NAFLD (Non-Alcoholic Fatty Liver Disease): an emerging problem?

Dr Lucy Garvey
Consultant HIV/GUM
St Mary’s Hospital

lucy.garvey@imperial.nhs.uk
@lucy_garvey
NAFLD SPECTRUM

‘Presence of hepatic steatosis (>5%) in absence of a secondary cause’
NAFLD – no secondary cause

• Significant alcohol consumption
  • UK (2016) >14 units/week *(previously 14u women, 21u men)*

• Drugs - amiodarone, methotrexate, corticosteroids, tamoxifen, antidepressants, antipsychotics, valproate, tetracyclines, **ddl and d4T (microvesicular steatosis)**

• Starvation and malnutrition, TPN
• Metabolic disorders (Wilson’s disease)
• HCV (G3)
• Fatty liver of pregnancy /HELPP
NAFLD PROGRESSION

Simple steatosis
• 80-90% no progressive liver disease
• Good prognosis

Two-way dynamic process
Interval re-staging needed

RISK FACTORS FOR NAFLD

- Obesity (BMI ≥ 30)
- Dyslipidaemia
  - high triglycerides (≥1.7mmol/L)
  - low HDL-cholesterol (<1mmol/L men, <1.3 women)
- Type 2 diabetes
- Metabolic syndrome
- Wide waist circumference (≥102 cm men, ≥88 cm women)

**Most NAFLD diagnosed following incidental findings (LFTs or US)**
**NICE guidelines on NAFLD anticipated June 2016 – move to targeting T2 DM and metabolic syndrome patients?**
NAFLD MORTALITY

- n=420 biopsy confirmed NAFLD, mean FU 7.6 yrs
- CVD and malignancy leading causes of death
- Liver disease 3rd cause of death (vs 13th in general population)
- Higher mortality with older age, impaired fasting glucose, liver stage/cirrhosis
NAFLD fibrosis F3+ had significantly increased mortality (HR 3.3, 95% CI 2.27-4.76, p< 0.001)
Death from CVD, HCC, infection, and cirrhosis all significantly increased compared to reference population

Ekstedt M et al Hepatology, Vol.61, No.5, 2015
Prevalence NAFLD ~20% in different global settings

Studies using a variety of criteria and diagnostic techniques
NAFLD IN UK

• Estimated 33% have NAFLD, and 2-5% have NASH\(^1\)
• Increasing indication for liver transplant (15-20%)
OBESITY INCREASING IN UK

PERCENTAGE OF ADULT POPULATION WHO ARE OBESE (WHO, 2014)

Map of excess weight


www.theguardian.com 4.2.14
THE METABOLIC SYNDROME

Heart Disease  Lipid Problems  Hypertension  Type 2 Diabetes

Dementia  Cancer  Polycystic Ovarian Syndrome  Non-Alcoholic Fatty Liver Disease
LIVER DISEASE IN HIV

HIV – NAFLD or NON-NAFLD?

• Pre-ART era (HIV wasting, opportunistic infections)

• Early ART era (mitochondrial toxicity, lipodystrophy and metabolic disorders from early ARVs – NRTIs / PIs)

• Excluded from most NAFLD studies......

• Modern CART era now recognised risk of ‘classic NAFLD’
  – BMI, waist circumference, abdominal visceral fat, IR, older age
  – ?ARV exposure ?immune activation ?PNPLA3 non-CC genotype
The Changing Epidemiology of Liver Disease in HIV Patients

Vincent Soriano¹, Pablo Barreiro¹ and Kenneth E. Sherman²

¹Department of Infectious Diseases, Hospital Carlos III, Madrid, Spain; ²Division of Digestive Diseases, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Figure 2. Time trends in liver disease etiologies in HIV patients. DAA: direct-acting antivirals; TDF: tenofovir; IDU: intravenous drug users; NAFLD: non-alcoholic fatty liver disease; DILI: drug-induced liver injury; HEV: hepatitis E virus.
## NAFLD PREVALENCE IN HIV

<table>
<thead>
<tr>
<th>COHORT</th>
<th>N</th>
<th>DIAGNOSTIC METHOD</th>
<th>PREVALENCE</th>
<th>NAFLD ASSOCIATIONS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price JC et al MACS 2007</td>
<td>n=465</td>
<td>CT liver-spleen attenuation ratio &lt;1</td>
<td>13%</td>
<td>Visceral fat HOMA-IR PNPLA3 non-CC genotype <strong>D-drug exposure</strong> Non—black ethnicity</td>
<td>92%ART 90%&lt;50 HCV 12% 35% on statin</td>
</tr>
<tr>
<td>Nishijima et al 2014 Japan</td>
<td>n=435</td>
<td>USS</td>
<td>31%</td>
<td>High BMI Dyslipidaemia Higher ALT/AST ratio <strong>No association ART/d-drugs</strong></td>
<td>~50% VL &lt;50</td>
</tr>
<tr>
<td>Guaraldi et al 2008 US</td>
<td>n=225</td>
<td>CT liver-spleen attenuation ratio &lt;1.1</td>
<td>37%</td>
<td><strong>Non-obese, lipoatrophic men</strong> ALT/AST ratio Waist circumference <strong>Longer NRTI exposure</strong></td>
<td>72% normal LFT</td>
</tr>
<tr>
<td>Crun-Cianflone et al 2011</td>
<td>n=223</td>
<td>CT liver-spleen attenuation ratio &lt;1</td>
<td>13%</td>
<td>Coronary artery calcification</td>
<td>96% male 83% ART</td>
</tr>
<tr>
<td>Crun-Cianflone et al 2009</td>
<td>n=216</td>
<td>USS (+ biopsy if indicated)</td>
<td><strong>31% NAFLD 20% of biopsies (n=55) =NASH</strong></td>
<td>Waist circumference High TGI Lower HDL Caucasian <strong>Past/current d4T (p=0.05)</strong></td>
<td>50% VL&lt;50 87% normal LFT</td>
</tr>
</tbody>
</table>
# NAFLD Prevalence in HIV

<table>
<thead>
<tr>
<th>COHORT</th>
<th>N</th>
<th>DIAGNOSTIC METHOD</th>
<th>PREVALENCE</th>
<th>NAFLD ASSOCIATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mohammed SS et al 2007</td>
<td>n=26 HIV+ n=25 HIV-</td>
<td>Liver biopsy</td>
<td>All included</td>
<td>HIV+ lower BMI (26 vs 30)</td>
</tr>
<tr>
<td>Toronto</td>
<td>all with NAFLD</td>
<td>proven</td>
<td></td>
<td>HIV+ more physical activity 'lean NASH' in HIV+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Similar fibrosis stage and IR</td>
</tr>
<tr>
<td>Morse et al NIH HIV/AIDS</td>
<td>n=62</td>
<td>Liver biopsy</td>
<td>NAFLD 73%</td>
<td>BMI</td>
</tr>
<tr>
<td>US 2015</td>
<td>Raised LFTS no other cause found</td>
<td></td>
<td>(NASH 55%, bridging fibrosis 17%)</td>
<td>Waist circumference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IGT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low HDL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PNPLA3 non-CC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>On CART&gt;1y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(median 13y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31% obese</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median ALT 72</td>
</tr>
</tbody>
</table>
Multiple potential targets for future treatment?
DIAGNOSIS/STAGING NAFLD

1. Steatosis
2. NASH
3. Fibrosis

• Predict prognosis for developing CLD
• Intervene (and halt/reverse)
• Screen cirrhotics for portal hypertension and HCC

• *Ideal test gives all 3 pieces of information....and is non-invasive...*
# DIAGNOSIS/STAGING NAFLD

<table>
<thead>
<tr>
<th></th>
<th>Steatosis</th>
<th>Steato-hepatitis (NASH)</th>
<th>Fibrosis/cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
<td><strong>US liver</strong></td>
<td><strong>MR spectroscopy?</strong></td>
<td><strong>Fibroscan ®</strong></td>
</tr>
<tr>
<td></td>
<td>Controlled Attenuation Parameter (CAP) score &gt;250</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR (fat fraction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR spectroscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td><strong>Fatty Liver Index (FLI) &gt;60</strong></td>
<td><strong>Cytokeratin-18</strong></td>
<td><strong>NAFLD fibrosis score</strong></td>
</tr>
<tr>
<td></td>
<td>SteatoTest</td>
<td>NashTest</td>
<td>FIB-4</td>
</tr>
<tr>
<td></td>
<td>NAFLD Liver Fat Score</td>
<td>ALT</td>
<td>APRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ELF test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FibroTest</td>
</tr>
<tr>
<td>Histology</td>
<td>Liver biopsy</td>
<td>Liver biopsy</td>
<td>Liver biopsy</td>
</tr>
</tbody>
</table>

Over two-thirds of NAFLD cases have a normal ALT
FATTY LIVER INDEX (FLI)

AUROC of 0.84 to detect liver steatosis in a general population with low prevalence of T2 DM
## DIAGNOSIS/STAGING NAFLD

<table>
<thead>
<tr>
<th></th>
<th>Steatosis</th>
<th>Steato-hepatitis (NASH)</th>
<th>Fibrosis/cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imaging</strong></td>
<td>US liver</td>
<td>MR spectroscopy?</td>
<td><strong>Fibroscan ®</strong></td>
</tr>
<tr>
<td></td>
<td>Controlled Attenuation Parameter (CAP) score &gt;250</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR (fat fraction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MR spectroscopy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>Fatty Liver Index (FLI) &gt;60</td>
<td>NashTest</td>
<td><strong>NAFLD fibrosis score</strong></td>
</tr>
<tr>
<td></td>
<td>SteatoTest</td>
<td>ALT</td>
<td>APRI</td>
</tr>
<tr>
<td></td>
<td>NAFLD Liver Fat Score</td>
<td>Cytokeratin-18</td>
<td>FIB-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ELF test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>FibroTest</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Liver biopsy</td>
<td>Liver biopsy</td>
<td>Liver biopsy</td>
</tr>
</tbody>
</table>
US elastography:
Measures velocity of 50MHz shear wave passing through liver and converted to a stiffness score (kPa)

Controlled Attenuation Parameter (CAP):
Measures decrease in US waves through liver
Expressed in decibel per meter (dB/m)
CAP scores > 250-280 dB/m suggest steatosis

BMI > 30kg/m²
FIBROSCAN® IN NAFLD

- Fibroscan® scoring card converts stiffness score to METAVIR fibrosis stage F0 (no fibrosis) to F4 (cirrhosis or advanced fibrosis)
LIVER BIOPSY

• Diagnostic:
  – Co-existing aetiologies of liver disease
  – Elevated iron
  – Persistent ALT elevation without cause

• To stage NAFLD:
  – Elevated non-invasive fibrosis measures
  – Patients at increased risk of NASH / fibrosis
  – Patients with metabolic syndrome
  – (?)HIV

AASLD Position Paper: Liver Biopsy. DC Rockey et al Hepatology 2009,
AASLD NAFLD Guidelines. Chalasani et al Hepatology 2012
TREATING NAFLD?
MANAGEMENT– DIET / EXERCISE

• 5% weight loss improves steatosis and LFTs\(^1,2\)
• 7-10% weight loss improves steatosis and NASH\(^1,2\)
• Exercise 3x week 30-60 mins reduced liver fat (MRS) –effect on NASH unknown\(^3-5\)
• Hepatic improvements are proportional to intensity of weight loss and/or exercise and must be sustained

• Significant decline in NAFLD prevalence plus NASH resolution @1 and 5 yrs following bariatric surgery in obese patients\(^6\)

EFFECT OF WEIGHT LOSS ON ALT

Fig. 2

### OTHER THERAPIES?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Evidence for use</th>
<th>Indicated for NAFLD/NASH?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong> (insulin sensitizer)</td>
<td>Small open label studies showed ↓ in AST and IR? weight loss confounded RCT vs placebo (n=48) no difference Meta-analysis no additional effect on ALT or histology versus lifestyle modification alone</td>
<td>Not recommended beyond DM</td>
</tr>
<tr>
<td><strong>Pioglitazone</strong> (insulin sensitizer)</td>
<td>PIVENs study 96 wk RCT in non-diabetic patients pioglitazone 30mg vs placebo vs vit E: Pioglitazone reduced steatosis and inflammation (not fibrosis) despite some weight gain(^1) Safety concerns due to increased congestive heart failure limit use</td>
<td>AASLD not recommended</td>
</tr>
<tr>
<td><strong>Vitamin E</strong> (antioxidant)</td>
<td>Multiple studies with various doses and formulations – reduction in transaminases, steatosis and inflammation. No effect on fibrosis. PIVENs study RCT vitamin 800 IU/day superior to placebo (42% vs 19% improvement in NASH histology) Safety concerns: meta-analysis associated with increase in all-cause mortality(^2,3) and haemorrhagic stroke(^4) Recently association to increased rate of prostate cancer reported(^5)</td>
<td>AASLD and BSG recommend with caution in non-diabetic patients with NASH (non-cirrhotic)</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>No trials with liver histological endpoints. Post-hoc analysis of CV outcomes study suggest improved LFTs and CVS outcomes in patients with likely NAFLD. No data to support use specifically for NASH.</td>
<td>Use for dyslipidaemia in NAFLD</td>
</tr>
</tbody>
</table>

THE DASH TO TREAT NASH?

• **Farnesoid X Receptor (FXR) Agonists** (increase BA synthesis):
  – Obeticholic acid (FLINT trial 2b) vs placebo in non-cirrhotic NASH improved NASH histology at 72 weeks (45% vs 21%) and fibrosis (35% vs 19%).
  – 25% pruritus, LDL increases in OCA arm

• **Simtuzumab** (monoclonal antibody as anti-fibrotic)
  – Phase 2 NASH cirrhosis

• **Cenicriviroc** (CCR5 and CCR2 blocker as anti-fibrotic)
  – HIV Phase 2b study comparing liver fibrosis biomarkers over 48 weeks (ELF score)
  – Phase 2 Treatment for NASH fibrosis (HIV negative)

• **Aramchol** (novel FA/BA conjugate) in HIV patients with NAFLD and lipodystrophy (MR study)

Fatty liver on US (incidental)

Persistent raised ALT (>6 months)

Exclude other causes of chronic liver disease

Assess BMI, waist circumference, lipids, HbA1c, BP, exercise, smoking

Assess fibrosis using non-invasive measure (eg Fibroscan®, NAFLD fibrosis score)

Consider biopsy if elevated: eg Fibroscan® >7kPa
Co-existing aetiologies

Cirrhosis
Screen for portal hypertension and HCC

Fibroscan® score <7kPa or low-risk of fibrosis
Advise weight loss 7-10%
Exercise 3+/week
Recommend CVS risk factor treatments
Reduce alcohol
Suppress HIV replication
[Recruit to trials?]

Re-assess at appropriate interval
SUMMARY

• Rising prevalence of NAFLD in general population

• Limited data suggest high rates of NAFLD fibrosis in HIV
  – Suspect if IGT/DM, obese, wide waist, dyslipidaemia, lipodystrophy
  – Atypical phenotype also observed – ‘lean NASH’

• Role of ART in pathogenesis unclear
SUMMARY

• In clinic:
  – persistently elevated LFTs should be ‘worked up’
  – Stage NAFLD, using non-invasive methods where possible (discuss arrangements locally)
  – Biopsy where uncertainty of diagnosis / fibrosis / high risk

• Lifestyle modifications and optimise CVS risk factors

• Likely clinical trials of therapeutic interventions in HIV in near future
ACKNOWLEDGEMENTS

James Maurice
Janice Main
Graham Cooke
Mark Nelson
Mark Thursz
Maud Lemoine
Linda Greene
Nicky Mackie