Non-alcoholic fatty liver disease in HIV-infected subjects

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St Mary’s Hospital
Imperial College London, UK

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8–9 December 2014
Queen Elizabeth II Conference Centre, London
DEFINITION

NON-ALCOHOLIC FATTY LIVER (NAFLD)

SIMPLE STEATOSIS

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

FIBROSIS CIRRHOSIS

Steatosis
+
Hepatocyte Ballooning at any degree
+
Lobular inflammation at any degree

With or without fibrosis

Brunt et al. Hepatology 2011
**NATURAL HISTORY**

- **Simple steatosis**
  - 15-20%

- **NASH**
  - 30-38%

- **Fibrosis**
  - 5-20% over 20 years

- **Cirrhosis**
  - 3-5%/year
  - HCC

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Adams, LA J Hepatol 2005
Ekstedt M, Hepatology 2006
Fassio, E Hepatology 2004
Harrison, SA Gastroenterol 2003
n = 420 with NAFLD
Mean Follow-up: 7.6 years
Overall mortality rate: 12.6 %

NAFLD IS ASSOCIATED WITH A HIGHER MORTALITY

Causes of Death: Cancers (28 %), Cardio-vascular (25 %), Liver (13 %)

Adams LA, Gastroenterology 2005
NAFLD IS ASSOCIATED WITH A HIGHER MORBIDITY

1) Higher cancer incidence, in particular HCC
   
   Baffy G, J Hepatol 2012

2) Increased incidence of DM and insulin requirement
   
   Ryysy L, Diabetes 2000, Fraser A Diab Care 2009

3) Increased prevalence and incidence of atherosclerosis and CVD
   

4) Higher rate of major complications and deaths after surgery
   
   de Meijer, Br J Surg 2012
**METABOLIC SYNDROME (MS): THE MAIN CAUSE OF NAFLD/NASH**

3 criteria out of five

| Central obesity | **Waist circumference:**  
|-----------------|-----------------------------  
|                 | Europeans: $\geq 94$ cm (M) ou $\geq 80$ cm (F)  
|                 | Americans: $\geq 102$ (M) $\geq 88$ cm (F)  
|                 | Asians: $\geq 90$ cm (M) $\geq 80$ cm (F)  
|                 | Sub-Saharan Africans $\geq 94$ cm (M) ou $\geq 80$ cm (F)  
| High Blood Pressure | **Arterial Pression** $\geq 130$ mmHg and/or $\geq 85$ mmHg  
|                  | or treated Hypertension  
| Low cholesterol HDL | $< 0,4$ g/L (1 mmol/L (M) ou $< 0,5$ g/L (1,3 mmol/L (F)  
|                  | ou treated Cholesterol  
| High blood triglycerides | $\geq 1,5$ g/L (1,7 mmol/L)  
|                  | or treated hyperTG  
| High blood glucose | **Glucose** $\geq 1$ g/L (5,6 mmol/L)  
|                  | or antidiabetic treatment  

Adapted from Alberti Circulation 2009
Metabolic syndrome prevalence in developed countries: 25%

Even more in subjects over 50 years

Global prevalence of overweight both sex -WHO 2008
GLOBAL EPIDEMIOLOGY OF NAFLD/NASH

France: NAFLD: 60 %  NASH: 33 %
De Ledinghen, J Hepatol 2006

Spain: NAFLD: 44%
Caballeria, Eur J Gastro 2012

India: NAFLD 32 %

Japan: NAFLD 29 %
Jimba S Diabet Med 2005

Brazil: NAFLD: 42%
NASH: 27%
27% severe fibrosis/cirrhosis
Cotrim HP, Ann Hepatol 2012

46 % NAFLD
12 % NASH
3 % severe fibrosis/cirrhosis
Texas
Williams Gastroenterology 2011
NASH: THE THIRD MOST COMMON INDICATION OF LIVER TRANSPLANTATION IN THE US

n = 35,781 patients with Liver Transplantation between 2001-2009

Charlton MR et al. Gastroenterology 2011
HIV PATIENTS ARE AGING

By 2015, 50% of HIV patients will be over 50 years

*United States estimates*

Effros, RB  CID 2008
HIV PATIENTS ARE GETTING OLD AND FAT

n = 1286
Follow-up: 1985-2004

Crum-Cianflone, N et al. PlosOne, 2010
MS PREVALENCE HAS GREATLY INCREASED IN HIV PATIENTS

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Number of patients under follow-up</td>
<td>24349</td>
<td>26615</td>
<td>28449</td>
<td>28661</td>
<td>26265</td>
<td>23853</td>
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<tr>
<td>% of patients under follow-up with</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DM</td>
<td>1008 (4.1)</td>
<td>1140 (4.3)</td>
<td>1303 (4.6)</td>
<td>1344 (4.7)</td>
<td>1275 (4.9)</td>
<td>1245 (5.2)</td>
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<tr>
<td>BMI</td>
<td>1469 (6.0)</td>
<td>1796 (6.8)</td>
<td>2094 (7.4)</td>
<td>2323 (8.1)</td>
<td>2343 (8.9)</td>
<td>2288 (9.6)</td>
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<tr>
<td>Triglycerides</td>
<td>16325 (67.1)</td>
<td>18283 (68.7)</td>
<td>19728 (69.4)</td>
<td>20842 (72.7)</td>
<td>19894 (75.7)</td>
<td>18826 (78.9)</td>
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<tr>
<td>HDL</td>
<td>11660 (47.9)</td>
<td>13671 (51.4)</td>
<td>15531 (54.6)</td>
<td>16896 (59.0)</td>
<td>16099 (61.3)</td>
<td>15583 (65.3)</td>
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<tr>
<td>Hypertension</td>
<td>7243 (29.8)</td>
<td>9069 (34.1)</td>
<td>10670 (37.5)</td>
<td>12429 (43.4)</td>
<td>12634 (48.1)</td>
<td>12998 (54.5)</td>
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<tr>
<td>n (%) with MS</td>
<td>4712 (19.4)</td>
<td>6328 (23.8)</td>
<td>7647 (26.9)</td>
<td>9121 (31.8)</td>
<td>9418 (35.9)</td>
<td>9913 (41.6)</td>
</tr>
</tbody>
</table>

Worm et al AIDS 2010, the D.A.D study group
# METABOLIC SYNDROME: A COMMON FEATURE IN HIV PATIENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>country</th>
<th>MS criteria</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gazzaruso, C Diabetes Care 2002</td>
<td>533</td>
<td>Italy</td>
<td>NCEP-ATPIII</td>
<td>45.4</td>
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<td>Bruno, R JAIDS 2002</td>
<td>201</td>
<td>Italy</td>
<td>EGIR</td>
<td>39.8</td>
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<tr>
<td>Jerico, C Diabetes Care 2005</td>
<td>710</td>
<td>Spain</td>
<td>NCEP-ATPIII</td>
<td>17</td>
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<tr>
<td>Bofanti, P JAIDS 2007</td>
<td>1243</td>
<td>Italy</td>
<td>NCEP-ATPIII</td>
<td>22</td>
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<tr>
<td>Samaras, K Diabetes Care, 2007</td>
<td>788</td>
<td>USA</td>
<td>IDF</td>
<td>14</td>
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<tr>
<td>Crum-Cianflone, N JAIDS 2009</td>
<td>216</td>
<td>USA</td>
<td>NCEP-ATPIII</td>
<td>75</td>
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<tr>
<td>Worm, SW AIDS 2010</td>
<td>23 853</td>
<td>Europe/Australia/USA D.A.D</td>
<td>NCEP</td>
<td>41.6</td>
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<tr>
<td>Alencastro, PR AIDS Res Ther, 2012</td>
<td>1240</td>
<td>Brazil</td>
<td>AHA/NHLBI</td>
<td>24.7</td>
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<tr>
<td>Wu, PY J Anti Chem 2012</td>
<td>877</td>
<td>Taiwan</td>
<td>NCEP-ATPIII</td>
<td>26.2</td>
</tr>
</tbody>
</table>
THE RISK OF MS IS TWICE IN HIV PATIENTS

Bofanti et al, JAIDS 2007
MS IS NOT ONLY OBSERVED IN HAART-TREATED PATIENTS

Bofanti et al, JAIDS 2007
# NAFLD IN HIV INFECTED PATIENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>country</th>
<th>n subjects</th>
<th>Steatosis assessment</th>
<th>Prevalence of NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadigan, C 2007 JAIDS</td>
<td>USA</td>
<td>33</td>
<td>MR spectrometry</td>
<td>42%</td>
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<tr>
<td>Moreno-Torres, A 2007 AVT</td>
<td>Spain</td>
<td>29</td>
<td>MR spectroscopy</td>
<td>58%</td>
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<tr>
<td>Mohammed, SS 2007 JAIDS</td>
<td>Canada</td>
<td>26</td>
<td>Liver Biopsy</td>
<td>45%</td>
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<tr>
<td>Guaraldi, G 2008 CID</td>
<td>Italy</td>
<td>225</td>
<td>CT</td>
<td>37%</td>
</tr>
<tr>
<td>Crum-Cianflone, P 2009 JAIDS</td>
<td>USA</td>
<td>216</td>
<td>Ultrasound</td>
<td>31%</td>
</tr>
<tr>
<td>Ingiliz, P 2009 Hepatol</td>
<td>France</td>
<td>30</td>
<td>Liver Biopsy</td>
<td>60%</td>
</tr>
<tr>
<td>Nishijima, T 2014 PlosOne</td>
<td>Japan</td>
<td>435</td>
<td>Ultrasound</td>
<td>31%</td>
</tr>
<tr>
<td>Price, JC 2014 Am J Gastro</td>
<td>USA</td>
<td>465 HIV and HIV HCV</td>
<td>CT</td>
<td>15%</td>
</tr>
<tr>
<td>Juan, M 2014 AIDS</td>
<td>Spain</td>
<td>505 HIV HCV/HBV</td>
<td>CAP™</td>
<td>40%</td>
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</table>
HIV monoinfected patients with unexplained elevated LFT

<table>
<thead>
<tr>
<th>Study</th>
<th>country</th>
<th>n subjects</th>
<th>NASH assessment</th>
<th>Prevalence of NASH</th>
<th>Significant fibrosis</th>
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</thead>
<tbody>
<tr>
<td>Lemoine, M AIDS 2006</td>
<td>France</td>
<td>14</td>
<td>Liver Biopsy</td>
<td>56%</td>
<td>29%</td>
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<tr>
<td>Mohammed, SS JAIDS 2007</td>
<td>Canada</td>
<td>26</td>
<td>Liver Biopsy</td>
<td>55%</td>
<td>-</td>
</tr>
<tr>
<td>Crum-Cianflone, N JAIDS</td>
<td>USA</td>
<td>55</td>
<td>Liver Biopsy</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>Ingiliz, P Hepatol 2009</td>
<td>France</td>
<td>30</td>
<td>Liver Biopsy</td>
<td>53%</td>
<td>30%</td>
</tr>
<tr>
<td>Sterling, RJ Clin Gastr 2013</td>
<td>USA</td>
<td>14</td>
<td>Liver Biopsy</td>
<td>26%</td>
<td>14%</td>
</tr>
</tbody>
</table>
FACTORS ASSOCIATED WITH NAFLD/NASH IN HIV

- Older age
- Overweight and waist circumference
- Lipodystrophy
- HAART use of NRTI (ddi, D4T, AZT) and/or PIs (indinavir, ritonavir)
- Insulin resistance

Crum-Cianflione N JAIDS 2009
Capeau J, AIDS 2012
**HIV INFECTION IS ASSOCIATED WITH HIGHER RISK OF INSULIN RESISTANCE**

<table>
<thead>
<tr>
<th></th>
<th>Cases HIV + n=927</th>
<th>Controls HIV- n=258</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with HOMA&gt;4</td>
<td>343 (37%)</td>
<td>70 (27%)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

After multivariable adjustment for adipose tissue depots, demographic, and lifestyle factors,

HIV infection was associated with greater insulin resistance:

**OR = 1.62 for having HOMA>4; 95% CI: 1.10 to 2.4; P = 0.015.**

_Grunfeld, C J AIDS 2007_
INSULIN RESISTANCE: A CENTRAL ACTOR

Key mediators:
- Adipose tissue
- Gut
- Mitochondria
- Endoplasmic reticulum
- Lysosomes

HIV

↑ Oxidative stress
Chronic inflammatory state

Insulin resistance

Metabolic disorders
NAFLD/NASH

Lemoine, M & Ingiliz, P Clin res Hepatol Gastroenterol 2012
Adipose tissue changes
Lipodystrophy and overweight

PPARγ
Adipokines
↑ Leptin, IL6, IL1, TNFα
↓ adiponectin

HIV
ART (NRTI, PIs)

Autophagy

Mitochondrial dysfunction
↓ mDNA

Endoplasmic Reticulum Stress

↑ SREBP-1 + lipogenesis

↑ LPS
↑ TNFα
↑ IL-1

Genetic?

Free Fatty acids

INSULIN RESISTANCE

Steatosis, inflammation, fibrosis

Lemoine, M & Ingiliz P Clin Res Hep Gastr 2012
How to make the diagnosis of NAFLD/NASH in HIV?

HIV + subjects
Met.S and/or Lipodystrophy and/or abnormal LFT

Exclude other causes of steatosis
HCV
Alcohol
Drugs
Chemotherapy...

Look for
Insulin resistance (HOMA index: glycemie x insulinemia/22.5)
Liver steatosis
Inflammation
Fibrosis

Consider Liver Biopsy in case of
Suspected significant liver fibrosis
Or
Undetermined diagnosis
## NON INVASIVE MARKERS OF STEATOSIS

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sonography</strong></td>
<td>Simple</td>
<td>not detect steatosis &lt; 30 %</td>
</tr>
<tr>
<td></td>
<td>Quick</td>
<td>operator- and machine-dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>poor reproducibility.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>challenging in obese patients</td>
</tr>
<tr>
<td><strong>Computed Tomography</strong></td>
<td>Better sensitivity than sonography</td>
<td>Errors in fat quantification (<em>iron, copper, glycogen, fibrosis or edema</em>)</td>
</tr>
<tr>
<td><strong>MR spectroscopy</strong></td>
<td>Good Sensitivity</td>
<td>Low sensitivity for mild-moderate steatosis</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>No irradiation</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Good Performances</td>
<td></td>
</tr>
<tr>
<td><strong>Steatotest</strong></td>
<td>Easy</td>
<td>Cost</td>
</tr>
<tr>
<td><strong>CAP</strong>&lt;sup&gt;TM&lt;/sup&gt;</td>
<td>Simple-Quick</td>
<td>Requirement of a recent Fibroscan machine</td>
</tr>
</tbody>
</table>
LIVER INFLAMMATION IS A RISK FACTOR OF FIBROSIS PROGRESSION

Argo J, Hepatol 2009

Inflamatory infiltrate = ↑ Risk of fibrosis progression by 2.5
TRANSAMINASES:
NOT A PERFECT MARKER OF LIVER INFLAMMATION IN NASH

n = 679 morbid obese patients

Bedossa P, Hepatol 2012
Diagnosis of Liver Inflammation & NASH

- Non-invasive serum markers can help, e.g., Nashtest

Liver biopsy remains the gold standard

3 criteria: Steatosis (A) + Ballooning (B) + inflammation (C)

Fibrosis is not a criteria for the diagnosis of NASH
257 patients with biopsy-proven NAFLD
Follow-up: 145 months. Hepatic-related deaths: 9%
NON INVASIVE MARKERS OF FIBROSIS

Fibroscan® (Elastography)

<table>
<thead>
<tr>
<th>Best cut-offs</th>
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</thead>
<tbody>
<tr>
<td>F2: 7 kPa</td>
<td>F3: 8.7 kPa</td>
<td>F4: 10.3 kPa</td>
<td></td>
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</tbody>
</table>

Wong et al. Hepatol 2010  n=246 non HIV subjects

Biochemical markers (FibroTest, Fibrometer, ELF score, APRI ...)
• **Weight loss**
  
  ⇒ At least 7% of baseline weight

• **Dietary changes** (avoid saturated fat and soft drinks)

• **Regular physical exercise**
  
  150 min/week moderate

---

_Nascimbeni F, J Hepatol 2013_  
_Ratziu V, J Hepatol, 2010_
Exercising improves

- Insulin resistance
- Steatosis
- Independently from the weight loss

In HIV (n=18)
Exercises (strength or endurance 3 times/wk)
- Improve insulin resistance and total liver fat
- Decrease LDL chol, CRPus, TNFα, IL6, IL18

Fatty Liver assessment by spectrometry

Johnson, Hepatology 2009
Helmerhost, Diabetes 2009

Lindegaard, B J Clin Endocrinol Metab 2008
PHARMACOLOGIC THERAPY

1- Treatment of metabolic disorders
HBP, Diabetes mellitus, Hyper TG, HyperChol

2- No approved medication for NASH
- **Metformine**: no effect  
  Musso G, Hepatol 2010-Meta-analysis
- **Thiazolidiones** (pioglitazone, rosiglitazone): removed from the market
- **UDCA** (Ursodeoxycholic acid): hepatoprotective effects, insulin sensitizing and possible antifibrogenic effects  
  Ratziu V, J Hepatol 2011
- **Vitamin E + UDCA**  
  Dufour JF, Liver Intern 2009
- Several drugs under investigation

=> FXR (obeticholic acid) or PPARα/δ agonists

3- No trials have been conducted in HIV patients with NAFLD/NASH
CONCLUSIONS

1- Metabolic disorders are frequent in HIV-infected subjects

2- HIV patients are at high risk of NAFLD/NASH

3- The physiopathology is complex

4- Even in the absence of approved drugs for NASH, it is critical to make a correct diagnosis and identify the most severe cases

5- Additional data are needed
The ECHAM study
European Cohort: HIV, Aging and Metabolic liver disease

Muticentric European study (clinicaltrial.org NCT-02093754 )

France, Germany, Belgium

ANRS-HIVERA funding CROSS SECTIONAL PROSPECTIVE STUDY

Primary objective:
To assess the proportion of HIV monoinfected patients with NAFLD & NASH
<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
<th>Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>France, Paris</td>
<td></td>
<td>Hayette Rougier, Jean-Luc Meynard, Pauline Campa, Jacqueline Capeau, Dominique Costaglioa, Lambert Assoumou, Pierre-Marie Girard, Karine Lacombe, Yves Menu, Vlad Ratziu, Lawrence Serfaty, Marc-Antoine Valantin</td>
</tr>
<tr>
<td>Germany, Berlin, Dusseldorf, Hambourg, Hannover</td>
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<td>Georg Behrens, Johana Eberhard, Patrick Ingiliz, Jan Van Luzen, Stefan Mauss</td>
</tr>
<tr>
<td>The UK, London</td>
<td></td>
<td>Janice Main, Lucy Garvey, Graham Cooke, Mark Thursz, Simon Taylor-Robinson, Sanjay Bhagani</td>
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<tr>
<td>Belgium, Brussels</td>
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<td>Stéphane De Wit, Coca Nescoi</td>
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<td>ANRS, Paris</td>
<td></td>
<td>Soizic Lemestre, Juliette Saillard, Jean-François Delfraissy</td>
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<tr>
<td>HIVERA</td>
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<td>Roxane Brachet</td>
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