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Neuropsychological performance in patients with asymptomatic HIV-1 infection

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ABSTRACT

Human immunodeficiency virus (HIV-1) infection and acquired immunodeficiency syndrome (AIDS) lead to neurocognitive disorders; however, there is still much knowledge to be gained regarding HIV-associated neurocognitive disorders. The purpose of this study was to assess the cognitive performance, instrumental activities of daily living, depression, and anxiety in patients with asymptomatic HIV-1 infections compared with seronegative participants without neurocognitive impairment. We studied a sample consisted of 60 patients with asymptomatic HIV-1 infections and 60 seronegative participants without neurocognitive impairment from the city of Barranquilla, Colombia, with a mean age of 36.07 years. A protocol of neuropsychological and psychopathological tests was applied to the participants. The group of patients with asymptomatic HIV infections significantly underperformed on tasks that assessed global cognitive screening, attention span, learning, phonemic verbal fluency, auditory-verbal comprehension, information processing speed, cognitive flexibility, and motor skills compared to the group of seronegative participants. No significant differences were found in memory, visual confrontation naming, vocabulary, inhibition, and instrumental activities of daily living. Additionally, the patients with asymptomatic HIV-1 infection had a higher anxiety index than the seronegative participants, but no significant difference was found in depression. A correlation was found between depression and anxiety. In conclusion, the patients with asymptomatic HIV-1 infection had lower cognitive performances than the seronegative participants in the cognitive functions mentioned above and more anxiety but still performed the instrumental activities of daily living.

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Introduction

Human immunodeficiency virus (HIV) is a neurotropic and immunotropic virus that compromises the immune system by infecting CD4 lymphocytes (Croucher & Winston, 2013), and can affect any cognitive function in individuals with HIV infection, although some are more commonly affected than others (Heaton et al., 2010). According to figures from ONUSIDA (2015a), 36.9 million people were living with HIV worldwide at the end of 2014, of which 120,000 resided in Colombia ONUSIDA (2015b). HIV-associated neurocognitive disorders (HAND) are one clinical manifestation of the virus (Antinori et al., 2007). These disorders are characterized by cognitive and behavioural disorders in which any cognitive function can be affected (Bragança & Palha, 2011).

HIV-associated neurocognitive disorders are classified as "*asymptomatic neurocognitive impairment (ANI)*", "*mild neurocognitive disorder (MND)*", and "*HIV-associated dementia (HAD)*" (Antinori et al., 2007; Guevara-Silva et al., 2014; Kalinowska, Trześniowska-Drukała, & Samochowiec, 2013). ANI is characterized by mild neurocognitive deficits (MND) without reported functional impairment (Antinori et al., 2007); MND is characterized by mild or moderate impairment of at least two neurocognitive areas with effects on the activities of daily living of the patient (Antinori et al., 2007), and HAD consists of moderate to severe impairment of at least two neurocognitive areas and severe functional impairment (Antinori et al., 2007). These disorders become more severe in the more advanced stages of the disease (Kalinowska et al., 2013 and Vally, 2011).

HIV-infected people may present with neurocognitive disorders at any stage of the infection (Bragança & Palha, 2011; Guevara-Silva et al., 2014), and HIV–infection is a risk factor for neurocognitive impairment (Abusamra et al., 2014; Custodio, Escobar, & Altamirano, 2006;

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Habib et al., 2013; Heaton et al., 2010; Galindo-Sainz, Rodríguez-Almanza, Sandoval-Ramírez, & Tejada-García, 2010; Rackstraw, 2011). Currently, one concern is the detection of early cognitive impairment (Ian et al., 2015) during the asymptomatic stage of the infection, which will help determine the treatment protocol. Despite of this situation, very few studies in Colombia have investigated neurocognitive disorders in patients with asymptomatic HIV-infection (Arciniegas, Malagón, Halliday, & Tovar-Cuevas, 2013). This topic should be considered relevant due to its implications not only for research but also for neuropsychological prevention and intervention, which should have more clearly defined roles in the comprehensive care of these patients. Although the HIV/AIDS guidelines in Colombia mention neuropsychological assessment (Ministerio de Salud y Protección Social y Fondo de Población de las Naciones Unidas, 2014), the procedure and protocols for diagnostic tests are not clear, and neuropsychological rehabilitation is not even contemplated (Pino-Melgarejo & Omar-Martínez, 2014) despite its potential effects (Bragança & Palha, 2011; Weber, Blackstone, & Woods, 2013). The aim of this investigation is to study the cognitive performance, instrumental activities of daily living, depression, and anxiety in patients with asymptomatic HIV- infection.

Subjects and methods

Subjects

The total sample consisted of 60 patients with asymptomatic HIV- infections and 60 seronegative participants without neurocognitive impairment (control group). The definition of asymptomatic HIV is released by the Centers for Disease Control and Prevention, USA (Castro et al., 1993), which refers to disease status and not to neurocognitive status. The inclusion criteria for the patients were as follows: (i) infected with HIV in the asymptomatic stage; (ii) age between 18 and 58 years; (iii) at least two years of education; (iv) time since HIV diagnosis of up to 9 years; and (v) no history of alcohol and/or drug use or neurological, neuropsychological, and/or psychopathological disorders prior to HIV -infection in the patient's medical record. The control group met the same inclusion criteria as the asymptomatic group with HIV infection but was not infected with HIV. Table 1 describes the sociodemographic characteristics of the participants.

Instruments

The cognitive performance of the participants was measured with a neuropsychological assessment battery that included cognitive screening, attention span, verbal learning and memory, visual memory, language, information processing speed, visuoconstructive skills, executive function, depression, and anxiety tests (See Table 2 and Supplementary Material). Anxiety state, depression, and instrumental activities of daily living were also evaluated (see Table 2 and Supplementary Material). These tests were selected based on the systematic review of different proposals for neuropsychological assessment batteries for the HIV-infected population (Ardila-Ardila et al., 2003; Ayuso-Mateos, 1997; Burgess et al., 1994; Butters et al., 1990; Maj, Starace, & Sartorius, 1991; Selnes & Miller, 1994).

Procedure

Informed written consent was obtained from all participants. This study was carried out in accordance with local review board approval. The neuropsychological tests were administered in two sessions. After all data were collected, the neuropsychological and psychopathological tests and the activities of daily living were graded.

Statistical analysis

Measures of central tendency and dispersion were estimated for the continuous variables, and frequencies and proportions were calculated for the categorical variables. The normality of the continuous variables was assessed using the Shapiro-Wilks test. The categorical variables were analyzed using the χ^2 test.

Student's *t*-test and the Mann–Whitney *U* test were performed to compare the means of the hypothesis tests. Cohen's standardized effect size (d) was calculated. To correct for potential confounding effects of the demographic variables, such as age, gender, and years of education, on the cognitive variables, analysis of covariance (ANCOVA) was used to compare the performances of the HIV-infected and seronegative individuals. In this case, the partial η^2 parameter was used to estimate the effect size. To explore potential relationships between neuropsychological tasks, we used Pearson's linear correlation coefficient. Because many statistical hypotheses were tested when comparing the neuropsychological performance of HIV-infected individuals with that of seronegative individuals, we used the False Discovery Rate (FDR) procedure (Benjamini & Hochberg, 1995) and a method based on extreme-value theory (Vélez, Correa, & Arcos-Burgos, 2014) to control for multiple comparisons. The FDR procedure was chosen as it controls the proportion of wrongly rejected null hypotheses amongst those that are rejected, not amongst all hypotheses being tested (Groppe, 2016; Storey & Tibshirani, 2003) and

Table 1. Sociodemographic characteristics of the participants.

Variable	Category	All individuals ($N = 120$) Mean ± SD	Patients with asymptomatic HIV infections ($N = 60$) Mean ± SD	Control group ($N = 60$) Mean ± SD	Statistic t (df)	P
Age (years)		36.07 ± 10.98	38.60 ± 9.48	33.53 ± 11.84	2.59 (118)	**0.011**
Years of education		9.02 ± 2.65	8.07 ± 2.85	9.97 ± 2.07	4.18 (118)	**< 0.0001**
		***n*(%)**	***n*(%)**	***n*(%)**	**χ^2(df)**	
Gender	Female	74 (61.7)	32 (53.3)	42 (70)	3.52 (1)	.060
	Male	46 (38.3)	28 (46.7)	18 (30)		
Sexual orientation	Heterosexual	111 (92.5)	53 (88.3)	58 (96.7)	4.42 (2)	.109
	Homosexual	5 (4.2)	3 (5)	2 (3.3)		
	Bisexual	4 (3.3)	4 (6.7)	0 (0)		
Hand preference	Left	6 (5)	0 (0)	6 (10)	6.32 (1)	**0.012**
	Right	114 (95)	60 (100)	54 (90)		

Note: Results significant at 5% are shown in bold. df = degrees of freedom; SD = standard deviation.

hence more powerful than Bonferroni's correction (Groppe, Urbach, & Kutas, 2011; Storey & Tibshirani, 2003; Vélez et al., 2014). Unless otherwise stated, all statistical analyses were performed in R version 3.3.3 (R Core Team, 2016).

Results

The mean time since diagnosis in the HIV- infection patients was 3.32 ± 2.5 years, and 81.67% of the patients were on antiretroviral therapy (ART). The mean number of CD4 cells was 310.2 ± 87.6 cells/μL. The median viral load was 11,260 copies/mL, and the average logarithm of the viral load was 9.136 ± 3. Significant differences were found ($P < 0.05$, Table 1) in hand preference, age, and years of education when comparing the compositions of the group of patients with asymptomatic HIV- infections and the seronegative controls.

Table 2. Variables (cognitive functions) and instruments used in the neuropsychological assessment battery. The Supplementary Material provides a detailed description of each of the tests used in the neuropsychological assessment battery.

Cognitive function	Test
Cognitive screening	Mini-Mental State Examination (Folstein, Folstein, & McHung, 1975).
Attention span	Wechsler Memory Scale Digit Span Subtest (Wechsler, 2004)
Verbal learning and memory	Rey Auditory Verbal Learning Test (Rey, 1964; Schmidt, 1996)
Visual memory	Rey Complex Figure Test (Rey, 2003)
Language	
Naming	Boston Naming Test (Kaplan, Goddglass, & Weintraub, 1983)
Phonemic verbal fluency	Controlled Word Association Test. (Spreen & Strauss, 1998)
Vocabulary	Wechsler Intelligence Scale Vocabulary Subtest (Wechsler, 2001)
Auditory-verbal comprehension	Language Comprehension Subtest of the Brief Neuropsychological Assessment in Spanish (Otrosky-Solis, Ardila, & Rosselli, 1999)
Information processing speed	Digit Symbol-Coding Subtest of the Wechsler Intelligence Scale (WAIS-III)
Visuoconstructive skills	Rey Complex Figure Test (Rey, 2003)
Executive functions	
Inhibition	STROOP Color-Word Test by Golden (2005)
Cognitive flexibility	Trail Making Test (TMT), Part B (Lezak, Howieson, & Loring, 1983)
Motor programming	Motor Skills Subtest of the Brief Neuropsychological Assessment in Spanish (NEUROPSI)
Instrumental activities of daily living	Lawton and Brody Scale (Lawton & Brody, 1969)
Depression	Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)
Anxiety	Trait-State Anxiety Inventory (STAI) (Spielberger & Díaz-Guerrero, 1975)

We observed that patients with asymptomatic HIV underperformed compared to the individuals in the control group in the global cognitive screening, attention span, learning, language (i.e., vocabulary), phonemic verbal fluency and auditory-verbal comprehension, information processing speed, cognitive flexibility, motor skills as part of the executive function, and anxiety tests ($P < 0.05$, Table 3). However, no differences were found in verbal and visual memory, naming, inhibition, and ability to perform instrumental activities of daily living, which were also conserved in patients with asymptomatic HIV ($P > 0.05$, Table 3). Additionally, patients with asymptomatic HIV had higher anxiety indices than the seronegative individuals, but no significant differences were found in the depression indices. Overall, laterality (i.e., being right-handed) improves the performance in the WAIS vocabulary subtest, and the total score of the Controlled Word Association Test, whilst years of education and age have a positive effect (i.e., there is an improvement) on 58% (25/43) of all cognitive tests, and on 9% (4/43) of memory and information processing speed neuropsychological tests (i.e., digit symbol-coding, test 3 and sum of tests 1–5 of the Rey Auditory-Verbal Learning Test, and the memory subtests of the Rey Complex Figure Test), respectively (Supplementary Table 1).

Figure 1(a) shows the mean corrected differences of the neuropsychological tests (β coefficient, Table 3) as a function of the P value. In this case, values of $\beta > 0$ imply that the individuals with asymptomatic HIV-1 infections have higher mean scores than the seronegative individuals, whereas values of $\beta < 0$ indicate that the

Table 3. Performance on neuropsychological tests of the individuals with asymptomatic HIV -infections and the controls.

Test	Description	Group		d	β(SE)	P	
		HIV	Control				
1	Minimental	27.55 (1.9)	29.05 (1.11)	0.964	−0.88 (0.27)	**0.002**	*
	WMS-III						
2	Digit span	9.48 (2.44)	11.38 (3.18)	0.671	−1.78 (0.56)	**0.002**	*
3	Digit span forward	6.38 (1.54)	7.32 (2.09)	0.509	−0.83 (0.36)	**0.024**	
4	Digits span backward	3.42 (1.73)	4.22 (1.84)	0.448	−0.66 (0.36)	0.066	
	Wechsler Intelligence Scale						
5	Vocabulary	21.18 (12.67)	28.17 (9.88)	0.614	−5.01 (2.12)	**0.020**	
6	Digit symbol-coding	38.65 (14.45)	52.93 (16.49)	0.921	−7.57 (2.54)	**0.003**	*
	Rey Auditory-Verbal Learning Test						
7	Test 1	4.87 (1.73)	5.47 (1.68)	0.351	−0.38 (0.33)	0.256	
8	Test 3	6.67 (2.06)	7.72 (2.12)	0.502	−0.43 (0.39)	0.278	
9	Test 3	7.5 (2.8)	9.37 (2.55)	0.698	−1.36 (0.52)	**0.010**	*
10	Test 4	9.28 (2.78)	10.4 (2.2)	0.445	−0.59 (0.47)	0.213	
11	Test 5	9.8 (2.87)	11.42 (2.08)	0.645	−1.06 (0.47)	**0.027**	
12	Sum of tests 1–5	38.25 (10.06)	44.48 (8.6)	0.666	−3.6 (1.71)	**0.038**	
13	Test 7	8.38 (3.01)	9.92 (2.49)	0.554	−0.53 (0.49)	0.286	
	Rey Complex Figure Test						
14	Copy	31.73 (5.91)	34.78 (3.19)	0.642	−1.85 (0.91)	**0.045**	
15	Type of copy	2.18 (1.5)	2 (1.43)	0.125	0.29 (0.29)	0.320	
16	Copy time	4.48 (1.78)	4.37 (1.65)	0.068	−0.45 (0.32)	0.161	
17	Recall copy	2.84 (1.54)	2.92 (1.49)	0.047	−0.26 (0.3)	0.397	
18	Memory	16.55 (8.25)	20.83 (8)	0.527	−1.41 (1.49)	0.348	
19	Recall time	3.28 (2.18)	2.82 (1.36)	0.257	0.45 (0.36)	0.217	
	Boston Naming Test						
20	Total score	47.83 (7.54)	50.07 (5.87)	0.331	−0.38 (1.29)	0.767	
21	Semantic clues	8.73 (5.85)	5.88 (3.66)	0.584	1.58 (0.94)	0.095	
22	Correct responses to semantic clues	3.1 (2.54)	3.33 (2.52)	0.092	−0.82 (0.49)	0.097	
23	Phonemic clues	5.63 (6.1)	2.53 (3.16)	0.638	2.41 (0.97)	**0.014**	*
24	Correct responses to phonemic clues	0.42 (0.93)	0.33 (1.17)	0.079	−0.03 (0.21)	0.880	
	Stroop						
25	Interference	−3.52 (8.82)	−5.85 (8.92)	0.264	2.06 (1.77)	0.246	
26	Word	85.27 (19.22)	97.15 (15.76)	0.676	−7.48 (3.36)	**0.028**	
27	Colour	61 (12.4)	69.28 (12.08)	0.677	−5.35 (2.36)	**0.025**	
28	Word-color	31.8 (8.72)	34.07 (8.46)	0.264	−0.98 (1.69)	0.563	
	Controlled Word Association Test						
29	Total score	33.73 (11.78)	42.37 (11.46)	0.743	−5.99 (2.12)	0.006	*
30	Words with P	13.1 (4.79)	15.7 (4.72)	0.547	−1.81 (0.91)	**0.049**	
31	Words with T	10.77 (4.5)	13.17 (3.98)	0.565	−1.36 (0.77)	0.082	
32	Words with M	10.13 (4.28)	13.28 (3.92)	0.768	−2.09 (0.75)	**0.006**	*
	Trail Making Test						
33	Part B errors	6.35 (4.95)	3.33 (3.3)	0.718	2.31 (0.84)	**0.007**	*
34	Part B time	22.77 (13.65)	23.3 (16.01)	0.035	0.18 (5.06)	0.972	
	NEUROPSI						
35	Motor skills 1	2.5 (1.23)	3.67 (0.6)	1.207	−0.97 (0.19)	$\mathbf{1.21 \times 10^{-6}}$	*
36	Motor skills 2	1.4 (0.76)	1.82 (0.47)	0.658	−0.31 (0.13)	**0.015**	*
37	Motor skills 3	1.37 (0.74)	1.8 (0.4)	0.730	−0.42 (0.12)	**0.001**	*
38	Motor skills total score	5.25 (1.85)	7.27 (1.09)	1.331	−1.71 (0.3)	$\mathbf{7.87 \times 10^{-5}}$	*
39	Auditory-verbal comprehension	5.12 (1.04)	5.92 (0.33)	1.033	−0.65 (0.15)	$\mathbf{3.95 \times 10^{-5}}$	*
40	Lawton and Brody scale	7.98 (0.13)	7.98 (0.13)	0.000	0.01 (0.03)	0.717	
41	Beck Depression Inventory	9.02 (9.28)	5.92 (5.54)	0.406	2.62 (1.55)	0.093	
	Anxiety Inventory						
42	State	36.6 (11.17)	31.75 (7.29)	0.514	4.69 (1.91)	**0.016**	*
43	Trait	41.77 (11.66)	35.38 (8.65)	0.622	6.63 (2.08)	**0.002**	*

Significant differences at the 5% level are shown in **bold,** and differences significant after correction for multiple testing using the false discovery rate (FDR) are marked with *. β: regression coefficient; d: Cohen's effect size; P: P-value; SE: standard error.

seronegative individuals have scored lower than the patients with asymptomatic HIV- infections (Figure 1 (a)). Particular attention is drawn to the following tests because the individuals with asymptomatic HIV- infections have lower performance scores: digit symbol-coding ($\beta = -7.566$, $P = 2.53 \times 10^{-3}$, Table 3); Stroop interference score ($\beta = -7.484$, $P = 0.0276$, Table 3); total score of the Controlled Word Association Test ($\beta = -5.992$, $P = 5.54 \times 10^{-3}$, Table 3); Stroop colour score ($\beta = -5.348$, $P = 0.0251$, Table 3); Trail Making Test Part B, number of errors ($\beta = 2.307$, $P = 0.0679$, Table 3); Boston Naming Test, phonemic clues ($\beta = 2.410$, $P = 0.0139$, Table 3)[1]; State Anxiety Inventory ($\beta = 4.687$, $P = 0.0158$, Table 3); and Trait Anxiety Inventory ($\beta = 6.633$, $P = 0.0018$, Table 3). Figure 1(b) shows the results for each of the neuropsychological variables that are relevant for the differentiation of individuals with asymptomatic HIV- infections from seronegative individuals. For each test, relevance was determined using the ratio between the value of β and its standard error. These

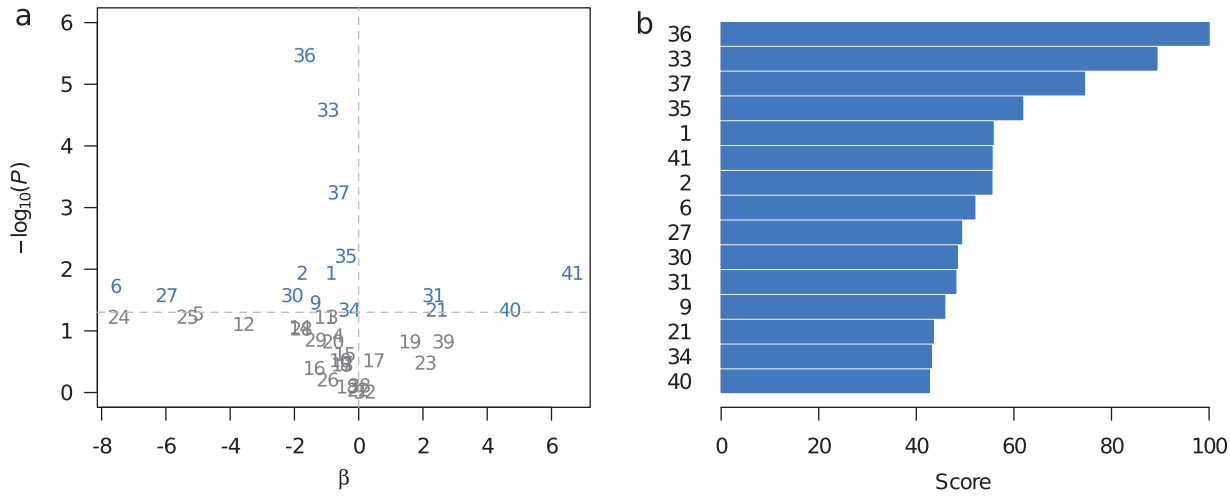

Figure 1. (a) $-\log_{10}(P)$ as a function of β, representing the corrected differences in the neuropsychological test; (b) importance of neuropsychological tests for the differentiation of the HIV asymptomatic individuals from the controls. The neuropsychological tests are numbered as described in Table 3.

results suggest that tasks 36, 33, 37, and 35 (see Table 3) are the most relevant for this differentiation. This result is consistent with previous research of HIV associated neurocognitive disorders, which have reported the impairment of cognitive flexibility (Venier, Murillo, & Godoy, 2012) and have established that motor skills are the first skills to be affected (GESIDA and SPNS, 2014; Vally, 2011).

Across all neuropsychological tasks, the average effect size d was 0.565 ± 0.304 (range 0–1.331; Table 3) and increased to 0.7475 ± 0.209 (range 0.508–1.331; Table 3) when only significant neuropsychological tasks that differed between the HIV asymptomatic and seronegative individuals were considered (Table 3 and Figure 1). These results indicate medium-to-large effect sizes of these tasks when contrasting the performances of the HIV asymptomatic and seronegative individuals.

We found that the Beck Depression Inventory, Anxiety Inventory (State) and Anxiety Inventory (Trait) are positively correlated with each other regardless of HIV status (Figure 2). In particular, the correlation Anxiety Inventory (State) and Anxiety Inventory (Trait) was 0.654 ($P_{FDR} < 0.0001$) in patients with HIV-infection and 0.844 in controls ($P_{FDR} < 0.0001$), whilst the correlation between Anxiety Inventory (State) and BDI was 0.629 ($P_{FDR} < 0.0001$) in patients with HIV-infection and 0.497 in controls ($P_{FDR} < 0.0001$), and between Anxiety Inventory (Trait) and BDI was 0.702 ($P_{FDR} < 0.0001$) in patients with HIV- infection and 0.638 in controls ($P_{FDR} < 0.0001$). In all cases, the resulting correlations differed between cases and controls ($P_{FDR} < 0.05$). There is a correlation between anxiety and depression. However, this correlation is stronger in the group of cases which may suggest that being infected with the HIV makes them more vulnerable to comorbid psychiatric disorders (Beckford Jarrett et al., 2017).

Discussion

The aim of this study was to evaluate the cognitive performance, instrumental activities of daily living, depression, and anxiety in patients with asymptomatic HIV- infections. The results show the existence of cognitive impairment in subjects with asymptomatic HIV-infections. This finding agrees with the results of other studies (Amador-Romero & Mayor-Ríos, 2005; Guevara-Silva et al., 2014; Salawu et al., 2008), which stated that cognitive dysfunction in patients with HIV might be present from the early stages of infection and might occur in neurologically asymptomatic patients.

The findings of the present study are in line with other studies that also reported poorer performances in patients with asymptomatic HIV -infections in the following variables: attention span (Amador-Romero & Mayor-Ríos, 2005; Arciniegas et al., 2013; information processing speed (Vally, 2011; Vázquez-Justo, 2001; Woods, Moore, Weber, & Grant, 2009); visuoconstructive skills (Guevara-Silva, 2013; Hesse et al., 2003; Villaseñor-Cabrera & Rizo-Curiel, 2003); learning (Cysique, Maruff, Darby, & Brew, 2006; Paul, Cohen, Navia, & Tashima, 2002), phonemic verbal fluency and auditory-verbal comprehension (Pino, 2015; GESIDA [Spanish AIDS study group] and SPNS [Spanish Secretariat for the National Plan on AIDS], 2014); and executive functions, especially cognitive flexibility (Venier et al., 2012) and motor skills (Amador, Mayor-Ríos, & Del Castillo-Martín, 2006; Vally, 2011). In addition to the significant differences between groups in these cognitive

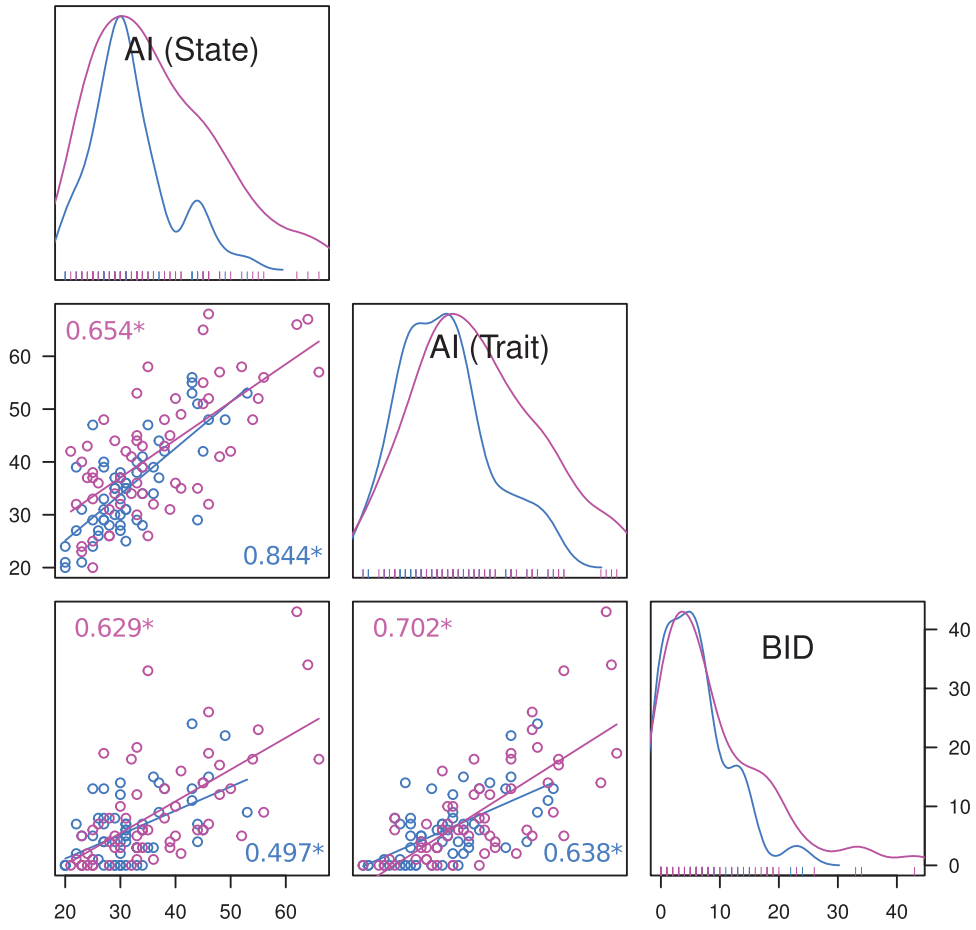

Figure 2. Scatterplot matrix of anxiety and depression neuropsychological tests in patients with asymptomatic HIV- infection (pink dots/lines) and controls (blue dots/lines). Estimated pairwise Pearson's linear correlation between tests are shown in the upper-left and bottom-right corners. Statistically significant correlations after correction for multiple testing using FDR are marked with *. AI: Anxiety Inventory; BDI: Beck Depression Inventory.

performances, medium-to-large effect sizes were also observed, which demonstrated the sensitivity of the neuropsychological tests used to differentiate patients with asymptomatic HIV- infections from the seronegative controls and associated poor performances with HIV-infection.

It calls our attention that, although some studies have found memory impairment (Faílde, Lameiras, Rodríguez, Carrera, & López, 2009; Heaton et al., 2010; Vally, 2011) as well as alterations in inhibitory control (Arciniegas et al., 2013), these findings do not agree with those of the present study. This discrepancy could be due to other factors associated with HIV or the methodology used herein. Regarding the factors associated with HIV (time since infection, viral load, CD4 cell count, and ART), the likelihood of cognitive dysfunction is hypothesized to increase as HIV-infection progresses. Although neurological complications seem to be closely related to the time elapsed since the infection was acquired (Guevara-Silva, 2013; Woods et al., 2009), this relationship is not clear-cut (Towgood et al., 2012; Woods et al., 2009). Another aspect that perhaps could explain this difference is the evaluation instrument used because HIV-infected individuals who present asymptomatic or mild neurocognitive disorders may have subtle changes in memory that remain undetected due to a lack of a well-defined clinical protocol (Manzanera, 2014; Parry, Zetler, Kentridge, Petrak, & Barber, 2017). However, Vergara, García, García, and Vergara (2010) reported that memory was generally intact and therefore preserved in the early stages of HIV-associated minor cognitive motor disorder. Regarding naming, there is no specific report in the scientific literature about this function in patients with HIV, probably because this issue has not been sufficiently studied or the condition is uncommon.

We found that patients with asymptomatic HIV-infections presented higher anxiety rates than seronegative individuals, which agreed with the findings of other studies (Martin Suarez et al., 2002; Vera-Villaroel, Pérez,

Moreno, & Allen de, 2004). However, evidence supporting the existence of this highly prevalent disorder in individuals with HIV (Elliott, 1998) is not consistent with other studies (McAllister et al., 1992; Mehta et al., 1996; Perdices, Dunbar, Grunseit, Hall, & Cooper, 1992; Pumpradit et al., 2010) that do not report anxiety. We found no significant differences in depression measures between the patients with asymptomatic HIV -infections and the seronegative controls which coincides with the findings of (Maj et al., 1991; Martin Suarez et al., 2002) who have found depression in some symptomatic HIV patients, unlike Custodio et al. (2006) who did not find depression. The presence or absence of psychiatric disorders may be determined by characteristics of the virus and / or other psychosocial factors (Hill & Lee, 2013; Sánchez-Fernández & Tomateo-Torvisco, 2014). In addition, a positive relationship between anxiety and depression was found, which was much stronger in the cases. This agrees with (Hill & Lee, 2013) who report a link between HIV- infection and psychiatric disorders. These findings may suggest that HIV- infection is a risk factor for the development of psychiatric disorders. As well as, in addition to infection, they may have comorbid psychiatric disorders that are neither diagnosed nor treated (Beckford Jarrett et al., 2017); although other psychosocial factors associated with anxiety and depression have also been reported (Laverick et al., 2017) which should be taken into account in future research.

The statistically significant correlation between anxiety and depression in HIV^{+} individuals (Figure 2) may potentially suggest that cognitive impairment could be associated with the presence of anxiety and depression disorders (Laverick et al., 2017). A recent systematic review urges for depression assessment in those with HIV infection as the appearance of depression is prior to HIV diagnosis (Sherr, Cluclas, Harding, Sibley, & Catalan, 2011). A similar study in Alzheimer's disease points out that depression and anxiety can trigger other psychiatric disorders (Jessen et al., 2014). Performance in daily living activities was preserved in assessed individuals, which agreed with Martin Suarez et al. (2002). The neurocognitive disorders already present in these subjects are most likely not severe enough to affect their functioning.

To the best of our knowledge, this study is the first in Colombia to assess the neuropsychological performances of individuals with asymptomatic HIV- infections which is a starting point for early diagnosis and decision-making regarding HAND treatment in our population. Mild cognitive impairment should be studied in its asymptomatic phase to detect individuals at risk of developing dementia and to perform the corresponding intervention (Acosta-López, Mattar Khalil, Riaño Garzon, Rincón Lozada, & Díaz Camargo, 2015). Additionally, the resulting observed power calculated based on these effect sizes and assuming 60 HIV-1 asymptomatic individuals, an equal number of seronegative controls, and a significance level of 5% (see Supplementary Material in Vélez et al., 2016 for more details) using the pwr package (Champely, 2017) in R, ranged from 78.9% (task 3) to > 99.9% (tasks 38 and 39), with an average of 94.47%.

The limitations of this study include not controlling for factors associated with HIV, such as the viral load and antiretroviral therapy, and how we were able to control for substance abuse, confounding medical conditions and psychiatric diagnoses. Clinical information from individuals that could potentially participate in this study was initially retrieved from medical records, which were carefully reviewed with the chief nurse of the *Programa de Atención Integral* of the two Health Institutions where the patients were recruited (see Acknowledgements section); this programme is monitored by the Ministerio de Salud y Protección Social de Colombia. In addition to reviewing these clinical records, potential candidates were further interviewed; this interview included clinical questions such as age, years of education, time elapsed since diagnosis, sexual orientation, neurological and neuropsychiatric disorders, and substance abuse.

In conclusion, HIV may cause neurocognitive deficits that could potentially affect functioning at personal, family, social and work-related environments, and limit their quality of life, treatment adherence, and prevention of risk behaviours in the understudied region/population of Barranquilla, Colombia.Our findings are a warning regarding the early onset and possible progression of cognitive impairment associated with HIV infection that require a precise and early diagnosis, which will contribute to the pharmacological and cognitive rehabilitation treatment. Future research studies should assess neurological and psychiatric information in individuals with HIV using standardized instruments and/or the protocol used in this study, and further replicate our findings in other regions of Colombia and/or other Latino and Non-Latino populations. Furthermore, longitudinal studies measuring cognitive performance and neurodegenerative processes in individuals with HIV are needed. These studies should include HIV-associated risk factors such as elapsed time since the infection, infection stage, viral load, CD4 count and antiretroviral treatment, in addition to neurological, psychiatric, psychosocial, ethnic and genetic data and its association with HAND (Marquine et al., 2017). In a subsequent stage of our research programme, we plan to perform genetic studies using high-throughput sequencing

technologies to better understand the contribution of virus-specific genetic variations and human-specific genetic variants to the differences in neurocognitive impairment our cohort of patients with HIV.

Note

1. Although it is promising that the phonemic clues subtest in the Boston Naming Test is the only subtest statistically significant after correction for multiple testing, this result is not enough to conclude that naming capacity is different between individuals with HIV infection and those with asymptomatic HIV.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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