^{18}F-FDG-PET/CT abnormalities are associated with higher risk of IRIS in HIV

Abstract # 238

National Institute of Allergy and Infectious Diseases

DA. Hammoud[1], GZ. Papadakis[2], A. Boulougoura[3], V. Sheikh[4], LE. Dodd[5], J. Wang[6], A. Kibiy[7], J. Micanl[3], C. Millo[2] and I. Sereti[3]

[1]Center for Infectious Disease Imaging, NIH, Bethesda, MD, USA, [2]Positron Emission Tomography Department, NIH, Bethesda, MD, USA, [3]National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA, [4]US Food and Drug Administration, Silver Spring, MD, USA, [5]National Institute of Allergy and Infectious Diseases, NIH, Rockville, MD, USA, [6]Leidos Biomedical Research, Rockville, MD, USA, [7]Leidos Biomedical Research, Bethesda, MD, USA

10 Center Drive, Bldg 10/11B07A
Bethesda, MD 20892
isereti@niaid.nih.gov
P: 301-496-5533

Background and Study Rationale

Immune reconstitution Inflammatory Syndrome (IRIS) in HIV infection represents the unexpected clinical deterioration that could be the result of either worsening (paradoxical) or uncovering (unmasking) of an infection or malignancy after the start of antiretroviral therapy (ART) despite control of HIV viremia. Major predictors of IRIS are low CD4+ cell count, high plasma HIV RNA level, opportunistic infections (OIs) when starting ART, and a short time between starting ART and treatment initiation for OIs. In addition, biomarkers associated with the coagulation cascade (D-dimer), monocyte activation (soluble [s] CD14), and inflammation (C-reactive protein [CRP] and proinflammatory or Th1 cytokines) have been associated with an increased risk of IRIS. We hypothesized that ^{18}F-FDG-PET/CT scan could be used to assess the acute effects of ART initiation on HIV+ patients with advanced disease, potentially correlate with the level of biomarkers and assist in defining a distinct pattern of those patients who are at high risk of developing IRIS.

Study Design & Methods

A. 30 HIV+/ART-naïve patients with CD4<100 cells were included in this prospective study.
B. Patients underwent ^{18}F-FDG-PET/CT scans pre-ART (baseline) and 4-8 weeks after ART initiation. Regions of interest (ROI) were delineated over liver, spleen, bone marrow (BM), axillary and inguinal lymph nodes (LN). SUV mean, SUVmax between baseline and post-ART among various groups were compared (Paired T-test). The lesion load was assessed as areas of non-physiologic FDG uptake (infectious/neoplastic) throughout the body with SUV > 4; Total glycolytic activity (TGA) values were obtained. Baseline TGA values and change from baseline values (between follow-up and baseline scans) were then compared between groups (Wilcoxon rank sum statistics).
C. ELISA-based assays were performed to obtain values for biomarkers at baseline and Post-ART.

Results

Table 1: Characteristics of study participants at baseline (median values reported with 25th and 75th percentile).

Study Groups	All patients (n=30)	Non-IRIS (n=20)	IRIS (n=10)	P-value IRIS vs Non-IRIS	Mycobacterial IRIS (N=6)	P-value Myco-IRIS vs Non-IRIS
Age, years	36 (32-39)	35.5 (32-38.5)	36.5 (33-41)	0.6277	36.5 (33-37)	0.7142
Female gender, n (%)	8 (26.7)	4 (20)	4 (40)	0.3841	3 (50%)	0.2929
Race, n (%)				0.4896		1
White	11 (36.7)	8 (40)	3 (30)	.	2 (33.3%)	.
African American	18 (60)	12 (60)	6 (60)	.	4 (66.7%)	.
Asian	1 (3.3)	0 (0)	1 (10)	.	0 (0%)	.
Hemoglobin g/dL	10.1 (9.3-11.5)	10.15 (9.8-11.5)	9.45 (8.1-10.6)	0.2012	8.75 (8-10.1)	0.0382
BMI	21.76 (19.29-25.13)	21.76 (19.33-24.81)	22.08 (18.52-25.47)	0.9474	23.54 (20.84-28.5)	0.4113
CD4+ T-cell%	3 (2-5)	2 (1-4.5)	3.5 (3-6)	0.1185	4 (3-6)	0.2055
CD4+ T-cells/µl	25 (13-36)	19 (10-30)	27.5 (18-48)	0.1795	27.5 (14-48)	0.3611
CD8+ T-cell%	69 (63-75)	66 (60-72)	70 (65-78)	0.1176	70 (69-76)	0.1796
CD8+ T-cells/µl	552.5 (340-682)	537.5 (361-679.5)	604 (334-825)	0.6129	604 (318-682)	0.9273
CD4/CD8 ratio	0.04 (0.02-0.07)	0.03 (0.02-0.06)	0.05 (0.04-0.09)	0.2437	0.05 (0.04-0.09)	0.3455
Plasma HIV RNA, log copies/mL	5.31 (4.94-5.86)	5.15 (4.81-5.74)	5.70 (5.36-5.99)	0.0679	5.95 (5.86-6.14)	0.0115

In our study population, 6 patients were diagnosed with Mycobacterial IRIS (5 M. Tuberculosis and 1 Mycobacterium avium complex), 2 patients with Kaposi's sarcoma-IRIS, 1 patient with CMV-IRIS and 1 patient with VZV-IRIS. Patients with Mycobacterial-IRIS had lower hemoglobin and higher plasma HIV RNA level at baseline compared to the Non-IRIS group (Table 1).

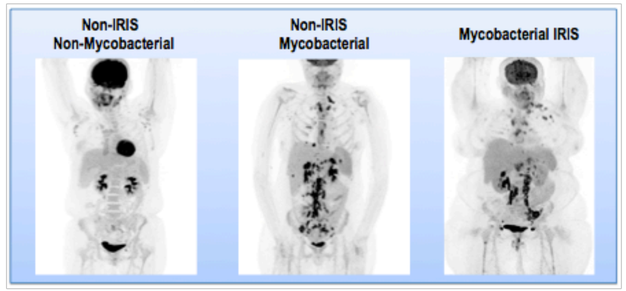
Results

At baseline, lesion load TGA and total volume were significantly higher in IRIS compared to non-IRIS group (>3X) and even more impressively in Mycobacterial-IRIS (>10X) compared to the patients who never developed IRIS (table 2 – figure 1).

Table 2. Comparison of whole body ^{18}F-FDG-PET/CT threshold values at baseline between study groups (median values reported with 25th and 75th percentile).

	All patients (n=30)	Non-IRIS (n=20)	IRIS (n=10)	P-value IRIS vs Non-IRIS	Mycobacterial IRIS (N=6)	P-value Mycobacterial IRIS vs Non-IRIS
SUVmax	14.06 (11.20,22.55)	12.08 (8.74-19.22)	19.99 (14.18-31.63)	0.0101	22.4 (19.72-31.63)	0.0081
SUVmean	5.78 (5.02, 6.42)	5.13 (4.68-6.39)	6.02 (5.68-6.42)	0.1083	6.15 (5.68-7.7)	0.0726
TGA	182.3 (50.32,559.4)	106.4 (20.14-328.8)	404.7 (170.1-3156)	0.0165	1858 (371.4-3821)	0.0097
Total Volume	30.92 (9.84, 87.18)	20.02 (4.16-58.6)	68.94 (28.39-482.0)	0.0294	284.6 (65.35-536.5)	0.0137

Figure 1. Baseline ^{18}F-FDG-PET/CT



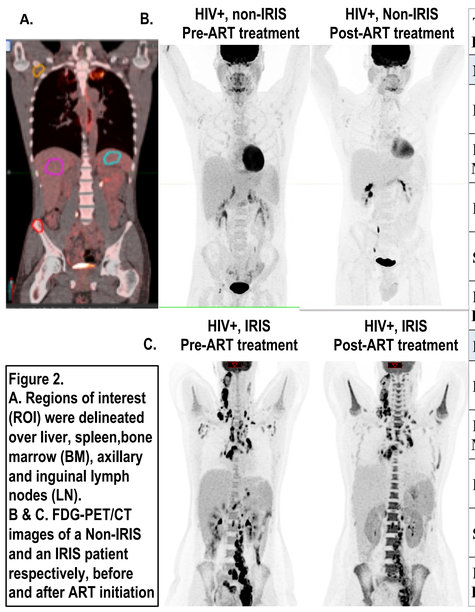
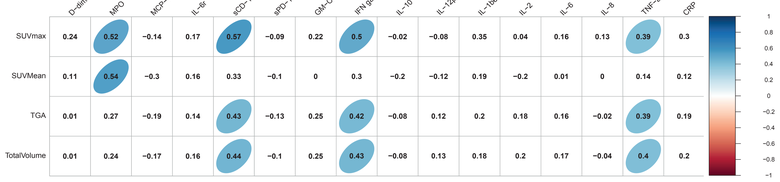


Figure 2.
A. Regions of interest (ROI) were delineated over liver, spleen,bone marrow (BM), axillary and inguinal lymph nodes (LN).
B & C. FDG-PET/CT images of a Non-IRIS and an IRIS patient respectively, before and after ART initiation

Table 3. Median (IQR) values of SUVmean ^{18}FDG-PET/CT measured in ROI at baseline and post-ART

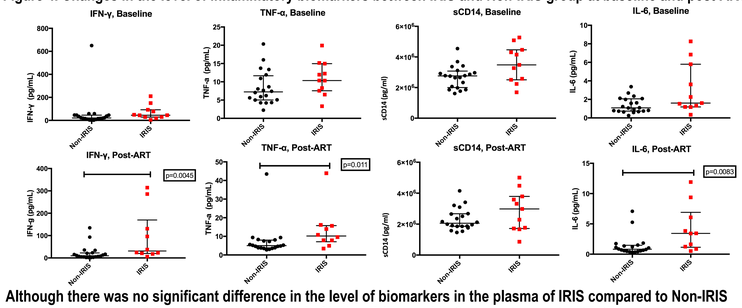
Non-IRIS			
ROI	Baseline	Post-ART	P-value
Bone Marrow	4.11 (3.32, 5.00)	3.38 (3.05, 4.23)	0.0037
Liver	1.96 (1.75, 2.10)	1.88 (1.68, 2.09)	0.4132
Spleen	2.07 (1.84, 2.36)	1.94 (1.64, 2.17)	0.0133
R/L Axillary LN	3.62 (2.47, 4.89)	3.67 (2.42, 4.69)	0.7879
IRIS			
ROI	Baseline	Post-ART	P-value
Bone Marrow	4.61 (3.53-5.33)	4.13 (3.46-4.39)	0.9504
Liver	1.92 (1.83-2.2)	1.8 (1.72-2.04)	0.2871
Spleen	2.39 (1.84-2.92)	1.94 (1.72-2.92)	0.1894
R/L Axillary LN	4.46 (3.32-5.74)	3.06 (2.06-3.23)	0.0148

Figure 3. Correlation of whole body ^{18}F-FDG-PET/CT with inflammatory biomarkers measured in the plasma of all patients at baseline (Spearman Correlation Rhos are shown, Ellipses were drawn at the cell where p-value<0.05).



At baseline, lesion load TGA/total volume/SUVmax positively correlated with TNF-α , IFN-γ and sCD14, and MPO levels

Figure 4. Changes in the level of inflammatory biomarkers between IRIS and Non-IRIS group at baseline and post-ART.



Although there was no significant difference in the level of biomarkers in the plasma of IRIS compared to Non-IRIS patients at baseline, IRIS group had higher level of IFN-γ, TNF-α and IL-6 during the post-ART PET scan time point.

Conclusion

- Our findings suggest that higher lesion load TGA/volume at baseline could indicate increased risk of developing IRIS after ART initiation; especially in mycobacterial/HIV co-infected patients.
- At baseline, a positive correlation was demonstrated between the whole body ^{18}F-FDG/PET-CT values and specific inflammatory biomarkers previously shown to be associated with IRIS pathogenesis.
- After the initiation of ART, there was an acute decrease in metabolic activity in spleen and BM in non-IRIS patients that could suggest an important role of these sites as tissue viral reservoirs.
- Further studies will be necessary to determine the possible role of ^{18}F-FDG-PET/CT in identifying paradoxical and/or unmasking IRIS as well as persistent residual inflammation after ART initiation.

This research was made possible by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH)