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

**Design:** 11C-PiB scanning, clinical assessment, and cerebrospinal fluid (CSF) analysis were performed. Both χ² 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 11C-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 11C-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 11C-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 11C-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. 11C-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 11C-PiB in older individuals with HAND.

Arch Neurol. 2012;69(1):72-77

---

**Human Immunodeficiency Virus–Associated Neurocognitive Disorder**

Older age has been associated with increased risk of HAND independent of the duration of HIV infection. 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 rather than neuritic 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. HAART may not provide sufficient protection to prevent the development of HAND.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cognitively Normal HIV-Positive Participants (n = 11)</th>
<th>HIV-Positive Participants With HAND (n = 5)</th>
<th>Cognitively Normal ADRC Participants (n = 8)</th>
<th>ADRC Participants With Symptomatic AD (n = 11)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SE), y</td>
<td>48 (3)</td>
<td>46 (3)</td>
<td>48 (1)</td>
<td>75 (2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>9 (82)</td>
<td>5 (100)</td>
<td>7 (88)</td>
<td>6 (55)</td>
<td>.14</td>
</tr>
<tr>
<td>Educational level, mean (SE), y</td>
<td>15 (1)</td>
<td>12 (1)</td>
<td>15 (1)</td>
<td>13 (1)</td>
<td>.19</td>
</tr>
<tr>
<td>Receiving HAART, No. (%)</td>
<td>9 (82)</td>
<td>4 (80)</td>
<td>NA</td>
<td>NA</td>
<td>.86</td>
</tr>
<tr>
<td>Presence of at least 1 APOE allele, No. (%)</td>
<td>5 (45)</td>
<td>2 (50)*</td>
<td>3 (38)</td>
<td>6 (55)</td>
<td>.91</td>
</tr>
<tr>
<td>Mean GDS</td>
<td>0.15 (0.19)</td>
<td>1.82 (0.51)</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CDR, No. (%)</td>
<td>NA</td>
<td>NA</td>
<td>8 (100)</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>0</td>
<td>0</td>
<td>8 (73)</td>
<td>3 (27)</td>
<td>.35</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, mean (quartiles), /µL</td>
<td>477 (335, 579)</td>
<td>645 (366, 905)</td>
<td>NA</td>
<td>NA</td>
<td>.35</td>
</tr>
<tr>
<td>Nadir CD4 cell count, mean (quartiles), /µL</td>
<td>194 (107, 265)</td>
<td>353 (161, 405)</td>
<td>NA</td>
<td>NA</td>
<td>.14</td>
</tr>
<tr>
<td>Log VL, mean (quartiles), copies/mm³</td>
<td>2.21 (1.69, 2.16)</td>
<td>2.39 (1.69, 2.20)</td>
<td>NA</td>
<td>NA</td>
<td>.76</td>
</tr>
<tr>
<td>CSF Ap42, mean (SE), pg/mL</td>
<td>615 (69)</td>
<td>730 (116)</td>
<td>699 (53)</td>
<td>353 (142)</td>
<td>.03</td>
</tr>
<tr>
<td>CSF tau, mean (SE), pg/mL</td>
<td>147 (19)</td>
<td>221 (43)</td>
<td>218 (24)</td>
<td>823 (173)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MCBP, mean (SE)</td>
<td>-0.004 (0.03)</td>
<td>-0.008 (0.05)</td>
<td>-0.02 (0.03)</td>
<td>0.77 (0.23)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: Ap42, 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.

*One patient did not undergo APOE testing.

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. 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.

11C-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. 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. A diagnosis of cognitive 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...
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. Cognitive normality was designated by a Clinical Dementia Rating of 0.

CSF EVALUATION

Collection of CSF was obtained as previously described, with 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.

11C-PiB IMAGING

Participants underwent 11C-PiB imaging as previously described. 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 11C-PiB scan for region of interest analysis. The cerebellum was used as a reference region. Logan graphic analyses were performed, and 11C-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) and the caudate. The caudate was chosen because this region has been previously shown to be affected by HAND.

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 11C-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

Figure 1. Magnetic resonance imaging (MRI) and carbon 11–labeled Pittsburgh Compound B (11C-PiB) imaging in 4 representative study participants. Representative structural MRIs and 11C-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 11C-PiB.
study\textsuperscript{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 \textsuperscript{11}C-PiB (Figure 1D).

We also assessed the relationship between fibrillar amyloid deposition using \textsuperscript{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 2A). 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).

We observed that HIV-positive participants (both cognitively unimpaired and those with HAND) did not have increased fibrillar brain amyloid deposition using \textsuperscript{11}C-PiB. Only the ADRC participants with symptomatic AD had elevated \textsuperscript{11}C-PiB MCBP values (>0.18 arbitrary units).\textsuperscript{24} No correlation existed between low CSF Aβ42 and \textsuperscript{11}C-PiB MCBP values for HIV-positive participants, whereas the ADRC participants with low CSF Aβ42 values typically had increased \textsuperscript{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 \textsuperscript{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 \textsuperscript{11}C-PiB MCBP values for symptomatic AD, as well as in cognitively normal individuals between 60 and 90 years of age.\textsuperscript{19,24,26,28,34} 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{40} have confirmed these observations, with the highest concentration of virus often found in the caudate. Previous neuroimaging studies\textsuperscript{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 \textsuperscript{11}C-PiB values within the caudate. These results are in agreement with previous \textsuperscript{11}C-PiB studies\textsuperscript{40,41} in symptomatic AD participants. These results suggest that symptomatic AD has both cortical and subcortical components.

\textit{APOE}, an apolipoprotein involved in lipid metabolism and transport, has been previously shown to modulate amyloid deposition neurodegeneration.\textsuperscript{31-42,45} The presence of at least 1 \textit{APOE4} allele is a potent risk factor for developing AD.\textsuperscript{35} In contrast, the role of \textit{APOE4} in HAND remains uncertain. An early study\textsuperscript{46} found no correlation between the presence of the \textit{APOE4} allele and HAND,
whereas a subsequent cohort study 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, (2) increased intraneuronal Aβ42 deposition, causing a reduction in overall extracellular concentrations, or (3) increased Aβ42 brain deposition in a more diffuse, nonfibrillar form that is 11C-PiB negative. Future longitudinal examinations, especially within older HIV-positive patients, are required to determine whether diffuse or oligomeric forms could with time subsequently become fibrillar (11C-PiB-positive) deposits. Our findings reinforce the importance of understanding amyloid metabolism in neurodegenerative disorders while confirming that 11C-PiB could be a useful biomarker for discriminating AD from HAND in HIV-positive patients in the age group studied.

Accepted for Publication: March 17, 2011.

Correspondence: Beau M. Ances, MD, PhD, Department of Neurology, Washington University in St Louis, Campus Box 8111, 660 S Euclid Ave, St Louis, MO 63110 (ances@wustl.edu).

Author Contributions: Study concept and design: Ances, Benzinger, and Clifford. Acquisition of data: Ances, Benzinger, Christensen, Thomas, Teshome, Venkat, and Alda. Analysis and interpretation of data: Ances, Benzinger, Christensen, Venkat, Fagan, Holtzman, Morris, and Clifford. Drafting of the manuscript: Ances. Critical revision of the manuscript for important intellectual content: Benzinger, Fagan, Morris, and Clifford. Statistical analysis: Ances, Thomas, and Venkat. Obtained funding: Ances and Morris. Administrative, technical, and material support: Christensen, Alda, and Teshome. Study supervision: Ances, Fagan, Holtzman, Morris, and Clifford.

Financial Disclosure: Dr Ances is currently participating in a clinical trial of antidementia drugs sponsored by Pfizer. Dr Benzinger consults for Biomedical Systems Inc and ICON Medical Imaging and receives research support from Avid Radiopharmaceuticals. Dr Holtzman reports consulting for Pfizer, Bristol-Myers Squibb, and Innogenetics and is on the scientific advisory board of En Vivo, Satori, and C2N Diagnostics. Dr Morris is currently participating in clinical trials of antidementia drugs sponsored by Janssen, Pfizer, and Eli Lilly Company. He reports consulting for AstraZeneca, Bristol-Myers Squibb, Eisai, Elan/Janssen Alzheimer Immunotherapy Program, Genentech, Lilly, Merck, Novartis, Otsuka Pharmaceuticals, Pfizer/Wyeth, and Schering Plough. Dr Clifford reports serving on data monitoring committees and/or as a scientific adviser to Biogen Idec, Elan, Pfizer, Roche, Forest Labs, Genentech, GlaxoSmithKline, Millennium, Schering Plough, Bristol-Myers Squibb, and Genzyme with research support from Pfizer, Schering Plough, Bavarian Nordic, NeurogesX, GlaxoSmithKline, Tibotec, Boehringer Ingelheim, Gilead, and Biogen Idec.

Funding/Support: This study was supported by pilot grant 3255 P50AG05681 from the ADRC (Drs Ances and Morris), grant K23MH081786 from the National Institute of Mental Health (Dr Ances), grant R01NR012657 from the National Institute of Nursing Research (Dr Ances), grant DF10052 from the Dana Foundation (Dr Ances), American Roentgen Ray Society Scholar Award (Dr Benzinger), grant 22005 from the National Institute of Mental Health (Central Nervous System Highly Activated Retroviral Therapy Effects Research) (Drs Ances and Clifford), and grants P01-AG026276 and P01-AG03991 from the National Institutes of Health (Dr Morris).

Additional Contribution: We acknowledge the assistance of the ADRC clinical, genetics, imaging, and psychometrics cores.

REFERENCES


