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Elevated Rates of Mild Cognitive Impairment in HIV Disease

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Abstract

With the rising number of individuals in their 50s and 60s who are infected with HIV, concerns have emerged about possible increases in the rates of non-HIV-associated dementias. The current study examined the prevalence of mild cognitive impairment (MCI) in older HIV-infected adults, since MCI is an intermediate state between typical cognitive aging and dementia that emerges in this age range. Participants included 75 adults with HIV disease aged 50 years and older who were on cART and had undetectable plasma viral loads and 80 demographically similar HIV seronegative comparison subjects. Participants completed a research neuropsychological evaluation that was used to classify MCI according to the comprehensive diagnostic scheme described by Bondi et al. (2014). HIV-infected persons were over seven times more likely to have an MCI designation (16%) than their seronegative counterparts (2.5%). Within the HIV+ cohort, MCI had minimal overlap with diagnoses of Asymptomatic Neurocognitive Impairment and was significantly associated with older age, lower Karnofsky Scale of Performance Scores, and mild difficulties performing instrumental activities of daily living (iADLs). HIV infection in older adults is associated with a notably elevated concurrent risk of MCI, which may increase the likelihood of developing non-HIV-associated dementias as this population ages further.

Keywords

HIV; MCI; Neuropsychology; Cognitive aging

The prevalence of older adults (aged ≥ 50) living with HIV has grown considerably in recent years (CDC 2012) and is predicted to rise to well over 50% by 2020 (Brooks et al. 2012). Advancing age in HIV+ adults carries an increased risk for HIV-associated, Non-AIDS (HANA) conditions (e.g., cardiovascular disease) and problems in multiple organ systems,

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including the central nervous system (High et al. 2012). In parallel, HIV-associated neurocognitive disorders (HAND) have persisted in the era of combination antiretroviral therapy (cART; Heaton et al. 2010). Older HIV+ adults are at a particularly increased risk for HAND (Valcour et al. 2004). Taken together, these factors have raised concerns that the HIV population may be increasingly vulnerable to developing non-HIV-associated dementias such as Alzheimer's disease (AD).

Although controversial (Iudicello et al. 2012), there is some evidence to suggest that HIV may precipitate a neuropathological process similar to that observed in AD. Biomarkers such as beta amyloid (Green et al. 2005; cf. Ances et al. 2012) and tau (Brew et al. 2005) can be altered in HIV disease. Older HIV+ adults who are carriers of ApoE ε 4 may be at higher risk of HAND (Valcour et al. 2004), especially in combination with amyloid beta plaques (Soontornniyomkij et al. 2012). HIV-associated neuropathologies in the medial temporal region may contribute to declines in delayed episodic memory—a hallmark feature of AD (Maki et al. 2009; Moore et al. 2006). Nevertheless, extant studies focus on HIV-infected persons in their early 50s (Scott et al. 2011), which is younger than the typical age of onset for most non-HIV-associated dementias. Thus, one potential approach to determining the risk of older HIV+ adults for incipient dementia is to draw from the typical cognitive aging literature and determine whether HIV is associated with elevated rates of Mild Cognitive Impairment (MCI).

MCI is a transitional state between typical cognitive aging and dementia (Petersen 2004) that may be observed in persons in their 50s (Anstey et al. 2013). Prevalence estimates of MCI in seronegative older adults range from 5 to 20% (Hänninen et al. 2002; Lopez et al. 2003; Petersen et al. 2010). There are several potential benefits to exploring the relevance of the MCI diagnostic criteria to older HIV+ adults. First, these criteria have been applied with great success to clinical populations with frontal systems pathology—most notably Parkinson's disease (Geurtsen et al. 2014; Goldman and Litvan 2011). Second, there is long-standing controversy surrounding the optimal way to diagnose milder forms of neurocognitive disorders in HIV disease (for review, see Nightingale et al. 2014), arguments about which have regained momentum in recent years specifically in regards to the utility of Asymptomatic Neurocognitive Impairment (ANI) (Grant et al. 2014; Su et al. 2015). Thus, considering the wealth of evidence in support of the MCI criteria both in typical and pathological aging (e.g., Parkinson's disease), an examination of their application to older HIV+ adults seems well justified. Therefore, we aimed to estimate the concurrent risk of MCI in older HIV+ adults, in whom we sought to determine the clinicodemographic and real-world correlates of MCI.

Methods

Participants

The study sample included 155 participants aged 50 years and older who were recruited from the greater San Diego community and local, urban HIV clinics. HIV serostatus for 75 HIV-seropositive (HIV+) and 80 HIV-seronegative comparison individuals (HIV-) was confirmed using standard Western blot and/or a point-of-care test (MedMira Inc., Nova Scotia, Canada). All HIV+ participants were prescribed cART and had undetectable viral

loads. Participants were excluded if they had histories of psychosis, current psychiatric disorders (e.g., depression, substance use), major neuromedical conditions (e.g., head injury with loss of consciousness > 30 min, stroke, seizure disorder, multiple sclerosis, non-HIV-associated dementia), estimated verbal IQs below 70 on the Wechsler Test of Adult Reading (WTAR; Psychological Corporation 2001), or positive Breathalyzer or urine toxicology screens for illicit drugs (except marijuana) on the day of testing. Consistent with MCI research diagnostic criteria (Bondi et al. 2014), we also excluded participants with clinical functional impairment as operationalized by 2 or more areas of "dependence": (1) unemployment (not due to elective retirement), (2) endorsed clinically notable declines in instrumental activities of daily living (iADLs) on a modified form of the Lawton and Brody (Lawton and Brody 1969) ADL Scale (i.e., finance management, purchasing groceries, cooking, using transportation, shopping, medication management, and social activity planning; (3) endorsed clinically notable declines in basic activities of daily living (bADLs) on a modified form of the Lawton and Brody ADL scale (i.e., housekeeping/cleaning, laundry, home repairs, bathing, and dressing); or (4) scores < 90 on the Karnofsky Scale of Performance Status (Karnofsky and Burchenal 1949), which is a scale that has been applied previously in HIV samples (Gandhi et al. 2011; Morgan et al. 2012). Thus, by these criteria any participants with Minor Neurocognitive Disorder (MND) or HIV-associated Dementia (HAD) using the Frascati criteria for HAND (Antinori et al. 2007) were excluded. 73% (n=55) of HIV-infected individuals were cognitively normal and 27% (n=20) met Frascati criteria for ANI (Antinori et al. 2007).

Materials and Procedure

All participants provided written, informed consent prior to completing a comprehensive medical, psychiatric, and neuropsychological research evaluation for which they received nominal financial compensation. The university's human subjects committee (IRB protocol numbers 081481 and 071656) approved the parent study from which these participants were drawn.

All participants were administered a comprehensive neuropsychological test battery by certified research assistants. Measures for MCI group classification were selected from the larger battery in order to examine domains that are typically considered in the MCI literature, including (1) *delayed memory*, Logical Memory subtest from the Wechsler Memory Scale, 3rd edition (WMS-III; Psychological Corporation 1997) and the long-delay free recall trial of the California Verbal Learning Test, 2nd edition (CVLT-II; Delis et al. 2000); (2) *executive functions*, Trailmaking Test, Part B (Army Individual Test Battery 1994) and the total moves score from the Tower of London Test (Drexel Version; Culbertson and Zillmer 1999); (3) *language*, Boston Naming Test (BNT; Goodglass et al. 2001) and verbal (action) fluency test (see Piatt et al. 1999 and Woods et al. 2006 for further details); (4) *attention*, WMS-III Digit Span and CVLT-II Trial 1; and (5) *speed of information processing*, Trailmaking Test, Part A and the Total Execution Time from the Tower of London Test.

MCI designations were made using comprehensive neuropsychological criteria as described by Bondi et al. (2014), as these criteria provide a balance of sensitivity and specificity and

are less susceptible to false-positive errors than conventional diagnostic criteria (Edmonds et al. 2014). MCI designation was operationalized by endorsement of cognitive symptoms > 1 SD above the normative mean on the cognitive symptoms scale of the Profile of Mood States (POMS; McNair et al. 1981) *and* either (1) scoring > 1 SD below the mean of normative data on both neuropsychological measures within one or more domains or (2) scoring > 1 SD below the mean of normative data on one test in each of at least three cognitive domains. The group of participants with MCI was further divided by MCI subtype (Petersen 2004), including (1) single domain amnestic (impaired only in the domain of delayed memory), (2) single domain non-amnestic (impaired in one non-memory domain), (3) multiple domain amnestic (impaired in the domain of delayed memory and one or more domains), or (4) multiple domain non-amnestic (impaired in multiple non-memory domains).

Finally, we also generated traditional neurocognitive summary scores and Frascati diagnoses of ANI from the complete evaluation (see Woods et al. 2013), which included measures of motor skills (Grooved Pegboard; Heaton et al. 2004; Kløve 1963) and learning (WMS-III Logical Memory I and CVLT-II Total Trials 1-5) to round out the test battery detailed above. Individual normed T-scores were converted into deficit scores (range = 0 [normal] to 5 [severe]; see Carey et al. 2004 for details) and averaged to generate neurocognitive domain scores and a Global Deficit Score (GDS; Carey et al. 2004) that were used to determine ANI per Frascati criteria.

Results

Descriptive demographic and clinical information for HIV+ and HIV- individuals is shown in Table 1. There were no serostatus group differences on any demographic or clinical variables (*p*s>.10). As shown in Figure 1, a chi-square test of independence showed a significant association between HIV serostatus and the likelihood of having an MCI designation, χ^2 (1) = 9.36, p = .004. Specifically, HIV+ individuals were at 7.43 (95% confidence interval = 1.60, 34.42) times greater odds to have MCI designation (total percentage of 16%) than were HIV- individuals (total percentage of 2.5%). In the entire HIV + group, 7 subjects met the criteria for multiple domain non-amnestic MCI (58% of those with MCI, 11% of the HIV+ sample), and 5 subjects met the criteria for multiple domain amnestic MCI (42% of those with MCI, 8% of the HIV+ sample). None of the HIV+ individuals with MCI had single domain non-amnestic or single domain amnestic MCI.

Next, we examined the clinicodemographic factors from Table 1 and functional outcomes that might be associated with MCI in HIV. All continuous variables were non-normally distributed (all Shapiro-Wilk W Tests *p*s <.05) so non-parametric Wilcoxon rank-sums tests were used for analyses. Among the HIV+ individuals, an MCI designation was associated with older age (χ^2 (1) = 8.01, p = .006), whereby individuals over the age of 60 were at 6.62 (95% confidence interval = 1.77, 24.75) times greater odds to have MCI (see Figure 1). In addition, MCI designations among the HIV+ individuals were significantly associated with lower continuous Karnofsky Scale of Performance Status scores (χ^2 (1) = 5.12, p = .024, Hedge's g = -.33), and greater mean endorsement of decline from a previous level of iADL ability (χ^2 (1) = 4.48, p = .034, Hedge's g = .46), but not bADL (p = .57). No other clinical

or demographic variables listed in Table 1 differed between individuals with or without MCI among individuals with HIV (all *p*s > .05).

Finally, we were also interested in the extent to which MCI diagnoses were associated with global deficit scores (GDS) and Frascati ANI diagnoses. HIV+ individuals with MCI had significantly higher continuous GDS values than HIV+ participants without MCI (χ^2 (1) = 9.15, p = .003, Hedge's g = -.98). Given the possibility that premorbid factors may influence MCI designations, we also covaried education and premorbid IQ (i.e., WTAR) in this analysis, which did not dampen the strong association between MCI and GDS (t(1) = -3.74, p < .001). However, the association between MCI and ANI was characterized by only a slight rate of agreement (i.e., Kappa = .14; see Table 2). Among the 20 persons with ANI, 5 were designated as having MCI (i.e., rate of positive diagnostic agreement = .31). Among the 55 persons without ANI, 48 were designated as not having MCI (i.e., rate of negative diagnostic agreement = .81).

Discussion

With the rising prevalence of adults in their 50s and 60s living with HIV disease, concerns have emerged about possible increases in the future risk of non-HIV-associated dementias in this population. This study examined the possibility that older individuals with HIV may have higher rates of MCI, which is widely considered to be an intermediate stage between normal cognitive aging and dementia. Findings showed that HIV infection was associated with a considerably elevated concurrent risk of meeting research diagnostic criteria for MCI. In fact, HIV infected individuals had an over 7-fold greater odds of being diagnosed with MCI than their seronegative counterparts, which was not better accounted for by clinicodemographic factors—including mood and substance use disorders—as the groups were comparable on these variables. The prevalence rate of MCI for HIV+ adults ages 60 to 70 years in the present study was increased nearly 4-fold than the rate observed in typically aging cohorts of the same age (Anstey et al. 2013). MCI designations among HIV+ individuals were also associated with greater difficulties in iADLs, which may be indicative of an increased risk for incipient dementia.

HIV-infected individuals with MCI were exclusively classified as having multiple domain subtypes of MCI that, compared to single domain subtypes, often are associated with increased risk for developing dementias (Ganguli et al. 2011). The lack of HIV+ individuals designated as having a single domain subtype also suggests that the HIV+ individuals with MCI may have a relatively robust diagnostic profile of cognitive impairments, as single domain subtypes are more likely to revert back to normal functioning at follow-up compared to multiple domain MCI (Bickel et al. 2006; Summers et al. 2012). Studies of MCI in typically aging populations have suggested that a non-amnestic MCI designation is associated with an increased risk of developing either AD or non-AD dementias (e.g., vascular dementia; Busse et al. 2006; Ferman et al. 2013; Roberts et al. 2010). In turn, individuals with non-amnestic MCI evidence increased reversion to normal functioning (Ganguli et al. 2011). By way of contrast, amnestic MCI is thought to be more closely associated with progression specifically to AD (Damian et al. 2013). The equal prevalence of amnestic and non-amnestic MCI in the present study suggests that the specific dementia

syndrome to which HIV infected individuals may be vulnerable remains to be determined, as it is possible that MCI may confer a risk of AD or non-AD dementias, including HIV-associated dementia. Indeed, this interpretation is not inconsistent with previous studies in HIV, which have found that HIV-associated neurocognitive deficits do not necessarily fit those that are observed in "cortical" dementias (Iudicello et al. 2012). Future studies should apply cluster and discriminant analyses to examine the profiles of statistically determined MCI phenotypes in HIV, with particular emphasis on determining whether these phenotypes parallel the deficits indicative of frontal-subcortical or cortical profiles.

Our findings suggest that HIV infection increases the risk for having an MCI designation, which in typically aging cohorts is less prevalent for adults in their 60s than in relatively older groups (Anstey et al. 2013). The findings of the present study suggest that HIV+ individuals may undergo accelerated cognitive aging. It has been shown, for example, that HIV+ individuals showed a similar pattern and level of cognitive performance as much older seronegatives (Van Gorp et al. 1989). Indeed, the present sample of HIV+ individuals in their 60s had prevalence rates of MCI that were similar to those typically observed in seronegative adults aged 70 and over (Ward et al. 2012). These cognitive deficits in the cART era appear to be driven by a rise in the prevalence of impairment in memory and executive functions among HIV+ individuals who are medically asymptomatic (Heaton et al. 2011). Moreover, older HIV+ adults are less likely than their younger or seronegative counterparts to experience "successful" neurocognitive aging (e.g., Moore et al. 2014), which is related to poorer everyday functioning (Malaspina et al. 2011) and lower health-related quality of life (Moore et al. 2014). As such, as HIV infected individuals continue to age, it will be increasingly important to determine whether an increased risk for MCI in HIV consequentially confers an increased likelihood of developing non-HIV-related dementias and more severe declines in everyday functioning.

The clinical relevance of the MCI diagnosis in HIV is supported by evidence that HIV+ subjects with MCI had lower clinician-rated functional status and reported mild declines in iADL. Although preserved independence in everyday functioning is required for an MCI designation, studies examining everyday functioning in typically aging samples have found that mild deficits in iADL abilities often exist in MCI (Schmitter-Edgecombe et al. 2009) and may be associated with baseline risk for developing dementia (Reppermund et al. 2013). Accordingly, some diagnostic schemes allow for mild declines in iADL (Winblad et al. 2004) or subtle interference with function such that tasks require more effort or take more time than they did previously (American Psychiatric Association 2013). While an MCI designation in the HIV+ individuals was associated with increased age, there was no significant association between age and everyday functioning in the HIV+ sample as a whole nor with the HIV+ MCI group specifically (ps > .10). As such, these data suggest that having an MCI designation is related to increased age, but that the functional deficits reported by these individuals are not age-related. In HIV, iADL deficits have been found to be associated with neuropsychological impairment (Heaton et al. 2004), and iADL deficits may be attributable to memory decline due to shallow encoding in older adults with HIV (Fazeli et al. 2014). While the present findings should be interpreted cautiously regarding dementia risk, the neuropsychological and everyday functioning profile of HIV+ individuals

with MCI in the present study is consistent with those that are considered to be at risk for developing dementia syndromes.

There are several limitations to this retrospective cross-sectional study that deserve consideration. Studies of MCI often explore whether particular biomarkers predict MCI prevalence in typically aging individuals (Anstey et al. 2013). Future investigations into MCI in HIV may therefore wish to explore various biomarkers relevant to HIV and MCI (e.g., CSF beta amyloid or tau levels, MRI markers of neurodegeneration), as well as genetic factors such as ApoE ε 4. Future longitudinal studies should examine the candidate pathways through which an individual with HIV infection could conceivably reach an MCI designation. HIV infection may directly initiate a biological cascade that results in vascular involvement or increased risk of developing amyloid-β plaques and neurofibrillary tangles, as seen in AD. Another possibility is that the biological and cognitive insult of HIV infection may decrease an individual's cognitive reserve, and combined with the effects of normal aging and/or very early vascular or AD-type neuropathology, may cause the individual to pass a threshold of impairment in one or more cognitive domains. Although HIV-associated neuropathologies are predominately frontostriatal (Plessis et al. 2014), the hippocampus and other medial temporal lobe structures may also be vulnerable to HIV infection (Pfefferbaum et al. 2014). These latter findings are not inconsistent with those found in MCI, which implicate medial and inferior temporal lobes, as well as temporoparietal structures (Jak et al. 2009). Further, MCI criteria have been reliably applied to aging populations with diseases that include frontal systems pathology such as Parkinson's disease (Geurtsen et al. 2014; Goldman and Litvan 2011). Future studies should address whether HIV infected individuals with MCI are particularly susceptible to structural or functional alterations in these regions, as such evidence would highlight the clinical utility of these criteria in aging individuals with HIV. While one may question the extent to which the present findings apply to a broader and more diverse HIV population, such as to individuals not prescribed cART and with detectable viral loads who were excluded from the present study, these exclusion criteria may offer increased utility to clinicians, as older individuals with these health profiles more often present in clinical settings. Another limitation is that by virtue of being a retrospective study specifically in HIV, we did not include tests of spatial cognition, including visuoperception and visual memory; future studies should aim to address the question of whether these particular domains are affected in HIV—as they have been shown to be affected in aging MCI studies (Clark et al. 2013).

Finally, a few words about the extent to which consideration of MCI in HIV disease is warranted given the widely used Frascati criteria (Antinori et al. 2007). Indeed, there are presently controversies about the extent to which milder forms of HAND represent clinically valuable diagnostic entities (Nightingale et al. 2014). The current nomenclature for diagnosing asymptomatic HAND (ANI) requires intact daily functioning and neurocognitive deficits in at least two domains that are attributable to HIV-infection (Antinori et al. 2007; Blackstone et al. 2012). A recent longitudinal study by Grant et al. (2014) demonstrated that ANI is associated with an increased risk for earlier development of symptomatic HAND, which requires that HIV-associated deficits interfere with functional capabilities. The finding that MCI designations were highly associated with GDS suggests that the MCI criteria correspond to commonly used psychometric approaches in HIV; however, our data

also show that the two criteria-based methods of determining impairment have only a very slight correspondence. Although the negative diagnostic agreement was strong (81%), the positive diagnostic agreement was quite weak (31%) with only 25% of ANI subjects also meeting MCI criteria. In addition to MCI criteria being more liberal, there are domains considered by MCI criteria but not by ANI (i.e., language, visuoperception), and domains included in ANI criteria but not in those for MCI (e.g., motor), which warrant additional inquiries into whether MCI-specific domains decline due to HIV infection. A few additional findings increase our confidence that the elevated MCI risk observed in this HIV+ cohort is not simply an alternate manifestation of ANI. First, there were no significant associations between MCI and traditional HIV disease markers (e.g., nadir CD4); in fact, there are a growing number of studies in the cART era showing that clinical factors other than HIV disease severity are more strongly predictive of neurocognitive impairment in infected cohorts (Becker et al. 2009). Second, and relatedly, this was a well-managed HIV+ sample that was on effective cART, thereby further decreasing the likelihood that the MCI findings are exclusively an artifact of ANI. Finally, we observed a strong age-associated risk of MCI in this HIV+ group, which is interpretively important because age is historically the strongest risk factor for MCI among seronegatives (for review, see Mariani et al. 2007). Moreover, a post-hoc analysis showed that older age (over 60 years) was *not* associated with ANI in this elderly HIV+ group, χ^2 (1) = 0.15, p = .903, thereby providing some evidence of dissociability of key predictors for ANI and MCI. Nevertheless, determining the extent to which MCI criteria maintain poor sensitivity or superior specificity relative to existing criteria should be a point of emphasis in future studies. Thus, it remains an empirical question whether these related systems have current and prognostic clinical value, and future longitudinal investigations should determine the extent to which MCI criteria allow for better predictions of non-HIV related dementias in persons living with HIV infection.

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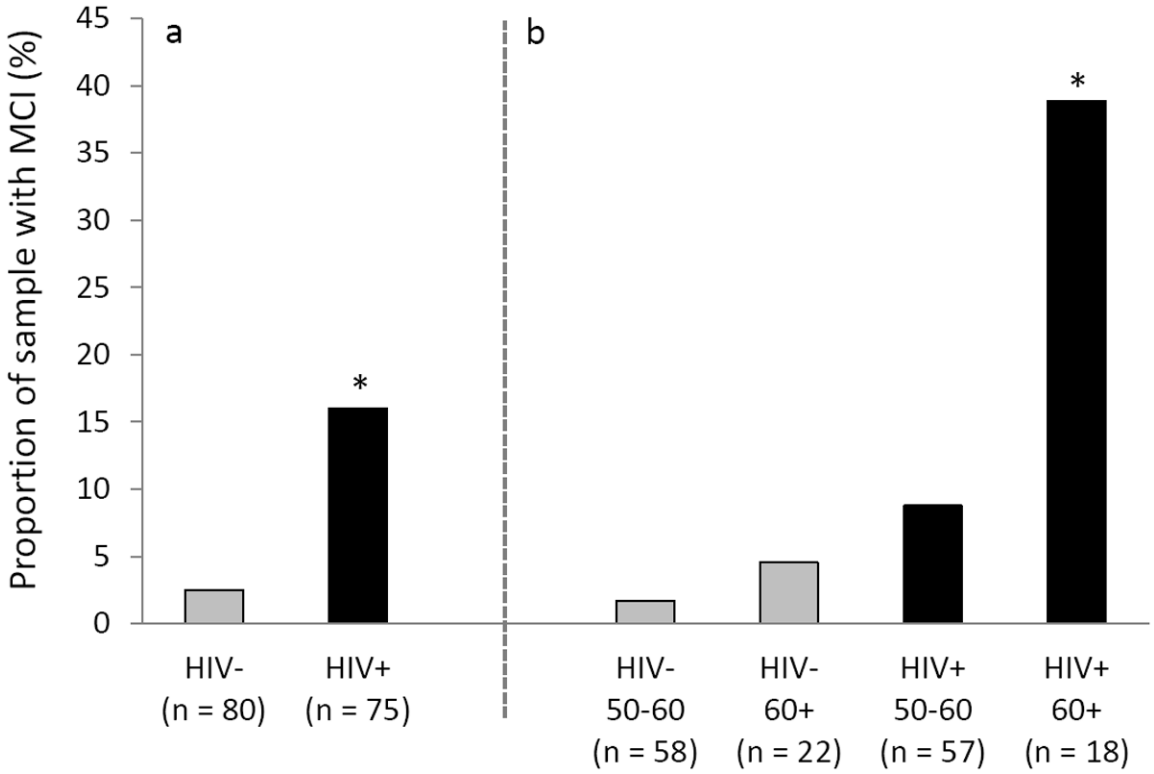

Fig. 1.

(a) Prevalence of MCI by HIV serostatus and (b) prevalence of MCI among serostatus by age group

* test is significant at $\alpha = 0.05$

Table 1

Mean (standard deviation) demographic and clinical information for HIV-Seronegative and HIV-Seropositive groups

Variable	HIV-Seronegative (n = 80)	HIV-Seropositive (n = 75)
Age (years)	56.71 (5.65)	56.38 (5.94)
Gender (% men)	73.75	84.00
Education (years)	14.50 (2.64)	14.28 (2.62)
Ethnicity		
Caucasian (%)	66.25	69.33
African American (%)	18.75	21.33
Hispanic (%)	13.75	9.33
Other (%)	1.25	0.00
Estimated verbal IQ (WTAR)	104.98 (10.12)	103.53 (12.19)
Major Depressive Disorder[a] (%)	33.75	41.33
Generalized Anxiety Disorder[a] (%)	5.00	10.67
POMS total (of 200)	40.97 (27.39)	46.82 (30.12)
Substance dependence[b] (%)	45.00	48.00
Medical		
HCV (%)	13.92	23.29
Estimated duration of infection (years)	--	16.81 (7.24)
Duration of regimen (months)	--	22.43 (21.71)
CPE Rank	--	5.63 (3.40)
Current CD4 count (cells/μL)	--	587.62 (327.74)
Nadir CD4 count (cells/μL)	--	155.27 (134.91)
AIDS (%)	--	65.33

Note. WTAR = Wechsler Test of Adult Reading; POMS = Profile of Mood States total mood disturbance score; HCV = hepatitis C virus; CPE Rank = CNS Penetration-Effectiveness Rank; CD4 = cluster of differentiation.

[a] Lifetime diagnosis.

[b] Any lifetime diagnosis of dependence on alcohol or illicit substances.

Table 2

MCI and asymptomatic neurocognitive impairment (ANI) designations for the HIV+ group

		ANI		
		Present	**Absent**	**Totals**
MCI	Present	5	7	12
	Absent	15	48	63
	Totals	20	55	75