

Is HDV/HBV more aggressive than HBV monoinfection?

R. PARANÁ

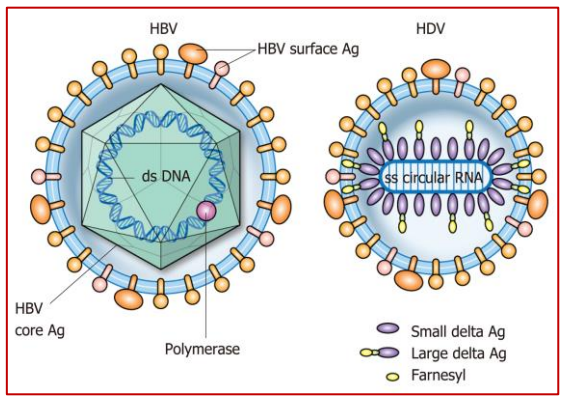
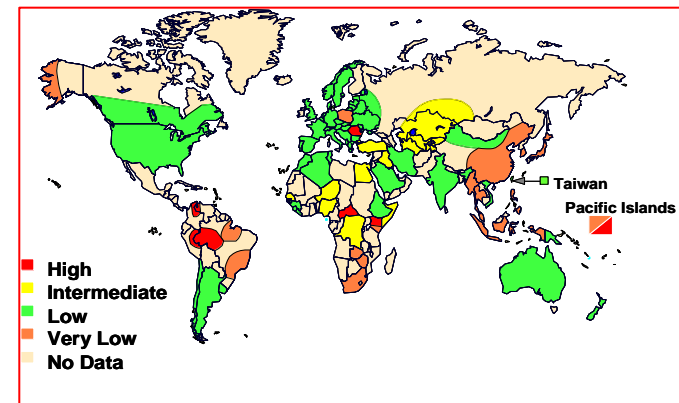


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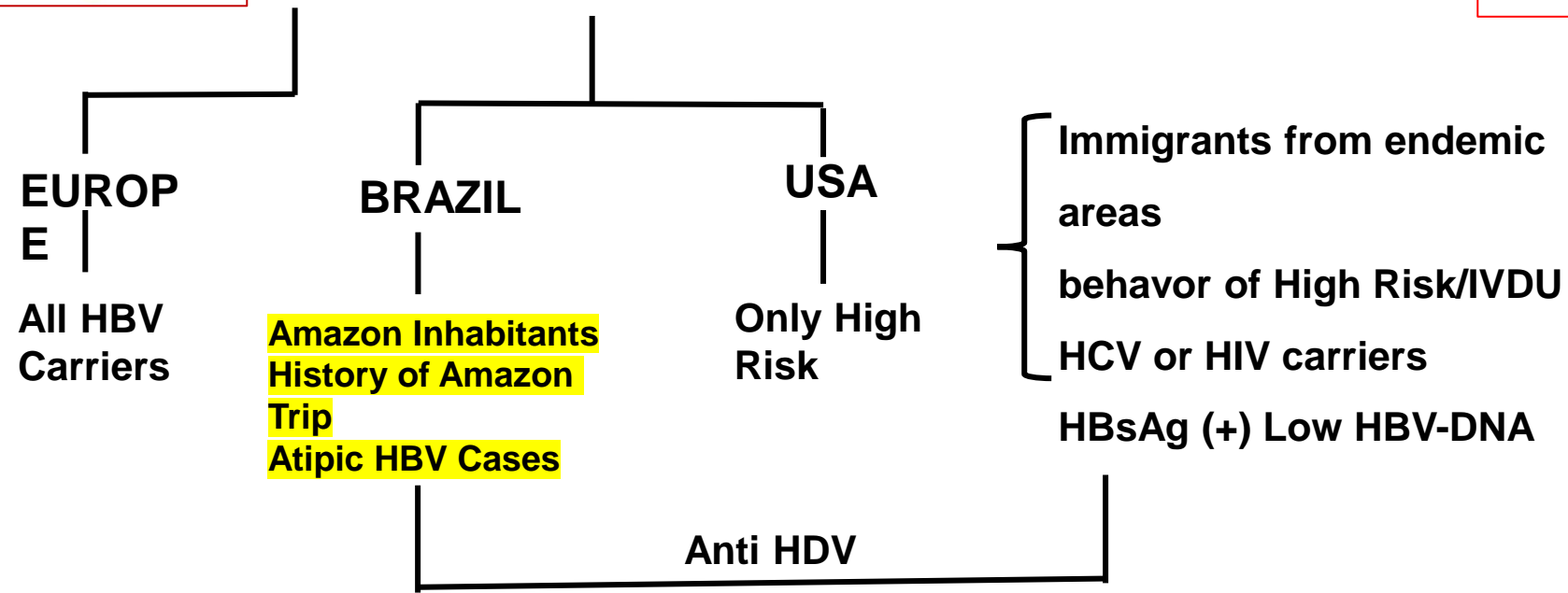


HDV is:

**Neglected
Underreported
underestimated**



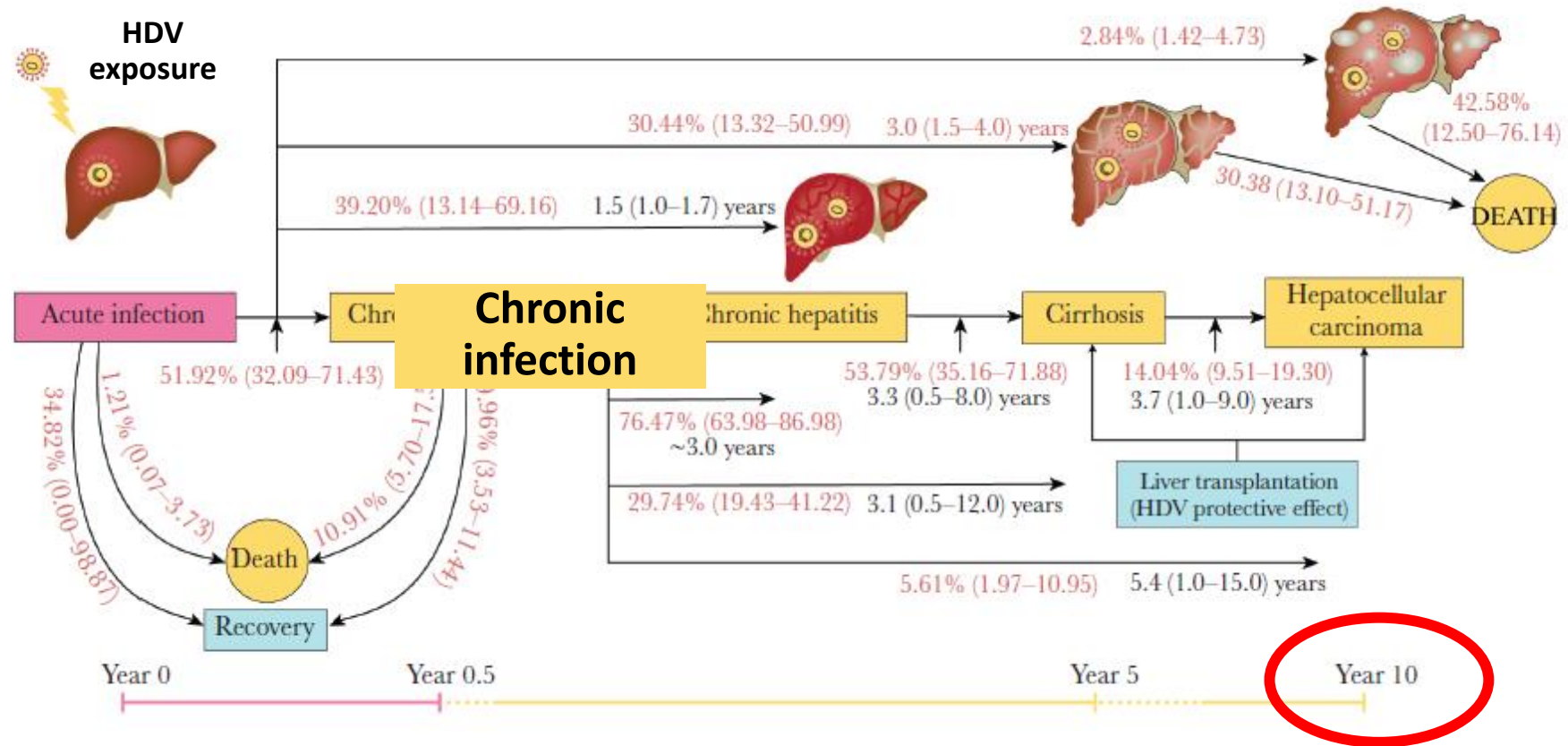
SCREENING



1. Diversity of genotypes
2. Interplay between HBV/HDV (Genotypes and Viral Load)
3. Diversity of Demographic factors
4. Diversity of natural History and Fibrosis progression
5. Most in poor or vulnerable population
6. Epidemiologic data not consolidated

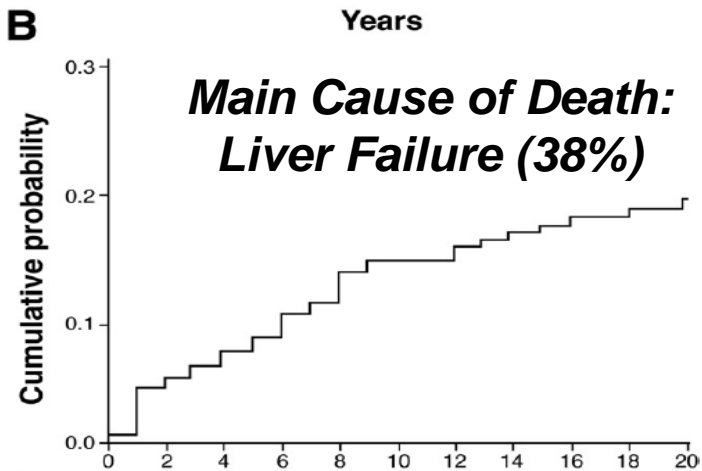
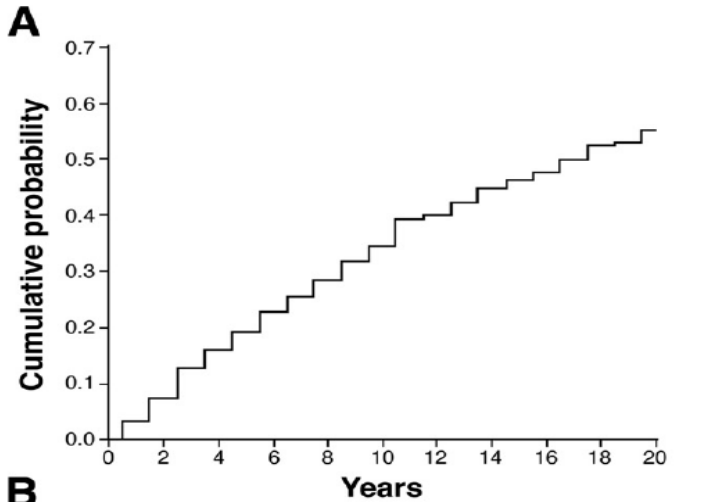
When the delta virus superinfects, liver disease progresses faster

Rapid Progression



- 2-3 x more cirrhosis than HBV monoinfection
- 3-6 x more HCC
- 2x more decompensation

“Healthy Carrier State” of HDV do Exist?



Population survey
on Rhodes

2479 screened



260 (10.5%) AgHBs positive



71 (27 %) Anti-HDV positive



42 (59 %)

Normal ALT
and biopsy



29 (41 %)

Liver
disease

Standardized HDV-RNA viral load
Fibrosis status change over time
HBV/HDV Genotype (HBV-C and F)
Ethnicity
Tertiary x secondary centers
Non – Cirrhotic x Cirrhotic enrolled
Few long term cohort studies
Few studies from highly endemic
areas
Older x newer studies
INF Treated x Non-Treated patients
HBV treatment with NUCs

Young patients: HDV Gen-3 HISTOLOGY AND PARAMETERS OF DISEASE STAGE

METAVIR

FIBROSIS

Necro-inflammation

STAGE	N (%)	TOTAL	GRADE	N (%)	TOTAL
F0	5 (4.6)	109	A0	9(8.2)	109
F1	27 (24.7)		A1	30(27.5)	
F2	28 (25.7)		A2	31(28.5)	
F3	25 (23.0)		A3	39(35.8)	
F4	24 (22.0)				

HDV SUPERINFECTION



	HBV	HDV HBV
CIRRHOSIS	> 10 y	5 – 10 y (70%) 3x MORE THAN HBV
DECOMPENSATION	< 3% ANNUAL	≥ 3% ANNUAL. OD 2,2
HCC	< 2%	> 2% OD 3,2

10-20%
STABLE DISEASE
HDV-RNA < 2 Log
HDV-RNA negative

4% ANNUAL RATE

3,6% DECOMPENSATION

HDV-RNA
> 2 LOGS

CIRRHOSIS

Few recent
studies > 60%
stable

HCC
2,8 – 4% ANNUAL RATE

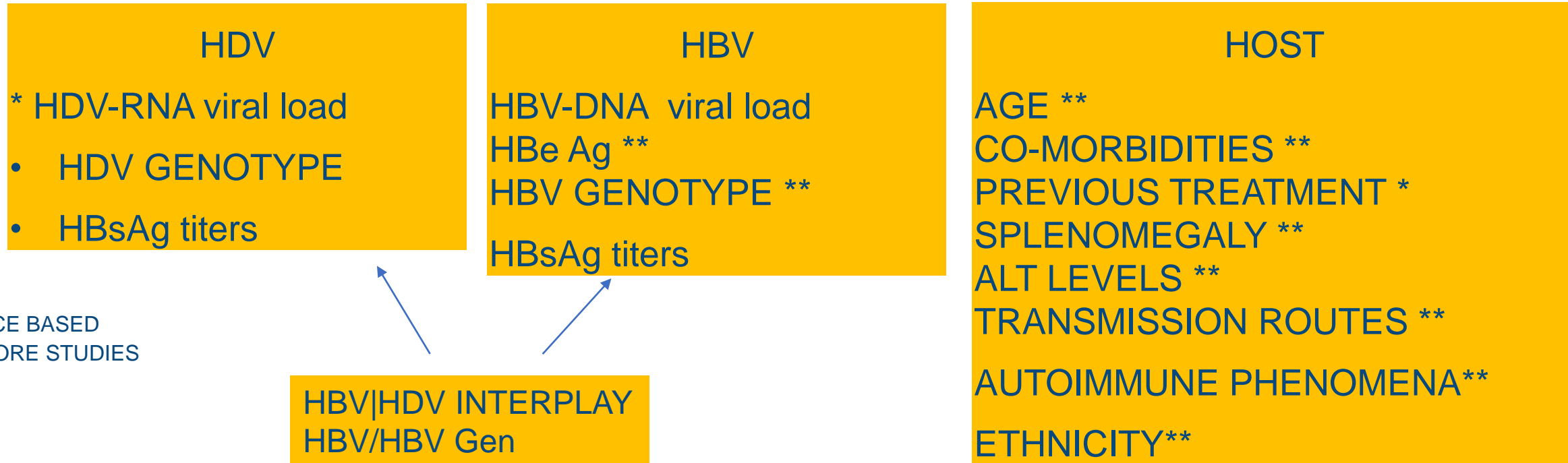
RIZZO et al, 2022
PAPATHEODORIS et al, 2008
DA BL et al, 2019
FATTOVICH et al, 2000
RIZZETTO et al, 2009
FARCI et al, 2021
KAMAL et al, 2020

Biti et al, 2011

Jachs et al, 2021

ROMEO et al, 2010
ALFAIATE et al, 2022
FATOVICH et al, 2002
GRABOWSKI et al, 2010

Variables that influence the natural history of the disease



* EVIDENCE BASED
** NEED MORE STUDIES

Role of HDV Genotypes

GEN 1

All continents but Europe and USA

Brazil (largest cities)

Severe disease +

↑
Cirrhosis

↑
HCC

GEN 2

East Asia

Milder Disease

↓
Cirrhosis

↓
HCC

Excepting 2b

GEN 3

South America

Severe Disease ++

Peculiar ALF

GEN 4

East Asia

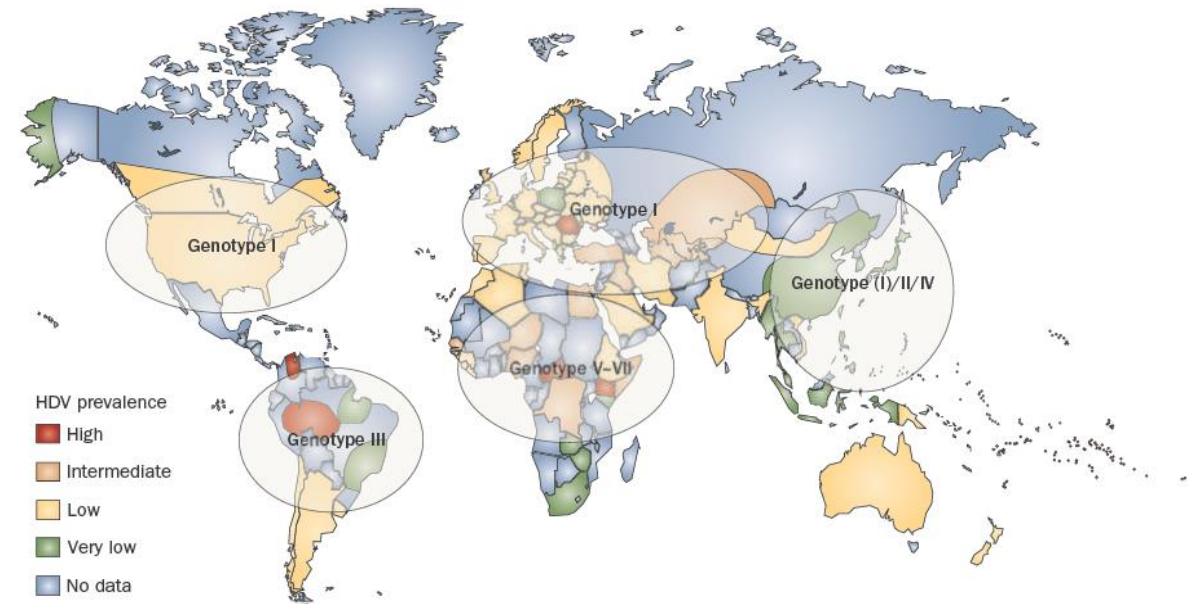
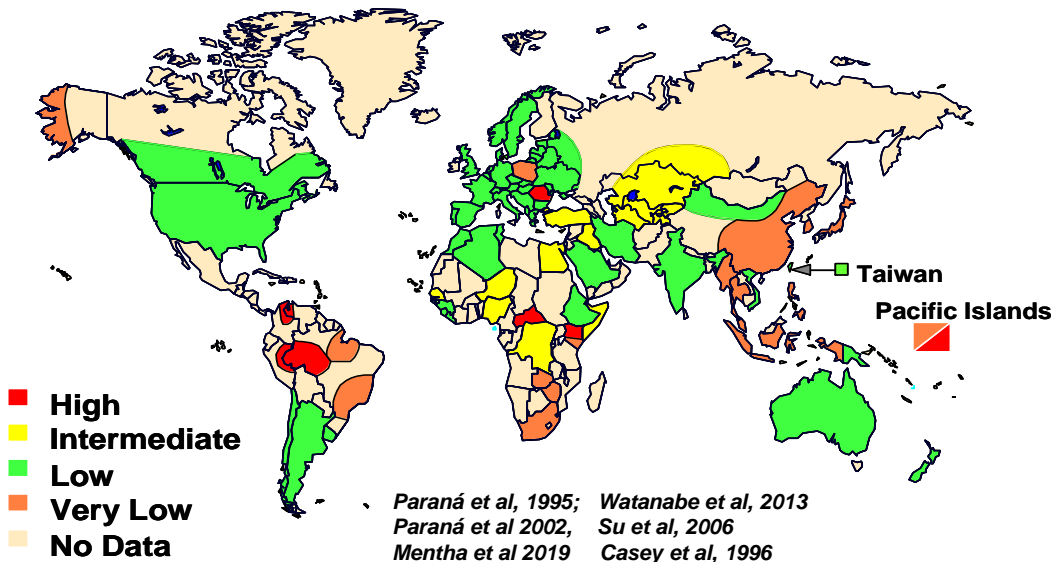
Milder Disease

GEN 5 - 8

Africa
Isolated Communities in Brazil (Gen 8)

Few data

Gen V severe disease, and ALF similar to Gen 3 from Amazonia



CO-INFECTION			SUPER-INFECTION	
	GENOTYPE	DOMINANCE	PREVALENT AREA	CLINICAL OUTCOME
SEVERE ACUTE HEPATITIS ↑ FHF	1	↑ HDV	MIDDLE EAST MEDITERRANEAN NORTH AMERICA PAKISTAN NORTH AFRICA	RAPIDLY PROGRESSIVE DISEASE SUPERINFECTION
ACUTE HEPATITIS ↓ FHF	2		EAST ASIA, RUSSIA	BETTER OUTCOME ↓ HCC CIRRHOSIS
PECULIAR AND SEVERE FHF	3	HDV HBV	AMAZON BASIN	MORE ACCESSIVITY GOOD RESPONSE TO PEG-INF
ACUTE HEPATITIS ↓ FHF	4		TAIWAN JAPAN	BETTER OUTCOME
PECULIAR AND SEVERE FHF	5-8		AFRICA CENTRAL AFRICA	MILDER DISEASE GOOD RESPONSE TO INF.

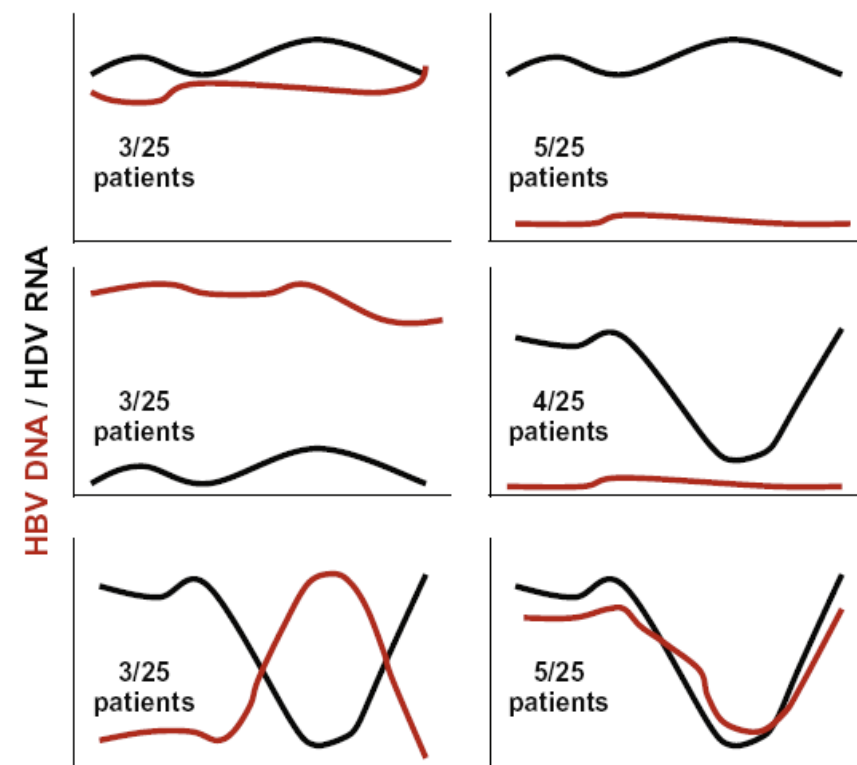


Fig. 1. Schematic representation of HBV DNA and HDV RNA patterns over time observed in the study by Schaper et al. [19].

HDV-3 HISTOLOGY AND PARAMETERS OF DISEASE STAGE

Advanced fibrosis and associated variables of the 64 patients with chronic HDV/HBV coinfection included in the study (multiple logistic regression)

Variable	N	Advanced fibrosis	%	OR	95%CI	p value	OR*	95%CI*	p value*
Total	64	32	50						
Gender									
M	43	23	53.5	1.53	0.53-4.38	0.42			
F	21	9	42.9						
Age group									
> 25	28	18	64.3	2.82	1.01-7.87	0.04	4.05	1.13-14.50	0.03
≤ 25	36	14	38.8						
Splenomegaly									
Y	36	23	63.9	3.73	1.31-10.61	0.01	2.41	0.75-7.78	0.13
N	28	9	32.1						
HBV viral load									
≥ 2 log	9	6	66.7	2.23	0.50-9.83	0.28			
< 2 log	55	26	47.3						
Delta predominance									
≥ 2 log	36	24	66.7	5.00	1.70-14.6	0.003	6.47	1.79-23.37	0.004
< 2 log	28	8	28.6						

* multiple logistic regression; N= number of subjects; OR= odds ratio; 95% CI= 95% confidence interval; Y= yes, N= no; Gender= M= male, F= female



HDV in referral centers of Viral Hepatitis in the Brazilian Amazonia

Big cities

TABLE 1
Demographic data according to HDV genotype group

Demographic parameters	HDV genotype percent (N)		P value
	Genotype I	Genotype III	
Sex			
Male	55.6% (15)	44.4% (12)	0.05*
Female	53.8% (7)	46.2% (6)	
Age (above and below median)			
< 38 years	31.6% (6)	68.4% (13)	0.01†
≥ 38 years	76.2% (16)	23.8% (5)	
Age strata			
11–20 years	66.7% (2)	33.3% (1)	> 0.05 (0.08)‡
21–30 years	23.1% (3)	76.9% (10)	
> 30 years	70.8% (17)	29.2% (7)	
Origins			
Non-amerindian	58.3% (21)	41.7% (15)	0.05*
Amerindian	25% (1)	75% (3)	

* Non-significant.
† χ^2 test.
‡ Linear-by-linear association.

TABLE 2
Genotype distribution regarding race, age and sex in symptomatic or asymptomatic patient

Demographic parameters	Clinical parameters percent (N)		P value
	Asymptomatic	Symptomatic	
Sex			
Male	76.9% (10)	23.1% (3)	< 0.08*
Female	40.7% (11)	59.3% (16)	
Age (above and below median)			
< 38 years	52.6% (10)	47.4% (9)	NS†
≥ 38 years	52.4% (11)	47.6% (10)	
Origins			
Non-amerindian →	58.3% (21)	41.7% (15)	< 0.05‡
Amerindian	0 (0)	100% (4)	
Genotype			
I	68.2% (15)	31.8% (7)	< 0.03§
III →	33.3% (6)	66.7% (12)	

* Yates.
† χ^2 test.
‡ Fisher test.
§ Not significant.

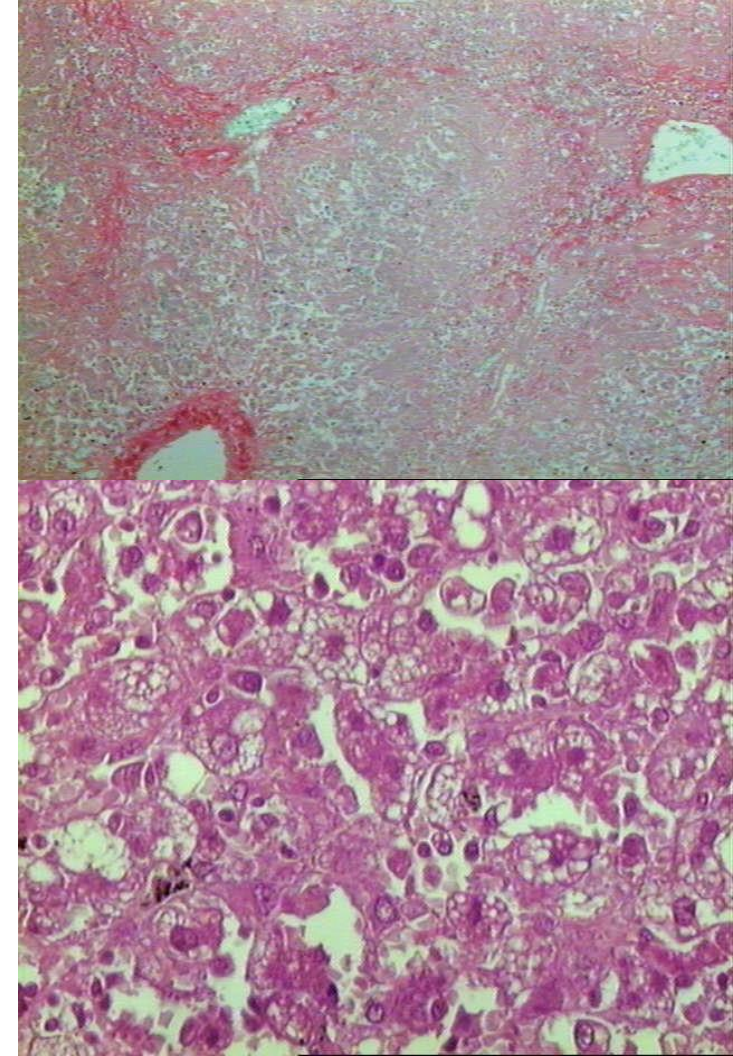
Paraná et al, Am J Trop Med Hyg,
74, 475-479 (2006)

- 👉 Genotype III is common in Brazil
- 👉 It has spread to the non-Amerindian population
- 👉 It gives more symptomatic disease

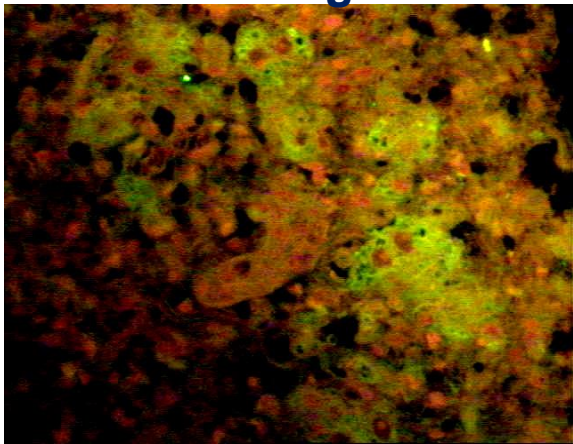
Genotype related direct cytotoxicity?

Histological Features of Labrea hepatitis/Spongiovitc Hepatitis, Yucpa Indians Hepatitis/etc

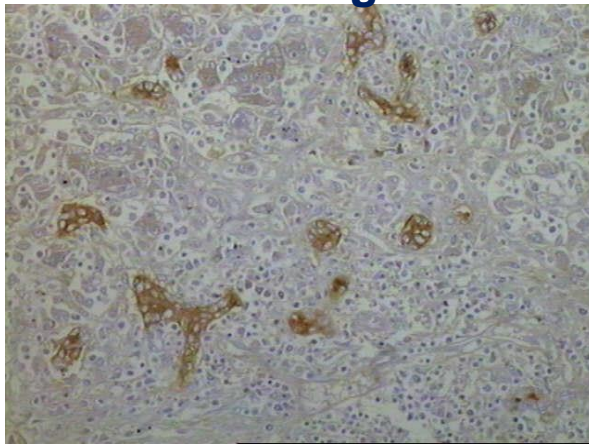
- Less Necrosis and Morula cells (“spongicytes”), ballooning cells, apoptosis, some degree of cholestasis, but no multilobular necrosis.



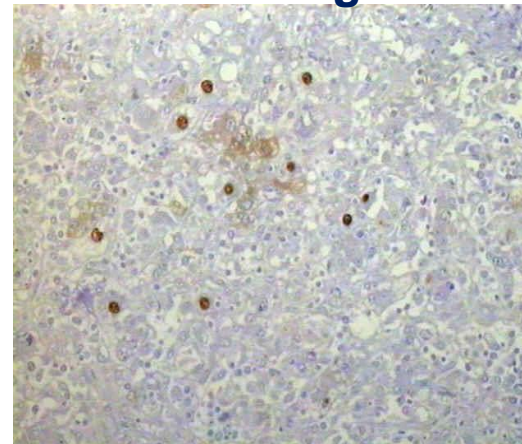
HDV Ag



HBsAg



HBcAg



Typical case of chronic HDV infection in Amazonia: Delta Ag over-expression

25 YO patient from Acre state

Anti-HCV: negative

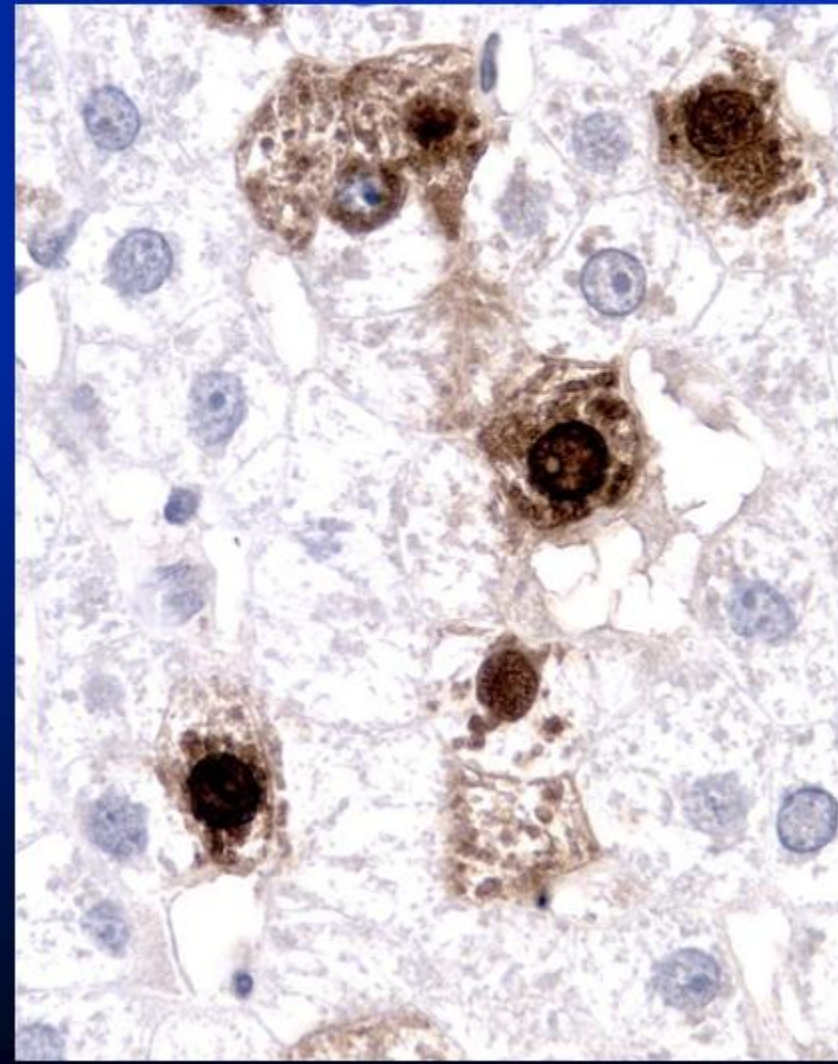
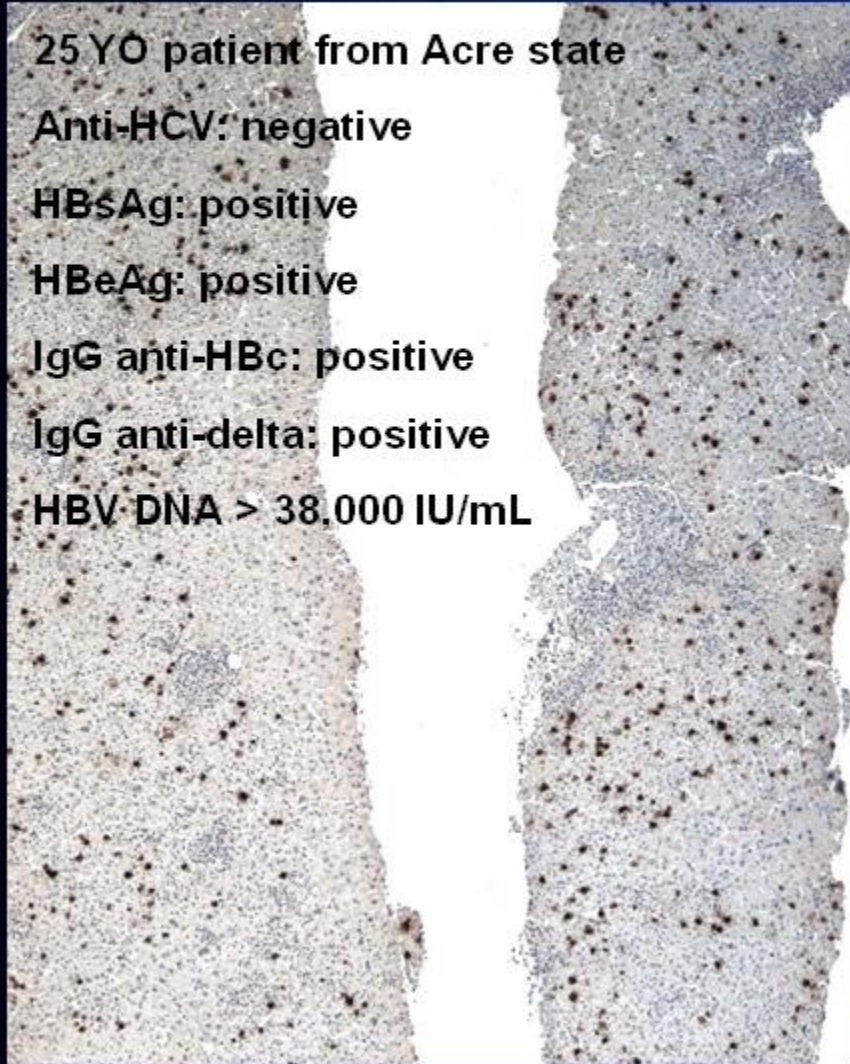
HBsAg: positive

HBeAg: positive

IgG anti-HBc: positive

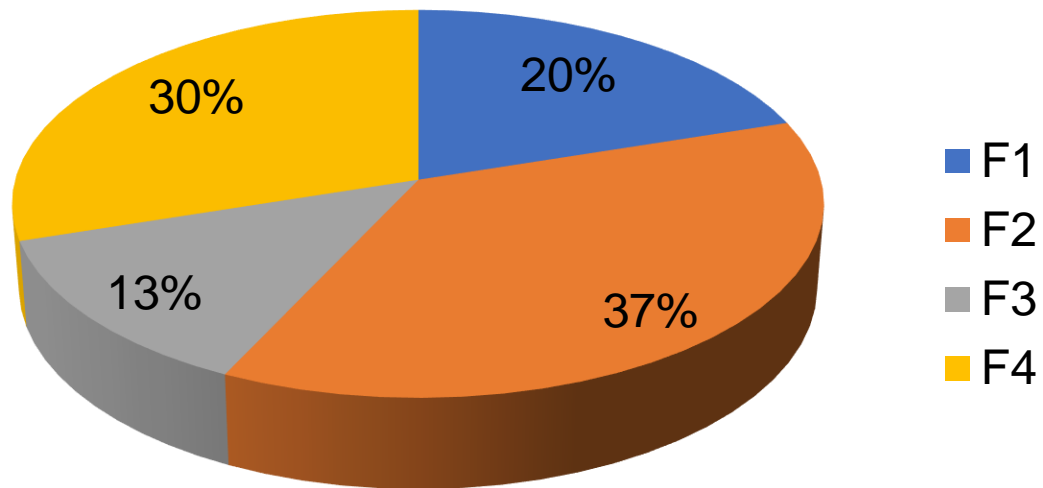
IgG anti-delta: positive

HBV DNA > 38,000 IU/mL



Delta Project

Liver biopsy



Usual Brazilian Chronic Delta Hepatitis Patient
12 yo, many family members HDV carriers
Large splenomegaly, High globulin, High
HBV-DNA and HDV-RNA levels



CHALLENGES TO COMPARE HBV – HBV/HDV

- MOST RETROSPECTIVE STUDIES
- ONLY RECENTLY COMERCIAL HDV-RNA
- NON-STANDARDIZED HDV-RNA TESTS
- HBV/HDV GENOTYPES NOT AVAILABLE IN MANY ENDEMIC AREAS
- HBV/HDV CLINICAL PRESENTATION RANGE FROM ASSINPTOMATIC TO RAPDLY PROGRESSIVE DISEASE
- CLINICAL FEATURES CHANGE OVER TIME
- HBV-DNA / HDV-RNA NOT EASILY AVAILABLE IN MANY ENDEMIC AREAS
- NEGLECTED DISEASE (NON-DIAGNOSED)
- STUDIES SHOULD BE CONDUCTED IN MANY ENDEMIC AREAS
- HOST IMMUNE RESPONSE PATTERN AND/OR DIRECT CITOTOXICITY MUST BE CONSIDERED
- ETHNICITY MUST BE STUDIED

SPECTRAL DISEASE

- MILD FORMS DEMONSTRATED in 10-20%
- Possibly more cases of stable disease
- MORE AGRESSIVE DISEASE IN MOST?
- HDV-RNA LEVEL METTERS
- HDV GENOTYPE METTERS
- Probably, many others variables metter

Democracy is not paradise, but it is the
furthest point from hell

Humanity must stay away from extremism

Amazonian Delta Hepatitis Project

- Referral centers: RIO BRANCO/CRUZEIRO DO SUL/PORTO VELHO/MANAUS
- Satelites centers: SENA MADUREIRA-AC/COARI-AM/TABATINGA-AM
- Amazonian Referral Centers

**Jiminawá Tribe
Purus River-ACRE state**



Manaus – Amazonas state



**Thank you
Merci
Gracias
Obrigado**