La storia naturale della coinfezione HIV-HCV

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Outline

- ✓ Pathogenesis of liver damage in HIV- coinfected patients
- ✓ Cofactors contributing to persistent inflammatory response
  - ✓ Metabolic syndrome
  - ✓ Microbial translocation
  - ✓ HIV
- ✓ Impact on natural history of HIV-and viral hepatitis coinfection

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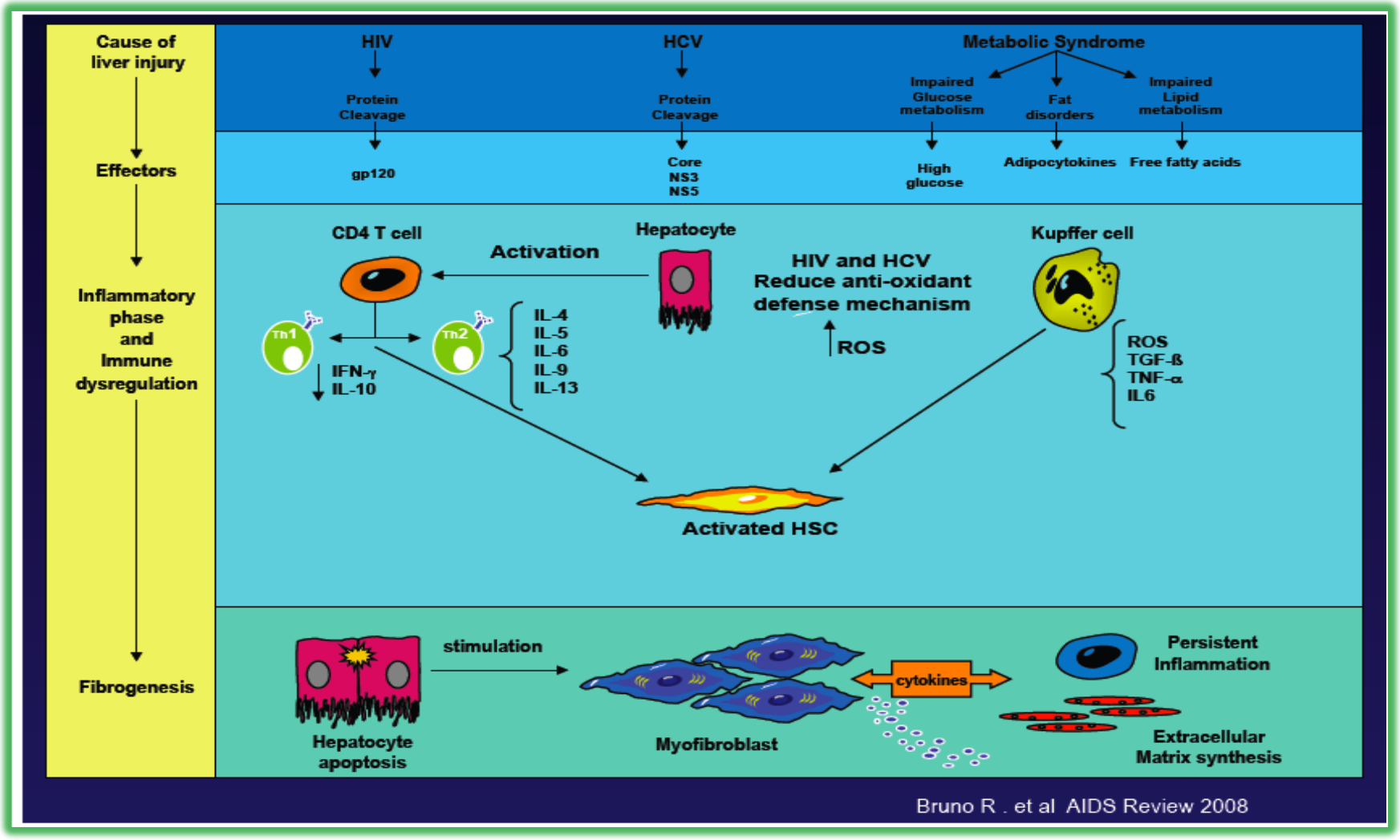
HCV and Cofactors such as metabolic syndrome activate an inflammatory response and immune dysregulation which accelerates liver fibrosis by triggering Hepatic Stellate Cells (HSC)



EASL JOURNAL OF HEPATOLOGY

Impaired CD4$^+$ T cell stimulation of NK cell anti-fibrotic activity may contribute to accelerated liver fibrosis progression in HIV/HCV patients

Andreas Glässner, Marianne Eisenhardt, Pavlos Kokordelis, Benjamin Krämer, Franziska Wolter, Hans Dieter Nischalke, Christoph Boesecke, Tilman Sauerbruch, Jürgen K. Rockstroh, Ulrich Spengler, Jacob Nattermann*

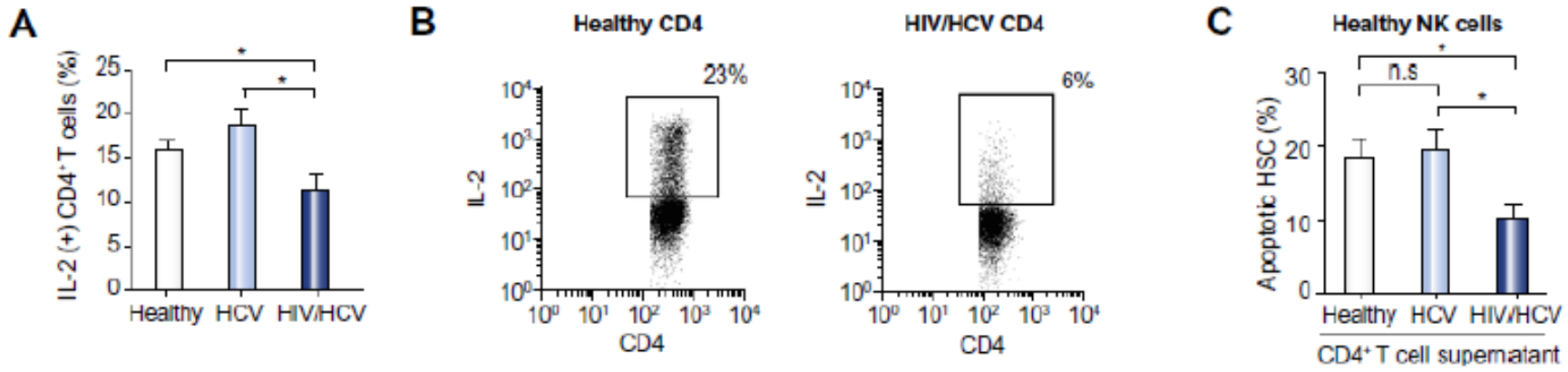


Fig. 4. CD4$^+$ T cells from HIV/HCV co-infected patients display an impaired capability to induce anti-fibrotic activity of NK cells. (A) CD4$^+$ T cells from HIV/HCV co-infected patients showed a reduced IL-2 secretion after stimulation with CD3/CD28-coated beads compared to healthy or HCV mono-infected patients ((healthy) = 13; (HCV) = 12; (HIV/HCV) = 9). (B) Representative dot plots from FACS measurements of IL-2 production in stimulated CD4$^+$ T cells from healthy and HIV/HCV co-infected individuals, respectively. (C) NK cells from healthy persons were stimulated with the supernatant of CD4$^+$ T cells obtained from HIV/HCV, HCV or healthy individuals (healthy: n = 9; HCV: n = 8; HIV/HCV: n = 8). Columns represent mean ± SEM; *$p < 0.05$; n.s., not significant.

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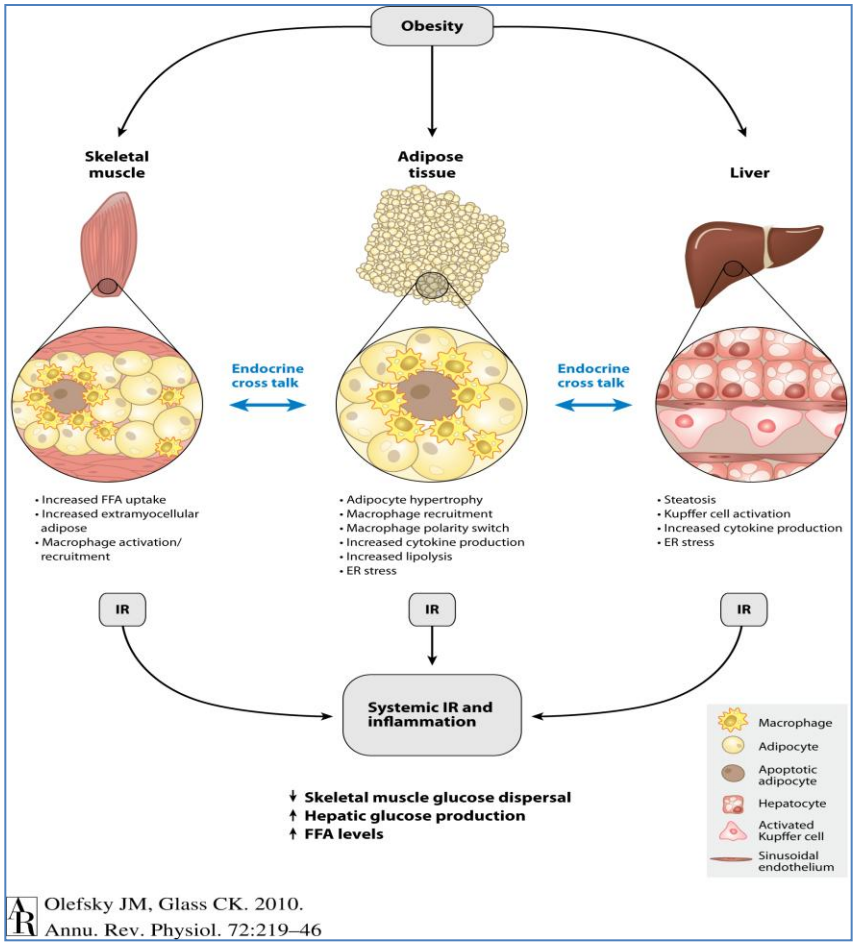
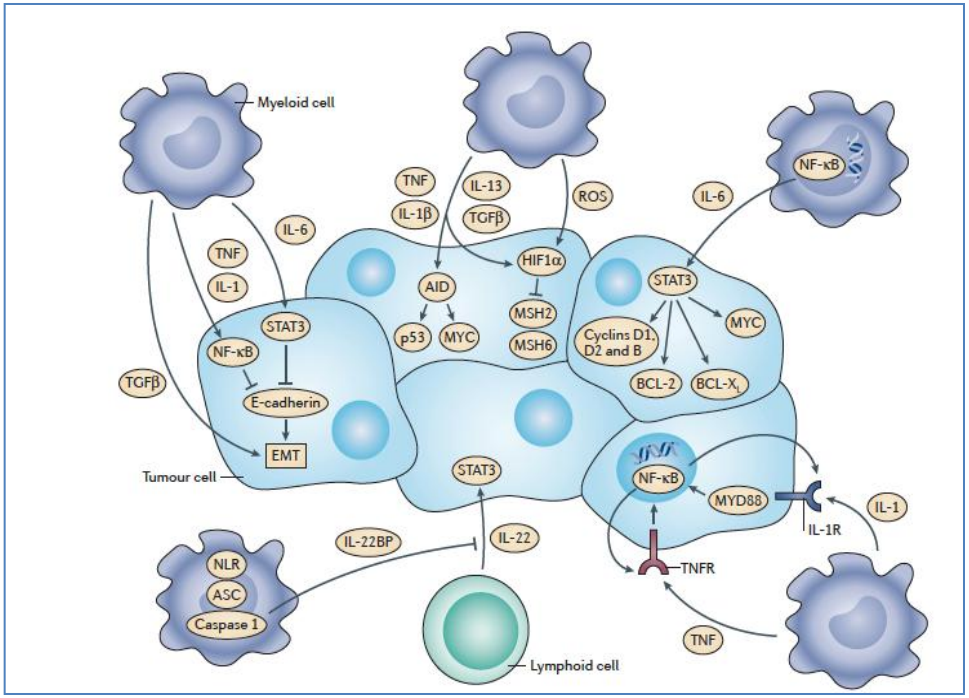
Inflammation and insuline resistance



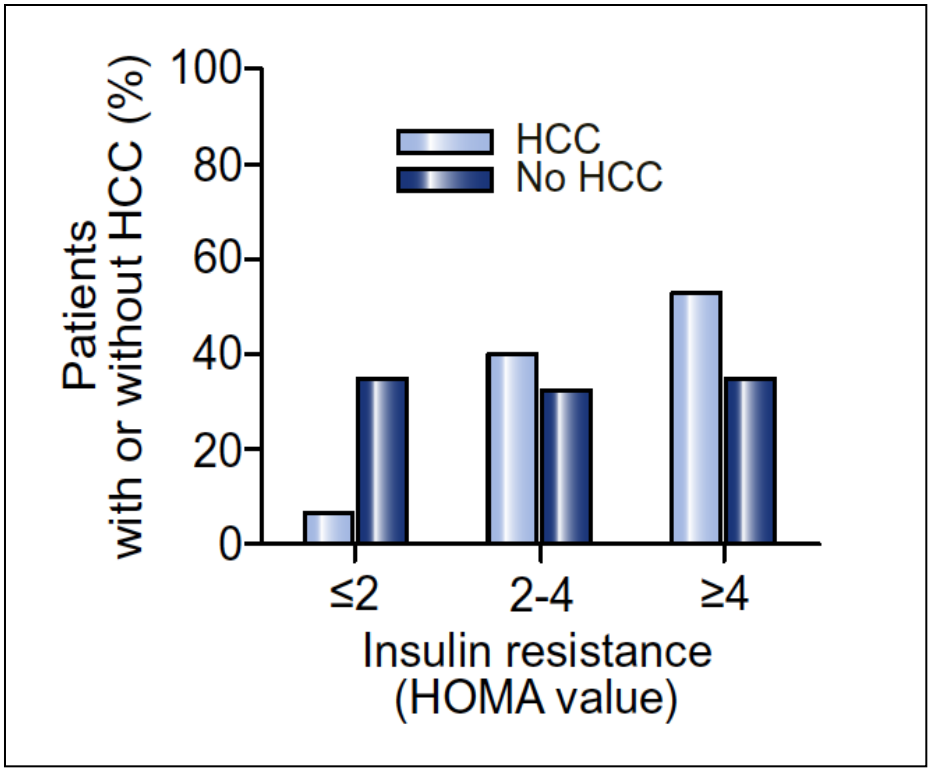
Olefsky JM, Glass CK. 2010.
Annu. Rev. Physiol. 72:219–46

Influence of inflammatory signalling on carcinogenesis



Insulin resistance is associated with a higher risk of hepatocellular carcinoma in cirrhotic HIV/HCV-co-infected patients: Results from ANRS CO13 HEPAVIH

- 244 HIV/HCV with cirrhosis (clinically or histologically proven cirrhosis or Liver Stiffness ≥ 12.5 KPa)
- 21 (8.6%) developed HCC during a mean follow up of 2.6 years (95% CI 1.8-3.5)
- Predictors of HCC by multivariate analysis:
  - Age > 50 yrs (ARR 3.2 95% CI 1.2-9) p=0.02
  - HOMA > 3.8 (ARR 3.4 95% CI 1.1-10.3) p = 0.03



Salmon D et al. J Hepatol 2012; 56 : 862-68

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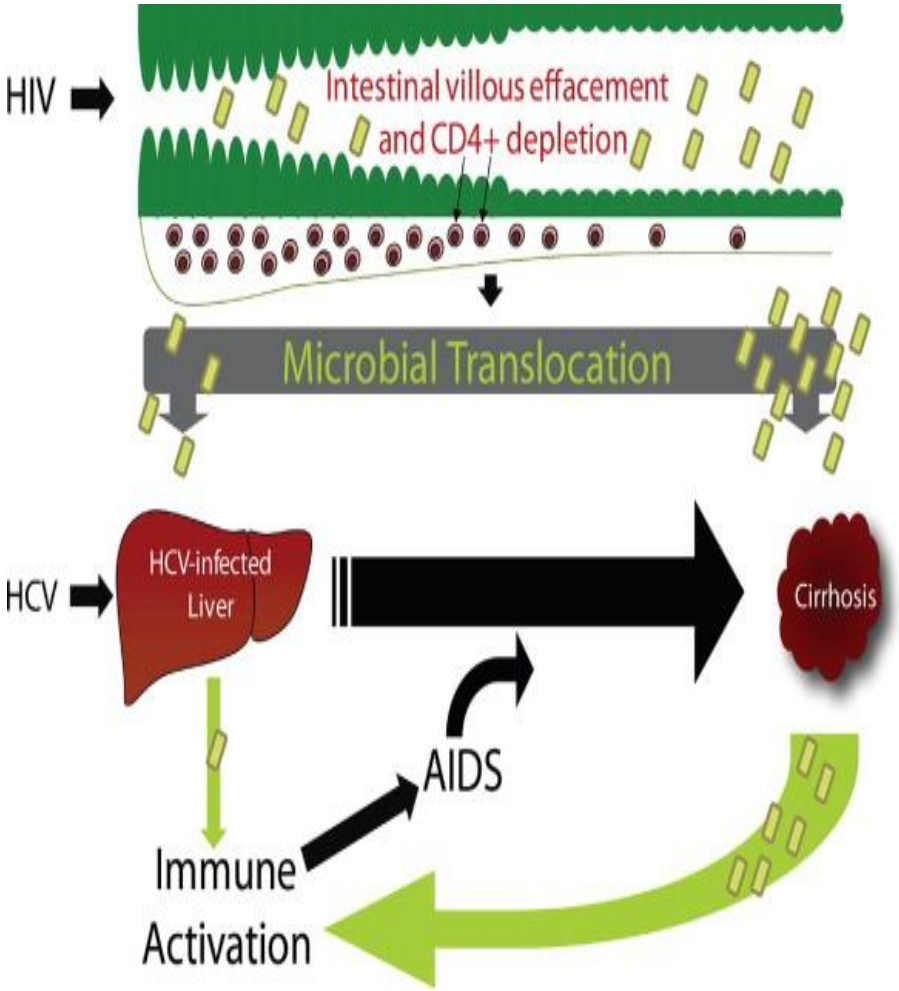
Human Immunodeficiency Virus-Related Microbial Translocation and Progression of Hepatitis C

Balagopal et.al GASTROENTEROLOGY 2008;135:226–233



- ✓ HIV-related intestinal CD4+ lymphocyte depletion and microbial translocation contribute to HCV progression.
- ✓ An integrated model shows that microbial translocation is dependent on HIV-related CD4+ lymphocyte depletion. Microbial translocation is critical for the development of immune activation and AIDS, but liver disease develops only in HCV coinfection.
- ✓ Microbial translocation in the host with cirrhosis will lead to less clearance of bacterial products and increased immune activation

Correlation Between the Levels of TGF-beta 1, Foxp3+ lymphocytes, Bacterial Traslocation Indexes and Liver Fibrosis Score in HIV+, HCV+, HIV+/HCV+ patients and Healthy Controls

P. Sacchi, S. Cima, M. Corbella, G. Comolli, A. Chiesa, F. Baldanti, C. Klersy, S. Novati, P. Mulatto , M. Mariconti, C. Baldi and R. Bruno

1) Dipartimento di Malattie Infettive, Fondazione IRCCS Policlinico San Matteo, Pavia 2) Unità di Virologia Molecolare, S.C. di Microbiologia e Virologia, Fondazione IRCCS Policlinico San Matteo, Pavia 3) Servizio di Biometria e Epidemiologia Clinica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy 4) Università degli Studi di Milano, Milano

DLD 2015

Aim

- A cross-sectional study was conducted on 80 subjects including HIV-monoinfected (n = 20), HCV monoinfected (n = 20) and HIV/HCV-co-infected (n = 20) patients, and healthy controls (n = 20) older than 18 years

- to investigate the correlation existing between blood levels of Foxp3, TGF-beta 1, IL-17, sCD14, bacterial-DNA products and liver fibrosis stage in HIV, HCV monoinfected, HIV/HCV coinfected patients and age matched healthy controls.

Sacchi P. et al DLD 2015

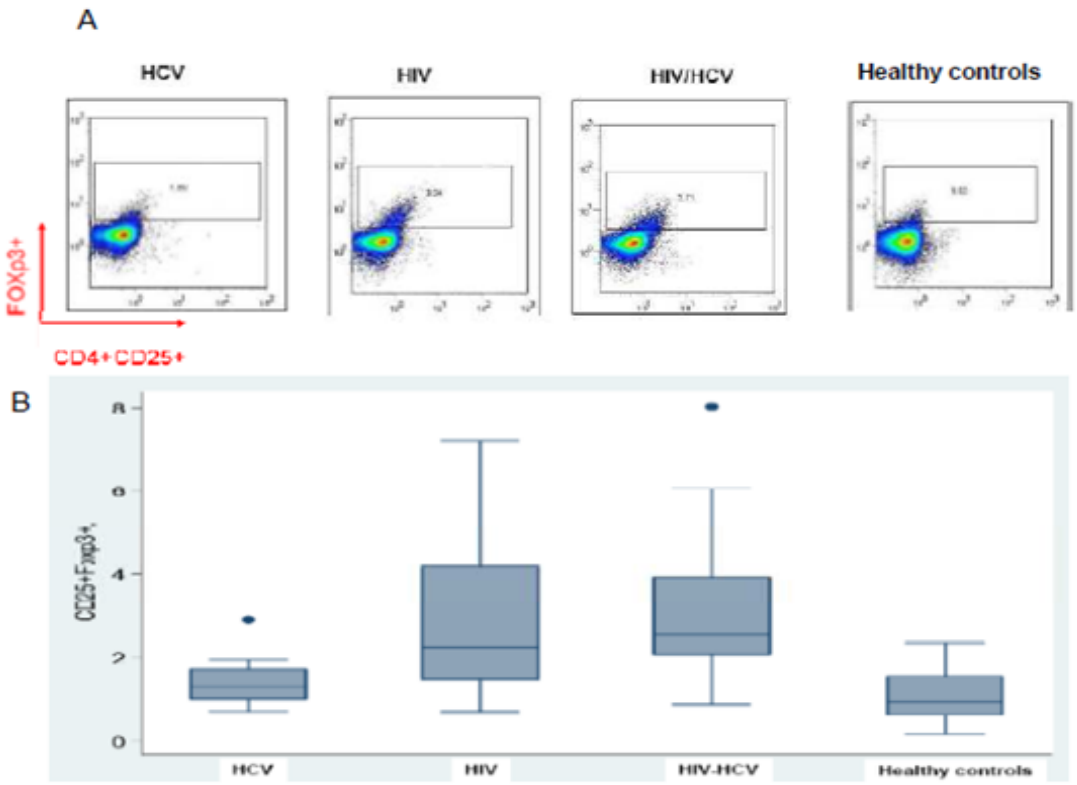
Methods

- $Foxp3^+$ and TGF-beta 1 levels were measured in peripheral blood and were correlated to liver fibrosis, measured either by biochemical score (FIB 4) or by elastometry

- $CD4^+CD25^+Foxp3^+$ and sCD14T-cell levels, were measured by Flow Cytometric analysis, Circulating TGF-beta1 and IL-17 concentrations in plasma by a commercial enzyme-linked immunosorbent assay ELISA kit Quantikine (R&D Systems) and complete 23S rDNA sequences from 50 bacterial species by 23S rDNA real-time PCR.

Sacchi P. et al DLD 2015

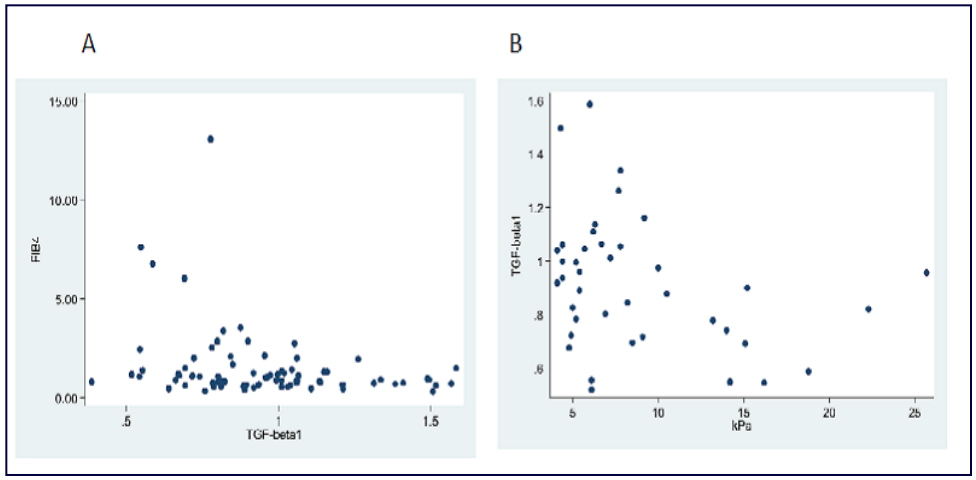
Main Findings 1/3



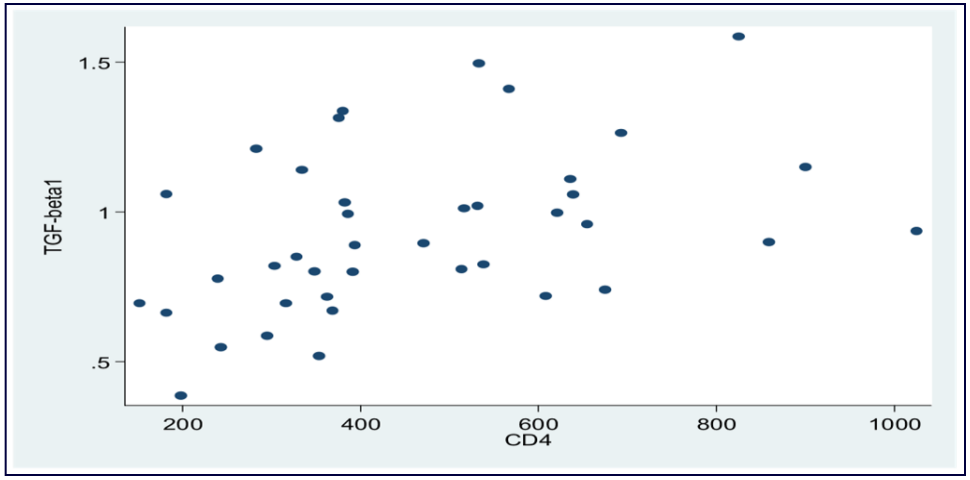
- Foxp3^{+} % levels were significant higher in HIV^{+} and HIV^{+}/HCV^{+} than in HCV^{+} and control group ($p < 0.0005$, Kruskal-Wallis test)

Sacchi P. et al DLD 2015

Main Findings 2/3



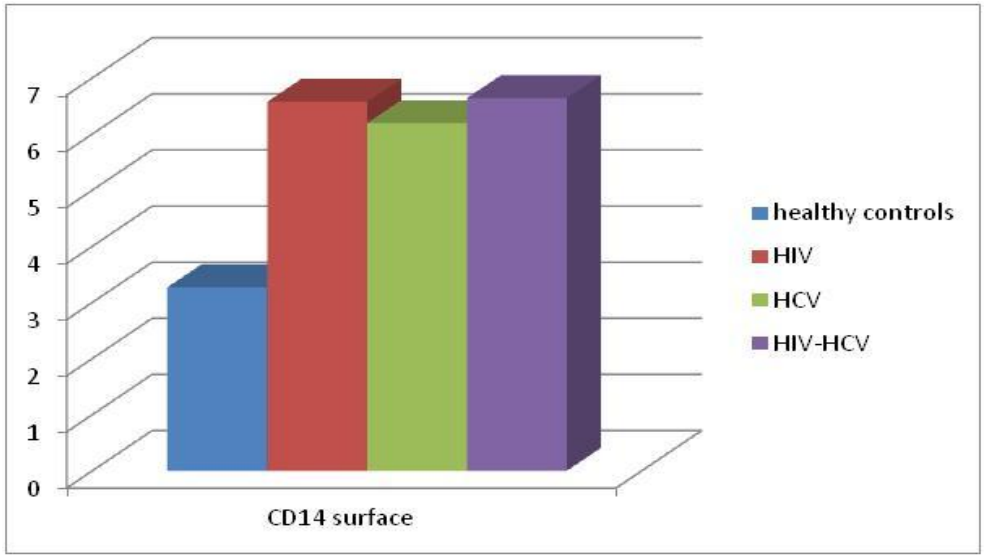
- FIB 4 values inversely correlated with TGF-beta1 (Rho -0.38; p=0.0155) as well as with liver stiffness values (Rho -0.31; p=0.0498



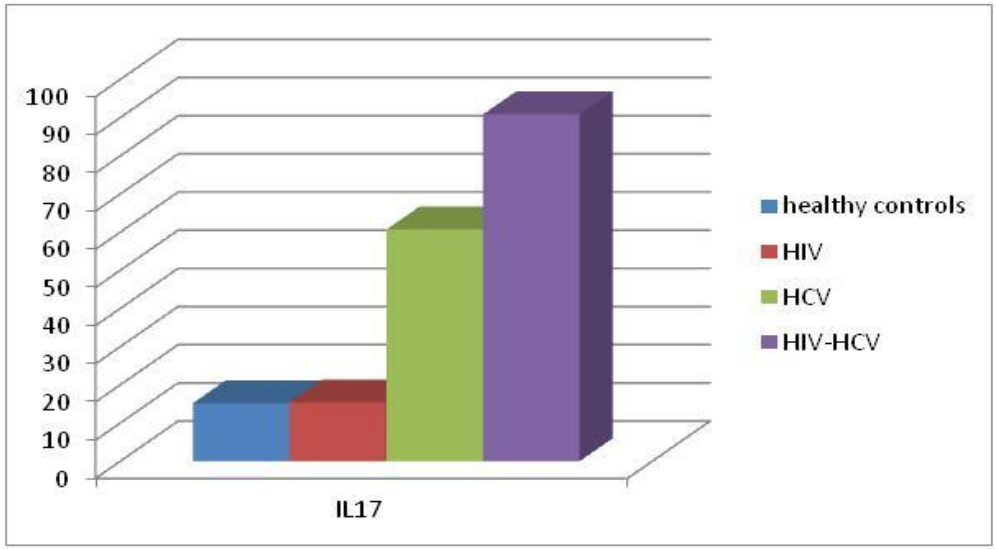
- TGF-beta1 levels directly correlated with CD4 cell count values in HIV and HIV/HCV coinfected patients
(Rho 0.4802; p=0.0017)

Sacchi P. et al DLD 2015

Main Findings 3/3



- CD14 (soluble and surface) levels were significantly different between HIV^+ vs the healthy controls , HIV^+/HCV^+ vs the healthy controls, HCV^+ vs HIV^+/HCV^+ ($p< 0.0001$)



- IL17 was significantly different between HCV^+ vs the others 3 groups.

Sacchi P. et al DLD 2015

Conclusions

- Foxp3^{+} levels are higher in patients with HIV, but they do not influence liver fibrosis stages.
- TGF-b1 levels inversely correlate with fibrosis and directly with CD4 cell count suggesting a protective effect of immune status against fibrosis.
- HIV^{+}/HCV^{+} patients have increased levels of bacterial DNA, CD14 (soluble and surface) and IL17 as compared with the others groups.
- The correlation between the translocation indexes(CD14,IL17) and FIB4 suggests that fibrosis stage may depend on immunoactivation caused by bacterial translocation.

Sacchi P. et al DLD 2015

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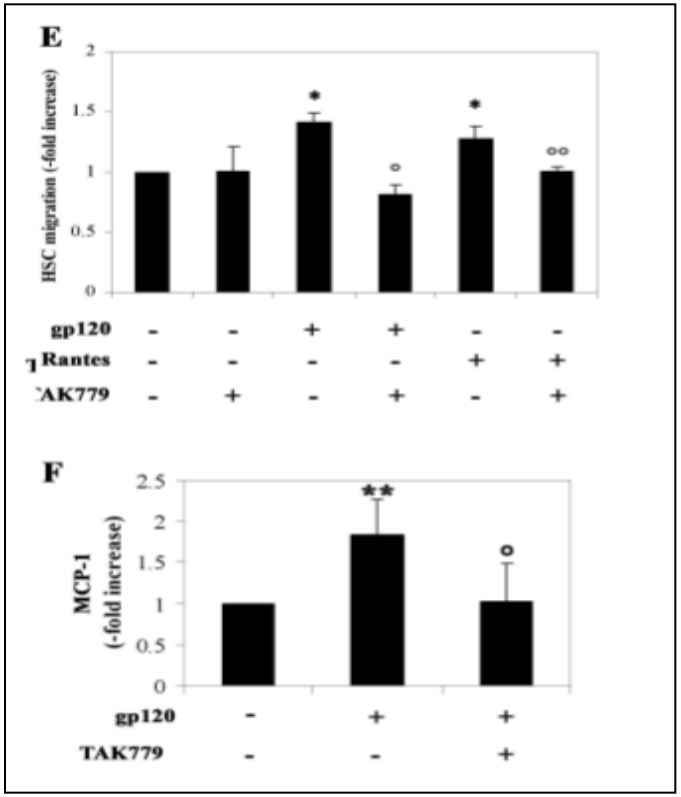
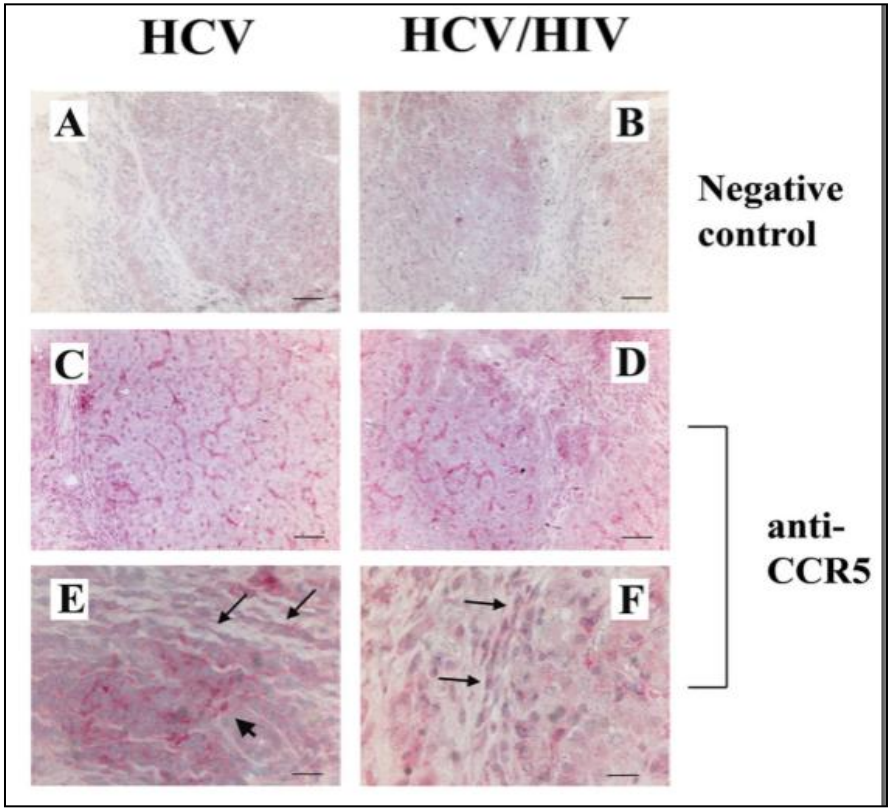
The HIV Envelope Protein gp120 Modulates The Biology of Human Hepatic Stellate Cells





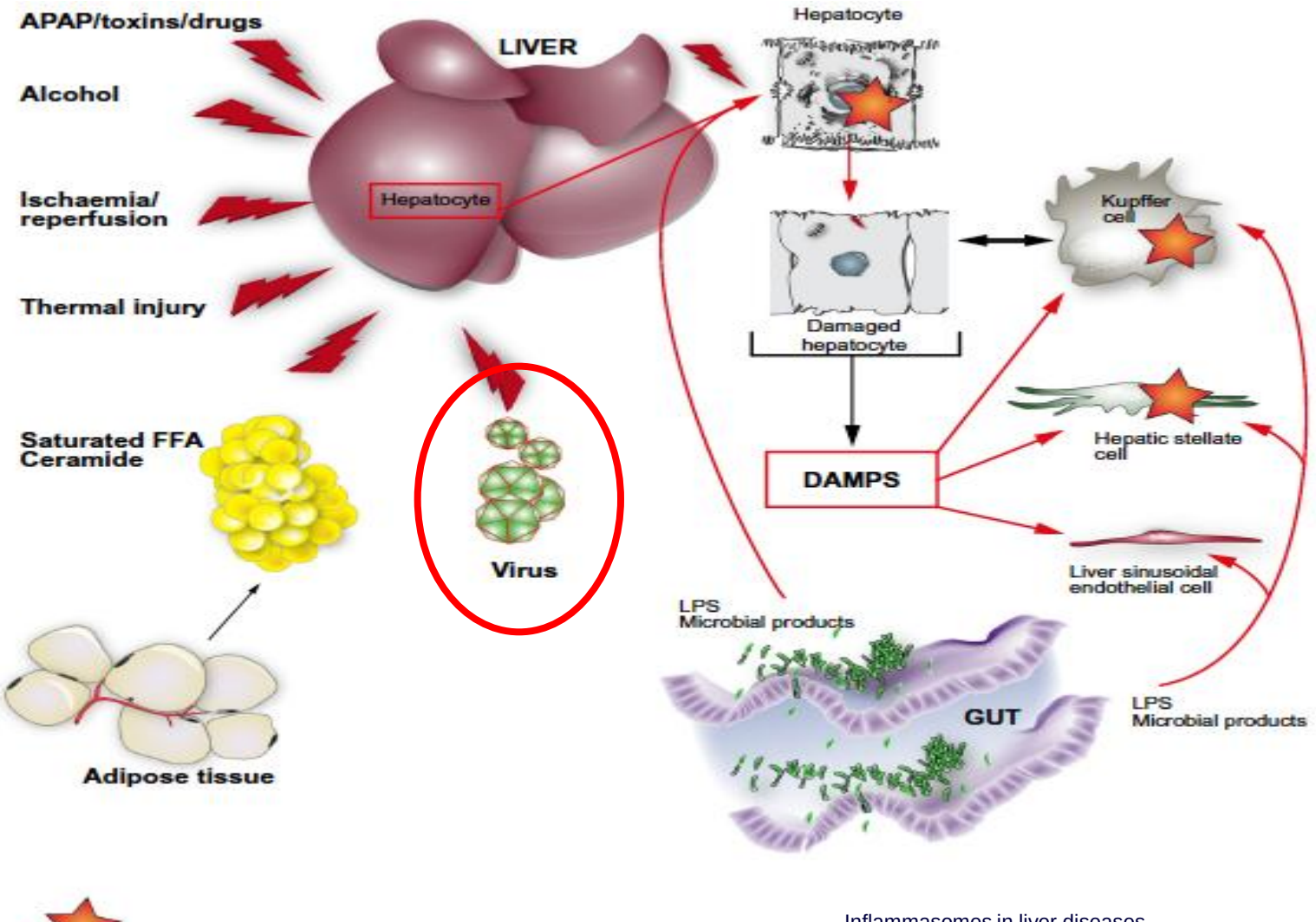
HIV-gp120 modulates different aspects of HSC biology, including directional cell movement and expression of pro-inflammatory cytokines by binding to CCR5r. These results identify a direct pathway possibly linking HIV infection with liver fibrogenesis via envelope proteins.

Bruno R et al. Gut 2010

Inflammasome

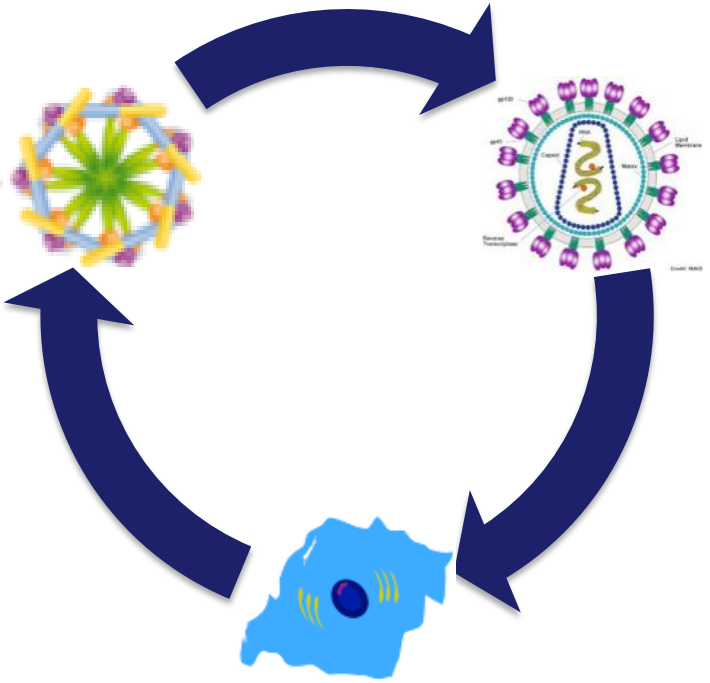
- The inflammasome is a multiprotein oligomer consisting of caspase 1, PYCARD, NALP and caspase 5.
- It is expressed in myeloid cells and is a component of the innate immune system. The exact composition of an inflammasome depends on the activator which initiates inflammasome assembly,
- The inflammasome promotes the maturation of the inflammatory cytokines Interleukin 1β (IL-1β) and Interleukin 18 (IL-18).
- The inflammasome is responsible for activation of inflammatory processes, and has been shown to induce cell pyroptosis, a process of programmed cell death distinct from apoptosis.

Triggers of inflammasome activation in liver diseases.



Inflammasomes in liver diseases
Gyongyi Szabo, Timea CsakJournal of Hepatology 2012 vol. 57 642–654

NALP3 inflammasome and HIV



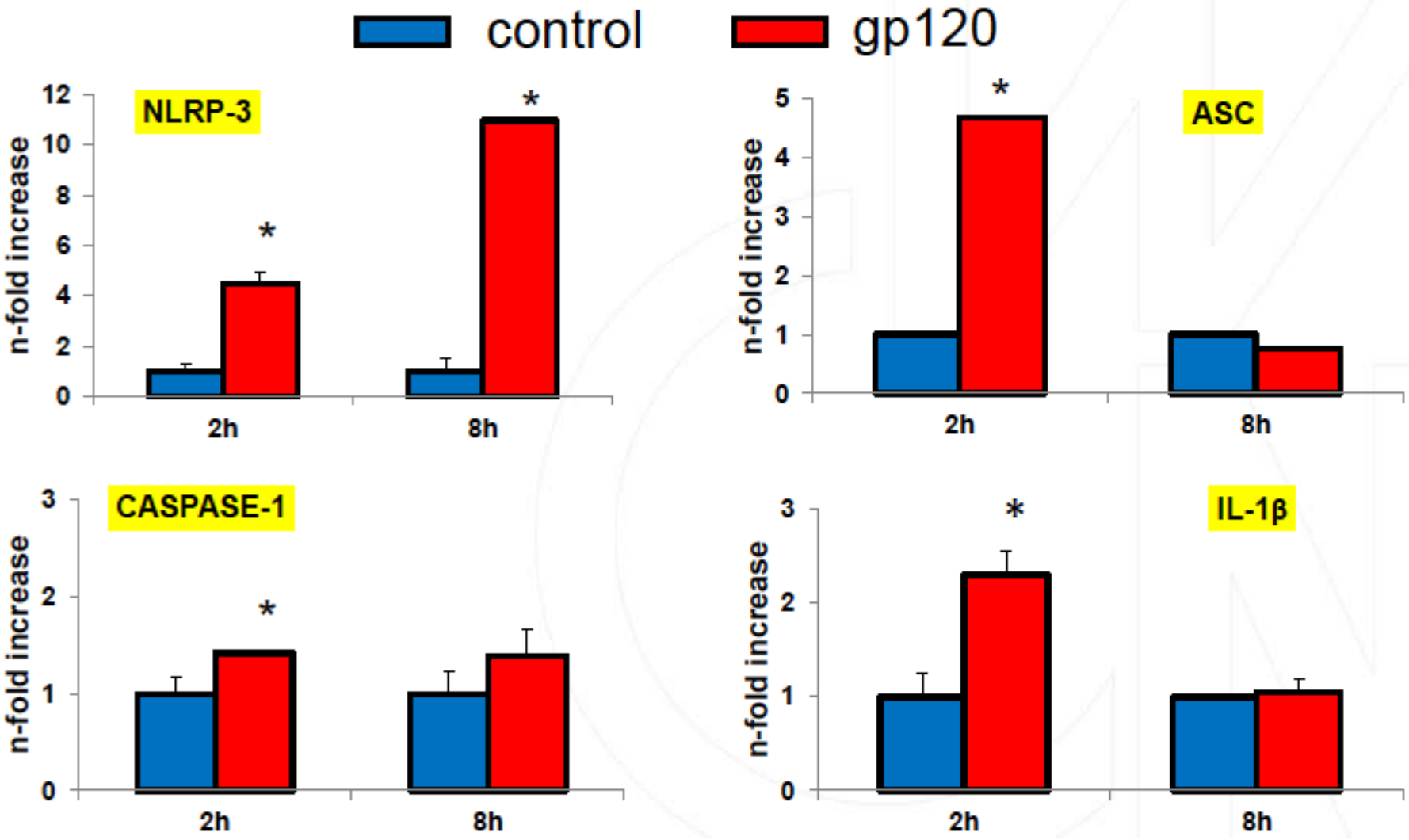
- A possible direct link between the inflammasome and HIV proteins is under evaluation

HIV-Envelope Protein Gp120 Actives the Nalp3-Inflammasome Through the Engagement of CCR5 Receptor in Human Hepatic Stellate Cells

A. Cappon*, R. Bruno**, S. Gessani***, A. Masotti°, and F. Marra
*University of Florence, Florence, Italy, **IRCCS, University of Pavia, Pavia, Italy, ***Istituto Superiore di Sanità, Rome, Italy, °Ospedale Pediatrico Bambino Gesù, Rome, Italy

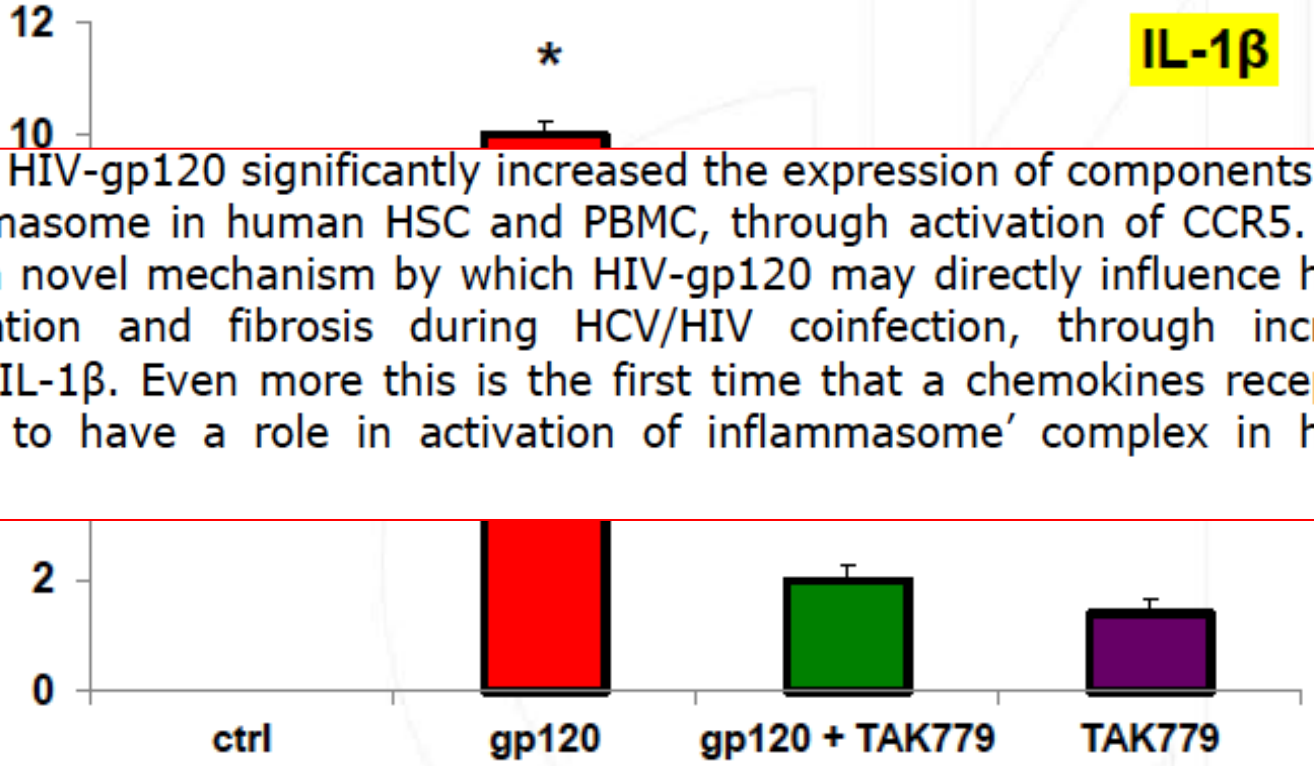
AASLD 2013

gp120 induces expression of inflammasome components and IL-1β production in PBMC



Cappon A et al AASLD 2013

GP120 activates the inflammasome pathway through engagement of CCR5 in PBMCs

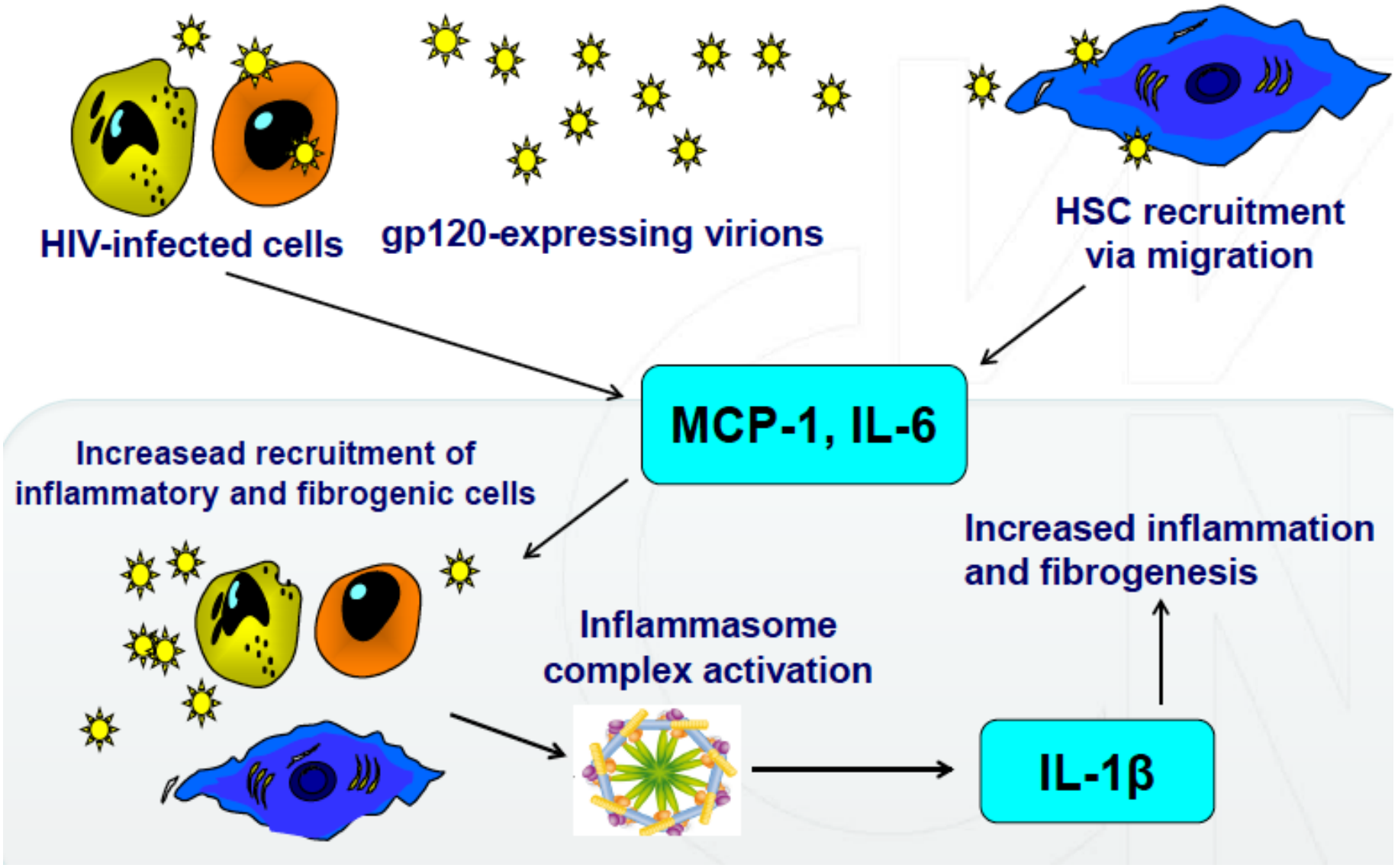


Conclusions: HIV-gp120 significantly increased the expression of components of the NALP3 inflammasome in human HSC and PBMC, through activation of CCR5. These data identify a novel mechanism by which HIV-gp120 may directly influence hepatic necroinflammation and fibrosis during HCV/HIV coinfection, through increased production of IL-1β. Even more this is the first time that a chemokines receptor is demonstrated to have a role in activation of inflammasome' complex in hepatic stellate cells.

*P<0.05 vs control; ^ P<0.05 vs gp120

Cappon A et al AASLD 2013

Conclusions



monocyte chemotactic protein 1 (MCP1)

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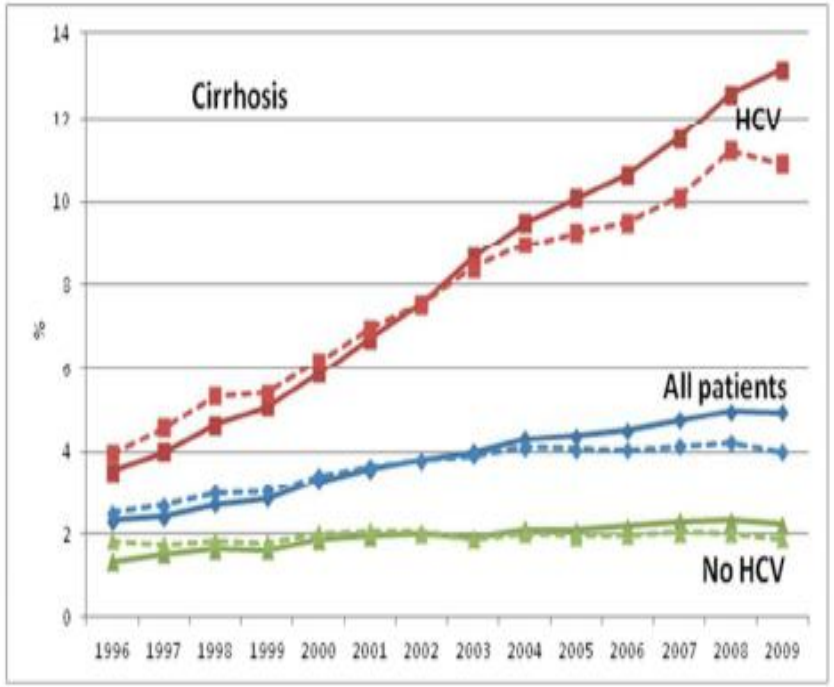
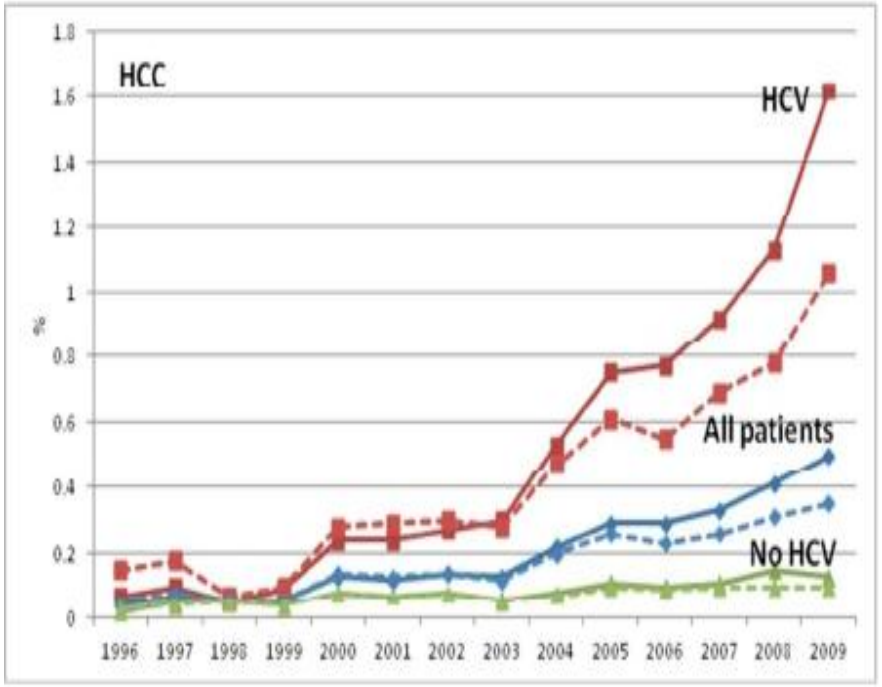
The prevalence of cirrhosis and hepatocellular carcinoma in patients with HIV infection

Patients received care in the Veterans Affairs (VA) healthcare system - 1996-2009 n=24,040





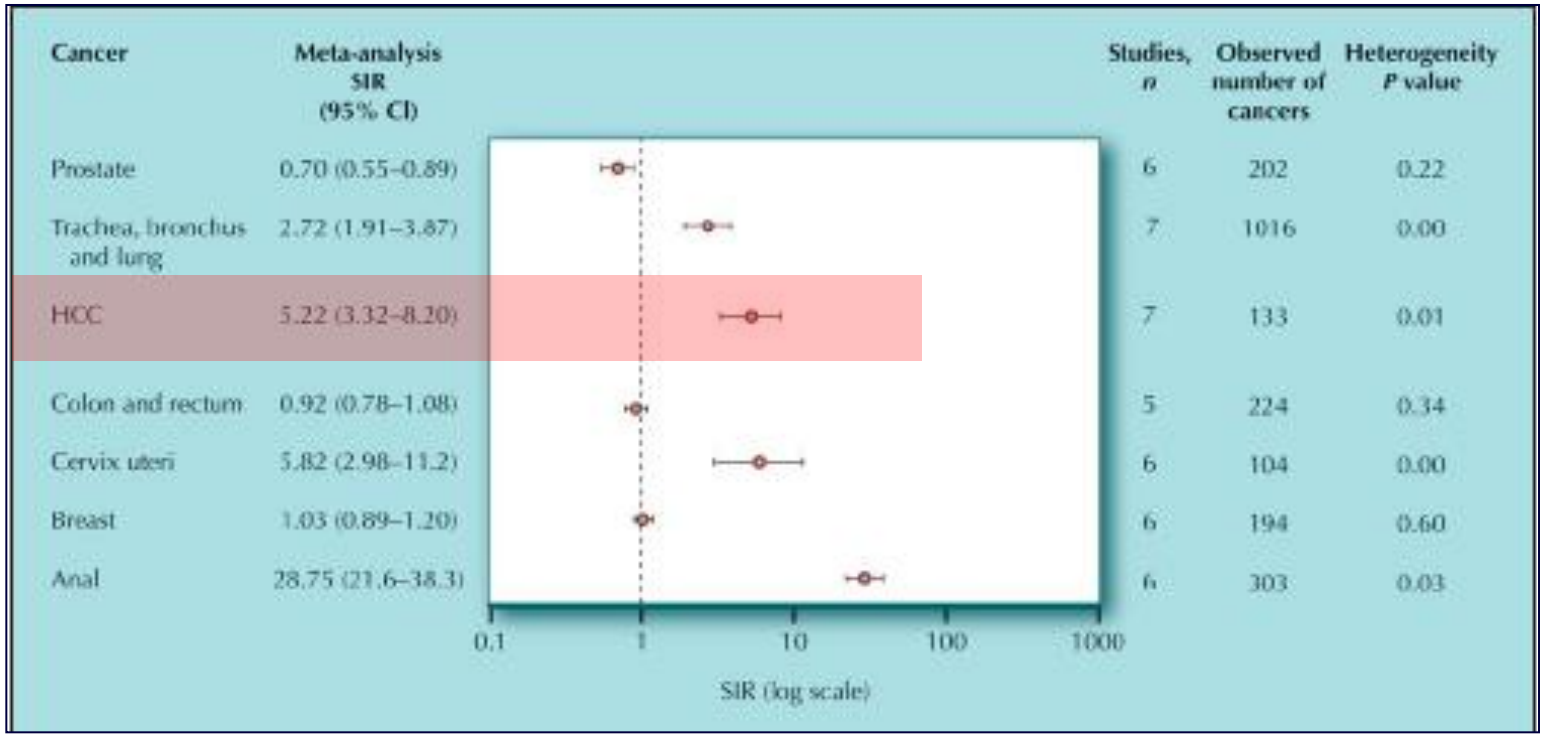
The prevalence of cirrhosis and HCC has increased dramatically among HIV-infected patients driven primarily by the HCV epidemic.

Ioannou GN et.al. Hepatology. 2012 Apr 24. [Epub ahead of print]

Screening HIV-Infected Patients for Non–AIDS-Defining Malignancies

Adrienne A. Phillips, MD, MPH, and Jessica E. Justman, MD

Curr HIV/AIDS Rep 2009;6(2):83–92



Incidence of HCC is higher in persons living with HIV with a ratio of 5.22 ranking second after cervix uterus neoplasia among non-AIDS defining cancers.

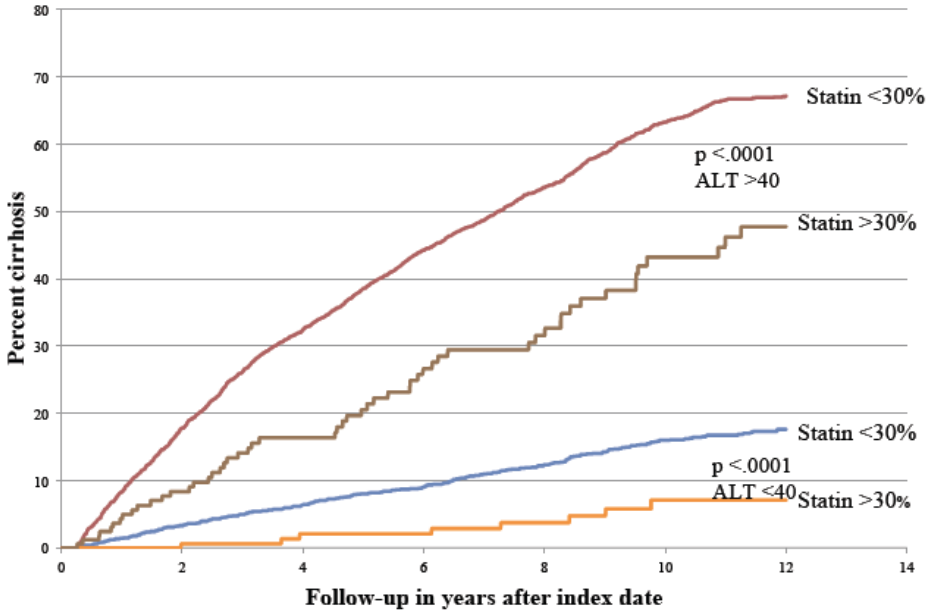
CROI 2016:
Hepatitis Viruses Coinfection

Statin Use and the Impact on Cirrhosis Progression in a HIV/HCV Co-infected Population

- 5985 VA HIV/HCV coinfected patients 273 (ALT < 40 IU/mL) and 1992 ALT > 40
- Although not used frequently in patients with underlying chronic liver disease (12.5% with ALT >40), among those with less severe liver disease (ALT < 40), statins have a significantly protective effect in the development of cirrhosis (p = 0.04), but loses significance for ALT>40 (may be due to small numbers on statins).
- Metabolic risk factors including low-HDL and diabetes are significantly associated with increased risk of cirrhosis among those with ALT > 40 .
- Hypertension was also associated with a non-significant increased risk.
- Older age, poorer HIV control with CD4 count <200 and less time with undetectable HIV VL confer significantly greater risk

	ALT* <40 IU/L N = 273		ALT* >40 IU/L N = 1992	
	HR (CI)	P-value	HR (CI)	P-value
Statin by 30% increment* (Point estimate)	0.68 (0.47-0.98)	-	0.95 (0.83-1.01)	-

Figure 1. Kaplan-Meier Cumulative Cirrhosis Incidence Among HIV/HCV Patients



Oliver NT et al CROI 2016 Poster # 550

Protective Effect of Coffee Intake on Mortality of French HIV-HCVInfected Patients (ANRS CO13 HEPAVIH Cohort)

- N=1,035 patients eligible for this study
- Median [interquartile range] follow-up duration: 5 [3.9-5.8] years, representing 4,693 person-years
- 77 deaths → Mortality incidence rate [95% confidence interval]: 1.64 [1.31-2.05] per 100 person-years

	N (%) §	n deaths	AHR [95% CI]	P-value
Gender				
Male	726 (70.1)	61	1	
Female	309 (29.9)	16	0.6 [0.3-1.0]	0.060
Having a steady partner §				
No	399 (38.5)	40	1	
Yes	631 (61.0)	37	0.6 [0.3-0.9]	0.014
Precarious housing §				
No	1,013 (97.9)	71	1	
Yes	18 (1.7)	6	3.7 [1.9-7.2]	$<10^{-3}$
HCV treatment status §				
Not yet treated	551 (53.2)	58	1	
Ongoing treatment	73 (7.0)	7	0.9 [0.4-1.9]	0.753
Treated and not cured	163 (15.7)	8	0.7 [0.3-1.4]	0.289
Treated and cured	248 (24.0)	4	0.2 [0.1-0.6]	0.004
HIV stage §				
1	462 (44.6)	18	1	
2	269 (26.0)	21	2.0 [1.0-4.0]	0.036
3	301 (29.1)	37	3.2 [1.8-5.7]	$<10^{-3}$
CD4+ cell count/mm^3 ≤ 200 §				
No	951 (91.9)	58	1	
Yes	84 (8.1)	19	3.2 [1.9-5.5]	$<10^{-3}$
Tobacco consumption §				
Past/current	905 (87.4)	73	1	
Never	122 (11.8)	3	0.3 [0.1-0.9]	0.039
Alcohol consumption § (AU/day)				
No consumption	325 (31.4)	27	1	
Low (≤ 1)	477 (46.1)	25	0.5 [0.3-0.9]	0.033
Moderate (> 1 and ≤ 4(3) for men(women))	161 (15.6)	14	0.7 [0.3-1.3]	0.228
Elevated (> 4(3) for men(women))	61 (5.9)	9	1.0 [0.4-2.4]	0.912

	N (%) §	n deaths	AHR [95% CI]	P-value
Coffee consumption §				
< 3 cups/day	762 (73.6)	65	1	
≥ 3 cups/day	272 (26.3)	12	0.5 [0.3-1.0]	0.045

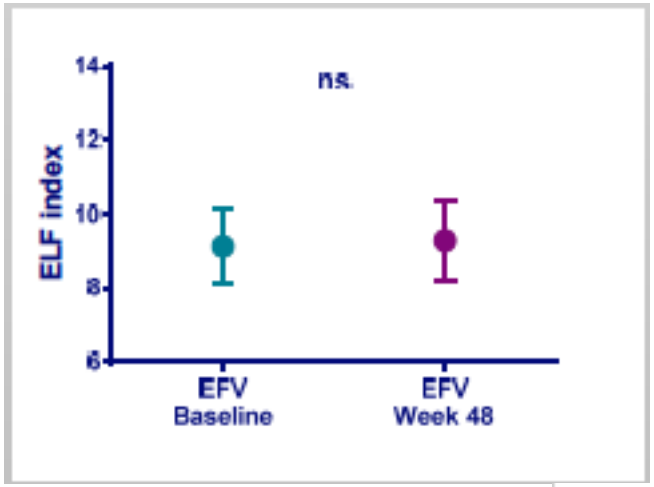
Carrieri MP et al CROI 2016 poster #549

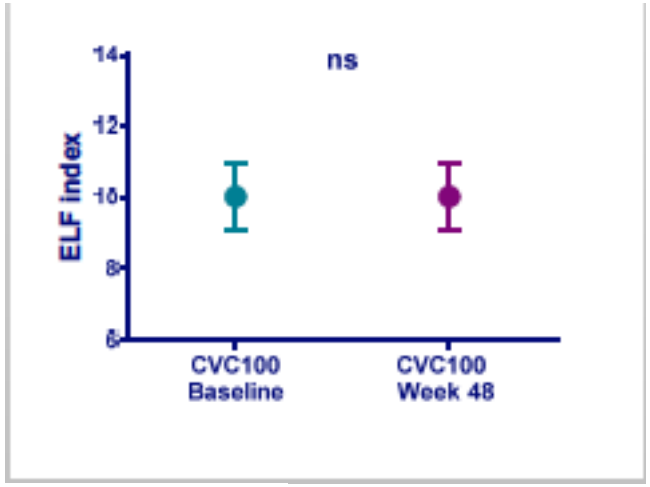
Risk factors for liver fibrosis progression in HIV/HCV

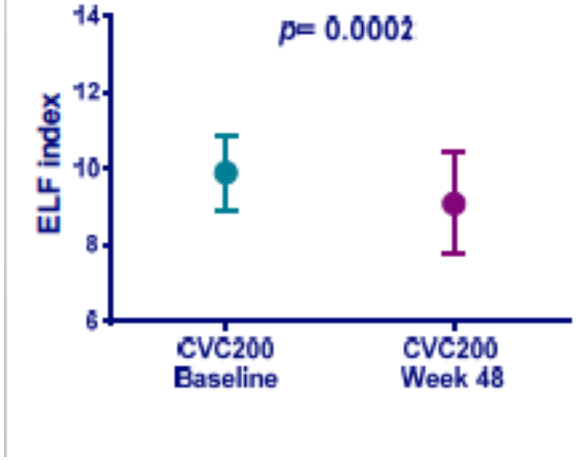
- 156 HIV/HCV fibrosis progression by LSM (Fibroscan) → HLA B18
- 168 HIV/HCV with liver biopsies
  - 68 HCV G3: PNPLA3 variants (I/M+M/M vs. I/I) and the CD4+ cell count were identified as the only predictors of severe steatosis for those with HCV-genotype non- 3
  - Cannabinoid Receptor 2 63 variant associated with more severe Hepatitis Acitivity Index

Frias M et al CROI 2016 poster# 555 Sagnelli C et al CROI 2016 Posters# 586 & 587

Assessment of Hepatic Antifibrotic Effect of Cenicriviroc in Patients With HIV







Abdelhameed E et al CROI 2016 Poster # 552

Eradication of HCV and Extrahepatic Comorbidities in HIV/HCV Coinfection

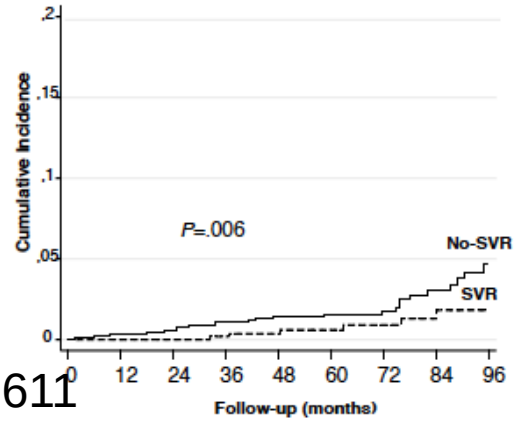
Hazard ratio of events during FU

Responders vs Non-responders

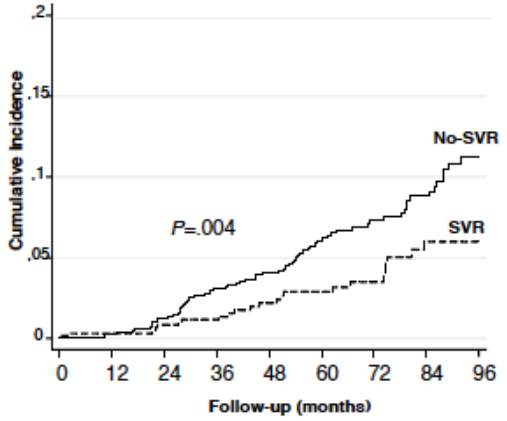
	Univariate analysis[a]		Multivariate analysis[a,b]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Overall deaths	0.35 (0.24 - 0.52)	<.001	0.37 (0.25 - 0.56)	<.001
	sHR (95% CI)		sHR (95% CI)	
Cause-specific deaths				
Liver-related deaths	0.12 (0.05 - 0.28)	<.001	0.13 (0.06 - 0.30)	<.001
Non-liver-related deaths	0.69 (0.43 - 1.1)	.119	0.73 (0.45 - 1.21)	.225
AIDS-related deaths	0.45 (0.09 - 2.22)	.325	0.36 (0.09 - 1.41)	.143
NLR-NAR deaths	0.73 (0.44 - 1.19)	.204	0.80 (0.47 - 1.36)	.406
New AIDS-defining events	0.34 (0.16 - 0.72)	.004	0.37 (0.17 - 0.80)	.011
Liver-related events				
Liver decompensation	0.09 (0.04 - 0.2)	<.001	0.10 (0.05 - 0.22)	<.001
Hepatocarcinoma	0.12 (0.03 - 0.5)	.004	0.13 (0.03 - 0.50)	.003
Liver transplantation	0.10 (0.01 - 0.77)	.027	0.12 (0.02 - 0.79)	.027
NLR-NAR events				
Diabetes mellitus	0.53 (0.33 - 0.84)	.007	0.56 (0.34 - 0.90)	.018
Cancer	0.91 (0.6 - 1.38)	.650	0.90 (0.57 - 1.43)	.665
Cardiovascular event	1.41 (0.93 - 2.13)	.105	1.56 (1 - 2.43)	.052
Sepsis requiring hospitalization	0.55 (0.33 - 0.92)	.024	0.90 (0.57 - 1.43)	.665
Bone event	1.39 (0.82 - 2.35)	.225	1.27 (0.69 - 2.33)	.442
Renal event	0.39 (0.16 - 0.95)	.038	0.38 (0.15 - 0.98)	.046

[a]Cox regression for comparison of the HR of overall death. Fine and Gray regression for comparison of the sHR of events, in the presence of competing risks.
[b]Adjusted for age, sex, prior AIDS-defining conditions (yes vs. no), HIV-transmission category (injection drug users vs. non–injection drug users), nadir CD4+ cell count, cART (yes vs. no), undetectable HIV-RNA at baseline (yes vs. no), FIB-4 ≥3.25 (yes vs. no), genotype (3 vs. other genotypes). **Abbreviations**: HR, hazard ratio; CI, confidence interval; sHR, subhazard ratio.

Renal event



Diabetes mellitus



Berenguer J et al CROI 2016 Poster # 611

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- ✓ Cofactors contributing to persistent inflammatory response
  - ✓ Metabolic syndrome
  - ✓ Microbial translocation
  - ✓ HIV
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- ✓ Inflammatory response driven either by metabolic factors, or microbial traslocation or HIV itself contribute to increase fibrogenesis
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