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Associations of cigarette smoking with viral immune and cognitive function in human immunodeficiency virus–seropositive women

Valerie Wojna,[1,2] Lizbeth Robles,[1] Richard L Skolasky,[3] Raul Mayo,[1,4] Ola Selnes,[5] Tania de la Torre,[1] Elizabeth Maldonado,[1] Avindra Nath,[5] Loyda M. Meléndez,[1,6] and Jose Lasalde-Dominicci[1,7]

[1]NeuroAIDS Program and [2]Departments of Internal Medicine, Neurology Section, [4]Physical Medicine and Rehabilitation, [6]Microbiology, and [7]Biology and Chemistry, University of Puerto Rico, San Juan, Puerto Rico; and Departments of [3]Orthopedic Surgery and [5]Neurology, Johns Hopkins University, Baltimore, Maryland, USA

Cigarette smoking alters the immune system and may improve cognitive deficits in neuropsychiatric disorders. Smoking prevalence is high in human immunodeficiency virus (HIV)–infected patients; however, its effect on HIV-associated cognitive impairment remains unknown in the era of antiretroviral treatment. The authors examined associations of smoking with viral immune profile and cognitive function in a cohort of HIV-seropositive women. This observational cross-sectional study included 56 women (36 HIV-seropositive and 20 HIV-seronegative) surveyed with a tobacco questionnaire: the Fagerström Test for Nicotine Dependency. Viral immune status was obtained 6 to 12 months before questioned. Neurocognitive testing (NP) assessed verbal memory, frontal/executive function, psychomotor speed, and motor speed. A reference group of HIV-seronegative women was used to calculate standardized z-scores. Cognitive impairment was classified using a modified American Academy of Neurology criteria, adding an asymptomatic group based on NP tests. Statistics included parametric and nonparametric tests. HIV-seropositive women were more likely to report a history of smoking ($P = 0.028$). Among them, current smoking correlated with higher plasma viral load ($P = 0.048$), and history of smoking correlated with lower CD4 cell count ($P = 0.027$). The authors observed no associations between cognitive impairment and either current or past history of smoking and no differences in neurocognitive domain scores between HIV-seropositive and -seronegative women or between those with and without a history of smoking. However, restricting analysis to HIV-seropositives showed a significant better performance on the frontal/executive domain in those with history of smoking. In summary, history of smoking correlated with better frontal/executive cognitive domain performance in HIV-seropositive women and with worse viral immune profile.
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Introduction

Cigarette smoking effect on the immune system function may depend on the smoker's duration of smoking, gender, and ethnicity (Tollerud *et al*, 1989; Tollerud *et al*, 1991; Sopori, 2002). In light and moderate smokers, the CD4 cell count increases; however, in heavy smokers, the count decreases (Holt, 1987). Nicotine, as one of the components of cigarette smoking, may be responsible for these immunological changes (Sopori, 2002). Furthermore, in the brain,

Address correspondence to Valerie Wojna, MD, NeuroAIDS Program, PO Box 365067, San Juan, Puerto Rico 00936-5067. E-mail: vwojna@rcm.upr.edu

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nicotine may have anti-inflammatory effects (Shytle *et al*, 2004; De Simone *et al*, 2005).

Human immunodeificiency virus (HIV)–seropositive patients (Burns *et al*, 1991; Mamary *et al*, 2002; Gritz *et al*, 2004), as well as schizophrenic patients (O'Farrell *et al*, 1983; Masterson and O'Shea, 1984; Hughes *et al*, 1986; Ziedonis *et al*, 1994; de Leon *et al*, 1995), have a higher prevalence of smoking. Most previous studies involving smoking in HIV-seropositive patients were performed in men without highly active antiretroviral treatment (HAART). In the pre-HAART era, men who smoked were more likely to seroconvert to HIV than were exposed men who did not smoke. Once infected, HIV-seropositive smokers presented a higher serum β2-microglobulin level and an increased CD4 cell count, which lasted approximately 2 years (Royce and Winkelstein, 1990; Burns *et al*, 1991). Studies performed in the post-HAART era, during which the incidence of opportunistic infections has decreased markedly, have found that smoking is associated with a decreased quality of life and an increased mortality (Page-Shafer *et al*, 1996; Turner *et al*, 2001; Crothers *et al*, 2005). Regardless of treatment modalities, no association between smoking and progression to acquired immunodeficiency syndrome (AIDS) was found (Burns *et al*, 1991; Conley *et al*, 1996; Furber *et al*, 2007).

Clinical studies on the effect of smoking on cognitive function have shown mixed or inconclusive results. Cross-sectional, longitudinal, and population-based studies involving healthy elderly subjects demonstrated that smoking is associated with poor performance in cognitively demanding tasks (Hill *et al*, 2003) and executive function (Razani *et al*, 2004) and with greater decline in the Mini-Mental Status Examination (Ott *et al*, 2004). Likewise, smoking presents a higher risk of late-life cognitive impairment (Galanis *et al*, 1997; Richards *et al*, 2003). Nonetheless, clinical studies involving nicotine administration in healthy smokers and nonsmokers have shown an enhancement of cognitive function, mostly involving attention and psychomotor speed domains (Sacco *et al*, 2004). The prevalence of smoking is higher in subjects with neuropsychiatric disorders, such as attention deficit hyperactivity disorder, affective disorders, schizophrenia, Parkinson's disease, and Alzheimer's disease. It is likely that smoking or nicotine may improve the neurocognitive deficits present in these disorders (Sacco *et al*, 2004, 2005; Olincy *et al*, 2006). Stimulation of central nicotinic receptors has been shown to enhance neurotransmitter release, modify circuit excitability, and influence synaptic plasticity (Dani and Bertrand, 2007).

There are limited clinical studies evaluating the effect of smoking on cognitive function in people with HIV infection. Prior to HAART, Burns *et al* found that current smokers were more likely to develop AIDS dementia complex (HIV-associated dementia) than those who never smoked. However, these patients were associated with intravenous drug abuse, lower CD4 cell counts, and decreased use of antiretroviral treatment (Burns *et al*, 1991). Animal studies performed by Gonzalez-Lira *et al*, using event-related potentials (indicators of cognitive processing), observed that HIV gp120 (glycoprotein derived from HIV) interfered with cholinergic neurotransmission and affected event-related potential and motor coordination, whereas the simultaneous nicotine administration obliterated this effect (Gonzalez-Lira *et al*, 2006). In an *in vitro* model for HIV dementia consisting of cultured microglial cells synergistically activated by the addition of interferon gamma (INFγ) and HIV gp120, pretreatment with nicotine and galantamine (nicotine agonist) attenuated microglial inflammatory response to gp120 and tat (Giunta *et al*, 2004).

At present, the effect of smoking on the course of HIV-associated cognitive impairment in the HAART era remains unknown. Studies performed in the pre-HAART era involved mostly men. However, women constitute the fastest growing group of persons with HIV/AIDS, and as a group, they remain far less studied, particularly those from minority populations. Studies addressing gender differences in the clinical presentation of HIV infection have shown greater disease progression in women despite HAART (Poundstone *et al*, 2001). In addition, recent studies from our group suggest that Hispanic women may be at greater risk of HIV-associated cognitive impairment (Wojna *et al*, 2006). In this study, we examined associations of smoking history and dependence with viral immune profile and cognitive function in a cohort of HIV-seropositive women.

Results

The 36 HIV-seropositive women tended to be older on average than the 20 HIV-seronegative women (39.8 years [SD = 6.3] versus 35.9 [6.2], $P = .030$), but there were no significant differences regarding years of education (12 years), or annual income (mode of <$5000) (Table 1). Of the 36 HIV-seropositive women, 27 presented with menstrual cycles (2 with irregular cycles, 1 with amenorrhea, and 24 with

Table 1 Demographic characteristics stratified by HIV serostatus

	HIV-1 seropositive ($n = 36$)	HIV-1 seronegative ($n = 20$)	P value[a]
Age, years[b]	39.8 (6.3)	35.9 (6.2)	.030
Education, years[b]	12.5 (1.7)	12.7 (1.9)	.741
Age started smoking[b]	15.3 (2.3)	18.1 (2.0)	.007
History of smoking[c]	24 (67%)	7 (35%)	.028
Current smoking[c]	15 (42%)	4 (20%)	.143

[a]Significant P value <0.05; [b]mean (SD); [c]number (percentage).

Table 2 Virologic and immune markers stratified by current smoking and history of smoking

	Current smoking[a]			History of smoking		
	Yes	No	*P* value[b]	Yes	No	*P* value
CD4 cell count, cells/mm^3	275.1 (164.5)	368.8 (221.0)	.174	277.7 (192.0)	433.8 (188.3)	.027
HIV viral load, $\log_{10}$ copies/ml						
Plasma	3.4 (1.4)	2.5 (1.1)	.048	3.1 (1.4)	2.5 (1.2)	.223
CSF	2.5 (1.1)	2.2 (0.8)	.399	2.3 (0.9)	2.4 (0.9)	.884

[a]Mean (SD); [b]significant *P* value <0.05.

regular menses), 6 had hysterectomy, and 3 had menopause. Two women were using hormonal replacement therapy (Provera) at the time of the evaluation. All HIV-seronegative women ($n = 20$) presented with regular menstrual cycles. History of smoking was reported in 31 (55%) women. HIV-seropositive women were more likely than seronegatives to report a history of smoking (24 of 36 versus 7 of 20, Fisher's exact $P = .028$). Among those with a history of smoking, HIV-seropositive women tended to begin smoking at a younger age (15.3 years [SD = 2.3] versus 18.1 [2.0], $P = .007$). History of smoking in the HIV-seropositive women correlated with lower CD4 cell count ($P = .027$), whereas current smoking correlated with higher plasma viral load RNA ($P = .048$). No correlations were observed between CSF viral load among HIV-seropositive women who had history or were currently smoking (Table 2). From the 15 HIV-seropositive women who reported to be current smokers, 10 specified the number of daily cigarettes. A majority (6/10) tended to smoke fewer than 10 cigarettes per day, whereas the others (4/10) reported smoking between 11 and 30 cigarettes per day.

Using the modified American Academy of Neurology (AAN), we classified individuals with asymptomatic impairment, minor cognitive motor disorder, and HIV-associated dementia as cognitively impaired. There were no associations observed between presence of cognitive impairment and either current smoking (Fisher's exact $P = 0.175$) or history of smoking (Fisher's exact $P = 0.293$). There were also no differences in neurocognitive domain test scores between HIV-seropositive and HIV-seronegative women or between those with and those without a history of smoking. However, when the analysis was restricted to HIV-seropositive women, those with a history of smoking had a significantly higher score (i.e., they performed better) on the frontal executive domain ($P = 0.007$) than did those without a history of smoking. There were no differences in cognitive domain performance when the data were stratified by current smoking. When analyzing performance among the individual tests/subtests, we observe that HIV-seropositive women with history of smoking performed better on the Stroop Color Word Test ($P = 0.005$) and the Symbol Digit Modality Test ($P = 0.004$) than those without history of smoking (Table 3). When stratified by current smoking we observed that HIV-seropositive women continued to perform better in the Stroop Color Word Test ($P = .041$) (not shown on Table 3). There were no differences among HIV-seropositive women with either history or current smoker regarding age, education, and annual income.

Discussion

Although women smoke less than men, the prevalence of cigarette smoking in young women is greater than among older women (Williams, 2002). Women who smoke, in contrast to men who smoke, have greater difficulty quitting (Perkins, 2001; MMWR 2006; Perkins *et al*, 2006). In the present study, the HIV-seropositive women began smoking at an earlier age (15.3 years) than the seronegative women. It is known that cigarette smoking is associated with other addictive behaviors (Burns *et al*, 1991; Mamary *et al*, 2002), which could predispose women smokers to risky behaviors such as drug abuse and sexual promiscuity, thus placing them at greater risk of developing HIV infection at an earlier age (CDC, 2006). Younger women with addictive behavior and HIV infection could present with increased risk of cognitive impairment later in life due to the additive effect of comorbid factors (e.g., drug abuse, aging, and HIV infection) (CDC, 2006; Wojna and Nath, 2006). Awareness of the problem and the identification of these women at risk of developing or presenting an addictive behavior could benefit from early intervention (Niaura *et al*, 2000).

Cigarette smoking alters the immune system function. Its effect may depend on the smoker's duration of smoking, gender, and ethnicity (Tollerud *et al*, 1989; Tollerud *et al*, 1991; Sopori, 2002). In our study, HIV-seropositive women with a history of smoking presented with a lower CD4 cell count. These findings are similar to those obtained in the Women's Interagency HIV Study (WIHS) (Feldman *et al*, 2006). Smoking may have an immunosuppressive effect on innate immunity by activating macrophages and adaptive immunity through altered production of antibodies and T-cell responsiveness

Table 3 Neurocognitive domain and neuropsychological tests/subtests scores, stratified by history of smoking

	HIV-seropositive		
	No	Yes	p-value[a]
	History of smoking		
I. NPZ[b]	−0.35 (0.60)	0.05 (0.65)	0.085
II. Neuropsychological tests/subtests			
1. Frontal Executive	−1.16 (0.95)	−0.20 (0.93)	0.007
a. Stroop Color Word Test	−1.845 (1.096)	−0.705 (1.077)	0.005
b. Trail Making B	−0.466 (1.431)	0.295 (1.122)	0.089
2. Psychomotor Speed	−0.32 (0.62)	0.08 (0.74)	0.122
a. Symbol Digit Modality Test	−1.019 (0.679)	−0.093 (0.901)	0.004
b. Visual Reaction Time non dominant hand	−0.090 (1.207)	0.124 (1.051)	0.511
c. Auditory Reaction Time non dominant hand	0.162 (0.459)	0.205 (0.682)	0.781
3. Verbal Memory (RAVLT[c])	−0.08 (0.77)	0.33 (0.61)	0.280
a. Trial 5	−0.497 (0.920)	−0.004 (0.714)	0.687
b. Memory Recall	0.263 (1.006)	0.420 (0.894)	0.608
c. Delayed Recognition	0.466 (0.737)	0.587 (0.584)	0.525
4. Motor Speed	−0.27 (0.83)	−0.10 (1.12)	0.637
a. Trail Making A	−0.383 (1.746)	0.177 (1.438)	0.400
b. Grooved Pegboard dominant hand	−0.077 (0.673)	−0.164 (0.882)	0.988
c. Grooved Pegboard non dominant hand	−0.352 (1.089)	−0.303 (1.613)	0.637
	Current smoking		
	HIV-seropositive		
	No	Yes	
I. NPZ	−0.15 (0.57)	0.01 (0.76)	0.454
II. Neuropsychological tests/subtests			
1. Frontal Executive	−0.72 (1.03)	−0.24 (0.99)	0.173
2. Psychomotor Speed	−0.06 (0.62)	−0.04 (0.87)	0.912
3. Verbal Memory	0.23 (0.64)	0.28 (0.72)	0.842
4. Motor Speed	−0.25 (0.85)	−0.02 (1.25)	0.521

[a]Comparisons made across history of smoking among HIV-1 seropositive using Student's t-test. Significant p value <0.05.
[b]NPZ= neuropsychological tests z-score.
[c]Rey Auditory Verbal Learning Test.

(Sopori, 2002). Nicotine, as an active compound of cigarette smoking, may also have neuroimmune immunosuppressive effects (Sopori, 2002). These immune changes may make HIV-seropositive women more vulnerable to HIV disease progression. We also found that the HIV-seropositive women in our study presented with higher plasma HIV viral load. Although poor antiretroviral treatment (ART) compliance could be one reason for these findings, nicotine may alter ART metabolism by increasing clearance and decreasing efficacy. The effect of cigarette smoking on ART may vary according to gender. In the Women's Interagency HIV Study (WIHS) longitudinal study, investigators found that HIV-seropositive HAART-compliant women, who were currently smoking, presented poorer viral and immunological response to HAART than did nonsmokers. These findings suggest that in HIV-seropositive women, cigarette smoking may decrease the efficacy of HAART. Contrary to studies involving mostly men in the pre-HAART era, HIV-seropositive women who smoke presented with a higher risk of death and development of AIDS (Feldman *et al*, 2006).

Another factor to consider when studying nicotine's effects in women is that estrogen may synergize with nicotine in neurocognitive function because neurons of the hippocampus have both estrogen and nicotinic receptors (Hosli *et al*, 2000). Estrogen interacts with the $\alpha 7$ nicotinic receptor by attenuating the toxicity induced by amyloid β, thus enhancing nicotine's neuroprotective effect (Svensson and Nordberg, 1999). It is noteworthy that estrogen increases the metabolism of nicotine (Mueck and Seeger, 2005; Benowitz *et al*, 2006).

Although no associations were observed between history of smoking and cognitive status as determined by the mAAN, when the analysis was restricted to HIV-seropositive women, smokers had a significantly higher score (performed better) on the frontal/executive domain (most likely driven by the Stroop Color Word Test performance) and in the Symbol Digit Modality Test, which forms part of our psychomotor speed cognitive domain. Interestingly the performance in the Stroop Color Word performance was maintained in HIV-seropositive women who were currently smoking than did nonsmokers. Comparing our findings with those observed by other investigators evaluating the effect of smoking and nicotine has on cognitive function is difficult because not all investigators use the same neuropsychological battery. However, when comparing our results with those seen in healthy smokers, wherein smoking improved selective attention (as determined by the Stroop Color Word Test) and psychomotor speed (as determined by Reaction Times) our findings are similar (Sacco *et al*, 2004).

Our observational study shows that women with HIV infection presented with an addictive behavior at a younger age, and those of this group who smoked presented with a more severely altered viral immune profile (lower CD4 cell counts and higher plasma viral loads). However, those HIV-seropositive women who had history of smoking performed better in the frontal/executive cognitive domain and in the Symbol Digit Modality Test as a measure of psychomotor speed. Whereas this finding needs to be confirmed in future studies, it is possible that nicotine may have a beneficial effect on cognition in HIV-seropositive

women while using HAART; still, smoking may be detrimental to their immune system. In view of the possible benefits nicotine may offer in improving cognitive performance, it is reasonable to consider studying the dose-response effects of nicotine on cognitive function and viral immune status. Using standardized nicotine dose and administration in clinical trials, we could assess these risk-benefit effects. Along these lines, it will be important to evaluate the use of nicotine in a safer form (e.g., patch, gum, etc.) on the cognitive performance of HIV-infected persons. Furthermore, the presence of nicotinic receptors in peripheral macrophages suggests that nicotine could potentially affect the cholinergic pathway, which might function as an important regulator of inflammation as well as immune responses (Tracey, 2002; Wang *et al*, 2003). Because new antiretroviral agents are available, it is possible that nicotine could serve as an adjuvant treatment in HIV-associated cognitive impairment. Although our study is limited by the sample size, the possibility of cigarette smoking effects on both the immune system and in cognitive function is worth studying further. Controlled clinical trials (e.g., nicotine patches) to evaluate independently the effects of nicotine on the viral immune profile in parallel with its effects on cognitive function in HIV-infected patients could clarify these effects in women with HIV infection.

Methods

Participants and study design
This study was conducted as part of the NeuroAIDS Specialized Neuroscience Research Program (SNRP) at the University of Puerto Rico Medical Sciences Campus. We evaluated 56 women, 20 HIV-seronegative and 36 HIV-seropositive women from the Hispanic-Latino Longitudinal Cohort of HIV-seropositive women, who fulfilled the inclusion criteria of (i) being 18 to 50 years old; (ii) having completed at least the 9th grade of education; and (iii) having a nadir CD4 cell count $\leq$500 cells/mm^3 during the past year. Excluded were women with a history of neurodegenerative diseases or prior central nervous system (CNS) infections (e.g., toxoplasmosis), psychiatric conditions, active infections, or head trauma.

Evaluation of participants
The evaluation or participants has been described previously (Wojna *et al*, 2006). 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, nadir and current CD4 cell counts, and menstrual history. Plasma and CSF viral load was determined via Ultrasensitive RNA Roche Amplicor at an Adult Clinical Trial Group (ACTG)-Certified Laboratory. A macroneurological evaluation, performed by the same neurologist (V.W.), 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 neurological evaluations of cranial nerves, cerebellar, motor, reflexes, and sensory evaluations. The evaluating neurologist was blinded to the smoking status. The psychosocial domain of the Menopause-Specific Quality of Life (MENQOL) questionnaire was used (Hilditch *et al*, 1996). The HIV-seronegative group underwent the same evaluations except for the viral and immune profile determinations.

Determination of nicotine use and dependence
The cohort completed a self-reported questionnaire intended to collect information about smoking history, including age of smoking onset, duration of smoking, and smoking interruption. Participants afterwards answered the Spanish translation of the Fagerström Test for Nicotine Dependence (FTND) (Becona and Vazquez, 1998).

Neurocognitive testing
The neuropsychological evaluation included the Wechsler Adult Intelligence Test—Vocabulary subtest and the Woodcock-Muñoz—Reading subtest modalities W31. 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 estimate the participants' premorbid cognitive ability status. The neurocognitive testing evaluation consisted of verbal memory (trial 5, delay recall, and recognition of the Rey Auditory Verbal Learning Test), frontal executive function (Stroop Color Word Test—word/color subtest and Trail Making B), psychomotor speed (Symbol Digit Modalities Test and Visual and Auditory Reaction Time nondominant hand), and motor speed (Trail Making A and Grooved Pegboard dominant and nondominant hand). All tests were conducted in Spanish on all patients. We calculated z-scores of the neuropsychological tests in Puerto Rican women, using a reference group of 34 HIV-seronegative women. This reference group did not differ from the HIV-seropositive women group with regard to age, education, and annual income. There were no differences in ethnicity and gender because all participants were Hispanic women. No statistical difference was observed in the premorbid cognitive ability between HIV-seropositive and

HIV-seronegative women. These women did not participate in the smoking questionnaire.

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 deficits (Wojna *et al*, 2006).

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 for significance of .05 was used to address the primary goal of the project: examine the associations of smoking history and dependence with viral immune profile and cognitive function in a cohort of HIV-seropositive women.

Following stratification of the cohort by HIV serostatus and history of smoking, group differences in neuropsychological raw scores were assessed by using a two-way analysis of variance (ANOVA). The two factors in this model were HIV serostatus and history of smoking. Among the HIV-seropositive women, differences in demographic characteristics and virologic and immune markers were assessed as a function of current smoking and history of smoking. Continuous variables were assessed using Student's *t* test, and categorical variables were assessed using Fisher's exact test. To test the influence that smoking may have on cognition, we examined differences in cognitive domain and neuropsychological tests/subtests scores using either current smoking or history of smoking as an independent variable. The null hypothesis of no difference was tested using a one-way ANOVA. To adjust for multiple comparisons across the five cognitive domains, we used a Bonferroni-adjusted *P* value of .01 for statistical significance.

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