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Elevated Lymph Node Metabolic Activity During Long-Term Antiretroviral Therapy

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BACKGROUND

Persistence and clonal expansion of HIV infected cells during long term antiretroviral therapy (ART) is a principal obstacle preventing virus eradication in persons with HIV (PWH). Although HIV infected cells are widely distributed in anatomic compartments, c. 98% lymphoid compartments distributed throughout The majority (c. 98%) of HIV infected cells persist in lymphoid tissue, especially lymph nodes despite antiretroviral therapy (ART).(1)

Only a small proportion of HIV infected cells (1-2%) contain replication-competent proviruses, which are responsible for rebound viremia if ART is discontinued; the majority of proviruses are defective, but all proviruses, regardless of replication competence, can contribute to elevated immune activation, which is associated with morbidity and mortality during ART. As a result, understanding the role of persistent HIV infected cell populations in immune activation is imperative, new approaches to evaluate immune activation in HIV will be useful.

Elevated immune activation and inflammation is associated with elevated metabolic activity in anatomic compartments, including lymph nodes, and can be detected in vivo using non invasive imaging approaches. Uptake of ^{18}F-deoxyglucose (FDG) correlates with glycolytic metabolic activity, is characteristic of elevated inflammation, and is highly elevated in inflammatory conditions and neoplastic diseases. FDG uptake can be non-invasively imaged using Positron Emission Tomography (PET). New PET imaging modalities are now available, which can be analyzed in the context of Computed tomography (CT) images; PET/CT image co-registration provides robust quantitative measurements of high resolution dimensional imaging of lymphoid structures, even lymph nodes < 1 cm in diameter. Here we are using PET/CT imaging to investigate levels of FDG uptake in individuals undergoing long term ART.

HYPOTHESIS

Metabolic activity of lymphoid tissue as measured by ^{18}FDG uptake will be detected in lymph nodes in PWH undergoing ART, but will not be greater than established clinical background uptake threshold.

METHODS

Study Participants

- Otherwise healthy PWH on suppressive ART with HIV RNA < 20 copies/mL for >3 years were enrolled in the IRB-approved protocol *Imaging and Biopsy of People with HIV-1 Undergoing Analytic Treatment Interruption (*NCT05419024)

Clinical Evaluation

- Clinical, demographic, virologic and immunologic data were collected for correlative analysis.

Non-invasive Imaging

- Study participants underwent ^{18}F-FDG-PET/CT imaging on the Siemens Biograph™ micro-computed tomography (mCT) and lymph nodes and regions of interest (ROIs) identified in Molecular Imaging in Medicine (MIM©). Volume and ^{18}F uptake levels were determined in regions of interest.

Image Analysis

- ^{18}F-FDG-PET/CT scans were analyzed with MIM®. After initial manual identification of lymph nodes, a board-certified Nuclear Medicine radiologist verified our findings. A semi-automatic MIM® workflow that identified regions of increased metabolic activity reduced reading time.
- Metabolic activity, represented by ^{18}F-FDG uptake, was calculated as standardized uptake value (SUV). SUVmax, location, total lesion glycolysis, and total lymph node volume were measured. An SUVmax $\geq$2.5 was considered elevated based on commonly used cancer thresholds.
- Descriptive statistics were calculated using GraphPad Prism®.

RESULTS

Participant Characteristics

Participant	Age (y)	Sex	Race/Ethnicity	Time on ART (y)	CD4 (cells/μL)	# of LNs
BATI-1	43	M	White/Hispanic	5	562	15
BATI-2	66	M	White/Non-Hispanic	27	413	0
BATI-3	58	M	White/Non-Hispanic	27	558	11
BATI-4	62	M	White/Non-Hispanic	14	547	1
BATI-5	62	M	White/Non-Hispanic	23	607	6
BATI-6	83	M	White/Non-Hispanic	31	310	4

Table 1: Participant Characteristics. Demographic and clinical information is shown at time of ^{18}F-FDG-PET/CT scan. Years (y).

^{18}F-FDG-PET Scans Reveal Lymph Nodes With Elevated Metabolic Activity

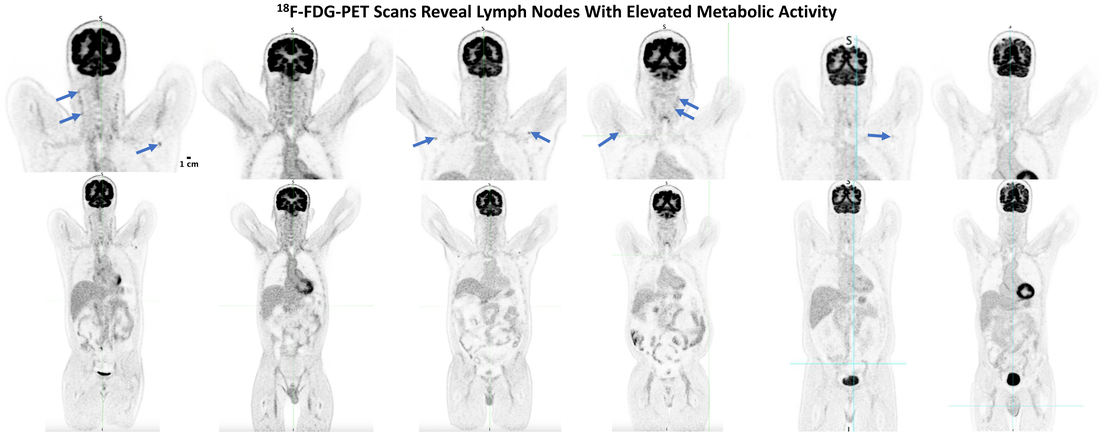


Figure 1: Coronal ^{18}F-FDG-PET images are shown for the whole body (bottom) and higher magnification section (above). LNs with elevated metabolic activity (SUV$\geq$2.5) are indicated with blue arrows.

Metabolic Activity Levels From an ^{18}F-FDG-PET Scan Can Be Visualized With Alternative Color Scales

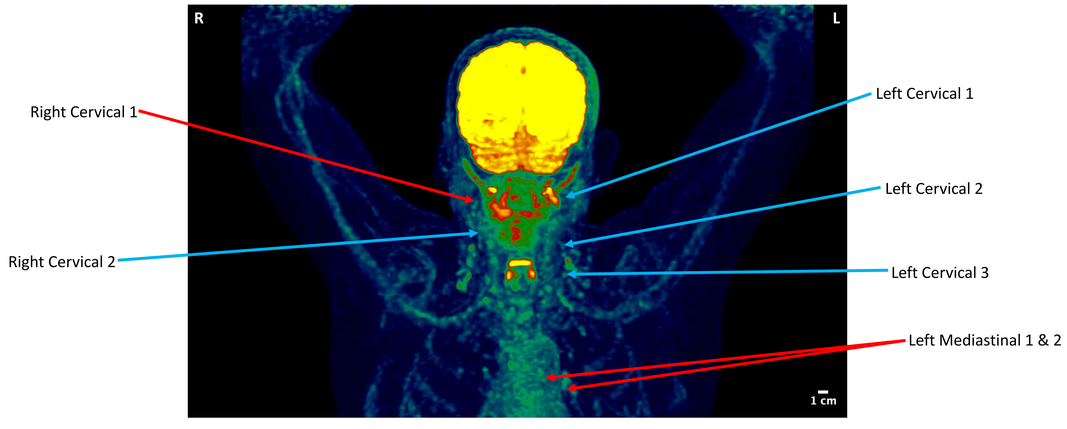


Figure 2: Cervical and Mediastinal Lymph Nodes with and without Elevated Metabolic Activity in ^{18}F-FDG-PET Scan for Participant 3. This PET scan has a different color scheme, which helps identify areas of elevated metabolic uptake more easily. Yellow indicates high levels of uptake. Blue is background uptake. LNs with elevated metabolic activity are indicated by the red arrows and LNs without elevated metabolic activity are denoted by blue arrows.

RESULTS

Lymph Node Metabolic Activity Varies Among PWH on ART

	Elevated Metabolic Activity (SUV ≥ 2.5)				Normal Metabolic Activity (SUV < 2.5)			
Participant	# of LNs	Mean (SUV_{bw})	Volume (mL)	TLG^{+} (SUV_{bw} x mL)	# of LNs	Mean (SUV_{bw})	Volume (mL)	TLG (SUV_{bw} x mL)
BATI-1	14	4.43	0.21	0.816	1	2.04	0.05	0.10
BATI-2	0	NA	NA	NA	0	NA	NA	NA
BATI-3	7	3.30	0.17	0.60	4	1.52	0.43	0.39
BATI-4	1	2.78	0.05	0.15	0	NA	NA	NA
BATI-5	2	2.87	0.03	0.09	4	1.37	0.35	0.47
BATI-6	0	NA	NA	NA	4	1.27	0.21	0.27

Table 2: ^{18}F-FDG-PET/CT Scan Results. LN were identified in 5/6 participants. For values with >1 LN, values are averaged. $^{+}$TLG Total Lesion Glycolysis

Total Lesion Glycolysis and Total Volume Trends Differ By Metabolic Activity

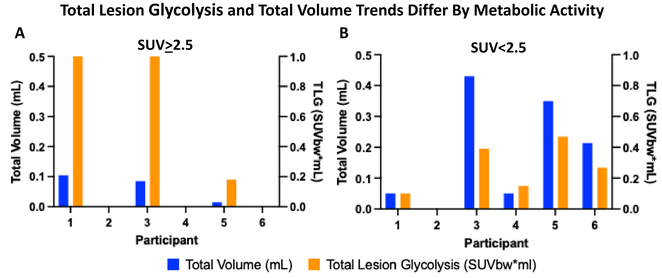


Figure 3: Average total lesion glycolysis (SUVbw*mL) vs. average total volume (mL) for (A) LNs with SUV_{max} $\geq$2.5 and (B) LNs with SUV_{max} < 2.5.

SUMMARY

- Elevated metabolic activity is present in LNs of PWH on long-term effective ART.
  - Suggests ongoing immune activation is detectable by PET/CT in PWH with elevated LN metabolic activity even when plasma HIV RNA < 20 copies/mL.
- Non-invasive functional imaging will facilitate evaluation of lymphoid tissues to determine mechanisms of immune and viral activation during ART.

FUTURE DIRECTIONS

- Assess immune and virologic correlates of LN metabolic activity during well-controlled HIV.
- Elucidate the mechanisms of ongoing immune activation and HIV persistence in lymphoid tissues, focusing on clonal expansion.
- Explore the effects of analytic treatment interruption (ATI) on lymphoid tissue metabolic uptake.
- Analyze uptake in both males and females, as well as by age.

ADDITIONAL KEY INFORMATION

Thank you to our participants!

1. Bronnimann et al., Frontiers in Immunology. 2018; 9(20)
2. Takahashi et al., Thoracic Cancer. 2019; 10(3)

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