FDG PET/CT Imaging of Lymph Nodes as a Measure of the HIV Reservoir in Humans

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Background

▪HIV persists indefinitely in the setting of combination antiretroviral therapy (ART), with most of the reservoir located in difficult-to-access lymphoid tissues.

▪There exists a complex association between HIV production/replication and inflammation during ART. HIV production/replication during ART is associated with higher levels of T cell activation and inflammation, while an inflammatory environment likely contributes to HIV persistence by (1) providing target cells for HIV spread, (2) blunting adaptive immune responses and/or (3) stimulating homeostatic proliferation.

▪Fluorodeoxyglucose Positron Emission Tomography - Computed Tomography (FDG PET/CT) is an imaging modality that quantifies inflammation in lymph node tissues

▪We assessed the association between lymph node inflammation and the frequency of CD4+ T cells harbouring integrated HIV DNA in blood (the "reservoir") in those with either therapeutic control of HIV (ART) or host-mediated control of HIV ("elite" controllers). HIV-uninfected controls and those with poorly controlled, untreated HIV disease were also studied.

Methods

▪74 participants, ages 40 and older, were recruited from the San Francisco-based SCOPE cohort.

- HIV-infected, on ART, with undetectable viral load (n=34)
- HIV-infected, off ART with undetectable viral load (n=7)
- HIV-infected, off ART with detectable viral load (n=3)
- HIV-uninfected controls matched by age, gender, race, and Framingham Score (n=29).

▪FDG uptake in the axillary lymph nodes (LN) was assessed as a mean standardized uptake value (SUV). Target to background ratio (TBR) for LN was generated by dividing LN SUV by blood background SUV.

▪Viral persistence was measured using frequency of cells harbouring integrated HIV DNA in CD+ T cells.

▪Inflammatory markers were measured by the Frederick National Laboratory for Cancer Research in Frederick, MD.

Results

Table 1: Baseline characteristics of participants stratified by HIV status

Parameter	HIV- (n=29)	HIV+ (n=45)	p-value
Demographic Factors			
Age (years)	53 (49, 59)	52 (46, 56)	0.143
Race			0.118
Caucasian	41%	67%	
African-American	48%	22%	
Latino	7%	9%	
Other	4%	2%	
Gender			-
Male	100%	100%	
Female	0%	0%	
BMI	27.0, (23.1, 29.2)	26.2 (24.0, 28.7)	0.550
Comorbidities			
Family History	10%	36%	0.015
Hypertension	21%	24%	0.708
Diabetes	0%	4%	0.250
Statins	5%	11%	0.238
Smoke ever	62%	64%	0.836
Aspirin use	10%	24%	0.131
Hx of MI or Stroke	4%	2%	0.751
Hep C	7%	22%	0.081
Labs			
Total Cholesterol	173 (154, 199)	178 (152, 206)	0.987
LDL	108 (84, 120)	110 (90, 129)	0.469
HDL	49 (44, 63)	46 (37, 53)	0.068
Triglycerides	85 (63, 117)	91 (70, 132)	0.499
Creatinine	0.91 (0.81, 1.04)	0.96 (0.86, 1.07)	0.189
Inflammatory Markers			
D-Dimer	0.39 (0.28, 0.53)	0.34 (0.25, 0.49)	0.410
CRP	1.19 (0.41, 5.08)	1.29 (0.53, 2.69)	0.834
sCD14	1.52 (1.34, 1.75)	1.75 (1.40, 1.95)	0.082
sCD163	307.46 (224.23, 431.61)	455.73 (344.37, 650.55)	**0.002**
IL-6	0.87 (0.61, 1.38)	0.86 (0.56, 1.76)	0.849
MCP 1	213.76 (158.53, 259.17)	210.09 (159.55, 360.06)	0.442
TF	71.66 (52.95, 81.96)	68.83 (55.30, 83.34)	0.995
Framingham Risk Score	5 (3, 9)	6 (3, 7)	0.986

p-values calculated using Chi-Square Goodness of Fit Tests and Wilcoxon non-Parametric tests

Results

Figure 1: FDG PET/CT Imaging of Node Activity

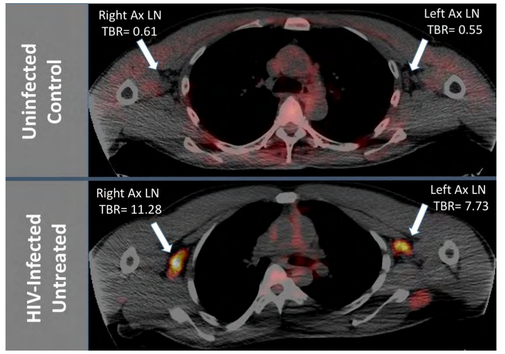


Table 2: Association of LN Activity to HIV reservoir, CD4+ T cell activation, and inflammatory marker

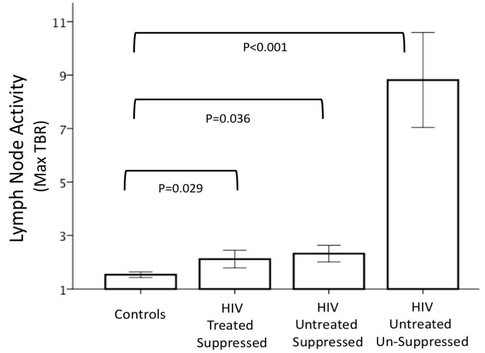
Group	Marker	Lymph node activation (maxmaxTBR)
Viral markers	Viral load	r = 0.556; p < 0.001
	Integrated HIV DNA	*r=0.85, p-0.015
Markers of Inflammation and thrombosis	D-dimer	r = 0.32; p = 0.044
	CRP	r = 0.15; p = 0.34
	IL6	r = 0.21; p = 0.19
CD4⁺ T cell markers	% CD4⁺ in total T cells	r = -0.341; p = 0.029
	% HLA-DR⁺CD38⁺ in CD4⁺ T cells	r = 0.434; p = 0.005
CD8⁺ T cell markers	% CD8⁺ in total T cells	r = 0.363; p = 0.020
	% HLA-DR⁺CD38⁺ in CD8⁺ T cells	r = 0.492; p = 0.001
	% CD28⁻CD57⁻ in CD8⁺ T cells	r = 0.374; p = 0.016
Monocyte Markers	% CD14⁺CD16⁺mono	r = 0.34; p = 0.035
	% CD14⁺CD16⁻ monocytes	r = -0.07; p = 0.68
	% CD14^{dim}CD16⁺ monocytes	r = 0.05; p = 0.78
	% CX3CR1⁺ monocytes	r = 0.21; p = 0.20
	% CCR2⁺ monocytes	r = -0.22; p = 0.16

* Integrated HIV correlation significant in subgroup of elite controllers only.

Disclosure: All authors report no conflict of interest.

Results

Figure 2: Plot of Lymph Node Activity in HIV infected individuals and HIV-uninfected controls



Conclusions

▪Lymph node activity as assessed by FDG PET/CT was higher among HIV-infected individuals on ART and in "elite" controllers as compared to matched HIV-uninfected adults.

▪Lymph node activity was associated with markers of viral persistence (HIV DNA) and T-cell activation.

▪Our findings support the hypothesis that HIV production (and perhaps replication) contribute to inflammation during ART and/or that a chronic inflammatory environment in lymphoid tissues contributes to persistence.

▪FDG PET/CT imaging of the axillary lymph nodes may provide a method to non-invasively measure reservoirs of viral persistence in HIV and assess response to different ART or anti-inflammatory interventions.

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