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Care of the aging HIV patient

ABSTRACT

Thanks to antiretroviral therapy, human immunodeficiency virus (HIV) infection has become a controllable chronic disease, and many infected patients are now living into their 60s and beyond. In addition, many patients with newly diagnosed HIV infection are over age 50. The subsequent rising prevalence of HIV infection in older adults presents several challenges for primary care clinicians. This article promotes increased HIV screening in older adults and highlights the need to recognize polypharmacy and the various comorbidities inherent in the aging HIV population.

KEY POINTS

Today, nearly 20% of newly diagnosed HIV-infected people and more than 50% of all HIV-infected people in the United States are over age 50.

The diagnosis and treatment of HIV tends to be delayed in elderly patients, with deleterious effects.

Antiretroviral drugs have a number of interactions with drugs commonly used in elderly patients.

Several diseases are more common in HIV-positive patients, including cardiovascular disease, diabetes mellitus, osteoporosis, dementia, and various malignant diseases. These merit aggressive screening and preventive measures.

IN THE 1980s, human immunodeficiency virus (HIV) infection was considered untreatable and predictably lethal. Today, with highly effective antiretroviral therapy, it has become a chronic condition in which patients have a life expectancy comparable to that in the general population.

This change has led to new challenges for primary care physicians, many of whom now find themselves either the sole medical provider for or the comanager of aging HIV-infected patients. Given that about one-fifth of new HIV diagnoses are now in people over the age of 50, it is crucial that primary care providers be able to recognize and diagnose the disease in this population. In addition, they need to effectively manage the polypharmacy and subsequent drug interactions prevalent in older HIV-infected patients. Finally, the clinician must address comorbid diseases common in the elderly, specifically neurologic, cardiovascular, metabolic, and endocrine disorders, as well as performing routine cancer screening.

Take-home point

- As the number of people age 50 and older with HIV infection increases, primary care providers must be able to both recognize and manage the condition.

■ RISING PREVALENCE OF HIV IN THE ELDERLY

Globally, about 2.5 million people received a new diagnosis of HIV infection in 2011, and about 35 million people worldwide are currently living with it.¹ An estimated 1.1 million Americans are living with HIV, and of these, about 16% do not know they are infected.²

Antiretroviral therapy has greatly improved the life expectancy of HIV-infected patients, and the number of HIV-infected people over age 50 continues to rise. A successfully

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HIV patients who adhere to treatment and achieve a CD4 count above 350 and a low viral load have a normal life expectancy

treated HIV-positive person with a CD4 count higher than $350 \times 10^6/L$ and a suppressed viral load now has a normal life expectancy.³ In 2011, nearly 20% of newly diagnosed HIV-infected people in the United States were over age 50, as were nearly 25% of those with a new diagnosis of acquired immune deficiency syndrome (AIDS).⁴ This year (2015), we expect that more than half of all HIV-infected people in the United States will be over age 50.⁵

The rising prevalence of HIV infection in this age group has prompted reevaluation of screening guidelines. The US Preventive Services Task Force recommends screening for HIV in all people ages 15 to 65, and also after age 65 in people at ongoing risk of infection.⁶ The American College of Physicians has suggested that the range for routine HIV screening be expanded to age 75.⁷ The cost-effectiveness of expanded and more frequent HIV testing appears to justify it.⁸

Take-home points

- An HIV-infected patient who is compliant with an appropriate antiretroviral regimen and has a CD4 count higher than $350 \times 10^6/L$ and a suppressed viral load now has a normal life expectancy.
- Today, nearly 20% of newly diagnosed HIV-infected people and more than 50% of all HIV-infected people in the United States are over the age of 50.
- The age range for routine screening for HIV infection should be expanded.

■ HIGH-RISK GROUPS AMONG THE ELDERLY

Early in the HIV epidemic, older patients acquired HIV from blood transfusions received because of hemophilia and other disorders. However, this rapidly ceased after blood banks began screening blood products. Today, people over age 50 who acquire HIV have many of the same risk factors as younger people.

Men who have sex with men are the largest subgroup of HIV-infected people in the United States, even among those over age 50. In particular, white men who have sex with men now constitute the largest demographic group among the HIV-infected elderly.⁴

Intravenous drug users make up about 15% of older people with HIV.

Women who have sex with infected men

or with men at risk of HIV infection make up the largest group of older women with HIV.⁴

Sex and the older person

Many older HIV-infected people remain sexually active and continue to engage in unprotected sexual intercourse far into advanced age. According to one survey, 53% of Americans ages 65 to 74 are engaging in sexual activity regularly; however, they are not using protective measures with up to 91% of casual partners and 70% of new partners.^{9,10} Many widowed and divorced people are dating again, and they may be unfamiliar with condom use or may be reluctant to use condoms because condoms can often make it difficult to maintain an erection.

Drugs for erectile dysfunction are making it easier for the elderly to engage in both vaginal and anal intercourse, but often without a condom.⁹ Older women who no longer worry about getting pregnant may be less likely to insist their partners use a condom and to practice safe sex. In addition, age-related thinning and dryness can cause vaginal tears, increasing the risk of HIV transmission.¹¹

Take-home points

- People older than 50 have risk factors for HIV similar to those in younger people.
- Men who have sex with men compose the largest group of HIV-infected individuals in the elderly population.
- Unprotected sexual intercourse is common in the elderly for several reasons: unfamiliarity with condom use, difficulty maintaining an erection, lack of concern about possible pregnancy, and vaginal thinning and dryness in women.

■ UNDERDIAGNOSIS AND LATE DIAGNOSIS IN THE ELDERLY

The cumulative number of AIDS cases in adults age 50 and older increased nearly nine-fold from 1990 to the end of 2009. Even more worrisome, one-half of HIV-positive adults over age 50 are diagnosed with AIDS simultaneously or within 1 year of their HIV diagnosis.⁴ This late diagnosis—and therefore late initiation of treatment—is associated with poorer health outcomes and more rapid disease progression.¹²

HIV infection in older adults often goes undiagnosed, for several reasons.

Providers may underestimate the risk in this population and therefore may not discuss HIV transmission or perform testing. Despite a US Centers for Disease Control and Prevention recommendation that people ages 13 to 64 be tested at least once, and more often if sexually active, only 35% of adults ages 45 to 64 have ever been tested for HIV infection.¹³

Older patients may not perceive themselves to be at risk of HIV infection because of lack of insight and information about its prevention and transmission. They are also less likely than younger adults to discuss their sexual habits or drug use with providers.¹⁴ In addition, compared with the young sexually active population, very little HIV prevention education is targeted to older people.¹⁵ Social stigmatization is also a concern for many HIV-infected elderly, as a perceived negative reputation within their community may prevent them from seeking care and disclosing their HIV status.

Take-home points

Reasons that HIV infection is underdiagnosed in the elderly include lack of:

- Provider recognition
- Insight and information about HIV prevention and transmission
- HIV-prevention education targeting the elderly
- Disclosure because of the social stigma of HIV infection.

■ HIV ACCELERATES AGING, AGING REDUCES IMMUNITY

Many HIV-positive people can expect to live as long as people in the general population, but those who are diagnosed late and thus are started on antiretroviral therapy later in the course of their infection have a reduced life expectancy. Longevity depends on both restoring the CD4 count to near-normal and suppressing the viral load to undetectable levels.^{3,16} This is especially important for older adults, as HIV may accelerate aging, and aging itself may speed the progression of HIV disease, so that therapy may result in delayed or only partial restoration of immunity.

Older age at the time of HIV infection is a strong predictor of accelerated HIV disease

progression in the absence of therapy.¹⁷ Left untreated, older patients with HIV lose CD4 cells and progress to AIDS and death faster than younger patients. The deleterious effects of chronic immune activation in the course of HIV infection, combined with the immune senescence of aging, are thought to promote this accelerated course.¹⁸

Recent data indicate that starting antiretroviral therapy early can help prevent the CD4-cell impairment that occurs with aging.¹⁹ However, in adults over age 50, the capacity to restore the CD4 count with antiretroviral therapy appears to be reduced, despite demonstrated viral load suppression and better adherence.²⁰ Although mean adherence rates appear higher in older HIV-infected patients, they are worse in those with neurocognitive impairment, highlighting the importance of evaluating neurocognition in this population.²¹

Decreased immune recovery and the subsequent increased risk of serious AIDS events are factors that now favor starting antiretroviral therapy in all HIV patients over age 50, regardless of CD4 count.

Take-home points

- Without treatment, HIV infection in older patients progresses more rapidly to AIDS and death than in younger patients.
- HIV-positive people over age 50 who have never received antiretroviral therapy should be strongly considered for it, regardless of the CD4 count.

■ SO MANY DRUGS, SO MANY INTERACTIONS

Since HIV patients are now living longer thanks to antiretroviral therapy, they are now experiencing more disease- and treatment-related problems. This has led to an increased likelihood of polypharmacy, defined here as the use of six or more medications.

In general, polypharmacy in the elderly is associated with adverse drug events, drug interactions, inappropriate medication use, delirium, falls, fractures, and poor medication adherence.^{22,23} But it becomes even more of a problem in HIV-infected elderly patients, as various drug interactions can alter the effectiveness of the antiretroviral regimen and can result in drug toxicity.

The age range for routine screening for HIV should be expanded

TABLE 1

Interactions between antiretrovirals and commonly prescribed medications in the elderly

Medication class	Interaction with antiretrovirals	Recommendations
Statin	Increased statin levels with protease inhibitor (PI) use	Avoid use of simvastatin and lovastatin with a PI Use lowest effective dose (maximum 20 mg/day) of atorvastatin with a PI
Proton pump inhibitor	Decreased absorption of rilpivirine and atazanavir	Contraindicated with unboosted atazanavir, rilpivirine Do not exceed 20 mg/day equivalent dose of omeprazole with use of atazanavir boosted with ritonavir (if patient has never taken a PI) Not recommended in patients who have taken a PI and are taking atazanavir boosted with ritonavir
Corticosteroid (systemic, intranasal, inhaled)	Increased fluticasone and budesonide levels with ritonavir Decreased levels of PI and nonnucleoside reverse transcriptase inhibitor (NNRTI) with dexamethasone	Use of fluticasone or budesonide with ritonavir can cause adrenal insufficiency, Cushing syndrome Avoid giving dexamethasone with rilpivirine
Calcium channel blocker	Increased calcium channel blocker levels and potential PR-interval prolongation on electrocardiography with PI use	Use PIs and calcium channel blockers with caution
Antiplatelet and anticoagulant	Decreased clopidogrel levels with etravirine Increased rivaroxaban levels with a PI Increased or decreased warfarin levels with both PIs and NNRTIs	Avoid clopidogrel with etravirine, if possible Avoid rivaroxaban and PI combination Closely monitor the international normalized ratio when starting or stopping a PI or NNRTI with warfarin
Opioid	Decreased methadone levels with NNRTI or PI boosted with ritonavir	Monitor closely for opioid withdrawal when methadone is combined with nevirapine, efavirenz, or PI boosted with ritonavir
Benzodiazepine	Increased midazolam and triazolam levels with efavirenz Increased diazepam levels with etravirine Increased benzodiazepine levels with PIs	Avoid coadministration of midazolam, alprazolam, diazepam, and triazolam with PIs, efavirenz, or etravirine Consider alternative benzodiazepines for use with a PI: lorazepam, oxazepam, temazepam
Antidepressant	Decreased bupropion and sertraline levels with efavirenz and select PIs Increased levels of trazodone and tricyclic antidepressants with select PIs	Titrate dose of selective serotonin reuptake inhibitor and bupropion to clinical effect with PIs Use lowest dose of trazodone and tricyclic antidepressant, and monitor for central nervous system and cardiovascular side effects with PIs

Derived from Greene et al,²⁵ 2013 US Department of Health and Human Services guidelines,²⁶ the HIV InSite website,²⁷ and the University of Liverpool Drug Interaction website.²⁸

The most common classes of medications used in the elderly are antihypertensives, lipid-lowering agents, antiplatelet medications, antidepressants, anxiolytics, sedatives, and analgesics, and many of these have notable interactions with current antiretroviral regimens.^{24,25} Most medications, including antiretrovirals, are cleared by the liver or kidneys, and the function of these organs often decreases with age, resulting in impaired elimination and in drug accumulation.

Information on drug interactions is readily available from the US Department of Health and Human Services,²⁶ drug interaction databases,^{27,28} and drug interaction software. The combination of antiretroviral therapy and preexisting polypharmacy significantly increases the risk of serious interactions, which can lead to drug toxicity, poorer adherence with antiretroviral therapy, loss of efficacy of the coadministered medication, or resurgence of HIV infection due to drug-drug interactions affecting the metabolism and ultimate efficacy of the antiretroviral therapy. An increased awareness of common drug-drug interactions can prevent coadministration of potentially harmful medications in elderly HIV patients.

Important interactions between antiretroviral drugs and other drug classes are summarized in **Table 1**.^{25–28} Most notably:

- Simvastatin and lovastatin are contraindicated with any protease inhibitor.
- Proton pump inhibitors are not recommended for patients taking ritonavir-boosted atazanavir. If a proton pump inhibitor is necessary, the daily dose should not exceed 20 mg of omeprazole or its equivalent in patients who have never taken a protease inhibitor, and it should be taken 12 hours before boosted atazanavir.²⁶
- Corticosteroids, whether systemic, inhaled, or intranasal (eg, fluticasone, budesonide), should be avoided in combination with any protease inhibitor, as they can cause iatrogenic Cushing syndrome and also pose the risk of adrenal crisis during acute illness.²⁷

Take-home points

- In cases of preexisting polypharmacy, antiretroviral therapy can lead to significant drug toxicity, poor adherence to medica-

tions, and resurgence of HIV infection.

- Increased provider awareness of common drug-drug interactions can prevent the prescribing of potentially harmful drug combinations to HIV-infected elderly patients.

COMORBIDITIES

In recent years, more than half of the deaths in HIV patients on antiretroviral therapy have been from noninfectious comorbidities such as cardiovascular disease, bone disease, and renal failure, which often coexist and are associated with advanced age.²⁹ In fact, both older age and each additional year of antiretroviral therapy are independent predictors of polypathology (simultaneous occurrence of two or more defined diseases).³⁰ The Antiretroviral Therapy Cohort Collaboration found that age greater than 50 was strongly associated with increasing rates of non-AIDS-related malignancy and cardiovascular disease.³¹

CARDIOVASCULAR DISEASE

With the increasing life expectancy of HIV-infected adults on antiretroviral therapy, cardiovascular disease has become an important concern. HIV-infected adults appear to have a significantly greater risk of myocardial infarction and coronary artery disease than age-matched HIV-negative individuals.³² Strikingly, being older than 50 itself increases the risk of hospitalization for cardiovascular disease fivefold (incidence rate ratio 5.01, 95% confidence interval 3.41–7.38).³³ In addition, HIV infection is associated with a risk of acute myocardial infarction 50% higher than that explained by recognized risk factors.³⁴

This high prevalence of coronary artery disease is likely from a combination of factors, including increasing age and the chronic inflammation and immune activation associated with HIV infection.³⁵ An association between untreated HIV disease and markers of risk for cardiovascular disease has been identified.^{36,37}

In addition, antiretroviral therapy is associated with dyslipidemia, which is most pronounced with protease inhibitor regimens. Whether specific lipid changes associated with individual antiretroviral drugs affect cardiovascular risk remains uncertain. In the Data

Age greater than 50 has been strongly associated with higher rates of non-AIDS-related cancers and cardiovascular disease

HIV is associated with a 50% higher risk of acute myocardial infarction beyond traditional risk factors

Collection on Adverse Events of Anti-HIV Drugs studies,³⁸ only cumulative exposure to indinavir, lopinavir-ritonavir, and didanosine was associated with an increased risk of myocardial infarction.³⁸

Traditional risk factors such as obesity, tobacco use, and genetic predisposition also apply to HIV-infected people.³⁹ In fact, the prevalence of traditional risk factors such as smoking and dyslipidemia is generally higher in HIV-infected people than in the general population, although this situation may be improving.⁴⁰

Science needs to elucidate the relationship between traditional and nontraditional risk factors for cardiovascular disease in older HIV-infected adults. In the meantime, older patients with HIV require aggressive management of modifiable risk factors.

Tools for assessing cardiovascular risk include the Framingham risk score⁴¹ and the Data Collection on Adverse Events of Anti-HIV Drugs 5-year risk calculator.⁴² The European AIDS Clinical Society guidelines recommend considering changing the antiretroviral regimen if the patient's 10-year risk of cardiovascular disease is more than 20%.⁴³ Recommended strategies for reducing cardiovascular risk in elderly patients with HIV infection include counseling about smoking cessation and weight loss at every clinic visit and optimally controlling dyslipidemia and hypertension using nationally accepted standardized guidelines.⁴⁴

Take-home points

- HIV infection is associated with a 50% higher risk of acute myocardial infarction beyond that explained by traditional risk factors.
- Chronic inflammation, immune activation, and dyslipidemia associated with antiretroviral therapy all contribute to cardiovascular disease in HIV-infected patients.
- HIV-infected elderly patients require aggressive management of modifiable risk factors for cardiovascular disease.

■ ENDOCRINE DISEASE

Diabetes mellitus

The estimated prevalence of diabetes mellitus is 3% in HIV-infected people who have never received antiretroviral therapy, but glucose

intolerance increases to the range of 10% to 25% in those who have started it.⁴⁵ Glucose disorders are associated with traditional risk factors as well as with HIV-associated factors such as lipodystrophy and antiretroviral therapy, specifically long-term use of protease inhibitors.⁴⁶ Although increasing age and obesity clearly play a role in the development of diabetes mellitus in this population, HIV-specific factors may also allow diabetes to develop at a lower level of adiposity than in people without HIV infection.⁴⁷

Strategies for preventing type 2 diabetes mellitus in HIV-infected patients focus on avoiding excessive weight gain, especially after starting antiretroviral therapy; regularly screening for diabetes using hemoglobin A_{1c}, both before and after starting antiretroviral therapy; and continuing to check hemoglobin A_{1c} every 6 months. The target hemoglobin A_{1c} should be less than 7.0%. This threshold should be increased to 8% in frail elderly adults if their anticipated life expectancy is less than 5 years, given their higher risk of hypoglycemia, polypharmacy, and drug interactions.⁴⁸ In addition, as in HIV-negative patients, diabetes screening should be performed if systolic blood pressure exceeds 135/80 mm Hg.

Insulin sensitizers such as metformin and thiazolidinediones should be considered for treating diabetes in HIV-infected patients if no contraindications exist. Consideration may also be given to switching the antiretroviral regimen from a protease inhibitor-based regimen to a nonnucleoside reverse transcriptase inhibitor-based regimen.⁴⁸

Take-home points

- Glucose intolerance has been associated with HIV-specific factors, including lipodystrophy and antiretroviral therapy.
- Avoiding excessive weight gain, use of insulin-sensitizing medications, and alteration in antiretroviral regimens should be considered for the treatment of diabetes mellitus in HIV infection.

Osteoporosis

Osteoporotic bone disease disproportionately affects patients with advanced HIV infection compared with patients of similar age.⁴⁹ Bone mineral density is lower and the fracture rate is higher in HIV-infected individuals.

The pathogenesis of bone disease appears to be multifactorial. Traditional risk factors include hypogonadism, smoking, alcohol use, and low body weight, while HIV-related risk factors include chronic immune activation and antiretroviral therapy.⁵⁰

Several antiretroviral regimens have been linked to clinically significant bone loss, including both tenofovir-based and protease inhibitor-based regimens.⁵¹ Most studies have shown that bone mineral density decreases by 2% to 6% in the first 2 years after starting these regimens⁵²; however, long-term effects on bone loss are unknown.

Questions remain. For example, what are the exact mechanisms that lead to the acute decrease in bone mineral density after starting antiretroviral therapy? And why is vitamin D deficiency is so prevalent in HIV infection, with low vitamin D levels seen in up to 60% to 75% of elderly HIV-infected patients?⁵³

Both the Work Group for the HIV and Aging Consensus Project⁵⁴ and the European AIDS Clinical Society⁴³ recommend screening for and treating causes of secondary low bone mineral density in HIV-infected men over age 50 and postmenopausal HIV-infected women. These causes include vitamin D deficiency. As of 2013, the National Osteoporosis Foundation guidelines include HIV infection and antiretroviral therapy as osteoporosis risk factors that should trigger screening for low bone mineral density with dual-energy x-ray absorptiometry (DXA).⁵⁵

As in the general population, the preferred treatment for low bone mineral density in people with HIV is a bisphosphonate, in addition to ensuring adequate calcium and vitamin D intake. It is important to repeat DXA imaging every 2 years and to reassess the need for continued bisphosphonate therapy after 3 to 5 years because of a possible increased risk of fracture with prolonged use.

Take-home points

- Osteoporosis and vitamin D deficiency both appear to be more prevalent with HIV infection.
- HIV infection and antiretroviral therapy are risk factors that should prompt DXA screening to evaluate for osteoporosis.

■ NEUROCOGNITIVE DISORDERS

HIV-associated neurocognitive disorders are common, with an estimated 50% of HIV-infected patients experiencing some degree of cognitive loss and some progressing to dementia.⁵⁶ Unfortunately, studies suggest that cognitive disorders can occur despite good HIV control with antiretroviral therapy, with one report demonstrating that 84% of patients with cognitive complaints and 64% without complaints were affected by an HIV-associated neurocognitive disorder.⁵⁷

HIV-associated dementia is often subcortical, with fluctuating symptoms such as psychomotor retardation, difficulty multitasking, and apathy. In contrast to dementia syndromes such as Alzheimer disease, relentless progression is less common in HIV-infected patients who receive antiretroviral therapy.

The Mini-Mental State Examination should not be used to screen for HIV-associated neurocognitive disorders, as it does not assess the domains that are typically impaired. The Montreal Cognitive Assessment has been suggested as the best screening instrument in elderly HIV-infected patients; it is available at no cost at www.mocatest.org.⁵⁸

As HIV-associated neurocognitive disorder is a diagnosis of exclusion, an evaluation for alternative diagnoses such as syphilis, hypothyroidism, and depression is recommended. If an HIV-associated neurocognitive disorder is diagnosed, referral to specialty care should be considered, as interventions such as lumbar puncture to assess cerebrospinal fluid viral escape and changing the antiretroviral regimen to improve central nervous system penetration are possible options under study.

Patients with poorly controlled HIV and a depressed CD4 count are at risk of a number of central nervous system complications in addition to HIV-associated neurocognitive disorders, eg, central nervous system toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and primary central nervous system lymphoma. Adherence to an effective antiretroviral regimen is the primary prevention strategy.

Take-home points

- HIV-associated neurocognitive disorders and dementia can occur despite appropri-

Osteoporosis and vitamin D deficiency appear to be more prevalent with HIV infection

TABLE 2

Non–AIDS-defining cancers in HIV-infected patients

Malignancy	Risk (standardized incidence ratio)	Screening recommendations
Anal	33.4–42.9	European AIDS Clinical Society: Consider digital rectal examination with or without a Papanicolaou smear every 1–3 years ^a
Hodgkin lymphoma	14.7–31.7	None
Liver	7.0–7.7	European AIDS Clinical Society: Ultrasonography, alpha fetoprotein every 6 months National Cancer Institute: No recommendation
Squamous cell carcinoma, basal cell carcinoma	3.2	European AIDS Clinical Society, National Cancer Institute: Consider routine whole-body skin examinations US Preventive Services Task Force: Insufficient evidence
Lung	2.2–6.6	American Cancer Society: Consider chest radiography in high-risk ^b patients National Cancer Institute, US Preventive Services Task Force: Consider low-dose computed tomography in high-risk ^b patients

^aSpecific to HIV-infected men who have sex with men; currently no national guidelines.

^bHigh-risk patients include those ages 55 to 74 in fairly good health who have a smoking history ≥ 30 pack-years AND are still smoking or have quit within the last 15 years.

Derived from Shiels et al,⁶⁵ Deeken et al,⁶⁶ Powles et al,⁶⁷ and Patel et al.⁶⁸

HIV-infected men are 4.5 to 10 times more likely than age-matched controls to be frail

ate HIV control and adherence to antiretroviral therapy.

- Adherence to antiretroviral therapy is the primary prevention against most central nervous system complications in HIV infection.

■ GERIATRIC SYNDROMES

The aging HIV-infected adult may also be at increased risk of geriatric syndromes.

In particular, a frailty-related phenotype of weight loss, exhaustion, slowness, and low physical activity was more common in HIV-infected elderly than in noninfected elderly.⁵⁹ HIV-infected men are 4.5 to 10 times more likely than age-matched controls to be frail, and the likelihood of frailty increases with age, duration of HIV infection, having a CD4 count lower than $350 \times 10^6/L$, and having uncontrolled HIV replication.^{60,61}

Other geriatric syndromes such as falls, urinary incontinence, and functional impairment have been identified in 25% to 56% of older HIV-infected patients.⁶² Indeed, the combination of HIV and older age may adversely affect performance of instrumental activities of daily living.⁶³ Also, as previously mentioned, nondisclosure, fear of HIV-related social stigmatization, and a desire to be self-reliant are all factors that perpetuate the social isolation that is common among the HIV-infected elderly.

For these reasons, a comprehensive approach involving a geriatrician, an infectious disease specialist, and community social workers is needed to manage the care of this aging population.

Take-home point

- Geriatric syndromes have an important impact on health in aging HIV patients.

CANCER SCREENING IN HIV PATIENTS

People with HIV have an elevated risk of cancer. Specifically, compared with the general population, their risk is:

- 3,640 times higher for Kaposi sarcoma
- 77 times higher for non-Hodgkin lymphomas
- 6 times higher for cervical cancer.^{64,65}

These cancers are considered “AIDS-defining,” and fortunately, the development of effective antiretroviral therapy in the 1990s has led to a marked reduction in their incidence. However, the aging HIV population is now experiencing a rise in the incidence of non-AIDS-defining cancers, such as cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin lymphoma.⁶⁶

Table 2 shows the standardized incidence ratio of selected non-AIDS-defining cancers in HIV-infected patients as reported in several large international studies.^{65,67,68} The etiology for the increased risk of non-AIDS-defining cancers in the HIV-infected population is not clear, but possible explanations include the virus itself, antiretroviral therapy, and co-infection with other viruses such as hepatitis B, hepatitis C, and Epstein-Barr virus.

Guidelines for cancer screening vary by organization, and the American Cancer Society, the National Cancer Institute, and the US Preventive Services Task Force do not have formal screening guidelines for the most common non-AIDS-defining cancers. The European AIDS Clinical Society, however, has proposed some screening recommendations for selected malignancies.⁴³

In general, screening recommendations are similar to those for HIV-negative patients.

A specific difference for HIV-infected patients is in cervical cancer screening. HIV-infected women should undergo a Papanicolaou smear at 6-month intervals during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter. There is no consensus as to whether human papillomavirus testing should be performed routinely on HIV-infected women.

At the time of this writing, there are no recommendations for routine screening for anal cancer, although some specialists recommend anal cytologic screening for HIV-positive men and women, and an annual digital anal examination may be useful to detect masses that could be anal cancer.⁶⁹

Take-home points

- The incidence of non-AIDS-defining cancers is rising in the aging HIV population.
- There are currently no formal recommendations for routine screening for anal cancer.

FINAL WORD

Because patients with HIV are living longer as a result of newer effective combination antiretroviral therapies, physicians face a new challenge of managing conditions in these patients that are traditionally associated with aging. Providers will need to improve their understanding of drug-drug interactions and polypharmacy issues and be able to address the complex medical and psychosocial issues in this growing population. As patients with HIV on effective antiretroviral therapy grow older, the burden of comorbid medical disease will continue to increase.

REFERENCES

1. World Health Organization. HIV/AIDS: fact sheet. www.who.int/media-centre/factsheets/fs360/en/. Accessed April 16, 2015.
2. Centers for Disease Control and Prevention (CDC). HIV/AIDS: basic statistics. www.cdc.gov/hiv/basics/statistics.html. Accessed April 16, 2015.
3. May MT, Gompels M, Delpech V, et al; UK Collaborative HIV Cohort (UK CHIC) Study. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS* 2014; 28:1193–1202.
4. Centers for Disease Control and Prevention (CDC). Diagnoses of HIV infection in the United States and dependent areas: HIV surveillance report. www.cdc.gov/hiv/library/reports/surveillance/2011/surveillance_Report_vol_23.html. Accessed April 16, 2015.
5. Effros RB, Fletcher CV, Gebo K, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis* 2008; 47:542–553.
6. Moyer VA; US Preventive Services Task Force. Screening for HIV: US Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2013; 159:51–60.
7. Qaseem A, Snow V, Shekelle P, Hopkins R Jr, Owens DK; Clinical Efficacy Assessment Subcommittee, American College of Physicians. Screening for HIV in health care settings: a guidance statement from the American College of Physicians and HIV Medicine Association. *Ann Intern Med* 2009; 150:125–131.
8. Lucas A, Armbruster B. The cost-effectiveness of expanded HIV screening in the United States. *AIDS* 2013; 27:795–801.
9. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007; 357:762–774.
10. Schick V, Herbenick D, Reece M, et al. Sexual behaviors, condom use, and sexual health of Americans over 50: implications for sexual health promotion for older adults. *J Sex Med* 2010; 7(suppl 5):315–329.
11. US Department of Health and Human Services, HIV/AIDS Bureau. The

- Ryan White HIV/AIDS program: population fact sheet: August 2010. Older adults. <http://hab.hrsa.gov/about/hab/populations/olderadultsfacts.pdf>. Accessed April 16, 2015.
12. May M, Gompels M, Delpech V, et al. Impact of late diagnosis and treatment on life expectancy in people with HIV-1: UK Collaborative HIV Cohort (UK CHIC) Study. *BMJ* 2011; 343:d6016.
13. Branson BM, Handsfield HH, Lampe MA, et al; Centers for Disease Control and Prevention (CDC). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep* 2006; 55:1–17.
14. Health Resources and Services Administration (HRSA); HIV/AIDS Bureau. HRSA CAREAction. The graying of HIV. <http://hab.hrsa.gov/newspublications/careactionnewsletter/february2009.pdf>. Accessed April 16, 2015.
15. AIDS InfoNet. Fact sheet number 616: Older people and HIV. http://aidsinfonet.org/fact_sheets/view/616. Accessed April 16, 2015.
16. Rodger AJ, Lodwick R, Schechter M, et al; INSIGHT SMART, ESPRIT Study Groups. Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. *AIDS* 2013; 27:973–979.
17. Kitahata MM, Gange SJ, Abraham AG, et al; NA-ACCORD Investigators. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009; 360:1815–1826.
18. Cao W, Jamieson BD, Hultin LE, Hultin PM, Effros RB, Detels R. Premature aging of T cells is associated with faster HIV-1 disease progression. *J Acquir Immune Defic Syndr* 2009; 50:137–147.
19. Allers K, Bösel D, Eppl HJ, et al. Effect of age on the CD4+ T-cell impairment in HIV-infected persons without and with cART. *J Acquir Immune Defic Syndr* 2014; 66:7–15.
20. Kalayjian RC, Spritzler J, Matining RM, et al. Older HIV-infected patients on antiretroviral therapy have B-cell expansion and attenuated CD4 cell increases with immune activation reduction. *AIDS* 2013; 27:1563–1571.
21. Althoff KN, Gebo KA, Gange SJ, et al; North American AIDS Cohort Collaboration on Research and Design. CD4 count at presentation for HIV care in the United States and Canada: are those over 50 years more likely to have a delayed presentation? *AIDS Res Ther* 2010; 7:45.
22. Freeland KN, Thompson AN, Zhao Y, Leal JE, Mauldin PD, Moran WP. Medication use and associated risk of falling in a geriatric outpatient population. *Ann Pharmacother* 2012; 46:1188–1192.
23. Steinman MA, Hanlon JT. Managing medications in clinically complex elders: “There’s got to be a happy medium.” *JAMA* 2010; 304:1592–1601.
24. Marzolini C, Elzi L, Gibbons S, et al; Swiss HIV Cohort Study. Prevalence of comedication and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* 2010; 15:413–423.
25. Greene M, Justice AC, Lampiris HW, Valcour V. Management of human immunodeficiency virus infection in advanced age. *JAMA* 2013; 309:1397–1405.
26. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed April 16, 2015.
27. UCSF Center for HIV Information. HIVinSite. Comprehensive, up-to-date information on HIV/AIDS treatment, prevention, and policy from the University of California San Francisco: database of antiretroviral drug interactions. <http://hivinsite.ucsf.edu/>. Accessed April 16, 2015.
28. The University of Liverpool. Drug interaction charts. www.hiv-druginteractions.org. Accessed April 16, 2015.
29. Vance DE, Mugavero M, Willig J, Raper JL, Saag MS. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *J Assoc Nurses AIDS Care* 2011; 22:17–25.
30. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011; 53:1120–1126.
31. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis* 2010; 50:1387–1396.
32. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003; 33:506–512.
33. Berry SA, Fleishman JA, Moore RD, Gebo KA; HIV Research Network. Trends in reasons for hospitalization in a multisite United States cohort of persons living with HIV, 2001–2008. *J Acquir Immune Defic Syndr* 2012; 59:368–375.
34. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* 2013; 173:614–622.
35. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007; 92:2506–2512.
36. Calmy A, Gayet-Ageron A, Montecucco F, et al; STACCATO Study Group. HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial. *AIDS* 2009; 23:929–939.
37. Phillips AN, Carr A, Neuhaus J, et al. Interruption of antiretroviral therapy and risk of cardiovascular disease in persons with HIV-1 infection: exploratory analyses from the SMART trial. *Antivir Ther* 2008; 13:177–187.
38. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *J Infect Dis* 2010; 201:318–330.
39. Lake JE, Currier JS. Metabolic disease in HIV infection. *Lancet Infect Dis* 2013; 13:964–975.
40. Data Collection on Adverse Events of Anti-HIV Drugs Study Group; Sabin CA, d’Arminio Monforte A, Friis-Møller N, et al. Changes over time in risk factors for cardiovascular disease and use of lipid-lowering drugs in HIV-infected individuals and impact on myocardial infarction. *Clin Infect Dis* 2008; 46:1101–1110.
41. Falcone EL, Mangili A, Skinner S, Alam A, Polak JF, Wanke CA. Framingham risk score and early markers of atherosclerosis in a cohort of adults infected with HIV. *Antivir Ther* 2011; 16:1–8.
42. Friis-Møller N, Thiebaut R, Reiss P, et al; DAD study group. Predicting the risk of cardiovascular disease in HIV-infected patients: the Data Collection on Adverse Effects of Anti-HIV Drugs study. *Eur J Cardiovasc Prev Rehabil* 2010; 17:491–501.
43. European AIDS Clinical Society Guidelines (EACS). www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed April 16, 2015.
44. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
45. Samaras K. The burden of diabetes and hyperlipidemia in treated HIV infection and approaches for cardiometabolic care. *Curr HIV/AIDS Rep* 2012; 9:206–217.
46. Rasmussen LD, Mathiesen ER, Kronborg G, Pedersen C, Gerstoft J, Obel N. Risk of diabetes mellitus in persons with and without HIV: a Danish nationwide population-based cohort study. *PLoS One* 2012; 7:e44575.
47. Capeau J, Bouteloup V, Katlama C, et al; ANRS C08 APROCO-COPILOTE Cohort Study Group. Ten-year diabetes incidence in 1,046 HIV-infected patients started on a combination antiretroviral treatment. *AIDS* 2012; 26:303–314.
48. American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care* 2013; 36(suppl 1):S11–S66.
49. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006; 20:2165–2174.
50. Rothman MS, Bessesen MT. HIV infection and osteoporosis: pathophysiology, diagnosis, and treatment options. *Curr Osteoporos Rep* 2012; 10:270–277.
51. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* 2012; 26:825–831.
52. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. *J Acquir Immune Defic Syndr* 2009; 51:554–561.
53. Rodriguez M, Daniels B, Gunawardene S, Robbins GK. High frequency of vitamin D deficiency in ambulatory HIV-positive patients. *AIDS Res Hum Retroviruses* 2009; 25:9–14.

54. **Work Group for HIV and Aging Consensus Project.** Summary report from the Human Immunodeficiency Virus and Aging Consensus Project: treatment strategies for clinicians managing older individuals with the human immunodeficiency virus. *J Am Geriatr Soc* 2012; 60:974–979.
55. **National Osteoporosis Foundation.** Clinician's guide to prevention and treatment of osteoporosis. 2013 Issue, Version 3. <http://nof.org/files/nof/public/content/file/2791/upload/919.pdf>. Accessed April 16, 2015.
56. **Heaton RK, Clifford DB, Franklin DR Jr, et al; CHARTER Group.** HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 2010; 75:2087–2096.
57. **Simioni S, Cavassini M, Annoni JM, et al.** Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS* 2010; 24:1243–1250.
58. **Valcour VG.** Evaluating cognitive impairment in the clinical setting: practical screening and assessment tools. *Top Antivir Med* 2011; 19:175–180.
59. **Desquilbet L, Jacobson LP, Fried LP, et al; Multicenter AIDS Cohort Study.** HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. *J Gerontol A Biol Sci Med Sci* 2007; 62:1279–1286.
60. **Desquilbet L, Jacobson LP, Fried LP, et al.** A frailty-related phenotype before HAART initiation as an independent risk factor for AIDS or death after HAART among HIV-infected men. *J Gerontol A Biol Sci Med Sci* 2011; 66:1030–1038.
61. **Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group.** Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56:M146–M156.
62. **Greene M, Valcour V, Miao Y, et al.** Geriatric syndromes are common among older HIV-infected adults. 21st Conference on Retroviruses and Opportunistic Infections (CROI) 2014 March 3–6, Boston MA.
63. **Morgan EE, Iudicello JE, Weber E, et al; HIV Neurobehavioral Research Program (HNRP) Group.** Synergistic effects of HIV infection and older age on daily functioning. *J Acquir Immune Defic Syndr* 2012; 61:341–348.
64. **Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM.** Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; 370:59–67.
65. **Shiels MS, Pfeiffer RM, Gail MH, et al.** Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst* 2011; 103:753–762.
66. **Deeken JF, Tjen-A-Looi A, Rudek MA, et al.** The rising challenge of non-AIDS-defining cancers in HIV-infected patients. *Clin Infect Dis* 2012; 55:1228–1235.
67. **Powles T, Robinson D, Stebbing J, et al.** Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J Clin Oncol* 2009; 27:884–890.
68. **Patel P, Hanson DL, Sullivan PS, et al; Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators.** Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med* 2008; 148:728–736.
69. **Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America.** Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009; 58:1–207.

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