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Cognitive impairment among Indonesia HIV naïve patients

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Abstract

Background: Antiretroviral treatment (ART) can decreased the incidence of HIV dementia, but milder cognitive impairment may not resolve when patients receive ART. In Indonesia, cognitive screening of HIV patients is not routinely performed before starting ART. Here we assess cognitive impairment in ART- naïve HIV patients beginning treatment in Jakarta. *Methods:* This is a cross sectional study with inclusion criteria: HIV positive, ART naïve, CD4 T-cells below 200 cells/uL, Karnofsky Performance Score (KPS) above 70. HIV-associated neurocognitive disorder (HAND) was defined by performance at least 1 Standard Deviation (SD) below the mean of demographically adjusted normative scores in at least two cognitive areas. *Results:* We studied 82 subjects with median (range) age 31 (19-48) years. Fifty six subjects (68%) were males. HAND was found in 42 subjects (51%). Eight subjects (19%) had impairment in 4 domains, 15 subjects (36%) in 3 and 19 (45%) in 2. The most common domain affected was memory (63%).
Conclusion: Our results show the prevalence of HAND is high among HIV naïve patients in Jakarta. This establishes the need for screening of cognitive function before initiating ART.

INTRODUCTION

HIV infection affects many systems including the central nervous system, and patients may display cognitive impairment, headache, seizures and/or manifestations of space occupying lesions.[1] Cognitive impairment can emerge in the early stages of HIV infection. In 2007, the National Institute of Mental Health, with the National Institute of Neurological Disease and Stroke, proposed revised nomenclature for HIV neurocognitive disorders, known as the Frascti Criteria. HIV-associated neurocognitive disorder (HAND) was categorized into 3 groups; HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND) and HIV-associated dementia (HAD). Under these criteria, HAND is defined by performance at least 1 standard deviation (SD) below the mean of demographically adjusted normative scores in at least two cognitive areas.[2]

Antiretroviral treatment (ART) can reduce the incidence of HIV dementia[3] and increase the quality of life, but less severe cognitive impairment may persist throughout a patient's life.[3]In 2013 totally there were 29,0376 HIV cases and 5,608 AIDS cases in Indonesia.[5] Most (70%) were aged 25-49 years, which are the productive years in a person's life. However ART is not available for all patients in need. Thus many patients begin treatment with advanced HIV disease[5], some of whom may have neurological deficits. Unfortunately cognitive screening is not routinely performed, so the extent of the problem is unclear. The aim of this study was to determine the prevalence of cognitive impairment in ART-naïve HIV patients beginning ART at an outpatient clinic in Jakarta.

METHODS

Study design

We present a cross sectional study of HIV patients (n=82), aged 18-50 years, attending the HIV clinic at Cipto Mangunkusumo Hospital, Jakarta, between March 2013 and March 2014. Inclusion criteria included HIV infection documented by ELISA, ART naïve, CD4 T-cells below 200 cells/uL, Karnofsky Performance Score (KPS) above 70. Exclusion criteria included active or known past opportunistic infection of the central nervous system (CNS), history of chronic neurological disease, head trauma, major depression, other

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psychiatric disease, antipsychotic treatment, pregnancy, breast feeding and physical deficits that would interfere with cognitive assessment (confirmed by examination). The study procedure was approved by Faculty of Medicine, University of Indonesia and Cipto Mangunkusumo Hospital ethics committees. Written consent was obtained from each subject after they understood the purpose and agreed to join the study. Subjects also completed blood counts and tests for anti-hepatitis C antibody, plasma HIV RNA load, chest X-ray and sputum acid bacilli smear.

Neurocognitive assessments

Demographic data and clinical history were collected by interviewing subjects using a questionnaire. This included date of birth, gender, education level, occupation, HIV transmission route, smoking habit, history of drug use, history of neurological illness and medications taken. Depression was assessed using Hamilton depression rating scale.Cognitive examinations were performed using established tools covering several cognitive domains[6] (Table 2) by a trained physician in a quiet room.

Normative values were taken from healthy subjects whose age and education were similar to the study subjects. Inclusion criteria for the healthy subjects included age 18-50 years and a normal Mini Mental State Examination score. Exclusion criteria included KPS less than 70, neurological disease (epilepsy, stroke, brain infection and brain tumor), excessive HIV risk (eg: drug use, prostitution), history of head injury, major depression, and disabilities likely to interfere with cognitive tests.

Statistical analyses

The results of cognitive examination from each area were transformed into Z scores by subtracting the test result from themean of normative value then dividing by the standard deviation of the normative value. Z scores for the Grooved Pegboard test were obtained from the mean of Z score of dominant and non-dominant hand. Cognitive function was defined as abnormal if there were 2 areas of cognitive domainwith Z scores less than 1.[2] Statistical analyses were performed using SPSS 17.0.Sex, education level, transmission route, hepatits C co-infection and pulmonary tuberculosis (TB) were presented as numbers of cases by percentage. Age, CD4 T-cell counts and plasma RNA levels were not normally distributed (Kolomogorov Smirnov test) and so are presented as median (range). Mean rank difference of these Z-score between HIV+ subjects and healthy control were analyzed using Mann-Whitney U tests. The effect size of the HIV status was also calculated using the Z scores, from U tests divided by the square root of the number of subjects. Categorical data were assessed using chi-square test (education level, sex, transmission route and hepatitis C co-infection). Age, plasma HIV RNA and CD4 T-cells were compared using Mann-Whitney U tests.

RESULTS

Subject characteristics

From March 2013 until March 2014, 82 HIV patients were eligible for this study (Table 1). Their median (range) age was 31 (19-48) years and 56 (68%) were males. The most common transmission route was heterosexual contact (50 subjects, 61%). The CD4 T-cell count was lowest in drug users (48 cells/ul). Anti-hepatitis C antibody and pulmonary TB were found in 41 (50%) and 18 (22%) subjects respectively. Subjects with Hepatitis C co-infection had lower median CD4 T-cell counts (30 vs 74 cells/uL, p=0.017). The median (range) age of healthy controls was 30.5 (18-50) years. The number of females was higher than in the HIV+ group, but their age and education were similar.

Neurocognitive performance

The raw scores of neurocognitive results transformed into Z-scores are shown in Table 2. In general, HIV subjects' results were inferior to those of healthy controls. There were significant differences in Forward Digit Span (FDS), Backward Digit Span (BDS), Animal Naming Test (ANT), Grooved Pegboard and assessments of memory. The clearest differences arose with delayed recall from Rey Auditory Verbal Learning Test in trial 7 (RAVLT-7) and Learning over training.The effect size was medium in the attention domains (FDS and BDS) and fluency (ANT). Based on cognitive domains, the most common impairment was in memory (63%), followed by fluency (40%) (Figure 1). There were 27 (33%) subjects with impairment in only 1 domain, 19 (23%) with 2 domains, 15 (18%) with 3 domains and 8 (10%) with 4 or more domains. The mean of Z total score of HIV subjects was -1.00 (0.096) with 20 (24%) subject having a score less than -1 and 12 (15%) of subjects less than -2.

Table 1: Characteristics of patients and controls

Parameter	Median (range), unless otherwise stated		p
	HIV+	Healthy control	
Age, years	31 (19-48)	30 (18-50)	0.48
Males, n(%)	56 (68)	39 (48)	0.01
Education more than 9 years, n(%)	64 (78)	70 (85)	0.31
Transmission route, n(%)			
• Homosexual	15 (18)		
• Heterosexual	50 (61)		
• IV drug user	15 (18)		
• Unknown	2 (2.4)		
CD4 T-cells/uL	62 (2-199)		
Plasma HIV RNA (log 10), copies/mL	5.1 (2.6-6.6)		
Pulmonary TB co-infection, n(%)	41 (50)		
Hepatitis C co-infection, n(%)	18 (22)		

There were 42 subjects (51%) who had impairment in 2 or more domains with Z score 1 SD below normative scores (HAND) with OR=16.2 (p<0.001; 95% CI 5.9-44). After adjustment for education, this association was still significant (p<0.001; OR=15.5, 95%CI 5.6-43).

Risk Factors for HAND

Among 42 subjects with HAND, 8 subjects (19%) had 4 domains impaired, 15 subjects (36%) had 3 domains and 19 (45%) had 2 domains. The most common domain affected was memory (88%). There were significant differences in the education level between HAND and non-HAND patients

Table 2: Neurocognitive test results (Z-Scores) for HIV patients

Ability domain	Cognitive test	*Z* Score Result (Median, range)	*P**	*r*
Attention	Forward Digit Span (FDS)	-0.80 (-2.8-1.2)	0.000	0.44
	Backward Digit Span (BDS)	-0.93 (-3.7-2.2)	0.000	0.49
Fluency	Animal Naming Test (ANT)	-0.67 (-0.78-2.9)	0.000	0.49
Executive Function	Trail Making A (secs)	0.23 (-6.4-1.6)	0.72	0.04
	Trail Making B (secs)	0.10 (-12-1.9)	0.34	0.10
Fine Motor Skills	Grooved Pegboard dominant hand (secs)	-0.28 (-20-4.2)	0.002	0.34
	Grooved Pegboard non-dominant hand (secs	-0.09 (-2.2-8.8)	0.017	0.26
Memory	Rey Auditory Verbal Learning Test			
	Immediate Recall (RAVLT-1)*	-0.47 (-3.0-1.5)	0.000	0.40
	Delayed Recall (RAVLT-7)**	-3.33 (-14-0.55)	0.000	0.99
	Learning over training***	-1.24 (-8.3-1.8)	0.000	0.71
Z Total		-0.83 (-4.5-0.51)	0.000	0.87

*Immediate Recall:, recall in the first trial, immediately after examiner read the list of words
**Delayed Recall: recall in the seventh trial after 20 minutes delay
***Learning over training, the total number of words recalled from all five trials minus five times the number of words obtained in the first trial.

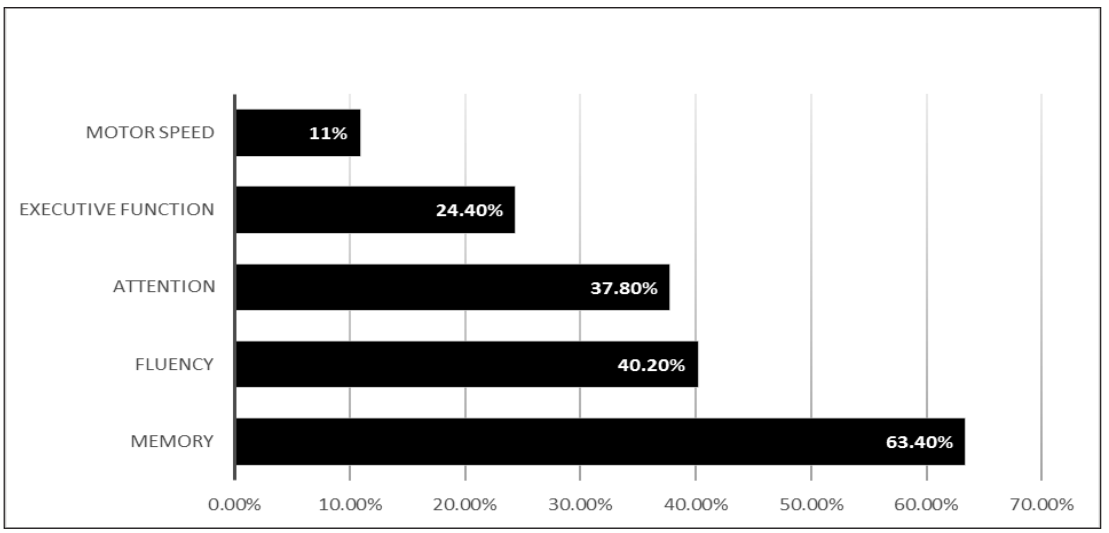

Fig. 1 Neurocognitive impairment pattern in HIV patients

(p=0.005). Lower education was associated with lower neurocognitive performance. Risk factor analyses for each domain showed that the education effect was pronounced in the fluency (p<0.001), executive function (p=0.04) and fine motor skill (p=0.05) domains (Table 3). The CD4 T-cell counts and plasma HIV RNA were similar in HAND and non-HAND patients (66.5 cells/uL vs 56.5 cells/uL). Median CD4 T-cell counts were lowest (63 cells/uL) among subjects with attention impairment compared to those with defects in other domains.

DISCUSSION

Patients were compared with healthy controls matched by demographic characteristics and ethnicity to theHIV+ subjects. Controls and patients were recruited from Cipto Mangunkusumo hospital area and were similar in age.However the age range was limited so there were no detectable effects of age on cognitive impairment.

In most cognitive domains, HIV subjects were significantly inferior to healthy controls. The exception is inthe trail making tests (executive function). There were smaller differences in fine motor speed performance between HIV+ subjects and healthy control. This agrees with Groove Peg Board data from Cameroon showing a small effect size between HIV+ and HIV- subjects.[7] Robertson *et al* found no significant different in fine and gross motor tests between Ugandan HIV+ and healthy controls, but these authors found impairment in subjects with AIDS dementia. This small difference in motor speed between patients and controls supportsthe current finding.[8]

The prevalence of HAND among Indonesian ART naïve HIV patients in our cohort was 51% (95% CI 34-56). This number was higher than was observed in a study by the Asia Pacific Neurology Network (APNAC) that included Indonesia as one study site. The APNAC study found the prevalence of cognitive impairment in Asia Pacific Region was 12% (Indonesia had 11%).[9] However the APNAC study included patients responding to ART, whilst our study focused on ART naïve patients. Nicholass *et al.* found the prevalence of cognitive impairment in young ART naïve patients (18-24 year-old) was 67%[10], whilst Hasbun *et al.* observed cognitive impairment in 75% of patients aged 22-64 years.[11] These individuals are slightly older than our patients. This suggests that the cognitive impairment seen in our study was not due to older age effect.

Subject with less than 9 years of education had a higher risk of developing HAND (OR=3.2). Wang *et al.* also reported that HAND was more prevalent in older subjects with lower education level.[12] We found no relationship between HAND and CD4 T-cell counts. Several studies also have failed to find the relationship between HAND and CD4 T-cell counts.[13-15] However Marcotte *et al.* found a relationship between nadir CD4 T-cell counts early after seroconversion and progression to cognitive impairment. Although 22% of subjects were taking ART, progression to cognitive impairment was similar in subjects receiving treatment and those who never treated.[14]

There were no significant associations between plasma HIV RNAand HAND, but HIV RNA levels were marginally higher in HAND subjects. Other

Table 3: Risk Factors for HAND

Parameter	Cognitive domain impairment					HAND n=42	Non-HAND n=40
	Memory	Fluency	Attention	Executive function	Fine Motor Skill		
Age, median	31	32	31	31	30	32.5	31
Education <9 yrs , n(%) Education ≥9 yrs, n(%)	12 (70.6) 40 (62.5)	11 (33.3)** 22 (66.7)	8 (25.8) 23 (74.2)	11 (55)* 9 (45)	4 (44.4) 5 (55.6)	13 (31) 29 (69)	5 (12.5) 35 (87.5)
Male, n(%) Female, n(%)	36 (64) 16 (64)	22 (67) 11 (33)	18 (58) 13 (42)	11 (55) 9 (45)	4 (44) 5 (56)	26 (61.9) 16 (38.1)	30 (75) 10 (25)
CD4 T cells/μL median (range)	73 (2-199)	74 (2-199)	63 (4-196)	59 (4-171)	85 (4-194)	83.2(2-199)	76.4(3-198)
Plasma HIV RNA log10, median (range)	4.9 (2.6-6.6)	5.2 (2.8-6.6)	5.2 (2.8-6.6)	4.7 (2.8-6.4)	5.2 (3.7-6.6)	4.9(2.8-6.6)	4.9(2.6-6.3)
Hepatitis C co-infection	10 (56)	7 (21)	6 (20)	4 (20)	1 (11)	7 (39)	11 (61)
PulmonaryTB co-infection	29 (71)	17 (51)	17 (55)	12 (60)	5 (56)	22 (54)	19 (46)

*p=0.000 chi square
**p=0.041 chi square

studies also failed to show the correlation between plasma HIV RNA and cognitive impairment[15,17], but CSF viral load appears to correlate with cognitive function and CNS dysfuction.[18,19]

The most common impairment in our study was memory (63%), followed by fluency (40%) and attention (38%).Similarly Gupta *et al.* showed 60% subject had mild to moderate cognitive impairment in fluency and memory.[20] Functional MRI showed greater activation in frontal lobe in HIV patients while performing complex tasks, compared to healthy controls. This indicated the use of more brain reserve due to fronto-striatal brain injury affecting the regions responsible for attention and working memory.[21]

Our results show that HAND is common among ART naïve HIV patients in Jakarta. This shows the need of cognitive function screening before initiating ART. Prospective studies are also needed to monitor cognitive changes after ART.

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DISCLOSURE

Conflict of interest: None

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