Service d'Immuno- Hématologie Clinique
Centre d'Information et de Soins de l'Immunodéficience Humaine et des Hépatites virales

Inflammation and HIV-HCV coinfection

Persistant Immune Activation during HIV/HCV Coinfection: A new treatment label ?

Dr I Poizot-Martin

CHU- Sainte Marguerite
Assistance Publique- Hôpitaux de Marseille

ISHEID, Marseille, 23 Mai 2012

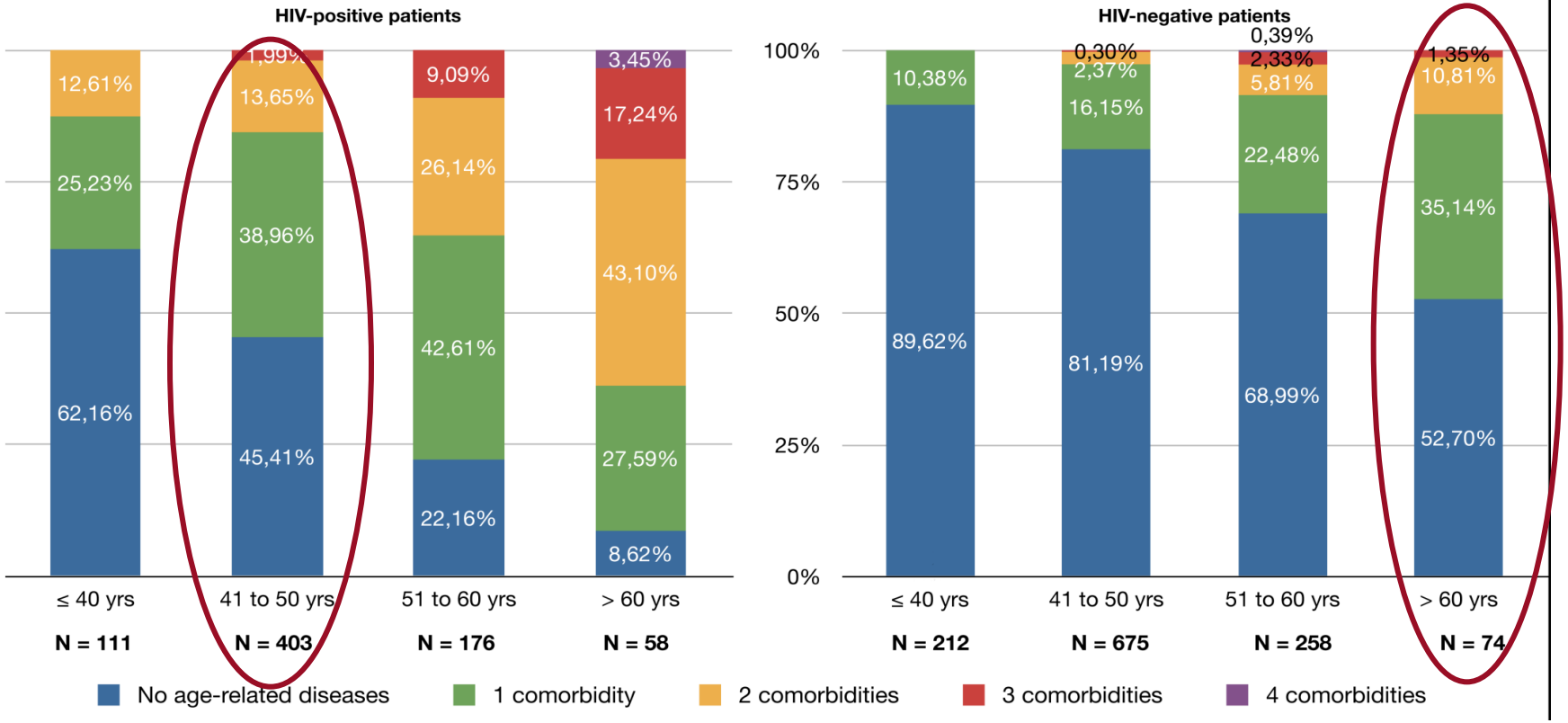
Effectively treated HIV infected patients have a higher than normal risk for developing noninfectious comorbidities including cardiovascular, renal disease and cancer.

Pre- HAART

Post- HAART !!!

Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the General Population

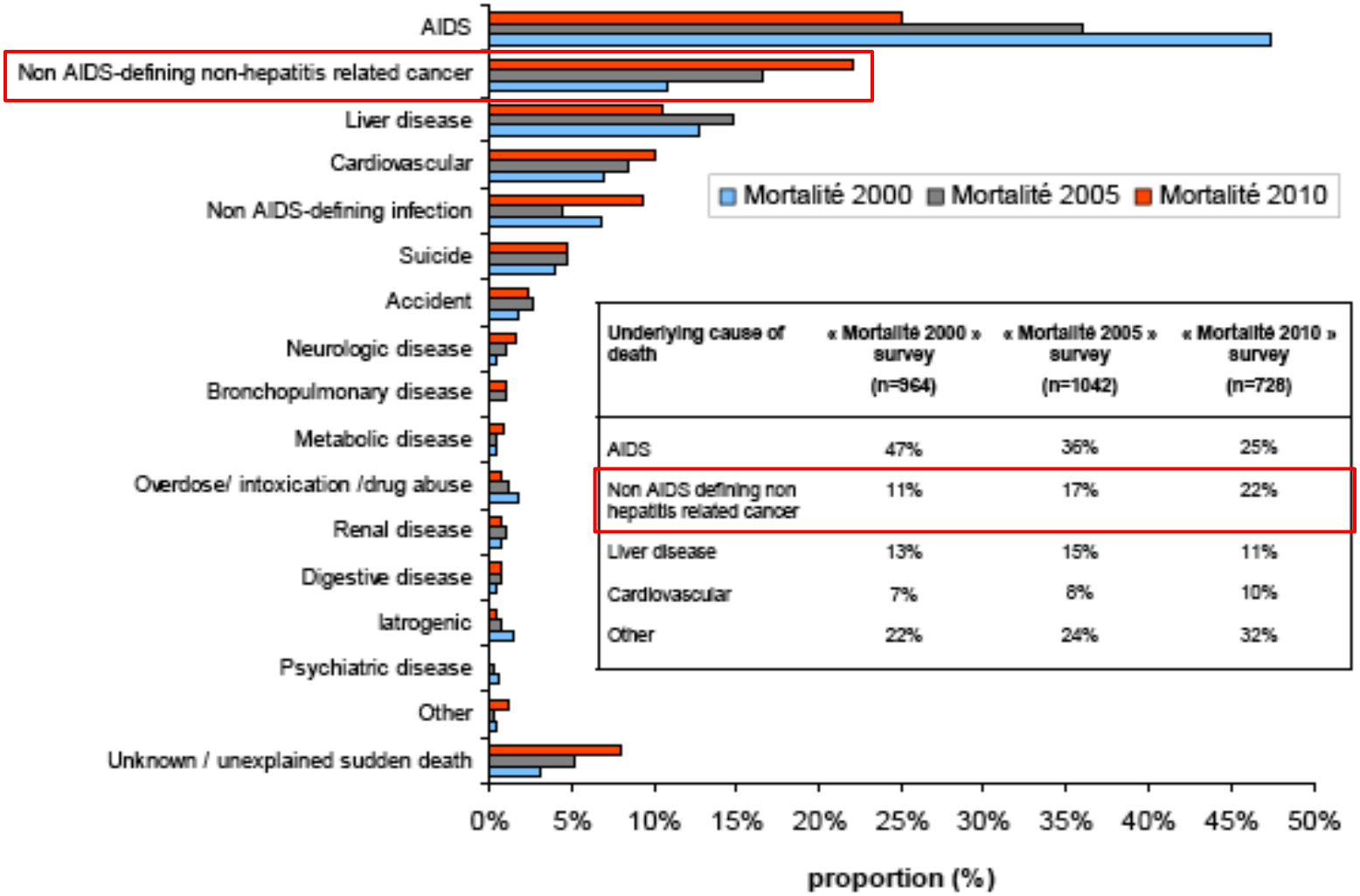
Comorbidities: Hypertension, Type 2 Diabetes, CardioVascular disease and osteoporosis



- Highly prevalence of non- infectious comorbidities in HIV-infected patients in all age strata compared with controls ($p<0.001$)
- The prevalence in 41-50 years old HIV-infected patients aged is similar to that observed among non HIV infected patients >60 years old age ($p=0.282$).

Guaraldi G et al; CID 2011; 53:1120-1126

Evolution of the Causes of Death among HIV-infected Patients between 2000 and 2010 : Results of the French National Survey "ANRS EN20 Mortalité 2010"

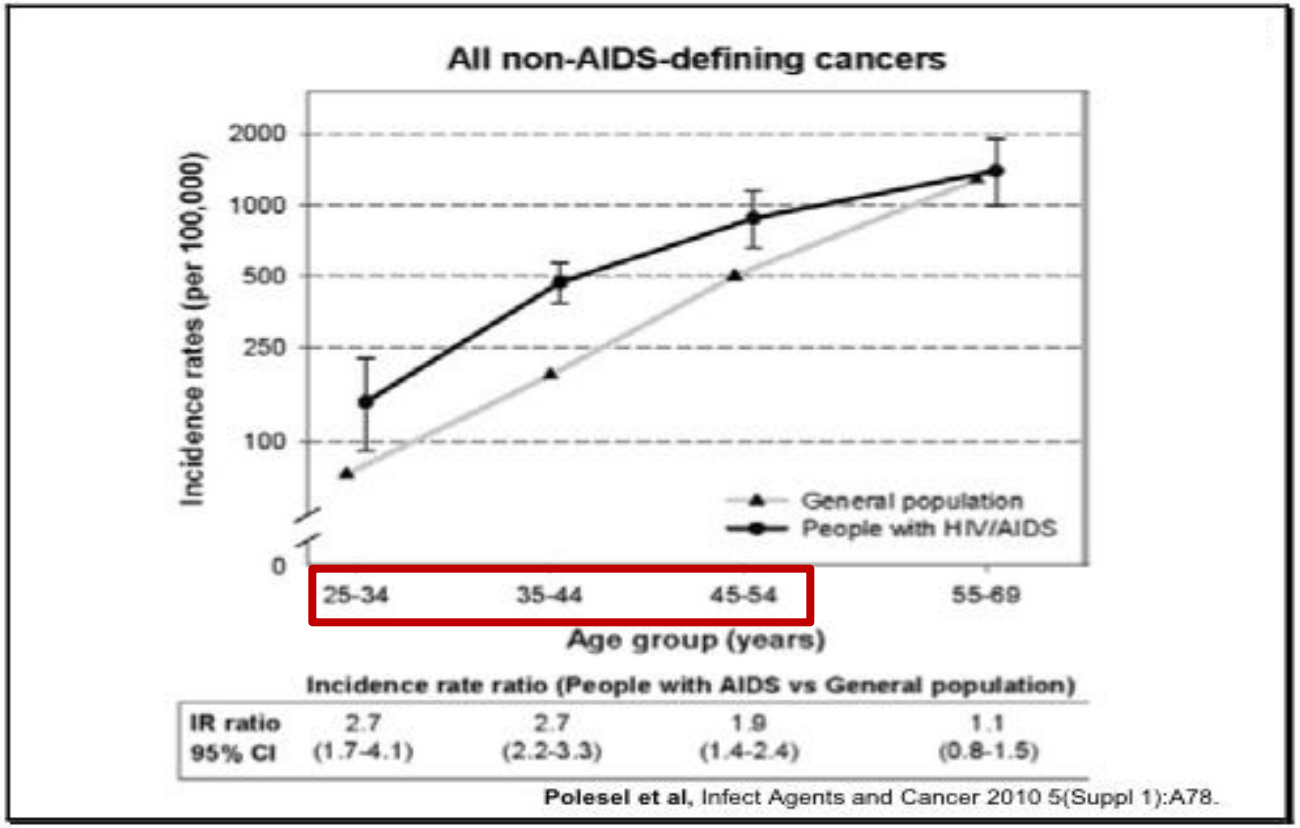


Underlying cause of death	« Mortalité 2000 » survey (n=964)	« Mortalité 2005 » survey (n=1042)	« Mortalité 2010 » survey (n=728)
AIDS	47%	36%	25%
Non AIDS defining non hepatitis related cancer	11%	17%	22%
Liver disease	13%	15%	11%
Cardiovascular	7%	8%	10%
Other	22%	24%	32%

Figure 1: Evolution of the distribution of the underlying cause of death in HIV-infected adults, 2000 (n=964), 2005 (n=1042) and 2010 (n=728)

P Morlat et al, Abstract 1130

High risk of non-AIDS-defining cancers in people with HIV/AIDS



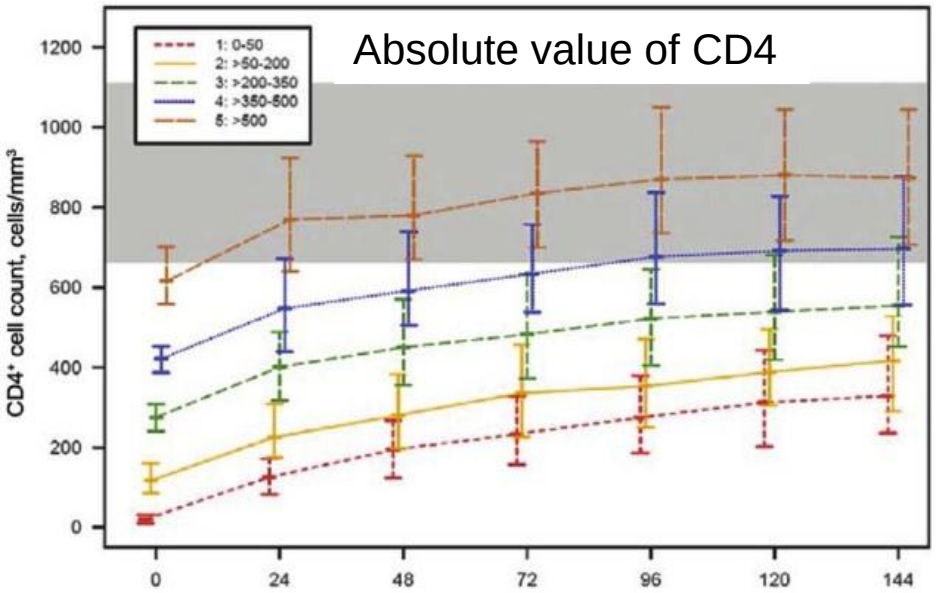
The excess of NADCs risk declined with age, peaking in HIV+ aged 25-44 years (IRs ratio: 2.7)

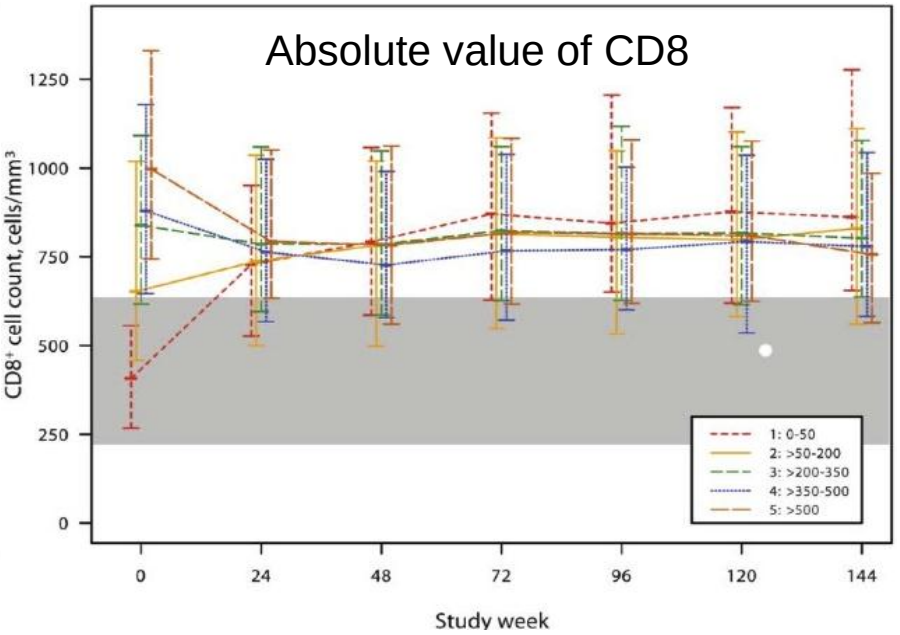
Despite effective viral suppression, **reconstitution of T cell subsets remains incomplete and chronic inflammation persists** at levels higher than in uninfected people.

Incomplete Reconstitution of T Cell Subsets on Combination Antiretroviral Therapy in the AIDS Clinical Trials Group Protocol 384

- 978 ART naive patients randomized: D4T/ddI vs ZDV/3TC + NFV or EFV or NFV+EFV
- T cell subsets performed for 623 patients (Median age: 36y (30-43)
  - naive $CD4^+$T cells, memory $CD4^+$ T cells, activated $CD4^+$ and $CD8^+$ T cells
  - at baseline, then every 24 weeks until W144
- Reference range for T cell subsets:

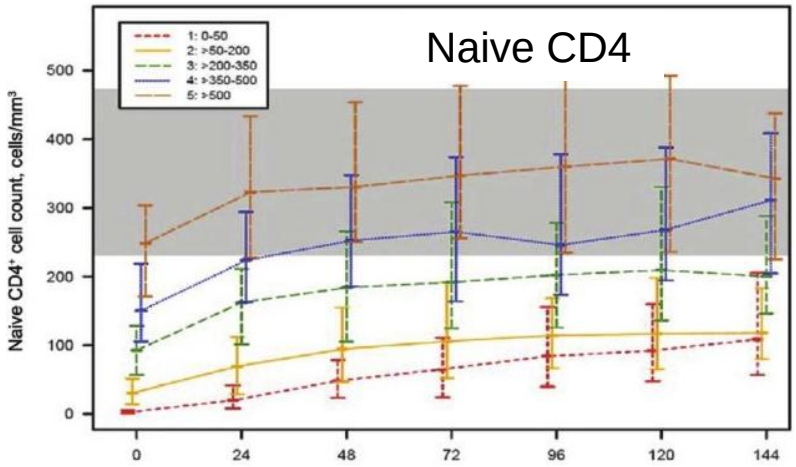
n= 48 HIV negative subjects (50% 18-30y; 50%>= 45 y)

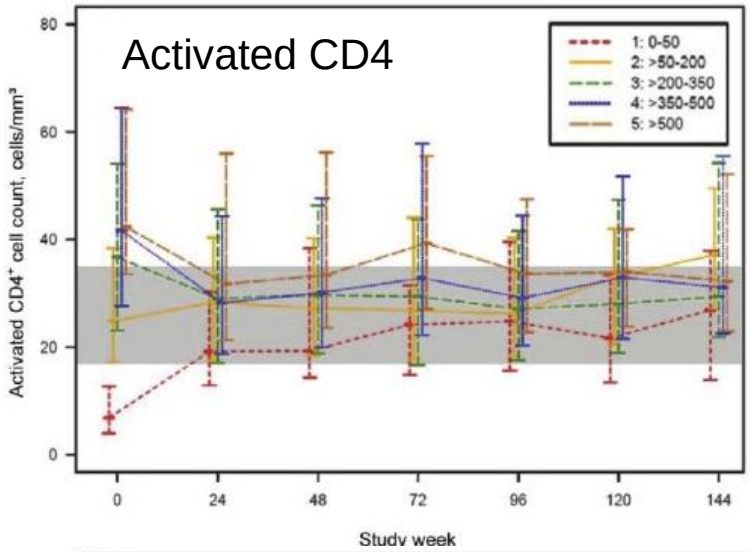


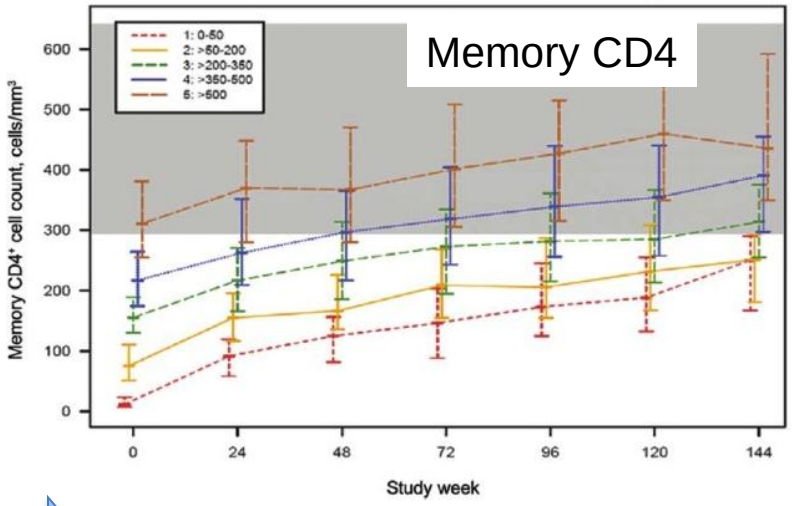


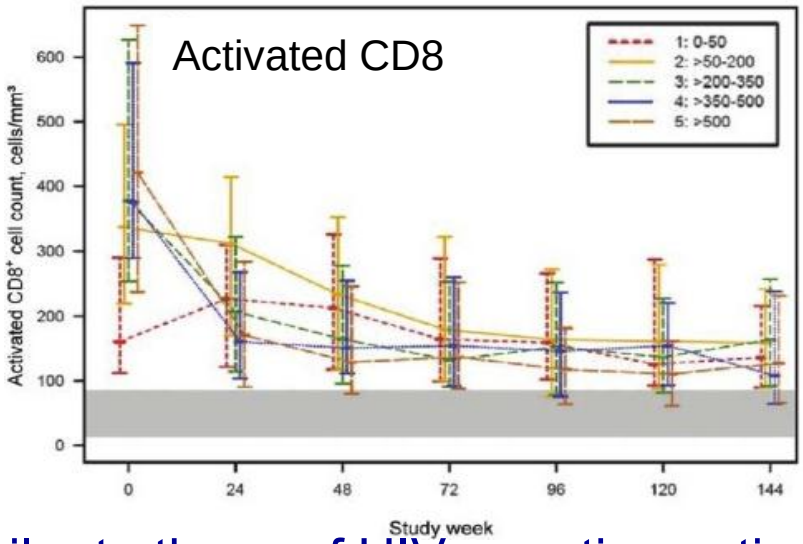
PGK Robbins et al. CID 2009;48: 350- 361

Incomplete Reconstitution of T Cell Subsets on Combination Antiretroviral Therapy in the AIDS Clinical Trials Group Protocol 384







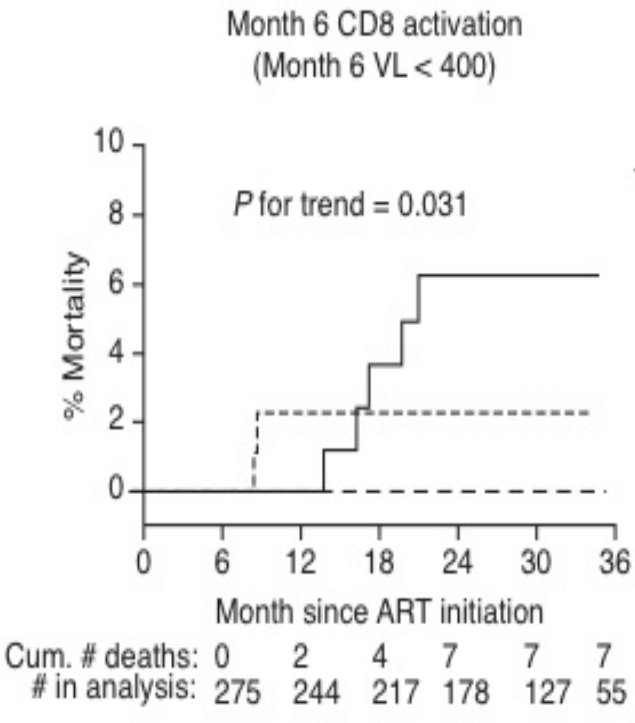


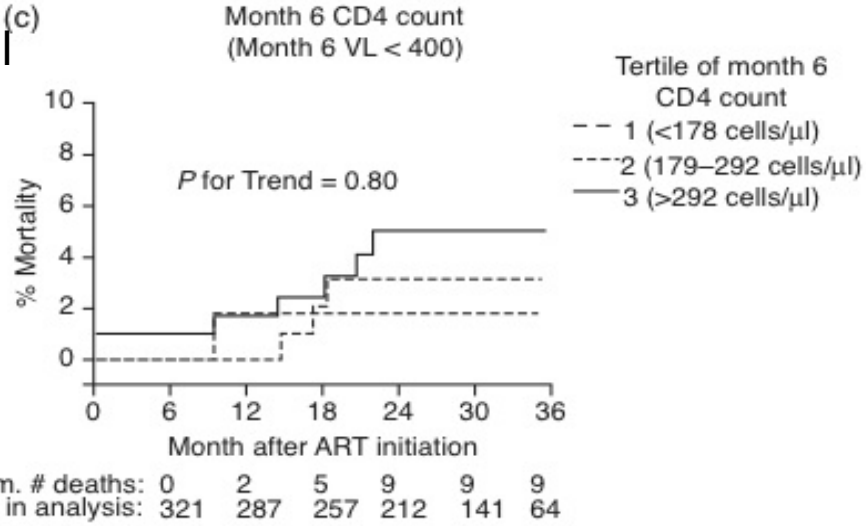
Activated CD8 did not achieve similar to those of HIV negative patients…

PGK Robbins et al. CID 2009;48: 350- 361

Impact of CD8$^+$ T-cell activation on CD4$^+$ T-cell recovery and mortality in HIV-infected Ugandans initiating antiretroviral therapy

- N= 451; 34y; CD4: 135 cells/ul;VL:5.1Log/ml
Six months: 93% VL<400 copies/ml
Median follow up: 24 months
Deaths: n= 34





- No relationship between month 6 CD4 and mortality

- Higher persistent CD8(+) T-cell activation during ART-mediated viral suppression independently predicts **increased mortality** among HIV-infected Ugandans.
- Each 5% increase in the frequency of HLA-DR+CD8+T cells was associated with a **1.3-fold increased hazard of death (p=0,022)**

P Hunt et al.AIDS 2011;25:2123-2131

Inflammatory or Coagulopathy Biomarkers Associated with Mortality in RCTs of HIV-infected Individuals

Biomarker	Odds ratios*: 1st vs 4th Quartile	Effect of HAART	Other HIV disease Associations
D-dimer	12.4 (SMART), 2.4 (FIRST) 2.6 (Phidisa)	Decreases	CVD
hs-CRP	2.0 (SMART), 2.1 (FIRST), 3.6 (Phidisa)	No decrease	CVD, OD
IL-6	8.3 (SMART), 1.8 (FIRST), 3.8 (Phidisa), 1.5** (ACTG 384 and 5015)	May decrease	CVD, OD
sCD14	6.0 (SMART)	Unknown	Microbial translocation

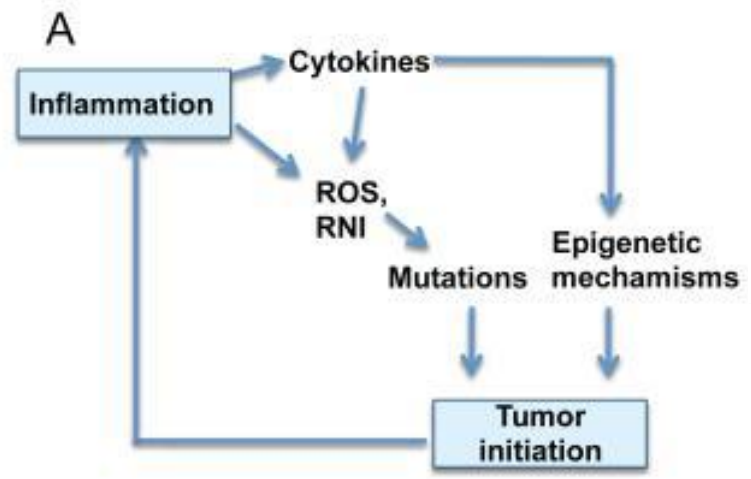
-While HAART partially reduces some biomarker levels, they may still remain elevated compared with healthy non-HIV infected individuals.

-Furthermore, inflammatory markers are more strongly associated with end organ disease and mortality than in HIV negative populations.

Adapted from Nixon and Landay, Curr Opin HIV/AIDS 2010

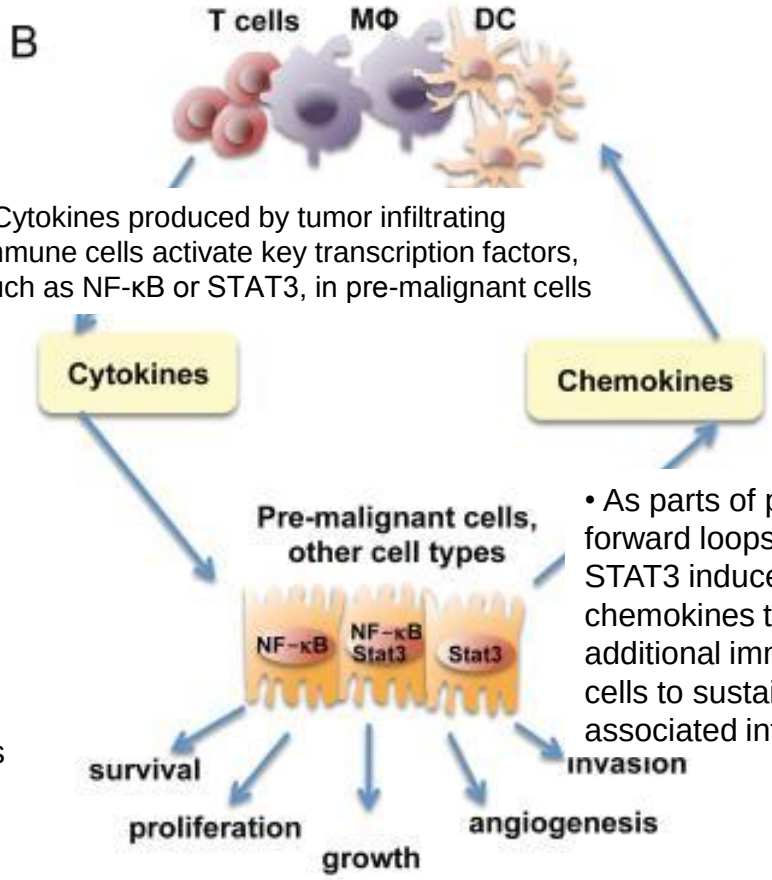
Immune activation, inflammation, and cancer !

- Inflammatory responses play decisive roles at different stages of tumor development and affects immune surveillance



- Reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) produced by inflammatory cells may cause mutations in epithelial cells.
- Cytokines produced by inflammatory cells can elevate intracellular ROS and RNI in pre-malignant cells.

In addition, inflammation can result in epigenetic changes that favor tumor initiation.



- Cytokines produced by tumor infiltrating immune cells activate key transcription factors, such as NF-κB or STAT3, in pre-malignant cells

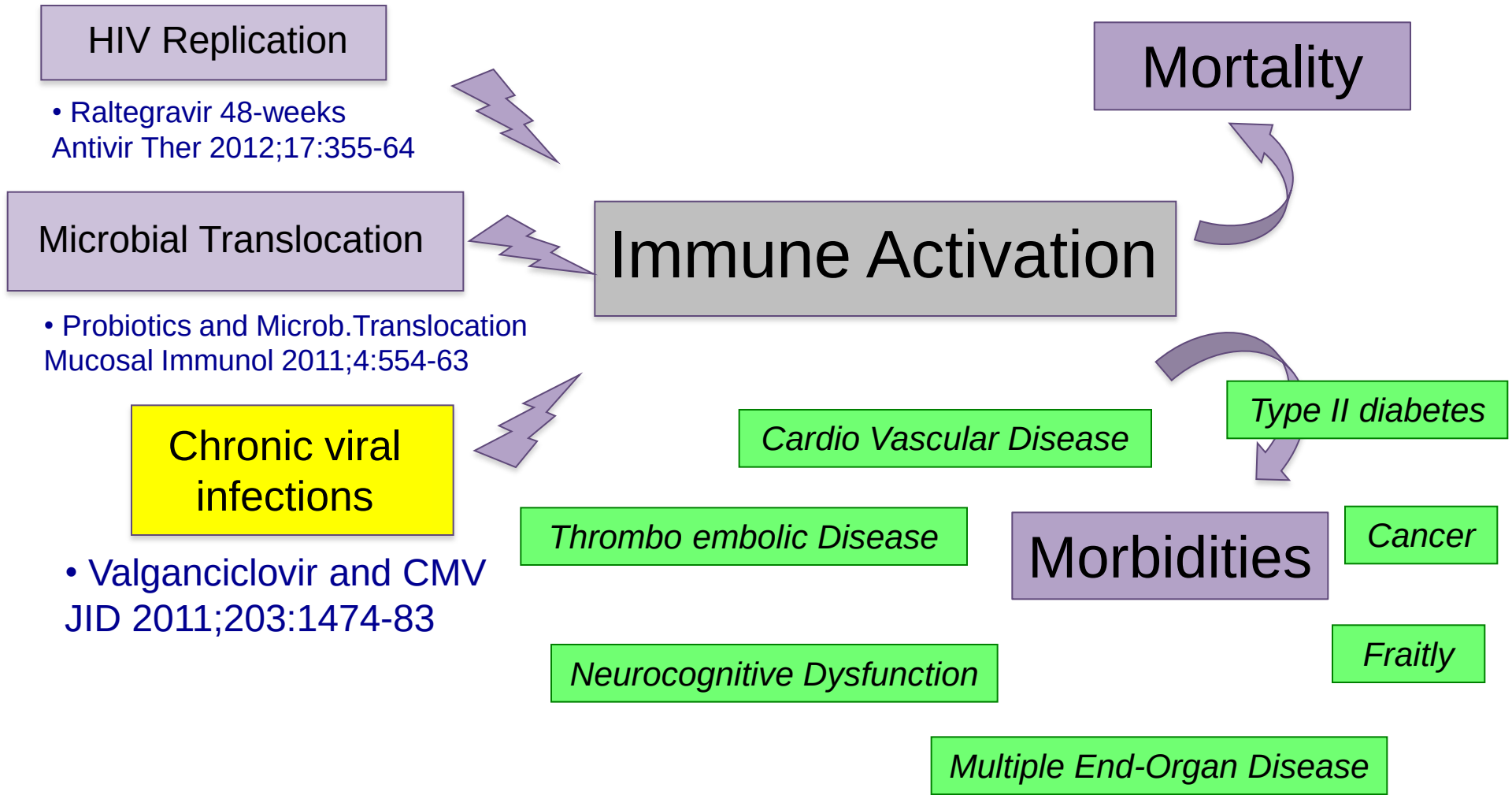
- As parts of positive feed-forward loops, NF-κB and STAT3 induce production of chemokines that attract additional immune/inflammatory cells to sustain tumor-associated inflammation.

Grivennikov NI et al.Cell 2010; 140: 883- 99

HIV and Inflammation: Mechanisms and Consequences

Peter W. Hunt

Curr HIV/AIDS Rep (2012) 9:139-147

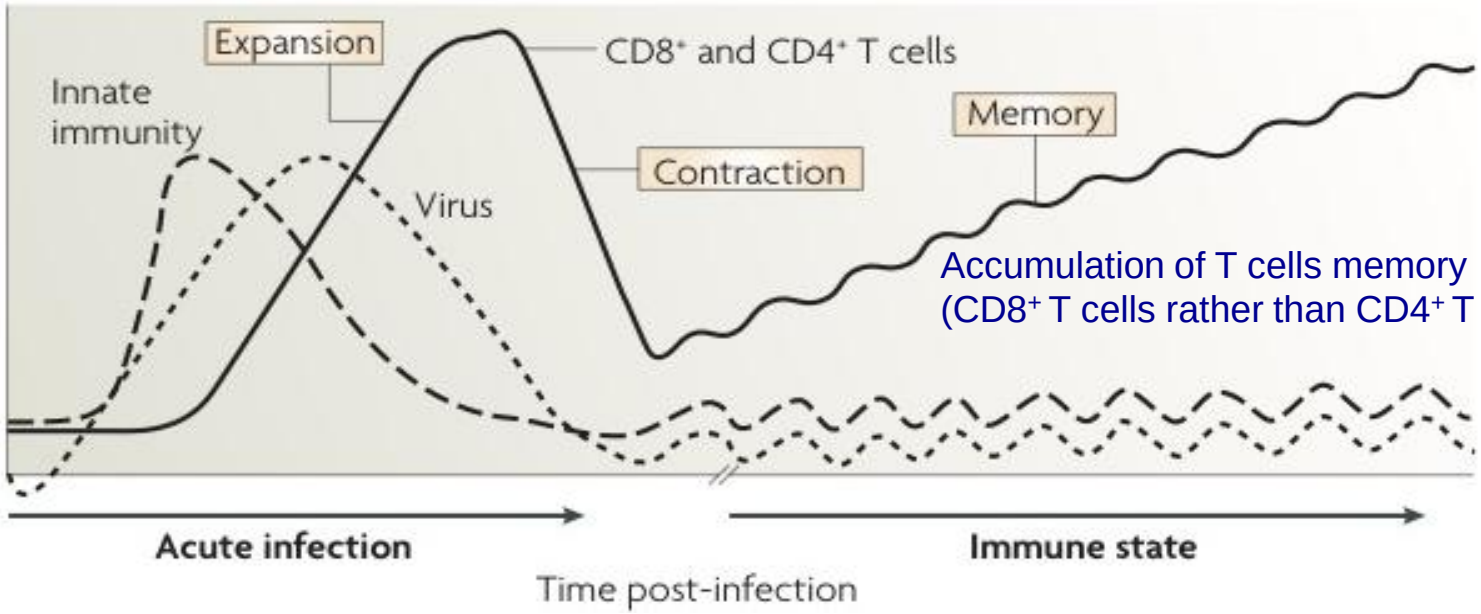


nature REVIEWS IMMUNOLOGY

Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections

J Nikolich-Zugich Nature Rev Immunol 2008; 8:512-522)

• Latent persistent pathogens (HSV, CMV) determine the extent of age associated immune deficiency ?



• During chronic infection (such as HIV, HCV) immune cells (including T cells) are constantly and systematically stimulated.**This persistent immune activation lead to a premature immunosenescence** and an exhaustion of immune resources.

V Appay et al. J Exp Gerontol 2007; 42: 432-437

Immune Senescence, Activation, and Abnormal T Cell Homeostasis despite Effective HAART, a Hallmark of Early Aging in HIV Disease

- ✓ 10 HIV-1-infected, HAART-suppressed individuals
  (median age 56 years, VL <50 copies/mL, median CD4 counts: 724 cells/mm^3)
  10 older HIV-negative subjects (median age: 88 years)
  5 HIV-negative, young controls (median age: 27 years)
- ✓ **Markers of immune senescence (CD57+CD28–)**,
  Markers of immune activation (CD38+HLA-DR+)
  Regulatory T cells (CD4+CD25hiCD127lo)

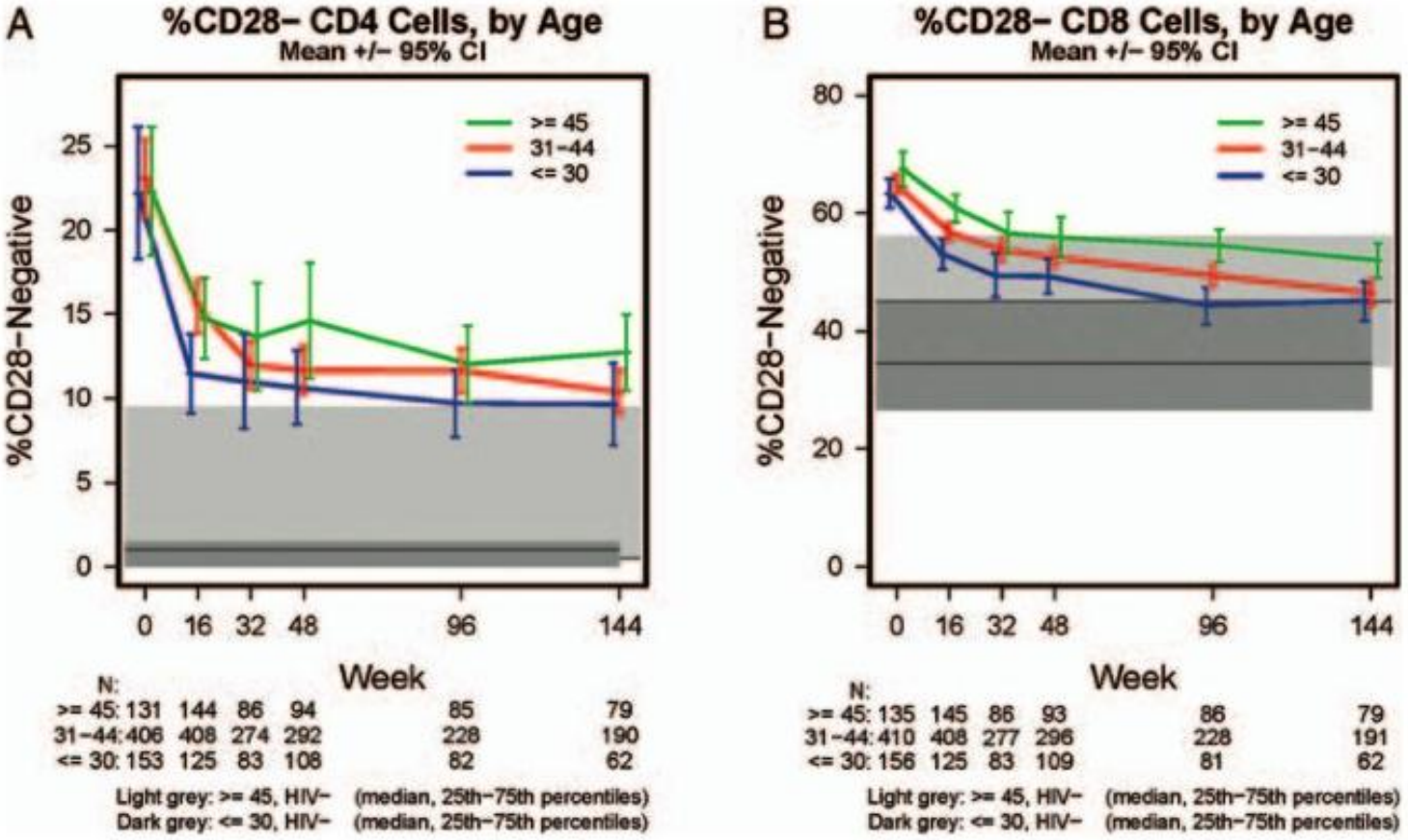
HIV-infected subjects (median 56 years) with good immune reconstitution and viral suppression had **immune changes comparable to older (median 88 years) HIV-negative subjects.**

Age-dependant changes in HIV-infected compared to young HIV-negative controls are more pronounced in CD8+ T cells, which exhibit **higher immune activation and senescence levels** and reduced naïve and central memory subsets.

S. Desai et al. CROI 2009 Abstract 381

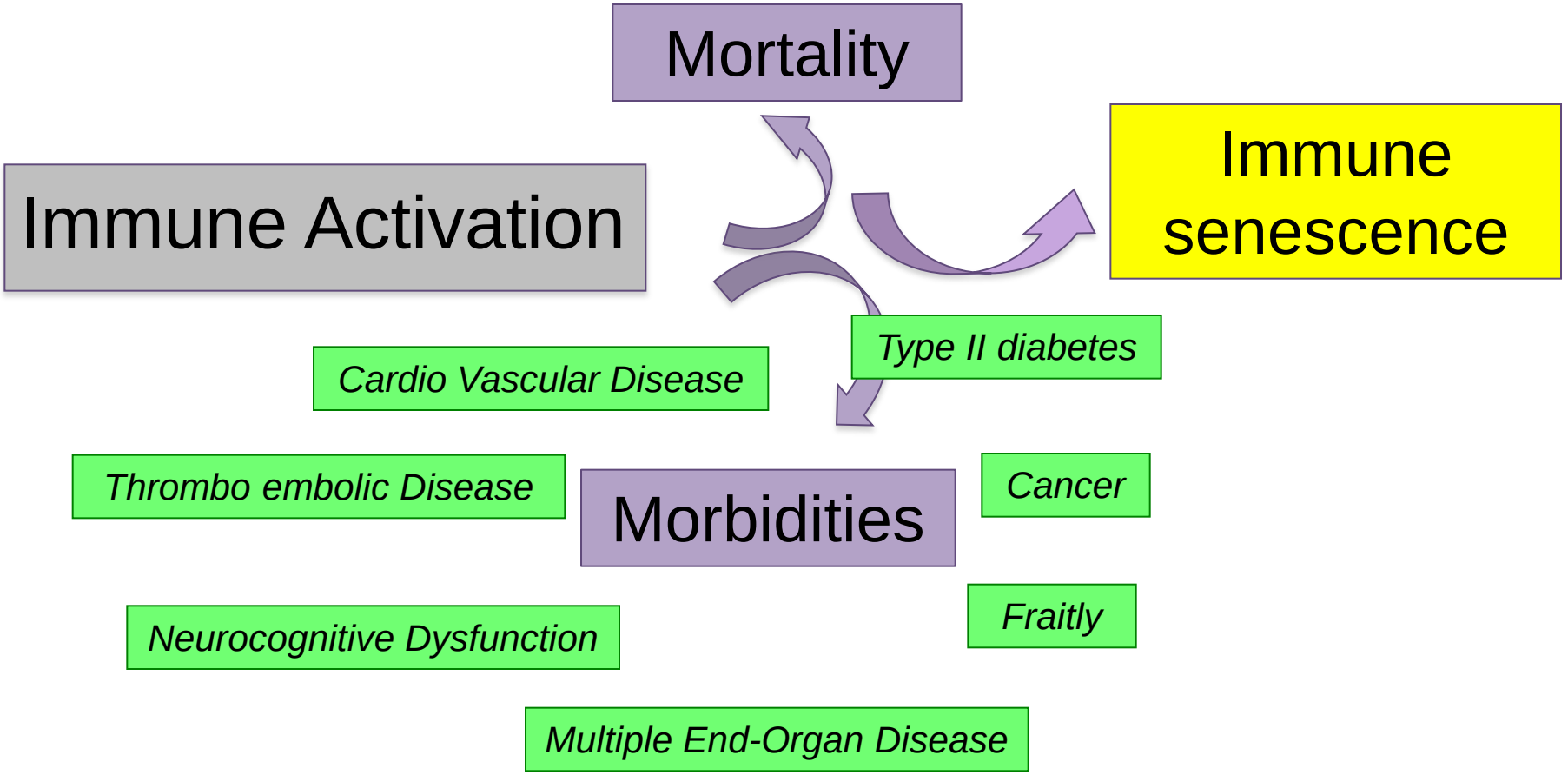
CD28-Negative $CD4^+$ and $CD8^+$ T Cells in Antiretroviral Therapy–Naive HIV-Infected Adults Enrolled in Adult Clinical Trials Group Studies

N= 1291 HIV infected treatment naive adults from 5 ACTG ART Studies and the ALLERT cohort vs 48 HIV negative adults (HIV negative control study 18-30 45-66y)



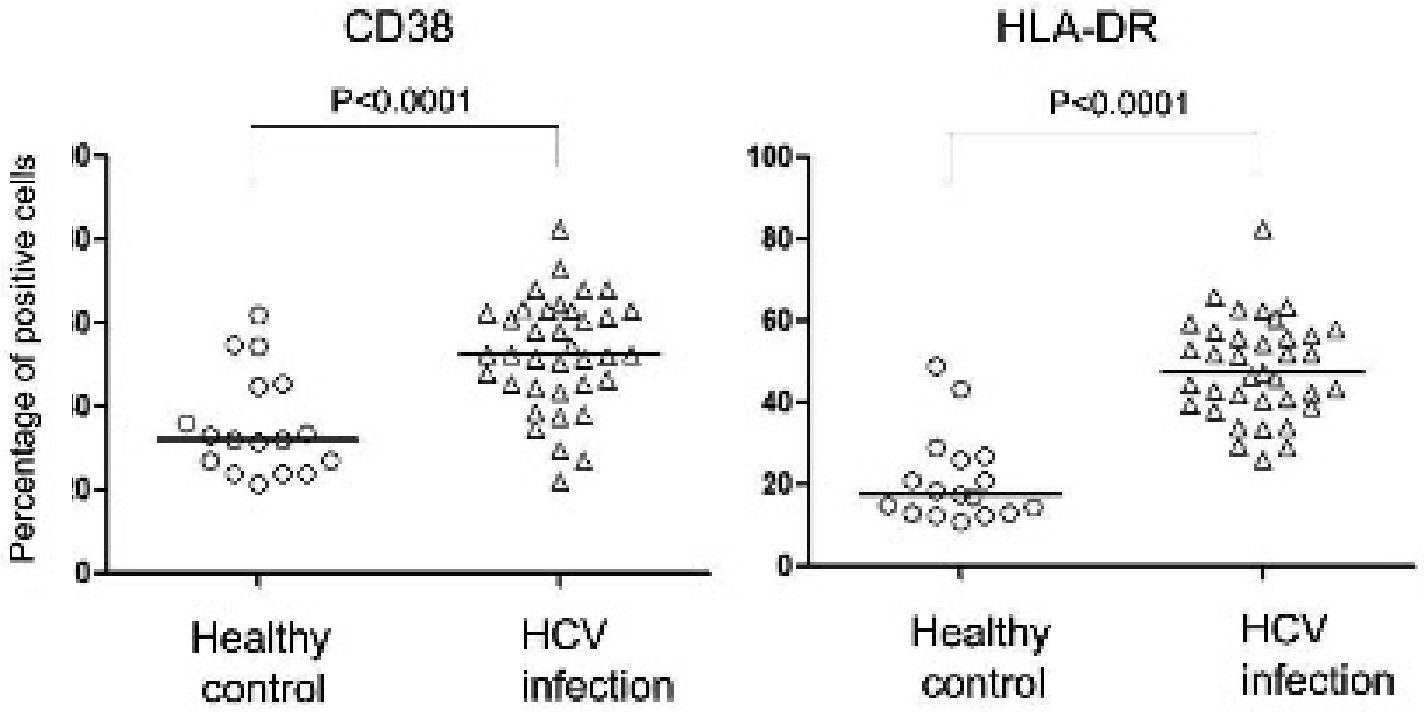
Tassiopoulos K et al JID 2012;April

HIV infection results in features characteristic of early aging of the immune system or **'immune senescence', driven by chronic antigen exposure and immune system activation.**



Chronic HCV infection induces CD8$^+$ T cell activation and impaired balance of T cell-homeostasis

- N= 37 HCV naive patients (G1/G2) vs 17 controls
- Mean age: 47 years vs 42 years



CD38, HLA-DR on total CD8+ T cells in HCV-infected patients.

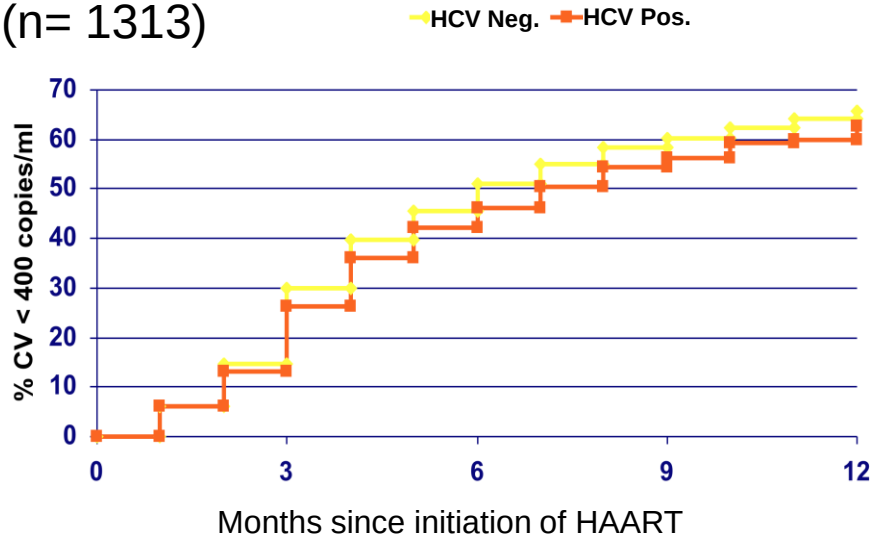
Influence of Hepatitis C Virus Infection on HIV-1 Disease Progression and Response to Highly Active Antiretroviral Therapy

- EuroSIDA Cohort

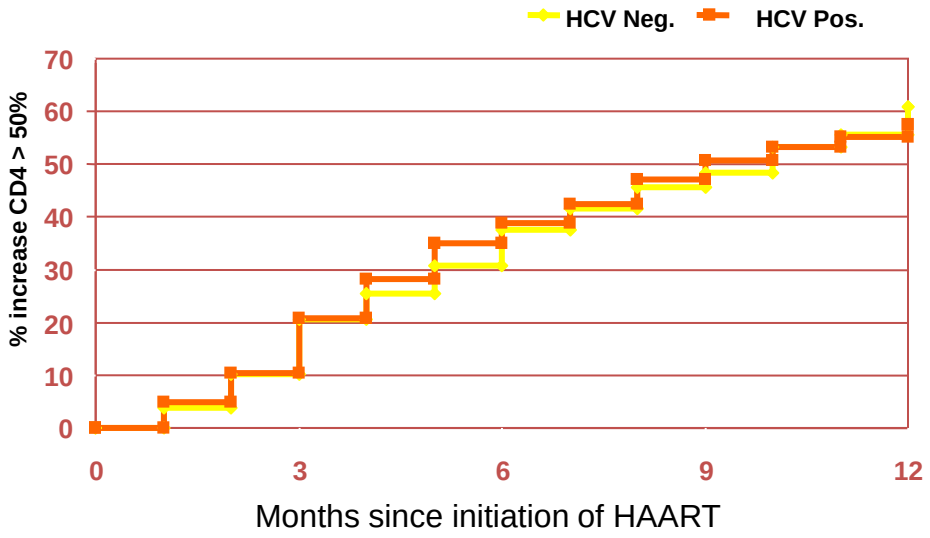
n= 5957 patients- 1960 HIV/HCV+ vs 3997 HIV+

Time to first achieve HIV-VL< 400 copies

(n= 1313)



Time to achieve >= 50 % increase in CD4 cell count (n= 1497)



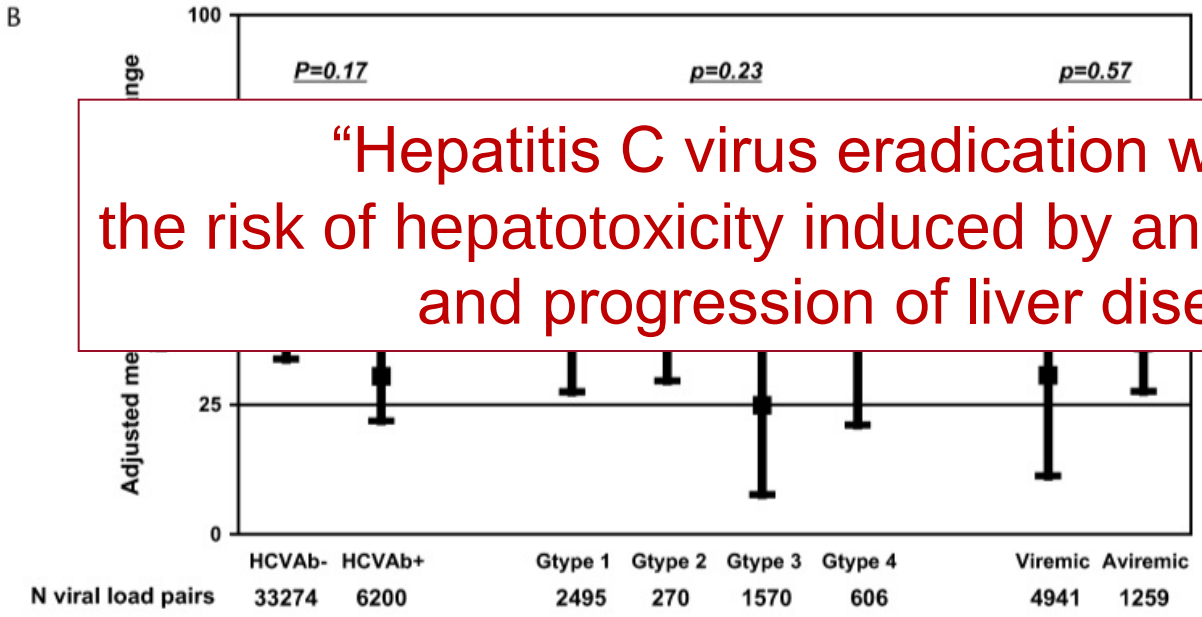
The overall virologic and immunologic responses to HAART is not affected by HCV serostatus.

Rockstroh JK et al,JID 2005;192:992-1002

Hepatitis C Virus Coinfection Does Not Influence the CD4 Cell Recovery in HIV-1–Infected Patients With Maximum Virologic Suppression

• EuroSIDA Cohort : 10 903 patients of whom 4803 with at least 2 consecutive undetectable HIV VL <50 copies/mL.
n= 4208 patients screened for HCV antibodies:
822 HIV/HCV+ and 78,8% with PCR+: G1: 51,2%- G3:31%- G4:13,6%- G2:4,2%

Annual Change in CD4 T cell count (mean/ y)	+35,5 (27,2- 43,9)	+38,3 (34,8- 41,9)	p=0,54



"Hepatitis C virus eradication will lower the risk of hepatotoxicity induced by antiretroviral drugs and progression of liver disease."

gain was
g distinct
V-RNA+
paring
HCV viremic vs. aviremic HCV-seropositive patients.

Peters L et al, J Acquir Immune Defic Syndr 2009;50:457-63

High Levels of Chronic Immune Activation in the T-Cell Compartments of Patients Coinfected with Hepatitis C Virus and Human Immunodeficiency Virus Type 1 and on Highly Active Antiretroviral Therapy Are Reverted by Alpha Interferon and Ribavirin Treatment▽

Veronica D. Gonzalez,[1] Karolin Falconer,[2] Kim G. Blom,[1] Olle Reichard,[2] Birgitte Mørn,[3] Alex Lund Laursen,[4] Nina Weis,[5,6] Annette Alaeus,[2] and Johan K. Sandberg[1]*

JOURNAL OF VIROLOGY, Nov. 2009, p. 11407–1141 Vol. 83, No. 21

Characteristic	Value for group[a]			
	HCV/HIV-1 coinfected	HCV monoinfected	HIV monoinfected	Healthy control
Subjects (*n*)	14	11	9	21
Sex [no. of patients (%)]				
Female	3 (21)	5 (50)	2 (22)	9 (43)
Male	11 (79)	6 (50)	7 (78)	12 (57)
Age (yr) (range)	43 (21–53)	52 (43–59)	46 (29–67)	45 (32–59)
CD4 absolute median (cells/μl) (range)	499 (250–1370)	729 (200–1746)	605 (370–720)	845 (441–1491)
CD4 median % (range)	27 (12–45)	44 (38–57)	30 (21–41)	46 (31–67)
CD8 absolute median (cells/μl) (range)	910 (530–2440)	666 (352–754)	770 (520–1770)	443 (195–776)
CD8 median % (range)	50 (24–70)	26 (15–39)	46 (24–64)	NA
HCV genotype [no. of patients (%)]				
1	10 (72)	2 (18)	NA	NA
2	2 (14)	4 (36)	NA	NA
3	2 (14)	5 (46)	NA	NA
Serum HCV RNA median (IU/ml) (range)	3.64×10^6 (0.068×10^6–20.0×10^6)	0.57×10^6 (0.023×10^6–3.65×10^6)	NA	NA

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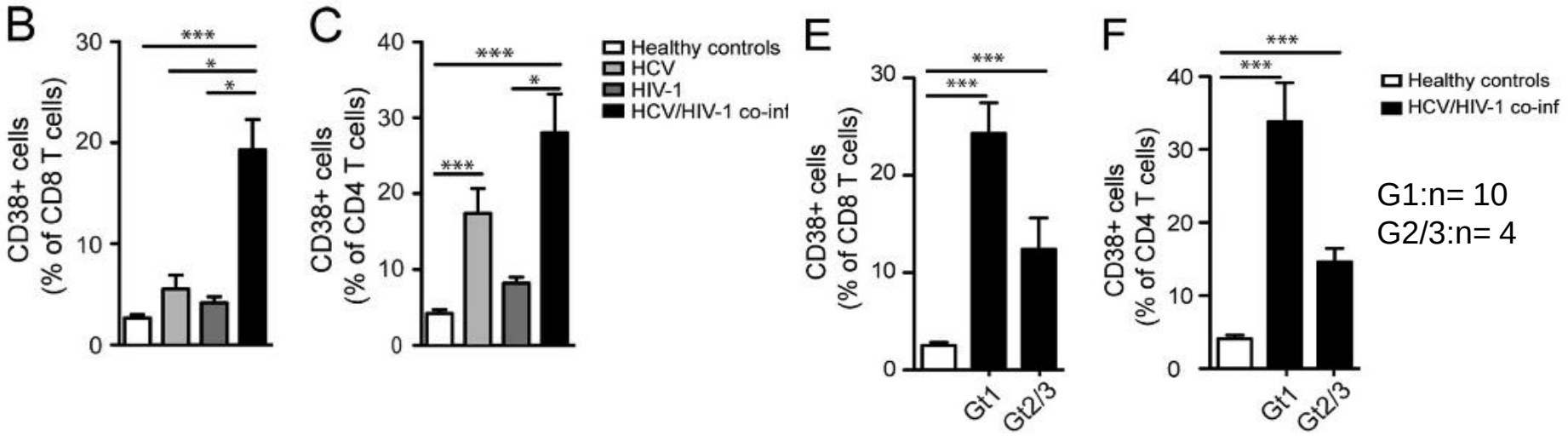

- HCV/HIV-1-coinfected patients have high levels of CD8 and CD4-T cell immune activation despite effective HAART –mediated suppression of HIV. This immune activation was higher than in mono infected HIV or HCV subjects and healthy controls
- CD38 expression in CD8 T cells and CD4 T cells tended to be more pronounced in HCV genotype 1 infection than genotype 2 or 3 infections (pNS)

High Levels of Chronic Immune Activation in the T-Cell Compartments of Patients Coinfected with Hepatitis C Virus and Human Immunodeficiency Virus Type 1 and on Highly Active Antiretroviral Therapy Are Reverted by Alpha Interferon and Ribavirin Treatment▽

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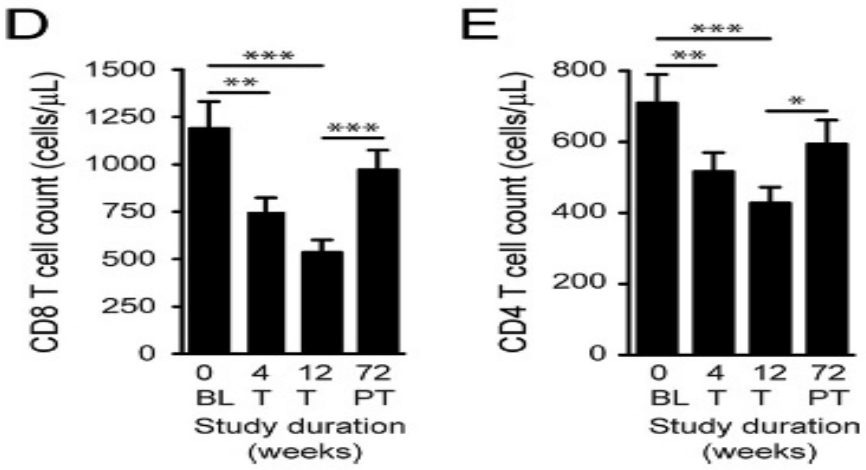
Significant reduction in CD38+CD4+ and CD38+CD8+T cell during PegIFN/Rbv treatment



Decrease in CD4 and CD8 T cell count during PegIFN/Rbv with a return to a normal condition at the end of treatment

Sustained virological response to interferon-α plus ribavirin decreases inflammation and endothelial dysfunction markers in HIV/HCV co-infected patients

María Guzmán-Fulgencio[1], Juan Berenguer[2], Isabel Fernandez de Castro[1], Dariela Micheloud[1,3], Juan Carlos López[2], Jaime Cosín[2], Pilar Miralles[2], Raquel Lorente[4], Teresa Aldamiz-Echevarría[3], M. Ángeles Muñoz-Fernández[4,5] and Salvador Resino[1]*

J Antimicrob Chemother 2011; **66**: 645–649

- N= 69 HCV/HIV coinfected patients on interferon (IFN)-α plus ribavirin

✓TNF-R1, sE-selectin, P-selectin, sICAM-1, sVCAM-1

	HIV patients (n=47), control group	HIV/HCV patients (n=69), IFN-α naive	P^a
CD4+ (cells/mm^3)	811 (659–1043)	440 (336–510)	<0.001
sTNF-R1 (ng/mL)	1.03 (0.5–4.2)	1.96 (1.5–2.6)	<0.001
sP-selectin (ng/mL)	1570 (792–3177)	1444 (1145–1915)	0.144
sE-selectin (ng/mL)	118 (24–280)	223 (150–288)	<0.001
sICAM-1 (ng/mL)	779 (207–3133)	1284 (1012–1722)	<0.001
sVCAM-1 (ng/mL)	1425 (417–2593)	1420 (1188–1644)	0.829

a: HIV vs HIV-HCV

HIV/HCV co-infected patients had higher values of soluble TNF-R1 (sTNF-R1), sE-selectin and sICAM-1 than HIV mono-infected patients ($p < 0.05$).

Guzman-Fulgencio M,J Antimicrob Chemother 2011;66:645-9

	HIV/HCV patients on HCV antiviral therapy								
	NR group ($n=34$)				SVR group ($n=35$)				
	baseline	W72	P^b	P^c	baseline	W72	P^b	P^c	P^d
CD4+ (cells/mm^3)	404 (283–469)	345 (283–444)	0.119	<0.001	460 (374–527)	450 (345–544)	0.260	<0.001	0.056
sTNF-R1 (ng/mL)	2.1 (0.6–4.5)	2.2 (1.1–4.5)	0.035	<0.001	1.8 (0.8–4.4)	1.5 (0.7–3.6)	0.065	0.001	0.003
sP-selectin (ng/mL)	1403 (365–3097)	1539 (314–2278)	0.837	0.255	1456 (819–3317)	1351 (504–2263)	0.013	0.005	0.126
sE-selectin (ng/mL)	220 (111–475)	211 (117–760)	0.739	<0.001	228 (57.6–515)	173 (7.03–501)	<0.001	0.001	0.011
sICAM-1 (ng/mL)	1255 (254–3694)	1223 (563–3167)	0.651	<0.001	1289 (667–3167)	1077 (318–2346)	<0.001	0.050	0.082
sVCAM-1 (ng/mL)	1407 (1130–1652)	1598 (1445–1691)	0.013	0.033	1445 (1231–1571)	1354 (1081–1569)	0.555	0.423	0.004

b= baseline vs w72;c: W72 and HIV; d:NR and SVR at W72

✓ SVR patients had **a decrease in sTNF-R1, sP-selectin, sE-selectin and sICAM-1** during anti-HCV treatment ($P<0.05$) and, at the end of treatment, **SVR patients had lower values** of sTNF-R1, sE-selectin and sVCAM-1 **than non-responder patients** ($P<0.05$), **although the values of sTNF-R1, sP-selectin, sE-selectin and sICAM-1 remained higher than in HIV mono-infected patients ($P<0.05$).**

- Chronic hepatitis C infection induces alterations of markers of inflammation and endothelial dysfunction.
- Eradication of HCV, following IFN-α and ribavirin therapy, reduces immune activation as well as markers of inflammation and endothelial dysfunction

Guzman-Fulgencio M,J Antimicrob Chemother 2011;66:645-9

HIV/Hepatitis C Virus Coinfection (Last updated March 27, 2012; last reviewed March 27, 2012)

Treating Both HIV and Hepatitis C Virus Infection

Concurrent treatment of HIV and HCV is feasible but may be complicated by high pill burden, drug interactions, and overlapping drug toxicities. In this context, the decision to treat chronic HCV should also include consideration of the medical need for such treatment on the basis of an assessment of HCV disease stage. Some clinicians may choose to defer HCV therapy in HIV/HCV-coinfected patients with no or minimal liver fibrosis. If treatment with PegIFN/RBV alone or in combination with one of the HCV NS3/4A PIs (boceprevir or telaprevir) is initiated, the ART regimen may need to be modified to reduce the potential for drug interactions and/or toxicities that may develop during the period of concurrent HIV and HCV treatment.

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Improving the Management of HIV Disease®

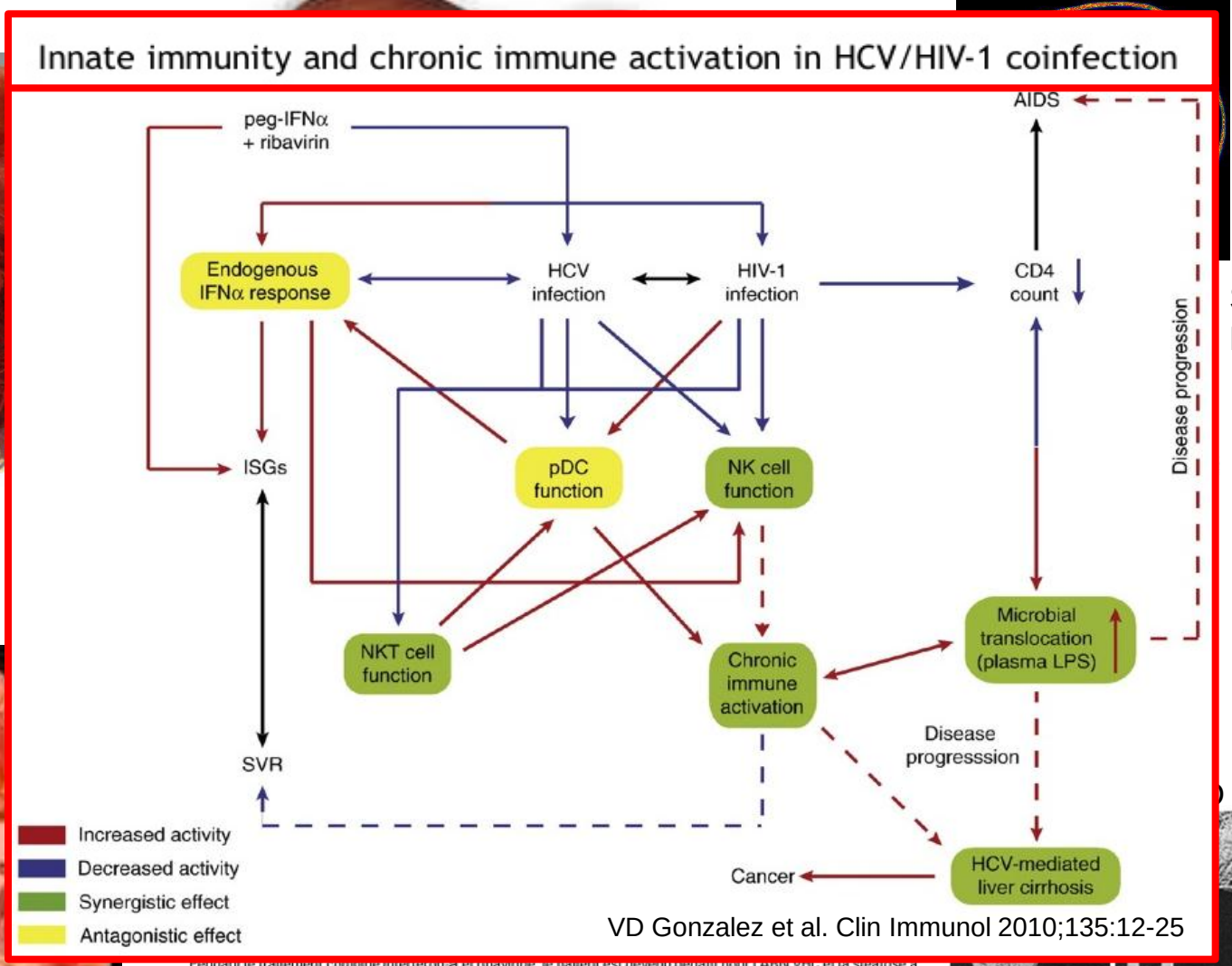
20TH Annual Advanced CME Course in HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

IAS–USA March 30, 2012
International Antiviral Society–USA

An HCV-HIV Coinfected patient ...

Tbles Neuro- Cognitifs

Syndrome Métabolique



VD Gonzalez et al. Clin Immunol 2010;135:12-25

Much more than a simple liver'story!!