NAFLD in HIV- infected patients

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Definition of NAFLD

Fatty liver
(≥5% steatotic hepatocytes)

Secondary FLD
- Alcohol
- Drugs
- Hereditary disorders

Non-alcoholic fatty liver disease (NAFLD)
- Non-alcoholic fatty liver (NAFL)
- Non-alcoholic steatohepatitis (NASH)

Body weight gain after ART

NA-ACCORD: 14,084 patients from 17 cohorts

NAFLD in HIV-infected patients

• Prevalence
• Natural history and risk of progression
• Factors associated with steatosis:
  – Metabolic risk factors
  – ART?
  – Genetics
• Management
Prevalence of steatosis in HIV/HCV coinfection: Liver biopsy

n 395 154 163 183 137 148 112
## Factors associated with steatosis in HCV/HIV coinfection: Liver biopsy

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>ART≥4 years</td>
<td>-</td>
<td>ART≥4 years</td>
<td>ddN (current)</td>
<td>d4T, No LPV-r</td>
<td>-</td>
<td>-</td>
<td>d4T (ever)</td>
</tr>
<tr>
<td>BMI</td>
<td>↑TG</td>
<td>-</td>
<td>Weight</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Weight, ↑ FPG</td>
</tr>
<tr>
<td>G3, HCV VL</td>
<td>-</td>
<td>-</td>
<td>Alcohol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ferritin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Caucasian race</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Fibrosis</td>
<td>Fibrosis</td>
<td>Inflammation</td>
<td></td>
</tr>
</tbody>
</table>

TG: Triglycerides; FPG: Fasting plasma glucose
Prevalence of hepatic steatosis measured by controlled attenuation parameter (CAP) in HIV infection


- **Patients**: Consecutive HIV-infected outpatients.

- **Methods**:
  - CAP measurements
  - Significant HS: CAP value ≥238 dB/m

Macías et al. AIDS 2014;28:1279-87
Relationship between hepatic steatosis and previous exposure to antiretroviral drugs

- **Nevirapine**
  - No (n=384): 43%
  - Yes (n=152): 32%
  - P=0.022

- **Ritonavir-boosted protease inhibitor**
  - No (n=216): 41%
  - Yes (n=284): 27%
  - P=0.042

- **Raltegravir**
  - No (n=412): 42%
  - Yes (n=87): 31%
  - P=0.064

- **Maraviroc**
  - No (n=459): 41%
  - Yes (n=41): 27%
  - P=0.077

Macías et al. AIDS 2014;28:1279-87
Frequency of hepatic steatosis according to body mass index category (N=505)

<table>
<thead>
<tr>
<th>Body mass index category</th>
<th>Patients with significant HS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal weight</td>
<td>90 (26%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>88 (64%)</td>
</tr>
<tr>
<td>Obesity grade I</td>
<td>20 (87%)</td>
</tr>
<tr>
<td>Obesity grade II</td>
<td>3 (100%)</td>
</tr>
</tbody>
</table>

$p<10^{-6}$

Macías et al. AIDS 2014;28:1279-87
Factors associated with hepatic steatosis: Multivariate analysis

**Adjusted odds ratio**

- %CD4 (per unit increase), p=0.200
- Plasma HIV (≤50 vs. >50 copies/ml), p=0.352
- DBP (mmHg, per unit increase), p=0.872
- FPG≤100 mg/dL, p=0.228
- TG<150 mg/dL, p=0.395
- TC (mg/dl, per unit increase), p=0.841
- LDL (mg/dl, per unit increase), p=0.824
- FMR (per unit increase), p=0.540
- BMI (k/m², per unit increase), p<10⁻⁶

Adjusted by age, gender, race, tobacco, IQR CAP, PI/r, MVC, RAL, NVP.

FMR: Fat mass ratio; %CD4: CD4 cell percentage.

Macías et al. AIDS 2014;28:1279-87
Prevalence of hepatic steatosis measured by CAP in HIV infection: German experience

- **Design**: Prospective cross-sectional study (Bonn University).
- **Patients**: Consecutive HIV-infected outpatients. Alcohol intake <30 g/day (men), <20 g/day (women).
- **N= 364**
- **Independent associations:**
  - BMI
  - Triglycerides
  - HbA1c

Prevalence of hepatic steatosis measured by CAP in HIV infection: Canadian experience

- **Design**: Prospective screening program for HS. Single center, Canada (Sept 2013-Sept 2016).
- **CAP thresholds**:  
  - HS (>10%): 248 dB/m  
  - Severe HS (>66%): 292 dB/m
- **Independent associations**:  
  - BMI  
  - Triglycerides

Prevalence of steatosis in HIV

• Frequent problem: 35%-40% of unselected populations

• Factors associated with steatosis:
  – Metabolic factors: BMI
  – ART
    • A problem of the past: ddX
    • Any role for “metabolic friendly” drugs
NAFLD in HIV-infected patients

- Prevalence
- Natural history and risk of progression
- Factors associated with NAFLD:
  - Metabolic risk factors
  - ART?
  - Genetics
- Management
Frequency of hepatic steatosis in paired liver biopsies

Retrospective cohort study (n=146): HIV/HCV coinfected patients with paired biopsies

Baseline
Median (Q1-Q3) time between biopsies: 3.3 (2-5.2) years

Follow-up

Macías et al. Hepatology 2012;56:1261-70
Frequency of patients with progression of hepatic steatosis

Macías et al. Hepatology 2012;56:1261-70
Progression of hepatic steatosis by the length of exposure to ddX, 3TC, EFV and NVP

% patients with HS progression

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt;2 years</th>
<th>2-4 years</th>
<th>&gt;4 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddX</td>
<td>10%</td>
<td>36%</td>
<td>88%</td>
</tr>
<tr>
<td>EFV</td>
<td>22%</td>
<td>38%</td>
<td>88%</td>
</tr>
<tr>
<td>3TC</td>
<td>38%</td>
<td>42%</td>
<td>53%</td>
</tr>
<tr>
<td>NVP</td>
<td>67%</td>
<td>21%</td>
<td>50%</td>
</tr>
</tbody>
</table>

n= 39 25 25 27 16 8 50 50 17 33 14 6

P<0.001 P=0.002 P=0.310 P=0.061

Macías et al. Hepatology 2012;56:1261-70
Factors associated with hepatic steatosis progression. Multivariate analysis

Odds ratio (95% CI)

- Time* on EFV (p=0.365)
- Time* on 3TC (p=0.069)
- Time* on ART (p=0.913)
- Time* on ddX (p<0.001)
- Change in glucose† (p=0.024)

†per 10 mg/mL increase; *per year

Macías et al. Hepatology 2012;56:1261-70
NASH: Changes in NAS score between biopsies

**Nonalcoholic fatty liver disease activity score (NAS)**

- **Steatosis: Brunt score.**
  - 0, absent steatosis
  - 1, <33%
  - 2, 33-66%
  - 3, ≥66%
- **Lobular inflammation:**
  - 0, no foci.
  - 1, <2 foci per 200× field.
  - 2, 2-4 foci per 200× field.
  - 3, >4 foci per 200× field.
- **Cytologic ballooning:**
  - 0, none.
  - 1, few balloon cells.
  - 2, many cells/prominent ballooning.

**Proportion of patients with change in NAS score**

- Decrease: 24%
- No change: 31%
- Increase: 45%

Macías et al. Hepatology 2012;56:1261-70
Persistence of or progression to NASH (NAS score ≥5)

Initial biopsy

NAS≥5
16% (n=24)

NAS<5
84% (n=122)

Final biopsy

Persistence of steatohepatitis
N = 9

Progression to steatohepatitis
N = 18

Fibrosis progression ≥1 stages was associated with persistence/progression to steatohepatitis (AOR [95% CI]=2.4 [1.01-5.7], p=0.047)

Macías et al. Hepatology 2012;56:1261-70
Changes in steatosis measured by CAP in HIV-infected

• **Design:** Prospective cohort study (November 30\(^{th}\), 2011-October 30\(^{th}\), 2013).

• **Patients:** Consecutive HIV-infected patients attended at 2 outpatient clinics (Spain).

• **Follow-up:** 12 months. Hepatic transient elastography examination with CAP scheduled every 6 months.

Baseline: Date of the first CAP measurement.

Macías et al. HIV Med 2016; 17:766-773
Factors associated with CAP changes

- BMI increase: Yes, 14; No, 4
- HIV RNA undetectable: Yes, 15; No, -1
- FPG increase: Yes, -30; No, -4
- Triglyceride increase: Yes, -11; No, 5
- Raltegravir: p=0.024; p<0.001; p=0.018

CAP median (Q1-Q3) change between baseline and 12 months

Multivariate analysis
Only BMI change associated with change in CAP [B (SD): 9.03 (1.9), p<0.001]

Macías et al. HIV Med 2016; 17:766-773
Changes in steatosis measured by CAP in HIV-infected patients: Canadian experience

- **Design**: Single center, Canada (Sept 2013-Sept 2016).
- **HS progression**:
  - Development of CAP>248 dB/m
  - Transition to severe HS, CAP<292 dB/m
- **Independent associations (hazard ratio)**:
  - BMI (per Kg/m²): 1.09 (1.03–1.17), p<0.05
  - HCV-coinfection (Yes vs. No): 0.51 (0.27–0.96), p <0.05

N=232
Changes in liver stiffness in HIV-infected patients with steatosis

- **Design**: Single center, Canada (Sept 2013-Sept 2016).
- **Fibrosis progression**:
  - Development of LSM >7.1 KPa
  - Transition >12.5 KPa
- **Independent associations (hazard ratio)**:
  - Any HS: 4.18 (1.21–14.5), p<0.05
  - Duration of HIV infection (per 10 yr): 1.43 (1.02–2.12), p <0.05

Natural history of steatosis (& NAFLD) in HIV

• Incomplete: Hard clinical end-points?

• Factors associated with steatosis progression:
  – Metabolic factors: BMI
  – ART
    • Obsolete: ddX
    • But, EFV?, INSTI?
NAFLD in HIV-infected patients

- Prevalence
- Natural history and risk of progression
- Factors associated with NAFLD:
  - Metabolic risk factors
  - ART?
  - Genetics
- Management
Changes in liver steatosis after switching efavirenz to raltegravir: The STERAL study

Randomized, controlled, open label, phase 4 clinical trial

- CAP ≥ 238 dB/m, indicative of steatosis involving >10% of hepatocytes.
- Daily alcohol intake < 50 g for men and < 40 g for women.
- Plasma HIV RNA < 50 copies/ml for ≥ 24 weeks in, at least, two visits.

![Diagram showing treatment regimens]

- **Baseline**
  - EFV + TDF/FTC or ABC/3TC

- **24 weeks**
  - RAL 400 mg BID + TDF/FTC or ABC+3TC

- **48 weeks**
  - EFV + TDF/FTC or ABC+3TC

CAP evaluations
Median CAP values during the follow-up by treatment group

- **Raltegravir group (N=19)**
  - Baseline: 260 dB/m
  - 24 weeks: 273 dB/m
  - 48 weeks: 250 dB/m

- **Efavirenz group (N=20)**
  - Baseline: 285 dB/m
  - 24 weeks: 273 dB/m
  - 48 weeks: 250 dB/m

**P-values:**
- Baseline to 24 weeks: P=0.607
- Baseline to 48 weeks: P=0.035
Proportion of patients without significant steatosis (CAP <238 dB/m) at week 48

- Raltegravir group: 9/19 (47%) with P=0.029
- Efavirenz group: 3/20 (15%)
Body mass index by treatment group at week 48

p=0.084

Median (Q1-Q3) BMI at 48 week

Raltegravir: 27.6 Kg/m² (24.3-31)
Efavirenz: 25.5 Kg/m² (23.8-29.9)
ART & FLD in HIV infection

- ddX are highly steatogenic, so what? Other ARV drugs might also be “steatotoxic”.

- Signals in previous studies obscured by metabolic factors.

- Steatosis can regress after switching to safer and less toxic drugs, i.e. from efavirenz to raltegravir.
NAFLD in HIV-infected patients

• Prevalence

• Natural history and risk of progression

• Factors associated with NAFLD:
  – Metabolic risk factors
  – ART?
  – Genetics

• Management
Adiponutrin: Yes or no?

- **PNPLA3** gene (SNP rs738409): Major genetic determinant of NAFLD. Replicated in the general population of different ethnicities.

- **Contradictory results in HIV infection:**
  - *PNPLA3*_rs738409 related to steatosis in HIV-infected MSM, but not among HIV-uninfected MSM\(^1\).
  - Not replicated in a larger sample of patients\(^2\).
  - Lack of association in HIV/HCV-coinfected patients\(^3,4\).

- GWAS in the HIV-infected population necessary.

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Management (NAFLD & FLD)

- Normal liver
- Fatty liver

Diet & exercise

Genetic factors

Fat accumulation in the cytosol

Mitochondria disfunction

Oxidative stress

Metabolic factors (Obesity, T2DM, dyslipidemia)

NRTI, EFV exposure

Secondary FLD

Summary

• Steatosis, mainly NAFLD, is frequent in HIV infection and can induce fibrosis progression.

• Factors associated with hepatic steatosis in HIV infection:
  – Metabolic factors: TRUE NAFLD
  – Antiretroviral drugs: Keep in mind
    • EFV, switching to RAL can induce regression
  – Specific genetics?

• Management = HIV-negative + Review ART
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