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Psychomotor slowing in HIV infection: a predictor of dementia, AIDS and death

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The objective of this study was to determine if sustained decline in psychomotor speed tests is associated with an increased risk of progression to dementia, acquired immunodeficiency syndrome (AIDS), or mortality in human immunodeficiency virus (HIV)-1-infected homosexual men in the Baltimore site of the Multicenter AIDS Cohort Study (MACS). Clinical and neuropsychological data were obtained on 291 HIV$^+$ homosexual men seen semi-annually over a nine year period (1986–1994). A proportional hazards model was used to assess the predictive value of sustained psychomotor slowing (defined as a 2.0 standard deviation (s.d.) decline in performance on either the Symbol Digit Modalities test or Trailmaking test at two consecutive evaluations). Time-dependent co-variates included in the model were sustained psychomotor slowing, number of attended visits, CD4$^+$ lymphocyte count, hemoglobin and antiretroviral medication use. HIV$^+$ participants with and without sustained psychomotor slowing were compared. Outcome variables were the development of dementia, AIDS and death. HIV$^+$ subjects with sustained psychomotor slowing had an increased hazard of dementia (Risk ratio (RR)=5.0, P=0.008), AIDS (RR=2.4, P=0.02), and death (RR=2.0, P=0.04). A similar analysis using sustained cognitive decline in one domain from a more extensive neuropsychological test battery failed to show any predictive value. Sustained decline in psychomotor performance in HIV infection was predictive of dementia, AIDS and death. This brief neuropsychological test battery may be useful for early detection of HIV$^+$ individuals with a poorer prognosis who may benefit from more aggressive treatment to prevent HIV dementia.

Keywords: HIV; dementia; predictor; psychomotor slowing

Introduction

HIV-1-associated dementia complex (HIV dementia) occurs in approximately 20% of HIV-infected individuals (Levy *et al*, 1985; McArthur, 1987; McArthur *et al*, 1993; Portegies *et al*, 1993) and has an incidence of approximately 7% per year among survivors after the development of AIDS (McArthur *et al*, 1993; Day *et al*, 1992). Typically, cognitive, behavioral and motor deterioration progresses over weeks or months once dementia develops (Navia *et al*, 1986). In particular, psychomotor slowing is a cardinal feature of HIV dementia. Two studies indicate that decline in performance on a psychomotor speed test is one of the earliest indicators of the development of dementia (Selnes *et al*, 1991; Van Gorp *et al*, 1989). Another longitudinal study found that during the period before and after the development of AIDS (1987 CDC definition, excluding HIV dementia), HIV dementia patients showed significant decline only on psychomotor speed tests (Selnes *et al*, 1995). The ability of a brief screening test of psychomotor speed to predict prognosis in HIV infection remains to be established. The present study examines whether sustained decline in performance on tests of psychomotor speed is associated with an increased risk of dementia, AIDS or death in 291 homosexual men.

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Methods

Study design and diagnostic criteria

The study was conducted in the Baltimore center of the MACS, a prospective study of the natural history of HIV infection among homosexual men. The design of this study has been described elsewhere

(Kaslow *et al*, 1987; Polk *et al*, 1987). Briefly, participants in the MACS undergo interview, clinical assessment, and laboratory measurements every six months. AIDS was defined according to the 1987 CDC criteria (Center for Disease Control, 1987). HIV dementia was defined by specific operational criteria which were modifications from those of the American Academy of Neurology (AAN) (Bacellar, 1994; McArthur *et al*, 1993; Working Group of American Academy of Neurology AIDS Task Force, 1991). The diagnosis of dementia was not made by neuropsychological testing criteria alone. Rather, a committee of neurologists and neuropsychologists used a combination of clinical abnormalities, functional impairments as well as neurological examination findings, radiological and cerebrospinal fluid results, and neuropsychological test abnormalities in several cognitive domains (memory, language, attention, as well as psychomotor speed), to establish a diagnosis of dementia. Detailed neurological and additional testing was performed as part of an active surveillance based on clinical reports of dementia, neurological symptoms, or neuropsychological decline in any domain. The timing of dementia was determined by the active surveillance system. In general, date of dementia was determined by when the neurological signs were overt and functionally limiting, and neurological assessment had been completed. These operational criteria have been published previously (McArthur *et al*, 1993).

Subjects

Longitudinal neuropsychological data was examined from 291 HIV^+ participants at the Baltimore site of the MACS. Data from January 1986 to December 1994 was included. The data set was censored on death or the last date of contact. 'Cognitive decline ever' was defined as a 2.0 s.d. deterioration on at least one neuropsychological test in an individual's testing compared to the same individual's previous best performance on the test (Figure 1a). Other cut-points also were examined, but 'a 2.0 s.d. deterioration on at least one test' was the best definition to discriminate between HIV^+ and HIV^- subjects. HIV^+ subjects with 'sustained cognitive decline' ($cogdec^+$) were compared to HIV^+ subjects with 'non-sustained decline' ($cogdec^-$). '$Cogdec^+$' was defined as a 2.0 s.d. deterioration on one neuropsychological test in an individual's testing that persisted for that individual's subsequent visit (occurring within a 1 year period) (Figure 1b). The onset of $cogdec^+$ was dated to the first visit of cognitive decline. '$Cogdec^-$' was defined as subjects who did not meet criteria for $cogdec^+$. In other words, individuals who never showed cognitive decline or individuals who had cognitive decline at one visit (cognitive decline ever), but it was not sustained at the subsequent visit, were defined as $cogdec^-$ (Figure 1c). In order to have an accurate description of whether an individual met criteria for sustained decline, if an individual without sustained decline did not attend at least 50% of the possible visits (and therefore was missing data which might have altered classification), that individual was excluded from the analysis.

Neuropsychological testing

Semi-annual neuropsychological evaluations were performed on approximately 65% of all HIV^+ participants (Miller *et al*, 1990). Two neuropsychological testing batteries were used to evaluate participants in the Baltimore site of the MACS.

The 'full-screen' battery was used to evaluate a subset of participants in the MACS. The full-screen included the Symbol Digit Modalities test (SDMT) (Smith, 1982) and the Trailmaking test (TM) Parts A and B (Reitan, 1958, 1979). The SDMT (written version) is a brief test of psychomotor speed and attention that requires the subject to substitute numbers for symbols according to a fixed key. The score is the total number of correct numbers completed in 90 s (maximum score=110). The TM is a test of perceptual motor speed, attention and visuospatial tracking. TM Part A requires the subject to consecutively connect numbers in sequence. TM Part B requires the subject to consecutively connect alternating numbers and letters in sequence, (e.g. 1-A, 2-B, 3-C, *etc*). The score is the time in seconds to complete the test. Other tests included in the full-screen were the Digit Span subtest (Forward and Backward) of the WAIS-R (Wechsler, 1981), the controlled Oral Word Association test (a verbal fluency test) (Benton and Hamsher, 1978; Benton *et al*, 1983), the Grooved Pegboard test (dominant and nondominant hands) (Klove, 1963; Matthews and Klove, 1964), and the Rey Auditory Verbal Learning test (Rey, 1964).

In 1991, a 'mini-screen' battery, administered to all MACS participants was initiated. The mini-screen included only two neuropsychological tests from the full-screen, the SDMT and TM. The longitudinal analysis of mini-screen performance included both data subsequent to 1991 and SDMT and TM data extracted from the full screen from 1986–1991, so that the mini-screen and full-screen analyses compared neuropsychological testing performance over the same time period (1986–1994). Thus, the mini-screen data analysis included both the SDMT and TM data extracted from the full-screen data and additional SDMT and TM data.

Data analysis

Univariate statistics were performed on the demographic data from the baseline visit, the initial visit of neuropsychological testing, to compare HIV^+ subjects who became $cogdec^+$ and subjects that remained $cogdec^-$. T-tests compared continuous data and chi-square tests compared proportions.

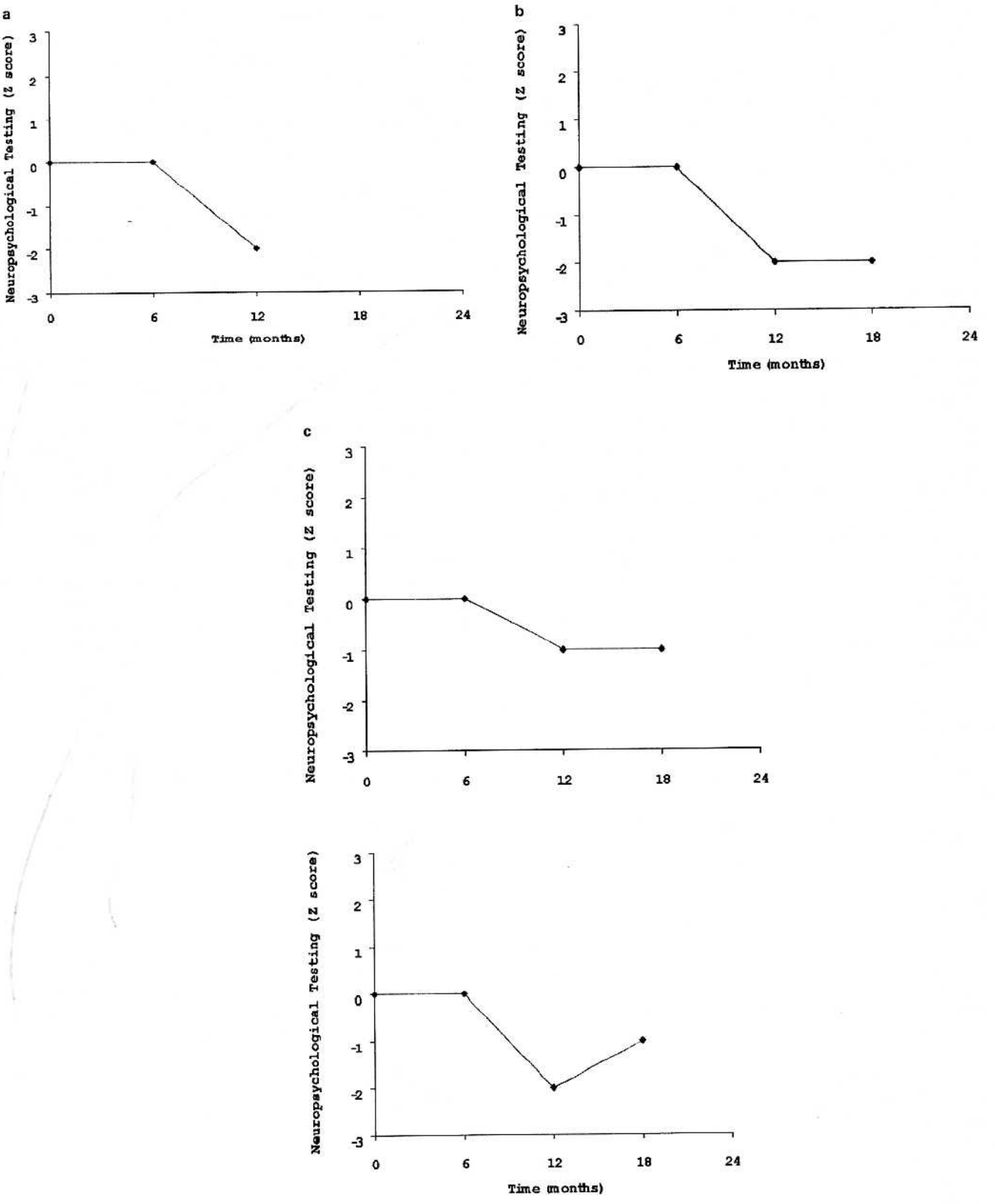

Figure 1 (a) Neuropsychological testing for 'cognitive decline ever'-example. (Neuropsychological testing in an individual declines by 2.0 s.d). (b) Neuropsychological testing for 'sustained cognitive decine' (cogdec^{+})-example. (Neuropsychological testing in an individual declines by 2.0 s.d. and is sustained at the next visit). (c) Neuropsychological testing for 'non-sustained cognitive decline' (cogdec^{-})-example. (Testing does not decline by 2.0 s.d. or 2.0 s.d. decline is not sustained at next visit).

Proportional hazards models (Cox, 1972) which used onset of cogdec$^+$ or 'cognitive decline ever' as a time-dependent covariate, were used to predict dementia, development of AIDS, and death. Other factors added to the models as time-dependent covariates included the number of attended visits, CD4$^+$ lymphocyte count, hemoglobin (Hb) and antiretroviral medication use (defined as any use of the reverse transcriptase inhibitors, AZT, DDI, DDC or D4T).

Results

Frequency of neuropsychological definitions
One hundred and nine (37%) of the 295 HIV$^+$ participants with neuropsychological testing from the mini-screen declined at least once ('cognitive decline ever'), (Table 1). Four patients with cognitive decline at their last documented visit never returned for further testing. Forty-three (15%) of the 291 HIV$^+$ subjects with longitudinal mini-screen neuropsychological data had sustained cognitive decline ('cogdec$^+$'). Longitudinal full-screen neuropsychological data was available on 234 patients. One hundred and forty-seven (62%) of the 234 HIV$^+$ subjects with longitudinal full-screen neuropsychological data were classified as 'cognitive decline ever'. Seventy-four (32%) of the 234 HIV$^+$ subjects with longitudinal full-screen neuropsychological data were classified as cogdec$^+$.

Demographic characteristics
The demographic characteristics of the mini-screen cogdec$^+$ and cogdec$^-$ subjects are described in Table 2. There were no significant differences in age, education, CD4$^+$ lymphocyte count or Hb at the baseline visit between the two groups.

Table 1 Frequency of neuropsychological definitions

	Mini-screen	*Full-screen*
Cognitive decline ever	37%	62%
Sustained cognitive decline cogdec$^+$)	15%	32%

Distribution of outcomes: mini-screen criteria
Twenty-three percent of the mini-screen cogdec$^+$ subjects developed dementia whereas only 6% of the cogdec$^-$ subjects developed dementia ($P<0.001$), (Table 3A). Six of the 10 mini-screen cogdec$^+$ subjects with dementia developed their sustained decline prior to the diagnosis of dementia (time range of decline prior to dementia: 6–24 months). Sixty-five percent of the mini-screen cogdec$^+$ subjects developed AIDS compared to 44% for the cogdec$^-$ subjects (P=0.01). Forty-nine percent of the mini-screen cogdec$^+$ died compared to 33% for the cogdec$^-$ subjects (P=0.05).

Distribution of outcomes: full-screen criteria
Eighteen percent of the full-screen cogdec$^+$ subjects developed dementia whereas only 6% of the cogdec$^-$ subjects developed dementia ($P<0.007$), (Table 3B). Fifty-seven percent of the full-screen cogdec$^+$ subjects developed AIDS compared to 50% for the cogdec$^-$ subjects (P=0.34). Forty-three percent of the full-screen cogdec$^+$ subjects died compared to 41% for the cogdec$^-$ subjects (P=0.77).

Outcomes as predicted by mini-screen 'cognitive decline ever' definition
A proportional hazards model including the number of attended visits, CD4$^+$ count, Hb and antiretroviral medication use as covariates, was used to determine if 'cognitive decline ever' (a decline in a single cognitive test) in the mini-screen predicted

Table 3 Distribution of outcomes for HIV$^+$ cogdec$^-$ and cogdec$^+$ subjects

	Cogdec$^-$	*Cogdec$^+$*	P *value*
A Mini-screen			
Dementia	6%	23%	0.001
AIDS	44%	65%	0.01
Death	33%	49%	0.05
B Full-screen			
Dementia	6%	18%	0.007
AIDS	50%	57%	0.34
Death	41%	43%	0.77

Table 2 Demographic characteristics of HIV$^+$ cogdec$^-$ and cogdec$^+$ groups (defined by mini-screen) at baseline visit

	Cogdec$^-$ Mean	*s.d.*	*Cogdec$^+$ Mean*	*s.d.*
Age (years)	37.1	(6.9)	39.1	(7.5)
CD4$^+$ count (cells/mm^3)	531.6	(337.2)	555.3	(272.4)
Hb (gm/dl)	14.2	(1.5)	14.6	(1.4)
	Cogdec$^-$		Cogdec$^+$	
Education (% college educated)	56		61	

the three primary outcomes (Table 4A). 'Cognitive decline ever' predicted dementia (RR=3.0, P=0.04), i.e., HIV$^+$ patients with cognitive decline at one visit were three times more likely to develop clinical dementia over a short time period than HIV$^+$ patients without cognitive decline. 'Cognitive decline ever' was neither associated with the development of AIDS nor death.

Outcomes as predicted by mini-screen sustained decline measure

A proportional hazards model using the mini-screen cogdec$^+$ definition as a time-dependent variable was performed in a similar manner as described above (Table 4B). After adjusting for number of attended visits, CD4$^+$ count, Hb, and antiretroviral medication use, mini-screen cogdec$^+$ predicted dementia (RR=5.0, P=0.008). Mini-screen cogdec$^+$ also had an increased risk of AIDS (RR=2.4, P=0.02) and an increased risk of death (RR=2.0, P=0.04). In other words, sustained cognitive decline on tests of psychomotor performance in HIV$^+$ patients was associated with a fivefold increased risk of dementia over a short interval, a 2.4-fold increased risk of AIDS, and a twofold increased risk of death, compared to HIV$^+$ patients without sustained cognitive impairment.

Outcomes as predicted by full-screen definition

A proportional hazards model using the full-screen cogdec$^+$ definition was also performed in a similar manner as described above (Table 4C). Full-screen cogdec$^+$ was neither associated with the development of dementia, AIDS, nor death. Full-screen 'cognitive decline ever' was also not associated with dementia, AIDS, or death.

Table 4 Dementia, AIDS, and death as predicted by neuropsychological testing decline in HIV$^+$ subjects (using a proportional hazards model adjusted for number of attended visits, CD4$^+$ count, hemoglobin and antiretroviral medication use)

	RR	P *value*
A Cognitive decline ever on the mini-screen		
Dementia	3.0	0.04
AIDS	1.4	0.23
Death	1.1	0.71
B Sustained decline (cogdec$^+$) on the mini-screen		
Dementia	5.0	0.008
AIDS	2.4	0.02
Death	2.0	0.04
C Sustained decline (cogdec$^+$) on the full-screen		
Dementia	1.7	0.33
AIDS	1.0	1.00
Death	0.9	0.66

Discussion

The present study indicates that sustained decline in psychomotor performance in HIV$^+$ homosexual men is associated with a significantly increased risk of dementia, AIDS, and death. Cognitive decline is a necessary component of dementia. However, the severity of the individual's measured cognitive deficits was not a part of the model; i.e., subjects with cogdec$^+$ could have met criteria for either HIV-1-associated minor cognitive/motor disorder or HIV-1-associated dementia complex (Working Group of American Academy of Neurology AIDS Task Force, 1991). Likewise, cogdec$^-$ subjects could also have met criteria for HIV-1-associated dementia complex, if they had poor neuropsychological test performance prior to enrollment in the cohort.

A single visit with decline in psychomotor performance was predictive of dementia but not AIDS or mortality. In order for the psychomotor speed factor to serve as a marker for all three outcomes, the decline in psychomotor performance needed to be sustained for two consecutive visits within a 1 year period.

The present analysis assumes that the Symbol Digit Modalities test (SDMT) and Trailmaking test (TM) are measurements of psychomotor speed. Other cognitive domains such as attention, concentration, and visuospatial tracking are also being assessed by these two tests. Since the SDMT and TM are sensitive indicators of subtle neuropsychological deficits (Smith, 1982; Reitan, 1958), it is possible that the mini-screen's sensitivity to more global cerebral dysfunction, rather than its capacity to measure solely psychomotor slowing, may make the battery a useful predictor of dementia, AIDS and death.

Non-sustained decline also could be due to several causes other than HIV infection which are potential confounding factors (Selnes *et al*, 1995). They include fatigue (Miller *et al*, 1991), sleep disturbance (Darko *et al*, 1992), vitamin deficiencies (Kieburtz *et al*, 1991), minor illnesses (Stewart *et al*, 1989; Smith *et al*, 1987; Smith, 1990), stress (Cohen *et al*, 1991), medication side effects (Lipowski, 1990), and depression (Hinkin *et al*, 1992; Perdices *et al*, 1992). Data on these potential confounders was not collected systematically on these patients, and we recognize that they could contribute, in part, to the non-sustained psychomotor slowing seen in our patients.

The proportional hazards model is a time-dependent model using all available neuropsychological testing. For example, if a subject with neuropsychological data from 1986–1994 developed decline in psychomotor performance in 1990, this individual was classified in the model as cogdec$^-$ from 1986–1990 and cogdec$^+$ from 1990–1994. Because increasing attendance at neuropsychological testing visits increases the like-

lihood of developing sustained cognitive decline, the number of attended visits was used as a covariate in the model. $CD4^+$ count was included as a covariate because numerous studies have shown an association between decreasing $CD4^+$ count and progression to AIDS and death (Polk *et al*, 1987; Prette *et al*, 1991). Hb was included as a covariate because of the previously reported association between lower Hb and HIV dementia (McArthur *et al*, 1993). Antiretroviral medication use was included to adjust for treatment effects.

After adjusting for the number of attended visits, $CD4^+$ count, Hb, and antiretroviral medication use, neither cognitive decline ever nor sustained decline ($cogdec^+$) in the full-screen battery predicted an increased risk of dementia, AIDS, or mortality. The full-screen battery includes tests of psychomotor speed as well as attention, verbal memory, verbal fluency, and manual dexterity. This result suggests that an abbreviated simple battery of two tests of psychomotor speed may be a useful screen for 'high-risk' patients with incipient dementia, AIDS, or death. It does not mean that a more comprehensive battery is not useful. Other risk factors for incipient dementia, from previous analyses within the MACS, include clinical symptoms, low Hb, and low body mass index (a measure of body weight) (McArthur *et al*, 1993).

The results from this study are consistent with prior observations that psychomotor speed performance is a sensitive measure for early detection of HIV dementia (Selnes *et al*, 1991; Van Gorp *et al*, 1989). Another study also suggests that the presence of cross-sectional cognitive impairment is associated with an increased risk of death (Mayeux *et al*, 1993). In that cross-sectional study (Mayeux *et al*, 1993), cognitive impairment was defined as a two or more s.d. decline below the mean of published norms on at least one cognitive area. Also, in that study (Mayeux *et al*, 1993), the prognostic significance of longitudinal decline in specific cognitive domains was not examined. Our study is the first longitudinal study to demonstrate that cognitive decline, specifically in psychomotor performance, rather than cross-sectional cognitive impairment, is associated with an increased individual risk of both death and AIDS.

This study was performed in a cohort of homosexual men, and it is unknown whether similar outcomes would be obtained in other groups of patients such as intravenous drug users. However, results from the ALIVE study (Selnes *et al*, 1992), a cohort of intravenous drug users, suggests that the clinical features of HIV dementia in this group are similar to those found in homosexual men.

The strength of the current study is in the definition of cognitive decline and in the active surveillance system for clinical dementia. Each individual's performance is compared to the same individual's previous best performance. Thus, each participant is serving as his own control. Cognitive performance is not being directly compared to population norms. Clinical use of a variable measuring longitudinal decline in an individual patient may appear complicated, but in practice can be automated simply using computer generated algorithms. Another strength to this study is the long (9 year) follow-up period used to evaluate each of the outcome variables.

As new therapies for treatment of HIV dementia become available, the selection of HIV^+ patients at risk for a worse cognitive outcome is critical to determine clinical efficacy. This simple screening battery for psychomotor performance, in combination with other clinical criteria, may be useful to select patients who may benefit from neurologically focused treatment.

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