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Short Communication

Improvement in HIV-associated motor slowing after antiretroviral therapy including protease inhibitors

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A study of neuropsychological performance was conducted in 33 HIV+ patients initiating highly active antiretroviral therapy (HAART). Grooved Pegboard (GP) non-dominant hand performance improved in 23/33 (70%) subjects (P=0.002). Among 23 patients with motor slowing (GP non-dominant hand z score < -1.0) at baseline, 18 (78%) improved on the GP non-dominant hand test after initiating HAART (P=0.001). GP non-dominant hand performance improved longitudinally in HIV+ patients initiating HAART, while matched HIV+ controls not on HAART did not change (P=0.045). Significant improvement in motor performance can occur after HAART in HIV+ patients with impairment. *Journal of NeuroVirology* (2000) **6,** 84–88.

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Highly active antiretroviral therapy (HAART) including protease inhibitors has resulted in durable suppression of plasma HIV RNA levels, improved survival, and a decreased incidence of HIV-1-associated dementia complex (HIV dementia) (Brodt *et al*, 1997). However, despite these advances, HIV dementia still develops in approximately 15% of individuals with late stage AIDS, and there is concern that the prevalence of dementia might increase as the pool of long term survivors with AIDS increases. The protease inhibitors, as a class, have relatively poor cerebrospinal fluid (CSF) penetration, although for some members of this class, CSF concentrations may be adequate to achieve virological suppression (Collier *et al*, 1997).

Motor and psychomotor slowing is a cardinal feature of HIV dementia, and decline in performance on tests of motor and psychomotor speed is one of the earliest indicators of the development of this condition (Van Gorp *et al*, 1989). The present study examines whether treatment with HAART including protease inhibitors is associated with improved motor performance in HIV+ patients, particularly those with motor slowing.

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The current investigation consisted of two aspects: (1) an uncontrolled, prospective study of neuropsychological test performance before and after initiation of HAART in HIV+ patients and (2) a comparison of changes in neuropsychological testing performance between HIV+ patients initiating HAART and HIV+ patients not on HAART who were matched for age, education, CD4 count, and the presence of AIDS and HIV dementia.

Initially, a prospective observational study was conducted in HIV+ patients followed in the Johns Hopkins HIV Neurology Outpatient Clinic. Neuropsychological testing data from August, 1995 to September, 1997 was included. Patients in this clinic receive a neuropsychological test, the Grooved Pegboard (GP) non-dominant and dominant hands, to screen for the presence of dementia (Klove, 1962; Matthews and Klove, 1964). The GP was performed before and following initiation of HAART including protease inhibitors in 33 HIV+ patients for the non-dominant hand test and 34 HIV+ patients for the dominant hand test. Sixty-seven per cent of the patients were on indinavir as part of their HAART. Subjects were excluded from the analysis if they did not have a GP test within 3 months of initiating HAART, if they had a concurrent central nervous system (CNS) opportunistic infection or neoplasm, or if they were participating

in a clinical trial for the treatment of HIV dementia. Age and education-adjusted z scores were used to evaluate change in GP performance after treatment initiation (Selnes *et al*, 1991; Concha *et al*, 1991).

The baseline was defined by the date of initiation of HAART. Cognitive impairment was defined as performance more than one standard deviation (s.d.) below the age and education-adjusted norm for the GP at baseline. Sixty-one per cent of the subjects in this study were diagnosed with HIV dementia at baseline using operational criteria from the American Academy of Neurology (Janssen *et al*, 1991). AIDS was defined according to the 1987 CDC criteria (Centers for Disease Control, 1987).

For each subject, the GP performance prior to initiation of HAART was compared to the last available GP performance within the study period. The tendency toward improvement or deterioration in the GP test was evaluated based upon the distribution of change scores among the participants. Subjects with a clinically meaningful response (i.e., 'responders') were defined using a threshold of z score change >0.5, (with clinically meaningful deterioration [i.e. 'non-responders'] defined as any z score change <-0.5).

Univariate statistics were calculated based on the demographic data from baseline (the visit within 3 months of HAART initiation), to facilitate the comparison of improvers and non-improvers. Two sample *t*-tests and chi-square tests were used to compare the distributions of continuous and categorical demographic variables, respectively. The Wilcoxon signed rank test was used to assess the significance of changes in cognitive test performance and CD4 lymphocyte counts. An exact sign test was performed to assess the probability of clinically meaningful response. All *P*-values reported correspond to two-sided tests.

In the second component of the study, HIV+ patients initiating HAART (cases) were compared to HIV+ patients not on HAART (controls) who receivd longitudinal GP non-dominant and dominant hand testing. Controls were selected from patients in the Johns Hopkins HIV Neurology Consultation Service database, and were matched individually to cases on age, education, CD4 count, and the presence of AIDS and HIV dementia. For age, cases and controls were stratified into one of four categories: (1) age=25–34 years; (2) age=35–44 years, (3) age=45–54 years, (4) age $\geqslant$ 55 years. For education, cases and controls were stratified into one of the following categories: <high school, high school, some college, college, or >college. For CD4 count, the following three groups were used: CD4 $\leqslant$ 200, CD4=201–350, CD4 >350. The presence of AIDS and HIV dementia were dichotomous variables. HIV+ controls had similar exclusion criteria as HIV+ cases. For the HIV+ controls, age and education-adjusted z scores were used to evaluate change in GP performance.

Controls were evaluated in a manner similar to cases initiating HAART with *t*-tests and chi-square tests to compare demographic data between improvers and non-improvers, the Wilcoxon signed rank test to assess the significance of changes in cognitive test performance, and the sign test to evaluate clinically meaningful change. To compare the GP changes among cases initiating HAART and controls, the difference in distributions between the case change scores and the control change scores was evaluated using the Wilcoxon signed rank test while accounting for the pairwise matching. To compare cases and controls on the basis of clinically meaningful improvement, a score of 1, −1, and 0, respectively, was assigned to those improving by >0.5 s.d.s, those deteriorating by >0.5 s.d.s, and those whose absolute change was <0.5 s.d.s. Differences in these scores between matched pairs was assessed via the Wilcoxon signed rank test.

There were no significant differences in age, education, gender, race, risk of transmission, the presence of AIDS or HIV dementia, or previous use of antiretroviral therapy at baseline visit between cases with z score change >0 and cases with z score change <0 or between controls with z score change >0 and controls with z score change <0 (see Table 1). Although controls were not using HAART, 82% of the controls had used some antiretroviral drugs prior to baseline. There was no significant difference in the time lag between GP testing dates for cases (mean number of days=259) and controls (mean number of days=214).

Longitudinal performance in HIV+ cases initiating HAART

GP non-dominant hand performance improved in 23 of 33 (70%) subjects initiating HAART (P=0.002) (see Figure 1A). Among 23 patients with cognitive impairment (GP non-dominant hand z score <-1.0 at baseline), 18 (78%) had better GP non-dominant hand test performance after initiating HAART (P=0.001). Substantial improvements of >5 s.d. were seen in four subjects. Improvement was maintained for at least 1 year after HAART initiation in five of seven (71%) subjects with a year or more of follow-up.

Using a threshold for clinically meaningful response of >0.5 s.d., there were 19 responders and five non-responders for GP non-dominant hand performance after HAART (P=0.007). Among subjects impaired at baseline, there were 17 responders and three non-responders (P=0.003).

Among subjects who showed improved performance on the GP non-dominant hand, CD4 cell counts also improved (mean increase in CD4 count=60 cells/mm^3, P=0.011). Plasma HIV RNA measurements were available in only 12 subjects. Of four subjects who achieved suppression of plasma HIV RNA levels to <1000 copies/ml subsequent to

Table 1 Demographic characteristics of HIV+ cases initiating highly active antiretroviral therapy (HAART) and controls not initiating HAART stratified by performance status on the Grooved Pegboard non-dominant hand test

	Cases with z score change >0 n=*23*	*Cases with z score change <0* n=*10*	*Controls with z score change >0* n=*18*	*Controls with z score change <0* n=*16*
Age: median (range)	37 (25–51)	40 (31–71)	37 (28–50)	42 (34–57)
Education in years: median (range)	14 (8–21)	12 (8–25)	12 (11–17)	15 (11–25)
Gender: % male	87	90	78	94
Race: % African/American	30	30	56	44
Risk of transmission				
Homosexual/bisexual	65	60	56	38
IV drug abuse	13	10	22	25
Heterosexual	9	0	6	19
Mixed risk factors/Unknown	12	30	16	18
Presence of AIDS at baseline visit %	74	80	78	69
Presence of HIV dementia at baseline visit %	57	70	61	63
Use of antiretroviral therapy prior to baseline visit %	87	90	83	81

HAART therapy, three subjects improved in their GP non-dominant performance.

GP dominant hand performance improved in 21 of 34 (62%) subjects (P=0.013). Among the 21 subjects who were impaired, (GP dominant hand z score < -1.0 at baseline) 15 (71%) had better GP dominant hand test performance (P=0.003). Using the threshold for clinically meaningful response of >0.5 s.d., there were 17 responders and seven non-responders for GP dominant hand change after HAART (P=0.064). Among subjects impaired at baseline, there were 14 responders and four non-responders (P=0.036).

There was insufficient data to evaluate the effect of HAART on performance in other tests of psychomotor speed or other neuropsychological tests [e.g., the Trail Making test Part B (Reitan, 1958), the Symbol Digit Modalities test (Smith, 1982), the HIV Dementia Scale (Power *et al*, 1995).]

Longitudinal performance in HIV+ controls not on HAART

There was no significant difference in GP non-dominant hand performance among controls, with 18 subjects with improvement in performance and 16 subjects with worse performance (see Figure 1B). Similarly, there was also no difference in GP dominant hand performance among HIV+ controls not on HAART.

Comparison of GP performance between cases initiating HAART and controls not on HAART

GP non-dominant hand performance showed a greater trend towards improvement (i.e., change scores were more positively distributed) in cases compared to matched controls (P=0.045). For the GP dominant hand, there was a trend for more favorable change scores among HIV+ patients initiating HAART compared to matched HIV+ controls, but statistical significance was not reached (P=0.068). The comparison of change scores to assess the tendency toward clinically meaningful improvement showed a significantly greater tendency for cases compared to controls on the GP dominant hand (P=0.035), and a trend in this direction on the GP non-dominant hand (P=0.061).

The present study suggests that significant improvement in motor performance in HIV+ patients with motor slowing can occur subsequent to HAART. This improvement can be quite striking with a z score change in some cases greater than five standard deviations. In addition, neuropsychological test improvements may occur in parallel with immunological benefit after HAART initiation.

The GP is a timed test that is sensitive to motor slowing and provides separate measures for both the non-dominant and dominant hands. Prior studies have found that patients with HIV-associated cognitive impairment tend to perform worse than controls on measures of psychomotor speed and manual dexterity such as the GP test (Van Gorp *et al*, 1989; Miller *et al*, 1990). In the Multicenter AIDS Cohort Study (Miller *et al*, 1990), measures of manual dexterity and psychomotor functioning (GP, the Symbol Digit Modalities test, the Trail Making Test Part B) were more sensitive than tests of verbal learning and memory, verbal fluency, and attention for discriminating symptomatic seropositive subjects from seronegative controls. Abnormalities on the GP test also correlate with subcortical atrophy as measured by magnetic resonance imaging in patients with HIV-associated cognitive impairment (Hestad *et al*, 1993). As there was insufficient data to evaluate the effect of HAART on performance in other neuropsychological tests, our study has limited its conclusion to motor performance improvement in HIV+ patients with motor slowing.

It is assumed that effective antiretroviral treatment for HIV dementia must have good CNS penetration. The protease inhibitors as a class have relatively poor CSF penetration (McArthur *et al*, 1999). However, indinavir, used by 67% of the HIV+ patients on

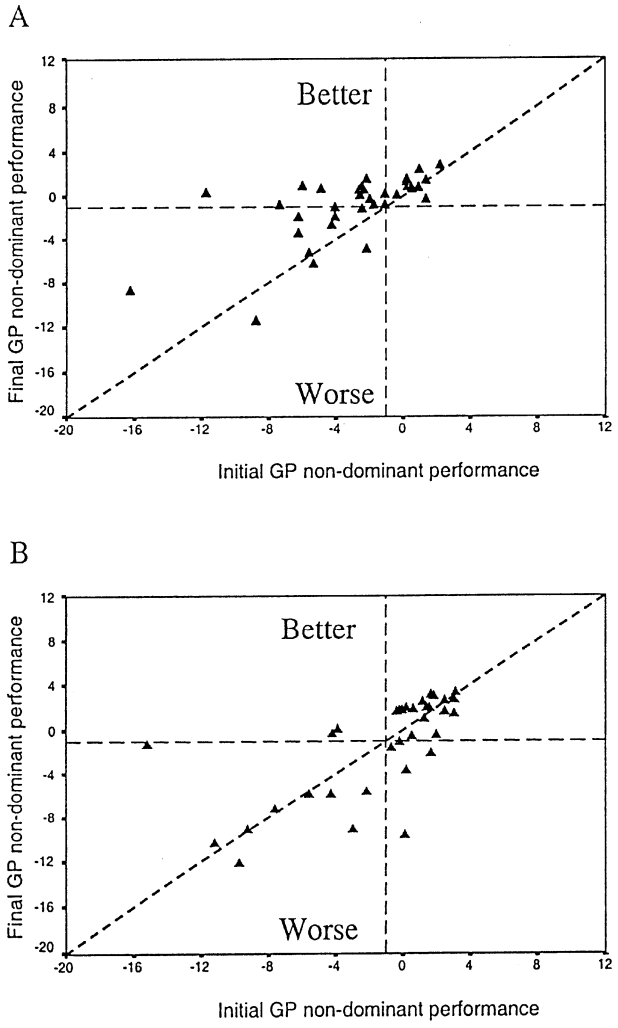

Figure 1 Grooved Pegboard (GP) non-dominant hand test performance. (**A**) Performance in HIV+ subjects after initiation of highly active antiretroviral therapy (HAART) (cases). GP non-dominant hand performance improved in 23 of 33 (70%) of subjects (P=0.002). (**B**) Performance in HIV+ subjects not on HAART (controls). GP non-dominant hand performance improved in 18 of 34 (53%) of subjects (P=0.738). Each triangle represents the performance of an HIV+ patient. The x and y axes correspond to z score performance. Subjects to the left of the vertical line represent patients with motor impairment at baseline, and subjects below the horizontal line represent patients with impairment at the follow-up visit. Subjects to the upper left of the diagonal line represent patients with improvement. Subjects to the lower right of the diagonal line are those with deterioration.

HAART, has a CSF:plasma concentration ratio of 0.02–0.06 (McArthur *et al*, 1999) which is higher than most other protease inhibitors. In addition, Collier (1997) reported that nine out of ten patients had a CSF HIV RNA less than 200 copies/ml after long-term indinavir therapy. These results suggest that even potent antiretroviral agents with putatively poor CNS penetration, such as the protease inhibitors, can still be effective treatment for HIV-associated cognitive impairment in some patients.

Two potential mechanisms may explain the association between HAART and improvement of HIV-associated motor slowing. Suppression of CNS viral replication may be due to direct CNS penetration of antiretroviral drugs. Also, suppression of plasma HIV viral load with potent combination antiretroviral therapy may reduce further CNS seeding, and thereby be effective treatment (Sacktor and McArthur, 1997), which would be consistent with the fact that plasma viral load is associated with the risk of dementia (Childs *et al*, 1999).

Improvements in neuropsychological performance in patients with HIV-associated cognitive impairment correlate with declines in CSF HIV RNA levels (Le Tendre *et al*, 1998). Unfortunately, there was insufficient data to evaluate for changes in CSF HIV RNA in the HIV+ patients initiating HAART in the current study.

Some subjects showed no neuropsychological test improvement after HAART initiation. Potential hypotheses for this lack of response are inadequate systemic viral load suppression with HAART, problems with adherence (due to forgetting doses or side effects from the antiretroviral medications), drug interactions reducing antiretroviral drug plasma levels, or the selection of a combination of CNS-impenetrable antiretroviral drugs (Condra and Emini, 1997).

The beneficial effect of HAART on motor performance is consistent with two recent studies evaluating the effect of HAART on neuropsychological test performance (Sacktor *et al*, 1999; Ferrando *et al*, 1998). In the Multicenter AIDS Cohort Study (Sacktor *et al*, 1999), combination antiretroviral regimens (with or without protease inhibitors) were associated with improved psychomotor speed performance in HIV+ homosexual men. In a cross-sectional study, Ferrando *et al* (1998) found that combination therapy with protease inhibitors was associated with a lower prevalence of neuropsychological impairment in HIV+ homosexual men compared to HIV+ homosexual men not taking protease inhibitors. Our study demonstrates that in a longitudinal assessment in HIV+ individuals with motor slowing, neuropsychological testing can improve after initiation of HAART.

The strengths of the current study are in the longitudinal assessment of individuals, the use of a neuropsychological test sensitive to HIV-associated cognitive impairment, the use of HIV+ subjects from multiple risk groups, and the use of a comparison group of HIV+ controls matched on age, education, CD4 count, and the presence of AIDS and HIV dementia.

In addition to the effect of HAART, there are several other explanations that could account for an improvement in neuropsychological testing performance. The GP improvement could be due to an

improvement in overall health status. Also, there may have been selective dropout of subjects with more advanced disease. Among clinic patients initiating HAART, there were no significant differences between the 33 subjects who returned after baseline for follow-up testing and the 17 subjects who failed to return for follow-up testing, with respect to age, education, gender, race, risk of transmission, presence of AIDS at baseline, or use of antiretroviral therapy prior to baseline. Subjects failing to return for a follow-up visit were actually less likely to have dementia at baseline (P=0.001). Neuropsychological testing improvement could also be due in part to regression to the mean or to practice effects. To evaluate this latter possibility, subjects with $\leqslant 2$ neuropsychological testing visits prior to baseline were compared to subjects with >2 neuropsychological testing visits with respect to GP non-dominant hand changes. There were no significant differences between these two groups. Biases due to drop-out or practice would seem to be less of a concern given that the influence of these effects were also possible among the control group, who showed no tendency toward cognitive improvement.

HAART was associated with improvement in motor speed performance, which was maintained for 1 year for some HIV+ individuals. Further studies are needed to determine the durability of this potential therapeutic effect, and to determine if this neuropsychological improvement is also associated with functional improvement.

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