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Hepatitis Delta – Optimal treatment
PEG-IFN monotherapy

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Conflicts of interest

- **Advisor: Abbvie, Albireo, Astra Zeneca, Elpen, Genesis, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Takeda**

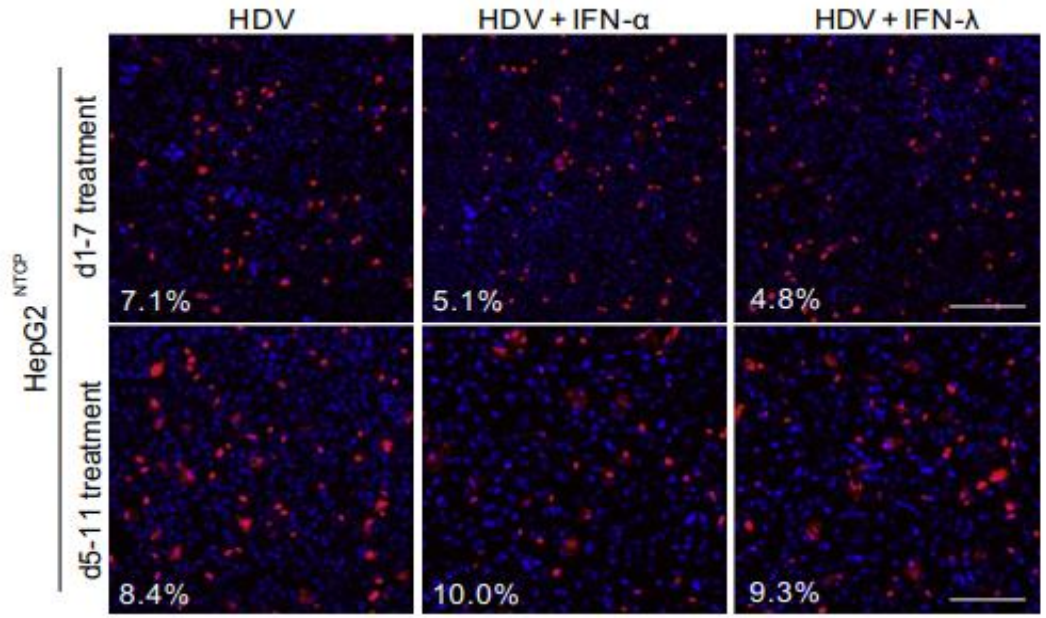
- **Lecturer: Abbvie, Astra Zeneca, Elpen, Genesis, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche**

- **Research grants: Abbvie, Gilead, Takeda, Vianex**

- **Clinical trials: Abbvie, Astellas, Bayer, Celgene, Eiger, Gilead, Janssen, Merck Sharp & Dohme, Noorik, Novartis, Novo Nordisk, Roche, Takeda**

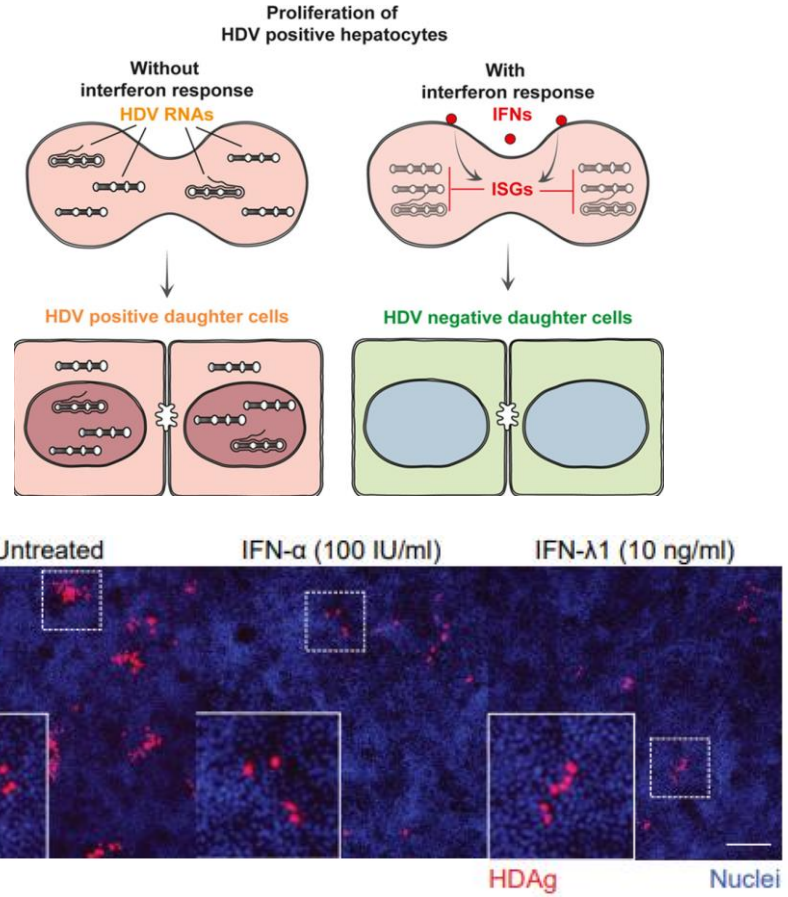
PEG-IFNa is not approved by EMA for the treatment of hepatitis delta

Novel IFN modes of action



- IFN-a and IFN-λ exhibited **only a moderate effect (<50% inhibition) on HDV replication**
- This inhibition was only observed when we treated the cells at **an early stage of infection (day 1–7) but no effect after the establishment of infection (day 5–11),** suggesting an inhibitory effect on viral entry.

Z Zhang et al, J Hepatol 2018; 69:25-35



- Both HDV-induced IFN response and exogenous IFN treatment suppress **cell division-mediated HDV spread**
- **More pronounced effect** of IFN therapy in patients with **lower HDV serum RNA levels**

Zhang et al, J Hepatol 2022; 77:957-966

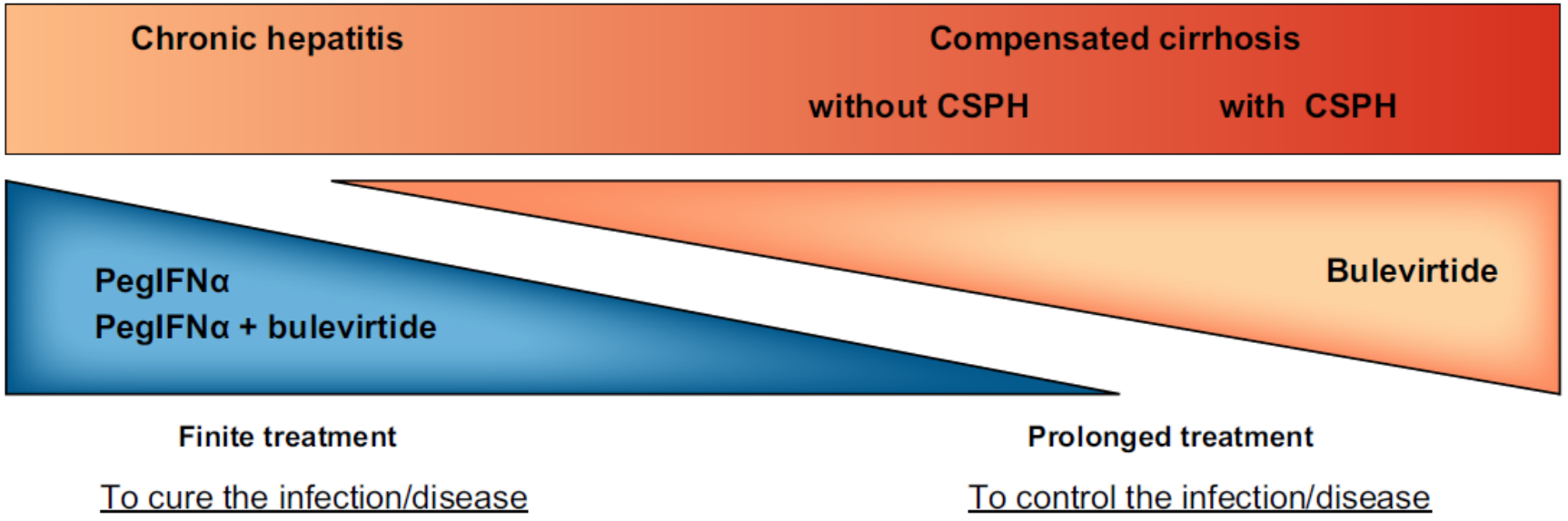
Which patients with CHD can be treated with PegIFNa?

Recommendations

- All patients with CHD and compensated liver disease, irrespective of whether they have cirrhosis or not, should be considered for treatment with PegIFNα **(LoE 2, strong recommendation, consensus).**
- PegIFNα for 48 weeks should be the preferred treatment schedule **(LoE 3, strong recommendation, consensus).**
- Personalised treatment durations may be considered based on HDV RNA and HBsAg kinetics and treatment tolerability **(LoE 3, weak recommendation, strong consensus).**

EASL HDV CPGs. J Hepatol 2023;79:433–460

Management of antiviral treatment in patients with CHD



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

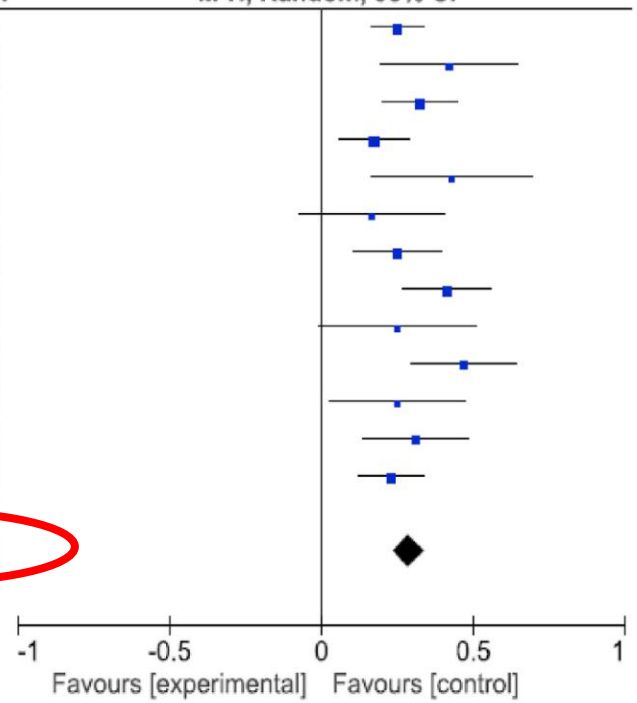
EASL HDV CPGs. J Hepatol 2023;79:433–460

PEG-IFNa in CHD: Meta-analysis
Virological response at 24 weeks after EOT

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)

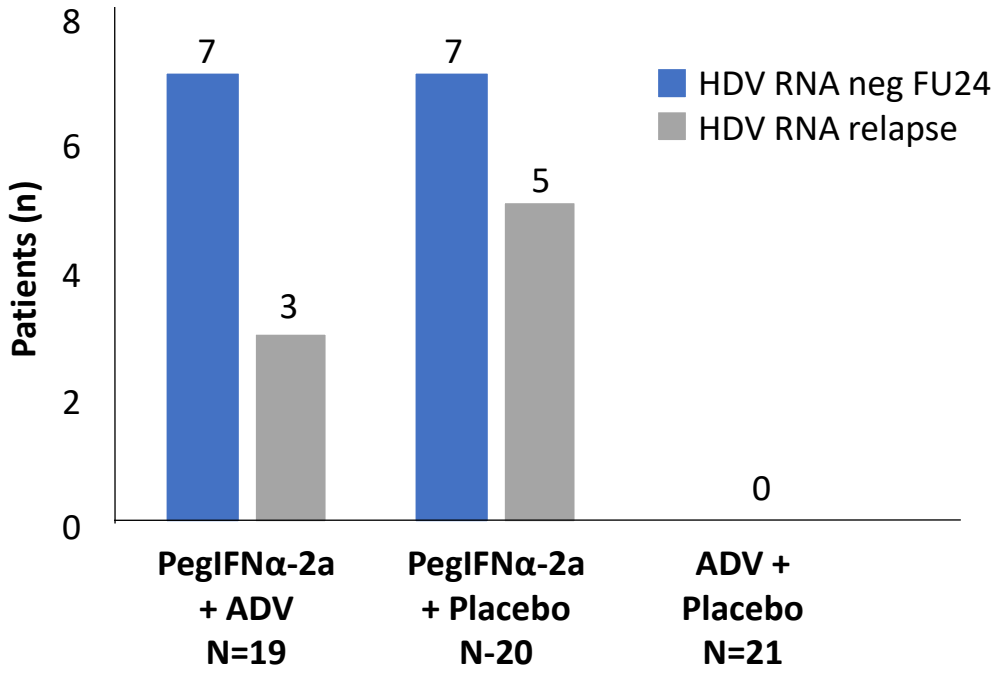


- **HDV RNA PCR with low sensitivity**
- **HDV RNA relapse >50%**

A Abdrakhman et al. Antiviral Res 2021;185:104995.

HIDIT-I: PEG-IFNα-2a ± ADV for 48 weeks

60 patients – median fup: 8.9 years



High rate of late relapses (8/14 patients [**57%**]) - between year 2 and 9

HDV RNA negative at 24 weeks post-EOT: not predictive of SVR

H Wedemeyer et al. N Engl J Med 2011;364:322-331. A Wranke et al. J Viral Hepat 2020;27:1359-1368.

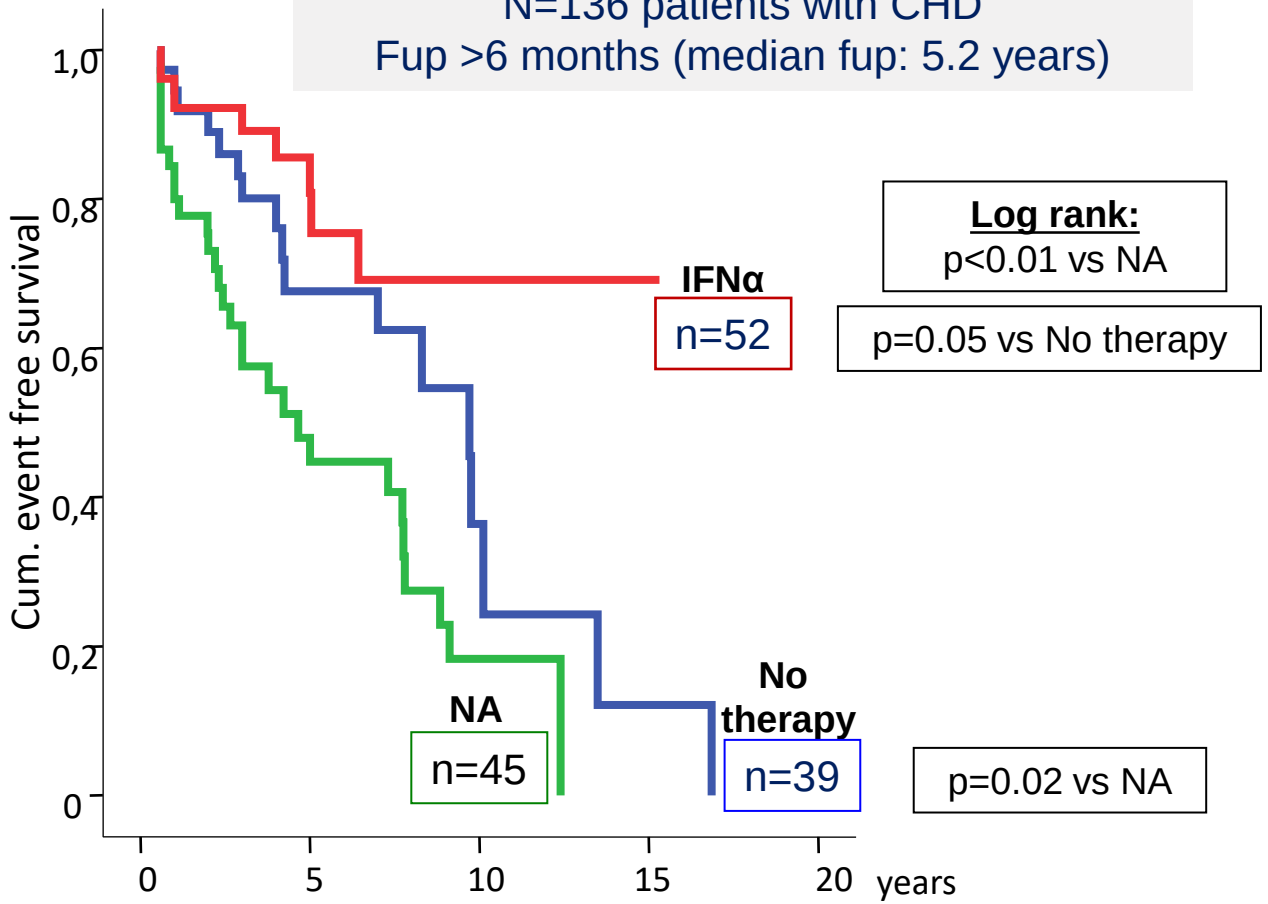
IFNα therapy is associated with improved clinical long-term outcome of CHD

Prospective Study from Greece
anti-HDV-positive N=90
anti-HDV negative: N=2047
13 years of follow-up

46 patients treated with IFNα

HR for liver related-events for IFNα-treated patients:
HR=0.14 (0.02-0.86); p=0.033

N=136 patients with CHD
Fup >6 months (median fup: 5.2 years)

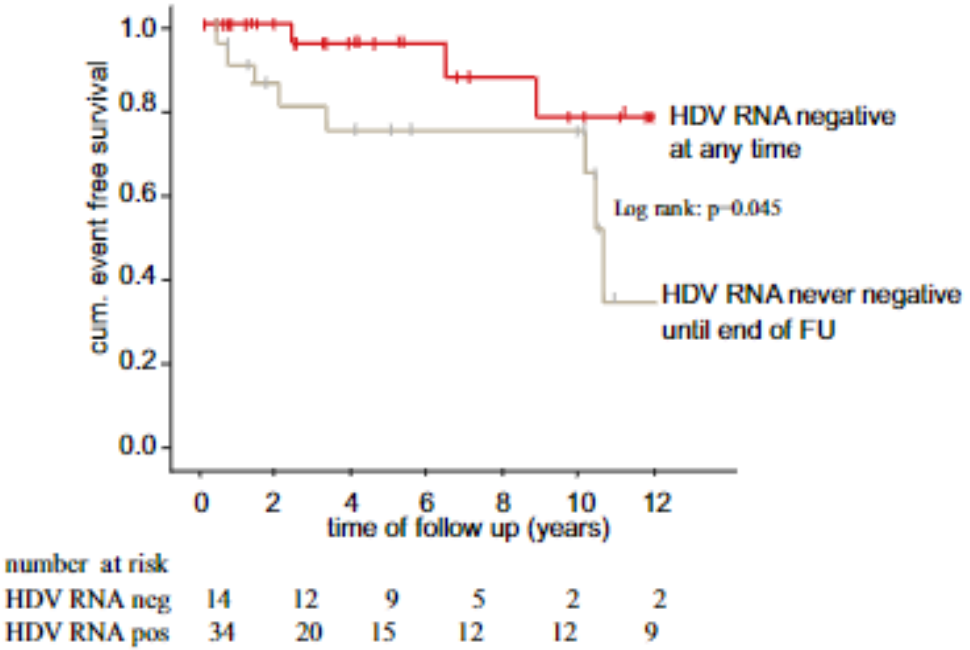


EK Manesis et al. J Hepatol 2013;59:949-956.

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

HIDIT-I: PegIFNα±ADV x48 wks

60 pts - 10 year fup

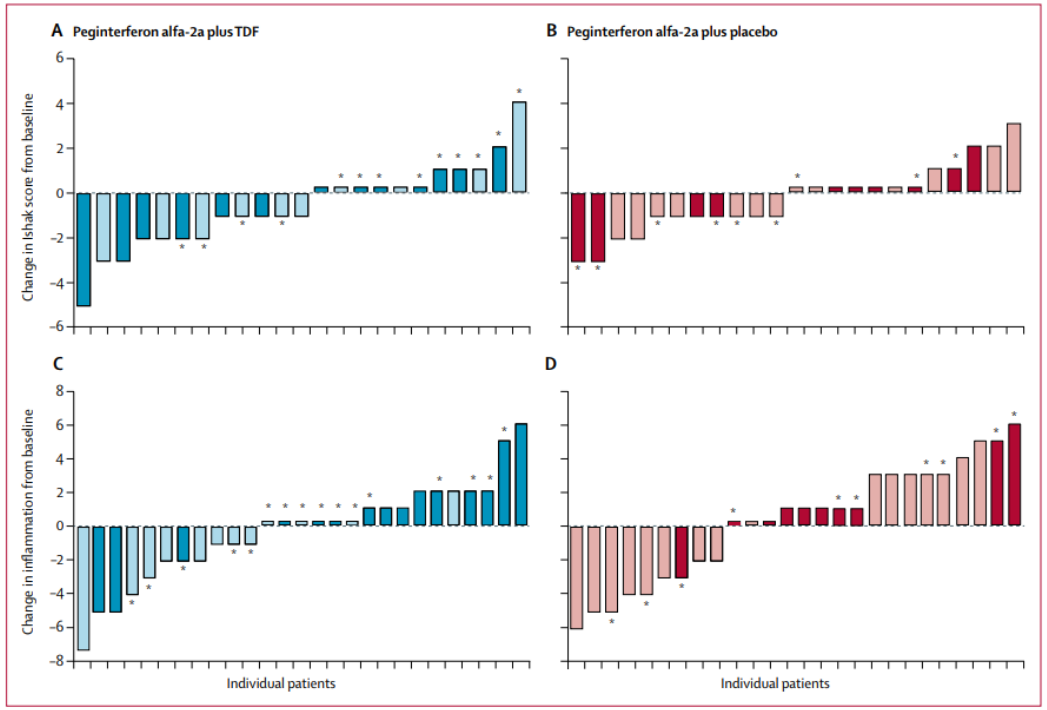


Off-treatment HDV RNA response after PegIFNα leads to improved long-term clinical outcome

A Wranke et al. J Viral Hepat 2020;27:1359-1368.

HIDIT-II: PegIFNα±TDF x96 wks

46 pts with paired liver biopsies



Administration of PegIFNα for 96 weeks resulted in improved histological fibrosis scores in most patients

H Wedemeyer. Lancet Infect Dis 2019;19:275-286.

Duration of IFNα therapy & Outcomes in CHD

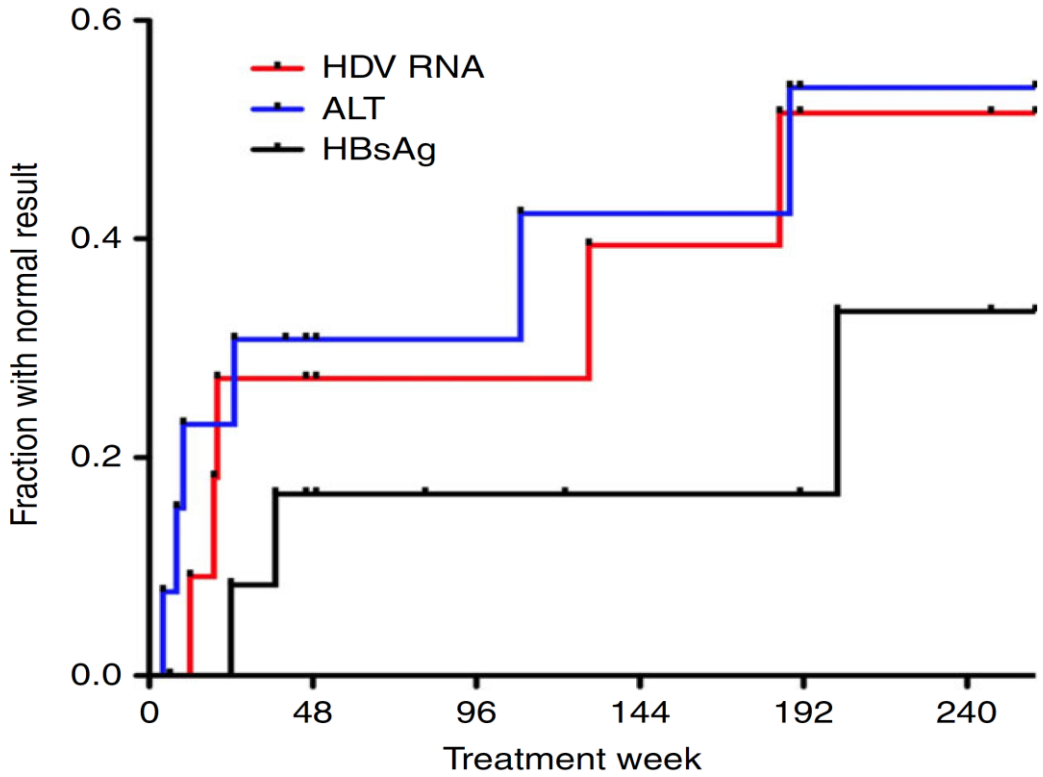
- 99 pts with ≥6 months of IFNα therapy
- IFNα - median duration: 24 (range 6-126) months, median courses: 2 (range 1-8)
- **Maintained virologic response (MVR): HDV RNA negative for 2 years after EOT**
- Post-treatment median follow-up: 55 (range: 24-225) months

- MVR: 35/99 (35%) pts - HBsAg clearance: 37% of pts with MVR
- **Cumulative probability of MVR: increased with treatment duration (50% at 5 yrs)**
- **MVR: less likely** to die from liver disease (P=0.032) or develop complications (P=0.006)
- **Predictors of adverse outcomes**: cirrhosis (OR:16.1) & no response to therapy (OR:5.2)

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

Long-term PegIFNα therapy in CHD

- 13 pts with CHD started with PegIFNα-2a (180 µg/wk with escalation up to 360 µg/wk)
- All 13 pts had bridging fibrosis – 1 pt discontinued therapy within month 2 for social reasons
- 12 patients were treated for median 140 wks (6–260) with median dose 180 µg/wk



- 25% (3/12): SAE - PegIFN interruption
- 25% (3/12): PegIFN dose reduction due to cytopenias

T Heller et al. Aliment Pharmacol Ther 2014;40:93-104.

Limitations of PegIFNα use

- **Limited response – High relapse rates**

- **Poor tolerance / Patients' unwillingness**
  - Concerns for adverse events
  - Poor quality of life during therapy (fatigue, weakness, flu-like syndrome, depression, ...)
  - Concerns for relapse after EOT

Very close on-treatment monitoring

- **Contraindications**
  - Decompensated cirrhosis
  - Advanced portal hypertension (cytopenias)
  - Serious psychiatric disorders
  - Serious comorbidities
  - Autoimmune diseases
  - Risk of autoimmune hepatitis (anti-LKM-3 pos.)

Baseline predictors of response to IFNα

Weak data (variability in study designs, HDV RNA assays, definitions and timing of responses)

- Low pretreatment HDV RNA serum levels
- Low pretreatment HBsAg serum levels
- HDV genotype 5

GA Niro et al. Aliment Pharmacol Ther 2016;44:620-628. C Yurdaydin et al, J Infect Dis 2018;217:1184-1192.

H Wedemeyer et al, Lancet Infect Dis 2019;19:275-286. M Spaan et al. J Hepatol 2020;72:1097-1104.

None with very high NPV

On-therapy Predictors of response to IFNα

Weak data (variability in study designs, HDV RNA assays, definitions and timing of responses)

Response: HDV RNA (-) at 24 wks after EOT, **no response**: HDV RNA decrease <1 log at EOT

- **HDV RNA (-) at wk 24 or EOT** for **response**: PPV 71% or 100%
- **HDV RNA decrease ≤1 log at 24 wk** for **no response**: 67% sens., 85% spec., 67% PPV, 91% NPV
- **HDV RNA decrease >2 log at wk 24** for **no response**: 95% NPV

No futility rule – Minimum duration of PegIFNα therapy: 48 wks

62 pts with CHD-GT1 treated with **PegIFNα ±NA for 15±4.8 mos**

At 5±2.9 yrs after EOT-**Response**: HDV RNA (-) ± HBsAg (-) (n=14/12), **No response**: HDV RNA (+) (n=36)

- **HDV RNA reduction at mo 6** predictive of **response** (-1.61 log: AUROC 0.791, sens. 86%, specif. 68%)
- **HBsAg reduction at mo 6** predictive of **response** (-0.105 log: AUROC 0.713, sens. 61%, specif. 87%)

GA Niro et al. Aliment Pharmacol Ther 2016;44:620-628.

HBsAg decline at wk 12: associated with on-PegIFNα response. T Heller et al. Aliment Pharmacol Ther 2014;40:93-104.

Serum HDV RNA levels at wk 24 appears to be the strongest predictor of response - EASL CPGs 2023

Prolongation or retreatment with IFNa

Currently, **prolongation or retreatment with IFNa may be considered** in patients with :

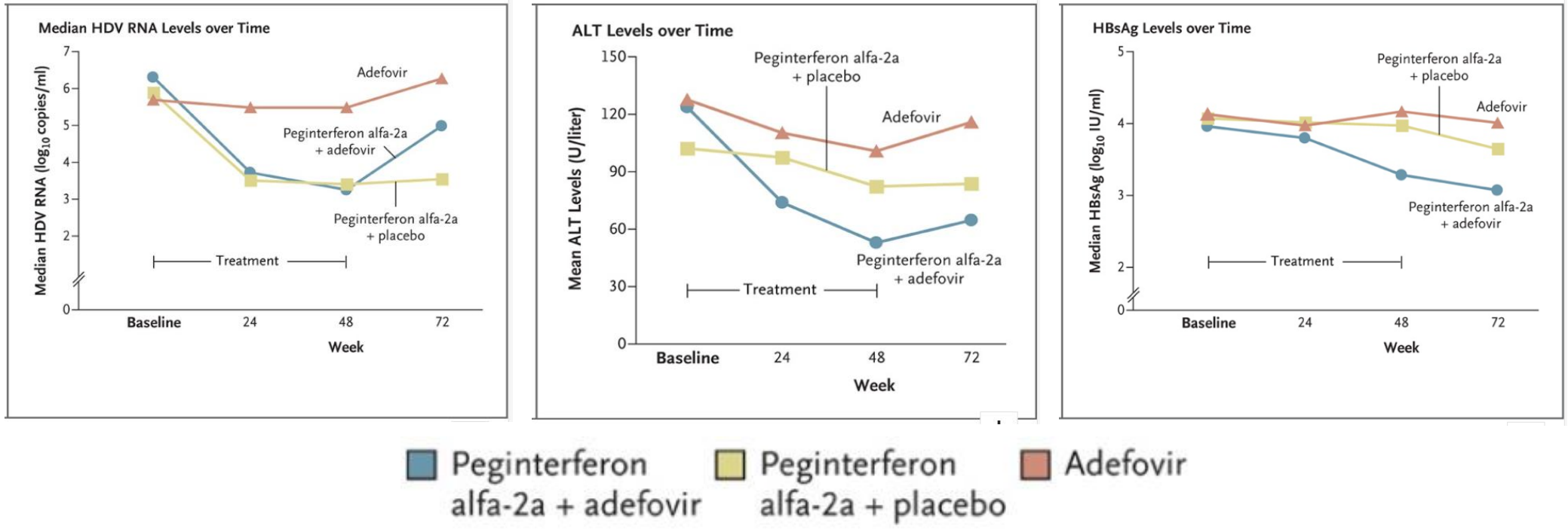
- Good compliance to treatment
- Slow virologic response (in a subset of patients, the decline in viral load becomes more pronounced after the first 24 weeks)
- Progressive HBsAg decline

EASL HDV CPGs. J Hepatol 2023;79:433–460

PegIFNα with or without NA?

HIDIT-I: PegIFNα ±ADV x48 wks in CHD

31 pts PegIFNα+ADV, 29 pts PegIFNα alone, 30 pts ADV alone



➢ **PegIFNα+ADV combination vs PegIFNα alone: higher rates of HBsAg decline**

H Wedermeyer et al. N Engl J Med 2011;364:322-331.

HIDIT-II: PegIFNα ±TDF x96 wks in CHD

61 pts PegIFNα alone, 59 pts PegIFNα + TDF

	Baseline	Week 12	Week 24	Week 48	Week 72	Week 96	Week 120
HDV RNA negative							
Peginterferon alfa-2a plus TDF (n=59)	1 (2%)	14 (24%)	21 (36%)	25 (42%)	23 (39%)	28 (48%)	18 (31%)
Peginterferon alfa-2a plus placebo (n=61)	1 (2%)	9 (15%)	18 (30%)	21 (34%)	19 (31%)	20 (33%)	14 (23%)
OR (95% CI), p value	..	1·71 (0·67–4·41), 0·26	1·32 (0·60–2·89), 0·49	1·60 (0·73–3·48), 0·24	1·66 (0·74–3·71), 0·22	1·84 (0.86–3·91), 0·1154	1·46 (0·64–3·31), 0·37
HBsAg decline ≥0·5% from baseline							
Peginterferon alfa-2a plus TDF (n=59)	..	4 (6·8%)	10 (16·9%)	14 (23·7%)	11 (18·6%)	17 (28·8%)	12 (20·3%)
Peginterferon alfa-2a plus placebo (n=61)	..	4 (6·6)	18 (29·5)	15 (24·6)	9 (14·8)	12 (19·7)	14 (23·0%)
OR (95% CI), p value	..	0·90 (0·21–3·90), 0·89	0·40 (0·15–1·03), 0·057	1·08 (0·41–2·86), 0·88	1·60 (0·54–4·67), 0·40	1·74 (0·67–4·51), 0·25	0·85 (0·32–2·26), 0·75
Normal ALT values							
Peginterferon alfa-2a plus TDF (n=59)	8 (14%)	12 (20%)	12 (20%)	18 (31%)	21 (36%)	26 (44%)	27 (46%)
Peginterferon alfa-2a plus placebo (n=61)	3 (5%)	10 (16%)	15 (25%)	16 (26%)	23 (38%)	23 (38%)	16 (26%)
OR (95% CI), p value	3·18 (0·79–12·82), 0·10	1·30 (0·51–3·34), 0·58	0·76 (0·30–1·94), 0·56	1·44 (0·61–3·37), 0·40	1·12 (0·49–2·57), 0·79	1·58 (0·72–3·48), 0·26	3·42 (1·38–8·47), 0·008

HDV=hepatitis D virus. TDF=tenofovir disoproxil fumarate. OR=odds ratio. ALT=alanine aminotransferase.

- **PegIFNα + TDF combination did not significantly affect end of-/off- treatment response rates**

H Wedemeyer. Lancet Infect Dis 2019;19:275-286.

When should NAs be used in patients with CHD?

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).**

EASL HDV CPGs. J Hepatol 2023;79:433–460

Peg-IFNα for CHD 2024 - Conclusions

- HDV RNA (-): 25-35% at 24-48 wks after EOT – decreasing over time
- HBsAg loss: <5%
- Long-term benefits in responders
- F
- Suboptimal safety and tolerability profile
- Frequent, even late, relapses

Only a minority of cases are currently treated with PegIFNα in countries with access to Bulevirtide

2022-2023 in 12 Greek liver centers: PegIFNa 3 (4%), BLV 76 (96%) patients


Thank you!