HIV and Aging

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Current Infectious Disease Reports 2006, **8:**241–247
Current Science Inc. ISSN 1523-3847

Approximately one in five individuals living with HIV infection in the United States is 50 years of age or older. This proportion continues to increase as HIV incidence remains stable and potent antiretroviral therapy has reduced the morbidity and mortality associated with HIV infection. Newly identified HIV-seropositive older individuals are proportionately more likely than younger persons to have AIDS at the time of diagnosis. Clinicians have to think about the possibility of HIV infection in older persons to avoid delays in diagnosis and treatment. Immunologic recovery in older individuals initiated on combination antiretroviral therapy is less robust in some studies compared with younger individuals. However, virologic suppression on treatment in young versus old antiretroviral naïve patients is comparable. Co-morbid conditions and their treatment pose a special challenge to health care providers with regard to drug metabolism and interactions with HIV medications. HIV prevention should be discussed with all at risk individuals. The HIV epidemic will only worsen if medical practitioners neglect to discuss sexual risk behavior with their older patients.

Introduction

For this paper, older persons with HIV will be defined as being 50 years of age or older. This somewhat arbitrary cut-off was chosen due to its adoption by most of the available studies and published material in this area, and as categorized by the United States National Institute on Aging [1]. Immunologically, this designation may be appropriate due to changes that occur in the maturation and senescence of adult immune function. However, immune function develops on a continuum and may be disconnected from chronologic age in years.

After a quarter of a century, the HIV/AIDS pandemic, and our understanding of it, continues to evolve. AIDS, and subsequently HIV infection, was initially recognized in the United States among individuals with well defined risk factors such as men who have sex with men (MSM), injection drug users (IDUs), blood product recipients, or children born of an HIV-infected mother. However, it was readily apparent that these limited "risk groups" did not necessarily apply to the worldwide epidemic and that HIV infection would be recognized in persons beyond these initially identified groups in the United States and Europe. Identification of transmission risk behavior is essential in combating HIV due to its long clinical incubation period. Categorizing individuals based on perception of their risk of HIV acquisition can lead to complacency among some persons who are at risk. Moreover, narrowly focused prevention and screening efforts on certain risk groups may hamper control of the epidemic and can engender stigmatization. Thus, education and prevention efforts should be focused on specific behaviors rather than "risk groups".

Despite efforts to educate the general population about HIV transmission, HIV incidence in the United States has not declined significantly in the past decade. The advent and availability of highly active antiretroviral therapy (HAART) has led to profound declines in deaths attributable to AIDS since the mid-1990s. The combination of the previous two trends underlies the reports of increasing HIV prevalence in the United States, surpassing 1 million persons living with HIV infection in 2003 [2]. Among groups that have experienced an increase in numbers during this period are older individuals. Older individuals may be at risk for HIV infection for a number of reasons, including: 1) aging of persons infected and diagnosed at a younger age due to improved survival through the use of HAART; 2) late recognition of HIV infection acquired at a younger age due to its long clinical incubation period; and 3) newly acquired infection at an older age. The last two categories may be affected by misperception of HIV acquisition risk on the part of older persons and their health care providers.

It is estimated that by the year 2030, the number of individuals older than 65 years of age in the United States will double to more than 70 million, and constitute 20% of the population. Distinguishing older persons with HIV infection for evaluation may be relevant if they, as a group, have unique morbidities, clinical course, epidemiologic trends, or public health issues.

Epidemiology of HIV/AIDS in Older Persons

In the United States, persons 50 years of age or older represent 14% (22,296) of the 157,468 individuals diagnosed with HIV infection between 2001 and 2004 in 35 areas with name-based reporting [3]. The rate of new HIV diagnoses among persons 50 years of age or older increased from 13.4% in 2001, to 13.6% in 2002, to 14.3% in 2003, and to 15.2% in 2004. By the end of the 1990s, 17% of all persons living with AIDS in the United States were over the age of 50 [4]. In New York City, where the epidemic in the United States is most mature, over 29% of all persons with HIV/AIDS are aged 50 years or older—possibly a harbinger for the rest of the country [5]. Among 42,514 persons diagnosed with AIDS in the United States in 2004, 18.6% were aged 50 years or older, which is higher than the 12.2% of 944,306 cumulative AIDS cases since the start of the epidemic [6••]. This is indicative of the increased trend in AIDS diagnoses among older persons as the epidemic evolves. Nearly 25% of those diagnosed with AIDS after the age of 55 years in the United States in 2004 were aged 65 or older [6••].

By the mid-1990s the rate of increase in AIDS cases in persons over the age of 50 years was among the highest in the United States. Up to two-thirds of AIDS cases in older persons in the United States are in MSM. Not all of these men would self-identify as "gay", "homosexual", or "bisexual". Unprotected heterosexual sex accounts for 15% of AIDS cases in this age group and is becoming increasingly more prevalent as the mode of HIV acquisition, especially among women. Current or past IDU has accounted for an increasing proportion of AIDS cases in older persons from the mid to late 1990s (11% in 1991 and 17% in 1996). This may represent a delay in clinical presentation for persons infected at a younger age and may decline in future surveys as a reflection of the decrease in this mode of transmission nationally due to needle exchange, drug rehabilitation services, and other harm reduction efforts directed at IDUs. Acquisition of HIV through receipt of infected blood products, as expected, is declining as a risk factor, accounting for 15% of AIDS cases in the 1980s and only 1.1% in 1999 [7]. A higher proportion of older persons (14%) with HIV infection report an "unknown" source of HIV acquisition than younger age groups. This difference may reflect a general unease among medical practitioners and their older patients to discuss sexual practices and risk behaviors.

The HIV Cost and Services Utilization Study interviewed 2857 HIV-infected adults statistically representative of the nationwide epidemic, of whom 11% were over the age of 50, concerning their health and socioeconomic status [8]. Respondents were grouped by HIV acquisition mode into three categories: MSM, IDU, and other (within which 72% of younger persons and 44% of older persons reported heterosexual contact, and 10% of younger persons and approximately 20% of older persons reported blood transfusion as their primary HIV risk factor). Among MSM, those over age 50 were more likely than younger men to be white, have had a college education, be disabled or unemployed, and have insurance. Among IDUs, those over the age of 50 were more likely than younger persons to be black and be disabled. Among those with "other" risk factors, those over the age of 50 were more likely than younger persons to have less than a high school education and be disabled or unemployed. Across all risk categories, older persons with HIV were more likely to live alone and were less free from conflict with family, friends, and contacts than younger persons. Older persons with HIV reported the same overall quality of life as younger persons. However, in a study of Australians with HIV, older persons reported less of a sense of well-being than younger persons [9]. Overall, such studies indicate that great diversity exists among older persons with HIV and that it might be best to approach each subpopulation individually.

HIV Acquisition and Transmission Among Older Persons

Attitudes about sex among older Americans are changing. The 1999 American Association of Retired Persons (AARP)/Modern Maturity survey on sexual attitudes and behavior reported that men and women age 45 to 59 were more accepting of sex between unmarried persons and of oral sex than the preceding generation [10]. Nearly 50% of all Americans age 60 or older engage in sexual activity at least once a month. These trends may reflect the aging of the more sexually liberal "baby boomers". Middle-aged women (between 45 and 64 years of age) remain sexually active, with approximately two-thirds having sex on a weekly basis [11]. Many middle aged and older women experience flux in their relationships and may engage in sex with new partners due to divorce or death of their spouse. This would place them at increased risk for sexually transmitted diseases, including HIV infection.

In the United States, more than 50% of persons living with HIV/AIDS over the age of 50 are black or Hispanic, and there is an increasing incidence for HIV/AIDS diagnoses among women [12]. Recognition of these trends is important in order to target resources to increase awareness of HIV and improve prevention efforts among subpopulations of older persons at highest risk for newly acquired or unrecognized HIV infection.

Factors that may contribute to HIV transmission among older persons include: 1) that this age group has historically not been a focus of the HIV prevention message or prevention efforts; 2) the notion that condom use is to prevent pregnancy and would be less important for a post-menopausal woman; 3) the availability of medications to treat erectile dysfunction; and 4) lack of knowledge about HIV among older persons leading to increased fear, stigma, and discrimination. Interviews with 24 HIV-infected older women (aged 45 to 71) found

that abuse of drugs and alcohol, ignorance of the HIV risk behavior of their sexual partners, domestic violence and other history of personal abuse, dependency on a male partner, and lack of knowledge about HIV transmission risk were the most important factors contributing to their acquisition of HIV [13].

The National AIDS Behavioral Survey of 14,000 adults, of whom 4797 were age 50 years or older conducted from 1990–1991 found that older persons with HIV risk factors were 80% less likely to have received HIV testing than young adults aged 20 to 29 [14]. Ninety percent never used condoms and 10% had one or more significant risk factors for HIV acquisition. Decline in condom use with advancing age is evidenced by a cross-sectional survey of Swiss adults, which revealed that older individuals (46–65 years) were significantly more likely not to use a condom than younger individuals (19–30 years, 53% vs 27%) [15]. Moreover, a 2004 AARP survey found that 22% of men over the age of 45 had used treatments for erectile dysfunction, such as sildenafil, tadalafil, or vardenafil hydrochloride [16]. However, the number of reported sexual partners decreases with age and over 95% of persons aged 50 to 75 report no sexual risk factors for HIV acquisition [17].

Up to one-third of older adults lack knowledge about HIV transmission. Older women (age > 45 years) responded incorrectly to almost half of 12 items on the AIDS Risk Behavior Knowledge Scale [18]. Furthermore, changes to the vaginal mucosa (drying and atrophy) may make older women more vulnerable to infections and trauma, which would also increase the efficiency of HIV transmission. MSM remain at high risk for acquiring HIV infection even when they are older. A cross-sectional survey of MSM residing in Florida found that almost 50% reported unprotected anal intercourse and that a significant predictor for this high-risk activity was associating the use of condoms with erectile problems [19]. The higher prevalence of erectile dysfunction among older men coupled with experiencing or perceiving that condoms will exacerbate erectile difficulties may contribute further to "condom fatigue" and heighten the risk for acquiring and transmitting HIV.

Aging Effects on the Immune System and HIV Infection

Older persons with HIV infection have been found to progress more rapidly to AIDS, have steeper decline in CD4 lymphocyte counts, suffer more from encephalopathy, are more likely to have an AIDS diagnosis at presentation, and have a shorter mean time from diagnosis to death (6.3 months compared with 16.5 months) than younger persons [20–25]. Some of these observations might be explained by delayed diagnosis of HIV infection in older persons due to low suspicion by their health care providers; however, the effects of aging on immune function may also contribute to poorer prognosis of HIV infection in older persons. The availability of HAART has impacted on the mortality of HIV/AIDS for all ages, however, it is possible that CD4 recovery on therapy may not be as robust or complete in older as in younger people.

HIV disease progression is associated with decrease in naïve and memory CD4+ T lymphocyte populations. The loss of CD4 helper function also affects the regulation of immunoglobulin production by B lymphocytes and natural killer (NK) cell function [26,27•]. Thus HIV affects both innate and adaptive immunity. Aging also affects immune function due to waning of immune surveillance, involution of the thymus, and declines in innate immunity [28]. This senescence of the immune system is manifest by the increased rates of reactivation of latent infections (such as tuberculosis and herpes zoster), increased susceptibility to pneumococcal disease, and increased cancer rates observed with aging [29••]. Aging has been associated with decreased naïve CD4 and CD8 lymphocyte counts, and loss of thymic volume [30]. Small et al. [31] reported on immune function in younger (< 40 years) compared with older (> 55 years) HIV-infected subjects on HAART therapy with viral suppression and found higher CD8 cells, CD4 cells that traffic to lymph nodes, and NK cell activity in the younger compared with older subjects. The combination of HIV infection and aging may have additive or synergistic effects on disease progression and may impact upon immune recovery after viral suppression.

The breadth of the T lymphocyte adaptive immune response is related to the diversity of the available T-cell receptors. The potential of having an immune response to a neoantigen is based on the pre-existence of a T-cell receptor on a naïve T-lymphocyte with which it will interact. Once a receptor has been stimulated, the immune response will mature resulting in clonal expansion and the development of memory T-lymphocytes, which remain in the tissues and circulation, ready to elicit rapidly a robust immune response when subsequently exposed to their specific antigen. Naïve T-lymphocytes have the potential to recognize up to 1 billion unique antigenic epitopes, while the memory T-cell repertoire is about 10,000 to 1 million [29••,32]. During the maturation of the immune system, naïve T lymphocytes are derived from the thymus. However, the involution of the thymus is advanced by the 2nd and 3rd decade of life, manifest by the poor reconstitution of thymus-derived naïve T cells following cancer chemotherapy in adults [33]. Estimates of thymic function measuring the concentration of episomal DNA fragments excised during T cell receptor gene rearrangement (referred to as T cell receptor excision circles [TRECs]) indicate that the production of naïve T cells by the thymus after the age of 55 years may be negligible [29••]. Therefore, the repertoire of the T cell immune response narrows to approximate

the memory pool with age as the potential for responses to neoantigens by naïve cells declines [29••]. This may have important implications on immune reconstitution in older HIV-infected subjects.

Immune reconstitution following HAART is complex and not yet fully understood. Recovery of CD4+ T-lymphocyte cell numbers is accounted for initially by redistribution and subsequently proliferation of the memory cell population. However, the potential for the immune repertoire to reconstitute fully from expansion of peripheral T lymphocytes (both memory and naïve cells) with little contribution from the thymus is not known. The Adult AIDS Clinical Trials Group (AACTG) study 5015 was a prospective trial of the effects of HAART on immune function and thymic volume in older (> 45 years of age) and younger (18–30 years of age) HIV-infected subjects [34••]. Results after 48 weeks of HAART therapy demonstrated inferior naïve CD4 and CD8 cell responses in the older subjects. Thymic volumes decreased significantly from baseline in the older subjects, which correlated with changes in total and naïve CD4 cell counts. Among subjects with low thymic volumes, IL-7 levels correlated with total and naïve CD4 counts. IL-7 is a cytokine that promotes T cell survival and expansion. These findings may indicate that, in the absence of significant thymic contribution, both total and naïve CD4 cell proliferation may be promoted in the peripheral circulation by IL-7 [34••]. Further study on the clinical implications of the differences in immune recovery between young and older HIV infected persons is needed. Such studies may lead to changes in treatment guidelines regarding the initiation of antiretroviral therapy based on age as well as absolute CD4 count and HIV viral load.

Diagnosis and Management of HIV in Older Persons

Clinicians should consider the possibility of HIV infection or AIDS-related conditions as part of the differential diagnosis in older persons. Older persons and their health care providers may not recognize that they are at risk for HIV infection and may not access HIV prevention and testing services. Unsuspected HIV infection was identified (by testing discarded serum) in 5% of patients older than 60 years of age who died in one New York City hospital [35]. Diagnosis of HIV in older persons may be complicated by the similarity of symptoms of HIV infection or opportunistic diseases with other more common conditions or signs of aging. For example, the symptoms of *Pneumocystis jiroveci* pneumonia such as insidious and progressive onset of dyspnea, a dry, hacking cough, symptoms exacerbated by exertion, and bilateral pulmonary infiltrates with or without fever may mimic congestive heart failure. Delay in diagnosis and treatment can lead to increased morbidity and death.

Since older persons with HIV infection appear to be at increased risk for disease progression and poorer survival, they may derive enhanced clinical benefit from antiretroviral therapy than younger persons even though age at initiation of HAART appears to be a predictor of less robust CD4 recovery. The EuroSIDA study examined the CD4 lymphocyte response to HAART therapy in 1956 patients (median age of 37.2 years) [36]. Subjects on HAART older than 44.5 years of age were 32% less likely to achieve a CD4 lymphocyte count increase of more than 200 cells/mL than those younger than 32.7 years of age ($P < 0.003$), adjusted for acquisition risk factor, AIDS status, baseline CD4, time on HAART, and most recent HIV plasma viral load. Younger patients achieved higher overall CD4 count and achieved their maximum CD4 count in less time than did older patients. The Swiss HIV Cohort study reported on 293 HIV-infected subjects after 5 years of virologically suppressive HAART of whom 105 failed to achieve a CD4+ T-cell count of approximately 500 cells/μL [37]. By multivariate analysis, factors associated with incomplete CD4 recovery were age (in 10 year increments), baseline CD4 count, and length of time of HIV infection (in 10 year increments). A retrospective US case control study of 101 older (median age 56.7, range 50 to 79 years) compared with 202 younger (median age 32.8, range 21-39 years) patients initiating HAART found only similar recovery of CD4 cell count over 29 months of follow-up, despite the observation that older subjects in this study had superior virologic suppression and significantly fewer treatment interruptions (ie, better adherence) than younger subjects [38]. In contrast, a smaller case control study from Italy of 58 older and 116 younger patients on HAART found equal rates of viral suppression and CD4 recovery between the groups even with the finding of lower pre-treatment baseline CD4 and presence of more co-morbid conditions among the older group [39].

Although reports may differ with respect to the magnitude of CD4 recovery on HAART in older compared with younger HIV-infected persons, older persons appear to derive significant clinical benefit from treatment. A study of 256 patients who initiated HAART at older than 50 years of age at the Johns Hopkins University found no difference in total CD4 increase (about 110 cells) or adverse drug events, than younger subjects after more than 3 years of follow-up [40]. Rates and durability of viral suppression of HIV were as good or better for patients over the age of 50 than for those aged 35 to 50 years (1322 patients) and those less than 35 years of age (895 patients). Death was more frequent in those older than 50 years of age (25%), but causes of death were less likely to be HIV-related in those aged 50 years or more (42%) compared with those aged 35 to 50 years (71%) and those younger than 35 years of age (79%; $P < 0.001$). Although the death rate was higher among older persons, these investigators have reported that the risk for death was significantly lower for HIV-infected persons over the age of 50 on HAART (0.28) compared with untreated older patients (2.4, reference was younger untreated patients) [41]. The benefits of HAART were present for

older persons, especially with regard to decreased AIDS-related mortality.

Virologic response rates to HAART among older persons appear to be as good or better than younger patients. Superior and more durable viral suppression in older subjects has been reported in a number of cohorts and prospective clinical trials [34••,36,38,40,41]. This appears related to superior adherence to antiretroviral therapy and better socioeconomic status among older subjects. Even though adherence to antiretroviral therapy for older HIV-infected persons in the aggregate appears to be good, there are, nevertheless, unique circumstances in the elderly that may impact treatment adherence on an individual basis. These factors include the availability of proper meals, poor eyesight, diminished cognition, lack of social support systems, depression, and poverty. Reluctance to disclose HIV-positive status to family and friends, or to accept the diagnosis themselves, can also lead to social isolation. Indeed, age itself may not be the most important issue related to adherence, but rather, other factors associated with aging such as lack of insurance, mobility, cognitive impairment, social isolation, knowledge about the medical regimen and fear about the severity of the condition under treatment [42].

A study of 100 HIV-infected persons aged 50 years or older prescribed antiretroviral therapy noted a self reported medication adherence rate of 94% and a strong negative correlation between reported adherence and HIV plasma viral load ($P = 0.005$) [43]. Factors reported by HIV-infected older persons leading to non-adherence with antiretroviral therapy were scheduling problems, adverse events, fatigue, and fear of revelation of HIV diagnosis [44].

Aging may alter pharmacokinetics of medication including antiretroviral therapy. Changes in body fat content may alter volume of distribution for drugs. In addition, decline in glomerular filtration with aging may affect clearance of renally excreted drugs such as tenofovir and zidovudine. Chronic viral hepatitis, excessive alcohol intake, hepatic steatosis, and other forms of chronic liver disease that slowly damage liver function over many years may lead to hepatic insufficiency manifest only in older persons. Several antiretroviral agents including abacavir, the non-nucleoside reverse transcriptase inhibitors, and the protease inhibitors are metabolized by the liver and may require dose adjustment or lead to increased hepatotoxicity in the presence of decreased liver function. HIV practitioners must be cognizant of these effects and utilize antiretroviral therapy carefully and monitor closely for adverse events in older persons.

More than a third of individuals in the United States will have a chronic health-related condition that will affect their normal functioning by the age of 65. HIV-infected individuals older than 55 years of age have nearly four times more chronic co-morbid conditions than those younger than 45 years of age. A study of 165 HIV-infected persons over the age of 55 years found they had an average of 2.4 co-morbid conditions for which an average of 2.7 chronic medications were used [45]. Medical conditions such as diabetes mellitus, hypertension, hyperlipidemia, fat atrophy and accumulation, atherosclerosis, and dementia are more prevalent with advancing age. These conditions may be exacerbated by HIV infection (dementia, atherosclerosis) or by the complications of long-term exposure to certain antiretroviral therapies (insulin resistance, dyslipidemia, body habitus changes, atherosclerosis). Co-morbid conditions such as diabetes and hypertension, which are more prevalent among blacks and persons of Hispanic origin, and hormonal changes associated with menopause in older women may complicate the management of HIV infection. Polypharmacy used in the management of co-morbid conditions associated with aging, including antihypertensives, lipid lowering agents, gastric anti-acid drugs, and anti-diabetes treatments, may lead to unrecognized drug interactions if a complete inventory of all medications (prescription and over-the-counter) is not obtained. Receipt of HAART, its discontinuation due to toxicity, and having an undetectable viral load has been shown not to be affected by comorbid conditions or concurrent medications used by older HIV-infected persons [45]. Nonetheless, HAART use, in particular protease inhibitors, has been associated with an increased risk for developing diabetes and cardiovascular disease. Older age may contribute to this risk. Systolic hypertension was significantly increased after 1 year of HAART use in a previously naïve cohort of HIV-positive subjects with a mean age of 40 years [46]. Moreover, this study also showed that each additional decade of age at baseline was associated with almost a 5 mm Hg greater increase in systolic blood pressure at 1 year. HIV specialists need to be vigilant to these added risks among their older patients and develop greater expertise in the management of the problems of aging and the specific interactions with chronic antiretroviral therapy that may arise.

Increasing age has been associated with the prevalence of low testosterone levels in men. Hypogonadism has also been observed among men with HIV infection, in particular those with AIDS. A cross-sectional study of HIV-positive men found that an HIV-1 viral load greater than 10,000 copies/mL was significantly associated with a testosterone level of less than 200 ng/dL [47]. Co-infection with hepatitis C virus was also highly associated with total testosterone deficiency. Hypogonadism, defined by this study as a low free androgen index, was also significantly associated with subjective ill-health, depressive symptoms, sexual disinterest, and osteopenia. Older men with HIV infection should be monitored for signs and symptoms of hypogonadism, and patients with clinical androgen deficiency, confirmed in particular by a low free testosterone level, should receive androgen replacement therapy. The possible re-emergence of sexual interest brought about by testosterone supplementation

should always prompt a discussion with patients about sexual risk behavior and prevention prior to the initiation of treatment.

Dementia and neurocognitive dysfunction has been associated with HIV infection and aging. HAART use has affected the epidemiology of HIV-associated neurocognitive disease and may delay its onset until older age or at higher CD4 count [48]. Age associated co-morbidities such as hypertension, diabetes, atherosclerosis, and hyperlipidemia are linked to the development of dementia. Distinguishing these factors as causative for neurocognitive decline in older HIV-infected persons is further complicated by the long-term metabolic toxicity of HAART. HIV-associated dementia was found to be 3.26 times more likely in a cohort of older (> 50 years) than in younger (20 to 39 years) HIV-infected persons, controlling for factors including race, CD4 count, HAART use, and depression score [49•]. A review of the records of 198 HIV-infected persons over the age of 55 years engaged in HIV primary care in New York City found that only 4% received neurocognitive screening [45]. Formal evaluation of mental status should be part of the routine care of HIV-infected persons of all ages, but especially for those over the age of 50.

With regard to health maintenance, clinicians who provide care to older persons with HIV infection should not only remember those conditions associated with HIV disease (eg, cervical neoplasia, and the importance of Papanicolaou smear screening) but also other appropriate health maintenance procedures (eg, mammography and colorectal cancer screening).

Conclusions

HIV is increasingly prevalent in persons over the age of 50 years. The aging process complicates immune function and HIV disease progression, yet co-morbid conditions and their treatments need not impede successful HIV treatment. The social implications of HIV disclosure, impact health care access, prevention efforts, and risk assessment. To increase awareness of HIV infection in older persons, and effectively enlighten older persons about the risk for acquiring HIV, health care providers and educators must remove barriers, especially sexual ones. "Tell me about the people you've had sex with recently" is an inquiry that should be posed to all patients, not just younger individuals. Planning for delivery of prevention and care services to address the increasing prevalence of older persons with HIV infection must consider the socio-economic conditions unique to this population [50]. Services to address physical, mental health, and social support issues should be incorporated into HIV primary care models for older persons.

Increased research in areas related to HIV in the elderly is needed. The trends of increasing prevalence of HIV/AIDS among older persons indicate the need for long-term planning to anticipate the impact on service needs. As the number of older persons with HIV infection continues to increase, especially those over the age of 65, the unique physical, social, and mental health needs of this population must be vigorously addressed.

Acknowledgments

This work was supported in part by the National Institute of Allergy and Infectious Diseases grant AI-46370 (DM).

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