

Management of Human Immunodeficiency Virus Infection in Advanced Age

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THE PATIENT'S STORY

Mr H is a 74-year-old man who was diagnosed with human immunodeficiency virus (HIV) in 1984. He has chronic fatigue and has experienced a 10-lb weight loss over the past 2 years. His current CD4⁺ T-lymphocyte count is 440 cells/ μ L, with a nadir of 140 cells/ μ L occurring in 1991. He has never had opportunistic infections. His plasma HIV RNA level (viral load) has been undetectable since 1996. Mr H participated in the original zidovudine (AZT) monotherapy clinical trial in 1988 and subsequently received a total of 7 nucleoside reverse transcriptase inhibitors (NRTIs) and 6 protease inhibitors before starting his current regimen of emtricitabine/tenofovir and ritonavir-boosted fosamprenavir. He receives treatment at an infectious disease clinic in an urban, tertiary care Veterans Affairs hospital, where his follow-up is led by Dr L and a team that includes an infectious diseases pharmacist, a nutritionist, and a social worker.

Mr H vigilantly adheres to his antiretroviral regimen. Even when offered new antiretroviral medications, he prefers to stay with his current regimen. He has hypertension, hyperlipidemia, osteoporosis, depression, atherosclerotic subclavian steal syndrome with stent placement, chronic kidney insufficiency, adenomatous colon polyps, and past anal squamous cell carcinoma. His other medications are rosuvastatin (hyperlipidemia), testosterone (low testosterone level), bupropion (depression), fenofibrate (hypertriglyceridemia), and lorazepam (anxiety; taken as needed). Due to episodic dizziness and fluctuating blood pressure, hydrochlorothiazide and metoprolol were recently discontinued.

Mr H was a computer systems analyst until his late 40s when he was diagnosed with HIV. He lives with a partner, but voices concerns for social isolation from the deaths of many HIV-positive acquaintances. He participates in a support group of older adults with HIV run by a psychologist. Mr H is a former smoker and drinks a glass of wine with dinner. He never drank alcohol heavily and never used recreational drugs. He is currently not sexually active.

Initial evaluation of his fatigue and weight loss revealed no anemia and his pharmacist found no medication-based association with his symptoms. Dr L discussed testing for malig-

Importance Human immunodeficiency virus (HIV)-positive patients treated with antiretroviral therapy now have increased life expectancy and develop chronic illnesses that are often seen in older HIV-negative patients.

Objective To address emerging issues related to aging with HIV. Screening older adults for HIV, diagnosis of concomitant diseases, management of multiple comorbid medical illnesses, social isolation, polypharmacy, and factors associated with end-of-life care are reviewed.

Evidence Acquisition Published guidelines and consensus statements were reviewed. PubMed and PsycINFO were searched between January 2000 and February 2013. Articles not appearing in the search that were referenced by reviewed articles were also evaluated.

Findings The population of older HIV-positive patients is rapidly expanding. It is estimated that by 2015 one-half of the individuals in the United States with HIV will be older than age 50. Older HIV-infected patients are prone to having similar chronic diseases as their HIV-negative counterparts, as well as illnesses associated with coinfections. Medical treatments associated with these conditions, when added to an antiretroviral regimen, increase risk for polypharmacy. Care of aging HIV-infected patients involves a need to balance a number of concurrent comorbid medical conditions.

Conclusions and Relevance HIV is no longer a fatal disease. Management of multiple comorbid diseases is a common feature associated with longer life expectancy in HIV-positive patients. There is a need to better understand how to optimize the care of these patients.

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nancy or other disorders causing weight loss, but Mr H initially declined. Mr H retains medical decision-making capacity and has specified that he not receive resuscitation or intubation should he experience a cardiopulmonary arrest.

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Mr H and Dr L were interviewed by a Care of the Aging Patient editor in 2012.

Perspective

Mr H: *When you got HIV in those days it was a death sentence. That was what was expected—you would die. To live even 5 years was a surprise to me.*

Dr L: *(I met Mr H) about 7 years ago . . . His HIV needs were fairly well controlled. But he was already middle aged and experiencing middle-aged types of medical issues. HIV is still something we address at each of our appointments but it really has retreated into the background.*

PUTTING MR H'S CARE INTO CONTEXT

Aging of the HIV-positive population is an unexpected development in the history of the HIV/AIDS epidemic. The first US case of HIV-1 was reported more than 3 decades ago. Progressive immunodeficiency with opportunistic infections, AIDS-related malignancies, and death were hallmark features until the mid-1990s when combination antiretroviral therapy (ART) produced durable reductions in mortality. Medication improvements resulted in better tolerability and reduced pill burden, which facilitated adherence with sustained immunologic and virologic responses. By 2005, a 20-year-old HIV-positive non-injection drug user from a high-income country could expect to live to age 65 years.¹ Longer life expectancy is seen in all settings where there is access to combination ART; it is estimated that one-half of HIV-positive individuals in the United States will be older than age 50 by 2015. Eleven percent of incident infections in the United States between 2006 and 2009 occurred among individuals older than age 50.² In the United States, HIV rates for older African Americans are 12 times higher than that of older white individuals and 70% of older HIV-positive women are African American or Hispanic/Latina.^{3,4}

In the modern era (since combination ART), AIDS has evolved into a chronic disease, and for older HIV-positive patients, there are new challenges with polypharmacy and comorbidity. We conceptualize the care of older HIV-positive patients into 3 stages: early care, which focuses on HIV screening, diagnosis, and initiation of treatment; chronic care, which emphasizes maintenance of HIV treatment and management of non-HIV comorbidities; and advanced care, which considers goals of care and end-of-life planning.

METHODS

We searched PubMed and PsychINFO (for social isolation) using MeSH terms *HIV infections* and *AIDS seropositivity*, with limits of English language, aged, middle aged, aged 80 and older, and articles published between January 2000 and February 2013. For the early-stage care section, MeSH terms were *diagnosis*, *screening*, *medication adherence*, and *patient compliance*; for polypharmacy, *inappropriate prescribing*, *polypharmacy*, *polymedical*, and *drug interactions*; for social isolation, *social isolation*, *social support*, and *loneliness*. All peer-reviewed articles were considered.

We selected articles that focused on older HIV-positive adults (defined as 50 years and older based on literature consensus), examined differences between older and younger HIV-positive individuals, or contained a significant sample of older HIV-positive adults. If necessary, we referenced articles of younger HIV-positive participants, HIV-negative older adults, and articles published before the combination ART era (late 1990s). Due to the relative infancy of published literature on the clinical care of aging HIV-positive patients, we included expert consensus guidelines. Additionally, we incorporated emerging data from the developing world whenever possible, although our work reflects that most existing data are based on studies from the developed world.

Early-Stage Care

Prevention and Screening. The diagnosis of HIV in older patients is often delayed, in part due to a perception that HIV is an infection of younger individuals, that sexual activity is uncommon in older adults, and by the nonspecific nature of HIV-presenting symptoms.⁵⁻⁷ After age 50, only 38% of US men and 22% of US women report discussing sexual activity with their physician.⁸ One-fourth of US adults older than age 50, without obvious risk for HIV acquisition, are screened for HIV.⁹ Older adults often lack an understanding of HIV transmission, do not perceive self-risk, and are less likely than younger individuals to use condoms—even when they have multiple sexual partners.⁹⁻¹² Among older drug users, some high-risk behaviors, such as needle sharing, may be less frequent than among younger individuals, but sexual risk taking, including sex in exchange for money or drugs, is not.¹³ In women, age-associated physiological changes including vaginal mucosa thinning and altered immunologic barriers increase HIV transmission risk.

Most US guidelines recommend HIV testing among high-risk groups regardless of age; however, routine screening recommendations differ. The US Preventive Services Task Force has no recommendation for or against routine screening for HIV in adolescents and adults who are not at increased risk for HIV infection.^{14,15} The Centers for Disease Control and Prevention (CDC) recommends that screening be offered to all patients aged 13 to 64 years and to all pregnant women, giving them the ability to opt out of testing if they do not want to be tested. Separate consent for HIV testing is not recommended and, according to the CDC, HIV testing should be covered under a general permission form (consent form) that is signed for all medical care.¹⁶ However, the joint American Academy of HIV Medicine, the American Geriatrics Society, and the AIDS Community Research Initiative of America guidelines recommend routine opt-out screening, regardless of age,¹⁷ because screening in adults up to age 75 is likely cost effective in settings where prevalence is 0.1% or higher,¹⁸ and clinicians may have difficulty estimating local prevalence and individual risk. HIV infection should be routinely considered in the differential diagnosis for unexplained systemic signs and symptoms, including atypical pneumonias, anemia, fever, weight loss, rapid cognitive decline, and fatigue (BOX).

Box. Disease-Stage Summary of Care**Early-Stage Care**

Clinicians should discuss sexual history with their patients

Routine screening for human immunodeficiency virus (HIV) in older adults is recommended

Clinicians should have increased awareness of atypical presentation of HIV in older adults

Antiretroviral therapy should be started in all older patients regardless of CD4 T-lymphocyte count

No specific guidelines exist for choosing antiretroviral drugs in older HIV-positive adults; the choice of antiretroviral drugs depends on factors such as pill burden, dosing frequency, comorbid diseases, drug interactions, and local drug availability

Education should be emphasized on HIV transmission reduction strategies, adherence with antiretroviral drugs, and retention in care

Chronic-Stage Care

Treatment should consider that HIV-associated non-AIDS conditions are more likely to impact mortality than HIV

Management of comorbidities should be prioritized (especially cardiovascular, hepatic, renal, bone, central nervous system)

Modifiable lifestyle risk factors, focusing on health maintenance and prevention, should be addressed

Risk for polypharmacy and drug-drug interactions in older HIV-positive adults should be considered

Risk for social isolation in older HIV-positive adults should be considered because social support can impact health outcomes

Advanced-Stage Care

Palliative care is reemerging as an important component in older HIV-positive patients

Best models of care are not well defined but will require integration of HIV, primary care, and geriatric expertise

Chronic- and Advanced-Stage Care

Prognosis becomes an increasingly important component of decision making related to screening, adding medications, and considering invasive treatments

Ongoing discussions and documentation of end-of-life preferences, choice of living environment, and safety should be completed

Initiating Treatment. Well-established guidelines for initiation of antiretroviral medication differ by country, with many adopting or modifying World Health Organization (WHO) guidelines.¹⁹ In the United States, clinicians typically adhere to the US Department of Health and Human Services or the International Antiviral Society-USA guidelines, both of which recommend initiation of therapy regardless of CD4 T-lymphocyte count for all ages.^{20,21}

The early CD4⁺ T-lymphocyte response to combination ART is blunted in older age. Differences in final CD4⁺ T-lymphocyte counts are partially attributable to lower values at treatment initiation, which emphasizes the importance of early diagnosis.²²⁻²⁴ In contrast, sustained virologic response is superior when compared with younger patients, a difference that may be explained by better treatment adherence.^{22,25} Cognitive disorders, common with older age, might diminish this difference since medication adherence may be reduced.²⁶

There are few studies to help guide selection of first-line antiretroviral regimens in terms of virologic or immunologic response in older patients.²⁰ Initial regimen choice should consider existing medications, comorbidities, and potential organ system injury—particularly liver and kidney disease (TABLE 1 and TABLE 2).^{19,21} These factors are important to consider in older patients since the age-associated pharmacokinetics and pharmacodynamics are poorly understood.²⁷ The first year of treatment is associated with a higher risk for treatment non-adherence and loss to follow-up, which increases mortality risk.²⁸ Consequently, loss to follow-up after initial diagnosis should be minimized for optimal outcomes. Once patients are consistently engaged in care and their HIV treatment is stabilized, the frequency for clinician follow-up is typically every 3 to 6 months depending on immunologic status and comorbidities.²⁹

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Maintenance (Chronic-Care) Stage

Mr H: *[HIV has] completely evolved into a manageable disease and I don't dwell on it; I live life like I don't have HIV.*

Dr L: *Clinicians increasingly [realize that having] HIV, even when it's well controlled, can impact other conditions including cardiovascular disease. The challenges of managing [treatment in] HIV patients are probably not so different than the management of [treatment in] other aging patients with multiple medical problems.*

Once patients have achieved viral suppression and are tolerating therapy, treatment priorities transition to managing comorbid non-HIV medical conditions, risk reduction, and preventive care (Box). These priorities include appropriately indicated screening examinations that are recommended for patients of a particular age. Disease screening itself can confer risk and may uncover conditions that require treatments associated with risks. Identification of new diseases may result in the addition of more medications, worsening polypharmacy in an already complex patient. Before embarking on screening, the consequences of treating newly diagnosed disease entities must be carefully considered.

Comorbid medical conditions: In the combination ART era, the proportion of AIDS-related deaths declined, while non-AIDS associated mortality increased. Large cohort studies have shown an association between the risk of non-AIDS conditions and CD4⁺ T-lymphocyte count.^{30,31} A randomized trial

of combination ART treatment interruption was terminated early because treatment interruption not only increased the risk of AIDS-related events, but also cardiovascular, renal, and hepatic events.³² HIV appears to increase the risk of many non-HIV conditions resulting in the use of a new term, HIV-associated non-AIDS (HANA) conditions. HANA conditions are illnesses, such as cardiovascular disease, associated with or exacerbated by HIV infection but are not AIDS-defining conditions (eg, opportunistic infections and AIDS malignancies).^{17,33} HANA conditions occur more frequently or are more severe with lower CD4⁺ T-lymphocyte counts or detectable viral loads, but can persist or develop among individuals with suppressed viral loads and high CD4⁺ T-lymphocyte counts. Although associated with HIV infection, HANA conditions have a multifactorial etiology including the long-term effects of HIV and preexisting coinfections, health behaviors (eg, substance use), and HIV treatments (TABLE 3).

Common preexisting coinfections contributing to HANA conditions include hepatitis B and hepatitis C viruses (liver cirrhosis and hepatoma) and human papilloma virus (cervical and anal cancer).^{34,35} Hepatitis C is responsible for more than 90% of liver-related deaths in HIV-positive patients.³⁶ The prevalence of human papillomavirus varies by demographic group, but may be greater than 90% in HIV-positive men who have sex with men.³⁷ HANA conditions are responsible for as many as 60% of deaths in developed-world HIV-positive cohorts, particularly from cardiovascular events, non-AIDS malignancies, and end-stage liver and kidney disease.³⁸ Addressing reversible risk factors through smoking cessation and hyperlipidemia treatment is associated with risk reduction for cardiovascular disease, providing management opportunities.³⁹

Assessing the relative contributions of HIV infection, combination ART, and traditional risk factors to the development of HANA conditions is difficult because HIV-positive and

Table 1. Treatment Considerations and Evidence Ratings for Use of Specific Antiretroviral Agents in HIV-Positive Patients

Characteristics for Starting Treatment	General Guidelines for Antiretroviral-Naive Patients		
	DHHS	IAS-USA	WHO
Patient inclusion criteria (evidence rating)	All patients regardless of CD4 T-lymphocyte count (AI-BIIA) ^a	All patients regardless of CD4 T-lymphocyte count (AI-BI) ^a	Asymptomatic patients with CD4 T-lymphocyte count <350 (BI) ^a ; Patients with severe disease regardless of CD4 T-lymphocyte count (CI)
Age-specific guidelines (evidence rating)	Any CD4 T-lymphocyte count if aged >50 years (BIIA) ^a	Any CD4 T-lymphocyte count if aged >60 years (BI) ^a	No age-specific guidelines
Medication	Efavirenz/tenofovir/emtricitabine Ritonavir-boosted atazanavir plus tenofovir/emtricitabine Ritonavir-boosted darunavir plus tenofovir/emtricitabine Raltegravir plus tenofovir/emtricitabine	Efavirenz plus tenofovir/emtricitabine or abacavir/lamivudine ^b Ritonavir-boosted atazanavir plus tenofovir/emtricitabine or abacavir/lamivudine ^b Ritonavir-boosted darunavir plus tenofovir/emtricitabine Raltegravir plus tenofovir/emtricitabine	Efavirenz or nevirapine plus tenofovir or zidovudine plus lamivudine or emtricitabine

Abbreviations: DHHS, US Department of Health and Human Services; HIV, human immunodeficiency virus; IAS-USA, International Antiviral Society-USA; WHO, World Health Organization.

^a All antiretroviral treatments listed under general guidelines have AI evidence rating and are not specific to older adults. Ratings for strength of recommendations and quality of evidence are based on the AHA system (<http://guidelines.gov/ontext.aspx?id=15560>) and are based on the consensus of DHHS (2013 Guidelines: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>), IAS-USA (2012 guidelines: <https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection-0>), and WHO (2010 guidelines: <http://www.who.int/hiv/pub/arv/adult2010/en/index.html>).

^b Avoid abacavir if patient is HLA-B*5701-positive or if HIV-RNA viral load is greater than 100 000 copies/mL.

Table 2. Disease-Specific Considerations and Evidence Ratings for Use of Specific Antiretroviral Agents in HIV-Positive Patients With Selected Comorbidities

Disease	Disease-Specific Considerations	Rating ^a
Renal insufficiency	Consider avoiding tenofovir because it may be associated with progression of chronic kidney disease	BIII ^{b,c}
Osteoporosis, fragility fractures	Consider avoiding tenofovir because it may be associated with greater decrease in bone mineral density	BIII ^{b,c}
Cardiovascular disease	Consider avoiding abacavir, ritonavir-boosted lopinavir, or ritonavir-boosted fosamprenavir	BIII ^{b,c}
Depression, sleep disturbance	Consider discontinuation of efavirenz if sleep disturbance or depression persist while receiving this agent	AIII ^c
End-stage liver disease	Avoid nevirapine; and use protease inhibitors with caution	CIII ^b CIII ^{b,c}
Hyperlipidemia	Use ritonavir-boosted protease inhibitors and efavirenz-based regimens with caution due to development or worsening of hyperlipidemia	AIII ^b
HIV-hepatitis B virus coinfection	Nucleoside component of initial therapy should include tenofovir and either emtricitabine or lamivudine in HIV-HBV coinfection	AI-BI ^{b,c,d}
HIV-tuberculosis coinfection	Efavirenz is the preferred NNRTI component of an antiretroviral regimen in patients receiving concurrent rifampin-based tuberculosis therapy	AI ^{b,c,d}
Cognitive dysfunction	Early initiation of antiretroviral therapy may delay or treat HIV-associated neurocognitive disorder	BIIb ^b

Abbreviations: HBV, hepatitis B virus; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; WHO, World Health Organization.

^a Ratings are for strength of recommendations and quality of evidence and are based on the AHA system (<http://guidelines.gov/ontext.aspx?id=15560>) and are based on the consensus of DHHS (2013 Guidelines: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>), IAS-USA (2012 guidelines: <https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection-0>), and WHO (2010 guidelines: <http://www.who.int/hiv/pub/arv/adult2010/en/index.html>).

^b Ratings based on DHHS guidelines.

^c Ratings based on IAS-USA guidelines.

^d Ratings based on WHO guidelines.

HIV-negative populations in research studies frequently have different behavioral risk factors and comorbid disease burden. Cohort studies suggest an increased risk for cardiovascular disease in HIV-positive patients but did not always fully control for traditional risk factors.⁴⁰ However, a recent study comparing demographically and behaviorally similar HIV-positive and HIV-negative adults showed substantial excess risk for acute myocardial infarction in the HIV-positive group after adjusting for Framingham risk factors, comorbidities, and substance use.⁴¹ Meta analyses comparing HIV-positive patients with HIV-negative groups have shown increased risk of other comorbid diseases often associated with aging, including malignancies and osteoporosis.^{42,43}

Functional Status. Maximizing everyday function is a major objective when treating aging HIV-positive patients. Chronic health conditions in HIV are associated with lower self-reported physical, social, and mental health functioning as assessed by SF-36 testing.⁴⁴ The combination of HIV and age may adversely affect performance of instrumental activities of daily living.⁴⁵ The Veteran's Aging Cohort Study (VACS) compared function among demographically matched HIV-infected and noninfected veterans, which found that overall function (measured by a 12-

question self report) was comparable. A 50-year-old HIV-positive individual and a 51.5-year-old uninfected individual have comparable function, but comorbidity was a stronger predictor of diminished physical function and disability than age, regardless of HIV status.⁴⁶ In the Multicenter AIDS Cohort Study, a frailty-related phenotype of weight loss, exhaustion, slowness, and low physical activity was more common in enrollees with HIV infection compared with those who did not have HIV infection, and it predicted mortality independently of CD4 T-lymphocyte count and viral load. But only a small number of individuals exhibited this frailty-related phenotype.^{47,48}

Polypharmacy. Having recently discontinued 2 antihypertensive therapies, Mr H now takes 9 medications including 4 antiretrovirals, 2 lipid-lowering agents, testosterone, an antidepressant, and an anxiolytic. In the Swiss Cohort Study, 14% of HIV-positive participants older than age 65 were taking 4 or more non-HIV medications.⁴⁹ Common classes of drugs include antihypertensive therapies, lipid-lowering agents, antiplatelet medications, antidepressants, anxiolytic/sedatives, non-HIV-related anti-infective medications, and analgesics.^{50,51} Supplements and herbal medications used by patients worsen this situation. In recent years, single-pill fixed-combination antiretro-

Table 3. Selected Emerging Comorbidities in Chronic HIV Infection^a

Comorbidity	Effect of HIV	Effect of Traditional Risk Factors in HIV-positive Populations	Effect of Antiretroviral Therapy
Cardiovascular disease	Increased risk of fatal and nonfatal cardiovascular events; acute coronary events associated with elevated levels of biomarkers of inflammation (IL-6, d-dimers, high-sensitivity C-reactive protein, sCD14); Increased preclinical markers of atherosclerosis such as carotid intima media thickness and computed tomography coronary angiography in HIV cohorts	Increased prevalence of traditional cardiovascular disease comorbidities: smoking, diabetes, hyperlipidemia, hypertension, and substance use in HIV cohorts	Hyperlipidemia associated with antiretroviral use (protease inhibitors, efavirenz, thymidine analogues); Possible contribution of abacavir to cardiovascular disease events
Kidney disease	Increased risk of renal disease progression in HIV-positive patients; Increased mortality associated with CKD; CKD associated with increased cardiovascular disease risk	Increased prevalence of renal comorbidities: hypertension, diabetes mellitus, hepatitis B virus, hepatitis C virus infection, smoking, in HIV cohorts; Higher incidence of end-stage renal disease in HIV-positive African Americans	CKD associated with tenofovir use and other antiretroviral agents
Liver disease	Increasing liver-related mortality in HIV cohorts	Rapid fibrosis progression in HIV/hepatitis B virus and HIV/hepatitis C virus coinfection; Increasing incidence of acute hepatitis C virus in HIV-positive population; Alcohol use; Steatohepatitis associated with insulin resistance and hepatitis C virus coinfection	Combination ART-associated hepatotoxicity (eg: didanosine, nevirapine, high-dose ritonavir); Steatohepatitis associated with nucleoside analogues (eg, didanosine and stavudine)
CNS disease	Direct CNS invasion early in HIV infection and associated neurologic syndromes; Microglial activation and CNS inflammation; Monocyte trafficking of HIV despite combination ART; Increased risk of cerebrovascular events	Possible contribution of concurrent hepatitis C virus infection, active and prior substance use, diabetes, alcohol, and cigarette smoking to neurocognitive function	CNS viral escape associated with poorer CNS penetration and possible worsening neurocognitive function; Associations with certain antiretrovirals (eg, efavirenz)
Bone disease	Increased risk of fragility fractures, osteopenia, and osteoporosis in HIV cohorts; Increased risk of osteonecrosis	High prevalence of comorbidities associated with decreased bone density (hypogonadism, smoking, alcohol, malnutrition, proton pump inhibitors use)	Effects of protease inhibitors on bone density; Effects of tenofovir on bone density; Decreased bone density associated with continuous antiretroviral therapy
Non-AIDS-associated malignancies	Impaired CD4 response to antiretrovirals; Chronic immune activation and dysregulation	Malignancies associated with coinfections (cervical, anal carcinoma, hepatitis B virus- and hepatitis C virus-associated hepatoma, Epstein-Barr virus-associated lymphoma, and non-Hodgkin's lymphoma; Increased lung cancer risk; Increased smoking and alcohol use in HIV-positive cohorts	Increased risk of drug interactions between nonnucleoside reverse transcriptase inhibitors or protease inhibitor-based combination ART and cancer chemotherapeutic agents as compared with raltegravir-based combination ART

Abbreviations: ART, antiretroviral therapy; CKD, chronic kidney disease; CNS, central nervous system; HIV, human immunodeficiency virus.

^aReferences, categorized by comorbidity, are included in the eAppendix.

viral therapy has decreased pill burden for HIV treatment, a benefit offset by increased use of nonantiretroviral medications.⁵²

Polypharmacy, defined as taking 5 or more chronic medications, is associated with adverse drug events, drug interactions, inappropriate medication use, delirium, falls, fractures, and poor medication adherence.⁵³ Criteria for inappropriate medication use in the general population exist; but, applicability among patients with HIV is unknown. Complex cytochrome P450 inhibition and induction effects, especially with protease inhibitors and nonnucleoside reverse transcriptase inhibitors, as well as effects on P-glycoprotein and other drug transporters, increase risk for interactions (TABLE 4).²⁷ Medication interactions can be quickly assessed using DHHS guidelines, drug interactions databases,⁵⁴ or drug interaction software.

Psychosocial Issues and Social Isolation. Social support and the psychosocial context of patients' lives are central to both HIV and geriatric care. While older HIV-positive adults

commonly live alone and may score higher on social isolation scales, the size of their social networks and the amount of support they receive from family and friends can be similar to that of younger HIV-positive individuals.⁵⁵ Nondisclosure, fear of HIV-related stigma, and a desire to be self-reliant are self-perceived barriers to accessing social support; but these factors vary greatly due to the heterogeneity of older HIV-positive adults by race/ethnicity, sex/gender, length of infection, and route of exposure.^{55,56} Loss of friends from AIDS further decreases support networks.⁵⁷

Self-perceived support and loneliness are linked to health outcomes in older adults who are HIV-negative and may become a determinant for HIV-positive individuals as they age. In HIV, social support is linked to mood, well-being, and medication adherence.^{58,59} Nonpharmacologic support groups, such as those in which Mr H participates, can ameliorate depression.⁶⁰ Life experiences result in improved coping strategies and resilience compared with younger pa-

Table 4. Common Drug Interactions Between Antiretroviral and Other Prescribed Medications

Class of Interacting Medication	Interaction With NNRTIs	Interaction With Protease Inhibitors	Comment
Cardiovascular agents (eg, calcium channel blockers, amiodarone)		Increased calcium channel blocker exposure, amiodarone exposure, and potential PR interval prolongation	Use calcium channel blockers and protease inhibitors with caution; Avoid coadministration of amiodarone and protease inhibitors
Cardiovascular agents (eg, lipid-lowering agents)	Decreased statin exposure with selected NNRTIs	Increased statin exposure with selected protease inhibitors	Lovastatin and simvastatin contraindicated with concurrent protease inhibitor use; Use minimally effective doses of atorvastatin (maximum 20 mg/d) with protease inhibitors; Use lowest effective dose of pravastatin with darunavir
Benzodiazepines	Increased midazolam and triazolam effect with efavirenz; Increased diazepam exposure with etravirine	Increased benzodiazepine effect	Do not administer midazolam, alprazolam, diazepam and triazolam with protease inhibitors and efavirenz; Lorazepam, oxazepam and temazepam have less interaction potential with protease inhibitors
Proton pump inhibitors	Decreased rilpivirine absorption	Decreased atazanavir absorption	Proton pump inhibitors contraindicated with rilpivirine, atazanavir (without use of ritonavir); Proton pump inhibitors should not exceed a dose equivalent to omeprazole (20 mg/d) in protease inhibitor-naïve patients receiving ritonavir-boosted atazanavir; Proton pump inhibitors are not recommended in protease inhibitor-experienced patients receiving ritonavir-boosted atazanavir
Opiates	Decreased methadone exposure with efavirenz and nevirapine	Decreased methadone exposure with ritonavir-boosted protease inhibitors	Opiate withdrawal may occur with methadone and concurrent ritonavir-boosted protease inhibitor, efavirenz, or nevirapine use
Corticosteroids (systemic, inhaled, or intranasal)	Dexamethasone can decrease NNRTI levels, especially rilpivirine	Increased fluticasone and budesonide exposure with ritonavir; decreased protease inhibitor levels with dexamethasone	Cushing syndrome and adrenal insufficiency reported with fluticasone and budesonide coadministration with ritonavir; Beclomethasone preferred alternative Avoid dexamethasone and rilpivirine coadministration
Antiplatelet and anticoagulant agents (eg, clopidogrel, warfarin, rivaroxaban)	Decreased clopidogrel exposure with etravirine; Increased or decreased warfarin effect with NNRTIs	Increased or decreased warfarin effect with protease inhibitors; Increased rivaroxaban exposure with protease inhibitors	Avoid clopidogrel and etravirine coadministration if possible; Monitor international normalized ratio closely when stopping or starting protease inhibitors and NNRTIs and adjust warfarin dose accordingly; Avoid rivaroxaban and protease inhibitor coadministration
Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil, avanafil)	Decreased phosphodiesterase type-5 inhibitor effect with etravirine	Increased phosphodiesterase type-5 inhibitor exposure with ritonavir-boosted protease inhibitors	Start with lowest effective dose with ritonavir-boosted protease inhibitors; Avoid coadministration of avanafil with NNRTIs or protease inhibitors
Antidepressants	Decreased bupropion and sertraline exposure with efavirenz	Decreased SSRI and bupropion exposure with selected protease inhibitors; Increased trazodone and tricyclic antidepressant effect with selected protease inhibitors	Titrate SSRI and bupropion doses based on clinical response in patients receiving protease inhibitors; Use lowest dose of trazodone and tricyclic antidepressants and monitor for central nervous system and cardiovascular adverse events in patients receiving protease inhibitors; Use of trazodone and saquinavir contraindicated

Abbreviations: NNRTI, nonnucleoside reverse transcriptase inhibitor; SSRI, selective serotonin reuptake inhibitor.

Derived from 2013 US Department of Health and Human Services guidelines, the HIV InSite website, and the University of Liverpool Drug interaction website (see Resources, available at <http://www.jama.com>).

tients, despite higher rates of comorbidity and psychosocial challenges.⁶¹

Health Care Maintenance and Prevention. The Infectious Diseases Society of America's HIV Primary Care Guidelines recommend following age-appropriate primary care screening guidelines as for the general population.²⁹ For an individual of Mr H's age, grade A and B recommendations from the US Preventive Services Task Force support screening for colorectal cancer, hypertension, depression, and hyperlipidemia; aspirin to prevent cardiovascular disease; smoking and alcohol screening and counseling; healthy diet counseling if cardiovascular risk factors are present; obesity screening and counseling; behavioral counseling for sexually transmitted infections; and diabetes screening if systolic blood pressure exceeds 135/80 mm Hg.⁶²

Caution is needed before applying screening and disease-specific practice guidelines for older patients with multiple comorbid diseases and polypharmacy since complications from treating those diseases or adding to the complexity of an older patient's medication requirements may outweigh benefits. Patients' overall goals and life expectancy should also be considered. Validated geriatric risk assessment tools incorporate measures of cognitive and physical functioning, symptoms, clinical diagnoses, and laboratory values to assess mortality risk⁶³; but the accuracy for these assessments in HIV is not known.

The Veterans Aging Cohort Study (VACS) developed an index that has been validated among cohorts from Europe and North America and is more accurate at predicting all-cause mortality (AIDS, non-AIDS, and cardiovascular) than age, CD4 T-lymphocyte count, and viral load alone.^{64,65} Building on typical HIV measures (CD4, viral load), it also includes routinely monitored indicators of organ system function including hemoglobin, platelet count, transaminases, creatinine, and hepatitis C serology. The VACS Index also predicts morbidities such as hospitalization and fragility fractures and is correlated with functional performance.^{66,67}

Advanced-Stage Care

Dr L: *We have little mini goals-of-care discussions at every visit. [For example,] Mr H actually has a lot of insight about what he's gone through and what he's willing to go through. During his last visit, we broached the idea of doing imaging to determine whether there could be a malignancy or something that would be responsible for his weight loss. He really felt that he didn't want to pursue that at this time.*

As evidenced by his age, increasing fatigue, and weight loss, Mr H may be reaching a crossroad. A single insult such as a fall, an episode of pneumonia, or an adverse drug event might shatter this patient's independence. Compared with when he was diagnosed with HIV, achieving excellent antiretroviral medication adherence and overcoming toxicities are no longer the major priorities for his care. For an HIV-uninfected individual similar to Mr H but without weight loss, life expectancy approximates 10 years. Coexisting HIV and weight

loss decrease estimated life expectancy. Advanced-stage care is characterized by individualized decisions to defer guideline-driven preventive interventions due to an unfavorable risk-benefit relationship in patients with limited life expectancy. Prognostic information is central to the dialogue with patients when conducting routine screening because many published recommendations are based on long-term benefits. For example, colon cancer screening is no longer recommended when life expectancy is less than 7 years because the harms from screening outweigh potential benefits.^{68,69}

According to a survey completed before widespread use of combination ART, one-half of HIV-positive patients in the United States had not discussed end-of-life preferences with their clinicians.⁷⁰ A smaller, recent study at an academic clinic showed only 47% of HIV-positive adults aged 45 to 65 years had documented advanced care planning.⁷¹ These findings highlight the need for greater attention to end-of-life preference discussions between older-HIV-positive patients and their physicians (Box). The imperative for advanced-care planning is even greater for older HIV-positive patients given their prevalent social isolation and given that advanced care may be provided by governmental and institutional organizations. Prognostic information and patient preferences factor into clinical decision making in cases like Mr H's, in which aggressive testing to evaluate weight loss may have a lower priority than symptom management. Palliative care, a critical factor in the early days of the HIV epidemic, may have an emerging role in improving quality of life for older patients.^{72,73} Although there are few data on which to make formal recommendations, even when a patient's life expectancy is less than 1 year, continuing antiretroviral medications and opportunistic infection prophylaxis may enhance palliation by minimizing symptoms from HIV-related diseases.⁷²

Mr H and Dr L initially chose a symptom-based approach to evaluating his fatigue and weight loss using focused investigations where benefits outweigh risks. His fatigue and weight loss were investigated by laboratory tests (eg, complete blood cell count, thyrotropin, testosterone); medications were assessed by a pharmacist; and alcohol intake, depressive symptoms, and the quality of his sleep were reviewed by Dr L. A regular exercise program was encouraged, which alone should have been beneficial.⁷⁴ Rosuvastatin was discontinued and he was switched to a single-tablet antiretroviral regimen (emtricitabine/tenofovir/rilpivirine) to reduce pill burden. Unfortunately the new regimen was associated with increased depressive symptoms and he was switched back to his prior antiretroviral regimen. In follow up, he has remained independent, continues to attend a support group, and has gained 6 lbs, although his fatigue persists.

Whether treating patients in the early, maintenance (chronic care), or advanced stages of care, clinicians should discuss patient preferences and goals, advise patients of available social support, and help determine the most appropriate level of care (eg, assisted living or nursing home). In the

advanced-care stage, the priority is to maintain independence and avoid prolonged hospitalizations.

Mr H's success may be attributable to an effective patient-physician alliance and a multidisciplinary approach; however, optimal models of care for older HIV-positive patients are not completely understood. A Cochrane review could not identify sufficient evidence to recommend any single model of care for HIV-positive patients irrespective of age. The reviewers did find that better case management may improve outcomes.⁷⁵ Published descriptive examples of clinics serving older HIV-positive adults focus on use of multidisciplinary teams and screening for specific complications such as polypharmacy and cognitive impairment.⁷⁶ Multidisciplinary models, such as the Ryan White Care Act–affiliated clinics,⁷⁷ may be beneficial and the integration of geriatric principles will likely be needed in all clinics where there are appreciable numbers of older HIV-positive patients. Internationally, HIV programs must consider the role of chronic diseases when serving an increasing population of older HIV-positive patients.⁷⁸

CONCLUSIONS

The transition of HIV infection from a terminal illness to a chronic manageable disease demonstrates the considerable gains in HIV treatment. Given these successes, management of aging HIV-positive patients is a relatively recent clinical problem clinicians worldwide must address. While HIV-positive patients have much in common with HIV-negative patients who are aging with attendant chronic diseases, issues of polypharmacy, care integration, social isolation, and end-of-life planning are complicated by HIV. A comprehensive care approach integrating principles from geriatric medicine is needed to manage the care of patients coping with multiple comorbid medical diseases. Optimal models of care must be identified—with HIV specialists, primary care clinicians, and geriatricians working together to make successful aging for this population achievable.

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