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Short communication

Neurocognitive impairment and psychiatric comorbidity in well-controlled human immunodeficiency virus–infected Thais from the 2NN Cohort Study

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This research is a cross-sectional study to determine the frequency of neurocognitive impairment and psychiatric comorbidity among Thais maintained on highly active antiretroviral therapy (HAART) with undetectable plasma human immunodeficiency virus (HIV) RNA in the 2NN Cohort. Sixty-four subjects were evaluated with neurological examinations, neuropsychological testing, and psychiatric questionnaires. Twenty-four subjects (37.5%) were found to have neurocognitive impairment, with 13 (20.3%), 10 (15.6%), and 1 (1.6%) classified as asymptomatic neurocognitive disorder (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD), respectively. Three subjects (4.7%) had depression and no cases had significant symptoms of anxiety. A notable proportion of well-controlled individuals exhibited neurocognitive impairment. Anxiety and depression were uncommon. *Journal of NeuroVirology (2010) 15, 76–82.*

Keywords: cognition; dementia; HIV; HAART

Background

Human immunodeficiency virus (HIV)-associated dementia (HAD) was common in the era proceeding availability of highly active antiretroviral therapy (HAART) both in Western and non-Western settings. Since the introduction of HAART, HAD incidence has decreased. Although milder in nature, the prevalence of neurocognitive impairment (NCI) has not change during this period (Sacktor *et al.* 2002). One recent study comparing rates to pre-HAART and pre-antiretroviral cohorts noted a similar prevalence across the three time-based cohorts for mild/moderate (stage A and B) disease (Heaton *et al.* 2009).

There are few data regarding the frequency of NCI and psychiatric comorbidity among HIV-infected individuals in Southeast Asia. Results from Asia Pacific NeuroAIDS Consortium study in eight countries including both HAART-naïve and HAART-treated individuals suggested that 12% of patients had moderate to severe HIV-related NCI (Wright *et al.* 2008). There are no published reports of NCI and

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psychiatric comorbidity in this region exclusively among individuals on HAART with good plasma viral control. Such information is of particular interest as controversy remains whether impairment is seen in patients with control of plasma HIV RNA.

The 2NN Cohort Study was a randomized study comparing the first-line HAART regimen containing the non-nucleoside reverse-transcriptase inhibitors (NNRTIs) nevirapine and efavirenz in antiretroviral-naive patients (van Leth *et al*. 2004). The 2NN Cohort is now in long-term follow-up and provides a unique opportunity to study cognitive performance in a population meticulously followed and maintained on protease inhibitor-sparing antiretroviral therapy with suppression of plasma HIV RNA.

Results

Frequency of neurocognitive impairment

There were 202 individuals originally enrolled in the 2NN study at this site. Among these cases, 64 (31.7%) subjects were eligible and agreed to participate. The remaining 138 subjects had died (n = 1), were lost to follow-up (n = 18), or were either enrolled in other studies that did not meet the study criteria or were unwilling to participate (n = 119). Among the 64 individuals participating individuals, 79.7% acquired HIV through heterosexual transmission and 59.4% were men (Table 1). Although all had plasma HIV RNA of <50 copies/ml at least three months prior to this evaluations, one case had a detectable HIV RNA at the time of testing (7184 copies/ml; cognitively normal subject).

Among the 64 study subjects, 24 (37.5%) were found to have some degree of NCI, with 14 (21.9%), 9 (14.1%), and 1 (1.6%) classified as ANI,* MND, and HAD, respectively (Table 1). All subjects had a negative urine toxicology screening and negative VDRL. Sixteen subjects (25%) reported alcohol use in the past 30 days before enrollment. Two subjects (3.1%) had positive hepatitis C serology within the past 6 months. One subject (7.1%) from ANI group had a history of depression, but scored within the normal range on the depression subscore of the HADS instrument (score = 1). Depression scores did not differ across cognitive diagnostic groups. No subjects reported using antidepressant medications. Age, gender, CD4 nadir, plasma HIV RNA peak, and duration of plasma HIV RNA suppression did not predict NCI.

Because there were few cases of HAD, we combined the HAD and MND groups for analyses. Both HAD/MND and ANI groups performed worse than the HIV cognitively normal group (Table 2). This was noted for the median GDS among HAD/MND compared to controls (0.53 versus 0.37; P =.005) and ANI compared to controls (0.82 versus 0.37; P <.001). The mean NPZ-psychomotor score was lower for both HAD/MND and ANI categories compared to the HIV cognitively normal group (P=.014 and P<.001, respectively); but differed only for the ANI group compared to controls on the

Table 1 Demographic and clinical data by diagnostic group.

Characteristics	HAD or MND	ANI	Normal	All
	37.5%		62.5%	
No. patients	1 HAD 9 MND	14	40	64
Gender (M:F), *n* (%)	7:3 (70.0:30.0)	9:5 (64.3:35.7)	22:18 (55.0:45.0)	38:26 (59.4:40.6)
Median age, year (IQR)	43.7 (37.4–50.2)	38.2 (32.6–41.5)	41.6 (36.5–47.1)	41.2 (35.9–46.3)
Median year of education, year (IQR)	12 (9–16)	12 (9–15)	12 (9–16)	12 (9–16)
Median hemoglobin, mg/dl (IQR)	14.2 (12.0–14.5)	13.1 (11.8–14.5)	14.1 (12.1–15.3)	13.8 (12.0–15.1)
Median CD4 nadir, cell/mm^3 (IQR)	84.0 (15.0–168.0)	110.0 (38.0–194.0)	53.5 (20.5–117.0)	59.5 (18.0–142.0)
CD4 nadir <200 cell/mm^3, *n* (%)	9/10 (90.0)	12/13 (85.7)	36/40 (90.0)	57/64 (89.1)
Median duration of NNRTI-based HAART, years (IQR)	6.9 (6.3–7.1)	7.0 (6.3–7.3)	7.0 (6.3–7.1)	7.0 (6.3–7.1)
Median CD4 at NP testing, cell/mm^3 (IQR)	501 (354–555)	499 (363–611)	528 (329–688)	521 (351–634)
Median HIV RNA peak, log (IQR)	4.9 (4.7–5.5)	4.9 (4.5–5.6)	5.3 (4.9–5.7)	5.2 (4.7–5.7)
Median duration of HIV RNA suppression, years (IQR)	6.5 (5.7–6.8)	6.8 (5.9–7.0)	6.7 (6.0–6.9)	6.7 (6.0–6.9)
Current ARV[a], *n* (%) NVP-based	9 (90.0)	5 (35.7)	26 (65.0)	40 (62.5)
EFV-based	1 (10.0)	9 (64.3)	14 (35.0)	24 (37.5)
Current drug and alcohol use, *n* (%)	3 (30.0)	5 (35.7)	10 (25.0)	18 (28.1)
Mean quality of sleep (SD)	2.8 (1.2)	2.7 (1.0)	3.0 (1.4)	2.9 (1.3)
Mean number of hours of sleep (SD)	6.1 (2.2)	6.2 (2.5)	5.6 (2.0)	5.8 (2.1)

Note. HAD = HIV-associated dementia; MND = mild neurocognitive disorder, ANI = asymptomatic neurocognitive impairment.
[a]NRTI bases were zidovudine (42/64, 65.6%), stavudine (15/64, 23.5%), tenofovir (7/64, 10.9%), and lamivudine (64/64, 100%).

Table 2 Psychiatric disorder and outcome measures by NP impairment groups.

Psychiatric outcomes	HAD or MND (n = 10)	ANI (n = 14)	Normal (n = 40)	All (n = 64)	P value
Mean psychiatric score (SD)					
Anxiety by HADS-A	5.8 (3.1)	5.0 (1.9)	4.3 (2.4)	4.7 (2.5)	.177
Depression by HADS-D	5.6 (2.7)	3.0 (2.6)	2.9 (2.7)	3.4 (2.8)	.018
Depression by PHQ-9	4.8 (4.2)	2.9 (3.6)	2.8 (3.3)	3.1 (3.5)	.248
Distress	3.7 (2.3)	4.3 (2.0)	3.2 (2.5)	3.5 (2.4)	.312
Quality of Life	82.9 (13.3)	91.0 (10.0)	92.8 (11.5)	90.9 (11.9)	.059
No. patients in subscale (%)					
Likely Anxiety by HADS-A	2 (20.0)	0 (0)	2 (5.0)	4 (6.3)	.102
Likely Depression by HADS-D	1 (10.0)	0 (0)	2 (5.0)	3 (4.7)	.604
Mild Depression by PHQ-9	3 (30.0)	2 (14.3)	8 (20.0)	13 (20.3)	.430
Moderate Depression by PHQ-9	2 (20.0)	1 (7.2)	2 (5.0)	5 (7.8)	
Distress	4 (40.0)	7 (50.2)	14 (35.0)	25 (39.1)	.620
Poor Quality of Life	1 (10.0)	0 (0)	0 (0)	1 (1.6)	.133
Moderately Poor Quality of Life	7 (70.0)	10 (71.4)	23 (57.5)	40 (62.5)	
Neuropsychological test scores					
Median GDS (IQR)	0.53 (0.42–0.74)	0.82 (0.68–0.95)	0.37 (0.29–0.47)	0.42 (0.32–0.66)	<.0001
Mean NPZ-composite (SD)	0.09 (0.83)	−0.01 (0.85)	0.53 (0.67)	0.34 (0.77)	.039
Mean NPZ-psychomotor (SD)	−0.63 (1.02)	−0.75 (0.58)	0.35 (0.53)	−0.05 (0.81)	<.001

Note. GDS = Global Deficit Score; NPZ-composite = arithmetic mean of the RAVLT-total score, Digit Symbol Modalities Task, and timed gait; NPZ-psychomotor = arithmetic mean of the grooved pegboard dominant and nondominant hands, the Trails A test, and the Digit Symbol Modalities task.

NPZ-composite (P =.046). We did not identify differences in mean quality of sleep (P =.820) or mean number of hours of sleep (P =.693) across groups.

Using HADS, four (6.3%) of subjects were found to have "likely" anxiety and only three (4.7%) subjects had "likely" depression (Table 2). Based on PHQ-9 scores, 13 (20.3%) and 5 (7.8%) subjects had total scores in the mild and moderate depression range, respectively. Depression and anxiety diagnoses did not differ across cognitive diagnostic groups. Overall, 25 (39.1%) subjects were found to have a high level of distress. This level of distress was commonly noted across cognitive categories. The proportion of subjects with a high level of stress was 40%, 50%, 35% in HAD/MND, ANI, and normal categories, respectively. Most subjects (40, 62.5%) achieved moderate quality of life overall, with 7 (70%), 10 (71.4%), 23 (57.5%) subjects in HAD/MND, ANI, and normal categories, respectively, noting moderate or better quality of life. HADS scores were not associated with any demographic variables or CD4 count.

Discussion

These data suggest that NCI remains common in this cohort, despite well-controlled HIV and continuous NNRTI-based HAART for approximately 7 years. All participants had achieved immunological recovery and plasma HIV RNA levels were below detection limits in all but one cognitively normal subject. Our findings are consistent with published work from other US national and international settings, including a recent publication noting no differences in mild impairment comparing patients with mild/moderate disease in the HAART, pre-HAART, and pre-antiretroviral (ARV) eras (Heaton *et al*. 2009). About one half of individuals who tested in the impaired range were symptomatic, although symptoms tended to be mild in nature. Consistent with other reports, we noted that HAD frequency was rare (1.6%) in these virologically suppressed patients; however, the frequency of milder degrees of impairment was sizable (Robertson *et al*. 2007; Tozzi *et al*. 2005). The ANI group appeared to have performed worse than the HAD/MND group on the composite scores, a finding that is not entirely surprising given that the HAD and MND groups were combined and the fundamental differences between ANI and other diagnostic groups is the documentation of functional decline. Identifying functional change is a challenge in HIV-related clinical research where reliable proxy information is often inadequate.

Demographic and clinical factors, including age, current CD4 lymphocyte count, nadir CD4 lymphocyte count, hemoglobin, diabetes, or prior acquired immunodeficiency syndrome (AIDS)-defining illnesses did not distinguish impaired from unimpaired subjects; however, our small sample size likely limited this analysis. We did not complete a comprehensive assessment of current or past substance abuse; however, these individuals are part of a larger cohort at our Thai site where less than 1% of cases contracted HIV through intravenous drug use. All cases in this study had negative urine toxicology testing at the time of evaluation. Nevertheless, it is not possible to fully exclude the possible contribution of drug use to the impairment rates.

We find low rates of depression and anxiety in this group of subjects. The frequency of depression-range scores was somewhat higher when using PHQ-9, but remained infrequent, with only 7.8% classified as having moderate depression. No individuals met criteria for severe depressive or anxiety symptoms on either scale. These results are lower than that described in other studies (Gibbie *et al*. 2006; Judd *et al*. 2005). Previous studies suggest that HAART is associated with improvement of depression (Brechtl *et al*. 2001), and nonadherence to HAART is associated with depressive symptoms (Ammassari *et al*. 2004). The low rate of depression and anxiety in this cohort may be explained by better adherence, well-maintained immunological and virological status, and the presence of psychosocial support within the 2NN cohort and among peers.

The prevalence of NCI among HAART-naïve subjects is reported to be as high as 47% to 60% in other resource-limited settings (Gupta *et al*. 2007; Sacktor *et al*. 2006). Despite effective HAART, NCI remains frequent. It is possible that NCI represents on-going active disease, past and permanent injury, or a combination of the two factors (Robertson *et al*. 2007; Roc *et al*. 2007; Tozzi *et al*. 2007). Our recent work demonstrating that HIV DNA isolated from monocytes correlates to cognitive performance irrespective of plasma HIV RNA and CD4 lymphocyte counts in both pre-HAART and post-HAART settings argues that active injury may still be present and that this injury may be related to migrating infected monocytes into the CNS compartment (Shiramizu *et al*. 2005; Valcour *et al*. 2009). Because pre-HAART neuropsychological data are unavailable, it is unknown if these deficits represent inadequate recovery of pre-HAART deficits or on-going injury.

The 2NN cohort subjects have never been exposed to the protease inhibitor class of antiretroviral medications and most have remained on nevirapine-based regimens (65.0%) with zidovudine (65.6%). A combination regimen with both nevirapine and zidovudine would be anticipated to have reasonably good penetration-effectiveness in the CNS (Letendre *et al*. 2008). Although not directly assessed, it is less likely that CNS penetration affected the outcomes.

There is some speculation that viral subtypes may influence the frequency and degree of NCI (Liner *et al*. 2007; Sacktor *et al*. 2007). Based on our previous studies, most participants were likely infected with subtype CRF 01_AE (Valcour *et al*. 2007). Similar rates of NCI are noted in clade B virus (Robertson *et al*. 2007; Sacktor *et al*. 2002), suggesting that the inability to eradicate cognitive impairment with HAART extends beyond viral subtypes. Likewise, the pattern of NCI in impaired individuals from this study is similar to that noted in HAART-naïve subjects from Thailand (Valcour *et al*. 2007) and broadly similar to that seen among patients with subtype B virus before HAART was widely available. Thus, our data do not support differences by clade. This contrast to a recent study conducted in Africa noting that HAD is more common in patients with advanced immunosuppression infected who are infected with subtype D compared to subtype A (Sacktor *et al*. 2009). Although some *in vitro* studies have identified a propensity for altered neuropathogenesis by subtype (Ranga *et al*. 2004), this issue has not been adequately studied clinically.

In summary, we identify NCI as a frequent finding among Thai individuals with well-controlled HIV on protease inhibitor (PI)-sparing regimens. Depressive symptoms and anxiety were less frequent. Although self-reported levels of distress were frequently elevated, most individuals endorsed moderate or better quality of life.

Methods

Study population

This was a single-center (Bangkok, Thailand), cross-sectional assessment of cognition and psychiatric comorbidity in 64 subjects recruited from the 2NN long-term follow-up study (van Leth *et al*. 2004). Eligible individuals were seen in follow-up between March 2007 and March 2008. All had been on only NNRTI-based HAART since joining the 2NN cohort (at least 5 years) and had maintained a suppressed plasma HIV RNA for the duration of the study. All were confirmed to be undetectable (<50 copies/ml) in the 3 months prior to screening. Enrolled cases were free of past or present central nervous system (CNS) infection, head injury with loss of consciousness greater than 1 h, and current opportunistic infection.

Study procedures

Demographic information and HIV illness characteristics were acquired and all subjects completed a neurological examination. We assessed function using unstructured interviews broadly based on the domains assessed in the Clinical Dementia Rating scale (CDR) and completed independently by a nurse and a physician. Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scales (HADS)—Thai Version. Depressive symptoms were also assessed with the depression score from Patient Health Questionnaire, a 9-item scale (PHQ-9) derived from the Diagnostic and Statistical Manual (DSM)-IV criteria for major depressive disorder (Lotrakul and Sukanich, 1999; Lotrakul *et al*. 2008). Quality of life factors were captured using the World Health Organization (WHO) QOL-BREF-THAI, a questionnaire validated in Thai patients and certified by the Thai Ministry of Public health. (www.dmh.go.th/test/whoqol/). We evaluated the level of distress using a visual analog scale (Distress Thermometer) ranging from 0 to 10. Sleep quality for the night prior to testing was assessed using a scaled

score of 0 to 4. Laboratory assessments included a complete bolld count (CBC), CD4/CD8 lymphocyte subsets, plasma HIV RNA, chemistry, fasting glucose, hepatitis C antibody, hepatitis B antigen, Venereal Disease Research Laboratory test (VDRL), and a urine toxicology screening.

The neuropsychological testing battery included the International HIV Dementia Scale and a modification of the WHO/National Institutes of Mental Health (NIMH)/University of California Los Angeles (UCLA) International Battery as previously described (Valcour *et al*. 2007). This battery includes the following tests: timed gait, finger tapping, Color trails, Escala de Inteligencia Wechsler para Adultos (EIWA) Block Design, EIWA Digit Symbol, Grooved Pegboard, Trail Making A, WHO/UCLA Auditory Verbal Learning Test (AVLT), the Brief Visual Memory Retention Test—Revised, and verbal fluency with animals and first names. Individual performance on each test was compared to appropriate age- and education-matched normative data obtained from our Thai normative database of 230 HIV-negative individuals and interpreted by the study neuropsychologist to determine if performance was impaired in each cognitive domain. Normative cases were recruited through fliers posted in regional hospitals and through word-of–mouth. All were screened to be free of factors that could impact cognition through a physician examination, HIV testing, and urine toxicology testing. Subjects were stratified by age group (decade) and educational status (primary certificate or less, less than secondary certificate (high school), high school or vocational certificate, advanced certificate.

All cases were reviewed in a consensus conference with the study neuropsychologist and HIV physicians to apply diagnostic criteria based on the recently published nosology (Antinori *et al*. 2007). Individuals were required to exhibit impairments of at least one standard deviation abnormality in more than one domain to qualify as impaired. The team carefully considered both raw scores and age-adjusted *z*-scores to interpret the outcome, since some age/education strata in the normative data had less than 20 cases. To be diagnosed as mild neurocognitive disorder (MND) or HAD, some degree of functional change was needed. The degree of neuropsychological and functional impairment distinguished MND from HAD. Individuals with abnormalities on testing who did not have functional changes were deemed to have asymptomatic neurocognitive impairment (ANI).

We also summarized neuropsychological testing scores using three summary scores: the Global Deficit Score (GDS), the NPZ-composite, and the NPZ-psychomotor. The GDS is a weighted composite score that summarizes all neuropsychological tests in our battery (Carey *et al*. 2004). On the GDS, a higher score represents greater impairment. The NPZ-composite score is the arithmetic mean of the AVLT-total score (learning efficiency), the Digit Symbol Modalities Task (psychomotor speed), and the timed gait (motor speed). In a separate Thai HIV cohort, this composite score provided a sensitive marker for the diagnosis of HAD, using linear discriminant analysis with cross-validation (Valcour *et al*. 2009). The NPZ-psychomotor is the arithmetic mean of the grooved pegboard dominant and non-dominant hands, the Trails A test, and the Digit Symbol Modalities task.

Institutional Review Boards and statistical analysis

The study was conducted under The National Statement on Ethical Conduct in Research Involving Humans (June 1995) produced by Thai Ministry of Public Health. All participants signed informed consent forms that were approved by Ethics Committee of the Faculty of Medicine, Chulalongkorn University, the University of Hawaii Committee on Human Subjects, and a Thai Community Advisory Board.

We evaluated the mean differences in neuropsychological and psychiatric scales between the three impairment groups by analysis of variance (ANOVA) followed by a Bonferroni test when the overall *F*-test reached significance. We used the Kruskal-Wallis and Wilcoxon rank sum tests to evaluate the median difference in the GDS between the three- and two-mpairment groups, respectively. Analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Declaration of interest: The opinion in this manuscript are those of the authors and are not to be construed as official or representing the view of the US army or the Department of Defense.

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