Arterial inflammation in young patients with human immunodeficiency virus infection: A cross-sectional study using F-18 FDG PET/CT

Ismaheel O. Lawal, MD,[a] Alfred O. Ankrah, MD,[a,b] Gbenga O. Popoola, MD,[c] Thabo Lengana, MD,[a] and Mike M. Sathekge, MD, PhD[a]

[a] Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Pretoria, South Africa
[b] Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[c] Department of Epidemiology and Community Health, University of Ilorin, Ilorin, Nigeria

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Background. **HIV infection is associated with the risk of development of atherosclerosis at a younger age. We compared arterial inflammation in HIV-infected and HIV-uninfected patients with otherwise low-risk factors for cardiovascular disease (CVD) using FDG PET/CT.**

Methods. **242 patients aged 18–40 years with low-risk factors for CVD consisting of 121 HIV-infected patients and 121 HIV-uninfected age- and gender-matched controls were studied, mean age = 34.95 ± 5.46 years. We calculated and compared the target-to-background ratio of FDG uptake in ascending aorta of HIV-infected and non-infected patients.**

Results. **Median CD4 count and viral load were 375.5 cells/mm^3 (range 2-1094) and 6391.00 copies/mL (range 24-1,348,622), respectively. There was slightly higher but significant overlap in the TBR between HIV-infected group compared with control (1.22, 0.87-2.02 vs. 1.12, 0.38-1.40, $P < 0.001$). TBR was neither affected by CD4 count levels nor the presence or absence of detectable viremia. We also found no significant difference in TBR between male and female patients with HIV infection. We found a weak positive correlation between TBR and CD4 count, TBR and duration of HIV infection, and a very weak negative correlation between TBR and viral load. There was no significant difference in TBR between patients on HAART and those not yet commenced on therapy.**

Conclusion. **Marginally higher TBR with a significant overlap exist in HIV-infected patients compared with control. Arterial F-18 FDG uptake is not affected by the CD 4 count, viral load, gender, or duration of HIV infection. (J Nucl Cardiol 2019;26:1258–65.)**

Key Words: FDG • PET/CT • HIV • inflammation • cardiovascular disease

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Reprint requests: Mike M. Sathekge, MD, PhD, Department of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, Private Bag X169, Pretoria 0001, South Africa; *mike.sathekge@up.ac.za*

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Abbreviations	
HAART	Highly active antiretroviral therapy
CD 4	Cluster of differentiation 4
CT	Computed tomography
CVD	Cardiovascular disease
FDG	Fluorodeoxyglucose
HIV	Human immunodeficiency virus
Hs-CRP	High-sensitivity C-reactive protein
PET	Positron emission tomography
SUV	Standardized uptake value
TBR	Target-to-background ratio

See related editorial, pp. 1266–1268

INTRODUCTION

Successful rollout of highly active antiretroviral therapy (HAART) in most regions of the world has led to a significant reduction in human immunodeficiency virus (HIV)-related mortality.[1] This reduction in mortality is partly due to the decrease in the incidence HIV-associated infections as well as HIV-defining cancers. Consequently, HIV infection is now recognized as a chronic medical condition.[2] Many observational studies have shown higher rates of cardiovascular diseases (CVD) among HIV-infected individuals compared with HIV-uninfected populations.[3,4] The pathophysiological basis of this increased risk is not entirely understood at present. Chronic immune activation in long-standing HIV infection is suspected to be the cause of arterial inflammation seen in HIV patients.

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has been used in the evaluation of several inflammatory conditions of the cardiovascular system.[5–7] Using arterial FDG uptake as a surrogate for vascular inflammation, a few studies have reported a higher incidence of vascular inflammation in HIV-infected cohorts compared to HIV-uninfected control groups.[8,9] These studies are limited by their modest patient populations. More importantly, all these studies were done in older patient populations with the average age greater than 50 years. HIV-associated CVD is, however, known to occur earlier, below the age of 50 years.[10] This may suggest that vascular inflammation, an early process in the pathogenesis of CVD, is present at even a younger age among HIV patients. The aim of this study was, therefore, to compare arterial inflammation in young HIV-infected with HIV-uninfected individuals with otherwise low or no risk for CVD using FGD PET/CT.

METHODS

Patients

We reviewed the scans of HIV patients imaged between September 2015 and June 2017 referred for oncological or inflammatory indications. We included patients aged between 18 and 40 years with no abnormality (finding suggestive of malignancy or inflammation/infection). Our exclusion criteria were patients with the following:

- Systemic hypertension (Systolic pressure $>$ 140 mmHg, Diastolic pressure $>$ 90 mmHg) documented.
- A history of type I or type II diabetes mellitus with/without use of oral antidiabetic agent or insulin.
- A history of acute or chronic renal failure.
- Vascular calcification noted on the CT component of the PET/CT study.
- A history cerebrovascular or cardiac/cardiovascular disease.
- Suspected or confirmed vasculitis.
- Smokers (at least one stick of cigarette per day).
- A history of peripheral vascular disease.
- Impaired lipid profile (Total cholesterol $\leq$ 5 mmol/L, low-density lipoprotein (LDL) cholesterol $\leq$ 3 mmol/L, high-density lipoprotein (HDL) cholesterol $>$ 1 mmol/L and Triglyceride $<$ 1.7 mmol/L).
- Statins use.

One hundred and twenty-one HIV-positive patients met our inclusion and exclusion criteria. We searched the electronic database of the hospital to identify HIV-negative patients who had F-18 FDG PET/CT scans from September 2015 and June 2017. We sought for patients with no abnormality detected on their images (inflammation/infection or malignancy), who met all the inclusion and exclusion criteria which we used for the HIV-positive patients. We selected patients from this group to be used as controls. A total of 274 HIV-negative individuals satisfied these criteria. An age- and gender-matched control was identified from the pool of the HIV-negative patients for each of the HIV-positive subjects. In total, 242 patients consisting of 121 HIV-positive patients and 121 HIV-negative patients (matched controls) were studied.

For each of the HIV-positive patients, the duration since diagnosis of HIV infection, whether or not the patient was on ART, CD 4 count, and viral load tested within four weeks of F18 PET/CT were recorded.

FDG PET/CT Imaging

Imaging was done as previously reported.[11] Briefly, all patients fasted for a minimum of six hours. Blood sugar before imaging was $\leq$ 11.0 mmol/L in all patients. The activity of FDG administered was weight-based, and calculated using the formula: Activity administered = [(body weight in Kg $\div$ 10)+1] $\times$ 37 Mega Becquerel (MBq). Imaging was

acquired on a Biograph 40 Truepoint PET/CT scanner (Siemens Medical Solution, Illinois, USA). Intravenous contrast, 100 mL Omnipaque 350 (GE Healthcare, Wisconsin, USA) was given after a scan delay time of 80 seconds. CT parameters were adjusted for patients' weight (120KeV, 40-150 mAs) with a section width of 5 mm and pitch of 0.8. Vertex to mid-thigh PET imaging was acquired in 3D mode at 3 minutes per bed position. Computed tomography data were used for attenuation correction. Image reconstruction was done with the ordered subset expectation maximization iterative reconstruction algorithm (4 iterations, 8 subsets). A Gaussian filter was applied at 5.0 mm full width at half maximum (FWHM).

Image Analysis

All images were analyzed by a single investigator who was blinded to the HIV status of the patients. Image analysis was done on a dedicated workstation equipped with a Syngo software (Siemens medical solutions, Illinois, USA). Image analysis was done as previously reported by Subramanian et al.[8] Briefly, the investigator drew five circular regions of interest enclosing the arterial wall at 5 mm intervals on the ascending aorta and recorded the maximum standardized uptake values (SUVmax). The mean of the SUVmax measurements of each patient was calculated to obtain the mean SUVmax aorta. Background activity was obtained by drawing five circular regions of interest within the lumen of the superior vena cava (SVC) to obtain SUV at the same levels as for the aorta. The mean of the SUV measurement taken within the SVC was then calculated and used as the background. We calculated target-to-background ratio (TBR) using the formula: TBR = mean aortic SUV ÷ mean SVC SUV. TBR was used as a measure of arterial inflammation.

Statistical Analysis

Descriptive statistics of the demographic and clinical characteristics of the study population were done. The independent samples *t* test was used to test for difference in TBR between the HIV-infected group and the control group and also to test if TBR was significantly different between HIV-infected patients with detectable viremia and those whose viral load was below the detectable limit. In addition, a sub-group analysis was done using independent samples *t* test to determine if there was a significant difference between male and female patients. Analysis of variance (ANOVA) was used to test if TBR is significantly different between the HIV-infected group and control as well as between those HIV-positive patients already on ART and those not yet on ART. The HIV-infected group was sub-categorized in sub-classes based on the CD4 count. Kruskal–Wallis test was used to test for significant difference in TBR between the various groups. Spearman correlation was used to evaluate for correlation between any of CD4 count, viral load, or duration of HIV infection and TBR. The statistical significance level was set at a P value of < 0.05. Statistical analysis was done using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, New York, USA).

RESULTS

Clinical characteristics of the study population are shown in Table 1. A total of 242 patients consisting of 121 HIV-infected patients and 121 HIV-uninfected controls were included, females = 190, males = 52. The mean age of patients was 34.95 ± 5.46 years. At the time of FDG PET/CT imaging, 81.80% of the HIV-infected patients were already on ART. The group's median CD4 count was 375.50 cells/mm^3 with the median time since HIV diagnosis of 42 months. Out of 121 HIV-infected patients, 58 patients had lower than detectable viral loads. In 63 patients with detectable viremia, the median viral load was 6391.00 copies/mL.

We found marginally higher but with a significant overlap in the TBR of the HIV-infected patients compared with control (1.22 ± 0.20 vs 1.12 ± 0.14, $P < 0.001$), Figure 1. Table 2 shows the distribution of TBR between the HIV-infected patients and the control. No statistically significant difference was seen in the TBR at different CD4 count levels (Table 3). We performed a sub-group analysis to determine the effect of gender on TBR (Table 4). There was higher TBR among males with HIV infection compared to non-infection cohorts ($P = 0.002$). Similarly, HIV-infected females show higher TBR compared to the females in the control group ($P = 0.001$). Among the HIV-infected

Table 1. Characteristics of the study population

Variables	Frequency	Percent
Age (years)		
Mean ± SD	34.95 ± 5.46	
Range	18–40	
Gender		
Male	52	21.5
Female	190	78.5
ART status		
On ART	99	81.8
Not on ART	22	18.2
CD4 count (cells/mm^3)		
Median (Range)	375.50 (2.00–1094.00)	
Viral load (copies/mL)		
Median (range)	6391.00 (24.00–1,348,622.00)	
Duration of HIV infection (months)		
Median (range)	42.00 (1.00–156.00)	

SD, standard deviation; *ART*, antiretroviral therapy; *CD4*, cluster of differentiation 4; *HIV*, human immunodeficiency virus

patients, no significant difference was demonstrated between males and females ($P = 0.727$). Representative images are shown in Figures 2 and 3.

The viral load in HIV patients did not seem to influence the TBR as both groups (patients with detectable viral load and those with undetectable viral loads) did not show any significant difference in TBR, $P = 0.367$ (Table 5). Table 6 shows a Spearman correlation demonstrating a very weak positive correlation between TBR vs duration of HIV infection, viral load, and CD4 count level. A weak negative correlation was found between TBR and viral load. None of these numerical correlations, however, reached a statistically significant level.

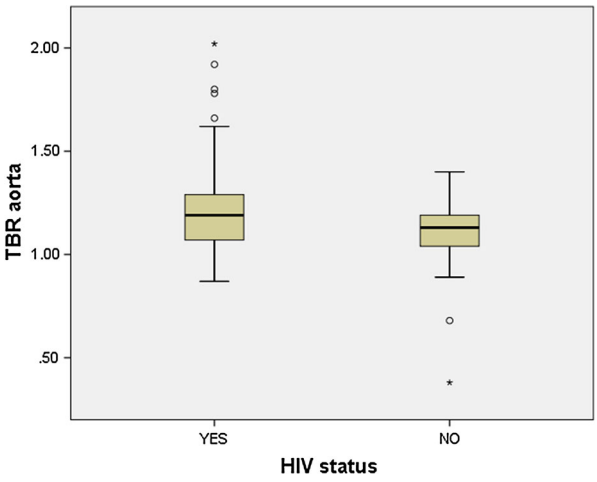

Figure 1. Box plot showing the distribution of TBR in the HIV-infected group and control.

We tested whether there was a difference in the TBR among HIV-infected patients on ART, HIV-infected patients not yet on ART, and control group using ANOVA, a significant difference in TBR was found among the three groups, $P < 0.001$ (Table 7). A post hoc analysis revealed that while a difference exists in TBR between the HIV-infected group and control, there was no difference between the two HIV-infected groups (i.e., those patients on ART vs those patients not yet commenced on ART).

DISCUSSION

Traditionally, individuals below age 40 years are not considered for routine screening for CVD. In this study, with the largest population so far published on the utility of FDG PET/CT in the evaluation of arterial inflammation in HIV patients, we found a marginally higher TBR in HIV-infected patients compared to their age- and gender-matched controls. There was, however, a significant overlap in the TBR between the two groups. Subramanian et al[8] compared aortic TBR of 27 patients with well-controlled HIV infection with two groups of HIV-uninfected controls. TBR was higher in the HIV-infected group compared with HIV-negative group but

Table 2. Comparison of TBR between HIV-infected patients and control group

Variable	HIV-infected	Control	*t*	*P* value
TBR				
Mean ± SD	1.22 ± 0.20	1.12 ± 0.14	4.515	< 0.001*
Range	0.87–2.02	0.38–1.40		

t, independent samples *t* test; *U*, Mann Whitney *U* test; *TBR*, target-to-background ratio
*P value < 0.05 (statistically significant)

Table 3. Relationship between TBR and CD4 count level

	CD4 count					
Variable	< 200	200–350	350–500	> 500	K	*P* value
TBR						
Median (range)	1.18 (0.87–2.02)	1.23 (1.02–1.78)	1.13 (1.01–1.49)	1.20 (0.94–1.80)	6.707	0.082

K, Kruskal–Wallis test; *TBR*, target-to-background ratio; *CD4*, cluster of differentiation 4

Table 4. Sub-group analysis showing the effect of gender on TBR

TBR	HIV-Infected Mean ± SD	Control Mean ± SD	*t*	*P* value
Males				
Mean ± SD	1.24 ± 0.24	1.04 ± 0.18	3.190	0.002*
Females				
Mean ± SD	1.22 ± 0.19	1.15 ± 0.12	3.314	0.001*
t (*P* value)	0.350 (0.727)	− 3.402 (0.001*)		

t independent samples *t* test
**P* value < 0.05 (statistically significant)

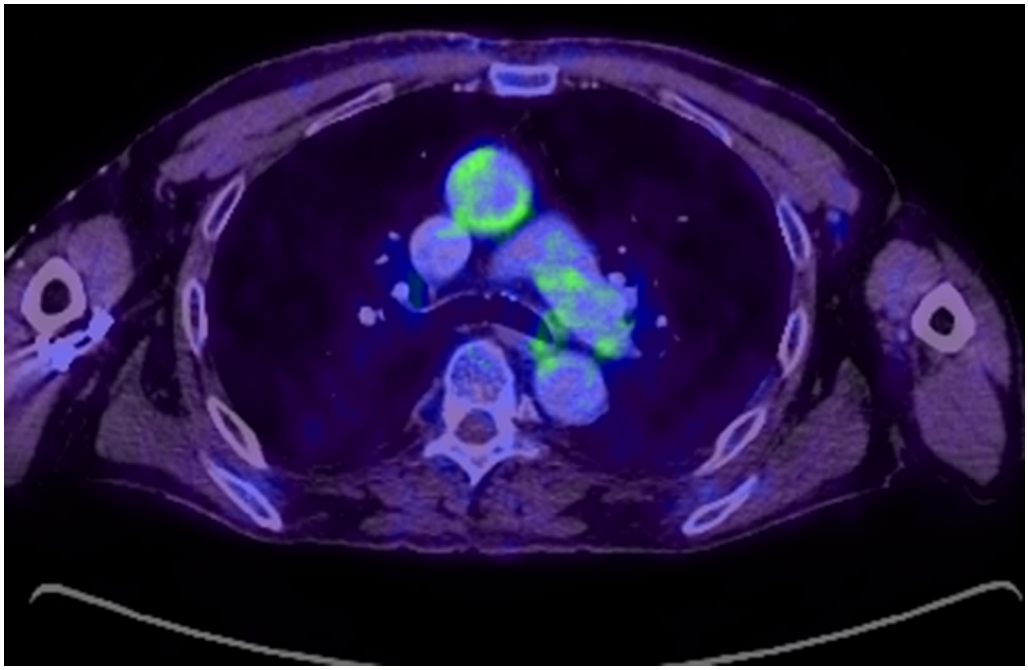

Figure 2. Axial slice of fused PET/CT image of an HIV-infected patient showing increased F-18 FDG uptake in the wall of the ascending aorta.

comparable to that in the group of patients with established atherosclerotic disease. This suggests that HIV infection may be associated with the same level of vascular inflammation as present in the vessels of those patients with established atherosclerotic disease. Another study with a smaller patient population found slightly higher aortic TBR in HIV-infected patients compared with HIV-negative patients, but the difference was not significant.[9] Knudsen et al failed to demonstrate any significant difference in aortic TBR between HIV-infected and HIV-negative patients.[12]

FDG uptake in the arterial wall is a reflection of vascular invasion by activated macrophages. Activated macrophages increase their use of glucose to meet the increased metabolic demand for energy. A study has shown that arterial uptake of FDG correlates well with the level of activated macrophage invasion.[13] Statins have an anti-inflammatory effect on vascular inflammation. However, a study which randomized 40 HIV-infected patients to 1 year of atorvastatin (19 patients) and a placebo (21 patients) did not find any significant difference in changes between the groups after 1 year.[14]

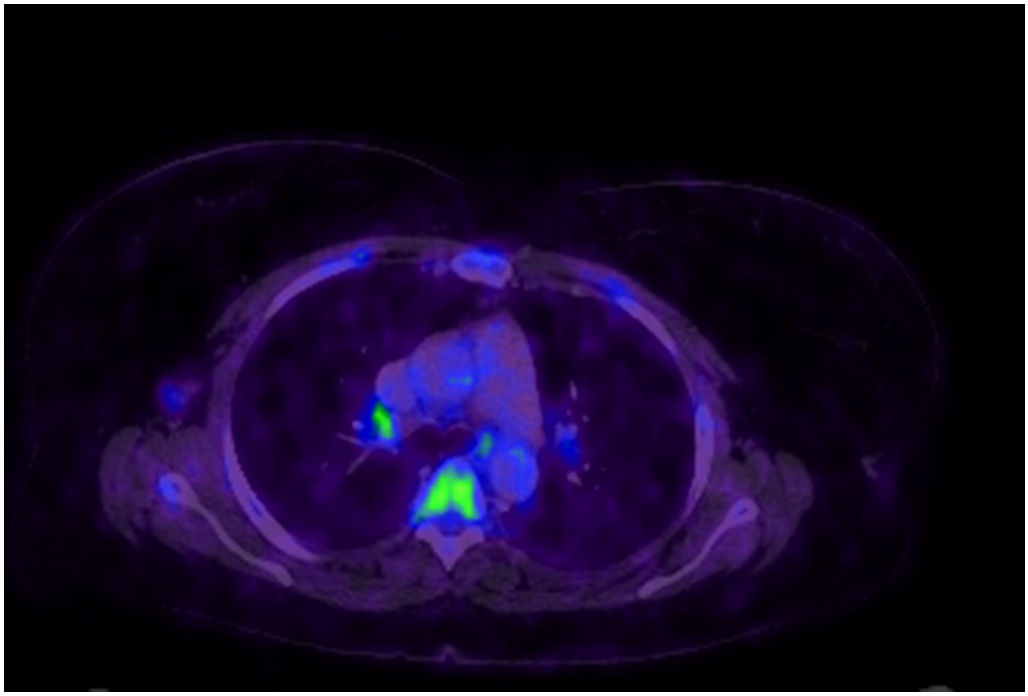

Figure 3. Axial slice of fused PET/CT image of an HIV-negative patient with no significantly increased F-18 FDG uptake in the wall of the ascending aorta.

Table 5. Effect of viral load on TBR

Variable	Viral load		*t*	*P* value
	Detectable	LDL		
TBR				
Mean ± SD	1.27 ± 0.29	1.22 ± 0.18	0.908	0.367

t, independent samples *t* test; *LDL*, lower than detectable limit; *TBR*, target-to-background ratio

In the context of vascular infection or inflammation, in other settings such as vasculitis, a reduction in PET signal following therapeutic intervention is associated with response to treatment.[6,15]

We found no significant effect of viral load on TBR. Similarly, CD4 count level did not influence the aortic TBR in our study. Our finding is consistent with the finding of a previous finding in a study by Zanni and colleagues. Zanni et al did not find any significant difference in TBR before, and six months after starting ART.[16] We demonstrated statistically significant differences in TBR among HIV-infected patients on ART, HIV-infected patients not yet on ART and HIV-uninfected control. A post hoc analysis, however, showed

Table 6. Correlation between TBR vs duration of HIV infection, CD4 count, and viral load of HIV-infected patients

Variable	TBR	
	r	*P* value
Duration of HIV (months)	0.088	0.407
CD4 COUNT	0.113	0.238
VIRAL LOAD	− 0.138	0.502

r, Spearman correlation coefficient; *HIV* human immunodeficiency virus; *TBR*, target-to-background ratio; *CD4*, cluster of differentiation 4

Table 7. Effect of ART use on TBR

Variable	On ART Mean ± SD	Not on ART Mean ± SD	Controls Mean ± SD	*F*	*P* value
TBR	1.27 ± 0.19[a]	1.21 ± 0.22[a]	1.12 ± 0.14[b]	10.308	< 0.001*

NB: different alphabets indicate a significant difference using least significant difference (LSD) post hoc test
F, analysis of variance (ANOVA); *ART*, antiretroviral therapy; *TBR*, target-to-background ratio
**P* value < 0.05

that this difference exists between the HIV-infected patients (whether on ART or not) and the HIV-uninfected control. There was no difference in TBR between the two HIV-infected sub-groups. This may suggest that HAART did not appear to affect TBR. The duration of HIV infection also did not appear to significantly influence aortic TBR. These findings may suggest that the risk for vascular inflammation as measured by TBR once established in HIV patients is not modified by the use of HAART. Larger prospective studies are needed to validate this.

Most studies evaluating the utility of FDG PET in the detection of vascular inflammation have used longer uptake time (time from FDG injection to the start of PET/CT imaging) of about 3 hours.[8,9,12,14] This retrospective study included patients imaged using standard oncologic/infection protocol where imaging is started earlier at 60 minutes' post-FDG injection. The likely implication for this is that there could be a lower FDG uptake in the arterial wall and high background activity at the time of imaging. We speculate that a later imaging at 2.5 hours or beyond may even demonstrate a more significant difference in the arterial FDG uptake between the HIV-infected group and the HIV-uninfected control. Bucerius and colleagues described a higher arterial FDG uptake in patients imaged after a longer uptake time (> 145 minutes) compared to patients who were scanned earlier (≥ 97 to ≤ 111 minutes).[17] In their study, while meanTBRmax showed a progressively increasing trend with uptake time, the SUVmax of FDG uptake in the aorta decrease with delayed imaging suggesting that improvement in meanTBRmax seen in the study was as a result of better background clearance on late imaging.

Patients included in this study were routinely imaged with intravenous contrast administered. Intravenous contrast, especially within large vessels such as the aorta, may cause up scaling of PET data on the attenuated corrected images leading to erroneously higher SUVmax. Since patients in both groups had intravenous contrast administered for imaging, the effect of over-correction of PET data may not impact significantly on the TBR.

Limitations

Our study has some limitations. The first limitation is its retrospective design. Another drawback is the lack of follow-up to identify which of these young patients to identify eventually developed a frank CVD. Again, imaging in this study was not optimized for arterial FDG uptake evaluation as it has been described in other studies. A longer uptake time may show higher TBR in HIV-infection patients compared with the control group. Patients included in this study were imaged for inflammation or malignancy. None of these patients showed abnormal FDG accumulation suggestive of the presence of malignancy or infection/inflammation. The absence of abnormal FDG accumulation, however, does not entirely rule out the fact that circulating cytokines may have influenced arterial uptake of FDG uptake in these patients. It is unknown the extent to which this could have impacted on our results.

CONCLUSION

Marginally higher TBR with significant overlap exists in HIV-infected patients compared with control. Arterial F-18 FDG uptake is not affected by the CD 4 count, viral load, duration of HIV infection, the use of and duration of HAART, and gender.

NEW KNOWLEDGE GAINED

The previous studies have demonstrated higher TBR in older HIV-infected patients in a few studies with modest patient populations compared with HIV-negative population. These studies included patients who have other risk factors for cardiovascular diseases. Our study, on the contrary, focuses on young HIV patients with no- or low-risk factors of cardiovascular disease. We demonstrate a marginally increase TBR risk in this

group that is unaffected by factors that usually modify HIV-associated conditions.

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Disclosures

Ismaheel O. Lawal, Alfred O. Ankrah, Gbenga O. Popoola, Thabo Lengana, and Mike M. Sathekge declares that they have no conflict of interest.

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