Clinical challenges in the development of HDV infection

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Novel HDV therapies: SWOT analysis

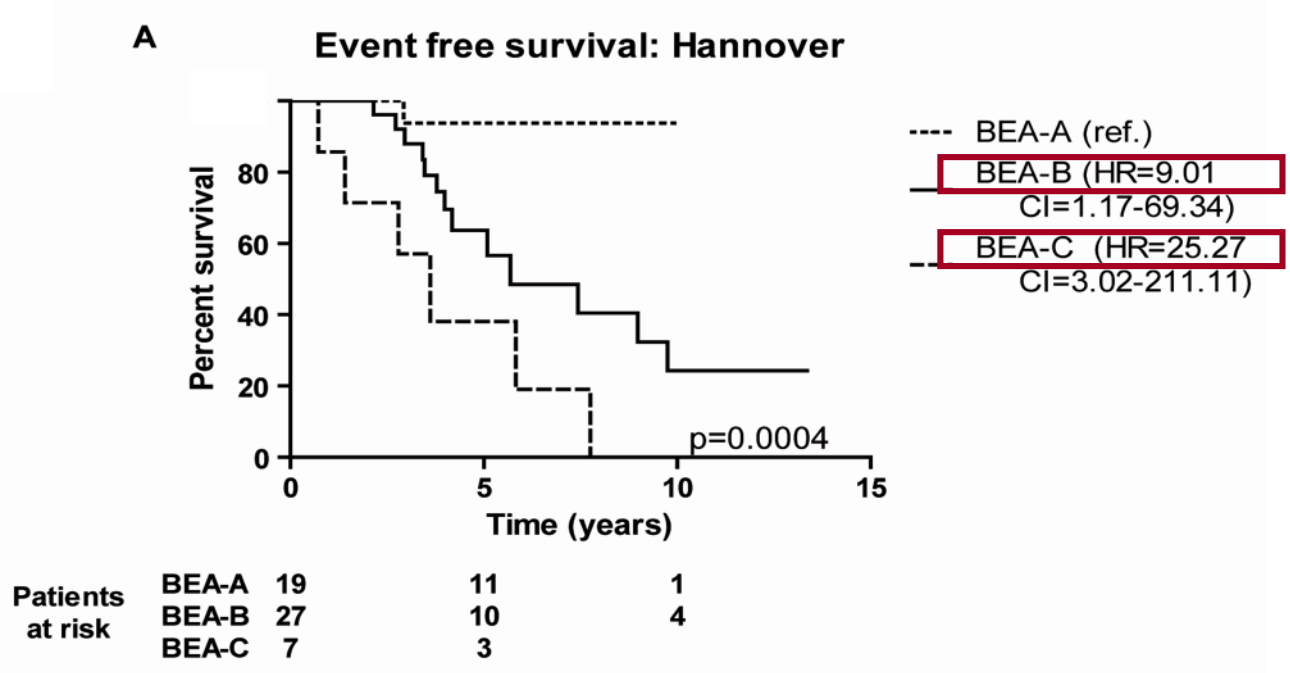
Strengths

- Standardized virological endpoints
- HDV RNA in addition to HBsAg + HBV DNA
- Liver biopsies are still performed
- Motivated patients

Opportunities

- High unmet medical need
- No approved therapy
- Some side effects acceptable
- HDV could help to develop HBV drugs

Survival according to the BEA-score



Calle Serrano et al. J Viral Hepatitis 2014

Treatment of Hepatitis Delta with PEG-IFNa-2a: ~25% HDV RNA suppression

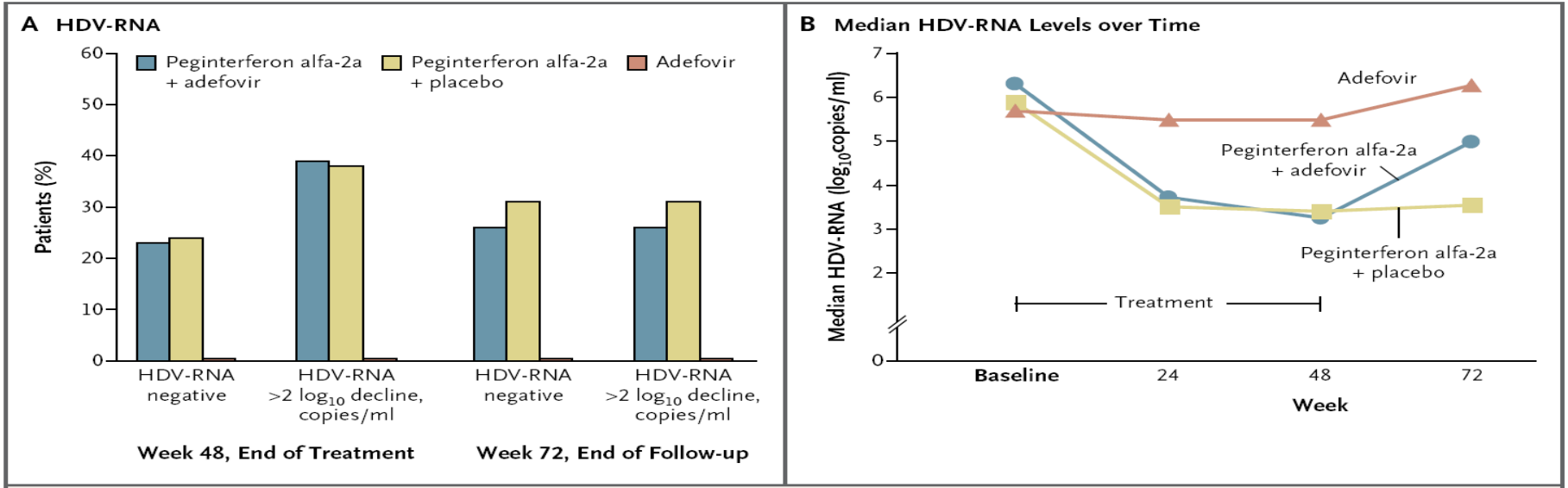
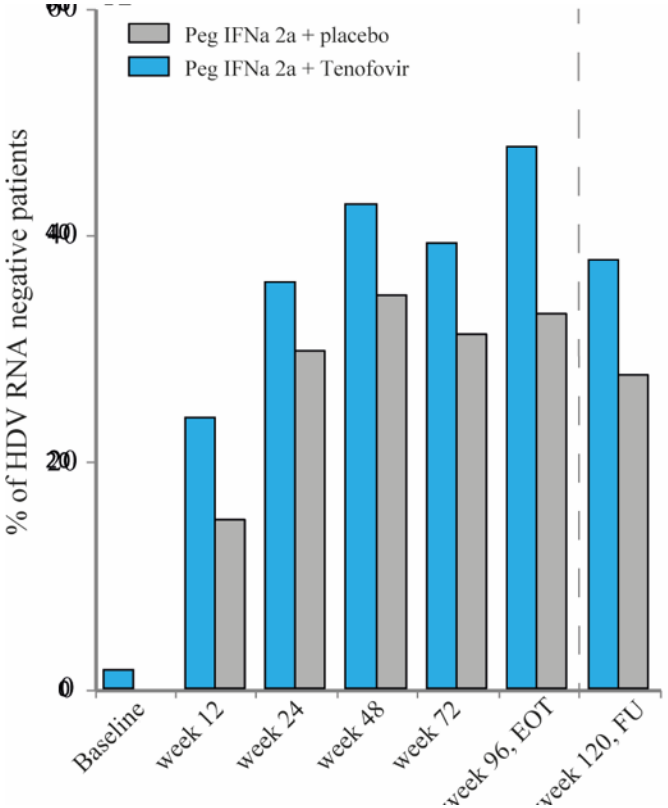
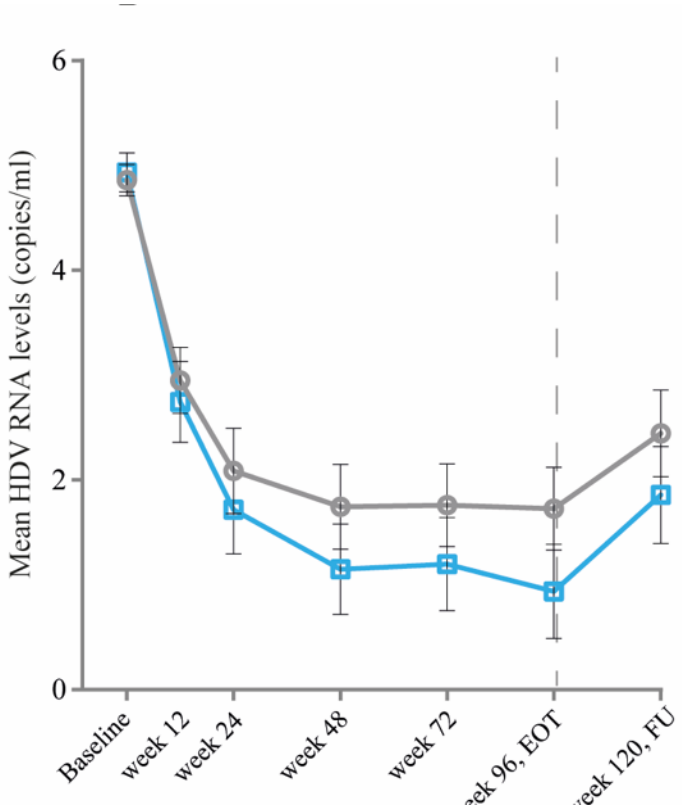


Figure 1. Virologic Response to Treatment as Determined by Serum Level of HDV RNA, According to Treatment Group.

Wedemeyer, Yurdaydin et al. NEJM 2011

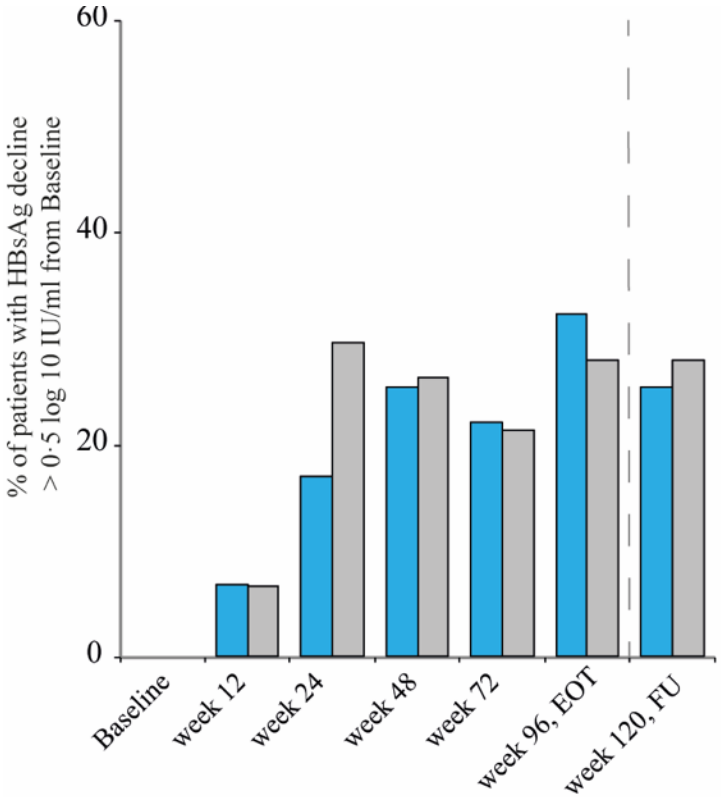
HDV-RNA relapses occur despited prolonged PEG-IFNa therapy

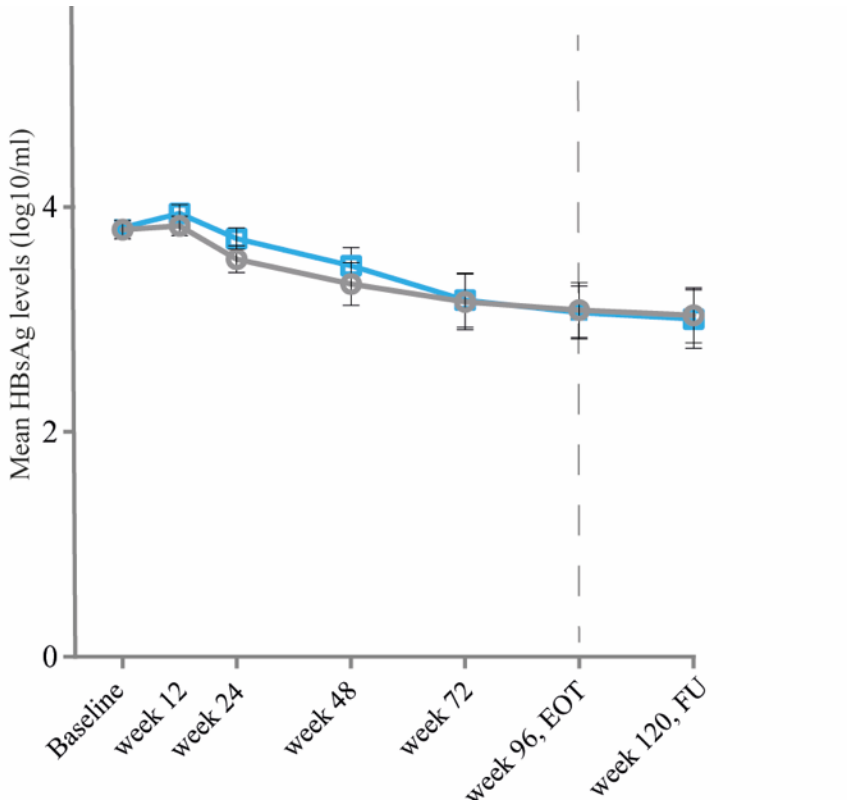




Wedemeyer, Yurdaydin et al. Lancet ID 2019, 19(3):275-286

No difference in HBsAg decline between PEG-IFNa + Placebi and PEG-IFNa + TDF





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

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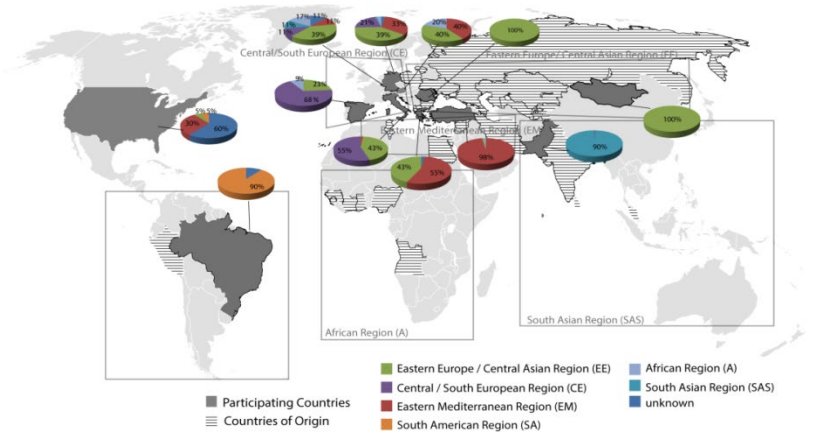
- Orphan Disease
- Heterogeneity
- Epidemiology of HDV infection
- Surrogates for clinical endpoints

Threats

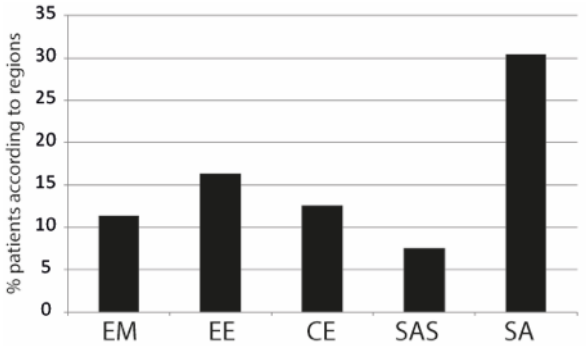
- Severity of liver disease
- Two infections
- Relapse after treatment (“SVR”?)
- PEG-IFNa backbone

Heterogeneity of hepatitis delta world-wide: the HDIN network

- The Hepatitis Delta International Network (HDIN)
- 1579 anti-HDV+ or HDV-RNA+ patients from 15 countries



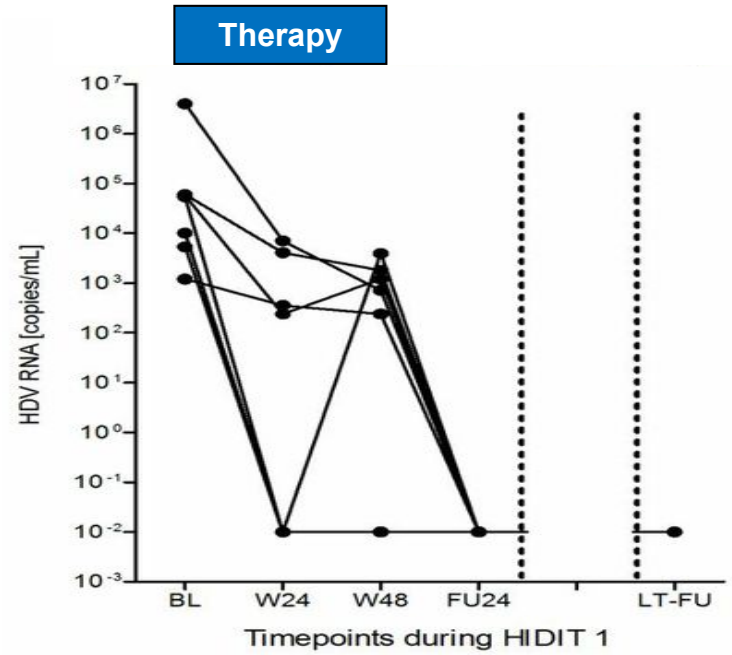
Hepatic clinical complications



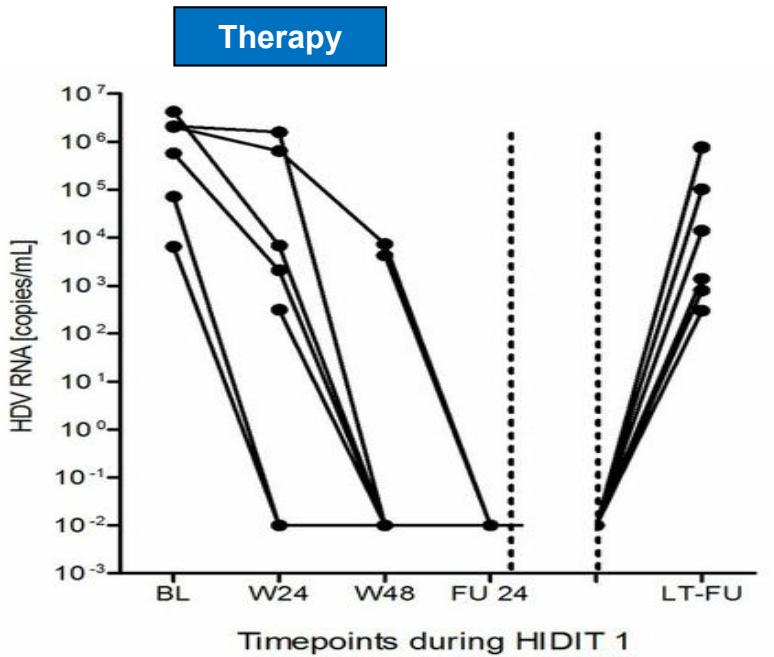
Wranke et al., Liver International 2018

Late Relapses after initial response! **No „SVR“ in hepatitis delta!**

Long Term Virological Response



Late Relapse



Heidrich et al., Hepatology 2014

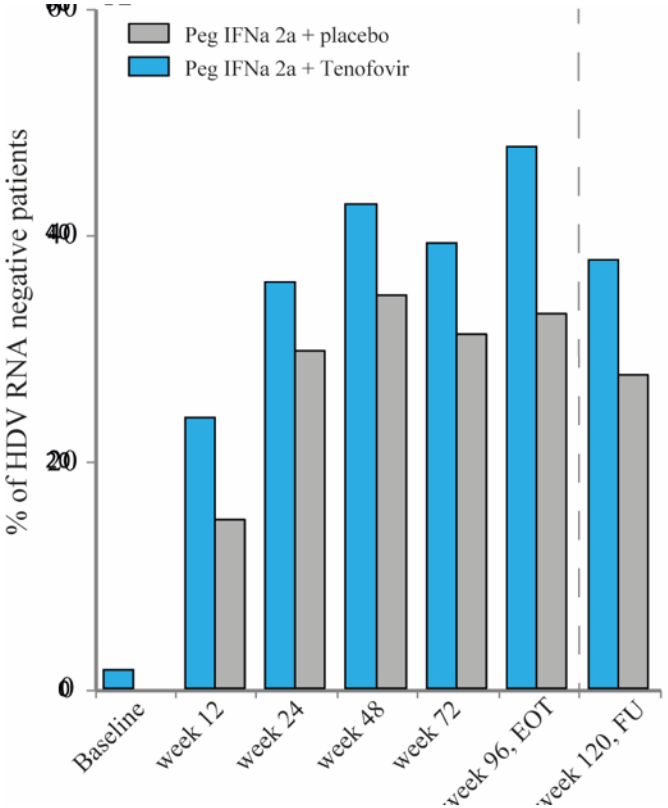
Giersch et al., Gut 2019; 68: 150-157

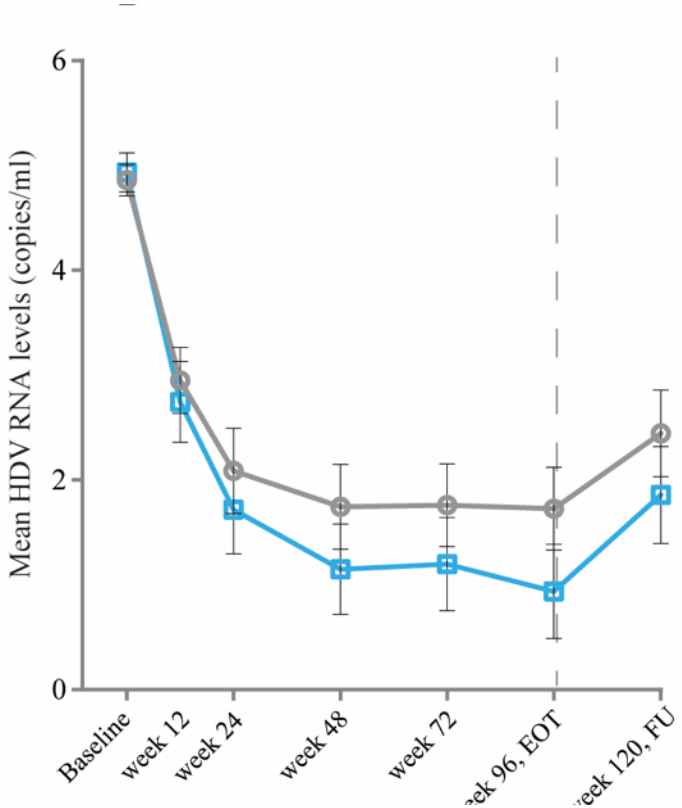
Hepatitis delta virus persists during liver regeneration and is amplified through cell division both in vitro and in vivo.

Mederacke et al., J Hepatol 2012; 56: 115-22

Rapid early HDV RNA decline in the peripheral blood but prolonged intrahepatic hepatitis delta antigen persistence after liver transplantation.

HDV-RNA relapses occur despited prolonged PEG-IFNa therapy





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

Treating chronic hepatitis delta: The need for surrogate markers of treatment efficacy

Cihan Yurdaydin[1,*], Zaigham Abbas[2], Maria Buti[3], Markus Cornberg[4], Rafael Esteban[3], Ohad Etzion[5], Edward J. Gane[6], Robert G. Gish[7], Jeffrey S. Glenn[7], Saeed Hamid[8], Theo Heller[9], Christopher Koh[9], Pietro Lampertico[10], Yoav Lurie[11], Michael Manns[4], Raymundo Parana[12], Mario Rizzetto[13], Stephan Urban[14], Heiner Wedemeyer[15], on behalf of the Hepatitis Delta International Network (HDIN)[†]

Yurdaydin et al., J Hepatol 2019 epub

Treatment goals in HBV/HDV coinfection

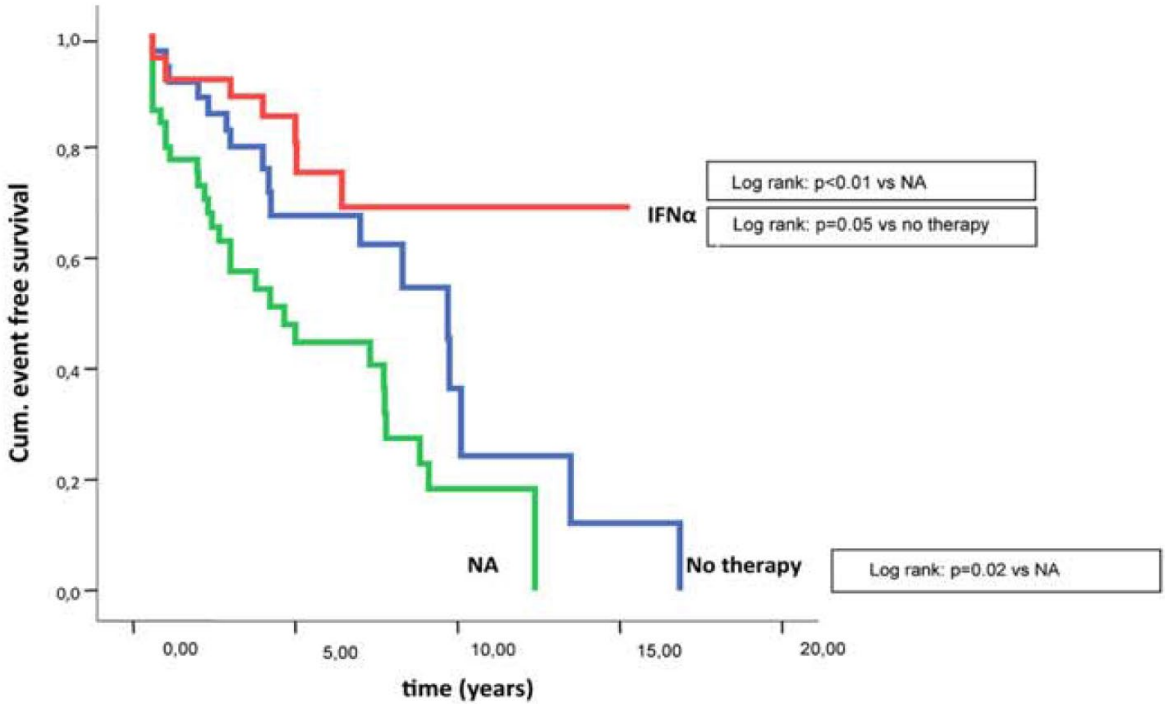
Table 1. Treatment goals for clinical trials in HBV/HDV coinfection.

Treatment goals	Parameter	Readout
Virologic efficacy during treatment	Relative HDV RNA decline during treatment compared to baseline levels	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity
Virologic efficacy off treatment	HDV RNA suppression/decline 24 weeks off-treatment and during further long-term follow-up	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity
Serological efficacy-1	HBsAg levels (log declines and loss) at end-of treatment and off treatment	validated quantitative HBsAg assay (IU/ml)
Serological efficacy-2	Seroconversion to anti-HBs at end-of treatment and off treatment	validated quantitative anti-HBs assay (IU/L)
Biochemical efficacy (1)	ALT normalisation at the end of treatment and off-treatment	Validated assays (IU/L)
Biochemical efficacy (2)	Relative ALT declines during treatment and off treatment	Validated assays (IU/L)
Combined virologic and biochemical response-1	HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) in combination with ALT normalisation at EOT	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.
Combined virologic and biochemical response-2	HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) in combination with ALT normalisation at 24 weeks off treatment and further during long-term follow-up	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.
Histological efficacy – grading	Improvement of HAI of at least 2 points	Total Ishak inflammation score (A + B + C + D); 0–18 points
Histological efficacy – staging	No worsening of fibrosis scores	Ishak score (0–6 points)
Safety – Drug-specific AEs	AEs and SAEs	Severity and relation ot study drug
Safety – Disease-specific AEs	HBV and HDV reactivation	HBV DNA, HDV RNA, ALT and other liver function parameters
ProQOLs	Quality of life during and after end of therapy	EQ5, SF-36, etc.

AEs, adverse events; ALT, alanine aminotransferase; cccDNA, covalently closed circular DNA; EOT, end of treatment; HBV, hepatitis B virus; HBsAg, HBV surface antigen; HDV, hepatitis D virus; SAEs, serious AEs.

Yurdaydin et al., J Hepatol 2019 epub

Improved outcome of hepatitis delta in IFNa-treated patients



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

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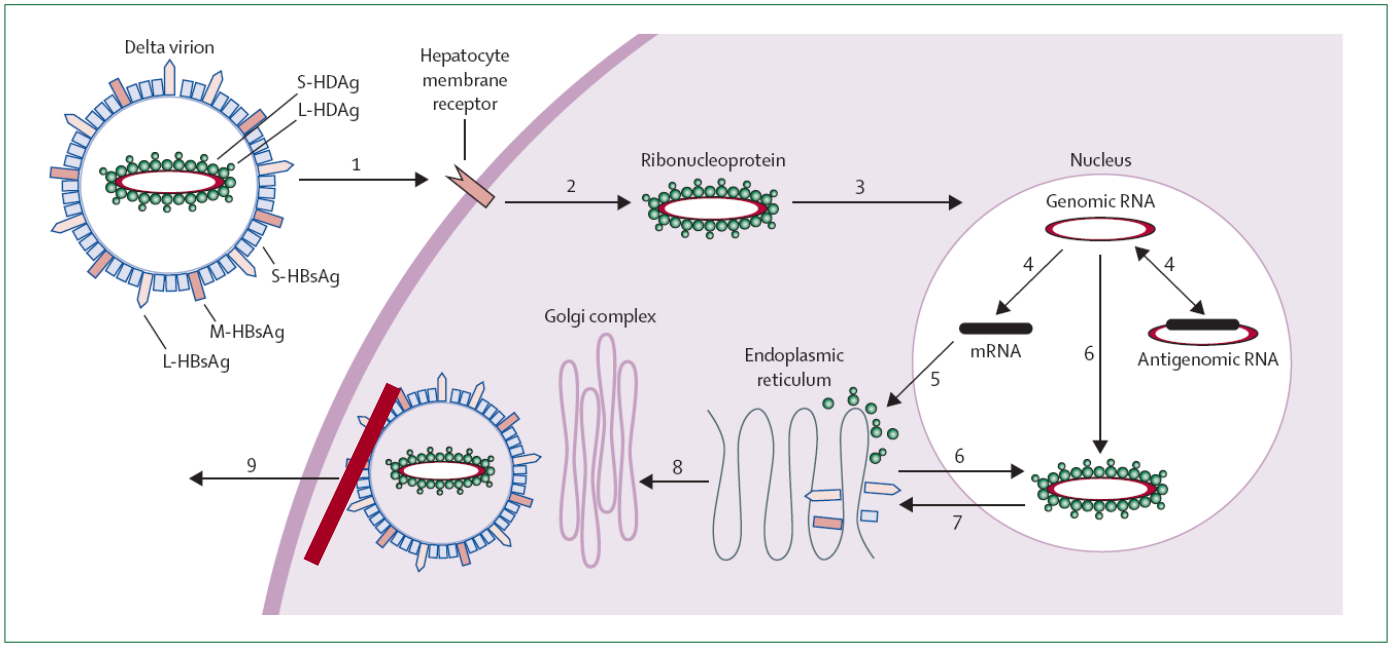
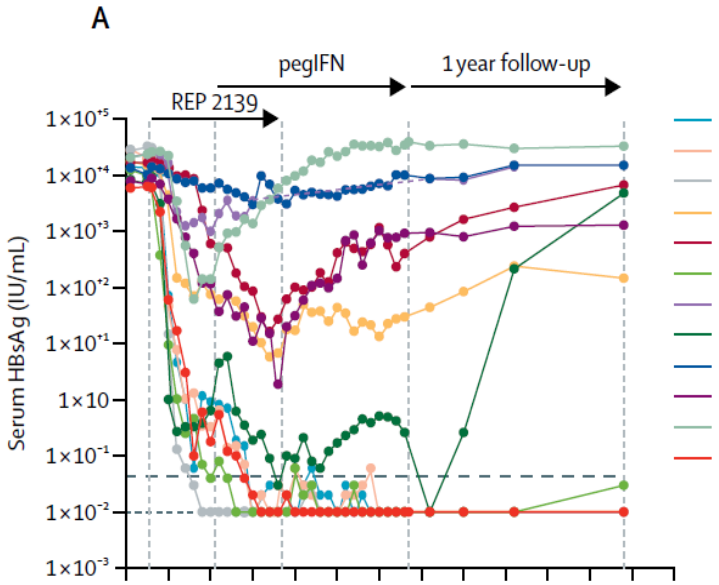
Blocking of subviral particle release



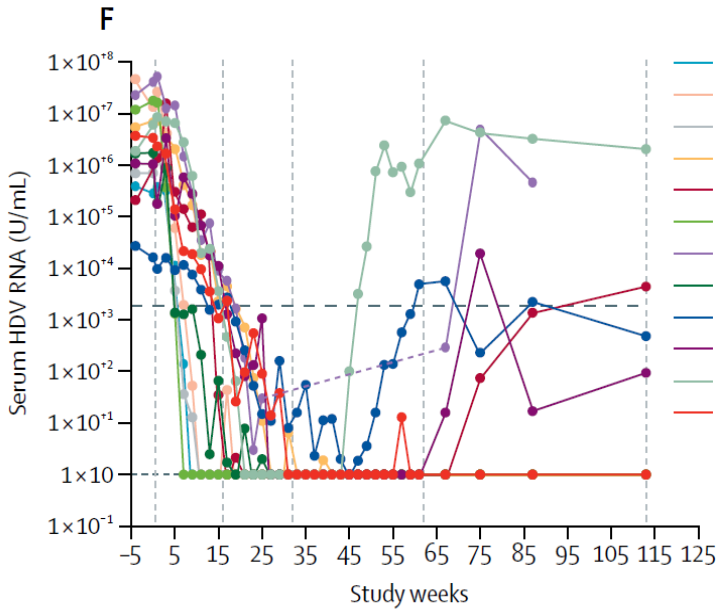
Nucleic Acid Polymers for HDV infection

Rep-3129 : blocking particle release

HBsAg

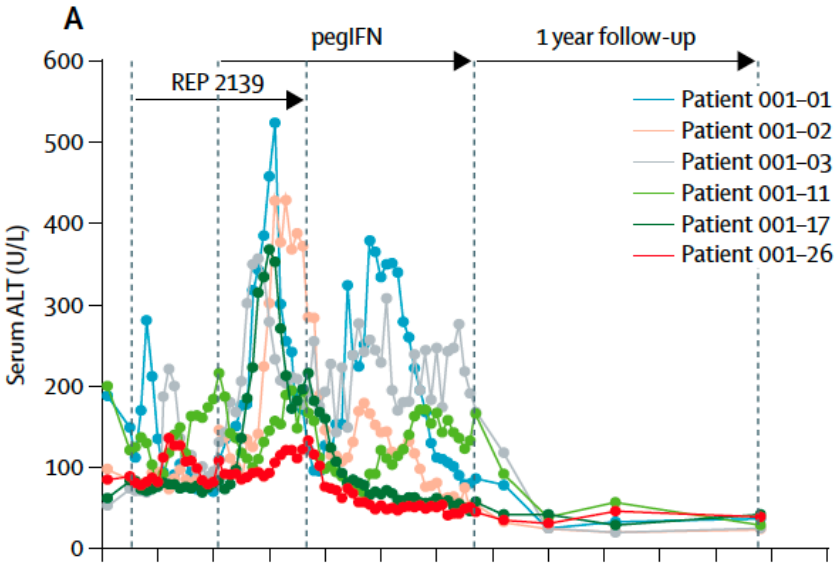


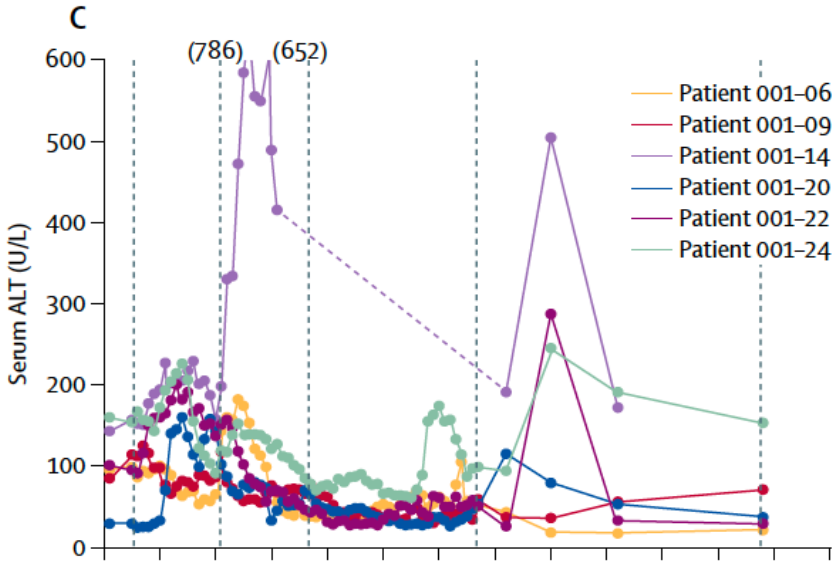
HDV RNA



Bazinet et al., Lancet Gastroenterol & Hepatol 2017

ALT flares during and after Nucleic Acid Polymers treatment





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Yurdaydin et al., J Hepatol 2019 epub