Measuring HIV Latency Over Time: Reservoir Stability and Assessing Interventions

Bateson R[1], Crooks AM[1],Cope AB[1], Dahl NP[1], Eron JJ[1], Gay CL[1], Kuruc JD[1], Margolis DM[1], Archin NM[1], Bosch RJ[2].

[1] The University of North Carolina, Chapel Hill, NC, USA; [2] Harvard University, Boston, MA, USA

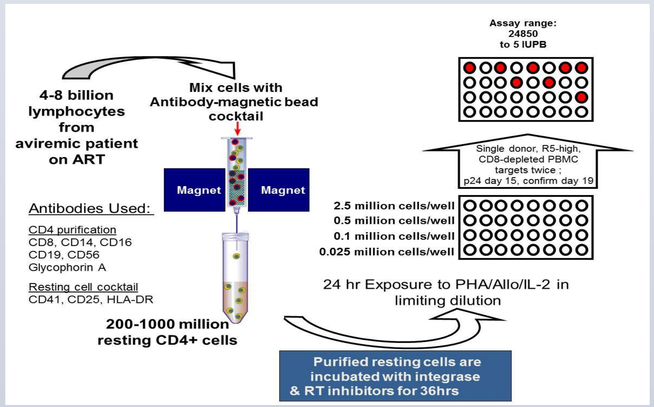
Background

Resting cell infection (RCI) is the major obstacle to an HIV cure, allowing the virus to persist even in patients on long-term antiretroviral therapy (ART). The quantitative viral outgrowth assay (QVOA) yields reliable measurement of RCI. However, the variability of RCI over time on ART, relevant to assess potential effects of anti-latency interventions, has not been fully described. As the ability to reliably measure RCI is necessary to assess potential effects of anti- latency interventions, RCI variability can provide data that will be helpful in determining a threshold for identifying these effects as well as power analyses for designing future cure studies.

Materials & Methods

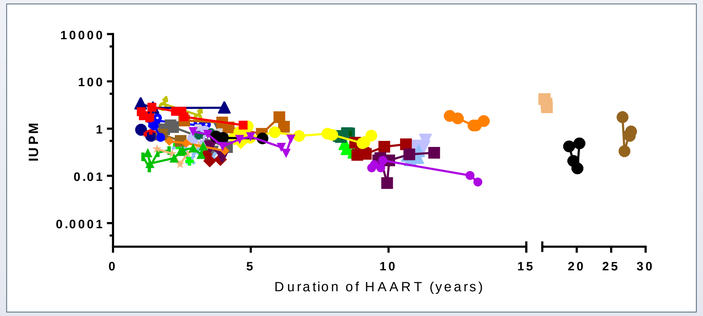
Using the QVOA, we measured RCI in 37 HIV+ participants, on stable suppressive ART who donated resting CD4+ T cells via leukapheresis, over a period of 6 years. Patients initiated ART in acute infection (AHI, n=17), or chronic infection (CHI, n=20) and were studied once HIV RNA was <50 copies/mL for ≥ 6 months. Random effects regression evaluated RCI decay and estimated sources of variability, restricting to 160 RCI measures obtained ≥12 months after ART. Residual plasma viremia was measured using a single copy assay with a limit of detection of <1 HIV RNA c/ml (SCA, Palmer et al, 2003).

The Quantitative Viral Outgrowth Assay



Results

Decay of resting CD4 T-cell infection in virally suppressed patients



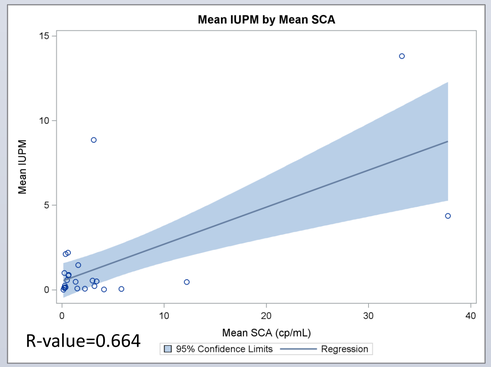
	Number of Patients	Number of RCI measurements*	Half Life (years)		
			Mean	95% confindence interval	p-value
Whole Cohort	37	160	3.6	2.3-8.1	p<0.001
Optimal Suppressed	21	91	3.3	2.0-8.0	p=0.002

*median of 4 measurements per patient with a median of 3 month intervals

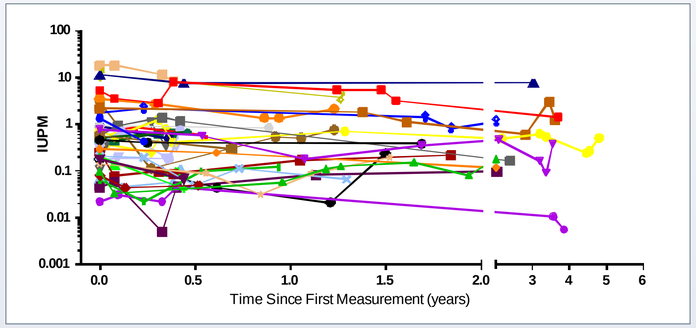
Between the group of optimally suppressed patients and the 16 subjects with viral blips or low-level viremia, there was no evidence that the half-life differed (p=0.68)

There was no evidence of more rapid decay for AHI vs. CHI (p=0.99) after ≥12 months of ART.

Correlation between low level viremia and the size of the resting CD4 reservoir



Reproducibility of the quantitative viral outgrowth assay



RCI reliably estimated longitudinal measurements. Most measurements show less than a two-fold change.

	Observed		Likelihood of decrease based upon model over 2 month period
	Number	Percent	
Pairs of consecutive RCI measurements	123	-	
<2 fold change	81	66%	
>2.5 fold decrease	21	17%	16%
>6 fold decrease	3	2.4%	2.3%

RCI decreases of less than six-fold were rare on stable suppressive ART, suggesting a potential threshold to identify effects of anti-latency therapeutics on RCI.

Conclusions

Consistent with prior studies, RCI decayed with a half-life of 3.6 years (43 months) and a correlation was observed between low level viremia and the size of the reservoir. Based on using large numbers of cells obtained via leukapheresis, RCI was reliably estimated with longitudinal measurements generally showing <2 fold variation from the previous measure. RCI decreases >6 fold were rare on stable suppressive ART, suggesting a potential threshold to identify effects of anti-latency therapeutics on RCI.

Acknowledgements

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