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SHORT REPORT

Screening for neurocognitive impairment, depression, and anxiety in HIV-infected patients in Western Europe and Canada

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CRANIum, a cross-sectional epidemiology study in Western Europe and Canada, was conducted to describe and compare the prevalence of a positive screen for neurocognitive impairment (NCI), depressive symptoms, and anxiety in an HIV-positive population either receiving combination antiretroviral therapy (cART) or who were naive to antiretroviral therapy (ART). HIV-positive patients ≥18 years of age attending a routine medical follow-up visit and able to complete the designated screening tools were eligible for study inclusion. The Brief Neurocognitive Screen was used to assess NCI; depressive and anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale. The evaluable patient population ($N = 2863$) included 1766 men (61.7%) and 1096 (38.3%) women. A total of 1969 patients were cART-experienced (68.8%), and 894 were ART-naive (31.2%). A positive screen for NCI was found in 41.5% of patients (cART-experienced, 42.5%; ART-naive, 39.4%; $p = 0.12$). A positive screen for depressive symptoms was found in 15.7% of patients (cART-experienced, 16.8%; ART-naive, 13.3%; $p = 0.01$), whereas 33.3% of patients screened positive for anxiety (cART-experienced, 33.5%; ART-naive, 32.8%; $p = 0.71$). A greater percentage of women compared with men screened positive for NCI (51.78% vs. 35.1%; $p < 0.0001$) and depressive symptoms (17.9% vs. 14.3%; $p = 0.01$). These data suggest that neurocognitive and mood disorders remain highly prevalent in HIV-infected patients. Regular mental health screening in this population is warranted.

Keywords: anxiety; combination antiretroviral therapy; depression; HIV; neurocognitive impairment

Introduction

Infection with HIV is often preceded or accompanied by neuropsychiatric conditions including mood and personality disorders and psychosis (Bennett, Joesch, Mazur, & Roy-Byrne, 2009; Gaynes, Pence, Eron, & Miller, 2008; Owe-Larsson, Sall, Salamon, & Allgulander, 2009). Depression is the most prevalent psychiatric disorder among patients infected with HIV with a prevalence up to four times that of the general population (Bing et al., 2001). Suicides and anxiety disorders are more common among patients with HIV than uninfected individuals (Hinkin, Castellon, Atkinson, & Goodkin, 2001; Keiser et al., 2010; Sewell et al., 2000). In addition, neurocognitive impairment (NCI) is often associated with HIV infection (Chan, Kandiah, & Chua, 2012; Heaton et al., 2010; Lawler et al., 2011; Robertson et al., 2007). These disorders may affect quality of life and can contribute

to increased morbidity and mortality (Andrinopoulos et al., 2011; Bing et al., 2000; Charles et al., 2012; Grov, Golub, Parsons, Brennan, & Karpiak, 2010; Hessol et al., 2007; Ickovics et al., 2001; Li, Lee, Thammawijaya, Jiraphongsa, & Rotheram-Borus, 2009; Reis et al., 2011; Tozzi et al., 2004; Wilkie et al., 1998; Wisniewski et al., 2005). A recently described meta-analysis found that the treatment of depression among HIV-infected individuals led to increases in antiretroviral adherence (Sin & DiMatteo, 2014).

This study was conducted to describe and compare the prevalence of a positive screening for NCI, anxiety, and/or depressive symptoms in an HIV-positive population receiving combination antiretroviral therapy (cART) versus antiretroviral therapy-naive (ART-naive) patients, and to explore potential associations between prevalence and sociodemographic and HIV disease characteristics.

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Methods

Study design

CRANIum (s**CR**een for **A**nxiety, depression, and **N**eurocognitive **I**mpairment in HIV+ patients) was a multinational, multicenter, cross-sectional epidemiology study, conducted among patients with HIV in Western Europe and Canada from October 2010 to June 2011. The study aimed to include ART-naive patients and patients treated with ritonavir-boosted protease inhibitors and nonnucleoside reverse transcriptase inhibitors in a 1:1:1 ratio. An a-priori recruitment target of 40% female subjects was set for the overall study population. The primary objective of the study was to describe and compare the prevalence of a positive screen for NCI, depression, and anxiety in an HIV-infected population either receiving or naive to cART.

Study population

Patients were eligible for enrollment if they were infected with HIV, ≥18 years of age, attending a routine medical follow-up visit, and able to complete the designated screening tools. Patients receiving cART were required to be on their current antiretroviral regimen for ≥9 months. Exclusion criteria included a current or active opportunistic infection or malignancy of the central nervous system (CNS) and alcohol (>5 units/day) or illicit substance abuse within the previous three months. The study protocol was approved by the appropriate institutional review boards or independent ethics committees. Approved informed consent was obtained from subjects before enrollment.

Variables and instruments

NCI was assessed by the Brief Neurocognitive Screen (BNCS), a validated, but limited, screening (not diagnostic) tool (Ellis et al., 2005; Reitan & Wolfson, 1985; Wechsler, 1981). A positive screen for NCI per individual patient was defined as a z-score of one standard deviation below the mean on two tests or two standard deviations below the mean on one test (Heaton, Miller, Taylor, & Grant, 2004). Depressive and anxiety symptomatology were assessed using the self-administered Hospital Anxiety and Depression Scale (HADS) questionnaire, which consists of seven items each relating to depression (HADS-D) and anxiety (HADS-A), respectively. A score of ≥8 on the HADS-D and HADS-A subscales (Zigmond & Snaith, 1983) was considered a positive screen.

Statistical analysis

A total of 2575 patients was determined to provide 80% power to detect a difference in prevalence of 20–25% between treatment groups at a 5% significance level. (See online Supplementary Text 1 for additional statistical details.)

Results

Patient characteristics

A total of 2884 patients from 15 countries in Western Europe and Canada were enrolled. The evaluable patient population ($n = 2863$) included 1766 men (61.7%) and 1096 women (38.3%; see online Supplementary Figure 1 for patient disposition). Demographic characteristics of patients are described in Table 1. The mean age of patients was 42.9 years (range, 19–83). Most patients were male ($n = 1766$ [61.7%] and white ($n = 2256$ [78.8%]), with a median HIV-1 RNA level of 633.5 copies/mL and a mean CD4+ T-cell nadir of 295 cells/μL.

Neurocognitive impairment

Among the evaluable patients, 41.5% screened positive for NCI. Of the ART-naive patients, 39.4% (352/894) screened positive for NCI, whereas 42.5% of cART-experienced patients (836/1969) screened positive for NCI ($p = 0.12$; Figure 1). Factors associated with NCI are shown in Figure 2A.

Depression and anxiety

Among the evaluable patients, 15.7% screened positive for depression and 33.3% screened positive for anxiety (Figure 1A). A significantly greater percentage of cART-experienced patients (326/1941 [16.8%]) screened positive for depression compared with ART-naive patients (117/882 [13.3%]; $p = 0.01$), whereas the percentage of patients screening positive for anxiety was similar between ART-naive (290/884 [32.8%]) and cART-experienced patients (648/1933 [33.5%]; $p = 0.71$). Factors associated with a positive screen for depressive symptoms and for anxiety are shown in Figure 2B and C, respectively.

Gender analysis

Women comprised nearly 40% of the study population. The proportion of black patients was significantly higher among women than men (25.8% vs. 5.9%; $p < 0.0001$). A greater proportion of men completed secondary or higher education (87.3% vs. 73.7%; $p < 0.0001$). Men were more likely to smoke or to use alcohol or illegal substances. Women who were cART-experienced had a significantly lower CD4+ T-cell count nadir (203.4 cells/μL) than cART-experienced men (228.2 cells/μL; $p = 0.0017$). Additional demographic data based on gender can be found in the online Supplementary Table 1.
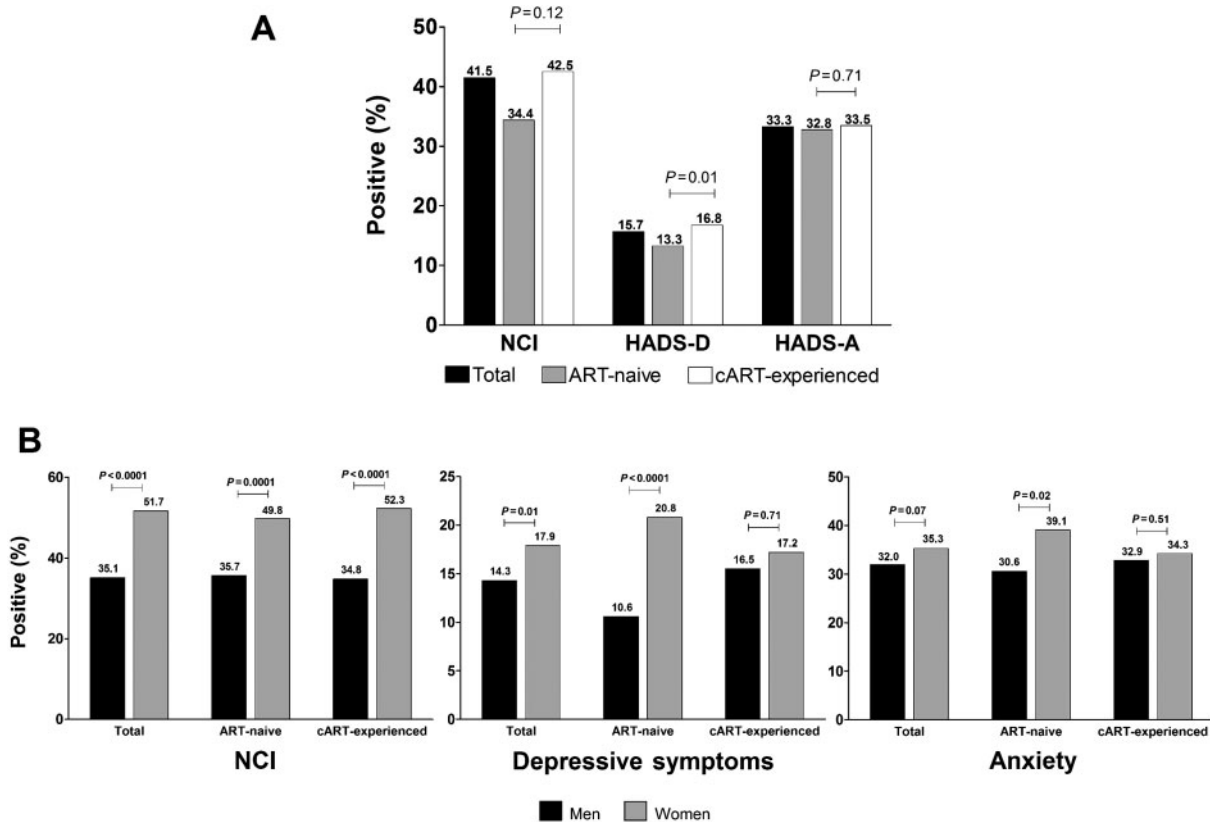
Figure 1. (A) Positive screen of total, ART-naive, and cART-experienced patients infected with HIV for NCI (BNCS), anxiety (HADS-A), or depression (HADS-D). (B) Neuropsychologic screen of total, ART-naive, and cART-experienced patients infected with HIV stratified by gender. Positive screen for NCI (left panel), positive screen for depressive symptoms (center panel), positive screen for anxiety (right panel); total ($n = 2863$), ART-naive ($n = 894$), cART-experienced ($n = 1969$). ART = antiretroviral therapy; cART = combination antiretroviral therapy; HADS = Hospital Anxiety and Depression Scale; NCI = neurocognitive impairment.

There was a significantly higher percentage of women with a positive screen for NCI compared with men (51.7% vs. 35.1%; $p < 0.0001$; Figure 1B). This difference was consistent among the cART-experienced (52.3% women vs. 34.8% men; $p < 0.0001$) and ART-naive populations (49.8% women vs. 35.7% men; $p < 0.0001$). In patients with a negative screen for depression (HADS-D < 8, $n = 2380$), 48.5% of women versus 33.7% of men ($p < 0.0001$) had a positive screen for NCI.

A significantly greater percentage of women screened positive for depression (17.9%) compared with men (14.3%; $p = 0.01$), driven by differences observed in the ART-naive group (20.8% women; 10.6% men; $p < 0.0001$; Figure 1B). Differences between genders for a positive screen for anxiety did not reach statistical significance overall (women 35.3%; men 32.0%; $p = 0.07$) but were significantly higher in the ART-naive group (39.1% women; 30.6% men; $p = 0.02$; Figure 1B).

Discussion

In CRANIum, more than 40% of the patients infected with HIV screened positive for NCI, similar to the rate reported in an earlier study (Heaton et al., 2011). The prevalence of a positive screen for NCI was not statistically different between patients who were cART-experienced and ART-naive; however, differences in demographics and disease characteristics between the groups should be considered. Patients treated with cART who had a lower viral load (≤ 50 copies/mL) were less likely to screen positive for NCI. Gender subgroup analysis demonstrated that women were significantly more likely to screen positive for NCI than men, independent of receipt of cART. Although significant differences in demographic and HIV disease characteristics were found between genders (a greater proportion of women were black and unemployed, and fewer women had a secondary or higher education), female gender was identified as a risk factor in the multivariate analysis.

Approximately one-third of the patients in this study screened positive for anxiety, and approximately 16% screened positive for depressive symptomatology. The percentage of patients who screened positive for depressive symptoms in this study is approximately twice

Table 1. Demographic data and disease characteristics.

	All subjects	ART-*naive*	cART-experienced	*P* value*
Evaluable subjects, *n* (%)	2863 (100)	894 (31.2)	1969 (68.8)	
Age (years), mean	42.9	38.0	45.2	<0.0001
Men (%)	61.7	73.7	56.2	<0.0001
Race (%)				0.1367
White	78.8	80.1	78.2	
Black	13.5	11.6	14.4	
Other	7.7	8.3	7.4	
Unemployed (%)	33.2	22.5	38.0	<0.0001
Marital status – single (%)	51.5	58.3	48.5	<0.0001
Any children (%)	39.4	28.1	44.5	<0.0001
Residence (%)				0.0144
Rural	9.3	7.7	10.0	
City	67.0	70.6	65.4	
Small/large town	22.9	21.4	22.6	
Secondary school or higher education (%)	82.1	86.8	80.1	<0.0001
Risk factor for acquiring *HIV* (%)				<0.0001
Homosexual	43.3	57.7	36.8	
Heterosexual	45.8	38.5	49.1	
Other/not known	10.9	3.8	14.1	
Duration of *HIV* infection (months), mean	98.1	42.5	126.9	<0.0001
Last-recorded *HIV*-1 RNA (c/mL), median	633.5	22,390	<50	<0.0001
Last-recorded CD4+ T-cell count (cells/µL), mean	587	554	600	<0.0001
CD4+ T-cell count nadir (cells/µL), mean	295	474	217	<0.0001
AIDS diagnosis (%)	17.5	2.5	24.4	<0.0001
Alcohol use (%)				<0.0001
None	38.8	30.7	42.5	
Intermittent (≤2 times/week)	46.3	52.8	43.4	
Regular (3–6 times/week)	9.1	12.0	7.8	
Daily	3.6	3.0	3.9	
Ex-drinker (none in the last three months)	2.2	1.5	2.5	
Illegal substance use in the previous 12 months (%)	11.2	17.5	8.4	<0.0001
Previous CNS infection (%)	4.5	0.6	6.3	<0.0001
Previous psychiatric diagnosis (%)	20.1	15.7	22.2	<0.0001
Other chronic diseases (%)				
Hepatitis C coinfection	12.4	5.3	15.6	<0.0001
Hepatitis B coinfection	4.8	2.8	5.7	0.0008
Diabetes	3.0	1.6	3.7	0.0020
Hyperlipidemia	12.3	4.5	15.8	<0.0001
High blood pressure	9.2	6.3	10.5	0.0003
Treated with antidepressives (%)	7.4	5.0	8.5	0.0009
Treated with anxiolytics (%)	5.0	3.7	5.6	0.0310

ART = antiretroviral therapy; cART = combination antiretroviral therapy; CNS = central nervous system.
*ART-naive vs. cART-experienced.
Rates may not add up to 100% because of rounding.

that previously reported for depression in the general European population (Ayuso-Mateos et al., 2001).

Compared with men, a higher proportion of women screened positive for depressive symptoms; however, significant differences in demographic and disease characteristics were found between the genders; being female was not an identified risk factor for a positive screen for depression in multivariate analysis. The prevalence of depressive symptoms among women infected with HIV in this study is nearly twice that reported for women in the general European population (Ayuso-Mateos et al., 2001). Previous studies have concluded that depression and depressive symptomatology seem more prevalent and severe in HIV-infected women compared with HIV-infected men (Kinyanda, Hoskins, Nakku, Nawaz, & Patel, 2011; Reis et al., 2011;
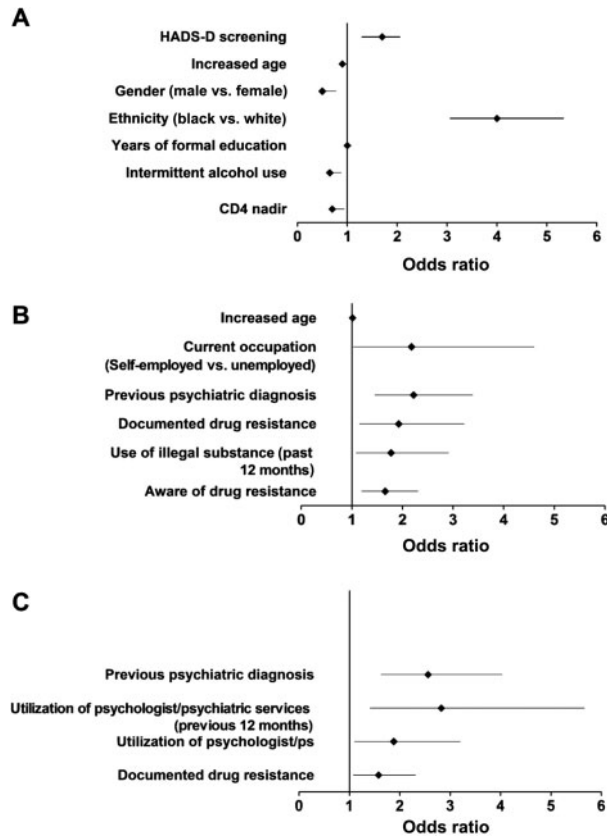
Figure 2. Multivariate analysis of all patients for the association of demographic characteristics with a positive screen for: (A) NCI, (B) depressive symptoms, or (C) anxiety. Variables included in the multivariate analysis were alcohol use (no alcohol use/ex-drinker vs. none), screen for NCI (positive screen vs. comparator), current occupation (unemployed/student vs. employed/self-employed), documented drug resistance (yes vs. no), ethnicity (black vs. other), gender (female vs. male), HADS depression score (negative screen vs. positive screen), hepatitis B virus or hepatitis C virus coinfection (no vs. yes), last recorded CD4+ T-cell count (<350 cells/mL vs. ≥350 cells/mL), marital status (single vs. not single), previous CNS infection (yes vs. no), previous psychiatric diagnosis (yes vs. no), residence (large town/city vs. rural/small town), smoking (smoker vs. never smoked/ex-smoker), time from HIV diagnosis (<5 years vs. ≥5 years), use of illegal substance/narcotics in the past 12 months (yes/response denied vs. no/not applicable), utilization of psychiatrist/psychologist service in the past 12 months (yes vs. no). Data are presented as odds ratios and 95% confidence intervals. HADS = Hospital Anxiety and Depression Scale; NCI = neurocognitive impairment.

Turner, Laine, Cosler, & Hauck, 2003). The high number and percentage of women included in this study (n = 1096, 38.3%) provide robust data.

Due to the cross-sectional nature of this study, the interpretation of predictive associations between risk factors and outcomes is difficult and does not demonstrate causality. Limitations of this study include the use of screening tools rather than structured or semistructured diagnostic interviews to diagnose depression and anxiety. Moreover, only three tests, and not a complete battery, were used to evaluate NCI. Additionally, this study used normalized data for the prevalence of neuropsychologic conditions from a US population; normative data from each of the countries that enrolled subjects in the study were not available, and the local differences in population risk may have an impact on the impairment assessed. Because the prevalence of NCI in the general population is most often provided for older adults, comparison of the population in this study (mean age 42.9 years) with an age-matched historical control is difficult.

Strengths of our study comprise both the large overall and female populations included. The subjects in this study were residents of a wide geographic area encompassing 15 countries, whereas most previous studies have tended to focus on individual countries (Chan et al., 2012; Gaynes et al., 2008; Kinyanda et al., 2011; Pappin, Wouters, & Booysen, 2012). Nonetheless, the rates of impairment observed in this study are comparable to those seen in other studies (Chan et al., 2012; Gaynes et al., 2008; Pappin et al., 2012).

Neuropsychological and psychiatric symptoms in the HIV population have obvious implications for treatment and serve as a reminder to health-care providers of the importance of comorbid mental health issues and neurocognitive functioning. Data in this study suggest that screenings for NCI, depression, and anxiety should be included in the routine clinical HIV management algorithms, especially for patients with identified risk factors.

Supplementary material

Supplementary (Figure 1/Table 1/content) is available via the 'Supplementary' tab on the article's online page (http://dx.doi.org/10.1080/09540121.2014.936813).

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Appendix

Austria: Dr. Vetter, Dr. Geit, Dr. Prammer; *Belgium:* Dr. Vandekerckhove, Prof. Moutschen, Prof. Vandercam; *Canada:* Dra. Loutfy, Dr. DeWet, Dr. Baril, Dr. Trottier, Dra. Walmsley, Dr. Gill; *France:* Dr. Bouchaud, Dr. De Truchis, Dr. Djerad, Dr. Gasnault, Dr. Gilquin, Dr. Hocqueloux, Dr. Hoen, Dra. Khuong, Dr. Lafeuillade, Dr. Le Moal, Dra. Leclercq, Dr. Molina, Dr. Patey, Dr. Pellegrin, Dr. Rogeaux, Dra. Salmon, Dr. Treilhou; *Germany:* Dr. Rockstroh, Dr. Schewe, Dr. Mayr, Dr. Pauli, Dr. Baumgarten, Dr. Lutz, Dr. Jäger, Dr. Knechten, Dr. Cordes; *Greece:* Dr. Gargalianos, Dra. Sabatakou, Dr. Katsabas, Dr. Skoutelis, Dr. Ploumidis; *Ireland:* Prof. Bergin, Dr. McNamara; *Israel:* Dr. Pollak, Dr. Elbirt, Dr. Maayan, Dr. Levy, Dr. Riesenberg; *Italy:* Dr. Antinori, Dr. Carosi, Dra. Mussini, Dr. Galli, Dra. Cinque, Dr. Parruti, Dr. Rizzardini, Dr. Viale; *Norway:* Dr. Leiva, Dr. Ringstad; *Portugal:* Dr. Serrão, Dr. Mansinho; *Spain:* Dr. Hernández-Quero, Dr. Colmenero, Dr. Terrón, Dr. Rodríguez-Baño, Dr. Lozano, Dr. de Zárraga, Dr. Llunch, Dr. Florez, Dra. Martínez, Dr. Rodriguez, Dra. Sepúlveda, Dr. Elizaga, Dr. Bahamonde, Dra. Garcínuño, Dr. Podzamczer, Dr. Mallolas, Dr. Clotet, Dr. Munoz, Dr. Domingo, Dr. Pedrol, Dr. Knobel, Dra. Omella, Dr. Aranda, Dr. Force, Dr. Barros, Dr. Martín, Dr. Arribas, Dr. Casado, Dr. Cuadrado, Dra. Oltra, Dr. Roca, Dr. Ortega, Dr. Fernández, Dr. Rodríguez, Dr. Morano, Dr. Canet, Dr. García-Henarejos, Dr. Cano, Dr. Goenaga, Dra. Muñoz, Dra. Goicoechea; *Sweden:* Prof. Nilsson Schönnesson, Dra. Schlaug, Dr. Flamholc, Dr. Bonnedahl, Dr. Briheim; *Switzerland:* Dr. Zimmerli, Dr. Vernazza, Dr. Cavassini; *UK:* Dr. Gompels, Prof. Lee, Dr. Price, Dr. Leen, Dr. Nelson, Prof. Johnson, Dr. Kulasegaram.