Acute HIV: a real gateway to post-treatment control?

Camilla Tincati, M.D., Ph.D

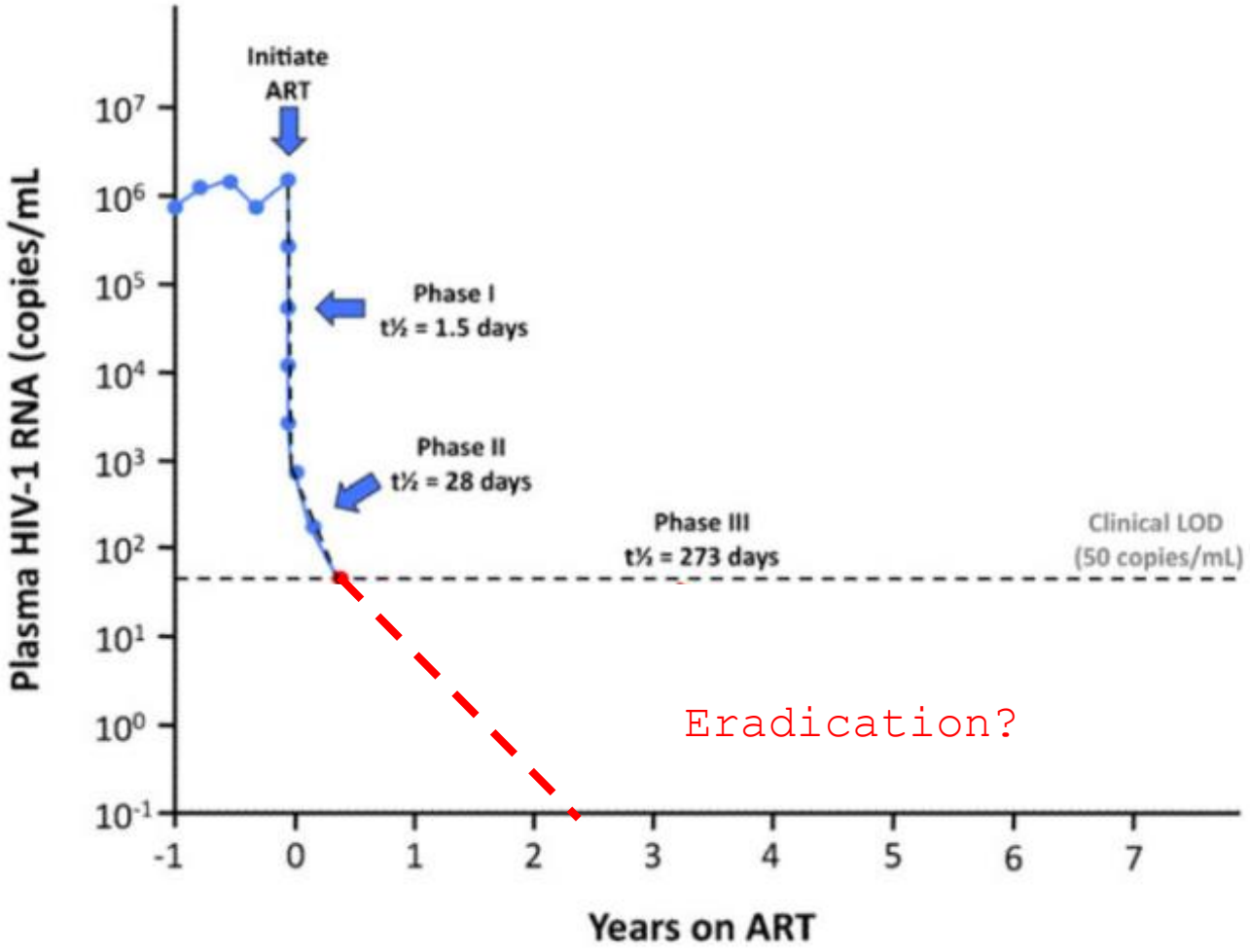
Department of Health Sciences

Clinic of Infectious Diseases

ASST Santi Paolo e Carlo

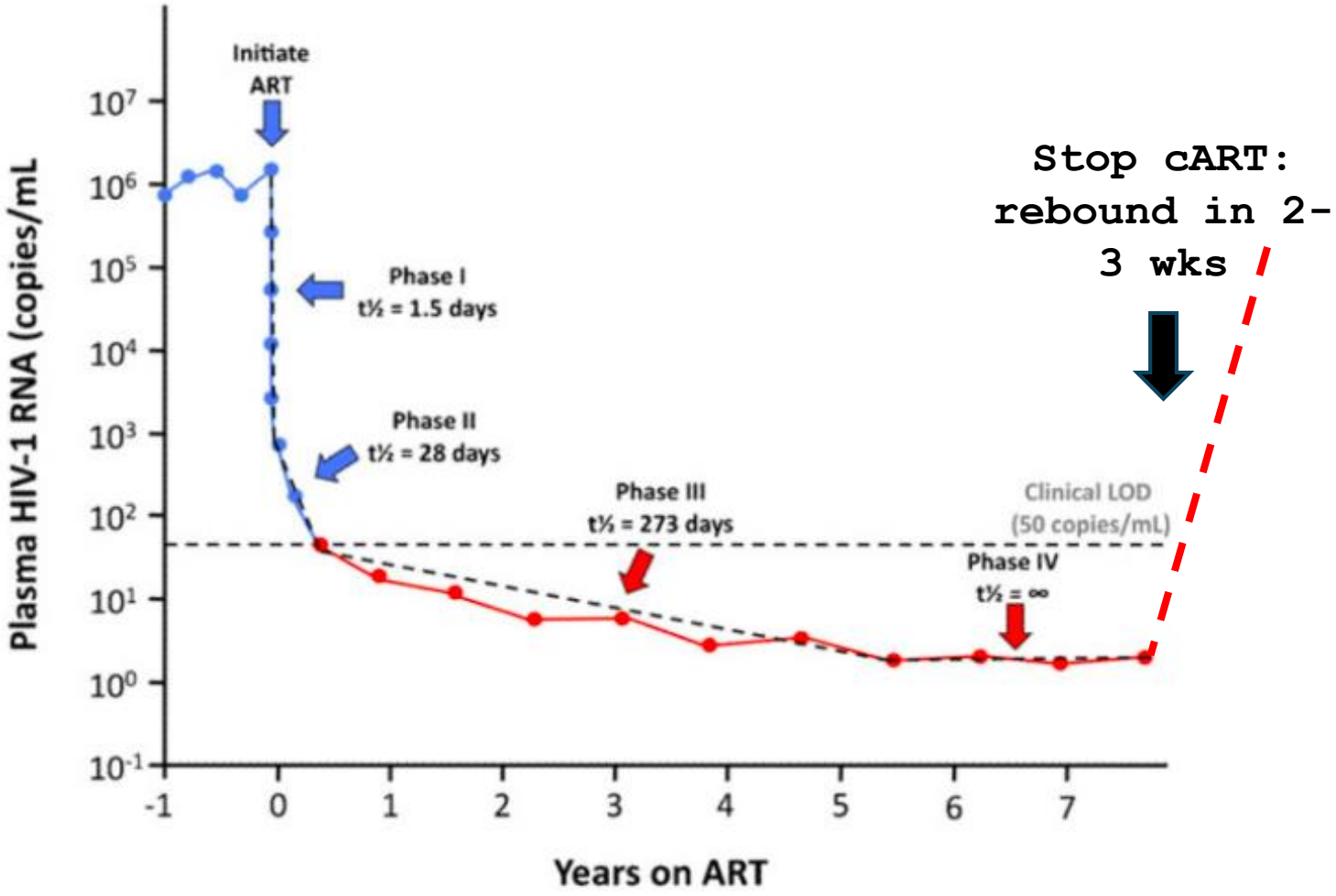
University of Milan

1996-1997: Cure possible with continued cART?



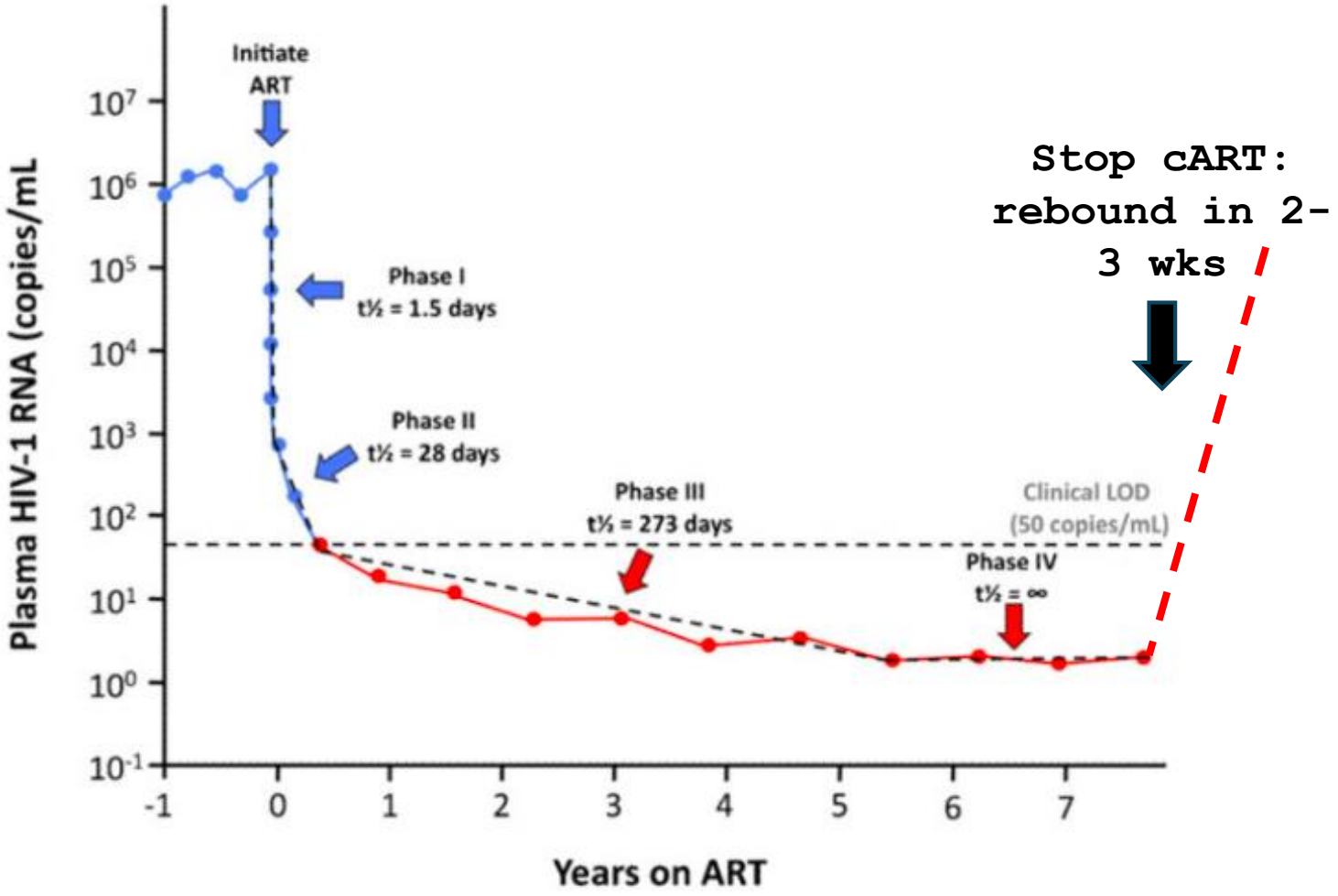
Perelson, Nature, 1997

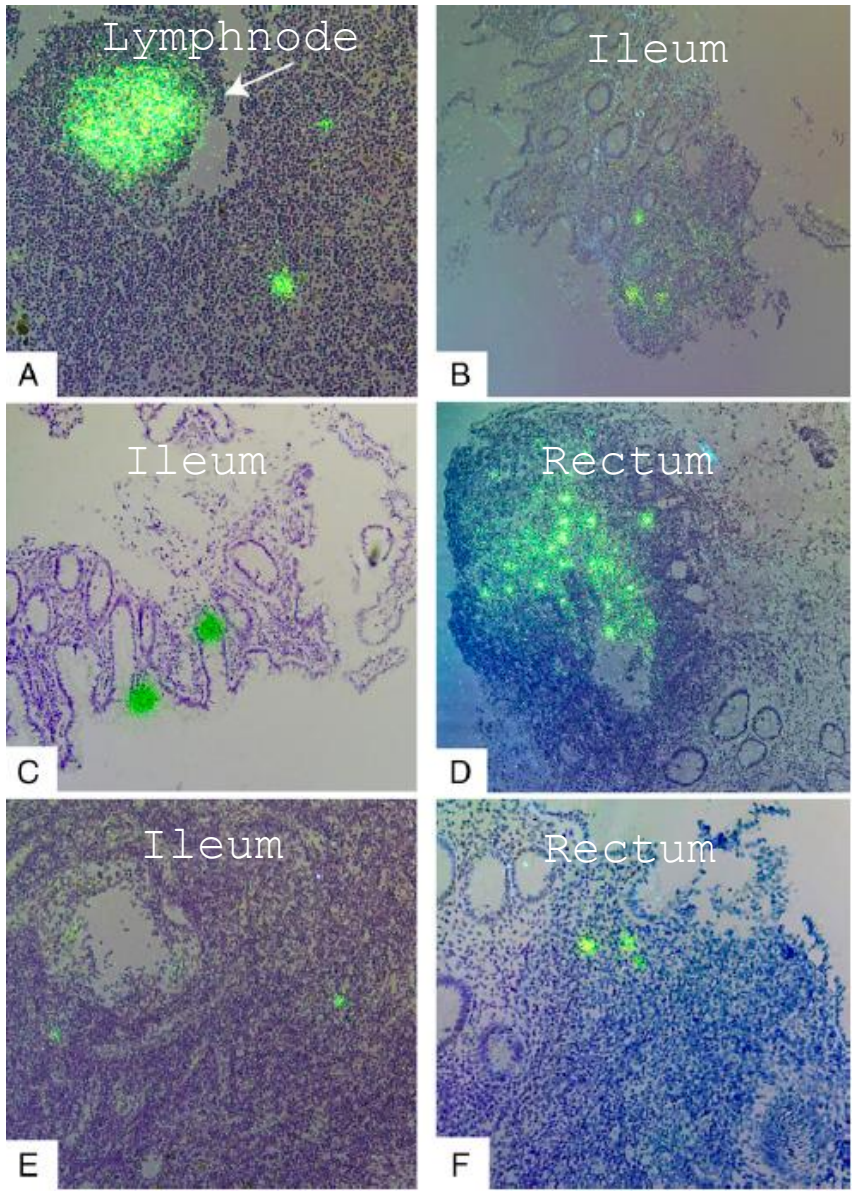
Cure possible with continued cART? No!



Dornadula et al. 1999; Yerly et al. 2000; Havlir et al. 2001; Palmer et al. 2008; and many more

The HIV reservoir causes rebound

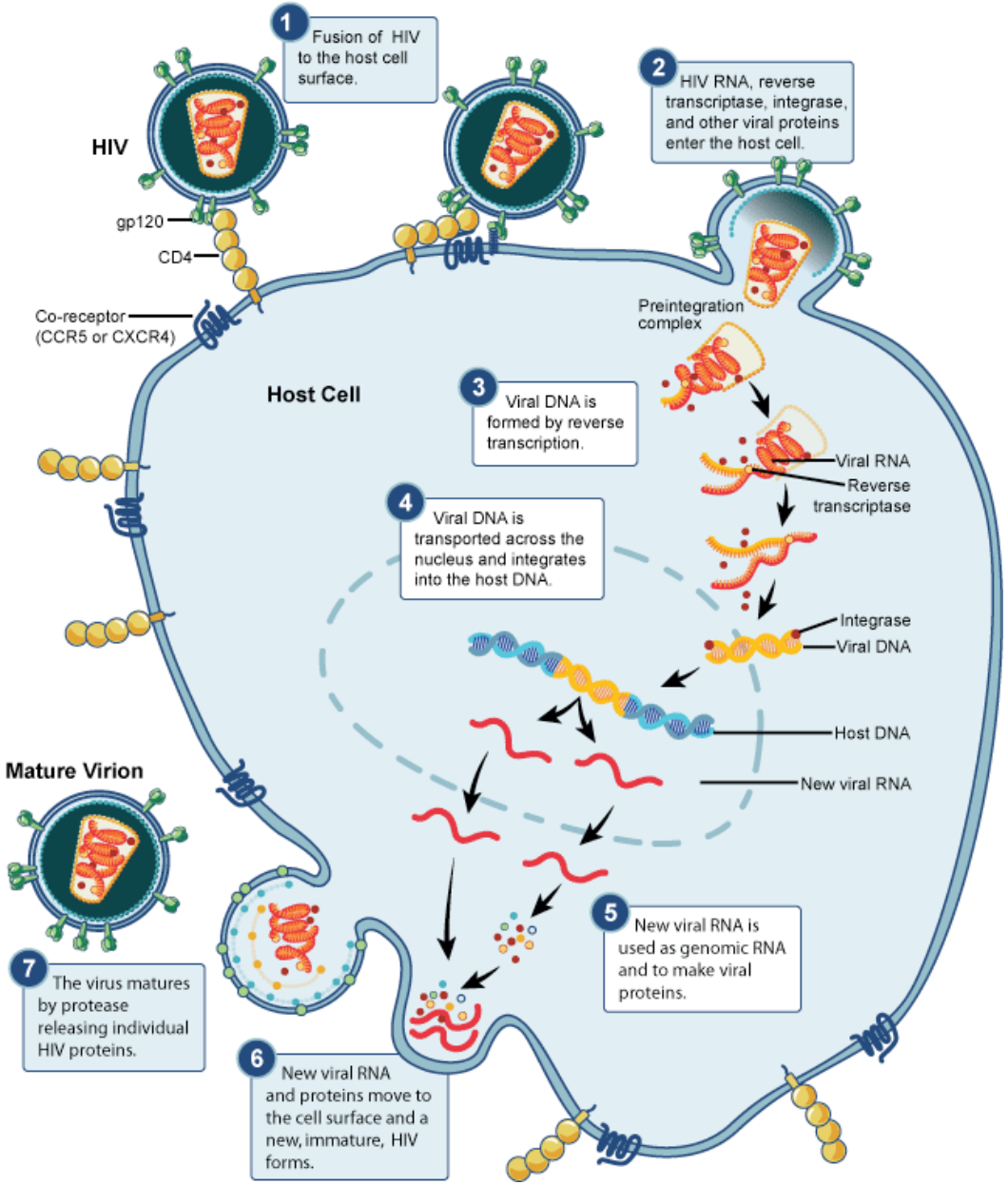




Rothenberger, PNAS 2015

Trends in Microbiology, May 2016, Vol. 24, No. 5

CellPress



Glossary

Cellular reservoir: cells that are infected with latent HIV-1.

Latent HIV-1: transcriptionally silent, but replication-competent HIV proviruses that persist during treatment with ART and are capable of resuming replication upon discontinuation of ART.

Tissue reservoir: anatomically defined structures that contain cells that harbor latent HIV-1.

//www.niaid.nih.gov

Reservoir=what causes rebound=obstacle

Cure vs Remission

Cure	Remission
Infectious Diseases model	Cancer model
Elimination of all HIV-infected cells: no replication-competent proviruses left	Long term health in absence of cART
HIV RNA < 1cp/ml	HIV RNA < 50 cp/ml
Eradication/Sterilising cure	Functional/Non-sterilizing cure

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Proof of Concept: cure strategies with bone marrow transplants

2008–2009



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

The Berlin Patient: T. Brown

2019



LETTER

https://doi.org/10.1038/s41586-019-1027-4

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K. Gupta[1,2,3,4,5]*, Sultan Abdul-Jawad[1], Laura E. McCoy[1], Hoi Ping Mok[4], Dimitra Peppa[3,6], Maria Salgado[7], Javier Martinez-Picado[7,8,9], Monique Nijhuis[10], Annemarie M. J. Wensing[10], Helen Lee[11], Paul Grant[12], Eleni Nastouli[12], Jonathan Lambert[13], Matthew Pace[6], Fanny Salasc[4], Christopher Monit[1], Andrew J. Innes[14,15], Luke Muir[1], Laura Waters[3], John Frater[6,16], Andrew M. L. Lever[4,17], Simon G. Edwards[3], Ian H. Gabriel[14,15,18,19] & Eduardo Olavarria[14,15,19]

The London Patient: A. Castillejo

2019–2023



nature medicine

Brief Communication

https://doi.org/10.1038/s41591-023-02213-x

In-depth virological and immunological characterization of HIV-1 cure after CCR5Δ32/Δ32 allogeneic hematopoietic stem cell transplantation

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Check for updates

Björn-Erik Ole Jensen[1,24], Elena Knops[2,3,24], Leon Cords[4,24], Nadine Lübke[5,24], Maria Salgado[6,7,23,24], Kathleen Busman-Sahay[8], Jacob D. Estes[8], Laura E. P. Huyveneers[9], Federico Perdomo-Celis[10], Melanie Wittner[4,11], Cristina Gálvez[6], Christiane Mummert[12,20], Caroline Passaes[10], Johanna M. Eberhard[4,11,21], Carsten Münk[1], Ilona Hauber[13], Joachim Hauber[11,13], Eva Heger[2,3], Jozefien De Clercq[14], Linos Vandekerckhove[14], Silke Bergmann[12], Gábor A. Dunay[11,13,22], Florian Klein[2,3], Dieter Häussinger[1], Johannes C. Fischer[15], Kathrin Nachtkamp[16], Joerg Timm[5], Rolf Kaiser[2,3], Thomas Harrer[12], Tom Luedde[1], Monique Nijhuis[9], Asier Sáez-Cirión[10,25], Julian Schulze zur Wiesch[4,11,20], Annemarie M. J. Wensing[8,17,25], Javier Martinez-Picado[6,7,18,19,25] & Guido Kobbe[16,25]

The Dusseldorf Patient: Marc

Cure vs Remission

Cure	Remission
Infectious Diseases model	Cancer model
Elimination of all HIV-infected cells: no replication-competent proviruses left	Long term health in absence of cART
HIV RNA < 1cp/ml	HIV RNA < 50 cp/ml
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Immune-mediated control without transplants

- Post-treatment controllers (PTC) (remission)
- Exceptional Elite Controllers (EEC)
- Natural Cure (very rare)

Immune-mediated control without transplants

- Post-treatment controllers (PTC) (remission)
- Exceptional Elite Controllers (EEC)
- Natural Cure (very rare)

PTCs represent a small subset of HIV-infected individuals able to maintain control of HIV-1 replication after stopping ART

Definition of PTC is heterogeneous

Supplementary Table S1. The summary of post-treatment controllers (PTCs) and viral control failure after treatment interruption (TI) definitions.

Study	Post-treatment control definition	Viral control failure definition
Hocqueloux, 2010 **(9)**	Viral load <50 copies/ml for at least 24 months post TI	2 consecutive viral rebound with viral load >50 copies/ml in 24 months post TI
Goujard, 2012 **(10)**	Viral load <50 copies/ml for more than 12 months post TI	2 consecutive viral rebound with viral load >50 copies/ml in at least 12 months post TI
Lodi, 2012 **(11)**	Viral load <50 copies/ml for in 24 months post TI	2 consecutive viral rebound with viral load >50 copies/ml in 24 months post TI
Saez-Cirion, 2013 **(7)**	Viral load <400 copies/ml for at least 24 months post TI	4 consecutive viral rebound with viral load >400 copies/ml in 24 months post TI
Stohr, 2013 **(12)**	Viral load <400 copies/ml for 12 weeks post TI	1 viral rebound with viral load >400 copies/ml in 12 weeks post TI
Van Gulk, 2012 **(15)**	Viral load <50 copies/ml for 6 months post TI	N/A
Assoumou, 2015 **(16)**	Viral load <400 copies/ml for 12 months post TI	2 consecutive or 1 plus treatment resumption viral rebound with viral load >400 copies/ml in 12 months post TI
Calin, 2016 **(17)**	Viral load <400 copies/ml for 56 weeks post TI	1 viral rebound with viral load >400 copies/ml in 56 weeks post TI
Perkins, 2017 **(18)**	Viral load <400 copies/ml for 6 months to 2 years post TI in transient controllers and more than 2 years for durable controllers	1 viral rebound with viral load >400 copies/ml (not specified exactly in how long post TI)
Fidler, 2017 **(19)**	Viral load <50 copies/ml for at least 24 months post TI	2 consecutive HIV-1 RNA viral load >50 copies/ml
Namazi, 2018 **(6)***	Viral load ≤400 copies/ml for two thirds or more of time points in at least 24 weeks post TI	Viral load >400 copies/ml were acceptable if the participant was subsequently able to suppress to ≤400 copies/ml in 24 weeks post TI

*The CHAMP study includes participants from 8 AIDS Clinical Trials Group (ACTG) studies (ACTG 371 (20), A5024 (21), A5068 (22), A5102 (23), A5130 (24), A5170 (25), A5187 (26), and A5197 (27)), the Montreal Primary HIV Infection Cohort (Montreal PIC) (28), the Seattle Primary Infection Program (SeaPIP) (13,29), the University of California San Diego Primary Infection Cohort (UCSD PIC) (14), a National Institutes of Health (NIH) therapeutic vaccine trial (31), the University of California San Francisco (UCSF) OPTIONS study (31), and the Ragon HIV Controllers cohort (32).

- virologic rebound
- duration of viral con

Etemad, Front Immunol, 2019

TABLE 1 | Post-treatment controller (PTC) frequency after treatment interruption reported from previously published studies.

References	Cohort	Timing of ART	PTC, Total, *N*	PTC Frequency (%)	VF threshold copies/ml	PTC duration
Hocqueloux et al. (9)	ANRS	Early	5	15.6	>50	75 months (median)
Goujard et al. (10)	ANRS PRIMO	Early	14	8.5	>50	4.5 years (median)
Lodi et al. (11)	CASCADE	Early	11	5.5	>50	24 months
Saez-Cirion et al. (7)	VISCONTI	Early	14	15.3	>400	89 months (median)
Stohr et al. (12)	SPARTAC	Early	4	2.4	>400	164–202 weeks
Van Gulck et al. (15)	Secondary Controllers	Chronic	4		>1,000	At least 6 months
Assoumou et al. (16)	ANRS SALTO	Chronic	7	4.2	>400	12 months (7 patients) 36 months (4 of the 7 patients)
Calin et al. (17)	ULTRASTOP	Early Chronic	1	10	>400	56 weeks
Perkins et al. (18)	NHS	Chronic	4	4.2	>400	267–1,058 days
Fidler et al. (19)	CASCADE	Early	22	2.8	>50	24 months
Namazi et al. (6)*	CHAMP	Early & Chronic	67	13 (Early) 4 (Chronic)	>400	24–804 weeks

**The CHAMP study includes participants from 8 AIDS Clinical Trials Group (ACTG) studies [ACTG 371 (20), A5024 (21), A5068 (22), A5102 (23), A5130 (24), A5170 (25), A5187 (26), and A5197 (27)], the Montreal Primary HIV Infection Cohort (Montreal PIC) (28), the Seattle Primary Infection Program (SeaPIP) (13, 29), the University of California San Diego Primary Infection Cohort (UCSD PIC) (14), a National Institutes of Health (NIH) therapeutic vaccine trial (30), the University of California San Francisco (UCSF) OPTIONS study (31), and the Ragon HIV Controllers cohort (32).*

ART, Anti Retroviral Therapy; VF, Viral Failure.

The observed frequency of PTCs ranged between 2.4 and 15.6% of patients undergoing TI
Median viral control 89 weeks; 22% of patients still suppressed after 5 years

Etemad, Front Immunol, 2019

Mastrangelo, Curr Opinion HIV AIDS,

PTC in ICoNA

Post-Treatment Controllers (PTCs)

Definition: PLWH with HIV-RNA less than 200 copies/mL for more than 1 year after treatment interruption

Characteristics	PTCs (*n*=17)
Age at enrollment (years), median (IQR)	39 (30–45)
Year of enrollment, median (IQR)	2008 (2002–2010)
Sex, *n* (%)	
Male	8 (47.1)
Female	9 (52.9)
Ethnicity, *n* (%)	
Italian	13 (76.5)
Non-Italian	4 (23.5)
Epidemiology	
MSM	2 (11.8)
MSW/WSM	8 (47.1)
IDU	5 (29.4)
Other/unknown	2 (11.8)
On ART (ever), *n* (%)	17 (100)
Years from ART start to PTC definition, median (IQR)	2 (0–4.5)
Years off-ART with HIV-RNA <50 copies/mL, median (IQR)	3 (2–5.5)
Off ART at last follow-up (2021–2023), *n* (%)	5 (29.4)
Still PTC (HIV-RNA <200 copies/mL while off ART) at last follow-up (2021–2023), *n* (%)	4 (23.5)
Active follow-up (2021–2023), *n* (%)	17 (100)
Immunologic parameters	
CD4 count at enrollment (cells/μL), median (IQR)	450 (90–672)
CD4 count strata at enrollment (cells/μL), *n* (%)	
<200	5 (29.4)
200–350	1 (5.9)
>350	11 (64.7)
CD4/CD8 ratio at enrollment, median (IQR)	0.7 (0.1–1.2)
CD4 count at ART start (cells/μL)[‡], median (IQR)	296 (90–474)
CD4 count strata at ART start (cells/μL)[‡], *n* (%)	
<200	5 (29.4)
200–349	5 (29.4)
350–500	3 (17.6)
>500	4 (23.5)
CD4/CD8 ratio at ART start[‡], median (IQR)	0.5 (0.1–1.1)
CD4 count at last follow-up (2021–2023) (cells/μL)[†], median (IQR)	654 (427–946)
CD4/CD8 ratio at last follow-up (2021–2023)[†], median (IQR)	0.9 (0.3–1.2)
Virologic parameters	
HIV-RNA at enrollment (log_{10} copies/mL), median (IQR)	4 (2–5)
HIV-RNA at ART start (log_{10} copies/mL)[‡], median (IQR)	4.4 (2.1–5)
HIV-RNA at ART start >100000 copies/m[‡], *n* (%)	5 (29.4)
HIV-RNA <50 copies/mL at last follow-up (2021–2023)[†], *n* (%)	14 (82.4)
HIV diagnosis during RHI, *n* (%)	0 (0)
AIDS (ever), *n* (%)	4 (23.5)

Marchetti, 10th ICoNA, 2024

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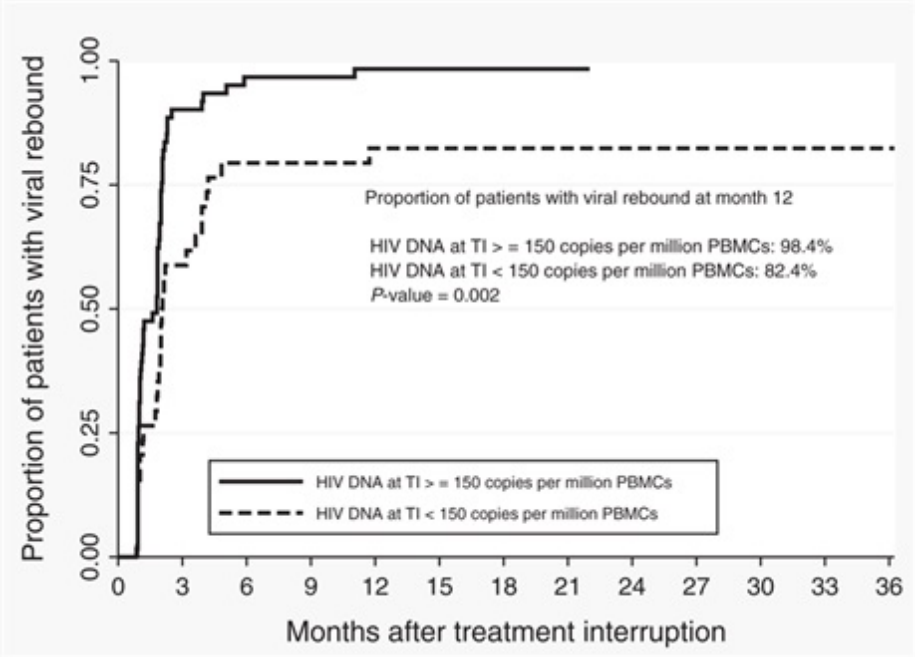
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Etemad, Front Immunol, 2019

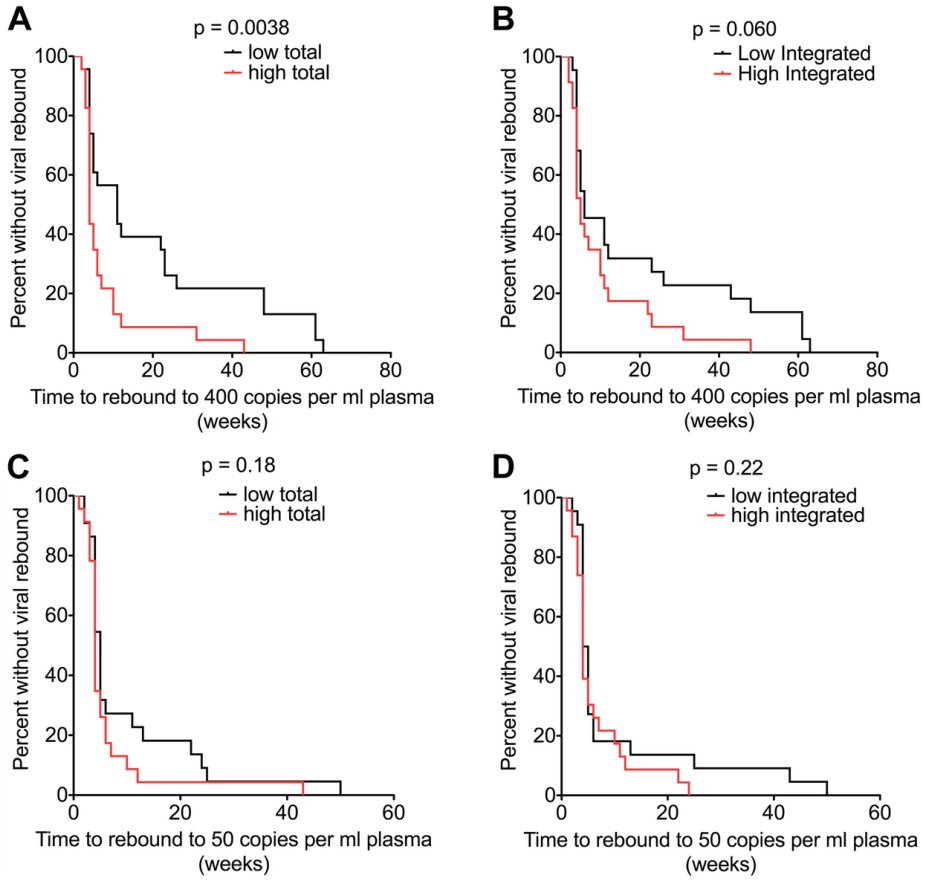
Mastrangelo, Curr Opinion HIV AIDS,

(A few) Reasons by which cART in acute HIV may account for post-treatment control

Low levels of pre-treatment interruption HIV proviral DNA predict delayed viral rebound

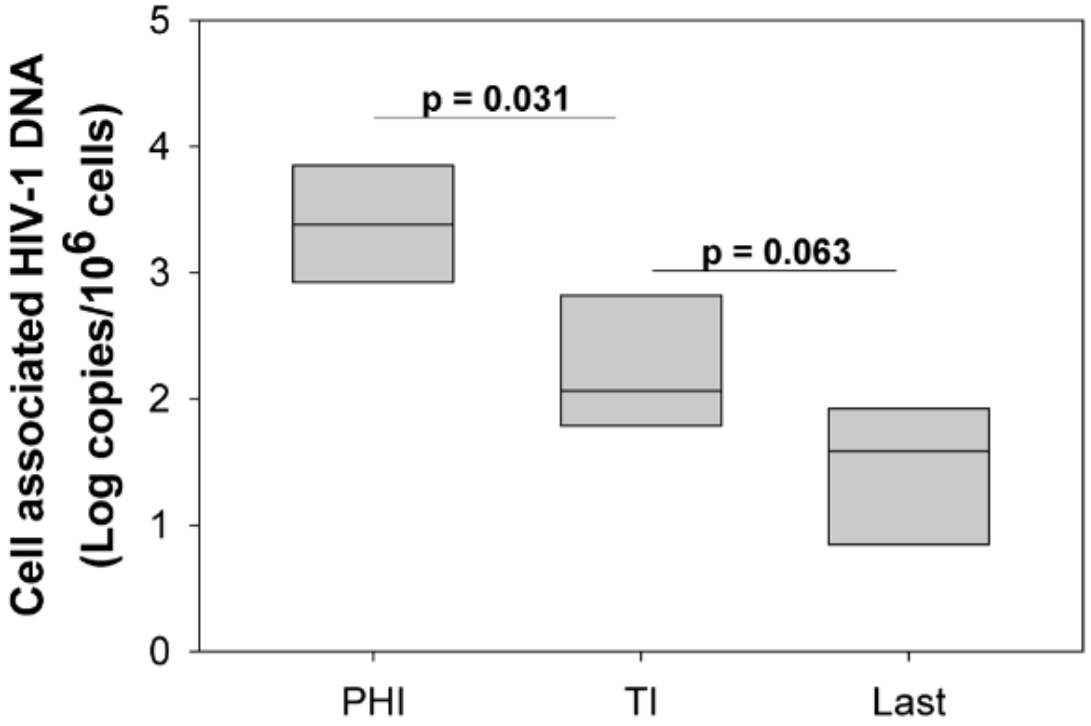


Lambert, AIDS, 2015

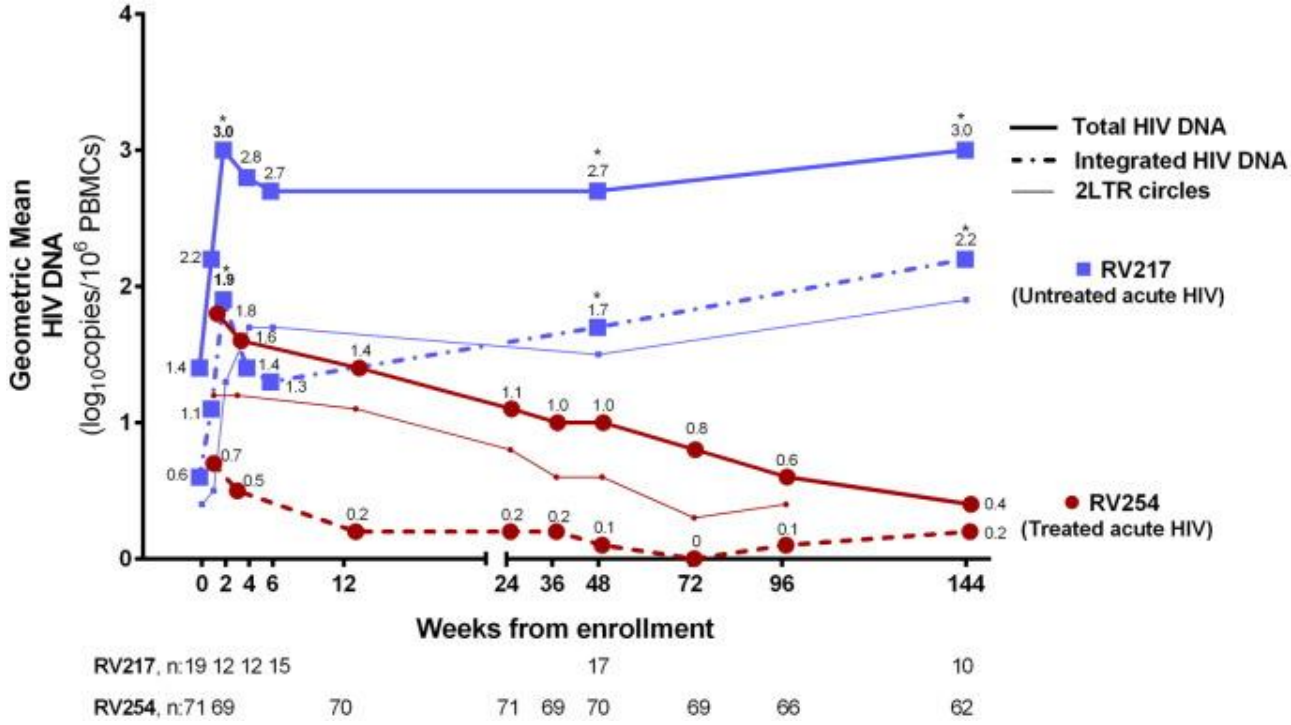


Williams, Elife, 2014

ART initiation during acute infection might reduce the cellular reservoir



Saez-Cirion, PlosPath, 2013

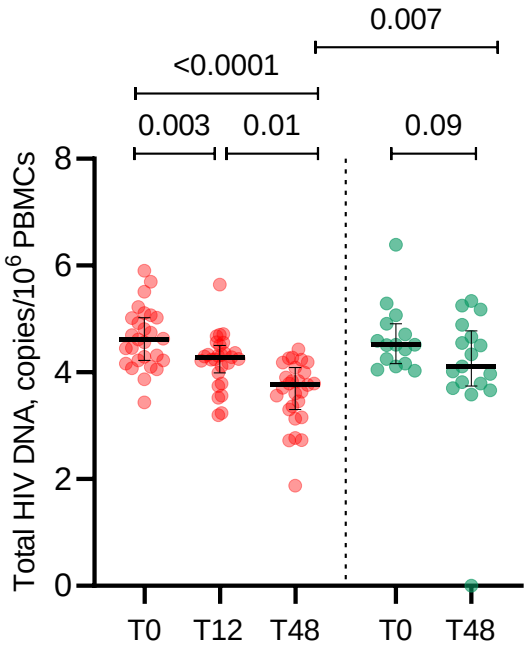


Ananworanich, EBioMedicine 2016

Lower cellular reservoir in cART-treated AHI than CHI

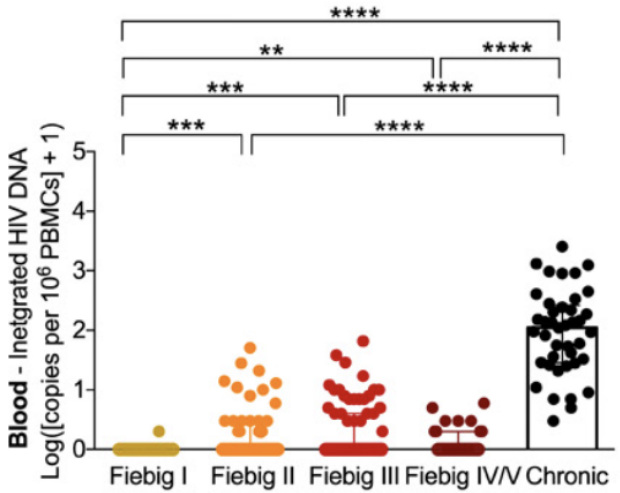
AHI

CHI



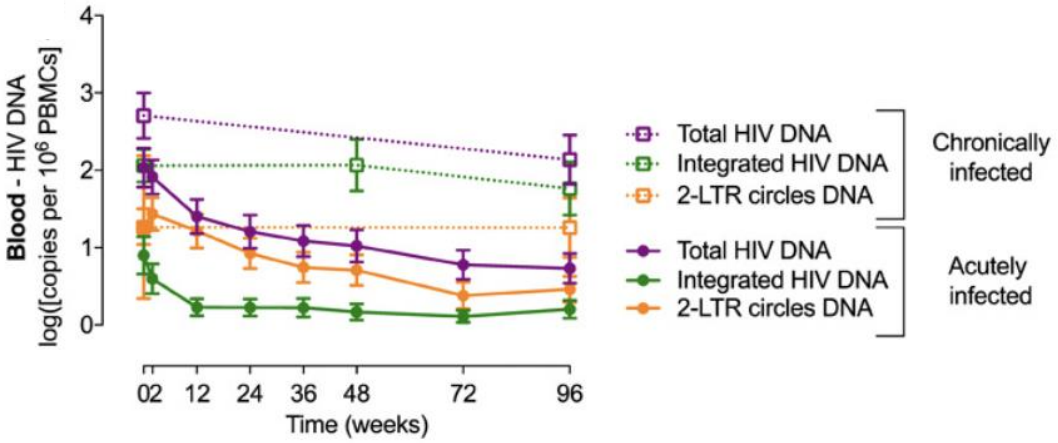
Baseline CD4 in CHI: 645/uL

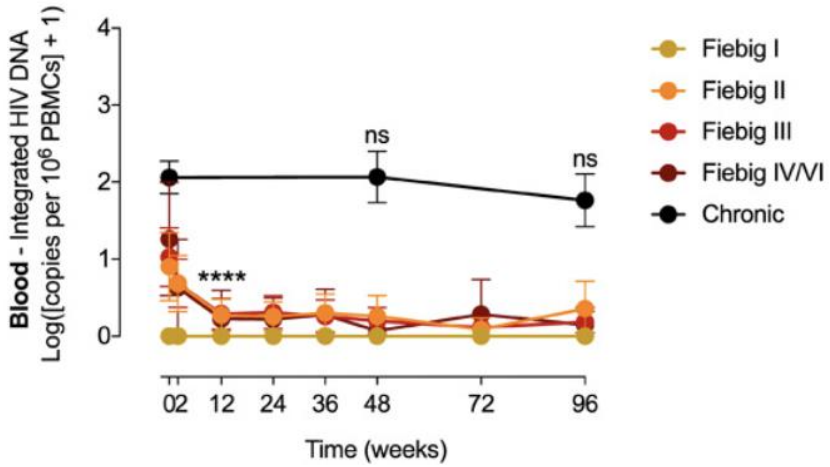
Bono, ICAR 2023; manuscript in preparation
See also: Bruzzesi, JMV, 2023



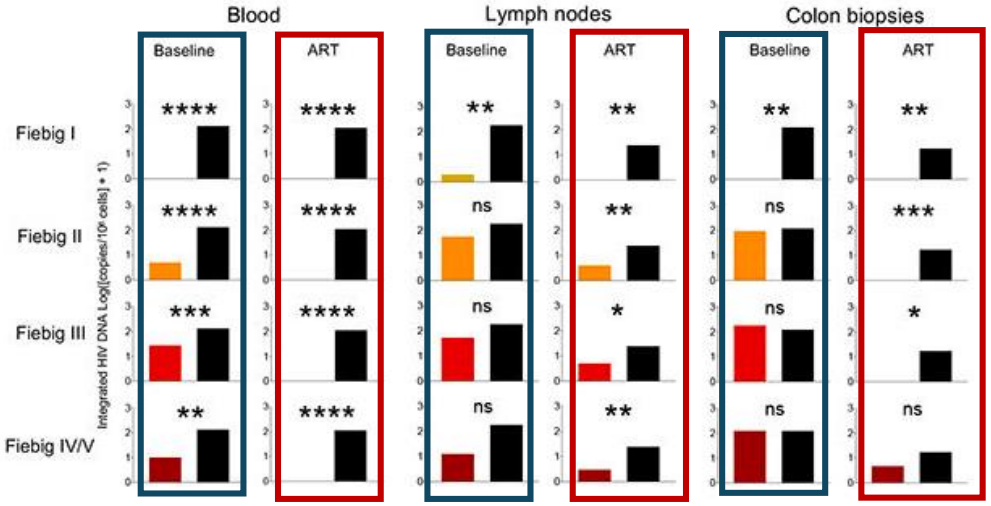
Baseline CD4 in CHI: 324/uL

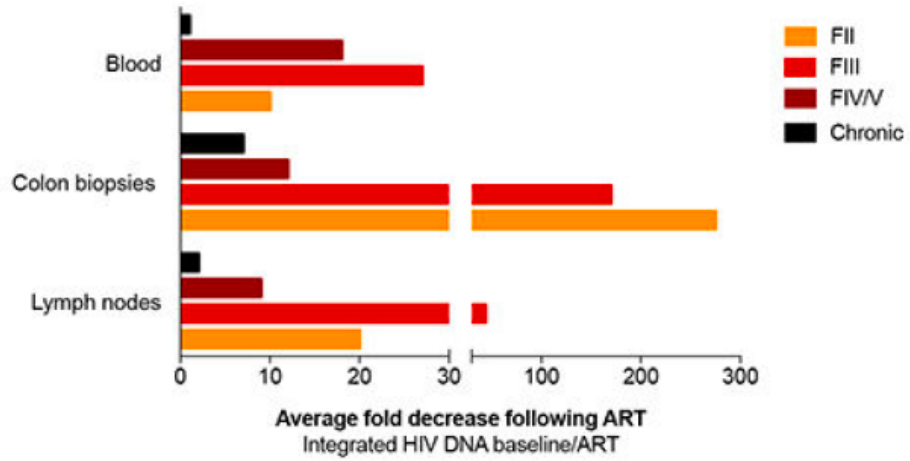
Leyre, Sci Transl Medicine 2020



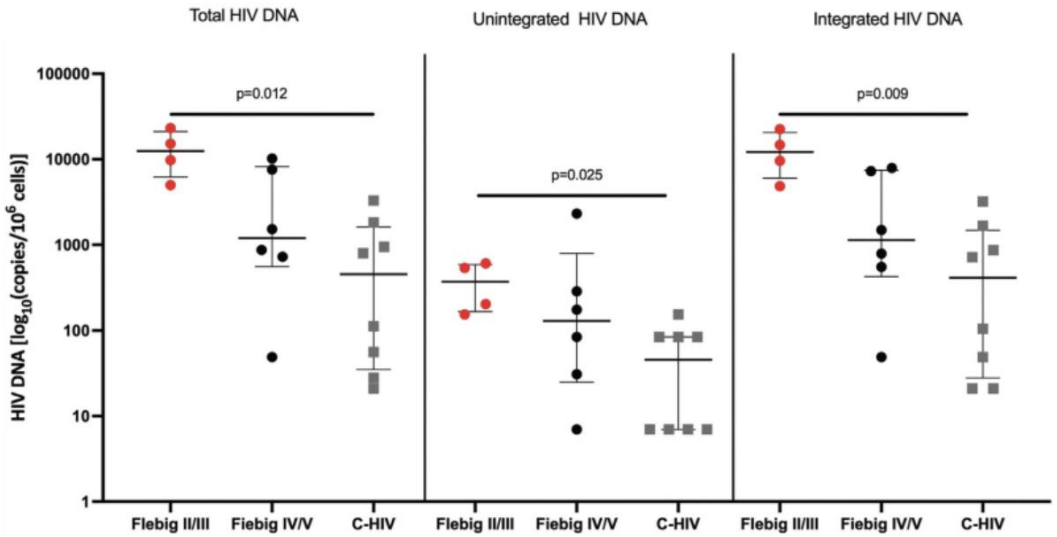


ART initiation during acute infection might reduce the size of the tissue reservoir, albeit great interindividual variability

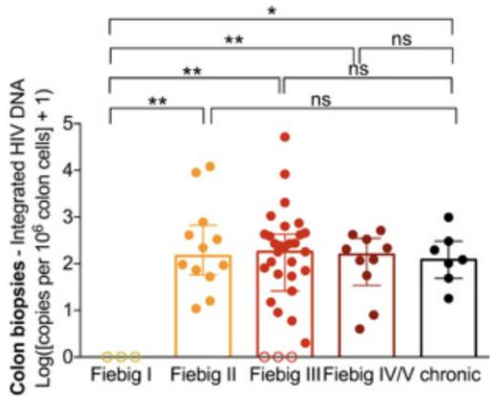




Leyre, Sci Transl Medicine 2020

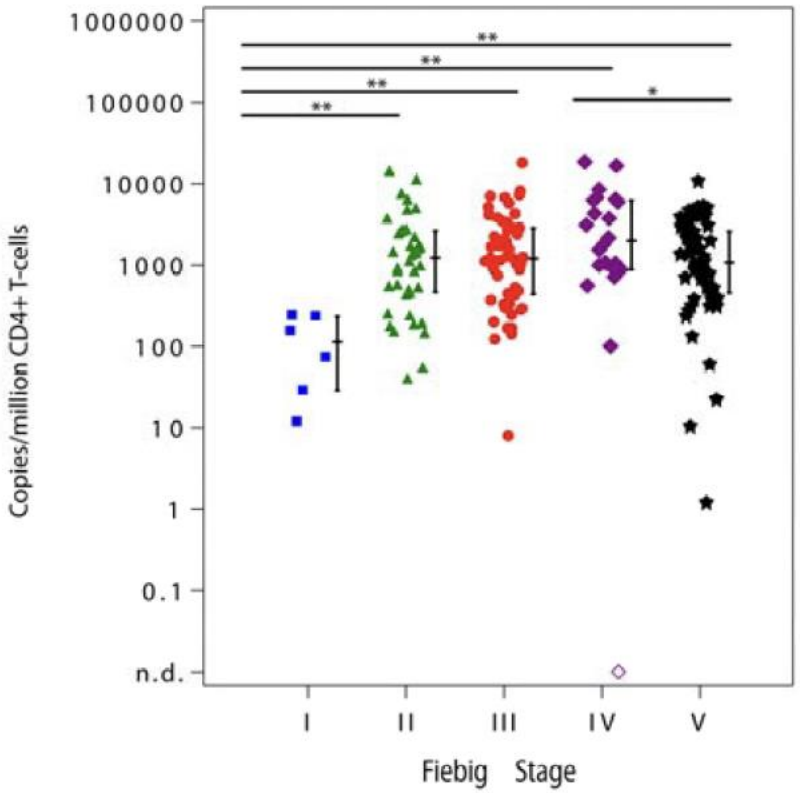


Tincati, AIDS, 2024

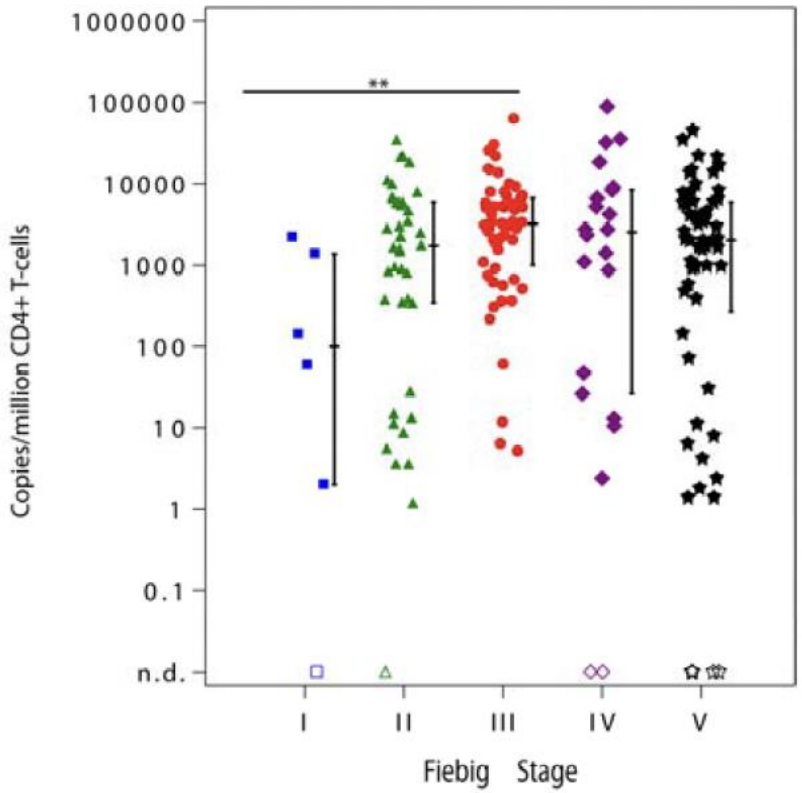


After 48 weeks of cART, HIV DNA* detected in the peripheral blood of all 188 partcipants

gag



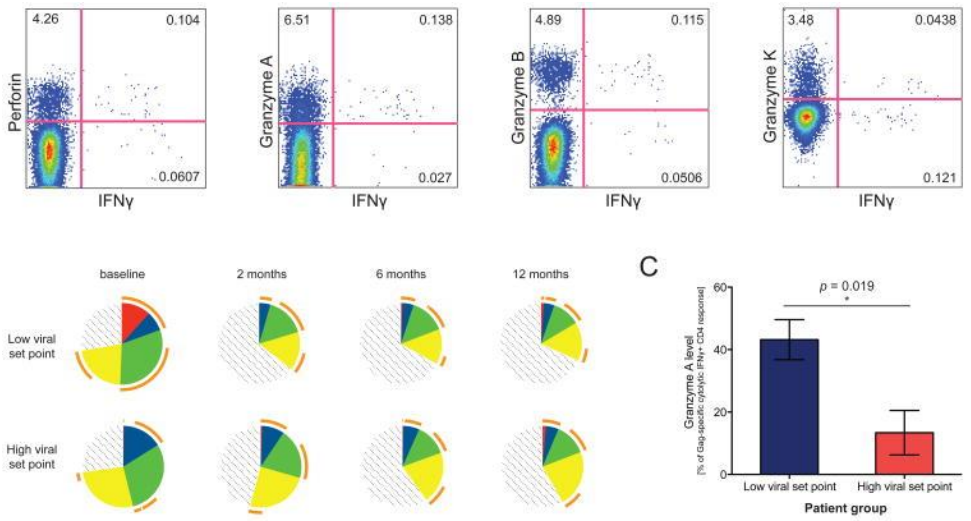
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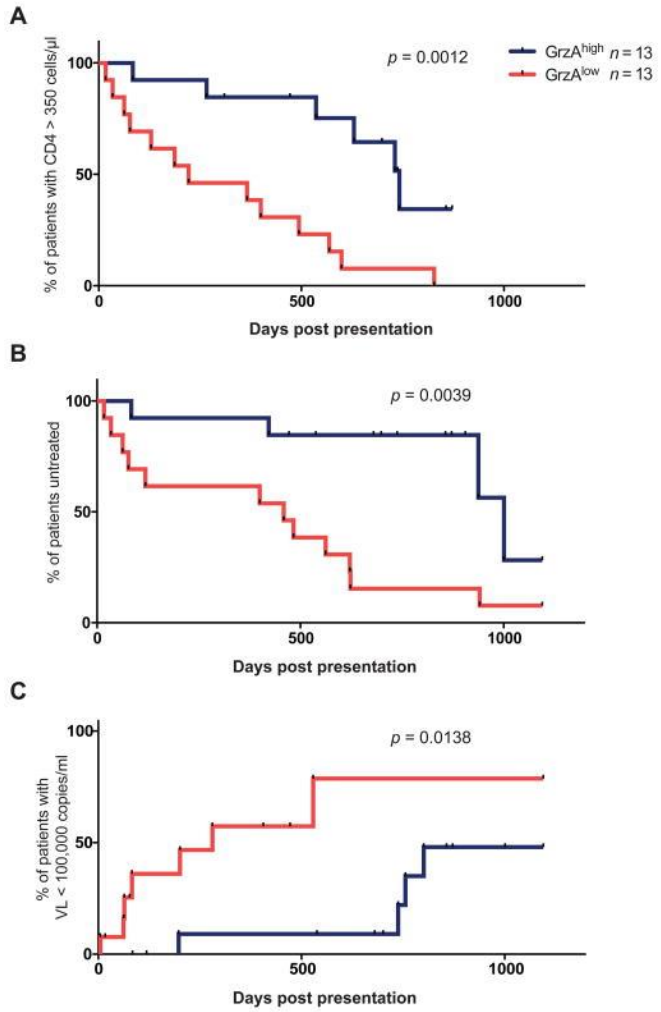


**measured by 5 million CD4+ T cells by sensitive qPCR assays targeting HIV gag and pol*

Crowell, AIDS, 2014

HIV-specific cytolytic CD4 T cell responses during acute HIV infection predict disease outcome





Immunological determinants associated to natural control of HIV-1 also feature superior attributes of:

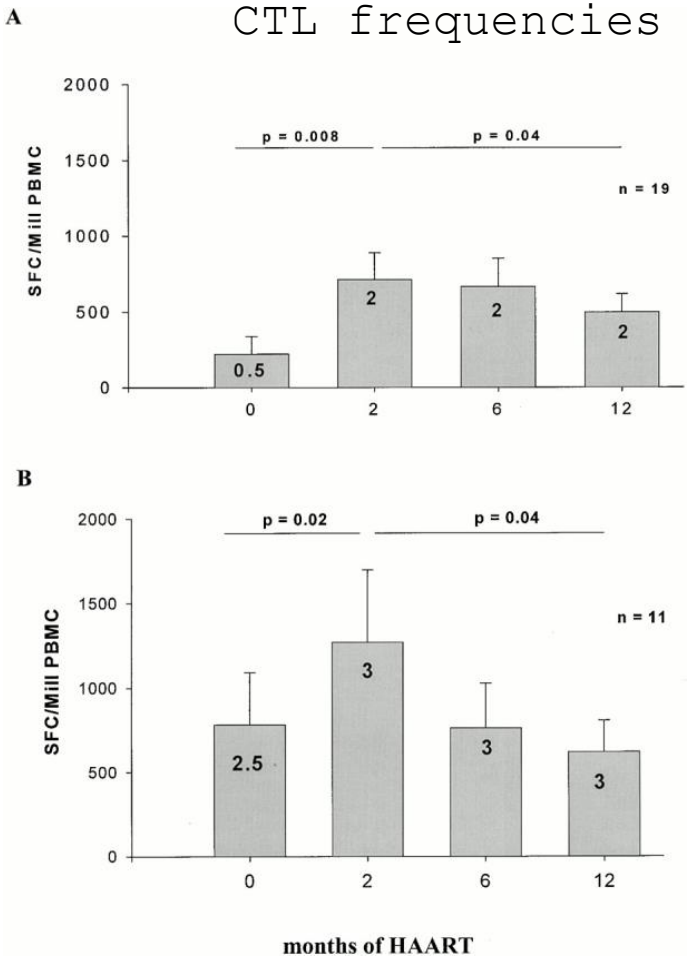
- HIV-specific CD8 T cells: frequency, breadth, polyfunctionality, stemness potential, trafficking to lymphoid tissues
- HIV-specific CD4 T-cell mediated responses: proliferative potential, polyfunctionality, T-follicular helper functions, cytotoxicity

Mastrangelo, Curr Opinion HIV AIDS, 2022

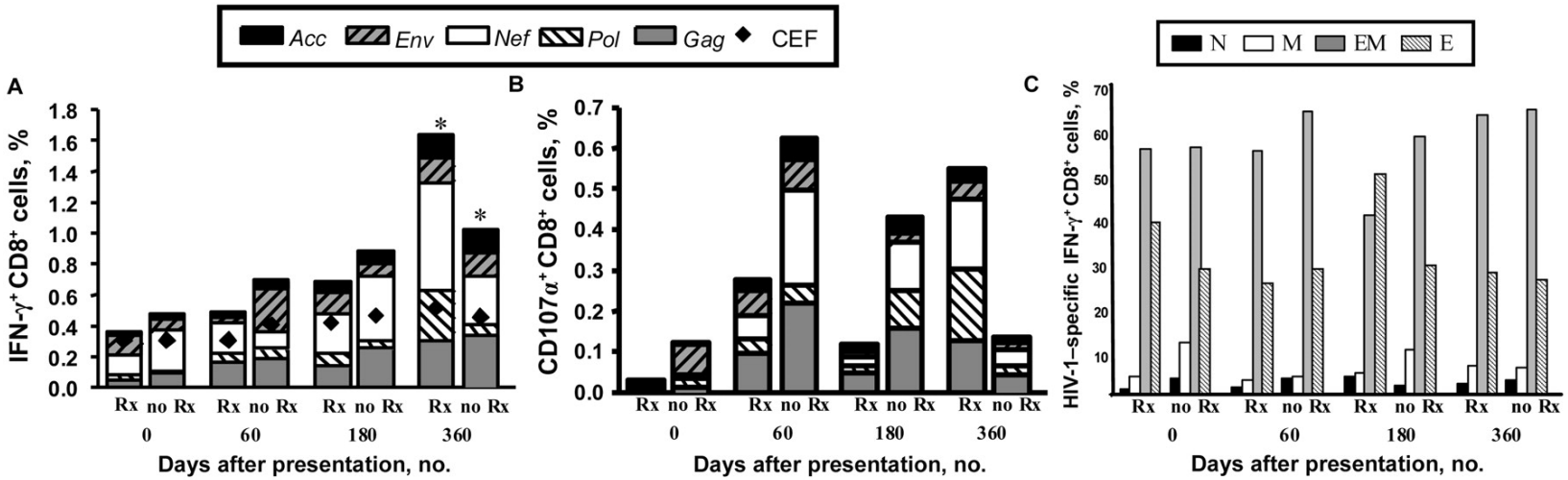
Soghian, Sci Transl Med, 2012

Early cART may preserve HIV-specific responses

CTL frequencies



HAART for 24 weeks



- enhanced differentiation of HIV-1–specific $CD8^+$ T cells from effector memory to effector cells at week 24
- significantly higher virus-specific interferon-γ^+ $CD8^+$ T cell responses after viral rebound

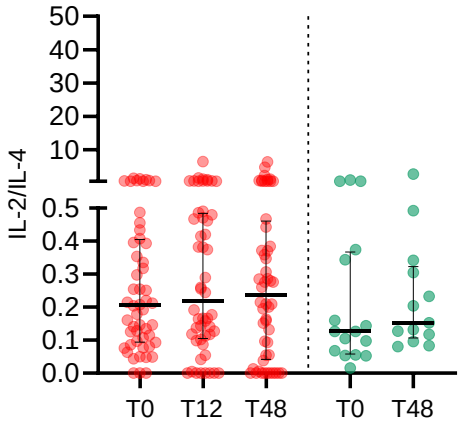
Streek, JID, 2006

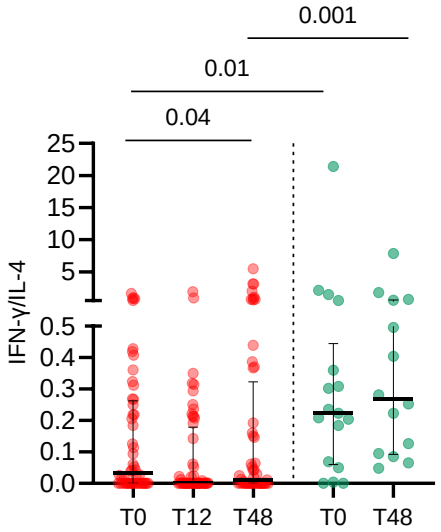
Altfeld, JEM, 2001
see also: Oxenius, PNAS, 2000

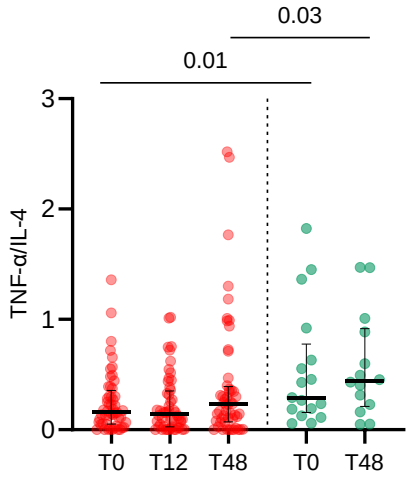
Lower circulating IFN-γ and TNF-α in AHI both prior to and following cART

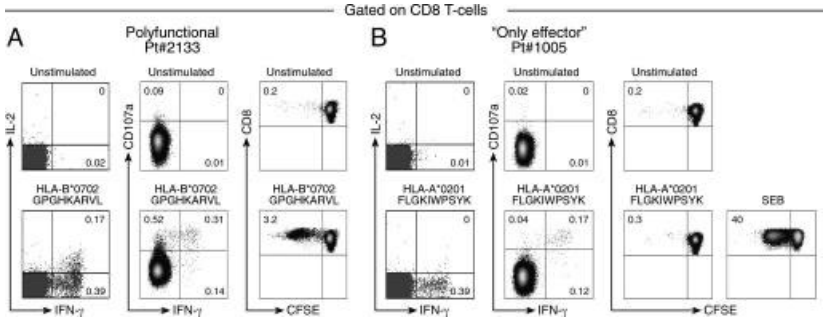
AHI

CHI



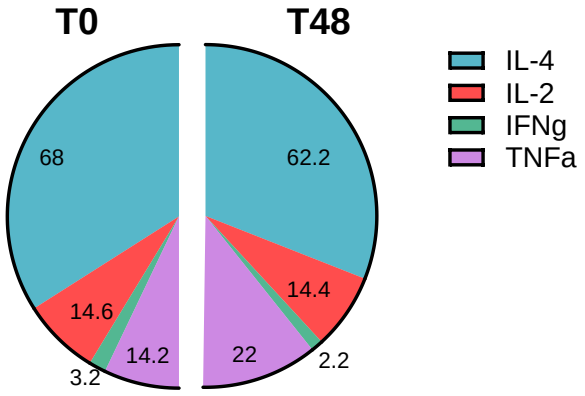




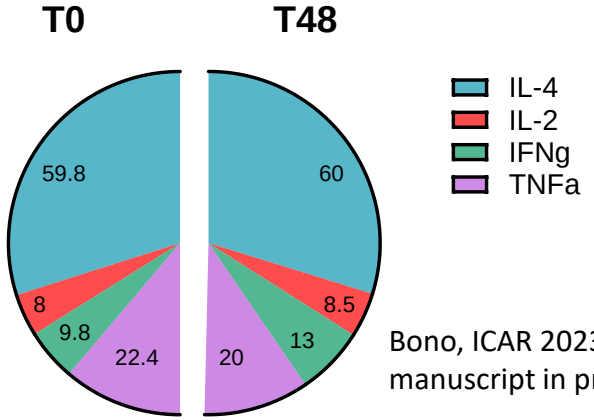


Harari, PNAS, 2007

PHI

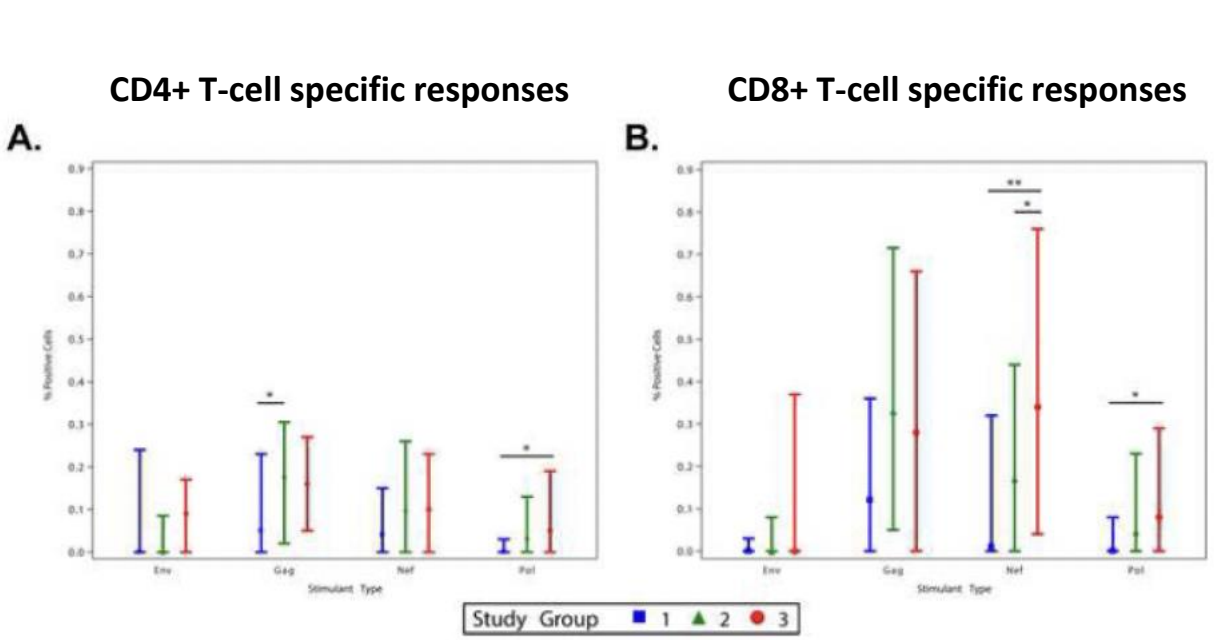


CHI

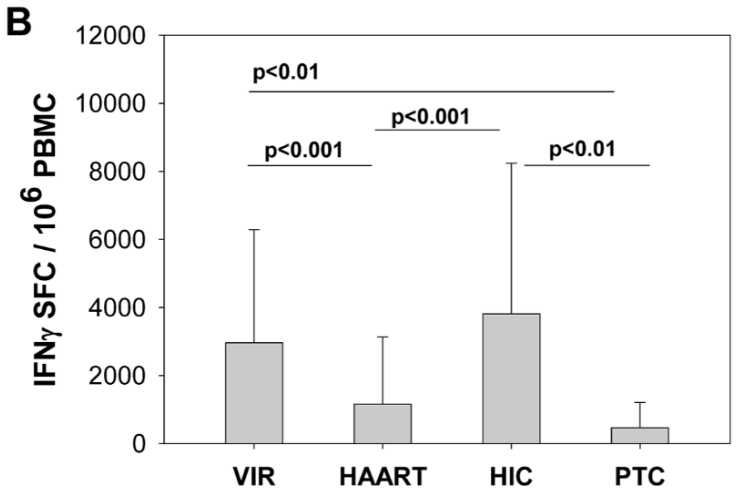


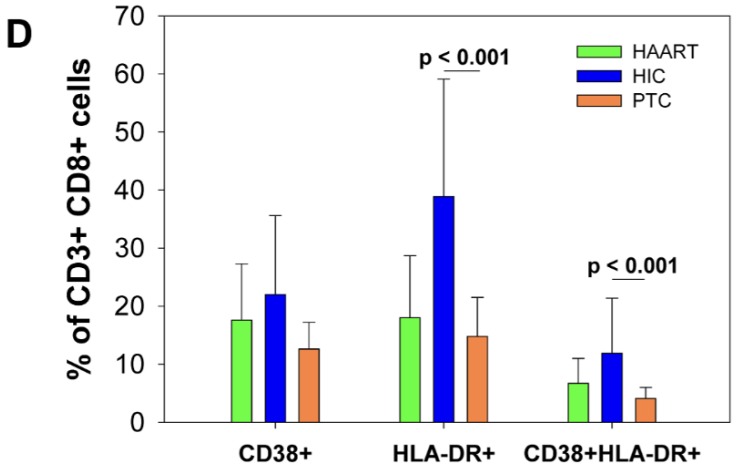
Bono, ICAR 2023; manuscript in preparation

Lower CD8 T-cell responses and activation in treated AHI and PTC



Study Group 1: Fiebig I/II
Study Group 2: Fiebig III/IV
Study Group 3: Fiebig V

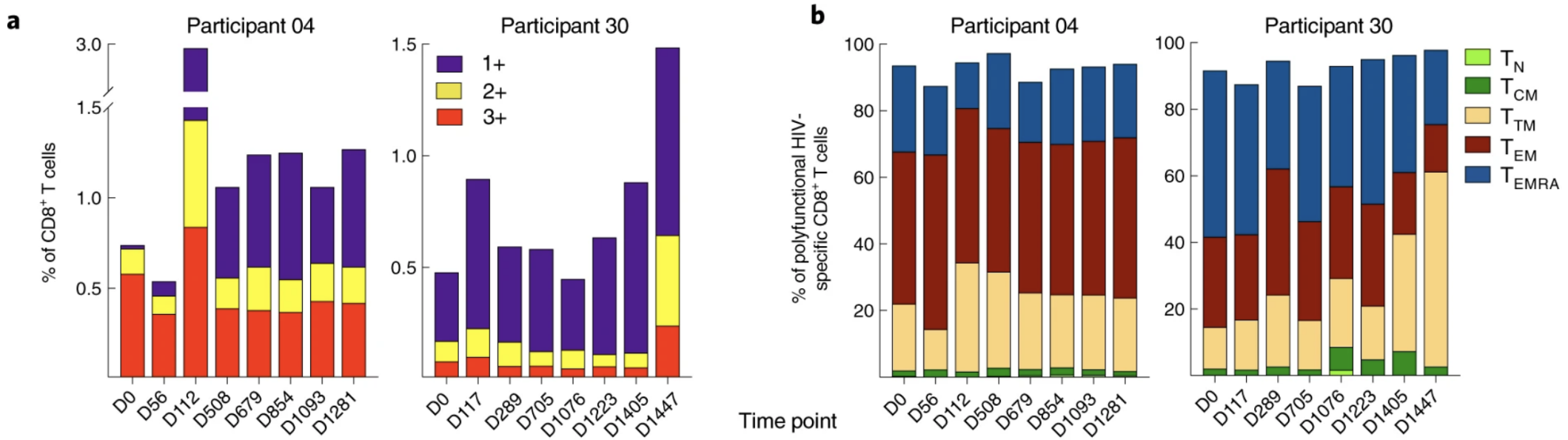




Distinct mechanisms of post-treatment interruption control

Higher frequencies of polyfunctional (IFN-γ⁺TNF-α⁺MIP-1ß⁺) HIV Gag-specific CD8⁺ T cells in Participant 04

The majority of responding cells in both study participants bore effector memory phenotypes

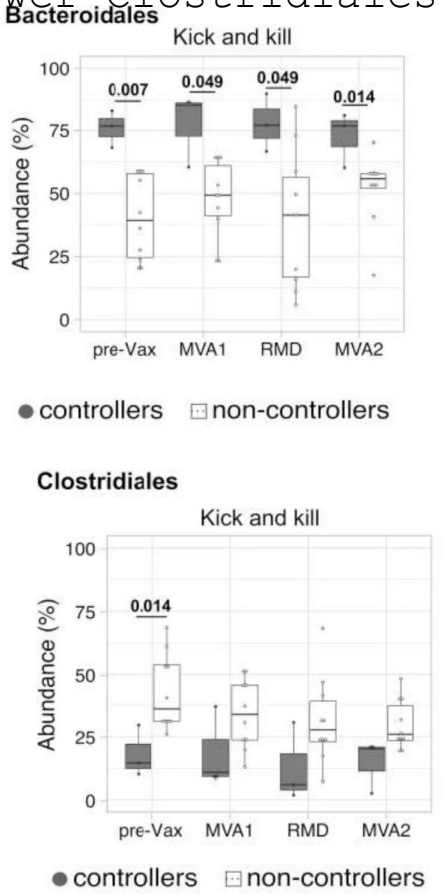


Blazkova, Nat Med, 2021

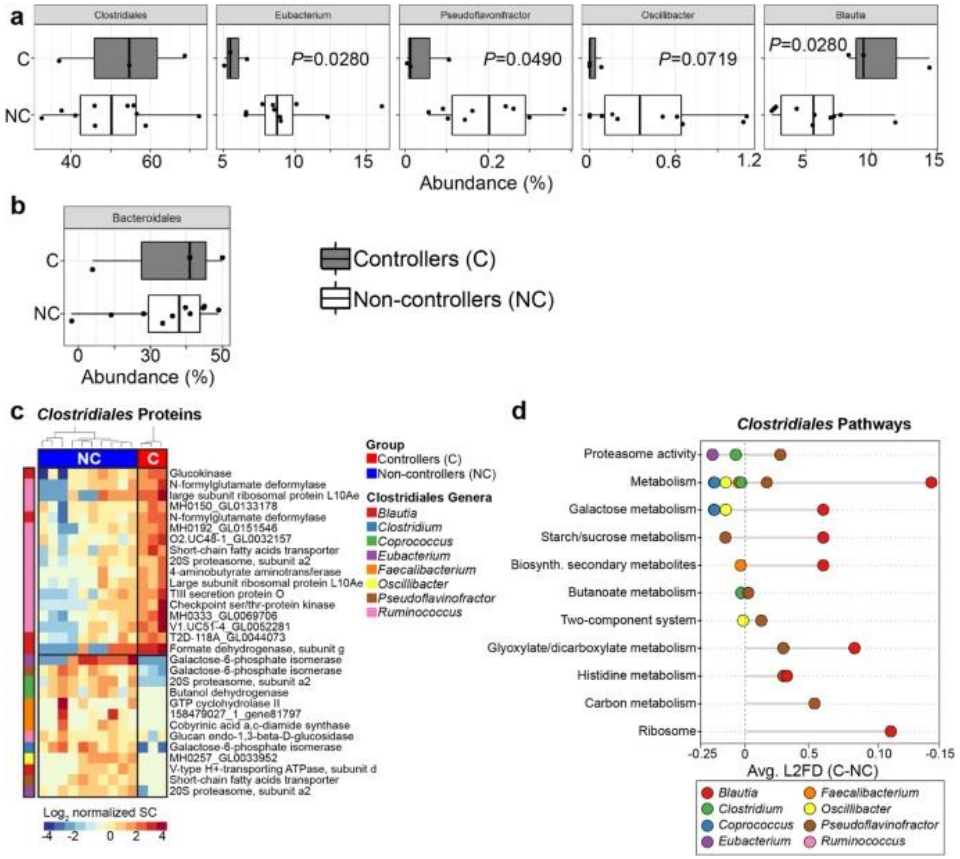
Role played by microbes in controlling HIV infection

- BCN02 clinical trial (NCT02616874) sub-study
- open-label, single-arm, phase I, proof-of-concept clinical trial
- 15 HIV-1-infected individuals with sustained viral suppression who started ART within the first 6 months after HIV transmission were enrolled to evaluate the safety, tolerability, immunogenicity, and effect on the viral reservoir of a **kick and kill strategy consisting of the combination of HIVconsv vaccines with romidepsin**

Viremic controllers showed higher Bacteroidales and lower Clostridiales

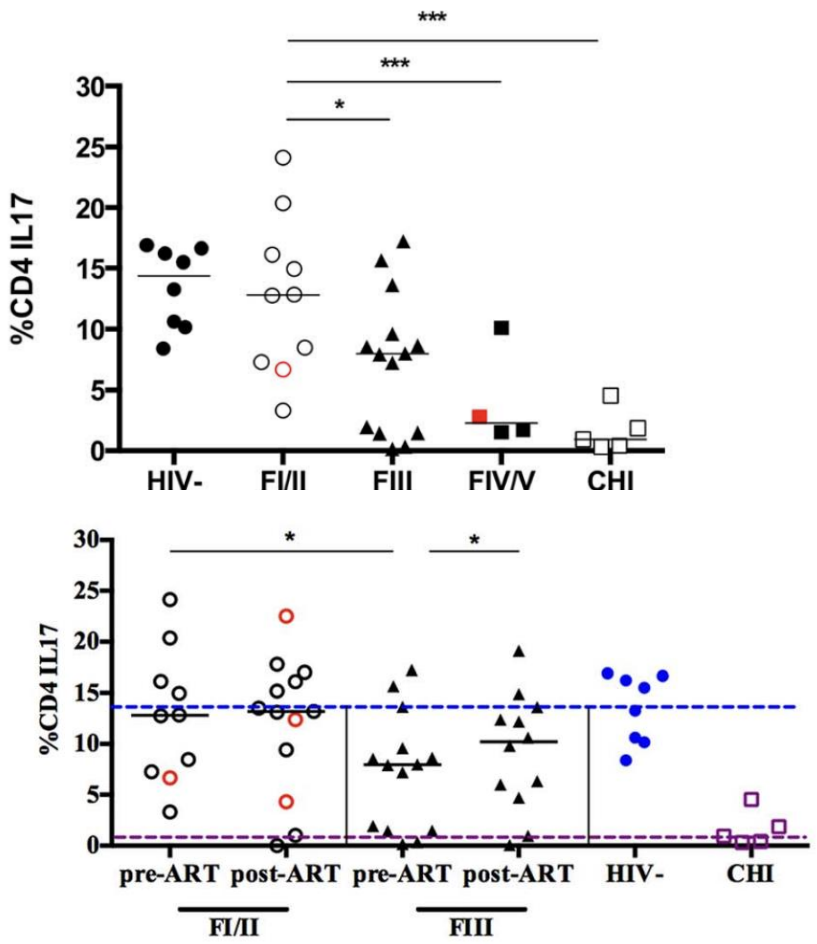


Distinct bacterial protein signatures associated with viremia control



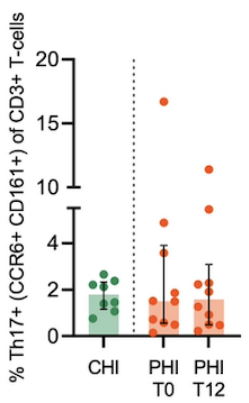
Borgognone, Microbiome, 2022

ART initiation during acute infection may not preserve mucosal integrity and immune functions

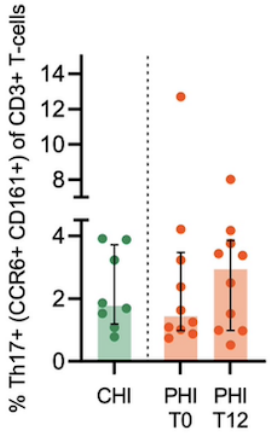


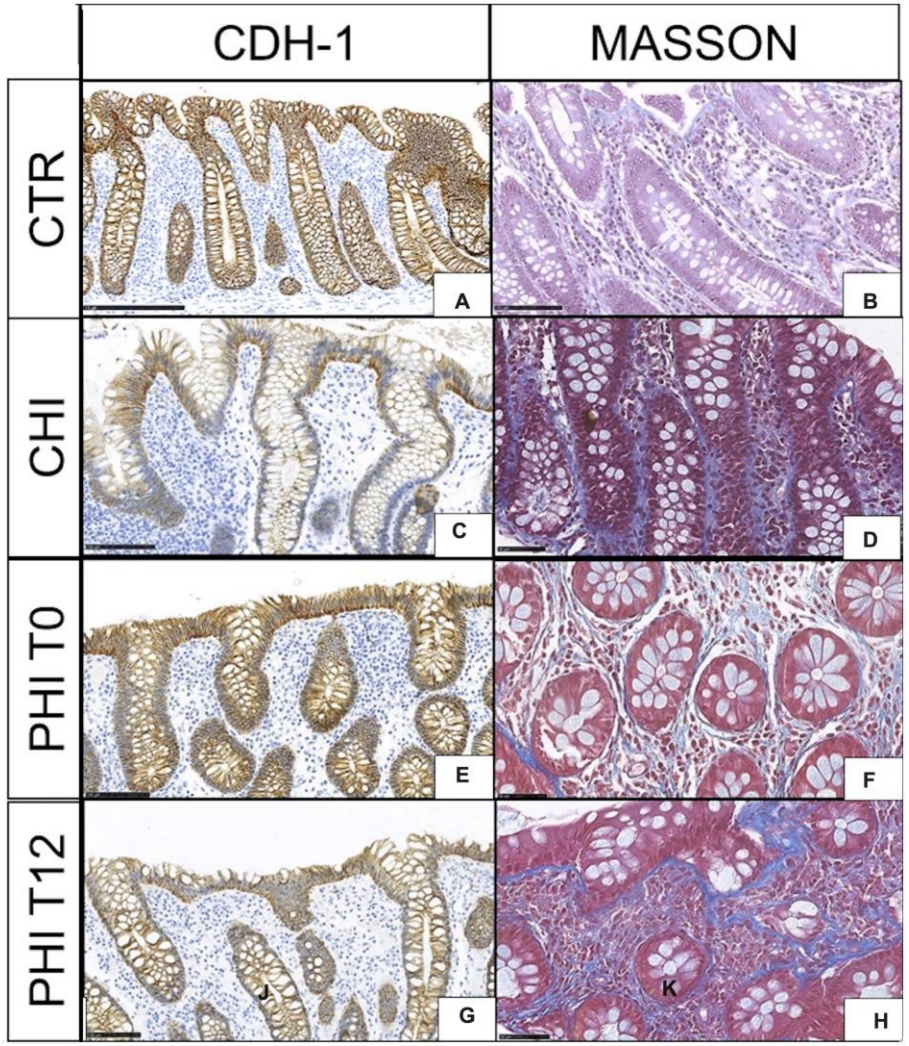
Schuetz, Plos Path, 2014

Colon Th17



Ileal Th17





Tincati, manuscript in preparation

Conclusions

- Treatment of acute HIV is likely a necessary, yet not sufficient condition of PTC

- HIV reservoirs are reduced, but not abated

- heterogenous T-cell specific responses

- features of the HIV virus (transcriptional activity) unknown

- cART alone is not able to account for PTC in acutely-infected individuals: role of bnAbs? New antivirals? Vaccine strategies?

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