Perché oggi siamo autorizzati a guardare oltre la viremia plasmatica non rilevabile?

ROMA 15 settembre 2016

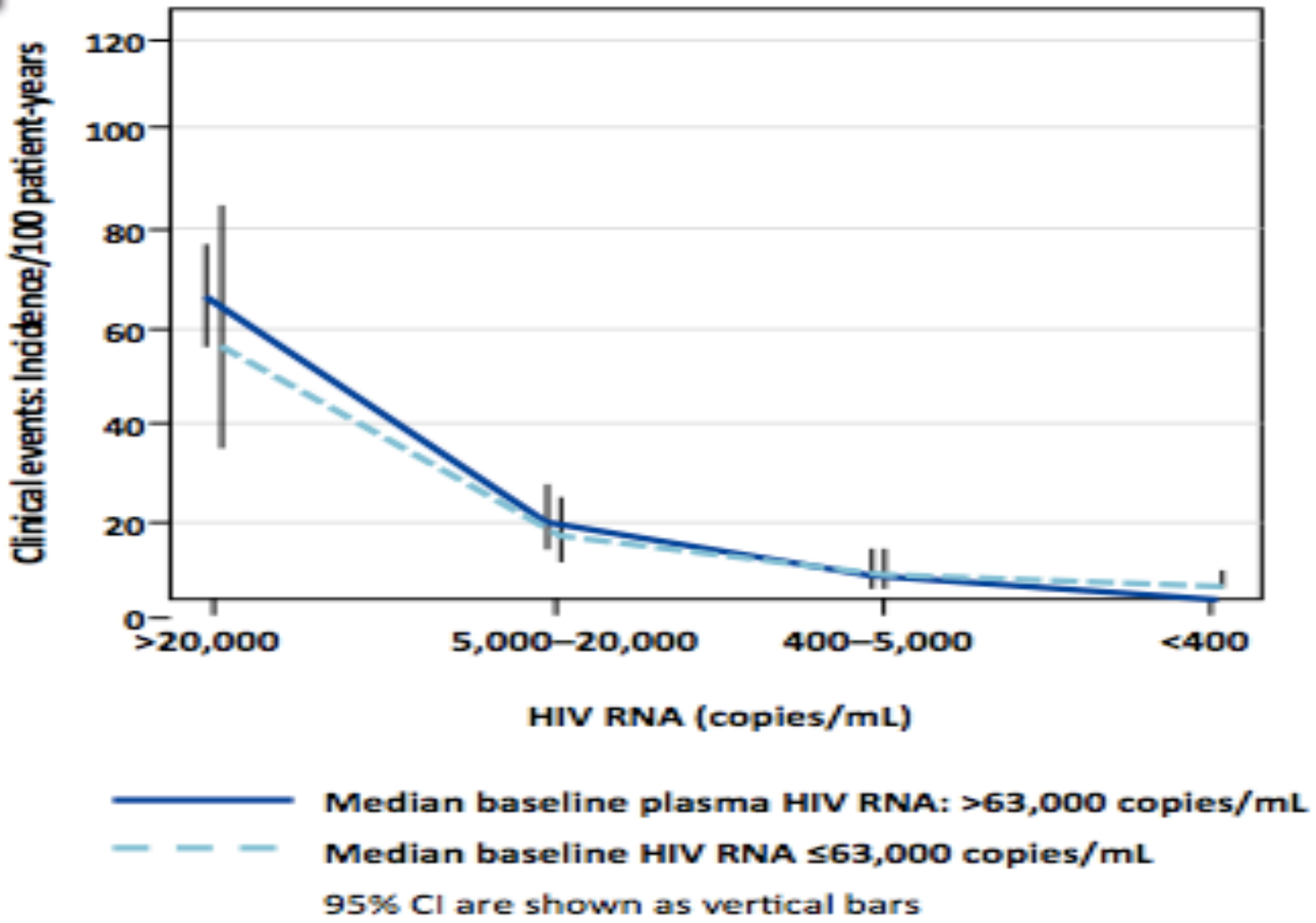
Università di Roma Tor Vergata

Massimo Andreoni

Cattedra di Malattie Infettive

PTV
Azienda Ospedaliera Univers
POLICLINICO TOR VERGATA

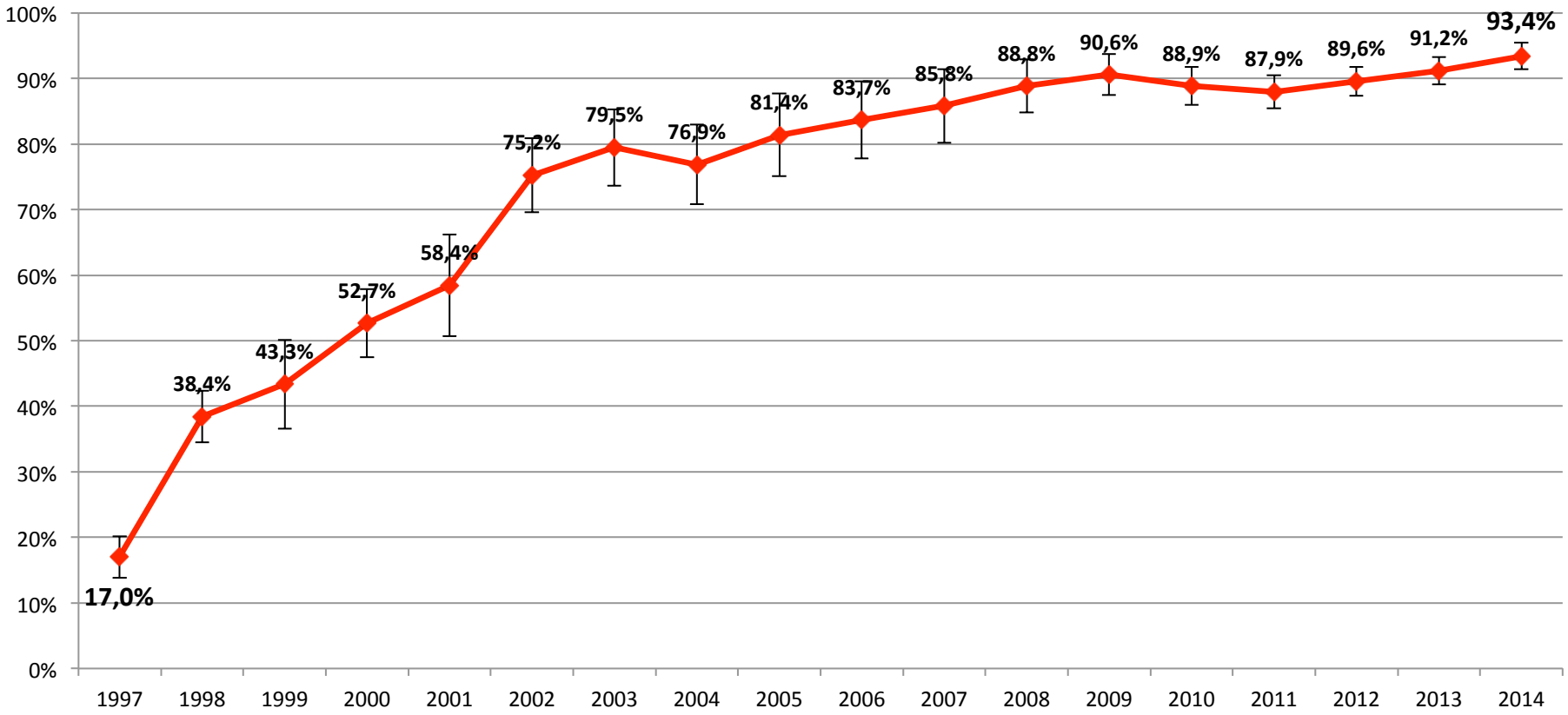
Viral suppression rates are associated with decreased clinical progression and improved clinical outcomes for patients



Murray JS et al. AIDS 1999;13(7):797–804;

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

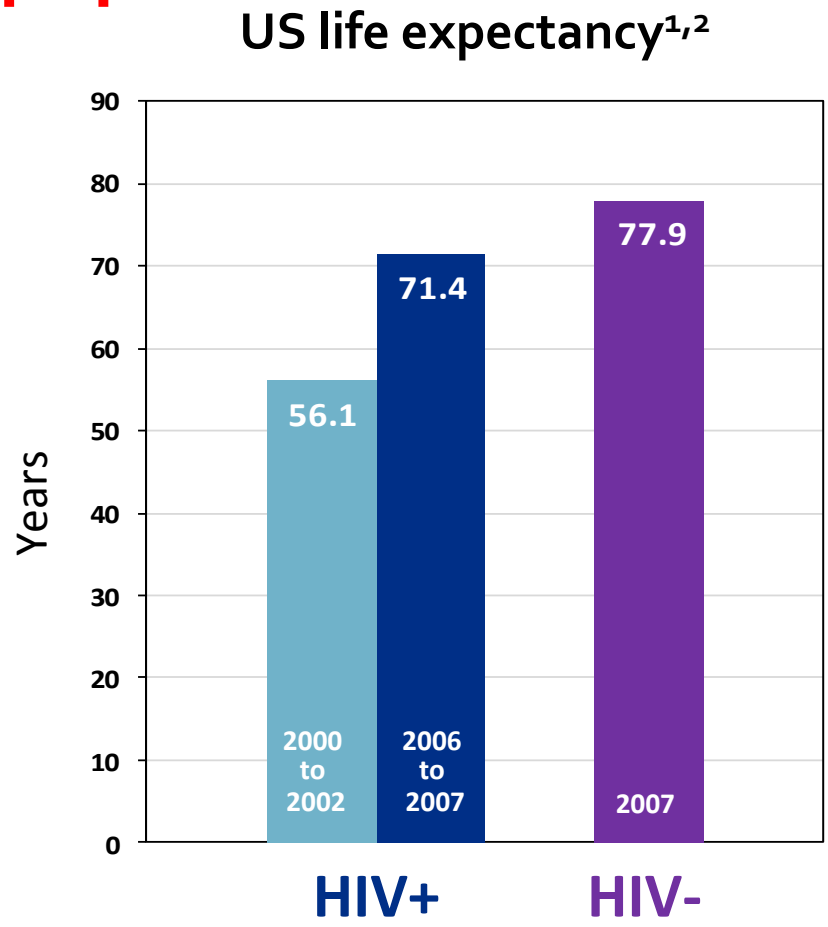
Proportion of patients with a VL<=80 copies/mL at 12 months from starting their first cART regimen by calendar year of initiation



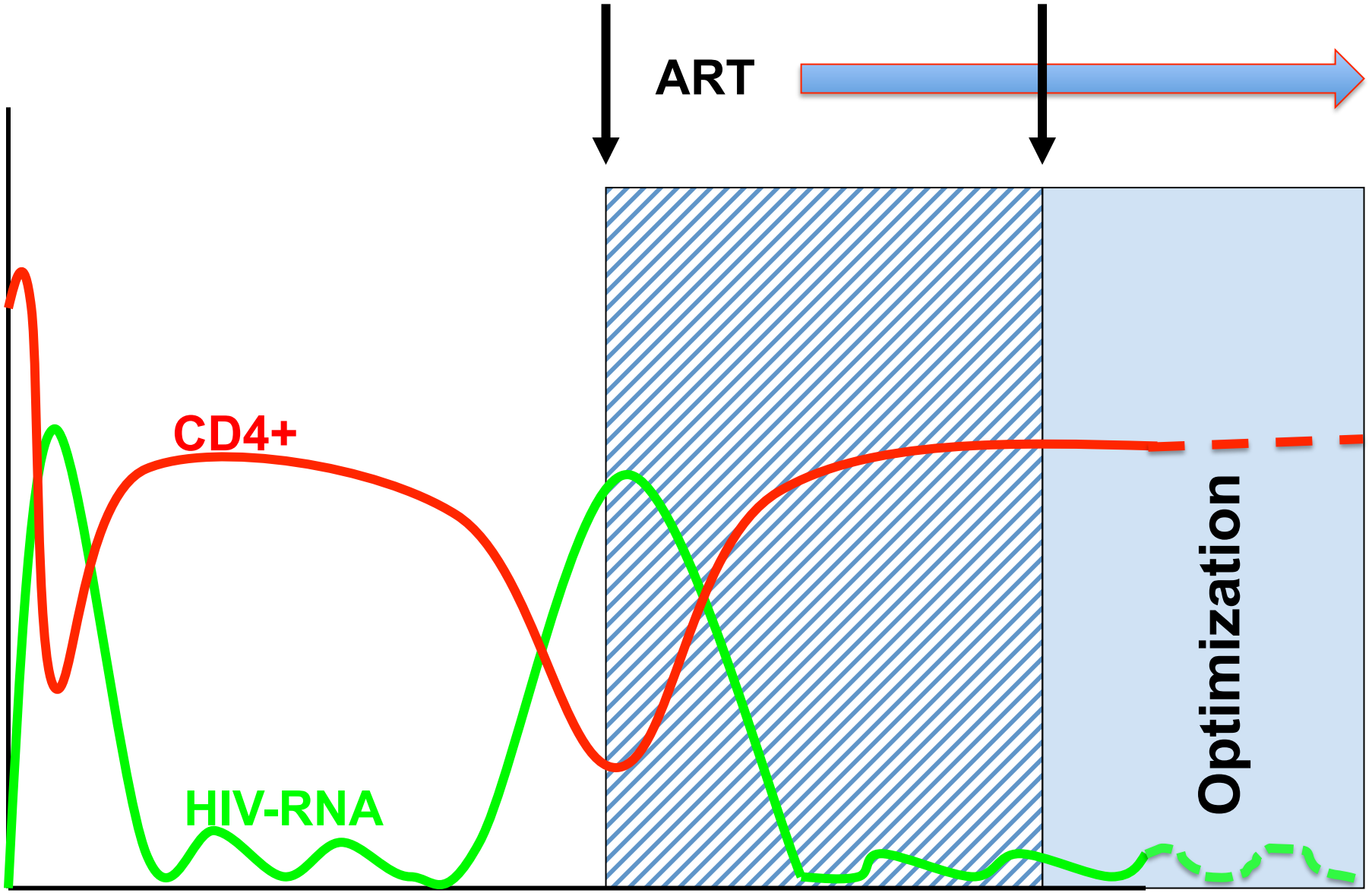
Jan 2016 Report

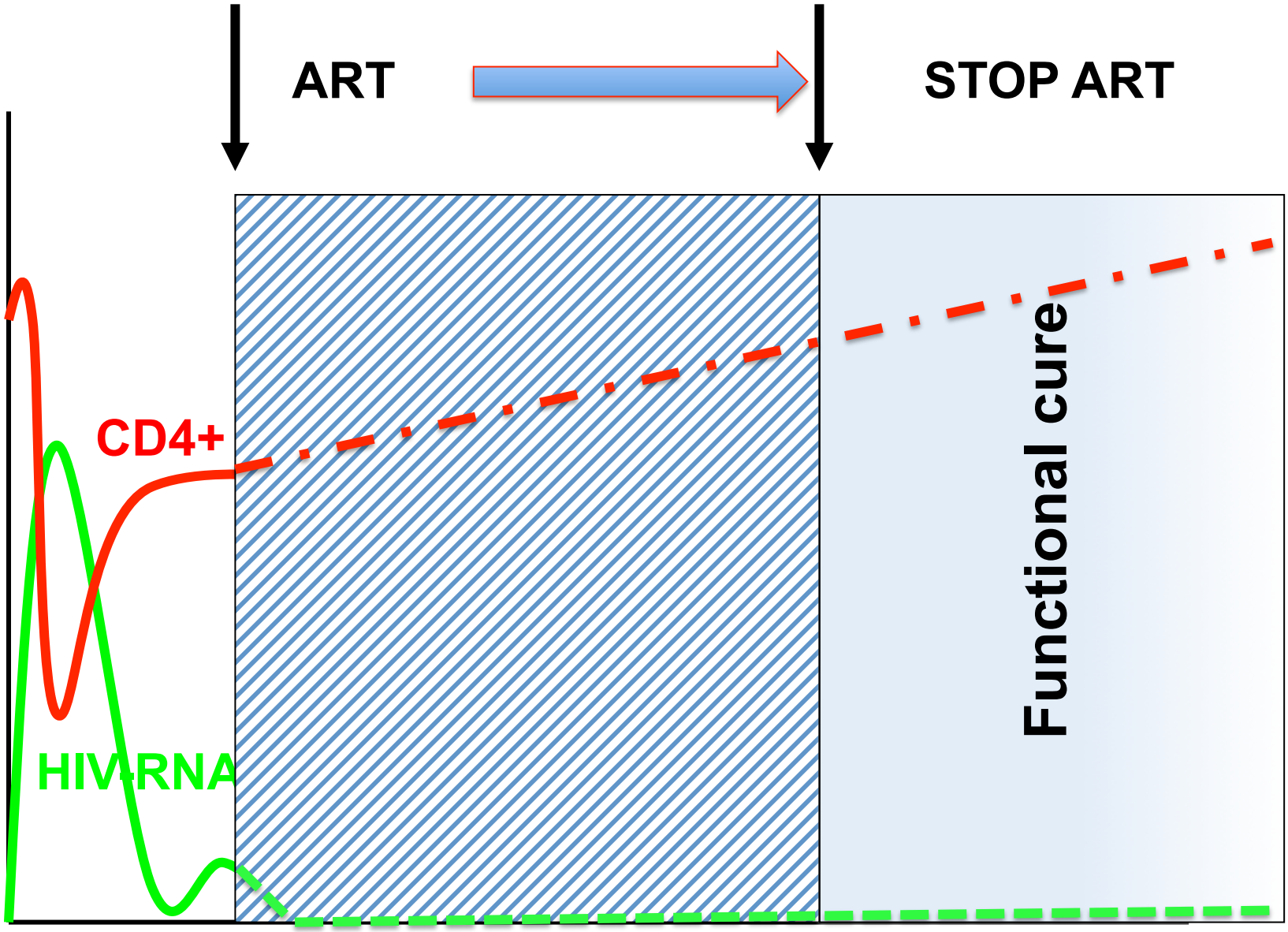
Average life expectancy of an HIV-positive patient is increasing but not yet reaching that of the uninfected population

Life expectancy for 20-year-old HIV-positive patients increased by 15 years from 2002 to 2007, but still falls short of the general population[4,5]



1. Samji H et al. 2013. PLoS One;8(12):e81355;
2. 2. Arias E. Natl Vital Stat Rep 2011;59:1-60.


ART
CD4+
HIV-RNA
Optimization


ART
STOP ART
CD4+
HIV-RNA
Functional cure

Mortality rates in patients with well-controlled HIV infection

Observed death rates and standardised mortality rates (SMRs) among 3,280 non-IDU HIV-positive patients, by age, sex and country
(SMART Study and ESPRIT Study[a])

	Most recent eligible CD4 count, cells/mm^3	
	350–499	>500
PY of follow-up	3,729	8,628
Observed deaths	28	34
Expected deaths[b]	15.86	33.96
SMR (95% CI)	1.77 (1.17–2.55)	1.00 (0.69–1.40)

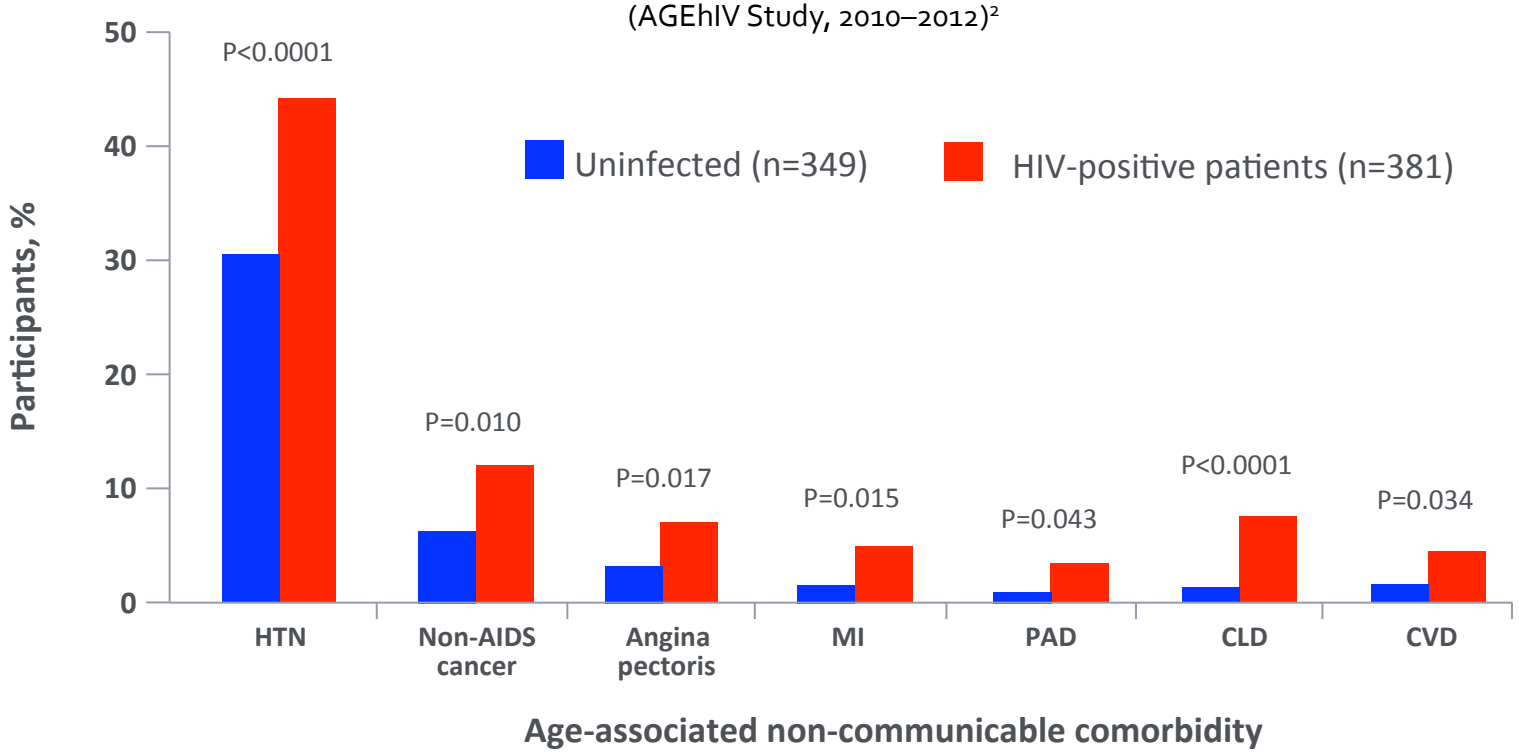
IDU, injection drug user.
[a] Continuous and control arms, respectively; [b] Based on general population mortality

Rodger A et al. AIDS 2013;27:973–979

Comorbidities are more prevalent in HIV-positive patients

- HIV infection may compress certain ageing processes, accelerating comorbidities and frailty[1]
- Duration of ART use (OR 1.24 per 5 additional years of ART use) and lower nadir CD_4 count (OR 1.12 per 100 less cells) were associated with an increased risk of a higher number of comorbidities

Subjects ≥45 years with age-associated non-communicable comorbidities, by HIV serostatus
(AGEhIV Study, 2010–2012)[2]

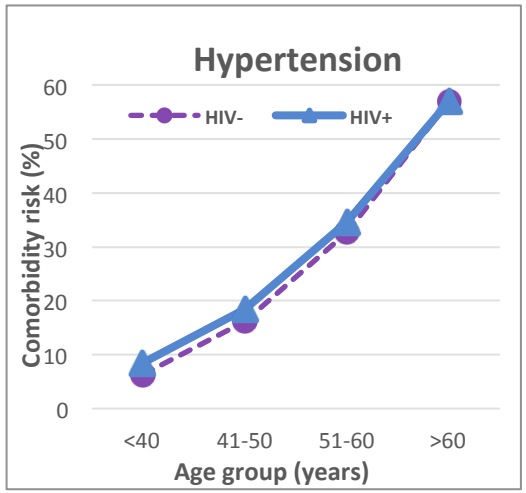


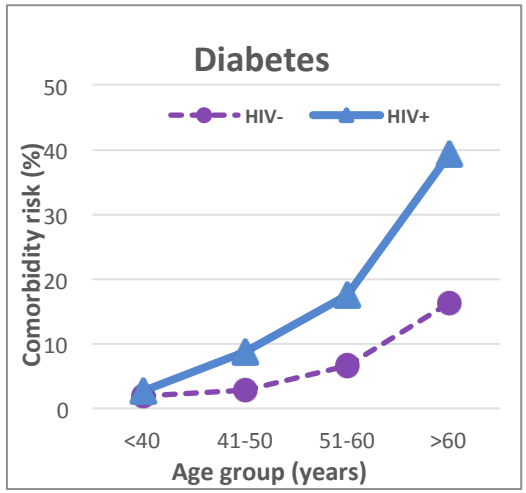
CLD, chronic liver disease; CVD, cerebrovascular disease; HTN, hypertension; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease

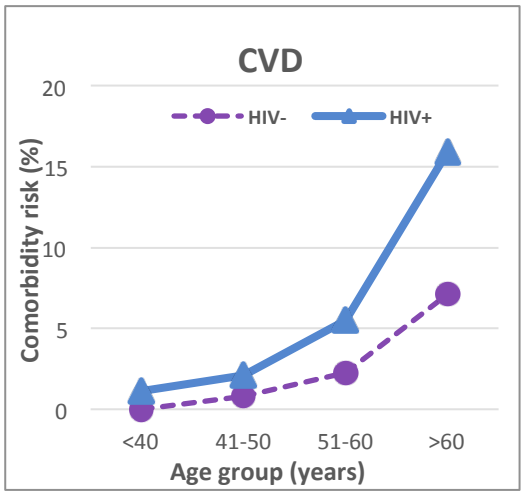
1. Effros RB et al. Clin Infect Dis 2008;47:542–553; 2. Schouten J et al. IAC 2012. Washington, DC. THAB0205

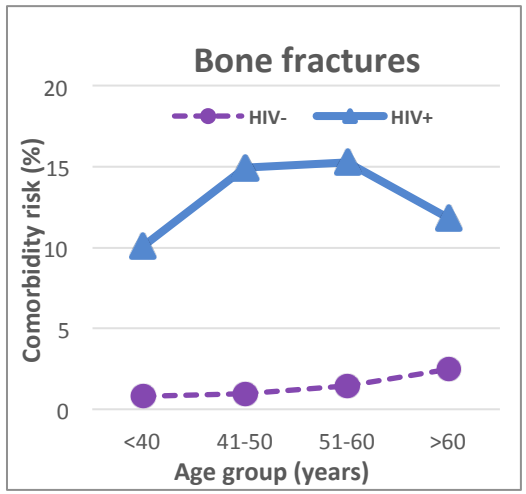
With increased life expectancy, management of non-HIV related comorbidities is now a significant area of focus

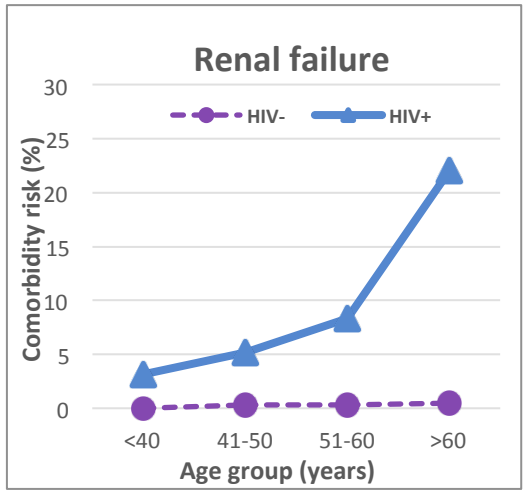
- **Patients with HIV are more susceptible to developing cardiovascular disease, bone fractures and renal failure than HIV-negative[2]**
  - In the 41–50-year-old cohort, HIV-positive patients are 24x more likely to develop renal failure; this increases to 63x for the >60-year-old cohort [1]
  - Bone fracture risk ranged between 12–16x more likely for HIV-positive vs uninfected in the <40–60-year-old range[1]
- **These comorbidities often develop earlier in HIV-positive patients[2]**









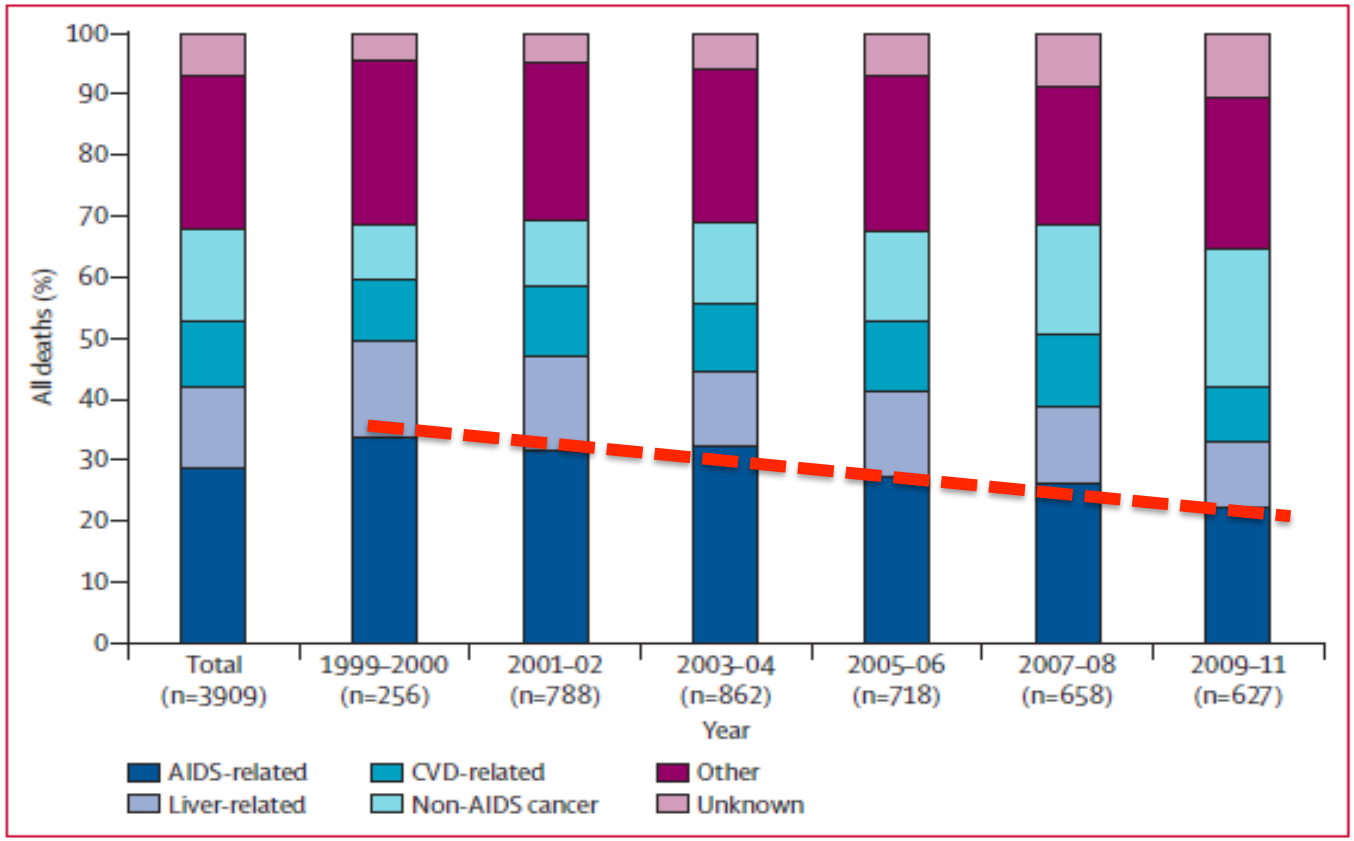


1. Adapted from Guaraldi G et al. Clinicoecon Outcomes Res 2013;5:481–488;
2. Guaraldi G et al. Clin Infect Dis 2011;53:1120–1126

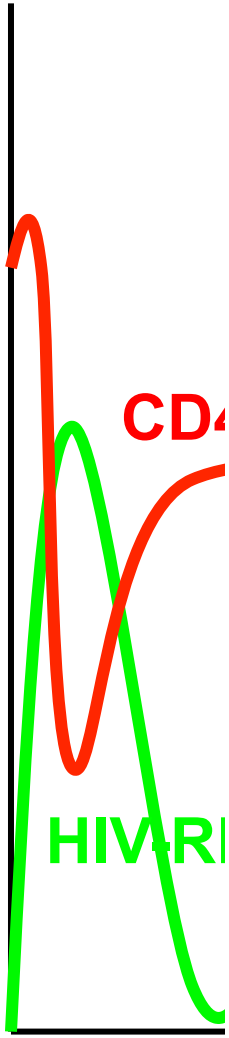
Causes of deaths in HIV patients between 1999 and 2011 (D:A:D study)

- 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



Smith CJ et al. Lancet 2014;384:241–248



PTV FONDAZIONE PTV POLICLINICO TOR VERGATA

Dipartimento Medicina interna Cognome G.

Unità Operativa Malattie infettive Nome MAURO

DATA: 12/09/2016 DATA:

ORE	2	4	7	8	9	10	11	12	13	14	15	16	18	20	22	24	2	4	7	8	9	10	11	12	13	14	15	16	18	20	22	24
T 41																																
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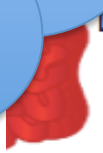
T 37,5																																
U 37														37																		
R 36,5																																
A 36			36																													

ORE	7	14	21
Alvo	+++		
Diuresi		1500 ml tot	
P.A. min/max	100/60		110/70
F.C.	74		70
Peso Kg.	97 %		98 %

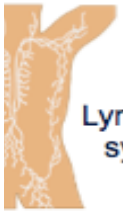
DIARIO CLINICO

TERAPIA:
Truvada 200/245 mg 1 cp/die R
Isentress 400 mg 1cp x2/die os R
Lyrica 150 mg 1 cp + 1 cp e ½ die os mod lyrica 150 mg 1 cp +2 cp/die os
Oramorph 6 gtt a/b max 3 volte die os R
Palexia 100 mg 2 cp x 2/die os R
Folina 5 mg 1 cp/die os R
Tachipirina 1 g a/b max x3/die os R
Venitrin 5 mg tts per 12 ore/die (dalle 8.00 alle 20.00) R
Ranitidina 300 mg 1 cp/die os R
Tranquirit XX gtt/die os R
Fluconazolo 200 mg 1 cp/die os R
Mycostatin 1 mis x3/die os R
KCl retard 600 mg 1 cp x2/die os R
Dilatrend 6,25 mg 1 cp/die os R
Cardioaspirina 100 mg 1 cp/die os R
~~Plavix 75 mg 1 cp/die os R~~
Resource Energy 1 brick x2/die os R
Clexane 6000 UI 1 fl x 2/die sc mod clexane 6000 UI 1 fl /die sc
Cefepime 1 g x 3/die ev R
Colistina 4,5 mln UI x2/die ev R

20 farmaci diversi!!!



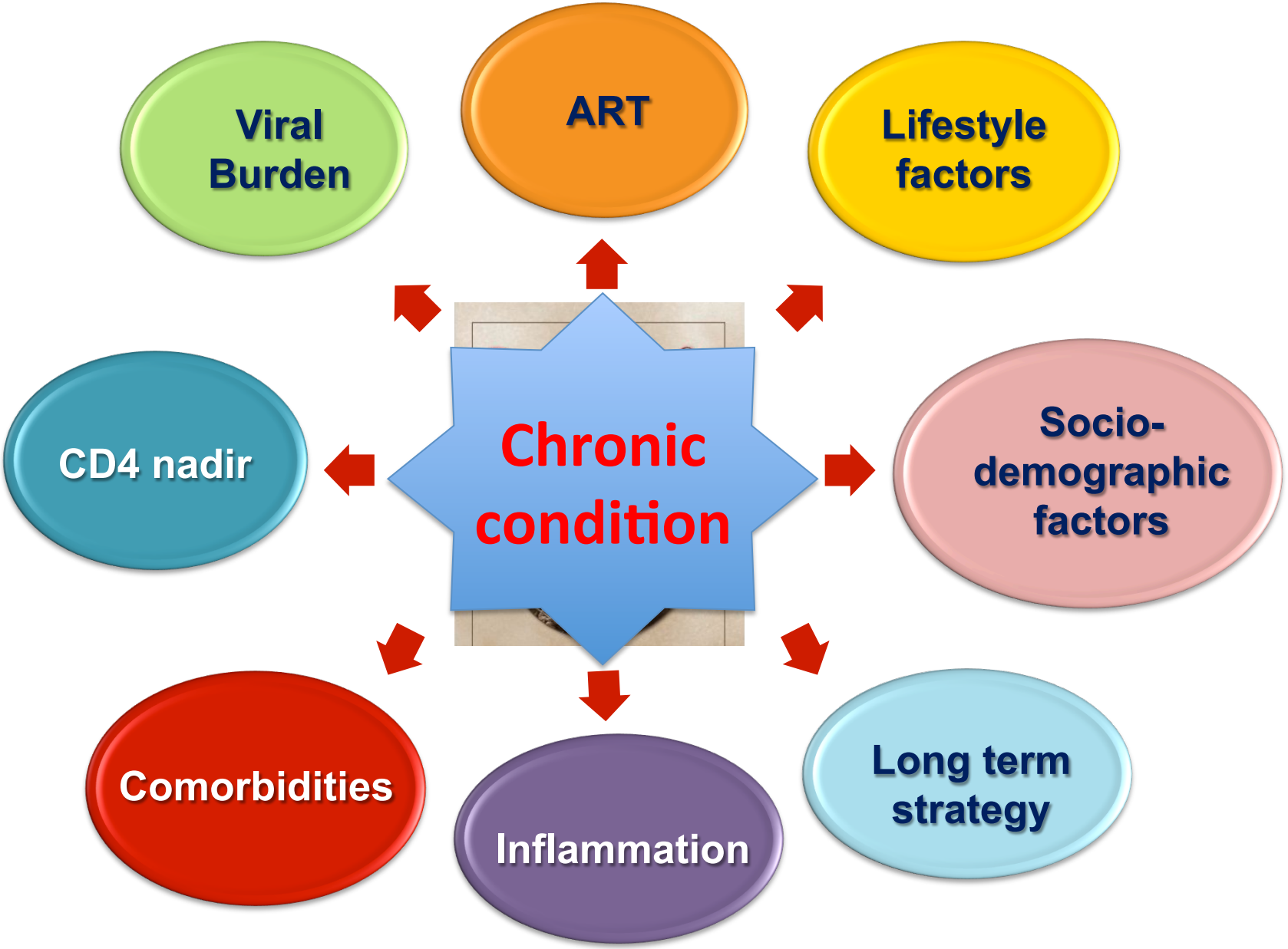
Digestive system



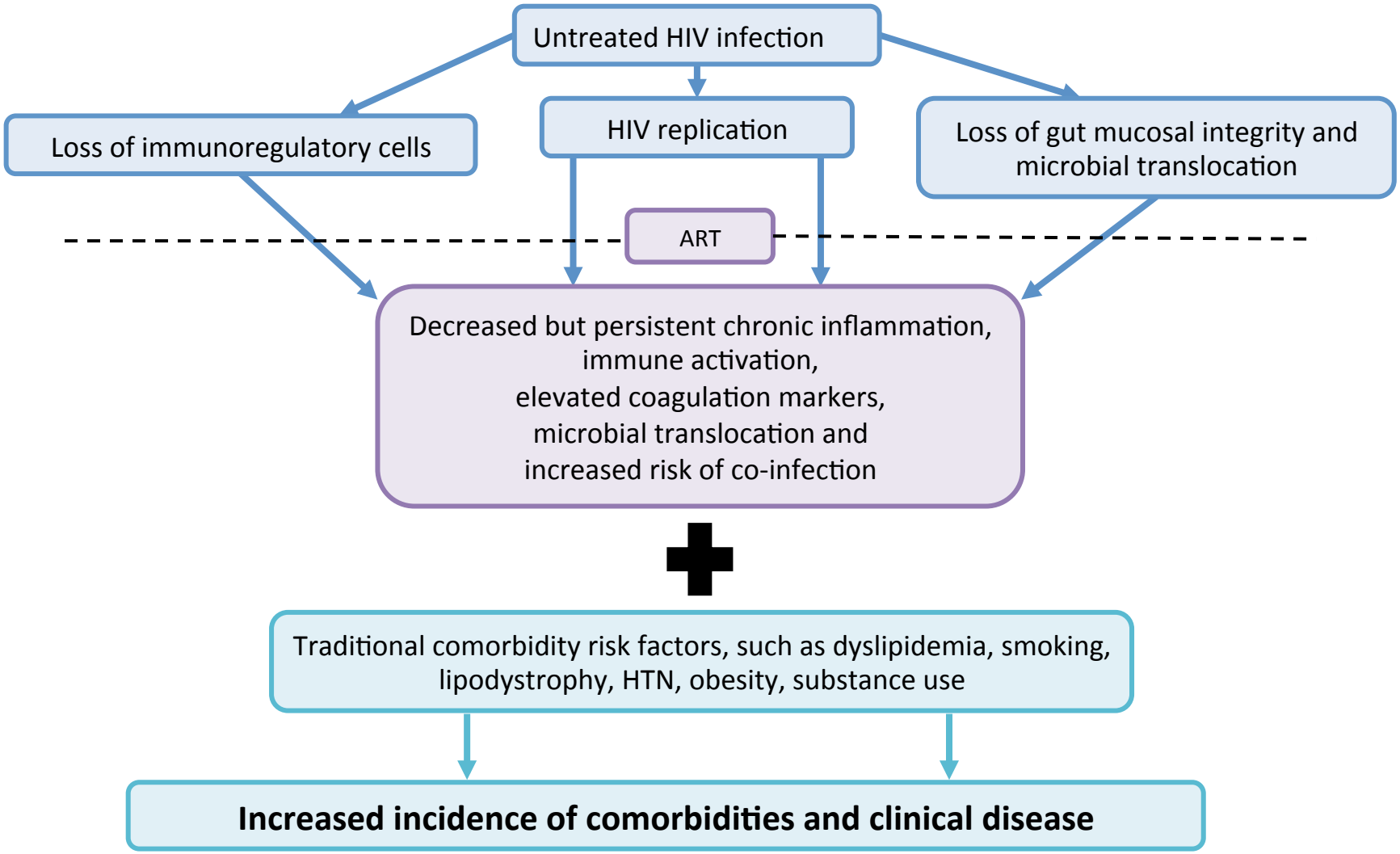
Lymphatic system

ndocrine system

Beyond undetectability: long term risk



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



Deeks SG. Annu Rev Med 2011;62:141–155

Inflammation predicts disease in treated HIV infection, as it does in the general population

- Mortality (Kuller, PLoS Med, 2008, Sandler JID 2011, Tien JAIDS 2011)
- Cardiovascular Disease (Baker, CROI 2013)
- Lymphoma (Breen, Cancer Epi Bio Prev, 2010)
- Venous Thromboembolism (Musselwhite, AIDS, 2011)
- Type II Diabetes (Brown, Diabetes Care, 2010)
- Cognitive Dysfunction (Burdo AIDS 2012)
- Frailty (Erlandson, JID 2013)

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Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection

Lewis H. Kuller[1], Russell Tracy[2], Waldo Belloso[3], Stephane De Wit[4], Fraser Drummond[5], H. Clifford Lane[6], Bruno Ledergerber[7], Jens Lundgren[8], Jacqueline Neuhaus[9], Daniel Nixon[10], Nicholas I. Paton[11], James D. Neaton[9*], for the INSIGHT SMART Study Group

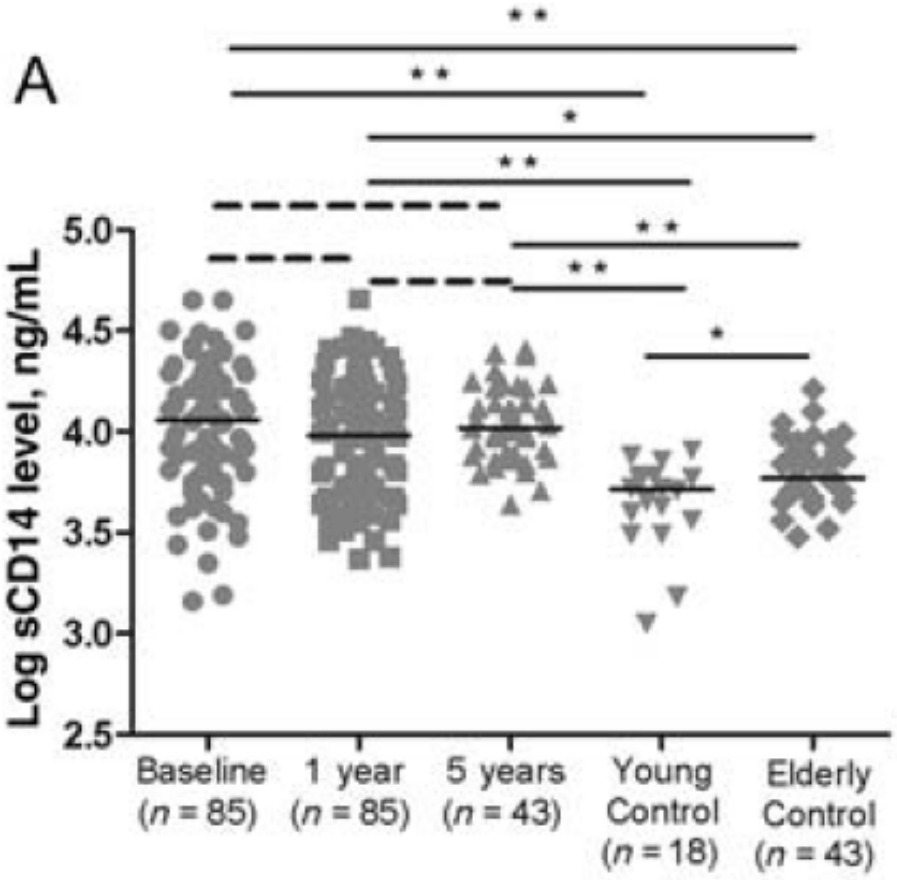
1 University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **2** University of Vermont, Burlington, Vermont, United States of America, **3** Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, **4** Saint-Pierre Hospital, Brussels, Belgium, **5** National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia, **6** National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, United States of America, **7** University Hospital, Zurich, Switzerland, **8** University of Copenhagen, Copenhagen, Denmark, **9** University of Minnesota, Minneapolis, Minnesota, United States of America, **10** Virginia Commonwealth University, Richmond, Virginia, United States of America, **11** Medical Research Council Clinical Trials Unit, London, United Kingdom

Biomarker and All-Cause Mortality Associations

Baseline Level	OR ($4^{th}/1^{st}$ QRT) Univariate	*P-value*
D-dimer	**12.4**	<0.0001
IL-6	**8.3**	<0.0001
hsCRP	**2.0**	0.05

February 4, 2013

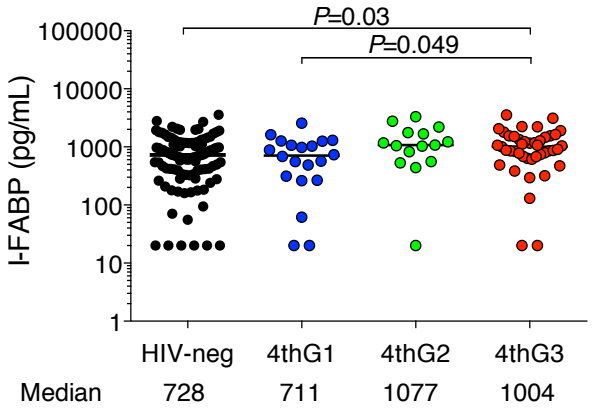
Long-Term Suppressive Combined Antiretroviral Treatment Does Not Normalize the Serum Level of Soluble CD14

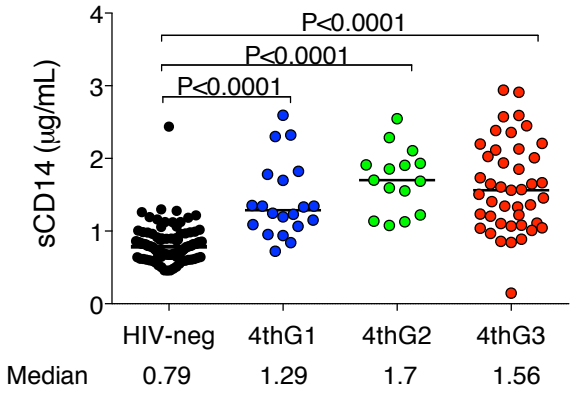


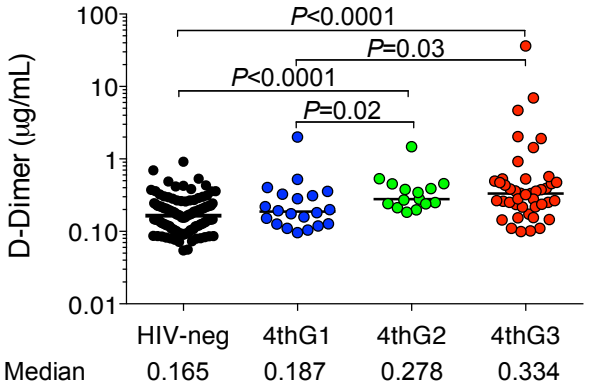
HIV-infected group displayed a significantly higher sCD14 level at baseline (ie, before cART initiation), 1 year and 5 years after cART initiation, compared with both control groups.

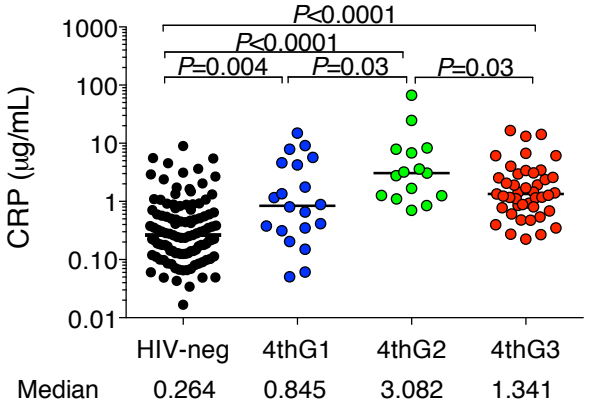
G. Mendez-Lagares

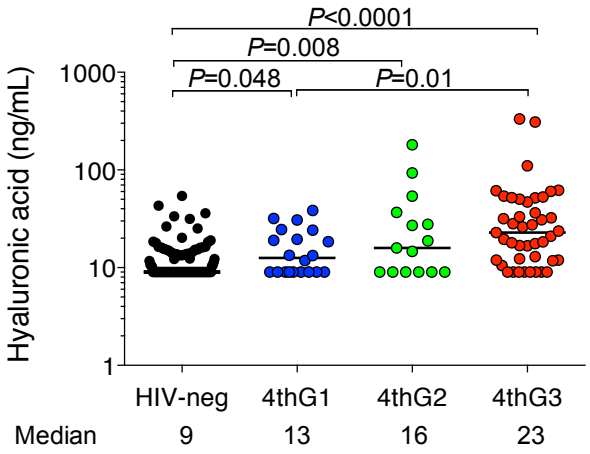
Inflammatory Biomarkers at Diagnosis of Acute HIV Infection









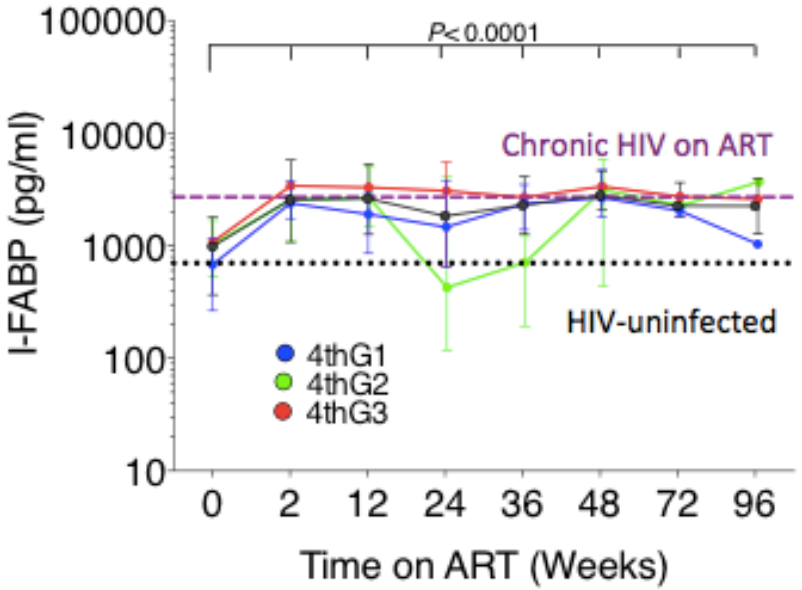


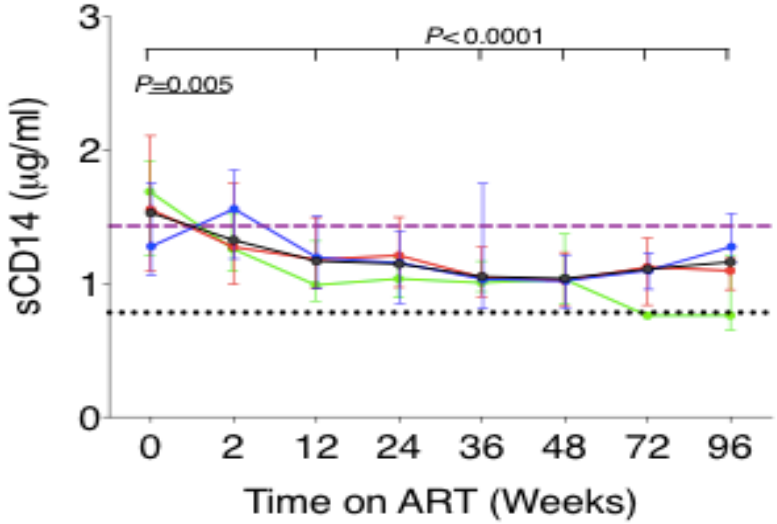
Compared to healthy controls, subjects with all stages of acute HIV infection have increased CRP, sCD14, and HA levels, and subjects with later stages of acute HIV infection have increased D-dimer and I-FABP levels.

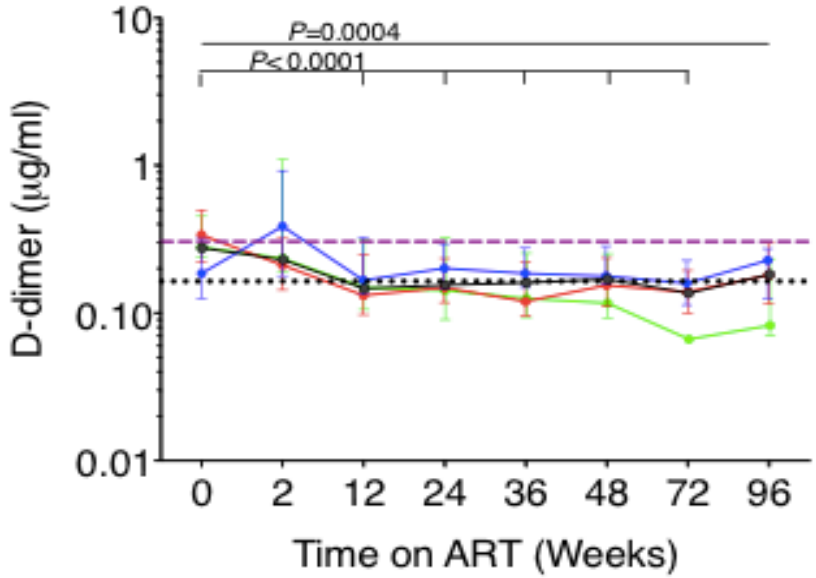
Sandler, CROI, 2014

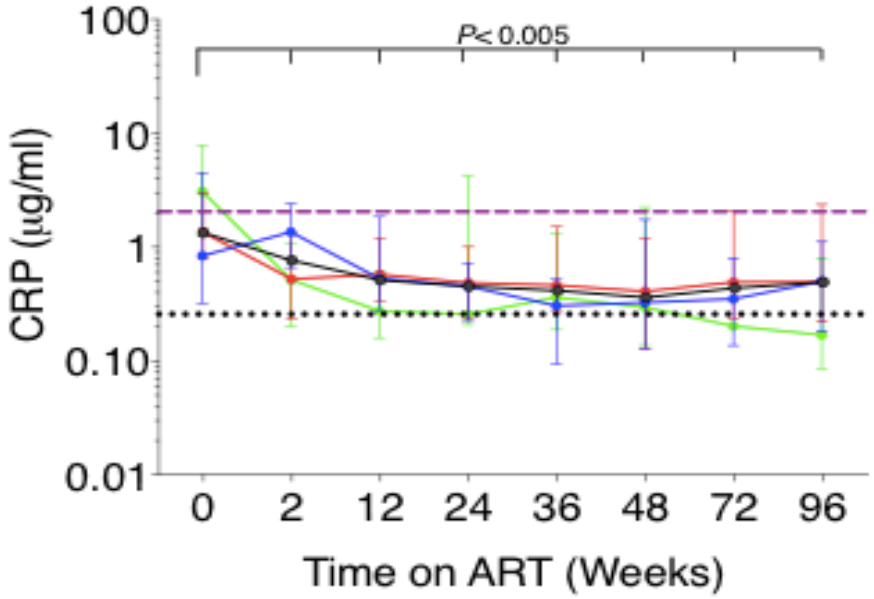
Inflammation persists despite early initiation of ART in acute HIV infection

NS Utay, CROI 2015

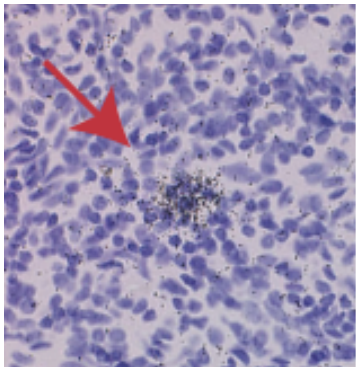




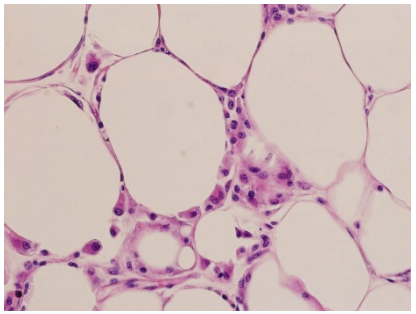




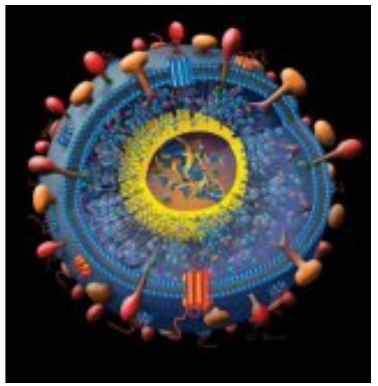
HIV production
HIV replication



HIV-associated fat
Metabolic syndrome

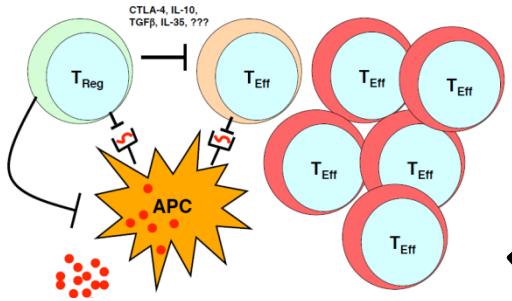


CMV/HCV
Excess pathogens

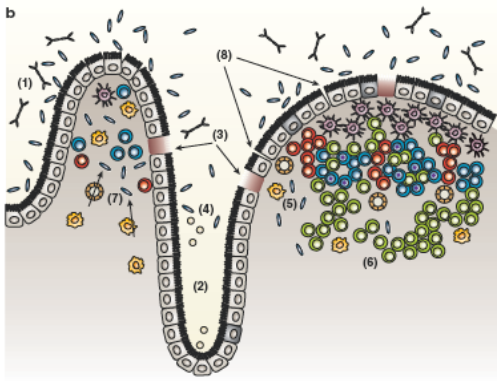


Inflammation

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

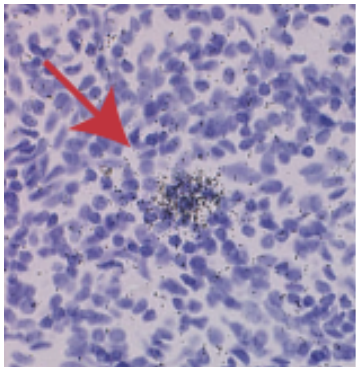


HIV-mediated loss of
regulatory cells (Tregs)



Microbial
translocation

HIV production
HIV replication



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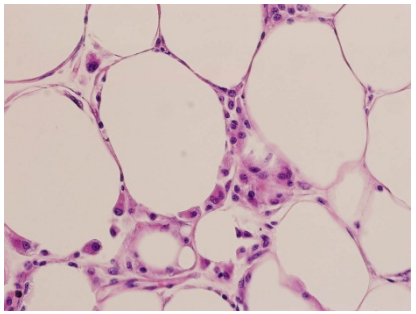

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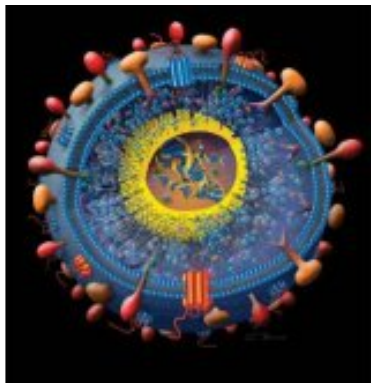

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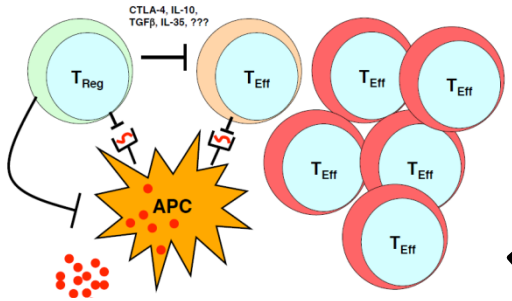

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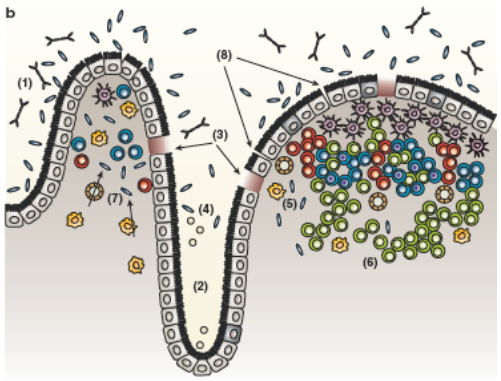
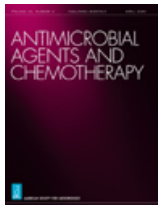


Microbial
translocation

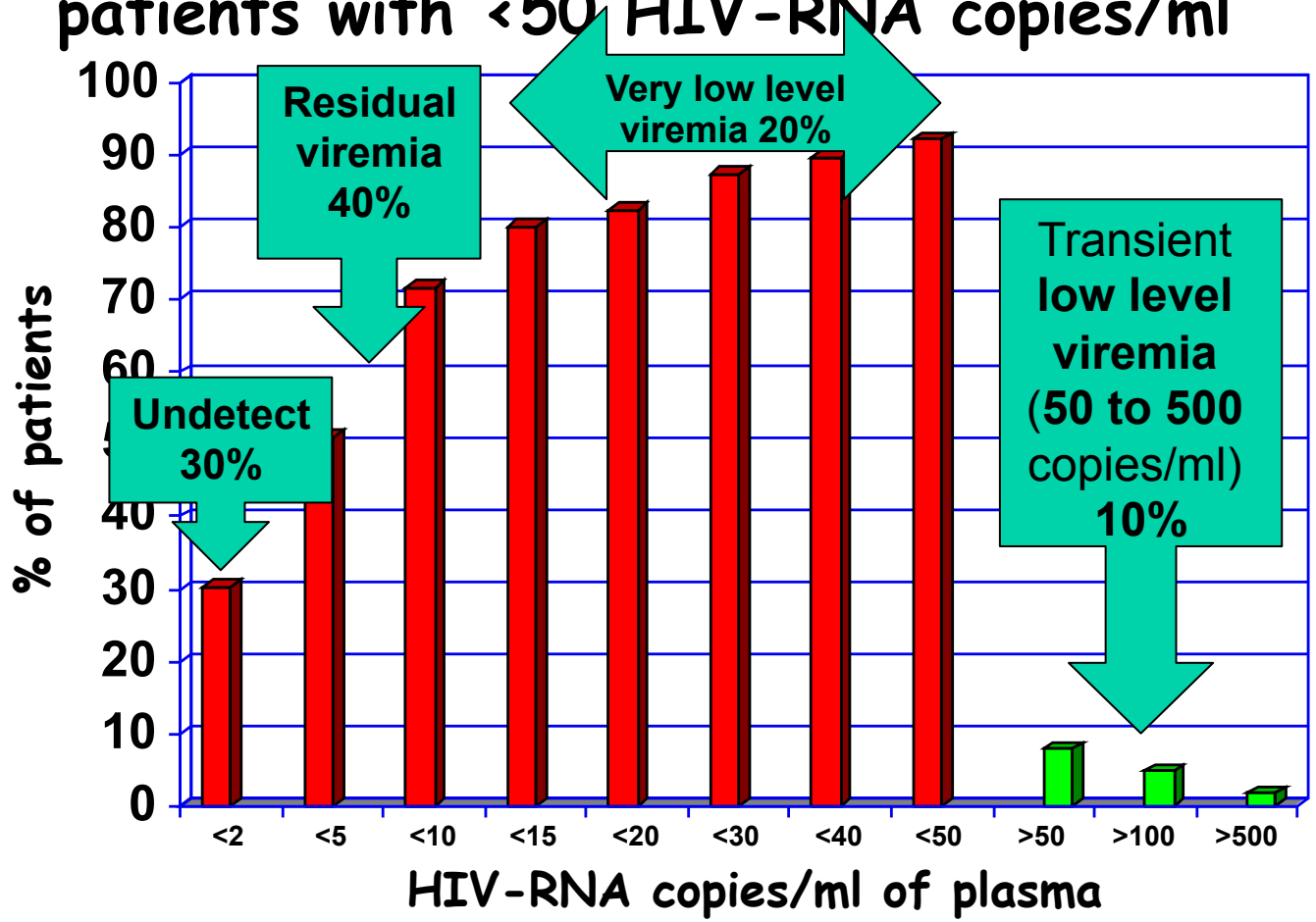


Nevirapine use, prolonged antiretroviral therapy and high CD4 nadir values are strongly correlated with undetectable HIV-DNA and -RNA levels and CD4 cell gain

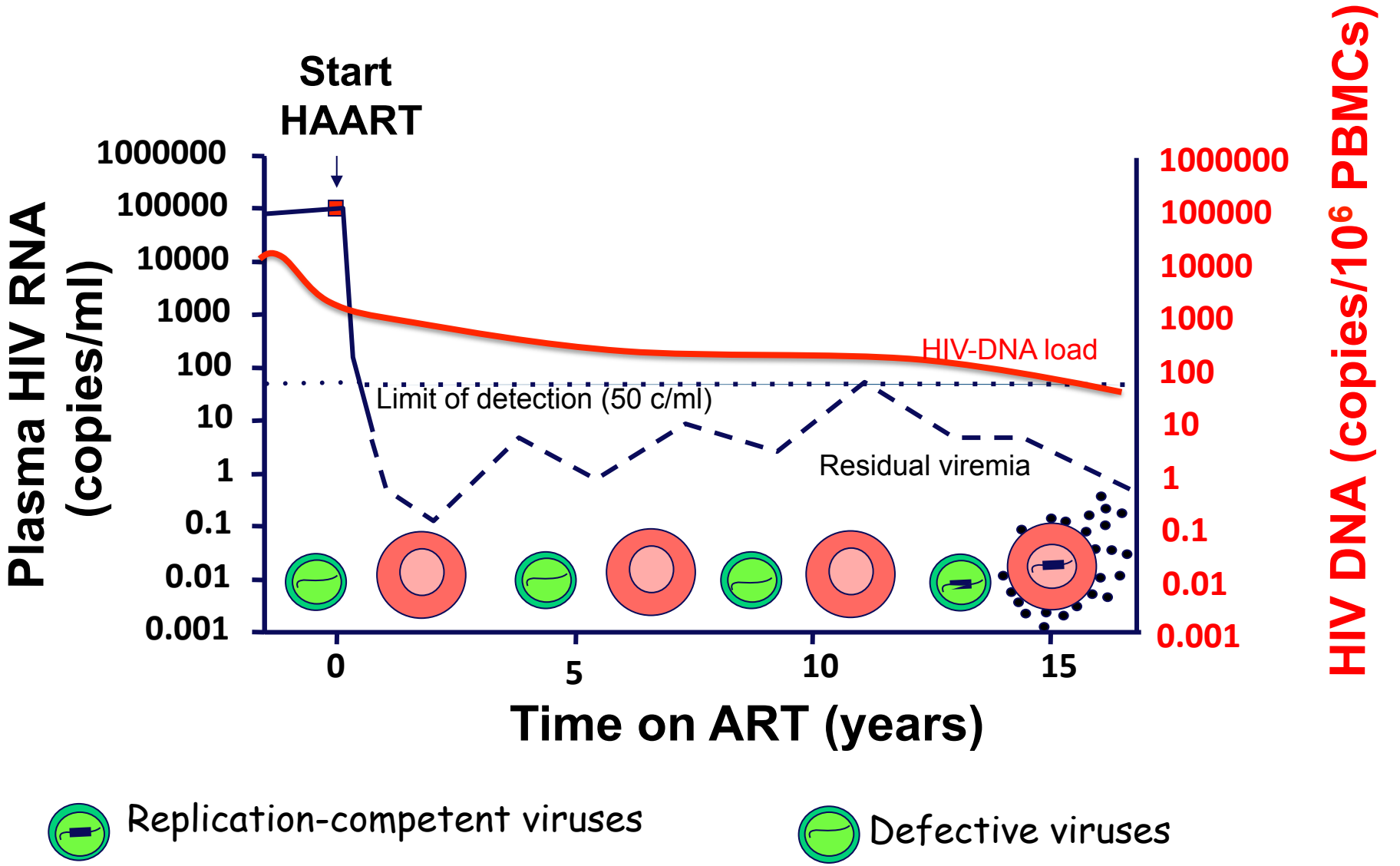
2012

Loredana Sarmati[1]*, Saverio Giuseppe Parisi[2], Marco Montano[1], Samantha Andreis[2], Renzo Scaggiante[3], Andrea Galgani[4], Magdalena Viscione[1], Gaetano Maffongelli[1], Alessandra Ricciardi[1], Carolina Andreoni[5], Stefano Boros[6], Giorgio Palù[2] and Massimo Andreoni[1]

Detection of viral load by ultrasensitive method in 420 patients with <50 HIV-RNA copies/ml



Long lived cells containing non-defective HIV are a very small fraction of total DNA positive-cells (<1%).



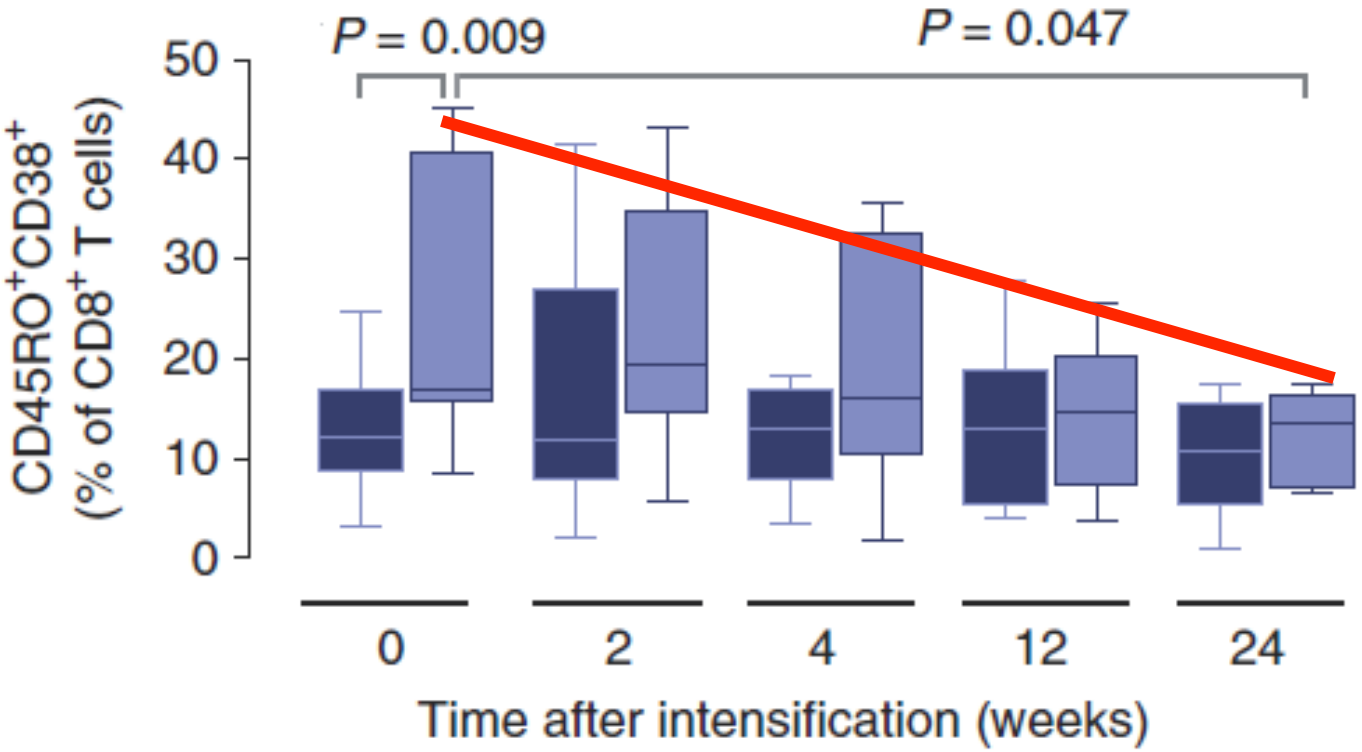
Andreoni Current HIV Medicine 2015

nature medicine

14 March 2010

HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

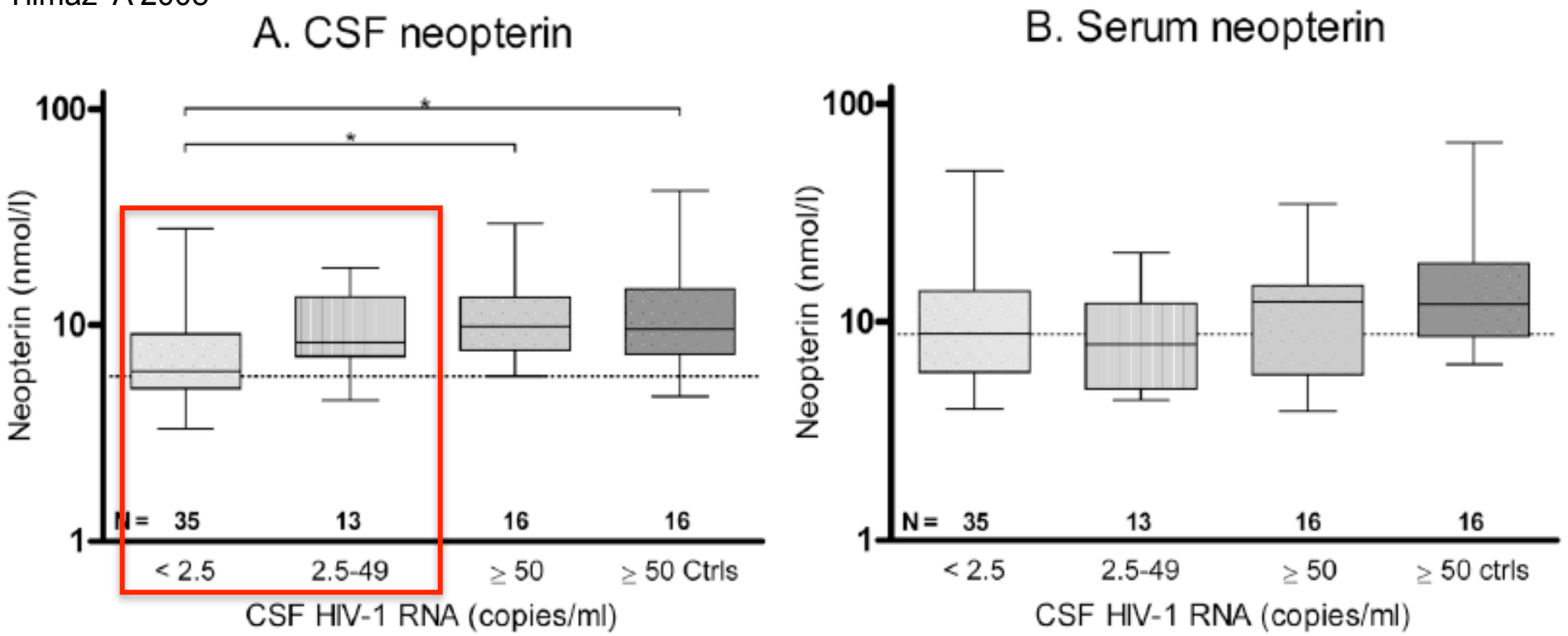
In subjects with increased episomal DNAs, immune activation was higher at baseline and was subsequently normalized after RAL intensification.



M.J.Buzon

Persistent intrathecal immune activation in HIV-1-infected individuals on antiretroviral therapy

Yilmaz A 2008

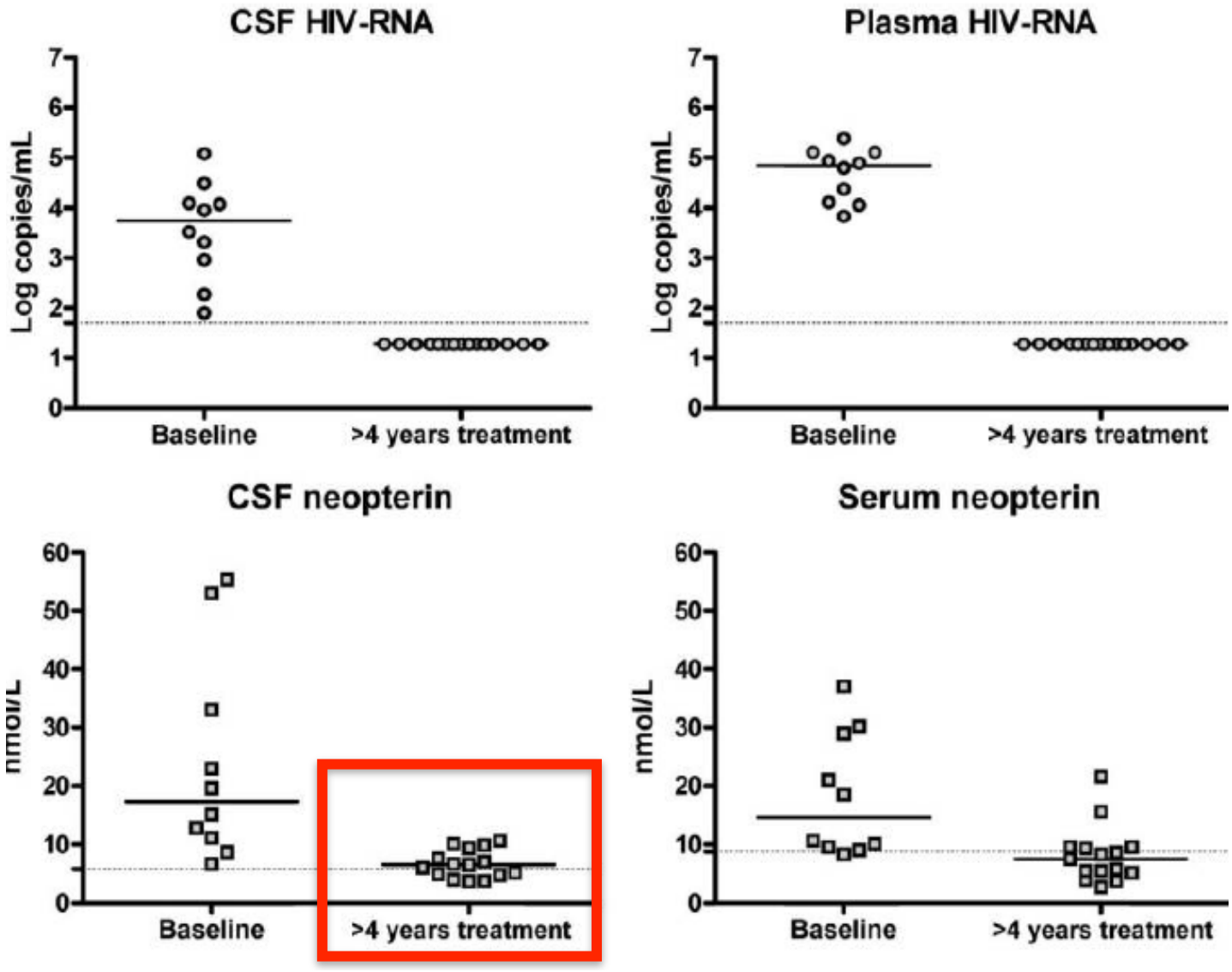


CSF and serum neopterin levels with different HIV-RNA levels during HAART

Immune activation of the central nervous system is still present after >4 years of effective HAART

Even A JID 2007

Neopterin levels in CSF decresed but were above normal value



RESEARCH ARTICLE

Association of Residual Plasma Viremia and Intima-Media Thickness in Antiretroviral-Treated Patients with Controlled Human Immunodeficiency Virus Infection

PLOS ONE
2014

Anders Boyd[1*], Jean-Luc Meynard[2,3], Laurence Morand-Joubert[4], Adrien Michon[5], Franck Boccara[2,6,7], Jean-Philippe Bastard[2,8], Assia Samri[2,9], Nabila Haddour[2,6], Ziad Mallat[10,11], Jacqueline Capeau[2,8], Moïse Desvarieux[12,13], Pierre-Marie Girard[1,2,3], for the Collaboration in HIV, Inflammation and Cardiovascular Disease Study

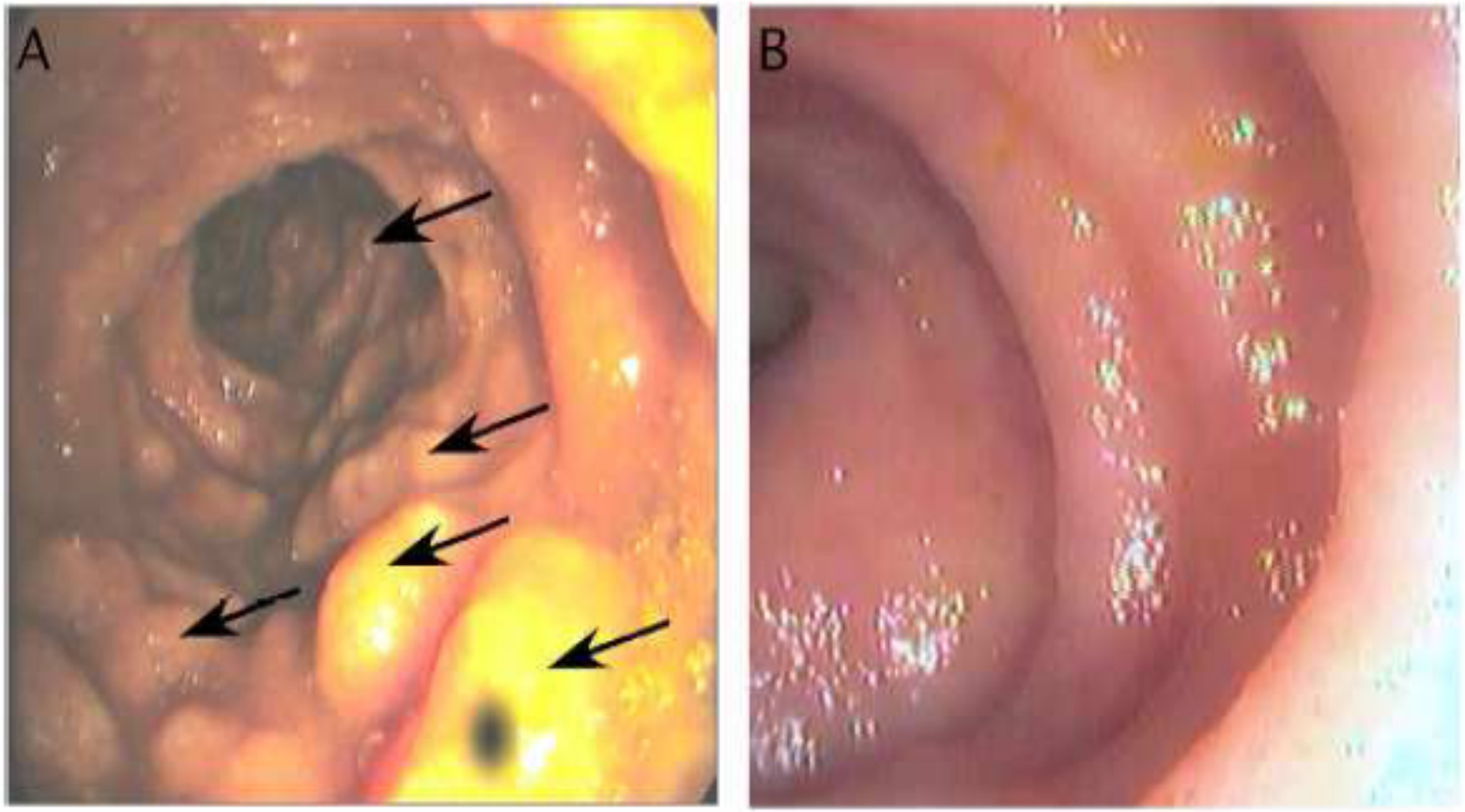
Background: While residual plasma viremia is commonly observed in HIV-infected patients undergoing antiretroviral treatment (ART), little is known about its subclinical consequences.

Methods: This cross-sectional study included 47 male, never-smoking, non-diabetic patients with >4 years of ART and controlled HIV-replication (HIV-viral load, VL <20 copies/mL for>1 year). Residual HIV-VL was measured using an ultrasensitive assay (quantification limit: 1 copy/ml). Patients were categorized as having detectable (D; 1-20 copies/mL, n=514) or undetectable (UD;,1 copies/mL, n=533) HIV-VL. Linear regression was used to model the difference in total carotid intima-media thickness [c-IMT, measures averaged across common carotid artery (cca), bifurcation, and internal carotid artery] and cca-IMT alone across detection groups. Multivariable models were constructed for each endpoint in a forward-stepwise approach. Results: No significant differences were observed between viremia groups with respect to median ART-duration (9.6 years, IQR56.8–10.9), nadir CD4+T-cell (208/ mm^3, IQR5143–378), and CD4+T-cell count (555/mm^3, IQR5458–707). Median adjusted inflammatory markers tended to be higher in patients with D- than UDviremia, with differences in IL-10 being significant (p=0.03). After adjustment on age, systolic blood pressure, and insulin resistance, **mean cca-IMT was significantly lower in patients with undetectable (0.668 mm±0.010) versus detectable viremia (0.727 mm±0.015, p=0.002).** Cca-IMT was also independently associated with age and insulin resistance. Mean adjusted total c-IMT was no different between viremia groups (p=0.2), however there was large variability in bifurcation c-IMT measurements.

Conclusions: Higher cca-IMT was observed in patients with detectable, compared to undetectable, HIV-VL in never-smoking ART-controlled patients, suggesting that residual HIV viremia may be linked to atherosclerosis.

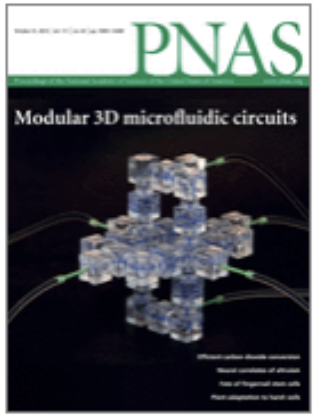
Terminal ileum, HIV uninfected

Terminal ileum, Week 3 HIV Infection



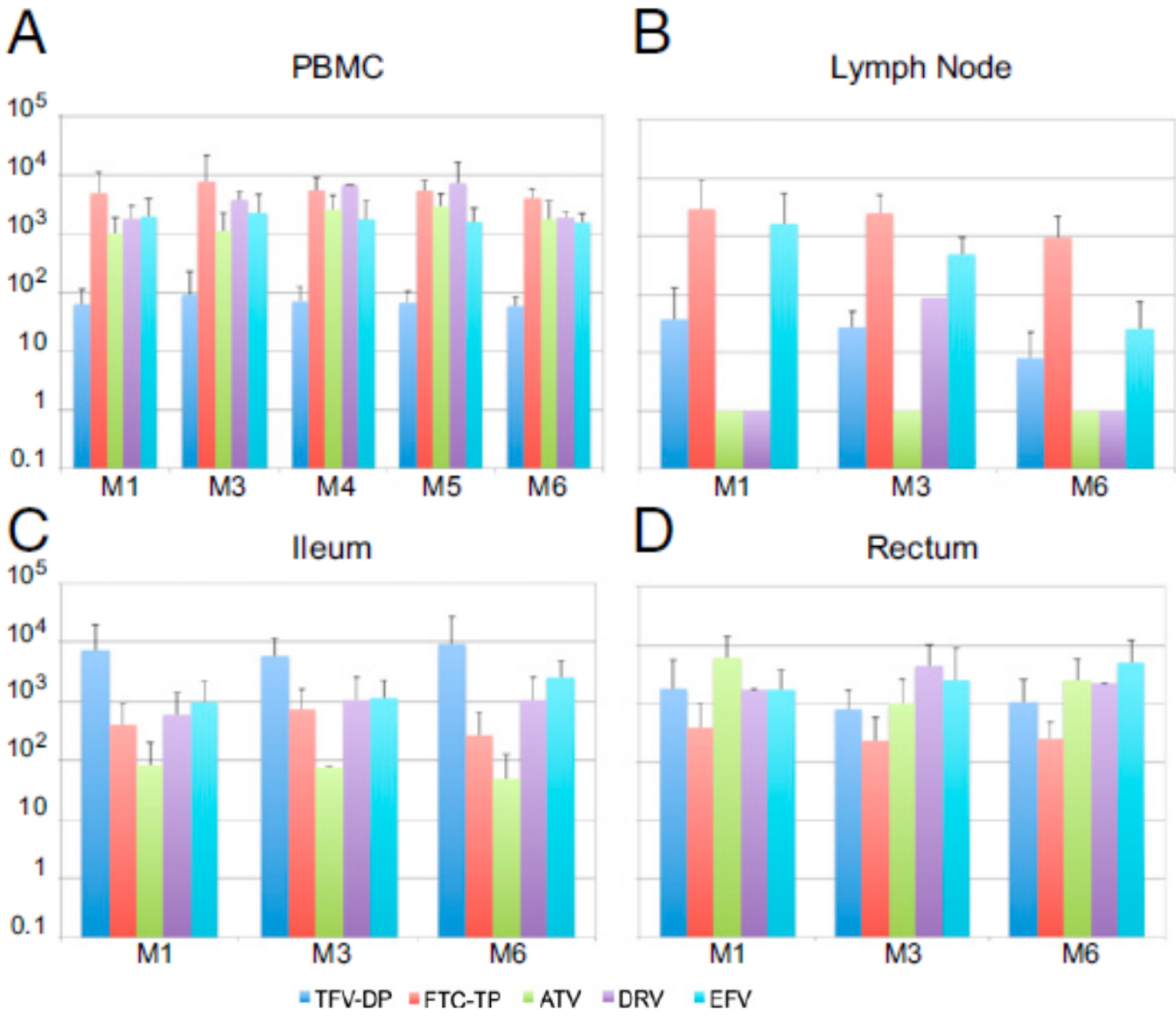
HIV infection results in a rapid and dramatic depletion of CCR5+ CD4+ memory T cells in gut (without evidence of increase activation/turnover)

Brenchley et al; J. Exp. Med 2004



Fletcher CV, 2014

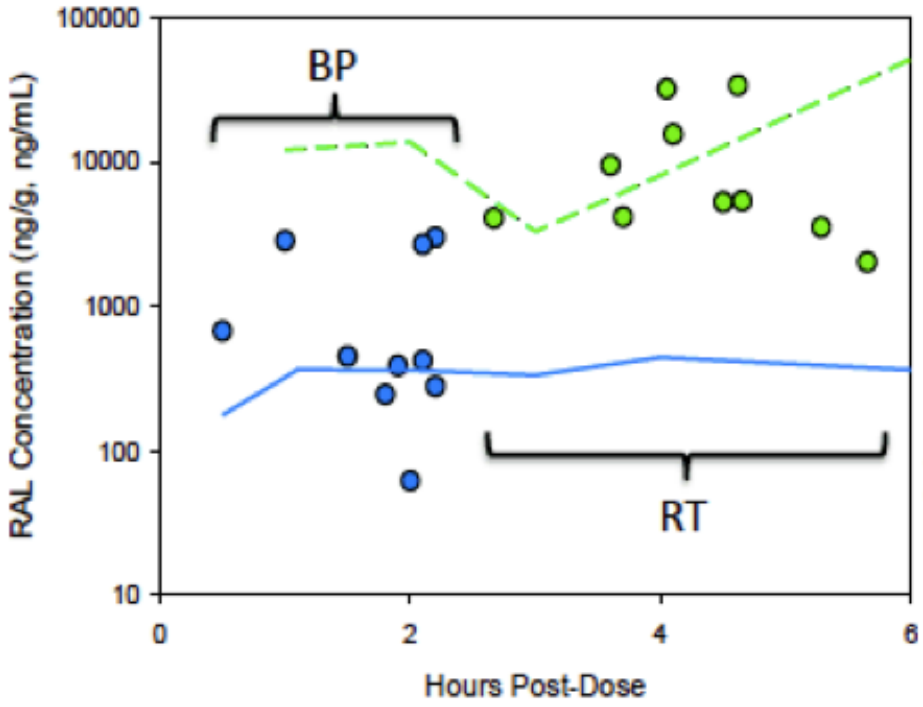
Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues



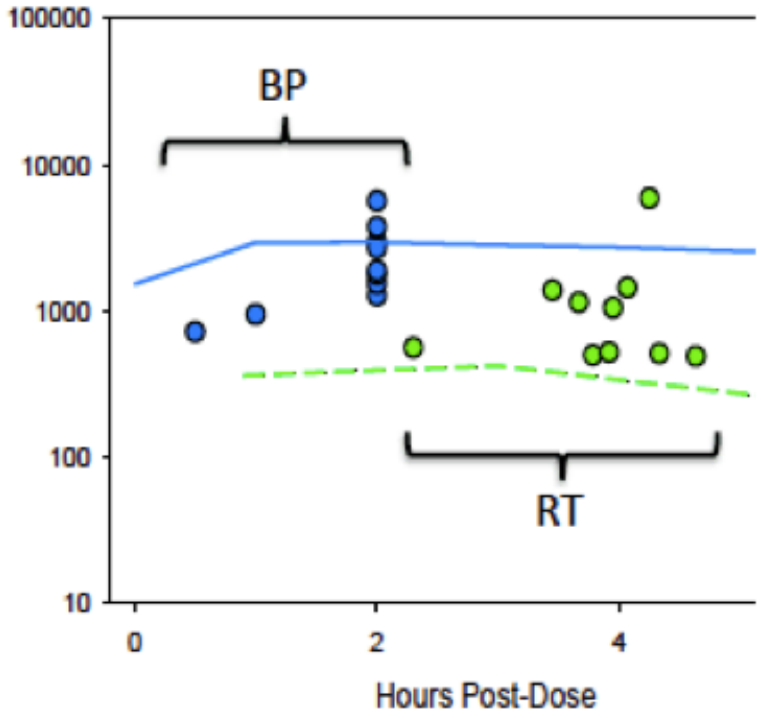
Virologic and Immunologic Responses to Raltegravir and Dolutegravir in GALT of HIV+ Men

Weber MD, 17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy June 8-10, 2016, Washington DC

Raltegravir



Dolutegravir



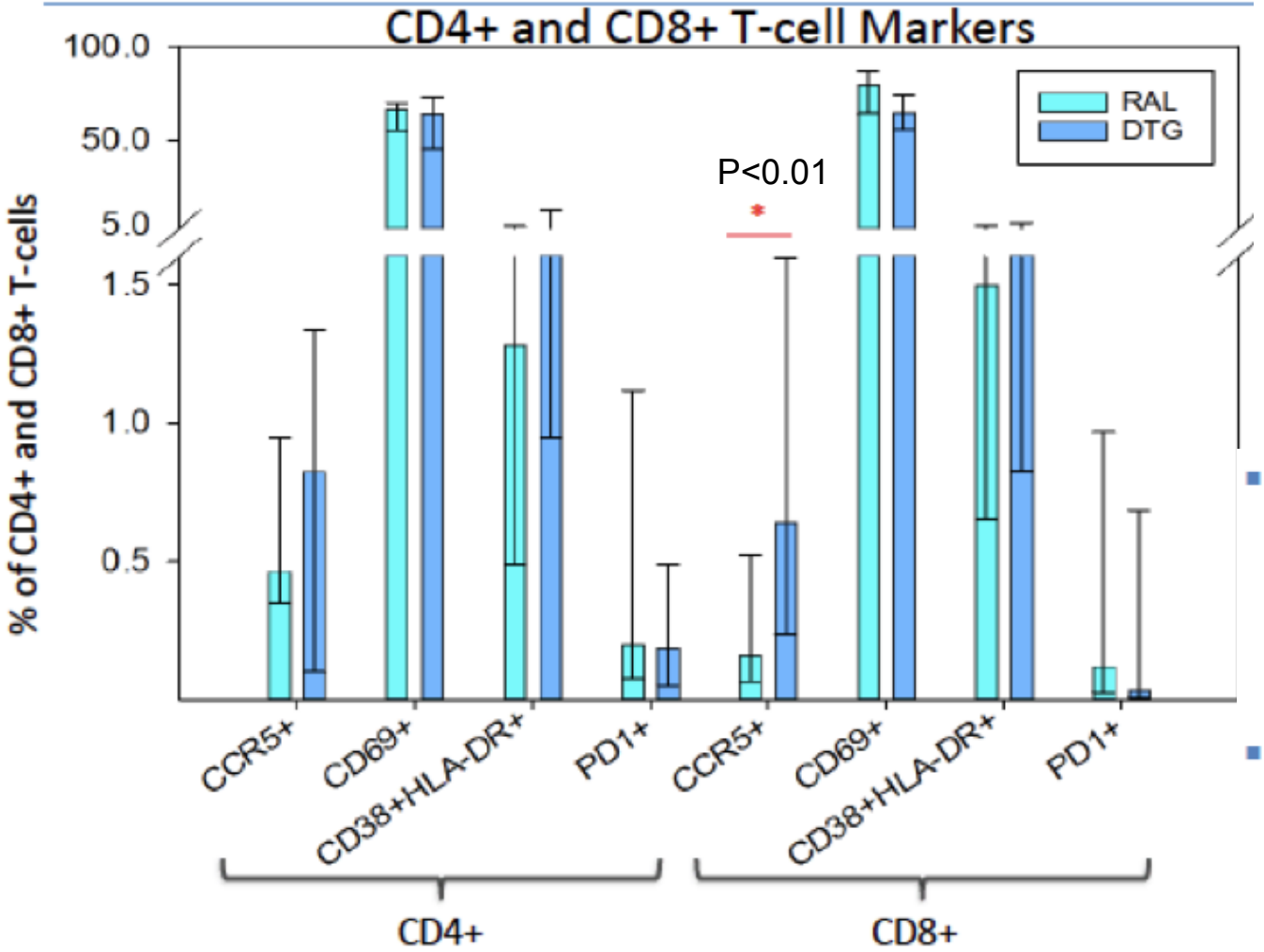
RAL producer higher tissue exposure

	RAL	DTG
Tissue Concentration	5,308ng/g (3,938-19,600)	810ng/g (510-1,408)
Tissue:plasma	11.3 (7.7-25.5)	0.44 (0.29-0.65)

Virologic and Immunologic Responses to Raltegravir and Dolutegravir in GALT of HIV+ Men

Weber MA, 17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy June 8-10, 2016, Washington DC

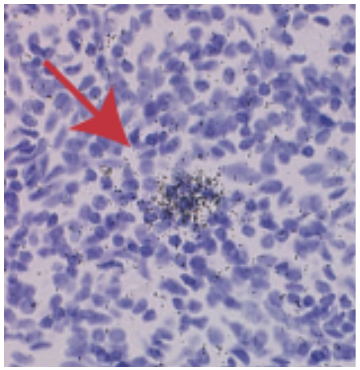
No significant difference in immunologic markers



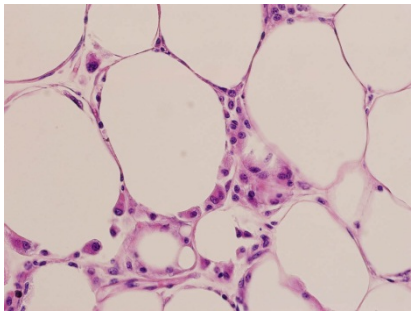
CCR5+	Marker of activation
CD69+	Marker of activation
CD38+HLA-DR+	Marker of activation
PD1+	Marker of exhaustion

- Markers of Activation
  - Increased activation is correlated with a slower immune reconstitution
- Marker of Exhaustion
  - Increased PD1+ is correlated with limited immune reconstitution

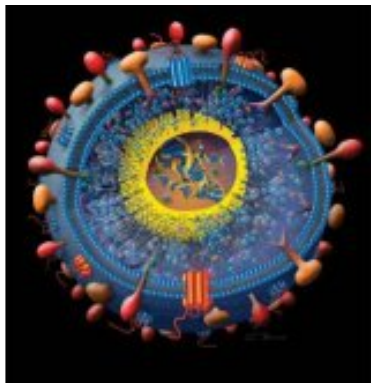
HIV production
HIV replication



HIV-associated fat
Metabolic syndrome

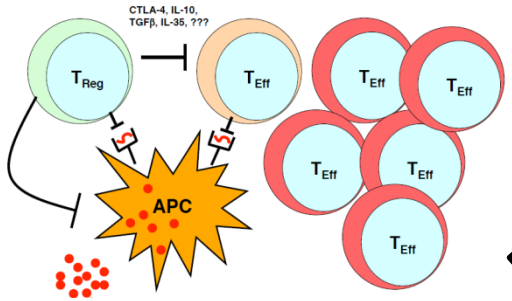


CMV/HCV
Excess pathogens

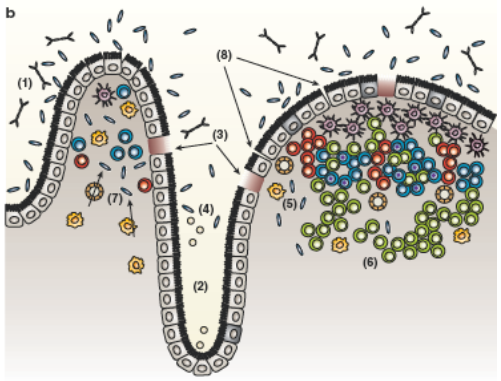


Inflammation

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

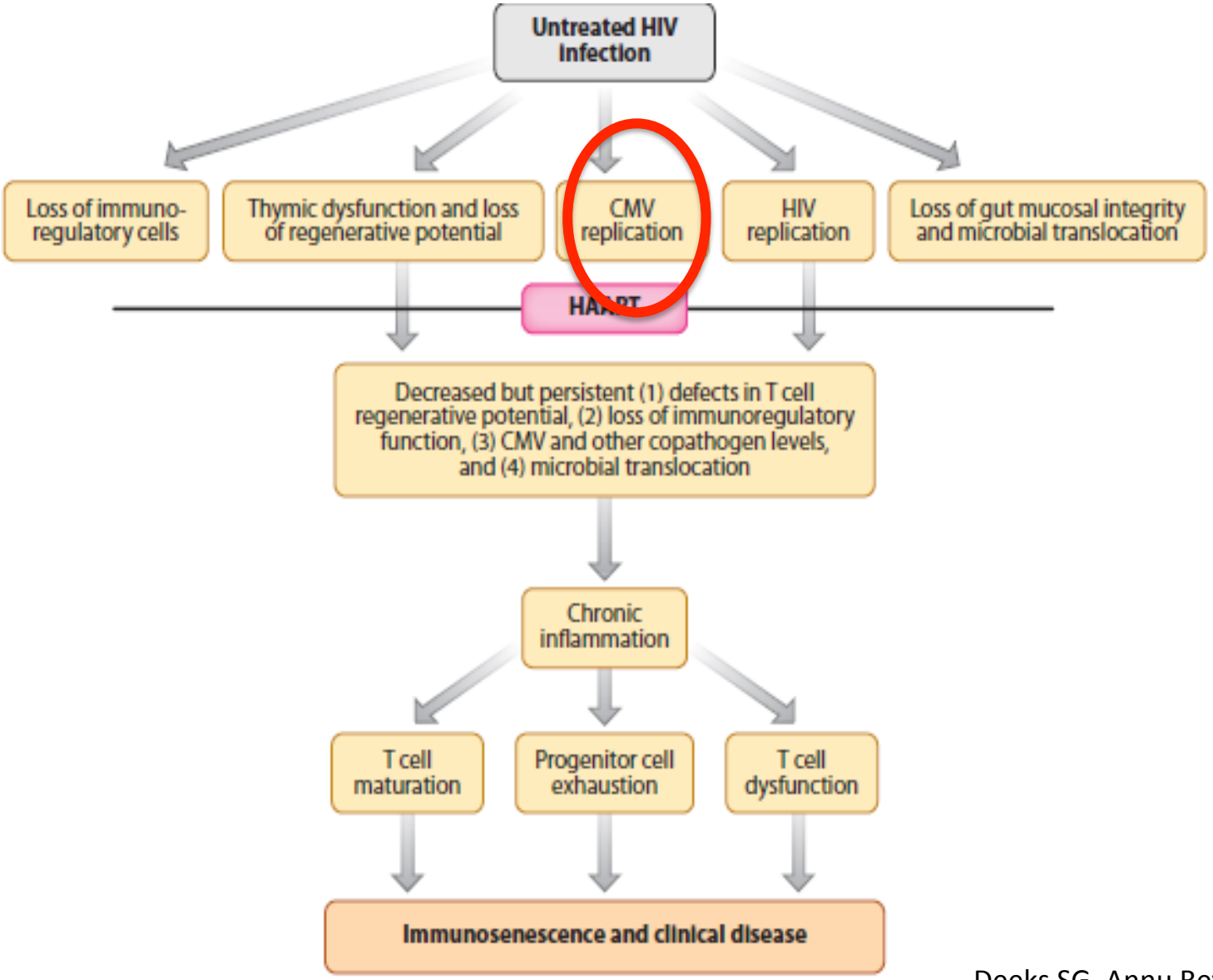


HIV-mediated loss of
regulatory cells (Tregs)

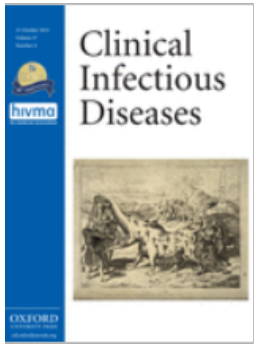


Microbial
translocation

The effect of HIV infection and its treatment on inflammation and immunosenescence



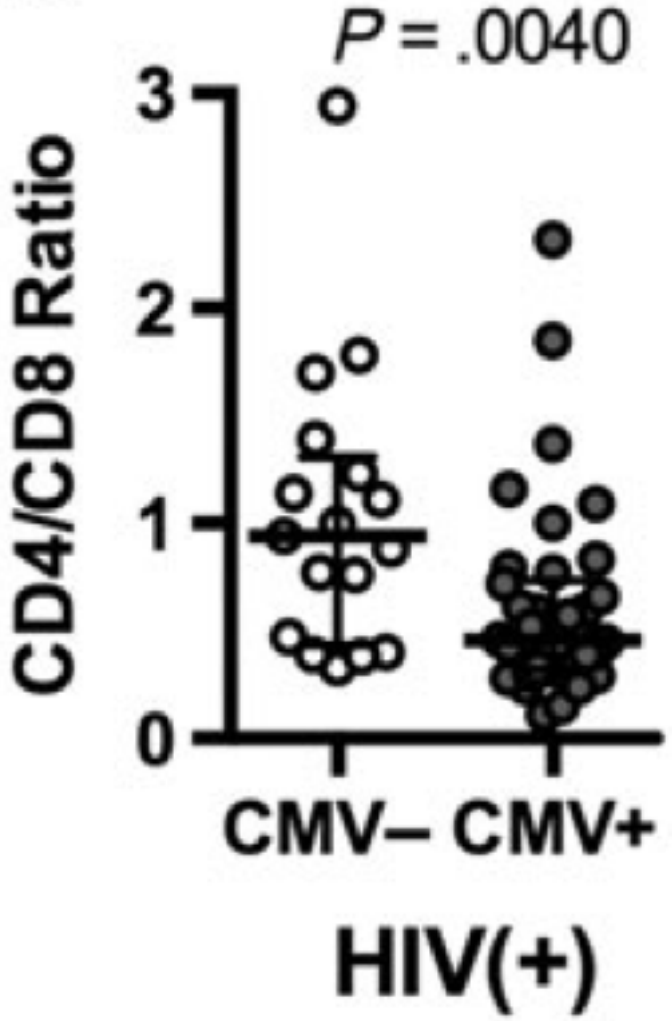
Deeks SG, Annu Rev Med, 2011



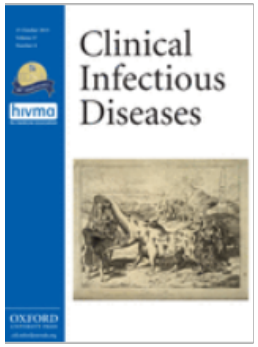
CD8 T-Cell Expansion and Inflammation Linked to CMV Coinfection in ART-treated HIV Infection

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. Lederman[1]

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.



CID 2016:62 (1 February)



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

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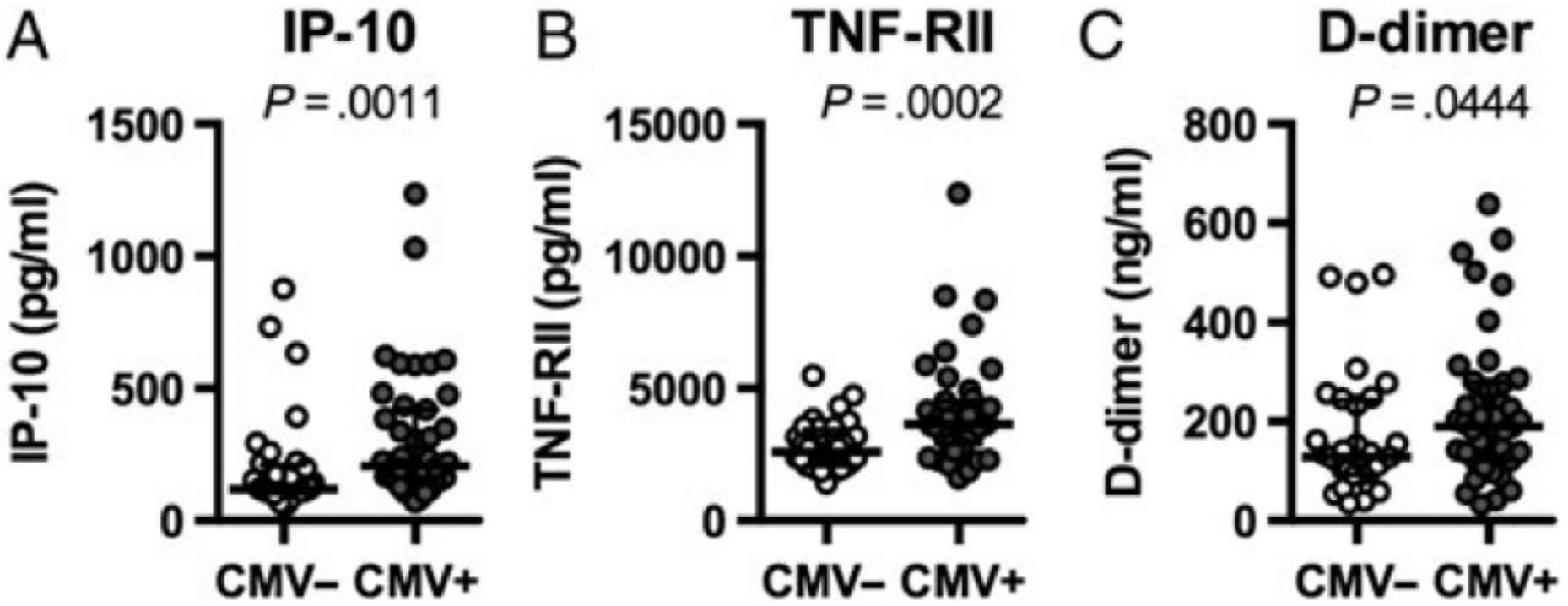
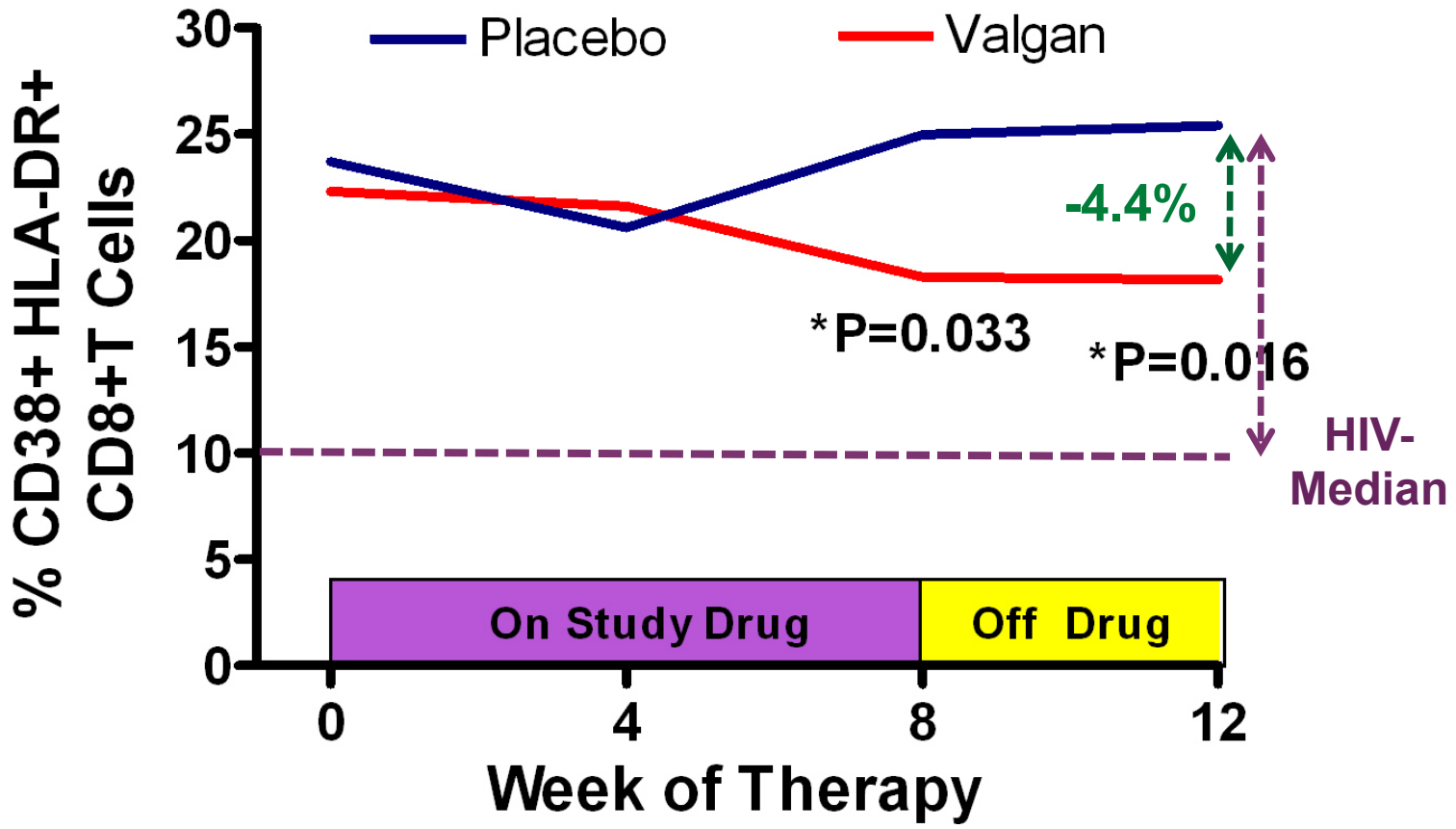


Higher plasma levels of IP-10, TNF-RII and D-dimer were found in coinfected patients than in HIV-positive/CMV-negative subjects.

CID 2016:62 (1 February)

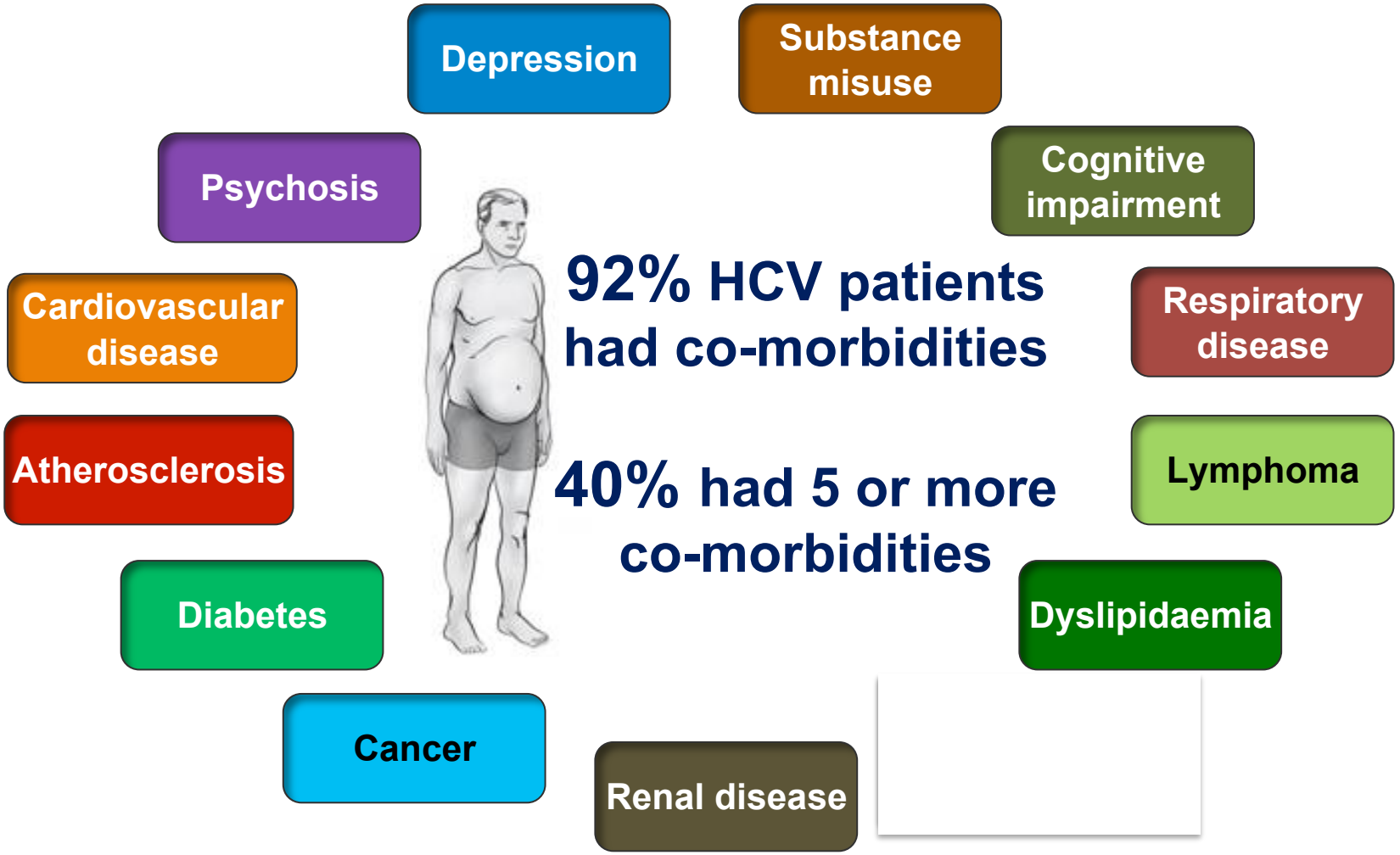
Decreasing Asymptomatic CMV Replication with Valganciclovir Decreases Immune Activation

in HIV+ Patients with CD4<350 despite ART



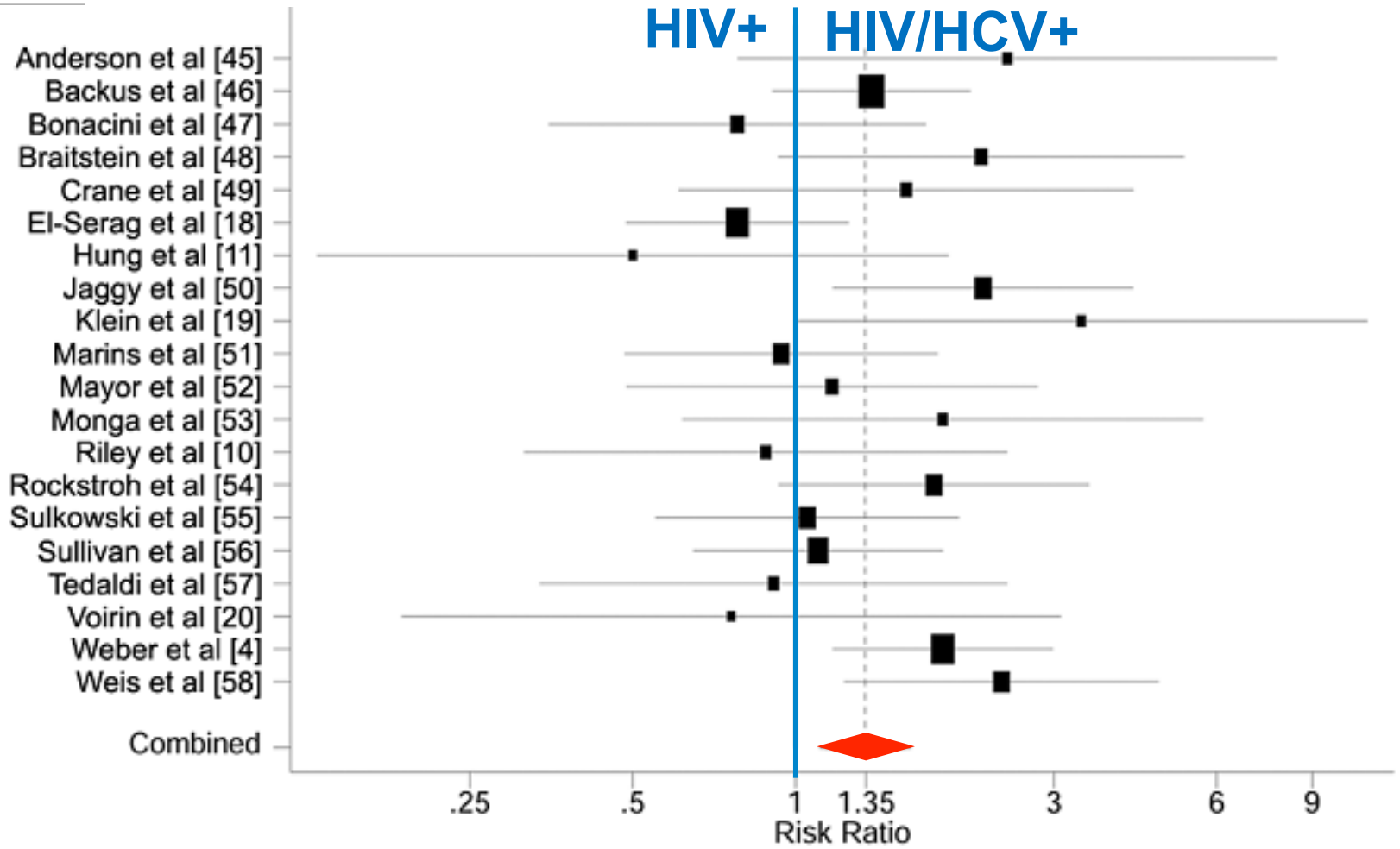
Hunt et al, JID, 2011

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



Vutien P, et al. AASLD 2014; Poster #1481.

HCV coinfection increases overall mortality

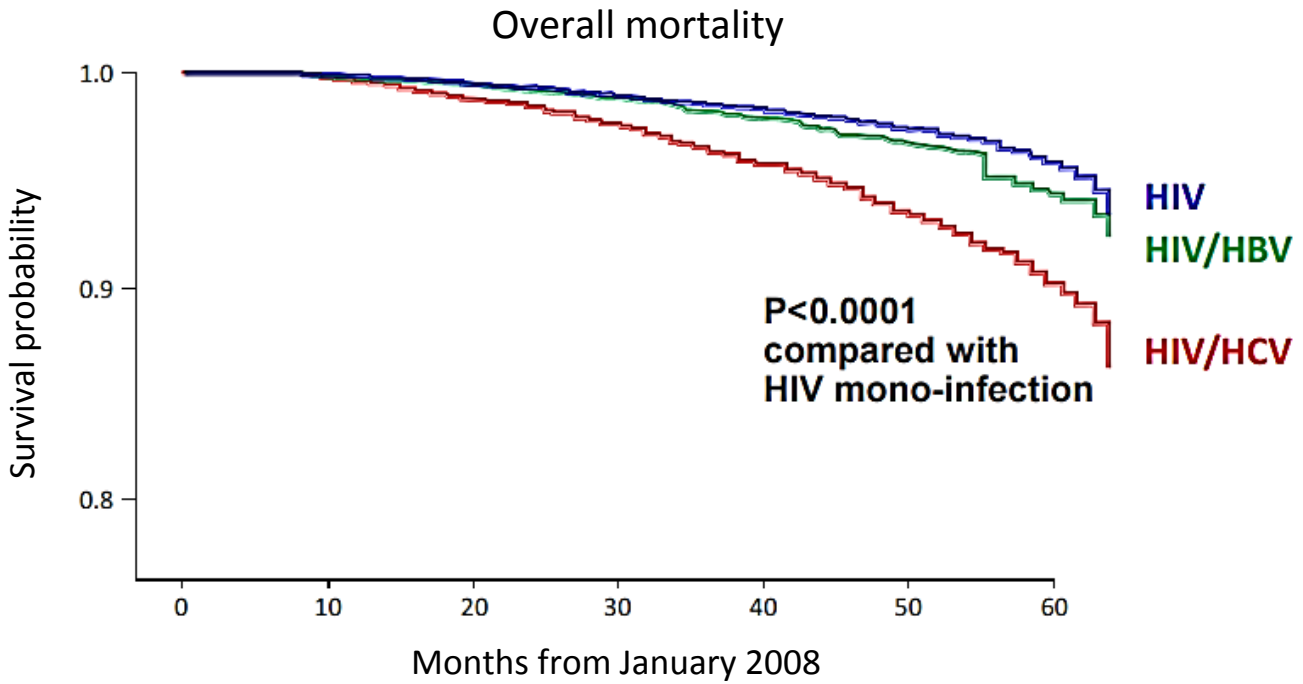


Overall mortality, HAART era

Chen, CID 2009

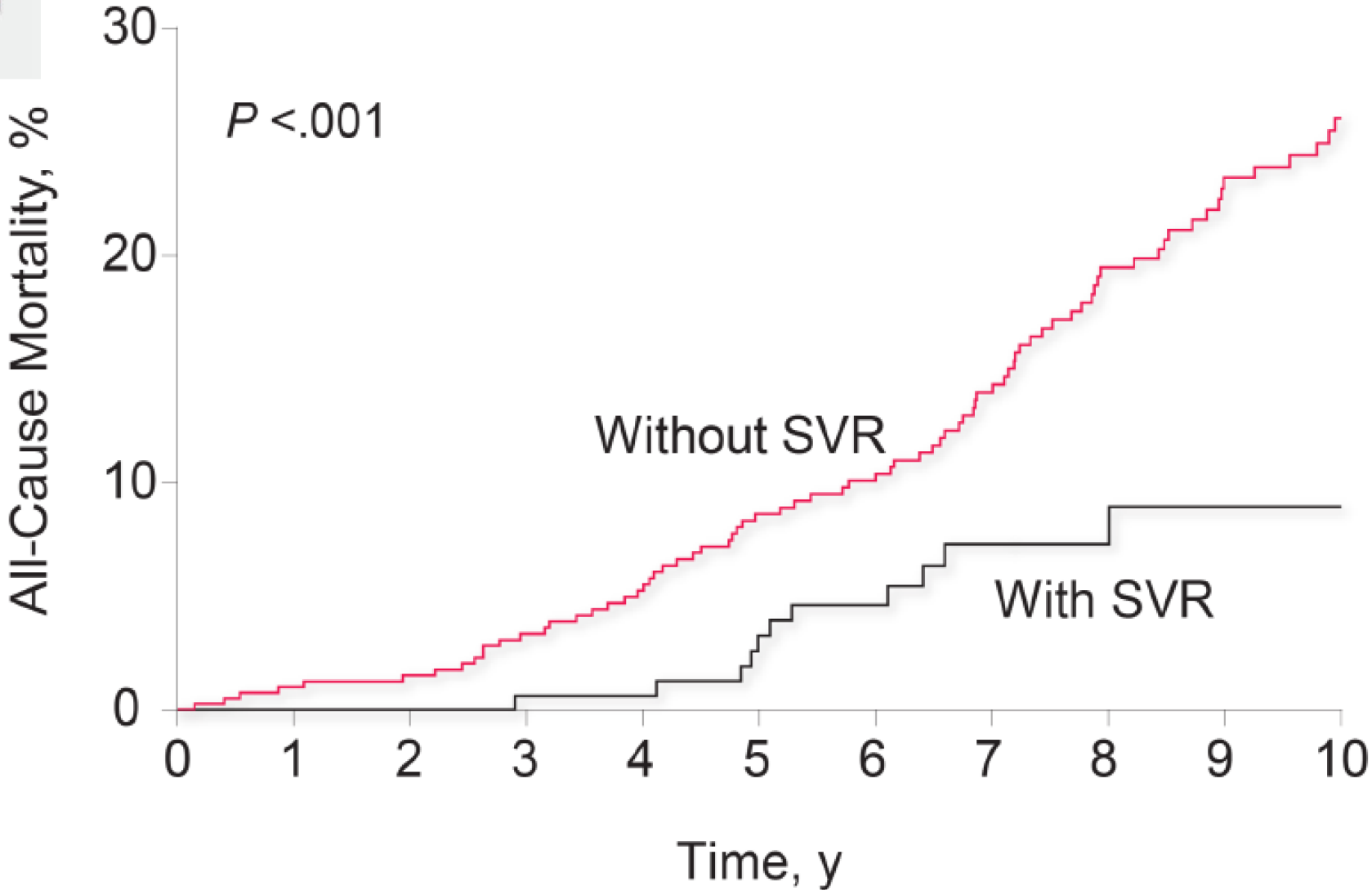
HCV increases overall and non-liver related mortality in HIV-infected patients[1]

- In a recent study, 2,385 out of 70,559 HIV-infected patients died in 248,885 patient-years
- Overall mortality was higher in 8,374 (7.5%) HIV/HCV patients compared with 60,016 (2.8%) HIV patients
- Non-liver-related as well as non-liver, non-AIDS-related mortality were higher in HIV/HCV co-infected patients (HR 1.40, P<0.0001 and HR 1.47, P<0.0001, respectively)



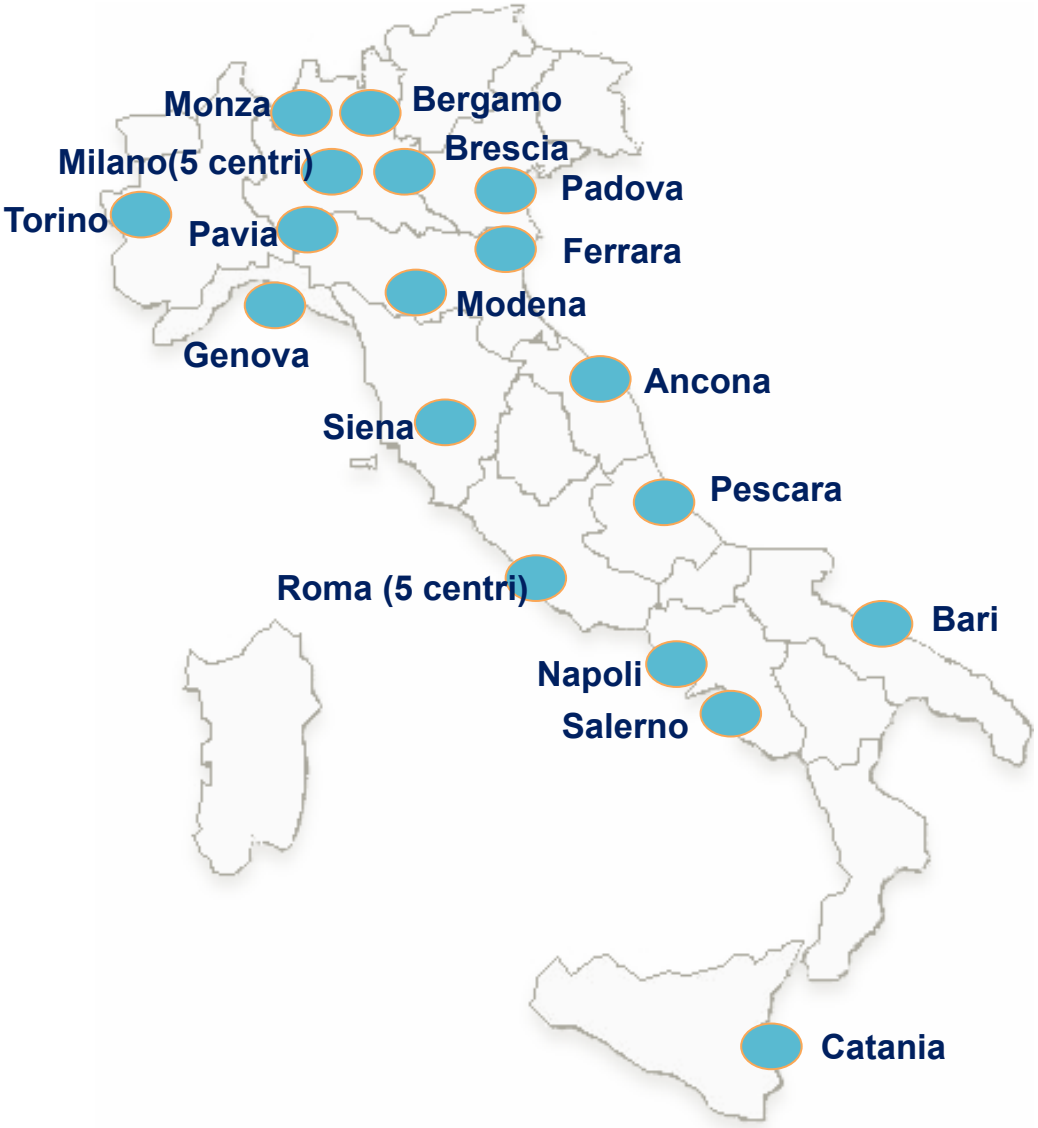
Mallet V et al. CROI 2014. Boston, MA. #690

SVR is associated with a reduction in all-cause mortality



Van Der Meer et Al, JAMA 2012; 308: 2584-93

SIMIT Compassionate Use Program



26 sites involved

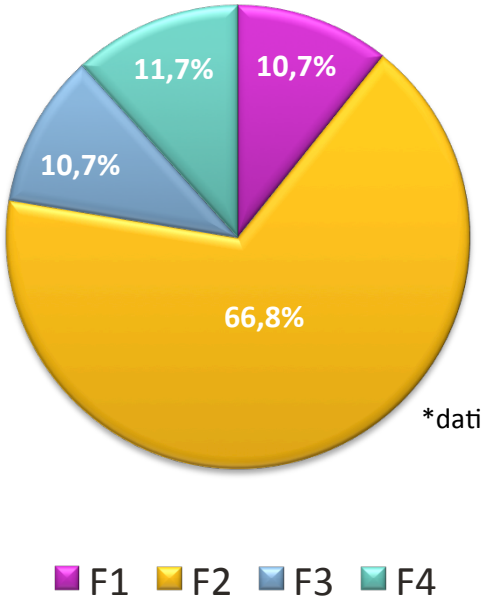
Trattamento di 214 Pazienti coinfetti HIV/HCV
Caratteristiche popolazione

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

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

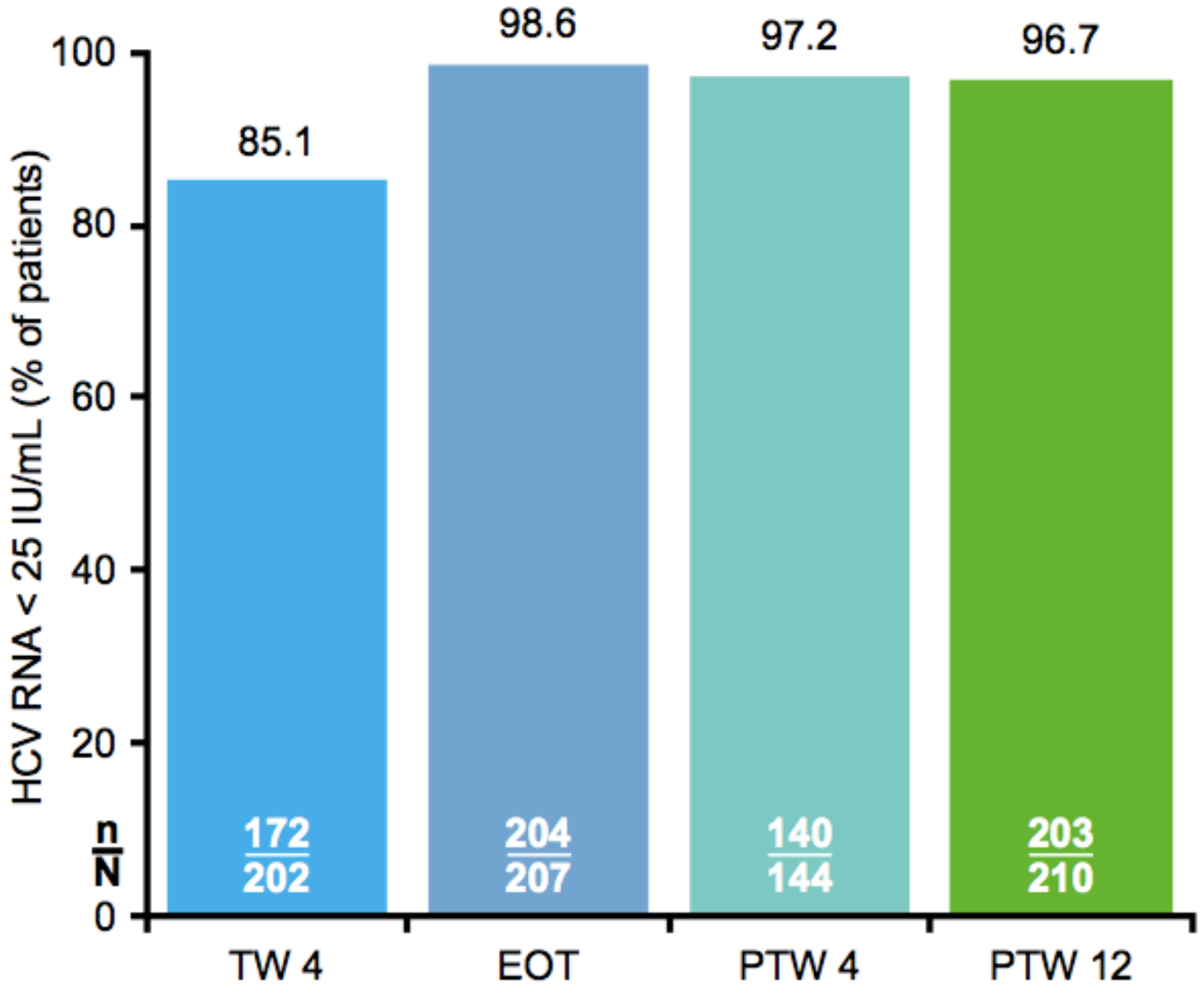
Genotipo	
GT 1a	**128**
GT 1b	**63**
GT1a/1b	**8**
GT1	**1**

Fibrosi (Fibroscan): n° pazienti 205*



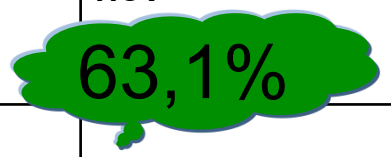
*dati mancanti in 8 pz

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



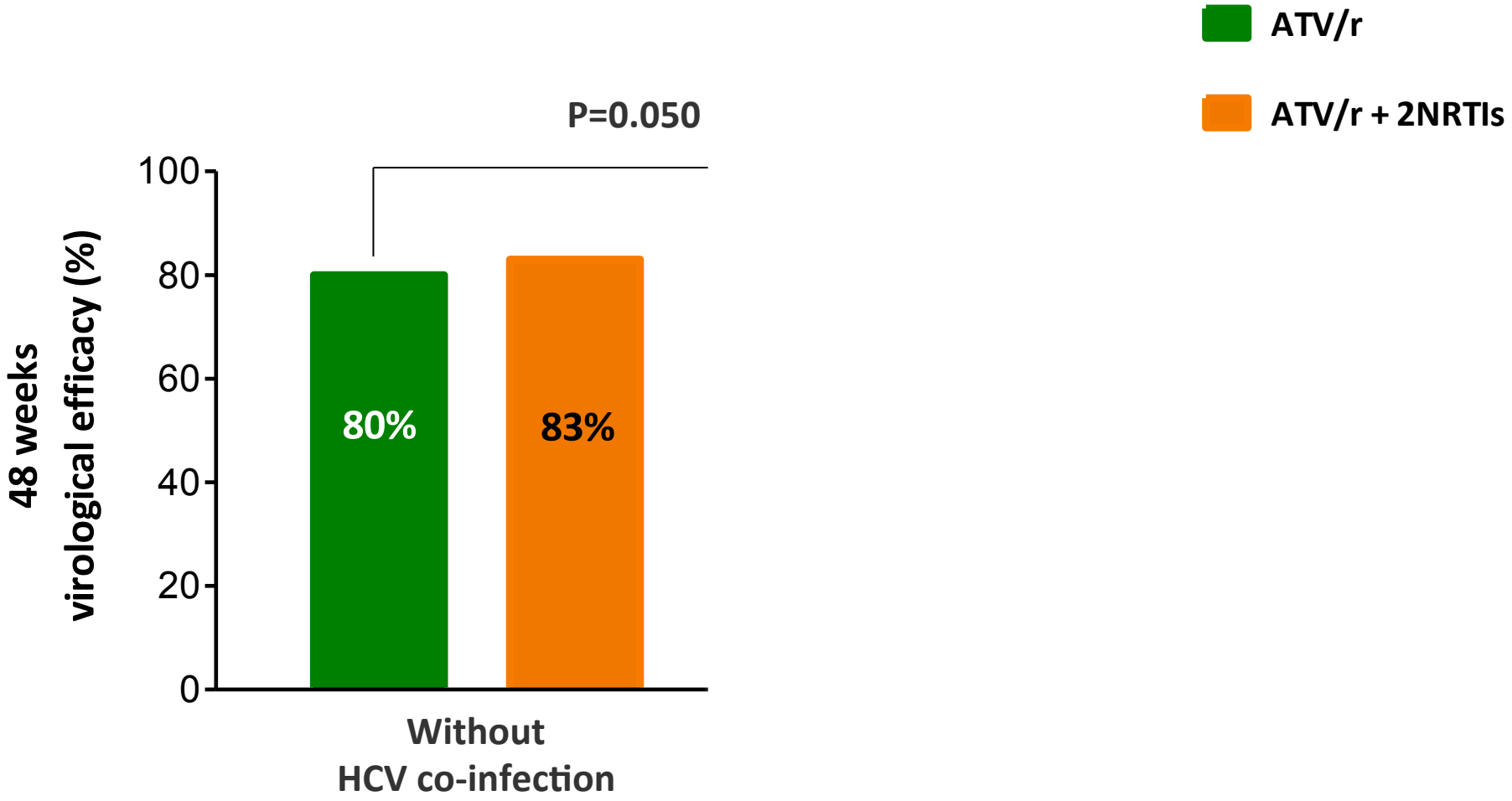
In treatment-naïve patients, HCV co-infection is associated with lower HIV RNA suppression rates. Difference = -11.1% (95% CI -6.5% to -15.6%, p<0.001)

Clinical trial	Treatment arm	% HCV+	HIV RNA <50 copies/mL HCV+	HIV RNA <50 copies/ mL HCV-
Naive patients				
Gilead 934	ZDV/3TC/EFV	7%	7/16 (44%)	164/228 (72%)
	TDF/FTC/EFV	4%	8/10 (80%)	186/233 (80%)
ECHO/THRIVE	2NRTI/EFV	9% (B/C)	50/63 (79%)**	497/602 (83%)**
	2NRTI/RPV	7% (B/C)	36/49 (74%)**	528/621 (85%)**
SENSE	2NRTI/EFV	10%	5/8 (63%)	53/70 (76%)
	2NRTI/ETR	11%	5/9 (56%)	55/70 (79%)
KLEAN	ABC/3TC/FPV/r	12%	20/47 (43%)*	277/358 (77%)*
	ABC/3TC/LPV/r	9%	23/38 (61%)*	282/386 (73%)*
ARTEMIS	TDF/FTC/DRV/r	8%	32/42 (76%)**	255/300 (85%)**
	TDF/FTC/LPV/r	9%	32/48 (67%)**	239/299 (80%)**
CASTLE	TDF/FTC/ATV/r	9%	42/61 (69%)**	300/378 (79%)**
	TDF/FTC/LPV/r	7%	37/51 (73%)**	301/397 (77%)**



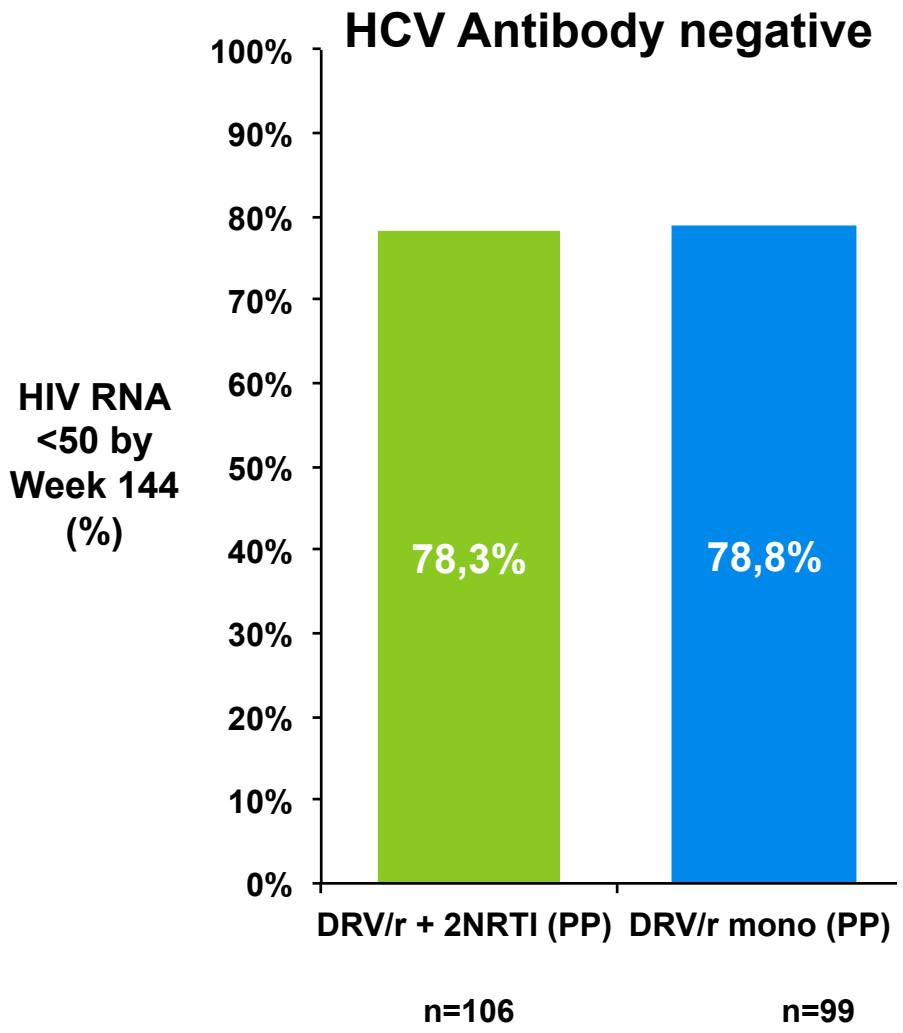
Ref: Pulido et al, AIDS Reviews, Vol 14, 2012

MODAt Virological efficacy according to HCV co-infection



Castagna A. et al, EACS 2013

Monet study: HIV RNA <50 copies/mL at Week 144 by HCV serology at baseline (PP, TLOVR, Switch=Failure)

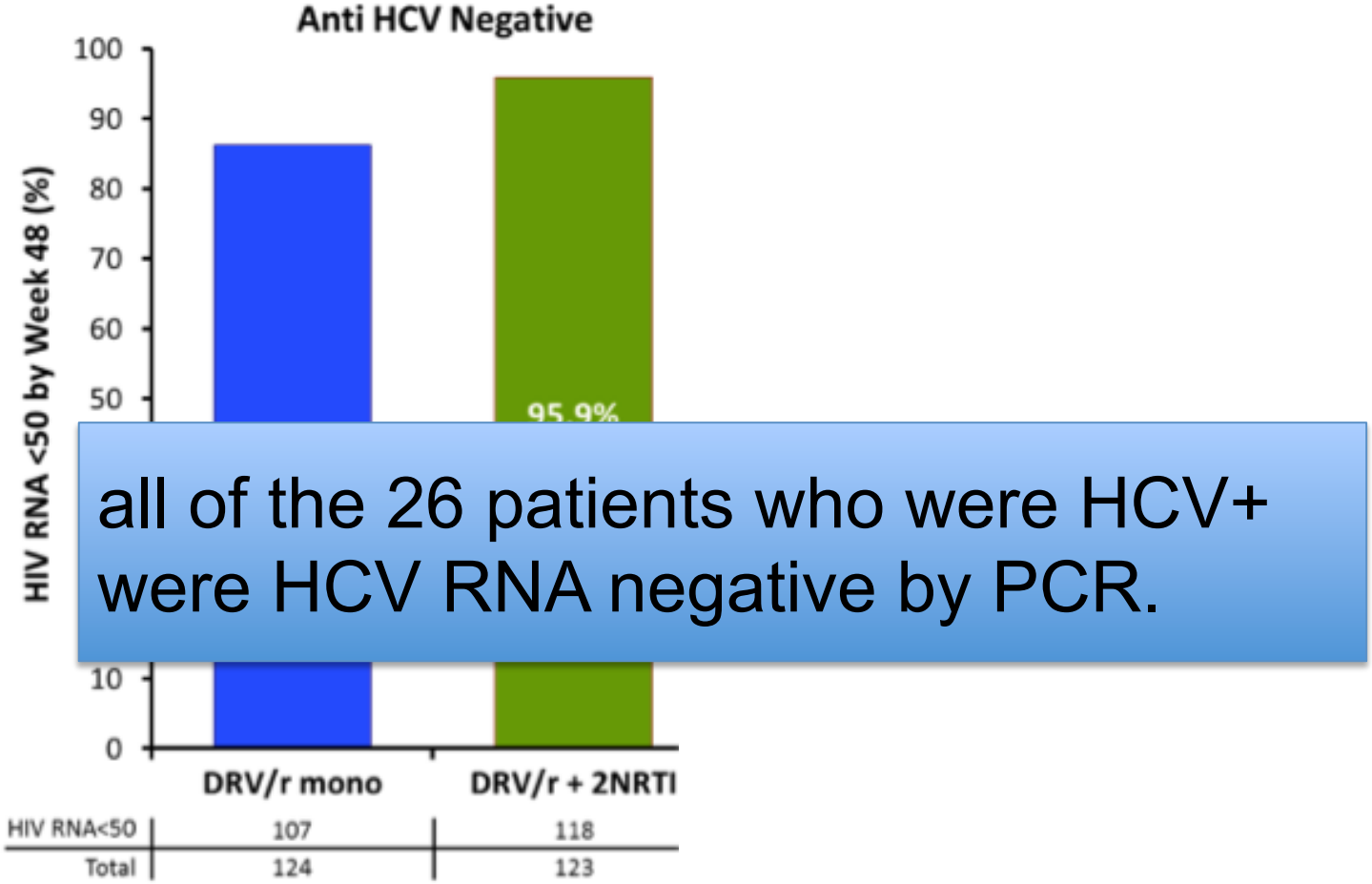


Ref: Arribas et al, HIV Medicine 2012, 13:398-405

Week 48 efficacy analysis of the PROTEA trial: darunavir/ritonavir monotherapy versus darunavir/ritonavir with two nucleoside analogues, for patients with HIV-1 RNA below 50 copies/mL at baseline

1. Andrea Antinori, National Institute of Infectious Diseases, Infectious Diseases, Rome, Italy 2. Jose Arribas, Hospital la Paz, IdiPAZ, Madrid, Spain 3. Jan Fehr, University Hospital, Zurich, Switzerland 4. Pierre-Marie Girard, Hopital Saint-Antoine, Paris, France 5. Andrzej Horban, Warsaw Medical University, Poland 6. Andrew Hill, Janssen, R&D, High Wycombe, United Kingdom 7. Yvon van Delft, Janssen, EMEA, Tilburg, Netherlands 8. Christiane Moecklinghoff, Janssen, EMEA, Neuss, Germany

Figure 4. HIV-1 RNA <50 copies/mL at Week 48, FDA snapshot, switch=failure, by HCV antibody status



all of the 26 patients who were HCV+ were HCV RNA negative by PCR.

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

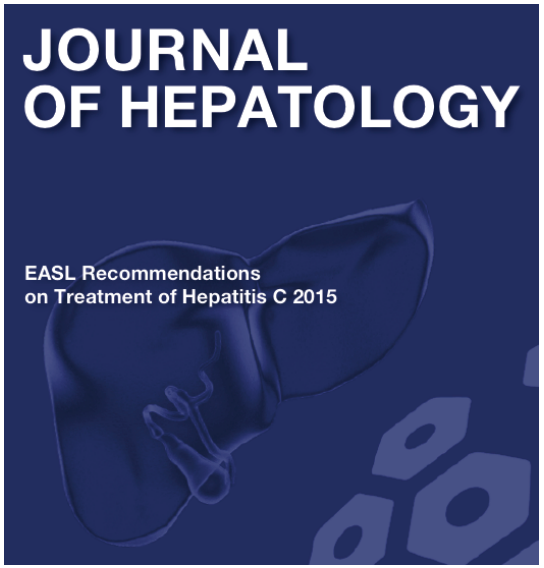


Table 2. Indications for treatment of chronic hepatitis C in 2015: Who should be treated and when?

Treatment priority	Patient group
Treatment is indicated	• All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
Treatment should be prioritized	• 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	• Patients with moderate fibrosis (F2)
Treatment can be deferred	• Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	• Patients with limited life expectancy due to non-liver related comorbidities

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

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.

HEPATOLOGY, Vol. 62, No. 3, 2015