Early Start of ART Affects Late Markers of Immune Senescence

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ABSTRACT:

Background

Despite a dramatic increase in life expectancy, people with HIV on antiretroviral therapy (ART) continue to suffer from higher risks of morbidity and mortality, often due to non-AIDS related illnesses. It is hypothesized that this increased risk is in part due to ongoing immune activation and premature immune senescence. We asked whether initiation of ART during primary HIV infection (PHI) correlated with improved markers of inflammation and immune senescence.

Methods

We recruited 32 subjects: 12 HIV+ men who started ART during PHI (Group 1), 10 HIV+ men who deferred ART until chronic HIV infection (CHI, Group 2) and 10 HIV-negative controls (Group 3). All subjects were men who have sex with men (MSM) between 18 - 45 years old with no comorbid chronic infections, immune modulating conditions/treatments, or IV drug use, and matched for EBV, CMV and RPR status. HIV-positive subjects were stably virologically suppressed. We used subject serum and plasma samples to perform ELISA, ECL, and xMAP assays to measure levels of soluble factors. We cryopreserved peripheral blood mononuclear cells (PBMCs) for flow cytometric measurements.

Results

Group 1 subjects began ART 31 ± 9 days after their estimated date of infection (EDOI) with HIV-1 and had been treated for 8.1 years at the time of screening. Group 2 began ART 3.7 ± 1.6 years after their EDOI and had been treated for 5.3 years. Group 1 subjects had higher CD4 counts (901 versus 605 cells/mm3 and CD4/CD8 T cell ratios (1.81 versus 0.89) compared to Group 2. The median plasma levels of inflammatory markers (CRP, fibrinogen, IL-1β, IL-6, TNF-α) were statistically the same between all groups (see table). Other markers of immune dysregulation (% monocytes, sCD14, CD8 T cell activation, Th17/Treg ratio) were equally abnormal in both HIV+ groups compared to the HIV-negative controls. However, Group 1 subjects did exhibit improved values in several markers of immune senescence (naïve/memory T cell ratio, % terminally differentiated CD8 T cells, % senescent CD4+ T cells, marker of vaccine response in CD4 T cells, CD8 T cell telomere lengths) compared to Group 2 subjects.

Conclusions

Initiation of ART during primary HIV-1 infection correlated with normalization of markers of immune senescence. Timing of ART initiation did not appear to correlate with any difference in select markers of inflammation or immune activation. These improvements in senescence markers may further support early treatment in patients with HIV.

INTRODUCTION:

- HIV+ people on ART continue to suffer higher morbidity and mortality, often due to non-AIDS defining illnesses, including:
  CVD, malignancies, liver disease, renal disease, neurocognitive decline, osteoporosis, age-related frailty
- This excess risk may be, in part, due to ongoing immune activation and premature immune senescence.
- Will starting ART during primary HIV infection alter markers of inflammation and immune senescence?

RESULTS:

	Group 1 HIV+ (PHI)	Group 2 HIV+ (CHI)	Group 3 HIV-negative	p-value
Age at screening (y)	40 ± 5	40 ± 5	34 ± 9	0.0414*
% Male	100	100	100	1.0000
% MSM	100	100	100	1.0000
% White (Non-Hispanic)	75	50	40	0.2292
% CMV IgG positive	92	90	60	0.1152
% EBV IgG positive	92	100	100	0.4231
% RPR NR	92	80	100	0.3044
Time to ART (days)	31 ± 5	1352 ± 587	NA	<0.0001
Time on ART (years)	8.1 ± 2.3	5.7 ± 3.5	NA	0.0272
CD4 count (cells/mm^3)	901 ± 206	605 ± 223	735 ±272	0.0201
CD4 %	48 ± 9	32 ± 11	42 ± 8	0.0013
CD4/CD8 ratio	1.81 ± 0.67	0.89 ± 0.51	1.42 ± 0.50	0.0033

Table 1: Demographics and initial lab results. Groups were statistically matched for age*, gender, HIV risk factor, race/ethnicity, EBV/CMV/RPR status. *3-way ANOVA showed a difference in age, which was not statistically significant between any 2 groups by t-tests to a level <0.05.

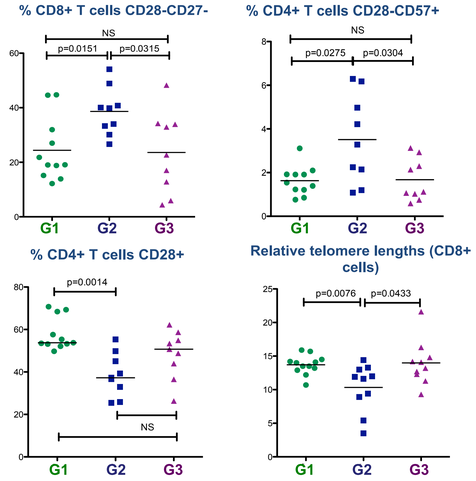
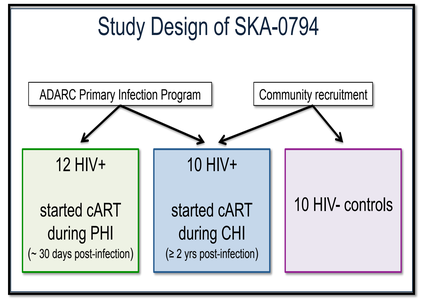


Figure 1 and Table 2: Results of experimental assays. Figure 1 demonstrates sample results from assays on markers of immune senescence, showing normalization/improvement in Group 1 (PHI) over Group 2 (CHI). Table 2 summarizes the main results of assays performed in this portion of the study, with medians and IQR (inter-quartile range) listed, as well as the p-value for 3-way ANOVA comparing all groups. The results column summarizes the conclusions drawn from pairwise statistical comparisons.

		Group 1 (HIV+, started ART during PHI)		Group 2 (HIV+, started ART during CHI)		Group 3 (HIV-negative)			
		Median	IQR	Median	IQR	Median	IQR	p-value	Results
Markers of immune senescence	Naïve/Memory T cell ratio	1.86	0.96 - 2.6	0.71	0.57 - 1.6	0.47	0.30 - 1.8	0.0360	G1 > G2/G3
	Terminally differentiated CD8+T cells (%CD27-CD28-)	19.1	15.2 - 32.0	39.1	30.0 - 44.8	22.7	9.4 - 34.1	0.0386	G2 > G1/G3
	Senescent CD4+ T cells (%CD28-CD57+)	1.54	1.2 - 1.9	3.29	1.7 - 5.6	1.12	0.89 - 2.6	0.0057	G2 > G1/G3
	Marker of vaccine response (%CD4+CD28+)	53.8	53.1 - 68.4	37.3	29.4 - 47.4	50.7	40.2 - 56.8	0.0006	G1 > G2
	Telomere lengths in CD8+ cells (relative to 1301 cells)	13.8	13.0 - 14.4	11.8	8.0 - 13.1	13.7	12.0 - 15.2	0.0116	G2 < G1/G3
Markers of immune activation / coagulation	Plasma CRP (mg/L)	0.36	0.19 - 0.95	0.24	0.13 - 0.32	0.22	0.13 - 0.60	0.2008	NS
	Plasma Fibrinogen (mg/dL)	207	165 - 444	196	180 - 325	175	147 - 247	0.3550	NS
	Plasma IL-1β (ng/mL)	0.26	0.18 - 0.32	0.23	0.08 - 0.34	0.23	0.15 - 0.38	0.5139	NS
	Plasma IL-6 (ng/mL)	0.93	0.54 - 1.2	1.02	0.76 - 1.6	0.90	0.62 - 1.0	0.2395	NS
	Plasma TNF-α (ng/mL)	6.18	5.0 - 8.2	6.38	5.7 - 8.8	5.00	4.2 - 5.4	0.9006	NS
	Monocytes (% of CD3- lymphocytes)	2.50	2.1 - 4.8	2.23	1.4 - 7.3	1.17	0.55 - 1.7	0.0300	G1/G2 > G3
	Serum sCD14 (ng/mL)	2035	1848 - 2280	1930	1805 - 2055	1510	1395 - 1605	0.0003	G1/G2 > G3
	Activated CD8+ T cells (% CD38+HLA-DR+)	1.45	1.2 - 2.5	1.80	1.2 - 2.6	1.11	0.60 - 1.4	0.0433	G1/G2 > G3
	Th17/Treg ratio	0.36	0.24 - 0.43	0.33	0.28 - 0.44	0.46	0.41 - 0.71	0.0145	G1/G2 < G3

METHODS :



All subjects were MSM, between 18-45 years old with no comorbid infections, immune modulating conditions/ treatments, or IV drug use. We matched for EBV, CMV and RPR status. HIV+ subjects were stably virologically suppressed. We performed ELISA, ECL, and xMAP assays on frozen serum/ plasma samples and cryopreserved PBMCs for flow cytometry.

Figure 2: Study design of SKA-0794. We recruited 12 HIV+ MSM who started ART during PHI (Group 1), 10 HIV+ MSM who deferred ART until chronic HIV infection (Group 2), and 10 HIV- MSM as controls.

CONCLUSIONS:

1. **Initiation of ART during primary HIV infection correlated with normalization or improvement of several markers of immune senescence.**
2. **Initiation of ART during primary HIV infection did not appear to correlate with any difference in select markers of inflammation or immune activation.**
3. **These data may further support early treatment in patients with HIV.**

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ACKOWLEDGEMENTS:

Supported in part by grant # UL1 TR000043 from the National Center for Advancing Translational Sciences (NCATS, National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program

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