ORIGINAL CONTRIBUTION

^{11}C-PiB Imaging of Human Immunodeficiency Virus–Associated Neurocognitive Disorder

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Objective: To evaluate whether the amyloid-binding agent carbon 11–labeled Pittsburgh Compound B (^{11}C-PiB) could differentiate Alzheimer disease (AD) from human immunodeficiency virus (HIV)–associated neurocognitive disorder (HAND) in middle-aged HIV-positive participants.

Design: ^{11}C-PiB scanning, clinical assessment, and cerebrospinal fluid (CSF) analysis were performed. Both χ^2 and *t* tests assessed differences in clinical and demographic variables between HIV-positive participants and community-living individuals observed at the Knight Alzheimer's Disease Research Center (ADRC). Analysis of variance assessed for regional differences in amyloid-β protein 1-42 (Aβ42) using ^{11}C-PiB.

Setting: An ADRC and HIV clinic.

Participants: Sixteen HIV-positive participants (11 cognitively normal and 5 with HAND) and 19 ADRC participants (8 cognitively normal and 11 with symptomatic AD).

Main Outcome Measures: Mean and regional ^{11}C-PiB binding potentials.

Results: Participants with symptomatic AD were older ($P<.001$), had lower CSF Aβ42 levels ($P<.001$), and had higher CSF tau levels ($P<.001$) than other groups. Regardless of degree of impairment, HIV-positive participants did not have increased ^{11}C-PiB levels. Mean and regional binding potentials were elevated for symptomatic AD participants ($P<.001$).

Conclusions: Middle-aged HIV-positive participants, even with HAND, do not exhibit increased ^{11}C-PiB levels, whereas symptomatic AD individuals have increased fibrillar Aβ42 deposition in cortical and subcortical regions. Observed dissimilarities between HAND and AD may reflect differences in Aβ42 metabolism. ^{11}C-PiB may provide a diagnostic biomarker for distinguishing symptomatic AD from HAND in middle-aged HIV-positive participants. Future cross-sectional and longitudinal studies are required to assess the utility of ^{11}C-PiB in older individuals with HAND.

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HUMAN IMMUNODEFICIENCY virus (HIV) can cause neurologic dysfunction, leading to HIV-associated neurocognitive disorder (HAND). HAND includes the previous designation of HIV-associated dementia and milder forms, such as mild neurocognitive disorder and asymptomatic neurocognitive impairment.[1] Before the advent of highly active antiretroviral therapy (HAART), HAND was present in approximately 50% of all HIV-positive individuals. HAART has led to a decrease in the incidence of HAND, but its prevalence (approximately 50%) remains unchanged,[2-4] with milder forms (both mild neurocognitive disorder and asymptomatic neurocognitive impairment) predominating. The proportion of cases of HAND with a CD4 cell count greater than 200/μL continues to increase in the post-HAART era.[5] These results suggest that HAND will continue to be a major issue for the HIV community as it ages.

Older age has been associated with increased risk of HAND independent of the duration of HIV infection.[6-8] Pathologic similarities exist between HAND and neurodegenerative disorders such as Alzheimer disease (AD), which is characterized by the presence of extracellular deposits of amyloid-β protein 1-42 (Aβ42) in the form of plaques and aggregations of microtubule-associated, tau-forming, neurofibrillary tangles. Typically, diffuse[9,10] rather than neuritic[11] plaques have been observed in HIV-positive individuals at autopsy compared with age-matched community participants. Observed pathologic changes within HIV-positive participants have been seen despite virologic control by HAART.[12] HAART may not provide sufficient protection to prevent the development of HAND.[13]

Multiple pathways could be responsible for increases in Aβ42 deposition in the setting of HIV. Transactivator of transcription (Tat) is a HIV protein that can inhibit the activity of neprilysin, a metal-

Table. Demographic, Clinical, and Laboratory Characteristics of the Study Participants

Characteristic	Cognitively Normal HIV-Positive Participants (n = 11)	HIV-Positive Participants With HAND (n = 5)	Cognitively Normal ADRC Participants (n = 8)	ADRC Participants With Symptomatic AD (n = 11)	*P* Value
Age, mean (SE), y	48 (3)	46 (3)	48 (1)	75 (2)	<.001
Male sex, No. (%)	9 (82)	5 (100)	7 (88)	6 (55)	.14
Educational level, mean (SE), y	15 (1)	13 (1)	15 (1)	13 (1)	.19
Receiving HAART, No. (%)	9 (82)	4 (80)	NA	NA	.86
Presence of at least 1 *APOE*4 allele, No. (%)	5 (45)	2 (50)[a]	3 (38)	6 (55)	.91
Mean GDS	0.15 (0.19)	1.82 (0.51)	NA	NA	<.001
CDR, No. (%)	NA	NA			<.001
0			8 (100)	0	
1			0	8 (73)	
2			0	3 (27)	
Laboratory tests					
CD4 cell count, mean (quartiles), /μL	477 (335, 579)	645 (366, 905)	NA	NA	.35
Nadir CD4 cell count, mean (quartiles), /μL	194 (107, 265)	353 (161, 405)	NA	NA	.14
Log VL, mean (quartiles), copies/mm^3	2.21 (1.69, 2.16)	2.39 (1.69, 2.20)	NA	NA	.76
CSF Aβ42, mean (SE), pg/mL	615 (69)	730 (116)	699 (53)	353 (142)	.03
CSF tau, mean (SE), pg/mL	147 (19)	221 (43)	218 (24)	823 (173)	<.001
MCBP, mean (SE)	−0.004 (0.03)	−0.008 (0.05)	−0.02 (0.03)	0.77 (0.23)	<.001

Abbreviations: Aβ42, amyloid-β protein 1-42; AD, Alzheimer disease; ADRC, Alzheimer's Disease Research Center; *APOE*, apolipoprotein E; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; GDS, Global Deficit Score; HAART, highly active antiretroviral therapy; HAND, HIV-associated neurocognitive disorder; HIV, human immunodeficiency virus; MCBP, mean cortical binding potential; NA, not applicable; VL, viral load.
[a] One patient did not undergo *APOE* testing.

loendoprotease involved in the degradation of Aβ42.[9] Tat can bind to lipoprotein receptor–related protein, leading to a decrease in Aβ42 clearance from the brain. Tat also attaches to the receptor for the advanced glycation end products, which may result in increased Aβ42 absorption from the blood.[14] Infected macrophages and microglia can also shed viral proteins, resulting in an upregulation of amyloidogenesis-promoting cytokines (ie, tumor necrosis factor and interleukin factor 1β).[15] These cytokines not only directly contribute to neurodegeneration but also promote an increase in Aβ42 generation by stimulating expression of the β site amyloid precursor protein cleaving enzyme 1.[16] HAND and AD may therefore share similar molecular mechanisms that lead to neurodegeneration.[17] What is not known is whether fibrillar cerebral amyloid plaques can be visualized in participants with HAND.

Cerebrospinal fluid (CSF) biomarkers can reflect pathogenic cerebral amyloid deposition. Decreased CSF Aβ42 and increased CSF tau can discriminate symptomatic AD participants and cognitively normal individuals at high risk for symptomatic AD from cognitively normal individuals at low risk for symptomatic AD.[18-20] At least some participants with HAND have CSF Aβ42 values comparable to symptomatic AD individuals.[21,22] Reductions in CSF Aβ42 have been shown to be present in almost all individuals with increased fibrillar amyloid deposition within the brain as assessed with positron emission tomography amyloid binding of carbon 11–labeled Pittsburgh Compound B (N-methyl-[^{11}C]2-[4-methylaminophenyl]-6-hydroxybenzothiazole) (^{11}C-PiB).[19,23-28] Mintun et al[29] previously demonstrated that ^{11}C-PiB has excellent sensitivity and specificity in diagnosing symptomatic AD in participants observed at the Knight Alzheimer's Disease Research Center (ADRC). This technique could serve as a supportive diagnostic biomarker. In this study we used ^{11}C-PiB to assess for the presence of fibrillar amyloid plaques in middle-aged HIV-positive participants with and without HAND.

METHODS

STUDY PARTICIPANT SELECTION

Participants positive for HIV (n=16) (age range, 38-67 years) with confirmed serologic status were selected from a cohort of the Central Nervous System Highly Activated Retroviral Therapy Effects Research study followed up at Washington University in St Louis, Missouri. The HIV-positive participants without HAND have previously been described.[30] Sex- and education-matched community participants (n=19) (age range, 48-89 years) were selected from a sample of community-living individuals involved in longitudinal studies of aging and dementia at the ADRC. Approval to conduct this study was obtained from our Human Research Protection Office. Written informed consent was obtained from all participants or their designee.

^{11}C-PiB imaging was performed within approximately 2 years of clinical assessment, as were lumbar puncture and genetic testing when possible. DNA was extracted from peripheral blood samples using standard procedures. Apolipoprotein E (*APOE*) genotyping was performed as previously described.[31] Cognitive status of HIV-positive participants was assessed using the previously validated Global Deficit Score, with a diagnosis of HAND given if the score was 0.5 or greater.[22] A diagnosis of cognitively normal was given to all HIV-positive participants if the Global Deficit Score was less than 0.5. A detailed medical history was obtained from all HIV-positive participants, with individuals excluded if they had a previous history of other neurologic illness or infections, cerebrovascular disease or strokes, or major psychiatric disorders. To ensure no recent use of any substances of abuse, we performed a urine toxicology screen (methamphetamine, cocaine, opiates, phenylcyclidine, and cannabis) before

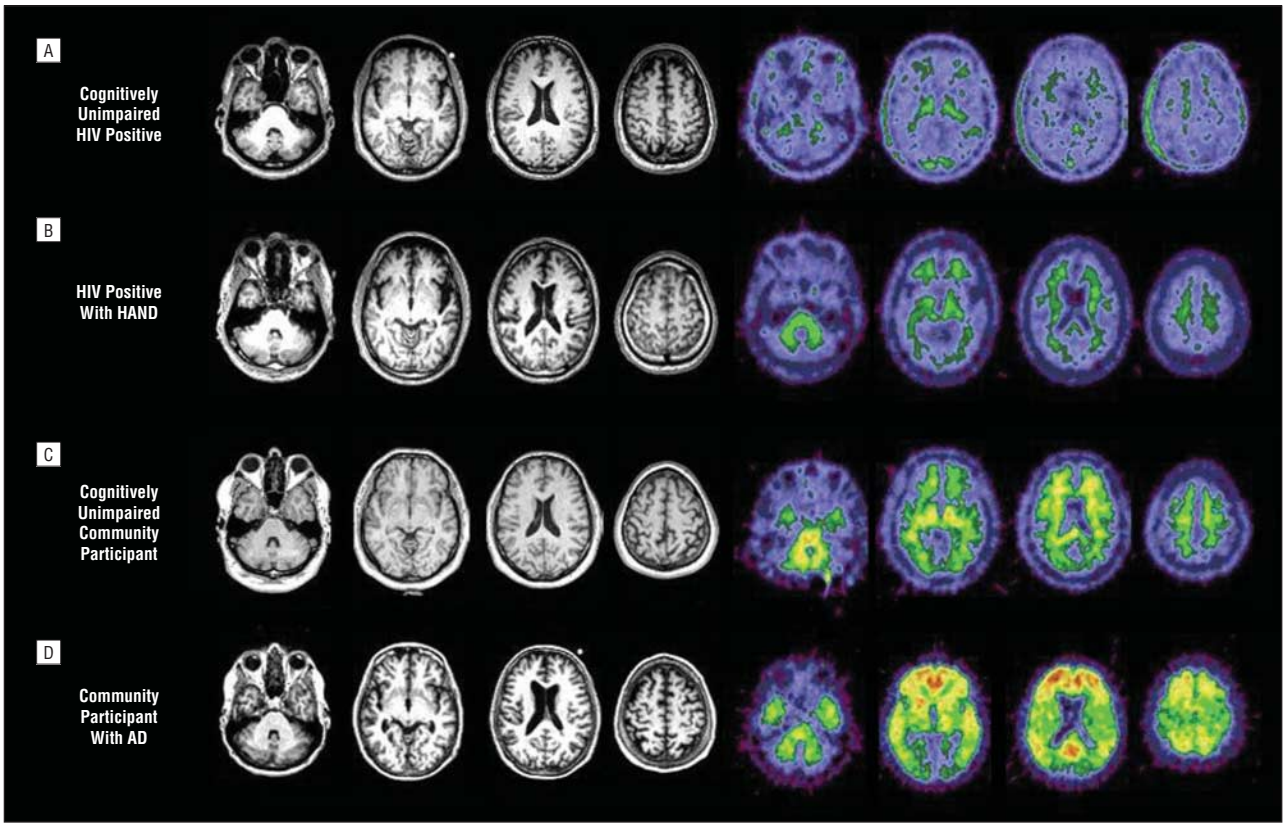

Figure 1. Magnetic resonance imaging (MRI) and carbon 11–labeled Pittsburgh Compound B (^{11}C-PiB) imaging in 4 representative study participants. Representative structural MRIs and ^{11}C-PiB images for a cognitively normal human immunodeficiency virus (HIV)–positive participant (A), an HIV-positive participant with HIV-associated neurocognitive disorder (HAND) (B), a cognitively normal Alzheimer's Disease Research Center (ADRC) participant (C), and ADRC participant with symptomatic Alzheimer disease (AD) (D). Only the symptomatic AD participants had increased fibrillar amyloid deposition using ^{11}C-PiB.

imaging for all HIV-positive participants. Only HIV-positive participants with a confirmed positive test result underwent imaging. For ADRC participants, dementia severity was assessed using the Clinical Dementia Rating scale; in this study, all participants with dementia had mild or moderate dementia (Clinical Dementia Rating of 1 and 2). The clinical diagnosis of AD was made in accordance with standard criteria.[32] Cognitive normality was designated by a Clinical Dementia Rating of 0.

CSF EVALUATION

Collection of CSF was obtained as previously described,[24] with Aβ42 and tau levels analyzed using a commercial enzyme-linked immunosorbent assay (Innogenetics). Samples were kept on ice, and assays were performed on aliquots after a single thaw.

^{11}C-PiB IMAGING

Participants underwent ^{11}C-PiB imaging as previously described.[29] In brief, the tracer was injected into the antecubital vein, and 60-minute, 3-dimensional, dynamic positron emission tomography was performed. Each participant also underwent T1-weighted anatomical magnetic resonance imaging, which was coregistered to the ^{11}C-PiB scan for region of interest analysis.[24] The cerebellum was used as a reference region.[29] Logan graphic analyses were performed, and ^{11}C-PiB distribution volumes were calculated for the regions involved in the calculation of mean cortical binding potential (MCBP; prefrontal, lateral temporal, precuneus, and gyrus rectus)[29] and the caudate. The caudate was chosen because this region has been previously shown to be affected by HAND.[33]

STATISTICAL ANALYSIS

Statistical differences for demographic and clinical values were assessed among HIV-positive unimpaired participants, HIV-positive individuals with HAND, unimpaired community participants, and community individuals with AD using analysis of variance. Analysis of variance with Bonferroni correction for multiple comparisons was also performed to determine whether MCBP and caudate binding potential for fibrillar amyloid plaque deposition varied among the 4 clinical groups.

RESULTS

Demographic variables, except for age, were similar for all groups (**Table**). The ADRC participants with symptomatic AD on average were older ($P<.001$). *APOE* genotyping was performed in 97% of the participants (1 HIV-positive participant did not undergo testing). No significant differences were present among the groups in regard to the presence of at least 1 *APOE4* allele.

Overall, 77% of the participants had a lumbar puncture performed. The ADRC participants with symptomatic AD had lower CSF Aβ42 ($P<.001$) and elevated tau ($P<.001$) levels (Table) compared with other groups. HIV-positive participants did not have evidence of increased fibrillar amyloid plaques according to ^{11}C-PiB imaging (**Figure 1**, A and B). This was observed despite the fact that 5 HIV-positive participants had CSF Aβ42 values less than 500 pg/mL, a level that has been shown in a previous

study[25] to be sensitive for distinguishing cognitively normal and symptomatic individuals who are PIB positive. No significant differences in CSF Aβ42 existed for HIV-positive participants, with 2 HIV-positive patients with HAND having values less than 500 pg/mL. Almost all ADRC participants with no cognitive impairment had CSF Aβ42 values greater than 500 pg/mL (Figure 1C). The ADRC participants with symptomatic AD had increased fibrillar amyloid plaques using ^{11}C-PiB (Figure 1D).

We also assessed the relationship between fibrillar amyloid deposition using ^{11}C-PiB and CSF Aβ42. A matrix was created using previously reported cutoffs for CSF Aβ42 (<500 pg/mL) and MCBP (>0.18 arbitrary units) (**Figure 2**A). Regardless of the degree of cognitive impairment, all HIV-positive participants had low MCBP values within the left upper and lower quadrants of the matrix. The ADRC participants with symptomatic AD typically had low CSF Aβ42 and elevated MCBP values. To determine whether variation existed in fibrillar amyloid deposition, binding potentials were assessed within each of the regions of interest involved in calculating the MCBP and the caudate region. Only ADRC participants with symptomatic AD had significantly higher binding potentials within the cortical and subcortical areas (Figure 2B).

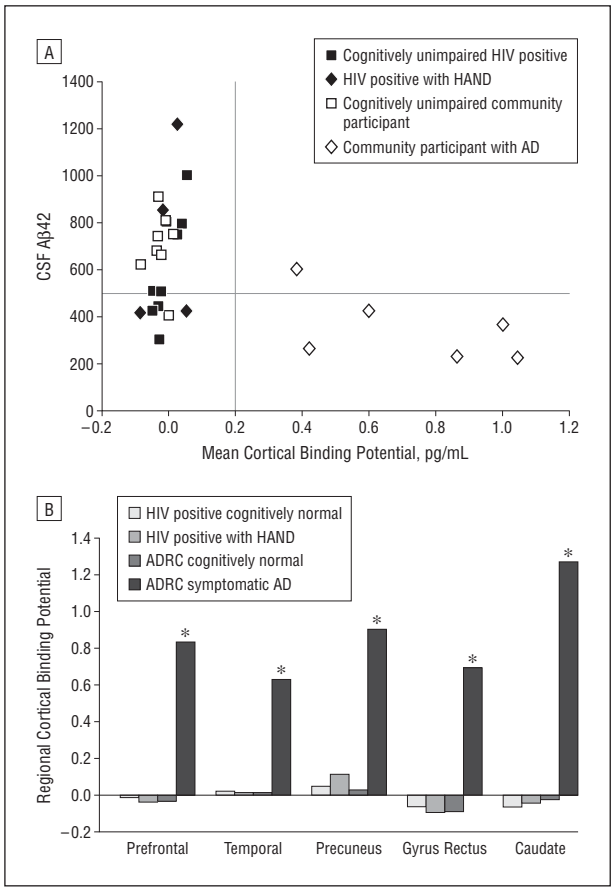

Figure 2. Mean cortical binding potential (MCBP) and regional binding potential for the 4 clinical groups. A, MCBP. A 2 × 2 matrix is created using cerebrospinal fluid (CSF) amyloid-β protein 1-42 (Aβ42) (<500 pg/mL) and MCBP (>0.18 arbitrary units). All human immunodeficiency virus (HIV)–positive participants, regardless of their degree of cognitive impairment, had normal carbon 11–labeled Pittsburgh Compound B imaging results (<0.18 arbitrary units). B, Regional cortical binding potential. For each region, symptomatic Alzheimer's Disease Research Center (ADRC) participants had higher binding potentials. AD indicates Alzheimer disease; HAND, human immunodeficiency virus–associated neurocognitive disorder; and asterisk, $P<.001$.

COMMENT

We observed that HIV-positive participants (both cognitively unimpaired and those with HAND) did not have increased fibrillar brain amyloid deposition using ^{11}C-PiB. Only the ADRC participants with symptomatic AD had elevated ^{11}C-PiB MCBP values (>0.18 arbitrary units).[24] No correlation existed between low CSF Aβ42 and ^{11}C-PiB MCBP values for HIV-positive participants, whereas the ADRC participants with low CSF Aβ42 values typically had increased ^{11}C-PiB MCBP values. Of the individuals studied in this small cohort, only symptomatic AD participants had significantly elevated CSF tau levels. Our findings suggest that ^{11}C-PiB MCBP can assist in differentiating HAND from AD. As the HIV-positive population continues to age, this distinction could be diagnostically important. A strong inverse correlation has previously been demonstrated between low CSF Aβ42 levels and increased ^{11}C-PiB MCBP values for symptomatic AD, as well as in cognitively normal individuals between 60 and 90 years of age.[19,24,26,28,34,35] In contrast, a low CSF Aβ42 level does not reliably predict elevated PIB binding in HIV-positive patients. In this study, only half of the HIV-positive participants with HAND had low CSF Aβ42 levels. We have previously reported that HAND participants can have low CSF Aβ42 levels.[22] Reasons for discrepancy between these studies may be due to the relatively small number of participants evaluated in this study, the age of participants, or differences in CSF collection methods because samples from a previous study were collected from multiple institutions.[22]

Because MCBP does not include subcortical areas, we also assessed fibrillar amyloid deposition within the caudate. We specifically chose the caudate because HAND is thought to heavily affect subcortical structures. Neuropathologic studies[36] have confirmed these observations, with the highest concentration of virus often found in the caudate. Previous neuroimaging studies[37-39] have also demonstrated hypermetabolism within subcortical structures in HIV-positive participants. What was surprising was that HIV-positive participants, regardless of their degree of impairment, did not have elevated amyloid-binding potentials within the caudate. Only symptomatic AD participants had significant elevations in ^{11}C-PiB values within the caudate. These results are in agreement with previous ^{11}C-PiB studies[40,41] in symptomatic AD participants. These results suggest that symptomatic AD has both cortical and subcortical components.

APOE, an apolipoprotein involved in lipid metabolism and transport, has been previously shown to modulate amyloid deposition neurodegeneration.[31,42-45] The presence of at least 1 *APOE4* allele is a potent risk factor for developing AD.[42] In contrast, the role of *APOE4* in HAND remains uncertain. An early study[46] found no correlation between the presence of the *APOE4* allele and HAND,

whereas a subsequent cohort study[47] observed an increase in the prevalence of HAND in *APOE4* HIV-positive individuals. These disparate results may reflect differences in the populations studied because *APOE4* genotype may modulate the risk of developing HAND, depending on age. In this study we did not observe a potential contribution of *APOE4* in developing HAND. This finding may reflect the younger age of HIV-positive participants with HAND who were assessed in our study. Future investigations of older HIV-positive participants with HAND are required.

The absence of elevated MCBP values in HIV-positive participants could result from (1) decreased Aβ42 production due to decreased synaptic activity[48]; (2) increased intraneuronal Aβ42 deposition, causing a reduction in overall extracellular concentrations[49]; or (3) increased Aβ42 brain deposition but in a more diffuse, nonfibrillar form that is ^{11}C-PiB negative.[10,50,51] Future longitudinal examinations, especially within older HIV-positive participants, are required to determine whether diffuse or oligomeric forms could with time subsequently become fibrillar (^{11}C-PiB–positive) deposits.[21,22] Our findings reinforce the importance of understanding amyloid metabolism in neurodegenerative disorders while confirming that ^{11}C-PiB could be a useful biomarker for discriminating AD from HAND in HIV-positive patients in the age group studied.

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