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Prevalence of HIV-associated Neurocognitive Disorder (HAND) and its subgroups among HIV-positive persons on anti-retroviral therapy in Iran

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This study aimed to determine the prevalence and determinants of HIV-associated neurocognitive disorder (HAND) and its subgroups in HIV-positive patients in Tehran, Iran. Ninety-three HIV-positive individuals were assessed; the majority were male (60%) and the mean age of patients was 36.5 years (*SD* = 9), with 8 years as the median duration of HIV infection. The relationship between demographic and clinical variables was examined using logistic regression analysis. The overall prevalences of HAND and cognitive complaints were 50.5% and 73%, respectively. Lower nadir CD4 counts (≤ 200), lower educational levels (≤ 12 years), longer disease duration (≥ 5years), and higher depression rates were positively associated with the presence of HAND. This study shows that the prevalence of HANDs in Iran is high, but similar to the prevalence levels found in Western societies. Further studies are needed to longitudinally evaluate the presence of HAND, in particularly to recognize new biomarkers and specific neurocognitive domains in HIV.

Key words: Human Immunodeficiency Virus (HIV), Neurocognitive Complaints, Depression.

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Highlights:

- Every second individual with HIV may have some neurocognitive impairment.
- The prevalence of HAND in Iran is similar to its prevalence in Europe.
- Depression represents a high risk for developing HAND.

The World Health Organization (WHO) estimates that 37.9 million people lived with the human immunodeficiency virus (HIV) at the end of 2018 (WHO, 2019). Cognitive impairments in HIV has become an important clinical and research challenge. These impairments are collectively known as HIV-associated neurocognitive disorder (HAND); with attention, memory, processing speed, executive functioning, learning, and memory difficulties and underlying cortical and subcortical brain dysfunctions (Saylor et al., 2016). In general, HAND significantly impacts the daily life (Hong & Banks, 2015; Nabha, Duong, & Timpone, 2013) of individuals suffering from it while it is associated with declines in social and occupational functioning and difficulty with activities of daily living. It may also lead to poorer anti-retroviral therapy (ART). (Farinpour et al., 2003; Garvey, Yerrakalva, & Winston, 2008; Garvey, Yerrakalva, & Winston, 2009; Heaton et al., 2010), quality of life (Tozzi et al., 2007), and the overall survival (Tozzi et al., 2007).

The prevalence of HAND is estimated to be between 20% and 50% (Heaton et al., 2010; Robertson et al., 2007). According to the most recent diagnostic standards (Antinori et al., 2007), patients with HAND are classified into three sub-groups: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). This classification is based on three parameters: performance during neuropsychological testing, functional impairments, and absence of any other condition explaining the existing symptoms (Saylor et al., 2016). The ANI is asymptomatic and it is defined as a condition of mild impairments in everyday functioning, while the MND is defined by the presence of at least two signs of decline in everyday functioning. Both require the presence of a mild neuropsychological impairment and inability to perform some functions in two or more in a physical domain, not attributable to comorbid conditions such as other infections, drug abuse, or other psychiatric or neurological conditions (Muñoz-Moreno et al., 2014; Saylor et al., 2016). The HAD is defined as an overt neuropsychological impairment of moderate severity that is not readily attributable to comorbid conditions. Screening for HAND among HIV individuals is essential for comprehensive care and effective treatments and the use of neuropsychological tests is widely recommended (European AIDS Clinical Society, 2017; Muñoz-Moreno et al., 2014; Saylor et al., 2016).

In September 2017, according to the report of the Iranian Ministry of Health (MoH), an estimate of 36,571 people was found to be infected with HIV in Iran (IRI-Country-Report, 2006; Mohammadi Firouzeh et al., 2016), of whom 67% were men. Currently, according to the WHO guideline and recommendations (WHO, 2019), ART should be initiated in Iran for all newly-diagnosed HIV patients, while before September 2016, ART was initiated when the patient's CD4 counts dropped to less than 500 cells/µl (IRI-Country-Report, 2006). Major epidemiological and public health aspects of HAND in Iran are unknown. In this regard, this study evaluated the clinical and socio-demographical factors associated with the neuropsychological performance of HIV-positive individuals and attempted to find the prevalence rates of HAND in Teheran, Iran.

Method

Participants

In the period between December 2016 and May 2017, 93 HIV-positive individuals who visited the Voluntary Counseling and Testing (VCT) center at Imam Khomeini Hospital, Tehran, were enrolled in this study. Inclusion criteria were age range 18–60 years and a confirmed HIV infection. Exclusion criteria were other infections of the brain over the past three years, any other opportunistic infection over the past 12 months, drug abuse, an abnormal level of vitamin B12, and thyroid gland dysfunctions, depression or bipolar disorders, and pregnancy. A total of 336 healthy individuals working at the university in Tehran participated as control subjects. The control group consisted of healthy people, 186 men and 150 women, aged between 20 to 55 years.

The main demographic variables registered were age, gender, and education. The clinical variables were HIV transmission routes, length of HIV infection, current CD4 T-cell count, nadir CD4 T-cell count (the person's lowest CD4 count), plasma viral load, past highest viral load, history of ART use, history of drugs/medications use, and comorbidities.

Neurocognitive Testing

HAND diagnosis was based on the Frascati neuropsychological criteria (Antinori et al., 2007) and using some neuropsychological test batteries. Neuropsychological batteries have been recommended for the assessment of neurocognitive disorders in HIV-positive individuals and it was suggested to include the following tests (European AIDS Clinical Society, 2017; Janssen, Bosch, Koopmans, & Kessels, 2015): Wisconsin Card Sorting Test – WCST (Grant, Sacktor, & McArthur, 2005; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), N–back test (Kundu, Sutterer, Emrich, & Postle, 2013; Salminen, Strobach, & Schubert, 2012); Go/No Go task (Redick, Calvo, Gay, & Engle, 2011), the part A of the Trail Making Test – TMT–A (Reitan & Wolfson, 1985); International HIV Dementia Scale (IHDS; Sacktor et al., 2005), and the Montreal Cognitive Test (MOCA; Simioni et al., 2010). The neuropsychological battery used in our study had already been standardized and validated in an Iranian population (Nejati, 2013). The MOCA and IHDS were used as suggested by an international consensus for HAND (Sanmarti et al., 2014). It should be noted that the HIV-positive group completed all six tests while the control group took four tests including WCST, N–back, Go/No Go task and the TMT–A, due to a limited access to the control group at the time of introduction of two newly developed NP tests.

Identification of Cognitive Complaints and Screening of Depression

Cognitive complaints were identified through a self-reported, multi-domain Cognitive Abilities Questionnaire, which has 30 questions for evaluating seven cognitive abilities: memory, selective attention, decision making, planning, sustaining attention, social cognition, and flexibility (Nejati, 2013). Responses to each question were scored on a five-point Likert scale ranging from *almost never, seldom, sometimes, often, and always* corresponding to scores 1–5. The total score was a sum of all answered scores and scires abive 70 were taken to indicate cognitive difficulties. For depression screening, the Beck Depression Inventory type II (BDI–II; (Beck, 1987), the Persian version (Ghassemzadeh, Mojtabai, Karamghadiri, & Ebrahimkhani, 2005) was used with suggested cut-off scores: 0–9 as *mild*, 10–15 as *moderate*, and > 16 as *severe* depressive symptoms (Kendall, Hollon, Beck, Hammen, & Ingram, 1987).

Ethical Considerations

The study was approved by the Ethical Committee of Tehran University of Medical Sciences. A written informed consent was obtained from all participants.

Statistical Analysis

Data were presented with means and standard deviations for quantitative, while frequency (percentage) for categorical variables. T-test was used to compare mean cognitive test scores of the two groups. Simple correlation and regression analyses were used to assess the relationship between demographical data and neurocognitive variables. Logistic regression analyses of all the statistically significant variables (gender, age, history of HIV, HCV co-infection), and variables of clinical interest (current CD4 cell count, nadir CD4 cell count, and HIV RNA) were performed in order to identify prospective predictors of HAND.

Results

Data were available for the analyses from 93 HIV-positive participants; 60.2% men, mean age 36.65 years (range 18–60, *SD* = 8.86). The median current CD4 count was 560 cells/μL (range = 50–1195) and median nadir CD4 count was 152.5 cells/μL (range: 8–900). Modes of HIV acquisition were sexual intercourse in 57 patients (61.3%), intravenous drug use in 26 (27.9%), mother-to-child transmission (MTCT) in 2 (2.2%) and other modes such as getting a tattoo or blood transfusion in 8 (8.6%). Sixty-eight (73.1%) of these patients had up to 12 years of education (*mean* = 10.74, *SD* = 4.17). The remaining demographic, clinical and neurocognitive characteristics are described in Table 1.

Table 1
Distribution of demographic and clinical features among control participants and HIV patients admitted in the VCT center, Tehran, Iran (2016–2017)

	HIV subjects *n* (%)	Control *n* (%)
Gender		
Men	56 (60.2)	186 (55.35)
Women	35 (37.6)	150 (44.65)
Transgender	2 (2.15)	-
Education		
< 12 years	68 (73.1)	125(37.2)
≥ 12 years	25 (26.9)	211(62.8)
Time since HIV diagnosis		
≤ 5 years	38 (41)	NA[a]
> 5 years	55 (59)	NA[a]
ART interruption patients	7 (7.5)	NA[a]
Co-infected with HCV	15 (16.1)	NA[a]
Standardized depression score*		
BDI–II (0–9)	13 (14)	-
BDI–II (10–15)	49 (52.7)	-
BDI–II (> 16)	31 (33.3)	-
Cognitive complaints (score ≥ 70)[b]		
≥ 70	30 (32.3)	268 (79.7)
< 70	63(67.7)	68 (20.3)
HAND positive	47(50.5)	NA[a]
Cognitive complaints with HAND	71(76.3)	NA[a]
HAND positive (Overlap)	47 (50.5)	NA[a]
HAND negative	24 (25.8)	NA[a]
Total	93 (100)	336 (100)

* The BDI test was not performed for control group.
[a] Not applicable.
[b] The difference was statistically significant between groups ($p < .05$).

Table 2
The mean time of ART, CD4 count, and cognitive complains scores

Variables	*Mean* (*SD*)
Time on current ART regimen (months)	50.96 (56.28)
CD4 T cell count (cells/ml)	536.47 (254.24)
Nadir CD4 T cell count (cells/ml)	231.03 (217.35)
Cognitive Abilities Questionnaire score (patient group)	79.80 (18.85)*
Cognitive Abilities Questionnaire score (control group)	65.79 (14.50)*

* The difference was statistically significant between groups ($p < .05$).

HAND Presence

The results concerning neuropsychological tests in HIV-positive individuals and in the control group are shown in Table 1. HANDs were present in 47 (50.53%) subjects; in particular, ANI was found in 22 (23.65%), whereas 17 (18.27%) and 8 (8.6%) subjects were diagnosed with MND and HAD, respectively.

Presence of Cognitive Complaints and Depression

Based on results of cognitive abilities questionnaire, cognitive complaints (score < 70 in cognitive ability test) were observed in 63 (67.7%) and 68 (20.3%) of HIV patients and control groups, respectively. The mean score of cognitive complains in the group of HIV-positive participants was 79.80 (*SD* = 18.85). This was significantly higher than the mean score of the control group of 65.79 (*SD* = 14.50). Overall, 47% of patients with cognitive complaints reached the threshold for HAND, whereas 24 (%) patients reported cognitive complaints, while their HAND results were normal.

The mean BDI score for HIV-positive participants was 17 (*SD* = 9.48). Applying the cut-off scores, 13 (14%) participants obtained scores in the range considered to indicate that they are not depressed (0–9), 31 (33.3%) in the range indicating that participants are dysphoric (10–15) and 49 (52.7%) in the range indicating that participants are depressed (≥ 16). The BDI was not administered to the control group in this study.

Predictors of HAND

Logistic regression analysis was performed in order to explore the association between clinical variables and HAND (Table 4). Patients with less than 12 years of education had a 3.3–fold greater rate of HAND than those with higher education degrees (Odds Ratio (*OR*) = .3; 95% CI [0.1–0.9]; $p = .034$). Low Nadir CD4 count (< 200) was 2.5 times more frequent than nadir CD4 cell counts > 200 (*OR* = .4; 95% CI [0.19–0.8]; $p = .047$), while a history of more than 5 years of HIV infection (*OR* = 3.1; 95% CI [1.3–7.4]; $p = .01$) was independently shown to be associated with HAND. In addition, after performing a complementary analysis in order to explore the association between a high BDI score and a low one to have HAND symptoms, we found an association (*OR* = 2.3; 95% CI [1.1–5.3]; $p = .045$) that was 2.3 times greater than a low BDI score (under score of 16). On the other hand, other variables such as HCV co-infection, gender, current CD4 cell count, and viral suppression did not show a statistically significant association with the occurrence of HAND.

Table 3
Neuropsychological testing results

	HIV subjects	Controls	
Tests	(*n* = 93)	(*n* = 336)	
	Mean (*SE*)	*Mean* (*SE*)	*p* value
WCST			
Preservation errors	18.67 (.84)	19.28 (.42)	.501
Cluster completed	2.90 (.10)	3.02 (.06)	.331
N–back			
Correct answers	20.67 (.58)	23.77 (.24)	.001*
Go/No Go task			
True numbers	21.69 (.37)	21.66 (.21)	.94
TMT–A			
Deficient number of seconds >78	60.73 (22)	50 (13.63)	.01*
MoCA			
Range	12–29	-	-
Mean cut off	22.76 (4.79)	-	-
IHDS			
Range	4–12	-	-
Mean cut off	8.72 (1.68)	-	-

* Statistically significant ($p < .05$).

Table 4
Results of the logistic regression analysis

	Negative	Positive	*B* (*SE*)	Wald	*OR* [95% CI]	*p* value
Gender						
Male	29	28			1	
Female	16	19	.2 (.4)	0.23	1.2[.5–2.9]	.631
Education						
≤ 12 years	29	39			1	
> 12 years	17	8	-1.1 (.5)	4.5	.3[.1–0.9]	.034**
Age						
≤ 40 years	36	32			1	
> 40 years	10	15	.5 (.4)	1.21	1.7[.7–4.3]	.271
Duration of HIV-infection						
≤ 5 years	25	13			1	
> 5 years	21	34	1.1 (.4)	6.65	3.1[1.3–7.4]	.010**
HCV co-infection						
No	36	37			1	
Yes	6	9	.4 (.6)	0.43	1.5[.5–4.5]	.512
Nadir CD4 cell count						
≤ 200	19	29			1	
> 200	27	18	-.8 (.4)	3.82	0.4[.19–0.8]	.047**

	Negative	Positive	*B* (*SE*)	Wald	*OR* [95% CI]	*p* value
Current CD4 cell count						
≤ 200	3	7			1	
> 200	33	33	-.8 (.7)	1.34	.4[.1–1.8]	.247
Transmission mode						
IDUs	11	16			1	
Sexual contact	32	24	-.7 (.5)	1.94	.5[.2–1.3]	.164
other	3	7	.5 (.8)	0.36	1.6[.3–7.5]	.551
BDI–II score						
Severe (> 16)	28	19			1	.045**
Viral load						
Undetectable	37	31			1	
Detected	4	10	1.1 (.6)	2.92	2.9[.85–10.45]	.087

**significantly associated.

Discussion

In the present study, the prevalence of HAND was 50.5%. This is in line with studies of other populations such as those in Germany (43%; Marin, Jessen, Kopp, Jessen, & Hahn, 2016); Spain (59%; Muñoz-Moreno et al., 2014); Ireland (51.5%; McNamara, Coen, Redmond, Doherty, & Bergin, 2016), and Italy (47%; Focà et al., 2016). However, our result showed a higher percentage than those observed in China (38%; Zhang et al., 2012) and India 33%; (Saini & Barar, 2014), but lower than those in Switzerland (84%; Simioni et al., 2010) and Cameron (85%; Atashili et al., 2013). Possible explanations for these fluctuations in the prevalence rates across different regions could be due to the differences in clinical variables such as nadir and current CD4 count, RNA viral loads and comorbidity factors or differences in general factors including age and educational level can influence the prevalence rate. Since normative standards applicable to specific linguistic, cultural and social groups can lead to variable diagnoses in HAND (Livelli et al., 2015; Zhang et al., 2012).

In our study, two thirds of people living with HIV complained about cognitive impairments, while only every fifth among healthy adults. In a study among HIV subjects with undetectable HIV RNA viral loads, there were 27% cognitive complains, even in patients with no HAND presentation, based on the evaluation of three main questions about memory, planning and attention (Simioni et al., 2010). In the present study, given the observation that about 75 percent of HIV positive individuals complained about cognitive impairments, it could be inferred that high incidence of cognitive complaints might be present at some (especially advanced) stages of neurological decline due to the infection.

Among the HAND group, ANI was diagnosed in 23.7%, whereas 18.3% of patients had MND and 8.6% met the criteria for HAD. Thus, the prevalence of ANI and MND was greater than the prevalence of HAD and these observations

were in agreement with the results from several previous studies reporting a higher prevalence of ANI compared to MND (Saini & Barar, 2014; Simioni et al., 2010). Moreover, the prevalence of HAD in all studied groups was less than 10% compared to other neurocognitive groups of ANI and MND (Sanmarti et al., 2014). Therefore, the worsening neurocognitive symptoms could be missed and the physician might not bring it to the attention of the patient (Sanmarti et al., 2014). Accordingly, the updated HAND algorithm effectively discriminates between patients at different levels of impairment, indicating adequate diagnostic utility. In our study, HIV patients performed worse than normal population on cognitive functioning tests including WCST, N–back, TMT–A and Go/No Go task. in previous studies, the MOCA and IHDS had shown a moderate to strong correlation with individual neuropsychological tests (Janssen et al., 2015; Sanmarti et al., 2014). As indicated in our results, among several risk factors associated with the occurrence of HAND, patients with low nadir CD4 count and low degree of education were more likely to have HAND. The probability of having HANDs among patients with high BDI scores was about two times higher than among patients with a low BDI score. We didn't find any significant association between HAND and age of patients,and this might be due to the limited number of patients over 50 in our sample. One study found that, in HIV-positive individuals over 50, the risk of developing a cognitive disorder increased three-fold compared to HIV-negative controls (Becker, Lopez, Dew, & Aizenstein, 2004).

According to available data and opinions, irreversible CNS damages would underlie HIV related neurocognitive impairment, and this would explain the persistence of the current neurologic disruption (De Ronchi et al., 2002; Fogel et al., 2015; Letendre et al., 2004; Muñoz-Moreno et al., 2008; Saylor et al., 2016). Viral loads in plasma and HCV co-infection were not associated with HAND in our study. In other studies, detectable levels of HIV in cerebrospinal fluid (CSF) had been observed, in spite of the presence of ART (Brew, 2004; Cysique et al., 2005). The question remains as to whether CNS inflammation that possibly contributes to HAND is sustained even when the initial stimulus derived from viral replication is suppressed by ART (Brew, 2004; Saylor et al., 2016). According to one hypothesis, the inflammatory responses initiated by HIV infection lead to cellular homeostasis and response to stress (Letendre et al., 2004; Peluso et al., 2013), resulting in an accumulation of a kind of proteasome or immune-proteasome that impedes the turnover of folded proteins in brain cells (Ferrington & Gregerson, 2012).

The present study has some limitations, which should be considered in future studies. First, the lack of follow-up data does not allow us to perform a longitudinal evaluation of the neurocognitive disorders and to investigate the effect of ART. Second, due to the observational nature of this study, we had a very heterogeneous population in terms of drug regimen, educational level, history of HIV infection and comorbidities. Third, the sample included individuals from only one part of Iran, with convenient sampling, and the results may not be generalizable to other parts. Finally, it was not possible to obtain neuroimaging data to validate our neuropsychological findings.

Conclusions

This is the first study using the standard criteria of HAND diagnosis to support a similarly high prevalence of HANDs in Iran and provides an indication for the correlation of HIV infection and neurocognitive impairment. Further studies should include monitoring with standard methods for biomarkers employed and specific neurocognitive domains among HIV individuals with HAND. We also recommend screening for HANDs in all HIV patients at early stages using neuropsychological tools.

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Prevalenca neurokognitivnog poremećaja povezanog sa HIV-om (HAND) i njegovih podgrupa kod HIV pozitivnih osoba na antiretroviralnoj terapiji u Iranu

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Cilj ove studije je da odredi prevalencu i determinante neurokognitivnog poremećaja povezanog sa HIV-om (HAND) i njegovih podgrupa kod HIV pozitivnih osoba u Teheranu, Iran. Devedeset tri HIV pozitivnih osoba je učestvovalo u istraživanju. Većina su bili muškarci (60%). Prosečna starost uzorka je bila 36.5 godina (*SD* = 9), dok je srednja dužina inficiranosti HIV-om bila osam godina. Povezanost demografskih i kliničkih varijabli je ispitivana korišćenjem logističke regresije. Ukupna prevalenca neurokognitivnog poremećaja povezanog sa HIV-om i žalbi na probleme u kognitivnom funkcionisanju bila je 50.5%, odnosno 73%. Niži broj CD4 limfocita u nadiru (≤ 200), niži nivo obrazovanja (≤ 12 godina), duže trajanje bolesti (≥ 5 godina) i viši nivo depresivnosti su bili pozitivno povezani sa prisustvom neurokognitivnog poremećaja. Rezultati ove studije ukazuju na visoku prevalencu neurokognitivnog poremećaja kod osoba zaraženih HIV-om u Iranu, ali se ona ne razlikuje u odnosu na onu u zapadnim društvima. Dodatne studije su potrebne da bi se longitudinalno procenilo prisustvo neurokognitivnog poremećaja kod osoba zaraženih HIV-om, posebno da bi se prepoznali novi biomarkeri i specifični neurokognitivni domeni koji su zahvaćeni kod HIV pozitivnih osoba.

Ključne reči: Humani virus imunodeficijencije (HIV), žalbe na probleme u neurokognitivnom funkcionisanju, depresija

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