Delta Hepatitis in South America:
Old disease with new paradigms

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School of Medicine
University Hospital – Gastro-Hepatology unit
Disclosure

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

Firstly described by Rizzetto et al, 1977

- > 15 million carriers worldwide
- 5% of the HBsAg carriers worldwide
- Neglected disease in many countries
  - HDV depends on the surface antigen of HBV (HBsAg) for transmission
  - Controlled in Western Europe / North America, but spreading in other countries
### Acute HDV Infection: co-infection x superinfection and the risk of chronicity

<table>
<thead>
<tr>
<th></th>
<th>CO-INFECTION</th>
<th>SUPERINFECTION</th>
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<tbody>
<tr>
<td>HBV infection</td>
<td>acute</td>
<td>chronic</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>1-2 %</td>
<td>1-5 %</td>
</tr>
<tr>
<td>Chronicity rate</td>
<td>2-7 %</td>
<td>70-90 %</td>
</tr>
</tbody>
</table>
HDV – Global distribution (CDC)
15 000 000 people infected in all continents

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

All HBV genotypes can support HDV

However, in many countries HDV infections are probably under-diagnosed unless a severe outbreak occurs
Hepatitis D: markers of disease progression

Clinical outcomes

Biochemistry
- LFT

Sorologic
- Anti HDV IgM

Histologic
- Liver Biopsy
- HDV Ag Immunostaining

Virologic
- HDV-RNA /HBV
- Quantitative
- Genotype/Subtype of HBV/HDV

Host
- Ethnicity
- Age
Evolution of Hepatitis D Compared to Hepatitis B and C
# HDV Gen-3 HISTOLOGY AND PARAMETERS OF DISEASE STAGE

## METAVIR

<table>
<thead>
<tr>
<th>FIBROSIS</th>
<th>N (%)</th>
<th>TOTAL</th>
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<tbody>
<tr>
<td>F0</td>
<td>5 (4.6)</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>27 (24.7)</td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td>28 (25.7)</td>
<td></td>
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<tr>
<td>F3</td>
<td>25 (23.0)</td>
<td></td>
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<tr>
<td>F4</td>
<td>24 (22.0)</td>
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</table>

<table>
<thead>
<tr>
<th>NECRO-INFLAMMATION</th>
<th>GRADE</th>
<th>N (%)</th>
<th>TOTAL</th>
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<tbody>
<tr>
<td></td>
<td>A0</td>
<td>9 (8.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A1</td>
<td>30 (27.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>31 (28.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A3</td>
<td>39 (35.8)</td>
<td></td>
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</tbody>
</table>

*Braga et al, 2014*
Advanced fibrosis and associated variables of the 64 patients with chronic HDV/HBV coinfection included in the study (multiple logistic regression)

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

* 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
Hep D is a spectral disease with many variables that are postulated to influence on the Natural History.
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
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 disease has been described in central Africa (Lesborde et al, 1990 and Andrade et al, 1992)

Similar disease reproduced 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
Emerging HDV Epidemiology

Gen VIII

- African descendants
- Isolated communities
- Run Way Slave Communities

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

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

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

Global epidemiology of HDV infection according to viral genotype. HDV genotype 1 is the most frequent genotype and is distributed throughout the world, especially in Europe, the Middle East, North America and North Africa. By contrast, HDV genotype 2 is observed in the Far East, and HDV genotype 3 is seen exclusively in the northern part of South America. Abbreviation: HDV, hepatitis D virus.
Phylogeny of HBV/HDV genotypes/subtypes

Su et al, gastroenterol 2006

Amazon Basin

HBV –C > HBV-A

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

Genotype III (3) is the most divergent


Su et al, gastroenterol 2006
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].
### Patient age, duration of clinical evolution and survival post transplantation in patients with cirrhosis HBV and Delta in Brazilian Amazonia

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Std. Deviation</th>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>31</td>
<td>27.06</td>
<td>3</td>
<td>49</td>
<td>12.641</td>
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<tr>
<td>Age in cirrhosis</td>
<td>30</td>
<td>31.43</td>
<td>4</td>
<td>58</td>
<td>13.733</td>
</tr>
<tr>
<td>Age in transplantation</td>
<td>31</td>
<td>34.74</td>
<td>7</td>
<td>59</td>
<td>13.130</td>
</tr>
<tr>
<td>Interval between the diagnosis of hepatites and cirrhosis in months</td>
<td>30</td>
<td>44.30</td>
<td>0</td>
<td>242</td>
<td>62.685</td>
</tr>
<tr>
<td>Survival post transplantation in months</td>
<td>31</td>
<td>50.71</td>
<td>1</td>
<td>171</td>
<td>47.361</td>
</tr>
<tr>
<td>Interval between the transplantation and loss of AgHBs in months</td>
<td>23</td>
<td>34.65</td>
<td>0</td>
<td>128</td>
<td>31.793</td>
</tr>
</tbody>
</table>

3. Death, 9, 17 and 26 months post transplantation: insufficiency hepática, septicemia, CHC recurrence, respectively.
Chronic HDV infection frequently suppresses HBV Replication (Wu JC, J Virol. 1991)

Status of HBV infection

<2.000UI/mL

IFN-PEG → 48 w

In Brazil

40%

>2.000UI/mL

IFN-PEG + NUCs → 48 w

60%

25% HBeAg+

Berzacov et al, in abstract
Typical case of chronic HDV infection in Amazonia: Delta Ag over-expression
Similar disease reproduced in the Woodchuck model inoculated with sera from Africans and Brazilian patients. HDVAg Display and histological characteristics were different in woodchucks infected with different inocula (FH from Lyon and FH from CAR).

Paraná et al, J Hepatol 1995
Novel HDV mutation described in HBV/HDV co-infected patients in western Brazilian Amazonia

Alan Kay¹, Edinete Melo da Silva¹, Hermes Pedreira², Suiane Negreiros³, Cirley Lobato³, Wornei Braga⁴, Richard Muwonge⁶, Paul Dény¹, Mitermayer Reis², Fabien Zoulim¹,⁵, Christian Trepo¹,⁵, Argemiro d’Oliveira Jr⁷, Juan Miguel Salcedo⁷, Maria Isabel Schinoni⁷ and Raymundo Parana²,⁷

<table>
<thead>
<tr>
<th>HBV Genotype</th>
<th>WT HDV</th>
<th>Mutant HDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>F</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>D</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not known</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Changes the 2nd from last aa of sΔAg from F (Phe) to Y (Tyr)
Hep D is a spectral disease with many variables that are postulated to influence on the Natural History. Host genetic background could interfere in the natural history chronic HDV infection?
Delta Project in Brazilian Amazonia: Amerindians from different ethnicities
Heterogeneity of HDV Distribution in Highly Endemic Regions

Is there a genetic susceptibility to HDV infection?

Rizzetto and Alavian 2013

Braga et al, 2014
Diversity of clinical presentation and virological characteristics of hepatitis delta in different regions world-wide: results of the Hepatitis Delta International network

ILC2017-RS-3818

Viral hepatitis: Hepatitis B and D - Clinical (therapy, new compounds, resistance)

Diversity of clinical presentation and virological characteristics of hepatitis delta indifferent regions world-wide: results of the Hepatitis Delta International network

Anika Wranke* 1, Svenja Hardtke1, 2, Lourdes M. Pinheiro Borzacov3, Raimundo Parana4, Cirley Lobato5, Saeed Hamid6, Emanoil Ceausu7, George N. Dalekos8, Mario Rizzetto9, Adela Turcanu10, Grazia Niro11, Tonya Hayden12, Minaam Abbas 13, Patrick Ingiliz14, Maria Buti15, Peter Ferenci16, Thomas Vanwolleghem17, Adriana Motoc7, Zaigham Abbas18, Cihan Yurdaydin19, Michael P. Manns1, 2, Heiner Wedemeyer1, 2 and Beatriz C. Serrano, Michael Wöbse, Benjamin Heidrich, Marion Muche, Nikolaos K. Gatselis, Kalliopi Zachou, Antonina Smedile, Robert Gish, Dana Obretin, Rafael Stern, Erwin Ho, Peter Michelsen, Obretin Dana, Valentina, Farheen Lubna, Rosanna Fontana

1Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, 2German Centre for Infection Research (DZIF), HepNet Study-House, Hannover, Germany, 3Research Center for Tropical Medicine of Rondônia, CEPEM/SESAU and Federal University of Rondônia, Rondônia, 4Hepatology Center of the University Hospital Professor Edgar Santos, Federal University of Bahia, Bahia, 5Hospital das Clínicas do Acre, Rio Branco, Brazil, 6Department of Hepatogastroenterology, Aga Khan University, Karachi, Pakistan, 7Infectious Diseases, Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania, 8Department of Medicine and Research Laboratory of Internal Medicine, Medical School, University of Thessaly, Larissa, Greece, 9Department of Internal Medicine - Gastroenterology, University of Turino, Turin, Italy, 10State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Moldova, Republic of, 11Divisione di Gastroenterologia, Ospedale Generale Regionale "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy, 12Centers for Disease Control and Prevention/Div of viral hepatitis, Atlanta, United States, 13School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom, 14Center for Infectiology Berlin (CIB), Berlin, 15Liver Unit, Valle d’Hebron (Ciberehd) University Hospital, Barcelona, Germany, 16Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria, 17Department of Gastroenterology and Hepatology, Antwerp University Hospital, Edegem, Belgium, 18Ziauddin University Hospital Karachi, Karachi, Pakistan, 19Medical Faculty, Ankara University, Ankara, Turkey

Corresponding author’s email: wranke.anika@mh-hannover.de

Background and Aims: Chronic delta hepatitis represents a major global health burden...
For where your treasure is, there also will your heart.
Tratamientos Futuros de VHB/HDV

AGENTES DIRIGIDOS AL HUÉSPED

ANTIVIRALES DE ACCIÓN DIRECTA

AGENTES INMUNOMODULADORES
<table>
<thead>
<tr>
<th></th>
<th>Study Title</th>
<th>Description</th>
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<tbody>
<tr>
<td>LBO-004</td>
<td>Safety, pharmacokinetics and antiviral activity of novel capsid assembly modulator JNJ-56136379 (JNJ-6379) in treatment-naive chronic hepatitis B patients without cirrhosis</td>
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<tr>
<td>PS-026</td>
<td>Novel and potent HBV capsid modulator reduces HBeAg and cccDNA in core site directed T109I mutant in HepNTCP cells</td>
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<tr>
<td>LBO-003</td>
<td>RO7049389, a core protein allostERIC modulator, demonstrates robust anti-HBV activity in chronic hepatitis B patients and is safe and well tolerated</td>
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<tr>
<td>PS-028</td>
<td>Combination treatment of a TLR7 agonist RO7020531 and a capsid assembly modulator RO7049389 achieved sustainable viral load suppression and HBsAg loss in an AAV-HBV mouse model</td>
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<td>PS-160</td>
<td>Effects of SB9200 (inarigivir) therapy on immune responses in patients with chronic hepatitis B</td>
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<tr>
<td>GS-005</td>
<td>Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with tenofovir in patients with chronic HBV/HDV coinfection</td>
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<tr>
<td>PS-025</td>
<td>Combinatorial RNAi/vaccination therapy for chronic hepatitis B achieves long-term functional cure in preclinical mouse model</td>
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<tr>
<td>PS-029</td>
<td>Durable inhibition of hepatitis B virus replication and antigenemia using subcutaneously administered siRNA agent AB-729 in preclinical models</td>
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<td>PS-030</td>
<td>Development of subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection</td>
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<tr>
<td>PS-032</td>
<td>Discovery of a novel core inhibitor EP-027367 with potent antiviral activity both in vitro and in a humanized mouse model</td>
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<tr>
<td>PS-027</td>
<td>Preclinical antiviral drug combination studies utilizing novel orally bioavailable investigational agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, a HBV RNA destabilizer</td>
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<td>PS-031</td>
<td>T cells grafted with HBV-specific T-cell receptors of high functional avidity achieve functional cure of HBV infection in humanized mice</td>
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</table>
Novas opções terapêuticas para HDV

Novel treatment options for HDV infection

<table>
<thead>
<tr>
<th>Novel antiviral strategies against HDV in clinical development</th>
<th>Target</th>
<th>Drug</th>
<th>Structure/function</th>
<th>Clinical Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry inhibitors</strong></td>
<td>• Sodium taurocholate co-transporting polypeptide (NTCP)</td>
<td>Myrcludex B</td>
<td>• Myristoylated lipopeptide obtaining 47 amino acids of the pre S1 domain of L-HBsAg</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Prenylation inhibitors</strong></td>
<td>• Farnesyl or geranylgeranyl prenyl lipids</td>
<td>Lonafamib</td>
<td>• Inhibitor of an essential step in viral propagation and assembly</td>
<td>Phase II</td>
</tr>
<tr>
<td><strong>Nucleic acid polymers</strong></td>
<td>• Amphiphatic alpha-helices in class I surface glycoproteins</td>
<td>REP 2139-Ca</td>
<td>• Blocks release of HBsAg particles: entry and post-entry antiviral activity</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Wranke & Wedemeyer, Current Opinion Virology 2016

- Buchmann et al., Thu-158: kinase inhibitors with activity against HDV
- Donkers et al., SAT-174: NTCP inhibitors (e.g. rosiglitazone)
- Bazinet et al., REP-2139 long-term follow-up; LBP-507
Lonafarnib for HDV infection

EASL-ILC 2017:
Wedemeyer et al., PS-039: -7 Lonafarnib dose escalation, treatment 24 weeks Yurdaydin et al., GS-008: -7 Lonafarnib dose finding, 12-24 weeks
Koh et al., LPB-519: -7 Lonafarnib once daily dosing, 24 weeks Yurdaydin et al., THU-161: -7 post-treatment HDV RNA clearance

- Antiviral efficacy confirmed for up to 24 weeks
- GI side effects are dose-limiting
- Off-treatment viral control is possible in some patients (can be associated with hepatitis flares)
- Longer therapies/combination therapies may be needed
Novas opções terapêuticas para HDV

Estudo fase II, lonafarnib (LNF), que inibe HDV ao inibir prénylação,

Diferentes esquemas: LNF dose de 25 ou 50 mg, VO e 2 x/dia, booster de ritonavir (RTV), Com ou sem Peg-IFNα semanal. Duração de 24 ou 48 semanas.
Idade média dos pts 50 anos, 44 % homens e 44 % já tratados com IFN.
36% dos pacientes tratados com LNF/RTV tiveram replicação < 3 log copie/mL (qPCR maison), contra 80 % dos pts que receberam só Peg-IFN, na RFT.
Poucos Pts com carga viral indetectável ao final do tratamento, 1 /21 no grupo LNF/RTV e 5 / 14 no grupo com IFN.

5/34 Eas graves e 30/34 EAs leve a moderado pp na esfera GI
Amazonean Delta Hepatitis Project

- Referral centers: RIO BRANCO/CRUZEIRO DO SUL/PORTO VELHO/MANAUS
- Satellites centers: SENA MADUREIRA-AC/COARI-AM/TABATINGA-AM
- Amazonean Annual Viral Hepatitis Meeting

Jiminawá Tribe
Purus River-ACRE state

Manaus – Amazonas state