Therapeutic Targets for NASH in HIV

Unique opportunities and challenges

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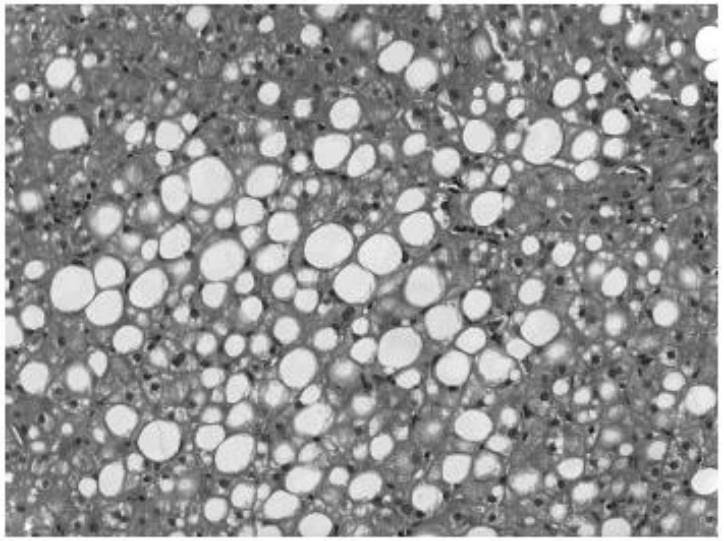


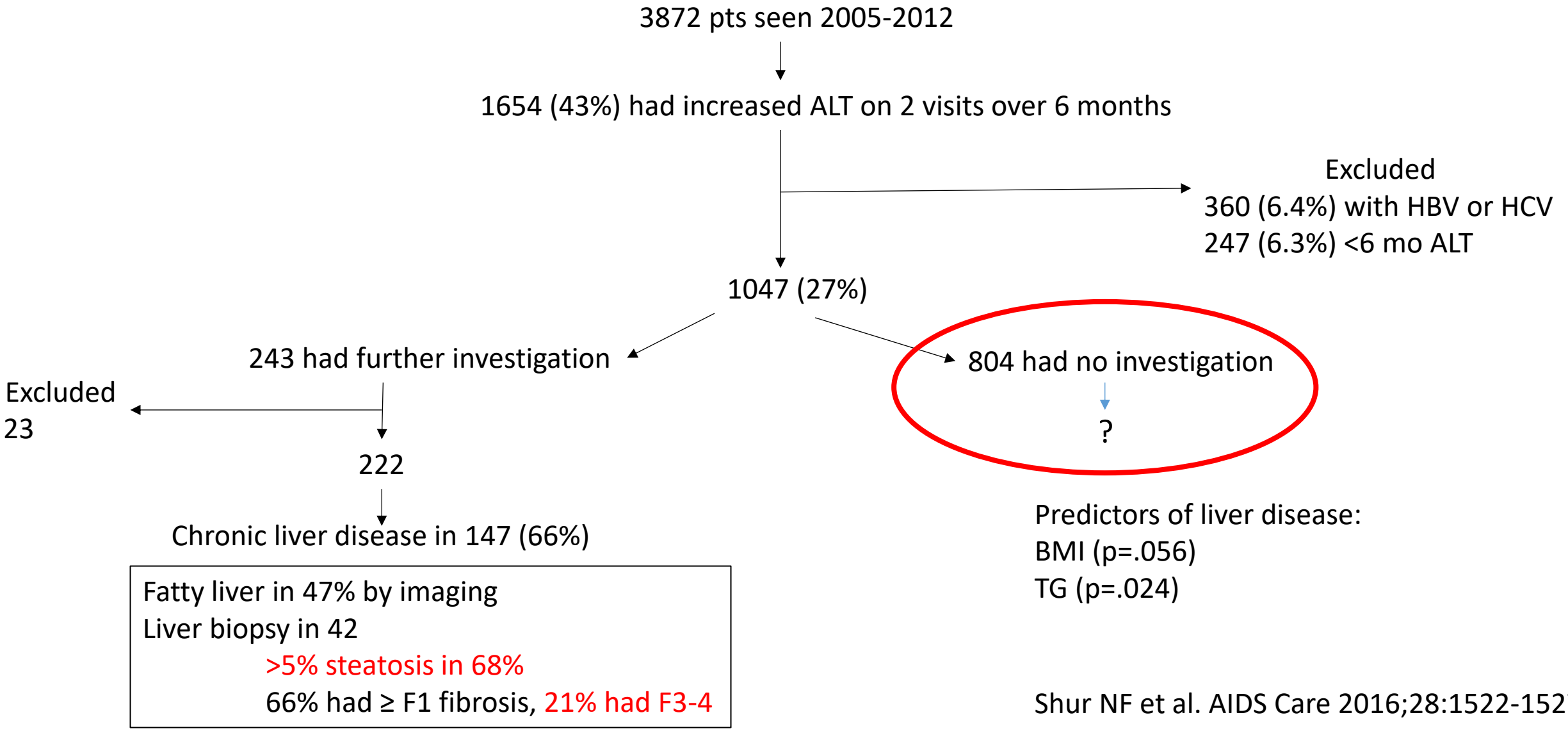
Conflicts of Interest in the last 12 months

- Advisory Board
  - Merck, Bayer, Salix, AbbVie, Gilead, ViiV, Baxter, Pfizer
- Research support
  - Roche/Genentech, Merck, BMS, AbbVie, Gilead, Abbott
- Speaker
  - None
- Stock/Financial interest
  - None

Outline

- What factors are associated with fatty liver in those with HIV ?
- What are the unique opportunities in treating NASH in HIV ?

Burden on non-viral liver disease in HIV



Shur NF et al. AIDS Care 2016;28:1522-1527

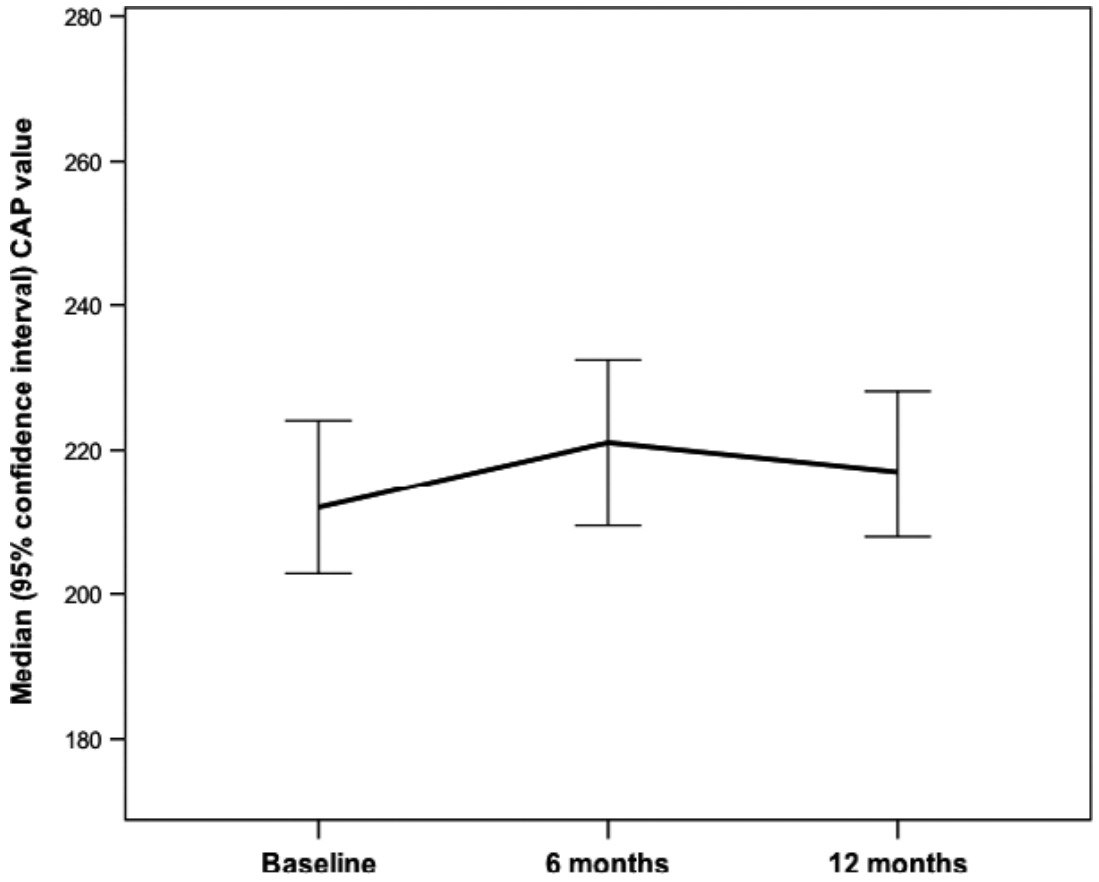
Incidence and Predictors of Steatosis in HIV

- 796 consecutive HIV+ without HCV or HBV observed for median 4.9 yrs
- Hepatic steatosis dx by index ≥36
  - 8 x AST/ALT + BMI (2+ if female; +2 if DM)
    Lee et al Dig Liver Dis 2010;42:503-508
  - AUC 0.88, Sen 86%, Spec 84% PPV 63% NPV 95%
- Hepatic fibrosis by FIB-4 (>3.25)
- Kaplan-Meier analysis for incidence
- Cox regression for predictors

- Incidence of steatosis 6.9/100 person yrs (95% CI 2.2-6.4) with 24% developing it over 5 yr period of observation
  - Steatosis predicted by black race (HR 2.18; 95% CI 1.58-3; p<.001), low albumin (HR 0.94; 95% CI 0.91-.97; p<.001).
- Incidence of advanced fibrosis 0.9/100 person yrs (95% CI 0.6-1.3) with 3.8% developing it over 5 yr period of observation
  - Fibrosis predicted by glucose (HR 1.22; 95% CI 1.2-1.3; p<.001) and lower albumin (HR 0.89; 95% CI 0.84-0.93; p<.001)

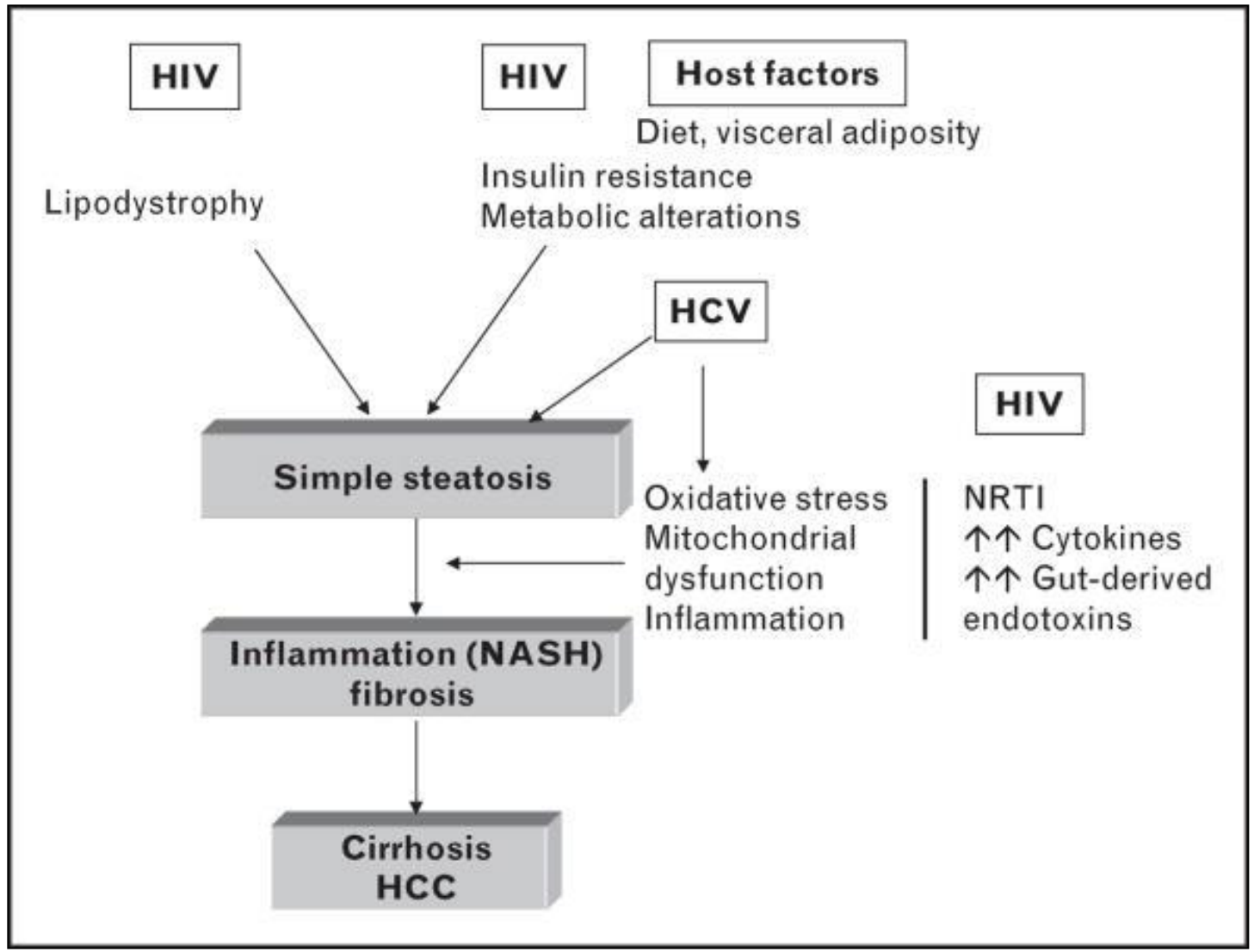
Sebastiani G et al. Open Forum in Infectious Diseases 2015

Changes in liver steatosis by VCTE/CAP in HIV

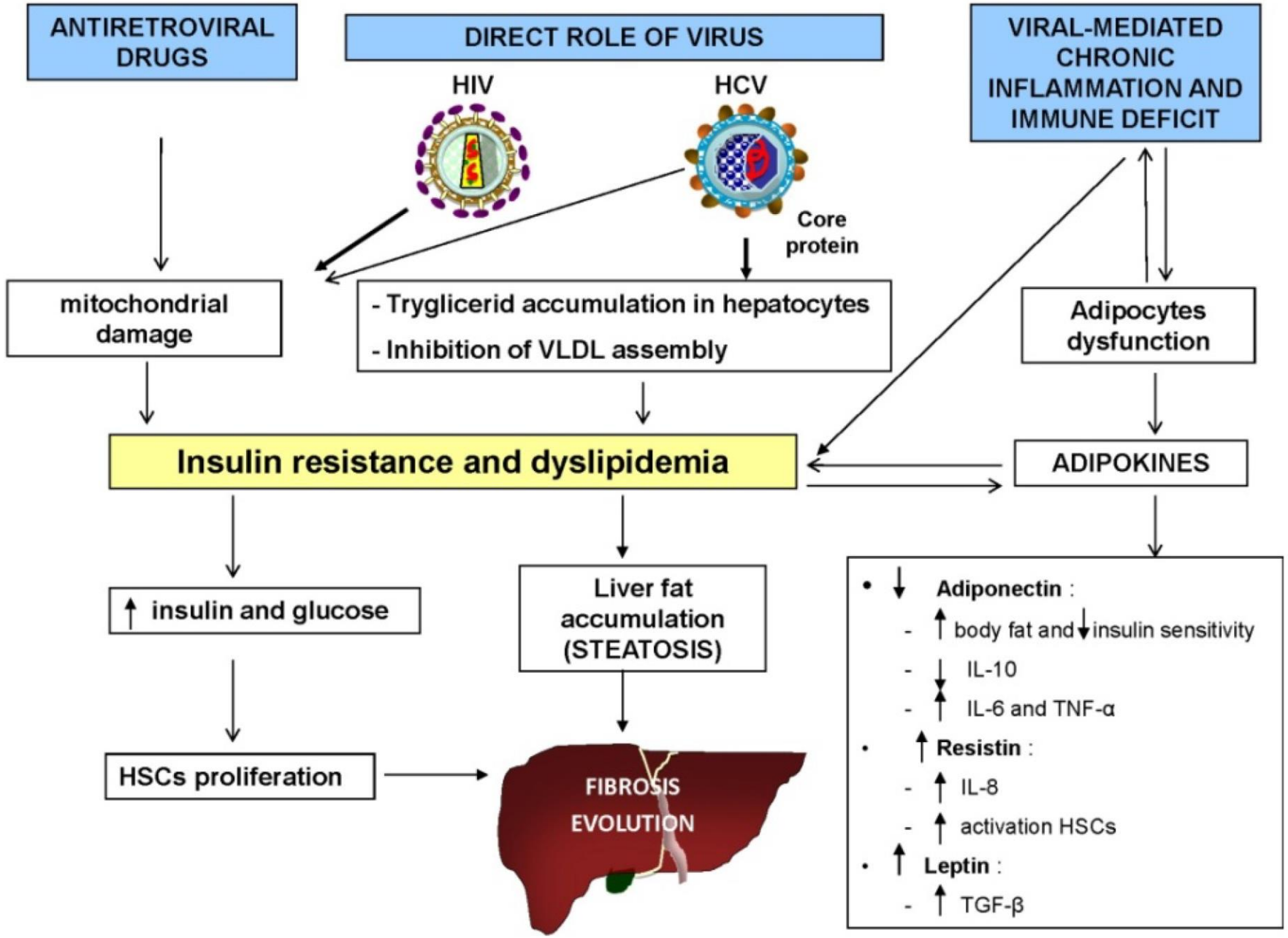


- 326 HIV+ patients undergoing CAP at baseline at mo 12
- Significant steatosis (≥ 238dB/m) was seen in 37% at baseline and not that different at follow-up
- Independent factors associated with increased CAP
  - Increase BMI

Macias J et al. HIV Medicine 2016;17:766-773



Lemoine, M et al. Current Opinion in Infectious Diseases. 25(1):10-16, February 2012.

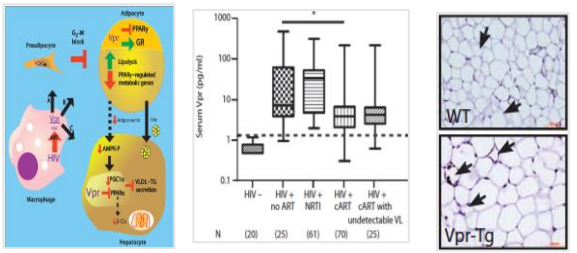


CM Mastroianni et al. Int J Mol Sci 2014;15:9184-9208

HIV Contribution to NASH

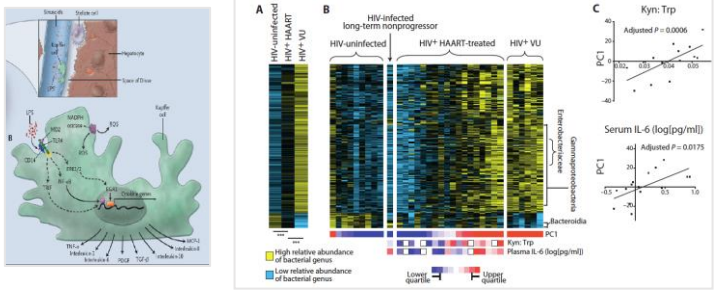
VPR

VPR-induced adipocyte hypertrophy and macrophage recruitment in adipose tissue in transgenic mice, including liver steatosis, insulin resistance



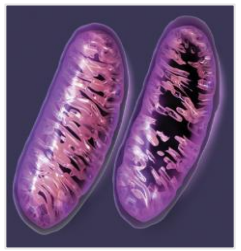
Microbial Dysbiosis

GALT depletion and altered microbiota to inflammatory profile attenuates translocation of endotoxins and Kupffer cell activation

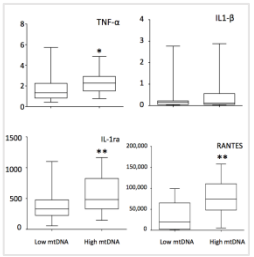


Mitochondrial Stress

NRTI and PI associated with mitochondrial toxicity and depletion. HIV also associated with mitochondrial stress and increased ROS. Clonal expansion of mutations

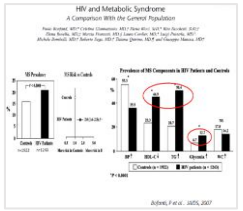


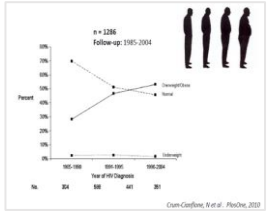
Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations



Metabolic Syndrome and Ageing

Metabolic syndrome (MetS) prevalence increased in HIV and ageing HIV population further increases risk of MetS and NASH

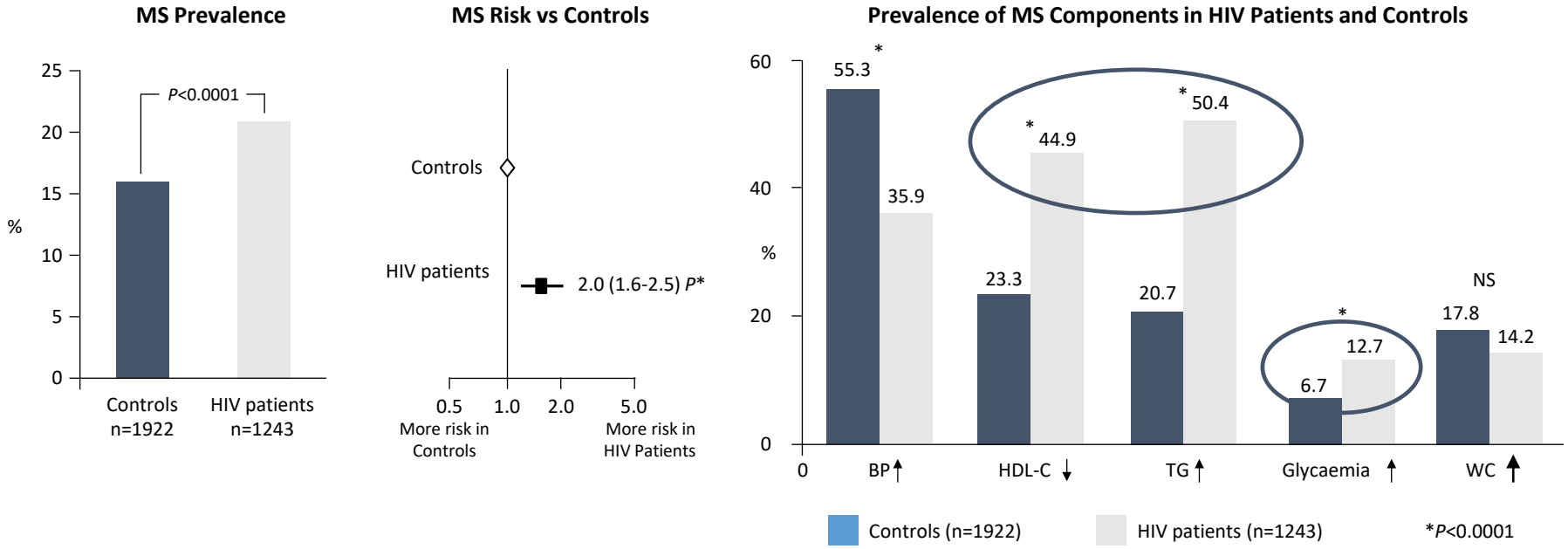




Deeks SG et al. Curr Opin Immunol 2012;24: 501–6. Vidal F et al. J Acquir Immune Defic Syndr 2012;61:131–7. Agarwal N et al. Sci Transl Med 2013;5:213ra164. Beaupere C. Aging Cell 2015;14:534–46. Delzenne NM et al. Microb Cell Fact 2011;10(Suppl 1):S10. Vujkovic-Cvijin I et al. Sci Transl Med 2013;5(193):193ra91

Patients with HIV are More Likely to Have Metabolic Syndrome

- Patients with HIV are more likely to develop metabolic disease
- Because of the close connection between metabolic syndrome and liver disease, there is also a higher risk of non-alcoholic liver disease in patients with HIV



BP, blood pressure; NS, not significant; WC, weight circumference.
Bonfanti P et al. J Acquir Immune Defic Syndr 2007;45:426–31

Metabolic syndrome is common in HIV patients

Study	n	country	MS criteria	Prevalence (%)
Gazzaruso, C Diabetes Care 2002	533	Italy	NCEP-ATPIII	**45.4**
Bruno, R JAIDS 2002	201	Italy	EGIR	**39.8**
Jerico, C Diabetes Care 2005	710	Spain	NCEP-ATPIII	**17**
Bonfanti, P JAIDS 2007	1243	Italy	NCEP-ATPIII	**21**
Samaras, K Diabetes Care, 2007	788	USA	IDF	**14**
Crum-Cianflone, N JAIDS 2009	216	USA	NCEP-ATPIII	**75**
Worm, SW AIDS 2010	23 853	Europe/Australia/USA D.A.D	NCEP	**41.6**
Alencastro, PR AIDS Res Ther, 2012	1240	Brazil	AHA/NHLBI	**24.7**
Wu, PY J Anti Chem 2012	877	Tawain	NCEP-ATPIII	**26.2**

Prevalence of Metabolic Syndrome has Greatly Increased in HIV Patients

- The prevalence of metabolic syndrome in patients with HIV increased significantly, from approximately 20% in 2000/2001 to over 40% in 2006/2007
  - During the same period, patients with higher BMI, hypertension, and elevated triglycerides also increased

	Calendar period					
Up to end of	2000/2001	2002	2003	2004	2005	2006/2007
Number of patient under follow-up	24 349	26 615	28 449	28 661	26 265	23 853
% of patients under follow-up with						
DM	1008 (4.1)	1140 (4.3)	1303 (4.6)	1344 (4.7)	1275 (4.9)	1245 (5.2)
BMI	1469 (6.0)	1796 (6.8)	2094 (7.4)	2323 (8.1)	2343 (8.9)	2288 (9.6)
Triglycerides	16 325 (67.1)	18 283 (68.7)	19 728 (69.4)	20 842 (72.7)	19 894 (75.7)	18 826 (78.9)
HDL	11 660 (47.9)	13 671 (51.4)	15 531 (54.6)	16 896 (59.0)	16 099 (61.3)	15 583 (65.3)
Hypertension	7243 (29.8)	9069 (34.1)	10 670 (37.5)	12 429 (43.4)	12 634 (48.1)	12 998 (54.5)
n (%) with MS	4712 (19.4)	6328 (23.8)	7647 (26.9)	9121 (31.8)	9418 (35.9)	9913 (41.6)

BMI, body mass index

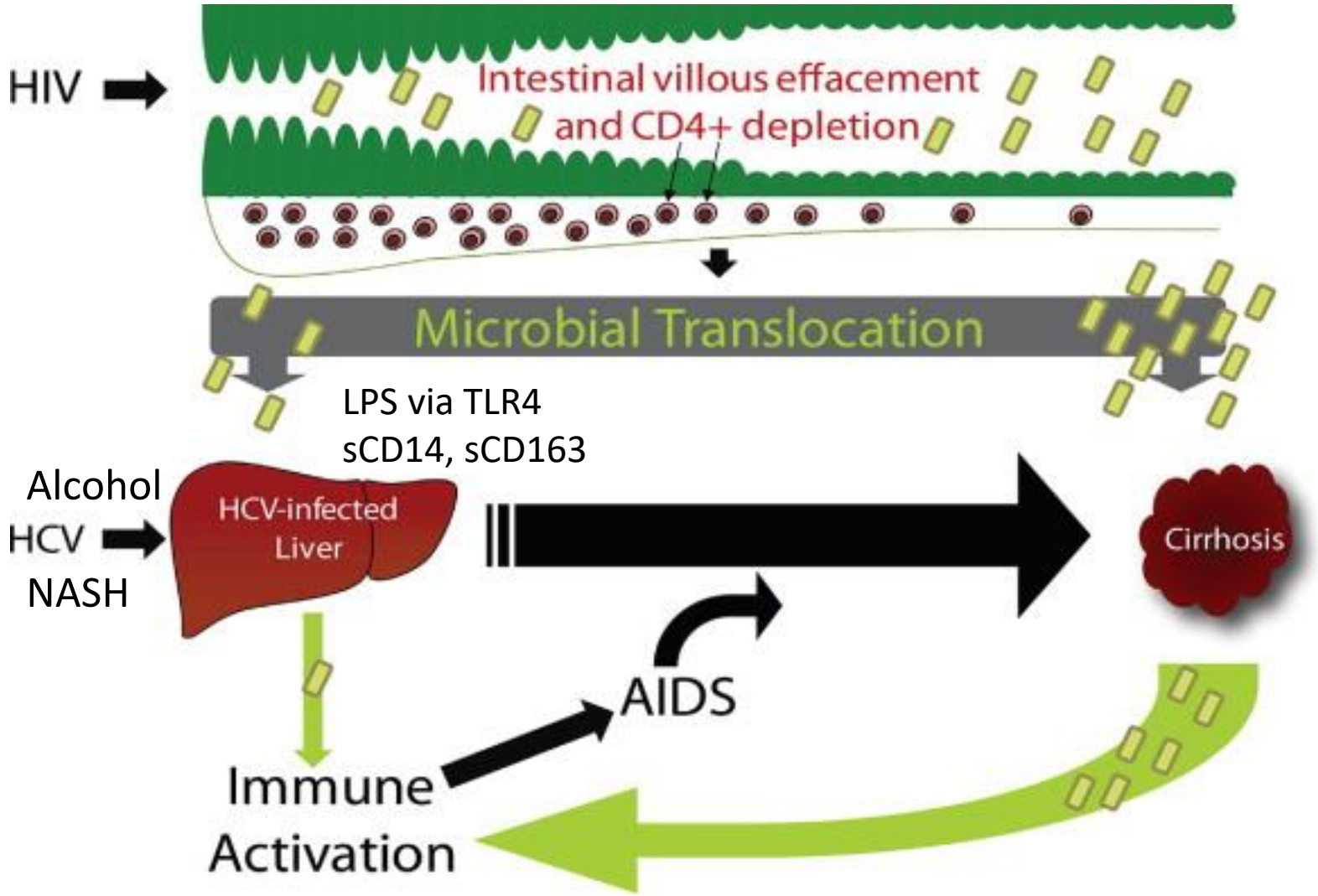
Worm SW et al. AIDS 2010;24(3):427–35

Factors associated with Metabolic Syndrome in HIV

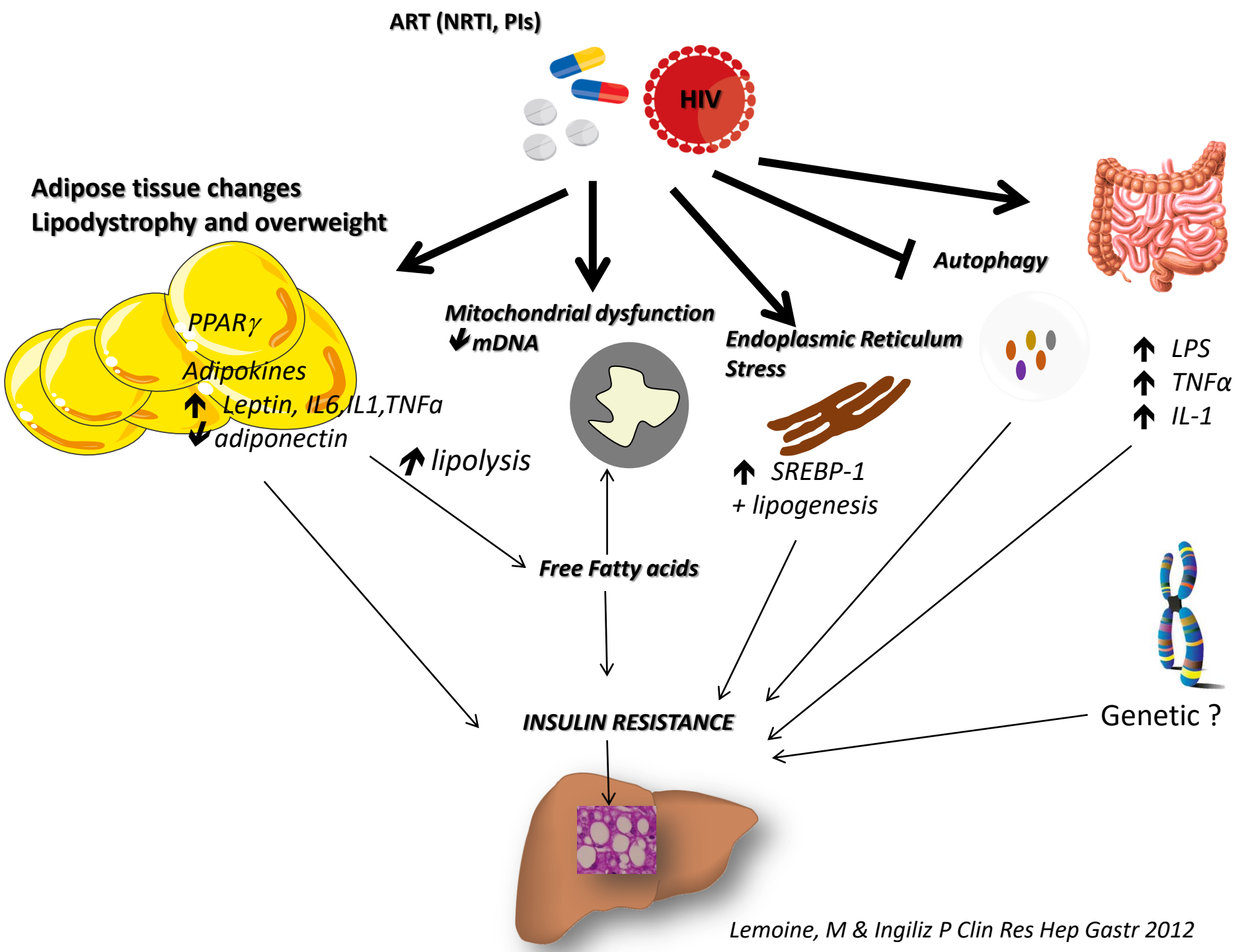
- Older age
- Overweight and waist circumference
- Lipodystrophy
- HAART use of NRTI (ddi, D4T) and/or PIs (indinavir, ritonavir)
- Insulin resistance

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

Bacterial Translocation is a driver of disease

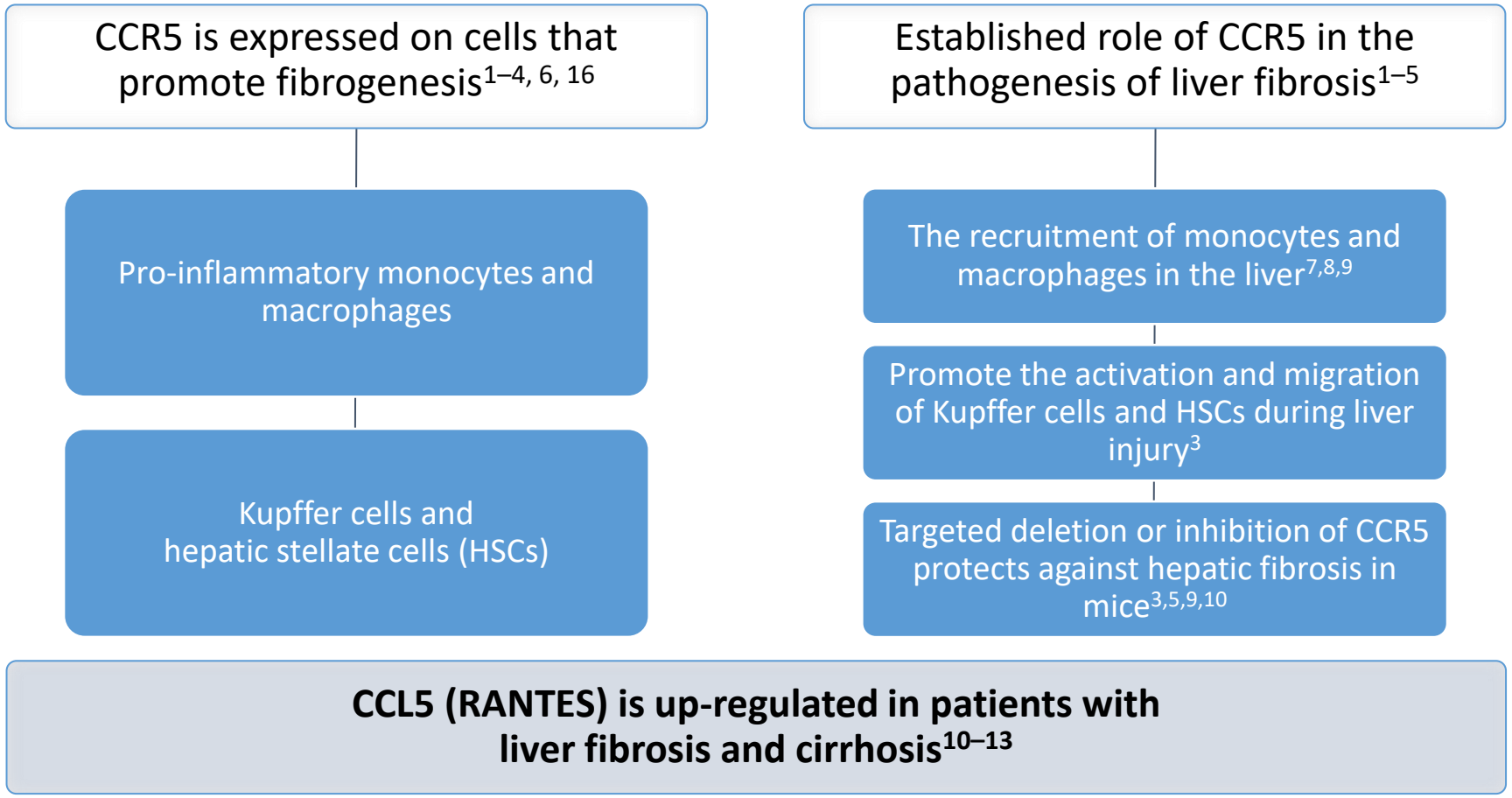


Adapted from Balagopal et al. Gastroenterology 2008;135:226-233



Lemoine, M & Ingiliz P Clin Res Hep Gastr 2012

Role of CCR5 in HIV-associated NASH



1. Saiman Y, Friedman SL. Front Physiol. 2012;3:213. **2.** Zimmermann HW, Tacke F. Inflamm Allergy Drug Targets. 2011;10:509-36. **3.** Seki E et al. J Clin Invest. 2009;119:1858-70. **4.** Schwabe RF et al. Am J Physiol Gastrointest Liver Physiol 2003;285:G949-58. **5.** Mitchell C et al. Am J Pathol. 2009;175:1929-37. **6.** Liaskou E et al. Hepatology 2013;57:385-98. **7**. Egan CE et al. PLoS One 20137;8:e65247. **8.** Baeck C et al. Gut 2012;61:416-26. **9**. Baeck C et al. Hepatology. 2014;59:1060-72. **10.** Bieche I et al. Virology 2005;332:130-44. **11.** Marra F et al. Am J Pathol 1998;152:423-30. **12**. Asselah T et al. Gastroenterology 2005;129:2064-75. **13.** Marra F and Tacke F. Gastroenterology. 2014;147:577-594

Maraviroc modifies gut microbiota

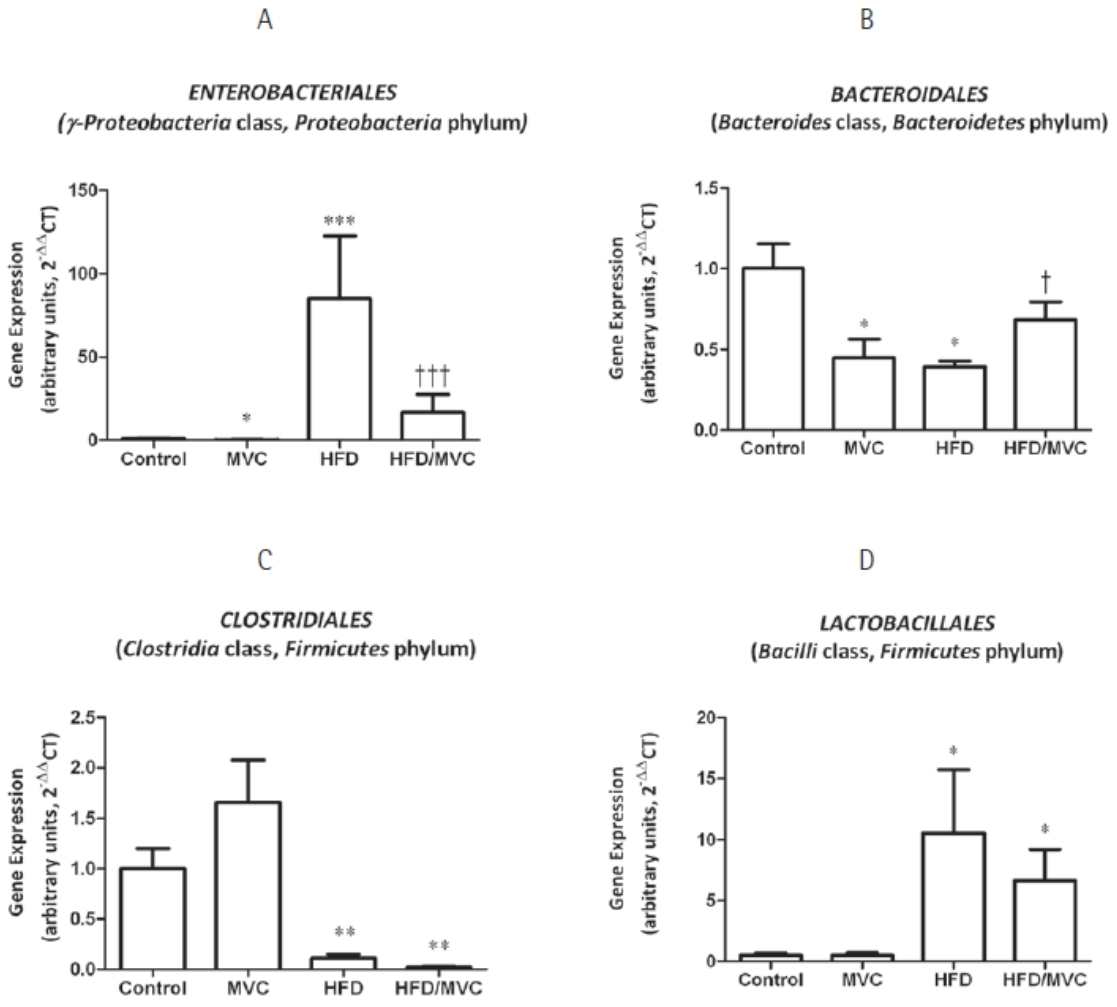
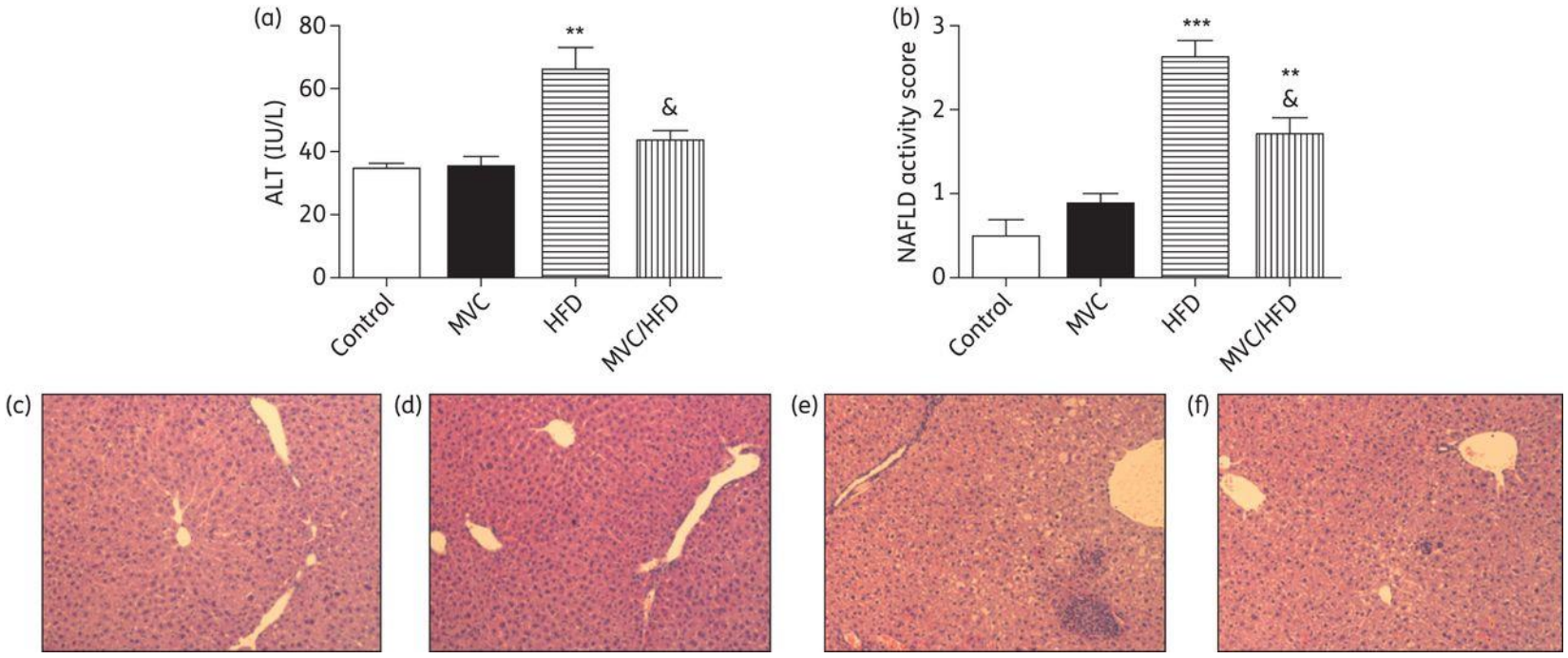


Figure 1 | Effects of MVC on the abundance of four bacterial orders from the most dominant phyla in gut. *P<0.05, **P<0.01 and ***P<0.001 with respect to the control group. †P<0.05, †††P<0.001 with respect to the HFD group.

	Control	MVC	HFD	HFD+MVC	p
Liver wt (g)	1.15±.04	1.13±.03	1.72±.10	1.28±.03	<.001
Liver TG (mg/g)	20.58	23.58	59.99	44.38	<.001
ALT (U/L)	34.5	32.57	66.0	42.71	<.001
HOMA-IR	9.8	17.5	124.8	69.0	<.001
TNF-α (pg/mL)	4.27	3.89	5.55	4.77	<.001

Perez-Matute et al. Rev Esp Quimioter 2015;28:200-206

ALT levels, NASH score index and histological images of liver sections stained with haematoxylin–eosin.



Laura Pérez-Martínez et al. J. Antimicrob. Chemother. 2014;69:1903-1910

Journal of Antimicrobial Chemotherapy

Summary: Role for Maraviroc in NAFLD

CCR5 has been shown to be a key modulator in hepatic repair system. CCL5 (RANTES) plays an important role in the progression of hepatic inflammation and fibrosis

- Monocytes key in fibrosis
- T-cell CCL5 (RANTES) pro-inflammatory
- CCR5 central role in liver matrix remodelling
- Recruit hepatic stellate cells, which synthesise collagen
- CCR5 antagonism limits and induces fibrosis regression

- Study 1098: no hepatic safety signal in HCV co-infected patients
- Clinical development programme: no increase in hepatobiliary events vs comparator
- MOTIVATE: no increase hepatic events in co-infected subjects

- Murine NASH model:
  - ✓ MVC significantly reduced ALT, steatosis, liver TG, reduced liver weight
- Murine HCC model:
  - ✓ Decreased fibrosis
  - ✓ MVC increased survival
  - ✓ Lower tumour burden

- Study 1098: reduction trend in hepatic stiffness at W48
- MAICOL study: 48W reduction of hyaluronic acid, marker of fibrosis
- HEFICO study: no progression in up to 2 years, 15% regression of fibrosis in HCV co-infection
- Resolution with ARV

HIV Infection is Associated with an Increased Risk of NAFLD and Hepatic Steatosis

Abnormal LFTs are common in patients with HIV

- 40–60% versus 8% in general population in absence of HCV/HBV
- Usually1.25–5 times the upper limits of normal

In HIV, steatosis is associated with:

- Elevated LFTs, LDL, TG
- Male gender
- Prolonged NRTI exposure
- Longer duration of HIC
- Increased waist circumference
- Insulin resistance
- PNPLA3 non-CC

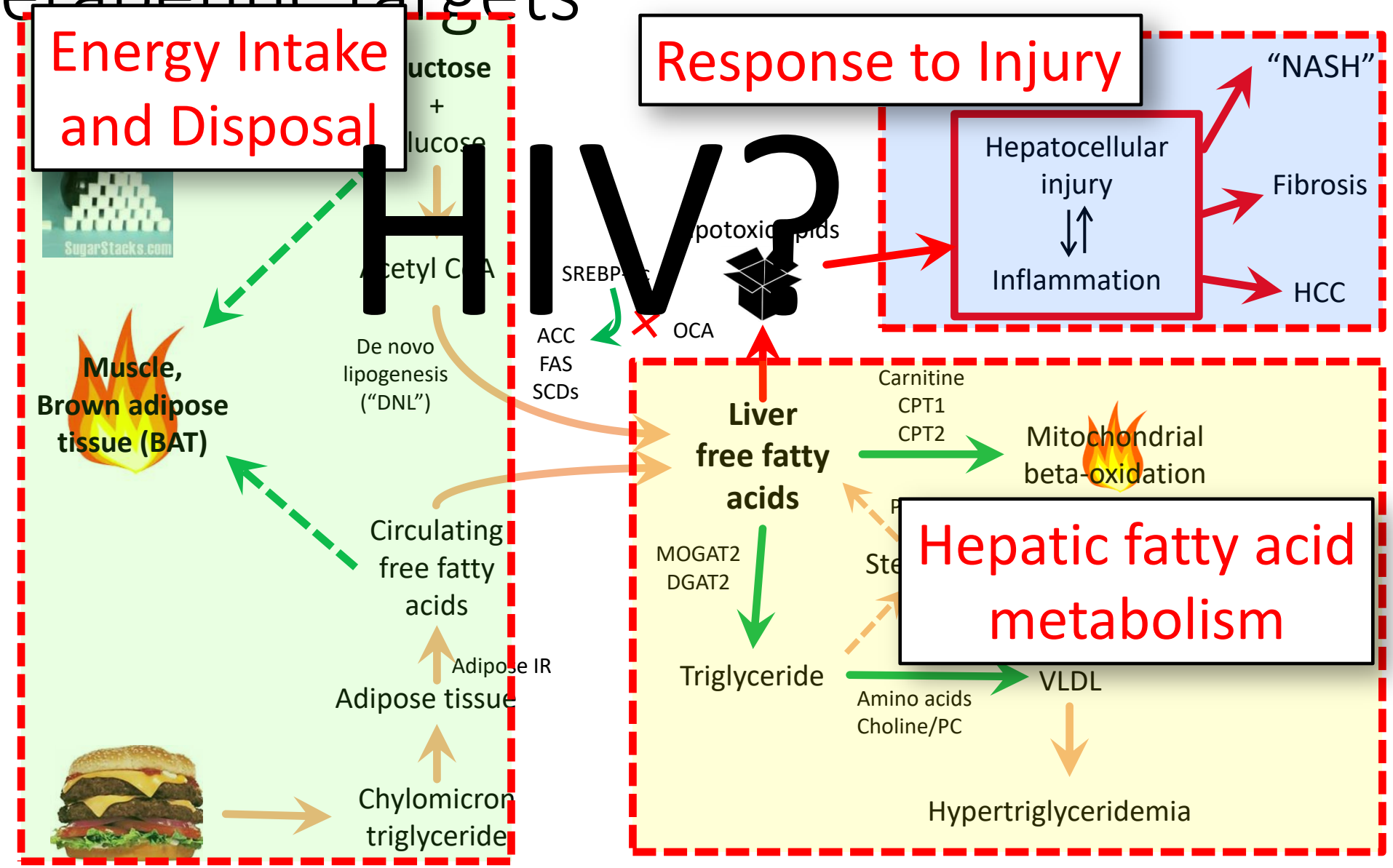
Biopsy data in patients with HIV (no HCV/HBV co-infection)

- 60–65% steatosis
- 26–53% NASH
- 60% evidence of fibrosis
- 13–20% severe fibrosis

LDL, low-density lipoprotein

Sterling RK et al. J Clin Gastroenterol 2013;47:182-7; Ingiliz P et al. Hepatology 2009;49:436-42; Crum-Cianflone N et al. J Acquir Immune Defic Syndr 2009;50:464-73; Morse CG CID 2015;60:1569-1578

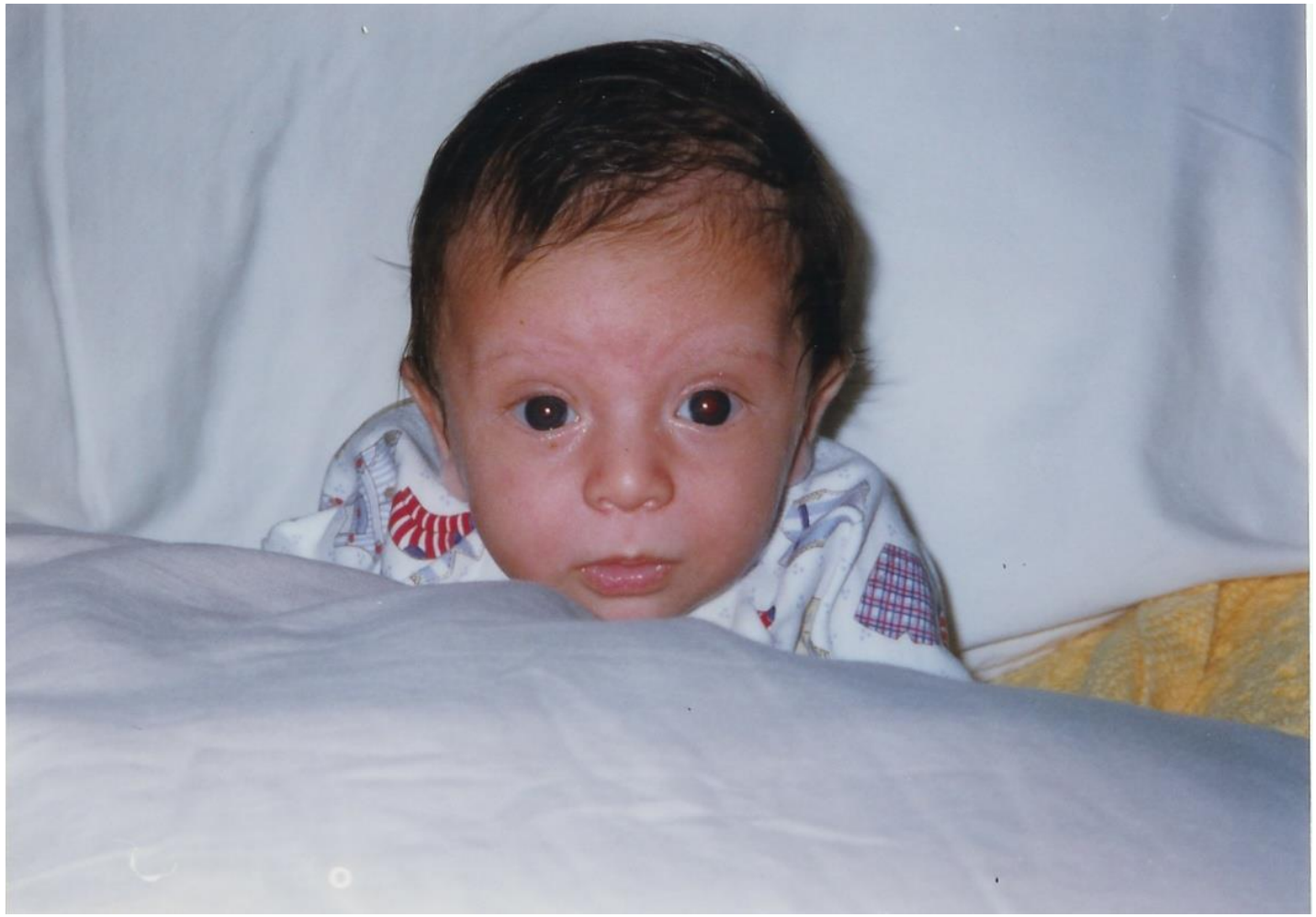
Therapeutic targets



Management Strategies for Steatosis in those with HIV

- Establish severity and presence of fibrosis
- Management of the metabolic syndrome
  - Weight loss
  - Control diabetes, hypertension, and hyperlipidemia
- Exercise
- Control HIV
- Switch cART off NRTIs (DDI, AZT, d4T) and boosted PIs
- Consider clinical trial (if available)
  - ? Reduce bacterial translocation
  - CCR5 antagonist

Discovery Comes to the Prepared Mind



Thank you for your attention

VCU Health System

MCV Hospitals and Physicians

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