Treatment of chronic hepatitis delta

Case report

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Disclosures

George Papatheodoridis:

- Advisor: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis, Roche, Spring-Bank
- Lecturer: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, Novartis, Roche
- Research grants: AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Roche
- Clinical trials: AbbVie, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Gilead Sciences, Janssen, Merck Sharp & Dohme, Noorik, Novartis, Novo Nordisk, Regulus, Roche

HDV case

Female, born in 1983

Initial evaluation at our center in 09/2013 (30 years old)

Origin: Moldavia

HBsAg+, HBeAg- known from the age of 15 years (1998) – no follow-up

2008: blood transfusion due to ferrum deficiency anaemia at a General Hospital of Greek NHS (no other guidance)

Alcohol: no, Smoking: no, PDU: no

Physical examination: no significant finding

AST 35 IU/L, ALT 49 IU/L, γGT 59 IU/L, ALP 100 U/L (UNL 120), Bil 1.2 mg/dl Total protein 8.2 g/dL, ALB 4.5 g/dL, INR 1.1, Hb 12 g/dl, PLT 160,000/mm3

HDV case - Continued

HBsAg (+), HBeAg (-), anti-HBe (+)

anti-HDV (+) – **(evaluated for 1st time in 2013!!!)**

anti-HCV (-)

anti-HAV (-) → vaccination initiated

anti-HIV (-)

HBV DNA: 1200 IU/ml, HBsAg 2200 IU/ml

HDV RNA: 567,657 cp/ml

US: heterogeneity of liver parenchyma, no focal lesion

Fibroscan: 12.6 kPa

HDV Case – Q1

What would you recommend?

Further follow-up

Liver biopsy

Therapy

HDV case - Continued

HBsAg (+), HBeAg (-), anti-HBe (+)

anti-HDV (+) – **(evaluated for 1st time in 2013!!!)**

anti-HCV (-)

anti-HAV (-) → vaccination initiated

anti-HIV (-)

HBV DNA: 1,200 IU/ml, HBsAg 2200 IU/ml

HDV RNA: 567,657 cp/ml

US: heterogeneity of liver parenchyma, no focal lesion

Fibroscan: 12.6 kPa

Liver Biopsy: Ishak's grade 2, stage 4

HDV Case – Q2

What would you recommend?

Further follow-up

Therapy with Peg-IFNa

Therapy with Peg-IFNa + NA

Other

Clinical studies for treatment of chronic hepatitis D until 2011

Ref.	Drug used	Dosage	No. of patients included	Main result (s)
Garripoli *et al*[45], 1994	Ribavirin monotherapy	15 mg/kg for 16 wk	9	Ribavirin did not show significant antiviral effects in chronic hepatitis D
Wolters *et al*[49], 2000	LAM + IFN add-on	LAM 100 mg at least for 24 wk; afterwards combination therapy with IFN 9 MU/d for 4 wk, followed by 9 MU 3 times/wk for 12 wk	8	Neither LAM alone nor the addition of IFN was capable of reducing HDV
Yurdaydin *et al*[47], 2002	Famciclovir	500 mg for 6 mo	15	Not effective
Farci *et al*[40], 2004	High-dose IFN *vs* no treatment	dose 3 million units 3 times/wk for 48 wk		significantly improves long term clinical outcome and survival
Kaymakoglu *et al*[46], 2005	IFN α + ribavirin	IFN 10 MU 3 times/wk, Ribavirin 1000-1200 mg/d for 24 mo	19	Addition of Ribavirin to IFN-α does not increase response rate in patients with CHD
Niro *et al*[36], 2005	LAM *vs* placebo	100 mg LAM for 52 wk	31	HDV viraemia was unaffected, even in patients when HBV replication was lowered by LAM therapy
Erhardt *et al*[43], 2006	PEG-IFN	1.5 μg/kg PEG-IFN per wk for 48 wk	12	PEG-IFN is a promising treatment option in chronic hepatitis D
Castelnau *et al*[41], 2006	PEG-IFN	1.5 μg/kg PEG-IFN per wk for 12 mo	14	PEG-IFN is safe and efficient for HDV treatment
Niro *et al*[42] 2006				
Yurdaydin *et al*[50], 200				nal
Mansour *et al*[52], 201				ore
Wedemeye *et al*[44], 2011	*vs* combination PEG-IFN + adefovir	48 wk		resulted in sustained HDV clearance in about 25%

Nucleos(t)ide analogues: ineffective

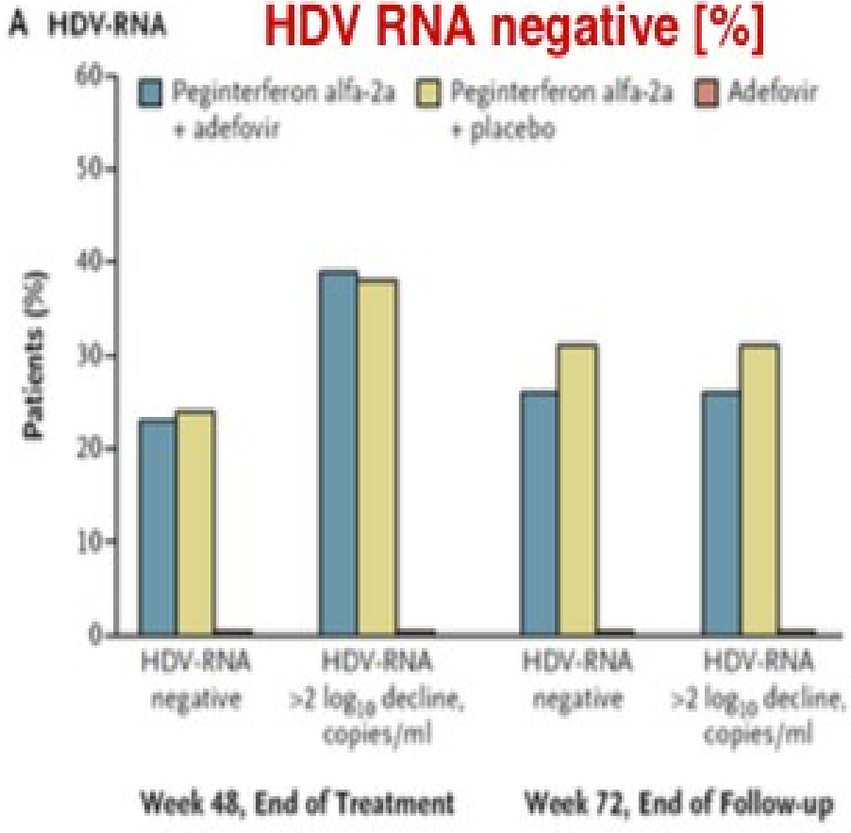
IFNα: sustained biochemical response 0-36%, treatment for >12 months required, treatment with high doses associated with better survival

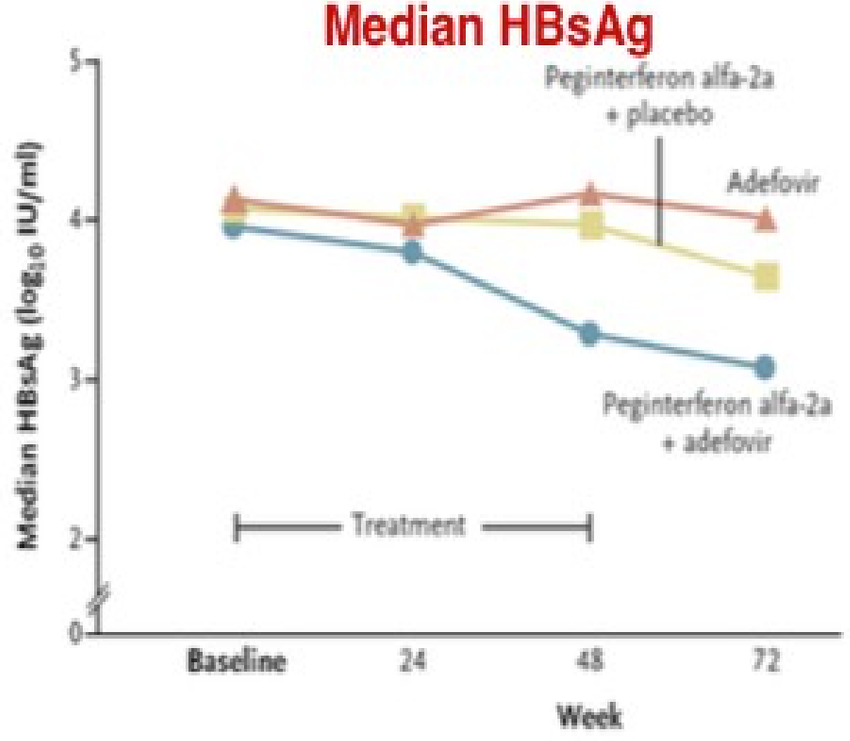
PegIFNa: SVR 17-43%

HIDIT-1: Peg-IFNa plus Adefovir vs. Either Drug Alone for Hepatitis D

Treatment Options for Hepatitis Delta

- HBV polymerase inhibitors are ineffective against HDV
- 48 weeks of PEG-IFNa leads to HDV RNA negativity in 25%-30%
- PEG-IFNa + adefovir may have advantages in HBsAg reduction





Wedemeyer H et al, N Engl J Med 2011; 364:322-31.

HIDIT-2: Peg-IFNa+TDF vs Peg-IFNa alone for Hepatitis D

120 patients, 96 weeks of therapy

	Peg-IFNa+TDF (n=59)	Peg-IFNa (n=61)
HDV RNA (-) at week 96	47%	33%
HDV RNA (-) at week 120	30%	23%
HBsAg (-)	6.7%	4.9%
HBsAg decline >0.5 log10 IU/ml	25%	29%

P≥0.10

Wedemeyer H, Yurdaydin C et al, EASL ILC 2014

Peg-IFNa+entecavir (ETV) vs Peg-IFNa alone for Hepatitis D

40 patients, 72 weeks of therapy

Stopping rules: <2 log reduction in HDV RNA levels at wk 24, detectable HDV RNA at wk 48

	Peg-IFNa+ETV (n=21)	Peg-IFNa (n=19)
HDV RNA (-) at EOT	38%	53%
HDV RNA (-) at 24 wks after EOT	33%	42%
HBsAg (-)	5%	0%

Abbas Z et al, World J Hepatol 2016;8:625–631.

Treatment of chronic hepatitis B + D
EASL recommendations

Recommendation	Grade of evidence	Grade of recommendation
PegIFNα for at least 48 weeks is the current treatment of choice in HDV/HBV co-infected patients with compensated liver disease	**I**	**1**
In HDV/HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered	**II-2**	**1**

NA treatment is recommended for those patients with HBV DNA levels being persistently above 2,000 IU/ml, and might be considered in order to block residual HBV replication in those with advanced liver disease. In patients with decompensated liver disease, PegIFNα should not be used and these patients should be evaluated for liver transplantation. NA should be considerd in all patients with decompensated disease if HBV DNA is detectable.

EASL CPG HBV. J Hepatol 2017;67:370–98

HDV Case – Q3

Peg-IFNa-2a (180 µg/week) was initiated in 11/2013. Do you use stopping rules for inefficacy?

No – minimum duration of therapy 48 weeks

HDV RNA at week 24

HDV RNA at week 48

Other

Treatment monitoring - The role of HDV RNA

- HIDIT-1: 41/50 patients, Peg-IFNa ± ADV for 48 wks & 24 wks follow-up

- Response: HDV RNA (-) at EOT or 24-wk fup,
  Null response: HDV RNA decline <1 log at EOT

- HDV RNA (-) at wk 24 or EOT—> PPV for Response 71% or 100%

- HDV RNA decline >2 log10 at wk 24 —> NPV for Null response 95%

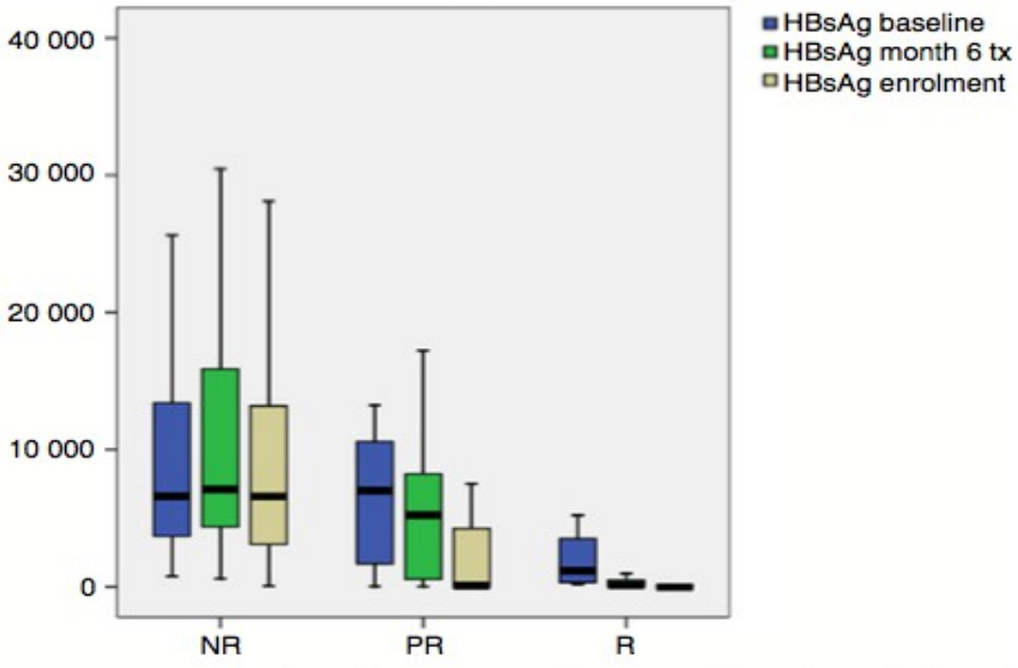
- HDV RNA decline <1 log10 & no HBsAg decline at wk 24 —>
  PPV for Null Response 83%

Keskin O et al, Clin Gastroenterol Hepatol 2015; 13:2342-2349

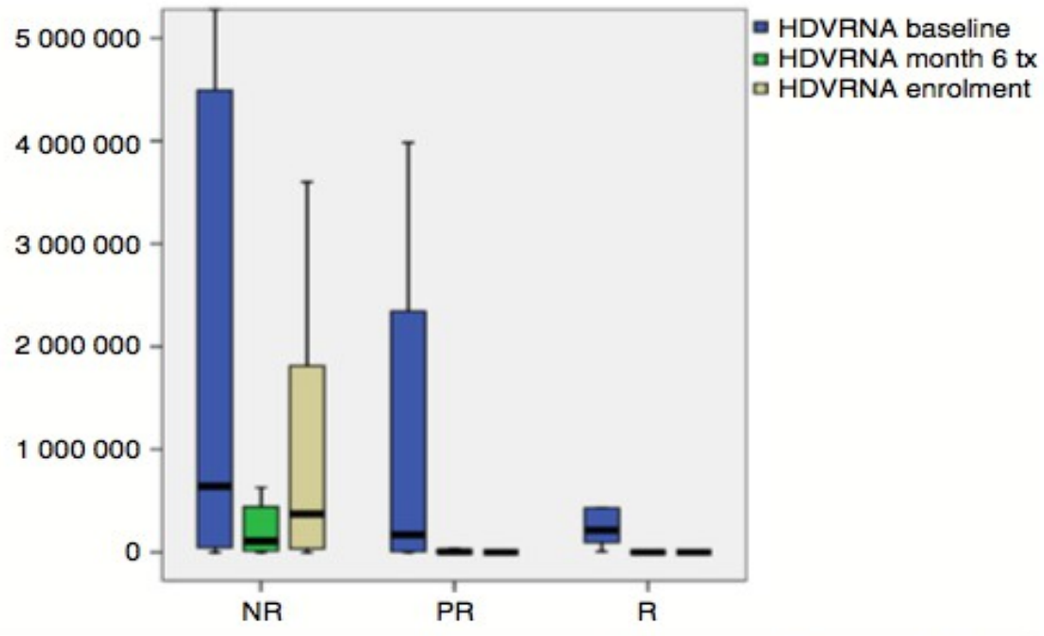
Treatment monitoring - The role of HBsAg

- 62 patients; ≥1 Peg-IFNa courses, mean fup after EOT: 5 years

At end of fup - Responders (R): HDV RNA & HBsAg (-) (n=14), partial responders (PR): HDV RNA (-) & HBsAg (+) (n=12), nonresponders (NR): HDV RNA & HBsAg (+) (n=36)



	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



	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

HBsAg <1000 IU/mL at month 6 discriminated responders and PR from NR (P < 0.001). By ROC curve, the threshold of **0.105 log reduction of HBsAg** associated with **1.610 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

Treatment of chronic hepatitis B + D
EASL recommendations

Recommendation	Grade of evidence	Grade of recommendation
PegIFNα for at least 48 weeks is the current treatment of choice in HDV/HBV co-infected patients with compensated liver disease	I	1
In HDV/HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered	II-2	1
PegIFNα treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated	**II-2**	**2**

EASL CPG HBV. J Hepatol 2017;67:370–98

HDV case – Q4

- 11/2013: started Peg-IFNa
- Relatively good tolerance – no lab adverse events
- 05/2014: ALT 34 IU/L, HBV DNA (-), HBsAg 1860 IU/ml,
  HDV RNA 7,200 cp/ml
- 08/2014: increasing fatigue
- 11/2014: ALT 34 IU/L, HBV DNA (-), HDV RNA (-), HBsAg (+),
  Fibroscan 11.2 kPa

Would you discontinue therapy?

Yes

No

Duration of IFNa therapy and sustained response in CHD

99 patients, ≥6 months of IFNa

Cumulative median IFNa: 24 months (range 6-126), median of 2 courses (range 1-8)

Maintained virologic response (MVR): HDV RNA (-) for 2 years after EOT

Post-treatment median follow-up: 55 months (24-225)

Cumulative probability of MVR increased with treatment duration (50% at 5 years)

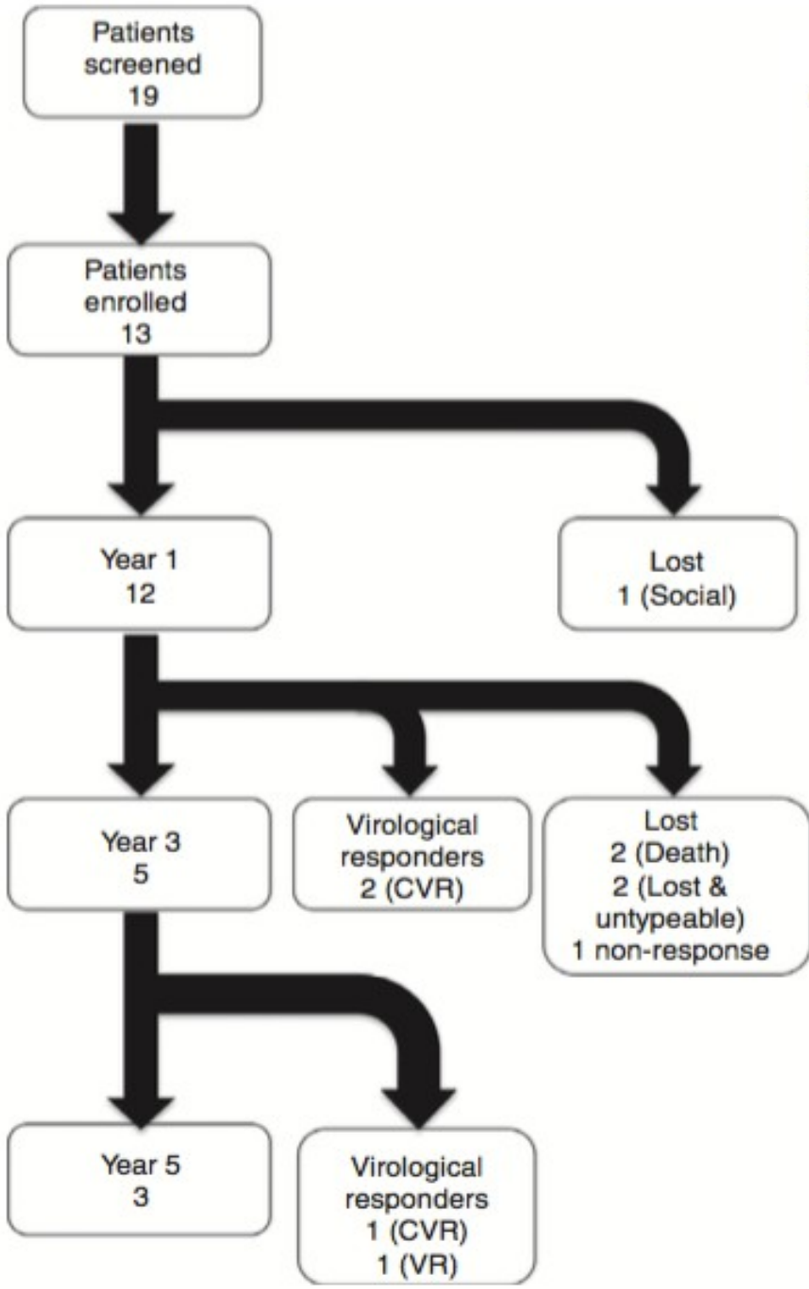
Patients with MVR: less likely to die from liver disease (P=0.032) or develop complications (P=0.006)

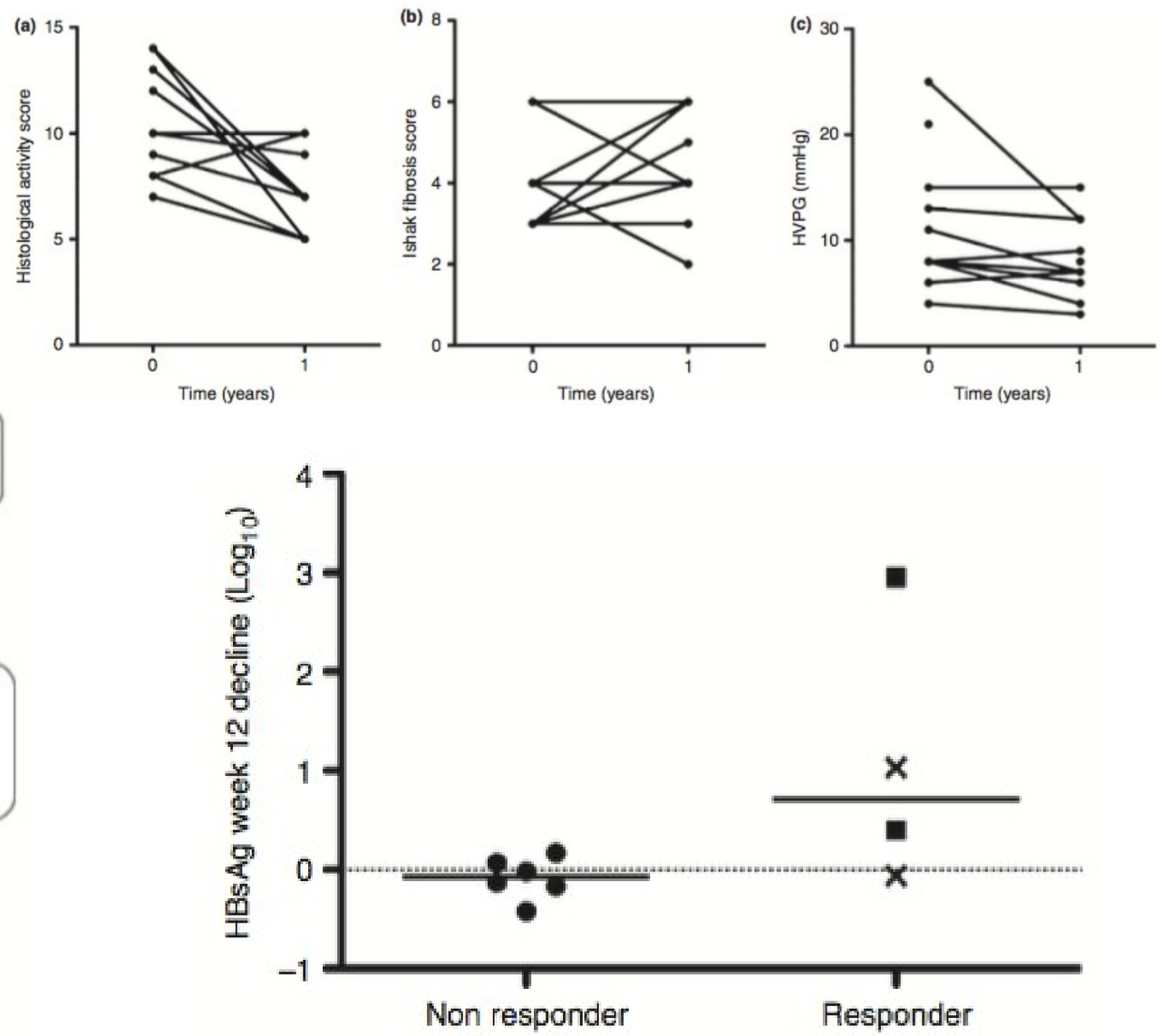
Adverse endpoint: associated with cirrhosis at baseline (OR: 16.10) and no response to therapy (OR: 5.23)

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

Long-term therapy of chronic hepatitis delta

Long-term therapy (5 years) of CHD with Peg-IFNα





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

Benefits from the use of IFNa for CHD

In HDV-coinfected patients, the effect of interferon was significant (HR = 0.14; 95% CI (0.02–0.86), p = 0.033), indicating a reduction of liver-related events in treated cases.

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

Benefits from the use of IFNa for CHD

Antiviral treatment and liver-related complications in hepatitis delta

- 136 CHD patients, single-center cohort
- Mean follow-up 5.2 years
- End-points (decompensation, HCC, LT, death): 40%
- IFNα-based therapies: less end-points than NA or no-therapy
- Loss of HDV RNA: more frequent in IFNα-treated patients, lower likelihood of end-points

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

HDV Case – Q5

➢Peg-IFNa-2a discontinued in 11/2014.

How would you follow the patient during the first year?

ALT & HDV RNA every 3 months

ALT every 3 months & HDV RNA every 6 months

ALT & HDV RNA every 6 months

ALT every 3 months & HDV RNA every 12 months or ALT flare

HDV Case – Q6

- Peg-IFNa-2a discontinued in 11/2014
- 02/2015-11/2015: ALT<ULN (4 occasions), HDV RNA (-) (2 occasions)

How would you follow the patient?

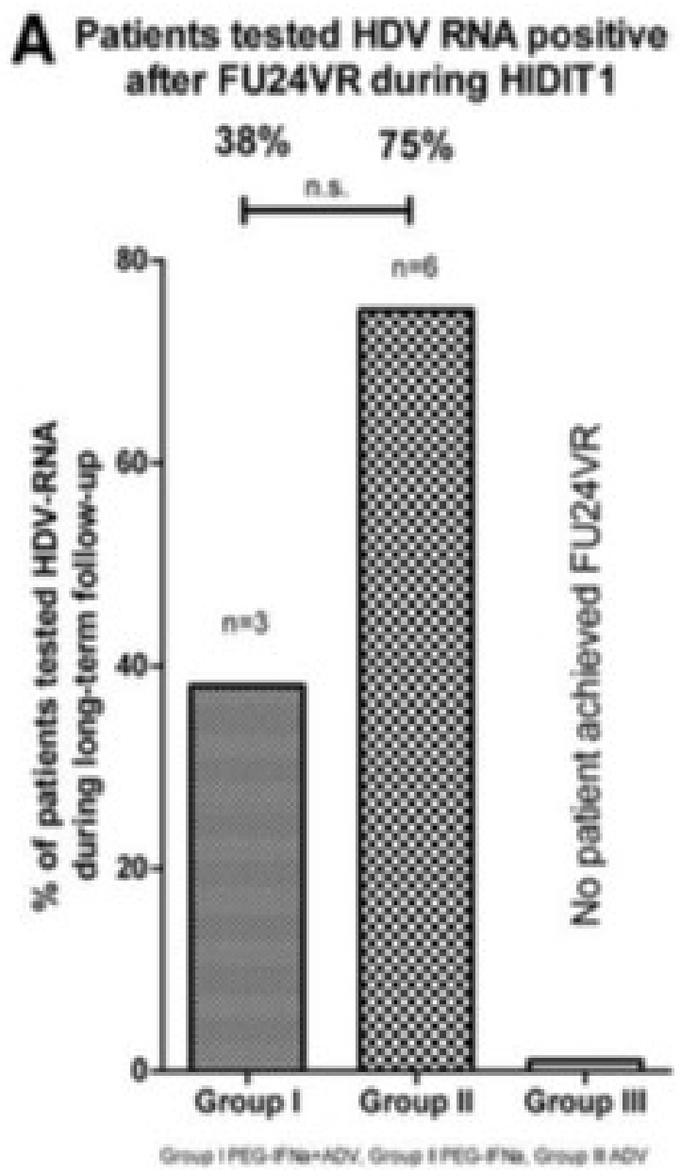
ALT & HDV RNA every 3 months

ALT every 3 months & HDV RNA every 6 months

ALT every 3 months & HDV RNA every 12 months

ALT every 6 months & HDV RNA every 6-12 months

Late relapses of HDV after Peg-IFNa therapy may occur



Among the 16 patients with HDV RNA (-) at wk 24 of fup who underwent long-term follow-up evaluation, 9 **(56%) experienced relapse of HDV replication**

Heidrich B et al, Hepatology 2014;60:87-97.

HDV Case – Q7

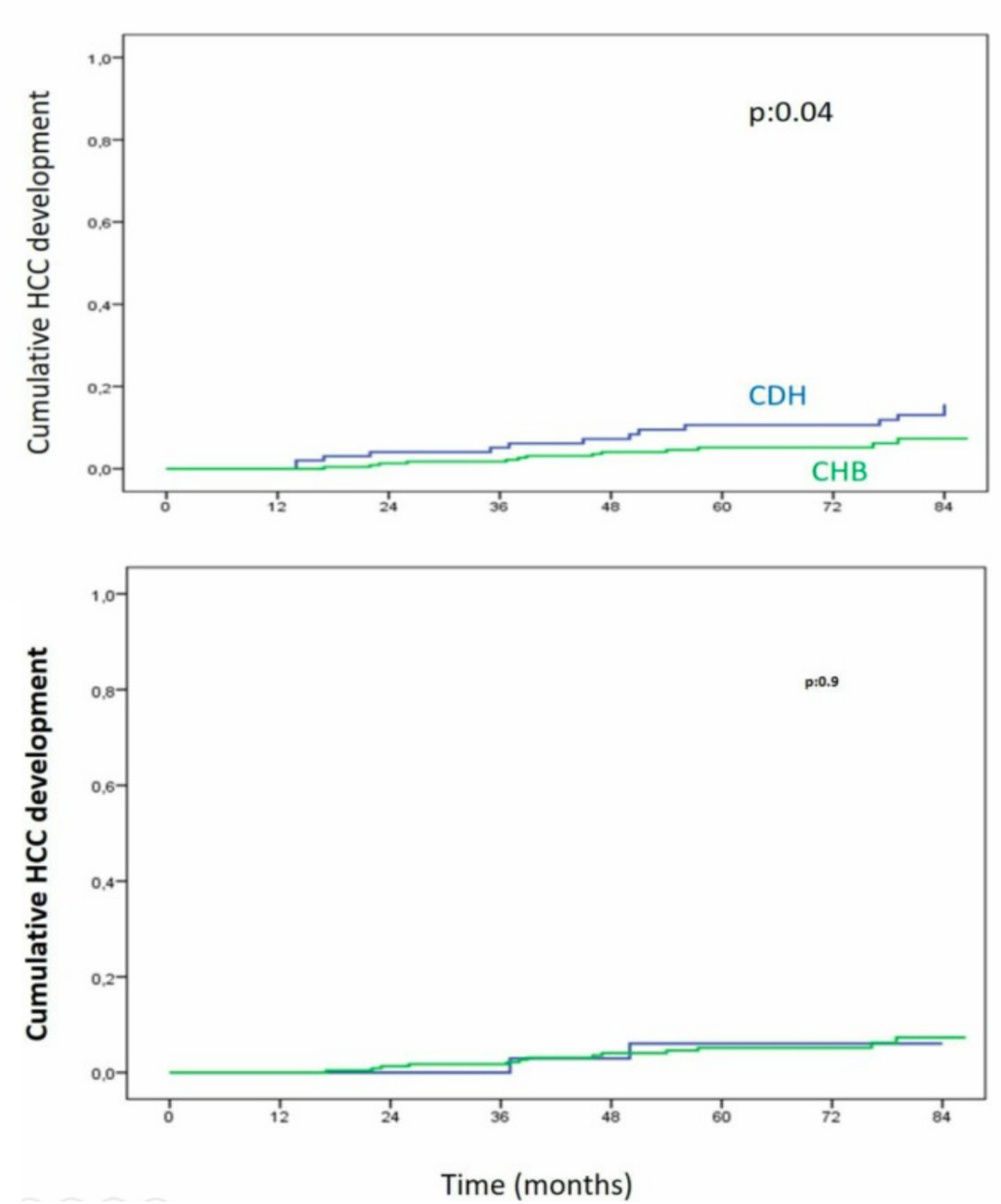
Would you recommend HCC surveillance?

Yes

No

In patients under treatment, CHD is a greater risk factor for HCC development than CHB

- HCC was more common in CHD vs CHB patients (P=0.04)
- Male sex (OR 7.3), CHD (OR 12.8), age (OR/year 1.1) were independent predictors of HCC development
- No significant difference in HCC incidence between CHB patients and CHD patients with MVR (cumulative 96-month probability of HCC: 7.6% for CHB vs 10% for CHD, P=0.09)



Keskin O et al, EASL ILC 2017

HDV Case – Q8

- The patient returned to the clinic in 11/2016
- ALT 320 IU/L, PLT 135,000/mm3
- HDV RNA 5,300,000 IU/ml, HBV DNA 1,800 IU/ml, HBsAg 2650 IU/ml
- Fibroscan 20 kPa

Treatment initiation was decided. Which regimen would you recommend?

Peg-IFNa (180 µg/week)

Peg-IFNa + ETV

Peg-IFNa + TDF

No therapy

Other

HDV Case – Q9

- 11/2016: Peg-IFNa + TDF initiated – Severe fatigue
- 05/2017: ALT 120 IU/L, PLT 85,000/mm3, HDV RNA 220,000 IU/ml, HBV DNA (-)
- 10/2017: Variceal bleeding, mild ascites, albumin 3.5 g/dl, INR 1.2, bilirubin 1.3 mg/dl, ALT 145 IU/L, PLT 80,000/mm3, HDV RNA 630,000 IU/ml, HBV DNA (-)

What would you recommend?

Stop Peg-IFNa, continue TDF

Stop Peg-IFNa & TDF

Other

Any of the above plus liver transplant evaluation

HDV Case – Q10

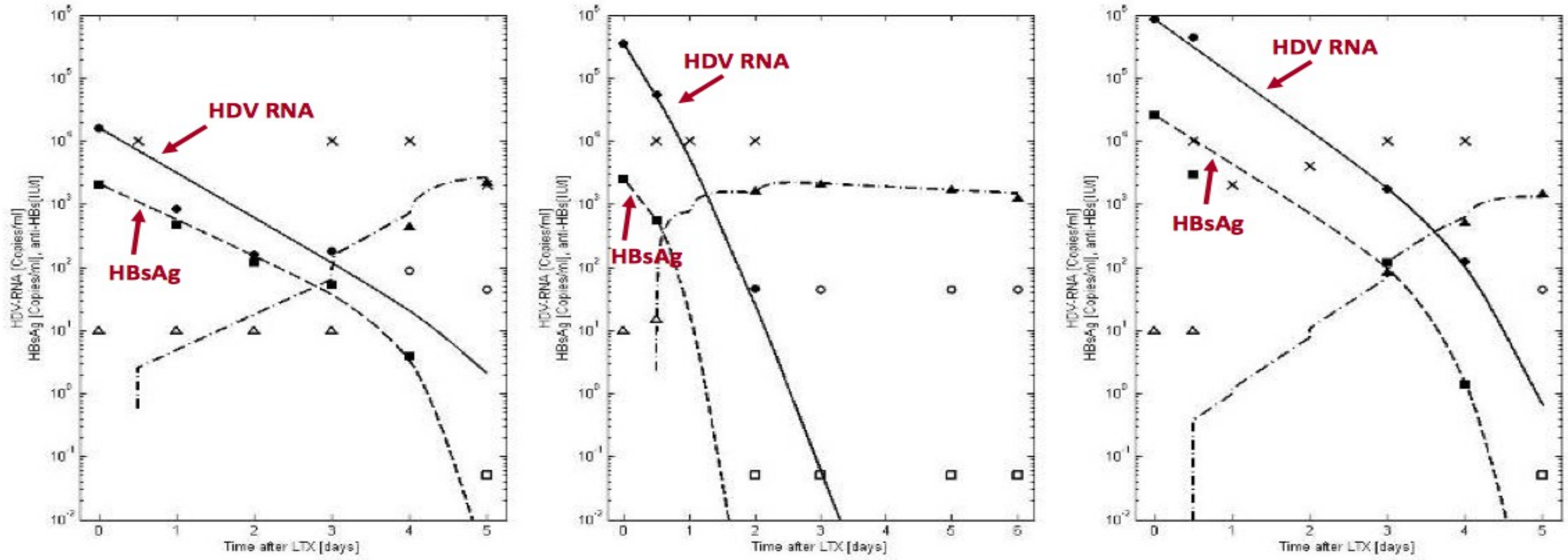
- 10/2017: Peg-IFNa discontinued - TDF continued (+spironolactone 50 mg/24h)
- 06/2018: Ascites worsened, albumin 3.1 g/dl, INR 1.5, bilirubin 2.1 mg/dl, ALT 145 IU/L, PLT 105,000/mm3, HDV RNA 1,130,000 IU/ml, HBV DNA (-)

Would you consider the patient for liver transplantation?

Yes

No

Liver transplantation: The final solution for CHD



- Rapid and parallel decline of HDV RNA and HBsAg after LT
- Rates of recurrent HBV-HDV infection: <5% using low dose HBIG + NA

Mederacke I et al, J Hepatol 2012;56:115-122. Roche B & Samuel D, Semin Liver Dis 2012;32:245-255.

HDV Case – Q11

Would you consider to discontinue HBIG and continue with NA monoprophylaxis in a patient who underwent liver transplantation for HBV+HDV related cirrhosis?

Yes

No

NA prophylaxis after HBIG withdrawal against HBV and HDV recurrence after liver transplantation

Clinical characteristics of patients with (*n* = 2) and those without (*n* = 32) hepatitis B/hepatitis D recurrence after liver transplantation (LT)

Variable (unit)	Patients with hepatitis B/hepatitis D recurrence (*n* = 2)	Patients without hepatitis B/hepatitis D recurrence (*n* = 32)	*P*-value
Age, mean ± SD (years)	31.5 ± 7	48 ± 15	0.24
Gender, male, *n* (%)	1 (50)	21 (72)	0.43
MELD at LT, mean ± SD	16 ± 3	17 ± 4	0.84
Detectable HBV DNA pre-LT	0 (0)	1 (3)	0.87
HDV RNA pre-LT, median (range), copies/mL	37,760 (12,520–63,000)	33,240 (192–853,500)	0.44
Pre-LT HCC, *n* (%)	0 (0)	5 (15.6)	0.54
Immunosuppressive regimen, *n* (%)			
CNIs+MMF	2 (100)	26 (81)	0.50
Antiviral prophylaxis with nucleotide (± nucleoside) analogs	2 (100)	21 (66)	0.31
Total dose of HBIG before discontinuation, median (range), IU/mL	79,000 (76,000–82,000)	89,000 (13,000–214,000)	0.83
Duration of HBIG administration before its discontinuation, median (range), months	9 (6–12)	28 (6–144)	0.008
Anti-HBs levels at the time of HBIG discontinuation, median (range), IU/mL	206 (196–215)	252 (97–1280)	0.23

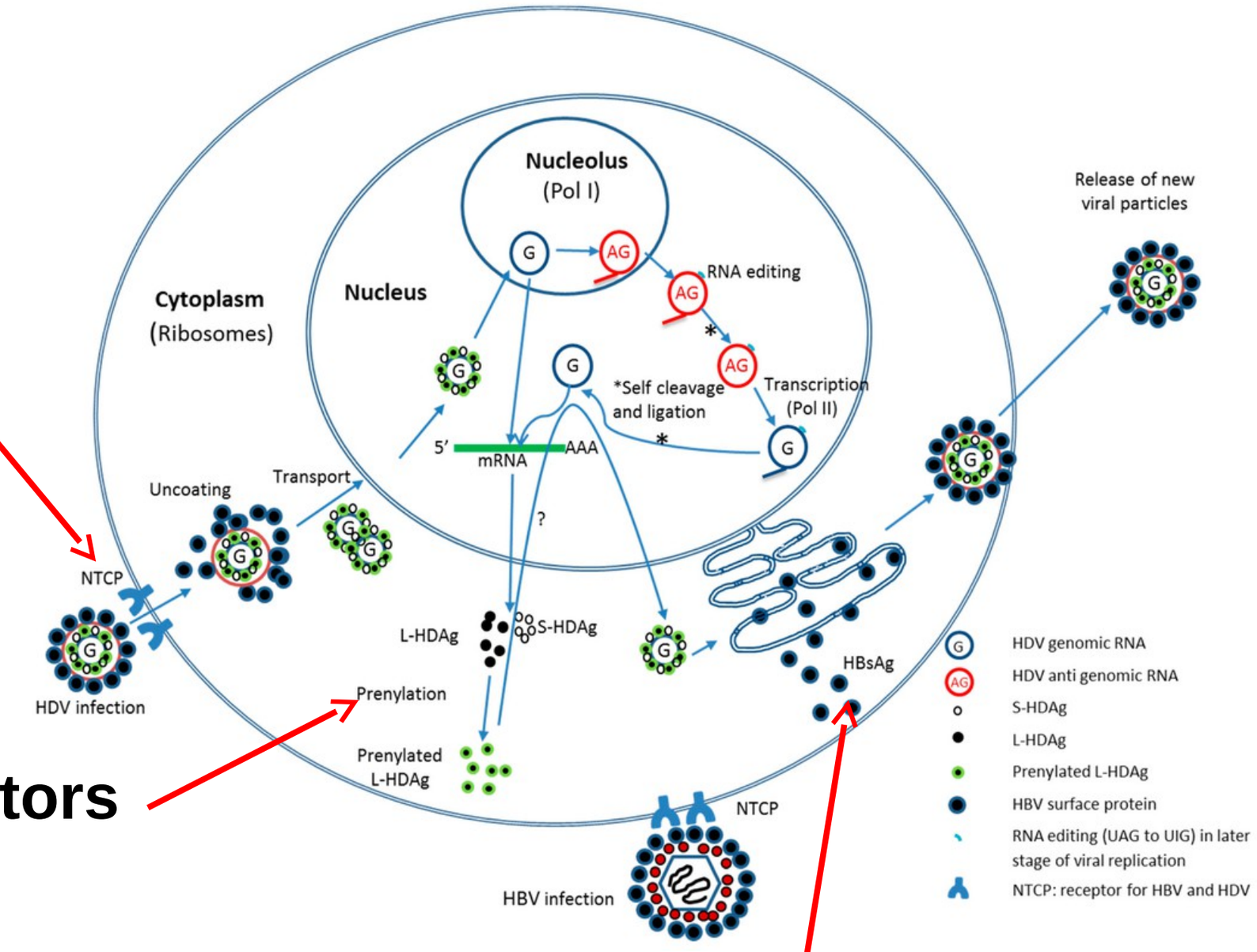
SD, standard deviation; MELD, model for end-stage liver disease; HBV, hepatitis B virus; HDV, hepatitis D virus; HCC, hepatocellular carcinoma; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; HBIG, hepatitis B immunoglobulin.

Cholongitas E et al, Transpl Infect Dis 2016;18:667-673.

HDV: Waiting for new therapies…

◆**Entry inhibitors (Myrcludex)**

◆**Prenylation inhibitors (Lorafarnib)**



◆**Nucleic acid polymers (REP 2139)**

Hepatitis Delta
Take home messages

- In order to treat CHD, it needs to be diagnosed
- Be aware of certain risk populations (immigrants, PDUs)
- The only effective treatment is interferon
- Treatment beyond 1 year is required in a significant proportion of patients
- Until new therapies are available, Peg-IFNa therapy duration has to be decided on an individual basis
- **New drugs: There is still a long way to go**

Thank you for your attention