Divergent effects of HIV and smoking on aortic inflammation

Abstract #628

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BACKGROUND

- ^{18}Flurodeoxyglucose positron emission tomography (FDG-PET) imaging targets metabolically active tissues such as malignancies, but may also reflect high levels of inflammatory cell infiltration. Uptake in the wall of large arteries has been proposed as a measure of vascular inflammation. Splenic uptake may reflect immune activation.
- HIV is associated with higher FDG uptake in one cross-sectional study, but the potential confounding effect of smoking has not been fully explored.

METHODS

Design: Cross-sectional

Subjects:

- 55 HIV+ adults on stable antiretroviral therapy
- 19 HIV-negative age-matched controls
- Subjects were free of CVD at baseline but had one or more of the following CVD risk factors (hypertension, low HDL or high total cholesterol, diabetes, or family history of premature coronary disease)

PET/CT

- All subjects underwent prospective FDG-PET/CT scanning using a protocol designed to optimize large vessel vascular imaging
- Participants were fasting for a minimum of 4 hours prior to the injection of FDG .
- Serum glucose was confirmed and if >200mg/dL, the study was rescheduled.
- Images were acquired from the orbits through the lower abdomen 3 hours +/- 10 minutes after FDG injection on a Philips Gemini TF Big Bore PET/CT.
- Standard uptake dose values (SUV) were defined per standard convention as the decay-corrected tissue concentration of 18F-FDG (in kBq/g) divided by the injected dose per body weight (in kBq/g).
- All measurements were performed offline on a dedicated workstation using MIM v. 6.6.6.
    - **Aorta**: Aortic target-to-background ratio was defined as the mean-mean aortic SUV measured from consecutive axial slices through the ascending aorta from the sinus of Valsalva to the aortic arch divided by the mean-mean superior vena cava blood pool SUV measured from the same axial slices. [Aortic SUV ÷ Superior vena cava SUV = Aortic TBR]
    - **Spleen**: A 3D region of interest tool was used to trace the borders of the spleen using 3 planes of view. The mean SUV was used for analysis
- All subjects also had coronary artery calcium score measured using the Agatston method.

Inflammation and Immune Activation (n=39 HIV+ and n=13 HIV-neg):

- Plasma markers of monocyte activation: Soluble CD163 and CD14
- Plasma markers of inflammation and endothelial activation: Interleukin-6, tumor necrosis factor-α receptor II, high sensitivity C-reactive protein, vascular cell adhesion molecules, and oxidized LDL

Statistics:

- Primary explanatory variables of interest: (a) HIV status and (b) Smoking status (current smokers vs. all others)
- Primary dependent variables of interest: (a) Aortic TBR and (b) Spleen SUV
- Unadjusted and multivariable adjusted linear regression models were used to explore these relationships
    - Model 1: HIV and smoking status only
    - Model 2: Model 1 + Age, gender, and race
    - Model 3: Model 2 + hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, body-mass index, and homeostatic model assessment of insulin resistance
- Exploratory analyses of the association between biomarkers of inflammation, CAC, and splenic/aortic FDG uptake were conducted using unadjusted and adjusted regression models.
    - Note: For CAC analyses, CAC>0 was the dependent variable and splenic SUV and aortic TBR were the primary explanatory variables in logistic regression models, with multivariable adjustment as in models 2 and 3 above.

RESULTS

Table 1: Baseline characteristics of study subjects by HIV status. Median (IQR) or %. HIV+ and HIV-neg groups were well-matched for demographics and clinical variables (p>0.2) except HIV+ were more likely to be African American (p=0.05) and to have hypertension (p=0.003).

	HIV+ (n=55)	HIV-negative (n=19)
Age (years)	49 (43-55)	50 (34-56)
Male gender	84%	74%
African American	73%	47%
Current smoker	55%	53%
Packs per day	0.5 (0.2-1)	1 (0.5-1)
Body mass index (kg/m^2)	26 (23-31)	27 (26-30)
Diabetes	1.8%	0%
HOMA-IR	3.1 (1.6-4.8)	2.1 (1.8-3.8)
Hypertension	56%	16%
Estimated GFR (mL/min/1.73m^2)	88 (76-102)	84 (73-107)
LDL cholesterol (mg/dL)	87 (70-114)	88 (76-116)
HDL cholesterol (mg/dL)	47 (37-60)	45 (35-58)
Coronary artery calcium >0	43%	39%
CD4+ T-cell count (cells/µl)	690 (443-818)	N/A
Nadir CD4+ T-cells (cells/µl)	189 (46-303)	N/A
HIV-1 RNA <20 copies/ml	88%	N/A
Current protease inhibitor	43%	N/A
Current abacavir	7%	N/A

Table 2: Inter-reader variability of aortic TBR and splenic SUV measurements. N=10 randomly selected cases were read by the two readers (CES and JM)

	Intraclass Correlation Coefficient (95% CI)
Mean-mean aortic TBR	0.979 (0.921-0.995)
Mean splenic SUV	0.995 (0.981-0.999)

Figure 1: [A] Aortic TBR = mean-mean aortic SUV (blue) ÷ superior vena cava SUV (red); [B] Mean splenic SUV measured using a 3D ROI (pink). Others have used an average of ROIs through the center of the spleen (green).

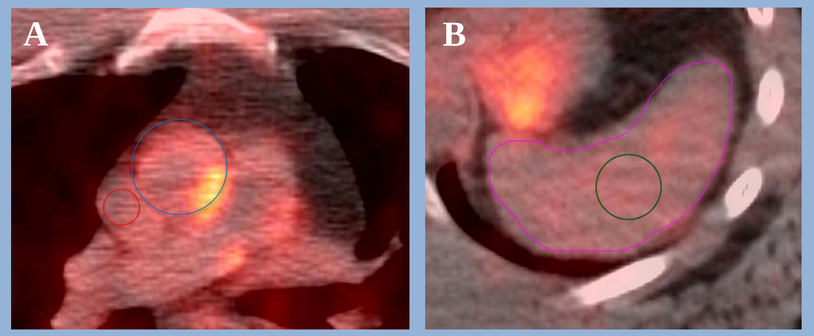
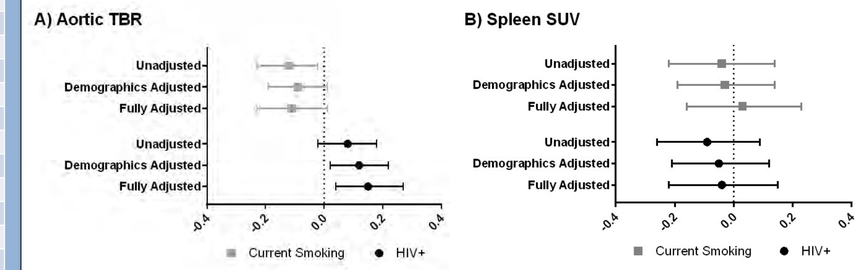


Figure 2: Effects of HIV and smoking status on (A) aortic and (B) splenic FDG-PET uptake. Symbols represent parameter estimates and error bars represent 95% confidence intervals. Unadjusted models include smoking and HIV status only. Demographics adjusted models include age, gender, and race. Fully adjusted models include demographics, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, body-mass index, and homeostatic model assessment of insulin resistance. There was no evidence for an HIV*smoking interaction for aortic TBR or spleen SUV models (all p>0.1). TBR, target-to-background ratio; SUV, standardized uptake value.



MORE RESULTS

Coronary Calcium Score (CAC)

- Mean spleen SUV was associated with higher odds of detectable CAC in a univariate logistic regression model [OR per 1 SD of spleen SUV 1.70 (95%CI 1.0-2.9); p=0.047]. After adjustment for age, sex, race, and traditional risk factors, the adjusted OR was similar, but the association was no longer statistically significant [OR 1.74 (95%CI 0.2-3.7); p=0.15].
- Aortic TBR was not associated with CAC>0 in univariate or multivariate models (all p>0.4)

Systemic Inflammation and immune activation

- Ln-transformed soluble CD163 was positively associated with spleen SUV in fully adjusted models (p=0.05), but not with aortic TBR (p=0.9).
- Ln-transformed hsCRP was positively associated with spleen SUV in unadjusted models (p=0.008), but adjustment for demographics (p=0.24) and further adjustment for traditional risk factors (p=0.61) significantly attenuated the relationship.
- None of the other biomarkers were associated with aortic TBR or spleen SUV in unadjusted or adjusted models at a level of p<0.05.

CONCLUSIONS

- **To our knowledge, this is the largest sample of HIV+ subjects studied by PET/CT to date, allowing us to explore important relationships with traditional and non-traditional risk factors.**
- **HIV is associated with increased aortic inflammation independent of traditional risk factors. In contrast, current smoking is marginally associated with lower aortic inflammation.**
- **More study is needed to determine whether tissue-specific FDG uptake is associated with clinical cardiovascular outcomes in this population**

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