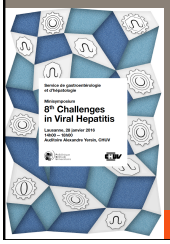
The challenge of hepatitis D in 2016

Heiner Wedemeyer, Markus Cornberg



Medizinische Hochschule Hannover

Hepatitis Delta: A typical case

- Waldemar, 42 years, born in Kazakhstan
- In 2008 routine check up at the primary care physician
- ALT 64 IU/l, AST 45 U/l, Bilirubin normal
- Platelets 160/nl

- HBsAg positiv, HBeAg negativ, HBV DNA 70 IU/ml
- HIV und anti-HCV negativ.
- "Moderate" alcohol.
- Primary care physician: *"Your Hepatitis B is encapsulated". "You should drink less alcohol and come back in 6 months".*

*This case is based on real patients but details have been changed and amalgamated to protect the patients.

3 years later

- 45 years, still elevated ALT
- ALT 67 IU/l, AST 78 U/l, Bilirubin normal
- Platelets 98/nl

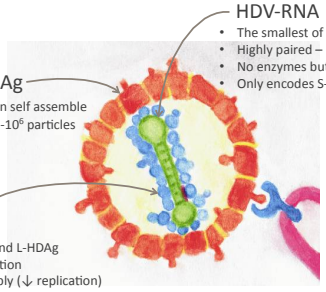
→ Referral to MHH

- HBsAg positive (21323 IU/ml), HBeAg negative
- HBV DNA 2334 IU/ml
- **Anti-HDV positive, HDV-RNA 7.3 log cop/ml**

- Ultrasound: Cirrhosis

*This case is based on real patients but details have been changed and amalgamated to protect the patients.

The Hepatitis Delta Virus

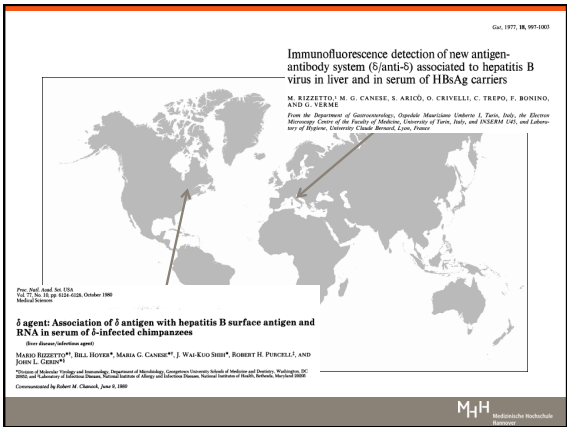


HDV-RNA
- The smallest of all animal viruses
- Highly paired – rod like structure
- No enzymes but Ribozymes
- Only encodes S-HDAg

HBsAg
- HBsAg particles can self assemble
- HBV: 1 virion x 10^3-10^6 particles

HDAg
- 2 forms: S-HDAg and L-HDAg
- S-HDAg: ↑ replication
- L-HDAg: ↑ assembly (↓ replication)

Calle Serrano, Manns & Wedemeyer, Seminars in Liver Disease 2012



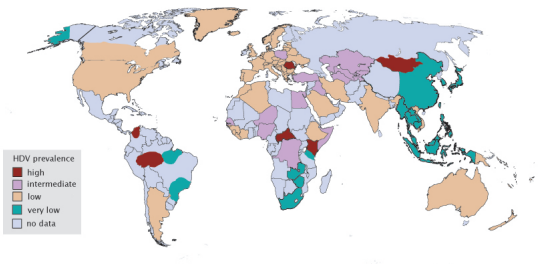
Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

M. RIZZETTO,† M. G. CANESE, S. ARICÒ, O. CRIVELLI, C. TREPO, F. BONINO, AND G. VERME

δ agent: Association of δ antigen with hepatitis B surface antigen and RNA in serum of δ-infected chimpanzees

MARIO RIZZETTO*†, BILL HOYER*, MARIA G. CANESE*†, J. WAI-KUO SHIH*, ROBERT H. PURCELL‡, AND JOHN L. GERIN*†

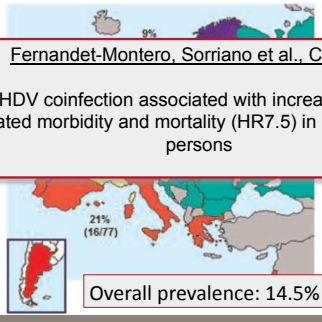
Prevalence of Hepatitis Delta



15-20 million patients with chronic Hepatitis Delta

www.hepatitis-delta.org

High anti-HDV prevalence in HBsAg-positive HIV-infected individuals

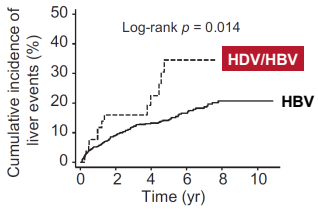


Fernandet-Montero, Sorriano et al., CID 2014

HDV coinfection associated with increased liver-related morbidity and mortality (HR7.5) in HIV-infected persons

Overall prevalence: 14.5%!

Hepatitis delta takes a more severe long-term course than HBV mono-infection



Number at risk						
HBV monoinfected	1091	685	434	266	123	36
HBV/HDV co-infected	53	33	24	7	2	2

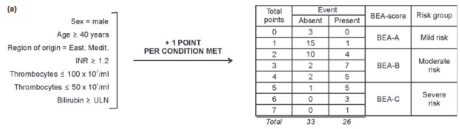
Identification of patients with a higher risk for disease progression

Who should be treated asap?

Journal of Viral Hepatitis, 2014 doi:10.1111/jvh.12251

Development and evaluation of a baseline-event-anticipation score for hepatitis delta

B. Calle Serrano,[1,2] A. Großhennig,[3] M. Homs,[4] B. Heidrich,[1,5] A. Erhardt,[6] K. Deterding,[1] J. Jaroszewicz,[1,7] B. Bremer,[1] A. Koch,[3] M. Cornberg,[1] M. P. Manns,[1,4] M. Buti[3] and H. Wedemeyer[1,2,4]
[1]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [2]German Center for Infection Research (DZIF), Partner Side HepNet Study-House, Hannover, Germany; [3]Institute for Biostatistics Hannover

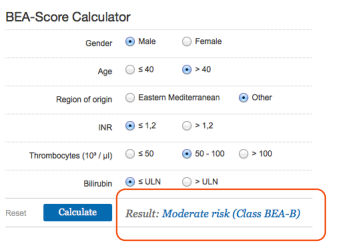


Total points	Event: Absent	Event: Present	BEA-score	Risk group
0	3	0	BEA-A	Mild risk
1	15	1		
2	10	4	BEA-B	Moderate risk
3	2	7		
4	2	5		
5	1	5	BEA-C	Severe risk
6	0	3		
7	0	1		
Total	33	26		

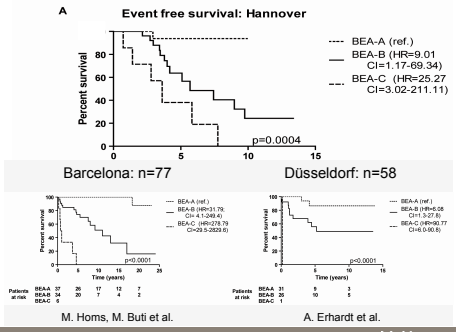
BEA-Score

http://hepatitis-delta.org/physicians-and-scientists/calculators/

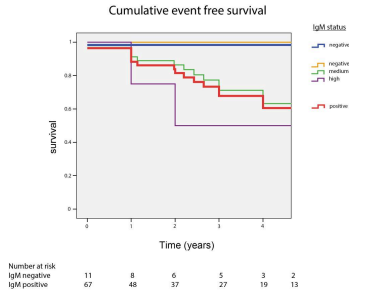
- Male
- 45 years
- Kazakhstan
- INR normal
- Platelets 98.000
- Bilirubin normal



BEA-Score B und C may benefit from treatment



Presence of anti-HDV IgM is associated with the development of clinical events



Wranke et al. PlosOne 2014

Treatment options for Hepatitis Delta

IFNa to treat HDV-Infection

Interferon alpha

- Sustained biochemical responses in 0-36% of patients
  Few Studies with virological endpoints
  treatment >12 months may be required

Farci et al., NEJM 1994
Di Marco et al., J Viral Hepatitis 1996
Niro et al., J Viral Hepatitis 2005; Yurdaydin et al., J Viral Hepatitis 2008

- Higher IFN doses were associated with better survival in small study cohort

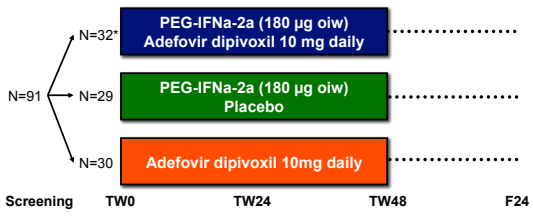
Farci et al., Gastroenterology 2004

PEG-Interferon alpha

- 48-96 weeks HDV RNA SVR 17-47%

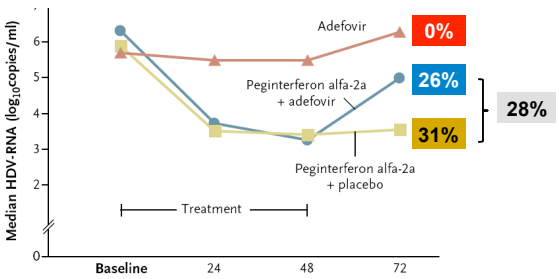
Erhardt Liver International 2006
Niro et al., Hepatology 2006
Castelnau et al., Hepatology 2006
Ormeci et al., Hepatogastroenterology 2011
Karaca C et al., Antiviral Therapy 2013

The Hep-Net/International Delta Hepatitis Intervention Trial (HIDIT-1)



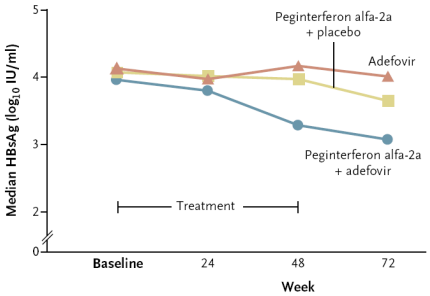
Wedemeyer, Yurdaydin et al. New Engl J Med 2011, 364(4); 322-31

Treatment of chronic hepatitis Delta: Only PEG-IFN leads to decline of HDV RNA



Wedemeyer, Yurdaydin et al. New Engl J Med 2011, 364(4); 322-31

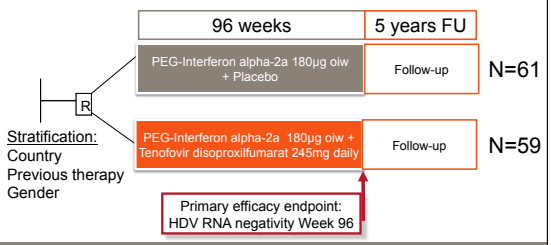
PEG-IFNa-2a – Adefovir combination resulted in a more pronounced HBsAg suppression



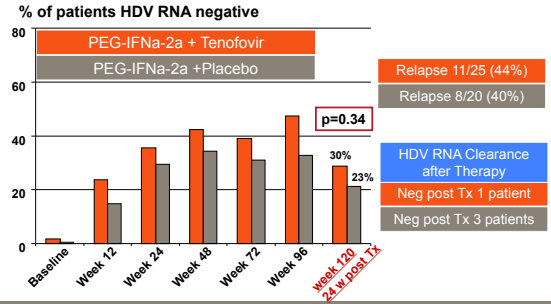
Wedemeyer, Yurdaydin et al. New Engl J Med 2011, 364(4); 322-31

The Hep-Net-International Delta-Hepatitis Intervention Trial 2: HIDIT-2

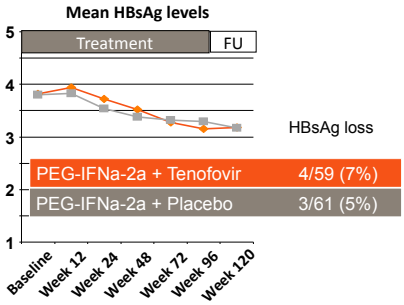
N=120 patients



Longer treatment with PEG-IFN does not increase response. No additional benefit of Tenofovir



Combination treatment of PEG-IFN and TDF does not lead to a stronger HBsAg decline compared to PEG-IFN alone



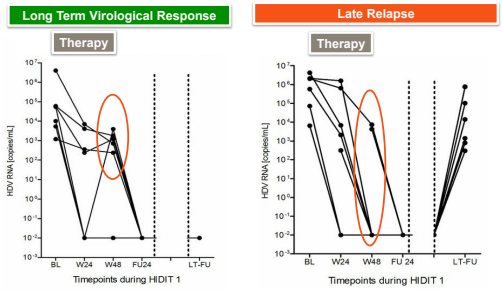
Factors associated with HDV RNA negativity at Week 120

Variable		Odds Ratio OR	95%-Confidence intervall		P value
Treatment Arm	Placebo vs. Tenofovir	0.961	0.441	2.085	0.92
Age	[years]	1.004	0.971	1.039	0.81
Gender	Female vs. Male	1.601	0.706	3.627	0.26
Cirrhosis at baseline	No vs. Yes	0.290	0.128	0.656	0.003
ALT [log U/L]				159	0.33
platelets [10*				506	
HBV-DNA at b				009	0.52
HDV-RNA at b				134	0.26
HBsAG at bas				031	0.074
HBsAG decline until week 96 ≥ 0.5 log IU/ml	yes vs. No	3.442	1.442	8.217	0.005
Country	Germany vs. Turkey	1.196	0.496	2.885	0.89
	Greece vs. Turkey	0.739	0.062	8.868	
	Romania vs. Turkey	1.457	0.489	4.341	
Previous Interferon-Therapy	yes vs. No	0.914	0.419	1.992	0.82

Week 120 HDV RNA Response:
Patients Cirrhosis: 51%
vs.
Non-cirrhotic patients: 25%

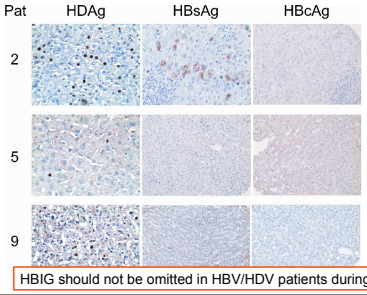
However, ...
HDV RNA negative at week 24 post treatment is not SVR

56% of patients with FU24 virological response in HIDIT1 became HDV RNA positive in the LTFU



N= 58 with a median time of follow-up of 4.5 (0.5-5.5) years

Prolonged intrahepatic persistence of HDAg after liver transplantation!

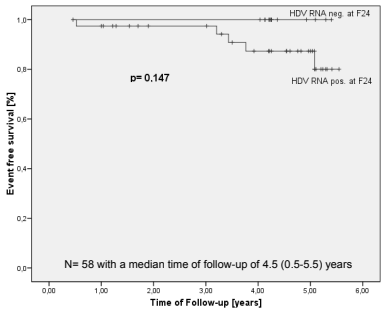


HDAg stained positive in transplanted livers in 6/26 patients in the absence of liver HBV DNA/cccDNA, serum-HBsAg, and HDV RNA for up to 19 months after LTX.

HBIG should not be omitted in HBV/HDV patients during and after transplantation

Mederacke et al., J Hepatol. 2012 Jan;56(1):115-22

HDV RNA negative during treatment *maybe* associated with better survival



Heidrich et al. Hepatology. 2014 Jul;60(1):87-97.

IFN-therapy is associated with improved clinical long-term outcome of hepatitis delta

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

↓

46 patients treatetd with interferon alfa

↓

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

Manesis et al., J Hepatol. 2013 Nov;59(5):949-56.

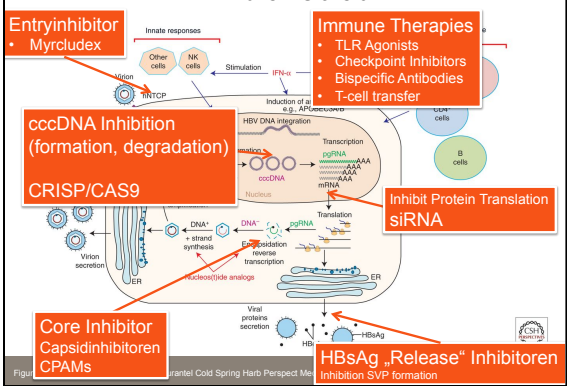
Current Management of Hepatitis Delta

- Patients with a very mild course *(possibly not requiring immediate treatment)* can be identified
  Clinical markers: Calle Serrano J Viral Hepatitis 2014
  Anti-HDV IgM Levels: Wranke et al., EASL 2013
  NK cell responses: Lunemann et al., GUT 2014
- PEG-IFNa remains the only effective treatment option against HDV
  – however, long-term follow-up is required
  → ***My*** recomendation: Treat Bea-B patients
- Treat HBV according to hepatitis B guidelines

Future treatment options?

HBV cure – HBsAg loss

HBV "Cure" is the aim!



New therapies have to be very safe (NUCs are the standard)

Easy accessible

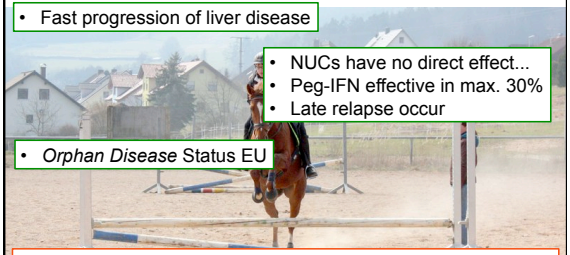
Low costs?!

Endpoints need to be defined
Definition „Cure“

Application should be easy
Ideally as oral treatment

Hepatitis Delta

- Fast progression of liver disease



- NUCs have no direct effect...
- Peg-IFN effective in max. 30%
- Late relapse occur

- *Orphan Disease* Status EU

- High diversity of HDV (8 Genotypes)
- No standardized assay*
- HDV can „survive“ without HBsAg via cell proliferation / liver regeneration **

* Le Gal et al., O013 EASL 2015, ** K Giersch et al., O012 EASL 2015

HBsAg Release Inhibitor?

M. Bazinet et al., LO2 EASL 2015

NUCLEIC ACID POLYMERS (NAP)

- block HBV entry (NAPs are heparin sulfate analogs)
- post entry activity: blocks subviral particle (SVP) formation
- production of virions is not targeted by NAPs

- NAPs may block HDV entry and or the production of HDV derived from a SVP-related assembly mechanism
- “liberated” anti-HBs may directly target HDV

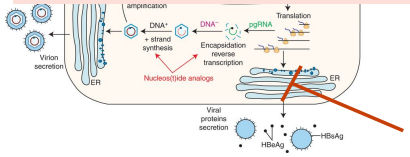
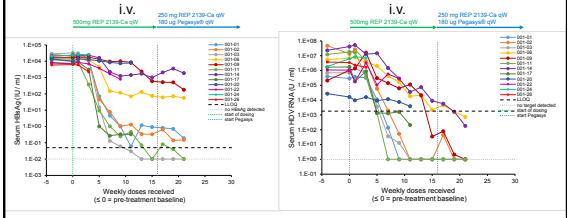


Figure from Fabien Zoulim, and David Durantel Cold Spring Harb Perspect Med 2015;5:a021501

REP 2139-Ca + PEG-IFNa2a lead to significant reduction of HBsAg and HDV-RNA in HBV / HDV co-infection

N=12 Caucasian HDV patients treated in Chişinău, Moldova
CRO monitored trial compliant with EU GCP
Clinicaltrials # NCT02233075

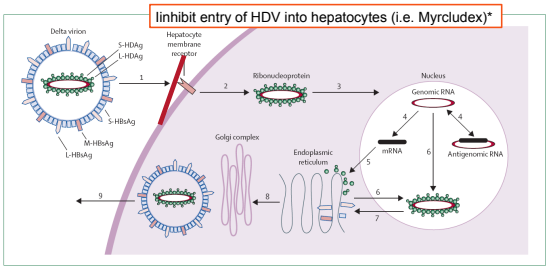
(REP 301)



Bazinet et al., LO2 EASL 2015

Targets for future anti-HDV treatments

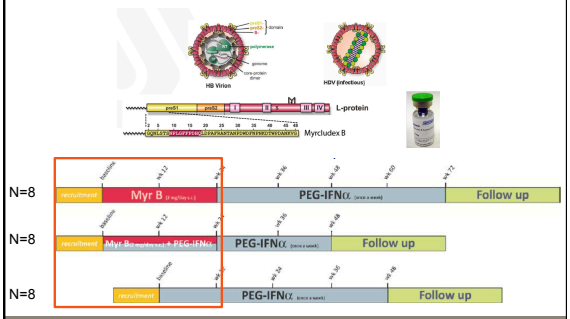
linhibit entry of HDV into hepatocytes (i.e. Myrcludex)*



*S. Urban et al., Gastroenterology. 2014 Jul;147(1):48-64.

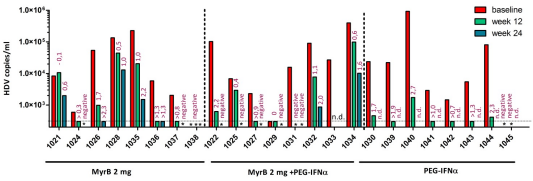
Review: Hughes, Wedemeyer, Harrison Lancet 2011

Myrcludex Pilot Study in HDV



P. Bogomolov, S. Urban et al., AASLD 2014; LB-20 (Poster am Montag)

Myrcludex B in Hepatitis Delta: Pilot Study



⇒ **6/7 patients experienced HDV RNA decline > 1log10 at week 24 during Myr B monotherapy.**

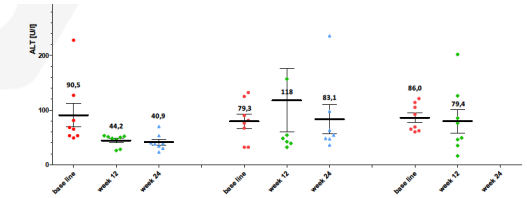
⇒ **7/7 patients experienced HDV RNA decline > 1log10 at week 24 during Myr B/PEG-IFNα combination therapy.**

⇒ **HDV RNA became negative in 2 patients during MyrB monotherapy and 5 patients in combination with PEG-IFNα.**

→ But no HBsAg decline with Myr

P. Bogomolov, S. Urban et al., AASLD 2014; LB-20

Normalization of ALT

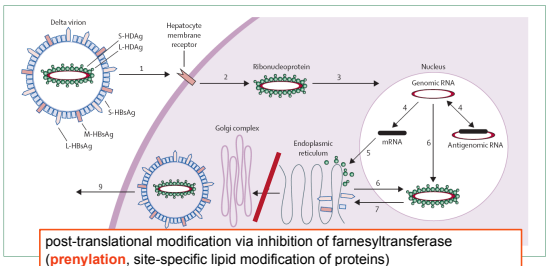


⇒ **Block of de novo infection with HBV and HDV results in normalization of ALT levels.**

→ Well tolerated
→ Increase of bile acids

P. Bogomolov, S. Urban et al., AASLD 2014; LB-20

Targets for future anti-HDV treatments



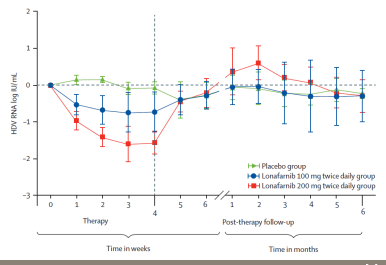
post-translational modification via inhibition of farnesyltransferase (**prenylation**, site-specific lipid modification of proteins)
→ Preventing prenylation abolishes virus particle formation.

*J. Glenn et al., J Virol. 1998 Nov;72(11):9303-6.
*J. Glenn et al., Science. 1992 May 29;256(5061):1331-3.

Review: Hughes, Wedemeyer, Harrison Lancet 2011

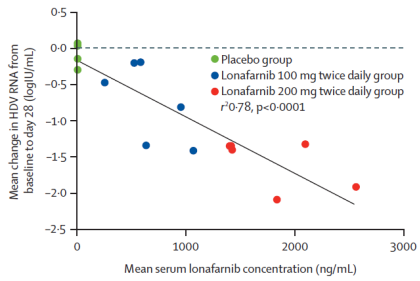
Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial

Christopher Koh*, Laetitia Canini, Harel Dahari, Xiongce Zhao, Susan L Uprichard, Vanessa Haynes-Williams, Mark A Winters, Gitanjali Subramanya, Stewart L Cooper, Peter Pinto, Erin F Wolff, Rachel Bishop, Ma Ai Thanda Han, Scott J Cotler, David E Kleiner, Onur Keskin, Ramazan Idilman, Cihan Yurdaydin, Jeffrey S Glenn*, Theo Heller*



Koh et al. Lancet ID 2015

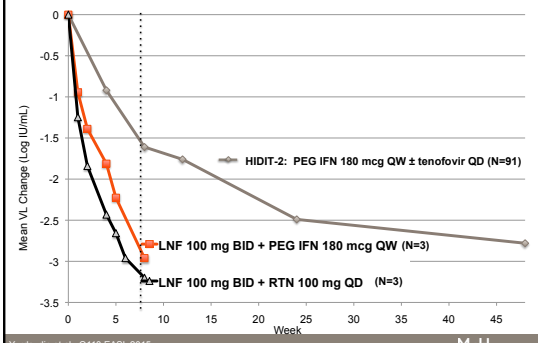
Serum lonafarnib concentrations correlate with HDV RNA decline



Koh et al. Lancet ID 2015

Earlier VL Decline with Lonafarnib Combination

Lonafarnib Combinations Display Biphasic Kinetics and More Rapid Onset*



Yurdaydin et al., O118 EASL 2015
Dahari et al., LP36 EASL 2015

Side effects

LOnafarnib **W**ith **R**itonavir in HDV

- Mainly GI side effects

	N=3				N=3				N=3				N=3			
	LNF 200 mg BID				LNF 300 mg BID				LNF 100 mg BID RTN 100 mg QD				LNF 100 mg BID PEG IFN 180 mcg QW			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Nausea		√				√			√					√		
Diarrhea		√				√				√			√			
Fatigue		√				√				√				√		
Wt Loss		√				√			√				√			
Anorexia		√				√				√				√		

- Observed in almost every patient. Graded according to **C**ommon **T**erminology **C**riteria for **A**dverse **E**vents
- Lonafarnib chronically dosed for 2 years in a pediatric population (Progeria - PNAS, *2012*, 16666)

Acknowledgements

- Heiner Wedemeyer, Cihan Yurdaydin & Michael Manns
- The HIDIT-1 and HIDIT-2 Study Groups
- The “Hepatitis-Team” at Hannover Medical School
- The Hep-Net Study House
- The Hepatitis Delta International Network