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HIV PERSPECTIVES AFTER 25 YEARS

Aging and HIV Infection

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ABSTRACT *With the advent of highly active antiretroviral therapy (HAART) in mid-1995, the prognosis for HIV-infected individuals has brightened dramatically. However, the conjunction of potent antiviral therapy and longer life expectancy may engender a variety of health risks that, heretofore, HIV specialists have not had to confront. The long-term effects of HIV infection itself and exposure to antiretroviral agents is unknown. Several aspects of aging, including psychiatric disease, neurocognitive impairment, and metabolic and hormonal disorders, may be influenced by chronic exposure to HIV and/or HIV therapeutics. In this paper, we discuss the health issues confronting HIV-infected older adults and areas for future research.*

KEYWORDS *Aging, HIV infection, Substance abuse, HAART*

BACKGROUND

The increased survival of HIV-infected individuals with the advent of HAART[1,2] has been accompanied by a steady increase in the number of older adults with HIV/AIDS. By the end of 2000, there were more than 60,000 persons living with AIDS >50 years of age.[3] From 2000 to 2003, the estimated number of HIV/AIDS cases in the United States increased among persons ≥45 years, whereas HIV/AIDS prevalence decreased or remained stable in the 25- to 44-year age group.[4] HIV-infected persons ≥45 years represented 28% of the HIV-infected population in the United States in 2000; this percentage increased to 35% by 2003.[4] An increased number of new HIV/AIDS diagnoses also accounts for the increasing prevalence among older adults. The proportion of new HIV/AIDS diagnoses among persons ≥45 years increased from 22% in 2000 to 25% in 2003.[4] The burden of HIV/AIDS

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among older adults is likely to continue to rise with widespread access to HAART and ongoing high-risk behavior.[5]

DIAGNOSIS OF HIV IN OLDER ADULTS

Despite the increasing burden of HIV among older adults, the prevalence is likely underestimated due to delayed screening and recognition of HIV.[6,7] Older persons are not a well-recognized HIV risk group, possibly due to a common perception of sexual inactivity among older adults[8] and an overall decline in drug use with age.[9] Education and prevention programs mainly target adolescents and young adults. Routine HIV testing commonly occurs at sexually transmitted disease clinics and drug treatment programs, which are sites not highly frequented by older persons.[10] In the National AIDS Behavioral Surveys, Stall and Catania reported that adults >50 years and at risk for HIV were one fifth as likely to have been HIV-tested than a comparison group of at-risk individuals in their 20s.[11] Studies have shown that the majority of older HIV-infected adults were diagnosed in the hospital,[10] which suggests that they are not tested until later in the course of disease.[7] Delayed diagnosis of HIV among older adults may have a negative impact on survival.[5,7]

The HIV Cost and Service Utilization Study and The Veterans Aging Cohort 3 Site Study observed that older patients with HIV consistently reported fewer symptoms than those under age 50,[12] which further hinders identification of HIV infection in older persons. Furthermore, physicians may be less likely to suspect HIV infection as a potential cause of fever, weight loss, anemia, neuropathy, and memory loss among older persons, perhaps due to the overlap of these symptoms with other age-associated diseases such as depression, Alzheimer's dementia, malignancy and chronic inflammatory states.[7,13]

RISK BEHAVIOR

When reviewing HIV/AIDS among older adults, special attention should be given to drug users. HIV/AIDS cases relating to injection drug use are increasing among older adults; from 1994 to 2000, injection drug-use-related HIV diagnoses increased 20% among persons 40–49 years of age.[14] In a sample of 198 HIV-infected persons ≥55 years in New York City, 30% gave a history of injection drug use.[15] Drug use, aside from its own attendant risk for HIV infection, is often accompanied by other high risk behavior. Kwiatkowski and Booth studied HIV risk behavior in 1508 active drug users >50 years and 1515 active drug users ≤50 years and found that, although drug users >50 years were less likely than their young counterparts to have had sex in the past month, those who did engaged in high risk sexual behavior, including sex with multiple partners, exchange of sex for money or drugs, and sex with an intravenous drug user.[16] Additional studies have revealed lower rates of condom use compared to younger persons.[7,11] Older adults have also been observed to be less knowledgeable about transmission of HIV.[17]

Although high-risk sexual behavior is associated with drug use, paradoxically, drug use behavior itself may become less risky as people age. Kwiatkowski and Booth observed that older drugs users were less likely to share needles and injected less often than younger drug users.[16] Crack users, however, were observed to continue to engage in high-risk behavior.[16] An overall decline in risky drug use practices is consistent with greater social isolation and decreased physical tolerance to drugs, which are commonly associated with aging.[10,16]

SUBSTANCE ABUSE AND PSYCHIATRIC ILLNESS

Record-high rates of alcohol and illicit drug use by the aging baby-boom cohort may offset secular trends in drug use behavior, such as a decline in substance abuse with age and a decrease in intravenous drug use due to higher purity of heroin.[9,18] As such, health care providers will need to specifically address substance abuse in the aging HIV-infected population. In the Veterans Aging Cohort Study, Justice et al. found that HIV-infected veterans had a higher prevalence of depression, alcohol abuse or dependence, and drug abuse or dependence than their age-matched uninfected counterparts.[19] Studies have shown that older substance abusers are less likely to have been offered substance abuse treatment compared to younger persons,[20,21] which does not portend well for the aging HIV-infected population.

Counseling and treatment must focus on unique features of drug abuse and mental health among older adults. Older adults are more likely to be separated, divorced, or widowed, which minimizes their social support.[10] Frequency of drug use may decline due to decreased physical tolerance.[16] Furthermore, the medical consequences of chronic drug use and dependence may complicate aging. Chronic drug use may lead to an increased risk of hepatitis C-induced liver disease, hypertension, cardiovascular disease, mental health problems, bacterial infections, and trauma.[22–25]

Substance abuse and psychiatric disorders frequently coexist; in a sample of 2864 HIV-infected adults receiving care in the United States, 47.9% screened positive for a psychiatric disorder, including major depression, dysthymia, generalized anxiety disorders, and panic attacks.[26] Illicit drug use and heavy alcohol use were independently associated with screening positive for a psychiatric disorder.[26] The two comorbidities may impair quality of life, foster social and medical disengagement, and compromise medication adherence.[27] In addition, untreated psychiatric illness can lead to substantial adverse health outcomes; in a multicenter longitudinal study of HIV-infected women in the United States, depression was independently associated with increased non-AIDS-related mortality.[28]

NEUROCOGNITIVE IMPAIRMENT

Although the incidence of HIV-associated dementia has decreased with the advent of HAART, numerous studies have reported an association between advanced age and increased risk of HIV-associated dementia as the first AIDS-defining illness.[5,29,30] Among non-HIV-infected persons, advanced age is associated with greater risk for Alzheimer's, Parkinson's, or vascular dementia.[31] However, the effect of HIV itself and duration of HIV infection on neurocognitive function remains unclear.

In a cross-sectional analysis, the Hawaii Aging with HIV-1 Cohort[31] conducted neuropsychological testing in 106 HIV-infected adults ≥50 years and in 96 adults between 20 and 39 years of age. The older group had a greater self-reported duration of HIV infection compared to participants between 20 and 39 years and had nearly three times the risk of dementia, after adjusting for education, race, substance abuse, HAART use, viral load, CD4 cell count, depression score, and duration of HIV infection.[31] In the Veterans Aging Cohort Study[19] of 1803 HIV-infected and uninfected veterans throughout the United States, HIV-infected subjects (median age 50 years) demonstrated a greater prevalence of depression and alcohol and drug abuse compared to age-matched HIV-negative subjects

(median age 55 years). After excluding persons with depression, memory problems increased with age in both groups.[19] These studies suggest that older HIV-infected adults are at increased risk for dementia, depression, and substance abuse. However, longitudinal research is needed to examine how substance abuse, psychiatric illness, duration of HIV infection, and immune function affect neurocognitive function in aging HIV-infected persons.

METABOLIC AND HORMONAL DISORDERS

Cross-sectional studies of HIV-infected persons have observed an increased risk for metabolic and hormonal disorders, including osteopenia, hypogonadism, diabetes mellitus, and dyslipidemia.[32–36] Many of these diseases have been associated with HIV itself, antiretroviral therapy, and opiate use.[32–38] As HIV-infected people approach midlife and beyond, the progression of metabolic and hormonal disorders may accelerate due to the aging process and chronic exposure to HIV and antiretroviral agents.

Bone Loss

An increased incidence of osteopenia and osteoporosis has been reported in HIV-infected men and women, although it is unclear if bone loss is a result of HIV infection or antiretroviral treatment.[33,39,40] Additional factors such as poor nutrition, wasting, steroid use, hypogonadism, and opiate use may decrease bone mineral density in HIV-infected persons.[40–42] Early literature suggested that protease inhibitors may be associated with reduced bone mineral density,[43] whereas other studies observed a protective effect of protease inhibitors on bone mineral density.[44,45] Recent studies, however, have refuted earlier reports and concluded that HIV infection, independent of antiretroviral therapy, is associated with reduced bone mineral density in both men and women.[33,46,47] In a cross-sectional analysis of 142 persons, there was a greater prevalence of osteopenia and osteoporosis among HIV-infected vs. HIV-uninfected persons.[33] Duration of HIV infection but not specific classes of antiretroviral agents was associated with decreased bone mineral density.[33]

In addition to these conflicting reports, our current understanding of bone metabolism in the aging HIV-infected population is limited given that most studies are cross-sectional and examine participants ≤45 years of age. Longitudinal data is needed to examine the effect of menopause on bone disease in HIV-infected women. Future studies also need to better address the effect of substance abuse on bone metabolism in aging HIV-infected persons.

Alendronate, in combination with vitamin D and calcium, has been shown to significantly increase bone mineral density in HIV-infected men and women with osteopenia and osteoporosis, compared to vitamin D and calcium alone.[40] Despite our poor understanding of the factors associated with reduced bone mineral density, screening and assessment for risk factors for bone loss should be undertaken to lessen morbidity from osteopenia and osteoporosis as the HIV-infected population matures.

Menopause

The presentation and natural history of menopause in HIV-infected women is an area of active research. Our knowledge of the interrelation of HIV, HAART, drug use, and immune function on the onset and symptoms of menopause is limited.

Recent studies have revealed that HIV-infected women, who are largely socioeconomically disadvantaged minorities, reach menopause between 46 and 47 years of age[32,38] which is in sharp contrast to the general population of women who have been estimated to reach menopause between 50 and 52 years of age.[49,50] In a cross-sectional analysis of 302 HIV-infected women in the Bronx, NY, Schoenbaum et al. reported a median age at menopause of 46 years; over 50% of this cohort of HIV-infected women used drugs, and drug use and immune status were independently associated with an earlier age at menopause.[32] The proportion of HIV-infected women reaching menopause increased as CD4 cell count declined, independent of age, HAART, and drug use.[32]

The observed earlier age at menopause may be partly attributed to smoking, physical stress, and low socioeconomic status, which is pervasive among HIV-infected women and has been associated with earlier menopause in the general population.[50–54] The effect of drug use on menopause needs further study, as one fourth of women in the US with HIV/AIDS have injected drugs and an even greater percentage have used drugs by other routes.[4] Whether the earlier age at menopause further increases the risk of osteopenia, atherosclerosis, dyslipidemia, and insulin resistance conferred by aging, HIV infection, HAART, and/or drug use requires further investigation.

Symptoms associated with menopause in the general population, such as hot flashes and insomnia, are prevalent in cohorts of HIV-infected women.[48,53] Yet, studies of postmenopausal HIV-infected women have revealed low rates of hormone replacement therapy.[5,48,51] This observation may be due to high pill burden, perceived poor compliance, and limited data on the effect of hormone replacement on menopausal symptoms and osteopenia in HIV-infected women.[48,51] Future studies are warranted, as one small study of 84 HIV-infected women over 40 years of age observed a trend towards improved survival among women on HRT.[51] Explanation for this finding are not obvious, but it is plausible that, thus far, hormone replacement therapy in the HIV-infected population is a marker of regular medical care.[51]

Hypogonadism

Decreased testosterone levels and hypogonadism have been noted in the HIV-infected population, and injection drug users, in particular, are at increased risk.[34,39] Stimulation of opiate receptors in the brain down-regulates the hypothalamus, leading to reduced synthesis of gonadotropin releasing hormone and decreased stimulation of the pituitary and gonads.[39] In a study of 502 HIV-infected and at-risk men with a median age of 54–55 years, the prevalence of low testosterone levels (<300 ng/dl) was 54%.[34] Injection drug use, hepatitis C virus seropositivity, and use of psychotropic medications were independently associated with low testosterone levels. HIV viral load >10,000 copies/ml, but not HIV itself, was associated with low testosterone levels, suggesting a direct effect of viral activity on gonadal function. Low testosterone levels were associated with symptoms suggestive of hypogonadism, including decreased libido, depression, poor overall health, and osteopenia.

Decreased sexual function, muscle mass, bone loss, fatigue, anemia, and disturbances in body fat patterns have been attributed to testosterone deficiency,[54–56] and testosterone replacement therapy is frequently prescribed.[57] However, the benefits and risks of testosterone replacement remain poorly defined, and the reported trials have shown mixed results,[58–60] possibly because responses to

testosterone supplementation may differ by age.[61] Low androgen levels may have adverse consequences, as total and free serum testosterone has been inversely correlated with coronary artery disease risk.[62] The effect of long-term testosterone replacement on atherosclerosis needs further study.

Diabetes Mellitus

The association between HIV infection itself and antiretroviral therapy with abnormal glucose metabolism has been well recognized.[36,63–65] The causative mechanisms leading to increased risk of diabetes mellitus are likely multifactorial.[66] Protease inhibitor use has been associated with a threefold increased risk of incident diabetes mellitus.[63] These antiviral agents have been shown to selectively inhibit Glut4, a cell membrane glucose transporter.[67] Not all studies, though, have observed detrimental effects of protease inhibitors on glucose metabolism.[37,65,68] Nucleoside reverse transcriptase inhibitors have also been observed to significantly increase the risk of diabetes mellitus in HIV-infected persons.[36] Recent data suggests that chronic low-grade elevations in serum lactate may be a factor in nucleoside reverse transcriptase inhibitor-induced insulin resistance.[64]

The interaction of advanced age on the risk and progression of diabetes among older HIV-infected adults with long-term exposure to antiretroviral agents requires further study. Early menopause may increase the risk of diabetes mellitus in HIV-infected women.[32] A history of chronic opiate use may also contribute to abnormal glucose metabolism among HIV-infected persons.[37] A study of HIV-infected and at-risk women found that methadone, heroin, and cocaine use were independently associated with lower insulin secretion.[37] Opiate use has been shown to reduce insulin response[69,70] and is also a marker of hepatitis C, which has also been associated with diabetes mellitus.[71]

A better understanding of the mechanisms leading to abnormal glucose metabolism in HIV-infected persons, along with an emphasis on primary and secondary prevention, is essential to optimize the long-term health of the aging HIV-infected population. A large multinational study of HIV-infected persons found that diabetes was an independent risk factor for cardiovascular disease.[35] Data suggests that metformin and rosiglitazone are effective in treating insulin resistance among HIV-infected persons,[72,73] but their effect on cardiovascular disease in this population is not known.

Dyslipidemia and Cardiovascular Disease

Serum lipid alterations have been associated with HIV infection and antiretroviral medications.[39] HIV infection has been shown to result in a decrease in total cholesterol and high-density lipoprotein (HDL).[74] Protease inhibitor-based HAART regimens may result in an increase in total cholesterol, triglycerides, and low-density lipoprotein (LDL).[75] Opiates may also have similar effects on lipid profiles; Maccari et al.[76] reported that HIV-uninfected heroin addicts had significantly lower total cholesterol and HDL values compared to age-matched controls.

HIV has been associated with premature atherosclerosis, which may be attributed to antiretroviral metabolic toxicity, including dyslipidemia and insulin resistance, and/or endothelial dysfunction.[5,77,78] The increased survival conferred by HAART has been accompanied by an increase in non-AIDS mortality, including cardiovascular disease.[25] The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study observed that persons receiving combination antiretroviral

therapy had a 26% relative increase in the rate of myocardial infarction per year of use.[35]

Health care providers must emphasize regular preventive care concurrent with treatment of HIV disease. Screening and management of dyslipidemia is a critical issue, as the DAD study found that an elevated total cholesterol and triglyceride level was associated with an increased risk of myocardial infarction.[35]

DRUG METABOLISM

An age-related decline in hepatic and renal function, combined with comorbid conditions and non-HIV-related medications, raises a concern of altered drug metabolism in older patients with HIV.[5,79–81] Few studies have examined the safety and optimal dose of antiretroviral agents in older adults. Knobel et al. found an increase in adverse events resulting in drug discontinuation with protease inhibitor use in persons >60 years compared to those <40 years.[82] The use of methadone, alcohol, illicit drugs, and complementary and alternative medicine may further complicate drug kinetics.[83–87] For example, St. John's wort, an alternative treatment for depression, has been shown to lower levels of antiretroviral drugs and to have interactions with numerous drugs.[88] As the HIV-infected population ages, pharmacokinetic data of the use of antiretroviral agents in older adults is warranted.

CONCLUSIONS

Older persons represent a substantial proportion of AIDS cases, and this number is likely to grow with the widespread availability of HAART and improved population screening. Current data demonstrates that HIV-infected persons are at heightened risk for psychiatric illness, neurocognitive impairment, psychiatric illness, osteopenia, hypogonadism, insulin resistance, and dyslipidemia. Longitudinal studies are needed to understand the interaction of advanced age, antiretroviral treatment, and substance abuse with diseases of aging in HIV-infected persons. Improved utilization of primary care services, concurrent with management of HIV/AIDS, is paramount to optimize longevity in this population.

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