Gli Immunological Non Responders (INR) oggi: patogenesi

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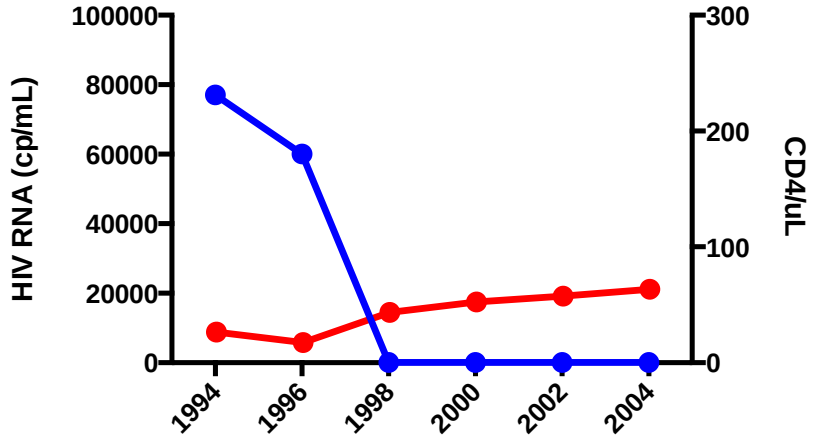
Case record: HIV-infected male, cook, age 59

- Previous IDU, **HCV co-infection**
- Diagnosis of HIV-seropositivity in **Sept 1994**; **nadir CD4: 26/uL**, no opportunistic infection
- First HAART regimen **1996: AZT+3TC+IDV**
- PJP Prophylaxis: Trimethoprim-sulfamethoxazole QD

Viro-immunological response to cART: “immunological-non-responder”



INR:
dimensione del problema, oggi

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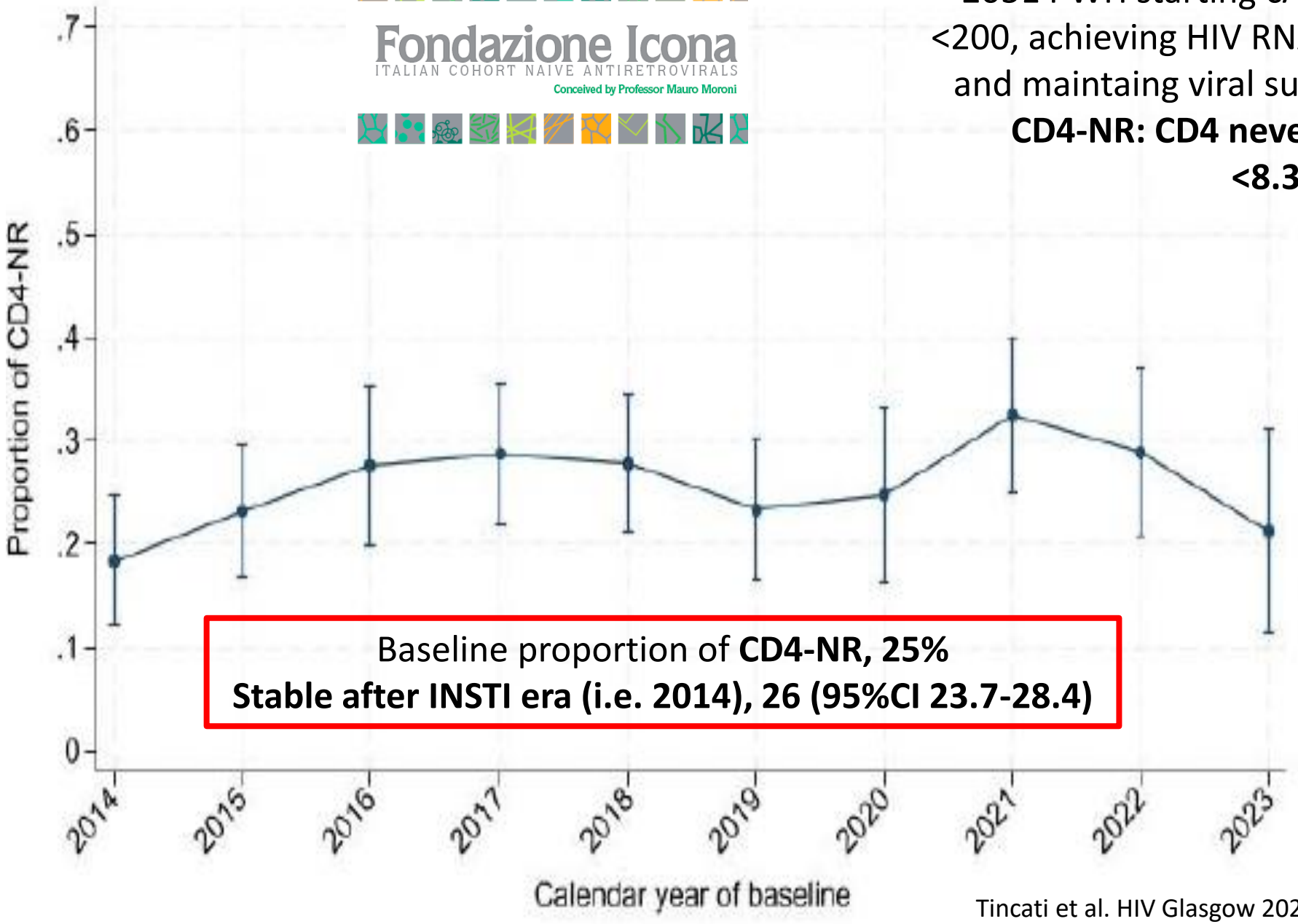
2051 PWH starting cART 1997-2021, CD4 nadir <200, achieving HIV RNA< 50cp/ml in 6-12 months and maintaing viral suppression for ≥24 months

CD4-NR: CD4 never >350 and CD4 slope <8.3/month



Baseline proportion of **CD4-NR, 25%**
Stable after INSTI era (i.e. 2014), 26 (95%CI 23.7-28.4)

Tincati et al. HIV Glasgow 2024

1784 U.S. Military HIV Natural History Study (NHS), **INR prevalence 10.8%** (enrolment started in 1986)

984 African Cohort Study (AFRICOS), **INR prevalence 25.8%** (enrolment started in 2013)

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INR:
rischio clinico

Increased clinical risk and immune activation in patients with scant CD4+ rescue on cART

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	Number of events	PYFU	Rate/ 100PYFU	95% CI	Rate ratio (95% CI) *P*		
					Unadjusted	Adjusted[a]	Adjusted[b]
INR							
All patients							
No	167	9095	1.84	1.58–2.14	1.00	1.00	1.00
Yes	55	1248	4.41	3.38–5.74	2.39 (1.77–3.25) <0.001	2.93 (2.06–4.16) <0.001	1.94 (1.39–2.72) <0.001
CD4 cell count							

Lapadula et al. AIDS 2013

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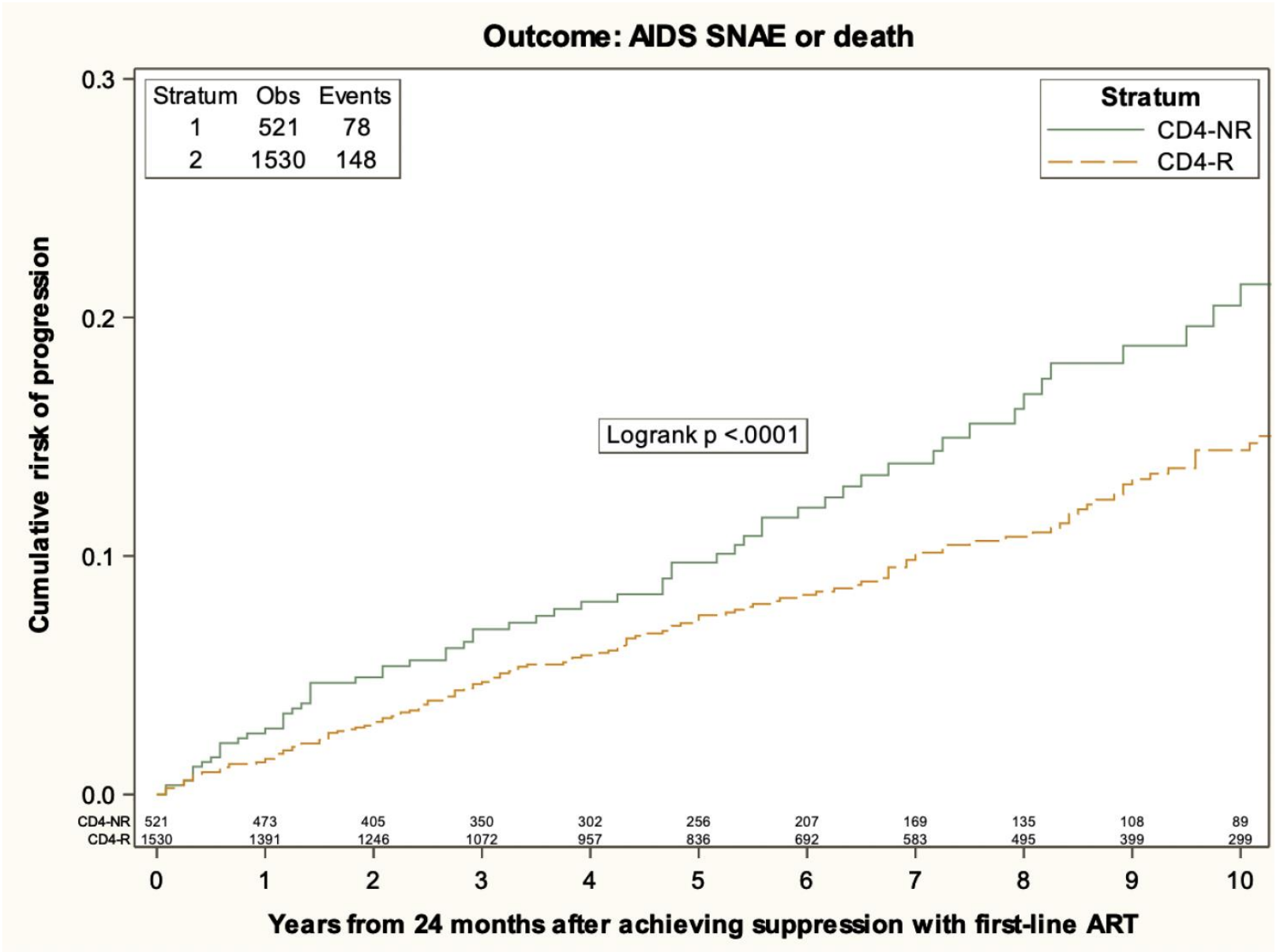
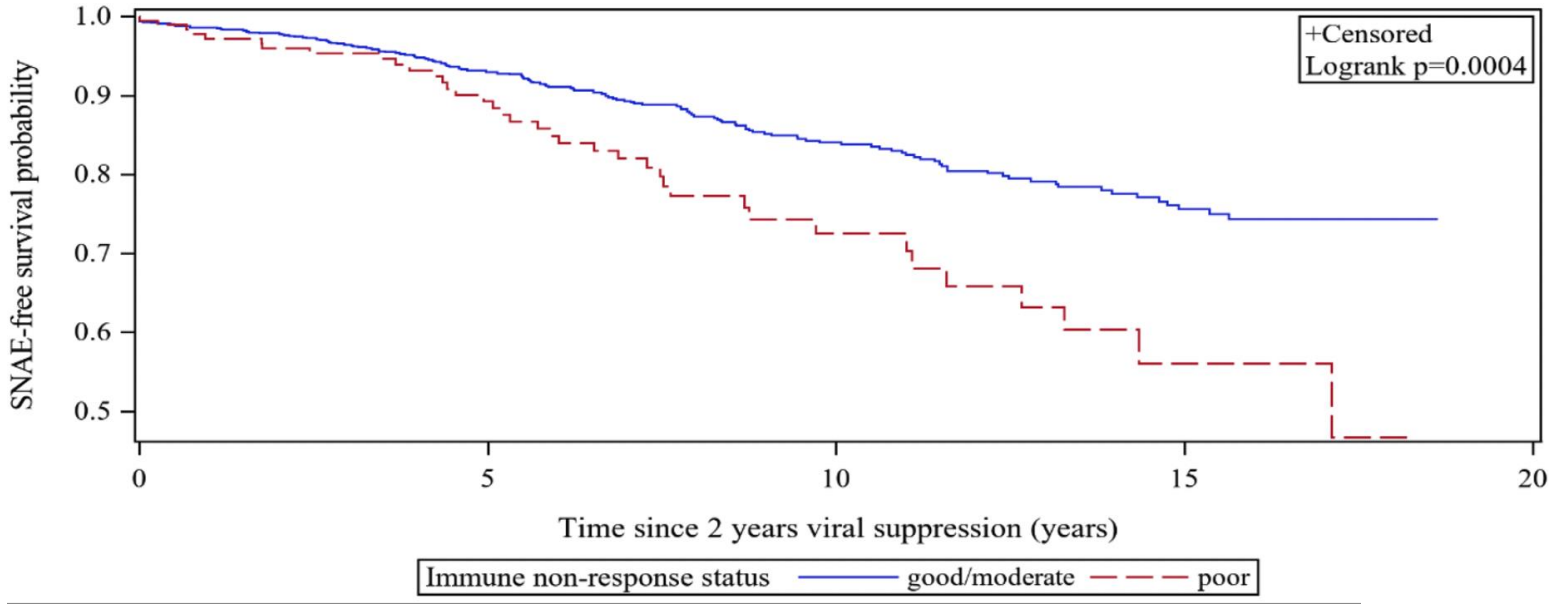
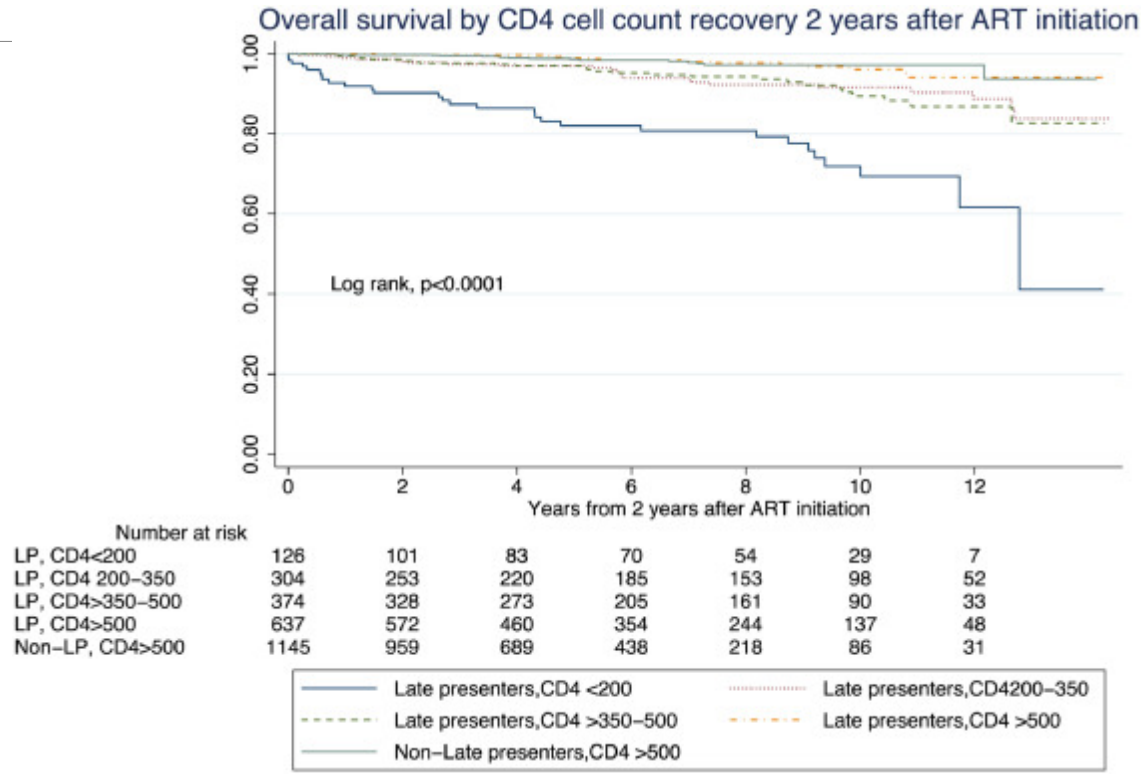


By 10 years from baseline, 21.4% (95% CI:15.9-26.9%) CD4-NR and 14.5% (95% CI:11.9-17.0%) CD4-R, developed AIDS, SNAE or death

Tincati et al. HIV Glasgow 2024



Noiman et al. Sci Reports 2022



Martin-Iguacel et al. eClinicalMedicine, 2022

INR:
fattori associati

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Characteristic	Total N=2051	CD4-NR N=521	CD4-R N=1530	p-value*
Gender, female, n(%)	463 (22.6%)	104 (20.0%)	359 (23.5%)	0.099
Mode of HIV Transmission, n (%)				**0.023**
PWID	202 (9.8%)	56 (10.7%)	146 (9.5%)	
Homosexual contacts	653 (31.8%)	140 (26.9%)	513 (33.5%)	
Heterosexual contacts	1046 (51.0%)	278 (53.4%)	768 (50.2%)	
Other/Unknown	150 (7.3%)	47 (9.0%)	103 (6.7%)	
Nationality, foreign, n(%)	390 (19.0%)	96 (18.4%)	294 (19.2%)	0.692
Calendar year of ART initiation, median (IQR)	2013 (2009, 2016)	2014 (2010, 2017)	2013 (2009, 2016)	0.054
Age, median (IQR), years	42 (35, 51)	46 (39, 55)	41 (34, 49)	**<.001**
CD4 count nadir, median (IQR) cells/mmc	85 (33, 148)	59 (28, 114)	97 (36, 156)	**<.001**
Baseline CD4 count, median (IQR) cells/mmc	394 (282, 535)	230 (179, 270)	460 (363, 580)	**<.001**
AIDS, yes, n(%)	727 (35.4%)	201 (38.6%)	526 (34.4%)	0.083
Viral load at ART, median (IQR) log10 copies/mL	5.04 (4.35, 5.53)	4.98 (4.24, 5.45)	5.07 (4.38, 5.56)	**0.037**
Co-infections, n (%)				
HCV+	217 (10.6%)	64 (12.3%)	153 (10.0%)	0.306
Not tested for HCV	292 (14.2%)	76 (14.6%)	216 (14.1%)	
HBV+	15 (0.7%)	5 (1.0%)	10 (0.7%)	0.769
Not tested for HBV	280 (13.7%)	72 (13.8%)	208 (13.6%)	
First-line ART				0.771
3 drugs	1984 (96.7%)	505 (96.9%)	1479 (96.7%)	
4+ drugs	67 (3.3%)	16 (3.1%)	51 (3.3%)	
Anchor drug in first ART regimen				0.154
PI/r	819 (39.9%)	188 (36.1%)	631 (41.2%)	
NNRTI	396 (19.3%)	105 (20.2%)	291 (19.0%)	
INSTI	630 (30.7%)	180 (34.5%)	450 (29.4%)	
other	67 (3.5%)	16 (3.3%)	51 (3.6%)	
Time from HIV diagnosis to cART, median (IQR), months	34 (33, 37)	34 (33, 36)	35 (33, 38)	**<.001**

*Chi-square or Kruskal-Wallis test as appropriate

Tincati et al. HIV Glasgow 2024

Characteristic	Adjusted OR (95% CI)	*p* value
Natural history study[a]		
Age at ART initiation (years)	1.00 (0.99, 1.03)	0.506
Sex		
Female	0.67 (0.34, 1.33)	0.254
Male	Reference	
CD4 nadir (cells/μl) (per 100 cells)	0.34 (0.28, 0.41)	< 0.001
History of diabetes[c]		
Yes	2.17 (1.11, 4.25)	0.024
No	Reference	
African Cohort Study[b]		
Age at ART initiation (years)	1.05 (1.03, 1.07)	< 0.001
Sex		< 0.001
Female	0.49 (0.35, 0.71)	
Male	Reference	
CD4 nadir (cells/μl) (per 100 cells)	0.46 (0.37, 0.56)	< 0.001
History of diabetes[c]		
Yes	0.87 (0.52, 1.46)	0.606
No	Reference	

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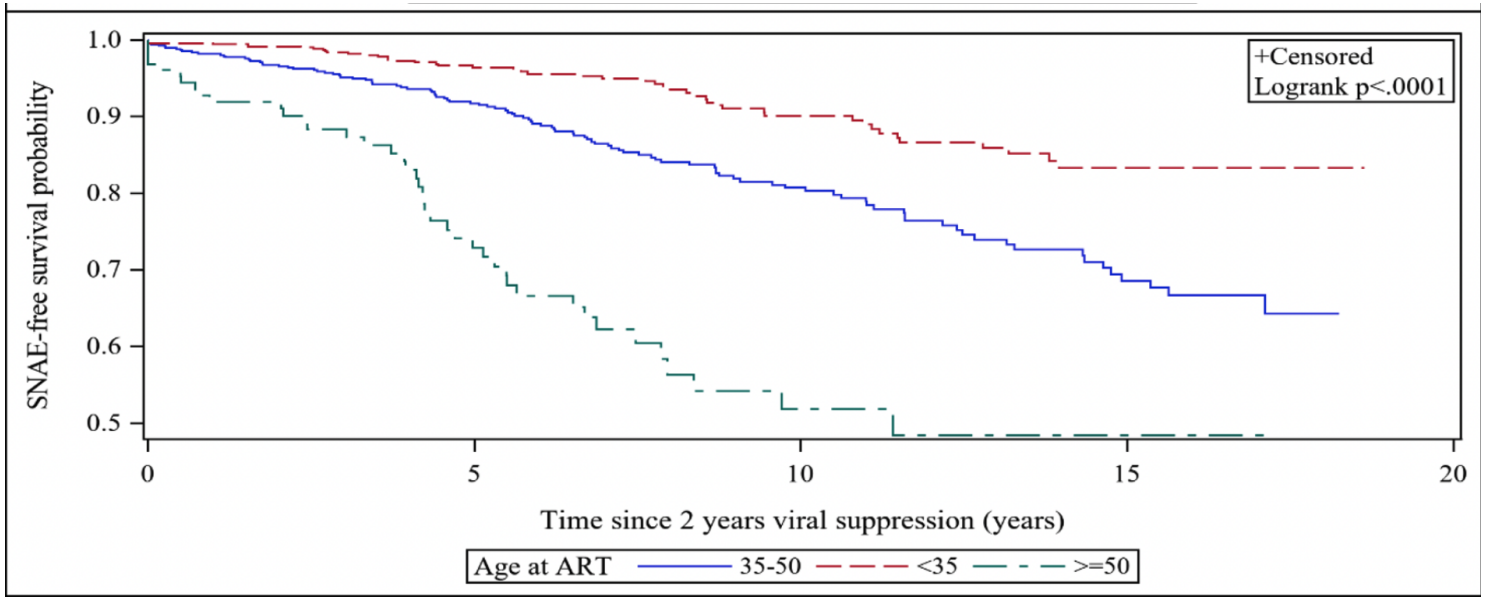
	Unadjusted RH (95% CI)	p-value	Adjusted[1] RH (95% CI)	p-value	Adjusted[2] RH (95% CI)	p-value
Outcome: new SNAE/death						
CD4-R	1		1		1	
CD4-NR	1.73(1.29, 2.33)	<.001	1.30 (0.96, 1.76)	0.085	1.28 (0.90, 1.84)	0.175
Outcome: new AIDS, SNAE/death						
CD4-R	1		1		1	
CD4-NR	1.75 (1.33, 2.30)	<.001	1.36 (1.02, 1.80)	0.033	1.33 (0.96, 1.86)	0.090

[1]for age

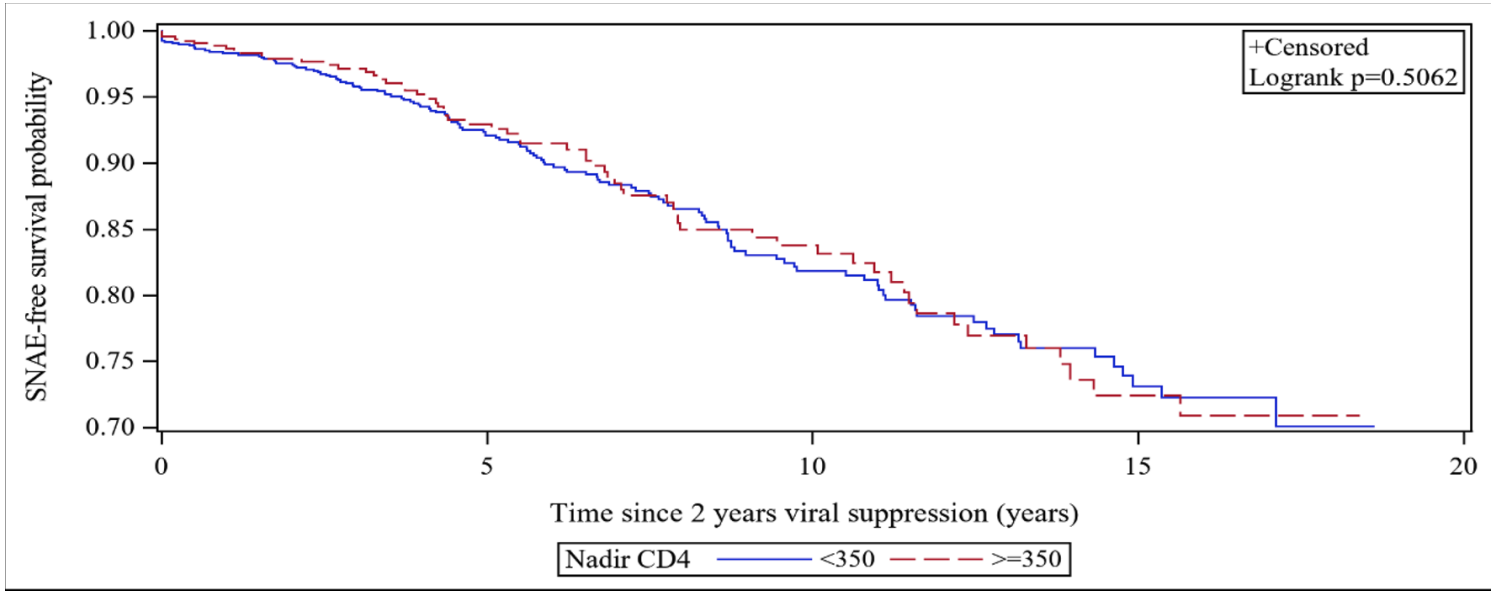
[2]for age, gender, nationality, mode of HIV transmission, year of baseline, CD4 nadir, baseline CD8 and at ART initiation, AIDS, INSTI use in first-line, hepatitis co-infection and VL blip before baseline

The relative hazard of AIDS, SNAE/death associated with CD4-NR was 1.33 (0.96-1.86; p=0.090) after controlling for key confounders.

Tincati et al. HIV Glasgow 2024



Increased clinical risk in INR appears largely explained by age (and other confounding factors)



Noiman et al. Sci Reports 2022

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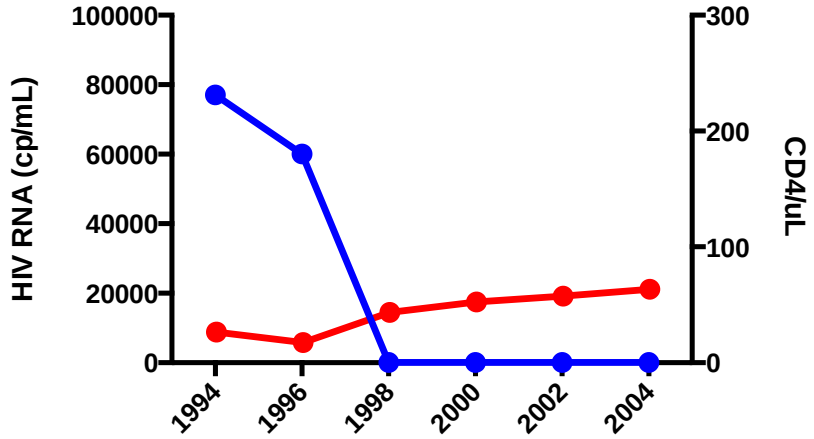
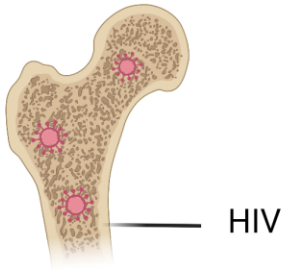


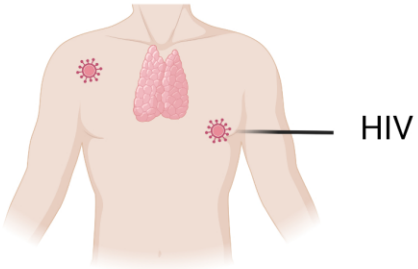
Years 2004-2013

Looking for pathogenetic pathway(s) for lack of CD4+ recovery in INRs

Depletion of progenitor cells in the bone marrow

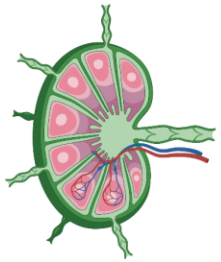


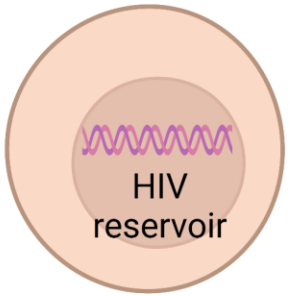
Reduced size and thymic output



Alteration in mitochondrial respiration

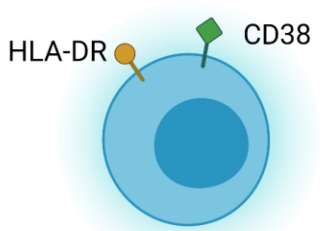
Lymphoid tissue fibrosis



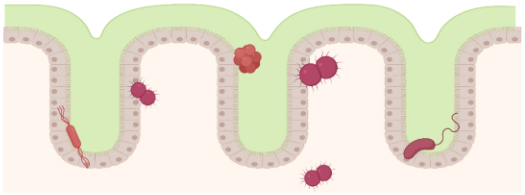


CD4+ T-cells

Persistent CD4+ T-cell hyperactivation



Gut barrier disruption, microbial translocation and gut dysbiosis



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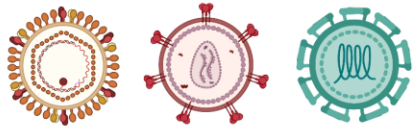
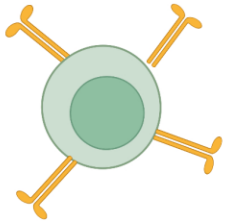


T-cell senescence and exhaustion



Bono V et al., New Microbiologica 2022

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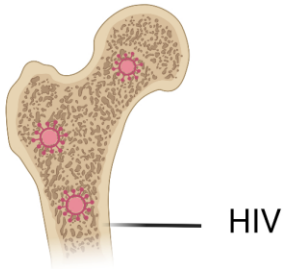

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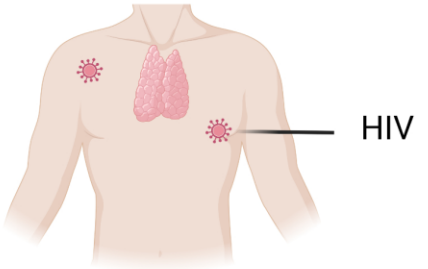

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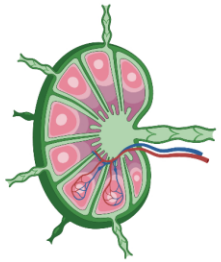

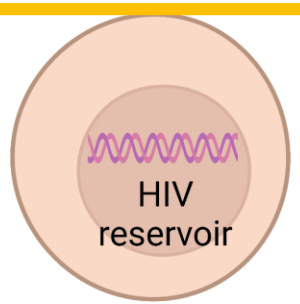

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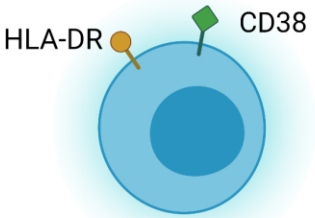

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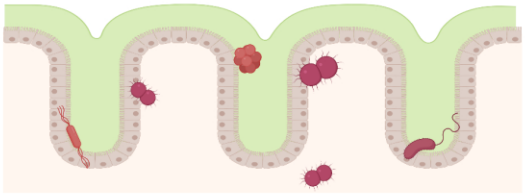

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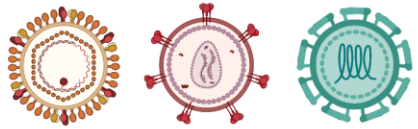
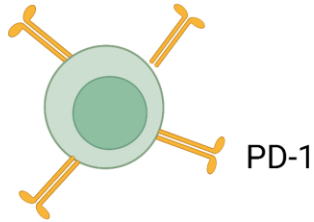
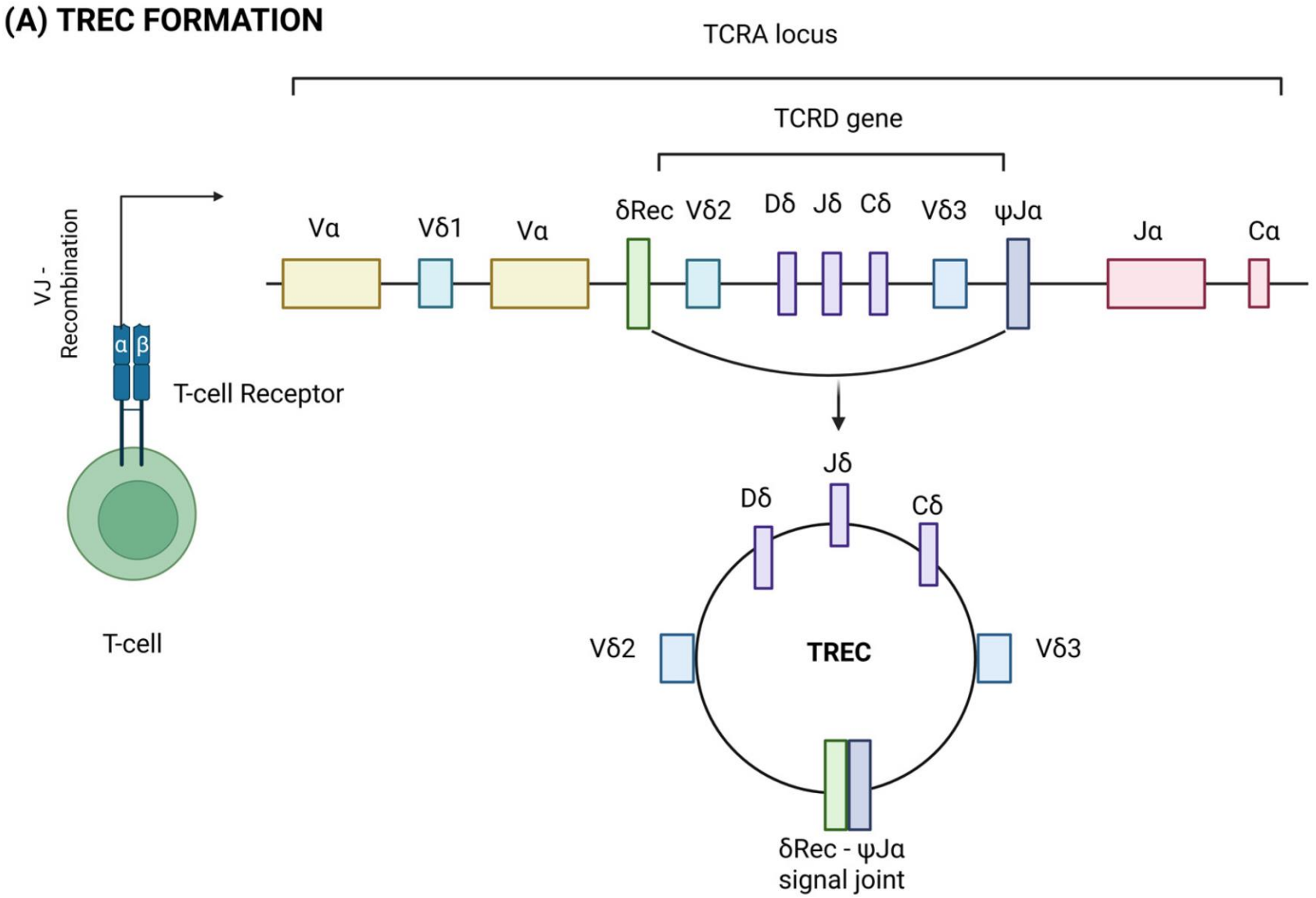


T-cell senescence and exhaustion

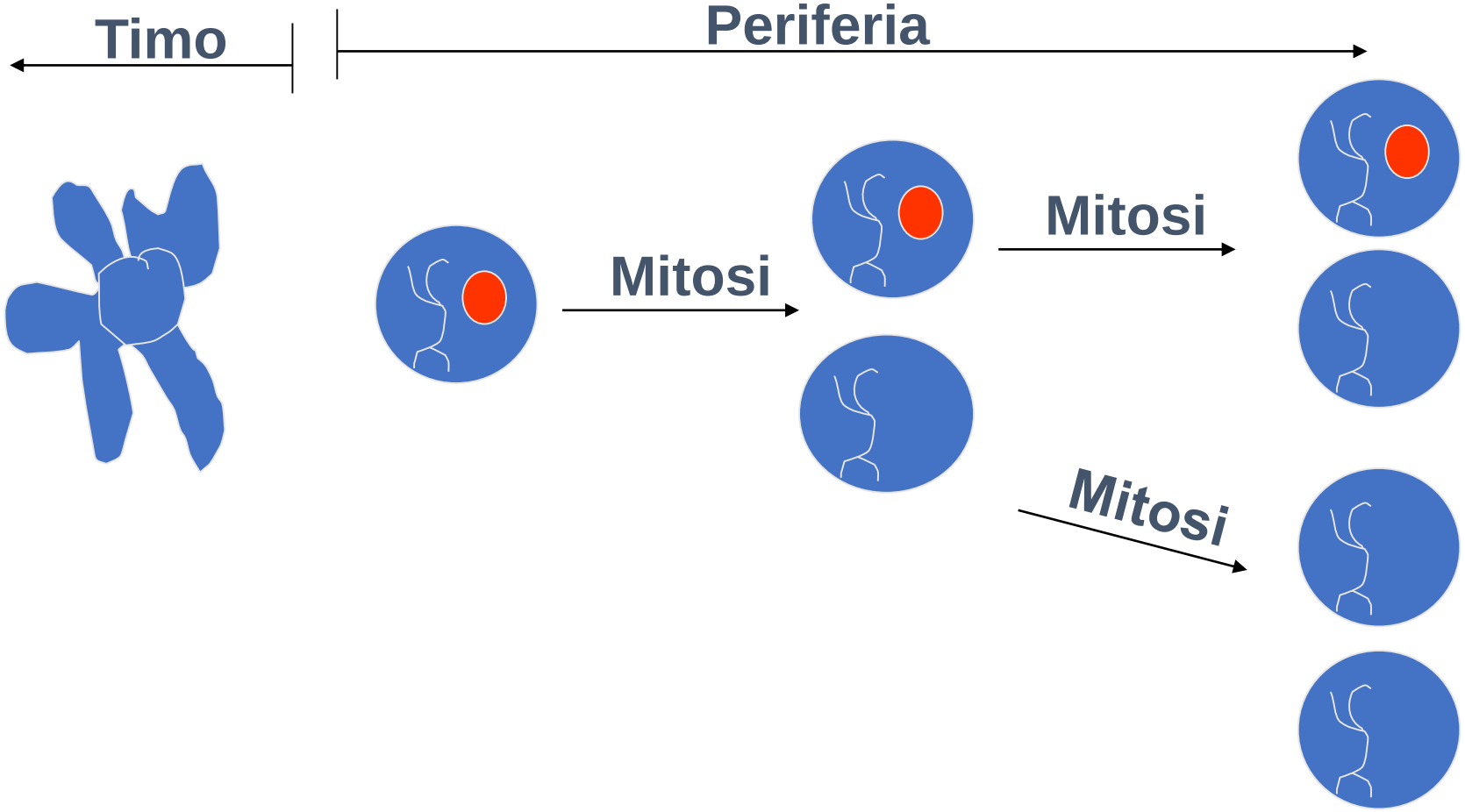


Bono V et al., New Microbiologica 2022

Studio della funzionalità timica (T-cell receptor excision circles-TRECs)



Meyers et al., Vaccines 2025


Timo
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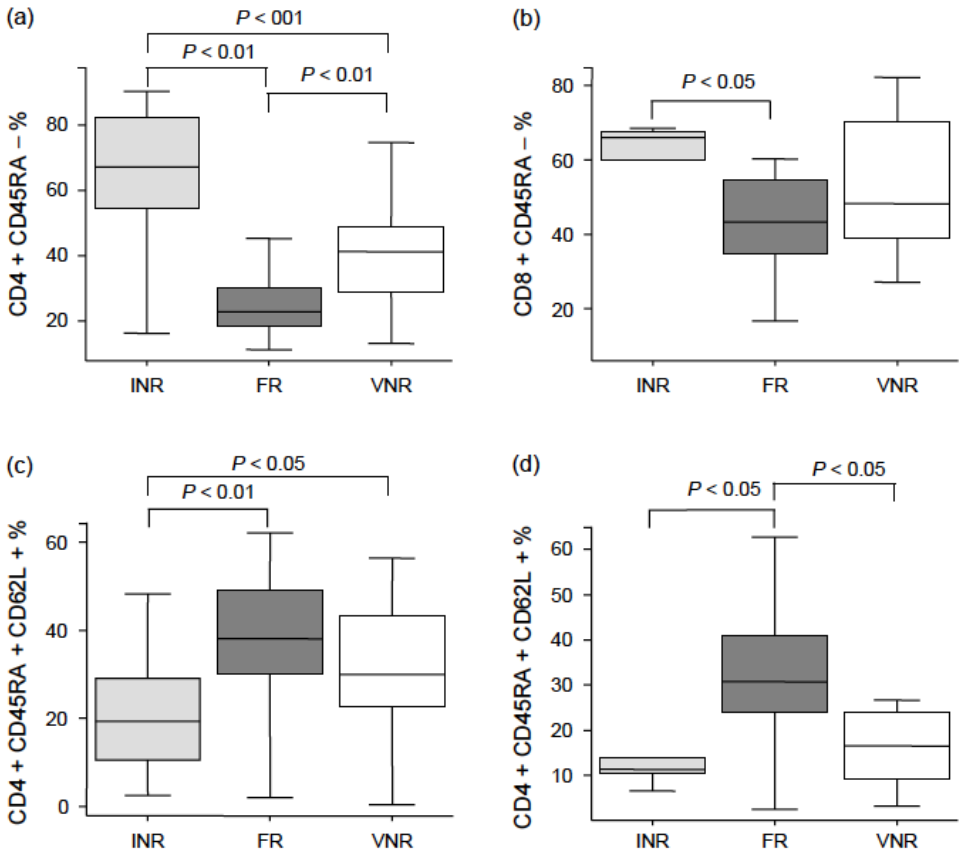
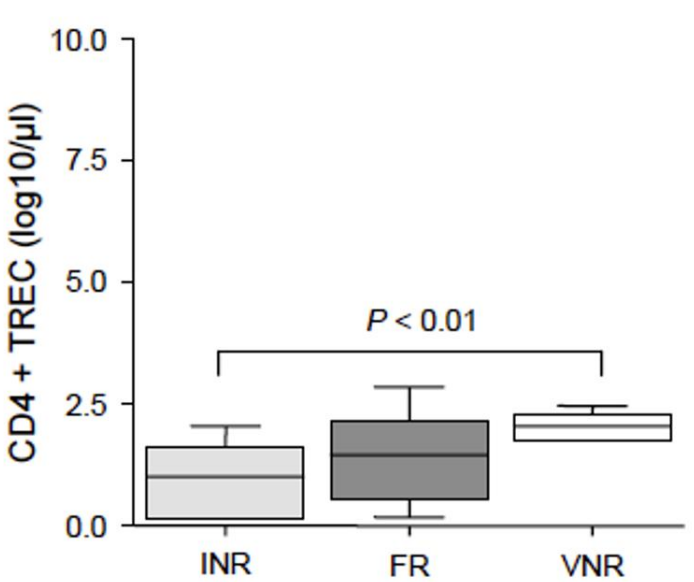
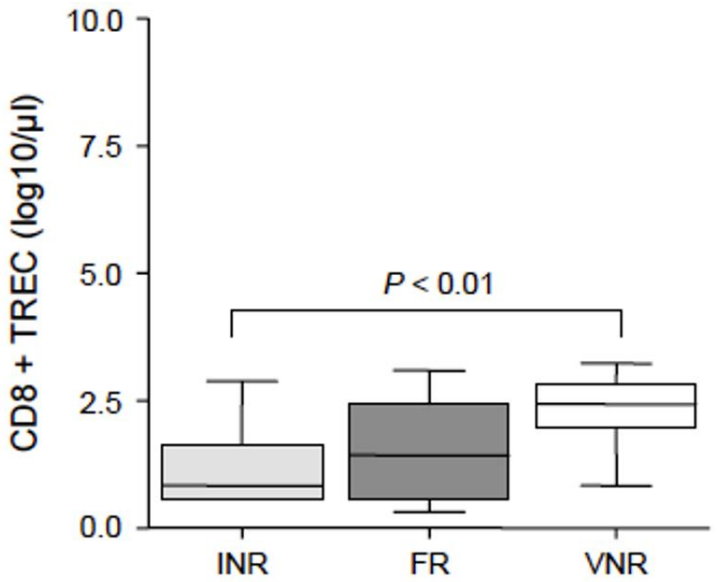
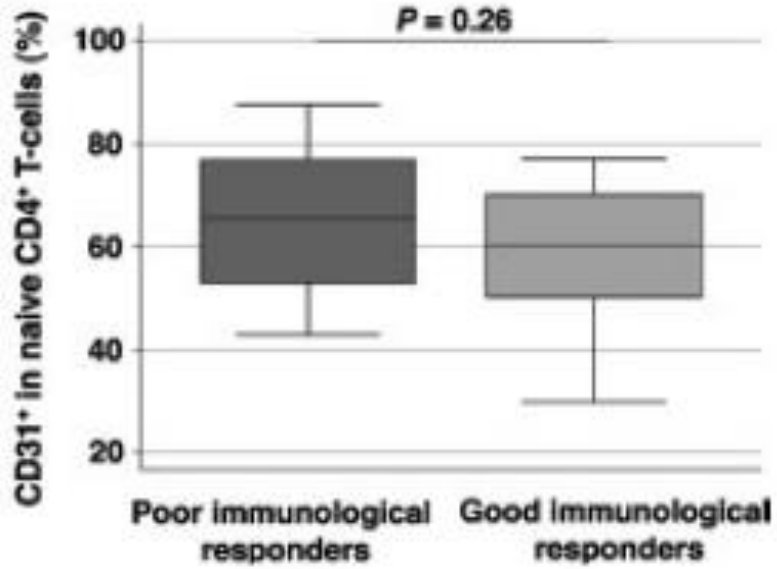
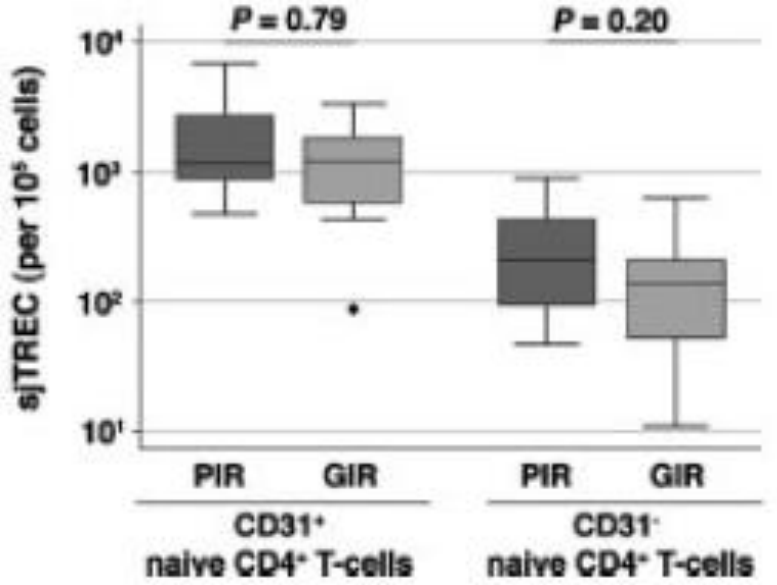




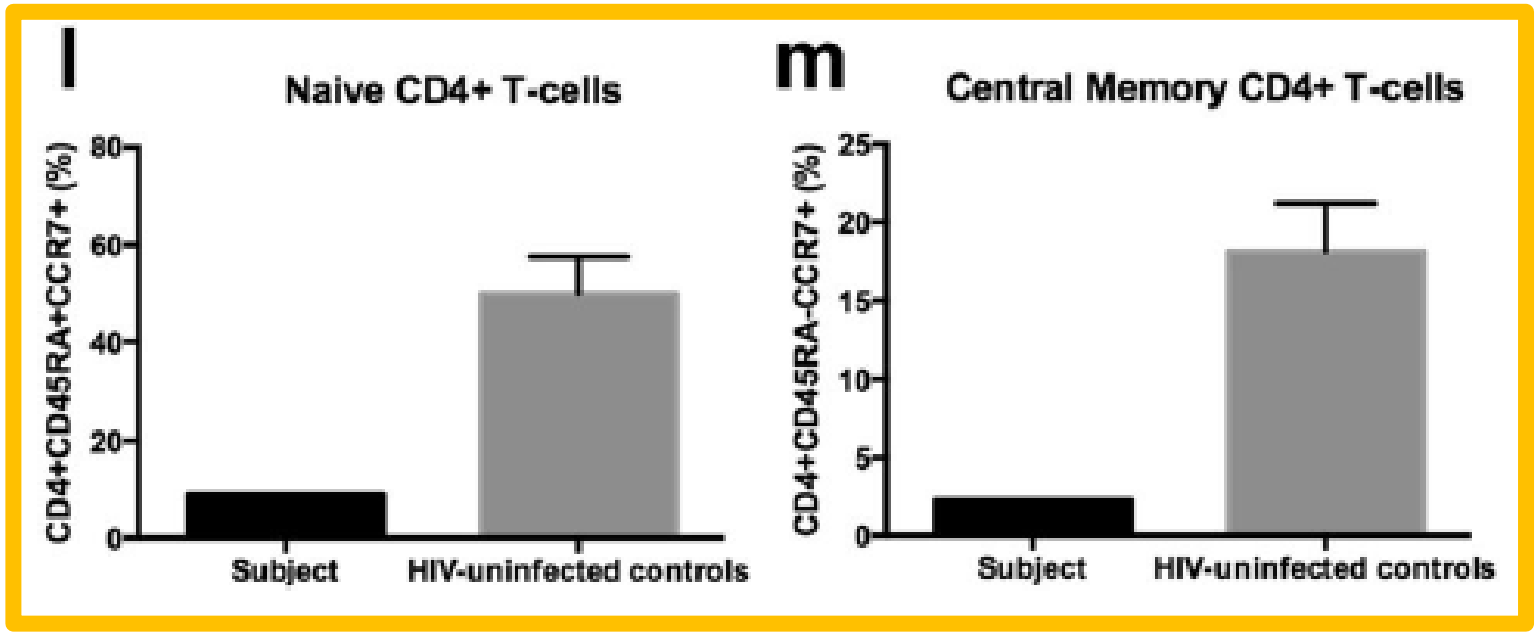


Marchetti et al., AIDS 2006; also Teixeira et al 2001



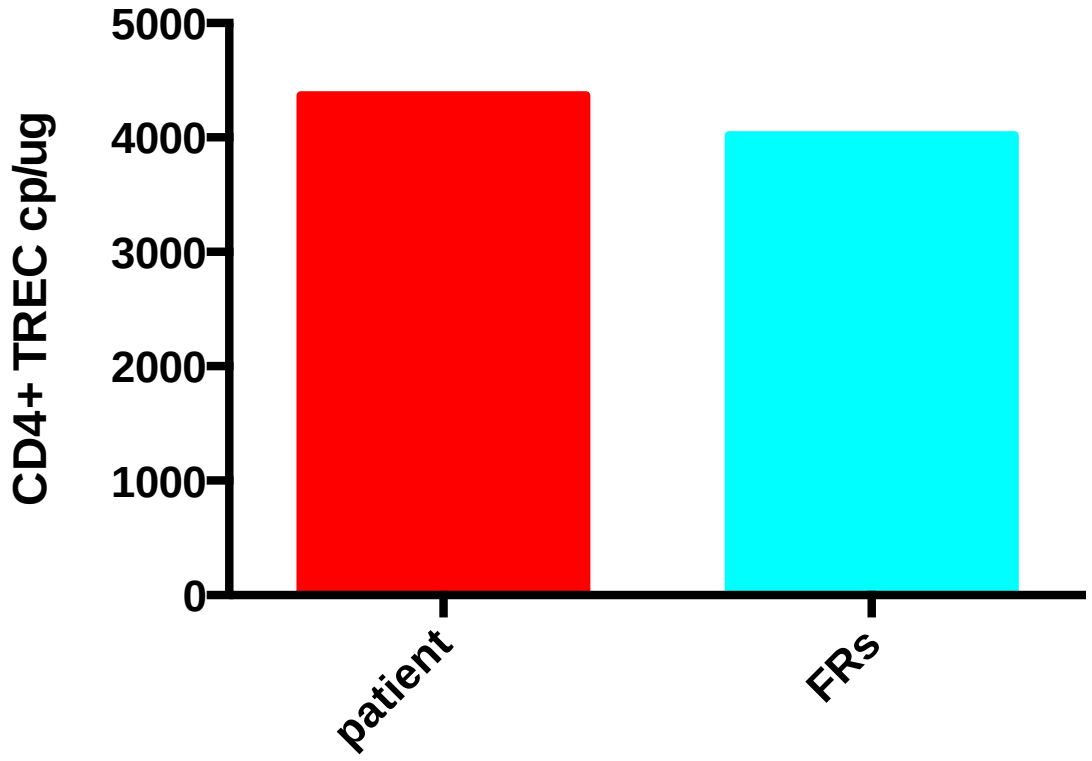


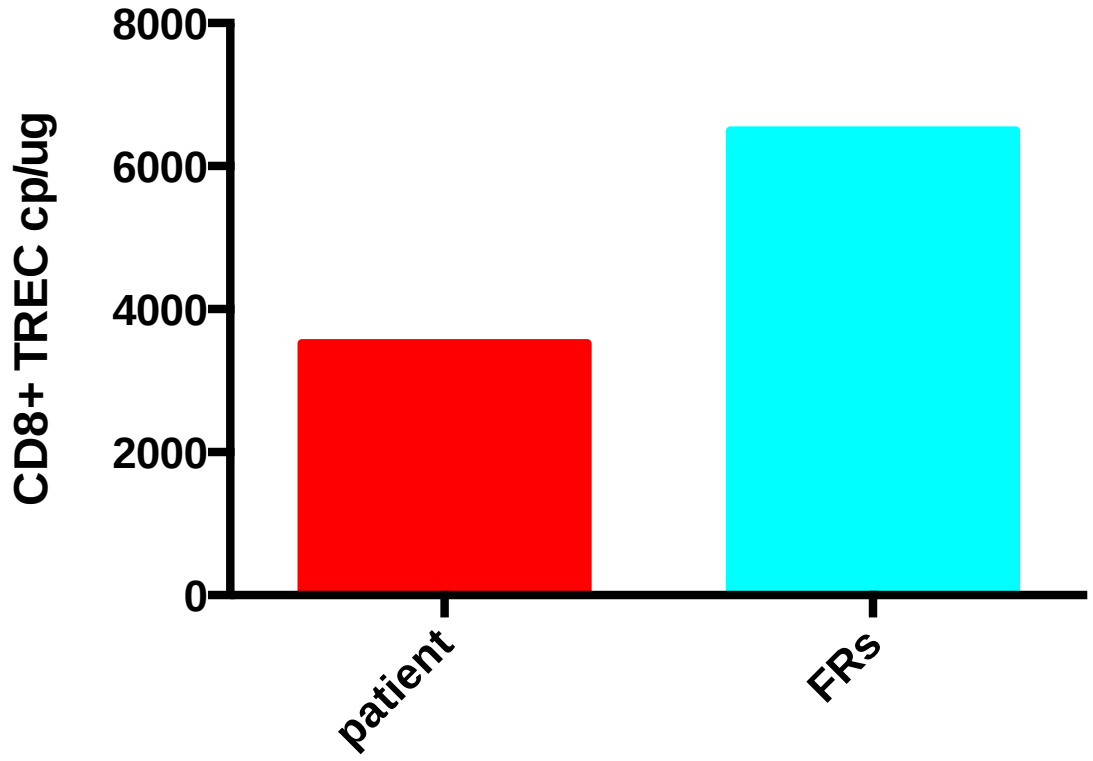
Delobel et al., J Virol 2006; also Cobos-Jimenez et al 2016



Tincati et al. BMC Infect Dis 2018

Thymic output (TREC content)





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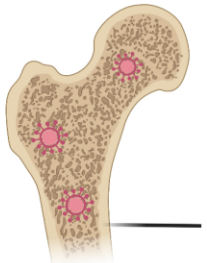

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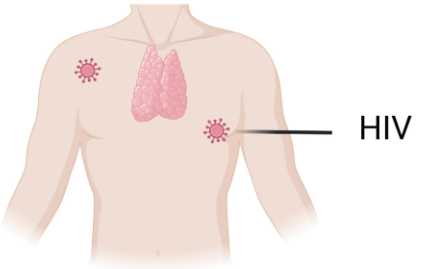

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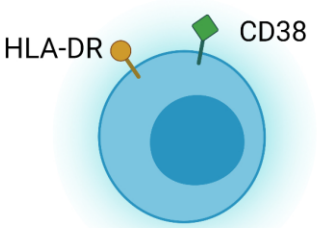

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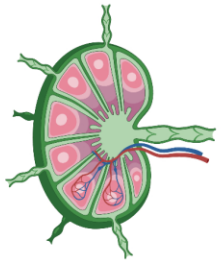

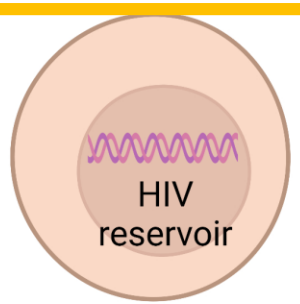

CD4+ T-cells

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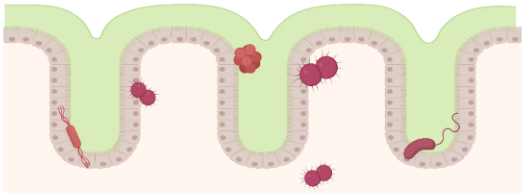
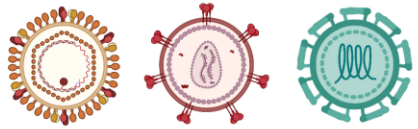
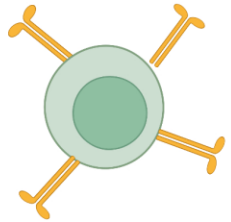


Coinfections

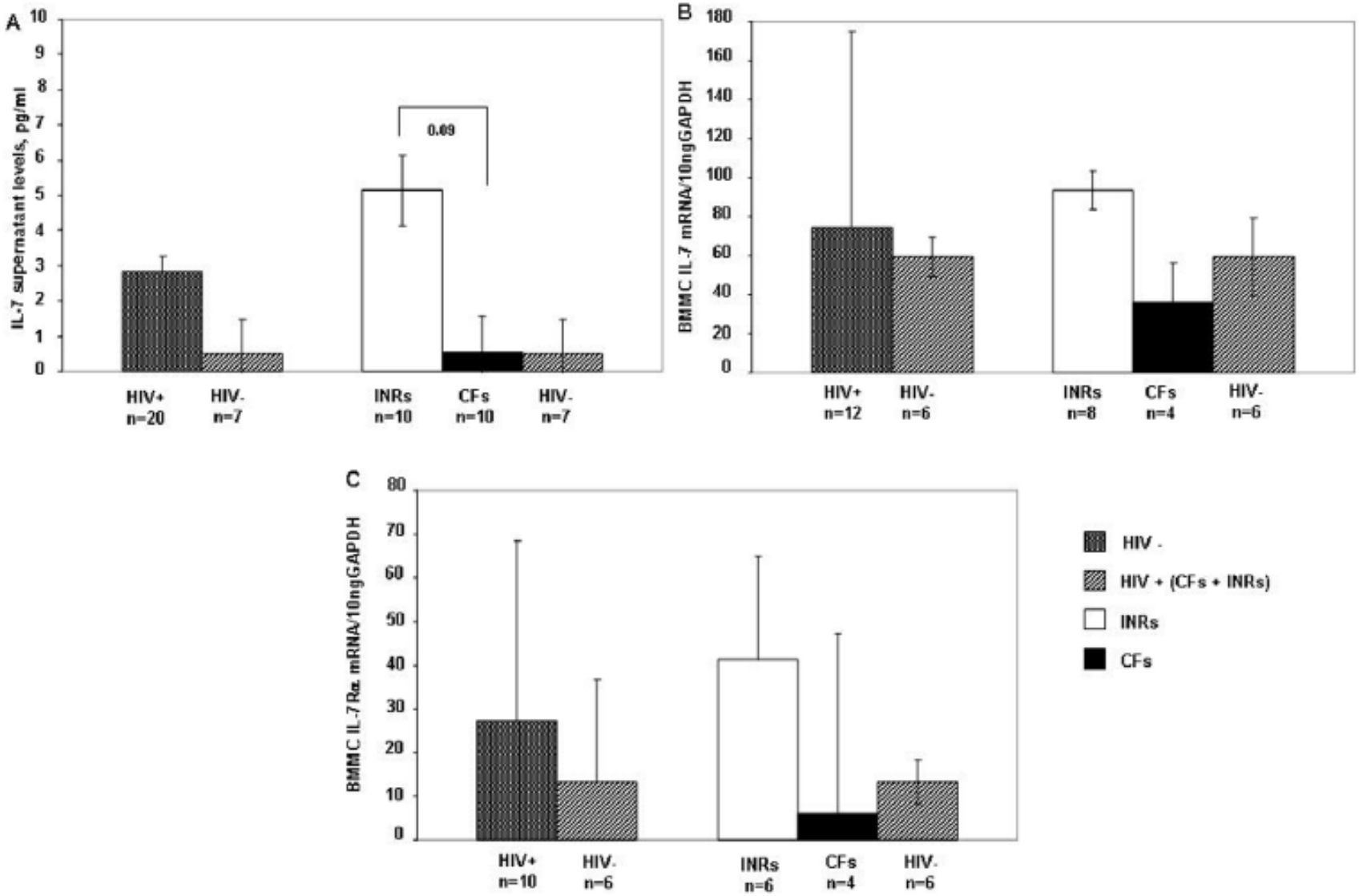


T-cell senescence and exhaustion



Bono V et al., New Microbiologica 2022

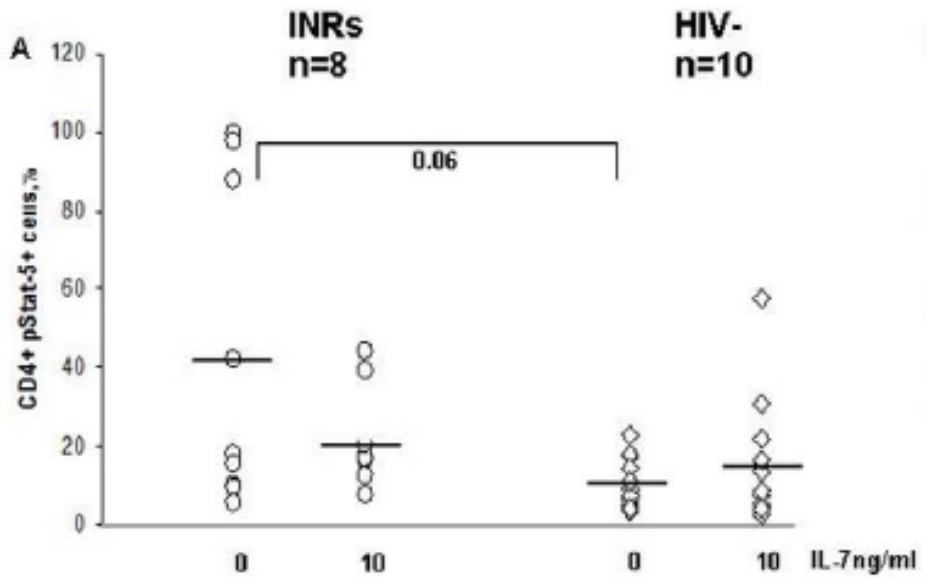
IL-7/IL-7R Axis

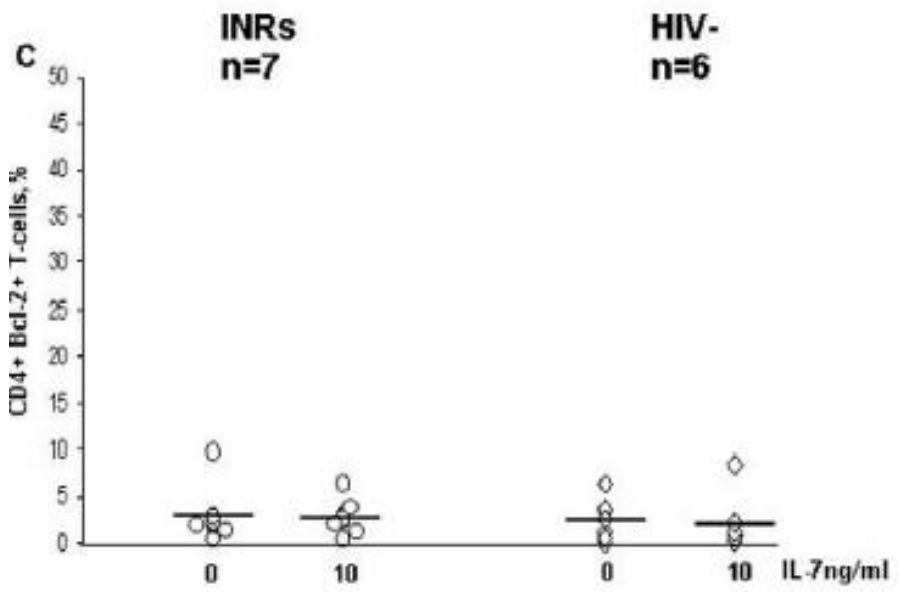


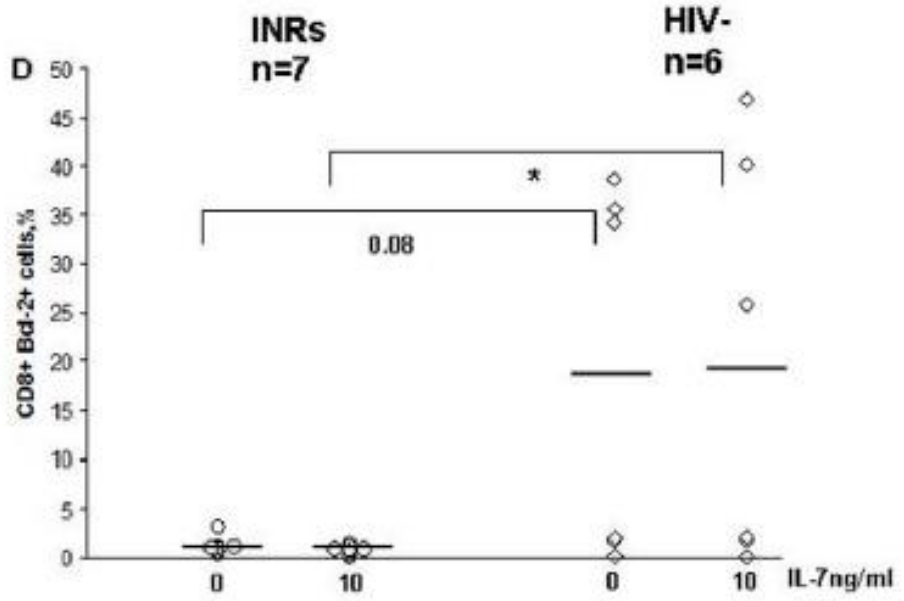
High IL-7/IL-7R production in the bone marrow in INRs,
but

Bellistrì G et al., Plos One 2010

reduced IL-7/IL-7R signalling in INRs





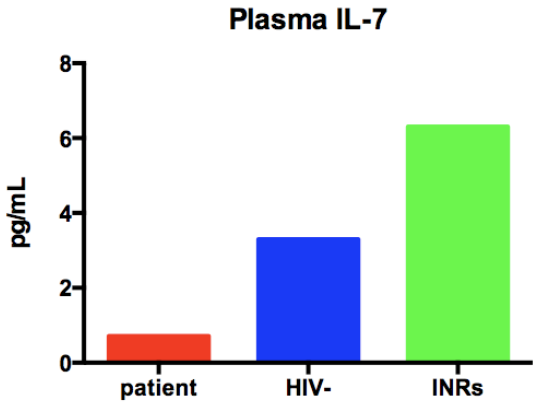


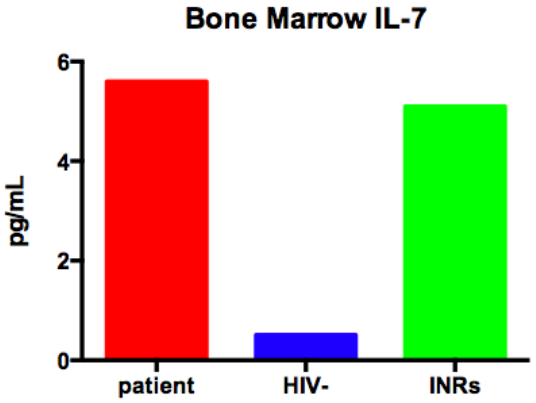
Bellistrì G et al., Plos One 2010

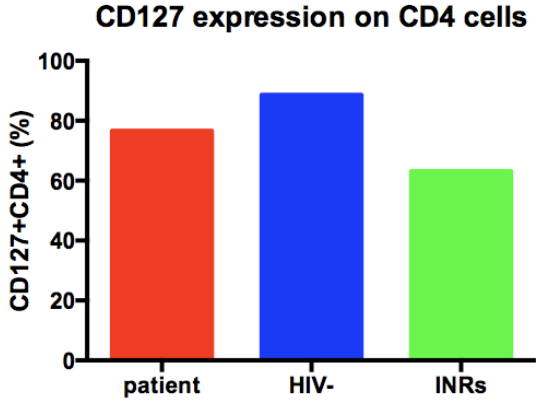
Tincati et al. BMC Infect Dis 2018

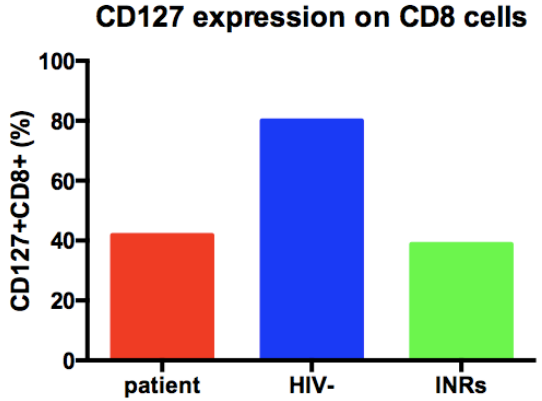
IL-7/IL-7R Axis

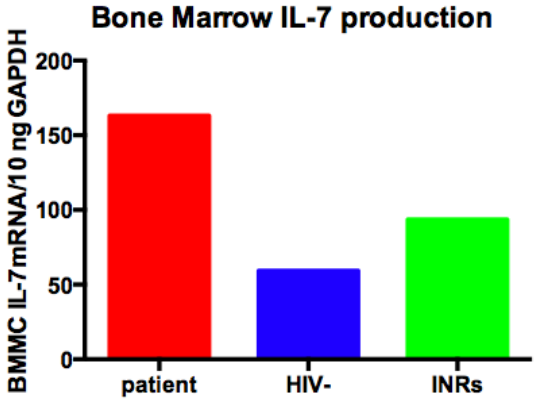
Peripheral blood

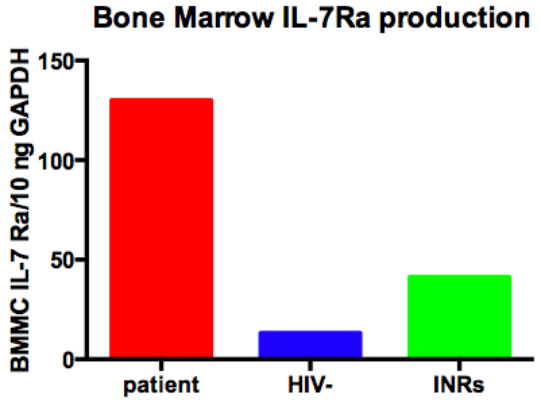






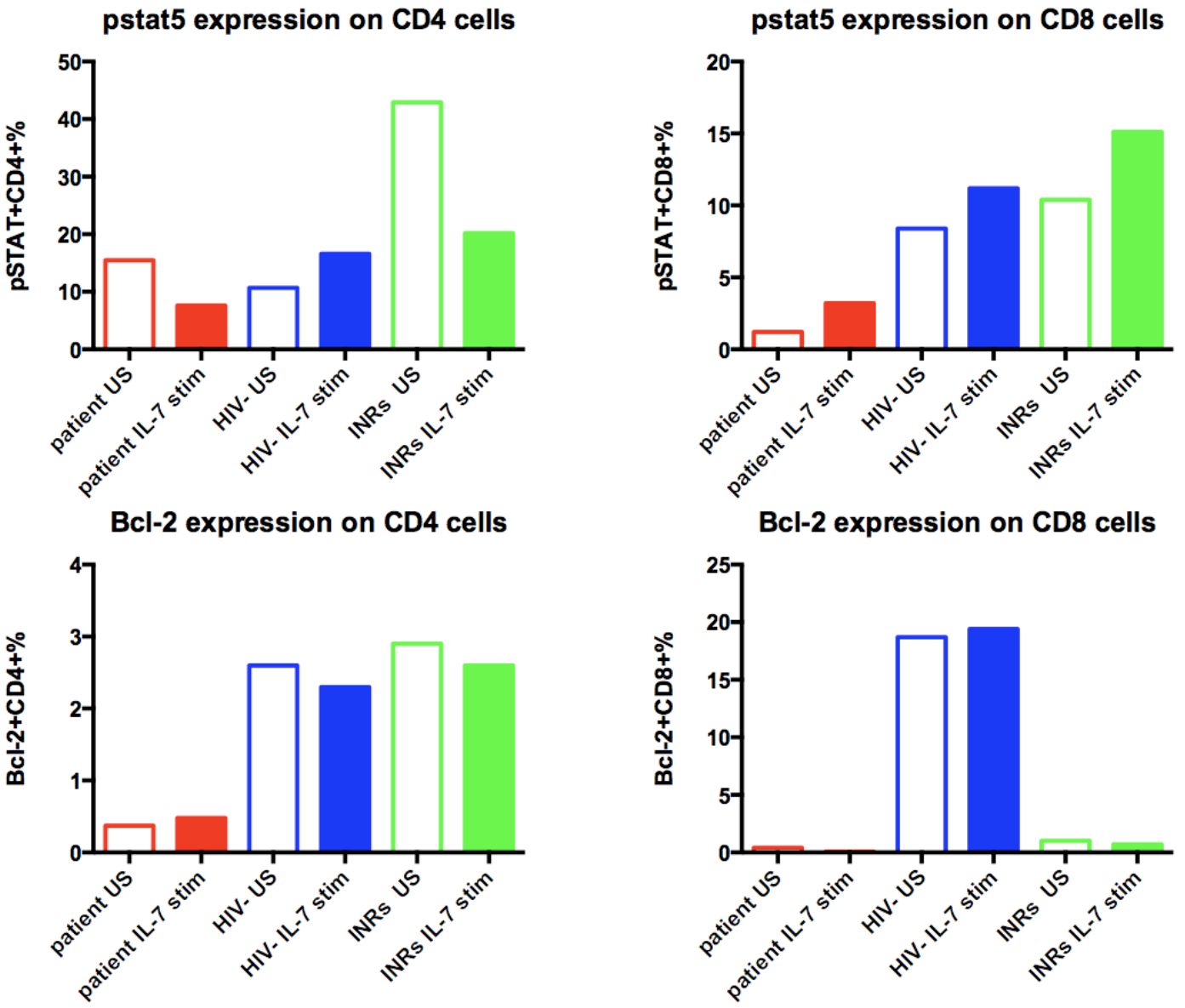






BM aspirate: *Severe dysplasia of myeloid, erythroid and platelet precursors, hypocellularity, matrix fibrosis*

IL-7 signaling in CD4+ and CD8+ T-cell subsets

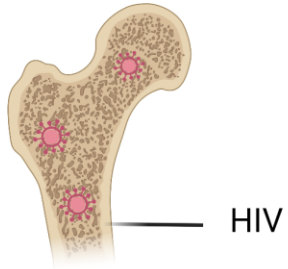


Tincati et al. BMC Infect Dis 2018

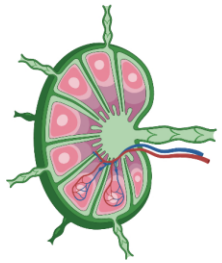
Years 2004-2013

Looking for pathogenetic pathway(s) for lack of CD4+ recovery in INRs

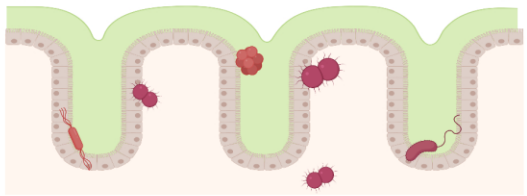
Depletion of progenitor cells in the bone marrow



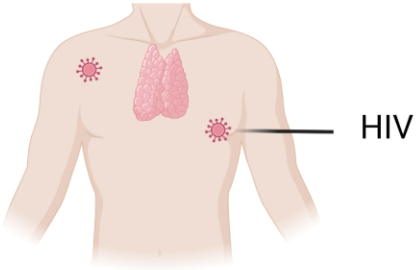
Lymphoid tissue fibrosis

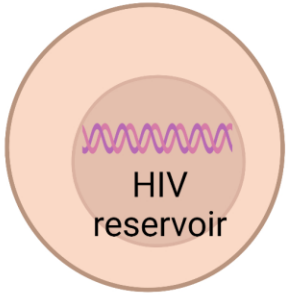


Gut barrier disruption, microbial translocation and gut dysbiosis



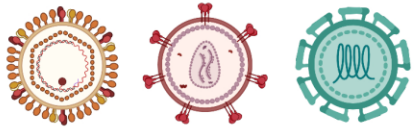
Reduced size and thymic output





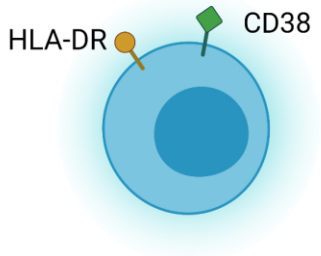
CD4+ T-cells

Coinfections

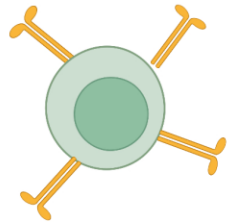


Alteration in mitochondrial respiration

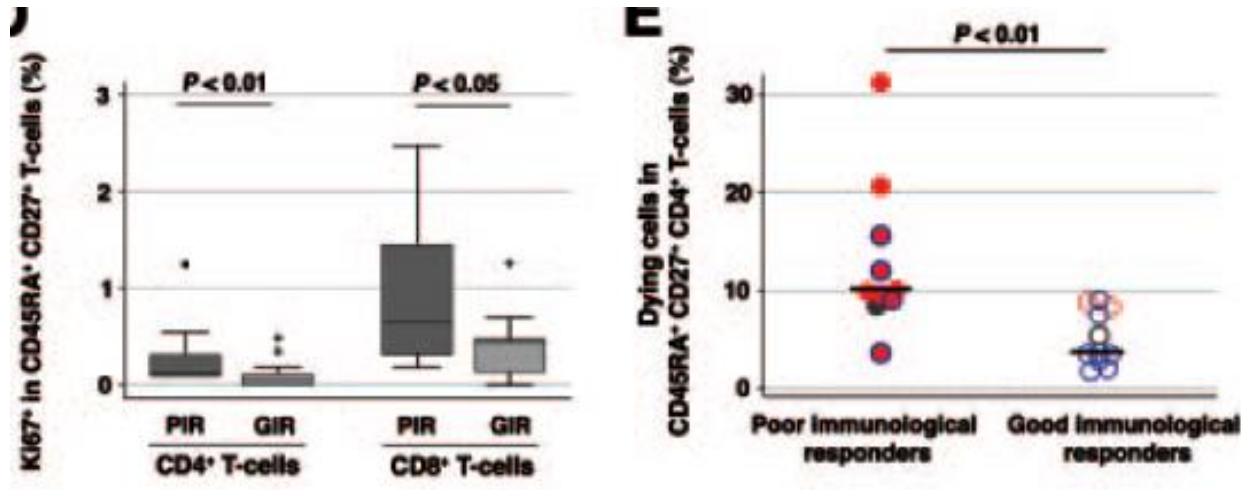
Persistent CD4+ T-cell hyperactivation

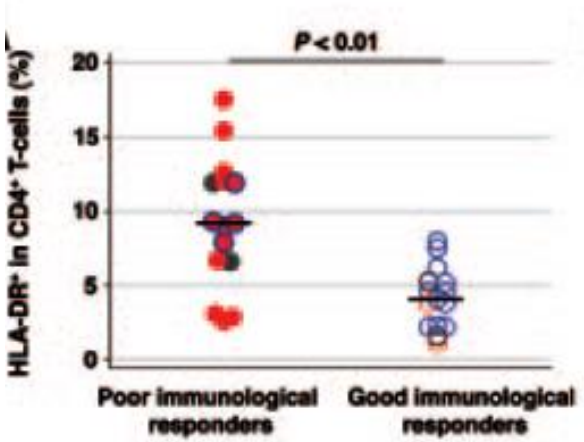


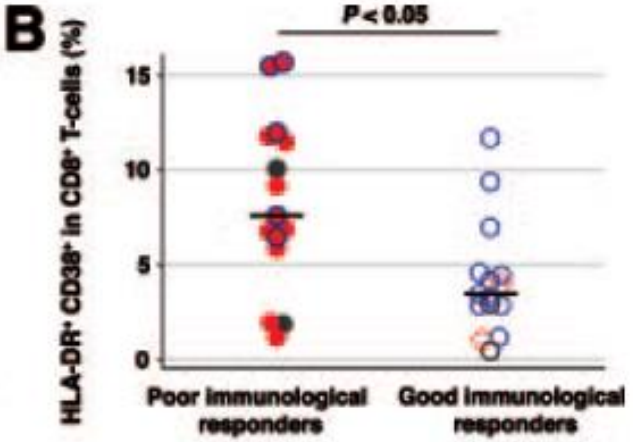
T-cell senescence and exhaustion



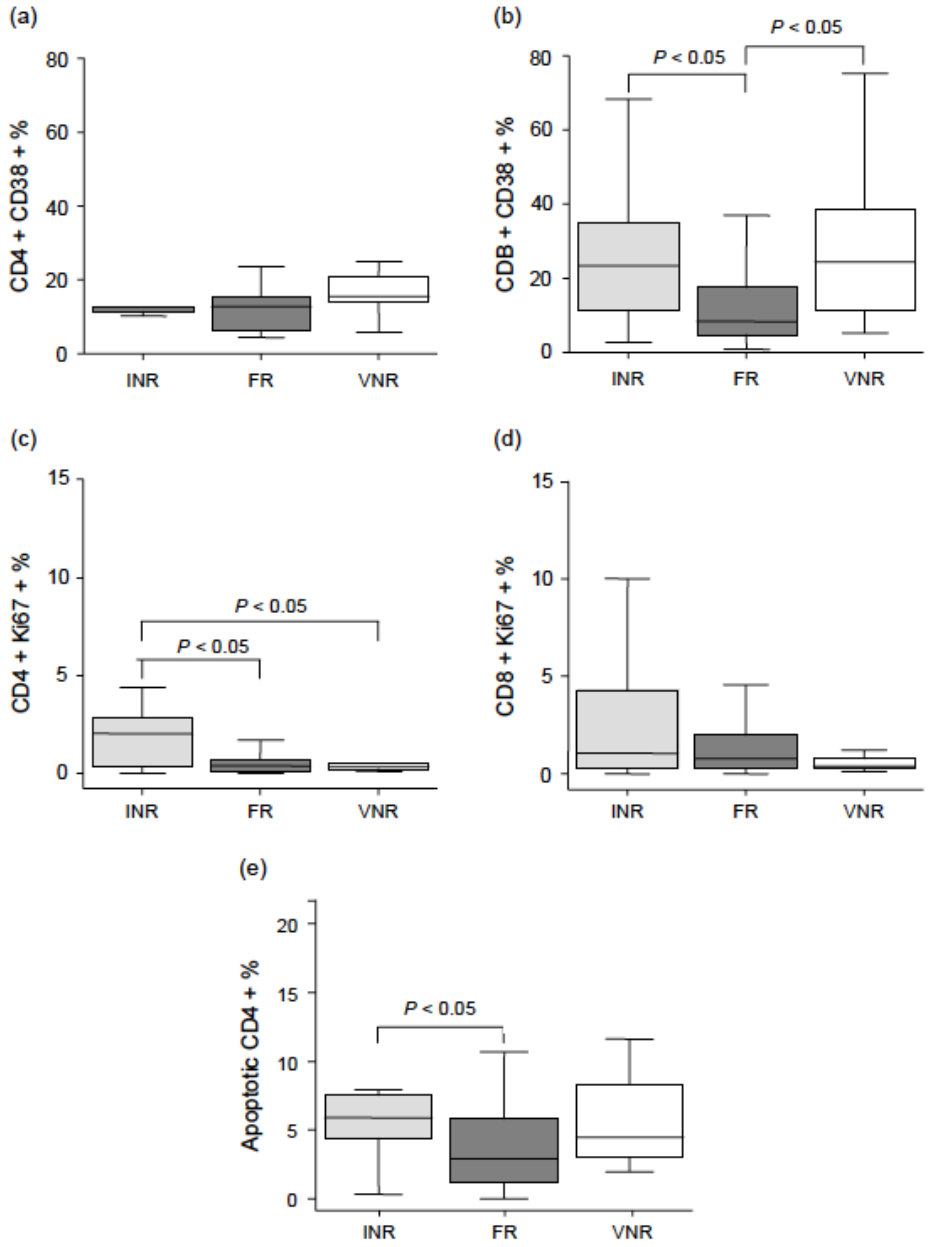
Bono V et al., New Microbiologica 2022







Delobel et al., J Virol 2006

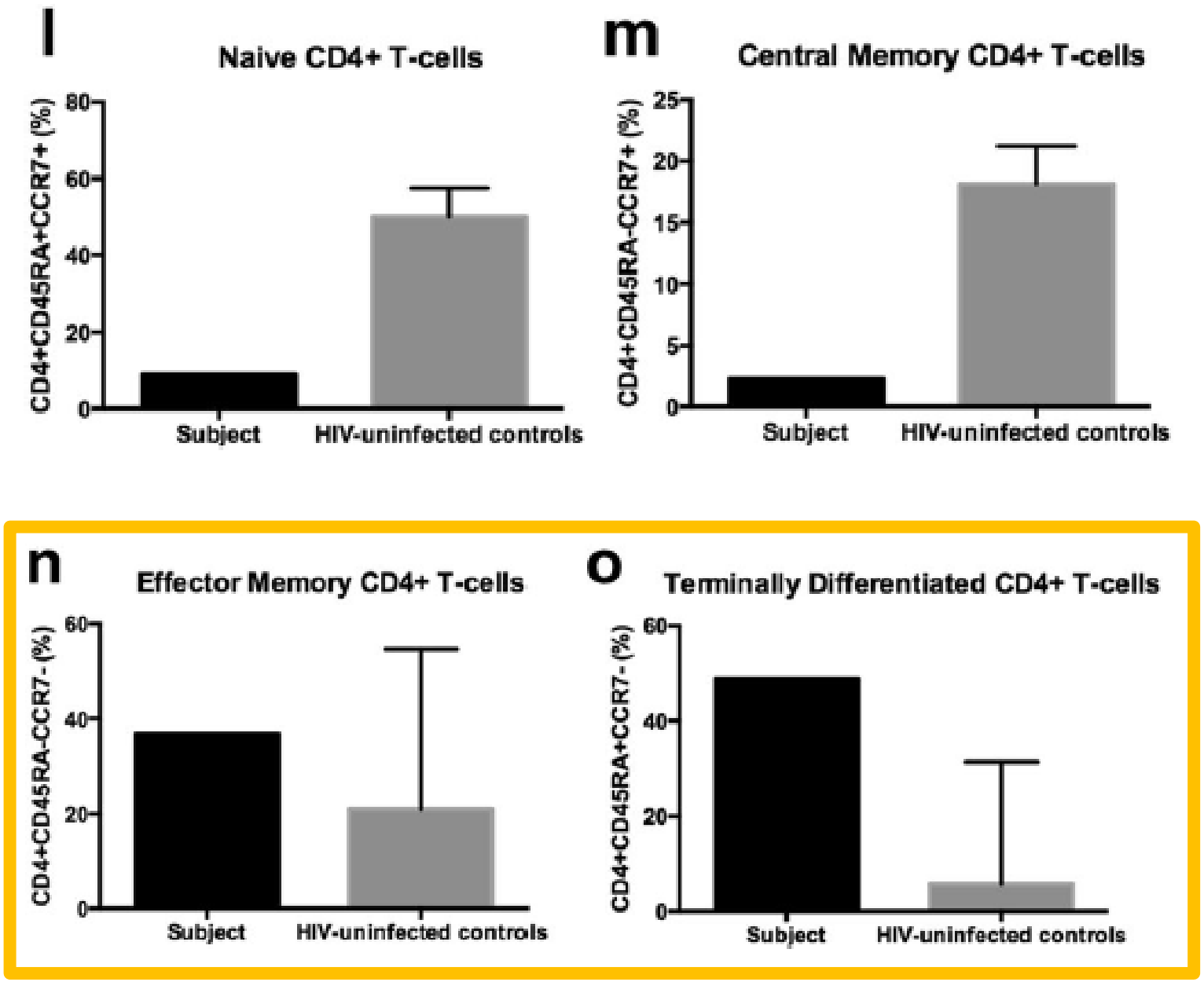


Marchetti et al., AIDS 2006

Table 2. Factors associated with late changes in CD4⁺ T cell gains in human immunodeficiency virus–infected patients.

Factor	Unadjusted analysis		Adjusted analysis[a]	
	Mean change (95% CI) in CD4⁺ T cell gains, cells/mm³	*P*	Mean change (95% CI) in CD4⁺ T cell gains, cells/mm³	*P*
Each 5-percentage-point increase in percentage of (CD38⁺HLA-DR⁺) CD8⁺ T cells	−45 (−64 to −25)	<.001	−35 (−62 to −20)	<.001
Each 5-percentage-point increase in percentage of (CD45RA⁺CD62L⁺) CD4⁺ T cells	+15 (4–26)	.01	+17 (7–26)	.001
Each 5-percentage-point increase in percentage of (CD38⁺HLA-DR⁺) CD4⁺ T cells	−61 (−108 to −14)	.01	+18 (−33 to 70)	.47
Each 1-month increase in the duration of viral suppression[b]	+6 (4–8)	<.001	+5 (3–7)	<.001
Each 10-year increase in age	−37 (−88 to 13)	.14	−50 (−90 to −7)	.02
Each increase of 100 cells/mm³ in pretherapy CD4⁺ T cell count	+10 (−10 to 32)	.30	−10 (−30 to 10)	.33
Each increase of 1 $\log_{10}$ copy/mL in pretherapy plasma HIV RNA level	+15 (−22 to 51)	.43	−3 (−36 to 30)	.85
Sex				
Male	Reference	—	Reference	—
Female	−19 (−137 to 99)	.75	−21 (−135 to 93)	.71
Hepatitis C virus antibody serostatus				
Negative	Reference	—	Reference	—
Positive	−14 (−95 to 67)	.73	+64 (−8 to 135)	.08
Each 10% increase in frequency of low-level viremia[c]	−2 (−3 to −0.5)	.007	+2 (−9 to 14)	.65

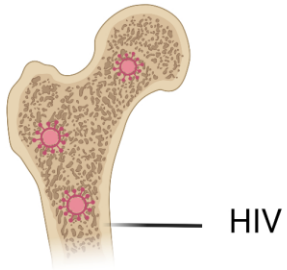
Hunt et al., JID 2003



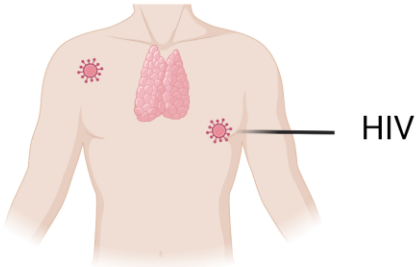
Tincati et al. BMC Infect Dis 2018

Causes of excessive immune activation

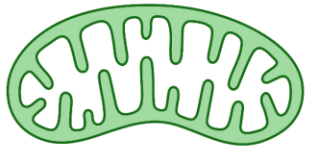
Depletion of progenitor cells in the bone marrow



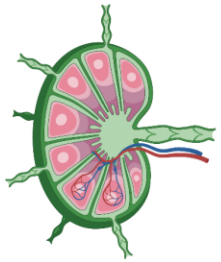
Reduced size and thymic output

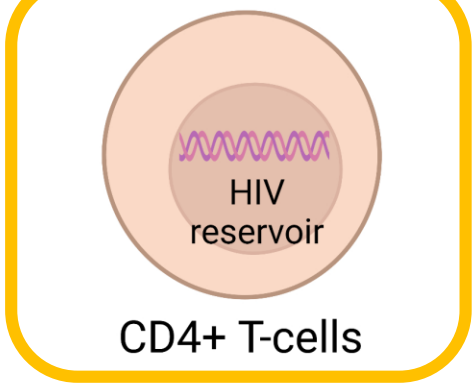


Alteration in mitochondrial respiration

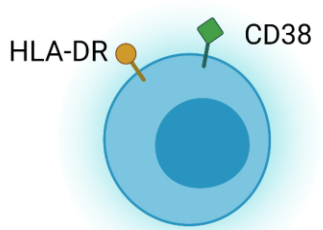


Lymphoid tissue fibrosis

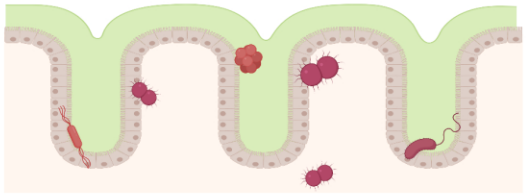




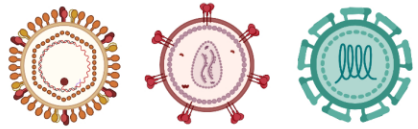
Persistent CD4+ T-cell hyperactivation



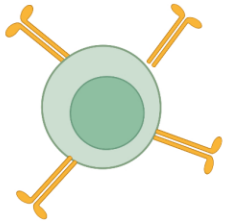
Gut barrier disruption, microbial translocation and gut dysbiosis



Coinfections



T-cell senescence and exhaustion



Bono V et al., New Microbiologica 2022

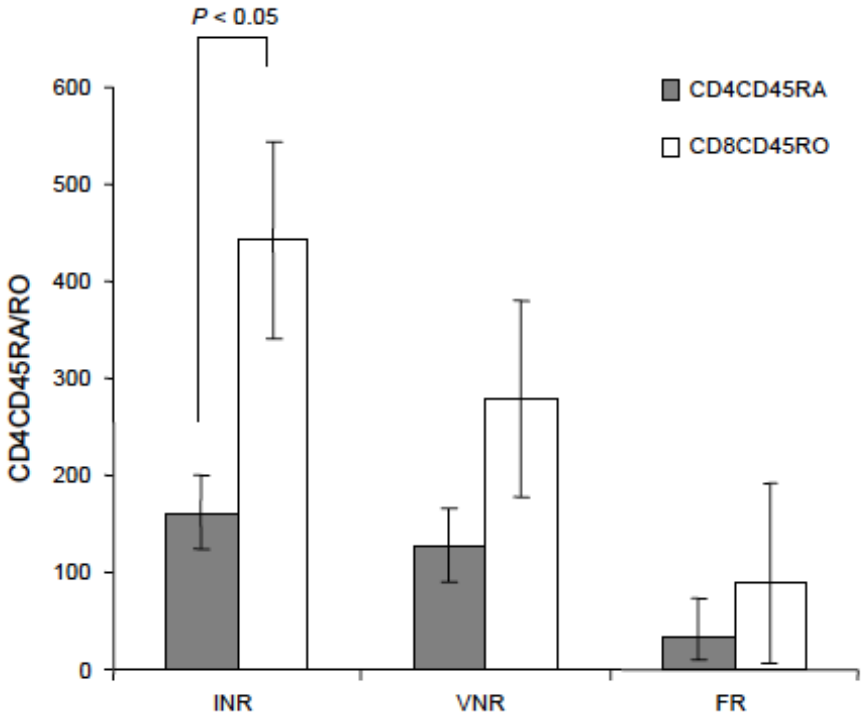
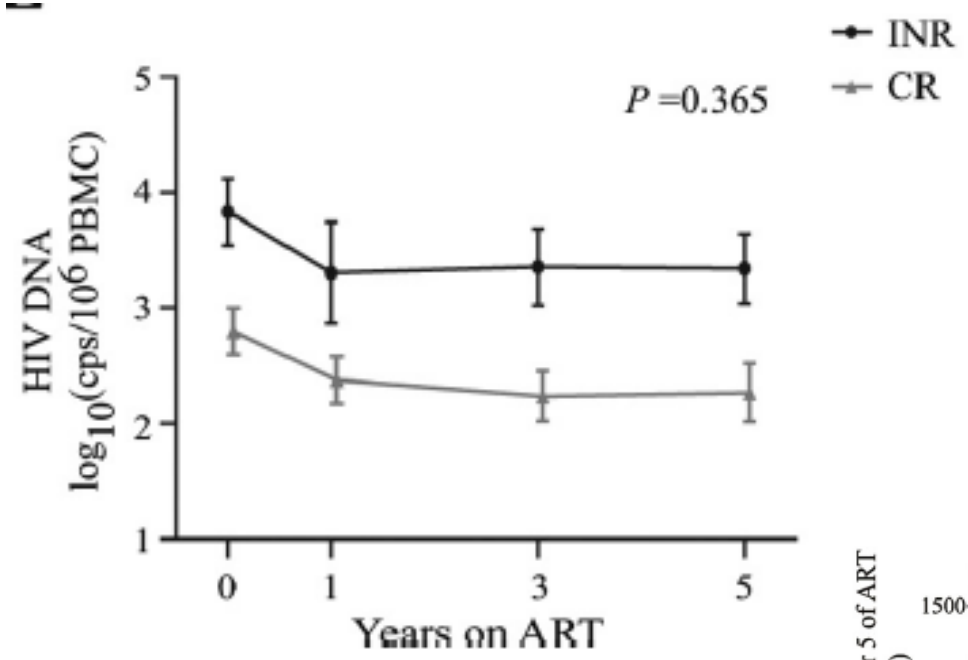
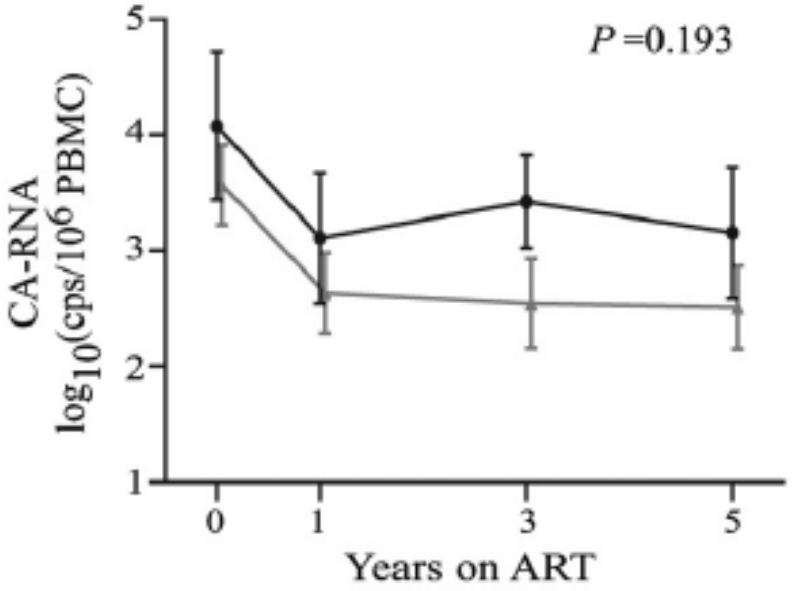
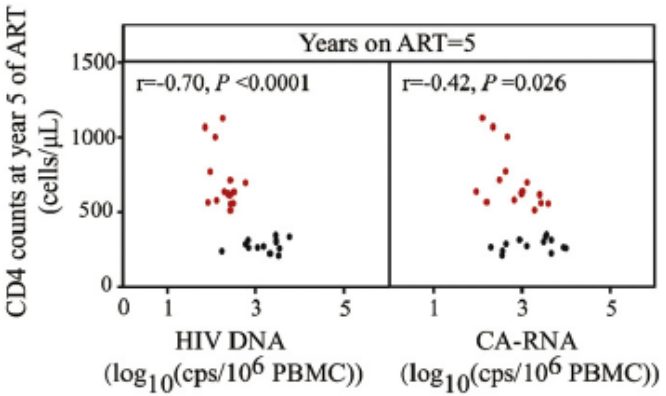


Fig. 4. Quantitation of intracellular HIV-DNA in CD4 in HIV-infected individuals with different responses to HAART.

Marchetti et al., AIDS 2006







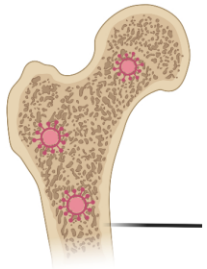
Zhang et al., AIDS 2006

Our patient: HIV Viral burden

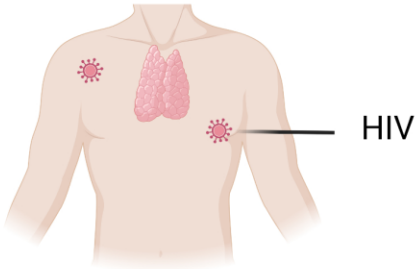
- HIV Residual Viremia <2 cp/ml
- HIV DNA
  - 2049cp/10^6CD4; integrated HIV DNA 268 cp/10^6CD4; 2LTR 199cp/10^6CD4
  - FR: tDNA 846[337-1148]cp/10^6CD4; iHIV-DNA 194[94-575]cp/10^6CD4; 2-LTR circles (5 [0-29]cp/10^6CD4)

Causes of excessive immune activation

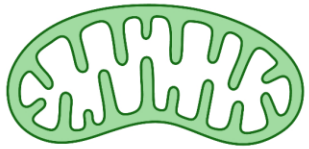
Depletion of progenitor cells in the bone marrow



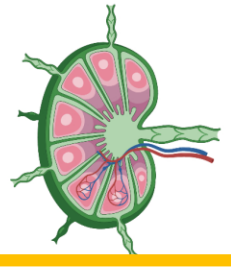
Reduced size and thymic output

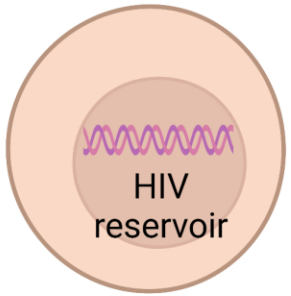


Alteration in mitochondrial respiration



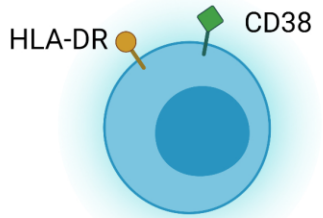
Lymphoid tissue fibrosis



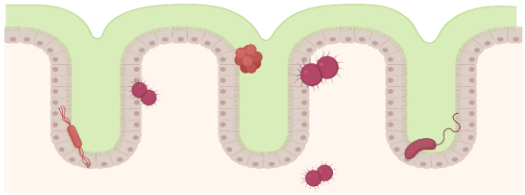


CD4+ T-cells

Persistent CD4+ T-cell hyperactivation



Gut barrier disruption, microbial translocation and gut dysbiosis



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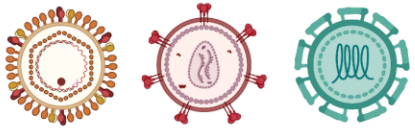
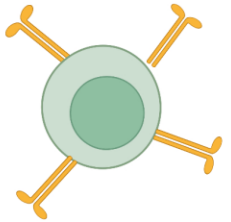


T-cell senescence and exhaustion

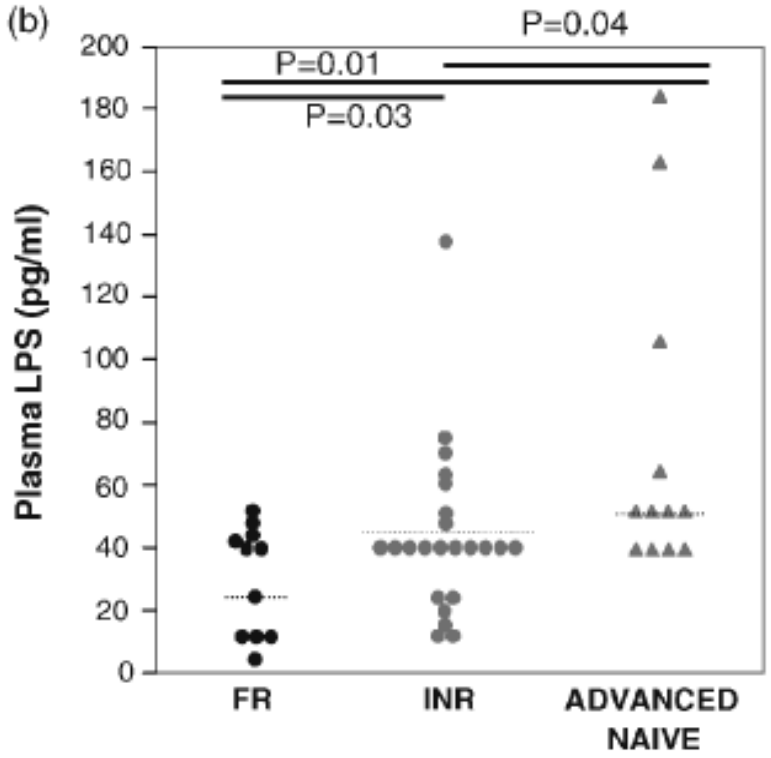


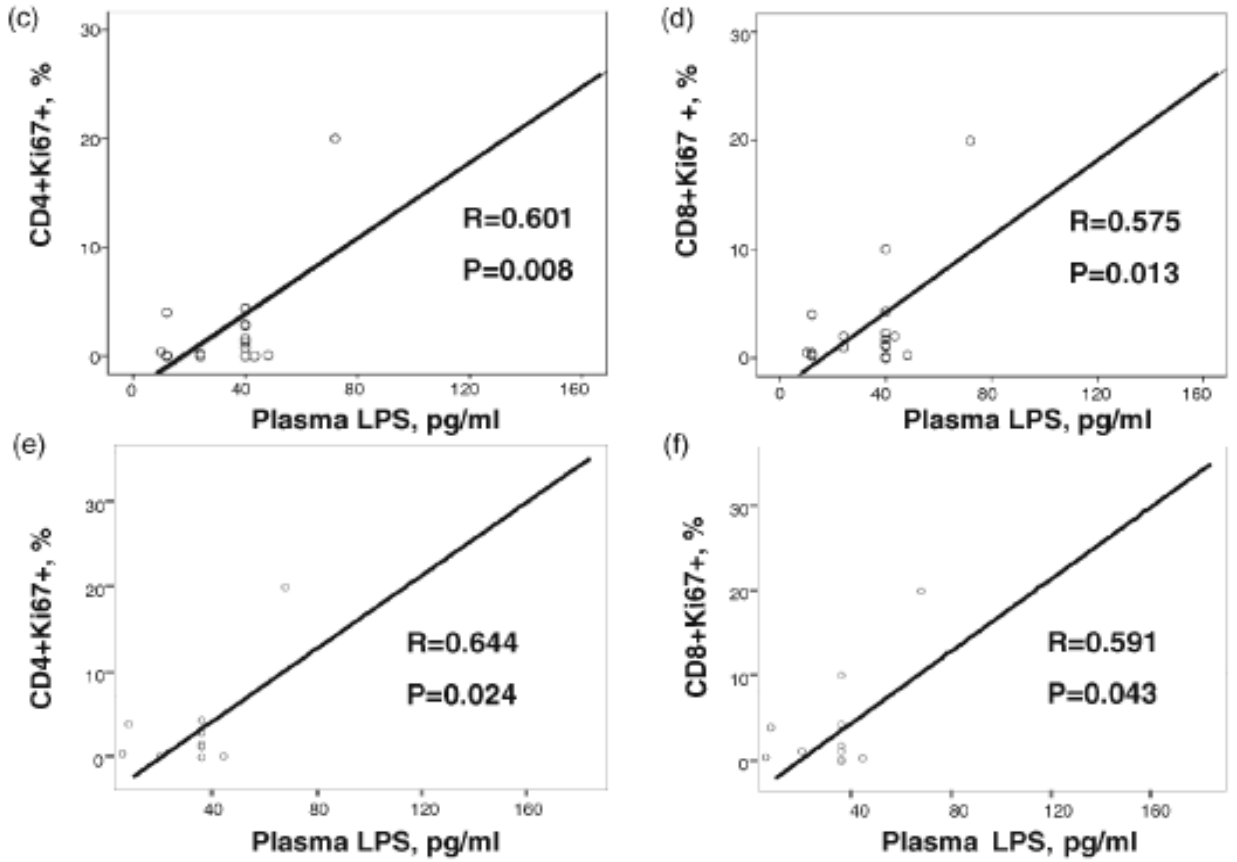
Bono V et al., New Microbiologica 2022

Higher microbial translocation in INRs

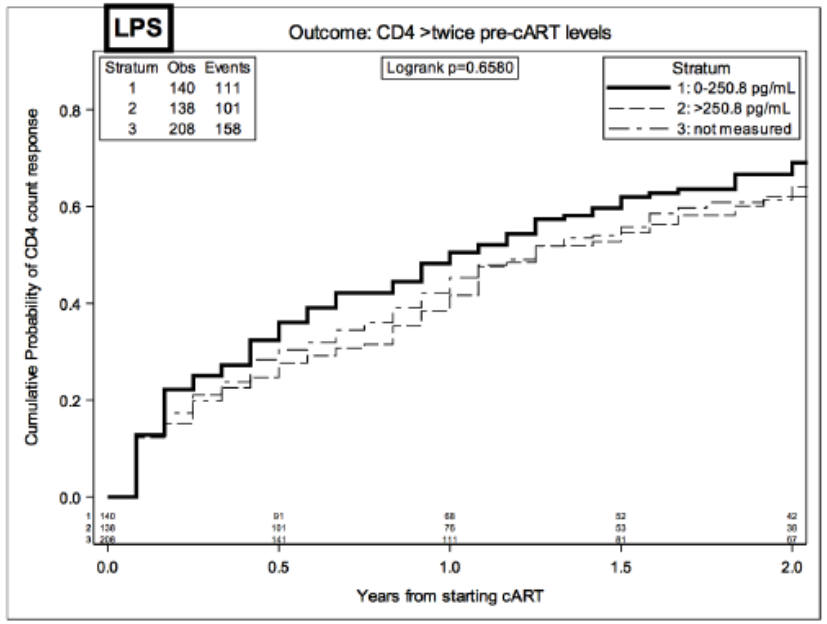
INRs:

CD4+ T-cell≤200; HIV-RNA≤50





Marchetti et al. AIDS 2008; also: Jiang et al. JID 2009



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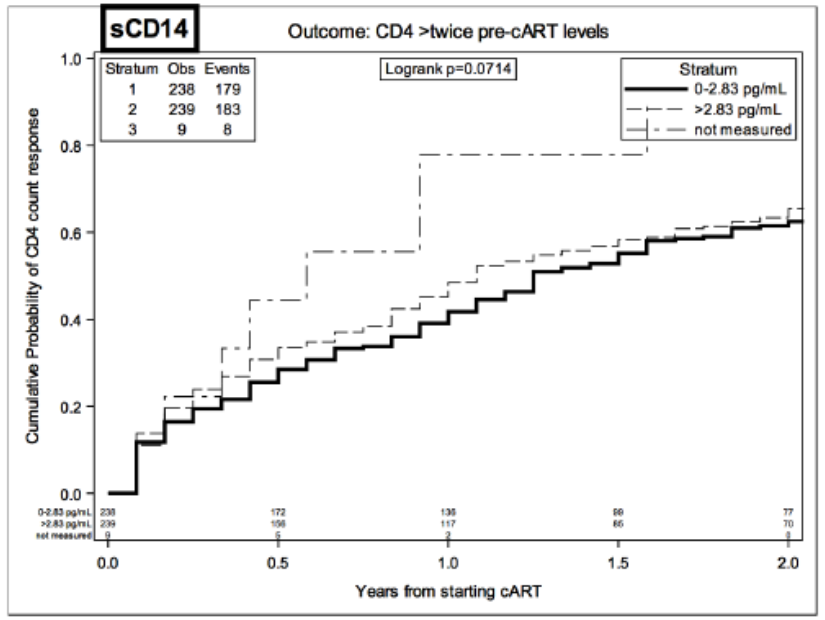
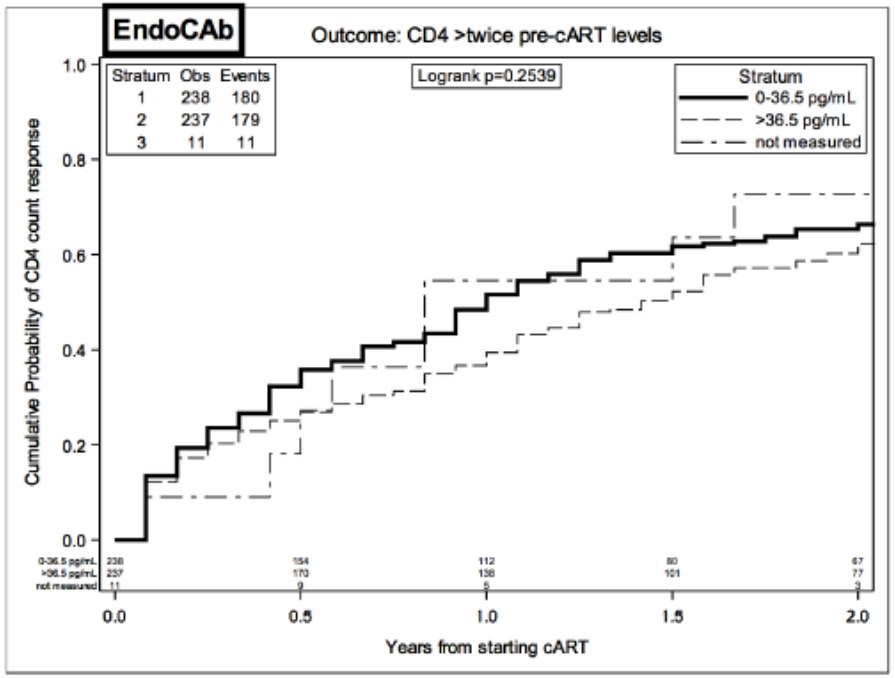


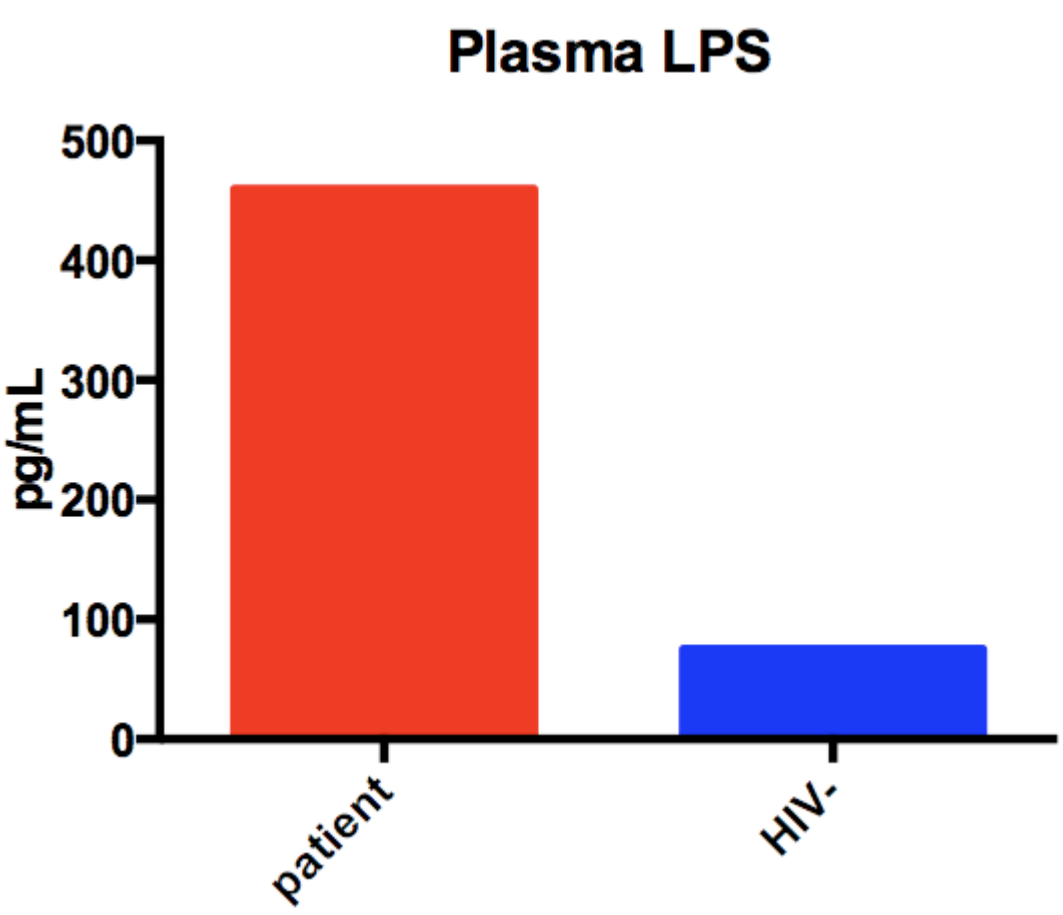


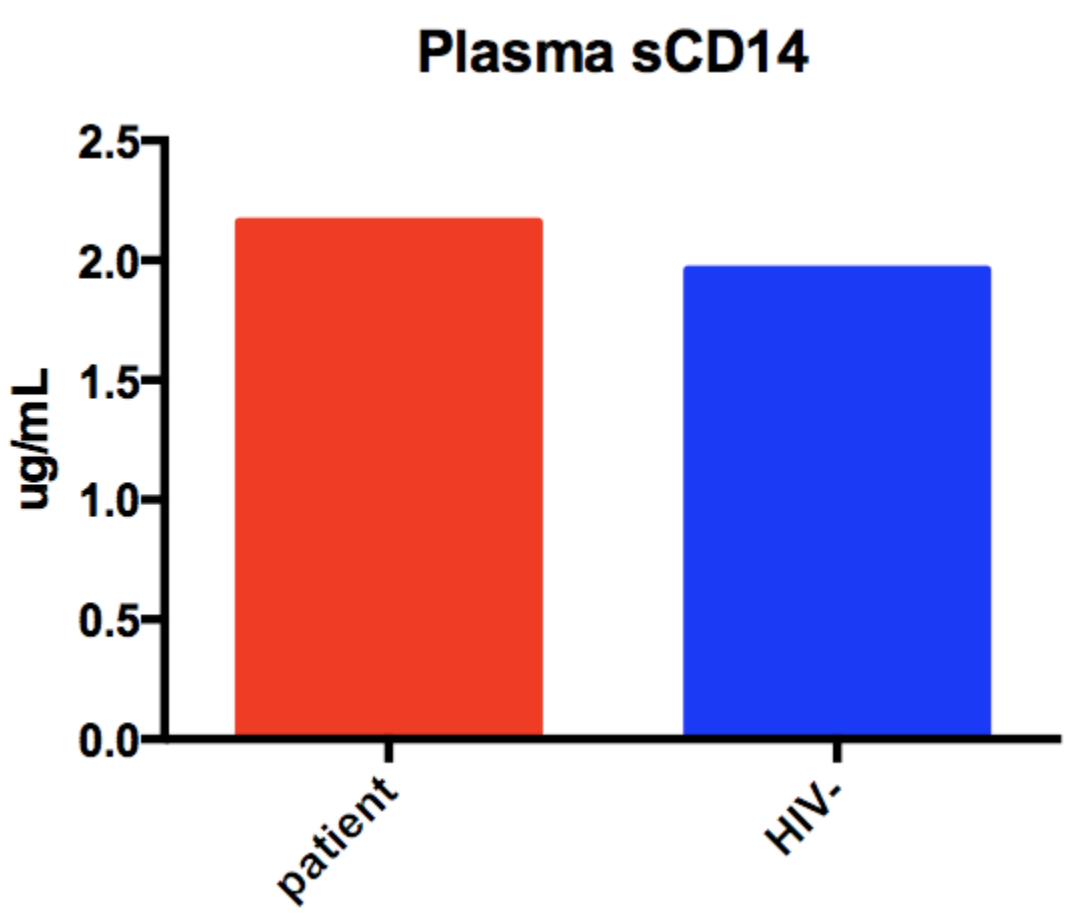
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS
Conceived by Professor Mauro Moroni

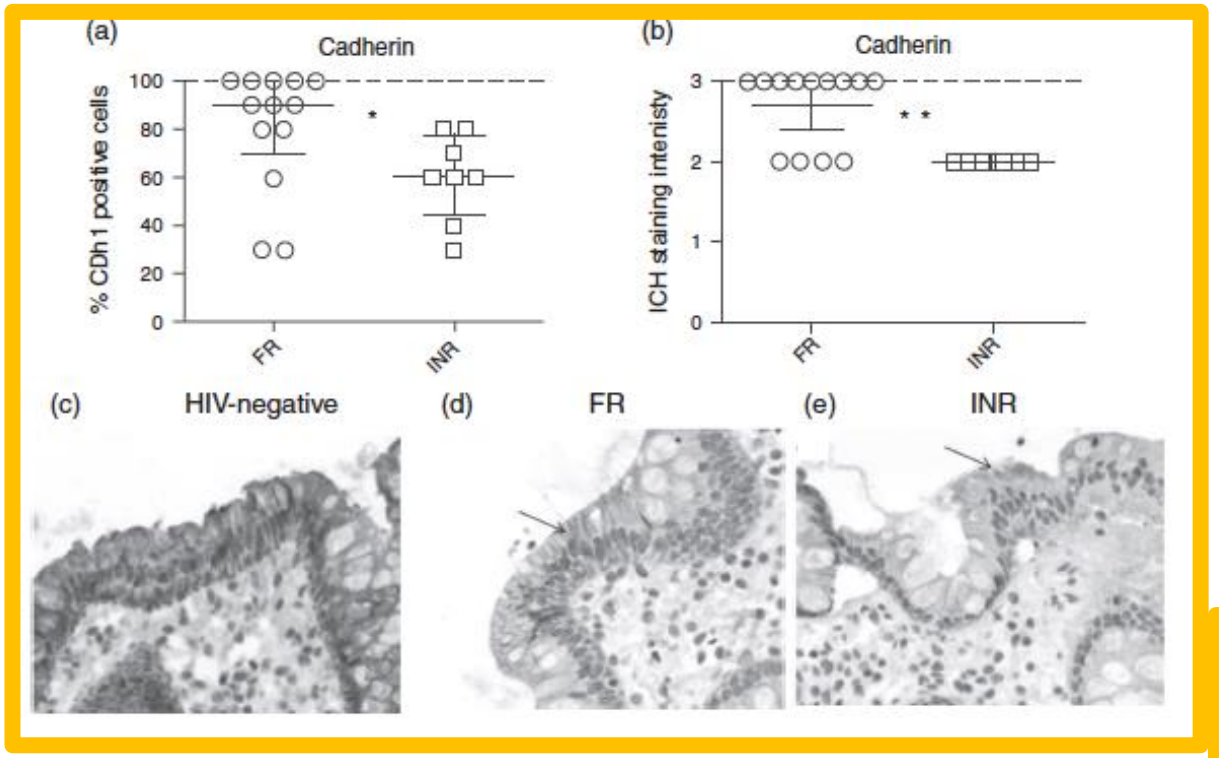
486 pts
No difference in the probability to reach CD4+ gain 2 times above pre-cART according to pre-ART microbial translocation

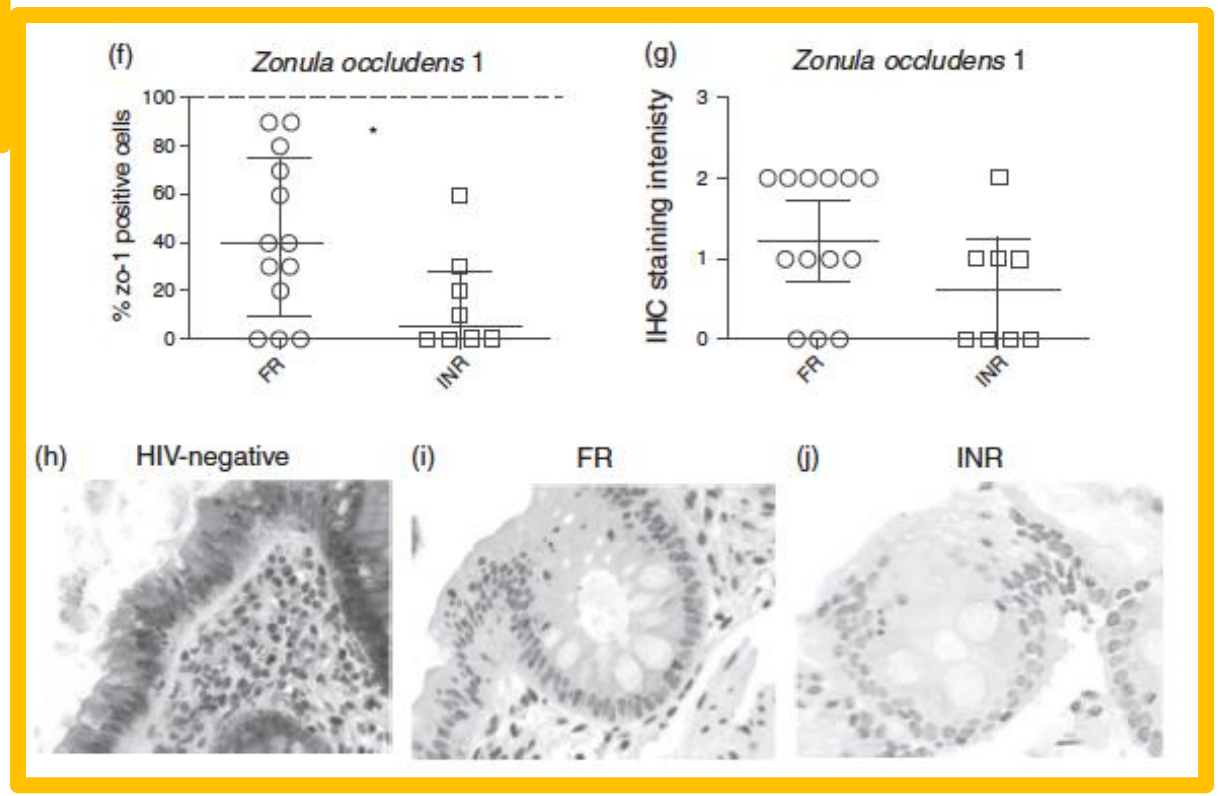
Merlini et al. BMC Infect Dis 2021

Microbial translocation



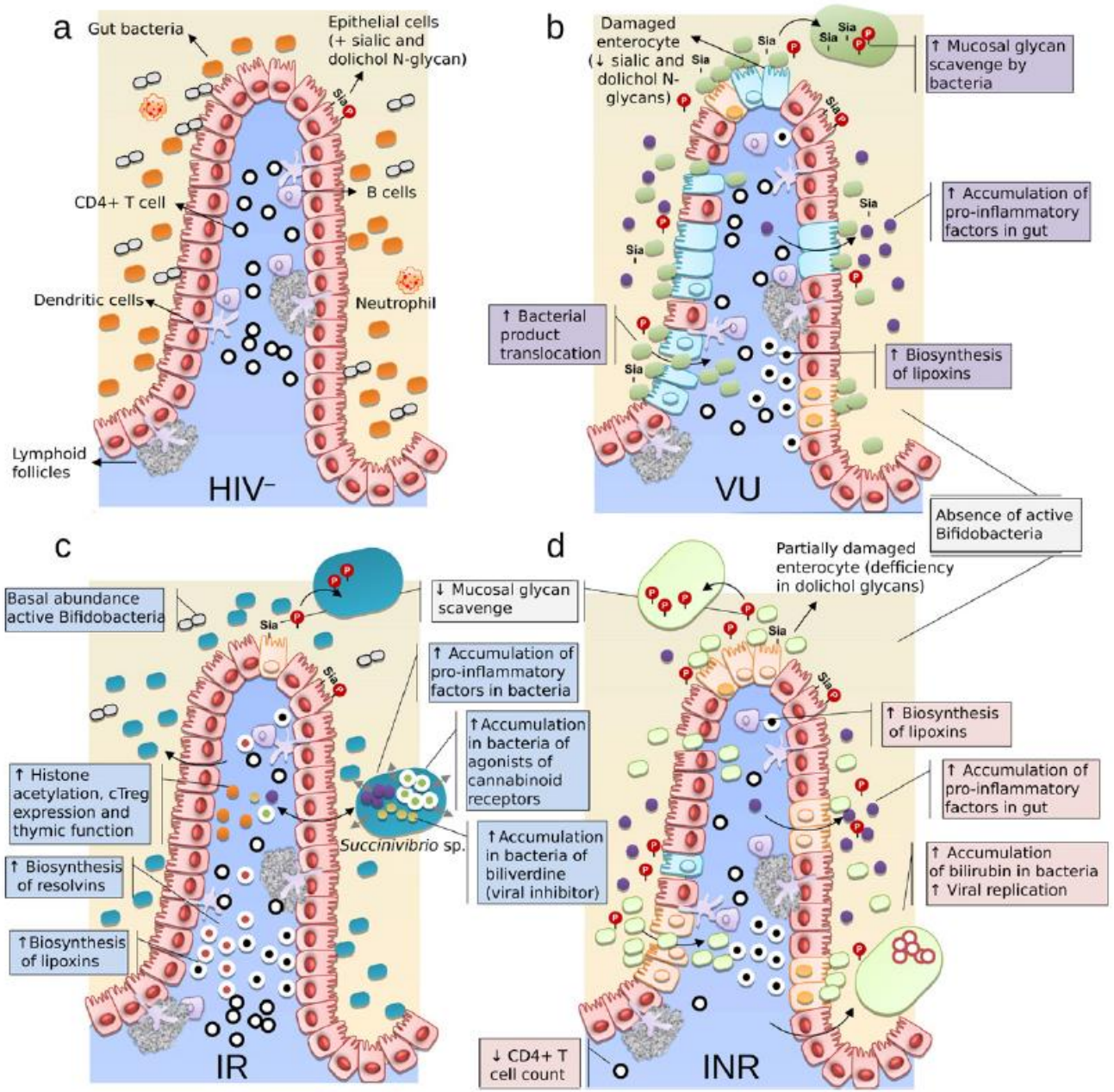






Tincati et al. AIDS, 2016

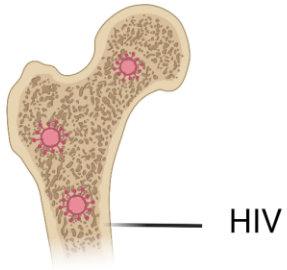
Complex gut damage in INRs



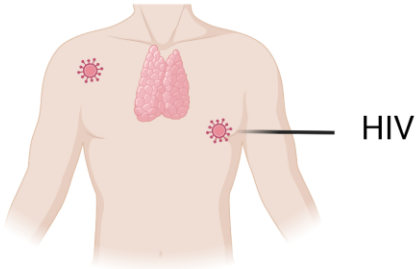
Sergio Serrano-Villar et al. eBiomedicine 2016

Causes of excessive immune activation

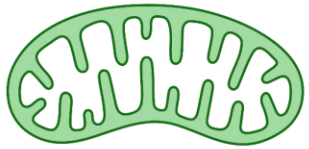
Depletion of progenitor cells in the bone marrow



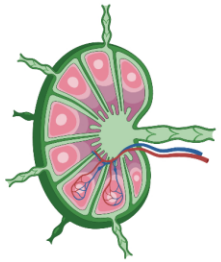
Reduced size and thymic output

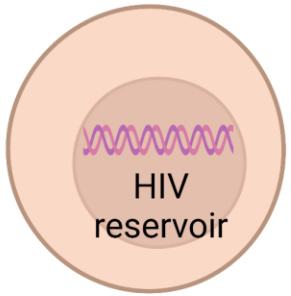


Alteration in mitochondrial respiration



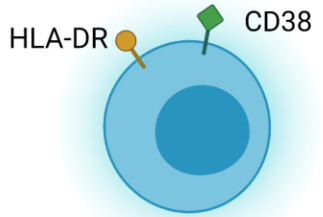
Lymphoid tissue fibrosis



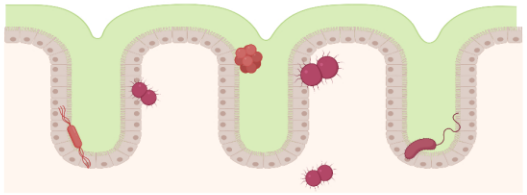


CD4+ T-cells

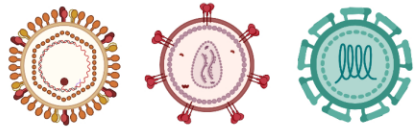
Persistent CD4+ T-cell hyperactivation



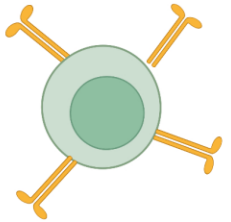
Gut barrier disruption, microbial translocation and gut dysbiosis



Coinfections



T-cell senescence and exhaustion



Bono V et al., New Microbiologica 2022

HCV co-infection is associated to higher T-lymphocyte activation on cART

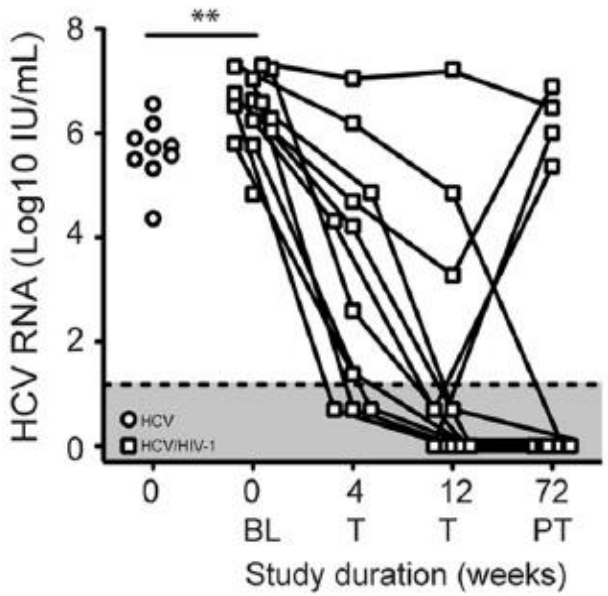
Table 3. Factors associated with changes in activated (CD38⁺HLA-DR⁺) T cell counts in 99 human immunodeficiency virus (HIV)–infected patients with sustained plasma HIV RNA levels ≤1000 copies/mL.

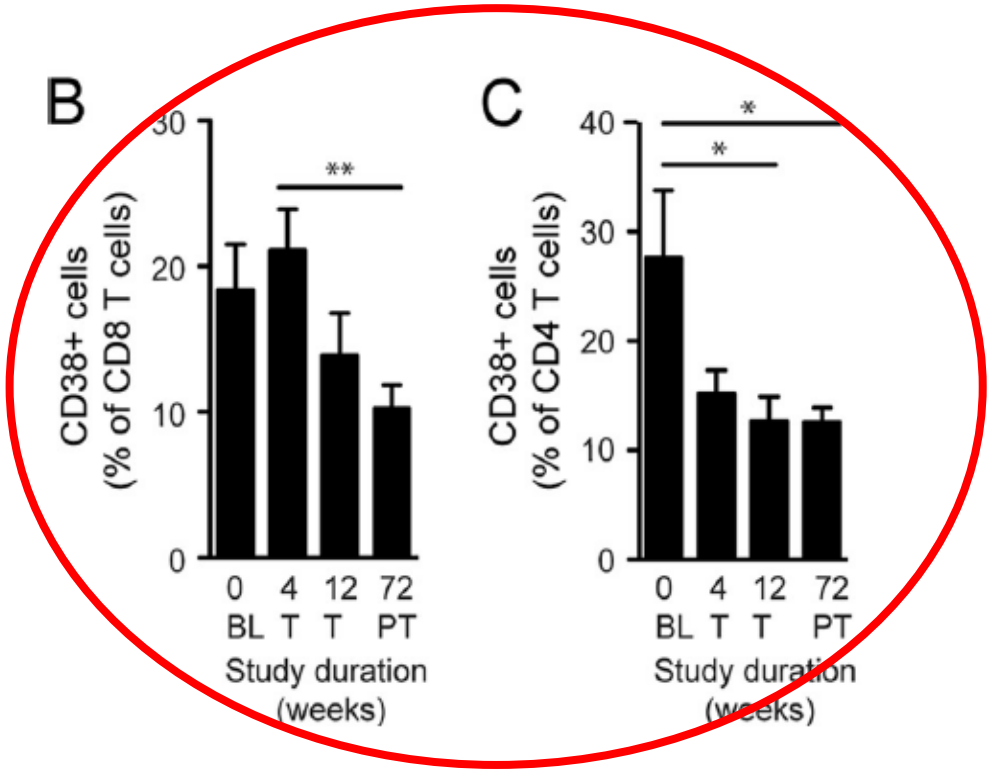
	CD4⁺ T cells				CD8⁺ T cells			
	Unadjusted analysis		Adjusted analysis[a]		Unadjusted analysis		Adjusted analysis[b]	
Factor	Mean change (95% CI) in activated T cells, %	*P*	Mean change (95% CI) in activated T cells, %	*P*	Mean change (95% CI) in activated T cells, %	*P*	Mean change (95% CI) in activated T cells, %	*P*
Each 1-month increase in duration of viral suppression[c]	−0.04 (−0.09 to 0.004)	.08	−0.06 (−0.1 to −0.005)	.03	−0.1 (−0.2 to −0.004)	.04	−0.1 (−0.2 to −0.01)	.04
Hepatitis C virus antibody status								
Negative	Reference	—	Reference	—	Reference	—	Reference	—
Positive	+2 (0.3–4)	.02	+2 (0.2–4)	.03	+6 (2–10)	.003	+5 (2–9)	.006
Frequency of low-level viremia in year before immunophenotyping[d]								
None	Reference	—	Reference	—	Reference	—	Reference	—
1%–50%	+0.1 (−2 to 2)	.96	−0.5 (−3 to 2)	.69	−1 (−6 to 4)	.74	−4 (−10 to 2)	.18
>50%	+3 (1–4)	.005	+2 (−0.2 to 4)	.07	+7 (3–11)	.001	+5 (0.5–10)	.03
Each increase of 100 cells/mm³ in nadir CD4⁺ T cell counts	−0.5 (−1.0 to 0.1)	.11	−1 (−2 to −0.3)	.003	−0.3 (−2 to 1)	.65	−1.5 (−3.0 to −0.03)	.05

Hunt et al. JID 2003; also Greub G Lancet 2000

Reduction of T-cell activation by anti-HCV treatment

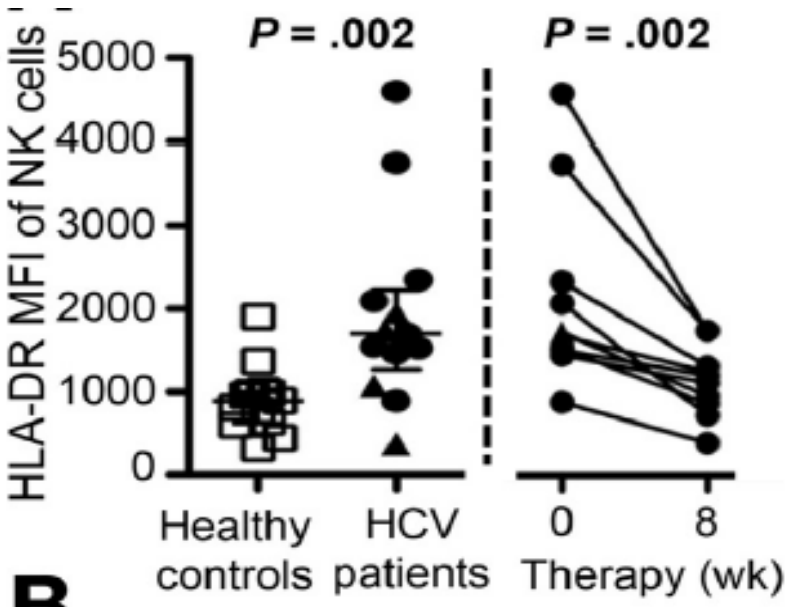
356 HIV+ cART-treated : 130 HCV co-infected

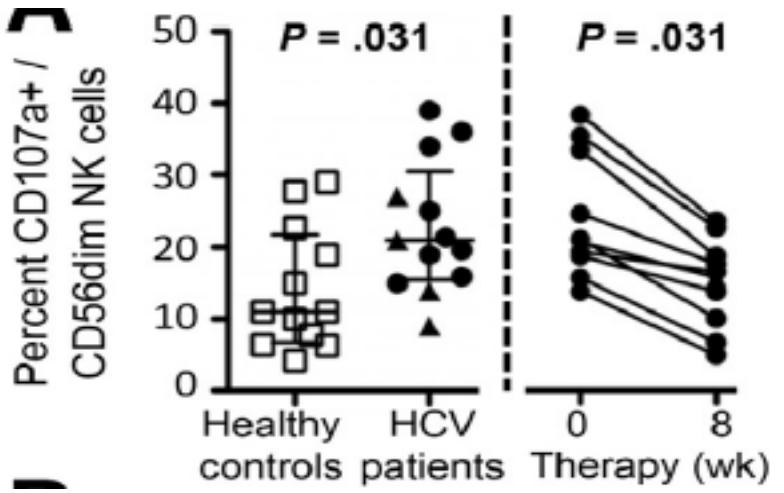




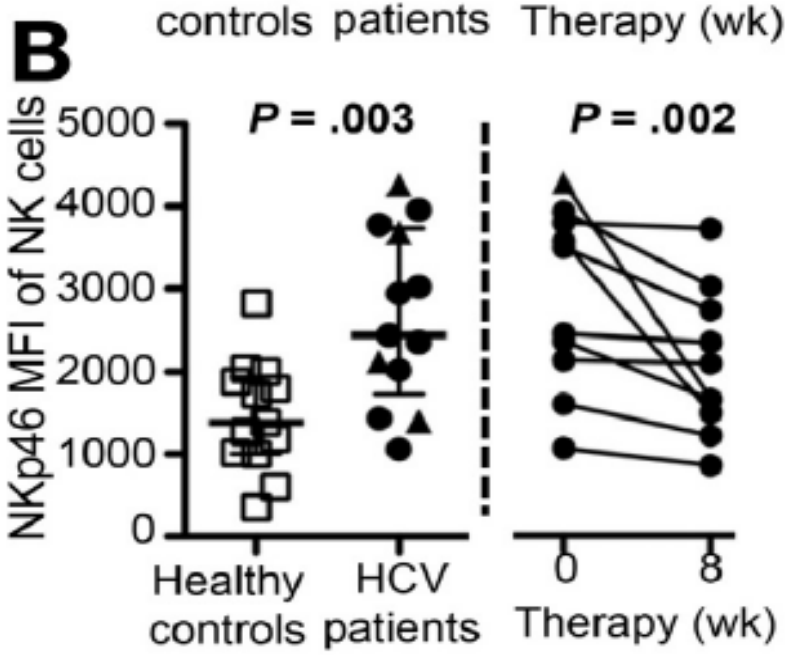
Gonzalez et al et al. J Virol 2009; also Massanella M et al. Antiviral Therapy 2010

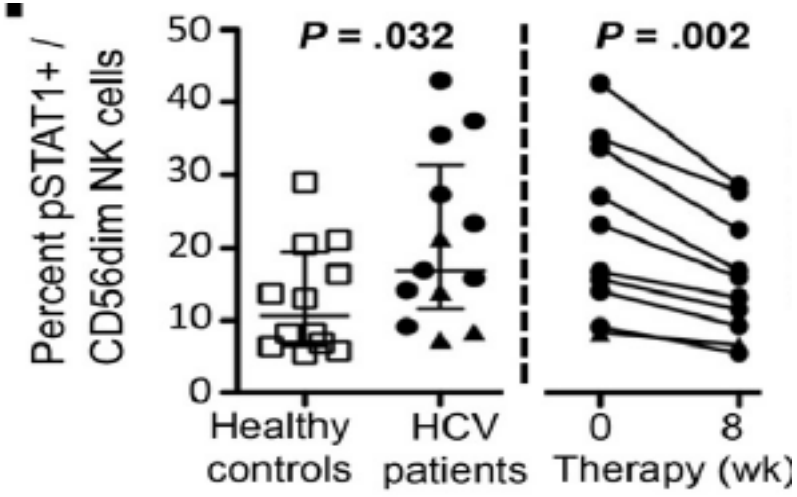
HCV: NK phenotype “normalization” under DAA





13 G1b NR to Peg-IFN/Riba NR, DCV/ASV





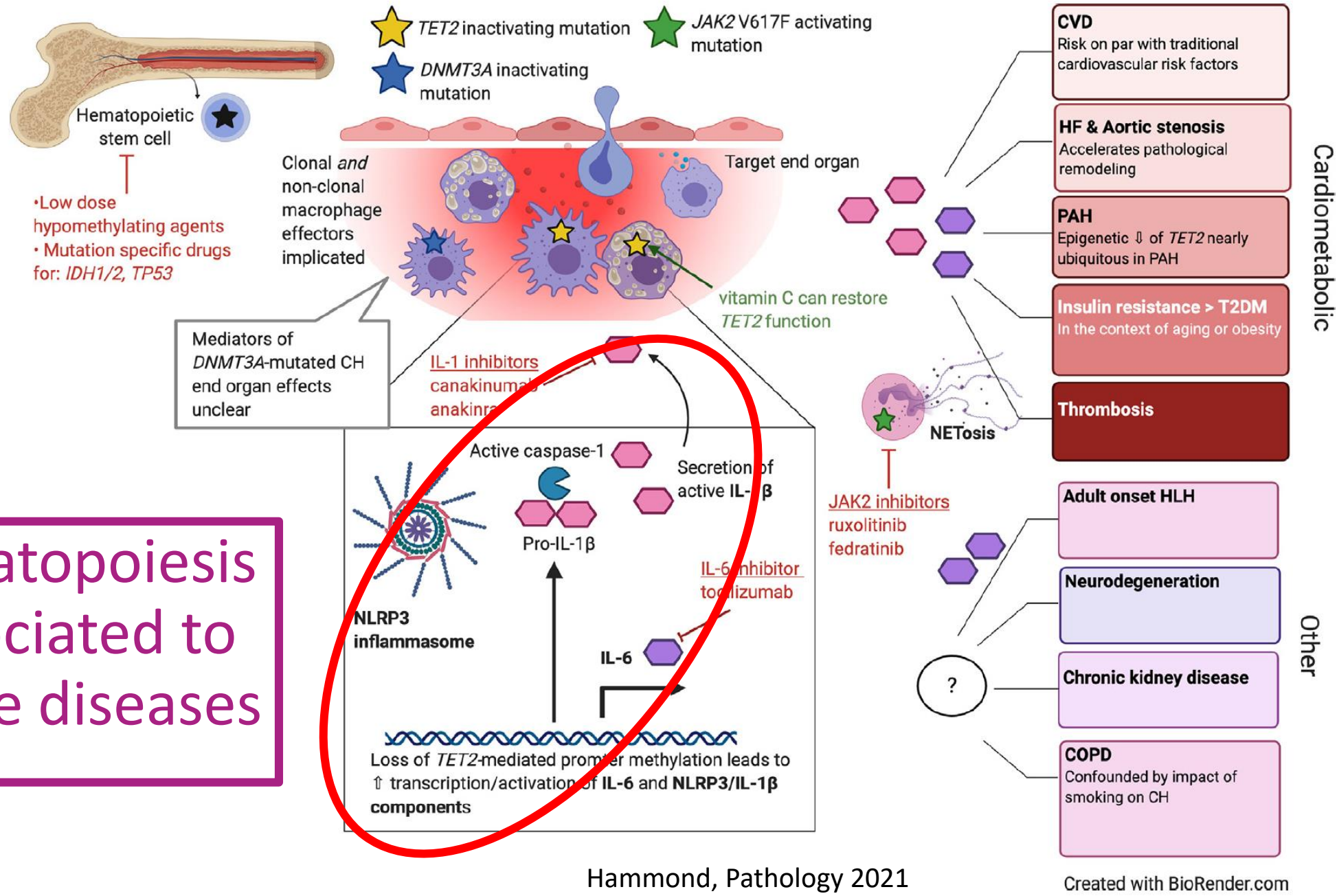
Serti E et al. Gastroenterology 2015

Clonal Hematopoiesis (CH) as driver of inflammation and disease

- Clonal hematopoiesis (CH): clonal expansion of hematopoietic stem cell (HSC) particularly myeloid-lineage cells with cancer-related mutations.

- Predominant CH mutations in epigenetic regulator genes DNMT3A, TET2, ASXL1; age-related phenomenon (about 90% of persons >50yo posess low level of these mutations); associated to inflammatory conditions

Clonal Hematopoiesis (CH) is associated to degenerative diseases

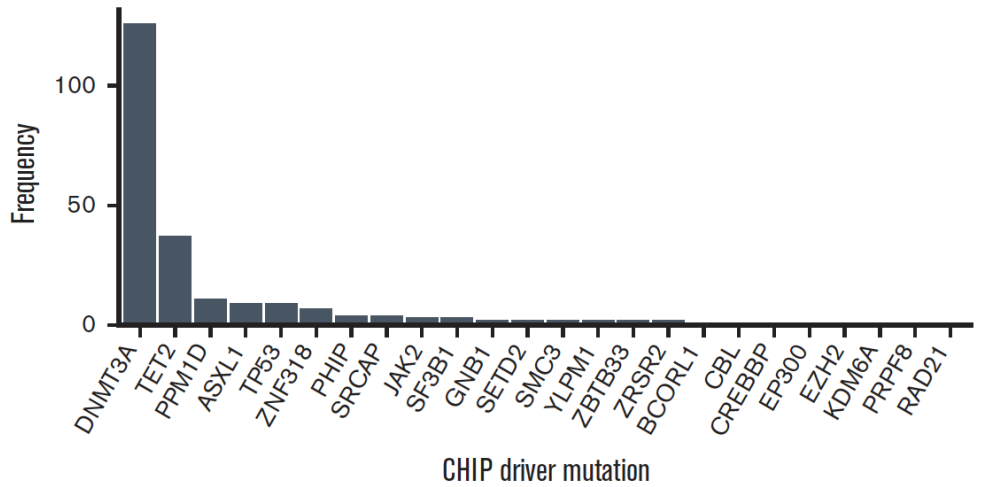


Hammond, Pathology 2021

4486 Reprieve patients

Body mass index, median (IQR)	25.3 (22.2-29.0)
Smoking status	
Current	980 (21.8%)
Former	964 (21.5%)
Never	2537 (56.6%)
Entry CD4 level (cells per mm^3), mean (SD)	654 (291)
ART duration, mean (SD), y	3.68 (3.52)
Baseline ART regimen (by class)	
NRTI + INSTI	896 (20.0%)
NRTI + NNRTI	2510 (56.0%)
NRTI + PI	781 (17.4%)
NRTI-sparing	93 (2.1%)
Other NRTI-containing	206 (4.6%)
eGFR (mL/min per 1.73 m^2), mean (SD)	99.1 (19.2)
On diabetic medications	13 (0.3%)
History of hypertension	1495 (33.3%)
Family history of CVD	673 (15.0%)
10-y ASCVD risk score (%)	
Median (IQR)	3.90 (1.70-6.60)
Total cholesterol (mg/dL)	
Mean (SD)	185 (36.3)
HDL cholesterol (mg/dL)	
Mean (SD)	51.5 (16.9)

A



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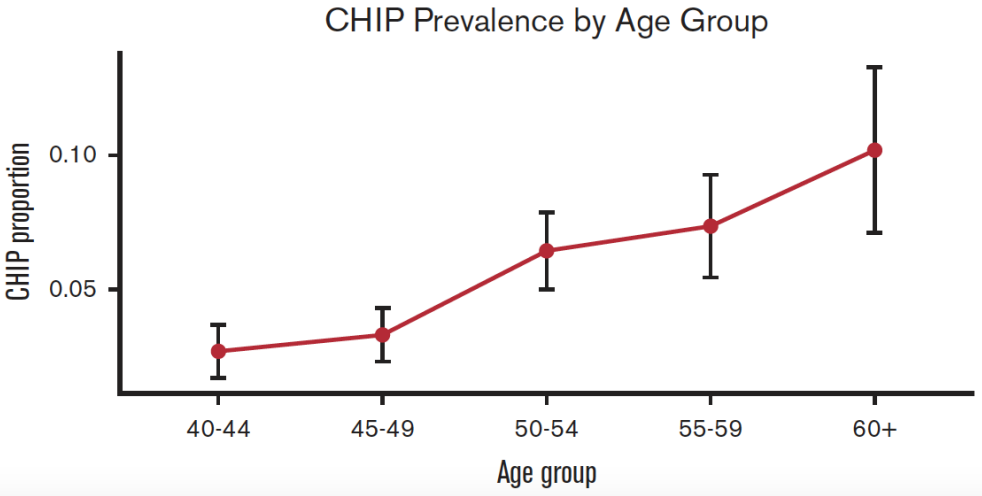
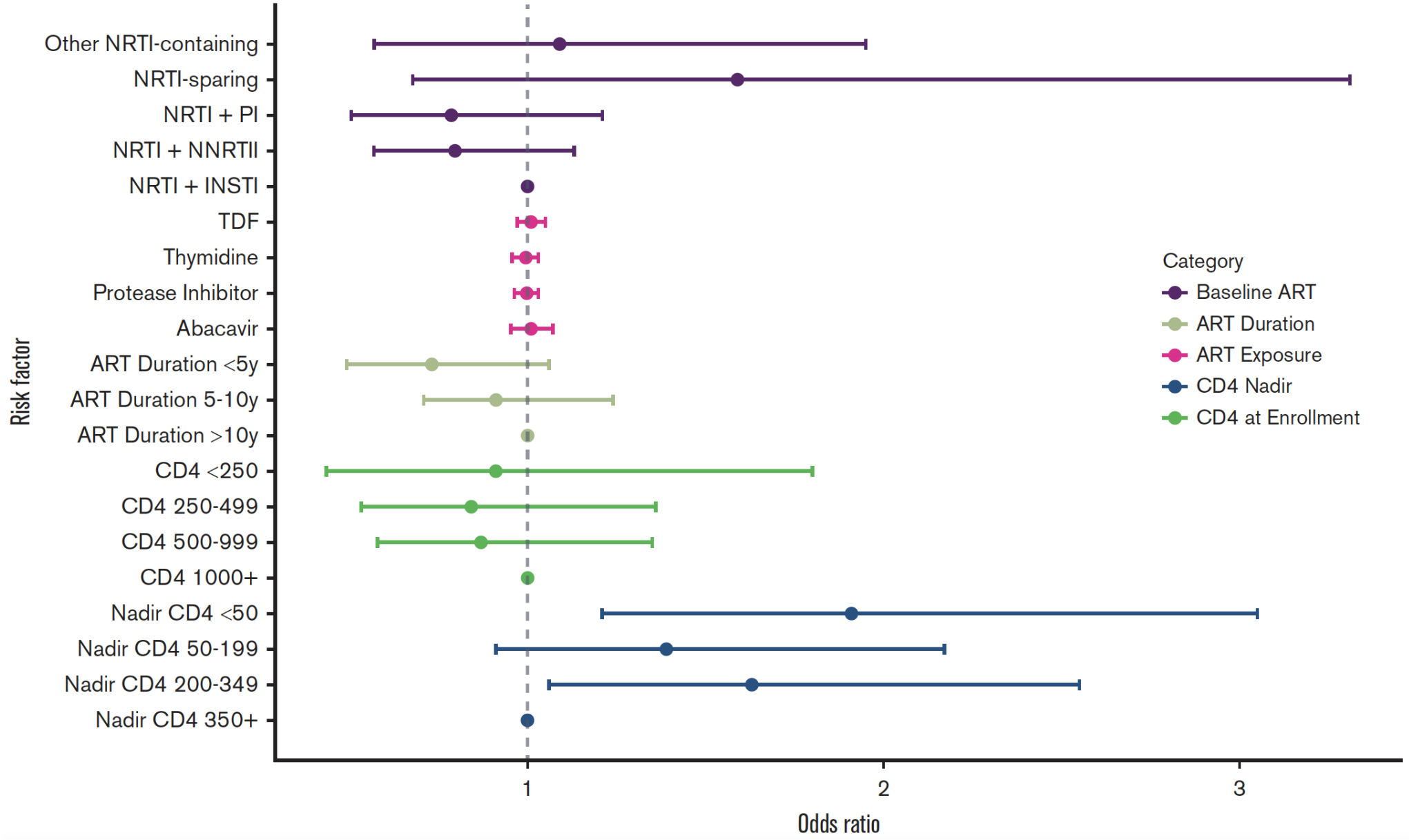
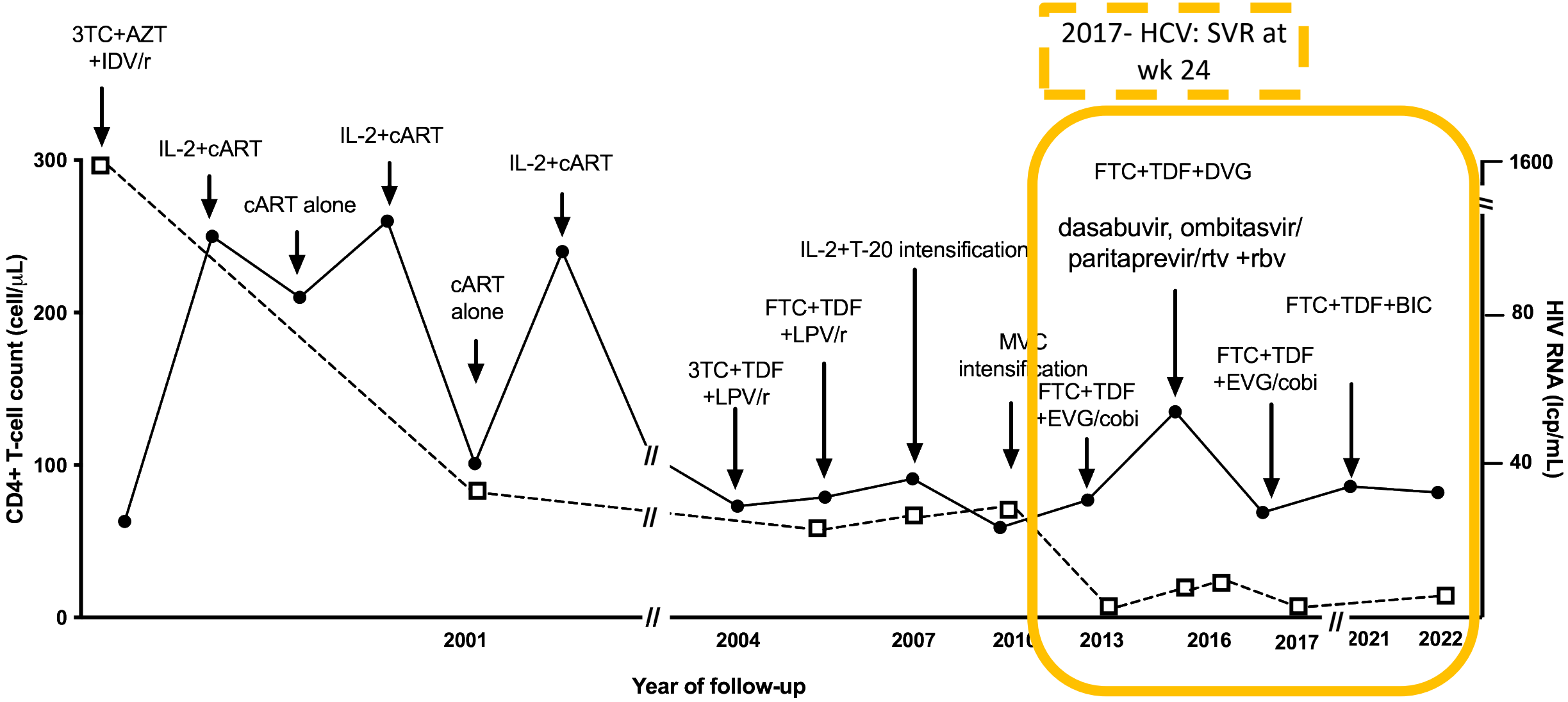


Bhattacharya, Blood Advances 2023



Bhattacharya, Blood Advances 2023



Tincati et al. BMC Infect Dis 2018