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Review

HIV and aging

Edward J. Wing *

The Miriam Hospital, Brown University, 164 Summit Avenue, Providence, RI 02906, USA

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ABSTRACT

With the wider availability of antiretrovirals, the world's HIV population is aging. More than 10% of the 34.5 million HIV-positive individuals worldwide are over the age of 50 years and the average age continues to increase. In the USA more than 50% of the 1.3 million people with HIV are over 50 years old and by the year 2030 it is estimated that 70% will be over the age of 50 years. Although the life expectancy of HIV-positive people has increased dramatically, it still lags behind that of HIV-negative individuals. There is controversy about whether HIV itself accelerates the aging process. Elevated rates of inflammation seen in people with HIV, even if their viral loads are suppressed and their CD4 counts are preserved, are associated with greater rates of cardiovascular, renal, neurocognitive, oncological, and osteoporotic disease. These conditions increase exponentially in the elderly and will represent a major challenge for HIV patients. In addition, conditions such as geriatric syndromes including frailty are also seen at higher rates. Management of the aging HIV patient includes an emphasis on early diagnosis and treatment, preventative measures for co-morbidities, and avoiding polypharmacy. Finally, the issue of quality of life, prioritization of medical issues, and end of life care become increasingly important as the patient grows older.

1. Introduction

The epidemic caused by the human immunodeficiency virus (HIV) was first recognized in the USA in the early 1980s and shortly afterwards throughout the world. It affected younger populations with devastating effects. Before effective combination antiretroviral therapy (cART) became available in the 1990s, most patients with HIV infection had an inexorable down-hill course dominated by infections, tumors, wasting, and death. Now, in most instances, patients with HIV treated with cART live with their disease successfully.

As people living with HIV age, they face a variety of new challenges including possible accelerated aging and higher rates of co-morbidities such as cardiovascular disease. They also develop geriatric syndromes and frailty earlier than uninfected people. Thus patients with HIV on cART have far less life-threatening acute illnesses, but must confront issues related to the aging process.

The problem of aging in the HIV-positive population has been recognized in high-income countries where the percentage of people over the age of 50 years has increased rapidly, in many cases to over 50%. Because much of the information on aging and HIV has come from these countries, this review will concentrate on reports from the USA and Western Europe. The same trends and the same issues will become important in middle- and low-income countries in the future. This review, therefore, will be increasingly relevant to the care of HIV-positive patients throughout the world.

This article is directed towards the general infectious diseases community, as well as physicians and other practitioners directly caring for patients with HIV. Issues covered include the epidemiology of aging, the question of accelerated aging, co-morbidities, geriatric syndromes and frailty, management, and the unique psychosocial issues facing HIV patients.

2. History

HIV was first recognized in the USA in 1981 as a fatal disease of young gay men and intravenous (IV) drug users. The virus was identified as the cause of HIV in 1983, and by 1985 there was a

* Corresponding author. Tel.: +1 401 793 4151.
E-mail address: Edward_Wing_MD@brown.edu

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serum test to identify infected individuals. The early history is tragically outlined in the *The Band Played On* by Randy Shilts, published in 1987. By 1996 in the USA and Western Europe, there was widespread use of effective combinations of antiretroviral drugs initially termed highly active antiretroviral therapy or HAART and now referred to as cART. The death rate from HIV began to fall in 1996 in the USA, and the further availability of cART worldwide saw a global decline in new cases for the first time in 2012. This remarkable reversal of the prognosis of HIV caused a dramatic shift in the demographics of people living with HIV.

3. Epidemiology of aging in people living with HIV

The age of people living with HIV has been rising steadily, largely due to the success of cART. An estimated 3.6 million of the 35.6 million people worldwide living with HIV are over the age of 50 years and this trend is increasing steadily.[1] In countries where the epidemic was recognized earlier and effective therapy was available in the mid-1990s, the age of people living with HIV has increased dramatically. For example, in the USA approximately 40% of people living with HIV in 2012 were over the age of 50 years and 11% were over the age of 60 years.[1] By 2015 it was estimated that 50% of people were over the age of 50 years. Less appreciated are data indicating that 18% of newly diagnosed patients are over the age of 50 years.[2] Both of these factors, aging and new acquisition later in life, have pushed up the average age of people living with HIV.

A geographically specific example of this rise is demonstrated by data from San Francisco, one of the epicenters of the epidemic in the 1980s and 1990s. In 1990, the percentage of people living with HIV in San Francisco who were over the age of 50 years was 10%. By 2010 it had reached 50%.[3] Similar data have been reported from New York City (New York City HIV/AIDS Annual Surveillance Statistics 2013) and France.[4]

The same trends, although delayed, have also been documented in low- and middle-income countries.[1]

4. Mortality and lifespan

There is great heterogeneity in the mortality figures and life expectancy of people with HIV, driven by factors such as patient virological suppression, CD4 nadir, time of diagnosis, and IV drug use. Nonetheless, the overall mortality rate has fallen dramatically.[5] Despite these advances, mortality rates in selected HIV-infected populations range from 1.7- to 7.0-times those of HIV-uninfected populations.[6–10] Of great interest, subgroup analyses indicate that mortality approaches the uninfected population if the diagnosis of HIV is made early in the course of the disease, the CD4 count is maintained at >350–500 cells/μl, and the viral load is suppressed.[6]

Similarly, calculated life expectancy, which is based on mortality data, has risen since the late 1990s, but it is still only two-thirds that of the general population.[7,11–16] As with mortality data, subgroup analyses indicate that those who achieve a CD4 count of above 350 cells/μl and viral suppression in the absence of other risk factors have a life expectancy that is similar to the general population.[16]

Caution regarding these studies, particularly the subgroup analyses, is warranted. Patients in some cohort analyses are not representative of the overall HIV-positive population, appropriate HIV-uninfected controls are difficult to identify, and data on aging are still preliminary for the HIV epidemic. In particular, it is difficult to control for differences in lifestyle factors, socio-economic status, risk factors for co-morbidities, nutrition, safe environment, ethnicity, social isolation, and chronic infections such as those caused by hepatitis and herpes viruses. The issues in identifying appropriate non-HIV-infected control populations has been reviewed recently.[17]

A recent article compared life expectancy of HIV-positive and matched HIV-negative individuals (rather than the general population) cared for in the Kaiser Permanente Health System in California from 1996 (at the beginning of widespread cART in the USA) to 2011.[18] The life expectancy at age 20 years of an HIV-positive individual rose from 19.1 years to 53.1 years by 2011, but was still less than that of HIV-negative individuals (64.9 years). After controlling for risk factors including cART therapy, smoking, substance abuse, and hepatitis virus infection, a gap between HIV-positive and HIV-negative individuals of almost 6 years of life expectancy was still demonstrated. Thus the best data, i.e. HIV-positive individuals compared to matched HIV-negative individuals rather than the general population, indicate a continuing gap in life expectancy for HIV-positive individuals compared to those who are uninfected.

5. Changing causes of death

Data on cause of death from six different cohorts in developed countries after 1996 have demonstrated a dramatic fall in the rate of AIDS-related infections and malignancies. The rate of non-AIDS-related causes of death has fallen as well, but not as dramatically.[5,19–23] These studies show widely varying causes of death depending on the characteristics of each cohort, but some important trends are clear. In the cART era, HIV-related causes of death remain important, but occur primarily in patients with delayed or ineffective treatment (non-adherence, drug resistance, poor CD4 recovery). The rates of liver disease, cardiovascular disease, and non-HIV-related infection have either fallen slightly or remained the same in the cART era. In contrast, the rate of death caused by non-HIV-related malignancies has increased.[19,23] Other causes of death in the cART era include non-AIDS-related infections, renal disease, substance abuse, violence, and suicide.[6,20]

6. Does HIV accelerate aging?

The data quoted above suggest that HIV itself may accelerate the aging process. Aging has been broadly defined as "the time-dependent functional decline that affects most living organisms."[24] Multiple biological mechanisms for aging have been described, some of which may affect HIV-positive individuals at higher rates.[24,25] These mechanisms are discussed in detail by Lopez-Otin et al.[24] and include genetic instability, telomere shortening, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. The latter includes abnormal endocrine and neuroendocrine signaling, as well as immune dysregulation. Immune dysregulation, immune cell senescence, and chronic inflammation found even in HIV-positive patients virally suppressed on cART appear to be most important. For example HIV-positive individuals have increased serum levels of interleukin (IL)-6, a marker of inflammation that is associated with chronic illnesses including cancer and cardiovascular disease, with overall fitness, as well as with increased mortality.[26–29] Other biomarkers have also been shown to be increased in HIV-positive patients, including D-dimer, a pro-thrombotic protein.[30,31] There are probably multiple mechanisms accounting for increased inflammation in HIV-positive individuals, as outlined below.

1. Low-level tissue viral infection with HIV, even in patients treated with effective cART who have undetectable serum virus. While controversial, recent evidence based on both tissue and

peripheral blood of patients on cART indicates ongoing tissue viral replication.[32–34] Both studies used genetic analysis to estimate viral evolution and mutation over time . In spite of cART, viral evolution continued for 6 months in one study and for 6 years in the other, suggesting ongoing tissue replication despite cART. It is important to note that viral evolution is not a direct measure of tissue viral replication. Analysis of the data from these studies required sophisticated statistical methods to infer tissue viral replication. Thus, further studies including more direct methods will be required to confirm these findings.
2. Chronic viral reactivation of herpes viruses, particularly cytomegalovirus, in HIV.[35]
3. Microbial translocation, i.e. penetration of gut microbes and their products into the systemic circulation due to abnormal gut immunity despite effective cART.[36]
4. Immune dysregulation and senescence with depletion of CD4+ T cells, increased numbers of senescent CD8 T cells (CD57 + CD28 −) that secrete cytokines, and increased monocyte activation.[37] Immune senescence occurs at a younger age in HIV-infected patients than in elderly non-HIV-infected persons. Functionally, this results in a decreased ability to respond immunologically to new antigens, pathogens, and vaccines, as well as an increased inflammatory state.

Interestingly, each of these mechanisms has also been described in elderly HIV-negative individuals as part of the normal aging process.[38]

Other biological mechanisms of aging have also been described in HIV-positive persons at higher rates, including mitochondrial dysfunction, dysfunction of the growth hormone/insulin-like growth factor/insulin pathway that regulates cell growth and metabolism, telomere shortening, and epigenetic changes.[24]

Whether these inflammatory and immune changes translate into accelerated aging is controversial.[38,39] It is important to emphasize that changes in inflammation, immune dysfunction, physical functional changes, e.g. geriatric syndromes and frailty (see below), and co-morbidities have not always been correlated. While each of these has been identified in HIV-positive populations, it is not clear that they cause accelerated aging.

Arguments supporting accelerated aging processes in HIV patients include the presence at younger ages of the following changes: (1) increased rates of chronic co-morbidities, (2) increased rates of geriatric syndromes and frailty, (3) senescent immune changes, and (4) persistent increased inflammatory markers termed inflamm-aging.[40] Consistent with these findings are the increased mortality and reduced lifespan of HIV-positive populations compared to the general population.

However, arguments against accelerated aging in HIV-positive patients include the fact that the life expectancy of HIV-positive patients with CD4 counts >500 cells/μl and suppressed viral loads on cART in some cohorts is no different to that of the general population.[7,15,16] In addition while co-morbidities occur at higher rates in the HIV population for any given age, the rate of co-morbidities does not increase with the length of time a person is infected with HIV. HIV may be a risk factor for co-morbidities, but does not appear to accelerate their occurrence over time.[41,42]

Further mechanistic and epidemiological data will be needed to clarify this ongoing controversy.

7. Increased risk of chronic non-AIDS diseases in HIV-positive patients

Patients with HIV have an increased number of co-morbidities compared to those without HIV.[43] These co-morbidities occur at high rates at all ages in HIV-positive patients, but will become increasingly important as this population ages. The following sections review data indicating increased risk in HIV-positive people for certain co-morbidities.

7.1. Cardiovascular disease and stroke

In the pre-cART era, HIV-positive patients were at risk of myocarditis and dilated cardiomyopathy, usually associated with a low CD4 count.[44] With the advent of effective cART, these conditions have faded, and HIV-positive patients are recognized to be at increased risk of chronic cardiovascular disease including coronary artery disease, myocardial fibrosis, congestive heart failure, and ischemic stroke.[45–47] For example, data from the Veteran Aging Cohort Study in HIV-positive individuals showed a 1.5-times increased risk of acute myocardial infection and a 1.17-times increased risk of stroke at all ages, even in those with suppressed viral loads.[48,49] Similar increased risks have been noted in other cohort studies, although the risk seems to have decreased in recent years, perhaps due to improved risk reduction through the use of statins.[50,51] Certain antiretroviral drugs may increase cardiovascular risk, including protease inhibitors, which induce a poor metabolic profile including hyperlipidemia compared to other drugs such as integrase inhibitors. The association of abacavir with cardiovascular disease noted in early studies has not been confirmed in all studies and remains controversial.[47] Other cardiovascular risk factors seen commonly in HIV-positive populations include smoking, hypertension, insulin resistance, increased inflammatory and thrombotic markers, and more recently obesity.

7.2. Osteoporosis and fracture

Osteopenia and osteoporosis in HIV patients are increased compared to the general population; the cause is likely multifactorial. Risk factors such as substance abuse (particularly alcohol), smoking, low body weight, and vitamin D deficiency contribute to the increased risk in HIV-positive patients.[52] In addition, the direct effects of cART, particularly those due to protease inhibitor-based and tenofovir-based regimens, predispose to loss of bone density.[53] Chronic HIV infection itself is also a contributor, as HIV infection appears to confer an increased risk of osteoporosis in cross-sectional cohort-based studies. The risk of fracture in HIV-infected individuals has been found to be increased almost three-fold.[42,54]

7.3. Metabolic syndrome and diabetes mellitus

The metabolic syndrome has been characterized by central obesity, hypertension, and metabolic abnormalities such as high fasting blood glucose and low high density lipoprotein levels, which confer a significant risk for cardiovascular disease and diabetes.[55,56] The risk of metabolic syndrome in HIV patients, relative to non-HIV patients, has been found to be increased in some studies and decreased in others.[56,57] Similarly, the risk of developing diabetes mellitus in HIV populations is not well established.[58] Studies earlier in the epidemic, when early cART regimens predominated, demonstrated an increased risk of diabetes mellitus in HIV-positive patients, whereas later studies have not consistently shown this relationship.[59]

7.4. Renal disease

Early in the HIV epidemic, a unique form of progressive renal disease was recognized primarily in African Americans, termed HIV nephropathy.[60] With the introduction of effective cART in the 1990s, the incidence of HIV nephropathy decreased markedly. However, the current prevalence of chronic renal disease remains

increased at all ages in HIV-positive individuals compared to uninfected individuals.[42,61] The prevalence of chronic kidney disease stage ≥3 (glomerular filtration rate of 30–59 ml/min) has ranged from 3.5% to 9.7%.[61] Risk factors for renal disease in HIV-positive individuals include age, black race, diabetes mellitus, hypertension, low CD4 counts, high viral loads, inflammatory markers, and certain cART drugs such as tenofovir.[62]

7.5. Chronic neurological complications

In the pre-cART era, neurological disease in AIDS patients was dominated by infectious complications of AIDS (CD4 <200 cells/μl), as well as HIV-associated dementia, myelopathy, and peripheral neuropathy.[63]

Despite a dramatic decrease in these conditions in the era of cART, HIV infection continues to be associated with neurocognitive disease termed HIV-associated neurocognitive disorders or HAND.[64] Approximately 50% of all HIV-positive individuals have some degree of neuropsychological impairment. Most are asymptomatic, but up to 12% may have mild and 2% severe disorders.[42,64] The risk of dementia in one cohort was increased for older HIV-infected patients (>50 years old) compared to younger HIV-infected patients (20–39 years old) by more than three-fold.[65] Changes seem to correspond to changes in brain volume.[66] Risk factors for HAND include age, history of immune suppression, other co-morbidities and disease indicators, psychiatric disorders, IQ, previous brain trauma, and infection, as well as co-infection with hepatitis C virus (HCV).[67,68] Unlike Alzheimer's disease, HAND is not necessarily progressive.[67,69] Treatment with both pharmacological and non-pharmacological approaches is an area of active research.[70,71] As the HIV-positive population ages, the intersection of HAND with age-related neurological conditions including dementia and Alzheimer's disease will be of great importance.

7.6. Malignancies

Increased rates of Kaposi's sarcoma and non-Hodgkin B cell lymphoma were recognized early in the HIV epidemic. Kaposi's sarcoma had rates of 1000 times and non-Hodgkin B cell lymphoma had rates 100 times those in non-HIV populations.[72] Subsequently other malignancies were noted to occur more frequently in HIV patients, including primary central nervous system lymphoma, invasive squamous cell carcinoma of the cervix, lung cancer, anal cancer, Hodgkin lymphoma, liver cancer, and head and neck squamous cell cancer. With the advent of effective cART in the mid-1990s, a dramatic fall in the incidence of many malignancies, particularly Kaposi's sarcoma and non-Hodgkin B cell lymphoma, was noted.[73–75] The incidence of other virally related cancers, however, has either remained the same or has increased somewhat.[42] Rates of skin and lung cancer remain high, but the rates of breast, colon, and prostate cancers are not increased when compared to the general population.[76,77]

As the HIV-positive population ages, the rates of all cancers, particularly lung, prostate, colorectal, and breast, will increase.[78] The estimated cumulative incidence of cancer by the age of 75 years for HIV-positive patients is increased for Kaposi's sarcoma, non-Hodgkin B cell lymphoma, lung cancer, anal cancer, liver cancer, and Hodgkin lymphoma, in HIV-positive individuals.[76] Furthermore, cancer-related mortality rates for HIV-positive patients remain high for many cancers.[79]

7.7. Quality of life in older patients with HIV

Older patients with HIV face a number of factors that affect their quality of life, including increasing physical disabilities and morbidities, psychiatric illnesses, losses of partners and friends, social isolation, and stigma. Added to this are additional stressors often experienced by older HIV patients, including unemployment, poverty, and crime. In a poignant qualitative study, the changes experienced by aging HIV-positive patients were categorized as physical challenges, internal changes, stigma, and in particular, a sense of lost community and social support described by one participant as "a shrinking kind of life".[80]

In a case-controlled study from San Diego, older HIV-positive patients were found to have worse physical and mental functioning and greater psychosocial stress than HIV-negative patients.[81] Interestingly, however, there were no differences in measures of optimism, personal mastery, and social support. In a separate study, HIV patients with strong resilience measures seemed to manage the stress of aging, including physical and emotional challenges, better than those who had weak resilience measures.[82] Interventions focusing on improving factors such as social support and resilience may improve the quality of life of HIV-positive patients who are aging.

7.8. Geriatric syndromes and frailty

The term 'geriatric syndromes' has been used to describe a wide variety of conditions associated with aging that predict adverse clinical outcomes.[83] For HIV patients, geriatric syndromes generally include the following: falls, urinary incontinence, difficulty with activities of daily living, slow gait, sensory deficits such as hearing and sight loss, and neurocognitive impairment.[84]

Studies have demonstrated a high incidence of geriatric syndromes in HIV-positive individuals over the age of 50 years.[84] In one study, more than half (53%) of the individuals had two or more geriatric syndromes, with the most frequent conditions being prefrailty (modified Fried criteria–see below), difficulty with activities of daily living (ADLs), and neurocognitive impairment.

Geriatric syndromes include frailty, which by itself confers a risk of morbidity, hospitalization, and mortality. The Fried criteria, which represent the most commonly accepted definition of frailty, are based on the assessment of weight loss, strength, endurance, walking speed, and activity level.[85] Multiple studies have demonstrated that patients with HIV are more susceptible to developing frailty at earlier ages than the general population,[86,87] and thus are more susceptible to adverse outcomes.[88] Risk factors for frailty include low current CD4 and low nadir CD4 counts, other co-morbidities such as hepatitis C, central obesity, and other geriatric syndromes, as well as social factors including lower education.[86]

As the HIV-positive population ages, the rates of frailty will increase and will represent an important challenge for clinicians. Although few data exist on the prevention or treatment of frailty, potential strategies include early diagnosis and treatment of HIV, identifying and treating co-morbidities, and exercise.[86,89]

8. Care of the patient

Recommended guidelines for the treatment of older patients with HIV can be found in the executive summary of the HIV and Aging Consensus Project, a joint project between the American Academy of HIV Medicine, the American Geriatrics Society, and the AIDS Community Research Initiative of America,[90] and in the guidelines for the treatment of HIV-positive individuals available from the Department of Health and Human Services (DHHS) (http://aidsinfo.nih.gov). An overall approach to the care of the older patient with HIV can be found in the article by Greene et al.[91] Also important for the care of the elderly patient are the *Primary Care Guidelines for the Management of Persons Infected with HIV: 2013 Update* by the HIV Medicine Association of the Infectious Diseases Society of America (IDSA).[92] The following are brief comments regarding the above guidelines for diagnosis and

Table 1
Suggested management guidelines for newly diagnosed HIV patients over 50 years of age[a]

	Recommendations	Comments
1.	Comprehensive history, including sexual history and physical examination	Include screening for hypertension, obesity, depression (e.g., Geriatric Depression Scale), smoking and substance abuse
2.	Complete blood and chemistry panel	
3.	Plasma HIV RNA (viral load)	Once stable on cART every 6 months
4.	Blood CD4 count and percentage	Once stable on cART every 6–12 months
5.	HIV resistance testing	Initially and for elevated viral load
6.	Treatment with cART for all patients by August 1, 2016 guidelines	Follow DHHS guidelines http://aidsinfo.nih.gov/guidlines
7.	Screening for syphilis, chlamydia, gonorrhea	Repeat periodically if indicated
8.	Fasting lipids and cardiovascular risk	Lipids initially and 3 months after starting cART; base treatment on ACC/AHA guidelines (http://www.nhlb.nih.gov)
9.	Urinalysis, creatinine clearance, and urine protein	Annually
10.	Hepatitis A, B, C screening	Vaccination (A, B) and treatment (C)
11.	Tuberculosis screening	Repeat if indicated
12.	Vaccination for influenza	Annually
13.	Vaccination for pneumococcal infection	
14.	Cervical Pap and HPV screen	Initially; if negative every 3 years; http://aidsinfo.nih.gov/guidelines
15	Baseline DEXA screen for men and women >50 years of age	
16.	Fasting blood glucose and HbA1c for diabetes	Initially, 1–3 months following initiation of cART, and then annually
17.	Mammography for women >50 years	Annually
18.	Colonoscopy	Age 50–75 years
19.	Low resolution lung CT cancer screening	>30 pack/year smoking history who smoke or quit in the last 15 years; age >55–80 years; annually
20.	Ultrasound for abdominal aortic aneurysm	Men age 65–75 years who have ever smoked
21.	Chest X-ray	If positive TB test or presence of other pre-existing lung condition

cART, combination antiretroviral therapy; DHHS, Department of Health and Human Services; ACC/AHA, American College of Cardiology/American Heart Association; HPV, human papillomavirus; DEXA, dual-energy X-ray absorptiometry; HbA1c, glycated hemoglobin; CT, computed tomography; TB, tuberculosis.
[a] Guidelines are based on Aberg et al.[92] and the Department of Health and Human Services guidelines (http://aidsinfo.nih.gov/guidelines for the care of patients with HIV).

treatment, behavioral risks, screening and prevention, and prioritization of elderly HIV-positive patients. Table 1 summarizes suggested management guidelines for newly diagnosed HIV patients over 50 years of age.

8.1. Diagnosis and treatment of HIV

The diagnosis of HIV remains a problem in older patients, as screening and diagnosis of older patients for HIV has not been emphasized and is frequently overlooked by both physicians and patients. Data indicate that 18% of newly diagnosed patients are over the age of 50 years.[2] Screening for HIV should be considered for all older adults.[90]

Treatment with cART should be offered to all HIV-positive patients unless there is a medical or pharmacological contraindication. A recent study indicated that patients in the age range 45–60 years have a higher mortality than younger patients if antiretroviral treatment is delayed.[93] Key considerations include the following:

1. All patients over age 50 years should be offered cART treatment for HIV. Guidelines are available at http://aidsinfo.nih.gov/guidelines.
2. The choice of cART will be influenced by underlying co-morbidities (e.g., renal disease).
3. Resistance testing should be performed at the time of initiation of cART.
4. cART side effects including bone, kidney, metabolic, cardiovascular, and liver are more common in the elderly, and side effects should be monitored carefully. Newer drug options, such as tenofovir alafenamide in place of tenofovir disoproxil fumarate, may reduce side effects such as bone and renal toxicity.[94]
5. Routine monitoring of CD4 count and HIV RNA levels should be done according to guidelines. CD4 responses to cART are reduced in older patients compared to younger patients, and this poor response may be related to greater clinical progression.[95,96] There are no differences in virological responses between older and younger patients.
6. Because of polypharmacy, older patients are more prone to drug–drug interactions. Drug–drug interactions have been reviewed recently.[97]
7. Although adherence by older adults may be better than younger ones,[98] a recent study using Medicaid data on over 5000 patients indicated that only 32% of participants had optimal adherence.[99] An increased number of co-morbidities and living in rural areas and small metropolitan areas were risk factors for lower adherence.

8.2. Behavioral risk factors for HIV

Many people with HIV have higher rates of smoking,[100] substance abuse including alcohol,[101] and low fitness and physical activity levels.[102] Each of these behaviors should be assessed at the initiation of care, and strategies to address these issues should be discussed with the patient. Smoking in particular has been shown to increase the risk of cardiovascular disease, chronic lung disease, and malignancy in HIV-positive individuals. With the rise in obesity, HIV individuals will be at risk of diabetes mellitus and hypertension. Nutritional advice and weight reduction programs should be offered.

A sexual history should be taken at each visit. As with other HIV-positive populations, and consistent with primary care guidelines, patients should be screened for high-risk sexual behavior and evidence of sexually transmitted infections at each visit. Prevention including behavioral and pharmacological approaches (pre-exposure prophylaxis or PrEP) should also be emphasized with this population if appropriate.

8.3. Screening and prevention for co-morbidities

Standard guidelines for HIV-negative individuals should be followed for the screening, risk assessment, and treatment of both cardiovascular disease and dyslipidemia for HIV-positive patients (for example the American College of Cardiology/American Heart Association risk calculator). Screening hyperlipidemia should be

performed before and 1–3 months after starting cART. Drug–drug interactions of hydroxymethylglutaryl coenzyme A (HMG co-A) reductase inhibitors with cART are a concern in HIV-positive individuals with indications for statins.[97] These can be minimized by using pravastatin, pitavastatin, and to some extent, low-dose atorvastatin and rosuvastatin.

Older patients with HIV are particularly prone to renal disease secondary to drugs (e.g., tenofovir), HIV itself (HIV nephropathy (HIVN)), hypertension, or diabetes. All HIV-positive patients should have annual measurements of serum creatinine and urinary protein excretion.

All HIV patients should be screened for hepatitis A, B, and C initially, and appropriate vaccinations should be given if the patients are not immune to hepatitis A virus or hepatitis B virus. Identification of hepatitis C has become particularly important, because patients co-infected with HIV and HCV have an increased risk of developing progressive cirrhosis as well as hepatocellular carcinoma. Because of the truly remarkable advances using oral treatment for hepatitis C, most patients co-infected with HIV and HCV should be considered for treatment.[103] Individuals co-infected with HIV and HCV have been listed as 'high priority' for treatment in the latest American Association for the Study of Liver Disease (AASLD) guidelines.

Other immunizations, including yearly influenza vaccination and appropriate vaccination for pneumococcal disease, are important preventative measures.

Cancer screening by current guidelines is important because of the increased risk of cancer as patients age (see above). DHHS guidelines recommend that HIV-infected women should have a cervical Pap test and human papillomavirus (HPV) testing initially, and if negative repeated every 3 years (DHHS guidelines at http://aidsinfo.nih.gov/guideliness). Although controversial, many practitioners recommend that HIV-infected men, HIV-infected women practicing receptive anal intercourse, and those with anal warts should have an annual anal Pap test.

Screening for osteoporosis by bone density scanning and assessment of the risk of fracture should be performed (e.g., FRAX calculator) in older patients, and treatment should be offered when appropriate.[104] IDSA guidelines recommend screening for osteoporosis at age 50 years for HIV-positive individuals, rather than age 65 years as recommended for the general population. Preventative therapy with vitamin D (HIV patients are often vitamin D deficient) and calcium should be routine in older HIV-positive patients.[105]

Dysregulation of endocrine pathways may occur in HIV individuals. Screening for diabetes mellitus consisting of a fasting blood glucose and glycated hemoglobin (HbA1c) should be obtained prior to and within 1–2 months after starting cART. Similarly, screening for hyperlipidemia should be performed before and 1–3 months after starting cART. Hypogonadism hallmarked by decreased libido and erectile dysfunction is common in elderly HIV-positive men, and, if indicated, should be screened for with a morning serum testosterone level. Androgen replacement therapy may be indicated if testosterone levels are low. Although controversial, hormone replacement therapy for menopausal women in those with severe menopausal symptoms can be considered.[92]

Older patients should be screened for depression (with tools such as the Geriatric Depression Scale), and, if present, treatment with selective serotonin reuptake inhibitors (SSRIs) or cognitive and behavior therapy should be considered as first-line therapy.[106] Non-benzodiazepine agents are preferred for the long-term treatment of anxiety, particularly because of concern for drug–drug interactions with benzodiazepine agents (especially diazepam, alprazolam, and midazolam). In addition, patients should be screened for neurocognitive impairment and referred for treatment if appropriate. A widely used although imperfect tool to determine neurocognitive impairment is the Montreal Cognitive Assessment.[107]

Polypharmacy is a major risk for HIV-positive patients because cART consists of at least three drugs and the treatment of co-morbidities often brings the total to 10 or more drugs. Data from non-HIV geriatric populations indicate that taking five or more drugs increases the risk of adverse drug events, drug interactions, inappropriate medication use, delirium, falls, fractures, and poor adherence. Medication interactions between cART and other medications are a major consideration, particularly the cytochrome p450 inhibition that occurs with protease inhibitors (e.g., darunavir) and non-nucleoside reverse transcription inhibitors (e.g., efavirenz). Regular review of all medications prescribed to a patient with regard to drug interactions, toxicity, and necessity is important.

8.4. Prioritization

Perhaps most important is to recognize that HIV-positive patients develop an increasing number of co-morbidities as they age. Stages of aging, priority driven care for co-morbidities, and issues of social isolation in the aging are discussed in more detail in the article by Greene et al.[91] The expectations of aging patients and the appropriate therapy for these patients will be different than those of younger patients and will evolve over time. For example, aggressive therapy of an advanced medical condition may be inappropriate for an older patient whose quality of life may be far more important than the potential benefit of treatment with risks and side effects. Communication between care givers and the patient becomes essential in establishing agreed-upon goals of treatment. Finally, advance directives are frequently overlooked in the care of HIV-positive patients, but take on increased importance for the elderly patients.

The prognosis of people living with HIV has improved dramatically over the past 20 years, but increased rates of co-morbidities as well as frailty and neurocognitive changes as they age pose challenges to patients and their caregivers. Early diagnosis, appropriate treatment and prevention, as well as appropriate geriatric care, will be essential to the wellbeing of this important patient population.

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