Prevalence of cognitive disorders differs as a function of age in HIV virus infection

James T. Becker, Oscar L. Lopez, Mary Amanda Dew and Howard J. Aizenstein

Objectives: Ten per cent of all new cases of AIDS in the United States are in persons older than 50 years. This is particularly problematical in the case of the neuropsychiatric consequences of HIV, because there are neuropsychiatric disorders which become common in older individuals in the absence of HIV. The purpose of this report is to describe the prevalence and incidence of cognitive impairment in HIV-infected individuals enrolled in a community-based study.

Design: The study consisted of community-based, sentinel survey physician referrals of HIV-infected patients, with volunteer recruitment of risk-appropriate seronegative controls. One-year longitudinal follow-up study.

Methods: Detailed neuropsychiatric evaluations were performed at study entry and after one year. A brief, interim visit tracked incident change. Each subject's neuropsychological test performance was classified as normal, demented, or cognitive impairment (not demented).

Results: The prevalence of cognitive disorder among HIV-positive individuals over 50 years was significantly greater than in individuals younger than 50 years. Among older participants, dementia was the more common classification (23%), whereas among younger participants, a milder form of cognitive impairment was more prevalent (22%). Alcohol abuse/dependence was a significant risk factor for a disorder, whereas greater education was a protective factor. The one-year incidence of disorder in the sample overall was low (7.3%), and age was not a significant risk factor. However, HIV viral load at study entry was significantly higher among those participants who had developed cognitive impairment one year later.

Conclusion: Age is a significant risk modifier for prevalent neuropsychological disorder.

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Introduction

The vast majority of neurobehavioral HIV research has focused on individuals younger than 50 years, in spite of the fact that 10% of all new cases are older. Older age is an important predictor of poor survival [1–3], and since the introduction of highly active antiretroviral therapy (HAART), age may be even more important to our understanding of the clinical manifestations of HIV infection. With the longer survival of AIDS patients, and the unrelenting increase in new cases of AIDS, the number of AIDS patients over 50 years of age is growing. Our lack of understanding about how age and HIV interact is becoming increasingly problematical, no more so than in the area of the neuropsychological manifestations of AIDS, because age is an

From the Departments of Psychiatry, Neurology, Psychology, and Epidemiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

Correspondence to James T. Becker, PhD, Neuropsychology Research Program, Suite 830, 3501 Forbes Avenue, Pittsburgh, PA 15213, USA.

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important predictor of neurobehavioral syndromes in its own right.

Relatively few data relate directly to the question of the possible synergism between age and HIV that would alter the clinical manifestations of AIDS, but in the studies that do examine such relationships, there is an increase in the rate of neuropsychological problems among older HIV-infected individuals. Janssen and colleagues [4] noted relatively early in the epidemic that HIV-associated dementia (HAD) was more often the AIDS-defining illness among older individuals. Furthermore, among individuals who already had AIDS, there was an age-associated increase in the risk of HAD [5]. More recently, Hardy (cited by Hinkin and colleagues [6]) examined the relationships among HIV disease stage, age and cognitive decline. Among HIV-positive individuals without AIDS, the rate of cognitive impairment rose from approximately 35% in those under 40 years, to approximately 50% in those over 40 years. Among individuals with AIDS, 50% of those under 50 years were impaired, whereas nearly 80% of those over 50 years were impaired. Goodkin and colleagues [7] reported that older HIV-positive adults have more symptoms of HIV-related minor cognitive/motor disorder [8] than younger HIV-positive adults. Therefore, aging, especially crossing the 50 year threshold, increases the risk of cognitive impairment.

The Multicenter AIDS Cohort Study (MACS) [9], however, failed to find a substantial age-by-HIV interaction. Among more than 1000 HIV-positive men and a similar number of HIV-negative controls, there were significant main effects of HIV serostatus and of age, but no significant interaction between HIV and age. There was a trend ($P = 0.056$) towards part B of the Trail Making Test to be more affected among older HIV-positive individuals than younger individuals, but the size of the effect was small. An analysis of a second, smaller cohort with a higher proportion of older individuals found, in addition to the trail B findings, a significant ($P = 0.015$) age-by-HIV status interaction on a measure of fine motor coordination (Grooved Pegboard, non-dominant hand). However, there were several limitations to the study; the sample of MACS participants contained only five who were older than 55 years, although 29 out of 76 of the HIV-positive individuals in the second study were older than 55 years. However, perhaps more importantly, these data were taken from the baseline data of the MACS Neuropsychological Study, which was conducted before the advent of HAART, and therefore, the significant medical complications and associated factors that were evident circa 1987/1988 may have masked any age-associated interactions.

The purpose of this report is to describe the prevalence of cognitive disorder in a sample of community residents from Western Pennsylvania, USA, who are infected with HIV compared with risk-appropriate HIV-negative controls. In particular, we were interested in knowing whether the prevalence and one-year incidence of disorder differed as a function of age, as well as serostatus. The study participants all completed a detailed neurobehavioral evaluation, and their neuropsychological performance was classified relative to study-specific norms. Each patient was classified with regard to cognitive dysfunction in order to examine prevalence rates of disorder, but without ascribing causality (i.e. age or AIDS-associated).

Methods

Subjects

The Allegheny County Neuropsychiatric Survey (ACNS) consists of 414 individuals recruited from the Greater Allegheny County community. Primary care physicians were asked to participate as 'sentinel survey sites' and to approach each of their HIV-infected patients about whether they would be interested in the study. As HIV-infected patients visited their physicians, they were invited to meet a study representative. Statements of information and brochures describing the study were presented and reviewed during this brief session. Questions and concerns regarding confidentiality, the research site and participant compensation were also addressed. Those patients who agreed then signed the informed consent form (approved by the University of Pittsburgh Institutional Review Board), and completed a brief questionnaire that recorded basic demographic, risk and health characteristics.

A total of 290 HIV-positive, and 124 HIV-negative individuals were recruited into the study. All participants were asked to refrain from psychoactive substance use (including alcohol) for 24 h before the evaluation, and a 24-h history of alcohol/drug use was taken when the subject arrived at the clinic. However, no blood or urine tests were completed to confirm the reported abstinence. The psychosocial, psychiatric, and neuropsychological methodology have been described previously [10–12]. Demographic and HIV-related characteristics of the study sample at baseline are shown in Table 1.

Neuropsychiatric evaluation

In addition to the neuropsychological test battery, our neuropsychiatric evaluation included a neurological examination, with a medical history and a psychiatric/psychosocial interview. The medical history, and physical and neurological examinations were conducted primarily by a research nurse, with supervision by a behavioral neurologist with experience in HIV and

Table 1. Demographic characteristics of Allegheny County Neuropsychiatric Survey sample.

	HIV-negative	HIV-positive
N	114	290
Age (years) (M, SD)	34.3 (82)	38.3 (8.2)*
Education (% high school)	79.7	64.4**
Sex (% male)	68.4	83.9*
Handedness (% right)	89.8	86.1
Race (% white)	78.1	78.1
Native language (% English)	97.9	97.4
CD4 cell count (M, SD)	n/a	388.8 (313.2)
HIV viral load (log_{10}) (M, SD)	n/a	4.14 (1.1)
AIDS (%)	n/a	65[a]
HAART (%)	n/a	17.0
Diagnosis (% lifetime)		
Depression	30.1	35.6
Anxiety	3.8	4.4
Alcohol abuse/dependence	17.7	33.0**
Substance abuse/dependence		
Cannabis	10.5	11.5
Stimulants	6.8	3.1**
Opiates	3.0	3.7
Cocaine	4.5	5.4
Poly-substance	1.5	2.0
Global Severity Index (brief symptom inventory)[b]	56.4 (15.3)	68.2 (21.6)*

HAART, Highly active antiretroviral therapy.
[a]4% were Centers for Disease Control grade C only.
[b]T-score.
*$P < 0.001$.
**$P < 0.05$.

dementing illness (O.L.L.). The personal history reflected data before seroconversion and the present/current medical status. The examination covered the entire nervous system, with particular emphasis placed on signs and symptoms relevant to HIV-associated neurological conditions.

Relevant laboratory studies were also completed. HIV antibody screen (enzyme-linked immunosorbent assay), HIV confirmation test (Western blot), lymphocyte phenotypes determined by flow cytometry, and viral loads were performed by local clinical research laboratories. There was no significant association between age and these measures of disease severity in the HIV-positive volunteers. There was thus no significant relationship between the decade of life and either absolute CD4 cell counts [$F(4,216) = 1.05$, $P = 0.38$] or log_{10} HIV RNA [$F(4,217) = 1.37$, $P = 0.25$].

Follow-up

Six and 12-month follow-up evaluations were completed to monitor the course of HIV infection and any subsequent cognitive, neurological or psychiatric signs or symptoms. Follow-up evaluations and interviews mirror those of the initial visits, with comparable information being confirmed or documented, but were tailored to cover only the period since the previous visit. In addition, the 12-month evaluation included a complete neuropsychological assessment, whereas at 6 months an abbreviated version was completed.

There were differences between the volunteers who completed both baseline and annual follow-up evaluations and those who did not. The HIV-positive volunteers who returned for follow-up were less likely to have used HAART at baseline than those who did not return (5.9 versus 35.8%, $\chi^2 = 44.1$, $df = 1$, $P < 0.001$), but there was no difference in baseline HIV viral load (logRNA = 4.12 and 4.14). Although the groups did not differ in terms of basic vocabulary knowledge (as measured by the WAIS-R Vocabulary Subtest), those who did not return for follow-up had significantly lower age-scaled scores on the Digit Symbol Test from the Wechsler Adult Intelligence Scale (Revised) (WAIS-R; 10.6 versus 9.06, $F(1298) = 23.6$, $P < 0.001$). The overall baseline classification of performance (see below) was more likely to be 'normal' among those volunteers who returned for follow-up (73.8 versus 58.6%; $\chi^2 = 10.1$, $df = 2$, $P = 0.006$). Furthermore, the volunteers who returned for follow-up were more likely to be right-handed than those who did not return (90.3 versus 79.1%, $\chi^2 = 5.82$, $P = 0.052$).

Neuropsychological testing

Neuropsychological testing was completed at all three study visits, with more extensive testing completed at study entry and after one year. The tests included in assessment covering a wide range of cognitive domains, including: premorbid intelligence (WAIS-R Vocabulary, and Information Subtests; National Adult Reading Test), motor skills (Pegboard, Grip Strength), visuospatial function (WAIS-R Block Design and Digit-symbol; Complex Figure Copy), verbal memory (California Verbal Learning Test; Memory Span), nonverbal memory (Complex Figure Recall), problem solving/reasoning (Booklet Category Test; WAIS-R Comprehension), language (Boston Naming Test), word generation (Letter and Category Cues), attention (Digit and Pointing Spans; Word Span) and executive functions (Trail Making; Continuous Performance Test; Stroop Screening).

The neuropsychological data were transformed into *z*-scores using age (± 40 years) and education (± high school)-appropriate normal values taken from the HIV-negative control individuals. Separate normative values were used for the baseline and annual follow-up testing to allow for correction for practice effects. The *z*-scores were then converted into summary values. All *z*-scores greater than zero were coded as 0; those between 0 and −1 were coded as 1; between −1 and −2 as 2, and less than −2 as 3. These summary values, as well as the subject's age and education, but without study identification number or serostatus, were then placed on a spreadsheet. This summary table was then reviewed by

one of us (J.T.B.) who classified each subject as either 'normal', 'dementia', or 'cognitively impaired, not dementia' (CIND) [13]. In order to be classified as a dementia case, the participant had to have ratings of 2 or 3 on two or more measures within each of two cognitive domains; it was not required that memory be one of those domains. In order to be classified as CIND, the participants had to have scores of 1 in more than one cognitive domain, or scores of 2 or 3 in a single cognitive domain (with scores of 0 elsewhere). Consistent with the nomenclature for the classification of HIV-related disorders [8], no reference was made to whether the patient complained of deficits in function for either a classification of dementia or CIND. All classifications were made without knowledge of whether it was a baseline or follow-up visit.

The *z*-transformed data were further reduced to domain scores using standard procedures [14,15]. Summary variables were created for each of the six domains by taking the mean of the *z*-scores of the test variables included in the domain (see Table 2). Each of these domain scores was then regressed on age, education, sex, race and the Global Severity Index from the Brief Symptom Inventory (BSI) in HIV-negative individuals. The resulting regression models were then used to calculate predicted *z*-scores for each domain for all subjects, regardless of serostatus. The difference between the actual domain *z*-score and the predicted domain *z*-score was then converted into a T-score, which reflects the deviation of the subject's performance from the expected value.

Table 2. Neuropsychological test scores [mean (SD)].

	HIV-negative	HIV-positive	F-ratio
Wechsler Adult Intelligence Scale, Revised (age scale)			
Information	11.4 (3.4)	10.6 (3.1)	2.85
Vocabulary	9.9 (3.1)	10.1 (3.1)	3.68*
Comprehension	11.3 (3.9)	10.4 (2.9)	5.53**
Block design	11.5 (3.2)	10.6 (3.1)	0.87
Digit-symbol	11.5 (2.4)	10.1 (2.8)	4.54*
Digit spans			
Forward	8.9 (2.0)	8.7 (3.9)	0.007
Backward	7.2 (2.4)	6.3 (2.2)	1.74
Visual pointing span			
Forward	8.77 (1.9)	8.11 (1.7)	2.00
Backward	8.05 (1.9)	7.64 (1.9)	0.50
Visual reproduction			
Copy	39.9 (1.5)	39.1 (3.4)	4.26*
Immediate recall	37.2 (3.9)	35.6 (5.3)	3.24
Delayed recall	35.7 (5.8)	32.4 (7.9)	5.02*
Verbal fluency			
Letters	45.4 (11.7)	41.2 (12.6)	3.91
Animals	22.7 (5.5)	20.8 (5.6)	8.07**
Trailmaking (time per connection)			
Part A	1.10 (.42)	1.24 (1.1)	0.288
Part B	2.39 (1.0)	3.06 (1.6)	0.310
B/A	2.28 (.85)	2.64 (1.0)	0.954
Booklet category (errors)	45.0 (31.1)	56.4 (31.7)	0.014
Logical memory			
Immediate	25.9 (7.2)	23.3 (7.0)	0.644
Delayed	22.0 (7.3)	19.0 (7.6)	0.776

*$P < 0.05$.
**$P < 0.01$.

Results

A multivariate analysis of variance was completed on the domain scores and revealed a significant effect of HIV serostatus on the scores overall [$F(8,405) = 2.47$, $P = 0.013$]. A multivariate analysis of variance was used rather than an analysis that included covariates (i.e. age, education, race, sex and BSI score) because these factors had already been taken into account in creating the factor scores. Of the individual domains, verbal skills [$F(1,405) = 7.46$, $P = 0.007$], attention [$F(1,405) = 6.51$, $P = 0.01$], fluency [$F(1,405) = 7.45$, $P = 0.007$], and executive functions [$F(1,405) = 8.06$, $P = 0.005$] all differed significantly between serostatus groups (see Table 3).

The distribution of baseline classifications (i.e. normal, CIND, demented) differed as a function of serostatus ($0^2 = 20.1$, df = 2, $P < 0.001$; see Table 4). The HIV-positive subjects were three times as likely to be impaired, either in terms of a dementia or CIND. A similar pattern was seen at follow-up ($\chi^2 = 6.541$, df = 2, $P = 0.038$), although not as dramatically as seen at study entry. Within the HIV-infected participants, there was a significant difference in the distribution of classifications as a function of age ($\chi^2 = 5.39$, df = 2, $P = 0.034$, one-tailed). Furthermore, the relative proportion of HIV-positive subjects classified as demented (i.e. 23%) relative to CIND (i.e. 14%) among the 50+ year-old age group at follow-up, was greater than that among the younger subjects (i.e. demented 9%; CIND 22%) ($\chi^2 = 4.42$, df = 2, $P = 0.036$).

The relative risk of dementia was affected by a history of alcohol abuse/dependence, which significantly increased the risk of dementia [relative risk (RR) 5.81, 95% confidence intervals (CI) 1.13–27.1], and by increasing education, which reduced the risk significantly (RR 0.26, 95% CI 0.12–0.57). Similar effects were seen when we calculated the risk of being classified with either dementia or CIND at study entry.

The one year incidence of cognitive impairment was calculated by examining the rates of classification among those participants who were classified as 'normal' at study entry. The rate of conversion was low overall, but among the HIV-positive participants younger than 50 years, 6.9% developed some form of impairment at one year; the rate of incident CIND was 6%, whereas only 1% converted to dementia. Among

Table 3. Standardized neuropsychological domain scores [mean (SD)].

	HIV-negative				HIV-positive			
	20s	30s	40s	50s	20s	30s	40s	50s
Verbal	49.7 (6.6)	49.3 (5.9)	51.8 (6.9)	46.2 (3.2)	44.2 (6.5)	47.5 (6.4)	50.3 (6.1)	47.0 (4.7)
Attention	50.1 (5.9)	49 (5.1)	50.1 (6.3)	48.8 (1.5)	46.0 (7.4)	47.3 (6.3)	50.0 (6.3)	50.0 (6.0)
Speed	49.0 (6.5)	50.5 (6.9)	48.9 (9.7)	49.7 (3.7)	46.1 (11.0)	50.1 (8.4)	49.3 (8.5)	48.9 (15.7)
Verbal memory	49.5 (5.6)	50.0 (6.4)	51.0 (7.8)	47.4 (2.1)	48.7 (6.7)	50.0 (7.6)	50.7 (6.7)	48.7 (8.3)
Non-verbal memory	50.2 (6.6)	50.0 (9.4)	49.5 (10.1)	54.9 (11.1)	47.6 (10.8)	48.1 (11.0)	48.5 (10.7)	38.5 (19.4)
Visuospatial	50.7 (6.3)	49.5 (7.9)	49.2 (7.4)	53.0 (9.2)	47.9 (7.8)	47.1 (13.5)	49.0 (10.1)	38.7 (30.0)
Fluency	49.6 (8.1)	49.6 (7.7)	49.0 (8.3)	56.2 (7.0)	44.6 (8.9)	46.5 (8.8)	49.2 (9.4)	47.7 (8.3)
Executive	50.7 (5.1)	49.5 (6.7)	50.4 (7.7)	49.2 (7.7)	48.3 (7.1)	46.2 (8.8)	47.1 (8.7)	47.6 (7.5)

Table 4. Classification of ACNS participants [N (%)].

	HIV-negative		HIV-positive	
Baseline (age, years)	< 50	50+	< 50	50+
Normal	107 (88)	3 (100)	185 (69)	14 (64)
CIND	10 (8)	0 (0)	60 (22)	3 (14)
Dementia	4 (4)	0 (0)	22 (9)	5 (22)
Annual follow-up				
Normal	73 (92)	3 (75)	124 (81)	10 (71)
CIND	5 (6)	1 (25)	23 (15)	3 (21)
Dementia	1 (2)	0 (0)	7 (4)	1 (7)

the older participants, only one converted to a cognitive impairment, and that was to CIND.

The incidence of cognitive impairment (both dementia and CIND) was not associated with age, although the number of cases was quite small ($\chi^2 = 0.53$, df = 1, $P = 0.47$). However, indices of HIV disease status were associated with subsequent impairment. In particular, viral load ($\log_{10}$) measured at study entry was higher among those who developed impairment (viral load 4.78) compared with those who did not (viral load 4.26; $t(110) = 1.80$, $P = 0.035$, one-tailed).

One important component of classifying individuals with reference to diagnosable disorders is whether the individual complains of cognitive impairment [8,16]. In general, independent reports of real-life performance are preferred, but in many cases reliable informants are not available. This was the case in the present study, so we asked each participant about their own perception of difficulties with cognitive function. Among all study participants, there was an increase in the proportion who complained of 'difficulty thinking' from the normal (7.2%), to the CIND (43.7%), to the individuals classified as demented (54.8%; $\chi^2 = 15.1$, df = 2, $P = 0.001$). Among the HIV-positive participants, the rate of complaints of 'difficulty thinking' (43.9%) was significantly elevated relative to the HIV-negative controls (4.8%; $\chi^2 = 61.5$, df = 1, $P < 0.001$), regardless of their actual cognitive impairment.

We created a summary variable for 'complaints' for those individuals who either complained of difficulty thinking, difficulty with memory, or difficulty with activities of daily living (ADL). Among all study participants, there was an increase in complaints from those participants classified as normal (35.8%), to those classified as CIND (53.4%), to those classified as demented (64.5%; $\chi^2 = 15.2$, df = 2, $P = 0.001$). The HIV-positive participants (54.0%) were significantly more likely to have complaints than the HIV-negative controls (10.2%; $\chi^2 = 71.4$, df = 2, $P < 0.001$). The proportion of the HIV-positive subjects complaining of 'difficulty with' thinking, memory, or ADL are shown in Table 5. Although the rate of complaints was generally higher among the patients classified with dementia (based on test scores), none of the differences

Table 5. Complaints of cognitive symptoms among HIV-positive participants at study entry [N (%)].

	Normal	CIND	Dementia	χ^2
Thinking	80 (40)	30 (50)	16 (59)	4.73
Memory	94 (47)	33 (55)	18 (67)	4.29
ADL	58 (29)	21 (35)	12 (44)	3.00
Summary[a]	102 (51)	37 (61)	19 (70)	3.00

ADL, Activities of daily living; CIND, cognitively impaired, not dementia.
[a]Either Thinking, Memory, or ADL difficulties.

in rates were statistically significant, even for the summary complaint score.

In order to be classified as either minor cognitive/motor disorder or HAD using research diagnostic criteria, there must be evidence of alteration in cognitive functions, or of alterations in ADL. In this study we could only rely on the subjects' self-report. When we combined each subject's classification based on their test performance with their summary of complaints (i.e. thinking, memory, ADL), 20 out of 31 of the participants classified as dementia based on their test performance also complained of altered mental status. Similarly, 39 out of 73 of the participants classified as CIND also complained of altered mental status. Put another way, of the participants whose performance was significantly impaired (i.e. > 1.0 s.d.) on multiple tests in multiple cognitive domains (i.e. dementia classification), 40% did not complain of significant alterations in mental status. When we examined the rates of impairment among those volunteers who did not complain, the rates did not differ from those seen in the entire sample.

Discussion

The neuropsychological manifestations of HIV have long been recognized as important for the management, survival, and quality of life of affected patients and their families [17]. However, despite the known links between age and various neuropsychiatric disorders, including dementia, it has only been recently that much attention has been paid to the possible interactions between HIV, aging and neuropsychiatric presentation [9,18,19]. The possible moderating effects of age on the neuropsychiatric manifestations of HIV becomes increasingly important, for example, as we learn more about the preclinical manifestations of Alzheimer's disease (AD) [20–23] or of the long-term effects of major depression on brain structure and function [24,25], both of which can affect HIV-infected individuals independent of HIV-related problems. Therefore, understanding the possible age-by-HIV synergy is of the highest priority [6,7,26].

The results of these analyses make two important points regarding the interaction of HIV and aging. First, the overall prevalence of disorder is related to the age of the HIV-infected individual, even when age-associated changes in test performance have been accounted for. In spite of the relatively small number of cases older than 50 years, these were the individuals at greatest risk of cognitive impairment, most particularly for the more severe form. Over the course of the one year of follow-up, new cognitive impairment developed in all age groups, but in older individuals it was more likely to be in the form of the milder impairment. This could reflect the natural progression from normalcy, through CIND to dementia, as would occur in aging. Alternatively, this might reflect the vacillation of cognitive function that can be seen in HIV-infected individuals. Although age was not significantly associated with incident severe impairment, measures of disease stage at baseline were significant predictors of subsequent impairment. This suggests that factors that may alter HIV-related health, even if they are not directly associated with HIV itself, can have an impact on cognitive function, and by extension, on the structure and function of the central nervous system (CNS).

Any future analyses of the interaction between HIV infection, age, and cognitive status, must deal with a variety of important factors. First and foremost is the issue of age-associated medical and neuropsychiatric co-morbid conditions. As individuals age, the rate of cardiovascular and cerebrovascular conditions increases, as does the prevalence of diabetes, thyroid dysfunction, and vitamin deficiencies (e.g. B12), which can, in and of themselves, alter cognition. Even if these conditions are no more prevalent in older HIV-infected individuals than in seronegative individuals of the same age, they nevertheless pose an independent risk of impairment that must be accounted for in future studies.

For example, in recent years greater attention has been paid to the role of inflammatory processes in the pathophysiology of AD and other degenerative disorders. Evidence of inflammation, especially in the region of the neuritic plaque, and the special role of microglia, has led to an increased understanding of the cascade of pathology, and has prompted therapeutic efforts with anti-inflammatory medications [27–30]. Inflammation appears to be associated with a variety of processes, including free radical formation, oxidative stress, disturbance of calcium homeostasis, and mitochondrial membrane disruption. One recent hypothesis [31] suggested that astrocytes, macrophages, and microglia are the common mediators of altered CNS structure and function in HAD, AD, and multiple sclerosis.

Recent work with SIV-infected monkeys suggested that there may be a relationship between the AD-associated mechanism of beta-amyloid precursor protein (β-APP) that may be involved in the CNS damage associated with HIV. In particular, among monkeys with elevated levels of β-APP, nine out of 10 also had SIV encephalitis [32]. The data further suggested that the accumulation of β-APP in the white matter of infected monkeys was related to viral replication. Furthermore, analysis of the brains of HIV-infected patients has revealed amyloid plaques and evidence of vascular pathology [33]. Therefore, factors that are more commonly associated with AD and other neuropathologies of the elderly may, in the end, also play a role in HAD.

After the introduction of HAART, the risk of HIV-related deaths declined, whereas the risk of non-HIV-related disorders, such as coronary artery disease, remained stable [34]. The risk of hyperlipidemia and hyperglycemia increased between 1993 and 2002 and the rate of myocardial infarctions increased after the introduction of protease inhibitors [35]. Recent reviews of the clinical and pathological characteristics of cardiomyopathy and HIV encephalopathy suggest a significant pathophysiological overlap [36,37]. The abnormal response of infected macrophages to virus leads to the release of large amounts of neurotoxic substances, which cause damage to the CNS [37]. For example, the neurotoxic effects of gp120 viral protein appear to be mediated by cytokines including tumor necrosis factor alpha and IL-6 [38,39], which are released by activated microglia and astrocytes. In one study, the intensity of tumor necrosis factor alpha immunostaining was increased in patients with HIV encephalopathy, and was related to the CD4 cell count, viral load, and a summary measure of mental status [36]. Factors that influence the risk of developing a dementia in uninfected individuals thus appear to have an independent association with the development of HIV-related dementia. Therefore, HIV-positive aging individuals have a 'double risk' associated with cytokines: that derived from their age-associated medical risks, and that derived from their HIV-associated risk. How these two related mechanisms interact to produce dementia syndromes in older HIV-positive adults, and the age at which the interaction begins to appear clinically, will be an important outcome of future research.

Current diagnostic criteria for dementia and related cognitive impairments in HIV and in aging are problematical when they must be applied simultaneously in the same patient. For example, no HIV-infected patient over 65 years of age can be diagnosed with 'probable' AD [40] because they have a medical condition that could, in and of itself, cause a dementia. Similarly, although not as clearly specified, we interpret the consensus diagnostic criteria of the American Academy of Neurology similarly to preclude a diagnosis of 'probable' HAD in older individuals, as age poses its own risk of impairment. Furthermore, all of these criteria require some independent evidence of altered ADL. In the present study, as in many involving HIV-infected individuals, such independent corroboration is not possible. As noted in this study, subjects' reports of their own function do not correspond to the neuropsychological test performance. Although complaints of impairment are necessary for a classification of mild cognitive impairment [20], such is not the case with dementia (i.e. Diagnostic and Statistical Manual of Mental Disorders, version IV). It is important to note that we cannot interpret a lack of complaint by a subject in this study as evidence of a lack of impairment; this requires independent observation.

This is not to suggest that such criteria could not be developed and validated, only that the current systems do not allow for the kinds of reliable differential diagnoses that are going to become more and more necessary in research and in clinical practice. For example, in the case of newly diagnosed dementia in a 70-year-old individual with HIV, should the physician treat it as if it were a case of AD (using cholinesterase inhibitors) or a case of HAD (using a calcium antagonist, for example), or both? This issue has been addressed indirectly by the recent approval by the Food and Drug Administration (USA) of memantine for use in moderate–severely demented AD patients, although it has been studied in HIV/AIDS for several years. Because of the decline in the incidence of HAD, the risk of an age-related cognitive disorder is probably more likely than an HIV-related disorder, especially in the absence of evidence of declining physical health (e.g. rising HIV viral load, lowered hematocrit [41–44]). The development of reliable diagnostic criteria will thus not only aid researchers, but also front-line clinicians.

In conclusion, these data demonstrate an increased risk of cognitive impairment among older HIV-positive adults. An increased risk of impairment was associated with age and alcohol abuse, and greater education was protective. The mechanism responsible for such an increased risk is unknown, but future research must focus on the interaction between age-associated medical co-morbidities, and HIV-associated neuropsychiatric disorders.

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