La Disfunzione del Sistema Immunitario Mediata da HIV è Influenzata dalla Terapia Antiretrovirale?

Camilla Tincati MD, PhD

Clinica di Malattie Infettive

Dipartimento di Scienze della Salute

ASST Santi Paolo e Carlo-Presidio San Paolo

Università degli Studi di Milano

Today’s agenda

- What is immune activation and what are its underlying causes?

- What are the clinical implications of persisting immune activation/inflammation on cART?

- poor CD4+ T-cell gain
- development of Serious Non AIDS Events (SNAEs)/mortality

- Can we dampen immune activation?

- adjuvant strategies (in INR)
- effect of different cART regimens on T-cell homeostasis/inflammation
- lessons learnt from acute HIV infection

Today’s agenda

- What is immune activation and what are its underlying causes?

- What are the clinical implications of persisting immune activation/inflammation on cART?

- poor CD4+ T-cell gain
- development of Serious Non AIDS Events (SNAEs)/mortality

- Can we dampen immune activation?

- adjuvant strategies (in INR)
- effect of different cART regimens on T-cell homeostasis/inflammation
- lessons learnt from acute HIV infection

The New England
Journal of Medicine

Volume 305 DECEMBER 10, 1981 Number 24

PNEUMOCYSTIS CARINII PNEUMONIA AND MUCOSAL CANDIDIASIS IN PREVIOUSLY HEALTHY HOMOSEXUAL MEN

Evidence of a New Acquired Cellular Immunodeficiency

MICHAEL S. GOTTLIEB, M.D., ROBERT SCHROFF, PH.D., HOWARD M. SCHANKER, M.D., JOEL D. WEISMAN, D.O., PENG THIM FAN, M.D., ROBERT A. WOLF, M.D., AND ANDREW SAXON, M.D.

Abstract Four previously healthy homosexual men contracted *Pneumocystis carinii* pneumonia, extensive mucosal candidiasis, and multiple viral infections. In three of the patients these infections followed prolonged fevers of unknown origin. In all four cytomegalovirus was recovered from secretions. Kaposi's sarcoma developed in one patient eight months after he presented with esophageal candidiasis. All patients were anergic and lymphopenic; they had no lymphocyte proliferative responses to soluble antigens, and their responses to phytohemagglutinin were markedly reduced. Monoclonal-antibody analysis of peripheral-blood T-cell subpopulations revealed virtual elimination of the Leu-3+ helper/inducer subset, an increased percentage of the Leu-2+ suppressor/cytotoxic subset, and an increased percentage of cells bearing the thymocyte-associated antigen T10. The inversion of the T helper to suppressor/cytotoxic ratio suggested that cytomegalovirus infection was an important factor in the pathogenesis of the immunodeficient state. A high level of exposure of male homosexuals to cytomegalovirus-infected secretions may account for the occurrence of this immune deficiency. (N Engl J Med. 1981; 305:1425-31.)

High levels of T10 expression

Table 3. Characterization of T-Lymphocyte Subsets.

Group	Lymphocyte Subset				Leu 3/ Leu 2 Ratio
	Leu 1	Leu 2	Leu 3	T10	
	per cent lymphocytes reactive with monoclonal antibodies				
Patients					
1	45	57	0	59	0
2	47	52	0	59	0
3	49	57	10	79	0.18
4	67	47	2	81	0.04
Mean ±S.D.	52 * ±10.1	53.3 † ±4.7	3.0 † ±4.76	69.5 † ±12.1	0.05 ±0.08 *
Normal subjects (n = 16 [mean ±S.D.])	71.0 ±10.0	28.0 ±8.0	46.0 ±12.0	15.0 ±6.6	1.6 ±0.74

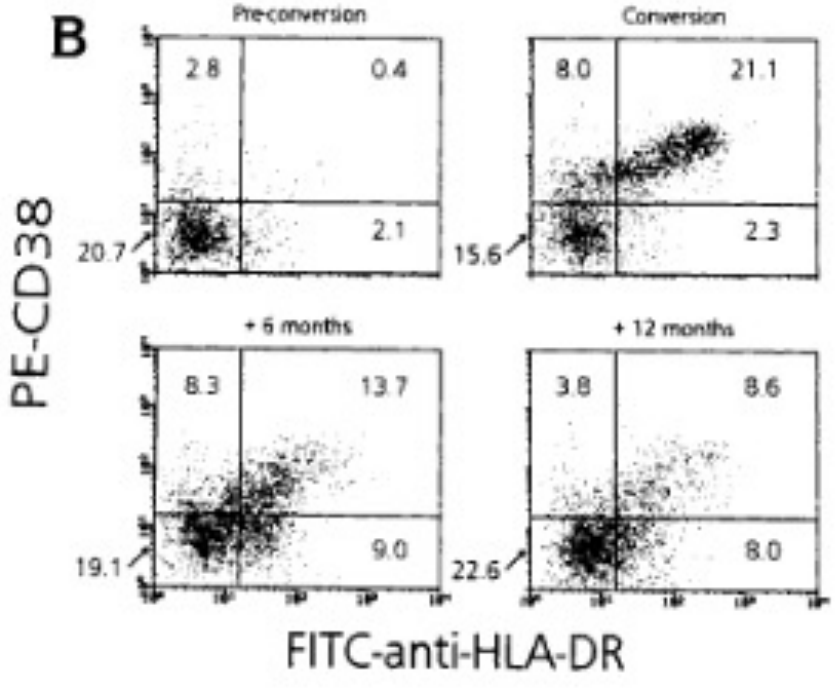
*Significantly different from value in normal subjects ($P<0.003$).
†Significantly different from value in normal subjects ($P<0.0001$).

Table 2. Stimulation of Mononuclear Cells by Antigens and Phytohemagglutinin in Normal Subjects and Patients.

Group	Stimulator			
	Medium Alone	Phytohemagglutinin	Candida Antigen	Streptokinase-Streptodornase
	counts per minute			
Normal subjects (n = 32 [mean ±S.D.])	1,312 ±565	155,983 ±53,652	74,500 ±38,759	87,408 ±24,365
Patients				
1 (3/18/81)	522	27,000	1,594	1,264
2 (4/21/81)	777	81,186	1,930	1,852
3 (5/8/81)	820	5,000	938	*
4 (6/5/81)	666	6,142	*	*

*Not determined.

Immune activation (CD8+CD38+HLADR+) is a feature of HIV infection and is linked to disease progression



Giorgi, JID, 1994

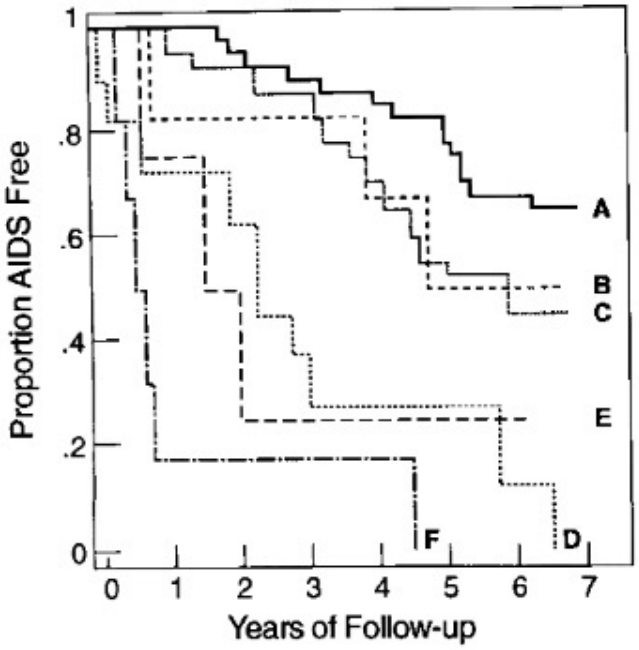


FIG. 3. Kaplan-Meier curves for the development of AIDS for the six groups of study participants stratified by $CD4^+$ cell number per mm^3 (CD4) and the mean fluorescence intensity of CD38 antigen expression on $CD8^+$ cells (RFI-CD38||$CD8^+$): group A, CD4>500, RFI-CD38||$CD8^+$ <6.1; group B, CD4 >500, RFI-CD38||$CD8^+$ ≥6.1; group C, CD4 = 200–500, RFI-CD38||$CD8^+$<6.1; group D, CD4 = 200–500, RFI-CD38||$CD8^+$ ≥6.1; group E, CD4 <200, RFI-CD38||$CD8^+$ <6.1; and group F, CD4 <200, RFI-CD38||$CD8^+$ ≥6.1.

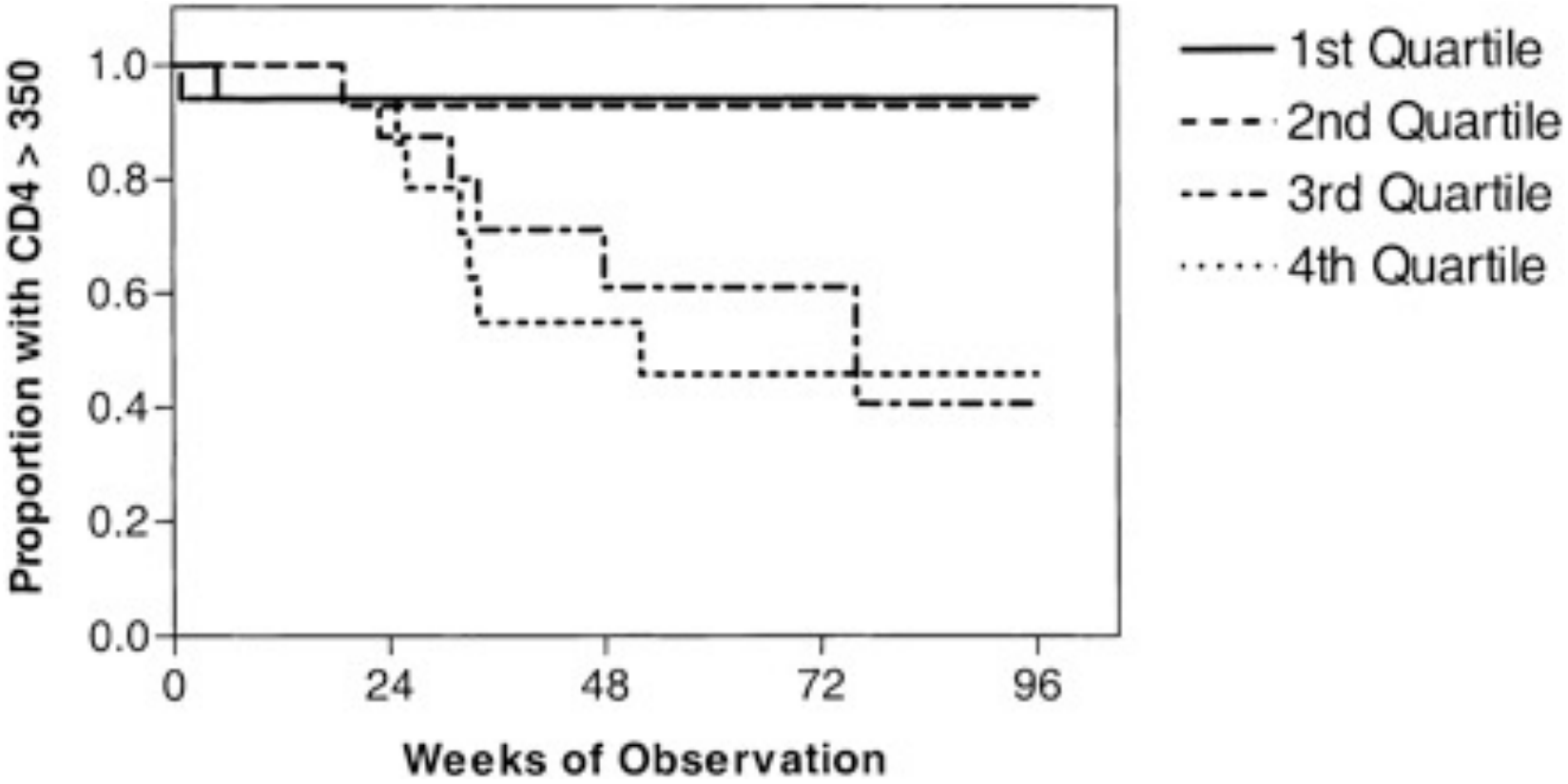
Group A:
highest CD4+ (< 500/Ul)
lowest CD8+CD38+

Group F:
lowest CD4+ (< 200/ul)
highest CD8+CD38+

Liu, Cytometry, 1996
See also Fahey, NEJM 1990)

Immune activation is a cause of CD4+ T-cell loss in untreated HIV

Individuals with higher baseline quartiles of CD8+ T-cell activation (P = .002 by the log-rank test) and viremia (P = .004) but not CD4+ T-cell activation (P = .21) **were more likely to experience subsequent CD4+ T-cell decline.**

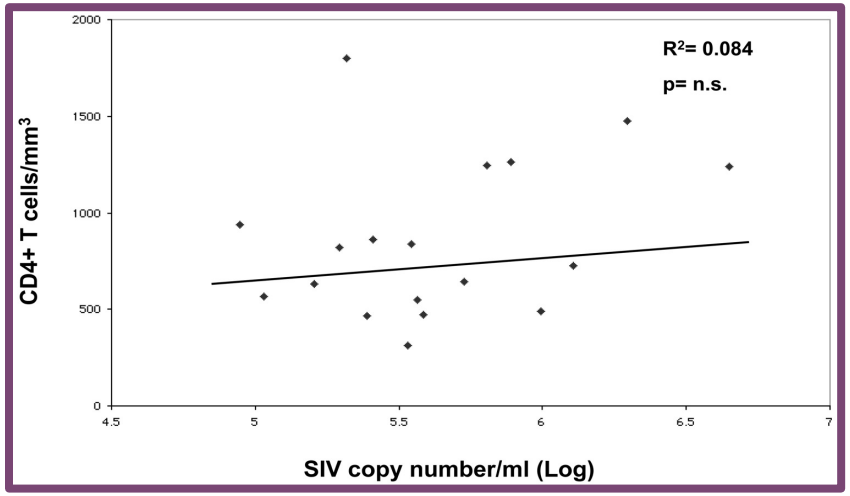


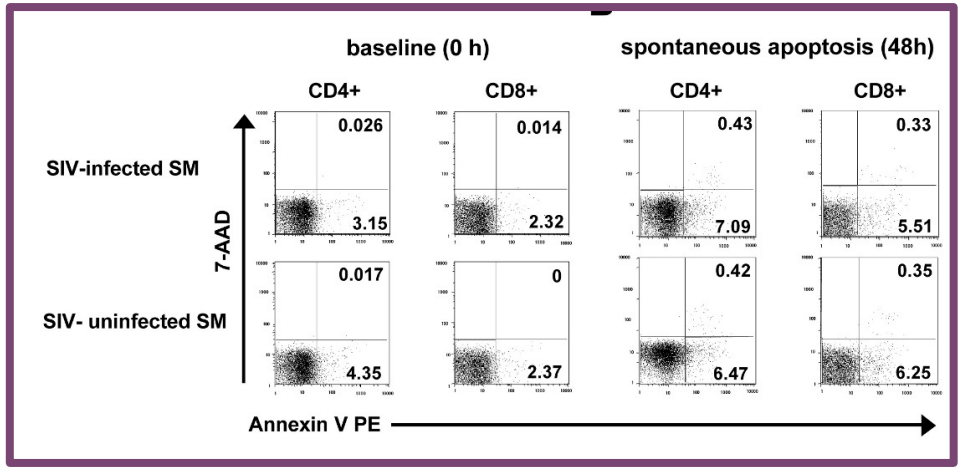
Deeks, Blood, 2004

Attenuated immune activation enables SIV-infected mangabeys to avoid the bystander damage seen in pathogenic infections and protects them from developing AIDS

Sooty mangabey
Natural Host
No AIDS

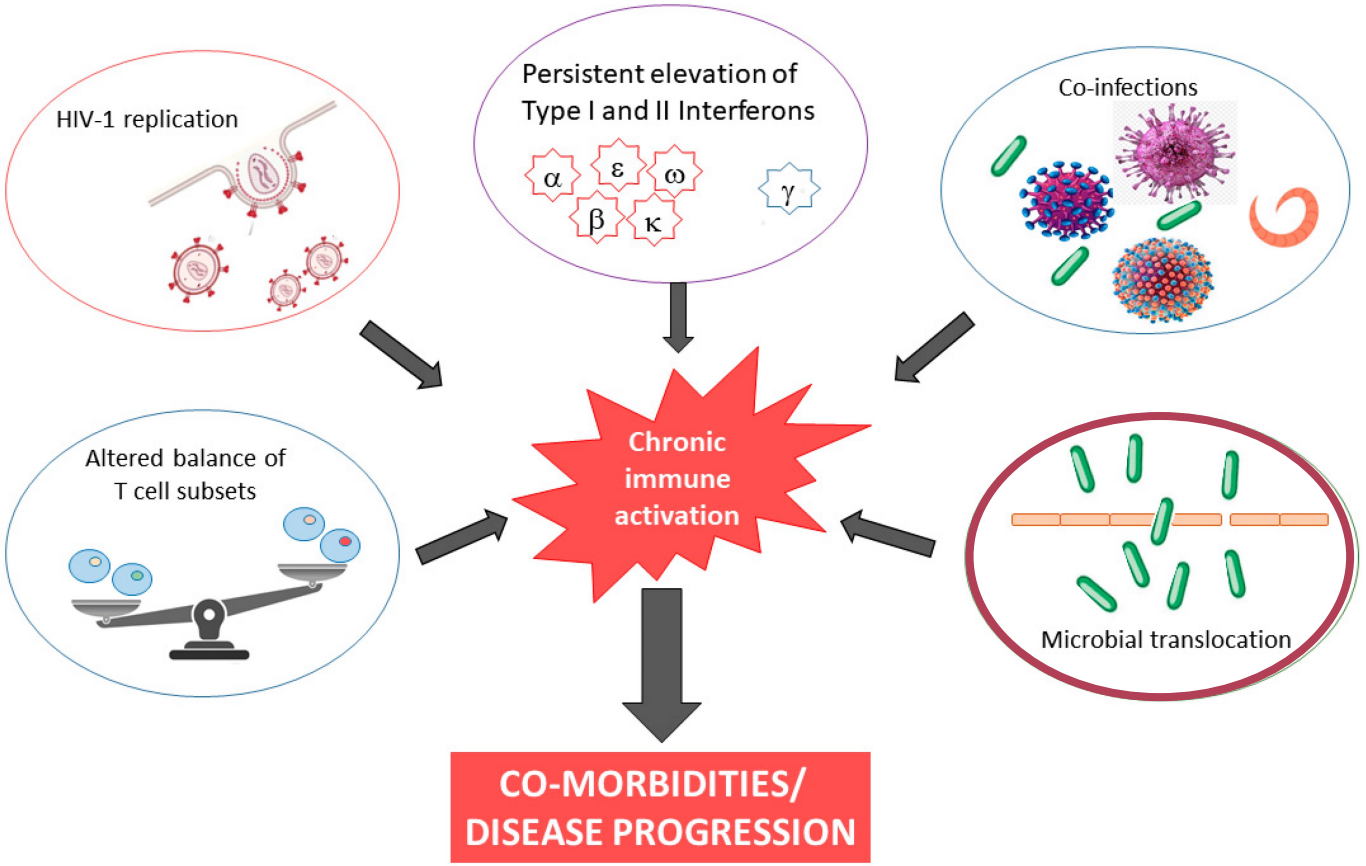
Rhesus macaques
Non-natural Host
AIDS





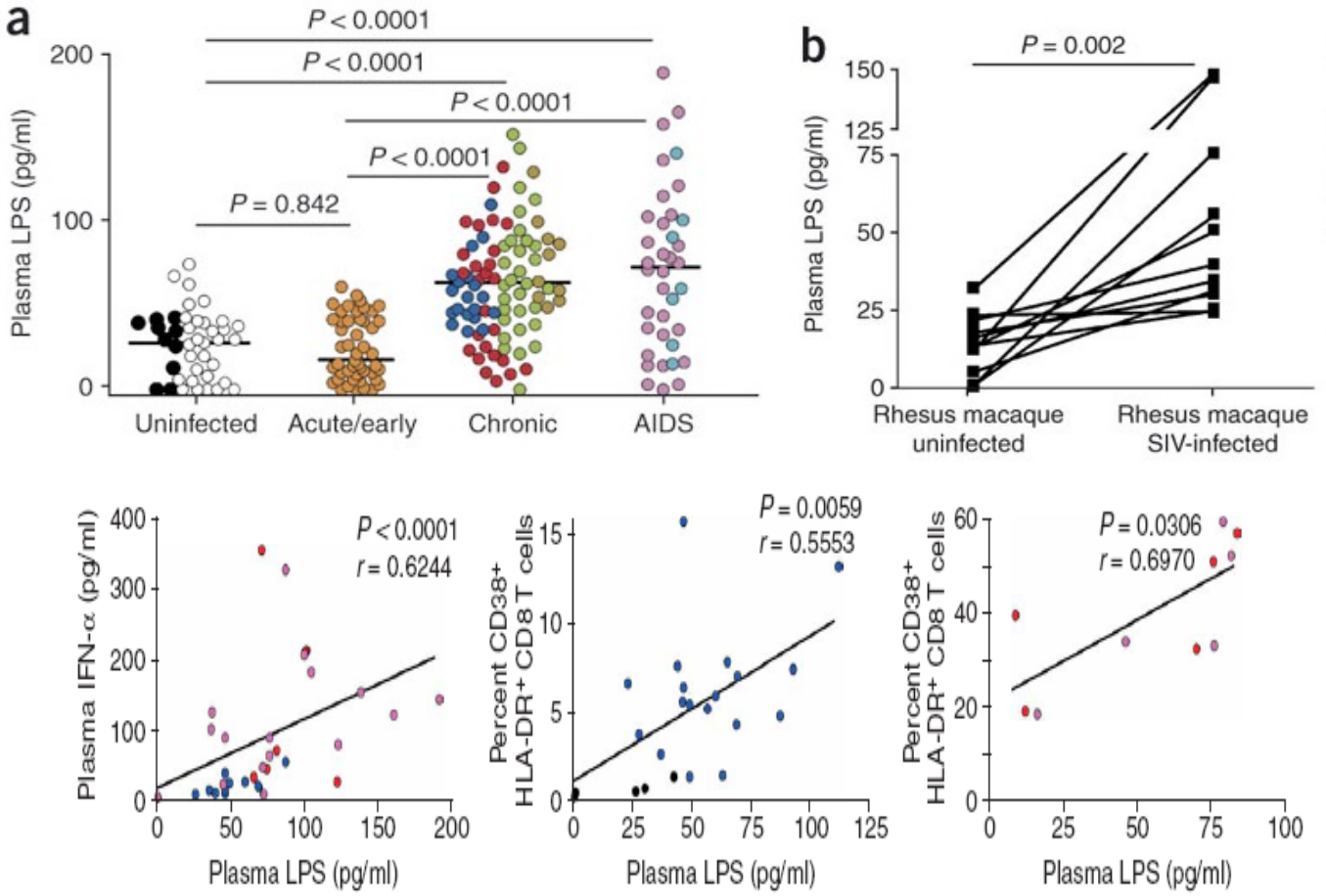
Silvestri, Immunity, 2003

Causes of Immune Activation in HIV/AIDS



Mazzuti, Biomedicines, 2023

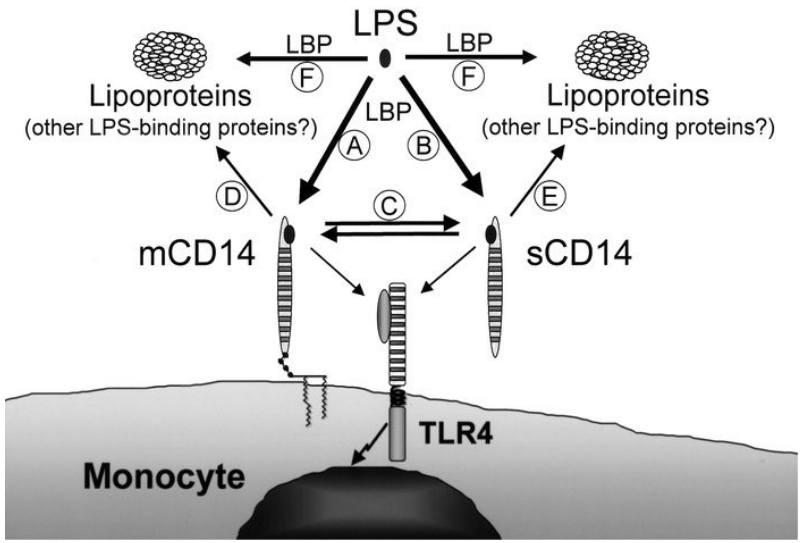
Microbial translocation features HIV/SIV and causes immune activation



Brenchley et al., Nat Med 2006

Markers of microbial transolcation:

- LPS
- LBP
- sCD14
- EndocAb

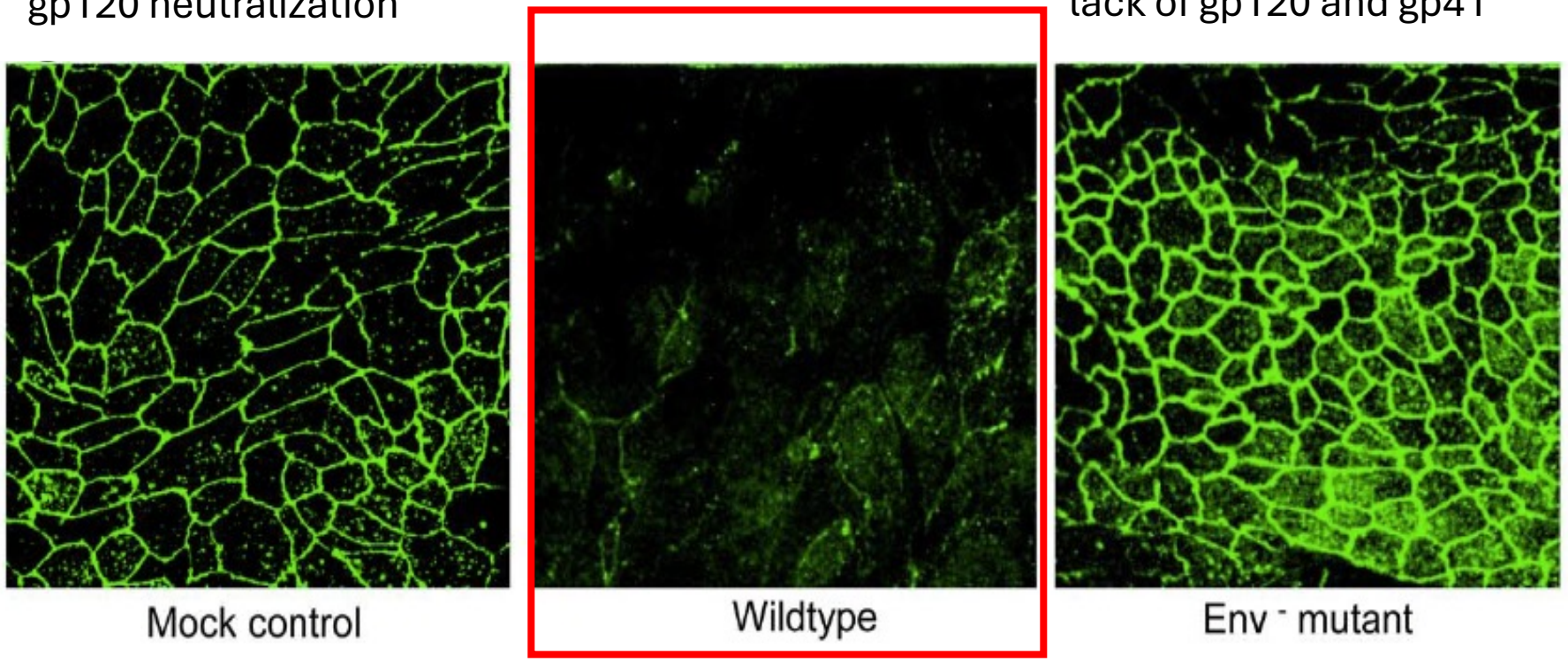


Kitchens, JCI, 2001

HIV causes direct damage of the gut barrier

gp120 neutralization

Env defective mutant:
lack of Env polyprotein→
lack of gp120 and gp41

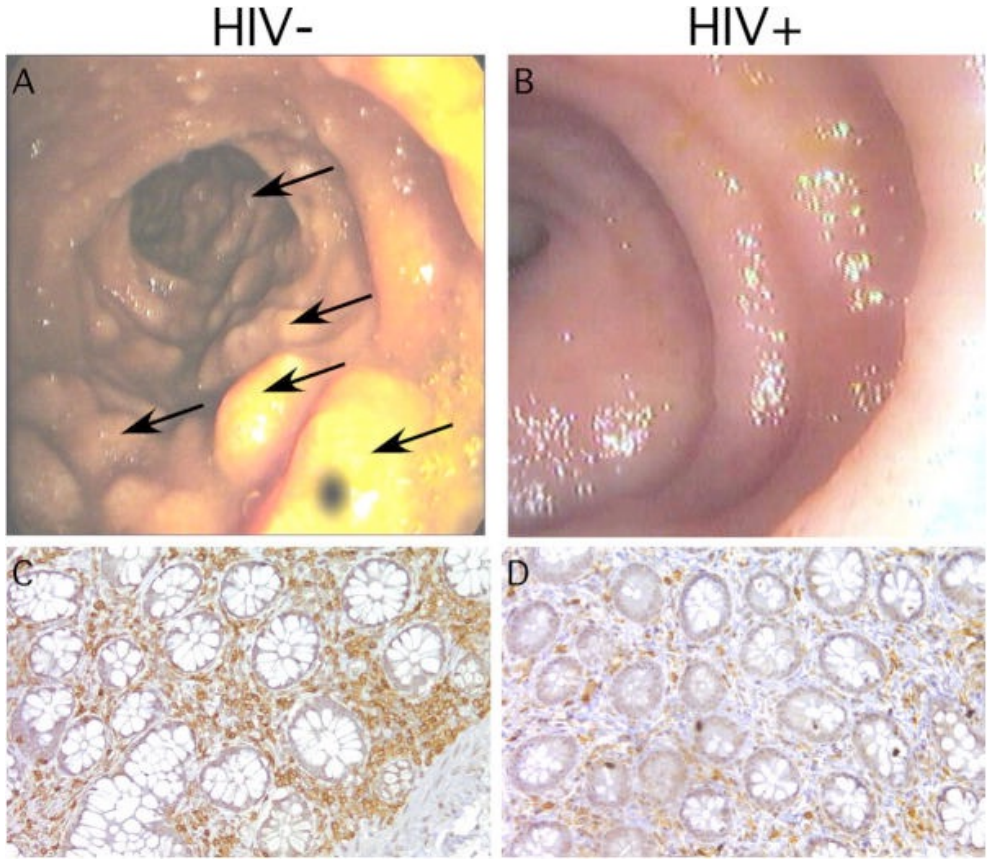


TER: transepitehlial resistance, measure of monolayer integrity

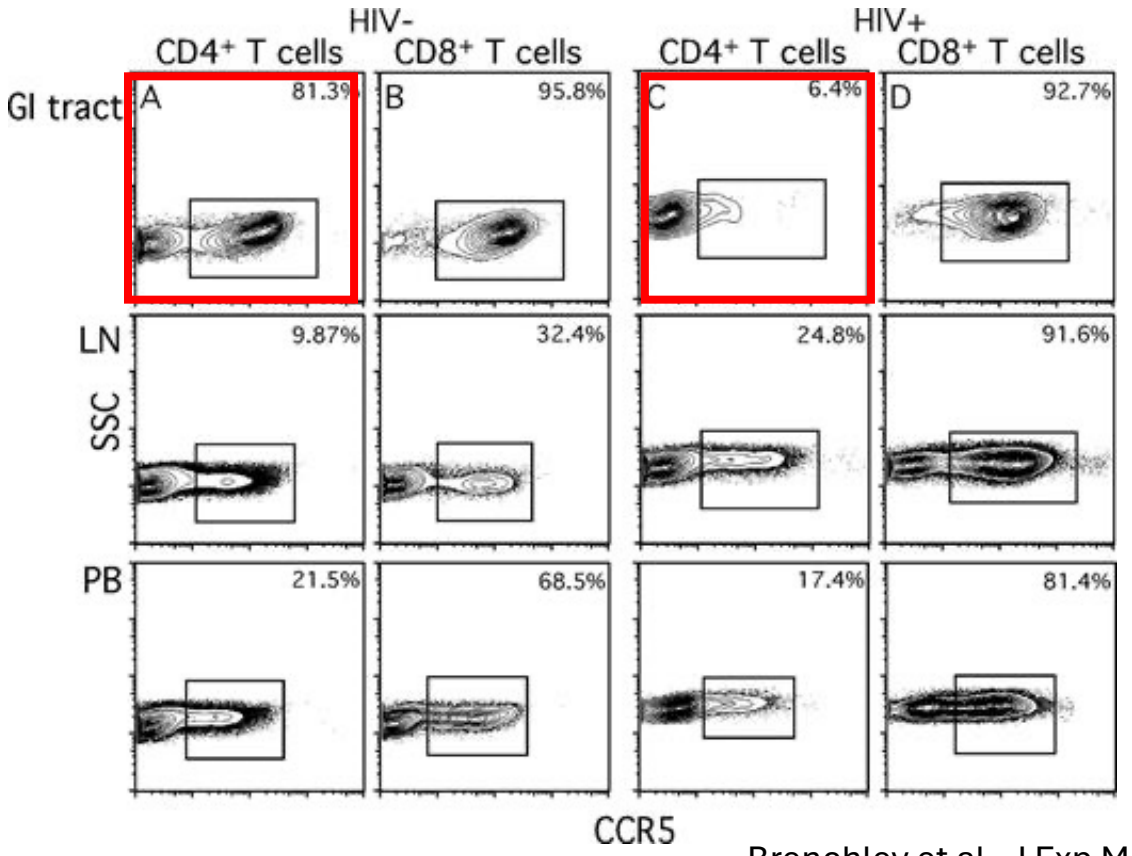
HIV-1 induced barrier permeability is dependent on virus envelope glycoprotein

Nazli et al., Plos Pathogens, 2010

CD4+ T-cell are preferentially lost in the gut during HIV infection



IHC staining for CD4+



Brenchley et al., J Exp Med 2004

Today's agenda

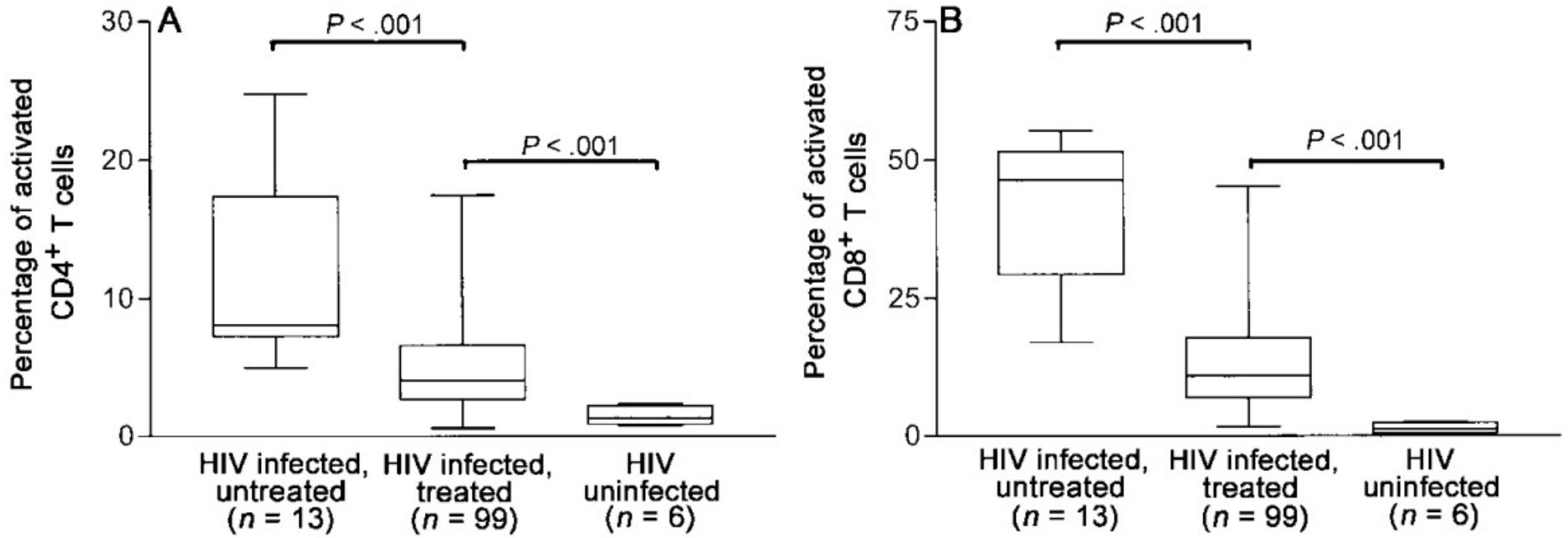
- What is immune activation and what are its underlying causes?

- What are the clinical implications of persisting immune activation/inflammation on cART?

- poor CD4+ T-cell gain
- development of Serious Non AIDS Events (SNAEs)/mortality

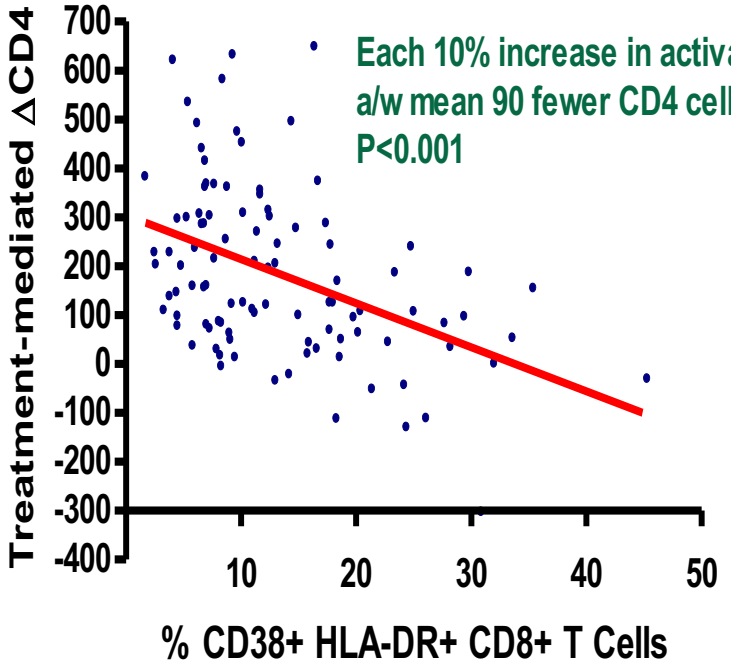
- Can we dampen immune activation?
- -adjuvant strategies (in INR)
- effect of different cART regimens on T-cell homeostasis/inflammation
- lessons learnt from acute HIV infection

Immune Activation Persists on cART

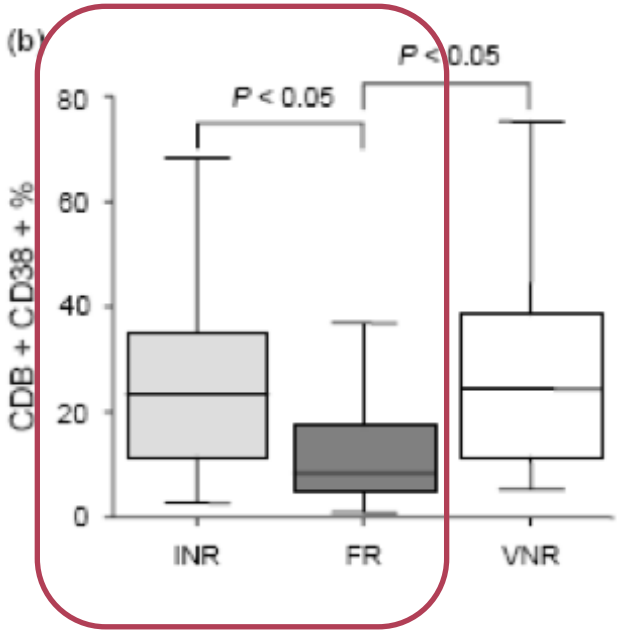


Hunt, JID, 2003

Persistent T-cell Activation is Linked to Poor CD4+ Gain on cART



Hunt, JID, 2003

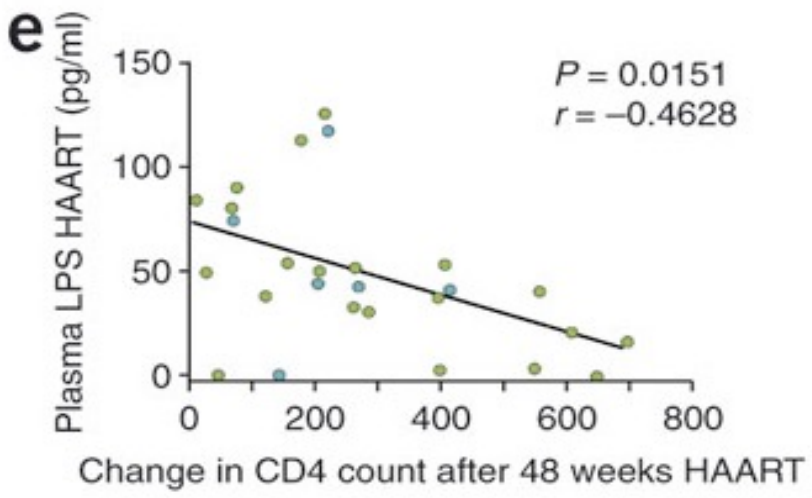


- **INR**: Immunological Non Responders
- **FR**: Full Responders

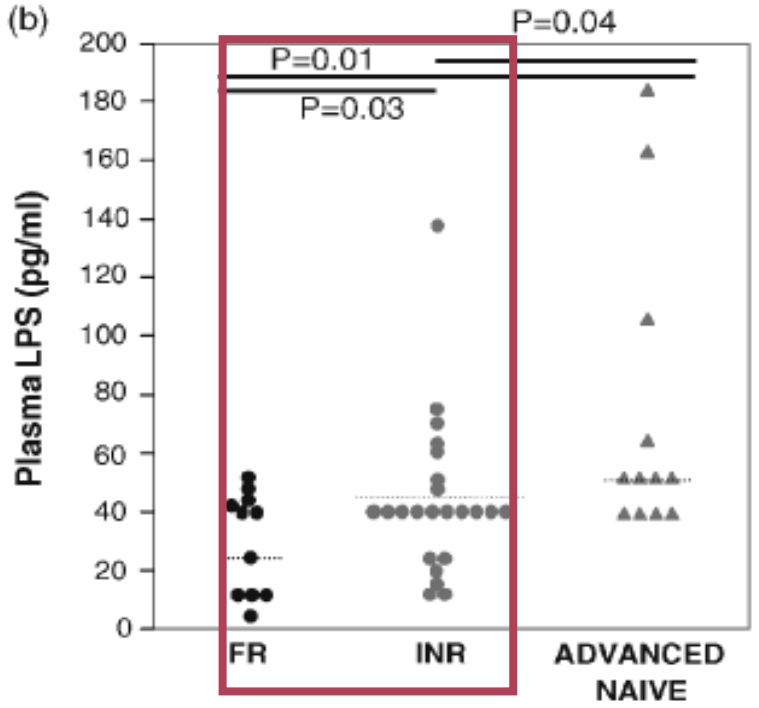
Marchetti et al., AIDS 2006

(see also Pitrak AIDS 2001)

Microbial translocation persists on cART and hampers CD4+ T-cell gain



Brenchley et al., Nat Med 2006

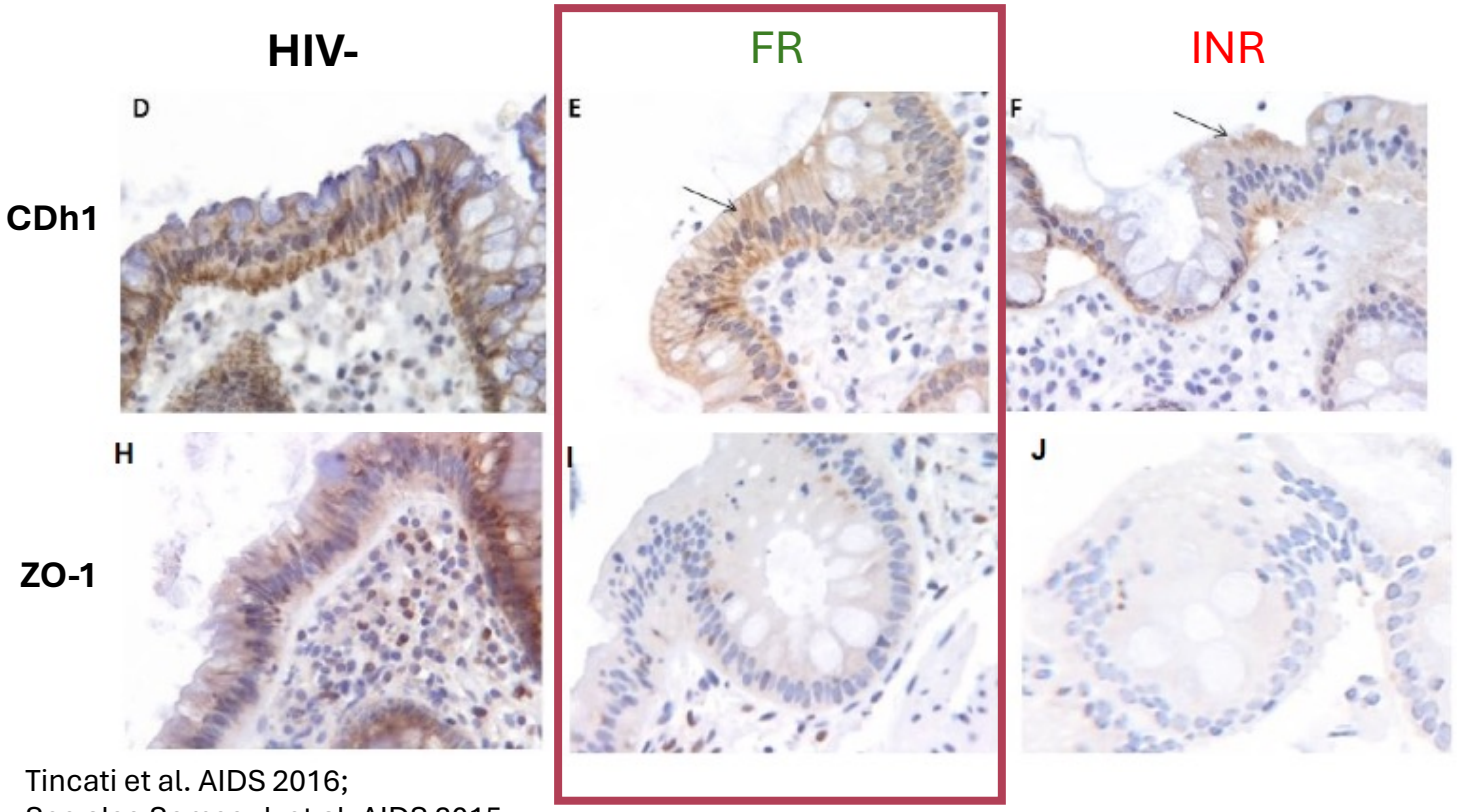


- **INR**: Immunological Non Responders
- **FR**: Full Responders

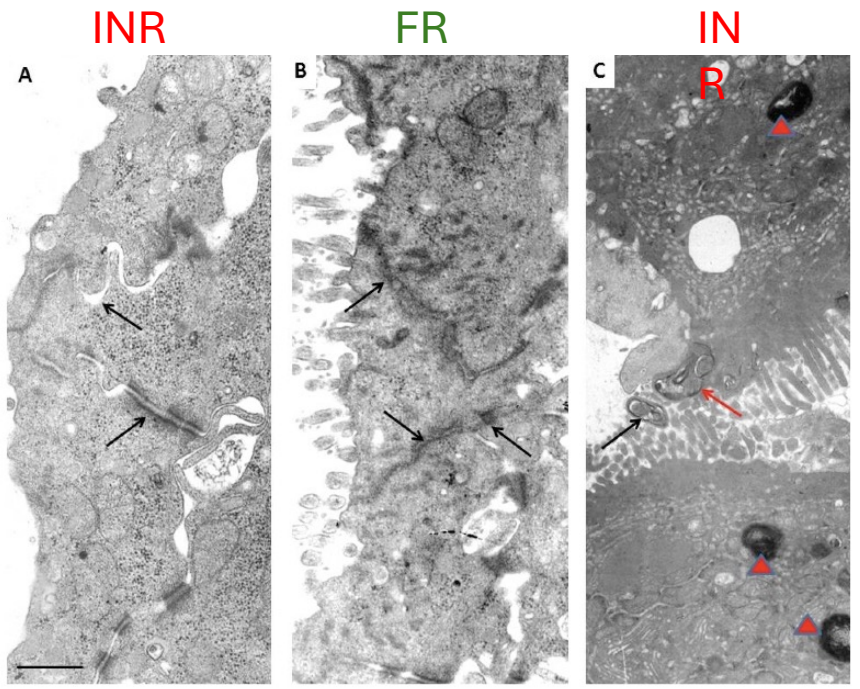
Marchetti et al., AIDS 2008

(see also Jiang JID 2009)

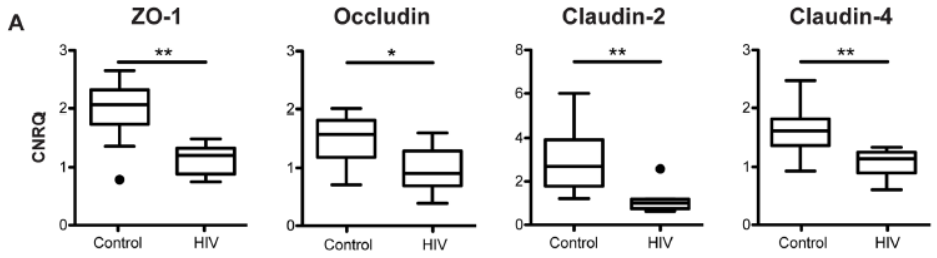
Gut damage in INR: low expression of junctional complex proteins



Tincati et al. AIDS 2016;
See also Somsouk et al, AIDS 2015

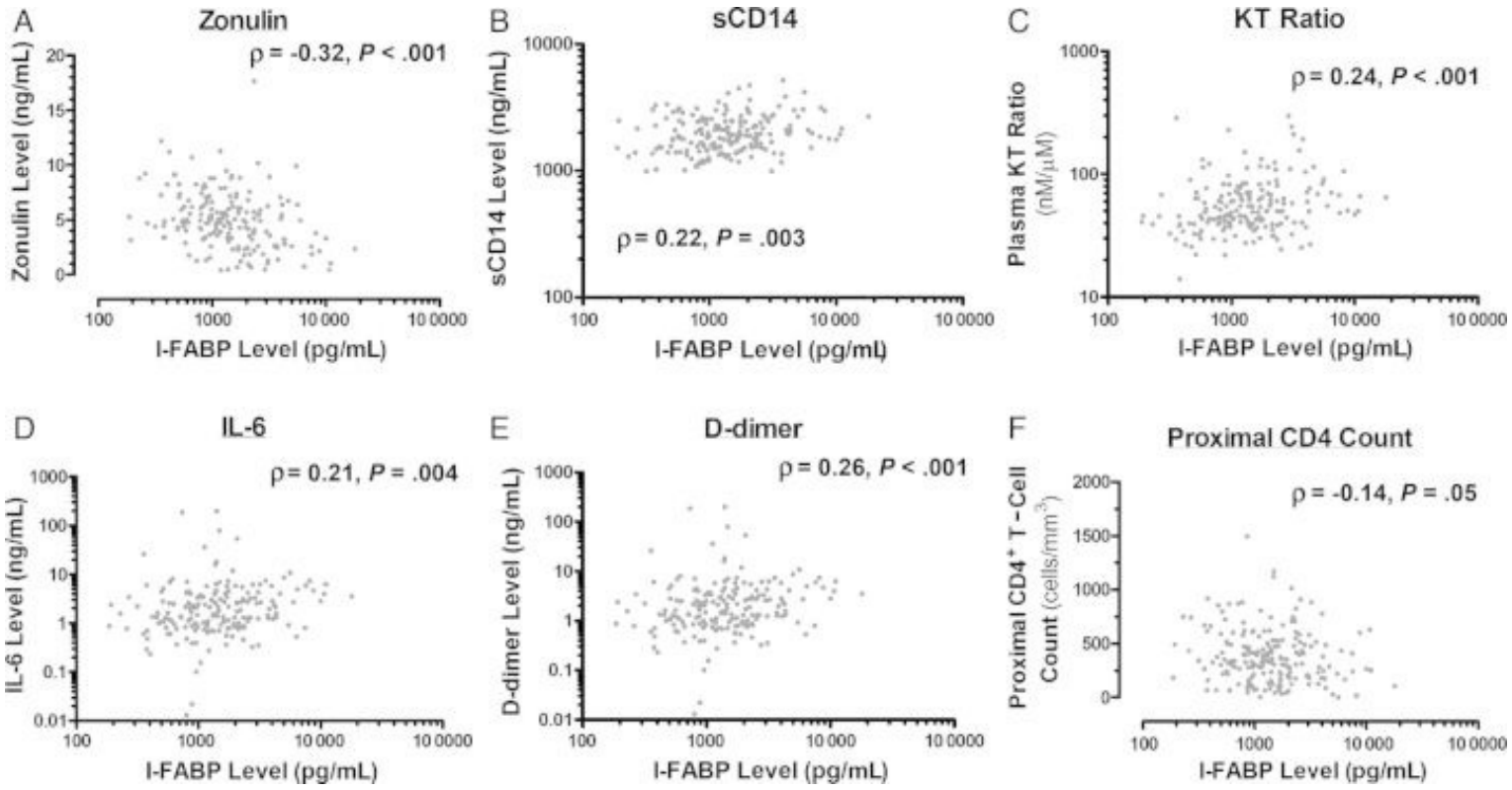


Tincati et al. AIDS 2016

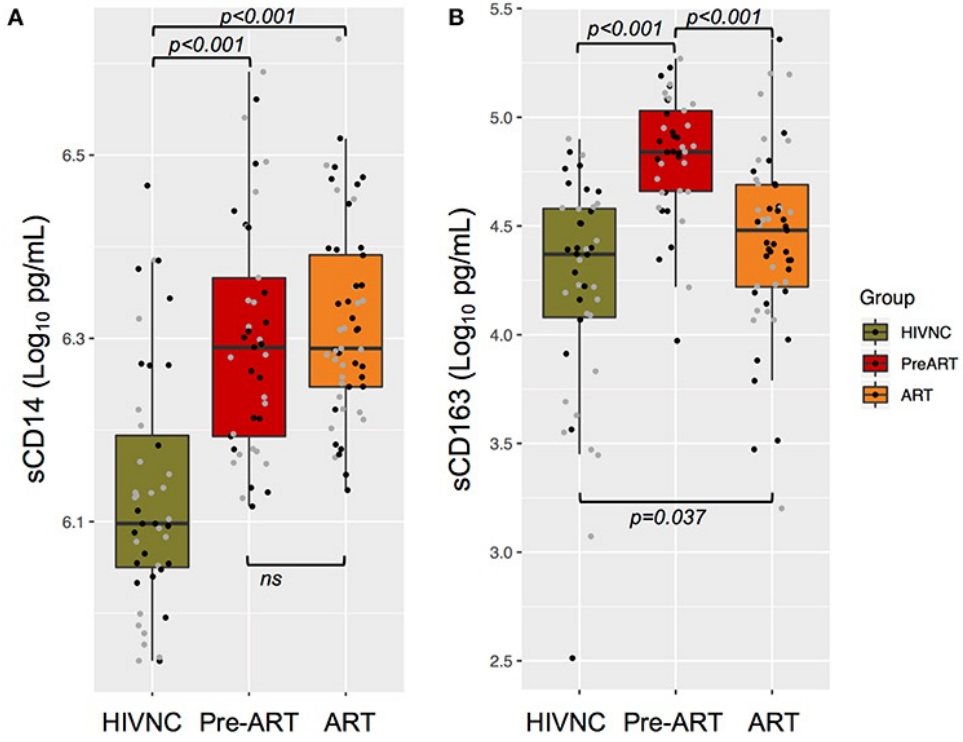


Chung et al., Plos Path , 2014

Link between plasma markers of gut epithelial barrier integrity and innate immune activation in cART-treated subjects



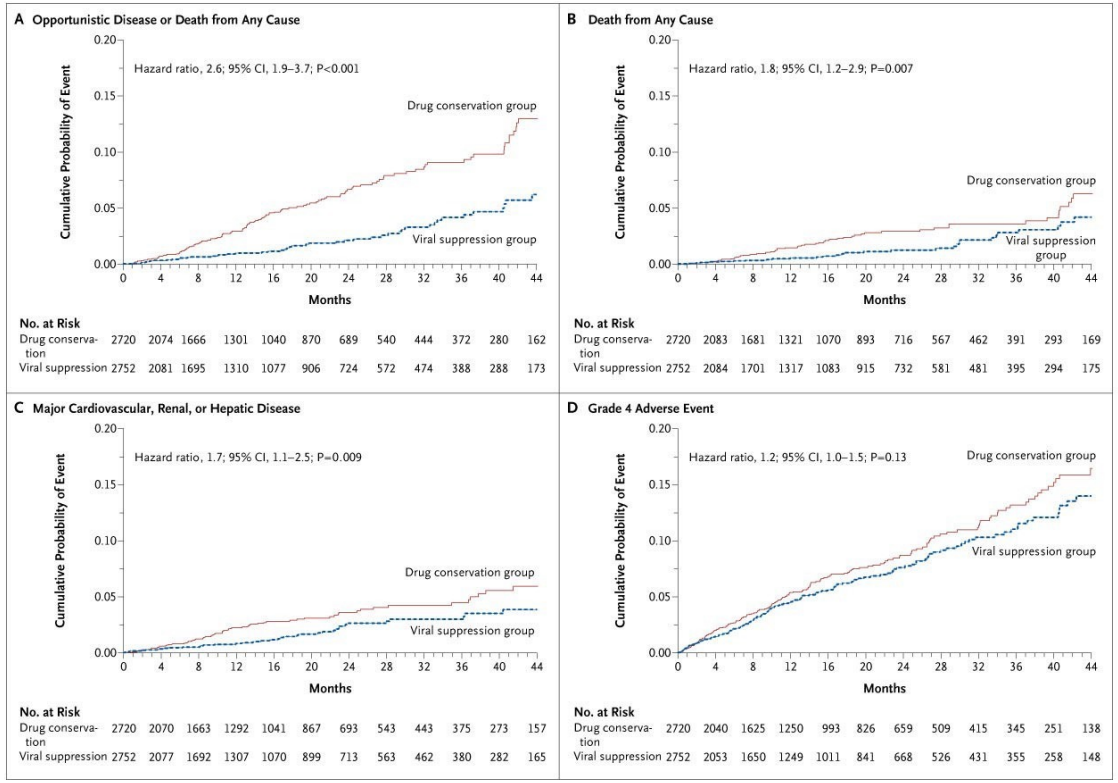
Hunt, JID, 2014



Babu, Front Immunol, 2019

I-FABP: intestinal fatty acid binding protein

Intermittent cART increases deaths from non-AIDS-related causes, secondary to (innate) immune activation



SMART study group, NEJM, 2006

Biomarker	<25th Percentile(Reference)	25th – 49th Percentile OR (95% CI)	*P*	50th – 74th Percentile OR (95% CI)	*P*	≥74th Percentile OR (95% CI)	*P*
sCD14 (×10^6 pg/mL)							
N (case patients/control subjects)	10/46	16/39		21/35		27/28	
Univariate	1.0	2.1 (0.8–5.7)	.12	3.3 (1.3– 8.6)	.01	6.0 (2.2–16.1)	<.001
Adjusted—risk factors[a]	1.0	2.8 (0.8–10.0)	.10	2.7 (.8–9.0)	.11	8.0 (2.0–31.9)	.003
Adjusted—inflammation[b]	1.0	2.3 (0.7–8.1)	.18	2.9 (.9–9.4)	.07	4.1 (1.2–13.9)	.02
LPS, pg/mL							
N (case patients/control subjects)	0	20/35		22/34		15/40	
Univariate	1.0	1.5 (0.6–3.5)	.39	1.6 (.7–3.7)	.25	0.9 (0.4–1.9)	.76
Adjusted—risk factors[a]	1.0	1.1 (0.4–3.1)	.82	1.3 (.5–3.5)	.63	0.4 (0.2–1.2)	.11
Adjusted—inflammation[b]	1.0	1.5 (0.5–4.7)	.45	1.4 (.5–4.4)	.55	1.2 (0.4–3.2)	.78
I-FABP, pg/mL							
N (case patients/control subjects)	23/59	9/20		19/36		23/32	
Univariate	1.0	1.1 (0.5–2.7)	.79	1.4 (.6–2.9)	.42	1.8 (0.9–3.7)	.10
Adjusted—risk factors[a]	1.0	1.2 (0.4–3.6)	.80	2.2 (.8–5.9)	.12	1.8 (0.7–4.4)	.20
Adjusted—inflammation[b]	1.0	1.5 (0.5–4.5)	.44	1.7 (.6–4.7)	.29	1.5 (0.6–3.9)	.38
16S rDNA, copies/μL							
N (case patients/control subjects)	24/32	13/42		16/39		21/34	
Univariate	1.0	0.4 (0.2–0.9)	.03	0.5 (.2–1.2)	.12	0.7 (0.3–1.7)	.45
Adjusted—risk factors[a]	1.0	0.2 (0.1–0.7)	.01	0.4 (.1–1.3)	.12	0.4 (0.1–1.2)	.10
Adjusted—inflammation[b]	1.0	0.4 (0.1–1.3)	.14	0.5 (.1–1.8)	.28	1.3 (0.4–4.1)	.60
EndoCAb, MMU/mL							
N (case patients/control subjects)	18/38	15/40		20/35		21/34	
Univariate	1.0	0.8 (0.3–1.9)	.60	1.2 (.5– 2.6)	.67	1.2 (0.5–2.8)	.61
Adjusted—risk factors[a]	1.0	0.8 (0.2–2.4)	.64	1.7 (.6–4.8)	.29	1.3 (0.4–4.2)	.62
Adjusted—inflammation[b]	1.0	1.1 (0.4–3.3)	.82	0.8 (.3–2.1)	.65	1.4 (0.5–4.0)	.48

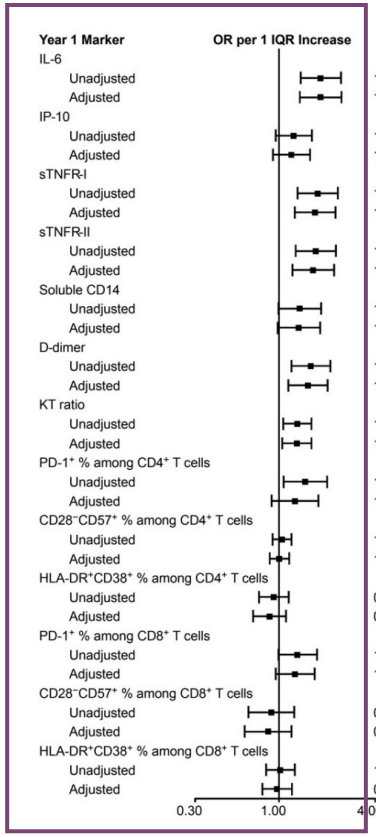
Sandler, JID, 2011

Clinical Implication of Persistent Inflammation: Development of Mortality/SNAEs on cART

Table 2. Soluble Biomarker Predictors of Mortality Among 192 Participants in the Longitudinal Study of the Ocular Complications of AIDS Who Had Antiretroviral Therapy–Suppressed Human Immunodeficiency Virus Infection

Characteristic, Analysis[a]	OR (95% CI) for Death, by Quartile[b]						OR per IQR Increase (95% CI)	P Value
	Second	P Value	Third	P Value	Fourth	P Value		
Proximal CD4+ T-cell count, cells/mm3								
Primary	0.50 (.22–1.1)	.099	0.41 (.17–.98)	.045	0.44 (.18–1.1)	.076	0.62 (.40–.95)	.030
I-FABP level, pg/mL								
Primary	1.76 (.61–5.1)	.30	4.5 (1.5–13.3)	.007	8.3 (2.8–25.1)	<.001	3.5 (2.0–6.1)	<.001
Adjusted	1.69 (.56–5.1)	.35	4.2 (1.4–12.8)	.011	8.6 (2.7–27.8)	<.001	3.5 (1.9–6.1)	<.001
Zonulin-1 level, ng/mL								
Primary	0.29 (.12–.69)	0.005	0.21 (.08–.53)	.001	0.24 (.09–.60)	.002	0.43 (.28–.64)	<.001
Adjusted	0.28 (.12–.69)	.005	0.20 (.08–.53)	.001	0.25 (.09–.64)	.004	0.43 (.28–.66)	<.001
sCD14 level, µg/mL								
Primary	2.7 (.82–9.1)	.10	7.7 (2.3–25.7)	.001	17.6 (4.4–55.1)	<.001	5.4 (2.8–10.4)	<.001
Adjusted	4.5 (1.09–18.6)	.038	11.4 (2.9–46)	.001	30.1 (6.2–145)	<.001	7.5 (3.4–16.5)	<.001
KT ratio, nM/µM								
Primary	1.48 (.51–4.3)	.47	2.3 (.82–6.5)	.11	4.6 (1.72–12.3)	.002	2.3 (1.45–3.5)	<.001
Adjusted	1.50 (.50–4.4)	.47	2.4 (.82–6.9)	.11	4.3 (1.51–12.4)	.006	2.3 (1.40–3.7)	.001
IL-6 level, pg/mL								
Primary	6.4 (1.33–30.6)	.020	9.8 (1.89–50.5)	.007	69.7 (12.4–392)	<.001	6.1 (2.9–12.9)	<.001
Adjusted	12.0 (1.42–102)	.023	17.8 (2.1–154)	.009	139 (14–1362)	<.001	6.6 (2.9–15.0)	<.001
sTNF-RI level, pg/mL								
Primary	1.42 (.44–4.5)	.55	3.8 (1.3–11.0)	.012	9.0 (3.1–26)	<.001	4.6 (2.5–8.5)	<.001
Adjusted	1.25 (.38–4.2)	.71	3.6 (1.23–10.8)	.02	10.2 (3.2–32)	<.001	5.2 (2.6–10.4)	<.001
hsCRP level, ng/mL								
Primary	1.61 (.57–4.6)	.37	2.1 (.78–5.6)	.14	10.9 (3.7–33)	<.001	3.7 (2.1–6.7)	<.001
Adjusted	1.58 (.53–4.7)	.42	2.3 (.81–6.6)	.12	10.9 (3.4–35)	<.001	3.8 (2.0–7.0)	<.001
D-dimer level, ng/mL								
Primary	1.33 (.35–5.1)	.68	5.9 (1.80–19.1)	.003	30.3 (7.2–128)	<.001	7.7 (3.6–16.7)	<.001
Adjusted	1.23 (.31–4.9)	.77	6.2 (1.8–21.3)	.003	29.4 (6.6–131)	<.001	7.7 (3.5–17.3)	<.001
CMV IgG index								
Primary	0.42 (.17–1.05)	.064	0.54 (.22–1.30)	.17	1.37 (.58–3.2)	0.47	0.91 (.80–1.05)	.19
Adjusted	0.38 (.15–.98)	.045	0.43 (.17–1.12)	.085	1.07 (.42–2.7)	.89	0.89 (.77–1.03)	.11

Hunt, JID, 2014



Year 1 Marker		P Value	OR at Year 1 for: Death	Cancer	MI/Stroke
IL-6					
Unadjusted	1.82 (1.37–2.44)	<.001	4.71**	1.65*	1.66
Adjusted	1.82 (1.35–2.45)	<.001	6.22**	1.68*	1.56
IP-10					
Unadjusted	1.24 (0.96–1.60)	.105	1.19	1.16	1.41
Adjusted	1.20 (0.92–1.56)	.182	1.10	1.24	1.36
sTNFR-I					
Unadjusted	1.74 (1.31–2.33)	<.001	2.24**	1.76*	2.02**
Adjusted	1.68 (1.25–2.24)	<.001	2.09*	1.74*	2.02**
sTNFR-II					
Unadjusted	1.70 (1.27–2.27)	<.001	3.08*	1.63	2.03**
Adjusted	1.63 (1.21–2.20)	.001	2.57*	1.71*	2.09**
Soluble CD14					
Unadjusted	1.35 (0.99–1.83)	.056	1.76	1.14	1.44
Adjusted	1.33 (0.98–1.81)	.069	1.54	1.13	1.39
D-dimer					
Unadjusted	1.58 (1.20–2.09)	.001	2.36*	1.51	1.73*
Adjusted	1.52 (1.15–2.02)	.004	2.80*	1.39	1.69*
KT ratio					
Unadjusted	1.30 (1.06–1.60)	.010	2.16*	1.17	1.41
Adjusted	1.30 (1.05–1.60)	.015	1.95	1.26	1.37
PD-1+ % among CD4+ T cells					
Unadjusted	1.46 (1.07–1.99)	.016	2.46	1.56	1.05
Adjusted	1.26 (0.90–1.76)	.180	2.27	1.45	0.87
CD28−CD57+ % among CD4+ T cells					
Unadjusted	1.05 (0.91–1.20)	.508	1.20	1.15	0.85
Adjusted	1.01 (0.87–1.16)	.940	1.17	1.10	0.82
HLA-DR+CD38+ % among CD4+ T cells					
Unadjusted	0.93 (0.75–1.15)	.498	1.54	0.87	0.59
Adjusted	0.87 (0.69–1.11)	.265	1.50	0.85	0.54
PD-1+ % among CD8+ T cells					
Unadjusted	1.31 (1.00–1.72)	.054	1.43	1.24	1.05
Adjusted	1.26 (0.96–1.67)	.101	1.41	1.23	1.00
CD28−CD57+ % among CD8+ T cells					
Unadjusted	0.90 (0.65–1.25)	.523	1.59	0.97	0.59
Adjusted	0.86 (0.61–1.20)	.361	1.54	0.93	0.62
HLA-DR+CD38+ % among CD8+ T cells					
Unadjusted	1.02 (0.83–1.26)	.846	1.70*	0.90	0.80
Adjusted	0.97 (0.79–1.20)	.805	1.62	0.87	0.76

Figure 4. Biomarker levels in specimens obtained at the visit approximately 1 year after ART initiation (year 1) and odds ratios (ORs) of having a non–AIDS-defining event. Adjusted analyses controlled for concurrent CD4+ T-cell count. *P = .01 to <.05; **P < .01. Abbreviations: IL-6, interleukin 6; IP-10, interferon γ–inducible protein 10; IQR, interquartile range; KT, kynurenine to tryptophan; MI, myocardial infarction; sTNFR, soluble tumor necrosis factor receptor.

Tenorio, JID, 2014

IL-6 and D-dimer are independent predictors of SNAE/death on suppressive cART

Table 1. Baseline characteristics [a].

Characteristic	Overall (n = 3766)	Median (IQR) or %	SMART (n = 1748)	ESPRIT (n = 1446)	SILCAAT (n = 572)
Age (years)	42	(37, 49)	45	40	41
Female (%)	21.2		25.8	17.4	16.6
Race/Ethnicity (%)					
Black	16.4		24.9	8.6	10.1
White/Latino/Other	83.6		75.1	91.4	89.9
Location of Enrollment (%)					
Asia	3.4		0.7	8.0	-
Australia, Europe, Israel	46.9		37.0	52.3	63.1
North America	37.4		49.0	23.5	36.9
South America	11.8		12.8	15.3	-
Africa	0.6		0.5	0.9	-
HIV-related factors					
CD4 cell count (cells/mm^3)	500	(365, 690)	654	452	205
Nadir CD4 (cells/mm^3)	181	(70, 290)	230	176	57
Prior AIDS (%)	27.1		24.9	28.1	31.3
Years since HIV diagnosis	7.3	(4.0, 11.4)	8.4	6.0	6.3
Duration of ART use (years)	4.9	(2.5, 8,0)	6.0	4.2	3.9
Current use of a PI (%)	47.8		42.1	47.9	64.9
Current use of a NNRTI (%)	50.8		52.0	51.7	44.8
BMI (kg/m^2)	24.1	(22.0, 26.6)	24.7	23.7	23.7
Biomarkers					
IL-6 (pg/mL)	1.7	(1.1, 2.7)	1.6	1.9	1.7
D-dimer (µg/mL)	0.22	(0.15, 0.35)	0.18	0.26	0.25
hsCRP (µg/mL)	1.54	(0.67, 3.60)	1.72	1.42	1.34

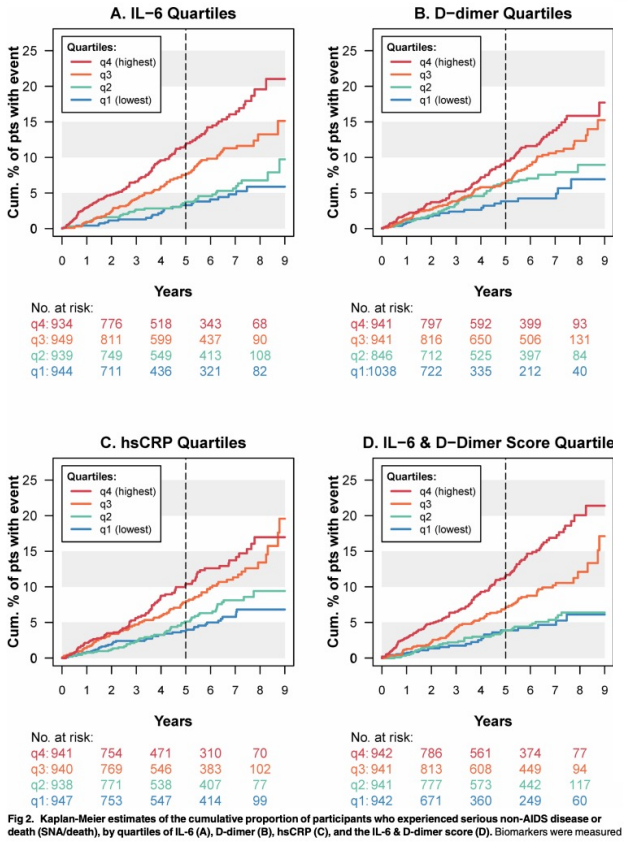
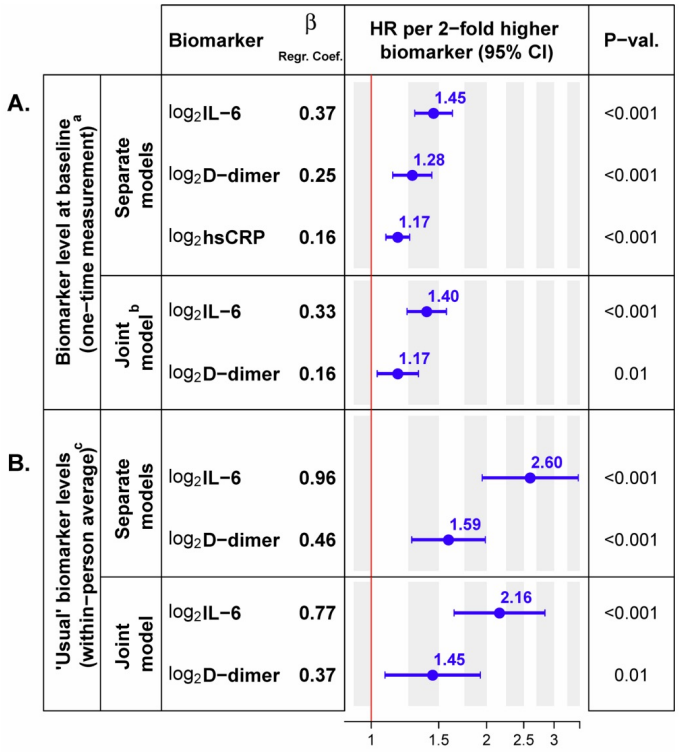
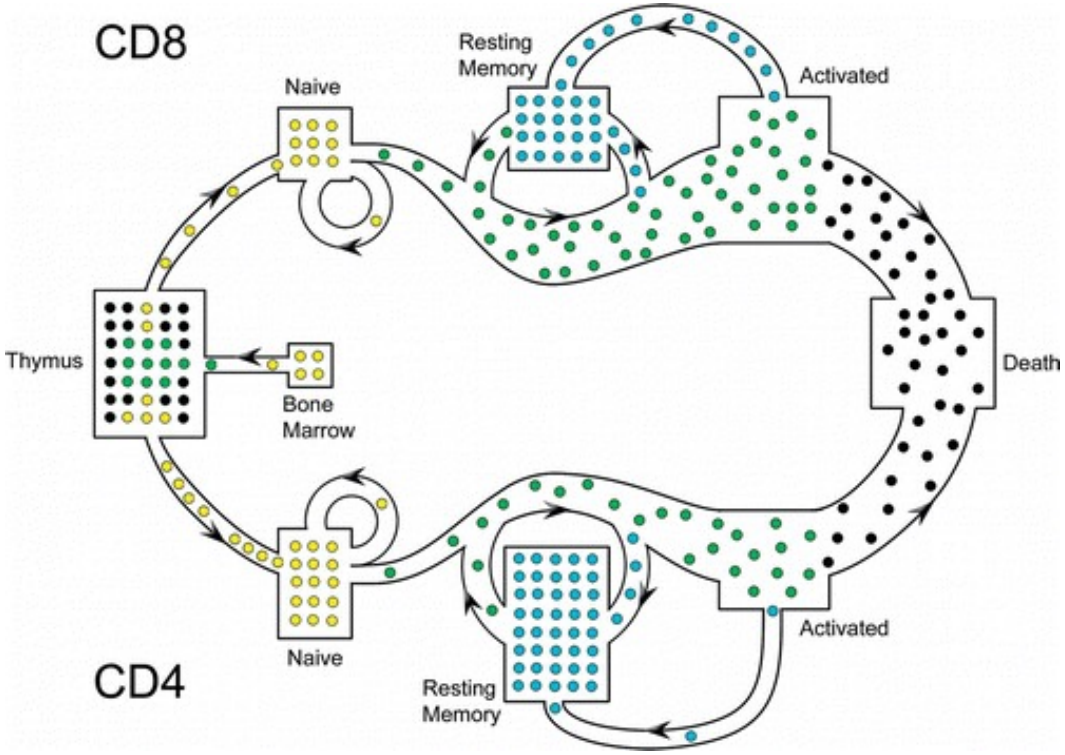


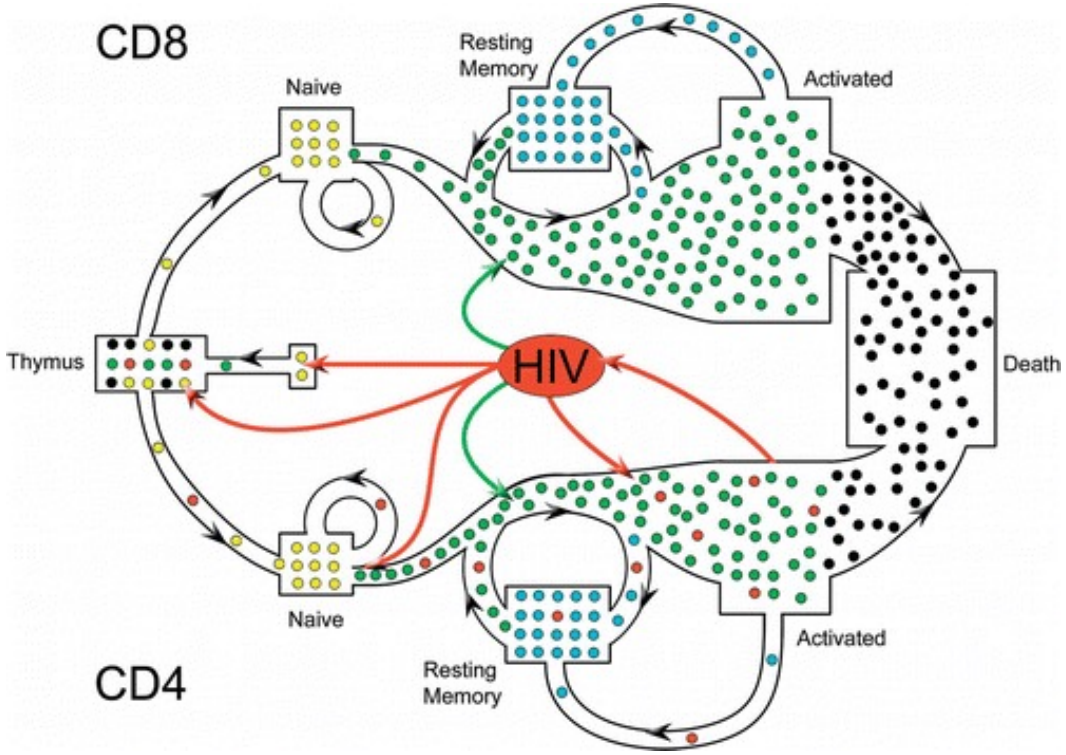
Fig 2. Kaplan-Meier estimates of the cumulative proportion of participants who experienced serious non-AIDS disease or death (SNA/death), by quartiles of IL-6 (A), D-dimer (B), hsCRP (C), and the IL-6 & D-dimer score (D). Biomarkers were measured



Grund, PlosOne, 2016

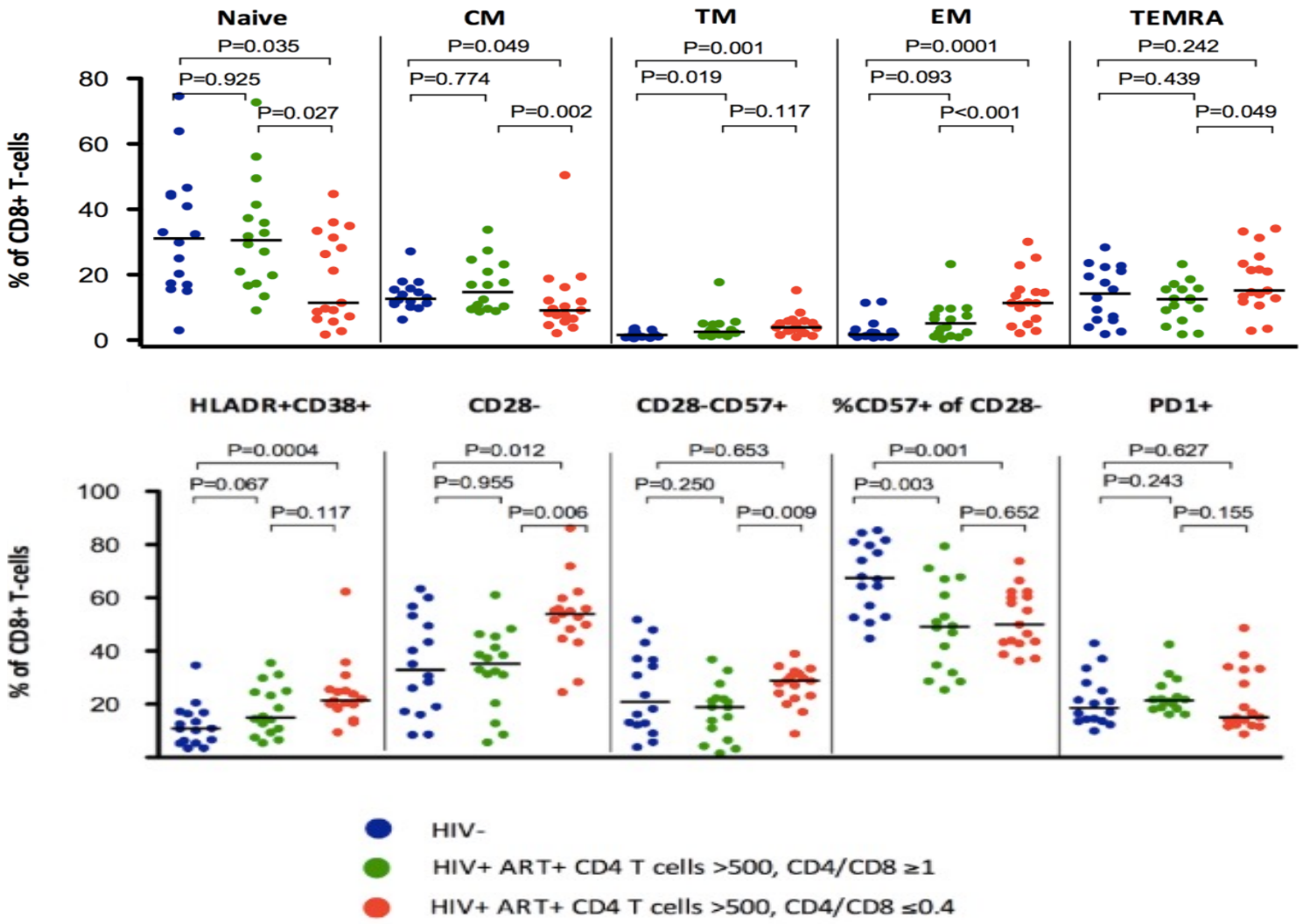
How can we capture persistent immune activation in clinical practice?





Douek, Annual Review Immunol, 2003

Low CD4/CD8 T-cell ratio mirrors peripheral immune defects



Serrano-Villar et al. PlosPath 2014

Clinical risk of patients with persistent immune impairment (low CD4/CD8 ratio)

	Univariable		Model 1 (AIC=3936)		Model 2 (AIC=3931)	
	RR (95% CI)	p value	ARR (95% CI)	p value	ARR (95% CI)	p value
Age (per 10 years older)	1·56 (1·41–1·73)	<0·0001	1·55 (1·38–1·74)	<0·0001	1·54 (1·37–1·74)	0·0001
Mode of HIV transmission						
Heterosexual contacts	1·00	..	1·00	..	1·00	..
Homosexual contacts with men	1·11 (0·84–1·46)	0·4589	1·15 (0·86–1·54)	0·3307	1·16 (0·87–1·55)	0·3231
Intravenous drug use	1·37 (1·07–1·80)	0·0147	1·36 (0·90–2·06)	0·1413	1·35 (0·89–2·04)	0·1546
Other or unknown	1·62 (1·07–2·44)	0·0221	1·51 (0·98–2·34)	0·0643	1·52 (0·98–2·35)	0·0612
Years of HIV infection (per 1 year longer)	1·02 (1·00–1·04)	0·0265	1·02 (0·99–1·04)	0·1285	1·02 (0·99–1·04)	0·1216
CD4 count at baseline (cells per µL)						
0–199	1·00	..	1·00	..	1·00	..
200–349	0·54 (0·40–0·73)	<0·0001	0·76 (0·54–1·06)	0·1024	0·81 (0·57–1·14)	0·2185
≥350	0·56 (0·43–0·72)	<0·0001	1·11 (0·79–1·56)	0·5645	1·18 (0·83–1·67)	0·3631
Months since ART start to first viral suppression (per 6 months longer)	1·03 (1·00–1·06)	0·0811	0·99 (0·96–1·03)	0·7333	0·99 (0·96–1·03)	0·6394
CDC stage category C (vs A and B)	1·73 (1·37–2·19)	<0·0001	1·37 (1·04–1·80	0·0250	1·34 (1·02–1·76)	0·0365
HCV-Ab status						
Negative	1·00	..	1·00	..	1·00	..
Positive	1·29 (1·02–1·64)	0·0362	1·05 (0·72–1·53)	0·8097	1·04 (0·71–1·52)	0·8397
Not known	1·33 (0·99–1·78)	0·0557	1·17 (0·85–1·60)	0·3437	1·15 (0·84–1·59)	0·3859
Current CD4 count (per 100 cells per µL higher)	0·87 (0·85–0·93)	<0·0001	0·90 (0·85–0·95)	<0·0001	0·93 (0·87–0·98)	0·0107
Current CD4/CD8 ratio						
>0·45	1·00	..	..	..	1·00	..
0·30–0·45	1·16 (0·86–1·58)	0·3362	..	..	0·95 (0·69–1·31)	0·7512
<0·30	2·25 (1·73–2·94)	<0·0001	..	..	1·51 (1·09–2·09)	0·0137

The model included all the study population (n=3236). Model 1 includes all significant variables in univariable analysis except for the CD4/CD8 ratio, model 2 included also the ratio. AIC=Akaike's information criterion. RR=relative risk. ARR=adjusted relative risk. ART=antiretroviral therapy. CDC=Centers for Disease Control and Prevention. HCV-Ab=HCV antibody.

Table 3: **Two different multivariable Poisson regression models analysing factors associated with clinical progression (defined as non-AIDS-defining event or death)**

	Univariable		Model 1 (AIC=1215)		Model 2 (AIC=1210)	
	RR (95% CI)	p value	ARR (95% CI)	p value	ARR (95% CI)	p value
White	0·33 (0·19–0·56)	<0·0001	0·32 (0·18–0·57)	<0·001	0·66 (0·43–1·00)	0·050
Baseline CD4 count (cells per µL)						
0–199	1·00	..	1·00	..	1·00	..
200–349	0·25 (0·14–0·45)	<0·0001	0·47 (0·24–0·92)	0·0267	0·52 (0·27–1·01)	0·0548
≥350	0·30 (0·19–0·47)	<0·0001	1·18 (0·64–2·17)	0·5998	1·27 (0·63–2·36)	0·4495
CDC stage category C (vs A and B)	2·82 (1·88–4·23)	<0·0001	2·22 (1·37–3·60)	0·0012	2·14 (1·32–3·47)	0·0020
Current CD4 count (per 100 cells per µL higher)	0·75 (0·68–0·84)	<0·0001	0·77 (0·69–0·87)	0·0001	0·85 (0·75–0·97)	0·0187
Current CD4/CD8 ratio						
>0·45	1·00	..	–	..	1·00	..
0·30–0·45	1·77 (0·96–3·25)	0·0655	–	..	1·30 (0·69–2·46)	0·4220
<0·30	4·96 (3·06–8·04)	<0·0001	–	..	2·56 (1·38–4·74)	0·0029

Model 1 includes all significant variables in univariable analysis except for the ratio, model 2 included also the ratio. The model included all the study population (n=3236). RR=relative risk. ARR=adjusted relative risk. ART=antiretroviral therapy. CDC=Centers for Disease Control and Prevention. AIC=Akaike's information criterion.

Table 4: **Two different multivariable Poisson regression models analysing factors associated with clinical progression (defined as AIDS event and death due to AIDS event)**

Mussini et al. Lancet HIV 2015

See also: Han et al. AIDS Res Ther., 2018; Lee et al. BMJ Open 2017; Trickey et al. CID 2017; Sauter et al. Medicine 2016; Hema et al. PlosOne 2016

Open Forum Infectious Diseases

MAJOR ARTICLE

Persistence of High Percentage of Peripheral Activated CD8+ T Cells Predict Cytologic HPV-Related Dysplasia in cART-Treated, HIV-Positive Subjects

Debora Mondatore,[1] Francesca Bai,[1] Matteo Augello,[1] Marco Giovenzana,[2] Andrea Pisani Ceretti,[2] Valeria Bono,[1] Enrico Opocher,[2] Antonella d'Arminio Monforte,[1] Giulia Carla Marchetti,[1] and Camilla Tincati[1]

Table 2. Parameters Independently Associated With Cytologic HPV-Related Dysplasia by Fitting 2 Models of Multivariable Logistic Regression Analyses

A, Model 1 of logistic regression analysis: association between CD8+ CD38+ T-cell percentages and HPV-related anal/cervical dysplasia

Parameter	aOR	95% CI	*P* Value
Log_{10} CD8+ CD38+ T cells, percentages, each additional unit	3.253	1.602–6.605	.001

B, Model 2 of logistic regression analysis: association between CD4/CD8 ratio and HPV-related anal/cervical dysplasia

Parameter	aOR	95% CI	*P* Value
CD4/CD8 ratio, each unit more	0.998	0.242–4.109	.997

Mondatore et al. OFID, 2022

Today's agenda

- What is immune activation and what are its underlying causes?

- What are the clinical implications of persisting immune activation/inflammation on cART?

- poor CD4+ T-cell gain
- development of Serious Non AIDS Events (SNAEs)/mortality

- Can we dampen immune activation?

- adjuvant strategies (in INR)
- effect of different cART regimens on T-cell homeostasis/inflammation
- lessons learnt from acute HIV infection

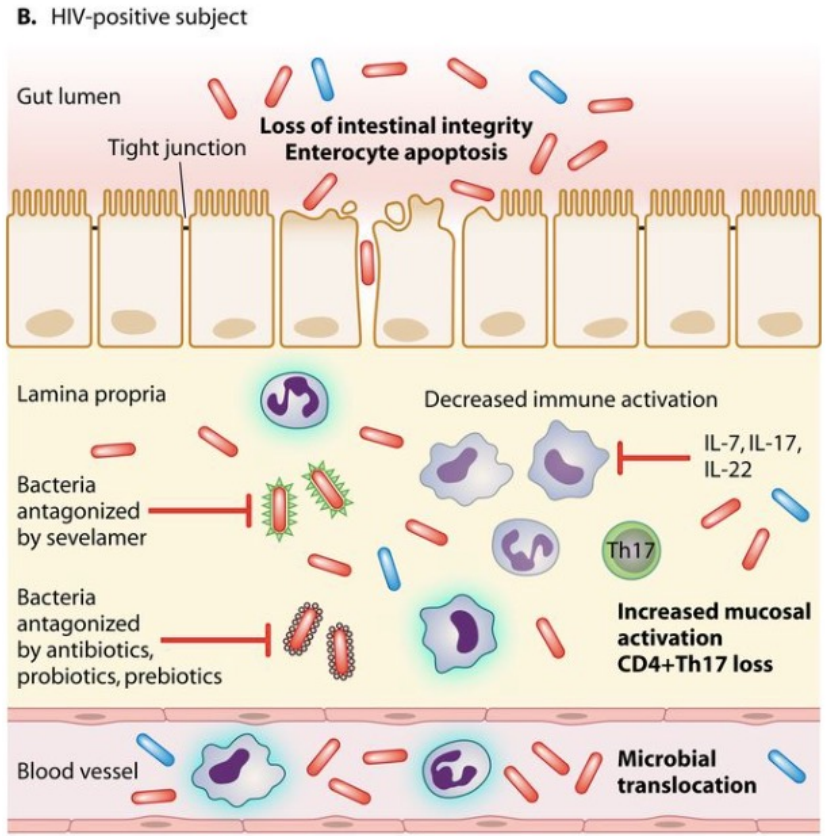
Past adjuvant strategies in the setting of poor immune recovery on cART

- Correction of T-cell homeostasis:
  - IL-2
  - IL7

- Abatement of reservoirs/low-level replication:
  - MVC
  - RAL

- Treatment of co-infections:
  - HCV
  - CMV

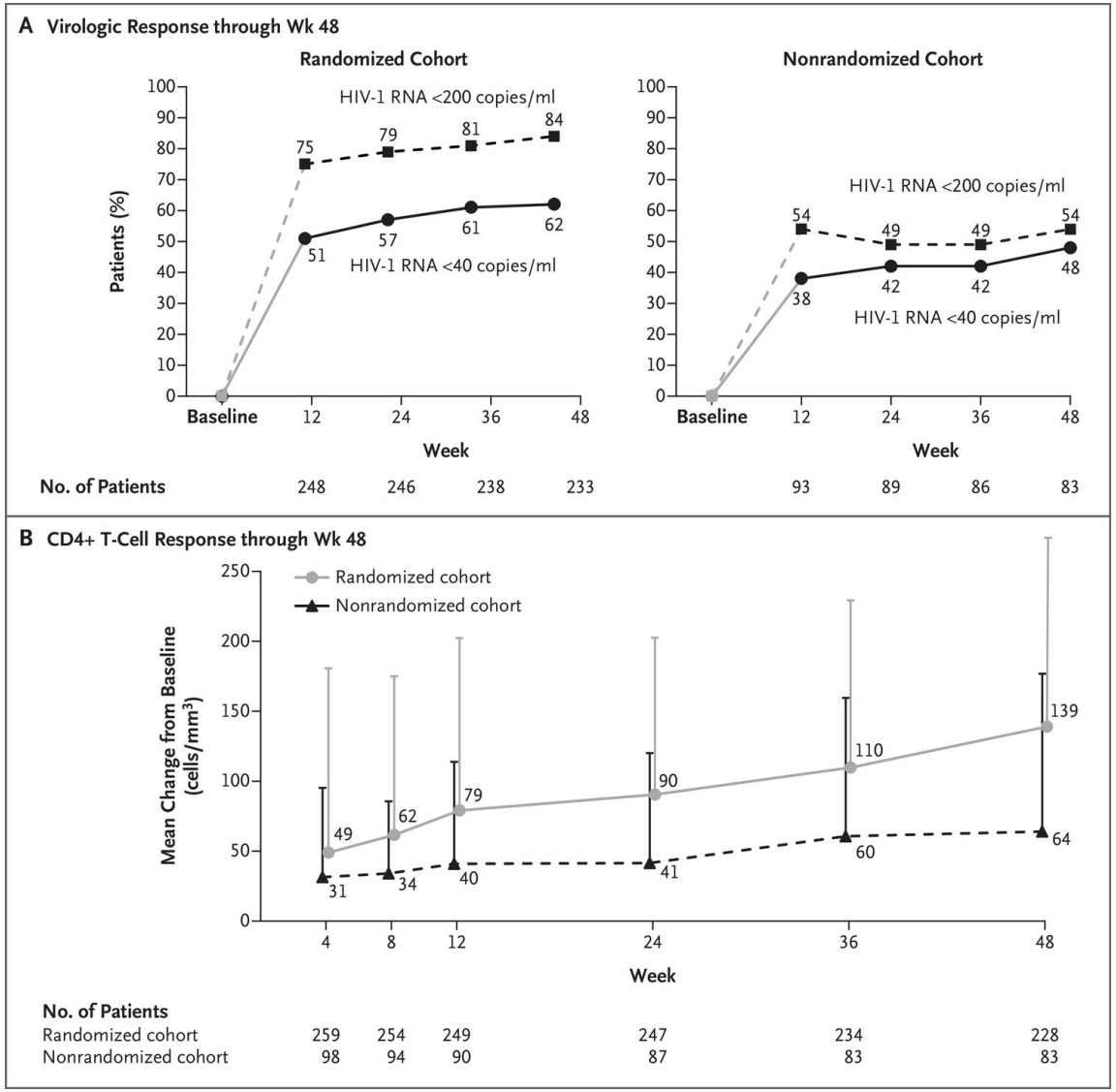
- Correction of dysbiosis:
  - Pre/probiotics
  - Fecal transplantation



Marchetti, Clin Microbiol Reviews, 2013

Fostemsavir

- Fostemsavir is the prodrug of temsavir, a first-in-class investigational HIV-1 attachment inhibitor.
- Temsavir binds the viral envelope protein gp120 on HIV-1, adjacent to the gp120-CD4+ binding site. In doing so, it prevents the conformational change required for attachment of HIV-1 to the host cell.



NIH U.S. National Library of Medicin

ClinicalTrials.gov

Previous Study | Return to List | Next Study

Changes in Immunologic Parameters Following the Addition of Fostemsavir in Virologically Suppressed Immunologic Non-responders Living With HIV-the RECOVER Study

Brief Summary:

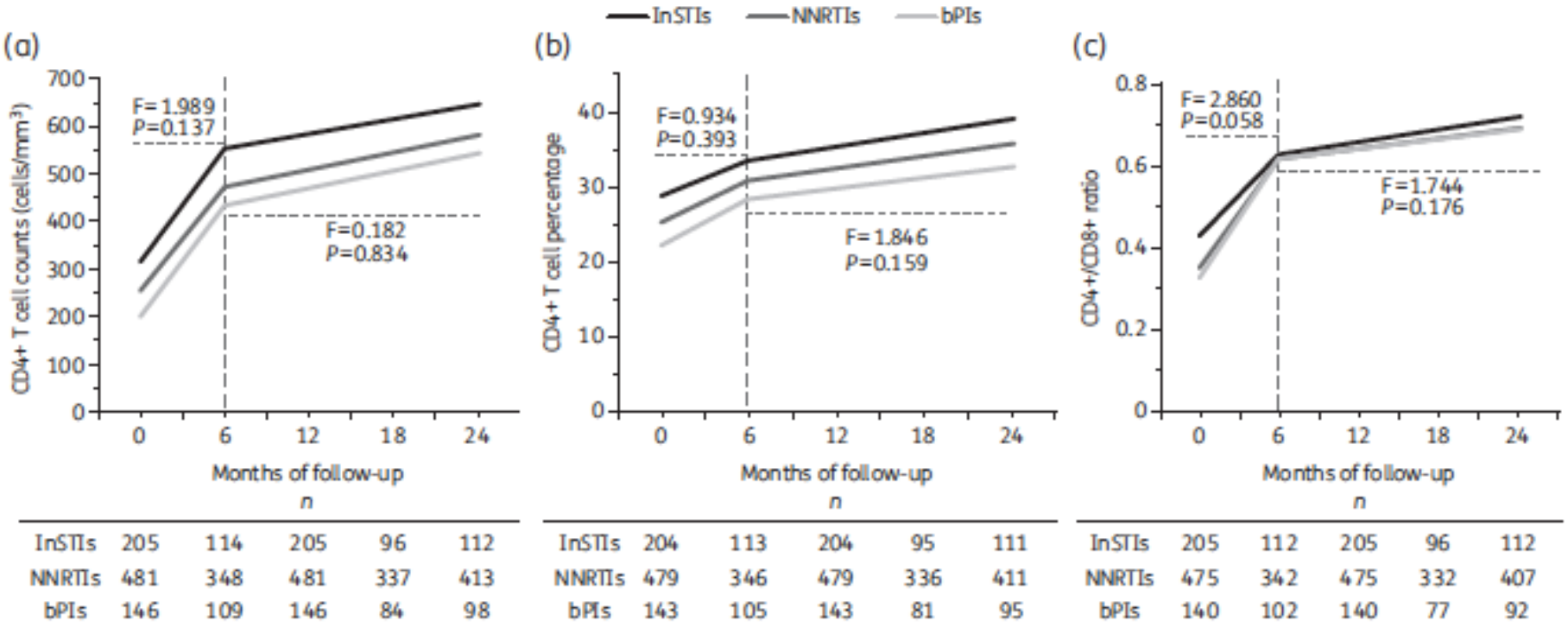
The RECOVER study is a self-controlled case series to evaluate whether the addition of **Fostemsavir** (Rukobia) to a stable HIV regimen in virologically suppressed patients living with HIV who never experience optimal CD4 T-cell count recovery can result in meaningful increases in different immunologic parameters such as CD4 T-cell count, CD4 T-cell percentage and CD4/CD8 ratio

Condition or disease	Intervention/treatment	Phase
HIV-1-infection	Drug: **Fostemsavir** 600 MG [Rukobia]	Phase 4

- Documented plasma HIV-1 RNA < 50 c/mL x 2 within the last year prior to screening
- Must be on a stable ARV regimen for ≥6 months prior to screening
- CD4+T-cell count<350 cells/mm3 while on ARVs for at least 2 years
- Must be willing to add FTR 600 mg twice daily to their current antiretroviral regimen

Immune restoration during 1st line cART is independent of third drug class when given with 2 NRTIs

N=836



n

InSTIs	205	114	205	96	112
NNRTIs	481	348	481	337	413
bPIs	146	109	146	84	98

n

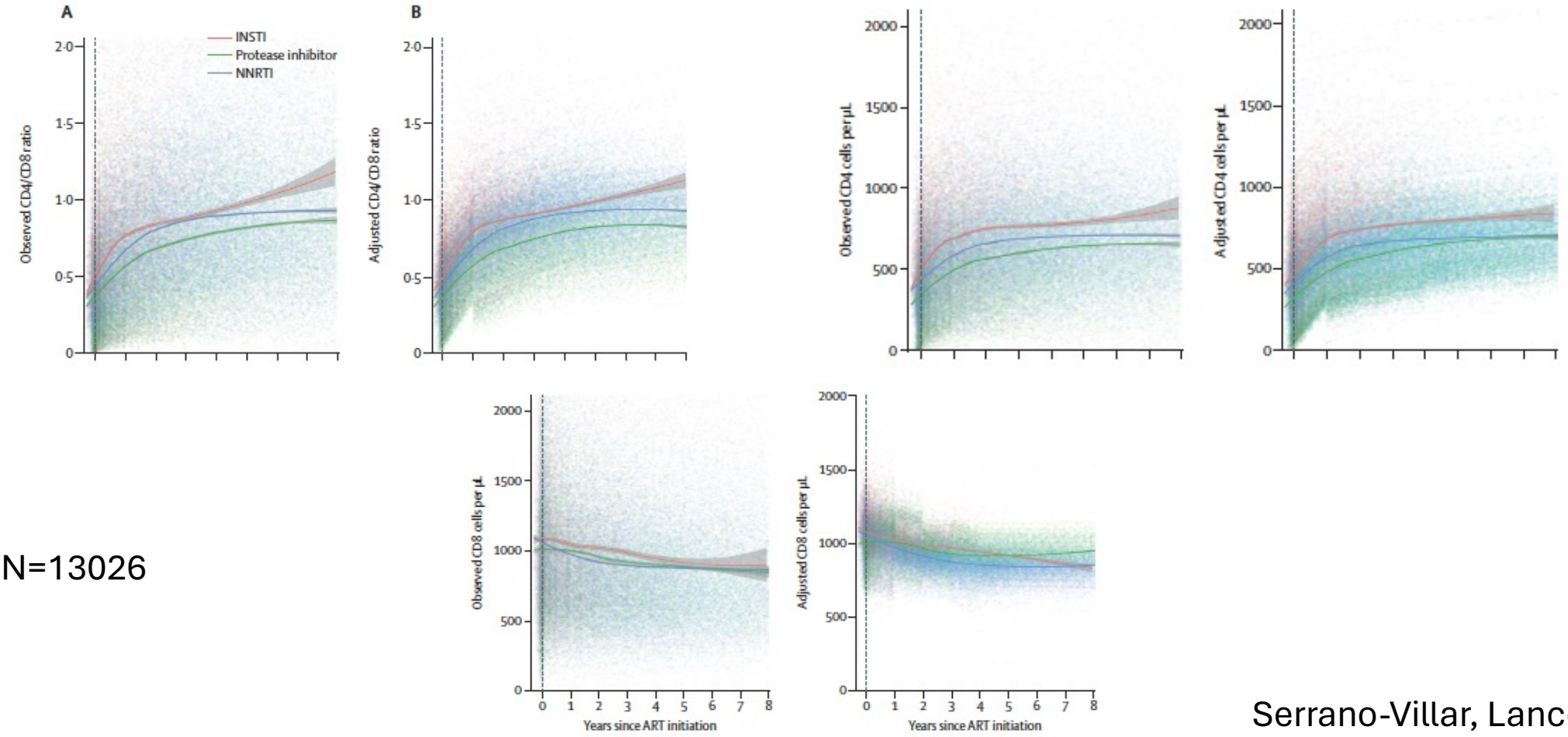
InSTIs	204	113	204	95	111
NNRTIs	479	346	479	336	411
bPIs	143	105	143	81	95

n

InSTIs	205	112	205	96	112
NNRTIs	475	342	475	332	407
bPIs	140	102	140	77	92

Milanes-Guisado, JAC , 2020

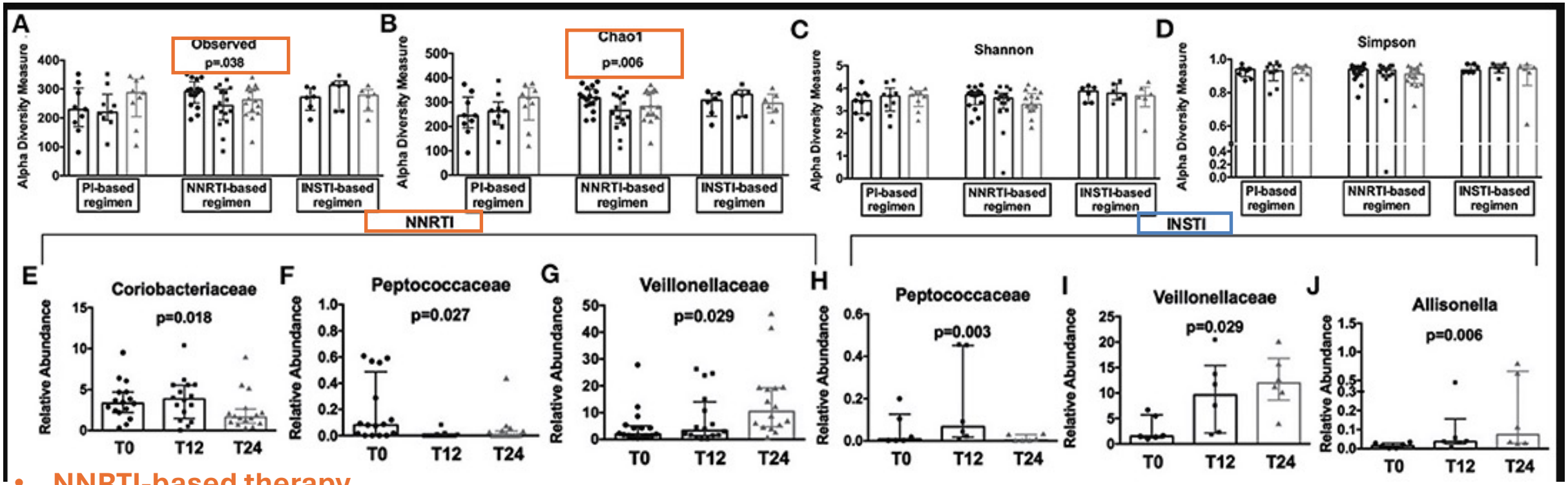
ART initiation with INSTI results in greater CD4/CD8 ratio recovery over time



N=13026

Serrano-Villar, Lancet HIV, 2020

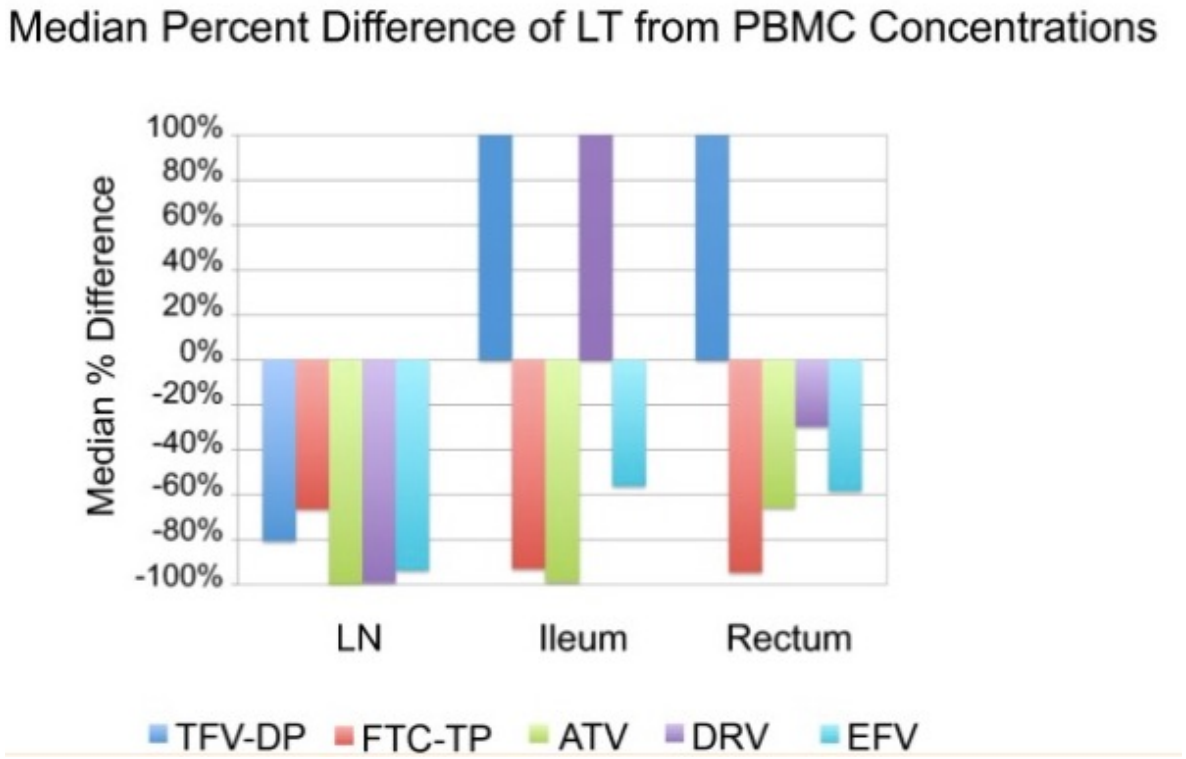
Changes in Fecal Microbiota Composition According to cART Class



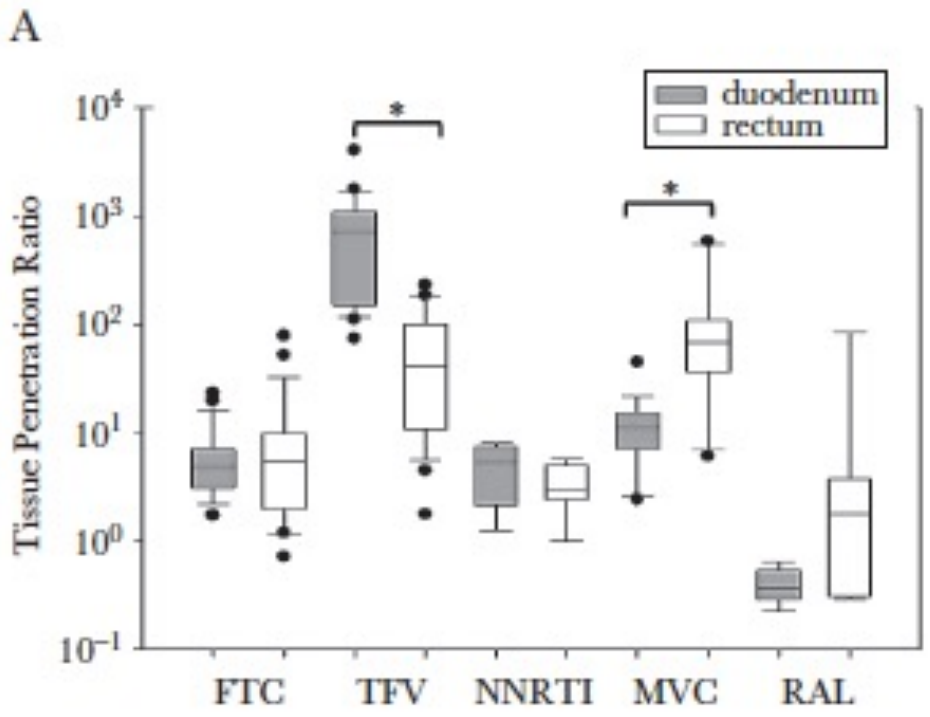
- **NNRTI-based therapy**
- reduced richness but not evenness indexes
- modified relative abundance: reduced Coriobacteriaceae, Peptococcaceae, increased Veillonellaceae
- **INSTI-based therapy**
- modified relative abundance: decreased Peptococcaceae, increased Veillonellaceae and Allisonella genus

Ancona et al. Front Immunol 2021

Possible different penetration of cART drugs in tissues



Fletcher, PNAS, 2013



Asmuth, JID, 2017

No changes in immune/inflammatory markers during switch to 3TC/DTG or 3TC+DRVc vs triple cART

Table 2
Evolution of immune activation, inflammation, and HIV reservoir parameters over follow up in patients with INSTI + 2 NRTIs, DTG/3TC, and DRVc/3TC of ITT population

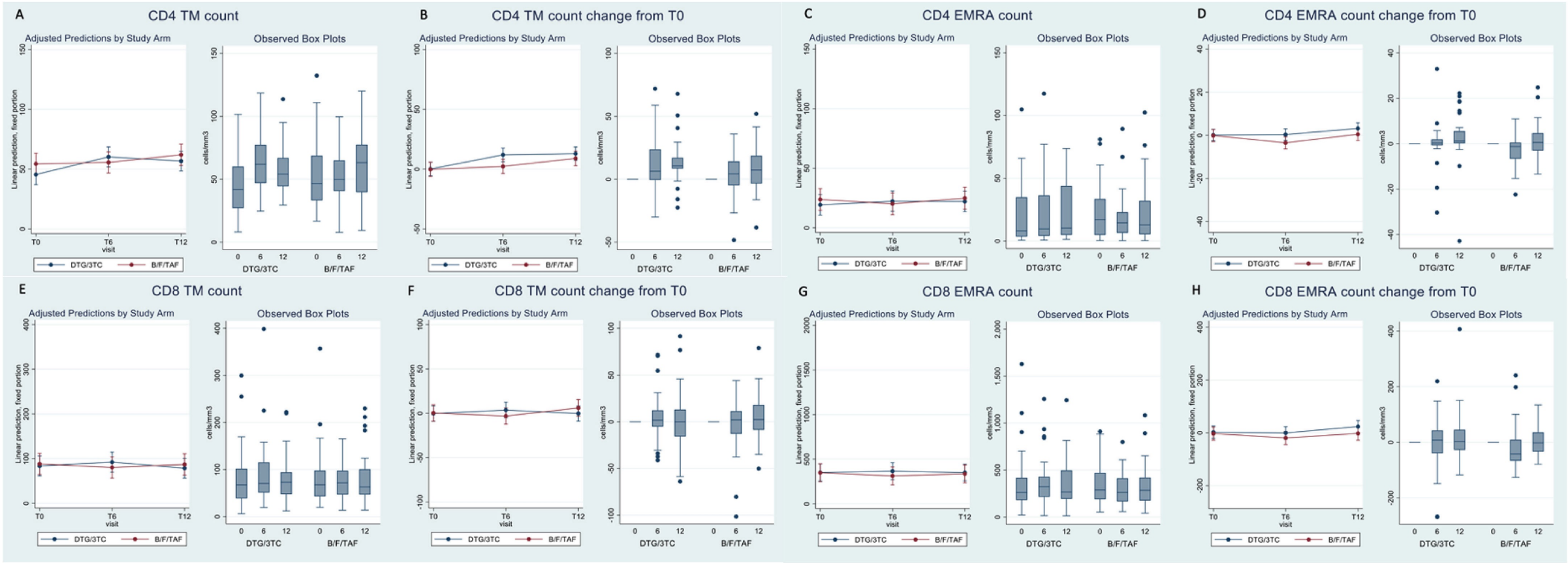
	INSTI + 2 NRTIs			DTG/3TC		DRVc/3TC				[a] p	[b] p
	Basal ($n = 53$)	Week 48 ($n = 51$)	Week 96 ($n = 49$)	Basal ($n = 50$)	Week 48 ($n = 48$)	Week 96 ($n = 47$)	Basal ($n = 48$)	Week 48 ($n = 44$)	Week 96 ($n = 41$)		
$CD4^+/CD8^+$ ratio	1.0 (0.7–1.4)	1.1 (0.7–1.6)	1.1 (0.8-1.6)	0.9 (0.6–1.1)	1.0 (0.7–1.3)	0.9 (0.6–1.2)	0.8 (0.6–1.2)	1.1 (0.8–1.3)	1.0 (0.7–1.3)	0.414	0.218
$CD4^+$ T cells											
HLA-DR^+CD38^+ (%)	1.2 (1.0–1.8)	1.2 (0.9–1.7)	1.1 (0.6–1.9)	1.5 (1.1–1.8)	1.4 (1.1–2.4)	1.5 (1.0–2.4)	1.7 (1.2–2.2)	1.4 (1.2–2.0)	1.7 (1.0–2.9)	0.086	0.333
$KI67^+$ (%)	0.7 (0.5–1.2)	0.9 (0.6–1.4)	1.2 (0.8–2.3)	0.8 (0.6–1.3)	0.9 (0.6–1.5)	1.7 (1.2–2.6)	0.9 (0.5–1.5)	0.9 (0.6–1.1)	2.0 (1.2–2.5)	0.307	0.446
$PD\text{-}1^+$ (%)	7.1 (5.0–12.7)	6.7 (4.4–9.9)	9.2 (5.9–17.3)	8.7 (6.8–12.9)	6.8 (5.2–10.9)	12.9 (6.4–18.2)	7.2 (5.4–11.9)	5.8 (4.1–8.3)	10.5 (5.5–15.8)	0.605	0.314
$CD28^-CD57^+$ (%)	5.6 (1.8–12.1)	6.8 (2.8–19.1)	3.4 (1.2–7.5)	3.1 (1.5–8.9)	8.1 (1.4–13.9)	2.6 (1.4–7.8)	4.7 (2.5–8.9)	5.7 (2.9–9.1)	4.9 (2.8–7.4)	0.236	0.863
Annexin V^+ (%)	0.6 (0.4–1.2)	0.9 (0.5–1.5)	2.2 (1.7–2.9)	0.8 (0.5–1.5)	0.9 (0.7–1.5)	2.0 (1.3–2.4)	0.7 (0.4–1.3)	1.2 (0.7–1.6)	2.1 (1.7–2.9)	0.529	0.316
$CD8^+$ T cells											
HLA-DR^+CD38^+ (%)	1.7 (1.1–2.6)	1.4 (0.8–2.2)	1.1 (0.6–2.0)	1.7 (1.0–2.9)	1.5 (0.9–2.4)	1.5 (0.9–2.3)	2.2 (1.6–3.9)	1.5 (1.1–2.5)	1.6 (0.9–2.4)	0.782	0.573
$KI67^+$ (%)	0.7 (0.4–1.0)	0.6 (0.3–0.9)	1.4 (0.9–1.9)	0.6 (0.4–0.9)	0.6 (0.4–0.9)	1.6 (1.0–2.1)	0.7 (0.4–1.0)	0.6 (0.4–0.8)	1.6 (1.4–2.0)	0.471	0.426
$PD\text{-}1^+$ (%)	8.2 (4.3–12.9)	7.9 (4.1–10.6)	13.6 (6.4–19.7)	8.2 (5.1–13.1)	8.0 (4.9–11.1)	12.9 (8.7–18.9)	7.8 (3.9–10.6)	6.2 (3.9–9.9)	9.9 (5.6–16.4)	0.801	0.297
$CD28^-CD57^+$ (%)	41.5 (30.6–51.9)	47.9 (36.1–57.9)	37.5 (24.8–49.7)	39.2 (33.2–46.6)	48.7 (33.5–59.7)	33.9 (25.7–40.9)	40.6 (32.9–51.9)	40.5 (29.5–53.9)	36.7 (28.2–49.6)	0.122	0.874
Annexin V^+ (%)	0.9 (0.7–1.8)	1.0 (0.6–1.7)	2.4 (1.7–2.8)	1.1 (0.7–2.2)	1.0 (0.7–1.7)	2.1 (1.4–2.6)	0.9 (0.5–1.6)	1.1 (0.8–1.6)	2.2 (1.5–2.7)	0.071	0.525
β2 microglobulin (mg/L)	1.9 (1.7–2.2)	1.9 (1.7–2.2)	2.0 (1.8–2.3)	1.9 (1.7–2.3)	1.9 (1.7–2.3)	2.0 (1.7–2.3)	2.1 (1.8–2.3)	1.9 (1.8–2.2)	2.1 (1.8–2.4)	0.886	0.744
sCD14 (μg/mL)	2.7 (1.9–3.6)	2.5 (1.7–3.5)	1.5 (1.3–1.9)	3.0 (2.1–3.6)	2.3 (1.6–3.5)	1.5 (1.2–1.8)	2.7 (1.8–3.6)	2.2 (1.8–3.1)	1.7 (1.2–1.9)	0.832	0.506
hsCRP (mg/L)	1.8 (0.9–3.6)	1.9 (0.9–3.9)	1.3 (0.7–3.2)	1.1 (0.7–2.9)	1.2 (0.7–2.0)	1.2 (0.6–3.4)	1.3 (0.7–2.6)	1.2 (0.7–1.9)	1.7 (0.9–2.9)	0.468	0.438
IL-6 (pg/mL)	1.7 (1.3–2.3)	1.7 (1.1–2.8)	2.5 (1.6–3.9)	1.9 (1.2–2.7)	1.9 (1.2–3.3)	2.5 (1.6–4.7)	1.7 (1.1–2.9)	1.7 (1.3–2.9)	2.5 (1.7–4.7)	0.390	0.982
TNF-α (pg/mL)	0.9 (0.6–1.2)	0.9 (0.6–1.3)	0.7 (0.6–0.9)	0.8 (0.7–1.2)	0.9 (0.7–1.2)	0.8 (0.6–1.1)	0.9 (0.8–1.2)	0.9 (0.8–1.2)	0.8 (0.7–1.2)	0.535	0.988
IP-10 (pg/mL)	81.4 (56.4–126.4)	76.2 (57.0–113.5)	77.2 (54.7–90.6)	81.2 (55.9–114.5)	86.3 (55.3–113.5)	80.3 (57.5–110.3)	100.7 (73.3–134.4)	94.1 (51.8–136.5)	81.7 (60.1–112.9)	0.553	0.195
D-Dimers (μg/L)	255.0 (200.0-372.5)	225.0 (170.0-305.0)	240.0 (185.0-305.0)	280.0 (220.0-350.0)	220.0 (170.0–370.0)	270.0 (220.0–382.5)	260.0 (205.0–367.5)	245.0 (170.0–347.5)	220.0 (190.0–295.0)	0.915	0.161
HIV-DNA $\log_{10}$ copies $/10^6$ PBMC	2.6 (2.3–3.0)	2.6 (2.4–2.9)	2.4 (2.3–2.6)	2.6 (2.4–2.9)	2.7 (2.6–2.9)	2.5 (2.2-2.7)	2.6 (2.4-2.9)	2.6 (2.3–2.9)	2.5 (2.2–2.9)	0.715	0.659
usHIV-RNA $\log_{10}$ copies $/10^6$ TBP	2.8 (2.5–3.1)	2.9 (2.6–3.3)	3.1 (2.8–3.6)	2.9 (2.7–3.3)	3.0 (2.7–3.2)	3.3 (3.0–3.6)	3.0 (2.4–3.3)	3.0 (2.5–3.5)	3.2 (2.6–3.7)	0.204	0.223

Data are expressed as median (IQR). INSTI, integrase inhibitor; NRTIs, nucleos(t)ide reverse transcriptase inhibitor; DTG, dolutegravir; 3TC, lamivudine; DRVc, darunavir/cobicistat.
[a] p value for differences between baseline and week 48 among TT, DTG/3TC, and DRVc/3TC treatment arms.
[b] p value for differences between baseline and week 96 among TT, DTG/3TC, and DRVc/3TC treatment arms.

Trujillo-Rodriguez, CMI, 2022

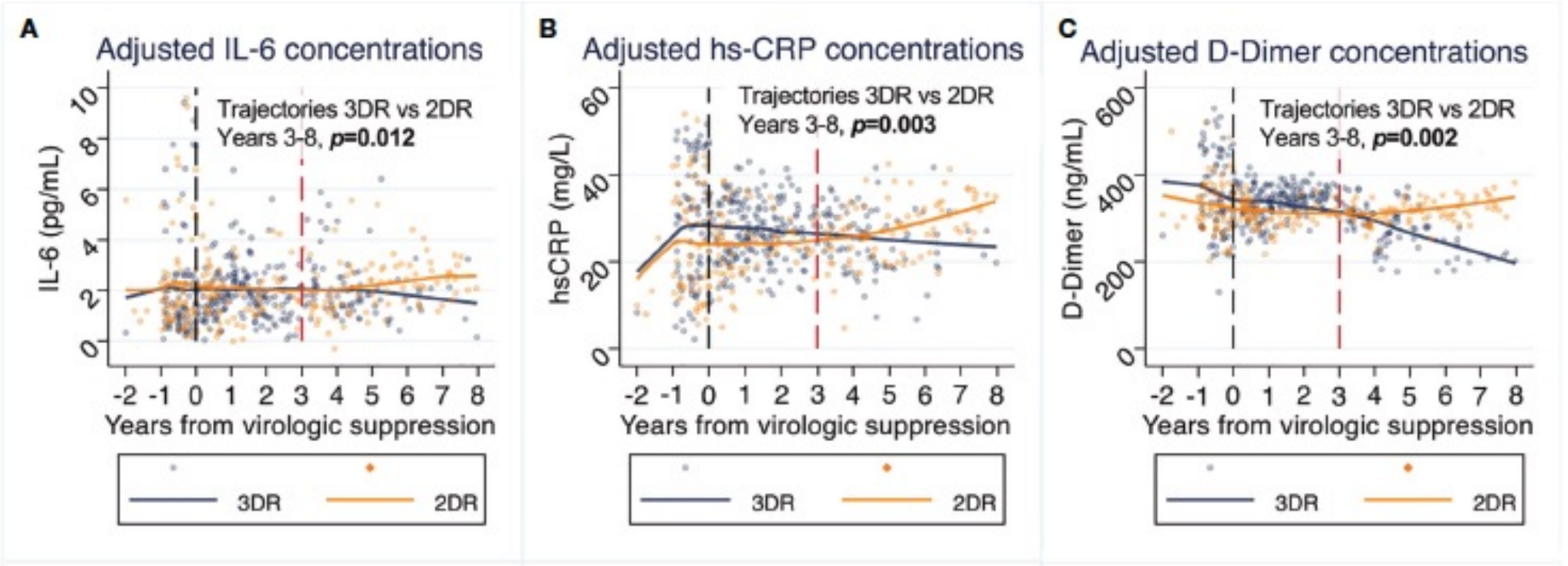
No major immune changes in 2DR vs 3DR

DEBATE: Open-label, prospective RCT enrolling PLWH receiving a 3DR who switched to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) or dolutegravir/lamivudine (DTG/3TC) was



Cossarizza et al, Front Immunol 2023

Higher inflammatory markers during switch to 2DR vs 3DR



N=148

- 3DR, N=90;
- 2DR, N=58

2DR:

- 3TC+bPI (15)
- 3TC+DTG (7)
- DTG+RPV (36)

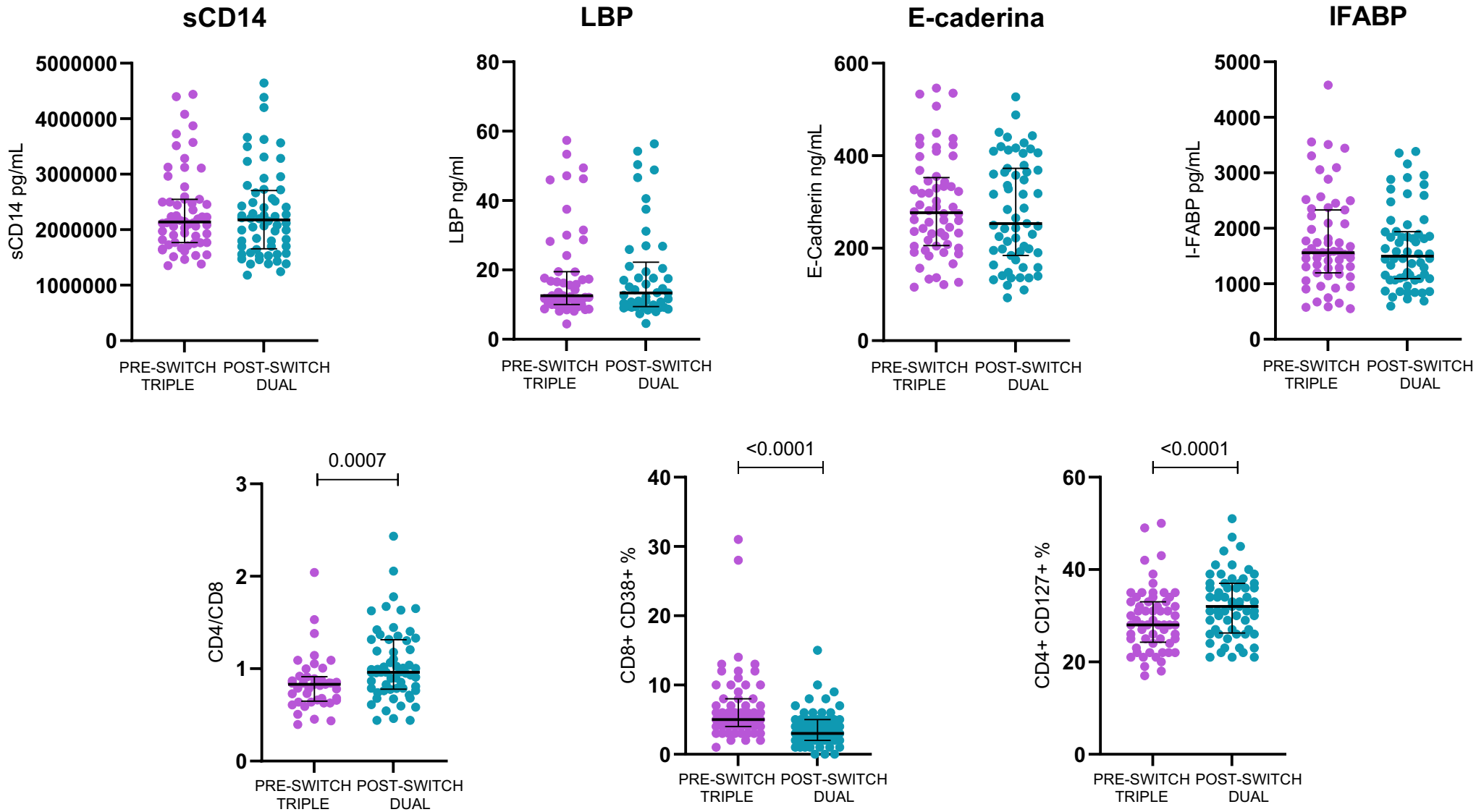
Serrano-Villar, Front Immunol, 2022

Study population

	PRE-SWITCH TRIPLE (n=60)
Age, years, median (IQR)	48 (42-58)
Sex, n (%)	
Male	50 (83.33%)
Female	10 (16.66%)
Ethnicity, n (%)	
Caucasian	55 (91.66%)
Asian	2 (3.33%)
Hispanic	3 (5%)
Risk factors for HIV infection, n (%)	
MSM	40 (66.66%)
Eterosexual	17 (28.33%)
IDU	3 (5%)
BMI, median (IQR)	25 (23-26.7)
Smokers, n (%)	20 (33.33%)
Alcohol use, n (%)	47 (78.33%)
Comorbidities	
History of cardiovascular diseases, n (%) (Dyslipidemia, HTA, Previous IMA, NAFLD ecc.)	20 (33.33%)
History of cancer, n(%)	19 (31.66%)
HBsAg (previous or vaccinated), n (%)	29 (48.33%)
Co-infection HCV, n (%)	4 (6.66%)
Time since HIV diagnosis (years), median (IQR)	14 (10-18)
Time from diagnosis to cART start (months), median (IQR)	0 (0-4)
Time on HAART (years), median (IQR)	13 (10-18)
Time from switch (months), median (IQR)	11 (8-14.7)
CD4 cell count nadir (cells/mm3), median (IQR)	275 (182.5-407.5)
HIV RNA (copie/mL) pre-switch, median (IQR)	0 (0-0)
Total time with viral load <50cps/mL (years), median (IQR)	9 (7-9)
Time since last viral load ⩾50cps/mL (years), median (IQR)	9 (7-9)
Previous virological failure, n (%)	1 (1.66%)
Past AIDS-defining events (CDC C), n (%)	9 (15%)
Number of cART lines prior to switch, n (%)	
0	1 (1.66%)
1	16 (26.66%)
2	20 (33.33%)
3	10 (16.66%)
4	8 (13.33%)
5	1 (1.66%)
6	1 (1.66%)
8	1 (1.66%)
Type of 3DR /Anchor drug in the triple therapy, n (%)	
INSTI-based	41 (68.33%)
NNRTI-based	14 (23.33%)
PI-based	4 (6.66)
INSTI + PI-based	1 (1.66%)

Bono et al., preliminary results (abstract in preparation for Glasgow 2024)

Stable microbial translocation, yet improved T-cell homeostasis in individuals switching froma triple to dual cART



Bono et al., preliminary results (abstract in preparation for Glasgow 2024)

SC 43

Modulation of Cytomegalovirus (CMV) T cells response in PLWH after switching to long-acting (LA) cabotegravir plus rilpivirine

ROMA 19-21 GIUGNO
UNIVERSITA' CATTOLICA DEL SACRO CUORE CENTRO CONGRESSI EUROPA
16° CONGRESSO NAZIONALE ICAR Italian Conference on AIDS and Antiviral Research

Authors

M. Guardiani[1], E. Tortellini[1], A. Carraro[1], M.A. Zingaropoli[1], F. Dominelli[1], C. Falvino[1], S. Garattini[1], P. Zuccalà[2], R. Marocco[2], G. Mancarella[2], F. Mengoni[1], O. Turriziani[3], V. Vullo[1], C.M. Mastroianni[1], C. Del Borgo[2], M. Lichtner[2,4]

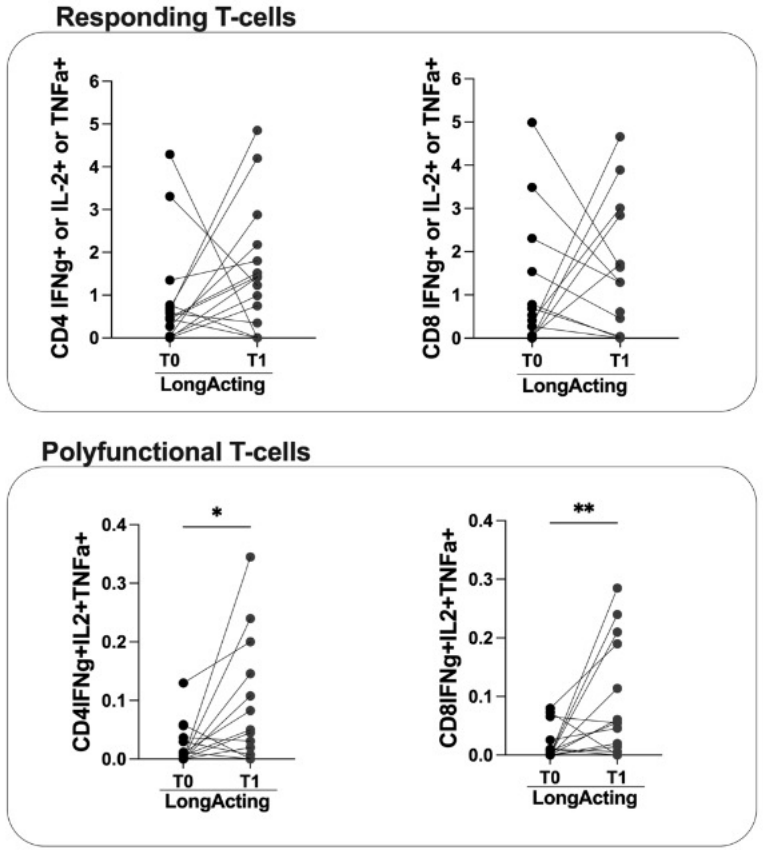
Affiliation

[1]Sapienza University of Rome, Department of Public Health and Infectious Diseases, Rome, Italy, [2]Sapienza University of Rome, Infectious Diseases Unit, SM Goretti Hospital, Latina, Italy, [3]Sapienza University of Rome, Laboratory of Virology, Department of Molecular Medicine, Rome, Italy, [4]Sapienza University of Rome, Department of Neurosciences, Mental Health, and Sense Organs, NESMOS, Rome, Italy

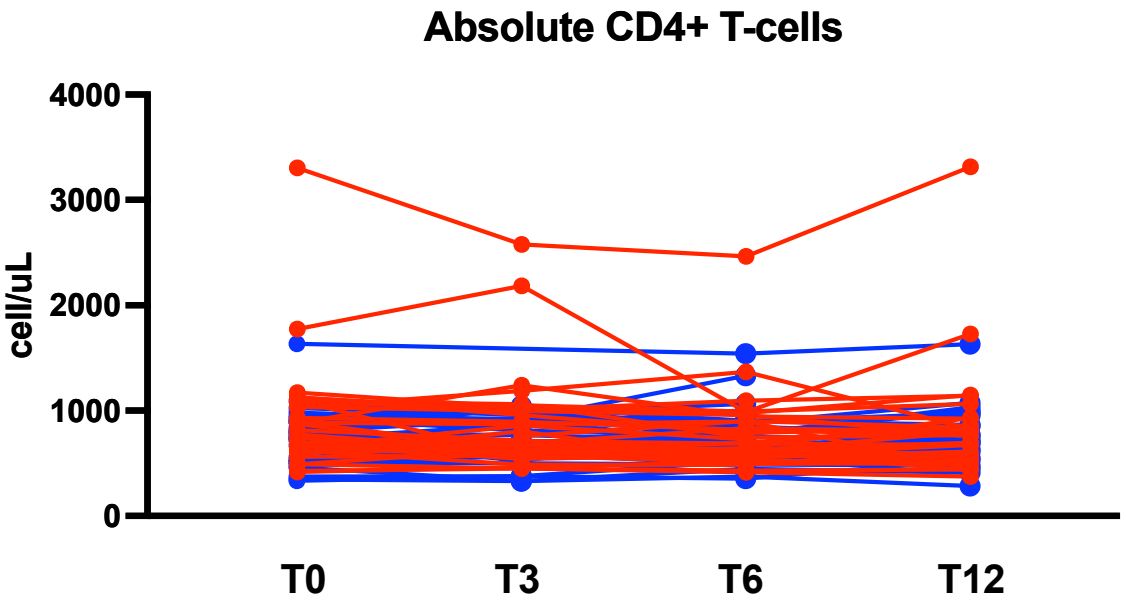
Table1: Clinical Findings

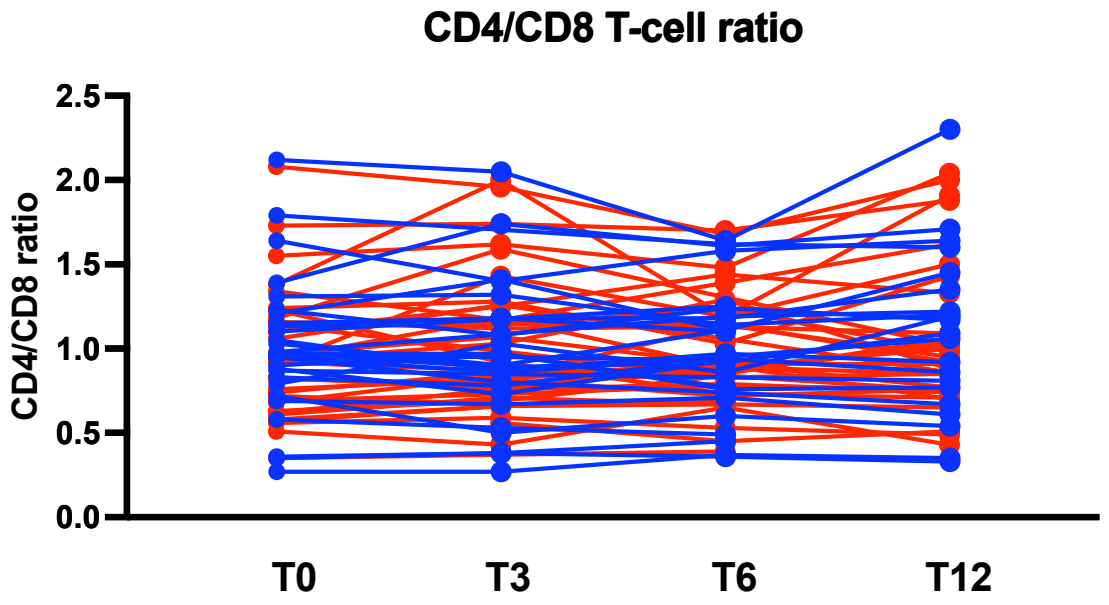
	PLWH-Long Acting		
Number	32		
Age, median (IQR) years	49(35-56)		
Male/Female	23/9		
Time elapsed from diagnosis median (IQR) years	12(5-20)		
Current CD4 cell count (cells/µl)	806.5(705.3-978.8)		
CD4+ cell count nadir, (cells/µl)	248.5(181.3-366.8)		
HIV-RNA zenith (cp/ml)	95720(10000-394823)		
HIV-RNA (cp/mL)	nr(100%)		
CD4 cell count, cells/mm³ (CD4 cell percentage)	**CDC classification (number of PLWH)(%)** **A[a]**	**B[B]**	**C[c]**
>500 (>29%)	A1(2/23) (8%)	B1 (1/23) (3%)	C1 (1/23) (3%)
200-500 (14%-28%)	A2 (6/23) (26%)	B2 (4/23)(17%)	C2(-/23)
<200(14%)	A3 (-/23)	B3 (4/23) (17%)	C3 (4/23)(17%)
ART			
Dual (%)	10/32(32%)		
Non-Dual (%)	22/32(68%)		
Comorbidities			
Any (%)	15/26(57%)		
More than one (%)	11/26(43%)		
CMV serostatus			
anti-CMV IgG positive (%)	29/32(90%)		
Smoke status			
No (%)	16/28(57%)		
Yes (%)	12/28(43%)		

Figure 2: Longitudinal evaluation of CD4 and CD8 T-cells



T-cell counts





switch to LAI from dual (n=44)

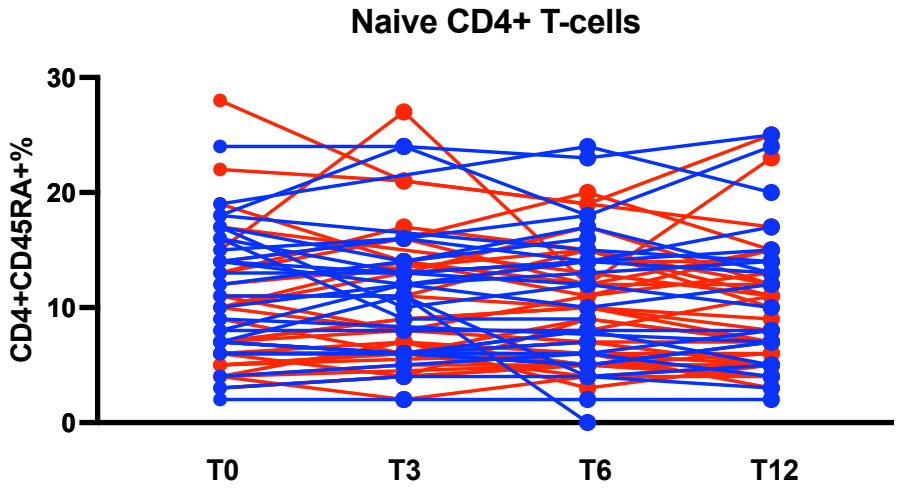
switch to LAI from triple (n=42)

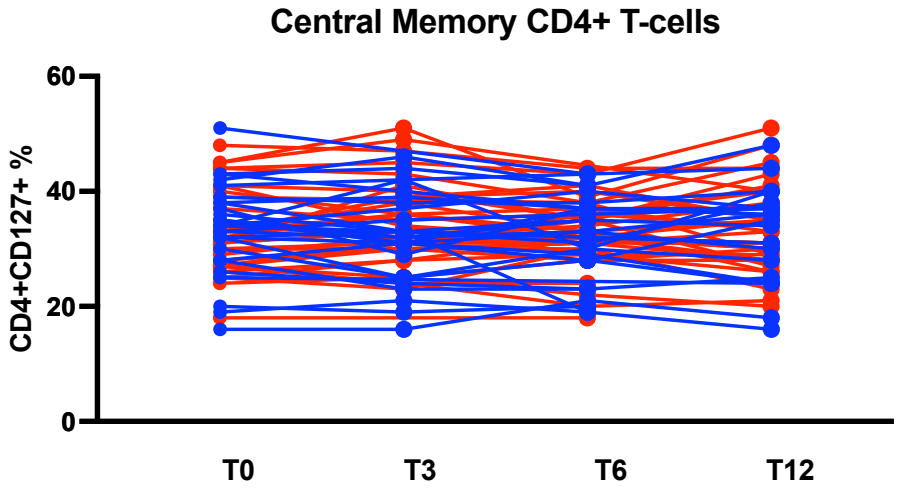
Rezzonico et al., preliminary results (abstract in preparation for Glasgow 2024)

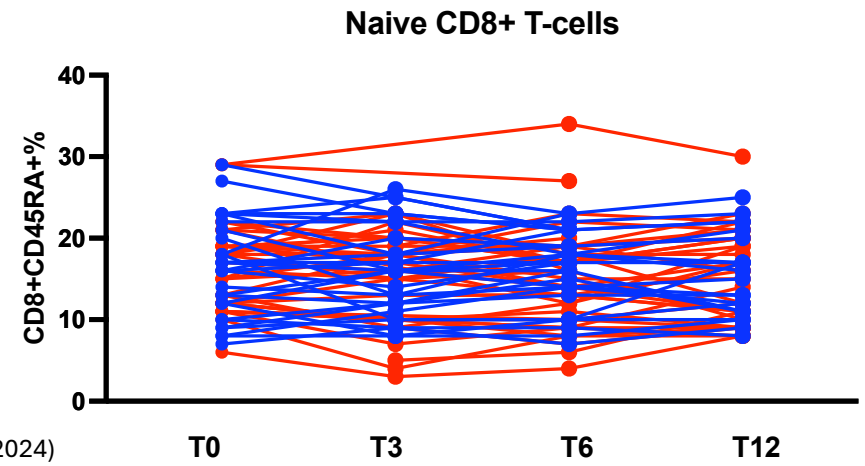
T-cell homeostasis

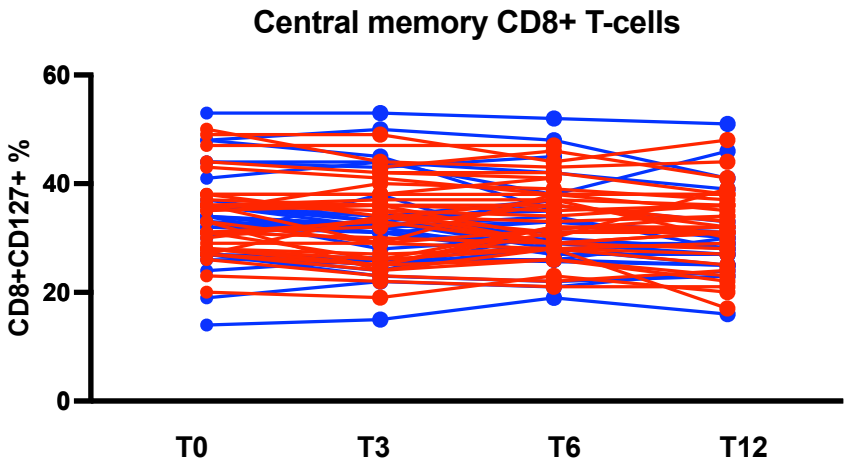
switch to LAI from dual (n=44)

switch to LAI from triple (n=42)







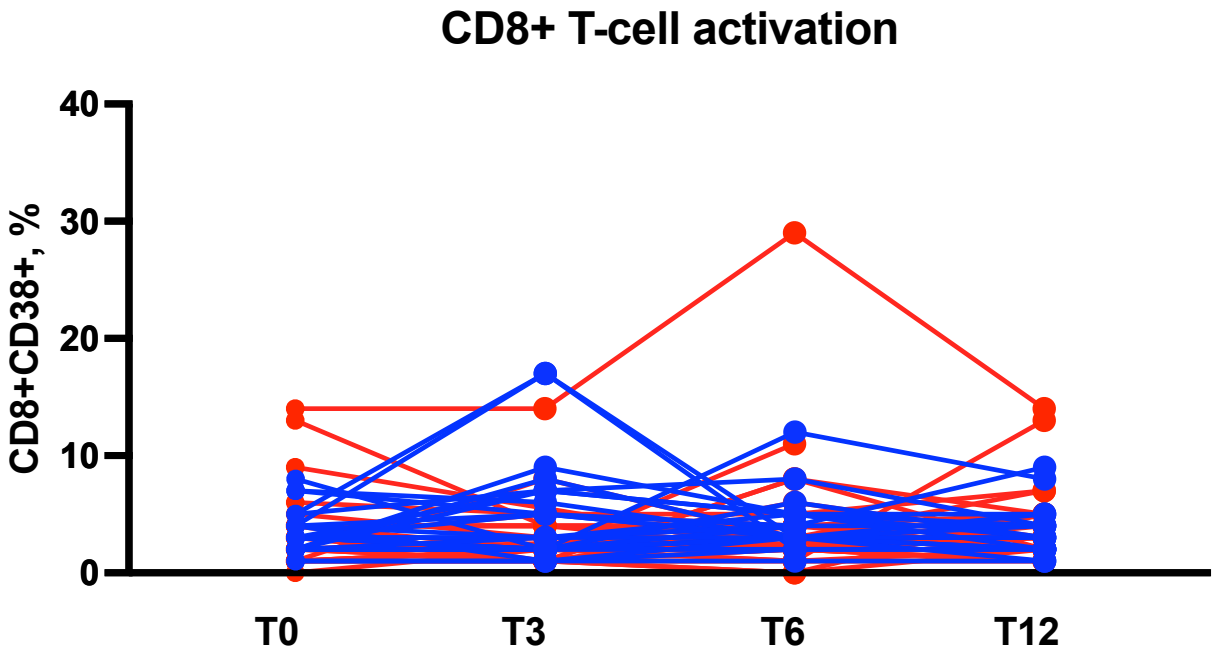


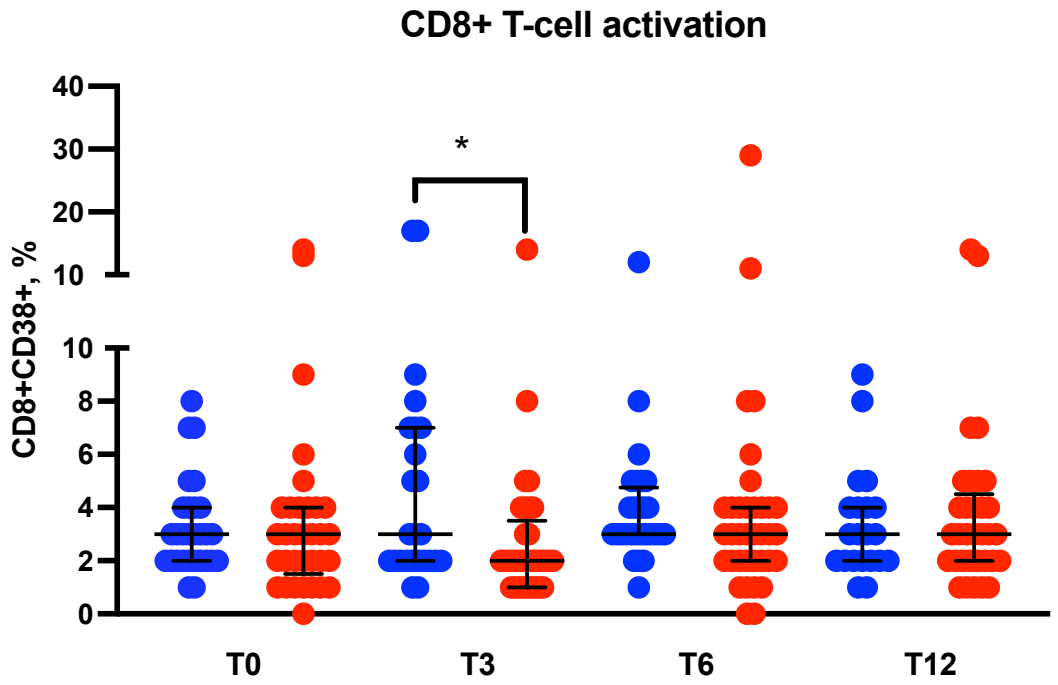
Rezzonico et al., preliminary results
(abstract in preparation for Glasgow 2024)

CD8+ T-cell activation

switch to LAI from dual (n=44)

switch to LAI from triple (n=42)





Rezzonico et al., preliminary results (abstract in preparation for Glasgow 2024)

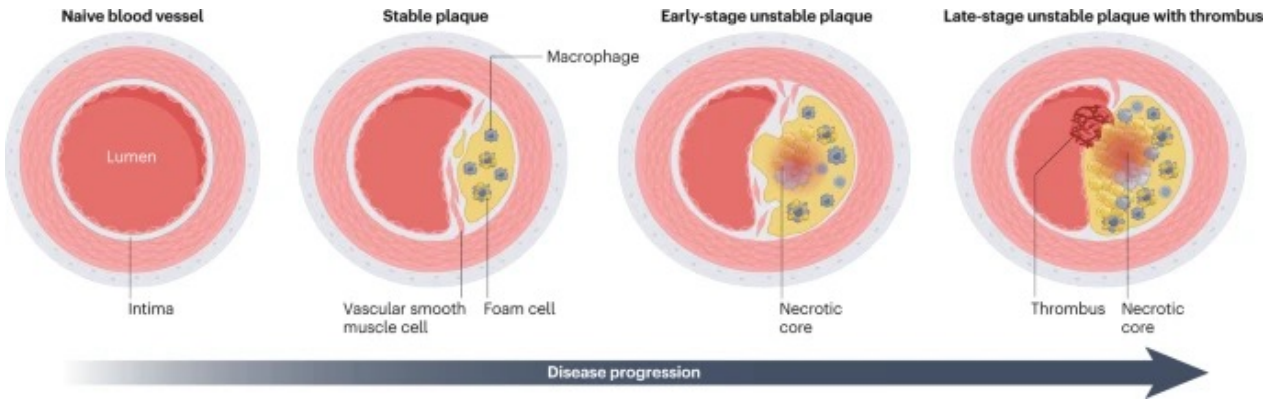
Rationale of the Reprieve Study

- Increased CVD in PLWH

- low- to-moderate traditional risk factors

- unique atherosclerotic phenotype: vulnerable, non-calcified plaque

- Hypothesis: statin could prevent CVD with pleiotropic effects beyond LDL lowering



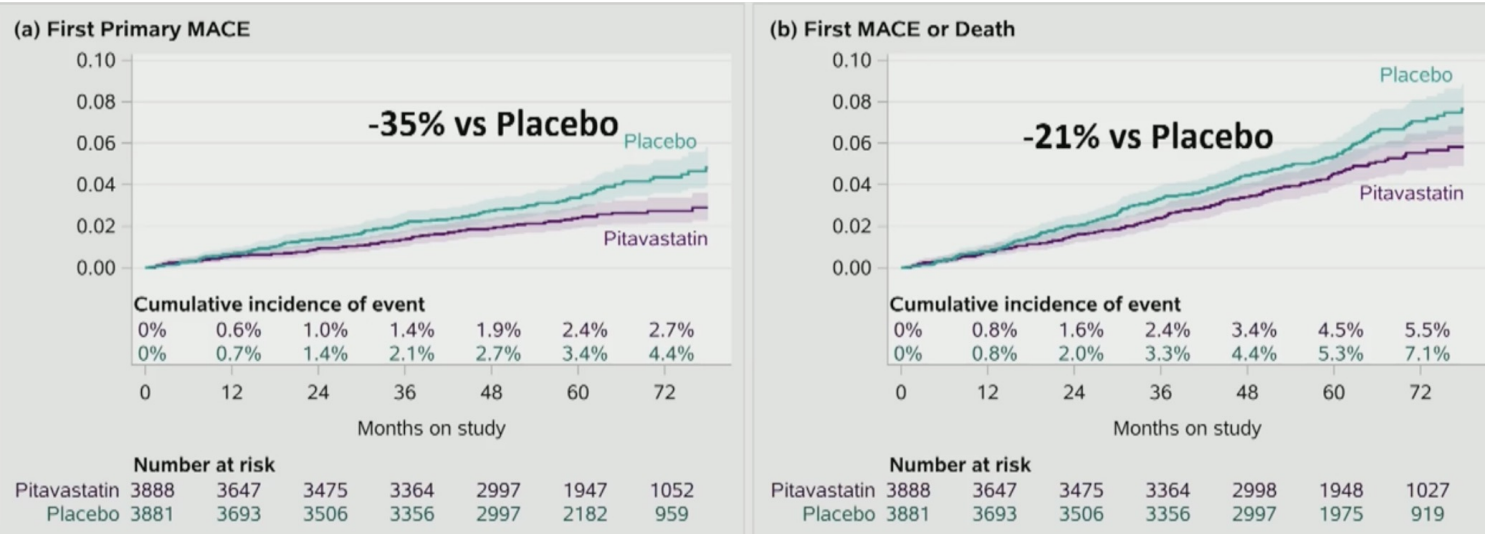
De Meyer, Nat Rev Cardiol, 2024

Primary and Key Secondary Endpoints

- RCT of 7769 participants, age 50, low to moderate Pooled Cohort Equation (PCE*) risk: 4.5%, LDL 108 mg/dL
- Trial stopped early for efficacy (average 5 year duration FU):

- first primary MACE: -35% vs placebo

- first MACE or death: -21% vs placebo



*estimates the risk of ASCVD within a 10-year period among patients who have never had one of these events in the past.

Grinspoon, NEJM, 2023

REPRIEVE in comparison with other key studies: larger effect size

SELECT:
-20%

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

Lincoff AM et al. DOI: 10.1056/NEJMoa2307563

CLINICAL PROBLEM

Glucagon-like peptide-1 (GLP-1) receptor agonists can reduce the risk of adverse cardiovascular events in patients with diabetes. Whether the GLP-1 receptor agonist semaglutide can also reduce cardiovascular risk in patients with overweight or obesity but without diabetes is unknown.

CLINICAL TRIAL

Design: An international, double-blind, event-driven, randomized, placebo-controlled, superiority trial assessed the safety and efficacy of semaglutide in patients with preexisting cardiovascular disease, overweight or obesity (body-mass index, ≥27), and no history of diabetes.

Intervention: 17,604 adults ≥45 years of age were assigned to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo. The primary cardiovascular end point was a composite of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis.

RESULTS

Efficacy: Semaglutide was superior to placebo in reducing the incidence of primary end-point events during a mean follow-up of approximately 40 months.

Safety: More patients discontinued semaglutide than placebo because of adverse events, a result driven largely by a higher incidence of gastrointestinal symptoms with semaglutide.

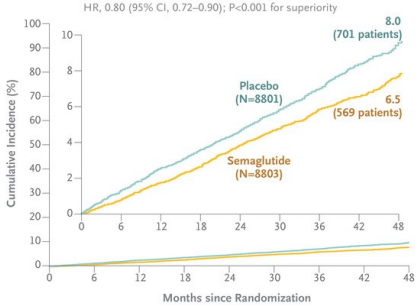
LIMITATIONS AND REMAINING QUESTIONS

- The trial was limited to patients with preexisting cardiovascular disease.
- The diversity of the trial population did not duplicate a globally representative population; specifically, women and patients identifying as Black were underrepresented.

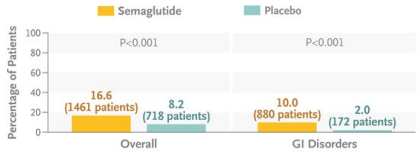
Links: Full Article | NEJM Quick Take | Editorial

Death from Cardiovascular Causes, Nonfatal MI, or Nonfatal Stroke

HR, 0.80 (95% CI, 0.72–0.90); P<0.001 for superiority



Adverse Events Leading to Permanent Discontinuation of Regimen



CONCLUSIONS

In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, once-weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke during a mean follow-up of approximately 40 months.

CANTOS:
-15%

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

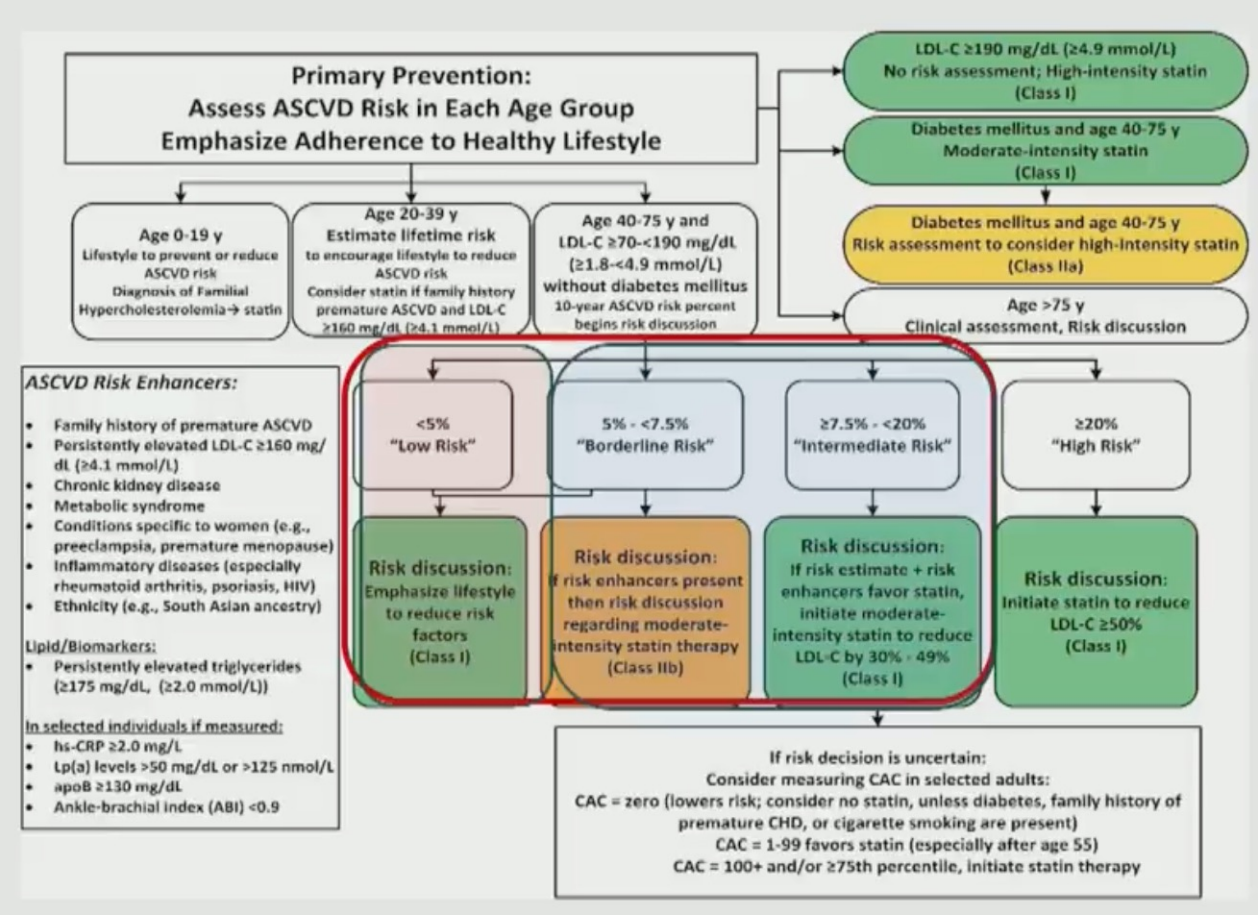
Authors: Paul M Ridker, M.D., Brendan M. Everett, M.D., Tom Thuren, M.D., Jean G. MacFadyen, B.A., William H. Chang, Ph.D., Christie Ballantyne, M.D., Francisco Fonseca, M.D., +21, for the CANTOS Trial Group* Author Info & Affiliations

Published September 21, 2017 | N Engl J Med 2017;377:1119-1131 | DOI: 10.1056/NEJMoa1707914
VOL. 377 NO. 12

CONCLUSIONS

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

DHHS/HIVMA/AHA/ACC Guidelines Expanded 29/2/24* to Include Data from REPRIEVE



AI Recommendation
Pitava 4 mg/d

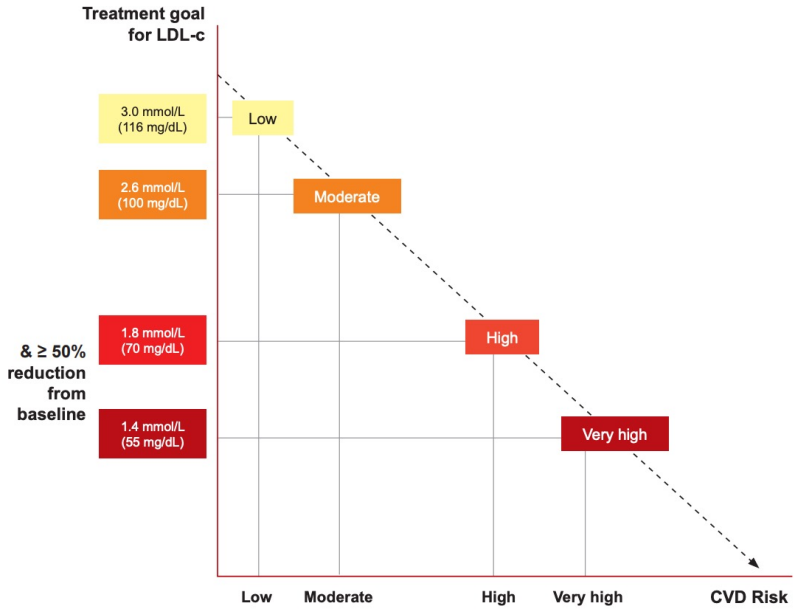
All Recommendation
Rosuva 10 mg/d
Atorva 20 mg/d

C1 Recommendation

*Before: unclear what to do between 5% and 20%

EACS 2023: statins should be used by all those with established vascular disease and in persons who are not at LDL-c goals considering their level of CVD risk, irrespective of lipid levels

Treatment Goals for LDL-c to Reduce Cardiovascular Risk Depending on CV Risk Estimation*



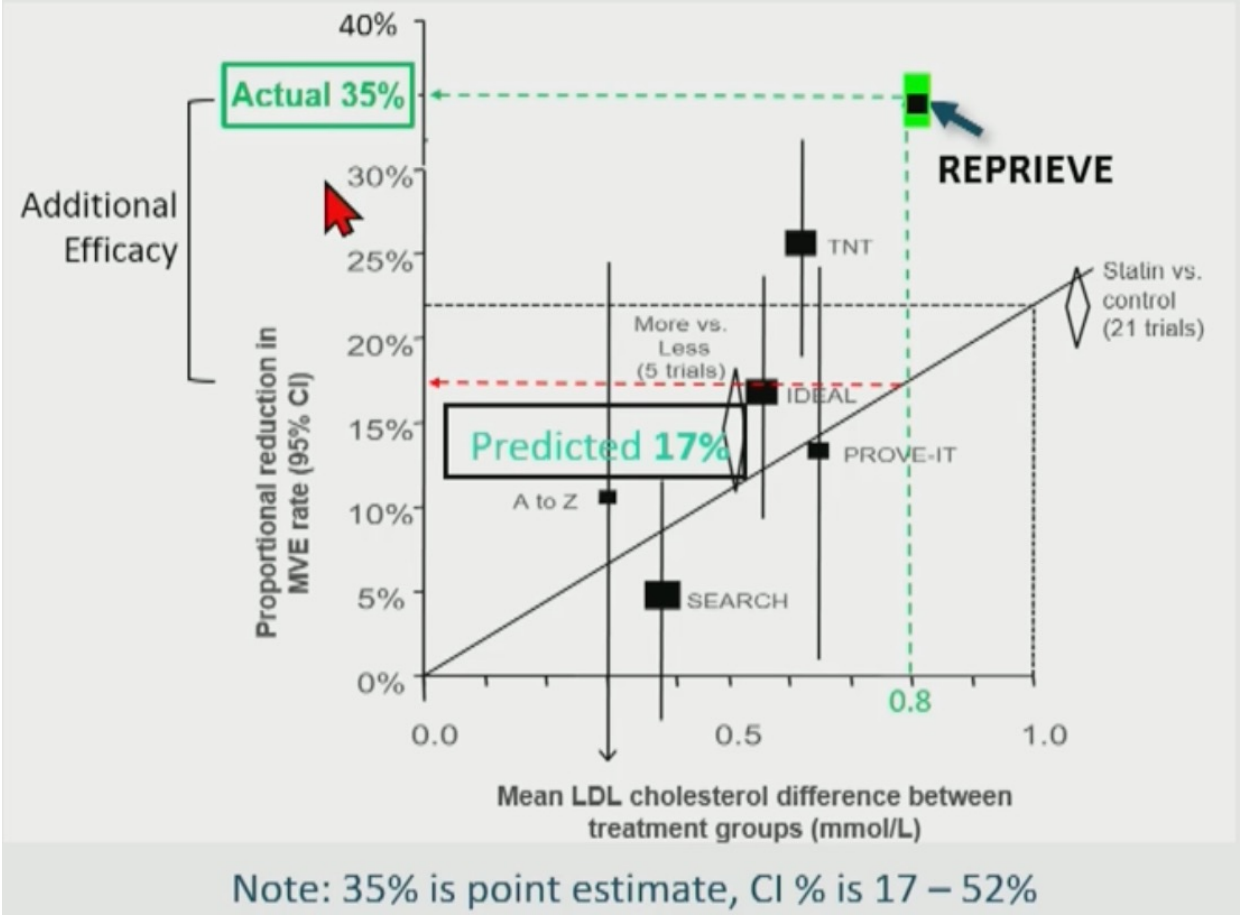
Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering*
Adapted from: 2019 ESC/EAS Guidelines for the management of dyslipidaemia: lipid modification to reduce cardiovascular risk. Eur Heart J 2020 Jan 1;41(1):111-188.

Drugs used to reduce cardiovascular risk by lowering LDL-c and triglycerides

Drug class	Drug	Dose	Adverse effects	Advice on use of lipid lowering therapy together with ART	
				use with PI/r	use with NNRTIs
Statin[i,viii]	Atorvastatin[ii]	10-80 mg qd	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Start with low dose[v] (max daily dose: 10 mg (ATV/r); 20 mg (LPV/r); 40 mg (DRV/r)	Consider higher dose[vi]
	Fluvastatin[iii]	20-80 mg qd		Consider higher dose[vi]	Consider higher dose[vi]
	Pravastatin[iii]	20-80 mg qd		Consider higher dose[vi,vii]	Consider higher dose[vi]
	Rosuvastatin[ii]	5-40 mg qd		Start with low dose[v] (max daily dose: 10 mg (ATV/r, LPV/r) 20 mg (DRV/r)	Start with low dose[v]
	Simvastatin[ii]	10-40 mg qd		Contraindicated	
	Pitavastatin[viii]	1-4 mg qd		No interaction expected	
Adenosine triphosphate citrate lyase inhibitor*	Bempedoic acid	180 mg qd	Gout, cholelithiasis	No interaction expected. Contraindicated with simvastatin > 40mg qd	
Intestinal cholesterol absorption inhibitor↓[i,ix]	Ezetimibe[iv]	10 mg qd	Gastrointestinal symptoms	No interaction expected	
PCSK9-inhibitors[x] Monoclonal antibodies	Evolocumab	140 mg 2 weekly or 420 mg monthly	Nil	No interaction expected	
	Alirocumab	75 mg or 150 mg 2 weekly or 300 mg monthly			
Fish oil, Omega-3	Icosapent ethyl[xi]	2 g bid	Atrial fibrillation, bleeding	No interaction expected	

Why was the study intervention in REPRIEVE so effective?

Effect Larger than Anticipated (17%) Based on Lowering LDL



In other words: LDL lowering matters but statin effect is beyond what is expected for LDL lowering alone

CTT collaborative;
Lancet, 2010; 376: 1670-1681

Mechanicistic study embedded in REPRIEVE

Designed to determine:

- potential statin effects to reduce noncalcified plaque volume and progression as assessed by entry and 2-year coronary computed tomography angiography (CTA)

- effects on lipid parameters and circulating biomarkers of inflammation: LDL and non–high-density lipoprotein cholesterol, hsCRP, LpPLA2, oxLDL, monocyte chemoattractant protein 1, IL-6, IL-10, IL-1β, IL-18, soluble CD14, and soluble CD163

Lu, JAMA Cardiology, 2024

Table 3. Distributions of Inflammatory and Immune Biomarkers at Entry and Month 24

Measure[a]	Median (IQR)				
	Entry		Month 24		
	Pitavastatin (n = 402)	Placebo (n = 402)	Pitavastatin (n = 349)	Placebo (n = 350)	P value
Inflammatory markers					
LpPLA2					
Total, No.	398	391	335	333	NA
LpPLA2 level, ng/mL	126 (94.8-169)	131 (89.6-163)	119 (84.0-160)	143 (105-186)	<.001
Change from baseline	NA	NA	−9.77 (−33.6 to 16.8)	19.9 (−5.6 to 43.0)	<.001
Mean fold change (95% CI)	NA	NA	0.93 (0.89-0.96)	1.14 (1.10-1.18)	NA
oxLDL					
Total, No.	398	392	335	333	NA
oxLDL level, U/L	53.0 (42.2-69.8)	53.6 (41.7-69.9)	37.6 (30.0-47.3)	48.2 (38.9-58.4)	<.001
Change from baseline	NA	NA	−14.9 (−28.9 to −3.93)	−6.45 (−20.2 to 5.26)	<.001
Mean fold change (95% CI)	NA	NA	0.71 (0.68-0.74)	0.87 (0.83-0.91)	NA
hsCRP[b]					
Total, No.	397	391	343	335	NA
hsCRP level, mg/dL	0.18 (0.08-0.39)	0.18 (0.09-0.33)	0.17 (0.07-0.36)	0.19 (0.10-0.40)	.02
Change from baseline	NA	NA	−0.01 (−0.10 to 0.08)	0.01 (−0.09 to 0.11)	.09
Mean fold change (95% CI)	NA	NA	0.89 (0.79-1.01)	1.06 (0.94-1.20)	NA
Immune markers					
MCP-1					
Total, No.	398	390	335	330	NA
MCP-1 level, pg/mL	189 (148-245)	183 (144-238)	192 (157-235)	193 (154-247)	.77
Change from baseline	NA	NA	2.11 (−37.8 to 47.5)	3.91 (−33.3 to 53.2)	.46
Mean fold change (95% CI)	NA	NA	1.02 (0.98-1.06)	1.05 (1.01-1.09)	NA
Soluble CD14					
Total, No.	398	392	335	333	NA
Soluble CD14 level, ng/mL	1840 (1544-2176)	1810 (1496-2200)	1541 (1284-1809)	1534 (1324-1850)	.52
Change from baseline	NA	NA	−289 (−588 to −5.08)	−237 (−528 to 36.1)	.54
Mean fold change (95% CI)	NA	NA	0.83 (0.81-0.86)	0.86 (0.83-0.88)	NA
Soluble CD163					
Total, No.	398	391	335	333	NA
Soluble CD163 level, ng/mL	849 (651-1163)	845 (613-1074)	1013 (728-1419)	1003 (745-1384)	.65
Change from baseline	NA	NA	149 (−60.8 to 420)	143 (−46.0 to 453)	.88
Mean fold change (95% CI)	NA	NA	1.21 (1.16-1.27)	1.23 (1.18-1.29)	NA
IL-6					
Total, No.	398	391	335	333	NA
IL-6 level, pg/mL	1.64 (0.99-2.76)	1.46 (0.98-2.59)	1.64 (0.99-2.73)	1.53 (0.93-2.62)	.24
Change from baseline	NA	NA	0 (−0.95 to 0.77)	−0.12 (−0.81 to 0.59)	.46
Mean fold change (95% CI)	NA	NA	0.98 (0.89-1.08)	0.94 (0.86-1.03)	NA
IL-1β					
Total, No.	377	375	320	320	NA
IL-1β level, fg/mL	75.9 (43.9-151)	87.0 (44.9-168)	88.6 (50.2-164)	96.4 (52.6-191)	.09
Change from baseline	NA	NA	2.01 (−41.4 to 58.1)	11.4 (−28.9 to 69.2)	.06
Mean fold change (95% CI)	NA	NA	1.05 (0.93-1.17)	1.19 (1.07-1.33)	NA
IL-18					
Total, No.	377	375	320	320	NA
IL-18 level, pg/mL	245 (179-330)	232 (169-310)	236 (169-310)	230 (176-308)	.79
Change from baseline	NA	NA	−8.53 (−48.2 to 35.3)	−3.77 (−43.3 to 44.1)	.26
Mean fold change (95% CI)	NA	NA	0.96 (0.92-1.00)	1.01 (0.97-1.04)	NA
IL-10					
Total, No.	363	353	305	300	NA
IL-10 level, pg/mL	0.24 (0.17-0.37)	0.22 (0.16-0.35)	0.21 (0.15-0.34)	0.22 (0.16-0.33)	.53
Change from baseline	NA	NA	−0.02 (−0.12 to 0.06)	0 (−0.09 to 0.09)	.08
Mean fold change (95% CI)	NA	NA	0.96 (0.87-1.05)	0.99 (0.91-1.07)	NA
Caspase-1					
Total, No.	377	375	320	320	NA
Caspase-1 level, pg/mL	66.6 (47.0-93.8)	69.6 (50.1-107)	69.6 (48.6-102)	74.2 (52.6-113)	.08
Change from baseline	NA	NA	−3.41 (−22.2 to 26.2)	5.61 (−18.6 to 30.5)	.07
Mean fold change (95% CI)	NA	NA	1.02 (0.94-1.10)	1.07 (0.98-1.16)	NA

Abbreviations: hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LpPLA2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein 1; NA, not applicable; oxLDL, oxidized low-density lipoprotein.

SI conversion factor: To convert hsCRP to mg/L, multiply by 10.

[a] Data are reported for all enrolled participants with available biomarker results.

[b] For hsCRP, censored values below the assay limit are randomly imputed based on a uniform distribution; otherwise, censored values below the assay limit are imputed as the result −0.01; values above the assay limit are imputed as result 0.1.

Pitavastatin reduced markers of lipid oxidation and arterial inflammation

Effects on localized plaque stabilization may be more important than systemic effects on inflammation

Lu, JAMA Cardiology, 2024

Pitavastatin reduced noncalcified plaque volume and progression

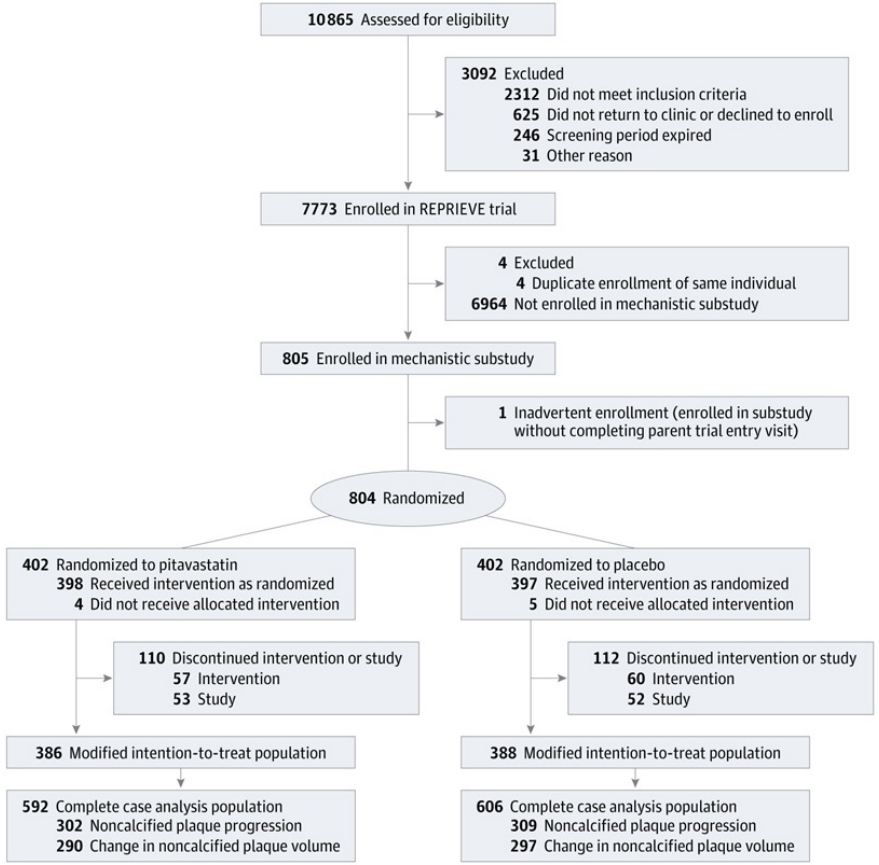


Table 2. Coronary Artery Plaque Changes by Treatment Arm[a]

Outcome	Treatment arm		Treatment effect[b]	
	Pitavastatin (n = 302)	Placebo (n = 309)	Estimated difference adjusted for baseline (95% CI)	*P* value
Primary outcomes				
NCP volume, mean (SD), mm^3[c]				
Baseline	52.3 (193.5)	57.7 (109.2)	NA	NA
Month 24	50.6 (192.8)	60.4 (113.7)	NA	NA
Change from baseline	−1.7 (25.2)	2.62 (27.1)	−4.3 (−8.6 to −0.1)	.04
Fold change from baseline (95% CI)	0.95 (0.91-1.00)	1.02 (0.99-1.05)	0.93 (0.88-0.99)	.02
Progression of NCP, No. (%)	53 (18)	85 (28)	0.67 (0.52-0.88)	.003
Secondary outcomes				
Total plaque volume, mean (SD), mm^3				
Baseline	65.6 (211.7)	72.2 (135.9)	NA	NA
Month 24	67.9 (218.4)	79.1 (149.1)	NA	NA
Change from baseline	2.34 (28.7)	6.89 (32.3)	−4.3 (−9.2 to 0.62)	NA
Progression of total plaque, No. (%)	80 (28)	100 (34)	0.89 (0.74-1.08)	NA
Reduction in NCP percentage, mean (SD)	−6.6% (14.3)	−2.6% (9.21)	−4.1% (−7.0 to −1.3)	NA
Exploratory outcomes				
Low-attenuation plaque volume, mean (SD), mm^3				
Baseline	3.32 (16.5)	4.25 (15.3)	NA	NA
Month 24	2.43 (9.91)	4.17 (12.8)	NA	NA
Change from baseline	−0.9 (9.97)	−0.1 (8.16)	−1.2 (−2.2 to −0.1)	NA

Abbreviations: NA, not applicable; NCP, noncalcified plaque.

[a] NCP defined as plaque voxels with attenuation <350 Hounsfield units. Total plaque includes all plaque voxels (noncalcified + calcified). Low-attenuation plaque defined as <30 Hounsfield units.

[b] For continuous outcomes, the treatment effect is given as the mean difference or relative fold change between treatment groups; for binary outcomes, it is a relative risk. All treatment effects and associated *P* values are adjusted for baseline values. Intention-to-treat analyses were conducted with the exception of reduction in NCP percentage, which is calculated in the subgroup with plaque present at baseline.

[c] Change in NCP volume could be assessed in a subset of 587 participants (297 in the pitavastatin arm and 290 in the placebo arm).

Lu, JAMA Cardiology, 2024

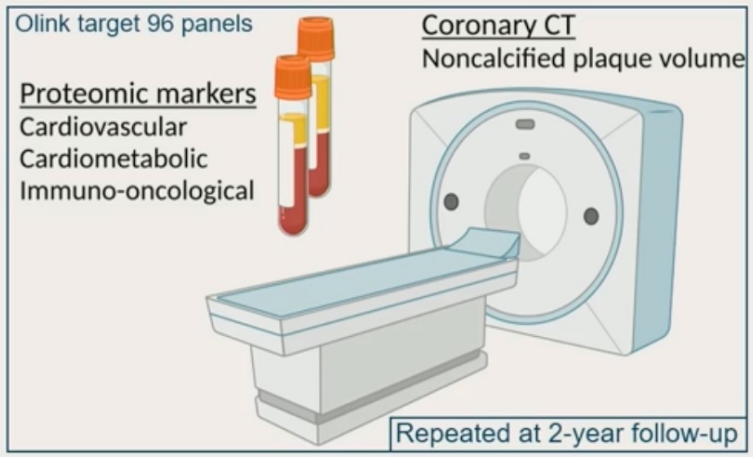
Effects on Novel Mechanistic Pathways

Primary objective

To investigate mechanistic pathways of statin effects on plaque in PWH

People with HIV

Randomized to pitavastatin or placebo



We first used a targeted approach to evaluate statin effects on plasma proteomic markers

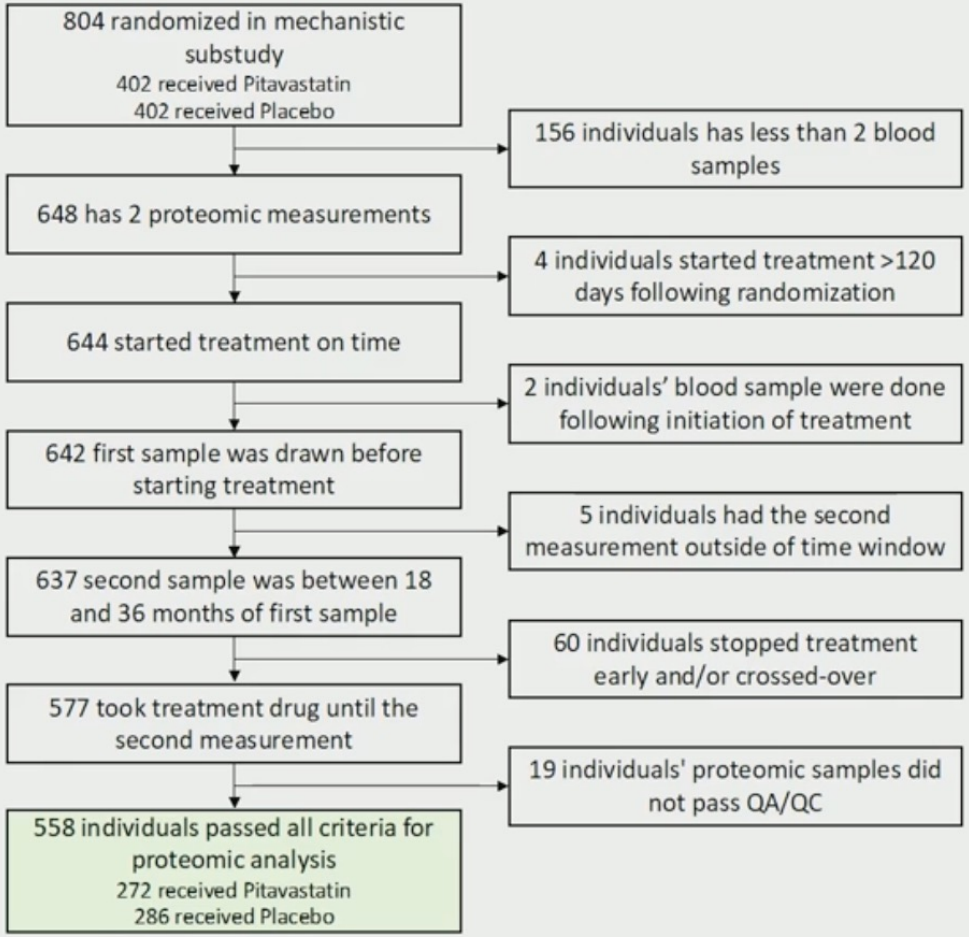
We then evaluated the association between changes in LDL / proteins and changes in coronary plaque

Finally, we investigated the degree to which changes in key proteins mediated statin effects on coronary plaque

CROI 2024

Kolossvary, CROI 2024

Participant characteristics

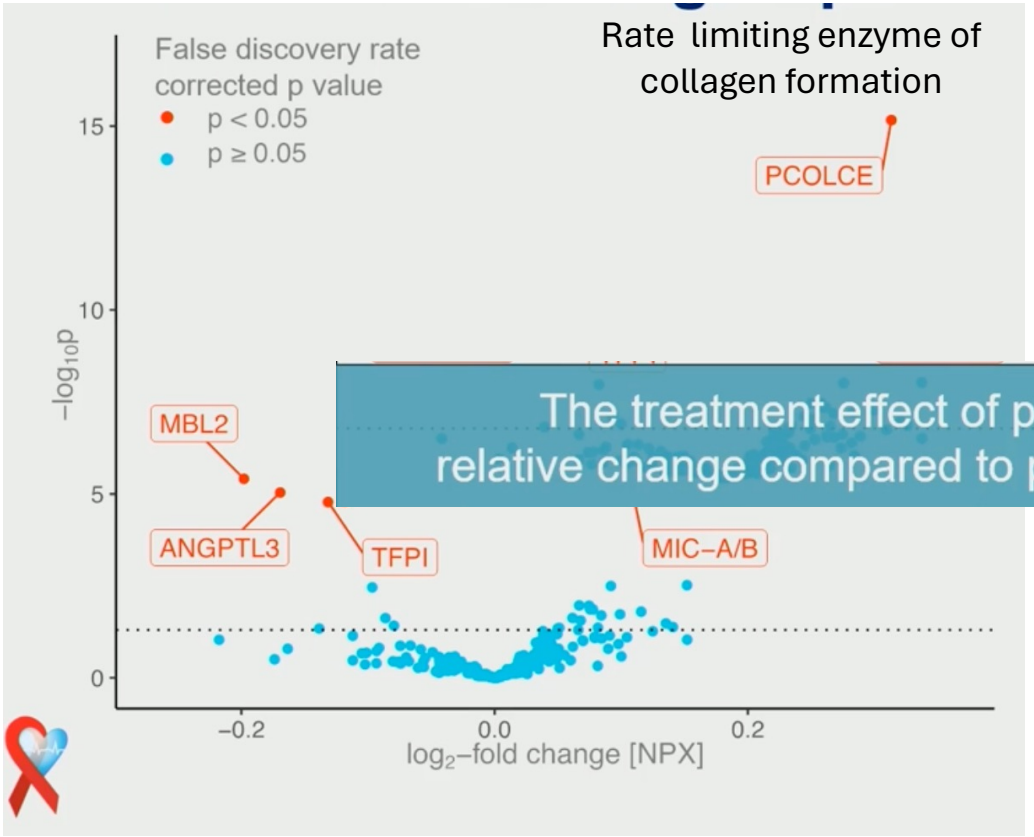


Variable	Overall N = 558	Placebo N = 286	Pitavastatin N = 272
Age (years)	51 ± 6	51 ± 6	51 ± 6
Male natal sex	455 (82%)	233 (81%)	222 (82%)
Race			
Asian	5 (1%)	4 (1%)	1 (0.3%)
Black or African American	206 (37%)	106 (37%)	100 (37%)
White	293 (53%)	154 (54%)	139 (51%)
Other	54 (10%)	22 (8%)	32 (11.7%)
Cardiovascular risk factors			
BMI (kg/m²)	27.3 ± 4.4	27.3 ± 4.3	27.3 ± 4.5
ASCVD risk score (%)	5.0 ± 3.1	4.9 ± 2.9	5.0 ± 3.2
Total cholesterol (mg/dL)	186 ± 36	186 ± 37	185 ± 35
LDL-C (mg/dL)	108± 30	108 ± 31	108 ± 29
Non-HDL-C (mg/dL)	134 ± 35	134 ± 36	134 ± 34
Triglycerides (mg/dL)	133 ± 74	133 ± 77	132 ± 72
HIV-related health history			
Total ART use (years)	12 ± 7	12 ± 6	12 ± 7
Nadir CD4 (cells/mm³)			
<50	116 (21%)	58 (21%)	58 (22%)
50-199	168 (31%)	92 (32%)	76 (28%)
200-349	155 (28%)	78 (28%)	77 (29%)
350+	106 (20%)	52 (19%)	54 (21%)
HIV-1 RNA (copies/mL)			
<LLQ	482 (88%)	245 (88%)	237 (88%)
LLQ -< 400	54 (10%)	29 (10%)	25 (9%)
400+	14 (2%)	6 (2%)	8 (3%)

CROI 2024

Kolossvary, CROI 2024

Proteins differentially expressed over time in the two treatment groups



The treatment effect of pitavastatin was largest on PCOLCE; relative change compared to placebo: 24% [95% CI: 18-31%, p<0.001]

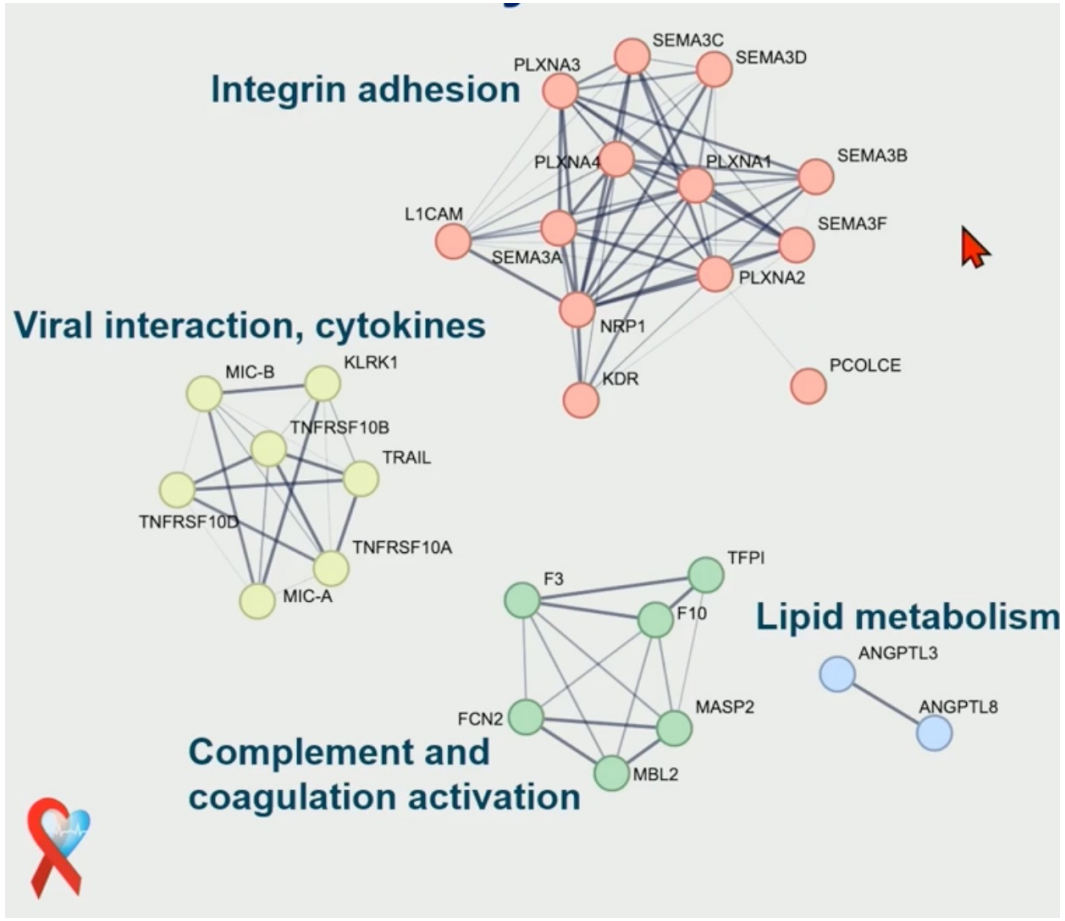
vs placebo

Proteins showing differential expression between treatment groups	
Decreased expression	
ANGPTL3	*Angiopoietin-related protein 3*: Involved in regulation of lipid and glucose metabolism.
MBL2	*Mannose-binding protein C*: Calcium-dependent lectin involved in innate immune defense.
	Tissue factor pathway inhibitor: Inhibits factor
	member 10: Induces apoptosis.
Increased expression	
MIC-A/B	*MHC class I polypeptide-related sequence A-B*: Acts as a stress-induced self-antigen that is recognized by gamma delta T-cells. Binding to KLRK1 leads to cell lysis.
NRP1	*Neuropilin-1*: Receptor involved in the development of the cardiovascular system, in angiogenesis.
PCOLCE	*Procollagen C-endopeptidase enhancer 1*: Binds to the C-terminal propeptide of type I procollagen and enhances procollagen C-proteinase activity

255 individual proteins

Kolossvary, CROI 2024

Network analysis of differentially expressed proteins



Proteins showing differential expression between treatment groups	
Decreased expression	
ANGPTL3	*Angiopoietin-related protein 3*: Involved in regulation of lipid and glucose metabolism.
MBL2	*Mannose-binding protein C*: Calcium-dependent lectin involved in innate immune defense.
TFPI	*Tissue factor pathway inhibitor*: Inhibits factor Xa directly. It possesses an antithrombotic action and the ability to associate with lipoproteins in plasma.
TRAIL	*Tumor necrosis factor ligand superfamily member 10*: Induces apoptosis.
Increased expression	
MIC-A/B	*MHC class I polypeptide-related sequence A-B*: Acts as a stress-induced self-antigen that is recognized by gamma delta T-cells. Binding to KLRK1 leads to cell lysis.
NRP1	*Neuropilin-1*: Receptor involved in the development of the cardiovascular system, in angiogenesis.
PCOLCE	*Procollagen C-endopeptidase enhancer 1*: Binds to the C-terminal propeptide of type I procollagen and enhances procollagen C-proteinase activity

CROI 2024

Kolossvary, CROI 2024

PCOLCE associates with reduced non-calcified plaque

Variable	Univariable regression			Multivariable regression		
	% change in NCP	95% Confidence interval	p	% change in NCP	95% Confidence interval	p
LDL	1.5	[-1.2; 4.3]	0.26	-0.1	[-3.0; 2.9]	0.95
ANGPTL3	-19.8	[-34.0; -2.6]	0.026	2.3	[-20.3; 31.3]	0.86
MBL2	-18.7	[-31.5; -3.5]	0.018	-11.0	[-26.9; 8.4]	0.25
MIC-A/B	-11.1	[-36.2; 23.7]	0.48	-	-	-
NRP1	-30.0	[-53.0; 4.3]	0.08	-	-	-
PCOLCE	-31.9	[-42.9; -18.7]	<0.001	-31.2	[-45.3; -13.4]	0.002

Doubling in PCOLCE expression was associated with a decrease in noncalcified plaque by -31%, [95%CI: -45%; -13%, p=0.002]

Model estimates are for per doubling in protein expression

CROI 2024

Kolossvary, CROI 2024

PCOLCE associates with plaque stabilization

Protein changes vs. plaque components changes

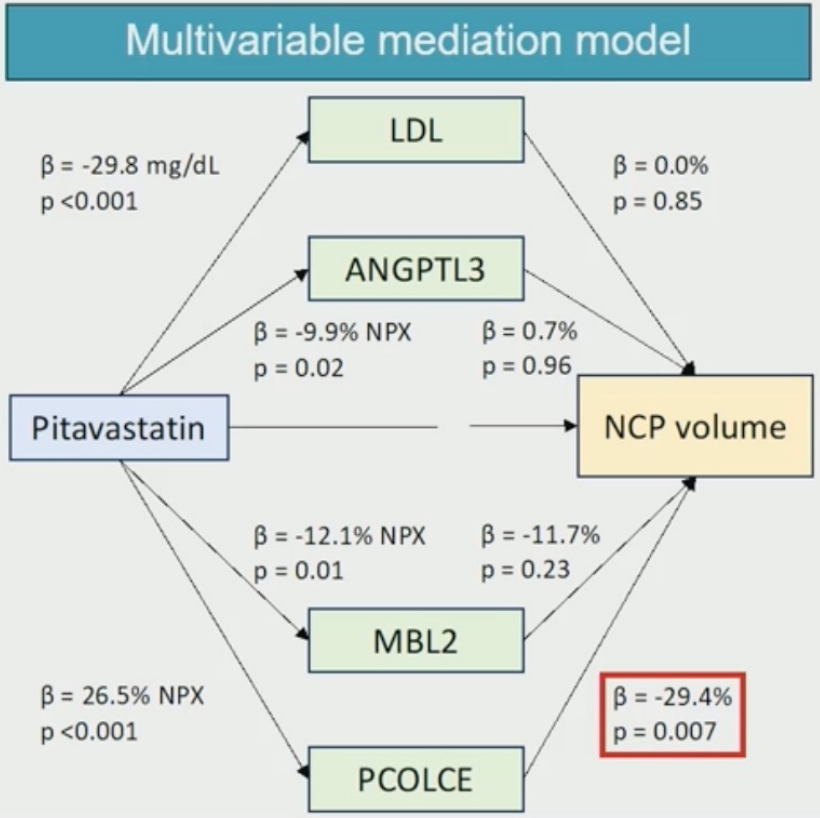
	Calcified plaque			Noncalcified plaque					
Variable	**Calcified plaque volume (>350HU)**			**Fibro-fatty plaque volume (<130HU)**			**Fibrous plaque volume (130-350HU)**		
	% change	95% Confidence interval	p	% change	95% Confidence interval	p	% change	95% Confidence interval	p
LDL	-3.7	[-9.5; 2.3]	0.22	6.1	[0.5; 11.8]	0.032	0.4	[-1.9; 2.6]	0.74
ANGPTL3	-1.2	[-33.8; 47.5]	0.95	-28.0	[-52.3; 8.9]	0.12	-20.7	[-32.3; -7.0]	0.004
MBL2	7.3	[-25.1; 53.6]	0.70	-25.9	[-48.5; 6.8]	0.11	-13.5	[-25.0; -0.4]	0.044
MIC-A/B	6.7	[-46.4; 112.3]	0.85	-25.7	[-63.0; 49.4]	0.40	-3.3	[-26.4; 27.1]	0.81
NRP1	13.8	[-50.1; 159.5]	0.76	-46.6	[-77.0; 24.1]	0.14	-13.9	[-38.1; 19.8]	0.37
PCOLCE	34.4	[-7.9; 96.2]	0.12	-38.5	[-58.1; -9.7]	0.013	-22.2	[-32.9; -9.7]	0.001
TFPI	77.3	[-0.4; 215.4]	0.051	-0.6	[-43.8; 75.8]	0.98	-8.1	[-26.4; 14.9]	0.46
TRAIL	9.6	[-40.2; 100.7]	0.77	18.2	[-37.7; 124.1]	0.61	-9.9	[-29.8; 15.6]	0.41

Increased PCOLCE expression was associated with a shift in plaque components promoting plaque stabilization

Model estimates are for per doubling in protein expression

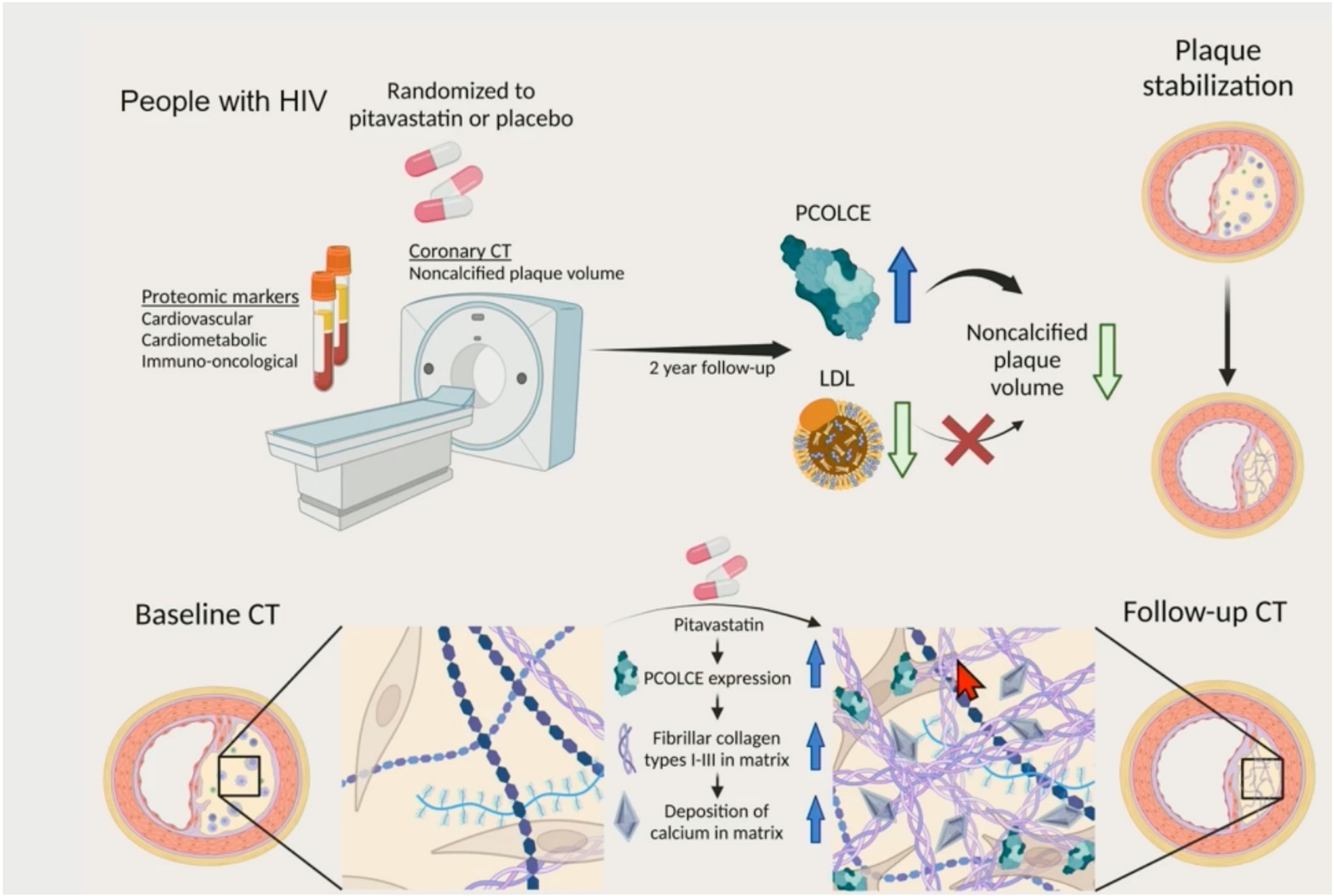
CROI 2024

Mediation analysis: PCOLCE mediates 84% of total effect of statins on non-calcified plaque volume, independent of LDL



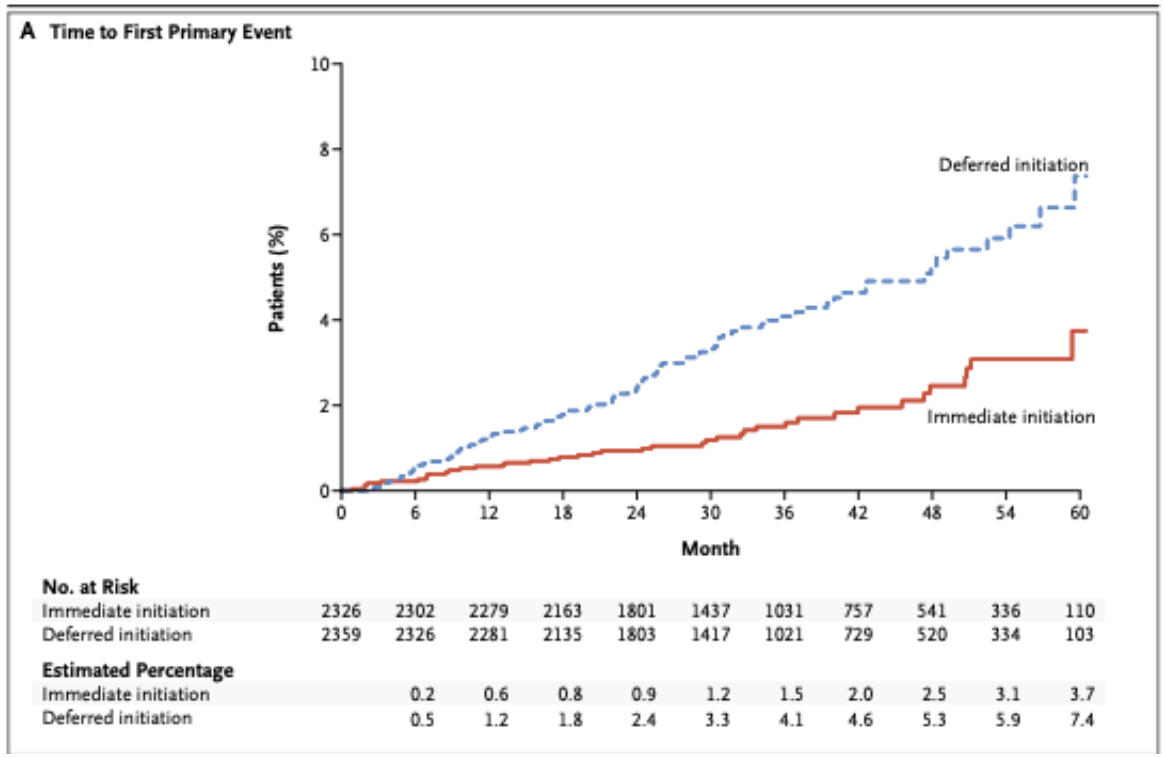
Variable	Multivariable mediation model		
	% change in NCP	95% Confidence interval	Proportion mediated
LDL	0.8	[-7.5; 9.8]	5.8%
ANGPTL3	-0.1	[-4.2; 3.9]	-0.6%
MBL2	2.0	[-0.7; 6.7]	14.2%
PCOLCE	-11.4	[-22.7; -1.2]	-83.8%

Kolossvary, CROI 2024

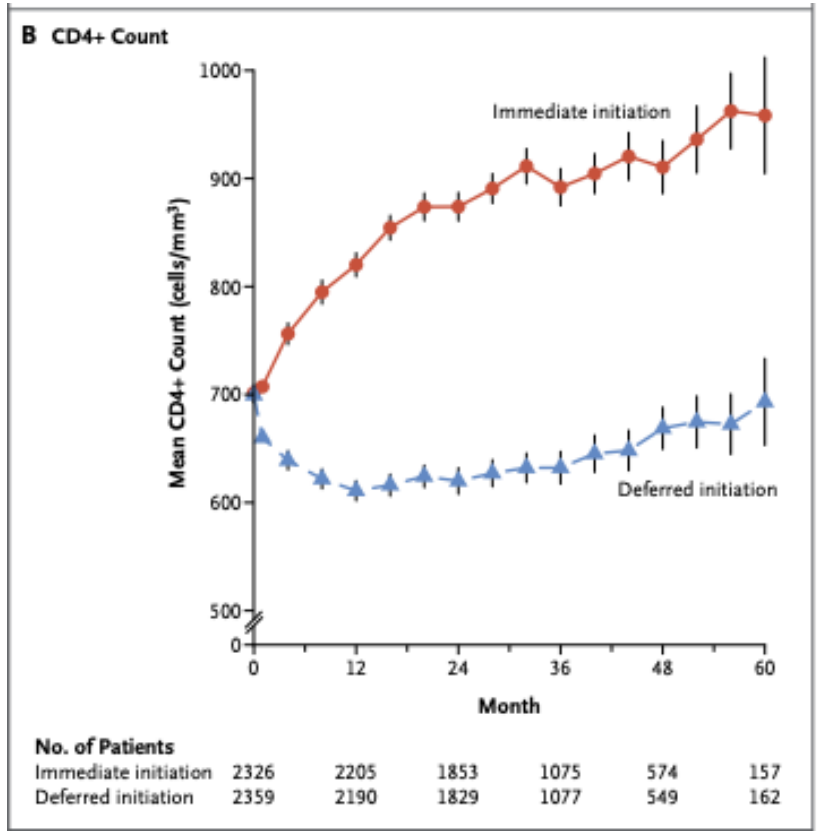


Kolossvary, CROI 2024

Low CD4+ T-cell nadir **(<500/uL)**: immune recovery and clinical outcome



Primary Event:
a serious AIDS-related or serious non–AIDS-related event, including death



INSIGHT START Study GroupNEJM, 2015

REVIEW

CURRENT OPINION

Can early therapy reduce inflammation?

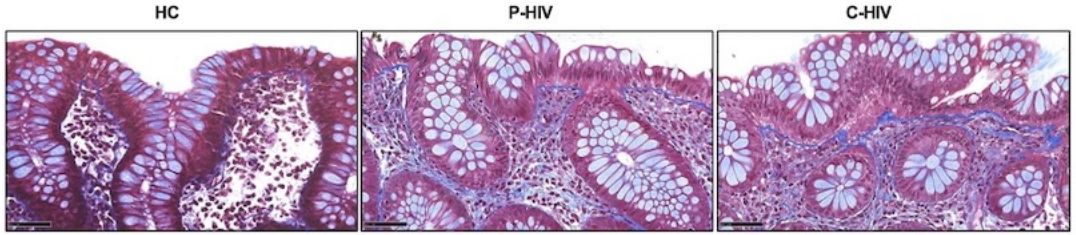
Netanya G. Sandler[a] *and Irini Sereti*[b]

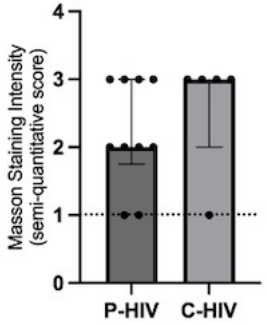
Volume 9 • Number 1 • January 2014

Early=PHI

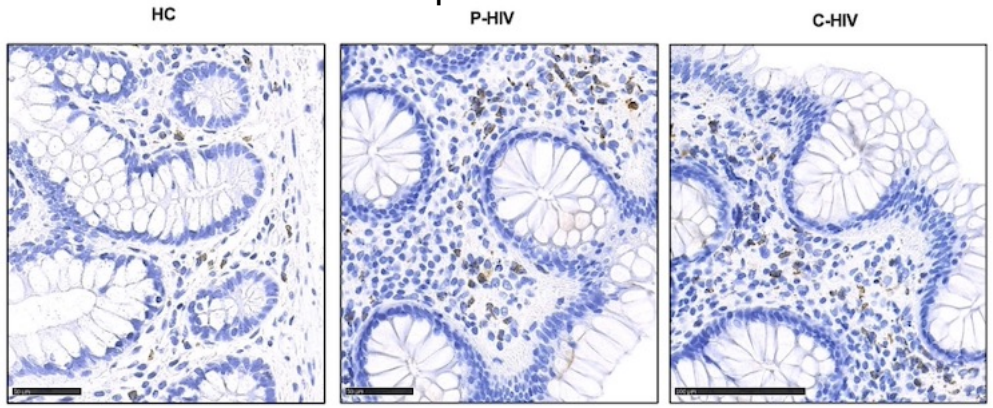
Collagen deposition, inflammation and barrier dysfunction in PHI

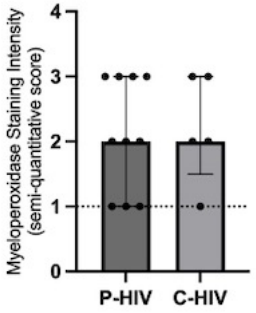
Collagen deposition



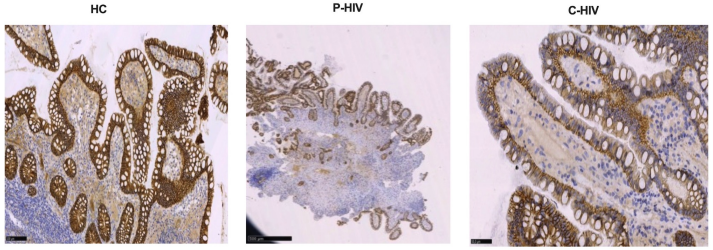


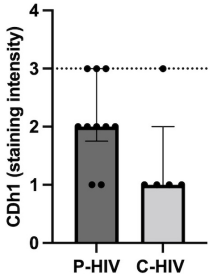
Neutrophil infiltration

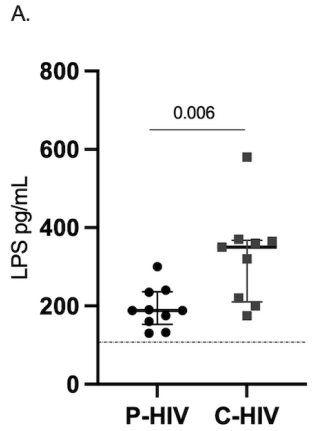


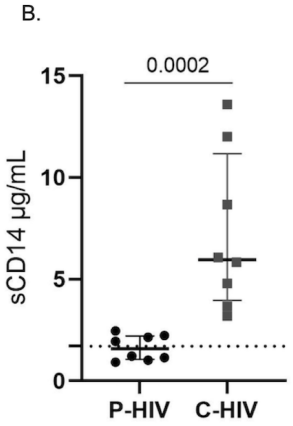


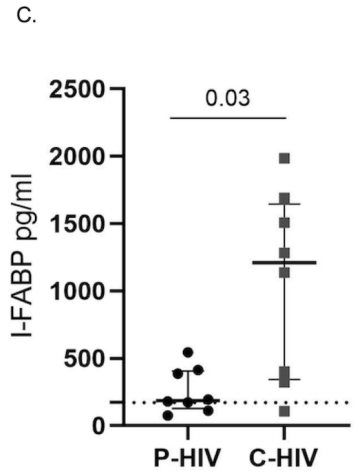
JC protein expression

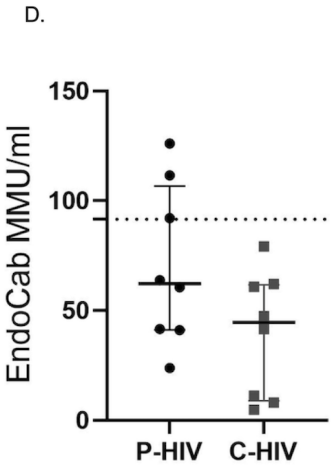




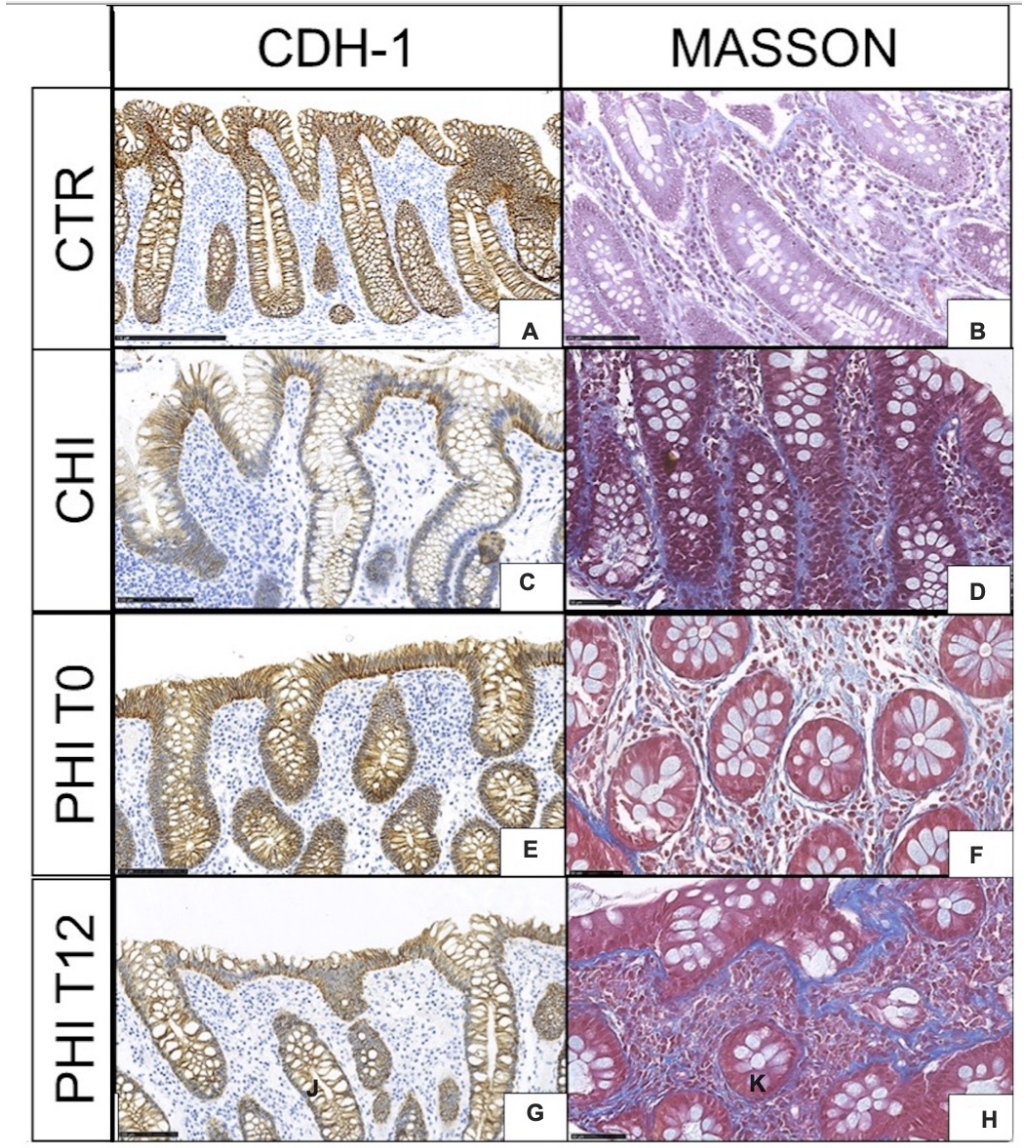








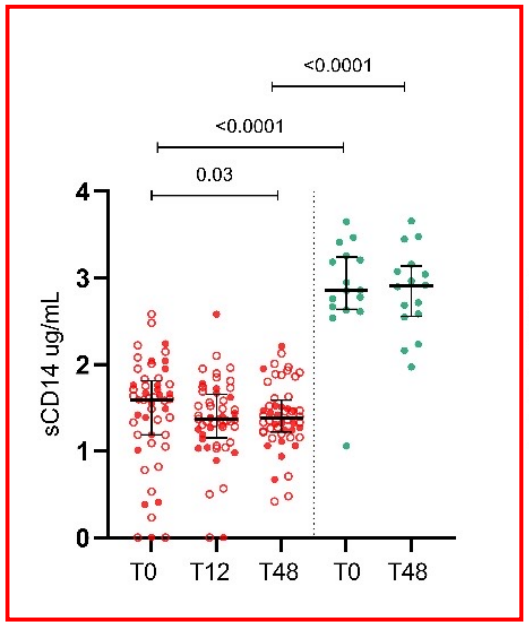
Tincati et al. AIDS, 2023

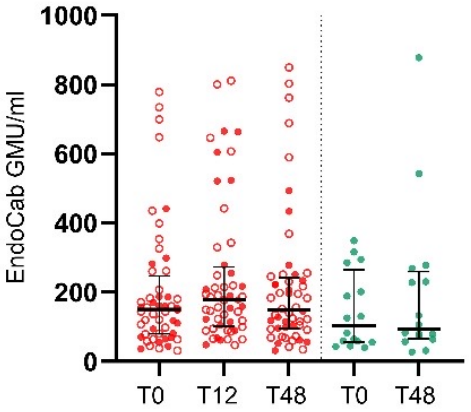


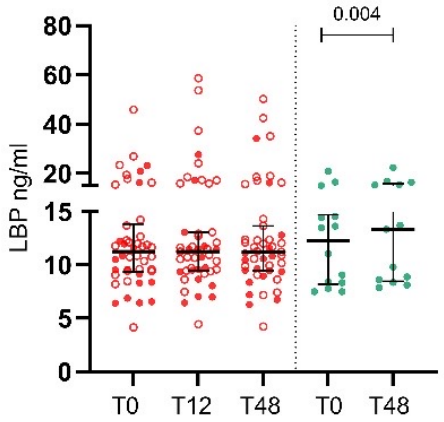
Little/no effect of early cART (PHI) in the gut

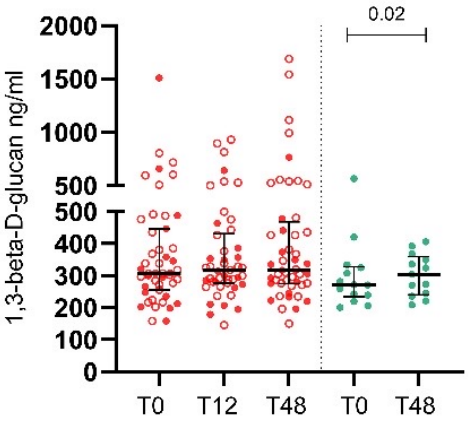
Tincati et al, HIV Glasgow 2022
mansuscript in preparation

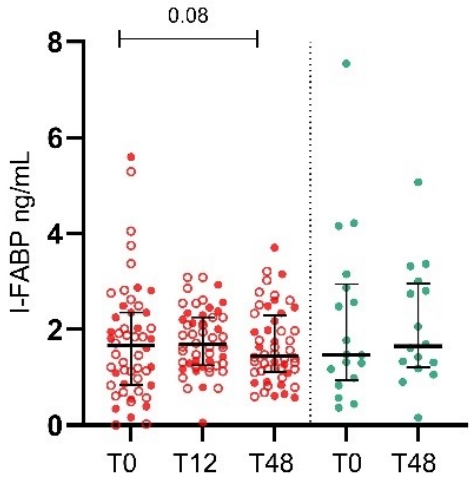
Reduced monocyte activation, stable microbial translocation and containment of intestinal barrier damage in treated PHI in treated PHI

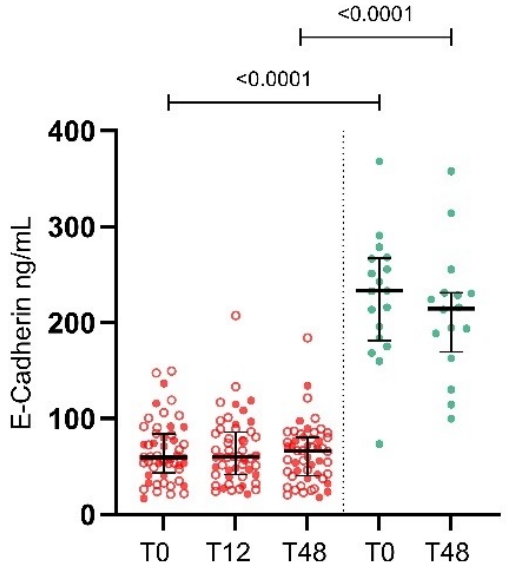












PHI (Fiebig I-III)
PHI (Fiebig IV-VI)
CHI

Bono et al, manuscript in preparation
See also Schintmann, JID, 2020

Conclusions

- HIV is characterized by a dysfunctional immune response, which drives disease progression by causing tissue damage and organ failure

- persists on cART

- current cART regimens appears to have similar effects on T-cell homeostasis/inflammation

- Early cART (PHI) may contribute to lowering peripheral markers of immune activation/inflammation

- whether this translates into a reduced risk of clinical events is currently unknown

- whether this has a beneficial effect on the GI tract (and other tissue reservoirs) is unknown

- Understanding the pathogenesis of HIV-related activation/inflammation is crucial to prevent disease progression

Acknowledgments

Clinica di Malattie Infettive
Dipartimento di Scienze della Salute
ASST Santi Paolo e Carlo-Presidio Ospedaliero San Paolo
Università degli Studi di Milano
Valeria Bono
Matteo Augello
Sabrina Marozin
Maria Sgarlata
Roberta Rovito
Giulia Marchetti*

*Funding: *Ministero della Salute* NET-2013-02355333-3

UO Anatomia Patologica
Dipartimento di Scienze della Salute
ASST Santi Paolo e Carlo-Presidio Ospedaliero San Paolo
Università degli Studi di Milano
Monica Falleni
Delfina Tosi

INACTION cohort group
Elena Bruzzesi (HSR, Milano)
Andrea Calcagno (UniTo)
Stefania Dispinseri (HSR, Milano)
Gabriella Scarlatti (HSR, Milano=
Andrea Giacomelli (H Sacco, Milano)
Andrea Gori (H Sacco, Milano)
Alessandra Bandera (IRCCS Ca' Granda, Milano
Antonio Muscatello (IRCCS Ca' Granda, Milano)
Silvia Nozza (HSR, Milano)
Stefano Rusconi (H Legnano, Unimi)