Delta Hepatitis:
Different Genotypes = Different Diseases?

Federal University of Bahia-Brazil
School of Medicine
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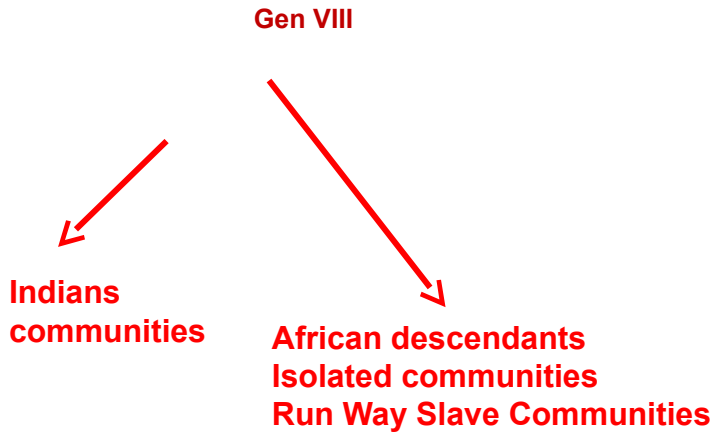
PHC 2018 - www.aphc.info

Disclosure

PI phase II and IIII studies: BMS, Janssen/Tibotec, Roche, BI, Jonhson&Jonhson Foundation
Speaker: ABBVIE/BMS/GILEAD
Board: Brazilian Health Ministry – HIV/Viral Hepatitis Department
Senior Researcher CNPq (Brazilian Agency for Research development)

Emerging HDV Epidemiology



Ferreira et al, 2011
Paraná et al, 2014, in abstract

- Amazonia
- Central Africa
- Western Europe (some areas)
- Isolated Pacific Islands
- India and Pakistan

- **Gen III associated with more severe disease and peculiar forms of FH**

Casey te al., J Infect Diseases 1996, Bensabath et al 1986, Parana et al, 2006

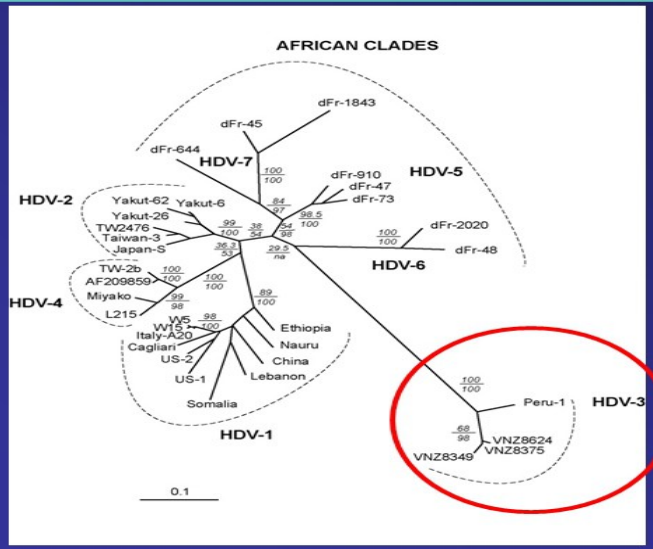
Phylogeny of HBV/HDV genotypes/subtypes

Amazon Basin

Kay & Zoulim, Virus Res, 127, 164-176 (2007)

Su et al, gastroenterol 2006

South America: Could the Severity of the disease be explained by phylogeny of HDV genotypes ?



Genotype III (3) is the most divergent

Radjef et al. J. Virol 2004

Heterogeneity of HDV Distribution in Highly Endemic Regions

Is there a genetic suceptibility ?

Braga et al, 2014

Is there a genetic of susceptibility to HDV infection? *Rizzetto and Alavian 2013*

HDV Gen-3 HISTOLOGY AND PARAMETERS OF DISEASE STAGE

METAVIR

FIBROSIS

STAGE	N (%)	TOTAL
F0	5 (4.6)	109
F1	27 (24.7)	
F2	28 (25.7)	
F3	25 (23.0)	
F4	24 (22.0)	

Necro-inflammation

GRADE	N (%)	TOTAL
A0	9(8.2)	109
A1	30(27.5)	
A2	31(28.5)	
A3	39(35.8)	

Braga et al, 2014

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						
≥ 2 log	36	24	66.7	5.00	1.70-14.6				
< 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

Braga et al., 2014. Journal of Hepatology

Patient age, duration of clinical evolution and survival post transplantation in patients with cirrhosis HBV and Delta in Brazilian Amazonia

	N	Mean	Minimum	Maximum	Std. Deviation
Age at diagnosis	31	27,06	3	49	12,641
Age in cirrhosis	30	31,43	4	58	13,733
Age in transplantation	31	34,74	7	59	13,130
Interval between the diagnosis of hepatites and cirrhosis in months	30	44,30	0	242	62,685
Survival post transplantation in months	31	50,71	1	171	47,361
Interval between the transplantation and loss of AgHBs in months	23	34,65	0	128	31,793

3 Death, 9, 17 and 26 months post transplantation: insufficiency hepática, septicemia, CHC recurrence, respectively.

Lobato et al, 2015, in abstract

Amazonian and European / US Delta Hepatitis D are different Diseases

Europe/US (Low endemicity)

- Almost restricted to group of Risk (IVDU)
- Immigrants from Endemic areas
- Vanishing Disease
- Gen I prevail
- Few patients with HBeAg pos status
- HBV-DNA inhibited by HDV

Amazon (High endemicity/Epidemic)

- **Autocthon cases, Not restricted to group of risk**
- **younger patients**
- **Gen III prevail mainly with HBV-F gen**
- **More severe chronic cases and peculiar forms**
- **Intrafamilial transmission**
- Probably adaptative mutations
- Peculiar Fulminant Hepatitis
- Severe Disease with splenomegaly
- Transmission routes unknown

Fluctuating Patterns of Viral Dominance in Hepatitis D

Most cases

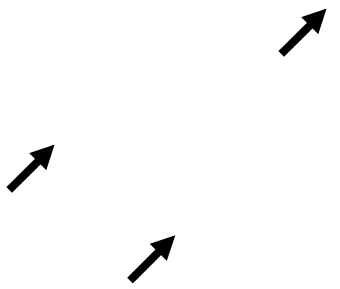
Peculiar histhologic forms of HEP D: morula cells means High mortality rate

- Outbreaks of fulminant hepatitis associated with HDV infection have been reported in Central Africa and the Amazonian countries

- These infections have a particular histopathology, microvesicular steatosis which results in ballooning hepatocytes with small fat droplets bunching around the nucleus giving them an aspect of sponges or morula (spongiocytes, Morula cells).

  Similar disaese has been described in central Africa (*Lesborde et al, 1990 and Andrade et al, 1992)*

  Similar disease reporduced in Woodchuck model inoculated with sera from Africans and Brazilian patients (*Parana et al, 1995)*



Amazonia and genotype III

- In Amazonia, mainly Amerindian communities are affected
- HDV genotype III seems to be directly implicated
- Venezuela - disease called Yucpa-Indian Fever
  Peru - Santa Marta Fever
  Brazil - Black Labrea Fever (Febre Negra de Lábrea)

SPONGIOCITIC Hepatitis in Central Africa

HDV related Labrea Fulminant Hepatites: Replication of both viruses (HDV III/HBV F)

Is HDV patogenicity due to a cytopathic or immunomediated lesion?

HDV Ag, HBcAg, HBS Ag are concentrated in the citoplasm of morula cells

Andrade and Parana, 2009

Mutant genotype III

☞ **Sequencing**

✦ **the sequenced samples showing anomalous hybridization have the same mutation in the region covered by the genotype III hybridization probes**

✦ **Wild type – 59 patients; Mutant – 25 patients**

☞ **Changes the 2nd from last aa of sΔAg from F (Phe) to Y (Tyr)**

Genotype III probe

CUGUUCCCAURGUAUGGGUUUACCCCGCCYCCCCCCGGGUAUUACUGGGUCCCAGGGUGCACCCAACAAUAAAG

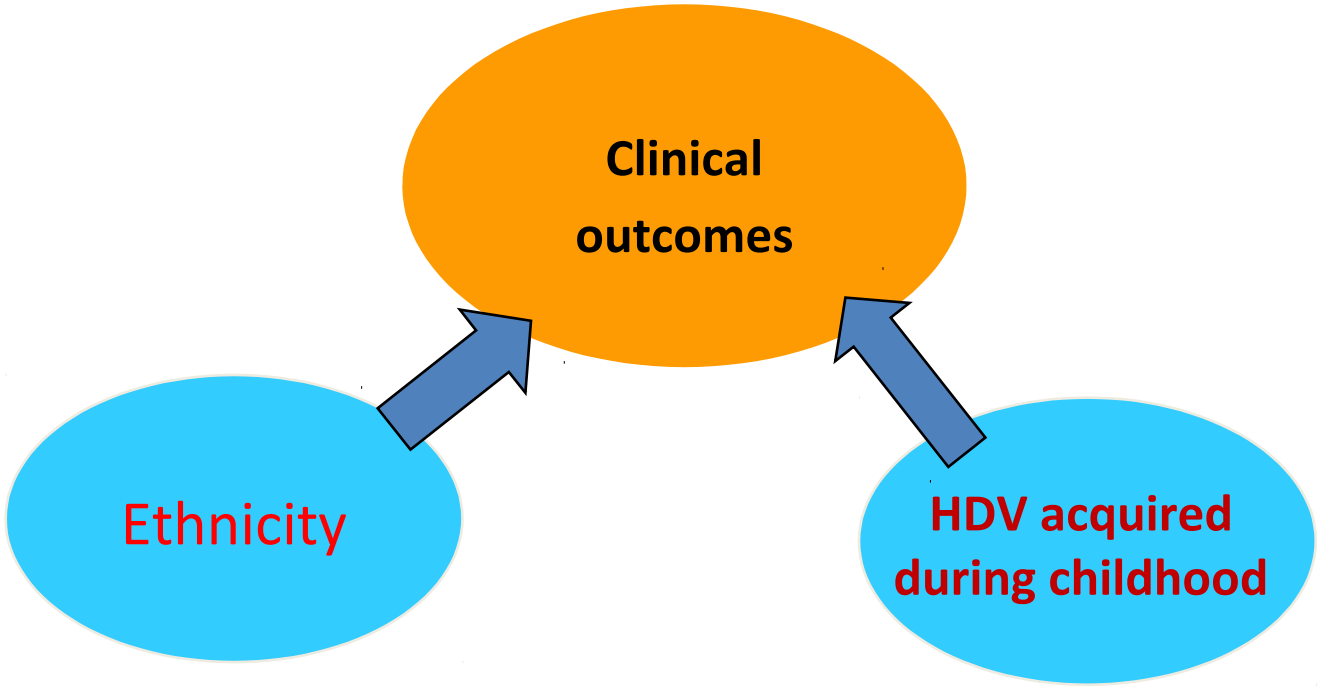
L F P Y/* Y G F T P P P P G Y Y W V P G C T Q Q *

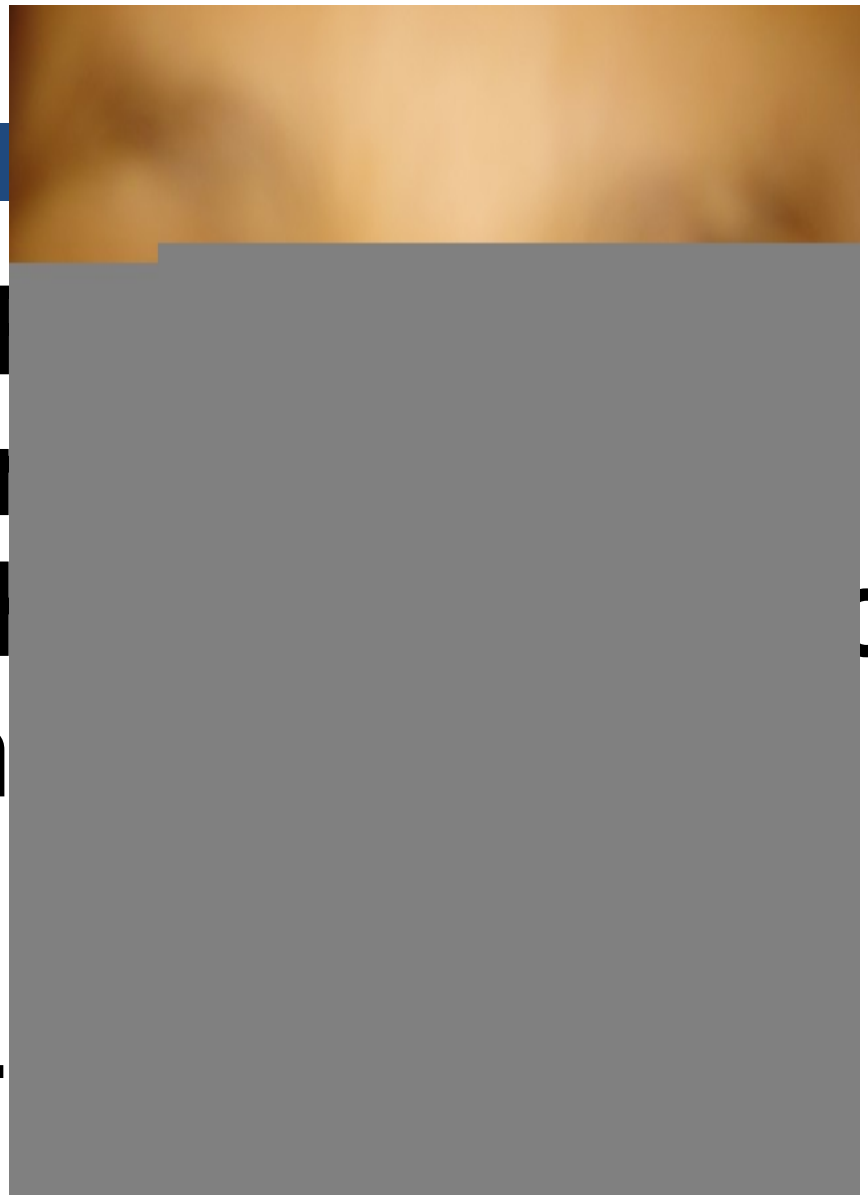
Y UAC

Kay et al , 2014

Hep D is a spectral disease with many variables that are postulated to influence on the Natural History

Host genetic backgound could interfere in the natural history chronic HDV infection?





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Questions?

- Ethnicity susceptibility?
- Concomitantly high HBV/HDV viral load?
- Some HDV Genotype are more pathogenic?
- Some HBV Genotypes with HDV are more pathogenic than others ?
- Children have a less favorable disease course ?

Clinical Case

- 22 yo male patient from Rondonia. Amerindian/Caucasian (Caboclo)
- 01 brother with HBV/HDV and 01 Brother died due to HCC 21yo. Presented fatigue . He was evaluated by the GP (Basic Health Assistence Program). Mother is under treatment with Tenofovie (AgHBs + / AgHBe -, High VL)

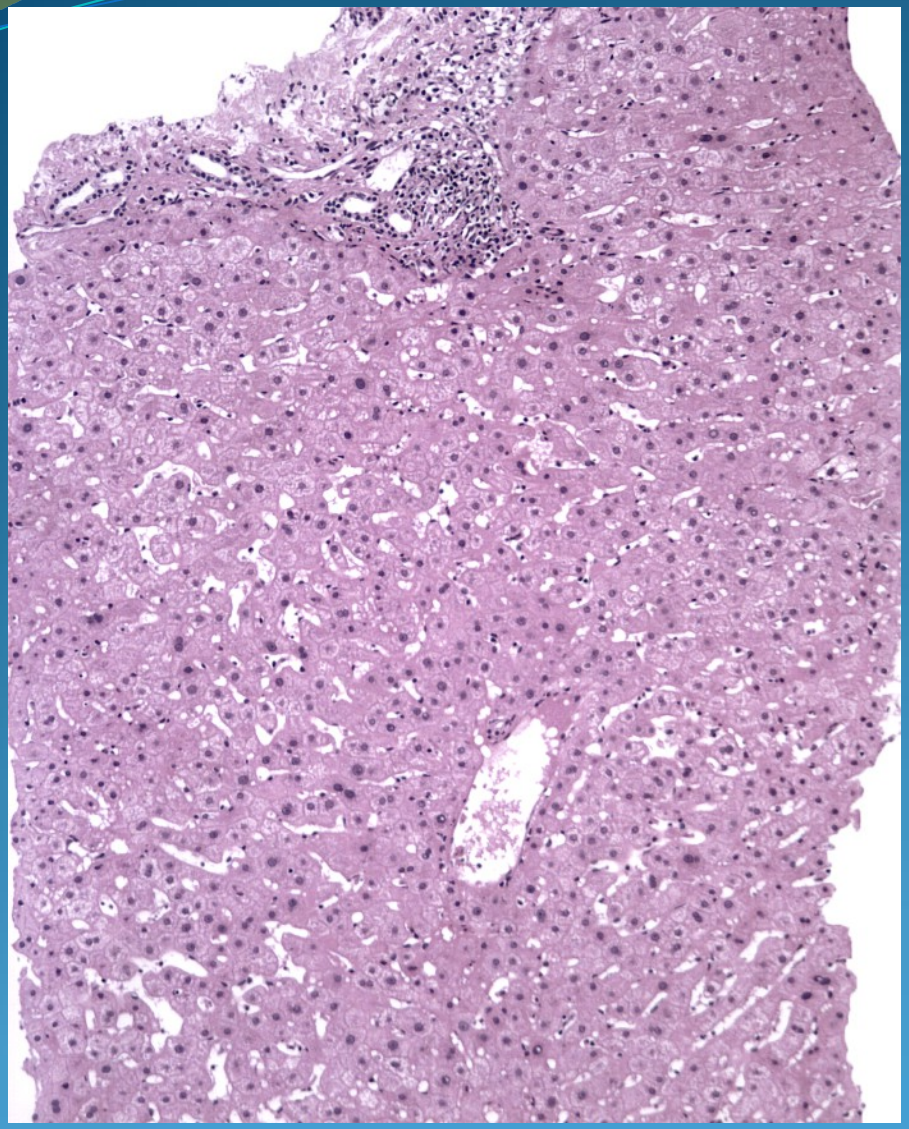
- Splenomegaly confirmed by US
- Mild jaundice

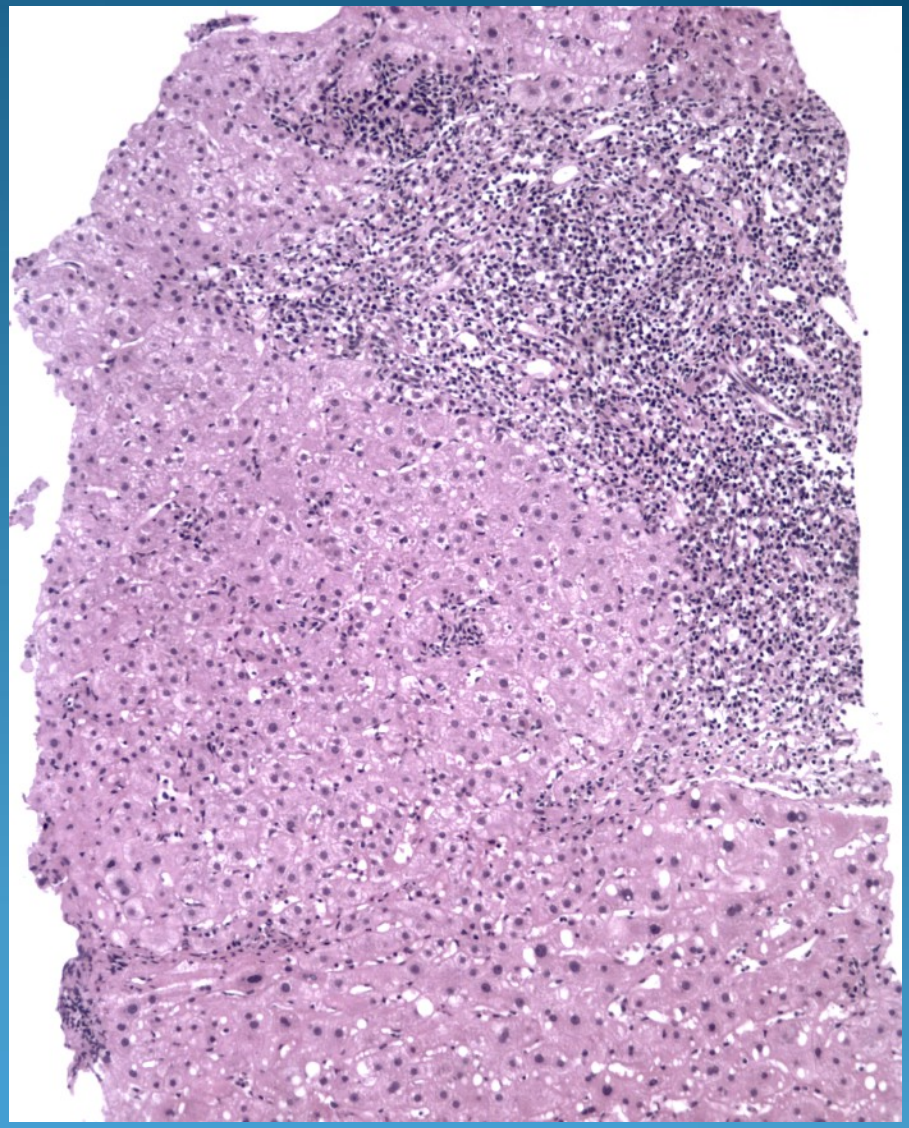
- Hb: 13 Ht 30, AST 4x UNL, ALT 6x ULL, GGT 1.5 x UNL

Alb 3,5, Glob 4.1 IgG 2950 (2400)

AgHBs +, AgHBe -. Anti HDV IgG +

Ecography: Crhonis liver disease and moderate splenomegaly
Endoscopy: No Varices





R 31 12

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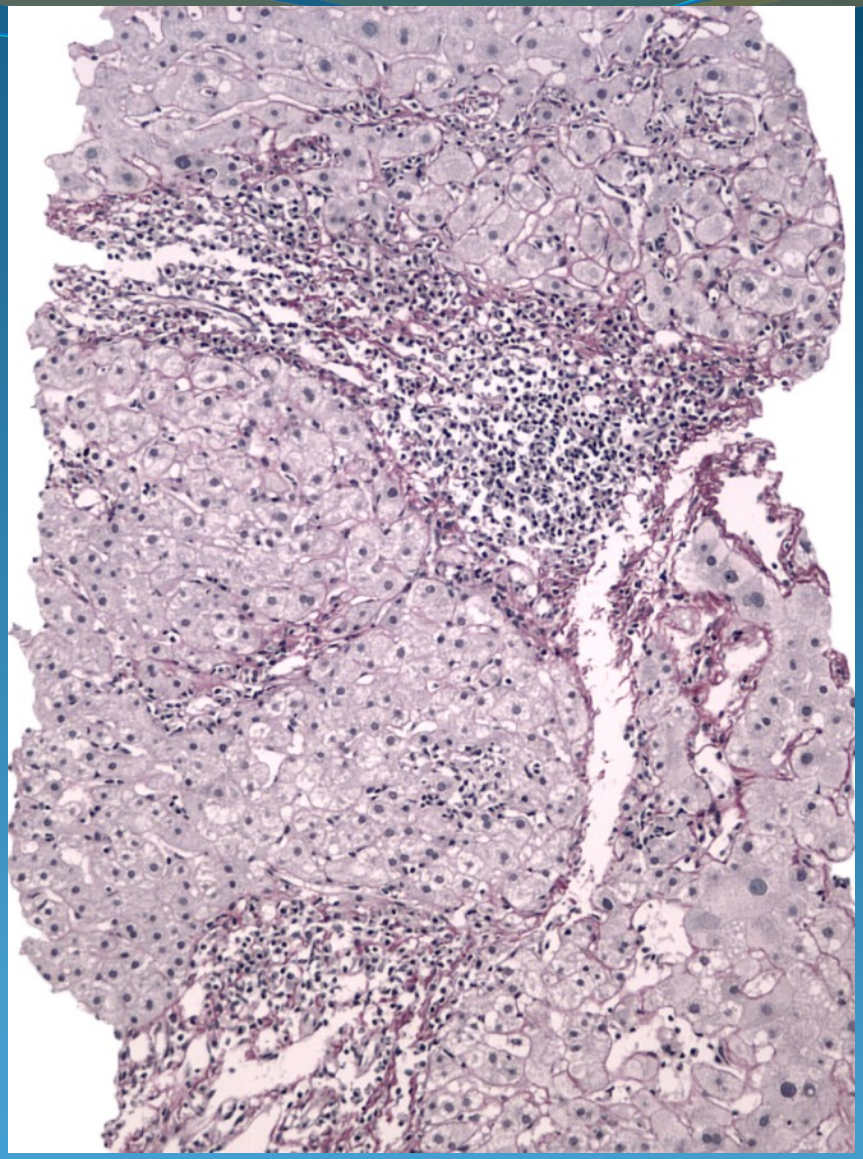
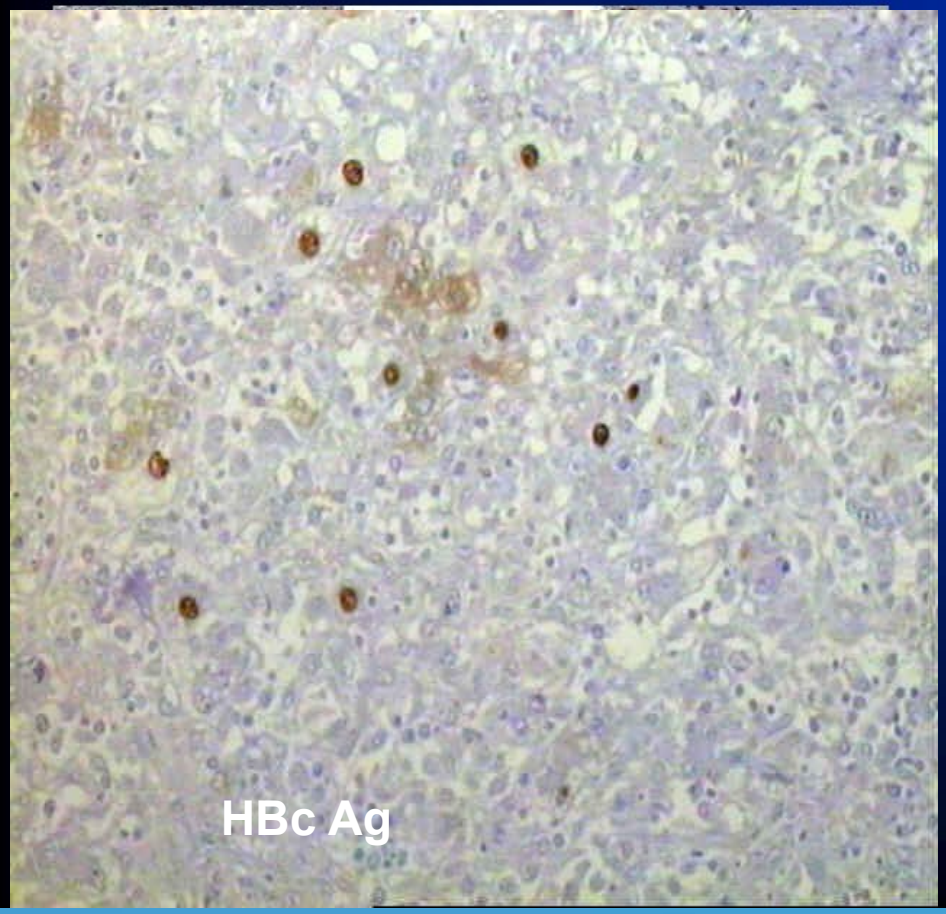
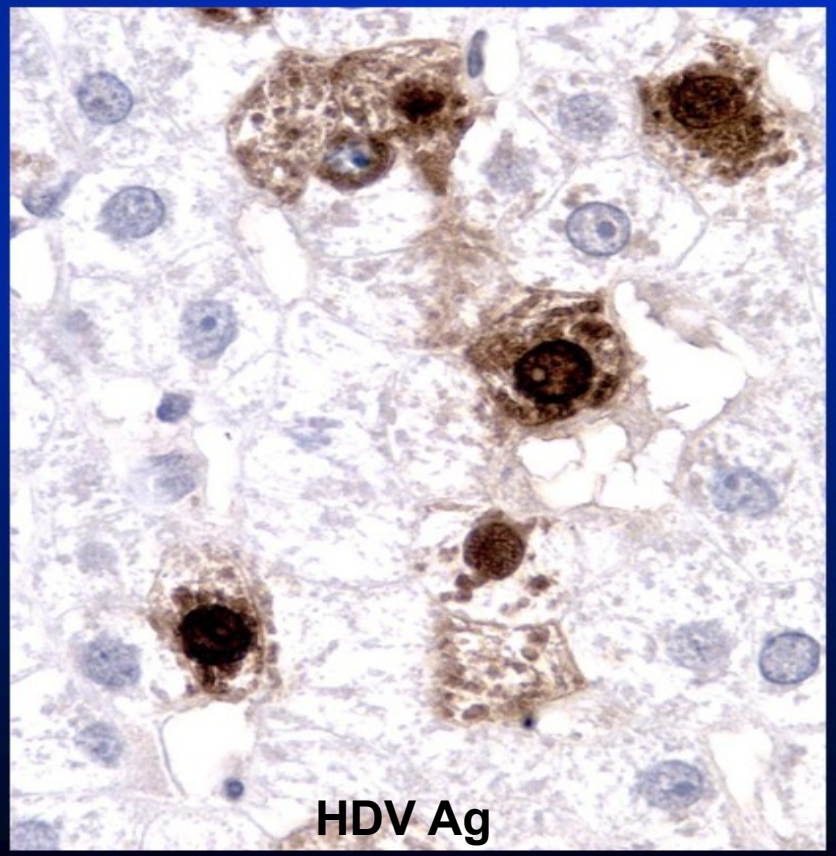


R 31 12

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





Question 2

- HBV-DNA 6,7 logs, HDV-RNA 3.1 logs

- Would you do HBV/HDV genotypes?

Does it metters regarding natural history or therapeutic decisions?

How about HBV F non –F /HDV III genotypes interplay?

Genotypes were performed

HDV gen 3

HBV F

Question 2

PEG-INF tratament

Or

Combo (Peg-INF + DAAs)

?

With Peg-INF monotheraphy: Lets discuss different scenarios

AgHBs Neg

HBV-DNA undetectable

HDV-RNA undetectable

Best scenario But very rare

HBsAg + Declene 1,8 log

HBV-DNA Decline < 2000 ui

HDV-RNA remains 3.5 logs

AgHBs + No decline

HBV-DNA > 2000 ui

HDV-RNA undetectable

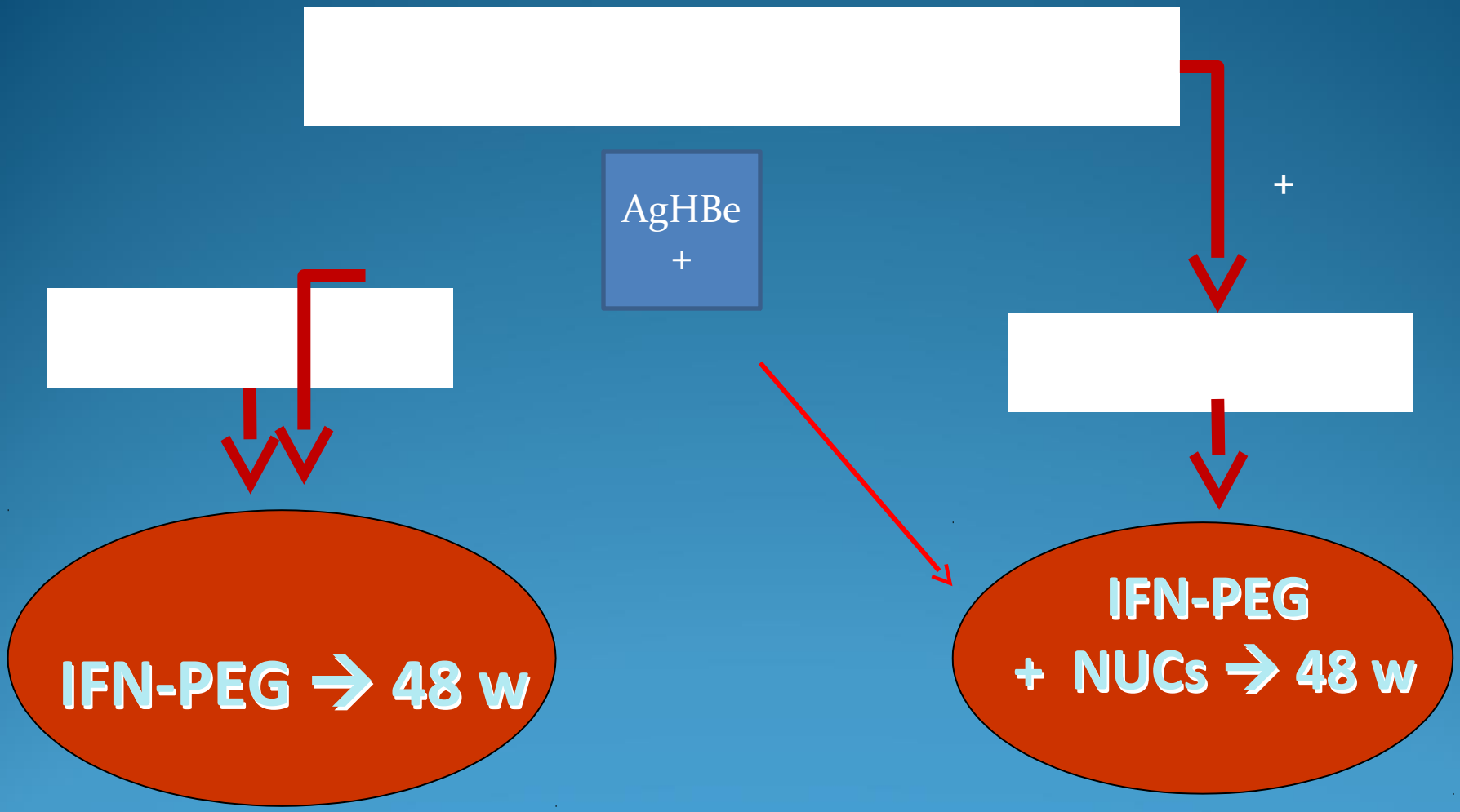
AgHBs Decline Strong

HBV-DNA (very low)

HDV-RNA 3.1 logs

Mow could we manage this patient accordind to these scenarios?

According to the Health Ministry Brazilian Protocol



PCDT- Brazilian Health Ministry

Real life: Outcomes

- Peg-INF + Entecavir started
- Week 24 HBV-DNA 22000 ui/ HDV – RNA not available
- Week 48 HBV-DNA undetectable/ HDV-RNA Undetectable
- Week 24 Follow up HBV-DNA undetectable/ HDV-RNA Undetectable, HBsAg NEGATIVE

What hapenned with this real patient?

AgHBs Neg

HBV-DNA undetectable

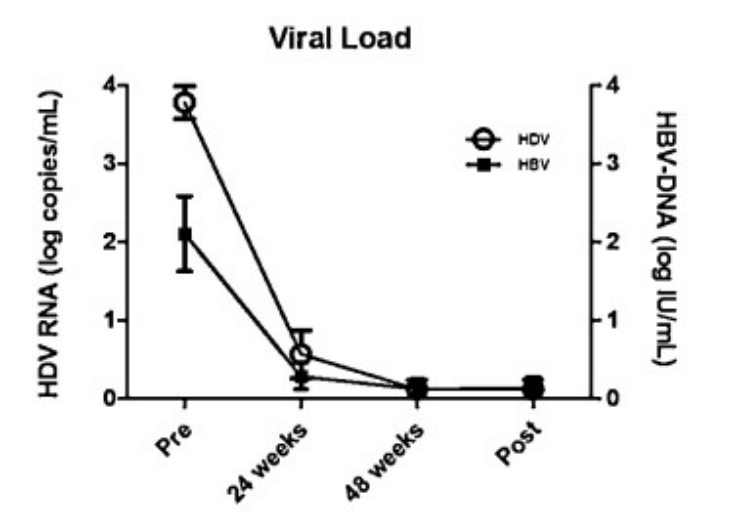
HDV-RNA undetectable

Best scenario But very rare

Treatment of hepatitis delta virus genotype 3 infection with peg-interferon and entecavir

Lourdes Maria Pinheiro et al Int J Inf Dis 2016

Real life study with 22 pts using Peg-INF + ETV , all Gen III



Only 9% of patientes With HBV-DNA detected at week 48 and the FU

3/22 Ptes became HBsAg Neg (14%)

Is Peg-INF + Nuc the best HDV therapy for Gen III pts?

www.hepatologiadomilenio.com.br

Check the international guests
Already confirmed on the site.

ACCOMPLISHMENT

SE7EAGA
Centro de Intercâmbio de Estudos Técnico-Científicos

ABEF
Associação Baiana para Estudo do Fígado

SUPPORT

ALEH

Sociedade Brasileira de Hepatologia

SBH

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Thank you

Merci