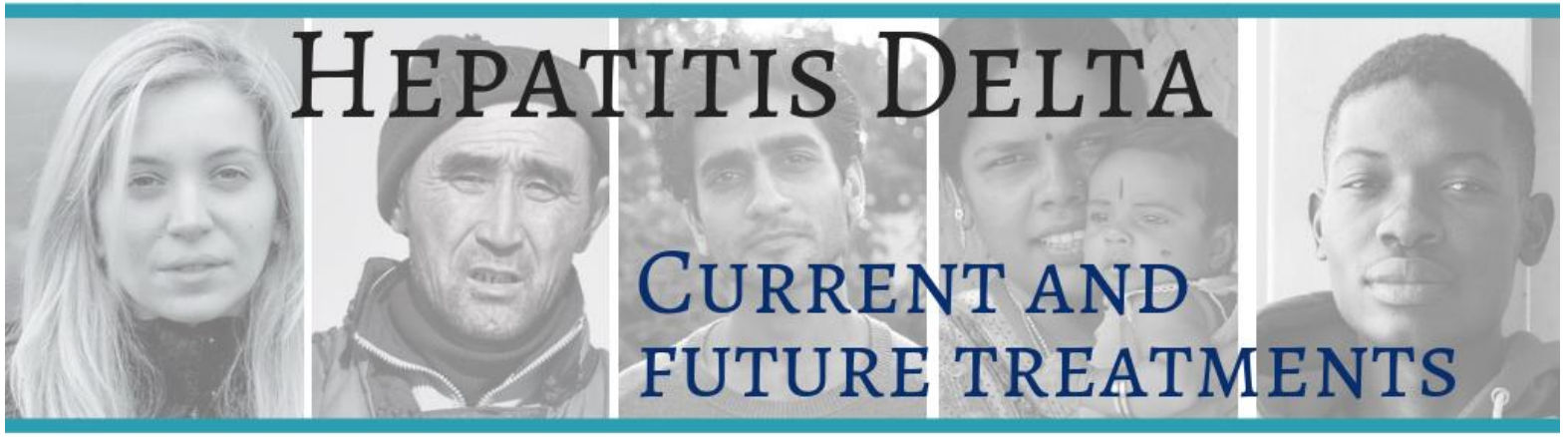

TUESDAY, JANUARY 8TH 2019
7:00 AM PT/ 10:00 AM ET

Cihan Yurdaydın, MD
Department of Gastroenterology
University of Ankara Medical
School, Ankara, Turkey

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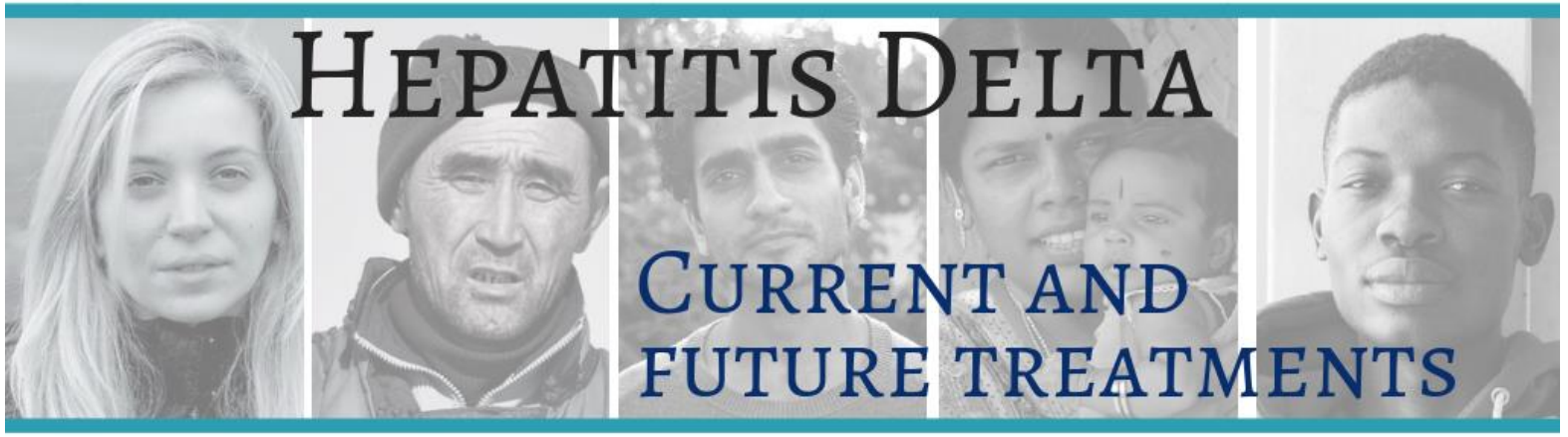
Have a Question?

Questions? Feel free to submit questions in the chat box at anytime throughout the webinar. We will have a 15 minute Q&A session at the end of the webinar.



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Disclosure

I have received consultancy and/or lecture fees from AbbVie, BMS, Gilead, Eiger, Roche, Merck, and have received grants from BMS, Eiger and Roche.

Outline

- The Problem
- Diagnosis
- Current Treatment
- Future Treatments

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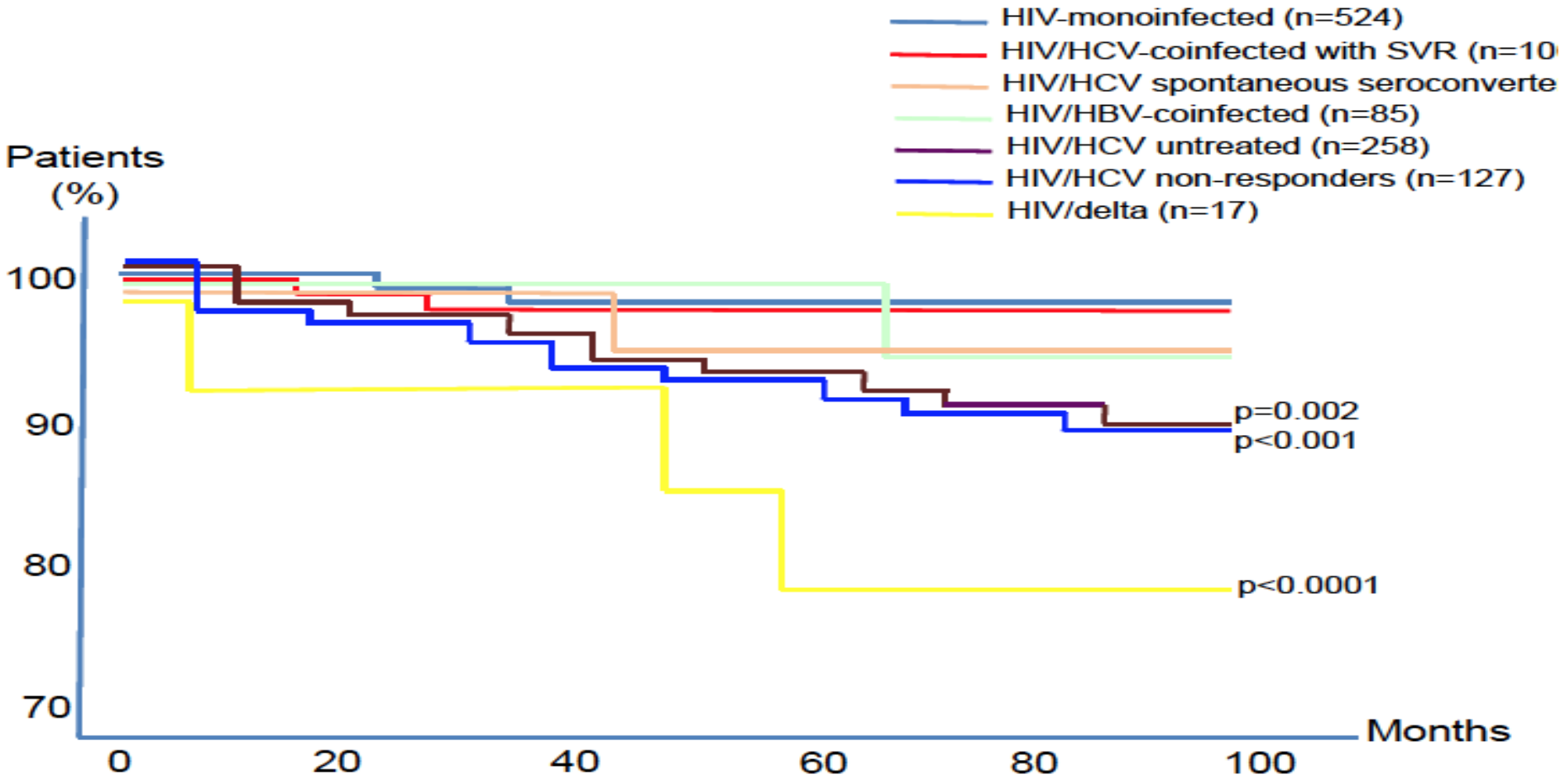
Introduction

- Chronic delta hepatitis (CDH) is the most severe form of viral hepatitis
- A disease of the developing or underdeveloped countries or regions
- Orphan disease in the EU and USA
- The only therapy of proven benefit is with interferons
- Biomedical Industry displays little interest: “not cost-effective”
- Liver injury in CDH is immune mediated

Time free from liver decompensation or death in HIV infected patients



Fernandez-Montero et al, Clin Infect Dis 2014

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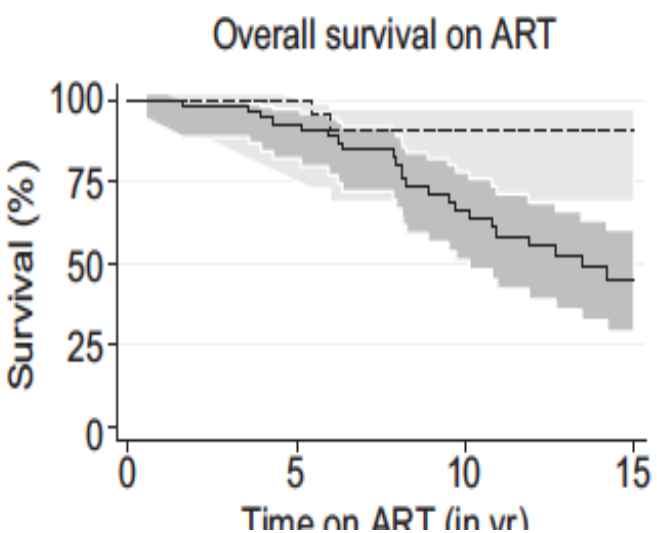
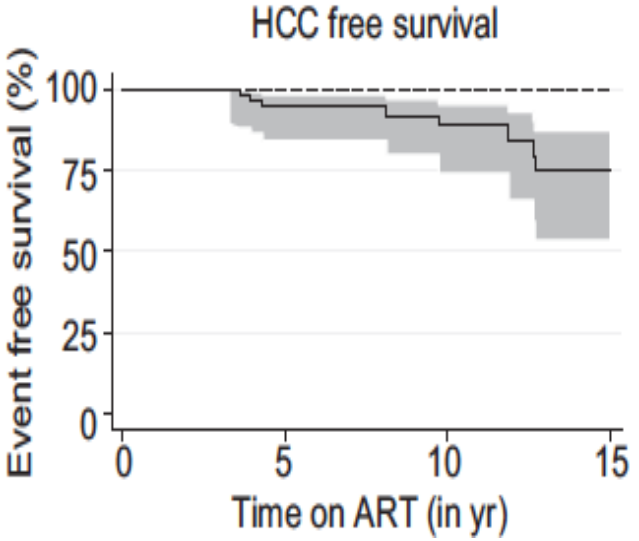
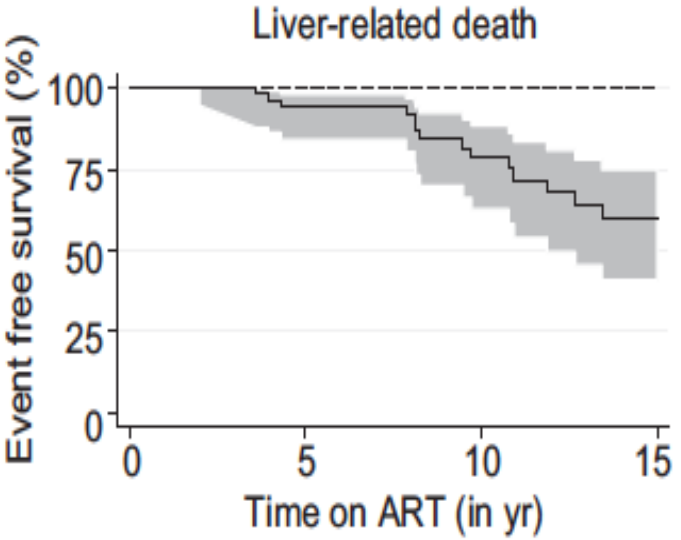
Overall, liver-related mortality and HCC development in HDV RNA (+) vs HDV RNA (-) HIV pts

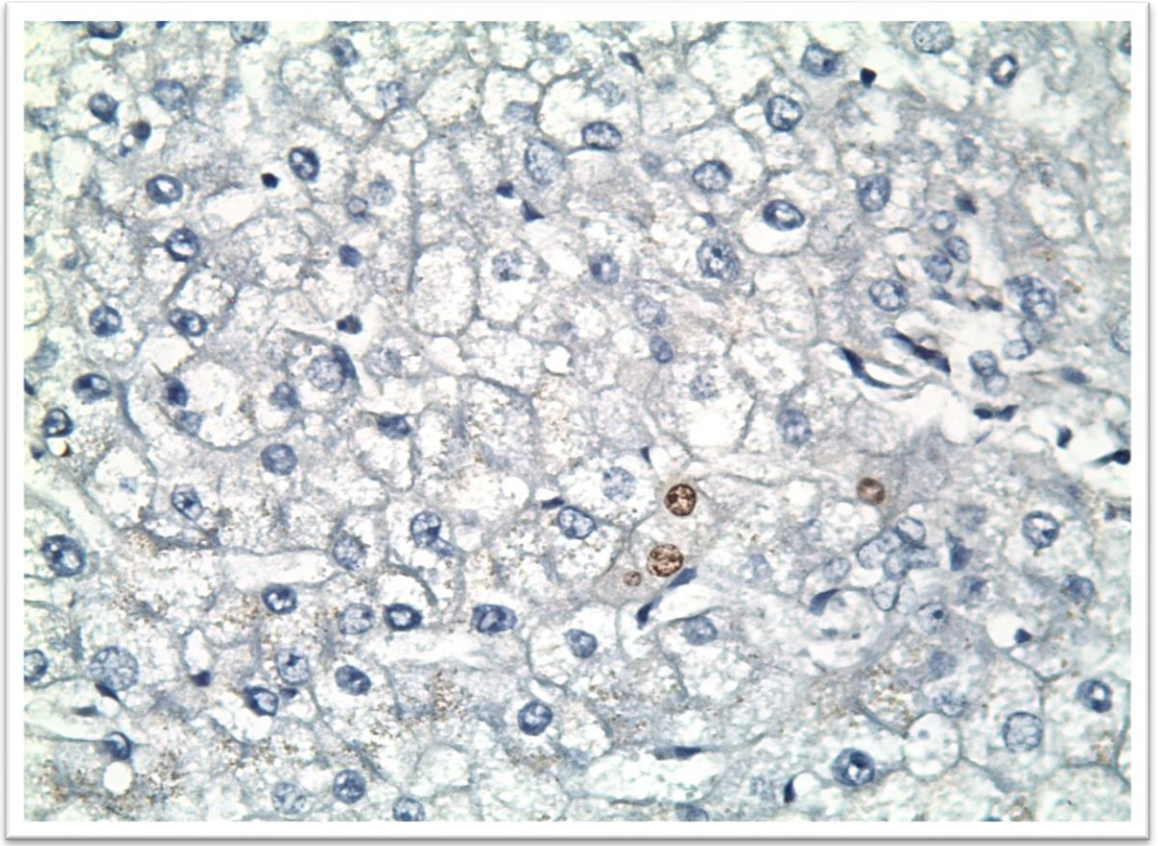






Moradpour et al, J Hepatol 2016

HBcAg IHC in CDH



- Nuclear localization
- No correlation with liver injury, even in HBV-HDV
- Co-dominant cases

Kabaçam et al, Liver Int 2013

Hepatitis D > Hepatitis B

Hepatitis D = Hepatitis B

Hepatitis D < Hepatitis B

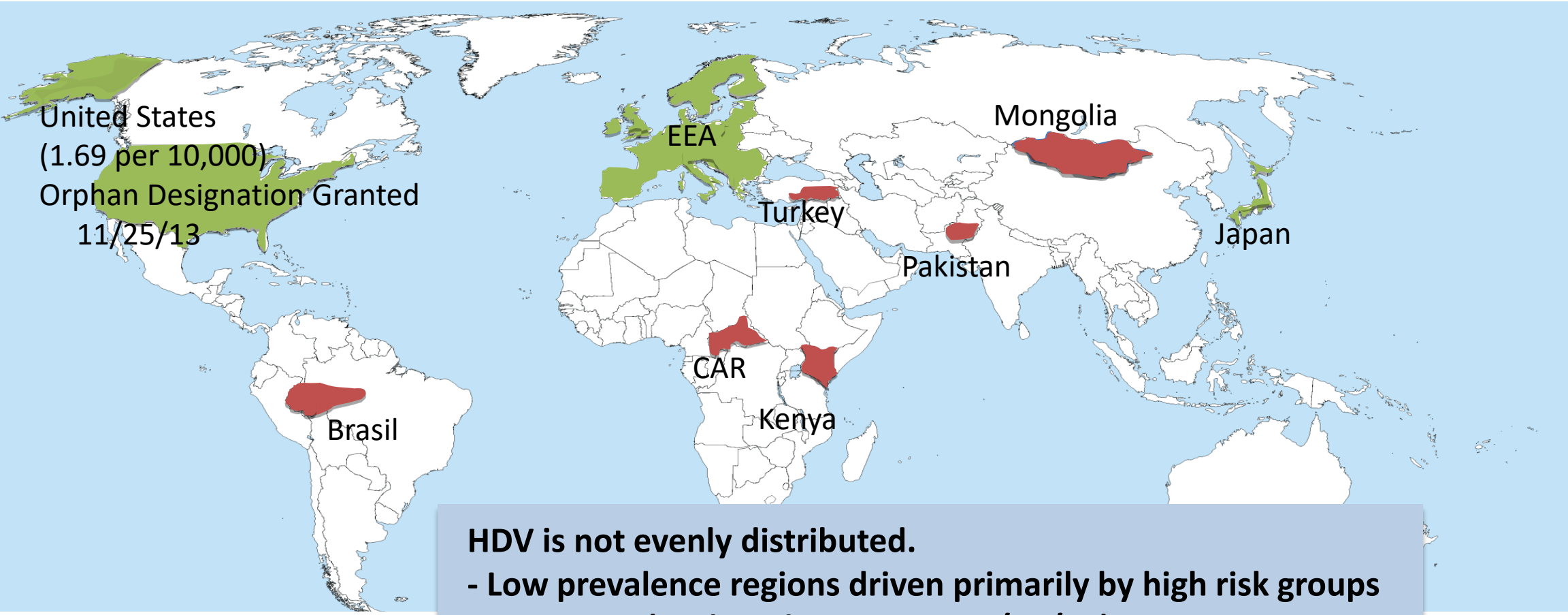
Delta Hepatitis

Early chimpanzee experiments disclosed:

- Suppression of HBV infection
  - Decline or disappearance of HBcAg in liver tissue
  - Decrease in HBsAg

- Typical patient with delta hepatitis:
  - HBeAg-negative, HBeAb-positive
  - HBV DNA low
  - High HDV RNA

Global overall estimated HDV prevalence: ~5% (4.7-5.3%) of patients with active HBV (240 million HBV cases worldwide--WHO)



HDV is not evenly distributed.

- **Low prevalence regions driven primarily by high risk groups**
  e.g. US (orphan designation 11/25/13), EU, Japan
- **Regions of higher prevalence--endemic**
  e.g. Mongolia, parts of Pakistan, Brasil, Africa, Turkey, etc.

Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis

Hai-Yan Chen,[1] Dan-Ting Shen,[1] Dong-Ze Ji,[2] Pei-Chun Han,[1] Wei-Ming Zhang,[2] Jian-Feng Ma,[1] Wen-Sen Chen,[3] Hemant Goyal,[4] Shiyang Pan,[1] Hua-Guo Xu[1]

Chen H-Y, *et al*. *Gut* 2018;**0**:1–10. doi:10.1136/gutjnl-2018-316601

Results From a total of 2717 initially identified studies, only 182 articles from 61 countries and regions met the final inclusion criteria. The overall prevalence of HDV was 0.98% (95% CI 0.61 to 1.42). In HBsAg-positive population, HDV pooled prevalence was 14.57% (95% CI 12.93 to 16.27): Seroprevalence was 10.58% (95% CI 9.14 to 12.11) in mixed population without risk factors of intravenous drug use (IVDU) and high-risk

EEA HDV Prevalence

Heavily impacted by Immigration and IVDU* Populations

	High Risk Group Proportion in HDV Population	IVDU HBsAg (+) Population[1]	Immigrant HBsAg (+) Population[2]	High Risk HBsAg (+) Population	% HDV Prevalence[3]	HDV subjects in High Risk Population
Spain	96%	1,686	155,459	157,145	6-9	11,786
Sweden	84%	4,466	50,593	55,059	2-5	1,927
France	83%	50,562	112,704	163,266	6-9	12,245
UK	74%	29,367	192,128	221,495	6-9	16,612
Germany	72%	9,394	282,256	291,650	10-12	32,082
Italy	56%	36,940	202,648	239,588	6-9	17,969

[1] IVDU population figures taken from EMCDDA (European Monitoring Center for Drugs and Drug Addiction)
[2] Immigrant population figures taken from Eurostat
[3] HDV prevalence from post-2006 country specific literature reports

- High risk group proportion in HDV population is 56-96%
  → For Spain, Sweden, France, UK, Germany, and Italy, HDV proportion of high risk groups are 96%, 84%, 83%, 74%, 72%, 56%, respectively (mean = 78%).
- Total HDV Population = HDV High Risk Group + HDV Low Risk Group
- HDV High Risk Group = [High risk group HBsAg(+) pop] x [% HDV Prevalence]
  → HBsAg(+) High Risk Group = HBsAg(+) Immigrant Pop + HBsAg(+) IVDU Pop

Spain: (Navascués et al, 1995; Buti et al, 2010], Sweden: [Ji et al, 2012], France: [Renard et al, 2011], UK: [Cross et al, 2008], Germany: [Heidrich et al, 2009; Reinheimer et al, 2012; Wedemeyer et al, 2007(a)], Italy: [Gaeta et al, 2003; Piccolo et al, 2009; Mele et al, 2007]

Ankara Uni.

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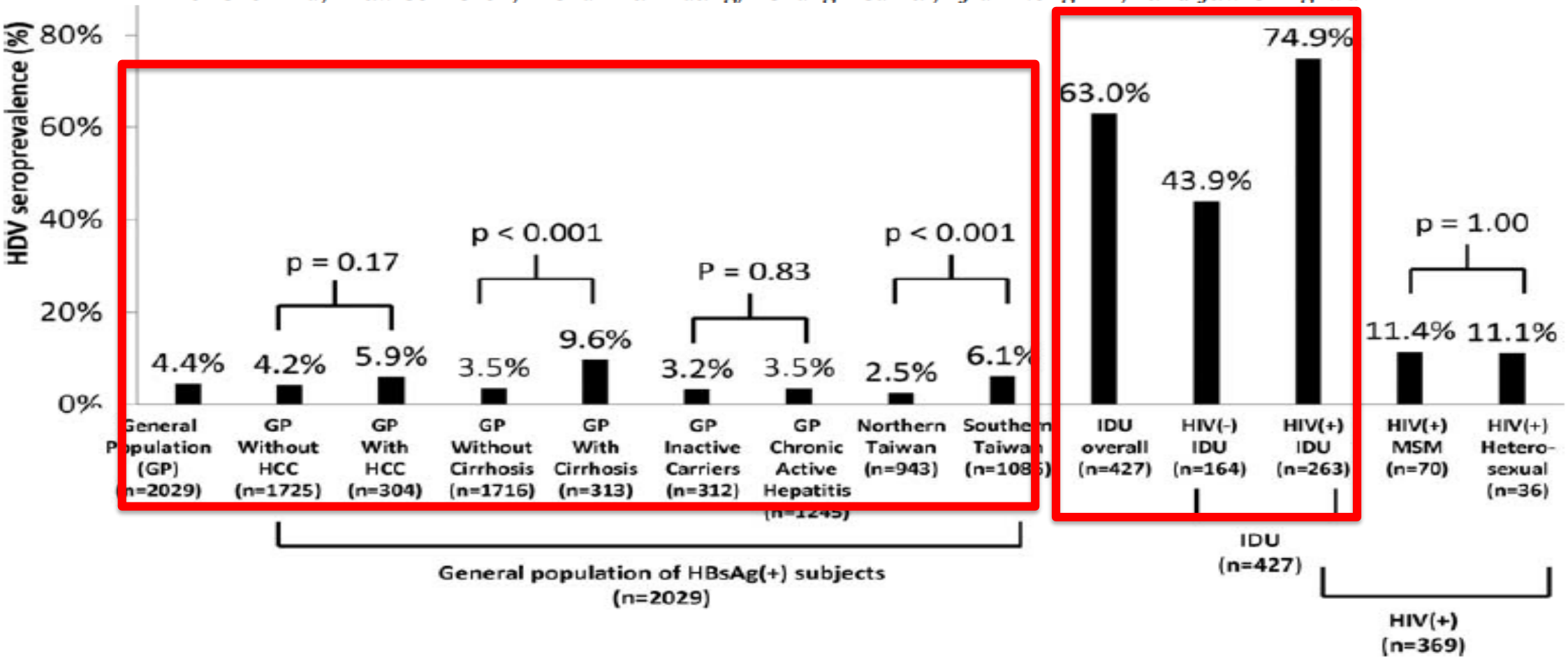
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Changing Hepatitis D Virus Epidemiology in a Hepatitis B Virus Endemic Area With a National Vaccination Program

Hsi-Hsun Lin,[1,2] Susan Shin-Jung Lee,[3,4] Ming-Lung Yu,[5*] Ting-Tsung Chang,[6,7*] Chien-Wei Su,[1,3,8] Bor-Shen Hu,[9] Yaw-Sen Chen,[10] Chun-Kai Huang,[2] Chung-Hsu Lai,[2] Jiun-Nong Lin,[2] and Jaw-Ching Wu[1,11]



Outline

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Delta Hepatitis - Diagnosis

- Anti HDV (IgG)
- Anti HDV IgM
- HDV RNA (qualitative, quantitative PCR)
- HDV Ag (immunohistochemistry)
- Quantitative HBsAg,
- HDV & HBV genotype determination

Anti HDV (or anti HDV IgG)

- First test to be used for searching for HDV
- Not a neutralizing Ab, depicts encounter with HDV
- HDV RNA testing necessary to establish active HDV infection
- Remains positive for years after successful tx including HBsAg clearance

HDV RNA

- Qualitative or quantitative
- Surrogate marker of tx efficacy
- Standardization was important
  - Now there is a WHO standard (Paul Ehrlich Institute); Labs should get it

Outline

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Treatment of Chronic Delta Hepatitis

- Evidence based successful treatment : interferon
- High dose, long treatment period (one year, or longer)
- Sustained virologic response LOW
- NAs ineffective

IFN treatment of CDH

- Interferon without effect in vitro in cell lines supporting HDV replication[1, 2]
- HDV impairs IFN-stimulated JAK-STAT signaling pathway [3]
- Interferon inhibits HDV infection at an early step of infection, at the level of hepatocyte entry [4]

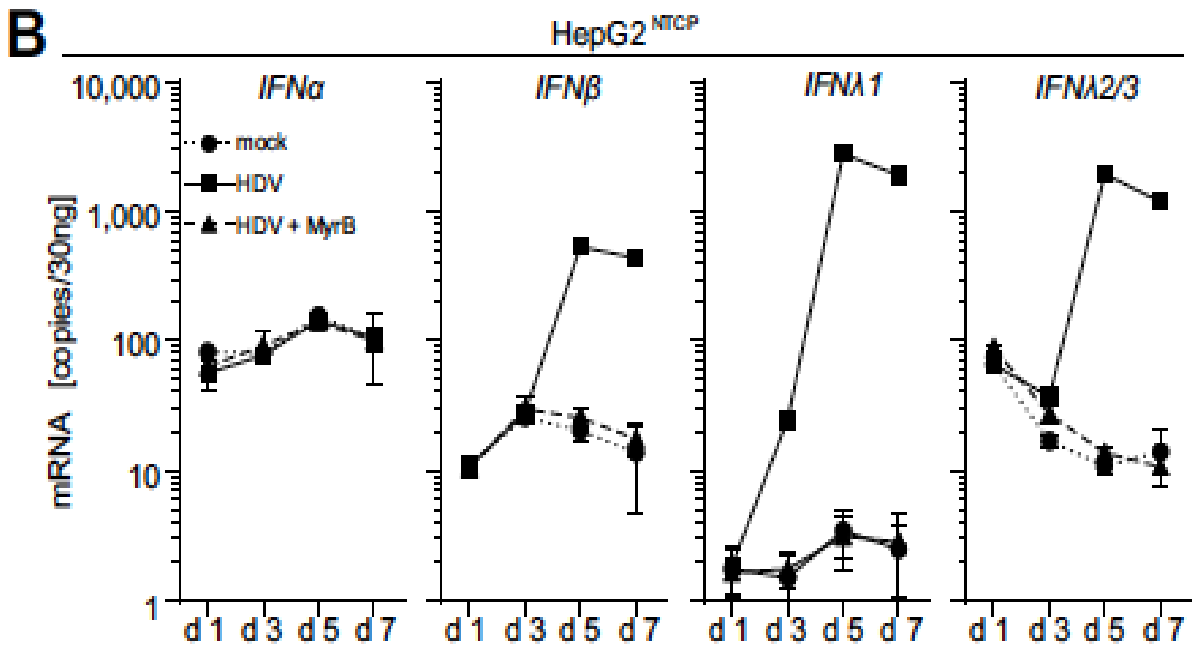
[1]Chang et al, J Virol 2006; [2]Ilan et al, JID 1992; [3]Pugnale et al, Hepatology 2009; [4]Han et al, Plos one 2011

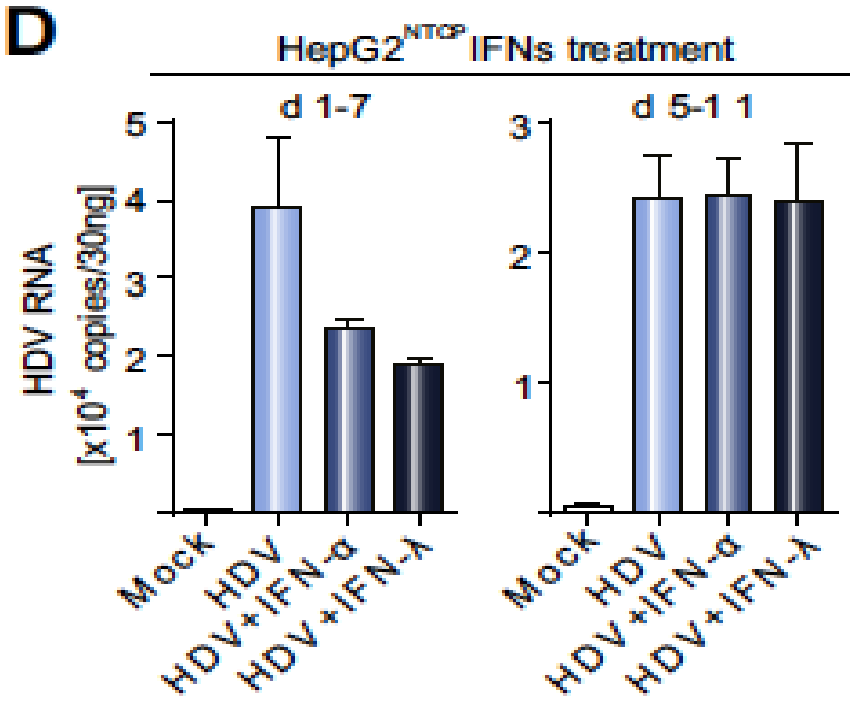
Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Hepatitis D virus replication is sensed by MDA5 and induces IFN-β/λ responses in hepatocytes

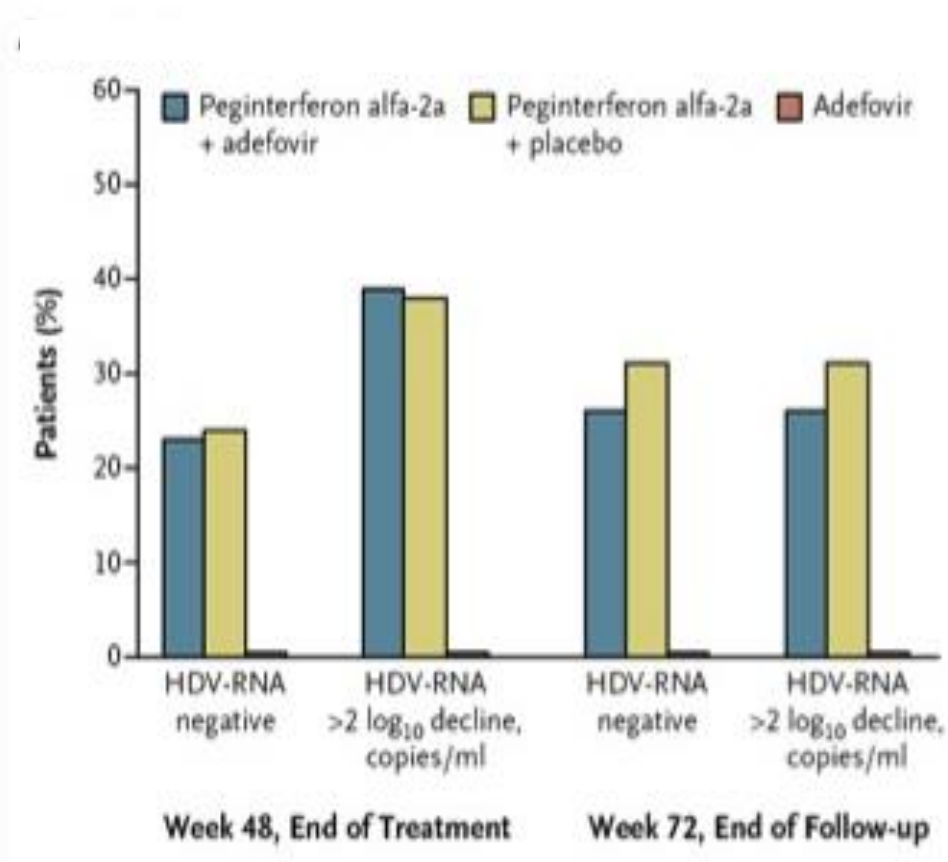
Zhenfeng Zhang[1], Christina Filzmayer[1], Yi Ni[1], Holger Sültmann[2,3,4], Pascal Mutz[1,8], Marie-Sophie Hiet[1], Florian W.R. Vondran[5,6], Ralf Bartenschlager[1,7,8], Stephan Urban[1,7,*]

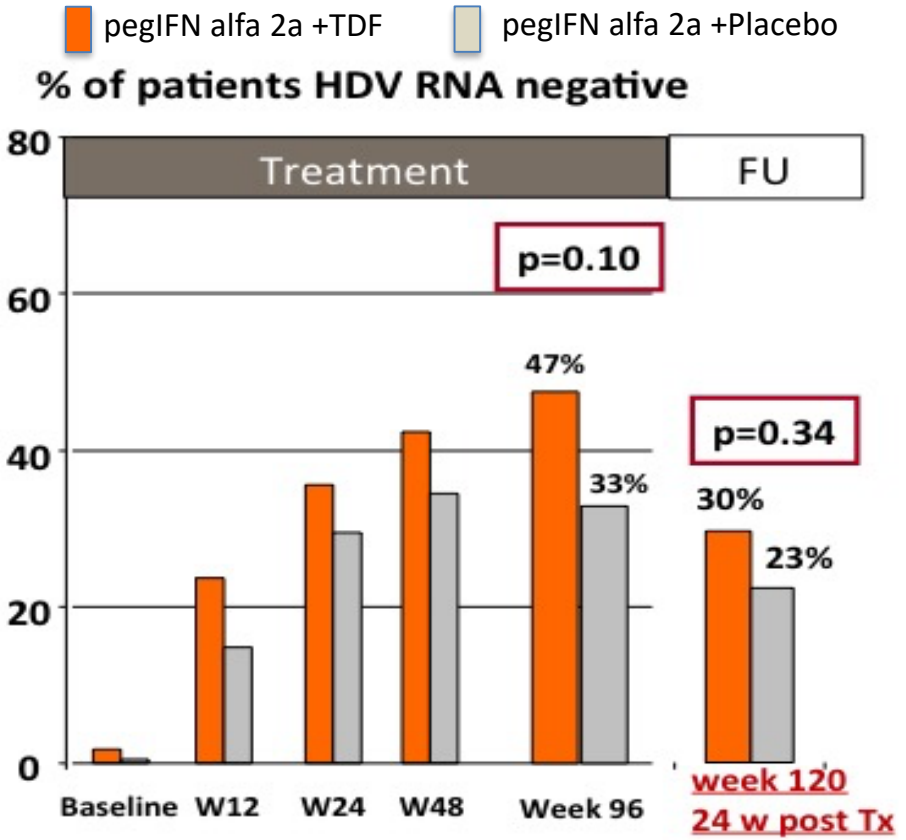




Results of Two Key Studies in CHD with pegIFN-α

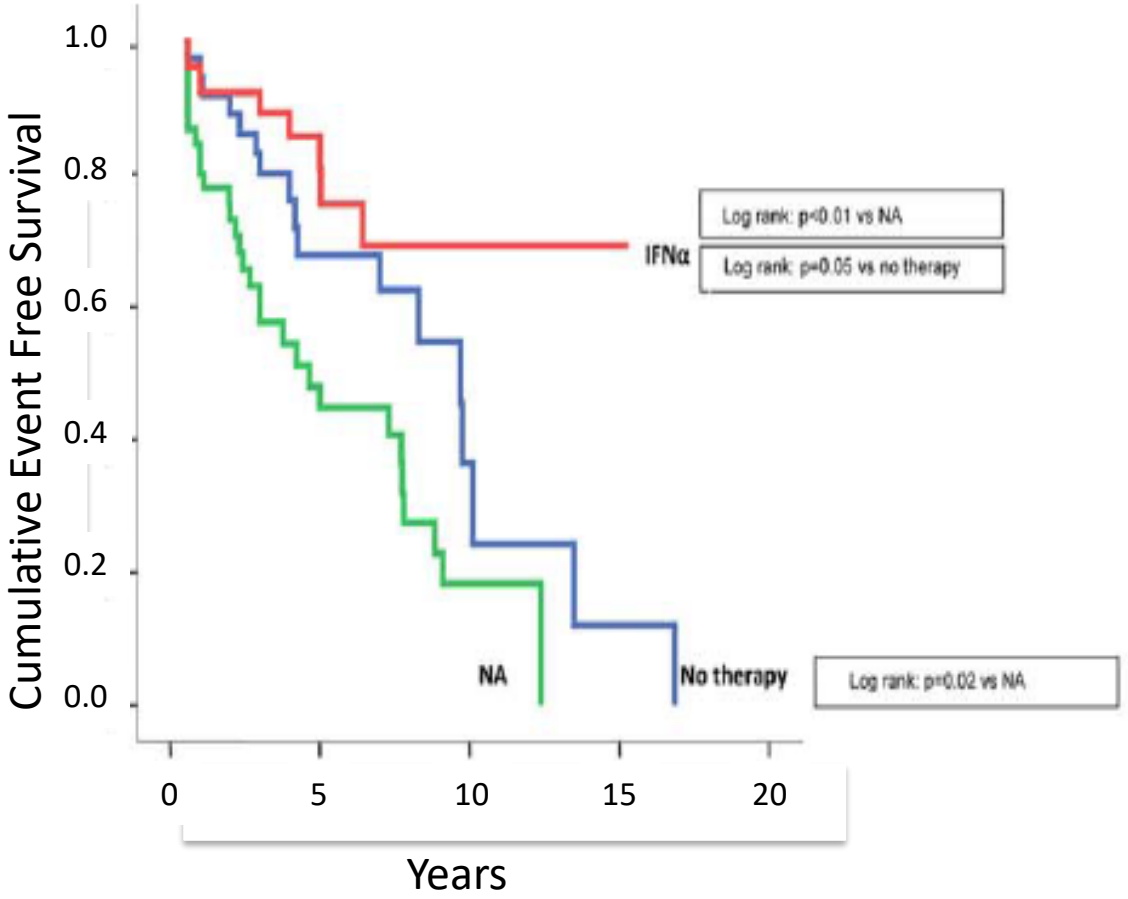
HIDIT I and HIDIT II



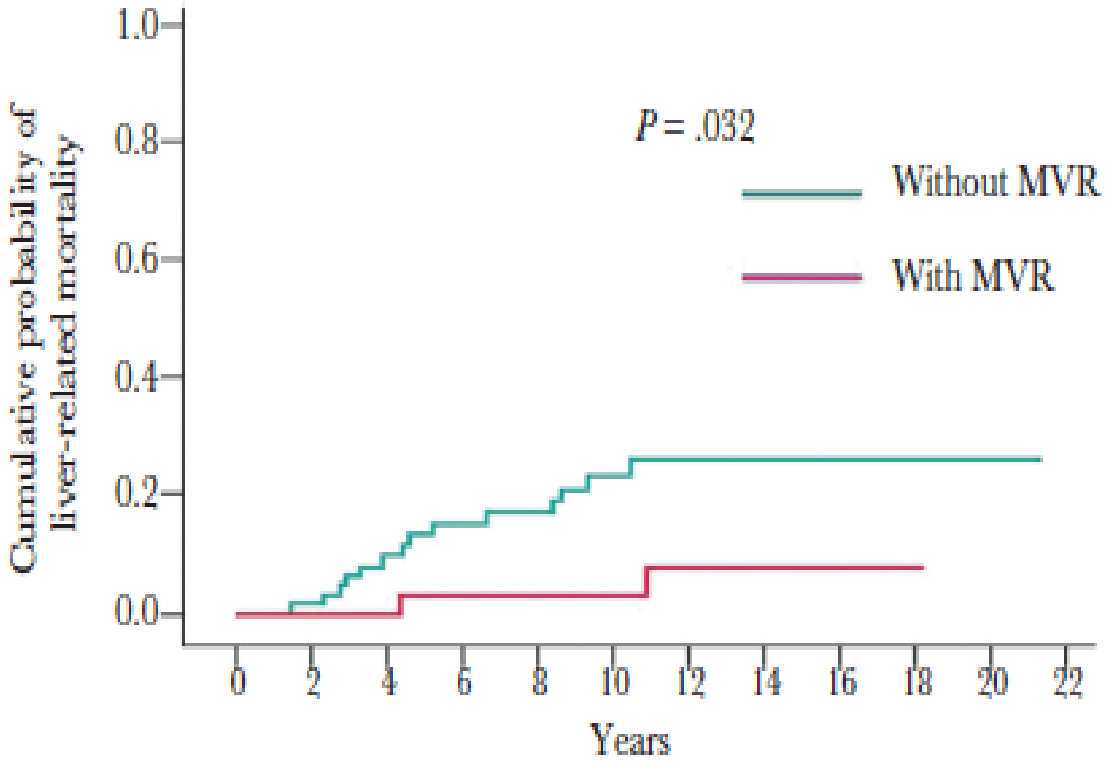


Wedemeyer, Yurdaydin et al, NEJM 2011 and Lancet Infect Dis 2019 in press

Long Term Benefit with HDV RNA Suppression



Wranke et al, Hepatology 2017



Yurdaydin et al, JID 2018

When to Start pegIFN-α Treatment?

HIDIT-1 Study

	Severe disease N= 31	Mild disease N=26	P-value
EOT HDV RNA (-)	29%	19%	0.54
EOFU HDV RNA (-)	32%	23%	0.56
Withdrawal due to AE	12%	3.6%	0.36

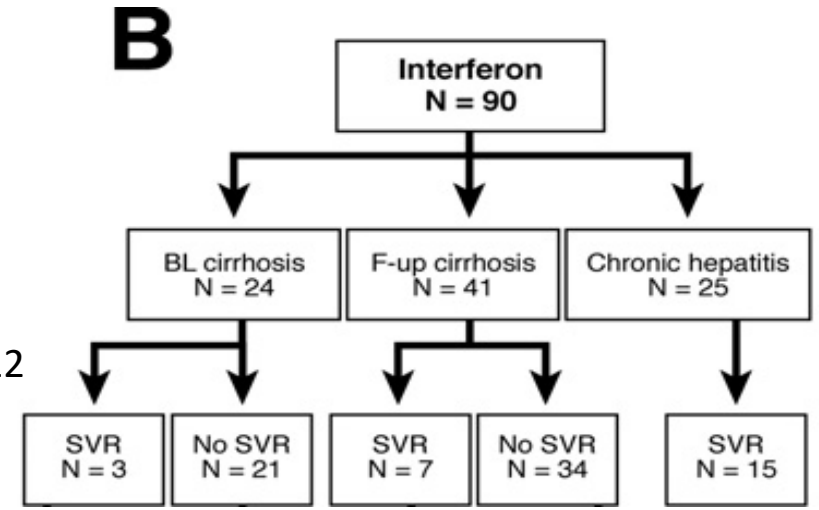
Kabacam et al, Turk J Gastroenterol 2012

HIDIT-2 Study

	Cirrhosis N= 49	No cirrhosis N=71	P-value
EOT HDV RNA (-)	45%	37%	0.288
EOFU HDV RNA (-)	37%	20%	0.041

Wedemeyer, Yurdaydin et al, Lancet Infect Dis 2019 in press

Romeo et al, Gastroenterology 2012



When to Start pegIFN-α Treatment?

	Overall (n = 99)	IFN responders (n = 35)	IFN nonresponders (n = 64)	*P* value
Age	40.0 ± 10.6	41.6 ± 9.4	39.2 ± 11.2	.28
Gender	70 M/29 F	24 M/11 F	46 M/18 F	.81
HDV RNA[a] (log_{10} IU/mL) (n = 59)	5.98 ± 1.4	6.1 ± 1.6	5.9 ± 1.3	.6
HBV DNA[a] (log_{10} IU/mL, median (range)(n = 63)	1.70 (1.0–7.62)	1.67 (1.0–4.90)	1.70 (1.0–7.62)	.34
HBeAg status	81 (–) / 15 (+)	29 (–) /4 (+)	52 (–) /11 (+)	.56
ALT (U/L)[b]	107 ± 108	97 ± 86	112 ± 119	.53
AST (U/L)[b]	76 ± 73	76 ± 76	77 ± 71	.9
ALP (U/L)[b]	115 ± 52	102 ± 52	123 ± 51	.07
GGT (U/L)[b]	83 ± 78	55 ± 53	100 ± 86	.007
PT (seconds)	13.3 ± 1.4	13.2 ± 1.4	13.3 ± 1.4	.6
Total bilirubin (mg/dL)	1.01 ± 0.5	0.89 ± 0.5	1.08 ± 0.6	.12
Platelet ($x10^9$/L)	161 ± 52	181 ± 54	150 ± 48	.004
HAI (n = 78)	10.9 ± 3.9	10.5 ± 4.7	11 ± 3.5	.56
Cirrhosis present	19/99 (19%)	5/35 (14%)	14/64 (22%)	.26
Fibrosis score (n = 78)	2.15 ± 1.4	1.97 ± 1.4	2.26 ± 1.3	.36
HBsAg (log_{10} IU/mL) (n = 49)	3.70 ± 0.66	3.40 ± 0.79	3.96 ± 0.35	.004

	Clinical event (+)	Clinical event (–)	*P* value
Age	43.5 ± 10.1	38.3 ± 10.5	.02
Gender	22 M/10 F	48 M/19 F	.81
HBeAg status	28 (–)/4 (+)	53 (–)/11 (+)	.67
ALT (U/L)	99.6 ± 69.5	111.1 ± 124	.56
AST (U/L)	78.5 ± 47.0	75.9 ± 83	.84
GGT (U/L)	107.7 ± 68.8	71.9 ± 81	.03
ALP (U/L)	119.0 ± 43.7	114.0 ± 56.2	.65
PT (seconds)	13.6 ± 1.5	13.1 ± 1.3	.19
Bilirubin (mg/dL)	1.11 ± 0.63	0.96 ± 0.53	.23
Platelet count ($x10^9$/L)	134 ± 41	174 ± 52	<.001
HAI (n = 78)	12.5 ± 3.3	10.2 ± 4.0	0.02
Fibrosis score (n = 78)	2.68 ± 1.35	1.95 ± 1.3	.04
HDV RNA (log_{10} IU/mL) (n = 59)	6.26 ± 1.4 (n = 18)	5.85 ± 1.4 (n = 41)	.31
HBV DNA (log_{10} IU/mL) (n = 63)	2.57 ± 1.5	2.0 ± 1.3	.2
Cirrhosis present	15/32	4 / 67	<.001
IFN response present	5/32	30/67	.006
HBsAg (log_{10} IU/mL) (n = 49)	9239 ± 6757	9252 ± 7965	.9

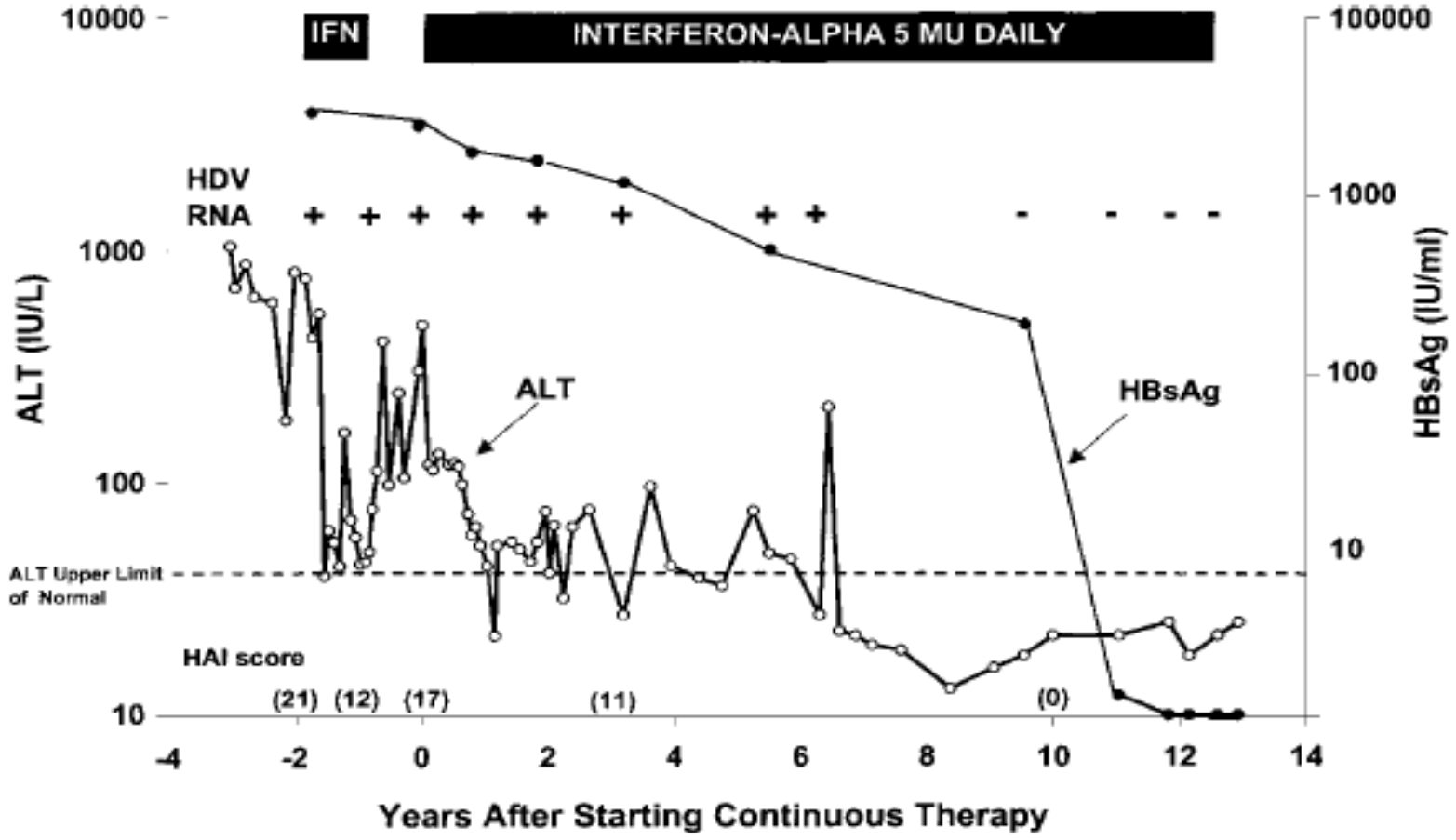
Yurdaydin et al, J Infect Dis 2018

Optimal Dose/Duration of Treatment with pegIFN-a in HDV

- Optimal dose:
  - 9 or 10 MU for conventional IFN[1,2]
  - 180 μg/qw for pegIFN-α
- Optimal duration: 1 year?
- 2 years of IFN no better than 1 year[3-6]
- 12-24 months better than ≤ 12 months[7]
- Some patients may benefit from prolonged treatment[8]
- Case report[9]

[1,2] Farci et al, NEJM 1994 and Gastroenterolopgy 2004; [3] Di Marco et al, JVH 1996;
[4] Gunsar et al, AVT 2005; [5] Yurdaydin et al, JVH 2007; [6] Wedemeyer, Yurdaydin submitted;
[7] Soyer et al, Postgrad Med 2016; [8] Heller et al, APT 2014; [9] Lau et al, Gastro 1999

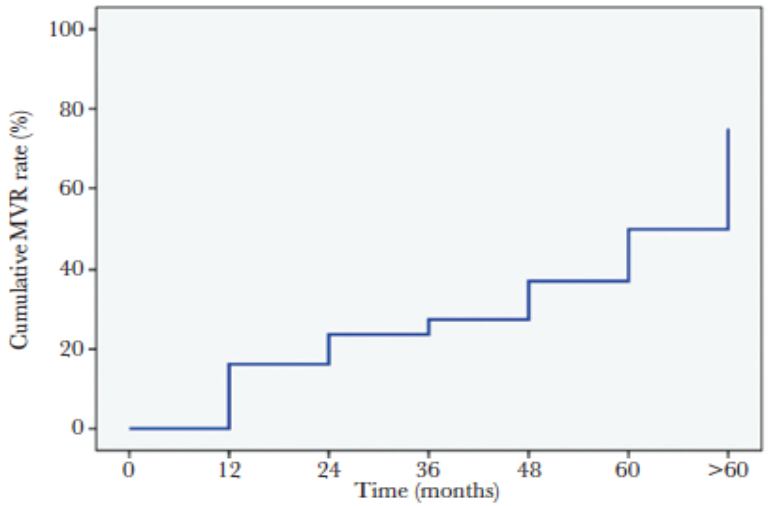
What is the Optimal Dose and Duration of Treatment with pegIFN-α in HDV?



Lau et al, Gastroenterology 1999

What is the Optimal Dose and Duration of Treatment with pegIFN-α in HDV?

n:99	n: 67	n: 41	n: 30	n: 15	n: 8
16 MVR (-) 16 MVR (+)	20 MVR (-) 6 MVR (+)	9 MVR (-) 2 MVR (+)	11 MVR (-) 4 MVR (+)	4 MVR (-) 3 MVR (+)	4 MVR (-) 4 MVR (+)



Yurdaydin et al, JID 2018

Interleukin 28B Polymorphism and response to IFN tx in CHD

Effects of Polymorphisms in *Interferon λ 3* (*Interleukin 28B*) on Sustained Virologic Response to Therapy in Patients With Chronic Hepatitis D Virus Infection

Emre Yilmaz, et L, CGH 2014

No impact of interleukin-28B polymorphisms on spontaneous or drug-induced hepatitis delta virus clearance☆

Ubaldo Visco-Comandini et al, Dig Live Dos 2014

HDV RNA and HBsAg Kinetics in HDV during pegIFN Tx

How can we follow response to treatment?

What is the role of viral kinetics (HDV RNA, quantitative HBsAg) (if any) during IFN-based therapy of hepatitis Delta?

Are there any factors predicting response or lack thereof?

Predictors of Viral Response

Subanalysis of HIDIT-I Study

	Virologic response	No virologic response	*P* value
Age (n = 41)	42 ± 8	42 ± 12	.93
Sex (n = 41)			.36
Male, %	37.5	62.5	
Female, %	47.1	52.9	
HDV RNA level, *log*$_{10}$ *copy/mL* (n = 32)	5.09 ± 1.17	5.98 ± 1.08	.03
Week 24 HDV RNA level, *log*$_{10}$ *copy/mL* (n = 35)	2.43 ± 2.03	5.01 ± 1.31	.00
HBsAg level, *IU/mL* (n = 39)	3.56 ± 0.79	3.96 ± 0.49	.06
Week 24 HBsAg level, *IU/mL* (n = 39)	3.32 ± 0.91	3.93 ± 0.66	.02
Week 48 HBsAg level, *IU/mL* (n = 37)	3.07 ± 1.27	3.80 ± 0.75	.04
ALT level, *U/L* (n = 40)	95 ± 48	85 ± 56	.53
HBeAg positive, %	33.3	66.7	1.00
HBeAg negative, %	44.1	55.9	
Week 24 ALT level, *U/L* (n = 39)	74 ± 53	98 ± 69	.23
HAI (n = 34)	7.4 ± 1.98	6.6 ± 2.23	.32
Fibrosis grade (n = 35)	3.3 ± 1.14	3.5 ± 1.60	.63
WBC, $\times 10^9$*/L* (n = 39)	6.12 ± 2.20	5.63 ± 1.90	.40
Platelets, $\times 10^9$*/L* (n = 39)	173 ± 54	166 ± 42	.29
AST level, *U/L* (n = 39)	64 ± 32	59 ± 30	.61
GGT level, *U/L* (n = 36)	56 ± 29	62 ± 68	.74
ALP level, *U/L* (n = 39)	138 ± 55	120 ± 96	.51
Albumin level, *g/dL* (n = 35)	4.12 ± 0.35	4.04 ± 0.42	.53
Previous IFN therapy	47.8	52.2	.51

Post-treatment week 24 response:

	OR	95% CI	p value
HDV RNA week 24	2.538	1.347 – 4.782	0.004

End of treatment response:

	OR	95% CI	p value
HDV RNA week 24	1.627	1.070 – 2.474	0.023
Baseline HAI	0.586	0.366 – 0.937	0.026

Earlier time points (week 4, 8, 12) perform less well compared to on-tx week 24

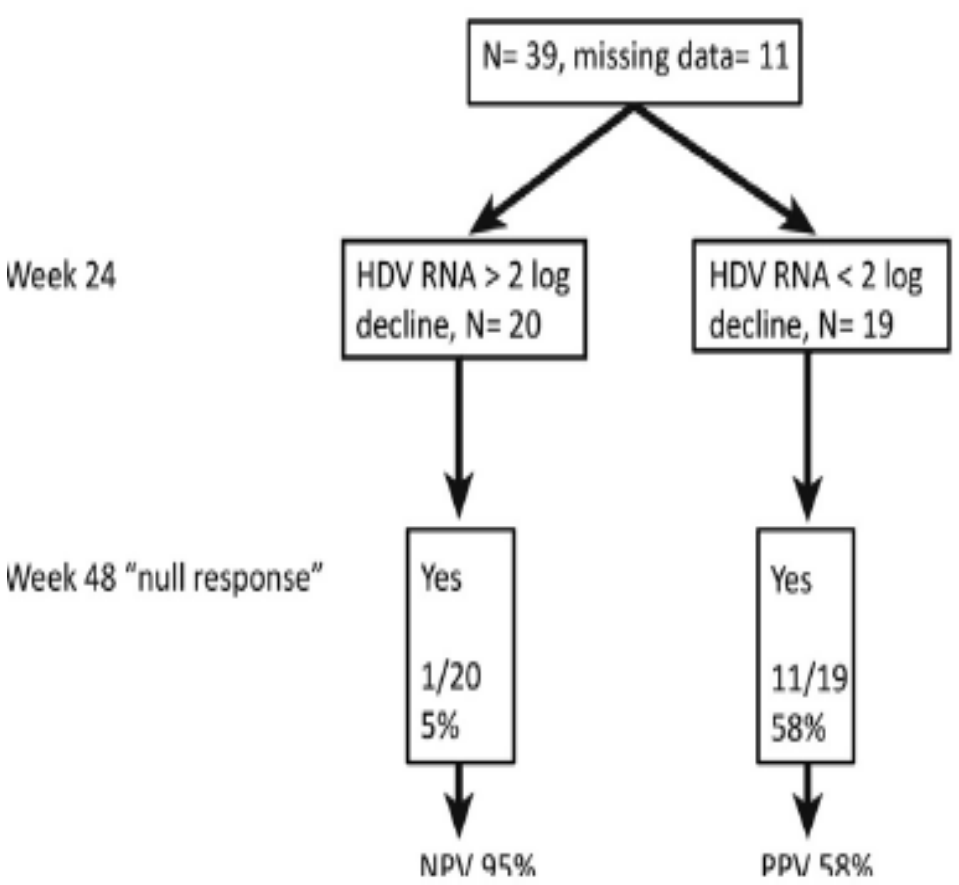
HIDIT-2 subanalysis; Wobse et al, AASLD 2014

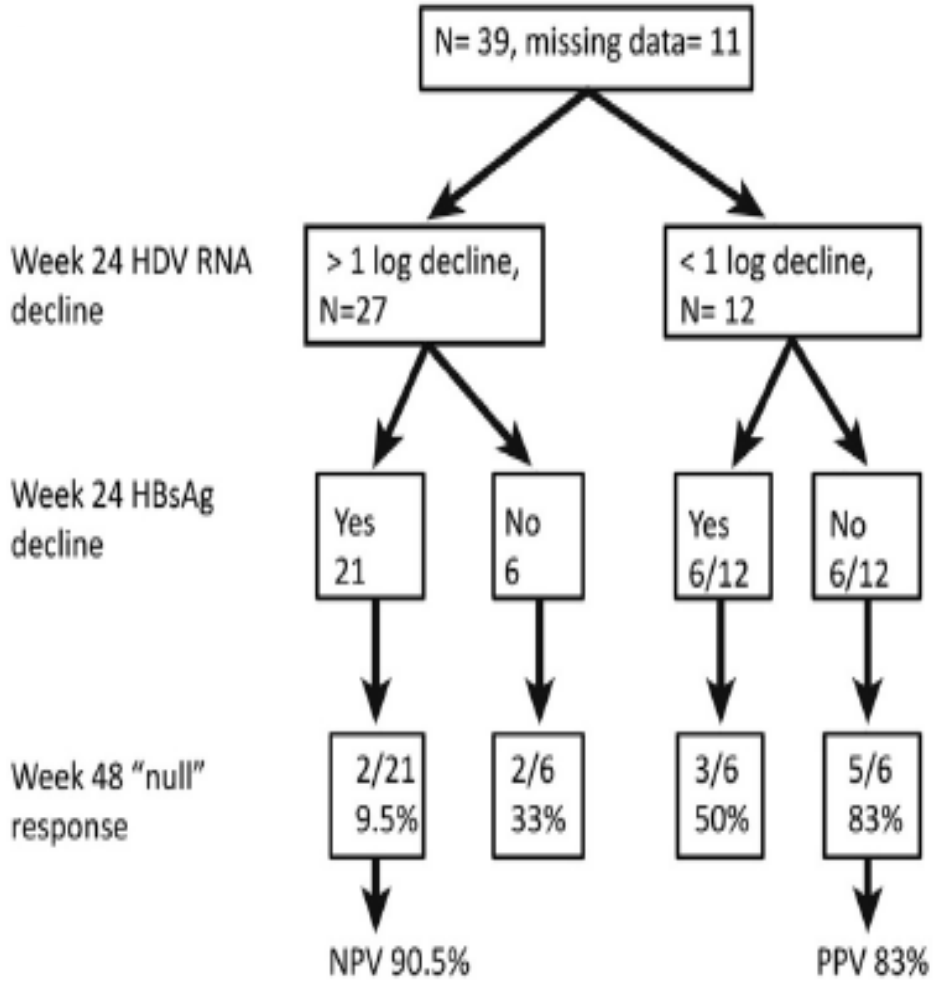
Keskin O, et al, Clin Gastroenterol Hepatol 2015

Predictors of Non-Responders (NR) to pegIFN-α

- EOT viral responders who relapse should not be considered NRs to pegIFN, in particular when pegIFN is the only available tx
- Patients without viral response (VR) at EOT should not be categorized as NRs to IFN.
  - HIDIT-1/2 Studies: half of patients with post-tx Week 24 response did not have VR at EOT
- <1 log decline after one year of pegIFN tx
  - Arbitrary definition of NR

Predictors of Null-Responders to pegIFN-α



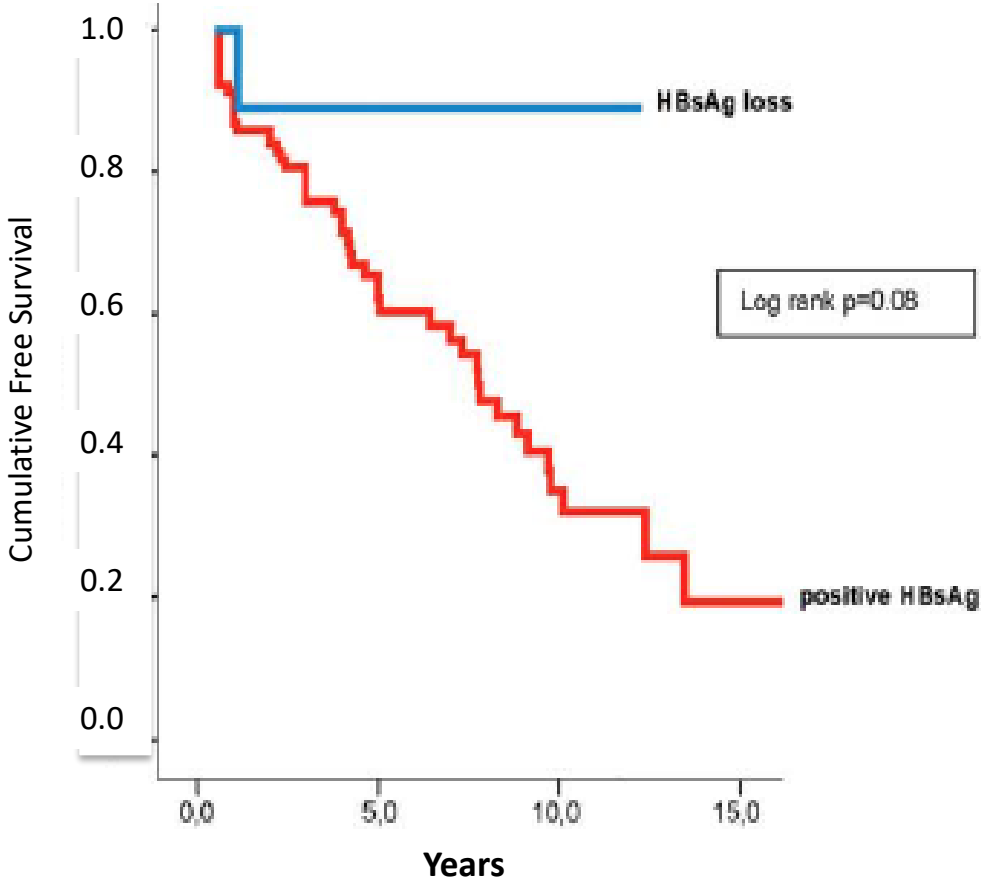


Keskin et al, CGH 2015

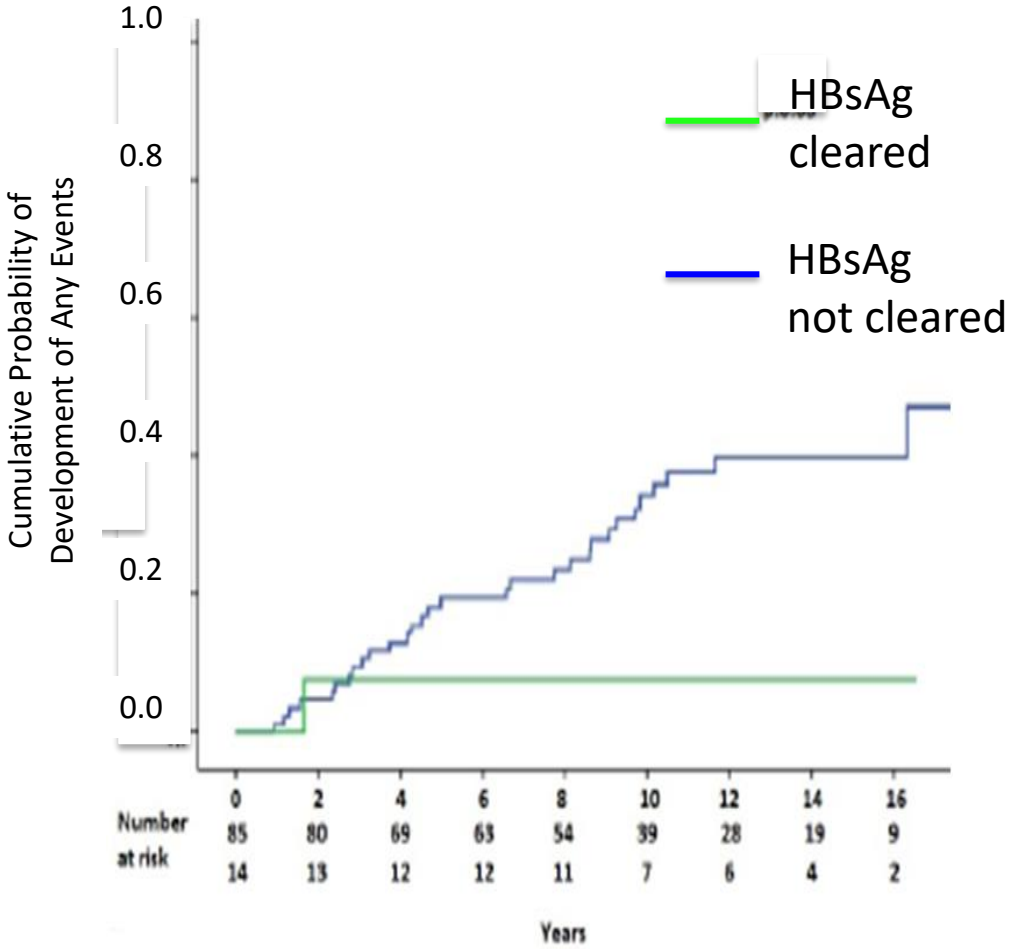
Endpoints in HDV Treatment

- Optimal endpoint: HBsAg (-), HBsAb (+)
  - Very good and very rare
- “Good” endpoints:
  - Post-Tx Week 24 undetectable HDV RNA
  - EOT undetectable HDV RNA
- Acceptable endpoint:
  - EOT $\geq$ 2 log decline ± normal ALT

HBsAg Clearance Improves Survival and Development of Liver Related Events

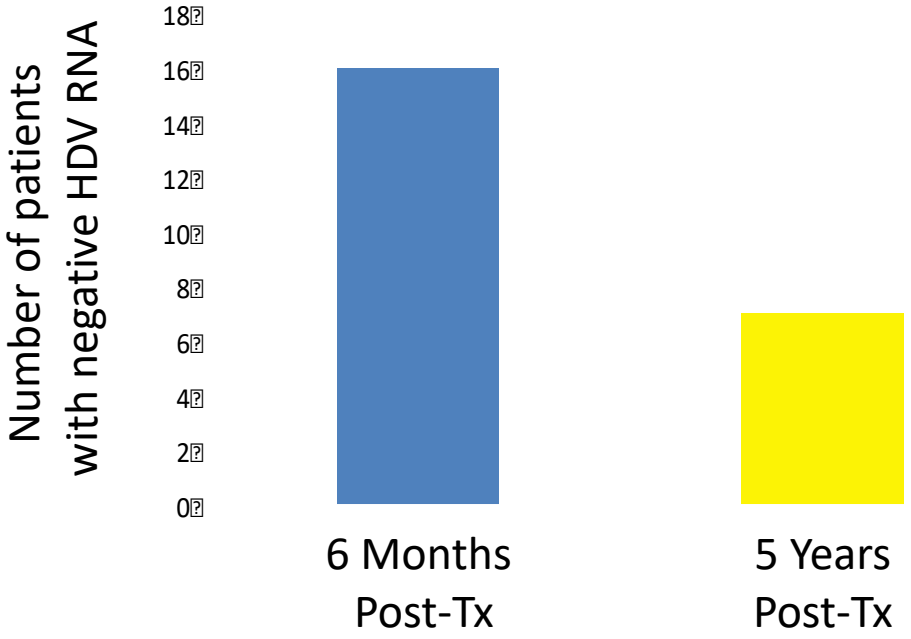


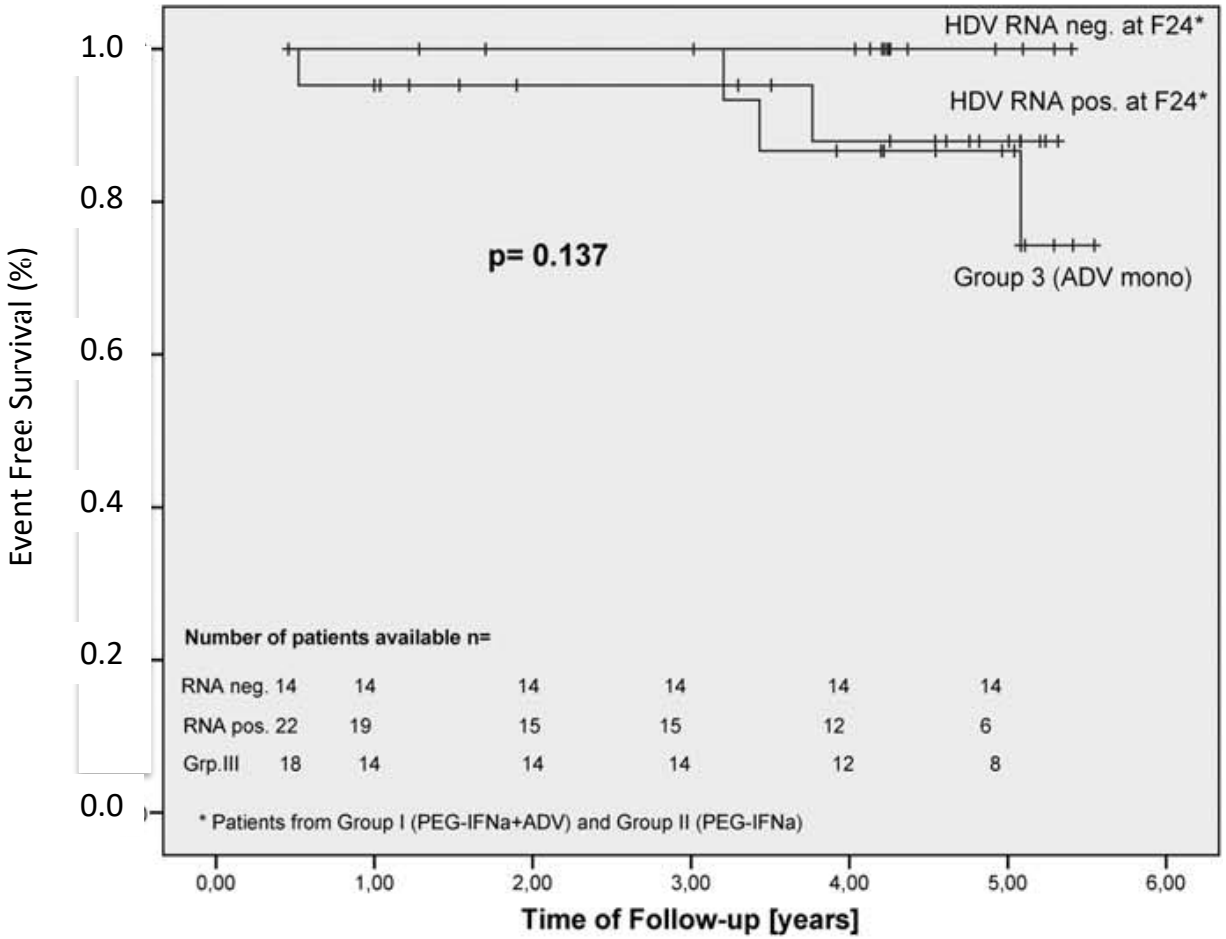
Wranke et al, Hepatology 2017



Yurdaydin et al, JID 2018

Post-Tx Week 24 HDV RNA Negative: Long Term Outcome





Heidrich et al, Hepatology 2014

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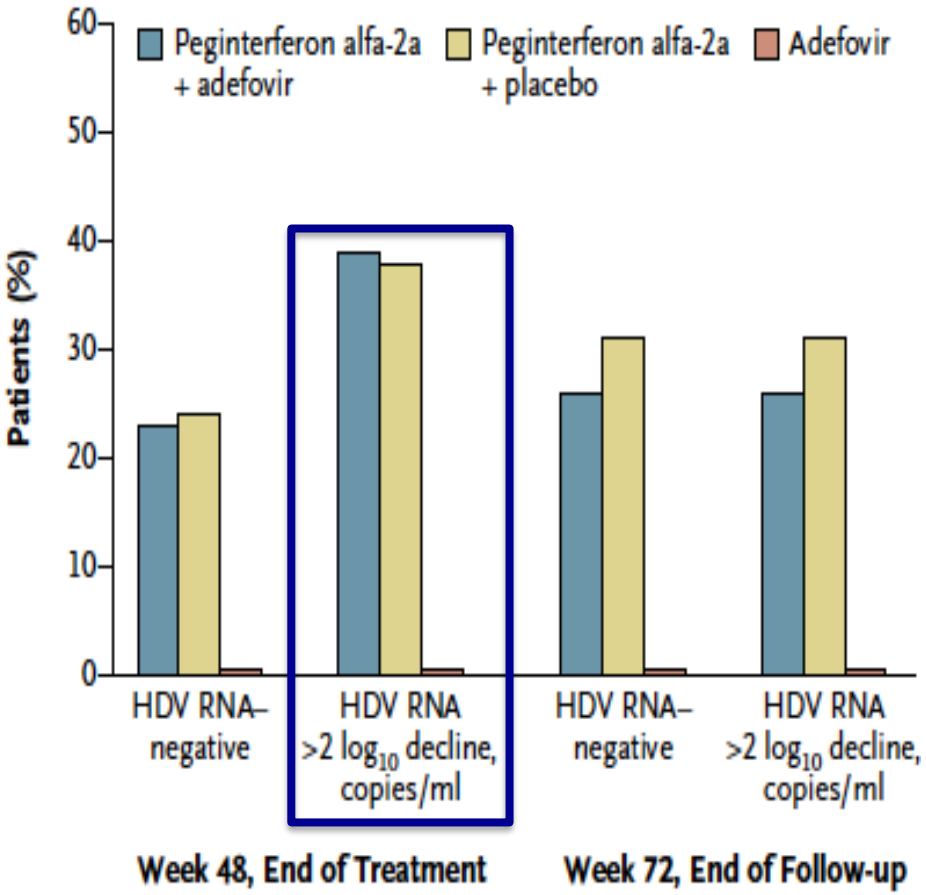
EOT (12-18 Months) HDV RNA Outcome Correlate Well with EOFU Viral Responses

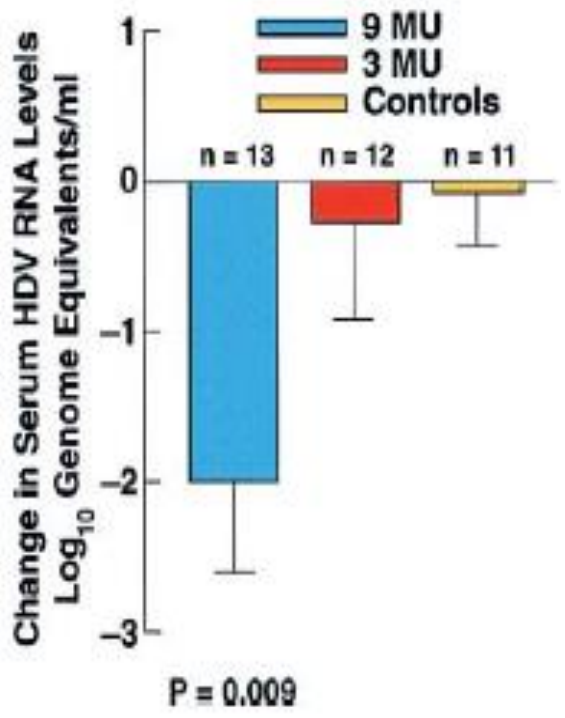
References	Treatment schedule	*N*	EOT VR	EOFU VR
Niro et al. 2006	Peg-IFNα-2b, 1.5 μg/kg, qw × 18 mo	16	19%	25%
	Peg-IFNα-2b, 1.5 μg/kg, qw × 18 mo + Ribavirin, 1-1.2g, qd × 12 mo	22	9%	18%
Castelnau et al. 2006	Peg-IFNα-2b, 1.5 μg/kg, qw × 12 mo	14	57%	43%[a]
Erhardt et al. 2006	Peg-IFNα-2b, 1.5 μg/kg, qw × 12 mo	12	17%	17%
Wedemeyer et al. 2011	Peg-IFNα-2a, 180 μg, qw × 12 mo	29	24%	26%
	Peg-IFNα-2b, 180 μg, qw × 12 mo + Adefovir, 10 mg, qd	31	23%	31%
Gheorge et al. 2011	Peg-IFNα-2b, 1.5 μg/kg, qw × 12 mo	48	33%	25%
Örmeci et al. 2011	Peg-IFNα-2b, 1.5 μg/kg, qw × 24 mo	9	56%	44%
	Peg-IFNα-2b, 1.5 μg/kg, qw × 12 mo	7	57%	100%
Abbas et al. 2014	Peg-IFNα-2a, 180 μg, qw × 12 mo	104	42%	23%
Karaca et al. 2013	Peg-IFNα-2a, 180 μg, or Peg-IFNα 2b, 1.5 ug/kg, qw × 24 mo	32	50%	47%[b]
Wedemeyer et al. 2014	Peg-IFNα-2a, 180 μg, qw × 24 mo	61	33%	21%
	Peg-IFNα-2a, 180 μg, qw × 24 mo + Tenofovir, 300 mg, qd	59	48%	29%

EOT HDV RNA ≥ 2 Log Decline May be Important



Wedemeyer, Yurdaydin et al, NEJM 2011

Of 17 pts with post-tx week 24 HDV RNA negativity,
9 were HDV RNA positive at EOT



Farci et al, Gastro 2004

The White Paper
Aim: Reasonable surrogate suggestion for treatments to come in HDV

Surrogate of initial treatment efficacy

- End of treatment ≥ 2 log decline compared to baseline recommended as surrogate for initial treatment efficacy
- Associated with ALT normalization

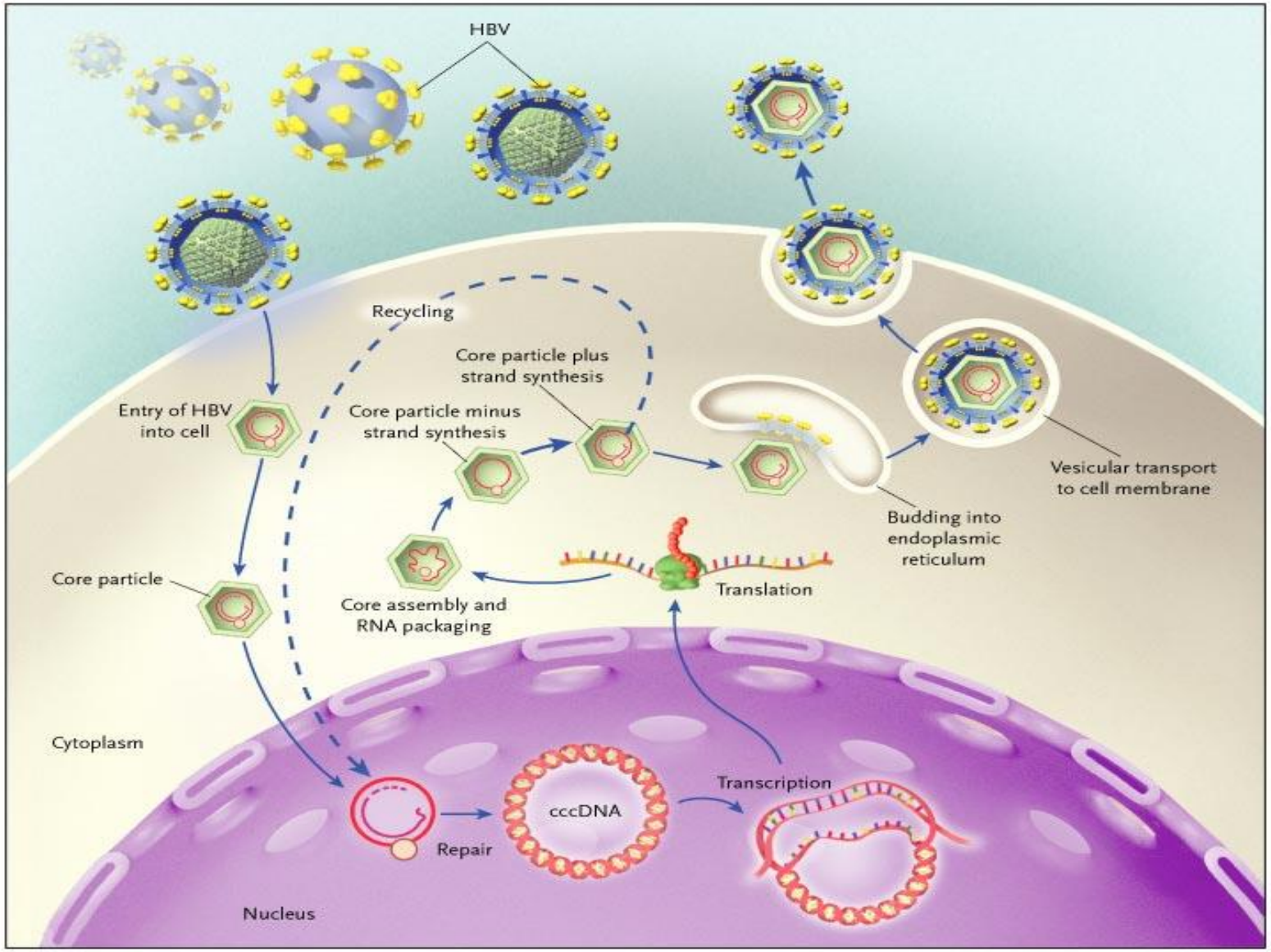
Nucleos(t)ides in HDV

LAMIVUDINE
FAMCICLOVIR
ADEFOVIR DIPIVOXIL
ENTECAVIR
CLEVUDINE

Tx duration: 6-18 months
No effect

TENOFOVIR — Median Tx duration: 6.1 YIL
Some efficacy

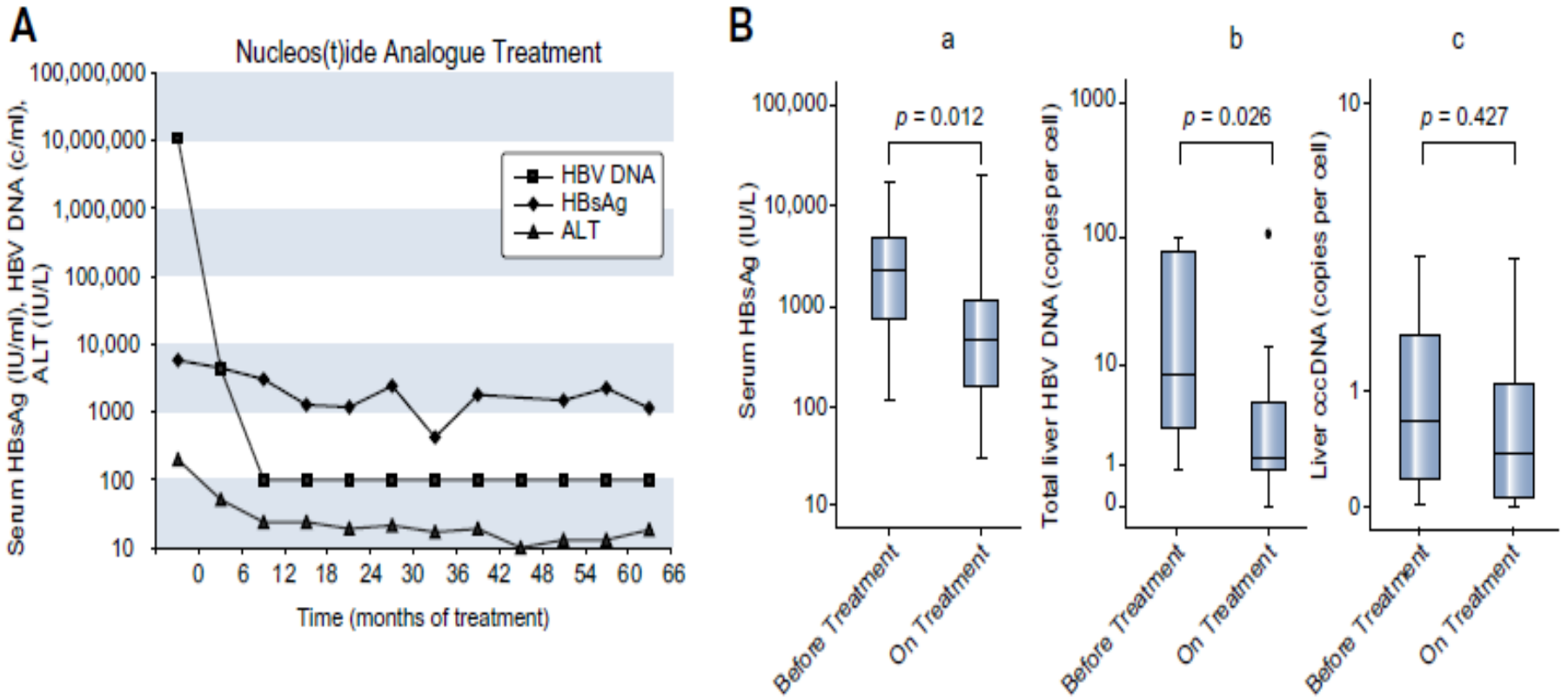
Lau et al, Hepatology 1999; Yurdaydin et al, J Hepatol 2002; Niro et al, APT 2006; Yurdaydin et al J Viral Hepat 2008; Wedemeyer et al, NEJM 2011; Kabacam et al CID 2012; Sheldon et al Antiviral Ther 2008



Ganem & Prince, NEJM 2004

Long-Term Treatment with NAs

Effect on cccDNA and HBsAg



Manesis et al, J Hepatol 2011

Effect of the Immune Status on HBsAg Levels in Patients with HIV-HBV Co-Infection

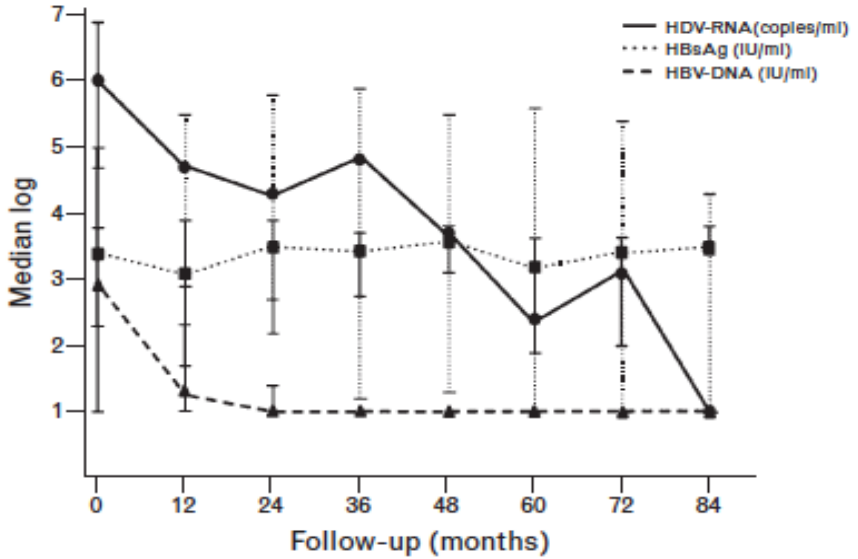
	All (n=51)	*HBsAg decrease[a] (n=25)*	*No HBsAg decrease (n=16)*	p *Value[b]*
Age, years	49.0±1.40	49.4±1.88	48.3±3.09	0.74
HBsAg, $\log_{10}$ IU/mL	3.57±0.17	3.49±0.20	3.87±0.17	0.34
Follow-up, months	43.3±3.84	44.1±5.70	43.5±6.30	0.76
HIV-RNA, copies/mL	2.55±0.18	2.67±0.27	2.25±0.27	0.58
Baseline CD4 count (cells/μL)	326±31	401±42	265±50	0.03
Baseline CD8 count (cells/μL)	1097±84	1130±106	1046±187	0.44
Last follow-up CD4 count (cells/μL)	411±32	506±39	310±51	0.01
Last follow-up CD8 count (cells/μL)	972±77	920±89	992±170	0.66
ART, n (%)	43 (84)	25 (100)	16 (100)	-
TDF, n (%)	36	22 (88)	12 (75)	0.28
AIDS, n (%)	19 (37)	9 (36)	6 (37)	0.92
HBeAg-positive, n (%)	17 (33)	8 (32)	6 (37)	0.90
HBV-DNA $\log_{10}$ IU/mL	3.64±0.60	4.08±0.92	4.44±1.13	0.86
ALT U/mL	58±10	63±13	46±11	0.26

Arendt et al, Viral Immunol 2012

Tenofovir for Extended Duration in HIV-HDV: Efficacy Data

Parameters	Baseline	End of follow-up	P value
CD4⁺T cell count, cells/mL	360 (160-471)	362 (263-761)	0.753
Plasma HIV RNA, log_{10} copies/mL	1.7 (1.7-4.3)	1.7 (1.7-2.9)	0.735
Serum HDV RNA, log_{10} copies/mL	7 (6.2-7.8)	5.8 (2-6.3)	0.011
Serum HBsAg, IU/mL	6899 (1793- 20086)	4428 (406- 6885)	0.424
Serum ALT, IU/mL	98 (67-147)	64 (33-111)	0.03

Sheldon et al, AVT 2008



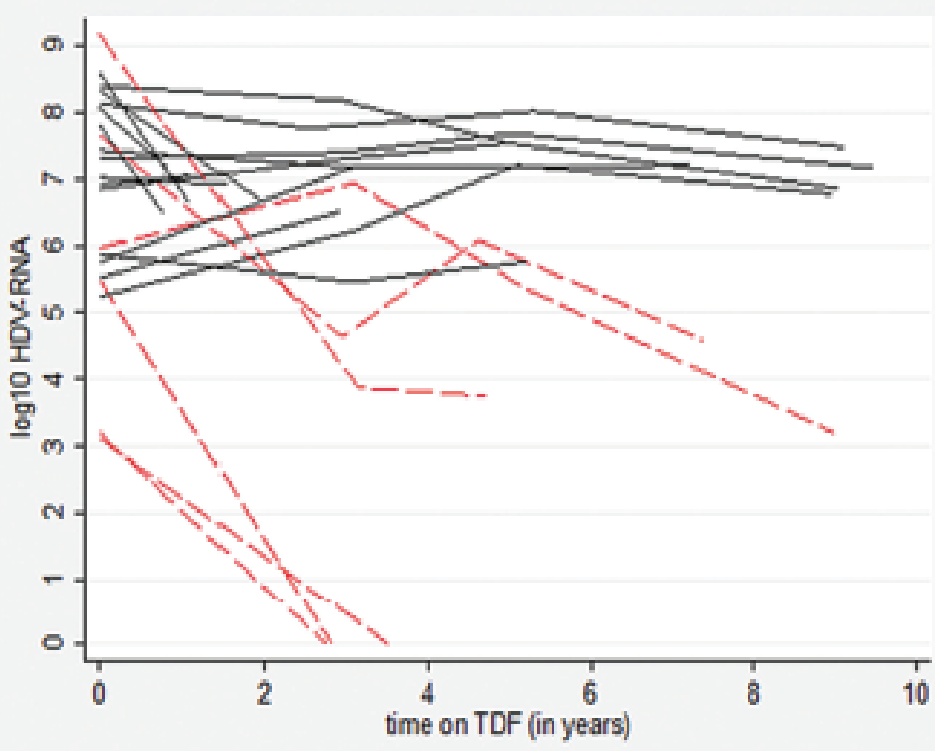
Median tx duration 58 months
10/19 are HDV RNA negative at EOFU
Medain delta decline in HDV RNA: 2.4 log

Soriano et al, AIDS 2014

Tenofovir for Extended Duration in HIV-HDV: Efficacy Data

Median tx duration 32 months
0/13 are HDV RNA negative at EOFU
Median delta decline in HDV RNA: 0.38 log/yr

Boyd et al, AIDS Res Hum Retroviruses 2013



Median tx duration 59 months
6/21 have a > 2log decline in HDV RNA
3/21 are HDV RNA negative at EOFU
Median delta decline in HDV RNA: 0.3 log

The 3 pts who lost HDV RNA had lower baseline HDV RNA and HBsAg (p=0.02 and, p=0.03)

Begueilin et al, CID 2017

Entecavir Tx for HDV for One Year

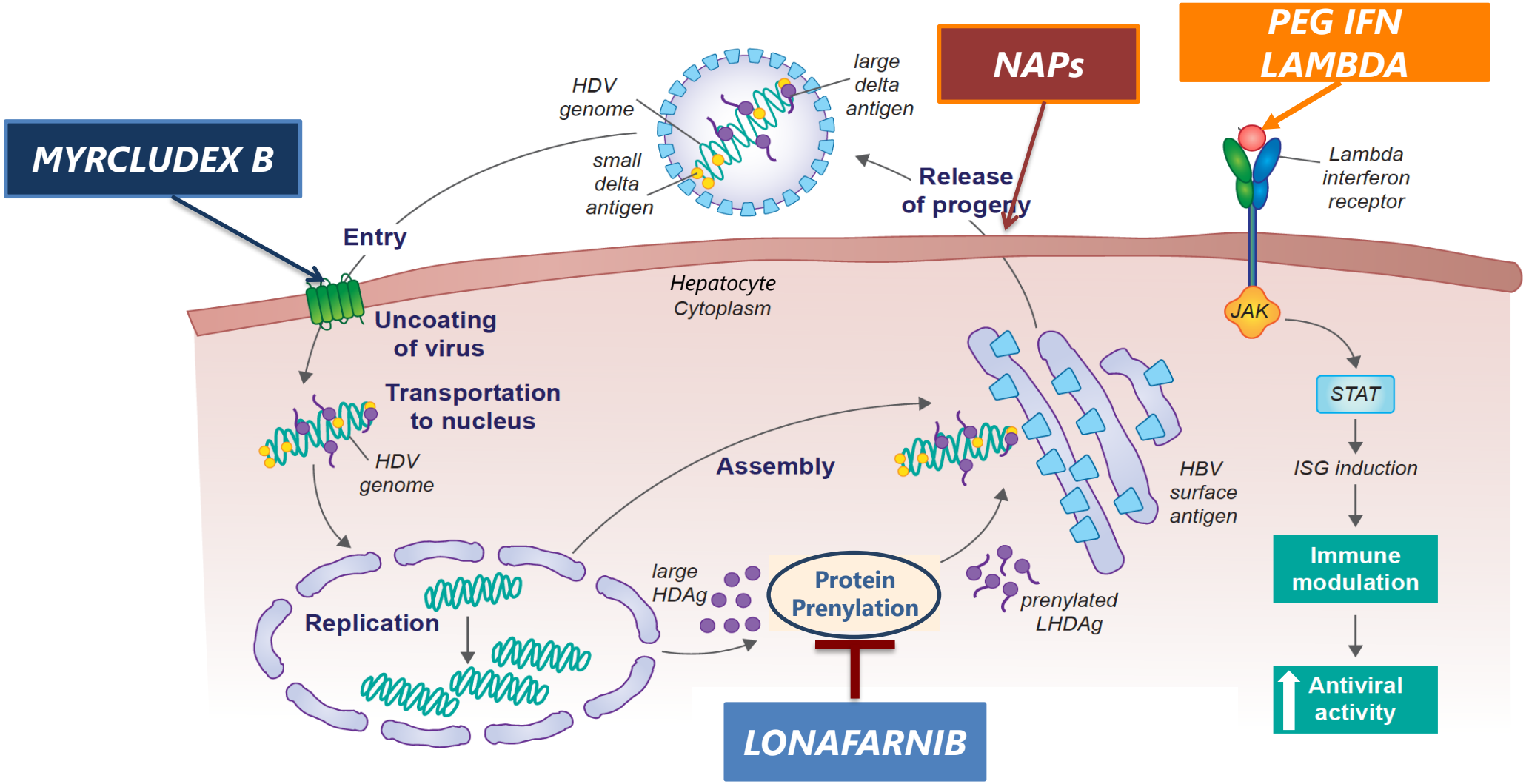
			ALT (IU/L)		HDV RNA, $\log_{10}$ Copies/mL		HBV DNA, $\log_{10}$ IU/mL		HBsAg		Fibrosis Grade[a]		HAI[a]	
Patient	HBeAg	HBeAb	BL	EOT	BL	EOT	BL	EOT	BL	EOT	BL	EOT	BL	EOT
1	Positive	Negative	79	51	5.1	5.24	4.23	UD	4.16	4.13	1	3	7	9
2	Negative	Positive	63	68	4.16	4.53	3.12	UD	4.29	4.26	0	4	10	16
3	Negative	Positive	61	66	4.16	4.63	UD	UD	4.11	4.27	4	4	9	9
4	Negative	Positive	94	103	3.82	4.16	UD	UD	3.37	4.29	5	5	10	12
5	Positive	Negative	54	39	5.49	5.33	4.79	UD	3.6	4.6	3	3	6	10
6	Positive	Negative	197	128	4.63	4.56	6.32	UD	2.17	2.18	3	NA	10	NA
7	Negative	Positive	69	42	5.72	5.53	UD	UD	4.18	4.14	1	3	6	10
8	Negative	Positive	250	54	2.85	2.98	4.84	UD	3.3	4.23	3	4	10	11
9	Negative	Positive	105	98	6.09	5.32	UD	UD	4.23	4.4	3	4	11	14
10	Positive	Positive	44	85	4.82	5.4	4.2	UD	3.55	4.26	4	3	11	10
11	Negative	Positive	32	23	2.23	UD	3.38	UD	2.05	1.95	NA	NA	NA	NA
12	Negative	Positive	400	23	3.62	UD	4.79	UD	NA	NA	NA	NA	NA	NA
13	Negative	Positive	201	18	3.12	UD	4.18	UD	NA	3.14	5	NA	11	NA

The 3 pts who lost HDV RNA had lower baseline HDV RNA (2.7 ± 1.3 vs. 4.6±1.2 p=0.028)

Kabaçam et al, CID 2012

Outline

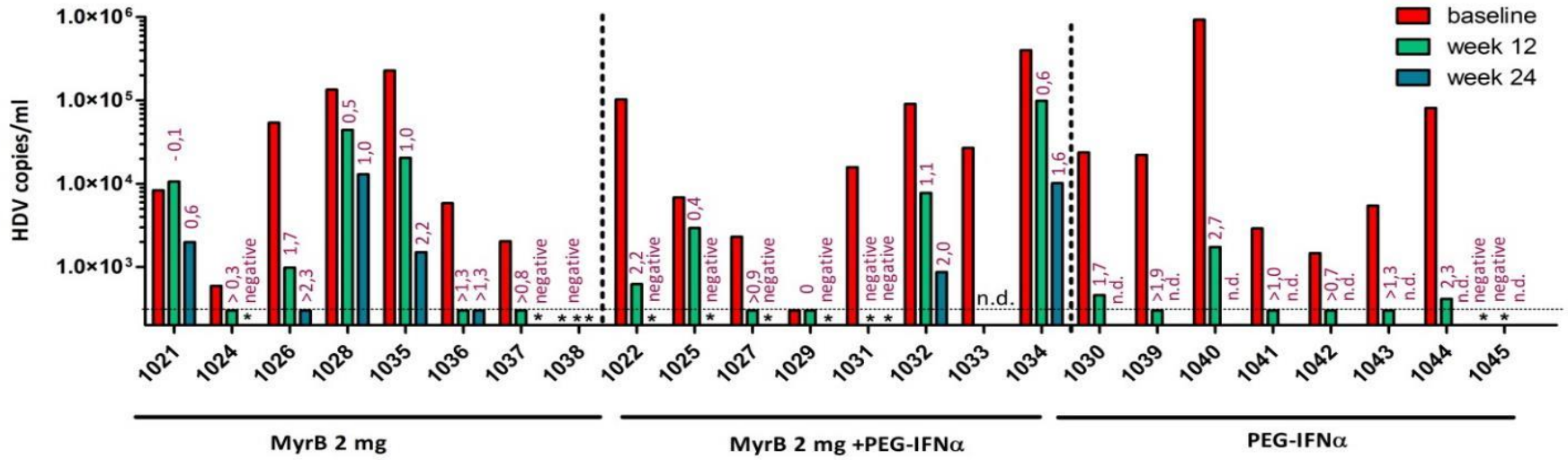
- The Problem
- Diagnosis
- Current Treatment
- Future Treatments


MYRCLUDEX B
NAPs
PEG IFN LAMBDA
HDV genome
large delta antigen
small delta antigen
Release of progeny
Lambda interferon receptor
Entry
Hepatocyte Cytoplasm
JAK
Uncoating of virus
STAT
Transportation to nucleus
HDV genome
Assembly
HBV surface antigen
ISG induction
Immune modulation
large HDAg
Protein Prenylation
prenylated LHDAg
Replication
Antiviral activity
LONAFARNIB

Characteristics of Novel Drug Treatment for HDV

Drug	Mode of action	Administration route,	Phase of study
Myrcludex B	Interferes with HDV entry into hepatocyte through NTCP inhibition	Subcutaneous, daily for 6 months, + Peg-IFN	Ib, II
Lonafarnib	Farnesyl transferase inhibitor, inhibits virion assembly	Oral, 2 to 12 months, + ritonavir + Peg-IFN	II
Rep-2139-Ca	Nucleic acid polymer, binds with high affinity to amphipathic proteins which are required at various stages of the viral life cycle	Intravenous infusion, once weekly for 4-6 months + Peg-IFN	II

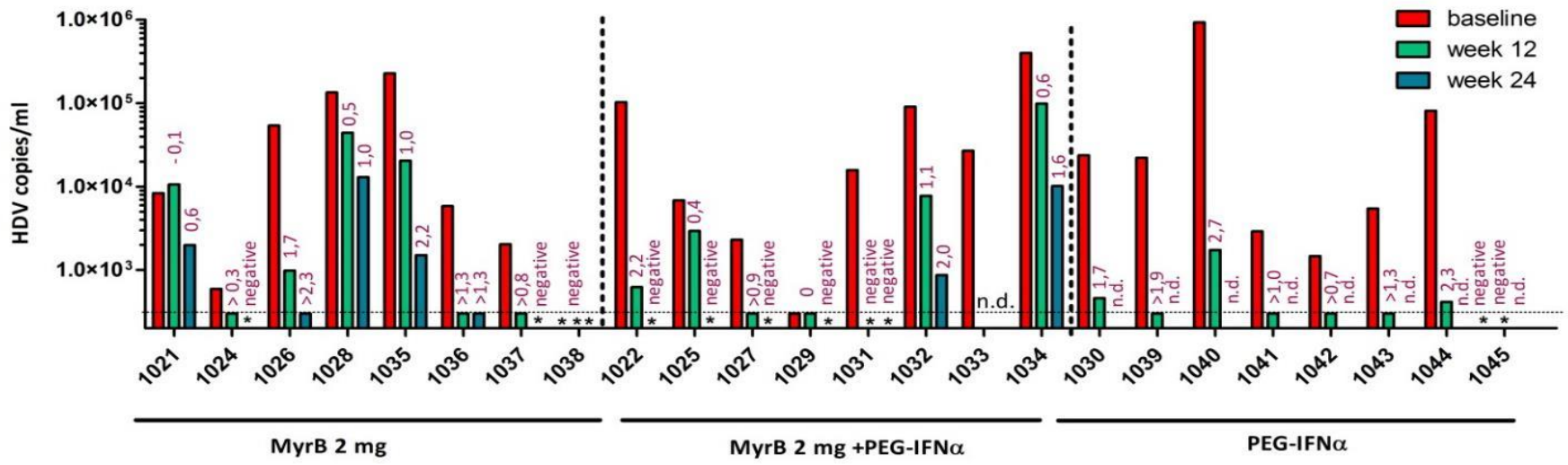
Entry Inhibitor: Myrcludex B



- 6 of 7 patients experienced HDV RNA decline >1 log_{10} at week 24 during Myr B monotherapy (mean log decline: 1.67 log_{10}copies/mL)
- 7 of 7 patients experienced HDV RNA decline >1 log_{10} at week 24 during Myr B/pegIFN-α combination therapy (mean log decline: 2.59 log_{10}copies/mL)
- HDV RNA became negative in 2 patients during MyrB monotherapy and in 5 patients in combination with pegIFN-α

Bogomolov et al, J Hepatol 2016

Entry Inhibitor: Myrcludex B



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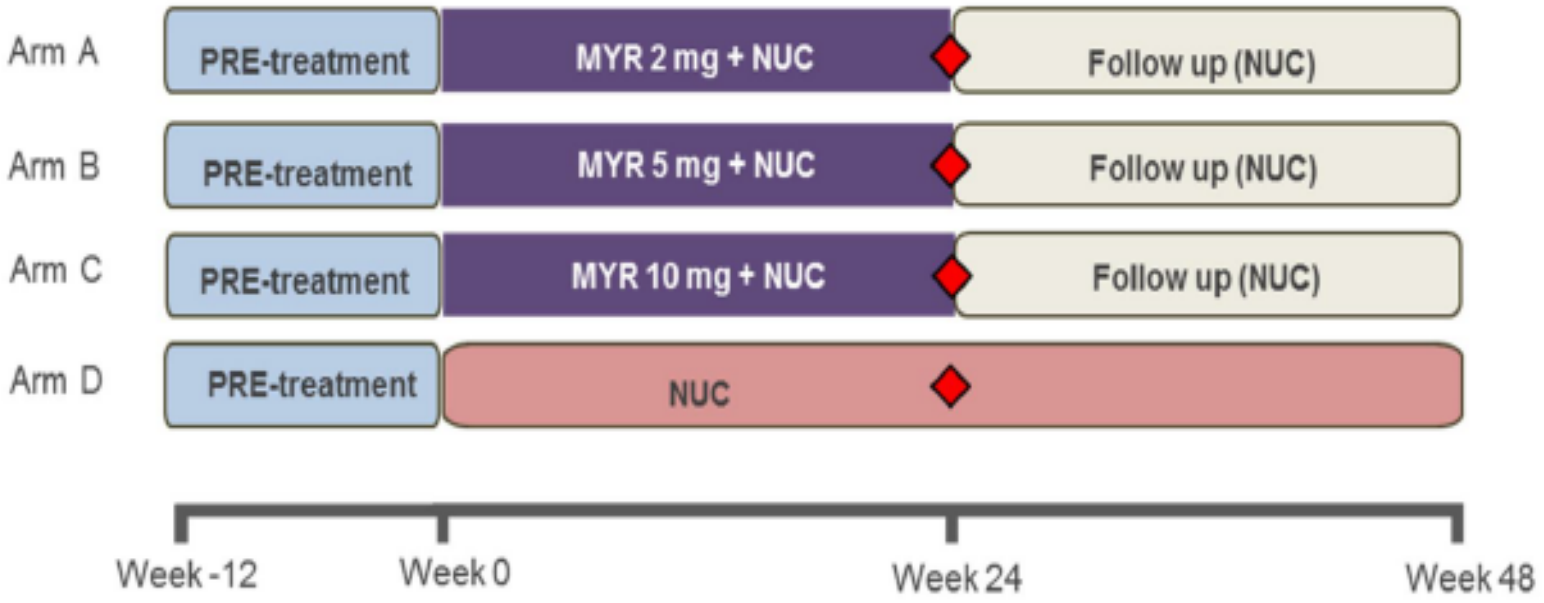
- HDV RNA became negative in 2 patients during MyrB monotherapy and in 5 patients in combination with pegIFN-α

Bogomolov et al, J Hepatol 2016

Myrcludex B Phase 2 Study

Daily Subcutaneous Injections

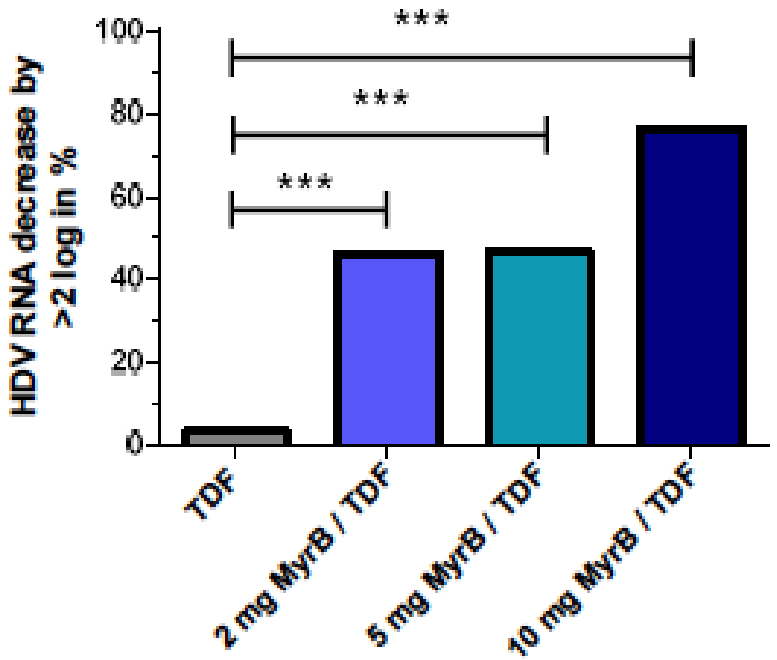
- 120 patients were randomized into 4 treatment arms in a ratio of 1:1:1:1 - 30 patients per arm
- Patients were pretreated with tenofovir for at least 12 weeks
- Myrcludex B was self administered by patients once daily s.c.
- All patients received tenofovir (oral qd) during the entire study period



Wedemeyer et al, AASLD 2017

Myrcludex B Phase 2 Results

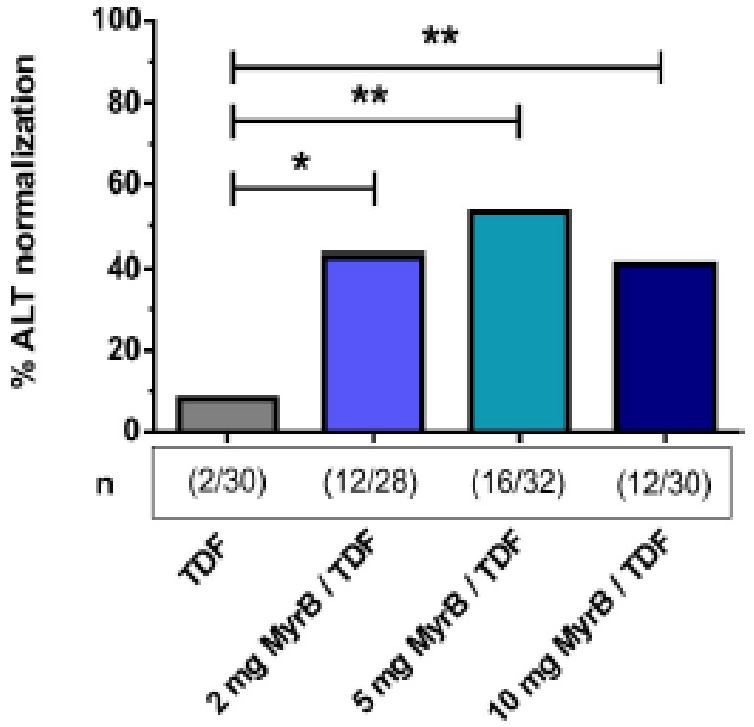
Primary endpoint:
2 log HDV RNA decline
or negativation week 24



Median RNA log10 change to BL

MyrB 2mg:	-1.75	MyrB 10mg:	-2.70
MyrB 5mg:	-1.60	TDF:	-0.18

ALT normalization (week 24)

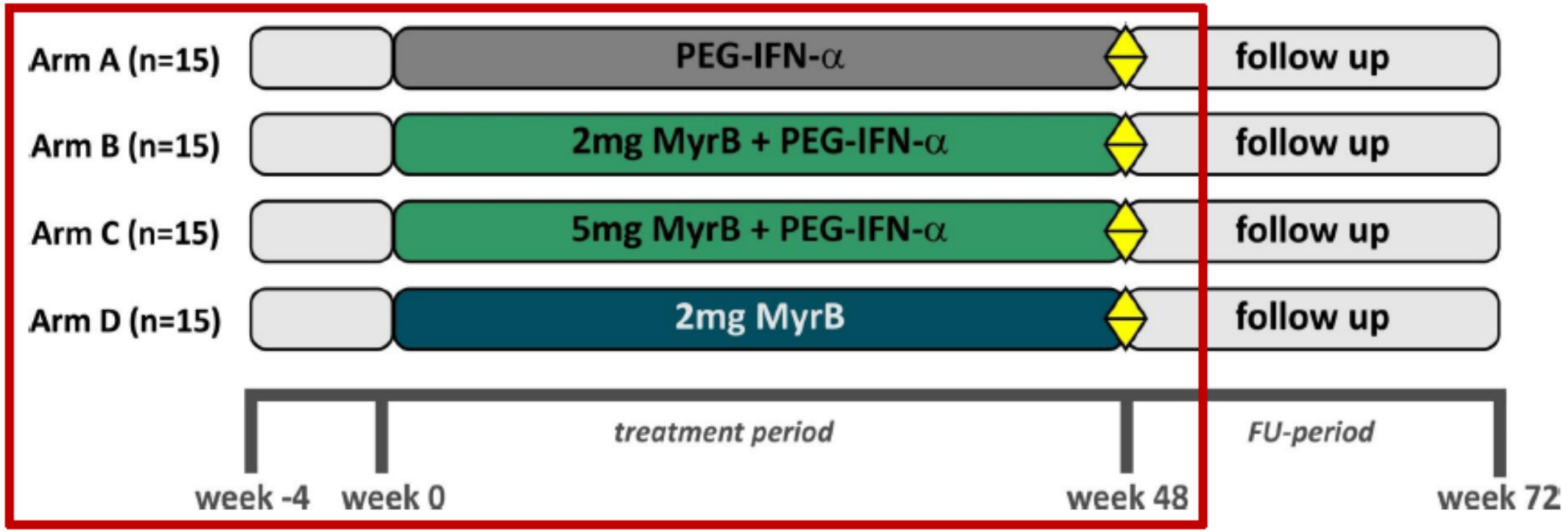


Wedemeyer et al, AASLD 2017

HEPATITIS B FOUNDATION

MYR203 Study Design

- 60 patients with chronic HBV/HDV co-infection were randomized into 4 treatment arms in a ratio of 1:1:1:1 - 15 patients per arm
- Myrcludex B was self administered by patients once daily s.c.

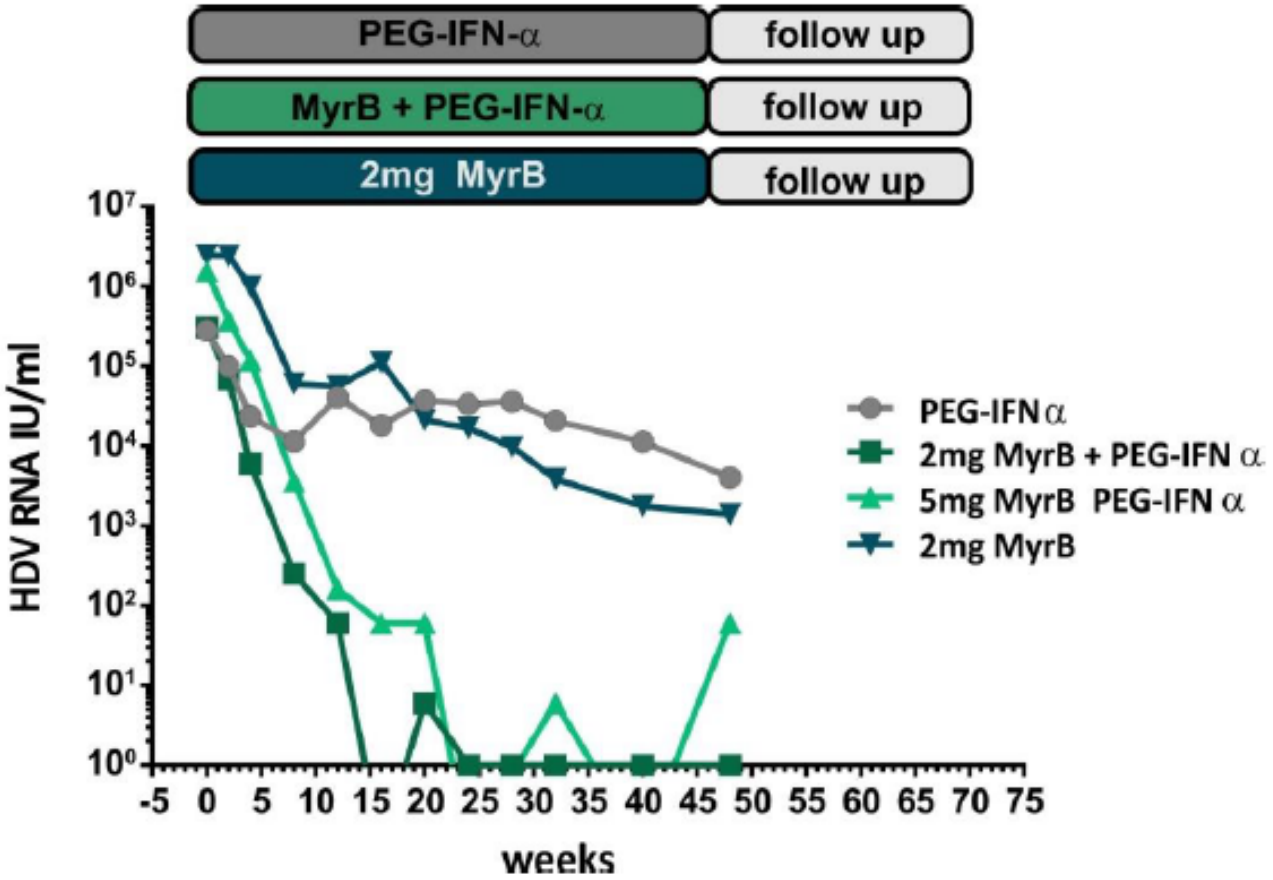


Wedemeyer et al, AASLD 2018

HEPATITIS B FOUNDATION

Virological Response (HDV RNA)

Median HDV RNA levels

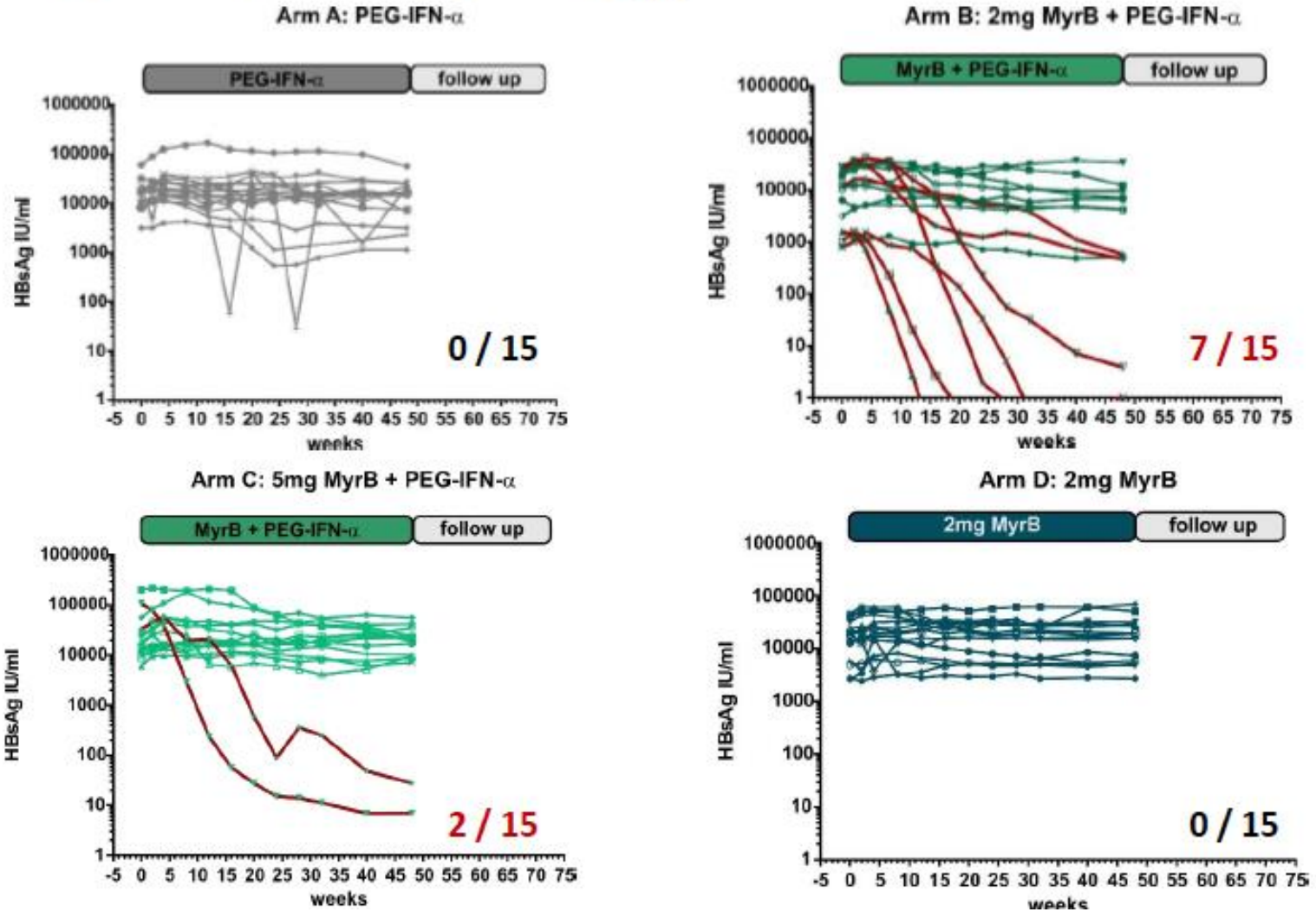


Median RNA log_{10} change to BL at week 48:

2mg MyrB/PEG-IFNα:	-3.62
5mg MyrB/PEG-IFNα:	-4.48
2mg MyrB:	-2.84
PEG-IFNα:	-1.14

Wedemeyer et al, AASLD 2018

HBsAg Response (≥1log$_{10}$ decline or undetectable)



Wedemeyer et al, AASLD 2018

HEPATITIS B FOUNDATION

Conclusions & Outlook

- Blocking HBV/HDV entry with myrcludex B is a safe and promising strategy to treat chronic hepatitis delta
- Prolonged myrcludex B monotherapy (2mg and 10mg for 2-3 years) will be studied in a phase 3 registration trial

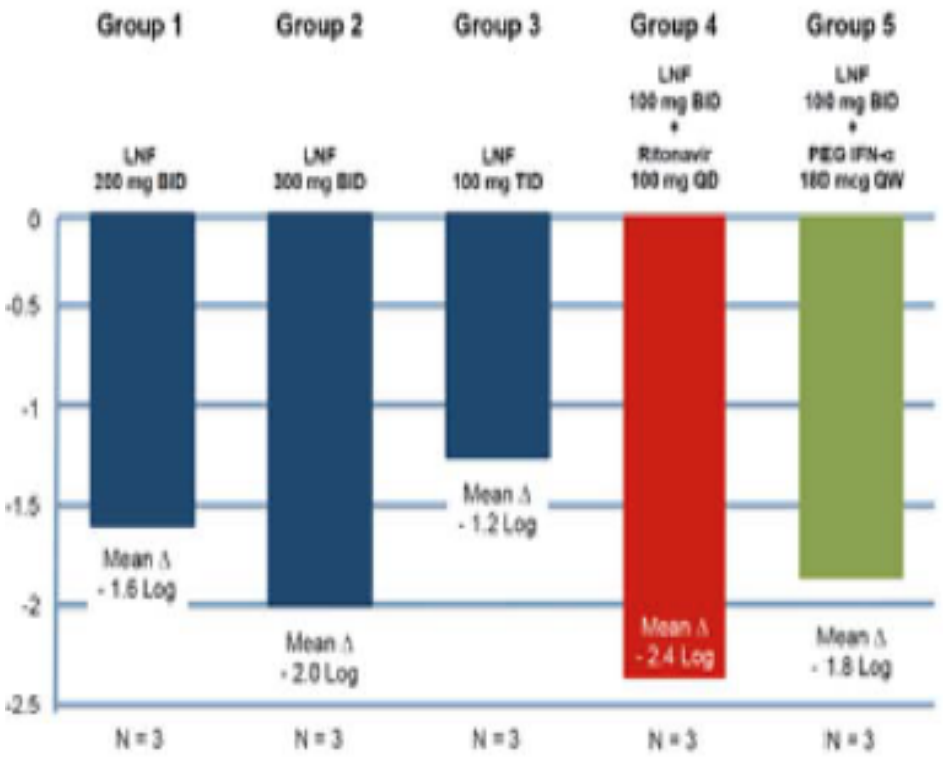
- Entry inhibition with myrcludex B in combination with PEG-IFNα bears curative potential in patients with hepatitis B/D coinfection
- Combination therapy will be tested in patients with HBV monoinfection

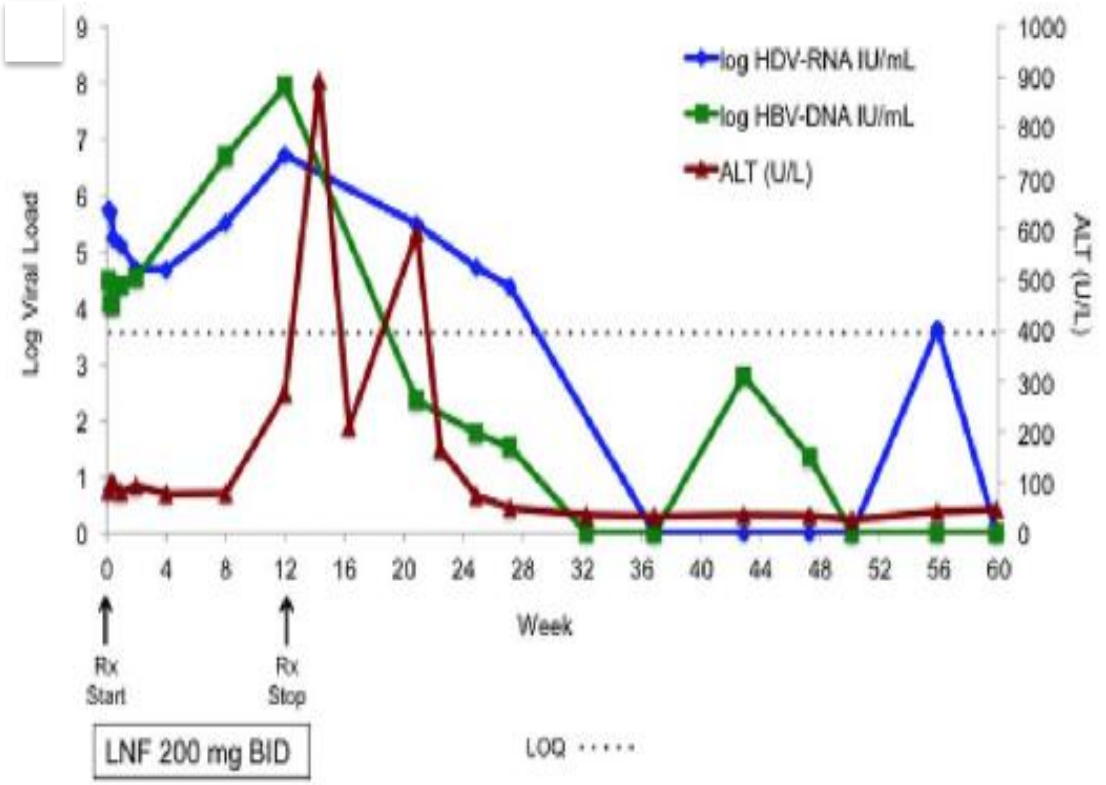
Wedemeyer et al, AASLD 2018

Prenylation Inhibitor: Lonafarnib (LNF)

Phase 2 LOWR-1 Study

Δ Log HDV RNA at Month 1



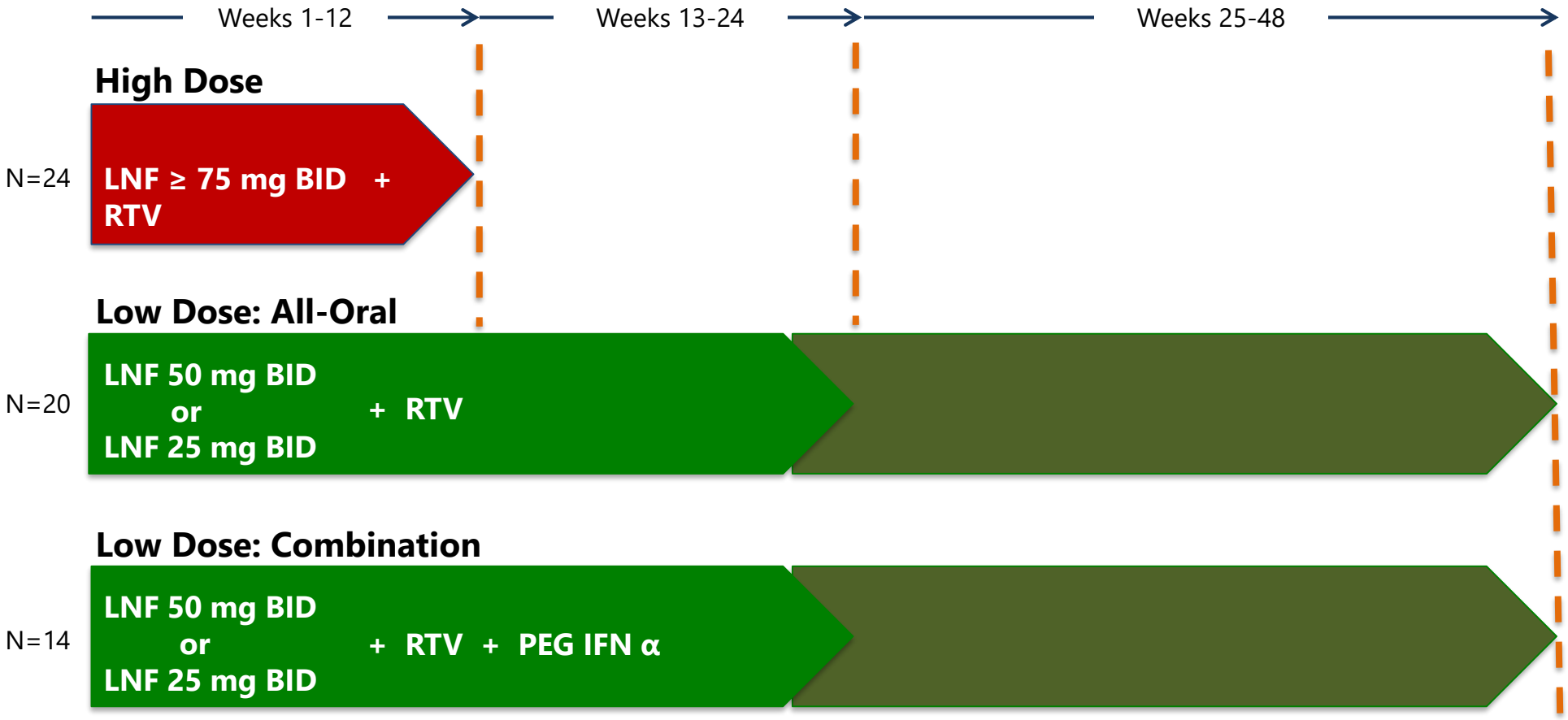


LOWR HDV = LOnafarnib With Ritonavir in HDV
Yurdaydin et al, Hepatology 2018

HEPATITIS B FOUNDATION

LOWR – 2: "DOSE OPTIMIZATION" STUDY

Dose and Regimen Identified for Registration

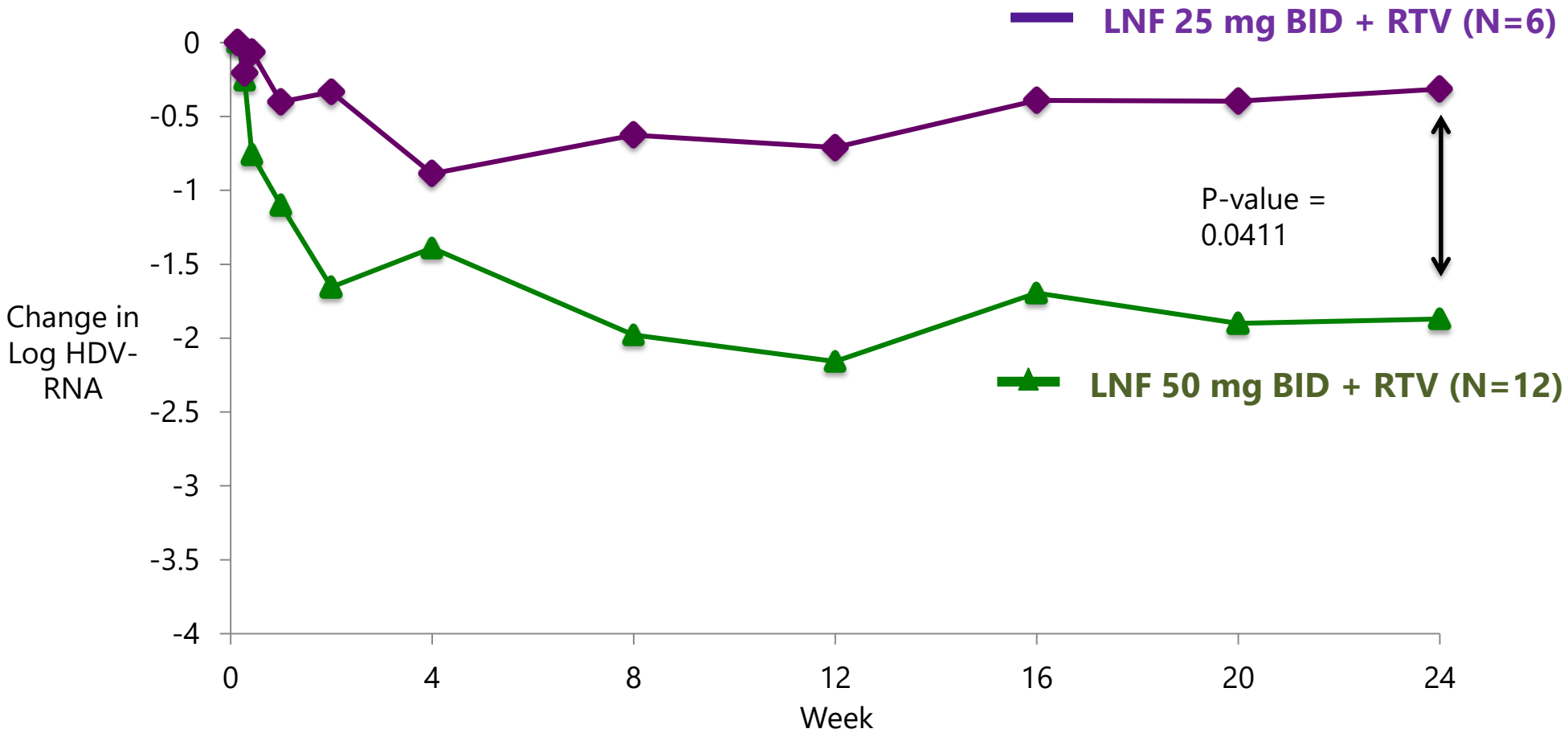


BETTER TOLERABILITY WITH LOW DOSE LONAFARNIB

Week 12								
LNF Dose	**N**	**HDV RNA Decline**	**# of D/C's**	**# of Dose Reductions**	**# of GI AEs**	**Grade 1**	**Grade 2**	**Grade 3**
High Dose[1]	17	-1.32 IU/mL	4	11	59	31	17	11
			23.5%	64.7%		52.5%	28.8%	18.7%
Low Dose[2]	**17**	**-2.09 IU/mL**	**1**	**0**	**62**	**53**	**5**	**4**
			5.9%	**0%**		**85.5%**	**8.0%**	**6.5%**

[1] LNF 100 mg BID + RTV 100 mg QD; LNF 100 mg QD + RTV 100 mg QD; LNF 100 mg BID + RTV 50 mg QD; LNF 150 mg QD + RTV 100 mg BID
[2] LNF 50 mg BID + RTV 100 mg BID (PEG IFN-alfa-2a added Week 13); LNF 50 mg BID + RTV 100 mg BID; LNF 25 mg BID + RTV 100 mg BID

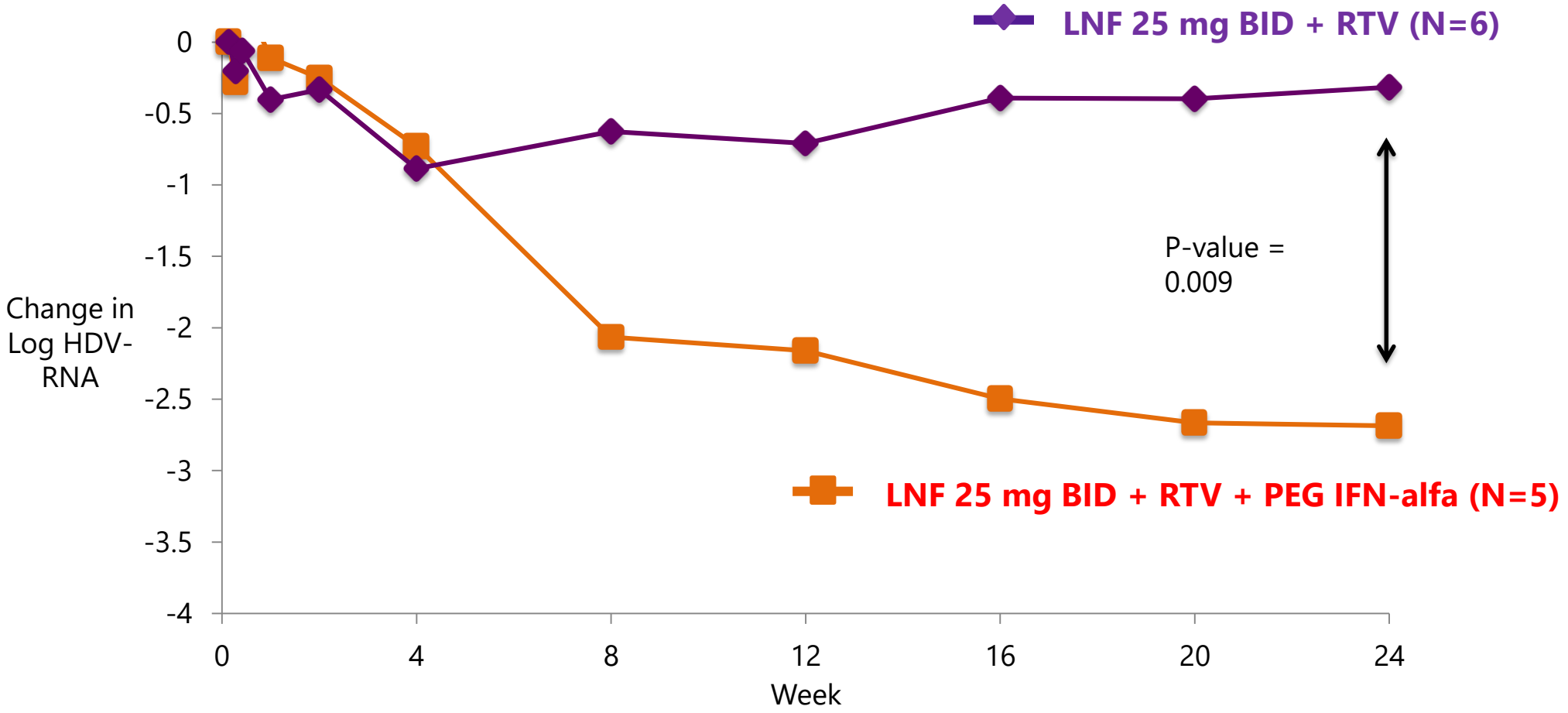
ALL-ORAL: LNF 50 MG BID + RTV vs. LNF 25 MG BID + RTV



Per protocol analysis

*Yurdaydin et al, J Hepatology **2018**, Abstract #PS-161*

COMBINATION: LNF 25 MG BID + RTV + PEG IFN-ALFA



Per protocol analysis
*Yurdaydin et al, J Hepatology **2018**, Abstract #PS-161*

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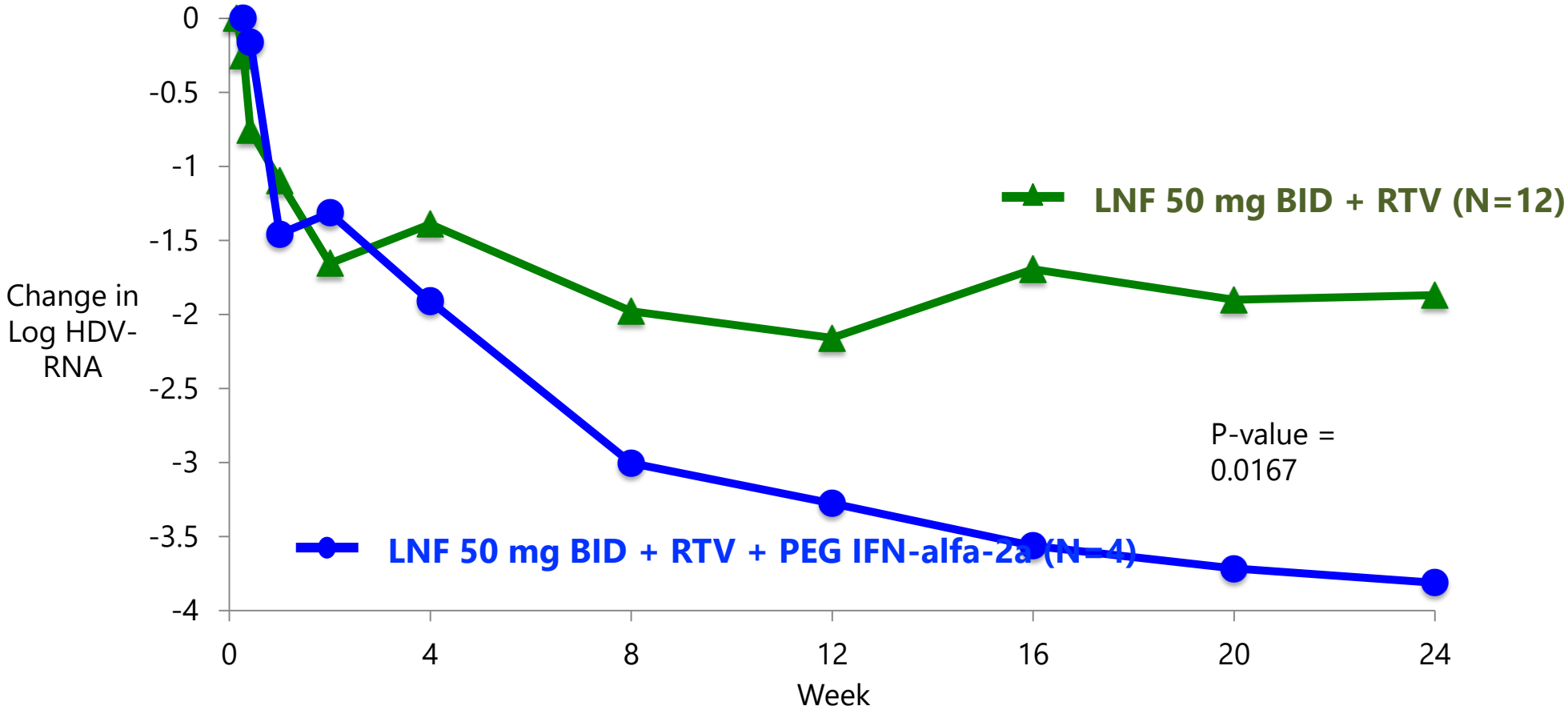
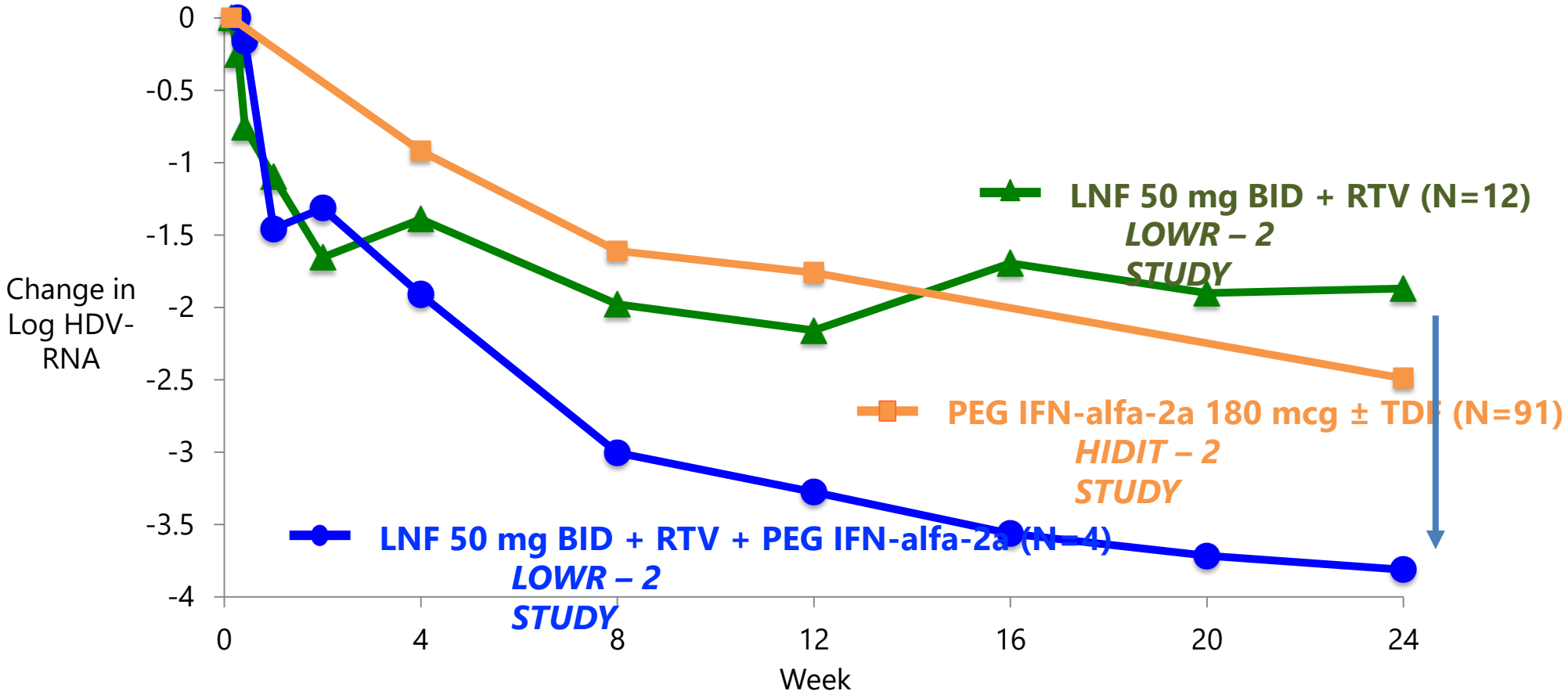


Per protocol analysis
*Yurdaydin et al, J Hepatology **2018**, Abstract #PS-161*

COMBO REGIMEN: GREATEST OBSERVED DECLINE IN HDV-RNA

Lonafarnib 50 mg BID + Ritonavir 100 mg BID + PEG IFN-alfa-2a



Per protocol analysis

*Yurdaydin et al, J Hepatology **2018**, Abstract #PS-161*

LONAFARNIB PHASE 2 HDV PROGRAM

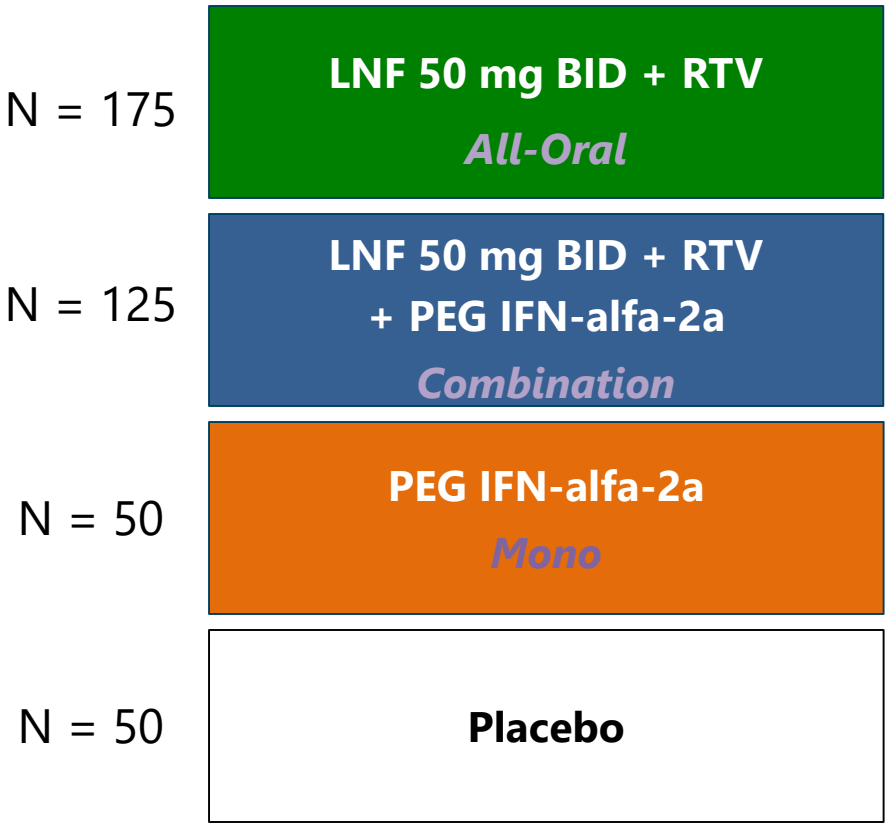
Dose, Combinations and Endpoints Defined

- **All-oral:** Lonafarnib boosted with Ritonavir
  - 33% (6 of 18) patients ≥ 2 log decline or BLQ at Week 24
  - 47% (7 of 15) patients normalized ALT at Week 24
  - **Composite endpoint: 29% (4 of 14)**
- **Combination:** Lonafarnib boosted with Ritonavir + PEG IFN-alfa-2a
  - 78% (7 of 9) patients ≥ 2 log decline or BLQ at Week 24
  - 88% (7 of 8) patients normalized ALT at Week 24
  - **Composite endpoint: 63% (5 of 8)**
- Predominant AEs were GI-related (mild / moderate)

*Yurdaydin et al, J Hepatology **2018**, Abstract #PS-161*
Most common reported AEs: nausea, diarrhea, fatigue, weight loss, anorexia, vomiting

D-LIVR : PHASE 3 STUDY INITIATING Q4 2018

Delta-Liver Improvement and Virologic Response in HDV



Primary Endpoint at Week 48

- ≥ 2 log decline in HDV RNA

  \+

- Normalization of ALT

Secondary Endpoint at Week 48

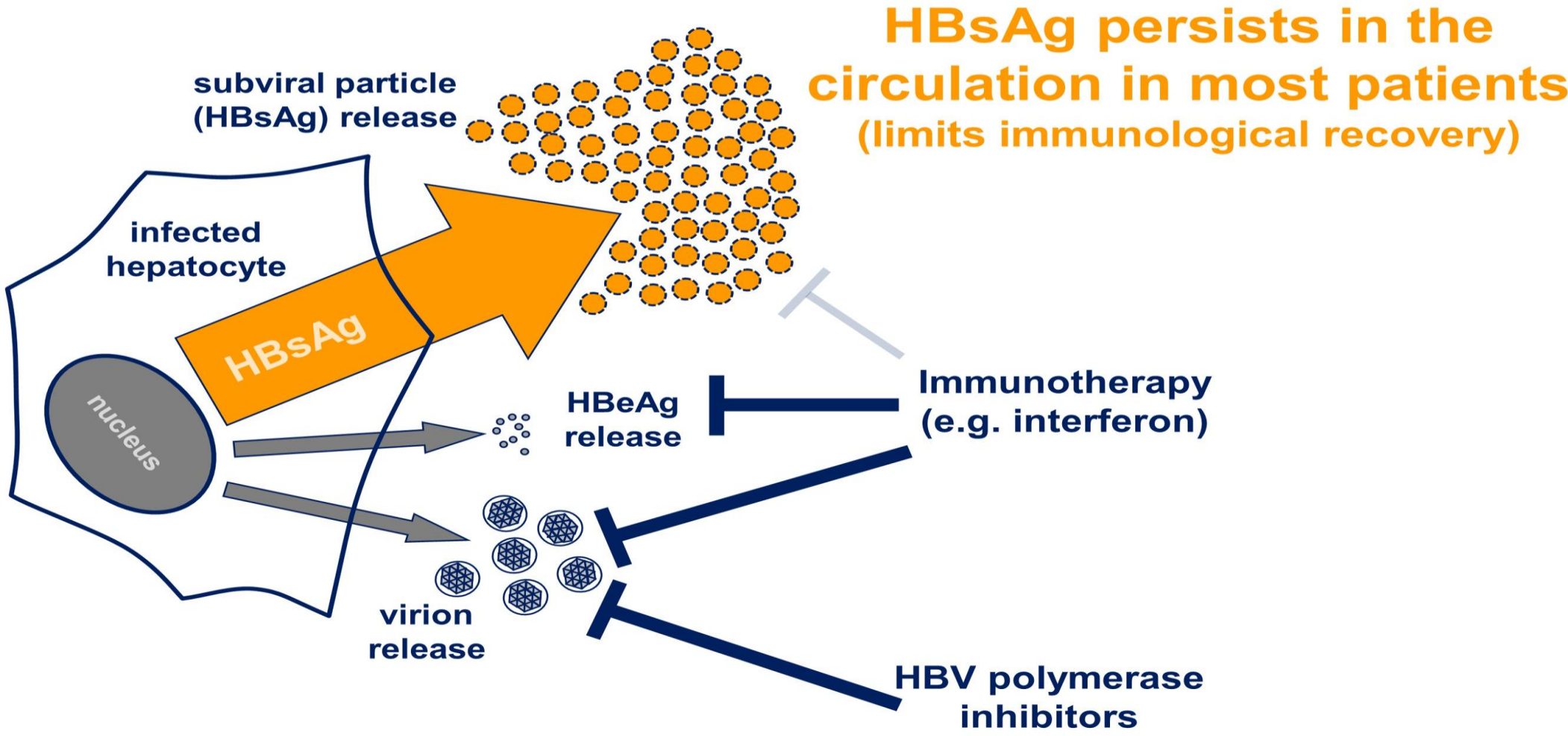
- Histologic improvement
  - > 2 point improvement in HAI inflammatory score
  - No progression in fibrosis
- Improvement of fibrosis

All patients will be run-in and maintained on background HBV nucleoside therapy

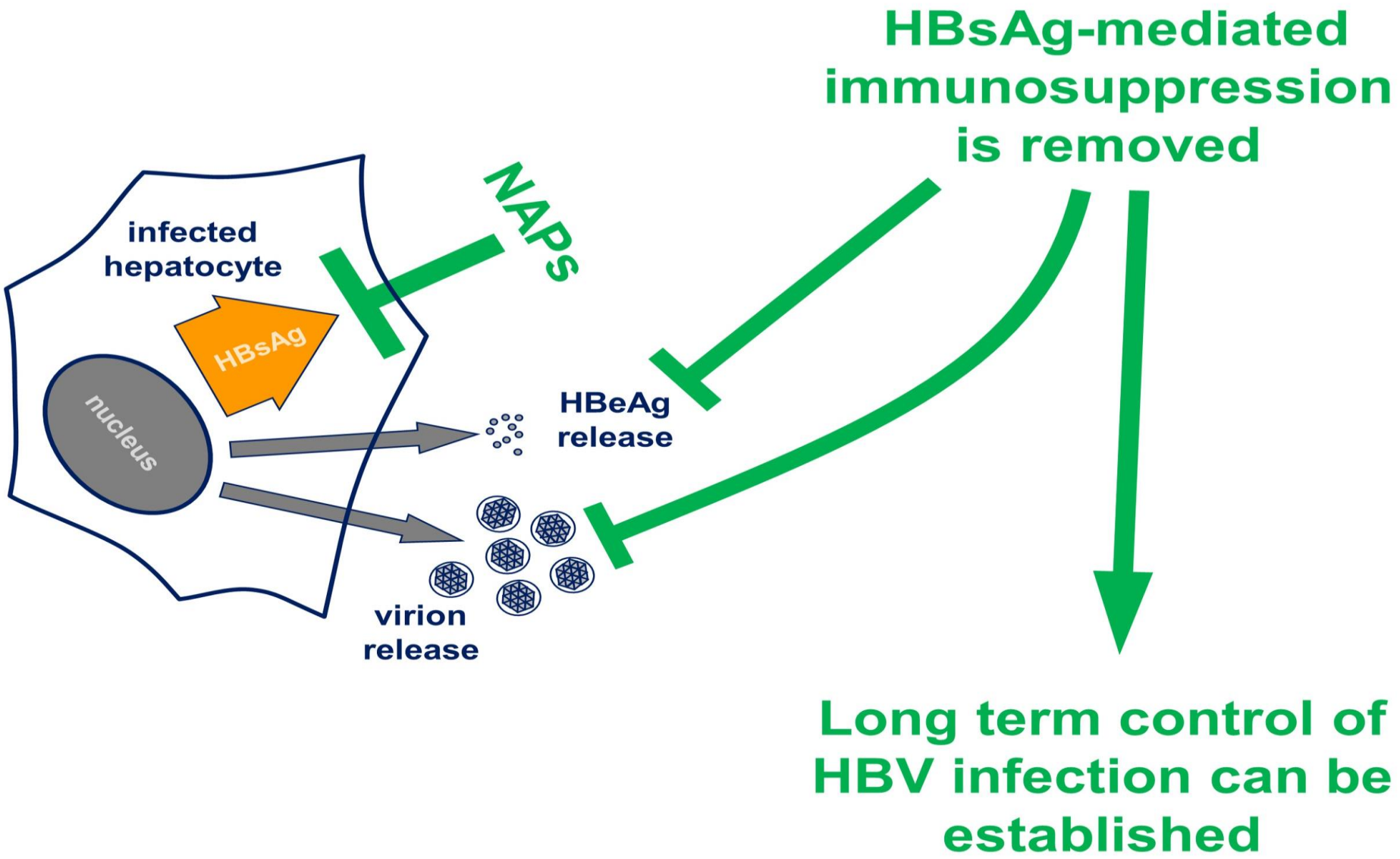
Nucleic Acid Polymers

- Nucleic acid polymers (NAPs) are sequence-independent phosphorothioated oligonucleotides which exert their pharmacological effect in a sequence independent manner.
- They bind with high affinity to amphipathic protein structures, a consequence of a hydrophobic-based interaction.
- Their mechanism of action is not entirely clear but it is suggested that NAPs inhibit assembly and/or secretion of subviral particles.

Limitation of current HBV antiviral therapies



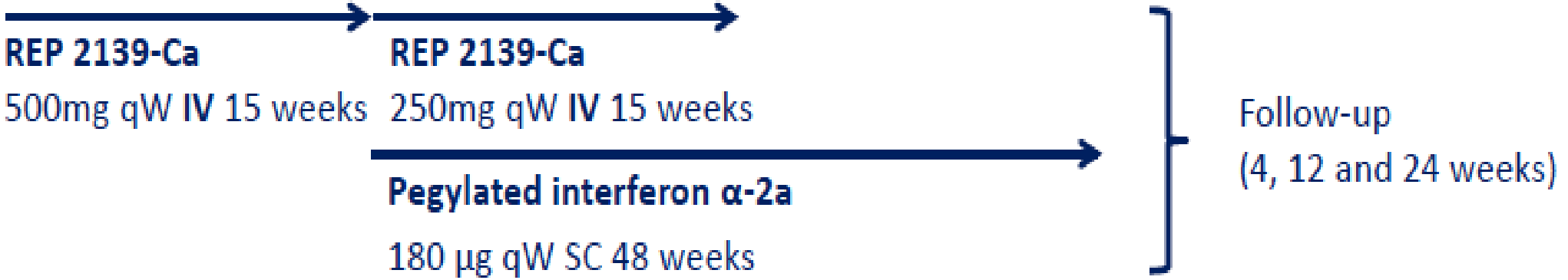
NAPs block the release of subviral particles



Nucleic Acid Polymers (NAPs): Phase 2 Study

Weekly IV Infusions

- 12 Caucasian patients with confirmed chronic HBV / HDV co-infection
- Clinicaltrials.org # NCT02233075



REP 301-LTF (NCT02876419): 3 year extension of follow-up (every 6 months)

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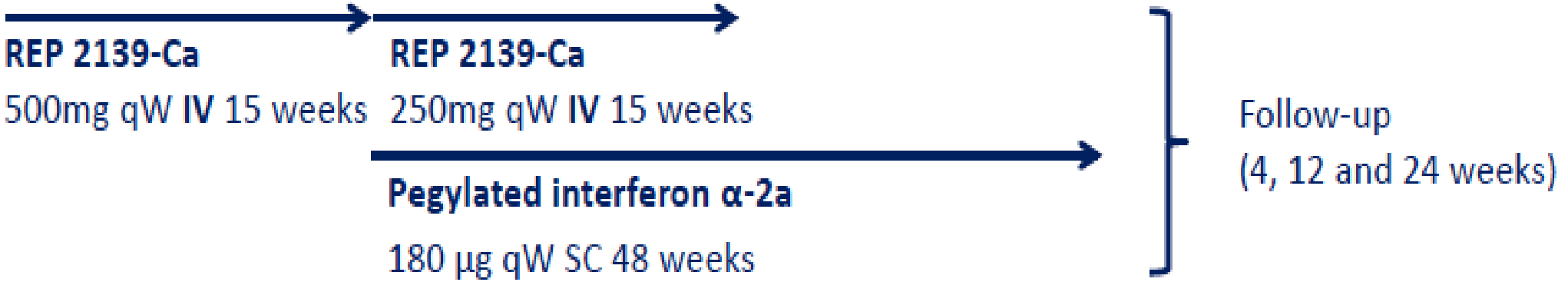
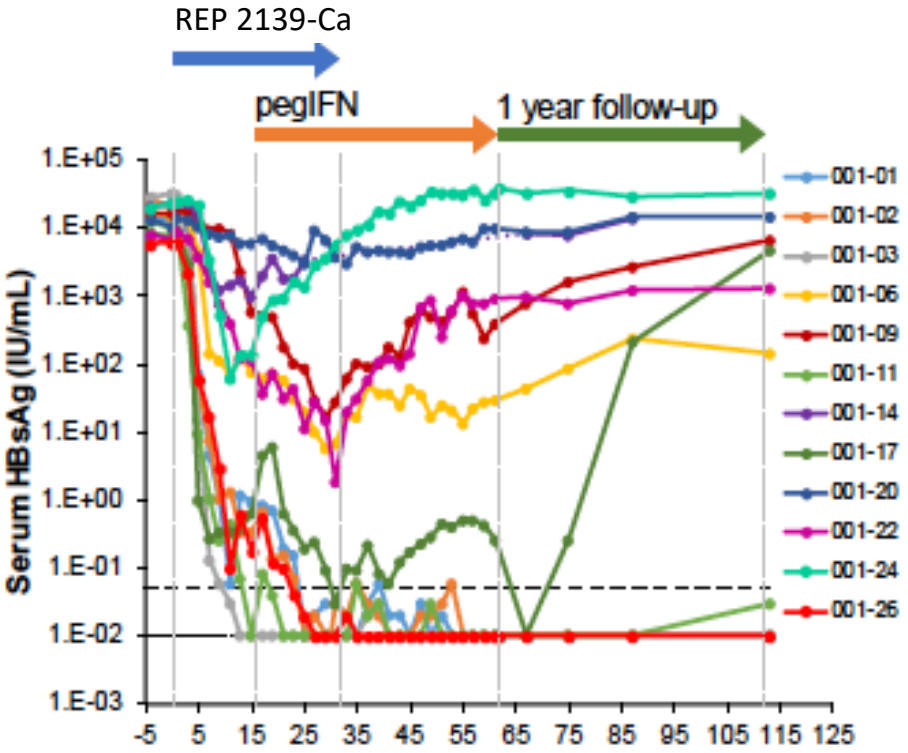
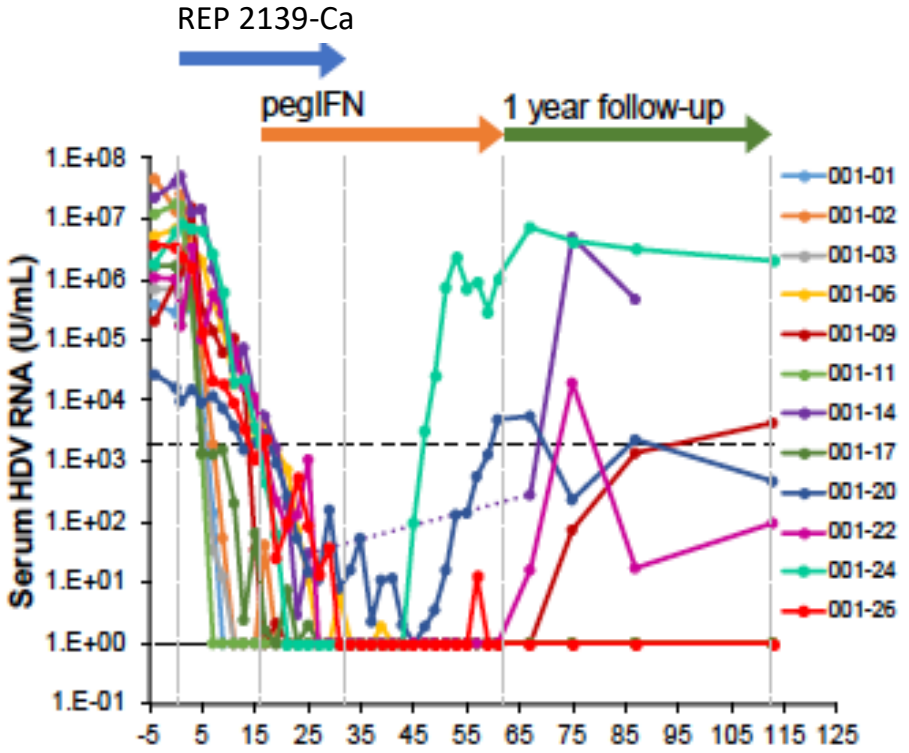


REP 301-LTF (NCT02876419): 3 year extension of follow-up (every 6 months)

Nucleic Acid Polymers (NAPs): Phase 2 Results

Weekly IV Infusions



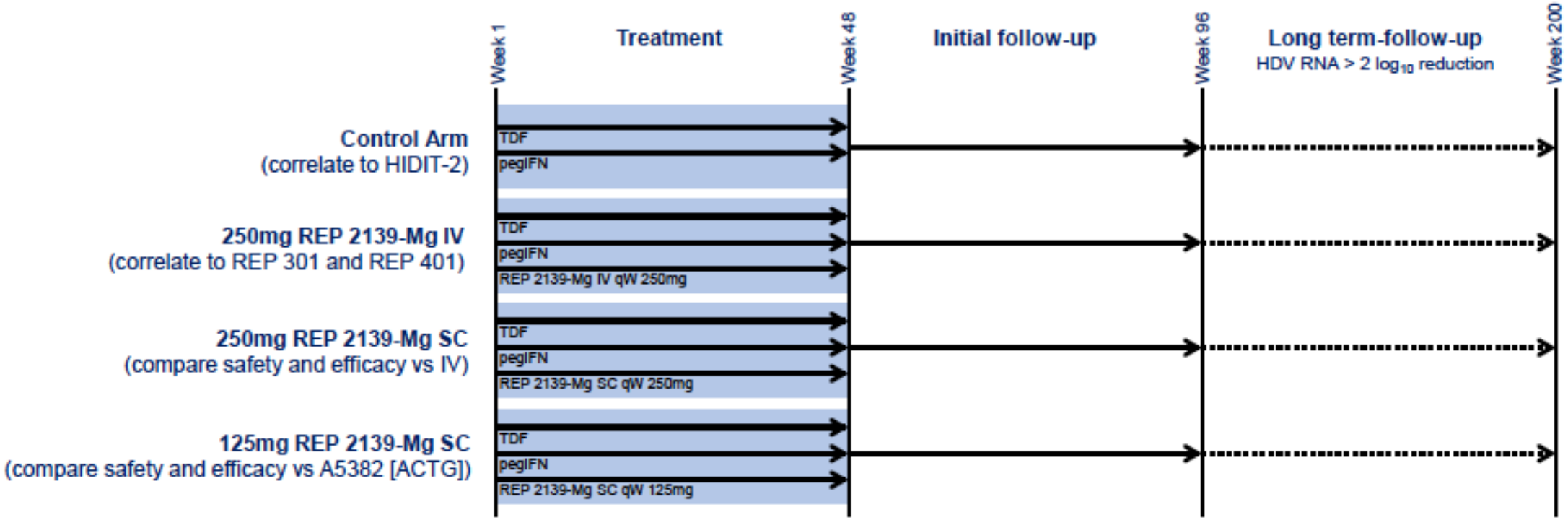


HDV RNA negative in 7/12 (58%)
HBsAg negative in 5/12 (42%)
Anti HBs positive at high titers in 5/12 (42%)

Bazinet et al, Lancet Gastroenterol Hepatol 2017

Transitioning REP 2139-Mg to SC administration

The REP 501 protocol:
Comparing safety and efficacy of REP 2139-Mg IV vs SC in combination with TDF and pegIFN

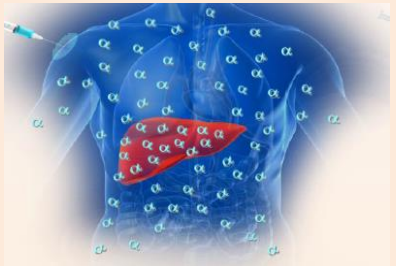


Pegylated Interferon Lambda

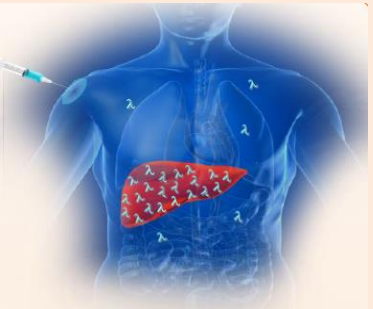
A Better Tolerated Interferon

- 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*

Alfa Receptor Expression



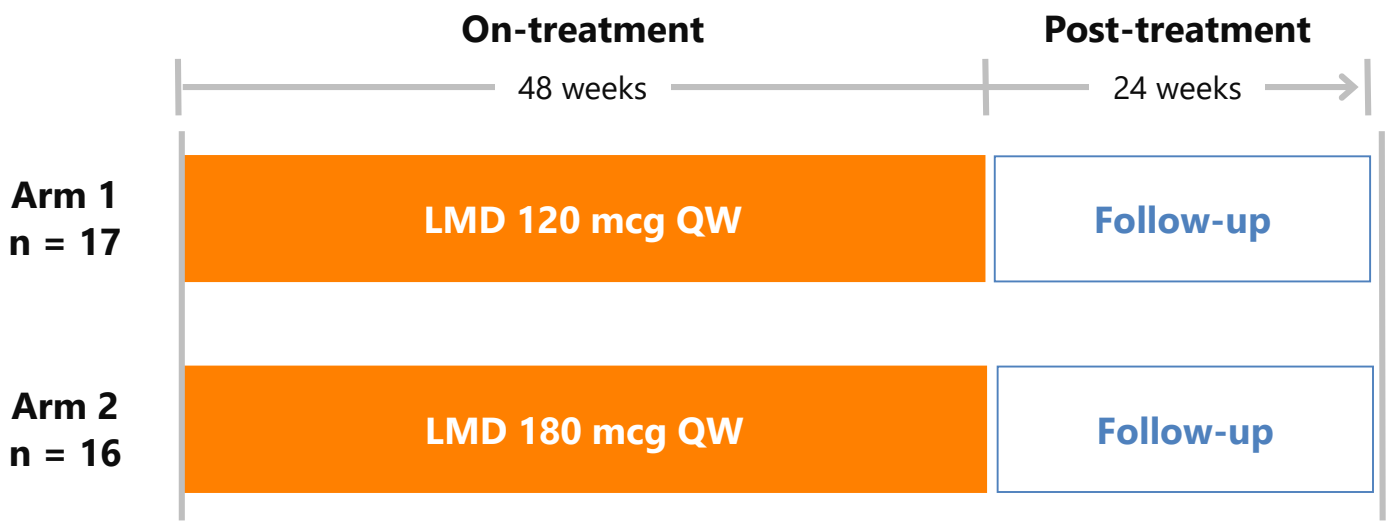
Lambda Receptor Expression



*Chan, HLY et al, J Hepatology 2016

Limt HDV “Mono”: Phase 2 Study

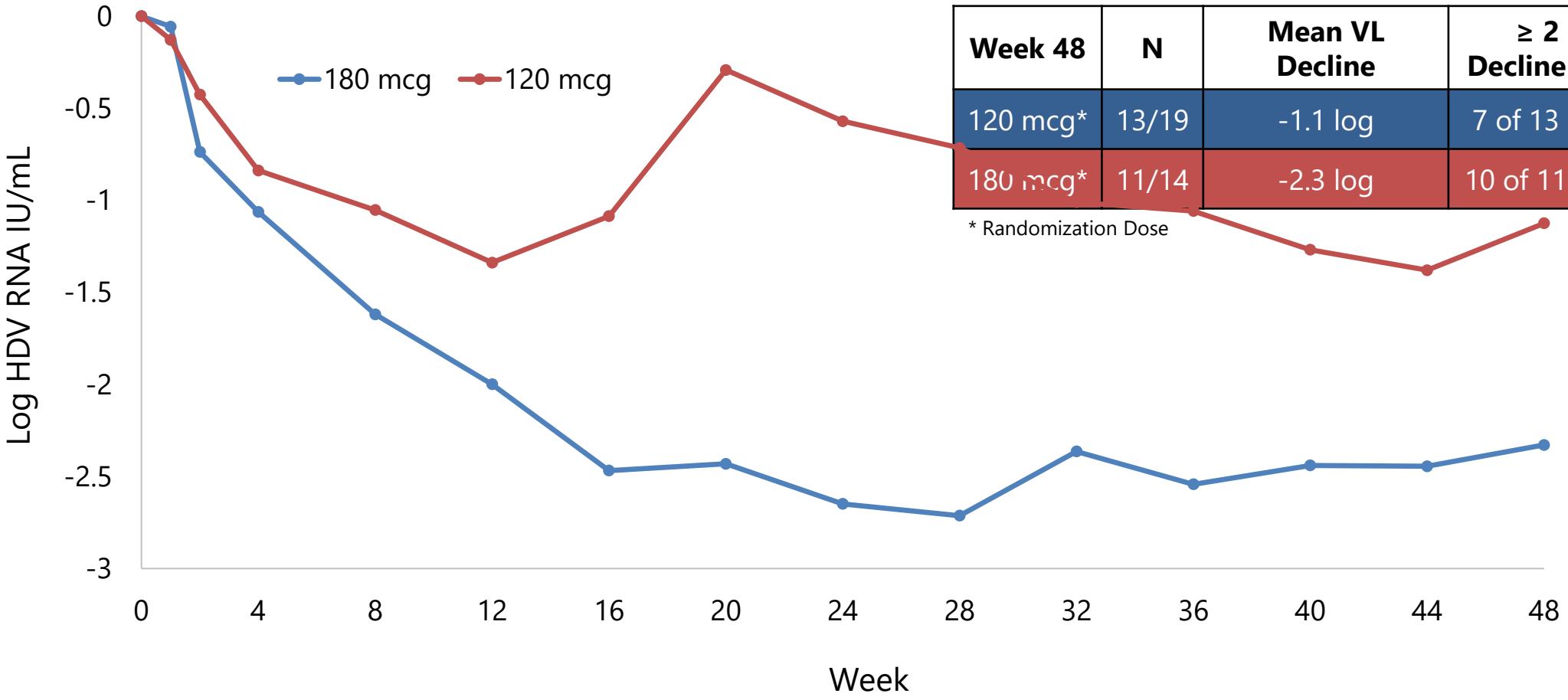
Lambda Interferon MonoTherapy Study in HDV



Etzion O, Hamid S et al.
Limit of quantification = 1.1 Log IU/mL

HDV-RNA REDUCTION WITH LAMBDA THRU WEEK 48

Dose Response Demonstrated



Week 48	N	Mean VL Decline	≥ 2 Log Decline or BLQ
120 mcg*	13/19	-1.1 log	7 of 13 (53.8%)
180 mcg*	11/14	-2.3 log	10 of 11 (90.1%)

* Randomization Dose

Etzion O, Hamid S et al.
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HEPATITIS B FOUNDATION

Reported Side Effects of New Drugs for CHD

Myrcludex B:

- Lipase, amylase elevation in phase I but not in phase II study
- Elevation of taurine- and glycine-conjugated bile acids- without apparent clinical consequences
- Thrombocytopenia, neutropenia, lymphopenia and eosinophilia: generally mild, transient

Lonafarnib (LNF):

- Gastrointestinal toxicity: anorexia, nausea ± vomiting, diarrhea, weight loss: dose dependent and in lower dose cohorts generally mild and well tolerated

Nucleic acid polymers (NAPs):

- Hair loss, dysphagia, anorexia, dysgeusia in HBV Study: related to heavy metal exposure at the trial site ?
- Administration route related side effects: peripheral grade 1 hyperemia, fever, chills, headache

New Drugs

- Registration studies expected to start soon for Myrcludex B and Lonafarnib
- Nucleic acid polymers: sc formula adaptation and small pilot study to be followed by registration study
- There are others:
  - Small interfering RNAs
  - Immunological approaches: Interferon lambda, TLR agonists, check point inhibitors, HBV vaccines
- Functional cure for HBV

Summary and Conclusions

- INFs are currently the only available drugs for the management of CHD
- They are effective in a subset of patients and appear to favorably modify complications of the disease
- NAs are ineffective when used for 6-18 months. Longer tx duration may be effective in a subset of pts as has been shown in HIV-HDV co-infected pts
- Mechanism of action not well understood:
  - Immune reconstitution?
  - Indirect effect on cccDNA and HBsAg synthesis
  - May be effective in pts with less HDV dominant CHD

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Summary and Conclusions

- In patients not responding or not tolerating IFN, new drugs are an urgent unmet need
- Good results with Myrcludex B, Lonafarnib and Nucleic Acid Polymers
- pegIFN-α may still be used as backbone
- We are expecting to enter a new area in the management of CHD

Thank you for your attention!

QUESTION & ANSWER

Please submit questions for Dr. Yurdaydin in the chat box!

HEPATITIS DELTA CONNECT
hepdconnect.org

A recording of the webinar will be emailed to you.

Please fill out the survey! Let us know if you'd like to opt in to receive future information from us.

For more information about the Hepatitis B Foundation's Hepatitis Delta Connect Program, visit our website *www.hepdconnect.org and email connect@hepdconnect.org with questions or collaborations.*