CIRCULATING IMMUNE PREDICTORS OF INTACT HIV RESERVOIR DECAY DURING LONG-TERM ART

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Sergio Serrano-Villar[1,2], Akshay Gala[3], Peter Bachetti[1], Clara di Germanio[3], Lillian B. Cohn[4], Peter W. Hunt[1], Greg Laird[5], Satish K. Pillai[3], Steven G. Deeks[1], and Michael Peluso[1]

[1]University of San Francisco California, US. [2] University Hospital Ramón y Cajal, IRYCIS, CIBERINFEC, Madrid, Spain [3]Vitalant Research Institute, San Francisco, California, US.

[4]Fred Hutchinson Cancer Research Center, Seattle, Washington, US. [5]Accelevir Diagnostics, Baltimore, MA, US, Spain.

BACKGROUND

- The HIV reservoir is not stable during antiretroviral therapy (ART).
- Cells harboring intact genomes decay more rapidly than those with defective genomes, particularly during the first several years of therapy.
- There is substantial variability in the intact reservoir dynamics across PWH (Peluso et al., JCI Insight 2020; Gandhi et al., JID 2020).
- The host factors associated with the rate of decay have not been characterized.
- We aimed to address whether a single baseline measurement of inflammatory biomarkers in ART-suppressed individuals can predict long-term changes in the frequency of intact proviruses over time and if changes in inflammatory biomarkers reflect concomitant changes in the frequency of intact proviruses.

METHODS

- Outcomes: Measured intact proviruses using IPDA (Accelevir Diagnostics) on cryopreserved PBMCs (UCSF SCOPE cohort) and fit linear spline models with a knot at seven years and a random intercept and slope up to the knot, as in prior study (Peluso et al., JCI Insight 2020).
- Predictors: 32 pro-inflammatory and regulatory cytokines in plasma measured using Luminex bead-based immunoassay
- We estimated the influence of baseline cytokine levels and trajectories on intact HIV kinetics during the first 7 years of ART

RESULTS

Characteristics of the study population	
Overall	(N=76)
Gender	
Female	3 (3.9%)
Male	72 (94.7%)
Transgender Women	1 (1.3%)
Age at baseline (years), mean (SD)	48.8 (9.6)
Race	
African American	9 (11.8%)
Asian	1 (1.3%)
Latino	6 (7.9%)
Mixed	1 (1.3%)
Pacific Islander	1 (1.3%)
White	57 (75%)
Year of HIV infection, median (min, max)	2000 (1980, 2010)
CD4 nadir (cells/uL), median (P25, P75)	186 (61, 320)
CD4 counts at baseline (cells/uL), median (P25, P75)	632 (460, 815)
CD8 counts at baseline (cells/uL), median (P25, P75)	921 (712, 1110)
CD4/CD8 ratio at baseline, median (P25, P75)	0.65 (0.46, 1.06)
Time from VS to first sample (years), median (P25, P75)	1.8 (0.3, 4.4)
Study follow-up (years), median (P25, P75)	7.0 (5.8, 8.3)
On ART	74 (100%)
HIV RNA <40 cop/mL	74 (100%)

Baseline galectin-9 was the marker most strongly associated with decay of the intact reservoir. For each 10-fold lower Gal-9, there was a 45% faster reservoir decay over the subsequent 7 years.

RESULTS

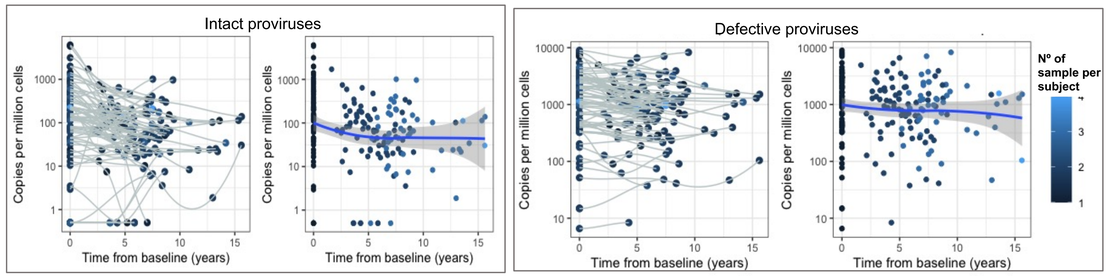


Figure 1. Overall intact (left panels) and defective (right panels) HIV genomes trajectories. The individual trajectories are shown in the left, and the smoothed mean and 95% confidence intervals generated using the loess function in R software (package ggplot) are shown on the right.

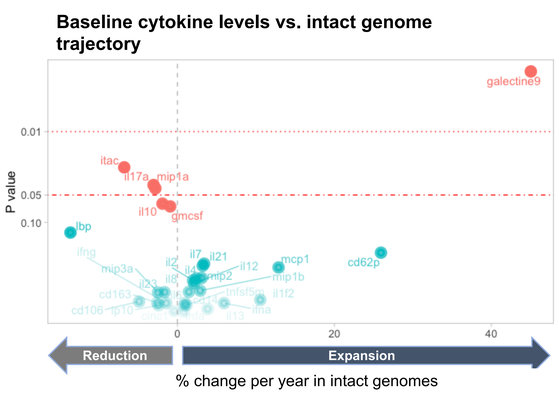


Figure 2. Effect of 10-fold higher baseline cytokine level on intact genome trajectories.
In red, cytokines with P values <0.10.
For each Gal9 10-fold increase at baseline, there was a mean 45% greater increase of intact HIV genomes per year (p = 0.0021). This corresponds to 45% faster decay for each 10-fold lower baseline Gal-9.

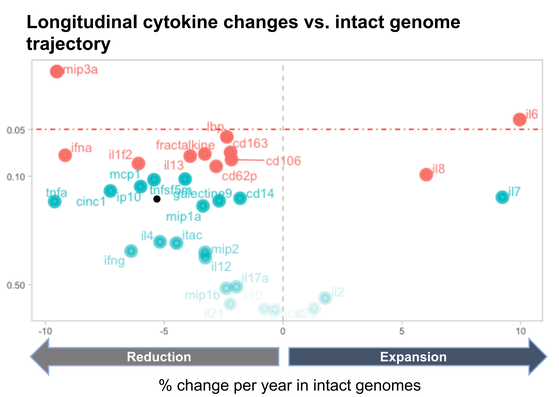


Figure 3. Effect of 10-fold higher cytokine changes on intact genome trajectories.
In red, cytokines with P values <0.10.
For each 10-fold increase of MIP-3α over time, we observed a concurrent 9.5% faster decay of intact HIV genomes (p=0.021), while for each 10-fold increased of IL-6, intact genomes increased 10% faster per year (p=0.043)

RESULTS

- We studied 76 PWH on effective ART for a median of 7 (IQR 6 - 8) years, providing a median of 3 (2 – 4) samples during the follow-up. Median nadir CD4 was 186 (61 – 320) cells/uL and median proximal CD4 counts at the first time point sampled were 632 cells/uL (480 – 815).
- Baseline galectin-9 was the most predictive marker of intact HIV kinetics.
- In contrast, lower baseline ITAC, IL-17, and MIP-1α were predictive of intact HIV increases (**figure 2**).
- MIP-3α and IL-6 exhibited the strongest associations between longitudinal changes in cytokine level during ART and intact HIV kinetics (**figure 3**).

CONCLUSIONS

- Galectin-9 was the host factor most strongly associated with subsequent intact HIV decay (lower initial Gal9 = greater viral decay over time), in alignment with its established roles in regulating HIV expression and cytotoxic immunity.
- MIP-3α and IL-6 changes over time correlated with intact HIV kinetics.

NEXT STEPS

- Investigate whether individuals with lower Gal-9 levels respond better to reservoir reduction strategies
- Consider investigations using Gal-9 inhibition in HIV cure strategies.

ADDITIONAL INFORMATION

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Author Contact Information

Sergio Serrano-Villar, MD, PhD
Department of Infectious Diseases, Hospital Universitario Ramón y Cajal, IRYCIS, CIBERINFEC
Madrid, Spain

sergio.serrano@salud.madrid.org
@serranovillar