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# Information processing and antiretroviral therapy in HIV-1 infection

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**Abstract**

Computerized reaction time (RT) tasks are sensitive measures of subclinical HIV-related mental slowing. We previously reported that nondemented HIV-seropositive patients on antiretroviral therapy at the time of testing had faster choice RTs compared to matched untreated seropositive participants. In the present study, we evaluated the performance of 163 nondemented HIV-seropositive participants on a reaction time version of the Stroop task as a function of antiretroviral status. Persons on antiretroviral therapy at the time of testing had significantly faster reaction times than untreated individuals, although treated asymptomatic participants showed significantly less Stroop interference than treated symptomatic participants. These effects could not be attributed to differences in demographic variables, disease status, substance abuse, or psychological distress. These data indicate that central information processing is faster for patients treated with antiretroviral compounds compared to untreated patients, and suggest that reaction time tasks may have significant potential utility in clinical trials of neuroprotective compounds. (*JINS*, 1998, *4*, 329–335.)

**Keywords:** HIV, AIDS, Dementia, Zidovudine, Reaction times, Antiretroviral, Neuropsychological tests

## INTRODUCTION

HIV-1 has an affinity for the CNS and neuropathology is evident in 80 to 90% of AIDS cases at autopsy (Navia et al., 1986a). HIV-1 infection causes a spectrum of neurobehavioral impairment ranging in severity from mildly slowed mentation to progressive dementia that has been well documented in studies of seropositive gay males and injection drug users (e.g., Heaton et al., 1995; Marder et al., 1992). Mental and motor slowing are the most prominent clinical features of HIV-related dementia, consistent with its primarily subcortical neuropathology (Navia et al., 1986b), and computerized reaction time tasks reliably detect subclinical mental slowing in nondemented HIV-seropositive persons (Bornstein et al., 1991; A. Martin et al., 1992; E. Martin et al., 1992b, 1995; Miller et al., 1991).

The reverse transcriptase inhibitor zidovudine (ZDV, AZT) crosses the blood–brain barrier (Klecker et al., 1987) and HIV-seropositive patients show improved neuropsychological test performance after antiretroviral therapy with zidovudine is initiated (Brouwers et al., 1990; Schmitt et al., 1988; Sidtis et al., 1993). We recently evaluated simple and choice reaction time performance in a group of nondemented HIV-seropositive patients on antiretroviral therapy (primarily zidovudine monotherapy) and a group of cohort-matched untreated seropositive patients (E. Martin et al., in press). We found that seropositive patients on antiretroviral therapy at the time of testing had significantly faster choice reaction times compared to untreated patients. These preliminary data suggested that central information processing is faster in patients on antiretroviral therapy compared with untreated patients and that these differences can be detected in patients without overt clinical mental status change.

This previous RT study employed relatively uncomplicated measures of simple and choice reaction time. In the current study, we investigated HIV-seropositive participants' performance of a more cognitively complex procedure, a reaction time version of the Stroop task (e.g., Henik et al., 1993; Stroop, 1935), in relation to their antiretroviral status. The RT Stroop measures voice-activated reaction

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**Table 1.** Demographic data for all participants

| Variable | Participant group | | |
|---|---|---|---|
| | Untreated | Treated asymptomatic | Treated symptomatic |
| *N* | 74 | 38 | 51 |
| Mean age in years (*SD*) | 37.4 (8.2) | 40.0 (8.1) | 39.0 (7.4) |
| Mean education in years (*SD*) | 12.9 (1.8) | 12.8 (1.8) | 12.9 (1.8) |
| Mean CD4 count/ml | 500***† (356) | 337*** (112) | 178 (144) |
| *N*/% female | 19/26 | 5/13* | 6/12* |
| *N*/% symptomatic | 27/36*** | 0*** | 51/100 |
| *N*/% AIDS diagnosis | 19/26*** | 5/14*** | 36/70 |
| *N*/% closed head injury | 11/15 | 4/11 | 7/14 |
| *N*/% psychiatric history | 23/32 | 5/13* | 8/16* |
| *N*/% psychiatric meds | 9/12 | 3/8 | 3/6 |
| *N*/% injection drug use | 36/49 | 17/45 | 21/41 |
| *N*/% drug abuse | 56/77 | 26/68 | 36/70 |
| *N*/% alcohol abuse | 34/46 | 17/45 | 25/49 |

*$p < .05$ *versus* untreated group.
†$p < .001$ *versus* treated asymptomatic group.
***$p < .001$ *versus* treated symptomatic.

times under three stimulus conditions varying in the demands made on controlled attentional processes (i.e., capacity-limited, effortful, and under voluntary control; Schneider et al., 1984), which are disrupted by HIV-1 infection (E. Martin et al., 1992a, 1995).

The RT Stroop has demonstrated sensitivity to HIV-related mental slowing in nondemented seropositive subjects (E. Martin et al., 1992a). In addition, the task requirement of a vocal rather than a keypress response is advantageous since potentially confounding effects of peripheral motor slowing due to neuropathy are minimized. A finding of faster RT Stroop performance in patients on antiretroviral therapy compared with untreated patients would thus provide stronger support for a hypothesis of faster mental processing in seropositive patients on antiretroviral therapy.

## METHODS

### Research Participants

We tested 132 male and 31 female HIV-seropositive patients recruited from infectious disease clinics at the Veteran Affairs Medical Center–West Side, Cook County Hospital, and the University of Illinois Hospital, and through community organizations. All participants were paid volunteers and were not referred because of neurobehavioral symptoms or signs. Participants had no evidence of overt dementia by history and on physician examination and all were capable of giving informed consent. Eighty-five subjects (52% of the total sample) were clinically asymptomatic or with lymphadenopathy only (CDC Stage A; Centers for Disease Control, 1992). The majority of the 78 symptomatic participants ($N = 52$) had constitutional disease or minor opportunistic conditions such as oral candidiasis (CDC Stage B); 26 participants (16% of the total sample) had a history of at least one AIDS-defining opportunistic illness, typically *Pneumocystis carinii* pneumonia, but no neurologic disease (including CMV retinitis). Thirty-four percent of all participants had AIDS-defining CD4 counts[1] (below 200). Approximately 45% of the total sample had a history of injection drug use, and 74% of all participants had a history of drug and/or alcohol abuse, with cocaine the most common drug of choice. The overall sample is 74% African American, 17% White, and 9% Hispanic. Potential study participants with a history of color blindness, closed head injury with loss of consciousness exceeding 1 hr, current neuroleptic treatment, history of schizophrenia, or any HIV-related neurologic condition other than neuropathy or aseptic meningitis were excluded from study.

Eighty-nine participants (55% of the total sample) were receiving antiretroviral therapy at the time of testing. The majority of these treated participants (72, or 81%) were on zidovudine monotherapy. The remaining subjects were treated with didanosine (ddI) or zalcitabine (ddC) alone (11%) or in combination with zidovudine (8%). Seventy-four participants had never been treated with antiretrovirals.

Table 1 shows demographic data for untreated, treated asymptomatic ($N = 38$) and treated symptomatic ($N = 51$) participants. Both asymptomatic and symptomatic patients receiving antiretroviral therapy were as expected more immunosuppressed compared with untreated patients as indexed by their significantly lower mean CD4 lymphocyte

[1]Data were collected prior to the development of viral load assay procedures.

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counts; further, mean CD4 counts for treated symptomatic patients were significantly lower than those for treated asymptomatic patients [$F(2,154) = 22.9$, $p < .0001$; $p < .01$ by the Duncan test for each comparison]. The asymptomatic treated group was slightly but not significantly older than the untreated and symptomatic treated groups [$F(2,160) = 2.52$, $p < .09$]. The three groups did not differ significantly in mean years of education [$F(2,160) = .07$, $p < .94$] or in ethnic composition [$\chi^2(4) = 3.65$, $p < .45$]; history of closed head injury ($\chi^2(2) = .35$, $p < .84$], or incidence of current antidepressant or anxiolytic treatment [$\chi^2(2) = 1.52$, $p < .47$).[2]

The three groups did not differ significantly in prevalence of drug abuse [$\chi^2(2) = 1.16$, $p < .56$], alcohol abuse [$\chi^2(2) = 0.19$, $p < .91$] or injection drug use [$\chi^2(2) = .69$, $p < .71$]. There were no differences between groups in mean years of drug abuse [$F(2,104) = .51$, $p < .61$] or alcohol abuse [$F(2,67) = .34$, $p < .71$], or in mean number of days since last drug use [$F(2,109) = 2.01$, $p < .14$] or alcohol use [$F(2,70) = 1.84$, $p < .17$] prior to testing. A positive psychiatric history (based on participant self-report when queried on interview about any history of mental health treatment in addition to substance abuse treatment) was more common among untreated participants [$\chi^2(2) = 6.71$, $p < .03$]. This latter finding may result from differences in gender composition for the treated and untreated groups: Compared to seropositive men, seropositive women were significantly less likely to be treated with antiretrovirals [$\chi^2(1) = 5.64$, $p < .02$] and significantly more likely to have a positive psychiatric history [$\chi^2(1) = 19.20$, $p < .001$].

## Procedure

We employed reaction time procedures identical to those reported by E. Martin et al. (1992a). We administered the Stroop task on an AT-compatible personal computer and VGA monitor with ATI VGA-Wonder graphics card, equipped with a Gerbrand voice-activated relay. The procedure consisted of a block of 48 practice trials followed by a single block of 192 test trials. At the start of each trial, a colored word appeared at central fixation and the participant's task was always to name the color while ignoring the word. The word remained on the screen for 3 s or until the participant responded. The computer recorded voice-activated reaction times while the examiner entered the participant's responses on an adjacent keyboard so that errors could be monitored. Twenty-five percent of stimuli were color-congruent (word and stimulus color the same, e.g., "RED" presented in red); 50% were neutral (animal names in color, such as "BEAR" in red); and 25% were color-incongruent (word and stimulus color different, e.g., "RED" presented in green). We used this probability manipulation because Stroop interference effects are maximal with 50% neutral trials (Tzelgov et al., 1992). Demands on controlled attentional processing are greatest in the color-incongruent condition and least in the color-congruent condition (Tzelgov et al., 1992). Four different colors and four different animal names were used to compose the stimuli, and stimulus order was randomly determined. We also administered the Beck Depression Inventory (Beck et al., 1961) and the State version of the State–Trait Anxiety Inventory (Spielberger et al., 1971) in order to monitor effects of psychological distress on RT performance.

## RESULTS

Mean error rates were approximately 4% and did not differ significantly between groups [$F(2,160) = .68$, $p < .51$]. Preliminary analyses indicated that mean RTs did not differ significantly between participants on zidovudine monotherapy compared with participants on other antiretroviral regimens [$F(1,87) = .11$, $p < .84$], so data for these groups were combined for analysis.

Figure 1 shows the mean of median reaction times for each Stroop condition. We analyzed RT data by mixed-design analysis of variance (ANOVA), with treatment group (untreated, treated asymptomatic, treated symptomatic) as the between-participants factor and Stroop condition (congruent, neutral, incongruent) as the within-participants factor. The expected significant main effect for Stroop condition is readily apparent in Figure 1 [$F(4,320) = 654.4$, $p < .0001$], confirming that reaction times increased systematically with greater demands on controlled attentional processing.

We found a significant main effect for treatment group [$F(2,160) = 5.34$, $p < .006$], with no significant interaction of Treatment Group × Stroop Condition [$F(4,320) = 1.54$, $p < .20$]. Compared with untreated participants, mean RTs for both asymptomatic and symptomatic treated participants were significantly faster in the congruent and neutral Stroop conditions [congruent: $F(2,160) = 4.55$, $p < .02$, $p < .05$ by the Duncan test for each comparison; neutral: $F(2,160) = 5.55$, $p < .005$, $p < .01$ by the Duncan test for each comparison]. RTs for asymptomatic treated participants were significantly faster compared with those of untreated participants in the incongruent condition, but RTs for symptomatic treated and untreated groups did not differ significantly [$F(2,160) = 4.77$, $p < .01$; $p < .01$ by the Duncan test for asymptomatic treated *vs.* untreated participants]. Mean RTs for treated asymptomatic and treated symptomatic participants did not differ significantly in any Stroop condition ($p > .05$ for each comparison).

Because of the greater number of women in the untreated group, we repeated the mixed-design analysis of RTs with gender and treatment group as between-participants factors. The main effect for treatment group again reached significance [$F(2,157) = 3.41$, $p < .05$]; the main effect for gender and the Treatment Group × Gender interaction were

[2] Estimated Verbal IQs by the AmNART (Grober & Sliwinski, 1991) were available for approximately 60% of the participants; mean age and education for the participants with AmNART scores were comparable to those for the full sample. Mean estimated IQs for asymptomatic treated participants ($M = 97.8$, $SD = 9.1$) were slightly but not significantly lower than those for untreated ($M = 103.2$, $SD = 9.5$) and treated symptomatic participants [$M = 101.7$, $SD = 7.9$; $F(2,94) = 2.36$, $p < .10$].

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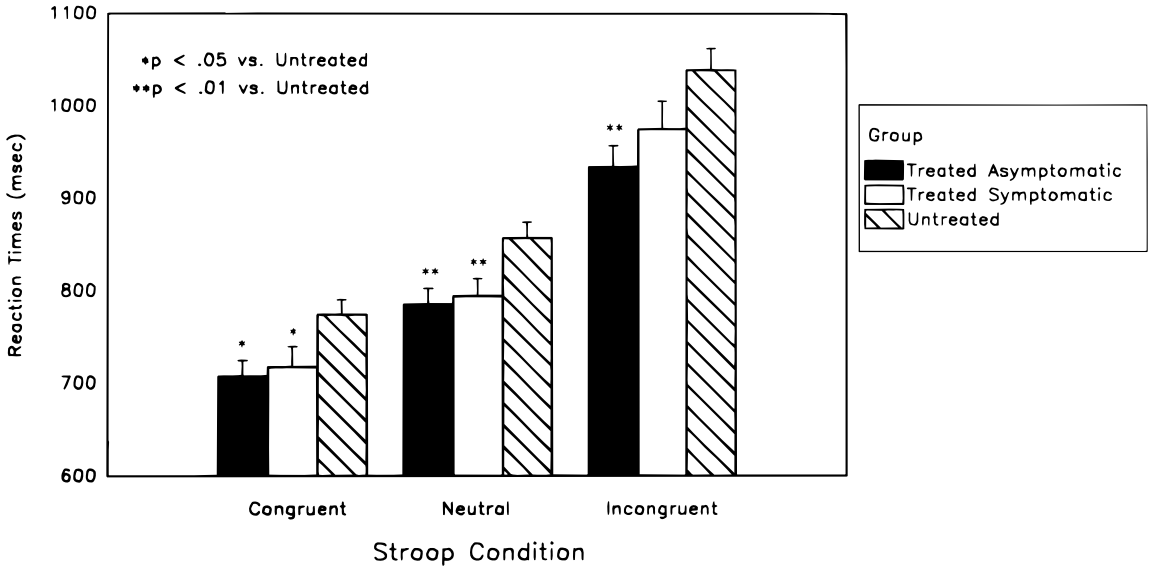


**Fig. 1.** Mean reaction times and standard errors (in milliseconds) for treated asymptomatic, treated symptomatic, and untreated HIV-seropositive groups in the three stimulus conditions of the Stroop task.

not significant [gender: $F(2,157) = .82$, $p < .37$; Group × Gender: $F(2,157) = .21$, $p < .82$]. Similarly, when we analyzed RTs using psychiatric history and treatment group as between-participants factors, the main effect for treatment group reached significance [$F(2,156) = 4.67$, $p < .02$], but the main effect for psychiatric history and the Treatment Group × Psychiatric History interaction were not significant [psychiatric history: $F(1,156) = .09$, $p < .77$; Group × Psychiatric History: $F(2,156) = 1.66$, $p < .20$].

Table 2 shows mean scores on psychological distress measures. Mean State–Trait Anxiety Inventory scores did not differ between groups significantly [$F(150) = 1.32$, $p < .19$]. We analyzed Beck Depression Inventory subjective and somatic subscores in addition to total scores. The treated symptomatic and untreated groups obtained significantly higher mean somatic subscores and total BDI scores compared with treated asymptomatic participants [somatic BDI: $F(2,149) = 6.07$, $p < .005$, $p < .05$ by the Duncan test for both comparisons; total BDI: $F(2,149) = 4.37$, $p < .02$, $p < .05$ by the Duncan test for each comparison]. Untreated and treated symptomatic groups showed a nonsignificant trend toward higher subjective subscores compared with the treated asymptomatic participants [$F(2,149) = 2.66$, $p < .08$].

We reanalyzed RTs with total BDI scores covaried in light of the significant group differences in self-reported depressive distress. The main effect for treatment group remained significant [$F(2,148) = 6.08$, $p < .005$], and the interaction of Treatment Group × Stroop Condition reached significance [$F(4,298) = 2.58$, $p < .05$]. The significant interaction appeared to be due to a difference in the pattern of RTs for treated asymptomatic and symptomatic participants. Mean RTs for both treated groups were significantly faster in all Stroop conditions compared to untreated participants ($p < .05$ for each comparison); mean RTs for the two treated groups did not differ significantly in the congruent and neutral conditions [congruent: $F(1,80) = .07$, $p < .80$; neutral: $F(1,80) = .02$, $p < .89$] but the asymptomatic treated group showed a nonsignificant trend toward

**Table 2.** Scores on psychological distress measures

| | Participant group | | |
|---|---|---|---|
| | Untreated | Asymptomatic treated | Symptomatic treated |
| Measure | *M* (*SD*) | *M* (*SD*) | *M* (*SD*) |
| Beck Depression Inventory | | | |
| Subjective items | 9.6 (8.4) | 6.2 (5.6) | 9.3 (7.1) |
| Somatic items | 5.8* (3.7) | 3.5 (2.5) | 5.6* (3.1) |
| Total | 15.4* (10.9) | 9.7 (6.9) | 15.0* (9.4) |
| State–Trait Anxiety Inventory | 38.4 (11.2) | 36.4 (9.4) | 36.1 (8.4) |

*$p < .05$ *versus* treated asymptomatic group.

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faster RTs in the incongruent condition compared with treated symptomatic participants [$F(1,80) = 2.12$, $p < .15$].

Correlations between RTs for the three Stroop conditions and the three BDI indices were not significant ($|r| < .12$ in each instance). We found small but significant correlations between STAI scores and RTs in the congruent ($r = .16$, $p < .04$) and incongruent conditions ($r = .18$, $p < .03$). We reanalyzed RTs with STAI scores covaried: the significant main effect for treatment group was unchanged [$F(2,148) = 6.06$, $p < .001$], and the Treatment Group × Stroop Condition interaction reached significance [$F(4,298) = 2.585$, $p < .05$]. Tests of the interaction indicated that mean RTs for treated asymptomatic subjects were significantly faster than RTs for untreated participants in all Stroop conditions [congruent: $F(1,100) = 7.26$, $p < .01$; neutral: $F(1,100) = 8.61$, $p < .005$; incongruent: $F(1,100) = 11.18$, $p < .001$]. Mean RTs for treated symptomatic participants were significantly faster compared to untreated participants in the congruent and neutral conditions [congruent: $F(1,115) = 5.14$, $p < .05$; neutral: $F(1,115) = 6.93$, $p < .01$] and showed a trend toward significance in the Incongruent condition [$F(1,115) = 3.84$, $p < .06$]. Mean RTs for treated asymptomatic and symptomatic participants did not differ significantly in any Stroop condition [congruent: $F < 1$, $p < .50$; neutral, $F < 1$, $p < .57$; incongruent: $F(1,80) = 2.39$, $p < .13$].

Stroop interference includes a "facilitation" and an "inhibition" component. The facilitation component or "benefit," indexed by the difference between RTs in the neutral and congruent conditions, is influenced primarily by automatic attentional processes; the inhibition component or "cost," indexed by the difference in RTs in the incongruent and neutral conditions, is influenced primarily by controlled processes (e.g., Henik et al., 1993). Stroop cost, but not benefit, is sensitive to HIV-related mental slowing (E. Martin et al., 1992a). Figure 2 shows mean facilitation and inhibition scores for the three treatment groups. Mean facilitation scores did not differ significantly between the three groups when scores were analyzed with BDI scores covaried [$F(2,148) = .46$, $p < .64$]. However, both the untreated and symptomatic treated participants showed significantly greater inhibition compared to the asymptomatic treated participants [$F(2,148) = 3.51$, $p < .05$, $p < .01$ by the Duncan test for each comparison]. Finally, correlations between RTs and absolute CD4 counts were not significant ($|r| < .09$ in each instance).

## DISCUSSION

We found that HIV-seropositive participants currently receiving antiretroviral therapy performed the RT Stroop task significantly faster than untreated participants, despite the treated participants' significantly more advanced immunosuppression. The groups were well matched on age, education, and substance abuse history, so the differences in reaction times cannot be attributed to these variables. Further, the group differences in RTs persisted when we repeated the analyses controlling for sex, psychiatric history, and psychological distress. These results are consistent with our previous finding of faster choice reaction times in treated compared to untreated individuals (E. Martin et al., in press). In addition, the current results provide stronger support for our hypothesis that central information processing is faster in antiretroviral-treated participants: The RT Stroop procedure requires only a vocal response and thus minimizes nonspecific effects of peripheral motor slowing, which are more likely to influence performance of tasks requiring a keypress response.

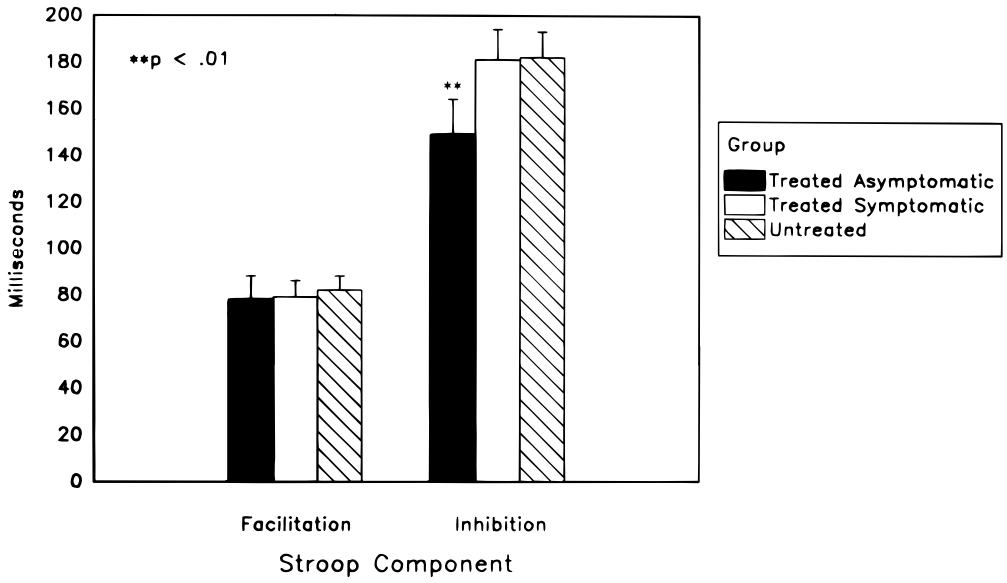


**Fig. 2.** Mean Stroop facilitation (left) and inhibition (right) in milliseconds for treated asymptomatic, treated symptomatic, and untreated groups.

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This study's cross-sectional design does not permit us to infer causation between antiretroviral treatment and cognitive function, although our data are consistent with previous reports that HIV-seropositive patients show evidence of improvement on neuropsychological tests and laboratory measures of CNS infection following initiation of antiretroviral therapy (e.g., Brouwers et al., 1997; Schmitt et al., 1988; Sidtis et al., 1993). Longitudinal data are needed to address this question and studies employing serial RT testing of participants pre- and postinitiation of antiretroviral therapy are currently in progress in our laboratory.

With these limits to interpretation in mind, several study findings deserve comment. We found faster Stroop RTs for both asymptomatic and symptomatic treated participants compared with untreated participants in the congruent and neutral stimulus conditions. However, mean RTs in the incongruent condition, which maximizes demands on controlled attentional processing, were consistently faster only for the treated asymptomatic participants compared to the untreated group. In addition, compared to untreated participants, only the asymptomatic treated individuals had significantly lower inhibition, the component of Stroop interference that is influenced primarily by controlled processes and is most sensitive to HIV-related mental slowing (E. Martin et al., 1992a).

It is difficult to attribute the differences in RT patterns and Stroop inhibition for the treated symptomatic and asymptomatic groups entirely to differences in disease progression: The symptomatic treated participants were also significantly more immunosuppressed than the untreated participants, yet their RTs were significantly faster compared to untreated participants. Group differences in duration of therapy may account in part for the differences in Stroop inhibition between the two treated groups. Neurobehavioral benefits associated with antiretroviral therapy are known to be time-limited, and it is reasonable to assume that on average duration of therapy is longer for symptomatic compared to asymptomatic patients. Improved neurocognitive function may be most apparent in patients on antiretroviral therapy for relatively brief periods[3] and one might speculate that decline in neurocognitive performance should be most evident on the most cognitively demanding components of test tasks. Longitudinal assessments will provide a rigorous test of this hypothesis as well.

We did not conduct detailed comparisons of RTs for patients treated with differing antiretroviral compounds, because only a very small number of those treated (11%) were not receiving zidovudine at RT testing, either as monotherapy or in combination with ddI or ddC; furthermore, the majority of patients on ddI or ddC monotherapy had been treated previously with zidovudine. However, antiretroviral compounds differ in their capacity to cross the blood–brain barrier (e.g., Portegies, 1995) and future studies should compare the neurobehavioral effects of compounds as a function of CNS penetrance.

Women in our sample were significantly less likely to receive antiretroviral therapy than men. This finding is consistent with reports from larger series of sex differences in rates of antiretroviral therapy (Guinan & Leviton, 1995; Moore et al., 1991). Investigators have speculated recently that HIV-seropositive women are more vulnerable to the development of dementia and other neurologic complications (e.g., Arendt et al., 1996) compared with seropositive males; these findings may reflect in part gender differences in access to antiretroviral therapy.

There is much interest in the development and application of pharmaceutical compounds with potential to ameliorate the signs and symptoms of HIV-related dementia or, ideally, to protect against CNS injury by HIV-1 infection. Drugs active against various processes implicated in the pathogenesis of HIV-associated neuropathology, such as NMDA receptor blockers, antioxidants, and calcium channel blockers are currently in various phases of clinical investigation (e.g., Lipton, 1994). Appropriate neurobehavioral outcome measures will be necessary to evaluate the effectiveness of putatively neuroprotective or neuropalliative agents. HIV-related dementia is a relatively late complication and patients with less advanced disease often have few or no overt deficits on clinical neuropsychological testing. Measures sensitive to the subclinical neurobehavioral effects of HIV will be needed to monitor drug response in patient groups with a broad spectrum of disease severity, and reaction time tasks are well suited for use in such protocols. We would recommend that protocols for clinical trials routinely employ RT measures varying in cognitive complexity, such as choice reaction time and the RT Stroop.

Impairments on standard neuropsychological tests are associated with decreased quality of life in HIV-seropositive patients (e.g., Heaton et al., 1994), but few studies have investigated the relation between slowed performance of RT tasks and daily function. This question must also be addressed if RT tasks are to be employed with maximal utility in monitoring quality of life and response to antiretroviral therapy.

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[3]We did not collect data on duration of therapy at the time of RT testing. However, based on chart reviews for 40 patients (45% of the treated participants), we estimate that mean duration of therapy was 6.2 months ($SD$ = 7.5) for asymptomatic subjects and 13.4 months ($SD$ = 15.1) for symptomatic subjects at RT testing. Although not a critical test, this finding is consistent with our hypothesis.

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