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Neuropsychological functioning in a cohort of HIV infected women: Importance of antiretroviral therapy

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Abstract

We evaluated neurocognitive function in 149 HIV-seropositive and 82 seronegative women enrolled in the Women's Interagency HIV Study (WIHS), a large multi-center study of disease progression in women living with HIV/AIDS. We evaluated the prevalence of abnormal neuropsychological (NP) test findings in HIV-seropositive and seronegative women and factors associated with increased risk of abnormal NP test performance. Risk of NP impairment was no higher for HIV positive women receiving antiretroviral therapy at testing than for HIV-negative women (*OR* = 1.00). However, the risk of abnormal NP performance increased significantly for seropositive women not receiving antiretroviral therapy (*OR* = 2.43). Further, treatment status was a significant predictor of NP impairment in a multivariate analysis that included viral load (*OR* = 1.48) and CD4 count (*OR* = 1.08) which were not significant. The multivariate analyses controlled for substance use, age, education, head injury, ethnicity, estimated IQ, and psychological distress. This study emphasizes the critical association of antiretroviral therapy with the risk of neurocognitive impairment in women living with HIV/AIDS. (*JINS*, 2002, *8*, 781–793.)

Keywords: HIV, AIDS, Women, Women's health, Neuropsychology, Memory, Dementia, Neuropsychological tests, Antiretroviral therapy, Zidovudine

INTRODUCTION

The types and prevalence of neuropsychological (NP) impairment associated with HIV have been well-described in studies of HIV-seropositive (HIV+) men who have sex with men (MSMs; Bornstein et al., 1993; Heaton et al., 1996; Miller et al., 1990) and in groups of primarily male injection drug users (Chiesi et al., 1996; but cf. Marder et al., 1992). Very few published data are available on the neurocognitive status of HIV+ women (Fox-Tierney et al., 1999). However, prevalence rates for neurocognitive impairment obtained from studies of HIV+ males cannot necessarily be applied to females with HIV. Compared to HIV+ males, women with HIV/AIDS are typically less educated, less likely to receive antiretroviral therapy and more likely to have a history of injection drug use, variables that appear to be associated with increased risk of HIV-related neurocognitive complications (Chiesi et al., 1996; Guinan & Leviton, 1995; Satz et al., 1993). Indeed, a study conducted in Europe reported that dementia was reported significantly more frequently as the AIDS-defining condition for women compared to men (Chiesi et al., 1996);

There are even fewer data available on the types and prevalence of NP defects in HIV+ women without dementia. One of the first published studies on NP performance in HIV+ women (Stern et al., 1998) reported no significant differences between groups of asymptomatic HIV+ and HIV− women on a battery of clinical tests. However, given the small sample size (total $n = 31$) and the asymptomatic status of the HIV+ women tested, the likelihood of Type II error might be substantial. Mason et al. (1998) reported

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evidence of psychomotor and memory defects in women carrying an AIDS diagnosis when compared to controls but noted no significant defects for women with less advanced disease. More recently, Durvasula et al. (2001) studied performance of a large cohort of HIV+ and HIV− women on a brief battery of NP measures. They report that analyses controlling for demographic and substance abuse variables indicated that HIV serostatus predicted impaired psychomotor speed but did not predict significantly motor speed or memory function.

Rates of HIV-associated NP impairment vary as a function of a number of factors, such as severity of disease as measured by CD4 counts and/or viral load (e.g., Chiesi et al., 1996; Heaton et al., 1995). Antiretroviral therapy also influences rates of NP deficits. Earlier studies examining reverse transcriptase inhibitors (typically zidovudine/AZT) typically showed an improved performance in treated compared with untreated patients on clinical measures of attention, memory, motor skills and general mental speed (Baldeweg et al., 1995; Brouwers et al., 1990; Chiesi et al., 1996; Damos et al., 1997; Elovaara et al., 1994; Martin et al., 1998; Reinvang et al., 1991; Schmitt et al., 1988; Sidtis et al., 1993). Recent cross-sectional studies of HIV+ drug abusers have reported that ZDV-treated subjects show faster reaction times when compared with untreated patients despite lower CD4 counts (Martin et al., 1998, 1999b). More recent cross-sectional and longitudinal studies also report evidence of NP benefits for persons on combination therapy with or without a protease inhibitor (Ferrando et al., 1998; Sacktor et al., 1999). Notably, a recent study reported that women treated with highly active antiretroviral therapy (HAART) showed significant improvement on a brief NP test battery compared to women who had not received HAART (Cohen et al., 2001).

In this paper, we report NP findings from a large sample of HIV+ and high-risk HIV− women enrolled in the Women's Interagency HIV Study (WIHS), a larger investigation of disease progression in women living with HIV/AIDS. WIHS is an ongoing NIH-funded multi-center study of approximately 2000 HIV+ and 550 HIV− women with centers in Los Angeles, San Francisco, Chicago, New York, and Washington, DC (Barkan et al., 1998). All women enrolled in the WIHS receive comprehensive medical and laboratory evaluations with a relatively brief assessment of psychological function every 6 months. In this article we report the results of a neuropsychological substudy of 231 WIHS subjects conducted at the Los Angeles and Chicago centers. We studied prevalence rates of NP deficits as a function of disease severity and antiretroviral therapy status.

METHODS

Research Participants

We tested 149 HIV seropositive (HIV+) and 82 seronegative (HIV−) women enrolled in the WIHS at Los Angeles ($n = 144$) or Chicago ($n = 87$) centers. Subjects were tested between April 1995 and April 1997. Detailed information on the national WIHS design and methods is reported elsewhere (Barkan et al., 1998). We recruited women for the NP substudy during their regular WIHS follow-up visit through referrals from WIHS personnel. In this article, we report results obtained with English speaking women[1] who were recruited and enrolled according to the following criteria: no history of AIDS defining neurological conditions, including clinical dementia[2]; no history of schizophrenia or bipolar disorder; no evidence of intoxication at testing; and no history of epilepsy. We tested 41 (28%) HIV+ women with immunologic AIDS (CD4 $\leq$ 200) and 108 (72%) women without an immunologic AIDS diagnosis. Eighty-two HIV+ women (55%) were receiving antiretroviral therapy (ART) at testing. The majority of treated women, 72 (88%) were receiving mono or combination therapy with reverse transcriptase inhibitors such as zidovudine, stavudine or lamivudine and the remaining 10 (12% of treated subjects) were on highly active antiretroviral therapy (HAART), combination regimens that included at least one protease inhibitor. All women were ambulatory without acute illness and we conducted all testing on an outpatient basis. Approximately 5% of the women approached refused to participate in the study. All women enrolled were capable of giving written informed consent. Participants received $25 compensation as well as $10 toward transportation costs. The study received IRB approval from each participating institution.

We queried subjects about types of street drugs used and their duration of abuse of each specific drug. We constructed an index of lifetime drug use by summing the years a subject used cannabis, opiates, and cocaine and years of abusive alcohol use, defined as 3 or more drinks per day. We classified subjects as having a *low* (accumulated 0–9 years), *medium* (10–30 years), or *high* (31–121 years) drug use history based on tertile cuts of these summary measures. Women also reported whether or not they had taken any medication with potentially sedating side effects, such as antihistamines, in the prior 24 hr.

Tables 1 and 2 show demographic data and mean CD4 cell counts for the HIV+ and HIV− groups. We present data for HIV+ subjects according to two different classifications: disease stage and antiretroviral treatment status, reflecting our prior decision to investigate each variable as a potential mediator of cognitive impairment. Given the extreme paucity of published NP data for HIV+ women, we report full details for both series of analyses. In Table 1, the HIV+ group is subdivided by disease status (HIV+/CD4 $>$ 200 and HIV+/CD4 $\leq$ 200). The HIV−, HIV+/CD4 $>$ 200 and HIV+/CD4 $\leq$ 200 groups did not differ

[1]A small sample of Hispanic women were tested with Spanish versions of the NP tests, but these data will be reported separately.

[2]The parent WIHS project excludes women with evidence of clinical dementia. Consequently study data pertain to the spectrum of cognitive dysfunction in women whose impairment fell short of frank dementia.

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Table 1. Demographics and covariate measures by disease status ($N = 231$)

Variable	HIV negative ($n = 82$) *M* (*SD*) (range)	HIV positive cd4 > 200 ($n = 108$) *M* (*SD*) (range)	HIV positive cd4 ≤ 200 ($n = 41$) *M* (*SD*) (range)	Significance test *F* (*p*)
Age in years	34.6 (8.8) b[1] (19–59)	36.3 (7.5) ab (19–55)	37.7 (7.2) a (25–53)	2.26 (.11)
Grade attained	11.9 (1.9) a (8–18)	11.3 (2.4) a (4–18)	12.1 (2.4) a (8–18)	2.44 (.09)
Mean CES–D	16.0 (12.7) b (0–50)	20.5 (14.4) ab (0–57)	21.6 (13.8) a (0–55)	3.36 (.04)
Estimated Verbal IQ	88.3 (11.4) a (70–116)	84.1 (11.6) a (52–116)	87.2 (12.5) a (70–125)	3.15 (.05)
CD4	1165 (430) a (275–2509)	524 (257) b (206–1319)	99 (55) c (5–196)	184 (.0001)
Variable	No. (%)	No. (%)	No. (%)	χ^2 (*p*)
Ethnicity				
African American	34 (41.5)	69 (63.9)	17 (40.5)	
White	16 (19.5)	20 (18.5)	8 (19.0)	
Hispanic	32 (39.0)	19 (17.6)	17 (40.5)	15.8 (.003)
Head Injury with LOC ≥ 1hr[3]				
No	74 (90.2)	99 (91.7)	38 (92.7)	
Yes	8 (9.8)	9 (8.3)	3 (7.3)	0.23 (.89)
Lifetime Drug use[2]				
Low	25 (30.5)	31 (28.7)	21 (51.2)	
Med	37 (45.1)	29 (26.9)	12 (29.3)	
High	20 (24.4)	48 (44.4)	8 (19.5)	18.1 (.001)
Sedating drug in last 24 hr[4]				
No	71 (86.6)	81 (75.0)	39 (95.1)	
Yes	11 (13.4)	27 (25.0)	2 (4.9)	9.76 (.008)

[1]Duncan Multiple Range test. Common subscripts indicate no significant difference between pairs.
[2]Tertile cuts of summed number of yrs used marijuana, cocaine, crack cocaine, heroin, or alcohol (3 or more glasses per day).
[3]LOC = Loss of consciousness.
[4]Women reported the medications they took in the prior 24 hr. These were reviewed individually and all medications that they listed and that produced drowsiness were identified, these included: diphenhydramine, clonidine, cimetidine, prochlorperazine, lithium, and methadone.

significantly on mean age, education, or history of closed head injury ($p > .09$ for each comparison; see Table 1 for details of significance tests). The HIV+/CD4 ≤ 200 group scored significantly higher on reported psychological distress as measured by CES-D scores compared to HIV− subjects ($p < .05$). Compared with the other two groups, the HIV+/CD4 > 200 group had a significantly higher percentage of African American subjects ($p < .005$) and the enrollees were significantly more likely to have taken licit or illicit drugs with potentially sedating side effects within 24 hr of testing ($p < .01$). The HIV+/CD4 > 200 group also reported greater estimated lifetime drug use compared with the HIV− and HIV+/CD4 ≤ 200 groups ($p < .05$). Estimated Verbal IQ using the Quick Test, a brief measure of sight-word vocabulary (Ammons & Ammons, 1962) was marginally lower for the HIV+/CD4 > 200 group ($p = .05$).

Table 2 indicates that demographic variables were more comparable across groups when HIV+ women were subdivided according to antiretroviral status at testing. These three comparison groups (*HIV−*, *HIV+/ART*, *HIV+/no ART*) did not differ significantly on mean age, education, estimated Verbal IQ, ethnicity, or history of head injury ($p > .07$ for each comparison). Both HIV+ groups scored significantly higher on Center for Epidemiologic Studies–Depression Scale (CES–D) mean scores compared with HIV− subjects, $p < .05$ (Weissman et al., 1977). Estimated lifetime drug use and use of potentially sedating medications within the past 24 hr period approached or reached marginal significance for HIV+ women not on ART, $p = .06$ and $p = .05$, respectively.

Measures and Procedures

Neurocognitive testing

All neuropsychological (NP) tests were administered by a doctoral level clinical psychologist or by a master's level psychometrician supervised by a board-certified neuropsychologist. Criteria for NP test selection included demonstrated sensitivity to HIV-related cognitive/motor

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Table 2. Demographics and covariate measures by HIV treatment status ($N = 231$)

Variable	HIV negative ($n = 82$) *M* (*SD*) (range)	HIV positive on ARTs[3] ($n = 82$) *M* (*SD*) (range)	HIV positive off ARTs ($n = 67$) *M* (*SD*) (range)	Significance test *F* (*p*)
Age in years	34.6 (8.8) a[1] (19–59)	37.0 (7.4) a (19–55)	36.4 (7.5) a (22–54)	1.9 (.14)
Grade reached	11.9 (1.9) a (8–18)	11.8 (2.3) a (7–18)	11.3 (2.5) a (4–18)	1.5 (.23)
Depression	16.0 (12.7) b (0–50)	20.5 (13.7) a (0–55)	21.2 (14.9) a (0–57)	3.3 (.04)
IQ	88.3 (11.4) a (70–116)	85.2 (12.3) a (52–125)	84.7 (11.5) a (70–116)	2.1 (.12)
CD4	1165 (429) a (275–2509)	321 (22.1) b (5–918)	512 (331) c (9–1319)	139 (.0001)
Variable	No. (%)	No. (%)	No. (%)	χ^2 (*p*)
Ethnicity				
African American	34 (41.5)	45 (54.9)	40 (59.7)	
White	16 (19.5)	14 (17.1)	14 (20.9)	
Hispanic	32 (39.0)	23 (28.0)	13 (19.4)	7.9 (.10)
Head injury with LOC ≥ 1 hr				
No	74 (90.2)	76 (92.7)	61 (91.0)	
Yes	8 (9.8)	6 (7.3)	6 (9.0)	.32 (.85)
Lifetime drug use[2]				
Low	25 (30.5)	30 (36.6)	22 (32.8)	
Med	37 (45.1)	24 (29.3)	17 (25.4)	
High	20 (24.4)	28 (34.2)	28 (41.8)	8.9 (.06)
Sedating drug in last 24 hrs				
No	71 (86.6)	71 (86.6)	49 (73.1)	
Yes	11 (13.4)	11 (13.4)	18 (26.9)	6.0 (.05)

[1]Duncan Multiple Range test. Common subscripts indicate no significant difference between pairs.
[2]Tertile cuts of summed number of yrs used marijuana, cocaine, crack cocaine, heroin, or alcohol (3 or more glasses per day).
[3]ART = Antiretroviral medications.

impairment (e.g., Heaton et al., 1995; Tross et al., 1988) brevity of administration and minimal dependence on literacy or language ability wherever feasible. We included several NP measures that have been employed successfully in cross-cultural studies of HIV and neurocognitive function in populations of varying education levels. The NP testing required approximately 45 min. Tests used at both sites included *Color Trails 1 and 2*, in order to measure divided attention, set-shifting, and psychomotor functioning (D'Elia et al., 1994; Maj et al, 1993); the *WHO/UCLA Auditory Verbal Learning Test* of multiple trial auditory verbal list learning under immediate and delayed recall conditions (Maj et al, 1993); the *Grooved Pegboard* to measure psychomotor speed and fine motor control (Kløve, 1963; Matthews & Kløve, 1964); the *Symbol Digit Modalities Test* of written coding that requires psychomotor speed, memory, attention, and concentration (Lezak, 1995; Smith, 1982) the *Visual Reproduction Subtest of the Wechsler Visual Memory Scale–Revised* for immediate and delayed recall of four geometric designs (Wechsler, 1987) and the *Mental Alternations Test*, an oral analogue of the Trail Making Test designed to assess divided attention and set shifting with minimal demand on motor function (Teng, 1994). The two sites employed different computerized measures of simple and choice reaction time (RT), and the Chicago protocol also included measures of verbal and spatial working memory (Martin et al., 1999a; Racenstein et al., 1999) and these data will be reported separately.

Intellectual Functioning and Psychological Distress

We evaluated premorbid verbal intellectual function using the Quick Test, a brief assessment of receptive vocabulary used to estimate verbal IQ (Ammons & Ammons, 1962). In order to evaluate mood we administered the Centers for Epidemiologic Studies Depression Scale (CESD; Radloff, 1992; Roberts, 1980; Weissman et al., 1977).

Laboratory studies

HIV serostatus was confirmed in all cases using FDA approved EIA and if repeatedly reactive, FDA approved

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Western blot HIV-1 confirmatory assay. Absolute CD4 lymphocyte count was determined by immunophenotyping and flow cytometric analysis. Laboratories performing flow cytometry testing were participating in the NIAID DAIDS Flow Cytometry Quality Assessment Program and followed Guidelines for Flow Cytometric Immunophenotyping (Centers for Disease Control, 1992). CD4 T cell count was stratified between CD4 $\leq$ 200, representing the CDC definition for immunologic AIDS, and CD4 $>$ 200.

The dichotomized AIDS diagnosis was based on CD4 lymphocytes over and under 200 rather than on AIDS defining illnesses. We use this because the WIHS collected blood samples and independently assessed CD4 count at each WIHS visit. AIDS defining illnesses are self identified on the questionnaire and verified by medical record abstract. The self-identification has validity problems due to recall issues, confusion about medical terminology etc, and the medical record abstract is incomplete. The CD4 is objective and accurate and a better indicator of disease progression than either of these other two measure in this cohort at this time.

Ultrafrozen sera from individual patients were tested for the detection and quantitation of HIV RNA copies (Bruisten et al., 1993; Vandamme et al., 1996) (viral load) using Nucleic Acid Sequence Based Amplification (NASBA^{TM}) which employs an isothermic RNA amplification method. Laboratories performing the NASBA testing were participants in the NIAID AIDS Program Virology Quality Assurance HIV RNA Proficiency Program of the NIH (Yen-Lieberman et al., 1996). Viral load was detectable at 4,000 copies/ml or greater using the NASBA method. A stratification of viral load was used that represented approximately equivalent number of women per category: viral load less than 4,000 copies/cc (the assay cut-off of detection), viral load 4,000 to 35,000 copies/cc, and viral load over 35,000 copies/cc.

RESULTS

Overview of Statistical Analyses

We administered and scored all NP tests according to standardized procedures and all analysis used raw scores. For each set of statistical analyses we compared groups according to (1) serostatus and AIDS diagnosis (HIV$-$, HIV$+$/CD4 $>$ 200, HIV$+$/CD4 $\leq$ 200; and (2) serostatus and antiretroviral therapy status (HIV$-$, HIV$+$/on ART, and HIV$+$/no ART). We classified each individual's test scores and overall protocol using procedures commonly employed in studies of NP performance in HIV/AIDS. We *z*-transformed each subject's raw NP scores using means and standard deviations for the HIV$-$ control group. We then classified a *z*-transformed NP *test score* as *impaired* if it fell at least 1 standard deviation below the mean of the control group (Baldeweg et al., 1995; Bornstein et al., 1993; Miller et al, 1990). We classified a subject's overall *protocol* as *abnormal* if it contained two or more unique test scores falling in the impaired range. *Unique* was defined as derived from separate tests; if a subject obtained two scores in the impaired range on components of the same test (e.g., Grooved Pegboard) these were counted as a single impaired score and insufficient for classifying a protocol as abnormal.

We evaluated the prevalence of *z*-transformed NP test scores in the *impaired* range for each group by chi-square analyses. The distributions of some test scores were skewed. We reran analyses of these data after log transforming the scores and the results were unchanged. We present untransformed scores in all study tables.

We employed a series of multivariate analyses that predicted prevalence of abnormal NP protocols, calculating odds ratios (*OR*s) and 95% confidence intervals (*CI*s; i.e., *p* values set at .05) using maximum likelihood estimates from logistic regression models, and employing education, age, ethnicity, history of head injuries, use of potentially sedating medications in the past 24 hr, lifetime drug use, psychological distress, and estimated verbal IQ as predictors. We also controlled for site of data collection (Los Angeles *vs.* Chicago) to adjust for differences in examiners and minimize effects of possible ascertainment bias (van Gorp et al., 1995). Finally, we employed a multivariate logistic regression, adjusted for the same variables listed above, to evaluate the risk for abnormal NP protocol associated with higher viral load levels, untreated therapy status, and lower CD4 counts.

Prevalence of Abnormal Individual NP Test Scores

We evaluated the proportion of impaired scores for subject groups on individual NP tests for exploratory purposes using chi-square tests. Table 3 shows the number and proportion of scores in the impaired range on specific NP tests for HIV$-$, HIV$+$/CD4 $>$ 200 and HIV$+$/CD4 $\leq$ 200 groups. Compared to controls, both HIV$+$ groups had higher proportions of abnormal scores on the Symbol Digit Modalities Test ($p = .03$). The HIV$+$/CD4 $>$ 200 group showed a significantly higher proportion of impaired scores compared with the HIV$-$ group on Color Trails 2 ($p = .03$) and on the Mental Alternations Test ($p = .04$). In contrast, group comparisons did not show a difference between the HIV$+$/CD4 $\leq$ 200 group and the HIV$-$ or between the HIV$+$ groups.

Table 4 shows the number and the proportion of ART-treated, untreated and control subjects that scored in the impaired range on individual NP measures. The HIV$+$ untreated group was more likely to score as impaired on the Mental Alternations and the Symbol Digit Modalities when compared to HIV$-$ or treated HIV$+$ groups ($p \leq .05$ for each comparison). Untreated HIV positive subjects also had a greater proportion of scores in the impaired range for the Color Trails 2 and the Grooved Pegboard nondominant hand trial ($p \leq .05$) compared with HIV$-$ controls but not when compared with the treated HIV$+$ subjects. A small number

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Table 3. Prevalence of scores in impaired range by disease status*

Measure	HIV− (n = 82) n (%)	HIV+/CD4 > 200 (n = 108) n (%)	HIV+/CD4 ≤ 200 (n = 41) n (%)	p
Color Trails 1	13 (15.9)	31 (28.7)	11 (26.8)	n.s.
Color Trails 2	8 (9.8)	26 (24.1)	6 (14.6)	.03
WMS–R Sum	11 (13.4)	25 (23.2)	6 (14.6)	n.s.
WMS–R Recall	13 (15.9)	25 (23.2)	8 (19.5)	n.s.
Grooved Pegboard (dominant)	14 (17.1)	22 (20.6)	8 (19.5)	n.s.
Grooved Pegboard (nondominant)	10 (12.2)	27 (25.2)	7 (17.5)	.08
Mental Alternations	15 (18.3)	38 (35.2)	11 (26.8)	.04
WHO AVLT Sum	14 (17.1)	20 (18.5)	10 (24.4)	n.s.
WHO AVLT Recall	10 (12.2)	18 (16.7)	5 (12.2)	n.s.
Symbol Digit	11 (13.4)	31 (28.7)	12 (29.3)	.03

*All raw scores represent percentage of women who score outside of 1 *SD* from the mean of the HIV negative control.

of comparisons (40% of tests in Table 3 and 50% in Table 4 were $p < .10$) showed evidence of group differences and thus must be interpreted conservatively.

Prevalence of Abnormal NP Protocols

We classified a study subject's NP test *protocol* as abnormal if it contained 2 or more of 10 individual NP scores in the impaired range. By this method, we classified protocols of 89 subjects (39% of the total sample) as abnormal. Figures 1a and 1b show the prevalence of abnormal NP test protocols for each study group. HIV+ groups both with or without an AIDS diagnosis showed a significantly higher proportion of abnormal NP protocols compared to controls ($\chi^2 = 6.1$, $p < .05$; Figure 1a). By contrast, the untreated HIV+ group had a significantly higher proportion of abnormal NP protocols compared with either HIV− or treated HIV+ subjects ($\chi^2 = 10.4$, $p < .01$; Figure 1b). Additionally, analyses showed no significant association between normal *versus* abnormal protocols and drug use or 24 hr sedating medication.

Risk Factors for Abnormal NP Protocols

We conducted a series of logistic regression analyses to evaluate the association of specific risk factors with abnormal NP protocols. These multivariate analyses included and controlled for serostatus, CD4 count, treatment status, test site, age, education, estimated verbal IQ, CES–D scores, use of potentially sedating medications within 24 hr of testing, history of head injury, ethnicity, and categorized lifetime substance use.

Table 5 shows results of logistic regression analyses with HIV+ subjects classified by CD4 lymphocyte count over or under 200. Univariate analyses showed that among those with a positive serostatus and higher CD4 cell count, older age, less education, lower estimated IQ, greater CESD score and African American ethnicity were associated with significantly increased risk of obtaining an abnormal NP protocol ($p < .05$ in each instance). Multivariate analyses controlling for all other variables (Table 5), indicated that older age, lower estimated verbal IQ, and greater CESD score were associated with significantly increased risk for

Table 4. Prevalence of scores in impaired range by treatment status*

Measure	HIV− (n = 82) M (SD)	HIV+ ART (n = 82) M (SD)	HIV+ No ART (n = 67) M (SD)	p
Color Trails 1	13 (15.9)	22 (26.8)	20 (29.9)	.10
Color Trails 2	8 (9.8)	15 (18.3)	17 (25.4)	.04
WMS–R Sum	11 (13.4)	15 (18.3)	16 (23.9)	n.s.
WMS–R Recall	13 (15.9)	18 (21.9)	15 (22.4)	n.s.
Grooved Pegboard (dominant hand)	14 (17.1)	13 (16.1)	17 (25.4)	n.s.
Grooved Pegboard (nondominant hand)	10 (12.2)	15 (18.8)	19 (28.4)	.03
Mental Alternations	15 (18.3)	21 (25.6)	28 (41.8)	.01
WHO AVLT Sum	14 (17.1)	14 (17.1)	16 (23.9)	n.s.
WHO AVLT Recall	10 (12.2)	13 (15.9)	10 (14.9)	n.s.
Symbol Digit	11 (13.4)	18 (21.9)	25 (37.3)	.003

*All raw scores represent percentage of women who score outside of 1 *SD* from the mean of the HIV negative control.

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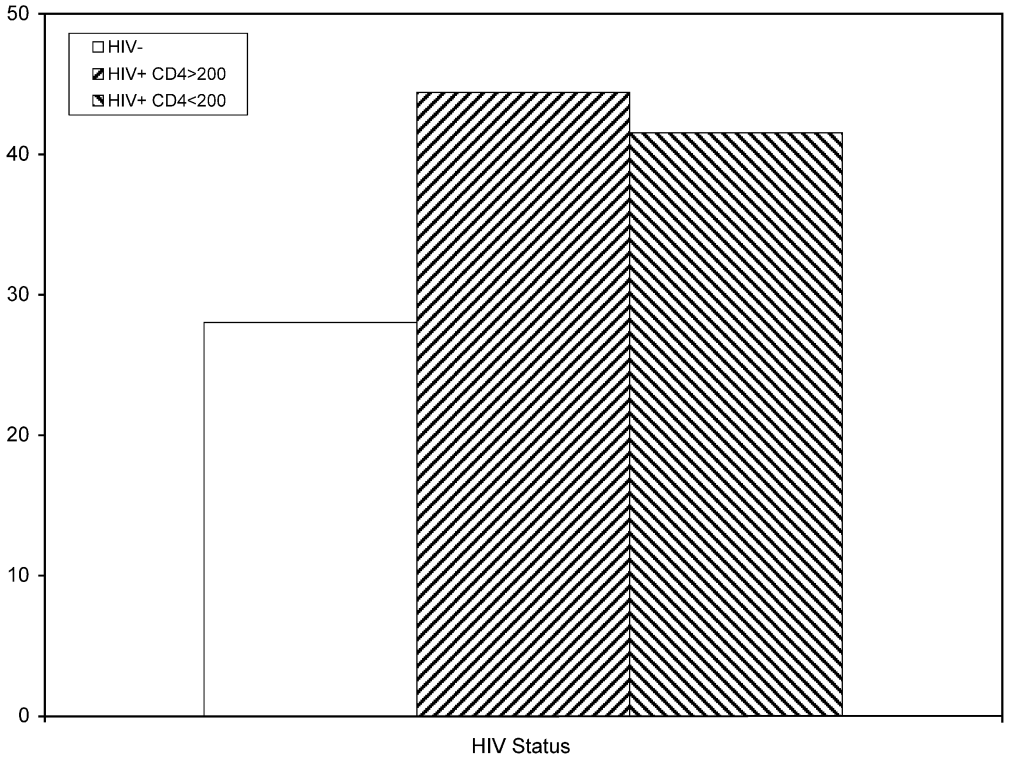

Fig. 1a. Proportion of abnormal NP protocols by HIV disease status: $\chi^2 = 6.1$, $p < .05$.

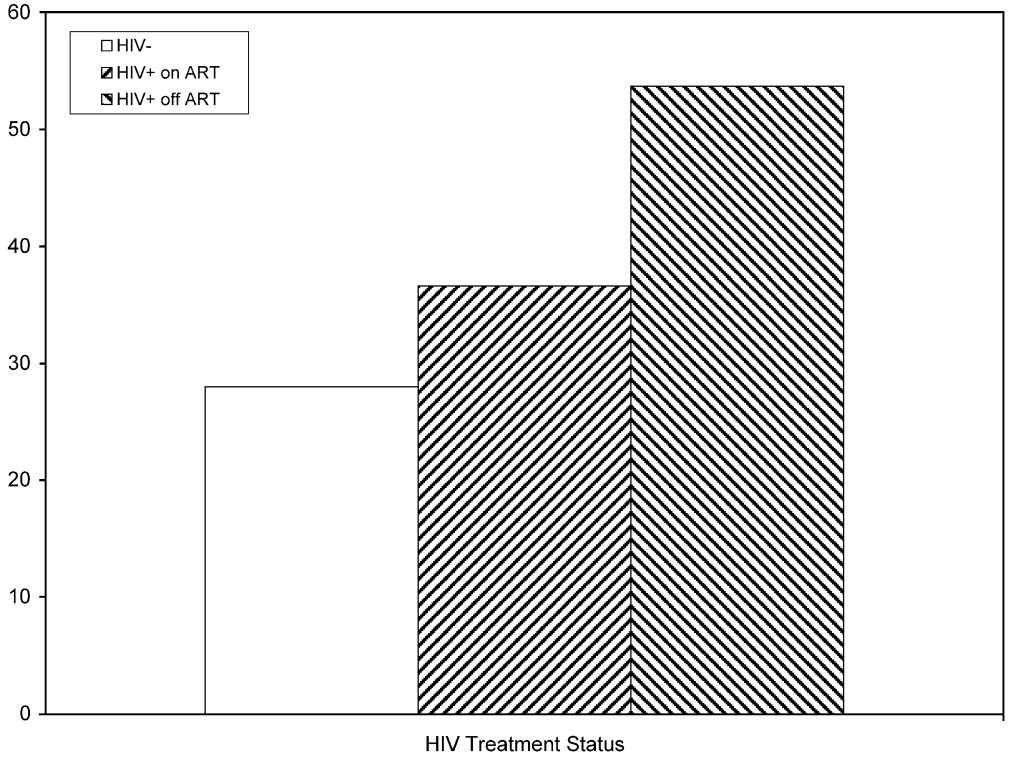

Fig. 1b. Proportion of abnormal NP protocols by treatment status: $\chi^2 = 10.4$, $p < .01$.

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Table 5. Predictors of abnormal NP protocols[1,2]

Variable	Normal No. (%)	Abnormal No. (%)	Univariate risk of NP abnormal protocol *OR* (95% *CI*)	Model I: Adjusted risk of NP abnormal protocol by disease status *OR* (95% *CI*)	Model II: Adjusted risk of NP abnormal protocol by treatment status *OR* (95% *CI*)
Disease status					
HIV negative	59 (72.0)	23 (28.0)	1.0		1.0
HIV pos–on ART	52 (63.4)	30 (36.6)	1.48 (0.77, 2.86)		1.00 (0.47,2.11)
HIV pos–off ART	31 (46.3)	36 (53.7)	2.98 (1.51, 5.88)**		2.43 (1.10,5.40)*
Treatment status					
HIV negative	59 (71.9)	23 (28.1)	1.0	1.0	
HIV pos CD4 > 200	59 (54.6)	49 (45.4)	2.13 (1.15, 3.93)*	1.54 (0.75,3.18)	
HIV pos CD4 ≤ 200	24 (58.5)	17 (41.5)	1.82 (.83, 3.99)	1.29 (0.53,3.13)	
Site					
Los Angeles	90 (62.5)	54 (37.5)	1.0	1.0	1.0
Chicago	52 (59.8)	35 (40.2)	1.12 (.65, 1.94)	0.81 (0.40,1.66)	0.71 (0.35,1.50)
Age					
≤ 29	44 (77.2)	13 (22.8)	1.0	1.0	1.0
30–39	69 (67.7)	33 (32.3)	1.62 (.77, 3.41)	1.62 (0.71,3.69)	1.63 (0.72,3.72)
≥ 40	29 (40.3)	43 (59.7)	5.02 (2.31, 10.92)†	5.77 (2.27,14.7)***	6.30 (2.48,16.1)***
Education					
HS or more	87 (68.0)	41 (32.0)	1.0	1.0	1.0
Less than HS	55 (53.4)	48 (46.6)	1.85 (1.08, 3.17)*	1.51 (0.76, 2.99)	1.54 (0.77, 3.08)
Estimated VIQ					
High	80 (70.2)	34 (29.8)	1.0	1.0	1.0
Low	62 (53.0)	55 (47.0)	2.09 (1.22, 3.59)**	2.10 (1.03, 4.28)*	2.00 (0.98, 4.11)
CES–D					
15 or under	74 (73.3)	27 (26.7)	1.0	1.0	1.0
16 or greater	68 (52.3)	62 (47.7)	2.50 (1.43, 4.37)***	2.08 (1.11, 3.90)*	2.17 (1.14, 4.11)*
Sedating drugs/24 hr					
No	122 (63.9)	69 (36.1)	1.0	1.0	1.0
Yes	20 (50.0)	20 (50.0)	1.77 (.89, 3.51)	1.64 (0.71, 3.82)	1.49 (0.64, 3.48)
Head injury w/LOC ≥ 1 hr					
No	130 (61.6)	81 (38.4)	1.0	1.0	1.0
Yes	12 (60.0)	8 (40.0)	1.07 (.42, 2.73)	0.96 (.33, 2.83)	0.97 (.32, 2.94)
Ethnicity					
White	65 (54.6)	54 (45.4)	1.0	1.0	1.0
African American	32 (72.7)	12 (27.3)	2.22 (1.04, 4.72)*	1.81 (0.74, 4.45)	1.96 (0.79, 4.89)
Hispanic	45 (66.2)	23 (33.8)	1.36 (0.59, 3.13)	0.96 (0.31, 2.60)	1.01 (0.37, 2.78)
Substance use/24 hr					
No	120 (61.2)	76 (38.8)	1.0	1.0	1.0
Yes	22 (62.9)	13 (37.1)	0.93 (.44, 1.96)	0.72 (.31,1.67)	0.72 (.30,1.69)
Lifetime drug use[2]					
Low	48 (62.3)	29 (37.7)	1.00	1.00	1.00
Med	53 (66.7)	26 (33.3)	0.82 (0.43,1.60)	0.68 (0.32,1.48)	0.70 (0.32,1.54)
High	42 (55.3)	34 (44.7)	1.34 (0.70,2.56)	0.61 (0.26,1.46)	0.61 (0.25,1.45)

*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$; †$p \leq .0001$.
[1]Multivariate analysis adjusted for all other variables listed in the model.
[2]Tertile cuts of summed number of years used marijuana, cocaine, heroin, or alcohol (3 or more glasses per day).

obtaining an abnormal NP score ($p < .05$). Serostatus in itself, was not associated significantly with NP function in the multivariate analysis.

Table 5 also shows results of multivariate analyses with HIV+ women classified according to treatment status at testing. Univariate analyses indicated that significant risk factors for obtaining an abnormal NP protocol included older age, less education, lower IQ, greater CESD score, African American ethnicity and absence of antiretroviral therapy ($p < .05$ in all instances). Multivariate analyses controlling for all other variables (Table 5), indicated that only greater CESD score, older age, and absence of anti-retroviral ther-

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Table 6. Predictors of abnormal NP protocols for seropositive women[1] ($N = 145$)

	Normal ($n = 83$) No. (%)	Abnormal ($n = 62$) No. (%)	Univariate risk of NP abnormal protocol *OR* (95% *CI*)	Adjusted risk of NP abnormal protocol *OR* (95% *CI*)
CD4				
>200	59 (56.2)	46 (43.8)	1.0	1.0
≤200	24 (60.0)	16 (40.0)	0.86(.41,1.79)	1.08 (0.37,3.18)
Viral load				
Undetectable (<4,000)	39 (63.9)	22 (36.1)	1.0	1.0
4,000–34,999	23 (52.3)	21 (47.7)	1.62 (.74, 3.56)	1.13 (0.44,2.94)
>35,000	21 (52.5)	19 (47.5)	1.60 (.71, 3.61)	1.48 (0.51,4.25)
Antiretroviral meds				
On ART	52 (63.4)	27 (34.2)	1.0	1.0
No ART	31 (46.3)	35 (53.0)	2.17 (1.11,4.25)*	2.24 (1.00,5.06)*

*$p \leq .05$.
[1]The model is adjusted for age, education, ethnicity, history of head injuries with LOC 1 hr or more, site of testing, Quick test, depression, years of substance use, and whether medications that produce drowsiness or illicit drugs or alcohol were taken within 24 hr before testing. Viral load, CD4 category and antiretroviral medications were also included in the model.

apy (ART) were significantly associated with abnormal NP performance. Women who were not on ART were 2.43 (*CI* = 1.10–5.40) times more likely to obtain abnormal scores than women receiving ART. The adjusted risk of NP impairment associated with untreated HIV status remained significant in multivariate analysis indicating that absence of antiretroviral therapy contributed unique variance in predicting impaired NP functioning. Also, test protocols of women 40 and older were 6.30 (*CI* = 2.48–16.1) times more likely to be classified as abnormal than those of women 20 to 30 years of age. Women with higher CESD scores were 2.17 (*CI* = 1.14–4.11) times more likely to obtain an abnormal NP protocol than those reporting lower CESD scores.

Disease and Treatment Risk Factors in HIV+ Women for Abnormal NP Protocols

Finally, we performed a series of analyses using data limited to the 145 HIV seropositive women[3] in order to evaluate the association of the risk of NP abnormalities with absolute CD4 cell count, antiretroviral therapy and HIV RNA levels (Table 6). First, we examined how viral load and CD4 were related to the use of ART among the HIV positive women. As expected, the proportion of women on ART varied by CD4; 48% of women with CD4 > 200 were on ART and 73% of women with CD4 ≤ 200 were on ART ($\chi^2 = 7.5$, $p = .006$). Of those with viral load under 4,000, 65% were currently receiving ART compared to 41% of those with viral load between 4,000 and 34,999 and 53% of those with viral load over 35,000 ($\chi^2 = 6.4$, $p = .042$). Viral load and CD4 counts were inversely related as expected. Of those without immunologic AIDS, 51% had a viral load below 4,000, 32% had from 4,000 to 34,999, and 16% over 35,000 as compared to women with an AIDS diagnosis who had 18%, 25%, and 58% respectively ($\chi^2 = 26.4$, $p < .001$.)

We examined simultaneously the joint association of disease status and ART therapy status with NP performance using multivariate analyses. Neither CD4 category nor viral load categories were significantly associated with prevalence of abnormal NP protocols (Table 6). In contrast, NP performance varied significantly with HIV treatment status. Protocols of untreated women were significantly more likely to be classified as abnormal in the univariate model (*OR* = 2.17; 95% *CI* = 1.11–4.25). In the multivariate model, after adjusting for age, education, ethnicity, depression, estimated Verbal IQ, head injuries, medications, lifetime substance use, sedating medications within 24 hr of testing, test site, CD4 and viral load, HIV positive untreated women were more than twice as likely to obtain abnormal NP protocols compared with seropositive women on ART at the time of testing (*OR* = 2.24; 95% *CI* = 1.00–5.06; see Table 6). Only 10 women in this sample were treated with HAART, consequently, we could not make reliable comparisons between NP performance of women on HAART *versus* therapy regimens that did not include a protease inhibitor ($n = 72$).

DISCUSSION

We evaluated neuropsychological (NP) test performance in a sample of 149 HIV seropositive (HIV+) women and 82 seronegative (HIV−) women at high risk for HIV exposure enrolled in a large multicenter study of disease progression in women living with HIV/AIDS. We classified each woman's NP protocol as abnormal if it contained two or more unique test scores that fell at least 1 standard deviation below the mean for the control group.

[3]Viral loads were not available for four women.

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Most notably, we found that HIV+ women who were not receiving antiretroviral therapy (ART) at the time of testing were 2.5 times more likely to obtain abnormal NP protocols compared with either antiretroviral-treated HIV+ or HIV− women. This pattern of findings was evident both on univariate and on multivariate analyses controlling for variables with potentially confounding effects on NP performance indicating that ART contributes unique variance to prediction of risk of abnormal NP performance.

This is among the first investigations to evaluate prevalence of NP impairment in a large sample of HIV+ women. We note that our overall rates of NP impairment among HIV+ women compared with matched HIV− controls appear roughly comparable to rates of NP impairment reported in previous studies of HIV+ males (McArthur & Grant, 1997); however we make this comparison with care given the difference in subject demographics and testing methods. Similarly, our data do not address directly the question of possible gender differences in prevalence and onset of *HIV-associated dementia* (HAD) since our parent study, the WIHS, excluded women with HAD from enrollment due to the demands of the study and need for full informed consent. Further, the cross-sectional design cannot provide information on decline in cognitive test performance over time, although these data will be presented in a separate article.

Notably, we found a *higher* prevalence of NP impairment among the HIV− women compared with rates reported for large samples of HIV− males (e.g., Heaton et al., 1995; Miller et al., 1990). For example, approximately 17% of the HIV− males studied by the HNRC group obtained abnormal NP protocols, compared with the 28% rate we observed in our control group. This discrepancy very likely reflects the high rates of substance abuse, head injury and other potentially confounding factors among our HIV− women and may explain Stern et al.'s (1998) previous finding showing no significant differences in NP performance between asymptomatic HIV+ women and HIV− controls (those authors did, in fact, note high rates of NP impairment among both subject groups on a number of tests). Given the greater overlap between HIV+ and HIV− women's NP test performance as an increased source of variance, the negative findings we report on individual NP tests and possibly those related to confounding variables such as head injury (see below) await independent replication. Further, this finding suggests that clinical NP tests may be less efficient in discriminating HIV− from HIV+ female groups. In this regard, we have presented preliminary evidence from the Chicago cohort that HIV+ women show reliably higher rates of impairment compared to HIV− controls on experimental measures of verbal and spatial working memory (Martin et al., 1999a; Racenstein et al., 2001).

We found no statistically significant difference in prevalence of abnormal NP protocols between HIV+ women with an immunologic AIDS diagnosis compared to women with less advanced disease. This finding is atypical compared with the body of literature on neurocognition and HIV. However, we tested a relatively small number of women with AIDS (28% of all seropositive subjects) and this finding awaits replication in an independent sample including a higher percentage of women with more advanced disease. Should future studies also fail to demonstrate differing prevalence rates for women with earlier *versus* advanced disease, this finding would provide tentative evidence consistent with speculation that NP deficits and/or dementia develop earlier in the course of disease for HIV+ women.

Notably, we found that antiretroviral treatment status, but not immunologic AIDS or viral load was a statistically significant predictor of NP impairment in the multivariate analysis. We measured only peripheral viral load in blood, which does not necessarily reflect CNS viral load; however, a significant relationship between viral load in CSF and neurocognition is most evident only in patients with advanced dementia (e.g., Ellis et al., 1997).

Our cross-sectional results are consistent with previous reports that patients treated with zidovudine show improved cognitive function following initiation of therapy (Schmitt et al., 1988), more recent studies that showed cognitive improvement following treatment with HAART (Cohen et al., 2001; Sacktor et al., 1999) and with cross sectional studies showing faster reaction times in patients receiving reverse transcriptase inhibitors (Martin et al., 1998) or highly active antiretroviral therapy (HAART) compared with untreated patients (Ferrando et al., 1998). Due to our cross-sectional design we must limit our conclusions to the observation of a strong statistical association between NP function and ART. Further, our conclusions must be tempered by the limitations imposed by reliability of our subjects' self-report of medications. Many of our subjects were unfamiliar with specific drug names and the core WIHS medication interview is guided by photographs of specific pills to aid recognition. Further, we did not measure rates of adherence among the treated women.

Exploratory analyses using scores from individual NP tests suggested decreased performance in HIV+ women compared to controls for the Color Trails 2, Mental Alternations, and the Symbol Digit Modalities, measures that all require speeded information processing. This pattern is quite consistent with reports of studies on neurocognition in HIV+ males (e.g., Heaton et al., 1995; Miller et al., 1990) and recent findings reported in Durvasula's study of HIV+ women (2001), which indicate that HIV+ subjects frequently show defects on speeded tasks with a cognitive component requiring the subject to divide and shift attention. Analyses of potentially confounding variables provided several notable results. We were unable to replicate the finding reported by Marder et al. (1992) that HIV+ subjects with a history of head injury were more likely to obtain abnormal protocols. However, the Marder study evaluated a large group of males and females with current or previous history of IDU as their primary risk factor, while risk factors were more varied for our study sample.

Surprisingly, we found no significant relationship between substance abuse severity and risk of NP impairment.

This finding is not unusual in the context of earlier studies of higher-functioning MSMs (e.g., Bornstein et al., 1993; Heaton et al., 1995), but our subjects' substance abuse histories were significantly more extensive and detailed. However, our negative finding may in part reflect current questions of which specific substance abuse parameters (e.g., recency of use, duration of abstinence, specific drug of choice) most reliably predict neuropsychological deficit and future studies must obtain additional data on substance abuse topography to revisit these findings.

Both psychological distress and older age were associated with an increased risk of NP impairment, which persisted in the multivariate model. These findings are consistent with those reported by others (Durvasula et al., 2001; McArthur et al, 1993). The literature on the association between psychological distress and NP function indicates that distress does not account completely for NP deficits in HIV+ (Bornstein et al., 1993; Heaton et al., 1995) but rather accounts for additional variance (Goggin et al., 1997). Further, depression is more common among HIV+ women compared with HIV+ males (Semple et al., 1993) suggesting that this variable might exert a more pervasive influence on cognition in the population of HIV+ women.

Both education and estimated Verbal IQ were associated significantly with NP performance for our subjects in the univariate analysis, although only Verbal IQ survived the multivariate model. The effects of lower education and estimated IQ as well as increased age are consistent with previous reports that vulnerability to HIV-related cognitive defects varies in part as a function of cognitive reserve, which can be indexed by education, age, or IQ (Racenstein et al., 2001; Satz et al., 1993; Stern et al., 1998; van Gorp et al., 1995).

Multiple factors account potentially for the association between antiretroviral therapy and NP performance and at present, we can not state equivocally that antiretroviral therapy directly lowers the risk of cognitive defects. It is quite possible, for example, that access to antiretroviral therapy and/or adherence rates with therapy regimens are lower for women with cognitive defects or related comorbidities. However, our results do provide preliminary indications that questions concerning cognitive impairment and its prevention or amelioration should be included in decision-making to initiate ART, particularly with older HIV+ women. Given that depression contributed unique variance to NP performance it would be prudent from a cognitive point of view to consider more aggressive treatment for depression as well.

Greater care is needed to ensure that women are offered antiretroviral therapies. Since women have traditionally had less access to care of ART than HIV infected men, further studies of health care services and service delivery with this population will be critical in order to determine specific barriers to therapy. In addition, it would appear that treatment of depression should be pursued more aggressively in HIV+ women.

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