Treatment of Delta Hepatitis

More questions than answers

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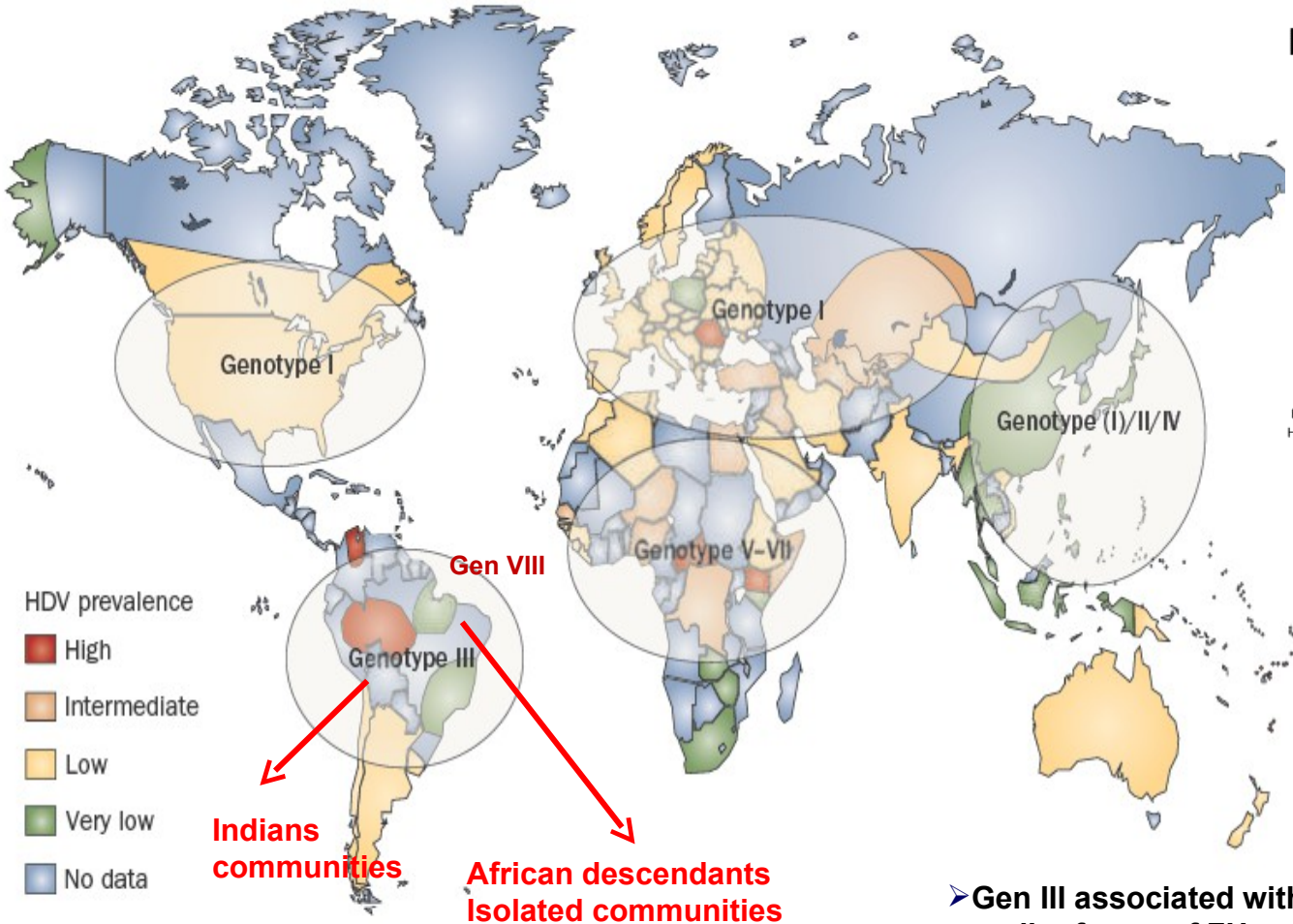
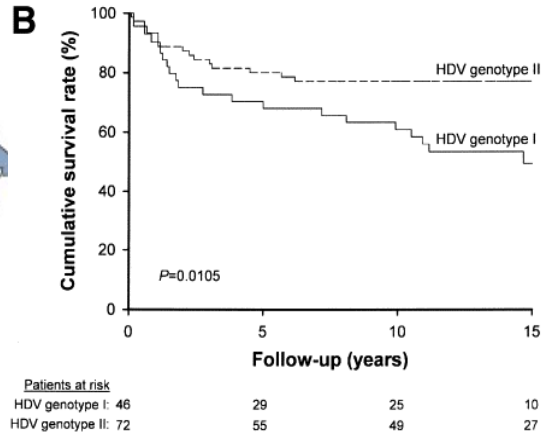
Emerging HDV Epidemiology





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

Indians communities

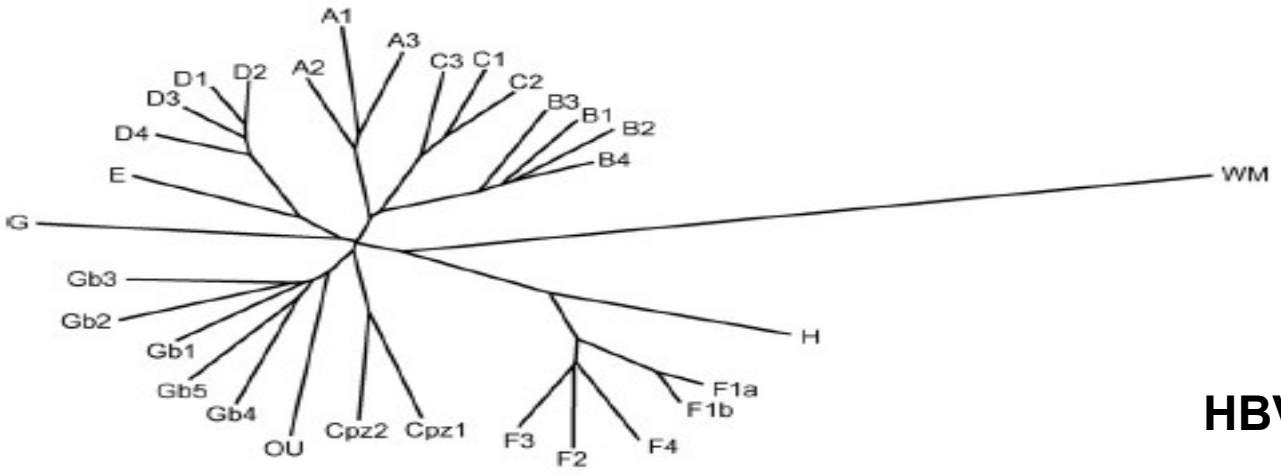
African descendants Isolated communities Run Way Slave Communities

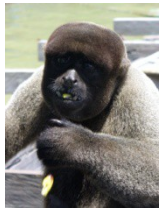
Ferreira et al, 2011
Paraná et al, 2014, in abstract

➢ **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





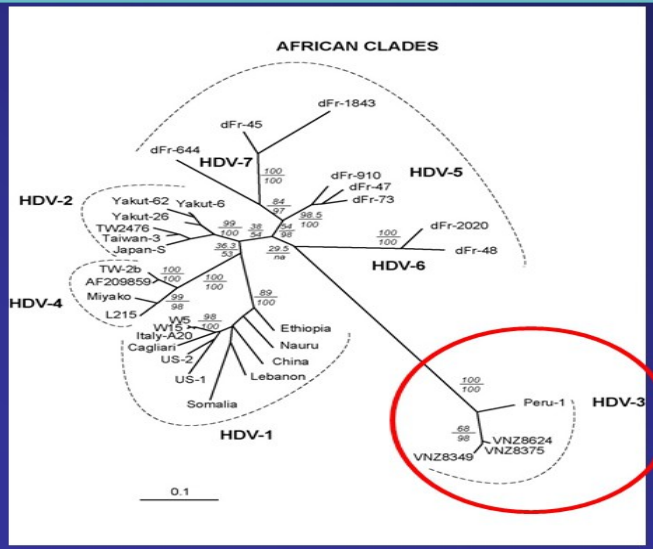
Amazon Basin

HBV –C > HBV-A

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

Su et al, gastroenterol 2006

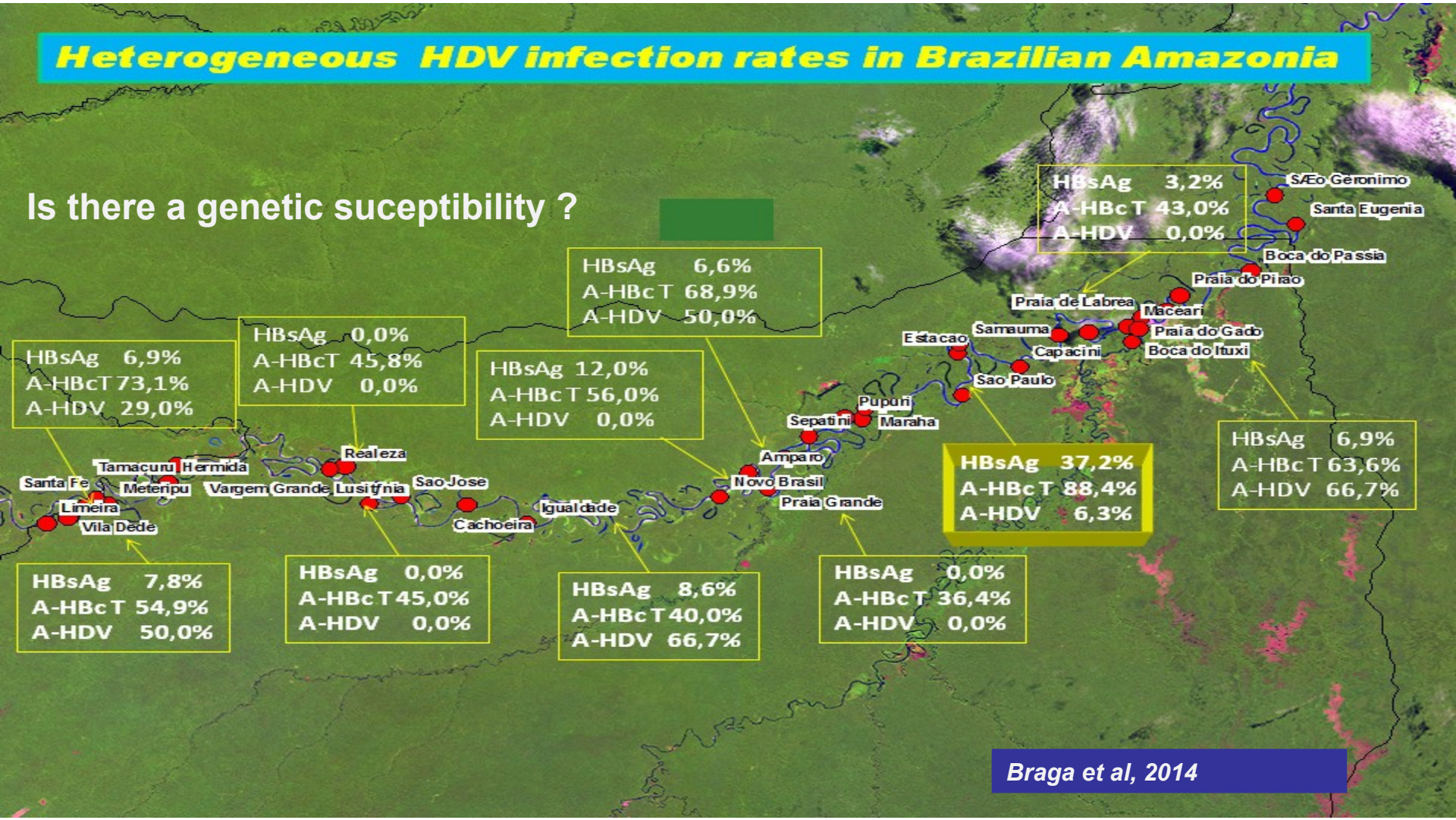
South America: Could the Severity of the disease be explained by phylogeny of HDV genotypes ?



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 of susceptibility to HDV infection? *Rizzetto and Alavian 2013*

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

Fluctuating Patterns of Viral Dominance in Hepatitis D

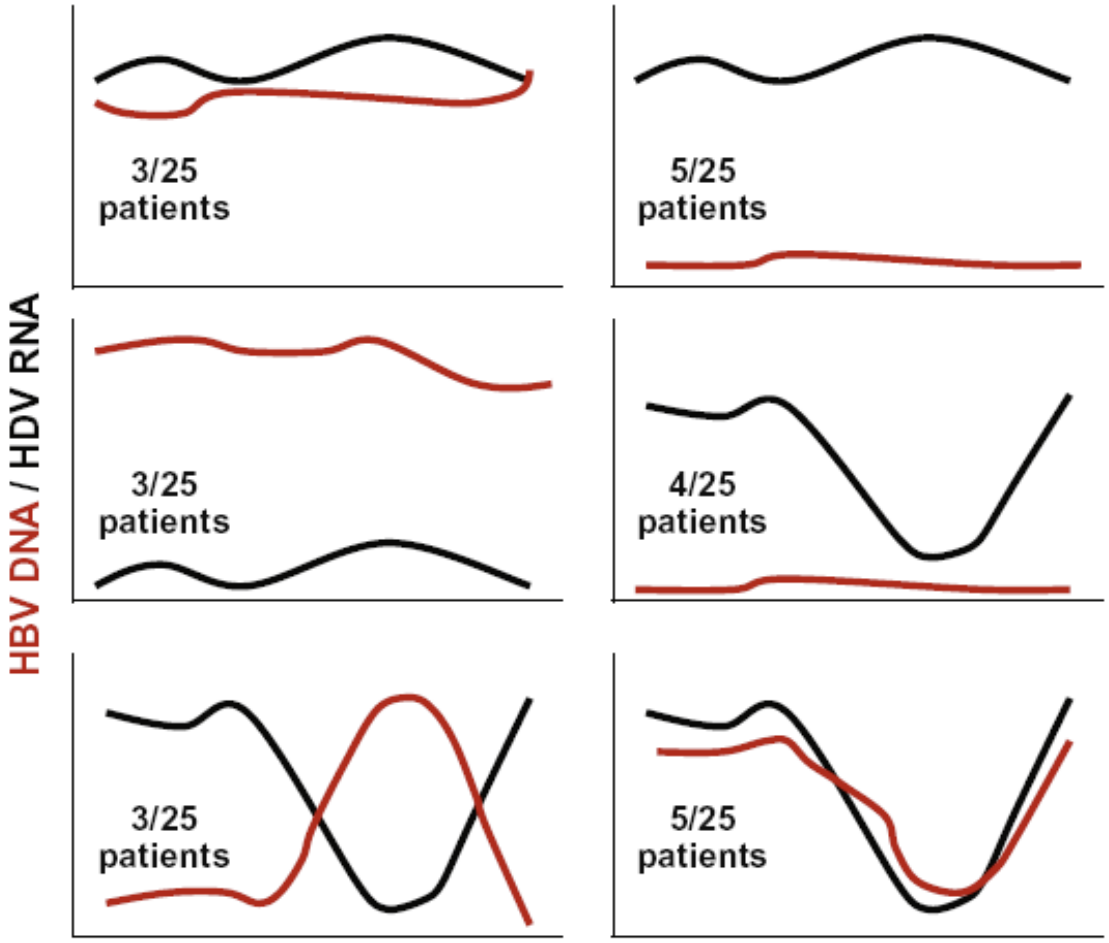


Fig. 1. Schematic representation of HBV DNA and HDV RNA patterns over time observed in the study by Schaper et al. [19].

MSO
Sexo: Male Age: 25 From: Acre (Amazonia)

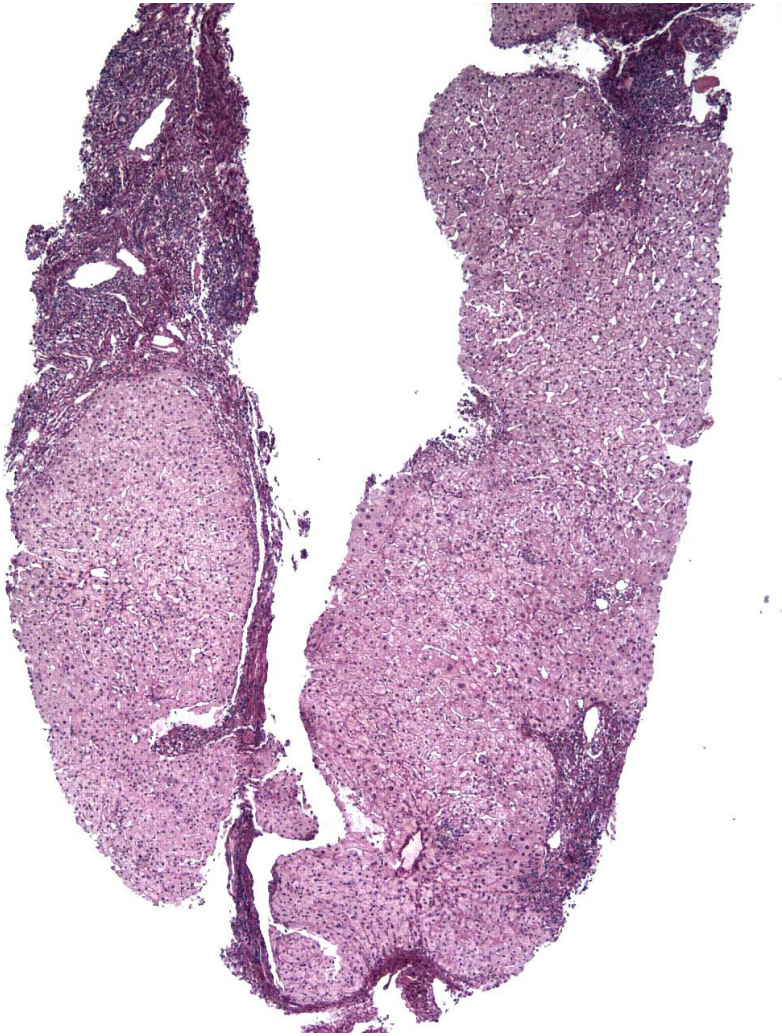
Chronic Hep B / Delta from *Jiminawa tribus*, Purus River, Amazonia.
He was referred to Rio Branco center of viral hepatitis

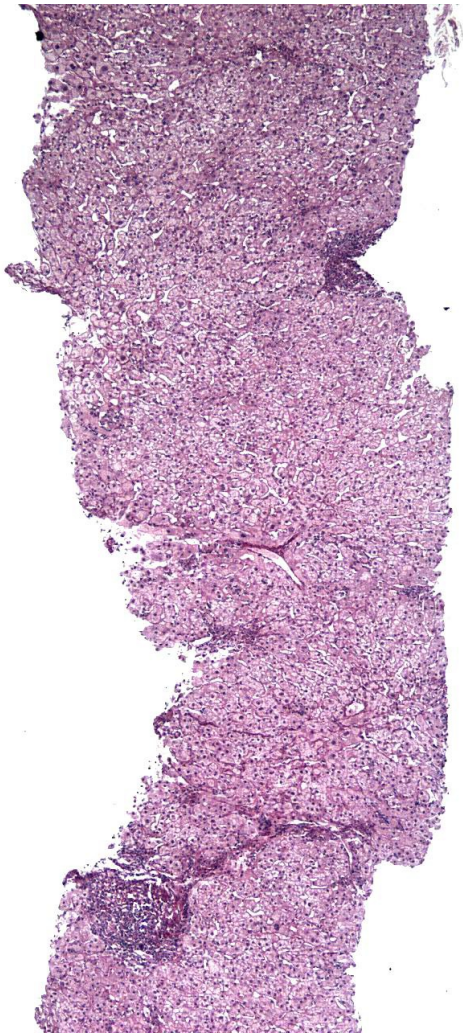
Two Brothers aged 18 and 17 yo died with liver Cirrhosis two years ago
Mother has been treated for Hep B with Tenofovir
Physical Exam: No stigma of CLD
Splenomegaly
Abdominal Echography: Moderate splenomegaly

US de abd: Normal, excepting Splenomegaly

HBeAg positive
HDV-RNA Pos (no quantitation)
HBV-DNA 280000ui/ml
AST 3x/UNL AST 2x GGT: 2x AP: 1,4 x
Bil: 1.1 PT (RNI) 11 Creat: 0.9 Alb: 4.2
HBV Gen F and HDV Gen III
Endoscopy: No varices

Proceed to Liver Biopsy





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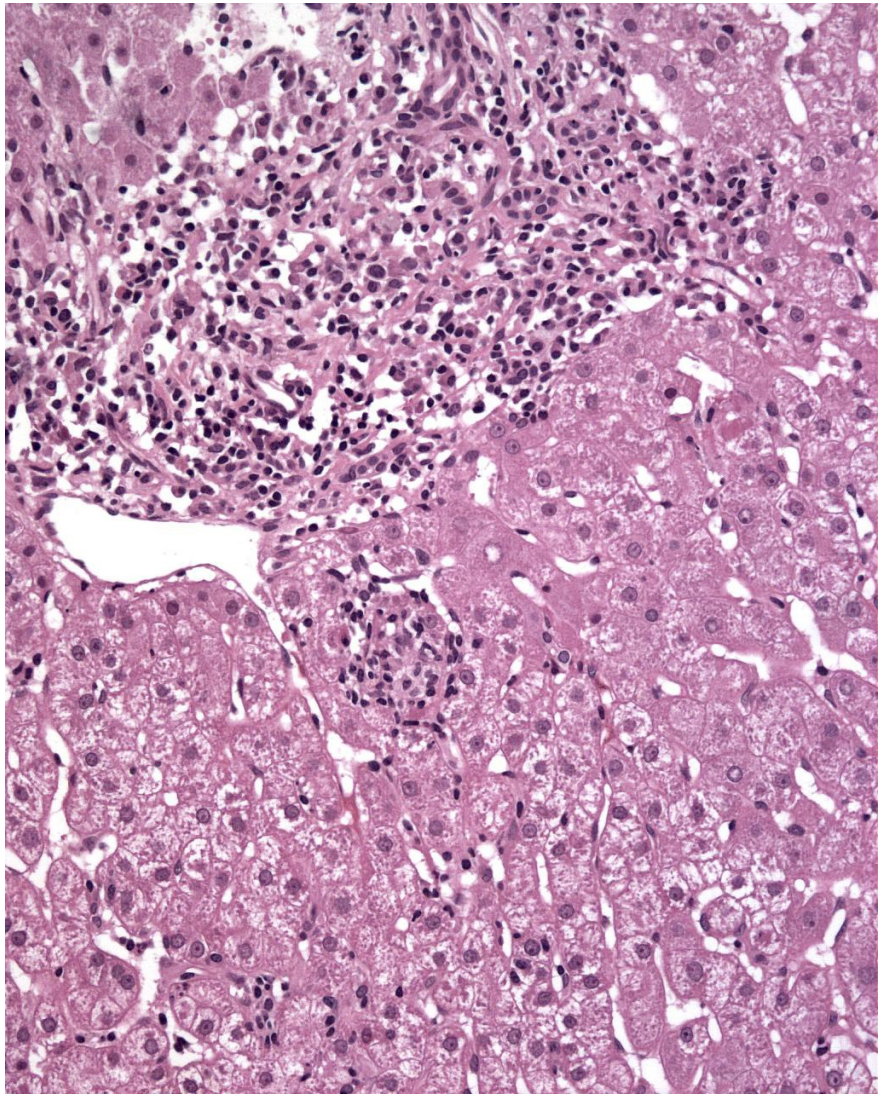

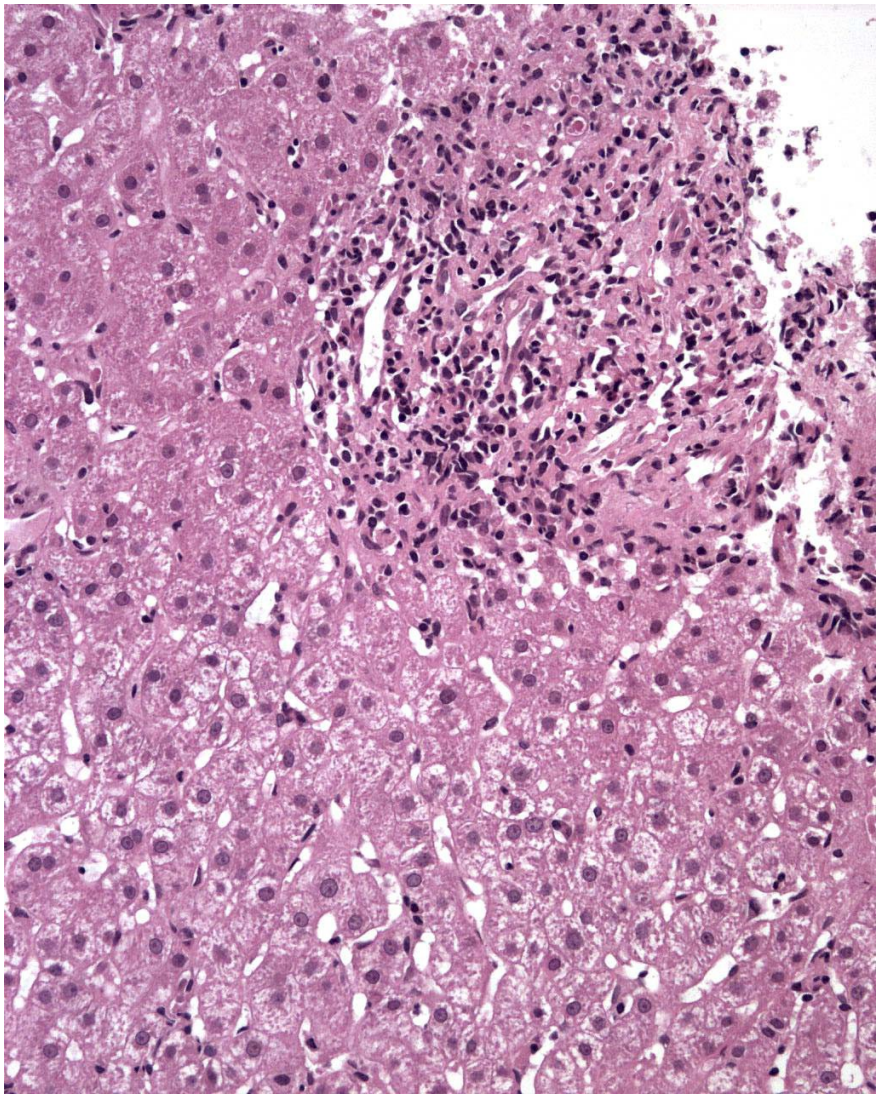

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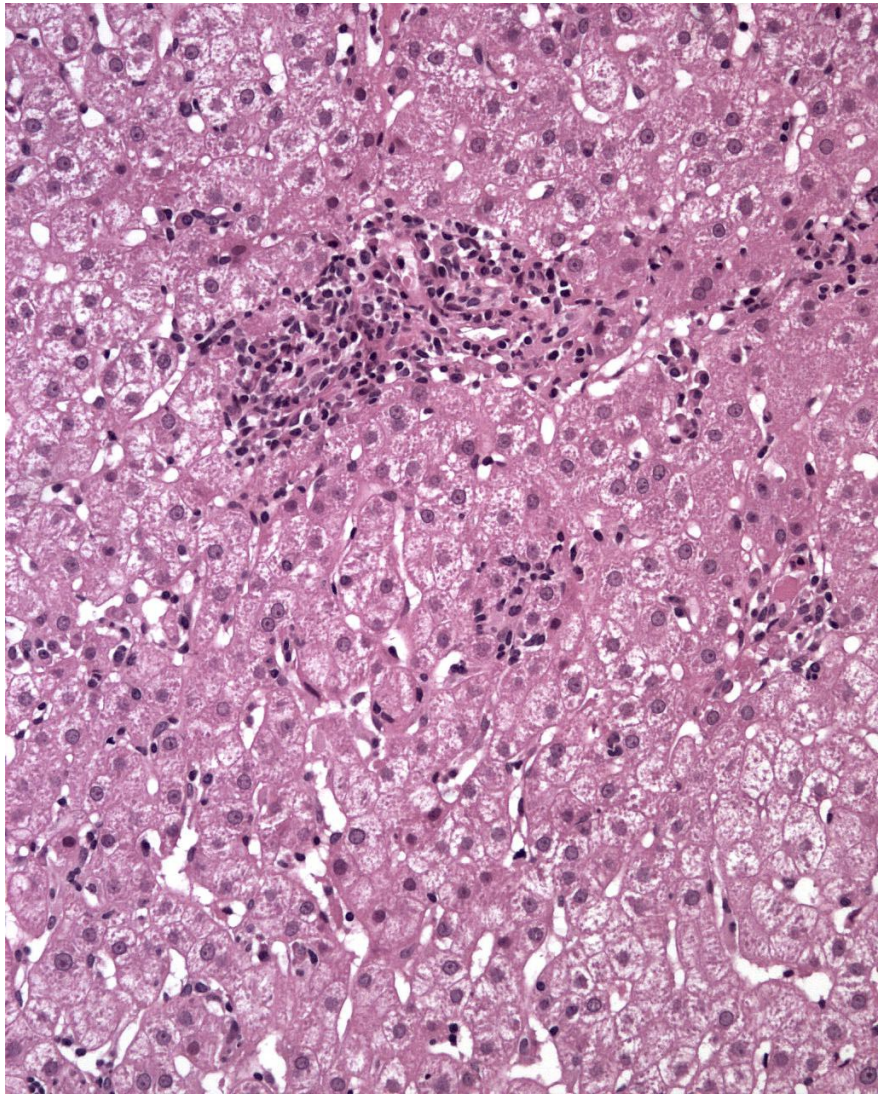

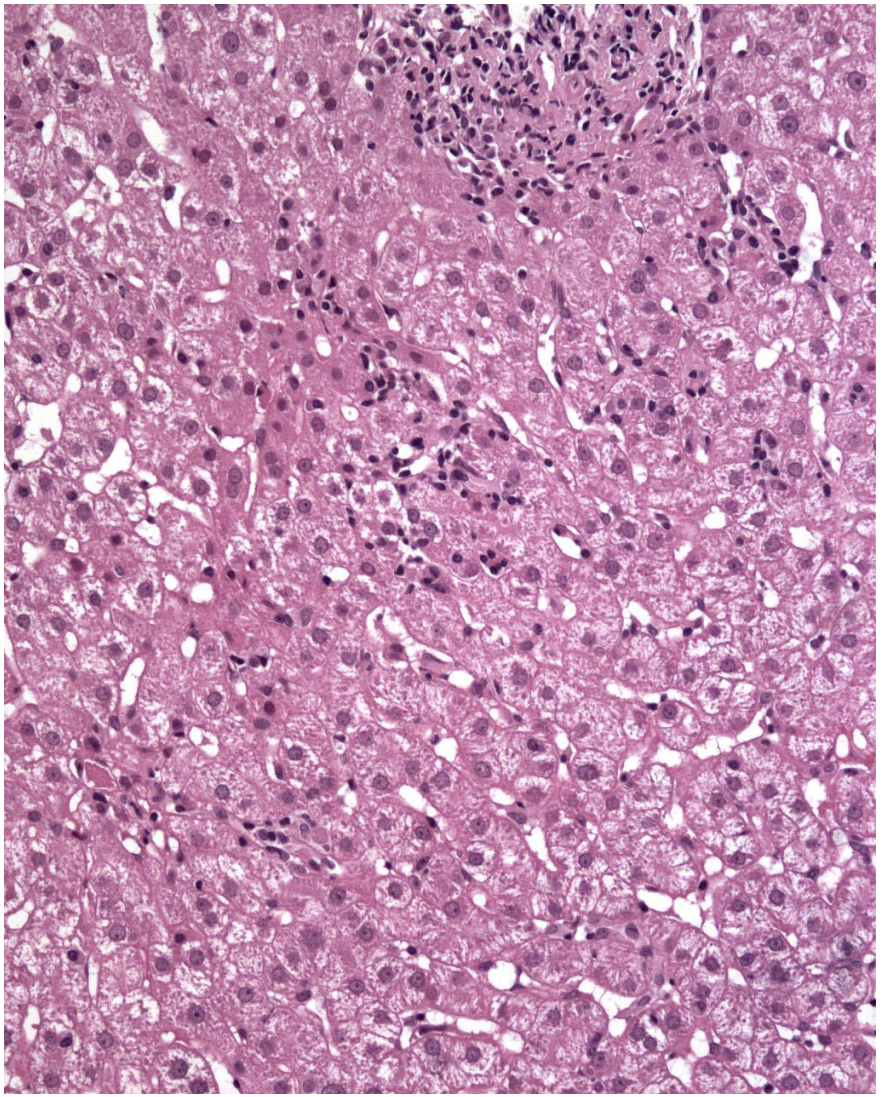

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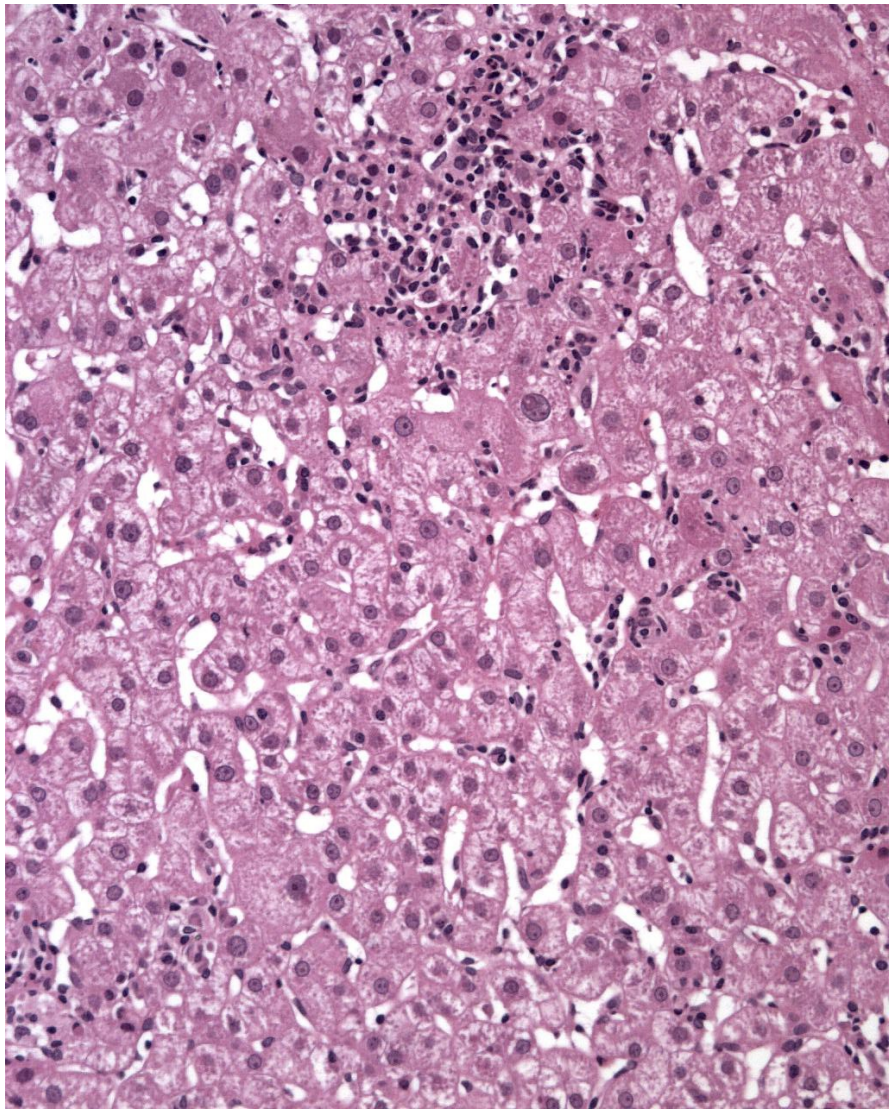

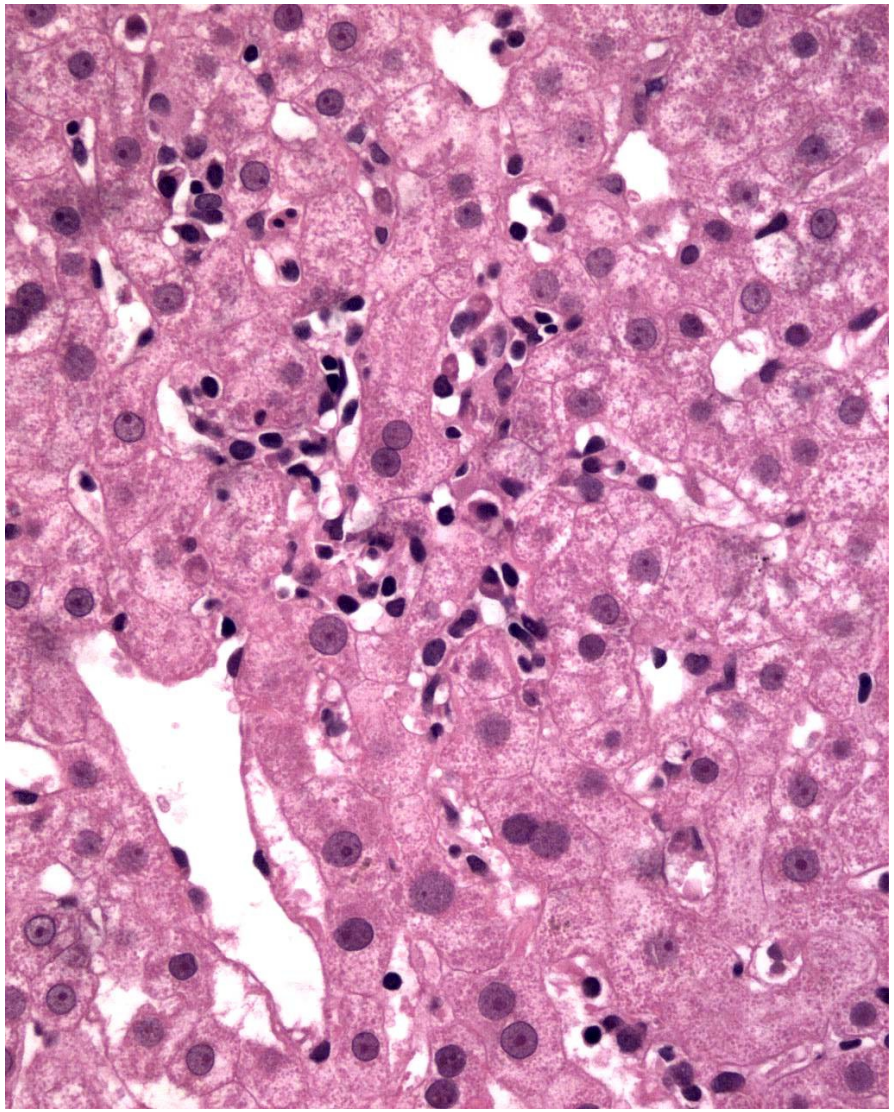

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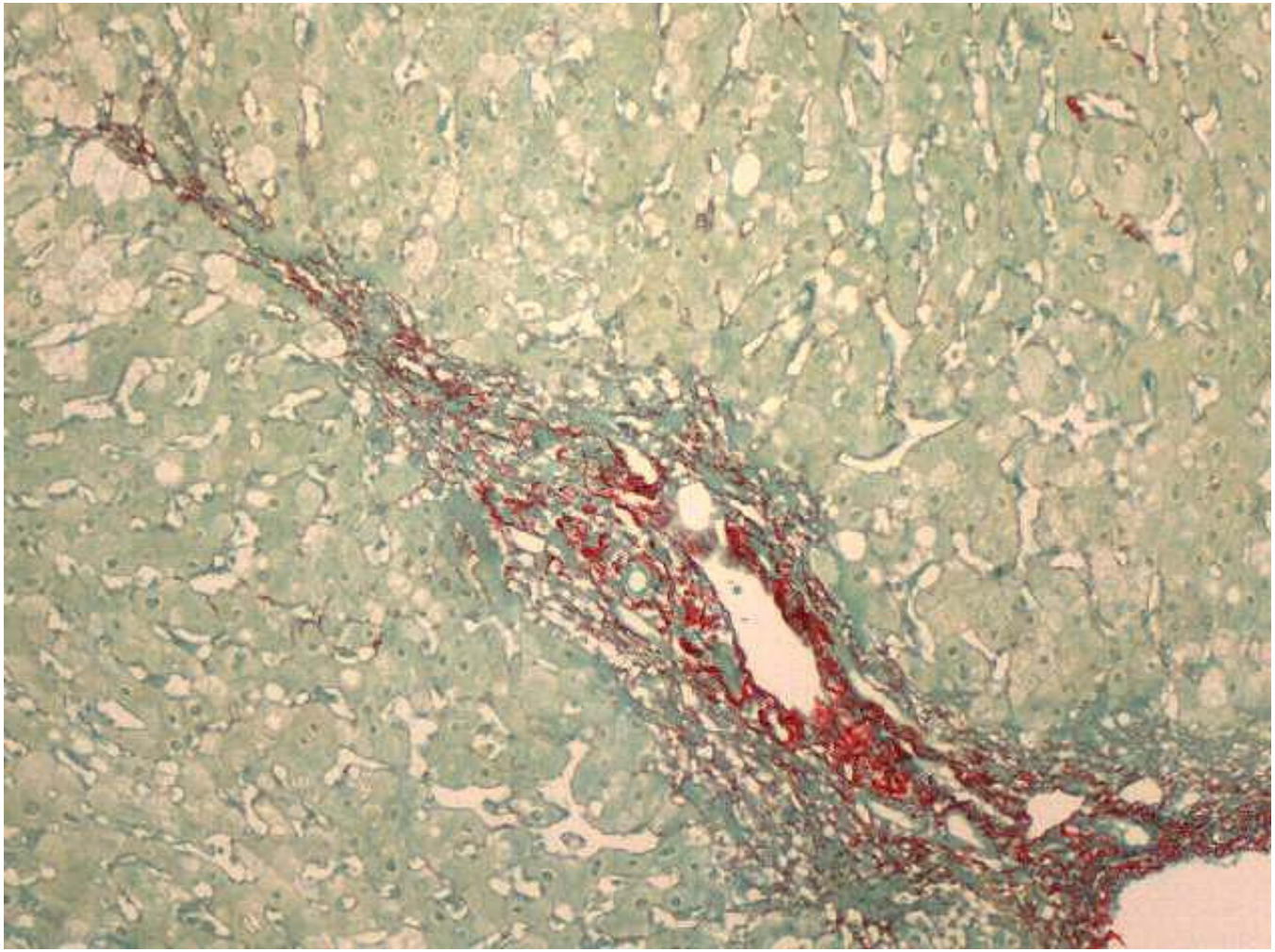
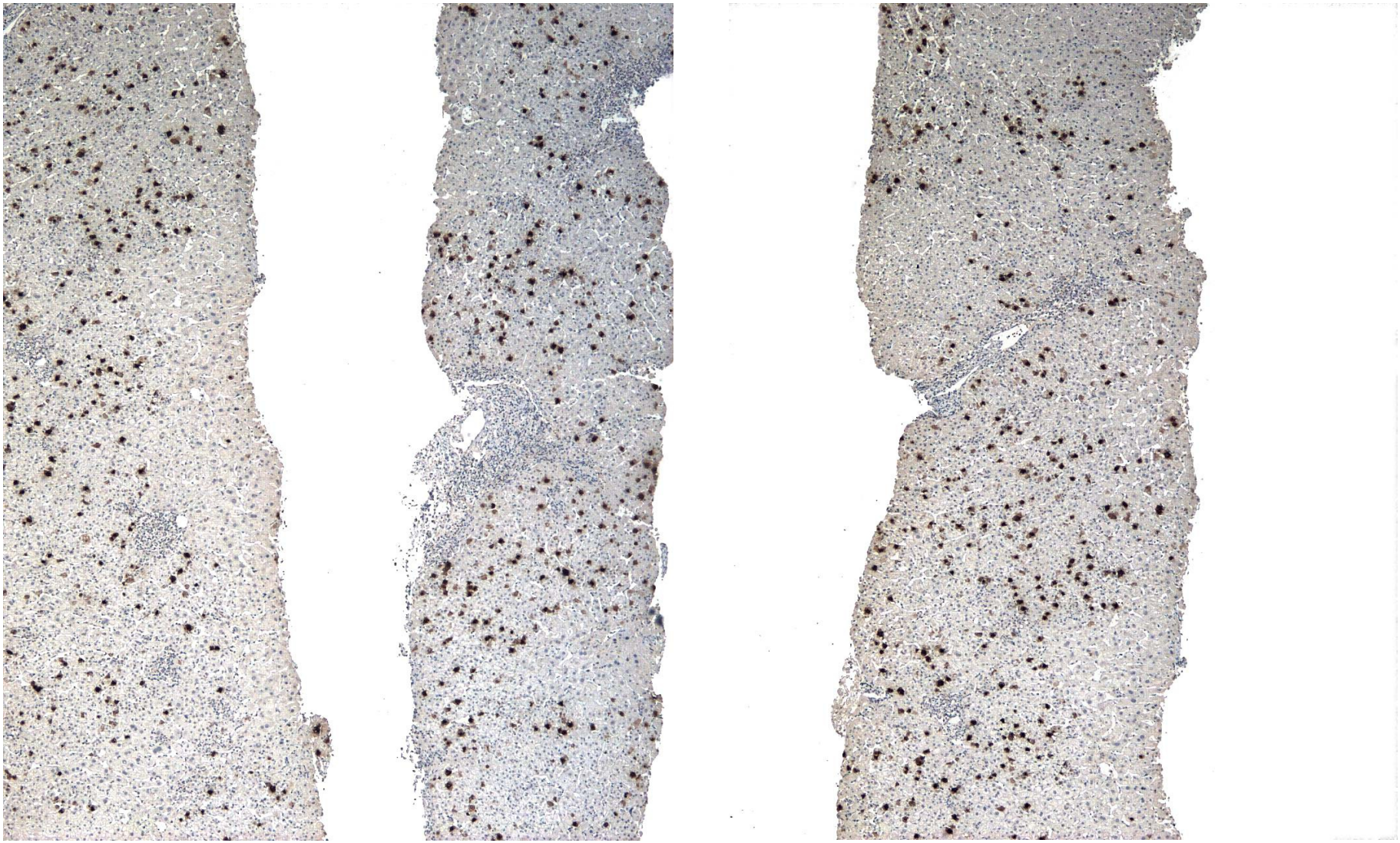


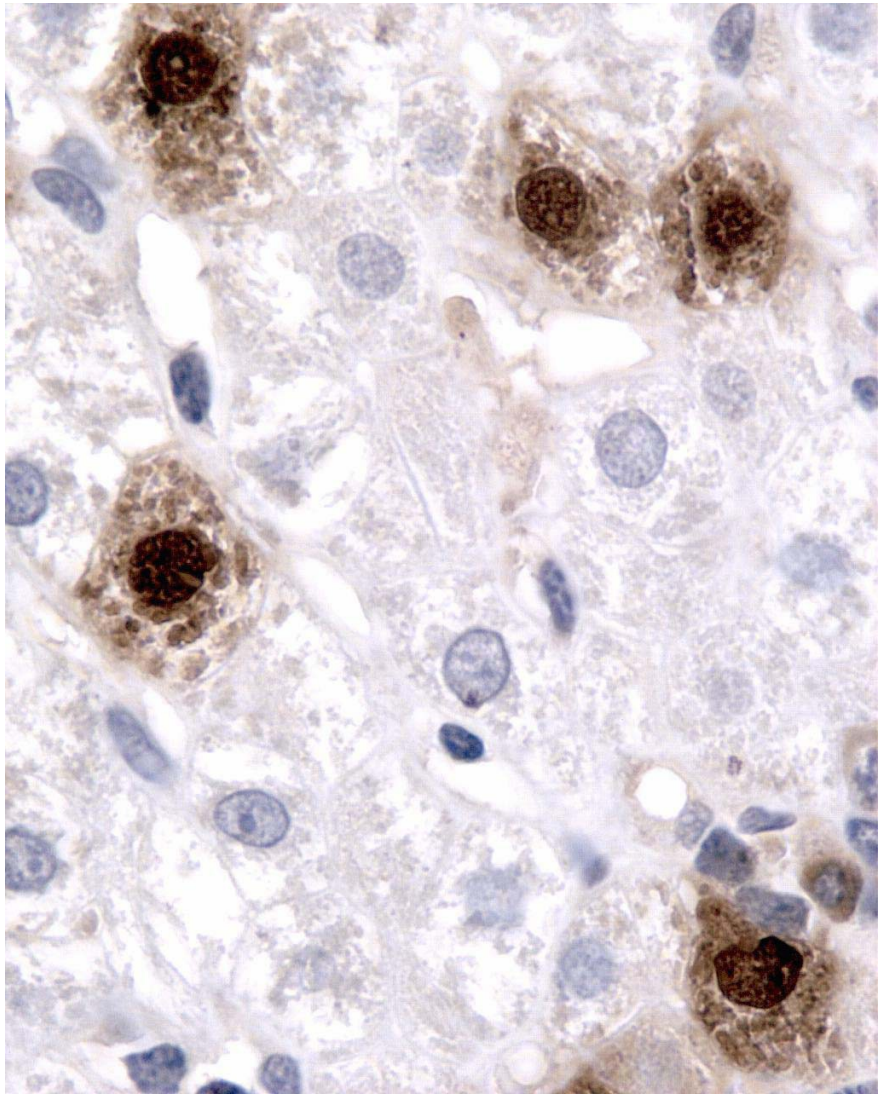
Chronic Hepatitis A2F2

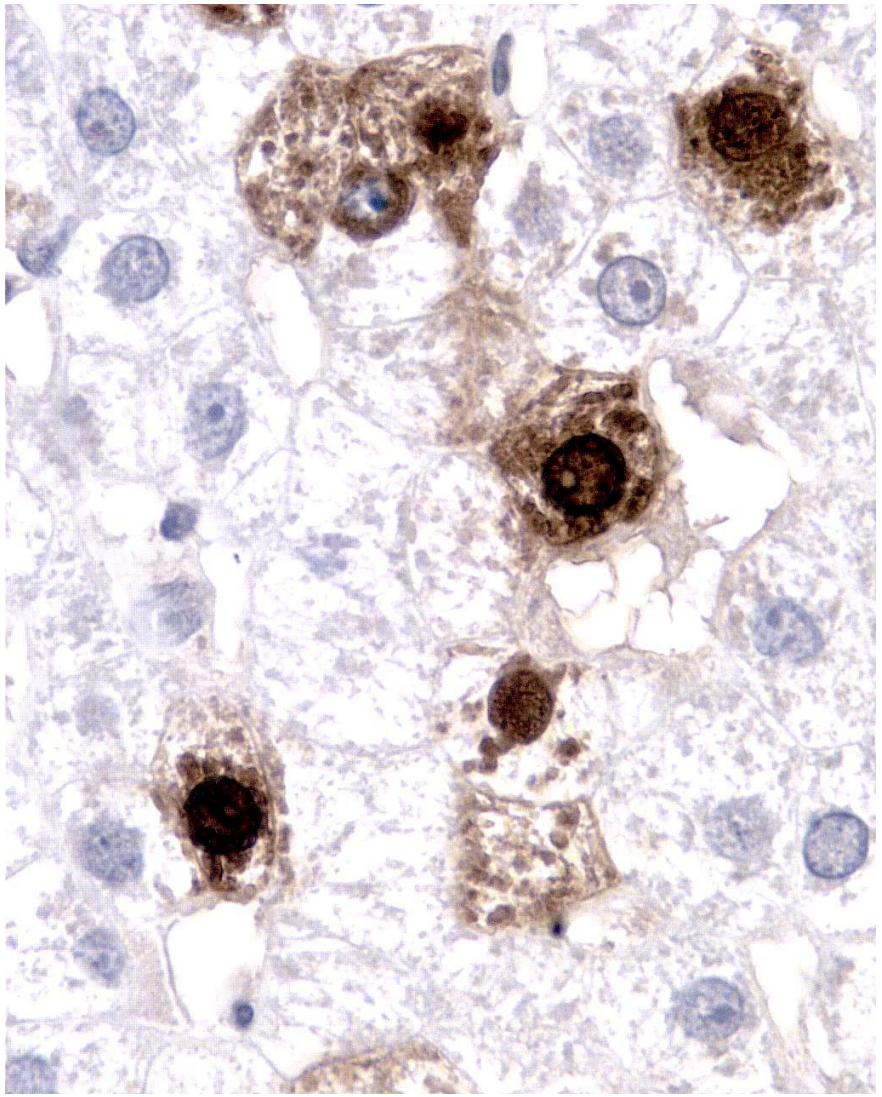
HBcAg



PC 08 15 Anti-HDV

HDV Ag





PC 08 15 Anti-HDV

1. Which virus predominate ?
2. Could we use non invasive fibrose stage in this case ?
3. Is there any role of Immunohistochemestry for HDV/HBV infection ?

What would be your conduct

1. Inf Conventional monohterapy (Long Duration) ?
2. Inf Convencional + NA ?
3. Interferon – Peg monotherapy ?
4. Interferon – Peg + NA ?
5. Only NUCs
6. No treatment at all

Which would be your aims

1. Normalize ALT and AST ?
2. HBV-DNA Negativation ?
3. HDV-RNA (negativation) ?
4. HBsAg loss?
5. Others

Possible scenarios among many others

1.ALT/AST Normalized, but HBV-DNA and HDV-DNA remained positive < 2000ui.
Would you stop INF or Keep INF for long duration treatment
In this case replace Peg-INF for Conventional INF?

2. AST/ALT Normalized, HDV-RNA detectable and HBV-DNA > 2000ui, No HBeAg seroconversion,
Keep INF? How long?
Add NUCs or keep on NUCs?

3. AST/ALT remain elevated, But HBV-DNA is now < 2000 ui , AgHBe negative/ Anti HBe Positive and HDV-RNA Positive
Keep INF? How Long

4. AST/ALT 2x, HBV-DNA < 20.000ui HBeAg positive, HDV-RNA undetectable
No acess to qHBsAg
Keep INF?
Replace Peg-INF for NUCs

According to the Brazilian Guidelines for HBV/HDV treatment, if HBV-DNA > 2000ui at baseline
Peg Inf + NUCs

Events during treatment

At 12 weeks ALT Normalized
At 24 weeks HBV-DNA Undetectable and seroconversion HBeAg/Anti Hbe
At week 48 HBV-DNA untedectable and HDV-RNA undetectable

Stop treatment ?
Keep on NuCs?
Keep on Peg-INF?
Keep on NuCs and Peg-INF?

According to the Brazilian Guidelines

Treatment was stopped and the patient were Monitored

Spenomegaly persisted but less pronounced .

At week 108 of Follow up

HBsAg clearance

Hepatotropic Viruses in the Brazilian Amazon: A Health Threat

Raymundo Paraná[1], Ludmila Vitvitski[2] and Joao Eduardo Pereira[3]
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Viral Hepatitis B, C and D are a serious public health problem in Brazil and other South American countries, mainly in the Amazonian region. Despite the paucity of clinical and epidemiological studies, a high prevalence of Hepatitis viruses has often been described in this area. Genotype F of Hepatitis B and Genotype III of Hepatitis D have been found to be quite prevalent in this area and preliminary studies have implicated both genotypes in carcinogenesis and peculiar pathogenic liver mechanisms. Initial epidemiological studies have further demonstrated a high prevalence of Hepatitis C in the western Brazilian Amazon. The geographic, cultural, ethnic and environmental aspects of this region may favor hepatotropic virus dissemination, as well as rendering difficult the implementation of governmental programs in the treatment of patients and prevention of disease dissemination.

Hepatitis D virus infection in the Western Brazilian Amazon - far from a vanishing disease

Wornei Silva Miranda Braga[1],[2], Márcia da Costa Castilho[1],[2], Fabiane Giovanella Borges[1], Jorge Roberto Di Tommaso Leão[2], Ana Cristina de Souza Martinho[1], Ivo Seixas Rodrigues[1], Eliete Pereira de Azevedo[1], Gildo Maia de Barros Júnior[1] and Raymundo Paraná[3]

Am. J. Trop. Med. Hyg., 75(3), 2006, pp. 475–479

HDV GENOTYPES IN THE WESTERN BRAZILIAN AMAZON REGION: A PRELIMINARY REPORT

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

Lourdes Maria Pinheiro Borzacov [a], Larissa Deadame de Figueiredo Nicolete [a], Luan Felipo Botelho Souza, Alcione Oliveira dos Santos, Deusilene Souza Vieira, Juan Miguel Villalobos Salcedo *

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SUMMARY

Objectives: Hepatitis delta virus (HDV) is recognized as the most pathogenic and infectious among the hepatotropic viruses. Studies on the treatment of HDV have predominantly included European patients and carriers of genotype 1 (HDV-1) in their clinical protocols. For the Amazon region, data show that infected individuals have mainly Native American ancestry and that >90% of HDV carriers have the genotype 3 (HDV-3). Thus combined therapy clinical protocols do not adequately address the treatment of these patients.

Methods: A prospective, non-randomized study was conducted in which 22 patients received 180 μg of pegylated interferon alpha 2a (PEG-IFN) plus entecavir at a dose of 0.5 mg for 48 weeks, with a subsequent 24-week follow-up. Throughout treatment, the patients were monitored for biochemical responses and the kinetics of hepatitis B virus (HBV) and HDV viral loads.

Results: Of the 22 patients treated, 15 presented normal alanine aminotransferase values at the end of treatment ($p = 0.002$). At week 24 of treatment, 86.4% of the patients did not present detectable HDV-RNA; at week 48, the rate of negative patients increased to >95% and remained the same after 6 months. With regard to HBV, only two patients (9%) still presented detectable HBV genetic material at the end of treatment, suggesting the effectiveness of combined therapy in combating the two viruses.

Conclusions: These findings support the use of this effective therapeutic protocol for HDV-3 in patients of non-European ethnicity and suggest a possible 'easy to treat' variant when compared to HDV-1.

What hapenned with this real patient?

AgHBs Neg

HBV-DNA undetectable

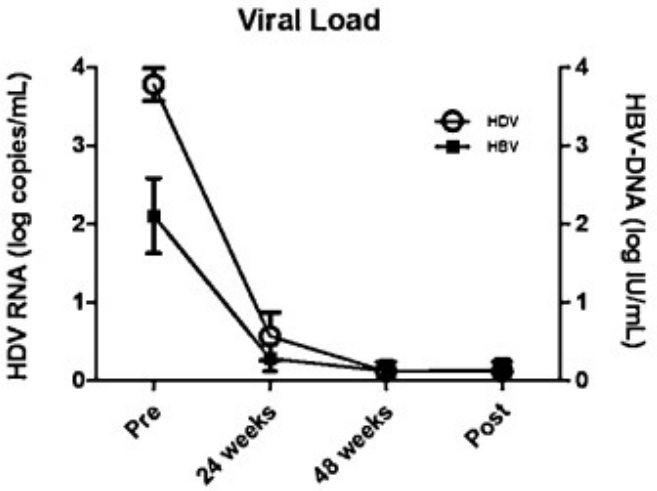
HDV-RNA undetectable

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

6 Ptes became HBsAg Neg

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

Salvador, Bahia

Amazonia

OBRIGADO
THANK YOU
MERCI