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Prevalence of human immunodeficiency virus–associated cognitive impairment in a group of Hispanic women at risk for neurological impairment

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Human immunodeficiency virus (HIV)–associated cognitive impairment, a significant cause of morbidity, affects up to 30% of HIV-infected people. Its prevalence doubled as patients began to live longer after the introduction of highly active retroviral therapy. Women are now one of the fastest growing groups with acquired immunodeficiency syndrome (AIDS) in the United States and Puerto Rico, but relatively little is known about the prevalence and characteristics of cognitive dysfunction in HIV-infected women. In this study the authors investigated its prevalence in a group of HIV-1–seropositive Hispanic women in Puerto Rico. Forty-nine women with a nadir CD4 cell count of $\leq$500 cells/mm^3 were enrolled. Cognitive impairment was defined according to the American Academy of Neurology criteria for HIV dementia as modified to identify an "asymptomatic cognitively impaired" group. Observed prevalence was compared with prevalence in other populations in United States, Europe, and Australia. Differences in clinical markers and neuropsychological test performance among the cohort stratified by cognitive impairment were tested. Cognitive impairment was observed in 77.6% (38/49) of cases; asymptomatic cognitive impairment in 32.7% (16/49); minor cognitive motor disorders in 16.3% (8/49); and HIV-associated dementia (HAD) in 28.6% (14/49). Cognitive impairment did not correlate with age, CD4 cell count, viral load, or treatment modality. The cross-sectional prevalence of HIV-associated cognitive impairment was 77.6% (28.6% for HAD). These findings should enhance awareness of the prevalence of HIV-associated cognitive impairment, both clinically apparent and "asymptomatic," in Hispanic women and lead to improvements in areas such as education and compliance and to reevaluation of treatment interventions. *Journal of NeuroVirology* (2006) **12,** 356–364.

Keywords: cognitive impairment; Hispanics; HIV; prevalence; women

Introduction

The epidemiology of human immunodeficiency virus (HIV)-1 infection in women has changed markedly worldwide since its onset. In 1981, HIV-1 was not recognized as a cause of death among women. Today, women now represent one of the fastest growing groups with acquired immunodeficiency syndrome (AIDS) in the United States (Cysique *et al*, 2004; Ojikutu and Stone, 2005). The 2004 Centers for Disease Control and Prevention (CDC, 2003) HIV/AIDS Surveillance Report stated that from 1999 through 2003, the number of AIDS cases increased

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15% among women and 1% among men, and the estimated number of deaths among persons with AIDS increased among Hispanics (CDC, 2004). The United Nations Program on HIV/AIDS has reported that women make up half of the adults living with HIV-1 in the Caribbean and one third in Latin America (UNAIDS, 2004a, 2004b). Puerto Rico has shown a similar increase in the population of HIV-infected women, rising from 18% before 1990 to 27.4% in the era of highly active antiretroviral treatment (HAART). This increase in the frequency of HIV infection among Puerto Rican women is mainly a consequence of heterosexual contact (61%), although intravenous drug abuse is also a contributing factor (37%) (PRAIDS-Surveillance, 2005).

There have been conflicting reports from studies assessing the influence of gender on clinical manifestations of HIV-1 infection. Some studies report that women with HIV-1 infection may have a lower viral load and a higher CD4 cell count at seroconversion (Prins *et al*, 1999), may experience no disease progression during pregnancy (Saada *et al*, 2000; Watts *et al*, 2003), and may be more prone to develop lipodystrophy than men (Galli *et al*, 2003). It has also been suggested that women may have a higher risk of developing AIDS than men at the same viral load and CD4 cell count (Farzadegan *et al*, 1998) and present a significantly younger age at death after HIV-1 infection (38.9 ± 1.0 years) than men (42.5 ± 0.64 years) (Morgello *et al*, 2002). These findings suggest a fundamental difference in the pathophysiology of HIV infection in women as compared with men. Hormonal changes in women may play a role in HIV susceptibility and their immune response to the infection (Quinn and Overbaugh, 2005).

One of the neurological complications of HIV infection is neurocognitive dysfunction. HIV-associated dementia (HAD) is characterized by disabling cognitive, behavioral, and motor dysfunctions (Janssen *et al*, 1991; McArthur *et al*, 2005). Although the incidence of HAD has dropped by approximately half since the advent of HAART, it continues to be a significant cause of morbidity in infected patients (McArthur *et al*, 1999; Sacktor *et al*, 2002). Its prevalence, on the other hand, has actually increased owing to the enhanced survival of HIV-1–infected patients receiving HAART (McArthur, 2004; Selnes, 2005).

The clinical manifestations of HAD have changed in the post-HAART era; it now presents in a milder form, with mixed cognitive phenotypes (subcortical and cortical features), higher CD4 cell count, and variable progression patterns (Sacktor *et al*, 2002; McArthur, 2004). Studies comparing HAD before and after HAART (Maschke *et al*, 2000; Sacktor *et al*, 2001) have found a higher range of CD4 cell count (i.e., 178 to 271 and 201 to 350 cells/cubic mm) in new cases of HAD. For that reason, we will use the term *HIV-associated cognitive impairment*, instead of HAD, when talking about cognitive dysfunction in HIV-infected patients.

To date, most neurological research on HIV infection has been conducted in Caucasian males. Women, as a group, remain far less well-studied, particularly those from minority groups. Specific information about women with HIV-associated cognitive impairment is lacking. Very few studies have adequately addressed the presence of cognitive impairment in women with HIV infection and their findings are contradictory (Chiesi *et al*, 1996; Clark and Bessinger, 1997; Robertson *et al*, 2004). In this study, we investigated the cross-sectional prevalence of HIV-associated cognitive impairment in a prospectively followed cohort of immunocompromised HIV-1 seropositive Hispanic women.

Results

As part of screening for the NeuroAIDS Program, we interviewed 100 women infected with HIV-1. Of these, 67 fulfilled the inclusion criteria and were assessed using the Memorial Sloan Kettering (MSK) (Demsky *et al*, 1998) scale for activities of daily living to determine the severity of HIV dementia and 49 of the 67 women agreed to participate in a longitudinal cohort (18 refused to participate because the study required a lumbar puncture). The demographics of the 49 patients in the longitudinal cohort were similar to those of the 67 patients who met the inclusion criteria and were as follows (mean $\pm$ SD): age 36 ± 6.5 years, CD4 nadir 218.7 ± 133.6 cells/mm^3, plasma HIV RNA 3.24 ± 1.14 $\log_{10}$ copies/mL, and cerebrospinal fluid (CSF) HIV RNA 2.13 ± 0.63 $\log_{10}$ copies/ml. The main mode of transmission was heterosexual contact in 37/49 (78.7%) of cases and intravenous drug abuse (IVDA) in 7/49 (14.9%). Coinfection with hepatitis C virus was present in 9/49 patients (18.4%). Plasma HIV RNA was detectable in 43/49 (87.8%) of cases and CSF HIV RNA in 46 cases with detectable levels of virus found in 21/46 (45.6%) (Table 1). Of the 18 patients who met inclusion criteria but did not enter the longitudinal study, 15 had a MSK score of 0 or 0.5 and hence were considered normal, whereas 3 had a MSK score ≥ 1 and thus were considered to have HIV-associated cognitive impairment. These proportions are similar to the original cohort of 67 patients, thus suggesting no selection bias between the patients who met the inclusion criteria and those who entered the longitudinal study.

Neurocognitive evaluation

Altered cognitive function was observed in 38/49 (77.6%) of cases, with asymptomatic cognitive impairment in 16/49 (32.7%), minor cognitive motor disturbance (MCMD) in 8/49 (16.3%), and HIV dementia in 14/49 (28.6%) cases. Following stratification of the cohort by modified American Academy of Neurology HIV-associated dementia (m-AAN)

Table 1 Demographic data[a] of women with HIV infection screened at their primary clinics using the Memorial Sloane Kettering (MSK) scale

	*Number of patients (*n = *47)*	*Age (years)*	*Education*	*Last CD4 cell count (cells/mm³)*	*Nadir CD4 cell count (cells/mm³)*	*Log_{10} plasma viral load (copies/ml)*
No dementia (MSK 0/0.5)	43 (64.2%)	34.6 (7.1)	11.9 (2.2)	295.7 (152.5)	228.3 (129.0)	3.2 (1.2)
Demented (MSK $\geq$ 1)	24 (35.8%)	36.8 (6.8)	12.2 (1.8)	310.5 (166.6)	194.2 (148.0)	3.3 (1.0)

[a]Data are given as mean (SD).

criteria demographic characteristics of the cohort of women were compared. There were no differences with respect to age, CD4 nadir, or plasma HIV RNA ($P > .05$). Although there appeared to be differences in the proportion of individuals with cognitive impairment when stratified by mode of HIV transmission or treatment modality, these differences were not statistically significant ($P = .136$ for mode of HIV transmission and $P = .557$ for treatment modalities) (Table 2). There were nine women positive for hepatitis C virus at baseline. Of these women, two presented normal cognition, two had asymptomatic cognitive impairment, two had MCMD, and three had HIV dementia. Using a Fisher's exact test, there was no difference between groups ($P = .882$).

Figure 1 shows the distribution of scores on the cognitive domains. There were significant differences in neuropsychological performance on the cognitive domains of verbal memory ($F_{3,47} = 3.90$, $P = .015$), frontal executive function ($F_{3,47} = 5.85$, $P = .002$), psychomotor speed ($F_{3,47} = 4.32$, $P = .009$), and motor speed ($F_{3,48} = 7.74$, $P < .001$) across the four groups. Posthoc analysis using Tukey's Multiple Comparison Procedures (MCP) revealed significant differences between those with normal cognition and those with either asymptomatic impairment or HIV dementia ($P < .05$) on verbal memory and frontal executive function; between those with normal cognition and those with HIV dementia on psychomotor speed ($P < .05$); and between those with normal cognition and those with either asymptomatic impairment, MCMD, or HIV dementia on motor speed ($P < .05$).

Prevalence of HIV-associated cognitive impairment

Neurocognitive impairment (asymptomatic impairment, MCMD, and HIV dementia) according to m-AAN scale was observed in 38/49 cases (observed prevalence: 77.6%; exact binomial 95% confidence interval: 63.4%, 88.2%). Symptomatic neurocognitive impairment (MCMD and HIV dementia) was observed in 22/49 participants (observed prevalence: 44.9%; exact binomial 95% confidence interval:

Table 2 Demographic characteristics of women with HIV infection by modified American Academy of Neurology diagnostic criteria for HIV-associated dementia

	m-AAN Criteria n = 49			
	Normal n = *11 (22.4%)*	*Asymptomatic cognitive impairment* n = *16 (32.7%)*	*MCMD* n = *8 (16.3%)*	*HAD* n = *14 (28.6%)*
Age (years)	34.8 ± 7.2	34.3 ± 6.9	38.5 ± 3.9	37.9 ± 6.4
Range (min, max)	23.0, 47.0	21.0, 44.0	33.0, 45.0	28.0, 49.0
Education (years)	12.7 ± 1.9	11.6 ± 2.1	11.9 ± 1.6	12.4 ± 1.7
Range (min, max)	10, 16	9, 15	9, 14	9, 14
CD4 nadir (cells/mm³)	207.9 ± 105.4	259.8 ± 152.5	240.5 ± 117.3	167.9 ± 133.5
Range (min, max)	28.0, 426.0	5.0, 415.0	50.0, 356.0	26.0, 459.0
Plasma HIV RNA (log_{10} copies/ml)	3.4 ± 1.2	3.2 ± 1.3	2.8 ± 0.9	3.4 ± 1.1
Range (min, max)	1.7, 4.53	1.7, 5.68	1.7, 4.21	1.7, 4.90
	ND 3	ND 4	ND 1	ND 2
CSF HIV RNA (log_{10} copies/ml)	2.5 ± 0.80	2.1 ± 0.6	1.8 ± 0.2	2.1 ± 0.6
Range (min, max)	1.7, 4.14	1.7, 3.45	1.7, 2.12	1.7, 3.50
	ND 5	ND 10	ND 4	ND 9
Mode of transmission				
Heterosexual contact	100% (11/11)	80% (12/15)	62.5% (5/8)	69.2% (9/13)
IVDA	0	13.3% (2/15)	37.5% (3/8)	15.4% (2/13)
Treatment				
Naïve	9.09% (1/11)	6.60% (1/15)	0	7.70% (1/13)
ART	9.09% (1/11)	33.3% (5/15)	0	7.70% (1/13)
HAART	81.81% (9/11)	60.00% (9/15)	100.00% (8/8)	84.60% (11/13)

Notes. m-AAN, modified American Academy of Neurology HIV-associated dementia; MCMD, HIV-associated minor cognitive-motor disturbance; HAD, HIV-associated dementia; IVDA, intravenous drug abuse; ART, antiretroviral treatment; HAART, highly active antiretroviral treatment; ND, not determined.

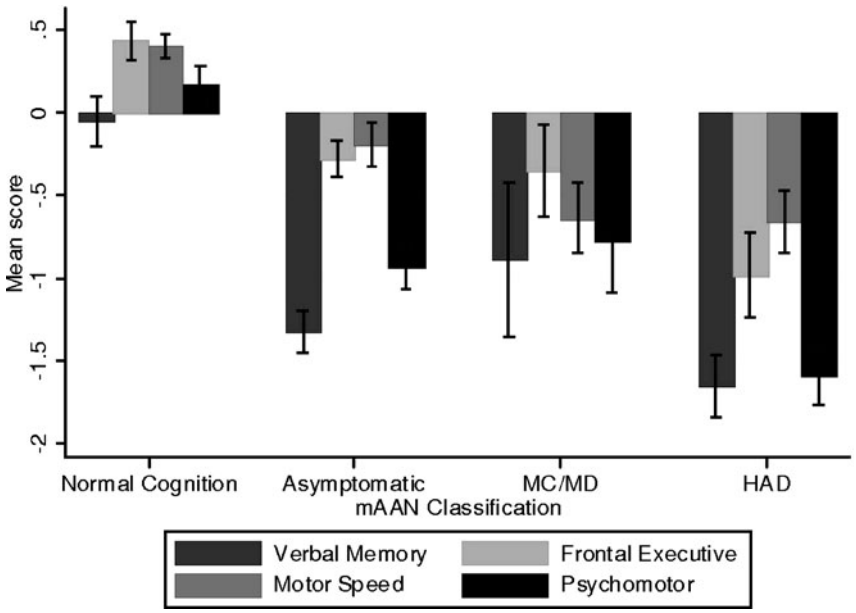

Figure 1 Neuropsychological performance by cognitive domain among women with HIV infection by modified American Academy of Neurology diagnostic criteria for HIV-associated dementia. mAAN Classification, modified American Academy of Neurology HIV-associated dementia criteria to include an asymptomatic cognitive impaired group defined as patients with abnormal neuropsychological tests (1 SD in two or more tests, or 2 SD in one or more tests, below the normal control group) but who failed to present self-reported functional/emotional disturbances in quality of life questionnaires or to present neurological findings; MCMD, HIV-associated minor cognitive-motor disorder; HAD, HIV-associated dementia.

30.7%, 59.8%). The prevalence of HIV dementia was 14/49 (28.6%; exact binomial 95% confidence interval: 16.6%, 43.3%). No significant difference was found regarding age, years of education, CD4 cell count, plasma HIV RNA levels, mode of HIV transmission, nor treatment modality between the patients with and those without HIV-associated cognitive impairment.

Discussion

Very few studies have adequately addressed the presence of HIV dementia in women. One study found no major gender differences in the development of HIV dementia (Robertson *et al*, 2004). However, in a retrospective multicenter longitudinal European study, among women with HIV-1 infection the rate of development of HIV dementia was more than double the rate among men (8.9% versus 4.1%) (Chiesi *et al*, 1996). In another retrospective study of HIV-infected women only, women aged 40 years and older had a higher incidence of HIV dementia (Clark and Bessinger, 1997). In our study, we did not find any significant difference in age groups of the patients with and without dementia (Tables 1 and 2), although the patients with dementia were slightly older than those without dementia. This could be due to the fact that we have a small sample size or that most of our patients are using HAART.

It appears that dementia is rare during the asymptomatic phase of HIV infection (McArthur *et al*, 1989) even among drug abusers (Selnes *et al*, 1990, 1992). In later stages of HIV infection, however, progression of neurocognitive deficits to frank dementia is more common. Since the introduction of HAART, the incidence of all AIDS-defining illnesses (including HIV dementia) has decreased (Dore *et al*, 1999; Sacktor *et al*, 2001). In contrast, the prevalence of HIV-associated cognitive impairment has increased, mostly because of the longer life expectancy of people with AIDS who use HAART (Sacktor *et al*, 2002; Dore *et al*, 2003; McArthur, 2004). In comparison to the findings of the North Eastern AIDS Dementia (NEAD) cohort—mostly men (66.5%)—whose patients were evaluated in a similar manner to those of the current study, we found a higher prevalence of HIV dementia (10% versus 28.6%), even though CD4 cell counts at recruitment into NEAD were lower (<200 cells/mm^3) than in our study (Sacktor *et al*, 2002).

The prevalence of HIV dementia in 28.6% of our cohort is higher than that observed in other studies performed in the United States, Europe, and Australia, where 70% to 94% of the subjects were men (Inungu *et al*, 2001; Schifitto *et al*, 2001; Sacktor *et al*, 2002; Dore *et al*, 2003; Valcour *et al*, 2004; Tozzi *et al*, 2005) (Table 3). In these studies the prevalence of HIV dementia was between 5.6% and 10.4%, and when participants were stratified by age, the younger

Table 3 Summary of prevalence studies of HIV cognitive impairment in post-HAART era and one from the pre-HAART era (Schifitto, 2001)

Study	*Cohort*	*Cohort description*	*Gender/mean (SD) age/sample size*	*Diagnostic criteria for cognitive function*	*Prevalence*
Cysique, 2004	Australia	HIV+ patients attending tertiary hospital clinics	Mostly men (99%)/47.4 ± 9.1 years/$n = 90$	2 SD below norms in 2 neuropsychological measures	CI 38.8%
Dore, 2003	Australian AIDS National Registry	All patients with AIDS	Mostly men (92%)/41 years/$n = 1754$	AAN	HAD 6.8%
Inungu, 2001	Michigan HIV/AIDS registry	All HIV/AIDS patients registered	Mostly men (82%)/>50 years/$n = 938$ 13–49 years/$n = 11676$	Specified in registry	HAD 5.6% HAD 3.3%
Sacktor, 2002	NEAD cohort	All HIV+ patients with CD4 <200 cells mm^3	Mostly men (66.5%)/41.4 (7.3) years/$n = 251$	AAN	MCMD 37% HAD 10.1% CI 47%
Schifitto, 2001	DANA cohort	High risk HIV + with CD4 < 200	Mostly men (80%)/40 years/$n = 329$	Modified AAN identifying a milder cognitive dysfunction by neuropsychological tests	Mild CI 28.9% MCMD 20.4% HAD 7.6% CI 56.9%
Tozzi, 2005	Italy	7-year survey	Mostly men (70.8%)/39.4 years/$n = 432$	Neuropsychological testing (NPZ)	HAD 10.4% CI 55.1%
Valcour, 2004	Hawaii	Longitudinal cohort of HIV+ patients	Mostly men >50 years (94% men)/$n = 103$ 20–39 years (70% men)/$n = 95$	AAN	HAD 25.2% HAD 13.7%

CI, cognitive impairment; AAN, American Academy of Neurology HIV-associated dementia criteria; HAD, HIV-associated dementia; NEAD, North Eastern AIDS Dementia; MCMD, HIV-associated minor cognitive-motor disturbance; NPZ is calculated as the mean of z-scores on neuropsychological tests.

group (13 to 49 years old) had the lowest prevalence (3.3%), suggesting that older age may be a risk factor for development of HIV dementia. In a cohort of older men (over 50 years) in Hawaii, HIV dementia was observed in 25.2% of patients using the AAN criteria (Valcour *et al*, 2004). This percentage is very similar to ours, but our population of Hispanic women was significantly younger.

The widespread use of HAART and the longest survival of HIV-1–infected patients has influenced the clinical manifestations of HIV-associated cognitive impairment (McArthur *et al*, 2003; McArthur, 2004). Cognitive impairment in the HAART era is milder with mixed phenotypes (subcortical and cortical features), higher CD4 cell count, and variable progression patterns (Sacktor *et al*, 2002; McArthur, 2004). It is likely that milder forms of HIV-associated cognitive impairment are missed or undiagnosed when assessed by established HIV dementia scales such as the AAN criteria. Notably, 77.6% of our cohort of women at risk for HIV dementia presented with some type of cognitive impairment by m-AAN criteria (asymptomatic cognitive impairment, 32.7%; MCMD, 16.3%; and HAD, 28.6%). This observed prevalence was significantly higher than that observed in other cohorts that take into account milder forms of HIV-associated cognitive impairment in the post-HAART era. These studies report a HIV-associated cognitive impairment prevalence of 38.8% to 47% (Sacktor *et al*, 2002; Cysique *et al*, 2004; Valcour *et al*, 2004; Tozzi *et al*, 2005). The higher prevalence of HIV-associated cognitive impairment observed in the DANA cohort was in patients with CD4 cell count <200 cell/mm^3 in the pre-HAART era (Schifitto *et al*, 2001); in the DANA cohort the prevalence of MCMD is similar to that observed in our cohort of Hispanic women (20.4%).

Although most of our HIV-infected women were receiving HAART, we observed that a considerable percentage of them presented with detectable plasma and CSF viral loads (plasma RNA in 82.3% and CSF RNA in 37.5%) while using an ultrasensitive kit. However, we did not find correlations between viral loads and cognitive impairment. The groups mentioned in Table 3 that report viral loads (Cysique *et al*, 2004; Valcour *et al*, 2004; Tozzi *et al*, 2005) did not observe correlations between viral loads and cognitive impairment, although they report detectable plasma viral loads. For example, Cysique *et al* (2004) used kit with similar sensitivity for viral load and reported detectable plasma viral load in 49% of patients, Tozzi *et al* (2005) reported that 67% of their population presented detectable plasma viral loads above 500 copies/ml, which are similar to our findings (67.3%), and Valcour *et al* (2004) reported a mean plasma viral load of 3.2 ± 1.5, which is very similar to our findings (3.4 ± 1.5). Therefore it is possible that in the HAART era plasma viral loads is not a good marker for cognitive impairment.

The higher prevalence observed in our cohort could be related to patient selection (HAART treatment failure), which would be anticipated to place

these women at higher risk of developing HIV-associated cognitive impairment. Because we did not evaluate men, we cannot conclude from our findings that gender plays a role in the development of cognitive impairment in HIV-infected populations. However, our findings do suggest that HIV-infected Hispanic women may be at a higher risk of developing cognitive impairment when compared with other cohorts of mostly men and merits further study because HIV-associated cognitive impairment is a significant cause of morbidity in HIV-infected patients (Welch and Morse, 2002; Cysique *et al*, 2004).

Although HAART has decreased the incidence of all AIDS-defining illnesses, once the disease is established the progression of the disease is greater among women than in men (Poundstone *et al*, 2001). Women have different healthcare utilization patterns. Fewer women obtaining care from a HIV specialist receive HAART (Moore *et al*, 2001; Gardner and Pande, 2002). However, once HAART is initiated, women can improve their immunologic function, suppress HIV-1 virus replication, and decrease morbidity and mortality (Gange *et al*, 2002). Although most of our participants were receiving HAART, 82.7% had a detectable plasma viral load and 37.5% had a detectable CSF viral load. These findings suggest poor infection control related to either gender, development of treatment resistance, different healthcare utilization patterns, or some combination of these factors.

Our findings suggest that women with HIV-1 infection may present with an increased prevalence of HIV-associated cognitive impairment when compared with other cohorts of mostly men. This difference justifies the need to further study the pathophysiology of HIV-1 infection in women. Sex hormones and sociocultural factors may play a role in the clinical presentation and/or progression of the infection. As the population of women with HIV-1 infection is increasing and living longer, these findings should enhance awareness of the problem of HIV-associated cognitive impairment in Hispanic women and, it is hoped, lead to improvement in education about the problem, compliance with treatment, and reevaluation of treatment interventions.

Methods

Participants and study design

This prospective cohort study was conducted as part of the NeuroAIDS Specialized Neuroscience Research Program (SNRP) at the University of Puerto Rico Medical Sciences Campus. Women participants were screened at their primary HIV clinics at the Puerto Rico Medical Center and the University of Puerto Rico Medical Sciences Campus. We interviewed 100 women infected with HIV-1 during 2002 to 2004 who fulfilled the inclusion criteria of (i) being 18 to 50 years old, (ii) completed at least the 9th grade of education, and (iii) having a nadir CD4 cell count $\leq$500 cells/mm^3 during the last year. Women with a history of neurodegenerative diseases or prior central nervous system (CNS) infections (e.g., toxoplasmosis), psychiatric conditions, active infections, or head trauma were excluded. These criteria identified a group of women with HIV-1 infection who were at risk of developing HIV-associated cognitive impairment (Maschke *et al*, 2000; Sacktor *et al*, 2001). The selection of participants did not relay on self-reported cognitive concerns. A control group of 34 seronegative healthy women with negative toxicology was evaluated as a reference group. The neurological and neuropsychological evaluations was performed by the same neurologist and neuropsychologist; both blinded to each other's findings.

Participant's evaluations

After giving their consent to take part in this institutional review board (IRB)-approved research project, individual participants were required to provide demographic and medical history information along with specimens for laboratory analysis. The information included age at enrollment, most likely mode of HIV-1 transmission, and nadir CD4 cell count. Plasma and CSF viral loads were determined via Ultrasensitive RNA Roche Amplicor at an AIDS Clinical Trial Group (ACTG)-certified laboratory. A macroneurological evaluation was performed by the same neurologist and consisted of a mental status examination, testing of sensory functions (including response slowing, speed of thought, and language), testing of behavior and mood, as well as standard neurologic evaluations of cranial nerves, cerebellar, motor, reflexes, and sensory evaluations. The psychosocial domain of the Menopause-Specific Quality of Life (MENQOL) questionnaire was used (Hilditch *et al*, 1996). The control group underwent the same evaluations except for the viral and immune profile determinations.

Table 4 Neurocognitive examination

Neuropaychological domain	*Test*	*Subtests*
Verbal memory	Rey Auditory Verbal Learning Test[a]	Trial 5
		Memory recall
		Delayed recognition
Frontal executive	Stroop	Word/color
	Trail Making B	Total score (seconds)
Psychomotor speed	Digit Symbol Modality Test	Total score
	Reaction Time	Visual and auditory nondominant hand
Motor speed	Trail Making A	Total score (seconds)
	Grooved Pegboard	Dominant and nondominant hand (seconds)
Visuoconstruction	Cube	Copy

[a]Spanish translation, standardized with a similar reference control group (see text description).

Table 5 Demographic factors[a] between HIV-infected and seronegative controls

	HIV-infected women	*Controls*	P values
Age	36.67 ± 6.26 (21–49)	34.24 ± 6.86 (22–49)	.097
Education	12.04 ± 1.99 (9–17)	12.68 ± 1.95 (9–16)	.153
Vocabulary subset of the Wechsler Adult Intelligent Test	51.4 ± 12.7 (26–74)	51.1 ± 15.6 (24–77)	.682
Reading subtest modality of the Woodcock-Muñoz (W 31)	25.7 ± 3.3 (17–31)	28.0 ± 1.5 (25–30)	<.001

[a]Data are mean ± SD, range in parenthesis.

Neurocognitive testing

The neuropsychological evaluation included the Wechsler Adult Intelligence Test (vocabulary subtest) and the Woodcock-Muñoz (reading subtest modalities). The second test is a Spanish substitution for the Wide Range Achievement Test previously validated for the Puerto Rican population (Davis and Rodriguez, 1979; Demsky *et al*, 1998). These tests were used to determine the pre-morbid vocabulary and reading scores (Table 4).

Neurocognitive testing performed on the 49 patients at baseline included tests of verbal memory (trial 5, delay recall, and recognition of the Rey Auditory Verbal Learning Test), frontal executive function (Stroop word/color and Trail Making B), psychomotor speed (Symbol Digit Modalities Test and visual and auditory reaction time nondominant hand), motor speed (Trail Making A and Grooved Pegboard dominant and nondominant hand), and Beck Depression Index (Bernal *et al*, 1995; Bonilla *et al*, 2004). All tests were conducted on all patients in Spanish. We calculated z-scores of the neuropsychological tests in Puerto Rican women, using the control group of 34 HIV-1–seronegative women. This control group did not differ from the HIV-infected group with regards to age, education, and sociodemographics status. No statistical difference was observed in the vocabulary premorbid status between seronegative controls and HIV-1–infected women. However, there was a significant difference in the premorbid reading status between seronegative controls and HIV-1–infected women (Table 5).

Ethnicity and education have been associated with differences in the neuropsychological performance (Durvasula *et al*, 2001; Ryan *et al*, 2005). Therefore, by recruiting a seronegative control group similar to our HIV-infected patients as a reference group for the neuropsychological performance analysis, we controled for language, educational background, and cultural issues. When comparing the neuropsychological raw scores between controls and HIV-infected groups, we observed a significant difference in motor speed (Trail Making A and Grooved Pegboard dominant and nondominant hand) and frontal executive functions (Stroop word/color and Trail Making B) scores. These findings in our HIV-infected women cohort are similar to those described in other cohorts of infected participants (Durvasula *et al*, 2001; Reger *et al*, 2002; Richardson *et al*, 2002; Selnes, 2005) (Table 6).

Cognitive impairment was determined using the American Academy of Neurology HIV dementia criteria (AAN criteria) (American Academy of Neurology AIDS Task Force 1991, 1996) modified to include an asymptomatic cognitively impaired group (m-AAN). This asymptomatic cognitively impaired group was defined as patients with abnormal neuropsychological tests (1 SD in two or more tests, or 2 SD in one or more tests, below the normal control group) but who failed to present self-reported functional/emotional disturbances in quality of life questionnaires or to present neurological findings.

Statistical analyses

All statistical analyses were performed with SAS version 8.02 (SAS Institute, Cary NC) and Intercooled Stata version 8 (StataCorp, College Station, TX). Two-sided hypothesis testing with a type I error threshold

Table 6 Comparison of the neuropsychological raw scores[a] between HIV-infected women and controls

	HIV-infected women	*Controls*	P *values*
RAVLT—trial 5	11.02 ± 2.91 (4–15)	11.76 ± 2.87 (4–15)	.257
RAVLT—memory recall	8.49 ± 3.19 (1–15)	9.65 ± 2.92 (4–15)	.099
RAVLT—delayed recognition	11.91 ± 2.76 (3–15)	12.21 ± 2.41 (6–15)	.623
Stroop (word/color)	31.30 ± 6.90 (18–49)	38.47 ± 5.83 (26–54)	<.001
Trail Making A	47.90 ± 18.90 (21–90)	35.94 ± 9.30 (20–57)	.001
Trail Making B	128.83 ± 59.54 (50–240)	92.71 ± 37.29 (44–190)	.002
Digit Symbol Modality Test	43.90 ± 16.33 (9–90)	49.41 ± 10.71 (28–67)	.069
Reaction Time—visual nondominant hand	.73 ± .16 (.50–1.40)	0.68 ± 0.12 (.42–.94)	.184
Reaction Time—auditory nondominant hand	.73 ± .27 (.30–2.00)	0.68 ± 0.16 (.20–1.10)	.380
Grooved Pegboard—dominant hand	74.44 ± 13.79 (50–102)	66.73 ± 14.41 (50–108)	.017
Grooved Pegboard—on dominant hand	83.08 ± 15.63 (55–117)	72.33 ± 12.78 (53–106)	.002
Cube (copying)	2.02 ± .99 (0–3)	2.03 ± 1.02 (0–3)	.968

[a]Data are mean ± SD, range in parenthesis.

for significance of .05 was used to address the primary goals of the project: to estimate the prevalence of HIV-associated cognitive impairment in a cohort of Hispanic women. Based on an a priori power analysis, it was estimated that we would need to recruit at least 45 women to be able to estimate a 95% confidence interval around an observed prevalence of 60% with a precision of ±10%. Thus, the current enrollment of 49 women is adequate to address this aim. However, posthoc power calculations for subgroup analyses (e.g., to estimate the prevalence of HIV-associated cognitive impairment among older versus younger HIV-seropositive Hispanic women) was not possible due to this sample size constraint.

Following stratification of the cohort by the presence of neurocognitive impairment, group differences were assessed with use of appropriate statistical tests. For continuous variables, such as age or CD4 cell count, Student *t* test was employed. For categorical variables, such as mode of transmission, chi-square test of association was used. All data are reported as mean ± SD.

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