

Motivazione e criteri di trattamento della coinfezione HCV nel paziente HIV-detenuto

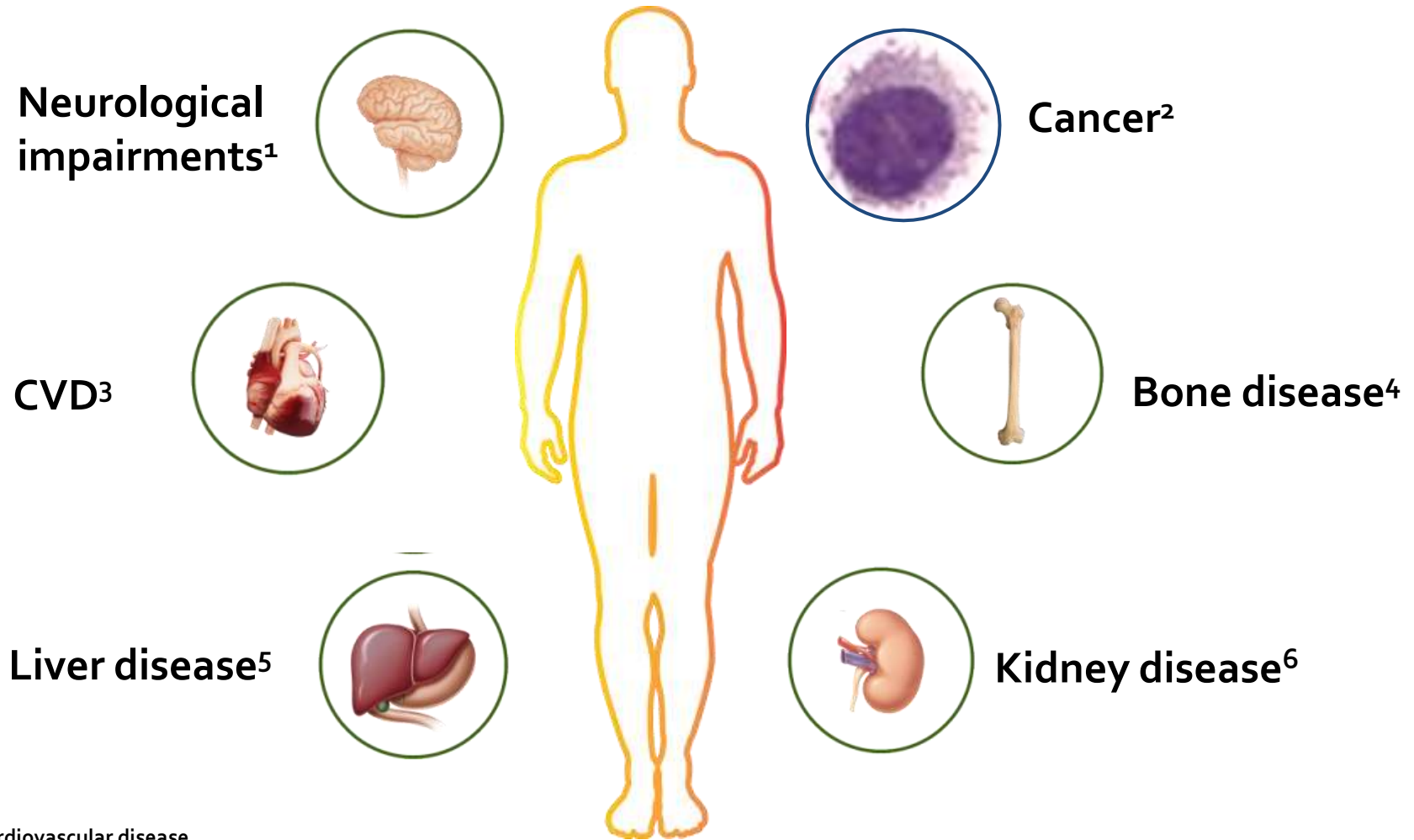
Roma 16 settembre 2016



Massimo Andreoni
Cattedra di Malattie Infettive



HIV infection can have long-term effects on numerous aspects of health

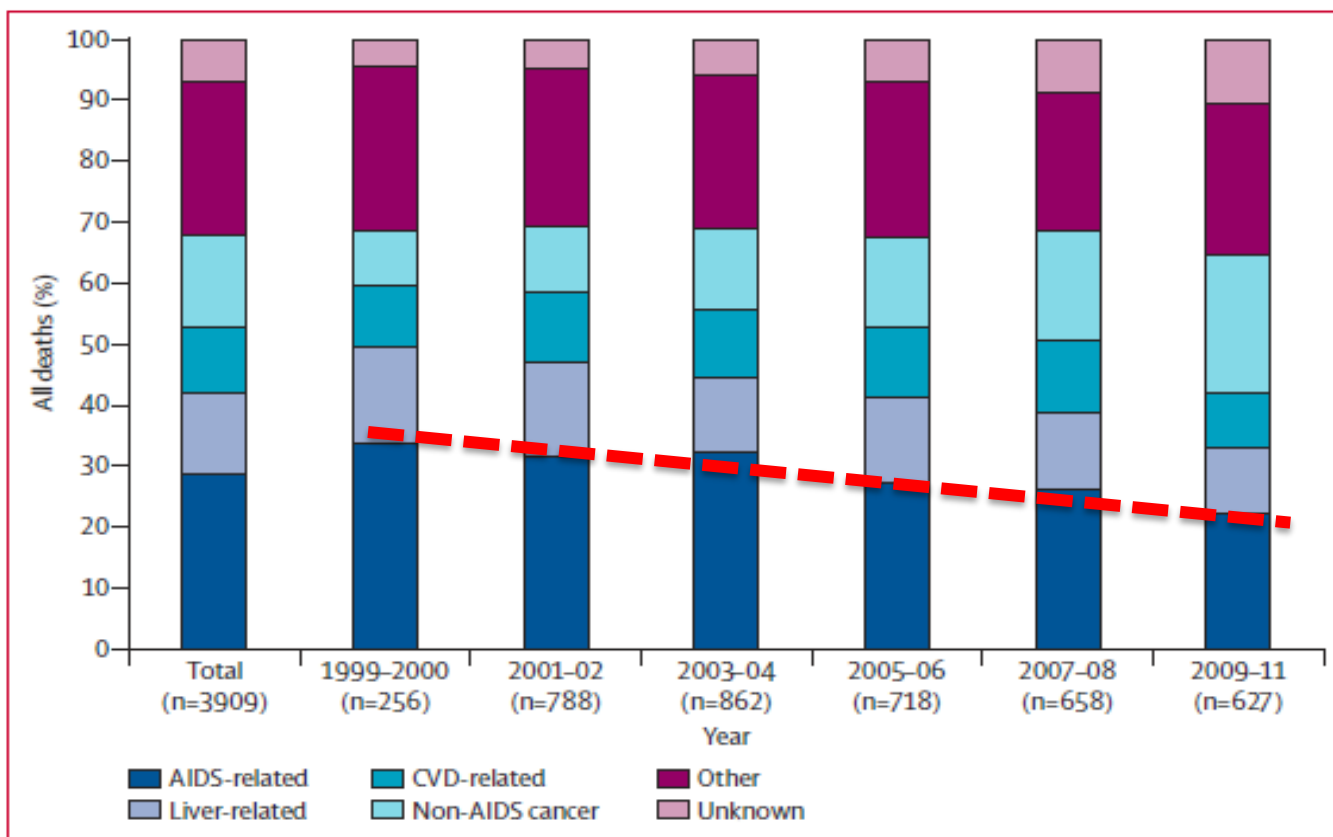


1. McArthur JC et al. Ann Neurol 2010;67:699–714; 2. Nguyen ML et al. 18th IAC. Vienna, Austria 2010. Abstract WEAB0105;
3. Freiberg MS et al. JAMA Intern Med 2013;173:614–622; 4. Brown TT et al. AIDS 2006;20:2165–2174;
5. Towner WJ et al. JAIDS 2012;60:321–327; 6. Lucas GM et al. Clin Infect Dis 2014;59:e96–e138

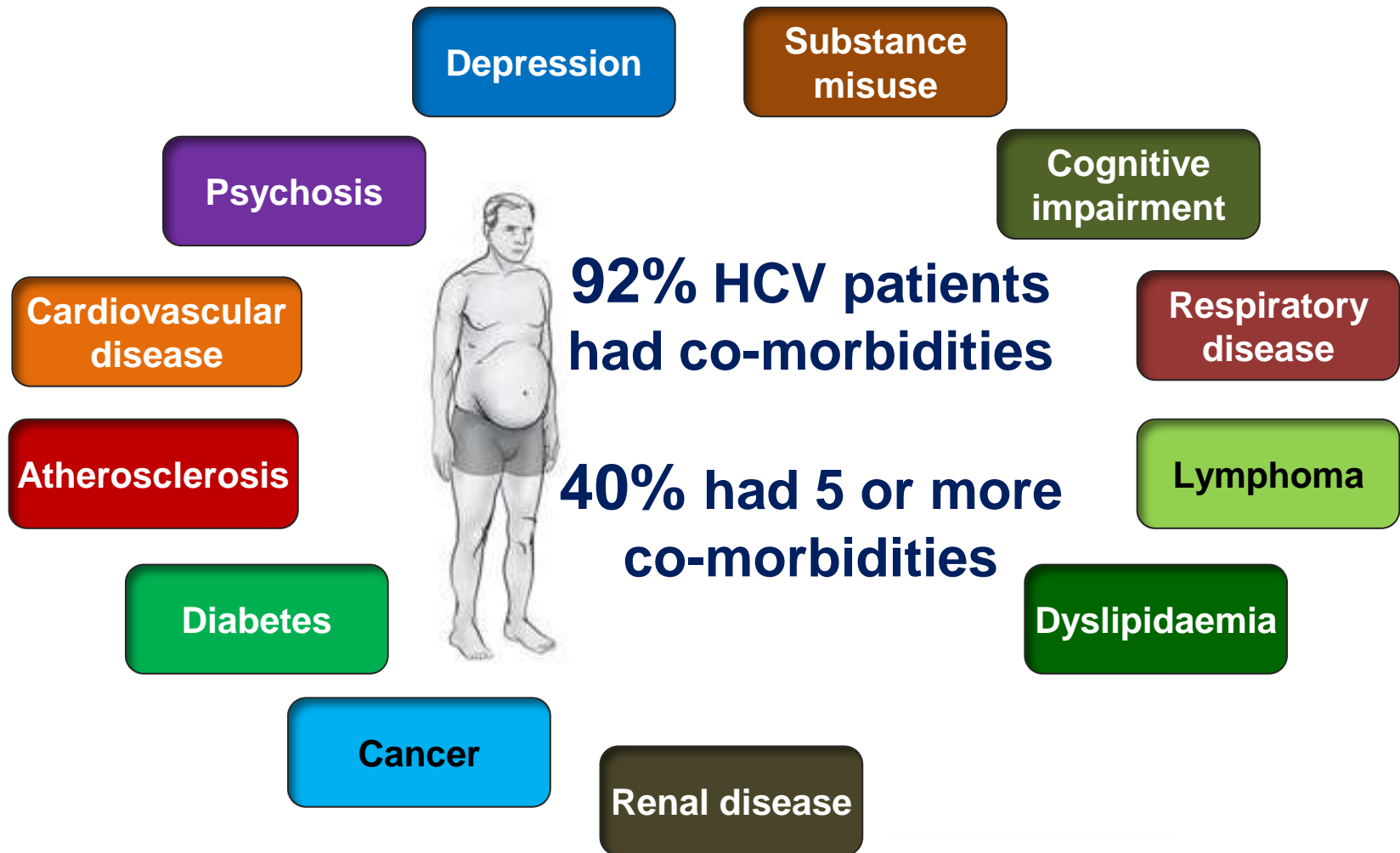
Causes of deaths in HIV patients between 1999 and 2011 (D:A:D study)

- 3,909 of the 49,731 D:A:D study participants died during the 308,719 person-years of follow-up (crude incidence mortality rate, 12.7 per 1,000 person-years [95% CI 12.3–13.1]) From March 1999 to February 2011

Most common causes of death in people with HIV



Co-morbidities in HCV patients are relevant – bringing potential for competing risks

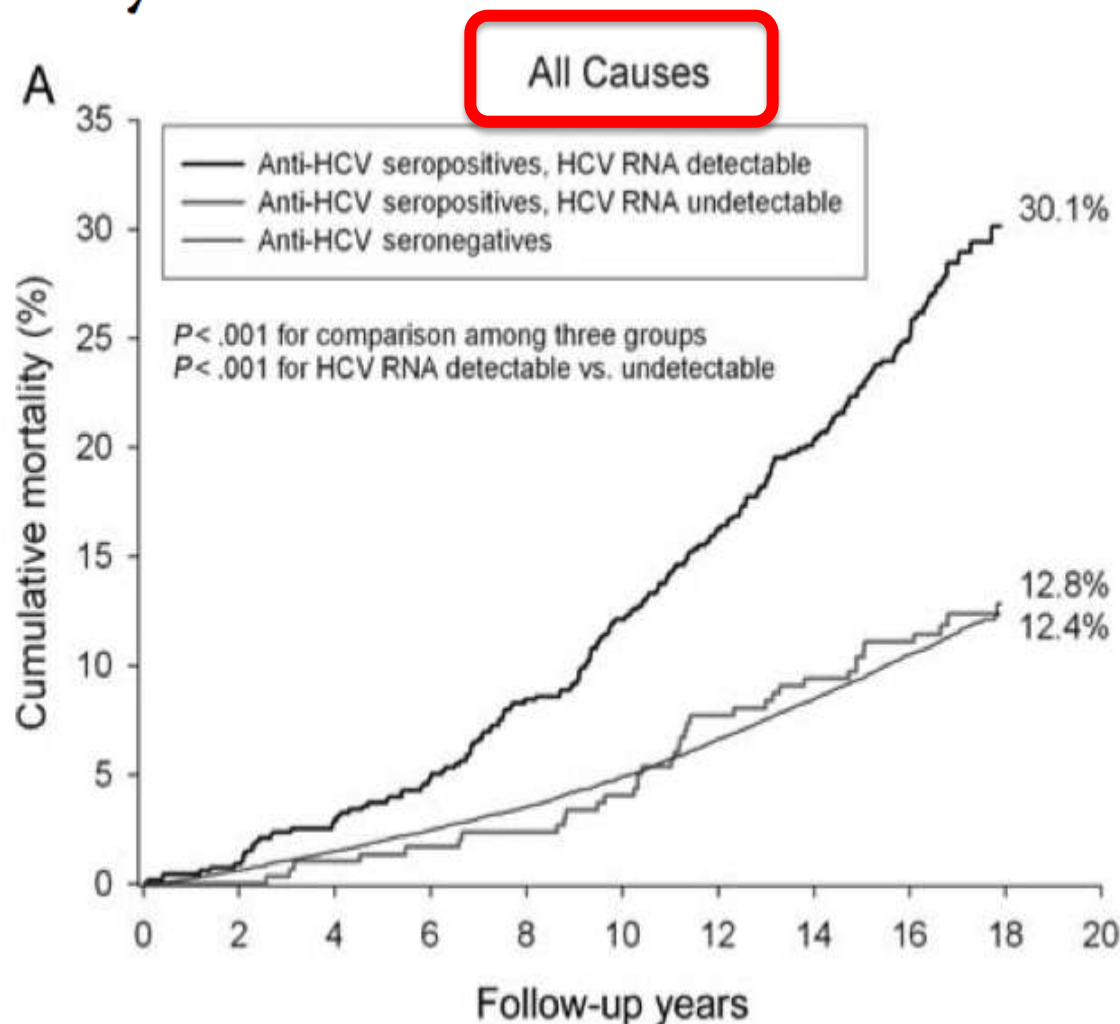




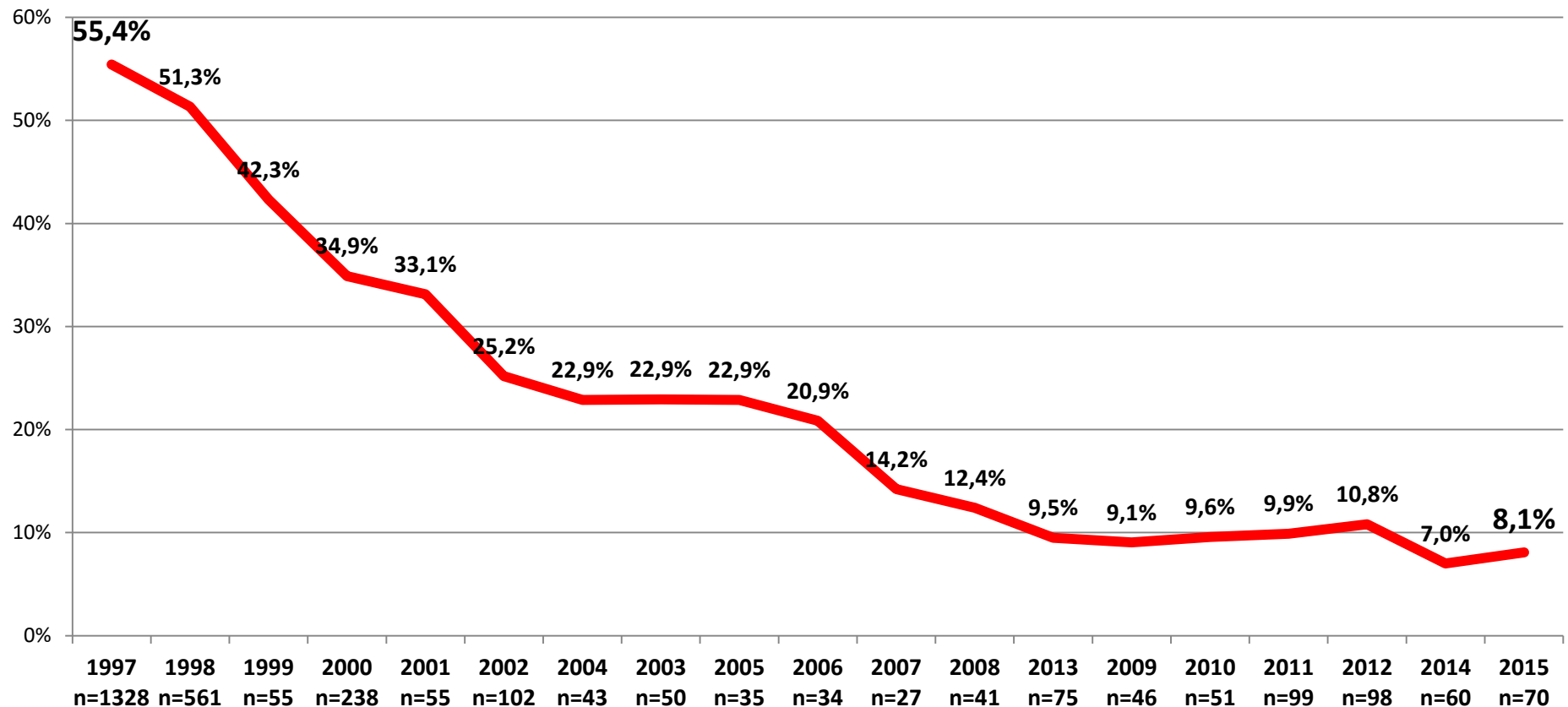
Chronic Hepatitis C Virus Infection Increases Mortality From Hepatic and Extrahepatic Diseases: A Community-Based Long-Term Prospective Study

Taiwan: 23.820 adults aged 30-65 years old enrolled during 1991-92

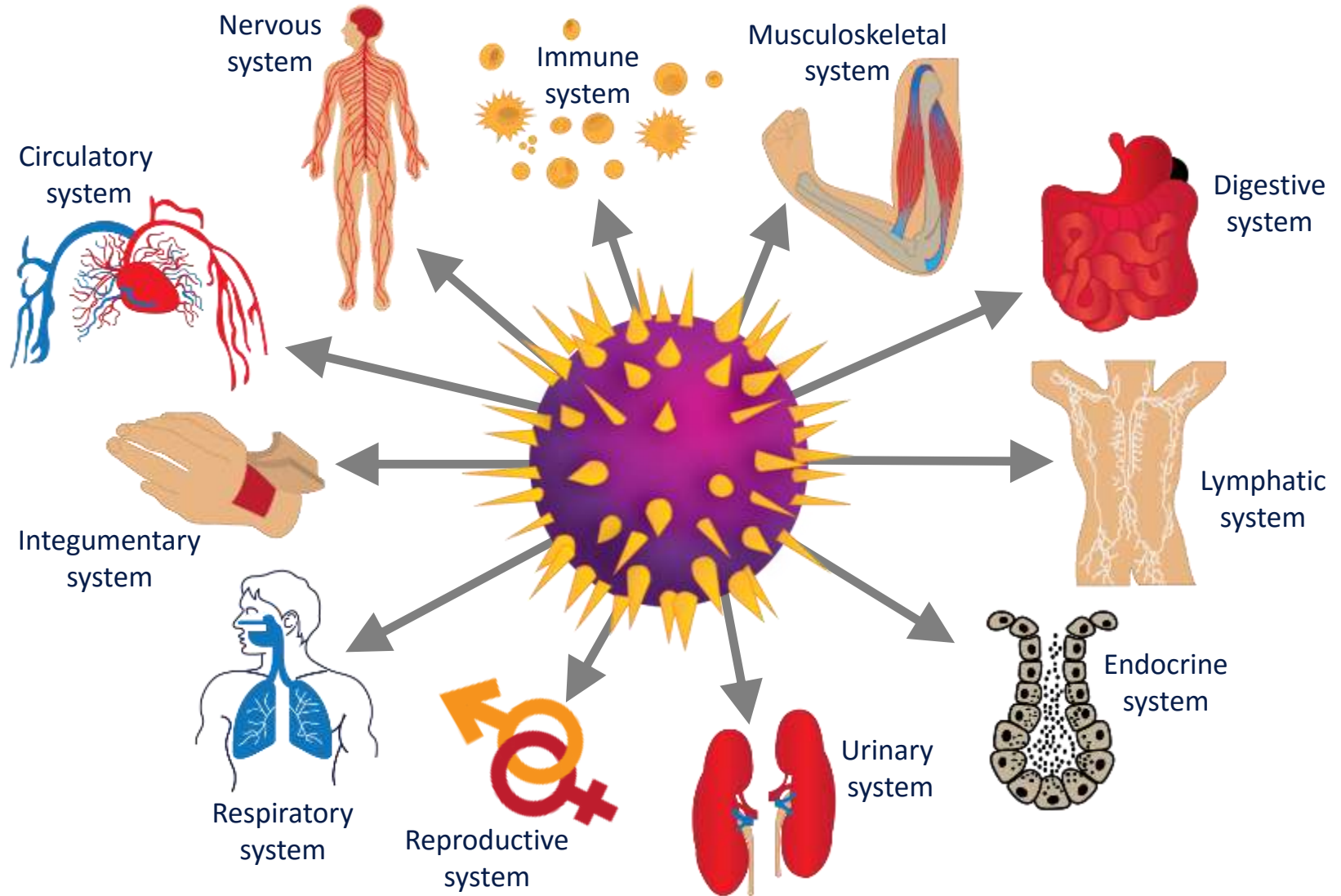
**19.636 HBsAg-neg,
18.541 anti-HCV-neg
1.095 anti- HCV-pos
(69,4% had detectable
HCV-RNA).**



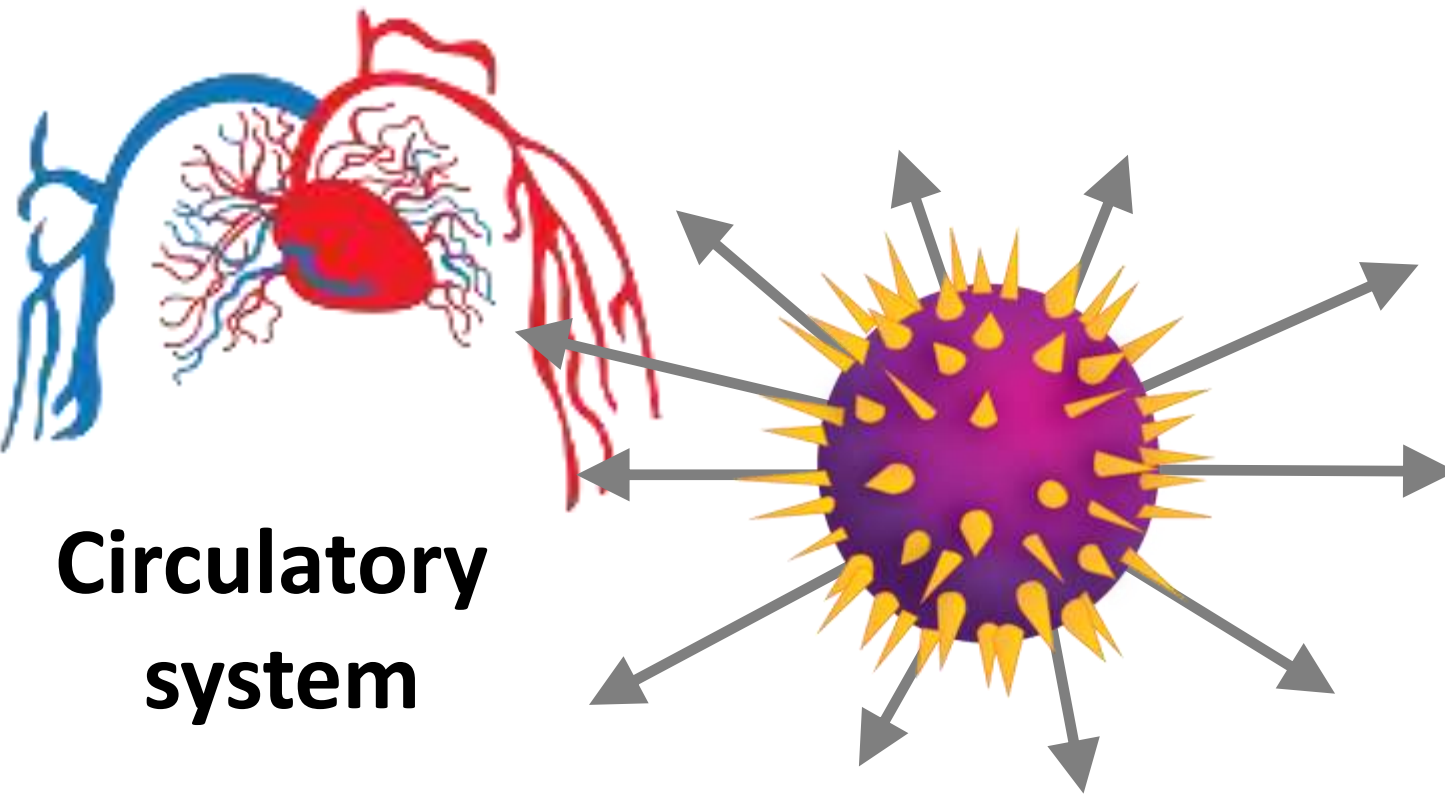
Proportion of patients with an HCVAb positive test within 1 year from enrolment, according to calendar year of enrolment



HIV and HCV are two Systemic Diseases Affecting Multiple Body Systems

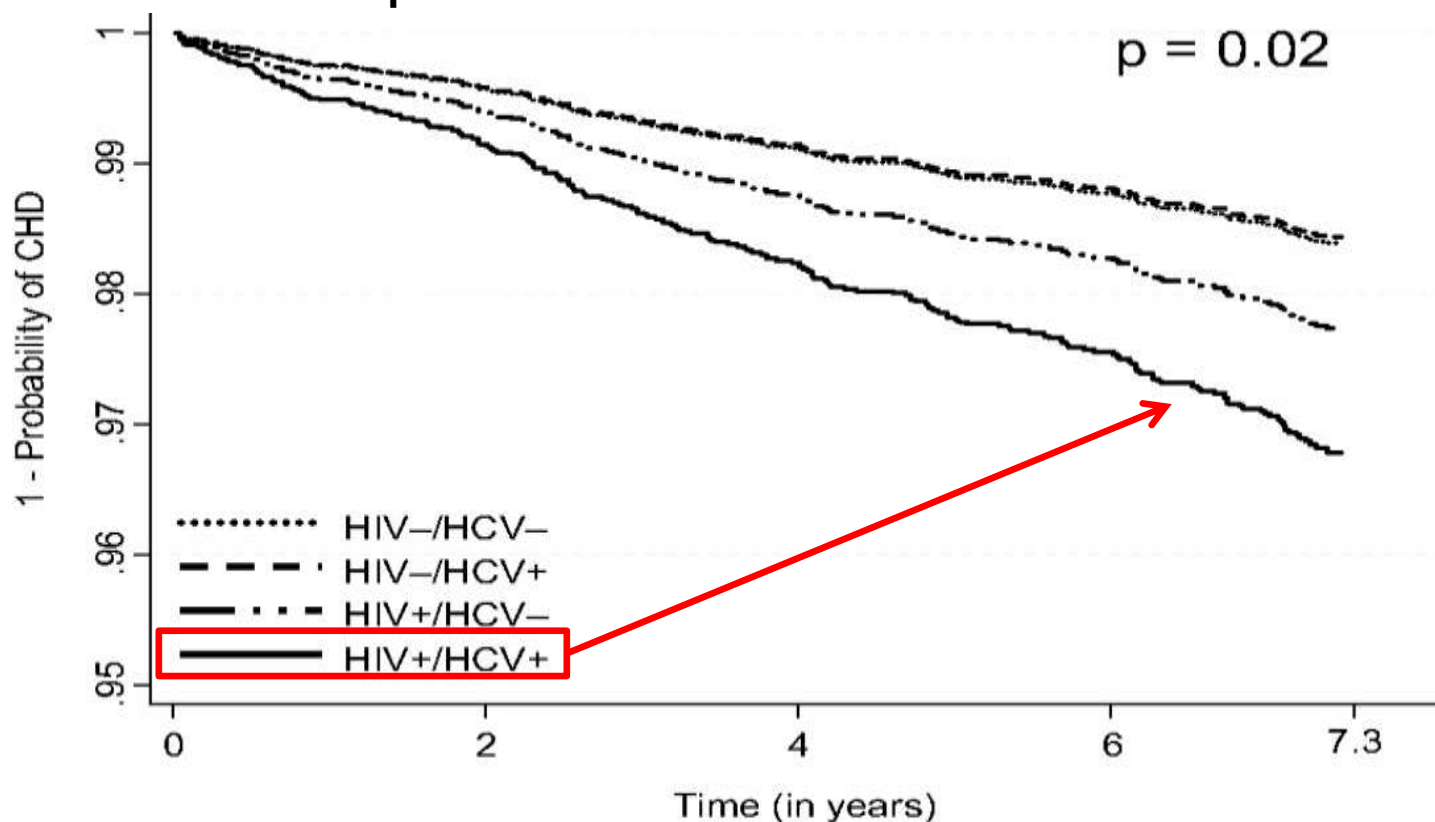


HIV and HCV are two Systemic Diseases Affecting Multiple Body Systems Beyond the Liver



Frailty of HIV/HCV co-infected patient: cardiovascular issues

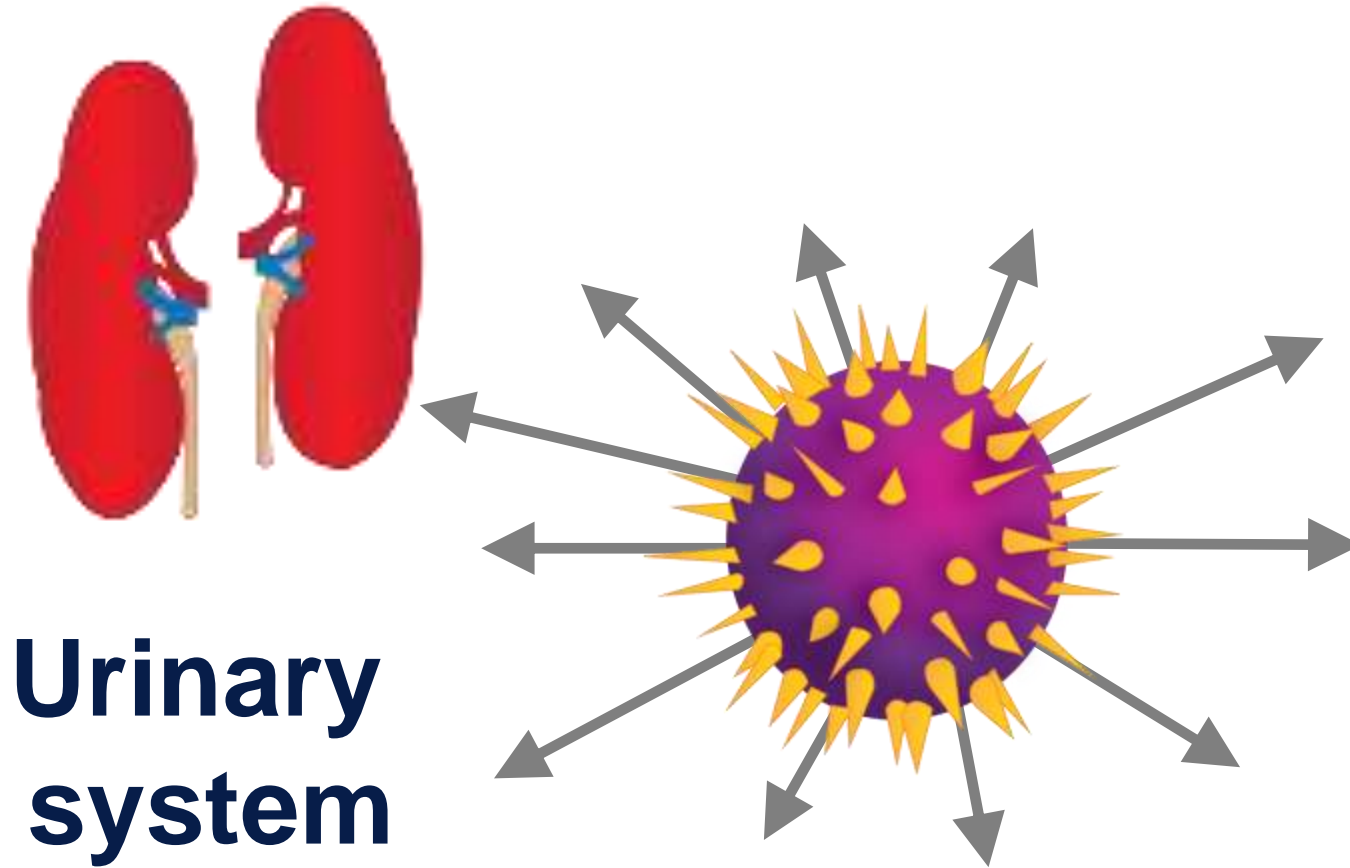
Adjusted survival curves from Cox proportional hazard models among HIV+HCV+, HIV+HCV-, HIV-HCV+, and HIV-HCV- Veterans and the risk of CHD. Solid line represents the risk for HIV+HCV+ Veterans.



No. at risk

HIV-/HCV-	5453	5212	4898	4435	2918
HIV-/HCV+	701	685	648	575	398
HIV+/HCV-	1687	1532	1379	1208	932
HIV+/HCV+	738	655	566	477	353

HIV and HCV are two Systemic Diseases Affecting Multiple Body Systems Beyond the Liver





HCV Co-infection is Associated with an Increased Risk of Chronic Kidney Disease Progression in Patients with HIV

CKD outcomes from 52,602 HCV seronegative, 9,508 HCV viremic and 913 HCV aviremic HIV-infected subjects from NA-ACCORD

Stage 3 CKD

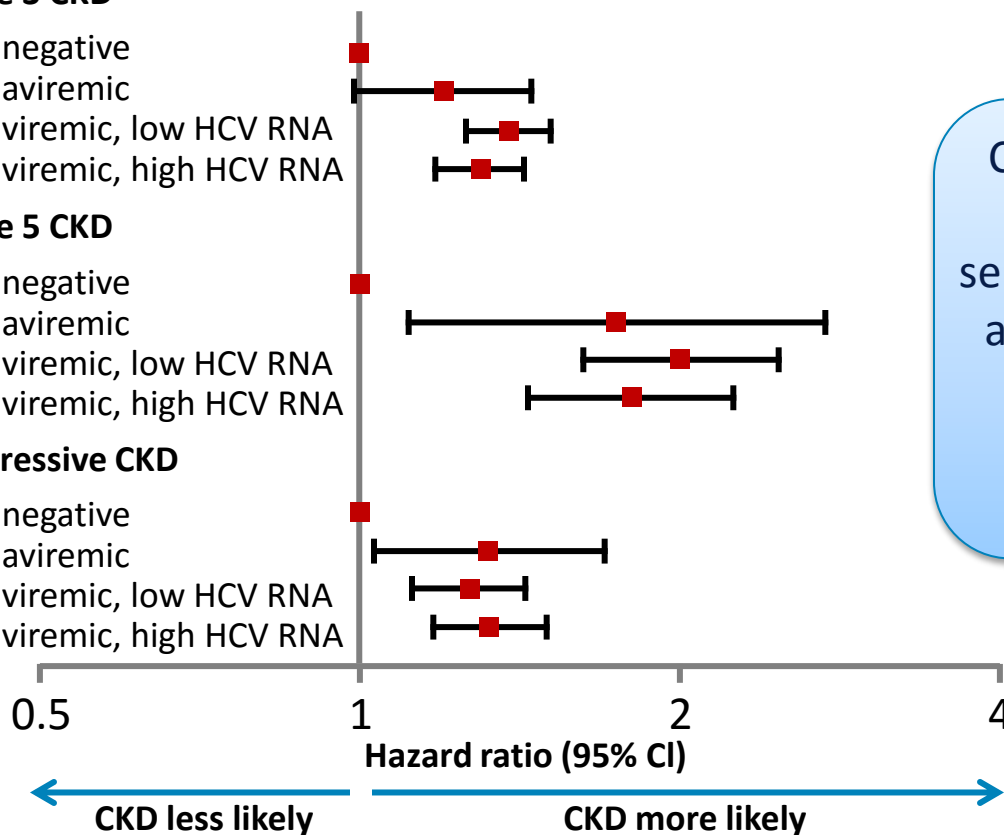
HCV negative
HCV aviremic
HCV viremic, low HCV RNA
HCV viremic, high HCV RNA

Stage 5 CKD

HCV negative
HCV aviremic
HCV viremic, low HCV RNA
HCV viremic, high HCV RNA

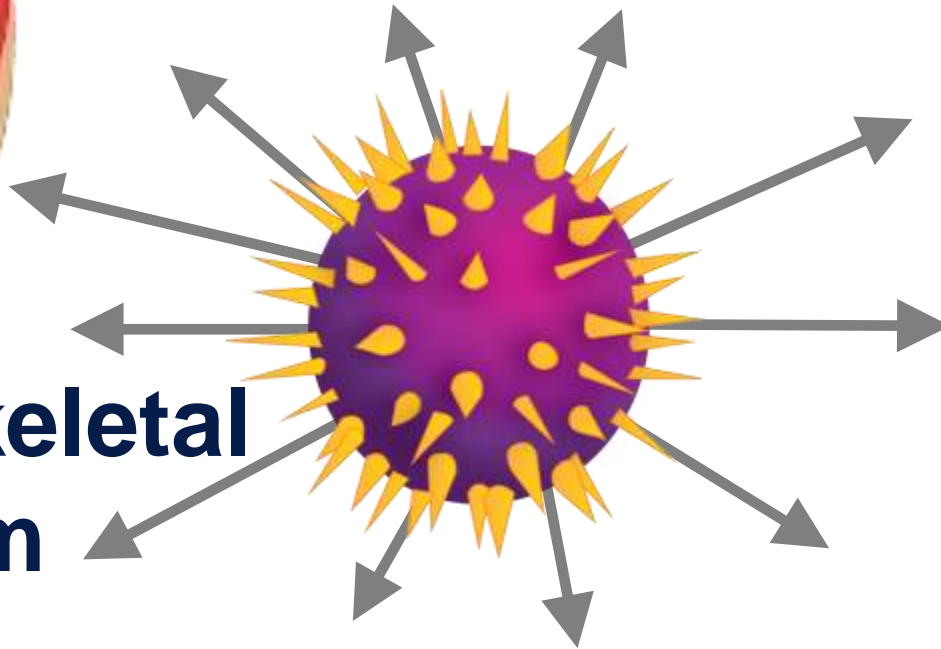
Progressive CKD

HCV negative
HCV aviremic
HCV viremic, low HCV RNA
HCV viremic, high HCV RNA



Compared with HIV-infected subjects who were HCV seronegative, both HCV viremic and HCV aviremic individuals were at increased risk for moderate, advanced and progressive CKD

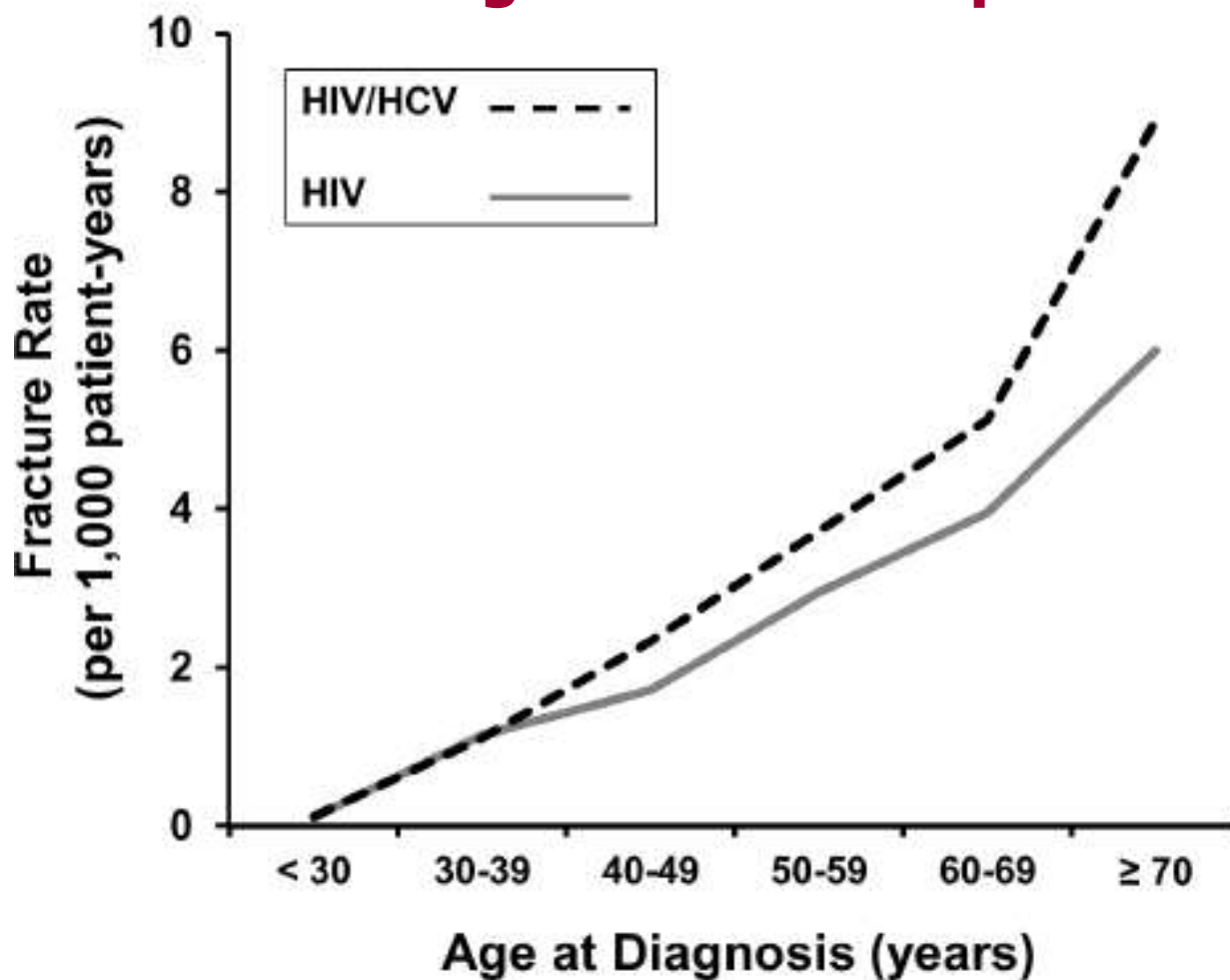
HIV and HCV are two Systemic Diseases Affecting Multiple Body Systems Beyond the Liver



**Musculoskeletal
system**

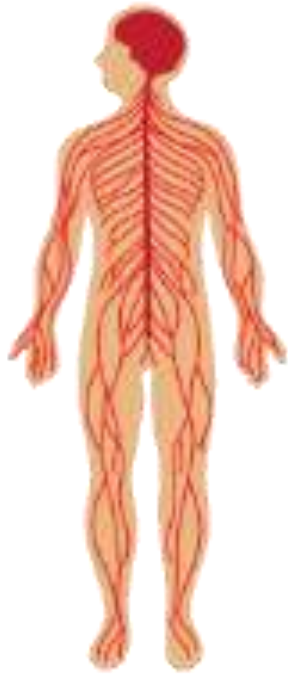


Hepatitis C co-infection and severity of liver disease as risk factors for osteoporotic fractures among HIV-infected patients

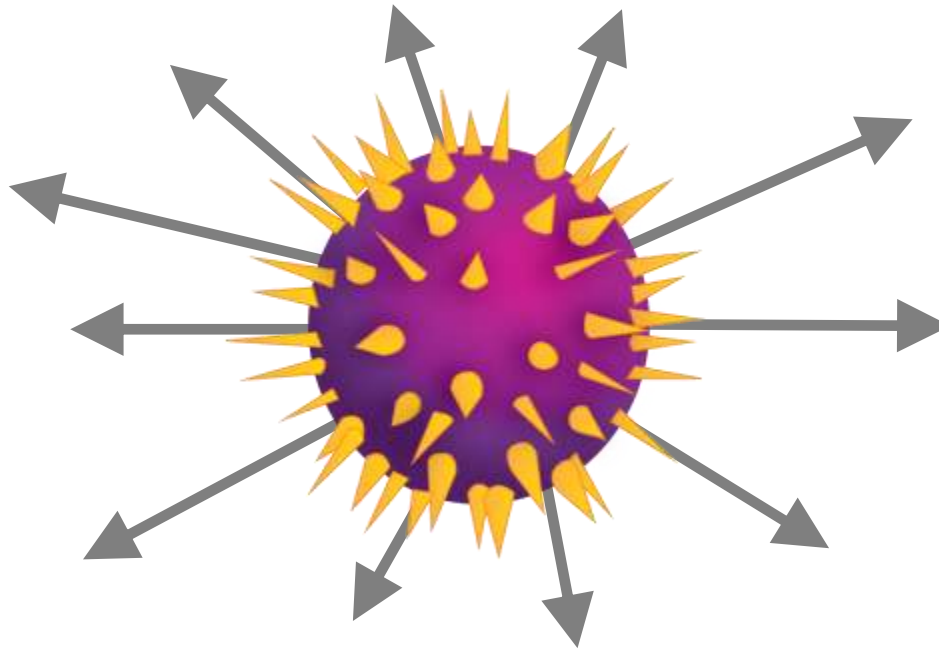


Fracture rates were significantly higher among HIV/HCV patients than HIV-only patients (2.57 versus 2.07/1000 patient-years, relative risk = 1.24, $p < 0.0001$).

HIV and HCV are two Systemic Diseases Affecting Multiple Body Systems Beyond the Liver



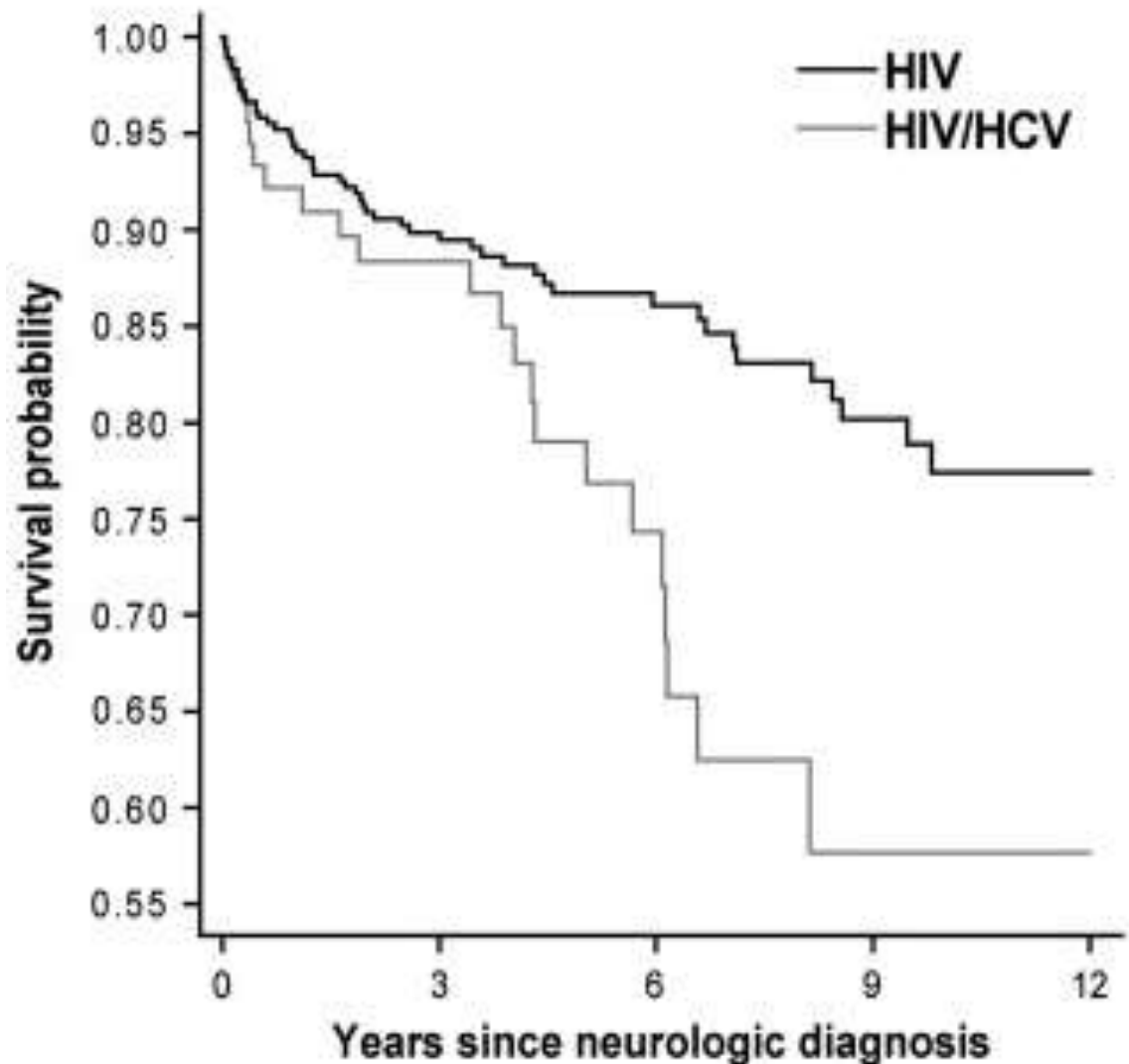
Nervous
system



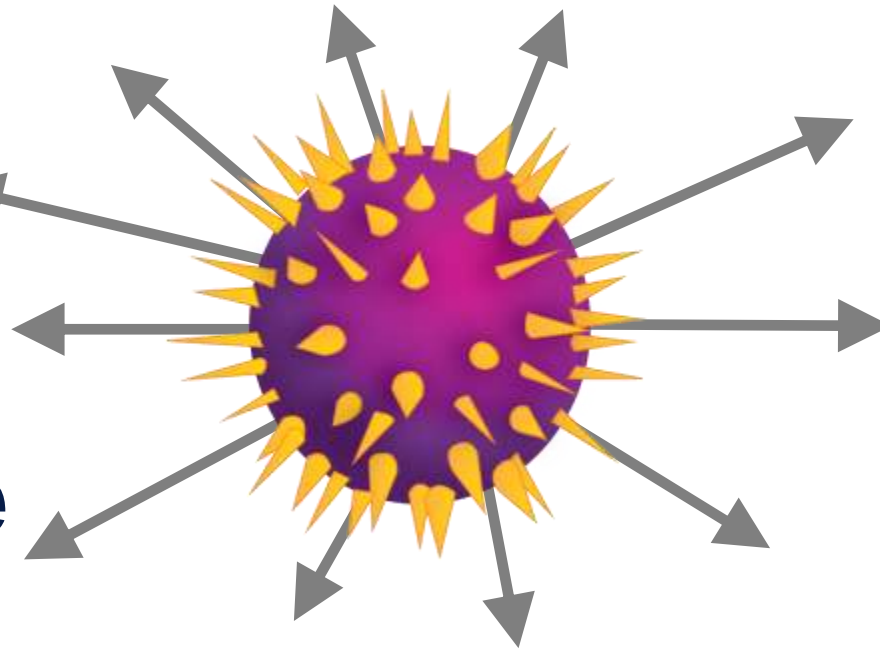
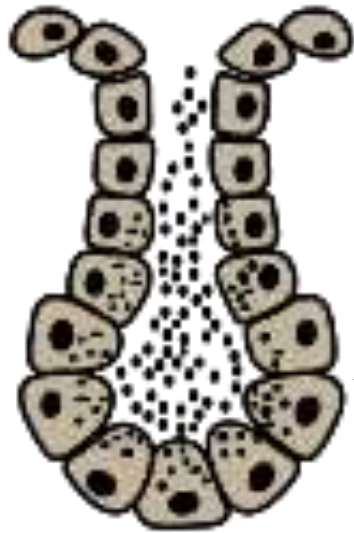


Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS

The presence of HCV co-infection among HIV-infected individuals increased neurologic disease burden and risk of death, underscoring HCV's capacity to affect the nervous system and survival of HIV-infected persons.



HIV and HCV are two Systemic Diseases Affecting Multiple Body Systems Beyond the Liver



**Endocrine
system**



Insulin resistance is associated with progression to hepatic fibrosis in a cohort of HIV/hepatitis C virus-coinfected patients

Table 2. Multivariate Cox proportional hazards model of factors associated with development of aspartate aminotransferase-to-platelet ratio index score of at least 1.5 during follow-up.

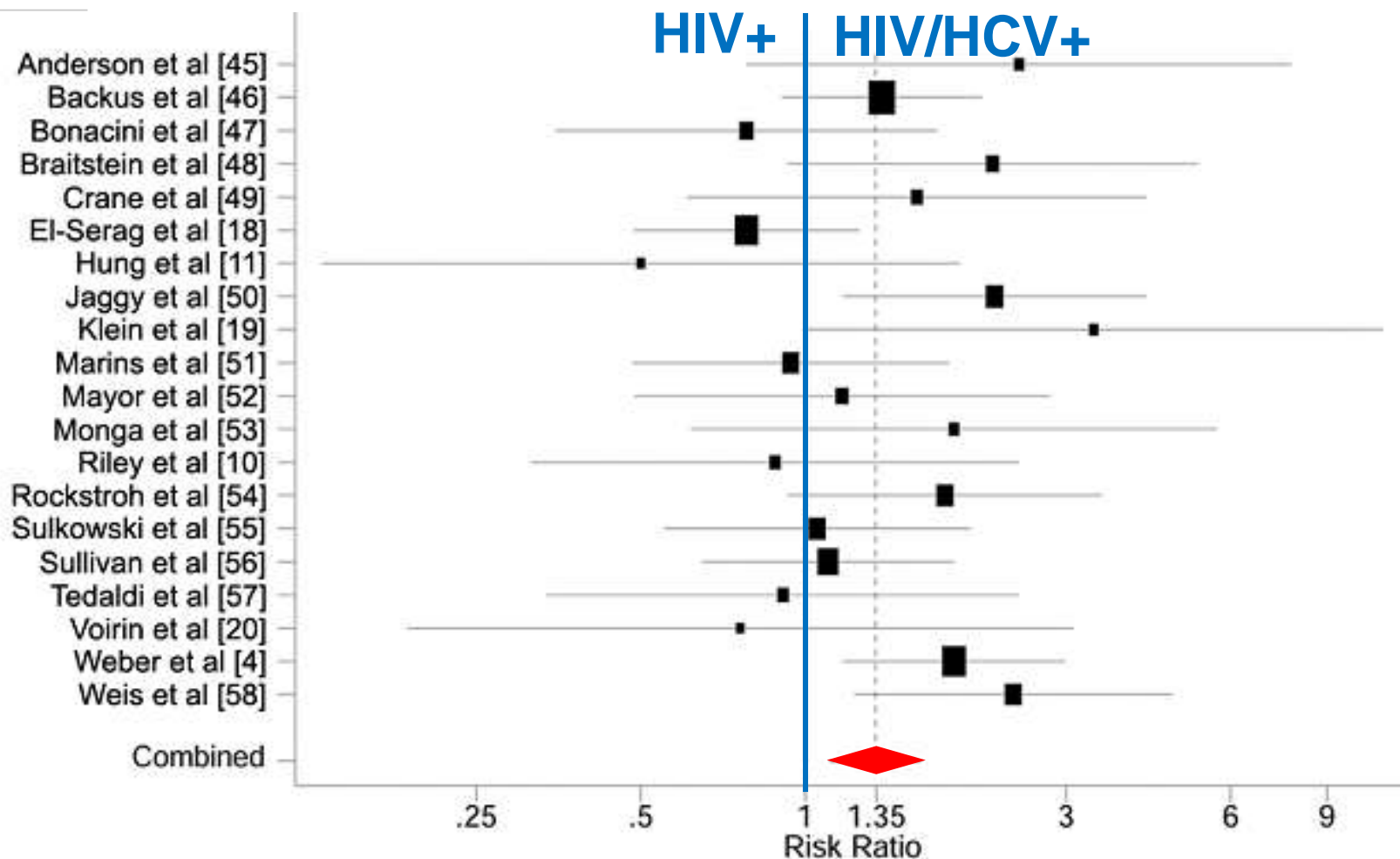
Variables	Adjusted hazard ratio	95% confidence interval
Insulin resistance modelled as HOMA-IR ≥ 2 vs. <2		
HOMA-IR >2	7.72	2.55–23.36
Age (years)	0.98	0.88–1.09
Female sex	0.85	0.27–2.63
Duration of HCV infection (per year)	1.05	0.99–1.12
BMI ≥ 25	0.73	0.24–2.28
Baseline APRI (ln)	7.92	1.94–32.42
Time updated CD4 cell count (per 100 cells/ μ l)	0.92	0.81–1.06
Time updated HIV viral load <50 copies/ml	0.74	0.24–2.29
Insulin resistance modelled with HOMA-IR as a continuous variable		
HOMA-IR (log-base 2)	1.48	1.12–1.86
Age (years)	1.00	0.91–1.09
Female sex	0.82	0.26–2.55
Duration of HCV infection (per year)	1.02	0.97–1.10
BMI ≥ 25	0.83	0.29–2.34
Baseline APRI (ln)	5.20	1.31–20.69
Time updated CD4 cell count (per 100 cells/ μ l)	0.92	0.79–1.08
Time updated HIV viral load <50 copies/ml	0.77	0.20–2.99

The population ($n = 85$) is defined as those with no baseline history of fibrosis or end-stage liver disease and confirmed presence of hepatitis C virus (HCV)-RNA. Median follow-up period was 1.4 years (interquartile range 1.0, 1.7 years). APRI, aspartate aminotransferase-to-platelet ratio index; HOMA-IR, homeostasis model for assessment of insulin resistance.

Conclusion: In this first longitudinal analysis, insulin resistance was very common among coinfectd patients and was associated with modifiable risk factors such as elevated BMI. Insulin resistance was found to be strongly associated with progression to hepatic fibrosis over time.



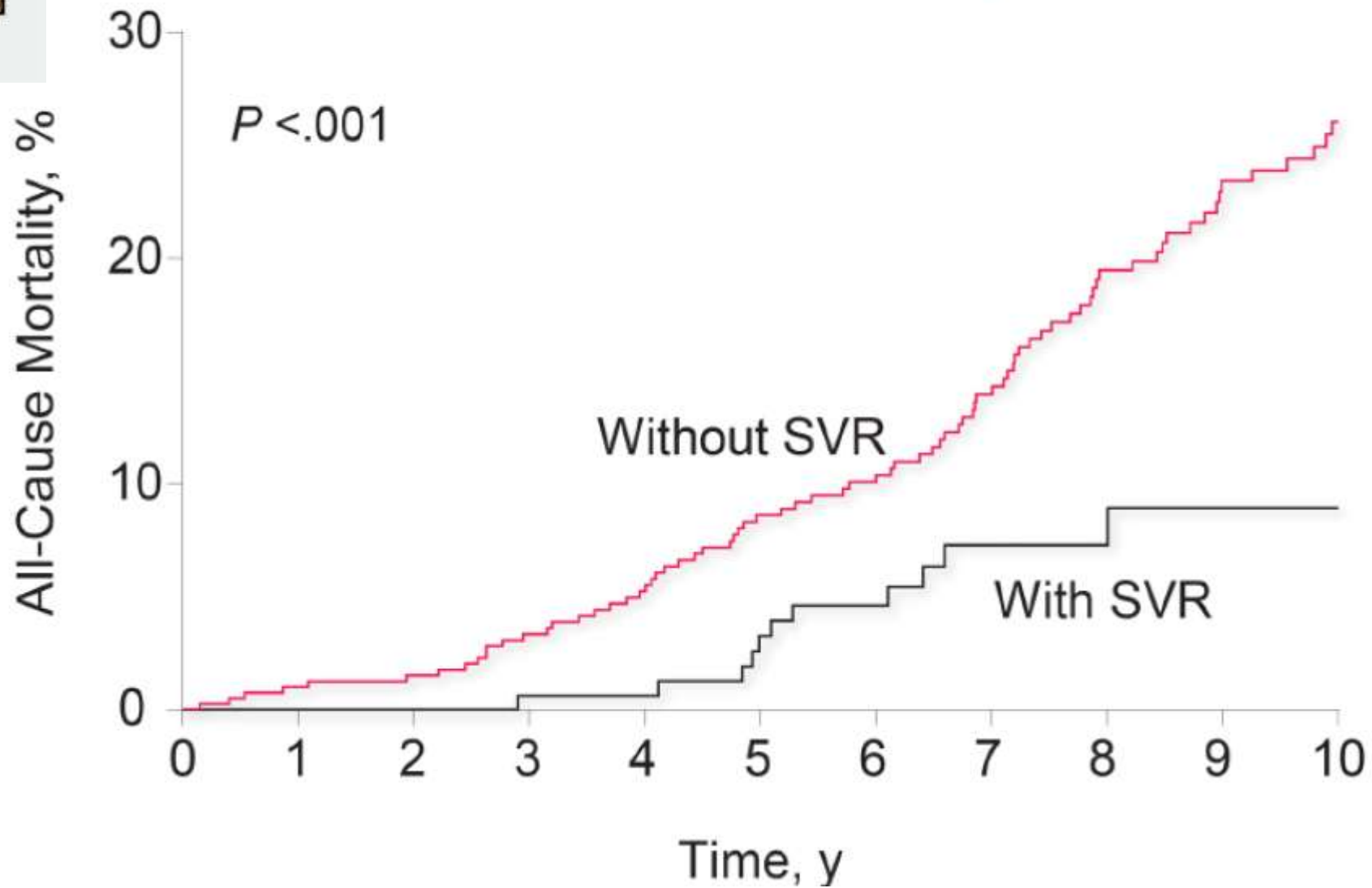
HCV coinfection increases overall mortality



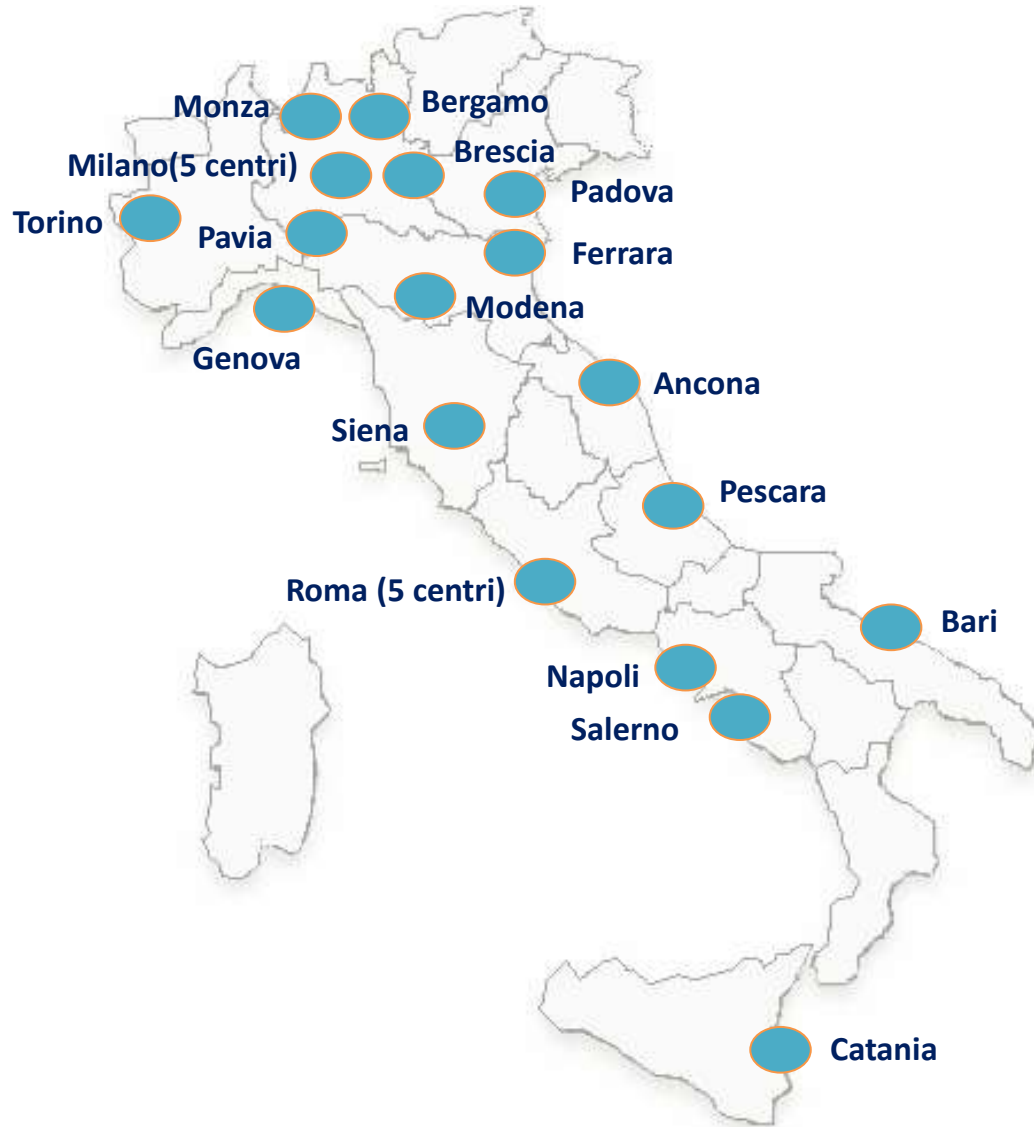
Overall mortality, HAART era



SVR is associated with a reduction in all-cause mortality



SIMIT Compassionate Use Program



26 sites involved

Trattamento di 214 Pazienti coinfecti HIV/HCV

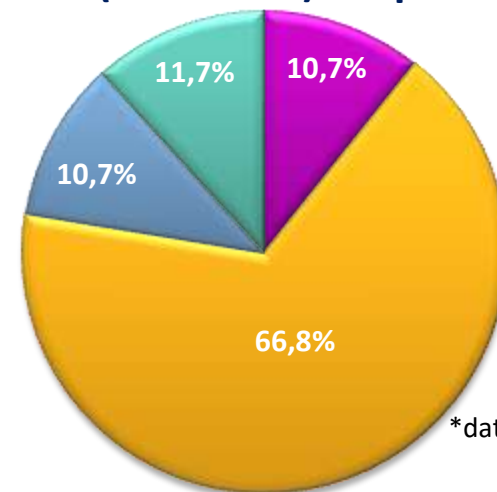
Caratteristiche popolazione

Mediana Età **52 anni** (min. 25 - max 77)

Naive **212**
Experienced **2**

Genotipo	
GT 1a	128
GT 1b	63
GT1a/1b	8
GT1	1

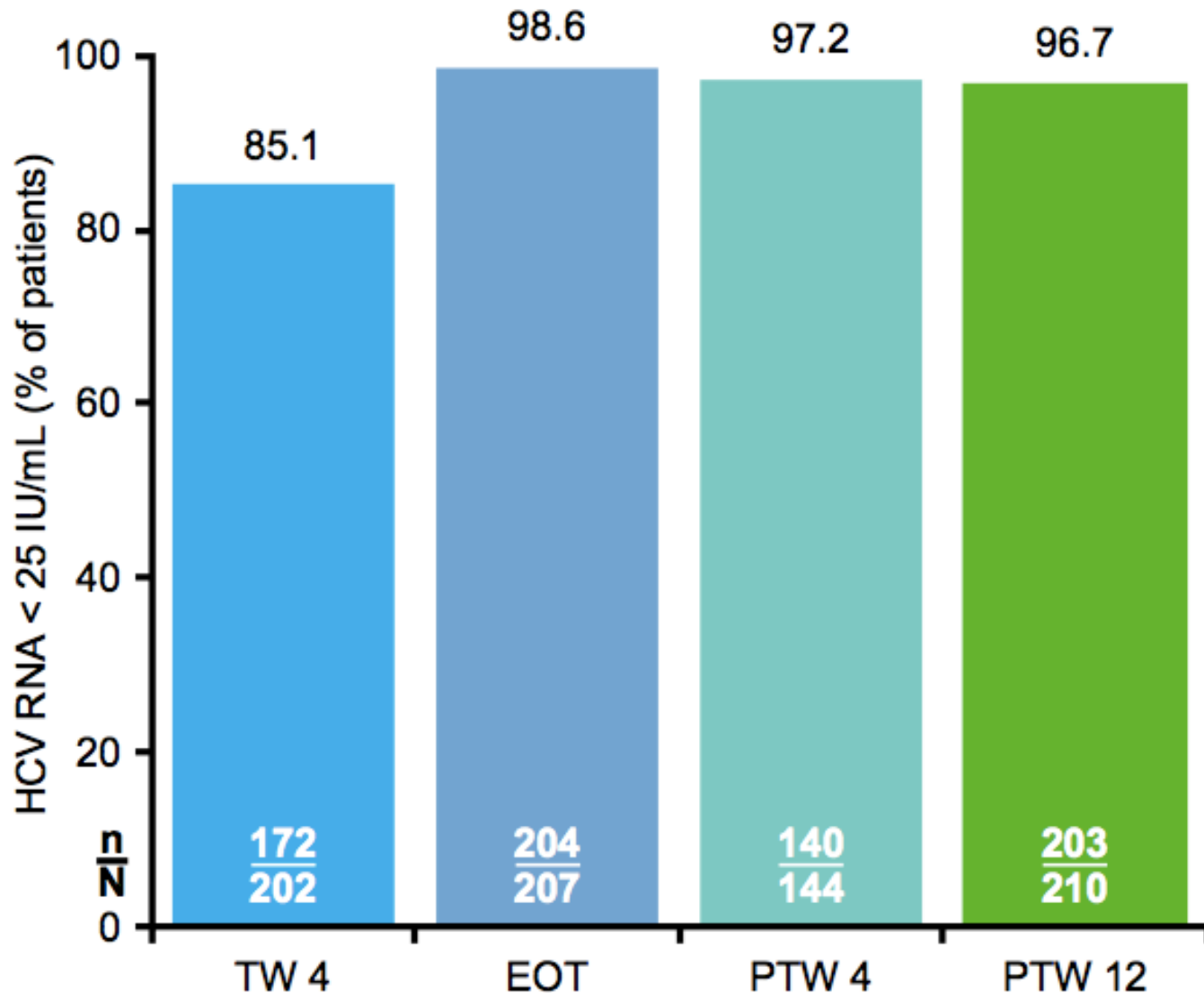
Fibrosi (Fibroscan): n° pazienti 205*



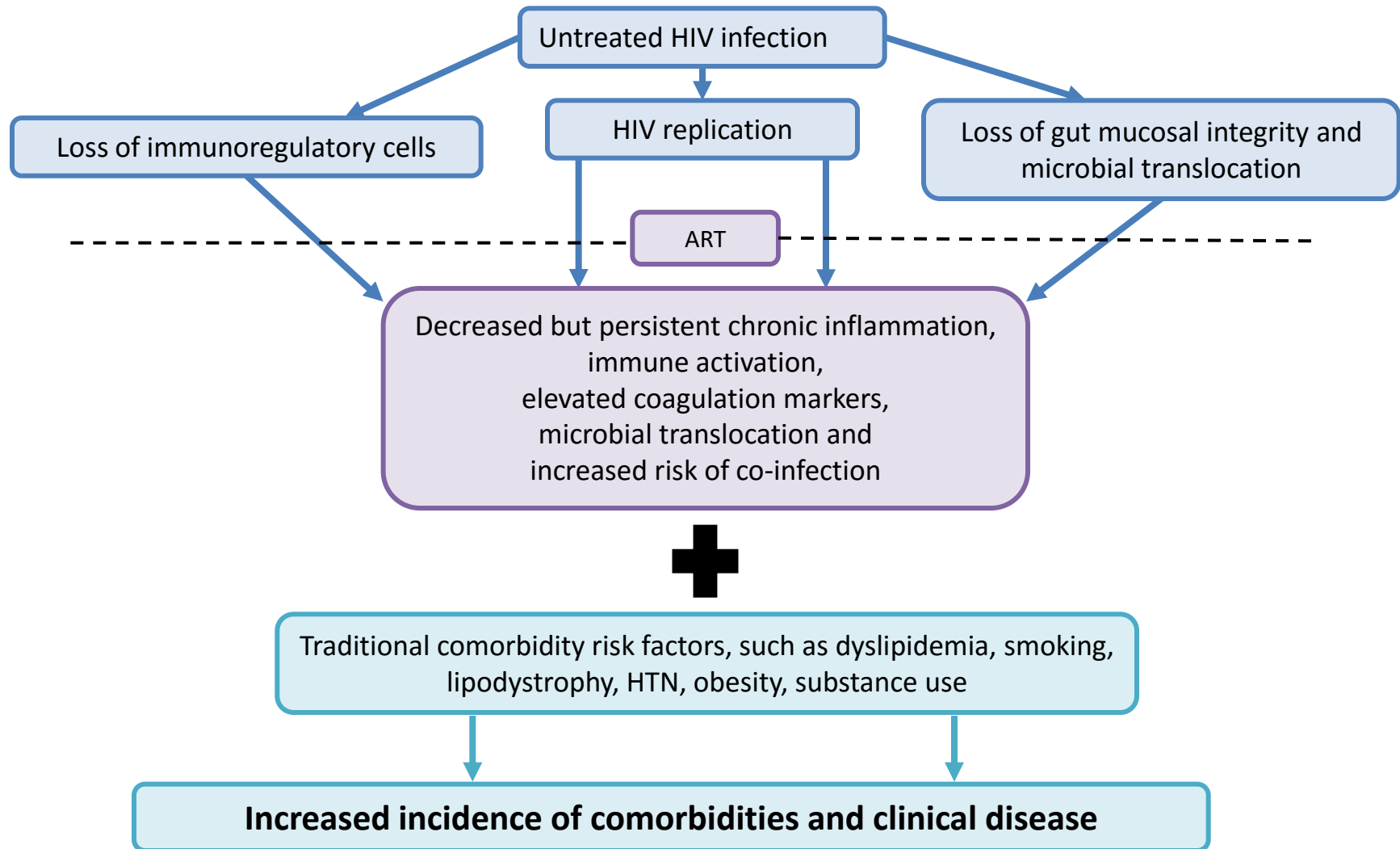
*dati mancanti in 8 pz

■ F1 ■ F2 ■ F3 ■ F4

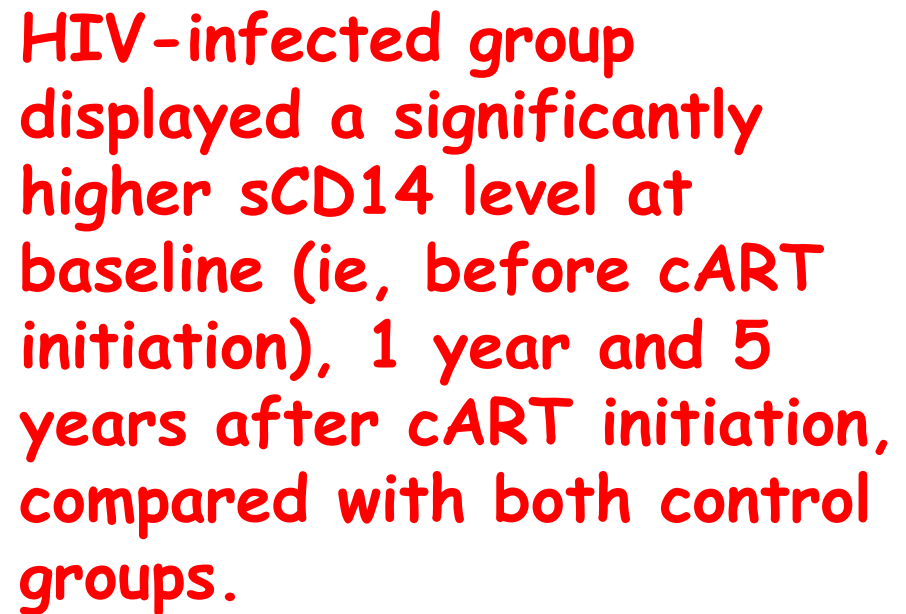
Percentages of patients with HCV RNA levels below the lower limit of quantification. ITT analysis



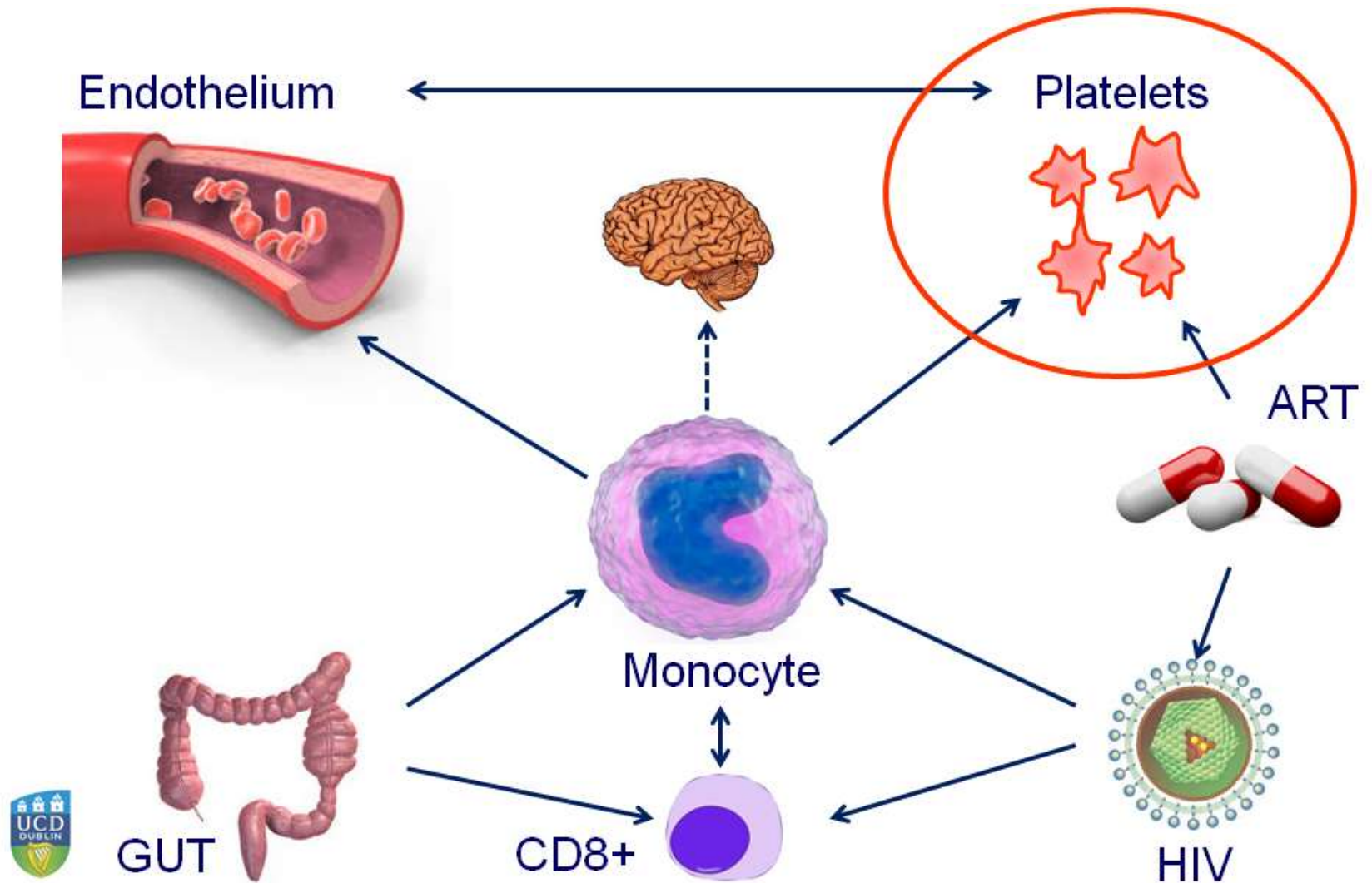
Chronic inflammation is associated with increased risk for comorbidities in HIV-positive patients



Long-Term Suppressive Combined Antiretroviral Treatment Does Not Normalize the Serum Level of Soluble CD14

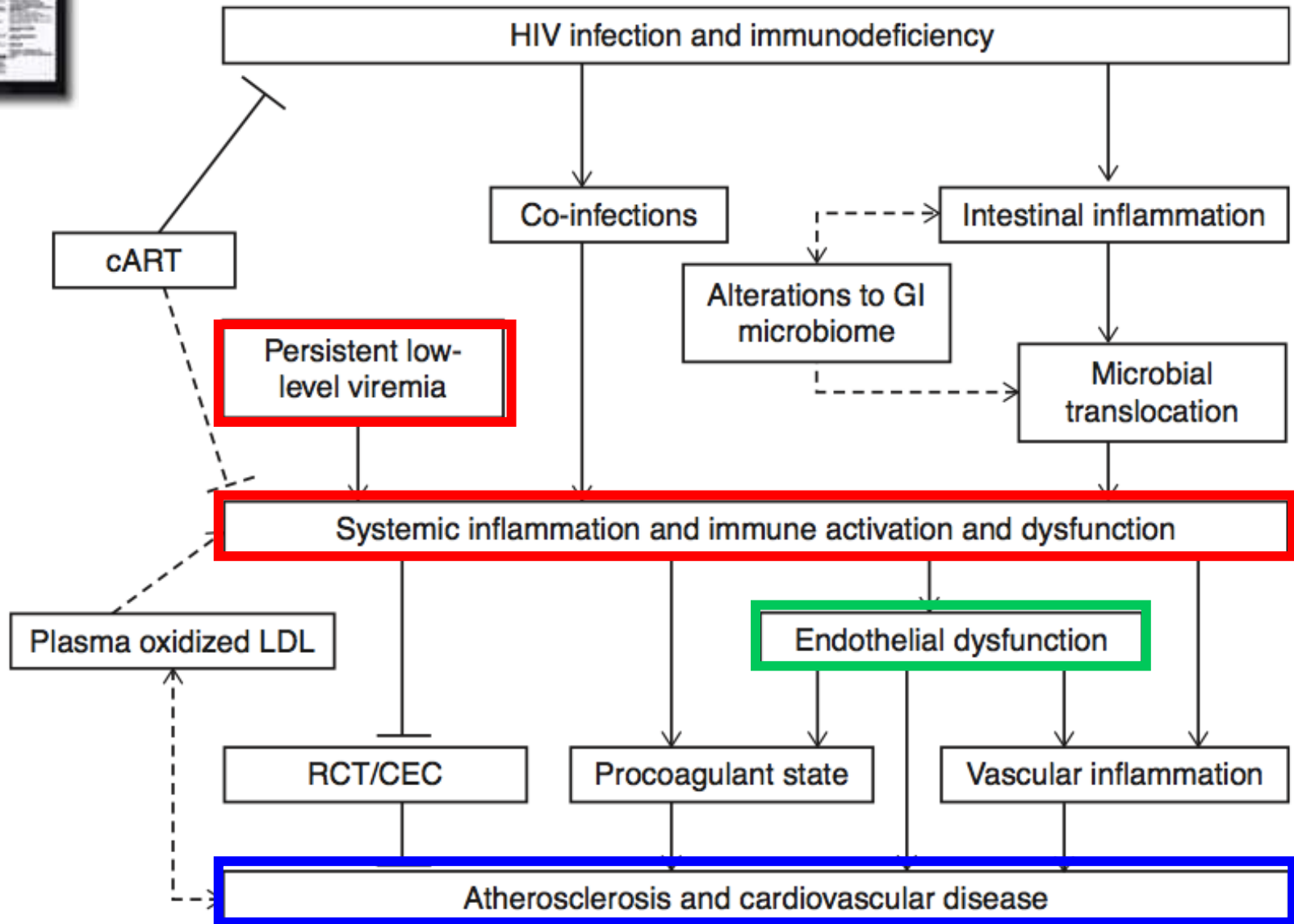


HIV and inflammation



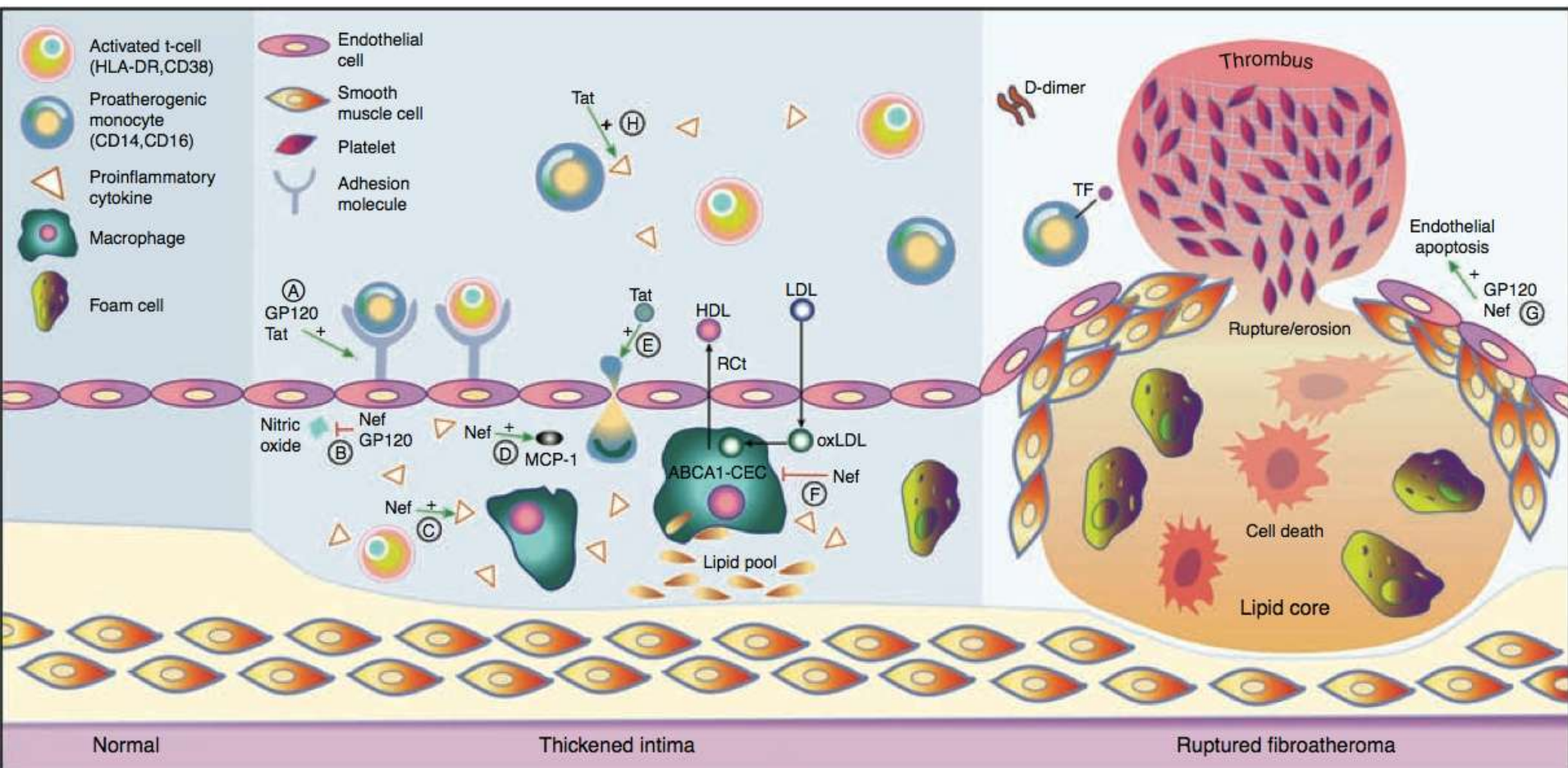


Pathways involved in the development of immune activation and atherosclerosis in HIV

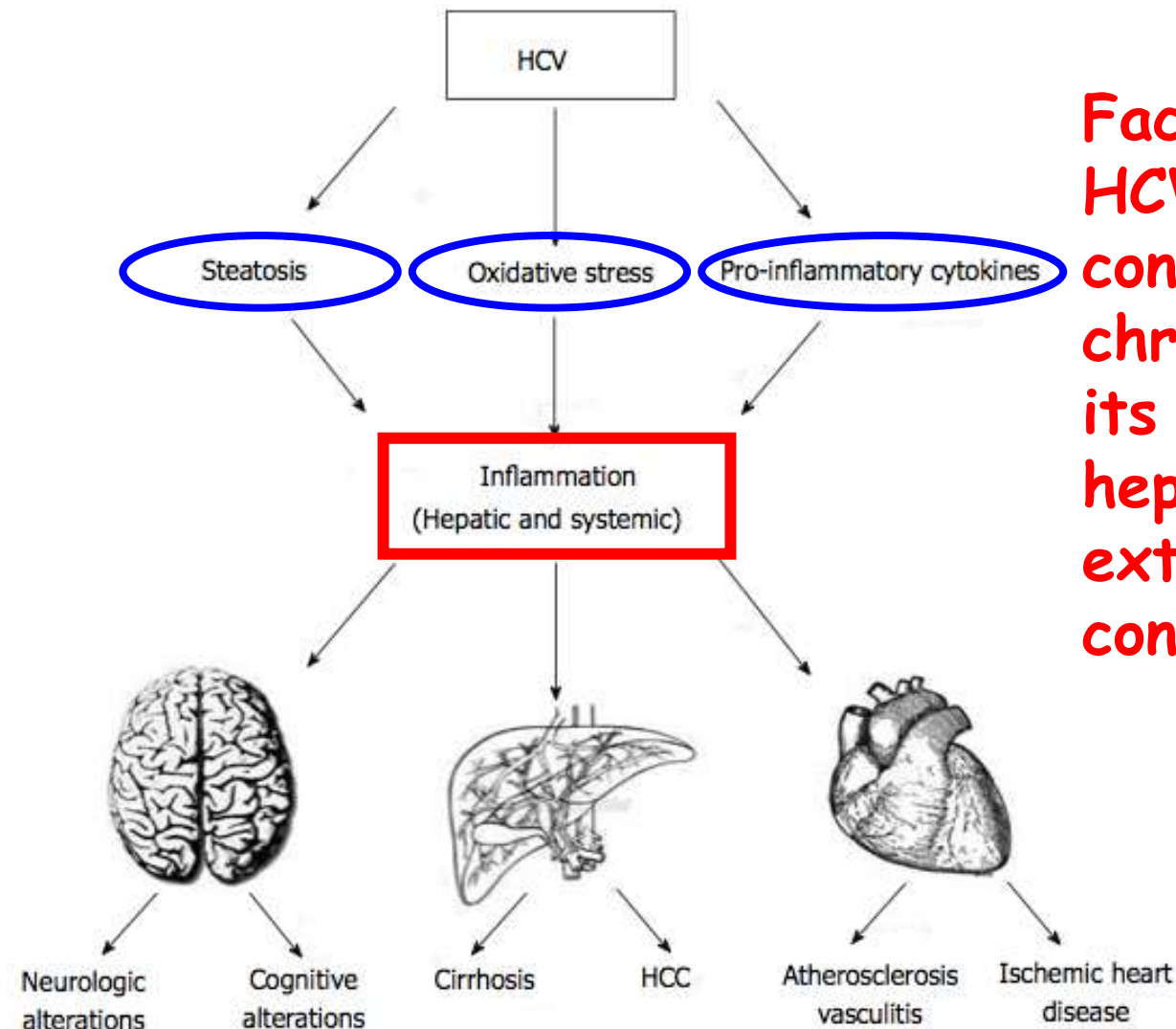




Effects of HIV viral proteins on the development of atherosclerosis

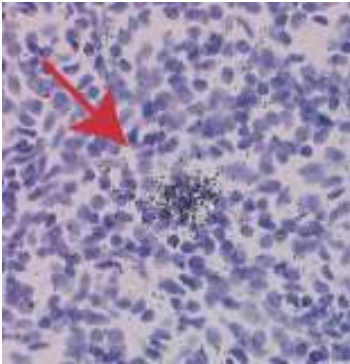


Chronic HCV infection and inflammation: Clinical impact on hepatic and extra-hepatic manifestations

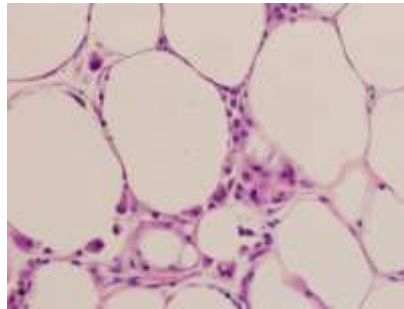


Factors associated with HCV infection that contributes to the chronic inflammation and its involvement in hepatic and extrahepatic clinical conditions.

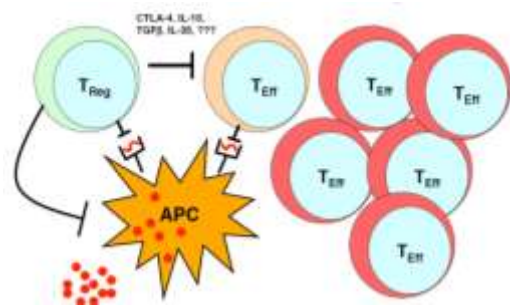
**HIV production
HIV replication**



**HIV-associated fat
Metabolic syndrome**

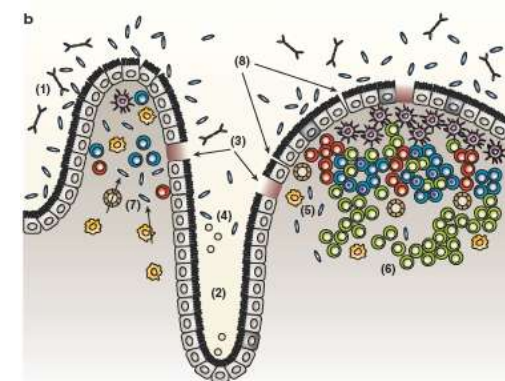


**CMV/HCV
Excess pathogens**



**HIV-mediated loss of
regulatory cells (Tregs)**

Inflammation
↑ Endothelium adhesion
↑ Monocyte activation
Dyslipidemia
Hypercoagulation/
thrombotic events
Endothelial dysfunction



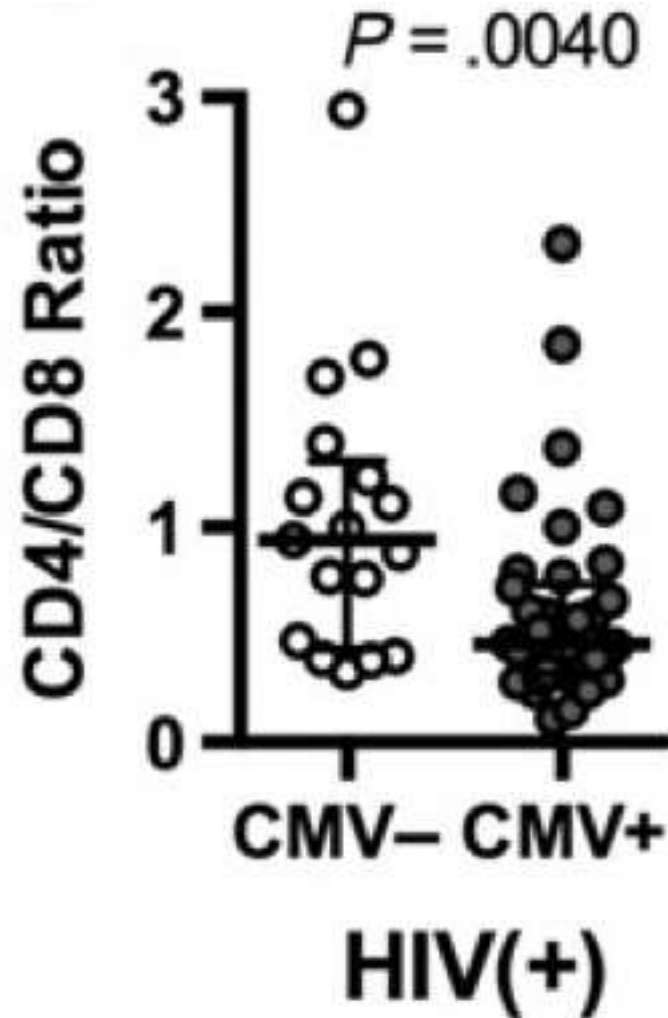
**Microbial
translocation**



CD8 T-Cell Expansion and Inflammation Linked to CMV Coinfection in ART-treated HIV Infection

Michael L. Freeman,^{1,a} Joseph C. Mudd,^{1,ab} Carey L. Shive,^{1,2} Souheil-Antoine Younes,¹ Soumya Panigrahi,¹ Scott F. Sieg,¹ Sulggi A. Lee,³ Peter W. Hunt,³ Leonard H. Calabrese,⁴ Sara Gianella,⁵ Benigno Rodriguez,¹ and Michael M. Lederman¹

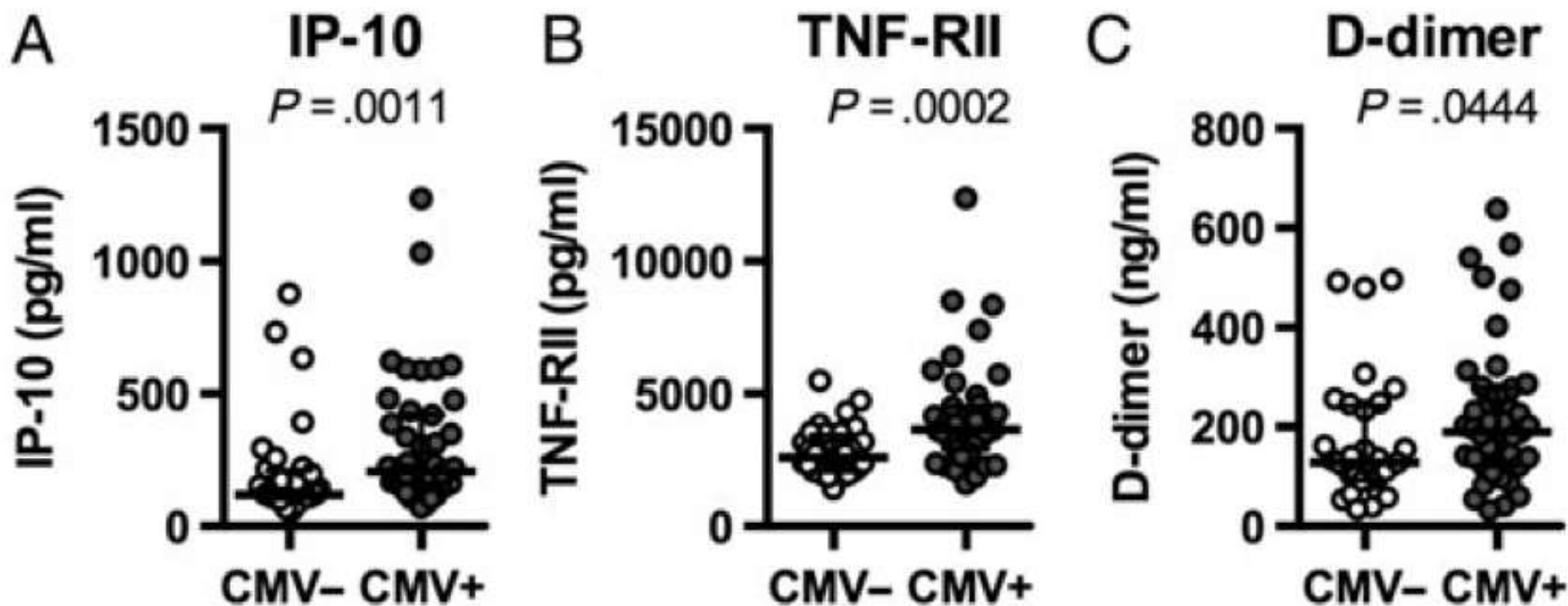
CMV infection is associated with lower CD4/CD8 ratios in ART-treated HIV infection. CMV infection may contribute to risk for morbid outcomes in treated HIV infection.





CD8 T-Cell Expansion and Inflammation Linked to CMV Coinfection in ART-treated HIV Infection

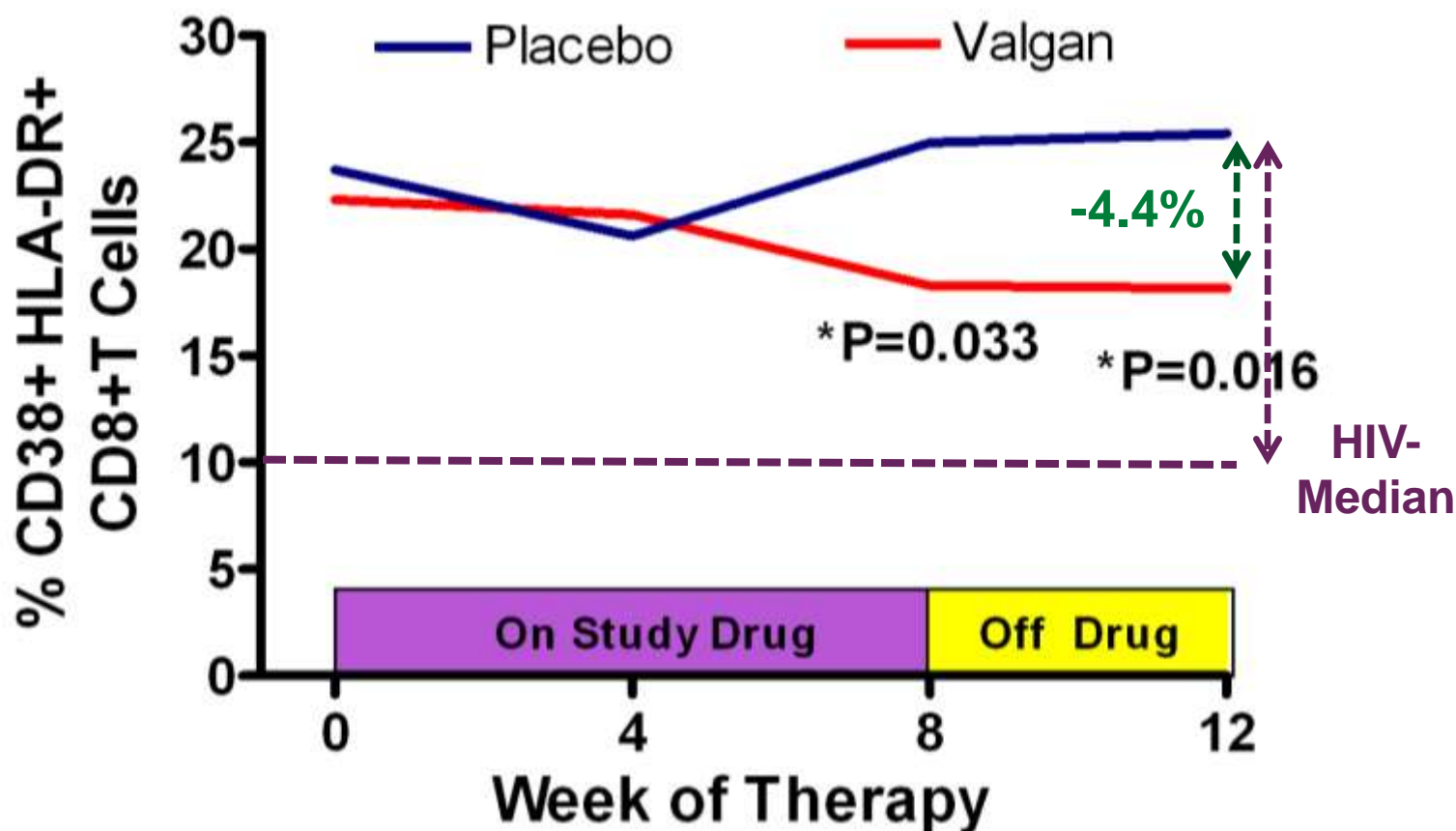
Michael L. Freeman,^{1,a} Joseph C. Mudd,^{1,ab} Carey L. Shive,^{1,2} Souheil-Antoine Younes,¹ Soumya Panigrahi,¹ Scott F. Sieg,¹ Sulggi A. Lee,³ Peter W. Hunt,³ Leonard H. Calabrese,⁴ Sara Gianella,⁵ Benigno Rodriguez,¹ and Michael M. Lederman¹

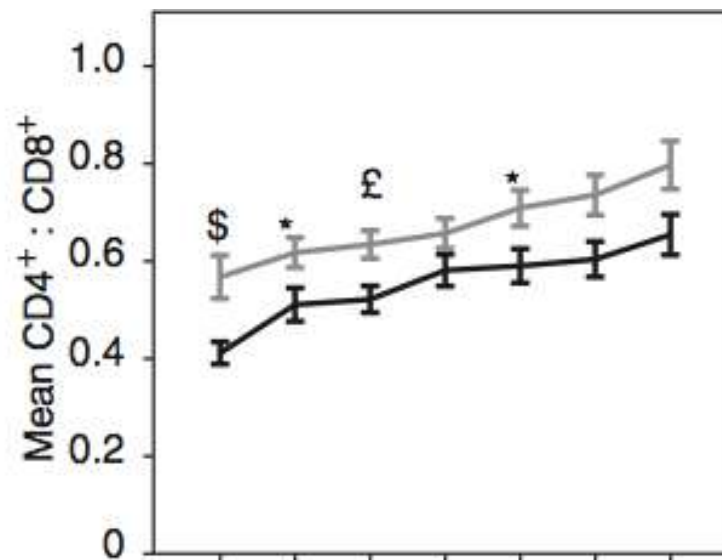
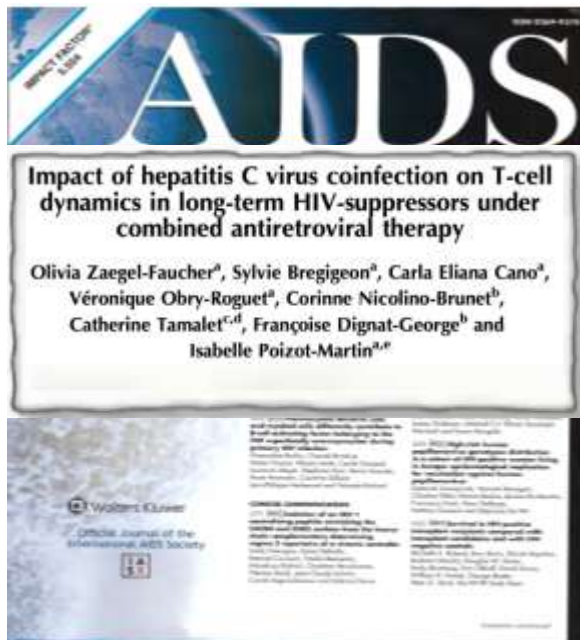


Higher plasma levels of IP-10, TNF-RII and D-dimer were found in coinfecting patients than in HIV-positive/CMV-negative subjects.

Decreasing Asymptomatic CMV Replication with Valganciclovir Decreases Immune Activation

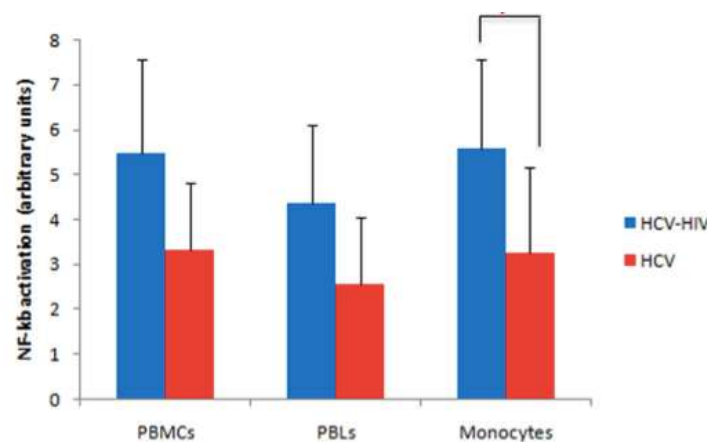
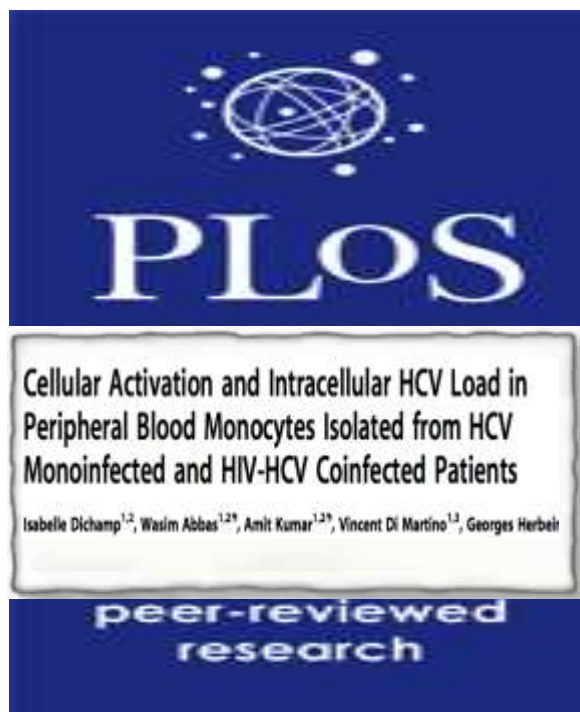
in HIV+ Patients with CD4<350 despite ART





The fraction of patients reaching CD4+ : CD8+ ratio + 1 was lower in group HIV/HCV than HIV infected patients (14 vs. 27.7%; $P < 0.05$).

AIDS 2015, 29:1505–1510



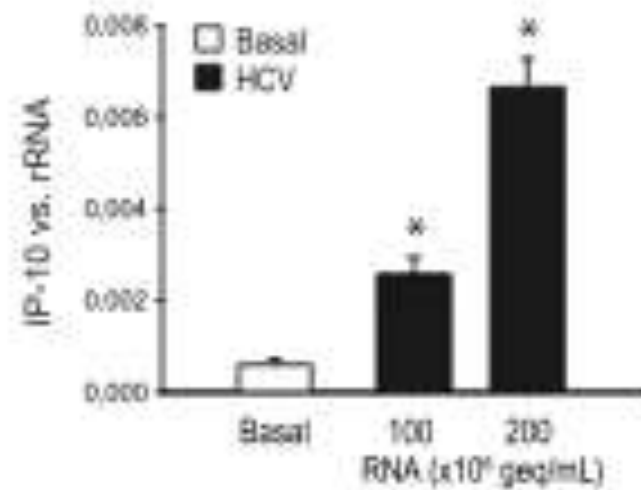
Cellular activation as measured by NF-kB activation was higher in monocytes isolated from HIV-HCV coinfecting patients than in those of monoinfected patients.

PLOS ONE May 2014, Volume 9, Issue 5

PLOS

Hepatitis C Virus Induced Endothelial Inflammatory Response Depends on the Functional Expression of TNF α Receptor Subtype 2

peer-reviewed research



HCV directly promotes activation, adhesion and infiltration of inflammatory cells into the vessel wall by activation of endothelial viral receptors.

J Pircher, November 24, 2014 1-23

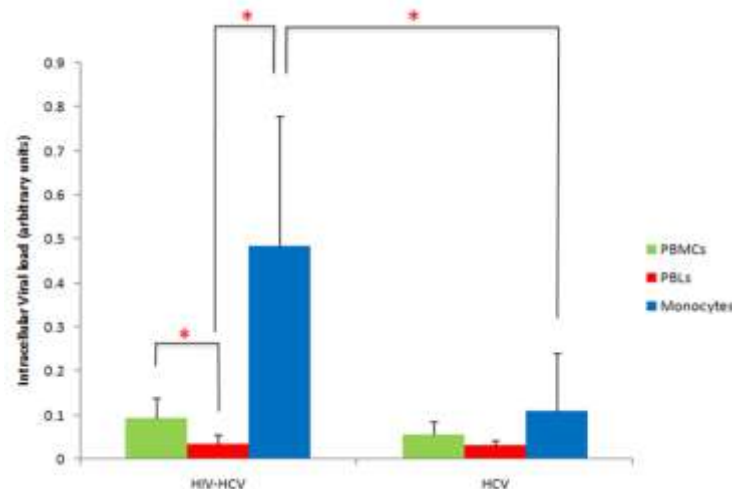
Human microvascular endothelial cells (HMEC) were stimulated with different concentrations of HCV RNA

PLOS

Cellular Activation and Intracellular HCV Load in Peripheral Blood Monocytes Isolated from HCV Monoinfected and HIV-HCV Coinfected Patients

Isabelle Dichamp^{1,2}, Wasim Abbas^{1,2*}, Amit Kumar^{1,2*}, Vincent Di Martino^{1,3}, Georges Herbeir

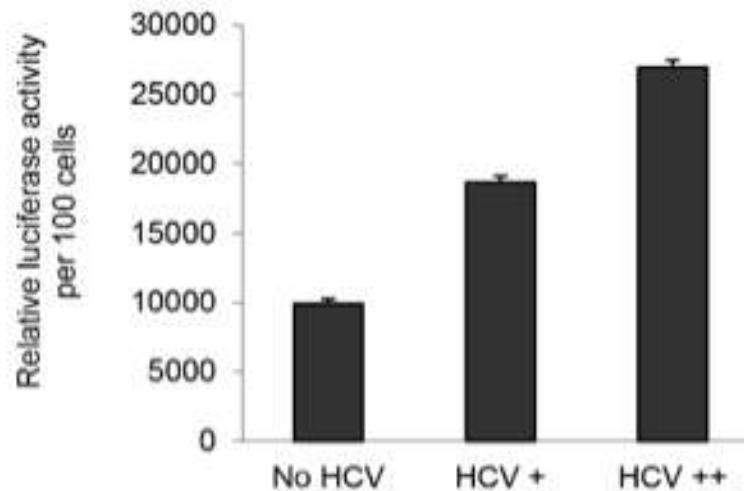
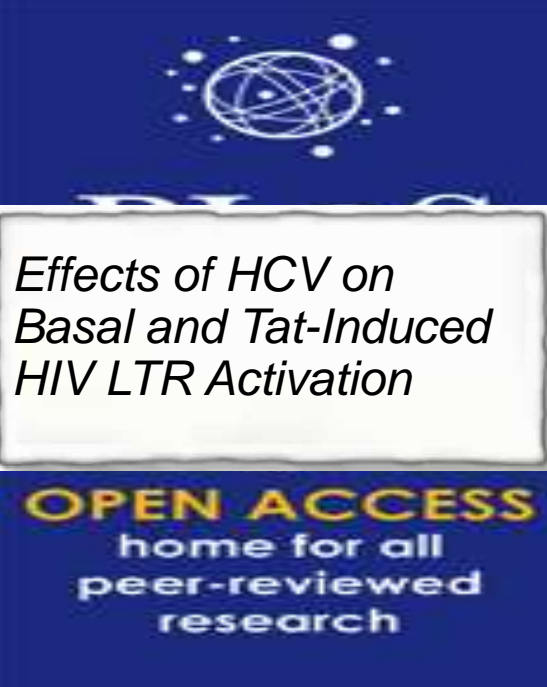
peer-reviewed research



Intracellular HCV loads were higher in monocytes isolated from HIV-HCV coinfecting patients than in those of monoinfected patients.

Peripheral blood monocytes are an important extrahepatic reservoir for HCV in HIV-HCV coinfecting patients

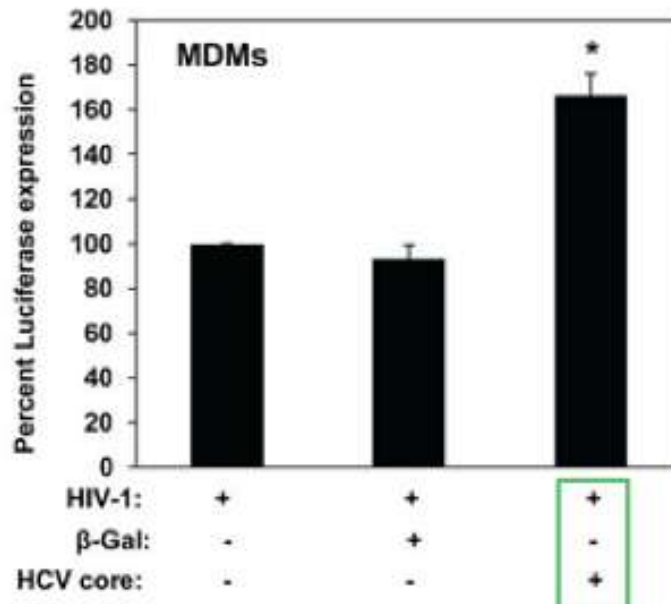
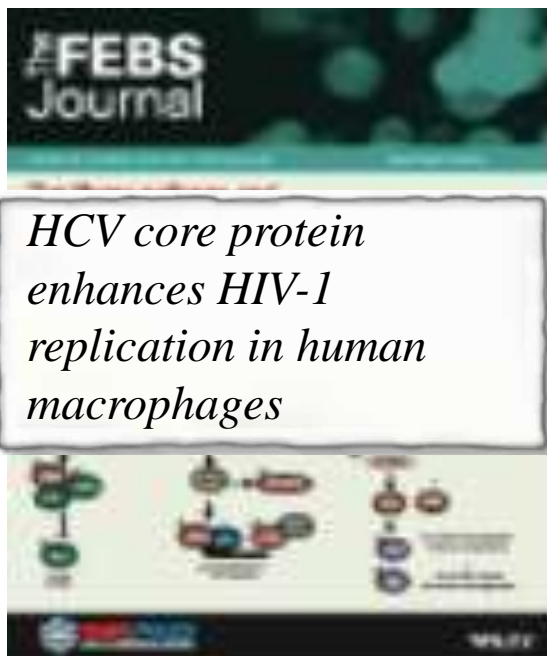
PLOS ONE May 2014, Volume 9, Issue 5



Activation of HIV LTR by HCV in Huh-7.5 cells in the presence of Tat

HCV replication activates HIV LTR expression in Huh-7.5 cells independently from Tat

Sengupta, PLoS ONE 2013



Primary human macrophages (MDMs) were stimulated with 5 μ g/ml of HCV core, or β -Gal recombinant protein control at 12 hours after HIV-1 BaL infection. LTR-driven Luciferase activity was measured 2 days after infection.

Swaminathan, FEBS Lett 2014

“Treatment should be prioritized regardless of the fibrosis stage in patients with HIV or HBV coinfection,(A1)“



Table 2. Indications for treatment of chronic hepatitis C in 2015: Who should be treated and when?

Treatment priority	Patient group
Treatment is indicated	<ul style="list-style-type: none"> • All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
Treatment should be prioritized	<ul style="list-style-type: none"> • Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis • Patients with HIV coinfection • Patients with HBV coinfection • Patients with an indication for liver transplantation • Patients with HCV recurrence after liver transplantation • Patients with clinically significant extra-hepatic manifestations • Patients with debilitating fatigue • Individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
Treatment is justified	<ul style="list-style-type: none"> • Patients with moderate fibrosis (F2)
Treatment can be deferred	<ul style="list-style-type: none"> • Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	<ul style="list-style-type: none"> • Patients with limited life expectancy due to non-liver related comorbidities

PRACTICE GUIDANCE

Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected With Hepatitis C Virus

AASLD/IDSA HCV Guidance Panel*

Cure of HCV infection may also reduce symptoms and mortality from severe extrahepatic manifestations.