Published in final edited form as:

J Neurovirol. 2013 February ; 19(1): 109–116. doi:10.1007/s13365-012-0147-5.

The Alzheimer Disease-8 and Montreal Cognitive Assessment as Screening Tools for Neurocognitive Impairment in HIV-Infected Persons

E. Turner Overton, MD¹, Tej Azad², Neva Parker², Debra Demarco-Shaw, RN³, Judy Frain, RN³, Teresa Spitz, RN³, Elizabeth Westerhaus, MA², Robert Paul, PhD⁴, David B. Clifford, MD², and Beau M. Ances, MD, PhD^{2,5}

¹Department of Medicine, University of Alabama Birmingham, Birmingham, AL

²Department of Neurology, Washington University in Saint Louis, Saint Louis, MO

³Department of Medicine, Washington University in Saint Louis, Saint Louis, MO

⁴Department of Psychology, University of Missouri in Saint Louis, Saint Louis, MO

⁵Department of Biomedical Engineering, Washington University in Saint Louis, Saint Louis, MO

Abstract

The diagnosis of HIV-associated neurocognitive impairment is time-intensive and often omitted in busy outpatient settings. Brief screening tools are needed. The Montreal Cognitive Assessment (MoCA) and the Alzheimer's disease (AD)-8 have been used in neurodegenerative disorders. We evaluated the sensitivity and specificity of these brief screening tools in HIV-infected persons. The AD-8, MoCA, and formal neuropsychological testing were administered to 200 HIV-infected patients followed at a single institution. Normalized scores on formal neuropsychological testing were used to define neurocognitive impairment. The sensitivity and specificity of the MoCA and AD-8 were assessed to diagnose impairment. Neurocognitive impairment was highly prevalent in this cohort: 127 persons (64%) were diagnosed with neurocognitive impairment based on formal testing. Using the AD-8 and MoCA, 113 (57%) and 101 (51%) persons were identified with neurocognitive impairment, respectively. The sensitivity and specificity of MoCA were 63% and 71%, respectively. The sensitivity and specificity of AD-8 were 61% and 51%, respectively. Our findings highlight that brief screening tools correlate with formal neuropsychological testing. However, the sensitivities of these screening tools are lower than desired. Nevertheless, given their ease in administration, these tools could assist as a first line for identifying individuals who may subsequently require formal neuropsychological testing.

Keywords

HIV; Neurocognitive Disorder; MoCA; AD-8; Neuropsychological Testing; Cognition

Corresponding Author: Turner Overton, MD, 908 20th St South, CCB Rm 325, Birmingham, AL 35294, toverton@uab.edu, Phone: (205) 934-5191, Fax: (205) 975-6027.

Preliminary results from this research were presented at the 18th Conference on Retroviruses and Opportunistic Infections in Boston, Massachusetts in 2011 as Poster #E-134.

Conflicts of Interest: No authors report conflicts of interest.

Introduction

Since the introduction of highly active antiretroviral therapy (HAART), HIV-associated dementia has markedly declined (Ances et al. 2007). However, subtle forms of neurocognitive impairment have become more prominent. A recent multi-site study demonstrated that 52% of HIV-infected adults had neurocognitive impairment (Heaton et al. 2011). These neurocognitive changes can greatly impact day-to-day functioning and cause significant morbidity and mortality (Vivithanaporn et al. 2010). The continued prevalence of neurocognitive impairment in the HAART era may reflect prolonged patient survival (Valcour et al. 2011a; Valcour et al. 2011b), chronic inflammation due to the inability of certain HAART regimens to adequately cross the blood-brain barrier (Cysique et al. 2011), and/or medication-induced neurotoxicity (Marra et al. 2009).

To adequately evaluate the extent of neurocognitive impairment, a battery of neuropsychological tests is typically administered (Heaton et al., 2010). However, these neuropsychological tests are neither cost effective nor time efficient in the outpatient clinical setting as they are often require several hours to complete and can be labor intensive requiring additional trained personnel to administer and correctly score (Koski et al. 2011; Robinson-Papp et al. 2009).

A number of relatively simple tests have been developed to assess neurocognitive impairment in the office (Valcour 2011c). The HIV Dementia Scale (HDS) consists of a brief series of tests that evaluate motor speed, memory, constructional praxis, and executive function (Davis et al. 2002; Power et al. 1995). The original 16 point HDS was modified for evaluations in international settings with limited resources (Lawler et al. 2010). The resulting International HIV Dementia Scale (IHDS) is scored out of a maximum score of 12, with less than 10 indicating dementia (Joska et al. 2011). While the HDS and IHDS can adequately identify more severe forms of neurocognitive impairment, specifically HIV-associated dementia, these tools are relatively insensitive in differentiating milder forms (Valcour et al. 2011a). In addition, these screening tests are influenced by the education level of the person (Waldrop-Valverde et al. 2010). Another method that evaluates multiple cognitive domains is a condensed version of formal neuropsychological testing in which scores from eight screening tests are combined into a single neuropsychological performance called the NPZ-8 (Clifford et al. 2002). This battery creates an aggregate score by averaging z-scores from the eight different tests after correcting for age and education. This approach has been used extensively in clinical trials for ease of data management but thresholds to identify neurocognitive impairment have not been established (Schifitto et al. 2006).

Screening tools that have been used to assess neurocognitive impairment in other neurodegenerative disorders (e.g., Alzheimer's disease (AD), Parkinson's disease, and Huntington's disease) may be useful in the HIV clinic, as many patients are living longer due to HAART (Wendelken and Valcour 2012). In particular, the AD-8 is an eight-item informant-based screen that reliably discriminates cognitively normal persons from demented persons, even at a very mild stage, and is sensitive to the earliest signs of neurocognitive impairment as reported by the individual person or an informant (often a spouse or life partner). (http://alzheimer.wustl.edu/About_Us/PDFs/AD8form2005.pdf) (Galvin et al. 2005; Galvin et al. 2006). The items focus on the individual's current and previous level of functioning and attempt to determine changes attributable to neurocognitive impairment (Galvin et al. 2007). An individual serves as his/her own control and this eliminates the need for preceding baseline evaluation. The AD-8 takes less than 2 minutes to complete and can be performed in the clinic waiting room (Galvin et al. 2010).

The person or his/her informant is asked to report changes in memory, problem-solving, orientation, and daily activities.

Another screening test that has been used by the AD community is the Montreal Cognitive Assessment (MoCA). The MoCA takes approximately 10 minutes to complete and consists of 30 items that encompass eight cognitive domains (Nasreddine et al. 2005). The MoCA is in the public domain, has been translated into multiple languages to facilitate global clinical application, can be administered by lay personnel, is easy to score, and requires a simple correction for years of education (www.mocatest.org) (Valcour et al. 2011a). It is more sensitive than the Mini-Mental Status Exam in differentiating neurocognitive impairment (Freitas et al. 2011; Paul et al. 2011). However, few studies have examined the utility of the MoCA in HIV-infected populations (Kaski et al. 2011; Chan et al. 2012).

In this study, we evaluated the utility of these two brief screening tools (AD-8 and MoCA) in assessing neurocognitive impairment within a cohort of 200 HIV-infected persons seen in the infectious diseases outpatient clinic of a single institution. In particular, we assessed the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the AD-8 and MoCA compared to more formal condensed neuropsychological performance testing using the NPZ-8.

Methods

Study Population

A total of 200 HIV-infected persons aged 18 to 65 were enrolled the outpatient infectious disease clinic at Washington University in St. Louis. All persons were on HAART and were virologically suppressed (plasma HIV viral load <400 copies/mL). Each person provided written consent approved by the Human Research Protection Office at Washington University in Saint Louis. Persons with a history of confounding neurological disorders including epilepsy, stroke, head injury with loss of consciousness greater than thirty minutes, history of opportunistic central nervous system infection, brain tumor, AIDS-defining opportunistic infections within forty-five days prior to study entry, major psychiatric disorders, or active substance abuse were excluded from participation. Demographic, clinical, and laboratory data was extracted from the clinic electronic medical record. Specifically, information regarding past medical history was gathered by medical chart abstraction and by self-report. Depression screening was performed using the PHQ-9, a standard screening tool for depression (Kroenke et al. 2001).

Neuropsychological Performance Evaluation

All persons completed a condensed battery of neuropsychological tests. This battery included Trail-Making Tests A & B, the Revised Hopkins Verbal Learning Test (HVLt-R), the Stroop Naming and Color Interference Task, Timed Gait, Grooved Pegboard for dominant and non-dominant hands, CalCAP Choice and Sequential Reaction Time Tests, and the Symbol Digit Substitution Test (Clifford et al. 2002). These tests examine multiple cognitive domains (including learning and memory, psychomotor speed, motor skills, and executive function) and have previously been used to assess neurocognitive impairment (Heaton et al. 2010; Van Gorp et al. 1989). Raw scores from each test were standardized using demographic (age, gender, race, education) adjusted normative means (Heaton et al. 2011). A standardized z-score was calculated by subtracting the appropriate normative mean from the raw score and then dividing by the normative standard deviation. A person was identified as having neurocognitive impairment if they had impairment in cognitive functioning in at least 2 domains as documented by z-scores ≤ -1.0 (Antinori et al. 2007). The NPZ-8 was calculated from the average z scores from the following eight tests

(CALCAP Choice and Sequential Reaction Times, Trail Making A and B, Digit Symbol Substitution Test, Timed Gait, and Grooved Pegboard non-dominant hands, and HVL-T-R delayed component).

MoCA

Each person completed the MoCA with scoring performed according to published instructions. The MoCA consists of 13 tasks organized into eight cognitive domains including visuospatial, executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. A total score was generated by summing scores across eight domains. One point was added for persons with 12 or fewer years of formal education (Nasreddine et al. 2005). The maximum possible score is 30 points with a score <26 considered as having neurocognitive impairment.

AD-8

Each person also completed the AD-8. This test consists of eight 'Yes/No' questions (repeats self (memory), reduced interest in hobbies and activities (apathy), trouble with judgment (executive), trouble operating appliances (executive), forgets correct month/year (orientation), trouble with finances (executive), forgets appointments (memory), daily problems with memory/thinking (general). The AD-8 yields a score from 0 to 8 depending on the number of positive responses. A score of ≥ 2 indicates neurocognitive impairment (Galvin et al. 2005).

Data Analysis

Baseline parameters for the neurocognitive impairment and cognitively normal persons, based on the criteria formulated by Antinori et al. (2007), were compared for possible differences using Student's T test, Chi-square test, or Mann-Whitney U tests. The following measures of binary classification were generated to evaluate the utility of the two screening tools (MoCA and AD-8) compared to the formal testing: sensitivity (the proportion of actual positives correctly identified), specificity (the proportion of actual negatives correctly identified), positive and negative predictive values (PPV, NPV) (measures of precision) and receiver operator curves (ROC) (a measure of the trade-off between sensitivity and specificity) (Metz 1978; Zweig and Campbell 1993). The Pearson Product Moment Correlation was obtained comparing the NPZ-8 to the AD-8 and MoCA (SPSS version 18, Chicago, Ill). We also evaluated different cutoff values for the MoCA to optimize sensitivity as has previously been performed for AD (Lee et al. 2008).

Results

The mean age of the 200 HIV-infected persons was 43 years, with 72% being male and African-Americans comprising the largest racial/ethnic group (67%). The median CD4 cell count was 538 c/mm³ (IQR: 361, 695) with all participants virologically suppressed on HAART (<400 copies/mL). Using formal neuropsychological testing, 127 of the 200 persons (64%) met criteria for neurocognitive impairment (z-score ≤ -1.0 in at least two domains). Neurocognitively impaired persons were more likely to be African-American, have lower education, currently use tobacco, and have higher total cholesterol and LDL compared to cognitively normal persons. Relevant demographic and clinical characteristics of the cohort are summarized in Table 1.

The MoCA identified 101 of 200 persons (51%) as neurocognitively impaired while the AD-8 identified 113 of 200 persons (57%) with neurocognitive impairment. Using the MoCA, 80 of the 127 neurocognitively impaired persons identified by formal testing and 52 of the 73 cognitively normal persons were correctly identified, yielding a sensitivity of 63%,

a specificity of 71%, a PPV of 79%, and a NPV of 53% (Table 2). When comparing the AD-8 to the formal testing results, 77 of the 127 neurocognitively impaired persons and 37 of the 73 cognitively normal persons were correctly identified, yielding a sensitivity of 61%, a specificity of 51%, a PPV of 68%, and a NPV of 43% (Table 3).

Evaluation of the two tests using ROC curves demonstrated that the MoCA differentiated neurocognitive impairment from normal cognition better than the AD-8 when compared to a condensed neuropsychological battery. The area under the curve (AUC) with 95% confidence Intervals was 0.67 (0.59, 0.75) for the MoCA and 0.56 (0.47, 0.64) for the AD-8 (Figure 1). These values are considered fair and poor, respectively, by a recent review of prognostic indicators (Yourman et al. 2012).

Both brief screening tests correlated with neurocognitive impairment as measured by the NPZ-8. In particular, the MoCA was positively correlated with the NPZ-8 ($R=0.65$, $p<0.001$) and accounted for 43% of the variation in NPZ-8 scores, while the AD-8 score was negatively correlated with the NPZ-8 ($R=-0.29$, $p=0.001$) and accounted for only 8% of the variation in the NPZ-8 scores.

To improve the utility of the MoCA as a screening tool for HAND, we evaluated the sensitivity, specificity, PPV, NPV, and ROC with different thresholds for detecting neurocognitive impairment (23, 24, 25, 26, and 27). Data to evaluate the different cutoffs are displayed in Table 4. By lowering the threshold to 23, we reduced false positive tests (i.e. improved specificity) at the cost of sensitivity. We found that raising the cutoff to 27 for neurocognitive impairment for the MoCA increased sensitivity to nearly 90% for identifying impairment. This marked improvement in sensitivity was accompanied by an expected loss of specificity. Interestingly, the areas under the ROC curves for these various MoCA threshold values (23, 24, 25, 26, or 27) were not notably different with overlapping 95% confidence intervals (Table 4).

We also examined whether a combination of both tests was better in discriminating neurocognitively impaired persons than either alone. A combination of the MoCA and AD-8 identified 51 of 127 cognitively impaired persons and 60 of 73 cognitively normal persons for a sensitivity of 40%, specificity of 82%, PPV of 80%, and NPV of 44%. The lower sensitivity of this combined approach likely reflects the fact that the two tests were weakly correlated ($r=0.140$, $p=0.048$).

Discussion

Among a group of HIV-infected persons who were virologically suppressed with HAART, neurocognitive impairment was highly prevalent (64%) when determined by a condensed battery of formal neuropsychological performance testing. Neurocognitive impairment was more prevalent within HIV-infected persons of African American race, and persons with lower educational attainment, higher cholesterol levels, and currently using tobacco. Both the MoCA and the AD-8, brief screening tests originally developed for AD, correlated with formal testing, but neither was particularly sensitive as a screening tool (63% for the MoCA and 61% for the AD-8). The combination of tests fared no better.

The relatively high proportion of persons identified with neurocognitive impairment in this study at a single site was similar to previous reports (Tozzi et al. 2007; Robertson et al. 2007). Others have identified a lower prevalence (Heaton et al., 2011; Cysique et al., 2004) reflecting either differences in the cohorts studied or neuropsychological battery used. For instance, the former study was comprised of individuals with significantly greater educational attainment than the present cohort and the latter study excluded all persons with HIV-associated dementia thus reducing the overall prevalence of neurocognitive

impairment. More importantly, the shift from HIV-associated dementia to the milder forms of neurocognitive impairment highlights the need for effective screening tests to identify these more subtle forms (Valcour et al. 2011a). Early identification is of critical importance with the recent recognition that even these less severe forms of neurocognitive impairment are associated with subsequent progressive cognitive decline and other health implications (Heaton et al. 2012; Watkins et al. 2012; Wendelken and Valcour 2012). Cost effective screening tools which require minimal performance time are clearly needed.

A challenge that has prevented the development of effective screening tools for HAND, is that multiple etiologies (including aberrant immune response (Cysique et al. 2011), medication neurotoxicity (Marra et al. 2009), comorbidities (diabetes and hypertension) (McCutchan et al. 2012), or genetic factors (Apolipoprotein E4 allele) (Chang et al. 2011)) may contribute. While this study was not specifically designed to evaluate other possible etiologies of neurocognitive impairment, the homogeneity of the sample population with regards to virologic suppression provided the opportunity to look at other factors. We observed that African American racial background, education level, total and LDL cholesterol, and current smoking use were associated with neurocognitive impairment. The relationship to race and education may reflect socioeconomic factors that are well known to impact cognitive functioning and likely serve as a marker of cognitive reserve. The cognitive reserve hypothesis suggests that individuals with greater cognitive reserve, i.e. higher education, exhibit higher resistance to neuropathologic damage (Roe et al. 2010; Roe et al. 2007). The associations with cholesterol and smoking are intriguing and suggest that atherosclerosis may contribute to neurocognitive impairment. An association between metabolic factors, most notably obesity, and cognitive impairment was recently reported in another large HIV-infected cohort (McCutchan et al. 2012). The pro-inflammatory milieu, attributable to HIV and obesity, likely engenders atherosclerotic changes and leads to an underlying vascular component that contributes to neurocognitive impairment (McMurtry et al. 2008). Cigarette smoking is much more prevalent among HIV-infected persons than the general population (Durazzo et al. 2007). The negative association of tobacco on cognition provides additional ammunition for care providers to counsel patients to stop smoking (Vellozzi et al. 2009; Chen et al. 2012). Further research is needed to understand how these different factors impact cognition in this at risk population.

The search for an effective screening tool for neurocognitive impairment remains a challenge. Our data illustrate that simple screening tools developed for AD may not provide the best discriminator in an HIV-infected population. We observed reduced sensitivity and specificity for the AD-8 compared to previous AD literature (Galvin et al. 2005). Given that different factors likely contribute to neurocognitive impairment in the current HIV-infected population, it is not surprising that the AD-8, a battery that assesses for functional impairment, performed poorly. The nature of the questions within the AD-8, specifically orientation and memory, make it less applicable to a subcortical process like HIV infection. The AD-8 has been validated in the AD community for either the person or their surrogate informant to complete, and thus, this tool lends itself to a third party assessment of the person's functional change. In contrast, HIV-infected persons often attend clinic appointments alone (Valcour et al. 2011a) and often have limited social support networks (Shippy and Karpiak 2005).

The MoCA performed better than the AD-8 as manifested within the ROC curves, yielding a fair prognostic score (0.60–0.69) compared to the poor prognostic score of the AD-8 (0.50–0.59) (Yourman et al. 2012). The MoCA tests 8 cognitive domains and is less likely to be affected by education, comorbidities, or reporting bias (Nasreddine et al. 2005). However, this screening tool alone failed to adequately distinguish HIV-infected persons with neurocognitive impairment from those with normal cognition. Unlike previous studies that

have used the MoCA in an HIV-infected cohort (Koski et al. 2011; Chan et al. 2012), ours is the first to compare this brief screening test to more formal neuropsychological testing. Notably, the sensitivity of the MoCA was improved to 90% by changing the threshold but the prognostic score remained in the *fair* range. While improved sensitivity may be preferable to the clinician, it will increase the number of persons referred for formal neurocognitive testing. Alternatively, the MoCA could be used to identify persons that should be repeatedly monitored. This tactic has been used with other screening tools with average sensitivity such as cervical cancer screening (Wheeler 2007).

There are several limitations to the current study. This study was cross-sectional, included persons from a single clinical site, and enrolled only persons whose HIV virus was suppressed with HAART. First, the use of a single site provided certainty that the testing was performed in a similar manner for all persons. Second, the inclusion of only HIV-infected persons who were virologically well controlled was specifically performed in an attempt to limit any confounding that could occur with uncontrolled HIV infection or undetected opportunistic infections. In addition, we did not include HIV uninfected persons within this study. Future studies are needed that include a wide range of HIV-infected persons as well as healthy controls. While the large proportion of African Americans may limit the generalizability, the inclusion of this minority population is highly relevant to the ongoing US HIV epidemic. We did not formally assess activities of daily living and could not make a formal diagnosis of HAND. Using recently developed criteria asymptomatic neurocognitive impairment is characterized by mild neuropsychological impairment in at least two cognitive domains but no functional decline, whereas mild neurocognitive disorder is defined by impairment of at least two domains and reported mild functional decline (Chen et al. 2012). HIV-associated dementia is defined as having deficits in at least two domains and significant impairment in activities of daily living. While we cannot classify individuals into different HAND categories (asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia), our results do not detract from the primary analysis to evaluate these batteries as screening tools for neurocognitive impairment.

In summary, our study confirms that a large proportion of HIV-infected persons have neurocognitive impairment as assessed by formal neuropsychological testing. The MoCA and AD-8 correlated with formal neurocognitive testing, but the sensitivity of each of these tests was lower than desired for a single screening test. The sensitivity of the MoCA can be improved by using a different threshold value although the number of false positives also increases. Furthermore, like other cognitive screening tests, performance on the MoCA does not define the etiology of neurocognitive impairment. HIV-infected persons with performances < 26 on the MoCA may still require a referral for more comprehensive neuropsychological assessments.

Acknowledgments

Funding Sources: This project was supported by an unrestricted research grant from the ViiV HIV Collaborative Investigator Research Award Program. BMA is currently receiving a grant (K23MH081786) from the National Institute of Mental Health at the National Institute of Health, the National Institute of Nursing Research at the National Institute of Health (R01NR012907 and R01NR012657).

References

- Ances BM, Ellis RJ. Dementia and neurocognitive disorders due to HIV-1 infection. *Seminars in Neurology*. 2007; 27:86–92. [PubMed: 17226745]
- Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn

- M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007; 69:1789–1799. [PubMed: 17914061]
- Chan LG, Kandiah N, Chua A. HIV-associated neurocognitive disorders (HAND) in a South Asian population - contextual application of the 2007 criteria. *BMJ Open*. 2012;10.1136/bmjopen-2011-000662
- Chang L, Andres M, Sadino J, Jiang CS, Nakama H, Miller E, Ernst T. Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. *Neuroimage*. 2011; 58:1017–1027. [PubMed: 21803164]
- Chen R, Zhang D, Chen Y, Hu Z, Wilson K. Passive smoking and risk of cognitive impairment in women who never smoke. *Archives of Internal Medicine*. 2012; 172:271–273. [PubMed: 22332161]
- Clifford DB, McArthur JC, Schifitto G, Kieburz K, McDermott MP, Letendre S, Cohen BA, Marder K, Ellis RJ, Marra CM. Neurologic AIDS Research Consortium (2002) A randomized clinical trial of CPI-1189 for HIV-associated cognitive-motor impairment. *Neurology*. 59:1568–1573. [PubMed: 12451199]
- Cysique LA, Maruff P, Brew BJ. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. *Journal of Neurovirology*. 2004; 10:350–357. [PubMed: 15765806]
- Cysique LA, Waters EK, Brew BJ. Central nervous system antiretroviral efficacy in HIV infection: a qualitative and quantitative review and implications for future research. *BMC Neurology*. 2011; 11:148. [PubMed: 22107790]
- Davis HF, Skolasky RL Jr, Selnes OA, Burgess DM, McArthur JC. Assessing HIV-associated dementia: modified HIV dementia scale versus the Grooved Pegboard. *AIDS Reader*. 2002; 12:29–31. [PubMed: 11862658]
- Durazzo TC, Rothlind JC, Cardenas VA, Studholme C, Weiner MW, Meyerhoff DJ. Chronic cigarette smoking and heavy drinking in human immunodeficiency virus: consequences for neurocognition and brain morphology. *Alcohol*. 2007; 41:489–501. [PubMed: 17923369]
- Freitas, S.; Simoes, MR.; Alves, L.; Santana, I. Alzheimer Disease & Associated Disorders. 2011. Montreal Cognitive Assessment: Validation Study for Mild Cognitive Impairment and Alzheimer Disease. [Epub ahead of print]
- Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC. The AD8: a brief informant interview to detect dementia. *Neurology*. 2005; 65:559–564. [PubMed: 16116116]
- Galvin JE, Roe CM, Xiong C, Morris JC. Validity and reliability of the AD8 informant interview in dementia. *Neurology*. 2006; 67:1942–1948. [PubMed: 17159098]
- Galvin JE, Roe CM, Coats MA, Morris JC. Patient's rating of cognitive ability: using the AD8, a brief informant interview, as a self-rating tool to detect dementia. *Archives of Neurology*. 2007; 64:725–730. [PubMed: 17502472]
- Galvin JE, Fagan AM, Holtzman DM, Mintun MA, Morris JC. Relationship of dementia screening tests with biomarkers of Alzheimer's disease. *Brain*. 2010; 133:3290–3300. [PubMed: 20823087]
- Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. CHARTER GROUP. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy CHARTER Study. *Neurology*. 2010; 75:2087–2096. [PubMed: 21135382]
- Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC, Marra CM, Morgello S, Mindt MR, Taylor MJ, Marcotte TD, Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. CHARTER Group; HRNC Group. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of Neurovirology*. 2011; 17:3–16. [PubMed: 21174240]

- Heaton, R.; Franklin, D.; Woods, S.; Marra, C.; Clifford, D.; Gelman, B.; McArthur, J.; Morgello, S.; McCutchan, A.; Grant, I. CHARTER Group. Asymptomatic Mild HIV-associated Neurocognitive Disorder Increases Risk for Future Symptomatic Decline: A CHARTER Longitudinal Study. 19th Conference on Retroviruses and Opportunistic Infections; Seattle, Washington. 2012 Mar.
- Joska JA, Westgarth-Taylor J, Hoare J, Thomas KG, Paul R, Myer L, Stein DJ. Validity of the International HIV Dementia Scale in South Africa. *AIDS Patient Care and STDs*. 2011; 25:95–101. [PubMed: 21214343]
- Koski L, Brouillette MJ, Lalonde R, Hello B, Wong E, Tsuchida A, Fellows L. Computerized testing augments pencil-and-paper tasks in measuring HIV-associated mild cognitive impairment. *HIV Medicine*. 2010; 12:472–480. [PubMed: 21395965]
- Kroenke K, Spitzer R, Williams J. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001; 16:606–613. [PubMed: 11556941]
- Lawler K, Mosepele M, Ratcliffe S, Seloiwe E, Steele K, Nthobatsang R, Steenhoff A. Neurocognitive impairment among HIV-positive individuals in Botswana: a pilot study. *Journal of the International AIDS Society*. 2010; 13:15. [PubMed: 20406460]
- Lee JY, Lee Dong Woo, Cho SJ, Na DL, Jeon Hong Jin, Kim SK, Lee You Ra, Youn JH, Kwon M, Lee JH, Cho Maeng Je. Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment. *Journal of Geriatric Psychiatry and Neurology*. 2008; 21:104–110. [PubMed: 18474719]
- Marra CM, Zhao Y, Clifford DB, Letendre S, Evans S, Henry K, Ellis RJ, Rodriguez B, Coombs RW, Schifitto G, McArthur JC, Robertson K. AIDS Clinical Trials Group 736 Study Team. Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. *AIDS*. 2009; 23:1359–1366. [PubMed: 19424052]
- McCutchan JA, Marquie-Beck JA, Fitzsimons CA, Letendre SL, Ellis RJ, Heaton RK, Wolfson T, Rosario D, Alexander TJ, Marra C, Ances BM, Grant I. CHARTER Group. Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder. *Neurology*. 2012; 78:485–492. [PubMed: 22330412]
- McMurtray A, Nakamoto B, Shikuma C, Valcour V. Cortical atrophy and white matter hyperintensities in HIV: the Hawaii Aging with HIV Cohort Study. *Journal of Stroke and Cerebrovascular Diseases*. 2008; 17:212–217. [PubMed: 18589342]
- Metz CE. Basic principles of ROC analysis. *Seminars in Nuclear Medicine*. 1978; 8:283–98. [PubMed: 112681]
- Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatric Society*. 2005; 53:695–699.
- Paul R, Lane EM, Tate DF, Heaps J, Romo DM, Akbudak E, Niehoff J, Conturo TE. Neuroimaging signatures and cognitive correlates of the Montreal cognitive assessment screen in a nonclinical elderly sample. *Archives of Clinical Neuropsychology*. 2011; 26:454–460. [PubMed: 21642663]
- Power C, Selnes OA, Grim JA, McArthur JC. HIV Dementia Scale: a rapid screening test. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology*. 1995; 8:273–278.
- Robertson KR, Smurzynski M, Parsons TD, Wu K, Bosch RJ, Wu J, McArthur JC, Collier AC, Evans SR, Ellis RJ. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*. 2007; 21:1915–1921. [PubMed: 17721099]
- Robinson-Papp J, Elliott KJ, Simpson DM. HIV-related neurocognitive impairment in the HAART era. *Current HIV/AIDS Report*. 2009; 6:146–152.
- Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology*. 2007; 68:223–228. [PubMed: 17224578]
- Roe CM, Mintun MA, Ghoshal N, Williams MM, Grant EA, Marcus DS, Morris JC. Alzheimer disease identification using amyloid imaging and reserve variables: proof of concept. *Neurology*. 2010; 75:42–48. [PubMed: 20603484]
- Schifitto G, Peterson DR, Zhong J, Ni H, Cruttenden K, Gaugh M, Gendelman HE, Boska M, Gelbard H. Valproic acid adjunctive therapy for HIV-associated cognitive impairment: a first report. *Neurology*. 2006; 66:919–21. [PubMed: 16510768]

- Shippy RA, Karpiak SE. The aging HIV/AIDS population: fragile social networks. *Aging Ment Health*. 2005; 9:246–54. [PubMed: 16019278]
- Tozzi V, Balestra P, Bellagamba R, Corpolongo A, Salvatori MF, Visco-Comandini U, Vlassi C, Giulianelli M, Galgani S, Antinori A, Narciso P. Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. *Journal of Acquired Immune Deficiency Syndrome*. 2007; 45:174–182.
- Valcour V, Paul R, Chiao S, Wendelken LA, Miller B. Screening for cognitive impairment in human immunodeficiency virus. *Clinical Infectious Diseases*. 2011a; 53:836–842. [PubMed: 21921226]
- Valcour V, Paul R, Neuhaus J, Shikuma C. The Effects of Age and HIV on Neuropsychological Performance. *Journal of the International Neuropsychological Society*. 2011b; 17:190–195. [PubMed: 21144102]
- Valcour VG. Evaluating cognitive impairment in the clinical setting: practical screening and assessment tools. *Topics in Antiviral Medicine*. 2011c; 19:175–180. [PubMed: 22298886]
- Van Gorp WG, Miller EN, Satz P, Visscher B. Neuropsychological performance in HIV-1 immunocompromised patients: a preliminary report. *Journal of Clinical Experimental Neuropsychology*. 1989; 11:763–773.
- Vivithanaporn P, Heo G, Gamble J, Krentz HB, Hoke A, Gill MJ, Power C. Neurologic disease burden in treated HIV/AIDS predicts survival: a population-based study. *Neurology*. 2010; 75:1150–1158. [PubMed: 20739646]
- Vellozzi C, Brooks JT, Bush TJ, Conley LJ, Henry K, Carpenter CC, Overton ET, Hammer J, Wood K, Holmberg SD. SUN Study Investigators. The study to understand the natural history of HIV and AIDS in the era of effective therapy (SUN Study). *American Journal of Epidemiology*. 2009; 169:642–652. [PubMed: 19074775]
- Waldrop-Valverde D, Nehra R, Sharma S, Malik A, Jones D, Kumar AM, Ownby RL, Wanchu A, Weiss S, Prabhakar S, Kumar M. Education effects on the International HIV Dementia Scale. *Journal of Neurovirology*. 2010; 16:264–267. [PubMed: 20578972]
- Watkins CC, Treisman GJ. Neuropsychiatric complications of aging with HIV. *Journal of Neurovirology*. 2012; 18:277–90. [PubMed: 22644745]
- Wendelken LA, Valcour V. Impact of HIV and aging on neuropsychological function. *Journal of Neurovirology*. 2012; 18:256–63. [PubMed: 22528478]
- Wheeler CM. Advances in primary and secondary interventions for cervical cancer: human papillomavirus prophylactic vaccines and testing. *Nature Clinical Practice Oncology*. 2007; 4:224–235.
- Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. *JAMA*. 2012; 307:182–92. [PubMed: 22235089]
- Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry*. 1993; 39:561–77. [PubMed: 8472349]

Figure 1. Receiver Operator Curves for MoCA and AD-8

Receiver operator characteristic curves (ROC) for the Montreal Cognitive Assessment (MoCA) and Alzheimer's disease (AD)-8 for identification of neurocognitive impairment. The MoCA had significantly greater area under the curve (AUC) (0.67, 95% CI: 0.59–0.75) compared to the AD-8 (0.56, 95% CI: 0.47–0.64)

Table 1

Baseline demographics of HIV-infected (HIV+) individuals

Variables	Overall (n=200)	Cognitively normal (n=73)	Neurocognitive impairment (n=127)	P value
Mean Age (years)	43.3 ± 10.7	42.1 ± 11.6	43.9 ± 10.1	0.260
Race				0.006
White (%)	65 (32%)	33 (45%)	32 (25%)	
African American (%)	133 (65%)	39 (53%)	94 (75%)	
Other (%)	1 (0.5%)	1 (2%)	-	
Missing (%)	1 (0.5%)			
Hispanic Ethnicity	1 (0.5%)	0 (0%)	1 (0.8%)	0.635
Sex (% Male)	143 (71.5%)	52 (71.2%)	91 (71.7%)	0.949
Mean Education (Years)	13.1 ± 2.6	14.2 ± 2.7	12.4 ± 2.3	<0.001
Mean Body Mass Index (BMI in kg/m ²)	28.5 ± 7.7	28.3 ± 7.2	28.7 ± 8.0	0.767
Median Nadir CD4 (cells/mm ³)	191 (70–300)	196 (88–317)	178 (50–290)	0.178
Median Baseline CD4 (cells/mm ³)	538 (361–695)	540 (367–658)	531 (351–745)	0.548
Baseline VL < 400cp/mL	200 (100%)	73 (100%)	127 (100%)	1.0
Hepatitis C Antibody reactive	16 (8.0%)	7 (9.9%)	9 (7.4%)	0.546
Hepatitis B surface antigen reactive	6 (3.0%)	1 (1.8%)	5 (6.3%)	0.212
Current Tobacco use	97 (48.5%)	27 (37.0%)	70 (55.1%)	0.014
Mean total cholesterol (mg/dL)	183.3 ± 43.4	174.4 ± 37.1	188.5 ± 46.0	0.031
Mean HDL (mg/dL)	51.4 ± 17.5	52.1 ± 19.2	51.1 ± 16.6	0.708
Mean LDL (mg/dL)	102.9 ± 33.1	95.7 ± 28.0	107.1 ± 35.2	0.023
Triglycerides	148.1 ± 87.1	135.7 ± 65.8	155.2 ± 96.7	0.137
Mean systolic blood pressure (mm Hg)	124.8 ± 14.9	125.5 ± 14.3	124.4 ± 15.2	0.625
Mean diastolic blood pressure (mm Hg)	74.9 ± 9.7	75.0 ± 9.2	74.9 ± 10.0	0.927
Waist Circumference (cm)				
Men	84.7 ± 18.6	86.7 ± 17.8	83.7 ± 20.0	0.353
Women	89.5 ± 28.4	85.3 ± 28.4	91.8 ± 28.5	0.409
Mean fasting glucose(mg/dL)	91.7 ± 18.9	91.1 ± 14.3	92.2 ± 21.2	0.704
Hypertension	74 (37%)	22 (30.1%)	52 (40.9%)	0.127

Variables	Overall (n=200)	Cognitively normal (n=73)	Neurocognitive impairment (n=127)	P value
Diabetes Mellitus	18 (9%)	4 (5.5%)	13 (11.0%)	0.187

T test, Chi² test, and Mann-Whitney U test as indicated.

Table 2

Comparison of the Montreal Cognitive Assessment (MoCA) to formal neuropsychological testing.

	Formal Testing		Total	Sensitivity	63%
	Cognitively normal	Neurocognitive impairment			
Impaired using the MoCA	21	80	101	Specificity	71%
Not Impaired using the MoCA	52	47	99	Positive Predictive Value	79%
Total	73	127	200	Negative Predictive Value	53%

Table 3

Comparison of the Alzheimer's Disease (AD)-8 to formal neuropsychological testing.

	Formal Testing		Total	Sensitivity	
	Cognitively normal	Neurocognitive impairment			
Impaired by AD8	36	77	113	Specificity	51%
Not Impaired by AD8	37	50	87	Positive Predictive Value	68%
Total	73	127	200	Negative Predictive Value	43%

Table 4

Evaluation of neurocognitive impairment for MoCA cutoff scores

	Threshold for Impairment by MoCA				
	27	26	25	24	23
Number Identified as Impaired	156	129	101	67	52
Sensitivity	89.8%	75.6%	63.0%	52.8%	37.8%
Specificity	42.5%	54.8%	71.2%	82.2%	94.5%
PPV	73.0%	74.4%	79.2%	83.8%	92.6%
NPV	70.4%	56.3%	52.5%	50.0%	46.6%
Area under ROC (95% CI)	0.66 (0.58–0.74)	0.65 (0.57–0.73)	0.67 (0.59–0.75)	0.68 (0.60–0.75)	0.66 (0.59–0.74)