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Cognitive impairment in older HIV-1-seropositive individuals: prevalence and potential mechanisms

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Abstract

Individuals over 50 years of age comprise 11% of AIDS cases reported to the Centers for Disease Control and Prevention. A higher prevalence of AIDS in older individuals has been reported in certain states including Hawaii (20%) and Florida (13%). Although life expectancy in individuals with AIDS has increased with advances in antiretroviral therapy, it is likely that there are health consequences both of long-term infection and chronic antiretroviral therapy. Given the general increase in neurological disorders with age and the relatively high prevalence of cognitive dysfunction associated with HIV itself, the risk of HIV-associated dementia (HAD) in this aging HIV-seropositive subgroup is of particular concern. Existing data suggest, but have not conclusively demonstrated, increased rates of HAD in older compared with younger seropositive individuals. Preliminary data from the Hawaii Aging with HIV Cohort, a prospective cohort study designed to address this issue definitively, are presented. Factors underlying this hypothesized susceptibility in older individuals are discussed, including a synergy among HAD and other dementias, the role of vascular co-pathology, HIV and age-related immunological changes, and detrimental neuroglial changes that limit the compensatory ability of the aging brain.

Keywords

aging; AIDS; cognition; dementia; HIV

Introduction

Over the past decade, changes have occurred in HIV/AIDS epidemiology within developed countries. Greater numbers of people are living with HIV as a chronic illness. In turn, there is an enhanced potential for an increased prevalence of HIV in older individuals compared with previous decades. Accompanying this change is a demographic shift in the United States as 'Baby Boomers' age, with increased risk behavior compared with their past counterparts. This combination of events is contributing to the emergence of a unique population of older HIV-seropositive individuals.

Centers for Disease Control and Prevention data may not adequately portray this evolving trend given the past reporting of AIDS and not HIV in many states. Because individuals with HIV treated with highly active antiretroviral therapy (HAART) live a relatively healthier existence

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than in the past, AIDS-defining illnesses are less useful to monitor chronic HIV infection. In some US states, the relative prevalence of HIV in older individuals is more apparent. In Florida, it is estimated that 19% of HIV cases involve individuals 50 years of age or older, despite an apparent lag in the reporting of AIDS cases (13% of cumulative reported AIDS cases occurred in this age group) [1,2]. In Hawaii, 20% of AIDS cases reported to the Department of Health in 2001 involved individuals 50 years of age or older compared with the national rate of 11% [3,4]. By conservative estimates, a quarter of HIV cases in Hawaii could be over 50 years old. Whereas the cognitive function of this older group is not yet well described, it appears likely that larger amounts of cognitive dysfunction will be observed. This hypothesis is currently being tested at several centers, including the University of Hawaii.

We have developed a model to facilitate the exploration of this hypothesis [5]. In this model, decreased brain reserve in older HIV-seropositive individuals occurs as a result of many factors: (i) the synergistic effect of neuropathology related to aging and age-associated degenerative diseases, e.g. Alzheimer's disease and Parkinson's disease; (ii) cerebrovascular disease resulting from hypertension, diabetes, hypercholesterolemia, cardiac disease, and potentially, antiretroviral medications; (iii) metabolic conditions such as hypothyroidism or vitamin B12 deficiency; (iv) age-associated changes in immune function, including the effect of chronic immune activation; and (v) detrimental neuroglial changes associated with aging. Genetic factors including apolipoprotein E4 expression associated with Alzheimer's disease are included in this model. In the following sections existing data are reviewed concerning the prevalence of cognitive dysfunction in older HIV-seropositive individuals, and some of the possible causative factors as they relate to this model are presented.

Prevalence of cognitive dysfunction with HIV and aging

Cognitive impairment associated with HIV infection has been categorized into two distinct entities: Minor cognitive motor disorder (MCMD) and HIV-associated dementia (HAD) [6]. In general, to meet diagnostic criteria necessitates an acquired deficit in a combination of cognitive ability including motor function (e.g. slowed movements, abnormal gait, hypertonia), behavior (e.g. apathy, irritability, emotional lability) and cognition (e.g. attention, concentration, memory, information processing, language). The primary difference between the two is the degree of impairment in daily function. Whereas all but the more demanding aspects of daily function are spared in MCMD, there is a greater degree of impairment in HAD.

HAD contributes to the morbidity of HIV infection and is an important risk factor for mortality [7]. Before the widespread use of HAART, up to 15% of individuals with AIDS had HAD and up to 15% experienced MCMD [8]. Advanced HIV infection is a risk factor for developing HAD in both the pre-HAART and post-HAART eras [9]. Correspondingly, there has been a decline in the reported incidence of HAD with the widespread use of HAART and associated immune reconstitution in developed countries [10].

Caution must be exercised in the interpretation of these findings as they underestimate the current impact of disease. There have been simultaneous reports of an increased HAD prevalence and an increased incidence of MCMD relative to HAD [11,12]. In addition, the proportion of individuals diagnosed with dementia while having a CD4 cell count greater than 200 mg/dl has increased, and the incidence of HAD as an AIDS-defining illness has increased [10,13]. HIV encephalopathy continues to be present in 25% of patients who succumb to autopsy, a rate that has not changed since the widespread use of HAART [14]. Taken together, these data suggest that HAD is a continuing important source of morbidity in HIV infection and may be associated with less severe stages of disease.

Reports to date indicate that the prevalence of HAD is probably higher for older compared with younger HIV-seropositive individuals. Centers for Disease Control and Prevention data

captured before the widespread use of HAART suggested that the highest rates of dementia are in the extremes of age, with a rate as high as 19% for patients 75 years of age or older with AIDS [15]. These data are subject to reporting biases such as the increased identification of dementia in older people, a propensity to report only first (AIDS-defining) illness, and the under-reporting (and perhaps under-detection) of mild disease. Epidemiological data from Europe similarly suggest a greater rate of HAD with advanced age [16]. An increased rate of MCMD symptoms in older seropositive individuals has been reported [17].

In 1994, data from the MultiCenter AIDS Cohort Study (MACS) revealed no effect of age on neuropsychological testing profiles when corrected for serostatus [18]. This analysis did show trends for differences by age chiefly in timed measures. The sample size, particularly for individuals over 50 years of age, may have been insufficient to show a more robust difference. Nevertheless, these data represent an early insight into the potential age-associated patterns of neurocognitive abnormality that could impact seropositive individuals. Psychomotor slowing has been described as a leading neurocognitive abnormality associated with HIV in younger individuals [7]. Psychomotor slowing is often characteristic of a subcortical pattern of cognitive loss similar to that of other age-associated dementias, including vascular dementia and the dementia of Parkinson's disease. The pattern of neuropsychological abnormality in older patients with HAD has not been delineated. A greater degree of psychomotor slowing may be seen, given the potential additive effects of converging neurodegenerative processes.

Therefore, existing data support increased rates of cognitive impairment in older compared with younger seropositive individuals. However, definitive data from prospective cohort studies aimed at evaluating this issue have not yet been reported.

Hawaii Aging with HIV Cohort

In the autumn of 2001, the University of Hawaii, in conjunction with Johns Hopkins University, began enrollment of the Hawaii Aging with HIV Cohort. The specific goal of this study is to characterize cognitive function in older (over 50 years of age) compared with younger HIV-seropositive individuals. Subjects in the cohort are recruited through broad community-based mechanisms involving physicians' offices, community centers, and AIDS resource organizations. Comparative groups of younger (20–40 years of age) seropositive individuals and two HIV-seronegative age groups are being enrolled simultaneously. Individual cases are brought to case conference on a weekly basis when they are reviewed by two neuropsychologists, two neurologists, and a geriatrician. Using American Academy of Neurology 1991 criteria, cases are categorized as normal, HAD, or MCMD. They are subsequently rated for severity using a modification of the Memorial Sloan Kettering scale (MSK) as described in the North East AIDS Dementia cohort (NEAD) [19].

A preliminary analysis of the first 47 older and 32 younger seropositive individuals was reported in June 2002 [20]. Although 88% of the younger group had normal or equivocal neuropsychological abnormalities (MSK 0 or 0.5), only 58% of the older group met these criteria ($P = 0.006$, chi square). In addition, a pattern of increasing severity of MSK was seen in the older compared with the younger impaired groups (Fig. 1).

These data are preliminary. A better understanding of cognitive dysfunction will require a larger sample. The planned enrollment of nearly 300 HIV-seropositive patients is underway.

Synergy between HIV-associated dementia and other dementias

Whereas HAD is distinguished from most other dementias by the identification of an infectious particle, it is not generally felt that the HIV virus itself plays a major direct role in the pathogenesis of the ensuing encephalopathy [21]. Many detrimental changes occur to neurons

in response to intermediaries such as cytokines and chemokines from the activated microglial system. Specific changes described in the neuron pool include apoptosis, neuronal dropout, and the decreased arborization of dendrites [21]. As indirect mechanisms appear to cause much of the damage in HAD, there is an increased likelihood that common pathways of various age-associated changes in the brain would contribute to more cognitive decline among older seropositive individuals.

The activation of the microglial system is a pathway shared by other dementias. It is seen in HAD, Alzheimer's disease, and dementia associated with Parkinson's disease [22]. Activated macrophages produce nitric oxide, superoxide anions, platelet activating factor, arachidonic acid metabolites, matrix metalloproteinases, and glutamate receptor antagonists, thus causing neuronal damage and apoptosis.

Some evidence suggests that the location of selective neuronal loss described in HAD mimics that of Alzheimer's disease, with larger degrees of hippocampal neuronal cell loss in the earlier stages [21,23]. Amyloid plaques have been identified in the brains of AIDS patients, with a significantly higher frequency in older compared with younger individuals [24]. In addition, in one series, apolipoprotein E4 expression, an accepted risk factor for Alzheimer's disease, was expressed twice as often in HIV-infected individuals with dementia compared with infected individuals without dementia [25].

A better understanding of the pathogenesis of HAD, particularly in older individuals, could augment our understanding of the pathogenesis of other dementias and direct treatment research. Currently, therapeutic modalities for HAD are limited, but there are important overlaps in research initiatives with those of other dementias. Selegiline, used for the treatment of Parkinson's disease, is currently being studied to treat the cognitive impairment associated with HIV infection in a multicenter trial of the AIDS Clinical Trials Group (ACTG 5090). Memantine, a non-competitive *N*-methyl-D-aspartate antagonist, has been studied for both HAD and Alzheimer's disease.

The role of vascular co-pathology

An important etiology for underlying neuropathology among older HIV-seropositive individuals is cerebrovascular disease. It may be caused either by non-HIV related risk factors or HIV-related risk factors.

Among HIV-seronegative individuals, the risk factors for cerebrovascular disease (hypertension, diabetes mellitus, cardiac disease, elevated cholesterol, and smoking) increase significantly with age. Similar patterns have been described with age in HIV-seropositive individuals [26]. Although both cerebrovascular disease and dementia are common disorders of aging, it is often uncertain whether stroke is directly causal, contributory, or merely coincidental to incident dementia. In addition to strategically placed infarctions in regions of higher cerebral function, multiple lacunes or diffuse white matter lesions can cause a dementia syndrome. The pathophysiological mechanisms of vascular dementia include cardioembolic phenomenon, atherosclerotic disease, white matter ischemia caused by hypertensive arteriopathy of penetrating arteries, distal field insufficiency, and a volume of infarct injury that overcomes the brain's compensatory capacities [27].

Cerebrovascular disease may also be a complication of HIV infection. Autopsy studies of patients with AIDS have revealed a prevalence of cerebral infarction of between 4 and 29% [28]. However, in one series, there were no excess vascular lesions in the brains of those with AIDS, suggesting that HIV infection does not cause cerebrovascular disease, but that stroke occurs in HIV-seropositive individuals as a secondary complication of systemic illness or of drug use [29].

Potential etiologies for vascular disease among AIDS patients include cardiac embolism from an underlying viral myocarditis, congestive cardiomyopathy, or infective endocarditis, atheroma and thromboembolism from arterial plaques, hematological disorders, including an antiphospholipid antibody syndrome, vasculitis secondary to opportunistic infections, or vasculitis secondary to substance abuse such as cocaine or heroin [30]. Decreased HDL-cholesterol and increased triglyceride levels as a result of an increase in VLDL are characteristic of changes seen with HIV-1 infection, independent of the effects of antiretroviral therapy. These metabolic changes may be proatherogenic [31–33]. Such alterations in the level and function of plasma lipids and lipoproteins may be induced by cytokines and other components of a prolonged acute-phase response to an inflammatory stimulus [34]. Protease inhibitors may also induce disorders of lipid metabolism, including elevations in LDL and triglycerides. These lipid abnormalities could add to accelerated atherosclerosis and an increased risk of cerebrovascular disease in HIV-seropositive individuals [17].

Therefore, as HIV-infected individuals live longer, the risk of vascular co-pathology may increase from HIV and non-HIV related events. It is hypothesized that this will contribute to an increased risk of cognitive decline. Early therapeutic interventions may need to be considered to reduce the risk of cerebrovascular disease-associated cognitive impairment.

Immunological changes with aging that potentiate risk of cognitive impairment

Knowledge about how age impacts HIV disease progression and immune dysfunction is incomplete. Older age is associated with a more rapid immunological decline, progression to AIDS following known dates of seroconversion, and poorer survival after the diagnosis of AIDS [35–39]. Whereas older individuals appear to have an HIV viral load decrease comparable with that of younger individuals after the initiation of HAART, some studies have shown a delayed or less favorable response in the CD4 lymphocyte increase [40–42]. Advanced age is associated with a lower magnitude of increase, specifically of naive CD4 cells [43]. It has been suggested that the poorer response in the elderly may be a function of thymus involution with age and the failure of thymic productivity. The level of increase in naive CD4 T lymphocyte counts after HAART has been correlated with the amount of residual thymus size assessed using computed tomography [44].

Many researchers have noted striking similarities in immune dysfunction associated with aging and that of HIV infection, which include a shift from a naive to a memory T-cell phenotype, a reduction in T-cell proliferative ability (associated with reduced telomere length and an increase in the CD8 cell population that are CD28-negative), and the decreased production of IL-2 and IL-2 receptors [45–49]. As a rough correlation exists between HIV immune dysfunction and the development of dementia, it is perhaps reasonable to hypothesize that the development of such similar immunological dysfunctions associated with the aging process may potentiate the risk for cognitive impairment.

No clear evidence currently links these age-related immune dysfunctions to the risk of neurocognitive decline. Therefore, discussions of the potential mechanisms whereby an increased risk may be manifested are highly speculative. Two potential mechanisms suggested in the literature may be worthy of note: the age-associated increase in CD8+CD28 cells, with the implication of replicative senescence in HIV pathogenesis, and the increase in the production of activated monocytes/macrophages (CD14/CD69) seen both in the context of HIV dementia and Alzheimer's disease.

Cytotoxic CD8 cells play a central role in the control of HIV infection. The CD28-negative phenotype characterizes CD8 cells that have reduced proliferative potential. An expanded

population of such CD8+CD28⁻ cells has been identified in aging humans. Studies of telomere length measurements in these cell populations have suggested that these cells have reached the irreversible state of replicative senescence [50,51]. Studies in patients with HIV have found a similar expansion of the CD8+CD28 cell subset with shortened telomeres [52]. Although the exact role that cytotoxic CD8 cells play in the development of HIV dementia is unknown, it can be hypothesized that a loss of the specific CD8 cytotoxic immune response to HIV may increase the risk of cognitive impairment. Furthermore, it has been reported that there is enhanced IFN- γ and TNF- α production by the CD8+CD28⁻ subset from both HIV-positive and aged donors [53]. By virtue of their inflammatory roles, such cytokines may play a role in the development of dementia.

The principal pathogenesis of HAD is believed to involve the activation of monocytic cells (macrophages and microglia) and their subsequent release of toxins that lead to neuronal and astrocytic dysfunction [12]. The activation of peripheral monocytes may enhance the transmigration of these cells into the brain, consequently allowing the initiation of inflammatory processes leading to HAD. Consistent with this hypothesis, an increased percentage of activated monocytes/macrophages (CD14/CD69) have been reported in the peripheral blood of individuals with HAD [54]. Interestingly, in the era of HAART, whereas CD14/CD69 cells continue to be elevated in individuals diagnosed with HAD, the levels are lower than those reported in similarly selected HAD individuals before the era of HAART. This has added to speculation that the clinical phenotype of HAD may be evolving from a subacute illness to a more protracted disorder [55]. Elevated levels of the activation marker, CD69, have been found on monocytes derived from patients with Alzheimer's disease [56]. This finding is consistent with our hypothesis of common shared pathways synergistically affecting cognitive function in older HIV-seropositive individuals.

Neuroglial changes associated with aging and HIV

Glial cells, with the extracellular matrix and blood vessels, comprise the microenvironment of the brain, and affect the plasticity of neural responses to aging and to disease. After entry into the brain of activated macrophages and the activation of microglial cells, the proliferation and activation of astrocytes (gliosis) occur [57,58]. The extent of astrogliosis tends to be more widespread than the distribution of the activated microglia, facilitated by gap junctions [59]. Gap junctions allow functional groupings of 10–100 astrocytes to communicate and exchange calcium signaling molecules, glucose, glutamate, and signals that propagate glial activation and apoptosis [60,61]. Such astrocytic upregulation results in an increase in numerous protective factors, including neurotrophic and neuroprotective cytokines, cytokines that enhance survival and differentiation of the oligodendrocytes, chemokines that recruit blood-derived inflammatory cells, cell adhesion molecules that facilitate leukocyte entry through the blood–brain barrier, extracellular matrix molecules that affect the migration of astrocytes and oligodendrocytes, and antioxidants involved in the elimination of free radicals and protection against oxidative stress [59,62]. As a result, the major role of the astrocyte in HAD may be in controlling inflammation and enabling a balance between tissue destruction and repair. With aging, this balance changes in several components.

Aging affects repair processes and induces a constant level of enhanced reactivity in both microglia and astrocytes. In older rats, signals from damaged cells are insufficient to activate further neuroprotection by astrogliosis, but are adequate for further activation of the microglia [63]. Furthermore, activated microglia in older rats lose their ability to upregulate neurotrophic molecules such as insulin-like growth factor 1 [64]. Insulin-like growth factor 1 is an important stimulator of proliferation and survival of neurons and oligodendrocytes [65]. In older human brains, astrocytic activation in response to ischemic injury has been shown to occur more slowly, to be less pronounced, and to persist for a shorter duration compared with younger

brains [66]. Aging rats also demonstrate a reduced capacity for neuronal sprouting [64]. Aging increases the microglial expression of proinflammatory cytokines, to include IL-1 in humans and IL-6 in mice, as well as the increased expression of CD4 cells and MHC-II within the white matter [67–71]. Therefore, the aging brain may be more vulnerable to HAD by favoring inflammatory microglial responses over neuroprotective microglial responses, while limiting protection and repair by neurons and astroglia.

Both astrocytes and microglia from older animals proliferate readily in culture, but are less responsive than cells from younger animals to controlling factors such as granulocyte–macrophage colony-stimulating factor and transforming growth factor beta 1 [72]. The loss of cytokine regulation of neural growth factors has been implicated in humans with HAD. IL-4 induces nerve growth factor secretion to enhance oligodendrocyte survival [73]. IL-4 messenger RNA has been shown to be undetectable in the autopsied brains of patients with HAD, but is easily detected in the brains of most non-demented HIV-positive and HIV-negative individuals [74].

Changes in the extracellular space can also affect glial and neuronal signaling. The loss of extracellular matrix macromolecules, the narrowing of the extracellular channels, and swelling of delicate astrocytic processes, with reduced non-synaptic astroglial uptake for glutamate, glycine, and -aminobutyric acid occur with aging [75]. Excitatory neurotoxicity would be further enhanced by an increase in intracellular calcium and a reduction in calcium channel antagonist receptors, which have been demonstrated to occur in the brains of aging mice [76]. Therefore, the aging brain may be at an increased risk of excitatory neurotoxicity. In HIV, excitatory neurotoxicity has been shown to be potentiated by gp120, Tat, and matrix metalloproteinases [77].

Macromolecules and proteins (prealbumin, albumin, alpha 2-macroglobulin, IgG) permeate the blood–brain barrier more freely with aging [78,79]. Choline and glucose permeability also changes with aging [80]. The significance of these changes in HAD is uncertain. However, age-associated increases in blood–brain barrier permeability could affect the delivery into the cerebrospinal fluid of antiretroviral agents possessing significant protein binding.

In conclusion, preliminary data from the Hawaii Aging with HIV Cohort, as well as other available existing data, support a growing concern that increased rates of cognitive impairment may be present in older compared with younger HIV-seropositive individuals. A need clearly exists to define the impact of aging on the prevalence and incidence of dementia and to determine the distinctive risk factors that may be associated with such a decline in this unique aging sub-group of HIV-seropositive individuals.

Whereas immune function probably plays a pivotal role in the pathogenesis of neurocognitive dysfunction, other factors including co-morbid neurodegenerative disorders, vascular co-pathology, and astrocytic function may also contribute. By skewing the microenvironment of the brain to one that favors the harmful effects of microglial activation, and limiting compensatory and adaptive neuroglial responses, one might expect the aging brain to be at increased risk of injury in HIV and other disorders that induce sustained microglial activation.

References

1. Bureau of HIV/AIDS. *HIV prevalence estimates* [Report]. Florida: Florida Department of Health; 2002. pp. 1–6.
2. The Florida Division of Disease Control. *Surveillance report (hepatitis, HIV/AIDS, STD and TB)*, Vol. 208. Florida: Florida Department of Health; 2001. pp. 24–25.
3. Hawaii Department of Health. HIV/AIDS surveillance quarterly report, cases to 31 December 2001. Hawaii: Hawaii Department of Health; 2001. pp. 1–6.

4. Centers For Disease Control and Prevention. *HIV/AIDS surveillance report*, Vol. 13(2). Atlanta, GA: Centers For Disease Control and Prevention; 2001. pp. 5–6.
5. Valcour V, Sacktor N. HIV-associated dementia and aging. *J Ment Health Aging* 2002;8:295–306.
6. Report of a Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. *Neurology* 1991;41:778–785. [PubMed: 2046917]
7. Sacktor NC, Bacellar H, Hoover DR, Nance-Sproson TE, Selnes OA, Miller EN, et al. Psychomotor slowing in HIV infection: a predictor of dementia, AIDS and death. *J Neurovirol* 1996;2:404–410. [PubMed: 8972422]
8. McArthur JC, Sacktor N, Selnes O. Human immunodeficiency virus-associated dementia. *Semin Neurol* 1999;19:129–150. [PubMed: 10718534]
9. Sacktor N, McDermott MP, Marder K, Schifitto G, Selnes OA, Miller EN, et al. HIV-associated cognitive impairment before and after the advent of combination therapy. *J Neurovirol* 2002;8:136–142. [PubMed: 11935465]
10. Sacktor N, Lyles RH, Skolasky R, Kleeberger C, Selnes OA, Miller EN, et al. HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990–1998. *Neurology* 2001;56:257–260. [PubMed: 11160967]
11. Sacktor N. The epidemiology of HIV-associated neurological disease in the era of highly active antiretroviral therapy [Abstract]. *J Neurovirol* 2002;8:39.
12. Kaul M, Garden GA, Lipton SA. Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature* 2001;410:988–994. [PubMed: 11309629]
13. Dore GJ, Correll PK, Li Y, Kaldor JM, Cooper DA, Brew BJ. Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS* 1999;13:1249–1253. [PubMed: 10416530]
14. Masliah E, DeTeresa RM, Mallory ME, Hansen LA. Changes in pathological findings at autopsy in AIDS cases for the last 15 years. *AIDS* 2000;14:69–74. [PubMed: 10714569]
15. Janssen RS, Nwanyanwu OC, Selik RM, Stehr-Green JK. Epidemiology of human immunodeficiency virus encephalopathy in the United States. *Neurology* 1992;42:1472–1476. [PubMed: 1641138]
16. Chiesi A, Vella S, Dally LG, Pedersen C, Danner S, Johnson AM, et al. AIDS in Europe Study Group. Epidemiology of AIDS dementia complex in Europe. *J Acquired Immune Defic Syndr Hum Retrovirol* 1996;11:39–44. [PubMed: 8528731]
17. Goodkin K, Wilkie FL, Concha M, Hinkin CH, Symes S, Baldewicz TT, et al. Aging and neuro-AIDS conditions and the changing spectrum of HIV-1-associated morbidity and mortality. *J Clin Epidemiol* 2001;54 (Suppl 1):S35–S43. [PubMed: 11750208]
18. van Gorp WG, Miller EN, Marcotte TD, Dixon W, Paz D, Selnes OA, et al. The relationship between age and cognitive impairment in HIV-1 infection: findings from the Multicenter AIDS Cohort Study and a clinical cohort. *Neurology* 1994;44:929–935. [PubMed: 8190299]
19. Marder K, Albert SM, McDermott MP, et al. Inter-rater reliability of a clinical staging of HIV-associated cognitive impairment. *Neurology* 2003;60:1467–1473. [PubMed: 12743233]
20. Valcour V, Shiramizu B, Shikuma C, Wu Poff P, Watters M, Grove J, et al. Neurocognitive function among older compared to younger HIV-1 seropositive individuals [Abstract]. *J Neurovirol* 2002;8 (Suppl 1):69. [PubMed: 11935459]
21. Lawrence DM, Major EO. HIV-1 and the brain: connections between HIV-1-associated dementia, neuropathology and neuroimmunology. *Microbes Infect* 2002;4:301–308. [PubMed: 11909740]
22. Williams KC, Hickey WF. Central nervous system damage, monocytes and macrophages, and neurological disorders in AIDS. *Annu Rev Neurosci* 2002;25:537–562. [PubMed: 12052920]
23. Cummings JL, Vinters HV, Cole GM, Khachaturian ZS. Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology* 1998;51 (Suppl 1):S2–S17. [PubMed: 9674758]
24. Esiri MM, Biddolph SC, Morris CS. Prevalence of Alzheimer plaques in AIDS. *J Neurol Neurosurg Psychiatry* 1998;65:29–33. [PubMed: 9667557]
25. Corder EH, Robertson K, Lannfelt L, et al. HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. *Nat Med* 1998;4:1182–1184. [PubMed: 9771753]

26. Kilbourne AM, Justice AC, Rabeneck L, Rodriguez-Barradas M, Weissman S. General medical and psychiatric comorbidity among HIV-infected veterans in the post-HAART era. *J Clin Epidemiol* 2001;54 (Suppl 1):S22–S28. [PubMed: 11750206]
27. Tatemichi T, Sacktor N, Mayeux R. **Dementia associated with cerebrovascular disease, other degenerative diseases, and metabolic disorders.** In: Katzman R, Bick K, editors. *Alzheimer disease* New York: Raven; 1994. pp. 123–166.
28. Connor MD, Lammie GA, Bell JE, Warlow CP, Simmonds P, Brett RD. Cerebral infarction in adult AIDS patients: observations from the Edinburgh HIV Autopsy Cohort. *Stroke* 2000;31:2117–2126. [PubMed: 10978040]
29. Berger JR, Harris JO, Gregorios J, Norenberg M. Cerebrovascular disease in AIDS: a case–control study. *AIDS* 1990;4:239–244. [PubMed: 2350443]
30. Harrison MJG, McArthur J. **Cerebrovascular disease.** In: *AIDS and Neurology* Edinburgh: Churchill Livingstone; 1995. pp. 197–206.
31. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1992;74:1045–1052. [PubMed: 1373735]
32. Constans J, Pellegrin JL, Peuchant E, Dumon MF, Pellegrin I, Sergeant C, et al. Plasma lipids in HIV-infected patients: a prospective study in 95 patients. *Eur J Clin Invest* 1994;24:416–420. [PubMed: 7957495]
33. Zangerle R, Sarcelletti M, Gallati H, Reibnegger G, Wachter H, Fuchs D. Decreased plasma concentrations of HDL cholesterol in HIV-infected individuals are associated with immune activation. *J Acquired Immune Defic Syndr* 1994;7:1149–1156. [PubMed: 7932082]
34. Khovidhunkit W, Memon RA, Feingold KR, Grunfeld C. Infection and inflammation-induced proatherogenic changes of lipoproteins. *J Infect Dis* 2000;181 (Suppl 3):S462–S472. [PubMed: 10839741]
35. Goedert JJ, Kessler CM, Aledort LM, Biggar RJ, Andes WA, White GC 2nd, et al. A prospective study of human immunodeficiency virus type 1 infection and the development of AIDS in subjects with hemophilia. *N Engl J Med* 1989;321:1141–1148. [PubMed: 2477702]
36. Phillips AN, Lee CA, Elford J, Webster A, Janossy G, Timms A, et al. More rapid progression to AIDS in older HIV-infected people: the role of CD4+ T-cell counts. *J Acquired Immune Defic Syndr* 1991;4:970–975. [PubMed: 1679845]
37. Gardner LI Jr, Brundage JF, McNeil JG, Milazzo MJ, Redfield RR, Aronson NE, et al. Predictors of HIV-1 disease progression in early- and late-stage patients: the US Army Natural History Cohort. Military Medical Consortium for Applied Retrovirology. *J Acquired Immune Defic Syndr* 1992;5:782–793. [PubMed: 1517964]
38. Operskalski EA, Stram DO, Lee H, Zhou Y, Donegan E, Busch MP, et al. Human immunodeficiency virus type 1 infection: relationship of risk group and age to rate of progression to AIDS. Transfusion Safety Study Group. *J Infect Dis* 1995;172:648–65. [PubMed: 7658055]
39. Rothenberg R, Woelfel M, Stoneburner R, Milberg J, Parker R, Truman B. Survival with the acquired immunodeficiency syndrome: experience with 5833 cases in New York City. *N Engl J Med* 1987;317:1297–1302. [PubMed: 3500409]
40. Yamashita TE, Phair JP, Munoz A, Margolick JB, Detels R, O'Brien SJ, et al. Immunologic and virologic response to highly active antiretroviral therapy in the Multicenter AIDS Cohort Study. *AIDS* 2001;15:735–746. [PubMed: 11371688]
41. Goetz MB, Boscardin WJ, Wiley D, Alkasspoles S. Decreased recovery of CD4 lymphocytes in older HIV-infected patients beginning highly active antiretroviral therapy. *AIDS* 2001;15:1576–1579. [PubMed: 11504992]
42. Viard JP, Mocroft A, Chiesi A, Kirk O, ROge B, Panos G. Influence of age on CD4 cell recovery in human immunodeficiency virus- infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis* 2001;183:1290–1294. [PubMed: 11262215]
43. Lederman MM, McKinnis R, Kelleher D, Cutrell A, Mellors J, Neisler M, et al. Cellular restoration in HIV infected persons treated with abacavir and a protease inhibitor: age inversely predicts naive CD4 cell count increase. *AIDS* 2000;14:2635–2642. [PubMed: 11125881]

44. Smith KY, Valdez H, Landay A, Spritzler J, Kessler HA, Connick E, et al. Thymic size and lymphocyte restoration in patients with human immunodeficiency virus infection after 48 weeks of zidovudine, lamivudine, and ritonavir therapy. *J Infect Dis* 2000;181:141–147. [PubMed: 10608760]
45. Fagnoni FF, Vescovini R, Passeri G, Bologna G, Pedrazzoni M, Lavagetto G, et al. Shortage of circulating naive CD8(+) T cells provides new insights on immunodeficiency in aging. *Blood* 2000;95:2860–2868. [PubMed: 10779432]
46. Negoro S, Hara H, Miyata S, Saiki O, Tanaka T, Yoshizaki K, et al. Age-related changes of the function of T cell subsets: predominant defect of the proliferative response in CD8 positive T cell subset in aged persons. *Mech Ageing Dev* 1987;39:263–279. [PubMed: 2887717]
47. Bestilny LJ, Gill MJ, Mody CH, Riabowol KT. Accelerated replicative senescence of the peripheral immune system induced by HIV infection. *AIDS* 2000;14:771–780. [PubMed: 10839584]
48. Valdez H, Connick E, Smith KY, Lederman MM, Bosch RJ, Kim RS, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. *AIDS* 2002;16:1859–1866. [PubMed: 12351945]
49. Negoro S, Hara H, Miyata S, Saiki O, Tanaka T, Yoshizaki K, et al. Mechanisms of age-related decline in antigen-specific T cell proliferative response: IL-2 receptor expression and recombinant IL-2 induced proliferative response of purified Tac-positive T cells. *Mech Ageing Dev* 1986;36:223–241. [PubMed: 3099104]
50. Fagnoni FF, Vescovini R, Mazzola M, Bologna G, Nigro E, Lavagetto G, et al. Expansion of cytotoxic CD8+ CD28- T cells in healthy ageing people, including centenarians. *Immunology* 1996;88:501–507. [PubMed: 8881749]
51. Reisberg B, Auer SR, Monteiro IM. Behavioral pathology in Alzheimer's disease (BEHAVE-AD) rating scale. *Int Psychogeriatr* 1996;8 (Suppl 3):301–308. [PubMed: 9154579]
52. Effros RB, Allsopp R, Chiu CP, Hausner MA, Hirji K, Wang L, et al. Shortened telomeres in the expanded CD28-CD8+ cell subset in HIV disease implicate replicative senescence in HIV pathogenesis. *AIDS* 1996;10:F17–F22. [PubMed: 8828735]
53. Eylar EH, Lefranc CE, Yamamura Y, et al. HIV infection and aging: enhanced interferon- and tumor necrosis factor-alpha production by the CD8+ BMC Immunol 2001;2:10. [PubMed: 11696237]<http://www.biomedcentral.com/1471-2172/2/10>
54. Pulliam L, Gascon R, Stubblebine M, McGuire D, McGrath MS. Unique monocyte subset in patients with AIDS dementia. *Lancet* 1997;349:692–695. [PubMed: 9078201]
55. Kusdra L, McGuire D, Pulliam L. Changes in monocyte/macrophage neurotoxicity in the era of HAART: implications for HIV-associated dementia. *AIDS* 2002;16:31–38. [PubMed: 11741160]
56. Kusdra L, Rempel H, Yaffe K, Pulliam L. Elevation of CD69+ monocyte/macrophages in patients with Alzheimer's disease. *Immunobiology* 2000;202:26–33. [PubMed: 10879686]
57. Balasingam V, Dickson K, Brade A, Yong VW. Astrocyte reactivity in neonatal mice: apparent dependence on the presence of reactive microglia/macrophages. *Glia* 1996;18:11–26. [PubMed: 8891688]
58. Hatten ME, Liem RK, Shelanski ML, Mason CA. Astroglia in CNS injury. *Glia* 1991;4:233–243. [PubMed: 1827781]
59. Howes E, Smith P. **Glial cell involvement in brain repair and the effects of aging.** In: de Vellis, editor. *Neuroglia in the aging brain* Totowa, NJ: Humana Press; 2002. pp. 113–134.
60. Hamon B, Glowinski J, Giaume C. **Intercellular diffusional coupling between glial cells in slices from the striatum.** In: de Vellis J, editor. *Neuroglia in the aging brain* Totowa, NJ: Humana Press; 2002. pp. 99–112.
61. Lin JH, Weigel H, Cotrina ML, Liu S, Bueno E, Hansen AJ, et al. Gap-junction-mediated propagation and amplification of cell injury. *Nat Neurosci* 1998;1:494–500. [PubMed: 10196547]
62. Merrill JE, Benveniste EN. Cytokines in inflammatory brain lesions: helpful and harmful. *Trends Neurosci* 1996;19:331–338. [PubMed: 8843602]
63. Gilmore SA, Kane CJ. Microglia, but not astrocytes, react to sciatic nerve injury in aging rats. *Brain Res* 1998;806:113–116. [PubMed: 9739119]
64. Woods AG, Guthrie KM, Kurlawalla MA, Gall CM. Deafferentation-induced increases in hippocampal insulin-like growth factor-1 messenger RNA expression are severely attenuated in middle aged and aged rats. *Neuroscience* 1998;83:663–668. [PubMed: 9483550]

65. Labourdette G, Eclancher F. **Glios growth factors in the adult and aging rat brain.** In: de Vellis J, editor. *Neuroglia in the aging brain* Totowa, NJ: Hamana Press; 2002. pp. 157–178.
66. Dziewulska D. Age-dependent changes in astroglial reactivity in human ischemic stroke. Immunohistochemical study. *Folia Neuropathol* 1997;35:99–106. [PubMed: 9377083]
67. Ye SM, Johnson RW. Increased interleukin-6 expression by microglia from brain of aged mice. *J Neuroimmunol* 1999;93:139–148. [PubMed: 10378877]
68. Sheng JG, Mrak RE, Griffin WS. Enlarged and phagocytic, but not primed, interleukin-1 alpha-immunoreactive microglia increase with age in normal human brain. *Acta Neuropathol (Berl)* 1998;95:229–234. [PubMed: 9542587]
69. Perry VH, Matyszak MK, Fearn S. Altered antigen expression of microglia in the aged rodent CNS. *Glia* 1993;7:60–67. [PubMed: 8423063]
70. Sheffield LG, Berman NE. Microglial expression of MHC class II increases in normal aging of nonhuman primates. *Neurobiol Aging* 1998;19:47–55. [PubMed: 9562503]
71. Barron KD. The microglial cell. A historical review. *J Neurol Sci* 1995;134 (Suppl):57–68. [PubMed: 8847546]
72. Rozovsky I, Finch CE, Morgan TE. Age-related activation of microglia and astrocytes: in vitro studies show persistent phenotypes of aging, increased proliferation, and resistance to down-regulation. *Neurobiol Aging* 1998;19:97–103. [PubMed: 9562510]
73. Brodie C, Goldreich N, Haiman T, Kazimirsky G. Functional IL-4 receptors on mouse astrocytes: IL-4 inhibits astrocyte activation and induces NGF secretion. *J Neuroimmunol* 1998;81:20–30. [PubMed: 9521602]
74. Griffin DE. Cytokines in the brain during viral infection: clues to HIV-associated dementia. *J Clin Invest* 1997;100:2948–2951. [PubMed: 9399939]
75. Sykova E. **Glia and extracellular space diffusion parameters in the injured and aging brain.** In: de Vellis J, editor. *Neuroglia in the aging brain* Totowa, NJ: Humana Press; 2002. pp. 77–98.
76. Kawamata T, Akiguchi I, Maeda K, Tanaka C, Higuchi K, Hosokawa M, et al. Age-related changes in the brains of senescence-accelerated mice (SAM): association with glial and endothelial reactions. *Microsc Res Tech* 1998;43:59–67. [PubMed: 9829460]
77. Diesing TS, Swindells S, Gelbard H, Gendelman HE. HIV-1-associated dementia: a basic science and clinical perspective. *AIDS Reader* 2002;12:358–368. [PubMed: 12229893]
78. Garton MJ, Keir G, Lakshmi MV, Thompson EJ. Age-related changes in cerebrospinal fluid protein concentrations. *J Neurol Sci* 1991;104:74–80. [PubMed: 1717663]
79. Kleine TO, Hackler R, Zofel P. Age-related alterations of the blood–brain-barrier (BBB) permeability to protein molecules of different size. *Z Gerontol* 1993;26:256–259. [PubMed: 7692679]
80. Shah GN, Mooradian AD. Age-related changes in the blood–brain barrier. *Exp Gerontol* 1997;32:501–519. [PubMed: 9315452]

Fig. 1. Cognitive functioning using the modified Memorial Sloan Kettering rating scale
MSK, Memorial Sloan Kettering. ■ Young; □ old.