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Delta hepatitis:
How to optimize current therapy with PEG IFN ?

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Disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN, SBRING BANK, MYR, EIGER

Outline of the presentation

- 48-week course of IFN or PegIFN
- Strategies to improve response to IFN
- Predictors of response
- Long-term outcome
- International guidelines

Response to PEG-IFN

IFN treatment for HDV - A review article

References	Type/dose	No. of patients	Duration of therapy	Duration of follow-up	Overall virological response at EOT (%)	SVR (%)
[28]	Peg-IFNα2b 1.5 μg/kg	14	12 months	16 months	57	43
[29]	Peg-IFNα2b 1.5 μg/kg	16	18 months	6 months	19	25
	Peg-IFNα2b 1.5 μg/kg + RBV	22	12 months	6 months	9	18
[30]	Peg-IFNα2b 1.5 μg/kg	12	12 months	12 months	–	17
[31]	Peg-IFNα2b 1.5 μg/kg	49	13 months	26 months	33	25
[32]	Peg-IFNα2b 1.5 μg/kg	11	24 months	6 months	56	–
		7	12 months	6 months	57	
[33]	Peg-IFNα2a 180 μg	29	12 months	6 months	24	31
	Peg-IFNα2a 180 μg + adefovir 10 mg/day	31	12 months	6 months	23	24
	Adefovir 10 mg/day	30	12 months	6 months	0	0
[34]	Peg-IFNα2b	277 enrolled (238 evaluated)	48 weeks	24 weeks	29.8	29.4
[35]	Peg-IFNα2a 180 μg or peg-IFNα2b 1.5 μg/kg	32	24 months	6 months	50	47
[36]	Peg-IFNα2a + tenofovir	59	96 weeks	24 weeks	48	29
	Peg-IFNα2a + placebo	61	96 weeks	24 weeks	33	21
[37]	Peg-IFNα2a 90–270 μg/week	13	6–240 weeks (median, 140 weeks)	–	–	39 (3 lost HBsAg)
[38] [a]	Peg-IFNα2a 180 μg + entecavir 0.5 mg/day	22	48 weeks	48 weeks	95	95
[39]	Peg-IFNα2a	41	12 months		39	37
	Peg-IFNα2b	15	12 months		13	13
[40]	IFN or peg-IFN	99	6–126 months (median, 24 months)	24–225 months (median, 55 months)	–	35.3

EOT, end of treatment; SVR, sustained virological response; RBV, ribavirin; HBsAg, hepatitis B surface antigen.
[a] South American study enrolling patients with HDV genotype 3.

Brancaccio G and Gaeta G. IJAA 2019;54:697–701

IFN treatment for HDV - A review article

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[31]	Peg-IFNα2b 1.5 μg/kg	49	13 months	26 months	33	25
[32]	Peg-IFNα2b 1.5					
[33]	Peg-IFNα2a 180					
	Peg-IFNα2a 180 μg + adefovir 10					
	Adefovir 10 mg/					
[34]	Peg-IFNα2b					4
[35]	Peg-IFNα2a 180					
	peg-IFNα2b 1.5					
[36]	Peg-IFNα2a + ter					
	Peg-IFNα2a + pla					
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Summary for a 48-week course of PegIFN in CHD:

- Number of studies: 7
- Number of patients: 22 (7-238)
- VR at EOT: 33% (13-57%)
- VR at EOF: 29% (13-43%)

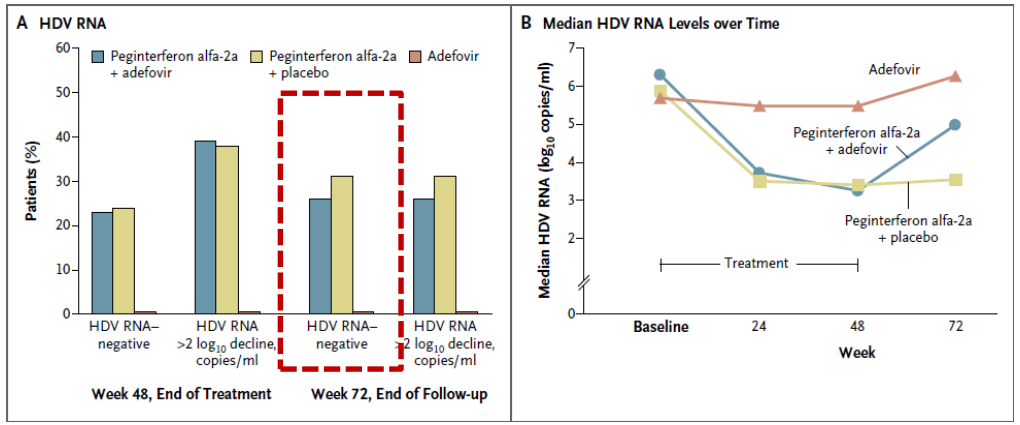
Brancaccio G and Gaeta G. IJAA 2019;54:697–701

Strategies to improve IFN response

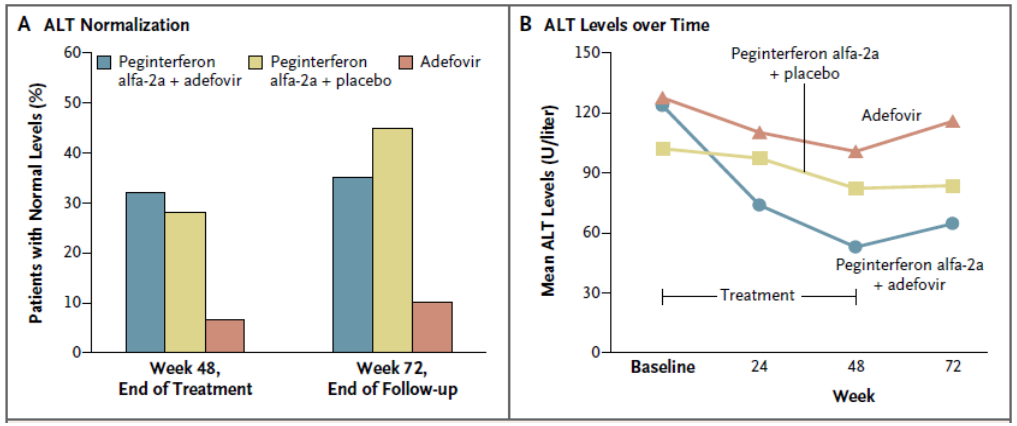
48-week PegIFN alfa-2a plus ADV versus either alone for Delta Hepatitis
A multicenter international RCT - the HIDIT-I study

90 CHD patients, age 40, 60% males, RNA 6 log cp, DNA 2 log, gt1 100%, cirr 20%; 48-week treatment and 24-week fup

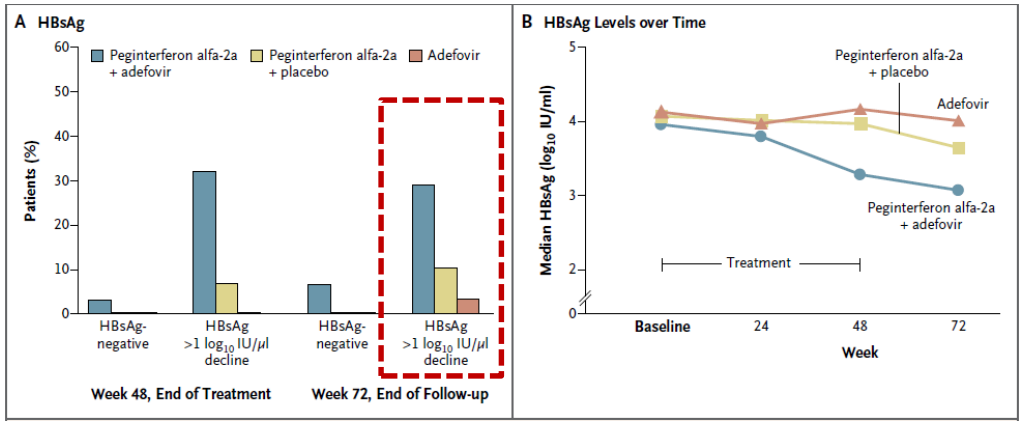
HDV-RNA response



ALT response



HBsAg response



Conclusions

Treatment with Peg-IFN alfa-2a for 48 weeks, with or without adefovir, resulted in **sustained HDV RNA clearance in about one quarter** of patients with HDV infection.

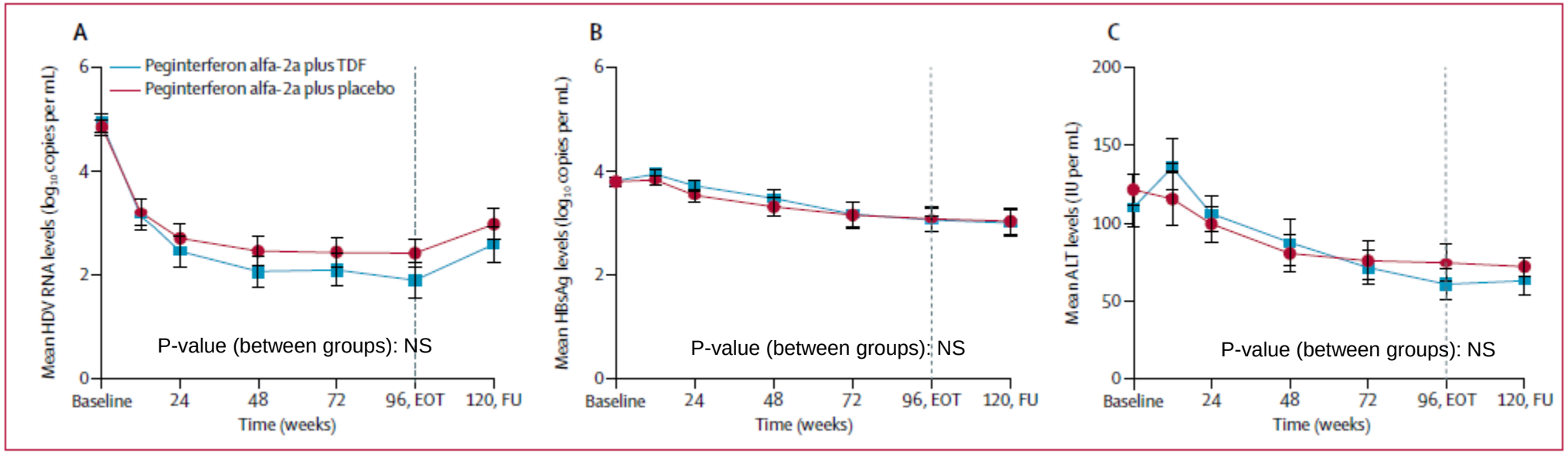
Faster HBsAg decline in the pegIFN + ADV group ?

Wedemeyer H et al NEJM 2011

96-week PegIFN alfa-2a plus TDF versus Peg-IFN alfa-2a mono for Delta Hepatitis
A multicenter international RCT - The HIDIT-II study

120 patients, age 40, 65% males, RNA 5 log cp, gt1 98%, HBsAg 3.8 log, DNA 2.8 log, cirr 40%

HDV-RNA levels | **HBsAg levels** | **ALT levels**



HDV-RNA negative at week 120:

31% vs 23% (p=NS)

HBsAg decline >0.5 log at week 120:

20% vs 23% (p=NS)

ALT normal at week 120:

46% vs 26% (p=0.008)

Conclusions:

Addition of TDF resulted in **no significant improvement** in HDV RNA response rates at the end of treatment.

Wedemeyer H et al. Lancet 2019

IFN for HDV: extension of treatment up to 5 years – The NIH study

13 patients with compensated HDV hepatitis treated with Peg-IFNa 2a for 120 weeks (6-260): age 42 yr, 85% male, HDV RNA 6.7 log, HBsAg 3.7 log

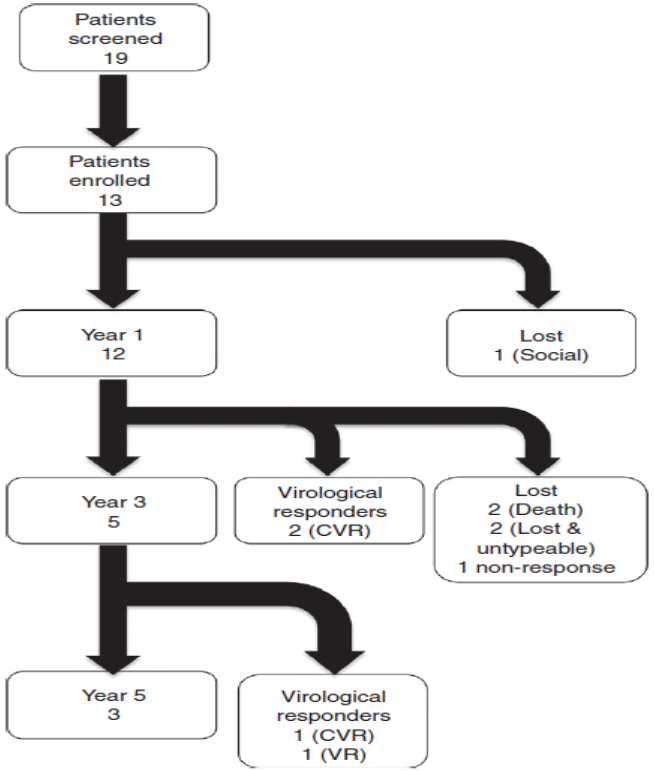
Table 1 | Baseline patient characteristics

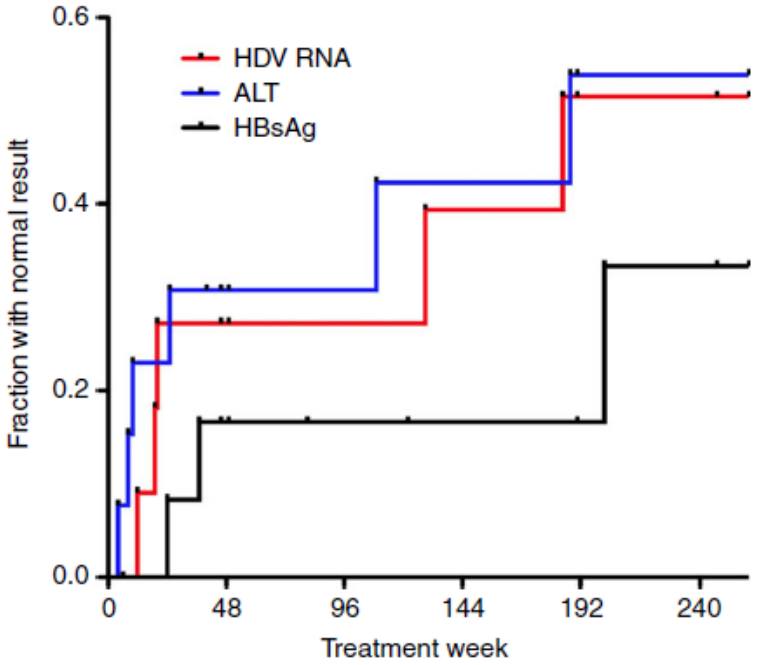
N	13
Age (years)*	42 (18–58)
Male gender	11 (85%)
Race (Caucasian/African-American)	11/2
Estimated duration of disease (years)*	25 (7–35)
Infection source†	
IV drug abuse	6 (46%)
Sexual	2 (15%)
Transfusion	2 (15%)
Endemic region	5 (39%)
ALT (U/L)*	141 (31–506)
HDV RNA (Log_{10} Genome Equivalent/mL)*	6.7 ± 1.2
HBsAg (Log_{10} IU/mL)*	3.7 ± 0.6
HBV DNA < 100 IU/mL	6 (46%)
HBV DNA (Log_{10} IU/mL)*‡	2.9 (2–4.9)
Fibrosis (median, range) (Ishak score)	3 (3-6)
HVPG (mmHg)*	11 (4-25)

* Mean (range).

† More than one suspected source possible.

‡ Limited to patients with HBV DNA >100 IU/mL.





- VR defined as the inability to detect HDV RNA in serum by quantitative measurements.
- CVR defined as the combination of HDV virological response with HBsAg seroconversion.
- HDV RNA undetectable: <100 genome equivalents (GE)/mL)

HBsAg loss: 3/13 (23%)

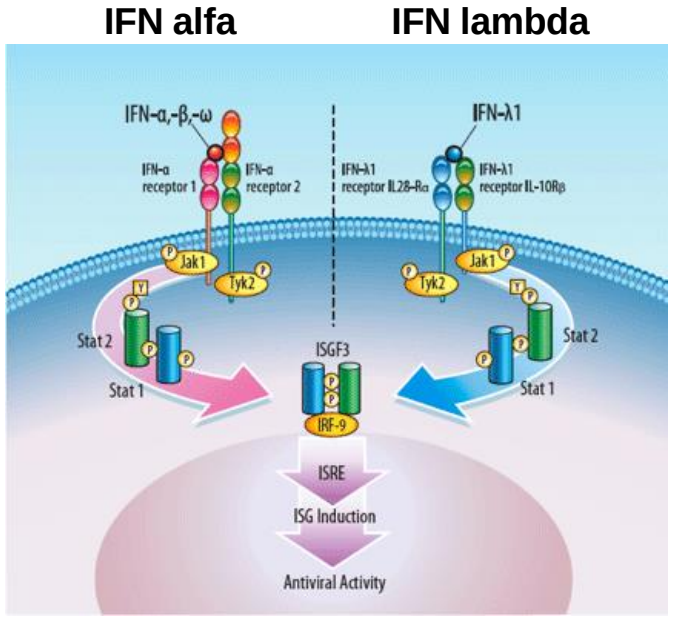
Conclusions:
Despite increased doses and duration of therapy, treatment of chronic HDV with Peg-IFN **remains unsatisfactory**

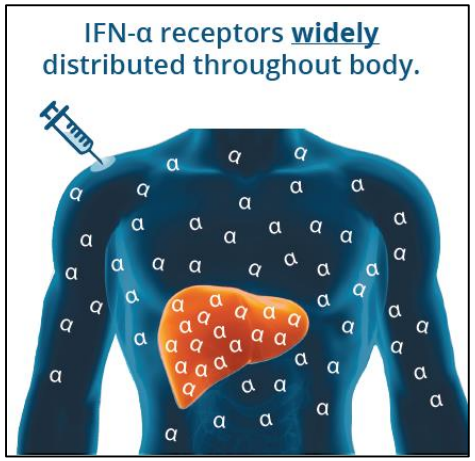
Heller T et al, Aliment Pharmacol Ther 2014; 40: 93–104

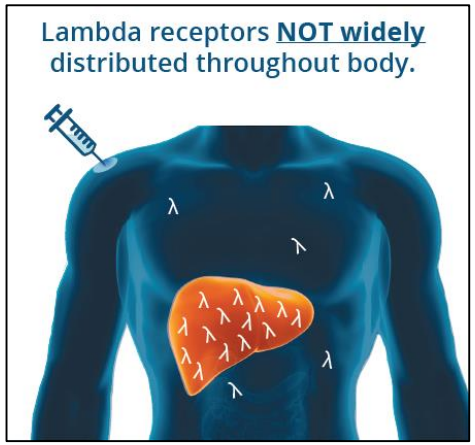
PegIFN Lambda for Delta Hepatitis

- A novel first in class Type III interferon
- Binds to a unique receptor versus Type I interferons
  - Highly expressed on hepatocytes
    - Limited expression on hematopoietic cells and CNS cells
- Uses similar downstream signaling pathway as Type I interferons
- Greater than 3,000 patients in 17 clinical trials (HCV / HBV)
- Comparable antiviral activity with less of the typical IFN alfa related side effects*

A better tolerated IFN ?



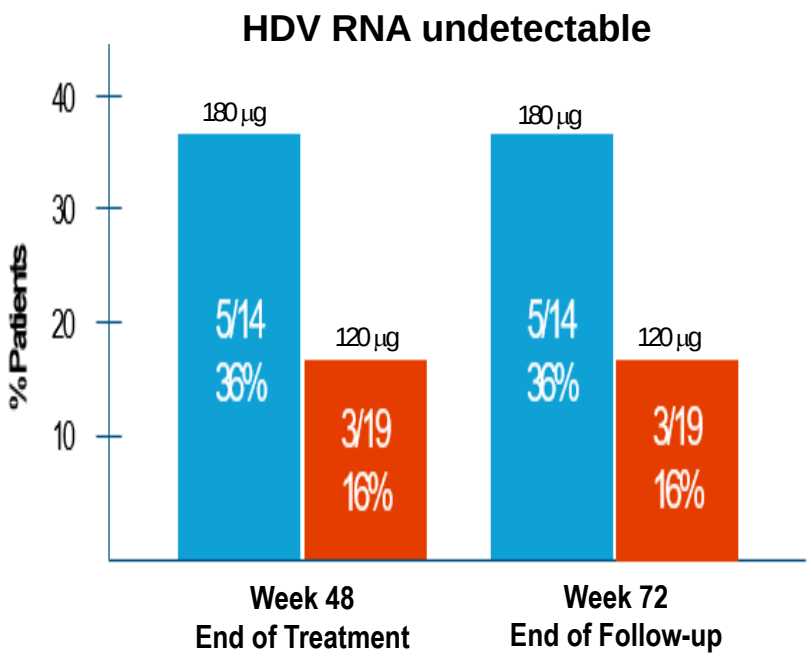


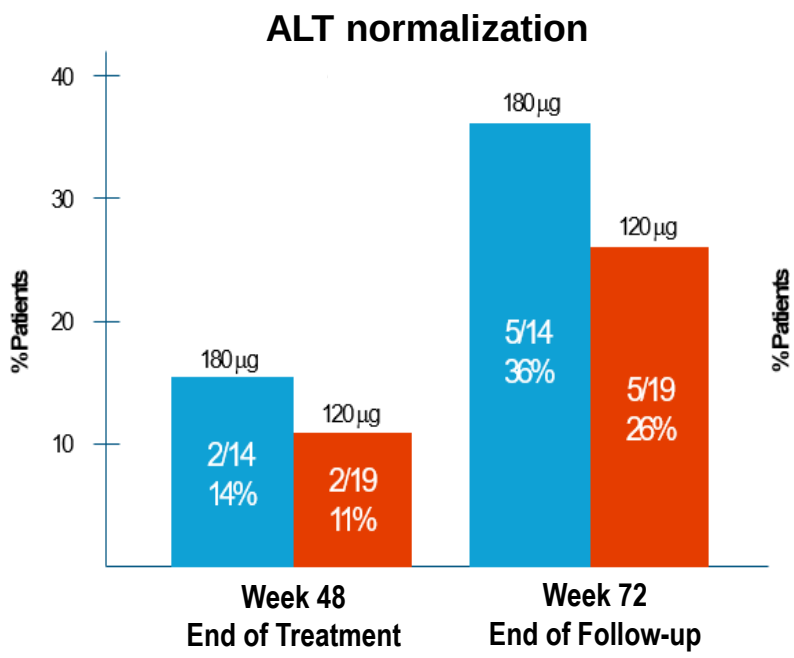


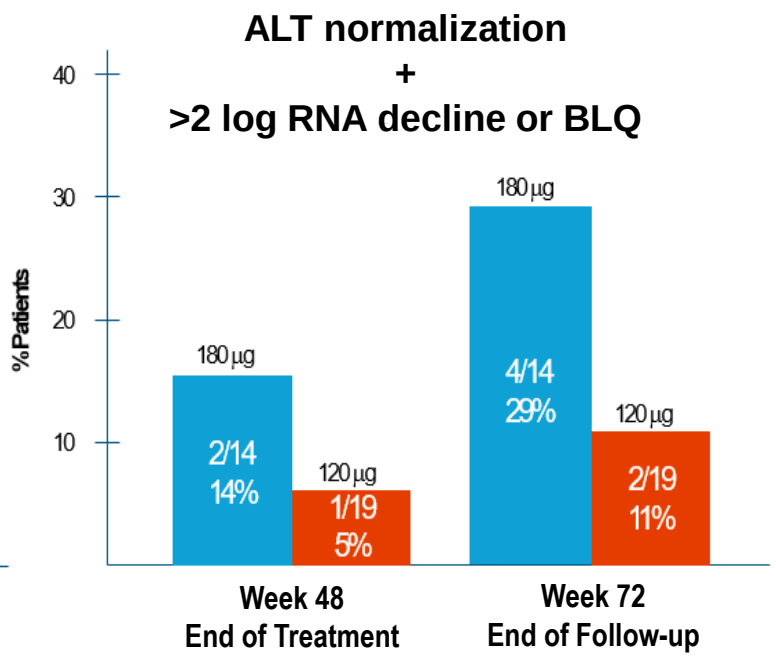
Chan, HLY et al, J Hepatology 2016

48 weeks of PEG-IFN Lambda monotherapy in HDV – A phase 2 study (Pakistan, Israel, New Zealand)

33 HDV patients enrolled (19 vs 21): 36 yrs, 67% males, RNA 4.1 log, ALT 106, 27% cirr; 48 weeks therapy and 24 weeks fup







Questions:

- Only 33 patients included (14 vs 19)
- No control group with Peg IFN alpha

Etzion O et al, EASL 2019

48 weeks of PEG-IFN Lambda monotherapy in HDV – A phase 2 study (Pakistan, Israel, New Zealand)

Classification	Adverse Event	Number of Patients Experiencing Grade of AE (N=33)			
		Gr 1	Gr 2	Gr 3	Gr 4
Constitutional	fatigue, asthenia	10	2	-	-
Flu-like	pyrexia, chills, chest pain, flu-like	21	5	-	-
Neurological	dizziness, headache	17	8	-	-
Musculoskeletal	arthralgia, myalgia, back pain, musculoskeletal pain	18	9	-	-
Psychiatric	depression, irritability, insomnia	1	-	-	-
Hematological	neutrophil count decreased	-	-	-	1**
Lab Abnormalities	bilirubin / ALT / AST / GGT increase	2	1	9	1**

* >1300 Weeks of Treatment
** non-serious

Conclusions:

- Milder flu-like and psychiatric symptoms with Lambda
- No thrombocytopenia events, no use of hematopoetic growth factors
- Elevated bilirubin and ALT levels normalized upon dose reduction or treatment discontinuation
- Jaundice observed in 3/15 (20%) Pakistani vs 0/18 (0%) non-Pakistani patients
- Transporter-based mechanism for bilirubin elevations?

Modified from Etzion O et al, EASL 2019

Predictors of IFN response

Association Between HDV-RNA Levels at Week 24 of Peg-IFN Therapy and Outcome in HDV patients (HIDIT-I sub-analysis)

50 patients with compensated HDV hepatitis treated with Peg-IFNa 2a, with or without ADV, for 48 weeks. Post-treatment fup: 24 weeks.

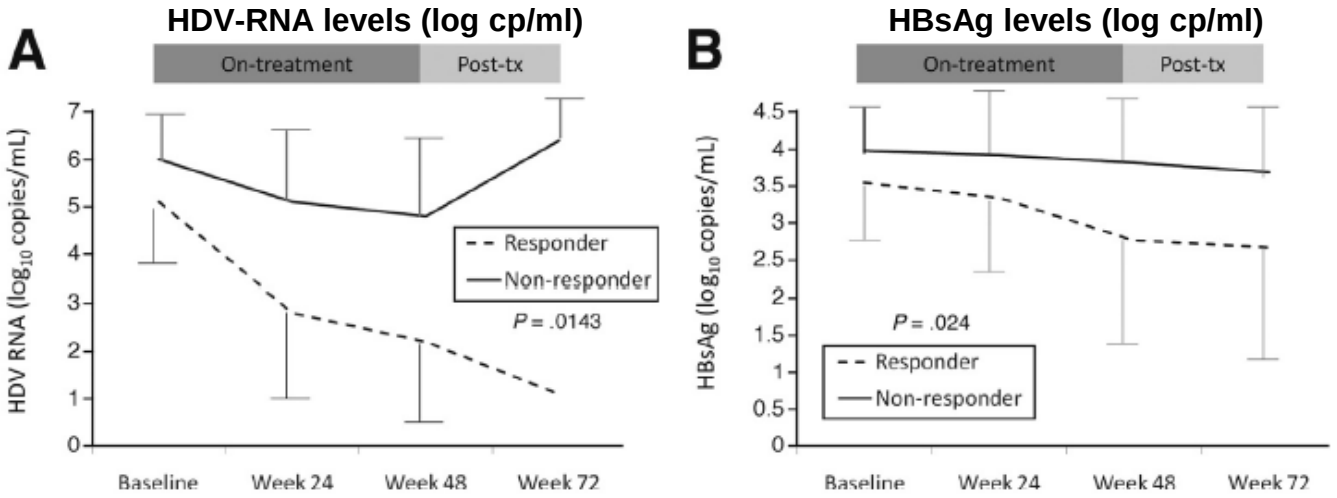
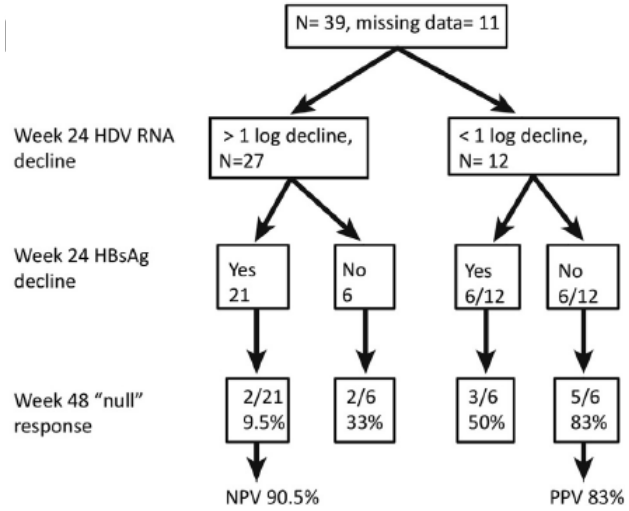


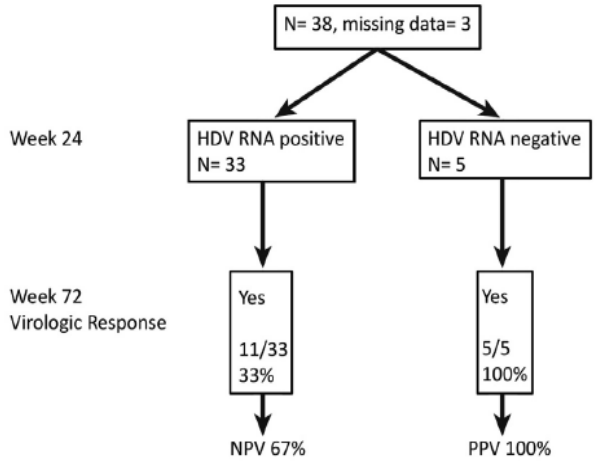
Table 2. Multivariate Logistic Regression Analysis Results for Predicting End-of-Treatment and End of Six Months Treatment-Free Follow-Up Virologic Response

	OR	95% CI	*P* value
End-of-treatment response			
HDV RNA week 24	1.627	1.070–2.474	.023
Baseline HAI	0.586	0.366–0.937	.026
End of 6-month treatment-free follow-up period			
HDV RNA week 24	2.538	1.347–4.782	.004

HAI, histologic activity index.

*HDV RNA lower detection limit: 120 copies/ml





Conclusions:

HDV RNA levels at week 24 of treatment with Peg-IFN, with or without ADV, for 48 weeks can identify patients who will test negative for HDV RNA 24 weeks after the end of treatment

Keskin O et al, CGH 2015;13:2342–2349

IFN for HDV: extension of treatment up to 5 years – The NIH study
Predictors of response

13 patients with compensated HDV hepatitis treated with Peg-IFNa 2a for 120 weeks (6-26): age 42 yr, 85% male, HDV RNA 6.7 log, HBsAg 3.7 log

On-treatment predictors of response

	Complete virological response*			Virological response†		
	Yes (n=3)	No (n=8)	*P*-value‡	Yes (n=5)	No (n=6)	*P*-value‡
HDV RNA 4 week slope (GE log_{10}/mL/week) §	−0.35 ± 0.15	−0.24 ± 0.08	0.43	−0.35 ± 0.15	−0.24 ± 0.09	0.75
HDV RNA week 12 decline (GE log_{10}/mL)§	3.6 ± 3.3	1.3 ± 1.6	0.31	3.0 ± 2.5	0.8 ± 1.8	0.20
HBsAg 4 week slope (IU log_{10}/mL/week) §	−0.04 ± 0.08	0.03 ± 0.04	0.12	−0.02 ± 0.06	0.03 ± 0.05	0.22
HBsAg week 12 decline (IU log_{10}/mL) §	1.7 ± 1.8	0.06 ± 0.5	0.07	1.5 ± 1.3	−0.1 ± 0.2	0.05

* Complete virological response = Undetectable HDV RNA in serum and seroconversion of HBsAg.

† Virological response = Undetectable HDV RNA in serum.

‡ Mann–Whitney test.

§ Mean ± s.d.

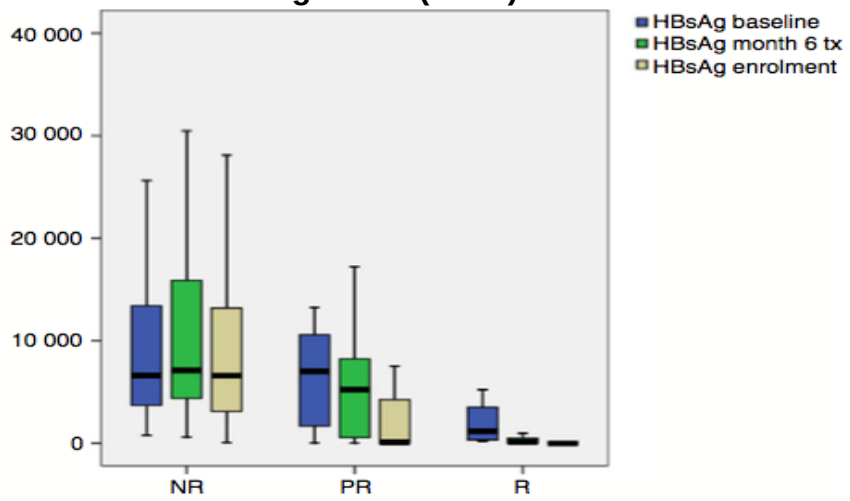
CVR: 3 vs 8 patients
VR: 5 vs 6 patients

Heller T et al, Aliment Pharmacol Ther 2014; 40: 93–104

IFN for HDV: treatment monitoring - The role of HBsAg

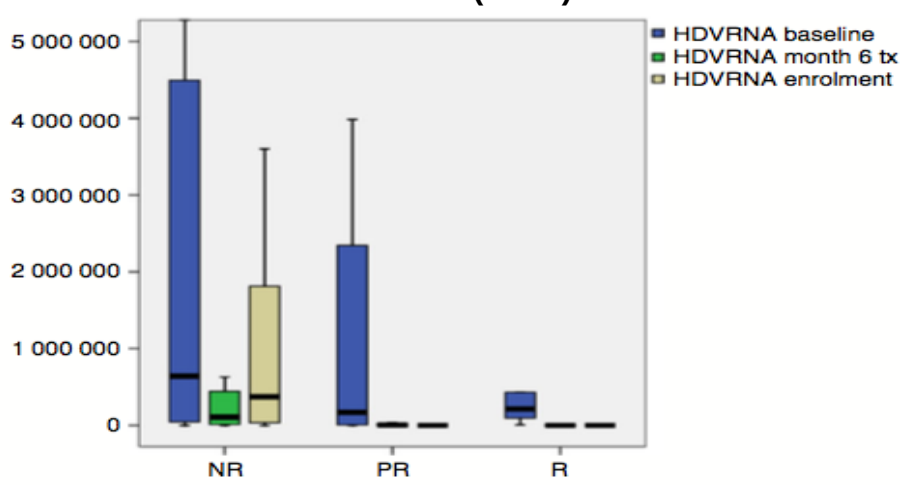
62 patients treated with ≥1 Peg-IFNa courses and followed for a mean of 5 years after EOT
End of fup: Responders (R): HDV RNA + HBsAg (-) (n=14), partial responders (PR): HDV RNA (-) but HBsAg (+) (n=12), nonresponders (NR): HDV RNA + HBsAg (+) (n=36)

HBsAg levels (IU/ml)



	NR	PR	R	*P* value
HBsAg baseline mv IU/mL	6577	7031	1187	0.020
HBsAg month 6 mv IU/mL	7073	5213	108	<0.001
HBsAg enrolment mv IU/mL	6559	62.5	0	<0.001

HDV-RNA levels (IU/ml)



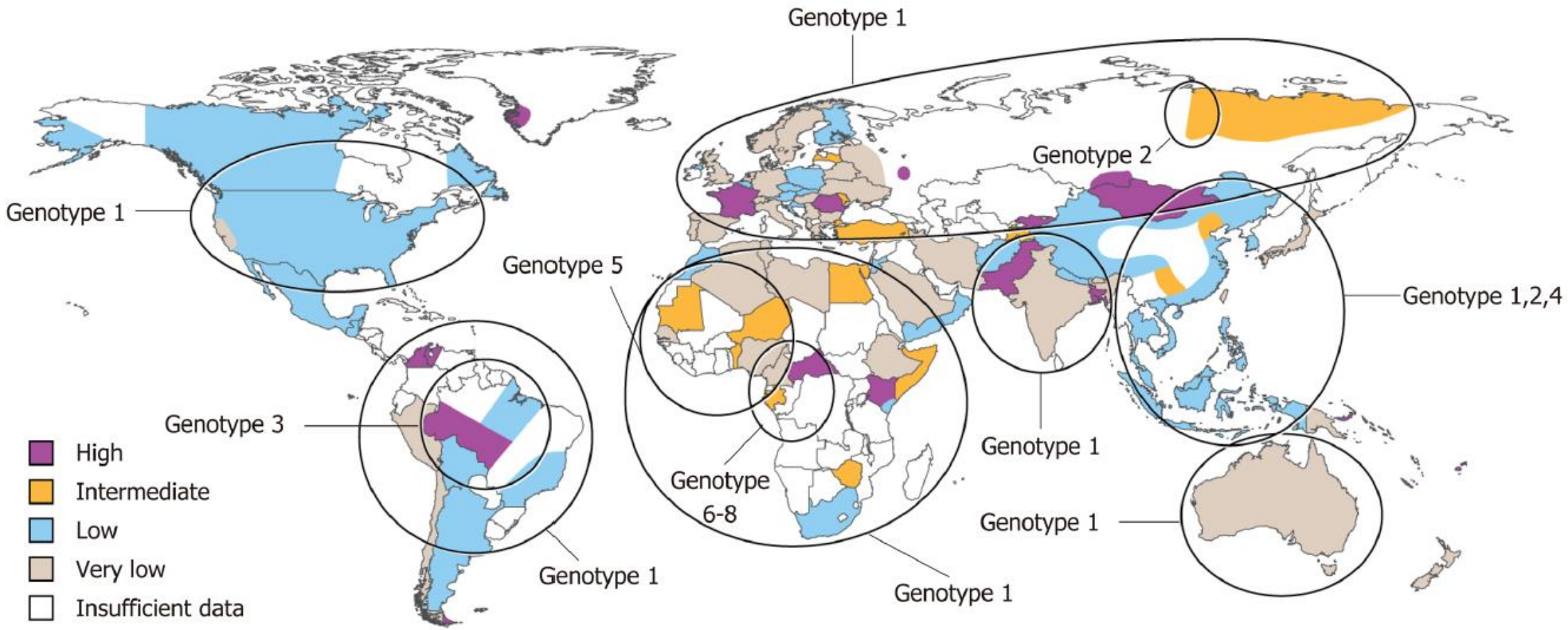
	NR	PR	R	*P* value
HDV-RNA baseline mv IU/mL	676 319	171 405	188 663	0.241
HDV-RNA month 6 mv IU/mL	107 000	2738	0	<0.001
HDV-RNA enrolment mv IU/mL	325 845	0	0	<0.001

Conclusions

HBsAg <1000 IU/mL at month 6 discriminated responders and PR from NR (P<0.001). The threshold of **0.10 log reduction of HBsAg** associated with **1.61 log reduction of HDV RNA** from **baseline to month 6** predicted the clearance of this marker

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

Estimated prevalence of hepatitis D virus infection with genotypic distribution

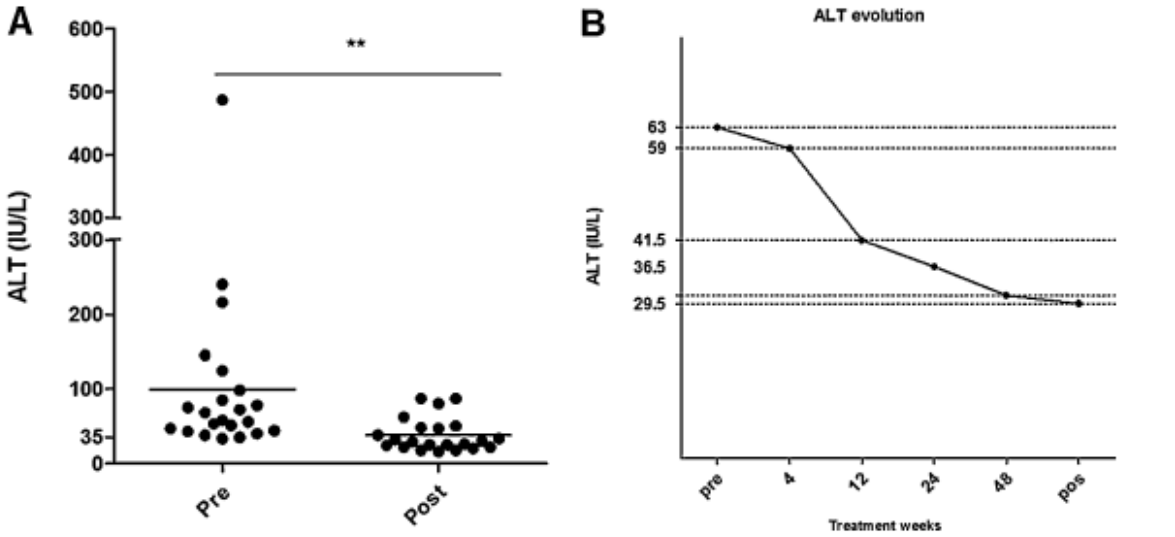


Gilman C et al World J Gastroenterol 2019;25:4580-4597

A 48-week course of PegIFN alfa-2a plus ETV for Genotype 3 – The Brazilian study

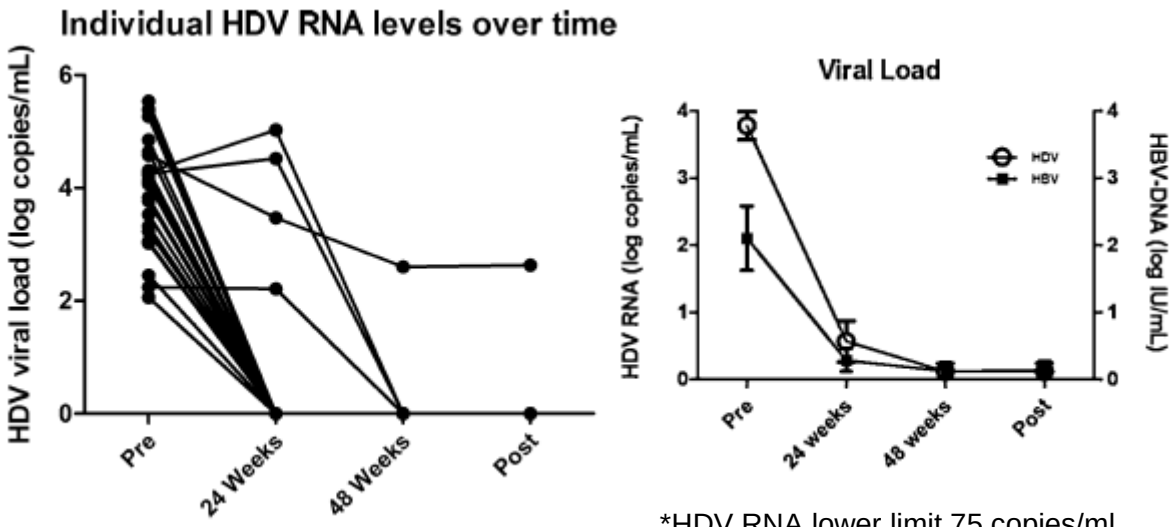
A prospective, non-randomized study, 22 patients treated for 48 weeks and followed post-treatment for 24 weeks. At baseline: age 45 yrs, 61% male, ALT 98, HDV RNA 3.8 log cp, HBV DNA 2.1 log, 100% GT 3, 52% Native American

ALT response



ALT normal at week 48: 15/22 (68%)
ALT normal 24 weeks fup: 14/22 (64%)

Viral load response



*HDV RNA lower limit 75 copies/ml

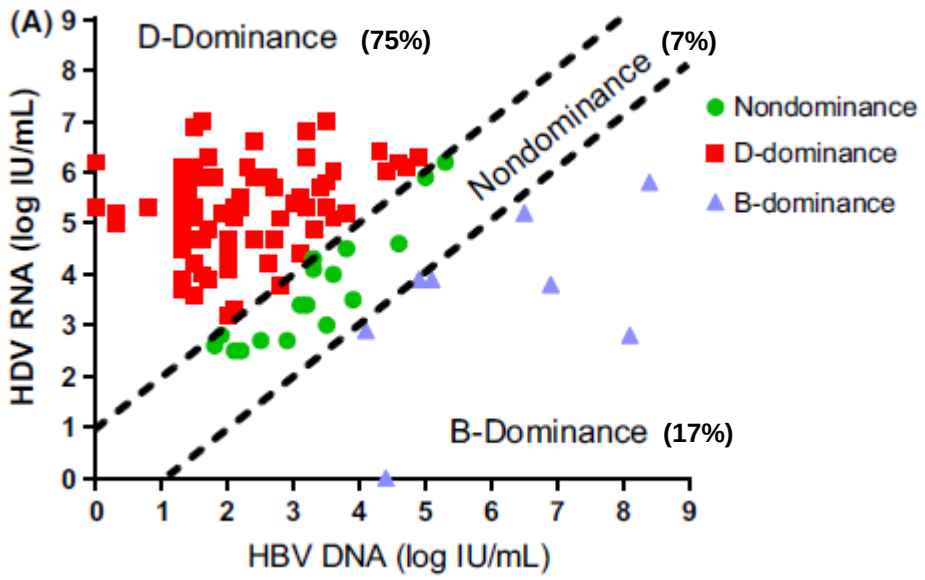
HDV RNA negative at week 48: 21/22 (95%)
HDV-RNA negative 24 weeks fup: 21/22 (95%)

Conclusions: These findings support the use of this effective therapeutic protocol for HDV-3 in patients of non-European ethnicity and suggest a **possible 'easy to treat' variant** when compared to HDV-1.

Borzacov LMP et al, IJID 2016;46:82–88

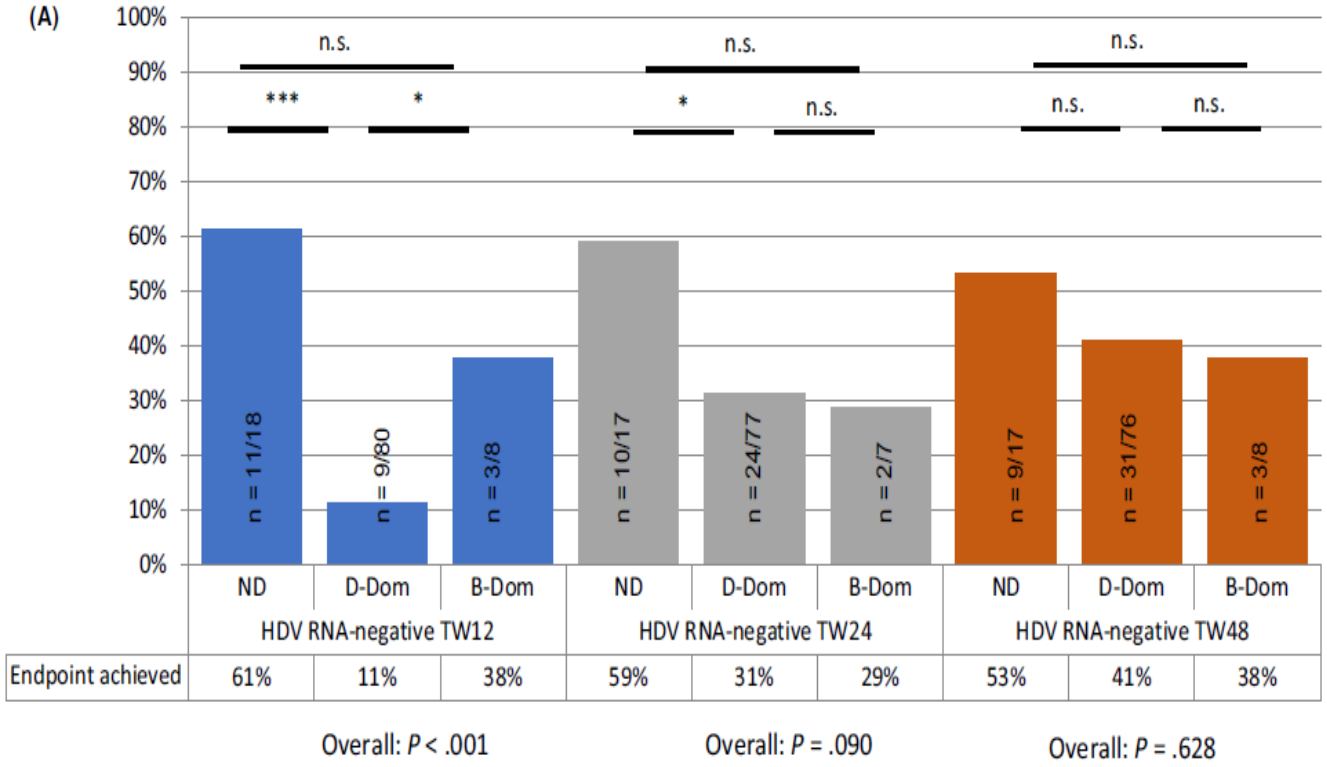
PegIFN for HDV: Viral dominance patterns determine early response therapy
A sub-analysis of the HIDIT-II study in 109 patients

Viral dominance



Definition:
Patients were classified as D- or B-dominant if the viral load of one virus exceeded that of the other virus by more than 1log10 according to Schaper and colleagues. Otherwise, nondominance (ND) was stated.

HDV-RNA negativity



Conclusions:
This study revealed **unexpected effects of viral dominance** on clinical and immunological features in CHD patients. Individualizing PEG-IFNa-2α treatment duration should consider viral dominance. Overall, our findings suggest an activated but exhausted IFN system in D-dominant patients.

Lutterkort GL et al, J Viral Hepat 2018;25:1384–1394

Long-term outcome of IFN treated patients

- Studies on the long-term effects of IFN or pegIFN on the natural history of HDV are limited
- IFN treatment has been associated with a significant improvent of the long-term outcome and survival
- Late and transient virological relapses have not been associated with clinical complications
- Some patients may clear HDV-RNA after therapy and this has been associated with improved outcomes
- Prolonged HDV-RNA negativity has been associated with favorable outcomes even in the absence of HBsAg loss
- Patients who receive more than 1 course of IFN are more likely to achieve a VR and clear HBsAg

Farci P and Niro GA, Gastroenterology and Hepatology 2018

Management of HDV hepatitis – International guidelines

APASL 2015

1) Patients should be treated **with PegIFNa for at 12-18 months** (A1)

2) **NUC might be considered** in some patients who have active HBV replication with persistent or fluctuating serum HBV DNA > 2000 IU/ml

3) Patients **should be monitored** for 6 months post-treatment and beyond (A1)

EASL 2017

1) **PegIFNa** for at least 48 weeks is the **current treatment of choice** in HDV-HBV co-infected patients with compensated liver disease. (Evidence level I, grade of recommendation 1)

2) In HDV-HBV co-infected patients with **ongoing HBV DNA replication, NA therapy should be considered**. (Evidence level II-2, grade of recommendation 1)

3) PegIFNa treatment **can be continued until week 48 irrespective** of on-treatment response pattern if well tolerated. (Evidence level II-2, grade of recommendation 2)

AASLD 2018

1) **Peg-IFN-a for 12 months is the recommended** therapy for those with elevated HDV-RNA levels and ALT elevation.

2) If HBV-DNA levels are elevated, **concurrent therapy with NA** using preferred drugs (ETV,TDF, or TAF) is indicated.

3) Assessment of HDV-RNA is warranted if ALT elevation occurs following treatment because of **the high rates of relapse**.

4) Given the limited efficacy of current therapies, it is reasonable **to refer patients to specialized centers** that offer access to experimental therapies for HDV.

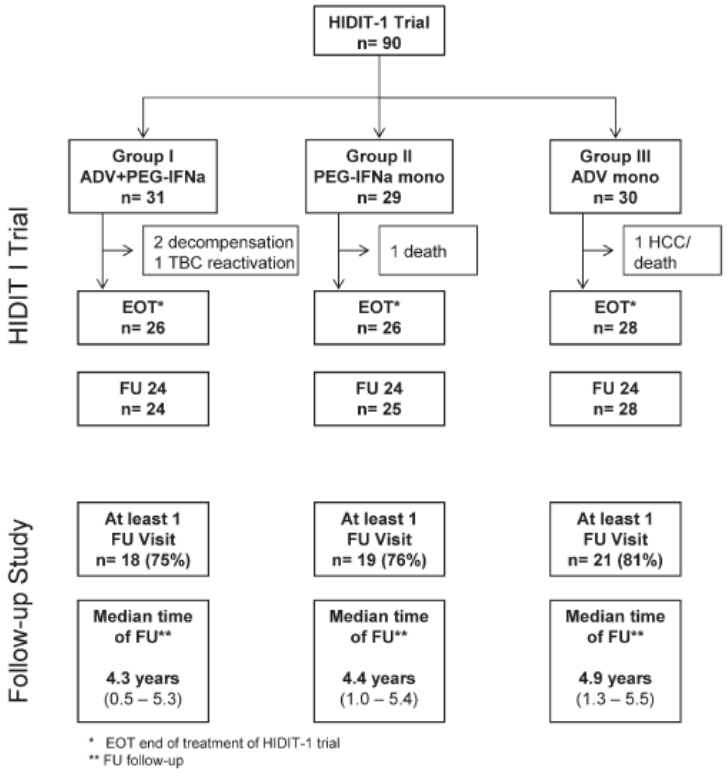
APASL 2015 HBV CPG, Hepatol Int 2017

EASL 2017 HBV CPG, J Hepatol 2017

AASLD 2018 HBV Guidance, Hepatology 2018

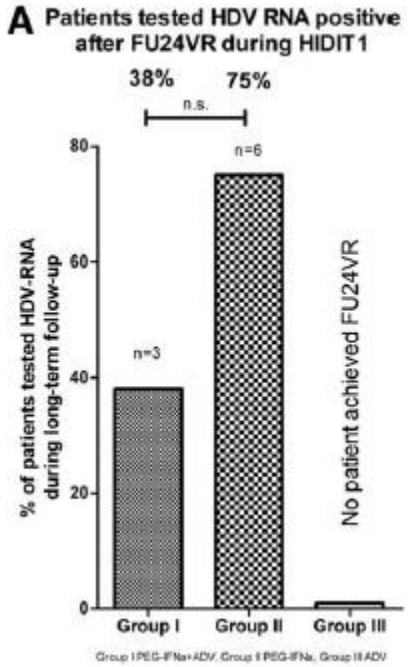
Late HDV-RNA relapse after PegIFN alfa-2a for Chronic Delta Hepatitis
A sub-analysis of the HIDIT-I study

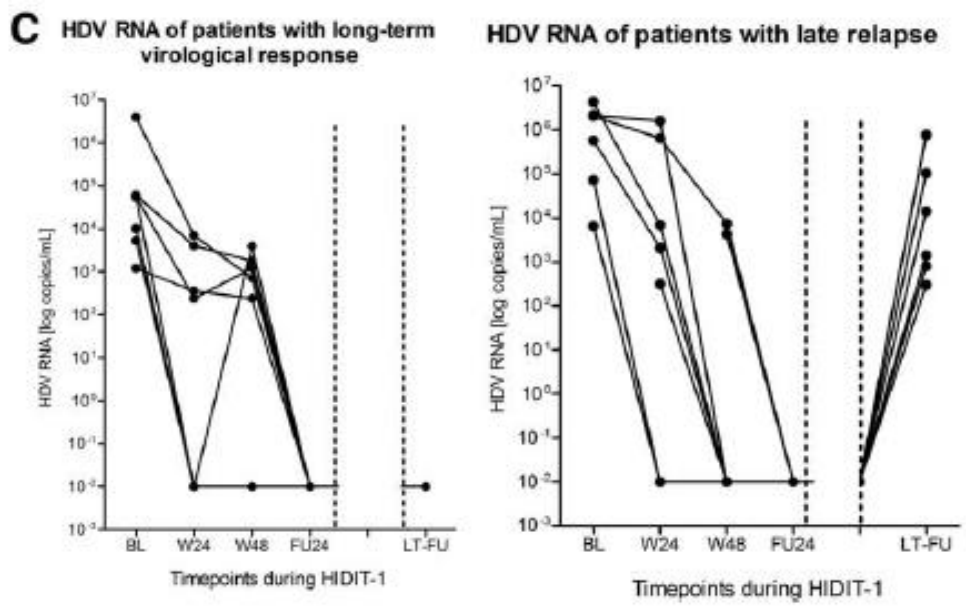
Study design



58 of 77 (75%) patients enrolled in the LTFUP study

Long-term outcome: late HDV-RNA relapse





Late HDV-RNA relapse: 9 of 16 (56%) SVR 24 patients

Conclusions:

Late HDV RNA relapses **(approx. 50-60%)** may occur after PEG-IFNa therapy of hepatitis delta and thus the term sustained virological response (SVR) should be avoided in HDV infection.

Heidrich B et al, Hepatology 2014

Interferon for Delta Hepatitis - Summary

- Off-label use of PegIFN (48 weeks) is currently the only recommended therapy by international guidelines
- Indications: chronic hepatits and compensated cirrhosis
- Virologic response: approx 20%-30% at week 24 post-treatment but high risk (50%?) of late relapse
- Strategies to improve effectiveness: combo with NUC, extension to 96 weeks, lambda IFN…….(no/limited evidence so far)
- Predictors of response: early on therapy decline of HBsAg and/or HDV-RNA (to be confirmed)
- Long-term outcome: improved in sustained responders
- New anti-HDV therapies are urgently needed (with pegIFN ?)

Back-up slides