

CHAPTER 4

HIV-Associated Dementia and Aging

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HIV/AIDS research over the past 2 decades has focused with near exclusion on younger individuals (less than 50 years of age). Research involving older HIV-seropositive individuals is notably lacking. By and large, this reflects the preponderance of disease in younger individuals, but may also reflect a selection bias due to study designs. Coexisting medical conditions, which are more common in older individuals, detrimentally affect participant enrollment. The presence of renal and liver dysfunction and other age-associated physiological changes, for example, may lead to exclusion more commonly for older compared with younger individuals (Linsk, 2000).

As the HIV epidemic in the United States enters its third decade, the research focus must broaden to better meet the needs of an emerging older HIV-seropositive population. We must expand our understanding of this infection as a chronic illness. Basic tenants of geriatric medical care focusing on functional assessment and management of multiple chronic conditions are becoming more applicable to the treatment of HIV infection.

As the population with HIV infection ages, a clearer awareness of age-associated illnesses that may synergistically and detrimentally affect known complications of HIV infection and related treatments is needed. Specific examples of interaction include:

1. age-associated and HIV-associated changes in immune function,
2. an increased presence of oxidative damage/mitochondrial dysfunction with both aging and with antiretroviral medication use,
3. accelerated atherosclerosis associated with both aging and (potentially) protease inhibitor medication use, and
4. both age- and HIV-correlated increased risk for cognitive impairment and dementia.

This chapter intends to address the impact of HIV infection on cognitive dysfunction in an aging population. We address current knowledge of medical treatment for HIV infection as it impacts older people and cognition. We present a model for the increased risk of cognitive dysfunction in older HIV-seropositive individuals.

AGING AND HIV—EPIDEMIOLOGY

A significant proportion of individuals with HIV infection are 50 years of age or older. AIDS, the clinical syndrome associated with HIV infection and representative of later stage, has traditionally been reported to Departments of Health and used as a surrogate marker for prevalence of HIV. About one tenth of all AIDS cases in the United States are reported to occur in the 50+ age group (Centers For Disease Control and Prevention, 2002).

Among HIV infected individuals over 50, about one quarter are thought to be over 60. It has been estimated that as many as 60,000 HIV-infected people over the age of 60 are living in the United States now (Linsk, 2000). Certain subsections of the country seem to be disproportionately affected by larger proportions of older HIV-seropositive people. Such is the case in Hawaii where the proportion has steadily increased over the past decade and 20% of new AIDS cases in 2001 were reported in individuals 50 years of age or greater (State of Hawaii, Department of Health, 2001).

It is likely that the number of older people living with HIV infection in the United States will increase over the next decade. This is in line with projected changes in the United States demographics. People over 65 are the fastest growing segment of the general population (Waite, 1996). During the period between 1995 and 2030, the elderly population in this country is expected to double (from 34 million to

more than 69 million) (Lubitz, Eggers, Gornick, & Villafrance, 1999). As a result, in 2030 one in five persons in the United States will be over age 65. Even if the rate of AIDS in older people were to remain at 10% nationally, the total number of people with AIDS would increase dramatically.

More importantly, new effective drug treatments for HIV infection (Highly Active Antiretroviral Therapy [HAART]) have decreased the mortality rate from HIV in developed countries (Brodt, Kamps, Gute, Knupp, Staszewski, Helm, 1997). This will impact the number of people who are surviving into advanced ages with infection.

This subgroup of older HIV-seropositive individuals may have unique complications of infection due to long-term existence of infection and extended treatment with antiretroviral medication. Protease inhibitor-associated changes in lipid metabolism and insulin resistance, for example, may be more prominent in this group. In turn this will likely contribute to accelerated cerebral atherosclerotic changes that could potentially affect cognitive function. There may be other global neurological changes associated with long-term HAART use that are yet to be fully characterized. A recently described series of brain pathologic changes (severe demyelinating leukoencephalopathy with intense perivascular monocyte/macrophage infiltrations) seen in a small autopsy series (7 patients) of individuals who had been failing HAART therapy suggests that factors associated with chronic infection may alter HIV-associated pathology in the brain (Langford et al., 2002). A corresponding change in clinical symptoms might be expected and can be evaluated with larger sample sizes.

With an increased prevalence of HIV infection in our older population, it is becoming critically important to address the fundamental neuroepidemiological characteristics of HIV infection and aging.

AGE-SPECIFIC ISSUES IN HIV CARE AND COGNITIVE FUNCTION

Predictive markers of incident cognitive decline are often markers of HIV disease progression itself, such as low CD4 lymphocyte count or poor suppression of virus in the blood (McArthur, Sacktor, & Selnes, 1999). Since cognitive status is so closely correlated to clinical status and particularly immune status it is important to review existing data in this area.

Medication Adherence. Critical factors associated with successful immune reconstitution and suppression of virus are access to treatment and treatment adherence. Few data are currently available concerning adherence rates for older HIV seropositive individuals. The limited data that exist suggests that self-reported adherence rates are the same or superior in older compared with younger HIV-seropositive individuals (Valcour, 2002; Knobel et al., 2001; Wellons, Edwards, Heald, Bartlett, & Schmander, 2000). This is found despite a larger number of reported adverse reactions in older HIV-seropositive individuals. For example, Knobel and colleagues reported a significantly greater number of adverse experiences in older compared with younger HIV-seropositive individuals (64.3% vs. 35% [$p < 0.001$]) yet there were no differences in rates of adherence, virological suppression, nor CD4 lymphocyte response. They also confirmed previous reports of significant differences in specific complications such as rates of reported lipodystrophic changes (63% for older vs. 33% for younger [$p = 0.003$]) suggesting that metabolic complications are more often present in older individuals (Safrin & Grunfeld, 1999).

One must use caution in interpreting adherence to a therapeutic regimen from research to that seen in clinical practice. True rates of adherence to these complicated antiretroviral regimens in clinical practice do not seem to be as high as those seen in clinical trials or in longitudinal cohorts. In an urban inner city clinic, only 37% of patients had undetectable plasma viral levels on aggressive drug therapy with HAART for a year. This is approximately one half the proportion with undetectable plasma viral levels seen in clinical trials (Lucas, Chaisson, & Moore, 1999). Further data are needed to clarify how these trends will affect incidence and prevalence rates of HIV-associated cognitive dysfunction in elderly HIV-seropositive individuals.

HAART and Neurocognitive Function. To date, HAART has had a tremendous impact on HIV-associated morbidity and mortality in people with access to treatment. Yet long-term consequences remain unknown. Short-term data suggest a favorable impact on neurocognitive function. In the Multicenter AIDS Cohort Study (MACS) the incidence of HIV dementia decreased by approximately 50% since widespread use of HAART (Sacktor et al., 2001).

Limited data suggest that HAART has a direct impact on cognitive function. A longitudinal study of 16 younger HIV-seropositive individuals, all with low CD4 lymphocyte counts at the time HAART was

initiated, showed improvement on neurocognitive testing over a 3-year period (Tozzi et al., 2001). Testing results, nevertheless, remained abnormal when compared with seronegative controls, and the beneficial changes leveled off after 15 months of therapy. This highlights a concern regarding completeness and durability of the response.

Medical Outcomes for Older HIV-Seropositive Individuals.

Outcomes for older HIV-seropositive individuals are often considered inferior when compared with younger individuals. Age has been associated with more rapid progression of disease and increased mortality for people with HIV infection (Babiker, Peto, Porter, Walker, & Darbyshire, 2001). Delay in diagnosis of infection for older individuals may be a significant confounding situation. Older individuals may simply have an advanced stage of disease at the time of diagnosis. Factors that may play a role in the delay include societal bias that HIV is a disease predominantly of the young, a variation in risk profile for infection in older individuals as compared with younger individuals, and misdiagnosis of other age-associated diseases due to a decreased suspicion of HIV infection in this age group.

Several studies support this concept. A review of CDC data suggests the percentage of individuals with a "late diagnosis" increased from 11% for people 13–19 to 58% for persons 50 or older (Neal & Fleming, 2002). In this analysis, late diagnosis was defined as developing AIDS the same year that HIV infection was detected.

Data from a retrospective evaluation of individuals at the Beth Israel Deaconess Medical Center in Boston suggested that the only predictor of survival after diagnosis of AIDS was antiretroviral therapy. Age was not predictive (Keller, Hausdorff, Kyne, & Wei, 1999). Recent data from the Moore Clinic at John Hopkins University suggest that mortality for older individuals without therapy, was double that of younger individuals without therapy, yet there were no differences between younger and older groups who received HAART (Perez & Moore, 2002). These data suggest that there would be similar outcomes if there is similar access to care and timely diagnosis.

One analysis suggests that age may play a greater role in later stage disease. In data from the French cohort study, SEROCO, where date of infection is documented (enrolled within 2 years of last seronegative test), age played no role in rate of progression to earlier stage disease (stage B disease, 1993 CDC revised classification) (Centers for Disease Control and Prevention, 1993). Conversely, age had a significant influ-

ence (relative risk: 1.97) on progression to a later stage (stage C disease) (Carre et al., 1994).

Age-associated changes in immune function likely play a role in the clinical course of HIV infection for older individuals. This can be evaluated by examining immunological response to HAART. Several studies indicate that CD4 T-lymphocyte response to HAART may be blunted. However, existing data do not universally support a decreased efficacy to HAART for older individuals (Goetz, Boscardin, Wiley, & Alkasspoles, 2001; Manfredi & Chiodo, 2000). Virological response appears to be similar in older and younger individuals as well.

In summary, there is insufficient evidence to support poorer outcomes for older individuals who receive timely diagnosis and have access to treatment. Further analysis of aging HIV-seropositive individuals is needed to confirm these findings and to better understand their role in cognitive function.

HIV DEMENTIA AND MINOR COGNITIVE MOTOR DISORDER

American Academy of Neurology Definitional Criteria for HIV Dementia and Minor Cognitive Motor Disorder (MC/MD).

Formal criteria are established for the diagnosis of cognitive syndromes in HIV infection (American Academy of Neurology AIDS Task Force, 1991). In general, these standards require: a change in at least 2 domains of thinking and the presence of (a) an abnormality on neurological exam consistent with a central nervous system impairment or (b) decline in motivation, emotional control, or behavior. These changes should affect daily function.

While detection of an abnormal neurological examination is fairly straightforward, detecting functional decline can be problematic, particularly in older individuals. Simply relying on changes in basic activities of daily living (e.g., change in ADLs or IADLs) is often insufficient. These basic daily functions are less likely to be affected in early stage illness. Assessment of changes in occupational or social functioning due to cognition may be more appropriate as they may be more sensitive in early disease.

Many HIV-seropositive individuals have disability due to physical illness that is independent of cognitive abilities confounding interpretation of function. The examiner must identify a change in function

that is due to cognitive decline, not physical impairment. Older individuals are more often retired and may have a baseline level of function that is lower than they had previously, further complicating interpretation. These changes make the assessment of an alteration in level of function due to cognition challenging.

Equally complex is the need to account for the occurrence of psychiatric illness that may be present in HIV-seropositive individuals (Hinkin, Castellon, Atkinson, & Goodkin, 2001). While not always a consequence of disease itself, psychiatric illness is a common occurrence in HIV-seropositive individuals. Depression is the most commonly encountered psychiatric illness in this setting. It shares common symptoms such as apathy, social withdrawal, and decreased psychomotor speed. It is imperative to identify and account for coexisting depression in a proper assessment of HIV dementia.

Characteristics and Epidemiology of HIV-Associated Cognitive Dysfunction in Younger Individuals. HIV dementia is characterized by cognitive symptoms (e.g., memory loss, poor concentration, mental slowing), behavioral symptoms (e.g., apathy, depression), and motor dysfunction (e.g., unsteady gait, poor coordination, tremor). The diagnosis of HIV dementia is established by a history of a progressive cognitive or behavioral decline with apathy, memory loss, or slowed mental processing and by appropriate ancillary studies. Neuropsychological assessment shows progressive deterioration on serial testing in at least two areas such as motor speed, frontal/executive functioning, and memory. Imaging studies in HIV dementia reveal diffuse cerebral atrophy with ill-defined white matter hyper-intensities on magnetic resonance imaging. Imaging studies are also performed to exclude any central nervous system opportunistic processes. Cerebrospinal fluid analysis is also useful to exclude cryptococcal meningitis or neurosyphilis.

The risk for HIV dementia is greater with advanced disease. In the early stages that are typically without symptoms, only 0.4% of HIV infected people have dementia (Bartholomew et al., 1987). In contrast, 15–20% of patients with AIDS develop dementia. Pre-HAART data from the Multicenter AIDS Cohort Study (MACS), a cohort of homosexual men, indicate a 7% annual incidence after the development of AIDS (McArthur et al., 1993). Incidence rates are higher in those with lower CD4+ T-lymphocyte counts (Bacellar et al., 1994).

The incidence of HIV dementia has declined by 50% in large epidemiological studies subsequent to widespread HAART use (Sacktor et

al., 2001). It is yet to be determined whether this change is permanent or simply a transient flattening of the curve due to a delay in presentation of symptoms. Factors that may contribute to a resurgence of HIV dementia include the development of resistance that occurs to antiretroviral medications and intolerance to medications due to side effects. Each could lead to poorer virological and immunological control and subsequently increased risk for dementia. To date, there is insufficient time of follow-up to fully answer these questions. Potential risk factors for dementia include low CD4 T-lymphocyte count, anemia, low body mass index, older age, the presence of more constitutional symptoms before AIDS, injection drug use, and female sex (Bacellar et al., 1994; Chiesi et al., 1996; Janssen, Nwanyanwu, Selik, & Stehr-Green, 1992).

The more subtle form of cognitive impairment, termed Minor Cognitive Motor Disorder (MC/MD), exists in 20% of symptomatic HIV-seropositive patients (Janssen, Cornblath, Epstein, McArthur, & Price, 1989). The risk for progression to dementia and prognostic impact of MC/MD is unclear. Several studies, however, have independently shown that the presence of cognitive impairment (MC/MD or dementia) in HIV infection is predictive of poor survival (Sacktor et al., 1996; Mayeux et al., 1993).

The progression of HIV dementia is variable. Some patients without antiretroviral treatment have a relatively rapid progression over 3 to 6 months. Patients, on HAART, however, may have a slow/stable course with minimal progression over years. Low CD4 T-lymphocyte count, injection drug use, and prominent psychomotor slowing may be associated with more rapid progression of neurological deficits (Bouwman et al., 1998).

HIV-ASSOCIATED COGNITIVE DYSFUNCTION AND AGING

Until recently, there has been little research examining the interaction of aging and HIV infection with regard to cognitive function. It seems intuitive that cognitive decline among older HIV-seropositive individuals would be more common. Published prospective data confirming this association are lacking.

This is not true for other forms of dementia. By and large, age is a strong risk factor for developing most forms of dementia. This is

particularly true for Alzheimer's disease where rates increase exponentially after the age of 65 (Geldmacher & Whitehouse, 1996).

Similarly, rates of dementia in individuals with Parkinson's disease increase with age. Mahieux and colleagues evaluated predictors of dementia in a cohort of initially non-demented patients with Parkinson's disease (Mahieux et al., 1998). The relative risk for age (> 60 years) was 4.1 ($p < 0.03$). There is also an increased risk of dementia in patients with onset of Parkinson's disease after age 50 ("late onset") compared to onset at a younger age ("early onset") (Hietanen & Tervainen, 1988; Katzen, Levin, & Llabre, 1998). The neurocognitive profile among Parkinson's disease cases is often characterized by greater deficits in psychomotor processing. This is a similar pattern to what is seen in HIV-associated cognitive decline (Sacktor et al., 1996).

Few data exist concerning prevalence of HIV dementia by age. CDC data suggest 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 greater and approaching 15% for children less than 15 years of age (Janssen et al., 1992). This higher rate is maintained when correcting for sex, race/ethnic group, exposure category, and region within the United States.

This report has limitations, however. The CDC data were collected in the pre-HAART era, and the analysis did not attempt to control for stage of disease. Additionally, accurate data from the CDC rely on proper recognition of symptoms and complete reporting by clinicians, which may be less than optimal. A bias due to increased reporting of AIDS defining illnesses (first illness) and less complete reporting of subsequent illnesses may affect rates. A bias toward increased reporting of cognitive symptoms in older individuals cannot be ruled out either.

In an analysis of data from the MultiCenter AIDS Cohort Study (MACS), trends were found in a number of cognitive tests, particularly in timed measures, with regard to age. No effect of age on neuropsychological testing profiles was found, however, when data were corrected for serostatus (van Gorp et al., 1994).

More recent preliminary data are beginning to reveal a pattern of marked increase in cognitive dysfunction among aged HIV-seropositive individuals. In one series, 87% of older AIDS patients were found to have abnormal neurocognitive testing results when compared with seronegative controls (Hinkin et al., 2001). In another series, older HIV-seropositive adults were found to have a significantly higher number of MC/MD symptoms when compared with younger individuals (Goodkin et al., 2001).

In the fall of 2001, the University of Hawaii, in conjunction with Johns Hopkins University, launched a prospective longitudinal study to evaluate the interaction of aging and HIV infection on neurocognitive function. Preliminary analysis of the first 35 individuals enrolled reveals a marked increase in neurocognitive dysfunction in the older group (ages 50 and greater) compared with the younger group (less than 40). Participants underwent a 4-hour interview including neuropsychological testing, a neurological examination, a substance use history, blood tests, and demographic information. A weekly consensus conference between the sites reviews all cases to provide diagnoses using the American Academy of Neurology criteria. Degree of cognitive impairment, when present, is rated using the Memorial Sloan Kettering scale (MSK) with scores of 0 (normal), 0.5 (equivocal), 1–4 (mild to severe dementia) (Price & Brew, 1988). None of the 35 individuals enrolled had an MSK rating of 3 or greater. Eleven percent of younger individuals (2/18) compared with 41% of older individuals (7/17) had mild to moderate dementia ($p = 0.0523$, fisher's exact test). A pattern of increasing degree of impairment was seen in the older compared with the younger individuals with impairment. These data are preliminary. Selection bias and applicability of utilized norms are possible limitations.

There are currently no published data on the patterns of cognitive impairment among older compared with younger HIV-seropositive individuals. Dependence upon currently defined characteristics of early cognitive dysfunction described predominantly from data on younger individuals may be insufficient. Age-associated and HIV-associated changes in psychomotor speed could produce a synergistic increase for psychomotor slowing in individuals with both risk factors. Additionally, the potential heterogeneity of neuropathology implicated in older individuals may lead to greater heterogeneity in symptoms of HIV-associated cognitive decline in older individuals. These are critical issues that are currently being addressed in several large cohort studies. Findings in these studies could play a pivotal role in appropriate detection of cognitive dysfunction in the emerging older HIV-seropositive population.

A MODEL FOR DEVELOPING HIV DEMENTIA IN OLDER INDIVIDUALS

As one ages, the number of age-associated medical illnesses increases, the number of medications taken increases, and the risk for poorer

outcomes to medical conditions generally increases. This holds true among HIV-seropositive individuals. In the Veterans Aging Cohort Study, older individuals were found to have had significantly greater amounts of reported hypertension, hyperlipidemia, diabetes, heart disease, strokes, peripheral vascular disease, and congestive heart failure (Kilbourne, Justice, Rabeneck, Rodriguez-Barradas, & Weissman, 2001). This multifaceted impact on health status implies a complex set of factors that impact disease in older people and is the cornerstone for proper care of older individuals. Interpretation of disease risk (as in risk for cognitive dysfunction) requires an understanding of these different factors and the interactions of each with the others.

The model for dementia in older HIV-seropositive individuals is proposed below (Figure 4.1). The model facilitates an approach to understanding the pathogenesis of dementia by accounting for multiple illnesses and conditions that may affect cognition in a synergistic manner.

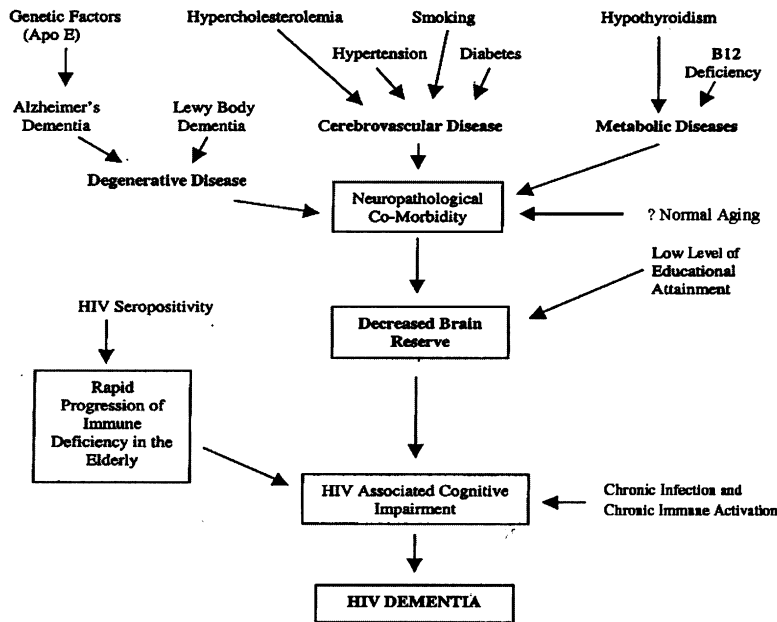


FIGURE 4.1 A model for development of HIV dementia in the elderly.

The symptoms of dementia among older HIV-seropositive individuals may be more prominent and/or may present earlier in individuals with neuropathological comorbidity. This neuropathological comorbidity could come from

1. underlying or sub-threshold degenerative disease such as Alzheimer's disease or Lewy Body dementia,
2. cerebrovascular disease resulting from hypertension, diabetes, hypercholesterolemia, or smoking,
3. metabolic disease (e.g., hypothyroidism, B12 deficiency), or
4. neuropathology associated with typical aging.

This underlying neuropathological comorbidity would lead to a decreased brain reserve.

Low education, head trauma, developmental factors, and genetic factors such as apolipoprotein E4, could also contribute to a decreased brain reserve (Abbott et al., 1998; Snowdon et al., 1996). For example, Satz and colleagues evaluated subgroups of well-educated and less well-educated HIV-seropositive and seronegative subjects (Satz et al., 1993). They found little difference within the well-educated group with regard to neuropsychological test profiles. In the less well-educated group, however, neuropsychological test profiles were significantly different between HIV-seropositive and seronegative individuals. This suggests that a low level of education may be associated with decreased brain reserve capacity.

Other factors which could play a role in increasing HIV-associated cognitive impairment among older HIV-seropositive individuals include age-associated changes in body immune function. In addition, cognitive impairment from underlying concurrent neurological or systemic medical diseases as described above, could also significantly impact antiretroviral medication adherence. Older individuals on multiple other medications, when started on HAART, may have decreased antiretroviral medication tolerance due to drug interactions. Age-related changes in pharmacodynamics of medications could also play a significant role in adherence. If older HIV-seropositive individuals are unable to take antiretroviral medications, they will have a decreased likelihood for viral suppression and an increased risk for HIV-associated cognitive impairment.

In summary, there are multiple factors that are more often present in older individuals and are synergistically capable of decreasing brain

reserve. This facilitates development of cognitive dysfunction due to HIV infection in older individuals.

CONCLUSIONS AND FUTURE DIRECTIONS

The changing epidemiology of HIV infection within the United States necessitates a broader focus, including evaluation of its interaction with aging and age-associated conditions. This is particularly important for our understanding of neurocognitive function. Simple extrapolation of characteristics of disease from younger populations to older populations is flawed.

The particular importance of age on neurocognitive complications in people with HIV infection springs from an age-associated coexistence of diseases that affect cognition and can thereby confound the identification and treatment of HIV-associated neurocognitive disease and increase its prevalence. Age-associated effects on antiretroviral medication tolerance and adherence may also play a role.

The frequency of cognitive dysfunction in older HIV-seropositive populations may be greater than that classically described in younger populations. As a result, it is increasingly important

1. to identify fundamental characteristics and the basic neuroepidemiology of HIV neurocognitive dysfunction for older individuals,
2. to determine whether advanced age and HIV infection have a synergistic effect in producing cognitive impairment among older individuals, and
3. to determine how cognitive impairment due to HIV itself can be distinguished from cognitive impairment due to other potential factors among older individuals.

New research is under way. The Veterans Cohort Study 3 (PI: A. Justice, University of Pittsburgh) is a multicenter trial at 3 centers (Cleveland, Houston, and Manhattan) (Smola et al., 2001). While this study is not currently focusing on cognition, it will provide valuable information concerning medical complications in older HIV-seropositive individuals. This may have direct applicability to understanding the factors associated with developing neuropathological comorbidity as described in the model.

Other cohorts of older individuals, such as the cohort in Hawaii (PI: V. Valcour), and a cohort at the University of Miami (PI: K. Goodkin), are designed to address the fundamental issues of presentation, clinical course, and risk profiles for neurocognitive decline. In the Hawaii cohort, brain imaging, assessment of genetic factors, and evaluation for metabolic diseases will shed light on other aspects of the proposed model concerning the development of neuropathological comorbidity as a focal point to increased risk for cognitive impairment in older HIV-seropositive individuals.

As HIV/AIDS research continues in the decade ahead, inclusion of studies with older individuals is paramount. Better characterization of disease in this cohort will provide the knowledge needed to detect neurocognitive complications, direct future research toward understanding its pathogenesis, and facilitate the identification of appropriate treatment modalities.

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