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Identifying Risk Factors for HIV-Associated Neurocognitive Disorders Using the International HIV Dementia Scale

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Abstract

HIV-associated neurocognitive disorders (HAND) persist despite great advancements in combination antiretroviral therapy (cART). The gold standard for diagnosing cognitive impairment consists of a time-consuming neuropsychological battery of tests given by a trained neuropsychologist, however in the outpatient HIV clinic this is not feasible. The International HIV Dementia Scale (IHDS) was developed to help identify individuals with cognitive impairment in the outpatient setting. The IHDS is moderately sensitive for detecting more symptomatic forms of HAND but sensitivity has been shown to be poor in mild impairment. The IHDS has not been evaluated in developed countries in large cohort populations. We conducted a prospective cross-sectional study of only HIV+ individuals in an urban clinic and evaluated the prevalence of HAND and associated risk factors for cognitive impairment using the IHDS. A total of 507 HIV+ individuals participated in the study of which the majority were male (65%) and African American (68%); and 41% had cognitive impairment. On multivariate analysis, African American race ($p=2.21$), older age ($p=1.03$), high school education or less ($p=2.03$) and depression ($p=1.05$) were associated with cognitive impairment. The high prevalence of HAND in this group suggests that more severe forms of HAND persist despite cART. Identified risk factors were non-HIV-related and suggest that environmental and sociodemographic factors have a significant impact on cognitive functioning and should be given more attention. The IHDS should be further evaluated in large cohort HIV+ and HIV– populations in the United States, as there remains a significant need to identify an effective brief screening tool for cognitive impairment.

Keywords

HIV; International HIV Dementia Scale (IHDS); HIV associated neurocognitive disorders (HAND)

Introduction

HIV enters the brain soon after seroconversion and leads to cognitive impairment (Ances and Ellis 2007). HIV associated neurocognitive disorders (HAND) are still prevalent (~50%) despite combination antiretroviral therapy (cART) (Heaton et al. 2010). While HIV-associated dementia (HAD), the most severe form of HAND, has decreased in the era of cART, milder versions of HAND [i.e. asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND)] predominate (Gelman et al. 2013). Symptomatic HAND (MND and HAD) may lead to unemployment, social disability, medication non-adherence, and poor quality of life (Hinkin et al. 2002; Hinkin et al. 2004). This process may induce a vicious cycle whereby reduced medication adherence results in detectable viremia and subsequent cognitive decline (the Mind Exchange Working Group 2013).

Revised HAND criteria are based on neuropsychometric performance (NP) testing and activities of daily living (ADLs) (Antinori et al. 2007). Both ANI and MND patients have NP deficits of at least 1 standard deviation (SD) below the mean within at least 2 cognitive domains for demographically adjusted normative scores. The two disorders are differentiated by performance of ADLs: individuals with MND have mild ADL deficits while ANI individuals having no impairment in completing ADLs. HIV-infected (HIV+) individuals with HAD have marked NP impairment (> 2 SD within at least 2 domains) and diminished ability to perform ADLs. Detailed NP testing is required to fully assess cognition and this process is both laborious and should be performed by trained personnel (Zipursky et al. 2013; Robinson-Papp et al. 2009; Overton et al. 2013).

Several brief screening tools for HAND have therefore been proposed to identify cognitively impaired individuals in the outpatient HIV clinic setting (Valcour 2011). One test that has gained popularity, especially internationally, is the International HIV Dementia Scale (Sacktor et al. 2005; Njamnshi et al. 2009; Joska et al. 2011). The IHDS consists of 3 parts: timed finger tapping, timed alternating hand sequence test, and recall of four items after two minutes. A perfect score is 12 and is derived from a maximum of 4 points from the 3 parts. The IHDS can be easily administered and has been extensively used in resource-limited settings. A score ≥ 10 has a sensitivity of 74% in identifying symptomatic HAND (Haddow et al. 2013). The IHDS has not been extensively evaluated in developed countries with the few studies performed consisting of relatively small cohorts (<100 HIV+ individuals) (Sacktor et al. 2005; Joska et al. 2011; Muniyandi et al. 2012).

Several risk factors have been associated with an increased risk of developing HAND. Previous studies have demonstrated that older age (Valcour et al. 2004), lower nadir CD4+ cell count (Ellis et al. 2011), metabolic syndrome (McCutchan et al. 2012), depression (Heaton et al. 2011), and hepatitis C co-infection (HCV) (Cherner et al. 2005) are associated with HAND. Socio-demographic factors such as age, race and education may also influence the likelihood of developing HAND. However, most studies have been conducted in research populations and not clinical cohorts that are more representative of the general HIV + community. The ability to identify HIV+ individuals at increased risk for cognitive decline may influence the choice of cART (Cysique et al. 2009).

We conducted a large prospective, cross-sectional study of only HIV+ individuals engaged in care at the Washington University in Saint Louis (WUSTL) infectious disease clinic. We evaluated the prevalence of HAND using the IHDS and identified potential risk factors associated with cognitive impairment in this HIV+ cohort.

Methods

Study population

Only HIV+ individuals 18 years old who presented for medical care between June and December 2008 were eligible for participation. In order to capture this clinic population, no exclusion criteria were employed. Informed consent was obtained from all individuals who agreed to participate in this study using forms approved by the WUSTL institutional review board.

Clinical and laboratory data

Clinical, medication data, laboratory data [e.g. current and nadir plasma CD4+ cell counts and plasma HIV viral load (VL)] and comorbid conditions were reviewed from available medical records. HCV was defined as seropositivity for hepatitis C antibody. Nadir CD4+ cell count was the lowest reported by the individual or was obtained from referral records or from laboratory data if care was at the WUSTL infectious disease clinic. Viral suppression was defined as plasma HIV RNA < 50 copies/mL.

International HIV Dementia Scale (IHDS)

Cognitive impairment was assessed by trained personnel using the IHDS. All scores ranged from 0–12 with a lower score reflecting greater cognitive impairment. First the examiner recited four words and asked the individual to immediately repeat the words. Four words were repeated by the examiner until the individual recited them correctly. Finger tapping was then assessed by counting the number of finger taps by the first and second fingers of the non-dominant hand during a 5 second period. Individuals were instructed to open and close the fingers as widely and quickly as possible during this period. A 4 point scale was used and greater than or equal to fifteen taps was considered normal. For the alternating hand test, individuals clenched his/her hand in a fist on a flat surface, then put the hand palm down flat on the surface, and finally put the hand perpendicular to the flat surface with the fifth digit against the surface. This was first demonstrated by the examiner, and the individual was allowed to practice this twice before performing the test over 10 seconds. A four point scale is used with four sequences in 10 seconds considered normal. After the finger tapping and alternating hand sequence subtests, the individual was then asked to recall the 4 words. For words not recalled, the instructor prompted the individual with a clue, such as “color” for the word red. The individual earned a half-point for a word that was recalled after receiving a clue. The number of words recalled was scored, with 4 being the highest score. Based on previous results, a score of 10 or less was indicative of cognitive impairment (Sacktor et al. 2005).

Questionnaires

Surveys were administered by trained interviewers while HIV+ individuals waited for their appointments. Interviewers were present throughout the study period. Questions assessed sociodemographic factors (race/ethnicity, employment status, level of education completed, and annual income), depressive symptoms using the Patient Health Questionnaire 9 (PHQ-9) (Tozzi et al. 2003), and risk behaviors (Risk Behavior Assessment) (Needle et al 1995). In particular, questions focused on consumption of alcohol (units consumed during a typical week), illicit drug use (within the last week/thirty days/twelve months/ever), current or past tobacco use, and sexual behaviors (current sexual relationship, recent sexual activity, condom use, type of sexual encounter, and number of sexual partners). Excess alcohol intake was defined as greater than seven drinks per week for women and greater than fourteen drinks per week for men (Centers for Disease Control and Prevention 2004; United States Department of Agriculture 2005). Major depression was defined by a score ≥ 10 on the PHQ-9 (Kroenke et al. 2001).

Antiretroviral therapy

cART was defined as three or more active antiretroviral agents from at least two classes. Antiretroviral treatment regimens were classified for central nervous system-penetrating effectiveness (CPE) using revised criteria (Letendre et al. 2010). Antiretrovirals were placed into one of four categories, with a score of 1 representing poorest penetration and a score of 4 representing significant penetration. A CPE score was calculated as the sum of the rankings for each drug in the individual's regimen. A high CPE scores was defined as ≥ 7 .

Statistical Analysis

Univariate analysis—Descriptive statistics were used to compare characteristics between cognitively impaired and cognitively unimpaired individuals using the IHDS score. All non-normally and normally distributed continuous variables were reported as medians with interquartile ranges (IQR) or means and standard error of the mean (SEM). Associations with cognitive impairment were assessed using the chi-square test for categorical variables. For normally distributed and non-normally distributed continuous variables, student's t-test and Mann-Whitney U tests were used, respectively. All p -values were 2-tailed and considered significant at $p < 0.05$. The variables education, employment, and income were dichotomized into $\leq$ high school vs. $>$ high school, employed vs. unemployed/disabled, and $\leq$ \$10,000/year and $>$ \$10,000/year, respectively.

Multivariate analysis—Variables associated with cognitive impairment at a p -values of < 0.10 in the univariate analysis were initially included in a multivariate logistic regression model. Variables which were non-significant in this multivariate model ($p < 0.05$) were then eliminated and the model refit. The Hosmer-Lemeshow test was used to assess the model's calibration (goodness of fit) (Hosmer et al. 1997). All analyses were performed using SPSS version 20.0 (Chicago, IL).

Results

From a sample of ~ 700 eligible HIV+ individuals, 507 were enrolled in to the study. No significant differences in race, sex, or education existed between individuals who did or did not participate. Of those who enrolled, the median age was 42 years (IQR 33–49) with a majority being male (65%) and African-American (68%) (Table 1). Most individuals who participated had at least a high school level education (55%), earned < \$10,000 per year (57%), and were unemployed or disabled (55%). Most of the participants were taking cART (~75%) and had suppressed plasma VL (< 50 copies) (67%). The median duration of HIV infection was 8 years and the median CD4+ cell count was 433 cells/mm³. A large proportion of participants was either current or former tobacco users (67%) and drank 2 alcoholic drinks per week. Marijuana was the most commonly used drug (64%). A percentage of participants were HCV+(11%). PHQ-9 score indicated that ~30 %t had major depression.

Overall, 41% of individuals had cognitive impairment. African American race was significantly associated with cognitive dysfunction ($p=0.03$). Higher education (at least some college), active employment, and an income > \$10,000 per year were protective (Table 2). A higher CPE was not associated with a higher IHDS score. Current or nadir CD4 cell count did not predict impairment. However participants with a nadir CD4 cell count < 200 cells/mm³ were more likely to be impaired ($p=0.06$). Smoking was also associated with cognitive impairment ($p=0.01$). No associations were observed between use of marijuana, cocaine, opiates, or methamphetamine and cognitive performance. Surprisingly, a history of ecstasy use was associated with a higher IHDS score.

While income was significant using a univariate analysis, this variable was not included in subsequent analyses due to missing data for some participants. On multivariate analysis, older age (adjusted odds ratio (aOR) 1.03; 95% confidence interval (CI) 1.02–1.05); African American race (aOR 2.21; 95% CI 1.41–3.46); high school education (aOR 2.03; 95% CI 1.36–3.23); and depression as determined by PHQ-9 score (aOR 1.05; 95% CI 1.02–1.09) were independently associated with cognitive impairment (Table 2).

Discussion

Using the IHDS, we performed a prospective cross-sectional study to investigate the prevalence of HAND and identify risk factors associated with cognitive impairment among HIV+ individuals who attend a general infectious disease clinic. Within this predominately middle-aged African American, male population with well-controlled HIV infection, symptomatic HAND remained highly prevalent (41%). Risk factors associated with cognitive impairment were older age, African-American race, lower education, and depression but not HIV laboratory measures (i.e. plasma CD4+ cell count or viral load).

The observed prevalence of HAND in this HIV+ cohort falls within the wide range reported in the literature (18–73%) (Zipursky et al. 2013; Haddow et al. 2013). The IHDS primarily captures more severe forms of symptomatic HAND (MND and HAD) and is insensitive for detecting milder forms (i.e. ANI). Notably, research studies in the United States that have

used formal neuropsychometric endpoints have observed a stable overall prevalence of HAND with greater preponderance of milder forms (Heaton et al. 2010; Lescure et al. 2011). However, these studies often do not represent the general HIV+ population in terms of sociodemographics and lifestyle behaviors (Sacktor et al. 2005; Becker et al. 2011; Overton et al. 2011; Richardson et al. 2005). Our study population was unique in that it was composed of all potential HIV+ individuals who attended a general infectious disease clinic. No exclusion criteria were utilized with participation offered to every patient that presented to the clinic. The relatively high prevalence of HAND in this group suggests that more severe forms of symptomatic cognitive impairment continue to occur despite cART and suppressed viremia. Interestingly, traditional risk factors for impaired cognition (age, race, education, depression, and income) were independently associated with cognitive dysfunction rather than HIV-specific parameters (i.e. HIV VL, CD4+ cell counts, or specific antiretrovirals). With the HIV epidemic in the United States now evolving into a disease affecting a greater proportion of individuals from lower socioeconomic status, these non-HIV factors may require additional attention.

The IHDS has limitations. A recent meta-analysis performed by Zipursky et al (2013) reported that the pooled sensitivity of the IHDS for detecting HAND was 0.62, and the general conclusion was that the IHDS is not an ideal tool for detecting HAND (Zipursky et al. 2013). Of the four studies included in that meta-analysis (Joska et al. 2011; Muniyandi et al. 2012; Sacktor et al. 2005; Singh et al. 2008), only one was performed in the United States. For all these studies, the numbers of participants included was small. The IHDS is relatively easy to administer, does not require a trained neuropsychometrist, and only takes a couple of minutes to complete. Additional applications of the IHDS, especially within the United States, are needed as portions of this test could still be useful for comparing across different cultures (Sacktor et al. 2005). Comparisons between the IHDS and formal neuropsychometric testing are still warranted.

In our study, African Americans had a higher prevalence of cognitive impairment. This racial group comprises 44% of all incident HIV infections while only comprising 13% of the entire US population (An et al. 2012). However, few studies have focused on the role of race as a potential risk factor for developing cognitive impairment. While race can be associated with potential confounders such as lower socioeconomic and educational level, we demonstrated that African American race was independently associated with HAND. These results are in agreement with previous studies that have shown that African American race is associated with cognitive impairment in the general population (Hawkins et al. 2012; Katz et al. 2012; Unverzagt 2011). Metabolic comorbidities, including cardiovascular disease and diabetes, are also more common in the African American population (Ford 2013). These comorbidities can further increase the risk of cognitive impairment (McCutchan et al. 2012; Fabbiani et al. 2013). Concerted efforts should focus not only on improving access to care and cognitive testing for HIV+ African American individuals, but also metabolic syndrome risk factors.

Low education attainment and unemployment were also associated with cognitive impairment in this study. Education may be a proxy for cognitive reserve and the mind's resiliency to neuropathologic damage. Cognitive reserve has been extensively studied within

the HIV+ population. In a cross-sectional analysis Stern and colleagues (Stern et al. 1996) demonstrated that HIV+ individuals with lower cognitive reserve had worse neuropsychometric performance. Longitudinal examination of HIV+ individuals (Basso and Bornstein 2000) has shown that individuals with more education (> 12 years) had less decline in executive performance over one year (Basso and Bornstein 2000). Recently Morgan and colleagues have demonstrated that HIV+ individuals with symptomatic HAND (i.e. MND and HAD) had reduced cognitive reserve compared to ANI or cognitively normal HIV+ participants (Morgan et al. 2012). These studies suggest that individuals with higher educational attainment can continue to function despite sustaining insults to cognitive ability due to HIV or associated factors (Andel et al. 2006; Basso and Bornstein 2000).

The association between unemployment and cognitive impairment has been recognized with HIV infection. Heaton et al (1994) performed a cross-sectional analysis on a group of 232 HIV-infected individuals and found that 8% of the cognitively unimpaired were unemployed compared to 18% unemployment in cognitively impaired individuals. These findings have been reinforced in subsequent studies (van Gorp et al. 1999, Kalechstein et al. 2003). We also observed that unemployed HIV+ individuals had higher rates of symptomatic HAND (i.e. MND and HAD). The exact etiology remains unknown but this may reflect differences in education or other unknown factors. Nevertheless, with a greater proportion of HIV+ individuals being unemployed, we may continue to see an unfortunate negative synergy with an ongoing increase in cognitive impairment in this population.

Depression was also independently associated with HAND in this study. Previously, Stern and colleagues have shown that cognitively normal HIV+ individuals with depression had an increased risk of developing HAND. Depression is a common feature of HAND and may precede the development of symptomatic cognitive impairment (Stern et al. 2001). The CHARTER study, a multi-center cohort that assesses cognitive impairment in HIV+ individuals, demonstrated that depressive symptoms are associated with cognitive impairment (Heaton et al. 2011) and may be a confounder impacting neuropsychometric testing performance (Antinori et al. 2007). Thus, it may be difficult to differentiate the effects of depression from HAND on neuropsychological performance (Cysique et al. 2007). If depression is an important variable associated with cognitive impairment, appropriate medical interventions should be considered.

Older age was also associated with cognitive impairment in this cohort. The effects of HIV and aging have been extensively studied (Robertson et al. 2007, Valcour et al. 2004, Kissel et al. 2005). HAD is more frequent in older HIV+ individuals (Valcour 2004) and advancing age is an important risk factor for dementia in HIV-seronegative individuals (Jorm and Jolley 1998). Research has focused on the potential interactions between HIV and aging on neuropsychometric performance. Within both longitudinal (Valcour et al. 2011) and cross sectional (Robertson et al. 2007, Kissel et al. 2005) analyses of HIV+ individuals, no interaction between age and neuropsychometric performance was observed. Age-related comorbidities as opposed to HIV-related factors could be responsible for the association between age and HAND.

Our current study had several limitations. We only included HIV+ individuals and did not have a HIV seronegative control group for comparison. However, the IHDS has been previously studied across a range of ages and does not require correction for age or education. Second, a formal neuropsychometric battery was not administered so comparisons to other studies could not be performed. Third, assessment of activities of daily living were not obtained, therefore limiting our ability to apply formal HAND criteria. Fourth, this study was cross-sectional. Larger, prospective studies of similar size are required. Finally, this study was performed in an urban academic center and results may not be generalizable to other HIV+ populations.

In conclusion, despite remarkable advancements in the cART era, HAND continues to be highly prevalent with potentially significant consequences including medication non-adherence and rebound HIV viremia. There remains a great need to identify an effective brief screening tool for cognitive impairment. Additionally, key risk factors for impairment need to be recognized so that at-risk patients are screened early and closely monitored. Larger longitudinal studies of HIV+ patients in the United States need to be performed using the IHDS and comparing results to formal neuropsychometric performance testing.

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Table 1

Characteristics of participants by cognitive impairment status according to IHDS score.

Characteristic, n (%)		<i>Cognitive Impairment present</i>	<i>Cognitive impairment absent</i>	
	All patients (n =507)	n = 209	n =298	P-value
<i>Demographics, n (%)</i>				
Age (years) *	42 (33–49)	44 (38–51)	41 (30–47)	<0.001
> 50 years	121 (24)	63 (30)	58 (19)	0.005
Male sex	329 (65)	144 (69)	185 (62)	0.113
<i>Sociodemographics, n (%)</i>				
Race				0.03
African American	351 (69)	159 (76)	192 (64)	
Caucasian	130 (26)	40 (19)	90 (30)	
Other [‡]	26 (5)	10 (5)	16 (5)	
Education				0.001
High School	279 (55)	135 (65)	144 (48)	
Some college	156 (31)	55 (26)	101 (34)	
Bachelor's degree or more	72 (14)	19 (9)	53 (18)	
Employment				<0.001
Unemployed	139 (27)	56 (27)	83 (28)	
Disabled	142 (28)	79 (38)	63 (30)	
Employed	206 (41)	66 (32)	140 (47)	
Annual income (n=489)				0.022
< \$10,000	279 (57)	124 (62)	155 (54)	
\$10,000–49,999	179 (37)	70 (35)	109 (38)	
\$50,000+	31 (6)	6 (3)	25 (9)	
<i>HIV-related variables, n (%)</i>				
Current-CD4+, cells/mm ³ *	433 (248–618)	403 (226–626)	439 (254–616)	0.64
CD4+ count < 200 cells/mm ³	96 (19)	46 (22)	50 (17)	0.14
CD4+ nadir, cells/mm ³ *	190 (53–344)	150 (34–319)	212 (64–349)	0.308
CD4+ nadir < 200 cells/mm ³	265 (52)	120 (57)	145 (50)	0.062
Duration of HIV infection, years *	8 (3–12)	8.88 ± 0.43	7.95 ± 0.36	0.10
On cART	380 (75)	160 (77)	220 (74)	0.28
CPE Rank [†]	7.18 ± 0.08	7.36 ± 0.14	7.05 ± 0.11	0.077
CNS penetrating regimen [§]	123 (32)	54 (34)	69 (31)	0.66

Characteristic, n (%)		<i>Cognitive Impairment present</i>	<i>Cognitive impairment absent</i>	
	All patients (n =507)	n = 209	n =298	P-value
Full viral suppression	255 (67)	103 (64)	152 (69)	0.38
<i>Lifestyle behaviors, n (%)</i>				
Tobacco use				
Ever smoked	339 (67)	153 (73)	186 (62)	0.01
Alcohol				
Total drinks/week *	2 (0–6)	1 (0–5)	2 (0–6)	0.509
Excess intake	65 (13)	25 (12)	40 (13)	0.38
Drug use				
Drug use ever	350 (69)	150 (72)	200 (67)	0.264
Drug use past thirty days	151 (30)	69 (33)	82 (29)	0.18
Marijuana use ever	326 (64)	139 (67)	187 (63)	0.40
Marijuana last thirty days	132 (26)	56 (27)	76 (26)	0.76
Cocaine use ever	149 (29)	63 (30)	86 (29)	0.77
Methamphetamine ever	37 (7)	15 (7)	22 (7)	1.00
Opiates ever	37 (7)	18 (9)	19 (6)	0.387
Inhalants ever	53 (10)	20 (10)	33 (11)	0.66
Ecstasy ever	43 (8)	8 (4)	35 (12)	0.001
<i>Comorbidities, n (%)</i>				
PHQ-9 Score*	5 (1–11)	7.6 ± 0.45	5.75 ± 0.33	0.001
Major Depression	144 (28)	76 (36)	68 (23)	0.001
Hepatitis C seropositivity	55 (11)	32 (15)	23 (8)	0.007
Statin use	43 (9)	22 (11)	21 (7)	0.195

* Median (Interquartile range)

† Mean ± standard error of mean

‡ Includes Hispanic (12), bi/multi-racial (5), American Indian (2), Asian (1), and unspecified (6)

§ CPE penetrating regimen: combined CPE score of 7

Table 2
Factors independently associated with cognitive impairment versus no cognitive impairment

Characteristics	Cognitive impairment (n =209)	No cognitive impairment (n =298)	Univariate analysis Cognitive Impairment versus no Cognitive Impairment			Multivariate analysis Cognitive Impairment versus no Cognitive Impairment		
			OR	95% CI	p-value	aOR	95% CI	p-value
<i>Sociodemographics, n</i>								
Age, years*	44 (38–51)	41 (30–47)			<0.001	1.03	1.02–1.05	<0.001
Male sex	144 (69%)	185 (62%)	1.35	0.93–1.97	0.113			
African American race	159 (76%)	192 (62%)	1.76	1.18–2.61	0.005	2.21	1.41–3.46	0.001
Unemployed/disabled	135 (65%)	146 (49%)	1.90	1.35–2.75	0.001			
High school education	144 (69%)	162 (54%)	1.88	1.29–2.72	0.001	2.03	1.36–3.23	<0.001
Income <\$10,000/year (n=489)	124 (62%)	155 (54%)	1.41	0.98–2.04	0.07			
<i>HIV-related, n</i>								
Current CD4+ count, cells/mm ³ *	403 (248–618)	439 (254–616)			0.64			
CD4+ nadir, cells/mm ³ *	150 (34–319)	212 (64–349)			0.31			
CD4+ nadir <200 cells/mm ³ *	120 (57%)	145 (50%)	0.71	0.50–1.02	0.06			
Duration of HIV infection, years*	8 (3.3–13)	7 (2.4–12)			0.10			
On cART	160 (77%)	220 (74%)	0.86	0.57–1.30	0.49			
CPE Rank [†]	7.36 ± 0.08	7.05 ± 0.11			0.08			
<i>Lifestyle behaviors</i>								
Ever smoked	153 (73%)	186 (62%)	1.65	1.12–2.42	0.01			
Total drinks alcohol/week*	1 (0–5)	2 (0–6)			0.51			
Drug use ever	150 (72%)	200 (67%)	1.25	0.85–1.83	0.28			
<i>Comorbidities</i>								
Major depression	76 (36%)	68 (23%)	1.93	1.31–2.86	0.001			
PHQ-9 score*	6 (2–12)	4 (1–9)			0.001	1.05	1.02–1.09	0.001
Hepatitis C seropositivity	32 (15%)	23 (8%)	2.16	1.23–3.82	0.007			

* Median (Interquartile range)

[†] Mean ± standard error of mean