Non-cirrhotic portal hypertension in HIV+ patients

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Liver disease burden in HIV

- Chronic hepatitis B and C
- Metabolic syndrome – NASH
- Drug-related hepatotoxicity
- Alcohol abuse
Clinical case

- Male, 56 years-old, MSM, Caucasian, business man
- HIV diagnosis in 1998. CD4: 133. HIV-RNA: 76,000
- ARV therapy since then, with good response.
- Mild liver enzyme elevations for the last couple of years. Exclusion of HBsAg, HCV-RNA, BMI>25 Kg/m², drugs other than ARVs, etc.
- Alcohol intake: “social”
- US: heterogeneous hepatic parenchyma & splenomegaly.
- FibroScan: F0F1 or F2 intermittently.

Unexplained liver disease in HIV - Exclusion

- HBV, HCV, HEV - overt or occult
- Alcohol abuse
- Insulin resistance, dislipidemias, NASH
- Hepatotoxic drugs
- Autoimmune hepatitis
- Metabolic diseases: hemochromatosis, Wilson
- Alfa1 antitripsin syndrome
- Inherited pro-coagulation disorders: protein S deficiency, etc
Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis.
Lack of hepatitis E virus infection in HIV patients with advanced immunodeficiency or idiopathic liver enzyme elevations

A. Madejón,1,2 E. Vispo,1 M. Bottecchia,1,2 M. Sánchez-Carrillo,1,2 J. García-Samaniego2 and V. Soriano1

1Department of Infectious Diseases; and 2Department of Hepatology, Hospital Carlos III and CIBERehd, Madrid, Spain

Journal of Viral Hepatitis, 2009

SUMMARY. Hepatitis E virus (HEV) is an enterically transmissible RNA agent that causes self-limited acute hepatitis. Recent reports have highlighted that organ-transplant recipients may develop chronic hepatitis E and progress to cirrhosis. Similar cases could occur in HIV patients. We have investigated 50 HIV-infected individuals with CD4 counts <200 cells/mm³ and 43 with cryptogenic hepatitis. None of them showed HEV viremia. Thus, HEV infection does not seem to be prevalent in the HIV population and accordingly universal HEV vaccination is not warranted in these patients.
Severe Liver Disease Associated With Prolonged Exposure to Antiretroviral Drugs

Ivana Maida, MD,*‡ Marina Núñez, MD, PhD,* Maria Jose Rios, MD,§ Luz Martín-Carbonero, MD, PhD,* Giovanni Sotgiu, MD,‡ Carlos Toro, MD, PhD,* Pablo Rivas, MD,* Pablo Barreiro, MD, PhD,* Maria Stella Mura, MD, PhD,‡ Sergio Babudieri, MD,‡ Javier Garcia-Samaniego, MD, PhD,† Juan González-Lahoz, MD, PhD,* and Vincent Soriano, MD, PhD*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Gender</th>
<th>Risk Group</th>
<th>Date of HIV Diagnosis</th>
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*didanosine
Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients

Vincent Malleta,b,e,*, Pierre Blanchardb,* , Virginie Verkarrea,c, Anaïs Vallet-Picharda,b,e, Hélène Fontaineb,e, Caroline Lascoux-Combed and Stanislas Pola,b,e


<table>
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<td>II</td>
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<tr>
<td>Ascites</td>
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<td>US: collateral venous derivation</td>
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<td>Total bilirubin (µmol/l)</td>
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<td>9</td>
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<td>Albumin (g/l)</td>
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<td>149</td>
<td>133</td>
<td>141</td>
<td>71</td>
<td>115</td>
<td>114</td>
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</table>
NCPH in the Swiss cohort

• 15 patients with NCPH, with proven esophageal varices and lack of cirrhosis on liver biopsy.

• Case-control study using 75 matched control patients.

• Risk factors: older age (OR 2.9), MSM (OR 4.5), CD4 <200 (OR 34.3), diabetes (8.8), ddI (OR 3.4). Only ddI exposure remained as independent risk factor in the multivariate analysis.

• 4 deaths (27%) due to bleeding or liver failure during a median follow-up of 12 years.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Histology</th>
<th>Etiology</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
</table>

* Laboratory (pancytopenia), clinical (GI bleeding) or endoscopic (esophageal varices)
Noncirrhotic portal hypertension in HIV-infected patients: unique clinical and pathological findings

Eugenia Vispo\textsuperscript{a}, Alberto Moreno\textsuperscript{b}, Ivana Maida\textsuperscript{a,c}, Pablo Barreiro\textsuperscript{a}, Adrián Cuevas\textsuperscript{b}, Sonia Albertos\textsuperscript{d} and Vincent Soriano\textsuperscript{a}

AIDS 2010, 24:1171–1176
Liver parenchyma

- Central vein
- Sinusoid
- Hepatic artery
- Portal vein
- Biliary vessel
- Disse's space
- Kupffer cells
- Liver cells

Portal tract
Normal portal tract (Masson)

Vispo et al. AIDS 2010
Portal vein showing dense fibrous thickening of the wall, centered by central stenotic lumen (H&E)
Portal tract without portal vein (Masson)

>60% of portal tracts vanished in these patients!

Vispo et al. AIDS 2010
Portal tract depicting small thin walled vessels replacing portal vein (Masson)
# Upper Gastrointestinal Bleeding May Unmask Didanosine-Associated Portal Hepatopathy in HIV/HCV Co-infected Patients

Eugenia Vispo, Ivana Maida, Pablo Barreiro, Victoria Moreno, and Vincent Soriano

<table>
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<tr>
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<th>Case 1</th>
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<tr>
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</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>Caucasian</td>
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<tr>
<td>Risk group</td>
<td>IDU</td>
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<tr>
<td>HCV genotype</td>
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<tr>
<td>HCV-RNA, IU/mL</td>
<td>1,380,000</td>
<td>989,000</td>
<td>17,200,000</td>
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<tr>
<td>GGT, IU/mL</td>
<td>46</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>Ph Alk, IU/mL</td>
<td>242</td>
<td>183</td>
<td>202</td>
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<tr>
<td>Current antiretroviral therapy</td>
<td>Tenofovir+emtricitabine +fosamprenavir/ritonavir</td>
<td>Abacavir+lamivudine +atazanavir</td>
<td>Abacavir+lamivudine +atazanavir</td>
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<tr>
<td>Prior didanosine exposure (months)</td>
<td>64</td>
<td>30</td>
<td>44</td>
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<td>CD4 count, cells/μL</td>
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<td>168</td>
<td>324</td>
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<tr>
<td>CD4 count nadir, cells/μL</td>
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<td>250</td>
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<td>Plasma HIV-RNA, copies/mL</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
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<tr>
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<td>F2 (9)</td>
<td>F3 (11.5)</td>
<td>F4 (15)</td>
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<tr>
<td>Metabolic disorders</td>
<td>No</td>
<td>No</td>
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NCPH in HIV-neg patients

Conditions:
• Leukemia
• Inflammatory bowel disease

Drugs:
• Azathioprine
• 6’-thioguanine
• mercaptopurine

Tuyama et al. J Crohn Colitis 2013
Hypothesis
“Two-hit” model for unexplained non-cirrhotic portal hypertension in HIV+ patients

Some metabolites emerging during ddl metabolism might cause damage in the endothelium of portal vessels.
**Purine metabolism**

- **Ribose 5-phosphate**
  - **Inosine Triphosphatase**
  - **5'-nucleotidase**
  - **Inosine-TP** → **Inosine-DP**
  - **5'-Phosphoribosyl 1-pyrophosphate**

- **DNA, RNA**
  - **Inosine-DP** → **Inosine-TP**

- **ATP** → **DNA, RNA**
  - **Nucleoside Diphosphate Kinase**
  - **AMP** → **DNA, RNA**
  - **Adenylate Kinase**
  - **Adenylosuccinate Lyase**
  - **Adenylosuccinate Synthetase**
  - **A.Succinate**

- **Inosine-MP** → **XMP** → **GMP**
  - **Guanylate Kinase**
  - **GDP** → **DNA, RNA**
  - **Nucleoside Diphosphate Kinase**

- **ddA-TP** → **ddA-DP** → **ddA-MP** → **ddI-MP**
  - **Adenylate Kinase**
  - **Inosine Triphosphatase**
  - **5'-nucleotidase**

- **Adenosine**
  - **Inosine**
  - **5'-nucleotidase**
  - **Inosine-MP**
  - **ddI**

- **Hypoxanthine**
  - **Xanthine Oxidase**
  - **Xanthine**
  - **Xanthine Oxidase**
  - **Uric acid**

- **AMP, ADP, ATP**
  - **DNA, RNA**
  - **Nucleoside Diphosphate Kinase**

**Abbreviations:**
- MP: monophosphate
- DP: diphosphate
- TP: triphosphate
- XMP: xanthosine monophosphate
- GMP, GDP, GTP: guanosine mono-, di-, tri- phosphate.
- AMP, ADP, ATP: adenosine mono-, di-, tri- phosphate.
- ddI: didanosine
- ddA: dideoxiadenosine
A genetic predisposition for NCPH in HIV?

- **Purine nucleoside phosphorylase (PNP)**
  - Variants show increased myelosuppression with azathioprine (organ transplantation) or its metabolite 6-mercaptopurine (autoimmune diseases and ALL).
  - Reduced activity in 11% of the general population.

- **ITPA (inosine triphosphatase) deficiency**
  - Variants increase the toxicity of purine analogues, but protect against RBV-induced hemolytic anemia.
  - 20% of Caucasians harbor the polymorphic trait.

- **5'-nucleotidase cytosolic II (NT5C2)**
  - Catalyses the first reaction of ddI activation to ddI monophosphate.

- **Xantine oxidase (XO)**
  - Primarily located in the intestinal mucosa and the liver. It catalyzes the oxidation of hypoxanthine to uric acid.

Fellay et al. Nature 2010; 464: 405-8._
NEAT project
Genetic markers involved in NCPH in HIV patients

• Juergen Rockstroh. University of Bonn, Bonn, Germany
• Mark Nelson. Chelsea & Westminster Hospital, London, UK
• Vincent Soriano. Hospital Carlos III, Madrid, Spain

Genetic Determinants of Idiopathic Noncirrhotic Portal Hypertension in HIV-Infected Patients

Eugenia Vispo,1 Muge Cevik,2 Juergen K. Rockstroh,3 Pablo Barreiro,1 Mark Nelson,2 Andrew Scourfield,2 Christoph Boesecke,3 Jan-Christian Wasmuth,3 and Vincent Soriano1; for the European Network of Clinical Trials (NEAT)

Clinical Infectious Diseases 2013
Methodology

• Retrospective case-control study conducted on HIV individuals living in Europe.

• HIV patients with prior exposure to ddI were split out into two categories: cases and controls with a 1:4 assignment (50 : 200). Demographics, clinical & therapeutic information recorded on a single CRF.

• Tagging SNPs at the ITPA, NT5C2, PNP and XO genes, tested using iPLEX microarrays technology and TaqMan 5’ assays.
## Genomic study design

<table>
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<th>Controls</th>
<th>HapMap Europeans</th>
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<tr>
<td>PNP</td>
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<td>ITPA</td>
<td>4 SNPs</td>
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<td>NT5C2</td>
<td>8 SNPs</td>
<td></td>
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</tr>
<tr>
<td>XO</td>
<td>22 SNPs</td>
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</table>

+ Four SNPs were represented at different rates in NCPH cases with respect to controls.
+ Two were at the NT5C2 and two at the XO
Impact of SNPs at 4 genes on the risk of NCPH

NCPH

- rs11191561
  - CC: 53, 17%
  - CG/GG: 27, 48%
  - TT: 32, 9%
  - TC/CC: 48, 19%
  - p=0.007

- rs11598702
  - CC: 53, 17%
  - CG/GG: 27, 48%
  - TT: 32, 9%
  - TC/CC: 48, 19%
  - p=0.007

5-nucleotidase

- rs1429376
  - AA: 7, 71%
  - AC/CC: 73, 23%
  - p=0.015

- rs1594160
  - AA: 7, 71%
  - AC/CC: 73, 23%
  - p=0.015

Xantin-oxidase

Impact of SNPs at 4 genes on the risk of NCPH
Cumulative risk of NCPH in HIV patients with SNPs

SNPs at XO and NT5C2

- 0 SNPs: 7%
- 1 SNP: 26%
- 2 SNPs: 42%
- 3 SNPs: 50%
- 4 SNPs: 100%
Summary

• Unexplained NCPH in HIV+ patients is a rare (~0.5-1.0%) but potentially life-threatening condition.

• Prolonged ddI exposure plays a key role. Inflammatory and thrombotic processes hypothetically triggered by metabolites of this purine analogue within the hepatic microvasculature might result in obliterative portal vein phenomena. NCPH is a vascular disease.

• Unique histological lesions characterized by massive absence of portal veins along with focal fibrous obliteration of these vessels.

• The condition may appear in subjects with genetic predisposition (SNPs) involving key enzymes in the metabolic purine pathway.

• It should be suspected when clinical, laboratory, ultrasonography and/or endoscopic signs of severe portal hypertension appear in subjects with null/mild liver parenchymal damage.
NCPH in HIV - Suspicion

• Prolonged/fluctuating mild liver enzyme elevations
• Splenomegaly & hypersplenism in US*
• Absence of advanced liver fibrosis/cirrhosis in FS
• Preserved hepatic synthetic function tests

*Esophageal varices in the upper GI endoscopy
NCPH in HIV - Management

- ddI removal
- esophageal band ligation
- TIPS
- (anticoagulation)
- (liver transplantation)
Acknowledgments

Hospital Carlos III, Madrid, Spain
• Eugenia Vispo
• Pablo Barreiro
• Vincent Soriano
• (Pablo Lapunzina)

University of Bonn, Bonn, Germany
• Christoph Boesecke
• Jan-Christian Wasmuth
• Juergen Rockstroh

Chelsea & Westminster Hospital, London, UK
• Muge Cevik
• Andrew Scourfield
• Mark Nelson