Global and regional brain hypometabolism on FDG-PET in treated HIV-infected individuals

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Abstract

Objective

To quantitatively measure brain glucose metabolism in treated HIV-positive individuals with [^{18}F]-labeled fluorodeoxyglucose (FDG) PET/CT.

Methods

We performed a cross-sectional comparison of FDG uptake in 47 treated HIV+ individuals, 10 age-matched controls (HIV−) sharing many of the comorbid conditions seen in the HIV+ group, and 19 age-matched healthy controls (HCs). We compared whole-brain (WB) and regional FDG standardized uptake values (SUVs) of select subcortical/central structures among the groups and correlated the values to clinical and neuropsychological assessments. A variable selection model was used to predict SUVs in HIV+ ($n = 47$) and in combined HIV+ and HIV− participants ($n = 57$).

Results

We found lower WB SUVmax in HIV+ participants compared to HCs but not to HIV− participants. Among the relative SUVmean measurements (regional SUVmean/WB SUVmean), only relative thalamic uptake values were lower in HIV+ compared to HIV− participants. When HIV+ and HIV− participants were grouped, cardiovascular disease risk scores best predicted WB SUVmean and SUVmax, while HIV status best predicted thalamic relative SUVmean.

Conclusions

We identified an important role for cardiovascular disease in neuronal loss/dysfunction, as measured by FDG-PET, in treated HIV+ patients. This underscores the need for shifting the focus of clinical intervention in this vulnerable population from HIV effects alone to a wider set of comorbid conditions, mainly cardiovascular disease. Only the thalamus showed significantly lower relative uptake in the HIV+ compared to the HC and HIV− groups. This needs to be further evaluated for underlying pathophysiology and potential association with memory, executive functioning, and attention deficits seen in the HIV+ population.

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Glossary

ART = antiretroviral therapy; **ASCVD** = atherosclerotic cardiovascular disease; **BMI** = body mass index; **CI** = confidence interval; **DBP** = diastolic blood pressure; **FBS** = fasting blood sugar; **FDG** = [^{18}F]-labeled fluorodeoxyglucose; **HAND** = HIV-associated neurocognitive disorders; **HC** = healthy control; **HCV** = hepatitis C; **SBP** = systolic blood pressure; **SUV** = standardized uptake value; **VL** = viral load; **VOI** = volume of interest; **WB** = whole brain.

Similar to simian immunodeficiency virus–infected monkeys,¹ it appears that the CNS harbors latent HIV-1 provirus despite long-term viral suppression by antiretroviral therapy (ART): HIV DNA was identified in >50% of brain tissues obtained from patients with low or undetectable viral load (VL) in the periphery before death.² With appropriate viral suppression, HIV reservoirs in the brain include latently infected cells such as perivascular macrophages, microglia, and astrocytes.³ Integrated HIV provirus within those cells results in the production of viral proteins, as has been shown with detectable levels of transactivator of transcription in the CSF of infected patients.⁴ In theory, the incomplete penetration of ART across the blood-brain barrier allows low-level production of those proteins, causing a subtle continuous process of brain injury, eventually leading to cognitive dysfunction.

Both hypometabolic and hypermetabolic brain abnormalities on [^{18}F]-labeled fluorodeoxyglucose (FDG) PET were described in the early days of the HIV epidemic,^{5–8} but only a few reports evaluated HIV+ patients in the recent ART era. In 1 report, 55% of patients exhibited varying mesial frontal reductions in glucose metabolism compared to a database of control PET scans.⁹ A second article reported small reductions in glucose uptake in the anterior cingulate cortex in HIV+ patients.¹⁰

In our study, we imaged a group of virologically suppressed HIV+ participants on ART for at least 1 year. One issue in such a population, however, is how much of the neurocognitive dysfunction is related to HIV vs commonly encountered comorbid conditions such as substance abuse, cardiovascular disease, and coinfections. To answer this question, we compared our HIV+ participants to 2 control groups: healthy controls with no significant comorbid conditions (HCs) and HIV-negative participants who were socioeconomically similar to the infected group with multiple comorbid conditions (HIV–). We assessed the neurocognitive status of HIV+ and HIV– participants and obtained multiple clinical and laboratory parameters to correlate with glucose metabolism measurements. Besides evaluating whole-brain (WB) metabolism and on the basis of pre-ART era findings,^{5,8} we specifically assessed glucose metabolism in brain subcortical/central structures, including the striatum and thalamus.

Methods

Standard protocol approvals, registrations, and patient consents

HIV+ and HIV– groups were scanned under protocol 13-N-0149. The study was reviewed and approved by the National

Institute for Allergy and Infectious Diseases Institutional Review Board. HCs were scanned under protocol 13-H-0194. The study was reviewed and approved by the National Heart, Lung, and Blood Institute Institutional Review Board. Both studies were approved by the NIH Radiation Safety Committee in keeping with the Declaration of Helsinki. All participants signed informed consent.

Participant groups

We recruited 47 HIV+ patients with serum VL <40 copies/mL for at least 1 year. Characteristics of the participants are summarized in table 1. The HIV– group included 10 participants recruited from the same geographic and socioeconomic areas as the HIV+ group. The HC group included 19 participants with no significant comorbid conditions and no history of psychiatric or neurocognitive abnormalities. HCs were selected carefully from a larger group to minimize comorbid conditions and to retain age matching.

Clinical and laboratory parameters

Data collected for HIV+ participants included estimated duration of HIV infection, nadir CD4 count, and estimated duration of infection before ART. For the HIV+ and HIV– groups, we performed detailed neurologic examination and psychiatric inventory,¹¹ including screens for drug abuse, posttraumatic shock disorder, anxiety, panic disorder, or major depression and history of previous or current use of psychiatric therapeutics. Prior drug abuse was determined by history as drug use that affected life or work. We also documented the type of drugs and approximate duration of use, recent drug use (in the last 6 months), history of smoking and current smoking, and past and current use of marijuana.

For the HC group, a medical history and examination were used to screen for current or past medical and psychiatric diagnoses and to evaluate prior drug or alcohol use. Data collected on all groups included body mass index (BMI), blood pressure (systolic [SBP] and diastolic [DBP]), cholesterol (high- and low-density lipoprotein), triglycerides, fasting blood sugar (FBS), and hemoglobin A_{1c} levels (when obtained). Atherosclerotic cardiovascular disease (ASCVD) risk scores were calculated for all groups (tools.acc.org/ASCVD-Risk-Estimator-Plus). In addition, HIV+ and HIV– participants underwent urine screening for amphetamines, benzodiazepines, cocaine metabolites, opiates, and cannabinoids at the time of scanning. Additional screening included hepatitis C (HCV) antibody, C-reactive protein, and D-dimer levels.

Table 1 Clinical and demographic characteristics of the 3 participant groups

Group	HIV+ (n = 47)	HIV– (n = 10)	HCS (n = 19)	Statistical analysis method and results
Age, y	53.6 ± 5.7	53.9 ± 4.7	50.6 ± 7.1	1-way ANOVA: NS
Sex, F:M, n	17:30	7:3	4:15	χ^2 test: $p = 0.034$
Ethnicity, white:other, n	20:27	8:2	11:8	χ^2 test: NS
Nadir CD4 count, 10 ⁶ cells/L	159 ± 162	NA	NA	NA
Estimated duration of infection, y	19 ± 8.8	NA	NA	NA
Estimated duration of infection before ART, y	6.2 ± 8.3	NA	NA	NA
HCV, yes:no, n (%)	11:36 (23)	1:9 (10)	0:19 (0)	χ^2 test: NS
History of drug abuse, yes:no, n (%)	28:19 (60)	2:8 (20)	0:19 (0)	χ^2 test: $p < 0.0001$
History of alcohol abuse, yes:no, n (%)	9:33 (21)	0:10 (0)	0:19 (0)	
BMI, kg/m ²	29.3	26.1	28.6	1-way ANOVA: NS
Diabetes mellitus, yes:no, n (%)	6:41 (13)	1:9 (10)	4:15 (21)	χ^2 test: NS
Mean ASCVD score, %	7.6 ± 5.6	3.8 ± 3.3	3.9 ± 2.8	1-way ANOVA: $p = 0.007$; Post hoc Dunnett test: HIV+ vs HIV–: $p = 0.047$; mean difference 3.82; 95% CI 0.05059–7.588 and HIV+ vs HC: $p = 0.012$; mean difference 3.685; 95% CI 0.7314–6.638

Abbreviations: ANOVA = analysis of variance; ART = antiretroviral therapy; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CI = confidence interval; HC = healthy control; HCV = hepatitis C; NA = not applicable.
For appropriate categories, values are reported as mean ± SD.

Neuropsychological testing

Detailed neuropsychological testing was performed on HIV+ and HIV– participants with 13 tests that resulted in 15 measures. Testing provided 3 primary cognitive variables: HIV-associated neurocognitive disorders (HAND) diagnosis (normal cognition vs asymptomatic neurocognitive impairment or mild neurocognitive dysfunction),¹² Global Deficit Score (a continuous score based on the number and severity of deficits in performance, with higher scores indicative of greater impairment), and overall T score (a continuous measurement of average neuropsychological test results across all measures, with lower scores indicating greater impairment).^{13,14}

HAND diagnosis was determined according to Antinori et al.¹² and Woods et al.¹⁵ First, each obtained raw score was converted to a demographically corrected T score based on norms such as those provided by Heaton et al.¹⁴ Next, each T score was converted to a clinical rating depending on the range in which it fell (e.g., low average, borderline, mild impairment). Finally, with the use of the algorithm provided by Woods et al., individual clinical ratings were combined to form a global rating and neurocognitive diagnosis.

Neuropsychological test results and psychiatric histories are summarized in table 2. We also assessed absolute and scaled values for attention, working memory, executive functioning,

information processing, verbal fluency, learning, psychomotor speed, and memory.

FDG-PET/CT scans

All participants were imaged over a period of 39 months on the same PET/CT scanner with the same acquisition and reconstruction techniques. After participants fasted for 6 hours, static PET emission scans were performed (Biograph PET/CT; Siemens Medical Solutions, Malvern, PA) 58 to 60 minutes after the administration of ≈ 5 to 10 mCi [¹⁸F]-FDG. A low-resolution transmission CT scan was acquired immediately before the emission scan. PET images were reconstructed with the use of an ordered subset expectation maximization algorithm and were attenuation and scatter corrected with a CT-based correction.

Spatial preprocessing and image analysis

WB standardized uptake values (SUVs) were measured with MIM 6.5 software (MIM Software Inc, Cleveland, OH). Briefly, each PET scan was uploaded to the analysis workstation and converted into SUV units. An inclusive volume of interest (VOI) was then applied automatically around the brain with a threshold-based method, excluding extracranial structures and the pituitary gland (figure 1). The caudal border of the VOI was set at the level of the foramen magnum to maintain consistency of included structures. We performed minor manual corrections of the VOI borders when needed. WB VOIs were then analyzed for SUVmean and SUVmax values.

Table 2 Neuropsychological testing and psychiatric history for HIV+ and HIV– participants

Group	HIV+ (n = 47)	HIV– (n = 10)	Statistical analysis method and results
Neurocognitive dysfunction, yes:no, n (%)	11:36 (23)	2:8 (20)	Fisher exact test: NS
HAND: normal/ANI/MND, n	36/6/5	8/2/0	Fisher exact test: NS
GDS	0.26 ± 0.25	0.15 ± 0.20	Mann-Whitney test: NS
Overall T score	49.9 ± 5.99	53.8 ± 8.7	Mann-Whitney test: NS
History of anxiety, yes:no, n	5:40	1:8	Fisher exact test: NS
History of depression, yes:no, n	3:42	0:9	Fisher exact test: NS
History of posttraumatic shock disorder, yes:no, n	8:37	1:8	Fisher exact test: NS
Taking psychiatric medicine, yes:no, n	18:27	3:7	Fisher exact test NS

Abbreviations: ANI = asymptomatic neurocognitive impairment; GDS = Global Deficit Score; HAND = HIV-associated neurocognitive disorders; MND = mild neurocognitive dysfunction .
For appropriate categories, values are reported as mean ± SD.

For regional analysis, we used PMOD 3.7 (PMOD Technologies LLC, Zurich, Switzerland). To generate regional SUVs for subcortical central regions (thalamus, caudate nuclei, and putamen) and cerebellum, we applied automatic template VOIs to the PET scan. The targeted VOIs were then manually adjusted as needed. The right and left VOIs for every region were first compared for statistically significant differences in all groups, separately and combined. The right and left VOIs were then averaged for each subregion, and mean SUVs were obtained. In addition, relative SUVmean values were obtained for all regions with the WB SUVmean used as the denominator.

Statistical analyses

We compared age, sex, and ethnicity using either 1-way analysis of variance or the χ^2 test. All results are reported as mean ± SD.

We compared FBS, SBP, DBP, cholesterol level, triglyceride level, BMI, and ASCVD risk score, as well as WB SUVmean/

max and absolute/relative SUVmean, for the caudate, putamen, thalamus, and cerebellum among groups using 1-way analysis of variance. If the overall model p value was <0.05, pairwise comparisons of HIV– and HC to HIV+ participants were performed, and the Dunnett multiple-comparisons test was used to adjust p values for multiple comparisons. We chose to perform the Dunnett test because the HIV+ group is our main target of comparison, thus comparing both HIV– and HC groups to HIV+ but not to each other.

Because of the high prevalence of HCV in our HIV+ group, we performed a subgroup comparison of SUVs after excluding HCV-infected participants from both the HIV+ and HIV– groups (36 HIV+ and 9 HIV– participants). In another subgroup analysis, we compared 15 HIV+ participants with no major comorbid conditions (negative HCV antibody and urine toxicology tests, no history of alcoholism or drug abuse, no diagnosis of diabetes mellitus, and

Figure 1 Example of volume of interest drawing (pink outline) to assess whole-brain standardized uptake values (mean and maximum) shown in (A) axial, (B) sagittal, and (C) coronal projections

no history of depression, anxiety, or psychosis) to 32 HIV+ participants with 1 or more of these comorbid conditions. We also separated 44 HIV+ participants into 2 groups based on their ASCVD risk scores (above and below an ASCVD score of 7.5%, the threshold for starting statin therapy as per the 2013 American College of Cardiology/American Heart Association guidelines¹⁶) and compared them. Finally, we compared HIV+ participants with a history of AIDS-defining illnesses ($n = 12$) to those without such a history ($n = 35$). Comparisons included WB SUVmean and SUVmax assessed with an unpaired Student t test.

We evaluated several continuous and categorical variables in terms of their association with SUVs in WB, thalamus, and caudate regions in the HIV+ and HIV- groups combined: HIV status (positive and negative), history of drug abuse, recent drug or alcohol abuse (within the last 6 months), history of alcoholism, diabetes mellitus status, ASCVD risk scores, age, and HCV coinfection. We also performed correlations in the HIV+ group separately with the addition of the following variables: estimated length of infection, estimated duration of infection before ART was started, and nadir CD4 value. Because multiple correlations were performed, a p value significance threshold of 0.01 was adopted.

We then determined the best set of predictive variables for the combined HIV+ and HIV- groups ($n = 57$) and the HIV+ group separately ($n = 47$) using 2 variable selection methods, Elastic Net¹⁷ and the stepwise model. The selection of the explanatory variables from the whole set of variables was based on a sequential process of variable elimination using Schwarz bayesian information criterion.

In the HC group, we performed correlations of WB SUVmean values with age and ASCVD risk scores separately.

For the neuropsychological testing categories, we first evaluated the values for normal distribution using the D'Agostino and Pearson normality test. For the categories that did not pass the normality test, we performed Spearman correlations (nonparametric) with SUVs, while for those that passed the normality tests, Pearson correlations with SUVs were performed. As a result of multiple correlations, only values of $p < 0.01$ were considered to be significant.

SAS version 9.4 (SAS Institute, Cary, NC) and Prism version 7.01 (GraphPad Software, Inc, San Diego, CA) were used for the statistical analyses.

Data availability statement

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Participant groups and clinical characteristics

Forty-seven HIV+ patients (age 53.4 ± 4.7 years) with at least 1 year of continuous ART and HIV VL below the limit of detection in both plasma (<40 copies/mL) and CSF (<20 copies/mL) at the time of scanning were recruited. Participants tested positive for HIV infection at a mean of 19 ± 8.8 years earlier. Their reported nadir CD4 count ranged from 0 to 676 (mean $159 \pm 162 \times 10^6$ cells/L). Ten HIV- participants (mean age 53.9 ± 4.7 years) and 19 HCs (mean age 50.6 ± 7.1 years) were included in the study.

The 3 groups were matched for age but not for sex or ethnicity (table 1). There were no differences in BMI, cholesterol, triglyceride, or FBS levels among the groups. SBP and DBP values were different among groups ($p < 0.0001$ for SBP, $p < 0.003$ for DBP). SBP was higher in the HIV+ and HIV- groups compared to the HC group ($p < 0.0001$ and $p < 0.0002$) but not different between the HIV+ and HIV- groups. DBP was higher in HIV+ compared to HC ($p = 0.002$) but not compared to HIV- participants. In addition, HCs showed lower ASCVD risk scores compared to HIV+ participants ($p = 0.012$).

Twenty-three percent of HIV+ and 10% of HIV- participants tested positive for the HCV antibody. HIV+ participants had a higher rate of drug abuse history compared to HIV- participants (60% vs 20%) and a higher rate of alcohol abuse history (21% vs 0%). In the HIV+ group, 28 participants reported drug use (≥ 1) that affected life or work (24 reported cocaine, 3 reported amphetamine, and 5 reported heroin use). Two of 10 HIV- participants reported a history of cocaine use. Thirty HIV+ and 2 HIV- participants reported a history of marijuana use. There was no reported drug or alcohol abuse history in the HC group. Approximately 32% of our HIV+ participants were current smokers compared to only 1 HIV- participant and 1 HC.

Neuropsychological testing results

There were no differences in the percentage of participants meeting criteria for HAND between HIV+ and HIV- participants (table 2). No neuropsychological testing was obtained for the HC group; however, no psychiatric or neurologic problems were reported.

WB SUVmean and SUVmax

There were no significant differences between groups for WB SUVmean ($p = 0.055$). Although the p value was not significant, we found a borderline difference between HIV+ and HC participants ($p = 0.047$, difference -0.7499 , 95% confidence interval [CI] -1.491 to -0.008942). For SUVmax, group differences were significant ($p = 0.011$), with HIV+ participants showing lower values compared to HCs ($p = 0.009$, difference -2.668 , 95% CI -4.724 to -0.6119) (figure 2).

Figure 2 (A.a, A.b) Whole-brain standardized uptake value (mean/maximum) and regional relative standardized uptake values for the (B) caudate, (C) thalamus, (D) putamen, and (E) cerebellum in healthy control, HIV+, and HIV- participants

Mean values are shown in red.

A subset analysis excluding patients with HCV showed similar results compared to the whole dataset: there were no differences between groups for WB SUVmean ($p = 0.08$), while for SUVmax, group differences were significant ($p = 0.018$), with HIV+ participants showing lower values compared to HCs ($p = 0.022$).

In another subset analysis, WB SUVmean and SUVmax were higher in HIV+ participants with no major comorbidity compared to those with ≥ 1 major comorbidity (unpaired t test, $p = 0.039$ and $p = 0.031$, respectively). In addition, WB SUVmean and SUVmax were higher in HIV+ participants with ASCVD risk scores $< 7.5\%$ compared to participants with scores $> 7.5\%$ ($p = 0.017$ and $p = 0.02$, respectively). There were, however, no differences in SUVs between HIV+ participants with a history of AIDS-defining illnesses vs those without such a history ($p > 0.05$).

WB SUV correlations

When HIV+ and HIV- participants were evaluated as 1 group, WB SUVmean and SUVmax correlated with ASCVD risk scores ($p = 0.004$, $r = -0.38$, $R^2 = 0.146$ for SUVmean; $p = 0.0019$, $r = -0.413$, $R^2 = 0.17$ for SUVmax) (figure 3). When HIV+ participants were evaluated separately, there were again significant correlations with ASCVD scores ($p = 0.0024$, $r = -0.454$, $R^2 = 0.199$ for SUVmean; $p = 0.002$, $r = -0.446$, $R^2 = 0.206$ for SUVmax) but no correlations with estimated length

of infection, estimated duration of infection before ART was started, or nadir CD4 value.

In the HC group, WB SUVmean values correlated with age ($p = 0.029$, $r = -0.50$, $R^2 = 0.25$) but not with ASCVD risk score ($p > 0.05$).

With the use of stepwise and elastic net variable selection methods, WB SUVmean and SUVmax were best predicted by ASCVD risk scores.

Subregional SUV measurements

There were no statistically significant differences between right and left VOIs in any region when the groups were assessed separately or when they were combined. All the results reported below reflect averaged right and left VOI values for each region.

Thalamic absolute and relative SUVmean values were significantly different between groups ($p < 0.0001$ for both). Absolute SUVmean values were lower in HIV+ compared to HC ($p = 0.0001$, difference -2.33 , 95% CI -3.371 to -1.29) but not to HIV- ($p = 0.73$, difference -0.3976 , 95% CI -1.73 to 0.9353) participants. Relative thalamic SUVmean values, however, were lower in HIV+ compared to HIV- ($p = 0.02$, difference -0.09103 , 95% CI -0.1701 to -0.012) and HC ($p = 0.0001$, difference -0.2083 , 95% CI -0.27 to -0.1466) (figure 2) participants. In some HIV+ patients, thalamic

Figure 3 Scatterplots of whole-brain standardized uptake values (A) mean and (B) maximum and atherosclerotic cardiovascular disease scores in HIV+ and HIV- participants combined

hypometabolism could be detected visually compared to nearby caudate and putamen metabolism (figures 4 and 5).

For the caudate, absolute SUVmean significantly differed between groups ($p = 0.008$), and pairwise comparisons showed that it was lower in HIV+ compared to HC ($p = 0.004$, difference -1.635 , 95% CI -2.788 to -0.4819) but not to HIV- ($p = 0.86$, difference -0.3017 , 95% CI -1.779 to 1.176) participants. Relative caudate SUVmean, on the other hand, was not different between groups ($p = 0.053$). Even though the p value was >0.05 , group comparisons showed borderline differences between HIV+ and HC participants ($p = 0.053$, difference -0.08926 , 95% CI -0.1794 to 0.0009341).

For the putamen, there were no differences in absolute or relative SUVmean values between the 3 groups ($p = 0.12$ and $p = 0.24$).

For the cerebellum, absolute SUVmean values of the 3 groups were significantly different ($p = 0.033$): lower in HIV+ compared to HC ($p = 0.021$, difference -0.8936 , 95% CI -1.669 to -0.1179) but not compared to HIV- participants. Cerebellum relative SUVmean values, however, were not different between groups ($p = 0.53$) (figure 2).

Subregional SUV correlations

Thalamus and caudate absolute SUVmean values correlated with ASCVD risk scores when HIV+ and HIV- participants

Figure 4 (A) Example of axial PET image from a HC and (B) close-up views of the basal ganglia and thalami in 1 HC, 1 HIV-, and 1 HIV+ participant

Top row shows axial PET images; bottom row shows 3-dimensional maximum intensity projection images encompassing the entirety of the basal ganglia and thalami from the same participants. Thalamic hypometabolism with respect to basal ganglia can be detected visually in the HIV+ participant, especially compared to the healthy control (HC).

Figure 5 Varying degrees of thalamic hypometabolism and heterogeneity in (A) 2 healthy controls compared to (B) 4 HIV+ participants

Top rows show axial PET images; bottom rows show 3-dimensional maximum intensity projection images encompassing the entirety of the basal ganglia and thalami from the same participants.

were evaluated together ($p = 0.0006$, $r = -0.45$, $R^2 = 0.20$ for thalamus; $p = 0.0016$, $r = -0.42$, $R^2 = 0.176$ for caudate). When HIV+ participants were evaluated separately (taking HIV status and adding 3 HIV-related variables: estimated length of infection, estimated duration of infection before ART was started, and nadir CD4 value), thalamus and caudate SUVmean values again correlated with ASCVD risk scores ($p = 0.0016$, $r = -0.463$, $R^2 = 0.210$ for thalamus; $p = 0.0026$, $r = -0.44$, $R^2 = 0.194$ for caudate) but not with the rest of the variables.

When HIV+ and HIV- participants were evaluated together, relative thalamic SUVmean values correlated with ASCVD risk scores ($p = 0.01$, $r = -0.347$, $R^2 = 0.12$), and participants with a history of drug use had borderline lower relative SUVmean values compared to participants who did not report a history of drug use ($p = 0.011$).

With the variable selection methods, absolute thalamic and caudate SUVmean values were best predicted by ASCVD risk scores in the HIV+ group and in the combined HIV+ and HIV- group.

Relative thalamic SUVmean values, on the other hand, were best predicted by HIV status when the HIV+ and HIV- groups were assessed in combination. No predictive variables were found when the HIV+ group was assessed separately. No variables were found to be predictive of relative caudate SUVs either.

Correlations of SUV with neurocognitive testing

There were no significant correlations between SUVs (WB SUVmean/max, regional absolute and relative SUVmean values) and the major neuropsychological test results (Global Deficit Score and overall T scores) or any of the absolute and scaled score values of individual domains.

Discussion

Limited literature is available on the use of brain FDG-PET to study the effects of chronic HIV-1 in the recent ART era. In 1 study, 55% of patients exhibited varying mesial frontal reductions in glucose metabolism,⁹ while a second study reported small reductions in glucose uptake in the anterior cingulate cortex in HIV+ patients.¹⁰ Both studies, however, evaluated relatively homogeneous patient populations, with most or all participants being white. In addition, neither study included participants with comorbid conditions commonly encountered in HIV+ patients.

Because our HIV+ patient population included many comorbid conditions, we chose HIV- participants with a comparable range of comorbid conditions for comparison, as well as HCs without significant comorbid conditions (table 1). While WB SUVmax was lower in HIV+ compared to HC participants, the values were best predicted by the ASCVD risk scores rather than HIV status, emphasizing the strong influence of cardiovascular disease on brain metabolism. Lower WB SUVmean and SUVmax in HIV+ participants with comorbid conditions compared to those without comorbid conditions and in participants with higher compared to those with lower ASCVD risk scores further demonstrate the importance of comorbid conditions, especially cardiovascular disease, on WB metabolism. Along similar lines, in an MRI study with combination ART-treated patients, white matter hyperintensities were more closely correlated with the participant's age and blood pressure than virologic parameters.¹⁸ Those findings, like ours, strongly underscore the effect of cardiovascular disease in this vulnerable patient population^{19–22} and the importance of better screening and control strategies^{23–25} to halt its associated neurocognitive decline. Our findings have significant clinical implications for the underlying pathophysiology of neurocognitive dysfunction in HIV+ participants and raise the burden on neurologists to

carefully assess HIV+ participants for cardiovascular disease rather than attribute their neurologic decline solely to persistent HIV effects on the brain despite optimal peripheral control of the infection. What complicates matters in this setting, however, is the known effect of HIV infection on cardiovascular disease related to factors such as obesity, dyslipidemia, and combination ART.^{26–28} Further studies are thus needed to better establish the interactions between HIV and comorbid conditions.

Our findings, however, also point to an identifiable HIV effect on subregional brain metabolism. We specifically chose subcortical/central brain regions to assess on the basis of reported glucose metabolism abnormalities in the pre-ART era.^{5,8,29,30} In our study, the thalamus showed the most significant hypometabolism in HIV+ participants, which could even be confirmed by qualitative visual observation in some HIV+ patients (figures 4 and 5). Relative thalamic SUVmean was lower in HIV+ compared to HIV– participants, suggesting that thalamic hypometabolism was slightly more pronounced with respect to WB metabolism in HIV+ compared to HIV– participants. Unlike FDG uptake in WB, which was best predicted by cardiovascular disease, relative thalamic SUVmean values were best predicted by HIV status. Caudate and cerebellar relative SUVmean, on the other hand, showed no difference between the groups, suggesting that those metabolism abnormalities are in line with global brain metabolism abnormalities.

It is generally agreed that the basal ganglia are especially vulnerable to the effects of the HIV-1 virus and were reported to show hypermetabolism in the early stages of infection,^{8,30} followed by volume loss and hypometabolism later in the disease process.^{29,30} Although it was not a major component of neuropathology in the pre-ART era, we believe that thalamic involvement plays a more central role in the post-ART era. In fact, thalamic volume loss in ART-treated patients has been identified in multiple volumetric MRI studies.^{31–34} Studies evaluating HIV+ patients with alcoholism found evidence of smaller thalamic volumes in HIV+ nonalcoholic participants,³² suggesting a virus-related effect. One study found substantial acceleration of volume loss with aging in cortical areas of HIV+ individuals and the thalamus, all regions supporting higher-order cognition and integration of function.³⁵

The thalamus is considered a major relay center of somatosensory spinal, cranial nerve, visual, auditory, basal ganglia, and cerebellar inputs to the cortex and a main subcortical component of arousal and alertness.³⁶ The thalamus also appears to control functional connectivity within and across cortical areas, thus determining how a cognitive process is implemented across distributed cortical microcircuits.³⁷ In support, executive dysfunction affecting higher-order cognitive constructs such as planning and organization can be caused by thalamic injury.³⁸ Although we did not find statistically significant correlations between thalamic SUVs and neuropsychological test scores in our participants, thalamic

hypometabolism could still potentially be related to subtle abnormalities noted in this patient population for the domains of concentration, attention, memory, and impaired executive function.³⁹

There was no correlation between our PET findings and estimated duration of infection, estimated duration of infection before treatment, or nadir CD4 count. Similar findings were also noted in morphometric studies.³³ This may be related to disease complexity, with underestimated duration of infection in many participants and incomplete documentation of nadir CD4 and other clinical variables. Although it seems reasonable to assume that the duration of infection before virologic suppression would have an effect on brain glucose metabolism, this is still poorly estimated because many of the participants do not recognize infection until late in the disease process, when treatment is generally started. Poor adherence to treatment also likely affects this measurement because treatment interruption could potentially reset the clock as far as virologic control.

Our results differ from 2 studies that reported FDG hypometabolism in treated HIV+ patients. This may be due to a combination of factors, including a longer duration of infection in our group (19 years vs 10 years¹⁰ or 12 years⁹), along with a more heterogeneous, multiracial patient population. Our study included HIV+ and HIV– participants with multiple comorbid conditions.

We observed heterogeneity of FDG uptake in the thalami, which has been described previously on FDG-PET imaging.⁴⁰ This likely reflects a combination of white and gray matter in this relay center, dividing the structure into multiple nuclei. Although we noted heterogeneous thalamic FDG uptake in all groups, it was most noticeable in the HIV+ group (figures 4 and 5). Heterogeneity could have affected the results of pixel-wise analyses used in previous studies^{9,10} because it is unlikely that uptake within the nuclei would be spatially identical between all participants. Heterogeneity of uptake in adjacent voxels could thus have masked thalamic FDG uptake changes in prior studies.

In a recent meta-analysis describing MRI findings attempting to measure HIV effects on brain macroarchitecture,⁴¹ publication year was associated with recent reductions in many neurostructural effects, which the authors attributed to improvement in treatment strategies in recent ART compared to early post-ART eras. Our patient population is similarly treated with state-of-the-art combination ART, which could potentially explain the lack of differences that we found in WB and other brain regions (except for the thalamus) between HIV+ and HIV– participants.

Our study is limited mainly by the small number of HIV– participants with comorbid conditions. Adding more HIV– participants might potentially differentiate HIV– from HIV+ participants as far as WB FDG uptake. Another

limitation is that the HIV+ and HIV− groups were not exactly matched for sex, ethnicity, or comorbid conditions (table 1). We believe, however, that it would be prohibitive to match all the variables between groups because of large variances, necessitating very large sample sizes. One more limitation is that the HC group received a higher FDG dose than either the HIV− or HIV+ group, but this should not influence SUV measurements. In fact, we did not demonstrate a difference between the groups in the putamen, which rules out a systematic error due to different dosing. In addition, our main finding was related to the thalamic relative SUVmean, which normalizes uptake in the thalamic VOI to that of the WB, further eliminating any systematic differences due to different dosing. We also did not have MRI scans for the HC group, which prevented us from performing partial volume correction on the PET scans. Although all participants obtained CT scans for attenuation correction purposes, they usually have very low resolution and cannot be used for segmentation and partial volume correction. Finally, although almost a third of our HIV+ participants were smokers, we did not include current smoking in the variable selection models, mainly because recent literature suggests no effect of smoking on brain FDG uptake.⁴² We believe, however, that the cardiovascular effects of smoking are probably still accounted for by the ASCVD calculation, which includes smoking as a factor.

We have identified glucose metabolism abnormalities in HIV+ and HIV− participants with comparable comorbid conditions, suggesting an important role of comorbid conditions, especially cardiovascular disease, in the global and regional deficits. Although brain hypometabolism has been described in association with hypertension and cardiovascular disease,^{43–46} it has not been evaluated in depth in HIV+ participants. Besides comorbid conditions, however, at least 1 area in the brain, the thalamus, seems to have more significant damage in HIV+ participants compared to HIV− participants, suggesting a possible role of the virus. The implications of this finding are unclear; however, it opens the door to more serious discussion about neurocognitive abnormalities still prevalent in HIV+ participants despite treatment and virologic suppression in both the periphery and brain.

Author contributions

D.A. Hammoud, E. Tramont, S.I. Rapoport, B.R. Smith, and A. Nath conceived of and designed the study. D.A. Hammoud, S. Sinharay, S. Steinbach, P.G. Wakim, K. Traino, K. Geanopoulos, A.K. Dey, J. Snow, N.N. Mehta, and B.R. Smith evaluated the study participants and/or collected the data. D.A. Hammoud and P.G. Wakim performed the statistical analysis. All authors participated in drafting the article and/or revising it critically for intellectual content. All authors gave final approval of the submitted manuscript.

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Disclosure

D. Hammoud, S. Sinharay, S. Steinbach, P. Wakim, K. Geanopoulos, K. Traino, A. Dey, E. Tramont, S. Rapoport, and J. Snow report no disclosures relevant to the manuscript. N. Mehta receives research grants to the National Heart, Lung, and Blood Institute from AbbVie, Janssen, Celgene, and Novartis. B. Smith and A. Nath report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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