Untangling the complex association between proliferation, activation and persistence

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Host environment and HIV persistence

- Should we stimulate or inhibit T cell activation?
- Should we stimulate or inhibit T cell proliferation/differentiation?

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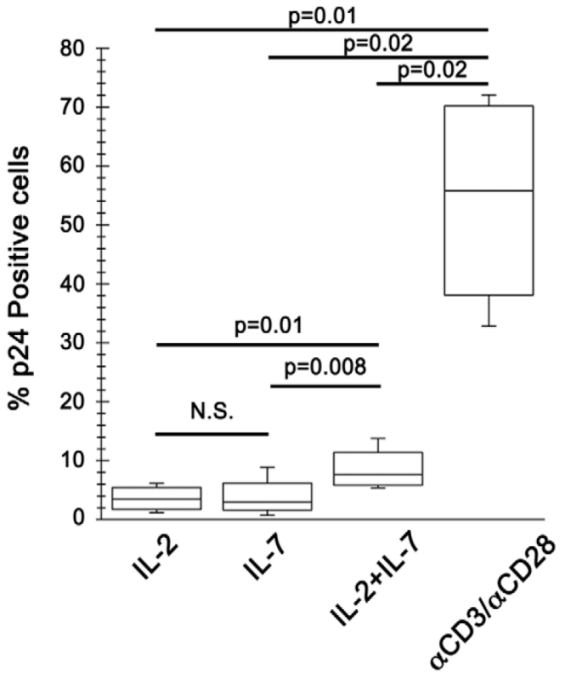
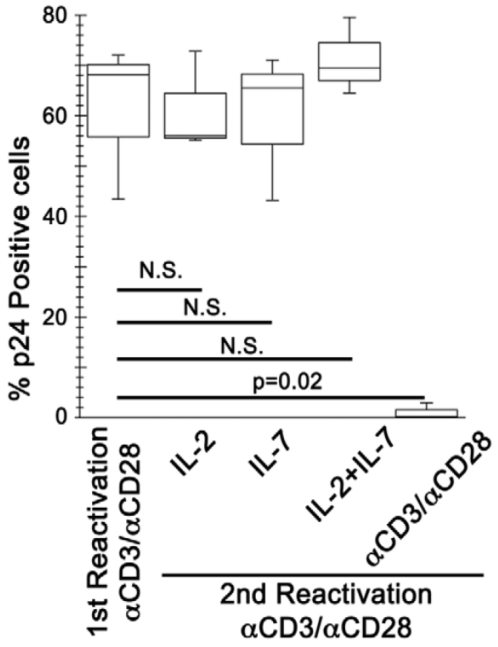
PLoS PATHOGENS

Homeostatic Proliferation Fails to Efficiently Reactivate HIV-1 Latently Infected Central Memory CD4+ T Cells

Alberto Bosque[1], Marylinda Famiglietti[1,2], Andrew S. Weyrich[3], Claudia Goulston[4], Vicente Planelles[1]*

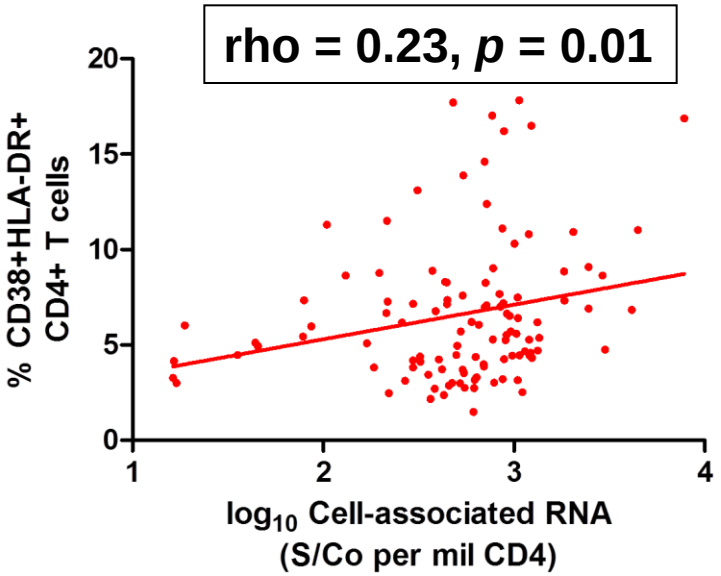


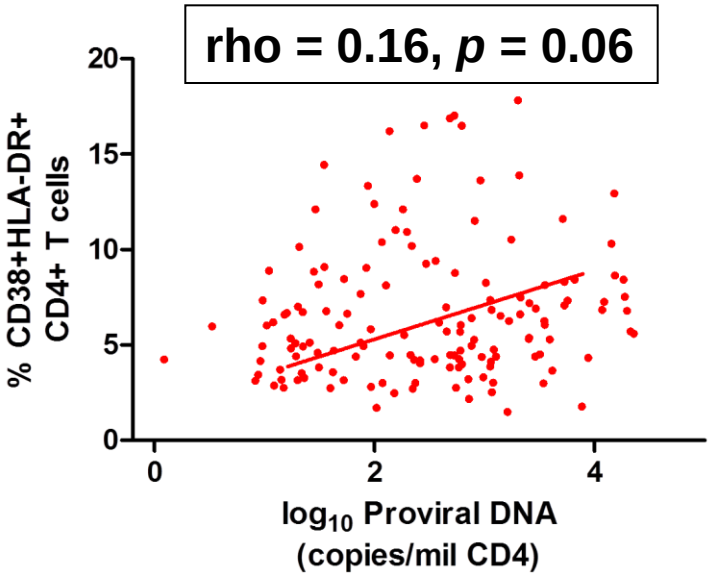


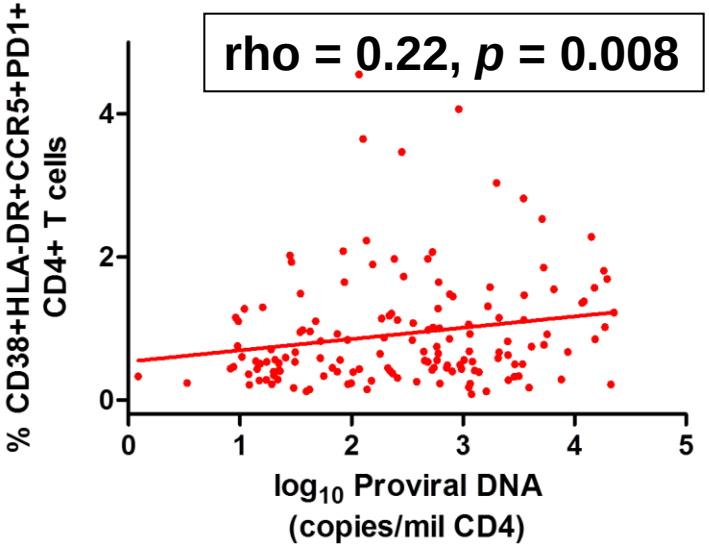
One round of broad, potent TCR activation (anti-CD3/CD28) but not IL-2/IL-7 clears HIV from central memory cells

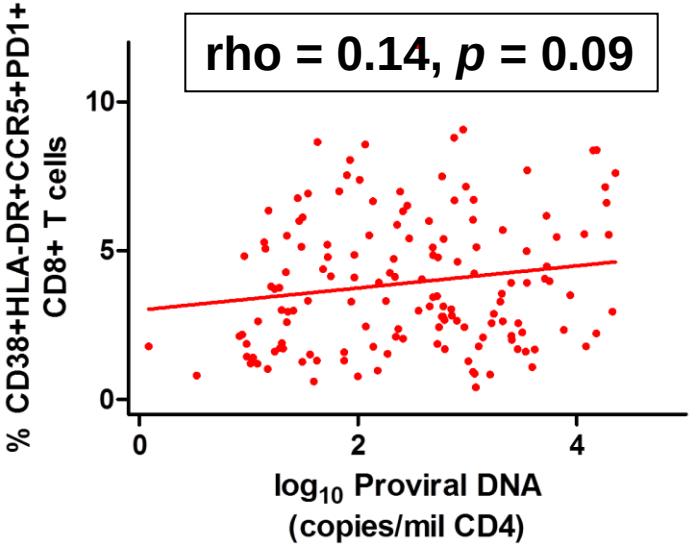
Does T cell activation and/or activation-induced cell proliferation contribute to persistence *in vivo*?

Weak association between cell-based measures of viral persistence (per million PBMCs) and T cell activation in blood









Hatano JID 2012

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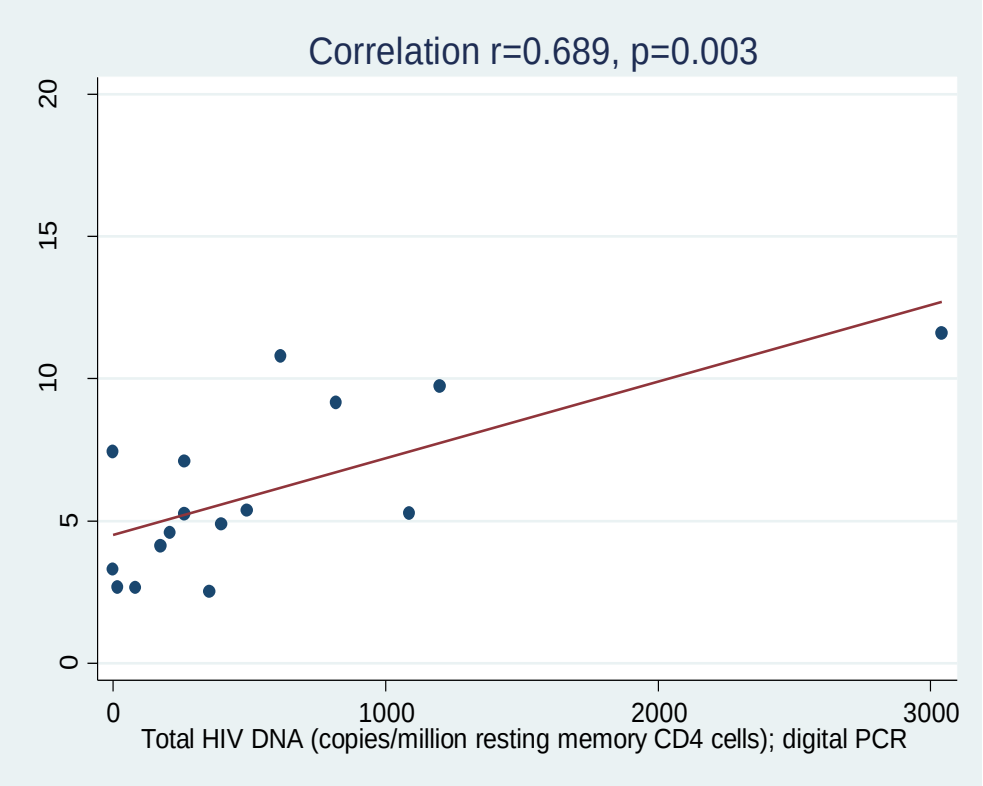
Comparative Analysis of Measures of Viral Reservoirs in HIV-1 Eradication Studies

Susanne Eriksson[1☯], Erin H. Graf[2☯], Viktor Dahl[1☯], Matthew C. Strain[3☯], Steven A. Yukl[4,5☯], Elena S. Lysenko[2], Ronald J. Bosch[6], Jun Lai[7], Stanley Chioma[7], Fatemeh Emad[7], Mohamed Abdel-Mohsen[5], Rebecca Hoh[5], Frederick Hecht[5], Peter Hunt[5], Ma Somsouk[5], Joseph Wong[4,5], Rowena Johnston[8], Robert F. Siliciano[7,9], Douglas D. Richman[3], Una O'Doherty[2], Sarah Palmer[1], Steven G. Deeks[5], Janet D. Siliciano[7]*



Frequency of HIV DNA-containing resting memory cells correlates with frequency of activated CD4+ T cells (rho=0.7, P=0.003)

ARCHE amfAR Research Consortium on HIV Eradication

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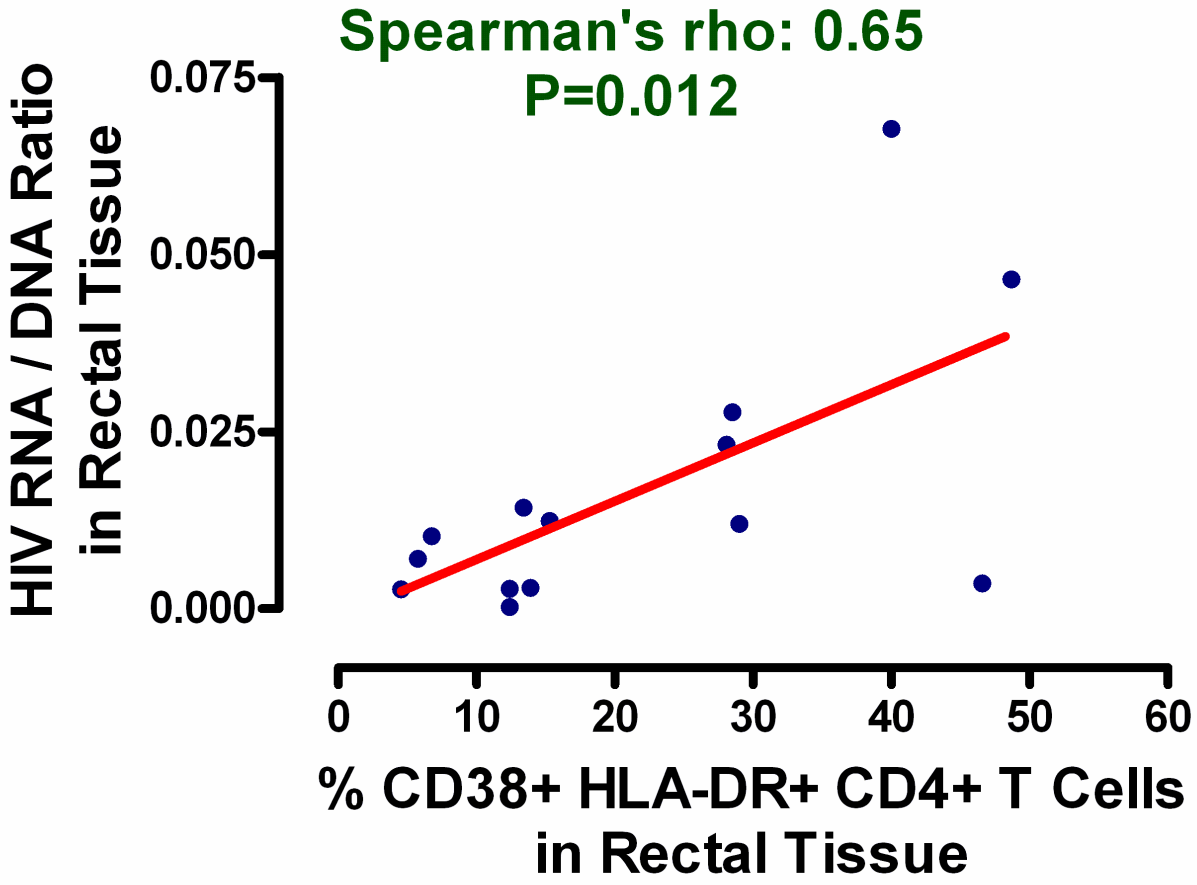
The association between these factors is much stronger in gut mucosa



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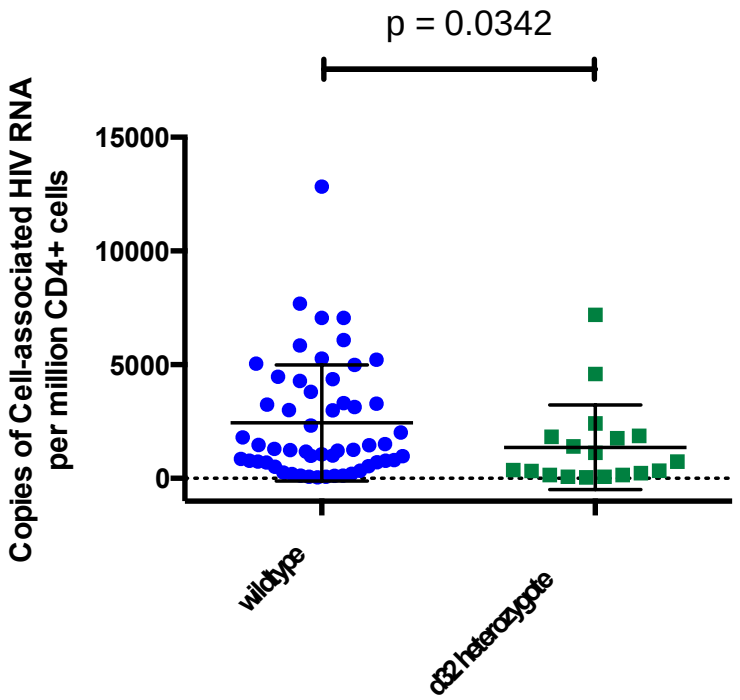
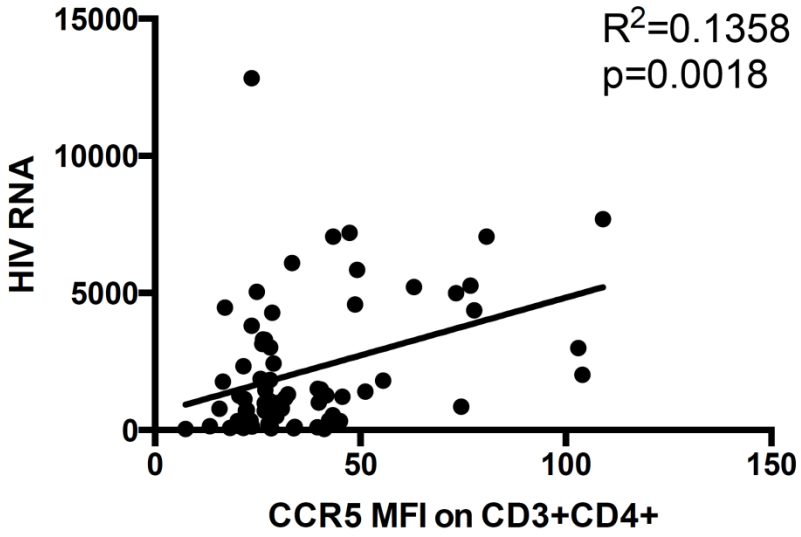
Hunt, Yukl and Wong

Cell-associated RNA (but not DNA) is lower in CCR5-delta 32 heterozygotes and positively correlated with frequency of CCR5-expressing cells and CCR5 MFI





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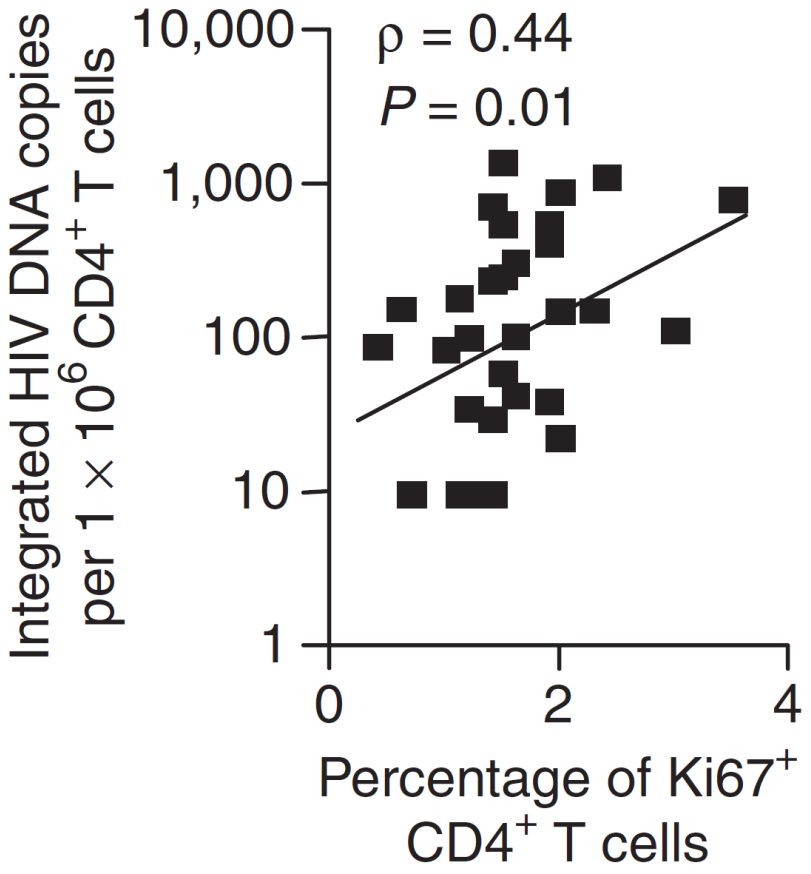
Wang and Pillai (unpublished)

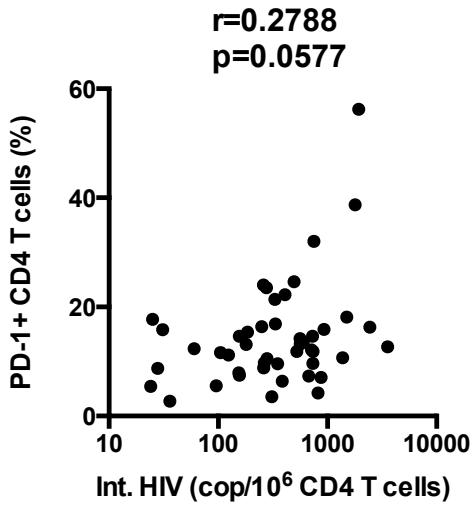
The frequency of proliferating cells also predicts size of reservoir (integrated DNA)



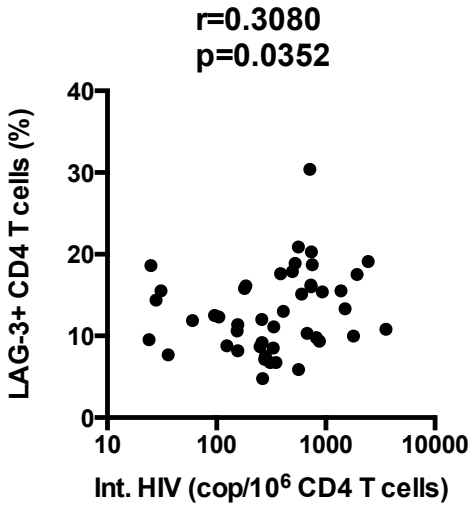
Chomont Nature Med 09

Immune “checkpoint” expression—which increase with cell proliferation/activation—also correlate with size of reservoir (integrated HIV DNA)

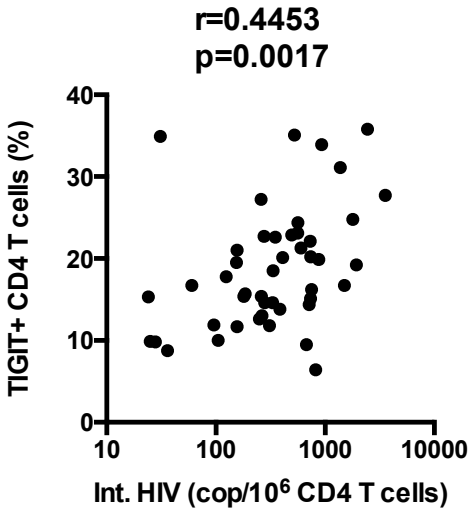
PD-1



LAG-3



TIGIT

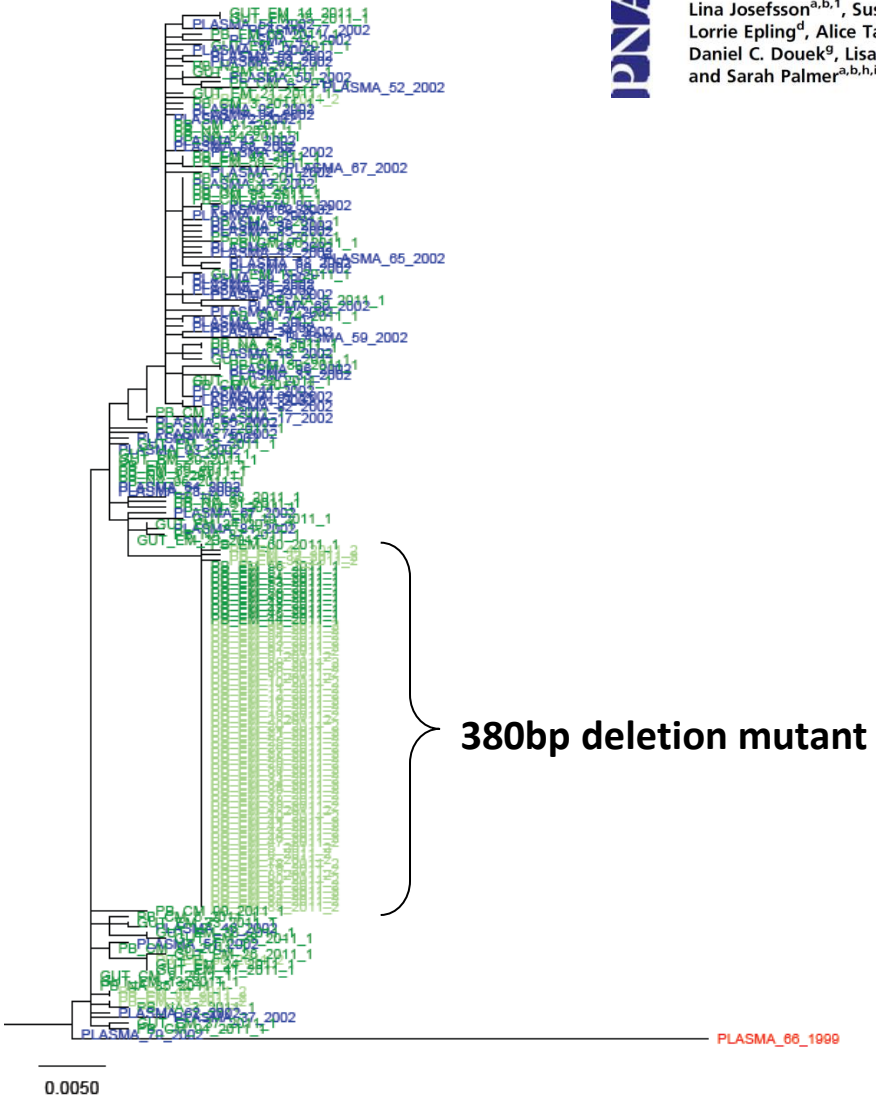


Fromentin and Chomont (unpublished)

PNAS PLUS

The HIV-1 reservoir in eight patients on long-term suppressive antiretroviral therapy is stable with few genetic changes over time

Lina Josefsson[a,b,1], Susanne von Stockenstrom[a,b], Nuno R. Faria[c], Elizabeth Sinclair[d], Peter Bacchetti[e], Maudi Killian[d], Lorrie Epling[d], Alice Tan[d], Terence Ho[d], Philippe Lemey[c], Wei Shao[f], Peter W. Hunt[d], Ma Somsouk[d], Will Wylie[g], Daniel C. Douek[g], Lisa Loeb[d], Jeff Custer[d], Rebecca Hoh[d], Lauren Poole[d], Steven G. Deeks[d], Frederick Hecht[d,2], and Sarah Palmer[a,b,h,i,2]



380bp deletion mutant

Clonal populations primarily in EM cells, including protease-deficient population

>10-fold higher rates of defective viral genomes in EM cells than either CM or TM cells (unpublished)

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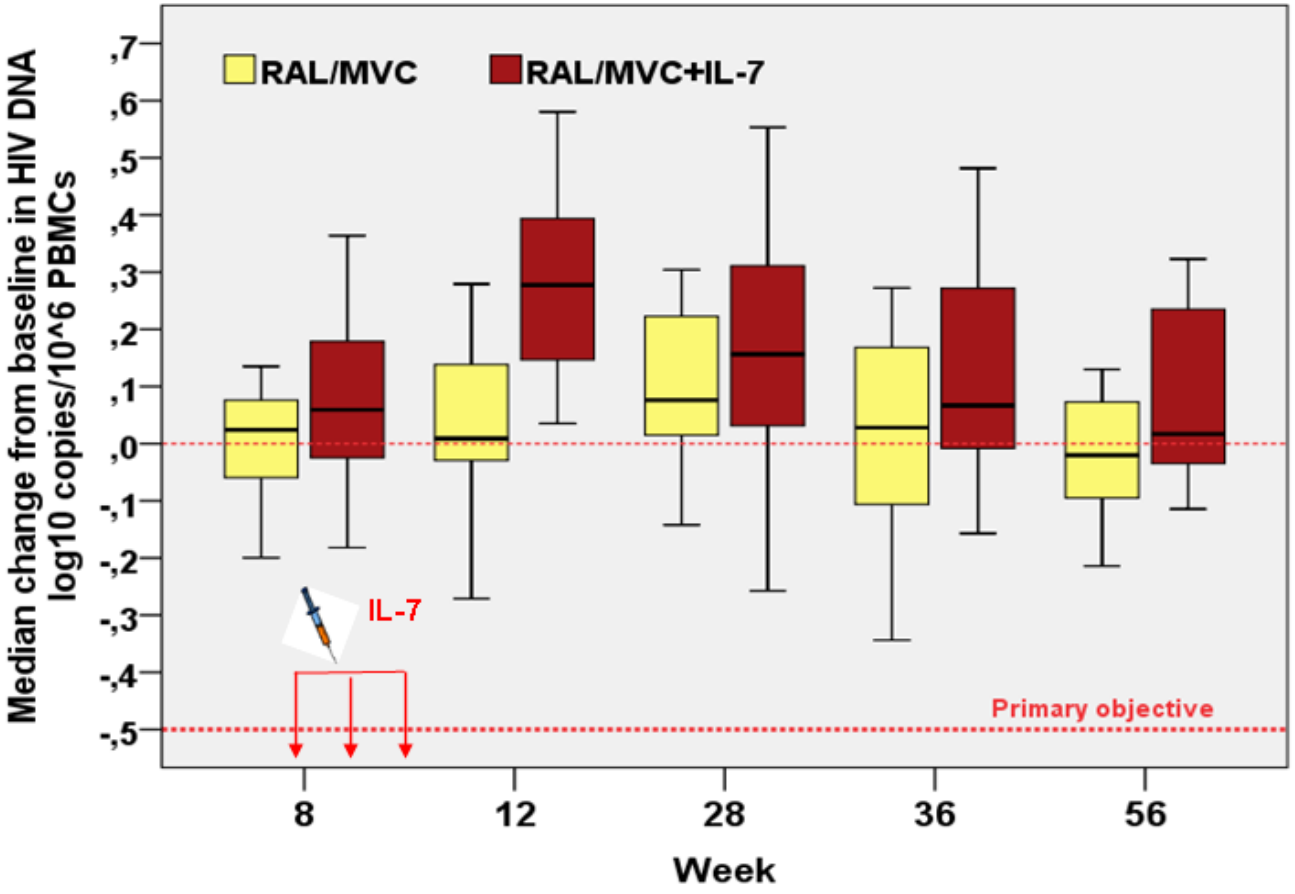
IL-7 causes proliferation of HIV-infected CD4+ T cells without obvious evidence of preferential clearance of these cells, either because virus is not induced or virus-producing cells are not cleared



Katlama et al, CROI 2013

HIV Persistence and Replication

T Cell Activation and Inflammation

nature medicine

HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects

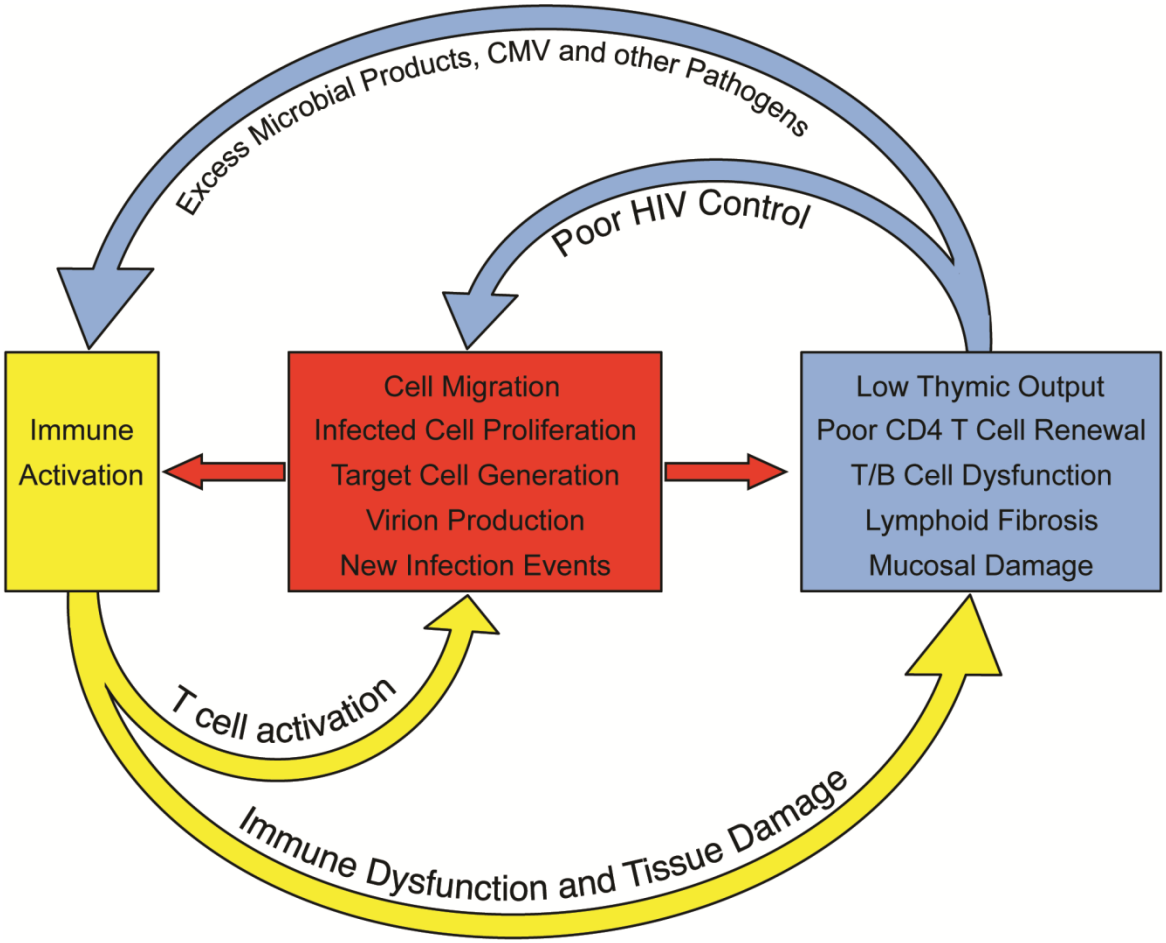
Maria J Buzón[1,9], Marta Massanella[1,9], Josep M Llibre[2], Anna Esteve[3], Viktor Dahl[4], Maria C Puertas[1], Josep M Gatell[5], Pere Domingo[6], Roger Paredes[1,2], Mark Sharkey[7], Sarah Palmer[4], Mario Stevenson[7], Bonaventura Clotet[1,2], Julià Blanco[1] & Javier Martinez-Picado[1,8]

The Journal of Infectious Diseases

Increase in 2–Long Terminal Repeat Circles and Decrease in D-dimer After Raltegravir Intensification in Patients With Treated HIV Infection: A Randomized, Placebo-Controlled Trial

Hiroyu Hatano,[1] Matthew C. Strain,[4,5] Rebecca Scherzer,[1,3] Peter Bacchetti,[2] Deborah Wentworth,[6] Rebecca Hoh,[1] Jeffrey N. Martin,[2] Joseph M. McCune,[1] James D. Neaton,[6] Russell P. Tracy,[7] Priscilla Y. Hsue,[1] Douglas D. Richman,[4,5] and Steven G. Deeks[1]

HIV-associated inflammation and immune dysfunction can cause HIV persistence through several potentially modifiable mechanisms



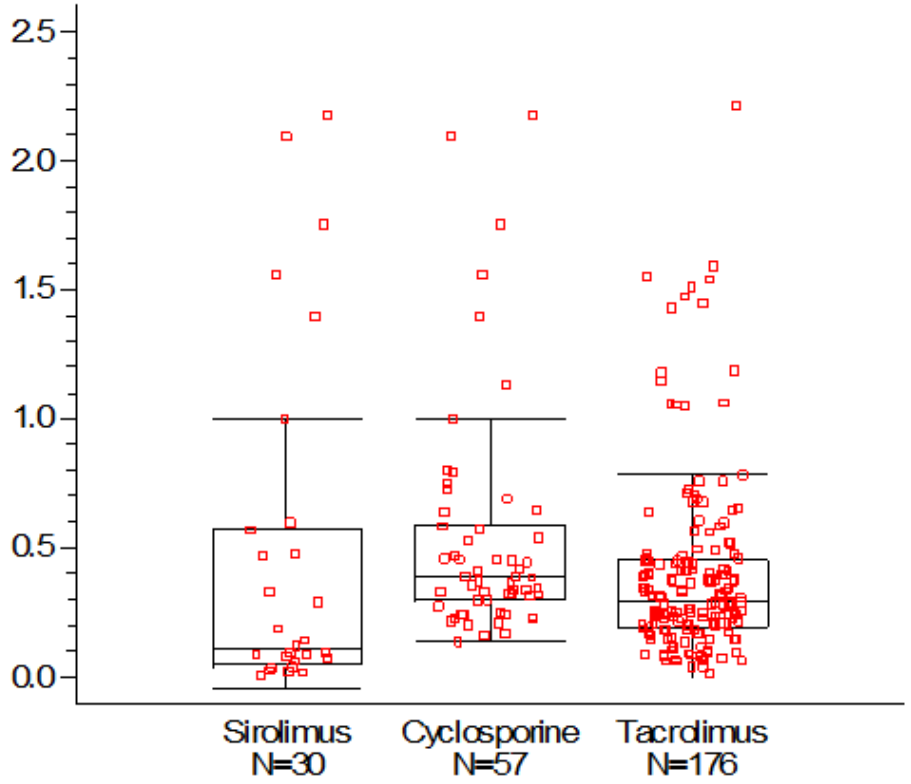
Klatt, Chomont, Douek, Deeks; Imm Rev 2013

Will inhibition of T cell activation and/or proliferation contribute to clearance of reservoir?

Sirolimus (rapamycin) and mTOR inhibition

- Sirolimus mimics a starvation signal, leading to mTOR inhibition and:
  - Cell cycle arrest in G1
  - Reduced T cell activation
  - Suppression of cell metabolism
  - Reduction in CCR5 expression

Sirolimus (rapamycin)—which reduces CCR5 expression, T cell activation and T cell proliferation—is associated with low reservoir size post-renal transplant



In the multivariate model, sirolimus use associated with lower HIV DNA levels (p=0.04)

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HIV+ SOLID ORGAN TRANSPLANT MULTI-SITE STUDY

ACTG: Proposed pilot study of sirolimus safety and efficacy for HIV-1 reservoir reduction (Hendrick)

- Study Design: Randomized open-label pilot study of sirolimus therapy or no sirolimus therapy for 3 months duration (randomized 3:1)
- Subjects: HIV-infected on non-protease inhibitor based regimen (HIV RNA < 40; CD4 > 350) (n=40)
- Primary objectives include: (1) PK, safety and tolerability, 2) replication competent HIV and HIV RNA, and (3) T cell function

POC IBT human studies in development

- IDO inhibitors (McCune)
- JAK inhibitors (Marconi/ACTG)
- Methotrexate (Hsue/ACTG)
- Mesalamine (Hunt/Somsouk)
- ACE inhibitors/ARBs (Hatano/Schacker/others)
- Anti-inferfeon-alpha (Hatano)
- Maraviroc (Stock)
- Aurofanofin (Savarino)
- Sirolimus (Henrich/ACTG)
- Anit-PD-1 (Hatano/ACTG)
- Anti-PDL-1 (Eron/ACTG)
- Caspase 1 inhibitors (Greene)

Conclusions

- The causal pathway for consistent association between HIV persistence and immune activation/proliferation is certainly complex, likely multi-directional, and may differ across patient groups (defined by age, gender, immunologic response)
- Rigorous controlled studies involving more potent antiretroviral strategies and immune-based therapeutics are needed to determine how immune environment contributes to persistence

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Janet Siliciano
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ARCHE
amfAR Research Consortium on HIV Eradication

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