HIV-associated cognitive disorders: Scientific discoveries through international collaborations in Thailand

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CHAPTER 3

NEUROPSYCHOLOGICAL ABNORMALITIES IN PATIENTS WITH DEMENTIA IN CRF 01_AE HIV-1 INFECTION

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Neuropsychological Abnormalities in Patients with Dementia in CRF 01_AE HIV-1 Infection

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Neurology

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Abstract
HIV-associated dementia (HAD) is not firmly established in patients with circulating recombinant form (CRF) 01_AE HIV-1. In this study, we compared neuropsychological performance among 15 Thai individuals with HAD, 15 Thai individuals without HAD, and 30 HIV-negative control subjects. HIV-1 participants were highly active anti-retroviral therapy (HAART)-naive and matched by age, education, and CD4 count. Neuropsychological testing abnormalities were identified in most cognitive domains among HAD vs. HIV-negative participants, confirming the presence of HAD in CRF01_AE.

Introduction
One-third to one-half of HIV-1-infected individuals develop cognitive disorders in the absence of highly active antiretroviral therapy (HAART) in the USA and Europe, where clade B HIV-1 predominates. This impairment influences disease progression, mortality, employability, and medication adherence. Some controversy remains concerning the frequency of such disorders in settings where clade B virus is uncommon. Recent reports indicate that neurocognitive consequences extend to regions of India (clade C) and central Africa (clades A and D). HIV-associated dementia (HAD) was not identified in a previous study attempting to estimate HAD prevalence in Thailand. Circulating recombinant form (CRF) 01_AE accounts for about 90% of HIV in Bangkok; the neuropathogenic properties of this subtype are almost completely unknown. In this study, we sought to identify patients who were HAART-naive, free of drug use and hepatitis C, and had been clinically diagnosed with HAD and then to confirm neuropsychological testing abnormalities among these individuals.

Methods
Thirty HIV-infected volunteers were enrolled at Phramongkutklao Hospital (PMK) in Bangkok, Thailand. All were HAART-naive and free of head injury, learning disability, major depression, active opportunistic infection, past or current CNS disease or infection, and hepatitis C. All had negative urine drug tests for marijuana, cocaine,
opiates, and amphetamines at screening and enrollment visits.

Fifteen of these individuals were clinically diagnosed with HAD by our study neurologist based on a neurologic examination, histories, bedside cognitive testing including the International HIV Dementia Scale, gadolinium-enhanced brain MRI, serology, and lumbar puncture, when indicated. The other 15 were age-, education-, gender-, and CD4-matched HIV-infected volunteers clinically determined to be free of HAD (non-demented [ND]) and meeting the same exclusion criteria. Thirty age-, gender-, and education-matched (2:1 matching) HIV-negative control subjects were then enrolled.

We completed neuropsychological (NP) testing after participants were enrolled since no Thai normative data were available, rendering such data unhelpful for primary diagnosis. The NP testing battery was modified from an international HIV battery with feasibility data from Bangkok. We substituted the Brief Visual Memory Test–Revised for the Picture Memory Test for logistical reasons. All personnel were trained in neuroAIDS assessments, and techniques were reassessed 6 months after study initiation. All but two HIV+ participants initiated HAART immediately after NP testing as they met guidelines for the Thai National Access to Antiretroviral Program for People Living with HIV/AIDS.

Viral subtype was determined by V3 peptide ELISA serotyping with confirmation by gene sequencing, when indicated.6 The protocol was approved by the Ethical Review Committees of the Royal Thai Army Medical Department (PMK) and the University of Hawaii. Prior to analyzing data, we validated the diagnoses of HAD by reviewing the first 27 HIV cases in a consensus panel consisting of an HIV neurologist, an HIV neuropsychologist, and the principal investigator. Case summaries were prepared including individual raw neuropsychological scores plotted over three box plot distributions of seronegative control subjects, ND individuals, and HAD individuals enrolled as of December 2005. Consensus diagnoses (HAD vs. non-HAD) were determined in a blinded fashion using American Academy of Neurology 1991 criteria. We then tested the hypothesis that the three enrolled groups differed using raw scores with an analysis-of-variance model, examining contrasts between groups if the omnibus models met significance at the 0.01 level (data from timed gait [p<0.011] and Trails A [p<0.014] are also presented). We controlled for the effects of CD4, education, gender, and age through matching.

RESULTS

All infections were with CRF01_AE. The three groups were well matched on all demographic parameters (Table 1). Most study volunteers were women.

<table>
<thead>
<tr>
<th>Table 1 Cohort baseline demographics</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Sample size, n</td>
</tr>
<tr>
<td>Mean age ± SD, y</td>
</tr>
<tr>
<td>% female</td>
</tr>
<tr>
<td>Education, mean ± SD, y</td>
</tr>
<tr>
<td>Risk category, n (%))</td>
</tr>
<tr>
<td>Homosexual only</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
<tr>
<td>Medical parameters</td>
</tr>
<tr>
<td>Current CD4 count ± SD</td>
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<tr>
<td>Log 10 viral load ± SD</td>
</tr>
<tr>
<td>Hemoglobin ± SD</td>
</tr>
<tr>
<td>TDI ± SD</td>
</tr>
</tbody>
</table>

Comparison of nondementia participants (ND) and dementia participants (HIV-associated dementia [HAD]) with HIV-seronegative control subjects (C). Statistical tests using Student t test or χ² analysis.

TDI = Thai Depression Inventory.
Previous non-CNS AIDS-defining illnesses were seen in 9 of 15 HAD compared with 8 of 15 ND patients. As a group, HAD compared with ND patients had higher Thai Depression Inventory (TDI) scores (18.1 vs. 12.7, p<0.001).

All HAD participants indicated limitations in function at the time of neurologist evaluation (screening). However, only one participant/proxy pair endorsed such limitation on a formal questionnaire. Nevertheless, differences were noted in nearly all self-reported symptoms of cognitive difficulty and only 5 of 15 HAD compared with 14 of 15 ND participants were employed (p<0.001).

The consensus conference concurred with the Thai neurologist on 100% of the ND cases and 10 of 14 HAD cases. The four non-congruent cases were judged to be mildly impaired but likely not quite meeting HAD criteria based on the raw neuropsychological data. The overall congruence exceeded 85%, allowing us to then proceed with evaluation of NP profiles by enrolled group.

We identified differences in a global composite score of all neuropsychological tests (p<0.001) identifying differences between the HAD group and controls (p<0.001) and between the ND group and controls (p=0.042) but not between the ND and HAD groups (p=0.217). We noted a pattern of deficit in nearly all tests for the HAD group when compared with controls (Figure 1) with mean z-scores of -1 or worse on Auditory Verbal Learning Test (AVLT) total learning, AVLT delayed recall, Color Trails 2, Escala de Inteligencia Wechsler para Adulto (EIWA) Digit Symbol Modalities Test, and EIWA Block Design total score when compared with the control subjects. By contrast, no mean z score reached -1 in the ND group. In statistical models, differences between the control and HAD groups were identified in verbal memory and recall, motor speed/fine motor control, selective attention, verbal fluency, and gross motor speed (Table 2).

**DISCUSSION**

Our work adds to recent work identifying cognitive impairment in non-clade B HIV-1 from Southeast Asia and is somewhat in contrast to a previous report of HAD prevalence in Bangkok, although methodological approaches differed. The earlier report relied on physician reporting but did identify neuropsychological testing abnormalities in participants enrolled. HIV-1 clade and hepatitis co-infection status were not reported, and the population studied in the previous work consisted

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group C vs ND</th>
<th>Group C vs HAD</th>
<th>Group HAD vs ND</th>
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<tbody>
<tr>
<td>AVLT total</td>
<td>11.32 &lt;0.001</td>
<td>7.14 0.010</td>
<td></td>
</tr>
<tr>
<td>AVLT long delay free recall</td>
<td>9.29 &lt;0.001</td>
<td>6.34 0.015</td>
<td></td>
</tr>
<tr>
<td>Color Trails 2</td>
<td>5.55 0.006</td>
<td>0.75 0.589</td>
<td></td>
</tr>
<tr>
<td>EIWA Digit Symbol</td>
<td>9.03 &lt;0.001</td>
<td>4.30 0.043</td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency First Names</td>
<td>7.26 0.002</td>
<td>0.95 0.333</td>
<td></td>
</tr>
<tr>
<td>Timed gait</td>
<td>4.68 0.011</td>
<td>2.68 0.107</td>
<td></td>
</tr>
<tr>
<td>Trails A</td>
<td>4.62 0.014</td>
<td>1.71 0.196</td>
<td></td>
</tr>
<tr>
<td>EIWA Block Design total</td>
<td>19.58 &lt;0.001</td>
<td>9.38 0.003</td>
<td></td>
</tr>
</tbody>
</table>

AVLT = Adult Verbal Learning Test; EIWA = Escala de Inteligencia Wechsler para Adulto.
predominantly of IV drug users.

Infections with non-clade B HIV-1 may be associated with a lower rate of neurocognitive abnormalities. This is supported by in vitro work whereby clade C-specific mutations in Tat appear to affect macrophage chemotaxis. Regarding CRF01-AE, experiments using in vitro CD4 cell models reveal subtype-specific tat-associated suppression of tumor necrosis factor production. Results from our study and other recent studies indicate that cognitive impairment does develop in patients with non-clade B HIV; however, future work should determine incidence rates and time to onset.

Most of our study volunteers were women. This is not reflective of HIV/AIDS in Thailand (the male/female ratio reported by the World Health Organization is 2.8:1). Although speculative, this may reflect a higher proportion of women being diagnosed late in disease or remaining untreated in Thailand. Other reasons for referral bias could exist. Our investigation raises practical questions regarding the assessment of everyday functioning in this setting. The measurement tools employed were less sensitive than that of the neurologist’s clinical assessments. Further research is needed. The finding of higher mean TDI scores among HAD patients is consistent with published data.

The most striking differences between HAD and control groups were evident on the EIWA Block Design, AVLT total learning and delayed recall, and EIWA Digit Symbol Test, with a notable exception in the grooved pegboard test. This pattern is somewhat different than that described in clade B virus prior to availability of HAART, as we did not identify fine motor deficits in our cohort. Importantly, the identified deficits in psychomotor speed, learning, and memory are consistent with the results from patients infected with clade B HIV-1. The differences may result from cultural factors, selection bias, or gender differences. It is also possible that clade-specific influences exist. Future work with this cohort will determine the degree to which treatment of HIV-1 improves NP performance in CRF01-AE, and new studies will attempt to define the prevalence of HAD in Thailand.

REFERENCES


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**DISCLOSURES**
The authors report no conflicts of interest.

**PERMISSIONS**
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