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Functional deficits and other psychiatric associations with abnormal scores on the Montreal Cognitive Assessment (MoCA) in older HIV-infected patients

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Abstract

Objective: The authors assessed the association of physical function, social variables, functional status, and psychiatric co-morbidity with cognitive function among older HIV-infected adults.

Design: From 2012–2014, a cross-sectional study was conducted among HIV-infected patients ages 50 or older who underwent comprehensive clinical geriatric assessment.

Setting: Two San Francisco HIV clinics.

Participants: 359 HIV-infected patients age 50 years or older

Measurements—Unadjusted and adjusted Poisson regression measured prevalence ratios and 95% confidence intervals for demographic, functional and psychiatric variables and their association with cognitive impairment using a Montreal Cognitive Assessment (MoCA) score < 26 as reflective of cognitive impairment.

Results—Thirty-four percent of participants had a MoCA score of < 26. In unadjusted analyses, the following variables were significantly associated with an abnormal MoCA score: born female,

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Description of authors' roles

Dr. Bourgeois designed the study and was primarily responsible for writing the paper. Dr. John assisted with study design and editing of the paper. Dr. Zepf was involved in data collection, study design, and editing of the paper. Dr. Greene assisted with editing of the paper. Dr. Frankel assisted with study design and editing the paper. Prof. Hessol conducted statistical analysis and interpretation and assisted in writing of the paper.

Conflicts of interest

The authors have no conflict of interests to report.

not identifying as homosexual, non-white race, high school or less educational attainment, annual income < $10,000, tobacco use, slower gait speed, reported problems with balance, and poor social support. In subsequent adjusted analysis, the following variables were significantly associated with an abnormal MoCA score: not identifying as homosexual, non-white race, longer 4-meter walk time, and poor social support. Psychiatric symptoms of depressive, anxiety, and post-traumatic stress disorders did not correlate with abnormal MoCA scores.

Conclusions: Cognitive impairment remains common in older HIV-infected patients. Counter to expectations, co-morbid psychiatric symptoms were not associated with cognitive impairment, suggesting that cognitive impairment in this sample may be due to neurocognitive disorders, not due to other psychiatric illness. The other conditions associated with cognitive impairment in this sample may warrant separate clinical and social interventions to optimize patient outcomes.

Keywords

HIV; HIV-associated neurocognitive disorder; Montreal Cognitive Assessment (MoCA); psychiatric co-morbidity; functional assessment

Introduction

In the era of effective antiretroviral therapy (ART) and management of HIV infection as a chronic condition, the proportion of people living with HIV (PLWH) in the United States who are age 50 and older has steadily increased (Centers for Disease Control and Prevention, 2014). In addition to increased longevity, many older PLWH have experienced polypharmacy and multiple other comorbidities (Centers for Disease Control and Prevention, 2014). People living with HIV are particularly vulnerable to neurocognitive disorders and other psychiatric comorbidities (depressive, anxiety, post-traumatic stress, and substance use disorders (Valcour, 2013; Ances and Ellis, 2007; Wang *et al.*, 2013). Even when HIV viral load (VL) is reduced to undetectable levels, HIV infection is still associated with neurological deficits and brain atrophy beyond that expected with normal aging (Becker *et al.*, 2011; Heaton *et al.*, 2010; MacArthur, 2004; Sacktor *et al.*, 2002).

Neurocognitive disorders in people living with HIV

HIV-Associated Neurocognitive Disorders (HAND) include (in increasing order of severity of functional impairment by the Frascati criteria) Asymptomatic Neurocognitive Impairment (ANI), HIV-Associated Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD) (Watkins and Treisman, 2015; Tedaldi *et al.*, 2015). The increased risk of cognitive disorders in HIV-infected patients may be attributed to various factors. These include: prolonged exposure to ART (especially early, more neurotoxic versions of ART), age-related changes in ART neurotoxicity, HIV-related neurotoxicity, age-dependent acceleration of HIV pathogenesis, interaction of HIV infection with other age-dependent neurological diseases, drug-drug interactions, immune activation, advanced clinical stage of HIV disease, low CD4 count, low hemoglobin concentration, individual genetic factors, and endocrine and/or vascular disease (Watkins and Treisman, 2015; Valcour *et al.*, 2004; Hong and Banks, 2015; Wendelken and Valcour, 2012; McCutchan *et al.*, 2012; Sattler *et al.*, 2015; Njamnshi *et al.*, 2009; Olivier *et al.*, 2018). Worse neurocognitive status in HIV has been

associated with lower HIV-1 RNA levels in the CSF and discordance in HIV-1 RNA detection between plasma and CSF, consistent with a compartmentalization effect (Anderson *et al.*, 2017)

HAND is associated with depressive and anxiety symptoms, regardless of ART treatment status or types (Ances and Ellis, 2007; Ammassari *et al.*, 2004). ART-treated individuals have decreased risk of more severe cognitive impairment, such as in HAD (MacArthur, 2004; Nath *et al.*, 2008). However, as PLWH age, the risk of mild and asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorders (MND) has increased to over 50%, even among those optimally treated with ART, even though *overall* prevalence of HAND remains unchanged (Ances and Ellis, 2007; Heaton *et al.*, 2011). In the "HIV over 60" cohort study, among 75 study participants with HIV the prevalence rate of ANI was 23%; 28% had MND, and 3% had HAD (Valcour *et al.*, 2012).

Depressive disorders, even in the absence of abnormal cognitive function, are a risk factor for impaired neuropsychological performance in HIV patients and are associated with poor concentration as well as lack of interest and apathy, overlapping with symptoms of neurocognitive disorders (Ammassari *et al.*, 2004). In neurocognitive disorders, there is a bi-directional relationship with co-morbid psychiatric illness, as other psychiatric syndromes may antedate and/or follow the development of the neurocognitive disorders. Following the diagnosis of HAND, apathy, depression, and mania may develop and complicate the management of the neurocognitive disorder (Paul *et al.*, 2005). Anti-HIV medication with significant penetration of the blood-brain barrier may help to mitigate the risk of central nervous system (CNS) injury from HIV disease (Letendre *et al.*, 2009), although studies are inconsistent, as a recent study showed higher CNS penetration by medication was associated with worse cognitive performance (Rackstraw *et al.*, 2018).

Other psychiatric comorbidities in people living with HIV

In addition to neurocognitive disorders, other associated psychiatric illnesses in PLWH have been described since the 1980s (Hammond and Treisman, 2007). As part of an overall study of geriatric conditions in older PLWH, Greene et al (2015) reported that of 155 participants with a median age of 57 who were 94% male, 40% exhibited scores consistent with clinical depression on the Center of Epidemiological Studies Depression (CES-D) Scale; 22% had mild depressive symptoms and 18% had moderate-to-severe depressive symptoms. The Research on Older Adults with HIV (ROAH) study included one thousand adults age 50 or older living with HIV and found 52% had a prior history of depressive disorders; on the CES-D, 20% scored a moderate level of depression, while 43% scored severe levels (Applebaum and Brennan, 2009). Pre-HIV history of substance use, depressive, or bipolar disorder is common in patients with HIV disease and can increase risk of HAND (Atkinson *et al.*, 2009; Weber *et al.*, 2013). These findings are particularly relevant for older PLWH, as depressive disorders in this group may directly lead to impaired function irrespective of separately diagnosed neurocognitive disorders and can complicate the management of neurocognitive disorders (Owora, 2018; Tymchuk *et al.*, 2018; Cross *et al.*, 2013). In addition, in older patients, depressive disorders may primarily present with significant cognitive complaints, which can improve with antidepressant treatment. It is therefore

important for patients with apparent cognitive impairment to receive a full assessment and treatment for depressive disorders to optimize clinical and social functioning.

Other factors related to cognitive status in people living with HIV

Other variables may be of importance regarding neurocognitive disorders in older patients with HIV who are at risk for dementing illness. Due to the subcortical neuroanatomy of much of HIV dementing illness, the level of physical functioning in many domains (e.g., manual dexterity, mobility, ability to physically accomplish self-care tasks) may be impacted by dementing illness, even antedating the development of cognitive deficits (Watkins and Treisman, 2015; Eggers *et al.*, 2017; Kallianpur *et al.*, 2016). Therefore, targeted physical skills assessment may offer early signs of subcortical dementing illness.

Educational attainment appears to be a protective factor against dementing illness. Higher levels of educational attainment are associated with later onset of dementing illness and more functional preservation (Cross *et al.*, 2013; Noble *et al.*, 2017). Therefore, level of educational attainment (and other measures of presumed premorbid intellectual function) is important for any study of neurocognitive disorders.

Social support often correlates with better functional status (Vance 2013). While this relationship can be somewhat indirect (e.g., a socially isolated patient may have more difficulty getting to clinic services and thus may be poorly compliant with medication treatment for a chronic illness and have poorer clinical outcomes), it can nonetheless be of great pragmatic impact. Importantly, once identified, social interventions for isolated patients could then result in greater engagement in clinical care. Higher levels of neighborhood socioeconomic status have been associated with higher cognitive function (Rosso *et al.*, 2018). Conversely, other social comorbidities such as loneliness, poverty, and prolonged exposure to traumatic stimuli are associated with impaired cognitive function (Tedaldi *et al.*, 2015; Han *et al.*, 2017).

Regarding sexual orientation and risk of HAND, De Ronchi *et al.* (2002) reported a higher odds ratio for the development on HIV-associated neurocognitive disorders in homosexual or bisexual subjects vs heterosexual subjects. Flatt *et al.* (2018) found subjective cognitive decline in 25% of LGBT older adults; being a person of color, depressed, or reporting functional impairment were correlated with subjective cognitive decline.

Given the likely complex and bidirectional relationships among the many variables associated with HIV and cognitive status, the objectives of this study were to explore the association among several geriatric measures, including physical, psychiatric, and social health, and cognitive impairment among older PLWH. We hypothesized that individuals who scored poorly on our geriatric social, physical, functional, and other psychiatric assessments would be more likely to experience cognitive impairment.

Method

Study sample

The study participants for this investigation were enrolled in the "Silver Project," a demonstration project created to understand and improve the care of HIV-infected adults 50 years of age and older. Details of the "Silver Project" have been previously published (Greene *et al.*, 2018; John *et al.*, 2016; Hessol *et al.*, 2017). The "Silver Project" took place at two clinical sites, 1) the University of California, San Francisco (UCSF) 360 Clinic, an outpatient HIV clinic that serves privately and marginally insured patients (n = 162), and 2) Ward 86, based at Zuckerberg San Francisco General Hospital (ZSFGH), a publicly funded San Francisco clinic serving publically insured and uninsured patients (n = 197).

Recruitment

Study participants were recruited by clinician or self-referral from flyers. To be eligible for the study, the patients were required to be English speaking, 50 years and older, and have HIV. The study protocol was approved by the UCSF IRB. Participants were assigned an individual study identification number, which was used on data collection forms to maintain confidentiality. As compensation, participants received a gift card upon completion of the study.

Cognitive assessment

For this investigation, our primary independent variable was cognitive impairment, as measured by the Montreal Cognitive Assessment (MoCA) score. The 12 questions used in the MoCA cover visuospatial/executive cognition, naming, memory, attention, language, abstraction, delayed recall, and orientation (Nasreddine, 2010). The test is scored out of a total of 30 points; one point is added for individuals with 12 years or fewer of formal education for up to a maximum of 30 points (as per MoCA protocol), with a score of 26 points or greater considered normal (the usual recommended cutoff score), and a score of 0 to 25 indicating cognitive impairment (Nasreddine, 2010). For statistical analysis, the MoCA score was dichotomized as "no impairment" (≥ 26) or "impaired" (< 26) (Nasreddine, 2010).

The MoCA has been used for screening of HIV-associated neurocognitive disorders, with moderate performance characteristics for cognitive screening in older HIV patients (Milanini *et al.*, 2014). Fazeli *et al.* (2017) studied the MoCA for identification of HAND in HIV infected patients over 50 by comparing the results on MoCA to a comprehensive neuromedical and neurocognitive battery. This study founded a cutoff for cognitive impairment of MoCA score less than or equal to 26 to yield a sensitivity of 84.2% and specificity of 55.8%, acceptable for a screening instrument. Janssen *et al.* (2015) studied the MoCA in HIV infected patients (mean age 48) and found a sensitivity for identification on HAND of 56% and specificity of 63%with a cutoff of less than 26, felt by the authors to be inadequately sensitive and specific for diagnosis of HAND as a sole instrument. Joska *et al.* (2016) compared the MoCA and several other brief cognitive screening tools to a neuropsychological battery. Using a cutoff of less than or equal to 26, they found sensitivity of 89% and specificity of 22% for distinguishing normal from HAND; this was high sensitivity but weak specificity. Mukherjee *et al.* (2018) studied the MoCA (using a cutoff

score of less than or equal to 26) on both HIV-infected and HIV-negative controls. While this study did not report conventional sensitivity and specificity values, the MoCA at this cutoff score identified significant cognitive impairment in both cohorts (69.3% in HIV-infected, 59% in controls); following correction for demographic variables, these rates were reduced to 23% and 14%, respectively.

Non-cognitive psychiatric assessments

Depressive symptoms were measured using the Patient Health Questionnaire (PHQ-9). The PHQ-9 is derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD) screen and consists of 9 items, each scored from 0–3, for a total possible score of 27. A score of 0–4 indicates no depression, 5–9 is mild, 10–14 is moderate, 15–19 is moderately severe, and 20–27 is severe (Kroenke *et al.*, 2001). Anxiety was assessed using the Generalized Anxiety Disorder (GAD)-7. The GAD-7 is also derived from the PRIME-MD screen and consists of 7 items, each scored from 0–3, for a total possible score of 21. A score of 0–4 indicates no evidence of anxiety, 5–9 is mild anxiety, 10–14 is moderate anxiety, and 15–21 is severe anxiety (Spitzer *et al.*, 2006). Post-traumatic stress disorder (PTSD) was measured using the Breslau short 7-item screening scale and dichotomized and 0–3 (no or mild) and 4–8 (requiring further evaluation) (Bohnert and Breslau, 2011).

Other functional assessments

The Veterans Aging Cohort Study (VACS) index, which uses age, sex, race, CD4 count, HIV-1 RNA, liver fibrosis-4 score (FIB), hemoglobin, renal function (eGFR), and hepatitis C co-infection to predict 5-year mortality in a weighted fashion, was calculated (Justice *et al.*, 2010). Falls were assessed by asking the participants if they had fallen in the past 12 months and if they had balance problems in the past 12 months. Responses to each of these two questions were dichotomized as “yes” or “no.’” Mobility was measured by the time it took for a 4-meter walk (gait speed), in seconds, at the subject’s usual pace (Guralnik *et al.*, 2000).

Other functional impairment was measured by self-reported Activities of Daily Living (ADLs), such as dressing and bathing, based on the Katz Index (Katz *et al.*, 1963), scored from 0–6, with higher scores indicating higher dependence. Scores were dichotomized as zero (independent on all tasks) or >/ = 1 (dependent in one or more ADLs), as done in prior cohort studies of older HIV-infected adults (Greene *et al.*, 2015).

Additionally, functional impairment was self-reported using the Lawton Instrumental Activities of Daily Living (IADL) scale which assessed eight tasks, such as shopping, managing medications and housework that were scored 0 (dependent) or 1 (independent) with totals ranging from 0 (dependent in all activities) to 8 (independent in all activities) (Lawton and Brody, 1969). Scores were then dichotomized to 8 (fully independent) versus 7 or lower (dependent in one or more IADLs), as reported previously (Greene *et al.*, 2015).

Social assessments

In the social domain, self-reported loneliness was measured using the UCLA 8-item Loneliness Scale (ULS) (Hays and DiMatteo, 1987). The scores from the 8-item scale are

categorized by degrees of loneliness: none (8–16), mild (17–20), moderate (21–24), or severe (> 24) and in this analysis were dichotomized as none (8–16) versus all other (> 16). Physical social support was measured using the Lubben Social Network Scale (LSNS), which assessed the numbers of relationships with family and friends and was dichotomized as little support (< 12) or normal support (> 12) (Lubben 1988). Perceived social support was assessed using the Social Provisions Scale with higher scores (36–60) indicating lower perceived social support (Cutrona *et al.*, 1986).

Substance use assessment

The CAGE-Adapted to Include Drugs (AID) screening tool was used to identify problem alcohol or drug use and was dichotomized as low risk (0–1) or at risk for problematic use (2 or greater) (Dhalla and Kopec, 2007; Brown and Rounds, 1995).

Other assessments

Health-related quality of life (HRQoL) was measured using self-reported answers to the question “how would you rate your current health?” (with answers on a five-point Likert scale from “poor” to “excellent”) and dichotomized as “poor/fair” vs. “good/very good/ excellent.” This single item question has been shown to be a reliable tool to assess HRQoL among HIV-infected adults (Crane *et al.*, 2006).

Self-reported information on socio-demographic variables (age, sex, race, ethnicity, relationship status, education, employment, and income), sexual orientation, and tobacco use were collected and assessed in bivariate and multivariate models. Study participants also had chart reviews performed to obtain HIV viral load copies (< 40 copies/mL was the lower limit of detectability) and CD4 cell counts, using laboratory results which occurred closest to and within 6 months of the study visit date; most laboratory results were within a 1-month window of the clinical assessment. Self-reports from the year of first HIV positive test was used to calculate the duration of HIV infection. After the study visit, participants were given a score card detailing information obtained from these batteries. The participant was instructed to bring this scorecard to the next primary care appointment to customize the treatment plan. Participant results were discussed in a meeting to arrange referrals to a psychiatrist, geriatrician, pharmacist, and/or dietician.

Statistical analysis

For this cross-sectional study, unadjusted and adjusted modified Poisson regression analyses were used to calculate prevalence ratios (PRs) and 95% confidence intervals (95% CIs) for each covariate and its association with abnormal MoCA scores (< 26) (Spiegelman and Hertzmark, 2005). Adjusted models included covariates that were significantly associated ($p < 0.05$) with cognitive impairment in unadjusted analyses and were performed using manual stepwise regression using backward elimination. At each step, each remaining predictor was examined for deletion from the model, and the one with the largest p-value was removed, until all predictors had a p-value of < 0.10. Each candidate model was run separately to avoid excessive case-wise deletion of observations that had missing values on other unselected candidate predictors. All statistical analyses were performed using SAS® software, version 9.4 (SAS Institute, 2014).

Results

A total of 359 participants were included in these analyses, of whom 33.7% (38% at UCSF and 30% at ZSFGH) scored below 26 on the MoCA, consistent with cognitive impairment. The majority of study participants were under 60 years old (68%; 62% at UCSF and 73% at ZSFGH), white race (57%; 65% at UCSF and 51% at ZSFGH), male (85%; 91% at UCSF and 80% at ZSFGH), identified as homosexual (66%; 77% at UCSF and 56% at ZSFGH), had at least some college education (72%; 83% at UCSF and 62% at ZSFGH), were unemployed (83%; 73% at UCSF and 91% at ZSFGH), had undetectable HIV viral load (82%; 83% at UCSF and 81% at ZSFGH), and reported good, very good, or excellent general health (70%; 73% at UCSF and 68% at ZSFGH; Table 1). Ninety-eight percent of participants reported taking ART in the past 30 days (99% at UCSF and 97% at ZSFGH).

In unadjusted analyses, the following variables were associated with a significantly increased risk of an abnormal MoCA score: non-white race compared to white race (PR = 2.17, 95% CI 1.51–3.14), less than a high school education (PR = 1.97, 95% CI 1.24–3.14) or high school diploma/GED (PR = 1.62, 95% CI 1.04–2.54) compared to some college or more, income < $10,000 per year compared to > $20,000 per year (PR = 2.12, 95% CI 1.35–3.34), current smoker of tobacco (PR = 1.59, 95% CI 1.10–2.29), longer 4 meter walk time (PR = 1.19, 95% CI 1.09–1.31), reported problems with balance (PR = 1.60, 95% CI 1.12–2.30), and poor social support (PR = 1.95, 95% CI 1.32–2.87). Male compared to female and transgender (PR = 0.54, 95% CI 0.36–0.81), identifying as homosexual compared to all others (P = 0.50, 95% CI 0.35–0.71), and being employed (either full or part time, PR = 0.50, 95% CI 0.27–0.92) were associated with a significantly decreased risk of having an abnormal MoCA score.

In the final adjusted model, the following variables were associated with a significantly increased risk of having an abnormal MoCA score: non-white race compared to white race (PR = 1 .78, 95% CI 1.17–2.70), longer 4-meter walk time (PR = 1.16, 95% CI 1.05–1.28), and poor social support (PR = 1.72, 95% CI 1.16–2.57; Table 1, column 3). Identifying as homosexual was associated with a 37% decreased risk of an abnormal MoCA score (PR = 0.63, 95% CI 0.42–0.94).

Discussion

The Silver Project was designed to study HIV-infected patients over age 50 presenting for care in our two clinics. Evaluation of several psychiatric variables (including cognitive status) was accomplished along with assessment of other clinical, social and functional variables. This study measured the association of an abnormal MoCA score with the other psychiatric, physical, social, and functional variables.

In this study, one-third of the study participants scored < 26 on the MoCA, consistent with mild cognitive impairment. Beyond screening with MoCA and similar instruments (e.g.,MiniMental State Examination, International HIV Dementia Scale, Simoni Symptom Questionnaire, Cognitive Assessment Tool-Rapid Version), a clinical diagnosis of neurocognitive disorder(s) requires a full clinical history and mental status examination. A

MoCA score by itself cannot itself distinguish HIV-associated neurocognitive disorders from other dementing illnesses. The conventional MoCA cutoff score of less than 26 for cognitive impairment was chosen for purposes of consistency with the general medical literature and the objectives of the designers of the MoCA instrument. While this cutoff may result in some patients being identified as “cognitively impaired” who are nonetheless functioning well, identification of cases of possible cognitive impairment, warranting full clinical assessment, is accomplished by such a “conservative” cutoff.

At the 360 clinic, there was a biweekly multispecialty and multidisciplinary case conference (participants include clinical nursing, infectious disease physician, HIV nurse practitioner, geriatric medicine, and HIV consultation-liaison psychiatrist). All new Silver Project cases and clinical data were discussed. In this meeting, plans for management of cases (e.g., recommendations for medication streamlining and adjustment to reduce cognitive risk from medications, physical/occupational therapy assessment, and/or for full consultation(s) with geriatric medicine and/or psychiatry) were developed. Cases subsequently seen by psychiatry for diagnosis and intervention were thereafter comanaged with infectious disease physicians for follow-up and monitoring of cognitive status.

Both of the clinics in this study had ready access to HIV consultation-liaison psychiatry for further assessment for neurocognitive disorders as needed. Patients seen in consultation received a full psychiatric interview and mental status examination. Additional assessments, including consideration of other psychiatric illness(es) possibly impacting cognitive performance (e.g., depressive disorders, substance use disorders), full laboratory evaluation for reversible causes of dementia (e.g., B12, vitamin D, TSH), neuroimaging, and (in selected cases) neuropsychology assessment were accomplished before rendering a diagnosis of neurocognitive disorder.

One variable associated with a 16% increased risk for an abnormal MoCA score in the adjusted analyses was poor performance on the 4-meter walk. The effect size was small, but potentially of theoretical interest. This association between gait speed and an abnormal MoCA score may be a proxy for neurologic impairment/movement disorders, thus serving as a peripheral marker for neurocognitive impairment. Such an association between motor deficits and neurocognitive impairment is quite common in dementia syndromes with a “subcortical” pattern, such as HAND (with degenerative disease at or below the level of the basal ganglia, in contrast to “cortical” dementia, such as Alzheimer’s disease) (Kallianpur *et al.*, 2016; Eggers *et al.*, 2017; Watkins and Treisman 2015).

The association with homosexual identity and the 37% lower risk of cognitive impairment may be nonspecific or of uncertain significance. In San Francisco during the period of this investigation, 74% of PLWH were men who have sex with men (MSM), while another 15% were MSM who also inject drugs (San Francisco Department of Public Health Population Health Division, 2018); hence the HIV transmission category of patients seen at the two clinics included in this investigation were reflective of the city at large. It has been reported that HIV-infected heterosexuals may experience more internalized HIV stigma, potentially leading to increased social challenges in dealing with illness. This could in turn affect retention in HIV care, leading to less robust compliance with anti-HIV medication regimens

and greater risk of progression of HIV associated cognitive disorders, and poorer clinical outcomes (Lee *et al.*, 2002).

An additional risk factor for dementing illness is level of educational attainment. Our study design made only a tripartite split regarding educational attainment among less than high school completion, high school or GED completion, and some college or more. Such a limited range of education attainment levels does not account for the presumed protective effect of even higher levels of educational attainment (e.g., completion of undergraduate degree, graduate degree(s)) that could serve as an important confounding variable. This could be especially relevant for homosexual subjects who had a higher level of higher educational attainment than non-homosexuals, a variable not included in our study paradigm. We did not address level of intelligence per se (e.g., IQ test results) where higher premorbid IQ could have a protective effect on the risk of dementing illness. Similarly, our research paradigm did not specifically address other dementia risk factors (e.g., family history of Alzheimer's or Parkinson's disease, APOE-4 allele) that could have resulted in residual confounding.

Similarly, the association between non-white race and the 78% increased risk of cognitive impairment is consistent with the study of Cross *et al.* (2013) who found a significantly higher rate of HIV-associated neurocognitive disorders in African Americans. Conversely, this finding may be the result of residual confounding due to other unspecified risk factors, such as differential educational attainment and/or skill at test taking (including the MoCA) (Noble *et al.*, 2017; Jackson *et al.*, 2017). Non-white race association with dementing illness can be partially attributed to the higher risk of vascular disease in non-white persons, a variable that independently increases the risk of dementing illness irrespective of HIV status. Our educational level of attainment variable does not differentiate between a subject who completed more than 11 years of school vs one with much lower educational attainment. This is a potential confounder for those with very limited access to educational resources. Finally, we were unable to account for those for whom English is a second language, a factor that could have a major affect performance on test-taking and other putatively objective measures.

The strong and clinically meaningful effect size for the association between poor social support and a 72% increased risk of cognitive impairment may be either a cause or effect in the genesis of dementing illness (Green *et al.*, 2008; Sims *et al.*, 2011). Poor social support is often imprecisely defined and thus difficult to compare across studies. Some patients with poor social support are less able to comply with clinical care by being unable to get to clinic appointments This relationship can of course be reciprocal; patients with poor cognitive performance more likely to be reclusive with cognitive impairment leading to less ability or confidence when seeking systems of social support. The communication difficulties of cognitively impaired patients may also be implicated in discouraging social support. Finally, patients with progression of cognitive impairment from any cause are more likely to experience paranoia, itself adding to social isolation. Paranoia and other psychotic symptoms were not specifically assessed in our research paradigm.

In summary, the social variables we found to be associated with cognitive impairment (non-white race, not identifying as homosexual, and social isolation) may have a greater relevance for dynamic, functional cognitive status than is conventionally appreciated. Study designs looking at such variables with greater "granularity" (e.g., more gradations among educational attainment, formal IQ testing, attitudes towards HIV disease, assessment of other risk factors for dementing illness, assessment for psychotic symptoms) could allow more elaboration of these details and hence more useful inferences. Further, our findings suggest that clinicians assessing for neurocognitive disorders should attend to the impact of these social variables in neurocognitive disorders workups. It is conventional practice to fully assess for co-morbid psychiatric illness in cases presenting with apparent cognitive impairment; our study suggests that attention to certain social variables may be similarly germane in dementia assessments.

Abnormal MoCA scores can also result from other neurocognitive disorders (e.g., delirium) as well as other classes of psychiatric disorders (e.g., depressive disorders), which similarly require comprehensive clinical evaluation for diagnostic confidence. Somewhat counter to expectations, few of the other psychiatric, physical, functional, or health-related variables were associated with an abnormal MoCA score on multivariate analysis. For example, depressive disorders often are associated with mild decreased cognitive performance on cognitive assessment, yet the increased PHQ-9 (indicative of significant depressive symptoms) did not significantly correlate with abnormal MoCA scores.

While anxiety and depression symptoms were not significantly associated with cognitive impairment, their prevalence ratios were elevated and with a larger sample size might have achieved statistical significance. It is common to find mild-moderate psychiatric illness presenting with a slightly decreased MoCA score (which often improves with psychiatric treatment). The lack of association between the markers of physical health and lower MoCA scores may also be due to the small sample size as the prevalence ratios for these markers were also elevated. The elevated but not significant association among single relationship status and loneliness with cognitive impairment supports the premise that social isolation may lead to depression and thus may be indirectly involved in causing impaired cognitive status. Consistent with this association, we did find those with low social support to have a 72% higher likelihood of impaired cognition.

There have been recent papers on the topic of HIV-associated neurocognitive disorders published in *International Psychogeriatrics*. Foley et al (2011) conducted a study of 210 HIV patients using the updated HIV-Associated Neurocognitive Disorders (HAND) diagnostic algorithm, using a comprehensive neurocognitive assessment. In the Foley *et al*. study, 32.8% of subjects had normal cognition, 21.4% had ANI, 34.3% had MND, and 11.4% had HAD. Fernandes Filho and de Melo (2012) studied HAND and depressive symptoms in older HIV patients, using the Mini-Mental State Examination and International HIV Dementia Scale for cognitive assessment. They found neurocognitive disorders in 36.5% of their cases, with 13.5% patients having dementia. Depressive symptoms were found in 34.6%; patients with depressive symptoms had greater degrees of functional impairment. Brito e Silva *et al*. (2011) studied eight HIV dementia patients, average age 71 years. Mild dementia was present in 87.5%; the "classic HIV Dementia triad" of cognitive impairment,

other psychiatric symptoms, and motor impairment was seen in this patient group. While not a study of HIV patients, Hughes *et al.* (2013) found that greater engagement in social activities was associated with a slower rate of cognitive decline in older patients with minimal cognitive impairment.

Our paper extends the prior work on HIV-associated neurocognitive disorders recently published in *International Psychogeriatrics* by including a standard cognitive assessment as part of a comprehensive assessment of multiple psychiatric, general medical, and social variables in older HIV-infected patients presenting for initial care in HIV-specific clinics. Such a comprehensive “up front” evaluation facilitates early identification of cognitive impairment on MoCA and associated other variables. The result of this type of evaluation is likely to be early case finding and prompt multispecialty and multidisciplinary assessment prior to comprehensive and ongoing clinical care.

While the focus of this paper was the association of other study variables with cognitive impairment, the findings on other psychiatric rating scales deserve mention. The triad of neurocognitive disorders, other neuropsychiatric syndromes (e.g., depressive disorders), and substance use disorders have been commonly associated with HIV disease (Watkins and Treisman, 2012; Kopinsky *et al.*, 2007; Weber *et al.*, 2013). Unsurprising in a HIV-infected population, the rate of substance use disorders based on the CAGE-AID was 30.9% and the rate of depressive disorders based on the PHQ-9 was 26.5%. While these rates are higher than expected on a general population basis, these variables did not correlate with cognitive impairment per se, arguing against substance use disorders or depressive disorders playing either a “cause” or “effect” role vis-à-vis cognitive disorders in this cohort,

Similarly, the rates of anxiety disorders (per the GAD-7) and PTSD-spectrum disorders (per the Breslau instrument) were 18.7%and 12.3% (respectively), higher than anticipated on a population basis, but, again, not correlated with cognitive impairment, the main study variable. Per the National Comorbidity Survey Replication (NCS-R), the rates of substance use disorder, major depressive disorder, generalized anxiety disorder, and PTSD were 11.2%, 7.0%, 3.4%, and 5.3%, respectively, for male subjects aged 45–59 (the NCS-R categories most comparable to our sample cohort) (NCS-R, 2005). While these rates were not analyzed statistically as was the data from our sample, on the surface, these rates from our sample are notably higher than population expectation, and will be the subject of further study in future analyses of our data.

Our results contribute to the growing body of literature evaluating cognitive and functional deficits in older adults living with HIV. As such, the strengths of this study include a thorough multicomponent assessment with validated screening tools used, comprehensive medical record data capture of enrolled participants, and inclusion of participants at two large San Francisco clinics that provide clinically up-to-date comprehensive HIV care to two distinctively representative patient populations.

There are limitations to our study. As with all cross-sectional studies, causal relationships among the variables of interest cannot be ascertained and the directionality of these relationships may be complex. Also, we considered 30 candidate dummy variables in our

unadjusted models and with a threshold of 0.05 there is a 78% chance that type I error may have occurred. The number of women and those over 65 year old in our sample was very low, which make our results less generalizable to those groups. This study sample was recruited at two clinics based in San Francisco and the participants may not be representative of PLWH who are not in care or who reside in other locations.

Additional limitations include the lack of neuroimaging and full psychiatric examination to validate diagnosis of neurocognitive disorders. The usually recommended MoCA cutoff score that we used may have classified as “cognitively impaired” many patients who are nonetheless functioning well. A choice of a lower MoCA cutoff score would likely have led to different results, as different MoCA scores are associated with different sensitivity and specificity in identification of cognitive impairment (Larner, 2015; Luis *et al.*, 2009; Lees *et al.*, 2013). Standardized psychiatric rating scales cannot ascertain specific individual factors in the experience of depressive, anxiety, and/or posttraumatic stress disorders.

The cognitive impact of medications, particularly psychotropic medications, which are intended to be disease modifying for the respective psychiatric illnesses, was not considered. This could have variable impact. Antidepressants and mood stabilizers, which may improve psychiatric status and thus improve cognitive performance, may have a “positive” effect on MoCA scores, while many other medications (e.g., sedatives, GABAergics, anticholinergics, opioids) may negatively impact cognitive status and thus MoCA score. Other systemic medical conditions besides HIV disease (e.g., thyroid, parathyroid, rheumatologic disease) which can impact various levels of psychiatric function (including cognitive performance as indicated by MoCA score) were not explicitly considered as separate items. A diagnosis of HIV-associated cognitive disorder (or any neurocognitive disorder) cannot be diagnosed solely by MoCA score, but a low MoCA score should motivate the physician for more thorough diagnostic assessment of neurocognitive disorders.

Despite the above-mentioned limitations, the study contributes potentially valuable information about the prevalence of cognitive impairment among older PLWH, depressive, anxiety, and cognitive characteristics associated with an abnormal MoCA score, and the relationship between cognitive impairment and age-related outcomes. Assessments of neurocognitive disorders in older patients, especially medically frail patients, would do well to focus on the many possible clinical and social variables and/or complications associated with the diagnosis and clinical management of neurocognitive disorders. The need to assess for psychiatric co-morbidity in neurocognitive disorders is particularly important, as competent management of psychiatric comorbid illness may improve patient function.

We aimed to learn more about the association among geriatric measures, including physical, psychiatric, and social health, and cognitive impairment among older PLWH. Toward that goal, we observed that 34% of our study participants had evidence of possible cognitive impairment as measured by scoring < 26 on the MoCA, and in multivariate models, slower gait speed and lack of social support were associated with an increased risk of cognitive impairment. Directionality among plausibly associated clinical variables cannot be assessed with a cross-sectional design. Cognitive impairment in this population may warrant separate clinical and social interventions to optimize patient outcomes. For optimal patient care of

PLWH, neurocognitive disorders should be assessed in a comprehensive manner that includes separate ascertainment of other psychiatric and other co-morbid illnesses. Ongoing assessment of social support and interventions to address other needs is also warranted.

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Table 1.

Unadjusted and adjusted prevalence ratios for factors associated with impaired cognition (MoCA<26)*, Silver Project participants, San Francisco

OUTCOME	UNADJUSTED PREVALENCE RATIO (95% CONFIDENCE INTERVAL) FOR IMPAIRED COGNITION	ADJUSTED PREVALENCE RATIO (95% CONFIDENCE INTERVAL) FOR IMPAIRED COGNITION
Age 50–59 (*n* = 244) vs >60 (*n* = 115)	1.07 (0.73–1.58)	
Mean = 57.4		
Standard deviation = 5.9		
Non-white (*n* = 153) vs white (*n* = 204)	**2.17 (1.51–3.14)**	**1.78 (1.17–2.70)**
Latino (*n* = 38) vs non-Latino (*n* = 318)	1.29 (0.76–2.18)	
Male (*n* = 305) vs all other (*n* = 54)	**0.54 (0.36–0.81)**	
Homosexual (*n* = 234) vs other (heterosexual, bisexual, other; *n* = 123)	**0.50 (0.35–0.71)**	**0.63 (0.42–0.94)**
Single relationship (*n* = 249) vs. all other (committed but not married, domestic partnership or civil union, married, other; *n* = 109)	1.22 (0.81–1.82)	
Education		
< high school (*n* = 44)	**1.97 (1.24–3.14)**	
High school or GED (*n* = 58)	**1.62 (1.04–2.54)**	
Some college or more (*n* = 257)	1.00 (reference)	
Employed (full/part-time) (*n* = 60) vs not employed (*n* = 297)	**0.50 (0.27–0.92)**	
Income		
< $10,000/year (*n* = 98)	**2.12 (1.35–3.34)**	
$10,000-$20,000/year (*n* = 121)	0.99 (0.60–1.65)	
>$20,000/year (*n* = 116)	1.00 (reference)	
CD4 count 0–199 cells/microliter) (*n* = 38) vs CD4+ count ≥ 200 cells/microliter (*n* = 310)	1.10 (0.63–1.92)	
Mean = 526.2		
Standard deviation = 285.4		
HIV viral load > 999 copies/mL (*n* = 10) vs viral load < 1000 copies/mL (*n* = 331)	1.19 (0.44–3.23)	
Median=< 40 copies		
Interquartile range=<40 - <40		
VACS per 10 unit (*n* = 348)	1.02 (0.92–1.13)	

OUTCOME	UNADJUSTED PREVALENCE RATIO (95% CONFIDENCE INTERVAL) FOR IMPAIRED COGNITION	ADJUSTED PREVALENCE RATIO (95% CONFIDENCE INTERVAL) FOR IMPAIRED COGNITION
Mean = 33.1		
Standard deviation = 17.4		
Smokes tobacco (*n* = 109) vs non-smoker (*n* = 247)	**1.59 (1.10–2.29)**	
# Years HIV infected (*n* = 308)	1.01 (0.98–1.03)	
Mean = 21		
Standard deviation = 8.1		
4 meter walk (seconds, *n* = 353)	**1.19 (1.09–1.31)**	**1.16 (1.05–1.28)**
Mean = 4.5		
Standard deviation = 1.4		
At risk alcohol or drug use	1.10 (0.75–1.62)	
CAGE-AID >2 (*n* = 111) vs CAGE-AIDS <2		
(*n* = 238)		
Fallen in the past year (*n* = 145) vs no falls (*n* = 211)	1.23 (0.85–1.76)	
Problems with balance (*n* = 134) vs no balance problems (*n* = 222)	**1.60 (1.12–2.30)**	
Poor/fair general health (*n* = 106) vs good/very good/ excellent (*n* = 250)	1.21 (0.83–1.76)	
Low physical social support		
LSNS 0–12 (*n* = 179) vs LSNS >12 (*n* = 180)	1.38 (0.96–1.98)	
Mean = 12.9		
Standard deviation = 7.0		
Social support abnormal		
SPS 36–60 (*n* = 78) vs normal	**1.95 (1.32–2.87)**	**1.72 (1.16–2.57)**
(SPS <36, *n* = 270)		
Mean = 29.4		
Standard deviation = 9.0		
Anxiety		
abnormal GAD7 >9 (*n* = 67) vs normal GAD7	1.33 (0.87–2.04)	
<9 (*n* = 287)		
Mean = 5.4		

OUTCOME	UNADJUSTED PREVALENCE RATIO (95% CONFIDENCE INTERVAL) FOR IMPAIRED COGNITION	ADJUSTED PREVALENCE RATIO (95% CONFIDENCE INTERVAL) FOR IMPAIRED COGNITION
Standard deviation = 5.1		
Depressive Symptoms		
None/mild (PHQ-9 <10, *n* = 260)	1.0 (reference)	
Moderate (PHQ-9 10–14, *n* = 52)	1.17 (0.71–1.93)	
Severe (PHQ-9 15–27, *n* = 43)	1.34 (0.81–2.24)	
Mean = 7.0		
Standard deviation = 6.2		
Loneliness	1.32 (0.90–1.92)	
ULS 17–40 (*n* = 206) vs ULS <17 (*n* = 150)		
Mean = 18.0		
Standard deviation = 5.2		
PTSD score	0.86 (0.49–1.54)	
Abnormal 4–7 (*n* = 44) vs normal 0–3 (*n* = 307		
Mean = 0.85		
Standard deviation = 1.9		
Dependent in ≥ 1 ADL (*n* = 43) vs independent (*n* = 310)	1.59 (0.99–2.56)	
Mean = 0.25		
Standard deviation = 0.82		
Dependent in ≥ 1 IADL (*n* = 136) vs independent (*n* = 214)	1.37 (0.95–1.98)	
Mean = 6.9		
Standard deviation = 1.7		

Significant prevalence ratios are bolded.

*MoCA: mean = 26 standard deviation = 3.7

The mean MoCA for the entire sample was 26.1, standard deviation 3.7, median 27, and interquartile range 24–29.