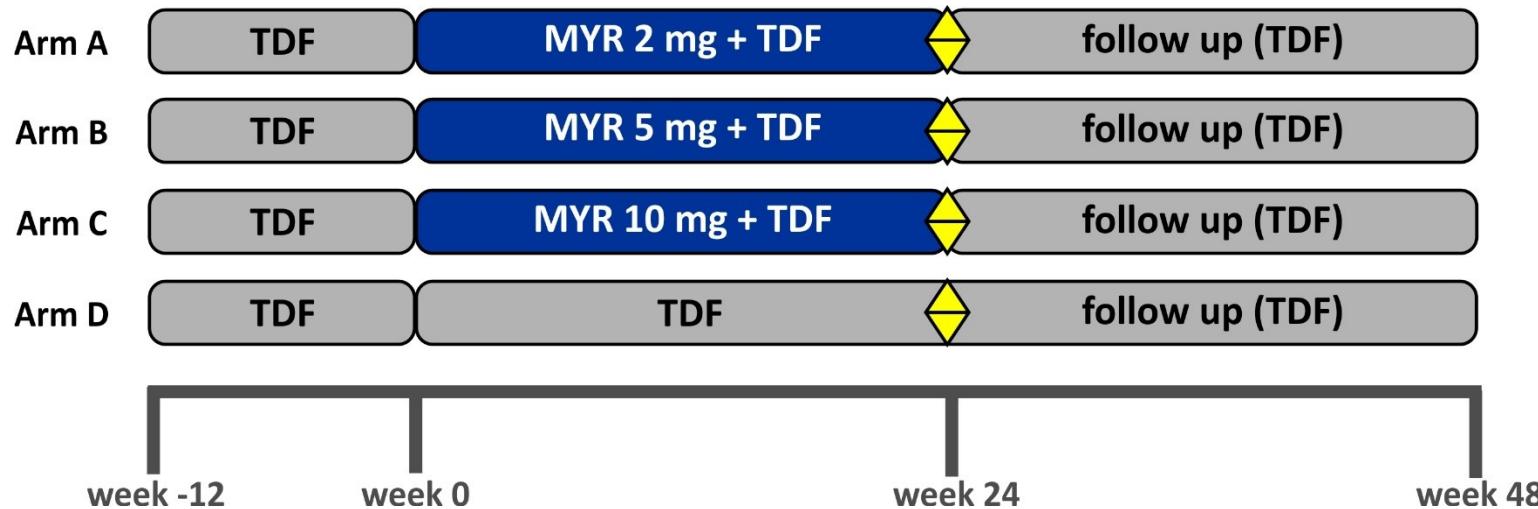


Entry Inhibitor „Myrcludex“

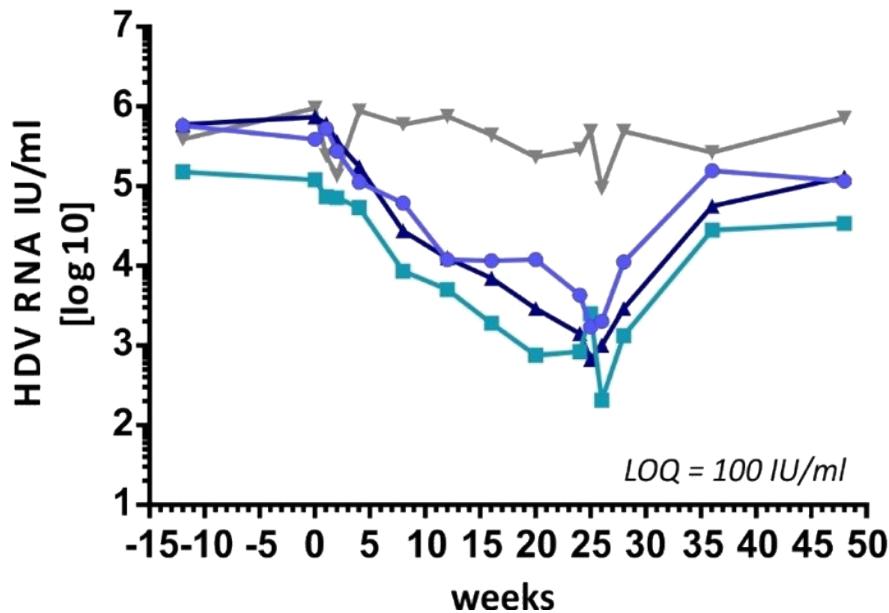


Myrcludex B 202 Study Design

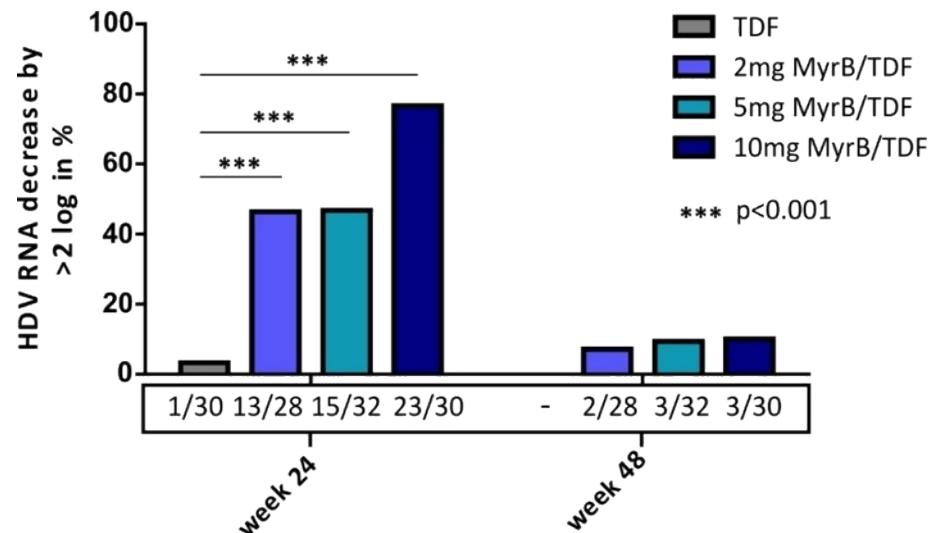
- 120 patients were randomized into 4 treatment arms in a ratio of 1:1:1:1 - 30 patients per arm
- Patients were pretreated with tenofovir for at least 12 weeks
- Myrcludex B was self administered by patients once daily s.c.
- All patients received tenofovir (oral qd) during the entire study period



Myrcludex B 202 Trial: Dose dependent HDV RNA decline



HDV RNA response: 2log decline or undetectable

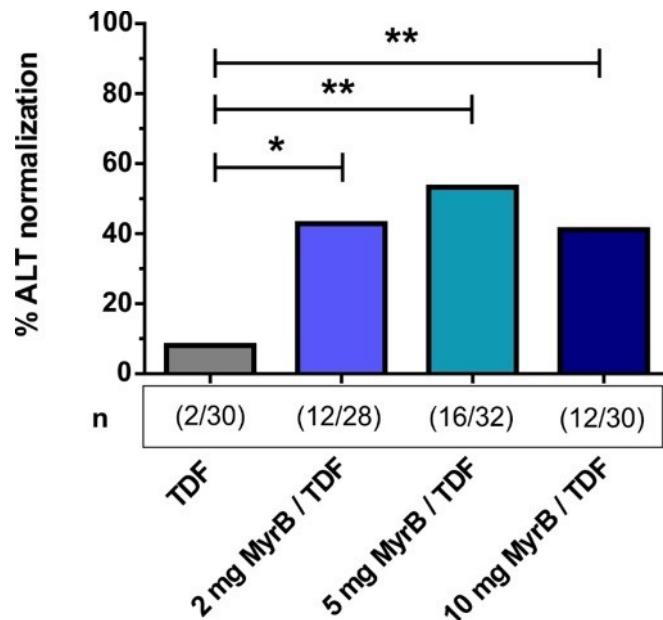


Wedemeyer et al. AASLD 2017 & EASL-ILC 2018



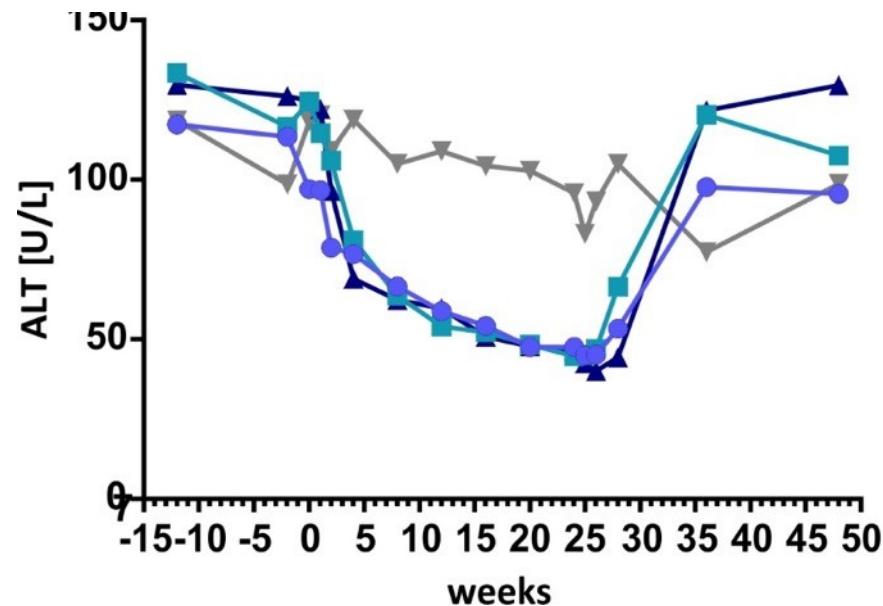
Myrcludex B 202 Trial: ALT decline is not dose-dependent

ALT normalization (week 24)

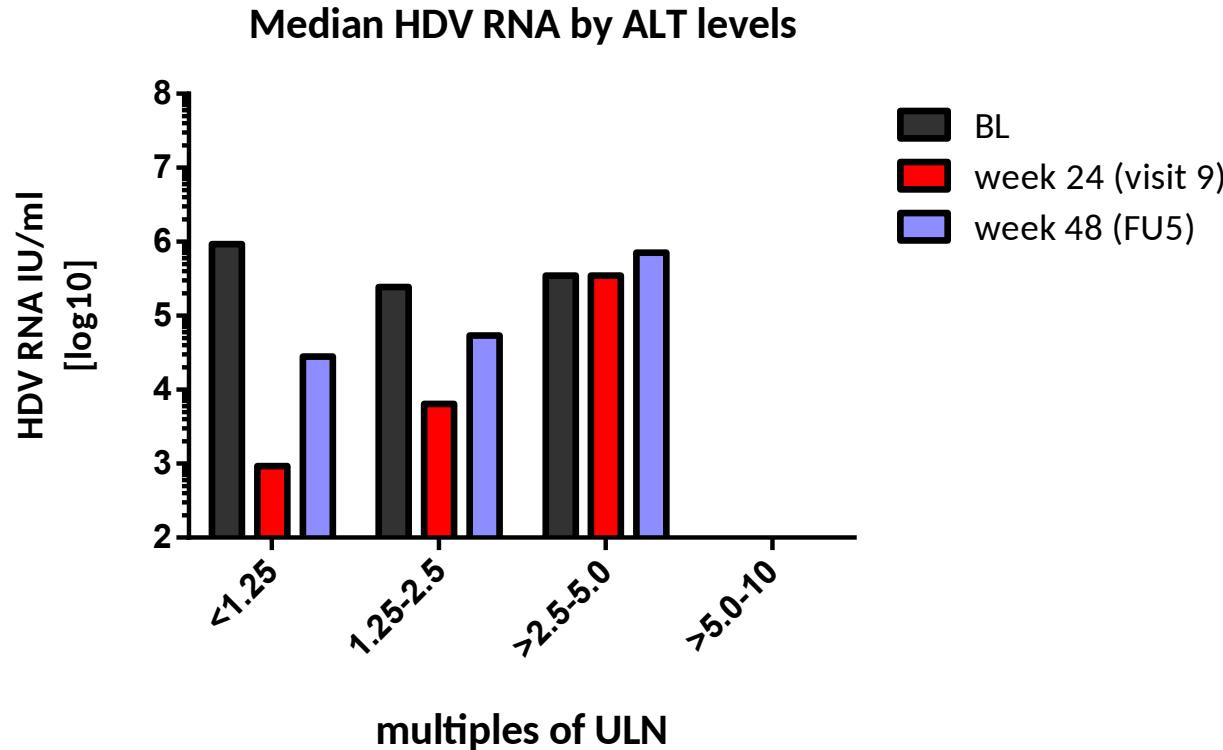


MyrB 2mg vs TDF * p=0.0013
MyrB 5mg vs TDF ** p=0.0002
MyrB 10mg vs TDF ** p=0.0023

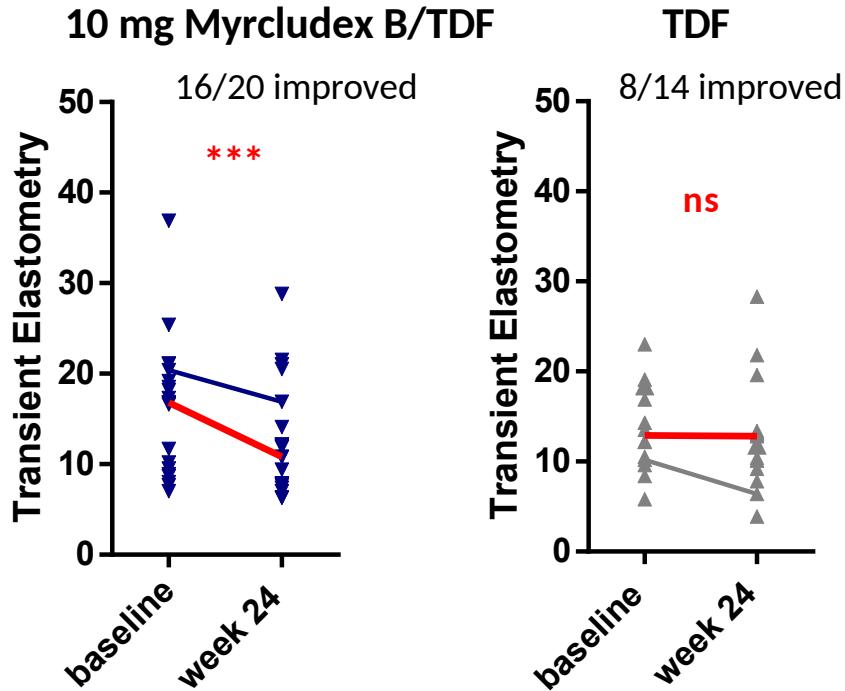
Mean ALT levels



Correlation between HDV RNA response and ALT decline



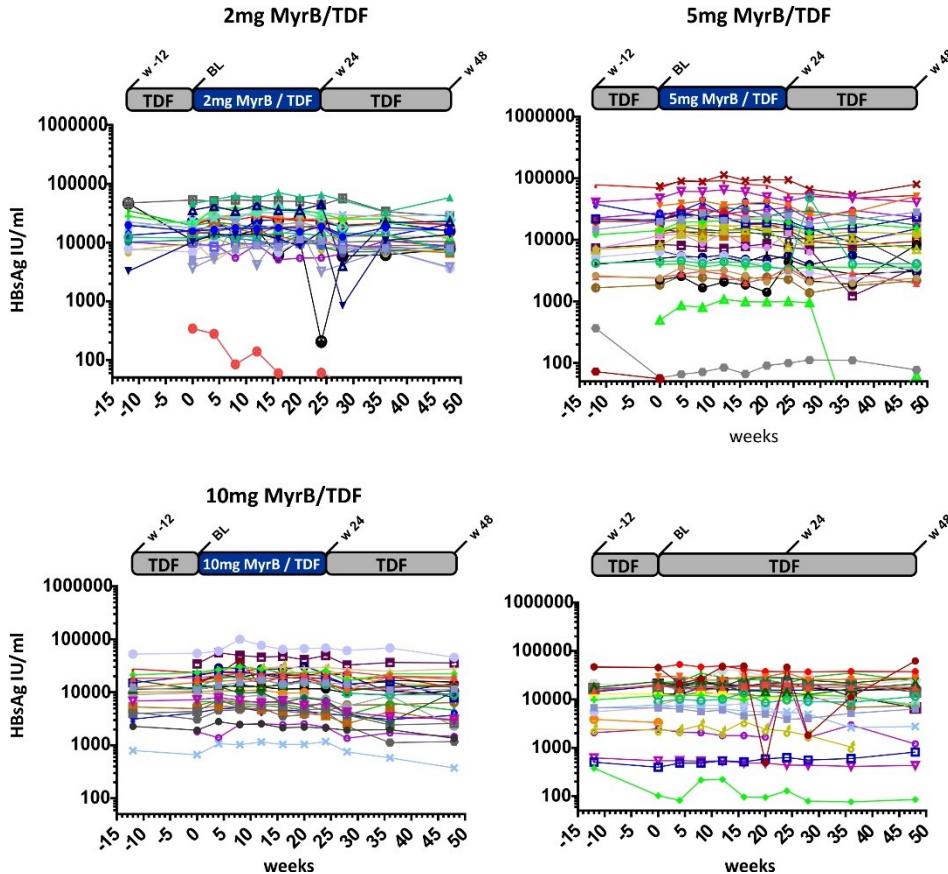
Fibroscan changes



*** p<0.001

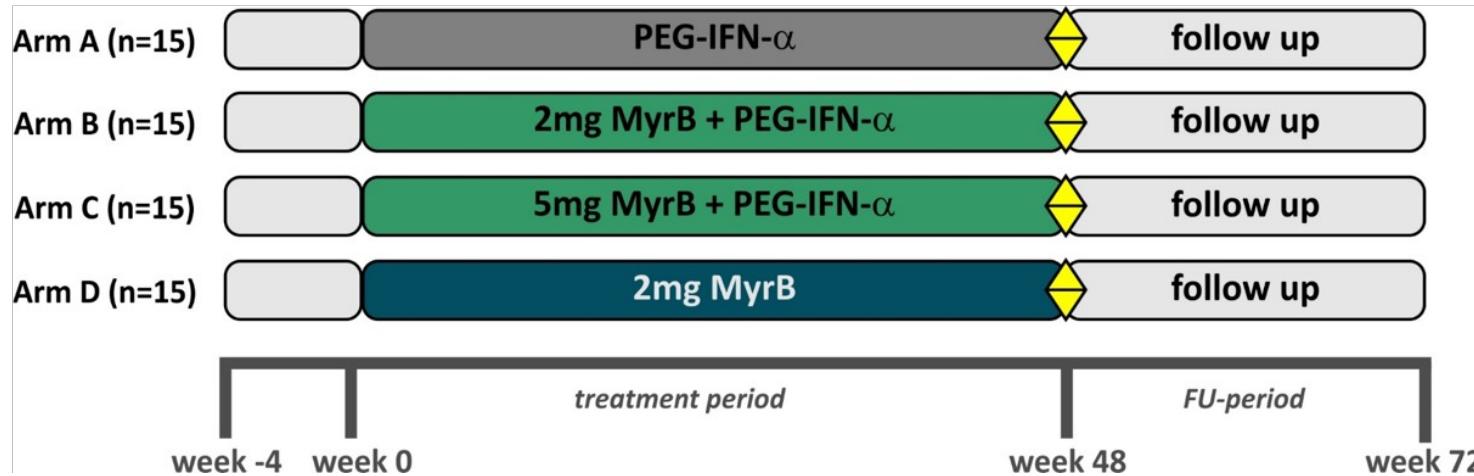


HBsAg response



Myrcludex B and PEG-IFNa combination: 203 Trial

- 60 patients with chronic HBV/HDV co-infection were randomized into 4 treatment arms in a ratio of 1:1:1:1 - 15 patients per arm
- Myrcludex B was self administered by patients once daily s.c.

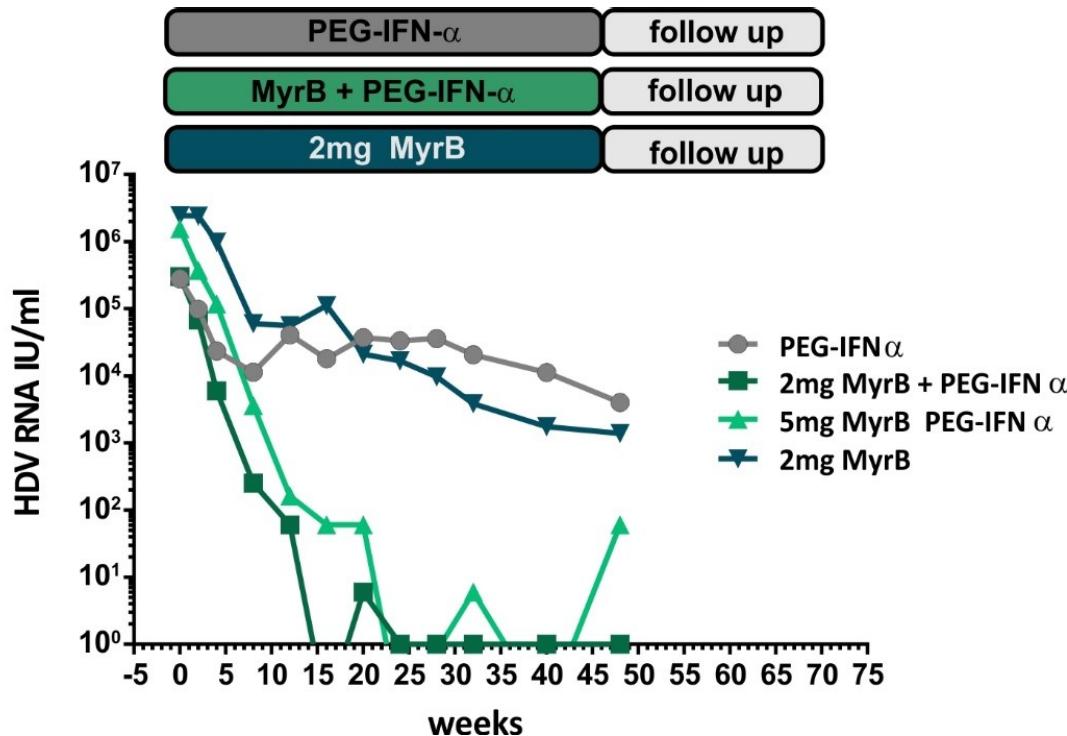


Wedemeyer et al. AASLD 2018



Virological Response (HDV RNA)

Median HDV RNA levels



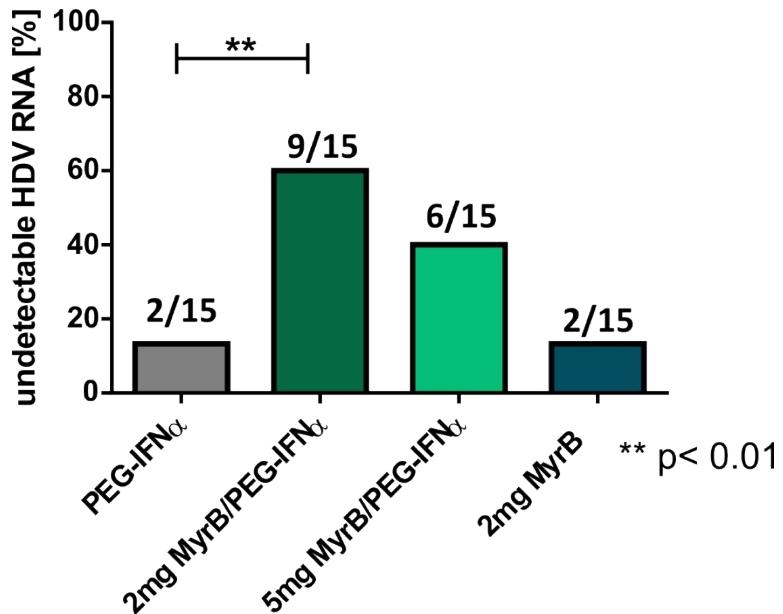
Median RNA \log_{10} change to BL
at week 48:

2mg MyrB/PEG-IFN α :	-3.62
5mg MyrB/PEG-IFN α :	-4.48
2mg MyrB:	-2.84
PEG-IFN α :	-1.14

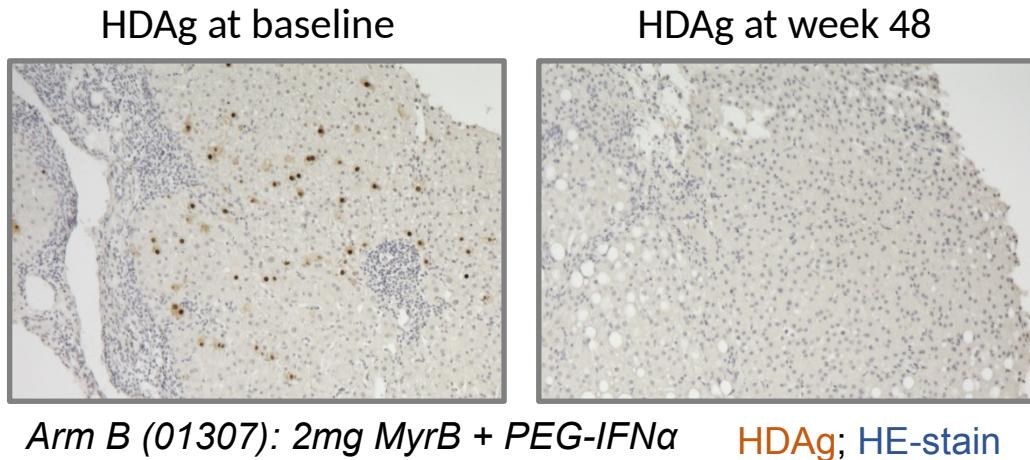


Virological Response (HDV RNA)

Secondary endpoint:
undetectable HDV RNA at week 48

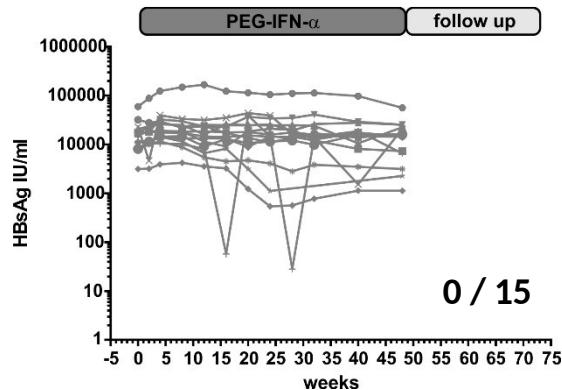


- Plasma HDV RNA decline correlated with intrahepatic decrease of HDV RNA replication and HDAg-positive cells

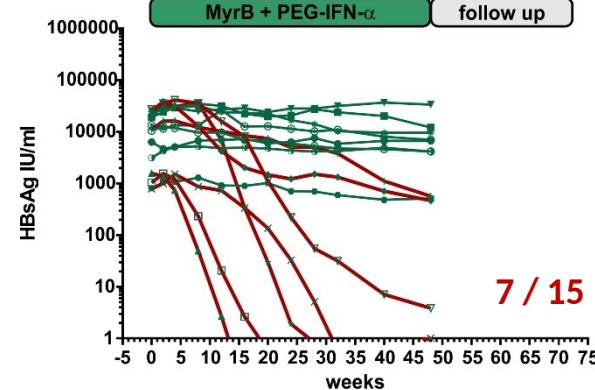


HBsAg Response ($\geq 1\log_{10}$ decline or undetectable)

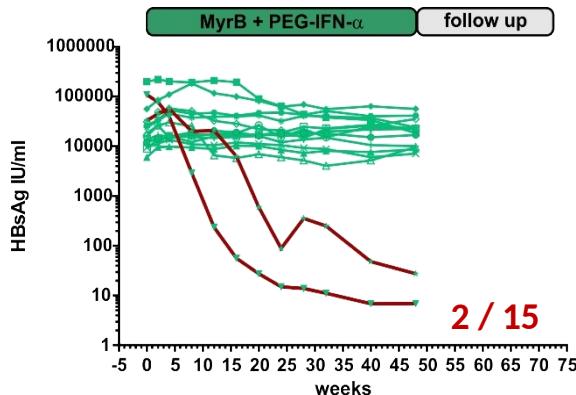
Arm A: PEG-IFN- α



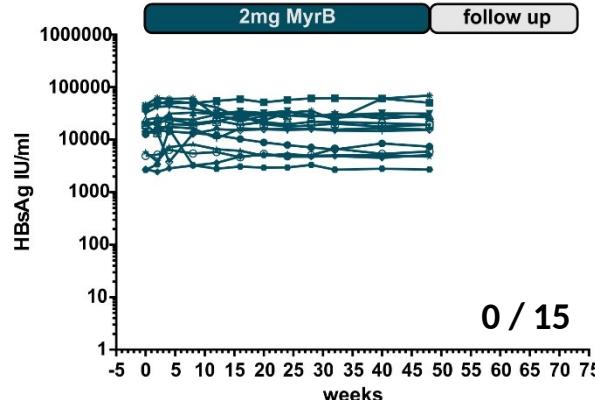
Arm B: 2mg MyrB + PEG-IFN- α



Arm C: 5mg MyrB + PEG-IFN- α



Arm D: 2mg MyrB



Summary 203 Study

- Myrcludex B therapy was safe and well tolerated
- **Myrcludex B monotherapy (2mg qd):**
 - continuous linear HDV RNA decline and ALT reduction over 48 weeks (combined response in 60% of patients)
- **Myrcludex B/PEG-IFNa combination therapy:**
 - HDV RNA undetectable in 15/30 patients (50%) (vs. 13% in PEG-IFNa mono)
 - $>1\log_{10}$ HBsAg decline in 47% (2mg/PEG-IFNa) and 13.3% (5mg/PEG-IFNa)



Summary

- PEG-IFNa is currently the only treatment option for HDV infection
- HBV entry inhibition, prenylation inhibition, block of particle formation and IFN-lambda may represent new treatment options
- Novel strategies to achieve HBsAg clearance need to be explored in hepatitis delta!

