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HBV/HDV-ACT Connect
(ADVANCING CURATIVE TREATMENTS)

Should All Patients With HDV Be Treated?

CLDF – HBV/HDV ACT Summit, March 26, 2023

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Disclosures:

- Advisory: Gilead, AbbVie, GSK, Bausch
- Research Support: Gilead

Delta Hepatitis

Viewed as one of the most severe forms of viral hepatitis when compared to HBV monoinfection:

- Higher risk for more severe liver disease
- Associated with an accelerated course of fibrosis progression
- Increased risk for hepatocellular carcinoma (HCC)
- Early decompensation in the setting of cirrhosis

Puigvehi M et al. *JHEP Rep*. 2019; 1(2): 120–130.

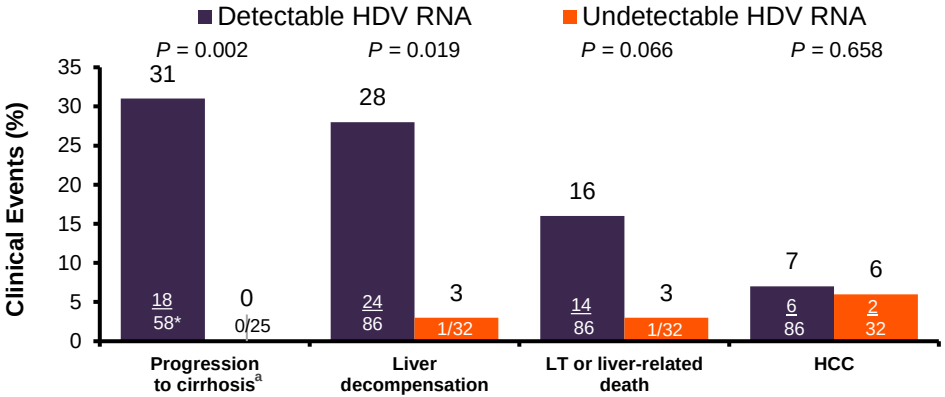
Persistent Viremia Impact on Clinical Outcomes

Multicenter study of HBsAg+, anti-HDV+ patients at 4 academic hospitals in Spain followed for ≥12 months (n = 118)

Baseline Characteristics

Parameters	All Cases (N = 118)	Detectable HDV RNA (N = 86)	Undetectable HDV RNA (N = 32)	P-Value
Male sex	68 (58%)	51 (59%)	17 (53%)	0.676
Age, y	49 (35–54)	47 (36–54)	50 (34–53)	0.227
Ethnicity				0.151
Caucasian	93 (79%)	71 (83%)	22 (69%)	
Black	23 (19%)	14 (16%)	9 (28%)	
Other	2 (2%)	1 (1%)	1 (3%)	
Risk Factors				0.844
IV drug users	23 (19%)	16 19%)	7 (22%)	
Vertical	12 (10%)	10 (12%)	2 (6%)	
Sexual	4 (3%)	3 (3%)	1 (3%)	
Unknown	79 (68%)	57 (66%)	22 (69%)	
ALT, IU/mL	55 (33–96)	65 (44–105)	21 (17–30)	< 0.001
Liver cirrhosis	35 (30%)	28 (33%)	7 (22%)	0.003
HBV DNA log IU/mL	2.2 (1.3–3.1)	2 (1.3–3)	2.8 (2.1–3.2)	0.158
Anti-HCV-positive	22 (19%)	17 (20%)	5 (16%)	0.428

Clinical outcomes based on detectable vs undetectable HDV RNA levels



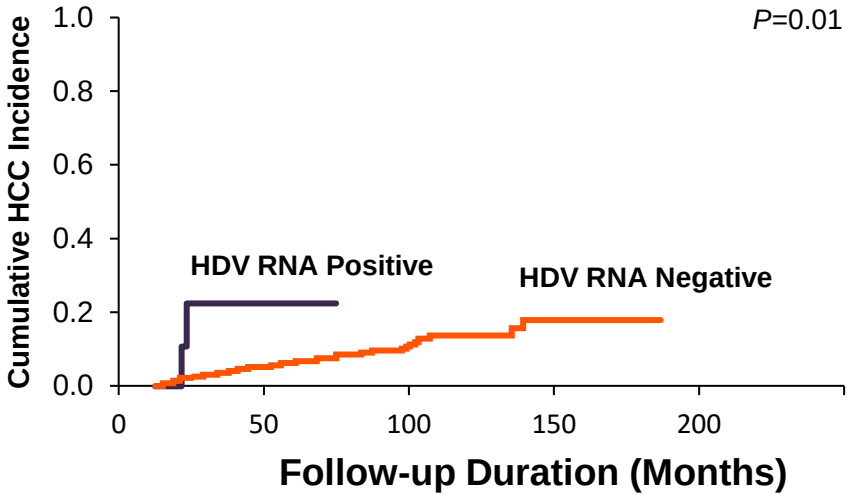
Subjects with persistently positive HDV RNA had a worse prognosis in terms of clinical events

[a]Progression to cirrhosis was assessed only in patients without initial liver cirrhosis. Palom A et al. *Aliment Pharmacol Ther.* 2020; 51(1): 158–166.

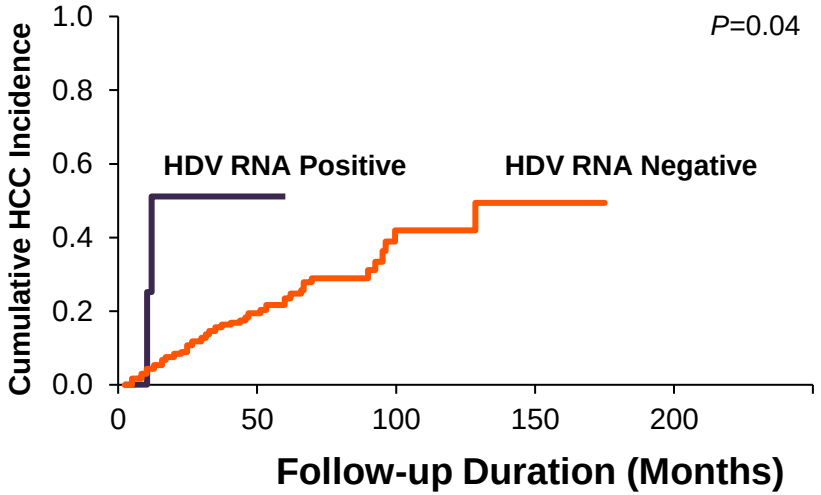
Cumulative Incidence of HCC in Chronic HBV/HDV Coinfection

Retrospective analysis of patients with chronic HBV in Taiwan from 2000-2018 (N=1349)

No Cirrhosis



Cirrhosis



The cumulative incidence of HCC in HBV/HDV coinfected patients was 7.5% at 5-year follow-up

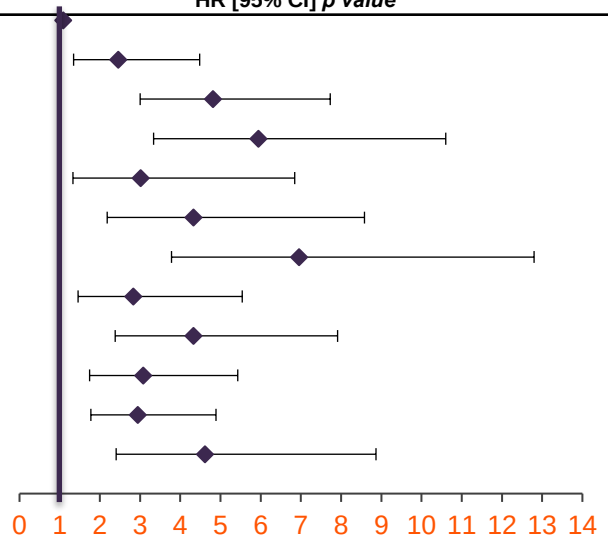
Jang T-Y et al. *Sci Rep*. 2021;11(1):8184.

Impact of Persistent HDV Viremia on Progression of Disease

French nationwide retrospective study of 1112 HDV patients with a median follow-up of 3.0 years

Clinical factors associated with the incidence of HCC

Features	No HCC n = 1004	HCC n = 72	Univariate analysis HR [95% CI] *ρ value*
Age at patient care (years)	35.5 [29.5-42.3]	41.9 [36.2-49.4]	1.09 [1.06, 1.11] **<0.001**
HDV RNA Positive (before endpoint)	552 (61.7)	45 (75.0)	2.46 [1.35, 4.48] **0.003**
Cirrhosis at referral	248 (24.8)	37 (51.4)	4.82 [3.00, 7.73] **<0.001**
Liver decompensation at referral	130 (13.0)	17 (23.6)	5.95 [3.34, 10.60] **<0.001**
AST (IU/L) >2ULN	362 (38.0)	32 (47.8)	3.02 [1.33, 6.85] **0.008**
GGT (IU/L) >2ULN	241 (16.4)	32 (51.6)	4.33 [2.18, 8.58] **<0.001**
Platelet count (10^3/mm^3) <100	216 (23.0)	32 (47.1)	6.96 [3.78, 12.80] **<0.001**
Platelet count (10^3/mm^3) [100; 150]	210 (22.4)	19 (27.9)	2.84 [1.46, 5.54] **0.002**
AFP (ng/ml) >ULN	85 (15.6)	17 (36.2)	4.33 [2.38, 7.91] **<0.001**
Albumin (g/L) ≤35	167 (24.0)	20 (37.0)	3.08 [1.75, 5.43] **<0.001**
Total bilirubin (µmol/L) >17	288 (32.8)	31 (49.2)	2.95 [1.78, 4.89] **<0.001**
Prothrombin time (%) ≤80	441 (51.1)	52 (81.3)	4.62 [2.41, 8.87] **<0.001**



AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; HCC, hepatocellular carcinoma; HR, hazard ratio.
In the multivariate analysis: only age, alcohol intake, GGT, platelet (10^3/mm^3) <100, and prothrombin time (INR) were considered statistically significant.
Roulot D et al. *J Hepatol*. 2020;73:1046-1062.

Patients With Chronic HDV Have Worse Patient-Reported Outcomes Than Those With Chronic HBV

Patients

Chronic HBV
n = 82

Chronic HDV
n = 43

Methods

QUESTIONNAIRES MATCHED GROUP

Chronic liver disease questionnaire

Functional assessment of chronic illness therapy-fatigue

Work productivity and activity impairment

Findings

PATIENTS WITH CHRONIC HDV REPORTED WORSE SCORES:

- **Worry** (*P* < 0.005)
- **Abdominal symptoms** (*P* < 0.05)
- **Physical well-being** (*P* < 0.005)
- **Emotional well-being** (*P* = 0.05)
- **Higher activity impairment** (P < 0.005)

Buti M et al. *JHEP Rep.* 2021; 3(3):100280.

Current Treatment Options for HDV

In EU in some countries: Bulevirtide[1,2]

- HDV entry inhibitor
- Daily subcutaneous injections
- EMA approved (commercially available in Germany and Russia; early access availability in France, Greece, Austria and Italy)

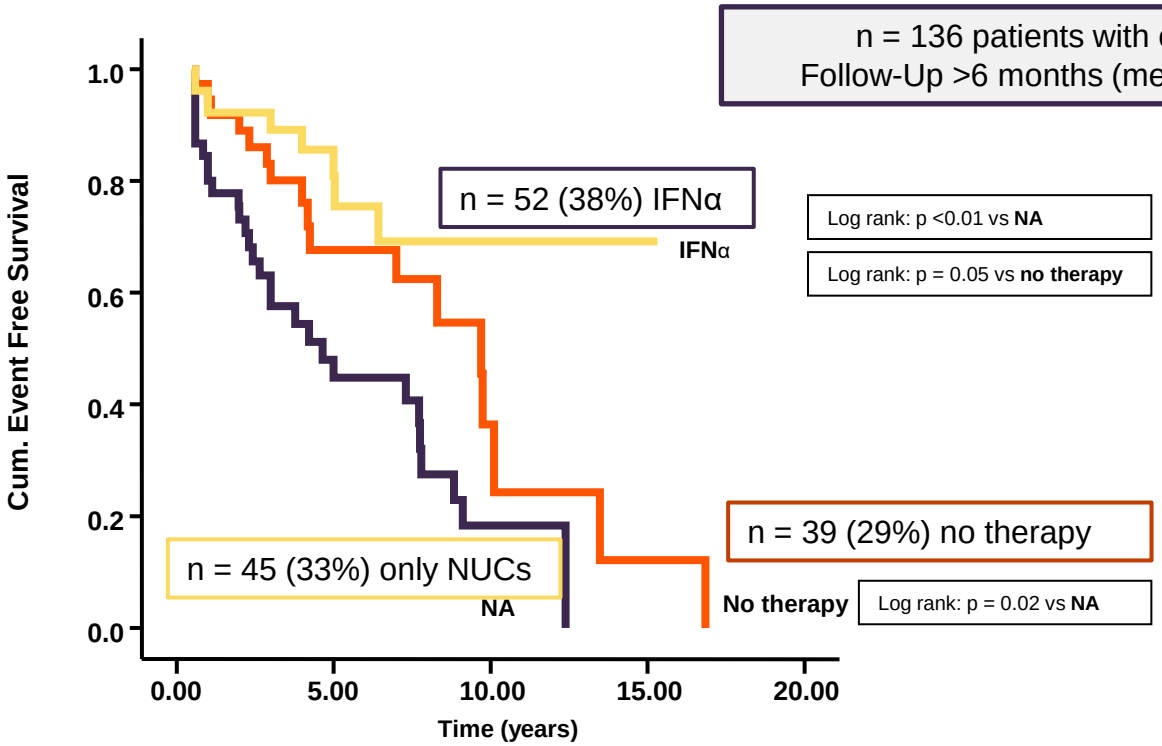
Global: PEG-IFNα[3,4]

- Immune modulator
- Weekly injections
- Off-label use

HDV: hepatitis D virus; EMA: European Medicines Agency; PEG-IFN: pegylated interferon.

1. EMA. Hepcludex. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex#authorisation-details-section. Accessed March 2021; 2. MYR GmbH. HEPCLUDEX▼ (bulevirtide), Summary of Product Characteristics. October 2020; 3. Terrault N et al. *Hepatology*. 2018; 67: 1560–99; 4. Wedemeyer H et al. *N Engl J Med*. 2011; 364: 322−31.

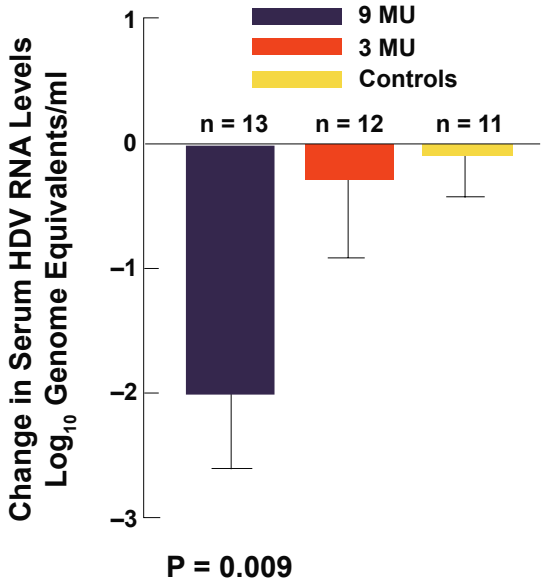
IFNα-Treated Patients Developed Clinical Endpoints Less Frequently

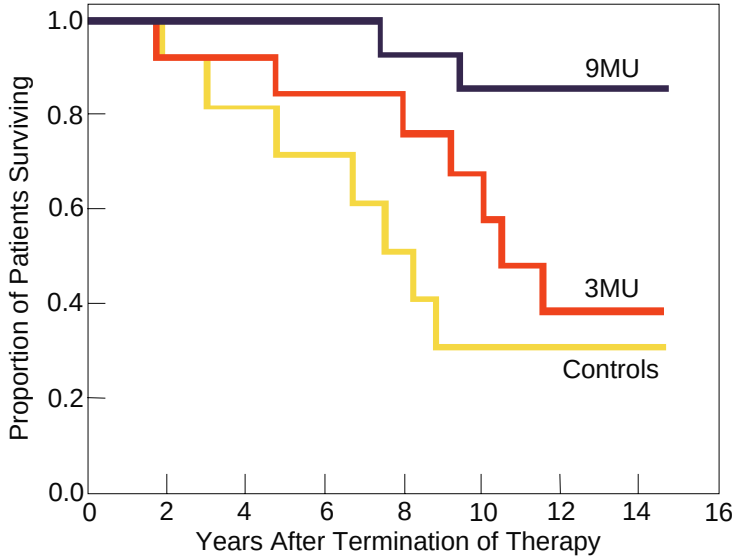


Wranke A et al. *Hepatology*. 2017 Feb; 65(2): 414–425.

EOT HDV RNA ≥2 Log Decline Improves Survival

36 patients with HDV
Randomized controlled trial of a 48-week course of high (9 million units) or low (3 million units) doses of interferon α or no treatment, followed for 2 to 14 years.





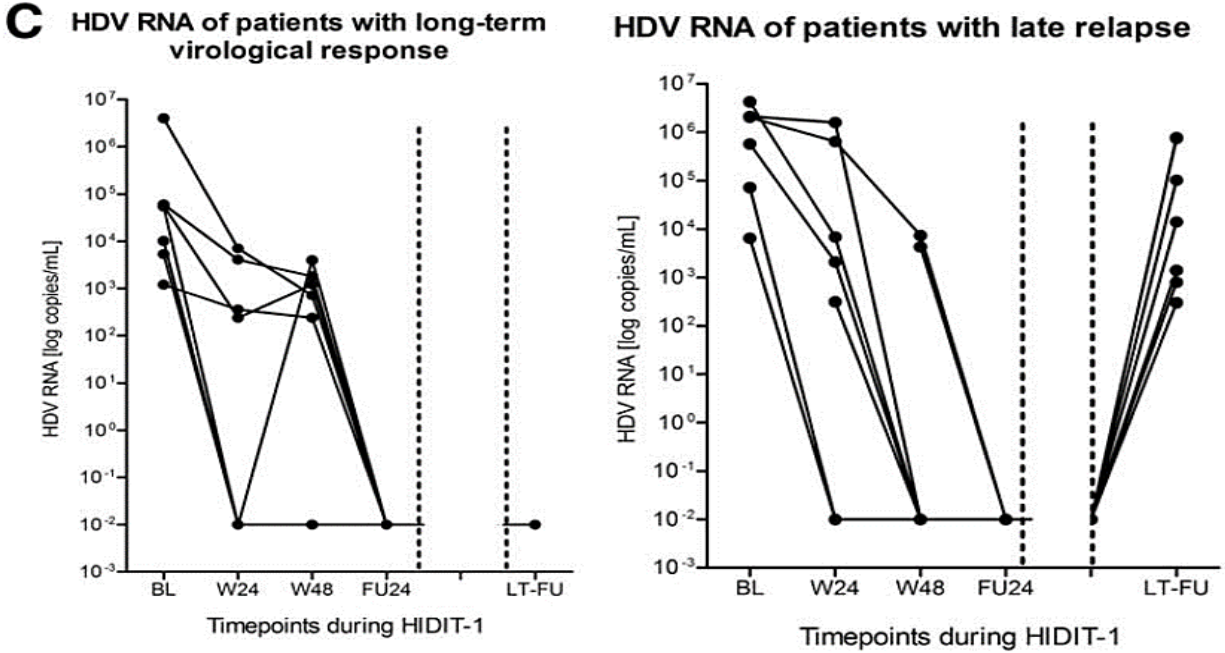
Farci et al. Gastro. 2004.

How Effective Is Peg-Interferon?

Study	Year	Dose	Study Arms and Duration	Number of patients	VR	SVR
Erhardt et al.	2006	1.5mcg/kg SC/ wk	48 weeks	12	NR	17%
Niro et al.	2006	1.5mcg/kg SC/ wk	72 weeks +/- ribavirin	38	13%	21%
Castelnau et al.	2006	1.5mcg/kg SC/ wk	48 weeks	14	57%	43%
Wedemeyer et al.	2011	180 mcg SC/wk	48 weeks +/- adefovir vs. placebo	90	23%	28%
Gheorghe et al.	2011	1.5mcg/kg SC/ wk	52 weeks	49	33%	25%

Adapted from Da B, Heller T, Koh H. *Gastroenterology Report*. 7(4), 2019, 231–245.

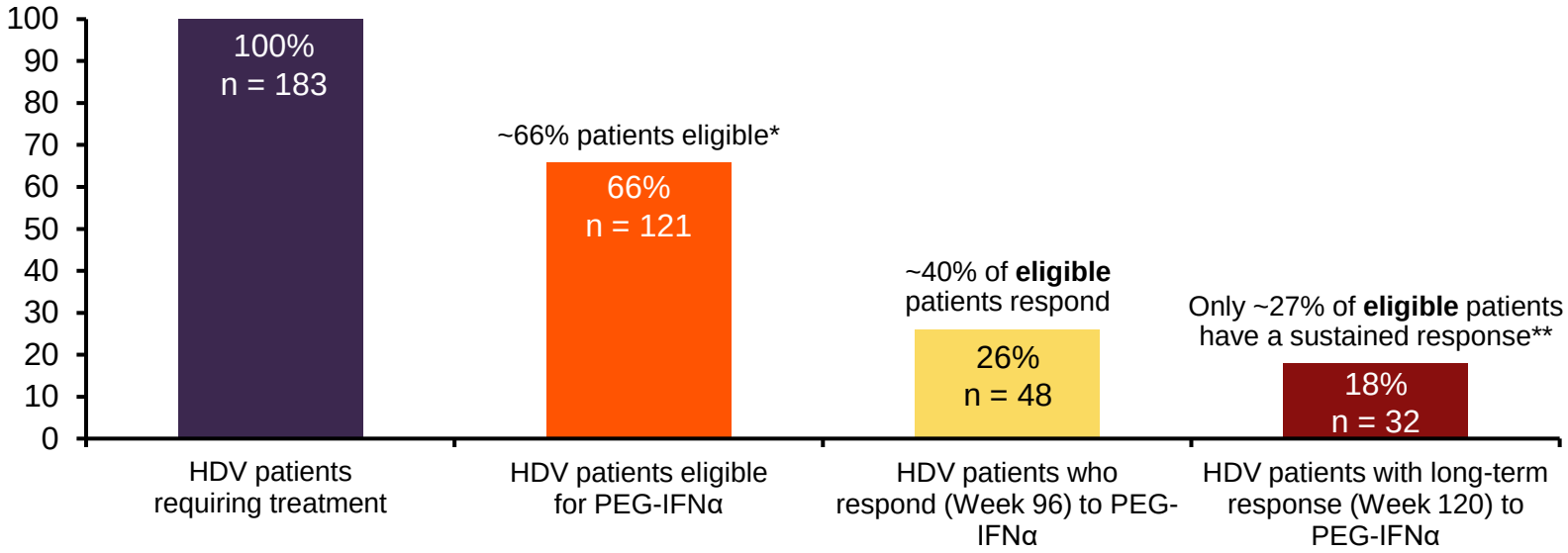
Late Relapse Is Common With PEG IFN Alpha



- Long term f/u of HIDIT-1
- Of 16 patients that were negative for HDV RNA at 6 months after therapy ended, 9 will test positive during long term f/u

Heidrich et al. *Hepatology.* 2014.

Response to PEG-IFNα Treatment



Only a subset of patients are treated with PEG-IFNα, of which a small proportion respond to treatment

*Ineligibility based on contraindications, intolerance and presence of advanced liver disease in HIDIT-II (62 of 183 screened did not meet inclusion criteria or met exclusion criteria) **Response defined as undetectable HDV RNA after 120 weeks of treatment.
HDV: hepatitis D virus; PEG-IFNα: pegylated interferon alpha. Wedemeyer H et al. *Lancet Infect Dis*. 2019; 19: 275–86.

Most Common Adverse Events Per Class

PEG-IFN α	PEG-IFN λ	Bulevirtide
Flu like symptoms Musculoskeletal pain Asthenia Alopecia Autoimmune disease Psychiatric disease Hematologic abnormalities Thyroid disease Injection site reactions PEG-IFN λ much better tolerated than PEG-IFN α		Bile acid elevation Hepatitis flares

Yardeni D et al. *JVH.* 2022.

Guideline Recommendations for Management of HDV – Treatment

	Treatment options	Treatment endpoint	Management
AASLD[1] (2018)	• PEG-IFNα for 1 year • Patients with elevated HDV RNA and ALT elevation	• Undetectable HDV RNA • ALT normalisation/ improved histology	• Test for HDV relapse if ALT increases • Manage in specialist centres
APASL[2] (2016)	• PEG-IFNα for ≥ 1 year • Optimal duration of therapy not well defined	• Undetectable HDV RNA	• Monitor for ≥ 6 months post-treatment
EASL[3] (2017)	• PEG-IFNα for ≥ 48 weeks • HDV/HBV patients with compensated liver disease	• Undetectable HDV RNA	• Long-term HDV RNA monitoring required
WHO[4] (2015)	• PEG-IFNα for ≥ 1 year	• Undetectable HDV RNA	No recommendation

NOTE: Treatment of HDV with PEG-IFNα is off-label. AASLD: American Association for the Study of Liver Diseases; ALT: alanine aminotransferase; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HDV: hepatitis D virus; PEG-IFN: pegylated interferon; RNA: ribonucleic acid; WHO: World Health Organization.

1. Terrault N et al. *Hepatology*. 2018; 67: 1560–99; 2. Sarin SK et al. *Hepatol Int*. 2016; 10: 1–98; 3. European Association for the Study of the Liver. *J Hepatol*. 2017; 67: 370–98; 4. WHO HBV guidelines. March 2015. Available at: https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf?sequence=1 (Accessed March 2021).

What Are the Guidelines on Who “Not” to Treat?

- In patients with decompensated liver disease, PegIFNa should not be used and these patients should be evaluated for liver transplantation. NA should be considered in all patients with decompensated disease if HBV DNA is detectable.

EASL (Lampertico P et al. 2016).

What Are the Guidelines for Nucleos(T)Ide Analogues for HDV Treatment?

	Recommendation
AASLD (Terrault et al. 2018)	1. If HBV-DNA levels are elevated, concurrent therapy with NA using preferred drugs (entecavir, TDF, or TAF) is indicated.
EASL (Lampertico P et al. 2016)	1. In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered (Evidence level II-2, grade of recommendation 1).
APASL (Sarin Sk et al. 2016)	In patients with coinfection of HBV and HDV, it is important to determine which virus is dominant and the patient should be treated accordingly with pegylated interferon alfa for 12–18 months. Patients should be monitored for 6 months posttreatment and beyond (A1).

So what Are the Pros and Cons of HDV Treatment?

- HDV aggressive disease course – hope to slow progression
- EOT viral response improves survival
- Bridge to newer more effective therapies
- Delay transplant?
- Feeling like we are “doing something”

- Longterm regimen
- Significant adverse effect profiles
- Injections
- Risk of disease relapse after treatment discontinuation
- Not available to patients with decompensated liver disease

Who Should We Treat for HDV?

- Patients with detectable viremia +/- elevated ALT
- Patients with evidence of advanced fibrosis or risk factors for more rapid fibrosis progression
- NOT patients with decompensated disease
- Patients who can tolerate peg-Interferon – no preexisting conditions
- Patients who have access to Bulevertide and/or access to clinical trials

Thank You!

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