

# Hepatic fat: Determinants, downstream effects and does HIV matter?

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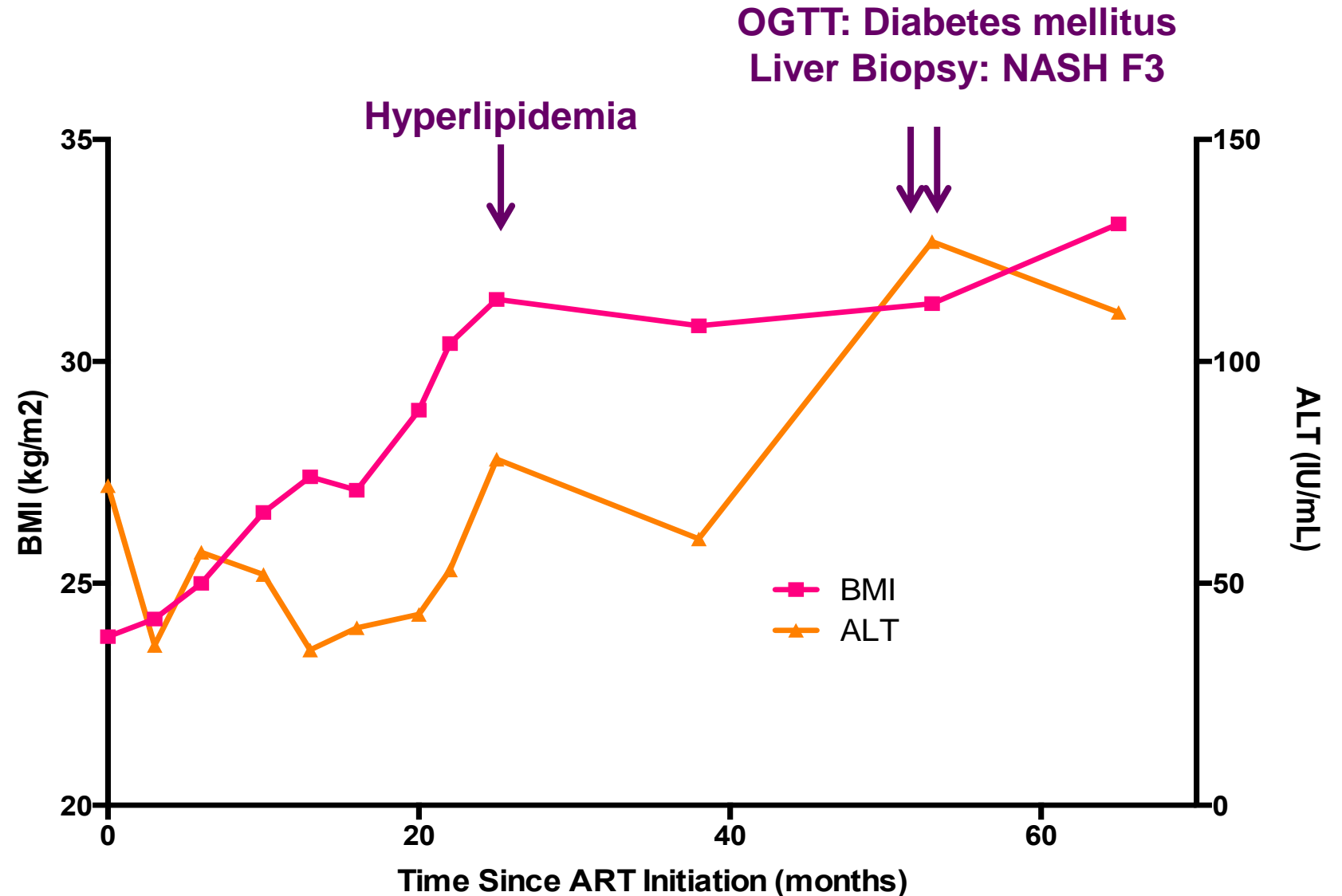


National Institutes  
of Health

*The speaker has no disclosures or conflicts to report*

# The price of success?

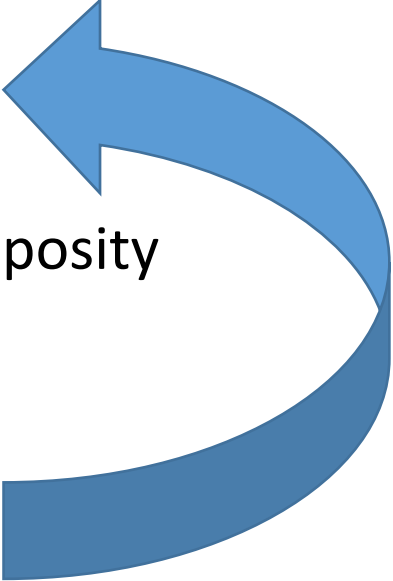
- 57 yo Hispanic male, HIV+ '09
- Cryptococcal meningitis
- CD4 nadir - 81
- 56 kg (BMI 24 kg/m<sup>2</sup>)
- Viral suppression & CD4 to 600-700  
but.....



# Mechanisms of NAFLD/NASH

## What is Unique in HIV?

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- Metabolic Factors
    - Insulin Resistance
    - Obesity/Visceral Adiposity
    - Hyperlipidemia
  - Genetic Factors
  - HIV Specific Factors
    - Antiretroviral Toxicity
    - Immunosuppression/Immune Activation/Chronic HIV
    - Opportunistic Infections
    - Co-infections - HCV
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# Obesity and Overweight in HIV: A Growing Problem

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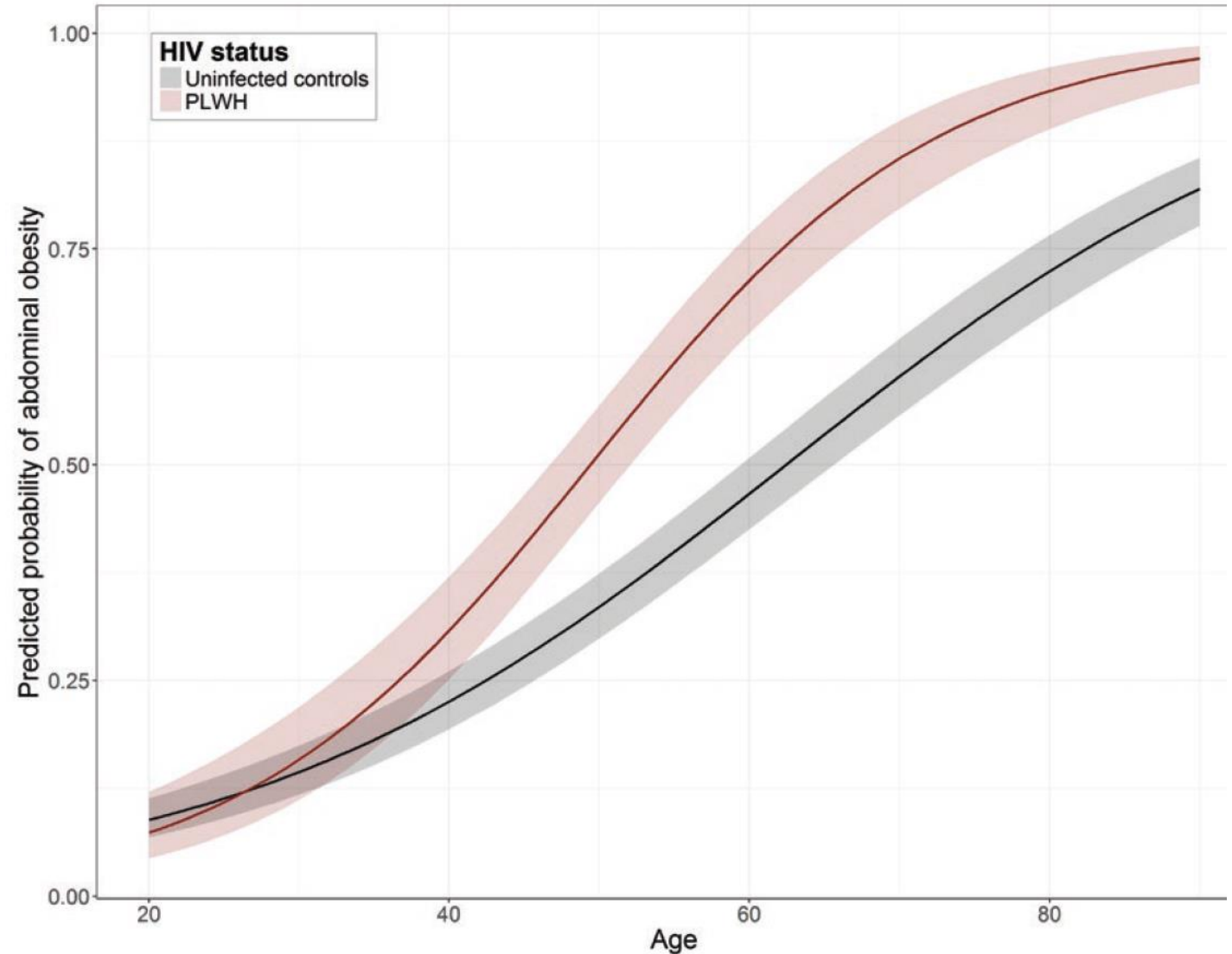
## NA-ACCORD Data

- Of >14 000 HIV+ in US & Canada
  - Obesity at ART initiation doubled from '98-'10
  - % obese at ART initiation increased 9% to 18%
- 3 years after ART initiation:
  - 22% with a normal BMI (18.5–25) at ART initiation became overweight
  - 18% of those overweight at ART initiation became obese

# Abdominal Obesity in HIV

- Copenhagen Comorbidity Cohort (COCOMO) cross-sectional data
- N=1099 HIV+, 12,161 matched controls
- Abdominal Obesity (WHO) by WHR
  - $\geq 0.90$  for men
  - $\geq 0.85$  women
- Factors associated with central obesity
  - CD4 nadir  $< 200$  (aOR 1.71)
  - Duration HIV (aOR 1.37)

Theory: short-term and long-term central adipose in weight recovery seen in anorexia nervosa and famine



# Prevalence and Risk for Fatty Liver in HIV

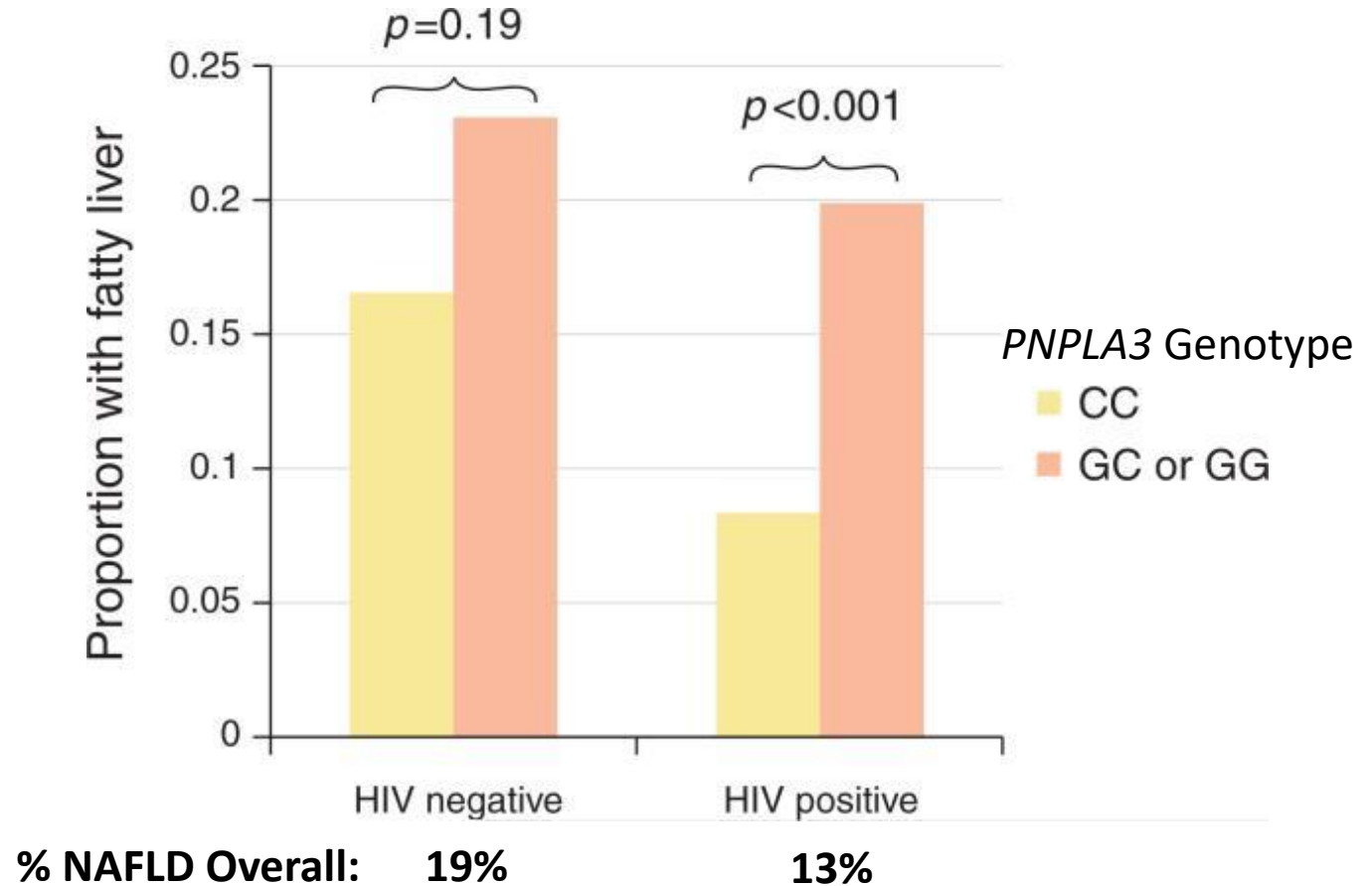
NAFLD prevalence 13-50% in HIV

Risk factors for NAFLD

- BMI > 25 kg/m<sup>2</sup>
- Insulin Resistance
- Dyslipidemia
- *PNPLA3* Genotype

MACS Cohort Data

- CT attenuation for NAFLD (n=719)
- NAFLD 19% HIV- vs 13% HIV+ (p=0.002)
- NAFLD increased with:
  - Visceral fat
  - Insulin resistance
  - *PNPLA3* genotype
  - Cumulative ddl exposure



Price et al., *Am J Gastroenterology*, 2014  
Vuille-Lessard et al., *AIDS*, 2016  
Sulyok et al., *Eur J Gastro & Hepatol*, 2015

# Prevalence and Risk for Fatty Liver in HIV

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## NAFLD/NASH in HIV: Meta-analysis HIV

### Ten studies identified

- 5/10 liver biopsy data (n=153)
- 2 large cohorts U/S or Fibroscan (n=516)

### Prevalence:

- NAFLD – 35%
- NASH – 42%
- Fibrosis ( $\geq$  F2) – 23%
  - 15-27% by kPa  $\geq$  7.0

### Risk factors for NAFLD

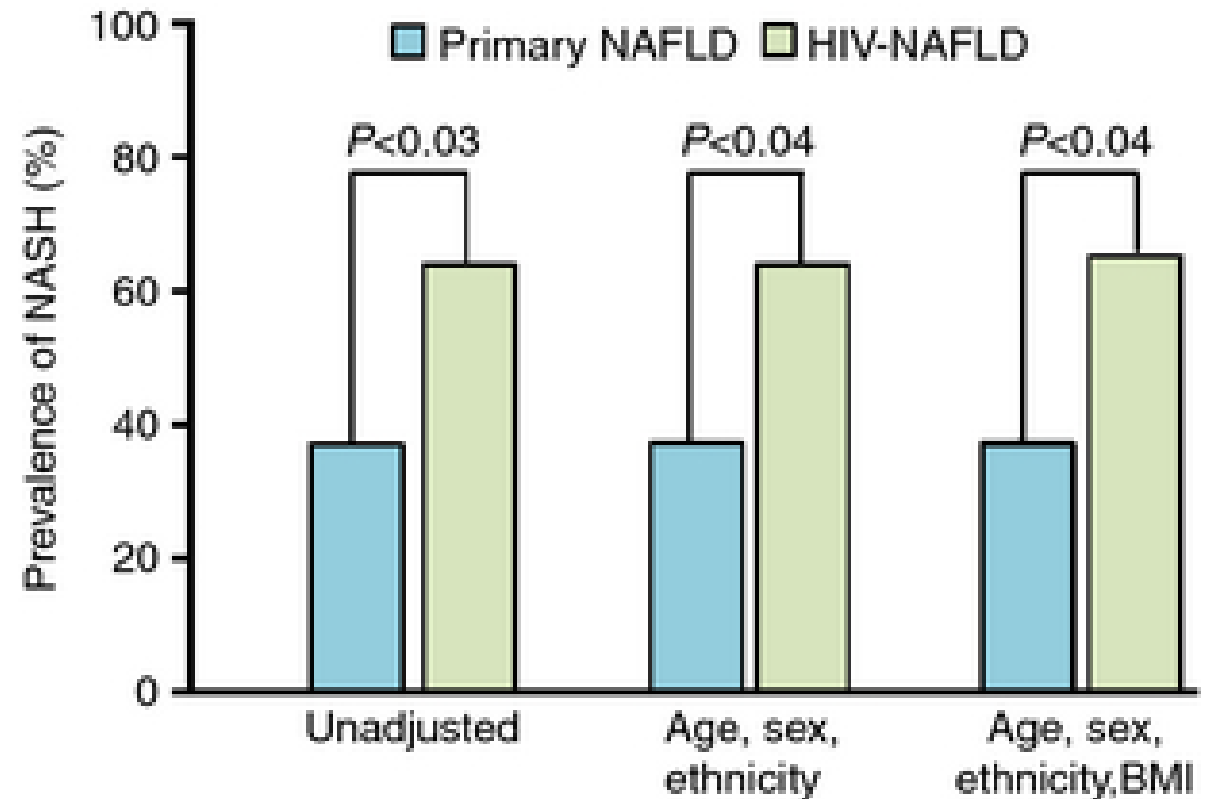
- BMI/waist circumference
- Diabetes
- Dyslipidemia
- HTN
- Transaminase elevation
- Higher CD4 count

### Risk Factors for Fibrosis

- BMI
- Glucose
- AST

# Is NAFLD Different in HIV?

- Case-Control study of biopsy identified NAFLD (HIV n=33, non-HIV n=33)
- HIV+ cases had higher aminotransferases, TG, and greater NAFLD activity scores vs. non-HIV
- Only duration of HIV was significantly associated with NASH, not CD4, VL or ARVs





# LIVEHIV Cohort

McGill Univ. Health Centre

2013-16

N=726 HIV+ w/o EtoH

22% HCV co-infected

N=313 w/ follow-up

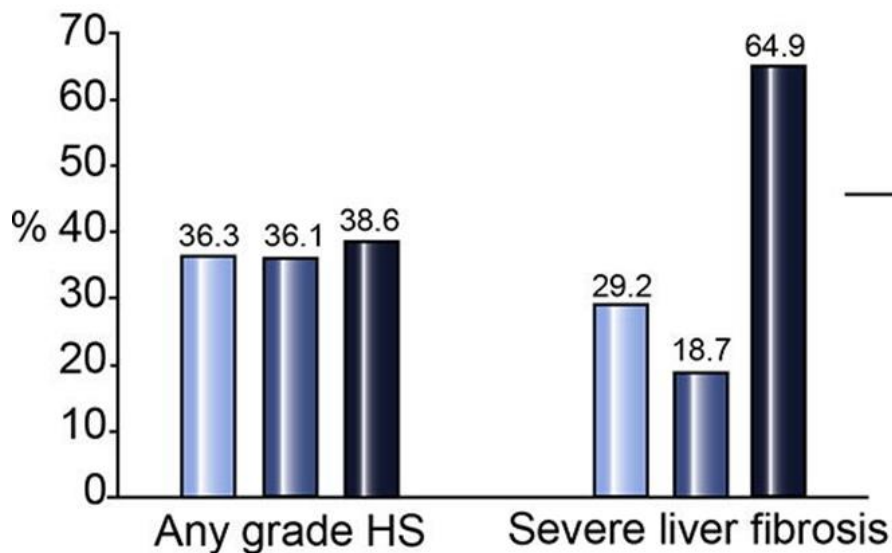
Annual fibroscan

Findings:

36% steatosis overall

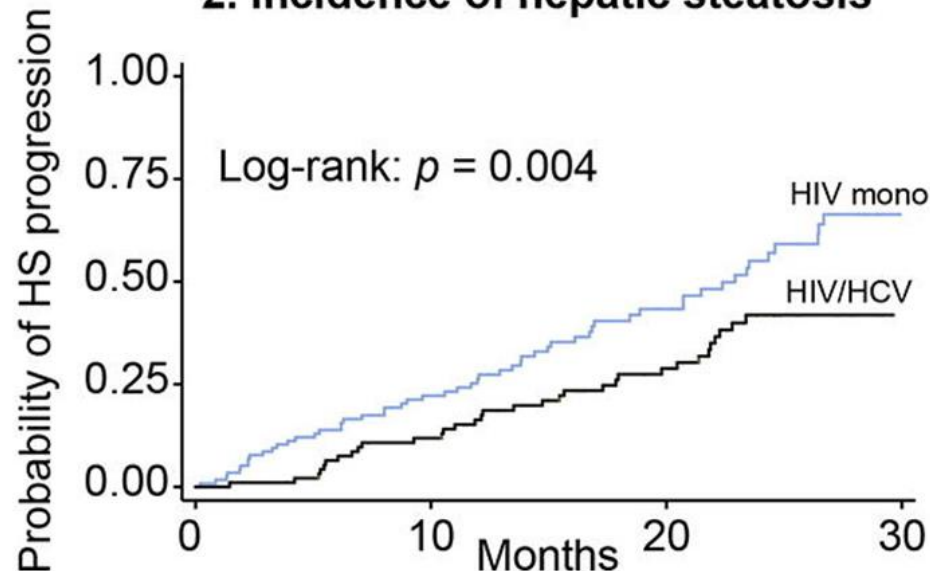
>= F2 fibrosis 30%

## 1. Prevalence of hepatic steatosis and significant fibrosis

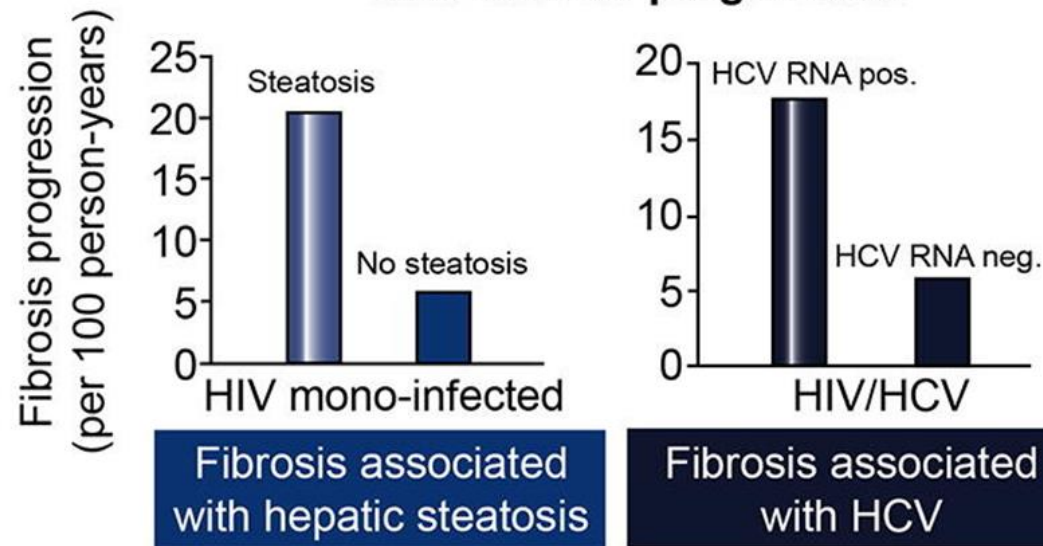


■ Prevalence (whole) cohort  
■ HIV mono-infected  
■ HIV/HCV

## 2. Incidence of hepatic steatosis



## 3. Independent predictor of liver fibrosis progression



Predictors of Steatosis Progression:

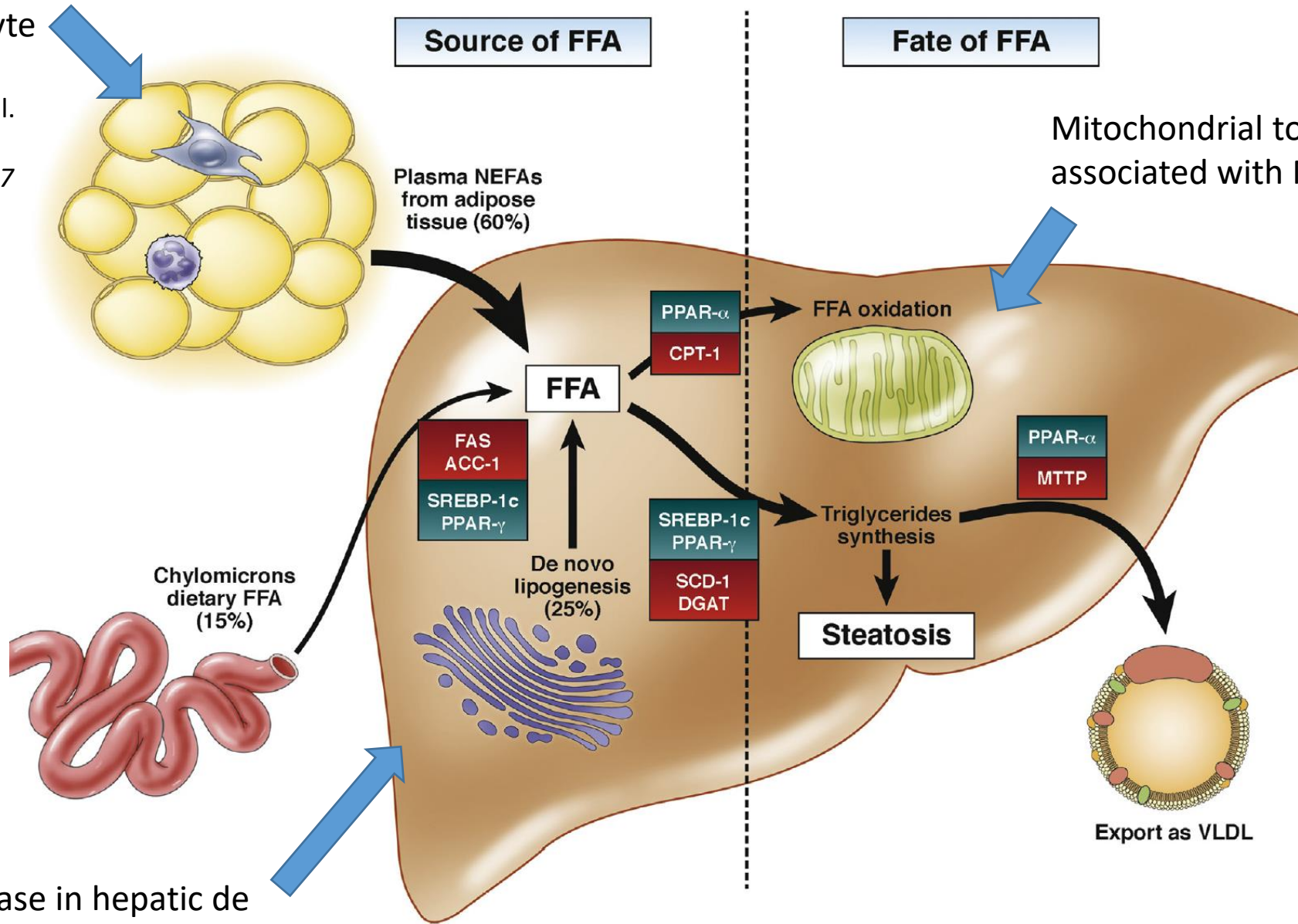
- BMI, HCV protective

Predictors of Fibrosis Progression

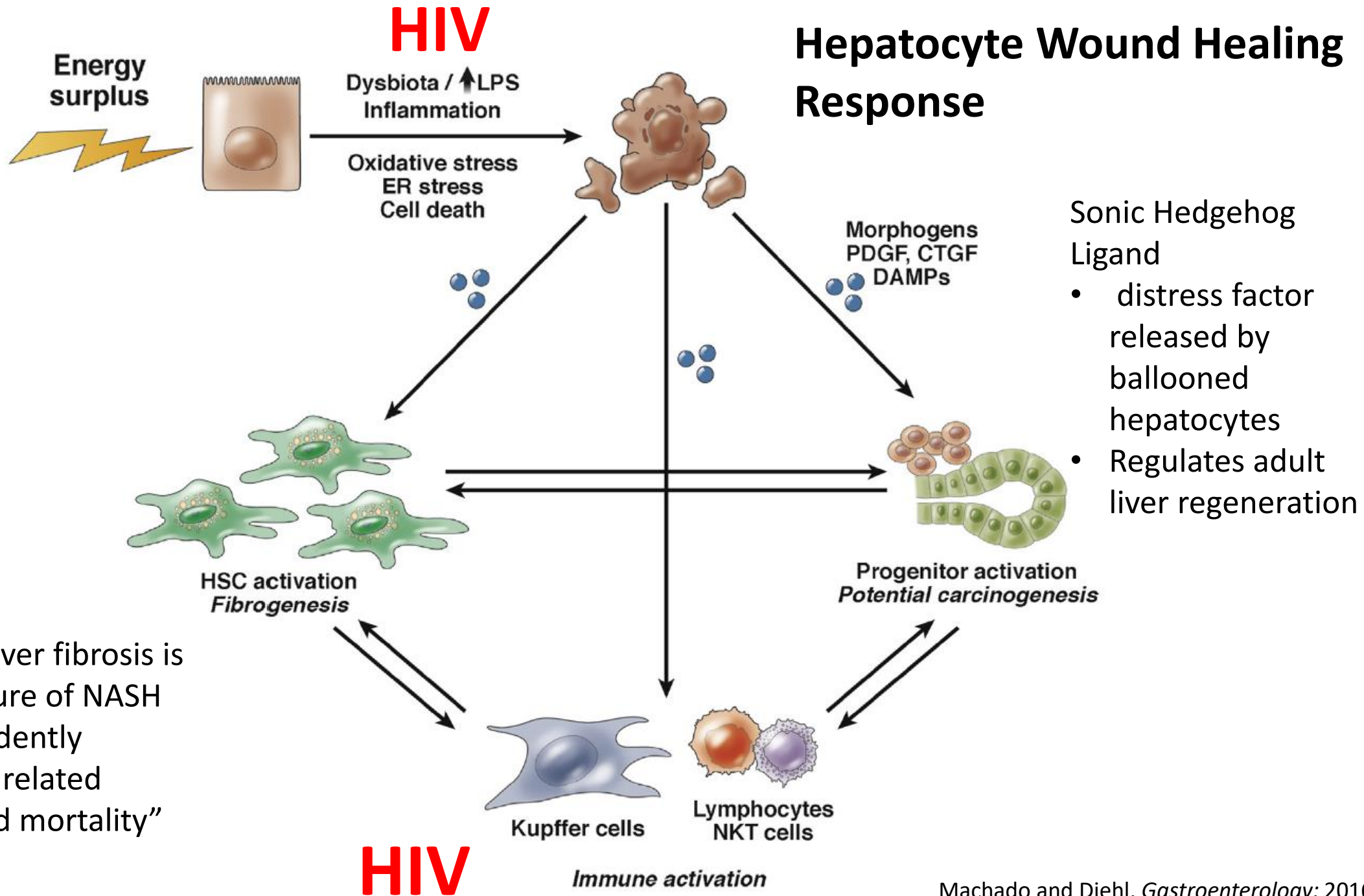
- HIV mono: duration HIV, steatosis
- HIV/HCV co-infected: HCV RNA+, ALT

## Protease Inhibitors increase adipocyte lipolysis

- Adler-Wailes et al. 2005, *JCEM*
- Kovans et al. 2007 *JBC*



3-4 fold increase in hepatic de novo lipogenesis in HIV infection  
- Hellerstein et al 1993 *JCEM*

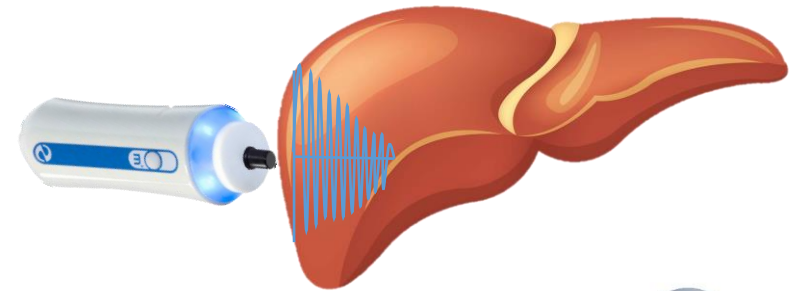


“Severity of liver fibrosis is the only feature of NASH that independently predicts liver related morbidity and mortality”

# Diagnosis

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- Non-invasive
  - Liver Ultrasound
  - Transient Elastography with CAP
    - Controlled Attenuation Parameter
  - MR Spectroscopy
  - MRI Proton Density Fat Fraction
- Invasive
  - Liver Biopsy



# Diagnosis: When to Biopsy?

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- AASLD recommendation
  - Increased risk of NASH/advanced fibrosis
  - Competing etiology or co-existing chronic liver disease **(HIV)**
- Fibrosis Testing - Non-invasive
  - NAFLD Fibrosis Score
    - $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (}\times 10^9/\text{l)} - 0.66 \times \text{albumin (g/dl)}$
  - Transient Elastography
  - MR Elastography

# Management

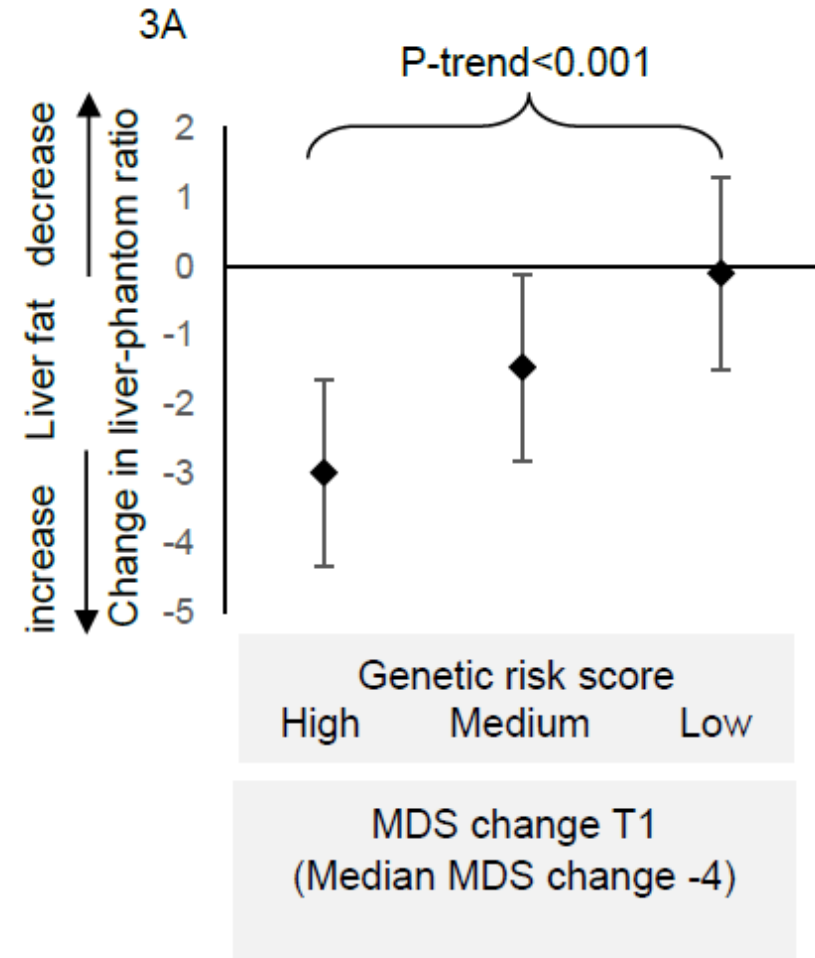
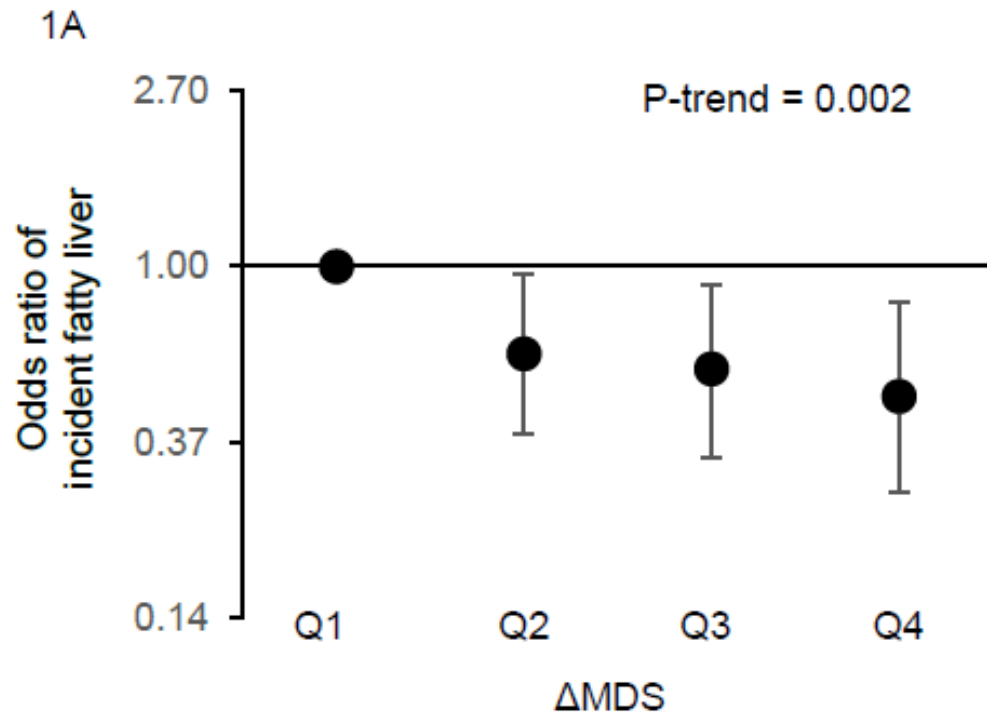
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There are no FDA approved treatments for NAFLD

Lifestyle Modification:

- 20 studies of diet/weight loss/exercise
  - 13/20 Rz-controlled trials
  - Duration 6-12 months
  - 18/20 subjects - obese/overweight
  - 19/20 showed reduction in liver fat

# Mediterranean style diet: Reduces risk of NALFD, particularly among those with genetic predisposition



- Framingham data (1998-2011), n=1521, F/U median 6 yrs
- CT estimates of liver fat, Food frequency questionnaire data
- PNPLA3 snips for genetic risk score

# NAFLD Management

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## AASLD Guidelines for NAFLD (2018):

- Weight loss 3-5%, up to 10%, of body weight
- Vit E 800 IU/day for non-diabetic, bx proven NASH
- Pioglitazone – consider in biopsy-proven NASH
- Avoid heavy alcohol intake
- CVD risk reduction (i.e. lipid lowering therapy) where indicated
- NASH w/ cirrhosis – variceal and HCC screening



# What is on the horizon that might apply in HIV and NASH?

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- PPAR- $\gamma$  agonist – Pioglitazone: What's old is new....
- PPAR- $\alpha/\delta$  – Elafibranor and the GOLDEN 505 Trial
- GLP-1 – Liraglutide – LEAN trial
- CCR2/CCR5 dual antagonist – Cenicriviroc- CENTAUR
- Tesamorelin – GHRH analogue

# Tesamorelin: GHRH for Visceral Fat in HIV

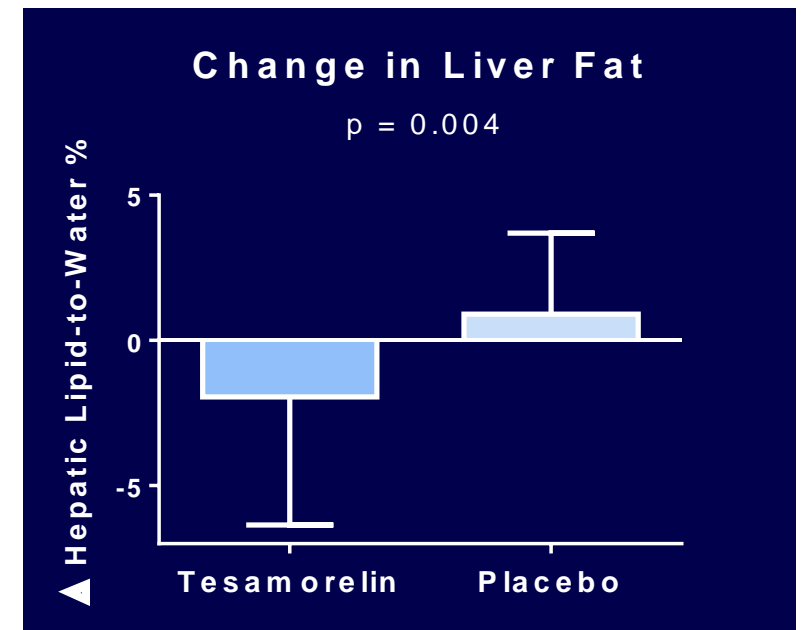
## What about the Liver?

- N=48 HIV+, ARV-treated, w/ increased visceral fat (VAT)
- Randomized: Tesamorelin 2mg SQ/day vs PBO for 6 mos
- Primary outcome: Change in VAT and Liver Fat

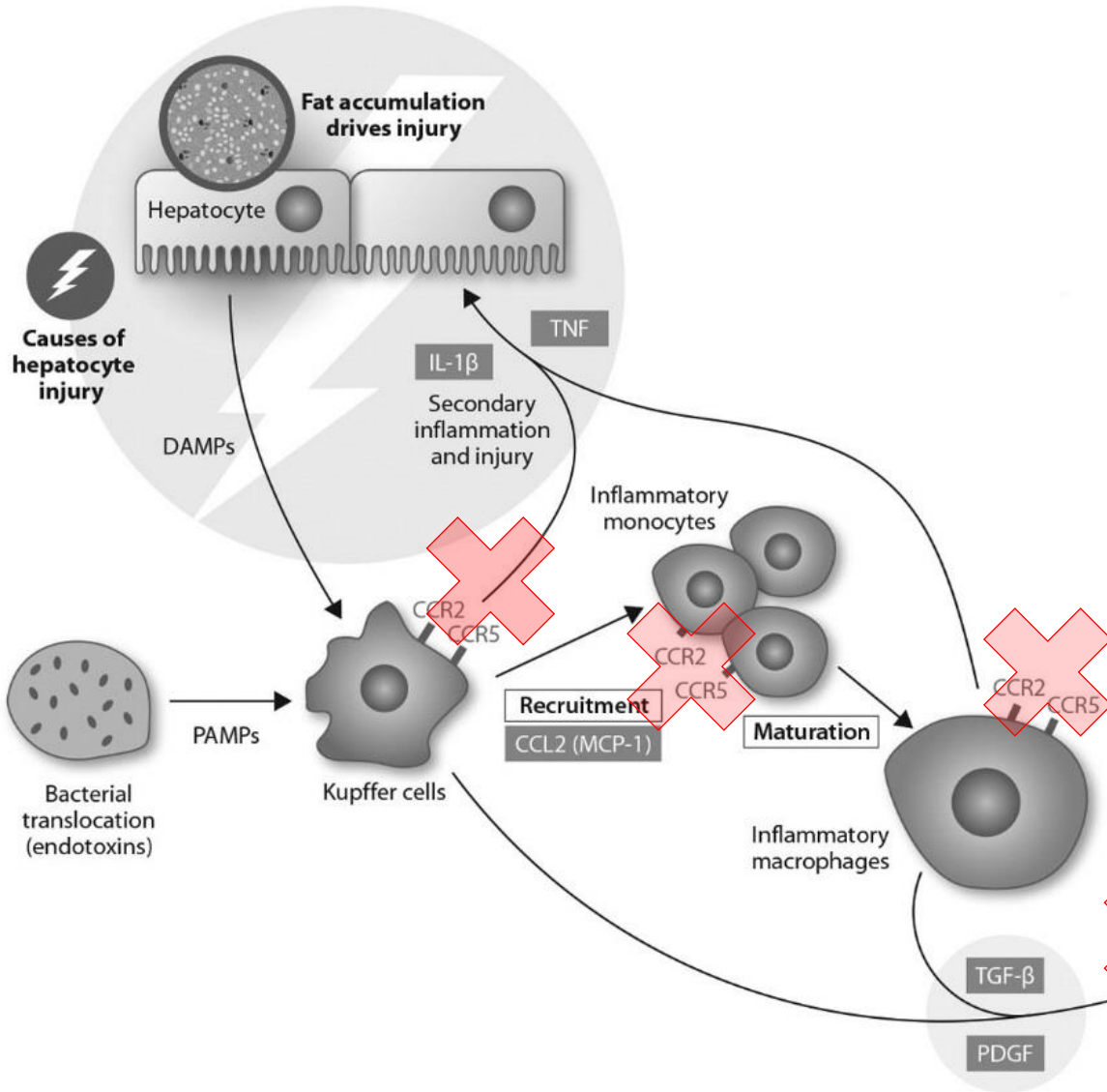
Mean Change in Body Fat at 6 Months

|                          | Tesamorelin<br>N=23 | Placebo<br>N=20 | P-value |
|--------------------------|---------------------|-----------------|---------|
| VAT (cm <sup>2</sup> )   | -34 ± 9             | 8 ± 11          | 0.005   |
| SAT (cm <sup>2</sup> )   | 2 ± 4               | 8 ± 6           | 0.37    |
| BMI (kg/m <sup>2</sup> ) | 0.3 [-0.3, 0.8]     | 0.3 [-0.2, 0.8] | 0.89    |

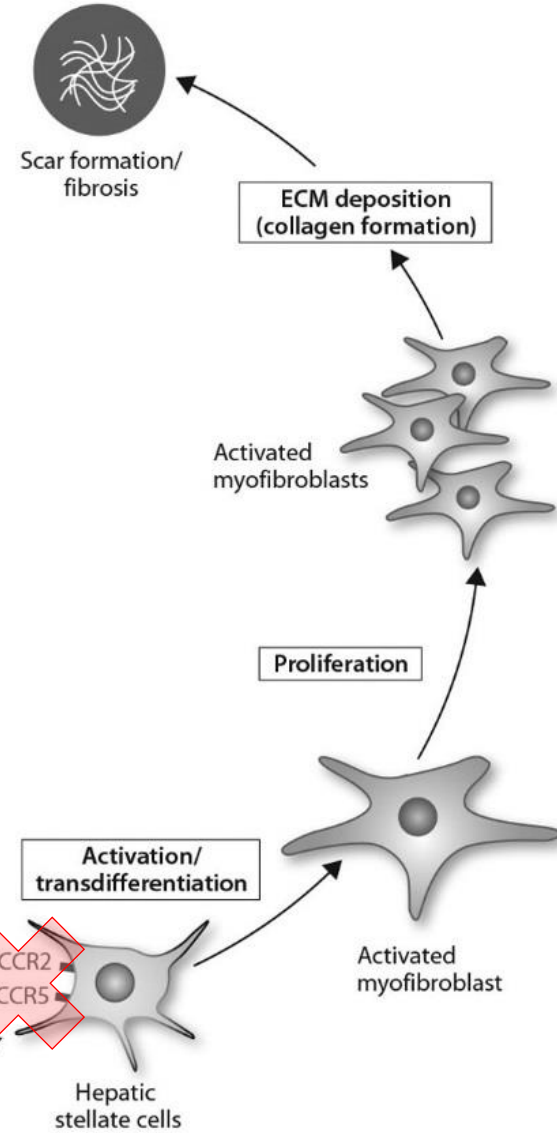
- Reductions in liver fat and AST
- No increase in glucose
- Study did not select for NAFLD



## Inflammatory response to hepatocyte injury



## Fibrogenesis



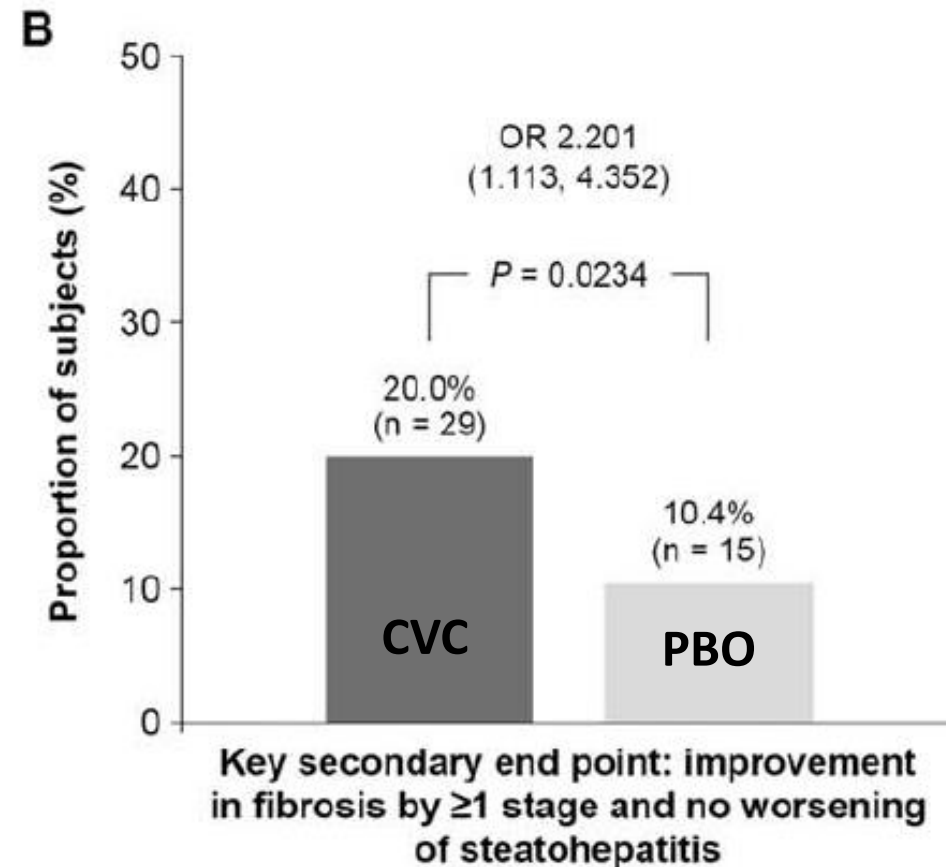
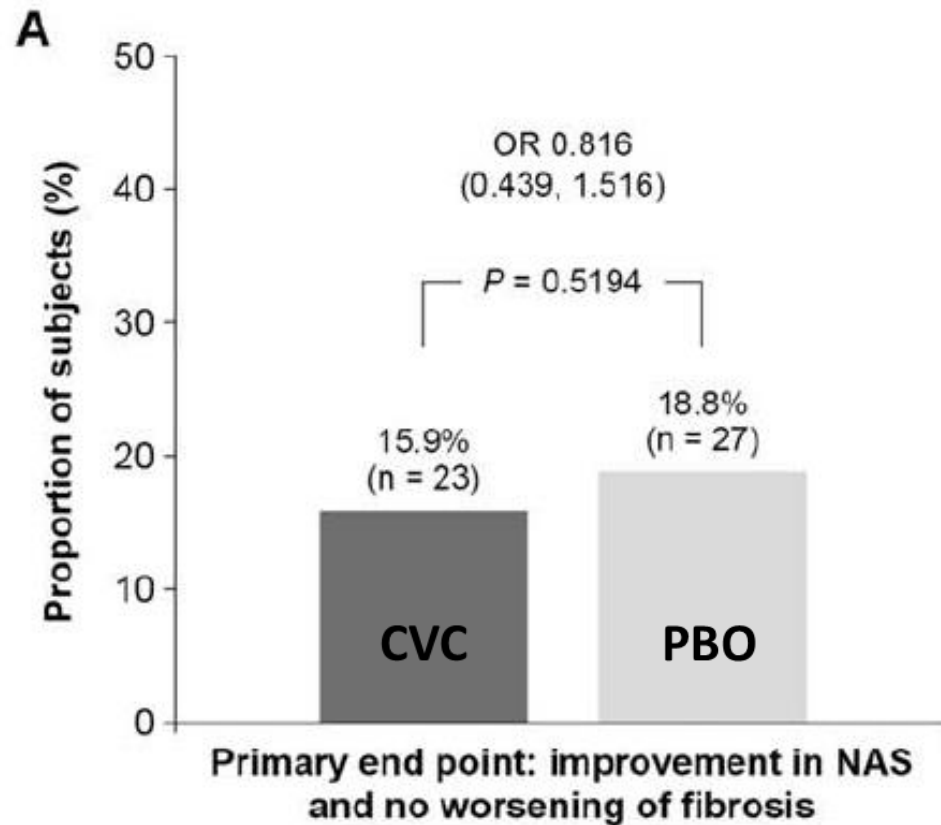
# CCR2/CCR5:

Potential mechanisms for CCR2/CCR5 antagonist to mediate NASH hepatic injury

- Monocyte/M $\phi$  recruitment
- HSC activation

Fig. 1. Inflammatory response to hepatocyte injury leading to fibrogenesis and CCL2, C-C chemokine ligand type 2; CCR2, C-C chemokine receptor type 2; CCR5, C-C chemokine receptor type 5; DAMPs, danger

# CENTAUR Trial



# Areas for Future Focus

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- Knowledge Gaps
  - Prevalence and Progression HIV vs non- HIV
  - Risk vs. benefit of low-moderate alcohol intake
- Prevention
  - Obesity
  - ART toxicity - may be less important in the future
- Measurement/End Points
  - Non-invasive tools – caveats and cost
  - Biopsy and Composite Scores
- Management
  - Obesity, Metabolic Syndrome, Alcohol Intake
  - Future Targets
    - PPARs, GLP-1
    - CCR2/CCR5
    - GHRH