

IMMUNOATTIVAZIONE ED INFIAMMAZIONE IN HIV E NEL COINFETTO HIV/HCV

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Today's agenda

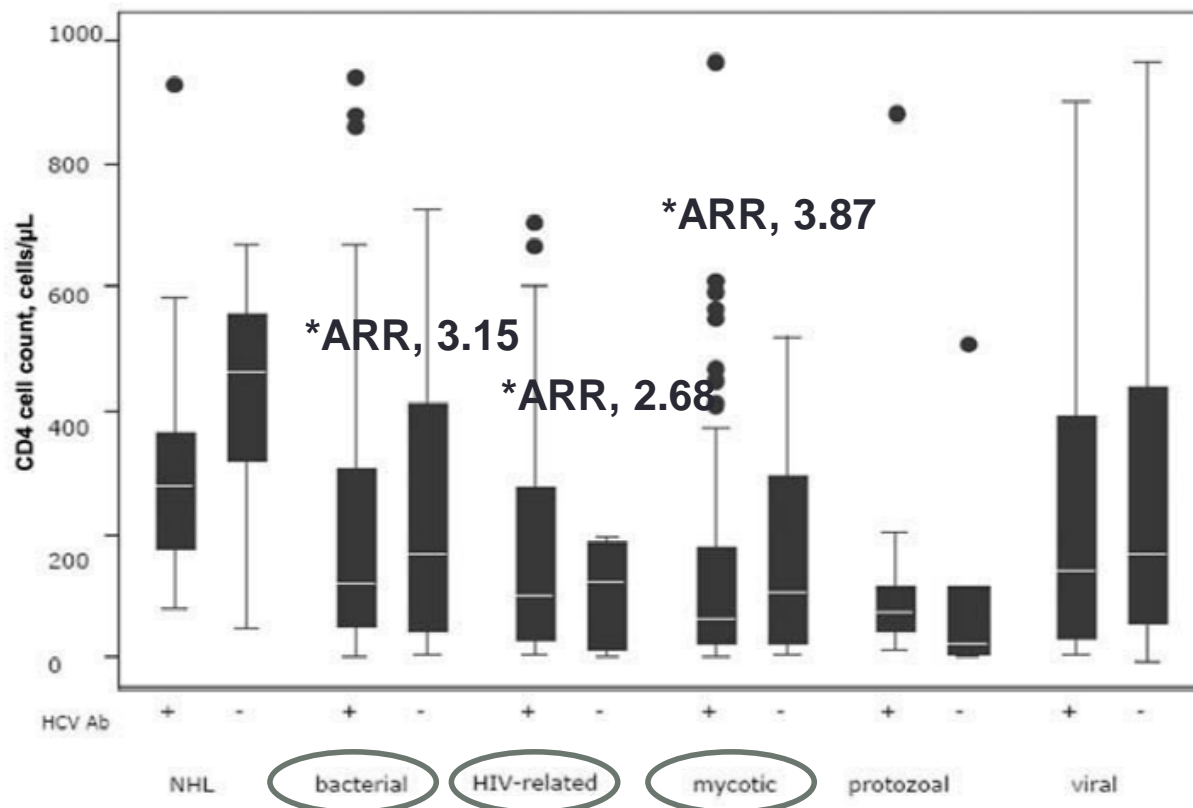
- **HCV & HIV : two challenges for the immune system**
- **HCV as driver of excess immune activation in treated HIV co-infection – biological pathways**
- **HCV as obstacle to cART immune reconstitution**

**HCV co-infection is
associated with
increased risk of HIV
disease progression**

Risk of Developing Specific AIDS-Defining Illnesses in Patients Coinfected with HIV and Hepatitis C Virus With or Without Liver Cirrhosis

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Clinical Infectious Diseases 2009;49:612–22

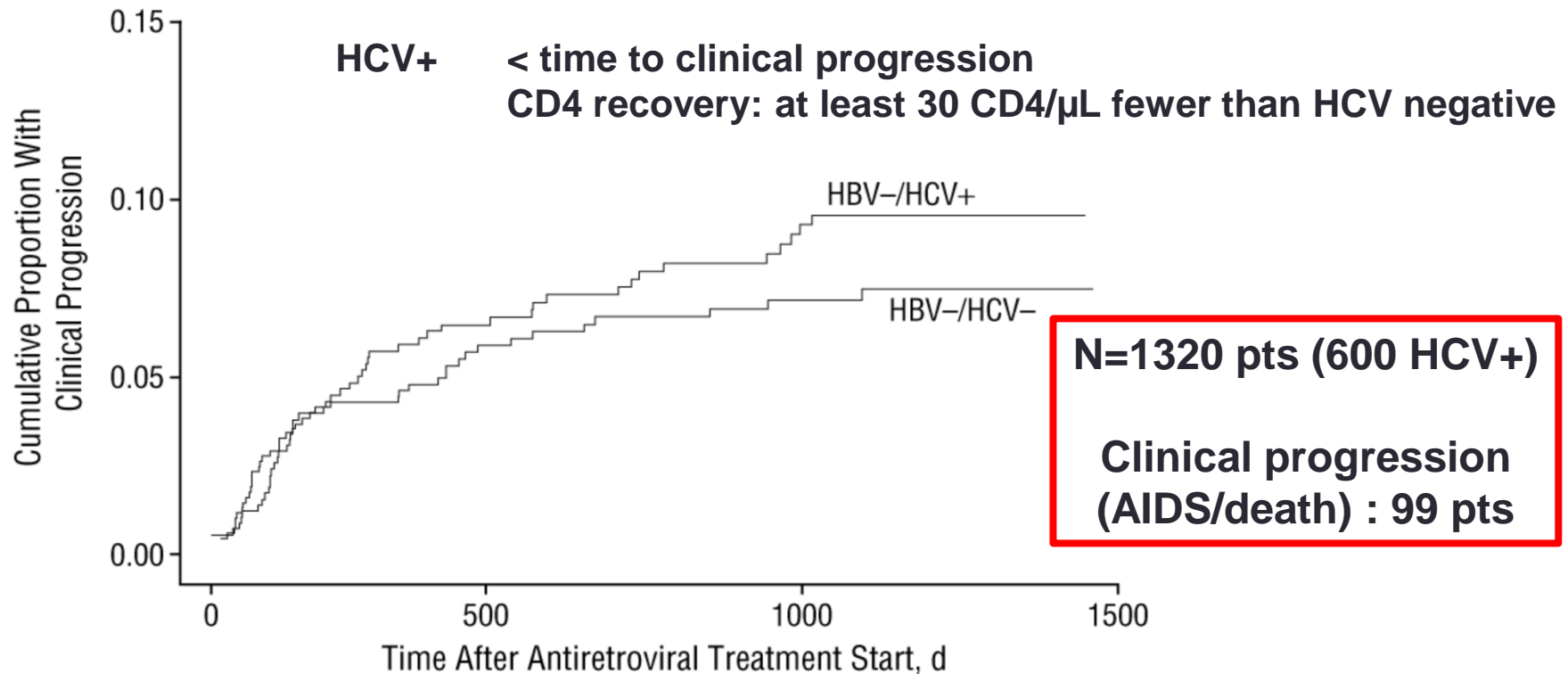


HCV coinfection was associated with increased risk of developing an ADI (adjusted relative rate [ARR], 2.61; 95% confidence interval [CI], 1.88–3.61)

Figure 1. CD4 cell counts at the time of AIDS diagnosis, according to hepatitis C virus antibody (HCV Ab) test result and type of AIDS-defining illness. HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma; +, positive for HCV Ab; -, negative for HCV Ab.

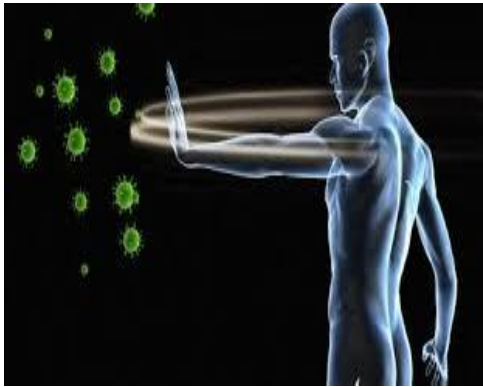
What the role of HCV co-infection on immune reconstitution and clinical progression upon cART?

Coinfection with hepatitis viruses and outcome of the initial ARV regimens in previously naive HIV infected subjects pts

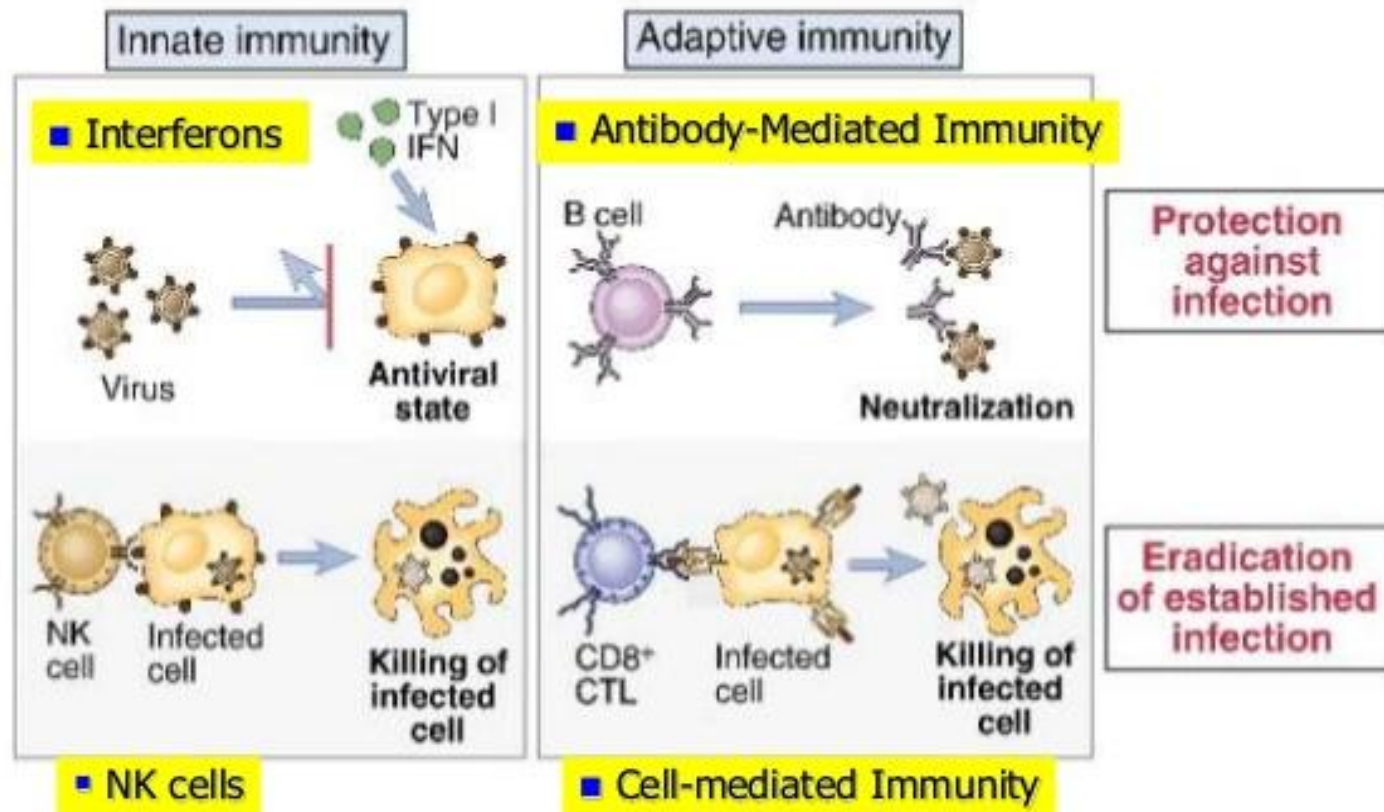


Cumulative proportion of human immunodeficiency virus-1-infected patients showing clinical progression after beginning potent antiretroviral therapy, by hepatitis virus serostatus. HBV-/HCV+ indicates hepatitis B virus-negative hepatitis C virus-positive; HBV-/HCV-, HBV-negative HCV-negative. The HBV-positive HCV-negative group and the HBV-positive HCV-positive group are not illustrated because of the limited number of clinical events (6 in each group).

**HCV as driver of excess
of morbidity/mortality in
treated HIV: via which
biologic mechanism(s)?**



HIV & HCV: double infectious strain to the immune system



HIV & HCV: double pro-inflammatory challenge

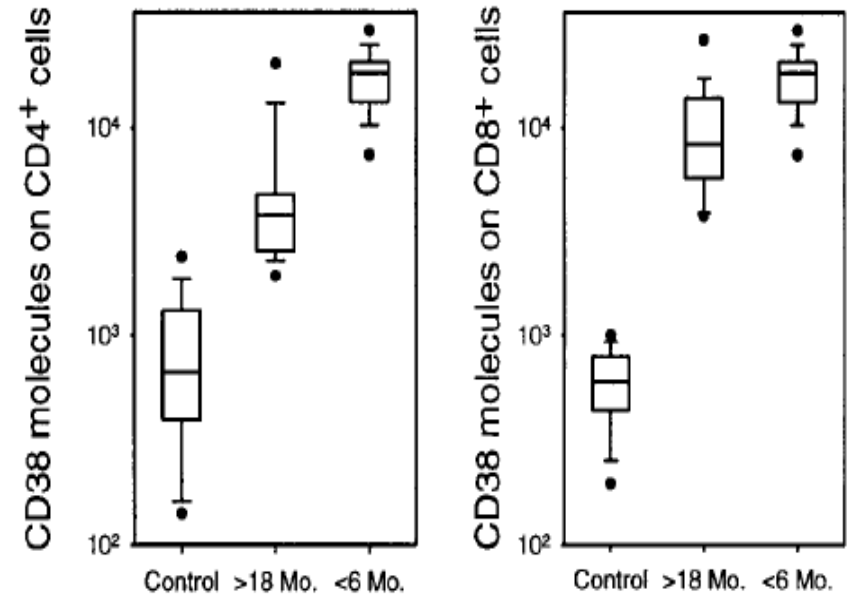
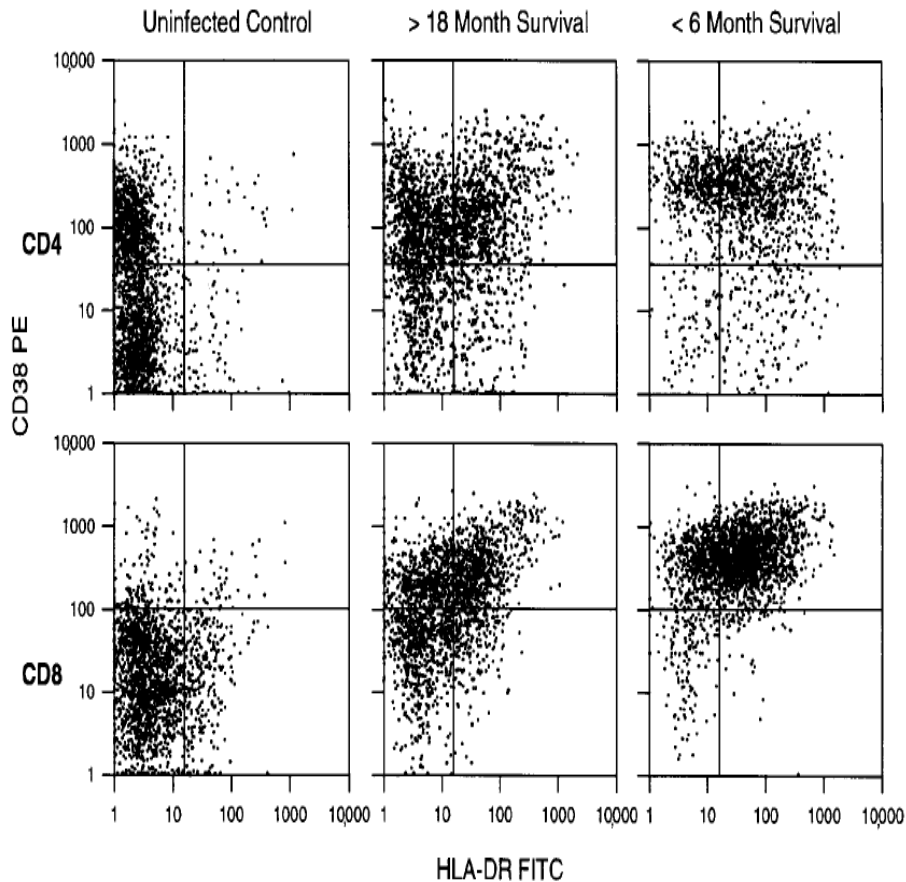
HIV as an inflammatory disease

- Acute HIV associated with rapid/intense release of pro-inflammatory cytokines (IL-6, IP-10, TNF- α) and dramatic increase of activated innate immune cells T-, B-cells
- Chronic HIV: T-cell activation steady state

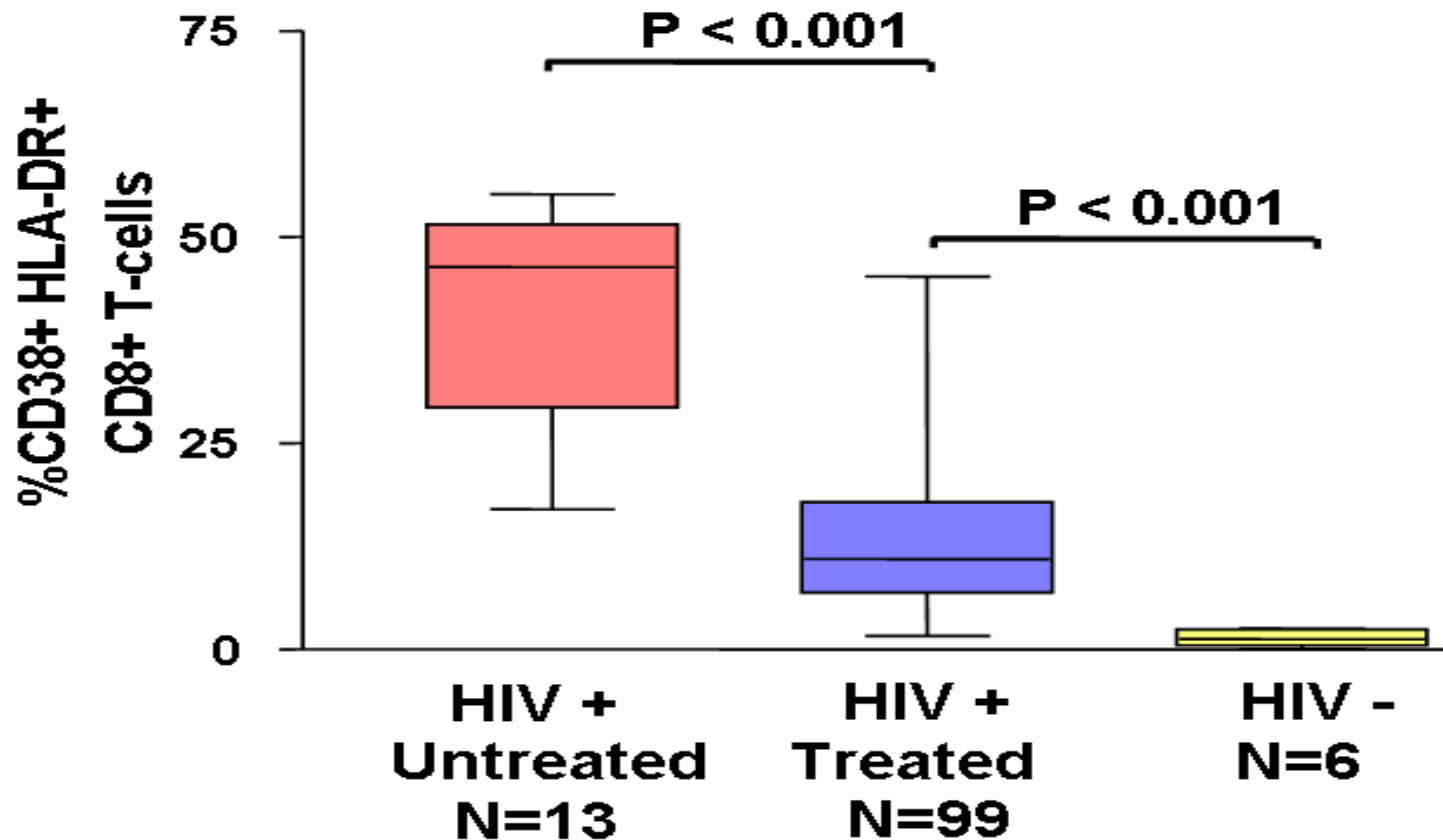
CD8 T-cell activation predicts CD4+ T-cell count over time

Parameter	Estimate	Standard error	<i>P</i>
Univariate model			
Plasma HIV RNA level, log ₁₀	-0.032	0.007	< .001
CD8 ⁺ T-cell activation, log ₁₀	-0.049	0.014	< .001
CD4 ⁺ T-cell activation, log ₁₀	-0.039	0.017	.021
Multivariate model			
Intercept	2.921	0.042	< .001
Plasma HIV RNA level, log ₁₀	-0.026	0.009	.005
CD8 ⁺ T-cell activation, log ₁₀	-0.033	0.015	.027
CD4 ⁺ T-cell activation, log ₁₀	-0.013	0.019	.474

Shorter survival is associated with T-lymphocyte activation



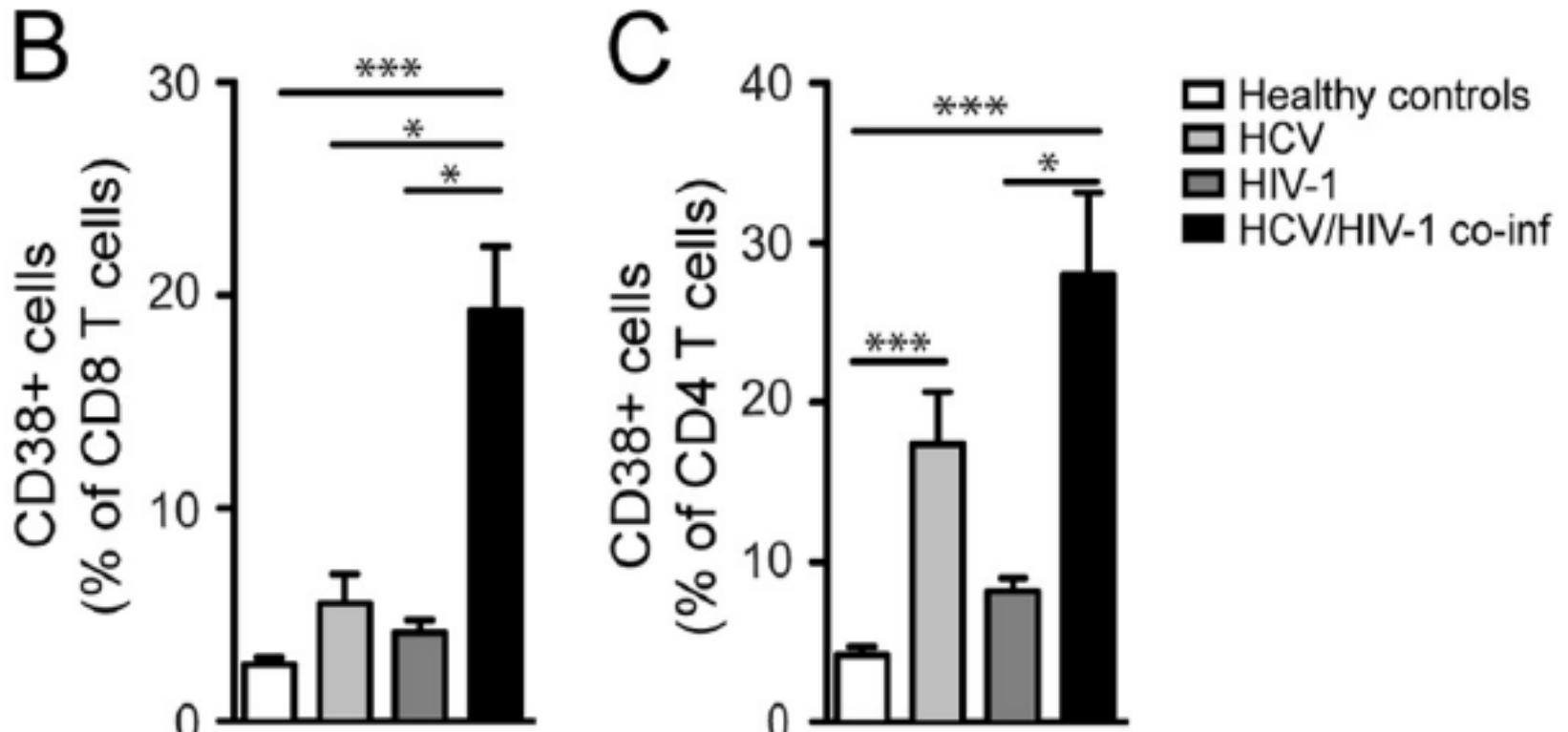
CD8+ T cell activation do not fully normalize during effective cART



HIV & HCV: double pro-inflammatory challenge

HCV co-infection as driver of immune activation in cART-treated HIV?

34 patients: 14 HCV+/HIV+ cART-treated; 11 HCV+; 9 HIV+ treated



HCV co-infection is associated to higher T-lymphocyte activation on cART

Table 3. Factors associated with changes in activated (CD38⁺HLA-DR⁺) T cell counts in 99 human immunodeficiency virus (HIV)-infected patients with sustained plasma HIV RNA levels \leq 1000 copies/mL.

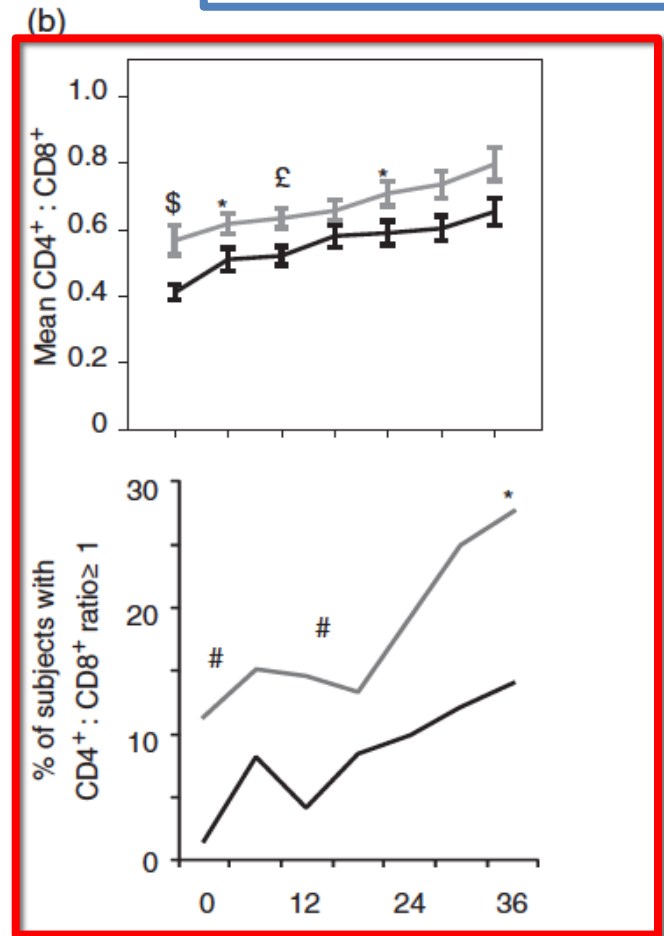
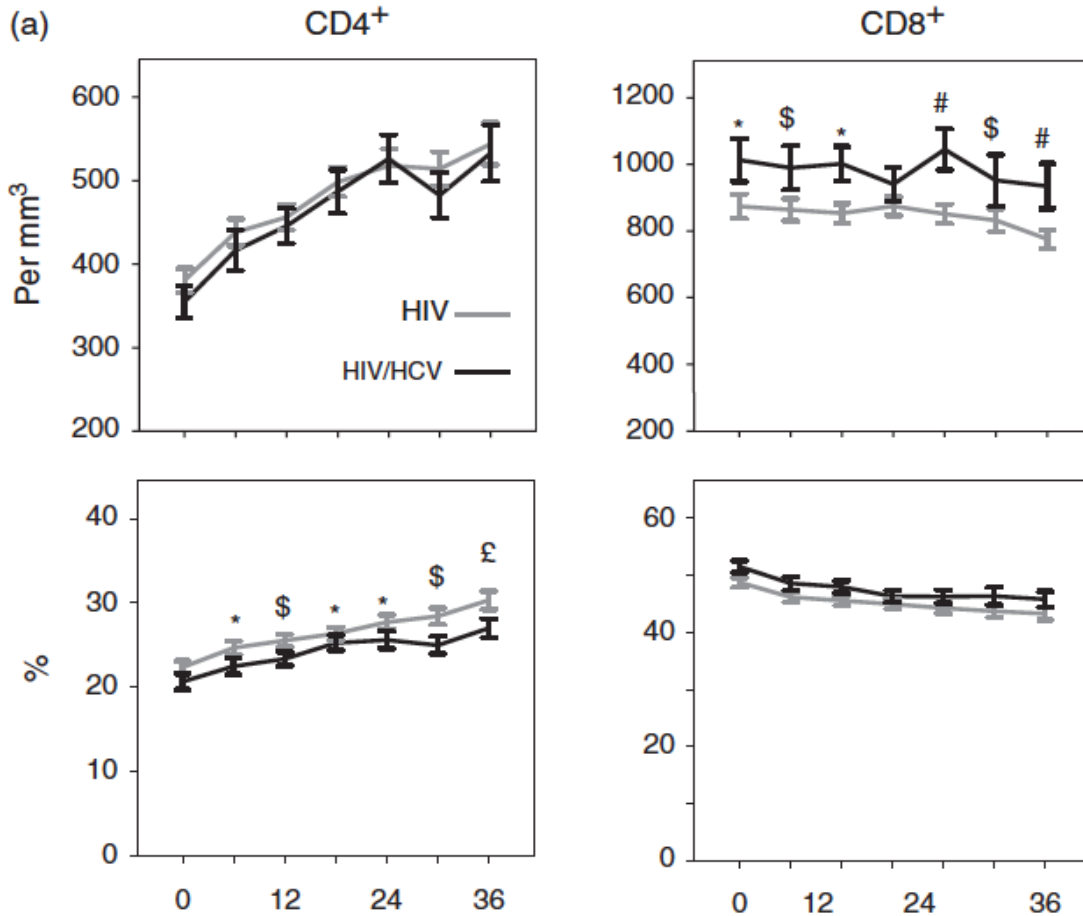
Factor	CD4 ⁺ T cells				CD8 ⁺ T cells			
	Unadjusted analysis		Adjusted analysis ^a		Unadjusted analysis		Adjusted analysis ^b	
	Mean change (95% CI) in activated T cells, %	P	Mean change (95% CI) in activated T cells, %	P	Mean change (95% CI) in activated T cells, %	P	Mean change (95% CI) in activated T cells, %	P
Each 1-month increase in duration of viral suppression ^c	-0.04 (-0.09 to 0.004)	.08	-0.06 (-0.1 to -0.005)	.03	-0.1 (-0.2 to -0.004)	.04	-0.1 (-0.2 to -0.01)	.04
Hepatitis C virus antibody status								
Negative	Reference	—	Reference	—	Reference	—	Reference	—
Positive	+2 (0.3-4)	.02	+2 (0.2-4)	.03	+6 (2-10)	.003	+5 (2-9)	.006
Frequency of low-level viremia in year before immunophenotyping^d								
None	Reference	—	Reference	—	Reference	—	Reference	—
1%-50%	+0.1 (-2 to 2)	.96	-0.5 (-3 to 2)	.69	-1 (-6 to 4)	.74	-4 (-10 to 2)	.18
>50%	+3 (1-4)	.005	+2 (-0.2 to 4)	.07	+7 (3-11)	.001	+5 (0.5-10)	.03
Each increase of 100 cells/mm ³ in nadir CD4 ⁺ T cell counts	-0.5 (-1.0 to 0.1)	.11	-1 (-2 to -0.3)	.003	-0.3 (-2 to 1)	.65	-1.5 (-3.0 to -0.03)	.05

HIV & HCV: double pro-inflammatory challenge

How does this affect immune reconstitution upon cART?

Hampered T-cell dynamics in HIV/HCV co-infected patients

356 HIV+ cART-treated : 130 HCV co-infected



Higher CD4/CD8 ratio on virologically-suppressive HAART is associated with lower T-cell activation

	CD4+ T cell count Rho (P value)	CD8+ T cell count Rho (P value)	CD4/CD8 ratio Rho (P value)
ALL SUBJECTS (n=95)			
%CD4+ T cells			
<i>Maturation subsets</i>			
Naïve	0.395 (<0.001)	-0.027 (0.798)	0.329 (0.001)
T _{CM}	-0.047 (0.656)	-0.069 (0.511)	-0.019 (0.857)
T _{TM}	-0.194 (0.065)	0.038 (0.720)	-0.179 (0.090)
T _{EM}	-0.366 (0.004)	-0.092 (0.931)	-0.219 (0.036)
T _{EMRA}	-0.051 (0.633)	-0.077(0.468)	0.021 (0.837)
<i>Activation phenotypes</i>			
HLADR+CD38+	-0.577 (<0.001)	0.008 (0.937)	-0.410 (<0.001)
CD28-CD57+	-0.209 (0.048)	-0.004 (0.968)	-0.149 (0.159)
PD1+	-0.565 (<0.001)	-0.037 (0.731)	-0.375 (<0.001)
%CD8+ T cells			
<i>Maturation subsets</i>			
Naïve	0.324 (0.002)	-0.252 (0.016)	0.437 (<0.001)
T _{CM}	0.011 (0.918)	-0.159 (0.131)	0.123 (0.245)
T _{TM}	0.037 (0.727)	0.239 (0.023)	0.203 (0.053)
T _{EM}	-0.167 (0.106)	0.319 (0.002)	-0.379 (<0.001)
T _{EMRA}	-0.185 (0.079)	0.167 (0.112)	-0.297 (0.004)
<i>Activation Phenotypes</i>			
HLADR+CD38+	-0.301 (0.003)	-0.159 (0.133)	-0.324 (0.002)

CD4/CD8 ratio predicts mortality

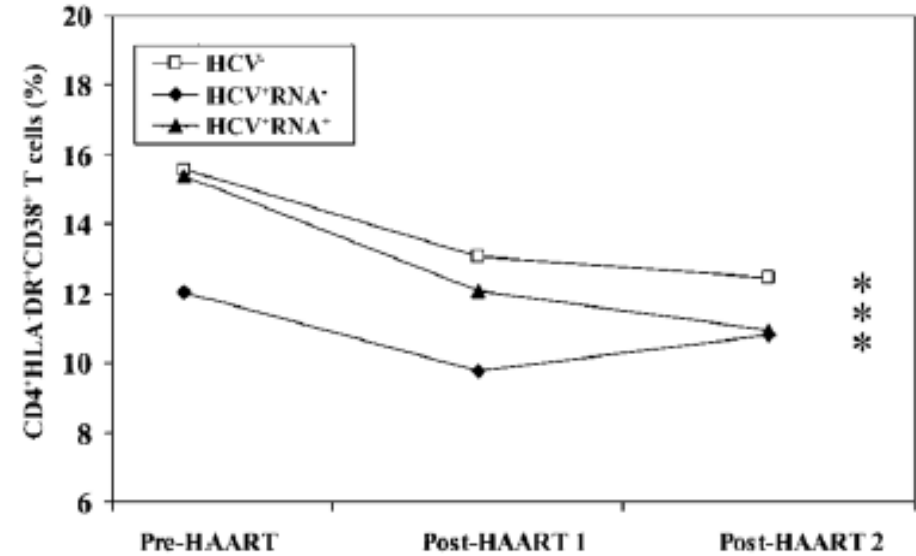
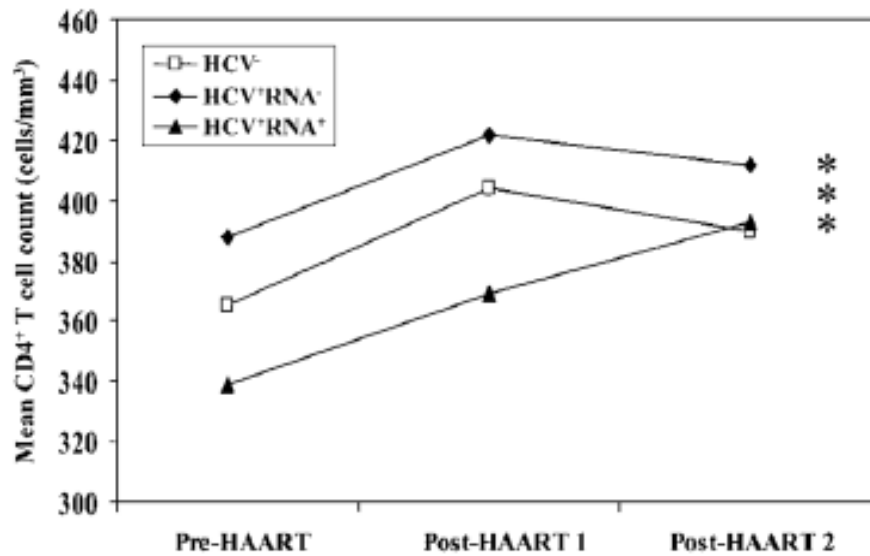
	Beta	Std. error	P value
Madrid cohort (N = 66) (all subjects CD4\geq500 cells/mm³)			
CD4+ T cells			
Unadjusted	-1.86	2.85	0.514
Adjusted by ART duration	-0.66	3.76	0.859
CD8+ T cells			
Unadjusted	2.80	1.12	0.013
Adjusted by ART duration	2.29	1.16	0.048
CD4/CD8 ratio			
Unadjusted	-6.23	2.48	0.012
Adjusted by ART duration	-5.08	2.53	0.045
SOCA cohort (N = 192)			
CD4+ T cells			
All subjects	-1.52	0.58	0.009
Subjects with CD4 \geq 500 cells/mm ³ *	-4.09	6.43	0.525
CD8+ T cells			
All subjects*	0.28	0.33	0.392
Subjects with CD4 \geq 500 cells/mm ³ *	2.37	2.05	0.246
CD4/CD8 ratio			
All subjects*	-1.38	0.55	0.012
Subjects with CD4 \geq 500 cells/mm ³ *	-5.04	3.88	0.194

**Chronic inflammation is
a much more important
determinant of
mortality in treated HIV**

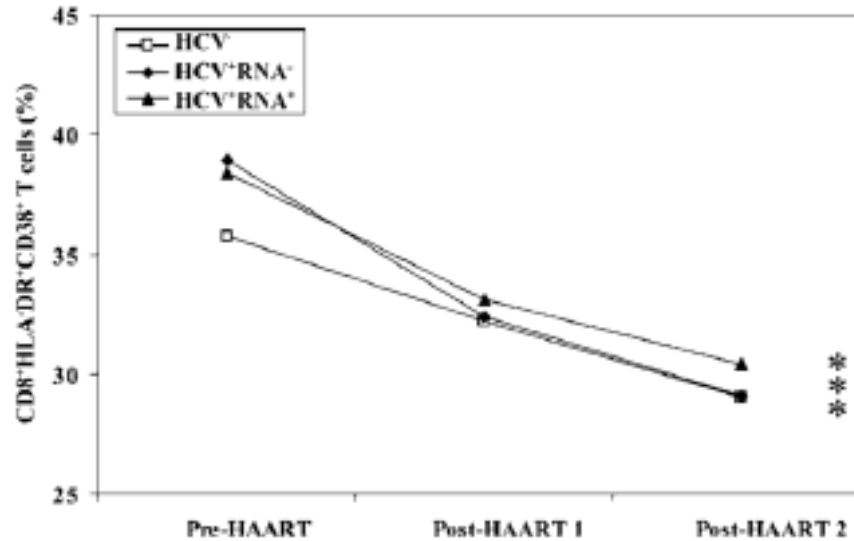
Kuller L PLOS Medicine 2008; also Hunt et al. AIDS 2011; Lok et al, AIDS 2013; Hunt et al. JID 2014; Tenorio et al JID 2014;

**HCV as (one of the)
driver(s) of excess of
morbidity/mortality in
treated HIV via excess
immune activation and
immune exhaustion**

HIV/HCV co-infected women recover CD4+ count and normalize T-cell activation upon cART



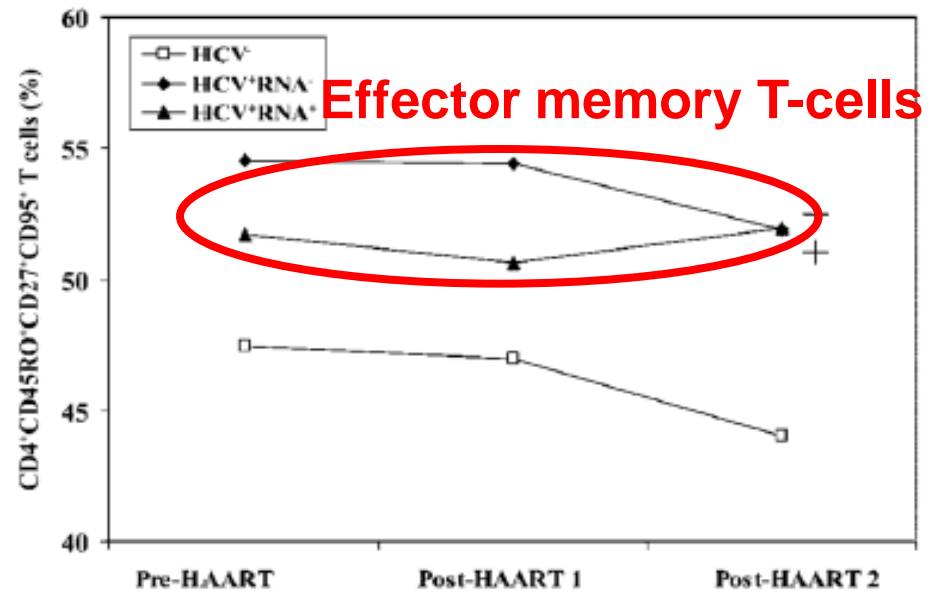
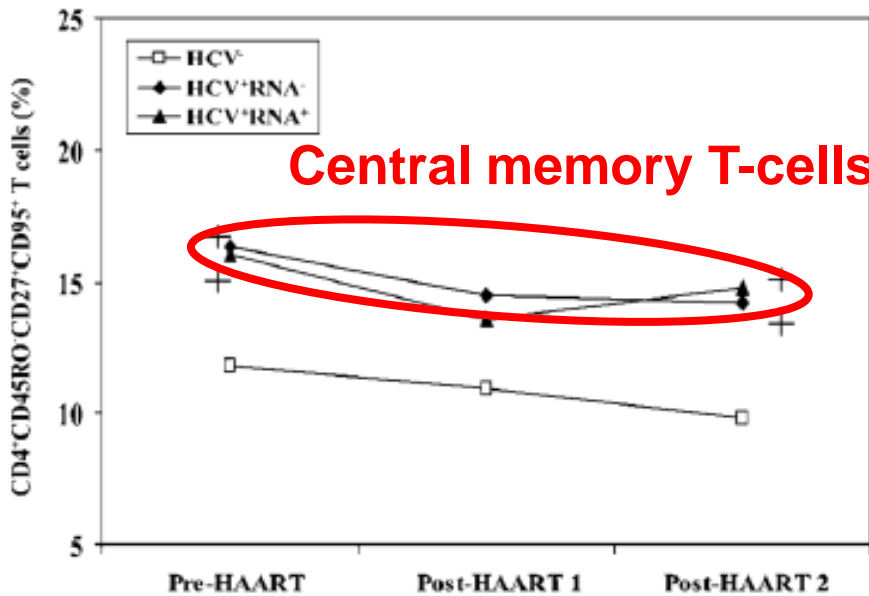
294 HIV-infected women- WIHS Study



T-cell activation

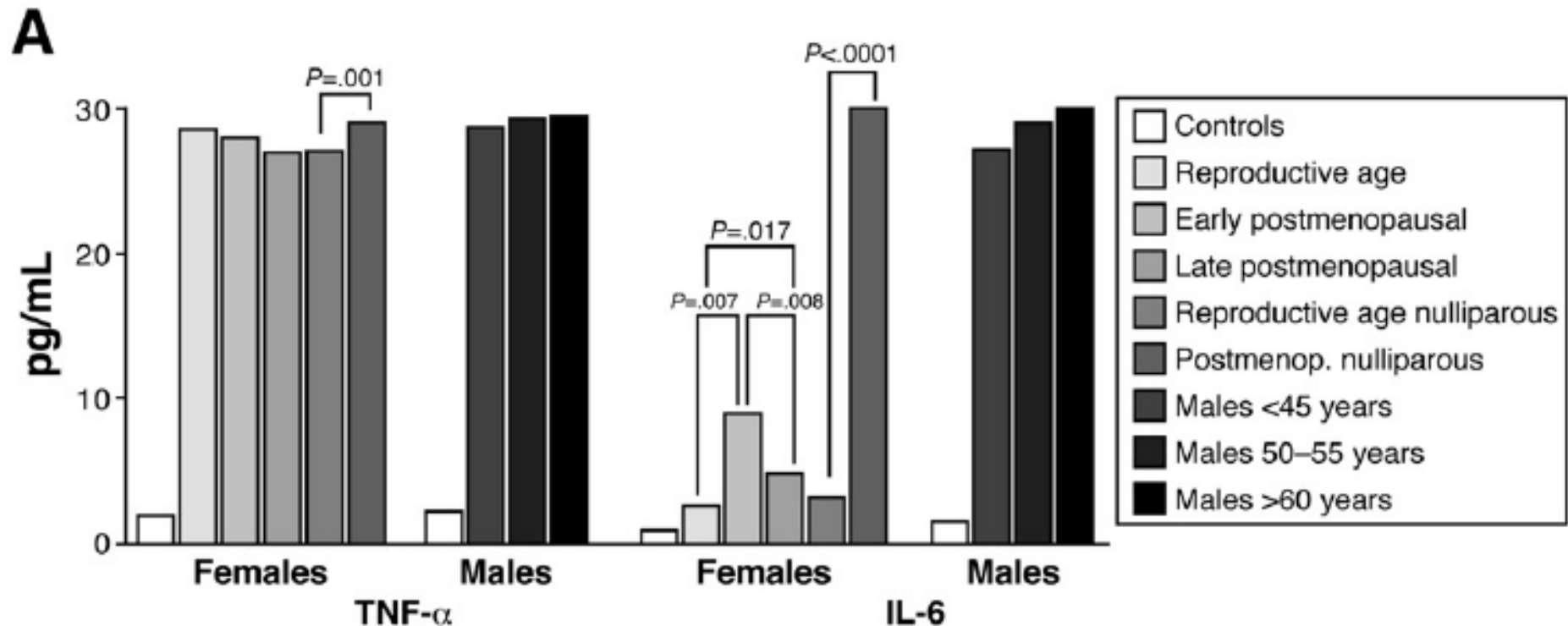
HIV/HCV co-infected women show higher central- and effector-memory T-cells

294 HIV-infected women- WIHS Study



**Gender-related
protection versus HCV-
driven impairment of
cART immune
reconstitution?**

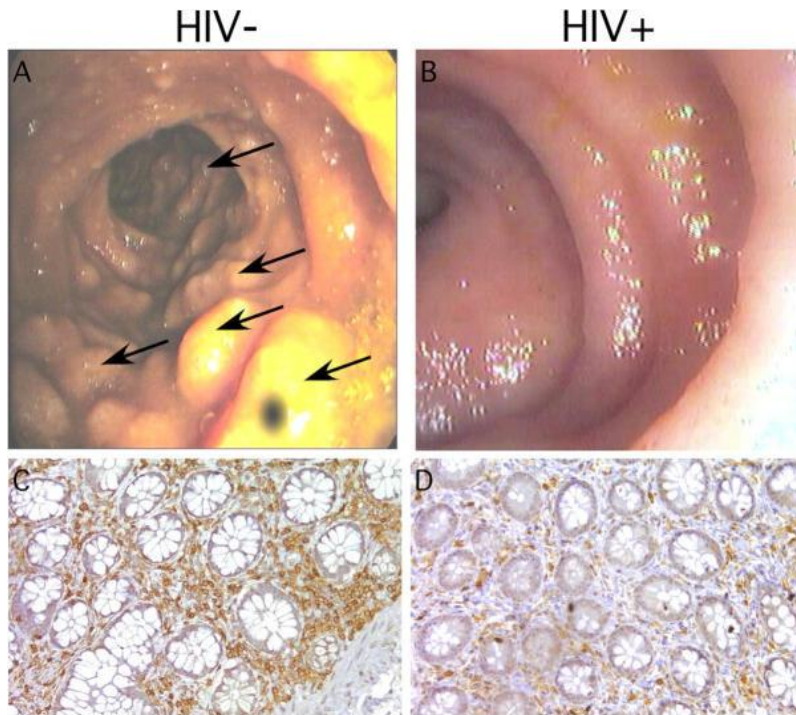
Pro-inflammatory *milieu* in HCV+ patients according to sex and menopause



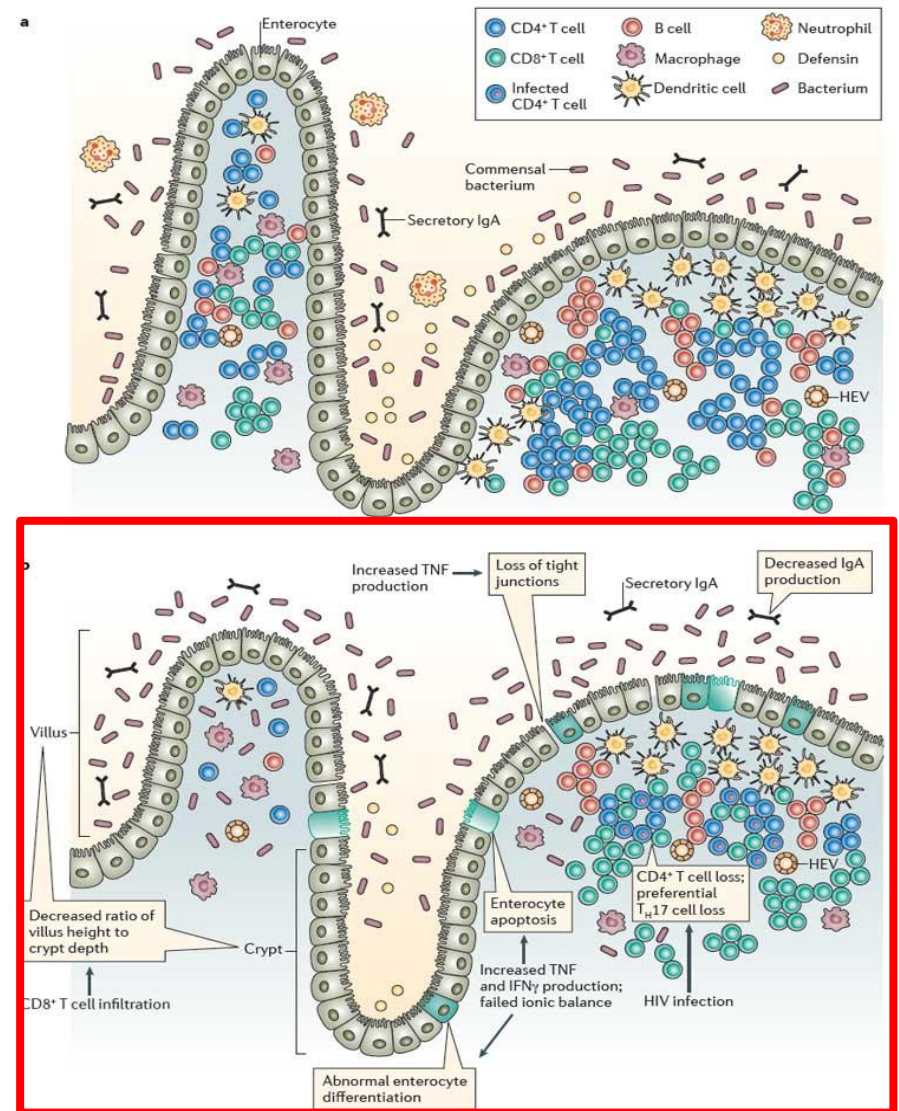
Only in menopausal women baseline IL-6 correlated with higher necroinflammation (OR 3.571; 95%CI 1.494-8.536, $p=.004$)

**HCV as driver of excess
of immune
activation/inflammation
in treated HIV: via which
biologic mechanism(s)?**

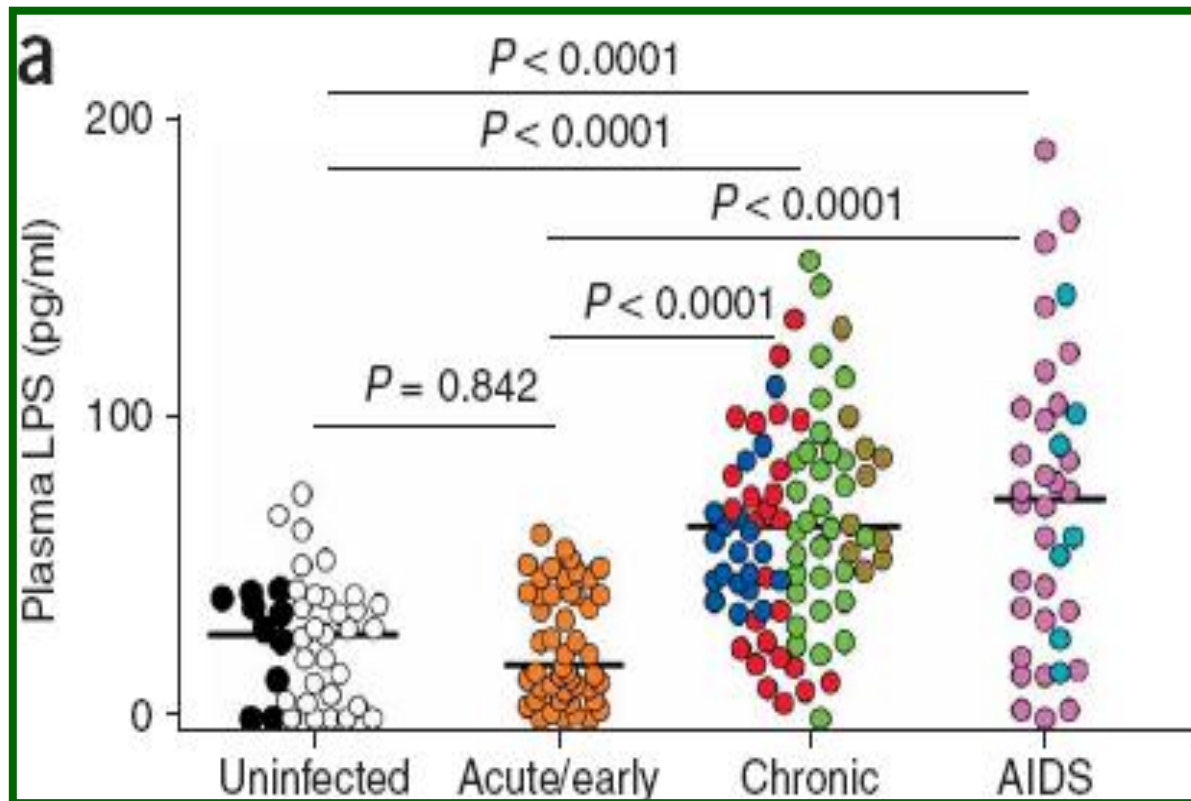
The GI tract as a site of HIV pathogenesis



Brenchley et al. Nat Med 2006

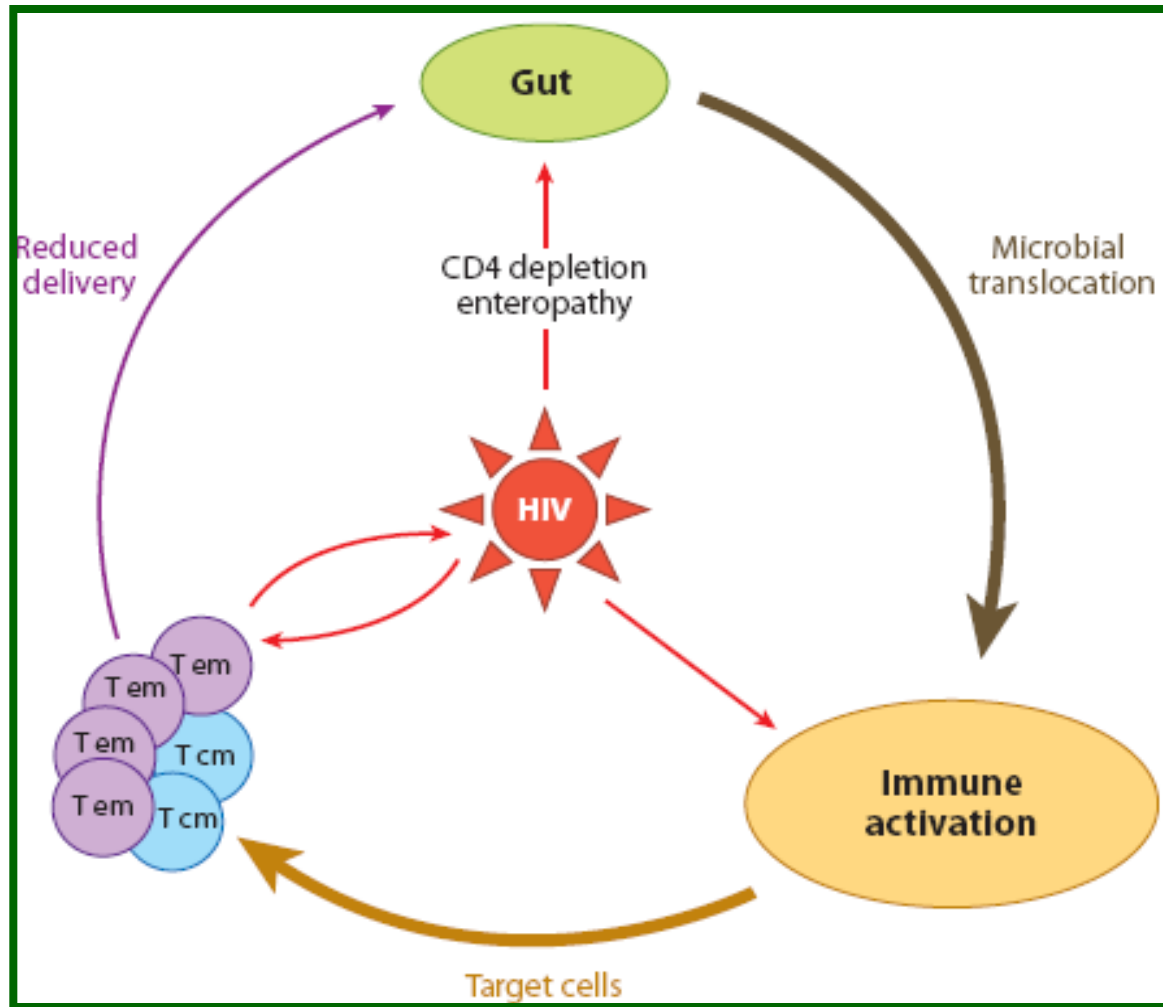


Microbial translocation in HIV

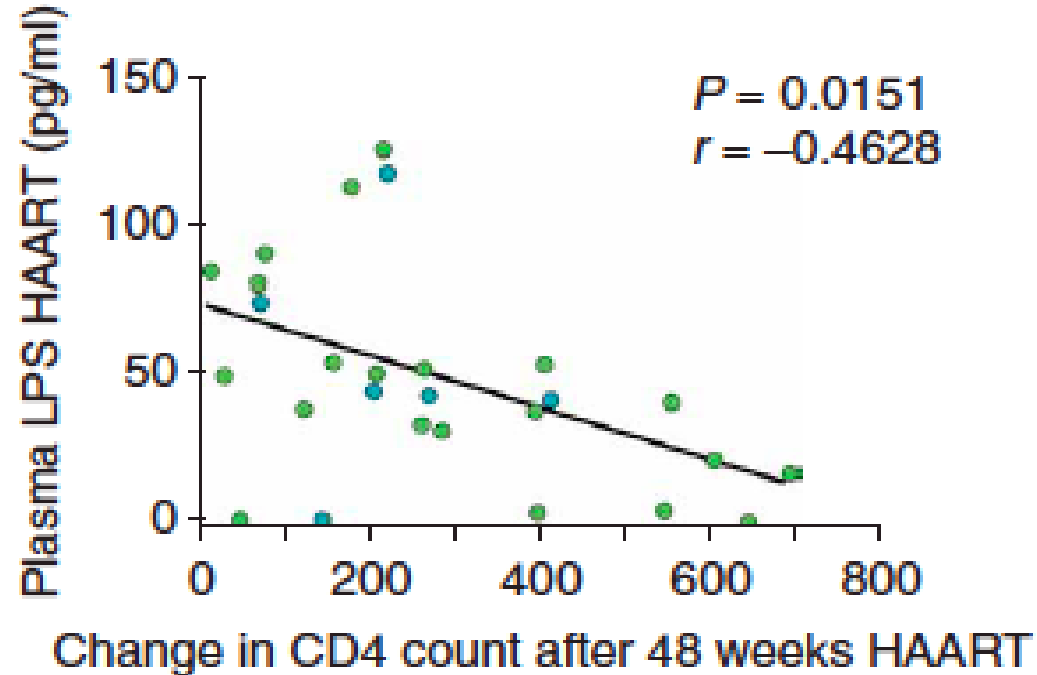
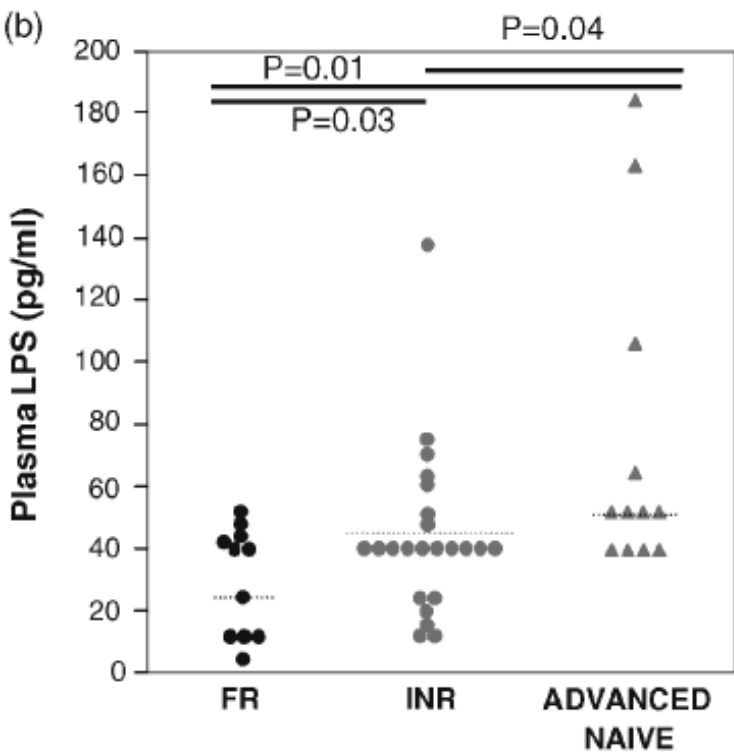


Brenchley et al. Nat Med 2006
also: Jiang et al. JID 2009

HIV, gut mucosa & immune activation



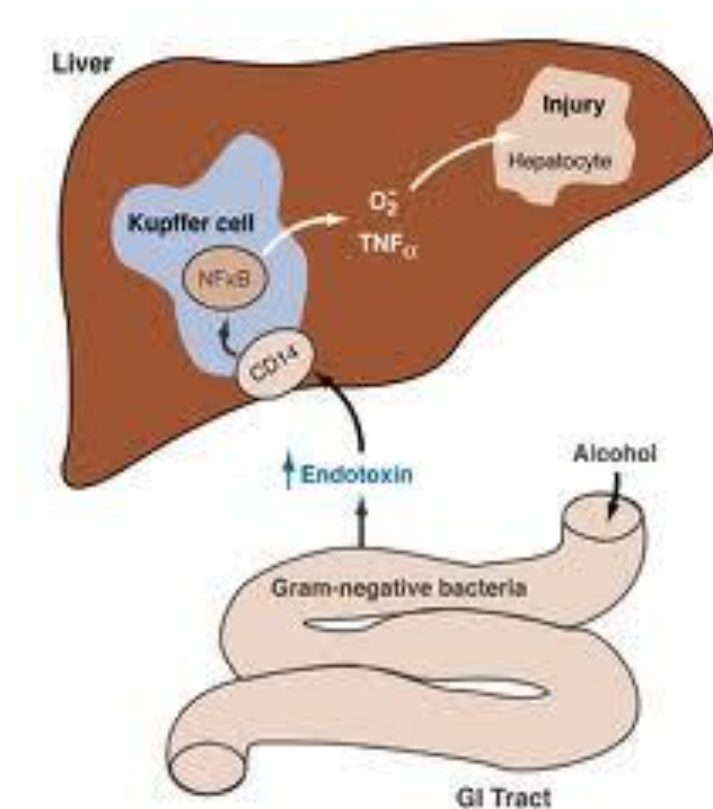
Microbial translocation hampers CD4+ T-cell recovery upon cART



**Microbial
translocation in
viral hepatitis?**

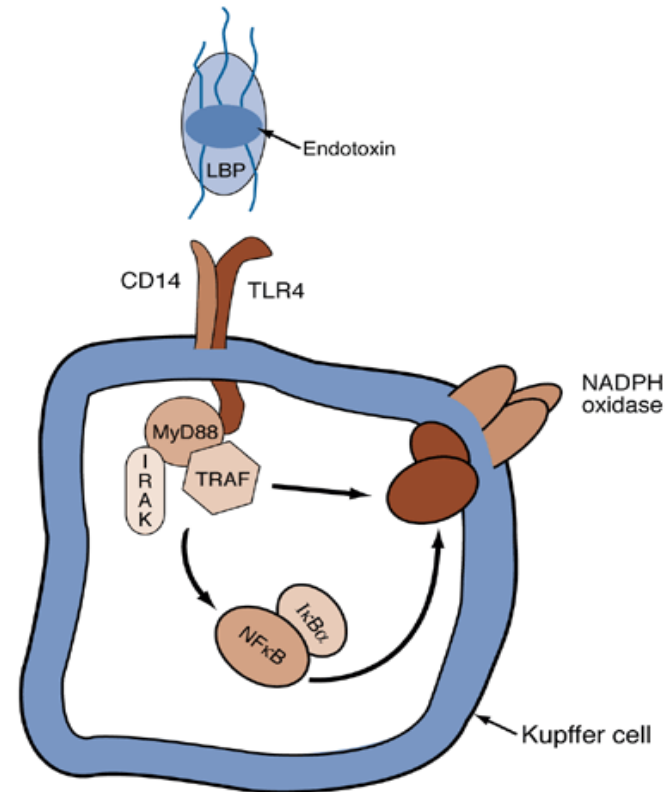
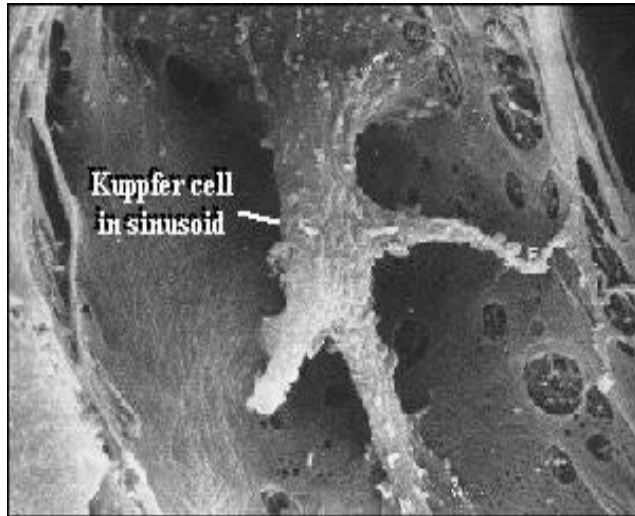
Microbial translocation is increased in liver disease

- Alcohol-induced liver disease
- Graft versus host disease
- Primary biliary cirrhosis



Thurman RG. Am J Physiol Gastrointest Liver Physiol 1998;
Paik YH. Hepatology 2003; Hill GR. Blood 1997; Feld JJ. Dig Dis Sci 2006

LPS and Kupffer cell activation



Up-regulation of pro-inflammatory, pro-fibrogenic cytokines (IL-6, TNF- α , IL-1, IL-12)

LPS independently predicts liver disease progression

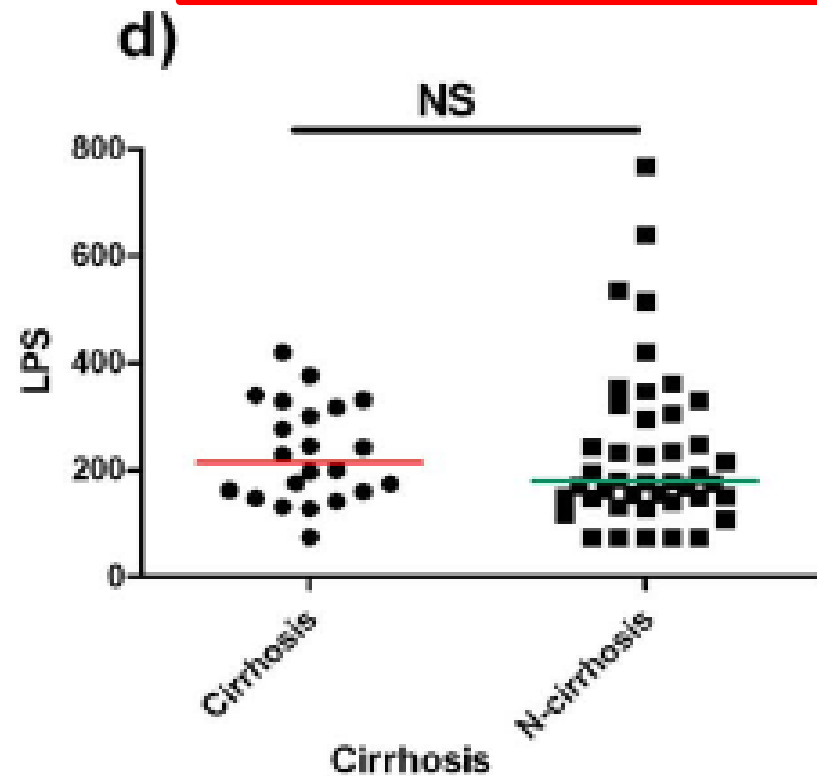
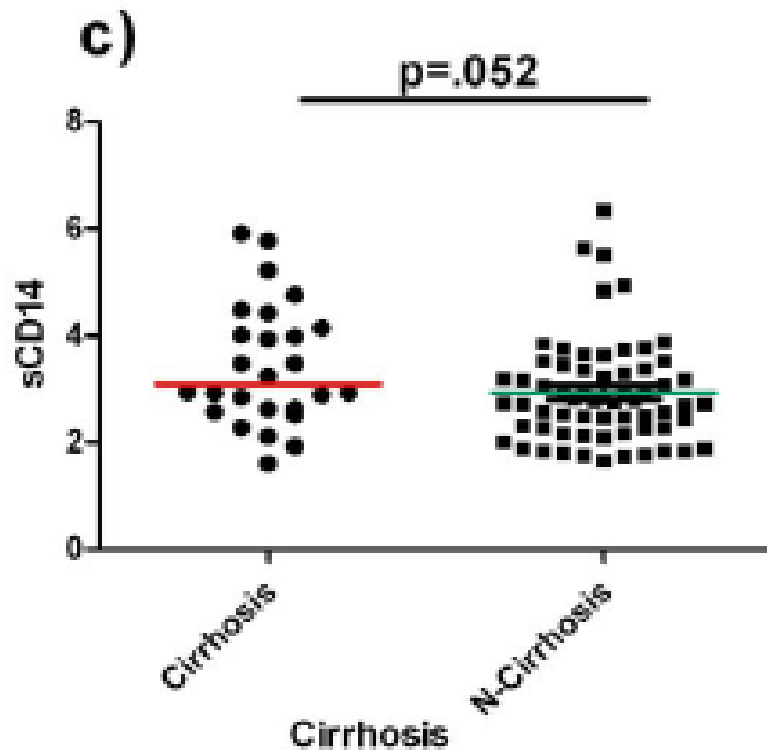
	Cirrhosis	Minimal disease
Total number	17	71
Mean age, y (\pm SD)	50.5 \pm 6.2	41.7 \pm 6.0
Sex, male, n (%)	10 (58.8)	60 (84.5)
Race, black, n (%)	16 (94.1)	69 (97.2)
HIV (%), n	8 (47.1)	20 (28.2)
Proportion injecting illicit drugs (in prior 6 mo)	7 (41.2)	39 (54.9)
Alcohol use, (%)		
None	11 (64.7)	26 (36.6)
>1 drink/day	5 (29.4)	38 (53.5)
7 days/wk	1 (5.9)	7 (9.9)

	OR	95% CI	P value
Univariate			
LPS \geq 42 pg/mL ^a	19.0	2.98–120.79	.0018
LBP (highest quartile)	5.02	1.63–15.48	.005
sCD14 (highest quartile) ^a	8.65	1.98–37.72	.0041
AAL \geq 5-fold above control ^a	27.77	5.64–136.71	< .0001
EndoCAb IgM (highest quartile)	0.15	0.02–1.20	.073
CD4 ⁺ lymphocyte <350/mm ^{3a}	7.02	1.36–36.31	.02
Multivariate^{a,b}			
LPS \geq 42 pg/mL	18.14	2.58–127.67	.0036
CD4 ⁺ lymphocyte <350/mm ³	6.50	1.02–41.23	.047

Cirrhosis: liver biopsy and/or clinical events (esophageal varices, ascites, or encephalopathy)

HIV/HCV co-infection

98 HIV/HCV co-infected patients on virologically-suppressive cART median CD4+ 430/mm³



RESEARCH ARTICLE

Open Access

Immune activation and microbial translocation in liver disease progression in HIV/hepatitis co-infected patients: results from the Icona Foundation study

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127 HIV-infected hepatitis viruses co-infected patients (118 HCV, 9 HBV)
- ART naïve, CD4 cell count >200/ μ l
- known date of prior HIV neg/pos tests

→immune activation (IA): **IL-6, TNF α**

→microbial translocation (MT): **LPS, sCD14**

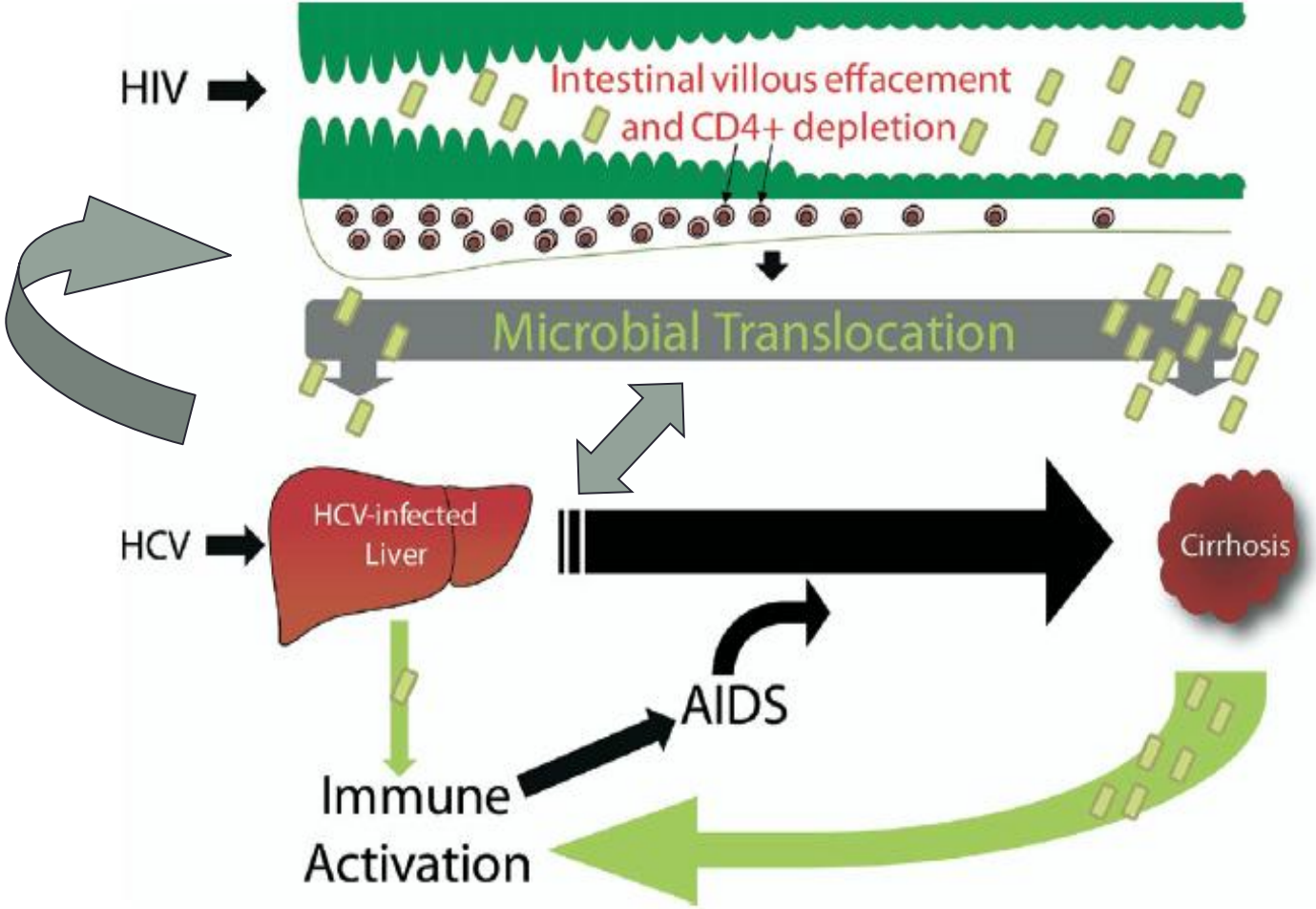
Hepatitis co-infected HIV + patients present higher circulating LPS (Icona Cohort)

118 HCV co-infected;
9 HBV co-infected

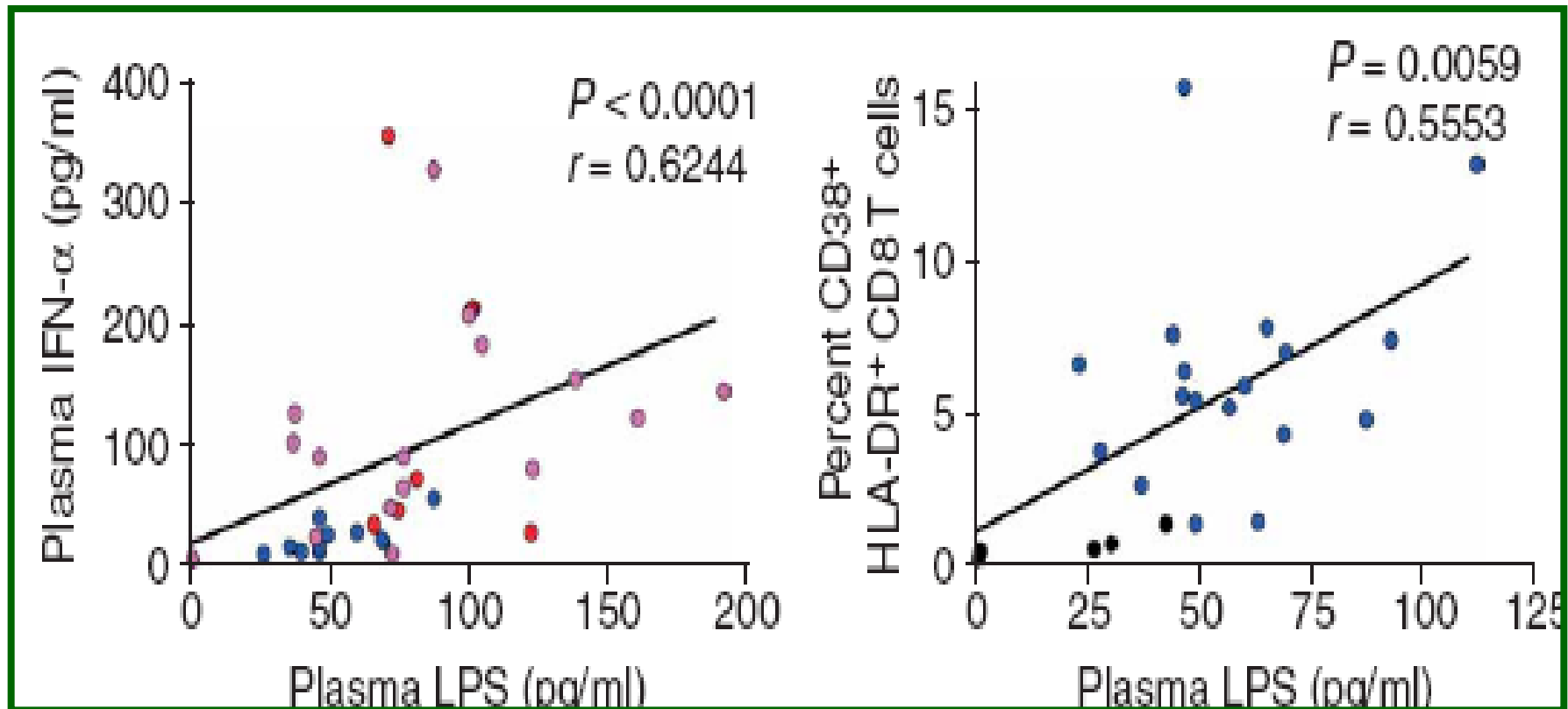
TABLE 1

Characteristics	Co-infection status		
	Hepatitis co-infected N= 127	HIV-monoinfected N= 241	Total N= 368
Gender, n(%)			
Female	44 (34.6%)	64 (26.6%)	108 (29.3%)
Age, years			
Median (range)	34 (23, 56)	33 (21, 58)	34 (21, 58)
Mode of HIV transmission, n(%)			
Homosexual contacts	18 (14.2%)	123 (51.0%)	141 (38.3%)
Heterosexual contacts	20 (15.7%)	101 (41.9%)	121 (32.9%)
IDU	85 (66.9%)	14 (5.8%)	99 (26.9%)
Other/unknown	4 (3.1%)	3 (1.2%)	7 (1.9%)
Viral load, log₁₀ copies/mL			
Median (IQR)	3.8 (3.1, 4.3)	4.0 (3.5, 4.5)	3.9 (3.3, 4.4)
CD4 count, cells/mm³			
Median (range)	596 (208, 1303)	579 (39, 1373)	580 (39, 1373)
Hepatitis C co-infection, n(%)			
Negative	9 (7.1%)	241 (100.0%)	250 (67.9%)
Positive	118 (92.9%)	0 (0.0%)	118 (32.1%)
Time from HIV seroconversion, years			
Median (range)	5 (0, 25)	3 (0, 16)	3 (0, 25)
Calendar year of sample			
Median (range)	1998 (1997, 2008)	2000 (1997, 2007)	1999 (1997, 2008)
Biomarkers			
CDBCD38+DR+, % (n=120)			
Median (IQR)	48.0 (25.2, 55.4)	45.0 (33.0, 54.7)	45.0 (32.6, 54.9)
IL-6, pg/ml (n=279)			
Median (IQR)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.1 (0.5, 2.0)
LPS, pg/ml (n=212)			
Median (IQR)	126.2 (75, 205.5)	75.3 (75, 198.0)	90.3 (75, 199.5)
sCD14, mg/ml (n=294)			
Median (IQR)	3.5 (2.0, 5.3)	3.6 (2.4, 5.1)	3.6 (2.3, 5.2)
TNF-alfa, pg/ml (n=286)			
Median (IQR)	2.3 (1.7, 3.4)	2.2 (1.6, 3.3)	2.3 (1.6, 3.3)
ALT, IU/l (n=360)			
Median (IQR)	41.0 (24.0, 64.0)	23.0 (17.0, 35.0)	25.5 (18.0, 43.0)

HIV/HCV co-infection, cirrhosis & microbial translocation



Microbial translocation as driver of immune activation/inflammation



**HCV might contribute to
the excess of immune
activation/inflammation
in treated HIV via
enhanced microbial
translocation**

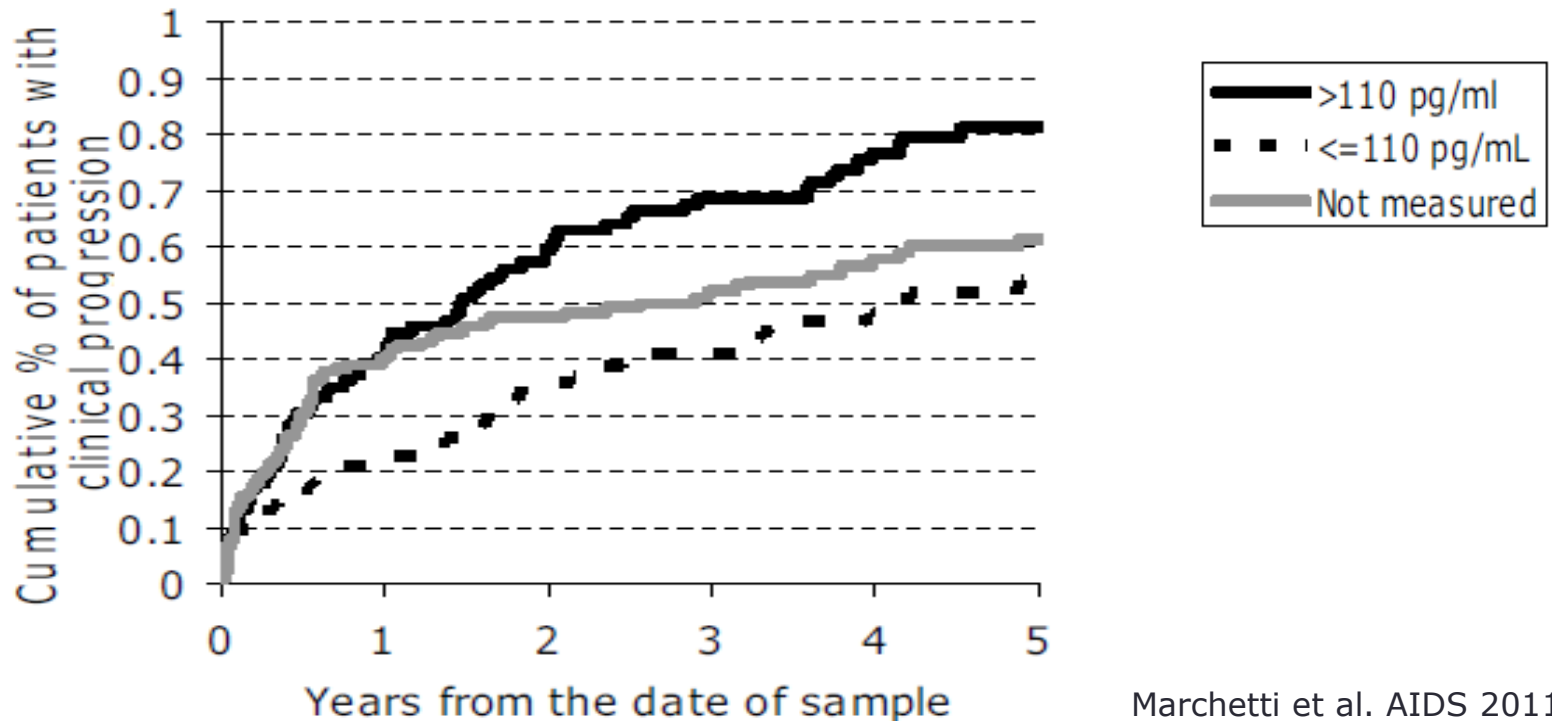
Endpoints: i) ALT >200 IU/ml or liver-related death; ii) Fib-4 > 1.45 or liver-related death

Crude and adjusted relative hazards of developing Fib>1.45

Biomarker	Crude RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value	Adjusted** RH (95% CI)	p-value
CD8CD38+DR+, %						
<=48%	1.0		1.0		1.0	
>48%	5.27 (0.59, 47.23)	0.137	4.62 (0.47, 45.35)	0.189	5.34 (0.31, 92.47)	0.250
not measured	2.82 (0.37, 21.58)	0.318	2.88 (0.35, 23.80)	0.327	1.71 (0.19, 15.66)	0.636
IL-6, pg/ml						
<=1.1	1.0		1.0		1.0	
>1.1	1.67 (0.59, 4.68)	0.333	1.62 (0.52, 5.05)	0.403	1.24 (0.34, 4.58)	0.747
not measured	0.71 (0.18, 2.84)	0.627	0.56 (0.13, 2.46)	0.443	§	0.992
LPS, pg/ml						
<=126	1.0		1.0		1.0	
>126	0.41 (0.11, 1.60)	0.200	0.36 (0.07, 1.78)	0.211	0.53 (0.08, 3.33)	0.497
not measured	0.53 (0.19, 1.46)	0.217	0.64 (0.21, 1.96)	0.431	0.71 (0.13, 3.89)	0.697
sCD14, mg/ml						
<=3.6	1.0		1.0		1.0	
>3.6	0.99 (0.36, 2.74)	0.987	0.46 (0.14, 1.53)	0.206	0.20 (0.04, 0.90)	0.036
not measured	0.69 (0.18, 2.61)	0.582	0.33 (0.08, 1.46)	0.145	§	0.992
TNF-alfa, pg/ml						
<=2.3	1.0		1.0		1.0	
>2.3	8.37 (1.90, 36.87)	0.005	15.17 (2.72, 84.76)	0.002	13.05 (2.43, 70.07)	0.003
not measured	1.70 (0.24, 12.11)	0.596	1.53 (0.17, 13.71)	0.702	0.29 (0.01, 10.81)	0.503

**What the correlates
of microbial
translocation in HIV
infection?**

Increased rate of disease progression in patients with heightened circulating LPS



Marchetti et al. AIDS 2011

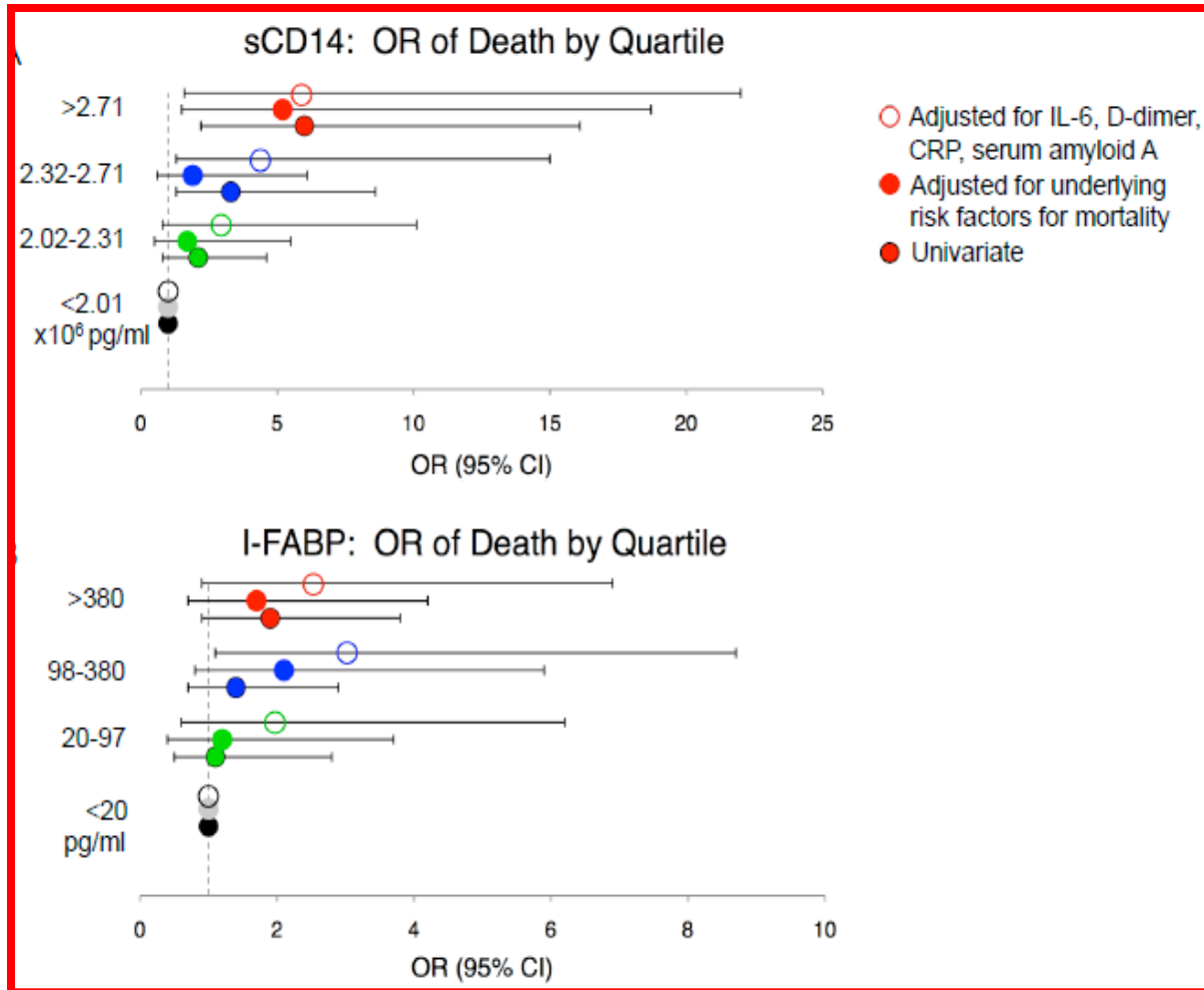
The median time to event was 4 years (95%CI:1-2) with $LPS \leq 110$ pg/mL vs 1.5 years (3.1-5.6) with $LPS > 110$ pg/mL

log-rank test $p=0.0002$

LPS independently predicts HIV disease progression

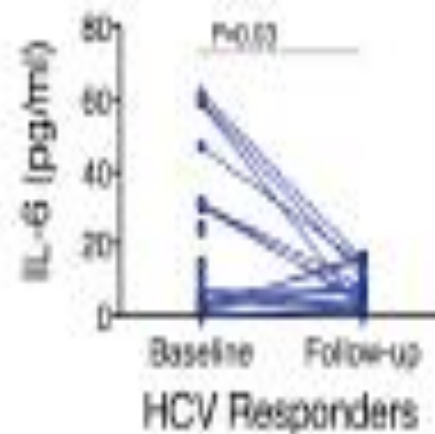
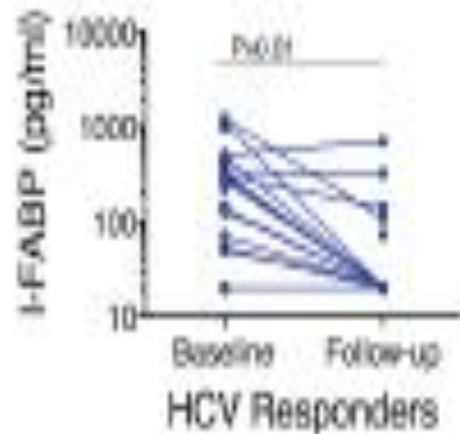
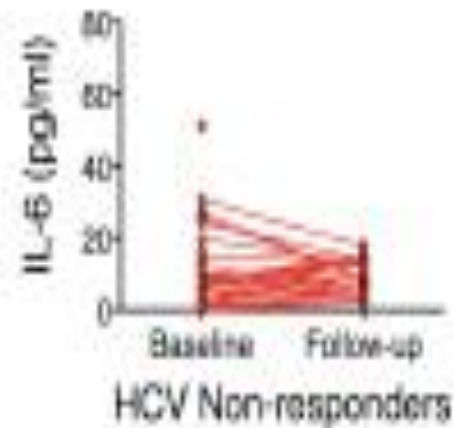
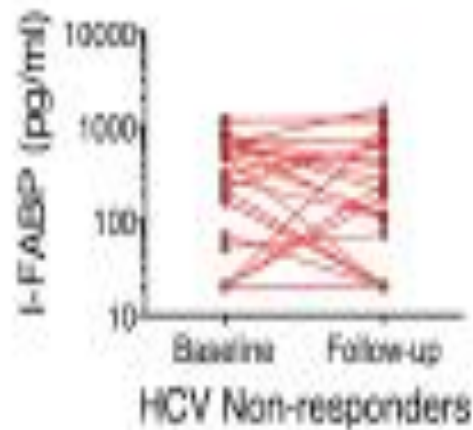
Biomarker	Crude and adjusted relative hazards of clinical progression					
	Crude RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value	Adjusted** RH (95% CI)	p-value
IL-6, pg/ml						
<=1	1.00		1.00		1.00	
>1	0.91 (0.69, 1.20)	0.507	1.12 (0.85, 1.47)	0.436	1.08 (0.80, 1.46)	0.600
not measured	1.03 (0.74, 1.45)	0.858	1.28 (0.91, 1.82)	0.157	1.28 (0.58, 2.82)	0.537
LPS, pg/ml						
<=110	1.00		1.00		1.00	
>110	1.90 (1.39, 2.60)	<.001	1.92 (1.39, 2.66)	<.001	1.85 (1.32, 2.58)	<.001
not measured	1.31 (0.97, 1.76)	0.077	1.32 (0.97, 1.79)	0.077	1.13 (0.78, 1.64)	0.504
sCD14, mg/ml						
<=3	1.00		1.00		1.0	
>3	1.32 (1.00, 1.74)	0.046	1.12 (0.84, 1.48)	0.439	1.14 (0.85, 1.52)	0.374
not measured	1.35 (0.95, 1.93)	0.098	1.28 (0.89, 1.84)	0.183	0.98 (0.41, 2.32)	0.967
TNF-alfa, pg/ml						
<=2.5	1.00		1.00		1.0	
>2.5	1.36 (1.03, 1.80)	0.033	1.22 (0.92, 1.62)	0.170	1.16 (0.86, 1.56)	0.342
not measured	1.54 (1.12, 2.11)	0.008	1.43 (1.04, 1.98)	0.028	1.28 (0.74, 2.24)	0.379

Immune activation due to microbial translocation independently predicts death



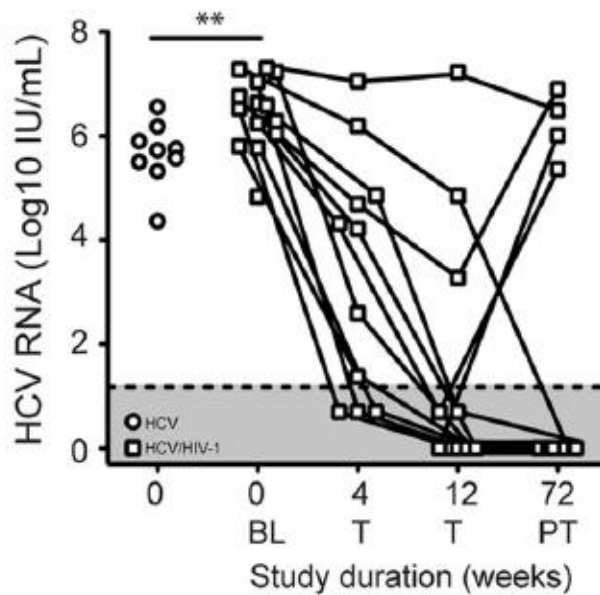
**HCV treatment
(IFN-ribavirin)
reduces immune
activation ?**

Successful anti-viral treatment is associated with decreased I-FABP and IL-6 levels

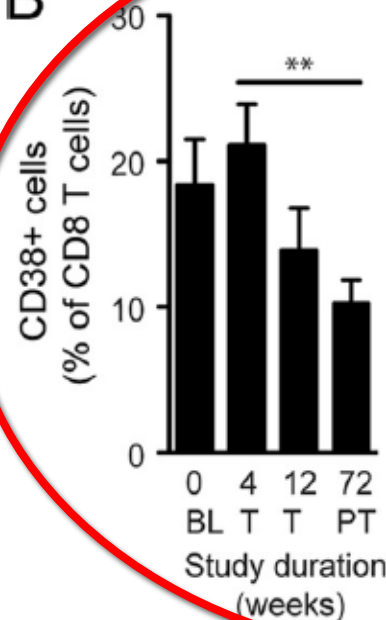


Reduction of T-cell activation by anti-HCV treatment

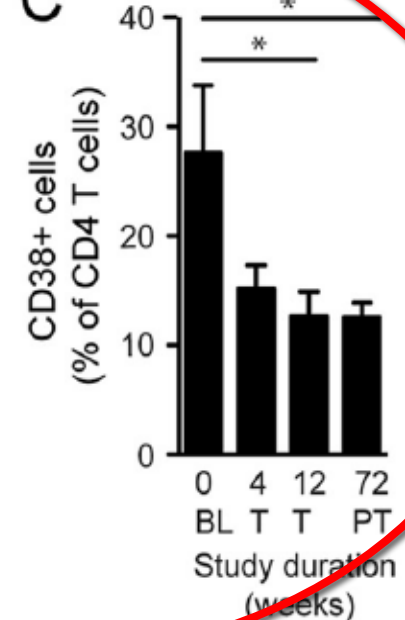
356 HIV+ cART-treated : 130 HCV co-infected



B



C



Gonzalez et al et al. J Virol 2009; also
Massanella M et al. Antiviral Therapy 2010

Predictors of EVR

98 HIV/HCV co-infected patients on virologically-suppressive cART median CD4+ 430/mm³

	Univariate			Multivariate		
	OR	95%CI	P	AOR	95%CI	p
LPS (pg/mL)	1.000	0.996–1.004	0.934	0.997	0.99–1.004	0.345
sCD14 (µg/mL)	0.419	0.252–0.695	0.001	0.145	0.031–0.688	0.015
HCV genotypes (1–4 vs 2–3)	0.109	0.037–0.324	0.0001	0.233	0.021–2.618	0.238
HCV-RNA (log ₁₀ IU/mL)	0.409	0.207–0.809	0.01	0.789	0.134–4.628	0.793
Fibrosis (advanced vs non advanced)	0.504	0.191–1.327	0.165	0.134	0.005–3.879	0.616
Cirrhosis (yes vs no)	0.382	0.148–0.99	0.048	0.185	0.007–4.623	0.304
Nadir CD4+ T cells/µL	1.003	0.999–1.006	0.155	1.007	0.998–1.016	0.134
CD4+ T cells/µL	0.999	0.997–1.002	0.518	0.996	0.990–1.001	0.112
Age, years	1.043	0.948–1.149	0.386	1.134	0.879–1.463	0.333
Sex, male vs female	0.509	0.134–1.934	0.321	0.215	0.007–6.926	0.385

Predictors of SVR

98 HIV/HCV co-infected patients on virologically-suppressive cART median CD4+ 430/mm³

	Univariate			Multivariate		
	OR	95%CI	p	AOR	95%CI	p
LPS (µg/ml)	0.996	0.990–1.001	0.106	1.000	0.980–1.003	0.129
sCD14 (µg/mL)	0.668	0.428–1.041	0.046	0.584	0.214–1.589	0.292
HCV genotypes (1–4 vs 2–3)	0.087	0.031–0.244	0.0001	0.022	0.001–0.469	0.014
HCV-RNA (log ₁₀ IU/mL)	0.423	0.224–0.798	0.008	0.778	0.309–10.231	0.519
Fibrosis (advanced vs non advanced)	0.498	0.200–1.194	0.116	0.553	0.026–11.663	0.703
Cirrhosis (yes vs no)	0.370	0.143–0.957	0.040	0.161	0.007–4.472	0.289
Nadir CD4+ T cells/µL	1.003	1.000–1.006	0.071	1.005	0.997–1.014	0.835
CD4+ T cells/µL	1.001	0.999–1.003	0.287	1.000	0.995–1.009	0.669
Age, years	0.996	0.908–1.093	0.996	0.942	0.719–1.236	0.870
Sex, male vs female	0.722	0.237–2.200	0.566	0.812	0.067–9.871	0.216

Patients

Three male HIV-HCV co-patients with:

- CD4+ count below 250/uL
- on stable, virologically-suppressive HAART
- requiring anti-HCV treatment

**MVC added to ongoing PI-based HAART
prior to anti-HCV treatment**

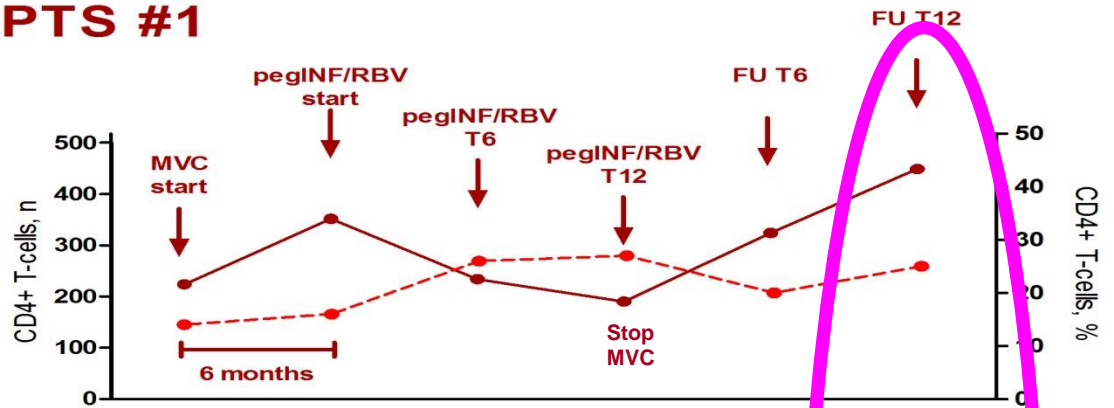
Clinical Characteristics	Patient 1	Patient 2	Patient 3
Age	47	37	50
Exposure	Ex-IDU	MSM	Ex-IDU
CDC	A3	A2	C3
CD4+ T-cells Nadir	111/uL	248/uL	63/uL
Current HAART	TDF+FPV/r	TDF+ATV/r	TDF+DRV/r
CD4+ t cell count at baseline before MVC intensification	224/uL	248/uL	209/uL
MVC intensification	300 mg bid	150 mg bid	150 mg bid
HCV Genotype	1b	1	1a
IL-28 polymorphism	C/C	C/T	C/C

All patients achieved SVR

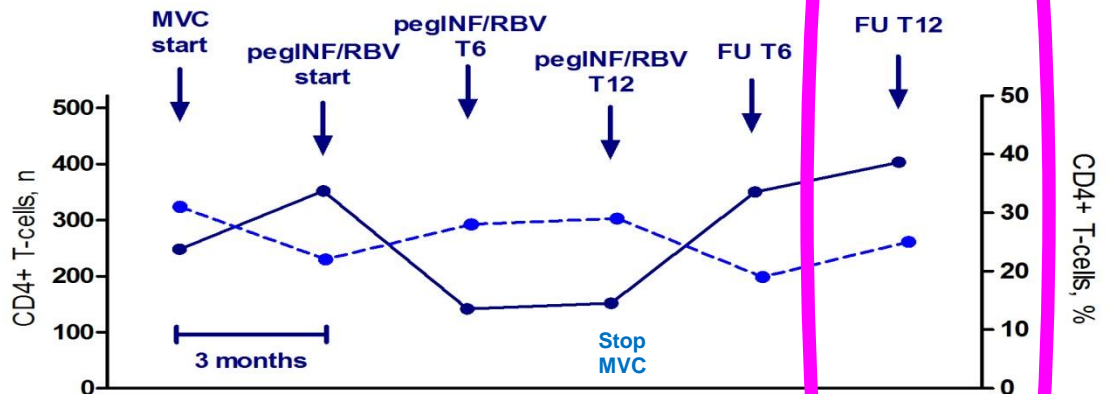
	MVC Start	IFN α /RBV Start	12 months follow-up	MVC Start	IFN α /RBV Start	12 months follow-up	MVC Start	IFN α /RBV Start	12 months follow-up
Fib-4 score	1.59	1.13	1.18	1.26	1.0	1.0	1.65	1.1	1.08
<u>Peripheral T-cells phenotypes</u>									
CD4+ T-cells n	224	352	449	248	352	403	209	261	299
CD4+ T-cells %	14	16	25	31	22	22	11	11	11
CD8+ T-cells n	880	1232	879	328	880	1107	1178	1529	1994
CD8+ T-cells %	55	56	50	41	55	60	62	67	73
CD8+CD127+ n	272	259	490	42	160	542	285	559	1023
CD8+CD127+T-cells %	17	21	28	13	10	30	15	24	37
CD8+CD38+T-cells n	32	12	41	5	48	74	57	46	175
CD8+CD38+T-cells %	2	1	3	1.5	3	5	3	2	7
CD4/CD8 ratio	0.25	0.29	0.51	0.76	0.4	0.36	0.18	0.17	0.15
HIV RNA cp/mL	<39	<39	<39	<39	<39	<39	<39	<39	<39
HCV RNA UI/mL		1492354	<12	282616	527921	<12	399556 1	2963732	<12
AST/ALT UI	163/60	59/34	41/39	39/107	38/27	19/27	54/51	38/27	20/30

All patients recovered CD4+ T-cell count

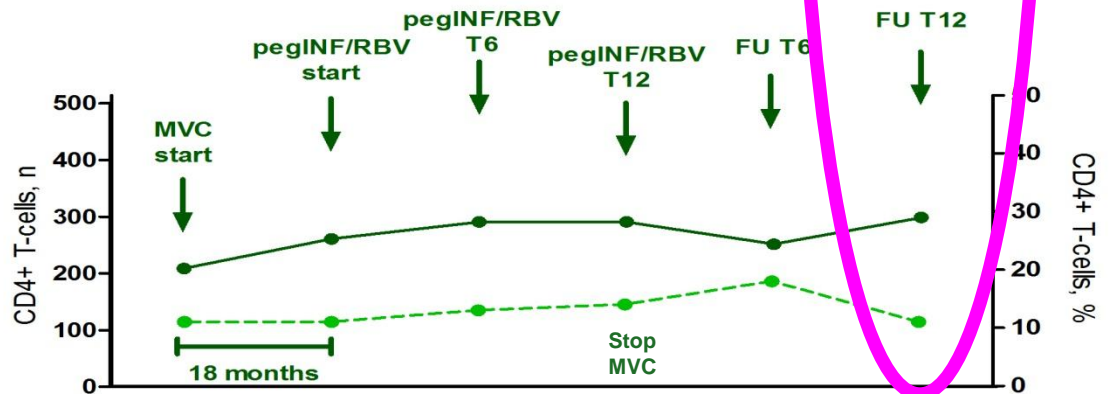
PTS #1



PTS #2



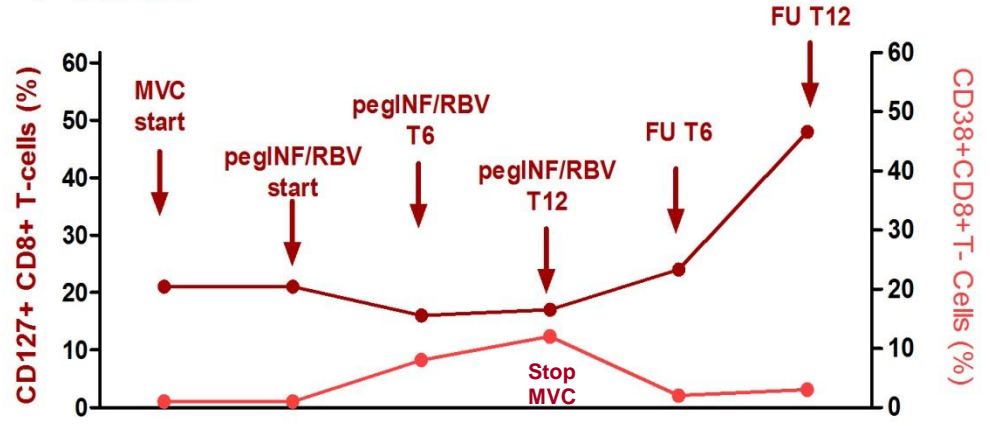
PTS #3



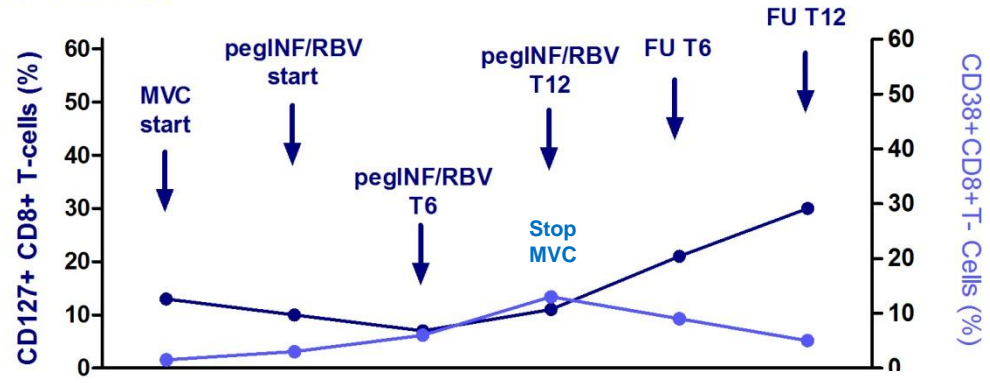
	MVC Start	IFN α /RBV Start	12 months follow- up	MVC Start	IFN α /RBV Start	12 months follow- up	MVC Start	IFN α /RBV Start	12 months follow- up
Fib-4 score	1.59	1.13	1.18	1.26	1.0	1.0	1.65	1.1	1.08
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HIV RNA cp/mL	<39	<39	<39	<39	<39	<39	<39	<39	<39
HCV RNA UI/mL		1492354	<12	282616	527921	<12	399336 1	2963732	<12
AST/ALT UI	163/60	59/34	41/39	39/107	38/27	19/27	54/51	38/27	20/30

Recovery of memory T-cells, rise in T-cell activation

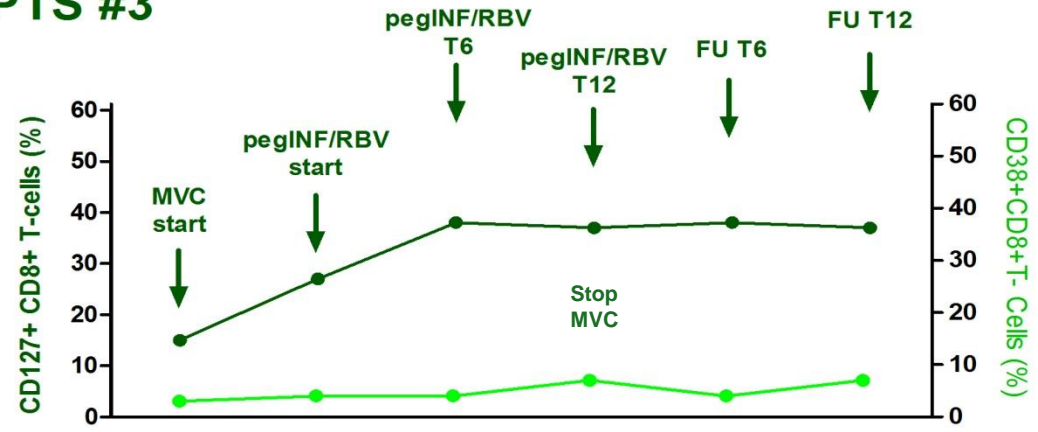
PTS #1



PTS #2



PTS #3

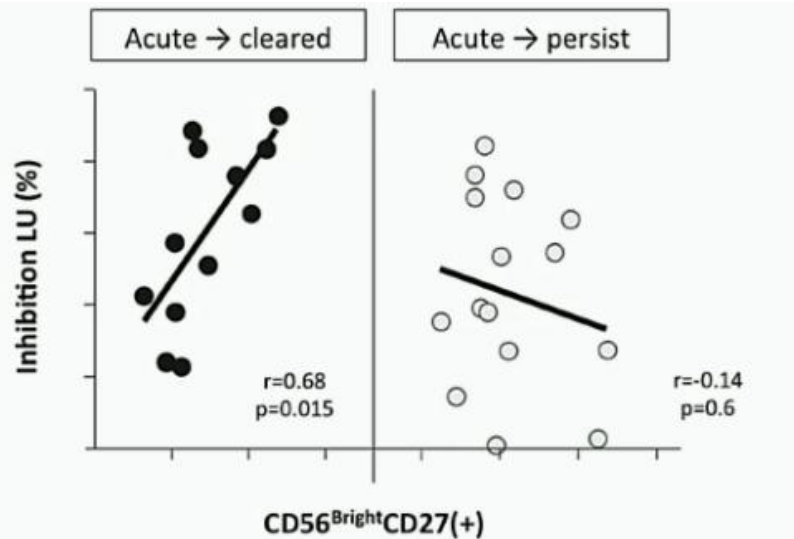
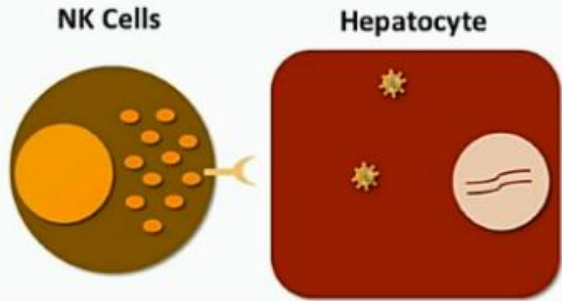


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HCV RNA UI/mL		1492354	<12	282616	527921	<12	399336 1	2963732	<12
AST/ALT UI	163/6 0	59/34	41/39	39/107	38/27	19/27	54/51	38/27	20/30

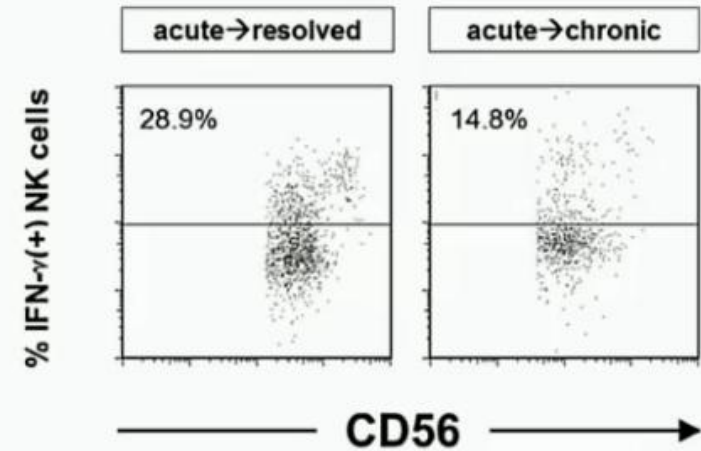
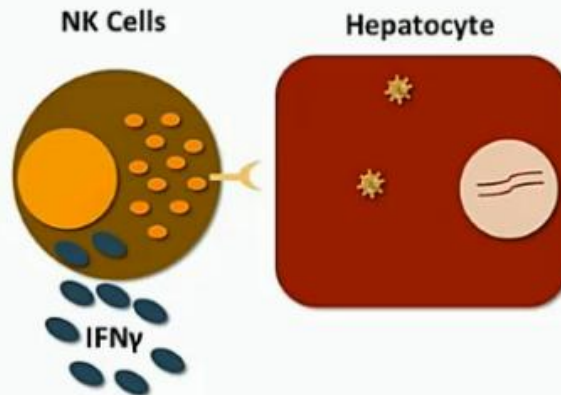
**What about the effect of
DAA-based HCV
treatment on immune
activation ?**

**NK cells are a crucial
component of HCV-
specific response**

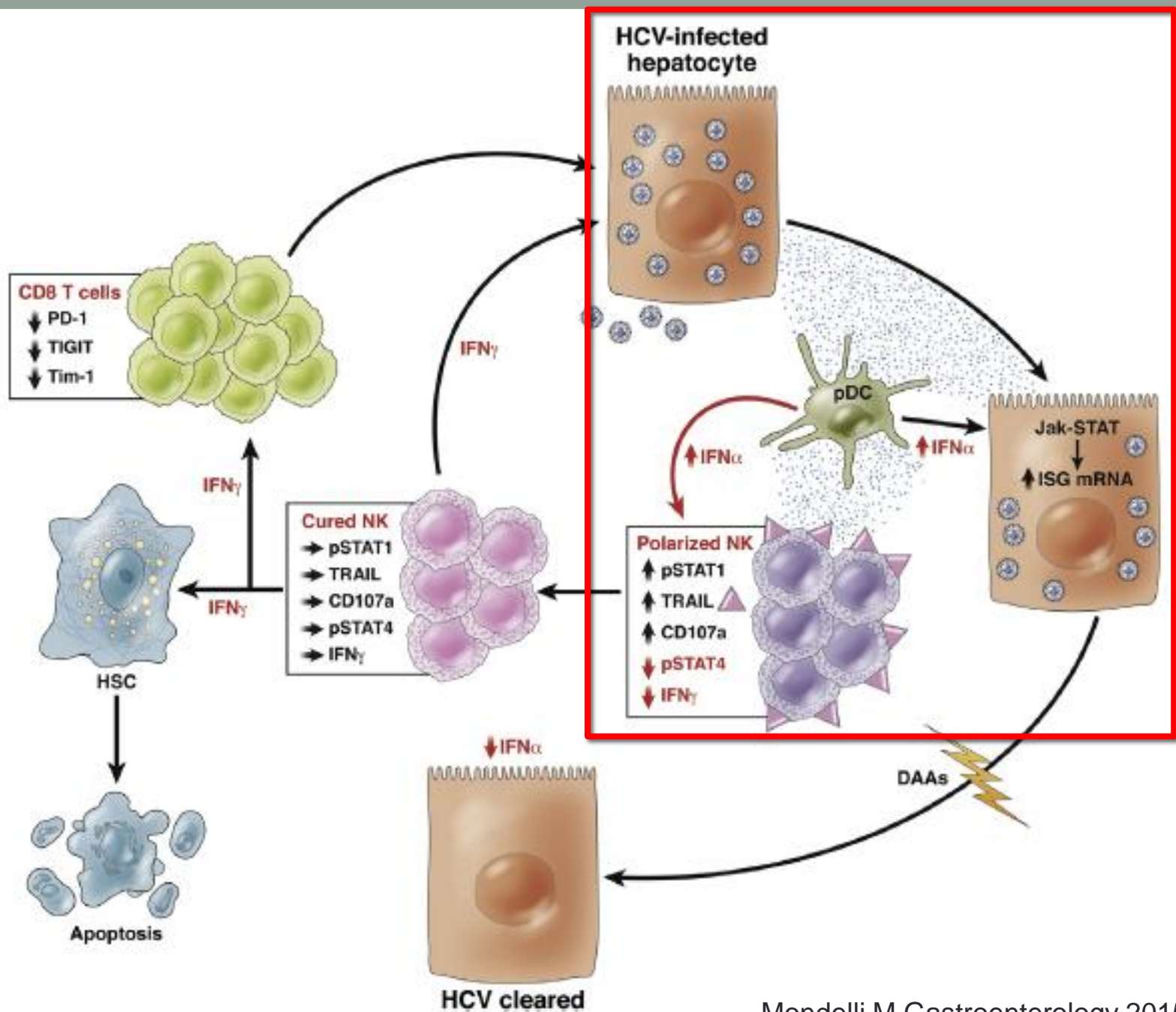
NK Cells Constrict HCV Replication



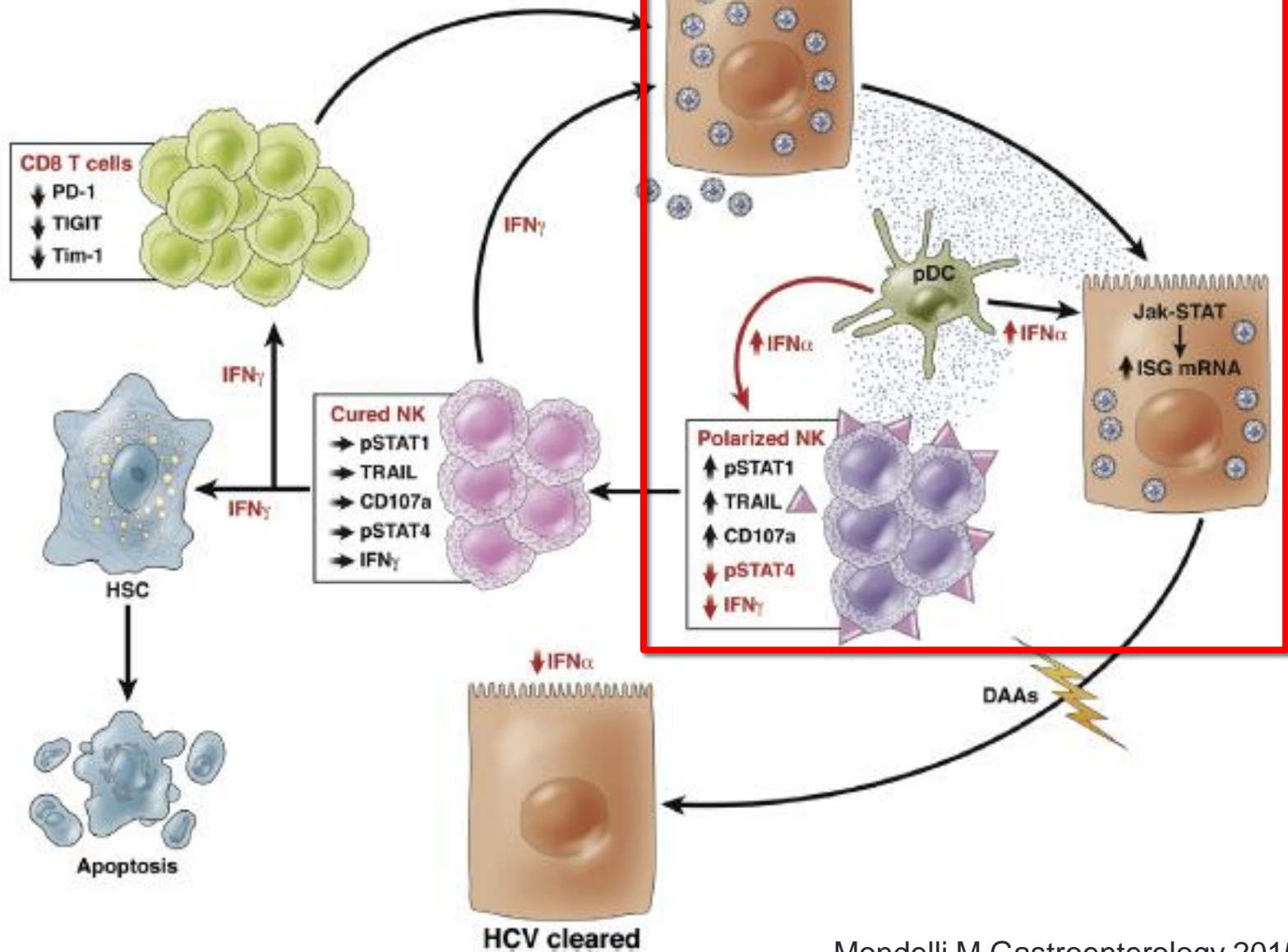
Eisenhardt M et al., *AIDS*, 2014
Golden-Mason et al., *PLoS One*, 2014



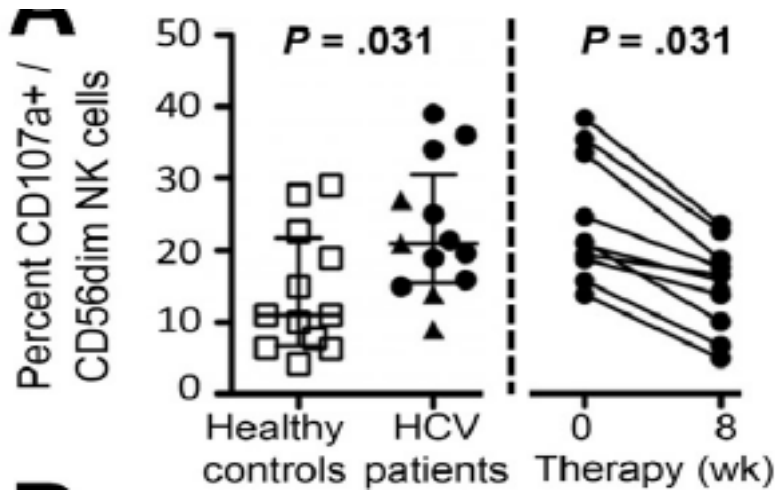
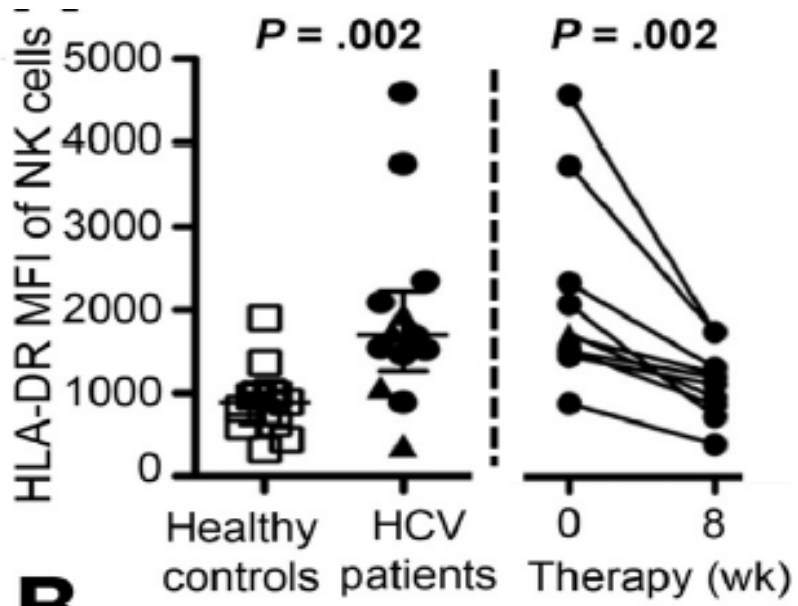
**In chronic HCV NK cells are
activated, polarized toward
cytotoxicity and deficient
IFN-g production
(functional dichotomy)**



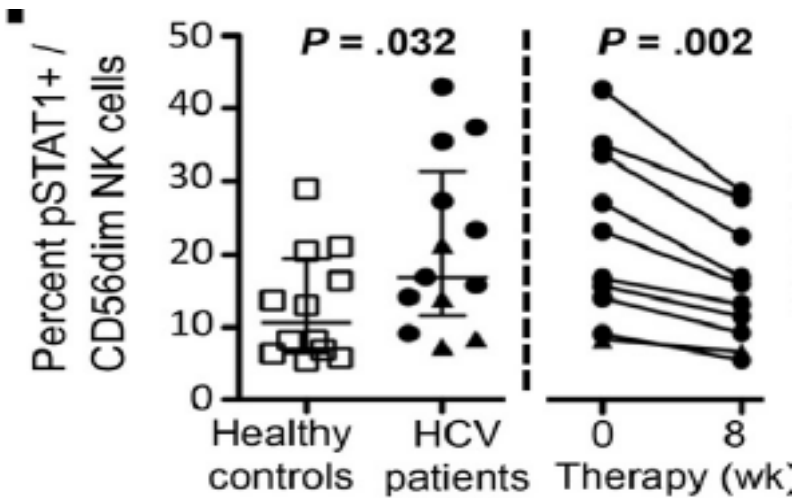
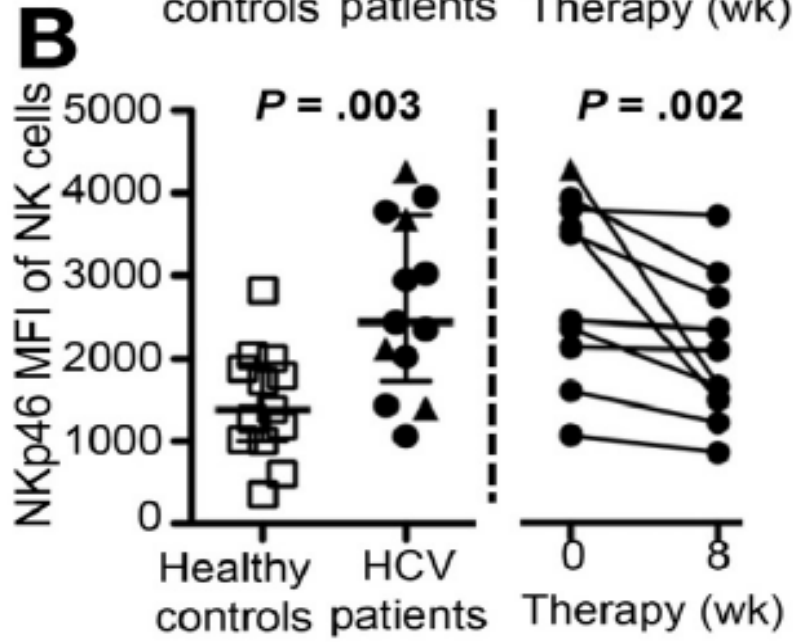
IFN-based therapy: viral cure ≠ immunologic cure



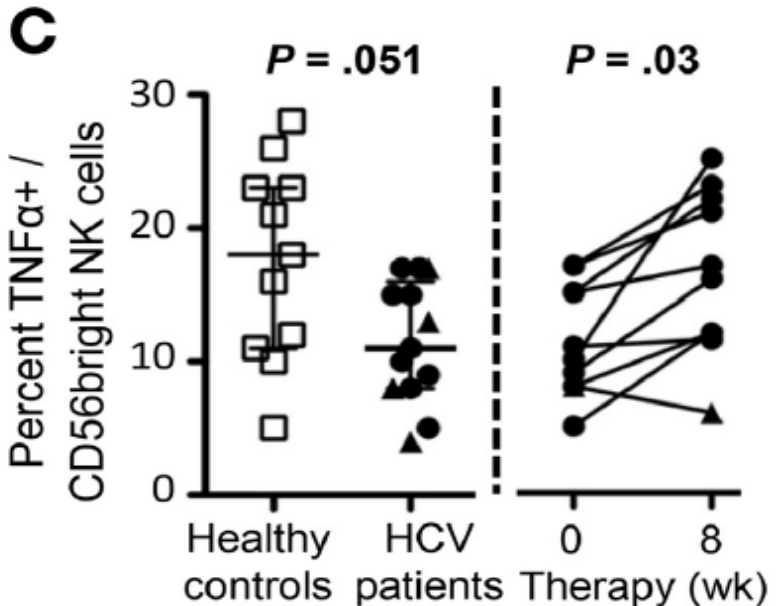
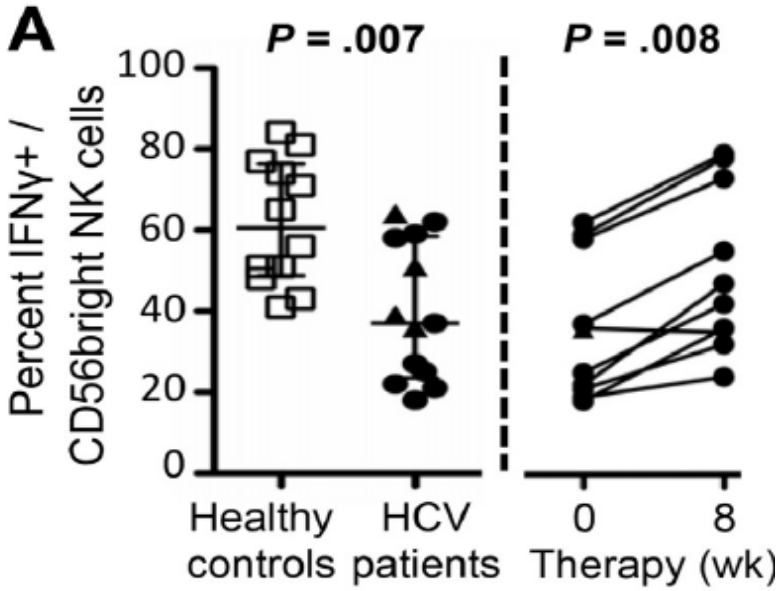
NK phenotype “normalization” under DAA regimes



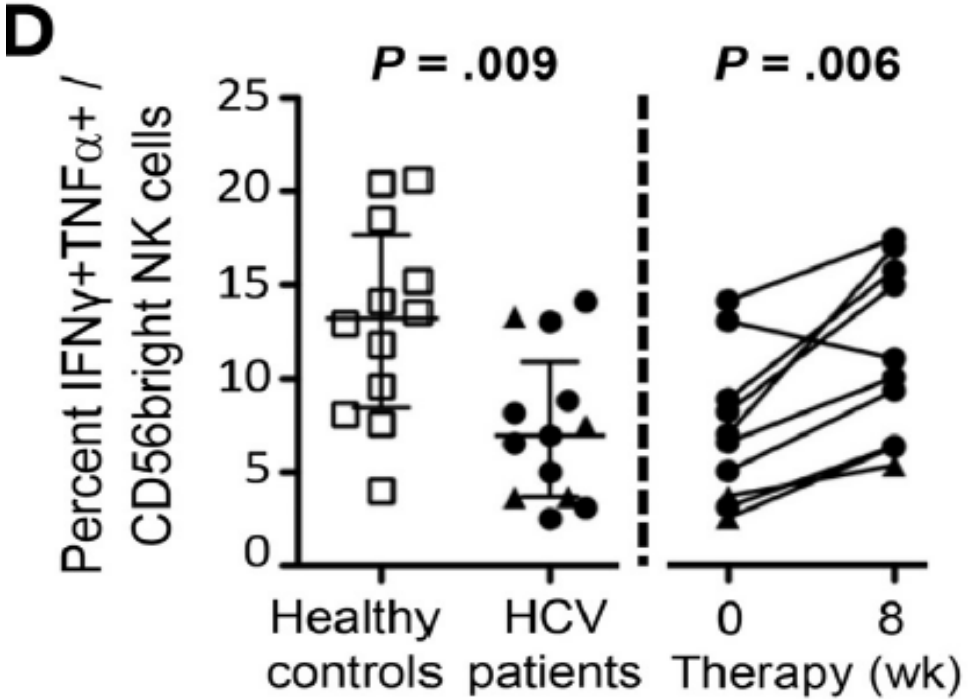
13 G1b NR to Peg-IFN/Riba NR, DCV/ASV

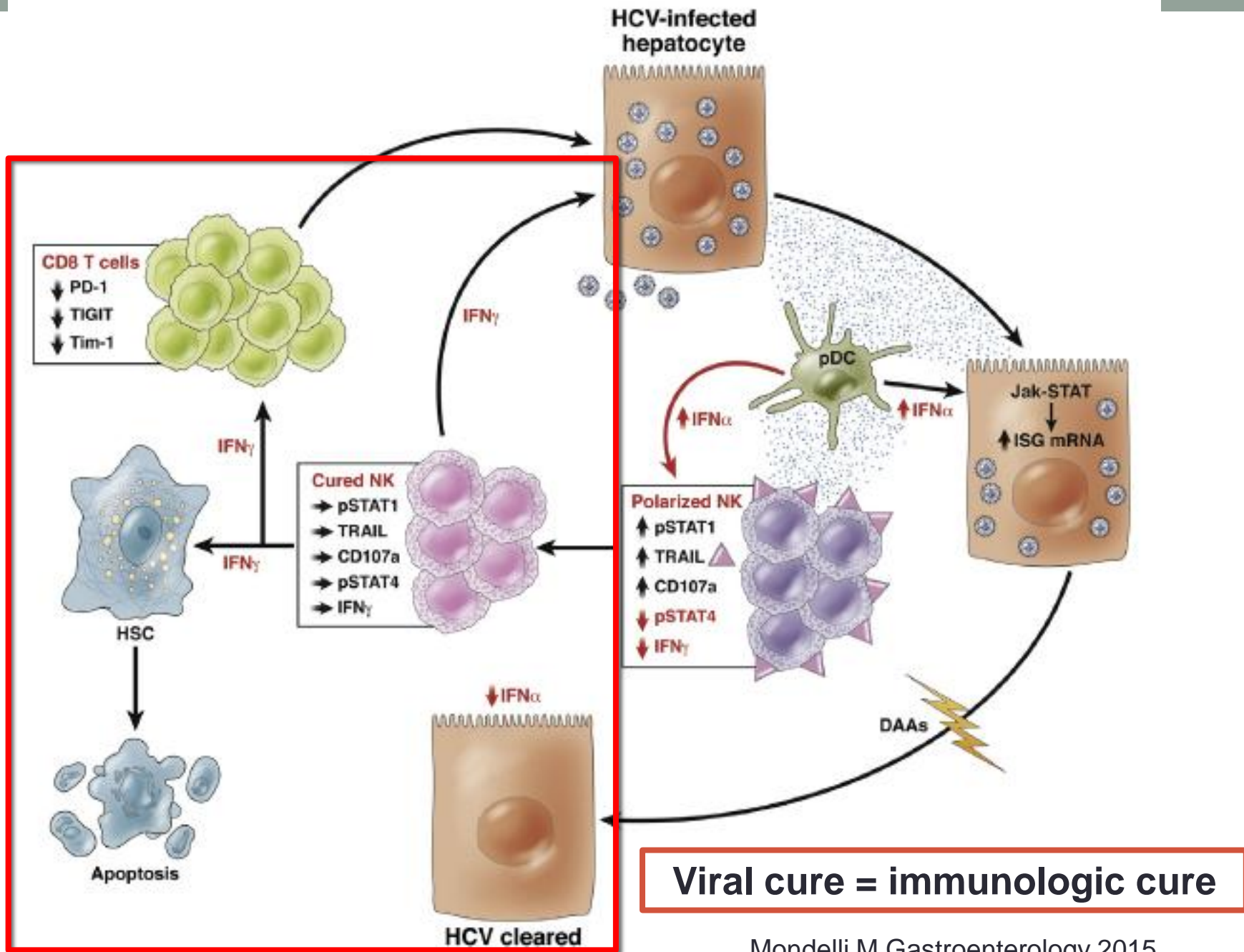


NK function “normalization” under DAA regimes



13 G1b NR to Peg-IFN/Riba NR, DCV/ASV

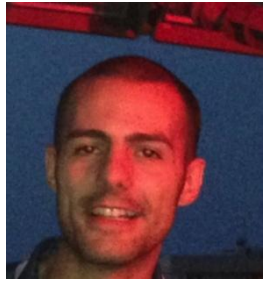




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- Antonella d'Arminio Monforte
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Massimo Puoti



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