Hepatology Highlights
for the HIV physician

What´s new in non-viral liver disease

London
June, 15th, 2016

Patrick Ingiliz, Berlin

Conflicts of interest

- Consultancy or speakers fees from abbVie, BMS, Gilead, Janssen, MSD, Roche, ViiV.

- Clinical trials with abbVie, Gilead, BMS, ViiV, Hologic, Janssen, MSD, Boehringer-Ingelheim.

Klaus, 51yo

- caucasian, MSM
- HIV infection, dx 1989, CDC B2
- presents for chronic ALT elevation:
- „since ages“

Klaus, medical history

- varicose veins
- PVD (femoro-popliteal bypass)
- hyperlipoproteinemia
- hyperuricemia

→ Meds: ASS, allopurinol

Klaus, ARV history

- 1997-2000: AZT, 3TC
- 2000-2002: 3TC, d4T
- 2002-2003: 3TC, d4T, EFV
- 2003-2011: TDF, 3TC, LPV/r (diarrhea)
- 2011-2012: TDF/FTC/ATV/r (LEE)
- 2012-2012: TDF/FTC/RPV (HIV-VL)
- since 2012: TDF/FTC/RAL

Klaus, 51yo

- 1,99m, 97kg, BMI 24,5 kg/m^2
- RR 110/60
- hip circumference: 101cm
- waist circumference 98cm
- ex-smoker

- physical exam: lipodystrophy syndrome

Klaus, lab results

- CD4 475/ul, 40%
- HIV <50 c/ml

- AST 85 U/L, ALT 93 U/L, GGT 123 U/L

- Thr 116 G/l

- Alb, Bili, INR within normal range

- TG 234mg/dL, Chol 143mg/dL, HDL 31mg/dL
- Glucose 111mg/dL

Klaus, hepatopathy screening

- **HBV: vaccinated**
- **HAV, HCV negative**
- **HEV: IgG positive, PCR negative**
- **No sign of autoimmune or hereditary liver disease**

- **US abd.: dense liver parenchyma suggesting steatosis, pancreas lipomatosis, spleen 19cm**

Klaus, liver staging

- **Fibroscan 23.9 kPa (IQR 3.1, SR 91%)**
- **CAP® 278 dB/m**

- **MRI (ECHAM trial): steatosis 6%**

- **Liver biopsy: 39mm, 25 portal tracts:**
- **steatosis ° I, hepatocytic ballooning, slight lobular inflammation. (NAS-Score 4)**
- **Fibrosis stage: F3 (partly F4) METAVIR**

Chronic ALT elevation in HIV monoinfection

2365 participants, 9972 person-years: incidence rate 3.9/100py

16%

Swiss cohort
Chronic ALT
No HCV/HBV

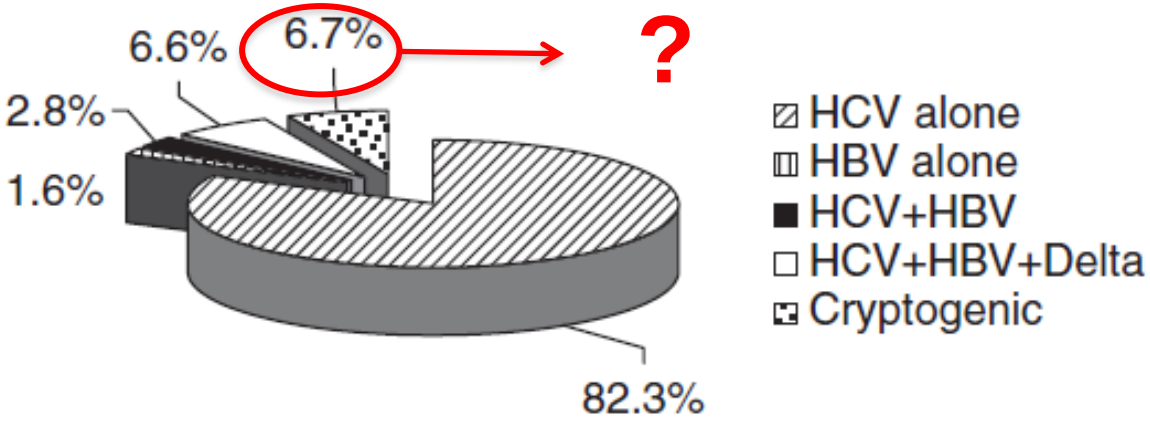
(high BMI, alcohol, HIV viral load > 100,000 c/mL, stavudine/zidovudine)

Kovari, CID 2010

Causes of cirrhosis in HIV patients

2,168 HIV patients
Cross sectional analysis
Transient elastography (TE, Fibroscan)

181/2168 (8.3%) with TE ≥ 12 kPa



No cirrhosis attributable to alcohol alone

Fig. 1 Aetiology of liver cirrhosis in the HIV study population.

Castellares C et al. J Viral Hep 2008

Non-virological factors associated to cirrhosis in HIV patients

US HIV positive veteran registry: n=24,040

Prevalence of cirrhosis in 2009: 5%

Non viral independent variables	Compensated cirrhosis n=1190	Decompensated cirrhosis n=565
Age	1.03 (1.02-1.04)	1.02 (1.01-1.03)
Hispanic ethnicity	1.76 (1.4-2.2)	1.96 (1.51-2.54)
Diabetes	1.79 (1.6-2.1)	1.91 (1.59-2.31)
Alcohol abuse	1.78 (1.5-2.1)	1.65 (1.32-2.08)

Ioannou et al. Hepatology 2013

Non-viral chronic liver diseases in HIV patients

Antiretroviral therapy (ART)

↓

Vascular liver disease

Alcohol abuse

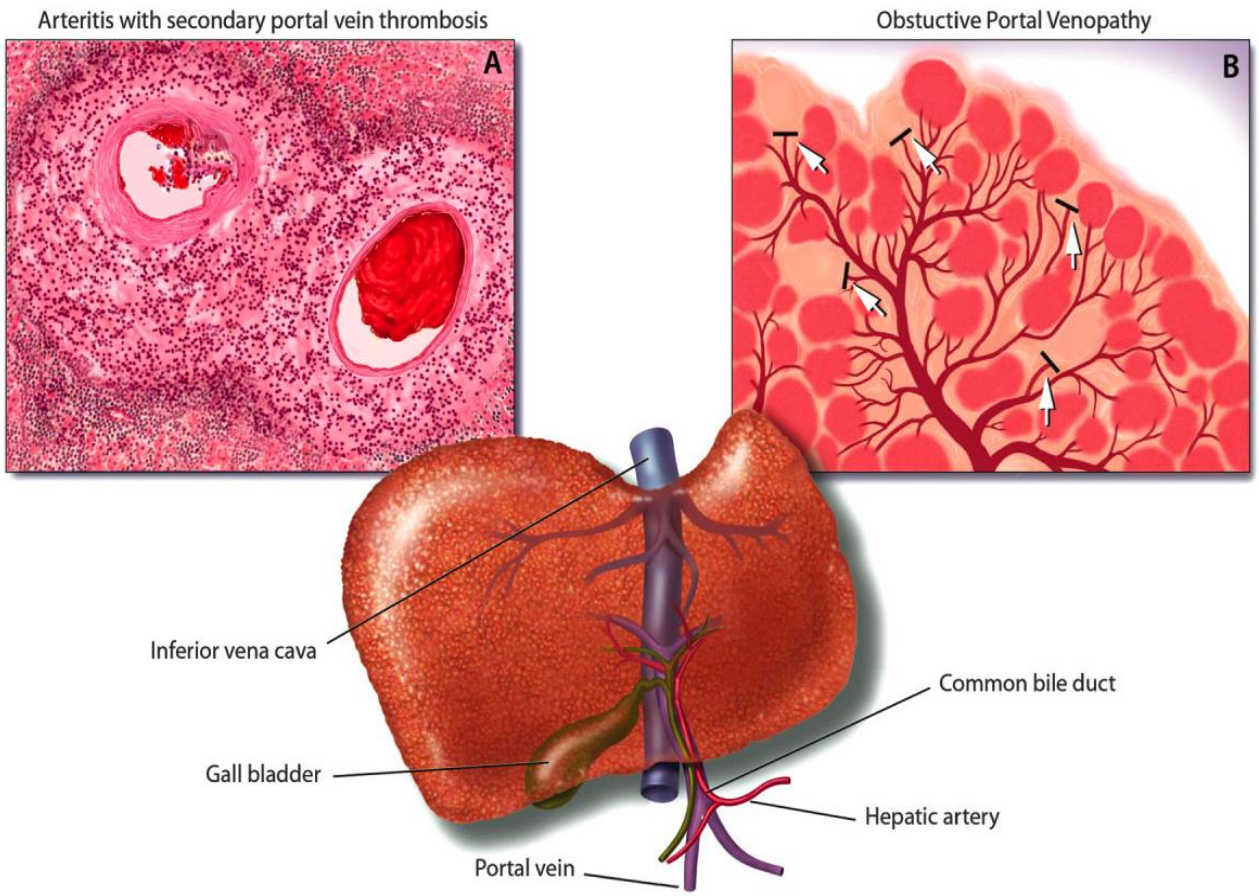
Metabolic disorders

Antiretroviral therapy (ART)

↓

Steatohepatitis +/- fibrosis

Nodular Regenerative Hyperplasia (NRH)



Main cause in non HIV:

Thrombophilia
Protein C deficiency,
Factor V Leiden….

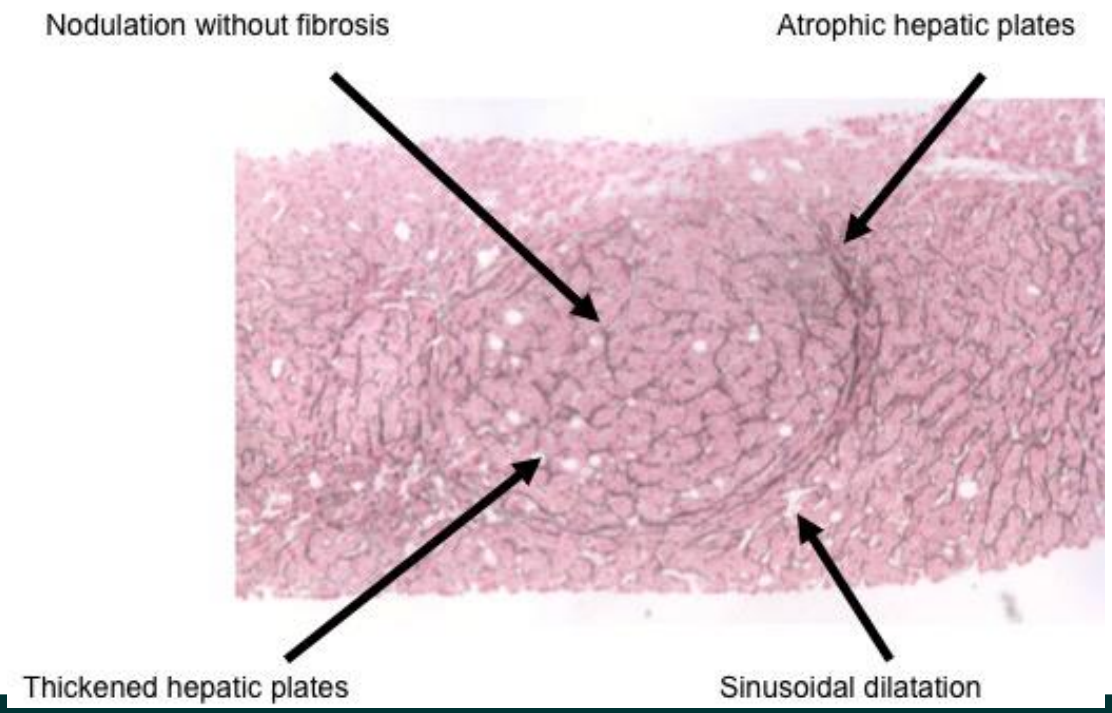
Reshamwala, 2004

Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients

Vincent Mallet[a,b,e,*], Pierre Blanchard[b,*], Virginie Verkarre[a,c], Anaïs Vallet-Pichard[a,b,e], Hélène Fontaine[b,e], Caroline Lascoux-Combe[d] and Stanislas Pol[a,b,e]

8 out of 97 HIV consecutive patients with unexplained persistent abnormal liver function tests and/or non-cirrhotic portal hypertension

⇒ Histologically confirmed NRH
⇒ Only causes: ddI exposure and HIV



Reshamwala, 2004
Mallet AIDS 2007

Noncirrhotic portal hypertension

Table 1. Literature Review on Noncirrhotic Portal Hypertension (NCPH) in HIV-Infected Persons

Author, year of publication	Case definition	Study design	No. of patients	Liver biopsy findings	Proposed risk factors for NCPH or elevated liver enzymes
Maida et al, 2006 [5]	Elevated liver enzymes of unknown origin	Case-control (1:1; matched by age, sex, CD4 cell count)	17 with elevated liver enzymes; suspected NCPH in 9 of 17	Biopsy in only 5 of 17: microvesicular steatosis in 5 of 5, mild fibrosis in 3 of 5, cirrhosis in 2 of 5	Prolonged DDI exposure
Mallet et al, 2007 [6]	Abnormal liver function tests or symptomatic PH of unknown origin	Case series	8	NRH in 7 of 8, sinusoidal dilatation in 1 of 8	DDI exposure (DDI in 8 of 8)
Arey et al, 2007 [7] (letter)		Case report	1	NRH	NVP (but patient with former DDI exposure)
Sandrine et al, 2007 [8] (letter)		Case report	1	NRH	Exposure to DDI and NVP
Garvey et al, 2007 [9] (letter)		Case series	6	NRH in 2 of 6, venous outflow obstruction in 3 of 6, normal in 1 of 6	DDI (in 5 of 6), coagulopathy (in 4 of 6)
Schiano et al, 2007 [10]	NCPH with variceal bleeding; HPS in biopsy; no etiology	Case series	4	HPS in 4 of 4	NVP (current therapy in 3 of 4); ART history not described
Maida et al, 2008 [11]	Elevated liver enzymes of unknown origin	Case series	32 with elevated liver enzymes; esophageal or gastric varices in 13 of 32	Biopsy in only 12 of 32: unspecific liver fibrosis in 3 of 12, NRH in 2 of 12, periportal fibrosis in 3 of 12	Prolonged DDI exposure, homosexual transmission modus
Tateo et al, 2008 [12]	Liver transplantation due to NCPH	Case series	3	NRH in 3 of 3	...
Saifee et al, 2008 [13]	NRH in wedge biopsies	Case series	11	NRH in 11 of 11	DDI in 11 of 11, coagulopathy in 8 of 10

NOTE. ART, antiretroviral therapy; DDI, didanosine; HIV, human immunodeficiency virus; HPS, hepatoportal sclerosis; NRH, nodular regenerative hyperplasia; NVP, nevirapine; PH, portal hypertension.

Kovari H et al., CID 2009

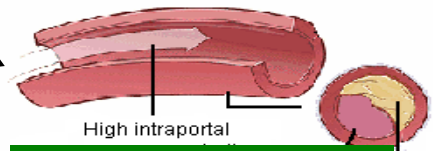
Non-cirrhotic portal hypertension

Unexplained:
- **↓platelets**
- **↑ transaminases**
- **↑ alkaline phosphatase, GGT**
- **E varices, ascites, splenomegaly**

Didanosine consumption

HIV

Hypercoagulability?



High intraportal drug concentration

Endothelial dysfunction?
Mitochondrial damage?

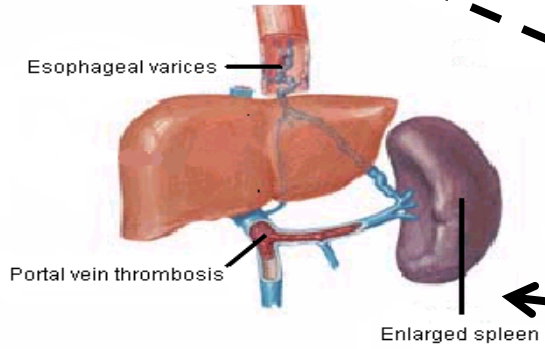
Heterogeneous liver perfusion

Periportal fibrosis

Partial nodular transformation

Nodular regenerative hyperplasia

Non-cirrhotic portal hypertension



Slide courtesy of Vicente Soriano

Chronic liver disease in non-alcoholic HIV mono-infected patients

Table 2. Histological Findings in Liver Biopsy of the 30 Patients with Aminotransferase Elevation of Unknown Origin

Fibrosis	n	%
F0	11	36.6
F1	13	43.3
F2	2	6.7
F3	1	3.3
F4	3	10
F1-4	19	63.3
Activity		
A0	14	46.7
A1-3	16	53.3
Steatosis		
≤5%	12	40
6-30%	9	30
>30%	9	30
Macrovesicular	12	66.6
Macrovesicular and microvesicular	6	33.3
Steatosis and inflammation		
Steatosis and inflammation (NASH)	16	53.3
Steatosis without inflammation	2	6.7
Inflammation without steatosis	8	26.6
No steatosis/no inflammation	4	13.3

Fibrosis and activity were classified according to the METAVIR score, and steatosis according to a 3-point scale.

n= 30 HIV mono-infected patients without alcohol abuse
<u>and</u>
persistent elevated transaminases (>ULN)

1 patient excluded because of nodular regenerative hyperplasia (NRH)

Ingiliz, P Hepatology 2009

Chronic liver disease in non-alcoholic HIV mono-infected patients

Table 2. Liver Biopsy Findings (n = 62)

Histologic Feature or Diagnosis	No. (%)
Steatosis	
None to trace (0) (<5%)	17 (27)
Mild (1) (5%–25%)	25 (40)
Moderate (2) (25%–50%)	13 (21)
Severe (3–4) (50%–75%)	7 (11)
Fibrosis score[a]	
None (0)	43 (69)
Mild (1)	7 (11)
Moderate (2)	1 (2)
Bridging (3–4)	11 (18)
Cirrhosis (5–6)	0 (0)
Diagnosis	
Nonspecific changes	22 (35)
Steatohepatitis	34 (55)
Steatohepatitis with any fibrosis	26 (42)
Steatohepatitis with bridging fibrosis	10 (16)
Fibrosis (Ishak stage ≥1) without evidence of steatohepatitis	3 (5)
Bridging fibrosis without steatohepatitis	1 (2)
Portal venopathy/nodular regenerative hyperplasia	3 (5)

All biopsies had at least 10 portal tracts for assessment. Median biopsy length was 15 mm (range, 7–24 mm); 59 of 62 (95%) biopsies were ≥10 mm in length.

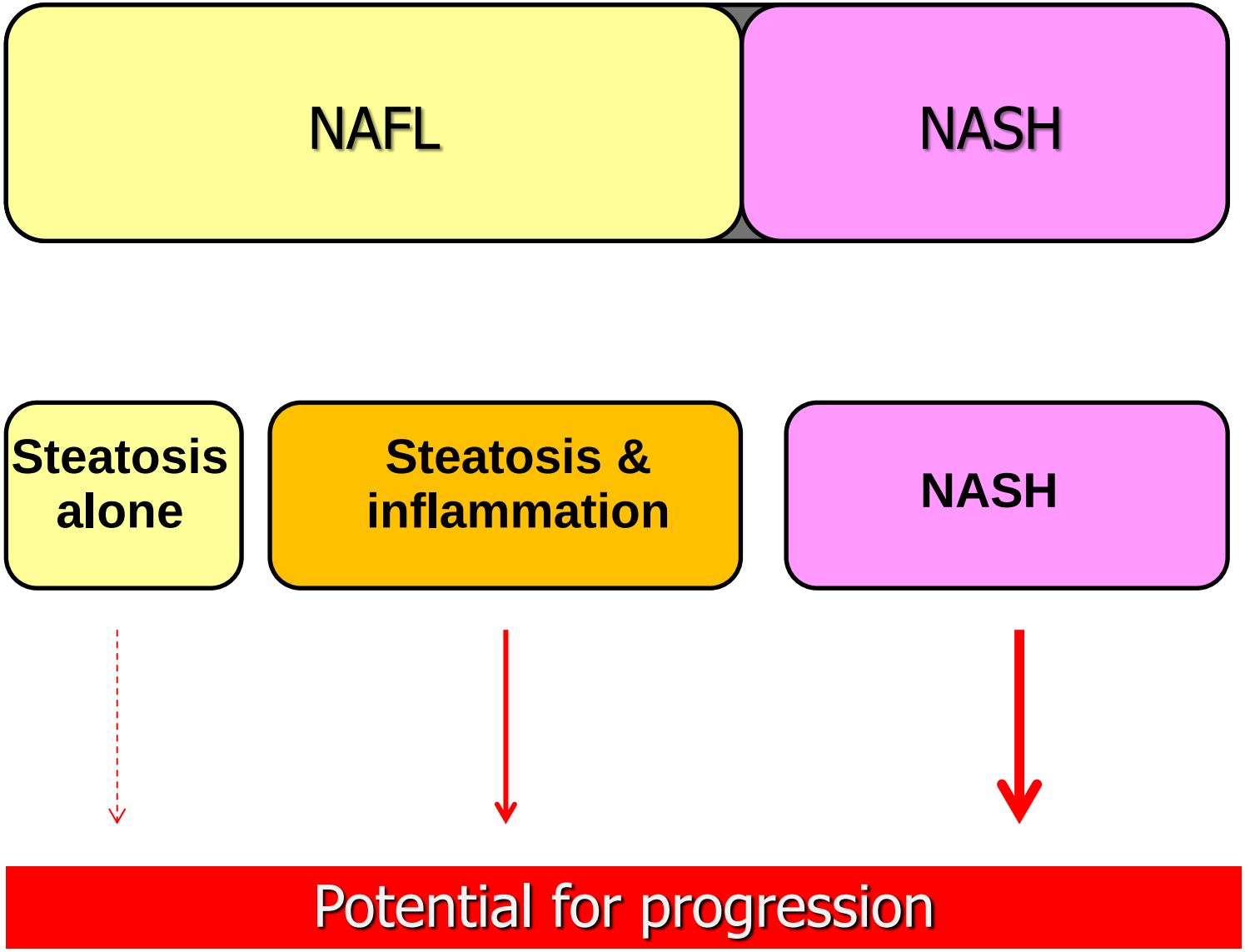
[a] Fibrosis classified according to the Ishak modified histology activity index scoring system [20].

62 HIV mono-infected patients (from USA)

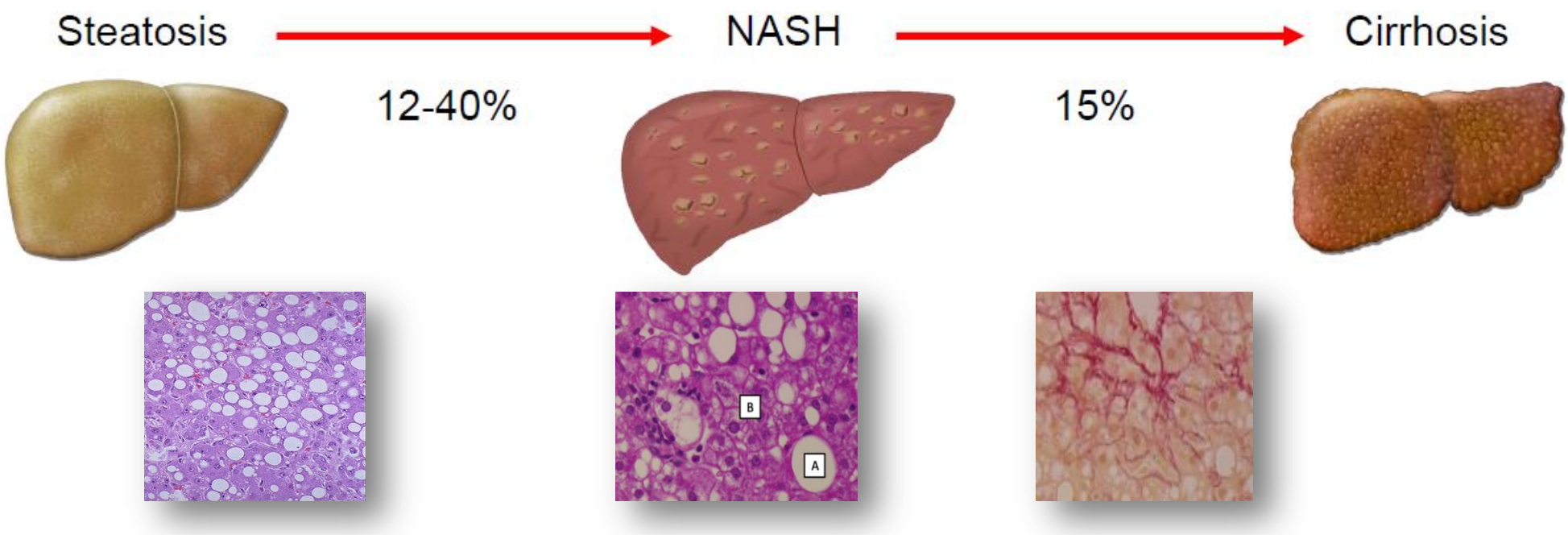
No alcohol abuse

With persistent elevated transaminases and liver histology

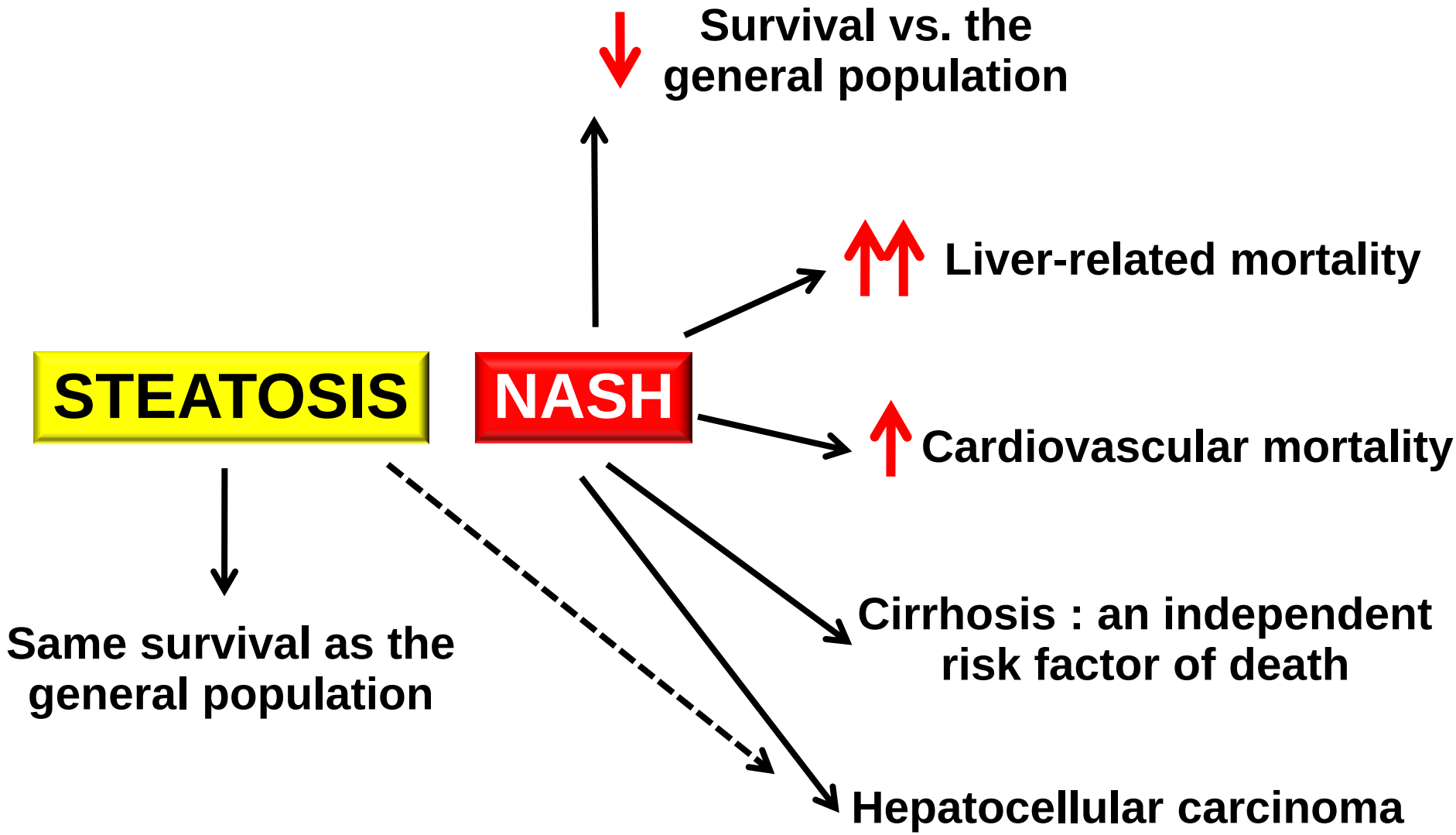
Morse, Clin Infect Dis 2015


NAFL
NASH
Steatosis alone
Steatosis & inflammation
NASH
Potential for progression

Natural history of NAFLD/NASH in non HIV subjects



NASH : reduced survival



Matteoni, Gastro 1999, Adams, Gastro 2005, Ekstedt, Hepatol 2006, Ong, J Hepatol 2008, Dunn AJG 2008, Sorderberg, Hepatology 2010 , Dyson J Hepatol 2014

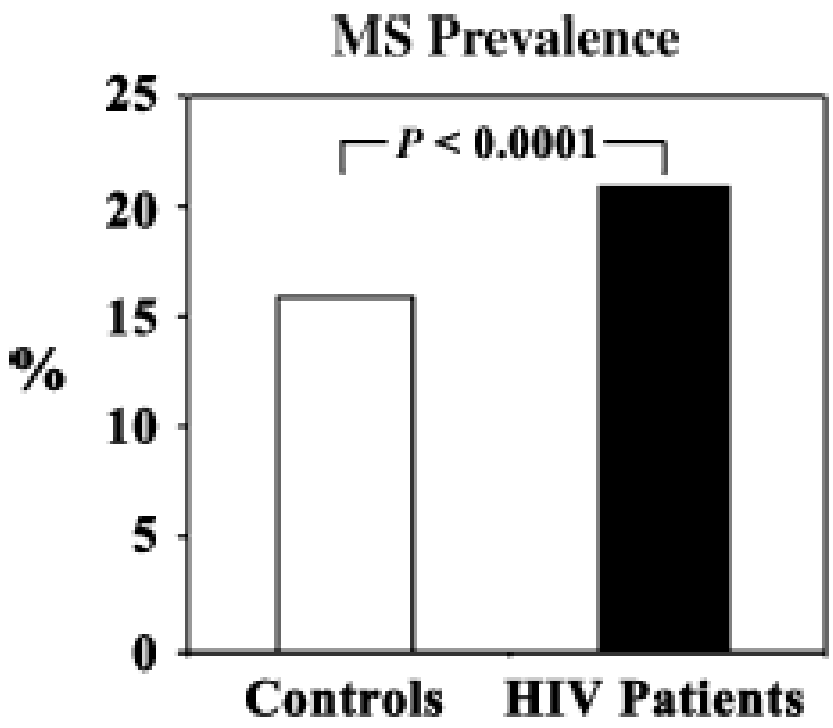
METABOLIC SYNDROME (MS) - A Joint definition

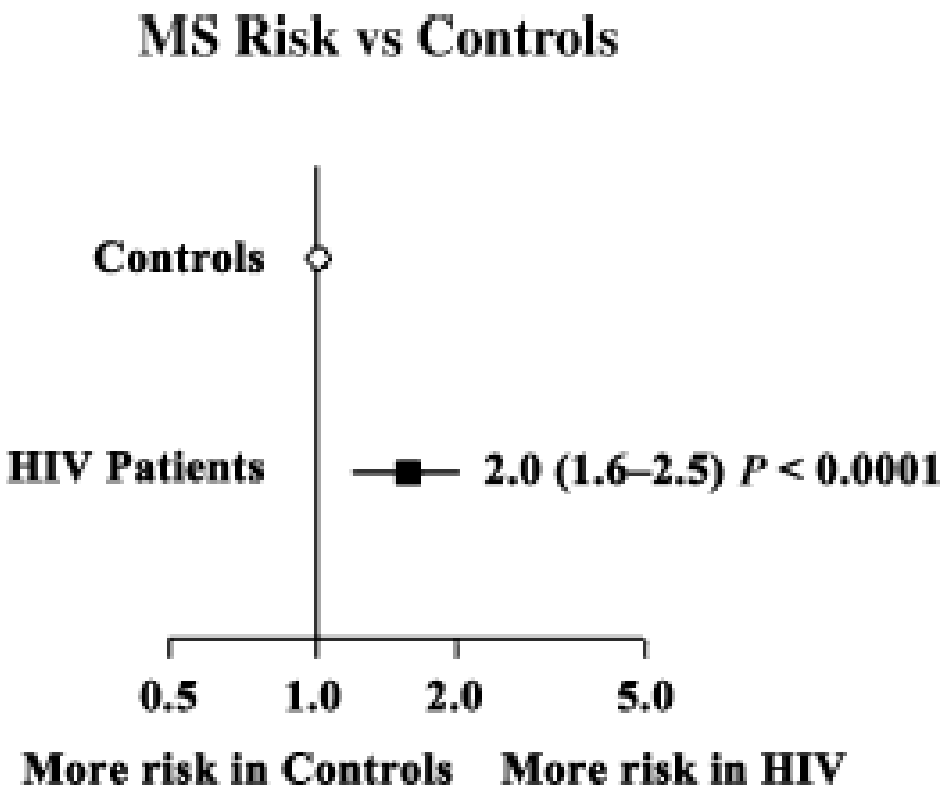
3 criteria out of five

Central obesity	**Waist circumference:** Europeans: ≥ 94 cm (M) ou ≥ 80 cm (F) Americans: ≥ 102 (M) ≥ 88 cm (F) Asians: ≥ 90 cm (M) ≥ 80 cm (F) Sub-Sahran African ≥ 94 cm (M) ou ≥ 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 treatment

Adapted from Alberti Circulation 2009

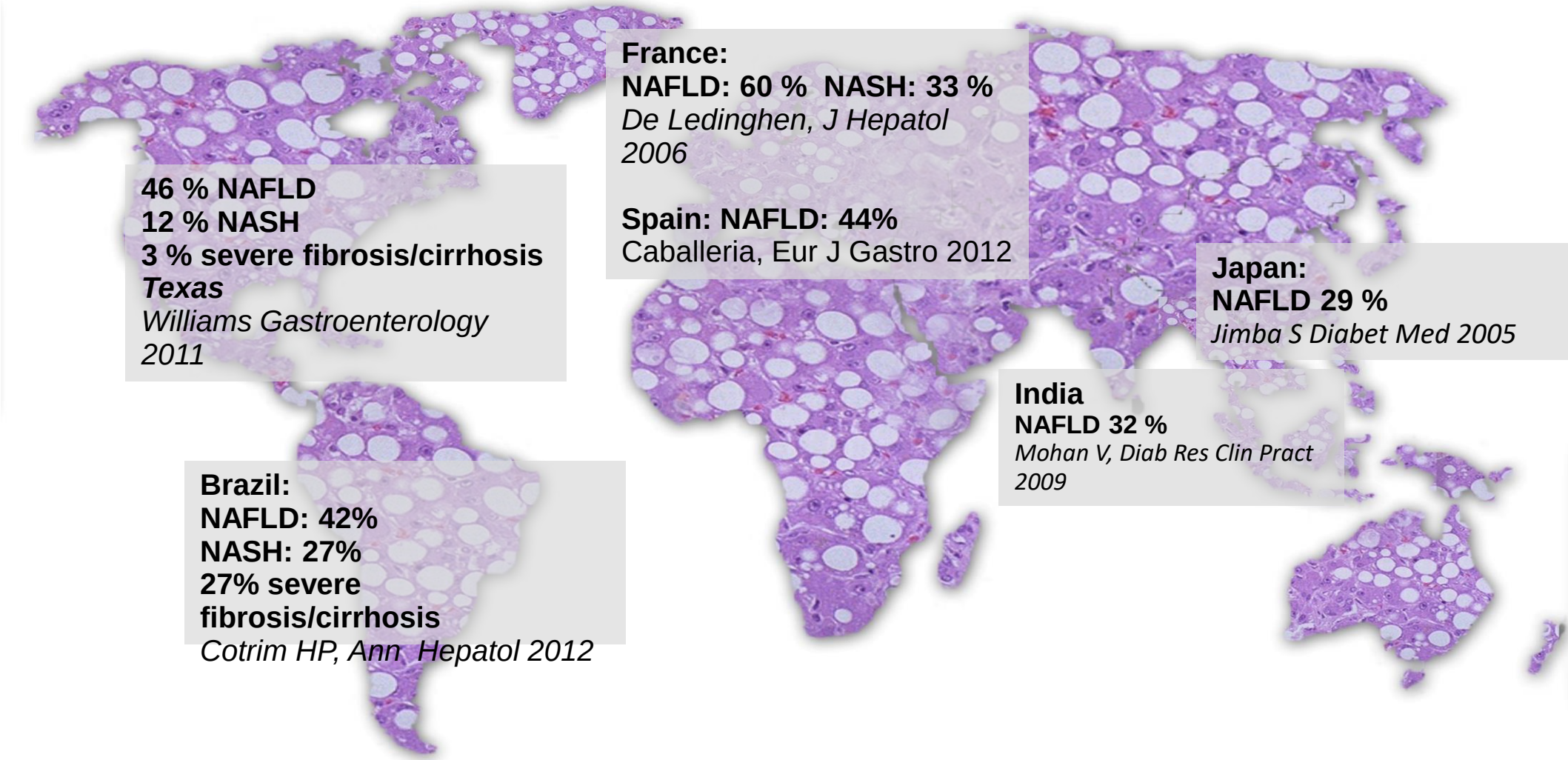
The risk of MS is twice in HIV patients





Bofanti et al, JAIDS 2007

Epidemiology of NAFLD/NASH



46 % NAFLD
12 % NASH
3 % severe fibrosis/cirrhosis
Texas
Williams Gastroenterology 2011

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

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

Japan:
NAFLD 29 %
Jimba S Diabet Med 2005

India
NAFLD 32 %
Mohan V, Diab Res Clin Pract 2009

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

Factors associated with the metabolic syndrome in HIV+ subjects

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

Crum-Cianflone N, JAIDS 2009
Capeau J, AIDS 2012

NAFLD in HIV patients

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

NASH and fibrosis in HIV patients

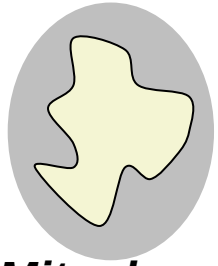
HIV monoinfected patients with unexplained elevated LFT

Study	country	n subjects	NASH assessment	Prevalence of NASH	Significant fibrosis
Lemoine, M AIDS 2006	France	14	Liver Biopsy	56%	29%
Mohammed, SS 2007 JAIDS	Canada	26	Liver Biopsy	55%	-
Crum-Cianflone, N 2009 JAIDS	USA	55	Liver Biopsy	20%	-
Ingiliz, P Hepatol 2009	France	30	Liver Biopsy	53%	30%
Sterling, R J Clin Gastr 2013	USA	14	Liver Biopsy	26%	14%
Morse, CG CID 2015	USA	62	Liver Biopsy	62%	18%
Vodkin, I APT 2015	USA	33	Liver Biopsy	63%	18.2%

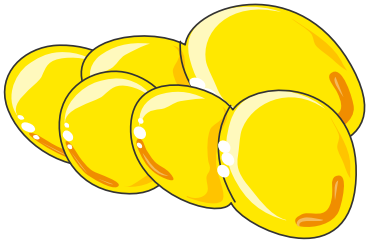
Non-alcoholic steatohepatitis (NASH) in HIV

Physiopathology

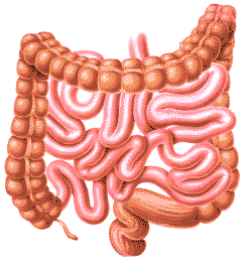
Key players



Mitochondria



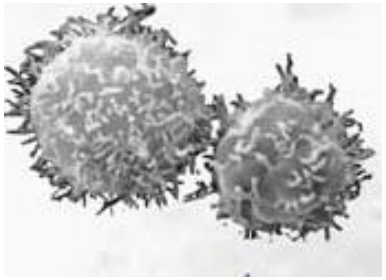
Adipose tissue



Gut

Lysosomes

Endoplasmic reticulum



Innate immune system

Genetic

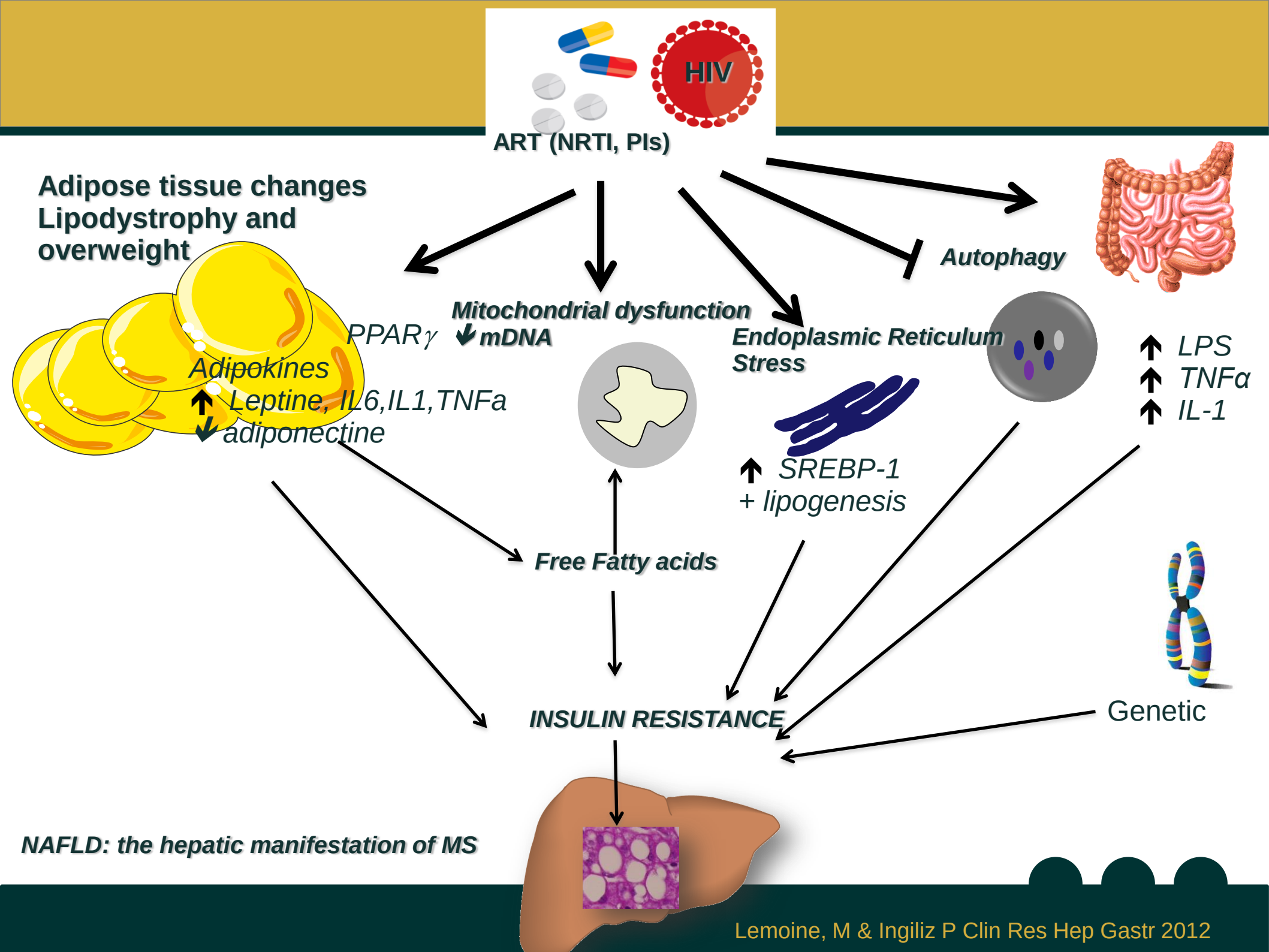
Insulinresistance is a key mediator

⇧ Oxidative stress
Chronic inflammation state

INSULIN RESISTANCE

Metabolic disorders

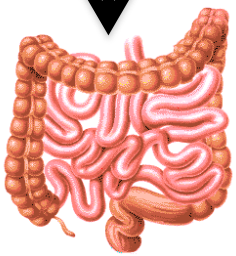
Lemoine, M & Ingiliz, P Clin res Hepatol Gastroenterol 2012



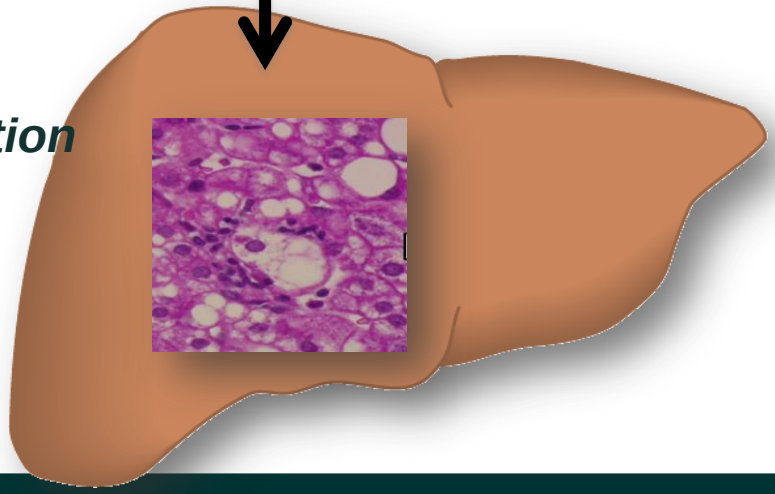
Lemoine, M & Ingiliz P Clin Res Hep Gastr 2012

Intestinal dysbiosis and microbial translocation

- ↑ *Dysbiosis (imbalance in microbiota)*
- ↑ *Intestinal permeability*
- ↑ *Microbial translocation*
- ↑ *sCD4 and LPS*
- ↑ *Immune activation (TLR)*
- ↑ *Inflammatory cytokines*



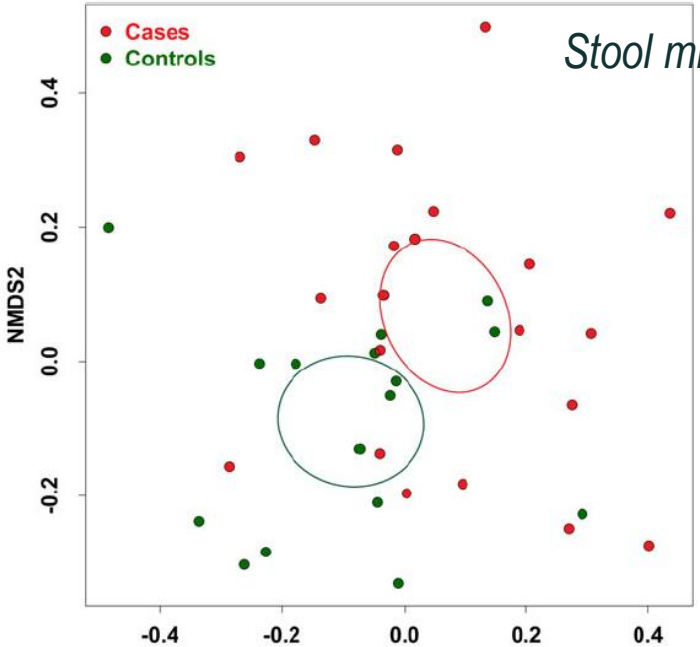
↑ *Systemic inflammation*



Liver inflammation & fibrosis

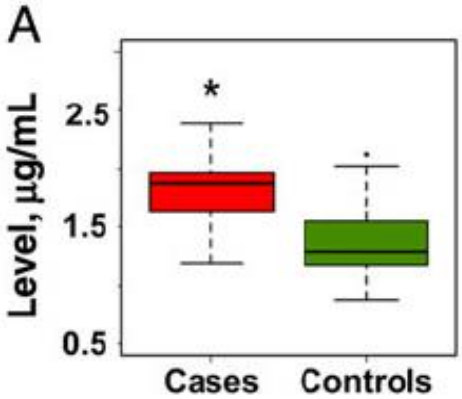
Dinh, DM JID 2015
Miele L et al. 2013

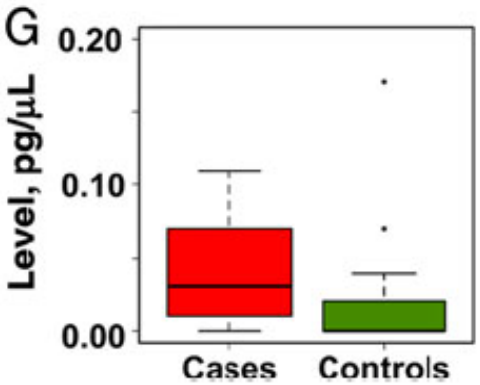
Intestinal dysbiosis and microbial translocation

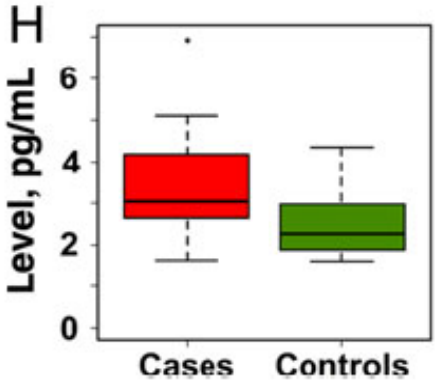


Stool microbiomal community

HIV neg controls (n=16)
Non obese HIV under HAART (n=21)







Dinh, DM JID 2015

Gene of Adiponutrin

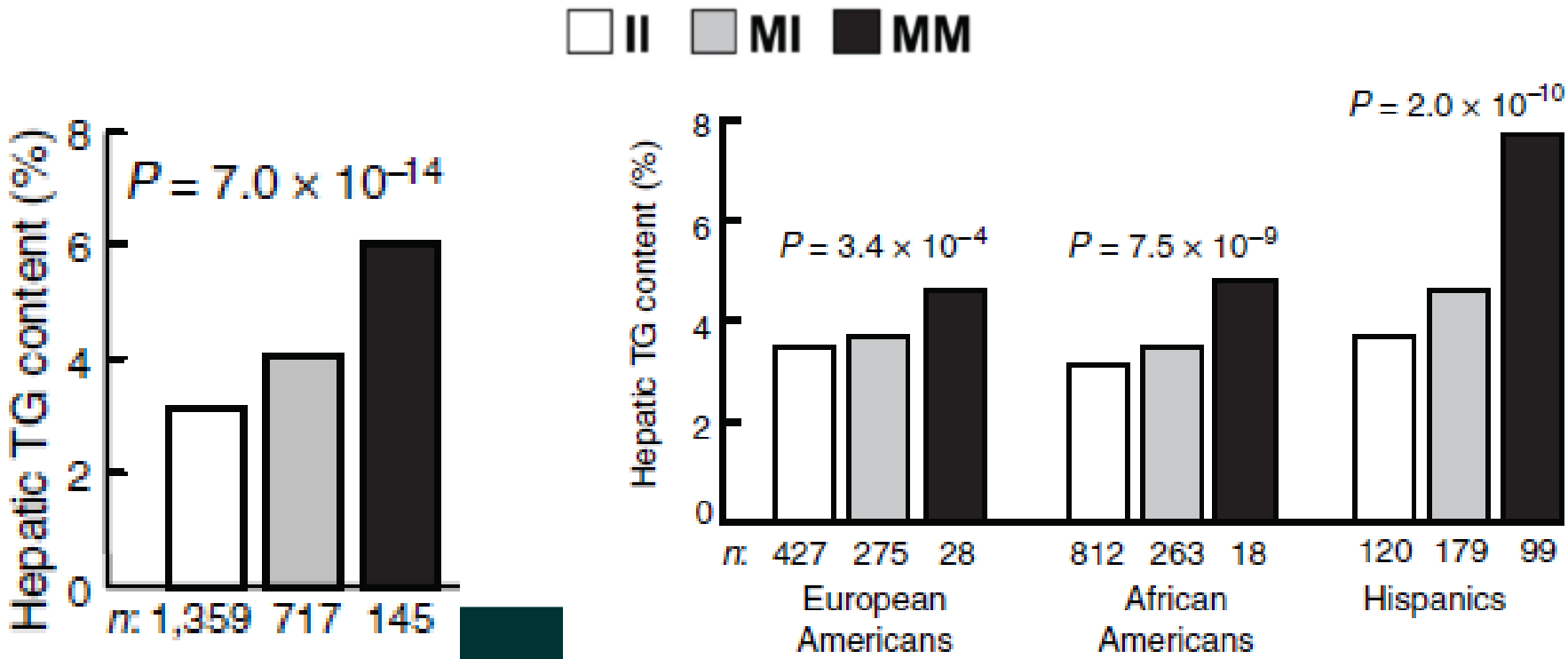
nature genetics

Genetic variation in *PNPLA3* confers susceptibility to nonalcoholic fatty liver disease

Stefano Romeo[1,8], Julia Kozlitina[2,3,8], Chao Xing[1,2], Alexander Pertsemlidis[1], David Cox[4], Len A Pennacchio[5], Eric Boerwinkle[6], Jonathan C Cohen[1] & Helen H Hobbs[1,7]

NATURE GENETICS | VOLUME 40 | NUMBER 12 | DECEMBER 2008

n = 2, 971
Liver Fat content (Spectrometry)
Genomic analysis



PNPLA3 and NAFLD in HIV

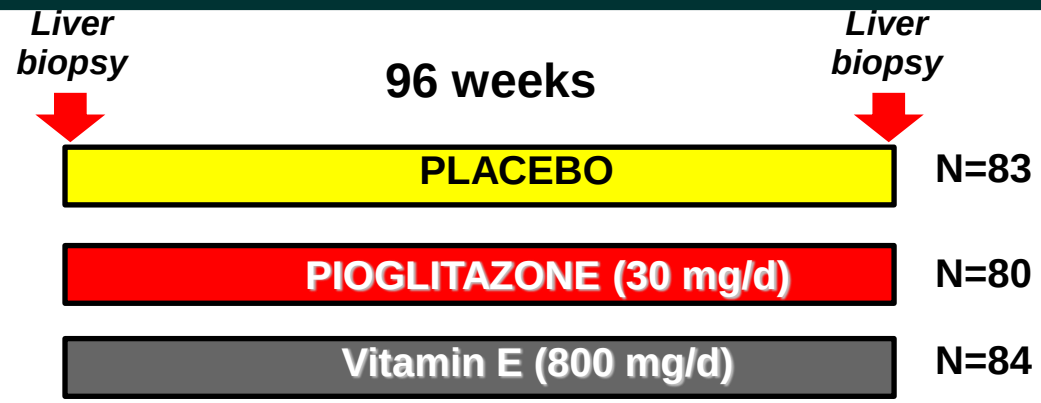
In two studies, **non-CC variant of rs738049** in the PNPLA3 gene has been shown to be associated with:

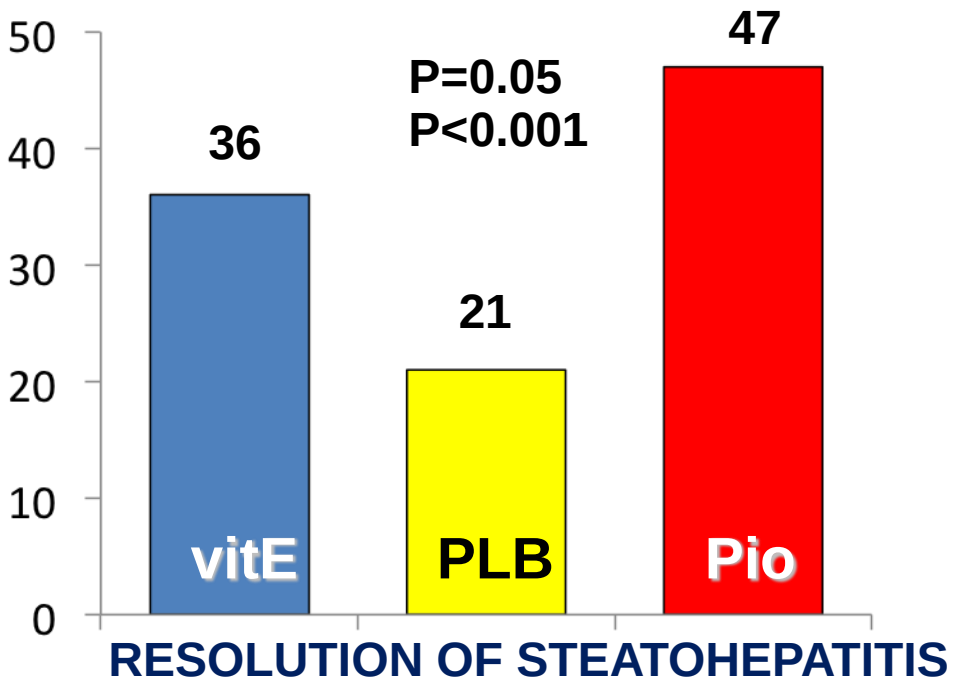
- ✓ Liver steatosis
- ✓ Fibrosis
- ✓ Levels of transminases

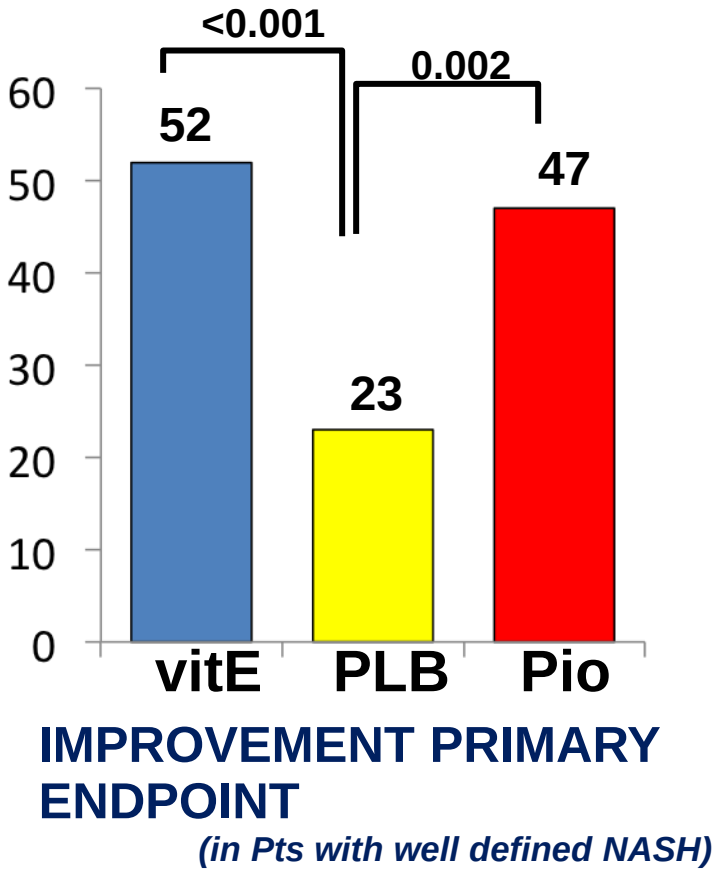
Morse, CG et al CID 2015
Price, JC Am J Gastroenterol 2014

Treatment for NASH

Results of the PIVENS trial in non-diabetic NASH







Pioglitazone improved :

- Steatosis
- Inflammation
- Ballooning
- NAS score

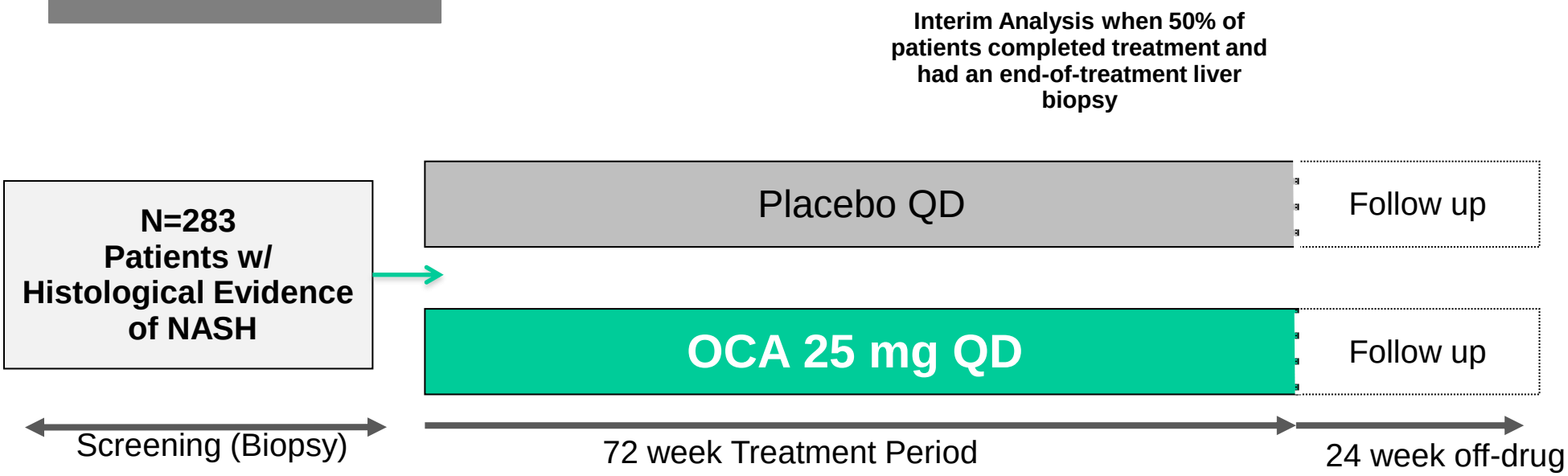
Sanyal, NASH CRN, NEJM 2010

FLINT Phase 2 Trial Design

The Farnesoid X Receptor Ligand Obeticholic Acid (OCA) in NASH Treatment

National Institute of Diabetes and Digestive and Kidney Diseases

NASH CRN



Primary endpoint: Histological improvement defined as:

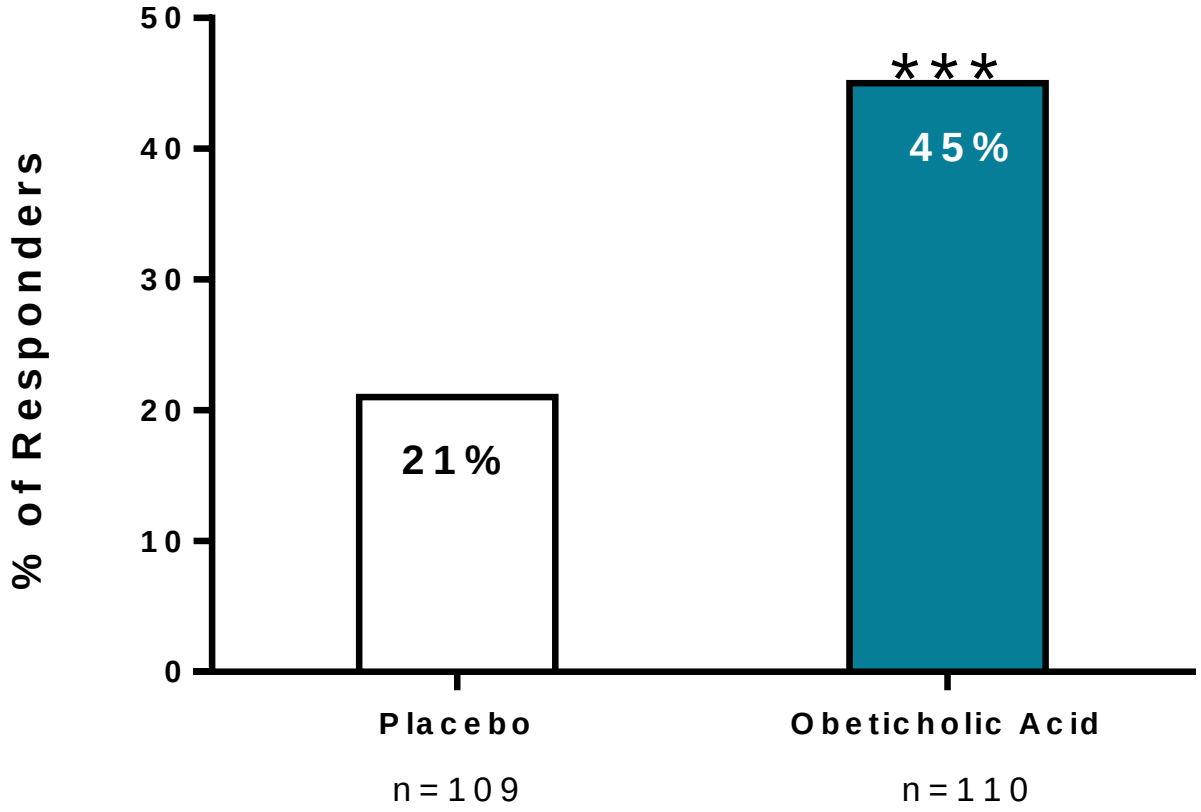
- No worsening in fibrosis; and
- Decrease in NAS of ≥ 2 points

Intercept

Tetri, Lancet 2014

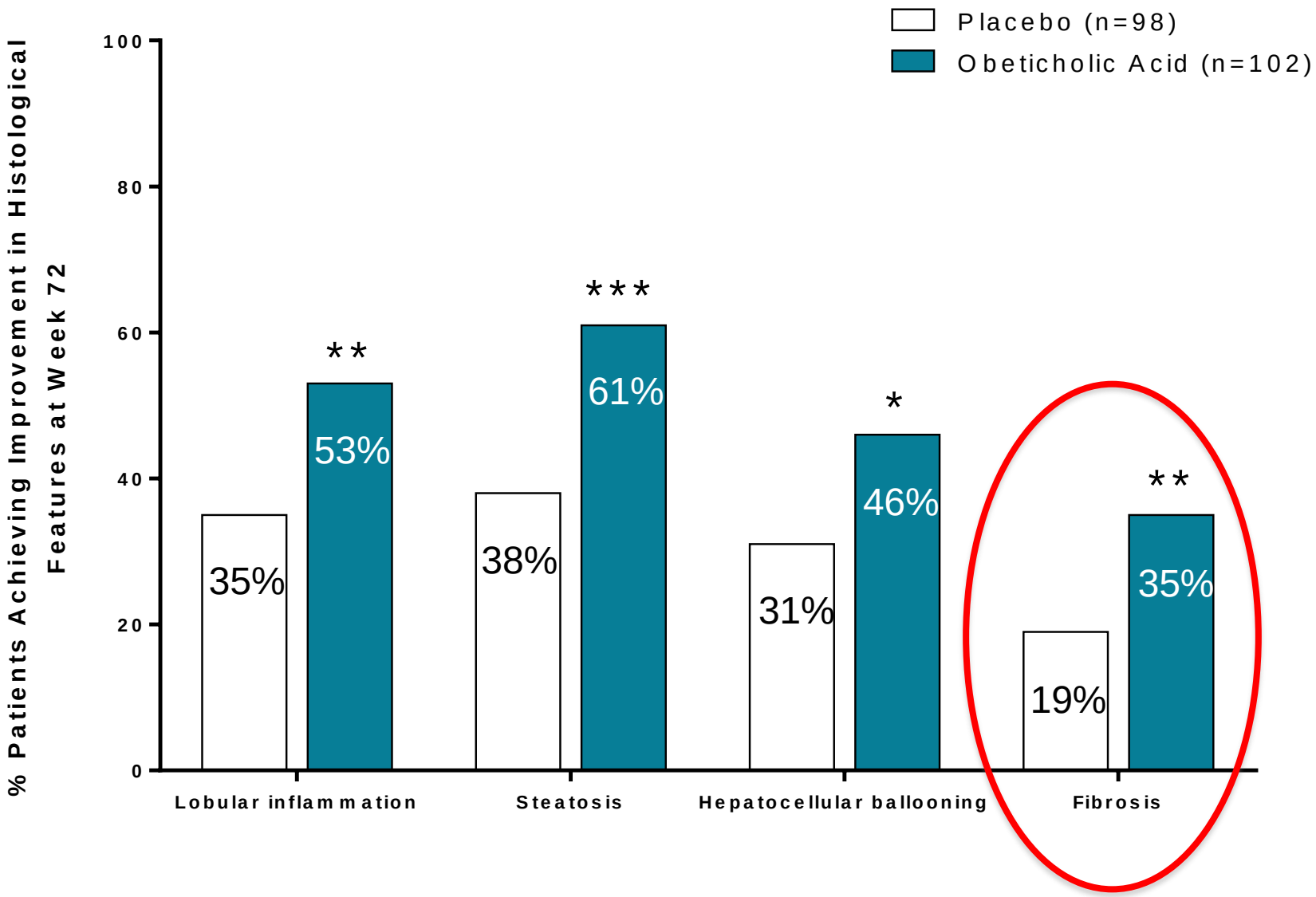
Primary Outcome: Improved Liver Histology after 72 Weeks of Treatment

Patients Achieving the Primary Outcome Measure
(2-point or greater improvement in NAFLD activity score without worsening of fibrosis)



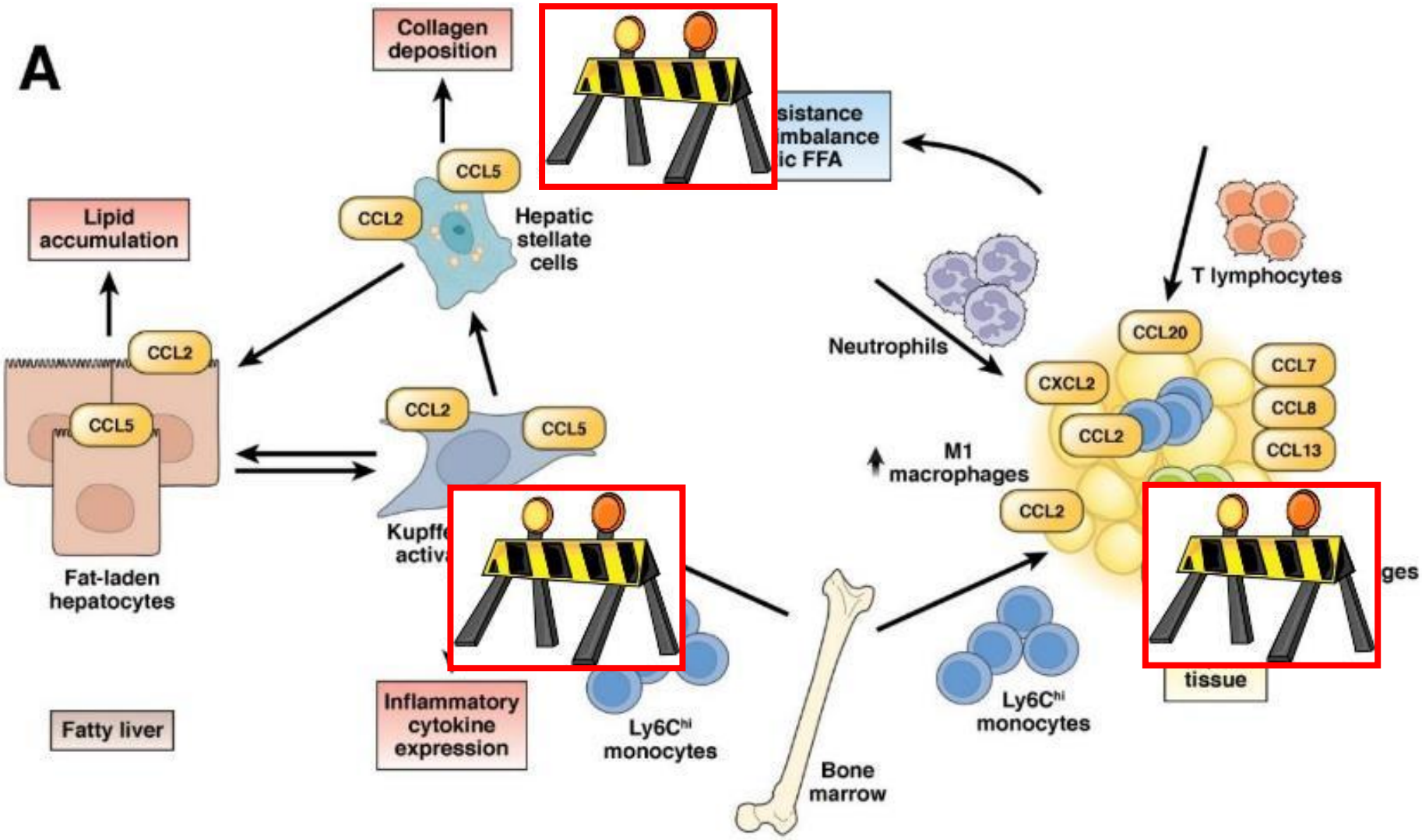
***p<0.001; Relative risk (95% CI): 1.9 (1.3 to 2.8); p-value and relative benefit were obtained using Cochran-Mantel-Haenszel Chi-square test stratified by center and diabetes status; Missing week 72 biopsy results were imputed as no improvement among patients at risk of week 72 biopsy; Neuschwander-Tetri BA, et al. *Lancet*. 2014:S0140-6736(14)61933-4.

Secondary Outcomes: Improvement in Histological Parameters



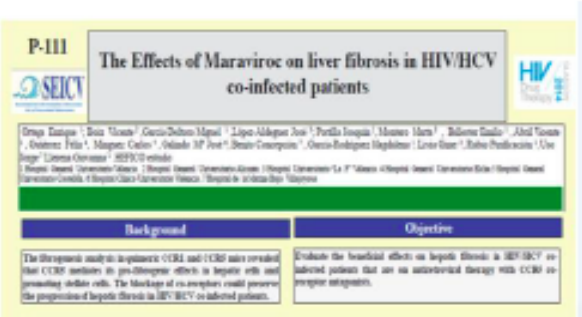
*p<0.05, **p<0.01, ***p<0.001; p-value was based on the Cochran-Mantel-Haenszel chi-square test stratified by center and diabetes status; Neuschwander-Tetri BA, et al. *Lancet*. 2014:S0140-6736(14)61933-4.

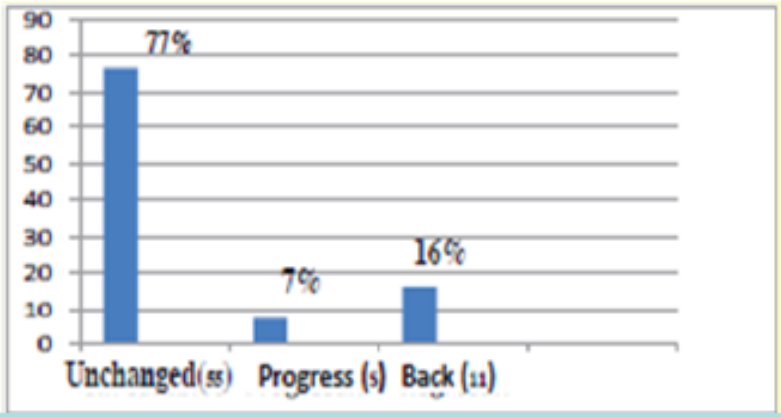
Monocytes and steatohepatitis

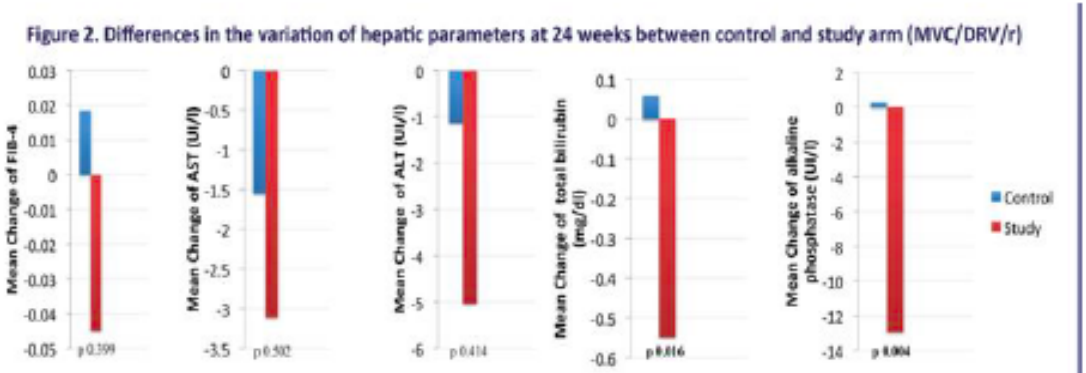


Marra F & Tacke F, Gastroenterology 2014

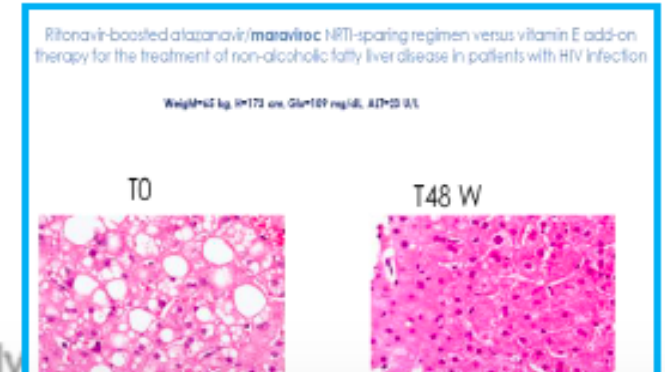
Clinical Data with MVC Evaluating Hepatic Fibrosis







NASH study comparing ATV/MVC with NRTI-ART +Vit E hitsological resolution at 48 weeks



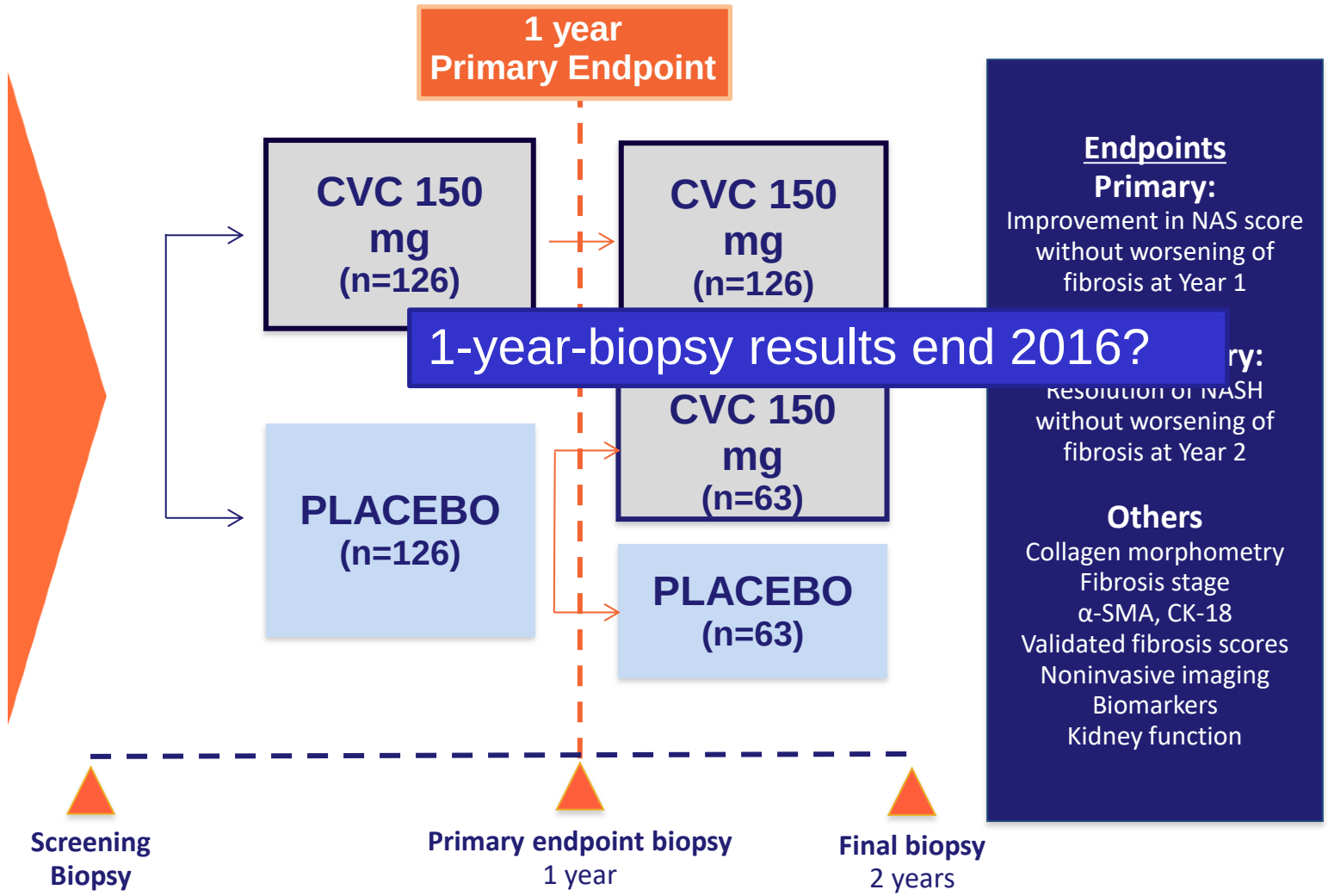
Phase II-study of the CCR2/CCR5 Inhibitors Cenicriviroc (CVC)

CENTAUR trial

Global phase 2b study, N = 289

Key Eligibility Criteria

- Biopsy diagnosis of NASH with fibrosis
- Enriched for patients with T2DM; high BMI with ≥ 1 criteria of metabolic syndrome; bridging fibrosis and/or definite NASH



NCT02217475; EudraCT number 2014-003164-21

CVC in steatohepatitis and fibrosis

MCD diet - progressive steatosis & fibrosis

0wks. — **4wks.** — **8wks.**

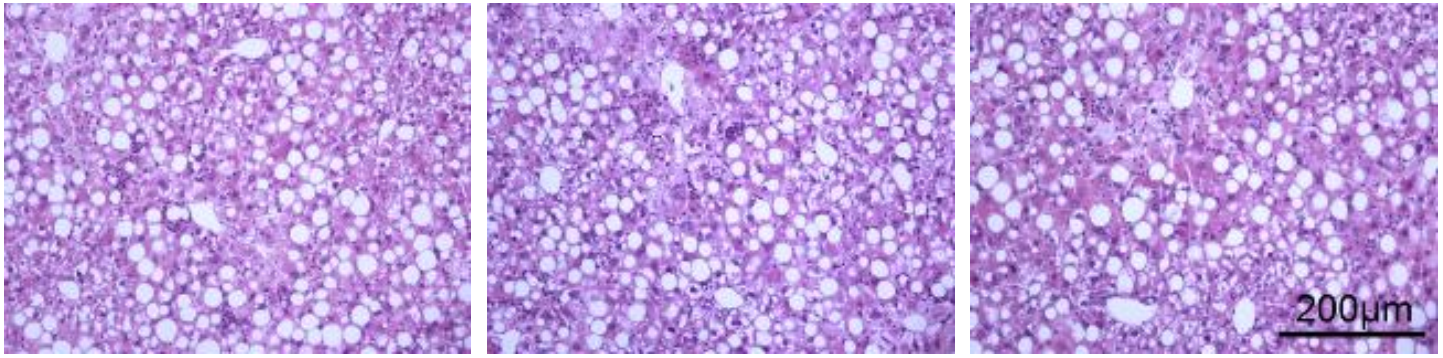
n = 8

Vhc. p.o. 1x/d

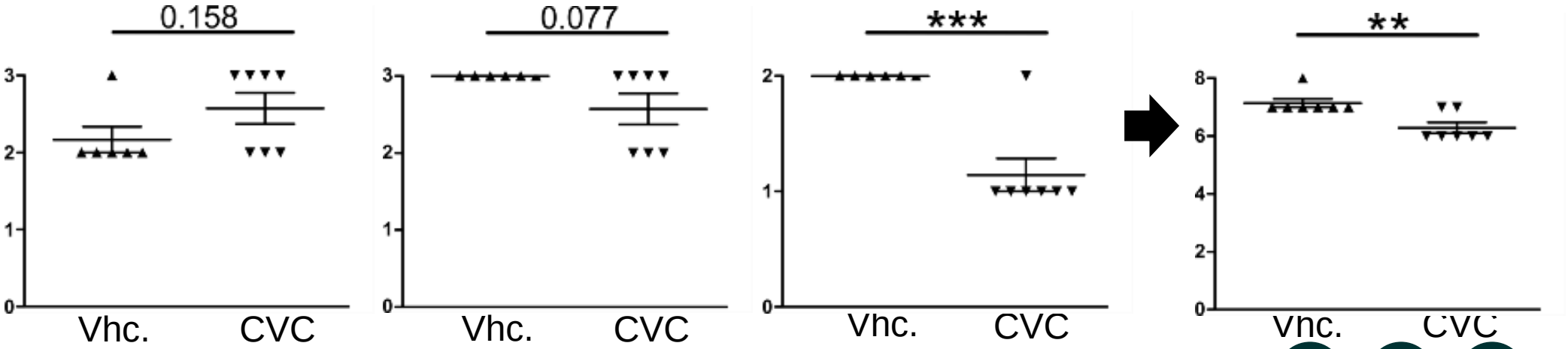
CVC p.o. 1x/d

8wks. **MCD diet** | +4wks. **Vhc.** | +4wks. **CVC**

H&E



Steatosis | **Lobular Inflammation** | **Hepatocyte Ballooning** | **NAFLD Activity Score**



Puengel T, et al., EASL 2016

Target-Based Drug Classes for NASH

Class	Drug	
Farnesoid X receptor (FXR) agonist	Obeticholic acid	Breakthrough status*
Anti-lysyl oxidase-like 2 monoclonal antibody	Simtuzumab	
Fatty acid/bile acid conjugate	Aramchol	Fast Track status*
Dual inhibitor of CCR2 and CCR5	Cenicriviroc	Fast Track status*
Dual peroxisome proliferator-activated receptor alpha/delta agonist	GFT505	Fast Track status*
Galectin-3-inhibitor	GR-MD-02	Fast Track status*

*US Food and Drug Administration.

Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with nonalcoholic fatty liver disease (NAFLD)

Winston Dunn, M.D[1,2], **Arun J. Sanyal, M.D.**[3], **Elizabeth M. Brunt, M.D.**[4], **Aynur Unalp-Arida, M.D., Ph.D.**[5], **Michael Donohue, Ph.D.**[6], **Arthur J. McCullough, M.D.**[7], and **Jeffrey B. Schwimmer, M.D**[8,9] **for the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)**[10]

J Hepatol. 2012 August ; 57(2): 384–391.