X Workshop Nazionale Innovazione e Ricerca per la Pratica Clinica

Firenze, 13-14 gennaio 2020

Update sulla terapia per HDV

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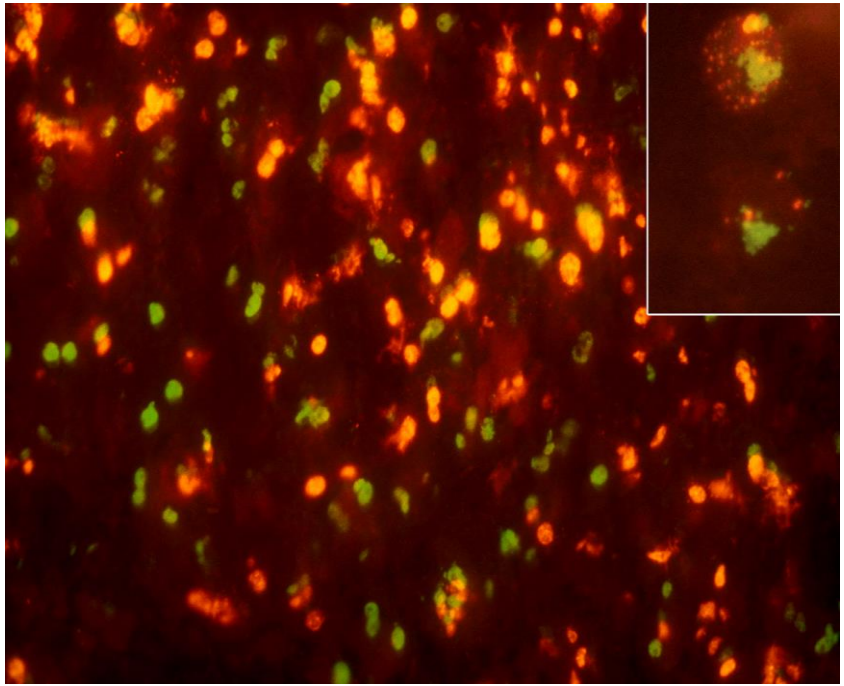
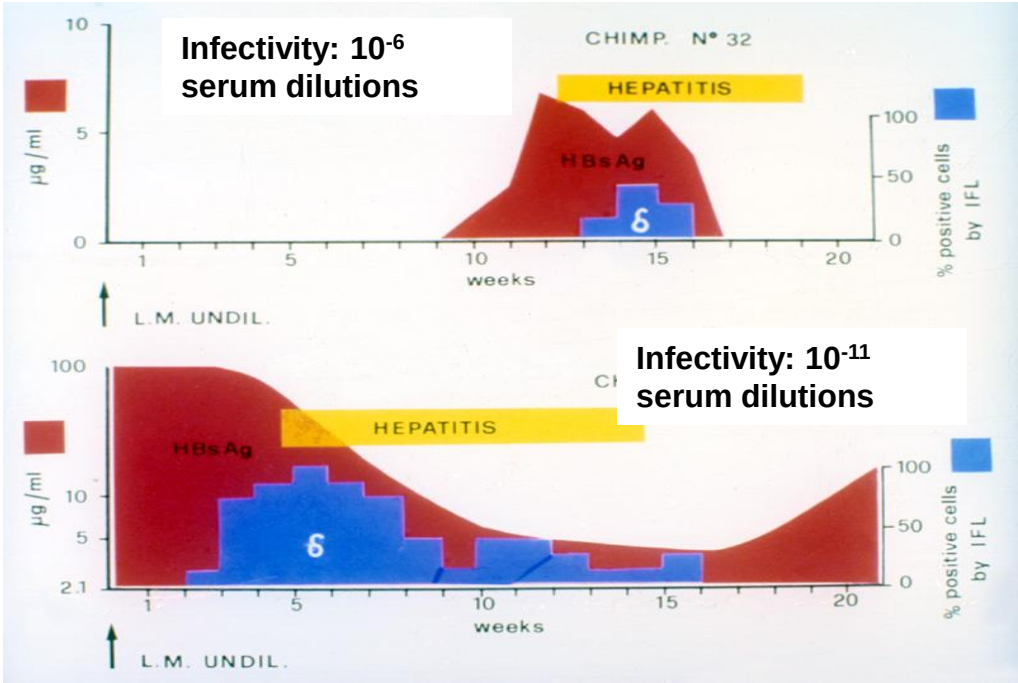
Immunofluorescence detection of new antigen-antibody system (δ/anti-δ) associated to hepatitis B virus in liver and in serum of HBsAg carriers

Gut, 1977

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





Courtesy Prof. Mario Rizzetto

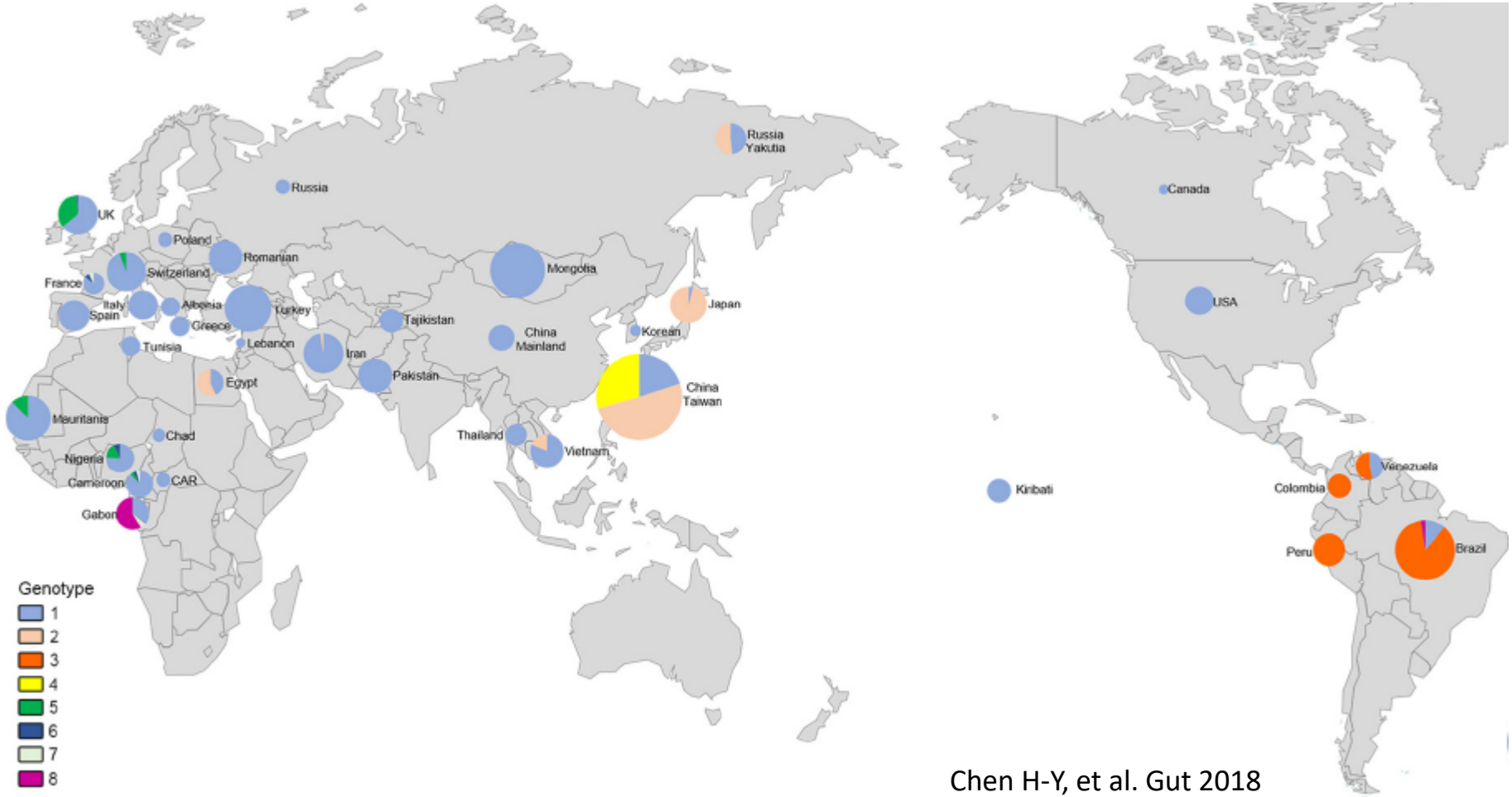
How many HDV infected individuals in the world ?

Classical reported estimate: 20-40 millions

- Clinically driven HDV testing
- Individuals recruited from hospital settings
- Blood donors
- Data from hyperendemic areas (Amerindians; Uzbekistan; Pakistan; etc)
- Anti-HDV IgG, IgM, HDV-RNA variably used to define HDV infection

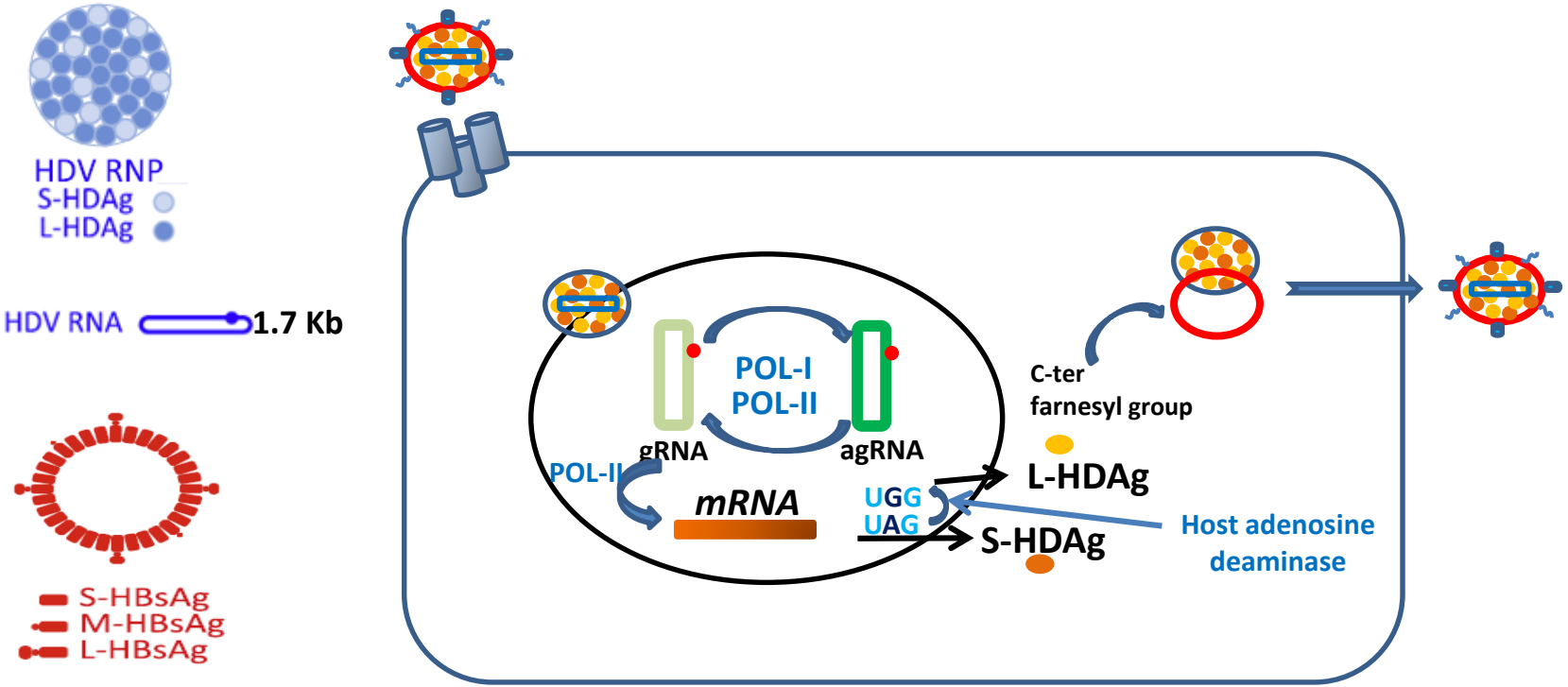
Chen HY, et al. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. Gut 2018:gutjnl-2018-316601
Stockdale et al., Gut, 2018

World distribution of HDV genotypes



Chen H-Y, et al. Gut 2018

Main steps of HDV replication cycle



Brancaccio G, Int J Antimicrob Agents 2019

nature COMMUNICATIONS

2019

Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo

Jimena Perez-Vargas[1], Fouzia Amirache[1], Bertrand Boson[1], Chloé Mialon[1], Natalia Freitas[1], Camille Sureau[2], Floriane Fusil[1] & François-Loïc Cosset[1]

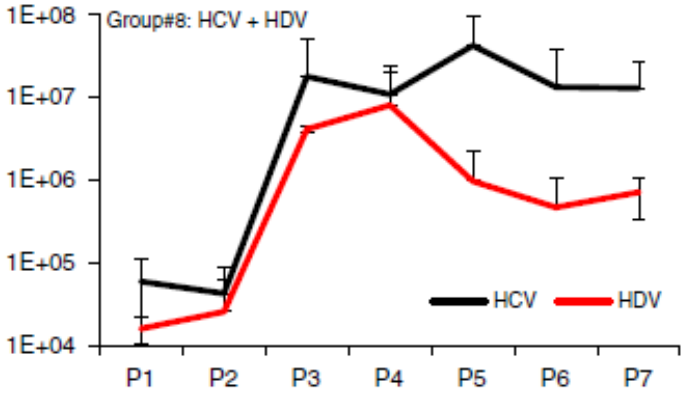
Alternative, HBV unrelated viruses can act as helper viruses for HDV.

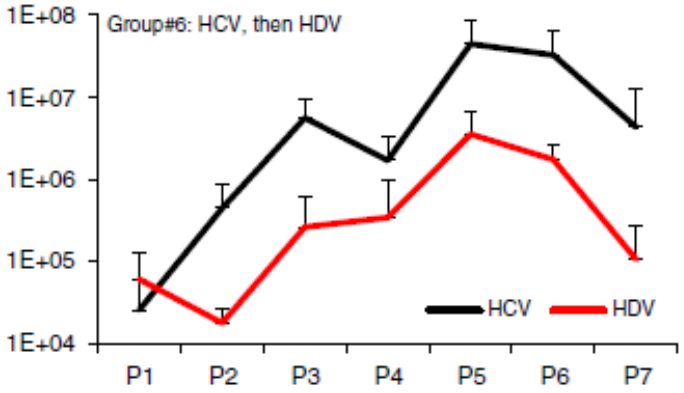
Vesiculovirus, flavivirus and hepacivirus, can package HDV RNPs, allowing efficient egress of HDV particles in the extracellular milieu of co-infected cells and subsequent entry into cells expressing the relevant receptors

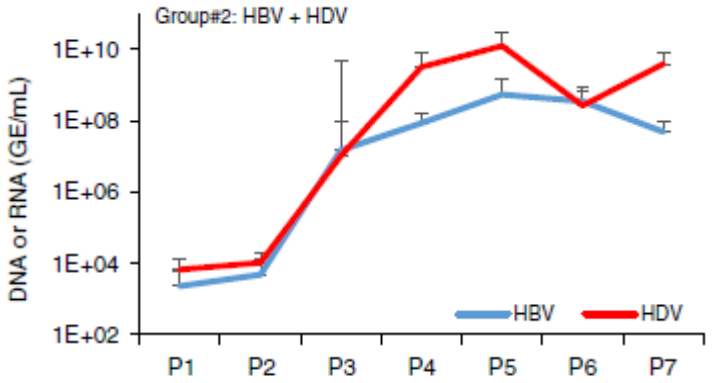
HCV can propagate HDV infection in the liver of co-infected humanized mice for several months

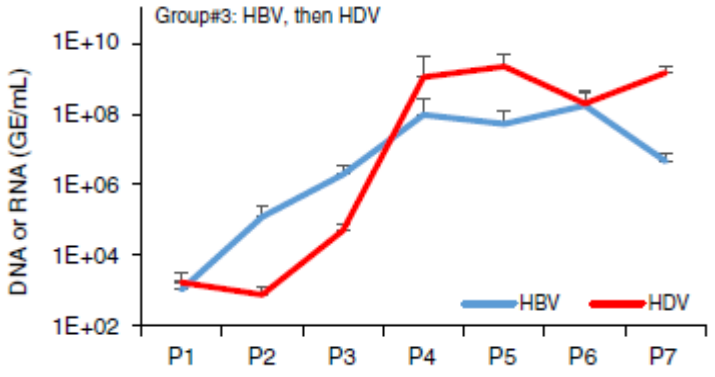
HCV propagates HDV particles in vivo

Experiments in Humanized mice



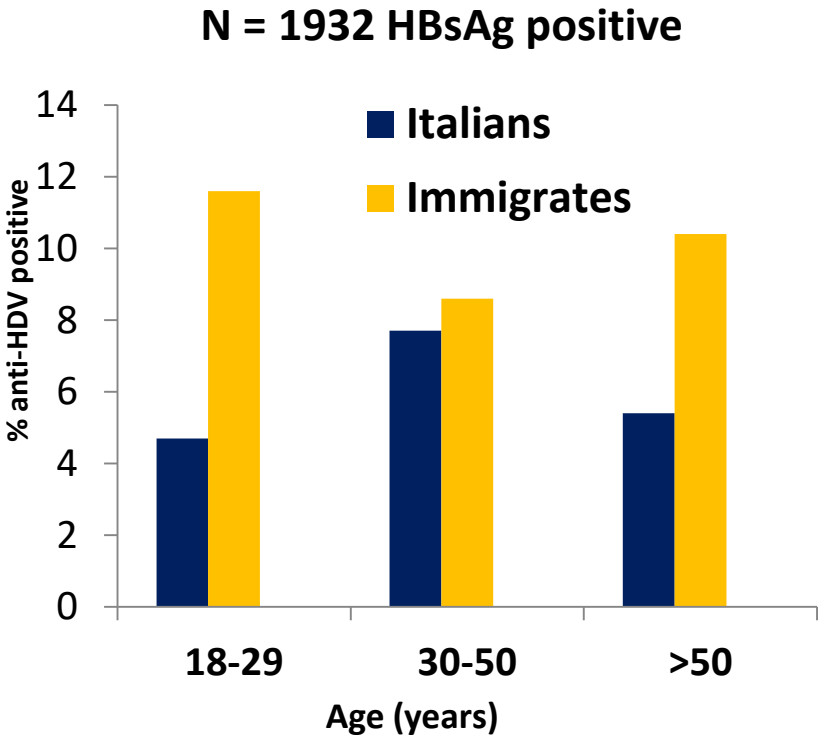




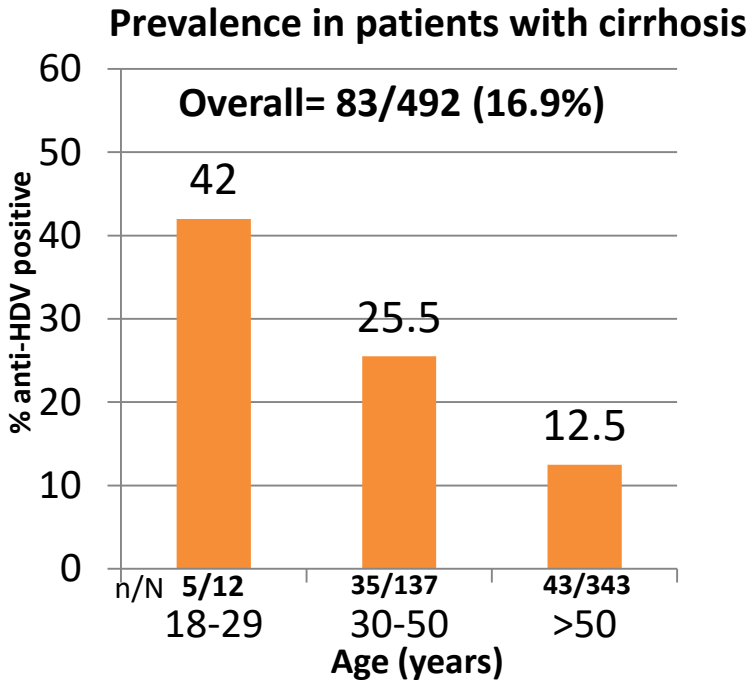


Perez-Vargas, Nature Comm, 2019

Age-specific prevalences of anti-HDV antibodies among Italian natives and non-Italian natives- MASTER-B cohort



Brancaccio et al, Dig Liver Dis, ePub 2018



Brancaccio et al, MASTER-B Cohort, unpublished

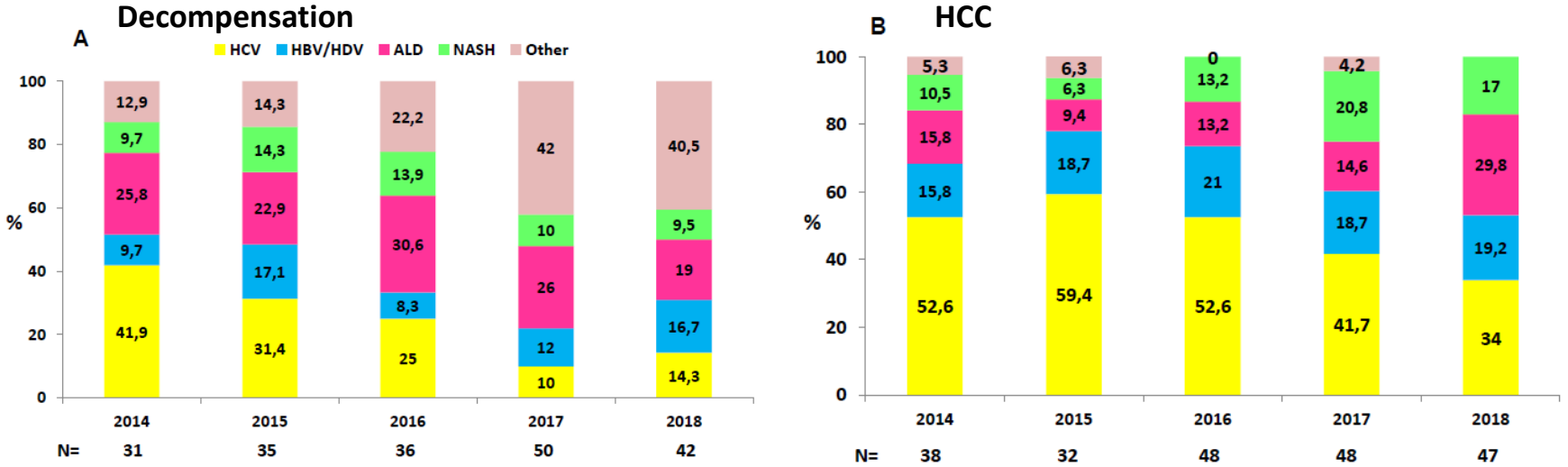
Prevalence of patients with HBsAg positive cirrhosis according to the presence of HDV and/or HCV coinfection

	Cirrhosis Y/N (%)	OR (95% C.I.)	P value
HDV-/HCV-	343/1554 (22.1)	reference	--
HDV+/HCV-	50/103 (48.5)	3.3 (2.2-5.0)	<0.0001
HDV-/HCV+	7/31 (22.6)	1	ns
HDV+/HCV+	17/26 (65.4)	6.7 (2.9-15.1)	<0.0001

From: MASTER-B cohort, APT in press

Causes for liver transplant – Padua, Italy

Adult patients at their first liver transplant



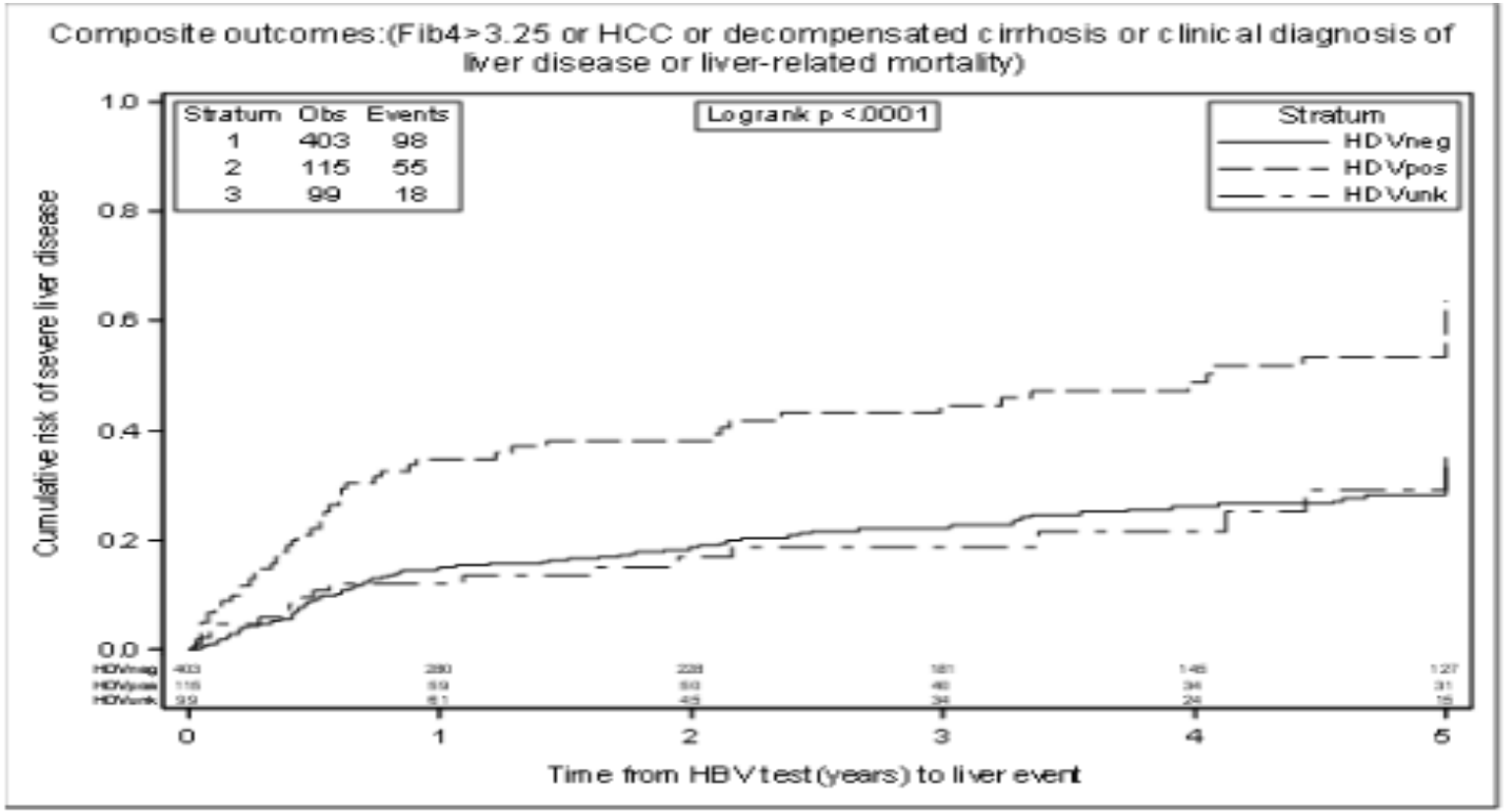
	HBV Entire cohort		HCC		Decompensation	
Year	N.HBV	N (%) HDV	N. HBV	N (%) HDV	N. HBV	N (%) HDV
2014	9	2 (22)	6	2 (33.3)	3	0 (0)
2015	12	4 (33.3)	6	2 (33.3)	6	2 (33.3)
2016	11	4 (36.4)	8	2 (25.0)	3	2 (66.6)
2017	15	4 (26.7)	9	0 (0)	6	4 (66.6)
2018	16	9 (56.2)	9	3(33.3)	7	6 (85.7)
All	63	23 (36.5)	38	9 (23.7)*	25	14 (56.0)*

*p<0.05

Brancaccio et al, submitted

Clinical outcome in a cohort of HIV/HBV/HDV coinfected patients

An analysis of the ICONA cohort



Gaeta, et al. CROI 2018

Endpoints of HDV treatment

Virological

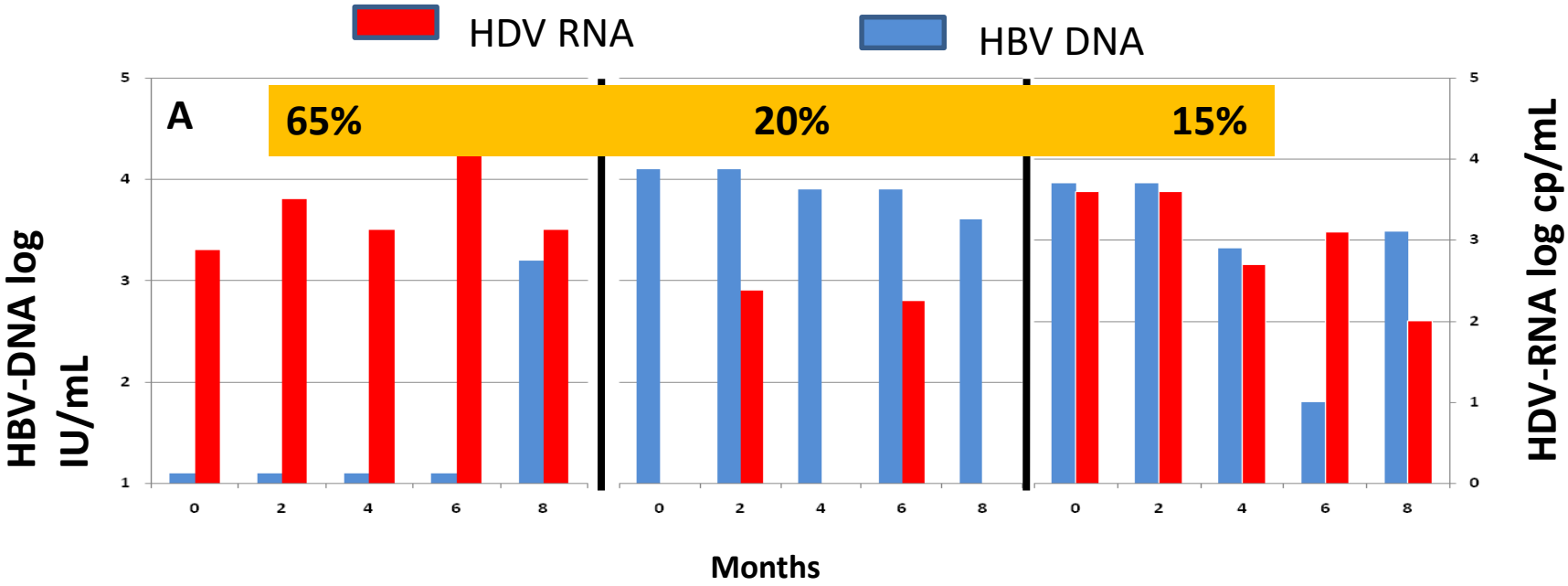
- ❑ HBsAg clearance stops HDV production
- ❑ Sustained plasma HDV RNA undetectability
- ❑ Reduction HDV RNA >2log and normal ALT

Clinical

- ❖ Stopping the progression of the liver disease
- ❖ Regression of fibrosis/cirrhosis

Yurdaydin C, J Hepatol 2019; 70:1008-1015

Longitudinal measurements of HBV DNA and HDV RNA in HDV untreated patients



Personal data

Anti HBV analogues for 6-12 months are not active against HDV

Lamivudine
Famciclovir
Adefovir
Adefovir+Peg-IFN
Tenofovir
Tenofovir+Peg-IFN

Suppress HBV replication
NO EFFICACY AGAINST HDV

To date, Peg-IFN is the only therapy available against HDV

Wedemeyer H et al, NEJM 2011; 364:322-31; Heidrich et al, Hepatology 2014; 60:87-97 ;
Niro et al, Aliment Pharmacol Ther. 2005; 22:227-232; Canbakan, , J Gastroenterol Hepatol 2006;21:657-63*;*
Yourdaydin, J Viral Hepat 2008;15:314-312; Kabacam, Clin Infect Dis 2012;55:645-50; Wedemeyer, Lancet Infect Dis. 2019;19:275-286

Long-term NUC treatment in Chronic HDV infection

56 patients with HDV
advanced fibrosis/cirrhosis
with persistent HBV replication

56 HBV monoinfected
1:1 matched by age, gender, platelet count, albumin level, bilirubin and INR

entecavir or tenofovir at standard dose
for a median of 50 months

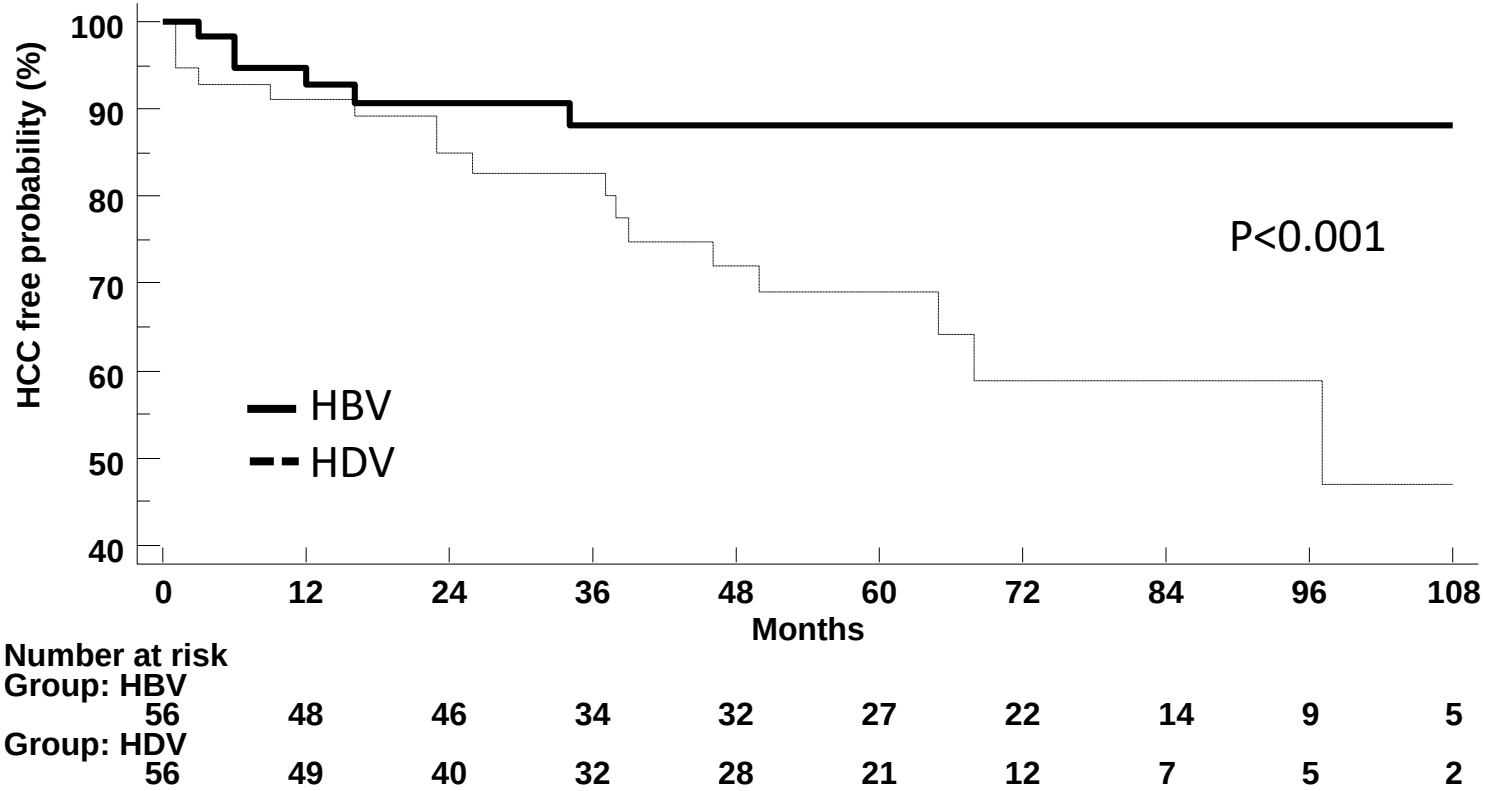
End points: death, OLT, decompensation, HCC

	Number of events	HDV Cases/1000 patient-months	HBV Cases/1000 patient-months	*P*-value*
Death/LT	19	2.92	0.38	0.001
Death	8	1.06	0.10	0.03
LT	11	3.44	0.78	0.016
Decompensation	13	1.53	0.13	0.015
HCC	23	3.12	1.12	0.02

HBV, hepatitis B virus; HDV, hepatitis D virus; LT, liver transplant.
*By log-rank test.

Brancaccio G et al, Aliment Pharmacol Ther. 2019; 49:1071-1076

Cumulative incidence of HCC in HDV patients and matched HBV monoinfected receiving NUCs



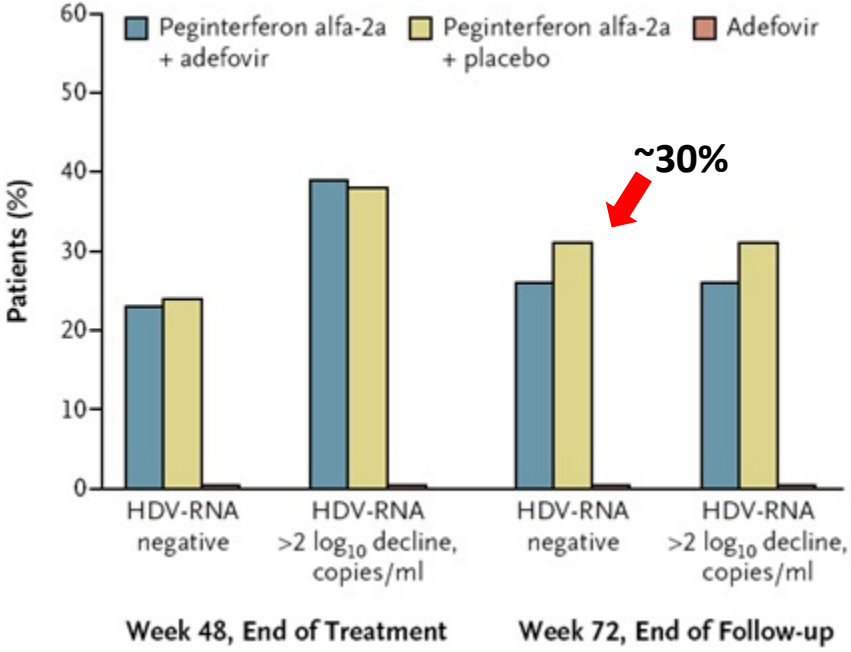
Brancaccio G et al. Aliment Pharmacol Ther. 2019; 49:1071-1076

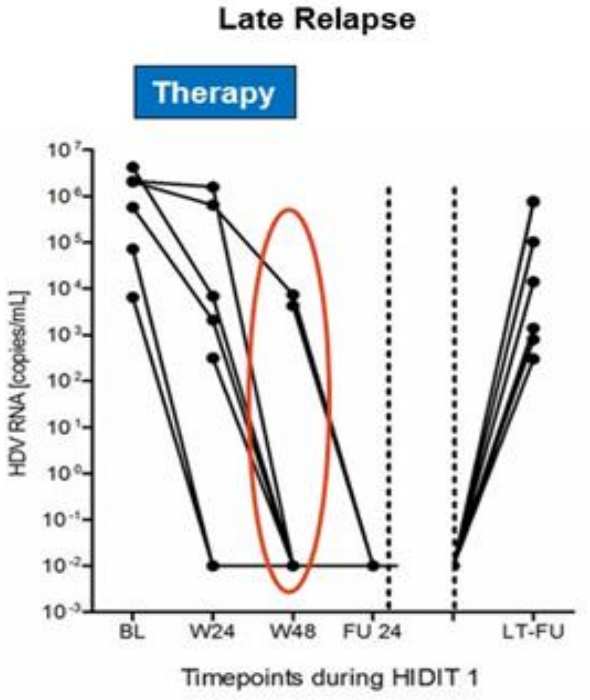
Studies with Peg-IFN in chronic hepatitis Delta

Ref	Type/Dose	N.Pts	Duration	Follow-up	EOT	SVR
Castelneau	Peg-IFNα2b 1.5µg/kg	14	12mo	16mo	57%	43%
Niro	Peg-IFNα2b 1.5µg/kg same+RBV	16 22	18mo 12mo	6mo 6mo	19% 9%	25% 18%
Erhardt	Peg-IFNα2b 1.5µg/kg	12	12mo	12mo	-	17%
Gheorghe	Peg-IFNα2b 1.5µg/kg	49	13mo	26mo	33%	25%
Ormeci	Peg-IFNα2b 1.5µg/kg	11 7	24mo 12mo	6mo 6mo	56% 57%	-
Samiullah	Peg-IFNα2b	277 enrolled 238 evaluated	48 weeks	24 weeks	29.8%	29.4%
Wedemeyer	Peg-IFNα2a 180µg or Peg-IFNα2b 1.5µg/kg	29 31	12 mo 12 mo	6 mo 6 mo	24% 23%	31% 24%
Karaca	Peg-IFNα2a 180µg or Peg-IFNα2b 1.5µg/kg	32	24mo	6mo	50%	47%
Wedemeyer	Peg-IFNα2a+ Tenofovir Peg-IFNα2a+ placebo	59 61	96 weeks	24 weeks	48% 33%	29% 21%
Heller	Peg-IFNα2a 90-270 µg/w	13	6-240 weeks median 140	--	--	39% 3 lost HBsAg
Borzacov	Peg-IFN α2a Peg-IFNα2b	41 15	12mo 12mo		39% 13%	37% 13%
Bahcecioglu	rIFN or	99	6-126 mo	24-225 mo	--	35.3%

- 12 studies
- Patients (n, range) 12-238
- Tx duration 48-240 weeks
- Response at EOT 9-57%
- SVR (24-104 weeks) 13-47%
- Heterogeneity in HDV-RNA detection methods

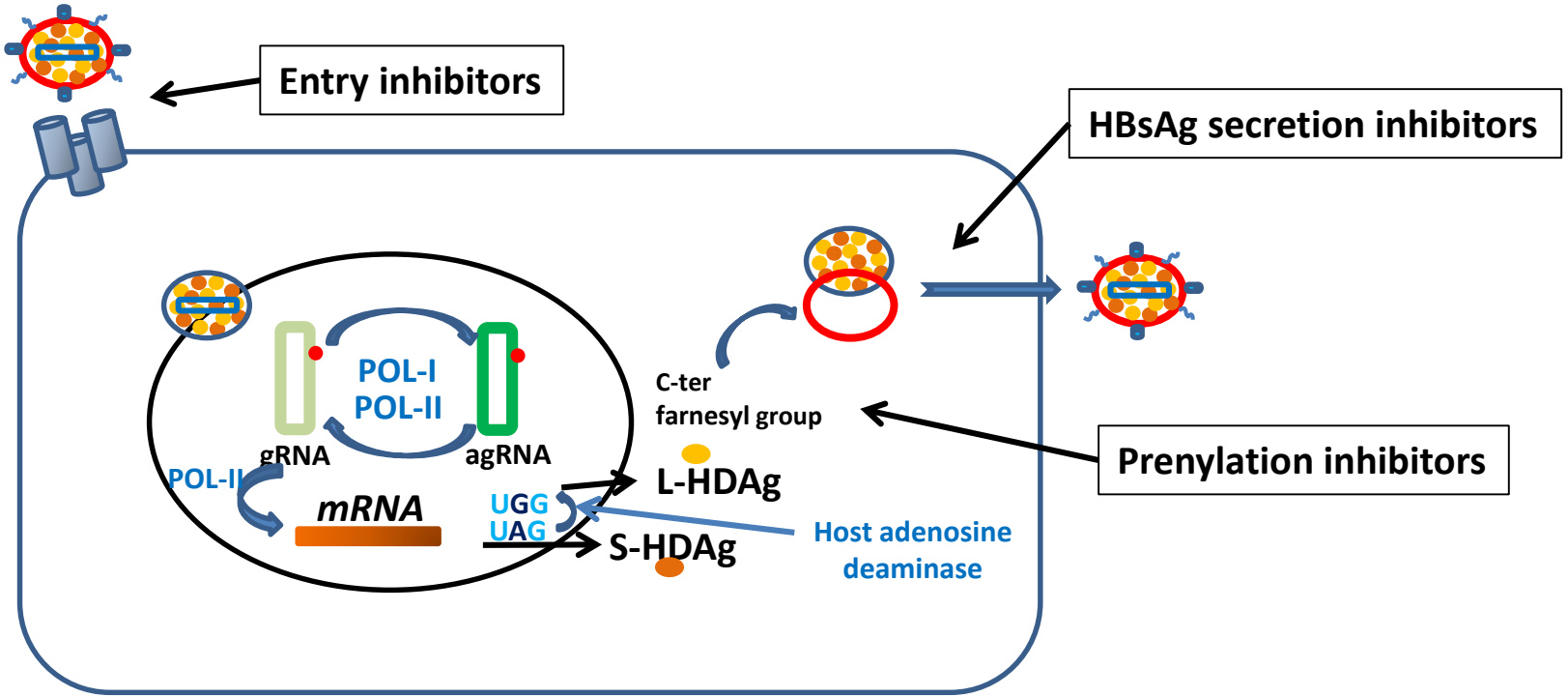
Lessons from the HIDIT-1 Study





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

Main steps of HDV replication cycle and targets of novel therapies



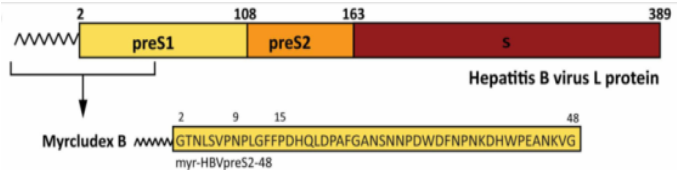
Brancaccio G, Int J Antimicrob Agents 2019

New therapeutical strategies

1. **Targetting HBsAg-dependent cell entry**

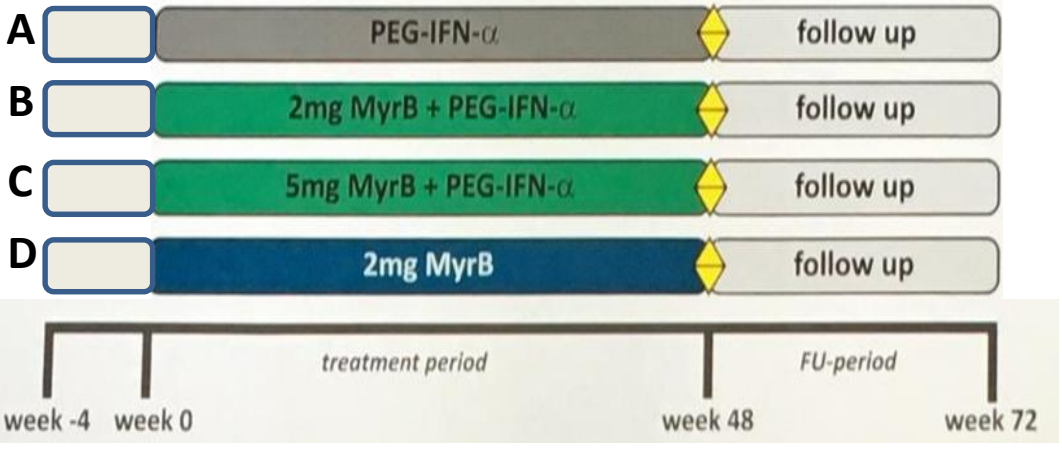
Myrcludex B (Bulevirtide) ± Peg-IFNα in chronic hepatitis Delta

MYR203 Study



60 patients with *chronic HBV/HDV infection were randomized into* 4 arms (1:1:1:1)-15 pts per arm

Myrcludex was self-administered once daily s.c.



Wedemeyer, AASLD 2018

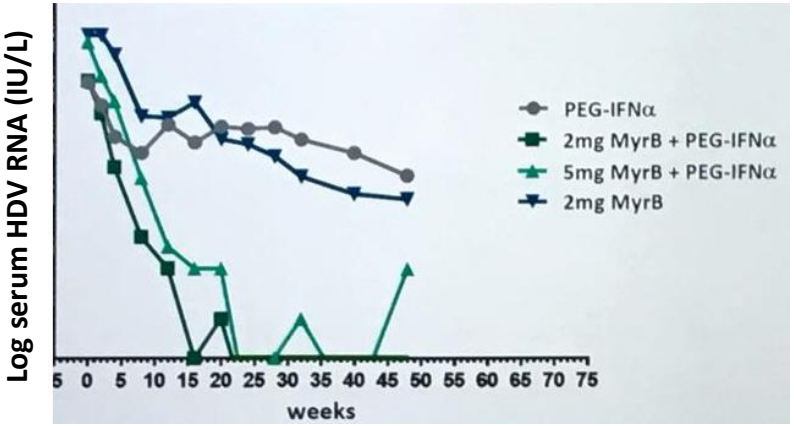
Key inclusion criteria

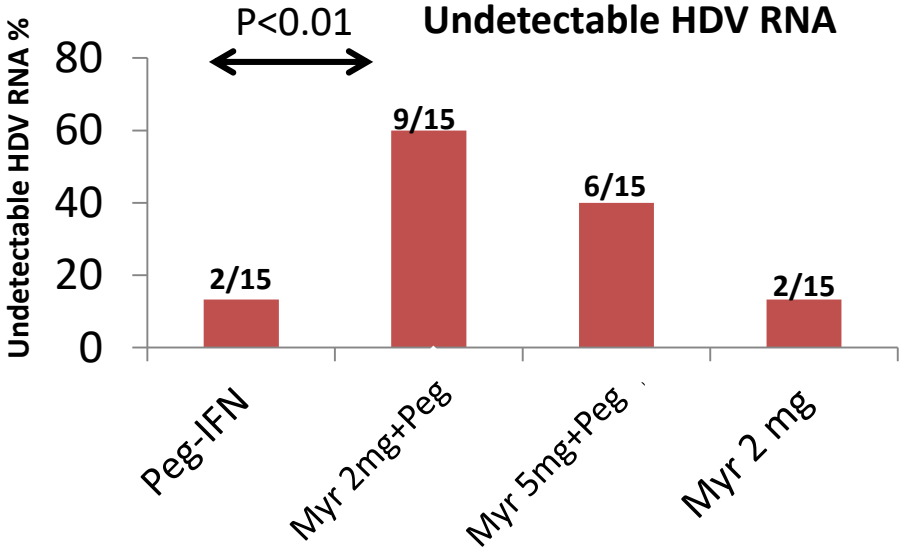
HBsAg +
Anti-HDAg+ >6 months
HDV RNA+ in serum
HBeAg+ or HBeAg-
ALT ≥ 1 but <10 ULN

Key exclusion criteria

HIV or HCV coinfection
Serum creatinine >1.5 ULN
T. Billirubin >34.2 µM/L
Decompensated liver disease
Platelet count <90,000/µl
HBV therapy in the last 6 mo.

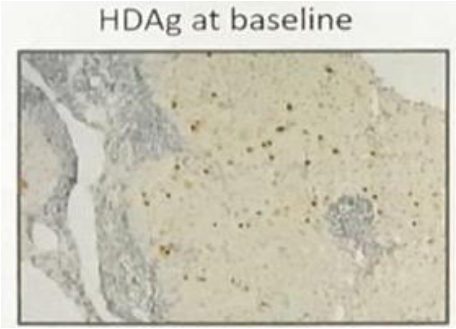
MYR203 Study – HDV RNA decline

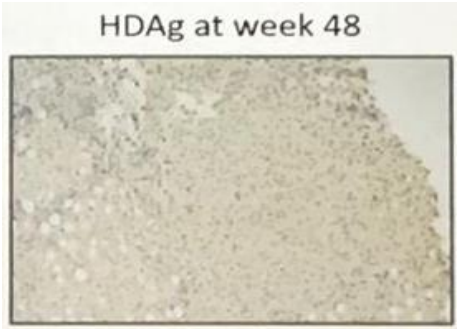




Median log HDV RNA decline

Myr 2mg +Peg-IFNα	-3.62
Myr 5mg +Peg-IFNα	-4.48
Myr 2mg	-2.84
Peg-IFNα	-1.14





Myr203 study - Safety

- 95% (57/60) completed 48 weeks of treatment
- 51.1% (23/45) Peg-IFN dose reduction/withdrawn
- 13.6% (6/44) reported missed Myrcludex doses

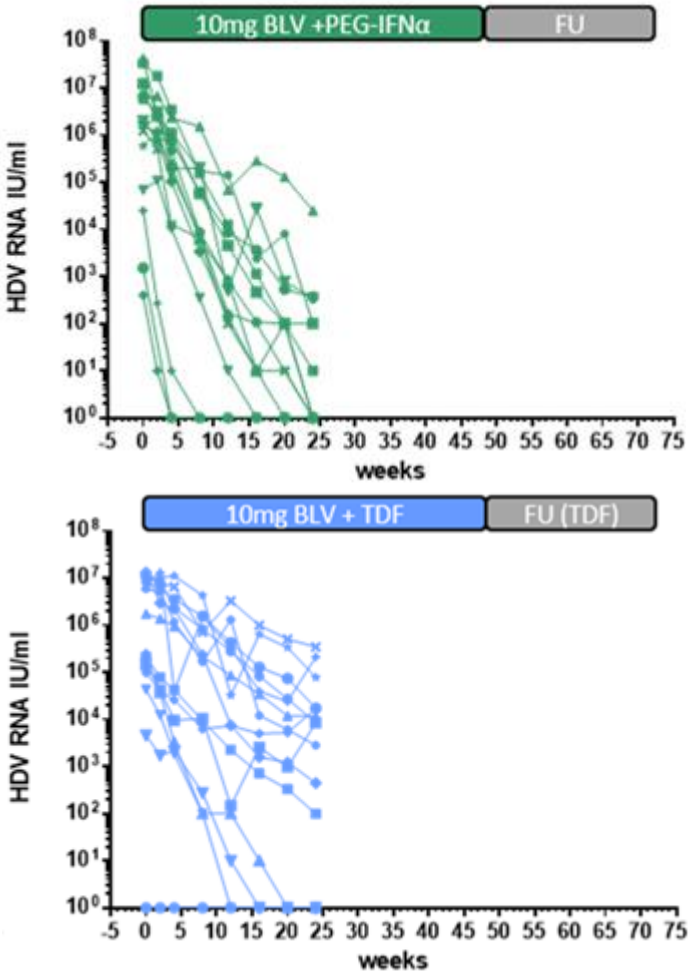
- No SAE related to Myrcludex B during treatment period
- No discontinuations because of AEs related to Myrcludex
- Asymptomatic bile salt increase in Myrcludex and Peg-IFN treated pts
- Myrcludex related AEs (n=130) were mild to moderate and resolved without sequelae or interventions; no dose dependency
- Majority of AEs were related to Peg-IFN treatment (n=484)
- High adherence to treatment

Safety and efficacy of Bulevirtide plus Peg-IFN or TDF in CHD patients. W24 interim results

30 HBeAg negative patients, with HDV infection

10 mg bulevirtide QID+Peg-IFN 180 µg/w OR
5 mg bulevirtide BID +Tenofovir standard dose
Duration: 48 weeks

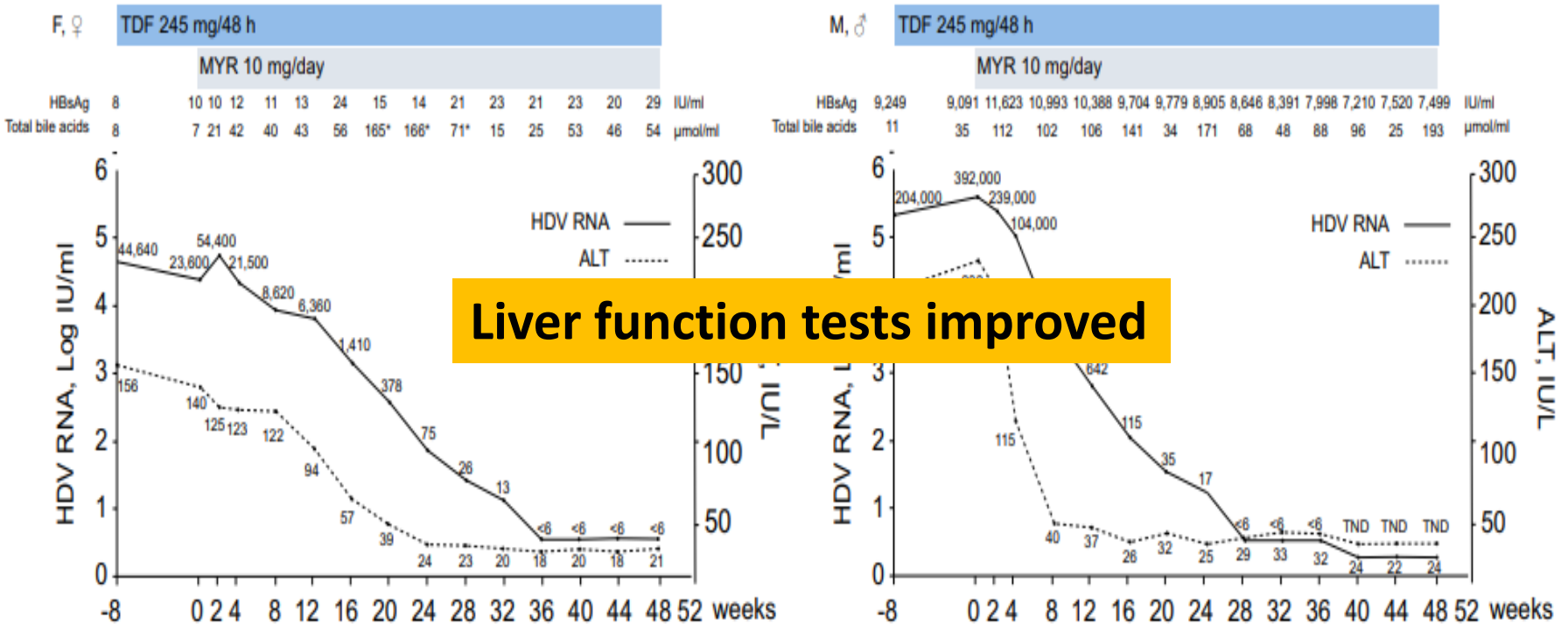
	MYR203 extension	
Virological response at w24	10 mg BLV q.d. + PEG-IFNα (n=15)	10 mg BLV (5 mg b.i.d.) + TDF (n=15)
Median HDV RNA log reduction [log_{10} IU/ml]	-4.84	-2.80
>2log decline or undetectable HDV RNA	100%	73.3%
Undetectable HDV RNA	60%	26.7%
ALT normalization	20%	60%
Combined endpoint*	13.3%	13.3%
HBsAg response**	6.7%	6.7%



Wedemeyer, AASLD 2019; abs 85

Myrcludex-B monotherapy for 48 weeks in HDV-related compensated cirrhosis – case reports

Myr-B 10 mg/day, 5mg sc bid



Liver function tests improved

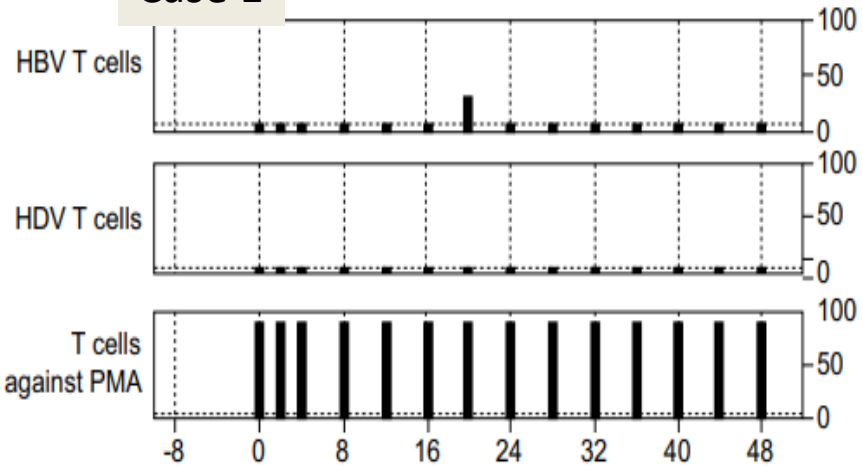
Loglio et al, J Hepatol 2019

Myrcludex therapy: open issues

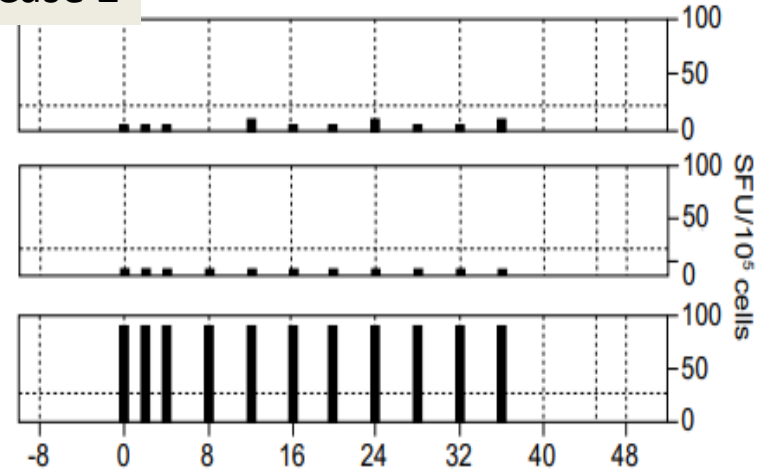
- Optimal dose in monotherapy

- Duration of therapy
  - Continuing at the same dose
  - Maintenance therapy at lower doses

Case 1



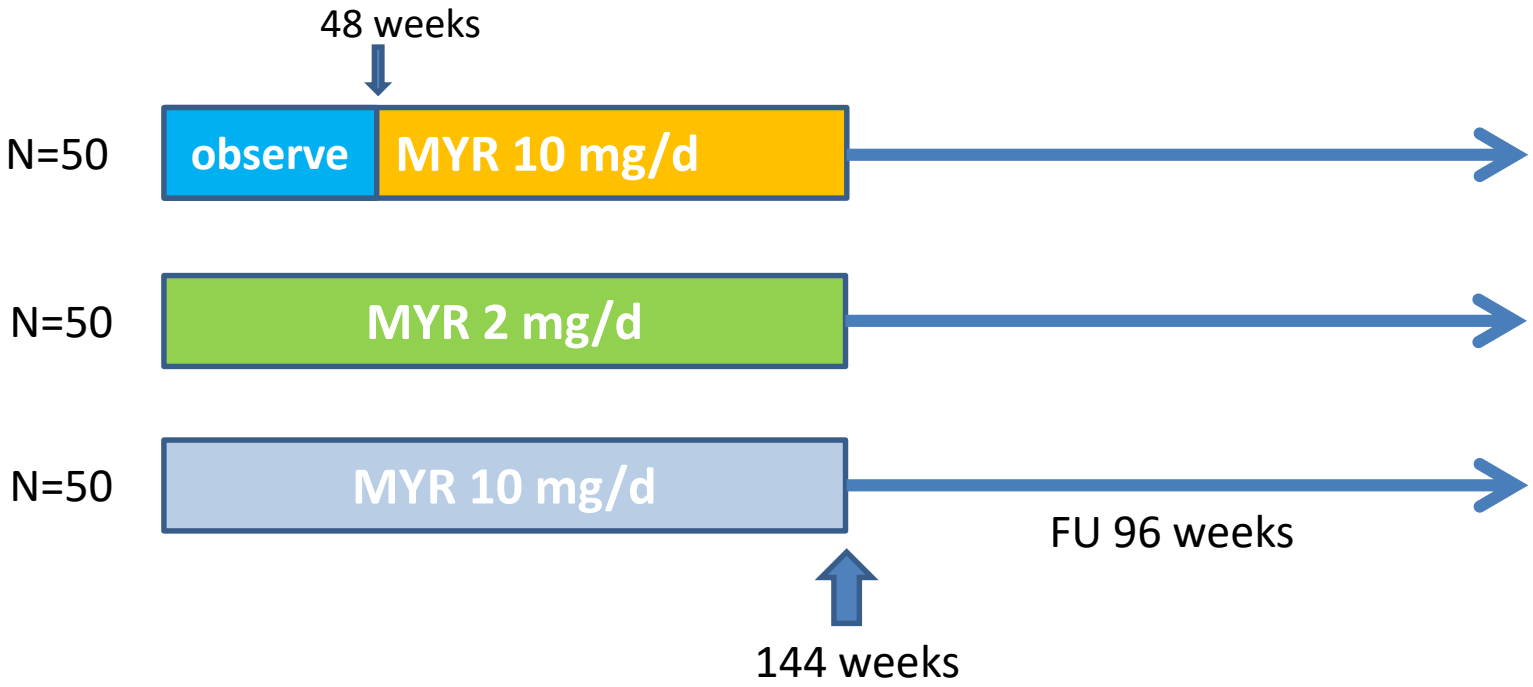
Case 2



Loglio et al, J Hepatol 2019

Phase 3 trial: long-term efficacy and safety of Bulevirtide in patients with chronic hepatitis Delta

Bulevirtide by sc injection; compensated cirrhosis allowed

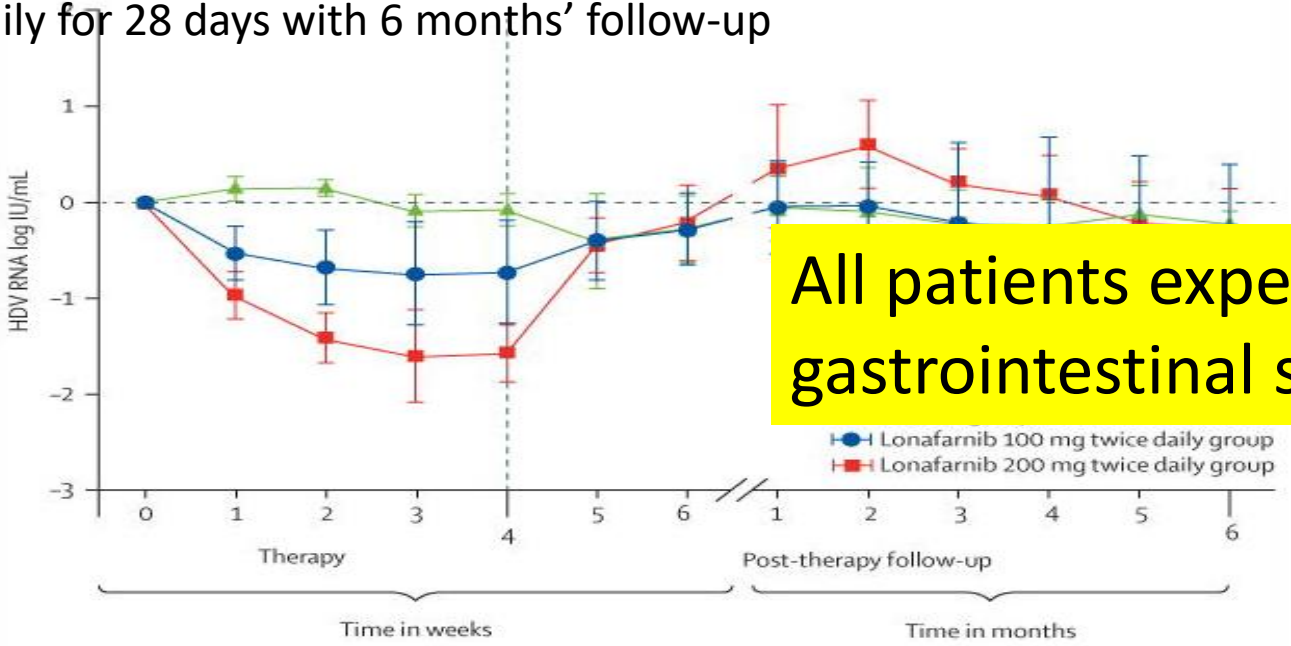


New therapeutical strategies

2. Direct targetting of HDV

Mean serum hepatitis delta virus RNA (SD) change during therapy with lonafarnib

phase 2A double-blind, randomised, placebo-controlled study. Patients aged ≥18 years with chronic HDV infection were randomly assigned (3:1 in group 1 and 2:1 in group 2) to receive oral lonafarnib 100 mg (group 1) or lonafarnib 200 mg (group 2) twice daily for 28 days with 6 months' follow-up



All patients experienced gastrointestinal symptoms

Koh et al. Lancet Infect Dis. 2015 Oct; 15(10): 1167–1174.

A phase 2 dose-escalation study of lonafarnib plus ritonavir in patients with chronic hepatitis D

Ritonavir 100 mg

LNF 50 mg → **LNF 75 mg** → **LNF 100 mg**

Follow-up (8 w)
one patient remained <LLOQ at wk 8 of FU;
5 patients had post-treatment ALT flares

0 — **weeks** — **24**

15 enrolled
12 on NUC

10 escaled
to 100 mg

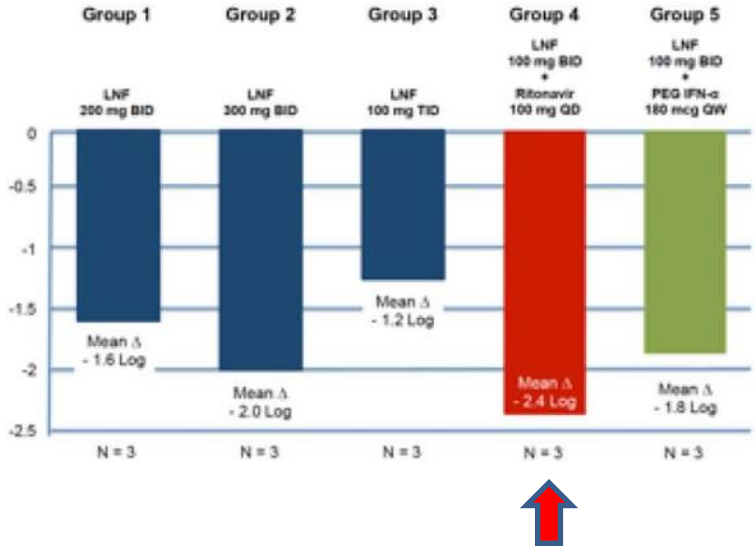
13 completed
24 weeks

HDV RNA decline

-1,58 ±1.38 log IU/ml
1 PCR negative
1 below LLOQ

Wedemeyer et al, EASL 2017; abs. PS 039

A proof of concept study

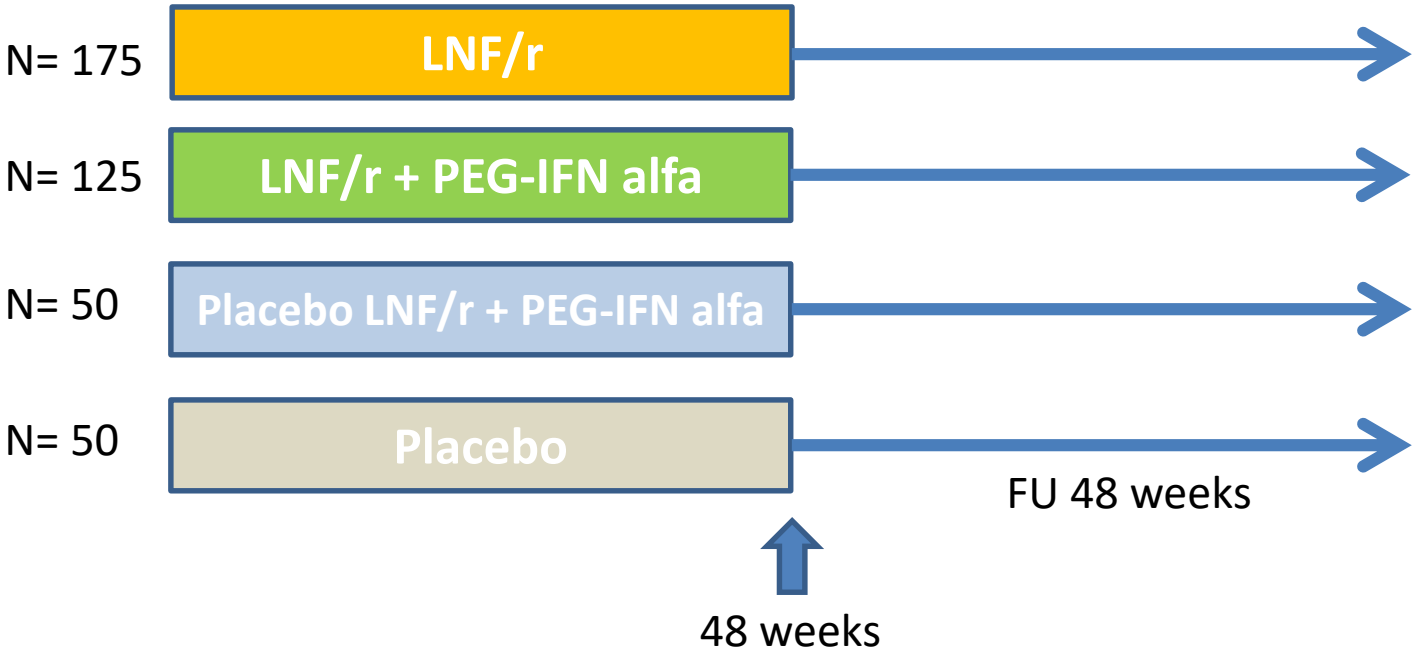


Yurdaydin, Hepatology, 2018

Phase 3 trial: lonafarnib ± Peg-IFN alfa

LNF 50 mg/RTV 100 mg, BID; PEG-IFN alfa 180 µg/week

HBV-DNA suppression with entecavir or tenofovir



Lonafarnib, ritonavir, and lambda interferon for HDV: interim end-of-treatment results – the LIFT study

Aims:

Evaluate the safety and antiviral effects of therapy with lonafarnib (LNF), ritonavir (RTV), and lambda interferon (LMD) in patients with chronic hepatitis D

Methods:

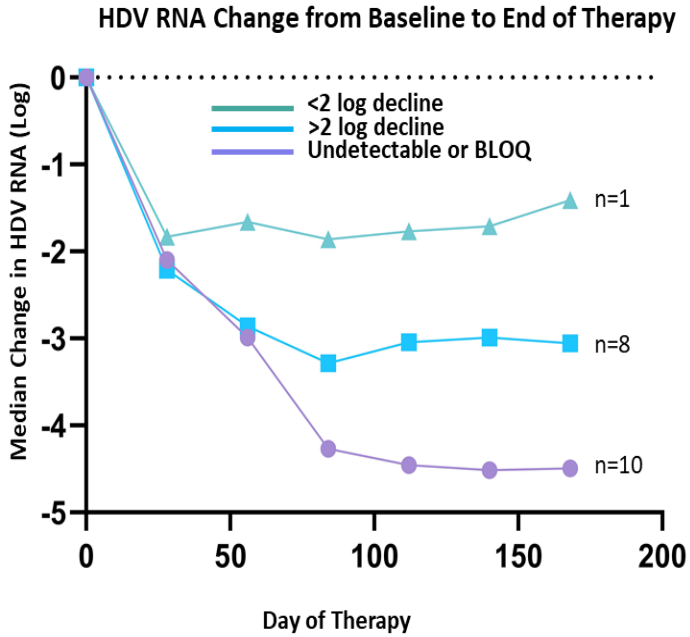
Phase 2a, open-label, prospective treatment trial in 26 patients for 24 weeks, with 24 weeks of post-therapy follow-up

Main Findings:

At the end of therapy (19 of 26 patients), the median HDV RNA decline was 3.4 log IU/ml (p<0.0001) with 10 (53%) patients achieving undetectable or BLOQ HDV RNA in serum.

Conclusions:

Triple combination therapy with LNF/RTV/LMD in chronic HDV patients appears to be safe and tolerable for up to 6 months in most patients.



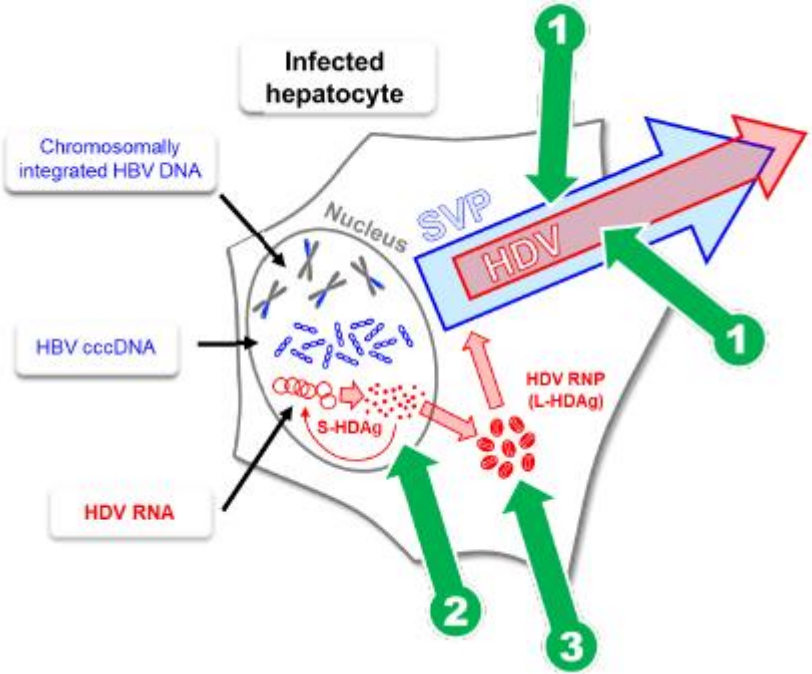
Koh C, et al., Abstract LO8

New therapeutical strategies

3. **Targetting HBV with drugs that induce HBsAg clearance**

NAPs - Nucleic Acid Polymers

Block the release of the hepatitis B virus surface antigen (HBsAg)
This effect restores functional control of HBV infection which persists after antiviral therapy is removed.



(1) Inhibition of HBV SVP and HDV assembly / secretion.

(2) Potential inhibition of HDV RNA synthesis via interaction with S-HDAg.

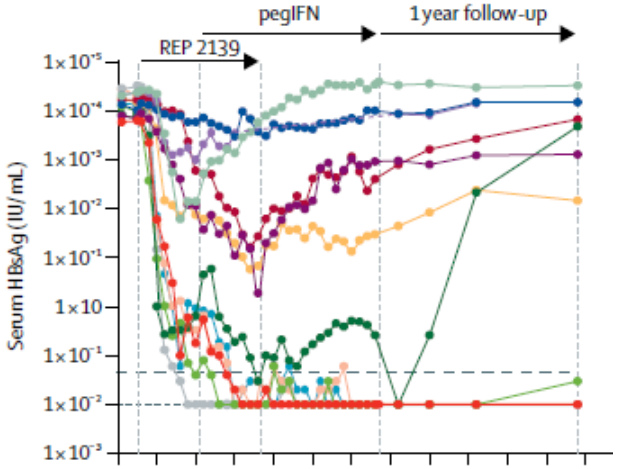
(3) Potential inhibition of HDV RNP formation via interaction with L-HDAg.

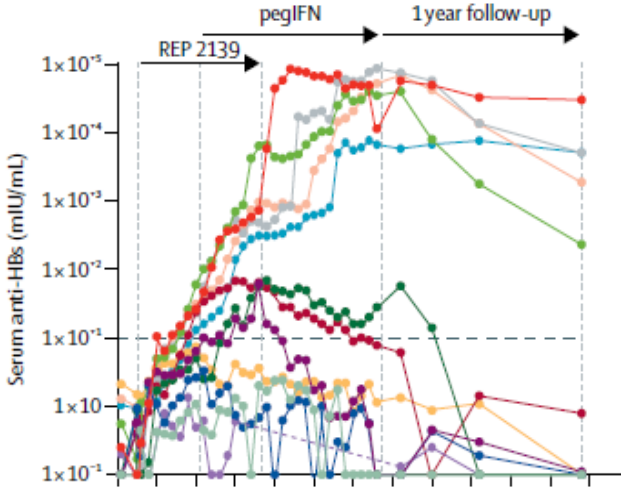
Vaillant, ACS Infect. Dis. 2019, 5, 5, 675-687

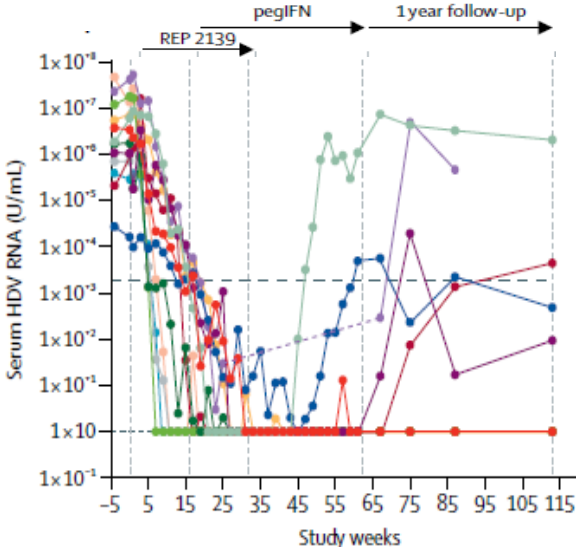
REP 2139 and pegylated interferon alfa-2a for treatment-naive patients with chronic hepatitis B virus and hepatitis D virus co-infection

REP2139 500 mg iv, weekly, 15 w;
REP2139 250 mg, iv, weekly, plus Peg-IFNα 180 µg, 15 w;
Peg-IFN α 180 µg, 33 w, alone

Open label
12 patients
No cirrhosis







At 1 yr post-Tx

8/12 HBV DNA undetectable; 5/12 HBsAg negative; 7/12 HDV-RNA negative

Bazinet, Lancet Gastroenterol Hepatol, 2017; 2:877-889

Conclusions

Chronic HDV infection is still presente in Italy as in Europe and is highly endemic in some countries

IFN-free therapy for HDV infection is desirable for all patients with chronic HDV infection and is crucial for patients with cirrhosis or those intolerant or non-responder to IFN

Two phase 3 trials are ongoing; in one trial (Myrcludex, Bulevirtide) all study arms are IFN-free