Clinical Review on Immunological non-responder

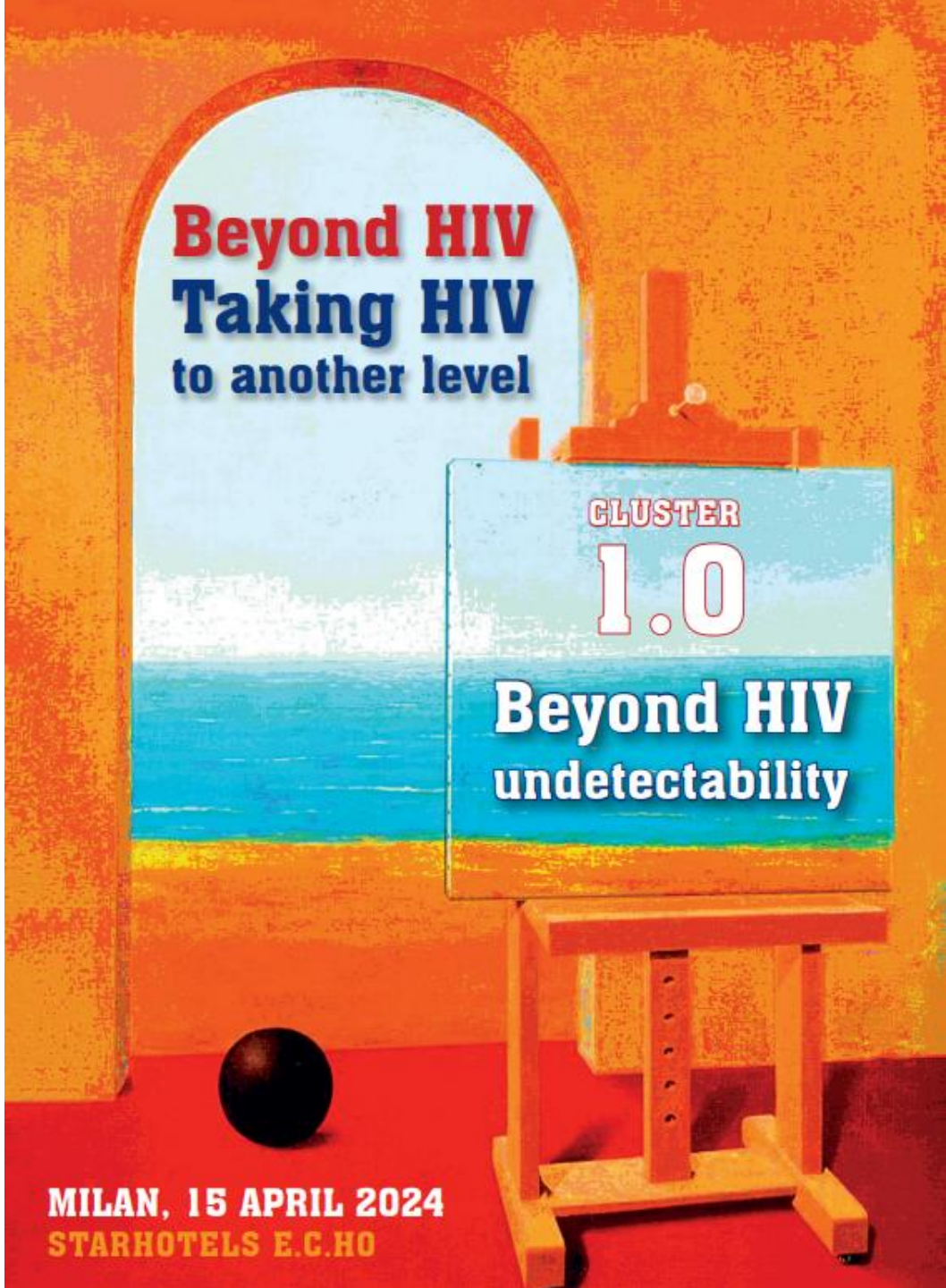
Valeria Bono, PhD candidate

Dep of Health Sciences

Clinic of Infectious Diseases

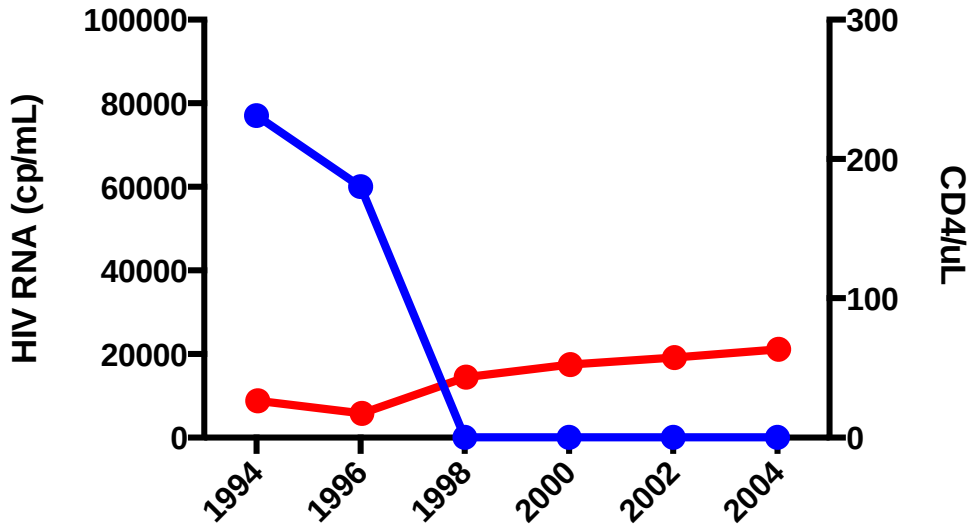
San Paolo Hospital

University of Milan



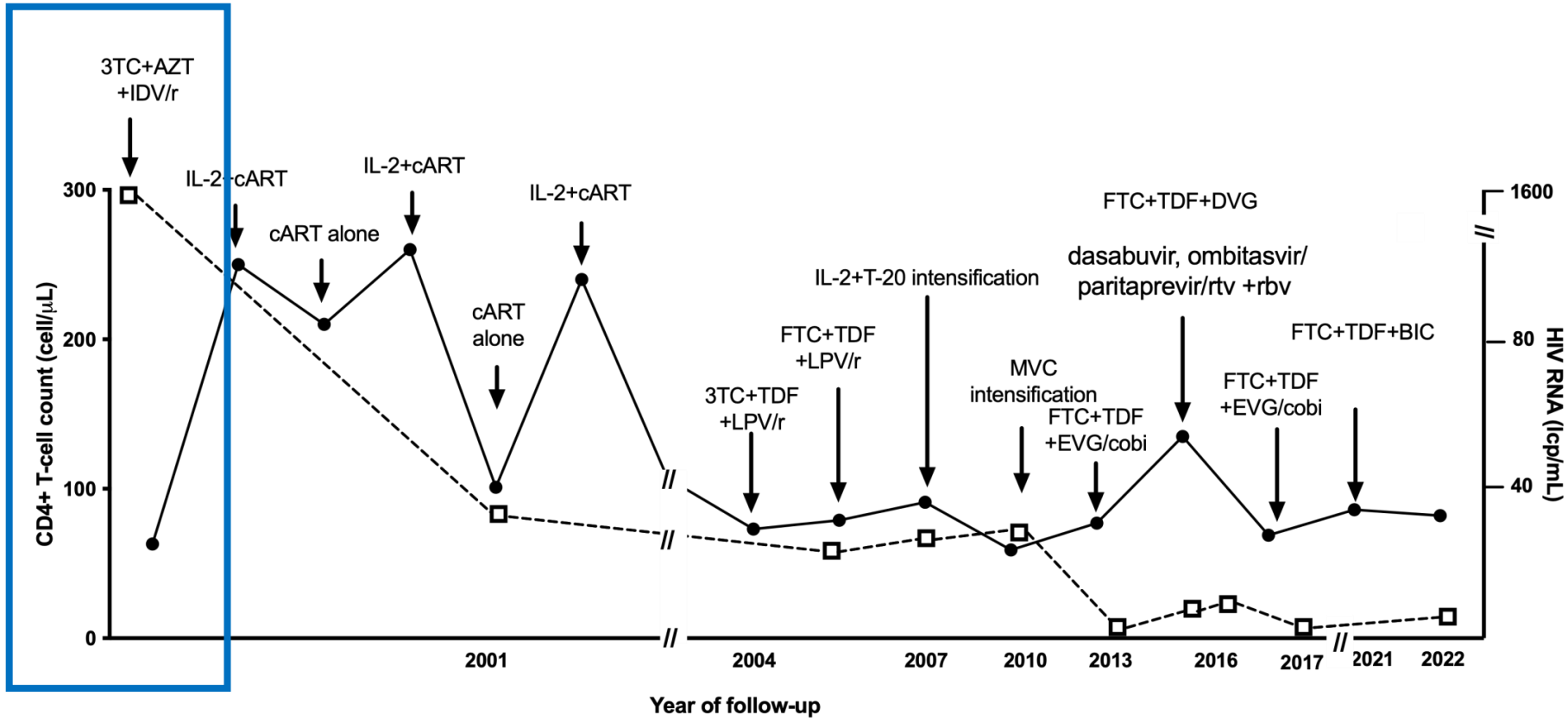
Case record: HIV-infected male, age 61

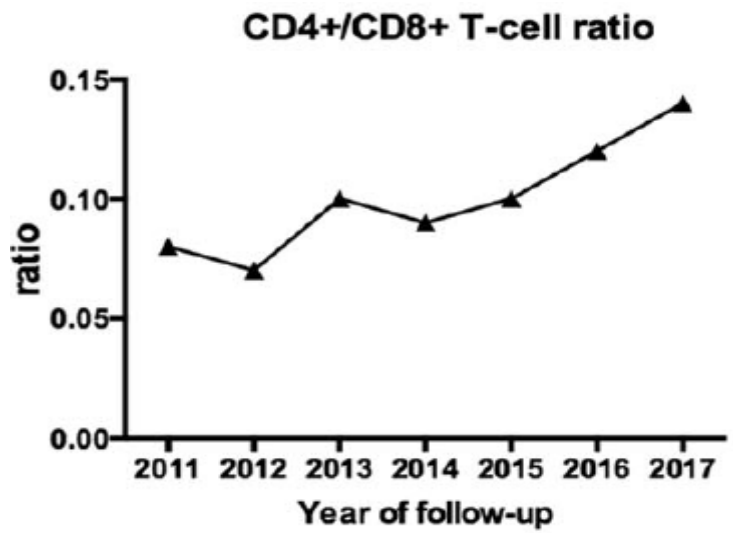
- Previous IDU, **HCV co-infection**
- Diagnosis of HIV-seropositivity in **Sept 1994; Nadir CD4: 26/uL,** no opportunistic infection
- First HAART regimen in **1996**
- PJP Prophylaxis: Trimethoprim-sulfamethoxazole QD



cART-treated PLWH fail to achieve CD4+ T-cell count normalization despite complete suppression of HIV replication

"Immunological-non-responder"





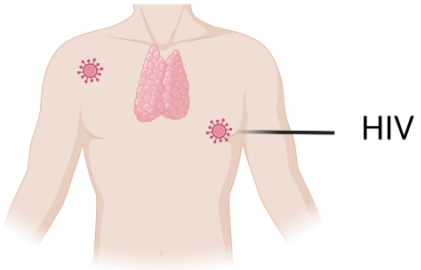
Tincati et al. BMC Infect

The pathogenetic mechanisms associated with an impaired immune reconstitution are multifactorial

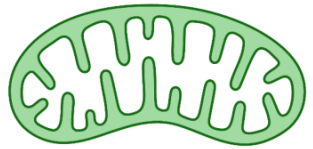
Depletion of progenitor cells in the bone marrow



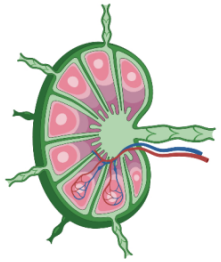
Reduced size and thymic output

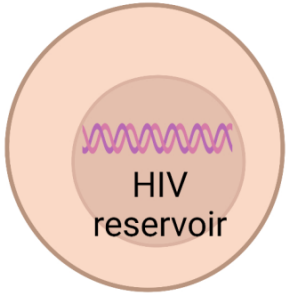


Alteration in mitochondrial respiration



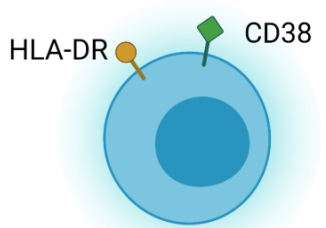
Lymphoid tissue fibrosis



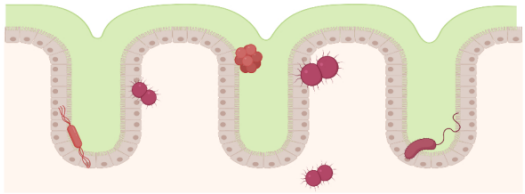


CD4+ T-cells

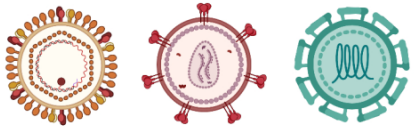
Persistent CD4+ T-cell hyperactivation



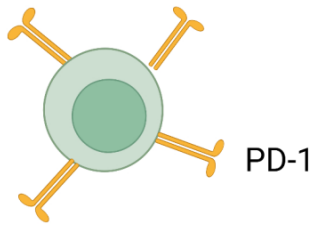
Gut barrier disruption, microbial translocation and gut dysbiosis



Coinfections



T-cell senescence and exhaustion



Bono V et al. New

A potential strategy: the use of interleukin-2 (IL-2) in combination with antiretroviral therapy (ART)

Clinical Trial > AIDS. 2003 Feb 14;17(3):343-51. doi: 10.1097/00002030-200302140-00008.

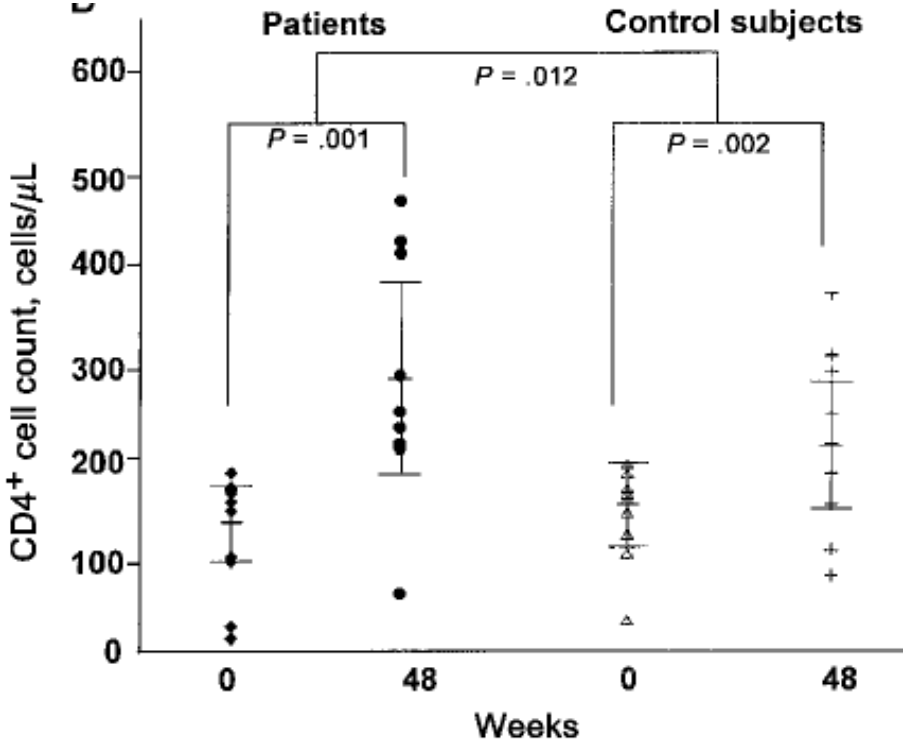
Effects of interleukin-2 therapy combined with highly active antiretroviral therapy on immune restoration in HIV-1 infection: a randomized controlled trial

Yves Levy [1], Christine Durier, Roman Krzysiek, Claire Rabian, Catherine Capitant, Anne-Sophie Lascaux, Christophe Michon, Eric Oksenhendler, Laurence Weiss, Jean-Albert Gastaut, Cécile Goujard, Christine Rouzioux, Jean Maral, Jean-François Delfraissy, Dominique Emilie, Jean-Pierre Aboulker; ANRS 079 Study Group

Clinical Trial > N Engl J Med. 1995 Mar 2;332(9):567-75. doi: 10.1056/NEJM199503023320904.

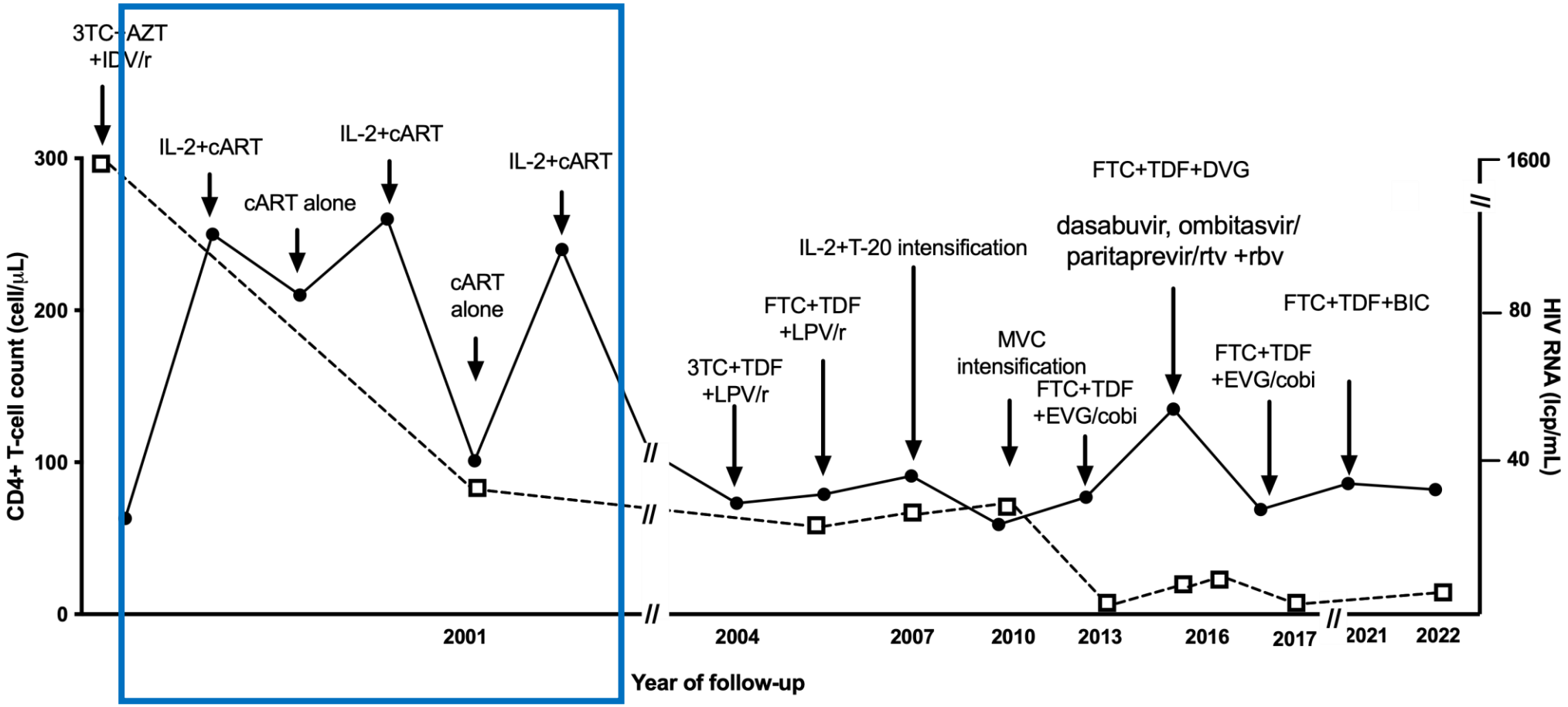
Increases in CD4 T lymphocytes with intermittent courses of interleukin-2 in patients with human immunodeficiency virus infection. A preliminary study

J A Kovacs [1], M Baseler, R J Dewar, S Vogel, R T Davey Jr, J Falloon, M A Polis, R E Walker, R Stevens, N P Salzman, H Clifford Lane



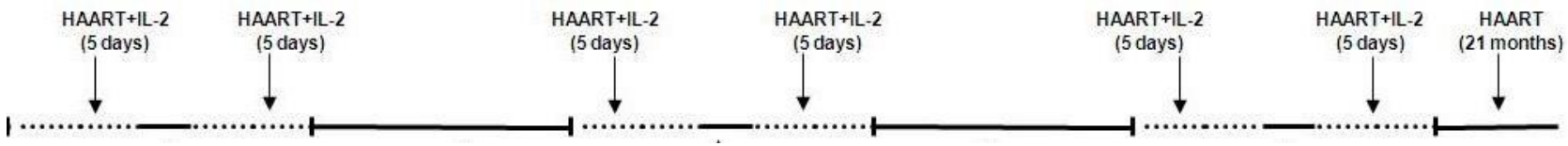
Marchetti et al., JID 2

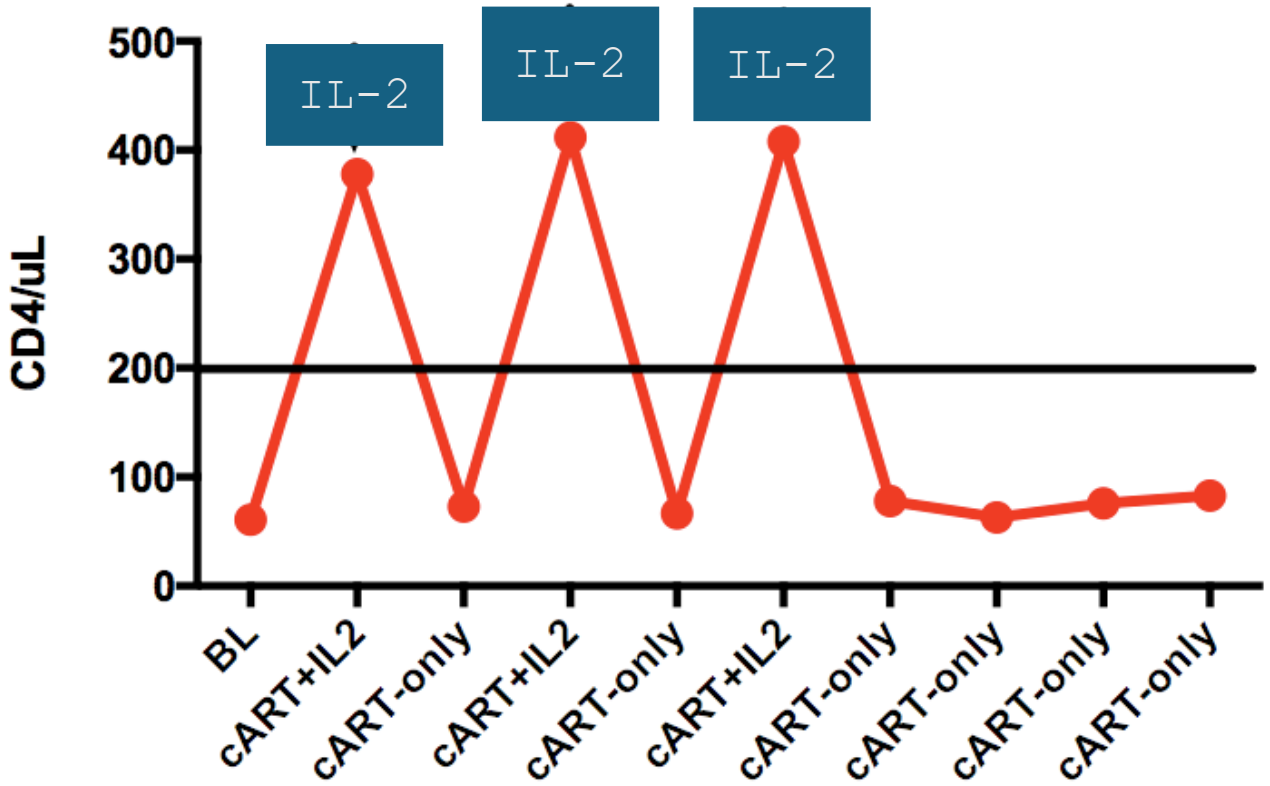
2001 → immune-adjuvant interleukin-2 (IL-2) therapy



Tincati et al. BMC Infect Dis 2018

Low-dose prolonged intermittent IL-2 schedule: 3 months total duration





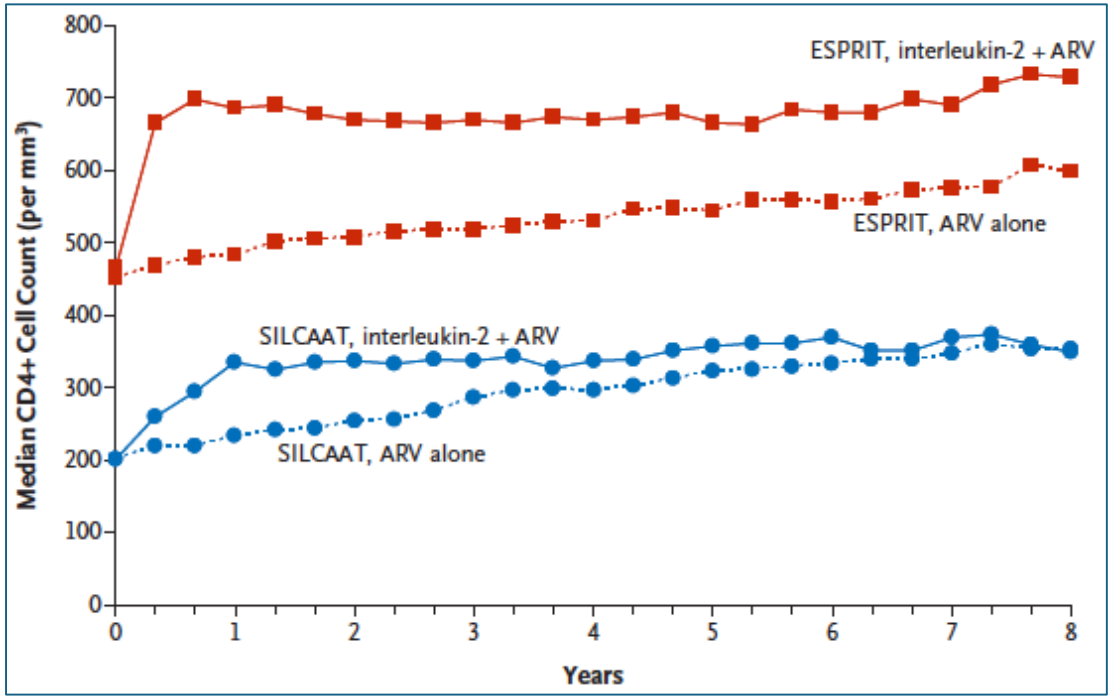
Year 2004:
ongoing cART
+ IL-2

HIV-RNA always

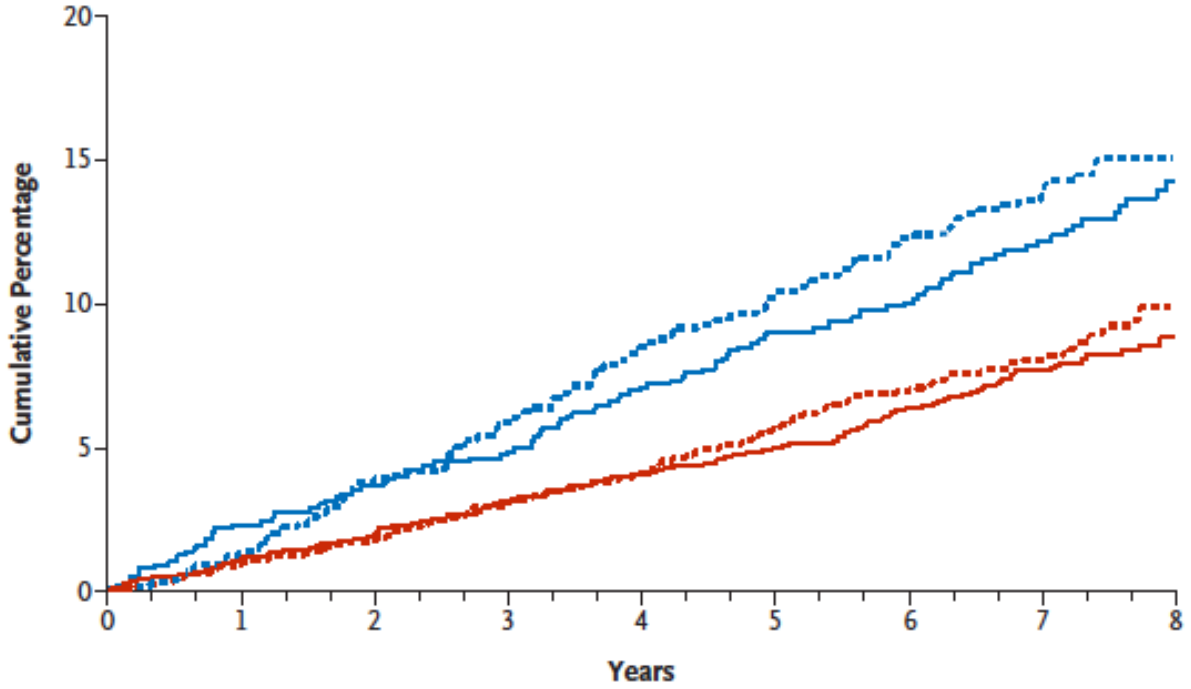
SILCAAT: median CD4+ T cell count 202 cells/mm3

ESPRIT: median CD4+ T cell count 457 cells/mm3

CD4 T cell count



Opportunistic disease or death from any



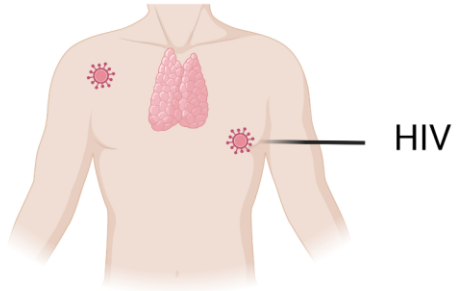
Adjuvant IL-2 in INRs: the failures

SILCCAT and ESPRIT, NEJM

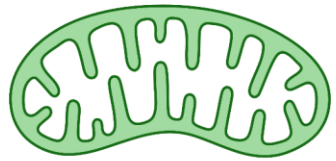
Depletion of progenitor cells in the bone marrow



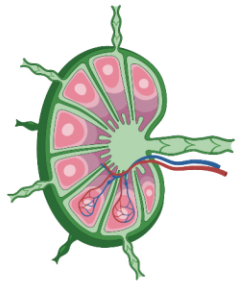
Reduced size and thymic output

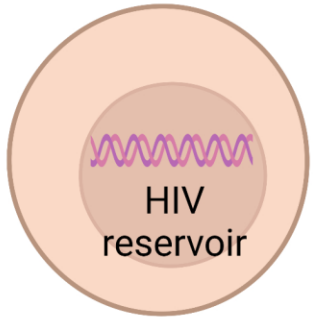


Alteration in mitochondrial respiration



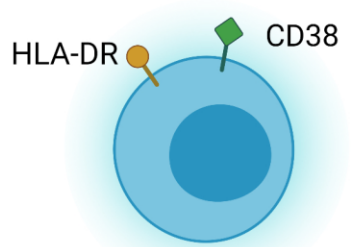
Lymphoid tissue fibrosis



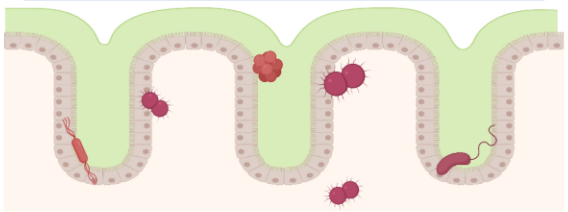


CD4+ T-cells

Persistent CD4+ T-cell hyperactivation



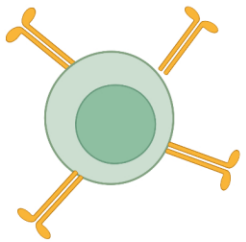
Gut barrier disruption, microbial translocation and gut dysbiosis



Coinfections



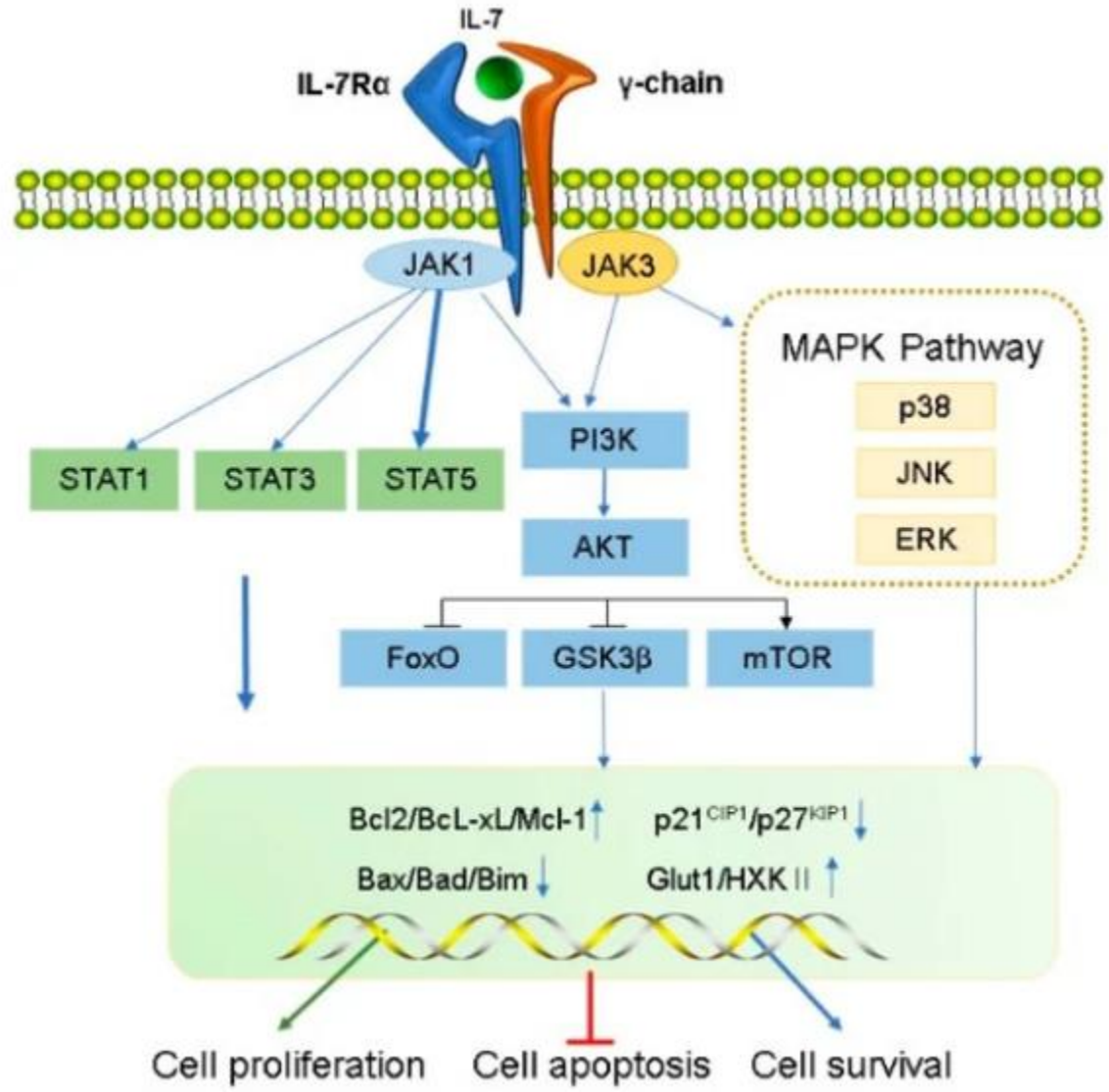
T-cell senescence and exhaustion



Bono V et al. New Microbiologica 2022

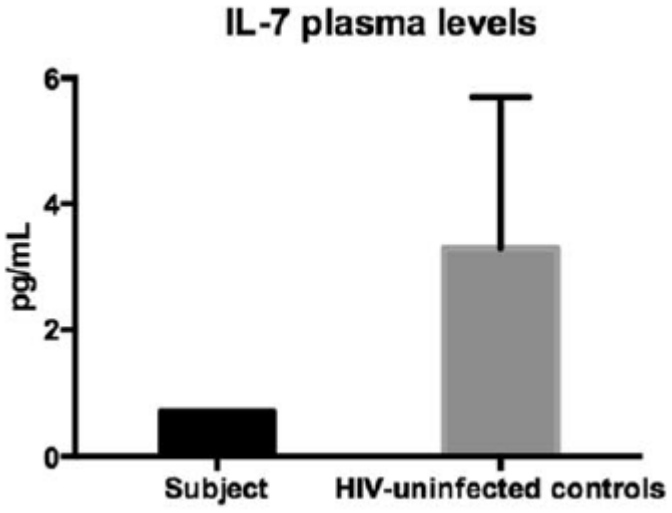
IL-7/IL-7R signaling

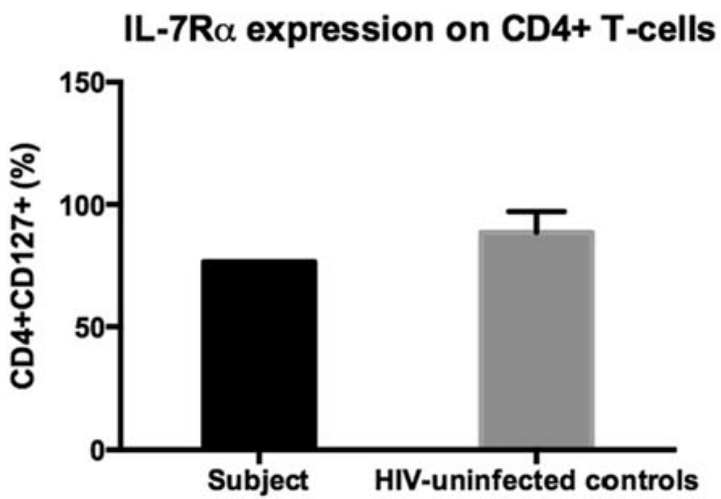
2006 → BM aspirate: *Severe dysplasia of myeloid, erythroid and platelet precursors, hypocellularity, matrix fibrosis*

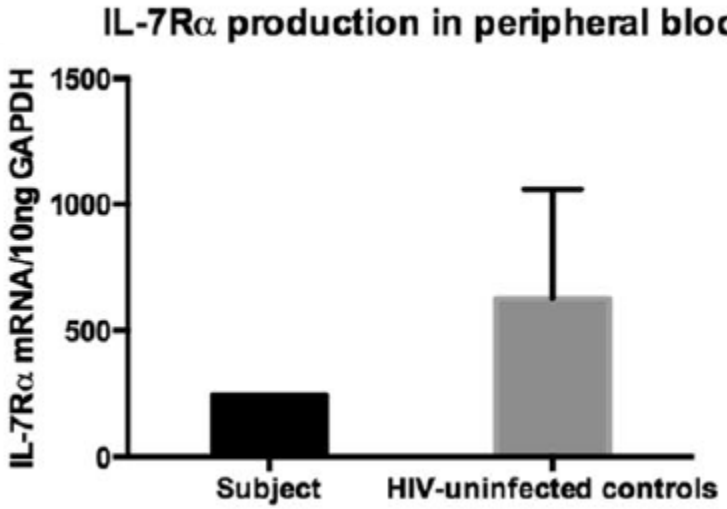


Wang et al. Int. J. Mol. Sci

IL-7/IL-7Rα levels in plasma

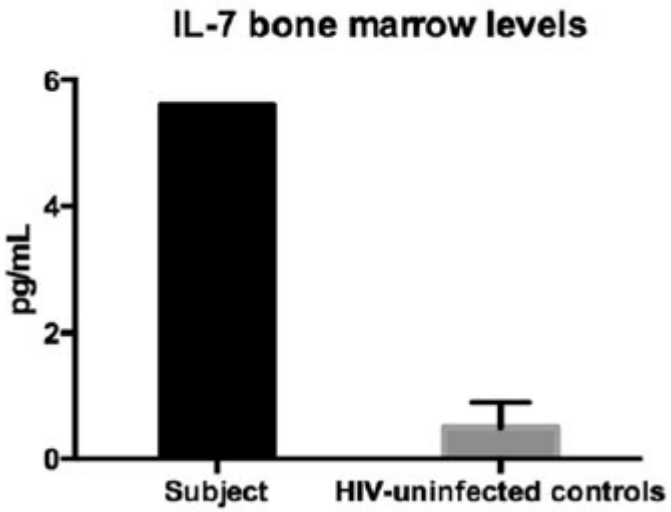


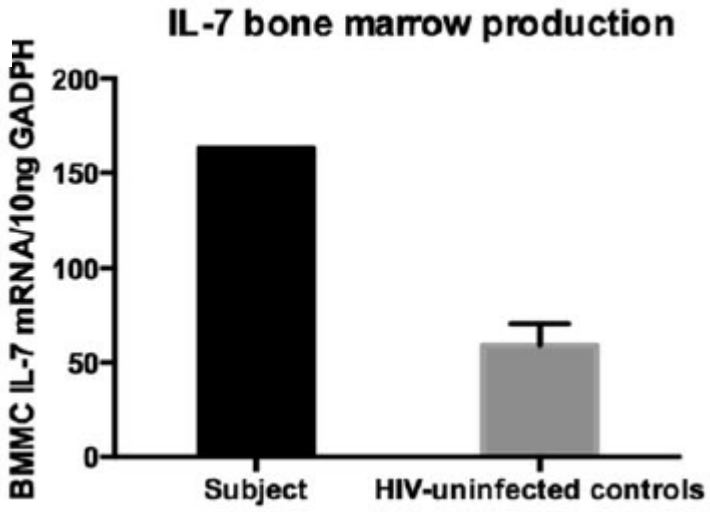


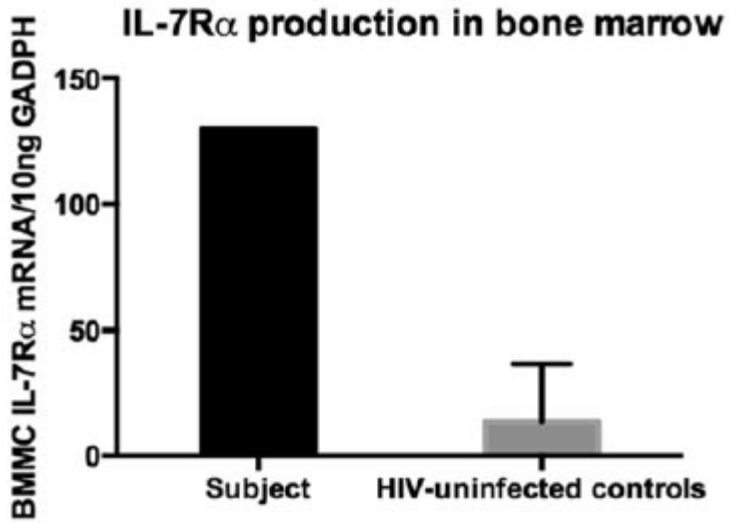


Tincati et al. BMC Infect

IL-7/IL-7Rα levels in in the bone marrow

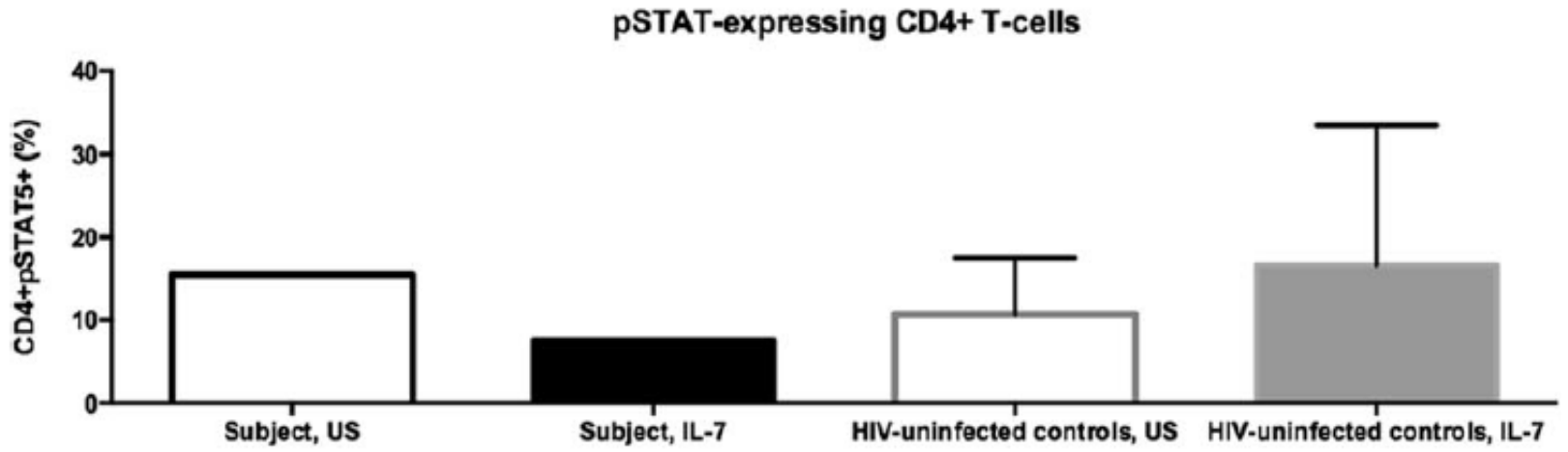


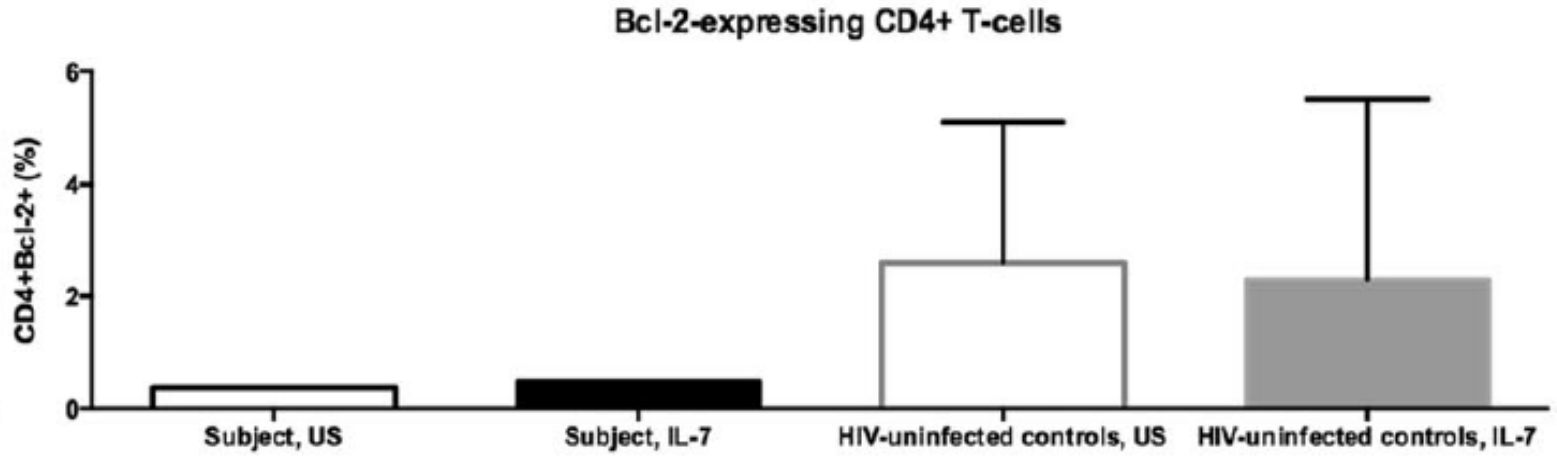




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IL-7 signaling in CD4 + T-cell subset



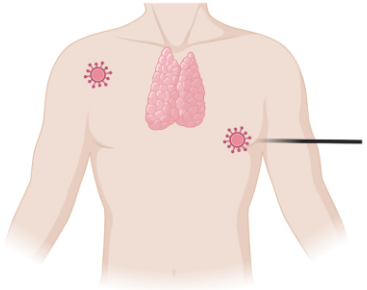


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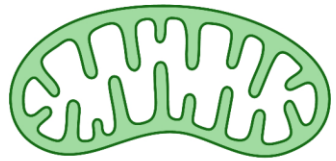
Depletion of progenitor cells in the bone marrow



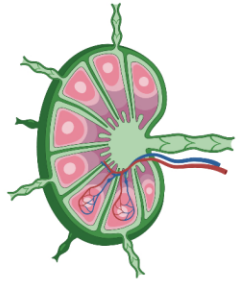
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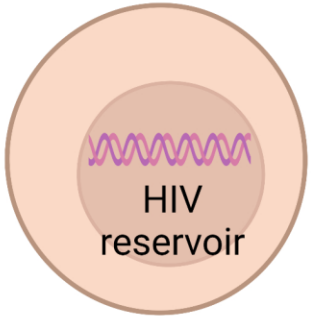


Alteration in mitochondrial respiration



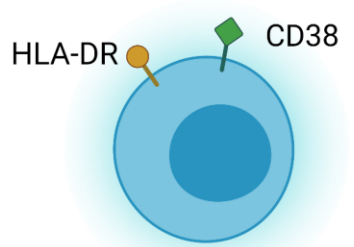
Lymphoid tissue fibrosis



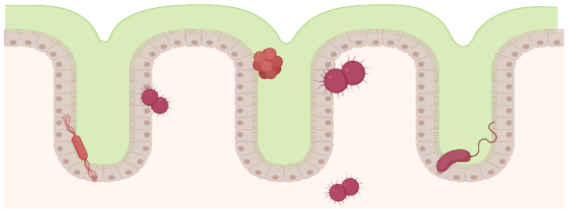


CD4+ T-cells

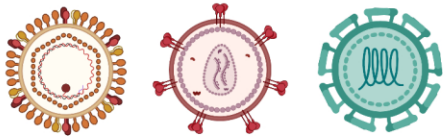
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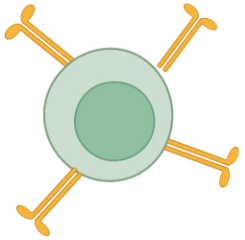
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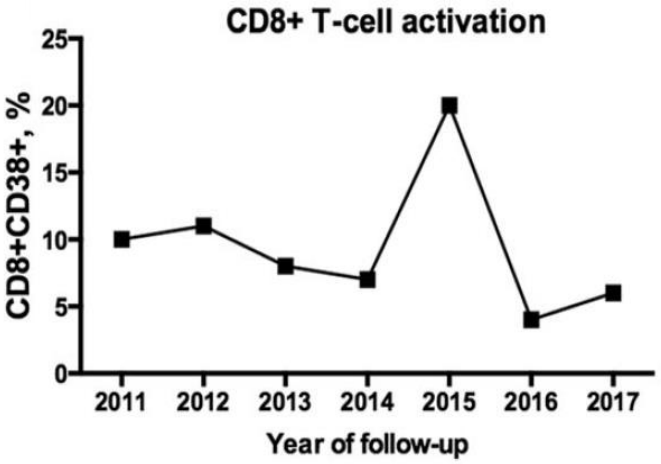


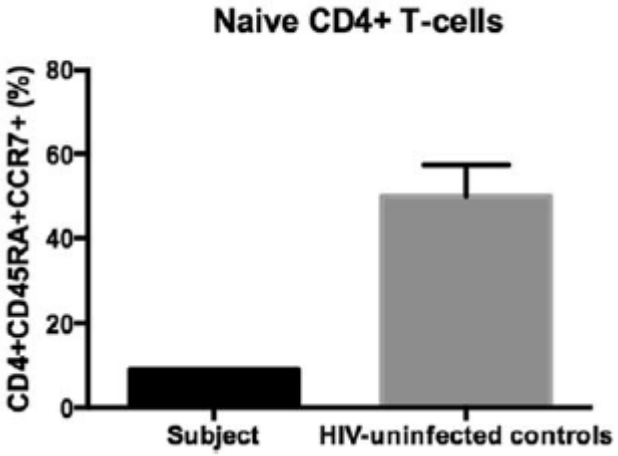
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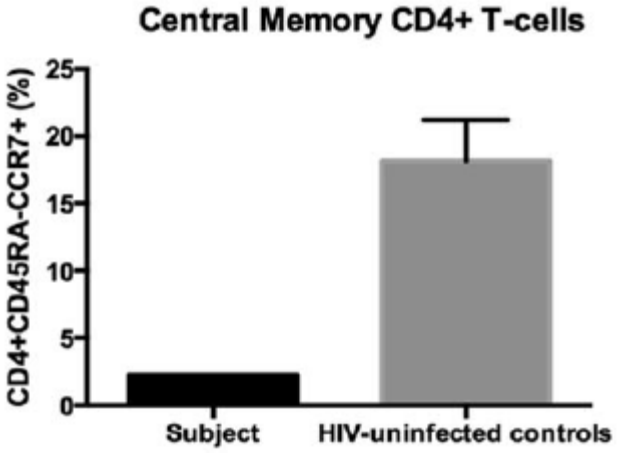


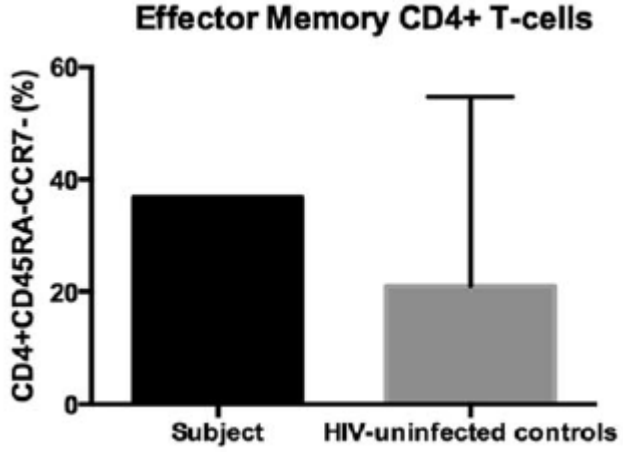
Bono V et al. New

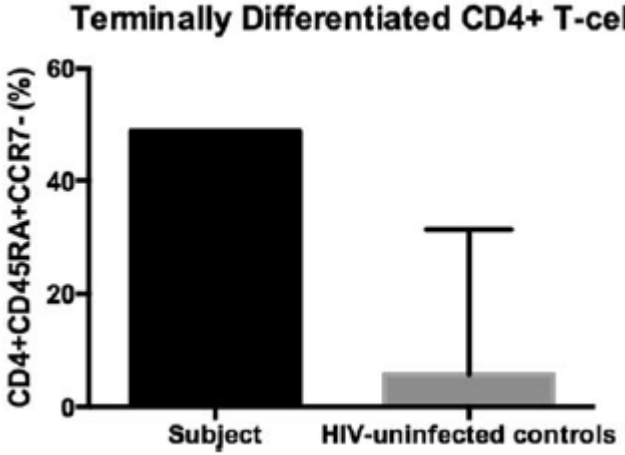
CD4 T-cell maturation phenotype





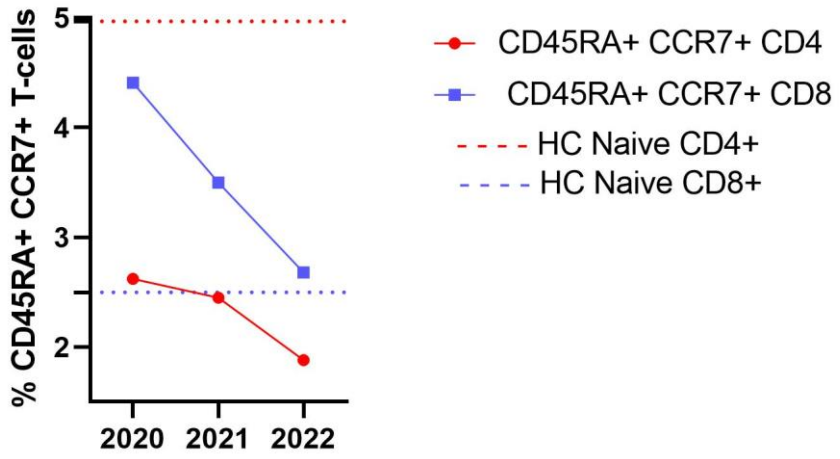




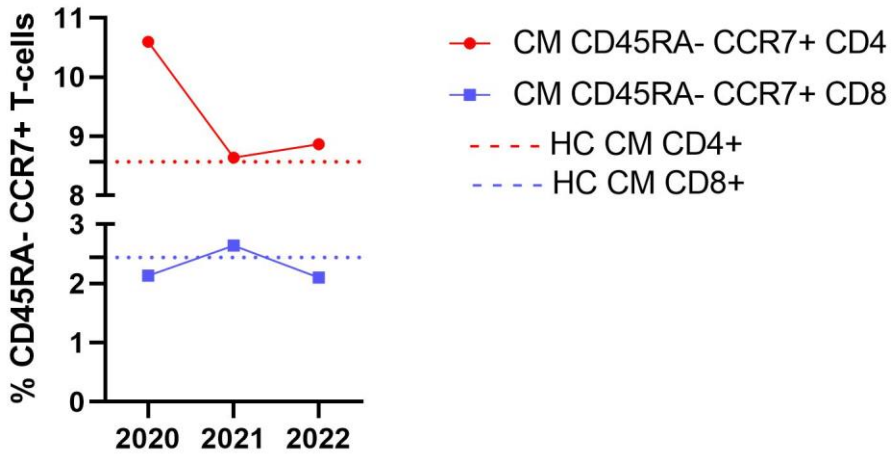


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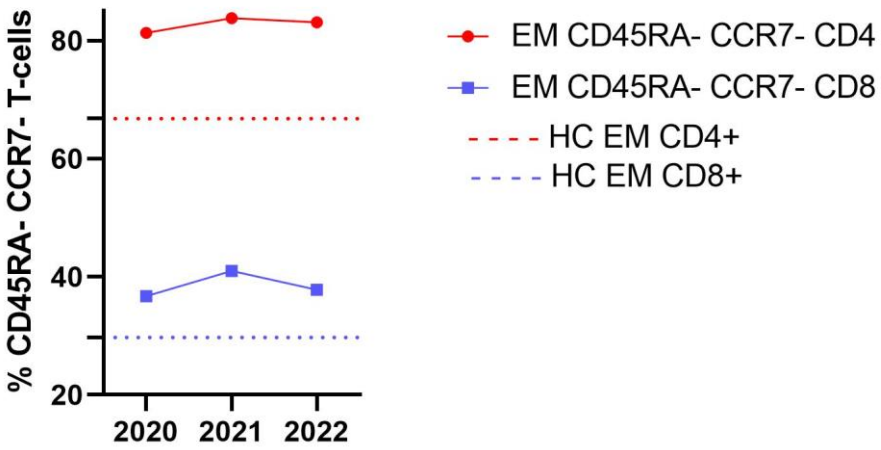
Naive CD4 and CD8 T-cells



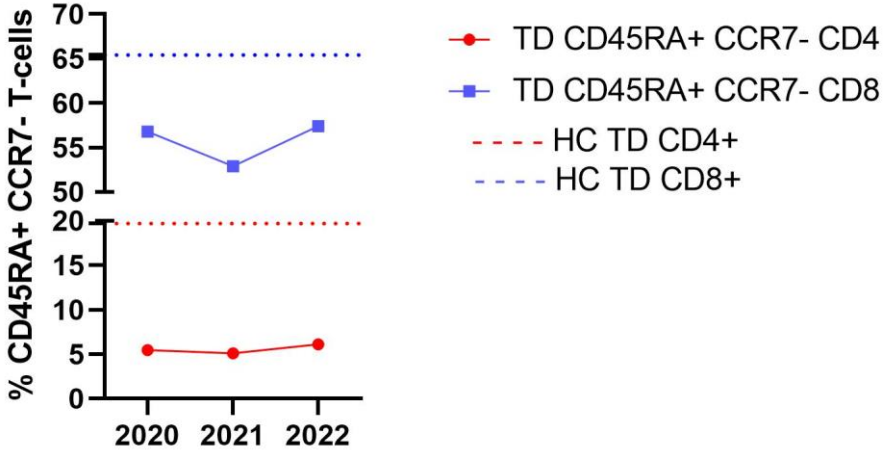
Central Memory CD4 and CD8 T-cells



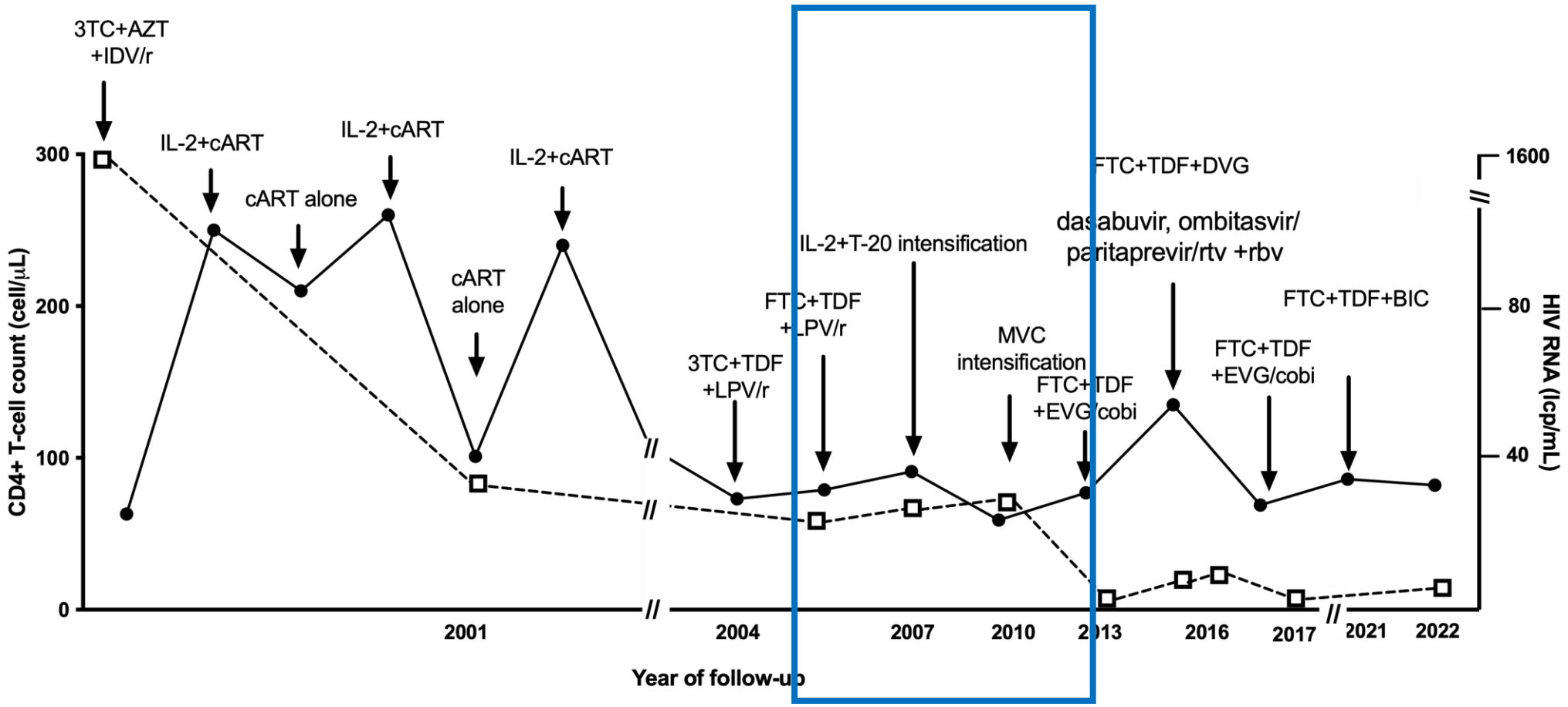
Effector Memory CD4 and CD8 T-cells



Terminally Differentiated CD4 and CD8 T-cells

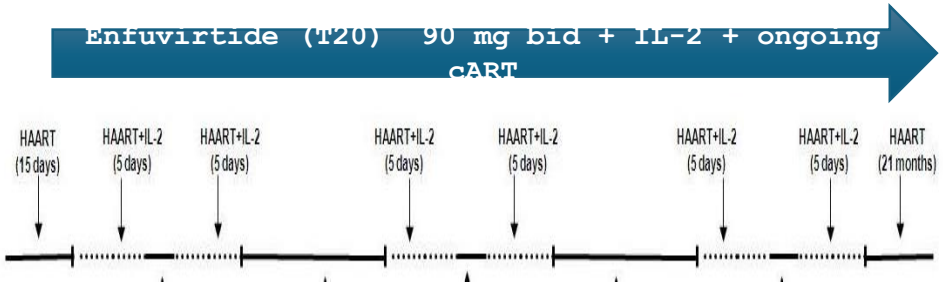


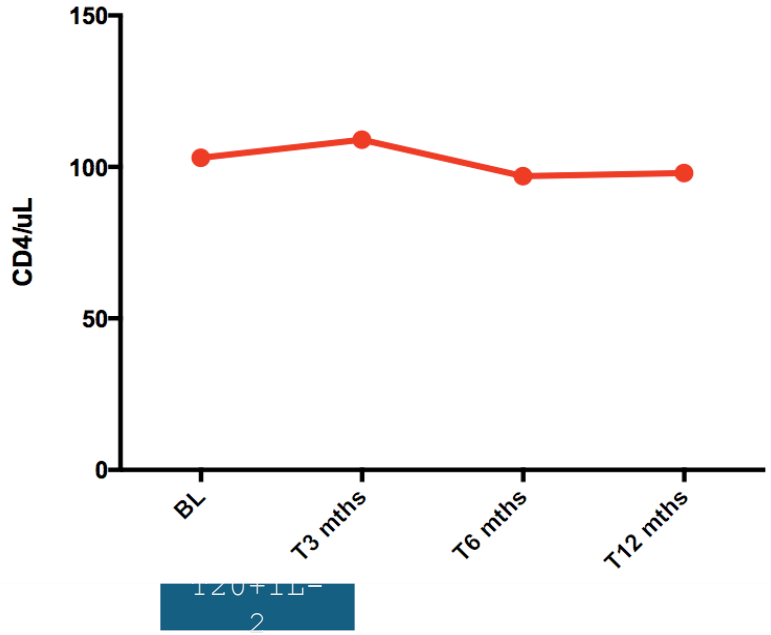
cART intensification



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Year 2007: cART Intensification (enfuvirtide-T20+IL-2)

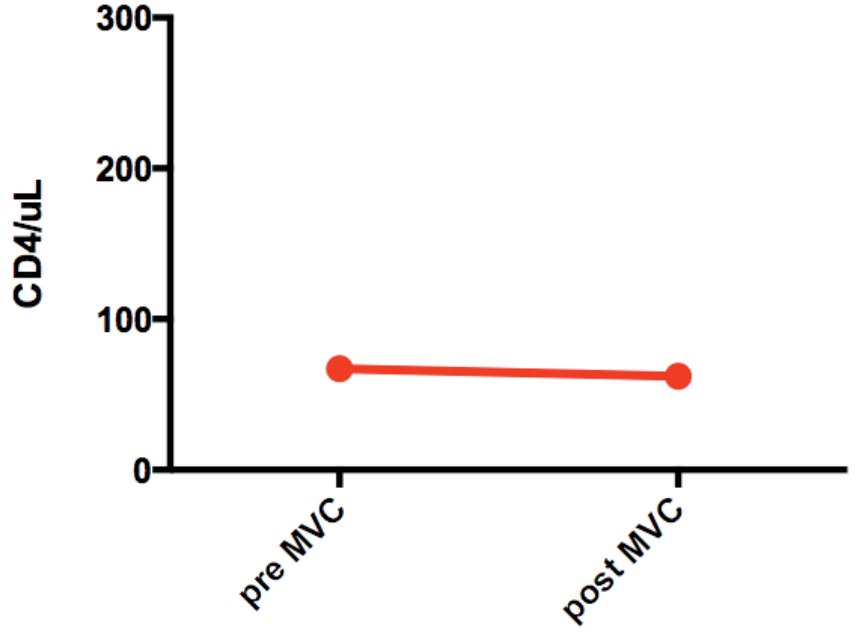




T20+IL-2

Year 2010: cART Intensification (maraviroc)

MVC: 150 mg bid + ongoing TDF+FTC+LPV/r



HIV-RNA always undetectable

Maraviroc

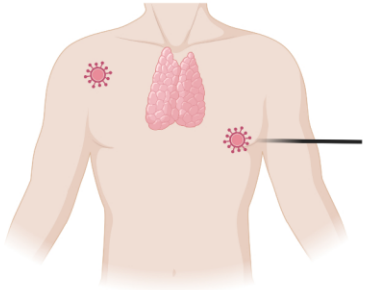
Rusconi *et al.* (2013)	RCT	97 INR pts (47 *vs* 50)	cART ± maraviroc	48 wks (48 wks)	No advantage in CD4 T-cell recovery; expansion of CD8 T-cell counts and activation (CD38+HLA-DR+); rise in plasma IL-7 and IL-7R expression on CD4 T cells
Hunt *et al.* (2013)	RCT	45 INR pts (23 *vs* 22)	cART + maraviroc or placebo	24 wks (36 wks)	No increase in CD4 T-cell count; rise in activated (CD38+HLA-DR+) CD8 T cells; expansion of activated T cells in rectal tissue
van Lelyveld *et al.* (2015)	RCT	85 INR pts (41 *vs* 44)	cART + maraviroc or placebo	48 wks (48 wks)	No rise in CD4 T-cell count; no changes in T-cell activation/proliferation (CD38+HLA-DR+/Ki-67+) and microbial translocation (sCD14); reduction of apoptotic (annexin-V+) T cells
Minami *et al.* (2017)	OS	32 INR pts (18 *vs* 14)	cART ± maraviroc	24 wks (24 wks)	Increase in CD4 T-cell count (>25%) in 12/18 pts (MVC-responders); decreased IFN-γ mRNA in CD4 T cells, especially in MVC-responders

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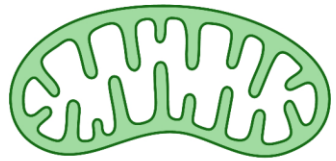
Depletion of progenitor cells in the bone marrow



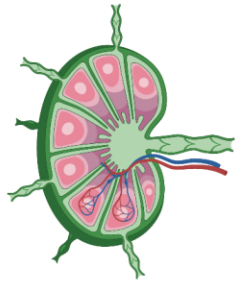
Reduced size and thymic output

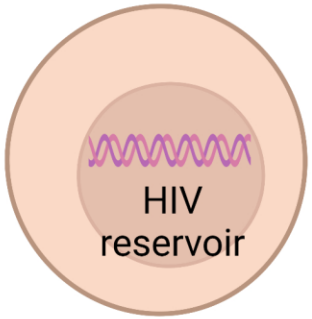


Alteration in mitochondrial respiration



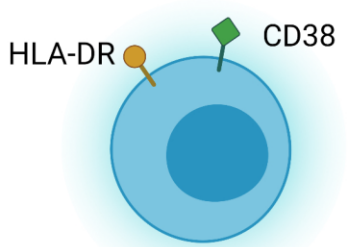
Lymphoid tissue fibrosis



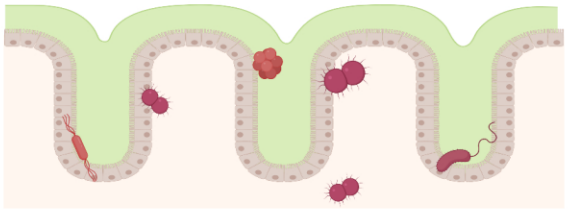


CD4+ T-cells

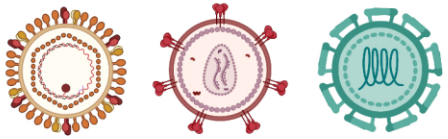
Persistent CD4+ T-cell hyperactivation



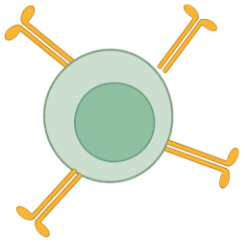
Gut barrier disruption, microbial translocation and gut dysbiosis



Coinfections



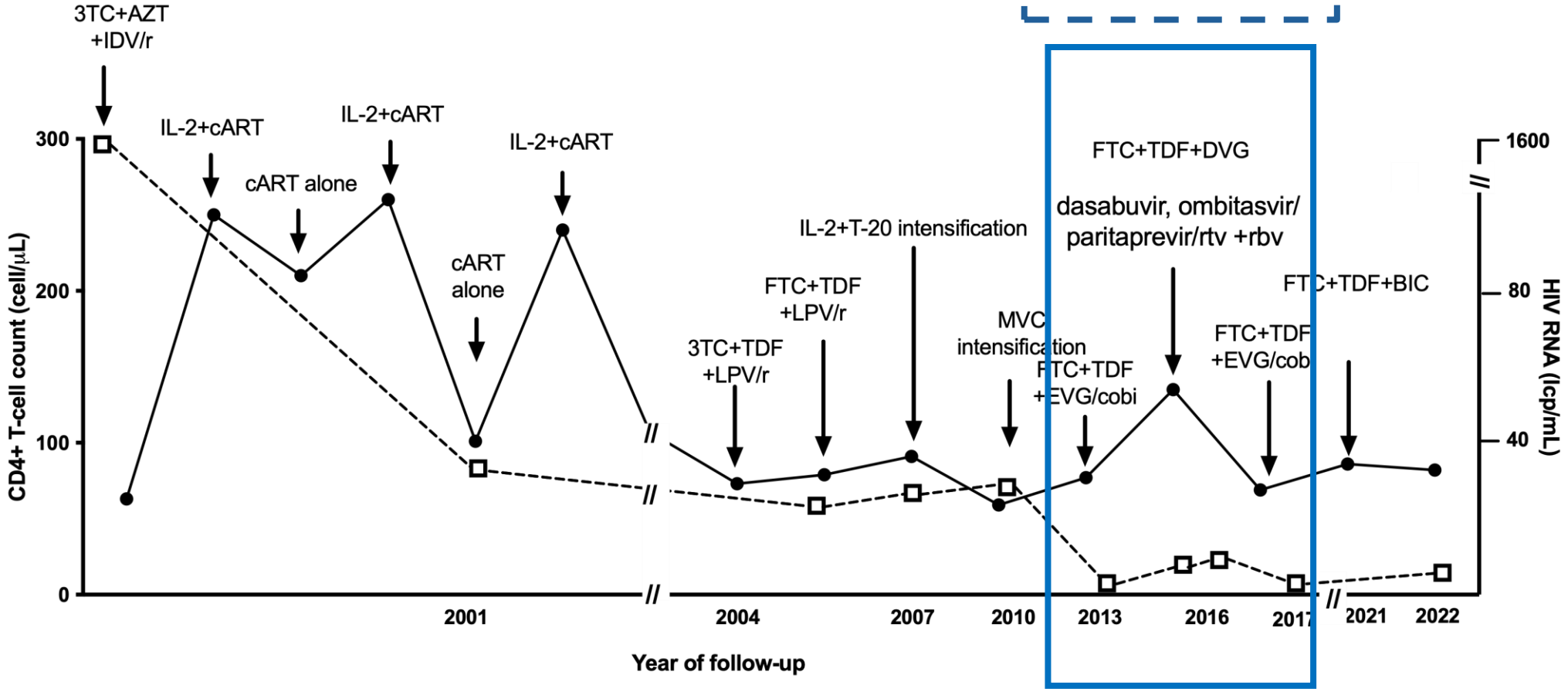
T-cell senescence and exhaustion



Bono V et al. New

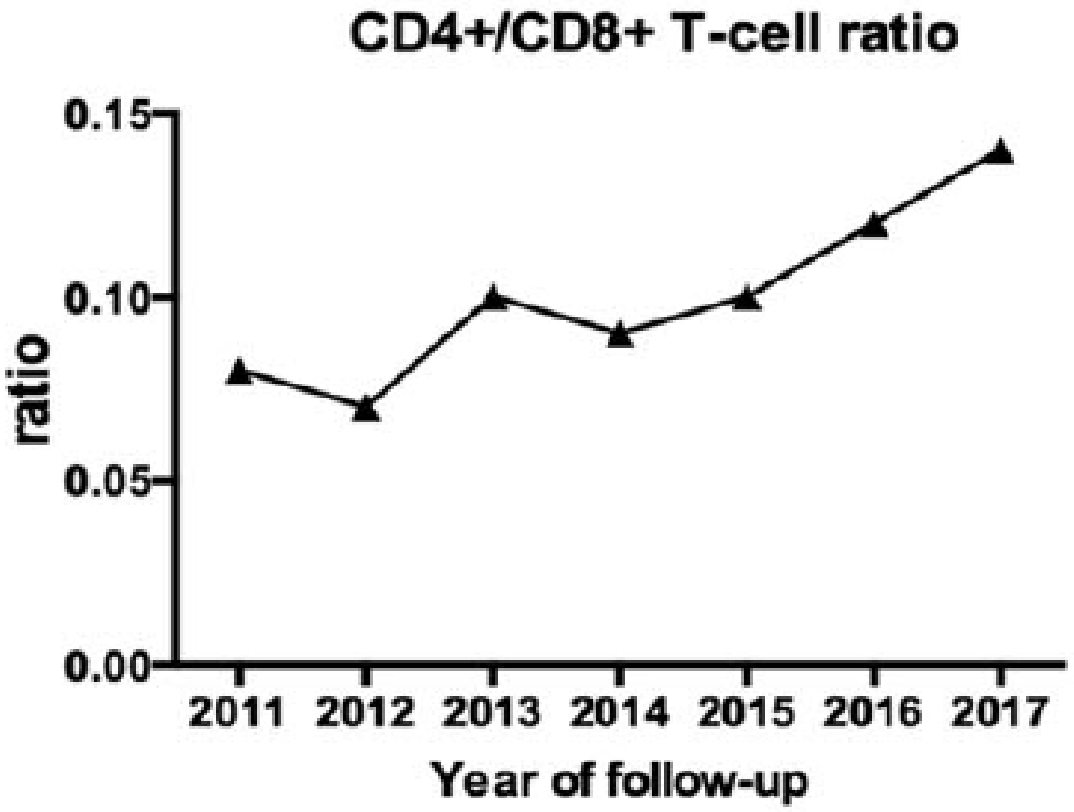
HCV genotype 1a, HCV RNA 359390 IU/ml

2017- HCV: SVR at wk 24



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Weak increase in CD4/CD8 T-cell ratio



CD4 135 cells/µl

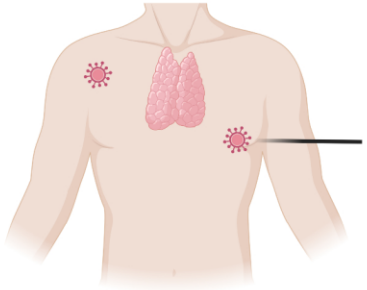
CD4/CD8 0.17

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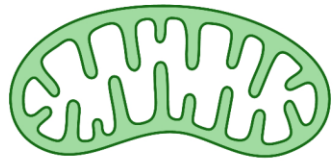
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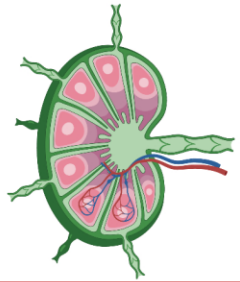
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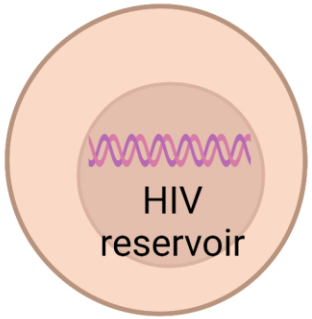


Alteration in mitochondrial respiration



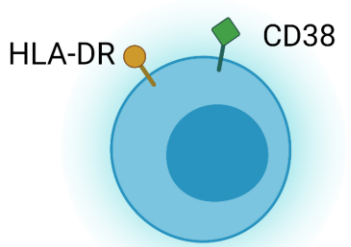
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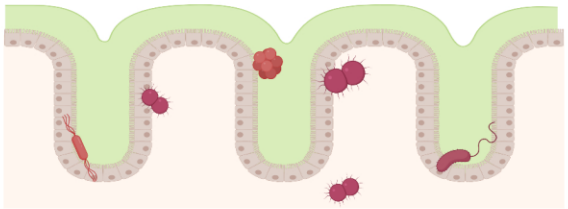


CD4+ T-cells

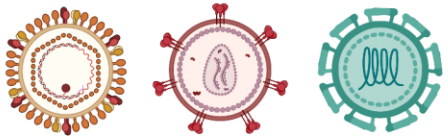
Persistent CD4+ T-cell hyperactivation



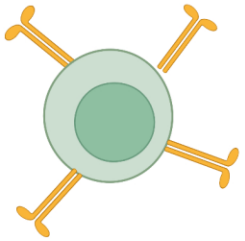
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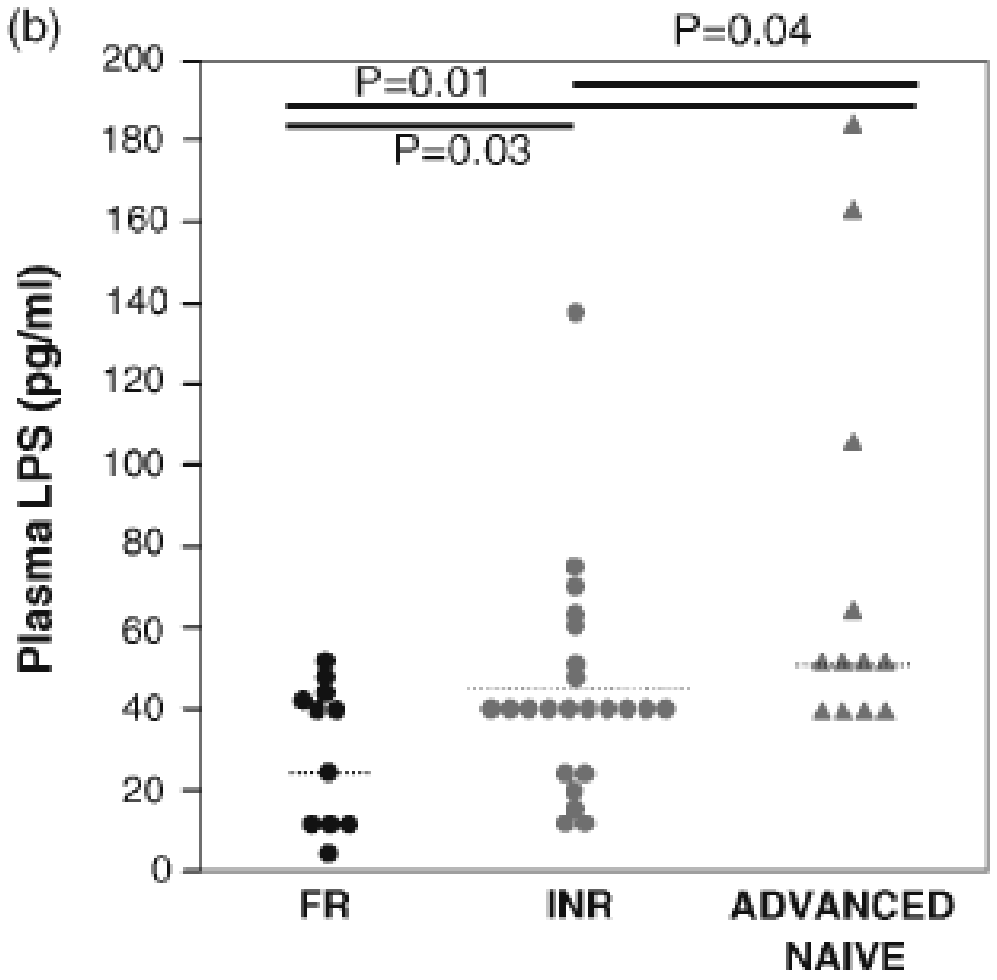


T-cell senescence and exhaustion



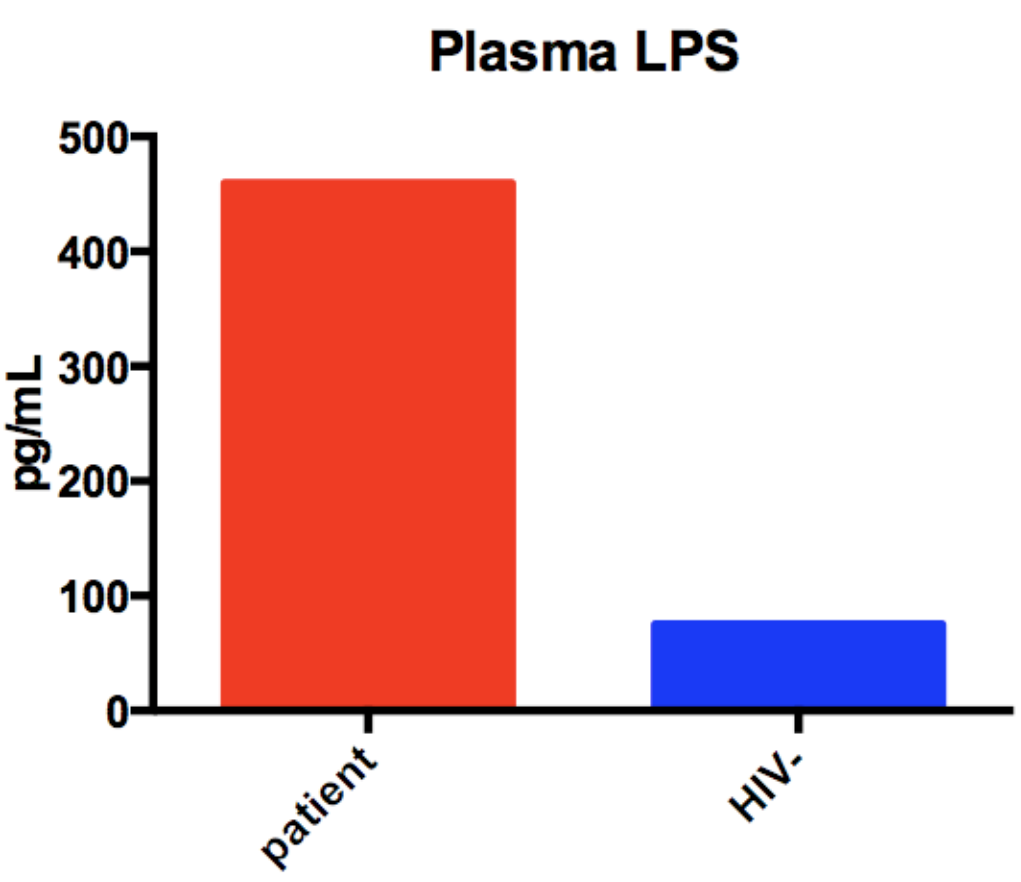
Bono V et al. New Microbiologica 2022

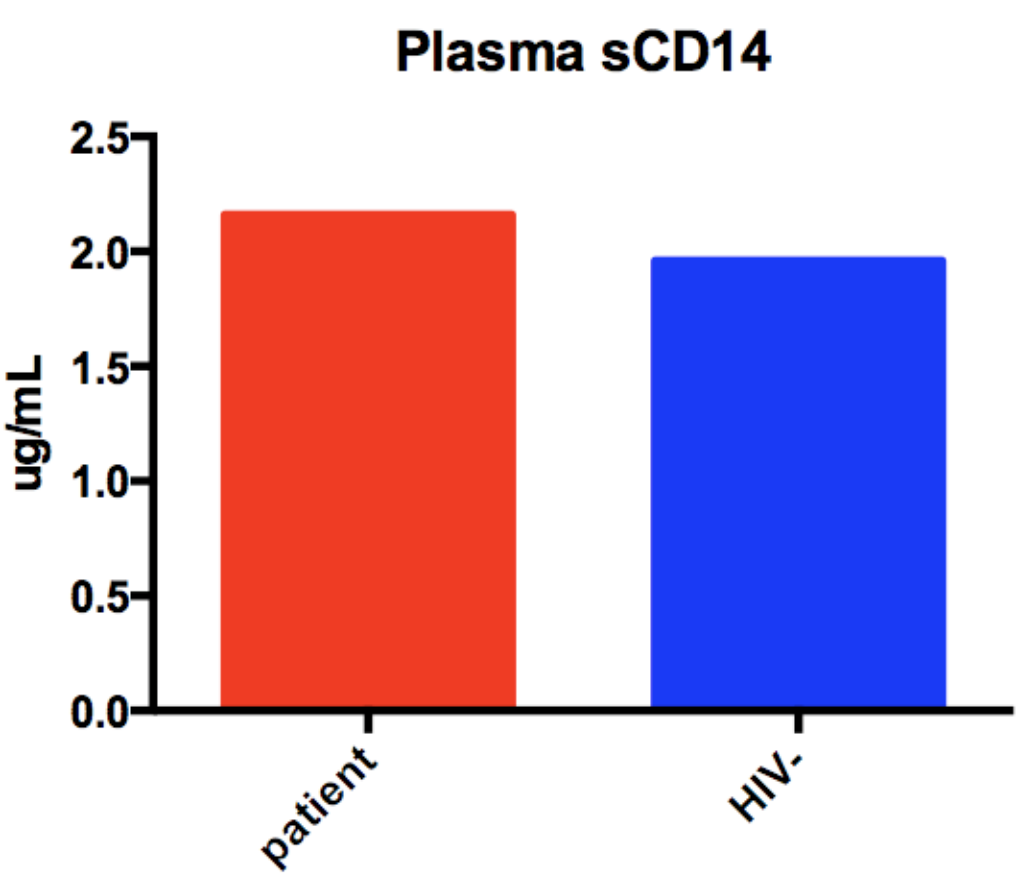
Higher microbial translocation in INRs



Marchetti et al. AIDS 2008

Microbial translocation

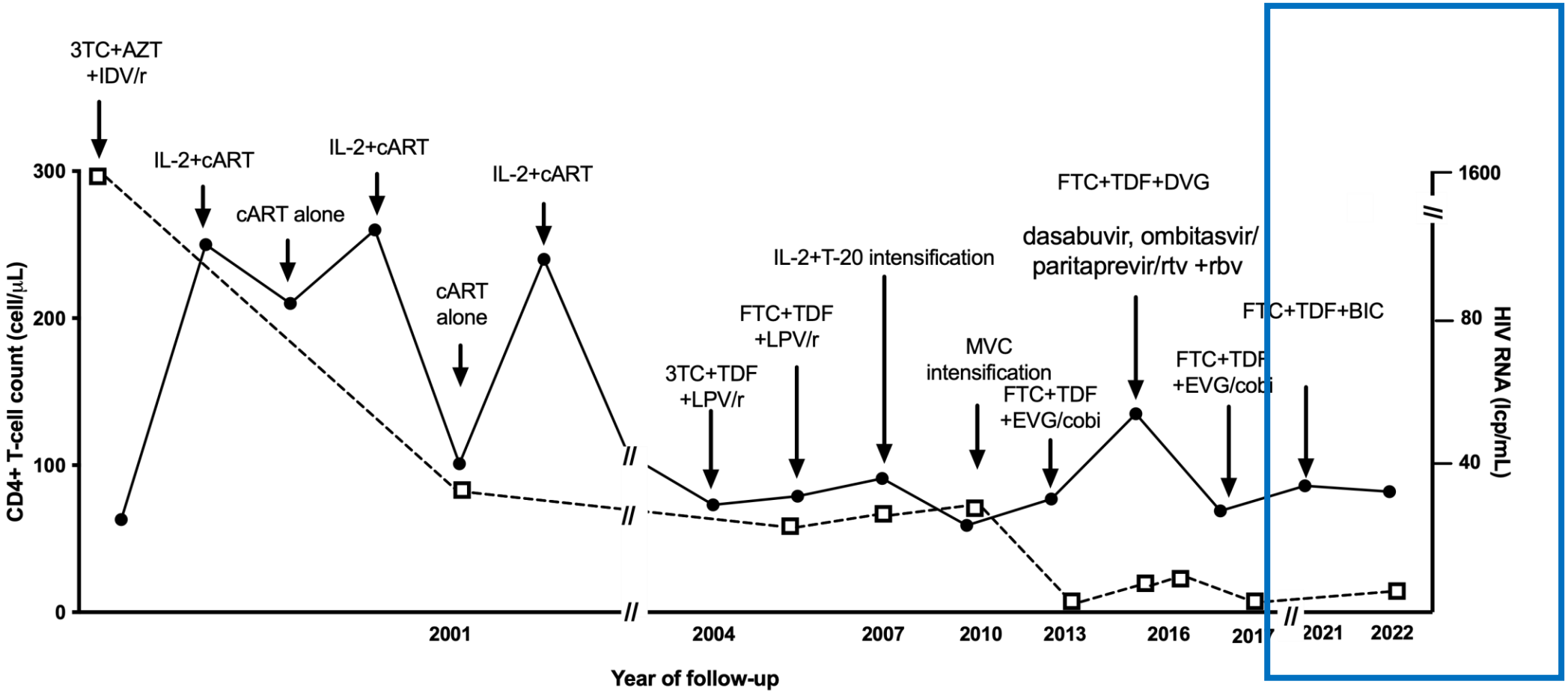




Rifaximin					
Tenorio *et al.* (2015)	RCT	65 INR pts (43 *vs* 22)	cART ± rifaximin	4 wks (8 wks)	No changes in CD4 T cells count or activation/ proliferation (CD38+HLA-DR+/Ki-67+); inhibition of CD8 T cells activation (CD38+HLA-DR+) increase; reduction of CD8 T cells proliferation (Ki-67+); weak and transient reduction of microbial translocation (LPS, sCD14); small reduction in plasma markers of inflammation (IL-6, CRP)

Bono V et al. New Microbiologica 2022

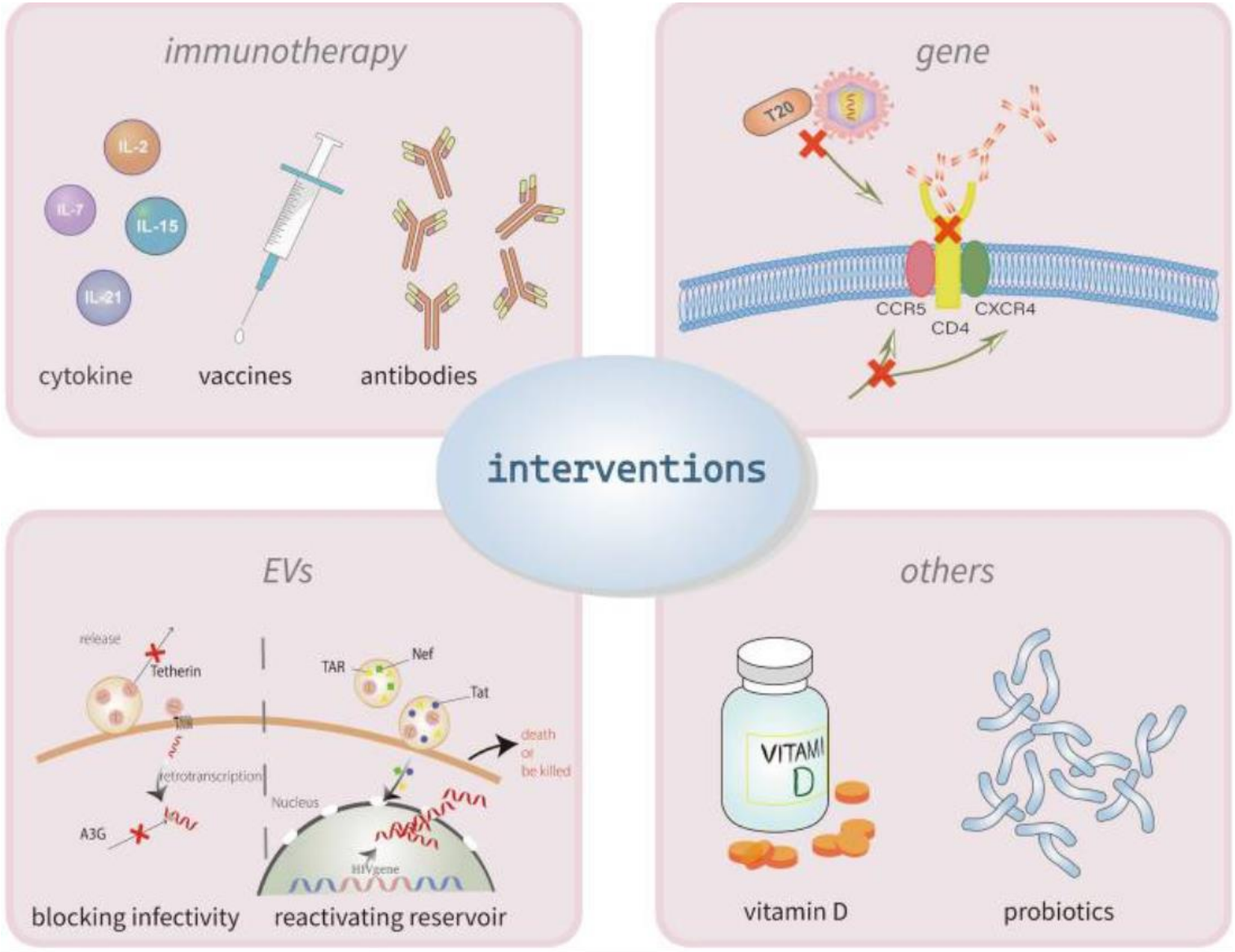
Conclusions



In 2024, viro-immunological parameters:
- HIV RNA undetectable
- CD4 T cell count 146 cells/µl

Tincati et al. BMC Infect

New therapeutic approaches



Zhang et al. Front Microbi

Acknowledgements

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  - Matteo Augello
  - Sabrina Marozin
  - Maria Sgarlata
  - Camilla Tincati
  - Giulia Marchetti



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