Fattori di patogenesi e di protezione: la risposta immune

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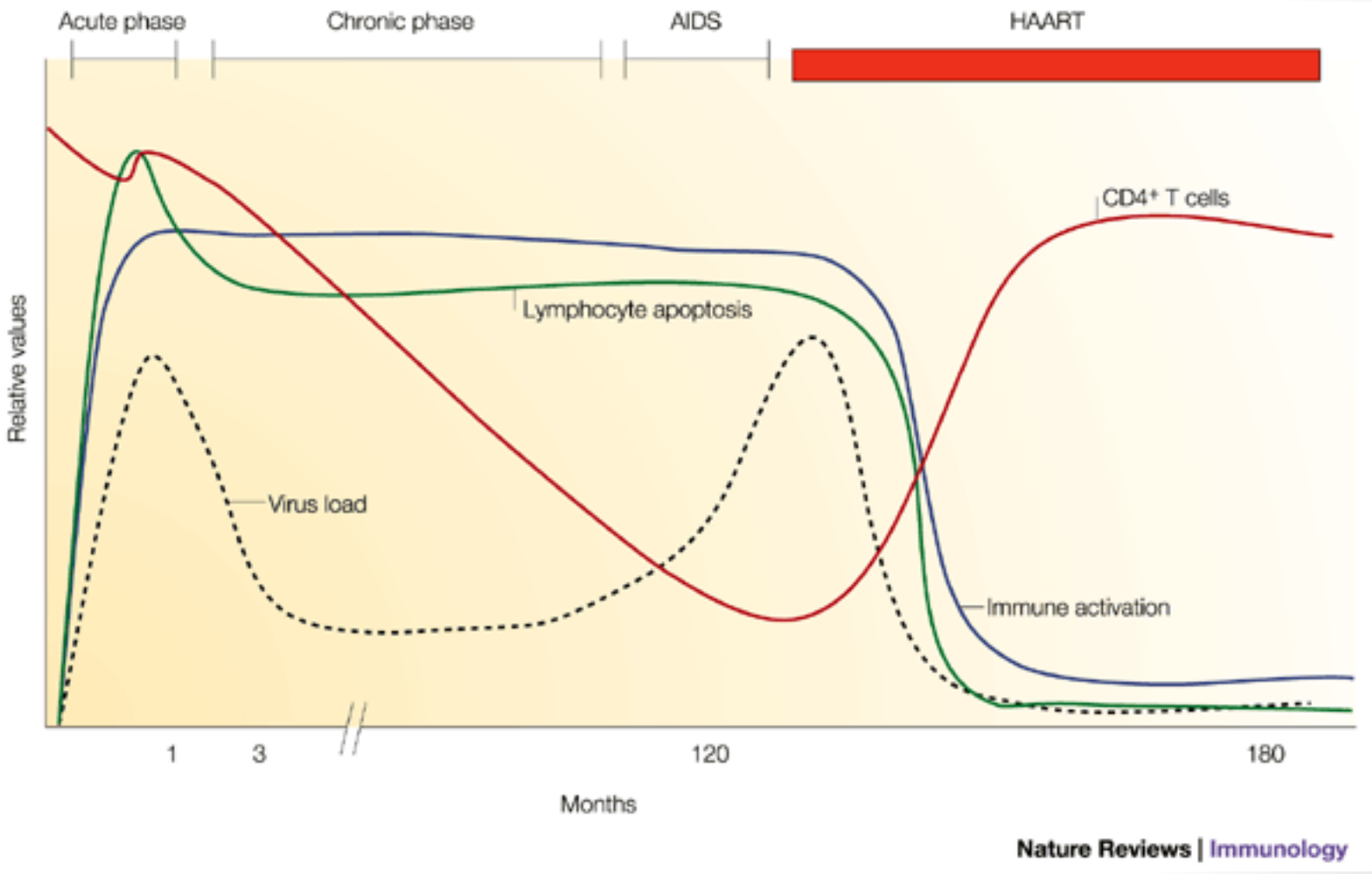
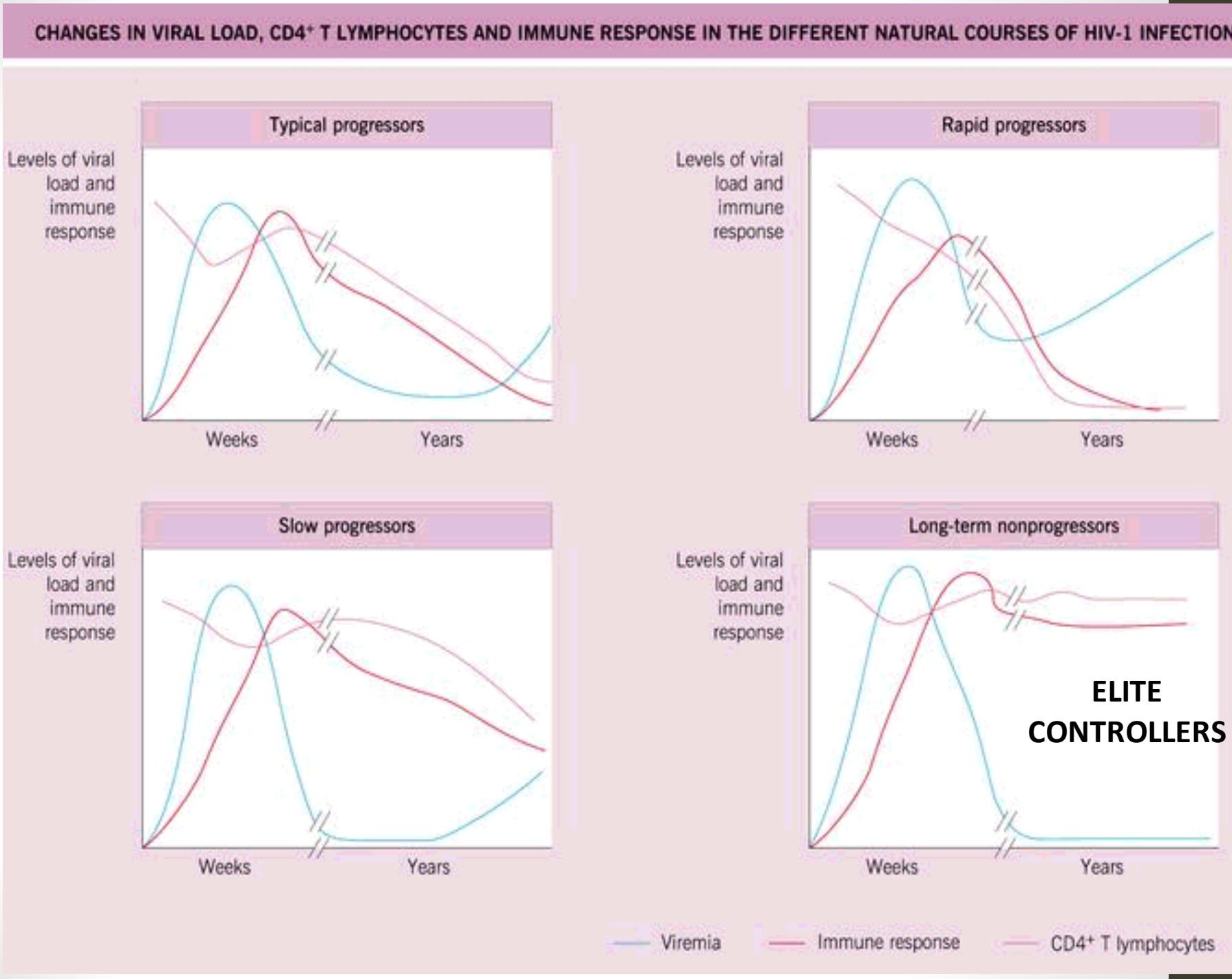
From pathogenesis to “clinical models” of disease progression

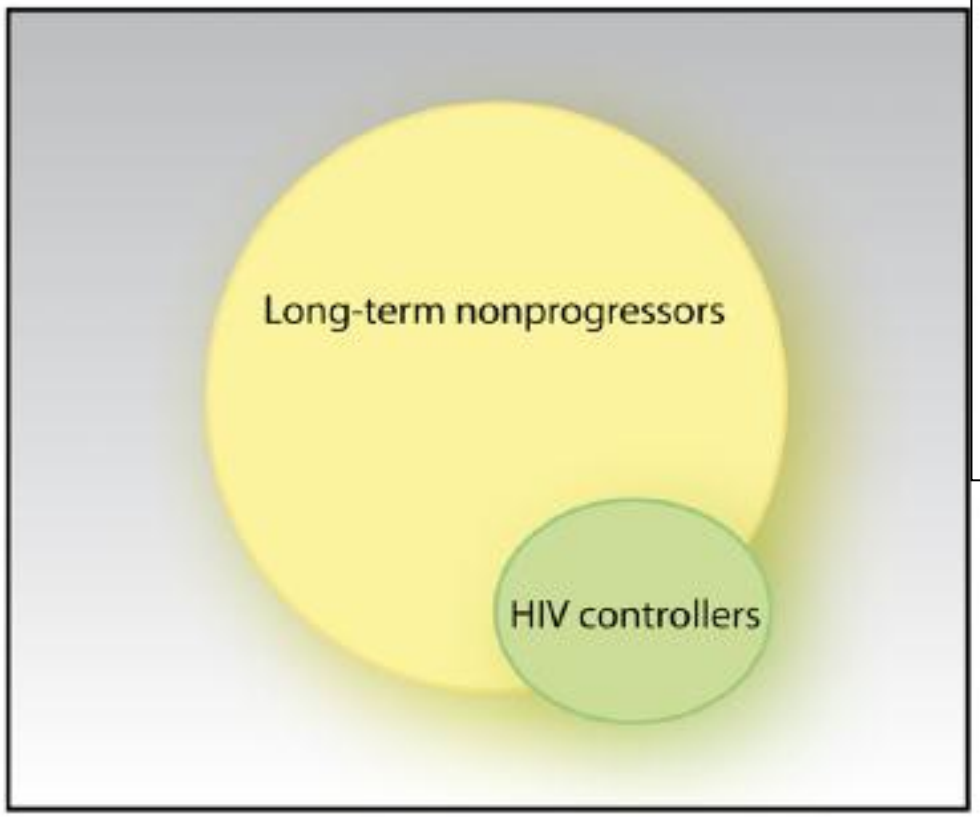
Clinical “models “ of disease progression

- Rapid/slow progressors
- Long-term non-progressors (LTNPs)/Elite controllers (ECs)
- Exposed yet non-infected individuals
- Animal models: natural hosts of SIV

Clinical progression of HIV




CHANGES IN VIRAL LOAD, CD4+ T LYMPHOCYTES AND IMMUNE RESPONSE IN THE DIFFERENT NATURAL COURSES OF HIV-1 INFECTION
Typical progressors
Levels of viral load and immune response
Weeks
Years
Rapid progressors
Levels of viral load and immune response
Weeks
Years
Slow progressors
Levels of viral load and immune response
Weeks
Years
Long-term nonprogressors
Levels of viral load and immune response
ELITE CONTROLLERS
Weeks
Years
Viremia
Immune response
CD4+ T lymphocytes



Elite Controllers

- HIV seropositive
- No detectable HIV RNA (< 50 copies/mL) for > 2 years
- Antiretroviral untreated

The proportion of individuals who become elite controllers is not known, but is estimated to be ~ 1%.


Viral factors
HIV
DISEASE
COURSE
Host factors

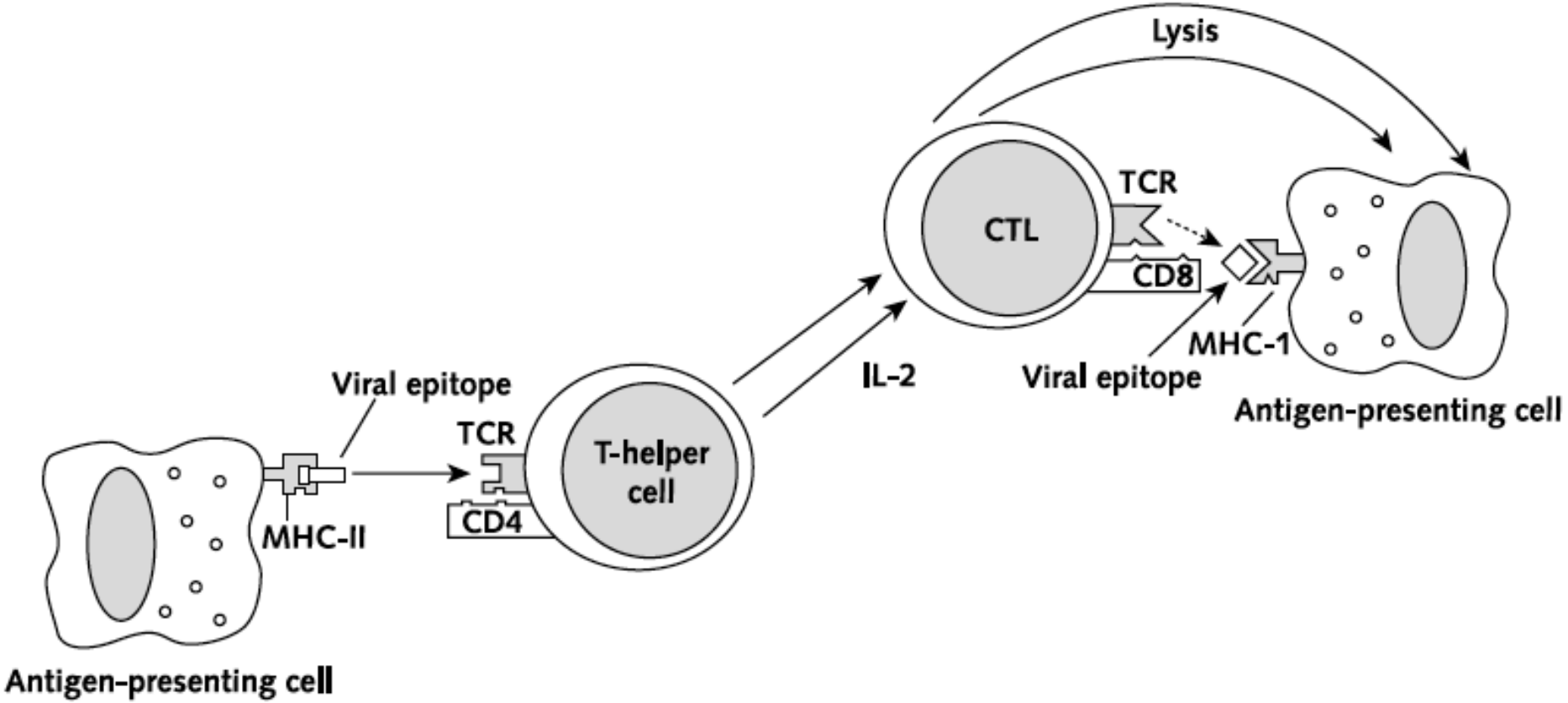
Host factors

Host Factors	Effects on HIV Transmission and Disease Progression
Cell-mediated immunity	
Cytotoxic T cells	Eliminate virions and virus-infected cells; play prominent role in initial control of viremia, slowing of disease progression, and perhaps prevention of infection
T-helper cell response	Preservation of this response may be vital to preservation of cytotoxic T lymphocyte response, and its importance provides theoretic rationale for early treatment
Humoral immunity	Role in prevention and control of disease progression is unclear
Local factors	
STDs and cytokine milieu	May upregulate HIV replication
Mucosal cytotoxic T lymphocytes and antibodies	Role in prevention of transmission and disease progression is unclear
Dendritic cells	Facilitate HIV infection of T cells by capturing and transporting HIV to lymph nodes and activating T cells
Chemokine receptors	
CCR5-Δ32	Homozygosity for this deletion is associated with decreased susceptibility to R5 virus infection; heterozygosity is associated with delayed progression to disease
CCR2-V64I	Heterozygosity is associated with delayed progression to disease
CCR5 promoter polymorphisms	Several genetic polymorphisms that may affect transmission or disease progression have been identified—for example, 59029-G homozygosity is associated with slower progression, and 59356-T homozygosity is associated with increased perinatal transmission
Chemokines	
SDF-1 3′α	Homozygosity may be associated with delayed progression to disease
Cytokines	Complex interplay of stimulatory and inhibitory cytokines affects HIV replication
Other soluble factors	Inhibit HIV replication in a noncytotoxic manner
Other genetic factors	
HLA alleles	Certain alleles are associated with differing susceptibilities to infection and rates of disease progression

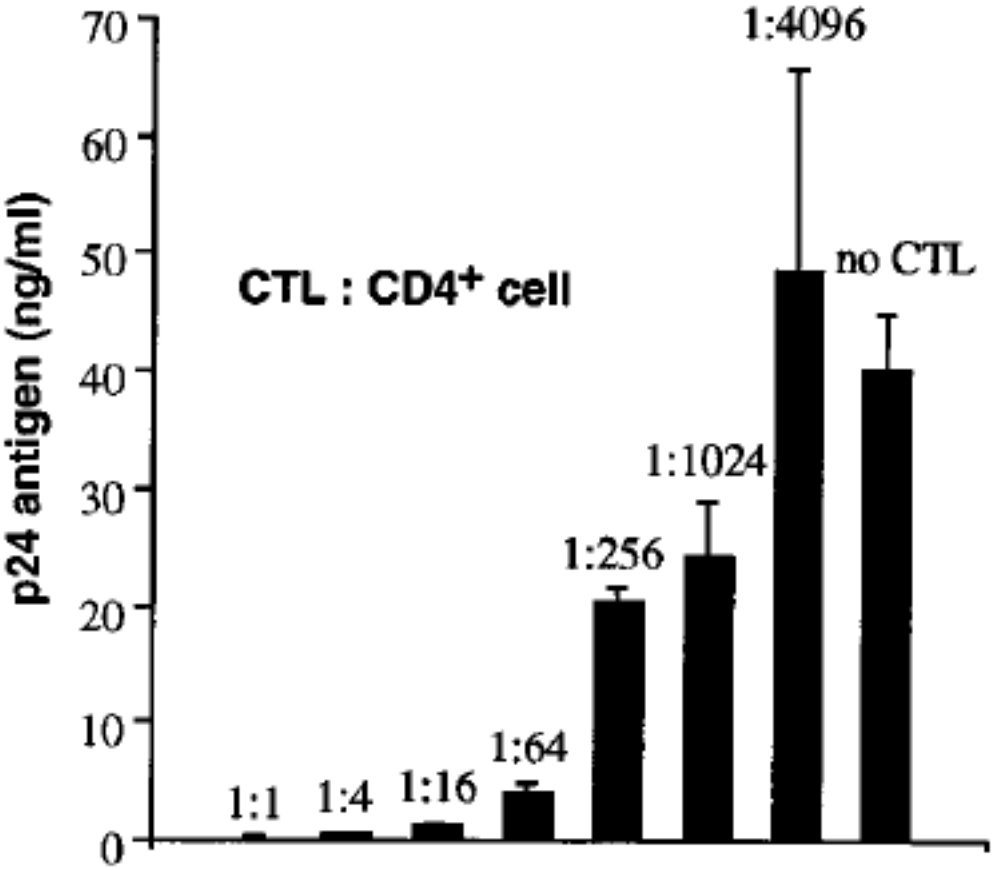
Viral factors that interact with the host to codetermine outcome

Viral Factor	Effect on HIV Transmission and Disease Progression
Escape from immune response	Under cellular and humoral immune pressure, mutations may arise in the *gag*, *pol*, and *env* genes, leading to escape from immune response
Attenuated viruses	*nef* viruses have been associated with long-term nonprogression in individual case reports and small cohorts
Tropism	Chemokine receptor use may determine tropism; progression from macrophage-tropic to T-cell–tropic viruses has been associated with increased pathogenicity and progressive disease
Subtypes	Different subtypes may have differing virulence and transmissibility

CTL response



In vitro inhibition of HIV replication by CTL

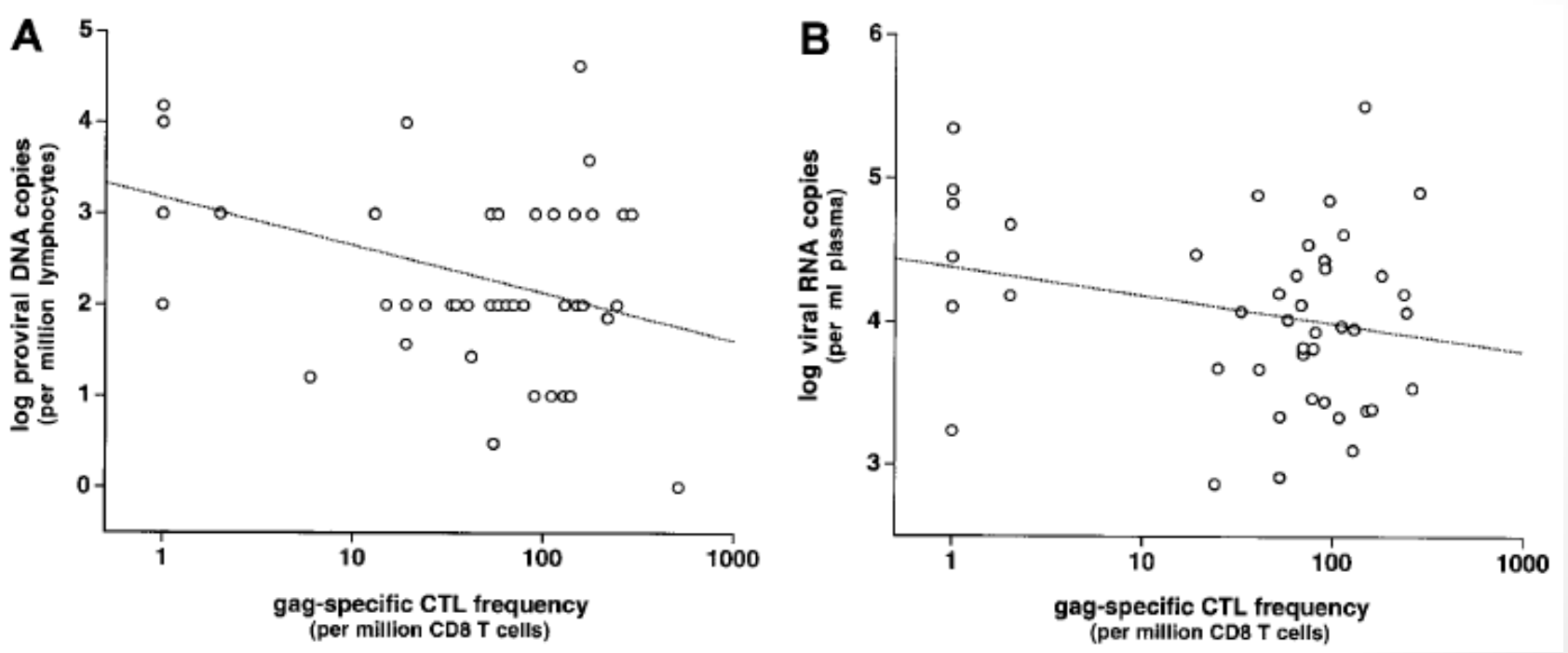


Yang et al. J Virol 1997

Gag-specific CTL response correlates with HIV proviral DNA

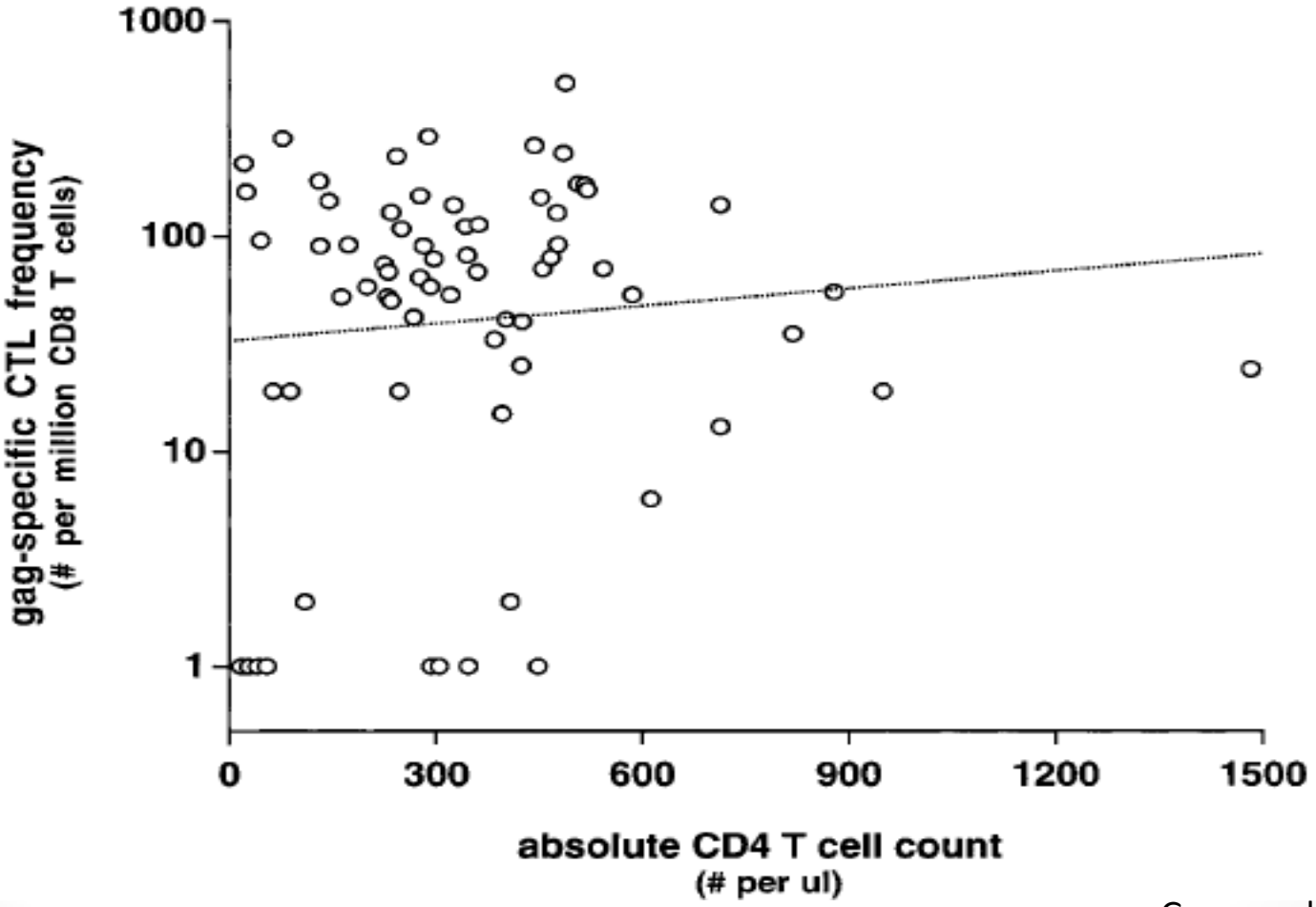
R=-.401, p=.005

R=-.241, p=.120



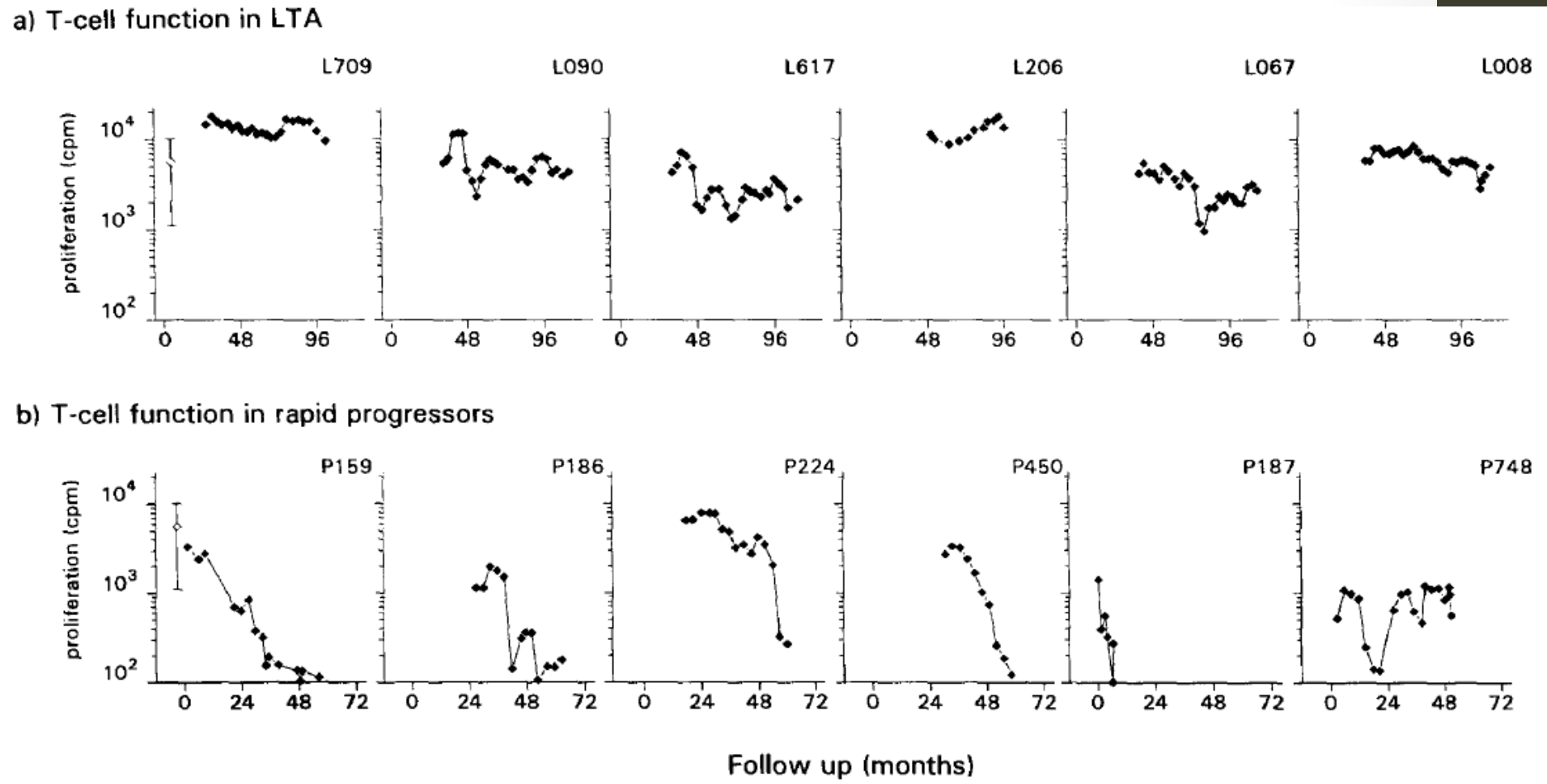
Greenough et al. JID 1997

Gag-specific CTL response and CD4+ count

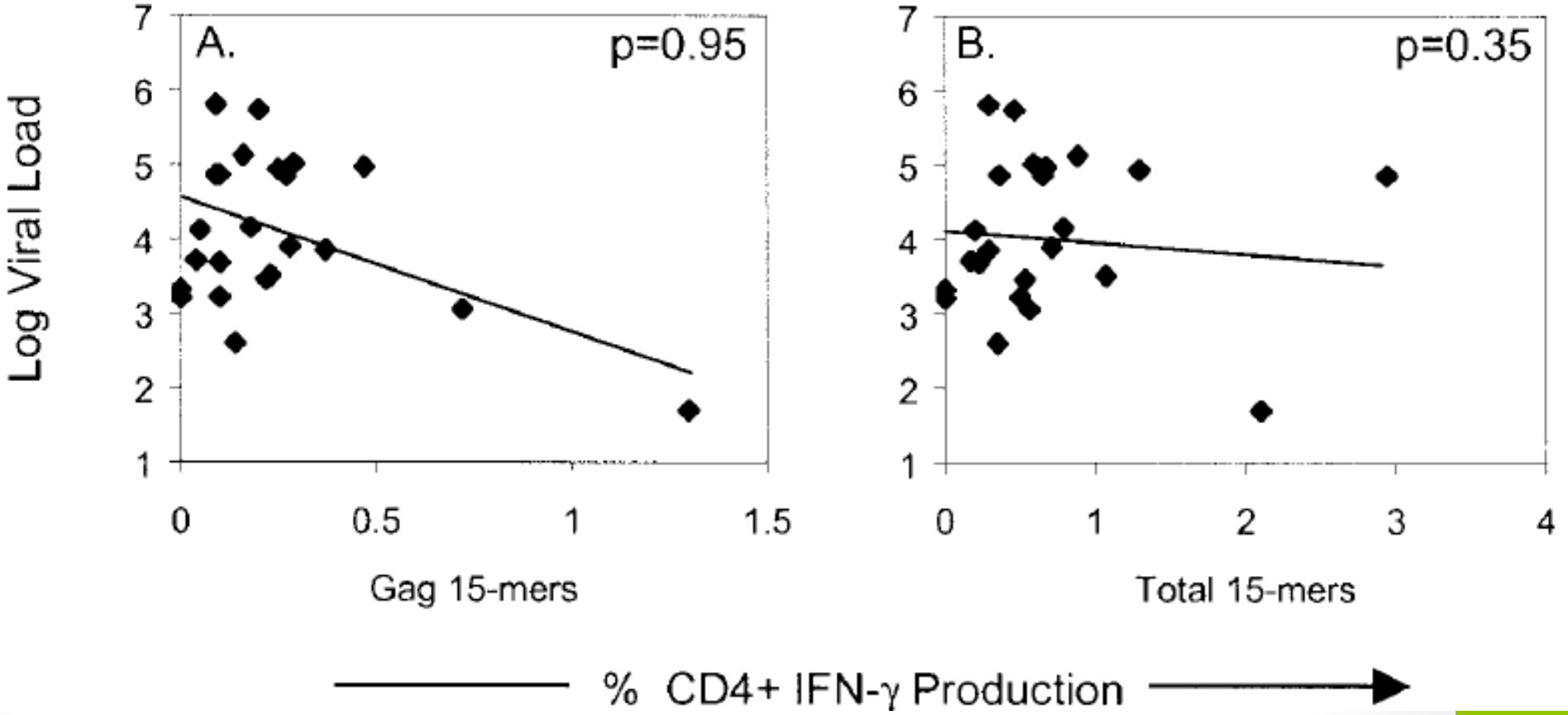


Greenough et al. JID 1997

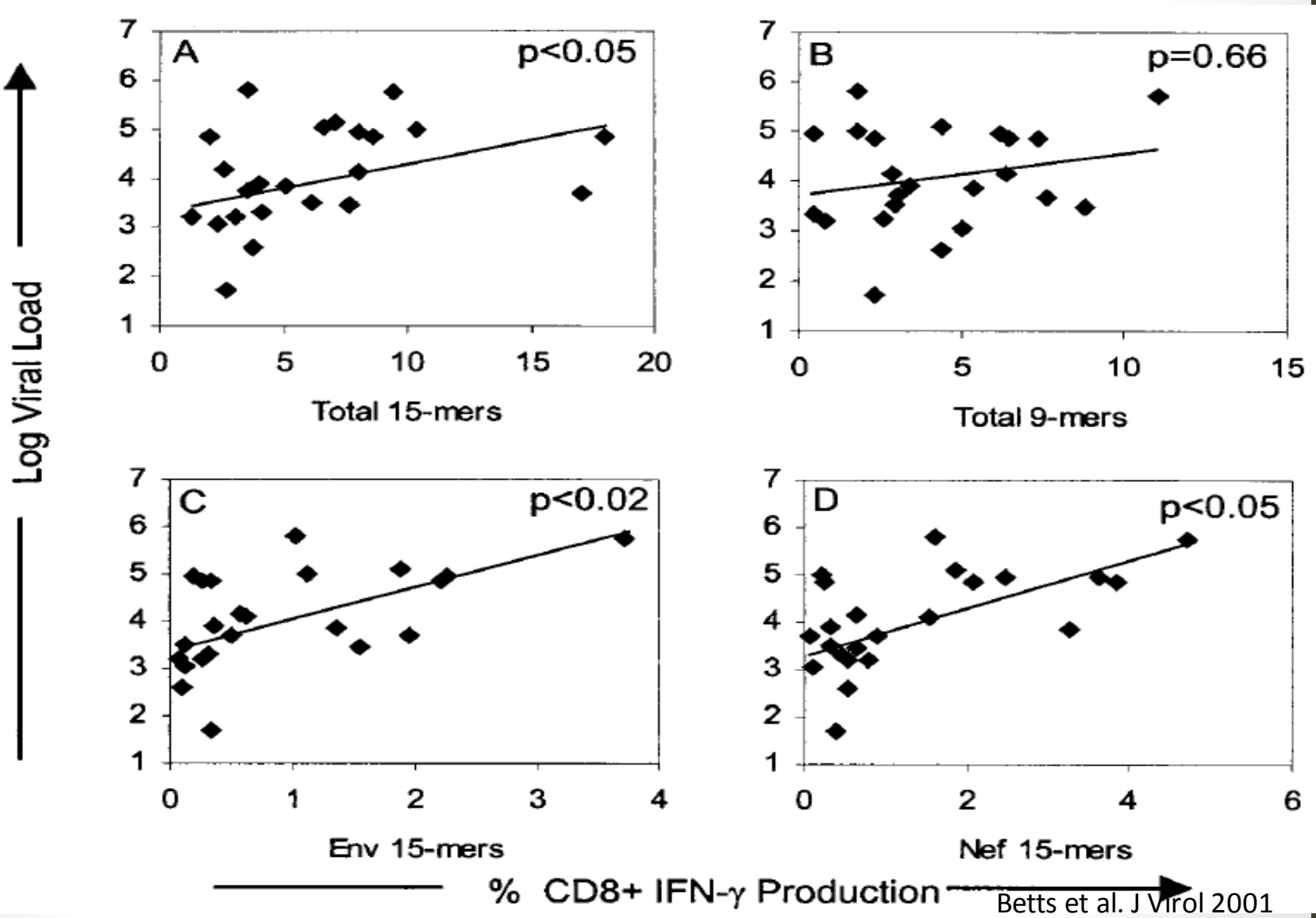
T-cell responses in progressors vs non-progressors



Klein et al J Exp Med 1995

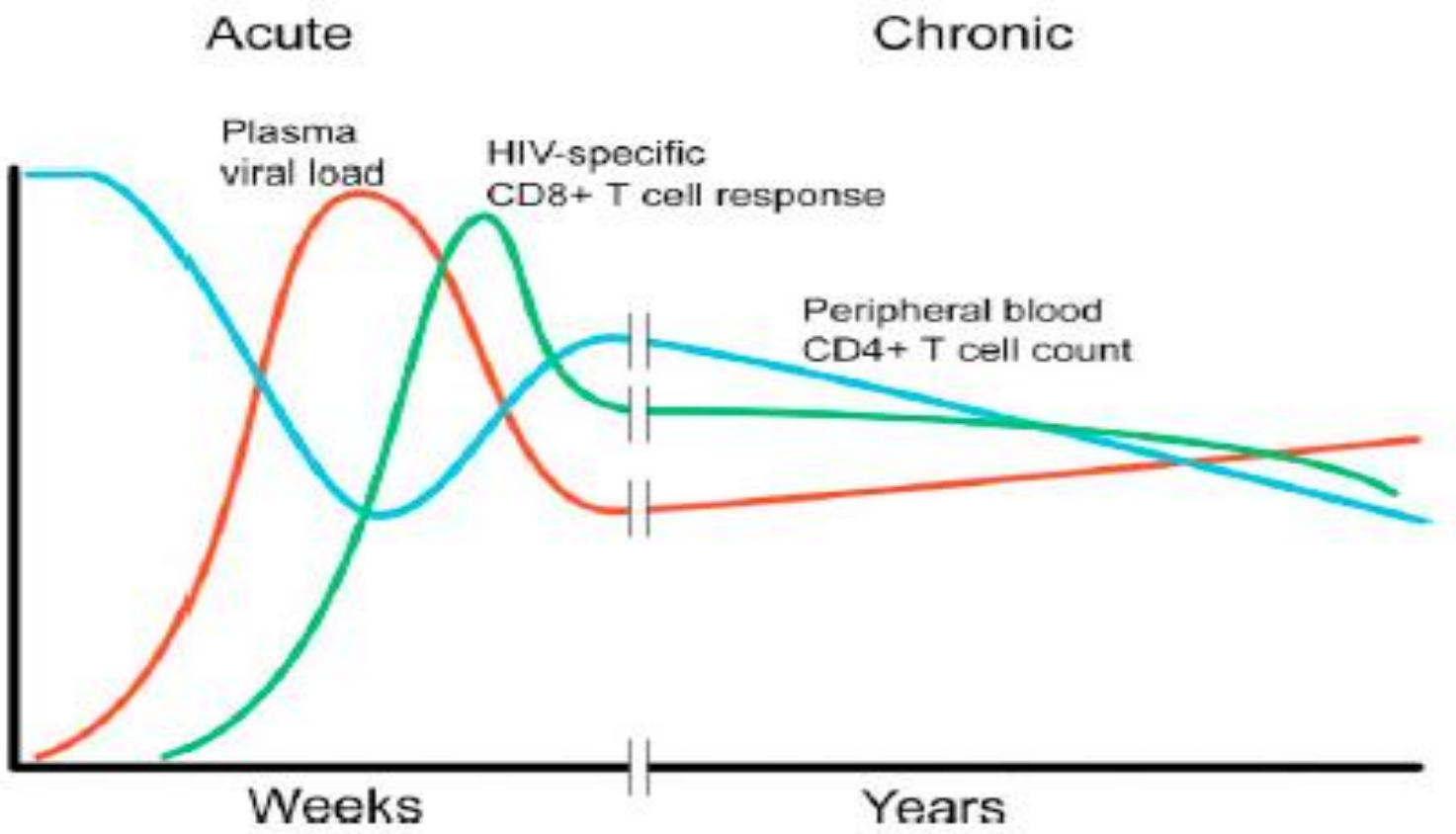


Betts et al. J Virol 2001

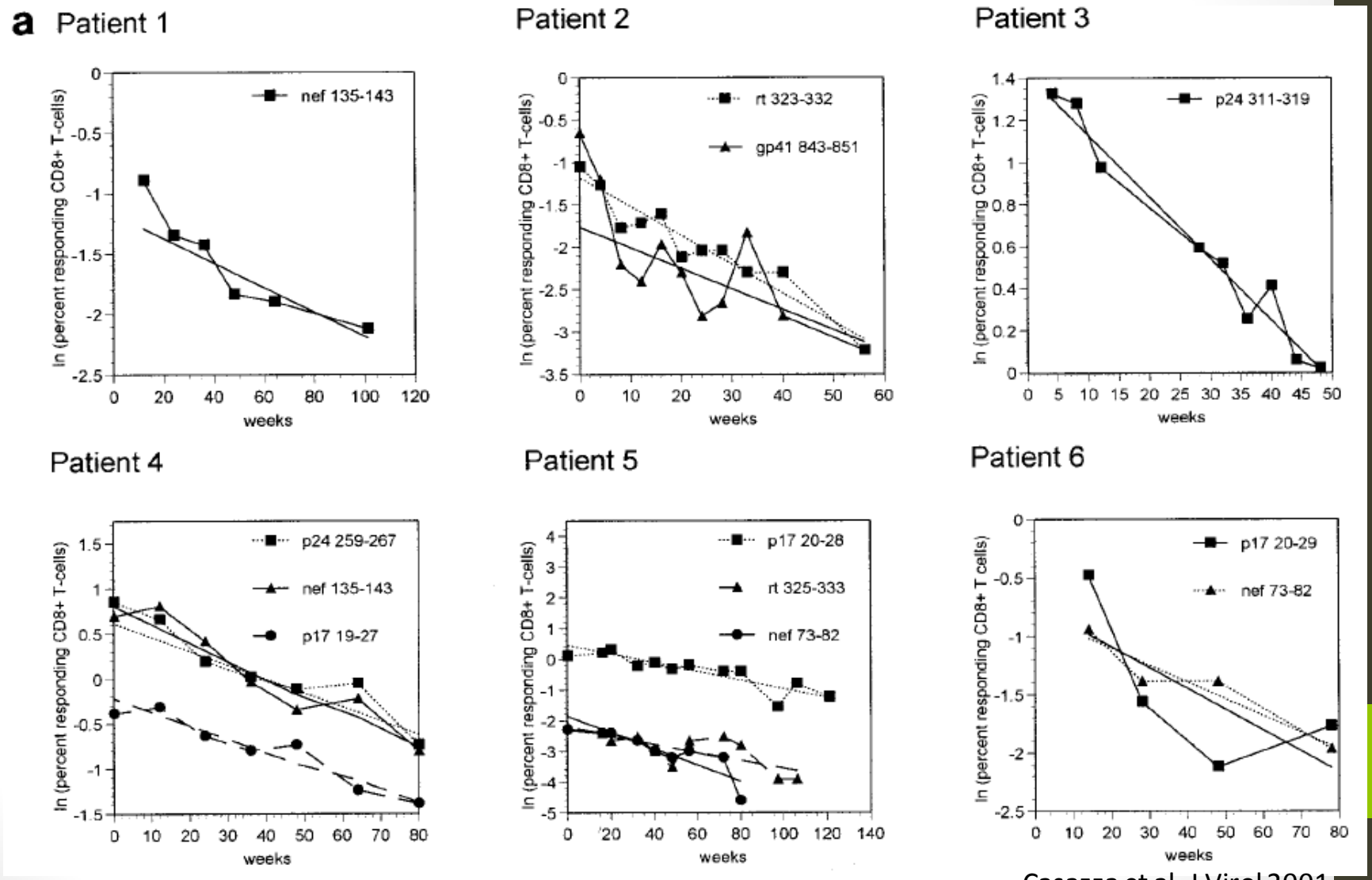


Betts et al. J Virol 2001

Persistent HIV replication in the face of vigorous CTL response



HIV viremia control by HAART reduces CTL response

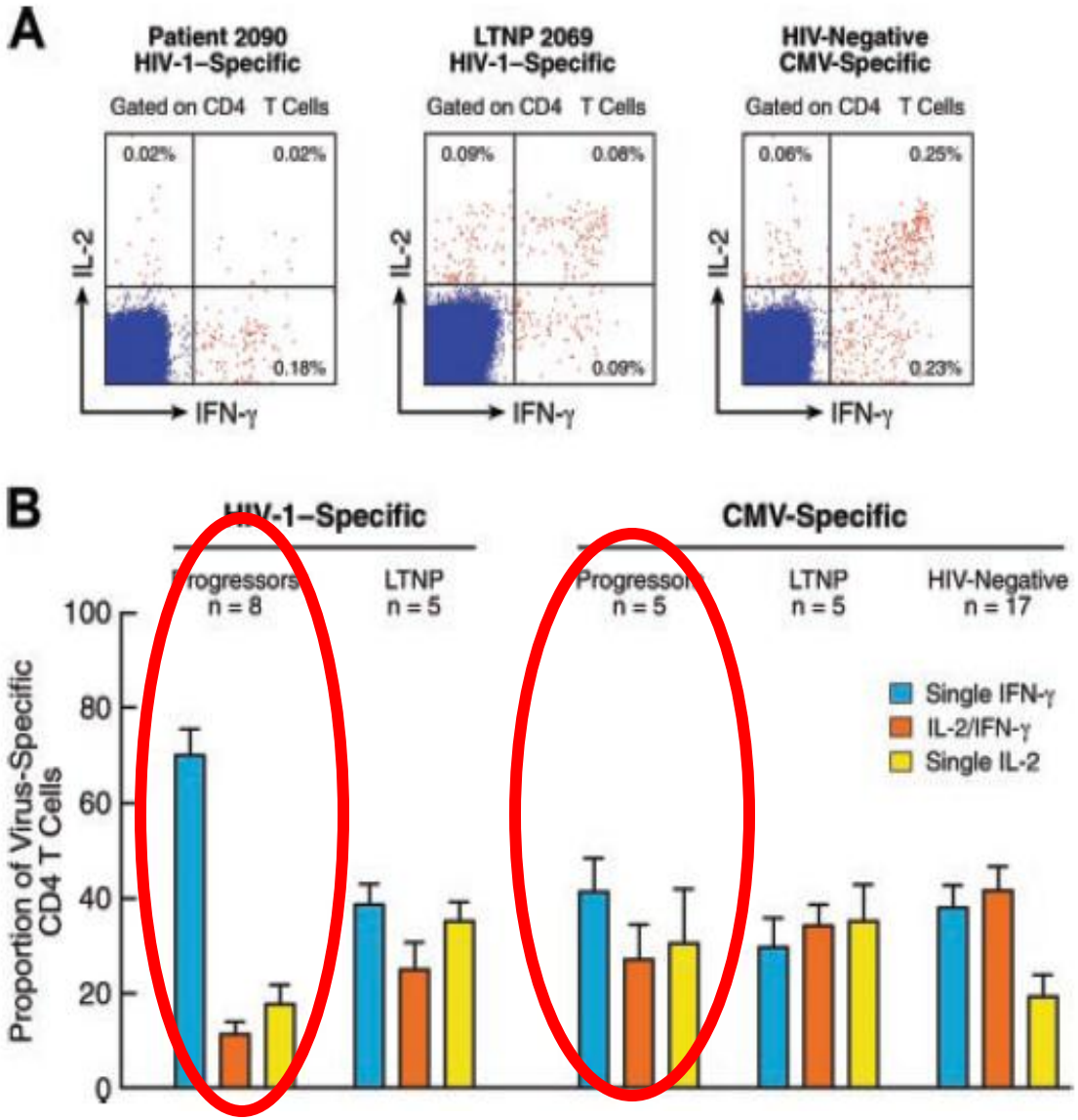


Casazza et al. J Virol 2001

No correlation between CD8 T-cell response to HIV and pathogenesis/clinical progression

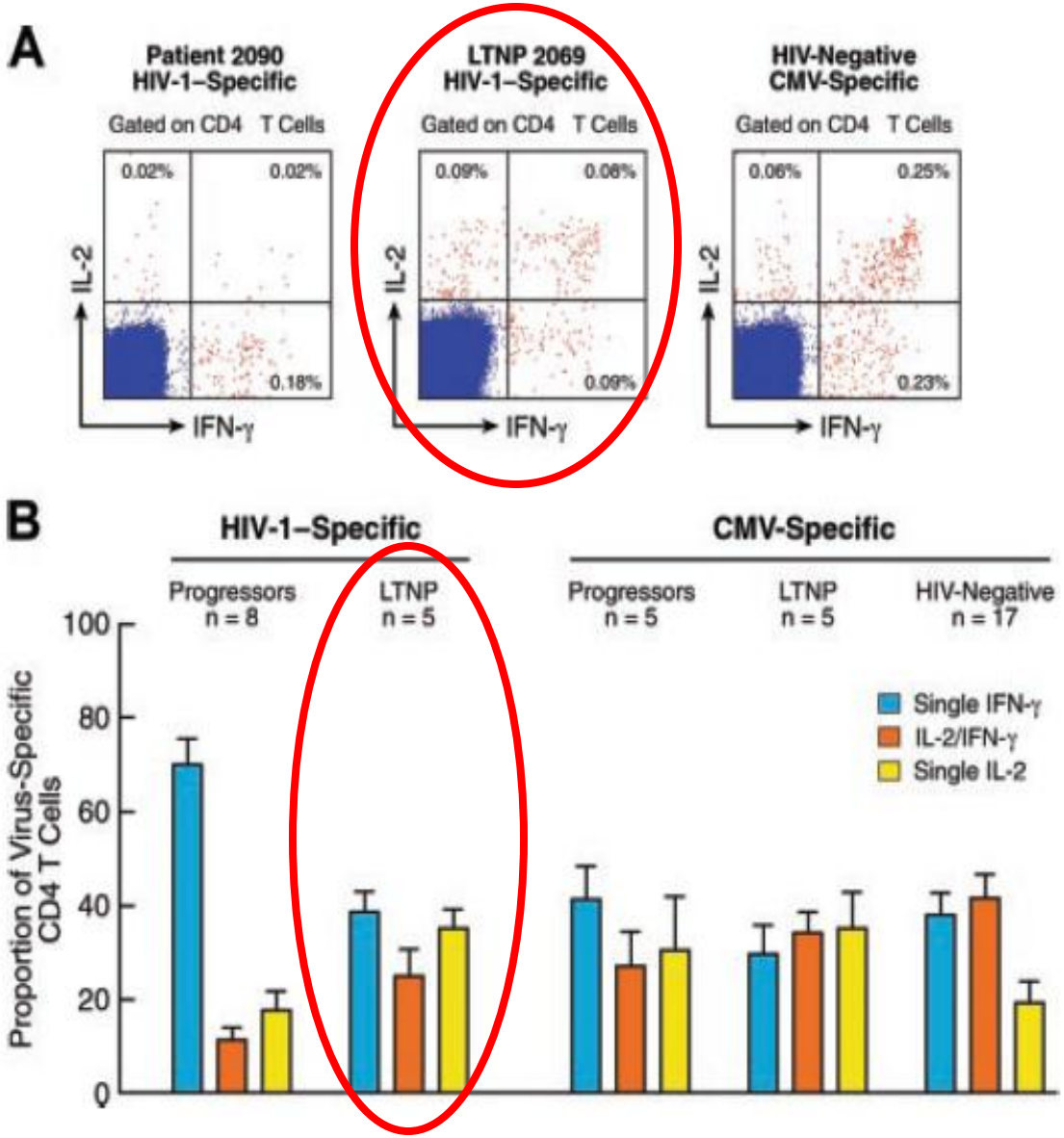
T-cell function in HIV pathogenesis

Functionally-distinct populations of HIV-specific CD4+



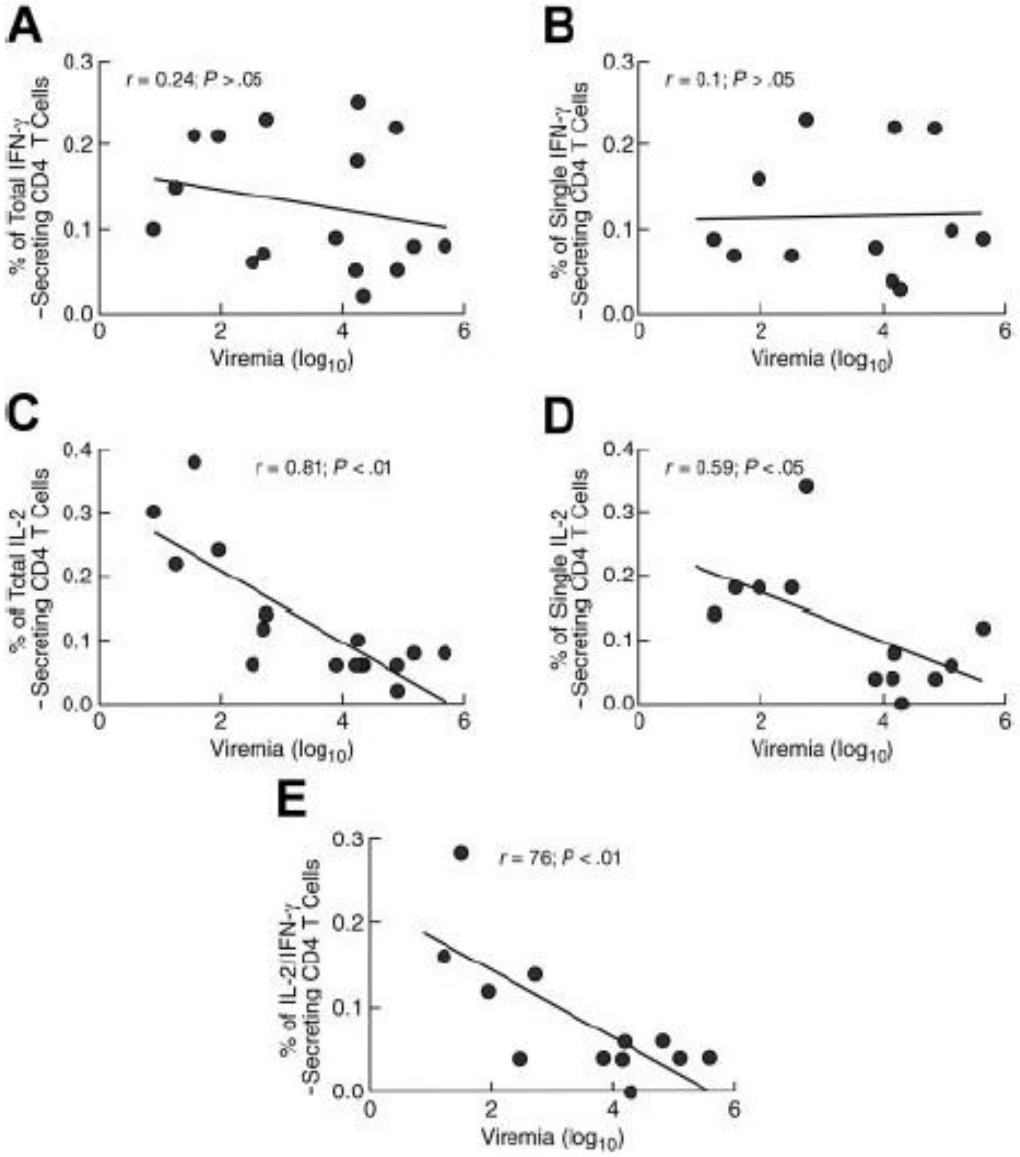
Harari A Blood 2004

HIV-specific CD4+ are equally distributed within different phenotypes in LTNPs



Harari A Blood 2004

Correlation of functionally-distinct populations of HIV-specific CD4+ and HIV RNA



Harari A Blood 2004

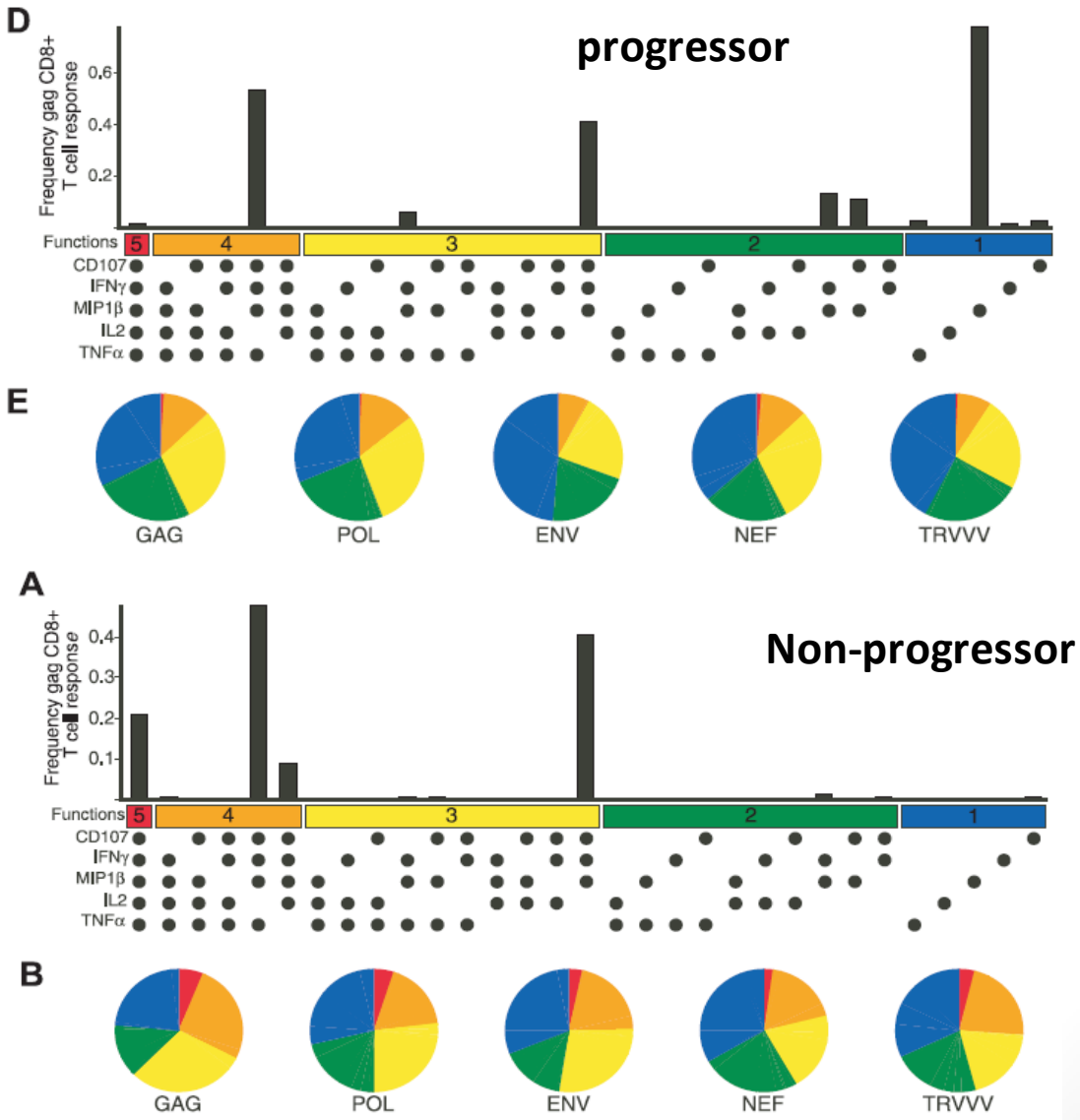
Single IL-2 response = antigen clearance

Single IFN-γ response = antigen persistence, high antigen load

Polyfunctional IL-2/ IFN-γ response = protracted antigen exposure, low antigen load

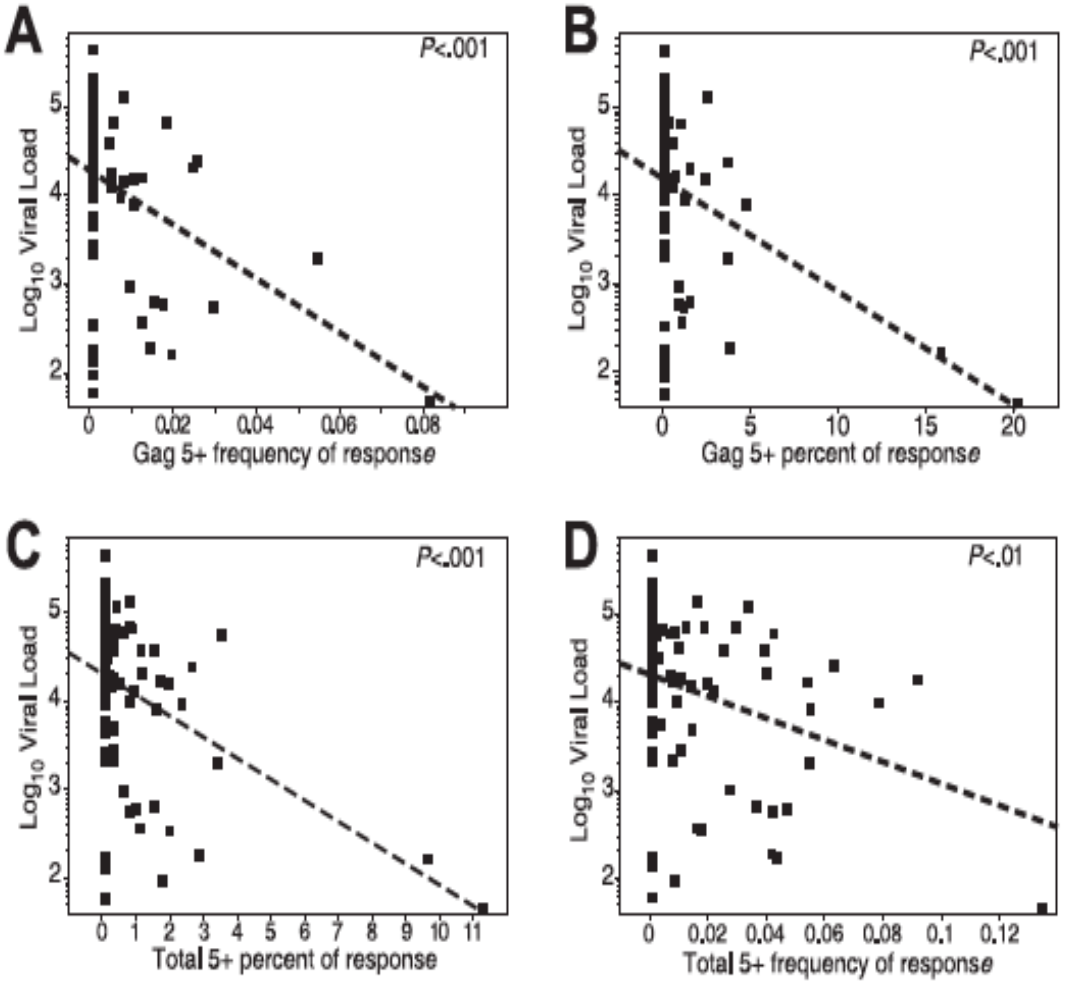
HIV-specific CD8+ functionality in HIV-infected progressors vs non-progressors

T-cell quality measured by 5 different function on cell-by-cell basis



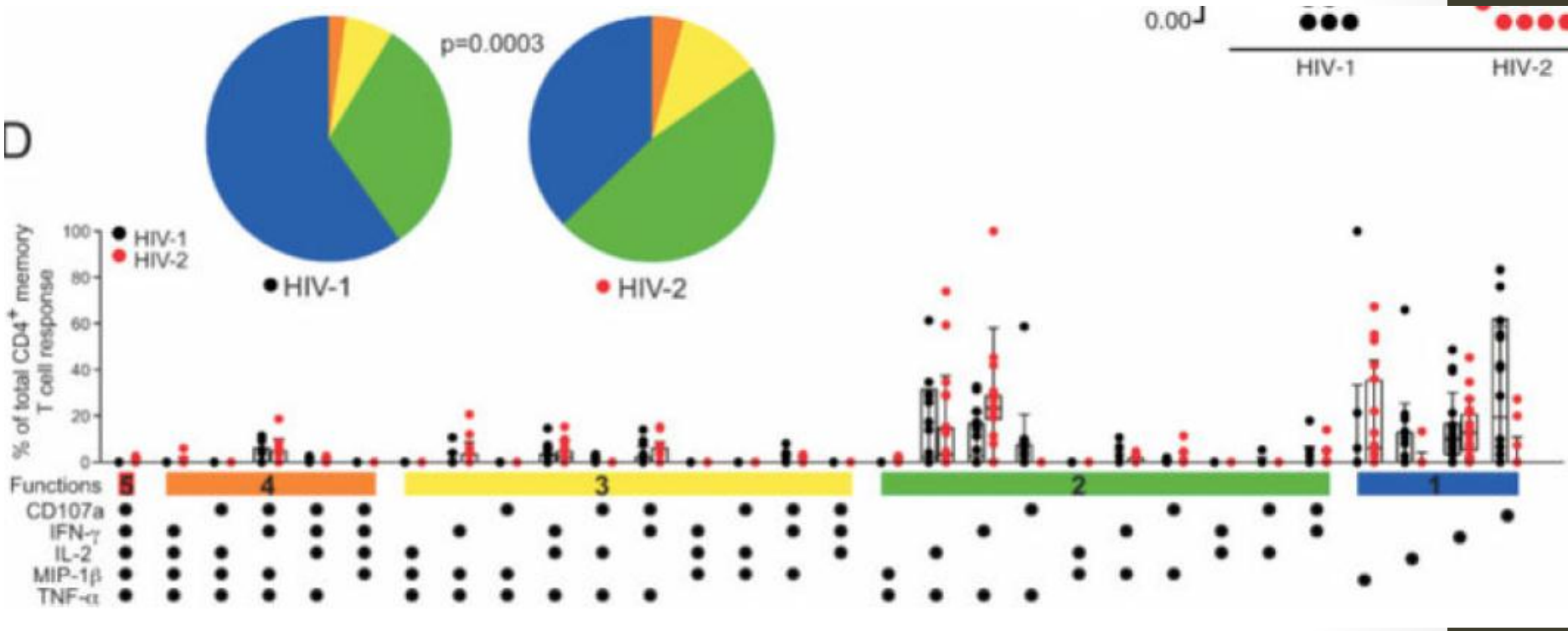
Betts M Blood 2006

The magnitude and proportion of HIV-spec CD8 negatively relate to HIV RNA



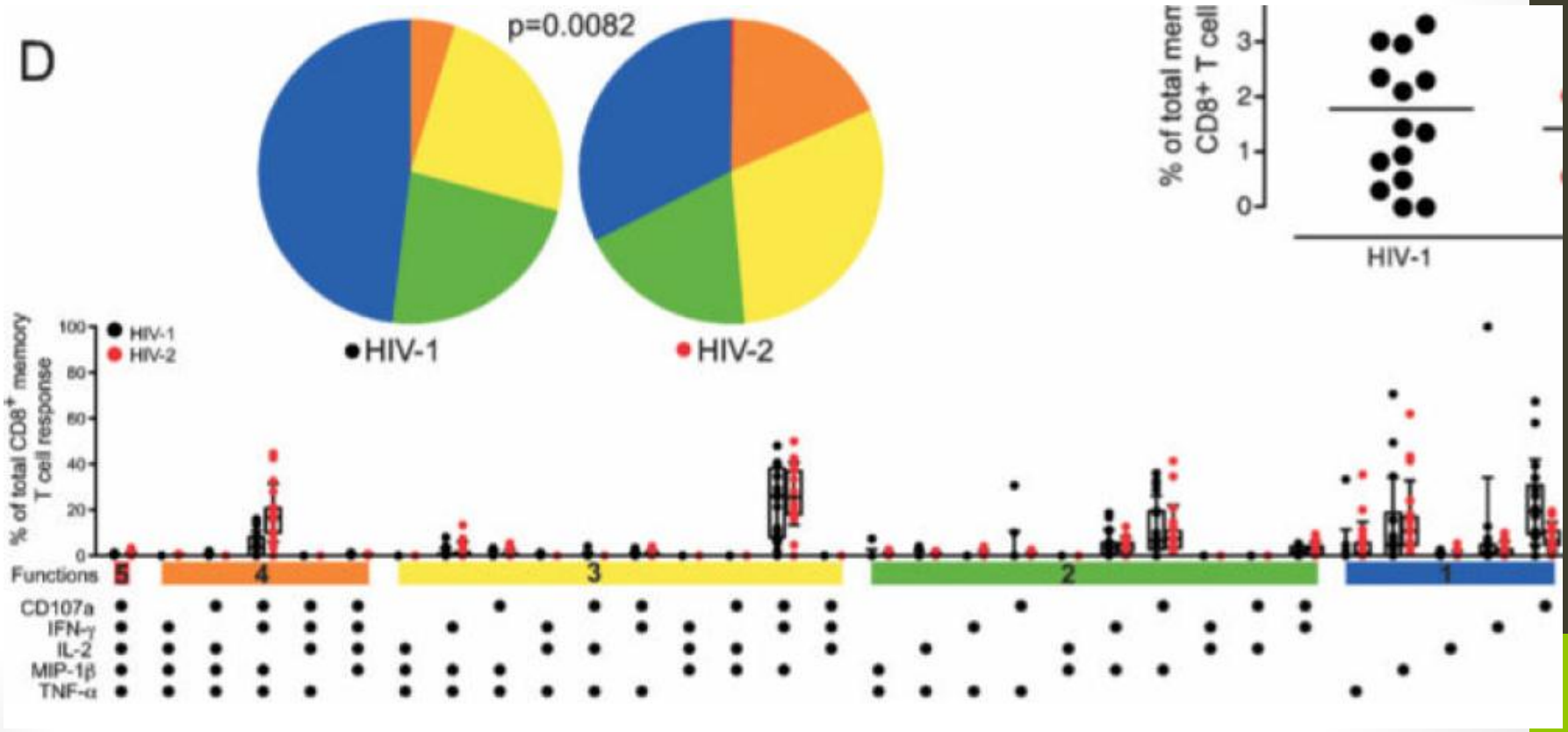
Betts M Blood 2006

Higher CD4+ T-cell polyfunctionality in HIV-2

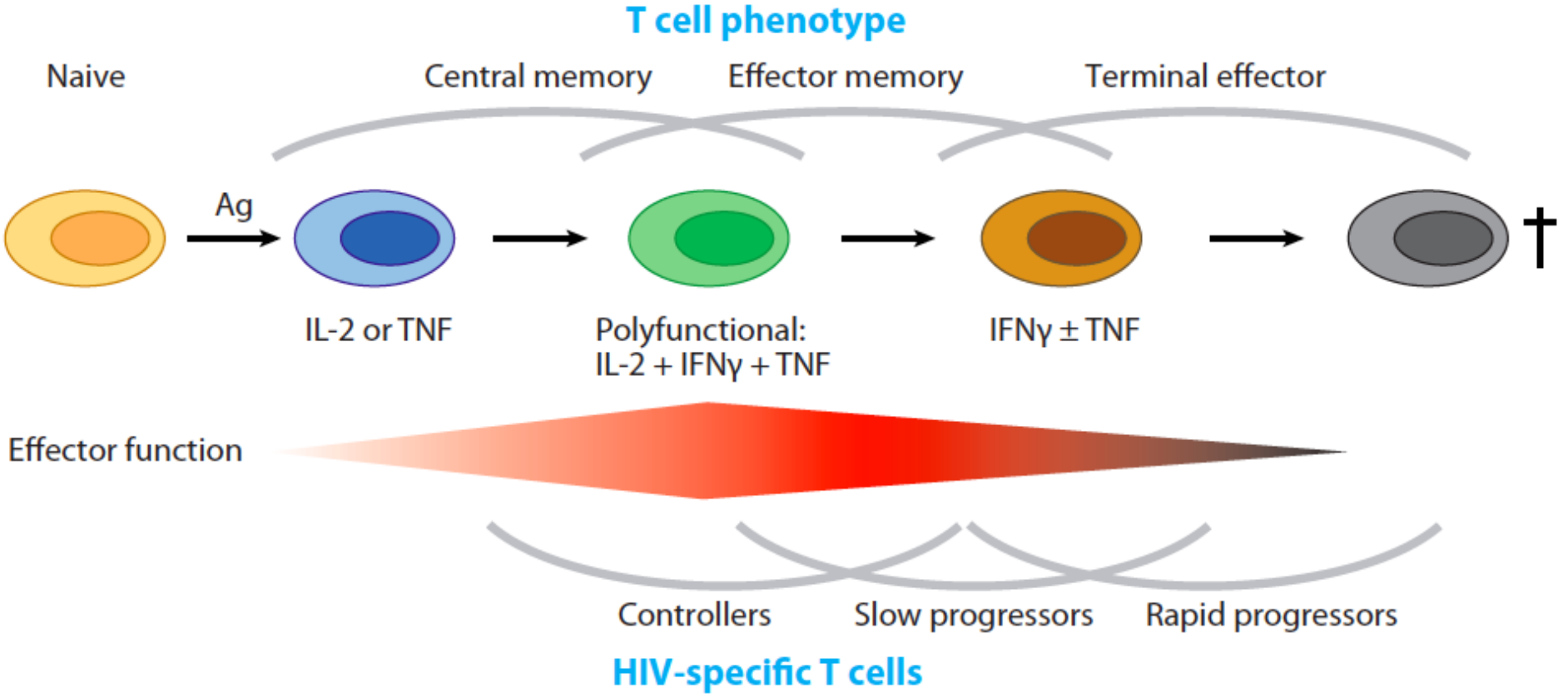


Duvall et al Eur J Immunol 2008

Higher CD8+ T-cell polyfunctionality in HIV-2

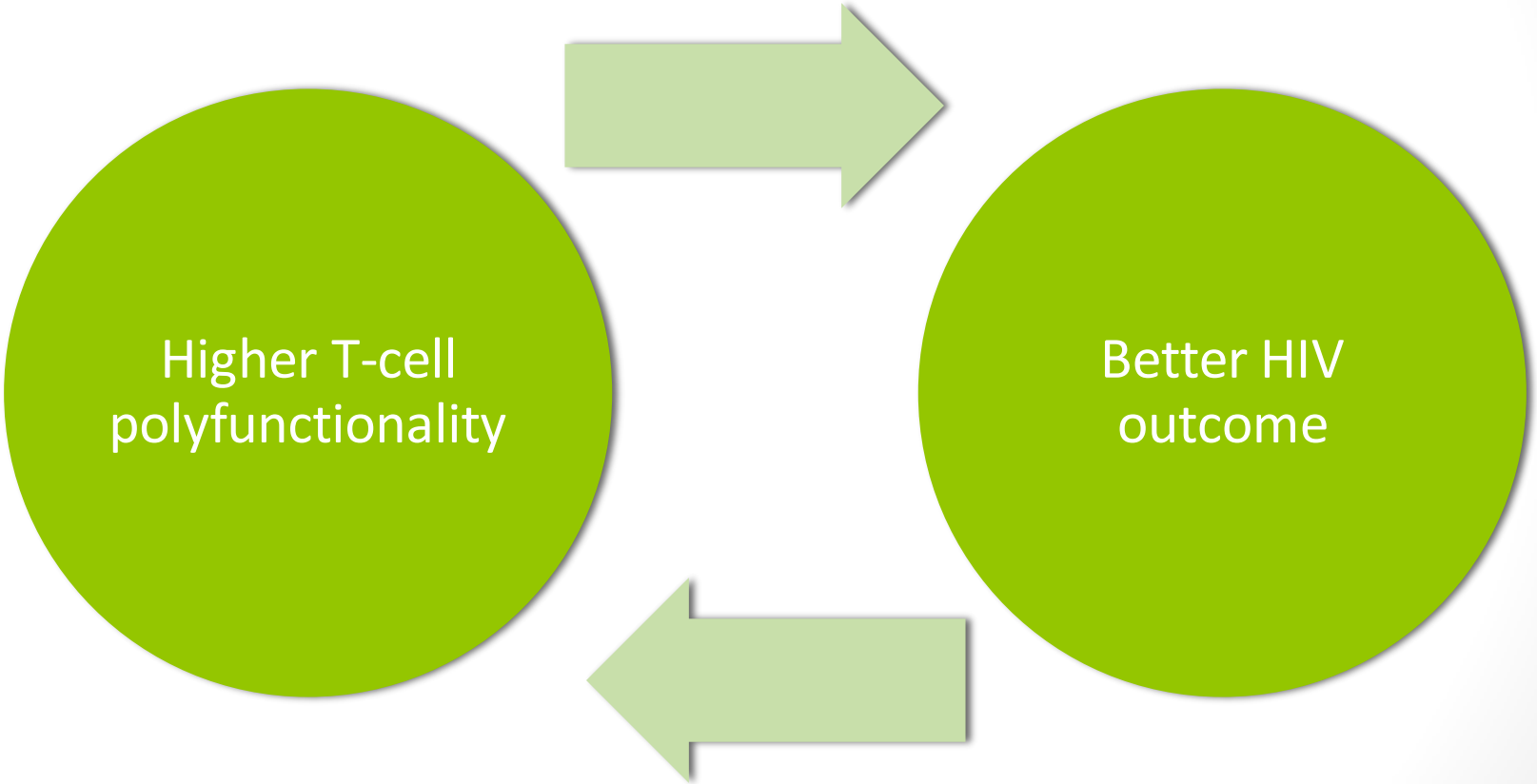


Duvall et al Eur J Immunol 2008



Douek et a. Annu Rev Med 2009

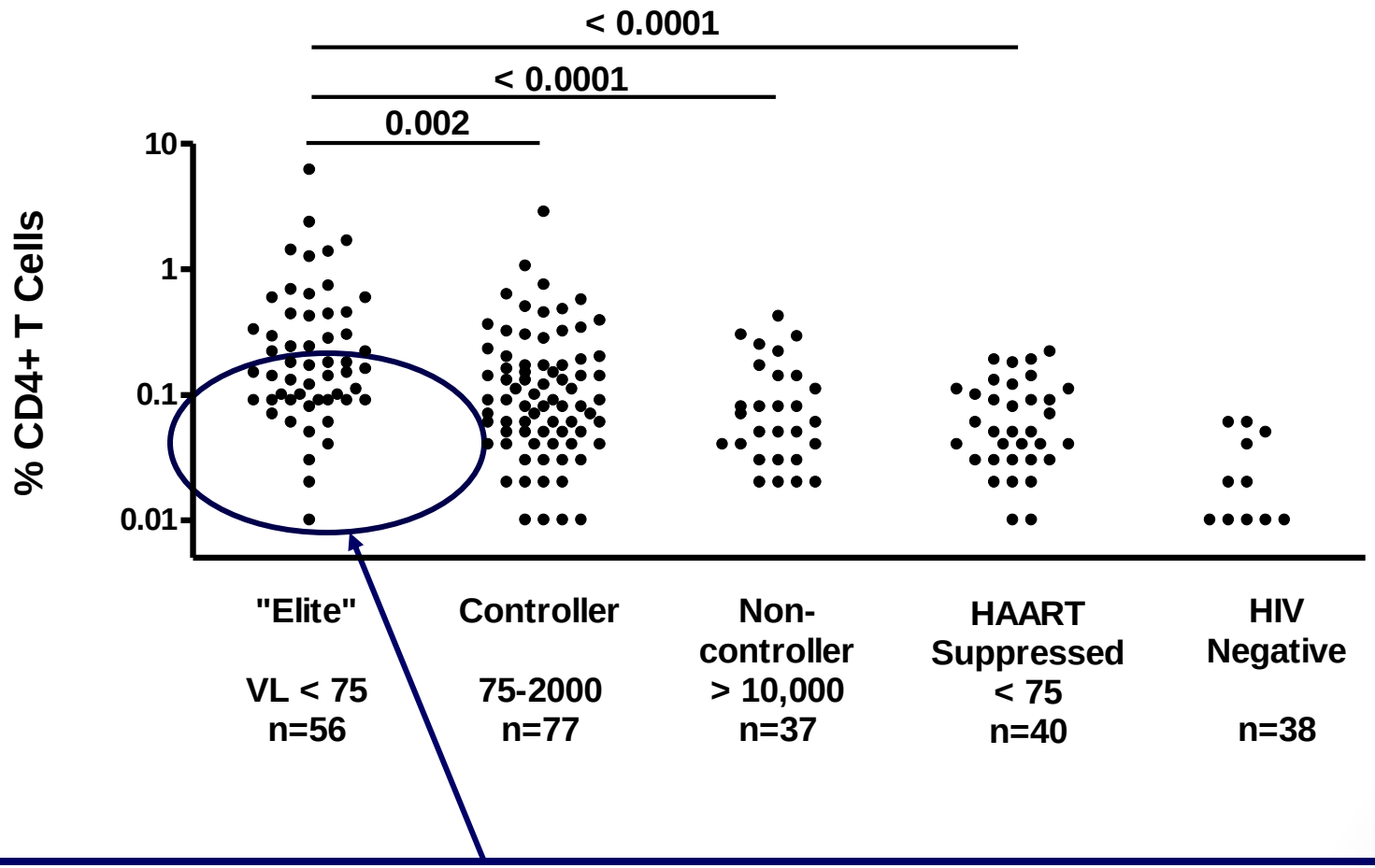
What is the cause and what is the effect?



Evidence in favour of T-cell polyfunctionality as causative of better control over HIV

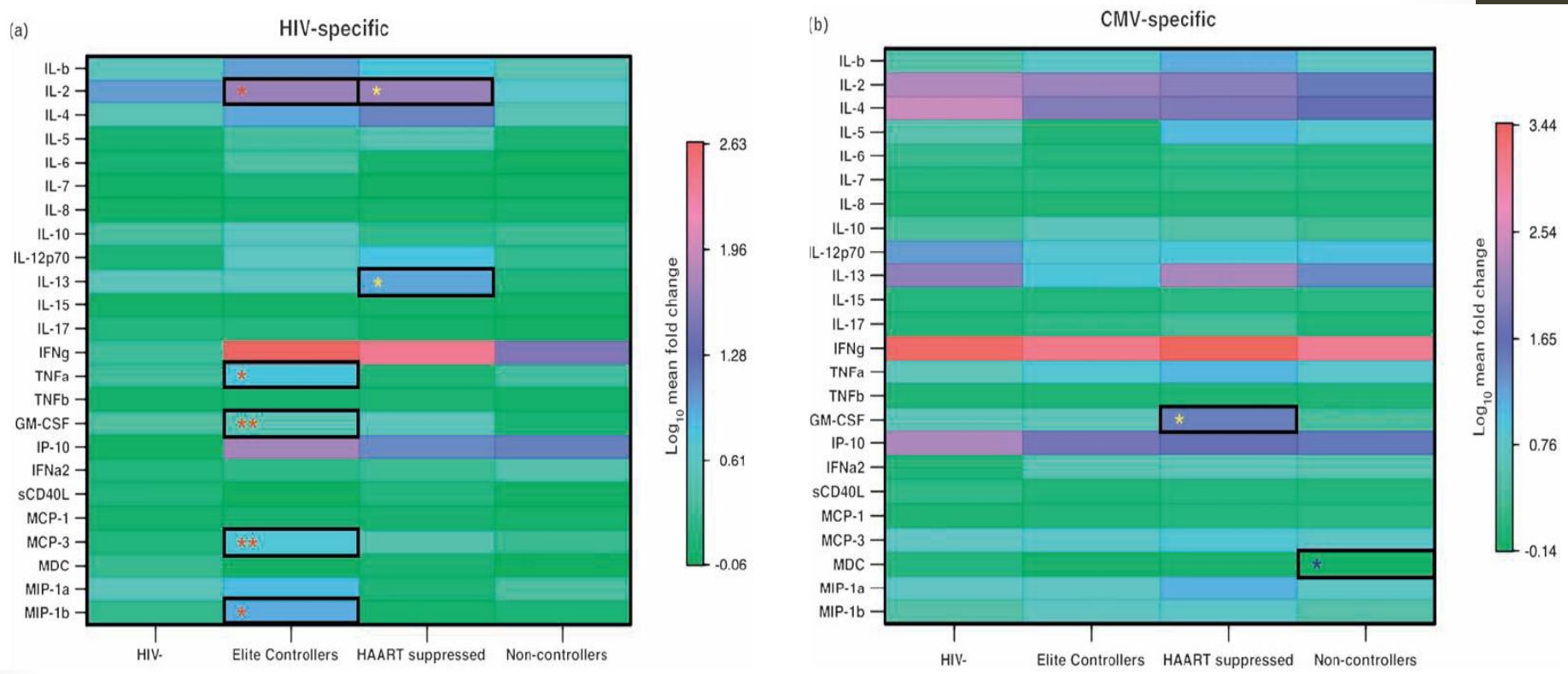
- Each polyfunctional cell elicits a wider repertoire of functions
- Each polyfunctional cell produces as much as 10-fold the amount of cytokine produced by monofunctional cells
- IL-2 production by polyfunctional cells makes them more prone to proliferation and effectiveness

Is the adaptive T cell response completely responsible for "elite" control?



Many controllers have HIV specific T cells that are low

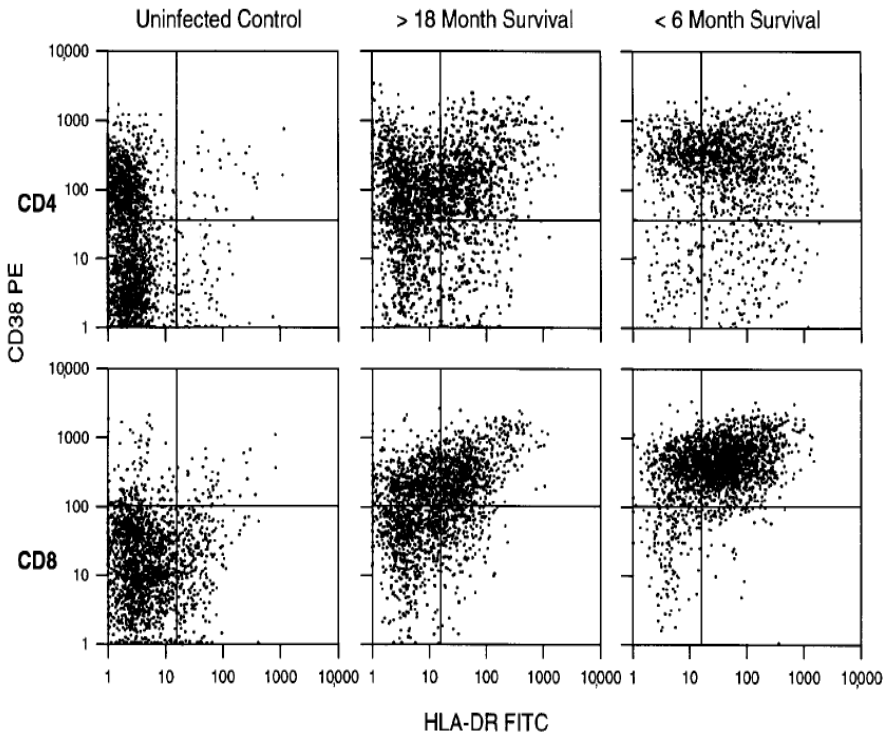
Elite controllers mount a broad and strong cytokine/chemokine response following HIV-specific stimulation

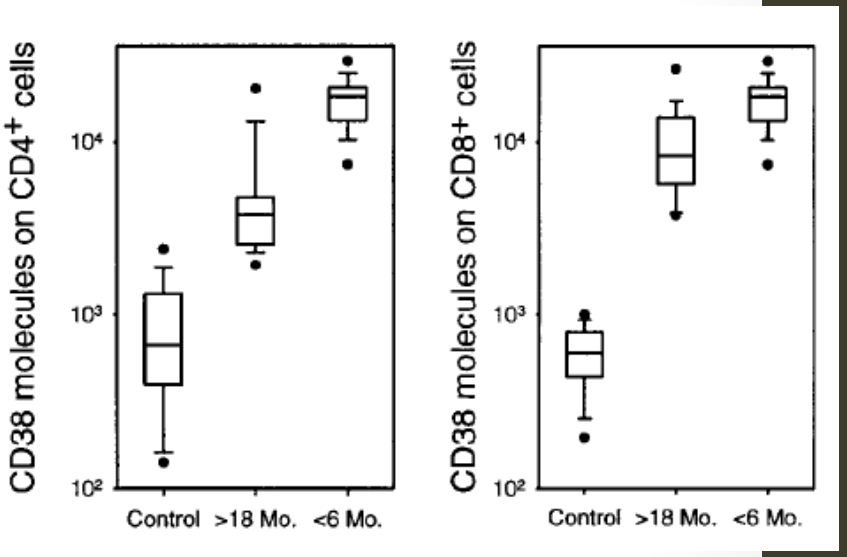


Owen et al. AIDS 2010

Immune activation in HIV pathogenesis

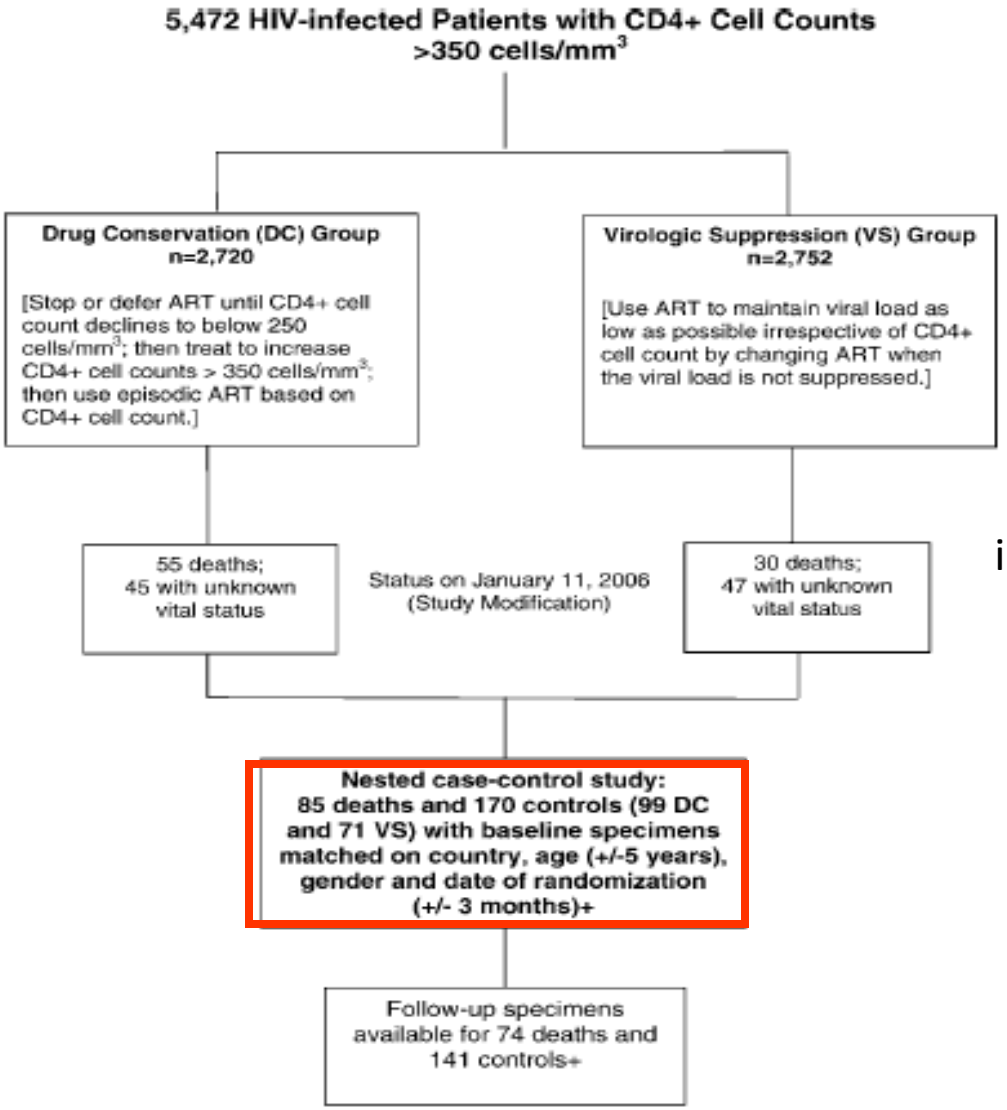
Shorter survival is associated with T-lymphocyte activation





Giorgi, J et al. JID 1999

The SMART Study



Analisi del rischio di morte in relazione a marcatori di infiammazione/coagulazione in pazienti in ART versus pazienti senza ART

Kuller L PLOS Medicine 2008

Rischio di morte associato a marcatori di infiammazione e coagulopatia

Biomarker	Type of Analysis	<25th Percentile (Reference)	25th–49th Percentile		50th–74th Percentile		≥75th Percentile		OR associated with One IQR Higher Biomarker Level after Log_{10} Transformation	
			OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
hsCRP (μg/ml)	No.[a]	16/45	9/42		20/28		40/55			
	Univariate	1.0 (ref.)	0.6 (0.2–1.5)	0.29	2.0 (0.9–4.6)	0.09	2.0 (1.0–4.1)	0.05	1.7 (1.2–2.4)	0.005
	Adjusted	1.0 (ref.)	0.7 (0.2–2.1)	0.50	2.5 (0.9–7.2)	0.08	3.1 (1.2–8.0)	0.02	2.3 (1.4–3.7)	0.001
Amyloid A (mg/l)	No.	11/46	17/35		28/33		29/56			
	Univariate	1.0 (ref.)	2.0 (0.8–5.2)	0.13	3.4 (1.5–7.7)	0.005	2.2 (0.9–5.2)	0.07	1.3 (0.9–1.7)	0.11
	Adjusted	1.0 (ref.)	3.4 (1.0–11.1)	0.04	3.5 (1.2–10.2)	0.02	3.1 (1.0–9.5)	0.05	1.3 (0.9–1.9)	0.12
Amyloid P (μg/ml)	No.	25/44	20/25		16/43		24/56			
	Univariate	1.0 (ref.)	1.5 (0.7–3.1)	0.32	0.7 (0.3–1.4)	0.32	0.7 (0.4–1.5)	0.39	0.7 (0.6–0.9)	0.009
	Adjusted	1.0 (ref.)	1.5 (0.6–4.0)	0.42	0.8 (0.3–2.0)	0.65	1.1 (0.4–3.0)	0.78	0.7 (0.5–1.0)	0.06
IL-6 (pg/ml)	No.	8/48	10/41		26/48		40/29			
	Univariate	1.0 (ref.)	1.3 (0.5–3.6)	0.62	3.2 (1.3–7.9)	0.01	8.3 (3.3–20.8)	<0.0001	3.4 (2.2–5.4)	<0.0001
	Adjusted	1.0 (ref.)	1.0 (0.3–3.6)	0.98	4.5 (1.4–14.2)	0.01	12.4 (3.6–42.0)	<0.0001	4.1 (2.3–7.3)	<0.0001
D-dimer (μg/ml)	No.	8/51	22/54		18/40		37/25			
	Univariate	1.0 (ref.)	3.2 (1.1–9.0)	0.03	4.0 (1.3–12.3)	0.02	12.4 (4.2–37.0)	<0.0001	3.9 (2.3–6.6)	<0.0001
	Adjusted	1.0 (ref.)	8.3 (1.9–36.8)	0.005	12.6 (2.4–65.1)	0.003	41.2 (7.5–225.6)	<0.0001	5.3 (2.6–10.9)	<0.0001

Kuller L PLOS Medicine 2008

Incremento di IL-6 e D-dimero

Braccio DC (drug conservation – ART CD4+-guidata)

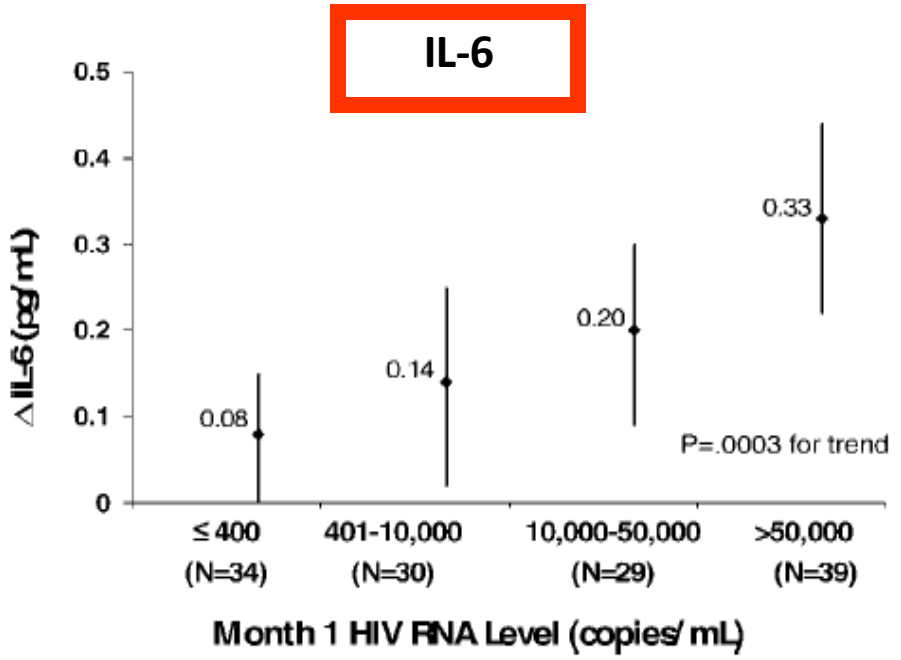
- IL-6= 30%
- D-dimero=16%

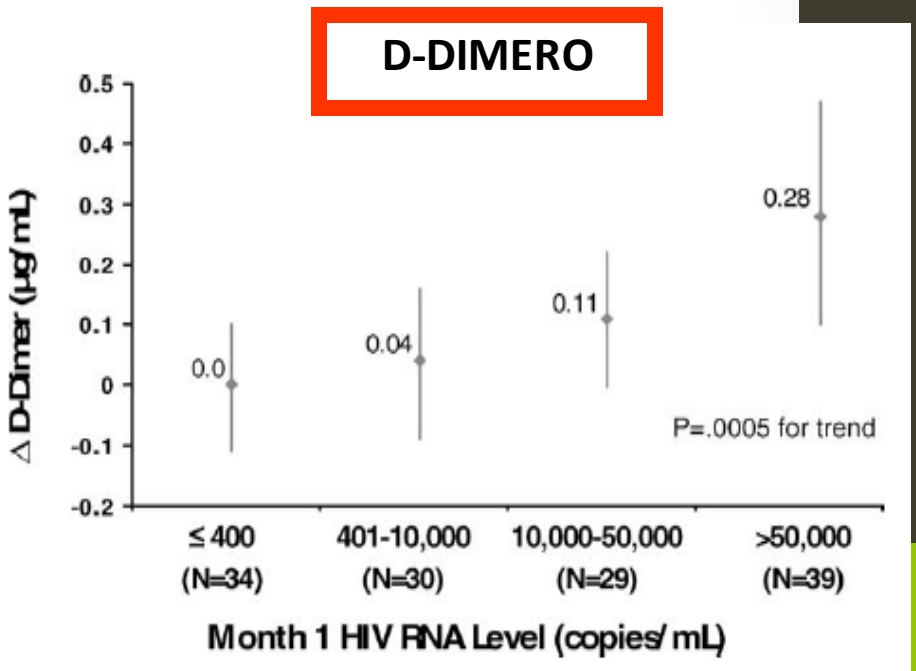
Braccio VS (virologic suppression)

- IL-6 =0%
- D-dimero=5%

P<.0001

Incremento di IL-6 e D-dimero nel braccio DC (drug conservation – ART CD4+-guidata)





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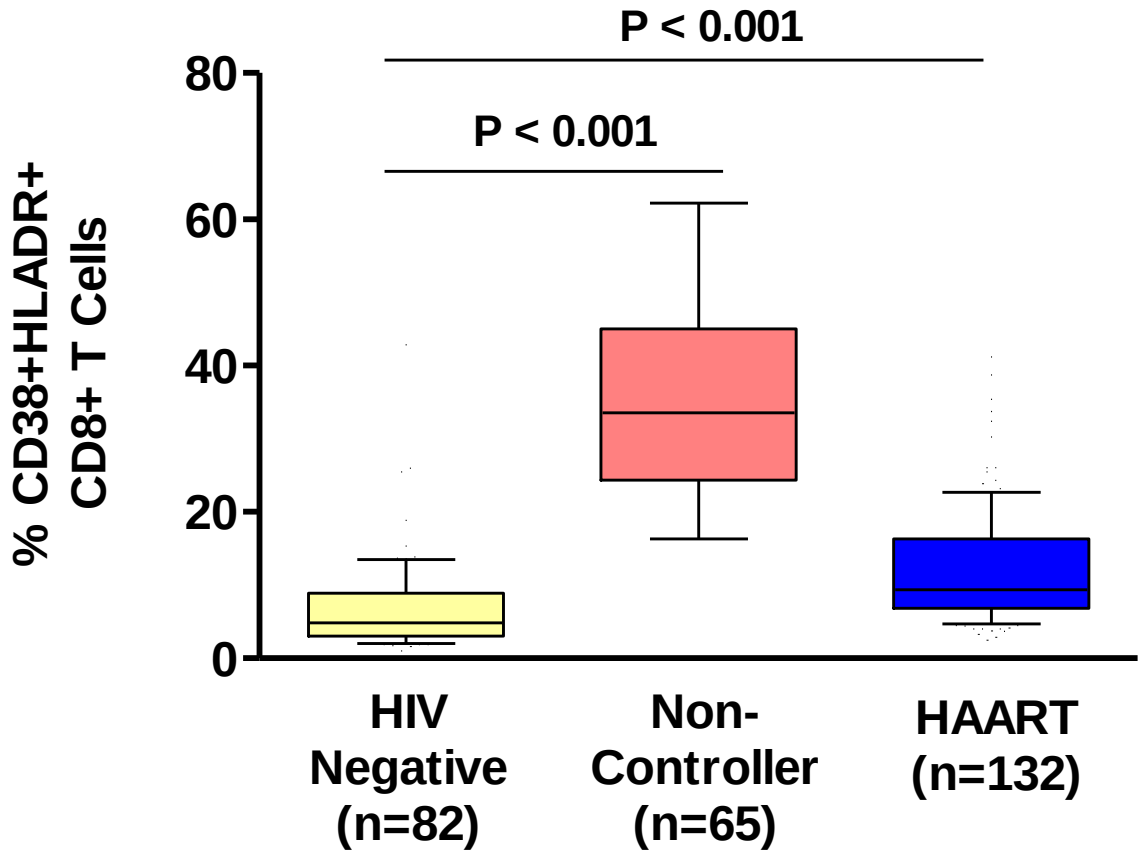
Rischio di morte associato a marcatori di infiammazione nei diversi bracci di trattamento

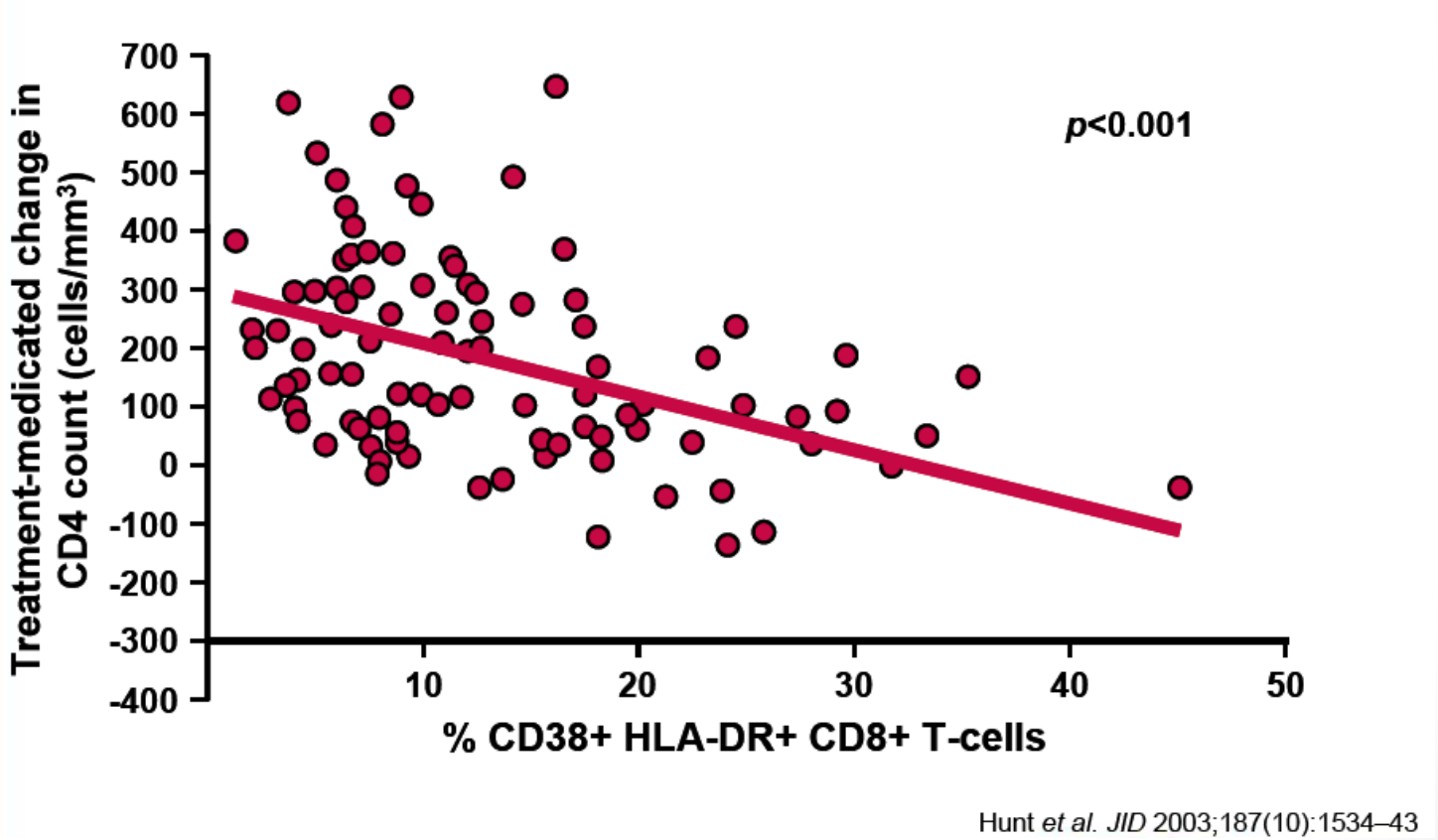
Biomarker	Type of Analysis	DC		VS		*p*-Value for Interaction[b]
		OR[a] (95% CI)	*p*-Value	OR[a] (95% CI)	*p*-Value	
hsCRP (µg/ml)	Univariate	2.0 (1.2–3.4)	0.01	1.8 (0.7–4.6)	0.18	0.41
	Adjusted[c]	2.3 (1.2–4.4)	0.01	2.7 (0.9–7.9)	0.08	0.44
Amyloid A (mg/l)	Univariate	1.6 (1.0–2.5)	0.06	1.2 (0.6–2.3)	0.67	0.08
	Adjusted[c]	1.6 (0.9–2.8)	0.11	1.5 (0.6–3.8)	0.40	0.11
Amyloid P (µg/ml)	Univariate	0.7 (0.5–1.1)	0.14	0.8 (0.4–1.4)	0.43	0.22
	Adjusted[c]	0.8 (0.5–1.3)	0.40	0.7 (0.3–1.6)	0.46	0.31
IL-6 (pg/ml)	Univariate	3.7 (2.1–6.4)	<0.0001	2.8 (1.3–6.1)	0.008	0.56
	Adjusted[c]	3.8 (2.1–7.2)	0.0002	2.4 (1.1–5.2)	0.03	0.33
D-dimer (µg/ml)	Univariate	3.6 (1.7–7.3)	0.0005	2.6 (0.7–9.1)	0.14	0.38
	Adjusted[c]	5.9 (1.9–18.7)	0.002	7.1 (0.8–63.2)	0.08	0.30
F1.2 (pmol/l)	Univariate	1.0 (0.6–1.6)	0.98	0.8 (0.3–2.2)	0.71	0.34
	Adjusted[c]	0.8 (0.4–1.5)	0.47	0.7 (0.2–2.2)	0.55	0.16

Persistente attivazione T-linfocitaria in corso di HAART virologicamente soppressiva



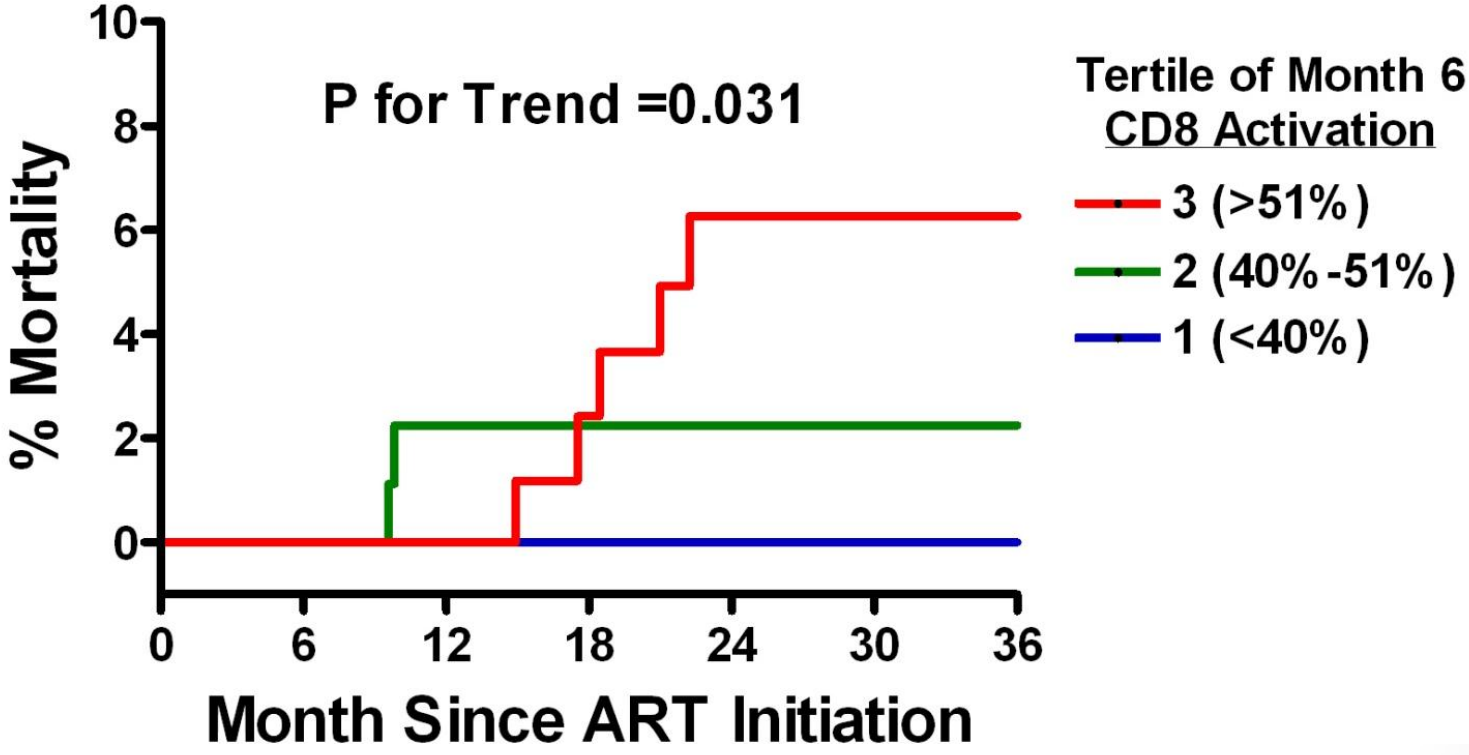
Hunt P et al. JID 2003

Immune activation hampers immune reconstitution on HAART



Hunt *et al. JID* 2003;187(10):1534–43

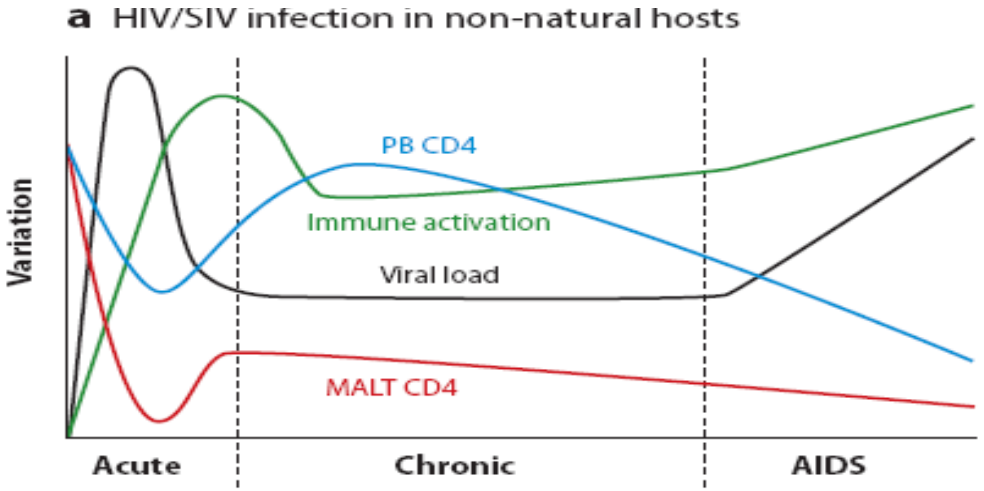
UARTO: alti livelli di attivazione CD8+ dopo 6 mesi di HAART predicono la mortalità in condizioni di HIV R <400



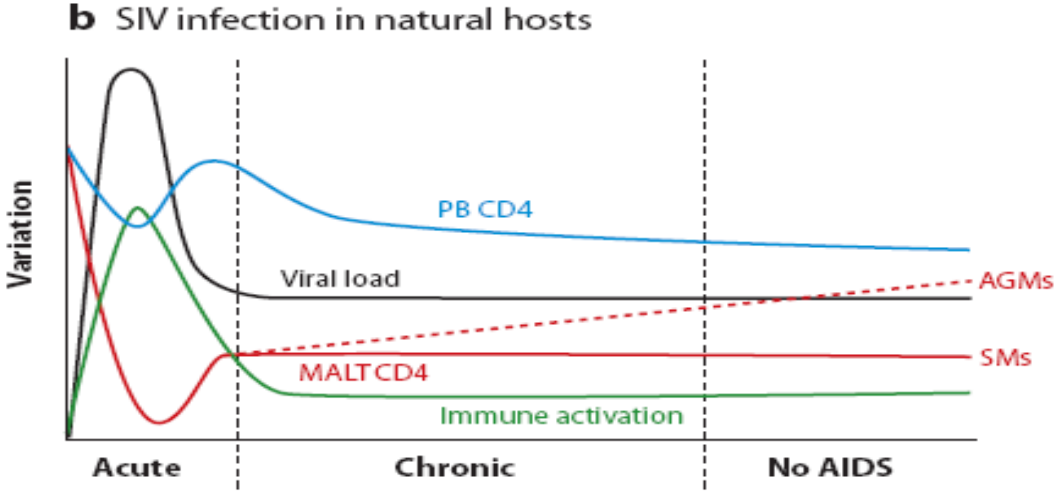
In Cox Proportional Hazards models, each 10% increase in the frequency of activated (%CD38+ HLA-DR+) CD8+ T cells was associated with an increased hazard of death even after adjustment for baseline CD4 count (HR: 1.62, P=0.048) or month 6 CD4 count (HR: 1.61, P=0.042).

Hunt et al, AIDS 2011 25:2123

Dynamics of immune activation in the Natural Hosts of HIV-Related Viruses



Rhesus macaques - RM



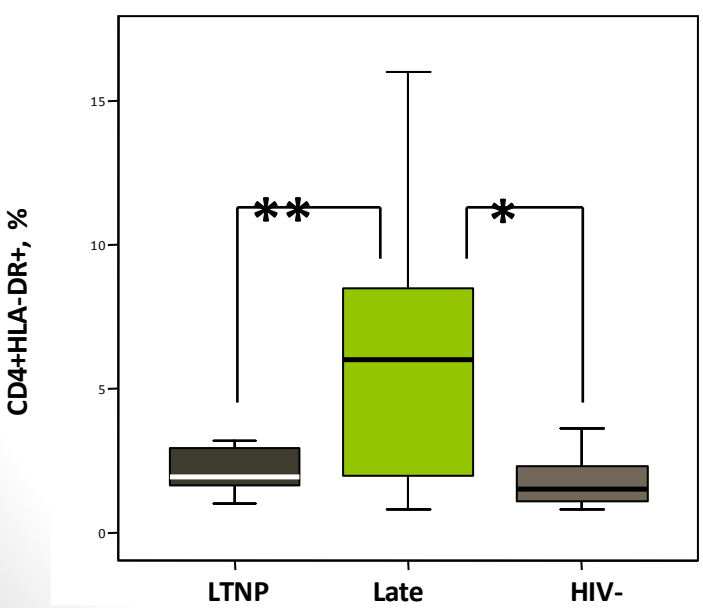
Sooty mangabeys - SM

Paiardini, M. Annu Rev Med. 2009;60:485-95.

I LTNPs presentano livelli di attivazione T-linfocitaria più contenuti rispetto a pazienti con progressione di infezione

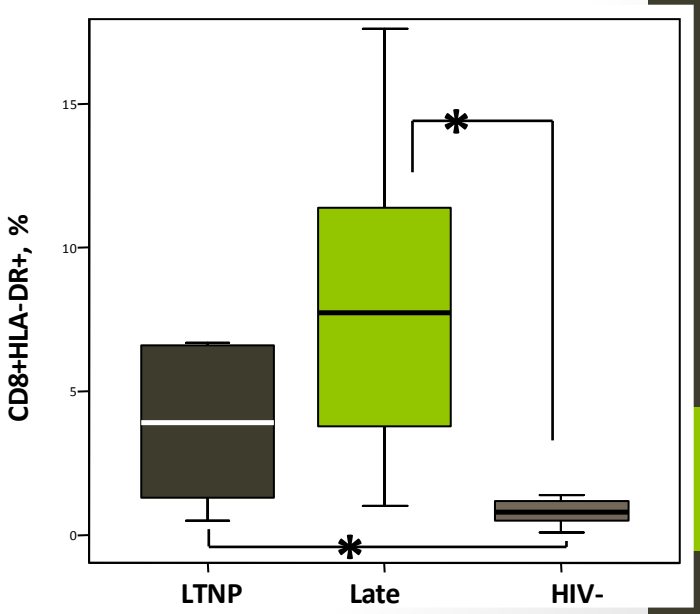
- Ridotti livelli di iperattivazione T-linfocitaria (in particolare CD4+CD38+ e CD8+CD38+)
- Ridotti livelli di apoptosi periferica

Vicenzi E, 1997 Blood; Perfetto SP, 1998 Cytometry; Richardson MW, 2003 AIDS



*p<0.01

**p<0.05



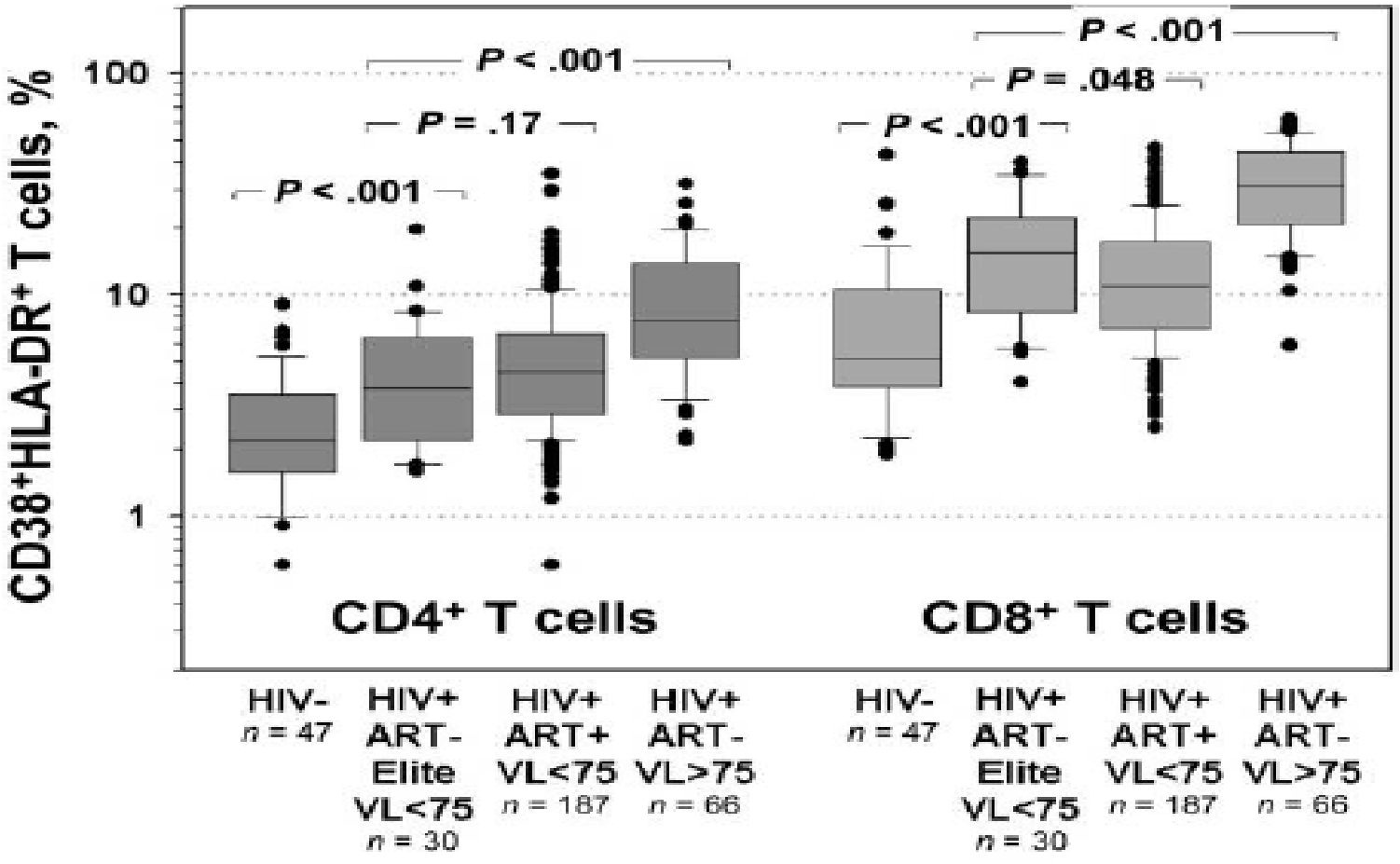
Marchetti et al HIV Med 2009

Elite controllers

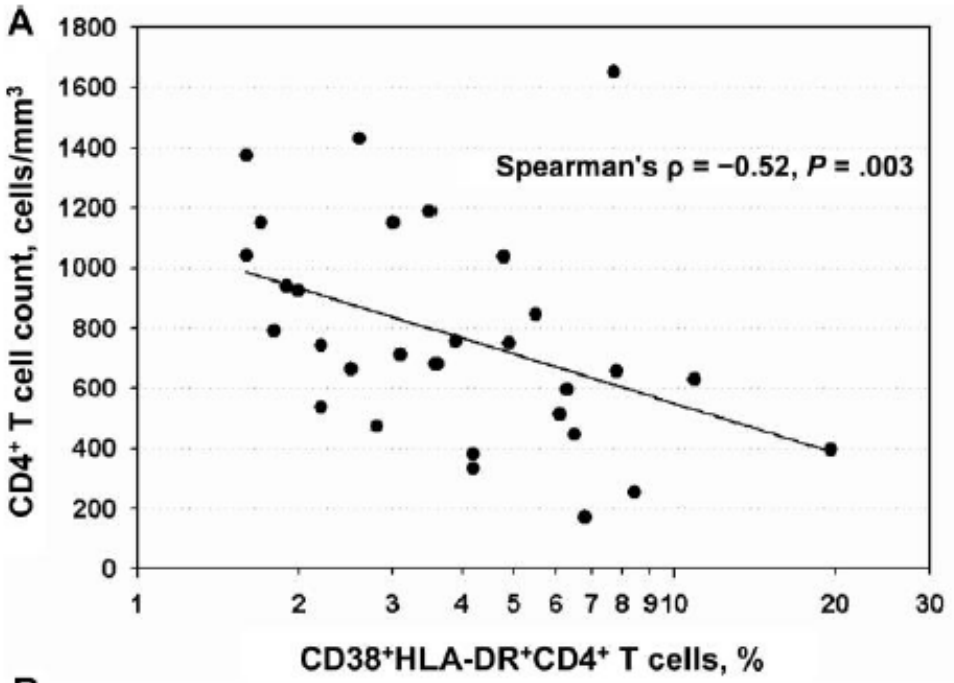
Characteristic	HIV-uninfected participants (n = 47)	HIV-infected controllers with VL<75 (n = 30)	HIV-infected antiretroviral-treated participants with VL<75 (n = 187)	HIV-infected untreated participants with VL>75 (n = 66)
Age, years	37 (30–43)	48 (45–51)	46 (41–51)	42 (37–48)
Female sex, no. (%)	0 (0)	12 (40)	32 (17)	14 (21)
CD4+ T cell count, cells/mm^3	943 (689–1058)[a]	727 (512–1037)	442 (274–633)	351 (250–511)
Plasma HIV RNA level, $\log_{10}$ copies/mL	. . .	<1.9 (. . .)	<1.9 (. . .)	4.0 (3.4–4.5)
Current AIDS diagnosis, no. (%)	0 (0)	2 (7)	25 (13)	12 (18)
Nadir CD4+ T cell count, cells/mm^3	. . .	496 (350–642)	114 (40–191)	270 (137–400)
Hepatitis C virus seropositive, no. (%)	0 (0)	19 (79)[b]	54 (29)	32 (48)

Hunt et al. JID 2008

Elite controllers display elevated T-cell activation

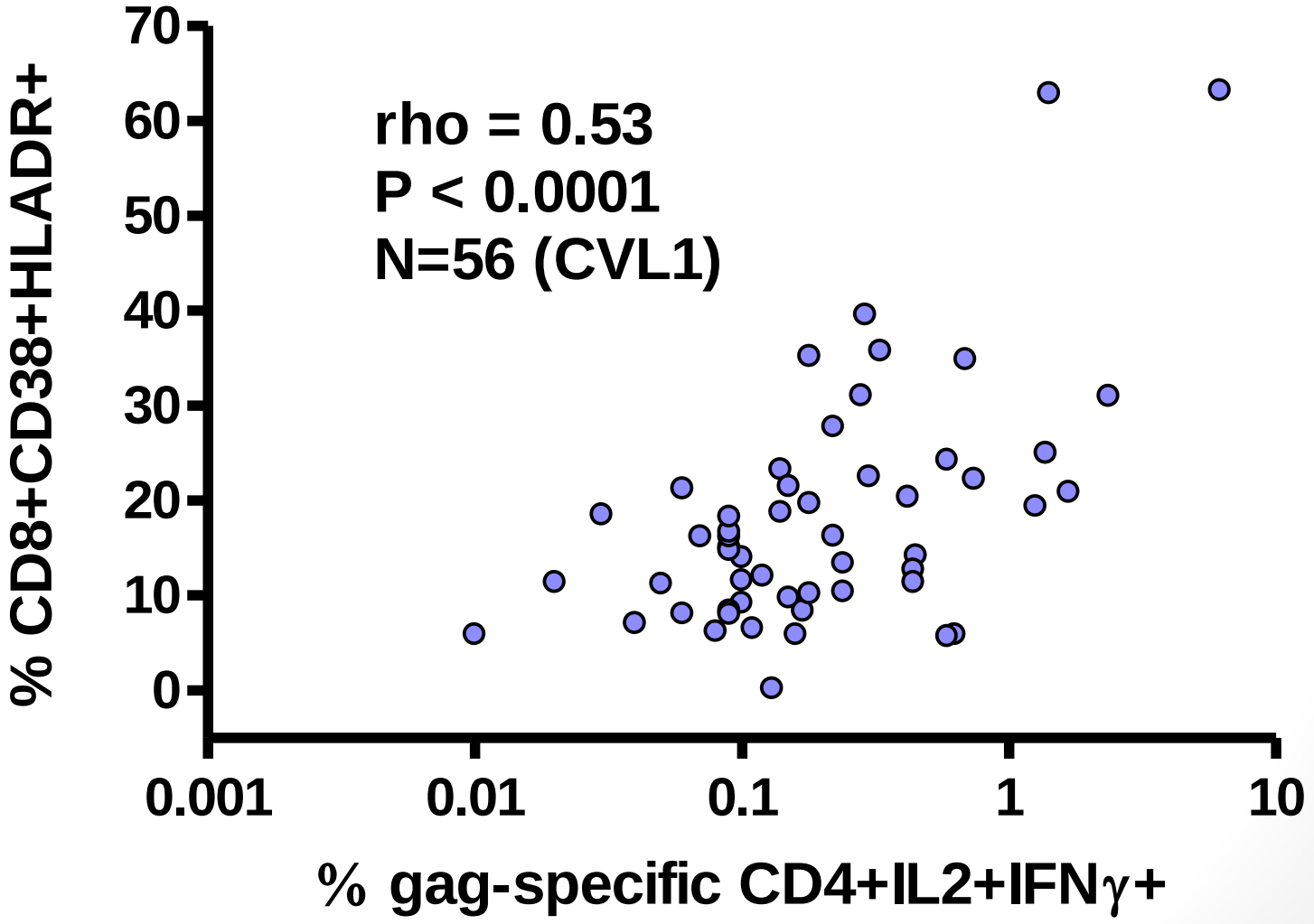


Hunt et al. JID 2008

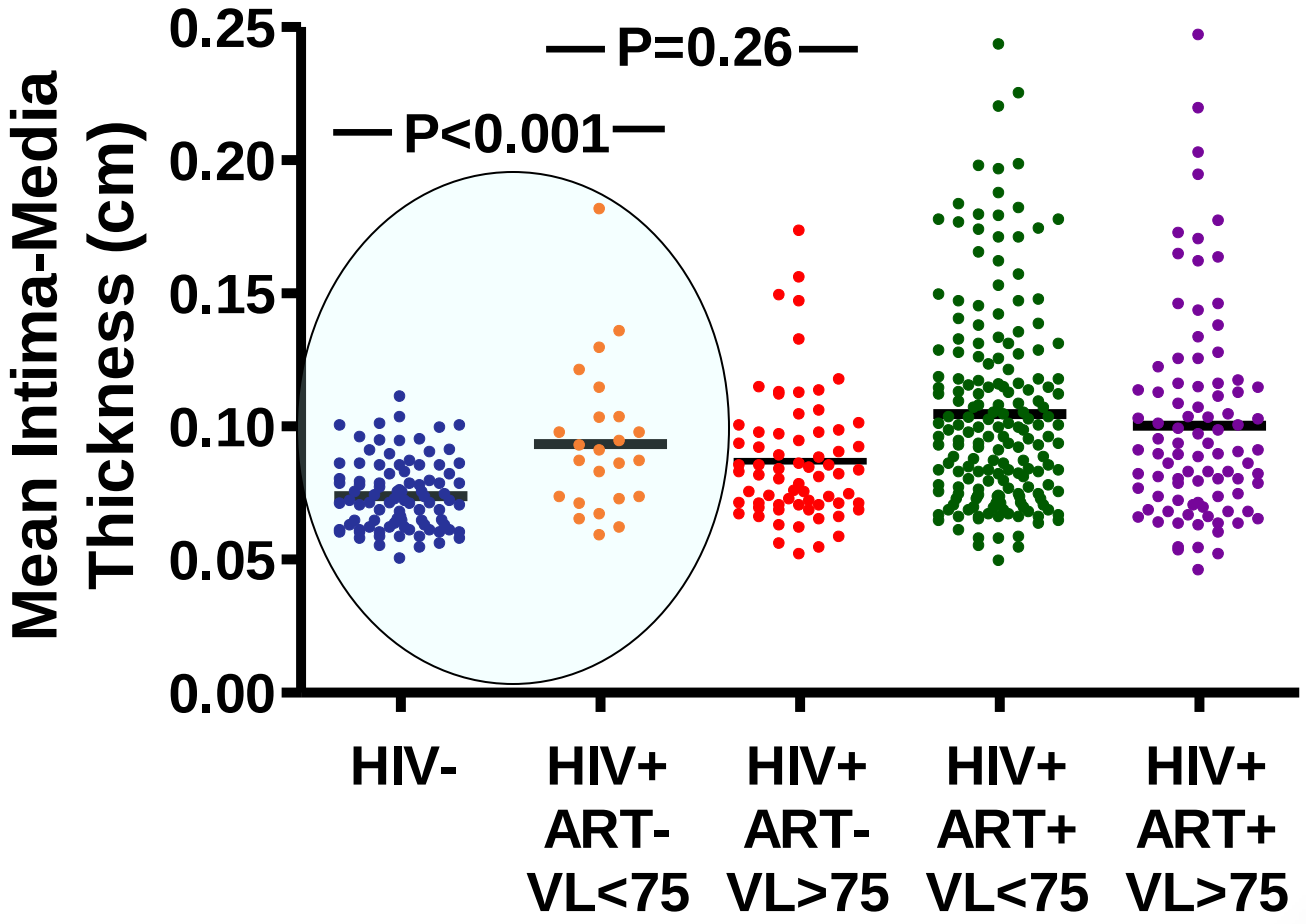


Hunt et al. JID 2008

High CD8+ T Cell Activation is Associated with High Gag-Specific CD4+ T cell Responses Among "Elite" Controllers



Elite controllers have higher levels of atherosclerosis than HIV negatives, after controlling for all known risk factors



P. Hsue

HIV "ELITE" CONTROLERS
Controlling virus comes at a cost?

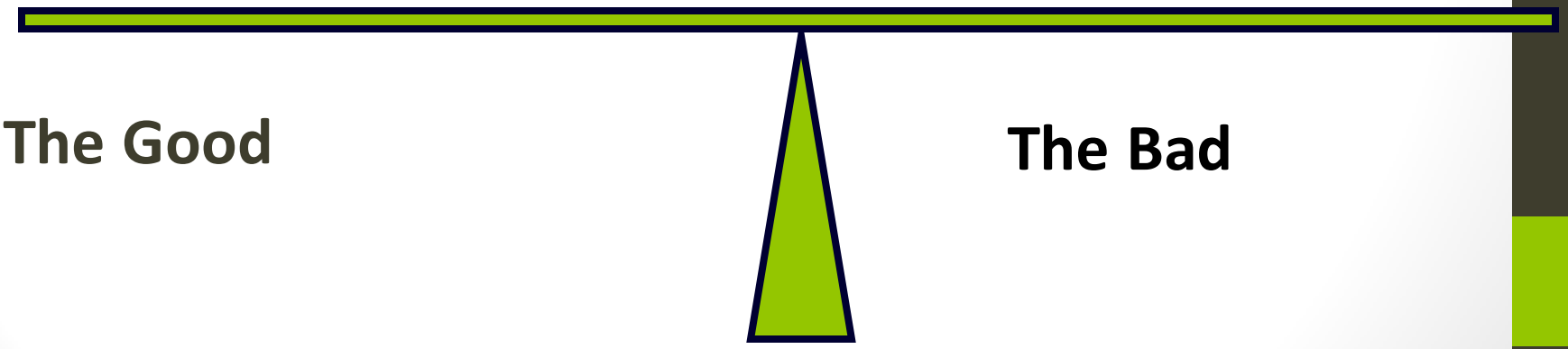
Strong HIV-specific CD8+ and CD4+ T cell responses

High NK Cell activation

Persistent inflammation

Progressive CD4 loss

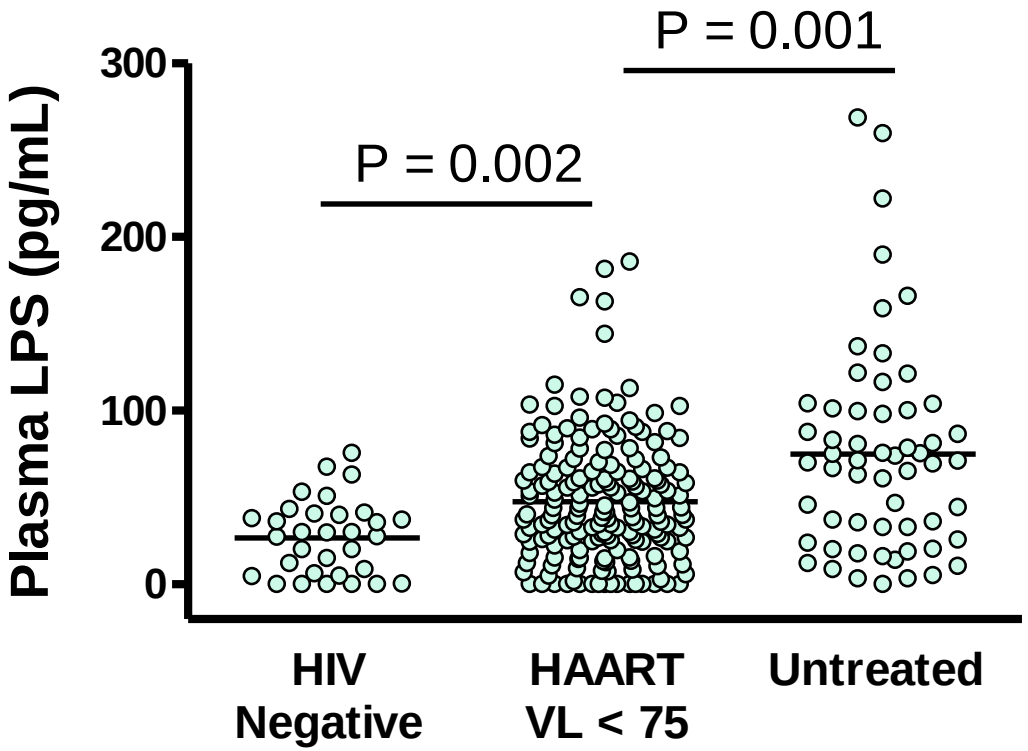
Higher risk of cardiovascular disease



The Good

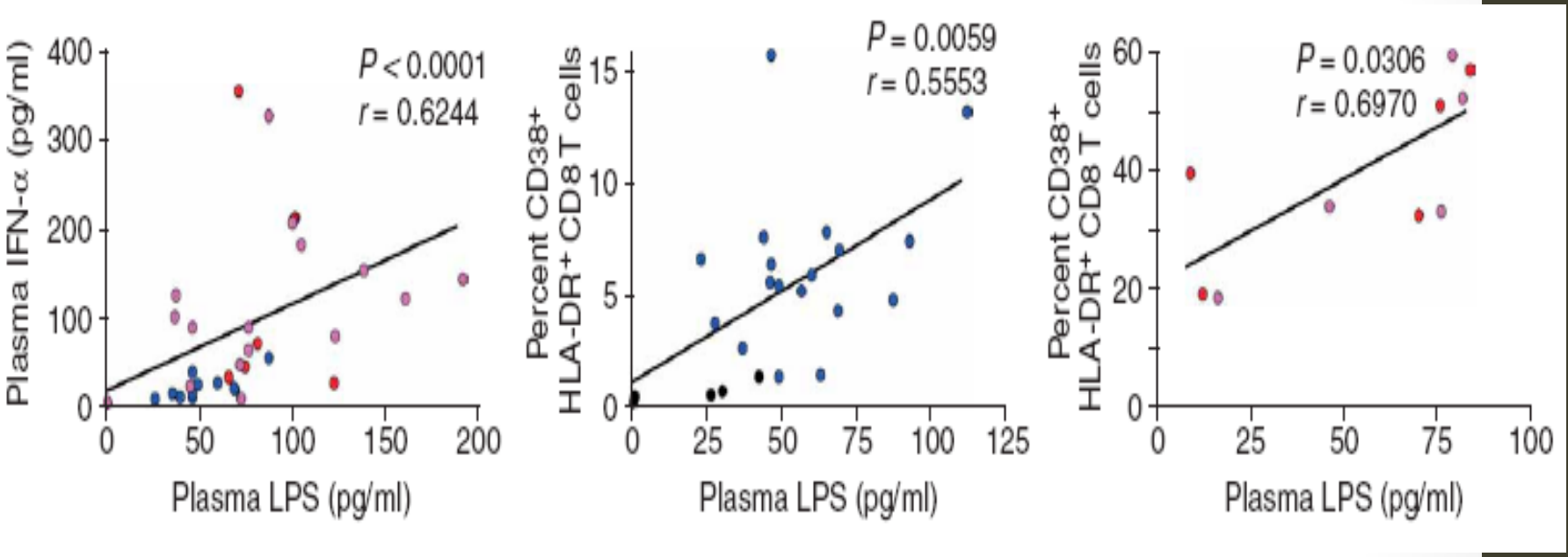
The Bad

Most (but not all) studies have shown that HIV infection results in mucosal damage, microbial translocation and inflammation; this effect persists during HAART



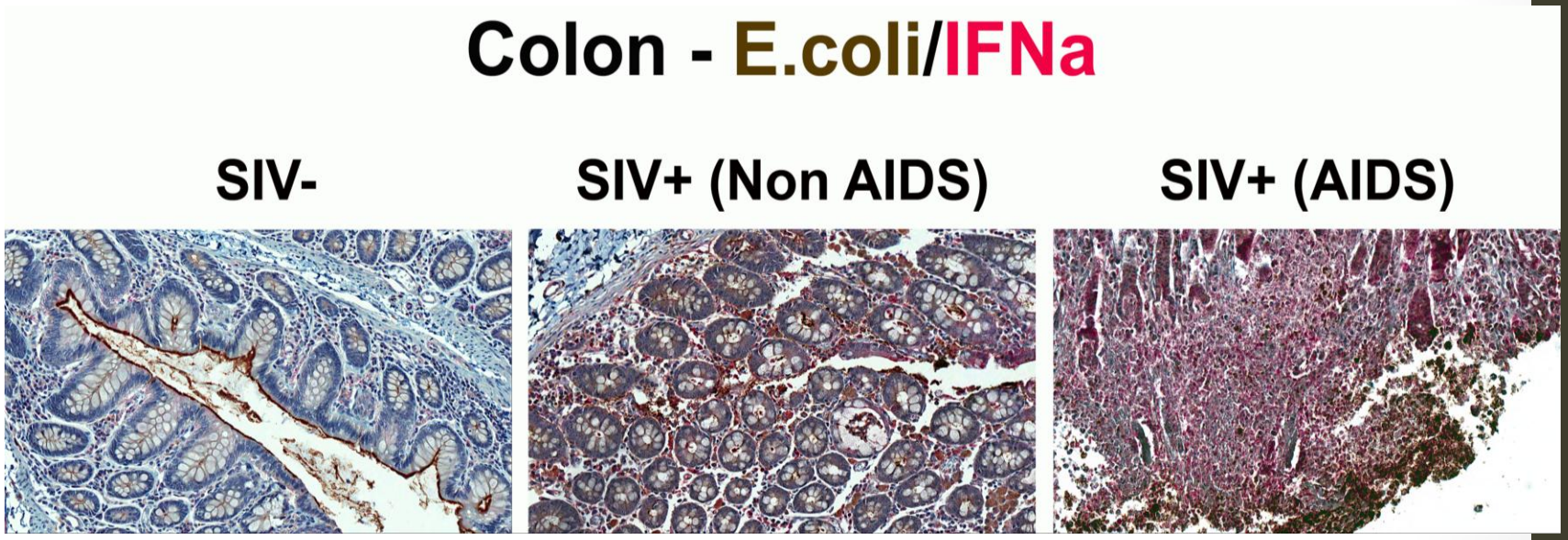
Brenchley JM Nature Medicine 2006

Microbial translocation is associated to immune activation



Brenchley Nat Med 2006

Microbial translocation causes immune activation (?): colocalization of *E.coli* and IFN-α in colon



Estes J et al. PLoS Pathogens 2010

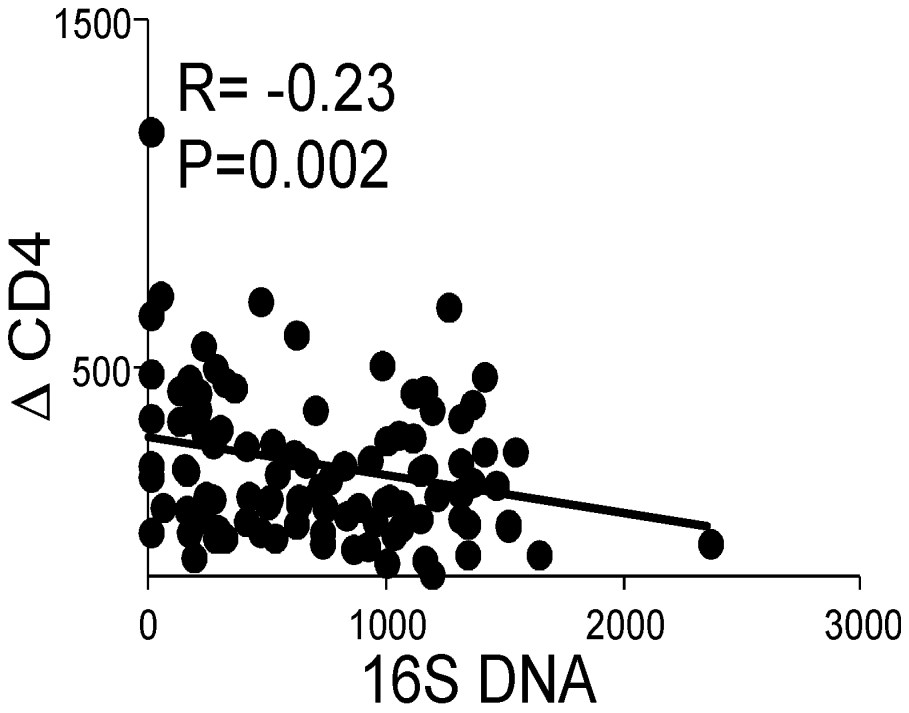
LPS independently predicts HIV disease progression

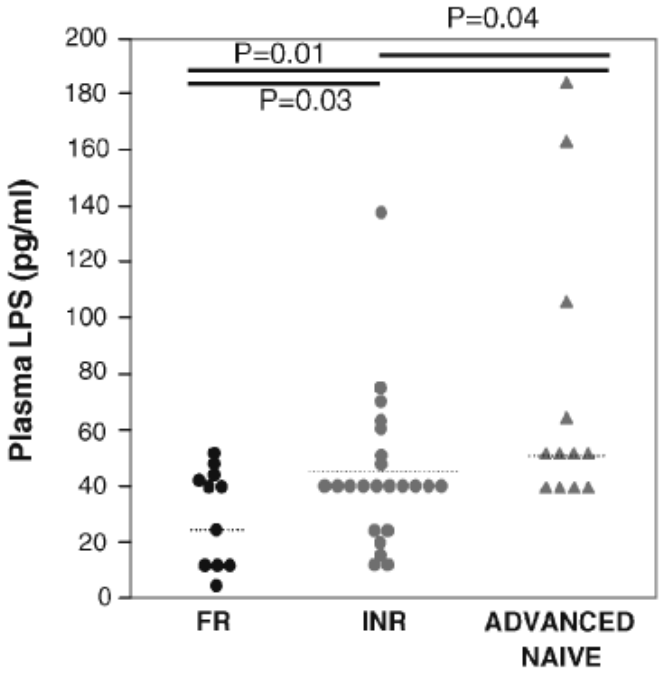
Biomarker	Crude and adjusted relative hazards of clinical progression					
	Crude RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value	Adjusted** RH (95% CI)	p-value
IL-6, pg/ml						
<=1	1.00		1.00		1.00	
>1	0.91 (0.69, 1.20)	0.507	1.12 (0.85, 1.47)	0.436	1.08 (0.80, 1.46)	0.600
not measured	1.03 (0.74, 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

*All models (a separate one for each biomarker) adjusted for age, CD4+, HIV RNA, HCV/HBV, year of test, duration of HIV infection at the date of the test; **Further mutually adjusted for all biomarkers

Marchetti et al. AIDS 2011

CD4 reconstitution during HAART is negatively associated with microbial translocation

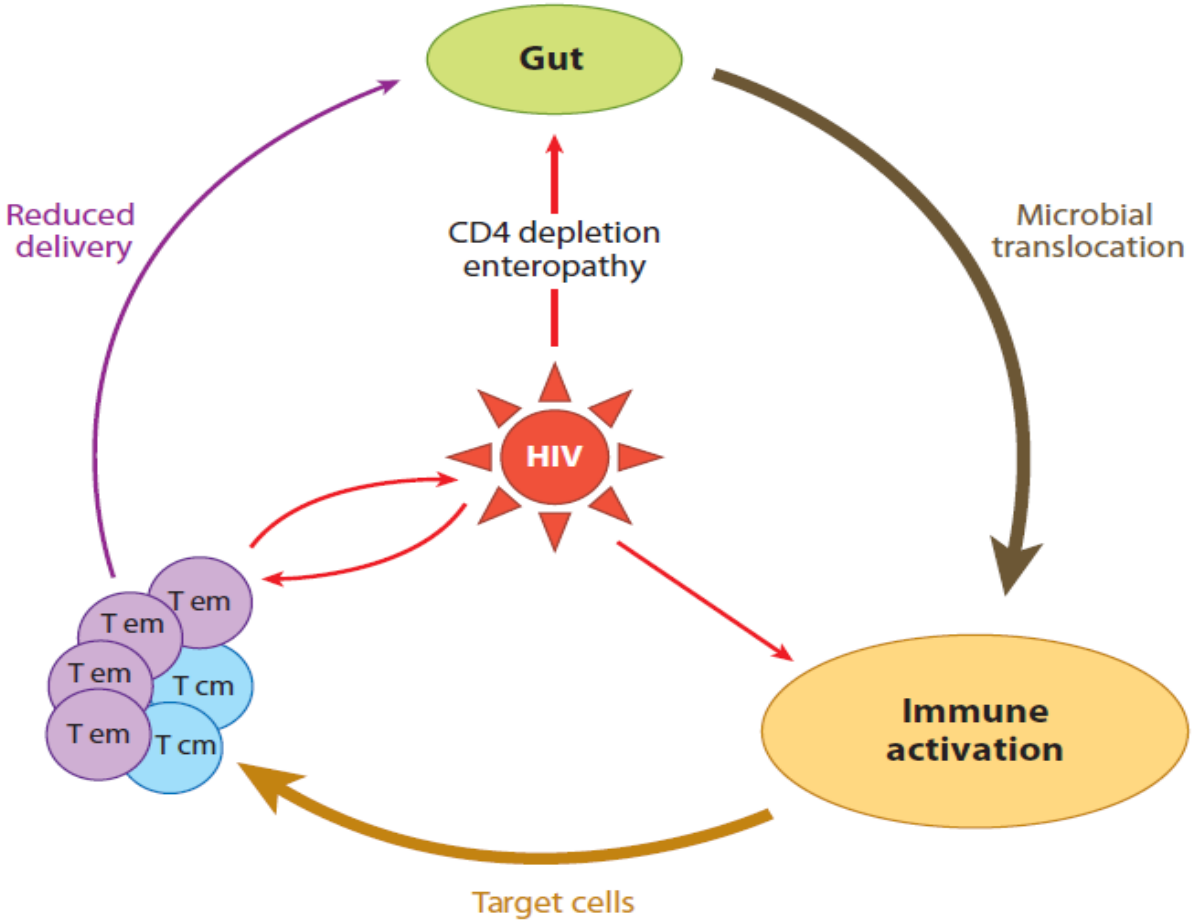




Jiang W, et al. J Infect Dis 2009;199:1177-1185

Marchetti G, et al; AIDS 2008; 22:2035-3028

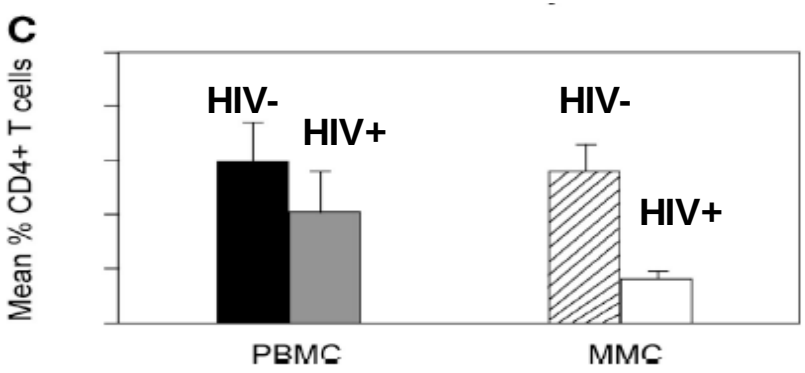
Microbial translocation and systemic immune activation: what the cause what the effect

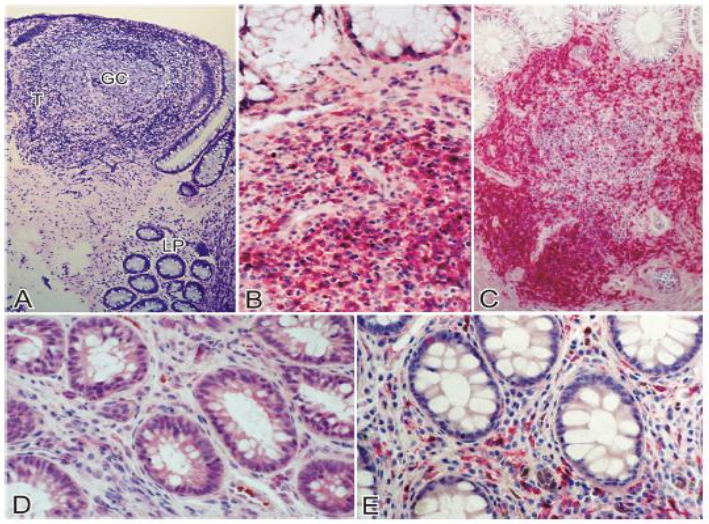


Douek et al. Annu. Rev. Med. 2009. 60:471–84

Gut CD4+ T-cell depletion in all stages of HIV infection

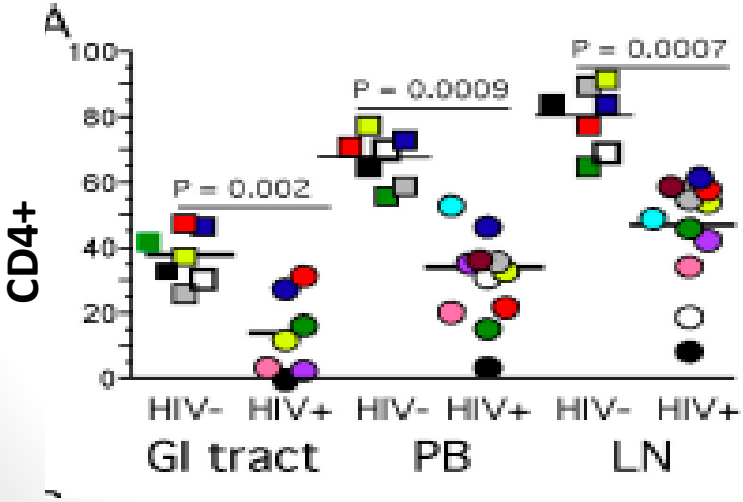
Acute and early HIV

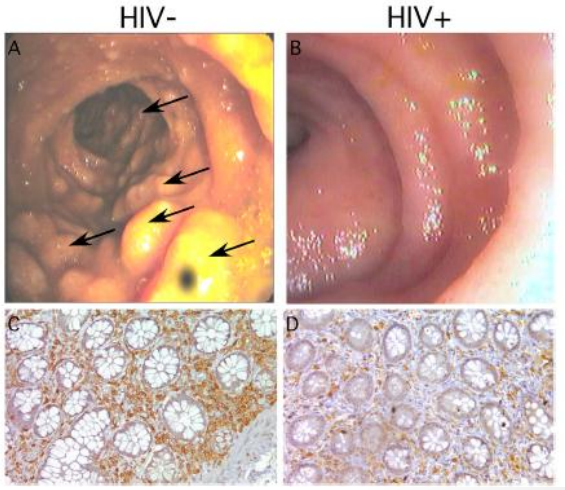




Red:CD4+

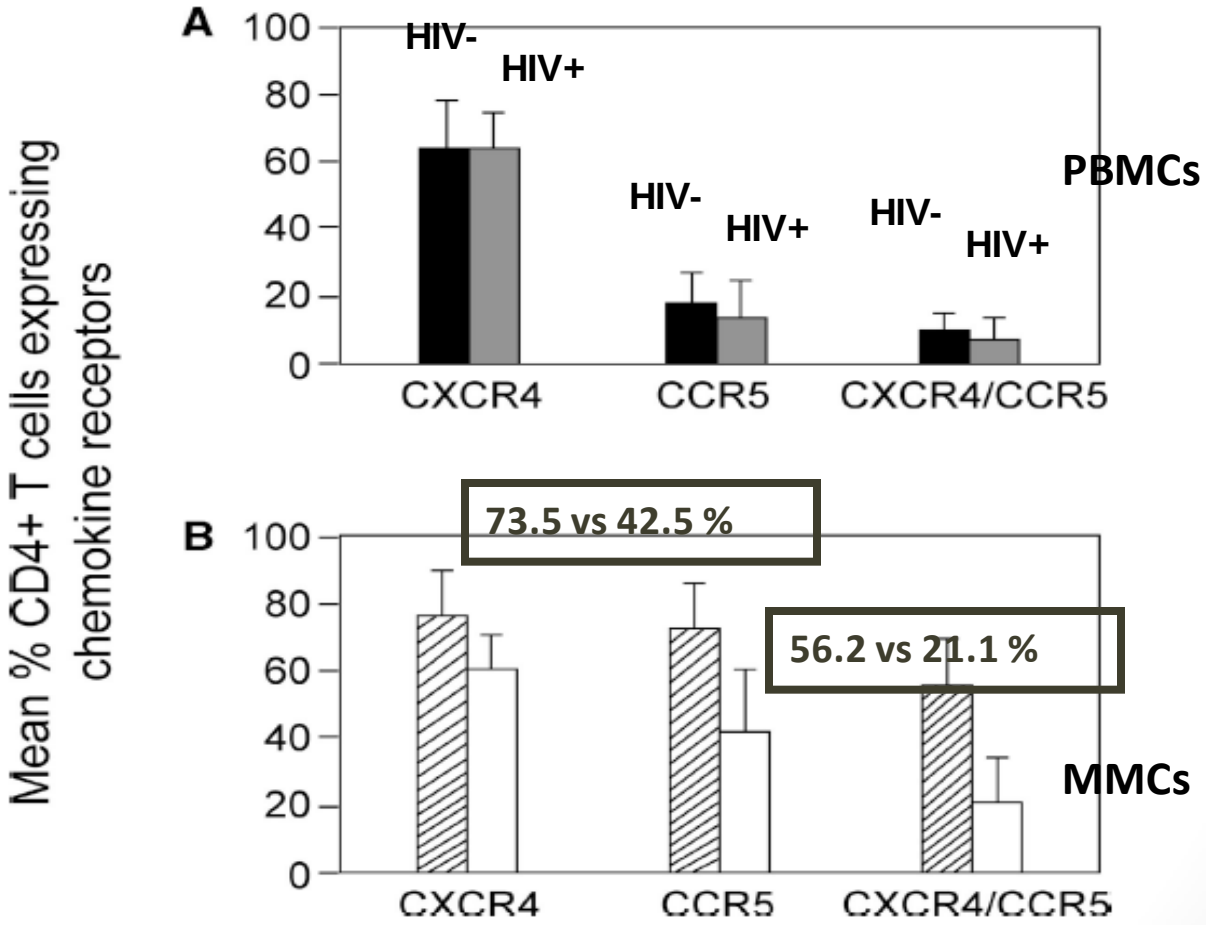
Mehandru et al.J Exp Med 2004





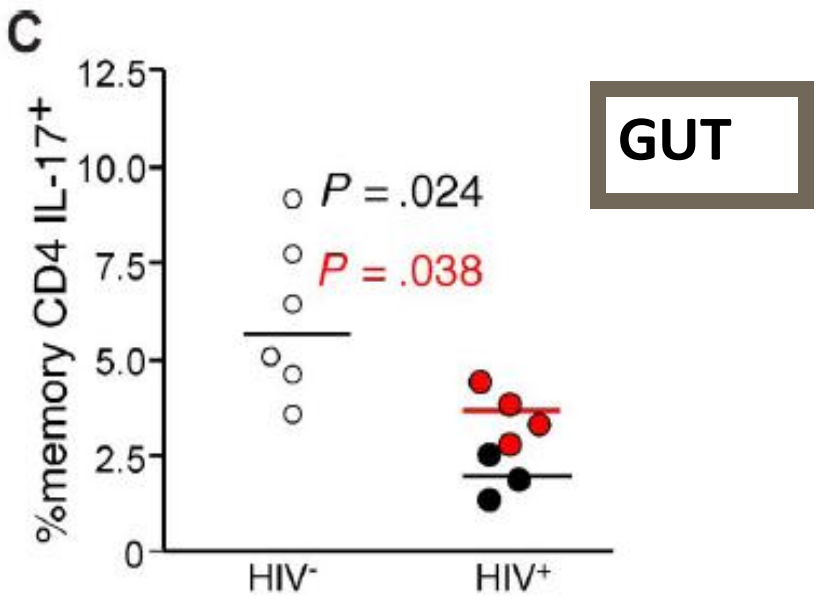
Brenchley J et al.J Exp Med 2004

Preferential depletion of CCR5-expressing CD4+ in the GI mucosa

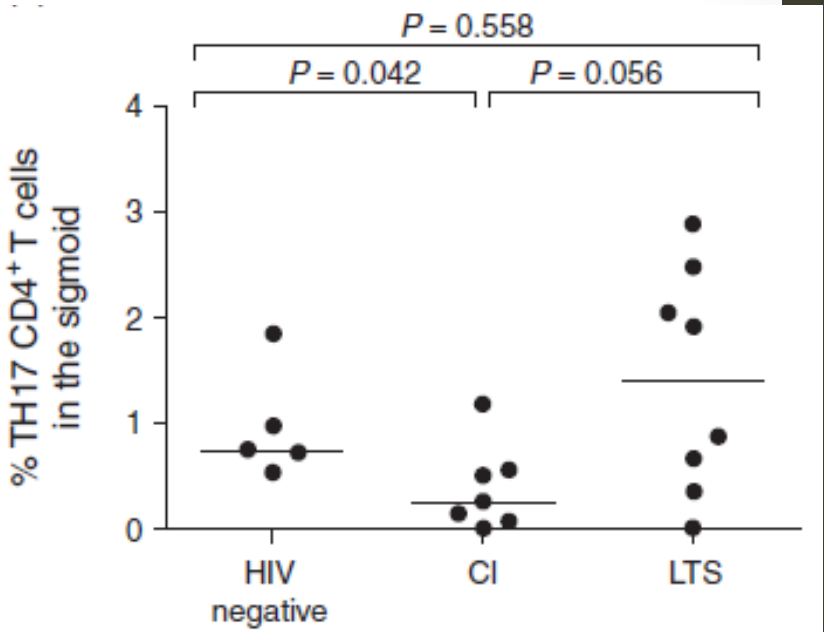


Mehandru et al.J Exp Med 2004; also: Brenchley J et al.J Exp Med 2004

Th17 cells are preferentially lost from the GI of HIV-infected patients



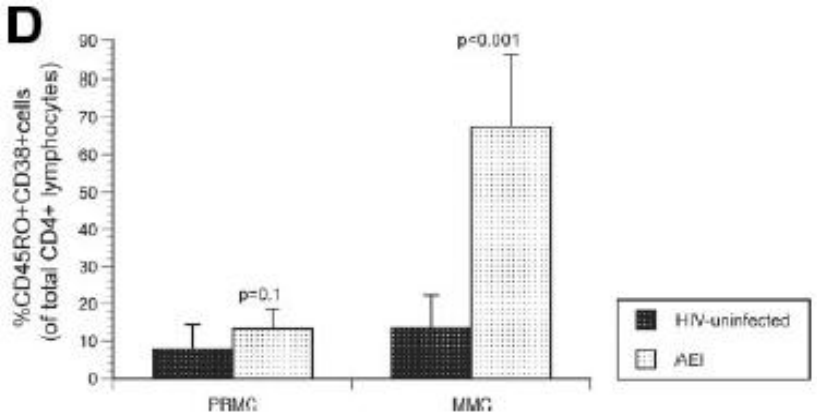
GUT



Brenchley J, Paiardini M et al. Blood 2008

Chege D et al. AIDS 2011

Early HIV infection: greater immune activation in the gut compared to peripheral blood

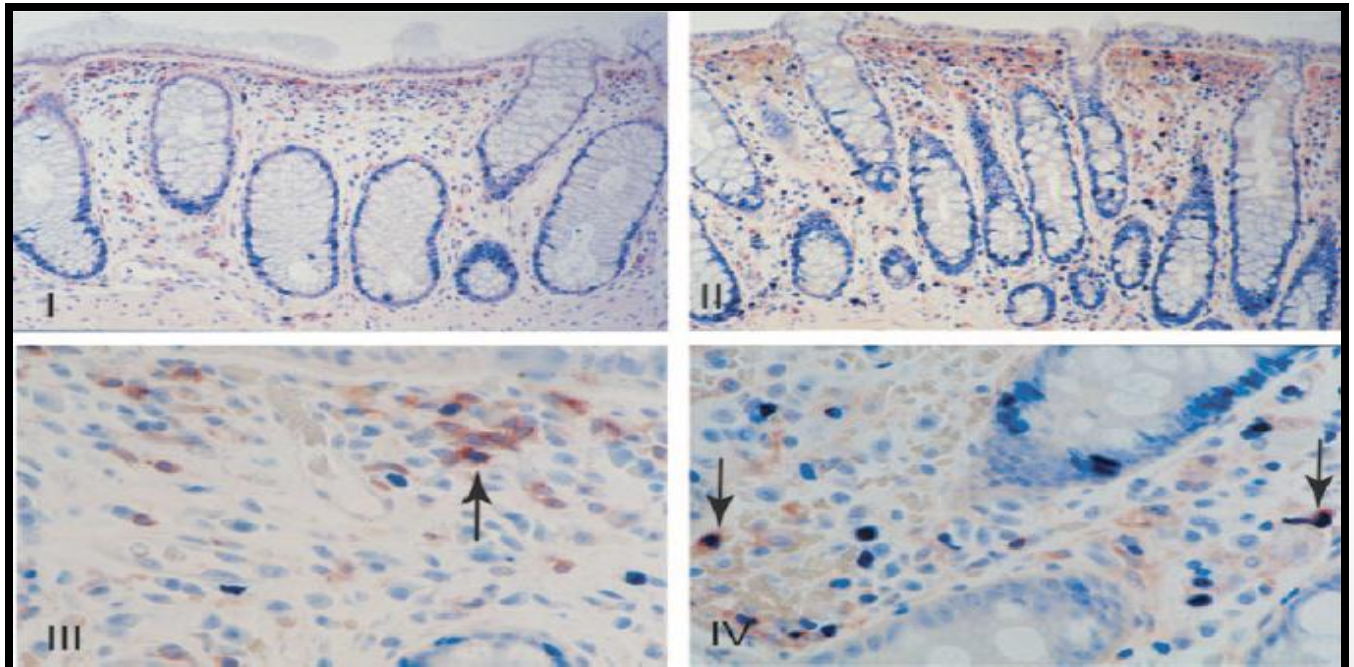


Mehandru S et al.J Virol 2007

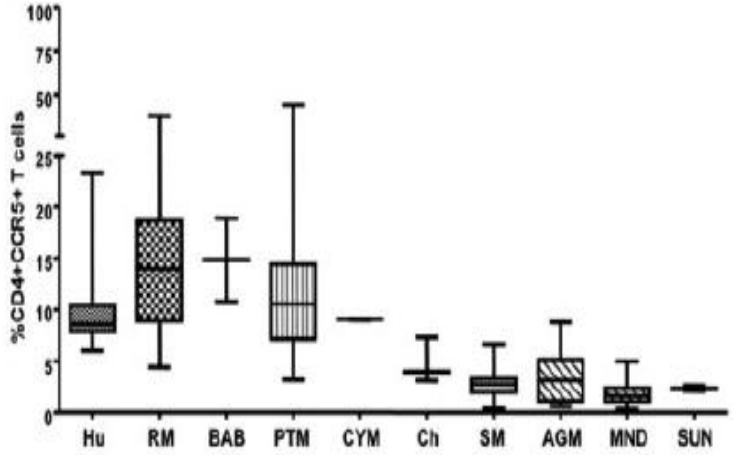
CD4+ in brown; Ki67+ in blue

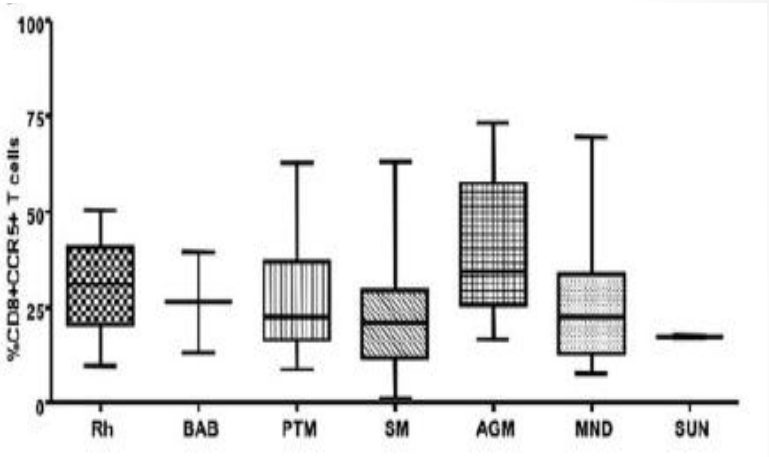
HIV -

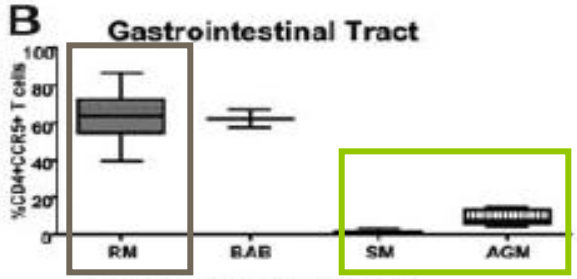
HIV +

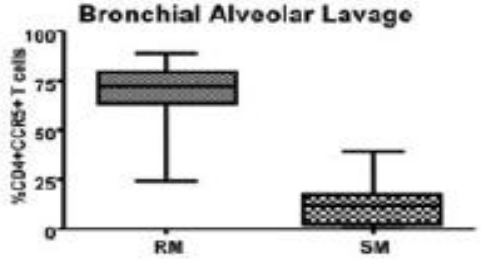


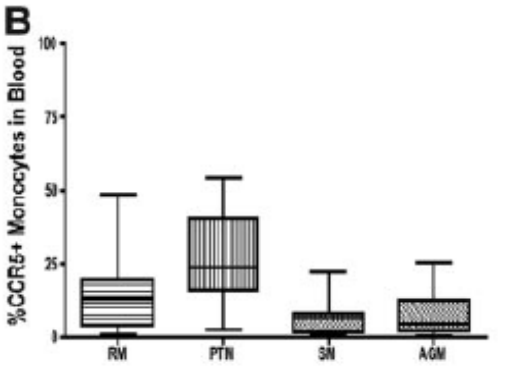
Lessons Learned from the Natural Hosts of HIV-Related Viruses: the experiment of "Mother Nature".











Pandrea I Blood 2007

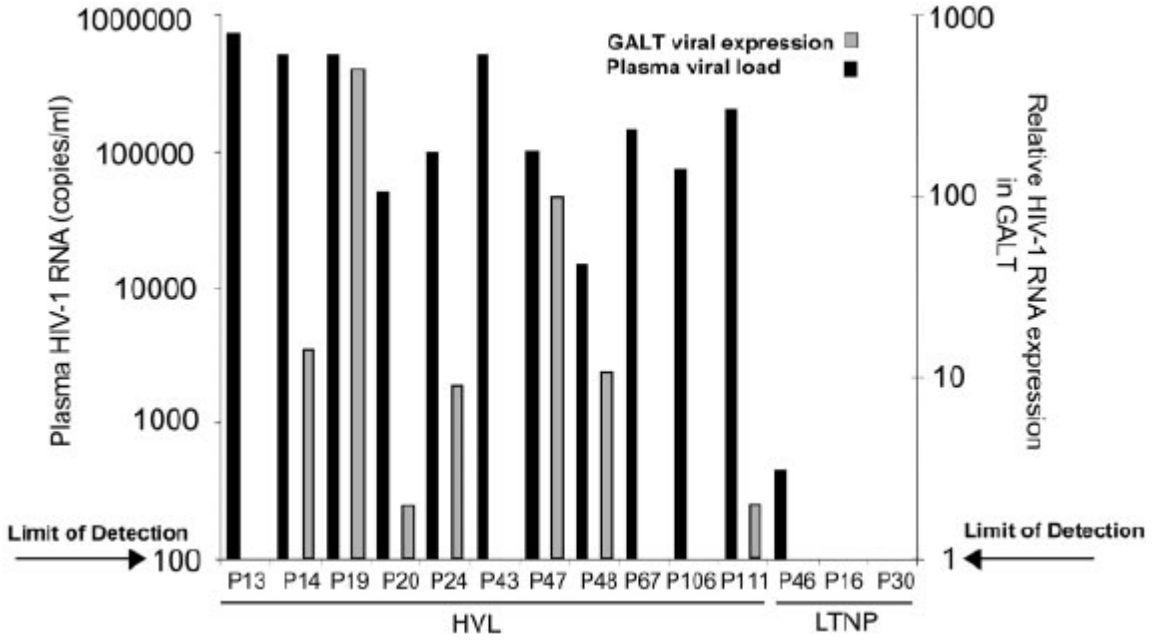
CCR5 and HIV: the less, the better

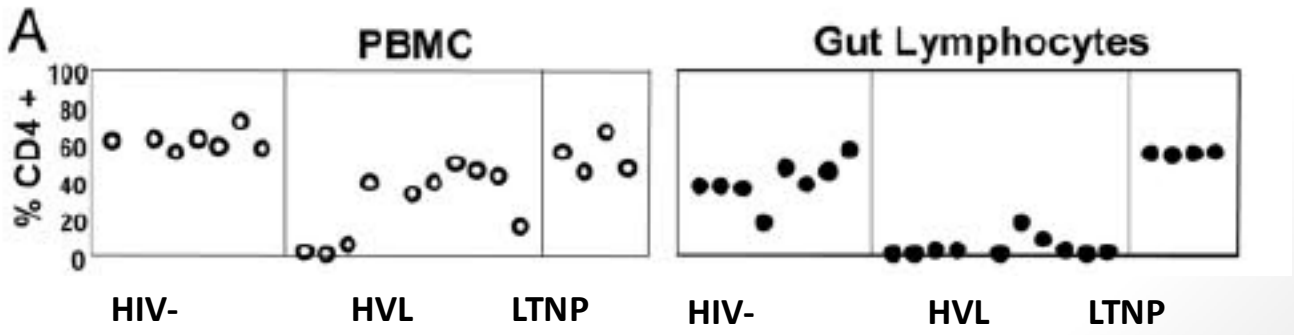
- Through natural selection, some species of primates exhibit lower levels of CCR5 cells in the gut, thereby escaping the massive immunopathogenesis and associated sequelae, allowing the host to maintain long-term nonprogression even in the face of relatively high plasma viremia.

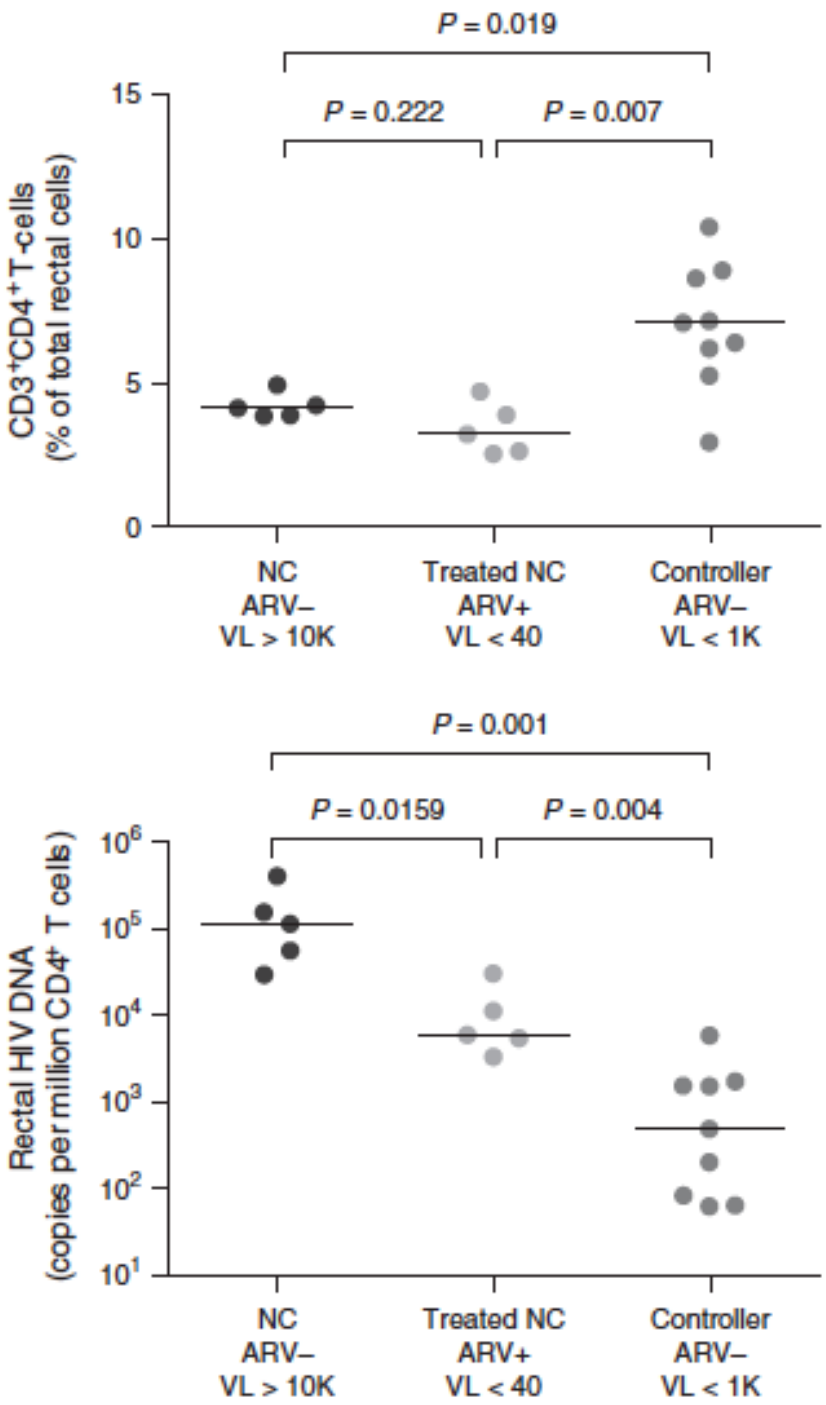
- Should HIV infection persist uncontrolled in humans, we might find our own subspecies undergoing a selection for low CCR5 expression.

Viral RNA is not detected in mucosa of LTNPs

Sankaran S et al.PNAS 2005; also Avettand-Fenoel et al. AIDS 2008

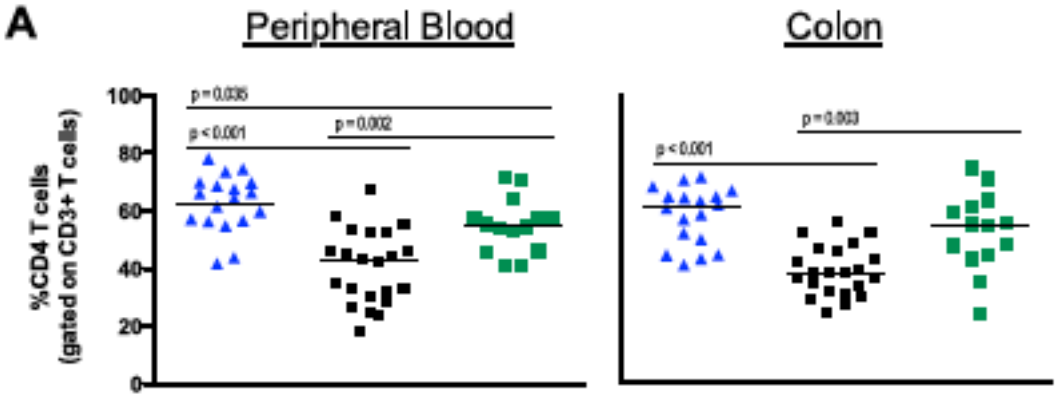


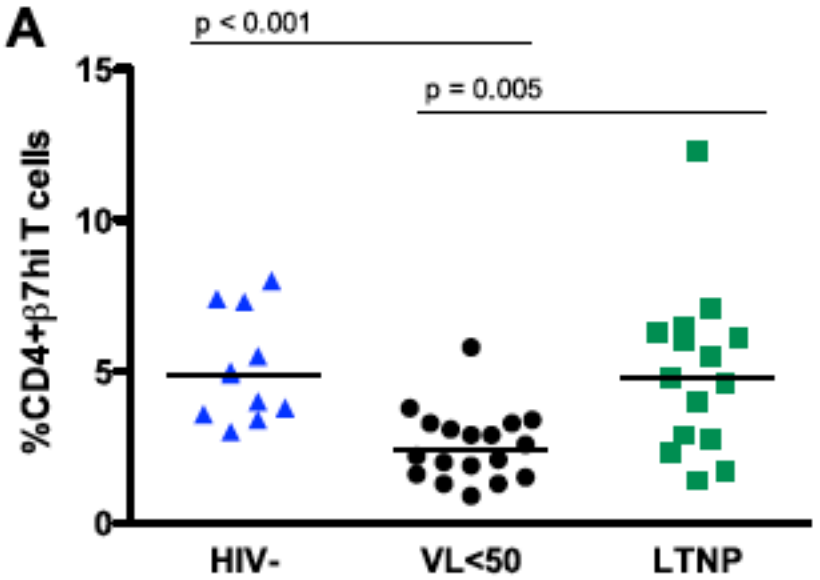




Hatano et al. AIDS 2013

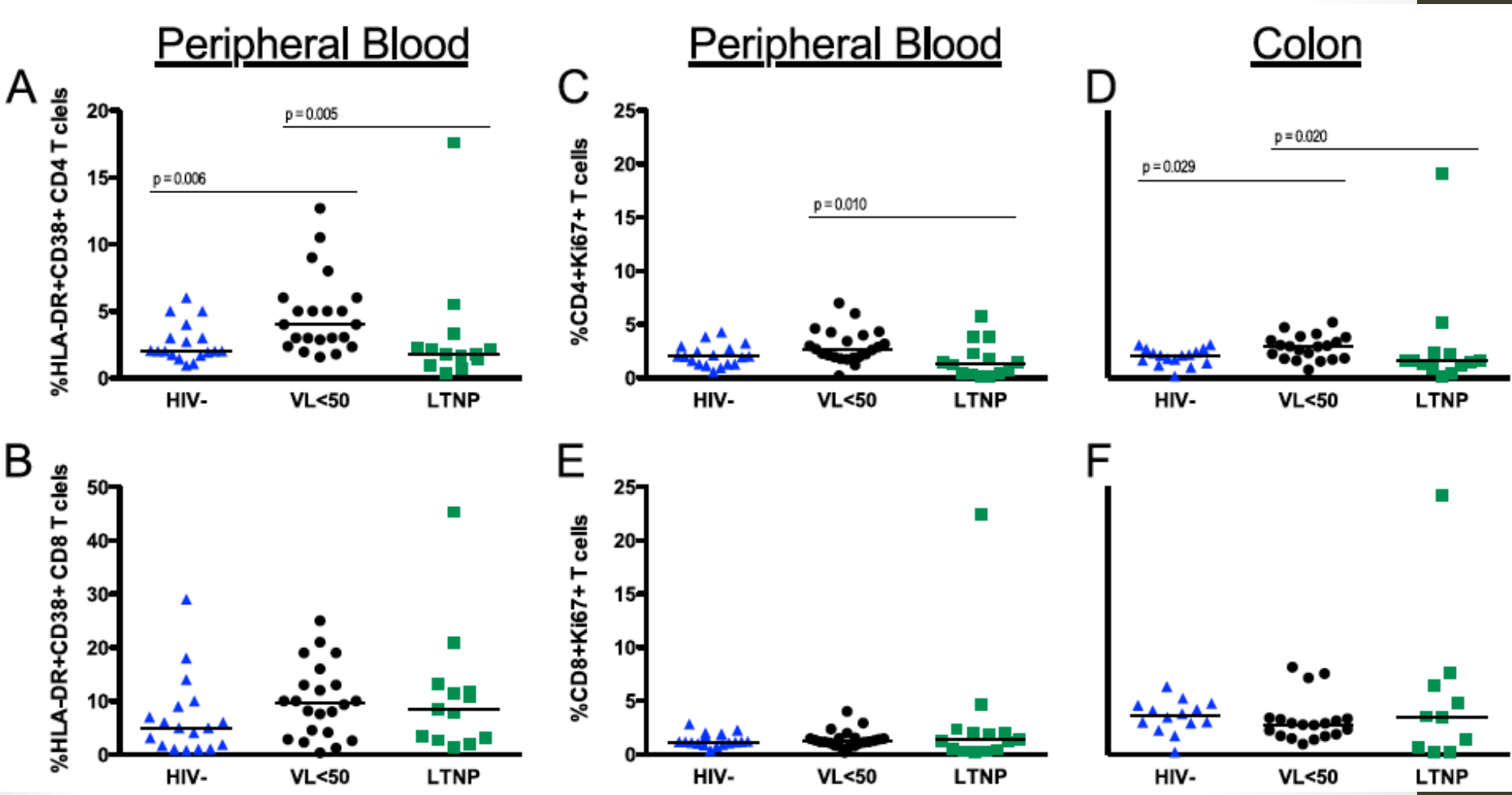
Colon CD4 are maintained in LTNPs





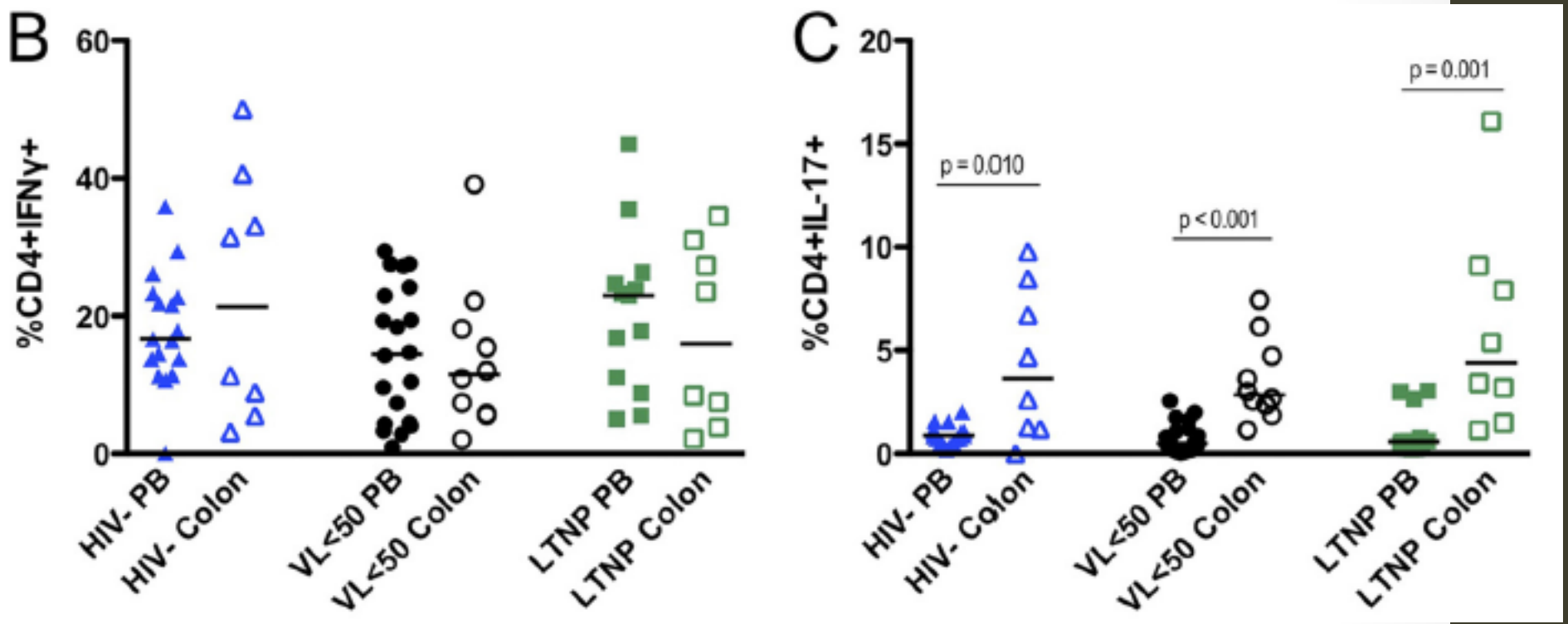
Ciccone et al. J Virol 2011

Lower T-cell activation in the gut of LTNPs



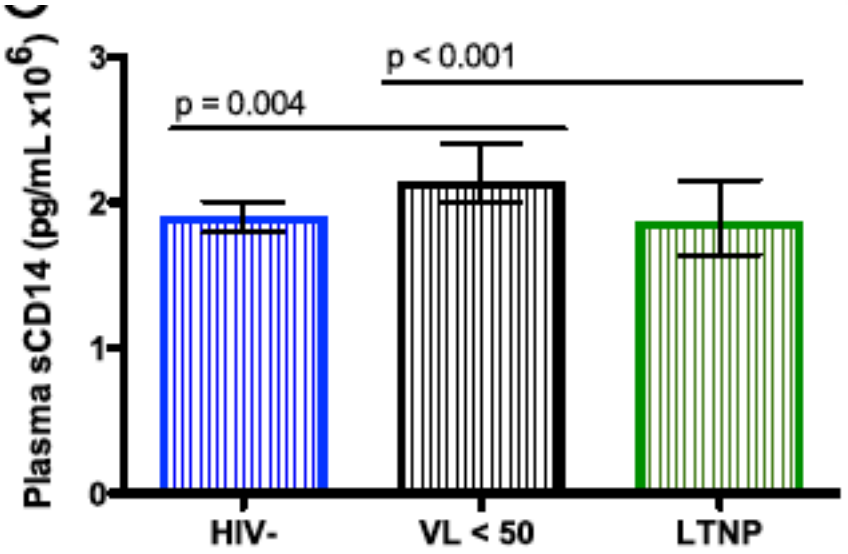
Ciccone et al. J Virol 2011

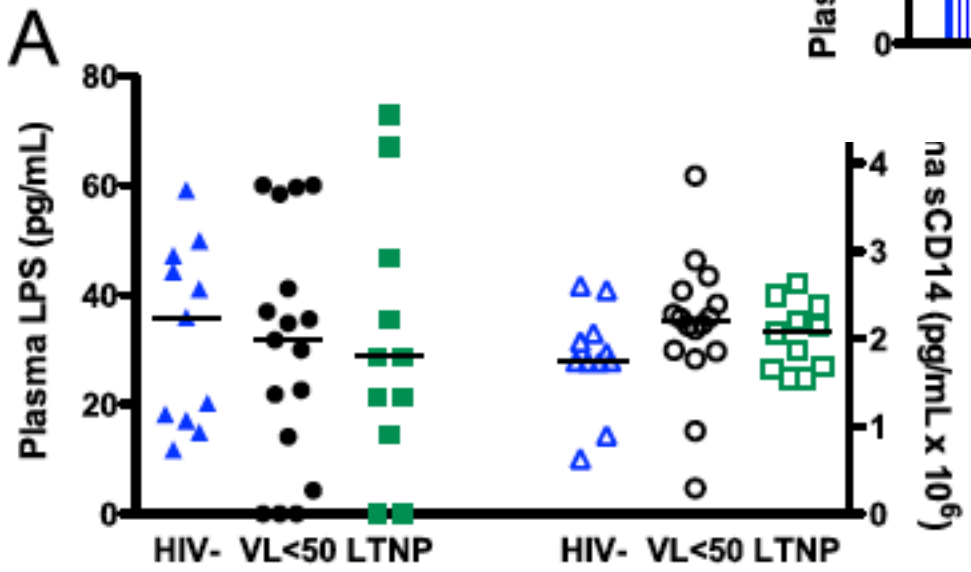
Higher colon Th17 in LTNPs



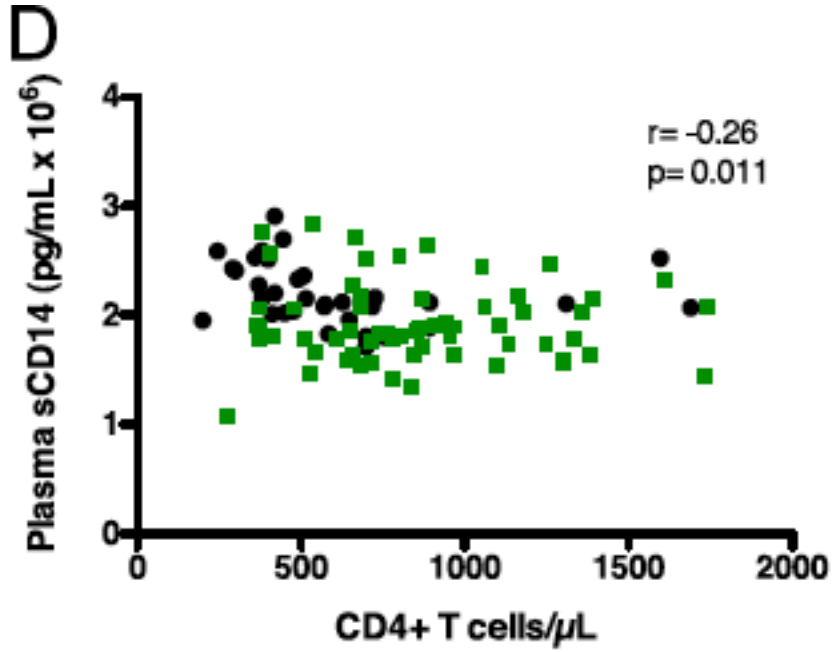
Ciccone et al. J Virol 2011

Lower immune activation due to microbial translocation in LTNPs



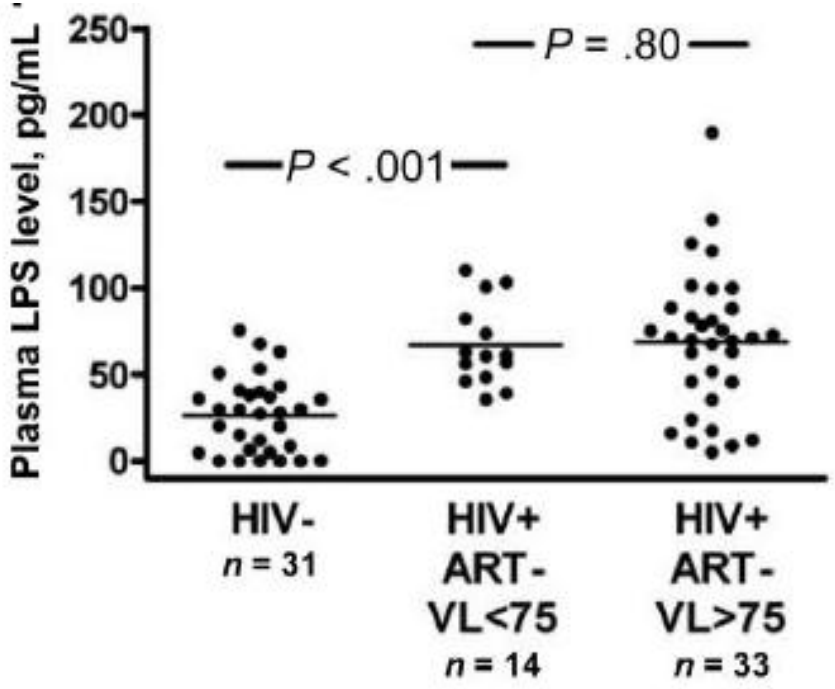


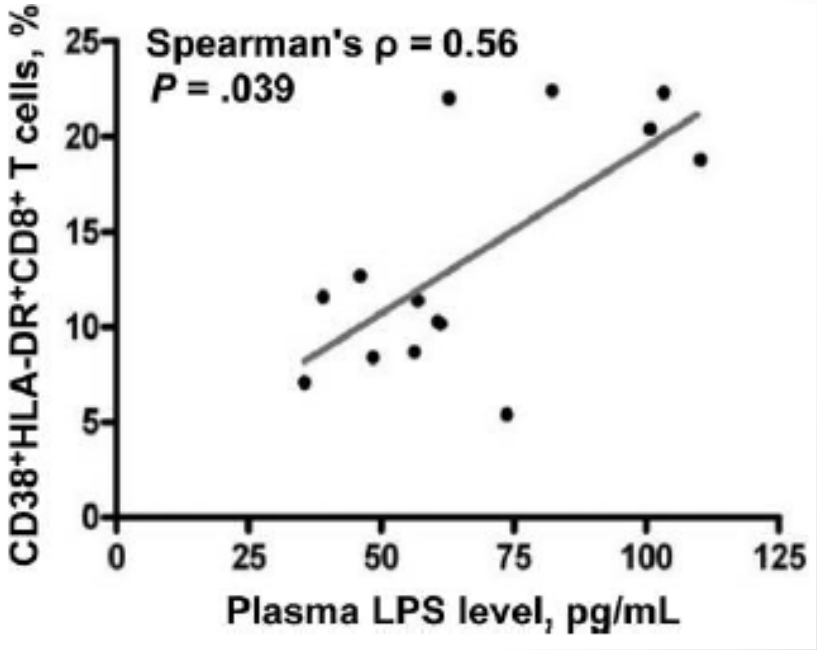
Ciccone et al. J Virol 2011



Ciccone et al. J Virol 2011

Elite controllers display elevated microbial translocation

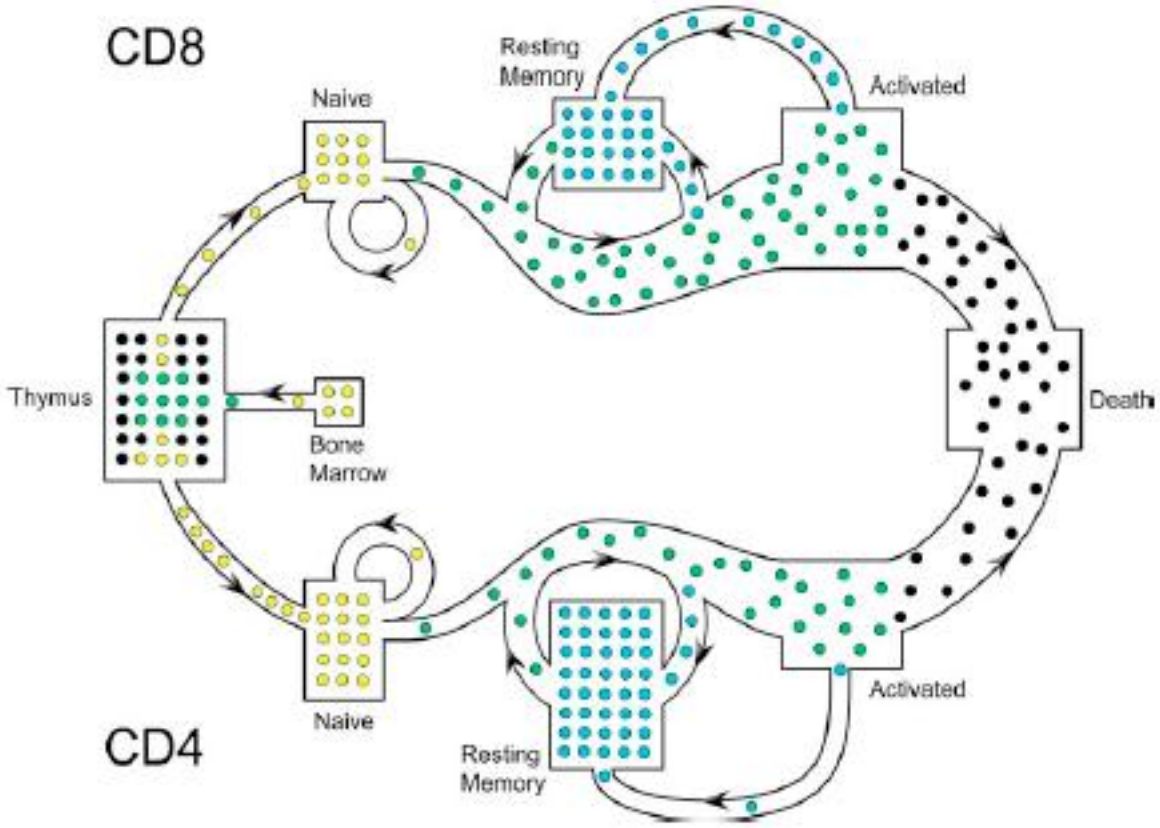




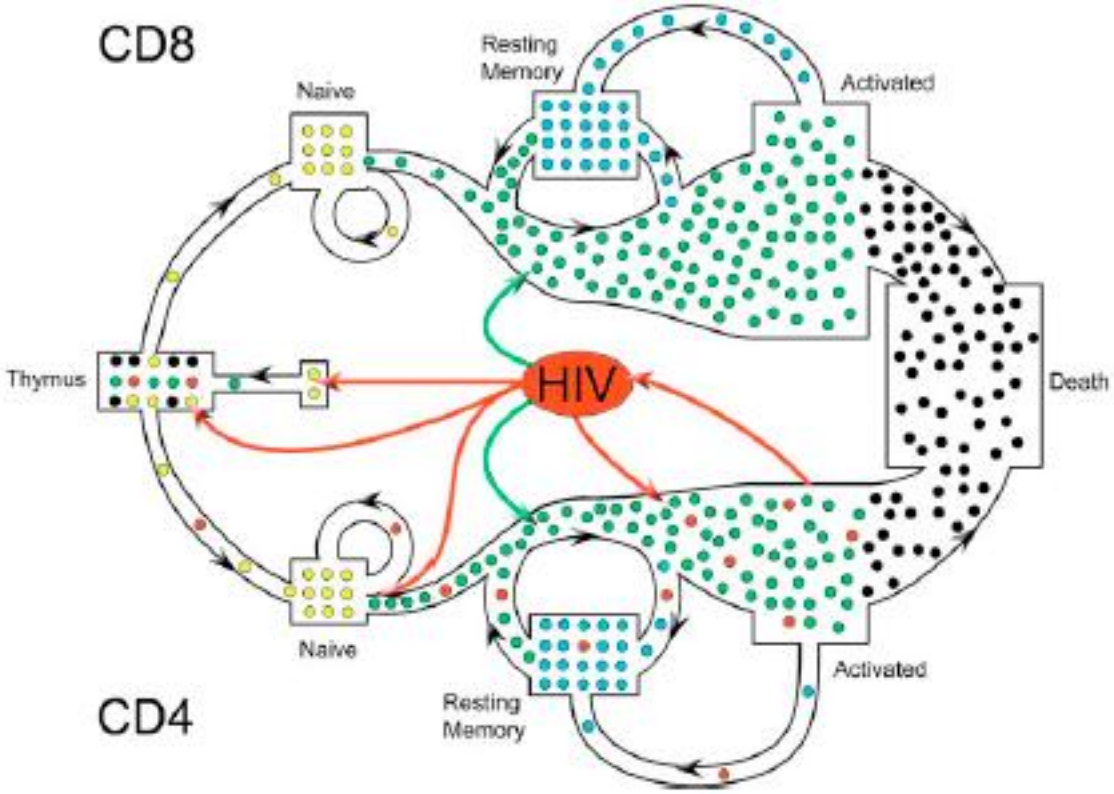
Hunt et al. JID 2008

T-cell homeostasis in HIV pathogenesis

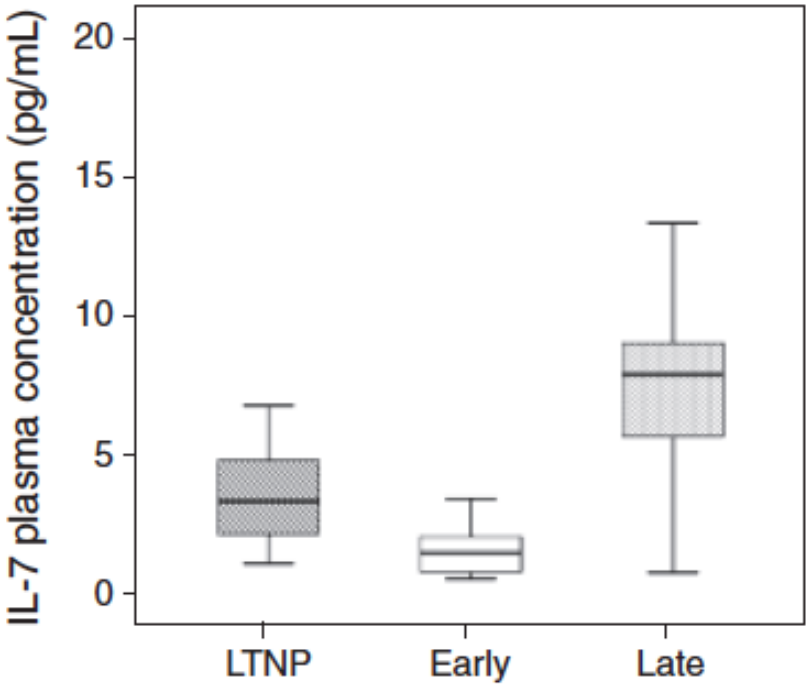
T-cell homeostasis in the healthy

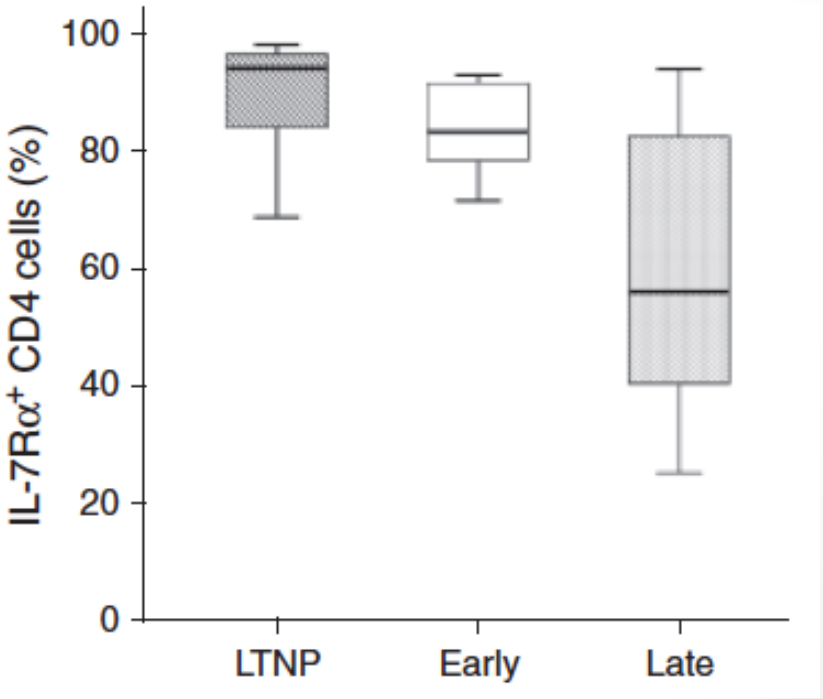


T-cell homeostasis in HIV



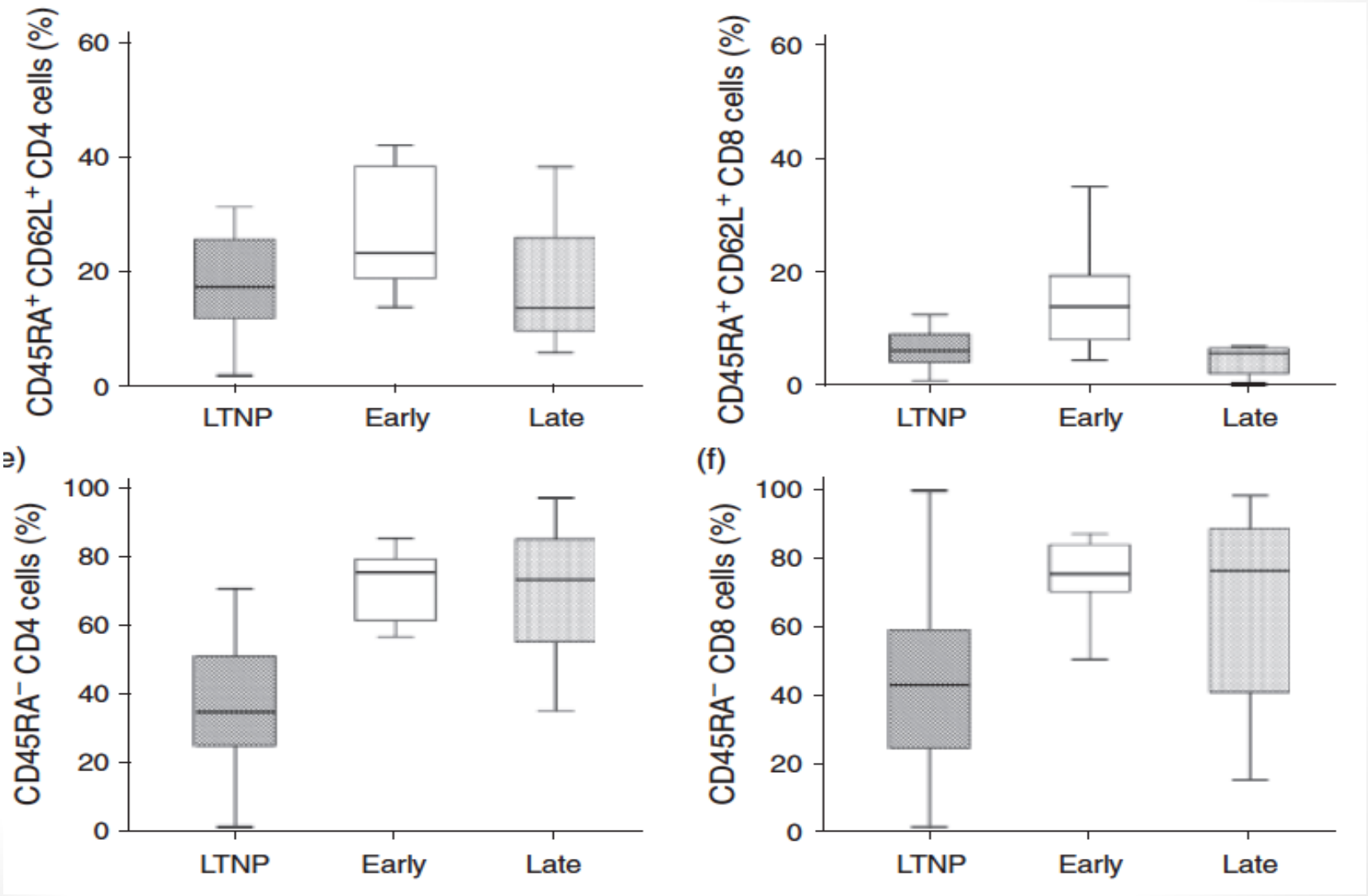
IL-7/IL-7R pathway in LTNPs



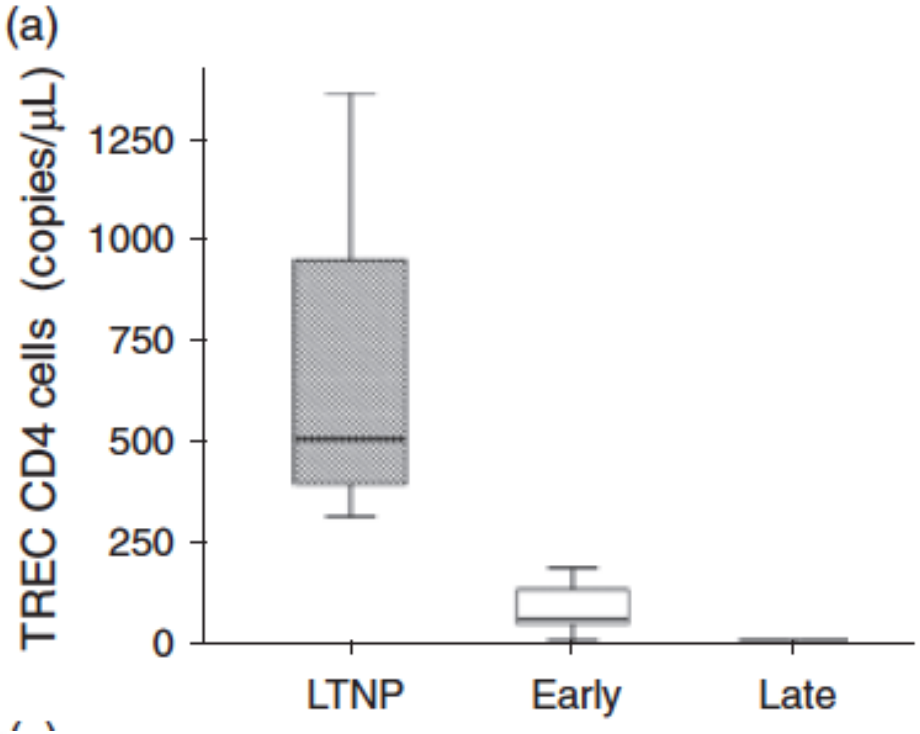


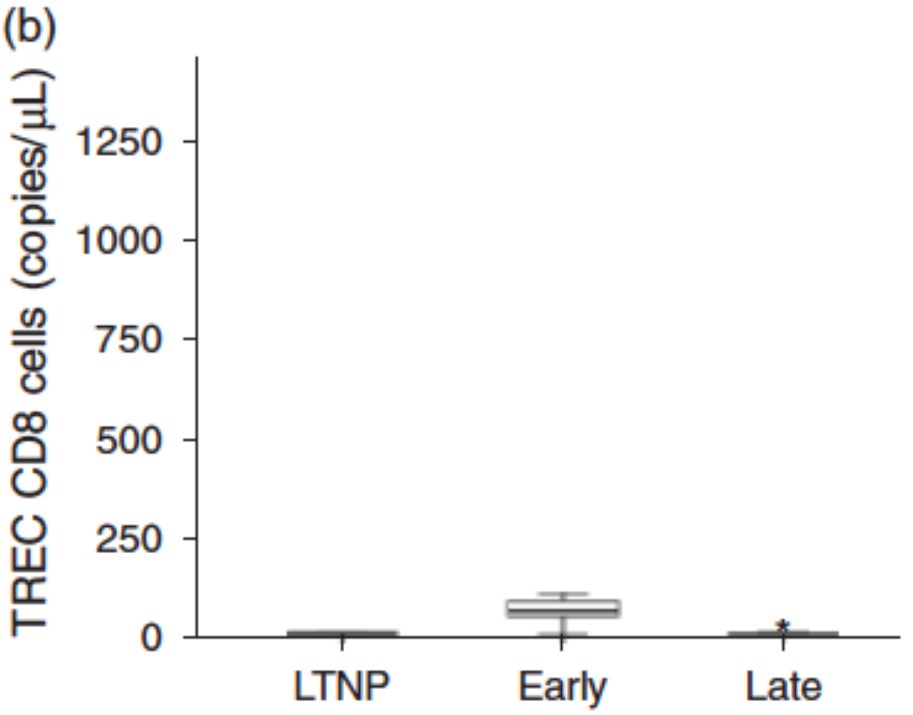
Marchetti et al. HIV Med

Naïve/memory T-cells in LTNPs



Thymic output in LTNPs





Open questions

- HIV infects apparently a small proportion of CD4 (1 in 100 to 1 in 100)- how can it still overwhelm T-cell renewal capacity of the host?
- Drivers of chronic immune activation?
- Persistent HIV replication in the face of vigorous CTL response?