HDV overview

Epidemiology, natural history, virology and a historical perspective on treatment

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LIFER Conference
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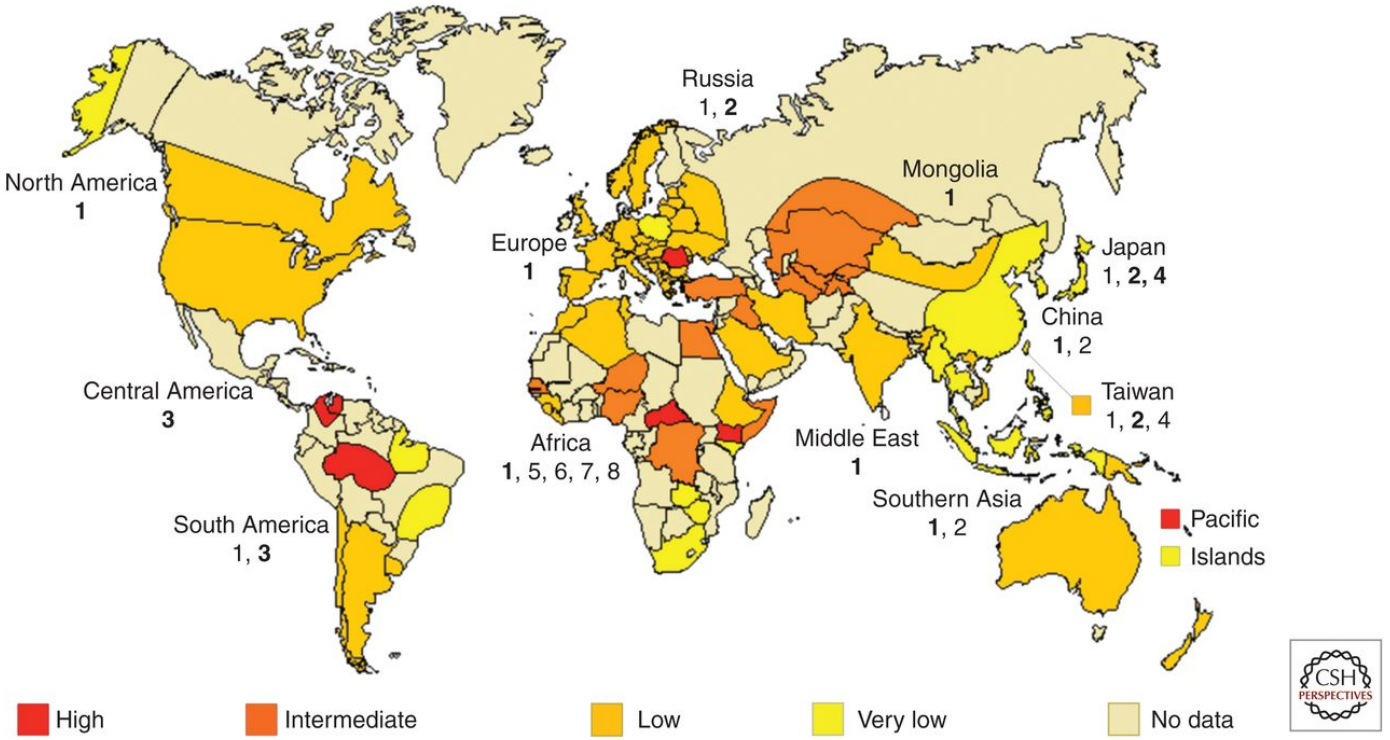
Epidemiology of Hepatitis Delta
Key messages

- An estimated 15-20 Million individuals are infected with HDV worldwide!
- Hepatitis Delta is the most severe form of chronic viral hepatitis
  → No testing – no identification of HDV infection!
- The clinical manifestations of hepatitis delta differs between regions and has changed during the last 3 decades
- Hepatitis Delta is a dynamic disease:
  - Both HBV and HDV contribute to disease progression
- Migrant populations and special risks groups show particular high HDV prevalence
- The HDV genotype matters

After: H Wedemeyer

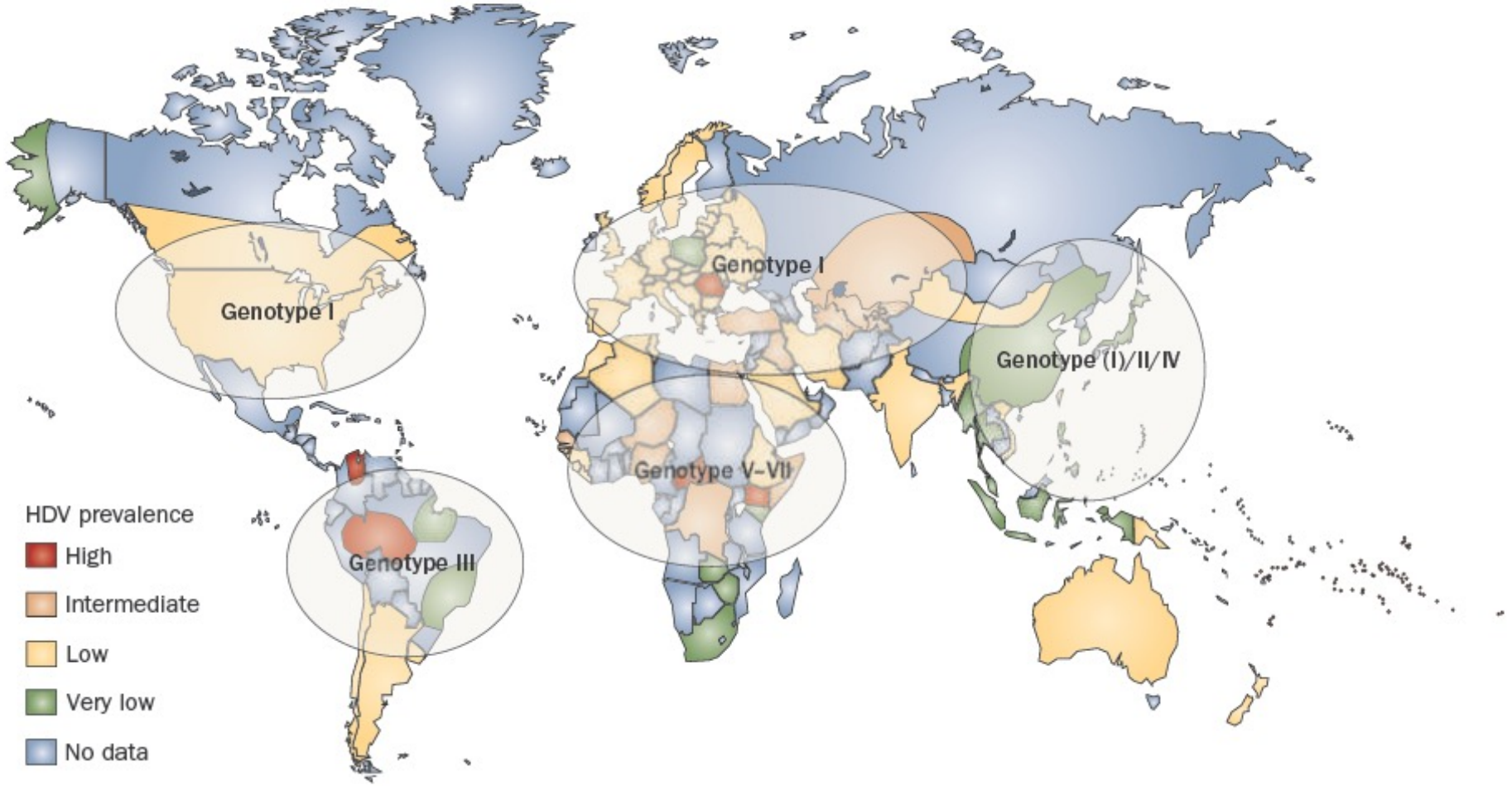
HDV epidemiology

- HDV = delta-virus, delta-agent
- Always found in association with HBV-infection
- Worldwide infection ≈15-20 million
- The most common routes of transmission
  - intravenous transmission (IDU)
  - percutaneous transmission (tattoo, piercing)
  - sexually transmission
  - intrafamilial transmission
- Endemic regions
  - Mongolia
  - Mediterranean countries (most often in children and young people)
  - Far East (infectiousness varies from 90% among HBsAg-carriers living in the Pacific Islands, up to 5% HBsAg-carriers in Japan)
  - Amazonia

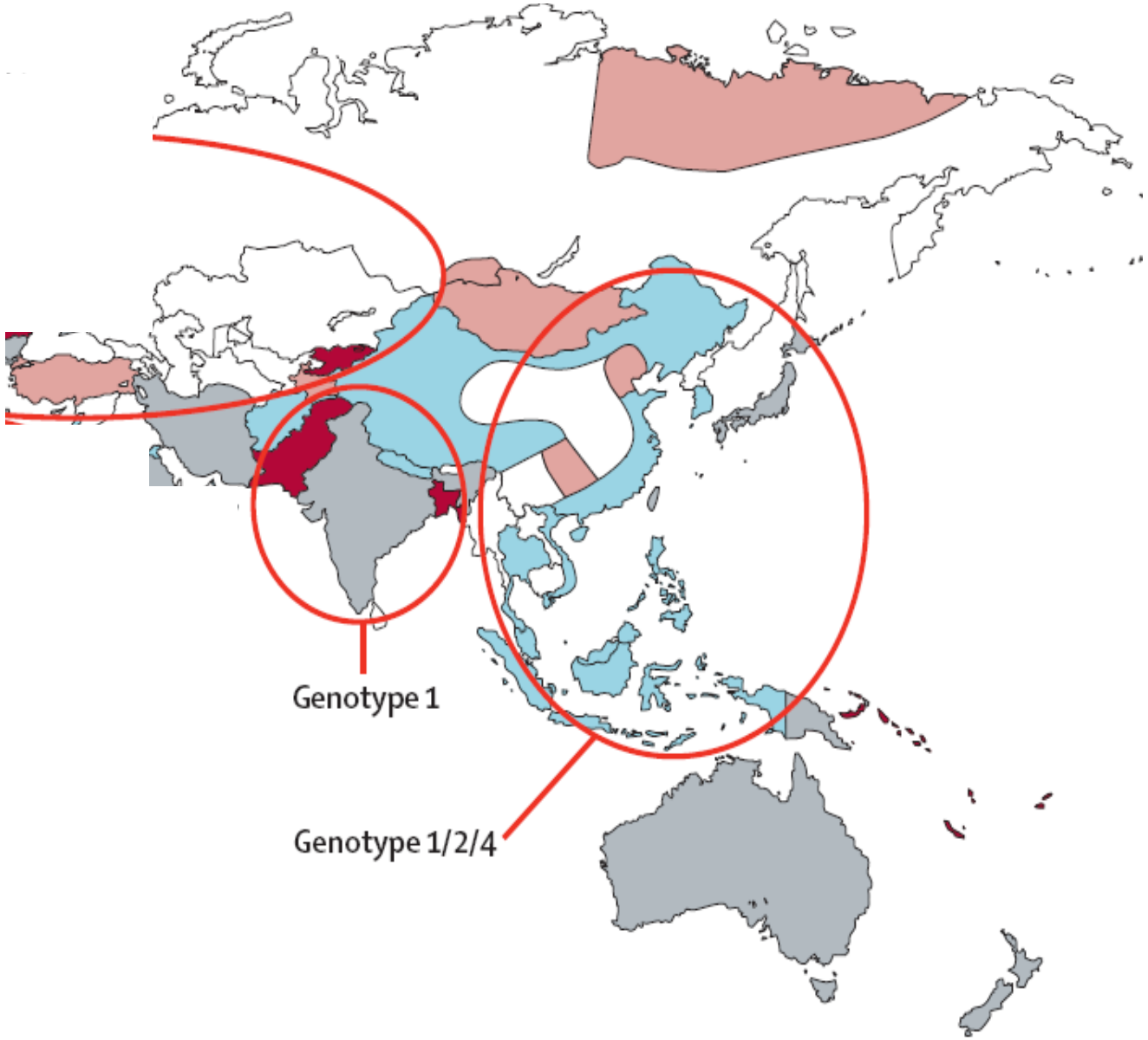


Mario Rizzetto Cold Spring Harb Perspect Med 2015;5:a021576

Different HDV genotypes in different regions!



Prevalence of Hepatitis Delta in the Asia-Pacific Region



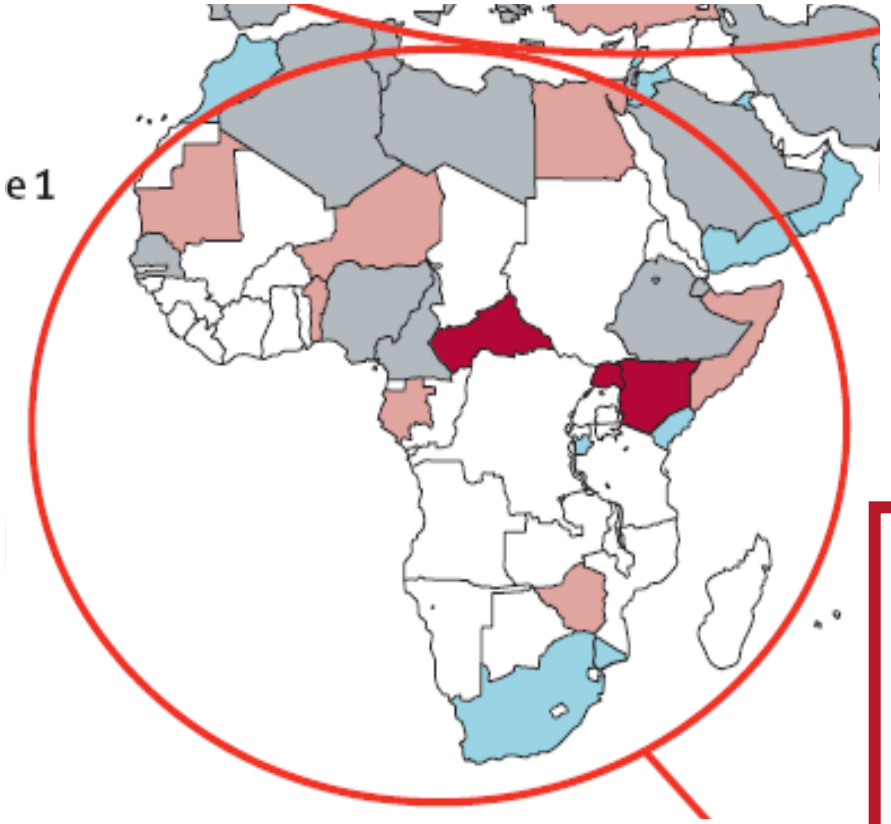
Hughes et al. The Lancet 2011; Abbas et al., World J Gastroenterol 2012

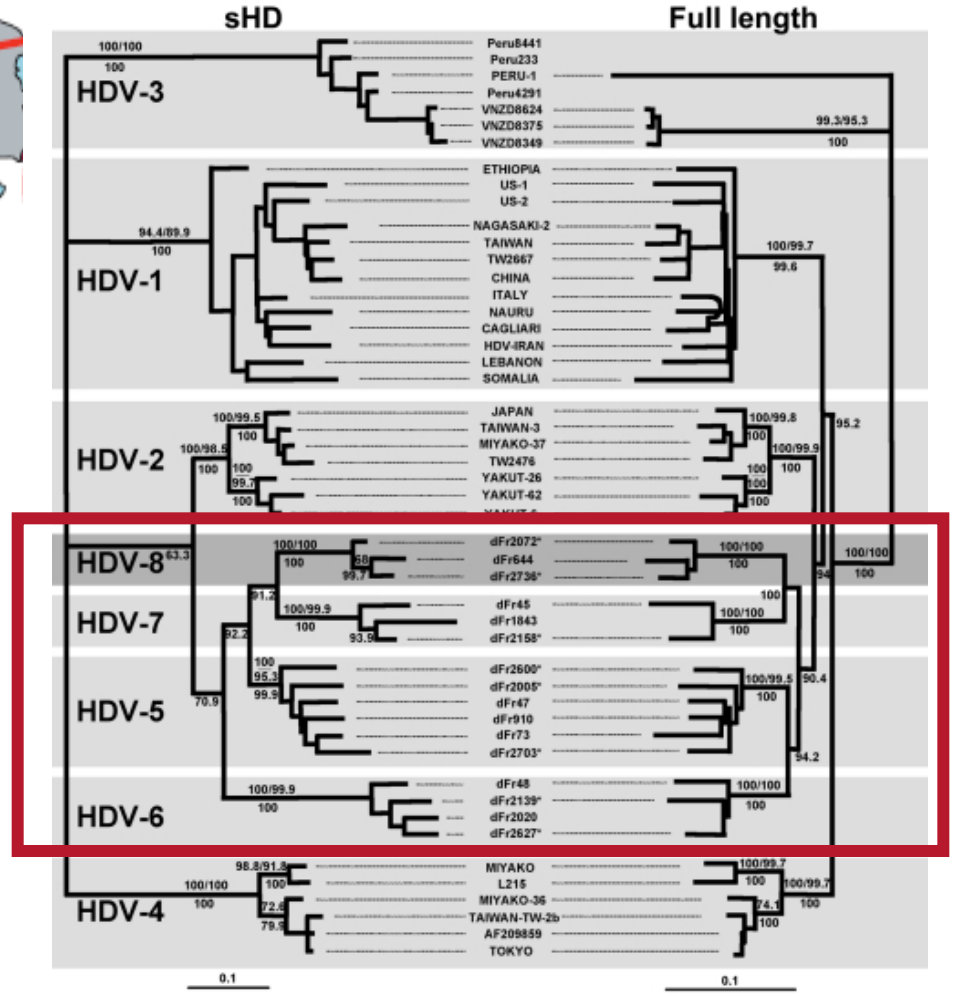
Prevalence of Hepatitis Delta in the Asia-Pacific Region
Data presented at the EASL Delta Conference 2010

Country	Prevalence	Author	Poster No
India	15.2% 10.9%	Raja W.A. et al. Asim M.	82 8
Korea	0.4% (OLT)	Jung Y. J. et al.	47
Pakistan	35.2% 45.3% 40.0% 45.3%	Mumtaz K. et al. Zaki M. et al. Bhatti T.A. et al. Memon M. S. et al.	71 7 13 95
Iran	7.6%	Azinmehr L. et al.	11
Turkey	2.5% (Izmir) 3.4% (Izmir) 8% (SE) 9% (Ddiyarbakir)	Köse S. et al Akpinar Z. . et al Turhanoglu M. et al. Gulsun S. et al.	26 40 41 58

Prevalence of Hepatitis Delta in Africa

- Genotypes 1, 5-8

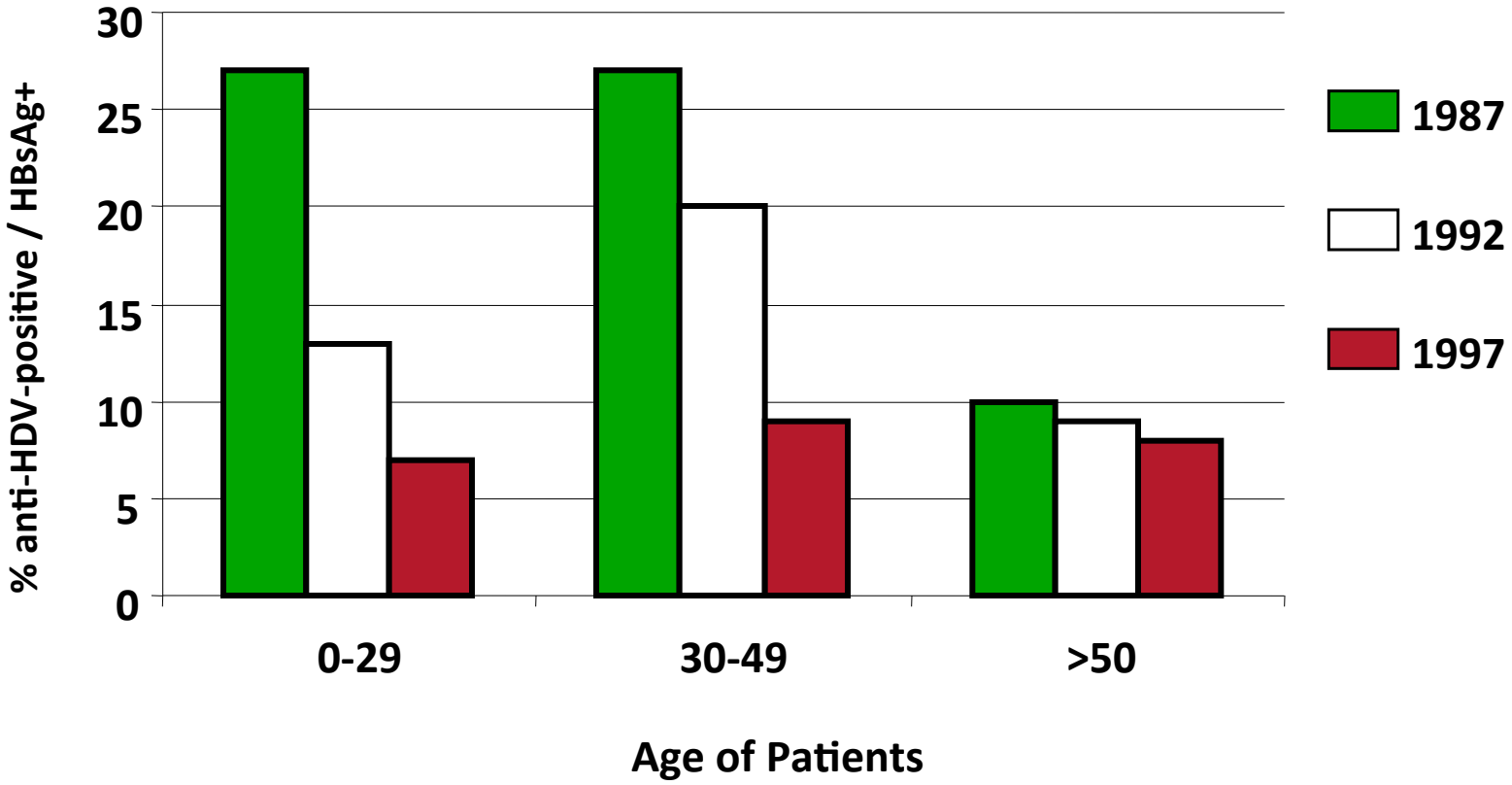




Le Gal et al., Emerg Infect Dis 2006

Anti-HDV Prevalence among HBsAg-positive patients in Europe (E.K. Manesis, EASL Special Conference 2010)

Decline of anti-HDV prevalence in Eastern Europe in the 1990ies



Gaeta, Rizzetto et al., Hepatology 2000

HDV Epidemiology in the USA

Highly variable: <1% to 30% among chronic HBV carriers!

Nath et al. Am J Epidemiol 1985:
Blood Donors: 1.4% Southeast to 12% Pacific region

Hershow et al. Ann Intern Med 1989:
Hepatitis B Carriers in Illinois: 30%

Weisfuse et al. Hepatology 1989:
Homosexual Men: 2%

Rizzetto et al. JID 1982; Troisi et al. Blood 1993:
Haemophiliacs: 19%; Female Prostitutes 21%

NHANES IV (CDC: 2003-2004)
1/28 HBsAg+ individuals was anti-HDV+ (3.6%)

Gish et al. JGH 2012:
N. Cal: outreach and clinic network: 8.4%

HDV Epidemiology in the USA:

Northern California

1296 HBsAg positive patients (incomplete data) → **82 (6.3%)** anti-HDV positive

499 HBsAg positive patients (complete data) → **42 (8.4%)** anti-HDV positive

- 71% male
- 54% non-hispanic Caucasians
- 28% asian-pac. immigrants
- 34% anti-HCV positive (with 67% cirrhosis)

Gish et al., 2012

HDV Epidemiology in the USA

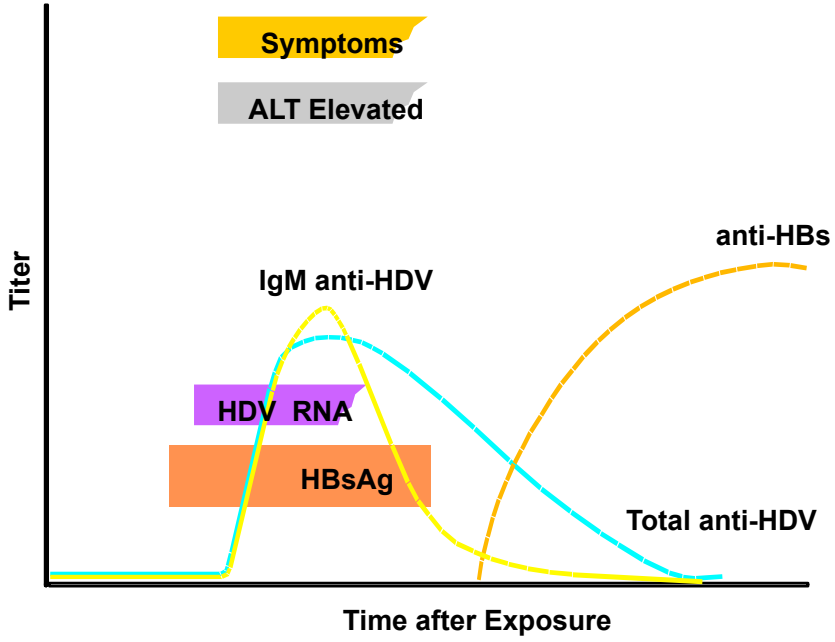
Prevalence, Correlates, and Viral Dynamics of Hepatitis Delta among Injection Drug Users

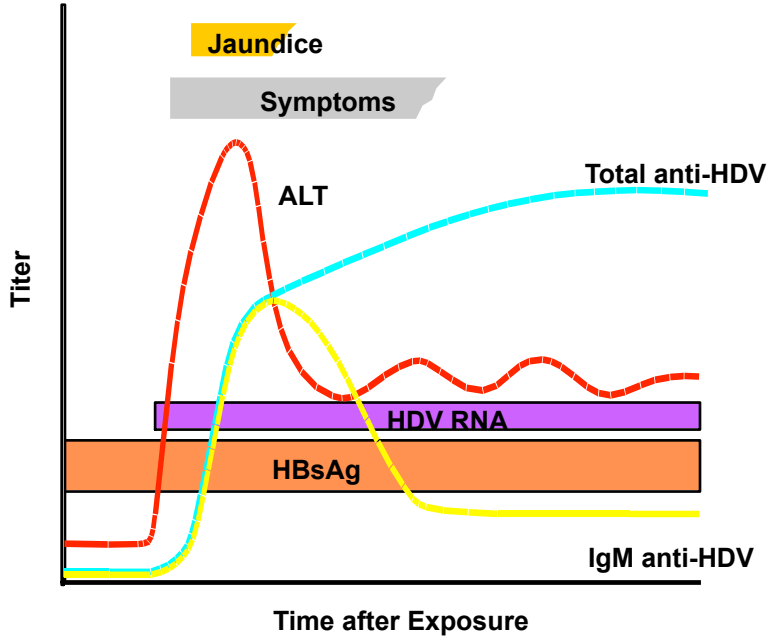
Lauren M. Kucirka,[2] Homayoon Farzadegan,[1] Jordan J. Feld,[5] Shruti H. Mehta,[1] Mark Winters,[4] Jeffrey S. Glenn,[4] Gregory D. Kirk,[1] Dorry L. Segev,[1,2] Kenrad E. Nelson,[1] Morgan Marks,[1] Theo Heller,[3] and Elizabeth T. Golub[1]

	Patients positive for HDAb				
	1988–1989		2005–2006		
HBV serology	Proportion of patients	Percentage of patients (Wald 95% CI)	Proportion of patients	Percentage of patients (Wald 95% CI)	*P* value
HBsAg positive	14/48	29 (16–42)	19/38	50 (34–66)	.048
HBsAg positive, adjusted				55 (40–71)[a]	.01[b]
HBsAg negative	16/146	11 (6–16)	6/220	3 (1–5)	.002
HBcAb and sAb positive	6/57	11 (3–19)	1/108	1 (0–2)	.003
HBcAb positive only	10/89	11 (4–18)	5/112	4 (1–8)	.07
All HBV categories	30/194	15 (10–21)	25/258	10 (6–24)	.2

Kurcirka et al., JID 2010

HDV co- and superinfection

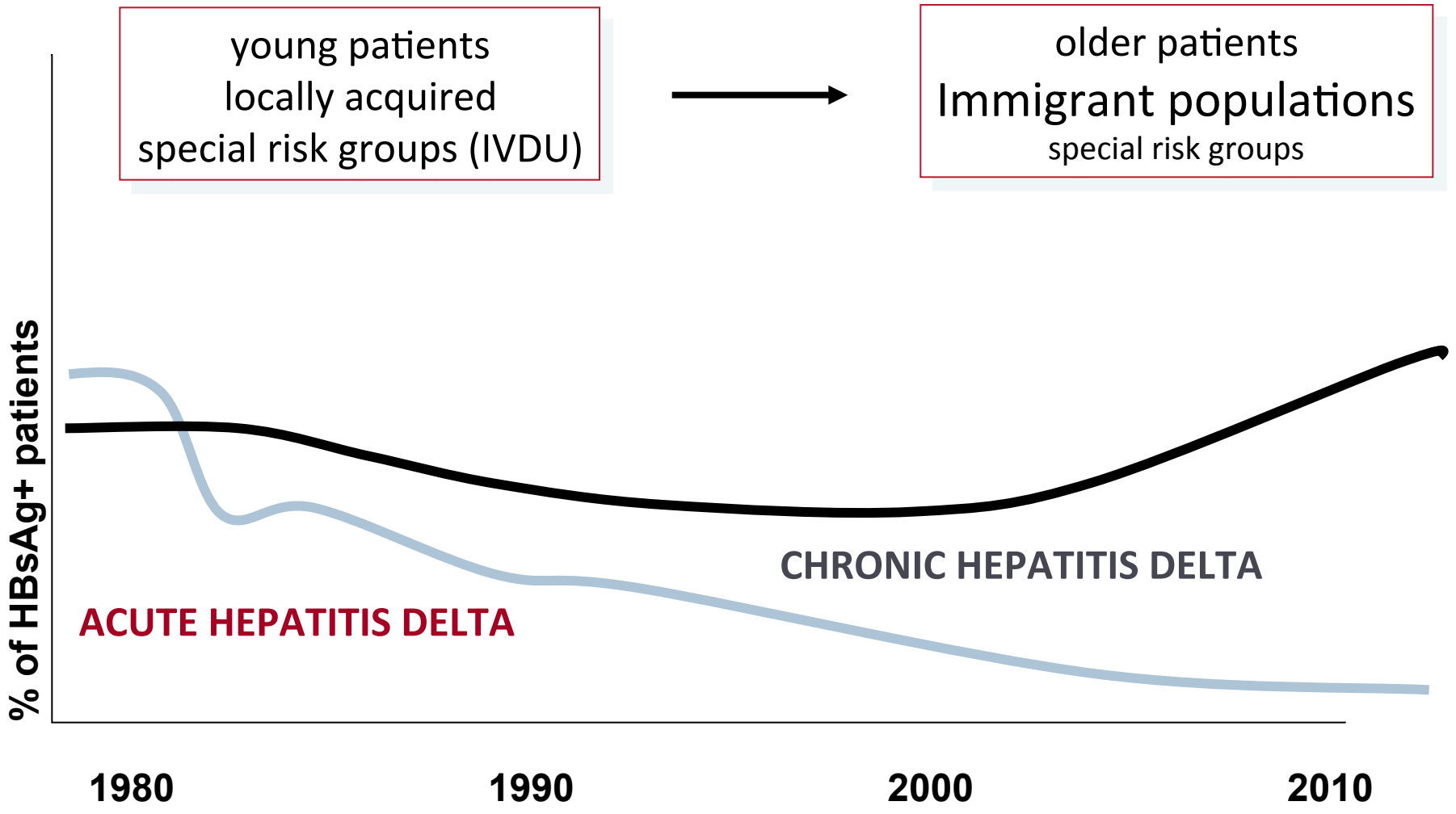




- Co-infection:
  - Clinically indistinguishable from acute HBV
- Usually acute and self-limited (95%), HDV and HBV clearance
- High frequency of acute liver failure in IDUs

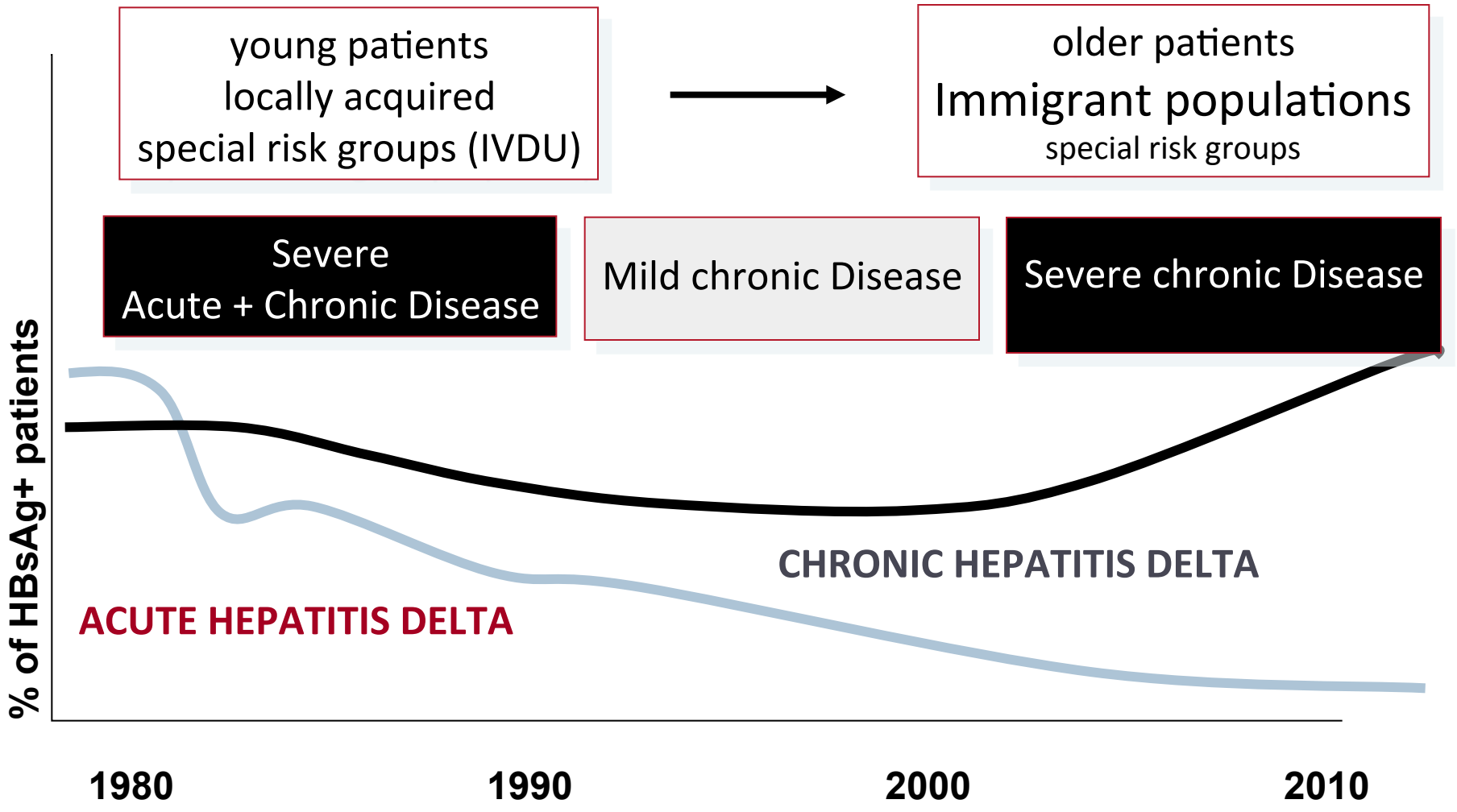
- Severe hepatitis in previously diagnosed HBsAg-carrier or exacerbation of a known chronic HBV
- HDV becomes chronic almost in 90%

Hepatitis delta: evolution of clinical presentation



After Wedemeyer

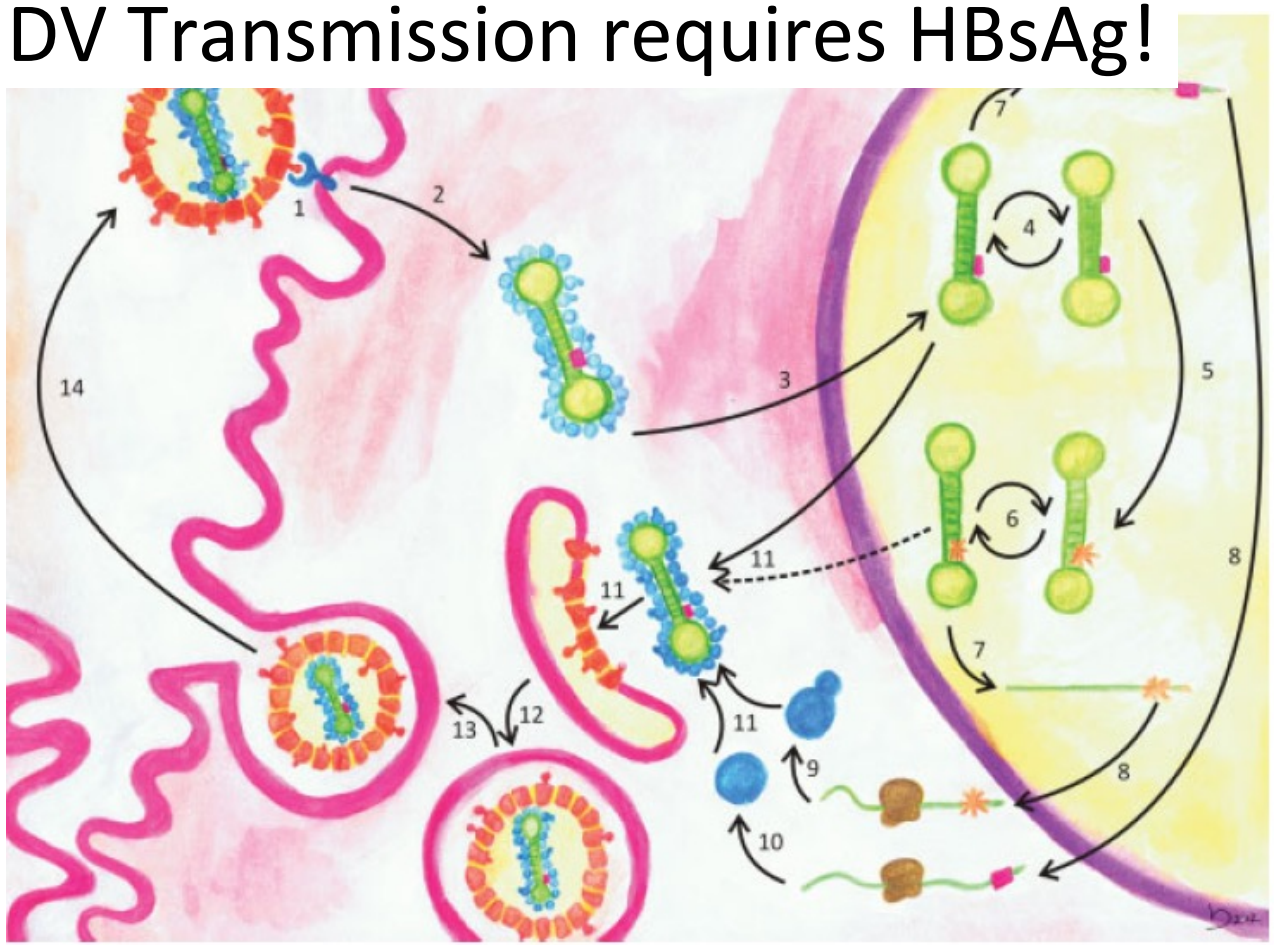
Hepatitis delta: evolution of clinical presentation



After Wedemeyer

HDV: Virology

- HDV Transmission requires HBsAg!



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

HDV: Modes of Transmissions

- HDV Transmission requires HBsAg!
- Intrafamilial transmission

  vertical & sexual transmission,

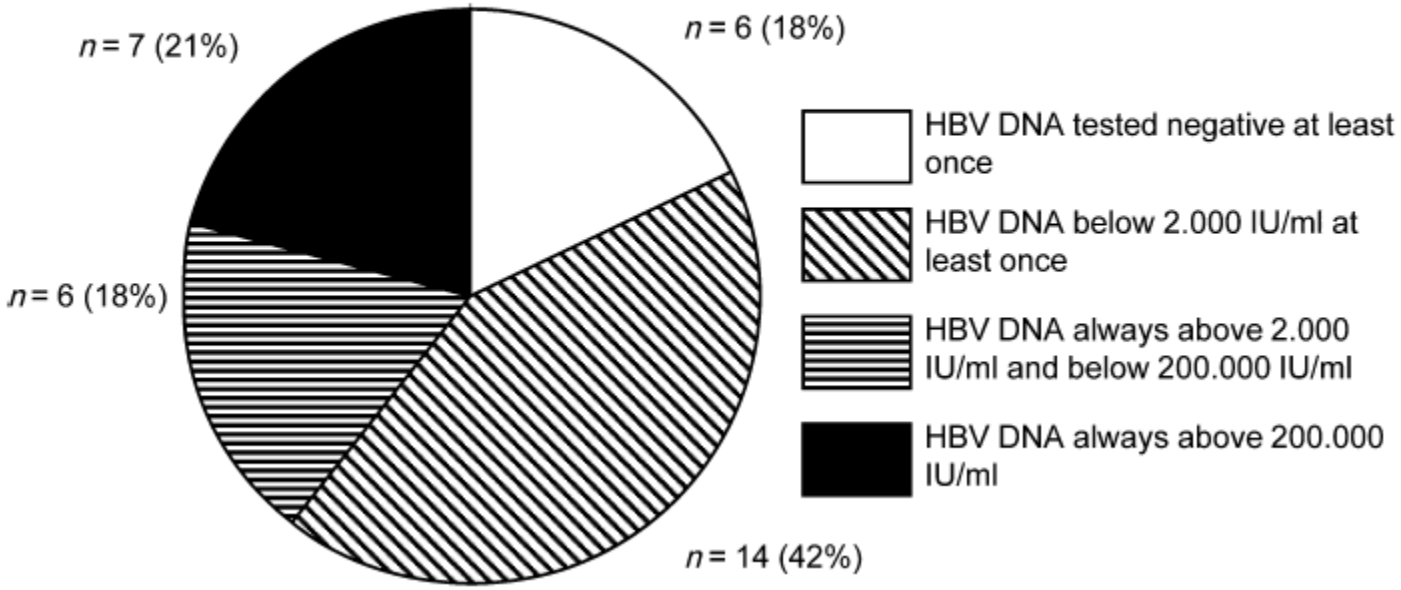
  infection during early childhood
- *Folk remedies, scarification, percutaneous exposure*
- Medical treatment

  blood transfusion, unsterile syringes, etc.
- Special risk groups

  IV drug user, dialysis, HIV+, hemophiliacs.
- HBV vaccination prevents from HDV infection!

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

HBV DNA is often suppressed by HDV, even in HBeAg-positive hepatitis



Heidrich et al., Liver International 2012

Fluctuating Patterns of Viral Dominance in Hepatitis D

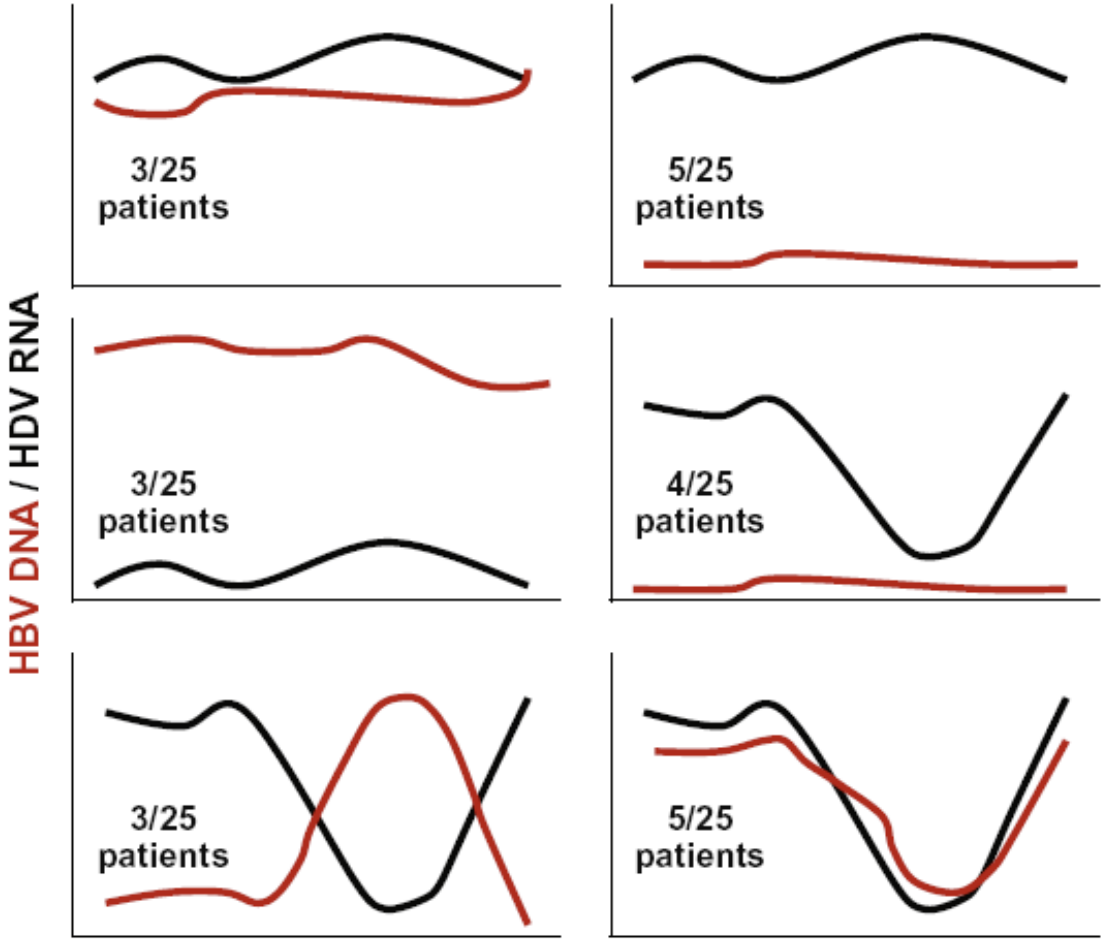
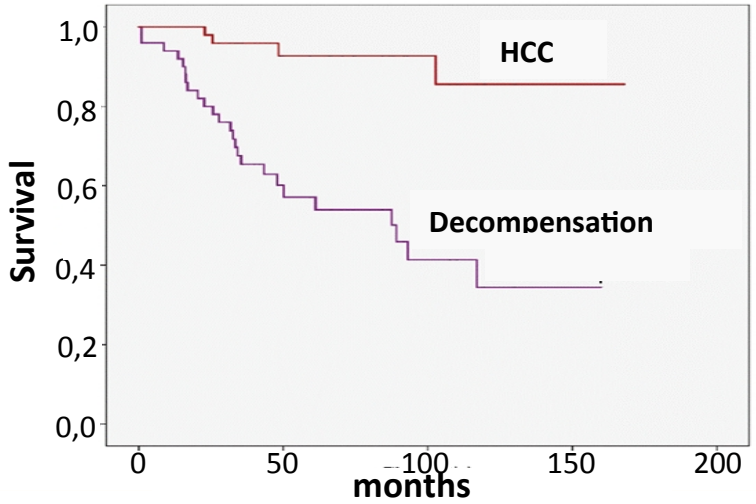


Fig. 1. Schematic representation of HBV DNA and HDV RNA patterns over time observed in the study by Schaper et al. [19].

Schaper, Buti et al., J Hepatol 2010; Wedemeyer J Hepatol 2010

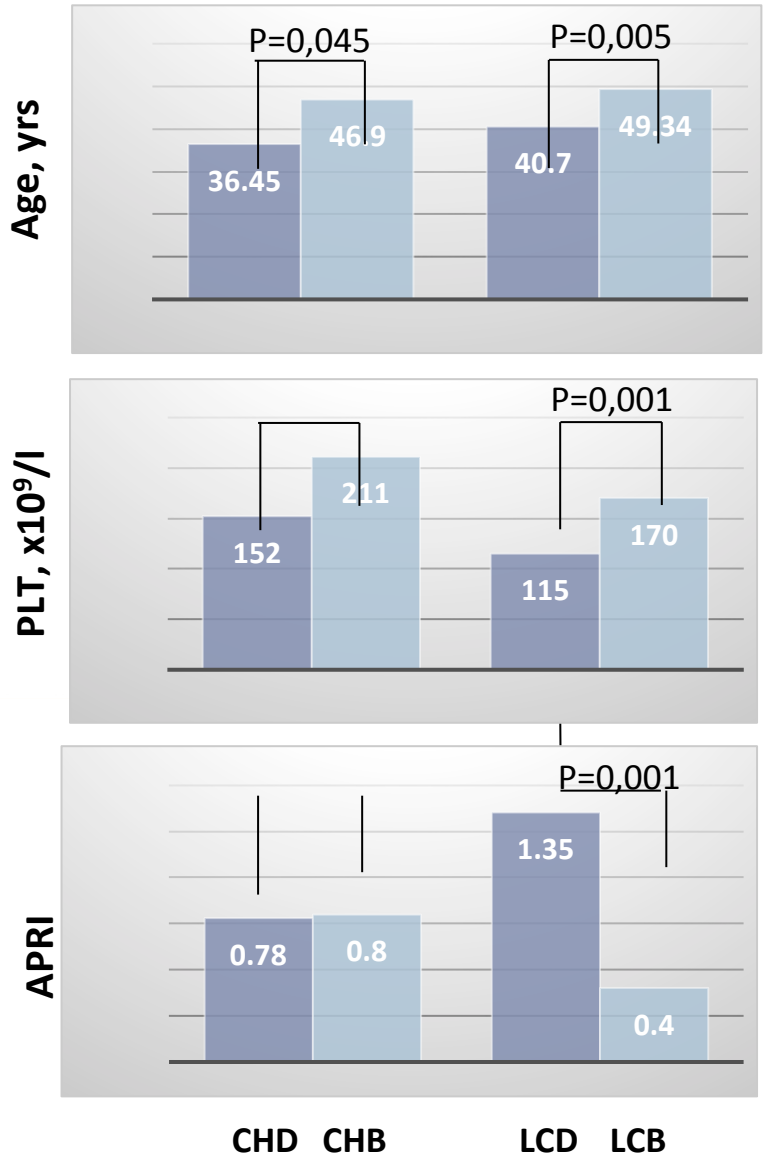
Liver disease progression

- 28-year prospective study in Italy: 25% with liver cirrhosis developed HCC, 59% - liver failure
- Study in Taiwan: 15% survival within 15 yrs



- The main cause of death in patients with CHD is the decompensation of progressive liver disease (38%) instead of hepatocellular carcinoma

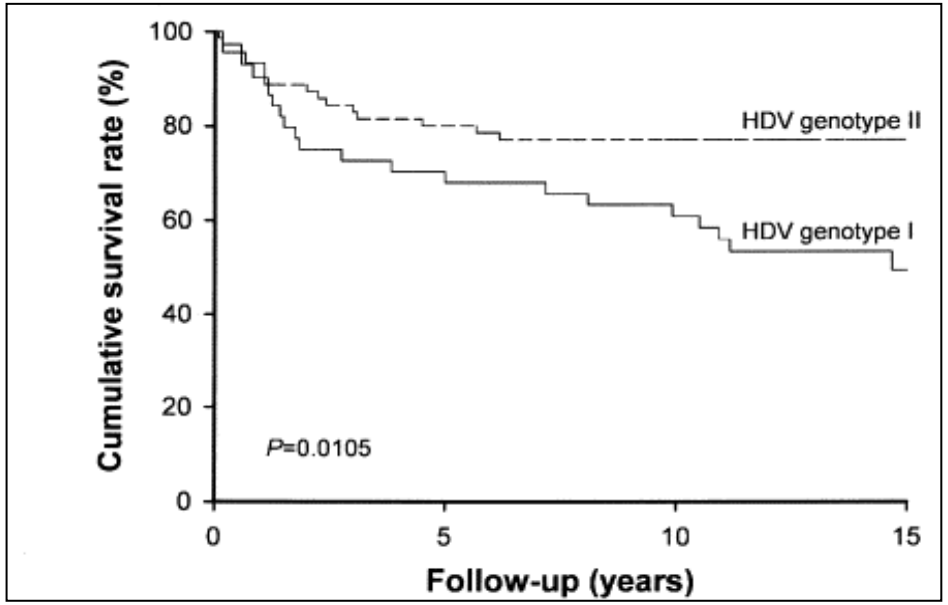
G Fattovich, G Giustina, E Christensen et al. Gut 2000;46:420–426; Farci P. EASL monothematic conference "Delta Hepatitis", Istanbul, Turkey, September 24-26, 2010, Oral; Bonino F, Negro F, Baldi M, et al. Prog Clin Biol Res. 1987;234:145-152; Romeo, R. et al. Gastroenterology 136, 1629–1638 (2009); Su, C. W. et al. Gastroenterology 130, 1625–1635 (2006); Calle-Serrano et al., AASLD 2009; Romeo et al., Gastroenterology 2009



- More rapid progression of HDV compare to HBV
  - Patients with CHD are as many as 10,5 years younger than those with CHB
  - Patients with LCD are as many as 8,7 years younger than those with LCB
- More frequent complications of LCD
  - Portal hypertension
  - HE
- More frequent / severe thrombocytopenia, more higher APRI

A.V. Nersesov, E.A. Izatullayev, L.K. Palgova et al. Clinical peculiarities of HDV infection in Kazakhstan. EASL Monothematic Conference: Delta Hepatitis, Istanbul, Turkey, Sept.r 24-26, 2010.- Abstracts.- P.133.

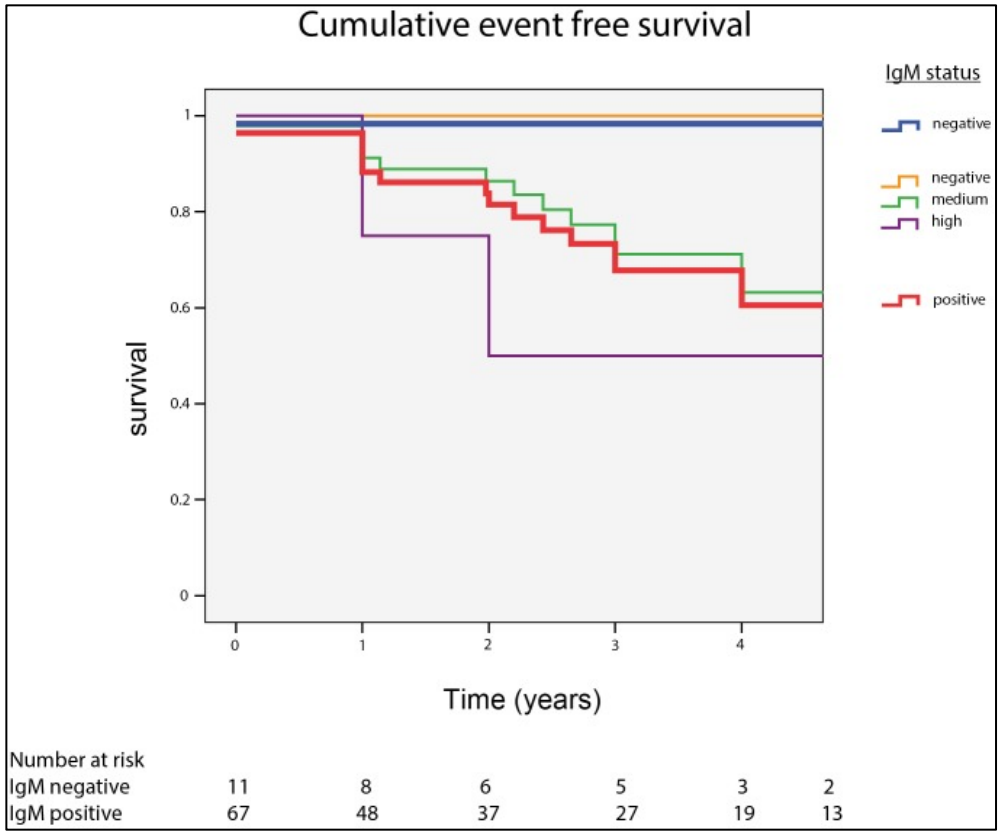
Outcomes of Hep D depends on HDV genotype



- G1 HDV in acute hepatitis
  - A risk of fulminant failure
- G1 HDV in chronic hepatitis
  - Rapid progression to cirrhosis
  - Risk of HCC is as many as 3 times higher
  - Mortality is as many as 2 times higher

Fattovich G et al. Gut 2000; 46:420 2. Wu Lancet 1995; 3. Su et al. Gastroenterol 2006; 4. Wu Curr Top Micobiol Immunol 2006

Anti-HDV IgM-status correlates with activity and outcomes of Hep D



- Serum anti-HDV IgM is a robust marker to determine disease activity in Hep D which has prognostic implications

Wranke A, Heidrich B, Ernst S et al. PLoS One. 2014 Jul 29;9(7):e101002. doi: 10.1371/journal.pone.0101002. eCollection 2014.

HDV RNA viral load did not correlate with activity

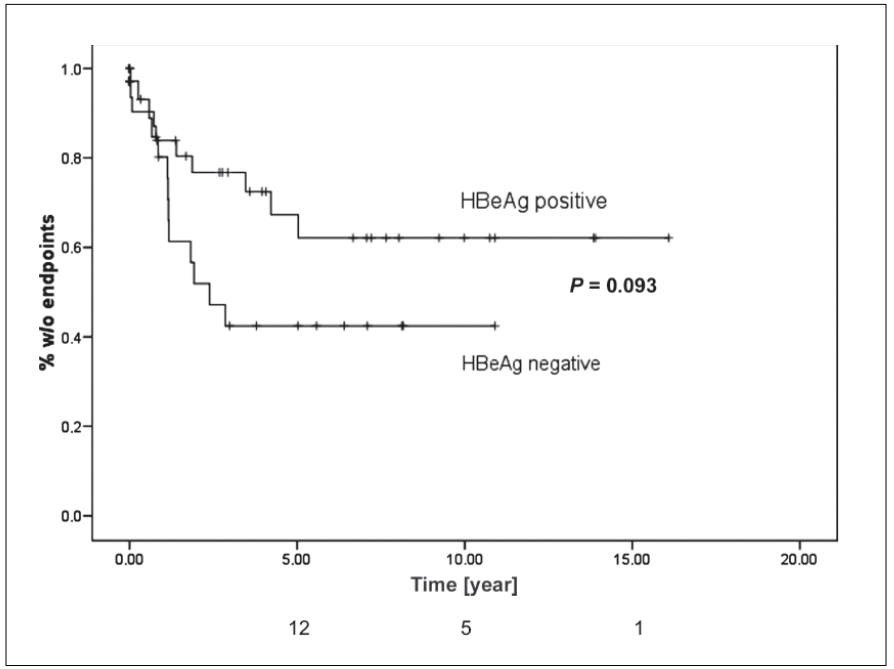
Table 4. Characteristics of hepatitis delta patients ($n = 73$) according to the histological activity index

	HAI 0–7 ($n = 38$)	HAI 8–18 ($n = 35$)	*P* value
Age	39 ± 11.8	37 ± 10	NS
Male (%)/female (%)	25 (65.8)/13 (34.2)	23 (65.7)/12 (34.3)	NS
WBC (10^9/L)	5.9 (1.9–10.9)	5 (2.8–7.6)	0.033
PLT (10^9/L)	183.6 ± 47.9	151.4 ± 45.5	0.005
AST (U/L)	65.5 ± 54.5	92.7 ± 60	0.046
ALT (U/L)	71 (27–332)	111 (42–660)	0.002
γ-GT (U/L)	34 (14–396)	68 (19–497)	0.003
ALP (U/L)	69 (36–234)	77 (47–286)	0.011
Bilirubin (mg/dl)	0.8 ± 0.4	0.8 ± 0.44	NS
Albumin (g/dl)	4.1 ± 0.46	4.1 ± 0.5	NS
HBsAg (IU/ml)	7.4×10^3 ($67–4.3 \times 10^4$) ($n = 35$)	1.4×10^4 ($668–7.9 \times 10^4$) ($n = 32$)	0.011
HBV DNA	1397 ($0–6.4 \times 10^8$) ($n = 35$)	148 ($0–4.4 \times 10^5$) ($n = 32$)	0.013
HDV-RNA (copies/ml)	5.7×10^5 ($1200–1.7 \times 10^7$) ($n = 35$)	9.7×10^5 ($1080–8.4 \times 10^7$) ($n = 32$)	NS
HBsAg expression ≥2+(%)	14 (40) ($n = 35$)	8 (24.2) ($n = 33$)	NS
HBcAg expression (%)	30 (85.7) ($n = 35$)	21 (63.6) ($n = 33$)	NS

Data are expressed as mean ± SD or median (range) as appropriate. Abbreviations are same as in Tables 1 and 2.
NS, non significant.

Zachou K., Yurdaydin C., Dienes H.P., Manns M.P. et al. *Liver Int. 2010 Mar; 30(3): 430-7.*

Outcome of CHD does not depend on HBeAg-status



Heidrich et al., Liver International 2012

Meta-analysis: antiviral treatment for chronic Hep D

- Sourses: Medline, Scopus, Cochrane Library, ISI Web of Knowledge

Group A	IFNa / absence of antiviral Tx	3 RCT; *n* = 137	IFNa was better for biochemical EOT [OR, 0.11 (95% CI, 0.04–0.2)] and virological EOT [OR, 0.08 (95% CI, 0.03–0.2)], but not for EOFUP VR
Group B	Low / high doses of IFNa	2 RCT; *n* = 60	High dose IFNa was better for biochemical EOT [OR, 0.24 (95% CI, 0.08–0.73)] and virological EOT [OR, 0.27 (95% CI, 0.1–0.74)]
Group C	IFNa ± LAM / LAM	2 RCT; *n* = 48	No benefits
Group D	PEG-IFNa) / other antivirals	2 RCT; *n* = 157	PEG-IFNa was better for virological EOT [OR, 0.419 (95% CI, 0.18–0.974)], EOFUP VR [OR, 0.404 (95% CI, 0.189–0.866)] and improvement in necroinflammatory activity [OR, 0.308 (95% CI, 0.129–0.732)]

C. Triantos, M. Kalafateli, V. Nikolopoulou, A. Burroughs. ***Alimentary Pharmacology & Therapeutics.*** *Volume 35, Issue 6, pages 663–673, March 2012*

Hep D Tx

- Endpoints
  - Eradication/suppression of HDV replication
  - Eradication (Functional cure) of HBV with HBsAg clearance /seroconversion
  - Normalization of biochemical tests and liver histology improvement
- Tx
  - PEG-IFN 48 wks (may require > 1 year due to some advantages)
  - AN therapy may be considered in patients with active HBV replication with a persistent or fluctuating HBV DNA > 2,000 IU / ml
  - VR can be evaluated after 3-6 months of therapy by measuring the level of HDV RNA
- Predictors of response
  - Non 1 genotype
  - Initial viral load < 10^6 copies/ml
  - PCR HDV RNA (--ve) at month 6 of Tx
  - Lower Initial HBsAg titer

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection. Journal of Hepatology, 2012 vol. 57 p. 167–185; Hughes S. EASL monothematic conference "Delta Hepatitis", Istanbul, Turkey, September 24-26, 2010, Abstr.138; Stern. EASL monothematic conference "Delta Hepatitis", Istanbul, Turkey, September 24-26, 2010, Abstr.186; Castelnau et al. Hepatology, 2006.

HDV Tx

- Trials with PEG-IFNa showed HDV RNA negativity rates of 25-30% 24 weeks after therapy
- Therapy up to 5 years can result in 35% long-term SVR
- Retrospective-prospective follow-up of 77 patients in the HIDIT-1 trial with a median time of follow-up of 4.5 (0.5-5.5) years
  - Out of 16 patients tested HDV RNA-negative 6 months after PEG-IFNa treatment, 9 individuals tested HDV RNA-positive in the long-term follow-up study

Heidrich B[1], Yurdaydın C, Kabaçam G et al. Hepatology. 2014 Jul;60(1):87-97. doi: 10.1002/hep.27102, Yurdaydin in press 2016

- Kazakhstan
  - 11 cases were analyzed
  - Tx
    - Peg-IFNα 2a, 180 µg/wk
    - 48 wks (in 1 case – 36 wks)
  - Efficacy
    - EOT VR – in 4 out of 11 pts (36,4%)
    - VR at 6 months follow up – in 3 pts (27,3%)
    - VR after 6 months follow up – in 2 pts (18,0%)

A. Nersesov, Zh. Kaibullayeva, A.Raissova, A.E.Dzhumabaeva, et al. The Liver Week 2014, Jeju, Korea, Abstract book, P. 176.

Late HDV RNA relapses may occur after PEG-IFNa therapy of hepatitis delta and thus the term sustained virological response should be avoided in HDV infection

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

Endpoints		Peg-IFN α2a + TDF	Peg-IFN α2a + Placebo	P
Not detected HDV RNA	At the end of 96 weeks of treatment	47%	33%	NS
	Of those who completed treatment	54%	41%	NS
24-week post-treatment sustained response		30%	23%	NS
Relapse		44%	40%	NS
↓HBsAg >0.5 log IU/mL	At week 96	30%	25%	NS
	At week120	22%	25%	NS

- Lower HDV RNA and lower HBsAg levels at baseline were associated with HDV sustained virological response
- People with cirrhosis had a higher HDV virological response rate compared with non-cirrhotics (51% vs 25%, respectively)
- Prolonged pegylated interferon plus tenofovir was difficult to tolerate and did not have any benefit
- All participants had at least 1 adverse event, and one-third had serious adverse events

H. Wedemeyer, C. Yurdaydin, S. Ernst, et al. EASL, 2014

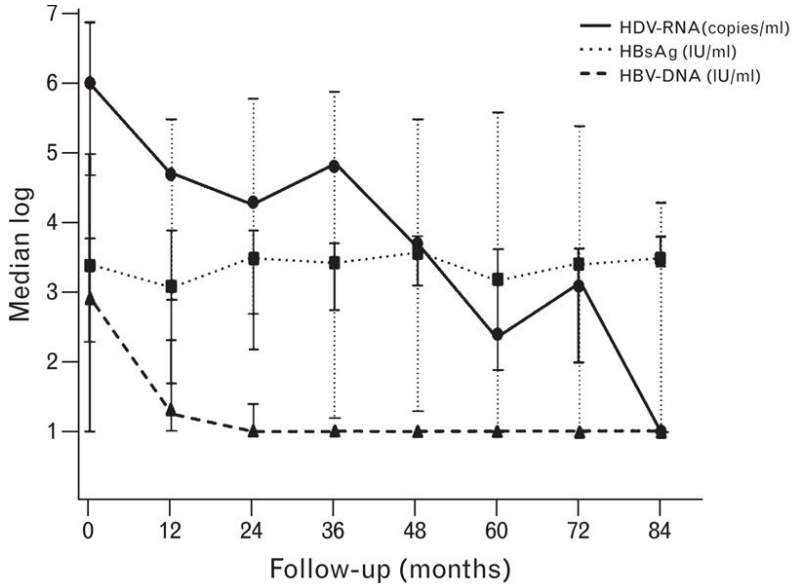
LT in HDV-infection

- The only available option for pts with FHF, end-stage liver disease and HDV-associated HCC who are not candidates for resection
- LT for HDV: The best outcomes amongst all other viral hepatitis (including HBV monoinfection)
- Compared to HBV monoinfection, in HDV infection the HBV graft infection risk is lower
- With the prophylactic HBIg and NAs, the incidence of HBV/HDV graft infection is 0-5%
- After LT the long term prophylaxis of HBV graft infection is recommended
- There is no any effective treatment of graft HDV infection

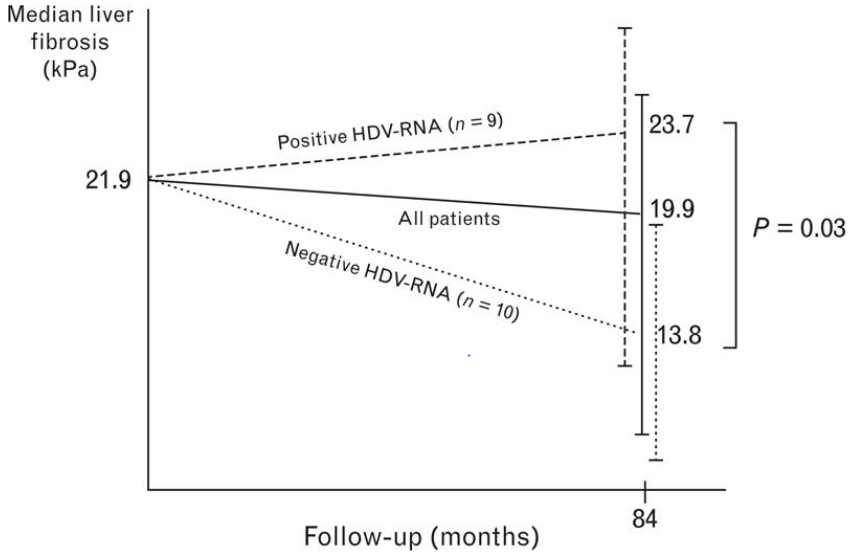
ten Kate FJ, Schalm SW, Willemse PJ et al. J Hepatol 14:2-3 1992 Mar: 168-75; Samuel D, Muller R, Alexander G et al. N Engl J Med 1993; 329:1842-7; Smedile A, Casey JL, Cote PJ et al. Hepatology 1998;27:1723-9; Rifai K, Wedemeyer H, Rosenau J et al. Clin Transplant. 2007; 21(2): 258$ *Roche B, Samuel D. Seminars in liver disease 32:3 2012 Aug pg 245-55; Wedemeyer H. Hepatology. Clinical textbook. Flying publisher, 2012. 546 p..*

Efficacy of prolonged tenofovir therapy on hepatitis delta in HIV-infected patients

AIDS
OFFICIAL JOURNAL OF THE INTERNATIONAL AIDS SOCIETY



After a median tenofovir exposure of 58 (34–93) months, all patients had undetectable HBV-DNA and 10 (53%) HDV-RNA less than 10 copies/ml. In the last group, the median time to reach undetectable HDV-RNA was 54 (33–72) months. In the remaining nine HDV viremic patients at the end of follow-up, the median HDV-RNA had dropped to 2.42 (1.27–3.09) log copies/ml



During tenofovir therapy, there was an overall reduction in liver stiffness from a median of 21.9 to 13.8 KPa (P = 0.34). More than 30% reduction in liver stiffness during the study period occurred in six out of 10 (60%) patients who achieved undetectable HDV-RNA. Regression of cirrhosis was recognized in five patients, all of whom had achieved undetectable HDV-RNA.

Conclusion: Long-term exposure to tenofovir significantly reduced serum HDV-RNA apart from completely suppressing HBV-DNA in HIV-infected patients with hepatitis delta. This virological benefit is accompanied by significant improvements in liver fibrosis.

Soriano, Vincent; Vispo, Eugenia; Sierra-Enguita, Rocío; Mendoza, Carmen de; Fernández-Montero, José V.; Labarga, Pablo; Barreiro, Pablo[a], AIDS, Issue: Volume 28(16), 23 October 2014, p2389–2394

HDV Assays in the US

- ARUP has launched a qHDV RNA test that is available at no cost to registered participants
- Launch of commercial assay to the general medical community occurred simultaneously

HDV Awareness and Testing Program Roles

EIGER BIOPHARMACEUTICALS → *Program sponsor*

Hepatitis B Foundation
Baruch S. Blumberg Institute → *Patient / HCP education*

ARUP LABORATORIES → *Centralized HDV testing*

You → *Test HBV patients*

Hepatitis Delta Testing

ARUP Laboratories

*Hepatitis Delta Total Antibody (IgM and IgG)**

- *Qualitative enzyme immunoassay*
- *Detects but does not differentiate IgM and IgG*
- *Results reported as 'negative', 'positive', or equivocal*
- *Performance characteristics are similar to other commercially available HDV antibody tests*

*HDV Viral Load by PCR**

- *Real time RT-PCR that quantifies HDV RNA*
- *Internal control monitors nucleic acid extraction and detects PCR inhibitors*
- *Calibrated to WHO standard*
- *Dynamic quantitative range of 120 - 5,800,000 IU/mL*
- *Lower limit of detection = 62 IU/mL*

*This test was developed and its performance characteristics determined by ARUP Laboratories. The U. S. Food and Drug Administration has not approved or cleared this test.

Perspectives of the Hep D therapy

- Other IFNs
  - IFN λ
  - (Albuferon)
- Combination therapy
  - IFN with NA, other agents
- Specific agents
  - Myrcludex B (inhibitor of HBV and HDV penetration)*
  - Prenylation inhibitors
- Improvement of LT medical support

- Lonafarnib trial
  - Oral prenylation inhibitor
  - 14 patients were enrolled, of whom eight were assigned to group 1 and six were assigned to group 2 (placebo control)
  - lonafarnib effectiveness in blocking HDV production was greater in group 2 than in group 1 (0·952 [SE 0·06] vs 0·739 [0·05], p<0·001), and the HDV half-life was 1·62 days (0·07)
  - There was no evidence of virological resistance
  - Adverse events were mainly mild to moderate; no treatment discontinuations occurred in any treatment groups

Koh C., Canini L, Dahari H, Zhao X. et al. The Lancet infectious diseases. Volume 15, No. 10, p1167–1174, October 2015

Conclusions

- HDV-infection plays an important role in the etiology of liver diseases in various parts of the world
- All HBsAg-positive patients should be tested for anti-HDV using serology and confirmation with HDV RNA by quant PCR
- Clinical outcomes of HDV-infection depend on time interval of HBV- and HDV-infections (co- or superinfection), viral and host factors
- Outcome of CHD superinfection is characterized by rapid progression to cirrhosis, end stage liver disease and HCC
- Peg-IFNα is the only approved antiviral for the "treatment" of CHD, and its efficacy is less than 15-25%
  - Although emerging data in Turkey may show up to a 35-40% MVR rate with treatment up to 5 years
- Prevention HDV = vaccination against HBV
- LT with CHD is characterized by better outcomes compare to other VH (including HBV monoinfection)
- SVR after 48-week PEG IFNa Tx is <25 %
- Most often HDV dominates over HBV, but in HBV DNA-positive cases can be used HBV-polymerase inhibitors
- Combination of PEG IFNa and NAs does not improve Tx results
- Late HDV RNA relapses may occur after PEG-IFNa therapy of hepatitis delta and thus the term sustained virological response (new term MVR Maintained Virologic Response) should be avoided in HDV infection
- Treatment up to 5 years would be consider optimal with on treatment monitoring of HDV RNA q until we have new oral/injectable therapies that can clear HBsAg or HDV RNA cure