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An initial screening for HIV-associated neurocognitive disorders of HIV-1 infected patients in China

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Abstract

HIV-associated neurocognitive disorders (HAND), characterized by cognitive, motor, and behavioral abnormalities, are common among people living with HIV and AIDS. In combined antiretroviral therapy era in Western countries, nearly 40% of HIV-infected patients continue to

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suffer from HAND, mainly with mild or asymptomatic cognitive impairment. However, the prevalence and the clinical features of HAND in China are still not well known. In this study, a multi-center cross-sectional study was performed to determine the prevalence and clinical features of HAND in 134 HIV-1 infected patients in China. The International HIV Dementia Scale and a neuropsychological test battery were administered for screening and diagnosis HAND. Subjective complaints, CD4 count and viral loads in both blood plasma and cerebrospinal fluid were correlated with diagnosis of HAND. The results showed that the prevalence of HAND was approximately 37% in these patients. CD4 counts at time of sampling were significant lower in the HAND group than in the non-HAND group. But the distribution of the HAND severity did not differ by CD4 count or viral load. The presence of HAND was associated with cognitive and behavior disorder complaints (4.9- and 4.1-fold higher than those without HAND, respectively). The present data suggest that CD4 count and viral load cannot predict the severity of HAND, although the prevalence of HAND is similar to previous report in these patients. Cognitive and behavioral disorder is major complaint rather than cognitive and motor impairment. A larger prospective study is needed to obtain better estimates of HAND in China.

Keywords

AIDS; Clinical manifestation; HIV-associated neurocognitive disorders; Prevalence

Introduction

Since the beginning of the HIV/AIDS epidemic, HIV-associated neurocognitive disorders (HAND) have been commonly observed in infected populations (Heaton et al. 1995, 2011). HAND is characterized by cognitive, motor, and behavioral abnormalities and severity is classified according to patient performance in areas of neurological and behavioral functioning and neuropsychological testing (Antinori et al. 2007b; Kaul et al. 2005). Prior to the widespread use of highly active antiretroviral therapy (HAART), 20–30% of individuals in Western countries with advanced HIV infection displayed symptoms of the most severe form of HAND, HIV-associated dementia (HAD) (Kaul et al. 2005). Even in the HAART era, nearly 40% of HIV-positive patients continue to suffer from HAND and a significant number of HIV-1 infected patients show progressive loss of cognitive abilities (Antinori et al. 2007b; Boisse et al. 2008; Minagar et al. 2008). Despite the decline of severe HAND incidence, neurological complications remain an important cause of disability and death, and the overall prevalence of HAND may increase as HIV-infected individuals live longer (Kandanearatchi et al. 2003).

HAND is clinically classified as asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and dementia (Antinori et al. 2007a). The International HIV Dementia Scale (IHDS) is widely used as screening test to identify individuals at risk for HIV-associated dementia (HAD) in both the industrialized world and the developing world, and full neuropsychological (NP) testing is often required to confirm a diagnosis of HAND (Sacktor et al. 2005). The NP assessment surveys the following abilities: verbal/language, attention/working memory, abstraction/executive, memory (learning; recall), speed of information processing, sensory/perception, and motor skills (Antinori et al. 2007a). Acquired impairment in cognitive functioning is defined as involving at least two ability domains, documented by performance of at least one standard deviation below the mean for age–education-appropriate norms on standardized NP tests.

By October 2010, over 370,000 people have been found to be infected with HIV in China. Sexual contact is becoming a major mode of HIV transmission, in particular among men who have sex with men (MSM), and ethnic minorities comprise the fastest growing segment

of the HIV-infected population (National Center for AIDS/STD Control and Prevention, China CDC). However, even though large numbers of people are infected in China, up to now, very few reports have documented the prevalence and the clinical features of HAND. In this study, we determined how frequently HAND could be detected in 134 HIV-1 infected patients in China, and how HAND was related to subjective complaints, CD4 counts and viral loads in blood plasma and cerebrospinal fluid (CSF).

Materials and methods

Patients

HIV-1 infected patients were selected from three sites participating in an AIDS Risk Cohort Program supported by Beijing Science and Technology Committee. These sites included the Infectious Diseases Hospital of Henan Province located in central China, Infectious Diseases Hospital of Yunnan Province located in southwest China, and the Beijing You An Hospital located in northern China. Exclusion criteria included age less than 18 years, an active or known past central nervous system (CNS) opportunistic infection, fever >37.5°C, a history of a chronic neurologic disorder, active psychiatric disorder, alcoholism, physical deficit (e.g., amputation), severe functional impairment, or severe medical illness that would interfere with the ability to perform the study evaluations. This study was approved by the Human Subjects Protection Committees of each participating hospital. Written informed consent was obtained from all study participants.

Clinical assessments

HIV-infected patients and/or primary care givers were randomly selected and subsequently questioned by an investigator about symptoms of: (1) cognitive impairments including memory dysfunction, difficulty with concentration, weak calculation, difficult to recognize his/her families, apathy, mutism, visual hallucinations, disorientation, inertia, social withdrawal and waning interest in work and hobbies; (2) motor impairments including poor hand writing, tendency to drop things easily, difficulty with hand coordination, holding instablity, insecure balance, difficulty with gait, postural tremor, dystonia, choreoathetoid movements, impairments of rapid eye movement and urinary or fecal incontinence; (3) change in behavior including change in personality, blunting of emotional responsiveness, agitation, mania and difficulties with activities of daily living or employment. Cognitive impairments and motor impairments contained 11 symptoms, respectively (each cumulative score 11), change in behavior containing five symptoms (cumulative score 5). Then these patients were evaluated using a screening test for HIV dementia (IHDS score ≤10) (Sacktor et al. 2005). The evaluations were translated into the local language, Chinese. Clinical assessments used standardized questionnaires assessing demographic information, including primary language and reading abilities, medical, psychiatric, and neurologic history, including an assessment of peripheral neuropathy symptoms, and a systematic neurological examination.

Neuropsychological and functional impairment in everyday life assessments

After questioning about neurocognitive symptoms and screening for HIV dementia, patients underwent standardized NP testing including Grooved Pegboard (dominant and non-dominant Hands), Trail Making Test: Parts A and B, and Wechsler Adult Intelligence Scale (WAIS-III) Digit Symbol. The Grooved Pegboard is a manipulative dexterity test. This unit consists of 25 holes with randomly positioned slots. Pegs, which have a key along one side, must be rotated to match the hole before the can be inserted. This test requires more complex visual–motor coordination than most pegboards. The Trail-making test is a neuropsychological test of visual attention and task switching. The task requires a subject to ‘connect-the-dots’ of 25 consecutive targets on a sheet of paper or computer screen. Two

versions are available: A, in which the targets are all numbers, and B, in which the subject alternates between numbers and letters. The goal of the subject is to finish the test as quickly as possible, and the time taken to complete the test is used as the primary performance metric. WAIS-III Digit Symbol is sensitive to brain damage, dementia, age and depression and consists of digit–symbol pairs followed by a list of digits. Under each digit, the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time is measured. The combination of Grooved Pegboard, Trail Making Test: Parts A and B, and Wechsler Adult Intelligence Scale (WAIS-III) Digit Symbol was confirmed to be more sensitive and accurate in detection HAND (Antinori et al. 2007a; Carey et al. 2004; Kim et al. 2001). Results of these NP tests were assessed in relation to previously reported normative data according to age and education (Kim et al. 2001). Based on these results, HAND was categorized as ANI, MND, or HAD, according to the Revised Research Criteria for HIV-associated Neurocognitive Disorders (Antinori et al. 2007a). Reports of cognitive difficulties in everyday life were assessed using Activity of Daily Living (ADL) scale (Gandhi et al. 2011). The ADL scale includes 20 items on which participants rate themselves as having neurobehavioral difficulties in their everyday lives. A total summed score is derived, with higher scores indicating more difficulty.

Laboratory assessments

HIV infection was diagnosed by enzyme-linked immunosorbent assay with Western blot confirmation. Complete blood counts and CD4+ T cells (flow cytometry) were performed. HIV RNA levels were measured in blood plasma and CSF by reverse transcriptase polymerase chain reaction (Roche Amplicor, v. 1.5; lower limit of quantization 50 copies per milliliter).

Data analysis

The results were evaluated as a mean with a standard deviation (SD) or other forms in accordance with the variable distribution. Statistical significance was determined by one-way ANOVA, with post hoc correction using the Tukey multiple comparison test. Chi-square test was used to compare the ratio change of different HAND types. Spearman correlation analysis was used to compare the relationship between two variables. Statistical software PASW statistics 18 was used in this study, and a value of $p<0.05$ was considered statistically significant.

Results

Participants

Among the three recruitment sites, 56 participants were selected from the Infectious Diseases Hospital of Henan Province and most reported being former plasma donors (FPD), 43 participants were selected from Infectious Diseases Hospital of Yunnan Province and most reported HIV risks of sexual contact and injection drug use (IDU), and 35 participants were selected from the Beijing You An Hospital and most reported HIV risks of MSM. Participant demographics are summarized in Table 1.

Among 134 subjects, 50 (37.31%) were found to have HAND based on IHDS and NP testing, significantly higher than normal population which was 17% (data not published). The HAND group had a mean (SD) age of 38.65 (9.46) years, which was not different from the non-HAND group who had a mean (SD) age of 36.77 (7.91) years. Women were over-represented in the HAND group (78% in HAND group vs. 22.62% in non-HAND group; chi-square test, $p<0.001$). There were no differences in reported HIV infection risks (MSM, IDU, FPD and Heterosexual contact), level of education, race ethnicity and estimated duration of infection. Among 134 HIV-1 infected patients, 98 administered HAART

including 59 (70.24%) in non-HAND group whose average therapy time was 13.26 months, and 39 (78%) in HAND group whose average therapy time was 12.03 months. No difference in HAART was found between two groups.

The prevalence of HIV-associated neurocognitive disorders

Participants were clinically classified into three grades according to the Centers for Disease Control (CDC) of the United States (CDC-A, CDC-B and CDC-C). Among the 134 participants, 26 were classified into CDC-A, 52 CDC-B and 56 CDC-C. There was a total of six HAND in CDC-A group (23.08%) including four with ANI (15.38%) and two with MND (7.69%). None in CDC-A group met criteria for HAD. For the CDC-B group, 20 participants demonstrated HAND (38.46%) including 13 with ANI (25%) and five with MND (9.62%) and two with HAD (3.85%). For the most advanced group, CDC-C, 24 participants had HAND (42.86%) and included 13 with ANI (23.21%), seven with MND (12.5%) and four with HAD (7.14%). As expected, the prevalence of HAND increased with the advanced stages of HIV disease, but statistical analysis showed no difference in the distribution of three HAND classifications among three CDC stages (chi-square test, $p>0.05$), likely secondary to sample size (Table 2).

The prevalence of HAND in three recruitment sites was also compared. In 50 HAND patients, 16 (45.71%) came from Beijing including ten with ANI (28.57%) and four with MND (11.43%) and two with HAD (5.71%); 15 (26.79%) came from Henan including eight with ANI (14.29%) and six with MND (10.71%) and only one with HAD (1.79%); and 19 (44.19%) from Yunnan including 12 with ANI (27.91%) and four with MND (9.3%) and three with HAD (6.98%). The rates of HAND in Beijing (45.71%) and Yunnan (44.19%) were close and higher than that in Henan (26.79%), but this difference was not significant (chi-square test, $p>0.05$) (Table 2).

Since HIV levels are a marker of disease status and can be used to monitor the effectiveness of HAART, we also evaluated blood viral loads in relation to the presence or absence of HAND. First, 134 participants were divided into 26 with blood plasma viral loads <50 copies/ml (undetectable) and 108 with viral loads ≥50 copies/ml). Among 50 patients with HAND, eight (30.77%) had undetectable blood viral loads including five with ANI (19.23%) and two with MND (7.69%) and one with HAD (3.85%), while 42 (38.89%) had detectable blood plasma viral loads including 25 with ANI (23.15%) and 14 with MND (12.96%) and three with HAD (2.78%). Prevalence of overall HAND and the constituent HAND types between two groups were not different (chi-square test, $p>0.05$) (Table 2).

The symptomatic features of HIV-associated neurocognitive disorders

In this study, we investigated the relationship of patient's complaints and NP results. The total symptom scores of cognitive and motor and behavior were 2.52 in non-HAND group, and 6.04 in HAND group (ANOVA, $p< 0.01$) (Fig. 1a); thereby, demonstrating that HAND was associated with greater participant symptomatology. Specifically, as expected the symptom of cognitive disorder was more significant in HAND group (3.19 vs. 0.65, ANOVA, $p<0.01$), followed by that of behavior disorder (1.60 vs. 0.39, ANOVA, $p<0.01$). But the symptom of motor impairment was not different between two groups (1.50 vs. 1.06, ANOVA, $p>0.05$) (Fig. 1b). The cumulative symptom scores were also different between ANI, MND and HAD (2.58 vs. 6.40 vs. 11.82, ANOVA, $p<0.01$) (Fig. 1c). Further analysis found that cognitive impairment scores (0.83 vs. 3.70 vs. 6.27, ANOVA, $p<0.01$) and behavior disorder scores (0.65 vs. 1.65 vs. 2.55, ANOVA, $p<0.05$) increased in the advanced stages of HIV disease, i.e., CDC classes. Although the symptom of motor impairment was more serious in HAD compared with that in ANI and MND (3.0 vs. 1.09 and 1.05, ANOVA, $p<0.01$), no difference was found between ANI and MND (Fig. 1d).

The relationship of HIV-associated neurocognitive disorders, CD4 count and HIV load

Among the cohort, average HIV loads (HIV RNA log10 copies/ml) were 3.87 (SD 1.50) in blood plasma and 3.36 (SD 1.41) in CSF. Blood and CSF viral loads were significantly correlated (Spearman correlation analysis, r=0.59, p<0.01), but no correlations were found between IHDS score and CSF viral load (Spearman correlation analysis, r=−0.046, p>0.05), IHDS score and blood viral load (Spearman correlation analysis, r=−0.219, p>0.05), and IHDS score and CD4 cell counts (Spearman correlation analysis, r=0.175, p>0.05). CD4 counts at time of sampling were significant lower in the HAND group (368.34±77.22) than in the non-HAND group (745.38±121.74) (ANOVA, p<0.05), but HIV loads in blood plasma or in CSF were not different between the two neurocognitive (NC) groups (ANOVA, p>0.05). Further analysis did not demonstrate any differences in the CD4 counts and blood plasma and CSF viral loads between the three HAND subgroups (ANI, MND and HAD; ANOVA, p>0.05, Table 3).

Discussion

Prior to the availability of HAART, HAND was relatively common among patients with advanced HIV disease. With the use of HAART, the prevalence of HAND decreased, and the overall health of HIV-infected patients improved; however, HAND is still a problem, even among patients receiving HAART and with good CD4+ counts and undetectable blood plasma viral load (Robinson-Papp et al. 2009). In fact, the prevalence of HAND has been described as close to 40% of HIV-positive patients in the HAART era (Antinori et al. 2007b; Boisse et al. 2008; Minagar et al. 2008). The results in this Chinese cohort were similar to these data, although a larger sample is needed to further confirm the results. Interestingly, compared with other two sites, the prevalence of HAND seemed to be lower at the Henan site where patients mainly consisted of patients with the FPD risk factor and had lower educational levels. This observation is significantly different from previous report (Heaton et al. 2008), although it did not reach statistical significance. Further, it is also different from previous report in our study that women were susceptible to HAND, which probably contributed to small sample size and variable treatment agents and time. Compared with male patients, lower education level in female patients probably affected NP results, although NP results have been normalized according to age and education.

Since HAND includes cognitive impairment, motor disorder and abnormal behavior, we evaluated the symptoms in each of these domains. In the pre-HAART era, HAND had more impairment in motor skills, cognitive speed, and verbal fluency, whereas in the HAART era HAND involved more memory (learning) and executive function impairment. This pattern is consistent with earliest involvement of subcortical or frontostriatal brain systems (Heaton et al. 1995). In HAART era, HIV-related HAND was generally mild and persisted at all stages of HIV infection, especially in the medically asymptomatic stage of infection, despite improved viral suppression and immune reconstitution with HAART (Heaton et al. 2011; Pascual-Sedano et al. 1999). One study reported that patients with HIV infection were at an increased risk of psychiatric illness, and that major depressive and anxiety disorder and substance abuse are more prevalent among HIV-infected individuals (Owe-Larsson et al. 2009). Our study even demonstrated that behavior disorder was more common than motor impairment, but cognitive impairment remained a persistently common complaint. Similar to a previous study in Switzerland (Simioni et al. 2010), in our study, symptoms also increased with successive HAND stages (ANI, MND, and HAD).

A previous cross-sectional cohort in the United States reported that among patients receiving HAART and with undetectable plasma HIV RNA, 38% had HAND (20%, 16%, and 2% with ANI, MND, and HAD, respectively) (Pumpradit et al. 2010). In comparison with participants who were NC normal and virally suppressed, individuals with HAND and viral

suppression had shorter duration of current HAART (Cysique and Brew 2011). A history of immunosuppression (nadir CD4 cell count <200 cells/ml) was associated with an increase in prevalent of HAND and CD4 nadir is a predictor of HAND in the era of combination antiretroviral therapy (Ellis et al. 2011a; Robertson et al. 2007). Neurocognitive performance is also linked to HIV disease stages, and in both pre-HAART and HAART eras, the HAND rate is increased with later disease stages (CDC stages A, B, and C) (Antinori et al. 2007a; Heaton et al. 2011; Woods et al. 2009). Further, low CD4 counts and high HIV RNA levels in the blood usually predict poorer outcome, and HAND has been consistently associated with nadir CD4 levels (Ellis et al. 2011b; Heaton et al. 2011; Simioni et al. 2010). Our multi-center cross-sectional study revealed that the overall prevalence of HAND was over one-third of HIV-1 infected patients in China. Interestingly, in our study, although CD4 counts were lower in HAND than non-HAND, it seemed not to correlate with the severity of HAND, which probably contributed to the relative short time on HAART resulting small proportion of HIV suppressed patients. Although not assessed, the CSF penetration of HAART and patients' adherence may have also affected the rate of HAND. Further, genotypic or phenotypic drug resistance assays were not performed, and these may have helped resolved some of the issues of possible drug resistance or infecting clade effect of HAND. Therefore, larger sample size, longitudinal observation and additional laboratory characterizations are needed to better characterize NC functioning among HIV-infected people in China.

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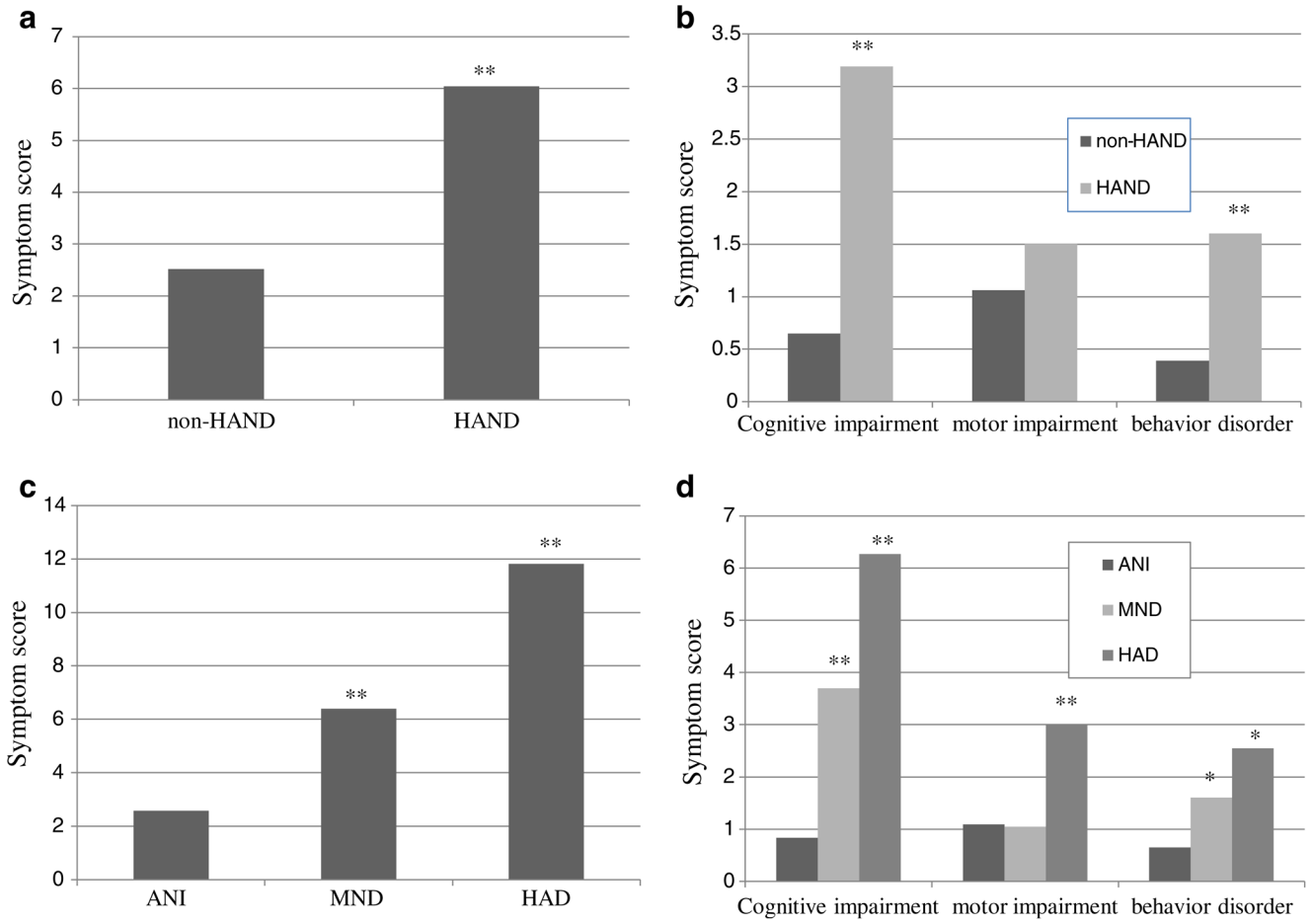

Fig. 1.

The symptomatic feature of HIV-associated neurocognitive disorders in these patients. **a** The total symptom score of HAND group was higher than that of non- HAND group (6.04 vs. 2.52). **b** The symptom score of cognitive impairment was very higher in HAND group (3.19 vs. 0.65), followed by that of behavior disorder (1.60 vs. 0.39). But the symptom score of motor impairment was not different between two groups (1.50 vs. 1.06). **c** The total symptom scores were different among ANI and MND and HAD (2.58 vs. 6.40 vs. 11.82). **d** Cognitive impairment scores increased as the disease development (0.83 vs. 3.70 vs. 6.27). Similarly, behavior disorder scores also increased as the disease development (0.65 vs. 1.65 vs. 2.55). Although the symptom score of motor impairment was higher in HAD compared with that in ANI and MND (3.0 vs. 1.09 and 1.05), no difference of that was found between ANI and MND. *Statistically significant at $p < 0.05$; **statistically significant at $p < 0.01$

Table 1

Participant demographics

	Non-HAND (*n*=84)	HAND (*n*=50)	*p* value
Age, years, mean (SD)	38.65(9.46)	36.77(7.91)	NS
Male, *n* (%)	65(77.38)	11(22)	<0.001
Education, years, mean (SD)	5.23(1.46)	4.85(1.24)	NS
Race/ethnicity — minority, *n* (%)	6(7.14)	3(6)	NS
Estimated infective time, years, mean (SD)	4.63(2.68)	5.16(3.24)	NS
ART treatment time, months, mean (SD)	13.26(3.25)	12.03(4.78)	NS
HIV infection risks			
MSM, *n* (%)	14(16.67)	8(16)	NS
IDU, *n* (%)	8(9.52)	3(6)	NS
Heterosexual, *n* (%)	27(32.14)	17(34)	NS
FPD, *n* (%)	32(38.1)	20(40)	NS
Others, *n* (%)	3(3.57)	2(4)	NS

HAND HIV-associated neurocognitive disorders, *ART* antiretroviral therapy, *MSM* men who have sex with men, *IDU* injecting drug user, *FPD* former plasma donors, *NS* non-significant at $p<0.05$

Table 2

Prevalence of HIV associated neurocognitive disorders

	Clinical stage			*p* value	Recruitment site			*p* value	Viral load (copies/ml)		*p* value
	CDC-A (*n*=26)	**CDC-B (*n*=52)**	**CDC-C (*n*=56)**		**Beijing (*n*=35)**	**Henan (*n*=56)**	**Yunnan 3 (*n*=43)**		**<50 (*n*=26)**	**> or =50 (*n*=108)**	
ANI, *n* (%)	4 (15.38)	13 (25)	13 (23.21)	NS	10 (28.57)	8 (14.29)	12 (27.91)	NS	5 (19.23)	25 (23.15)	NS
MND, *n* (%)	2 (7.69)	5 (9.62)	7 (12.5)	NS	4 (11.43)	6 (10.71)	4 (9.3)	NS	2 (7.69)	14 (12.96)	NS
HAD, *n* (%)	0 (0)	2 (3.85)	4 (7.14)	NS	2 (5.71)	1 (1.79)	3 (6.98)	NS	1 (3.85)	3 (2.78)	NS
HAND, *n* (%)	6 (23.08)	20 (38.46)	24 (42.86)	NS	16 (45.71)	15 (26.79)	19 (44.19)	NS	8 (30.77)	42 (38.89)	NS

CDC the Centers for Disease Control of the United States, *ANI* asymptomatic neurocognitive impairment, *MND* mild neurocognitive disorder, *HAD* HIV-associated dementia, *HAND* HIV associated neurocognitive disorders, *NS* non-significant at $p<0.05$

Table 3

Relationships between HIV associated neurocognitive disorders, CD4 count and HIV load

	Groups		*p* value	HAND Subtypes			*P* value
	Non-HAND	HAND		ANI	MND	HAD	
CD4 count (10^6/l), mean (SD)	745.38 (121.74)	368.34 (77.22)	<0.05	415.07 (111.85)	316.48 (96.5)	286.36 (56.97)	NS
HIV load in plasma (log_{10} copies/ml), mean (SD)	3.48 (1.42)	4.13 (1.51)	NS	4.08 (1.40)	4.35 (1.62)	4.24 (1.73)	NS
HIV load in CSF (log_{10} copies/ml), mean (SD)[a]	3.32 (1.45)	3.38 (1.40)	NS	3.32 (1.46)	3.36 (1.33)	3.65 (1.48)	NS

HAND HIV-associated neurocognitive disorders, *SD* standard deviation, *ANI* asymptomatic neurocognitive impairment, *MND* mild neurocognitive disorder, *HAD* HIV-associated dementia, *CSF* cerebrospinal fluid, *NS* non-significant

[a]Correlation of HIV load between blood plasma and CSF