Professor Mark Thursz

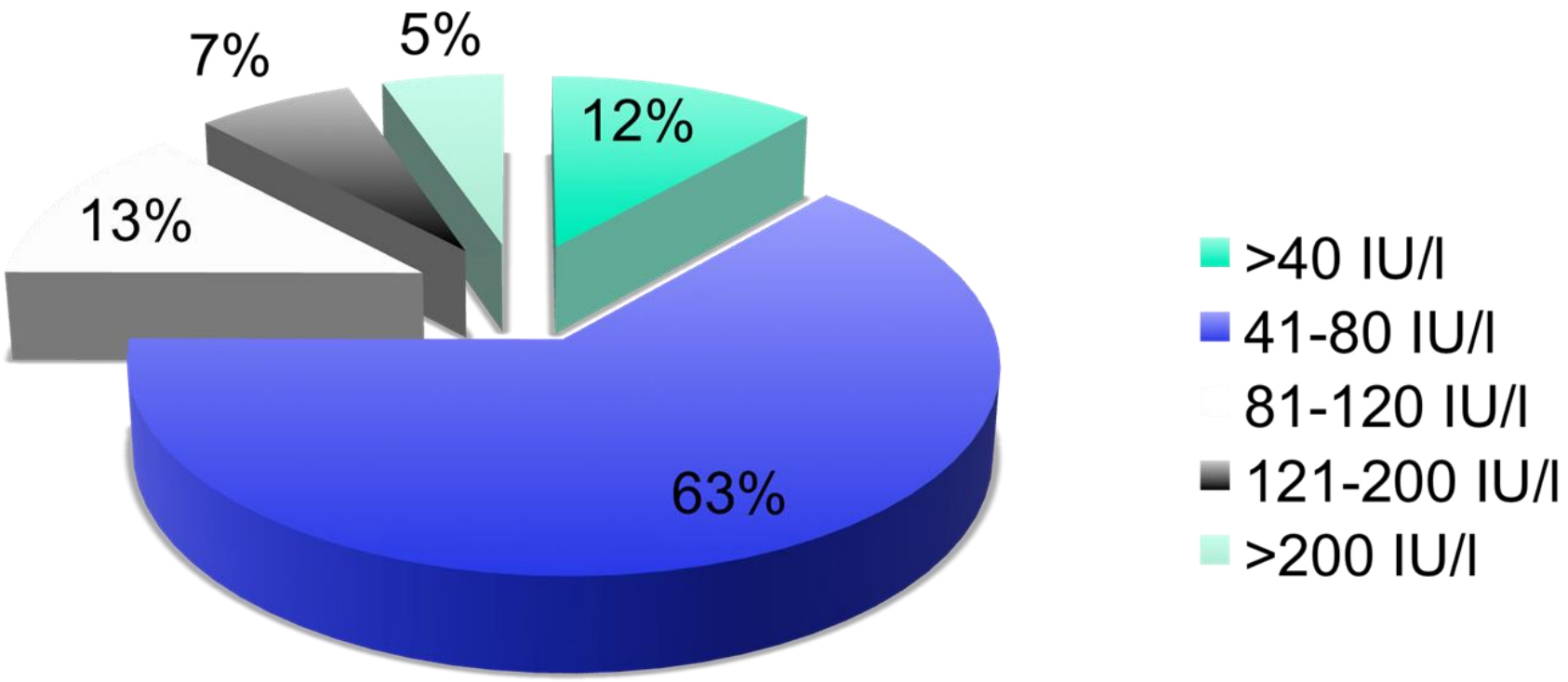
Imperial College Healthcare NHS Trust, London

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Prof Mark Thursz	Consultancy / Speaker fees from Janssen, Gilead, BMS, Abbott
Date	**November 2013**

Treating NASH in HIV infection

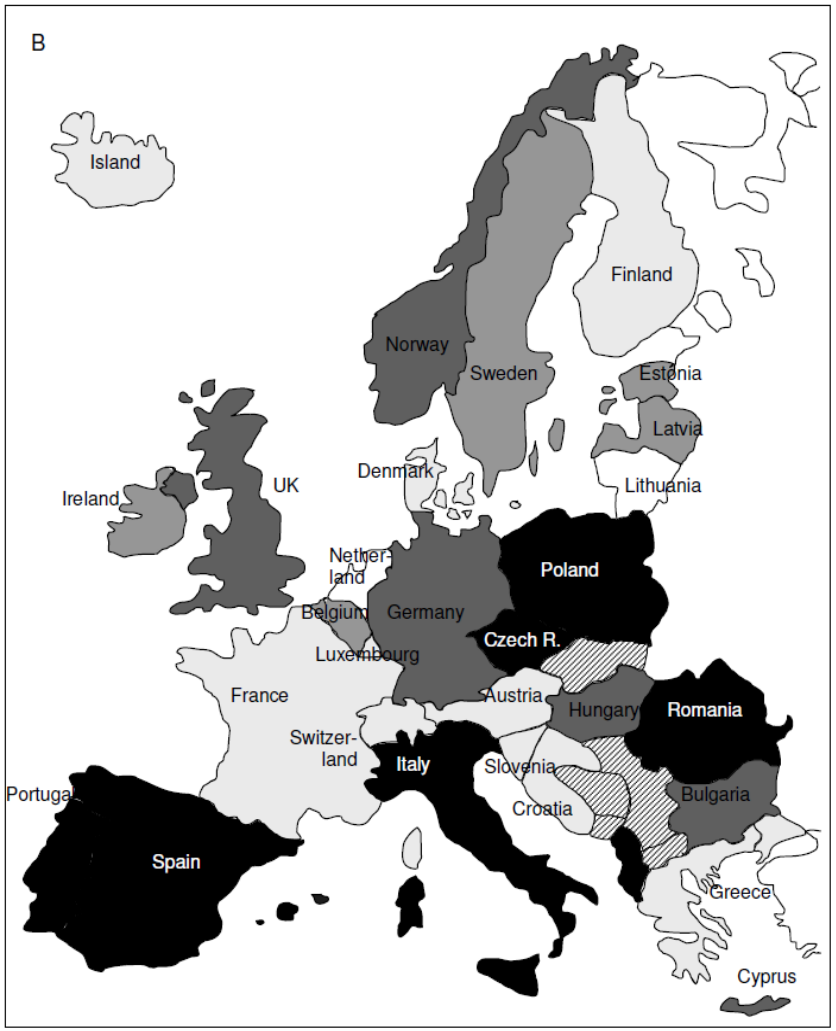
Mark Thursz
Imperial College

ALT



42%of abnormal ALT was attributable to coinfection with HBV or HCV
28% of those scanned had fatty liver.
16% had bridging fibrosis or cirrhosis

European Epidemic of Obesity



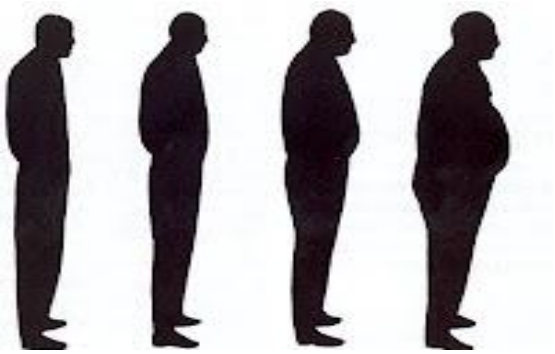
% obese (BMI ≥ 30)

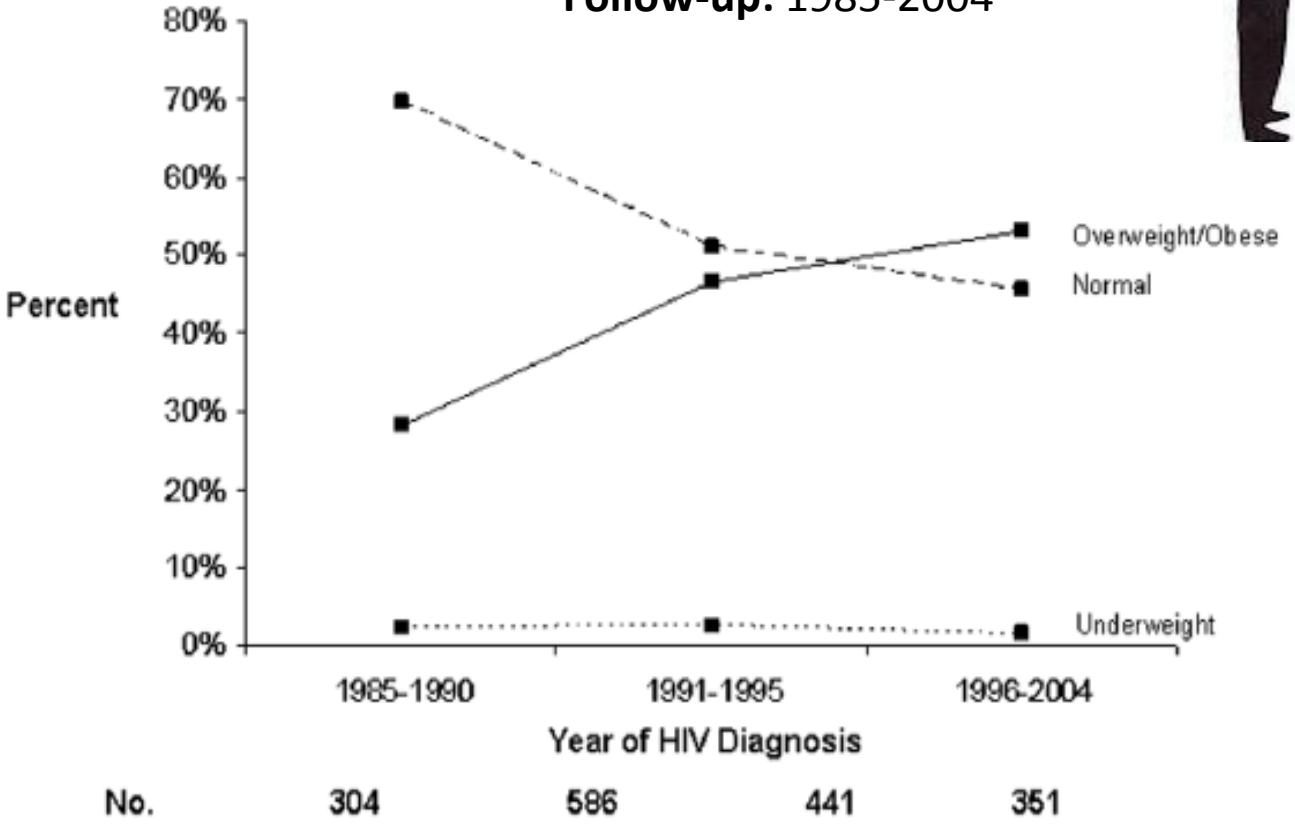
≤ 10	10.1-15	15.1-20	20.1-25	> 25	no data

Berghoefer et al. BMC Public Health 2008;8:200

HIV infected individuals are getting old and fat

n = 1286
Follow-up: 1985-2004



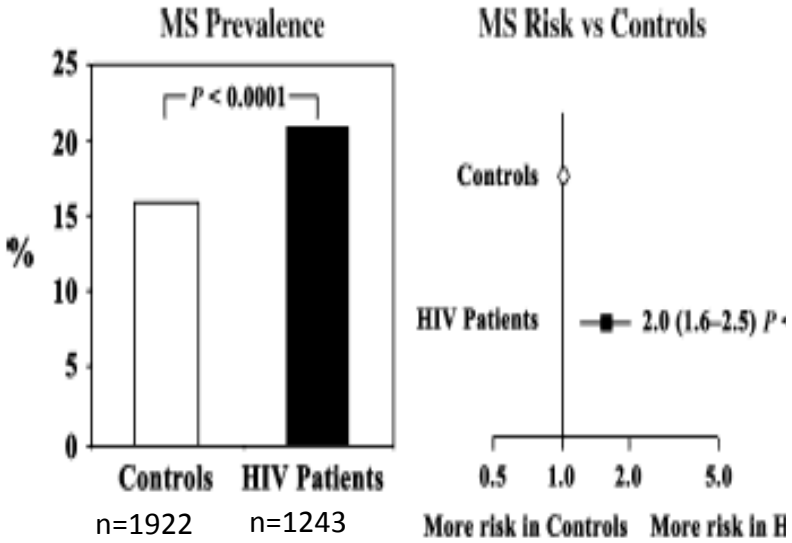


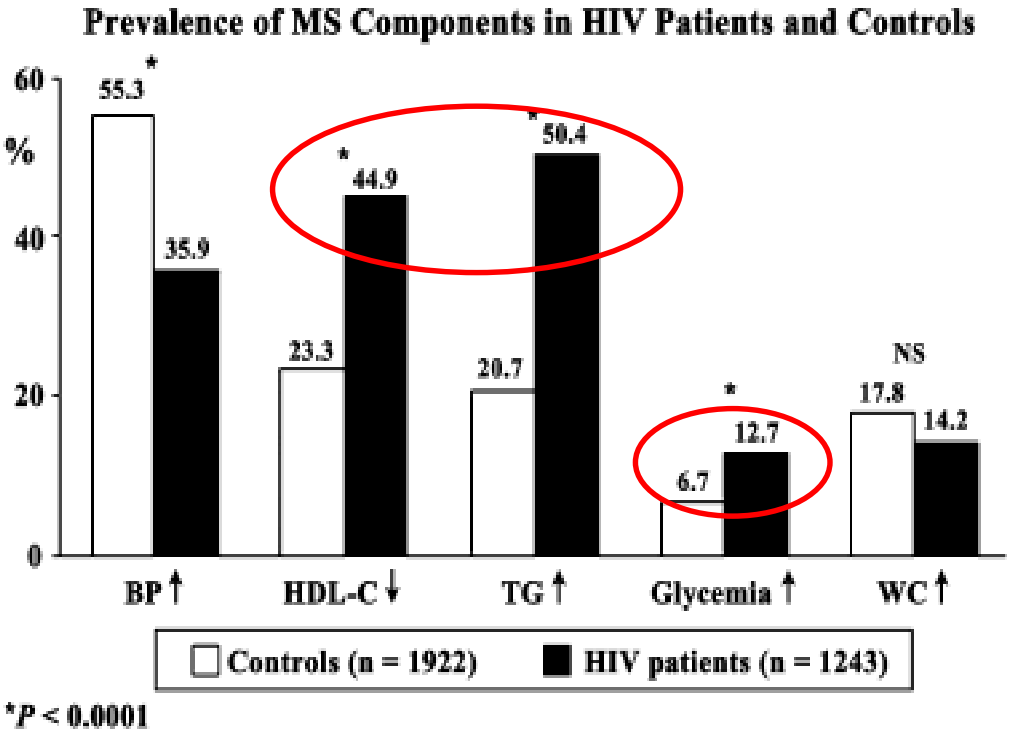
Crum-Cianflone, N et al . PlosOne, 2010

HIV and Metabolic Syndrome

A Comparison With the General Population

Paolo Bonfanti, MD, Cristina Giannattasio, MD,† Elena Ricci, ScD,* Rita Facchetti, ScD,†*
Elena Rosella, MD,‡ Marzia Franzetti, MD,§ Laura Cordier, MD, Luigi Pusterla, MD,‖*
Michele Bombelli, MD,† Roberto Sega, MD,† Tiziana Quirino, MD,¶ and Giuseppe Mancia, MD†

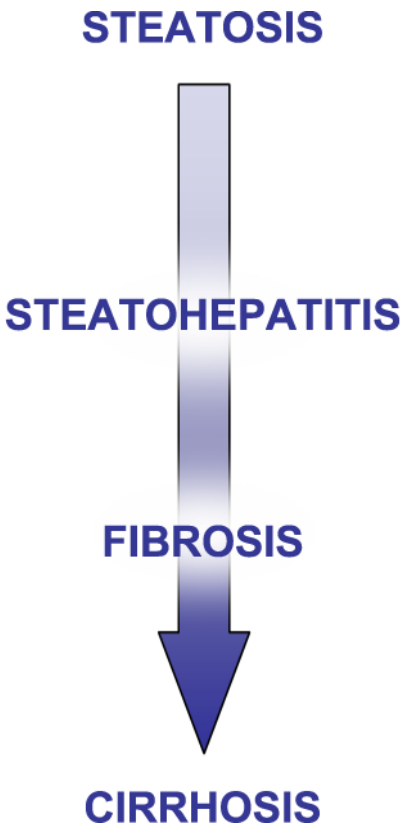




Bofanti, P et al . JAIDS, 2007

NON-ALCOHOLIC FATTY LIVER DISEASE

- NAFLD represents a spectrum of progressive fatty liver disease.
- NASH Clinical Features:
  - Frequently asymptomatic
  - A fluctuating elevation of ALT and AST.
  - A characteristic histological appearance **in the absence of a history of alcohol abuse**.
    - Ideally almost no alcohol intake (<40g/week)
    - Realistically, 210/140g/week M/F

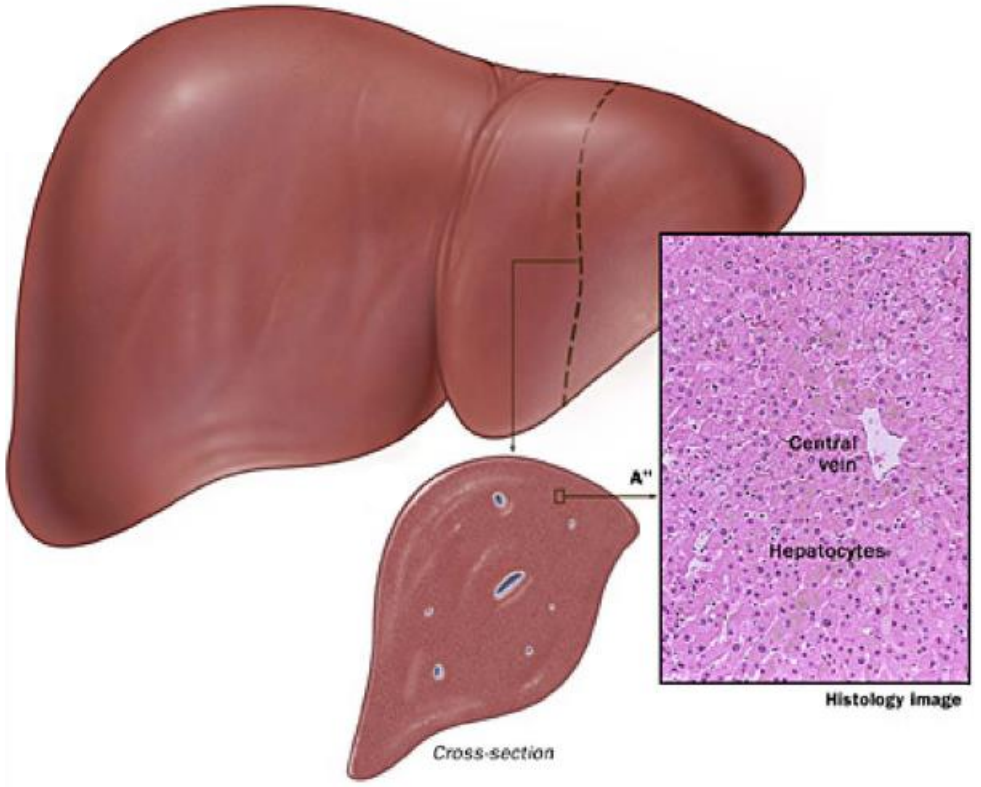


STEATOSIS

STEATOHEPATITIS

FIBROSIS

CIRRHOSIS



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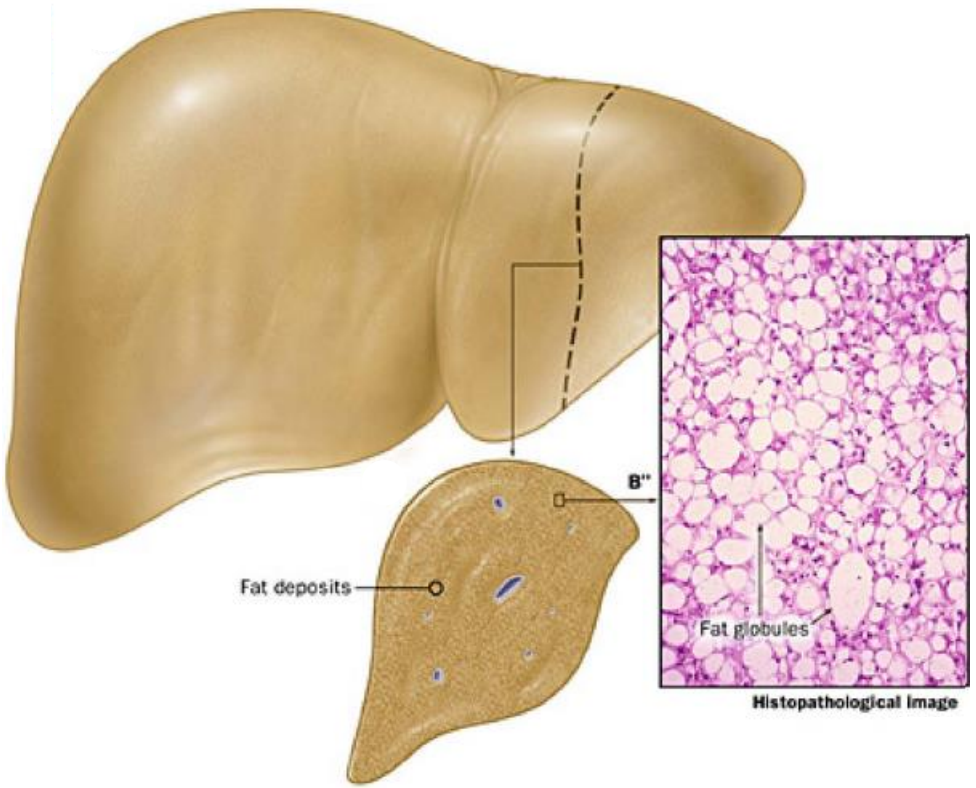

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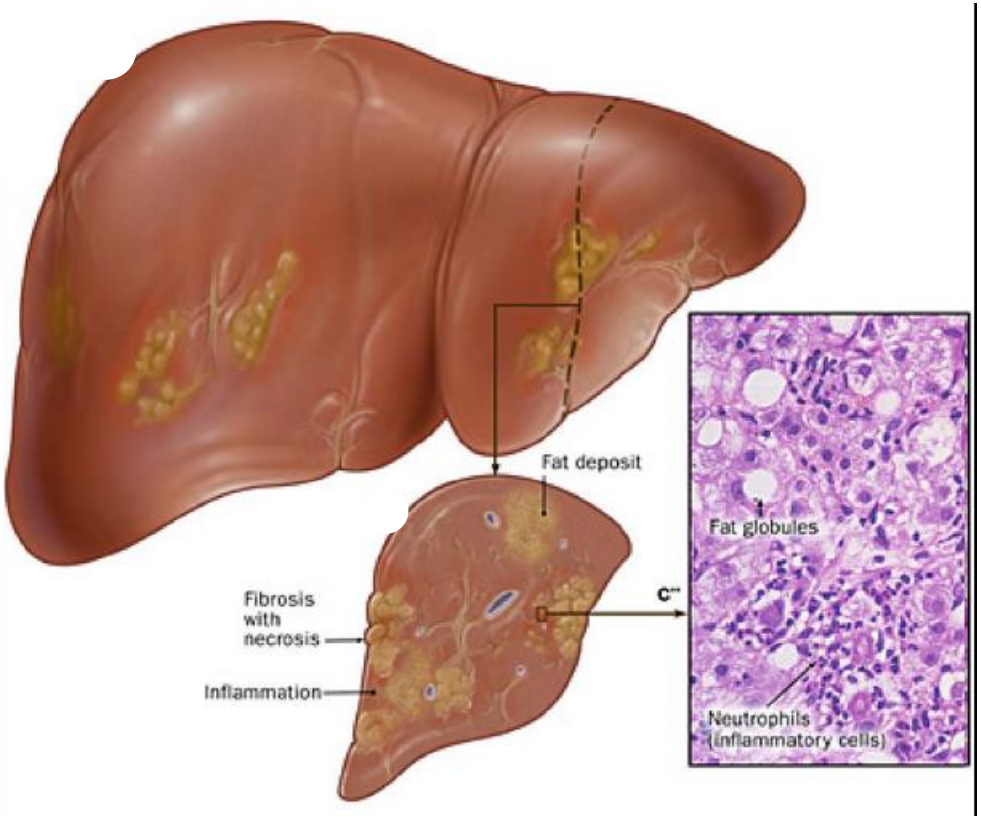

STEATOSIS

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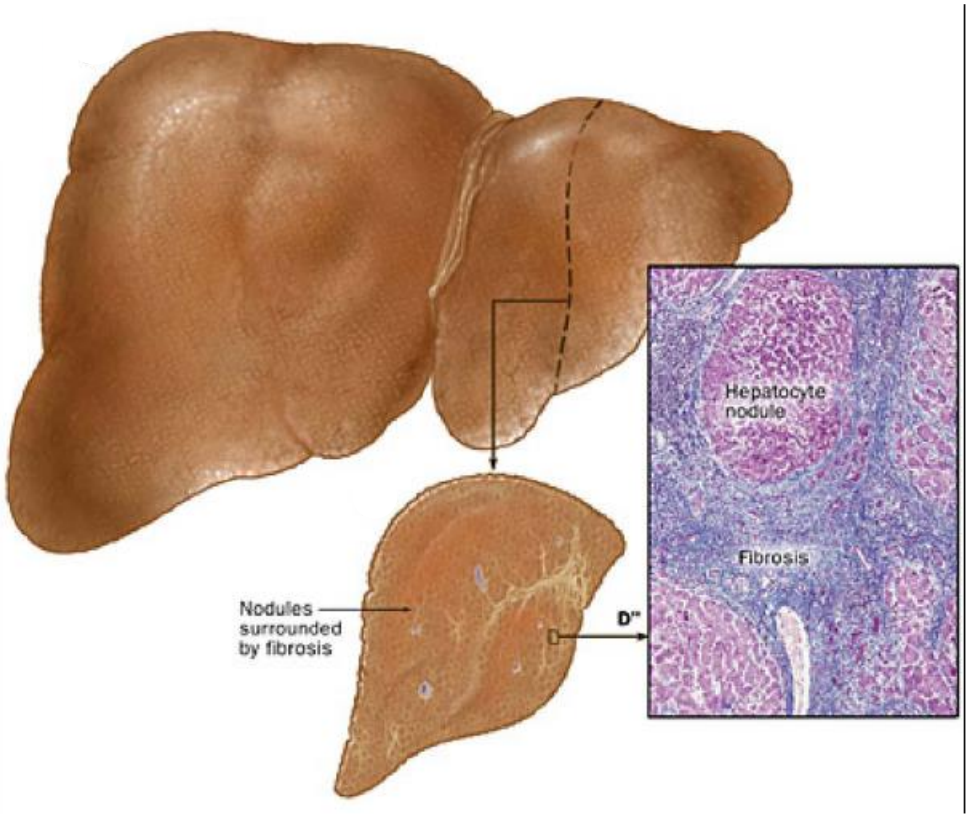
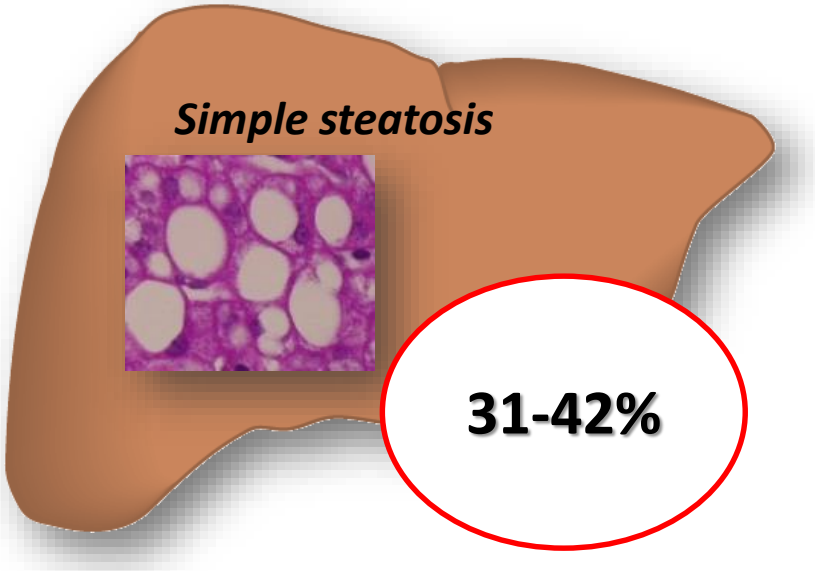
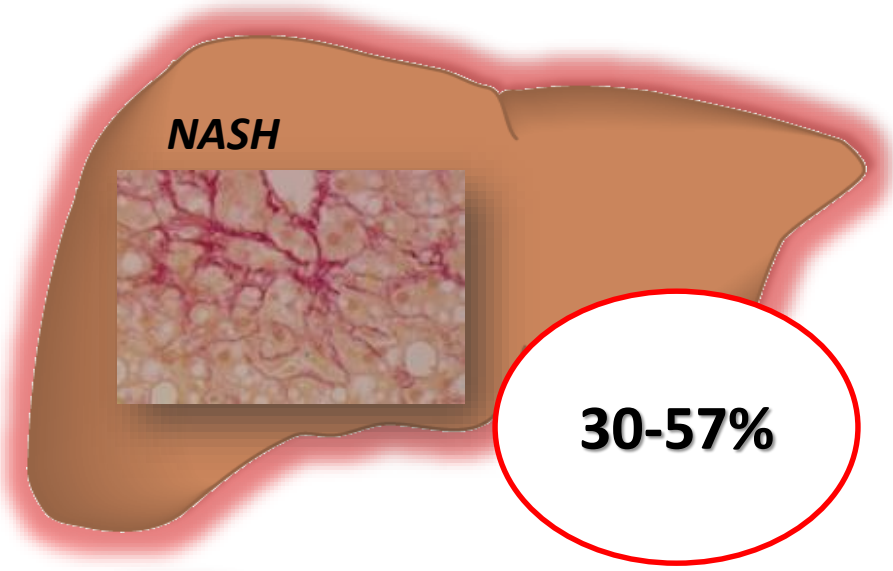
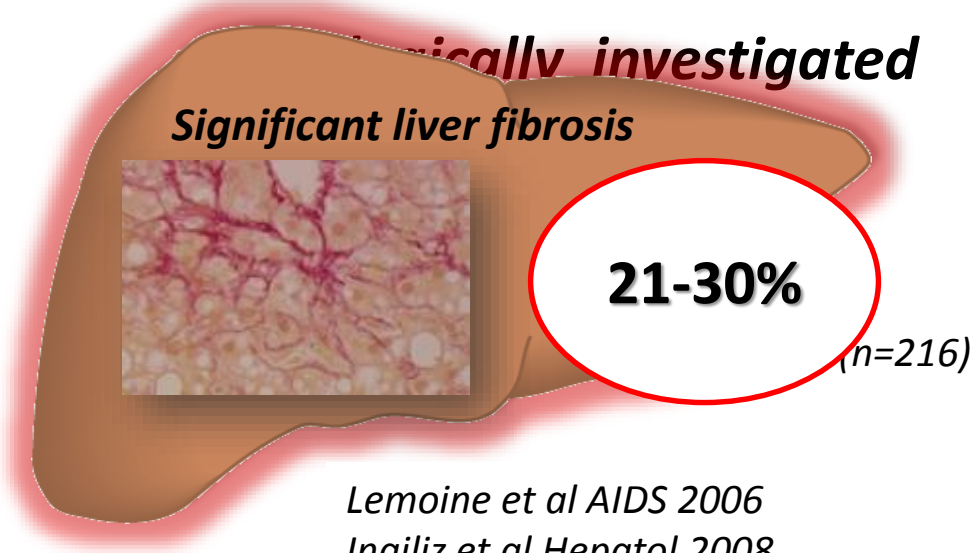






Radiologically investigated

Hadigan et al. J AIDS 2007 (n=33)
Guaraldi CID 2008 (n=225)
Crum-Cianflone N et al. JAIDS 2009 (n=216)



...gically investigated

...(n=216)

Lemoine et al AIDS 2006
Ingiliz et al Hepatol 2008
Mohammed, SS JAIDS 2007

Causes of Death in HIV-infected patients

n = 1876 1996-2006

Cause of death (N = 1597)	N (%)	Incidence rate (95% CI) per 1000 years
AIDS	**792 (49.6)**	**5.12 (4.78-5.49)**
Non-specified AIDS	190 (11.9)	1.23 (1.07-1.42)
AIDS infection	366 (22.9)	2.37 (2.14-2.62)
AIDS malignancy	236 (14.8)	1.52 (1.34-1.73)
Non AIDS malignancy	**189 (11.8)**	**1.22 (1.06-1.41)**
Non-AIDS infection	**131 (8.2)**	**0.85 (0.71-1.01**
CVD[1]	**126 (7.9)**	**0.81 (0.68-0.97)**
MI/IHD[2]	51 (3.2)	0.33 (0.25-0.43)
Stroke	23 (1.4)	0.15 (0.10-0.22)
Other heart disease	52 (3.3)	0.34 (0.26-0.44)
Violence[3]	**124 (7.8)**	**0.80 (0.67-0.96)**
Suicide	48 (3.0)	0.31 (0.23-0.41)
Substance abuse	42 (2.6)	0.41 (0.32-0.52)
Other violent death	34 (2.1)	0.22 (0.16-0.31)
Liver-related	**113 (7.1)**	**0.73 (0.61-0.88)**
Hepatitis-related	63 (3.9)	0.41 (0.32-0.52)
Other liver-related	50 (3.1)	0.32 (0.25-0.43)
Respiratory disease	**25 (1.6)**	**0.16 (0.11-0.24)**
Renal failure	**24 (1.5)**	**0.16 (0.10-0.23)**
Other causes with N<20	**73 (4.6)**	**0.47 (0.38-0.59)**

NAFLD/NASH ?

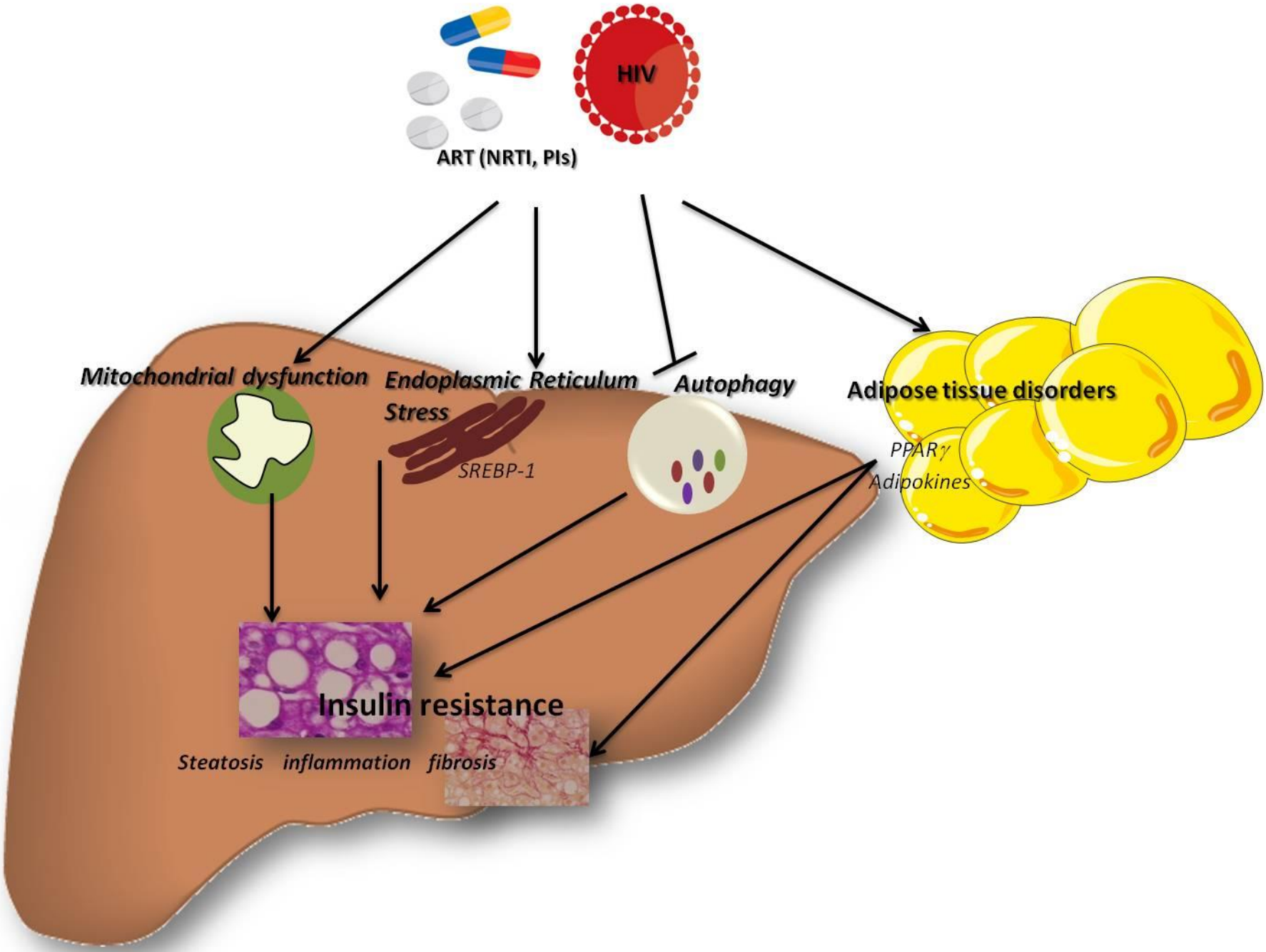
[1]CVD cardiovascular disease (includes MI/IHD, stroke, heart failure/unspecified and other heart disease)

[2]MI/IHD myocardial infarction/ischemic heart disease

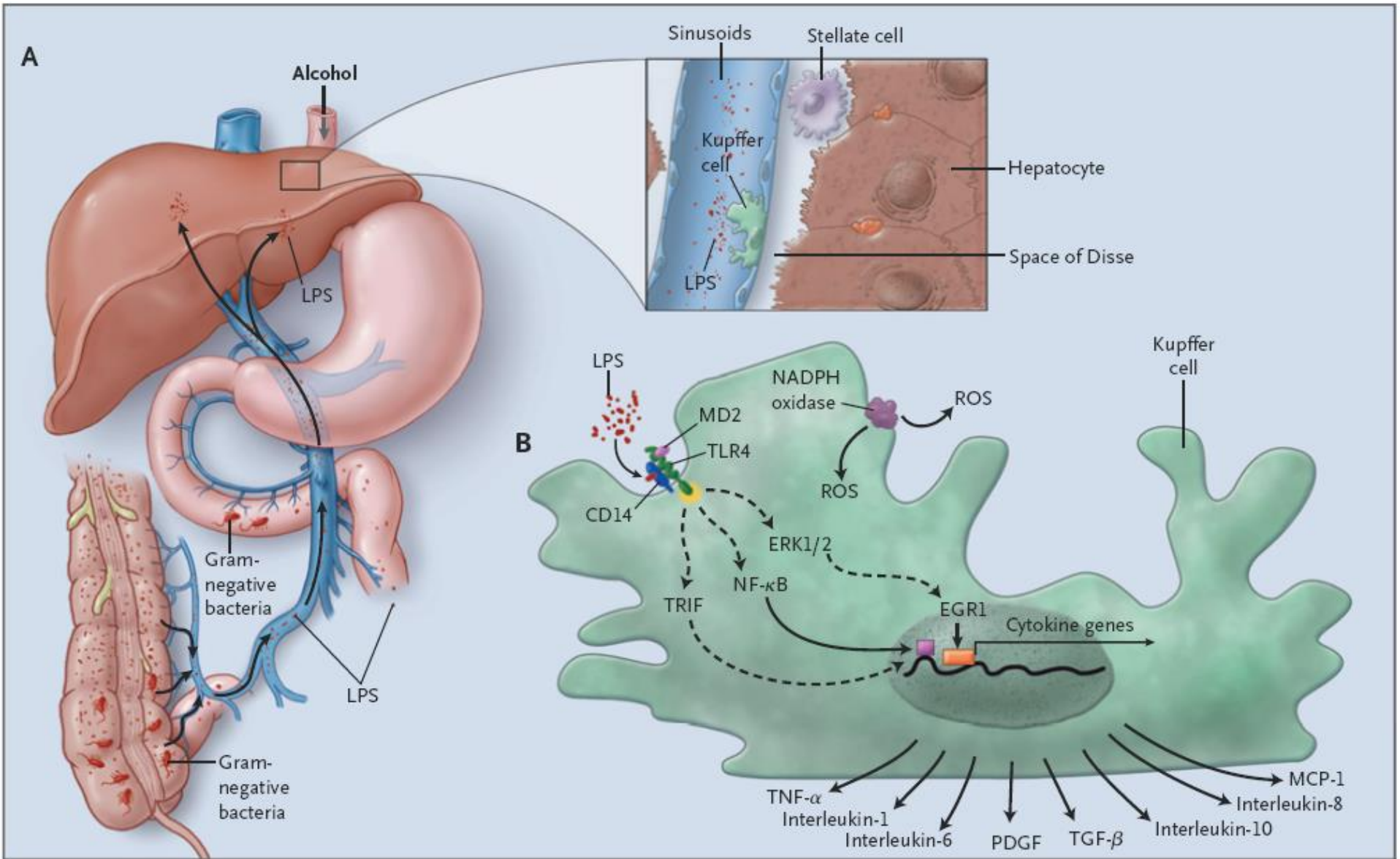
[3]Violent includes homicide, accident, suicide and substance abuse as well as ill-defined violent deaths.

Clin Infect Dis. 2010;50:1387-1396

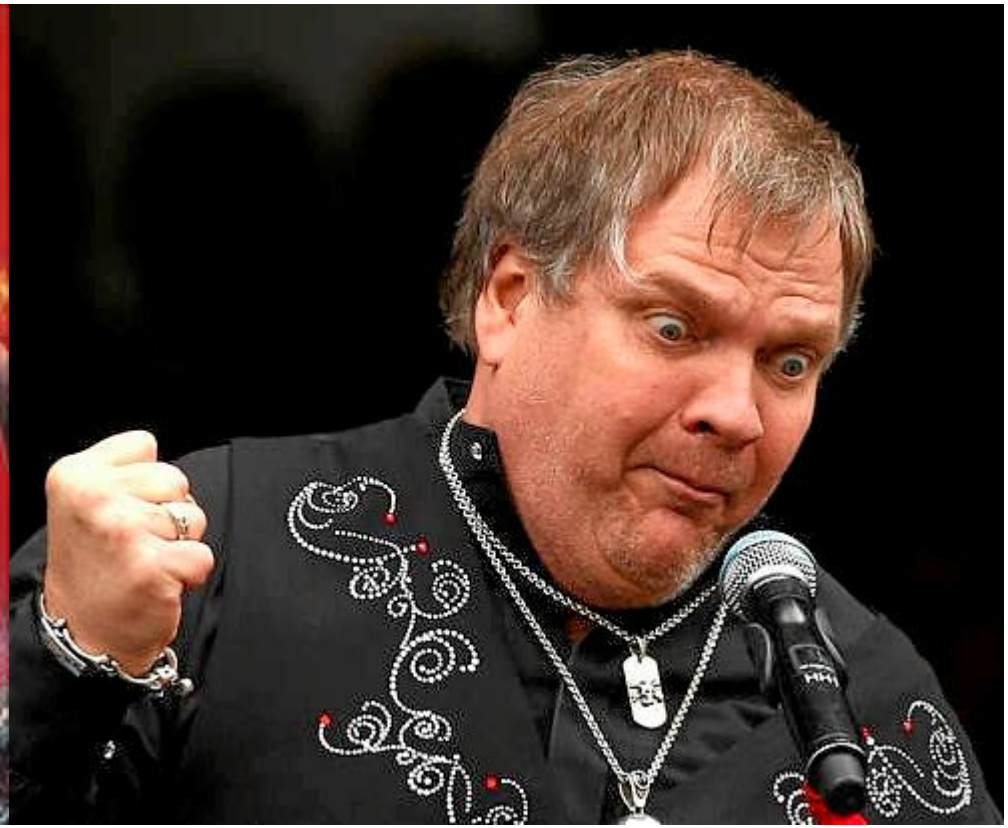
The Antiretroviral therapy Collaboration, CID 2010, May


HIV
ART (NRTI, PIs)
Mitochondrial dysfunction
Endoplasmic Reticulum Stress
SREBP-1
Autophagy
Adipose tissue disorders
PPARγ
Adipokines
Insulin resistance
Steatosis
inflammation
fibrosis

Gut Translocation Exacerbates NAFLD



MEATLOAF



Management

Make the diagnosis

Establish metabolic syndrome components

Assess lifestyle

Therapeutic approaches

Liver specific therapies

Offer clinical trials

Advice and targets

Follow-up

Management MEATLOAF

Make the diagnosis

- Raised ALT and/or steatosis on ultrasound examination
- Low to moderate alcohol c
- No hepatotoxic drugs
- Negative chronic liver dise

Establish metabolic syndrome

Assess lifestyle

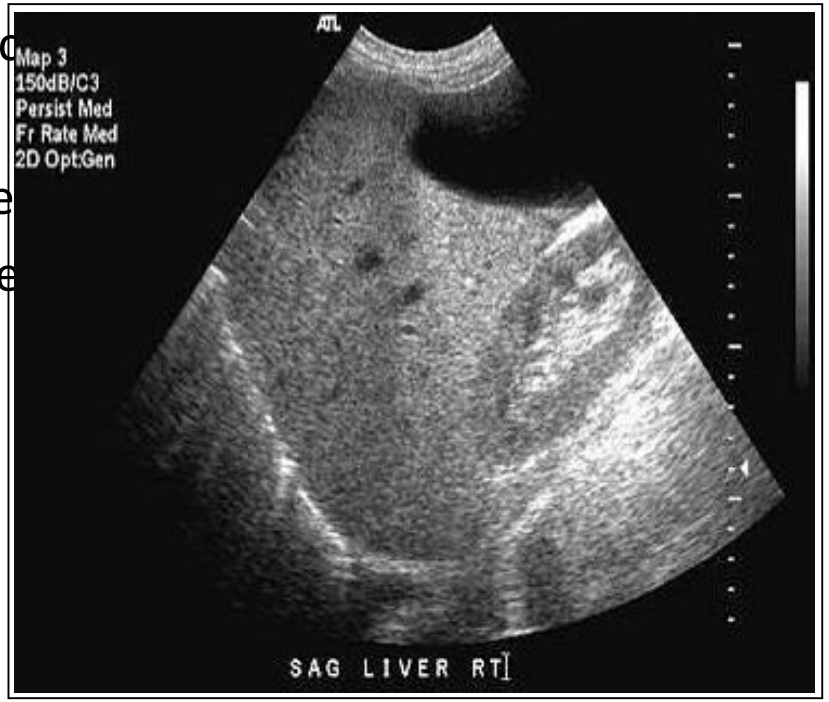
Therapeutic approaches

Liver specific therapies

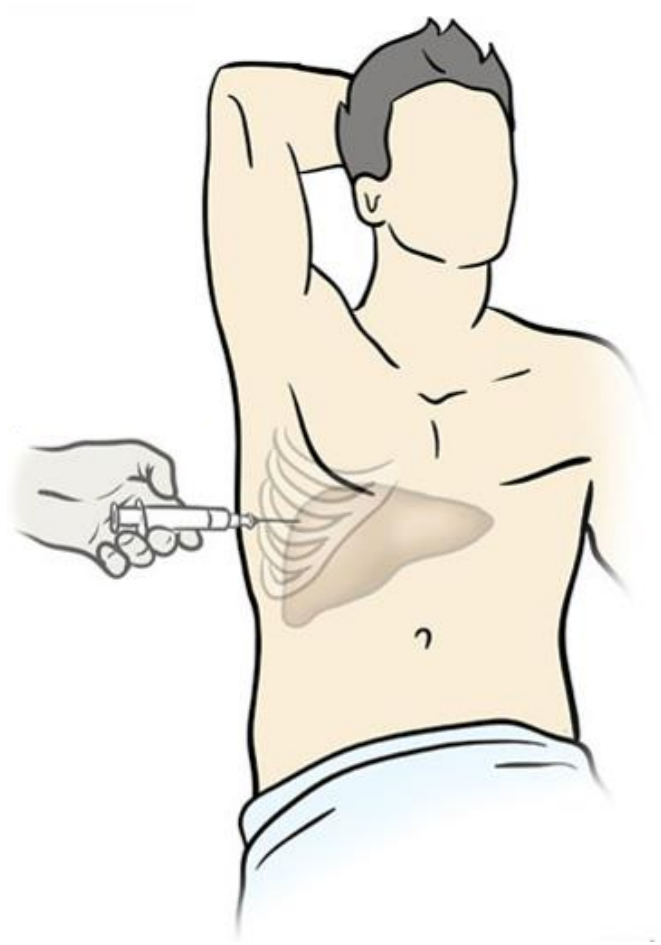
Offer clinical trials

Advice and targets

Follow-up



Is a Biopsy Always Necessary?



- Not always necessary but may be helpful.
- Calculate non-invasive scores
- Consider transient elastography
- Biopsy if:
  - Diagnosis uncertain/poor response
  - Indeterminant or high-risk non-invasive markers
  - ALT > 2 x ULN 3 months
  - Obese or DM or age <50
  - ALT values >80 IU/ml on two occasions.
  - Exclude alternative/secondary pathology
  - Stratify disease progression risk

NASH ACTIVITY SCORE (NAS)

- NAFLD Fibrosis Score=

  -1.675

  + 0.037 x **Age (years)**

  + 0.094 x **BMI (kg/m2)**

  + 1.13 x **IFG/diabetes (yes = 1, no = 0)**

  + 0.99 x **AST/ALT ratio**

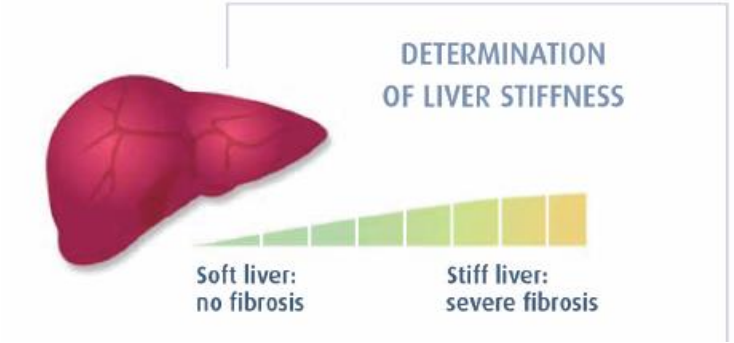
  - 0.013 x **platelet (x109/l)**

  - 0.66 x **Albumin (g/dl)**.

- < -1.455 excludes fibrosis (NPV 88-93%).
- > 0.676 predicts fibrosis (PPV 82-90%).

Angulo et al, Hepatology, 2007

FIBROSCAN


DETERMINATION
OF LIVER STIFFNESS
Soft liver:
no fibrosis
Stiff liver:
severe fibrosis

Management MEATLOAF

Make the diagnosis

Establish metabolic syndrome components

- Hypertension
- Dyslipidaemia
- Obesity
- Diabetes/impaired glucose tolerance

Assess lifestyle

Therapeutic approaches

Liver specific therapies

Offer clinical trials

Advice and targets

Follow-up

NAFLD, the hepatic manisfestation of the Metabolic Syndrome

Central obesity	**Abdominal circumference:** Europeans≥ 94 cm (M) ou ≥ 80 cm (F) Americans: ≥ 102 (M) ≥ 88 cm (F) Asians: ≥≥ 90 cm (M) ≥ 80 cm (F)
High Blood Pressure	Arterial Pression ≥ 130 mmHg and/or ≥ 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 Chol
High blood triglycerides	≥ 1,5 g/L (1,7 mmol/L) or treated hyperTG
High Blood glucose	Glucose ≥ 1 g/L (5,6 mmol/L) or antidiabetic treatement

Alberti, circulation 2009

Management MEATLOAF

Make the diagnosis

Establish metabolic syndrome components

Assess lifestyle

- Detailed dietary history (consider food frequency questionnaire, 7-day food diary)
- Daily activity/occupation
- Formal exercise (type, frequency, duration, intensity)

Therapeutic approaches

Liver specific therapies

Offer clinical trials

Advice and targets

Follow-up

Management MEATLOAF

Make the diagnosis

Establish metabolic syndrome components

Assess lifestyle

Therapeutic approaches

- Dietary advice/dietetic consultation
- Exercise counselling/gym referral
- Pharmacological modification to each component of the metabolic syndrome as per guidelines (eg, NICE)
- Adjust medications according to potential secondary benefit (eg, angiotensin receptor blockers may have antifibrotic effects, GLP-1 agonists may promote weight loss)

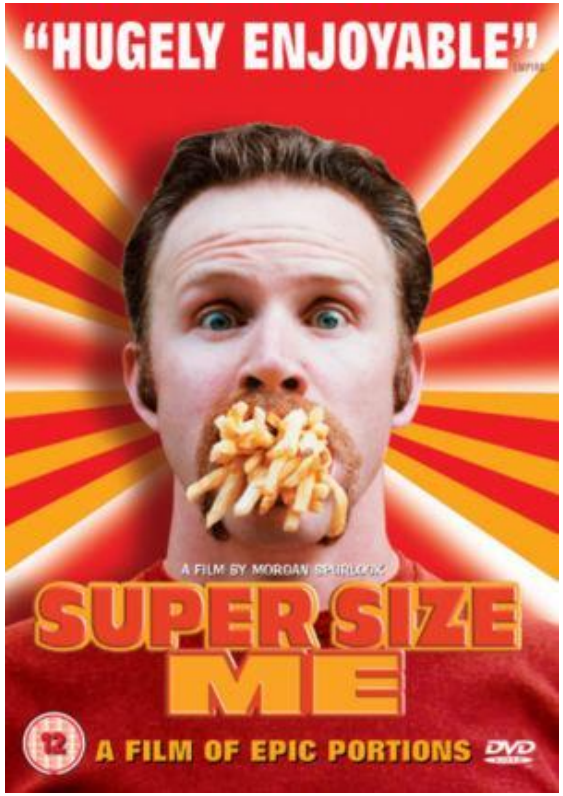
Liver specific therapies

Offer clinical trials

Advice and targets

Follow-up

Diet



- **Dietary Factors**
  - Antioxidant vitamins (Vitamins C & E)
  - Fruit & vegetables
  - Omega-3-fatty acids
  - Fructose content
- **Obesity**
  - Energy (food) intake > Energy expenditure
  - Food portion size

Lifestyle Modification

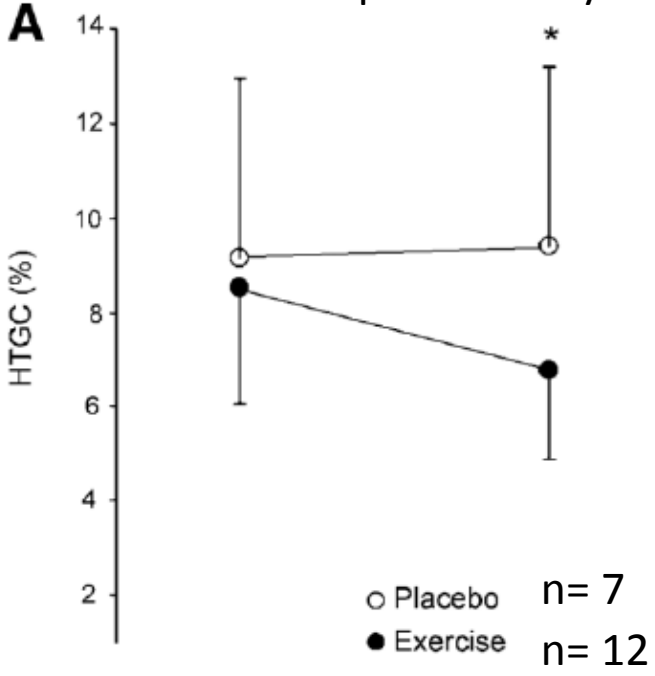
- **Exercise**
  - Pedometers
  - Subsidised gym in hospital for group ‘get fit’ sessions
  - Resistance vs aerobic exercise
- **Behavioural Therapy**
  - Clear Targets
  - Positive Feedback

Regular Exercise

Exercising improves

- Insulin resistance
- Steatosis
- **Independently from the weight loss**

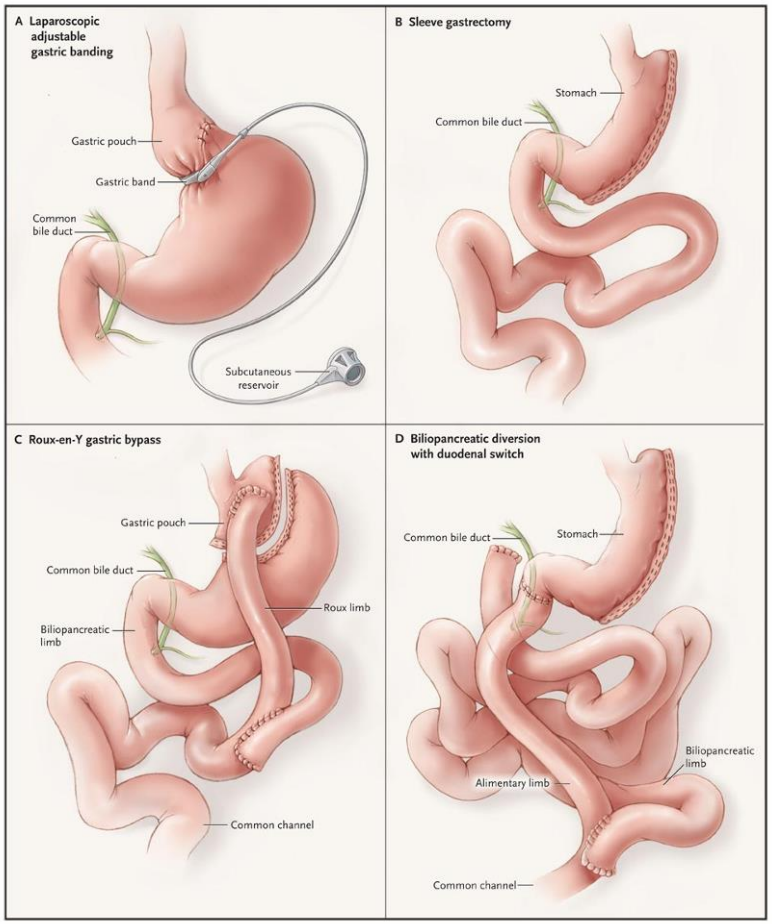
Fatty Liver assessment by spectrometry



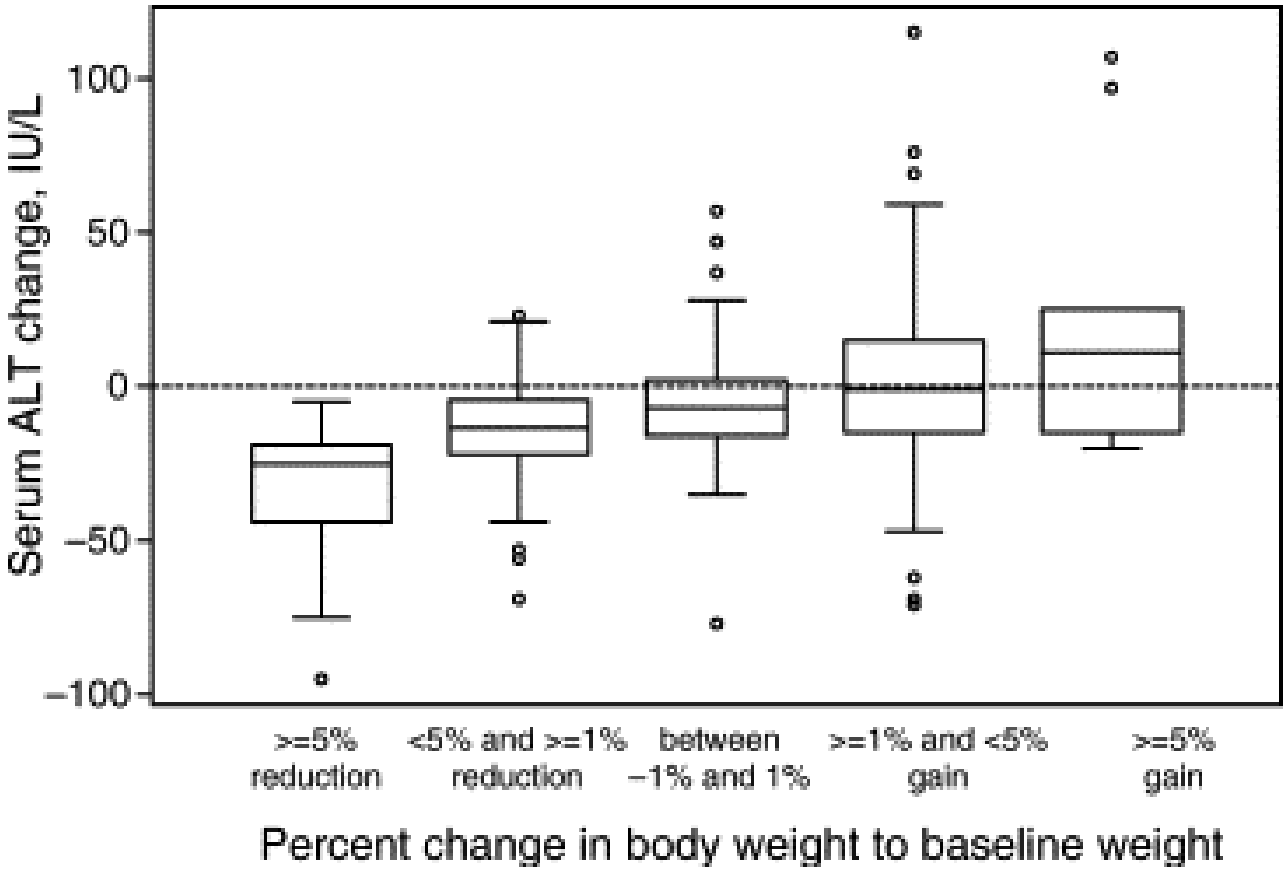
Johnson,Hepatology 2009
Helmerhost , Diabetes 2009

Treating Obesity

- **Central appetite suppressants**
  - Rimonabant (Acomplia)
    - Cannaboid receptor antagonist
    - No longer available
- **Slowing absorption**
  - Orlistat (Xenical)
    - Lipase inhibitor
    - Reduces dietary fat absorption
    - BMI >30 or >28 plus Metabolic Syndrome
    - May cause steatorrhoea
- **Bariatric Surgery**



Effect of Weight Loss on ALT



Suzuki et al. J. Hepatol 2005

Statins and LFTs

- Statins do cause ^LFTs
- Statins do not cause liver failure
- Statins are **not** contraindicated in patients with
  - ^LFTs
  - Cirrhosis
  - NASH
- Statins **are** contraindicated in decompensated liver disease

- Check LFTs before starting statin therapy
- Do not monitor LFTs
  - Do as patients to report jaundice, fatigue, malaise

- An Assessment of Statin Safety by Hepatologists. Am.J. Cardiol 2006:

- NB DDI with Protease Inhibitors!

Management MEATLOAF

Make the diagnosis

Establish metabolic syndrome components

Assess lifestyle

Therapeutic approaches

Liver specific therapies

- Pioglitazone or
- Vitamin E

Offer clinical trials

Advice and targets

Follow-up

PIVENS Trial - Endpoint

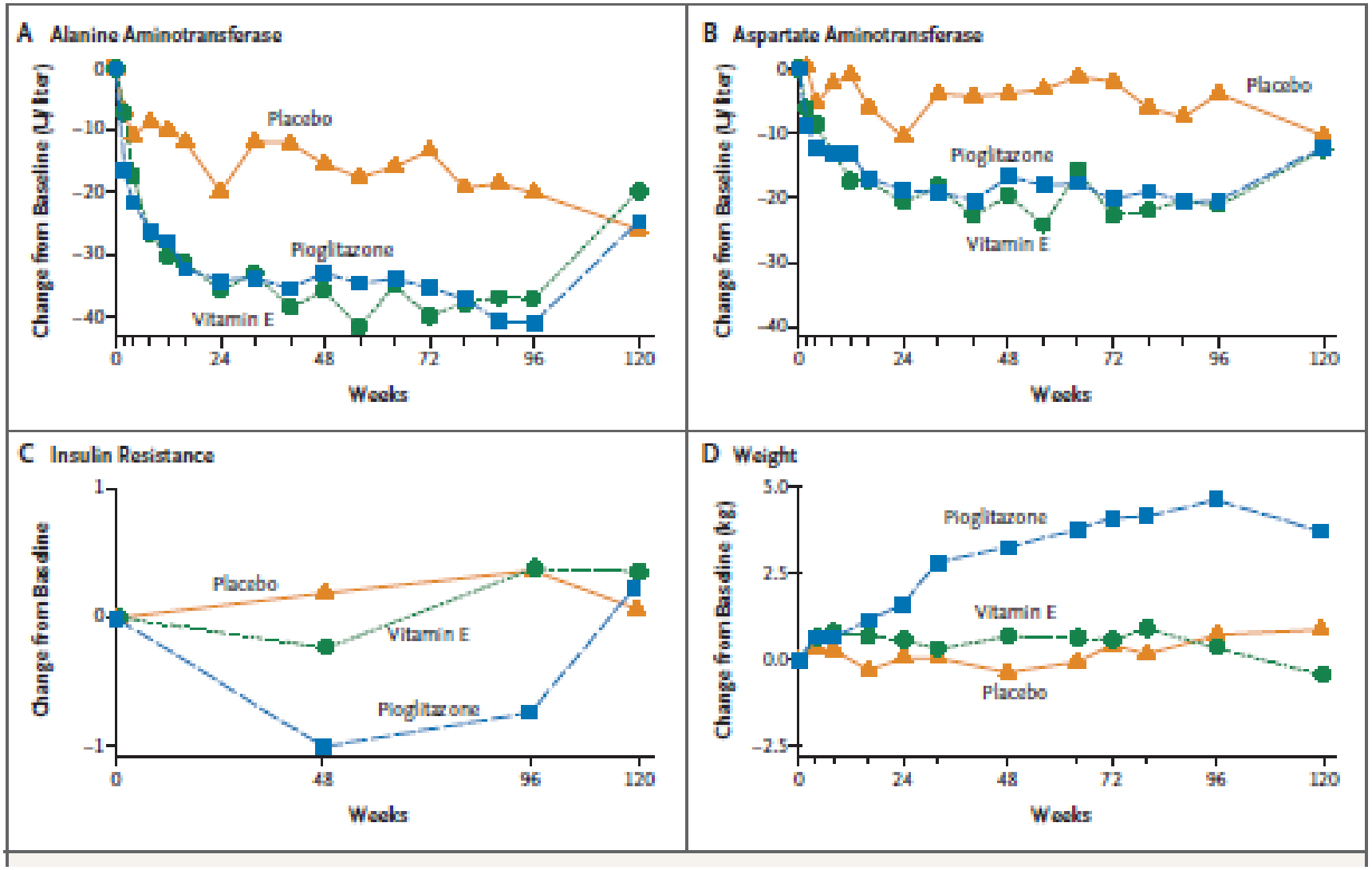
- Primary Endpoint
  - >/= 1 point improvement on ballooning
  - No increase in fibrosis
  - Decrease in NAS >/= 2 points or decrease 2 points with >/= 1 point decrease in lobular inflammation or steatosis
- Secondary
  - Change in NAS score
  - Change in ALT
  - Insulin resistance
  - Lipid profiles

PIVENS Results

Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

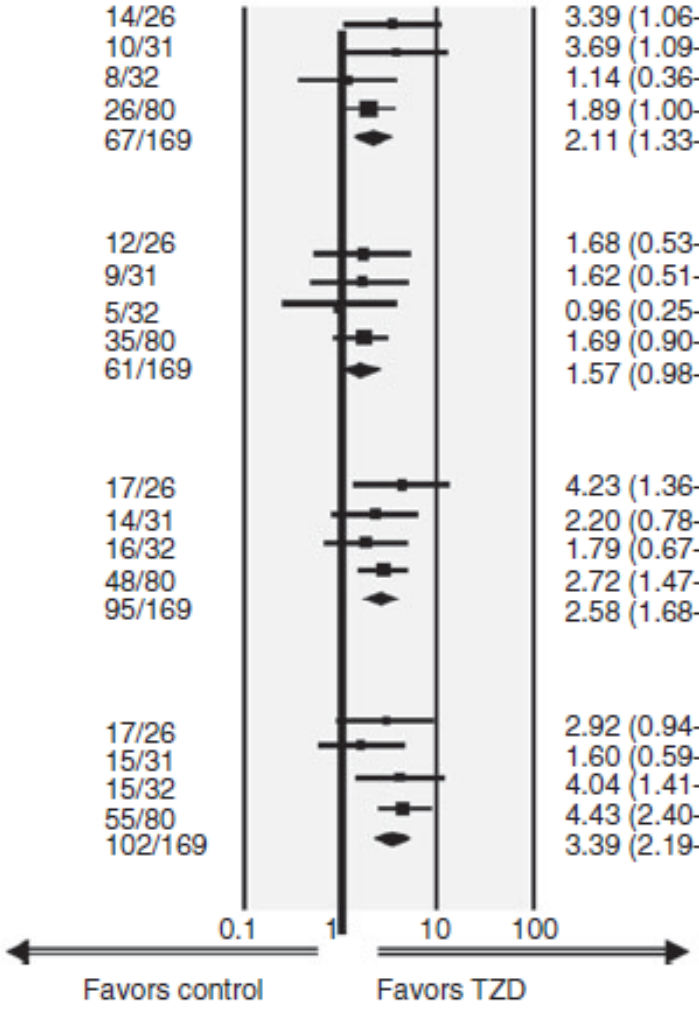
Variable	Placebo	Vitamin E	Pioglitazone	P Value*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	–0.1	–0.7	–0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.004
Mean change in score	–0.2	–0.6	–0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	–0.2	–0.5	–0.4	0.03	0.01
Total NAFLD activity score (mean change)	–0.5	–1.9	–1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	–0.1	–0.3	–0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

PIVENS Results 2



Pioglitazone Meta-analysis

Study, year[Reference]	Improved(*n*)/Total (*N*)		Peto OR (95% CI)	*P*-value
	Control	TZD		
Ballooning				
Belfort (2006)[23]	5/21	14/26	3.39 (1.06–10.80)	0.039
Aithal (2008)[22]	3/30	10/31	3.69 (1.09–12.44)	0.035
Ratziu (2008)[30]	7/31	8/32	1.14 (0.36–3.60)	0.823
Sanyal (2010)[25]	24/83	26/80	1.89 (1.00–3.58)	0.050
Summary	39/165	67/169	2.11 (1.33–3.36)	0.002
Fibrosis				
Belfort (2006)[23]	7/21	12/26	1.68 (0.53–5.37)	0.378
Aithal (2008)[22]	6/30	9/31	1.62 (0.51–5.13)	0.417
Ratziu (2008)[30]	5/31	5/32	0.96 (0.25–3.68)	0.957
Sanyal (2010)[25]	26/83	35/80	1.69 (0.90–3.19)	0.102
Summary	44/165	61/169	1.57 (0.98–2.51	0.060
Lobular inflammation				
Belfort (2006)[23]	6/21	17/26	4.23 (1.36–13.20)	0.013
Aithal (2008)[22]	8/30	14/31	2.20 (0.78–6.21)	0.136
Ratziu (2008)[30]	11/31	16/32	1.79 (0.67–4.82)	0.248
Sanyal (2010)[25]	29/83	48/80	2.72 (1.47–5.02)	0.001
Summary	54/165	95/169	2.58 (1.68–3.97)	0.000
Steatosis				
Belfort (2006)[23]	8/21	17/26	2.92 (0.94–9.14)	0.065
Aithal (2008)[22]	11/30	15/31	1.60 (0.59–4.38)	0.359
Ratziu (2008)[30]	5/31	15/32	4.04 (1.41–11.58)	0.009
Sanyal (2010)[25]	26/83	55/80	4.43 (2.40–8.17)	0.000
Summary	50/165	102/169	3.39 (2.19–5.25)	0.000



Boettcher APT 2011

Management MEATLOAF

Make the diagnosis

Establish metabolic syndrome components

Assess lifestyle

Therapeutic approaches

Liver specific therapies

Offer clinical trials

- Investigator-led studies
- Commercial trials of novel agents or ‘repurposing’ of existing therapies

Advice and targets

Follow-up

Management MEATLOAF

Make the diagnosis

Establish metabolic syndrome components

Assess lifestyle

Therapeutic approaches

Liver specific therapies

Offer clinical trials

Advice and targets

- Provide targets (if appropriate) to patient and primary care physician
  - Weight / waist circumference
  - BP,
  - cholesterol /triglyceride,
  - HbA1c
- Provide information leaflets

Follow-up

Management MEATLOAF

Make the diagnosis

Establish metabolic syndrome components

Assess lifestyle

Therapeutic approaches

Liver specific therapies

Offer clinical trials

Advice and targets

Follow-up

- 3–6 months if major therapeutic changes
- 6 months if NASH/significant fibrosis/compensated cirrhosis
- 6–12 months if stable on therapy
- 12 months or discharge if simple steatosis or very low risk on non-invasive tests

RESEARCH

Piloting a multidisciplinary clinic for the management of non-alcoholic fatty liver disease: initial 5-year experience

Jeremy F L Cobbold,[1] Sarrah Raveendran,[1] Christopher M Peake,[1] Quentin M Anstee,[2] Michael S Yee,[3] Mark R Thursz[1]

Table 2 Change in variables from baseline to latest clinic visit for the total cohort

Measure	N=	Baseline	Recent	Δ (%)	p Value
ALT, U/l	180	61 (12–270)	50 (11–221)	−18	**<0.001**
Weight, kg	180	90.5 (42.7–175.0)	87.3 (45.9–175.3)	−3.5	**<0.001**
HbA1c, mmol/mol	121	46.5 (27–120)	45.4 (22–105)	−2.4	0.73
tchol, mmol/l	140	4.47 (2.30–7.95)	4.36 (2.01–7.12)	−2.5	**0.001**
HDL, mmol/l	140	1.09 (0.59–1.75)	1.08 (0.53–2.70)	−0.9	0.80
TG, mmol/l	140	1.83 (0.26–7.85)	1.67 (0.32–7.94)	−8.7	0.41
SBP, mm Hg	154	135 (98–191)	134 (100–176)	−0.4	0.36
DBP, mm Hg	154	82 (57–114)	82 (59–111)	0	0.64

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Summary

- NASH is an increasing cause of liver mortality in HIV+/HIV-
- It is important to identify those at risk
- Lifestyle modifications are the key to management
- Vit E, Pioglitazone and Bariatric surgery may be used with caution

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