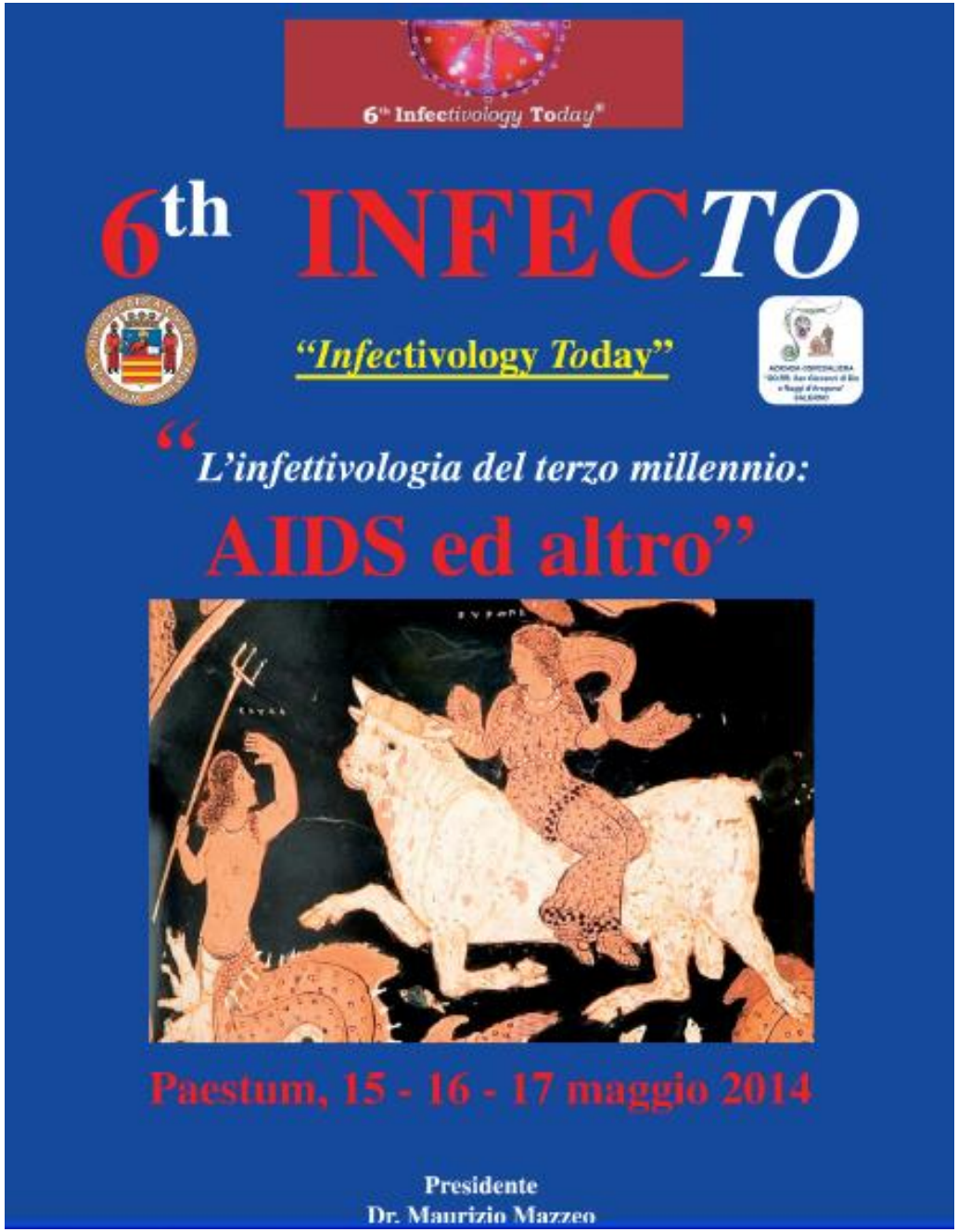
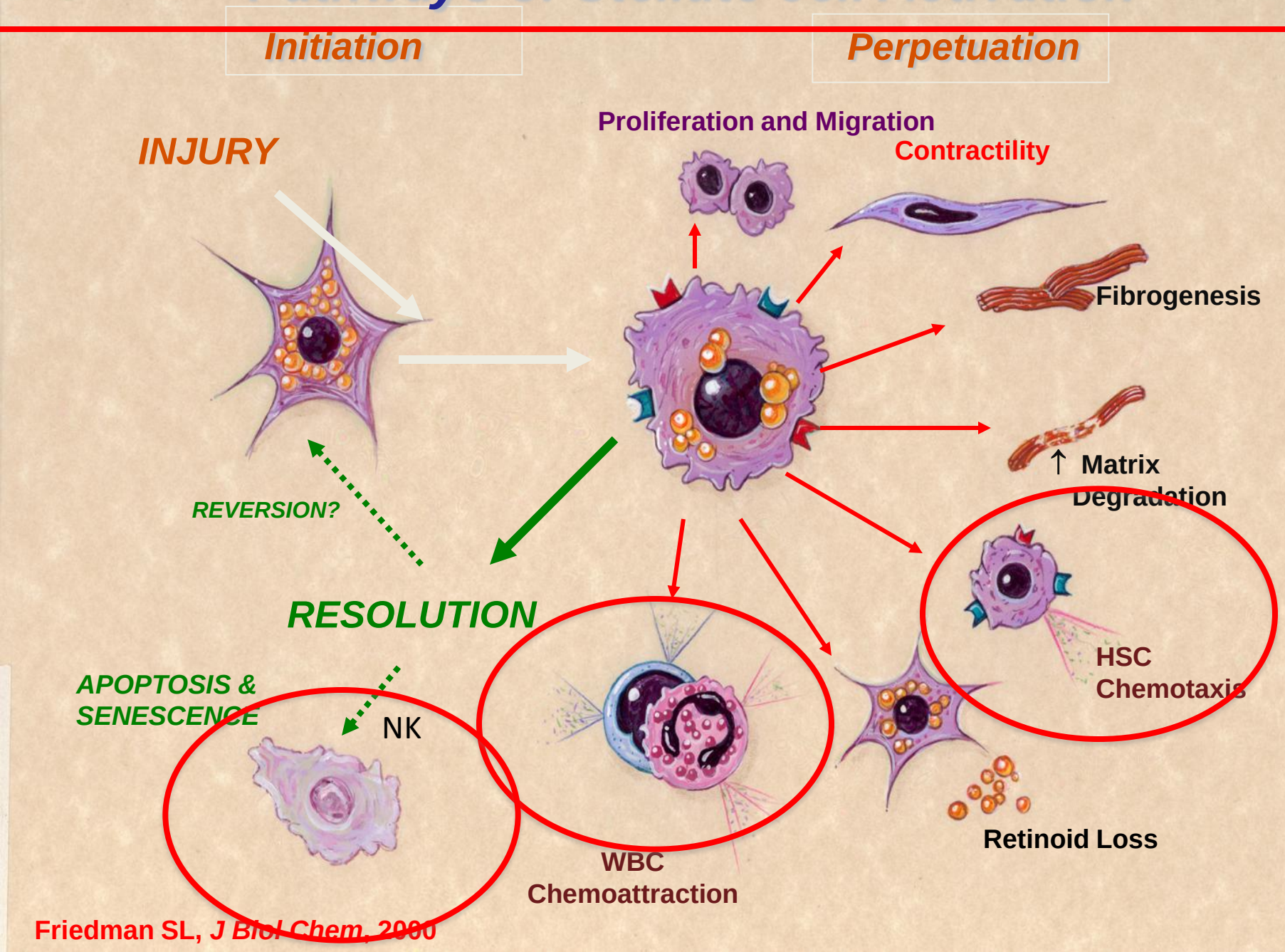


Maraviroc e Fibrosi

Paola Nasta
Clinica di Malattie Infettive

Spedali Civili di Brescia

Pathways of Stellate cell Activation



Friedman SL, *J Biol Chem*, 2000

CCR5 and liver fibrosis

Hepatic fibrosis develops as a response to chronic liver injury and almost exclusively occurs in a pro-inflammatory environment.
(Friedman Sl. et al. Physiol rev; 2008)

However, the role of inflammatory mediators in fibrogenic responses of the liver is only poorly understood

Hepatic stellate cells (HSCs), the main fibrogenic cell population of the liver, are a key player in the fibrotic response. (Friedman Sl. et al. Physiol rev; 2008)

CCR5 is highly expressed on HSCs membrane, promotes their migration to the site of injury, leads the recruitment of other cell types including Kupffer cells and subsequent HSCs activation. *(Schwabe RF et al.,2003; Ekiro S. etal. J Clin Invest,2009)*

- VIRUS
- FAT
- INFLAMMATION

HIV and liver fibrosis

Feng Y, Broder C, Kennedy P, Berger E. HIV-1 entry co-factor:functional cDNA cloning of a seven-transmembrane, G-protein coupled receptor. Science. 1996;272:872–877.

Balasubramanian S, Ganju R, Groopman J. Hepatitis C virus and HIV envelope proteins collaboratively mediate interleukin-8 secretion through activation of p38 MAP kinase and SHP2 in hepatocytes. J Biol Chem. 2003;278:35755–35766

Lin W, Weinberg E, Tai A, Peng L, Brockman M, et al. HIV Increases HCV Replication in a TGF-b1-Dependent Manner. Gastroenterology. 2008;134:803–811.

Tuyama AC, Hong F, Saiman Y, Wang C, Ozkok D, et al. Human immunodeficiency virus (HIV)-1 infects human hepatic stellate cells and promotes collagen I and monocyte chemoattractant protein-1 expression: implications for the pathogenesis of HIV/hepatitis C virus-induced liver fibrosis. Hepatology. 2010;52:612–622

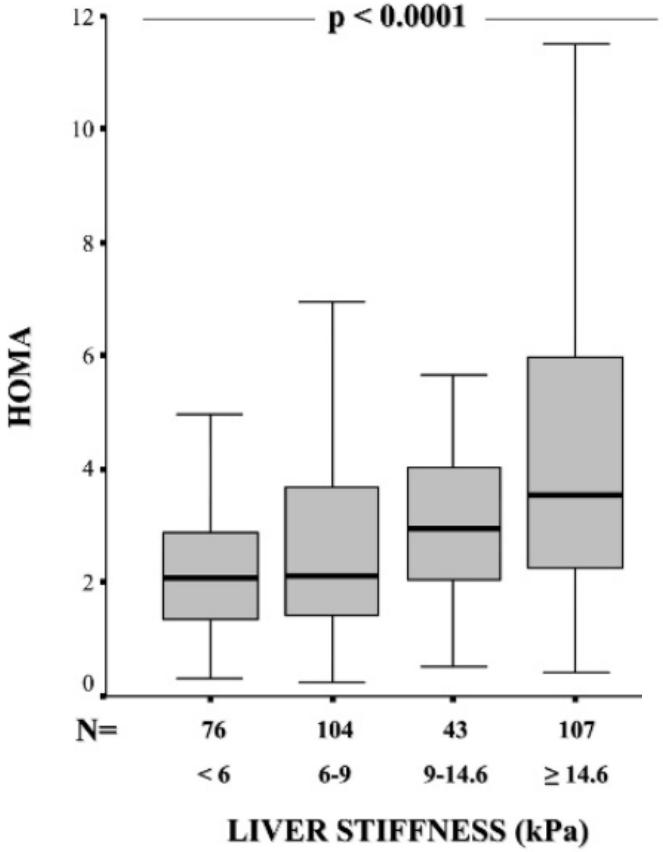
Feng H, Saiman Y, Chuanping Si et al .X4 Human Immunodeficiency Virus Type 1 gp120 Promotes Human Hepatic Stellate Cell Activation and Collagen I Expression through Interactions with CXCR4 PLoS One. 2012; 7(3): e33659

Bruno R, Galastri S, Sacchi P, Cima S, Caligiuri A, et al. gp120 modulates the biology of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. Gut. 2010;59:513–520

- VIRUS
- FAT
- INFLAMMATION

Insulin resistance is associated with liver stiffness in HIV/HCV co-infected patients

N Merchante,[1] A Rivero,[2] I de los Santos-Gil,[3] D Merino,[4] M Márquez,[5] M Á López-Ruz,[6] J Rodríguez-Baño,[7] J del Valle,[8] Á Camacho,[9] J Sanz-Sanz,[10] J Macías,[11] I Pérez-Camacho,[12] J Gómez-Mateos,[13] A Moro,[14] J A Pineda[1]



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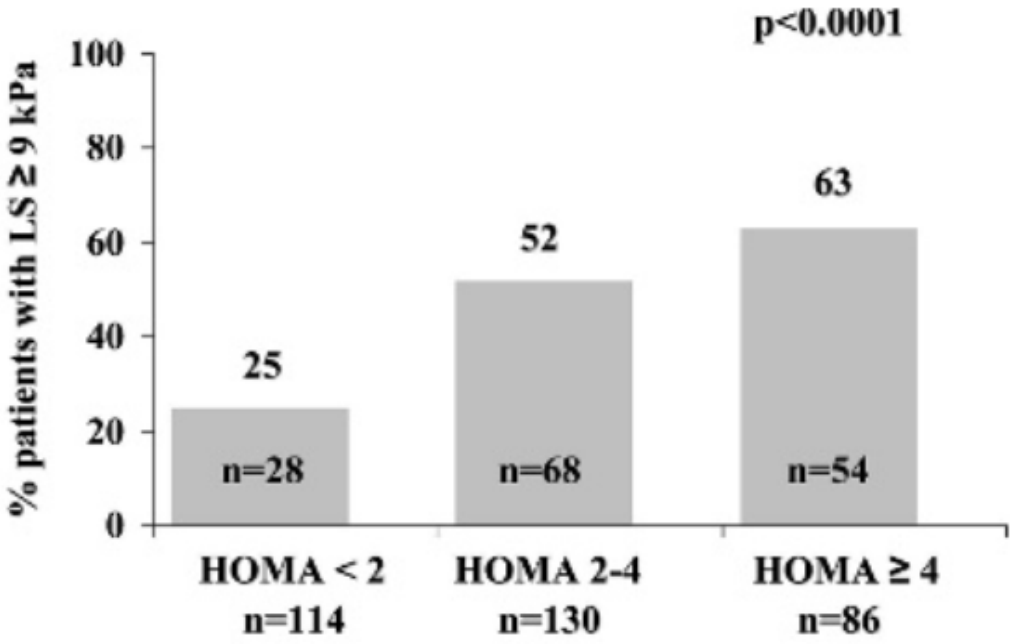


Gut 2009;58:1654–1660.

Insulin Resistance in Chronic Hepatitis C: Association With Genotypes 1 and 4, Serum HCV RNA Level, and Liver Fibrosis

RAMI MOUCARI,* TARIK ASSELAH,* DOMINIQUE CAZALS–HATEM,‡ HÉLÈNE VOITOT,§ NATHALIE BOYER,* MARIE–PIERRE RIPAULT,* RODOLPHE SOBESKY,* MICHÈLE MARTINOT–PEIGNOUX,* SARAH MAYLIN,‖ MARIE–HÉLÈNE NICOLAS–CHANOINE,‖ VALÉRIE PARADIS,‡ MICHEL VIDAUD,§ DOMINIQUE VALLA,* PIERRE BEDOSSA,‡ and PATRICK MARCELLIN*

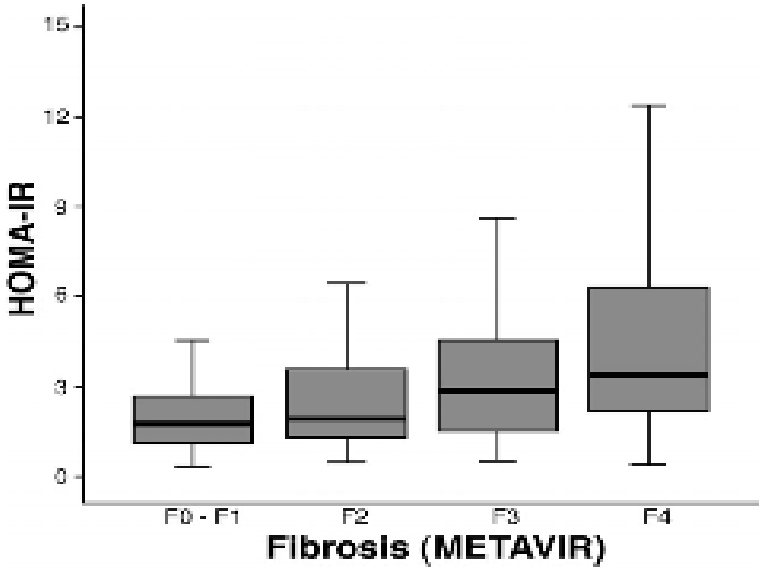


Figure 1. Significant increase of HOMA-IR, parallel with increasing fibrosis stage, in 462 nondiabetic chronic hepatitis C patients ($P < .001$). *Box plots* represent median, quartiles, and ranges of HOMA-IR.

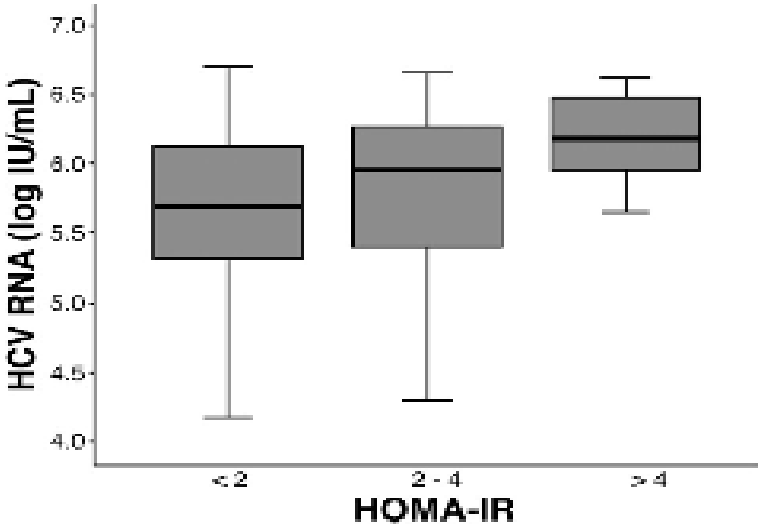


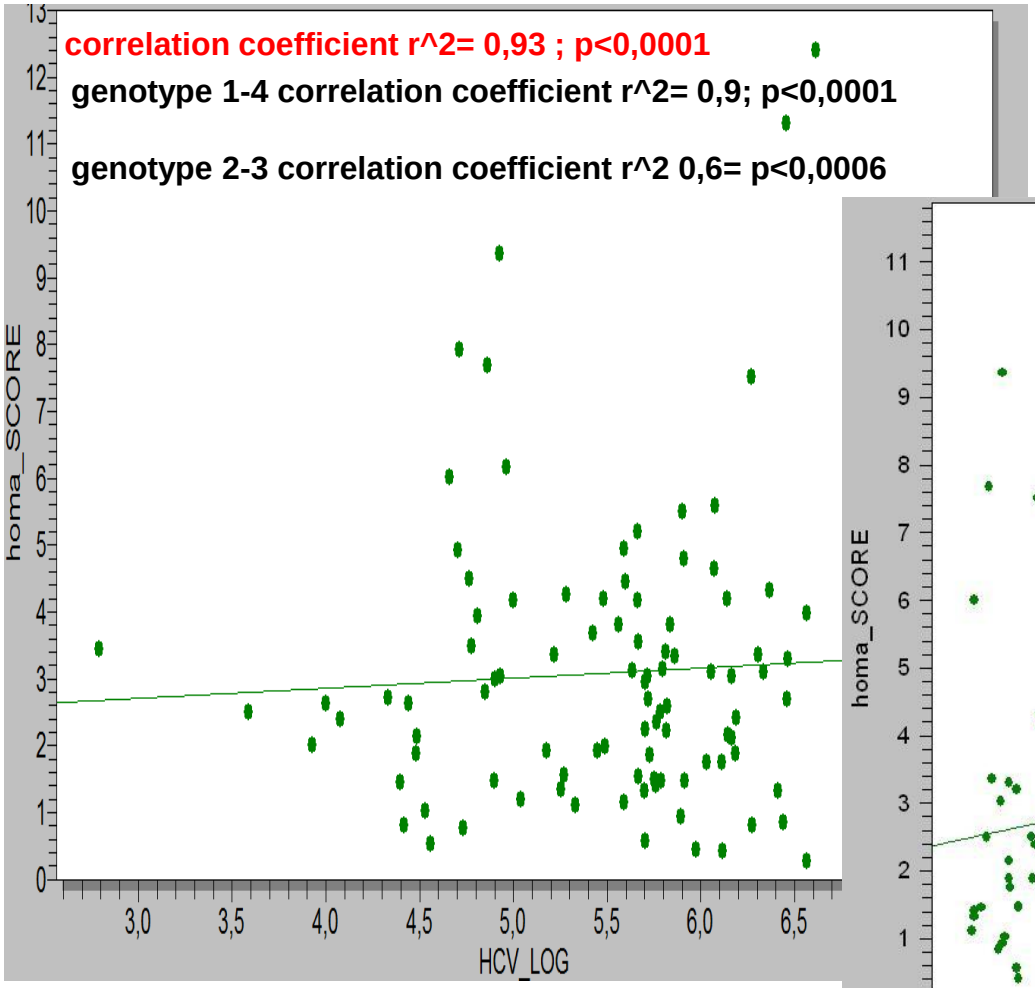
Figure 2. Significant increase in serum HCV RNA, parallel with increasing HOMA-IR, in 145 chronic hepatitis C patients without metabolic disorders or significant fibrosis ($P = .007$). *Box plots* represent median, quartiles, and ranges of $\log_{10}$ serum HCV RNA.

600 patients: 500 HCV and 100 HBV positive
IR is a specific feature of CHC, associated with genotype 1 and 4 and HCV RNA level.
Significant fibrosis is associated with IR independent from steatosis

GASTROENTEROLOGY 2008;134:416–423

HOMA score is associated with Hepatitis C Viremia (Hsui SC et al. 2010)

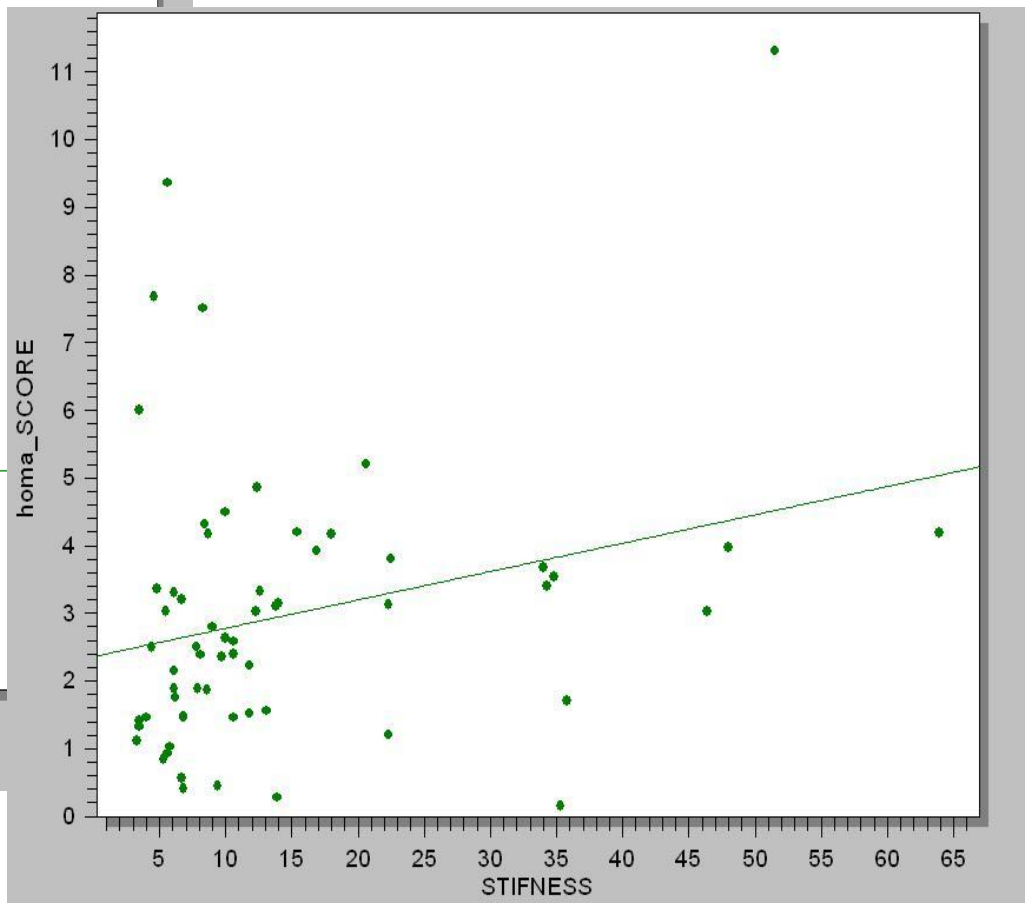
N 107 pts HIV/HCV who started PegIFN/RBV, 49,5% G 1 ,HOMA IR 3,2(±2,9), Cirrhosis 33%



Nasta P et al, ICAAC 2010, ABS H 1673

… and with Liver Stiffness

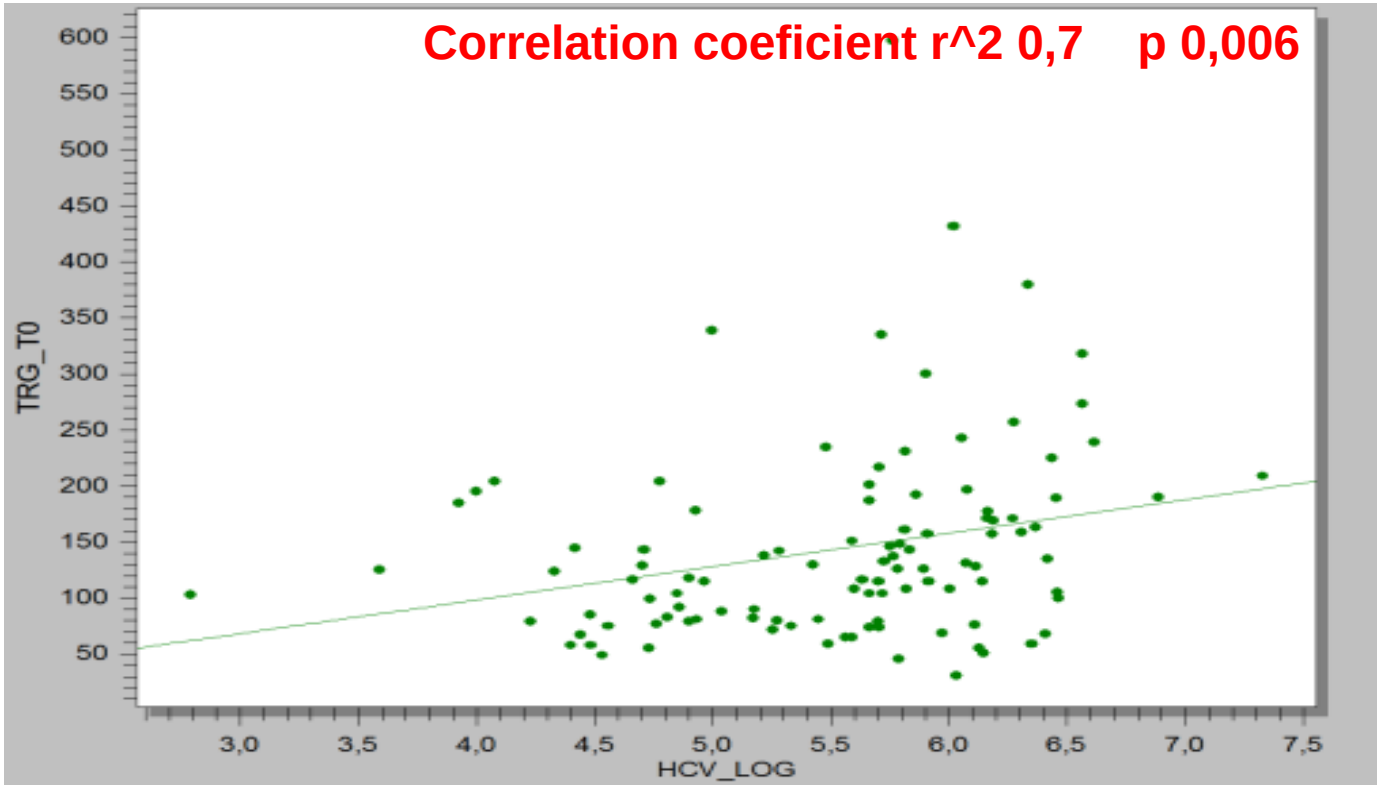
(N Merchante et al, 2010



Nasta P et al. ICAR 2010 (#91)
Nasta P er al, CROI submitted

Triglyceride level is associated with HCV RNA

N 107 pts HIV/HCV who started PegIFN/RBV
49,5% G 1
Cirrhosis 33%
Median TRG level 125 (82-181)mg/dl , TRG>150 mg/dl 34,5%



There is a linear correlation between trglyceride plasma level and HCV-RNA

Nasta P

ANNALS OF HEPATOLOGY
ORIGINAL ARTICLE
July-August, Vol. 11 No.4, 2012: 487-494

Association between metabolic abnormalities and hepatitis C-related hepatocellular carcinoma

Mahmoud A. Khattab,* Mohammed Eslam,* Yousef I. Mousa,* Nosa Ela-adawy,* Shimaa Fathy,* Mohammed Shatat,* Hesham Abd-Aalhalim,* Amal Kamal,* Mohammed A. Sharawe*

Comparison of metabolic parameters

- HCC patients (n=147)
- Matched CHC patients (n=147)
- Controls (n=320)

HCC group:

- higher levels of insulin, glucose, HOMA-IR and adiponectin
- lower levels of total cholesterol, HDL-C, LDL-C, triglycerides

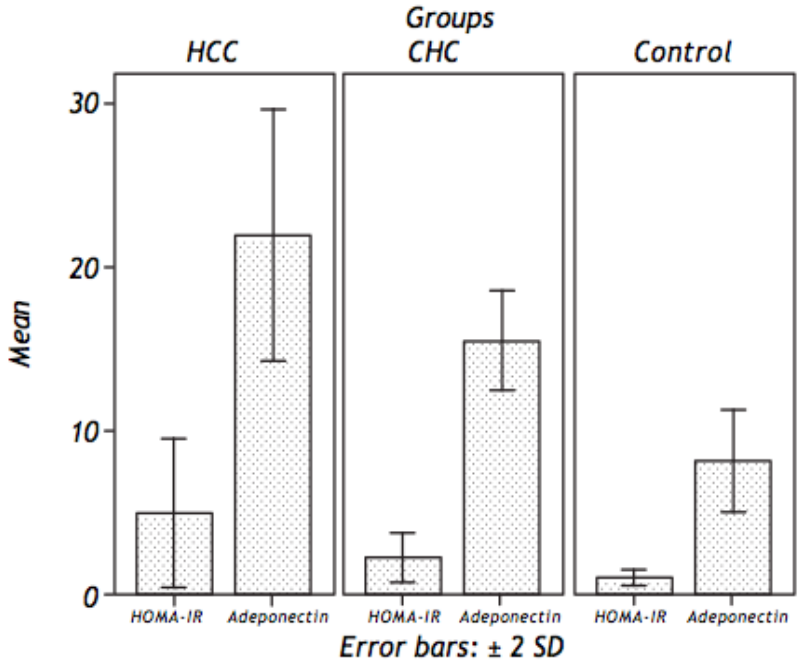


Table 3. Stepwise logistic regression analysis of factors associated with hepatocellular carcinoma (HCC).

	OR	95% CI	P value
Age (per 10year old)	1.456	1.072-1.979	0.01
HOMA-IR (per unit)	2.50	1.70-3.69	0.001
Adiponectin (> 14 µg/mL)	1.585	1.269-1.980	0.001

Khattab MA, et al. Ann Hepatol. 2012; 11:487–94

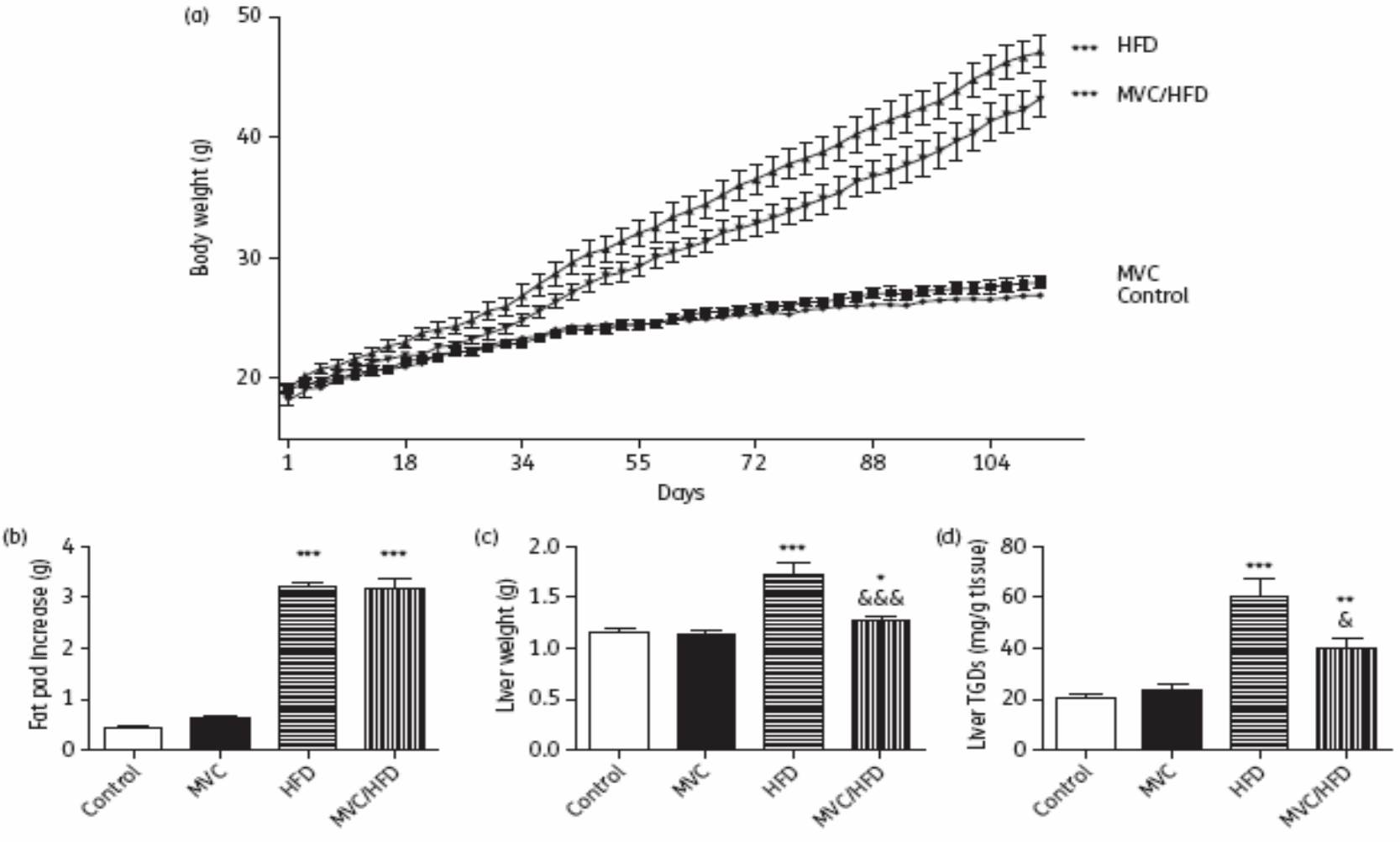
Journal of Antimicrobial Chemotherapy Advance Access published March 20, 2014

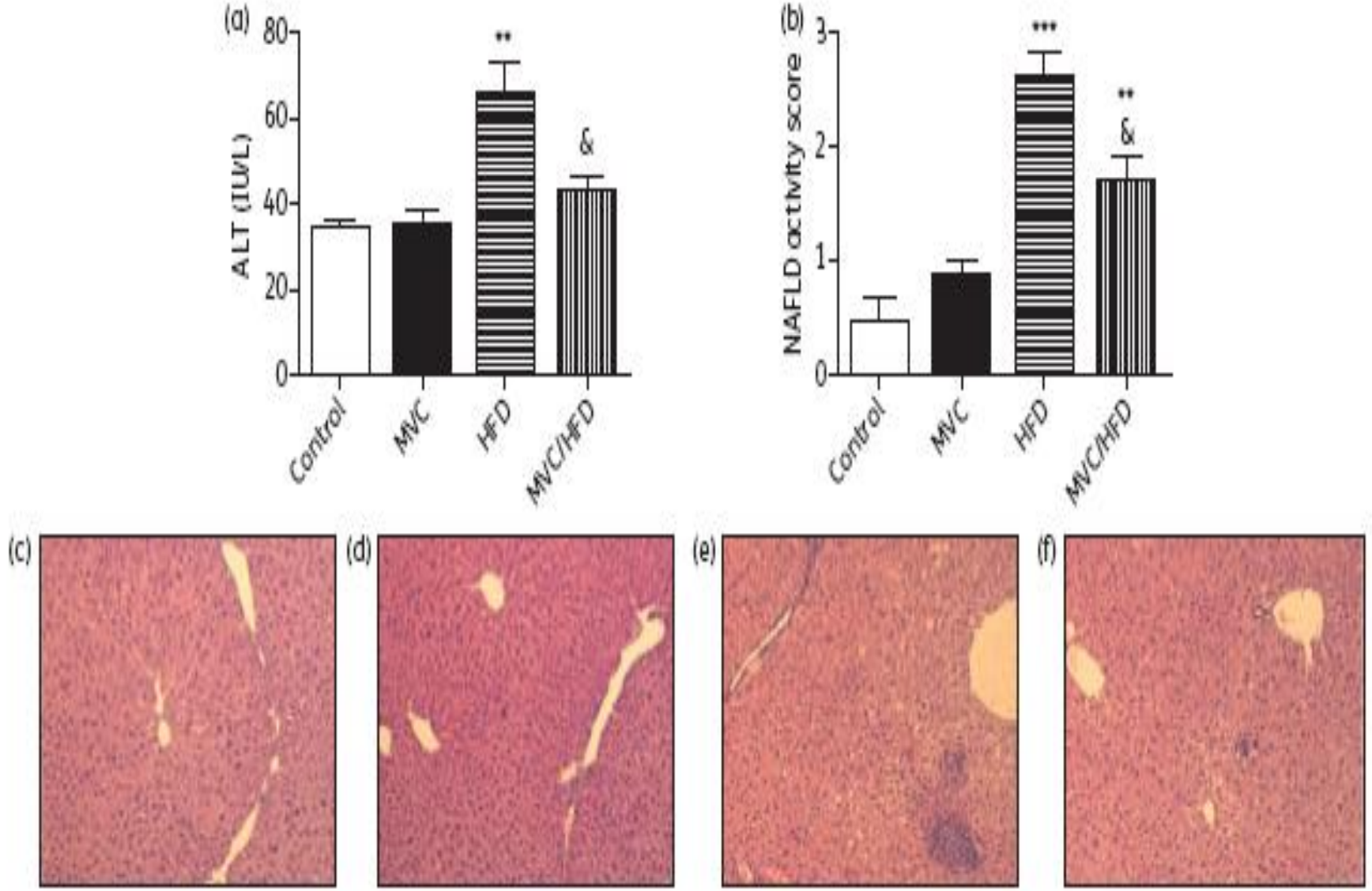
J Antimicrob Chemother
doi:10.1093/jac/dku071

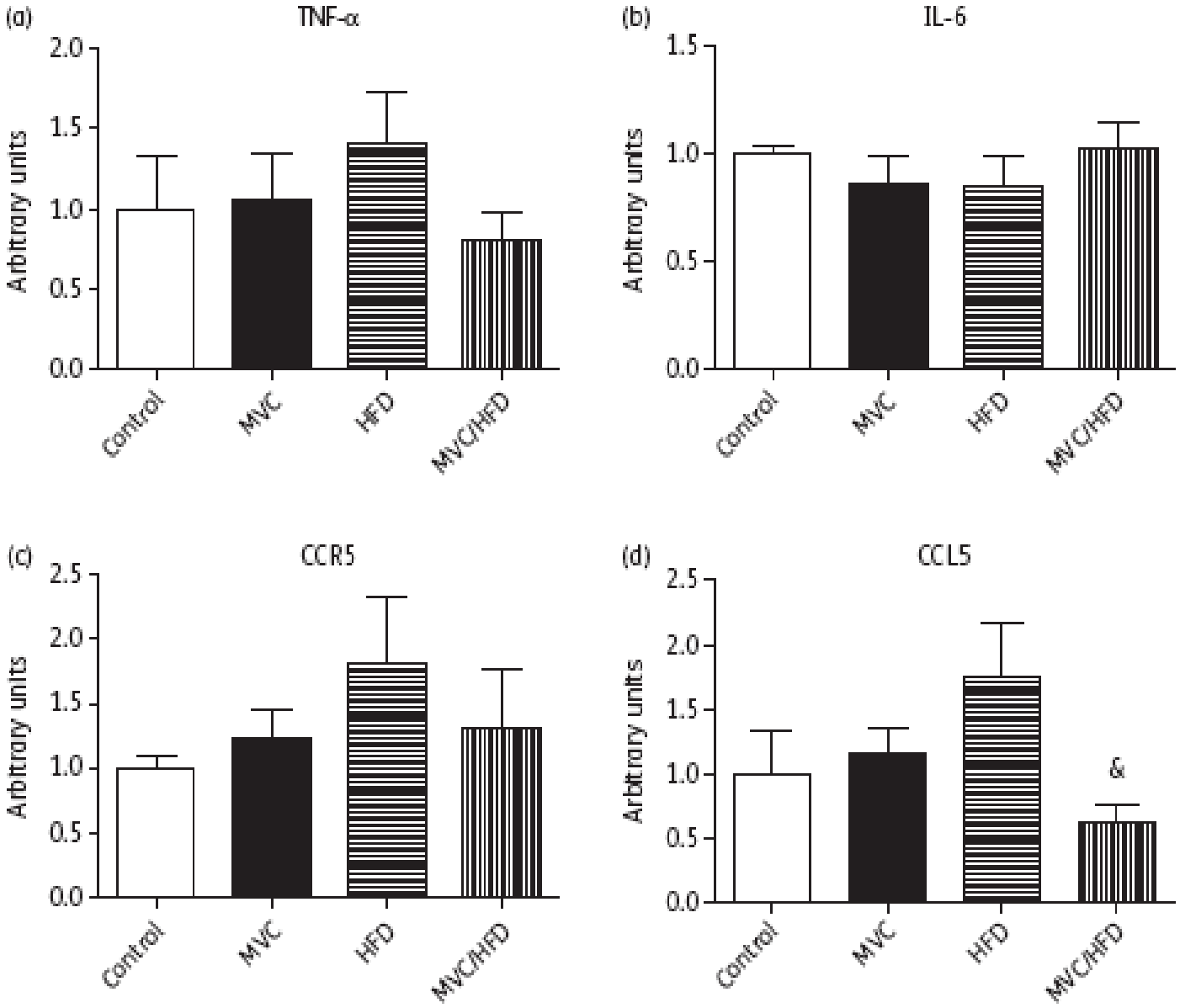
Journal of Antimicrobial Chemotherapy

Maraviroc, a CCR5 antagonist, ameliorates the development of hepatic steatosis in a mouse model of non-alcoholic fatty liver disease (NAFLD)

Laura Pérez-Martínez[1], Patricia Pérez-Matute[1], Javier Aguilera-Lizarraga[1], Susana Rubio-Mediavilla[2], Judit Narro[3], Emma Recio[1], Laura Ochoa-Callejero[3], José-Antonio Oteo[1] and José-Ramón Blanco[1]*




(a)
ALT (IU/L)
80
60
40
20
0
**
&
Control
MVC
HFD
MVC/HFD
(b)
NAFLD activity score
3
2
1
0
***
**
&
Control
MVC
HFD
MVC/HFD
(c)
(d)
(e)
(f)


(a)
TNF-α
Arbitrary units
2.0
1.5
1.0
0.5
0.0
control
MVC
HFD
MVC/HFD
(b)
IL-6
Arbitrary units
1.5
1.0
0.5
0.0
control
MVC
HFD
MVC/HFD
(c)
CCR5
Arbitrary units
2.5
2.0
1.5
1.0
0.5
0.0
control
MVC
HFD
MVC/HFD
(d)
CCL5
Arbitrary units
2.5
2.0
1.5
1.0
0.5
0.0
&
control
MVC
HFD
MVC/HFD

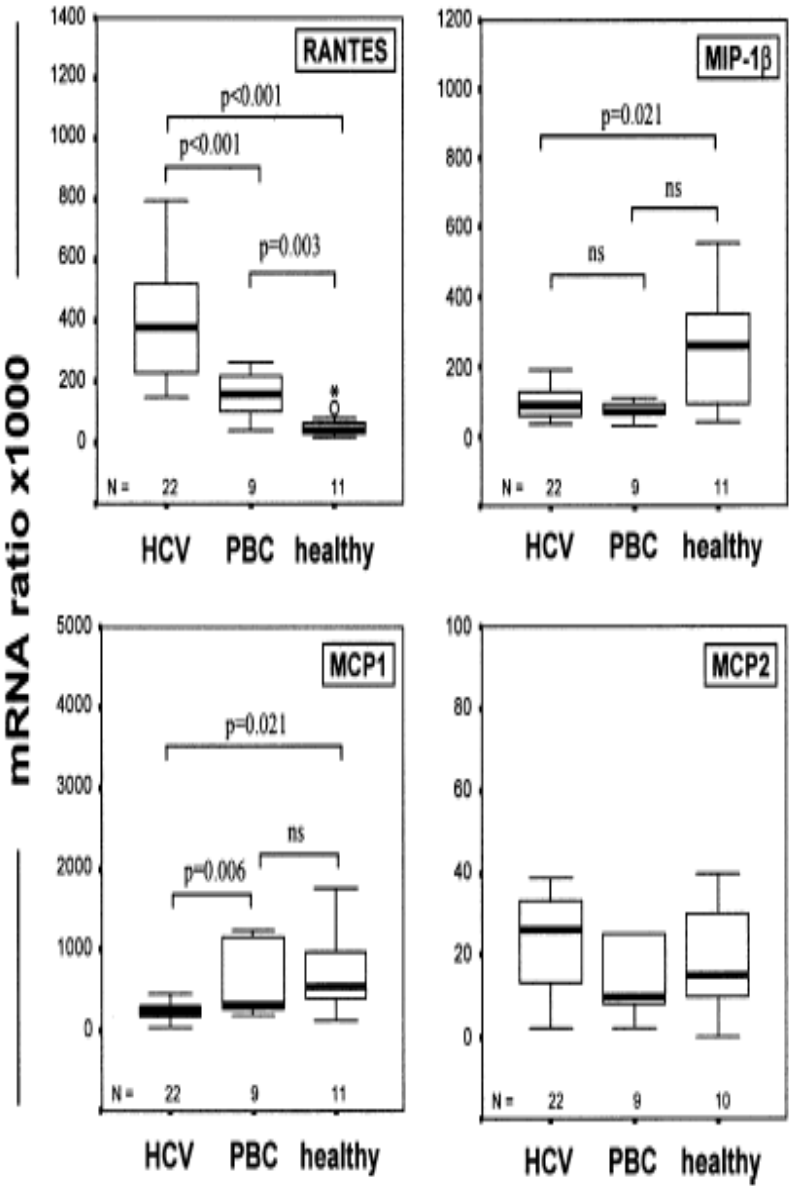
- VIRUS
- FAT
- INFLAMMATION

Semiquantitative analysis of intrahepatic CC-chemokine mRNAs in chronic hepatitis C*

Hans Dieter Nischalke[1], Jacob Nattermann[1], Hans-Peter Fischer[2], Tilman Sauerbruch[1], Ulrich Spengler[1] and Franz Ludwig Dumoulin[CA]

Higher intrahepatic RANTES mRNA levels in chronic hepatitis C.

enhanced expression of RANTES mRNA correlates to CD8 gene expression and to the extent of liver damage, suggesting that a release of proinflammatory cytokines by activated T cells contributes to immunemediated liver damage in hepatitis C



Mediators of Inflammation
Volume 13 (2004), Issue 5-6, Pages 357-359

Antagonism of the chemokine Ccl5 ameliorates experimental liver fibrosis in mice

Marie-Luise Berres,[1] Rory R. Koenen,[2] Anna Rueland,[1] Mirko Moreno Zaldivar,[1] Daniel Heinrichs,[1] Hacer Sahin,[1] Petra Schmitz,[1] Konrad L. Streetz,[1] Thomas Berg,[3] Nikolaus Gassler,[4] Ralf Weiskirchen,[5] Amanda Proudfoot,[6] Christian Weber,[2] Christian Trautwein,[1] and Hermann E. Wasmuth[1]

we identify the chemokine CCL5 (also known as RANTES), which is induced in murine and human liver after injury, as a central mediator of this interaction.

First, we showed in patients with liver fibrosis that *CCL5* haplotypes and intrahepatic *CCL5* mRNA expression were associated with severe liver fibrosis.

Consistent with this, we detected *Ccl5* mRNA and CCL5 protein in 2 mouse models of liver fibrosis, induced by either injection of carbon tetrachloride (CCl4) or feeding on a methionine and choline–deficient (MCD) diet. In these models,

***Ccl5*–/– mice exhibited decreased hepatic fibrosis, with reduced stellate cell activation and immune cell infiltration.**

Transplantation of *Ccl5*-deficient bone marrow into WT recipients attenuated liver fibrosis, identifying infiltrating hematopoietic cells as the main source of Ccl5.

We then showed that treatment with the CCL5 receptor antagonist Met-CCL5 inhibited cultured stellate cell migration, proliferation, and chemokine and collagen secretion. Importantly, in vivo administration of Met-CCL5 greatly ameliorated liver fibrosis in mice and was able to accelerate fibrosis regression.

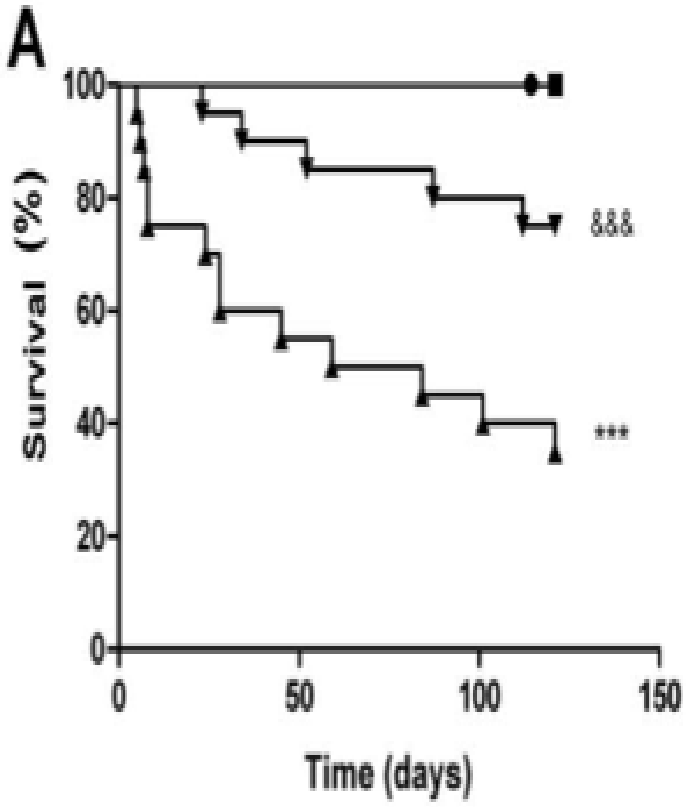
Our results define a successful therapeutic approach to reduce experimental liver fibrosis by antagonizing Ccl5 receptors.

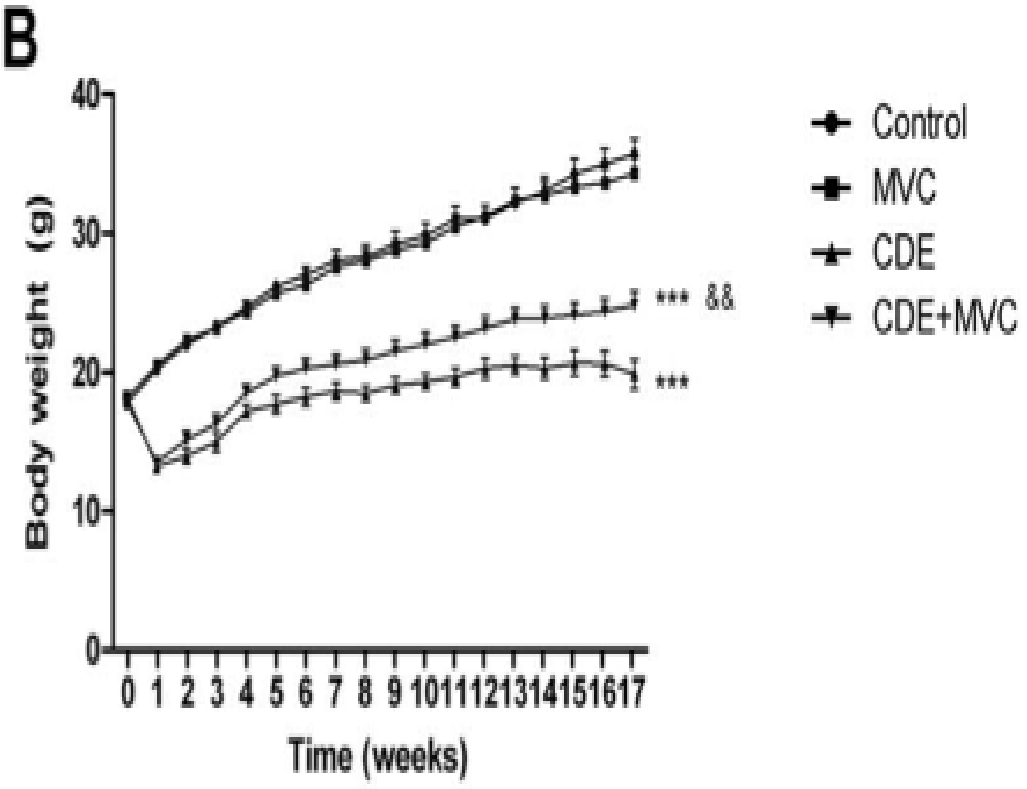
J Clin Invest , 2010, 120:4129-40

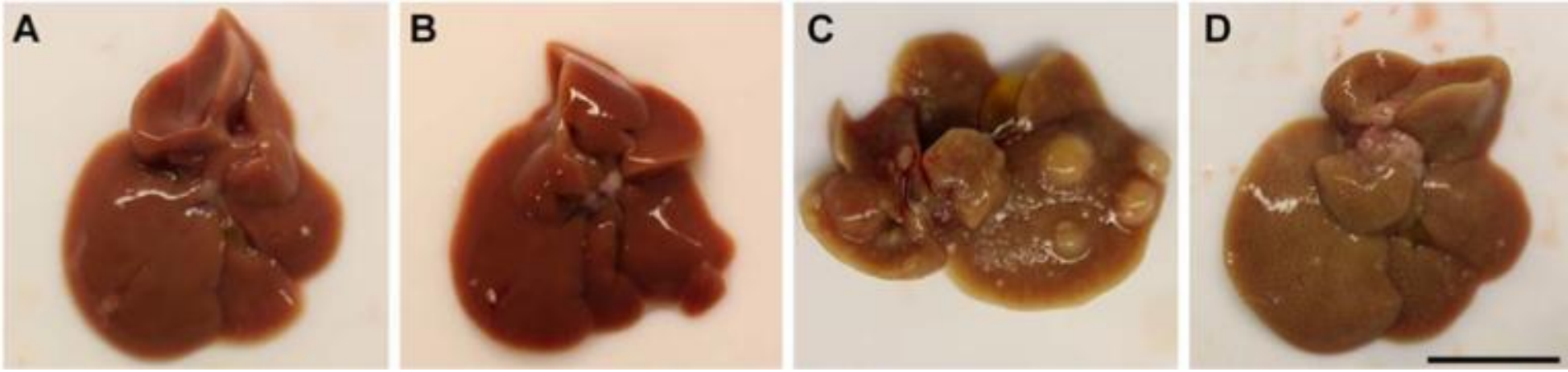
Maraviroc, a CCR5 Antagonist, Prevents Development of Hepatocellular Carcinoma in a Mouse Model

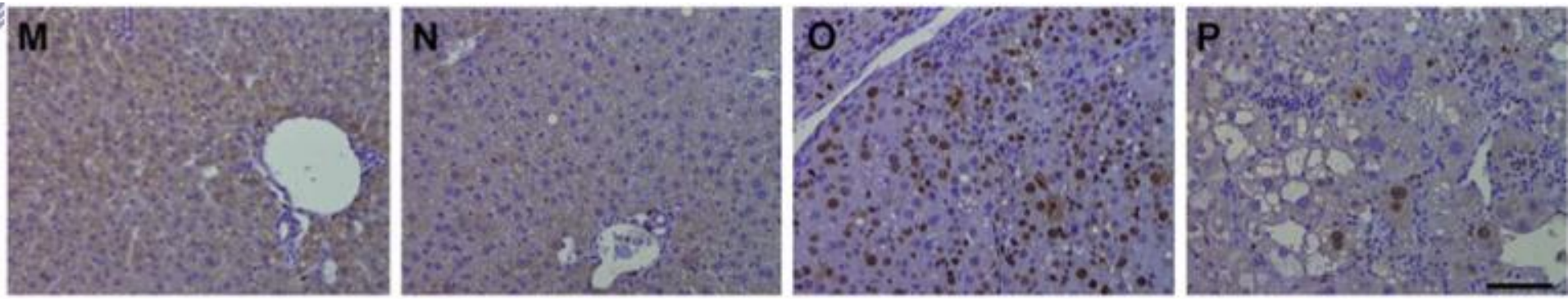
Laura Ochoa-Callejero[1], Laura Pérez-Martínez[2], Susana Rubio-Mediavilla[3], José A. Oteo[2], Alfredo Martínez[1]*, José R. Blanco[2]

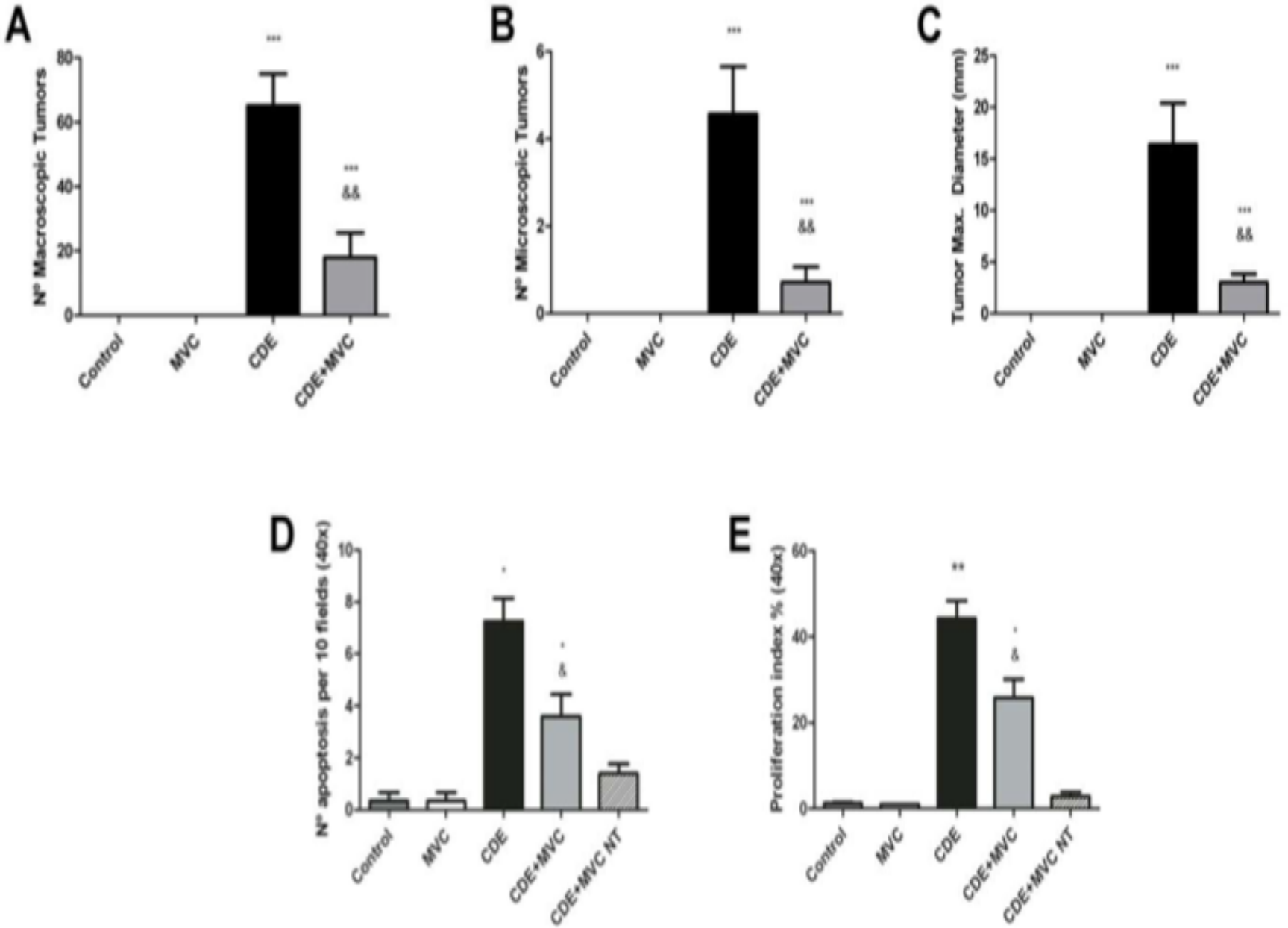
1 Oncology Area, Center for Biomedical Research of La Rioja (CIBIR), Logroño, Spain, **2** Infectious Diseases Area, Center for Biomedical Research of La Rioja (CIBIR), Logroño, Spain, **3** Pathology Service, Hospital San Pedro, Logroño, Spain



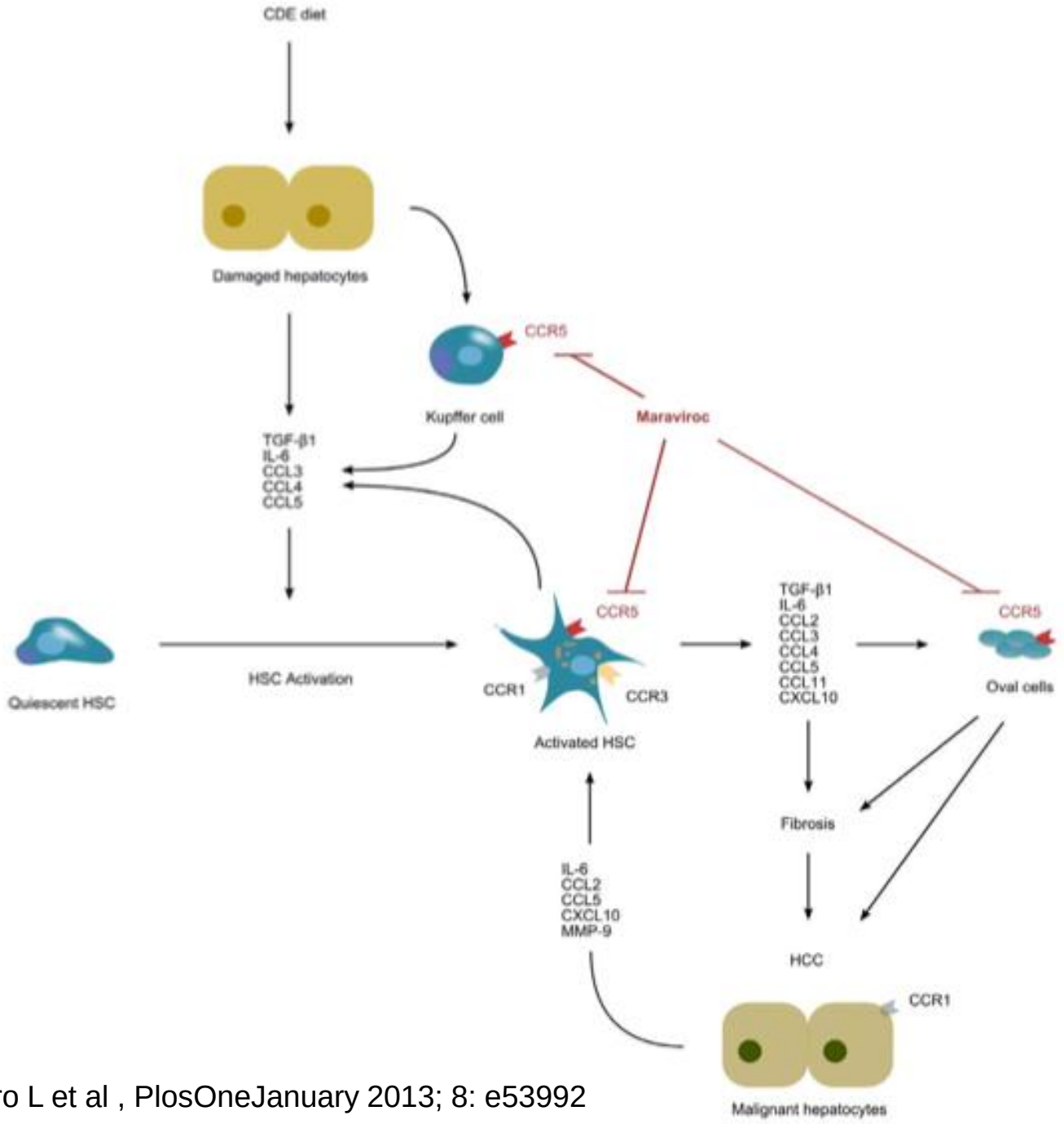



A
B
C
D


M
N
O
P



Ochoa Callheiro L et al , PlosOneJanuary 2013; 8: e53992



Ochoa Callheiro L et al , PlosOneJanuary 2013; 8: e53992

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Anti-retroviral drugs do not facilitate hepatitis C virus (HCV) infection *in vitro*

Lisa Sandmann [a], Matthew Wilson [a], David Back [b], Heiner Wedemeyer [a], Michael P. Manns [a], Eike Steinmann [c], Thomas Pietschmann [c], Thomas von Hahn [a,d], Sandra Ciesek [a,c,*]

una coltura cellulare di Huh-7.5

transfettata con genomi di HCV (5 lg Luc-Jc1 contenti luciferasi o Luc-Con1 ET).

Dopo 5 ore dalla transfezione , sono state aggiunte differenti concentrazioni di farmaci antiretrovirali

dopo 48 ore è stata valutata la replicazione di HCV quantificando l'attività della luciferasi.

Per analizzare la capacità di assemblamento e rilascio di nuove particelle di HCVcc, è stato raccolto il supernatante e usato per infettare altre cellule target.

La capacità infettante del supernatante è stata valutata quantificando l'attività della luciferasi

Table 1
Antiretroviral drugs.

Mode of action	Compound	Concentrations (μg/ml)	Toxic concentration (μg/ml)	Plasma in vivo concentration (therapeutic dosage) (μg/ml)
Protease inhibitors	Atazanavir	0–25	125	3.152
	Darunavir	0–50	250	6.5
	Lopinavir	0–50	10	9.4 ± 4.4
	Ritonavir	0–2	20	0.89
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	Efavirenz	0–10	10	4.07
	Nevirapine	0–100	100	5.74
	Rilpivirine	0–2	100	0.204
Nucleoside reverse-transcriptase inhibitors (NRTIs)	Abacavir	0–50	500	4.26
	Emtricitabine	0–20	500	1.8
	Tenofovir	0–30	300	0.326
Integrase inhibitor	Raltegravir	0–50	>100	2.17
CCR5 receptor antagonist	Maraviroc	0–50	500	0.888

Antiviral Research 96 (2012) 51–58

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

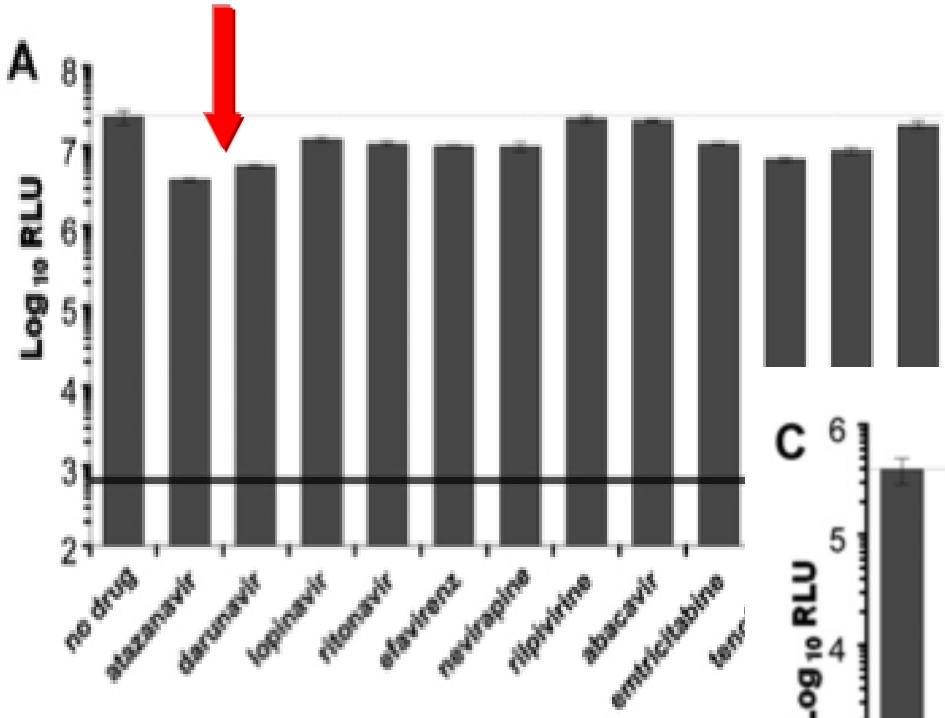
Antiretroviral drugs do not promote HCV replication

Since none of the antiretroviral drugs enhance HCV entry,

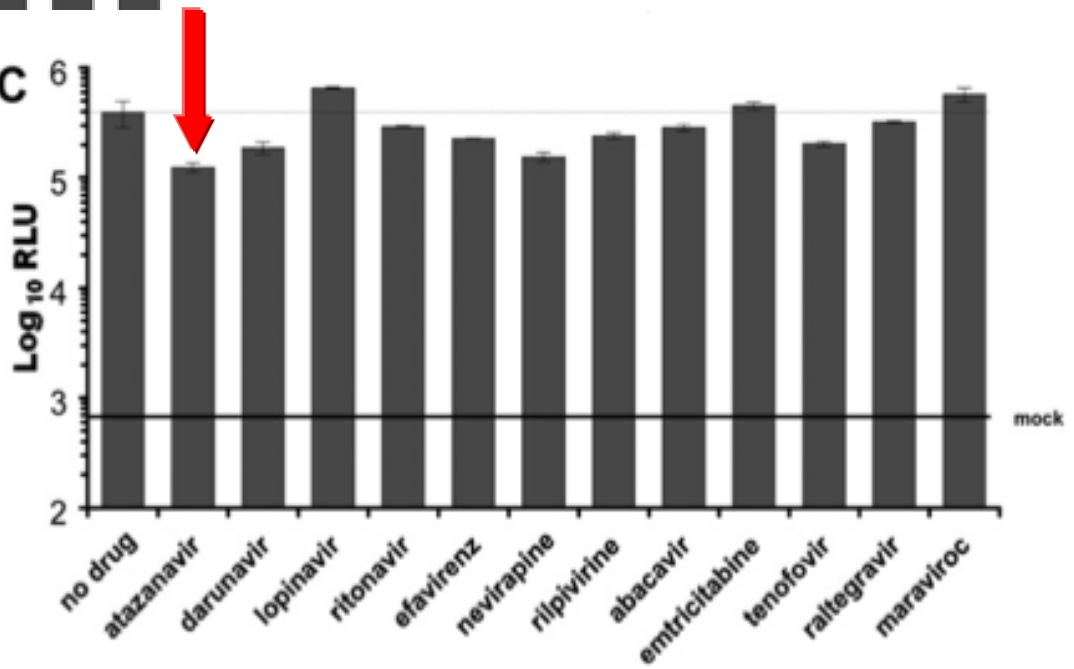
Anti-retroviral drugs do not facilitate hepatitis C virus (HCV) infection *in vitro*

Lisa Sandmann[a], Matthew Wilson[a], David Back[b], Heiner Wedemeyer[a], Michael P. Manns[a], Eike Steinmann[c], Thomas Pietschmann[c], Thomas von Hahn[a,d], Sandra Ciesek[a,c,*]

Atazanavir induced the most prominent inhibitory effect



and more evident reduction in HCVcc particle release



Antiviral Research 96 (2012) 51–58

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Anti-retroviral drugs do not facilitate hepatitis C virus (HCV) infection *in vitro*

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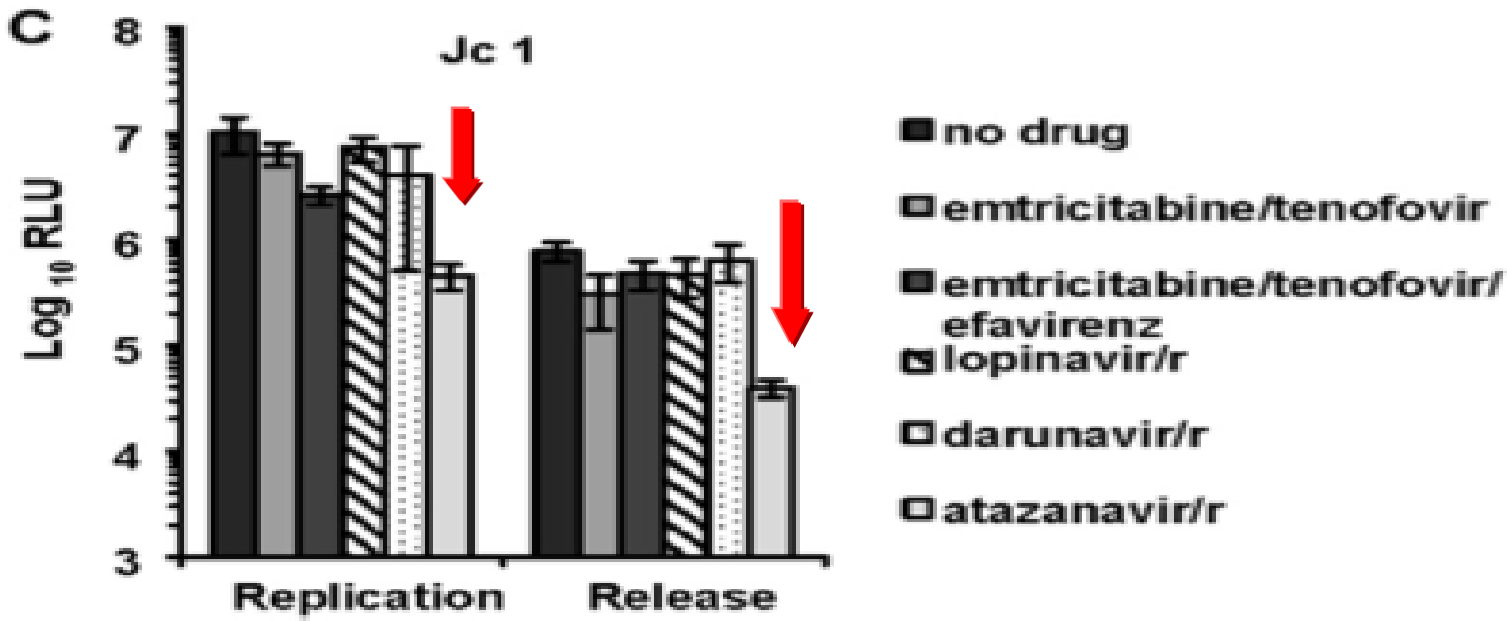

the combination of ritonavir with atazanavir reduced Luc-Jc1replication by more than 10-fold at the highest tested doses Likely as a consequence of reduced RNA rep-lication, the de novo production of infectious viral progeny was also impaired by ca. 10-fold

Antiviral Research 96 (2012) 51–58

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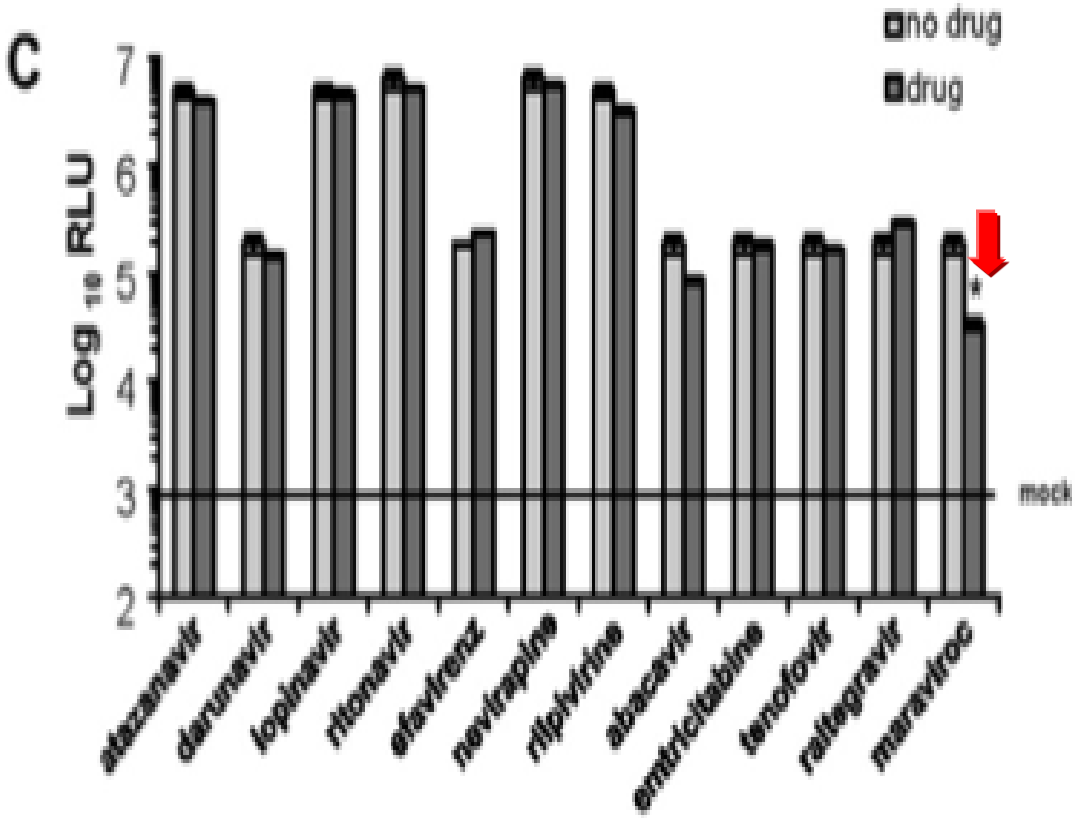
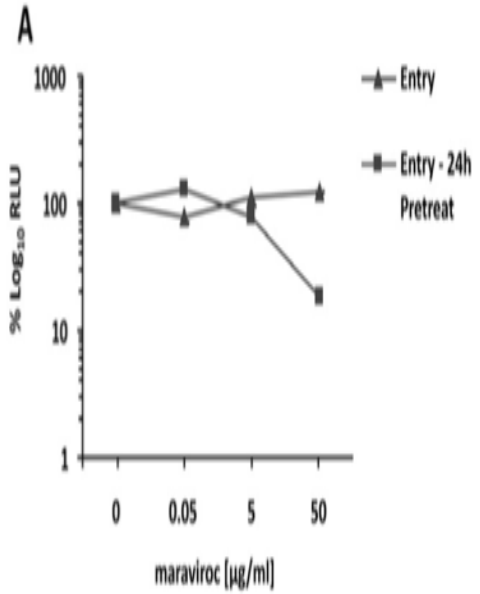
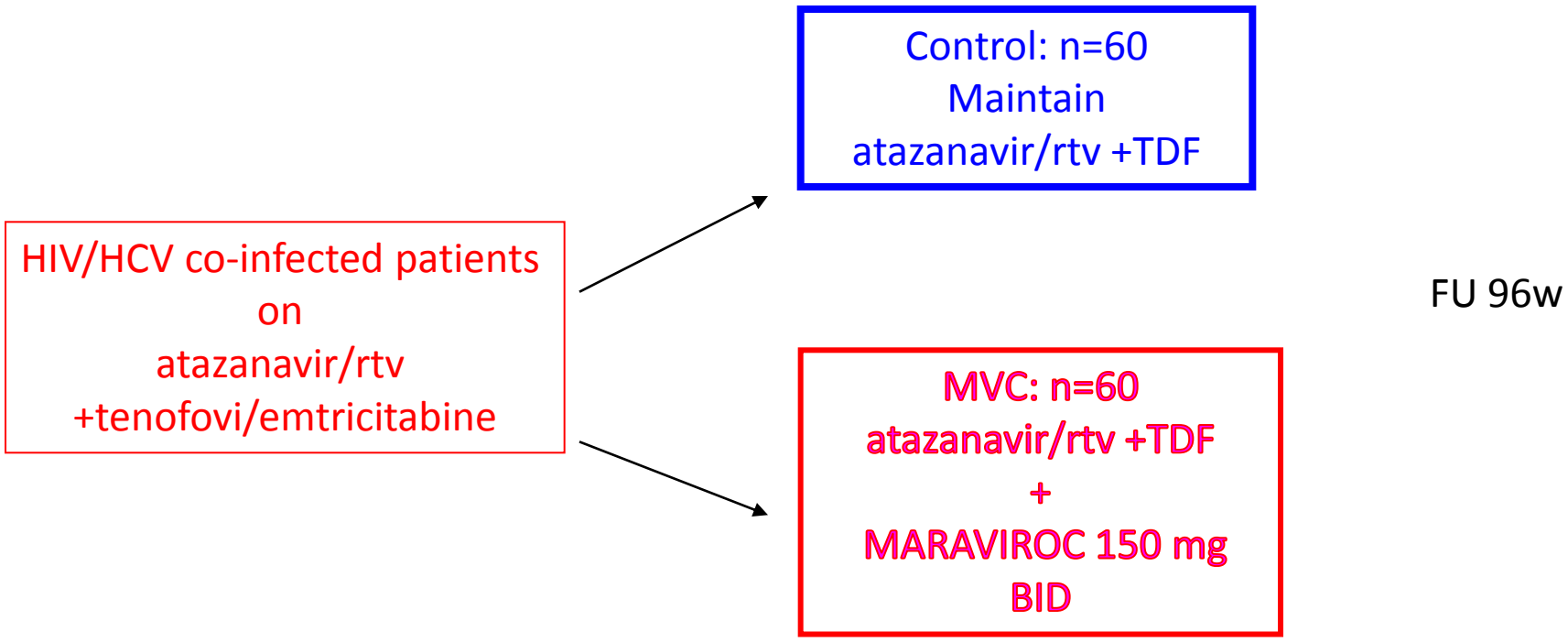
While most of the drugs did not have an effect on HCV entry even after 24 h pre-treatment, pre-treatment with the CCR5 receptor antagonist maraviroc showed an 8 to 10-fold reduction of HCVcc entry .





STUDY DESIGN

- Phase III, proof of concept, prospective, open label, randomized, controlled trial
- HIV/HCV co-infected subject with undectable HIV-RNA (< 50 copies/ml - bDNA) taking HAART based on Atazanavir 300 /ritonavir 100 qd plus Truvada®
- Patients will be screened and randomized 1:1 in two arm:



* Safety analysis of the intervention was planned on the first 60 patients enrolled before continuing enrolment in the study

KEY INCLUSION CRITERIA

•Patient with HIV-1/HCV (HCV-RNA detectable at quantitative analysis) co-infection

•Currently receiving a PI based HAART for at least 24 week based on Tenofovir/emtricitabine + Atazanavir 300mg/ritonavir 100 mg

•HIV-RNA < 50 copies/ml confirmed in two consecutive examination in the previous 3 months

•Without cirrhosis (based on hystological or echographycal or clinical signs)

KEY EXCLUSION CRITERIA

•Alcool intake >2 glasses daily

•Previous us of anti HCV treatment

•Need to use PegIFN/RBV in the next two years

•Child Pugh liver function classification > A 6

•HBsAg+ co-infection

•Grade ¾ laboratory abnormalities defined by DAIDS grading table

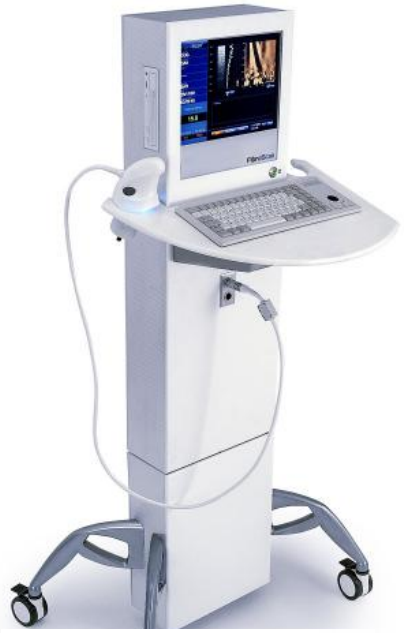
•Co-medication with statins or hypoglycaemic drugs

Primary end point

Proportion of patients with or without change in fibrosis stage at week 48 and at week 96 determined with transient Elastometry- Fibroscan® *(Castera L. et al, Gastroenterology; 2005)* *and Fibrotest* ®(Halfon P. et al. Am J Gastroenterol,2006)

Stage	Fibroscan : Liver Stiffness Kpa	Fibrotest
I (F0-1)	<7,1	0,22-0,27
II (F2)	7,1-9,4	0,49-0,58
III(F3)	9,5-12,4	0,59-0,72
IV(F4)	≥12,5	0,75-1

LIVER STIFFNESS MEASUREMENT:FIBROSCAN®



An officially trained physician performed
Livers Siffness measurement using Fibroscan® on fasting patients
The median value of 10 successful measurement
and success rate (defined as ratio of successful measurement) of at least 60% were only considered for evaluation

Secondary end point

1) Proportion of patient with reduction of ≥50 ng/ml of Hyaluronic acid plasma concentration from BL at week 24,48, 96

2) Change from baseline at week 24,48,96 of:

- AST/ALT, ALP, GGT, Bil tot,PLT, ALB (direct and indirect)
- Quantitative HCV-RNA ,HIV-RNA
- PCR, Alfa 1 antitripsin, fibrinogen,
- Total Cholesterol, LDL, HDL, triglycerides, HOMA score
- T CD4+ cell count and CD8+T cell count

Antivir Ther. 2011 ; 16(5): 667–675. doi:10.3851/IMP1815.

Hyaluronic Acid Levels Predict Increased Risk of Non-AIDS Death in Hepatitis Coinfected Persons Interrupting Antiretroviral Therapy in the SMART Study

Lars Peters[1], Jacqueline Neuhaus[2], Amanda Mocroft[3], Vincent Soriano[4], Jürgen Rockstroh[5], Gregory Dore[6], Massimo Puoti[7], Ellen Tedaldi[8], Bonaventura Clotet[9], Bernd Kupfer[5], Jens D Lundgren[1,10], and Marina B Klein[11] for the INSIGHT SMART Study Group

Probaility of NON AIDS death according with HA at BL

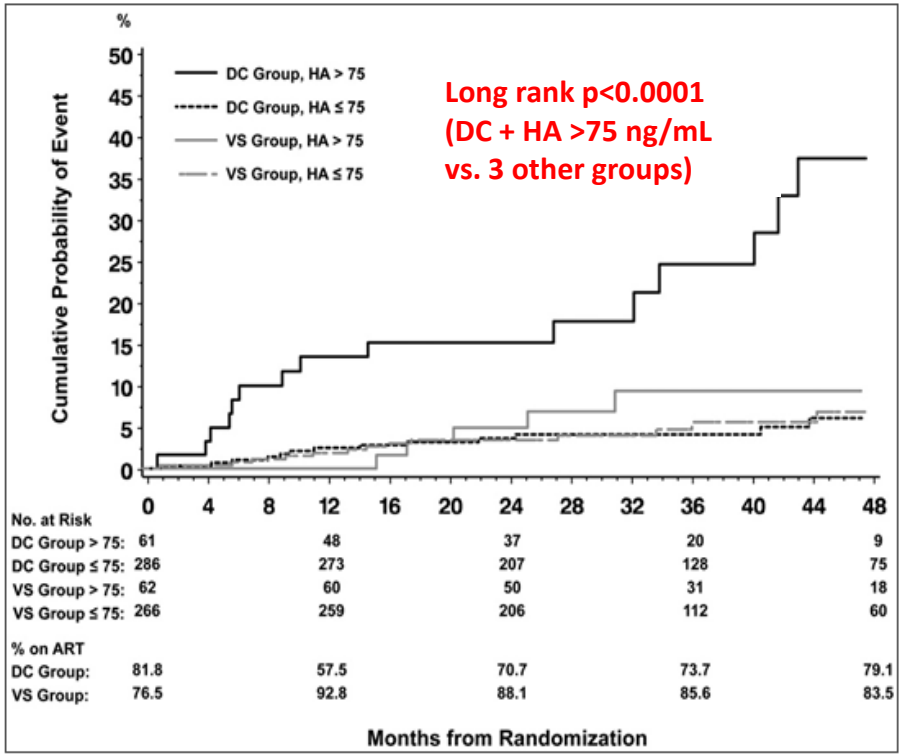


Figure 1
Cumulative probability of non-AIDS death according to randomization group and baseline hyaluronic acid (HA) (ng/mL) level in coinfected participants

Probability of Liver related death according with HA at BL

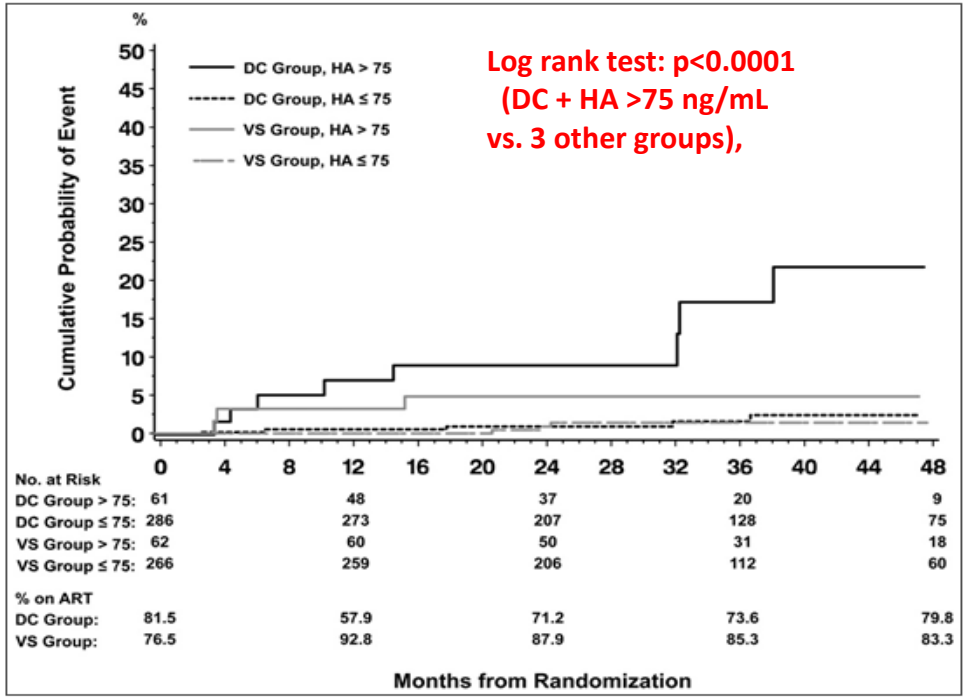


Figure 2
Cumulative probability of liver-related death or development of cirrhosis according to randomization group and baseline hyaluronic acid (HA) (ng/mL) level in coinfected participants

DC: drug conservation,
VS: viral suppression

Hyaluronic acid measurement

HA was measured in stored plasma samples at baseline and at 24,48 and 96 week using a commmecial ELISA-assay (Echelon Biosciences Inc®) with a HA range in a healthy population between 50–120 ng/mL.

Planned preliminary 96 week analysis on first 60 patients enrolled : patient disposition

Pts enrolled	Controls : n 28	MVC : n 35
Drop		
Rettry CI	1	2
SIDE EFFECT	0	7
Lost to FU	5	2
Start PegIFN	1	0
Final analysis	21	24

Baseline Characterstics

Parameters (median,IQR;n/%)	Control (n=28)	Maraviroc (n=35)	p
Age (yrs)	45(43-47)	46(43-49)	0,9
Female gender	5(18%)	8(23%)	0,3
IVDU	25(89%)	25(71%)	0,3
Body mass index	22.5(20.5-25.9)	24.2(21.2-30.9)	0,6
Alcool consumption	10(35%)	15(43%)	0,2
HIV exposure (yrs)	19.5(12.5-22.5)	19(13-23)	0,9
ARV exposure (yrs)	12(8.5-15)	13(9-14)	0,9
PI exposure (yrs)	10(6.5-12)	10(5-13)	0,9
CD4+ T cell count nadir (cell/mm3)	175(99.5-243)	241(73-410)	0,3
CD4+ T cell count at BL (cell/mm3)	552(371-857)	496(426-618)	0,3
CD4+ T cell %at BL	31,6(24.7-38.1)	29,7(25.7-36.4)	0,1
CD8+ T cell count at BL (cell/mm3)	728(605-918)	693(482-826)	0,4
CD8+ T cell% at BL	38,4(33.2-43.9)	40.2(31.3-48.7)	0,6
CD4/CD8	0.8(0.6-1.1)	0.8(0.5-1.0)	0,6

Baseline Characterstics

Parameter (median,IQR;n/%)	Control (n=28)	Maraviroc (n=35)	p
HCV Genotype, 1-4 2-3	 27(96%) 3 (10%)	 28 (80%) 1(3%)	 0,3
HCV RNA load (log_{10} IU/mL)	5.9(5.4-6.3)	5.3(5.2-6.0)	0,1
AST (IU/ml)	43(33-59)	42(29-58)	0,5
ALT(IU/ml)	64(44-109)	66(46-106)	0,5
GGT (mg/dl)	58(24-91)	51(38-123)	0,5
ALB (g/l)	4.5(4.4-4.6)	4.4(4.1-4.6)	0,1
PT%	104(98-109)	105(94-108)	0,4
PLT (cell/mm3)	168(142-200)	159(132-213)	0,8
Stiffness Kpa (n 57:26 ctr, 31 MVC) IQR Success rate (%)	7.2(5.7-9.3) 1(0.5-2.4) 100	7.3(5.4-10) 1(0.5-1.8) 100	0,9 0,9
Fibrotest (n 52:25cont;27MVC)	0.8(0.6-0.9)	0.7(0,6-0,8)	0,1
HA (ng/ml)	253(153-445)	257,4(179-375)	0,6

Parameter's variation at week 96

Control n=21 — Maraviroc n=24

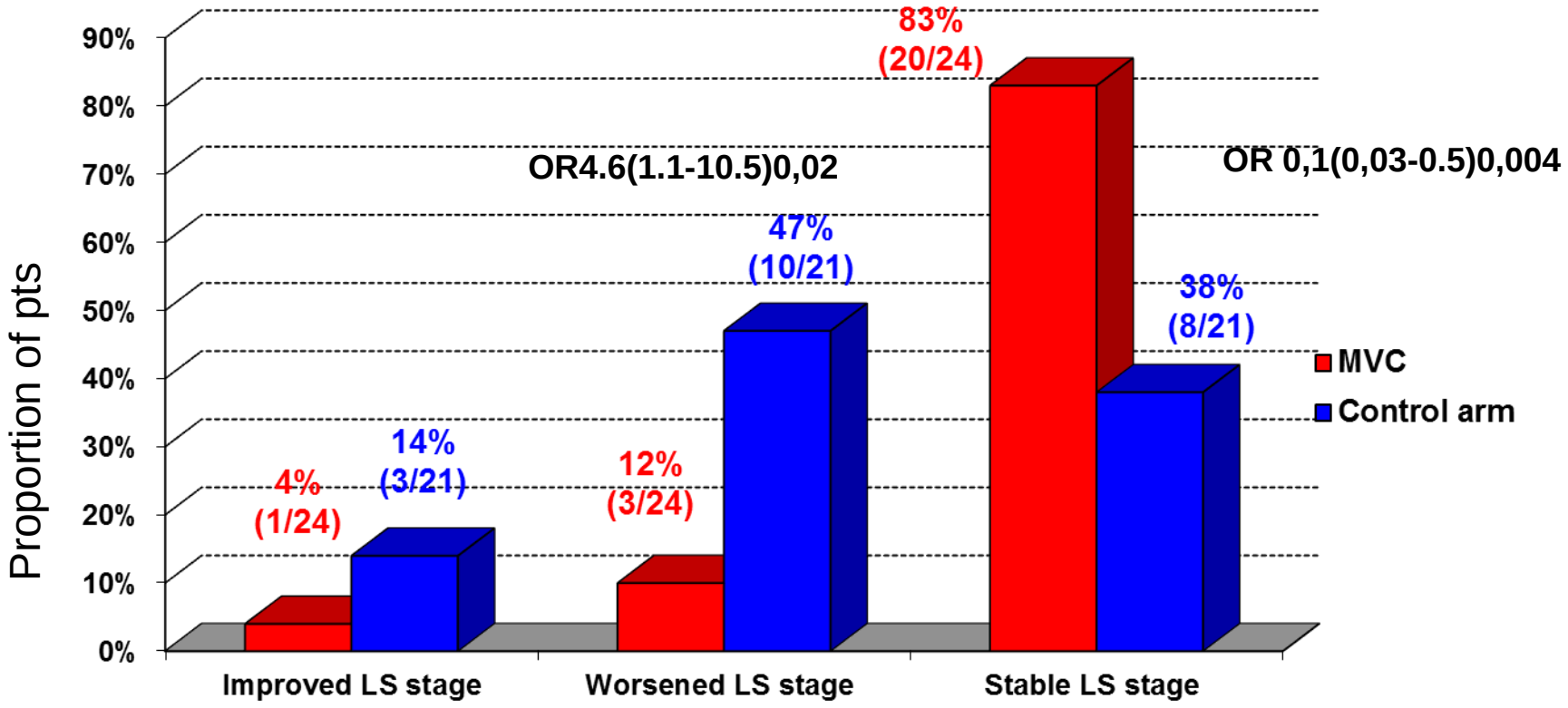
Parameters (median IQR)	Baseline	Week 96	P	Baseline	Week 96	P	P w 96 (Ctr vs MVC
HCV RNA load (log_{10} IU/mL)	5,7(5,2-6)	5,8(5,3-6,2)	NS	5,7(5,2-6)	5,8(5,6-6,2)	NS	0,7
HIV-RNA (cps/ml)	<37	<37	NS	<37	<37	NS	
CD4+T cell count(cell/mm^3)	553(385-908)	641(467-701)	NS	496(420-621)	580(387-646)	NS	0,1
CD8+T cell count(cell/mm^3)	752(628-976)	698(601-862)	NS	711(508-868)	752(565-884)	NS	0,6
AST (IU/l)	46(34-59)	48(34-57)	NS	40(29-60)	51(31-77)	NS	0,5
ALT(IU/l)	67(45-127)	71(49-106)	NS	70(52-96)	81(51-114)	NS	0,3
PLT(10^9/ml)	163(137-189)	162(136-190)	NS	159(127-213)	173(114-222)	NS	0,9
Adverse event		5(23.8%)			8(33,3%)		

Metabolic and inflammation parameter's variation at week 96

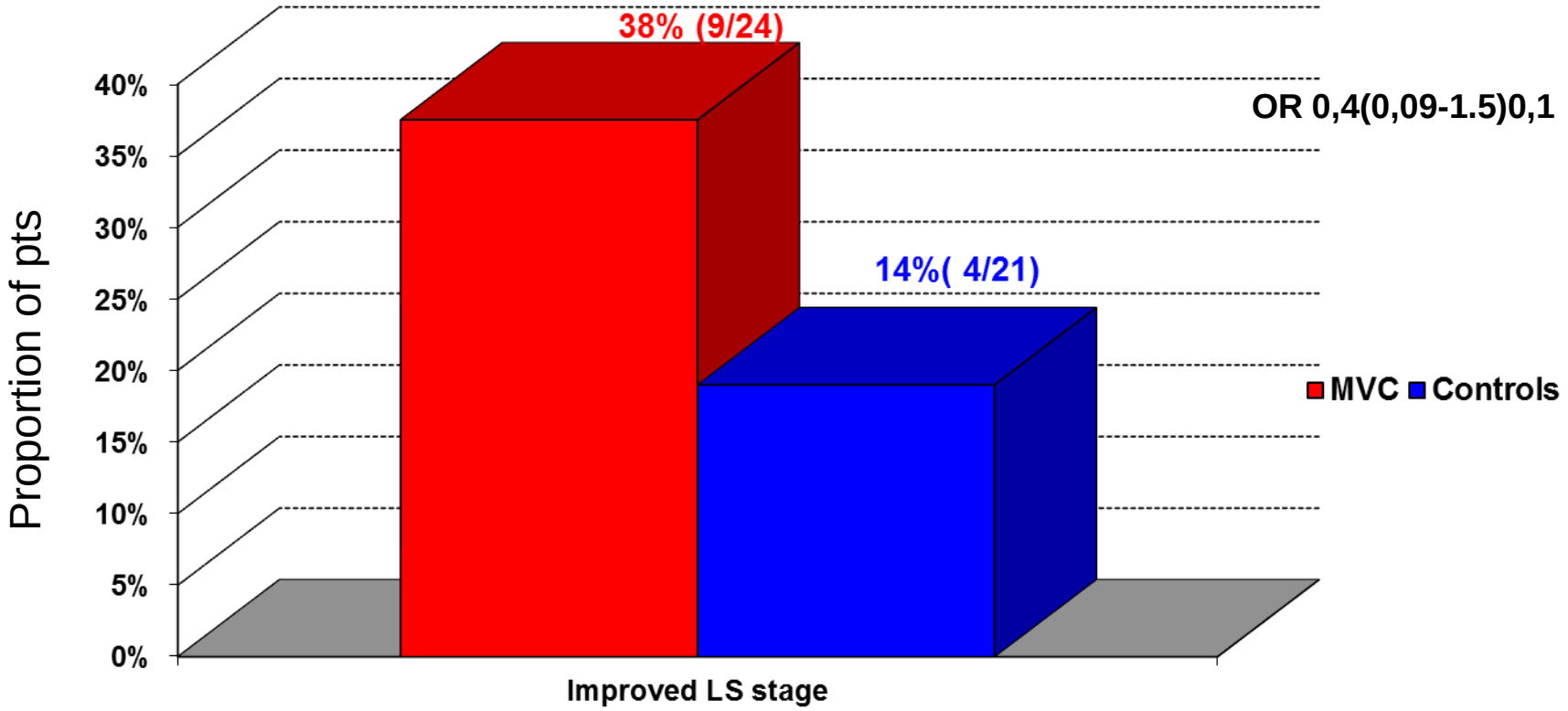
Control n=21 Maraviroc n=24

Parameters (median IQR)	Baseline	Week 96	P	Baseline	Week 96	p	P w 96 (Ctr vs MVC
Col tot (mg/dl)	165(133-193)	159(135-208)	NS	150(131-160)	153(127-180)	NS	0,4
Col LDL (mg/dl)	87(74-113)	92(69-126)	NS	82(67-98)	90(61-122)	NS	0,4
Col HDL (mg/dl)	38(33-47)	39(35-46)	NS	36(33-47)	45(34-53)	NS	0,4
TGD (mg/dl)	141(95-212)	116(88-163)	NS	130(81-155)	104(80-148)	NS	0,1
HOMA score	2,8(1,6-4,1)	2,5(1,5-4,8)	NS	3,8(2,0-6,2)	2,6(1,9-4,3)	NS	0,2
PCR	0,7(0,7-0,7)	0,7(0,7-0,7)	NS	0,7(0,7-0,8)	0,7(0,7-0,7)	NS	0,2
Alfa1antitripsin	158(152-192)	157(134-183)	NS	162(141-176)	156(138-183)	NS	0,8
Fibrinogen	267(237-289)	249(214-294)	NS	271(233-309)	260(236-290)	NS	0,4

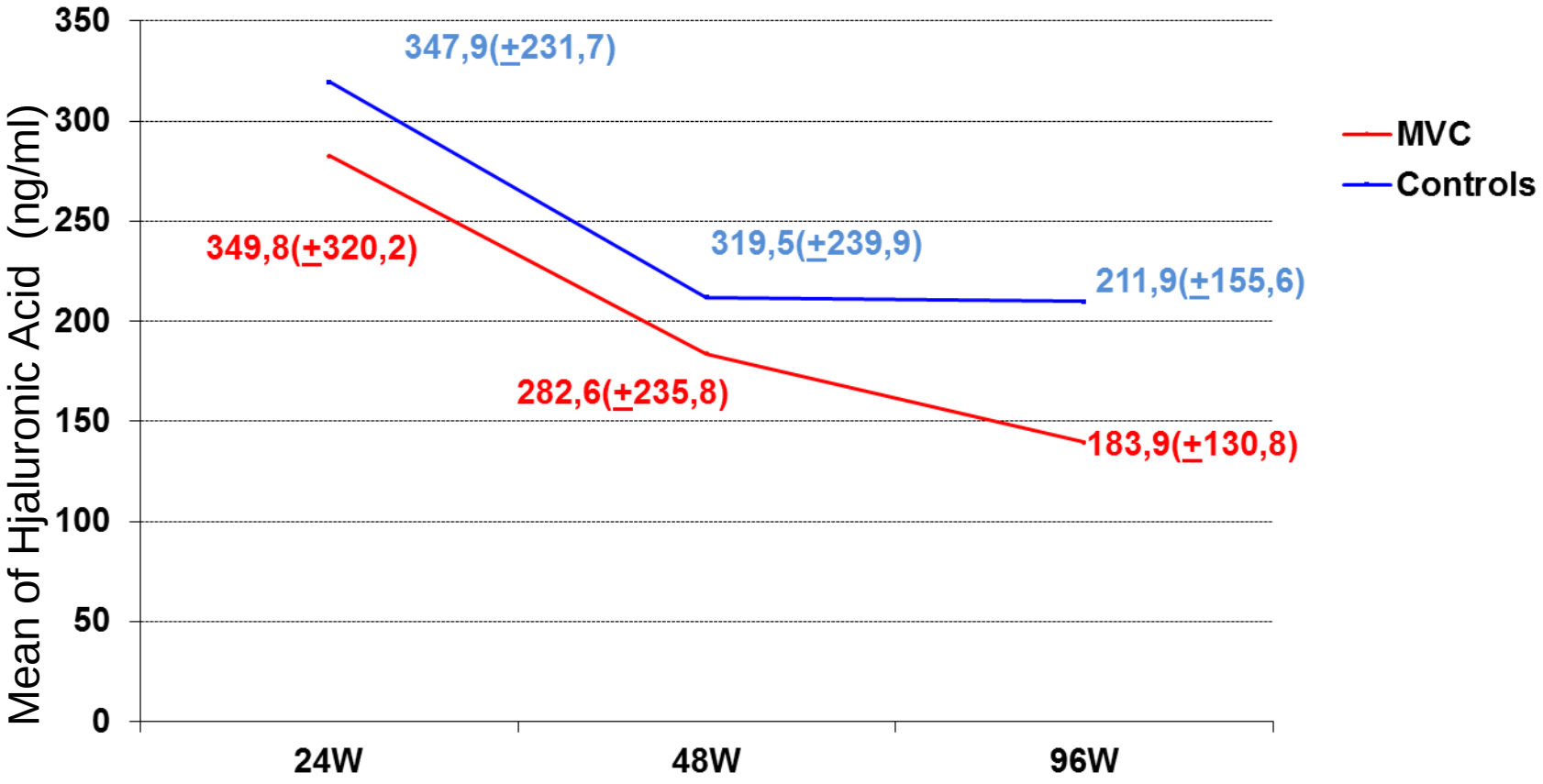
Proportion of patients with Liver Stiffness(LS) stage variation from BL through week 96



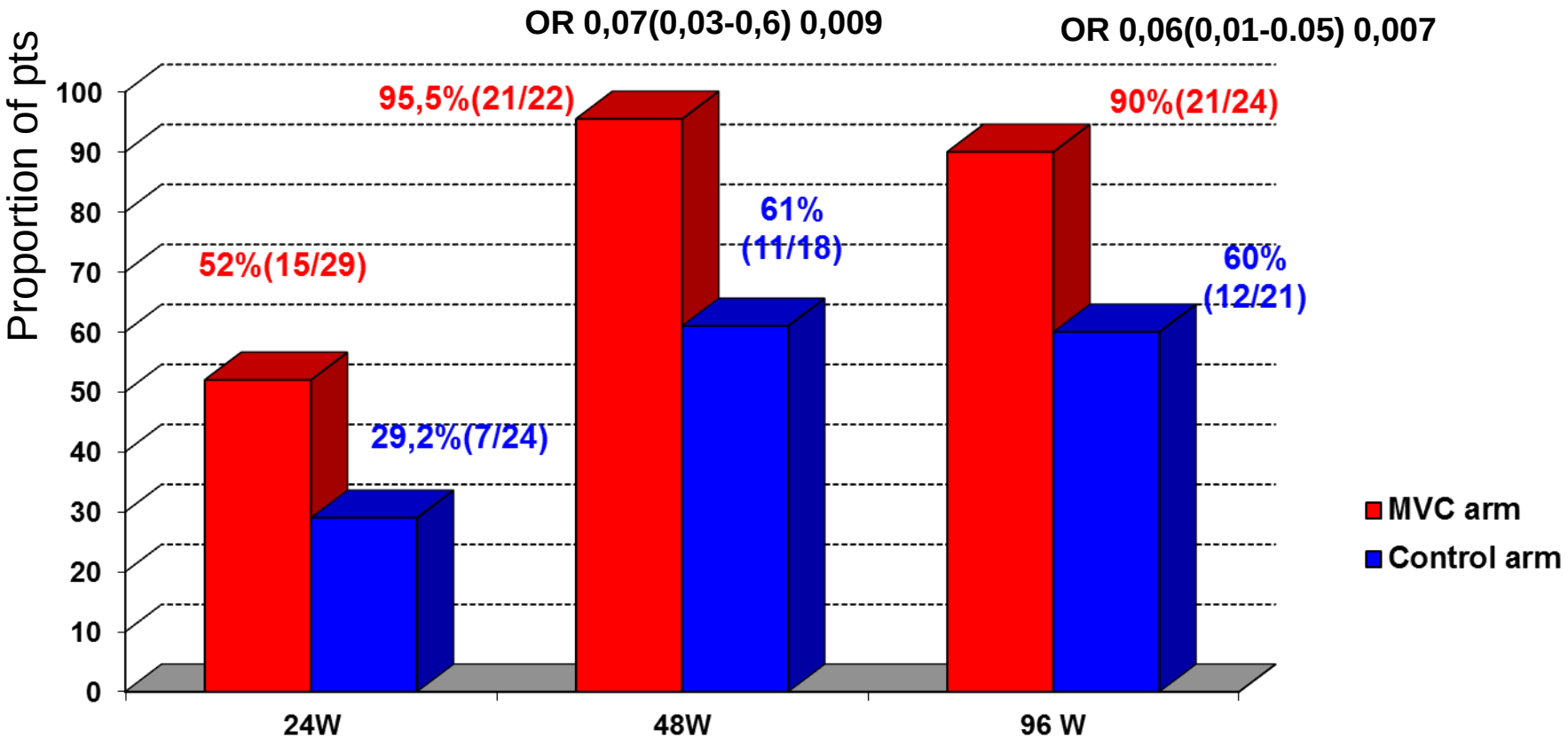
Proportion of patients with Fibrotest improvement from BL through week 96



Hjaluronic acid variation from BL through week 24,48 and 96



Proportion of patients with Hyaluronic acid reduction >50ng/ml from BL to 24 , 48 and 96 week



Multivariate analysis

Variables related with LS stabilty	AOR	IC 95%	p
No MVC use	0,1	0,02-0,7	0,002
BMI >23	0,4	0,07-2,6	0,73
Sex	0,1	0,01-1,6	0,1
Age>40yrs	0,2	0,006-6,1	0,3
HCV-RNA at BL	1,0	(0,3-1,4)	0,4
CD4 nadir	1,0	(0,9-1,6)	0,5

Variables related with Fibrotest improvement	AOR	IC 95%	p
No MVC use	0,1	0,02-0,8	0,03
BMI >23	0,4	0,08-2,6	0,4
Sex	0,2	0,02-3,5	0,3
Age>40yrs	0,5	0,05-4,9	0,5

Variables related with HA improvement	AOR	IC 95%	p
No MVC use	0,06	0,005-0,6	0,01
Advance fibrosis(F4)*	1,4	0,1-11,4	0,7
Sex	0,5	0,03-9,0	0,6
Age>40yrs	0,3	0,03-2,6	0,2

Maraviroc in patients with chronich liver diseases

Several HIV/HCV co-infected patients shall remain non eligible to receiving peginterferon/ribavirin and may not have or even anti HCV treatment option in the next future

Many patient will have a cirrhosis when IFN free regimens will be achievable and, also after HCV eradication, will remain at risk for HCC development (Berenguer ,2013)

A liver friendly antiretroviral therapy could be the only barrier, to the rapidly progressive liver disease

Maraviroc have a large evidence of good efficacy and safety in HIV/HCV co-infected patients and may represent a reasonable choice in this fragile population