NASH - The New Epidemic in HIV-Coinfected Patients?

ICVH, Chicago, October 10th, 2017

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Associate Professor of Clinical Medicine
University of California, San Diego
Outline:

• Case definition and HIV effects
• Epidemiology
• Diagnostic modalities- CAP considerations
• Practical management implications for HIV providers
• Issues on ART management
September 2015: The Intake appointment


HIV history:
- 2002-2006: TDF + 3TC + Lopinavir/ritonavir
- 2007-2014: coformulated Atripla

Physical Exam:
BP 133/85 mmHg | Pulse 88 | Temp 96.8 F (36 C) | Resp 18 | Ht 5' 10" (1.778 m) | Wt 97.523 kg (215 lb) | BMI 30.85 kg/m2

Besides mild central fat accumulation his physical exam was unremarkable.
## Main laboratory intake results

<table>
<thead>
<tr>
<th>Metabolic profile</th>
<th>General hematologic parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Total cholesterol: 152 mg/dl</td>
<td>• WBC: 5.7</td>
</tr>
<tr>
<td>• Triglycerides: 217 mg/dl (H)</td>
<td>• HGB: 15.90</td>
</tr>
<tr>
<td>• Direct LDL: 102 mg/dl</td>
<td>• PLT: 267</td>
</tr>
<tr>
<td>• Glucose: 80</td>
<td>• INR: 1.0</td>
</tr>
<tr>
<td>• SCr: 1.00</td>
<td></td>
</tr>
<tr>
<td>• Albumin: 4.40</td>
<td></td>
</tr>
<tr>
<td>• T. Bilirubin: 0.5</td>
<td></td>
</tr>
<tr>
<td>• ALP: 77</td>
<td></td>
</tr>
<tr>
<td>• AST: 53 (H)</td>
<td></td>
</tr>
<tr>
<td>• ALT: 111 (H)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver profile</th>
<th>Common causes of infectious hepatitis part of routine HIV intake labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hepatitis A Ab IgG: Reactive</td>
<td>• Hepatitis A Ab IgG: Reactive</td>
</tr>
<tr>
<td>• Hepatitis C Ab: Non-reactive</td>
<td>• Hepatitis C Ab: Non-reactive</td>
</tr>
<tr>
<td>• Hepatitis B Ig Core: Non-reactive</td>
<td>• Hepatitis B Ig Core: Non-reactive</td>
</tr>
<tr>
<td>• Hepatitis B s Antigen: Non-reactive</td>
<td>• Hepatitis B s Antigen: Non-reactive</td>
</tr>
<tr>
<td>• Hepatitis B s Ab: Reactive (164 )</td>
<td>• Hepatitis B s Ab: Reactive (164 )</td>
</tr>
<tr>
<td>• Syphilis EIA: Non-reactive</td>
<td>• Syphilis EIA: Non-reactive</td>
</tr>
</tbody>
</table>
November 2015: Liver ultrasound

The liver measures 16.6 cm in long axis. It is increased in echogenicity. There is no intra or extra hepatic bile duct dilation. The common bile duct measures for 9 mm. The gallbladder is normal with no calculi, sludge or wall thickening. No ascites is seen.

The visualized aorta and inferior vena cava are within normal limits.

**IMPRESSION:**
Mild hepatomegaly with fatty infiltration of the liver.
Does this case remind you of what you are seeing in your clinical practice?
NAFLD definition

• A clinicopathologic disorder defined by the presence of fat in >5% of hepatocytes in the absence of other secondary causes (e.g. alcohol use, hereditary disorders, steatogenic medications, or viral hepatitis)
The changing epidemiology of Liver Disease in HIV patients

Clinical liver-related complications

- IDU
- Delta
- HBV
- DILI
- HEV?
- HCV
- NAFLD
- DAA

More than 50% of Persons Living with HIV are overweight during the ART era.

Trends in Weight Categories at HIV Diagnosis during the HIV Epidemic.

Year of HIV Diagnosis

Risk factors for NAFLD

• Ethnic predisposition
  – More common in Asian Indians>Hispanics>Caucasians>African Americans

• Risk factors include metabolic syndrome
  – Obesity, hypertension, hypertriglyceridemia, insulin resistance and diabetes
  – PNPLA3 genotype
Are the metabolic consequences of obesity different in HIV+ patients?

**Consistent:**

- Obese HIV+ subjects have a higher trunk-to-appendicular fat ratio, a predictor of cardiovascular disease, compared to obese non-HIV controls.

- Higher calculated visceral fat.

**Variable:**

- Severity of peripheral resistance to the insulin
- Magnitude of lipid elevation
- Effects of biomarker and endovascular inflammation: ICAM-1, sCD14, TNFαR2

Koethe et al. AIDS. 2016;30:83-91
Price et al. Open Forum Infect Dis. 2017;4:ofx153
NAFLD prevalence

Prevalence (%)

HIV Navy Clinic-San Diego, USA (n = 216)
Metabolic Clinic, Modena-Italy (n = 225)
HIV Metabolic Clinic, Hong-Kong (n = 80)
HIV Clinic. U/S 2004-13, Japan (n = 455)
HIV Clinic. Consecutive pts, Canada (n = 300)

Prevalence (95% CI)

31.02% (29.92 – 37.65)
36.89% (30.57 – 43.56)
28.75% (19.18 – 39.95)
31.03% (26.71 – 25.62)
48.00% (42.22 – 53.82)

35.32% (28.80 – 42.45)

I² = 85.3%, Tau = 0.0947, p <0.0001)

Maurice JB et al. AIDS 2017; 31:1621-1632
How to diagnose it?

• Liver biopsy: Invasive, observer variation, heterogeneous fat distribution
• Liver ultrasound: Low sensitivity-threshold 30%.
• Fibroscan- Controlled Attenuated parameter - Caveats
• MRI
Forest plots of sensitivity and specificity of controlled attenuation parameter (CAP) for the detection of stage 1 (S1) hepatic steatosis

<table>
<thead>
<tr>
<th>CAP cut-off (dB/m)</th>
<th>Study ID</th>
<th>Sensitivity (95% CI)</th>
<th>Study ID</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>219</td>
<td>Ferraioli 2014</td>
<td>0.90 [0.68 – 0.99]</td>
<td>Ferraioli 2014</td>
<td>0.52 [0.33 – 0.71]</td>
</tr>
<tr>
<td>250</td>
<td>Chon 2014</td>
<td>0.73 [0.61 – 0.84]</td>
<td>Chon 2014</td>
<td>0.97 [0.82 – 1.00]</td>
</tr>
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<td>263</td>
<td>Chan 2014</td>
<td>0.92 [0.82 – 0.97]</td>
<td>Chan 2014</td>
<td>0.95 [0.82 – 0.99]</td>
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<tr>
<td>253</td>
<td>Shen 2014</td>
<td>0.88 [0.77 – 0.96]</td>
<td>Shen 2014</td>
<td>0.83 [0.67 – 0.94]</td>
</tr>
<tr>
<td>220</td>
<td>Wang 2014</td>
<td>0.69 [0.50 – 0.84]</td>
<td>Wang 2014</td>
<td>0.64 [0.43 – 0.82]</td>
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<tr>
<td>280</td>
<td>Masaki 2013</td>
<td>0.88 [0.69 – 0.97]</td>
<td>Masaki 2013</td>
<td>0.76 [0.56 – 0.90]</td>
</tr>
<tr>
<td>224</td>
<td>Kumar-2 2013</td>
<td>0.56 [0.35 – 0.76]</td>
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<td>0.74 [0.54 – 0.89]</td>
</tr>
<tr>
<td>214</td>
<td>Kumar-1 2013</td>
<td>0.65 [0.48 – 0.79]</td>
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<td>0.64 [0.46 – 0.79]</td>
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<tr>
<td>222</td>
<td>Sasso 2012</td>
<td>0.76 [0.63 – 0.86]</td>
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<td>0.70 [0.62 – 0.78]</td>
</tr>
<tr>
<td>266</td>
<td>Ledinghen 2012</td>
<td>0.70 [0.50 – 0.86]</td>
<td>Ledinghen 2012</td>
<td>0.85 [0.66 – 0.96]</td>
</tr>
<tr>
<td>289</td>
<td>Myers 2012</td>
<td>0.68 [0.57 – 0.78]</td>
<td>Myers 2012</td>
<td>0.87 [0.66 – 0.96]</td>
</tr>
<tr>
<td>238</td>
<td>Sasso 2010</td>
<td>0.93 [0.76 – 0.99]</td>
<td>Sasso 2010</td>
<td>0.81 [0.58 – 0.95]</td>
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<tr>
<td><strong>COMBINED</strong></td>
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<td>0.79 [0.70 – 0.86]</td>
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  Q = 34.57, df = 11, p = 0.00  
  I² = 68.18 [49.04 – 87.31]

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  Q = 37.93, df = 11, p = 0.00  
  I² = 71.00 [53.95 – 88.05]
Distribution of CAP measurements stratified by hepatic fat content

Higher CAP value using XL compared to M probe when MRI < 10%

Kruskal-wallis

P<0.0001

M probe
XL probe

n=28 n=7
n=17 n=11
n=37 n=19

Caussy et al Clinical Gastroenterology 2017. In press
## NASH prevalence

### Prevalence (95% CI)

<table>
<thead>
<tr>
<th>Location</th>
<th>Prevalence (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Navy Clinic-San Diego, USA (n = 55)</td>
<td>7.27%</td>
<td>(2.02 – 17.59)</td>
</tr>
<tr>
<td>Metabolic Clinic, Modena-Italy (n = 225)</td>
<td>36.89%</td>
<td>(30.57 – 43.56)</td>
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<td>48.00%</td>
<td>(42.22 – 53.82)</td>
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### Summary

*Prevalence overall: 35.32% (28.80 – 42.45)*

- $I^2 = 85.3\%$, $\tau = 0.0947$, $p < 0.0001$

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Maurice JB et al. AIDS 2017; 31:1621-1632
Natural history of NAFLD

Healthy Liver

~ 30%

NAFLD

~ 33%

(12-40%)

NASH

15-25%

Cirrhosis

50%

5%

Hepatocellular carcinoma

Death unless liver transplant

ICVH 2017
INTERNATIONAL CONFERENCE ON VIRAL HEPATITIS
May 2016: our patient modified his diet and has started exercising!

**September 2015**: Wt 97.523 kg (215 lb) | BMI 30.85 kg/m²

ALT

AST

**May 2016**: Wt 83.28 kg (183 lb 9.6 oz) | BMI 26.34 kg/m²
Aramchol for HIV-associated nonalcoholic fatty liver disease and lipodystrophy

Dear [Name],

Please find enclosed your MRI results from your recent visit.

The fat fraction of your liver was 2.92%, MR elastography 3.64 kPa of and fibroscan 25.4 kPa.

A fat fraction >5% is indicative of fatty liver disease, and Fibroscan score of > 7 kPa is indicative of fibrosis, >14 may suggest cirrhosis. MR elastography > 3.0 kPa may suggest advanced cirrhosis. Please show these results to your Primary Care provider.

If you have any questions, please feel free to call me at [phone number] or email me at [email address].

Thanks.
Management implications for HIV providers

• Staging for complications of portal Hypertension: EGD
• HCC screening
• Verify immunization status:
  + Viral hepatitis HAV, HBV
  + Invasive pneumococcal infections
  
  * Counseling: Behavioral, medications, life-style
Non-invasive online tools for liver fibrosis: practical tips.

Available at: http://nafldscore.com/index.php
Fibrosis progression rate in NAFLD

- FPR in NAFL: 14 years/stage
- FPR in NASH: 7 years/stage
- 20% of those who progress are “Rapid Progressors”

Singh et al. CGH 2014
Multivariable-adjusted risk of NASH in HIV-associated NAFLD

Risk of NASH is significantly higher in HIV than primary NAFLD independent of age, sex, ethnicity and BMI.
Are there HIV predictors of NASH and Fibrosis?

<table>
<thead>
<tr>
<th>HIV-related factors</th>
<th>Ishak Fibrosis Score on Liver biopsy</th>
<th>P</th>
<th>Biopsy Diagnosis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 ( n = 47)</td>
<td></td>
<td>Non-specific (n=22)</td>
<td></td>
</tr>
<tr>
<td>Time from HIV Diagnosis</td>
<td>17.5 (2.3 -27.8)</td>
<td>.72</td>
<td>18.2 (2.7 -24.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.1 (3.8 -24.8)</td>
<td></td>
<td>16.3 (2.3-27.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 2 ( n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CD4+</td>
<td>539 (105-1631)</td>
<td>.62</td>
<td>498 (1105-115)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>592 (138 -1525)</td>
<td></td>
<td>580 (138-1631)</td>
<td>.4</td>
</tr>
<tr>
<td>CD4+ %</td>
<td>30 (7-49)</td>
<td>.67</td>
<td>31 (8-49)</td>
<td>.19</td>
</tr>
<tr>
<td>CD4+ nadir</td>
<td>195 (&lt; 10-599)</td>
<td>.75</td>
<td>189 (12-561)</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>160 (&lt; 10-423)</td>
<td></td>
<td>178 (6-599)</td>
<td></td>
</tr>
<tr>
<td>History of opportunistic infections</td>
<td>21 (45%)</td>
<td>.48</td>
<td>8 (36%)</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>4 (33%)</td>
<td></td>
<td>17 (50%)</td>
<td></td>
</tr>
<tr>
<td>ART duration at biopsy</td>
<td>12.4 (1.7 -22.8)</td>
<td>.96</td>
<td>12.9 (3.2-20.6)</td>
<td>.33</td>
</tr>
<tr>
<td></td>
<td>13.0 (2.7-21.6)</td>
<td></td>
<td>11.1 (1.7-22.8)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Morse et al. CID 2015; 60: 1569-1578
Does it matter which antiretroviral regimen we choose?
328 patients were randomized (90% male, 44% white non-Hispanic). Overall, at week 96, increases in limb fat (13.4%), subcutaneous (19.9%) and visceral abdominal fat (25.8%), trunk fat (18%), and lean mass (1.8%) were apparent (P < .001 for changes within each arm).

Changes for all fat and lean outcomes were not different between the PI arms or between the RAL and the combined PI arms.
What about after someone is diagnosed with NAFLD?

Macias J. et al Clin Infect Dis 2017; 65:1012-1019
A window of opportunity: Liver fat as barometer of metabolic complications in an aging HIV population.

- NAFLD
- Diabetes mellitus\(^2\)
  - OR: 3.1 @ 5 years
- Cardiovascular disease\(^1\)
- Bone metabolism alteration\(^3\)
  - OR: 2.5↑
- Cognitive impairment?\(^4\)

3. JCEM 2012, 97: 2033-8
4. JAIDS 2015, 28: 281-288
“The July 2017 AASLD NAFLD guidelines do not comment on unique needs of HIV+ patients. This is a practical, albeit incomplete algorithm for the HIV provider.”
Summary:

• Persons living with HIV (PLWH) are at high risk for developing NAFLD/NASH
• Following diagnosis of ‘fatty liver’ is also essential to investigate liver fibrosis stage
• In the absence of specific treatment for NASH, HIV providers must focus on preventive efforts addressing weight and insulin resistance
• Emerging data suggest that reassessing ARV class might be a consideration for management of NAFLD in PLWH
• Think of NAFLD/NASH not only a marker but also as a mediator, for multiple future adverse health outcomes
Acknowledgements:

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• Rohit Loomba- UCSD
• Lucas Hill- UCSD
• Lisa Richards- UCSD
• ICVH organizing committee