Circulating immune predictors of intact HIV reservoir decay during long-term ART

Michael Peluso, MD
Assistant Professor of Medicine
Division of HIV, Infectious Diseases, and Global Medicine
University of California, San Francisco

Study Team: Sergio Serrano-Villar, Akshay Gala, Peter Bacchetti, Clara Di Germanio, Lillian Cohn, Peter Hunt, Greg Laird, Satish Pillai, Steven Deeks

CONFLICTS OF INTEREST

Dr. Peluso serves on a data safety monitoring board for American Gene Technologies.

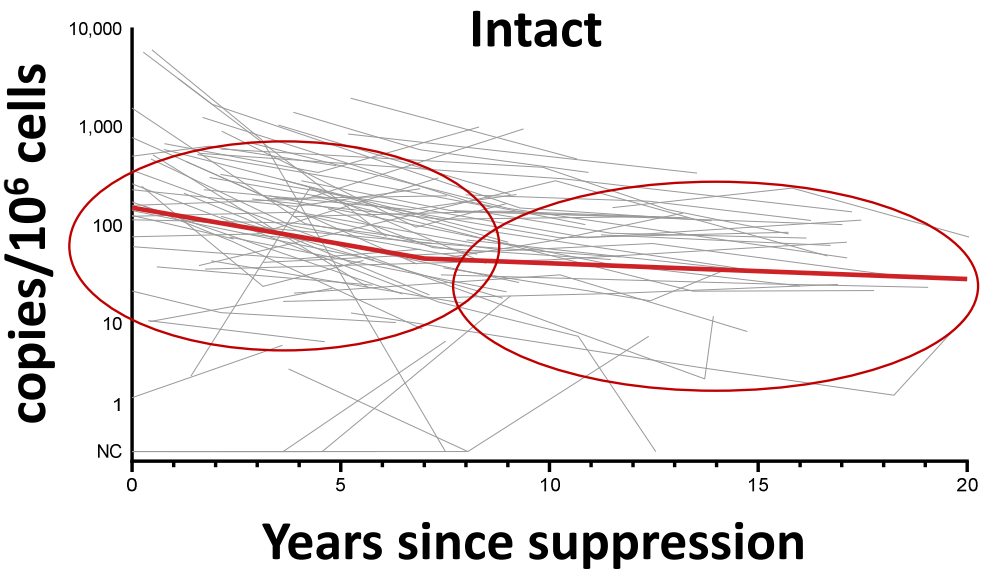
- Question: Does the level of inflammatory markers at baseline predict changes in the frequency of the intact HIV reservoir over time?

- Results: Baseline galectin-9 was the marker most strongly associated with reservoir decay. Lower Gal-9 was associated with faster HIV decay over the first 7 years.

- Next Steps: Examine correlates of defective reservoir decay, consider role of Gal-9-related agents in cure studies.

Background

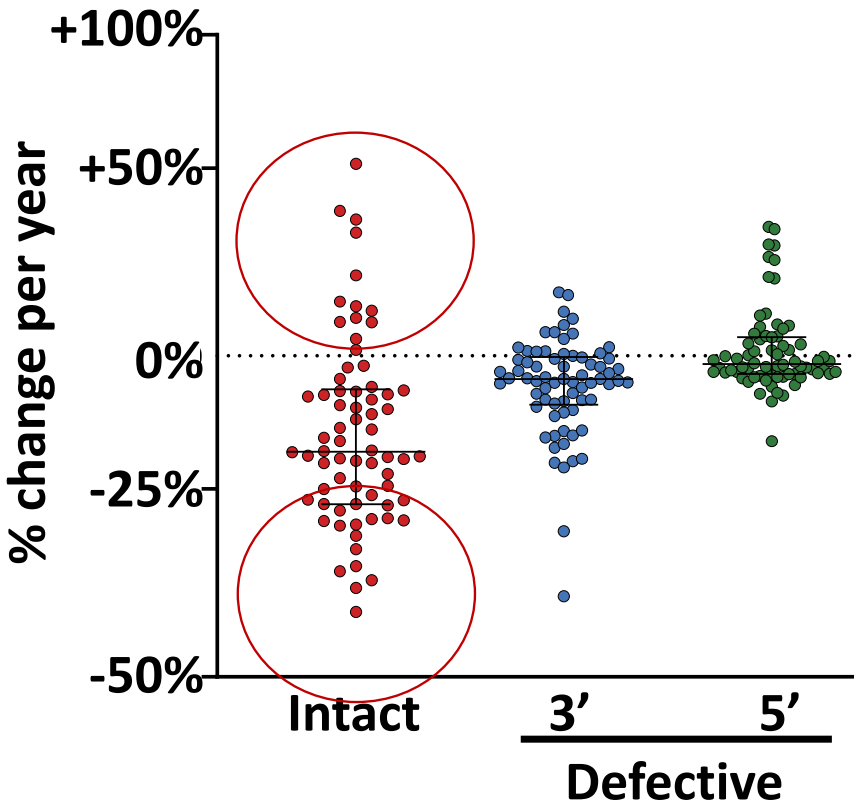
- The HIV reservoir is not stable during ART
- Cells harboring intact genomes decay more rapidly than those with defective genomes, particularly during the first several years on ART



	Through year 7	After year 7
Decay per year	-15.8%	-3.6%
Half life	4 years	19 years

Peluso et al JCI Insight 2020, Gandhi et al J Infect Dis 2021

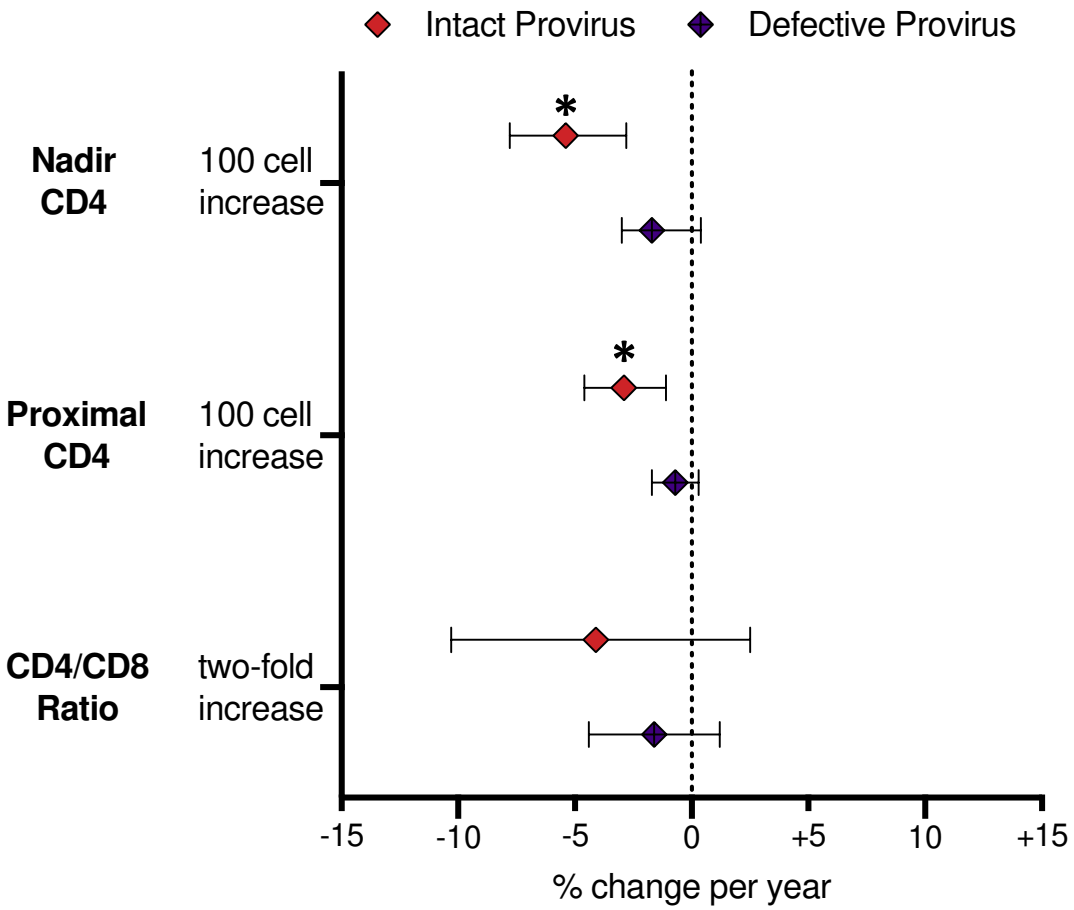
Background



- Substantial variability in rate of decline to year seven
- Sub-group had expansion
- Sub-group decayed very rapidly

Peluso et al JCI Insight 2020.

Background



- Individuals with higher CD4 nadir and proximal CD4 count had more rapid decay
- Age, race, gender, duration of infection, protective HLA alleles, CCR5 heterozygosity had no substantial effect
- Other immunologic factors associated with variability in decay have not been explored

Peluso et al JCI Insight 2020

Research Questions

- Can a single baseline measurement of inflammatory biomarkers in ART-suppressed individuals predict long-term changes in the frequency of intact proviruses over time?

- Do changes in inflammatory biomarkers over time reflect changes that are occuring in the frequency of intact proviruses over that same time period?

Methods

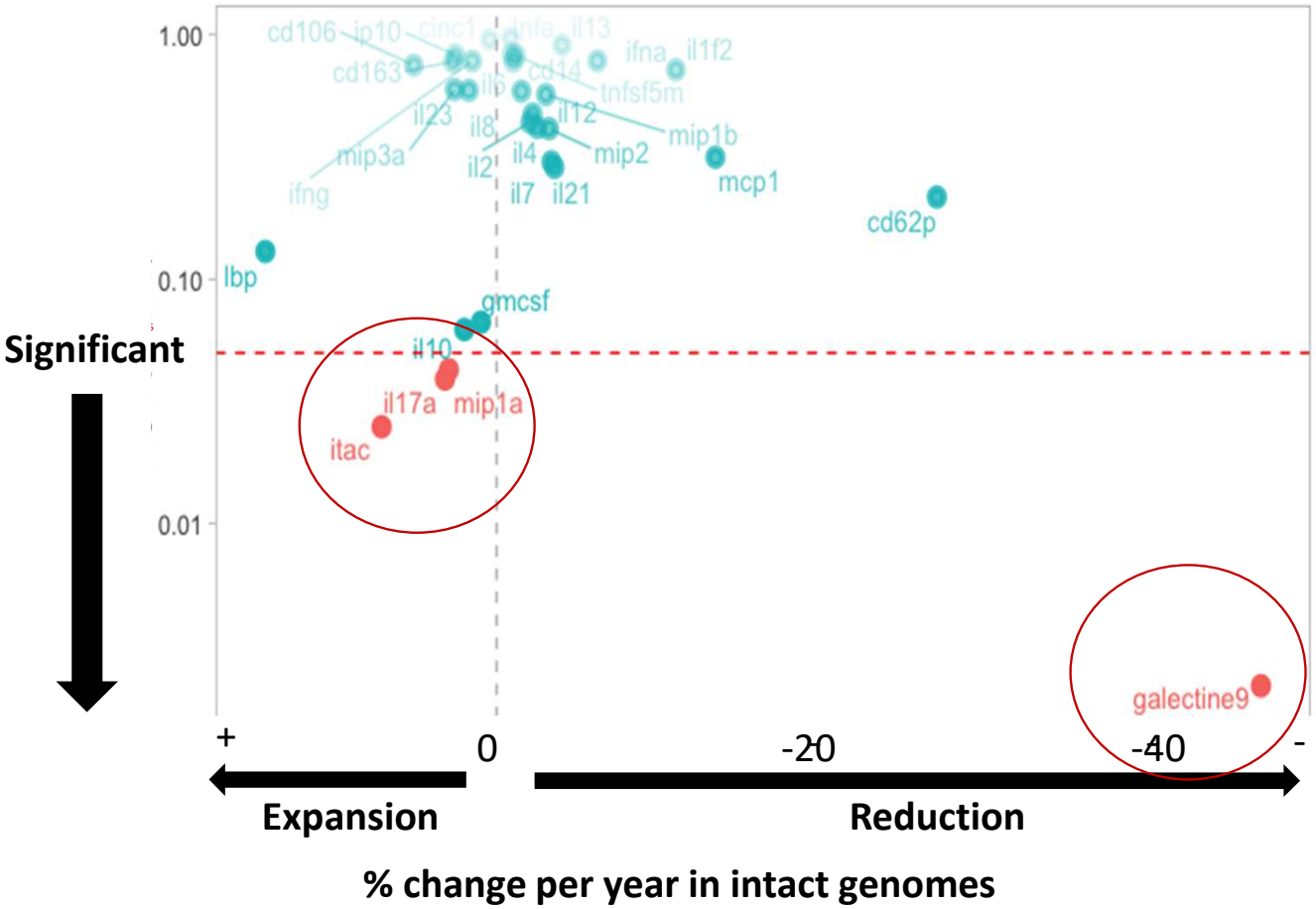
- Outcomes: Measured intact proviruses using IPDA in peripheral blood and fit linear spline models, as in prior study
- Predictors: 32 pro-inflammatory and regulatory cytokines in plasma measured using Luminex bead-based immunoassay
- Estimated influence of baseline cytokine levels and trajectories on intact HIV kinetics

Study Population

Characteristic	
Male	95%
Age, median (IQR)	49.5 (25-75)
Race	
White	65%
Black	12%
Latino	8%
Asian	1%
Native American	1%
Pacific Islander	1%
Multiple races	1%
CD4 Nadir	180 (59-315) cells/uL
Baseline CD4	591 (472-736) cells/uL
Baseline CD4/CD8	0.85 (0.17, 2.7)
Study follow up	7 (6-8) years

- UCSF SCOPE cohort
- 76 individuals on suppressive ART, 2-4 samples per person
- Variability in CD4 nadir, CD4 baseline, and ratio
- Focused on first 7 years on ART

Effect of baseline cytokine levels on intact genome trajectories



Baseline Gal-9 most predictive marker of intact HIV kinetics

Lower Gal-9 predicted more rapid intact decay

Each 10-fold ▼ Gal-9 = 45% greater decay in intact HIV genomes / year (p=0.002; adj p=0.005)

Lower baseline MIP-1a, ITAC, IL-17 predicted intact HIV increases

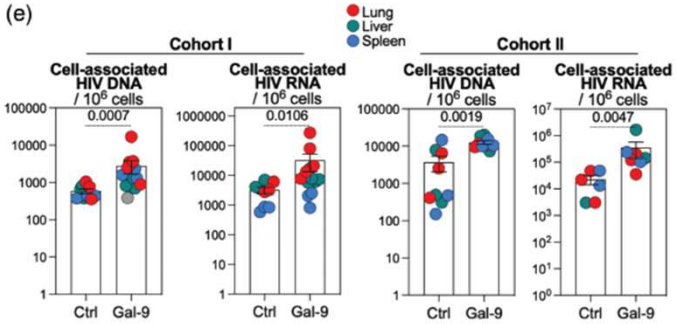
Marker	Relationship Observed	Function (published literature)
Galectin-9	▼ initial level = greater decay	Mixed data on benefits/harms during HIV infection May make CD4 cells less susceptible to infection Induces transcription/reverses latency in vitro Maintains chronic immune activation

AIDS

Human galectin-9 promotes the expansion of HIV reservoirs *in vivo* in humanized mice

Yuan, Zhe[a]; Giron, Leila B.[a]; Hart, Colin[e]; Gyampoh, Akwasi[a]; Koshy, Jane[a]; Hong, Kai Ying[a]; Niki, Toshiro[b]; Premeaux, Thomas A.[c]; Ndhlovu, Lishomwa C.[c]; Deleage, Claire[d]; Montaner, Luis J.[a]; Abdel-Mohsen, Mohamed[a]

Gal9 can directly expand HIV reservoirs in tissues



PLOS BIOLOGY

Neutrophils promote T-cell activation through the regulated release of CD44-bound Galectin-9 from the cell surface during HIV infection

Garett Dunsmore, Eliana Perez Rosero, Shima Shahbaz, Deanna M. Santer, Juan Jovel, Paige Lacy, Stan Houston, Shokrollah Elahi

Gal9 activates T cells and myeloid cells

frontiers

Galectin-9 Mediates HIV Transcription by Inducing TCR-Dependent ERK Signaling

Florent Colomb [1], Leila B Giron [1], Thomas A Premeaux [2], Brooks I Mitchell [2], Toshiro Niki [3] [4], Emmanouil Papasavvas [1], Luis J Montaner [1], Lishomwa C Ndhlovu [2], Mohamed Abdel-Mohsen [1]

Gal9 activates T cells by inducing non-specific TCR signaling, which can be harmful

Marker	Relationship Observed	Function (published literature)
MIP-1a	▼ initial level = expansion	B-chemokine produced by CD8+ T cells, binds to CCR5, higher levels may be associated with better HIV clinical status
ITAC	▼ initial level = expansion	Higher levels shown to be associated with protection from HIV infection in discordant couples
IL-17	▼ initial level = expansion	Lower expression associated with more exhaustion and immune activation

PNAS

Higher macrophage inflammatory protein (MIP)-1α and MIP-1β levels from CD8$^+$ T cells are associated with asymptomatic HIV-1 infection

Fiorenza Cocchi,[*†] Anthony L. DeVico,[*] Robert Yarchoan,[‡] Robert Redfield,[*] Farley Cleghorn,[*] William A. Blattner,[*] Alfredo Garzino-Demo,[*] Sandra Colombini-Hatch,[*] David Margolis,[*] and Robert C. Gallo[*]

Retrovirology

Elevated levels of inflammatory plasma biomarkers are associated with risk of HIV infection

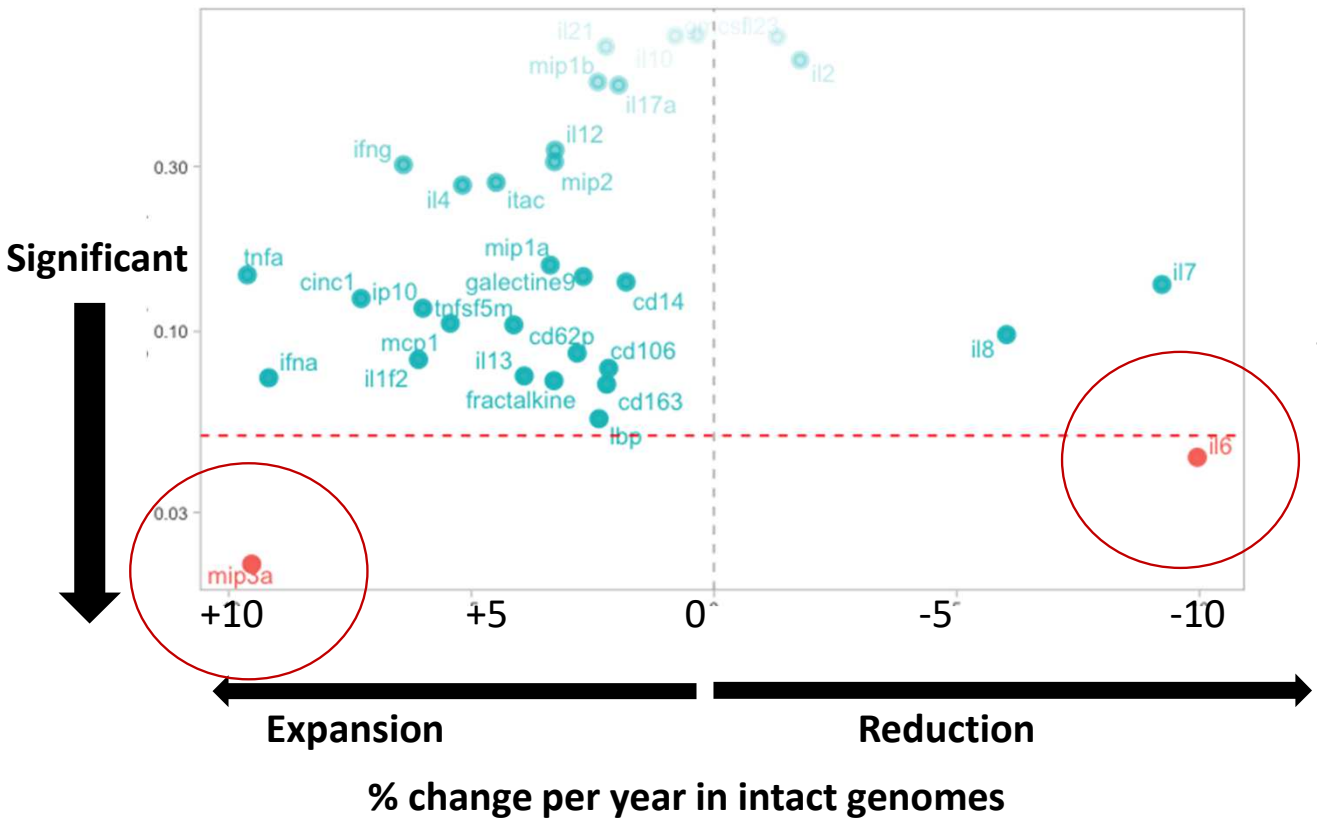
Samantha McInally, Kristin Wall, Tianwei Yu, Rabindra Tirouvanziam, William Kilembe, Jill Gilmour, Susan A. Allen & Eric Hunter

frontiers

A Low Frequency of IL-17-Producing CD8$^+$ T-Cells Is Associated With Persistent Immune Activation in People Living With HIV Despite HAART-Induced Viral Suppression

Federico Perdomo-Celis[1], Manuel G. Feria[1], Natalia A. Taborda[1,2] and Maria T. Rugeles[1*]

Effects of longitudinal cytokine changes on intact genome trajectories



For each 10-fold increase of MIP-3a over time, there was a concurrent 9.5% greater decay per year of intact genomes (p=0.02)

For each 10-fold reduction of IL-6, there was a concurrent 10% greater decay per year of intact genomes (0=0.043)

Marker	Relationship Observed	Function (published literature)
MIP-3a	▲ levels over time = greater decay	Potential antiviral and microbicidal properties
IL-6	▼ levels over time = greater decay	Levels linked to adverse outcomes in HIV

Note: The direction of causation is less clear for covariates that change over time.

ORIGINAL ARTICLE: CCL20/MIP3α is a Novel Anti-HIV-1 Molecule of the Human Female Reproductive Tract

Mimi Ghosh, Zheng Shen, Todd M. Schaefer, John V. Fahey, Phalguni Gupta, Charles R. Wira

Factors Associated With Plasma IL-6 Levels During HIV Infection

Álvaro H. Borges,[1] Jemma L. O'Connor,[2] Andrew N. Phillips,[2] Frederikke F. Rönsholt,[3] Sarah Pett,[2,4,5] Michael J. Vjecha,[6] Martyn A. French,[7,8] and Jens D. Lundgren[1], for the INSIGHT SMART and ESPRIT Study Groups and the SILCAAT Scientific Committee

Summary

- The extent of HIV decay was predicted by baseline galectin-9 levels (lower initial Gal-9 = greater viral decay over time).

- Galectin-9 was the host factor most strongly associated with subsequent intact HIV decay, in alignment with its established roles in regulation of HIV expression and cytotoxic immunity.

- MIP-3a and IL-6 kinetics correlated with intact HIV kinetics.

- Next steps:
  - Distinguish factors associated with defective decay dynamics
  - Investigate whether individuals with lower Gal-9 levels respond better to reservoir reduction strategies
  - Consider investigations using Gal-9 inhibition in HIV cure strategies

THANK YOU!

Acknowledgements

UCSF Division of HIV/ID/GM
- Steve Deeks
- Diane Havlir
- Monica Gandhi
- **Sergio Serrano-Villar**

UCSF Division of Exp Med
- Tim Henrich
- Peter Hunt
- Rachel Rutishauser

UCSF Dept of Biostatistics
- **Peter Bacchetti**
- Jeff Martin

Pillai Lab / VRI
- **Satish Pillai**
- Clara DiGermanio
- Akshay Gupta

SCOPE Team
- **Becky Hoh**
- Viva Tai

Johns Hopkins SOM
- Robert Siliciano
- Janet Siliciano
- Subul Beg
- Jun Lai

Accelevir Diagnostics
- Greg Laird
- Kristen Ritter

Grant Support
- K23 A137522
- DARE Collaboratory
  - AI096109
  - A127966
- UCSF/Gladstone CFAR
  - P30 AI027763
  - R24 AI067039
- amfAR Institute
  - 109301
- I4C Collaboratory
- Beat-HIV Collaboratory
- HHMI
- Gates Foundation

We are grateful to the SCOPE study participants!