HIV-associated neurocognitive disorder in HIV-infected Koreans: Korean NeuroAIDS Project

Nam Su Ku[1], **Youngjoon Lee**[2], **Jin Young Ahn**[1], **Je Eun Song**[1], **Min Hyung Kim**[1], **Sun Bean Kim**[1], **Su Jin Jeong**[1], **Kyung-Wook Hong**[3], **Eosu Kim**[2], **Sang Hoon Han**[1], **Joon Young Song**[3], **Hee Jin Cheong**[3], **Young Goo Song**[1], **Woo Joo Kim**[3], **June Myung Kim**[1], **Davey M. Smith**[4,5], and **Jun Yong Choi**[1,†]

[1]Department of Internal Medicine and AIDS Research Institute, Seoul, South Korea

[2]Department of Psychiatry, Institute of Behavioral Science in Mednce, Yonsei University College of Medicine, Seoul, South Korea

[3]Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea

[4]Department of Medicine, University of California San Diego, La Jolla, CA 92093-0679

[5]Veterans Affairs San Diego Healthcare System, San Diego, CA 92161

Abstract

Background—HIV-associated neurocognitive disorder (HAND) is an independent predictor of early mortality and is associated with many difficulties in activities of daily living. We sought to determine the prevalence of and risk factors for HAND in HIV-infected Koreans. In addition, we investigated the performance of screening tools and components of neuropsychological (NP) tests for diagnosing HAND.

Methods—HIV-infected patients were enrolled consecutively from two different urban teaching hospitals in Seoul, South Korea between March 2012 and September 2012. Participants completed a detailed NP assessment of six cognitive domains commonly affected by HIV. The *Frascati* criteria were used for diagnosing HAND. Four key questions, international HIV dementia scale (IHDS) and MoCA-K were also assessed as potential tools for screening for HAND.

Results—Among the 194 participants, the prevalence of HAND was 26.3%. Asymptomatic neurocognitive impairment, minor neurocognitive disorder accounted for 52.9% and 47.1% of the patients with HAND, respectively. In multivariate analysis, hemoglobin levels ≤ 13g/dL (*p*=0.046) and the current use of protease inhibitor-based regimen (*p*=0.031) were independent risk factors for HAND. The sensitivity and specificity of IHDS were 72.6% and 60.8%, and MoCA-K were 52.9% and 73.4%, respectively. IHDS (p<0.001) and MoCA-K (p<0.001) were both useful for screening for HAND. Among NP tests, the sensitivity and specificity of the Grooved Pegboard Test were 90.2% and 72.0%, and the Wisconsin Card Sorting Test were 61.2% and 84.4%, respectively.

†Corresponding author: Jun Yong Choi, M.D., Ph.D. Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul, 120-752, Republic of Korea. Tel.: +82-2-2228-1974, Fax: +82-2-393-6884, seran@yuhs.ac.
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Conclusions—HAND is a prevalent comorbidity in HIV-infected Koreans. Active screening and diagnosis with useful tools, like IHDS, MoCA-K and Grooved Pegboard Test, could be used to identify this important complication.

Keywords

HAND; HIV; risk factors; screening tool; NP tests

Introduction

Human immunodeficiency virus (HIV) may enter the central nervous system (CNS) early after infection [1], and although it does not directly infect neurons, it is frequently associated with structural and functional brain abnormalities [2-5]. This CNS infection can lead to neurocognitive impairment. This HIV-associated neurocognitive disorder (HAND) strongly predicts a wide variety of difficulties in activities of daily living, like employment, automobile driving, medication adherence, financial management, shopping, cooking, and use of public transportation [6]. Moreover, viral levels in the cerebrospinal fluid (CSF) have been associated with HAND in HIV-unsuppressed patients with AIDS [7], while a suppression of CSF HIV can correspond with improvement in cognition [8]. However, in the era of combination antiretroviral therapy (cART), HAND in Western countries is still common (16~52%), even when cART is successful with suppression of viral load [9-14]. The extent to which cART leads to a reduction in the incidence and prevalence of HIV-related cognitive impairment remains unclear. Additionally, most neurocognitive research in HIV-infected individuals has been conducted from western populations, and the burden of HAND in Korean HIV-infected individuals is so far unknown. Furthermore, there are few studies concerning how to screen HIV-infected individuals for HAND and the diagnostic validation of neuropsychological (NP) tests for diagnosing HAND among HIV-infected Asian persons.

Methods

Study design

Two hundred HIV-infected patients who were 18 years old or older were recruited consecutively in Severance Hospital and Korea University Guro Hospital between March 2012 and September 2012 in Seoul, Korea. All subjects received and acknowledged informed consent and received standardized neurological, NP, and functional assessments at two study sites. This study was approved by the Institutional Review Board of the hospital (IRB #4-2011-0630).

The exclusion criteria were (1) recent and/or significant traumatic brain injury; (2) neurologic disorder not related to HIV infection; (3) infections that can affect the CNS; (4) significant CNS opportunistic infection based upon history and/or neuromedical examination; (5) current or past psychotic disorder; (6) significant substance use, including greater than three alcoholic drinks per day daily over the last month, or recreational drug use greater than one time per week during the last month; (7) symptoms of a current, active infection, body temperature of > 38.5°C at the time of recruitment or current treatment for a

serious, systemic infection within 3 months; (8) color blindness; (9) hearing deficit that appears to affect auditory comprehension [15].

Six of two hundred subjects were excluded due to five confounding comorbidity and one withdrawing early from the study. Enrolled participants had demographical, clinical, and neuropsychological assessments. At baseline visits, neuromedical history and standardized exam, neurobehavioral testing, structured evaluation of selected psychiatric variables were evaluated. The following variables were also assessed: age at first visit, gender, body mass index (BMI), hemoglobin (Hb) level, degree of education, duration of HIV diagnosis, Centers for Disease Control and Prevention (CDC) classification, reported mode of transmission, prior acquired immunodeficiency syndrome (AIDS) diagnosis, hepatitis B or C co-infection, antiretroviral therapy regimen (2 nucleoside analog reverse transcriptase inhibitors (NRTIs) + non-nucleoside reverse transcriptase inhibitor (NNRTI), 2 NRTIs + protease inhibitor (PI), or other combination), CNS penetration effectiveness (CPE) score[16], initial $CD4^+$ T cell count, pre-cART $CD4^+$ T cell count, current $CD4^+$ T cell count, lowest $CD4^+$ T cell count, initial viral load (VL), pre-cART VL, current VL, and highest VL. Additionally, a clinician administered the depression questionnaire[17] and interview for assessing depression and substance use history. The Karnofsky performance status scale[18] was used to assess functional impairments. Also, eight questions designed by authors in Korean based on the suggestions of Antinori *et al*.[15] were used to assess functional activities; these were translated as: "Is it hard to take medication in correct dosages at correct time?"; "Is it hard to manage financial matters independently (budgets, writes checks, pays rent and bills, goes to bank)?"; "Is it hard to maintain house alone or with occasional assistance?"; "Is it hard to maintain personal schedules?"; "Do you have more mistakes in business?"; "Do you need more times than ever for finishing the same amount of work?; "Do you need more efforts than ever for doing well?; "Are you poorer at best working?".

Neuromedical evaluation

Neuromedical assessments were standardized between study sites and included multiple, linked evaluations. These evaluations included the following elements:

1. *Medical history*: Standardized forms to record medical and neurological symptoms. Medical conditions were classified using an International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) codes, and HIV disease stage was classified according to 1993 CDC guidelines[19]. Staff also administered a brief questionnaire to collect information about HIV risk behavior.

2. *Current Medications, Medication History, and Adherence*: A clinician recorded prescribed medications taken for longer than one month. Detailed information about past and present ART use was completed. Each site used the Adherence Scale to Anti-HIV Medications form to collect ART adherence data [20].

3. *Neurological and General Physical Examinations*: The research clinician performed a standardized neurological, medical examination that included assessment of vital signs height and weight, mental status, cranial nerves, motor,

sensory and cerebellar function, reflexes and gait. The medical staff also performs a general physical examination and note health-related functioning.

Assessment of screening tool

Four key questions proposed by the Asia, Australia, Africa and Middle East (AAAME) HAND Advisory Board as a screening tool (unpublished data) to evaluate an early potential of neurocognitive impairment and depression were applied to participants: "Are you slower in your thinking processes?"; "Are you more forgetful?"; "Is it harder to organize things?" and "Are you less able to find pleasure in things you used to enjoy?" Also, international HIV dementia scale (IHDS) [21] and Montreal Cognitive Assessment (MoCA)–K [22] were evaluated as screening tools for diagnosing HAND. The most useful cut-off values of each screening tests was also investigated.

Neuropsychological tests

In order to establish rates of HAND, we used NP test norms based upon the HIV-negative participants[23-27]. The neurobehavioral evaluation assessed six ability domains (Supplement table 1). These are well-established measures that have been used in numerous studies of HIV/AIDS. In addition to individual NP test results, the battery facilitates a clinical determination of level of impairment within each domain, as well as on global level of impairment based upon the population-specific normative standards. This approach has shown good inter-rater reliability, even across raters at different institutions [28].

Diagnosis of HAND

Subjects completed a detailed NP assessment measuring their functioning in six cognitive domains known to be commonly affected by HIV. The *Frascati criteria* were used for diagnosing HAND, classified into asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND) and HIV-associated dementia (HAD) [15].

Statistical analyses

Independent *t*-test or Chi-square test was used to measure differences of each variable between neurocognitive impaired and non-impaired subjects. To identify independent factors associated with HAND, multivariate logistic regression analysis was performed with the variables that had a significant association with HAND on univariate analysis ($p<0.05$). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were then calculated in comparison with the reference diagnosis, which was based on cases of HAND. In addition, we conducted a receiver operating characteristic (ROC) curve analysis to compare the predictive accuracy of screening tools and the area under the curve (AUC) was calculated. The 95% confidence interval (CI) was calculated using the Wilson score method. All *p*-values will be 2-tailed and $p<0.05$ will be considered statistically significant. All analyses will be performed using SPSS for Windows 12.0 (SPSS, Chicago, Illinois, USA).

Results

General characteristics of study subjects

Of the 194 enrolled subjects, 93.8% were male, and the mean age (range) was 45.12 (21-72) years. The most common exposure category was men having sex with men (MSM) (52.6%), followed by heterosexual contact (27.3%). The duration of education (mean±standard deviation (SD)) was 13.4±3.3 years, and 31.9%, and 27.9% of the subjects were at the clinical CDC stages B and C of HIV disease, respectively. Average current $CD4^+$ T cell counts (cells/mm^3, mean±SD) were 481.4±236.0 and current viral load (mean±SD, log10 copies/mL) were 2.0±1.4 (Table 1).

Prevalence and clinical characteristics of HAND

The overall prevalence of HAND in the study cohort was 26.3%. Of the 51 participants with HAND, ANI and MND comprised 52.9% and 47.1%, respectively. No individuals were diagnosed with HAD. Of those with HAND, the mean age (range) was 44.39 (21-70) years, and 96.1% of them were male. The most common exposure category was MSM (47.1%), followed by heterosexual contact (33.3%). The duration of education (mean±SD) was 12.8±3.4 years. The mean hemoglobin (Hb) level was 13.6±1.8 g/dL with 15% having Hb below 13.0g/dL. Initial and current CD4+ T cell counts (cells/mm^3, mean±SD) were 233.8±220.7 and 444.5±259.2, respectively. Initial and current viral load (mean±SD, log10 copies/mL) were 4.7±1.3 and 2.4±1.7, respectively, and 71.7% had the cART regimen of 2NRTI+PI (Table 1). Also, 82% of study participants with HAND receiving cART in our cohort had suppressed viral loads (<50 copies/ml). Among six domains in cognitive functioning in the individuals with HAND, impairment of sensory perceptual/motor skills were the most common (90.2%), followed by abstraction/executive (78.0%) and memory (learning and recall) (48.0%) (Table 2).

In univariate analysis, Hb levels 13g/dL (p=0.029) and current use of a PI-based regimen (p=0.043) were the only factors significantly associated with HAND. The observed significance remained for both Hb levels (p=0.046) and current use of PI-based regimen in multivariate analysis, (p=0.031) (Table 1).

The performance of screening tests for HAND

The sensitivity and specificity of IHDS were 72.6% and 60.8%, and MoCA-K were 52.9% and 73.4%, respectively (Table 3). The MoCA-K and IHDS screening tests significantly correlated with HAND, and a cut-off value of 25 and 10 was the most useful in diagnosing HAND, respectively (Table 3 and Supplement Tables 2 and 3). To compare the predictive accuracy of MoCA-K and IHDS as screening tools, a ROC analysis was performed (Figure 1), which demonstrated that the area under the curves of IHDS and MoCA-K for diagnosing HAND were 0.678 (p<0.001) and 0.666 (p<0.001), respectively. However, the developed 'four key questions' used as a screening tool did not significantly correlate with diagnosis of HAND by standard methods (Supplement Table 4).

NP tests for diagnosing HAND

Diagnostic characteristics for each NP test for diagnosing HAND in HIV-infected Koreans are provided in Table 4. Among NP tests, the Grooved Pegboard Test had the highest sensitivity and modest specificity (90.2% and 72.0%). The next highest scoring NP test was the Wisconsin Card Sorting Test, which had a sensitivity and specificity of 61.2% and 84.4%, respectively. The other NP tests had much lower sensitivity but higher specificity.

Discussion

This is the first study of the prevalence of HAND in HIV-infected patients in Korea, and we found that approximately a quarter of our patients had HAND (26.3%). Of these individuals 52.9% had ANI and 47.1% had MND. Of those with HAND, 82% were receiving cART with suppressed viral loads, suggesting that suppressing HIV replication might be not sufficient to treat HAND. These results are similar to reports from Western countries, with the reported prevalence of HAND of 16~38% in the era of cART [9-13].

Our study also found lower Hb levels and use of a current PI-based cART regimen to be independent risk factors for HAND. Although low Hb levels may represent underlying chronic disease, the specific mechanism of the effect of low Hb on the occurrence of HAND is unclear, although previous studies have also noted low Hb level as a risk factor for HAND [29] and HAD [30]. The reason behind the observed significant correlation between the current use of a PI-based cART regimen and HAND is unclear, but it may represent the possibility of clinician's effort for treatment of HAND rather than independent factor of it. In other words, we think that cART might have been switched to a PI-based regimen because of memory impairment of HIV-infected patients. This is because NNRTI such as efavirenz were reported risk factors of HAND [31] and PIs have mostly high CPE scores [32]. Thus, in our study, HIV-infected patients with HAND seemed to have more PI-based regimen than them without HAND. Another reason for the association between PI and HAND would be that perhaps clinicians tend to prescribe PI-based cART regimens for the more ill patients rather than NNRTI-based regimen.

Some studies of Western cohorts have reported that nadir CD4+ T cell counts were an independent risk factor of HAND [33-35], but this was not observed in our cohort. In our study, interquartile ranges of nadir CD4+ T cell counts of all participants were 69-277 cells/mm^3, and especially, 25% quartile was higher than that of other study [33]. This might be because cART had a tendency to be started earlier in Korea; thus, we think that nadir CD4+ T cell count was not significantly associated with HAND because of the overall higher CD4+ counts in our population. Since the prevalence of HAND in our population was similar to these Western reports, this finding may provide insight that nadir CD4+ count may in fact be a confounder with and not a predictor of HAND.

In our study, the IHDS and MoCA-K measures used as screening tools for HAND had better performance than the developed 'four key questions'. Since IHDS is widely used as a screening tool for HAD[21], it has the potential to be a useful screening instrument for HAND. For our study, participants who were classified with neurocognitive impairment on the IHDS also performed significantly lower on other tests of cognitive function, especially

processing speed and verbal learning/memory [36]. Alternatively, MoCA is a brief cognitive screening tool with high sensitivity and specificity for detecting mild cognitive impairment or dementia [22,37], and in our study, a cut-off value of 26 (scores of 25 or below indicate impairment) yielded the best balance between sensitivity and specificity for the HAND. Since clinicians often depend on patients to self-report memory complaints, especially in the early stages of cognitive impairment, we attempted to develop a screening tool with four questions, but this tool was not found to be reliable. We think that this was because enrolled patients might not have answered the questions frankly.

Beyond screening tools, we also evaluated which NP tests had the best test characteristics for diagnosing HAND. We found that the Grooved Pegboard Test and Wisconsin Card Sorting Test had the best sensitivity and specificity in our study population. Specifically, the Grooved Pegboard Test is commonly used measure of psychomotor slowing used with HIV-positive populations [38], and it has been reported that it can significantly differentiate demented from non-demented HIV-infected patients [39]. Therefore, the Grooved Pegboard Test might be useful in diagnosing HAND in HIV infected Koreans.

Our study had some limitations. First, although there were 194 well-characterized participants in the study, the sample size of those with HAND was only 51. The small sample size has the possibility to influence results due to an unequal distribution of impairment and to determine risk factors for HAND. Second, there was no HAD in this study. This might represent a selection bias, i.e. those with HAD would not have been able to find their way to consent and participate. Third, our results were not applicable to females with HIV because 93.8% of enrolled patients were men; however, the study sample was representative of the Korean HIV-infected population[40]. Fourth, this study was conducted among HIV-infected patients in an urban outpatient clinic in Korean, which may not be representative of HIV-infected individuals in community and rural setting or to the general Korean population. Lastly, the presence of peripheral neuropathy in HAND influencing NP tests, especially the Grooved Pegboard was not excluded by neurologic examination.

In conclusion, HAND is a prevalent comorbidity among HIV-infected Koreans. Active screening and diagnosis with useful tools like IHDS, MoCA-K and Grooved Pegboard Test likely should be performed not to overlook this important complication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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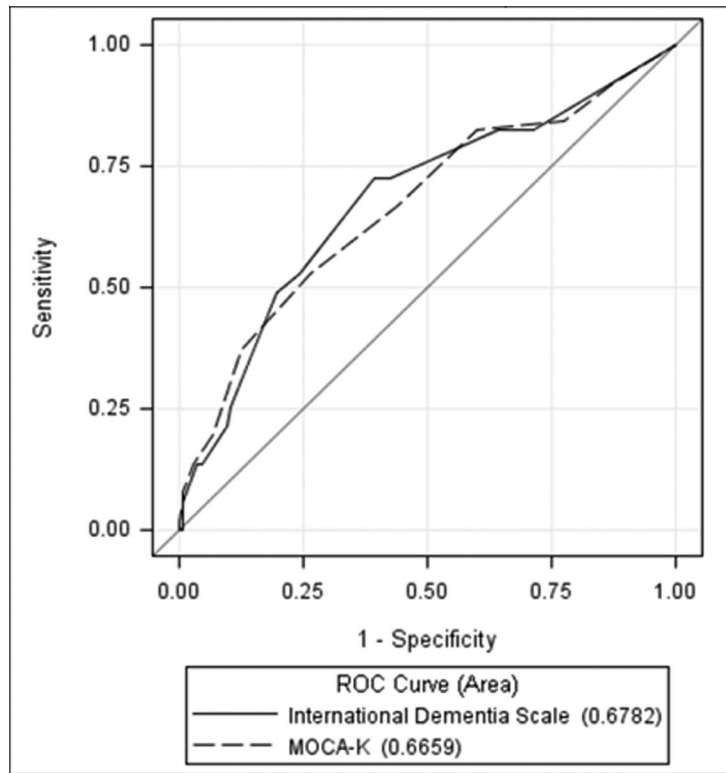40. 2011 Annual Report on the Notified HIV/AIDS in Korea. PHWR. 2012; 5:11–14.

Figure 1. The AUCs of IHDS and MoCA-K for diagnosing HAND

Table 1

Baseline characteristics and factors associated HAND in HIV-infected individuals

Variables	Total (N=194)	HAND (N=51)	No HAND (N= 143)	p-value	Multivariate analysis Odds ratio (95% CI)	p-value
Age (years, range)	45.12 (21-72)	44.39 (21-70)	45.38 (25-72)	0.581		
Male gender (%)	182 (93.8)	49 (96.1)	133 (93.0)	0.735		
BMI (Kg/mm²)	23.0±4.5	22.1±2.9	23.3±4.9	0.105		
Hemoglobin 13.0g/dL (%)		15 (29.4)	22 (15.4)	0.029	2.287 (1.014-5.162)	0.046
Education						
Mean (years)	13.4±3.3	12.8±3.4	13.6±3.3	0.188		
Mode of transmission (%)						
Homosexual contacts	102 (52.6)	24 (47.1)	78 (54.5)	0.358		
Heterosexual contacts	53 (27.3)	17 (33.3)	36 (25.2)	0.262		
Unknown and others	39 (20.1)	10 (19.6)	29 (20.3)			
Duration of HIV infection (years)	77.7±70.1	73.4±52.5	79.3±75.5	0.606		
Previous AIDS diagnosis	55 (28.4)	18 (35.3)	37 (25.9)	0.200		
AIDS at diagnosis						
No	**76**	**17 (33.3)**	**59 (41.3)**	**0.320**		
Yes	**118**	**34 (66.7)**	**84 (58.7)**	**0.320**		
Initial CD4$^+$ T cell count, mean±SD, cells/mm³	243.8±188.3	233.8±220.7	247.3±176.0	0.668		
Initial VL, mean±SD, log10 copies/mL	4.8±1.2	4.7±1.3	4.8±176.0	0.797		
Pre-cART CD4$^+$ T cell count, mean±SD, cells/mm³	186.4±136.0	176.5±167.5	189.8±123.8	0.601		
Pre-cART VL, mean±SD, log10 copies/mL	5.0±0.9	5.0±0.9	5.0±0.9	0.965		
Current CD4$^+$ T cell count, mean±SD, cells/mm³	481.4±236.0	444.5±259.2	494.6±226.6	0.194	0.999 (0.997-1.001)	0.225
Current VL, mean±SD, log10 copies/mL	2.0±1.4	2.4±1.7	1.9±1.2	0.069		
Nadir CD4$^+$ T cell count, mean±SD, cells/mm³	187.0±138.0	171.8±167.2	192.4±126.3	0.365		
Highest VL, mean±SD, log10 copies/mL	5.0±0.9	5.0±0.9	4.9±1.0	0.566		
Current cART (%)						
No treatment	20 (10.3)	7 (13.7)	13 (9.1)	0.350		
2NRTI+PI	104 (59.8)	32 (72.7)	72 (55.4)	0.043	2.323 (1.078-5.005)	0.031
2NRTI+NNRTI	49 (28.2)	7 (15.9)	42 (32.3)	0.037		

Variables	Total (N=194)	HAND (N= 51)	No HAND (N= 143)	*p*-value	Multivariate analysis	
					Odds ratio (95% CI)	*p*-value
2NRTI+II	12 (6.9)	3 (6.8)	9 (6.9)	1.000		
3NRTI	3 (1.7)	0 (0.0)	3 (2.3)	0.572		
Other	6 (3.4)	2 (4.5)	4 (3.1)			
CPE rank		6.7±1.3	6.7±1.1	0.961		
HCV co-infection (%)	6 (3.7)	3 (6.7)	3 (2.6)	0.350		
HBV co-infection (%)	9 (5.3)	2 (4.3)	7 (5.6)	1.000		

HAND, HIV associated neurocognitive disorder; BMI, body mass index; AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; cART, combination antiretroviral therapy; IQR, interquartile range; VL, viral load; PI, protease inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; II, integrase inhibitor; CPE, central nervous system penetration effectiveness; HCV, hepatitis C virus; HBV, hepatitis B virus

Table 2

Impairment of 6 domains in cognitive functioning in 51 Korean HIV-infected individuals with HAND

Domain	No. of impairment (%) in HAND
Verbal/language	2 (3.9)
Attention/Working Memory	3 (5.9)
Abstraction/Executive	39 (78.0)
Memory (learning and recall)	24 (48.0)
Speed of information processing	1 (2.0)
Sensory perceptual/motor skills	46 (90.2)

HAND, HIV-associated neurocognitive disorder

Table 3

Diagnostic performance of IHDS and MoCA-K

NP test	Sensitivity	Specificity	Accuracy
IHDS 10	72.55(60.30-84.80)	60.84(52.84-68.84)	63.92(57.16-70.68)
MoCA-K 25	52.94(39.24-66.64)	73.43(66.19-80.67)	68.04(61.48-74.60)
p-value for comparison	0.0244	0.0071	0.3134

IHDS, International HIV dementia scale; MoCA-K, Montreal Cognitive Assessment -K

Table 4

Diagnostic value of neuropsychological test for diagnosing HAND in Korean HIV-infected individuals

Cognitive Domain and Neuropsychological Test	Sensitivity	Specificity	PPV	NPV	Accuracy
Speed of Information Processing					
K-WAIS Digit Symbol Subtest	1.96(0.00-5.77)	99.30(97.93-100.00)	50.00(0.00-100.00)	73.96(67.75-80.17)	73.71(67.52-79.91)
Trail Making Test, Part A	0.00(0.00-0.00)	100.00(100.00-100.00)	-	73.71(67.52-79.91)	73.71(67.52-79.91)
Memory (learning and recall)					
K-Auditory Verbal Learning Test (K-AVLT)	6.00(0.00-12.58)	99.30(97.93-100.00)	75.00(32.56-100.00)	75.13(68.97-81.29)	75.13(69.03-81.23)
K-Complex Figure Test (K-CFT)	9.80(1.64-17.97)	99.30(97.93-100.00)	83.33(53.51-100.00)	75.53(69.39-81.68)	75.77(69.74-81.80)
Abstraction/Executive					
Wisconsin Card Sorting Test (128-item)	61.22(47.58-74.87)	84.40(78.41-90.39)	57.69(44.26-71.12)	86.23(80.48-91.98)	78.42(72.57-84.27)
K-WAIS Similarity Subtest	4.00(0.00-9.43)	100.00(100.00-100.00)	100.00(100.00-100.00)	74.74(68.56-80.92)	75.00(68.88-81.13)
Trail Making Test, Part B	32.00(19.07-44.93)	95.10(91.57-98.64)	69.57(50.76-88.37)	80.00(73.99-86.01)	78.76(72.99-84.53)
Attention/Working Memory					
K-WAIS Digit Span Subtest	5.88(0.00-12.34)	99.30(97.93-100.00)	75.00(32.56-100.00)	74.74(68.56-80.92)	74.74(68.63-80.86)
Sensory perceptual/motor skills					
Grooved Pegboard Test (Dominant and Non-dominant Test)	90.20(82.03-98.36)	72.03(64.67-79.39)	53.49(42.95-64.03)	95.37(91.41-99.33)	76.80(70.86-82.74)
Verbal/language					
K-WAIS Vocabulary Subtest	3.92(0.00-9.25)	100.00(100.00-100.00)	100.00(100.00-100.00)	74.48(68.31-80.65)	74.74(68.63-80.86)

HAND, HIV-associated neurocognitive disorder; K-WAIS, K-Wechsler Adult Intelligence Scale