Select Host Restriction Factors Are Associated with HIV Persistence During Antiretroviral Therapy

Mohamed Abdel-Mohsen[1,2], Leonard Chavez[1], Charlene Wang[1,3], Matthew C. Strain[4,5], Xutao Deng[1], Christopher D. Pilcher[2], Teri Liegler[2], Douglas D. Richman[4,5], Steven G. Deeks[2], and Satish K. Pillai[1,6]

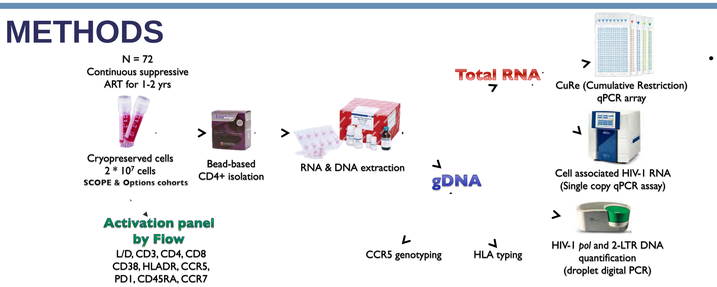
[1]Blood Systems Research Institute, San Francisco, CA; [2]Department of Medicine, University of California, San Francisco, CA; [3]Emory University, Atlanta, GA; [4]University of California, San Diego, La Jolla, CA; [5]Veterans Affairs San Diego Healthcare System, San Diego, CA; [6]Department of Laboratory Medicine, University of California, San Francisco, CA

Contact: Satish.Pillai@ucsf.edu

OBJECTIVE

- Although antiretroviral therapy (ART) results in sustained inhibition of HIV replication, the virus may continue to spread at low levels. Moreover, ART has no effect on the "latent" reservoir, composed of previously infected resting CD4+ cells.
- Identifying host determinants governing latency, viral production and reservoir size *in vivo* is an important step in developing effective strategies to clear the latent reservoir and cure HIV infection. The potential impact of cell-intrinsic immunity on viral persistence during antiretroviral therapy (ART) is unknown.
- We investigated the relevance of a comprehensive panel of anti-HIV-1 host restriction factors to multiple established virologic and immunologic measures of viral persistence in a cohort of 72 HIV-infected, ART-suppressed individuals.

METHODS



- **Spearman's rho, two-tailed Mann-Whitney tests, and Bonferroni correction were used to determine statistical significance.**

RESULTS

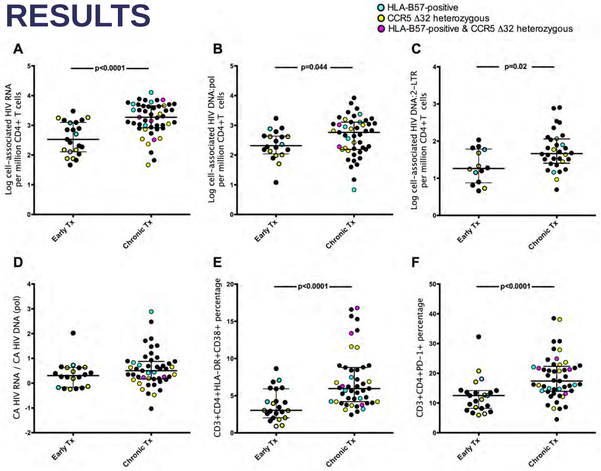


Figure 1. HIV reservoir measurements are highly variable across individuals. Multiple virologic and immunologic measures of the HIV reservoir are displayed for 72 individuals on suppressive ART. Early Tx and Chronic Tx labels represent individuals who initiated ART <1 year after infection and >1 year after infection, respectively. Individuals who were heterozygous for the CCR5 delta-32 mutation are highlighted in yellow, individuals carrying the HLA-B57 allele are highlighted in cyan, and individuals with both of these genetic features are highlighted in pink. Lines and error bars represent median and interquartile range. P values were obtained using Mann–Whitney tests. CA, cell-associated.

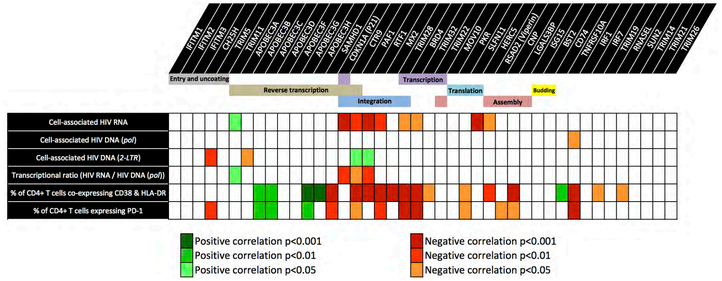


Figure 2: Select host restriction factors are associated with measures of HIV persistence during ART. Restriction factors are arranged by targeted viral life cycle stage (when known), displayed under factor names. The Bonferroni-corrected p-value threshold is p<0.0012; correlations highlighted in dark green and dark red were significant after correction. Correlations were evaluated using Spearman's rank correlation coefficient tests.

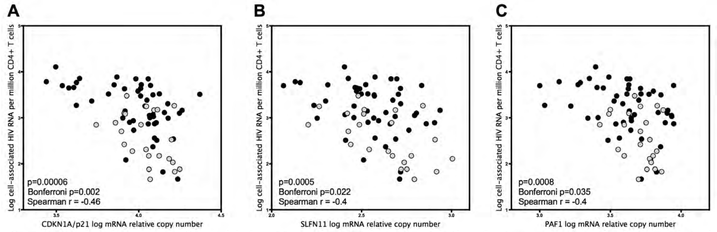


Figure 3. Expression levels of p21, schlafen 11, and PAF1 host restriction factors are negatively correlated with CD4+ T cell-associated HIV RNA in ART-suppressed individuals. Both raw and Bonferroni-corrected p-values are displayed for each correlation. Individuals who initiated ART during early and chronic infection are labeled with silver and black dots, respectively. p21 and schlafen 11 have been previously associated with HIV elite control.

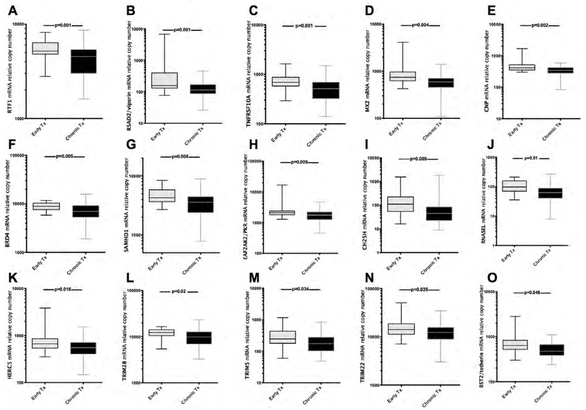


Figure 4. Host restriction factor expression is elevated in individuals who initiated ART during early infection. Early Tx and Chronic Tx labels represent individuals who initiated ART <1 year after infection and >1 year after infection, respectively. Whisker bars represent minimum to maximum range. All statistical comparisons were performed using a Mann–Whitney test.

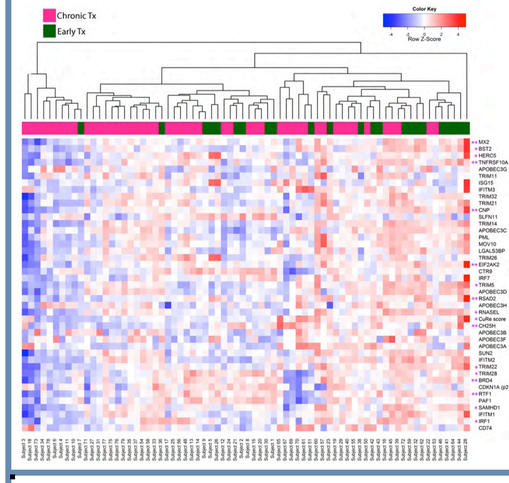


Figure 5. Heat map and dendrogram depicting host restriction factor gene expression patterns in 72 HIV-infected individuals on suppressive ART. Heat colors show standardized Z-scores across samples; red indicates upregulated expression, and blue indicates downregulated expression. The dendrogram depicting relatedness between individual gene expression profiles was generated using hierarchical clustering with complete linkage.

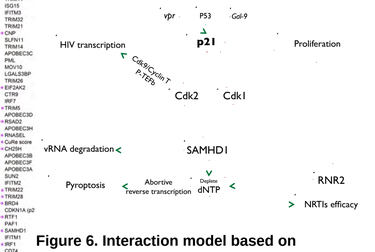


Figure 6. Interaction model based on published, experimentally determined roles of p21 in HIV pathogenesis.

CONCLUSIONS

- A few select intrinsic immune responses modulate HIV persistence during suppressive ART, and may be manipulated to both enhance the efficacy of ART and promote viral eradication through reversal of latency in vivo.
- ART perturbs the regulatory relationship between CD4+ T cell activation and restriction factor expression.
- The enhanced intrinsic immune responses observed in early ART initiators provides another possible justification for universal early administration of ART.
- Eradication efforts may exploit p21, schlafen 11 and PAF1 activity.

Please see our publication for more details: **Abdel-Mohsen *et al.*, AIDS. 2015 Feb 20;29(4):411-20.**

ACKNOWLEDGMENTS

amfAR: 108545-53-RGRL; NIH: R21 AI108503, U19 AI096109, P30 AI027763