Immunotherapy and an HIV Cure
Targeting T cell proliferation

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ACTG AIDS CLINICAL TRIALS GROUP

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All models of durable SIV/HIV remission - including elite controllers, post-treatment controllers and the cured monkey studies - suggest that the sustained control of HIV will require

(1) a low reservoir size

(2) an effective and durable host response

(3) low inflammation

Enhancing host immunity

Leveraging HIV prevention products (vaccines, bNAbs) and cancer immunotherapy (ICBs, CAR-T cells)

- Vaccines (UCSF/DARE/amfAR)
  - HIV DNA vaccine (Inovio): Enrolled (n=60)
  - CE DNA +TLR agonist + bNAbs: Approved, starting soon
  - CE DNA + PD-1 blockade: In development
  - mRNA vaccine (CureVac): NHPs
  - CMV/SIV vaccine: NHPs
- CAR-T cells (Lentigen/UCSF)
  - Duo-CAR: In development

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Can we reduce the reservoir?

Can we reduce the inflammatory environment?

Assumption: An understanding of the mechanism that accounts for how HIV is maintained during long-term ART will lead to effective interventions

T cell proliferation is the main cause of persistence

Science

Specific HIV integration sites are linked to clonal expansion and persistence of infected cells

F. Maldarelli,[1]* X. Wu,[2]* L. Su,[2] F. R. Simonetti,[1,3] W. Shao,[2] S. Hill,[1] J. Spindler,[1] A. L. Ferris,[1] J. W. Mellors,[4] M. F. Kearney,[1] J. M. Coffin,[5] S. H. Hughes[1]†

Science

Proliferation of cells with HIV integrated into cancer genes contributes to persistent infection

Thor A. Wagner,[1,2]* Sherry McLaughlin,[1,2]* Kavita Garg,[3] Charles Y. K. Cheung,[3] Brendan B. Larsen,[2] Sheila Styrchak,[1] Hannah C. Huang,[1] Paul T. Edlefsen,[2,3] James I. Mullins,[2]* Lisa M. Frenkel[1,2]*†

Cell PRESS

HIV-1 Integration Landscape during Latent and Active Infection

Lillian B. Cohn,[1] Israel T. Silva,[1,2] Thiago Y. Oliveira,[1] Rafael A. Rosales,[3] Erica H. Parrish,[4] Gerald H. Learn,[4] Beatrice H. Hahn,[4] Julie L. Czartoski,[5] M. Juliana McElrath,[5] Clara Lehmann,[6,7] Florian Klein,[1] Marina Caskey,[1] Bruce D. Walker,[8,9] Janet D. Siliciano,[10] Robert F. Siliciano,[9,10] Mila Jankovic,[1] and Michel C. Nussenzweig[1,9,*]

The Journal of Infectious Diseases

Longitudinal Genetic Characterization Reveals That Cell Proliferation Maintains a Persistent HIV Type 1 DNA Pool During Effective HIV Therapy

Susanne von Stockenstrom,[1,2] Lina Odevall,[1] Eunok Lee,[3,4] Elizabeth Sinclair,[5] Peter Bacchetti,[6] Maudi Killian,[5] Lorrie Epling,[5] Wei Shao,[7] Rebecca Hoh,[5] Terence Ho,[5] Nuno R. Faria,[9] Philippe Lemey,[9] Jan Albert,[1,2] Peter Hunt,[5] Lisa Loeb,[5] Christopher Pilcher,[5] Lauren Poole,[5] Hiroyu Hatano,[5] Ma Somsouk,[5] Daniel Douek,[8] Eli Boritz,[8] Steven G. Deeks,[5] Frederick M. Hecht,[5,a] and Sarah Palmer[1,3,4,a]

Infected cells maintained by those factors that dictate normal memory T cell homeostasis

HIV integration near growth genes may be selectively maintained


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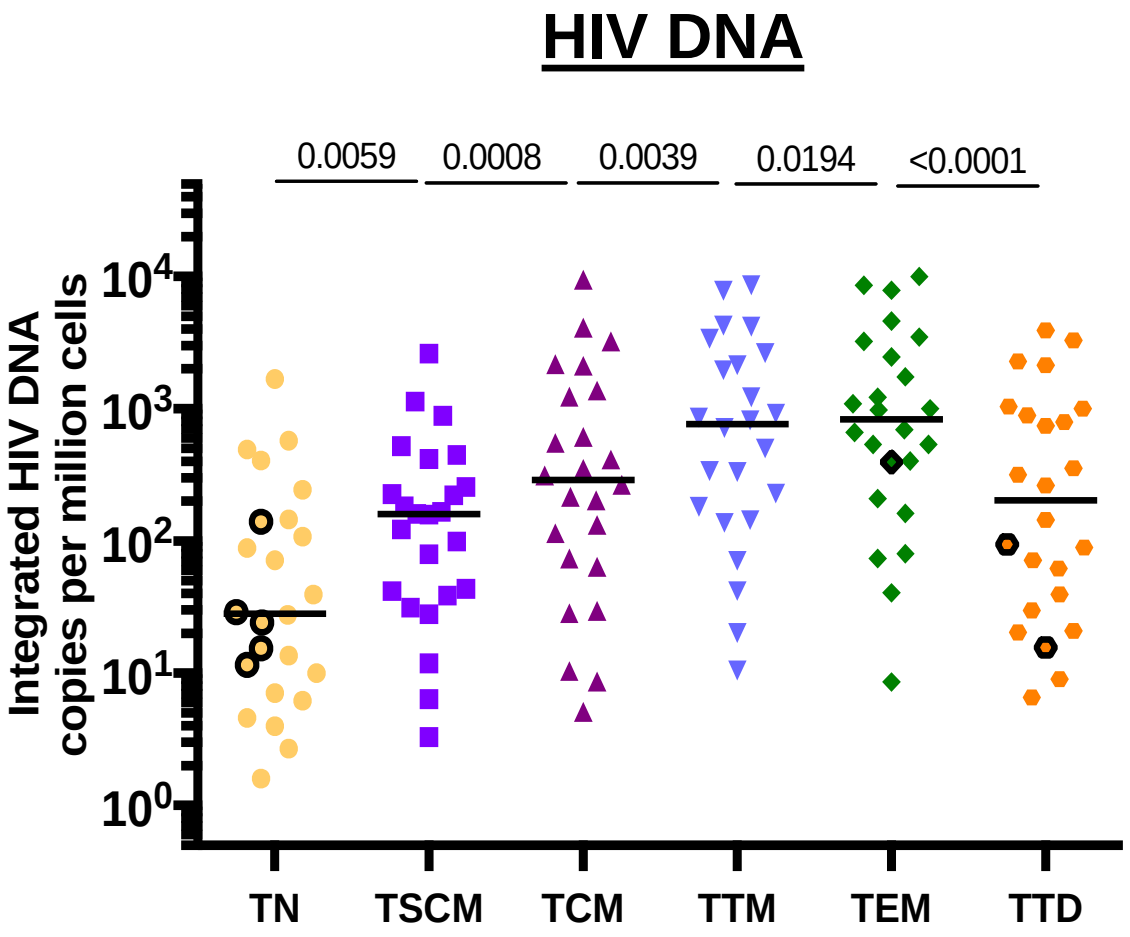
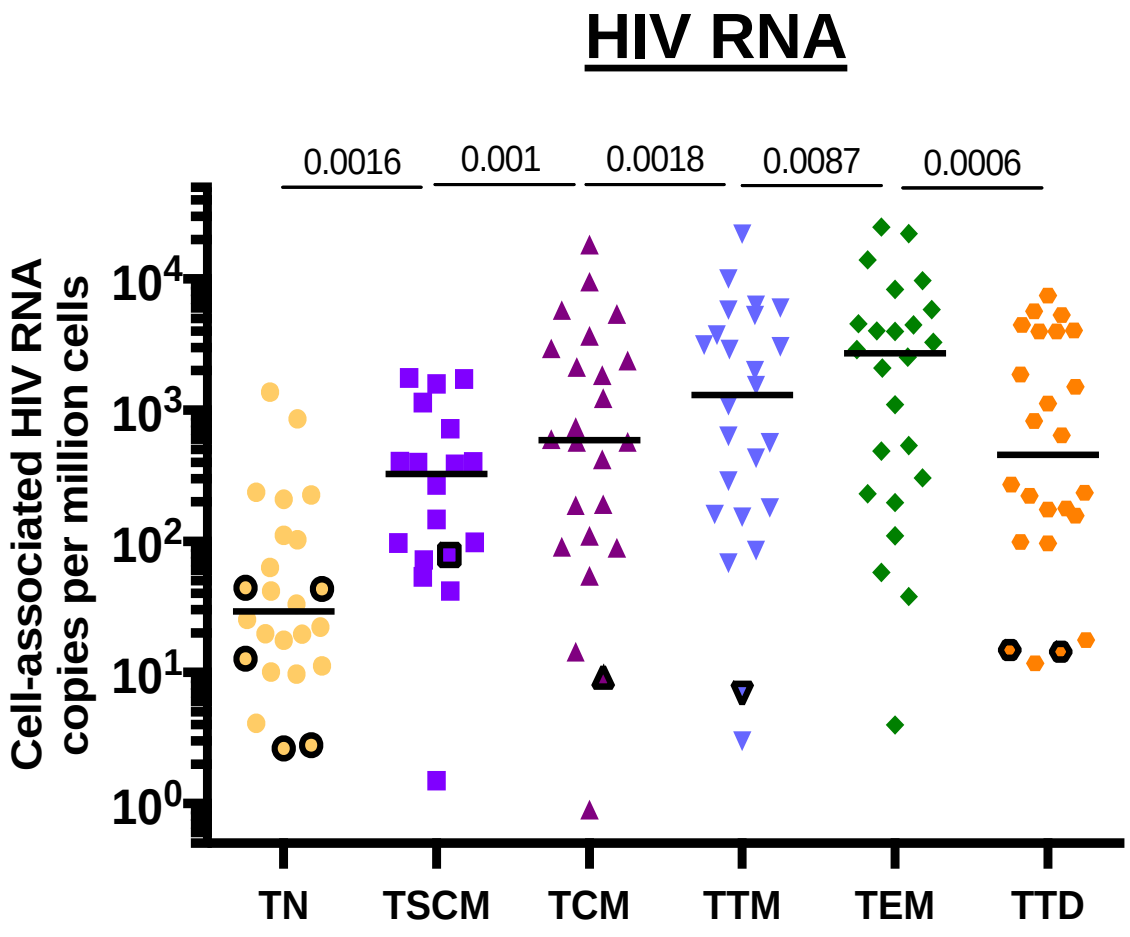
Enrichment for HIV in more differentiated cells





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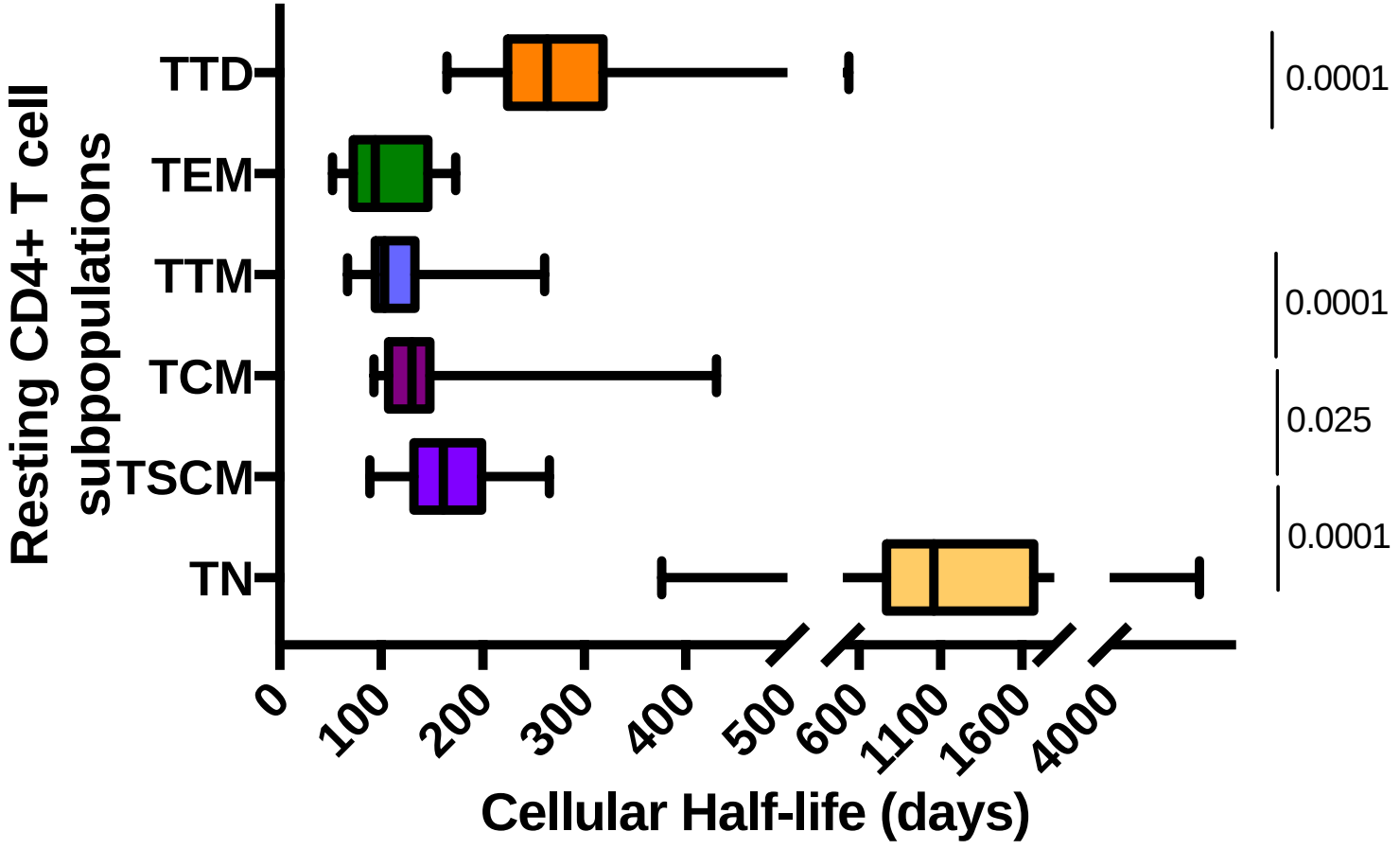
HOPE: CD4+ T cell half-lives (replacement rates) measured *in vivo* with deuterium labeling (treated HIV, n = 24)



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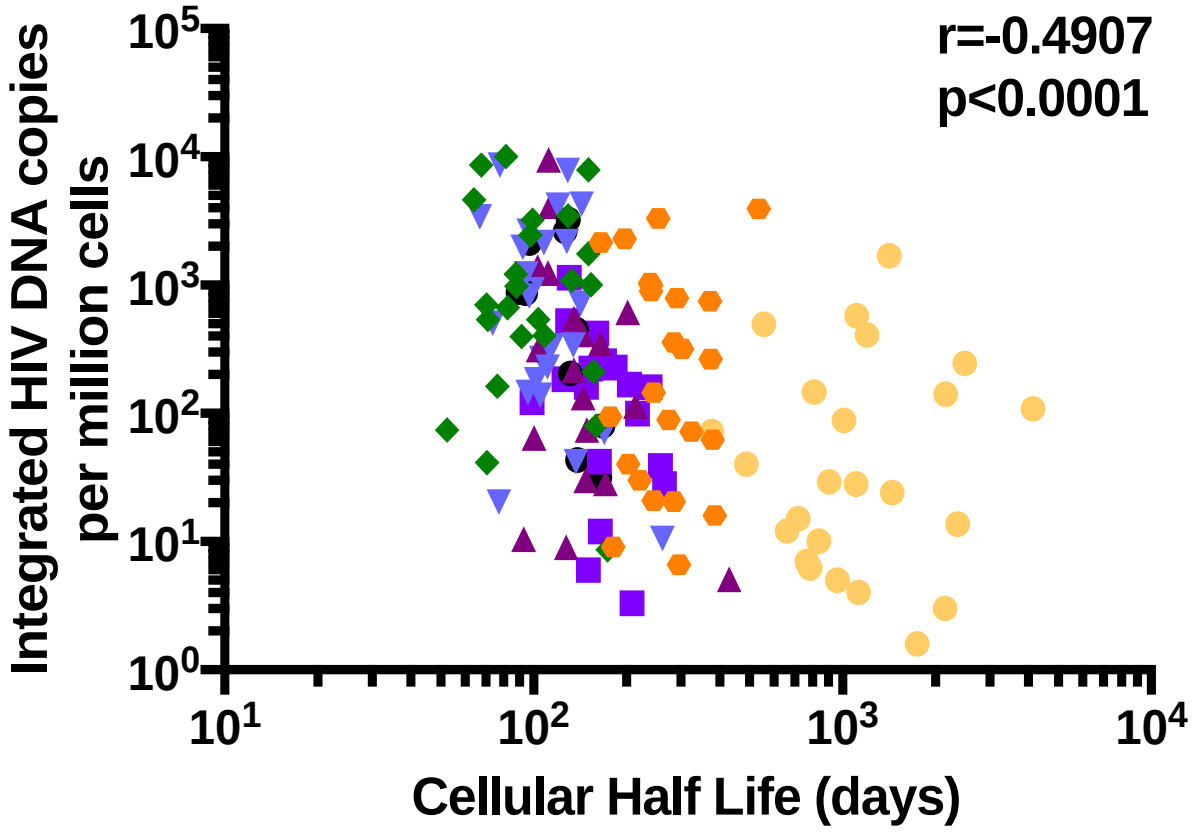
HOPE Cohort: Intact genomes are enriched in more differentiated cells with higher turnover rates



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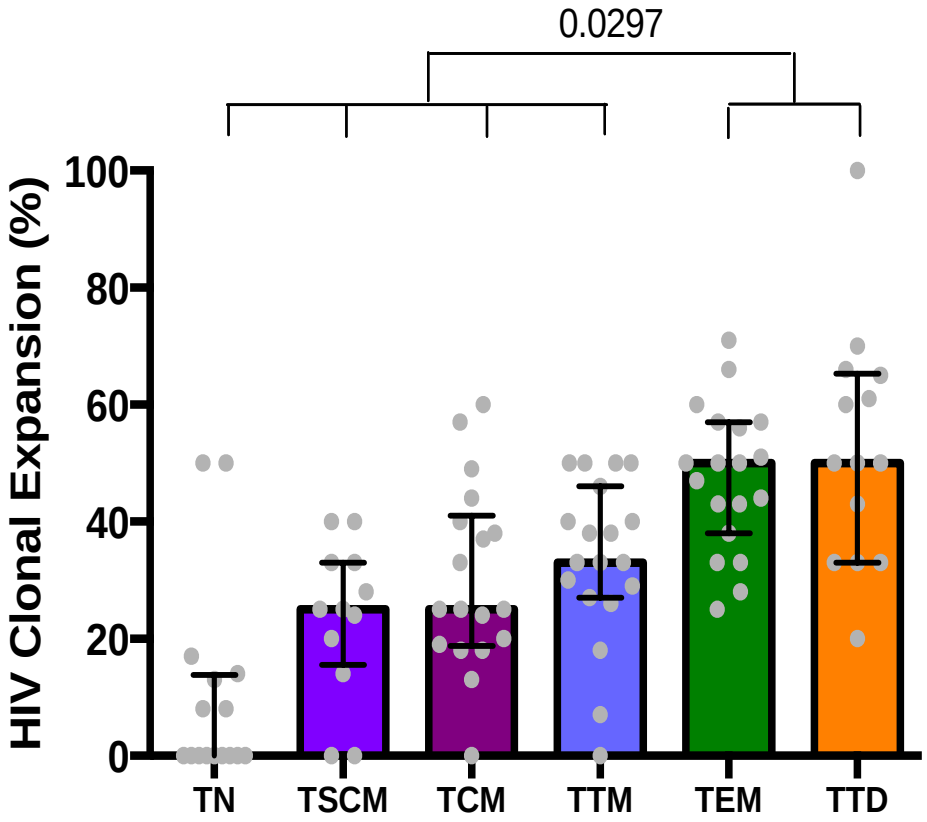
HOPE: Clonality increases with CD4+ T cell differentiation

Unique clones with same integration site were found across all states of differentiation



In larger clones (>10%), HIV integration in cancer genes, suggesting proliferating cells should be enriched for the virus

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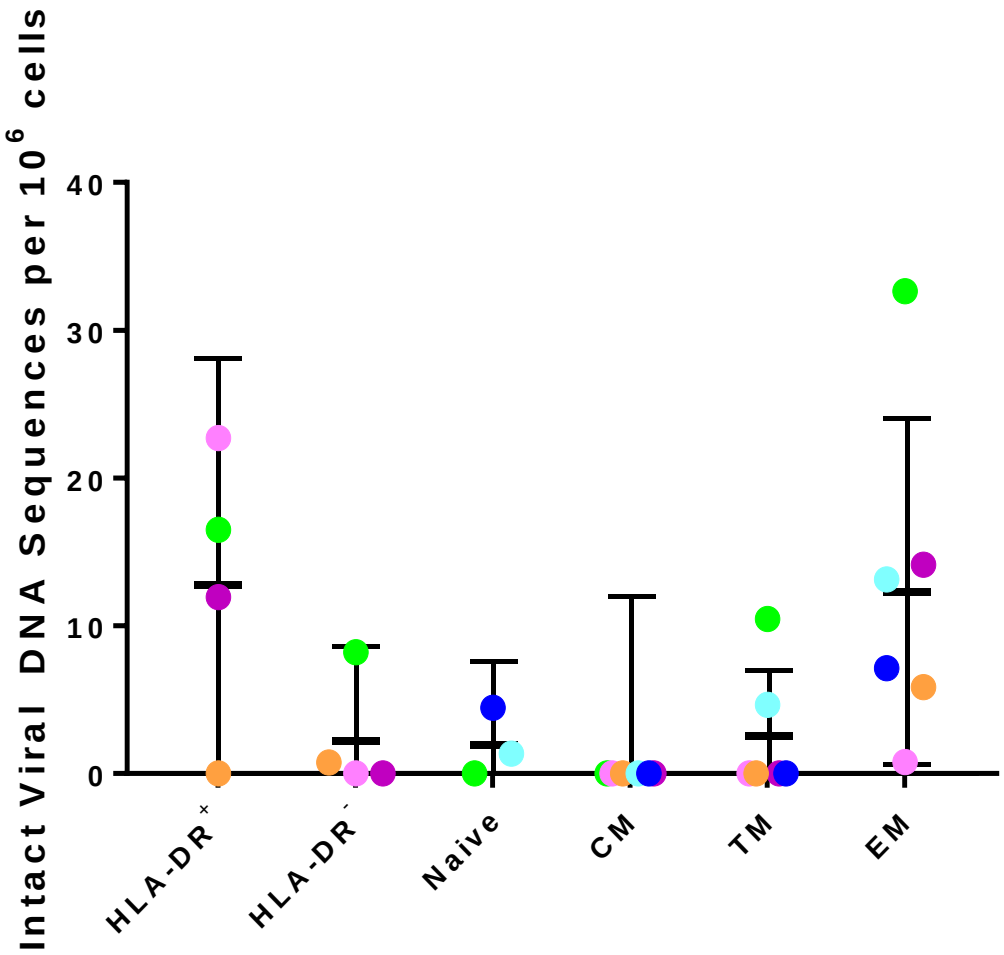

Cell Reports

Identification of Genetically Intact HIV-1 Proviruses in Specific CD4+ T Cells from Effectively Treated Participants

Bonnie Hiener,[1,9,*] Bethany A. Horsburgh,[1] John-Sebastian Eden,[1,2] Kirston Barton,[1] Timothy E. Schlub,[3] Eunok Lee,[1] Susanne von Stockenstrom,[4] Lina Odevall,[4] Jeffrey M. Milush,[5] Teri Liegler,[5] Elizabeth Sinclair,[5] Rebecca Hoh,[5] Eli A. Boritz,[6] Daniel Douek,[7] Rémi Fromentin,[8] Nicolas Chomont,[8] Steven G. Deeks,[5] Frederick M. Hecht,[5] and Sarah Palmer[1]

Intact genomes (FLIPS) are enriched in HLA-DR+ and effector memory CD4+ T cells





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DARE: HIV enriched in PD-1 expressing cells; inhibition of this pathway causes latency reversal

nature COMMUNICATIONS

PD-1 blockade potentiates HIV latency reversal ex vivo in CD4+ T cells from ART-suppressed individuals

Rémi Fromentin[1], Sandrina DaFonseca[2], Cecilia T. Costiniuk[3], Mohamed El-Far[1], Francesco Andrea Procopio[4], Frederick M. Hecht[5], Rebecca Hoh[5], Steven G. Deeks[5], Daria J. Hazuda[6], Sharon R. Lewin[7,8], Jean-Pierre Routy[3], Rafick-Pierre Sékaly[9] & Nicolas Chomont[1,10]

The Journal of Infectious Diseases

Human Immunodeficiency Virus Persistence and T-Cell Activation in Blood, Rectal, and Lymph Node Tissue in Human Immunodeficiency Virus–Infected Individuals Receiving Suppressive Antiretroviral Therapy

Gabriela Khoury,[1,2] Rémi Fromentin,[3] Ajantha Solomon,[1,2] Wendy Hartogensis,[5] Marisela Killian,[5] Rebecca Hoh,[5] Ma Somsouk,[5] Peter W. Hunt,[5] Valerie Girling,[5] Elizabeth Sinclair,[5] Peter Bacchetti,[6] Jenny L. Anderson,[1,2] Frederick M. Hecht,[5] Steven G. Deeks,[5] Paul U. Cameron,[1,2] Nicolas Chomont,[3,4] and Sharon R. Lewin[1,2]

PLOS | PATHOGENS

CD4+ T Cells Expressing PD-1, TIGIT and LAG-3 Contribute to HIV Persistence during ART

Rémi Fromentin[1], Wendy Bakeman[2], Mariam B. Lawani[2], Gabriela Khoury[3,4], Wendy Hartogensis[5], Sandrina DaFonseca[2], Marisela Killian[6], Lorrie Epling[6], Rebecca Hoh[6], Elizabeth Sinclair[6], Frederick M. Hecht[6], Peter Bacchetti[5], Steven G. Deeks[6], Sharon R. Lewin[3,4], Rafick-Pierre Sékaly[7], Nicolas Chomont[1,2,8]*

PLOS | PATHOGENS

TIGIT Marks Exhausted T Cells, Correlates with Disease Progression, and Serves as a Target for Immune Restoration in HIV and SIV Infection

Glen M. Chew[1], Tsuyoshi Fujita[1,2], Gabriela M. Webb[3,4], Benjamin J. Burwitz[3,4], Helen L. Wu[3,4], Jason S. Reed[3,4], Katherine B. Hammond[3,4], Kiera L. Clayton[5], Naoto Ishii[2], Mohamed Abdel-Mohsen[6], Teri Liegler[6], Brooks I. Mitchell[1], Frederick M. Hecht[7], Mario Ostrowski[5], Cecilia M. Shikuma[1], Scott G. Hansen[3,4], Mark Maurer[8], Alan J. Korman[8], Steven G. Deeks[7], Jonah B. Sacha[3,4‡], Lishomwa C. Ndhlovu[1‡]*

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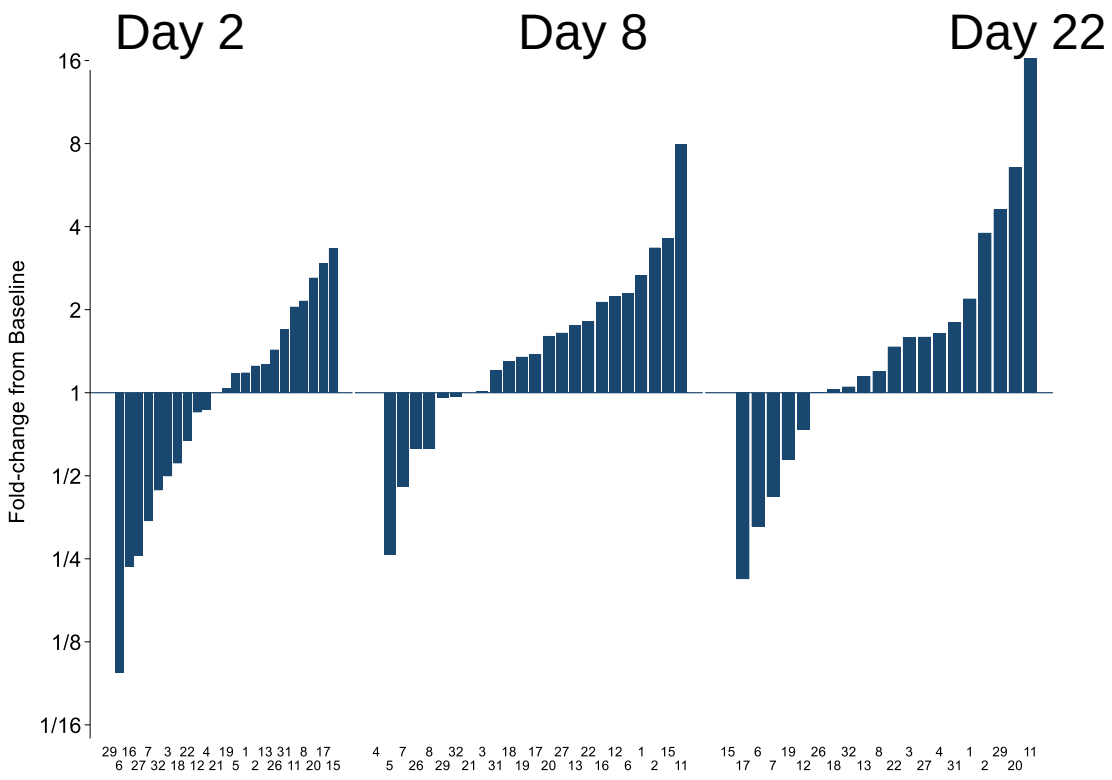
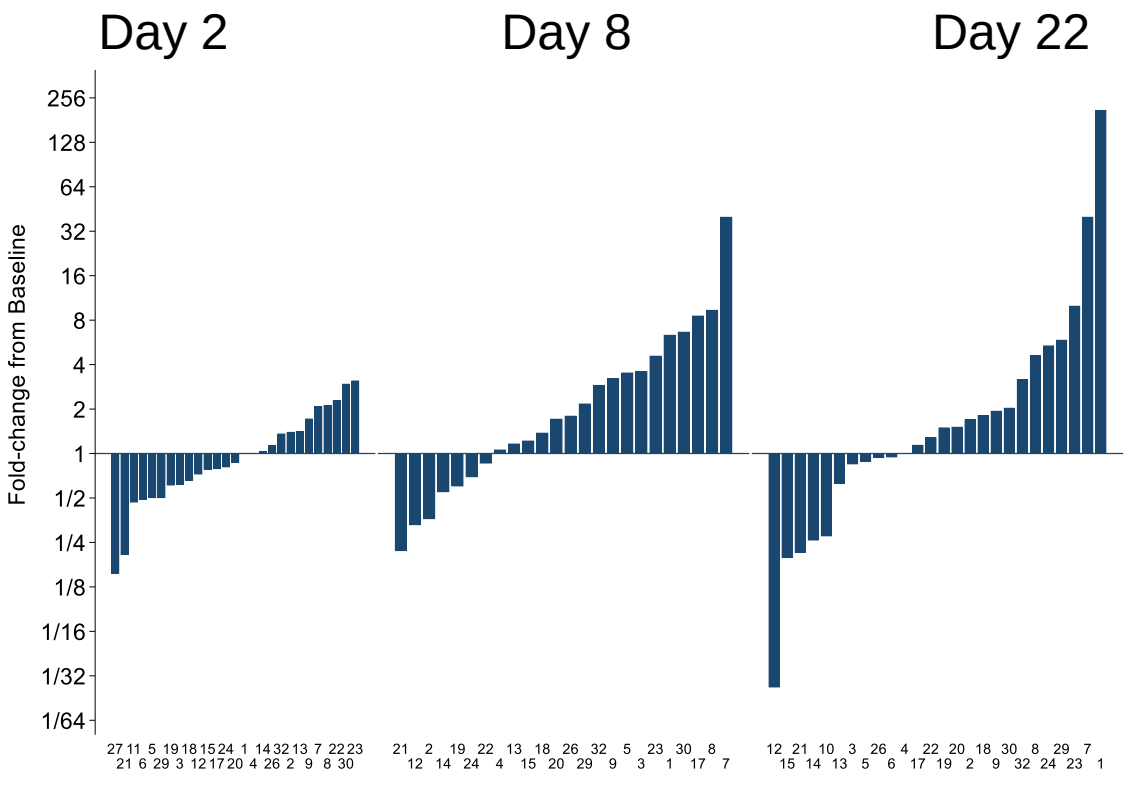
CITN: PD-1 blockade (pembrolizumab) increases cellular and plasma HIV in individuals on ART with cancer (n=32)

Unspliced Intracellular HIV RNA

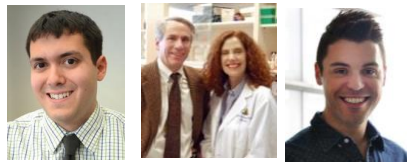


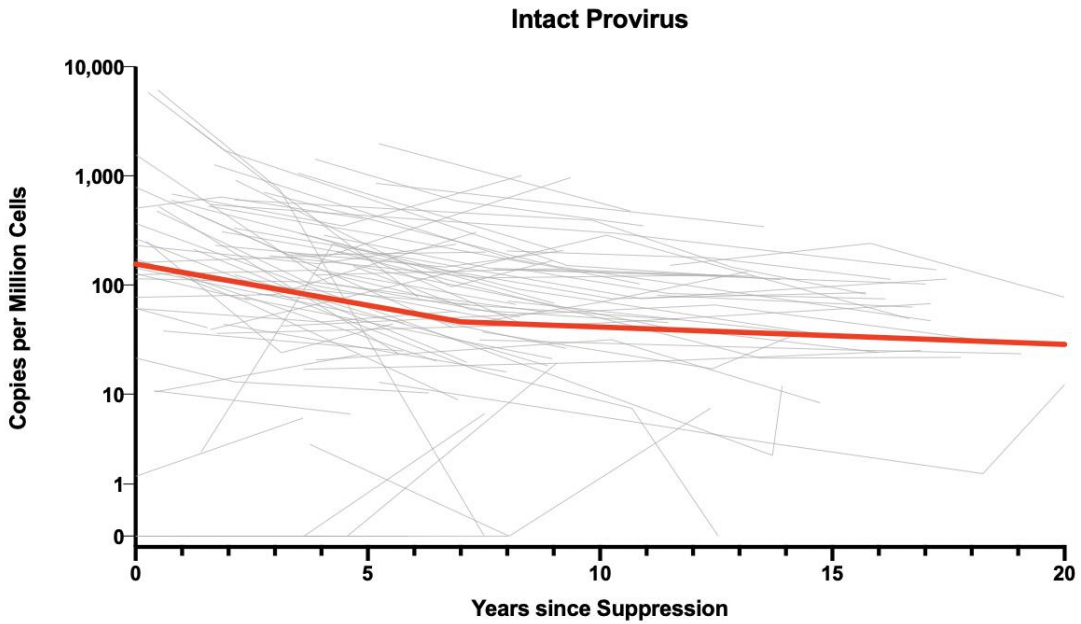
Plasma HIV RNA

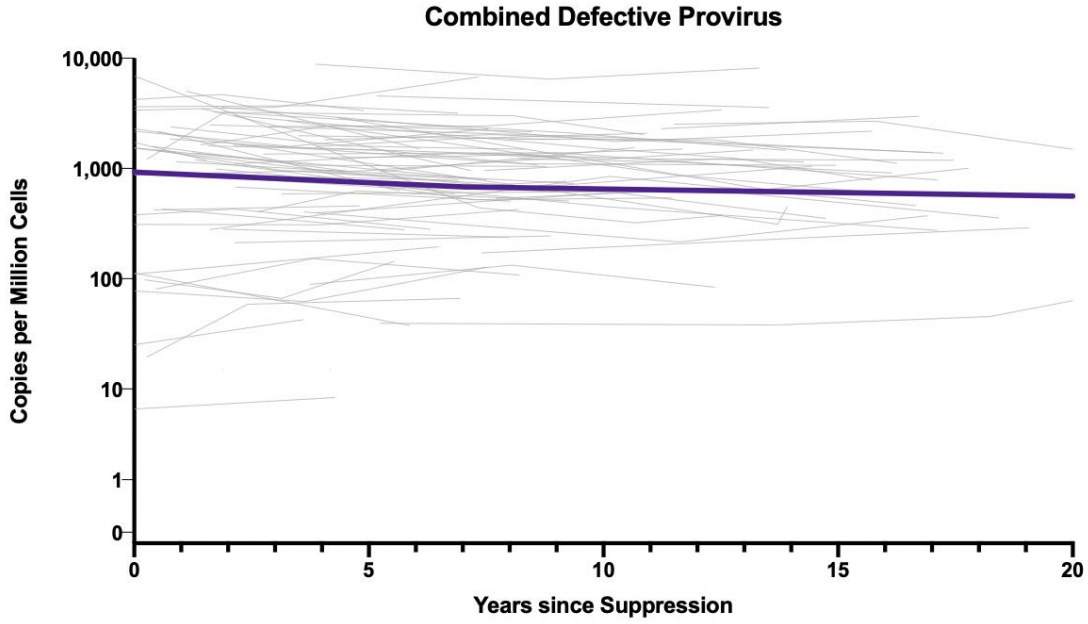


Does the size, distribution, inducibility, intactness and/or clonality of the reservoir evolve during long-term (> 10 years) of ART?

DARE/SCOPE: Intact genomes (IPDA) decay more rapidly than defective one during first seven years







$t_{1/2}$ = 4.0 years through year 7
$t_{1/2}$ = 19.0 years after year 7

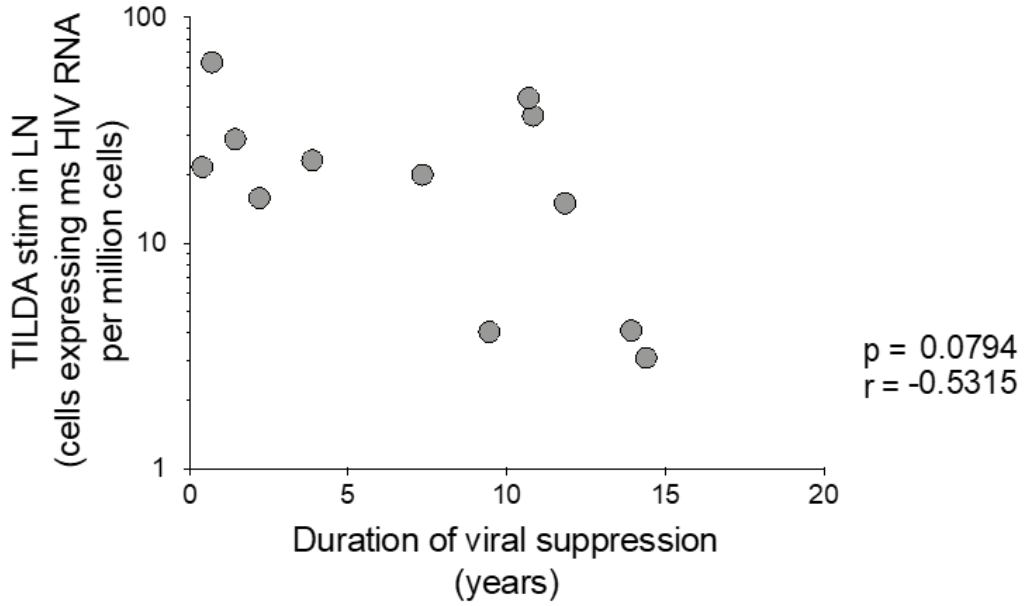
$t_{1/2}$ = 15.8 years through year 7
$t_{1/2}$ = 47.3 years after year 7

nature

A quantitative approach for measuring the reservoir of latent HIV-1 proviruses

Katherine M. Bruner[1,8,10], Zheng Wang[1,10], Francesco R. Simonetti[1], Alexandra M. Bender[1], Kyungyoon J. Kwon[1], Srona Sengupta[1], Emily J. Fray[1], Subul A. Beg[1], Annukka A. R. Antar[1], Katharine M. Jenike[1], Lynn N. Bertagnolli[1], Adam A. Capoferri[1], Joshua T. Kufera[1], Andrew Timmons[1], Christopher Nobles[2], John Gregg[2], Nikolas Wada[3], Ya-Chi Ho[1,9], Hao Zhang[4], Joseph B. Margolick[4], Joel N. Blankson[1], Steven G. Deeks[5], Frederic D. Bushman[2], Janet D. Siliciano[1], Gregory M. Laird[6] & Robert F. Siliciano[1,7]*

The frequency of “active” HIV reservoir in lymph tissues declines during long-term ART



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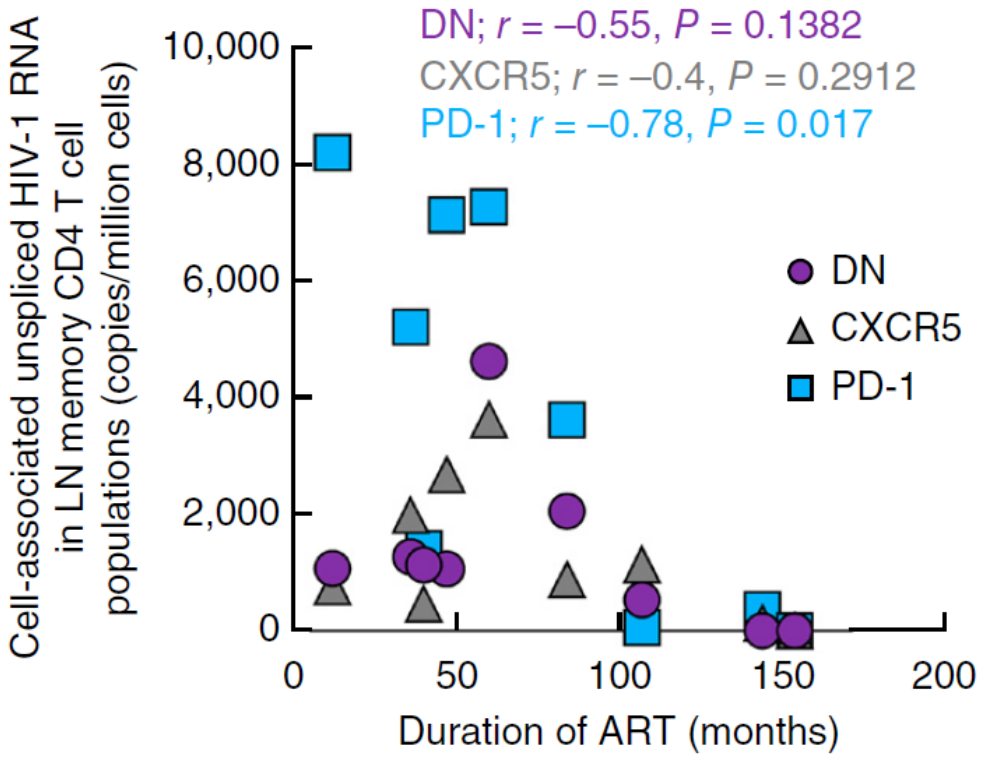
nature medicine

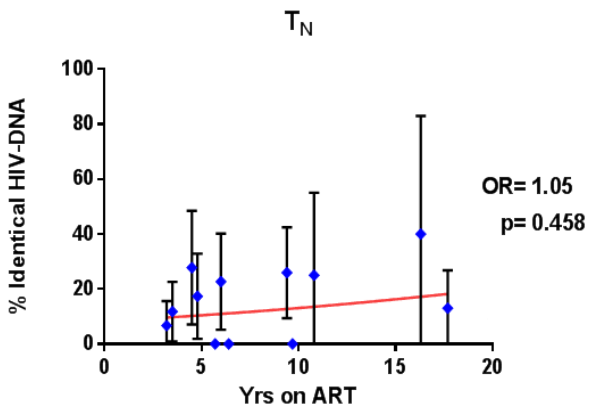
PD-1$^+$ and follicular helper T cells are responsible for persistent HIV-1 transcription in treated aviremic individuals

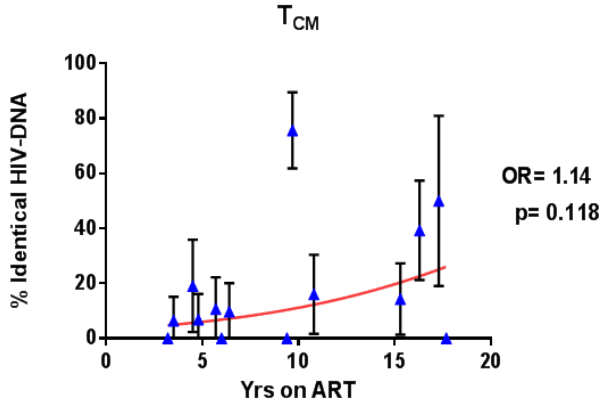
Riddhima Banga[1], Francesco Andrea Procopio[1], Alessandra Noto[1], Georgios Pollakis[2], Matthias Cavassini[3], Khalid Ohmiti[1], Jean-Marc Corpataux[4], Laurence de Leval[5], Giuseppe Pantaleo[1,6] & Matthieu Perreau[1]

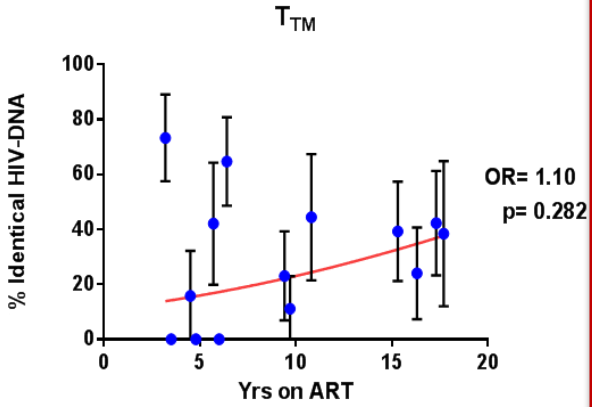


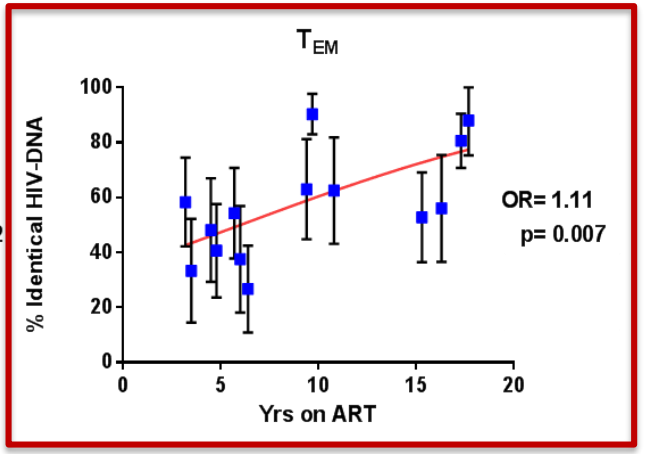
The "active" reservoir in nodes declines over time and appears to be correlated with the level of lymphoid inflammation (germinal centers)

FLIPS: The number of expansions of identical HIV-DNA sequences increases over time in T_{EM} cells









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During long term ART, the reservoir becomes increasingly clonal and difficult to reactivate

JEM

Proliferation of latently infected CD4$^+$ T cells carrying replication-competent HIV-1: Potential role in latent reservoir dynamics

Nina N. Hosmane,[1] Kyungyoon J. Kwon,[1] Katherine M. Bruner,[1] Adam A. Capoferri,[1] Subul Beg,[1] Daniel I.S. Rosenbloom,[2] Brandon F. Keele,[3] Ya-Chi Ho,[1] Janet D. Siliciano,[1] and Robert F. Siliciano[1,4]

JCI

Intact HIV-1 proviruses accumulate at distinct chromosomal positions during prolonged antiretroviral therapy

Kevin B. Einkauf,[1,2] Guinevere Q. Lee,[1,2] Ce Gao,[2] Radwa Sharaf,[1] Xiaoming Sun,[2] Stephane Hua,[2] Samantha M.Y. Chen,[2] Chenyang Jiang,[1,2] Xiaodong Lian,[1,2] Fatema Z. Chowdhury,[2] Eric S. Rosenberg,[3] Tae-Wook Chun,[4] Jonathan Z. Li,[1] Xu G. Yu,[1,2,5] and Mathias Lichterfeld[1,2,5]

nature COMMUNICATIONS

Longitudinal HIV sequencing reveals reservoir expression leading to decay which is obscured by clonal expansion

Marilia Rita Pinzone[1], D. Jake VanBelzen[1,2], Sam Weissman[1], Maria Paola Bertuccio[1], LaMont Cannon[1], Emmanuele Venanzi-Rullo[1,3], Stephen Migueles[4], R. Brad Jones[5], Talia Mota[5], Sarah B. Joseph[6], Kevin Groen[7], Alexander O. Pasternak[7], Wei-Ting Hwang[8], Brad Sherman[9], Anastasios Vourekas[1], Giuseppe Nunnari[3] & Una O'Doherty[1]

eLIFE elifesciences.org

Distinct chromatin functional states correlate with HIV latency reactivation in infected primary CD4$^+$ T cells

Emilie Battivelli[1,2,3], Matthew S Dahabieh[1,2], Mohamed Abdel-Mohsen[4,5,6], J Peter Svensson[7], Israel Tojal Da Silva[8,9], Lillian B Cohn[8], Andrea Gramatica[1,2,10], Steven Deeks[2], Warner C Greene[1,2,10], Satish K Pillai[4,5], Eric Verdin[1,2,3]*

Cell PRESS

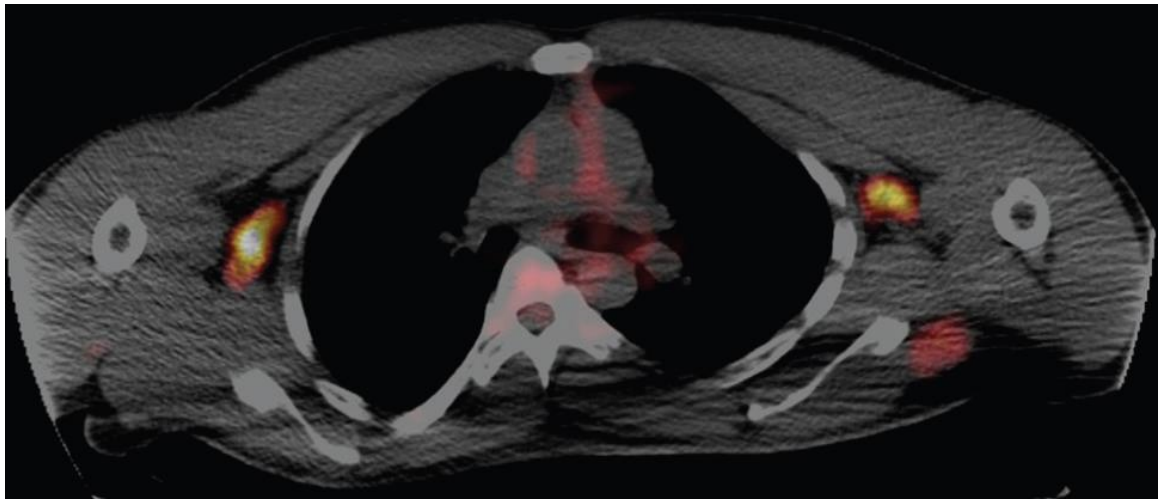
HIV-1 Integration Landscape during Latent and Active Infection

Lillian B. Cohn,[1] Israel T. Silva,[1,2] Thiago Y. Oliveira,[1] Rafael A. Rosales,[3] Erica H. Parrish,[4] Gerald H. Learn,[4] Beatrice H. Hahn,[4] Julie L. Czartoski,[5] M. Juliana McElrath,[5] Clara Lehmann,[6,7] Florian Klein,[1] Marina Caskey,[1] Bruce D. Walker,[8,9] Janet D. Siliciano,[10] Robert F. Siliciano,[9,10] Mila Jankovic,[1] and Michel C. Nussenzweig[1,9,*]

JAMA Cardiology

Association of Arterial and Lymph Node Inflammation With Distinct Inflammatory Pathways in Human Immunodeficiency Virus Infection

Ahmed Tawakol, MD; Amorina Ishai, MD; Danny Li, BS; Richard A. P. Takx, MD, MSc, PhD; Sophia Hur, MPH; Yannick Kaiser, BS; Miguel Pampaloni, MD, PhD; Adam Rupert, MT; Denise Hsu, PhD; Irini Sereti, MD; Rémi Fromentin, PharmD, PhD; Nicolas Chomont, PhD; Peter Ganz, MD; Steven G. Deeks, MD; Priscilla Y. Hsue, MD



Lymph node inflammation persists during ART and associated with higher viral burden, lower CD4/CD8 ratio, higher CD4+ T cell activation and (in controllers) HIV DNA

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Summary and therapeutic implications

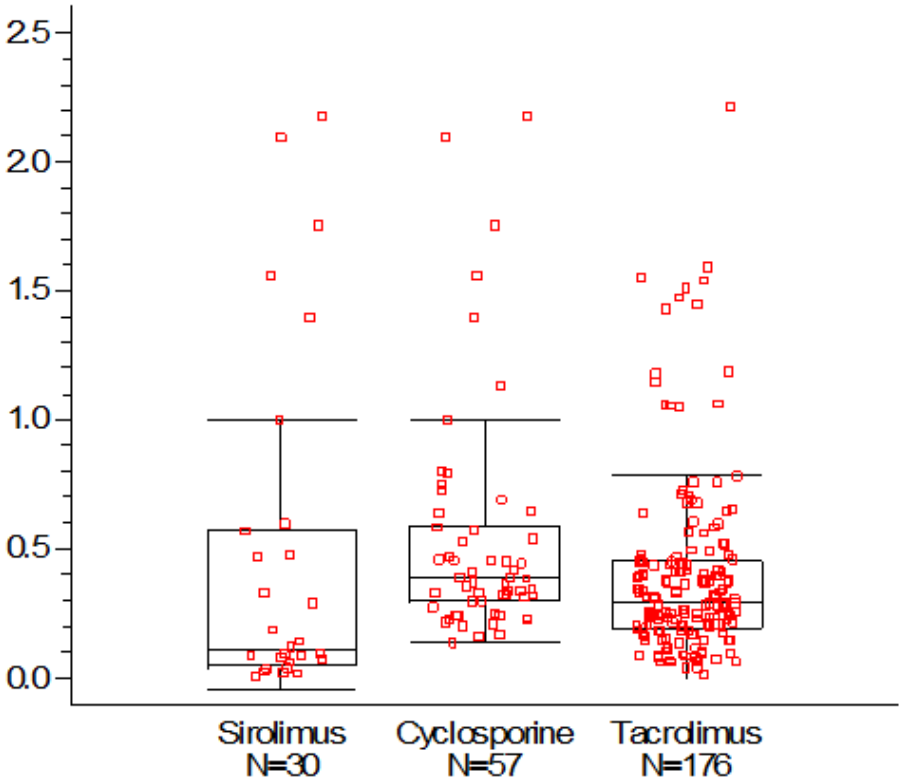
- HIV enriched in more differentiated, rapidly turning over cells
  - PD-1, HLA-DR, Tfh markers
- Clonal HIV integrated in genes associated with cell proliferation
- Reservoir during ART is not stable
  - Intact genomes decline more rapidly than defective ones
  - Reservoir increasingly clonal over time, with more in effector cells
- Reservoir may become increasingly difficult to reactivate, providing some rationale for “block and lock strategies”

If the reservoir is preferentially maintained in cells that are rapidly turning over (high replacement rates) then would sustained inhibition of this process lead to a measurable decay in the reservoir?

AJT

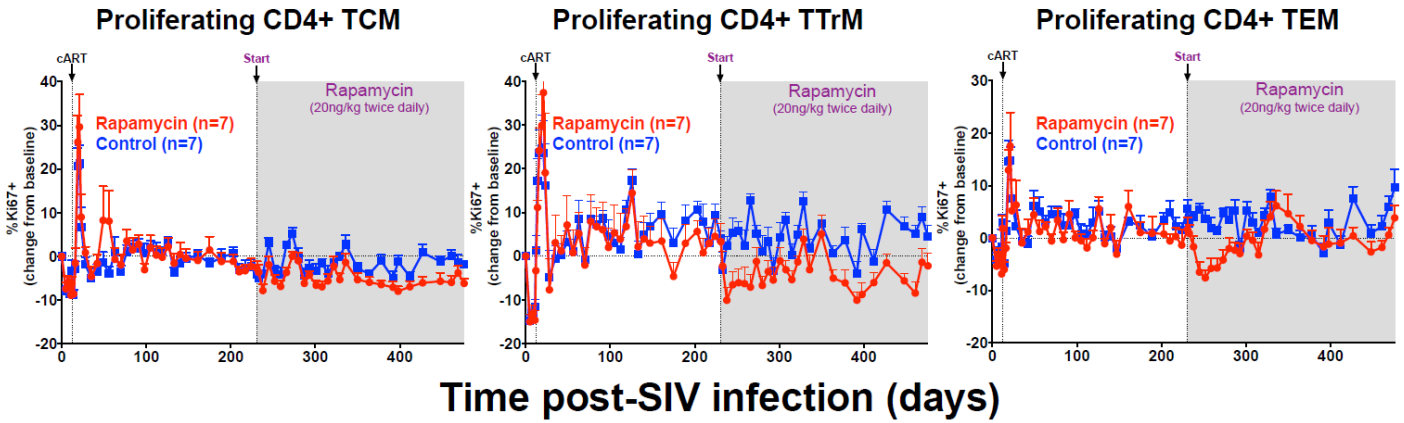
Reduction of HIV Persistence Following Transplantation in HIV-Infected Kidney Transplant Recipients

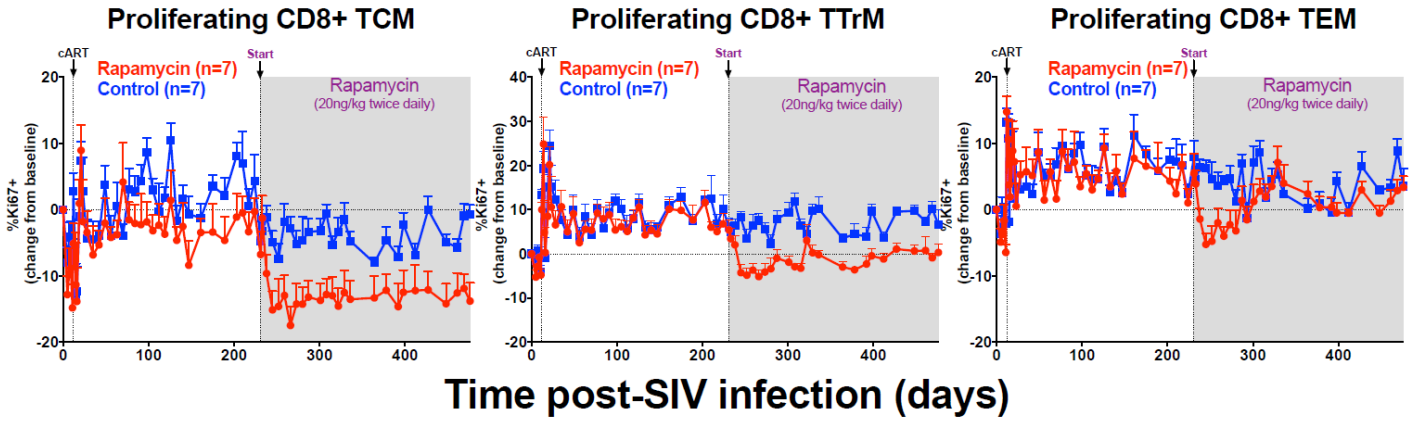
P. G. Stock[1], B. Barin[2], H. Hatano[3], R. L. Rogers[1], M. E. Roland[3], T.-H. Lee[4], M. Busch[4], and S. G. Deeks[3,*] for Solid Organ Transplantation in HIV Study Investigators



Sirolimus (rapamycin)—which reduces T cell activation and T cell proliferation and enhances generation of memory—is associated with low “reservoir” size post-renal transplant

mTOR inhibitors (sirolimus) induces decrease in proliferating T cells








A5337: Sirolimus decreased the frequency of CD4+ T cells expressing a marker of cell cycling (Ki67) (primary population, 20 weeks of treatment, n=16)

Outcome	Mean	95% Confidence Interval	P-Value
%CCR5+ CD4+ T-Cells	-1.67	(-3.76, 0.42)	0.11
%CD27+ CD4+ T-Cells	-0.30	(-2.38, 1.77)	0.76
%CD69+ CD4+ T-Cells	-0.17	(-0.97, 0.63)	0.65
Central Memory (%CD45RA-CCR7+) CD4+ T-Cells	-0.01	(-2.18, 2.17)	1.00
Effector Memory (%CD45RA-CCR7-) CD4+ T-Cells	2.20	(-0.50, 4.90)	0.10
%Ki67+ CD4+ T-Cells	-0.51	(-0.97, -0.05)	**0.031**
Naive (%CD45RA+CCR7+) CD4+ T-Cells	-2.16	(-5.46, 1.15)	0.18
%PD1+ CD4+ T-Cells	0.42	(-1.81, 2.66)	0.69
Terminally Differentiated (%CD45RA+CCR7-) CD4+ T-Cells	-0.04	(-1.21, 1.14)	0.95

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A5337: Sirolimus decreased the frequency of CD8+ T cells expressing CCR5, Ki67 and PD-1 (primary population, 20 weeks of treatment, n=16)

Outcome	Mean	95% Confidence Interval	P-Value
%CCR5+ CD8+ T-Cells	-3.92	(-5.99, -1.85)	**0.001**
%CD27+ CD8+ T-Cells	0.15	(-3.67, 3.98)	0.93
%CD69+ CD8+ T-Cells	-0.52	(-1.38, 0.35)	0.22
Central Memory (%CD45RA-CCR7+) CD8+ T-Cells	-0.87	(-1.82, 0.08)	0.07
Effector Memory (%CD45RA-CCR7-) CD8+ T-Cells	-0.58	(-3.02, 1.86)	0.62
%Ki67+ CD8+ T-Cells	-0.54	(-0.90, -0.19)	**0.005**
Naive (%CD45RA+CCR7+) CD8+ T-Cells	0.75	(-3.61, 5.12)	0.72
%PD1+ CD8+ T-Cells	-2.85	(-4.85, -0.86)	**0.008**
Terminally Differentiated (%CD45RA+CCR7-) CD8+ T-Cells	0.68	(-2.82, 4.18)	0.69

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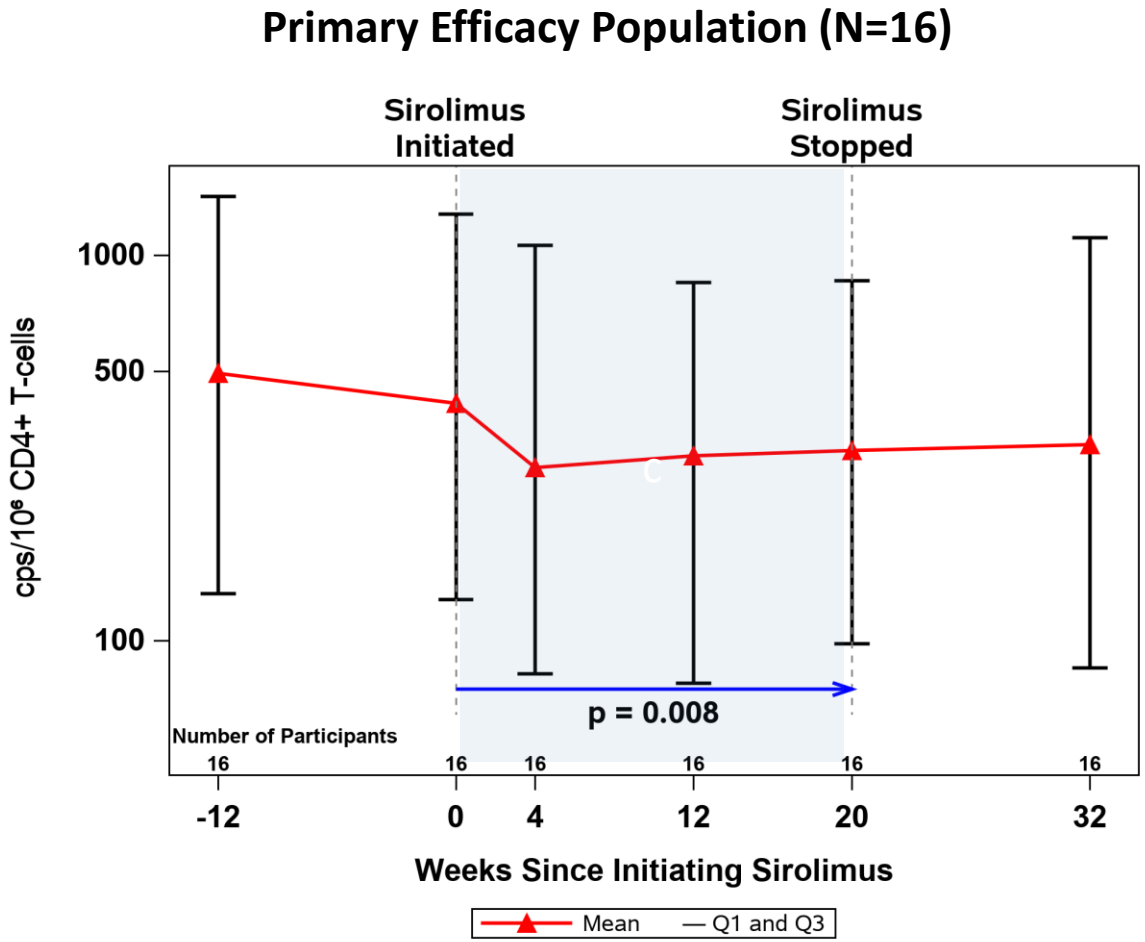
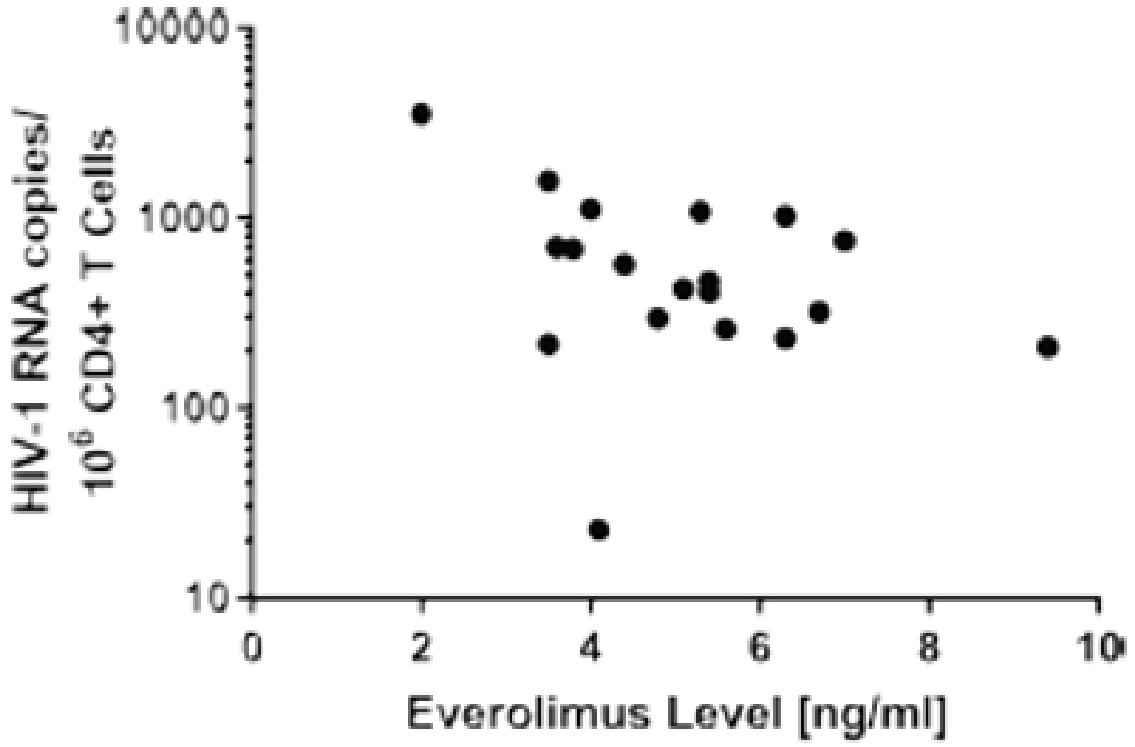
A5337: Sirolimus reduced HIV DNA levels (mean 0.16 log_{10} copies DNA/mL)

Although the effect was modest, this may be the first drug shown to affect this outcome



Higher levels of exposure to everolimus associated with greater reductions in cell-associated RNA (bulk)



Gene expression studies (pathway analyses): The greater the degree of mTOR inhibition the greater the reduction in cell-associated RNA

Cell
Host & Microbe

The mTOR Complex Controls HIV Latency

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Conclusions

- Reservoir: Long-term ART
  - HIV increasing enriched in rapidly turning more differentiated cells
  - Singlets may more likely to be a state of deeper latency
- HIV Remission: Reduce and control
  - Control: Active and robust experimental medicine program
  - Reduce: May need to target proliferating (clonal) population
- Cell proliferation as a target
  - Will prevention of proliferation lead to decay in these cells?
  - mTOR inhibition shows *in vivo* activity (rare in human studies)
  - Other options being pursued (IL1-beta inhibition, JAK/STAT inhibitors)