Hepatitis E in HIV

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DISCLOSURES RELEVANT TO THIS PRESENTATION

• NONE

• Off label use of drugs will be discussed
Case Presentation

• A 54 yo man with chronic HBV/HIV has abrupt onset of peripheral edema and increasing abdominal girth. He has also developed scleral icterus
• HBV well controlled on efavirenz/lam/AZT
• Symptoms began a few weeks after staying with sister on farm in central Ohio.
• HBsAg +, HBV DNA neg, anti-core IgM neg, HCV Ab and PCR neg, anti-HAV IgG+
• Listed for OTLTx but rapidly decompensated and died
• HEV IgM+ reported one week later
OVERVIEW OF PRESENTATION

• VIROLOGY
• EPIDEMIOLOGY
• CLINICAL OUTCOMES OF INFECTION
• HEV IN CHRONIC LIVER DISEASE
• PREVALENCE & SIGNIFICANCE IN HIV
• CHRONICITY & PROGRESSIVE LIVER DISEASE
• TREATMENT OF CHRONIC HEV DISEASE
• DISEASE PREVENTION
VIROLOGY of HEPATITIS E

- Enterically transmitted zoonotic RNA virus in the genus Hepevirus
  - 7200 bases
  - 3 ORFs

- There are 4 genotypes capable of human infection and up to 7 or more total genotypes
Hepatitis E Genotypes

Debing Y et al. J. Hepatol. 2016, 65: 200-212
Geographic Distribution of Primary Human HEV Genotypes
Based on 148 bp of the ORF2 gene
EPIDEMIOLOGY

• OLD SCHOOL
  – Occurs Only in Resource Limited Areas with Poor Sanitation
  – Associated with Refugee Camps, Monsoon
  – High Mortality in Pregnant Women

• NEW SCHOOL
  – Found Worldwide
  – Genotype Important
  – Not Just An Acute Disease Process
  – Mortality in Pregnancy Varies by Region
Typical Clinical/Serological Course

- **IgG anti-HEV**
- **IgM anti-HEV**
- **Virus in stool**
- **Symptoms**
- **ALT**
- **Virus in sera**

Weeks after Exposure:
- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13

CDC
HEV in Immunosuppressed Host
CHRONIC Clinical/Serological Course

Symptoms

Virus in stool

ALT

IgG anti-HEV

IgM anti-HEV

Virus in sera

Weeks after Exposure

Titer

0 1 2 3 4 5 6 7 8 9 10 11 12 13
DIAGNOSTIC MODALITIES

SEROLOGIC

• No FDA Approved Test in US
• Unreliable diagnostic kits
• Low specificity and sensitivity of anti-HEV IgM kits
• Short duration of anti-HEV IgM positivity
Comparison of serologic Assays Specific to Immunoglobulin M Antibodies against Hepatitis E Virus

Correlation between anti-HEV IgM kits

Unpublished from Shata/Sherman

Drobeniuc et al, Clinical Infectious Diseases 2010; 51(3):e24–e27
Evaluation of HEV-specific immune responses in HEV infected subjects

DIAGNOSIS

Virologic

• Blood
  – Short Window of Viremia

• Stool
  – Longer period of shedding
  – Generally not available in existing cohorts
HEV REAL TIME PCR
PROPOSED DIAGNOSTIC CRITERIA

• ACUTE HEV INFECTION
  – ALT>2x baseline + HEV IgM Reactive using 2 different assays or
  – ALT> 2x baseline + HEV IgM Reactive + HEV RNA detected in stool or blood (LOD 10 copies/ml) or
  – ALT> 2x baseline + HEV IgG x 2 weeks apart with > 5-fold increase in titer or
  – ALT> 2x baseline + HEV IgM Reactive + IFN-gamma ELISPOT for HEV (>50 HEV-specific spots/10^6 cells

• CHRONIC HEV INFECTION
  – HEV RNA detected twice over 6 months in stool or blood

Anwar & Sherman, SCIENTIFIC AMERICAN GASTRO 2017
# CLINICAL OUTCOMES

<table>
<thead>
<tr>
<th></th>
<th>ACUTE DISEASE</th>
<th>CHRONIC DISEASE</th>
<th>MORTALITY</th>
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<tbody>
<tr>
<td>Immunocompetent</td>
<td>YES</td>
<td>NO</td>
<td>LOW</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>YES</td>
<td>NO</td>
<td>VARIABLE</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>YES</td>
<td>NO</td>
<td>HIGH</td>
</tr>
<tr>
<td>Immunosuppressed - HIV - Post-Transplant - Cancer Chemotx</td>
<td>YES</td>
<td>YES</td>
<td>VARIABLE</td>
</tr>
</tbody>
</table>

? Immune Trigger- PBC, Guillain-Barre
Anwar et al, HEPATOLOGY Supp 2013 Abs 1195
Pas et al, Abs 66 HEPATOLOGY Supp 2013
HEV

Acute on Chronic Decompensation

Kumar et al., IND J GASTRO, 2004
HEV IN HIV-INFECTED PATIENTS
<table>
<thead>
<tr>
<th>Country</th>
<th>IgG HEV% (positive/tested)</th>
<th>IgM HEV% (positive/tested)</th>
<th>Chronicity</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>France</td>
<td>4.4% (8/184)</td>
<td>1.6% (3/184)</td>
<td>POS</td>
<td>Kaba et al. [21]</td>
</tr>
<tr>
<td>Spain</td>
<td>9% (22/238)</td>
<td>0%</td>
<td>POS</td>
<td>Jardi et al. [22]</td>
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<tr>
<td>Spain</td>
<td>9.2% (22/238)</td>
<td>ND</td>
<td>NEG</td>
<td>Riveiro Barciela et al. [23]</td>
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<td>Spain</td>
<td>10.4% (45/448)</td>
<td>7% (3/45)</td>
<td>NEG</td>
<td>Mateos-Lindemann et al. [24]</td>
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<td>Spain</td>
<td>21% (189/894)</td>
<td>ND2</td>
<td>NEG</td>
<td>Rivero Juarez et al. [16]</td>
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<tr>
<td>Spain</td>
<td>26% (161/613)</td>
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<td>NEG</td>
<td>Pineda et al. [15]</td>
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<td>Italy</td>
<td>19.4% (14/72)</td>
<td>50% (1/2)</td>
<td>NEG</td>
<td>Scotto et al. [26]</td>
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<td>Italy</td>
<td>6.7% (34/509)</td>
<td>14.7% (5/34)</td>
<td>NEG</td>
<td>Scotto et al. [27]</td>
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<td>Greece</td>
<td>7.3% (18/243)</td>
<td>0</td>
<td>NR</td>
<td>Politou et al. [41]</td>
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<td>France</td>
<td>9% (22/245)</td>
<td>2.25% (5/245)</td>
<td>NEG</td>
<td>Renou et al. [45]</td>
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<td>France</td>
<td>3.7% (4/108)1</td>
<td>0.9% (1/108)2&lt;comma&gt;8</td>
<td>NEG</td>
<td>Sellier et al. [63]</td>
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<tr>
<td>France</td>
<td>1.5% (4/261)</td>
<td>0%</td>
<td>NEG</td>
<td>Maylin et al. [64]</td>
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<td>Scotland</td>
<td>1.04% (1/94)</td>
<td>100 (1/1)</td>
<td>NR</td>
<td>Bradley Stewart et al. [17]</td>
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<td>England</td>
<td>9.4% (13/184)</td>
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<td>Keane et al. [32]</td>
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<td>Switzerland</td>
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<td>ND7</td>
<td>POS</td>
<td>Kenfak Fougouena et al. [30]</td>
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<td>Holland</td>
<td>11.7% (30/256)</td>
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<td>Hassing et al. [65]</td>
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<td>Croatia</td>
<td>1.1% (1/88)</td>
<td>12.5% (11/88)</td>
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<td>Dakovic Rode et al. [18]</td>
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<td>Gabón</td>
<td>7.1% (13/183)</td>
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<td>NEG</td>
<td>Caron et al. [66]</td>
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<td>Ghana</td>
<td>45.3% (182/402)</td>
<td>0.7% (1/182)</td>
<td>NEG</td>
<td>Feldt et al. [19]</td>
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<td>Cameroon</td>
<td>14.2% (42/289)</td>
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<td>NEG</td>
<td>Feldt et al. [19]</td>
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<td>Nigeria</td>
<td>30% (24/80)</td>
<td>4.2% (1/24)</td>
<td>NR</td>
<td>Junaid et al. [20]</td>
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<td>Cambodia</td>
<td>30% (247/825)</td>
<td>1.1 (9/825)</td>
<td>NEG</td>
<td>Nouhin et al. [29]</td>
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<tr>
<td>Malaysia</td>
<td>10.3% (15/145)</td>
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<td>Ng et al. [42]</td>
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<td>Australia</td>
<td>6.3% (12/191)</td>
<td>ND3</td>
<td>NEG</td>
<td>Yong et al. [61]</td>
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<td>USA</td>
<td>19% (32/166)</td>
<td>0.9% (2/133)</td>
<td>NR</td>
<td>Sherman et al. [28]</td>
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<tr>
<td>USA</td>
<td>4% (7/194)</td>
<td>3% (5/194)</td>
<td>NEG</td>
<td>Crum-Cianflone et al. [46]</td>
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<tr>
<td>Argentina</td>
<td>6.6% (32/484)</td>
<td>ND</td>
<td>NR</td>
<td>Fainboim et al. [67]</td>
</tr>
</tbody>
</table>

Adapted from JD Debes et al., J CLIN VIROL 2016
ACUTE HEV in HIV U.S. Military

- 4410 HIV positive persons followed for 32,468 person years
- 458 had ALT increase c/w acute hepatitis event
- 194 tested for HEV
- Conclusion: HEV is in the differential of acute hepatitis in HIV-infected patients

Crum-Cianflone et al, EMERG INF DIS, 2012
• 166 pre-transplant subjects
  – 113 awaiting liver transplant
    Including 10 dual organ candidates
  – 53 awaiting kidney transplant
• Adaltis and Wantai EIA
• ORF1-2 PCR Amplification
  – No positives at baseline
  – Stool not available
HEV IN SOT COHORT

Sherman et al, J VIRAL HEP 2014
HEV Prevalence
HEPRES/HEPPRO Cohorts

% HEV IgG Among HCV/HIV

16%

IgG neg
IgG positive

Sherman KE et al, AASLD, 2016
HEV Prevalence
Cumulative Risk by Age

HEV IgG Positive Cumulative Distribution

age (years)

Sherman KE et al, AASLD, 2016
### Laboratory Data for a Patient with Coinfection with Human Immunodeficiency Virus (HIV) and Hepatitis E Virus (HEV)

<table>
<thead>
<tr>
<th>Test</th>
<th>September</th>
<th>October</th>
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<td>Wantai HEV IgG</td>
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<td>Wantai HEV IgM</td>
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<td>Biokit HEV IgG</td>
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<td>HEV PCR assay — plasma</td>
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<td>HEV PCR assay — feces</td>
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<td>+</td>
</tr>
</tbody>
</table>
HEV
WIHS/MACS

WIHS: N = 1607
MACS:N = 190
HEV NAT Testing with Serologic Evaluation of Positives

Kuniholm et al, HEPATOLOGY 2016
CHRONIC HEV IN HIV
Progression to “Cryptogenic” Cirrhosis

Gurmit K. et al.
Journal of Infection 2011
TREATMENT OF CHRONIC HEV

• Pegylated Interferon
• Ribavirin
• Withdrawal of Immunosuppression
  – 18/56 Cleared HEV with reduced immunosuppression (Kamar et al, GASTRO, 2011)
HEV TREATMENT
Ribavirin

• Retrospective, Multicenter Case Series
• N= 59
• Organ Transplant Recipients
• Chronic HEV Identified
• Treatment
  – Ribavirin Median Dose 600 mg/day
  – Median Duration 3 months

Kamar et. al, NEJM, 2014
HEV in HIV
Ribavirin Treatment

- First Case Report
- 39 yo man with HIV
  - Lopinavir/abacavir/lam
  - Ate raw pork-liver sausage
  - CD4= 51, HIV undetectable
- HEV RNA +, Genotype 3
- Jaundiced with coagulopathy
- Riba 1200 mg x 12 weeks started
  - Viral load dropped
  - Liver parameters improved
  - Patient clear 1.5 months post treatment

Robbins et al, J CLIN VIROL, 2014
HEV VACCINE

• Recombinant HEV Vaccine
• Studied in Nepal
  – N= 2000
  – Randomized 1:1
  – 3 doses vaccine or Placebo
  – Median F/U 804 days

Sresthra et. al., NEJM 2007
Hepatitis E: Summary

HEV Exposure

Clearance

Acute HEV

Immunocompetent

Resolution

Long lived Immunity

Innate Immunity

Memory T cell responses

Neutralizing antibodies

Immunosuppressed

Pregnancy

High Viremia

Impaired T cells

Quasispecies

Genotype 3

Innate response

T cell response

T-reg

ALF

Chronicity
CONCLUSION

• WHAT WE KNOW
  – HEV is prevalent in Western countries where it was previously unsuspected
  – HEV Prevalence in HIV Infected Persons MAY be higher than general population
  – HEV is under-diagnosed in HIV-infected patients due to
    • Low clinical suspicion
    • Poor assays
    • Low availability of assays
  – There is a low risk of Chronicity but when it occurs, it could be associated with progressive liver disease

• WHAT WE DON’T KNOW
  – Are HIV+ patients at greater risk of infection?
  – Have we misclassified HEV as DILI in HIV+ patients?
  – How does CD4 affect risk of chronicity-? More common < 200 cells/mm³
  – How are humoral titers, avidity and CTL response altered in Immunosuppressed Hosts
  – Can/Should those with HIV be vaccinated?