October 4th, 2017 12:00 PDT/ 3:00 EDT

Diagnosing Hepatitis Delta in the U.S.

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HEPATITIS B FOUNDATION

Phone/Audio Option

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Audio PIN: Shown after joining the webinar

Access Code: 642-605-645

All attendees are muted.

Questions?

Questions? Feel free to submit questions in the chat box at anytime throughout the webinar.

Disclosures

- Dr. Robert Gish is a Medical Consultant for Eiger Pharmaceuticals

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 Significance

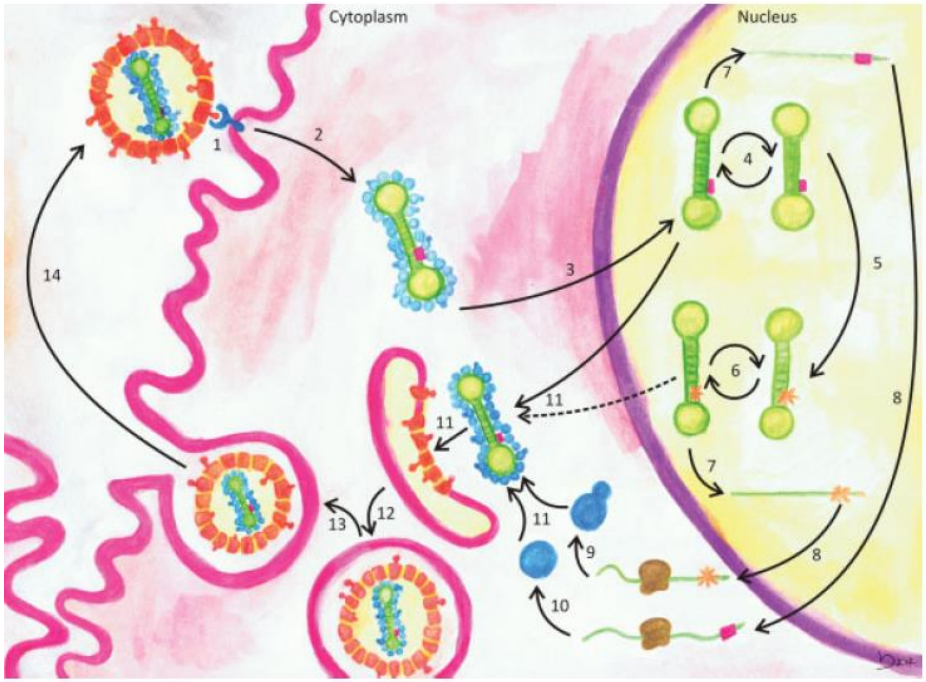
- HDV infection is associated with
  - Increased liver disease severity in setting of both superinfection and coinfection with HBV
  - More rapid rates of disease progression and early cirrhosis.

    Wang-Huei Sheng et al; Clin Infect Dis. 2007 Apr 1;44(7):988-95. Epub 2007 Feb 20.
  - Increased risk of HCC (up to 3x fold in HBV-cirrhosis)

    Fattovich G, Giustina G, Christensen E, Pantalena M, Zagni I, Realdi G, Schalm SW. Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep) Gut. 2000;46:420–426

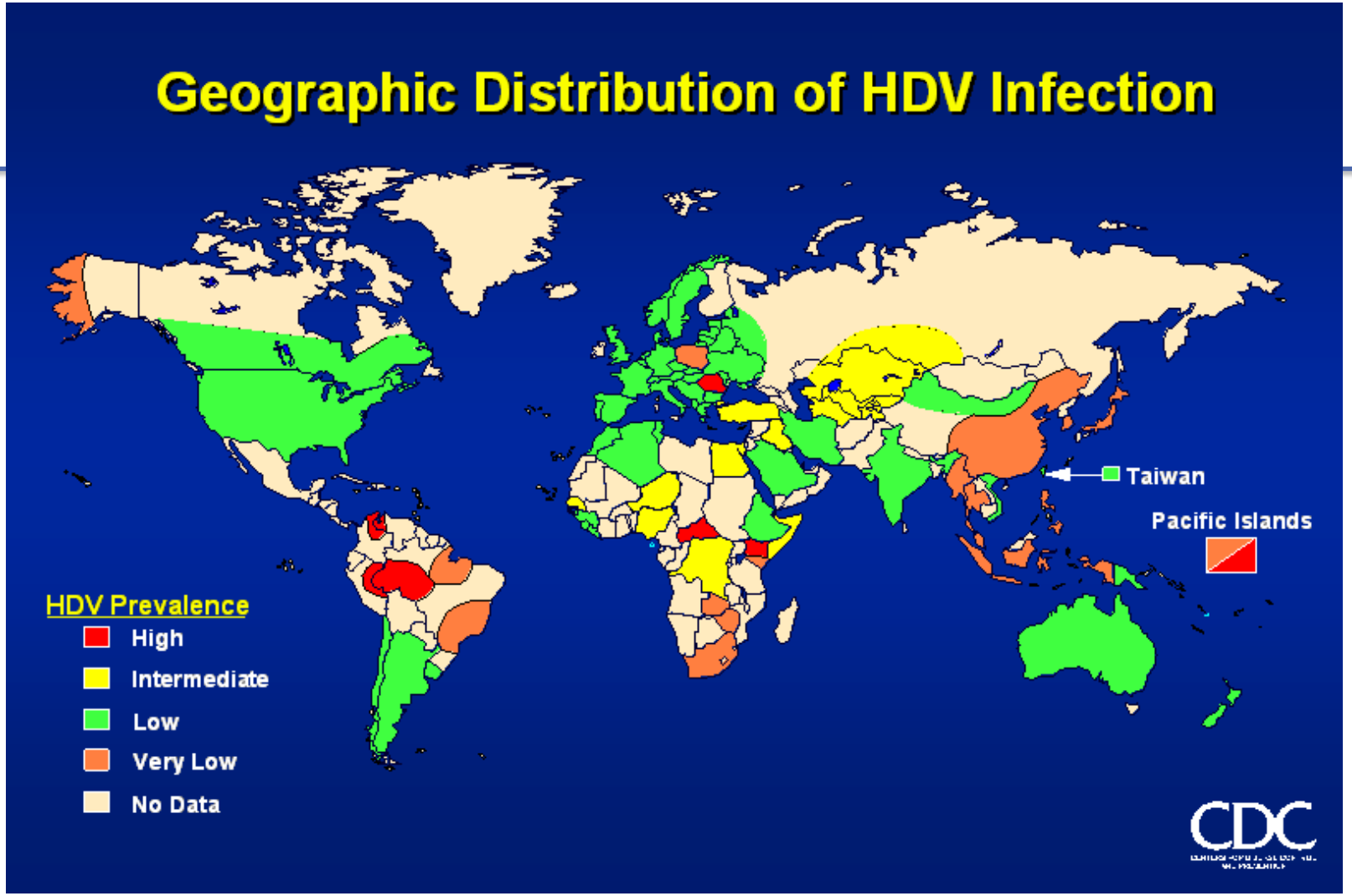
HDV: Virology

- HDV Transmission requires HBsAg!



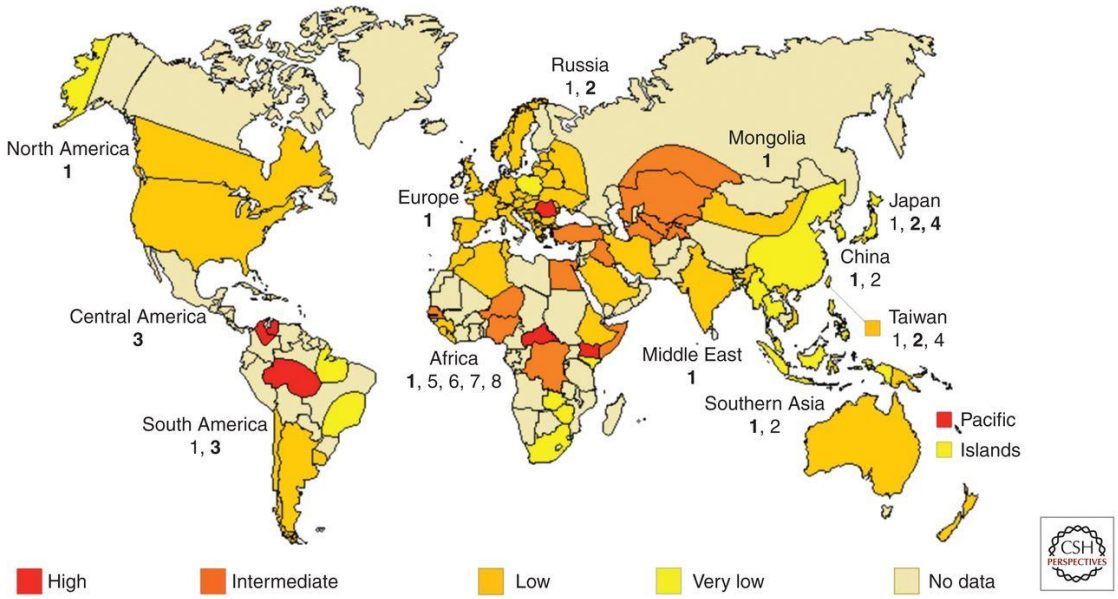
Calle Serrano, Manns & Wedemeyer, Seminars in Liver Disease 2012

Geographic Distribution of HDV Infection



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

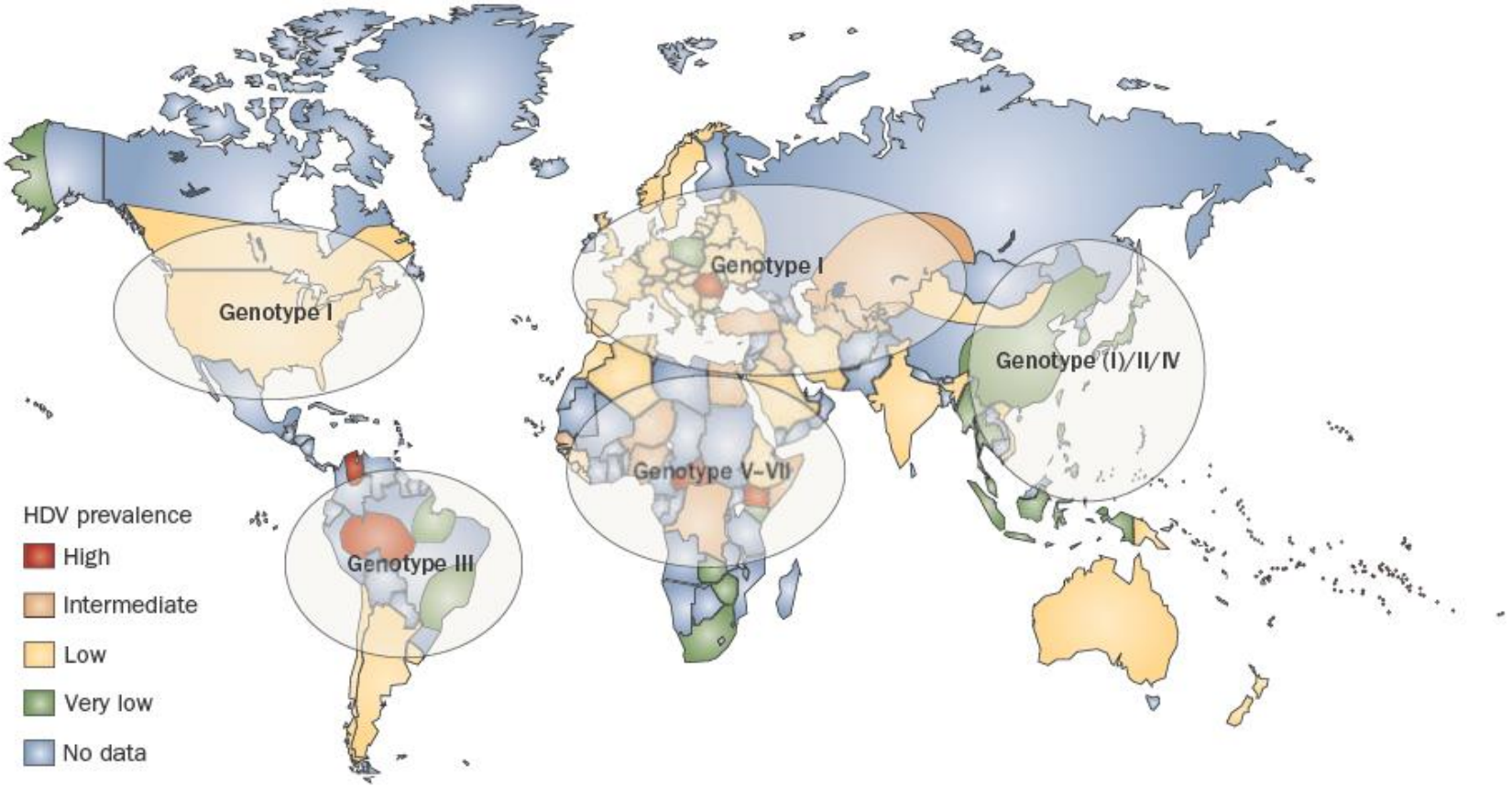
HDV TESTING RECOMMENDATIONS among HBsAg+ Individuals

- **AASLD Guidelines:** "Laboratory tests should include assessment of liver disease, markers of HBV replication, and tests for coinfection with HCV, HDV, or HIV in those at risk" which includes all individuals from HDV endemic areas and those with history of IDU".

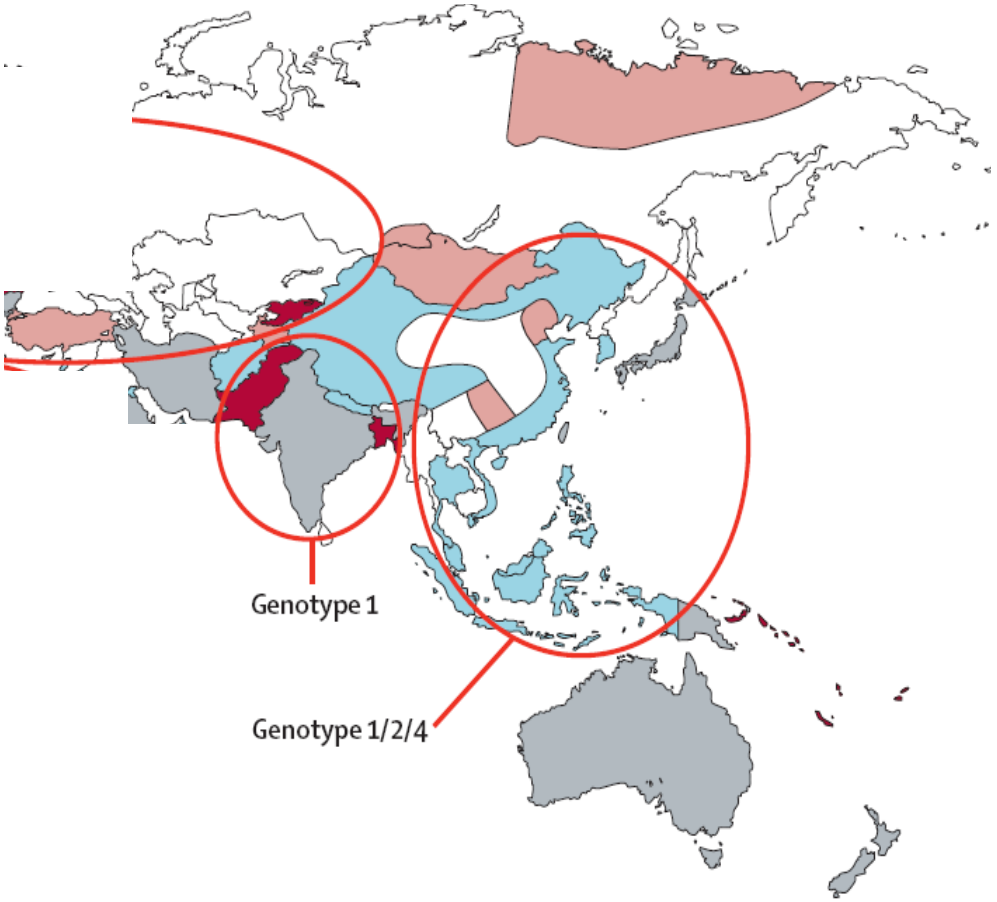
- **EASL Guidelines:** "Other causes of chronic liver disease should be systematically looked for including co-infections with HDV, HCV. and/or HIV (A1)"

- **APASL Guidelines:** "Other causes of chronic liver disease should be systematically looked for, including coinfections with HDV".

Different HDV Genotypes in Different Regions!



Prevalence of Hepatitis Delta by Genotype in the Asia-Pacific Region

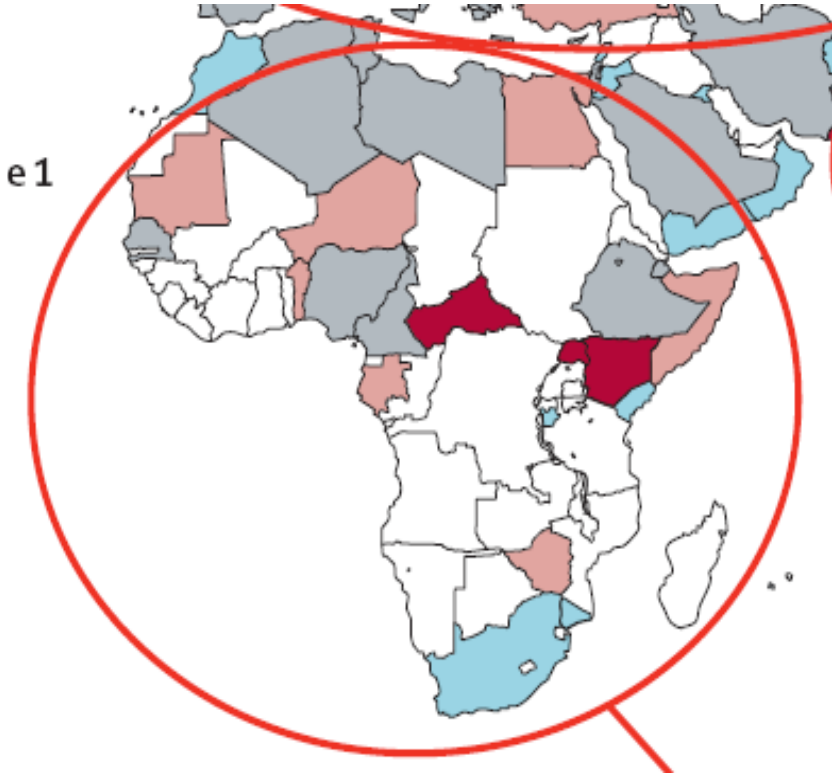


Hughes et al. The Lancet 2011; Abbas et al., World J Gastroenterol 2012

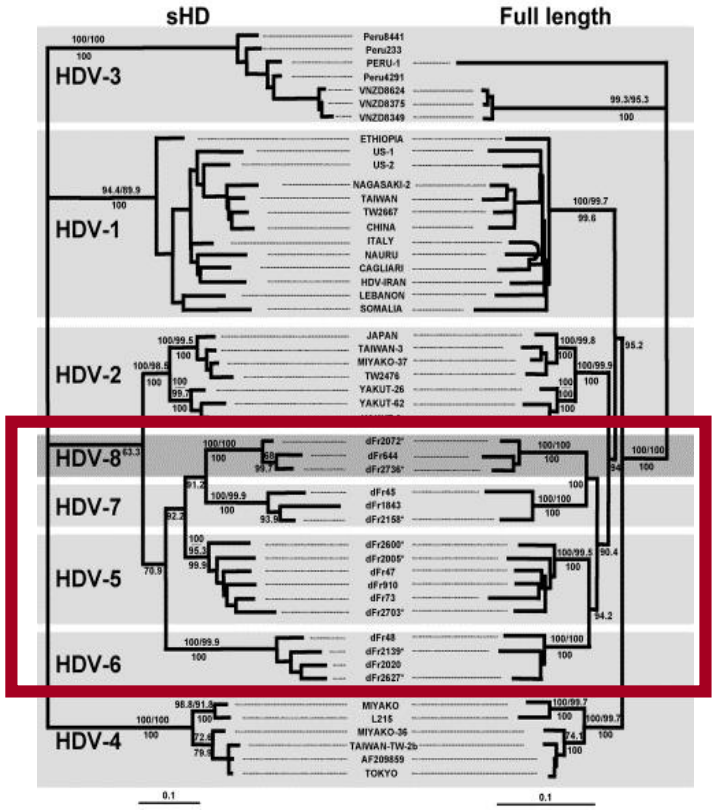
Prevalence of Hepatitis Delta in the Asia-Pacific Region Data presented at the EASL Delta Conference 2010

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



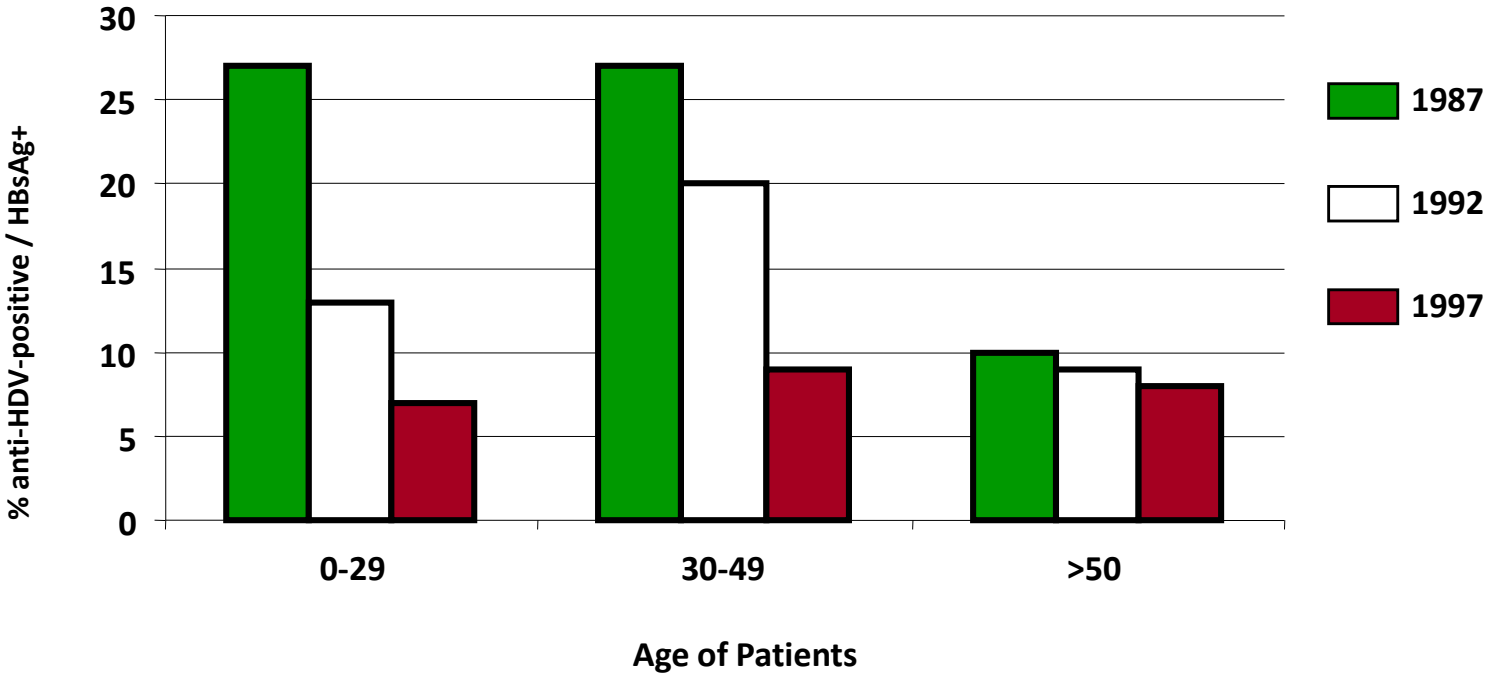
➢Genotypes 1, 5-8



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 1990's



Gaeta, Rizzetto et al., Hepatology 2000

Older Data:
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%)

From 1999 to 2012, data on 71,916 individuals were obtained, with 52,209 (72.6%) receiving HDV testing. The overall prevalence of HDV in the United States was 0.02% (10/52209), with a mean age of 52.1 ± 14.0 years and 60% males. Table 1 summarizes our results.

Njei Hepatology 2016

TABLE 1. Patient Demographics and Clinical Characteristics Stratified by HDV Status

Variable	HDV-Negative, % (n = 52,199)	HDV-Positive (%) (n = 10)	*P*
Mean age, years (SD)	36.6 (23.01)	52.1 (14.01)	**0.02**
Sex			
Male	49.2	60.0	0.54
Female	50.8	40.0	
Race/ethnicity			
Mexican American	23.3	10.0	**0.01**
Other Hispanic	7.1	0	
Non-Hispanic white	40.3	10.0	
Non-Hispanic black	23.3	50.0	
Other race, including multiracial	6.0	30.0	
HCV antibody			
Positive	1.2	20	0.08
Negative	98.8	80	
HIV status			
Positive	0.5	20	**0.03**
Negative	99.5	80	
Injection drug use			
Yes	2.8	0	0.99
No	97.2	100	
Homosexual men			
Yes	5.2	25	0.19
No	94.8	75	

Fisher's exact test was used for categorical variables and the Mann-Whitney test for continuous variables.
Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

Njei Hepatology 2016

HDV infections in the US population

- **Recent indications that HDV prevalence is increasing**
- **HDV prevalence in US was not assessed widely**

- Baltimore (n=194/258): prevalence declined from 15% to 11% in IVD between 1988-1989 and 2005-2006[2]
- US Veterans (n=2175 HBsAg + and tested for HDV): 3.4% positive[3]
- NHANES 1999-2012 weighted data: 0.02% prevalence

- 8% HDV in HBV patients San Francisco (2012)
- Need for improved surveillance in the US

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)

Journal of Gastroenterology and Hepatology
Gish et al., 2013

HDV in the US VA

- 3.5% of HBsAg+ who where tested were anti-HDV positive

- Predictors of being HDV tested included
- male gender (4.5 vs. 1.3%, p <0.001)
- Asian ethnicity (8.5 vs. ≤5% any other*, p <0.001)
- HBcIgM+ status (29 vs. 9.0% of HBcIgM-*, p<0.001)
- HBeAg+ (21.3 vs. 13.0% HBeAg-*, p<0.001)
- HCVAb+ (5.3 vs. 4.3% HCVAb-*, p<0.001)
- HIV+ (9.4 vs. 4.0% HIV-* p<0.001)
- ALT (peak ± 180d, 383 vs. 95u/l, p<0.001)
- HBV DNA > 2000 IU/ml (21.8 vs. 14.7%%*, p< 0.001)[

Kushner AASLD 2015 (see notes)

HDV in the US VA (part 2)

- 74 HDV+ individuals
  - 43 (58%) were HCVAb+
  - 7 (9.5%) HIV-coinfected
  - There was no difference in age, ethnicity, or comorbidity in HDV+ and HDV-subjects
  - 69% of HDV+ were HBeAg-, 74% HBeAb+, and 23/26 (88%) had HBV DNA titers <2000 IU/ml.

Kushner AASLD 2015

HDV Epidemiology in the US

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

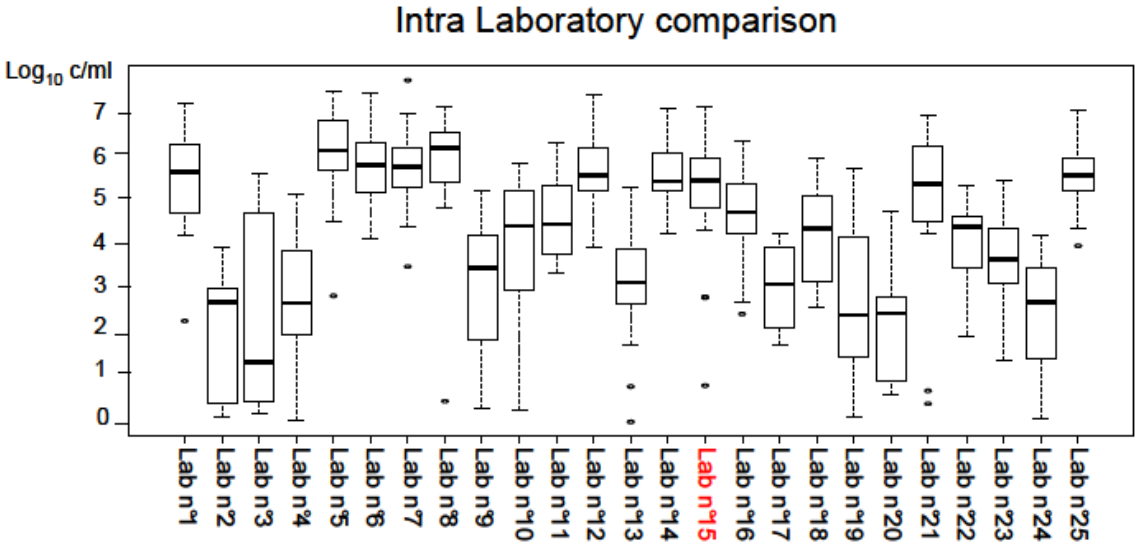
Lauren M. Kucirka,[2] Homayoon Farzadegan,[1] Jordan J. Feld,[5] Shruti H. Mehta,[1] Mark Winters,[4] Jeffrey S. Glenn,[4] Gregory D. Kirk,[1] Dorry L. Segev,[1,2] Kenrad E. Nelson,[1] Morgan Marks,[1] Theo Heller,[3] and Elizabeth T. Golub[1]

	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

Participation in the 1st International Quality Control for HDV RNA Quantitation (2013)

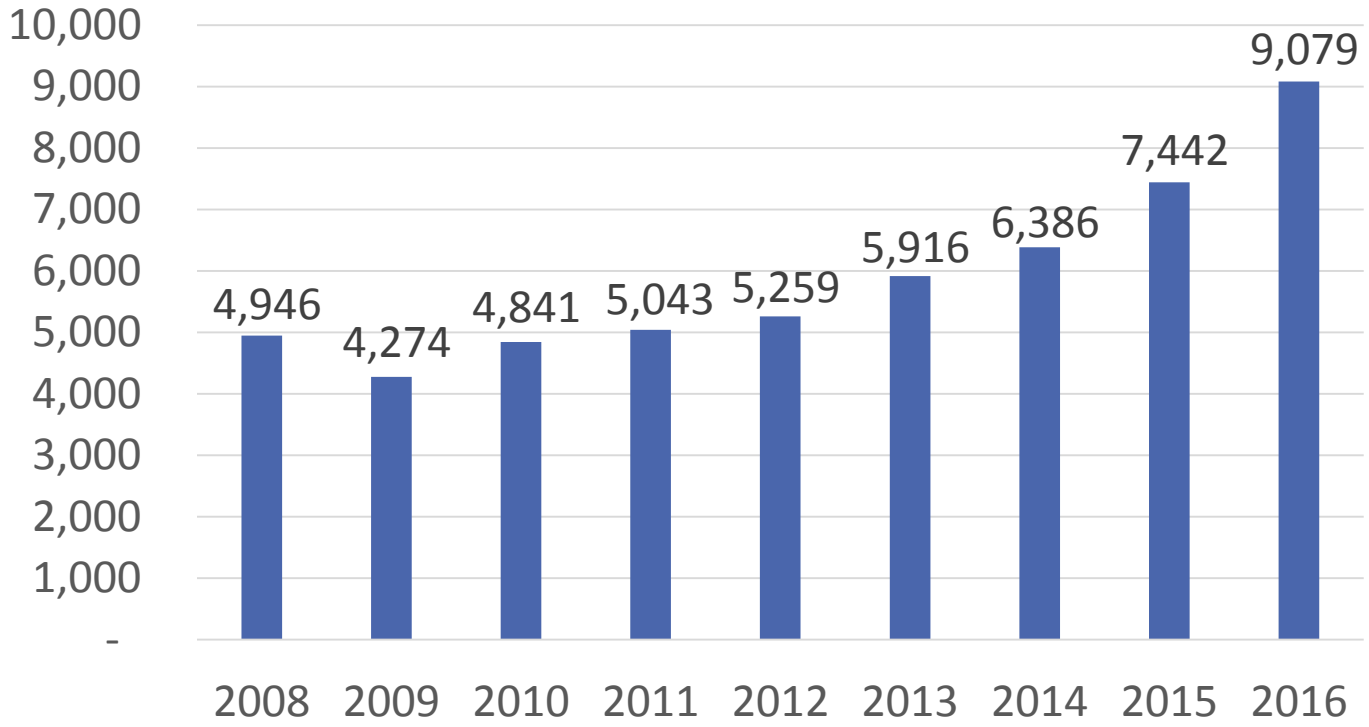
Figure 2



Hayden HDIN AASLD 2016

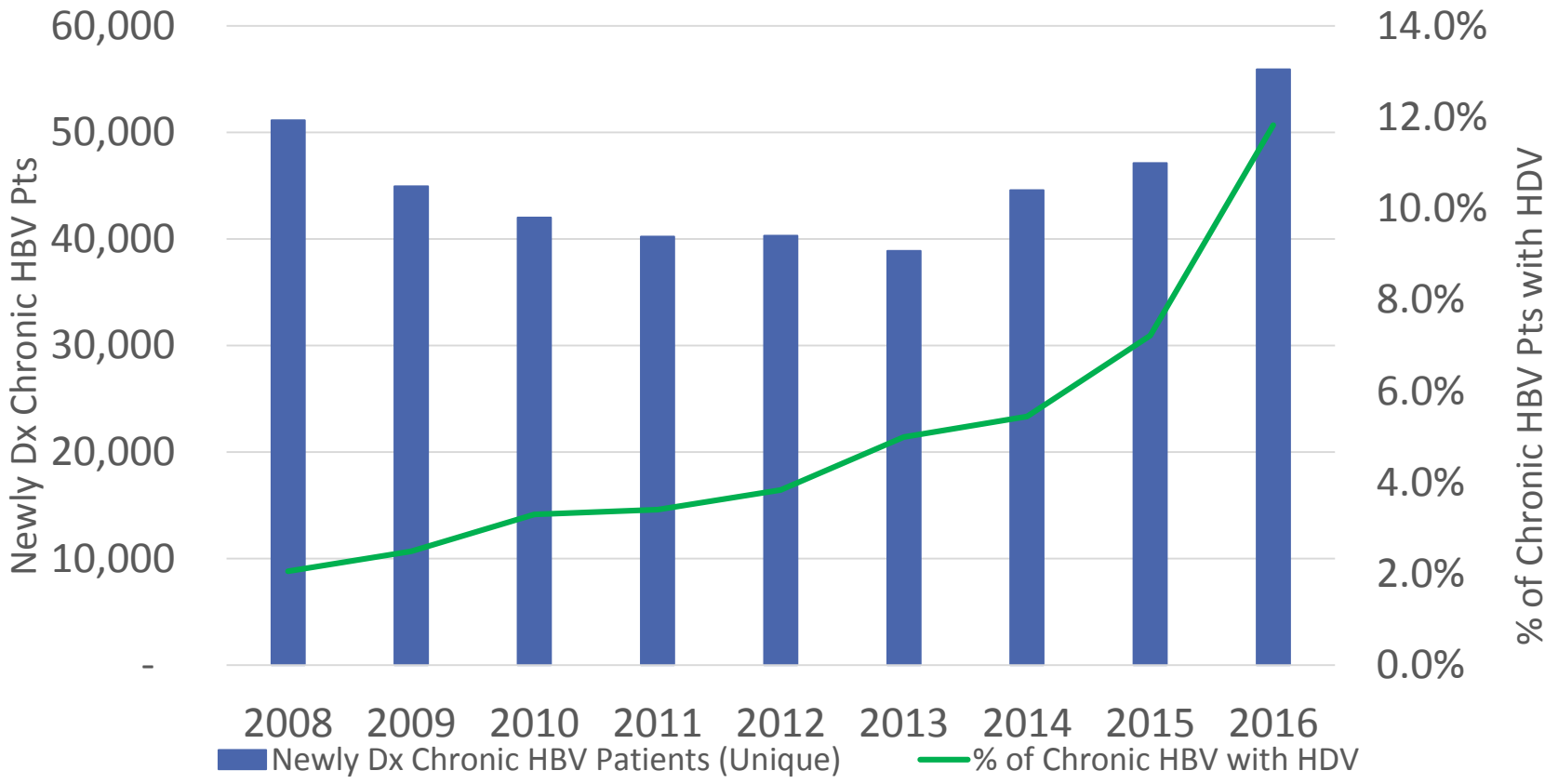
Newly Diagnosed HDV Patients in the US

(Unique Patients)



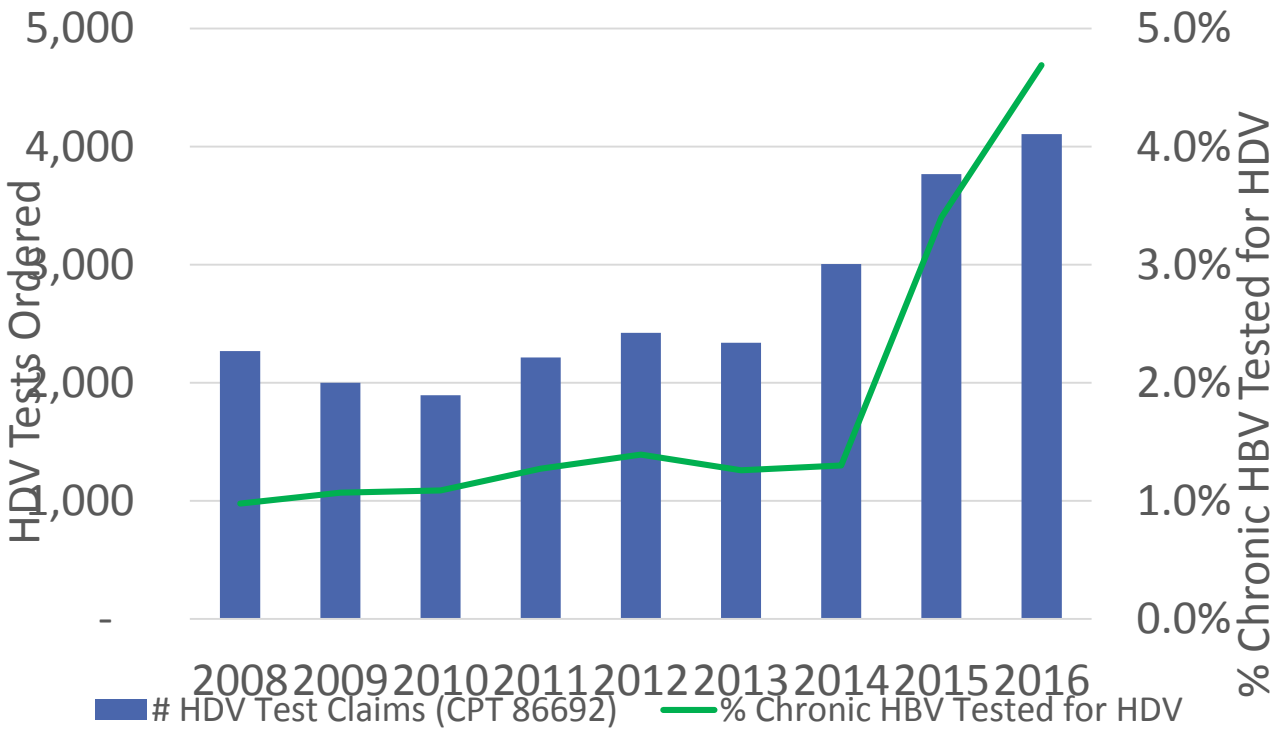
Source: Martins, E and Glenn, J. Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10 Review. Poster Sa1486 DDW May 2017.

Chronic HBV Pts and % Pts with HDV



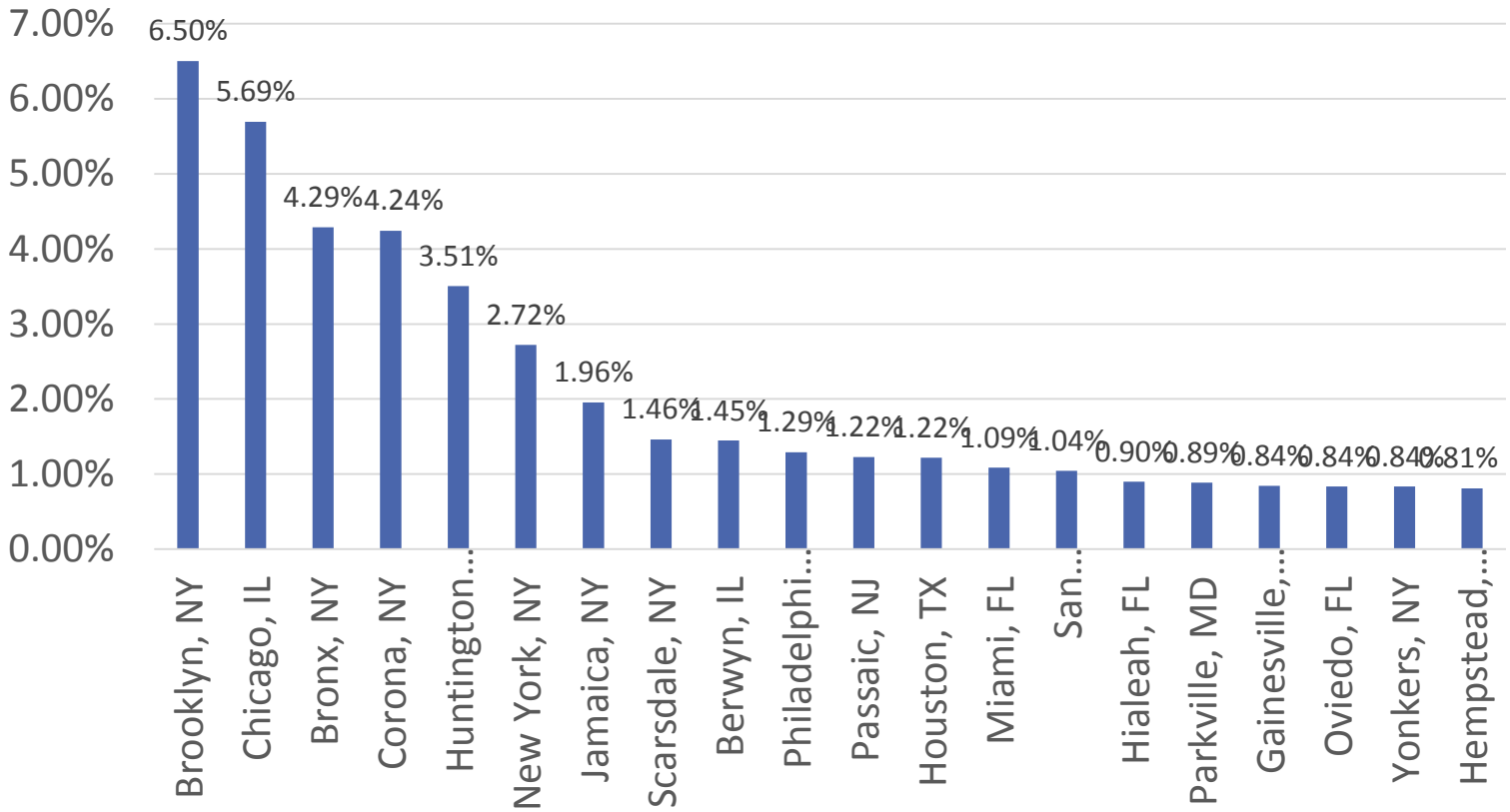
Source: Martins, E and Glenn, J. Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10 Review. Poster Sa1486 DDW May 2017.

HDV Tests Ordered and % Chronic HBV Patients Tested for HDV



Source: Martins, E and Glenn, J. Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10 Review. Poster Sa1486 DDW May 2017.

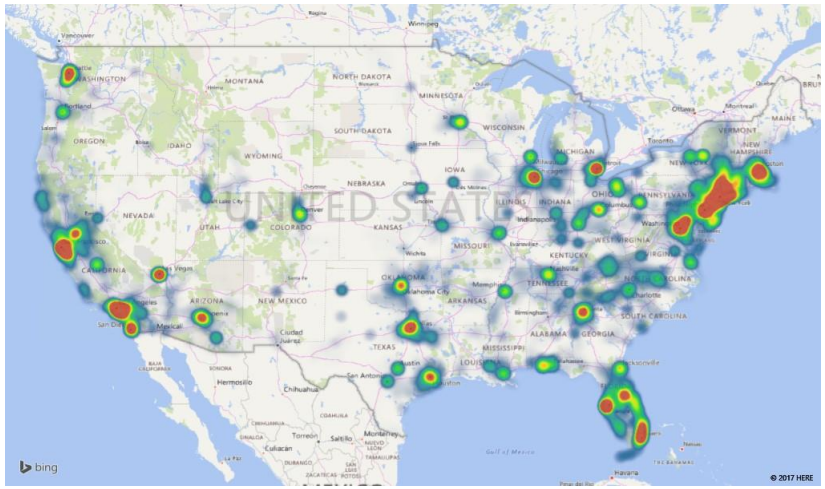
Top 20 US Geographies for HDV Patients



Source: Martins, E and Glenn, J. Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10 Review. Poster Sa1486 DDW May 2017.

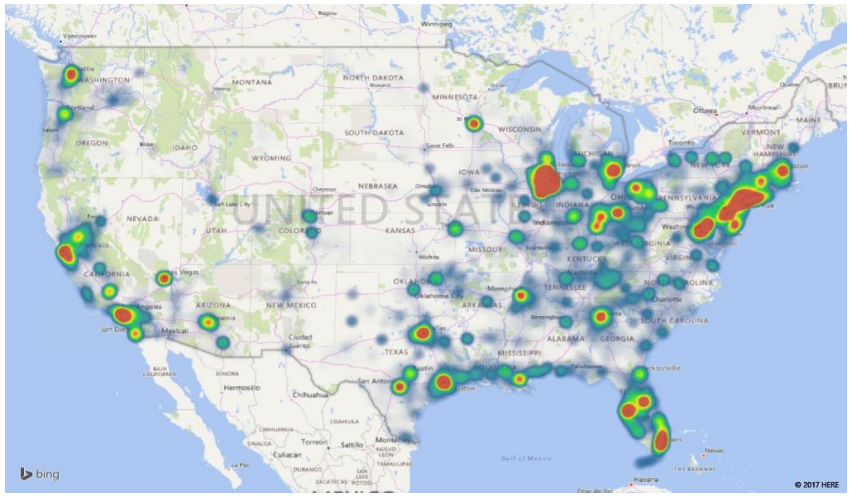
Comparison of HDV Patient Footprint 2008 vs 2016 and Top 20 Geographies for Each Year

2008



1. Brooklyn, NY	6. Bronx, NY	11. La Puente, CA	16. Chicago, IL
2. New York, NY	7. Philadelphia, PA	12. St. Petersburg, FL	17. Franklin, MA
3. Yonkers, NY	8. Jamaica, NY	13. Staten Island, NY	18. Las Vegas, NV
4. Corona, NY	9. San Francisco, CA	14. Pittsburg, CA	19. Newburgh, NY
5. Scarsdale, NY	10. Passaic, NJ	15. Detroit, MI	20. Huntington ST, NY

2016



1. Chicago, IL	6. New York, NY	11. Huntington ST, NY	16. Cicero, IL
2. Berwyn, IL	7. Bronx, NY	12. Philadelphia, PA	17. Parkville, MD
3. Brooklyn, NY	8. Jamaica, NY	13. Houston, TX	18. Miami, FL
4. Corona, NY	9. Lombard, NY	14. Passaic, NJ	19. Hialeah, FL
5. Waukegan, IL	10. Aurora, IL	15. Staten Island, NY	20. Las Vegas, NV

Source: Martins, E and Glenn, J. Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10 Review. Poster Sa1486 DDW May 2017.

HDV in a “low prevalence” country

- Vietnam

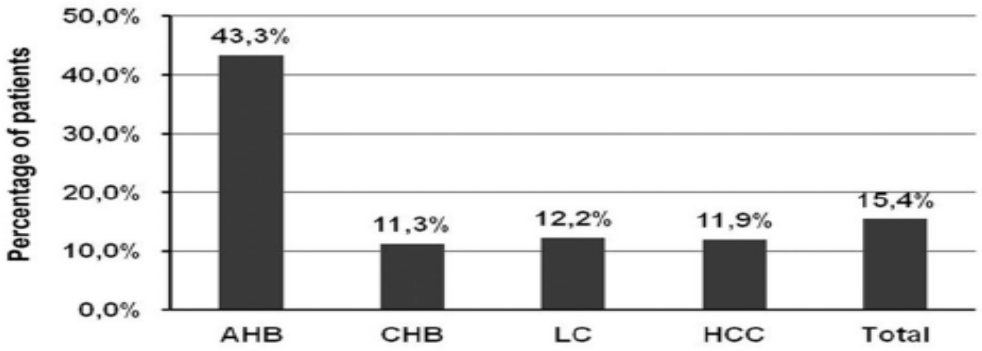
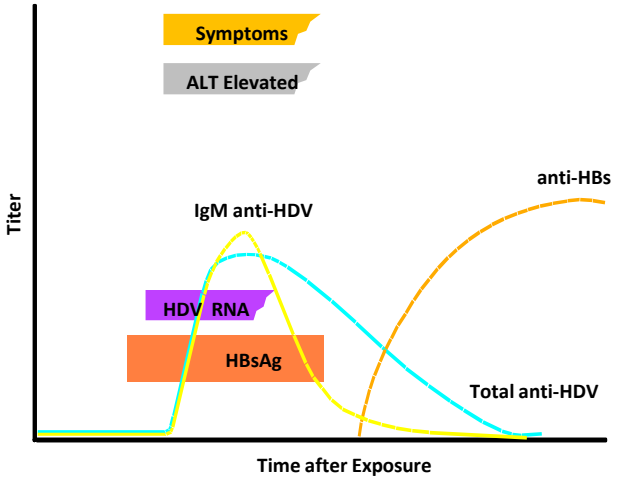


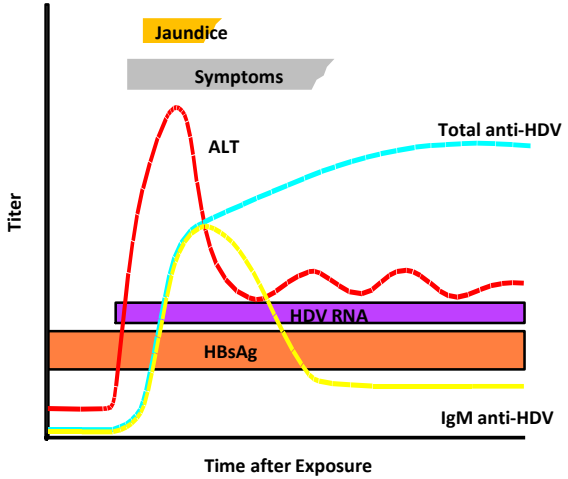
Figure 2. Prevalence of HDV genomes in the HBsAg-positive Vietnamese patients. The prevalence of HDV infection in AHB group was significantly higher in comparison to the CHB, LC and HCC groups (OR =0.19 (CI95 [0.23-0.66]), 0.20 (CI95 [0.08-0.54]), 0.25 (CI95 [0.22-0.71]), respectively; two tailed Fisher’s exact test, $p<0.01$). Overall, the HDV-prevalence of all patient groups was 15.4% (CI95 [11.1-19.8]) (Total).

doi: 10.1371/journal.pone.0078094.g002

Tien, 2013

HDV Co- and Superinfection

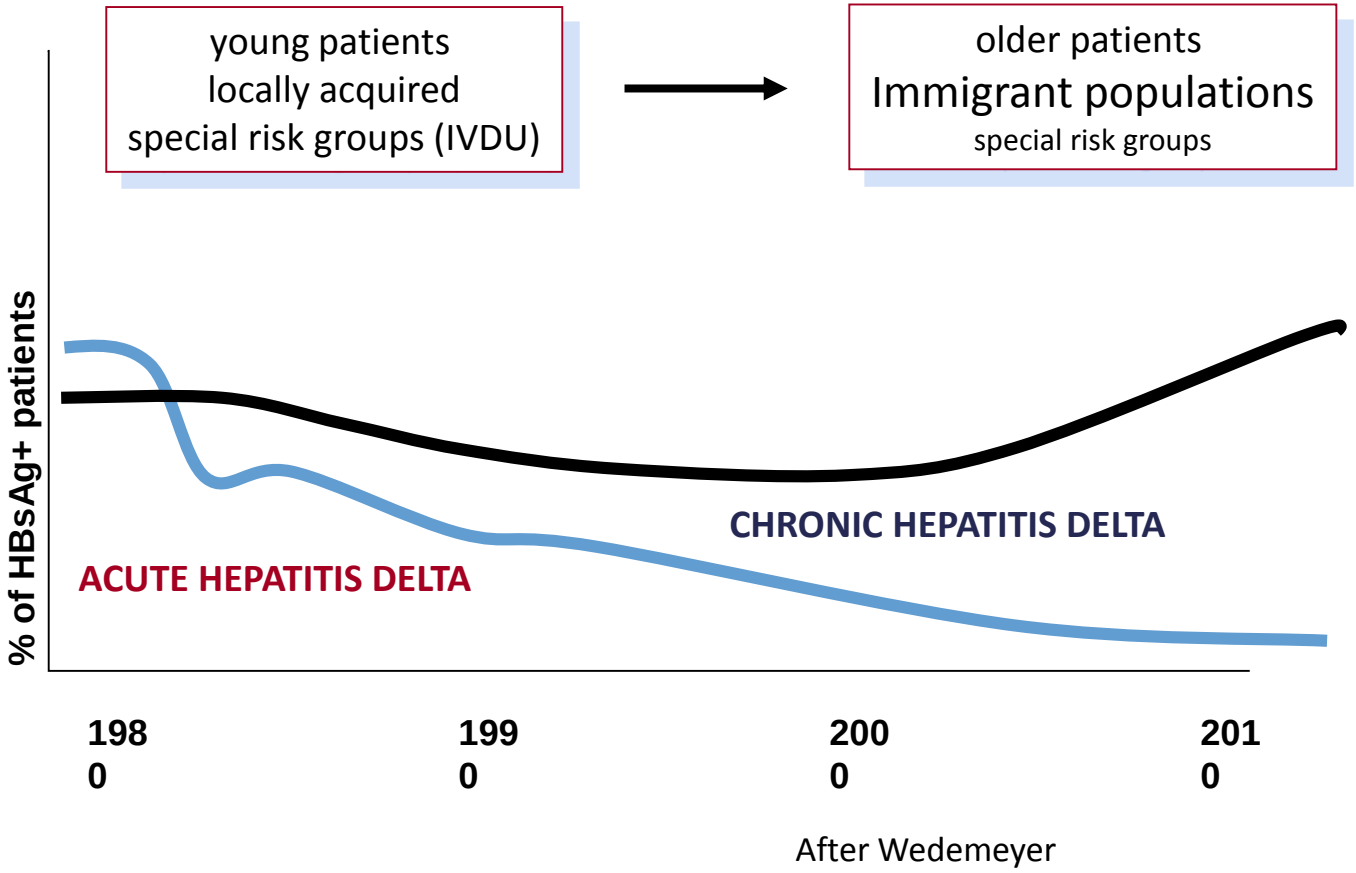




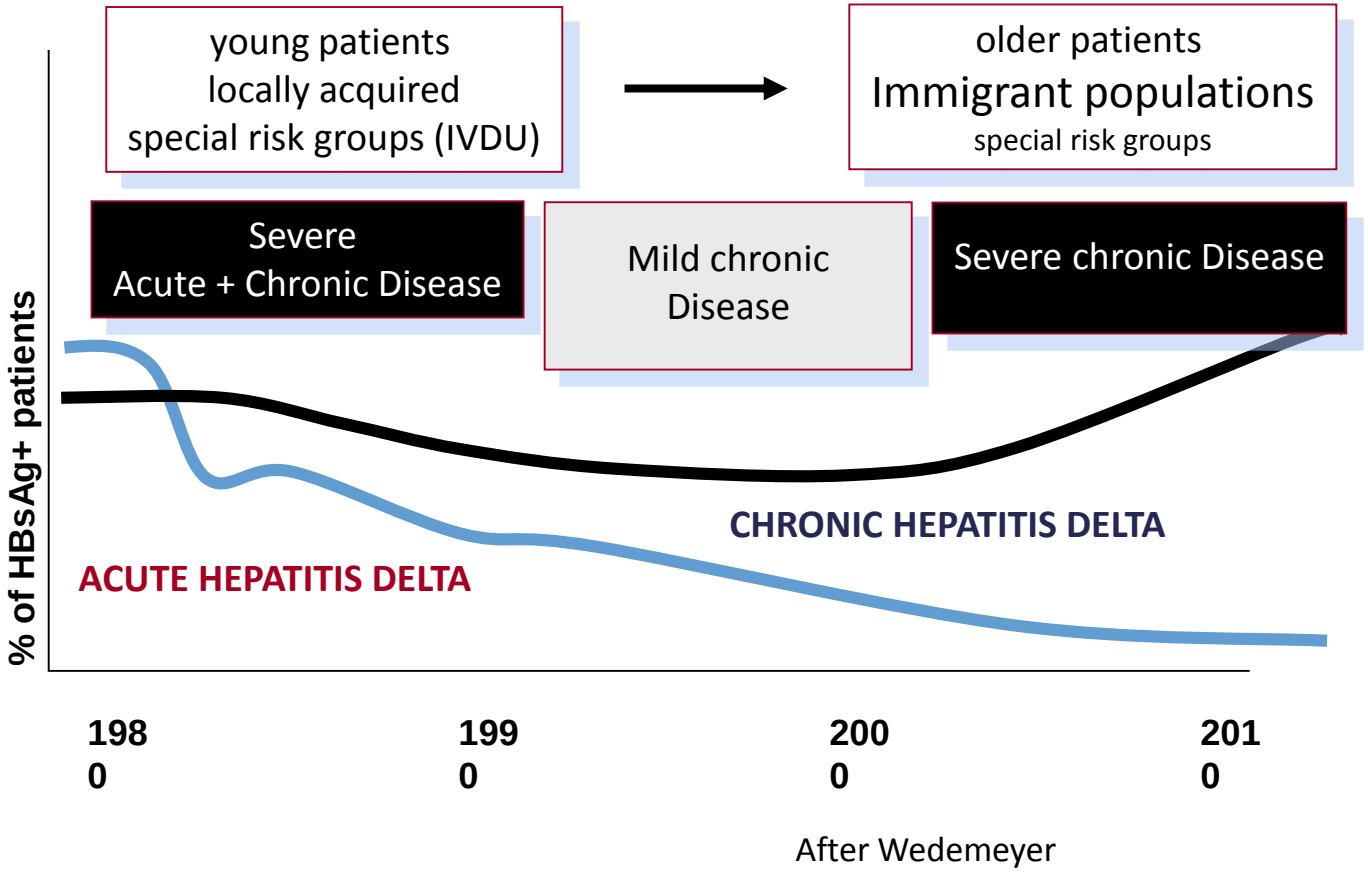
- Co-infection:
  - Clinically indistinguishable from acute HBV
- Usually acute and self-limited (95%), HDV and HBV clearance
- High frequency of acute liver failure in IDUs

- 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



Hepatitis Delta: Evolution of Clinical Presentation (Cont.)



HDV: Modes of Transmission

- HDV Transmission requires HBsAg!
- Intrafamilial transmission

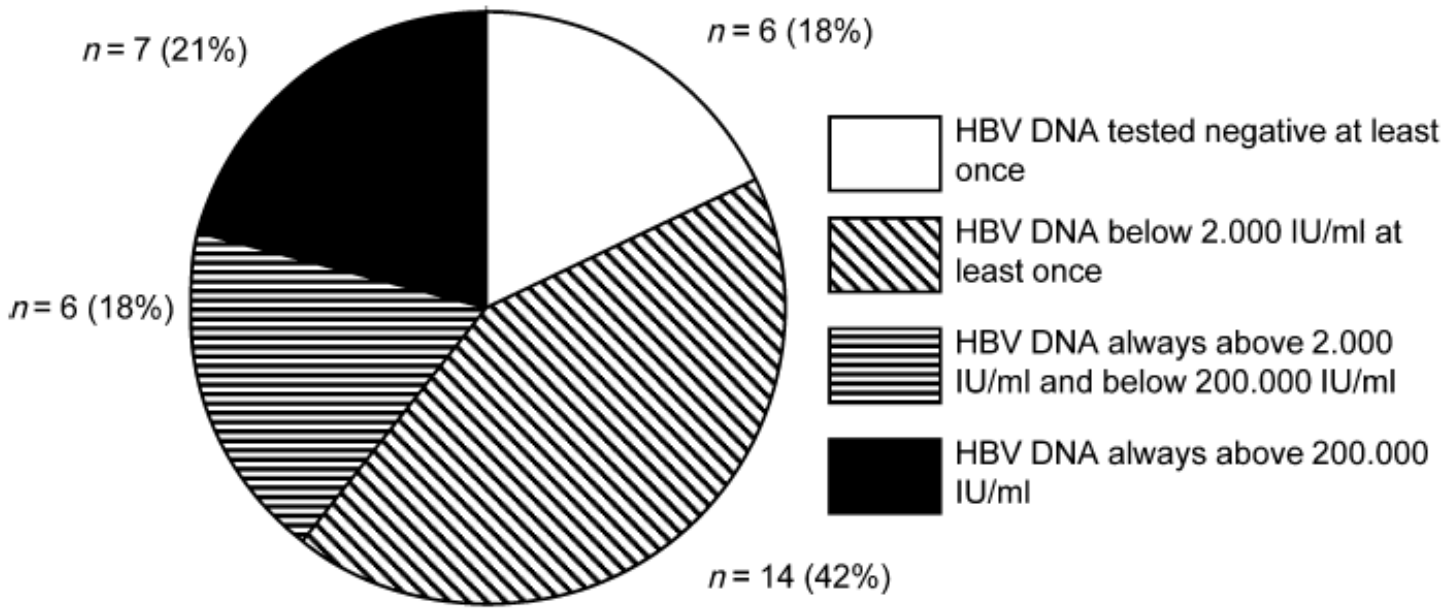
  vertical & sexual transmission,
  infection during early childhood
- *Folk remedies, scarification, percutaneous exposure*
- Medical treatment

  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

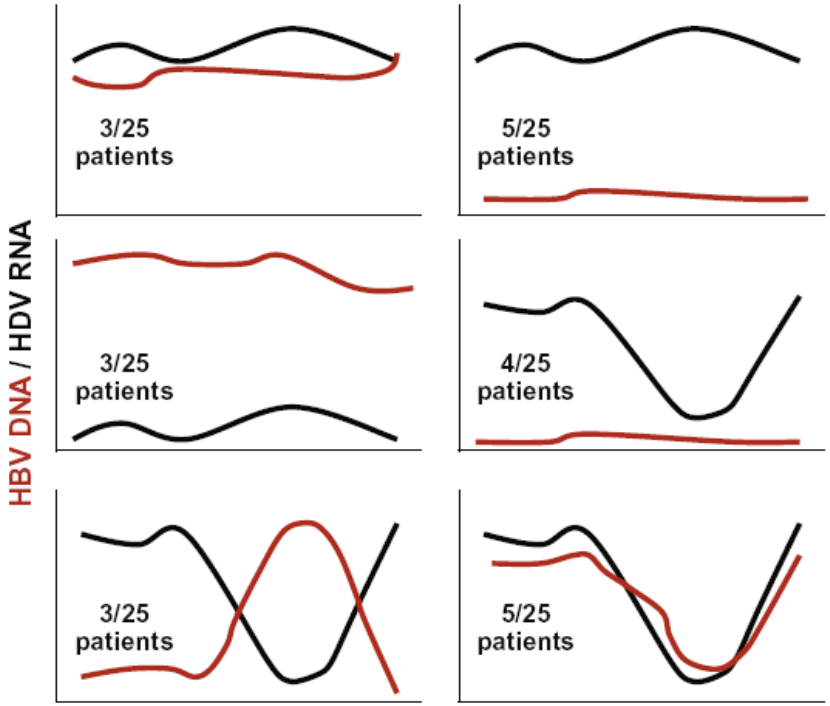
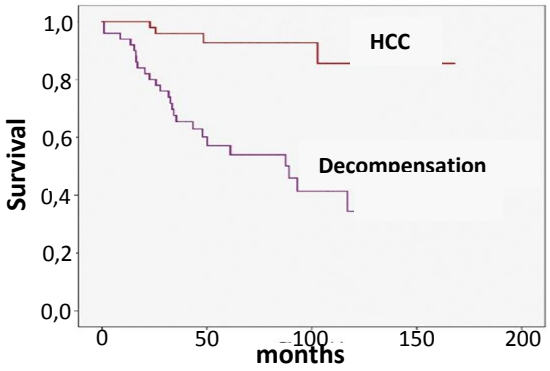


Fig. 1. Schematic representation of HBV DNA and HDV RNA patterns over time observed in the study by Schaper et al. [19].

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

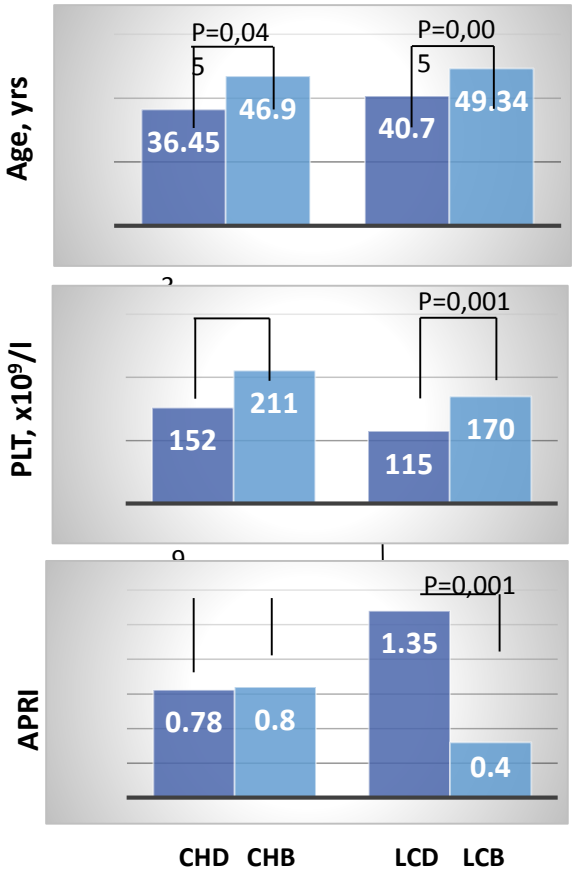
Liver Disease Progression

- 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

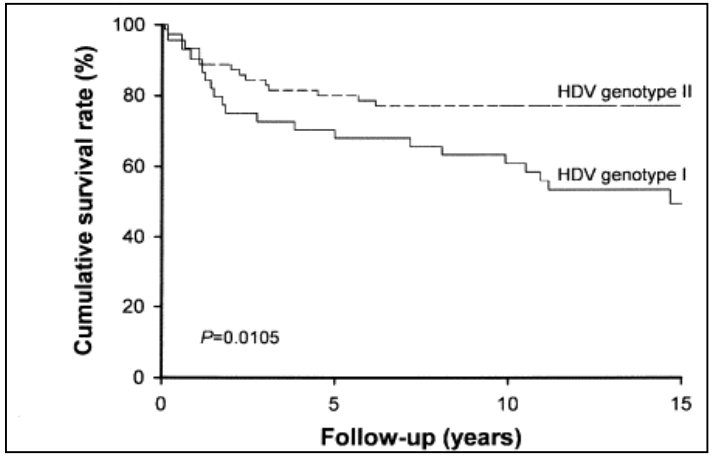
G Fattovich, G Giustina, E Christensen et al. Gut 2000;46:420–426; Farci P. EASL monothematic conference "Delta Hepatitis", Istanbul, Turkey, September 24-26, 2010, Oral; Bonino F, Negro F, Baldi M, et al. Prog Clin Biol Res. 1987;234:145-152; Romeo, R. et al. Gastroenterology 136, 1629–1638 (2009);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

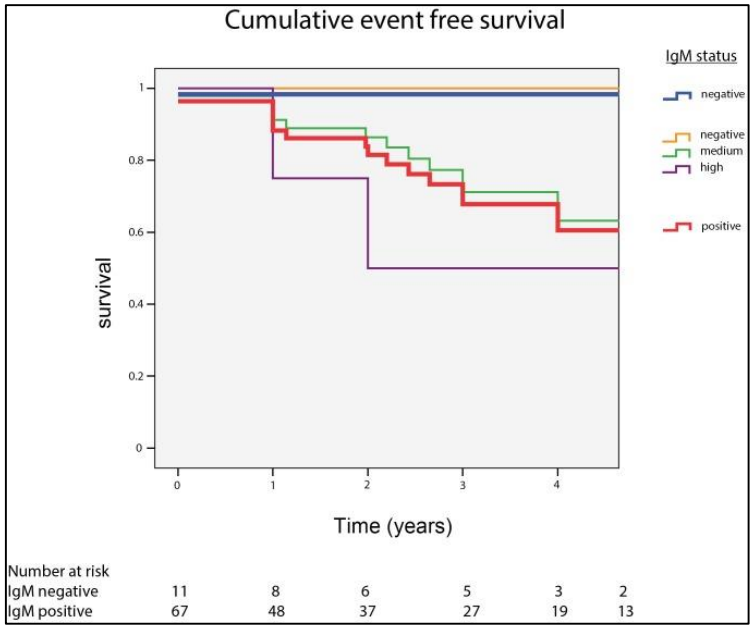
Outcomes of Hep D depends on HDV genotype



- 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

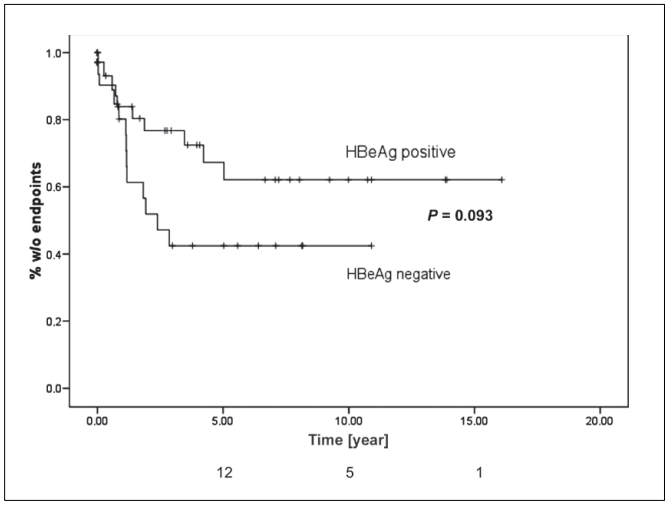
Table 4. Characteristics of hepatitis delta patients ($n = 73$) according to the histological activity index

	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

HDIN 11 2016

- 1605 patients in the database
- Need cholinesterase for HDIN BEA fibrosis score
- Test for liver function or hepatic reserves, synthesized in hepatocytes, 11 variants, 20 individual variations, diff stage of F0-F3 from F4, correlates with CTP, MELD correlation, (Pakistan AASLD 2016)
- 63% male
- Median age 36
- 85% RNA +
- 25% HBeAg(+)
- 70% plt below 100 000 in 60%
- INR high in 70%
- 75 % received INF therapy
- 25% Nuc only

Warnke AASLD 2016

CDC 11 2016

- Aby Diasorin increasing prevalence via NHANEs
- PCR: LOQ is 500 copies
- 1 step assay taqMan primers in the region of the large HDV Ag
- 75 copies LOD
- Range: 100 and 100 M of quant
- 49 samples since Oct 2014
  - 73% were male
  - Median age 39 10-70 range
  - Ethnicity: wide range
  - States: in US: PA 33 cases dominated
  - Genotypes at CDC G 1 and 5 (15 cases)

Meta-analysis: antiviral treatment for chronic Hep D

- Sources: 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
  - Reset HDV RNA level, reset ALT level
- 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 (Cont.)

- 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

New treatments ?

- The drug, Ezetimibe, which is currently known to lower cholesterol, is being used in a trial in Pakistan for patients with chronic HDV (phase II): https://clinicaltrials.gov/ct2/show/NCT03099278?term=hepatitis+D&rank=4

Liver Transplant for 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..*

Under Utilization of Hepatitis D Virus Testing among HBV Monoinfected and HBV/HIV Coinfected Patients

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Isaac Privatera
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UNIVERSITY OF Cincinnati

HEPATITIS B FOUNDATION

Goals/Hypothesis

- Determine frequency of testing for HDV among those with HBV infection.
- Whether HIV-infected persons will have higher rates of testing than those without HIV.
- Whether Gastroenterologists/Hepatologists will order HDV tests more frequently than other physician groups.
- Determine prevalence of HDV among tested HBsAg positive persons.

Methods

- Extracted de-identified data of all subjects with a positive HBsAg in our electronic medical record system (EPIC).

- Examined characteristics of individuals with and without testing for multiple parameters, including:
  - Age
  - Gender
  - Race
  - Relationship with serum aminotransferases
  - HBeAg-status
  - HBV DNA
  - IVDU
  - Clinician by which the HDV antibody testing was ordered

Statistics

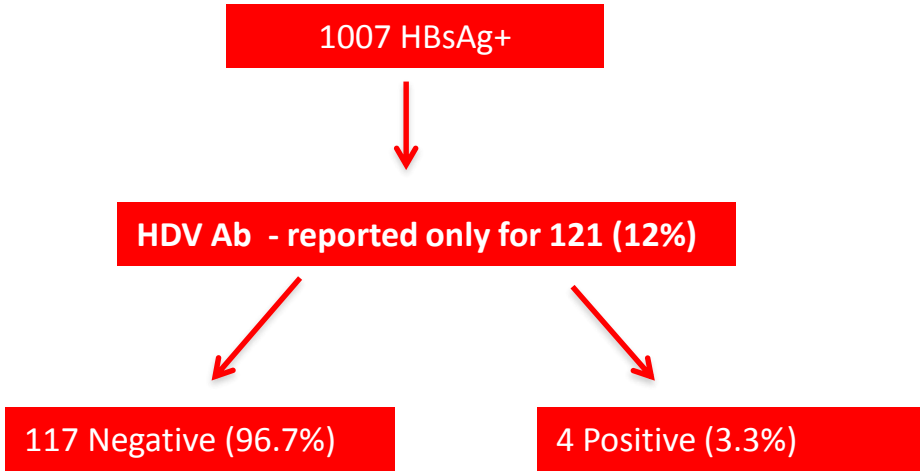
- Parametric and non-parametric comparisons were performed as appropriate to the data using Statistix 10.0.

- A p-value of 0.05 was considered significant.

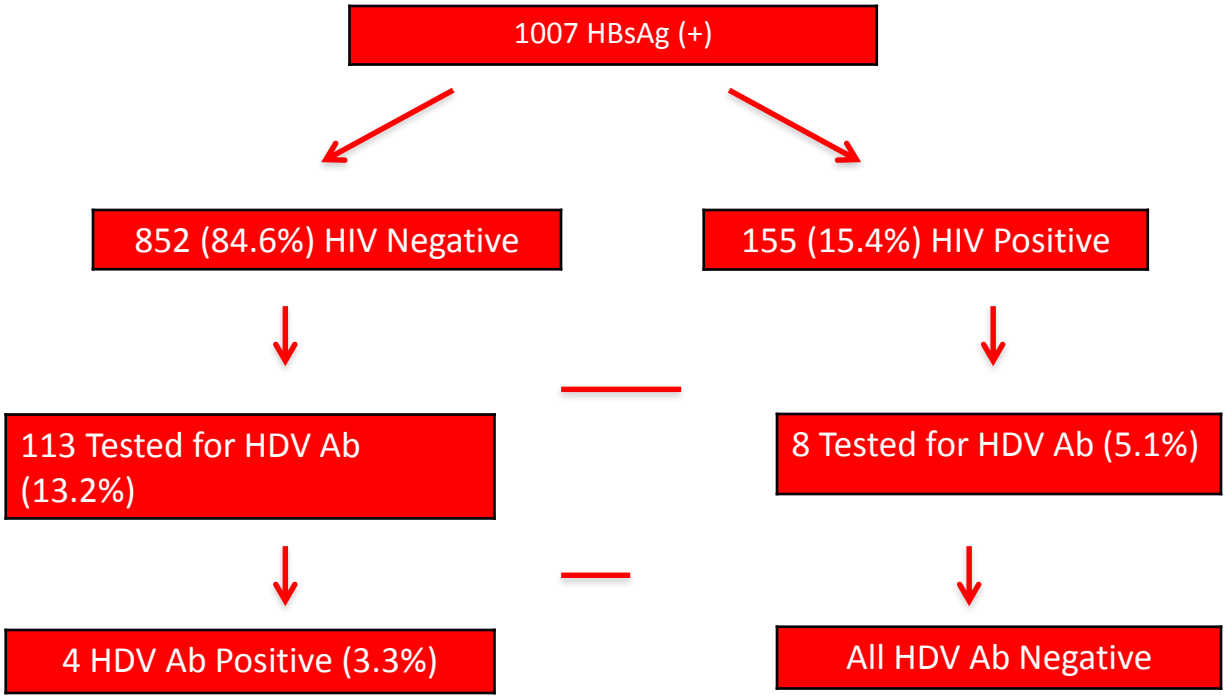
RESULTS
Demographics

N= 1007 HBsAg Positive Persons	
Gender	386 Females (38%) **621 Males (61%)**
Race	**Whites (53%)** Black (29%) Asian & Others (18%)
IVDU –reported for 886 (88%)	**7 IVDU (0.8%)** 879 non-IVDU (99.2%)
Female partners - reported for 886 (88%)	85 (9.6%)
Male partners - reported for 886 (88%)	103 (11.6%)
HIV status	**HIV Positive 155 (15.4%)** HIV Negative 852 (84.6%)
HBeAg status - reported for 482 (48%)	**287 Negative (59.5%)** 195 Positive (40.5%)
HBeAb status – reported for 455 (45%)	195 Negative (42%) **260 Positive (57.1%)**

RESULTS


1007 HBsAg+
HDV Ab - reported only for 121 (12%)
117 Negative (96.7%)
4 Positive (3.3%)

RESULTS (Cont.)



CHACTERISTICS by HDV STATUS

(for the 121 subjects tested for HDV, which includes 8 HIV+ subjects)

Groups	HDV Ab (+) N= 4	HDV Ab (-) N= 117	P value
Age	57	45.8	ns
ALT (Mean)	343 (SE ± 447.08)	314 (SE± 82.6)	ns
IVDU	0	2	ns

Groups	HDV Ab (+) N= 4	HDV Ab (-) N= 81	P value
HBV DNA (Available for 85 patients)	6.25 IU/mL (Mean)	4.27×10^6 IU/mL (Mean)	0.02

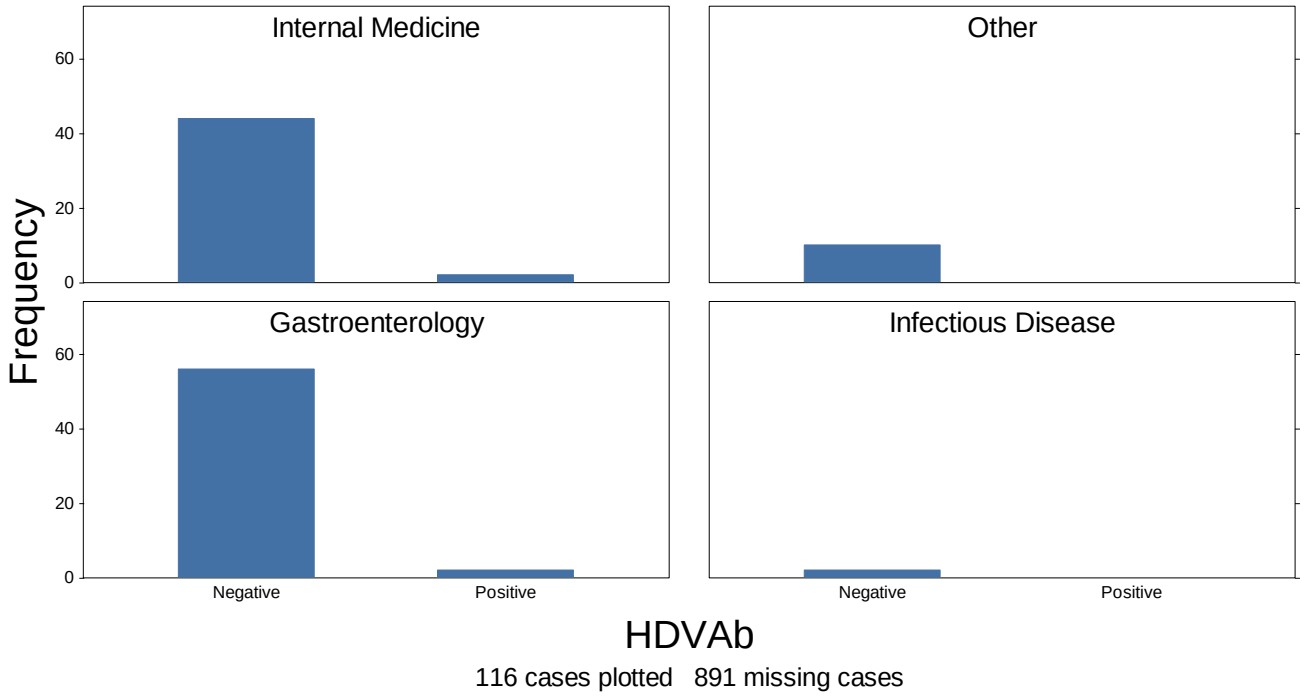
CHACTERISTICS by HDV STATUS

(for the 121 total subjects tested for HDV, which includes 8 HIV+ subjects)

Groups	HDV Ab (+) N= 4	HDV Ab (-) N= 117	P value
HBeAg Negative	3	46	0.04
HBeAg Positive	0	64	

Groups	HDV Ab (+) N= 4	HDV Ab (-) N= 117	P value
HBeAb Negative	0	48	ns
HBe Ab Positive	3	48	

TESTING By Specialty



Summary: Sherman et al

- HDV testing is rarely performed in HBsAg+ subjects in our system.
- Patients with HIV are less likely to have been tested than those without HIV.
- Gastroenterologist/Hepatologists are more likely to order HDV testing than other health care providers.
- The rate of HDV positivity in a mid western city was 3.3% (95% C.I. range 0.9% - 8.2%).

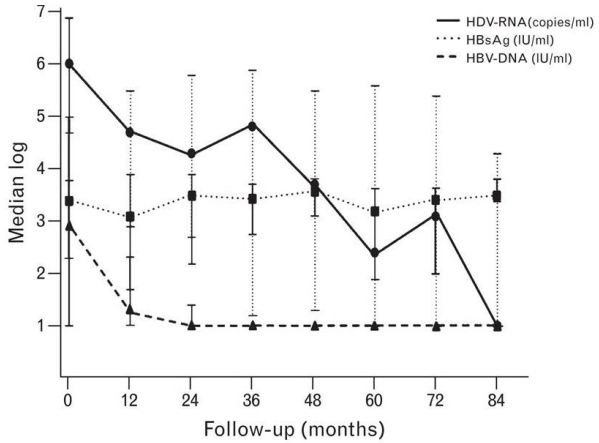
Conclusions

- HDV antibody test performance is inadequate in all groups.
  - Among tested persons, rates of HDV Ab among HBsAg+ persons are higher than would be expected.

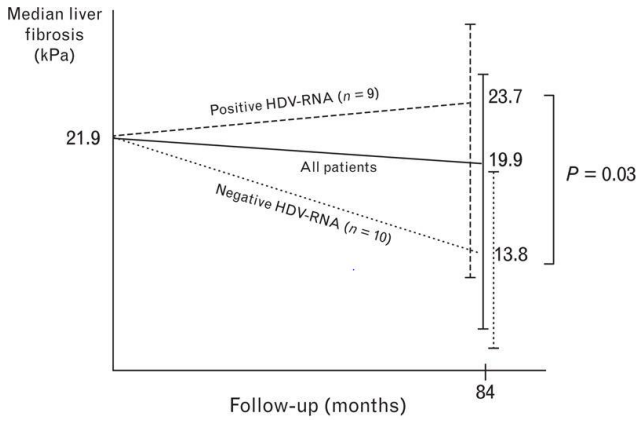
  Limitations of the study:
  - We do not know if the tested group was selected because of higher putative prevalence of HDV.
  - HDV RNA testing is not available routinely at many institutions, including our own, and should be considered.

- Targeted reminders may play a role in improving testing performance.

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



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

Functional control and clinical benefit 1 year following completion of REP 2139 / peg-IFN therapy in patients with chronic HBV / HDV co-infection

M. Bazinet, V. Pântea, V. Cebotarescu, L. Cojuhari, P. Jimbei, A. Krawczyk, A. Vaillant

13th HDIN Meeting in Amsterdam (EASL) April 19th 2017

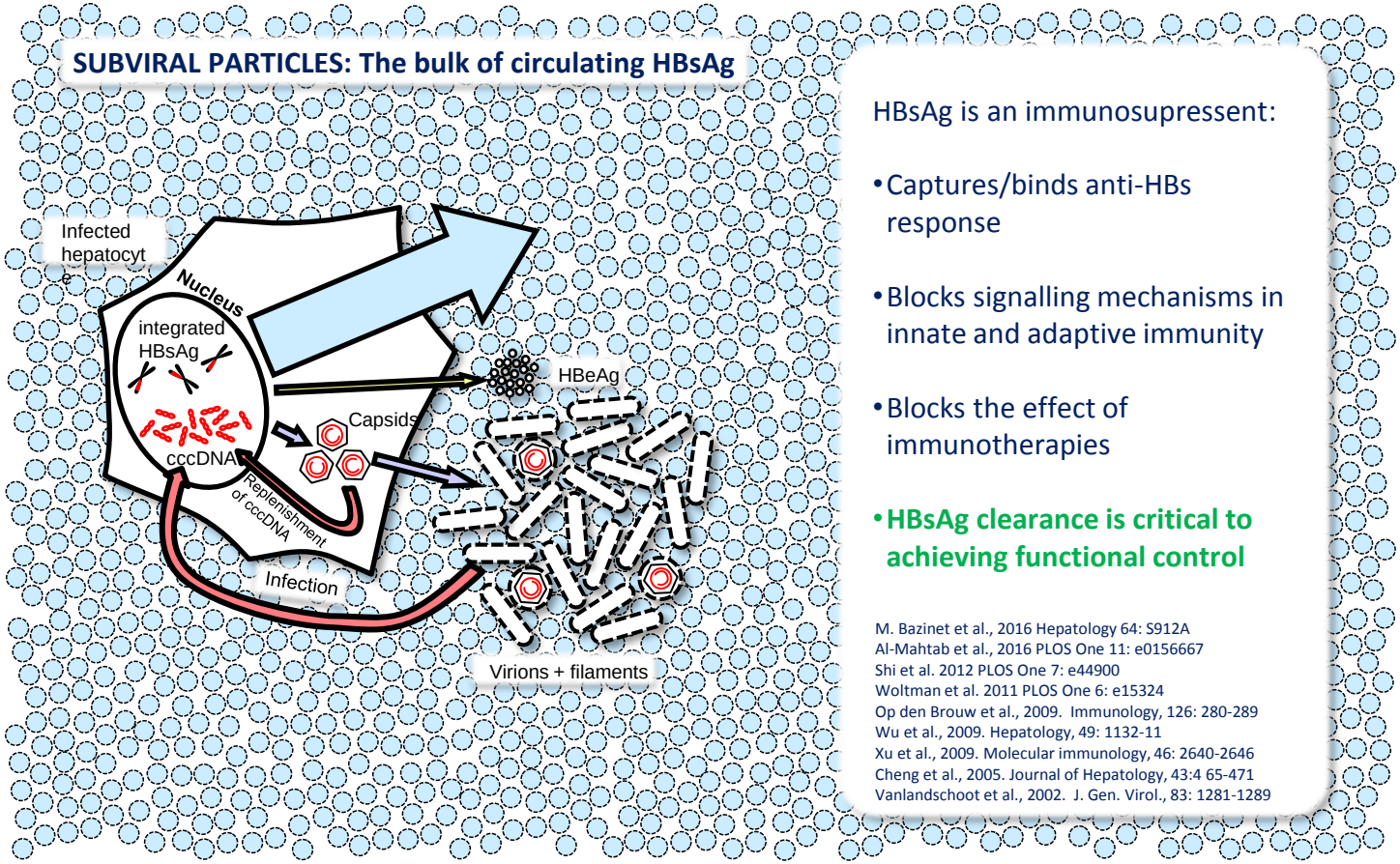
replicor

Infectious Disease Clinic
Toma Ciorbă Hospital

Universitätsklinikum Essen

Hepatitis B Foundation

Particle production in HBV



HBsAg is an immunosupressent:

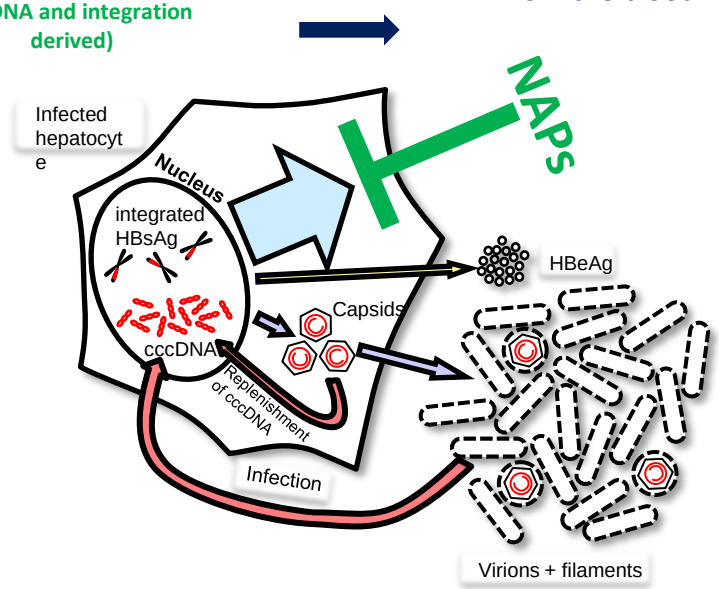
- Captures/binds anti-HBs response
- Blocks signalling mechanisms in innate and adaptive immunity
- Blocks the effect of immunotherapies
- **HBsAg clearance is critical to achieving functional control**

M. Bazinet et al., 2016 Hepatology 64: S912A
Al-Mahtab et al., 2016 PLOS One 11: e0156667
Shi et al. 2012 PLOS One 7: e44900
Woltman et al. 2011 PLOS One 6: e15324
Op den Brouw et al., 2009. Immunology, 126: 280-289
Wu et al., 2009. Hepatology, 49: 1132-11
Xu et al., 2009. Molecular immunology, 46: 2640-2646
Cheng et al., 2005. Journal of Hepatology, 43:4 65-471
Vanlandschoot et al., 2002. J. Gen. Virol., 83: 1281-1289

Nucleic Acid Polymers (NAPs)

NAPs block subviral particle release **(cccDNA and integration derived)**

Efficient HBsAg clearance from the blood

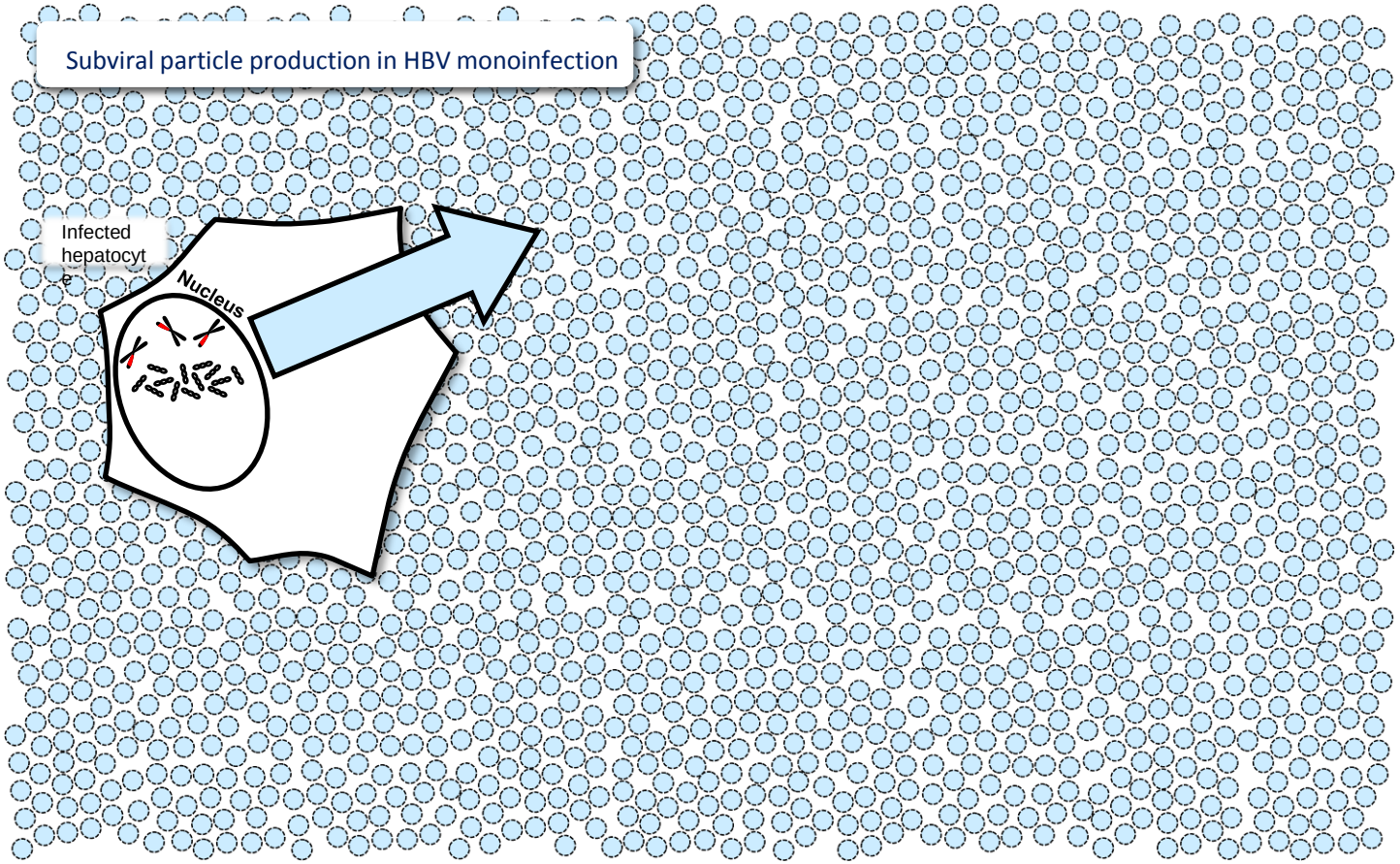


Critical effects of HBsAg clearance:

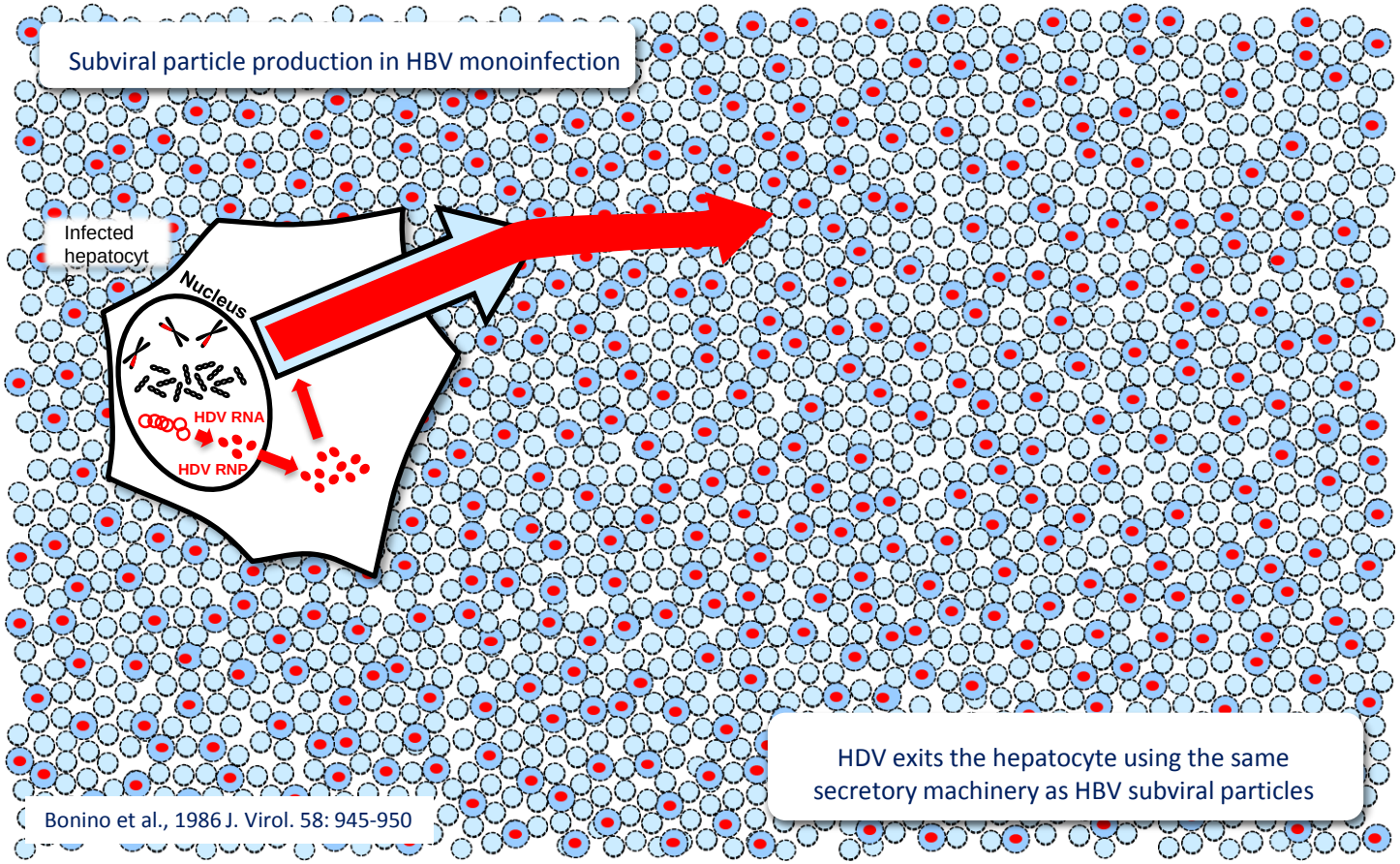
- Unmasking anti-HBs response; do anti-HBs have an effect on immune control: not proven
- Modulation of HBsAg mediated immunosuppression
- May improved response to immunotherapy
- **Functional control may be established in more patients**

Vaillant, 2016. Antiviral Res. 133: 32-40
Al-Mahtab et al., 2016 PLOS One 11: e0156667
M. Bazinet et al., 2016 AASLD Abstract 1848.
Reesink et al., 2016 Hepatol. Int. 10: S2
Noordeen et al., 2015 PLOS One 10: e0140909

HBV vs HBV / HDV co-infection

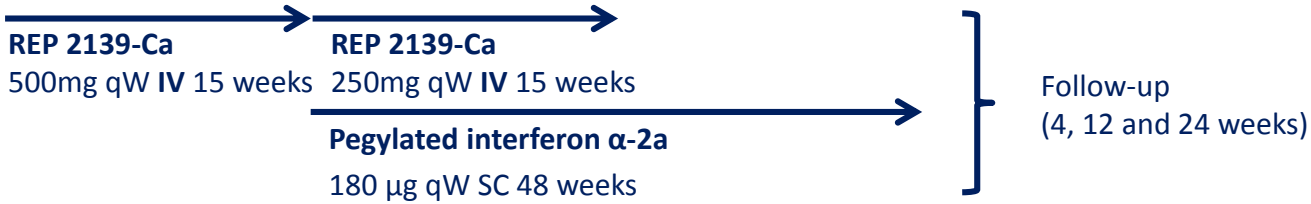


HBV vs HBV / HDV co-infection



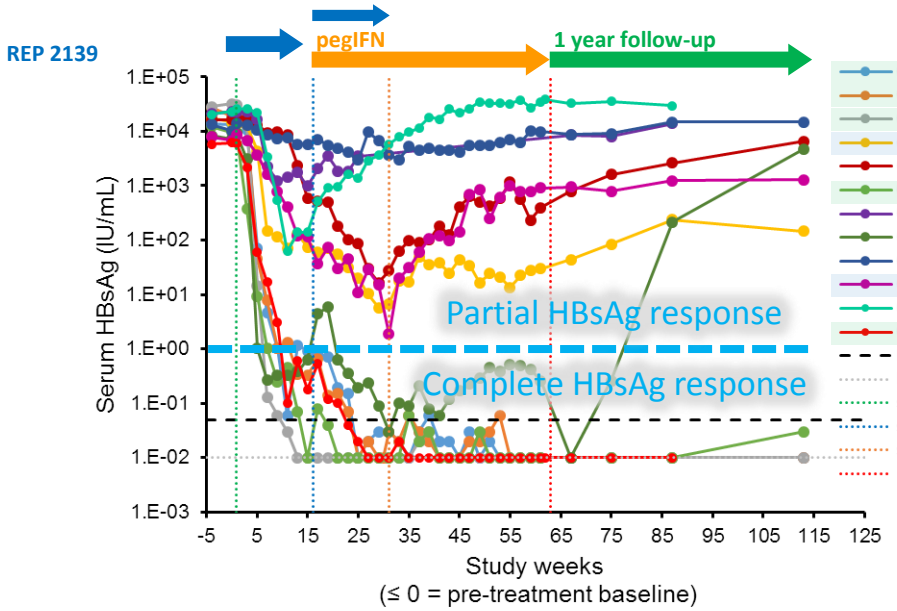
REP 301 / 301-LTF studies

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



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

Serum HBsAg



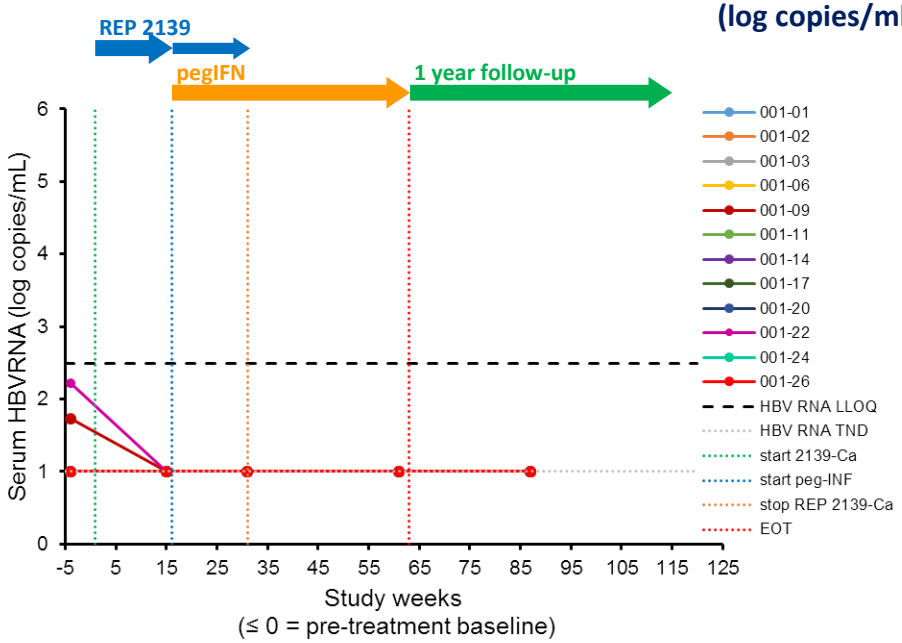
HBsAg status (IU/mL)	Baseline	24W follow-up	1 year follow-up
001-01	13998	0.00	0.00
001-02	27264	0.00	0.01
001-03	28261	0.00	0.01
001-06	17511	239	146
001-09	16426	2646	6621
001-11	12382	0.00	0.03
001-14	20869	13896	*
001-17	8314	214	4754
001-20	13430	14943	14917
001-22	7836	1225	1281
001-24	20473	29724	pending
001-26	5854	0.00	pending

5/12 patients with HBsAg control at 24W – 1 year follow-up.

An additional 2 patients have established a new HBsAg baseline

LLOQ = lower limit of quantification, TND = target not detected (0.00 IU/mL), EOT = end of treatment, * not enrolled in REP 301-LTF

Serum HBV RNA



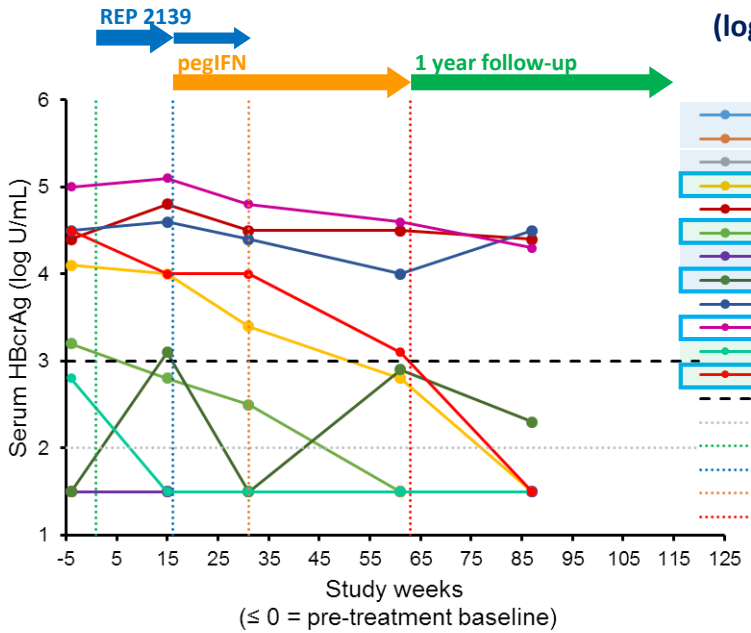
HBV RNA status* (log copies/ml)	Baseline	24W follow-up	HBsAg Baseline (IU/mL)
001-01	TND	TND	13998
001-02	TND	TND	27264
001-03	TND	TND	28261
001-06	TND	TND	17511
001-09	< LLOQ	TND	16426
001-11	TND	TND	12382
001-14	TND	TND	20869
001-17	TND	TND	8314
001-20	TND	TND	13430
001-22	< LLOQ	TND	7836
001-24	TND	TND	20473
001-26	TND	TND	5854

Baseline HBV RNA is either not quantifiable or not detectable in all patients

despite significant HBsAg levels

*DDL Diagnostic, Rijswijk, The Netherlands, TND = target not detected, LLOQ = lower limit of quantification (2.49 log copies/mL)

Serum HBcrAg



HBcrAg status* (log U/mL)	Baseline	REP 2139 mono	HBsAg log reduction REP 2139 mono	24W follow-up
001-01	< LLOD	< LLOD	4.18	< LLOD
001-02	< LLOD	< LLOD	4.92	< LLOD
001-03	< LLOD	< LLOD	6.45	< LLOD
001-06	4.1	4	2.37	< LLOD
001-09	4.4	4.8	1.44	4.4
001-11	3.2	2.8	6.09	< LLOD
001-14	< LLOD	< LLOD	1.32	< LLOD
001-17	< LLOD	3.1	4.11	2.3
001-20	4.5	4.6	0.36	4.5
001-22	5	5.1	1.83	4.3
001-24	2.8	1.5	2.17	< LLOD
001-26	4.5	4	4.51	< LLOD

HBcrAg LLOQ
HBcrAg LLOD
start 2139-Ca
start peg-INF
stop REP 2139-Ca
EOT

Baseline HBcrAg is undetectable in 5/12 patients at baseline

HBcrAg levels are unchanged during REP 2139 monotherapy despite substantial decreases in HBsAg (selective targeting of SVPs)

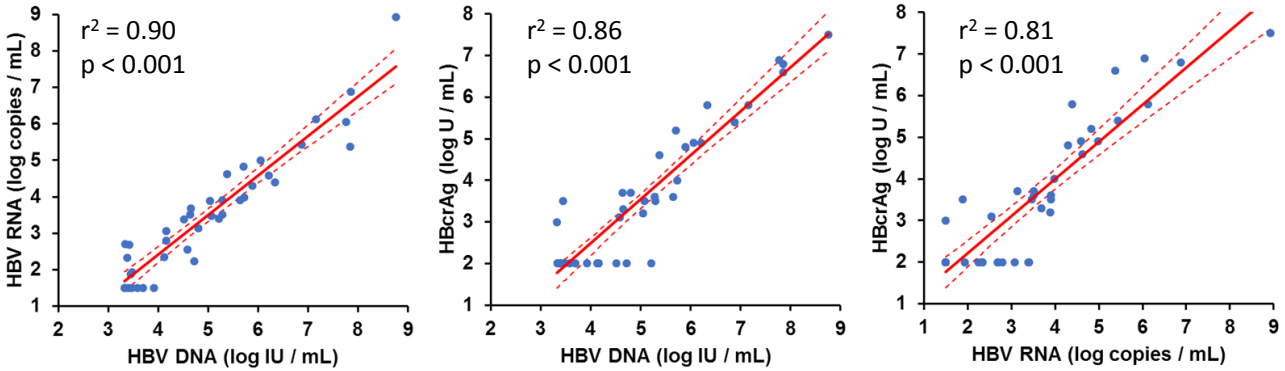
pegIFN results in HBcrAg < LLOD in 4/5 patients with HBsAg reduction > 2 log

*Fujirebio Lumipulse® (DDL Diagnostic, Rijswijk, The Netherlands), LLOD = lower limit of detection (2 log U/mL)

Serum HBV RNA / HBcrAg

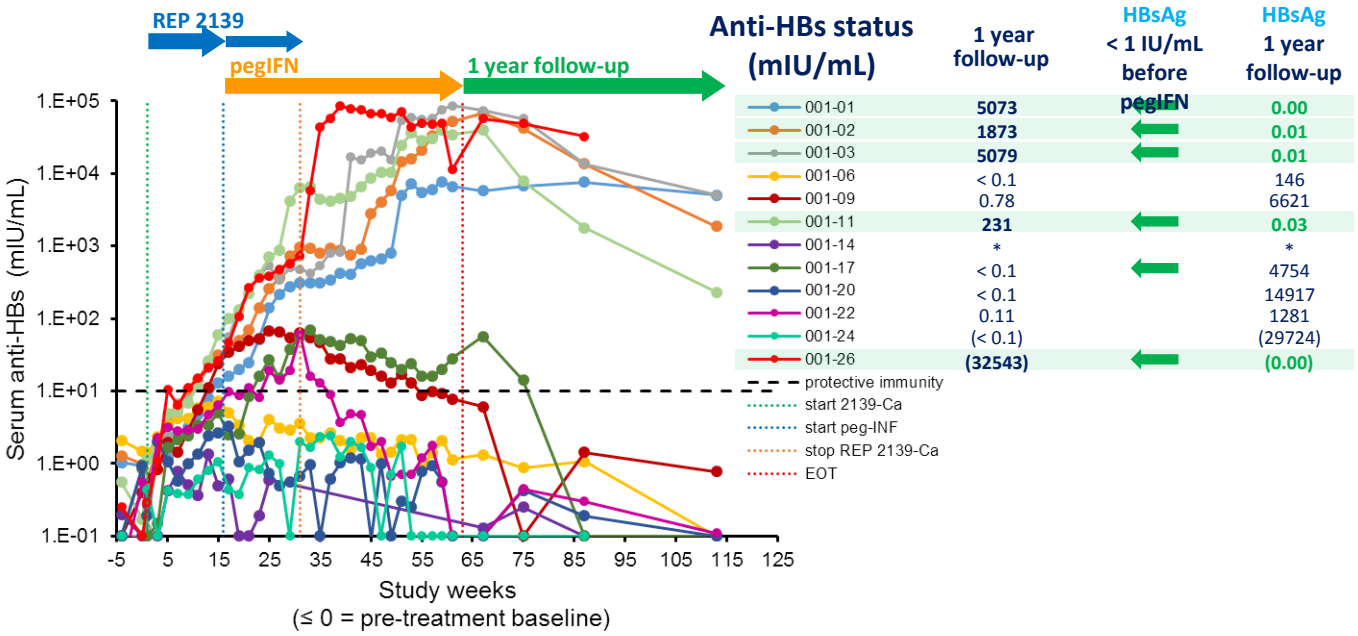
(HBeAg negative HBV mono-infection)

Baseline measurements of 40 HBeAg- HBV mono-infected patients
(REP 401 protocol, poster THU-154)



HBV RNA deficit is specific for chronic co-infection with HDV

Anti-HBs maintenance off treatment versus HBsAg response

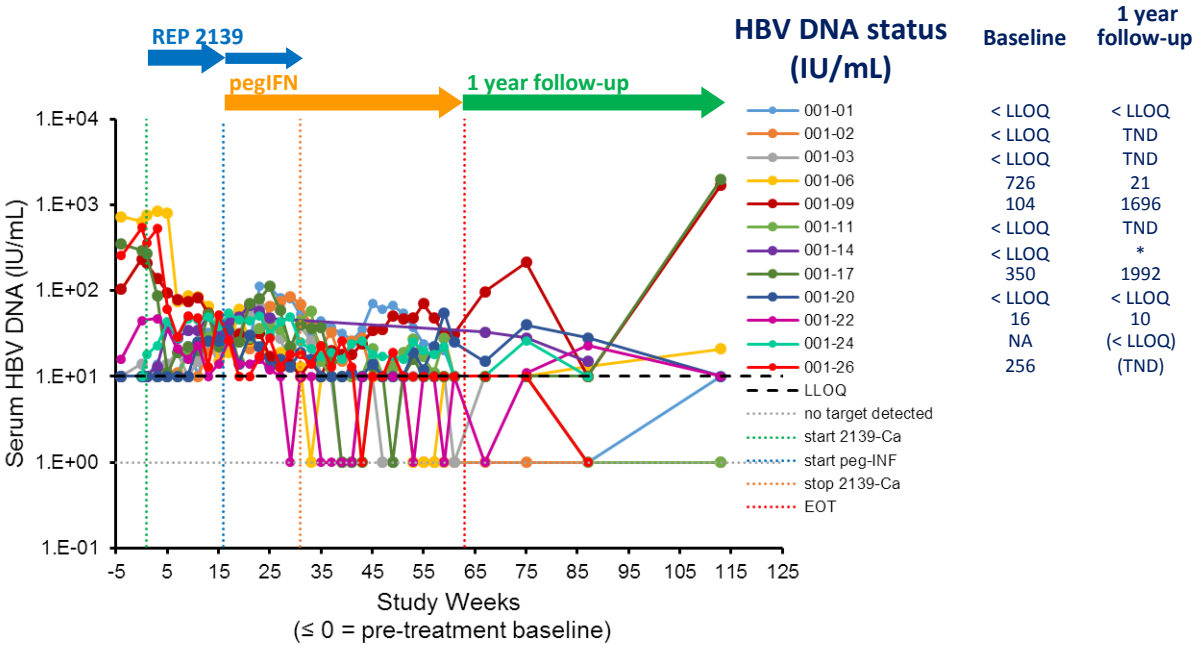


Anti-HBs status (mIU/mL)	1 year follow-up	HBsAg < 1 IU/mL before pegIFN	HBsAg 1 year follow-up
001-01	**5073**	⟵	**0.00**
001-02	**1873**	⟵	**0.01**
001-03	**5079**	⟵	**0.01**
001-06	< 0.1		146
001-09	0.78		6621
001-11	**231**	⟵	**0.03**
001-14	*		*
001-17	< 0.1	⟵	4754
001-20	< 0.1		14917
001-22	0.11		1281
001-24	(< 0.1)		(29724)
001-26	**(32543)**	⟵	**(0.00)**

Maintenance of anti-HBs titers at 1 year follow-up is correlated with serum HBsAg < 1 IU / at the start of peg-INF therapy

EOT = end of treatment, * not enrolled in REP 301-LTF, (24W follow-up result, 1 year follow-up result pending)

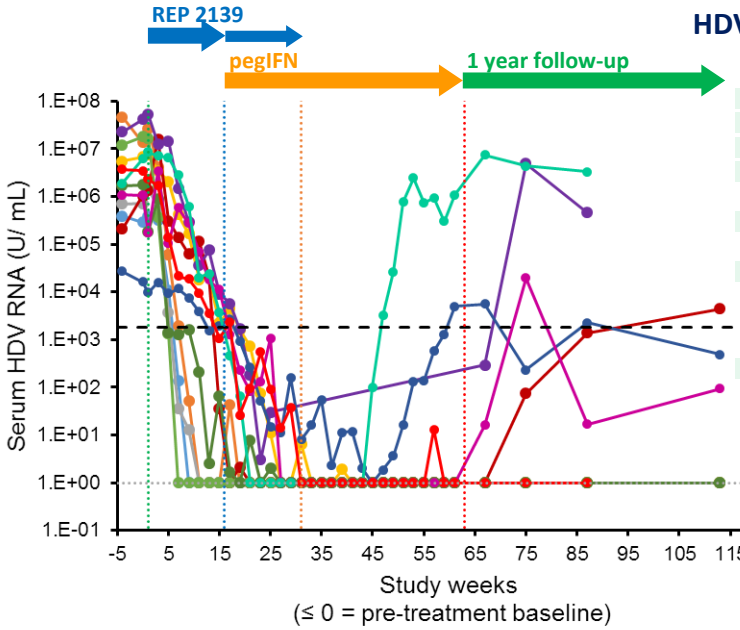
HBV DNA



HBV DNA status (IU/mL)	Baseline	1 year follow-up
001-01	< LLOQ	< LLOQ
001-02	< LLOQ	TND
001-03	< LLOQ	TND
001-06	726	21
001-09	104	1696
001-11	< LLOQ	TND
001-14	< LLOQ	*
001-17	350	1992
001-20	< LLOQ	< LLOQ
001-22	16	10
001-24	NA	(< LLOQ)
001-26	256	(TND)

EOT = end of treatment, * not enrolled in REP 301-LTF, LLOQ = lower limit of quantitation (10 IU/mL), TND = target not detected
NA = PCR result not available- inhibition observed, (24W follow-up result, 1 year follow-up result pending)

Serum HDV RNA



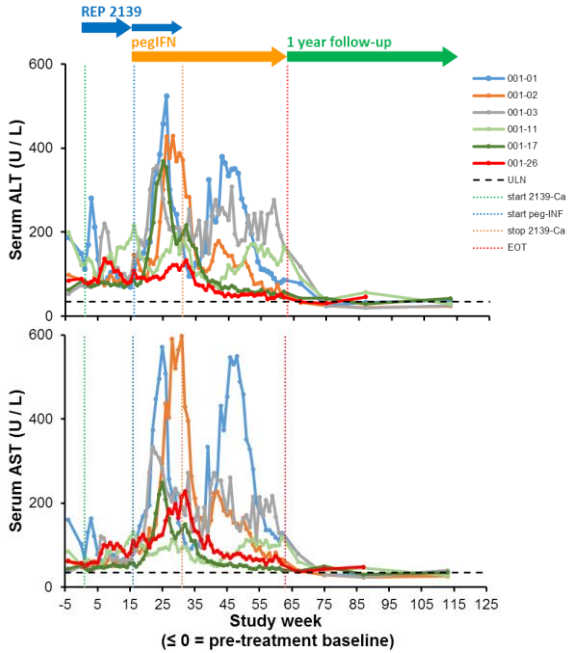
HDV RNA status (U/mL)	Baseline	EOT	24 week follow-up	1 year follow-up
001-01	$3.94x10^4$	TND	TND	TND
001-02	$4.71x10^7$	TND	TND	TND
001-03	$6.97x10^5$	TND	TND	TND
001-06	$5.59x10^6$	TND	TND	TND
001-09	$2.11x10^4$	TND	1390	4438
001-11	$1.21x10^7$	TND	TND	TND
001-14	$2.30x10^7$	*	$4.65x10^5$	*
001-17	$1.68x10^6$	TND	TND	TND
001-20	$2.74x10^4$	4920	2250	485
001-22	$1.09x10^6$	TND	17	94
001-24	$1.89x10^6$	$1.09x10^6$	$3.28x10^6$	pending
001-26	$3.76x10^6$	TND	TND	pending

Complete absence of HDV RNA observed at 24 weeks follow-up in 7/12 patients is stable at 1 year follow-up

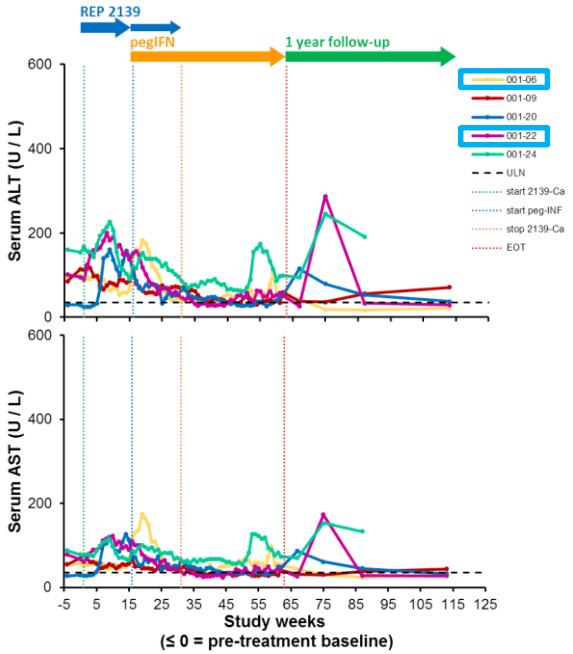
EOT = end of treatment, * early entry into REP 301 follow-up - not enrolled in REP 301-LTF, TND = target not detected

Serum ALT / AST

HBsAg < 1IU/mL prior to pegIFN



HBsAg > 1IU/mL prior to pegIFN



Serum transaminases normalize in 8/12 patients during follow-up

Serum transaminases normalize in 2 patients with lower HBsAg set points

EOT = end of treatment, ULN = upper limit of normal

A Phase 2 Dose-Optimization Study of Lonafarnib with Ritonavir for the Treatment *of Chronic* Delta Hepatitis —*End of* Treatment Results from the LOWR HDV-2 Study

C Yurdaydin[1], R Idilman[1], C Kalkan[1], F Karakaya[1], A Caliskan[1], O Keskin[1], E Yurdcu[1], S Karatayli[1], M Bozdayi[1], C Koh[2], T Heller[2], JS Glenn[3]

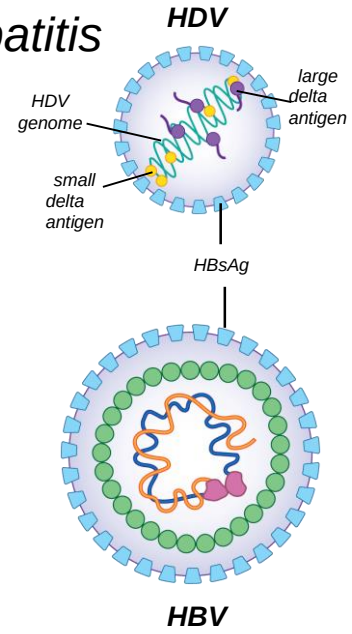
[1]Division of Gastroenterology, University of Ankara Medical School, Ankara, Turkey; [2]Liver Diseases Branch, National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bethesda, Maryland; [3]Division of Gastroenterology and Hepatology, Stanford University School of Medicine

April 21, 2017

Hepatitis Delta Virus

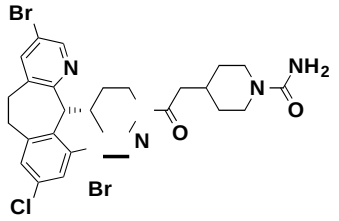
Leads to the Most Severe Form of Viral Hepatitis

- *HDV leads to the most severe form of viral hepatitis*
  - *More rapid progression to liver cirrhosis*
  - *5-7x more likely to develop cirrhosis and HCC vs HBV*
- *HDV is always associated with HBV infection*
  - *HDV steals HBsAg from HBV for envelopment*
- *Final step in replication involves prenylation*
  - *HDV hijacks prenylation, a host process*
- *No FDA approved Rx for HDV*
  - *PEG IFN-α demonstrates modest benefit*
- *HDV worldwide prevalence is 15 - 20 million*
  - *Approximately 4-6% of HBV worldwide population is infected with HDV*
  - *Orphan status in US and EU*



Sarasar® (lonafarnib) for HDV

Well-Characterized Clinical Stage Lead Compound

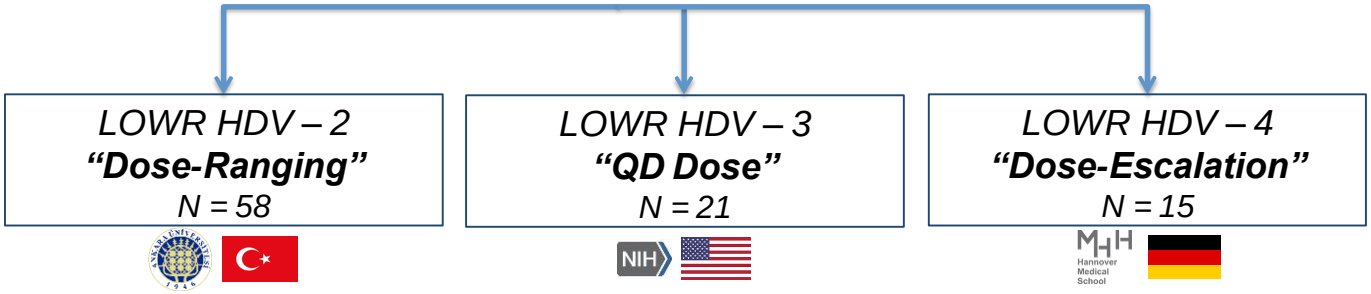


- *Small molecule, oral, prenylation inhibitor*
- *Well-characterized through Phase 3*
  - *>2,000 patients dosed in oncology program by Merck (Schering)*
  - *Dose limiting toxicity is GI (class effect)*
- *Prenylation is a host target; potential high barrier to resistance*
- *Over 120 HDV patients dosed across international sites*
  - *NIH Phase 2 study results published in Lancet Infectious Diseases 2015**
- *Orphan Designation in US & EU, Fast Track in US*

** Koh et al, Lancet Infect Dis, 2015.*

LOWR HDV - 2, - 3, - 4

Week 48 Results Presented at EASL 2017



LOWR HDV – 2

- *Identify LNF-RTV combination +/- PEG IFN*

*LOWR HDV – 3**

- *Once-daily dosing*

*LOWR HDV – 4***

- *Is rapid dose-escalation possible and / or required?*

** Koh et al., EASL 2017 Abstract #LBP-519, ** Wedemeyer et al., EASL 2017 Abstract #PS-039*

LOWR HDV – 2 Study

LOnafarnib With Ritonavir ± PEG IFN-α

Purpose

- *To identify combination regimens of **LNF and RTV ± PEG IFN-α** which demonstrate efficacy and tolerability for longer term dosing to enable HDV-RNA clearance.*

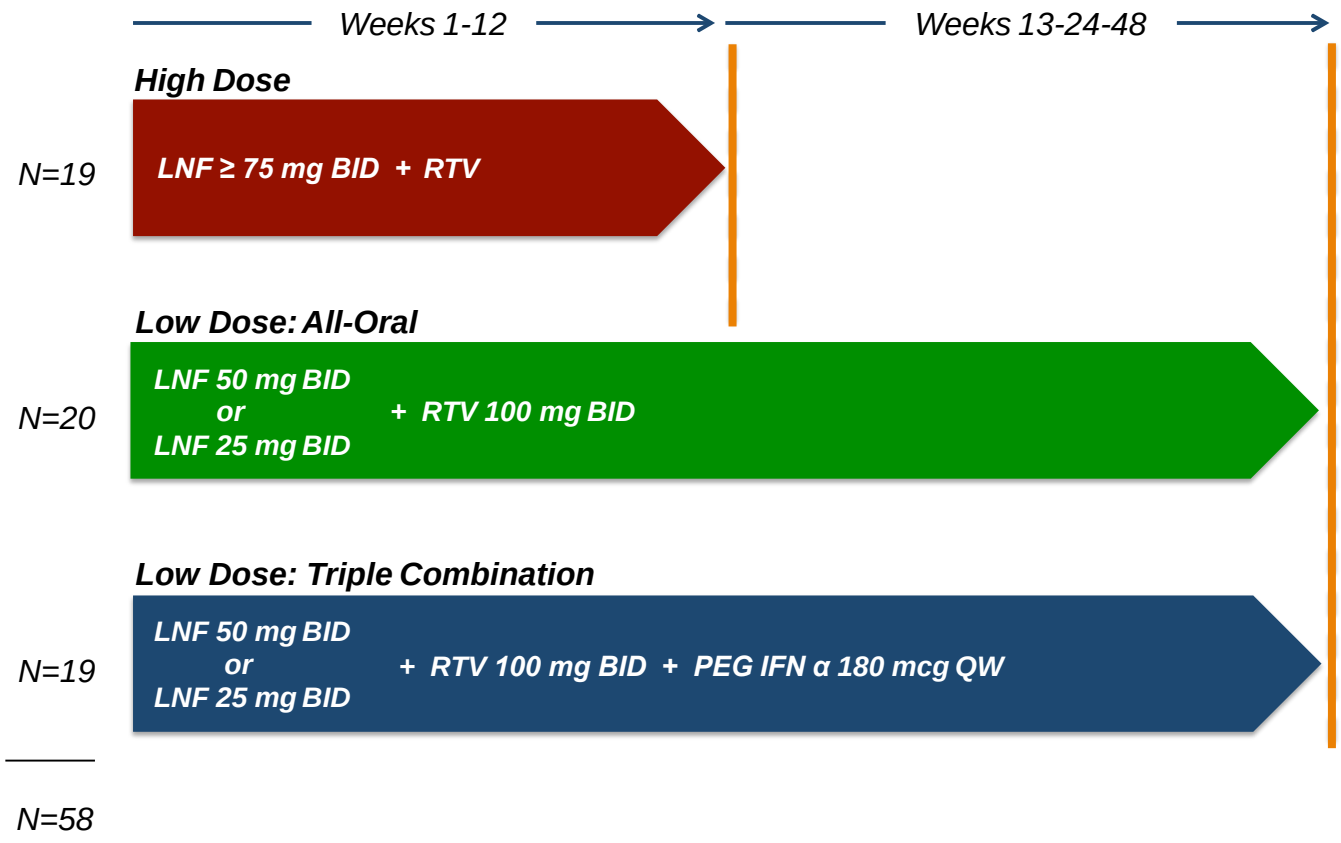
Patients and Methods

- *Treatment duration 12 or 24 or 48 weeks*
- *72 hour PK and PD evaluation on day 1 and day 28*
- *Testing frequency: days 1, 2, 3, 7, 14, 28 and then 4W*
  - *Biochemical parameters, HBV DNA*
  - *HDV-RNA (by in-house qPCR with LOQ ~ 3 log copies/mL)*

LOQ = limit of quantitation

LOWR HDV – 2: "Dose Finding" Study

Tolerability, Longer Dosing, and Triple Combination



LOWR HDV – 2: "Dose Finding" Study

Low Doses Tested for Longer Durations

	Regimen	Duration (Weeks)	# Patients	# Discontinuations Due to AE
High Dose	L100B + R100Q	12	4	1
	L150Q + R100Q	12	3	0
	L100B + R50B	12	4	0
	L100Q + R100Q	12	5	2
	L75B + R100B (+ P180QW on Wk 12)	24	3	0
Low Dose N = 34	L50B + R100B (+ P180QW on Wk 12)	24	5	1
	L50B + R100B	24	12	0
		48	2	0
	L25B + R100B	24	1	0
		48	5	0
	L50B + R100B + P180QW	24	3	1
		48	2	0
	L25B + R100B + P180QW	24	6	1
		48	3	0
	Total		58	6

L=LNF in mg, R=RTV in mg, P=PEG IFN-α in mcg, B=BID, Q=QD

Baseline Characteristics

LOWR HDV – 2: Low Dose Groups

Characteristic	Values
N	*27**
Median age, years (range)	*50 (24 - 59)*
Male, n (%)	*12 (44%)*
Race, n (%) *White*	*27 (100%)*
Median BMI, kg/m^2 (range)	*24.5 (18.5 – 33.9)*
Median HDV-RNA, log$_{10}$ copies/mL (range)	*5.36 (3.30 – 6.94)*
Median ALT, U/mL (range)	*64 (24 - 229)*
Prior interferon treatment, n (%)	*12 (44%)*

** Excludes 7 patients < LOQ at baseline*

LOWR HDV – 2: Efficacy

As-Treated Analysis: Patients Dosed for 24 Weeks

	# of Patients			
	All-Oral Rx		Triple Rx	
	LNF 25 mg BID + RTV	LNF 50 mg BID + RTV	LNF 25 mg BID + RTV + PEG	LNF 50 mg BID + RTV + PEG
Week 24	**N = 6**	**N = 8**	**N = 5**	**N = 4**
HDV-RNA < LOQ	3 / 6	2 / 8	4 / 5	3 / 4
HDV-RNA PCR negative	0 / 6	1 / 8	3 / 5	0 / 4
> 2 log decline*	3 / 5	1 / 3	3 / 4	3 / 3

24 Week Dosing

- *All-oral LNF 25 and 50 mg BID + RTV suppress HDV-RNA < LOQ in 36% of patients*
- *Addition of PEG IFN to LNF 25 mg BID + RTV enhances antiviral activity*

* *Patients with high baseline viral load (HDV RNA > 5 log copies/mL)*

LNF 25 mg BID + RTV + PEG

2 Patients HDV-RNA negative at EOT (Week 24) and Week 48

	# of Patients			
	All-Oral Rx		Triple Rx	
	LNF 25 mg BID + RTV	LNF 50 mg BID + RTV	LNF 25 mg BID + RTV + PEG	LNF 50 mg BID + RTV + PEG
Week 24	**N = 6**	**N = 8**	**N = 5**	**N = 4**
HDV-RNA < LOQ	3 / 6	2 / 8	4 / 5	3 / 4
HDV-RNA PCR negative	0 / 6	1 / 8	**3 / 5**	0 / 4
> 2 log decline*	3 / 5	1 / 3	3 / 4	3 / 3

- *3 of 5 patients (60%) PCR-negative at Week 24*
  - *2 had low viremia off-therapy, PCR-negative at 24 weeks post-treatment*
  - *1 continued treatment for another 24 weeks*

** Patients with high baseline viral load (HDV RNA > 5 log copies/mL)*

LOWR HDV – 2: Efficacy

As-Treated Analysis: Patients Dosed for 48 Weeks

	# of Patients			
	All-Oral Rx		Triple Rx	
	LNF 25 mg BID + RTV	LNF 50 mg BID + RTV	LNF 25 mg BID + RTV + PEG	LNF 50 mg BID + RTV + PEG
Week 24	N = 6	N = 8	N = 5	N = 4
HDV-RNA < LOQ	3 / 6	2 / 8	4 / 5	3 / 4
HDV-RNA PCR negative	0 / 6	1 / 8	3 / 5	0 / 4
> 2 log decline*	3 / 5	1 / 3	3 / 4	3 / 3
Week 48	**N = 5**	**N = 2**	**N = 3**	**N = 2**
HDV-RNA < LOQ	2 / 5	1 / 2[u]	2 / 3	0 / 2
HDV-RNA PCR negative	0 / 5	0 / 2[u]	2 / 3	0 / 2
> 2 log decline*	1 / 4	0 / 0	3 / 3	0 / 2

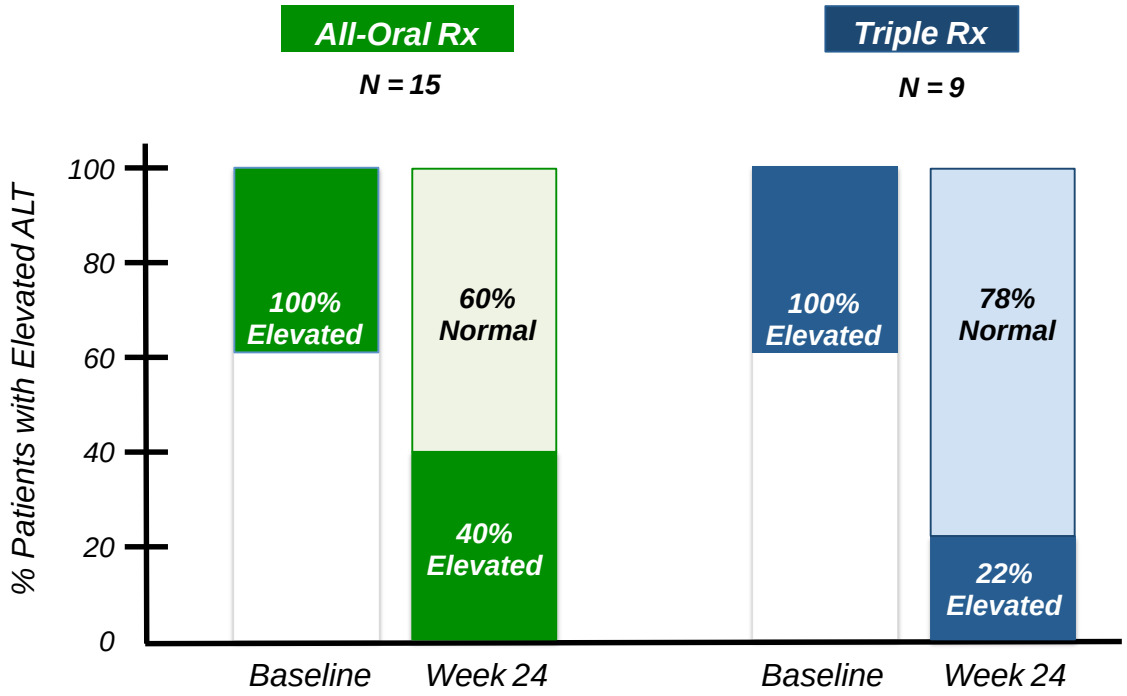
48 Week Dosing

- *All-oral LNF: 3 of 7 patients (43%) < LOQ*
- *Triple LNF 25 mg BID + RTV + PEG: 2 of 3 patients (67%) PCR-negative*

** Patients with high baseline viral load (HDV RNA > 5 log copies/mL); w Week 40-44 data*

60-78% of Patients Normalized ALT at Wk 24*

Addition of PEG Improves ALT Normalization



** LNF 25 and 50 mg BID regimens with elevated ALT at baseline*

All-Oral Rx = LNF 25/50 mg BID + RTV 100 mg BID; Triple Rx = LNF 25/50 mg BID + RTV 100 mg BID + PEG IFN 180 mcg QW

Adverse Events: Low Dose LNF

LNF 25 / 50 mg Regimens Demonstrate Tolerability

- *AEs predominantly mild / moderate for LNF 25 / 50 mg regimens*
- *Generally tolerable through Week 48*

	# of Patients Experiencing AE[1]			
	All-Oral Rx		Triple Rx	
AE Grade	LNF 25 mg BID + RTV N = 6	LNF 50 mg BID + RTV N = 14	LNF 25 mg BID + RTV + PEG N = 9	LNF 50 mg BID + RTV + PEG[2] N = 10
Grade 1	3	8	4	5
Grade 2	1	3	2	4
Grade 3	2	2	0	1
SAE[3]	1	2	1	1

Highest grade GI AE reported

[1] *Most common and severe reported AEs: nausea, diarrhea, fatigue, weight loss, anorexia, vomiting*

[2] *Includes cohort: LNF 50 mg BID + RTV for first 12 weeks + PEG for second 12 weeks*

[3] *All reported to be "unlikely related to LNF"*

LOWR HDV – 2

Conclusions

- *All-oral LNF 25 or 50 mg BID + RTV suppresses HDV-RNA < LOQ*
  - *5 of 14 (36%) patients < LOQ at Week 24*
  - *1 patient PCR-negative at Week 24*
- *Addition of PEG IFN to LNF 25 mg BID + RTV results in highest response*
  - *4 of 5 (80%) patients < LOQ at Week 24*
  - *3 of 5 (60%) patients PCR-negative at Week 24*
    - *2 patients PCR-negative at 24 weeks post-treatment*
- *60-78% of patients normalized ALT at Week 24*
- *> 2 log decline AND normalized ALT warrants evaluation for clinical benefit*
- *AEs predominantly mild / moderate for LNF 25 / 50 mg regimens*

Summary

- HDV suppression of HBV may target HBV pregenomic RNA.
- HDV infection can persist in the absence of active cccDNA probably using integrated HBV DNA and mRNA transcripts to make HBsAg
- Bulk of HBsAg in chronic co-infected patients is derived from integrated HBsAg.
- REP 2139 simultaneously reduces HBsAg and HDV RNA.
- **HBsAg clearance threshold for activation of immunotherapy appears to be < 1 IU / ml.**
- Functional control of HBV infection in 5/12 patients and control of HDV infection in 7/12 patients is stable 1 year off-treatment.
- **Functional control rate expected to be higher with longer concomitant therapy with REP 2139 and peg-IFN and including TDF.**

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*

Providers → *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, lonafarnib
  - Replicor, NAP release inhibitor
- Improvement of liver transplant outcomes
- Hepatology and 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 1

- HDV-infection plays an important role in the etiology of liver diseases in various parts of the world
- All at risk HBsAg-positive patients should be tested for anti-HDV using serology and confirmation with HDV RNA by quant PCR, cirrhosis, geography, risk behavior, abnl ALT on nuc suppressed HBV patients
- 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 antiviral for the “treatment” of CHD, and its efficacy (cure rate) is less than 15-25% with one year of treatment
  - Although emerging data in Turkey may show up to a 35-40% MVR rate with treatment up to 5 years
  - New reset: HDV RNA suppression by 1-2 logs off treatment with normal or improved ALT and improved histology

Conclusions 2

- Prevention HDV = vaccination against HBV and harm reduction
- HDV LT with CHD is characterized by better outcomes compare to other HBV monoinfection
- HDV SVR after 48-week PEG IFNa Tx is <25 %
- Most often HDV dominates over HBV, but in HBV DNA-positive cases providers can use HBV-polymerase inhibitors
- Combination of PEG IFNa and NAs does not improve treatment 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

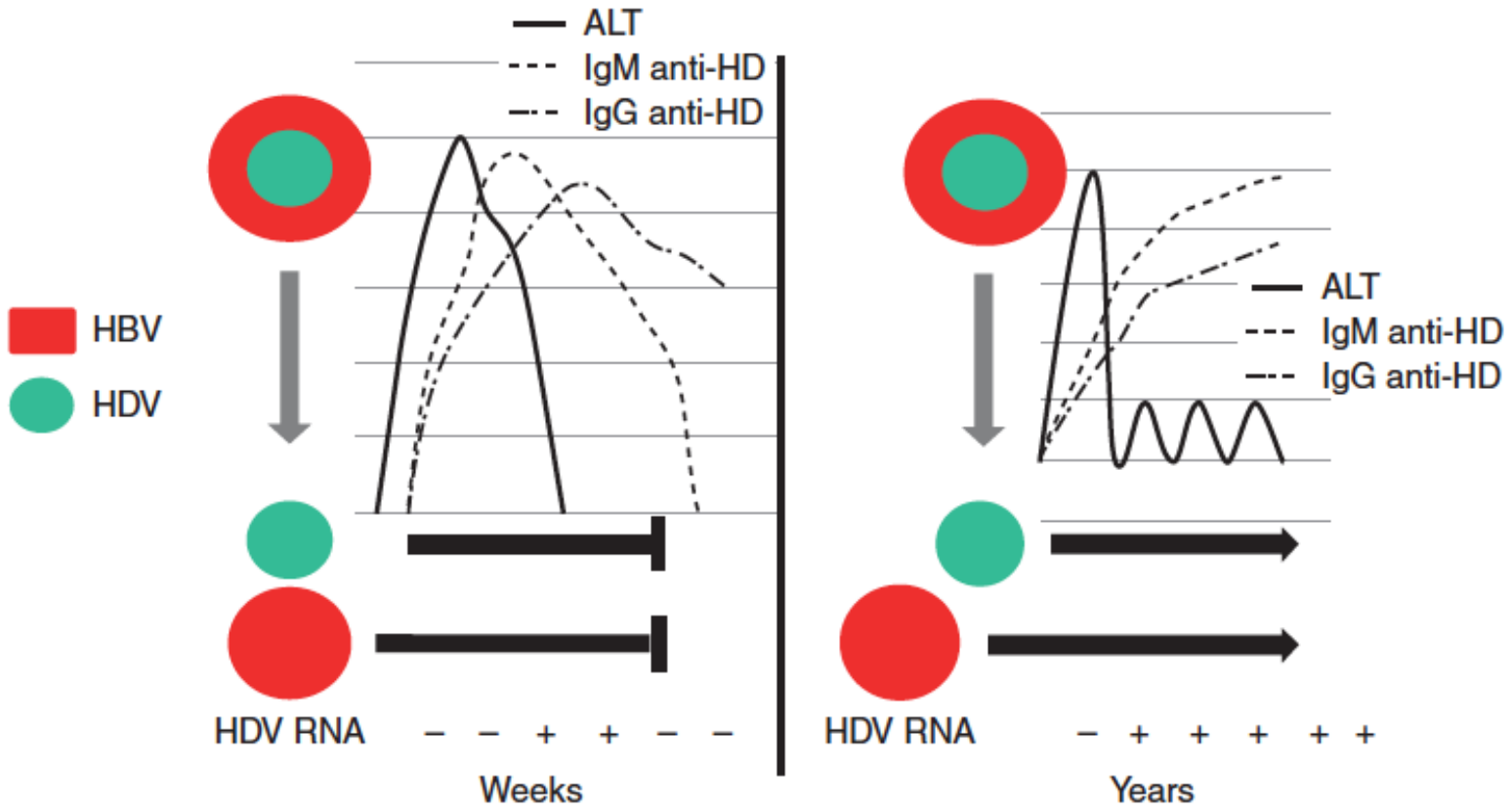
HDV Testing

Dr. David Hillyard

Laboratory Tools for HDV Diagnosis and Monitoring

- Screen with sensitive antibody assay
  - IgG and IgM
- Confirm with sensitive RNA assay
  - pan-genotypic -calibrated to WHO standard
- Reflex Antibody to RNA assay streamlines testing
- Monitor therapeutic response with quantitative RNA assay

Virologic and Serologic Markers of HDV Infection

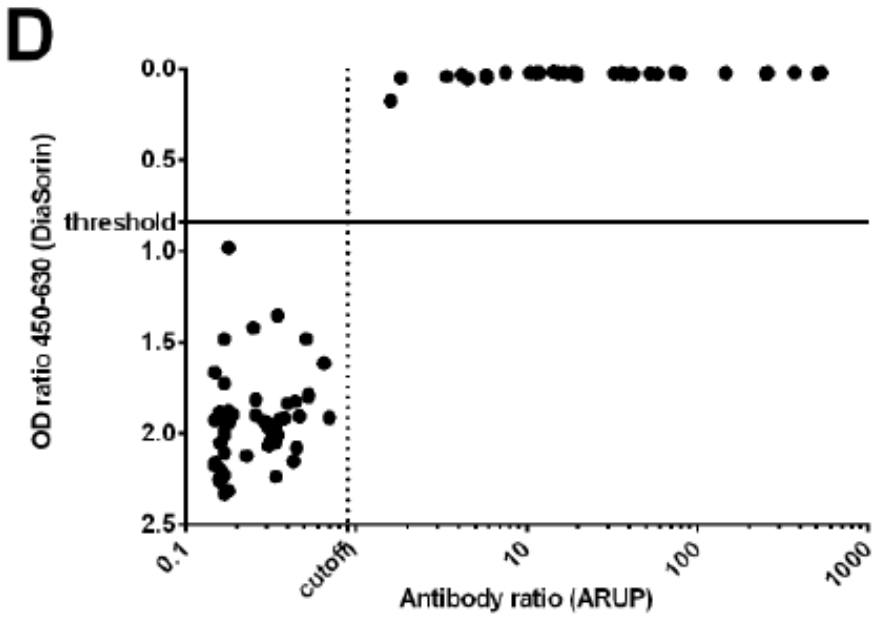


Coinfection

Superinfection

M Rizzetto Cold Spring Harbor Perspect Med 2015;5:a021576

Comparison HDV Enzyme Immunoassays



- Diasorin research assay is standard of performance (not available for clinical testing)
- ARUP assay (International Immuno-Diagnostics)
- And Focus LDT test both performed well, with different cutoffs

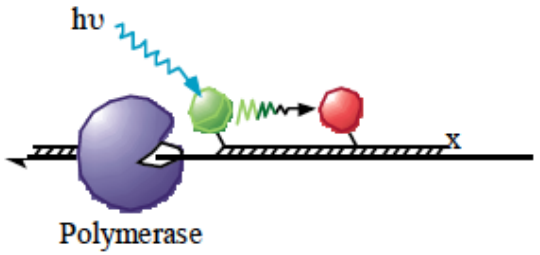
Siu-Kei et al August 2016 Volume 23 Number 8 Clinical and Vaccine Immunology

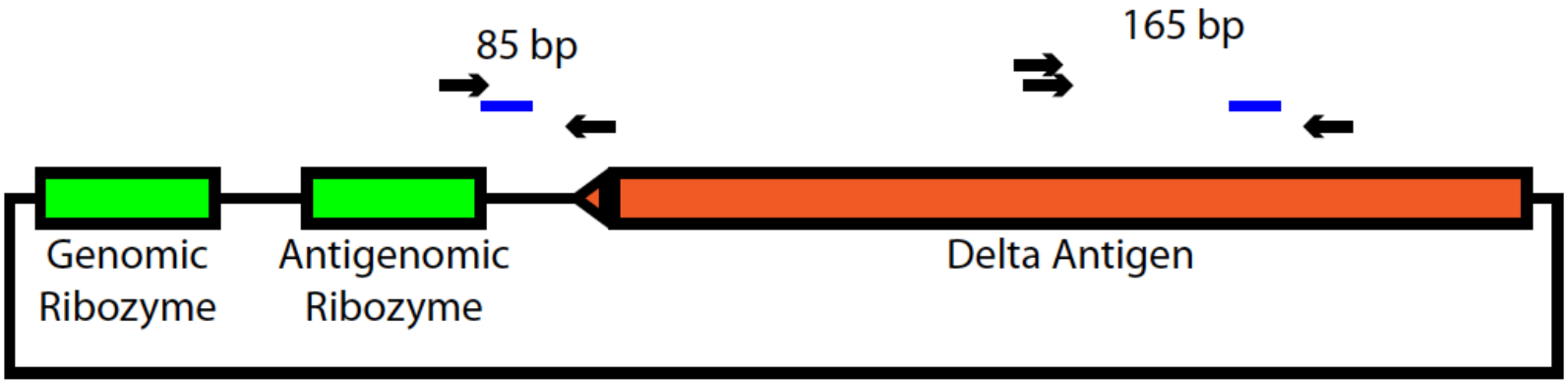
HDV RNA Testing

- Confirm serology
- Provide baseline for monitoring course of treatment
- Result expressed in international units (I.U.)
- Calibrated to WHO international Standard
  - Lyophilized patient plasma sample
  - Vials back gassed (stable for years)
  - Limited availability
  - Secondary standards calibrated by qPCR or digital PCR)
- Genotyping: Epidemiology only

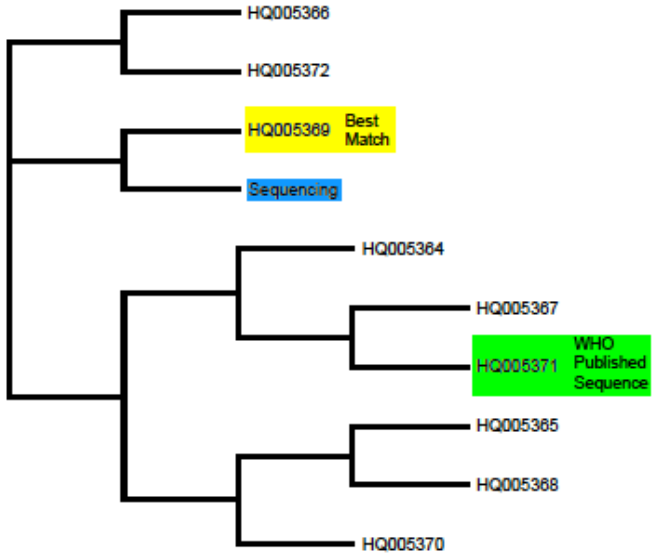
ARUP HDV RNA Assay

- Two Target TaqMan qPCR
- Calibrated to WHO standard
- Secondary standards stored liquid nitrogen



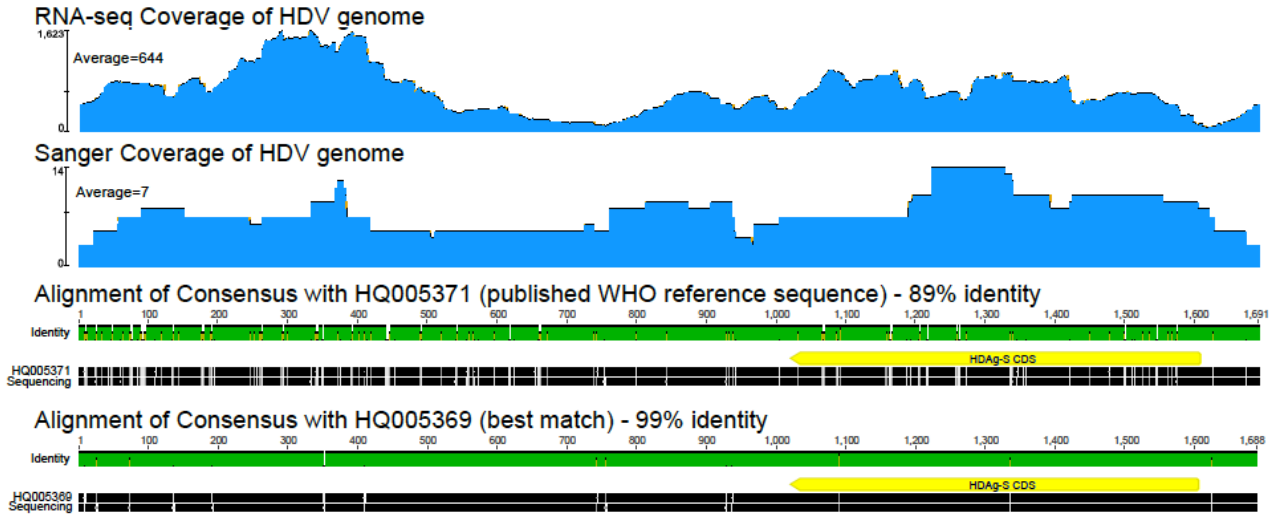


HDV International Standard:



Accurately characterized by Sanger and NGS sequencing

Patient sample (genotype I)
I.U is average of RNA copy assays
1 I.U. is ~ 10 RNA copies



Pyne et al J Clin Virol. 2017 May;90:52-56

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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
- quantitative range 120-6,800,000 IU/ml
- detects as few as 62 IU/ml

Hepatitis Delta Testing
ARUP Laboratories

When to order testing

- Recent diagnosis of acute HBV
- Recent presentation of acute hepatitis in a chronic HBV carrier
- HBsAg positive patient with chronic liver disease

Features and benefits of HDV testing at ARUP

- HDV seropositive samples are automatically reflexed to PCR
- Confirm active infection and monitor viral replication
- Medical Director review and consultation available

Hepatitis Delta Viral Load Assay

ARUP Laboratories

Hepatitis D Testing Details

Hepatitis D testing should only be performed in patients with documented acute or chronic Hepatitis B.

Specimen

Frozen (preferred) or refrigerated serum (2 ml)

Test Code	Test Name	Method
2013880	Hepatitis Delta Virus Antibody (IgG and IgM) Reflex to: Hepatitis Delta Viral Load by PCR	Enzyme Immunoassay Quantitative RT-PCR

Reflex Testing

Samples that are positive for HDV antibodies will automatically be tested by quantitative PCR for HDV RNA

Hepatitis Delta Viral Load Assay
ARUP Laboratories

Hepatitis D Testing Details

Hepatitis D testing should only be performed in patients with documented acute or chronic Hepatitis B.

Specimen

Frozen serum (2ml)

Test Code	Test Name	Method
2013880	Hepatitis Delta Virus Antibody (IgG and IgM)	Enzyme Immunoassay
	Reflex to	
	Hepatitis Delta Viral Load by PCR	Quantitative RT-PCR

Reflex Testing

Samples that are positive for HDV antibodies will automatically be tested by quantitative PCR.

Please submit questions for Dr. Gish and Dr. Hillyard in the chat box!

Q & A

THANK YOU!

For more information about the Hepatitis B Foundation's Hepatitis Delta Connect Program, visit our website *www.hepdconnect.org*

HEPATITIS DELTA CONNECT

hepdconnect.org

@hepdconnect

HEPATITIS B FOUNDATION