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NEU Screen Shows High Accuracy in Detecting Cognitive Impairment in Older Persons Living With HIV

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Abstract

The NEUrocognitive (NEU) Screen is a practical tool proposed to screen for HIV-associated cognitive impairment in the clinical setting. This is a pencil-and-paper method that can be applied rapidly (≤10 minutes for administration) and has no copyright limitations. In this study, we aimed at investigating its diagnostic accuracy in an older population of persons living with HIV (PLWH), with cutoffs set at 30, 40, 50, and 60 years. Data were collected from a sample of 368 PLWH who underwent a comprehensive neuropsychological tests battery (*gold standard*). Results of statistical tests showed that accuracy of the NEU Screen increased with age of the participants. The highest degree of precision, with a sensitivity of 91% and specificity of 92%, was obtained for people aged 60 years or older (correct classification: 91%). These optimal results point to the great potential of the NEU Screen as a tool for detecting cognitive disorders in older PLWH.

Key words: aging, cognitive impairment, HIV infection, older population, screening

The cerebral manifestations of HIV infection remain an issue of concern in the everyday practice of HIV medicine. Despite current widespread access to combination antiretroviral therapy, a large percentage of chronically infected persons living with HIV (PLWH) exhibit HIV-associated neurocognitive disorders (HAND; Eggers et al., 2017). HIV-associated neurocognitive disorders are linked to a poorer quality of life, worse daily functioning, higher rates of unemployment, greater use of health system resources, and diminished adherence to combination antiretroviral therapy (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009). As a result, the detection, prevention, and treatment of HAND have become research priorities in the field of HIV.

To date, several different methods to screen for cognitive impairment in PLWH have been proposed (Kamminga, Cysique, Lu, Batchelor, & Brew, 2013; Zipursky et al., 2013). One of the most widely used is the HIV Dementia Scale (Power, Selnes, Grim, & McArthur, 1995) and its derivative form, the International HIV Dementia Scale (Sacktor et al., 2005). However, several studies have shown that although both instruments are useful for detecting HIV-related dementia, they are less sensitive for milder HAND (Bottiggi et al., 2007; Valcour, Paul, Chiao, Wendelken, & Miller, 2011). Other studies have assessed the accuracy of the Montreal Cognitive Assessment instrument (Nasreddine et al., 2005), an easily accessible exploratory tool, in detecting cognitive impairment associated with HIV. However, although different cutoff points for the detection of cognitive disruption by this tool have been proposed, none of them yield rates for both sensitivity and specificity greater than 70% (Fazeli et al., 2017; Hasbun et al., 2012; Janssen, Bosch, Koopmans, & Kessels, 2015; Kim et al., 2016; Milanini et al., 2016, 2014; Overton et al., 2013). Finally, the Brief Neurocognitive Screen (Ellis

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Preliminary results of the work have been presented in the 14th International Symposium on Neurovirology, October 25–28, 2016, Toronto, Ontario, Canada (Abstract P114).

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et al., 2005), which includes the Trail Making Test (TMT) Parts A and B (Reitan & Davidson, 1974) and the Wechsler Adult Intelligence Scale (WAIS) III Digit Symbol test (Wechsler, 1999), has been shown to achieve a sensitivity of 65% and specificity of 72%. Nonetheless, none of these tools appears to have gained widespread acceptance in routine clinical practice. There are various possible reasons for this, among them, the time required for their administration, the lack of clinical studies as opposed to merely research-based studies, and, above all, the inadequate levels of diagnostic accuracy that most of them have revealed (Valcour, 2011).

The NEUrocognitive (NEU) Screen is a method that was developed to detect cognitive impairment in PLWH in day-to-day clinical practice (Muñoz-Moreno et al., 2013). For its development, we analyzed which combinations of neuropsychological tests were most sensitive and specific in the detection of cognitive disorders in a sample of 114 people with HIV from different treatment centers in Catalonia, Spain. The combinations were decided upon taking into account that their administration time had to be short (<10 minutes) and simple (without needing anything other than paper and pencil). The combination with the best sensitivity and specificity (74% and 81%, respectively) made up the NEU Screen.

Given that the population of PLWH is steadily aging, there is a growing need to be able to obtain information quickly and easily about not only the physical, but also the mental status of older adults living with HIV. However, at present, there is a significant lack of information about tools that can screen for cognitive impairment in this population. To help fill that gap, in this study, we investigated the accuracy of the NEU Screen for an older HIV population at different stages of aging.

Methods

Study Population and Design

We used clinical information from a voluntary sample of 368 PLWH receiving outpatient services at seven hospitals in Barcelona, Catalonia, Spain. Demographic, medical, and neurocognitive data were available for all participants. They were all at least 18 years of age, had confirmed HIV infection, and had undergone a comprehensive neuropsychological assessment. As the measures that make up the NEU Screen had been included in the comprehensive evaluation, we were able to use the data thus obtained to perform the present investigation. The work was conducted in compliance with the Helsinki Declaration of 1964 (1996 revision) and Good Clinical Practice guidelines, and all participants provided written informed consent. The information collected for data analyses was obtained from January 2004 to December 2015.

Measures

The measures included in the comprehensive battery of neuropsychological tests covered seven domains, comprising a total of 15 scores. The specific tests used were as follows: the Letter-Numbers and Digits tests of the WAIS III (Wechsler, 1999) for attention/working memory; the TMT Part A (Reitan & Davidson, 1974) and the Symbol Digit Modalities Test (Smith, 2002) for information processing speed; the California Verbal Learning Test–Part II (Delis, Kramer, Kaplan, & Ober, 2000) for verbal memory and learning; the TMT Part B (Reitan & Davidson, 1974), the Stroop Test (Golden, 2001), the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and the Tower of London test (Culbertson & Zillmer, 2001) for executive functions; the Controlled Oral Word Association Test (Benton, Hamsher, & Sivan, 1994) and the Animals Test (Kertesz, 1982) for verbal fluency; and the Grooved Pegboard Test (Reitan & Wolfson, 1985) for motor function. Of these, three (the TMT Parts A and B and the Controlled Oral Word Association Test) comprised the NEU Screen, which consequently covered three domains: attention/working memory, executive functions, and verbal fluency. Table 1 shows the characteristics of the NEU Screen (available at www.flsida.org/NEU). In both methods, scores were adjusted for age, gender, and educational level, according to the available local normative data. [T1]

Cognitive impairment was defined as performing at least one standard deviation in standardized *t* scores below the normative mean in at least two cognitive domains in the comprehensive neuropsychological battery and at least one standard deviation in standardized *t* scores below the normative mean in at least one cognitive domain in the NEU Screen.

Premorbid intelligence was evaluated by the Vocabulary test of the WAIS III. Depressive symptoms were evaluated by the Beck Depression Inventory II (Beck, Steer, & Brown, 1996). Potentially confounding comorbidities for cognitive impairment were recorded as a clinical variable, based on international consensus in the field, as was their degree of severity (Antinori et al., 2007). Such comorbidities included current or previous ~~CNS~~-related disease, current or previous psychiatric disorder, current use of psychopharmacological medication, use of illicit drugs, coinfection with hepatitis C virus, and non–HIV-related neurologic condition.

central nervous system (CNS)

Table 1. Characteristics of the NEU Screen

Cognitive Domain	Test	Score	Approximate Duration, minutes
Information processing speed	TMT-A	Total time	2
Executive functioning	TMT-B	Total time	3
Verbal fluency	COWAT	Total score	5

Adapted from J.A. Muñoz-Moreno, et al. (2013). A brief and feasible paper-based method to screen for cognitive impairment in HIV-infected patients: the NEU Screen. , JAIDS, 63(5), 589. The NEU Screen is available at www.flsida.org/NEU.
Note. COWAT = Controlled Oral Word Association Test; TMT-A = Trail Making Test-Part A; TMT-B = Trail Making Test-Part B.

Data Analyses

The statistical characteristics of the NEU Screen were compared for different age cutoffs, specifically less than 30 versus at least 30, less than 40 versus at least 40, less than 50 versus at least 50, and less than 60 versus at least 60 years old. Sensitivity, specificity, and negative and positive predictive values (PPV and NPV) were calculated relative to the *gold standard* as obtained by the comprehensive neuropsychological assessment. The percentage of correct classification was also calculated, with 95% confidence intervals offered for all age cutoffs. Variables associated with cognitive impairment were described and descriptive statistics, t tests, and ~~ANOVA~~ tests were used for data analyses. All comparisons were univariate and two-tailed, and statistical significance was set at $p < .05$. All analyses were performed using SPSS Statistics v15 (SPSS Inc., Chicago, IL).

AQ:3 analysis of variance (ANOVA)

Results

Characteristics of the Sample

Participants were mostly men (80%), who had acquired infection via men having sex with men (51%) and had a median (interquartile range) age of 43 (37; 48) years and 11 (9; 15) years of education. Most of them were on antiretroviral treatment (77%) and presented an undetectable plasma viral load (70%) with a median current CD4+ T-cell count of 511 (375; 720) cells/μL and a median nadir CD4+ T-cell count of 223 (101; 360) cells/μL. A total of 18 (5%) individuals presented potentially confounding comorbidities for cognitive impairment. The remaining demographic and clinical characteristics are displayed in Table 2. [T2]

Cognitive impairment was present in 188 (51%) participants, according to the comprehensive neuropsychological battery, and was associated with fewer years of education ($p = .004$), lower nadir CD4+ T-cell count ($p = .003$), lower premorbid intellectual level ($p < .001$), presence of comorbidities for cognitive impairment ($p = .001$), and the severity of those comorbidities ($p = .001$).

Comparison of Age-Based Cutoff Points

Some of the comparisons found demographic and clinical variables to be unequally distributed among groups. The most important factor revealed was the nadir CD4+ T-cell count, which was unbalanced across all the subgroups. The cutoff that showed the greatest difference was 40 years, with people aged 40 or older showing more years since HIV diagnosis ($p < .001$), fewer years of education ($p = .009$), a greater presence of cognitive complaints ($p = .046$), more instances of an undetectable viral load ($p < .001$), and a lower nadir CD4+ T-cell count ($p < .001$). The comparison that indicated least unbalance was the 60-year cutoff, with people aged 60 or older showing lower nadir CD4+ T-cell counts ($p = .031$). Of note, comorbidities were distributed uniformly across all the age subgroups.

With regard to the accuracy of the NEU Screen, sensitivity became higher as age increased, except for the 50-year cutoff. The same effect occurred for specificity, with the exception of the 30-year cutoff. The lowest values detected were in the subgroup of people younger than 30 years (<30 vs. ≥ 30): sensitivity 69.3% versus 75.4%; specificity 65.0% versus 73.7%; PPV 56.2% versus 75.8%; NPV 76.4% versus 73.2%. The greatest accuracy was revealed in the subgroup of people aged 60 or older (<60 vs. ≥ 60): sensitivity 74.0% versus 90.9%; specificity 71.2% versus 92.3%; PPV 73.1% versus 90.9%; NPV 72.1% versus 92.3%. The correct classifications at that cutoff were 72.6% versus 91.6%, respectively. Table 3 shows the results for all the age subgroups. [T3]

Discussion

The goal of the present investigation was to determine the diagnostic accuracy of the NEU Screen for detecting

Table 2. Demographic and Clinical Characteristics of Study Participants

	***N* = 368**
Gender, *n* (%)	
Male	295 (80)
Female	73 (20)
Age, years, median (IQR)	43 (37–49)
Infection route, *n* (%)	
MSM	185 (50)
Heterosexual	72 (20)
Injecting drug user	62 (17)
Other	13 (3)
Unknown	36 (10)
Education, years, median (IQR)	11 (9–15)
Time since HIV diagnosis, years, median (IQR)	10 (3–15)
On ART, *n* (%)	283 (77)
CD4+ T-cell count, cells/μL, median (IQR)	511 (375–720)
Nadir CD4+ T-cell count, cells/μL, median (IQR)	223 (101–360)
Undetectable viral load, *n* (%)[a]	251 (70)
Highest viral load, copies/ml, median (IQR)	86,500 (17,000–226,500)
HCV coinfection, *n* (%)	
Yes	70 (20)
No	263 (73)
Unknown	26 (7)
Premorbid intelligence, mean (SD)[b]	54 (8)
Depressive symptoms, mean (SD)[c]	11 (10)
Self-reported cognitive complaints, *n* (%)	191 (52)
Cognitive impairment, *n* (%)	188 (51)
Comorbidities for cognitive impairment, *n* (%)[d]	145 (39)
Severity of comorbidities, *n* (%)[d]	
None	223 (61)
Contributing	127 (34)
Confounding	18 (5)
HAND, *n* (%)[e]	
Asymptomatic neurocognitive impairment	66 (45)
Mild neurocognitive disorder	80 (54)
HIV-associated dementia	1 (1)

Note. ART = antiretroviral therapy; HAND = HIV-associated neurocognitive disorder; HCV = hepatitis C virus; IQR = interquartile range; MSM = men who had sex with men; SD = standard deviation.
[a] Detection limit of 50 copies/ml.
[b] Assessed by the Wechsler Adult Intelligence Scale III Vocabulary test (Wechsler, 1999). Standardized *t* score: *mean* 50; SD 10.
[c] Assessed by the Beck Depression Inventory II (Beck, Steer, & Brown, 1996). Raw score: range from 0 to 63; ≥17 is a cutoff for major depression in people living with HIV in the United States (Hobkirk et al., 2015).
[d] Based on the Frascati criteria (Antinori et al., 2007).
[e] From those participants with cognitive impairment and without confounding comorbidities.

cognitive impairment in PLWH at different ages. To make our study sample more representative, we included PLWH with diverse clinical conditions. Consequently, a high rate (51%) of cognitive impairment was detected. A considerable percentage of participants in the sample were not receiving antiretroviral treatment (23%), were not virally suppressed (30%), and presented a potential confounding comorbidity for cognitive impairment (5%), all circumstances that could be related to this high frequency of cognitive disruption. Nonetheless, this rate of impairment was similar to that seen in other studies that have included PLWH with comorbidities and diverse clinical conditions (Bonet et al., 2013; Heaton et al., 2010). The variables related to cognitive impairment that we found were mostly the same as those found traditionally in the field: low premorbid intellectual level, few years of education, presence of comorbidities, severity of those comorbidities, and low nadir CD4+ T-cell count (Heaton et al., 2010; Morgan et al., 2012; Muñoz-Moreno et al., 2014; Patel et al., 2013).

The NEU Screen showed the greatest degree of diagnostic accuracy in adults aged 60 years or older with HIV, with a sensitivity score of 91% and a specificity

Table 3. Accuracy of the NEU Screen According to the Different Age Cutoffs

Age Subgroup	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Correct Classification
<30 years (n = 33)	69.3 (38.8–89.6)	65.0 (40.9–83.6)	56.2 (30.5–79.2)	76.4 (49.7–92.1)	66.6
≥30 years (n = 355)	75.4 (68.3–81.4)	73.7 (66.1–80.2)	75.8 (68.6–81,8)	73.2 (65.6–79.8)	74.6
<40 years (n = 129)	70.1 (57.5–80.4)	72.5 (59.5–82.7)	73.4 (60.6–83.3)	69.2 (56.4–79.7)	71.3
≥40 years (n = 239)	77.6 (69.0–84.5)	72.8 (63.7–80.4)	74.6 (65.9–81.7)	76.1 (66.9–83.4)	75.3
<50 years (n = 289)	76.1 (68.3–82.5)	71.8 (63.5–78.8)	73.6 (65.8–80.3)	74.4 (66.1–81.3)	74.0
≥50 years (n = 79)	70.7 (54.2–83.3)	76.3 (59.3–87.9)	76.3 (59.3–87.9)	70.7 (54.2–83.3)	73.4
<60 years (n = 344)	74.0 (66.7–80.1)	71.2 (63.6–77.8)	73.1 (65.9–79.3)	72.1 (64.5–78.6)	72.6
≥60 years (n = 24)	90.9 (57.1–99.5)	92.3 (62.0–99.6)	90.9 (57.1–99.5)	92.3 (62.0–99.6)	91.6

Note. CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value. Values expressed as percentages except when indicated.

score of 92%. These values are remarkable, given that values over 90% for either sensitivity or specificity are truly uncommon among screening tools for HIV-related cognitive impairment. This may be of particular usefulness for health care providers who are caring for older adults living with HIV, as is the case of nurses, because they are in a key position to know which of their care recipients are at risk of developing cognitive impairment.

It is important to note that our stratification into age subgroups for purposes of comparison led to smaller-sized groups, resulting in a diminished statistical power. This was particularly important for the subgroup of people aged 60 years or older (n = 24). Nonetheless, the number of participants outside this group (i.e., younger than 60) was higher as a result (n = 344), and the general trend observed across all cutoffs was mostly clear-cut, detecting greater accuracy with increasing age for the remaining age cutoffs overall. Another effect of the stratification by age cutoffs was the unequal distribution among groups of some clinical variables that have been related to cognitive disorders in PLWH. This may have affected in some way the results observed.

Of previous studies, the Montreal Cognitive Assessment instrument test has been assessed in terms of its accuracy in detecting impairment in people older than 60 years with HIV, with results showing a sensitivity of 72% and specificity of 67% (Milanini et al., 2014). Both values were lower than those claimed for the NEU Screen when it was first described, namely 74% and 81%, respectively (Muñoz-Moreno et al., 2013). And, as we have seen here, when applied specifically to older people with HIV, the NEU Screen yields significantly higher accuracy scores, 91% and 92%, respectively. Nevertheless, these results can only be generalized to similar populations. In this regard, our study sample considered variable clinical conditions, comprising in particular people on and off treatment, as well as people with potential confounding comorbidities. Although we have attempted to take into account these and other potentially relevant variables in our data analyses, they may have had an impact on our results that we did not control for.

Conclusion

This is one of the first studies investigating the properties of a screening method for cognitive impairment in an aging HIV population. Some fairly optimal characteristics are revealed, suggesting that the NEU Screen can be of great utility in the clinical context as a screening tool for detecting cognitive dysfunction in HIV populations. Nurses and other qualified professionals can play an important role in this regard because they are in a good position to detect cognitive changes in adults aging with HIV. This will help them detect potential impairments, as well as be ready for possible interventions. Our findings are also of particular relevance because the HIV population as a whole is aging. In a few years, most people with HIV will be older than 50 years, and age-related morbidities will appear in this population complementarily to the long-term effects of HIV. Such comorbidities can include a wide range of potential malignancies, including oncologic, metabolic, and bone complications, and also brain disorders. The availability of a practical and reliable screening method such as the NEU Screen to detect at an early stage the presence of

Key Considerations

- There is a current need to incorporate the use of practical screening tools to detect cognitive impairment in aging PLWH.
- The NEU Screen appears to be a reliable and useful instrument to screen for HIV-associated cognitive impairment.
- The results from this study indicate that the accuracy of this method increases as the HIV population ages, particularly in PLWH aged 60 years or older.
- Nurses and other health care providers can play an important role in the detection of HAND.

neurological decline in the aging HIV population thus fulfills an urgent need in today's clinical context.

Disclosures

The authors declare not to have any potential financial conflict with the publication of the study.

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