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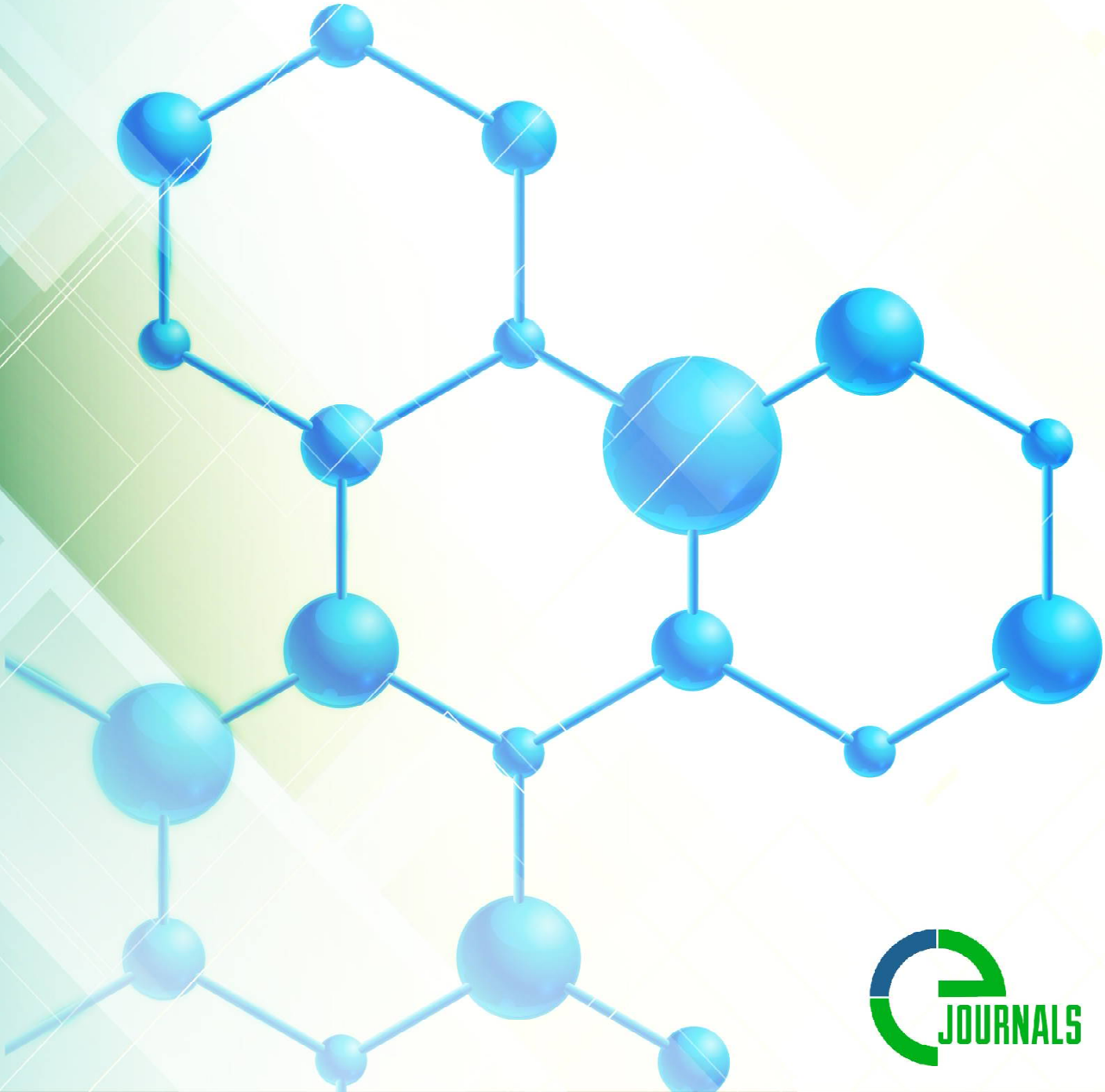
# MOLECULAR MEDICINE



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# DIAGNOSTICS OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND) BY USING PAPER TYPE SCREENING TOOLS

**Sokhiba K. Utegenova,**
**Allabergan K. Bayjanov**
Research Institute of Virology of the Republican Specialized Scientific Medical Center for Epidemiology, Microbiology, Infectious and Parasitic Diseases of the Republic of Uzbekistan
dr.utegenova@gmail.com
drbayjanov@mail.ru



## Introduction

The development of modern medical science and the widespread use of highly active antiretroviral therapy (HAART) at the current stage of HIV treatment has reduced the number of severe organic lesions of the central nervous system but brought neurocognitive disorders to the fore. The first mentions of neurocognitive deficits were published 25 years ago. Since then, a huge amount of research has been done on the pathogenesis, clinical picture, and diagnostic methods of HIV-associated neurocognitive disorders (HAND). Such a high interest in HAND is due to the social and medical significance of cognitive impairments, which are frequent and sometimes the only signs of organic brain pathology [1].

Risk factors (albeit nonspecific) for the occurrence of VANP are immunosuppression [2] and the presence of comorbidities, including co-infection with hepatitis C [3] and substance abuse disorders. Moreover, HAND tends to make its debut in the initial stages of HIV infection or against the background of combination antiretroviral therapy (HAART) - during the period of immunological and virological well-being [4].

The most used classification of HIV-associated neurocognitive disorders was proposed in 2007 and includes 3 categories: asymptomatic HAND (ANI) - insignificantly affect daily life and difficulties arise only when performing complex professional activities; light HAND (MND) - significantly disrupt professional activities, partly household and social activities; severe HAND - HIV-associated dementia (HAD) - a disabling form, a person needs outside care [5,6]. The diagnosis of neurocognitive disorders includes a set of studies depending on each specific case [7]: neurological examination and neuropsychological testing; examination to detect opportunistic infections, especially if the patient has a low CD4 cell count, in the absence of HAART; CD4 lymphocyte counts, HIV RNA, neuroimaging methods, lumbar puncture, CSF examination, etc.

The urgency of the problem and the lack of specific methods for detecting HAND in the early stages has led to the need to create special HIV-specific screening tools for neurocognitive disorders based on the results of numerous clinical studies.

Performing all diagnostic tests to detect neurocognitive impairment in HIV-infected patients often requires enormous resources and time. Especially the above makes sense when diagnosing mild or asymptomatic HAND variants.

In Uzbekistan, given the social significance of HIV infection, all patients receive free anonymous diagnostics, treatment, and prevention of complications of this disease. In these conditions, the early detection of neurocognitive impairment and their prevention is included as the important goal. In this regard, our group decided to compare the diagnostic effectiveness of tools such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment Test (MOCA) and the International HIV Dementia

Scale (IHDS).

**Materials and methods**

The study was conducted between May 2018 and May 2019 in the clinic of Scientific research institute of Virology, Tashkent, Uzbekistan. A total of 68 HIV-infected patients were recruited for the main group from the HIV department of above-mentioned clinic. All those patients had the different stages of HAND: asymptomatic neurocognitive impairment (ANI) - 19 patients, HIV-associated mild neurocognitive disorder (MND) - 18 patients and HIV-associated dementia (HAD) - 31 patients. The eligibility criteria included HIV infection III and IV clinical stages, age above 18 years old. The same criteria were used for the control group, which included 35 HIV patients without HAND.Patients who decided not to participate, were excluded from the study.All study participants provided written informed consent and the study was approved by the Ethical Committee of Scientific research institute of Virology.

Basic demographic data such as age, gender, race, bad habits as well as comorbidities were collected from all participants.All participants and control group members were required to complete MMSE, MOCA, IHDS cognitive tests. Cognitive impairment was defined based on 2007 Frascati criteria [Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69:1789-99.].

The collected data was entered and analyzed by using IBM SPSS 26.0 (Chicago, IL, USA). The level of statistical significance was set at 0.05 for all tests. To determine the best of the three tests, we performed binary logistic regression analyses with absence of cognitive impairment as the dependent variable and the cognitive tests as independent variables. Based on predicted probabilities of a logistic regression model, each test produced a propensity score. Sensitivity was plotted against specificity across varying cut-offs, generating a Receiver Operating Curve (ROC). Accordingly, each score corresponded to an ROC curve that illustrates the sensitivity and specificity of the combination for detecting cognitive impairment. The area under the curve (AUC), an index of effect size, was the primary result of the ROC analysis, and AUC summarizes the entire location of the ROC curve rather than depending on a specific operating point .

In short, AUC indicates the combined measurement of sensitivity and specificity of the relevant test. An area of 1.0 represents a perfect test and an area of 0.5 denotes an unfeasible test (95% confidence intervals [95% CI]).

**Results**

| | Control group | ANI | MND | HAD |
|---|---|---|---|---|
| | ♀/♂ | ♀/♂ | ♀/♂ | ♀/♂ |
| **Sex** | 15/20 | 7/12 | 6/12 | 19/12 |
| | **Single/ married** | **Single/ married** | **Single/ Married** | **Single/ married** |
| **Marital status** | 9/26 | 13/6** | 12/6** | 11/20 |
| | III / IV | III / IV | III / IV | III / IV |
| **HIV clinical stage** | 16/19 | 5/14 | 9/9 | 22/9 |
| | No/Yes | No/Yes | No/Yes | No/Yes |
| **Employment** | 28/7 | 17/2 | 14/4 | 22/9 |
| **PWID** | 26/9 | 14/5 | 14/4 | 26/5 |
| **More than 30 ml alcohol/day** | 26/9 | 16/3 | 12/6 | 21/10 |
| **Sleep disorders** | 31/4 | 3/16** | 0/18** | 2/29** |
| **Stress** | 28/7 | 13/6 | 14/4 | 20/11 |
| **Chronic diarrhea** | 20/15 | 9/10 | 3/15** | 18/13 |
| **Fever** | 16/19 | 9/10 | 3/15* | 24/7** |
| **Recurrent infection** | 18/17 | 14/5 | 3/15* | 20/11 |
| **Lymphadenopathy** | 27/8 | 12/7 | 11/7 | 26/5 |
| **Oropharyngeal candidiasis (OC)** | 23/12 | 8/11 | 8/10 | 9/22** |
| **Recurrent aphthous stomatitis (RAS)** | 31/4 | 12/7* | 14/4 | 6/25** |
| | 31/4 | 13/6 | 15/3 | 4/27 |
| **Angular cheilitis (AC)** | 31/4 | 16/3 | 17/1 | 22/9 |
| **Kaposi's sarcoma (KS)** | 33/2 | 15/4 | 17/1 | 12/19** |
| **Weight loss more than 10 %** | 26/9 | 10/9 | 6/12** | 28/3 |
| **Lung tuberculosis** | 31/4 | 17/2 | 16/2 | 28/3 |
| **Chronic hepatitis C (CHC)** | 24/11 | 16/3 | 11/7 | 30/1** |
| **Chronic hepatitis B (CHB)** | 33/2 | 18/1 | 16/2 | 17/14** |
| **MMSE** | 29 (28;30) | 26 (20;27) | 18 (15;20.25) | 15 (9;18) |
| **MOCA** | 29 (28;29) | 24 (17;24) | 15 (13.75;17.25) | 18 (17;19) |
| **IHDS** | 12 (11;12) | 9 (7;12) | 7 (6;8) | 6 (5;8) |

***p (significant difference between control group) < 0.05**
**** p (significant difference between control group) < 0.01**

Figure 1.Roc-curves for test in ANI patients

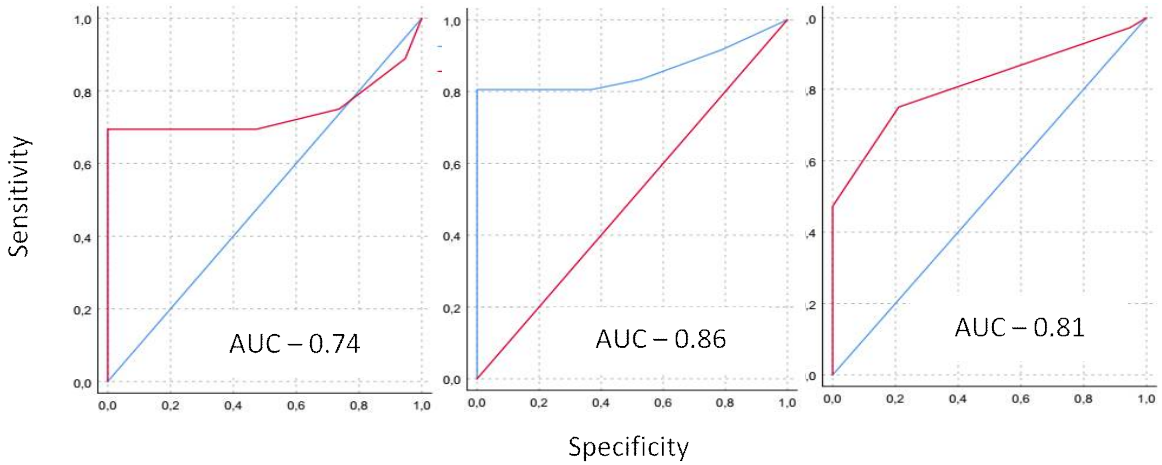


Figure 2.Roc-curves for test in MND patients

MMSE 95% CI (0.6-0.87) MOCA (0.68-0.93) IHDS (0.69-0.92)

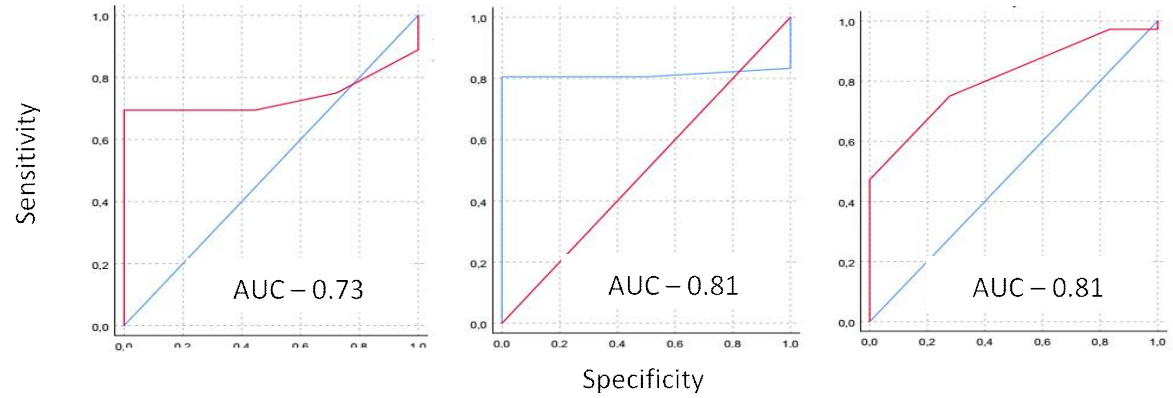


Figure 3.Roc-curves for test in HAD patients

MMSE 95% CI (0.89-0.99) MOCA (0.92-0.99) IHDS (0.87-0.99)

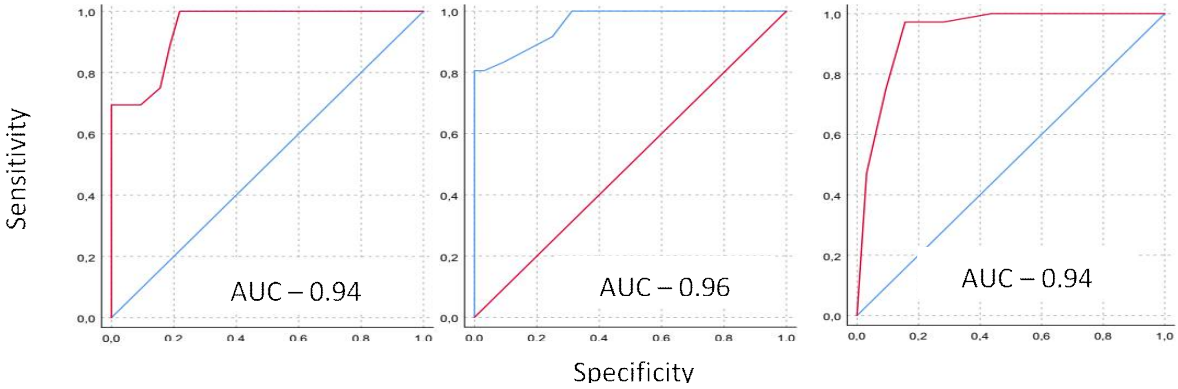


Table 1 provides an overview of the characteristics of the main and control groups of HIV-infected patients recruited to the study. Also, the table reflects social status, bad habits, clinical parameters as the stage of HIV infection and comorbid background. Interesting were the results of comparing the family status in patients with asymptomatic and mild neurocognitive impairment with a predominance of singles among these groups,

while the group with dementia did not differ from the control group. Our study also found a significantly higher incidence of sleep disturbances, even in patients with asymptomatic neurocognitive impairments. A higher incidence of co-infection was expected in persons with dementia, while fever was more common in those in the control group. The group with dementia suffered most from Kaposi's sarcoma.

To assess the degree of CNS damage, three types of tests were used: MMSE, MOCA, IHDS. The MMSE test showed good efficacy in patients with dementia (AUC - 0.94), while the MOCA test showed asymptomatic, along with mild and severe dementia. The IHDS test showed good results in all groups, behind the MOCA.

**Discussion**

This research was primarily aimed at assessing the possibility of using specially designed, concise, and convenient test systems for detecting HAND. Early detection of neurocognitive impairment will provide tremendous opportunities for the physician to potentially reverse the progression of HAND by initiating the appropriate therapy, and for the patient to improve the quality of life. The use of tests for HIV-infected patients to assess neurocognitive impairment is an infrequent occurrence in our healthcare system, which adds value to our study.

Our study had several limitations in the form of small sample size, lack of randomization, cross-sectional design, and limitation of conducting the study in one center.

Currently mini mental state examination is the most widely used first-line test for mild to severe HIV dementia. It is known that MMSE is not the best for detecting early dementia, limiting its use especially in the elderly [8-10].

We suppose that the MoCA's better results are conditioned by more words, less learning trials, and a longer delay before recall than the MMSE. Executive functions, complex language abilities, and visuospatial processing can make some more difficulties for neurocognitive impaired participants and are assessed by the MoCA with more numerous and demanding tasks than the MMSE. When evaluating the test scorers, we noticed adiscrepancy in the MMSE, MoCA and IHDS scores for the same participants. Most participants with asymptomatic and mild neurocognitive changes scored nearly the same score, while the MoCA identified asymptomatic patients, where the results of the other two tests showed scores corresponding to the normal ranges. Along with this, MoCA had a higher sensitivity in relation to those neurocognitive disorders in which the physical manifestations of these disorders were absent.

The IHDS is a screening tool specifically designed to detect HIV-associated dementia. The tool was excellent for identifying clinically manifest forms of neurocognitive impairment. Our results demonstrate that the IHDS poorly detects mild neurocognitive impairments as well as de Almeida, although it must be admitted that the test is easy to use and requires minimal time and material costs [11].

Finally, we found that the overall MMSE and IHDS scores are highly dependent on the length of study. This highlights the need to take education years into account when interpreting abovementioned scores, as failure to do so is likely to seriously affect the accuracy of last indicators.

Thus, current trends require the development and application of new or effective methods for detecting cognitive impairment in HIV-infected patients. Over time, the rapid and accurate diagnosis of cognitive impairment will become an increasingly important topic for clinicians. MoCA is one of the simplest tools for the early detection of cognitive impairment with superior sensitivity. The test touches important cognitive areas, detecting minimal changes, and can be done in 10 minutes on a single sheet of paper. These advantages make this test a priority level when there are limitations to the

use of other clinical methods. At the same time, we also made sure that the use of a complex of several tests significantly increased the diagnosis of neurocognitive disorders.

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