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Primary Care of Women Aging with HIV

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Abstract

Women are living longer with HIV infection, but their life expectancy is shorter than for women in the general population. How best to manage the multiple comorbidities and polypharmacy that are common in HIV infected individuals has not been studied.

This paper explores areas where the primary care of women with HIV may differ from that of aging women in the general population. We also discuss aspects of care that may not commonly be considered in those under the age of 65, specifically multimorbidity and polypharmacy.

Incorporating a gerontologic approach in the care of these women may optimize outcomes until research provides more definitive answers as to how best to collaborate with women with HIV to provide them with optimal care.

Keywords

HIV; aging; polypharmacy; multimorbidity; primary care

INTRODUCTION

Since the advent of antiretroviral therapy (ART), HIV infection has become a chronic disease, managed with medications that have ever-increasing efficacy and decreased toxicity. This has resulted in the aging of the HIV epidemic: by 2015, more than 50% of individuals with HIV in the United States will be over the age of 50. In the current treatment era, conditions that are not AIDS-associated, such as cardiovascular disease, diabetes, substance abuse, and depression, drive morbidity and mortality among individuals with HIV, and health care visits focus on primary care rather than HIV-specific care.[1] Thus, a number of

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experts suggest that primary care (rather than specialty HIV) clinics should be the healthcare home for individuals living with HIV, as it is for individuals living with other chronic illnesses. More primary care providers, including midwives and nurse practitioners, will be needed to provide primary care to these patients, particularly as they age.

Guidelines for HIV primary care have multiplied, providing numerous sources of guidance on topics such as diagnosis and management of dyslipidemia, decreased bone mineral density, and cervical cancer screening. Recently, the Infectious Disease Society of America published a comprehensive guide to HIV primary care, addressing both HIV-specific and general primary care concerns for patients living with HIV.[2] These guidelines, however, do not address certain issues that are of key importance to women, such as anemia, nor do they address issues of growing importance to all individuals aging with HIV such as multimorbidity (the co-existence of two or more long-term conditions in an individual) and polypharmacy (the use of five or more medications, including prescribed, over-the-counter, and complementary).

Multimorbidity and polypharmacy are traditionally associated with the elderly, and providers are accustomed to thinking of the elderly as being over the age of 65. However, among HIV-infected individuals, those 50 years of age and older are considered elderly. This terminology reflects that even with ART, HIV-infected individuals do not have a normal lifespan. Preliminary estimates suggest that women infected with HIV may lose 13 to 16 years of life compared to their uninfected counterparts (Table 1), three years more than HIV-infected men lose relative to uninfected men.[3] It is not yet clear what implications this shortened lifespan, or women's survival disadvantage relative to men, should have for patient care, but incorporating gerontologic principles into the care that we provide for our older HIV-infected patients may be a useful approach.

This review will address routine primary care issues that women's health care providers will encounter with their older patients with HIV, focusing on areas where care differs from that of women in the general population, younger women with HIV, and from men with HIV. For example, recommendations for screening for sexually transmitted infections, including hepatitis B virus infection, will not be reviewed in detail as they are not specific to older women. In addition, the limitations of individual guidelines for patients with multiple chronic diseases will be discussed. Recommendations are discussed at length in the text and are summarized with references in Table 2.

MENOPAUSE

Women in the United States who are HIV-infected have a number of risk factors for early menopause, including black race, lower body mass index, smoking, stress, less education, methadone use, illicit substance use (particularly opiates and cocaine) and use of psychotropic drugs.[4] However, when compared to demographically similar uninfected women, those with HIV do not experience menopause at an earlier age.[5] There is a high prevalence of menstrual irregularities among women living with HIV, secondary to illicit substance abuse; medications including psychotropics, narcotics, methadone, or corticosteroids; and comorbid conditions including diabetes, kidney disease, or liver

disease.[6,7] This makes the diagnosis of menopause challenging. In this population, rather than relying solely on 12 months of amenorrhea, providers might wish to assess timed serum follicle-stimulating hormone (FSH) and estradiol concentrations to confirm or disprove ovarian failure as the source of the amenorrhea.[8] Particularly for a woman in her very early 50s who has HIV, pregnancy must be considered when she presents with amenorrhea.

Recent guidelines recommend against the use of hormone replacement therapy (HRT) for disease prevention among women with HIV,[2] as is true for the general population of women. There is evidence, however, that these women experience more, and more severe, menopausal symptoms than their uninfected counterparts, thus supporting the use of HRT for symptom management.[4]

Hot flashes, night sweats in particular, need to be differentiated from HIV-associated conditions.[4] While a common experience for postmenopausal women, night sweats could also be a marker for tuberculosis or non-Hodgkins lymphoma. Evaluation should include a careful history for possible exposure to tuberculosis, and testing to rule out tuberculosis using a QuantiFERON test or the purified protein derivative (PPD) tuberculin skin test. Note that a reaction ≥ 5 mm of induration indicates tuberculin positivity for HIV infected individuals.[9] Physical and laboratory examinations assessing for fever, weight loss, a rapidly growing mass, hepatomegaly, splenomegaly, cytopenias, current CD4 count and HIV-RNA, may be indicated as well, depending on the woman's history.

Women may also experience memory loss during or after menopause. Among women with HIV, providers should be aware that memory loss could also be related to HIV infection, particularly if the HIV viral load is elevated. This topic will be developed further in the "Mental Health/Neurology" section of this paper.

Once alternative etiologies have been ruled out, symptomatic treatment should be considered. Hormone replacement therapy at the lowest effective dose for the shortest period of time is a reasonable approach.[2,4] However, ART often interacts with estrogen and progestins, although the hormones likely do not interfere with the metabolism of ART. Most of this research has focused on hormonal contraception and ART. For example, protease inhibitor-based regimens that include ritonavir (the vast majority of protease inhibitor-based regimens) typically cause a reduction in ethinyl estradiol area under the curve and may decrease efficacy.[10] Similar interaction may also result in decreased progestin concentrations. Alternative formulations, such as the patch, demonstrate similar outcomes.[11] However, as the formulations and doses of hormones used differ between hormonal contraception and hormone replacement therapy, identical interactions cannot be assumed. Therefore, focusing on resolution of menopausal *symptoms* is key to determining appropriate dosing, and women with HIV who are on ART may require higher doses of estrogen and progestin than other women to achieve similar relief. Checking medication interactions on the AIDSinfo website (Table 3) is always indicated for the most up-to-date information.

A number of alternatives exist for addressing menopausal symptoms; these may also provide additional benefits. For example, selective serotonin reuptake inhibitors such as fluoxetine,

and venlafaxine, a serotonin and norepinephrine reuptake inhibitor, have been shown to reduce the absolute risk of hot flashes by 19–60%.[12,13] Gabapentin (titrated to 2400 mg over 12 days) has also shown efficacy on par with that of estrogen in treating moderate to severe hot flashes.[14] High rates of depression and peripheral neuropathy among individuals living with HIV may make one of these options attractive, as one medication could be used to treat more than one condition.

MENTAL HEALTH/NEUROLOGY

Depression

Individuals with HIV experience depressive symptoms at a rate of 2–4 times that of the general population.[15] Whether or not women with HIV experience higher rates of depression than men is open to debate; some studies report higher rates in women[16] while others do not.[17] However the connection between depression and poor outcomes among individuals with HIV, and the improvement seen with treatment of depression, is clear, at least in part due to the improved adherence that is seen when depression is adequately treated.[18]

Older women with HIV may be at particular risk for depression associated with HIV-related stigma and loneliness.[19] Women of color who are HIV-infected may be at particular risk.[20] Why this is the case is not clear, but attitudes towards race and gender, as well as socioeconomic status, need to be considered when screening for and addressing stigma and depression in these populations.

Screening, diagnosis, and treatment of depression are thus key among older women with HIV. The New York State Department of Health (Table 3) suggests screening for depression at baseline and ongoing assessment at every visit.[21]

Substance abuse

The prevalence of alcohol use in the HIV-infected population may be as high as twice that found in the general population.[22] The prevalence of illicit substance use among individuals with HIV was 81% in 2009, and at least 25% of those with HIV were in need of treatment for alcohol or illicit drug abuse in the same year.[23] Substance use, particularly alcohol and illicit substance abuse, are associated with poor adherence to ART[24] and risky sexual behavior, which may increase the risk of HIV transmission.[25] Furthermore, substance abuse is associated with higher mortality among individuals with HIV, perhaps in part because substance use can decrease CD4 count.[26] In the general population, hepatic consequences of alcohol abuse are more pronounced in women than in men, and women may be more susceptible to alcohol-induced brain damage than men.[27,28] Women with HIV are also more likely than men to experience negative outcomes of substance use, including lower rates of adherence to antiretroviral therapy.[29] Therefore, screening for alcohol and substance abuse is indicated at baseline and at least annually so that patients who have problems with substance abuse can be linked with treatment programs.

Cognitive impairment

As yet, no gender differences have been identified for HIV-associated dementia.[30] However, as most of the women in these studies are premenopausal, little is known about cognitive decline among postmenopausal women with HIV.[31]

Among older individuals with HIV, 68% have reported some degree of cognitive impairment. Causes are doubtless multifactorial and include HIV-specific risk factors including low nadir CD4+ lymphocyte count and perhaps the use of antiretroviral regimens with poor central nervous system penetration, as well as those found in the general population, including older age, chronic HCV co-infection, polypharmacy, and frailty, and, perhaps, the use of antiretroviral regimens with poor central nervous system penetration.[32] However, uncontrolled HIV is the most important risk factor for HIV-associated dementia. Thus being sure that patients have initiated ART and are adherent is of key importance.[32]

Persons with HIV may be cognitively impaired for reasons other than HIV infection; for example they may also have Alzheimer's disease as well as vascular dementias. A full work-up to identify the cause of the dementia, including MRI of the brain and neuropsychological testing, is indicated, particularly among people on ART with fully suppressed HIV-RNA.

CANCER

Cervical cancer

The incidence of AIDS-defining cancers, including cervical cancer, has declined three-fold between 1995 and 2005.[33] Women with HIV should be screened for cervical cancer when diagnosed with HIV, again six months later, and then annually if these initial tests are negative.[2,34] There are, as yet, no guidelines for discontinuing cervical cancer screening among women over the age of 65 who are HIV infected, or among those who have had a hysterectomy unrelated to abnormal cervical cytology.

There are no guidelines that address human papilloma virus (HPV) screening for older women with HIV. Keller and colleagues found that the five-year cumulative incidence of high-grade squamous intraepithelial lesions (HSIL) or grade 2 or higher cervical intraepithelial neoplasia (CIN2+) was similar in women with HIV and their uninfected counterparts who were cytologically normal and oncogenic HPV-negative at baseline.[35] However, the mean age of women in this study was 34, and studies need to be done exploring HPV screening in older women with HIV.

Anal cancer

Rates of anal cancer are much higher among women with HIV compared with those who are uninfected.[36] There is also more than a four-fold increased risk for having concomitant (anus and cervix) oncogenic HPV infection comparing women with HIV with uninfected women.[8] Both oncogenic and nononcogenic HPV types were more prevalent in the anus than in the cervix in women with HIV. Use of ART has not been associated with a decreased risk of concomitant HPV infection.[36] Among women with HIV, those with a CD4 count less than

200 cells/μL were more likely to have detectable oncogenic and nononcogenic HPV types in both the cervix and anus than those with higher CD4 counts.[36]

The recent HIV primary care guidelines from the Infectious Disease Society of America[2] recommend anal pap smears for women with HIV who have a history of anal receptive intercourse, or who have had abnormal cervical cytology or anogenital warts. This is a weak recommendation with moderate quality evidence. Other organization-based guidelines do not recommend anal cancer screening for women with HIV.[37] Opinions against routine screening typically focus on the lack of evidence that screening programs reduce the morbidity and mortality associated with anal cancer, and that there are few trials that have evaluated the efficacy and safety of current treatment modalities for precancerous anal lesions, particularly regarding complications or side effects of treatment.[37]

CARDIOVASCULAR DISEASE AND METABOLIC DISORDERS

Cardiovascular disease

Rates of cardiovascular disease are higher among women with HIV compared with uninfected women.[38] While higher rates are, in part, associated with greater prevalence of Framingham risk factors (smoking, hypertension, and dyslipidemia), HIV infection does appear to be an independent risk factor for cardiovascular disease.[38,39] Mechanisms that drive the association between HIV infection and cardiovascular disease remain to be elucidated but may include inflammation, CD4 cell count depletion, hypercoagulability, dyslipidemia, altered arterial elasticity, and endothelial dysfunction. Cardiovascular disease is known to be an inflammatory disease.[40] HIV is an important cause of inflammation even with fully suppressed virus, although mechanisms and pathways for this inflammation are not well understood. These may include ongoing viral replication and/or microbial translocation from the gut into surrounding tissues and blood.[41] Antiretroviral therapy may also contribute to increased cardiovascular risk through associated metabolic changes and alterations in fat distribution such as lipodystrophy. However, the SMART study highlights the predominant contribution of HIV over ART.[39] Briefly, the SMART study was designed to compare continuous treatment on antiretroviral therapy to CD4 count-guided scheduled treatment interruptions. This study conclusively demonstrated that intermittent treatment, compared with continuous antiretroviral treatment, was associated with increased risks of HIV disease progression and death, serious HIV disease progression, and severe complications. In particular, despite greater exposure to antiretroviral therapy, cardiovascular complications were less common in the continuous treatment group than in the intermittent treatment group.[42]

Possibly because of this independent effect of HIV, the Framingham risk calculator may underestimate the true cardiovascular disease risk in this population. However, as many of the Framingham risk factors are modifiable, particular attention should be paid to reducing these risk factors among women with HIV. As noted earlier, smoking is endemic in the HIV-infected population. Each point of contact with a provider should be an opportunity for assessing readiness to quit smoking and to provide counseling regarding smoking cessation and aids that can facilitate quitting.

Because of heightened concern about long-term cardiovascular disease morbidity and mortality in this population, new primary care guidelines from the Infectious Disease Society of America[2] suggest that a fasting lipid profile, fasting blood sugar, and hemoglobin A1c be done at initiation of HIV care,[2] prior to initiation of ART, and within 1–3 months after starting ART.[2] Metabolic abnormalities among individuals with HIV are common, resulting from a number of different factors including: direct effects of HIV itself, toxicities of ART, body composition changes, restoration to health, as well as traditional risk factors found in the general population. While increased LDL appears to be the result of restoration to health, hypertriglyceridemia and reduced HDL cholesterol are likely linked to direct effect of the virus.[43] Specific antiretroviral medications have also been associated with dyslipidemia, specifically full-dose ritonavir, ritonavir-boosted regimens (ritonavir plus lopinavir or tipranavir or fosamprenavir), efavirenz, and stavudine. Ritonavir-boosted regimens also may decrease HDL concentrations.[43] Indinavir transiently blocks the glucose transporter GLUT4 which results in elevated serum blood glucose levels.[8] The nucleoside reverse transcriptase inhibitors such as zidovudine, stavudine, and didanosine, through their impact on mitochondrial toxicity, may contribute to insulin resistance.[44] There are too few data on the newer drugs and classes of ART to draw conclusions about their effects on metabolism.

Blood pressure should be checked annually in all patients.[2] Subsequent management should follow guidelines established for the general population.

A key concern among individuals on ART is the potential for pharmacokinetic interactions between medications used to treat comorbid conditions and protease inhibitors and non-nucleoside reverse transcriptase inhibitors, two of the most commonly used classes of ART. Lipid-lowering medications, especially statins, are of particular concern. Protease inhibitors inhibit metabolism of statins, thus increasing the potential for statin toxicity. Pitavastatin and pravastatin are exceptions as they are metabolized through glucuronidation, and can be used safely with protease inhibitors.[8] Atorvastatin and rosuvastatin may also be used in patients taking protease inhibitors, but the initial dose should be low with careful titration to achieve the desired effect without toxicity. Cobicistat, one of the ingredients in a new single pill antiretroviral therapy (commonly called the “quad pill”) likely interacts with statins in a manner similar to protease inhibitors, but this has not been well-explored. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, induces statin metabolism, resulting in lower statin levels. Careful review of package inserts prior to prescribing lipid lowering medications is always indicated to rule out potential interactions.

Dihydropyridine calcium channel blockers can also be problematic. All protease inhibitors can increase levels of these medications, thus they should be used with caution. In particular, electrocardiogram (ECG) monitoring is recommended when a calcium channel blocker is used with atazanavir.[10]

Osteoporosis

Osteoporosis is more common among individuals with HIV compared with uninfected individuals[45,46] as are fragility fractures.[47] However there is little agreement regarding the primary risk factors for fractures in this population. Some authors have focused on the

contribution of traditional risk factors found in the general population, including increasing age, white race, alcohol use, liver disease, corticosteroid use, current or past smoking, proton pump inhibitor use, body mass index, and decreased hemoglobin.[47,48] Others have focused more on the contribution of HIV-specific factors, particularly tenofovir use and protease inhibitor use.[49] Mundy and colleagues, however, have recently demonstrated an overall decreased fracture risk for individuals with HIV who are on ART, compared with those who are not.[50] Drug-specific risk estimates for fracture demonstrated an increased risk for fracture with darunavir (adjusted odds ratio [aOR] 1.93, 95% confidence interval [CI] 1.05, 3.56). These results are consistent with other studies pointing to a possible association between protease inhibitors and fracture risk.[50] Likely, all of these factors, traditional risk factors, HIV and ART, contribute to the risk of osteoporosis in this population.

Recent guidelines[2] suggest that osteoporosis screening include a baseline bone densitometry for all postmenopausal women. However, as T-scores are diagnostic thresholds for osteoporosis and osteopenia only,[51] pharmacologic intervention should be based on absolute fracture risk that includes clinical fragility fracture risk factors. An algorithm most commonly used to calculate fracture risk (FRAX) (Table 3) integrates clinical risk factors for fractures with bone mineral density at the femoral neck to determine the 10-year probability of both hip and major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).[51]

ANEMIA

Anemia has been an important concern for individuals infected with HIV since the early years of the epidemic when it was typically severe and driven by direct effects on the bone marrow of HIV, opportunistic infections, and zidovudine.[52] Currently, ART is associated with resolution of and protection against anemia. Nonetheless, 30% of individuals with HIV are anemic.[53] This anemia is usually mild, although it is associated with decreased survival. The SMART study[53] explored the relationship between anemia and death in approximately 2000 individuals with HIV, 28% of whom were women. Anemia was defined as less than 12 g/dL in women and less than 14 in men. Over the five years of follow-up, those who were anemic had more than twice the risk of death as those who were not (adjusted relative risk 2.31; 95% CI, 1.34–3.98). There were 0.54 deaths per 100 person years of follow-up in the group with normal hemoglobin, and 1.95 deaths per 100 person years of follow-up in the anemic group.

Pathogenesis of HIV-related anemia is multifactorial but may be driven by persistent inflammation, although all routine causes of anemia should be ruled out. Women, blacks, intravenous drug users, and older individuals are at greatest risk for anemia.[54]

In the elderly general population, anemia is also associated with decreased survival, impaired functional status and poor quality of life. It is associated with reduced physical performance, fatigue, functional dependence, disability, declining muscle strength and density, declining executive function and cognitive impairment (particularly in older women), and an increased risk of falls and frailty. These outcomes require further exploration in the HIV-infected population.

CO-INFECTION WITH HEPATITIS C VIRUS

In the United States, one-quarter of people living with HIV are co-infected with hepatitis C virus (HCV).[55] Given the “age wave” of chronic HCV seen in baby boomers,[56] it is particularly important for older individuals newly diagnosed with HIV to also be assessed for HCV. Annual testing should continue for those at risk, including those with ongoing injection drug use, and chronic hemodialysis.[2] Those who test positive for HCV antibodies should have a confirmatory test using a sensitive quantitative assay to measure plasma HCV RNA.[2] Those who are HCV seropositive and not immune to or infected with hepatitis B should be vaccinated. Those without immunity to hepatitis A should also be vaccinated. Counselling regarding cessation of alcohol use is also of central importance.

Recent advances in treatment for HCV have improved so dramatically that all coinfected patients should be referred to an experienced specialist for treatment. Watchful waiting to determine the need for treatment is no longer appropriate. Patients who abuse intravenous substances should be educated about safer injection practices and encouraged to stop using altogether as post-treatment reinfection with hepatitis C is possible.[8]

All individuals with HCV should be cautioned about use or overuse of medications that could be harmful to the liver, thus exacerbating the risk of liver damage. Acetaminophen use is of particular concern.[8] Providers should also ask about all over-the-counter or alternative therapies so that their impact on the liver can be reviewed.

IMMUNIZATIONS

Women with HIV are eligible for all routine immunizations recommended by the Centers for Disease Control and Prevention, on the same schedule as their uninfected counterparts, with one exception: live virus vaccines are contraindicated in individuals with CD4 counts less than 200 cells/μL.[2,57] Varicella and measles-mumps-rubella vaccines (MMR) are recommended as in uninfected individuals when CD4 counts are above 200 cells/μL[57].

The zoster vaccine, (Zostavax, Merck & Co., Inc, Whitehouse Station, New Jersey), is more problematic: there are as yet only minimal data suggesting that the zoster vaccine is safe and effective for individuals with HIV who have CD4 counts > 200 cells/μL. An AIDS Clinical Trial Group study explored the safety and efficacy of the zoster vaccine among individuals with HIV who had fully suppressed HIV-RNA, were on ART, had CD4 cell counts greater than 200 cells/μL, and had positive baseline varicella titers. This study measured varicella zoster virus (VZV) antibody titers at six and 12 weeks post-immunization and found that the participants who received the zoster vaccine had significantly higher varicella titers than those who did not. Investigators had decided *a priori* that use of the zoster vaccine would be considered safe if no more than 18 of the 295 (6.1%) people receiving the vaccine experienced a severe side effect. While the severe adverse events were not described in the study, prior research has identified asthma exacerbations, polymyalgia rheumatica, anaphylaxis and Goodpasture’s Syndrome as possible post-vaccine complications.[58] Seventeen of the patients (5%) in the zoster vaccine group met this endpoint compared to 2 (2.1%) of the 97 patients in the placebo group. The difference was not statistically

significant, and the authors concluded that two doses of the zoster vaccine were “generally safe” in the individuals with HIV who met inclusion criteria.[59]

The Advisory Committee on Immunization Practices and the Infectious Disease Society of America do not recommend for or against use of the zoster vaccine in patients with HIV who have CD4 counts greater than 200 cells/μL. And yet, vaccinating individuals with HIV against zoster, if the vaccine is safe and effective, may provide significant benefit, given the high prevalence of zoster and associated high rates of complications, both acute neuralgia and post-herpetic neuralgia, in this population[60] even in the ART era.[61]

Because the concentration of attenuated varicella virus is 14 times higher in the zoster vaccine than in the chicken pox vaccine (Varivax, Merck & Co., Inc, Whitehouse Station, New Jersey)[62] it is generally agreed that checking for antibodies to varicella virus prior to vaccinating with the zoster vaccine is important, as individuals who are varicella virus seronegative should be vaccinated with the varicella, not the zoster, vaccine.[58]

Given these complexities, primary care providers caring for women with HIV over the age of 60 who have with CD4 counts well over 200 cells/μL, fully suppressed viral loads, and evidence of exposure to chickenpox, might consider consulting with the patient’s HIV provider to discuss immunization with the zoster vaccine and optimal treatment should the vaccine result in symptomatic zoster. If HIV-RNA is detectable, if an individual is not on ART, or if the CD4 count is lower than or quite close to 200 cells/μL, immunization should be deferred.

MULTIMORBIDITY AND POLYPHARMACY

The high prevalence of multimorbidity among individuals with HIV has been well documented.[63] Multimorbidity may be related to HIV itself, to immunosuppression, to antiretroviral medications, and/or to an increased prevalence of traditional risk factors among individuals with HIV. Salter and colleagues[63] found that the risk of multimorbidity in this population increased with advanced immunosuppression and HIV viremia. Their study addressed seven non-AIDS defining chronic diseases: diabetes, obstructive lung disease, liver disease, anemia, obesity, kidney dysfunction and hypertension. In contrast, Kim and colleagues[64] found that obesity was associated with a higher likelihood of multimorbidity among individuals with HIV. While little is known about multimorbidity among women with HIV, Salter and colleagues[63] suggest that women with HIV may be more likely to experience multimorbidity than men with HIV, although why this may be the case is not yet understood.

In the general population, multimorbidity is associated with decreased functional status and quality of life, increased adverse drug events, medical costs, disability, and mortality.[65] These outcomes have not been explored among individuals with HIV, but are likely similar.[66]

Polypharmacy may contribute to morbidity and mortality through its association with non-adherence, the presence of pre-existing organ system injury that may be aggravated by the toxicity from additional medications, drug-drug interactions, and ongoing substance use.[67]

Polypharmacy has been associated with poor health outcomes including hospitalization and mortality in the general population,[68] but until recently has received little attention in the context of HIV. In the Veterans Aging Cohort Study, 55% of individuals with HIV who were over the age of 50 took five or more daily medications.[67] Women in the general population typically experience a higher prevalence of polypharmacy than men,[68] possibly because women visit health care providers more often than men,[69] although this difference may resolve with increasing age. Patterns of polypharmacy are as yet unexplored in HIV-infected populations.

CONCLUSION

Guideline-based care presents particular challenges. Most practice guidelines target a single, index condition. Aberg and colleagues present at least 13 different guidelines that should be considered when managing the care of older women with HIV. This focus on single-disease guidelines may result in treatment plans that are inefficient, ineffective, and potentially harmful to patients.[65,70] Few guidelines exist to help primary care providers manage and prevent chronic disease in these complex patients, as most clinical trials exclude those with multimorbidity, particularly those with HIV infection.

Management of multimorbidity should include understanding and incorporating patient preferences, shifting priorities and healthcare goals into the care plan. This should involve discussions with patients around their priorities, reviewing their current plan of care, and their ability to adhere to the current plan. Providers then need to consider the patient's preferences in the context of relevant evidence that supports the achievement of these outcomes. Interactions within and among treatments and conditions should be considered, and providers should weigh benefits and harms of components of the treatment plan with the patient.[71] Ideally, this discussion would take place with the specialty providers and the patient, together with the primary care provider. This level of collaboration is difficult to achieve in our health care system, thus primary care providers need to communicate with specialists, and patients need to be empowered to communicate their priorities to all of their providers along with any concerns that they may have regarding how specific treatments may interfere with these priorities.

Primary care of women with HIV is similar to that of women in the general population, but there are issues particular to HIV, the understanding of which can enhance the provision of quality care. These issues are summarized in Table 2. An initial response to the complexity of care for women with HIV has been an increased number of guidelines and recommendations for what should be done to prevent undesired consequences. However, shortened life expectancy and the high prevalence of multimorbidity and polypharmacy make guideline-based care a difficult proposition. The dangers of using multiple single-disease guidelines for the care of patients with multimorbidity are well established.[70] For example, in a patient with osteoarthritis and hypertension, non-steroidal anti-inflammatories are recommended to treat the osteoarthritis but may worsen the hypertension and decrease the efficacy of a diuretic if it is used.

Providers need to talk with their patients to identify healthcare priorities so that treatment can be adjusted to enhance these outcomes. That patients' preferences change is well-documented, so this conversation about goals for care needs to be ongoing, with changes to the care plan reflecting the evolution of preferences.

However, we do not understand how best to partner with patients to help them be advocates for themselves and their families. Including patients as full participants and decision-makers in their healthcare is important but difficult to implement: their healthcare is often so complex that even providers often do not fully understand the technicalities of every aspect of the patient's care. Understanding what self-management means in this context, and how to incorporate friends and family members into this process requires further research. Unfortunately, because of the persistent stigma associated with HIV infection, many patients may not have disclosed their HIV status even to their closest friends and family. How to provide care for these more isolated individuals is an important area of research and clinical concern.

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Quick points

- Women with HIV are aging, but their life expectancy is still shorter than that of their uninfected counterparts.
- Optimal management of women infected with HIV should take into consideration multimorbidity and polypharmacy, but no research exists to guide patients and providers.
- Providers and patients may benefit from incorporating a gerontology perspective in the primary care of aging women with HIV.

Table 1

Life Expectancy for Men and Women in the General Population Compared with those who are HIV infected.

General population (HIV−)	**Men**	**Women**	**Difference in life expectancy**
A 20 year old will live to be (years)	76	80	Women live 4 years longer than men
A 35 year old will live to be (years)	77	81	Women live 4 years longer than men
HIV+ at ART initiation			
A 20 year old will live to be (years, adjusted)	63	64	Women live 1 year longer than men
A 35 year old will live to be (years, adjusted)	67	68	Women live 1 year longer than men
Years of life lost for HIV infected individuals			
20 year old	13	16	HIV+ women lose, on average, 3 years of life more than men.
35 year old	10	13	HIV+ women lose, on average, 3 years of life more than men.

Table 2

Summary of primary care recommendations for women with HIV

Aspects of care	Recommendations for women with HIV	Differences from the general population	Gender-specific issues
Menopause[2,4]			
	Similar to women in the general population.	HIV may be associated with earlier onset of menopause. May need more than 12 months amenorrhea to diagnose (for example, serum FSH and estrogen concentrations may be helpful). Likely associated with more severe symptoms. HRT and non-hormonal alternatives may be considered. Effective dosing of HRT may be higher than in the general population because of drug/drug interactions.	NA
Mental Health/Neurology			
Depression[1820]	Screening at diagnosis and then at least annually.	Rates of depression much higher among women with HIV than in the general population	Rates of depression twice as high in women with HIV as in men with HIV. Role of stigma should be explored.
Substance abuse[232728]	Screen at baseline and at least annually for both alcohol and drug use/abuse. Refer for treatment as indicated.	Increases risk of HIV transmission. Also has direct effect on the immune system: lowers CD4 count.	Hepatic consequences of alcohol abuse more pronounced in women than men, women may be more susceptible to alcohol-induced brain damage than men.
Cognitive impairment[3031]		Untreated HIV is likely most important HIV-related cause. Rule out other causes found in general population, including Alzheimer's and vascular dementias.	As yet, no gender differences have been identified for HIV-associated dementia. However most of the women in these studies are premenopausal, thus not much is known about cognitive decline among postmenopausal, HIV infected women.
Cancer			
Cervical[3424]	Cervical cancer screening at diagnosis and again 6 months later. If normal, annual screening.	No explicit guidelines regarding incorporation of co-testing (cytology and HPV).	NA
Anal[2]	Screen women with abnormal cervical testing, with history of anal-receptive intercourse, and with anogenital warts.	Screening not recommended for women in the general population.	High rates of anal cancer in both HIV+ men-who-have-sex-with-men and in women with HIV
Cardiovascular disease and metabolic disorders			
Cardiovascular disease (CVD)[2]	See individual guidelines below for hypertension, dyslipidemia and diabetes.	Framingham risk score likely underestimates true CVD risk, but addressing these risk factors is a good place to start.	Current research indicates that in terms of CVD risk in women with HIV vs men, there are few differences. However, the numbers of women with HIV who have with CVD are limited (most cohorts are composed of younger women), limiting our knowledge on this point.

Aspects of care	Recommendations for women with HIV	Differences from the general population	Gender-specific issues
Hypertension[2]	Annual screening. Management same as in general population.	Be aware of possible drug/drug interactions.	None
Dyslipidemia[2]	Screen at initial visit, before starting ART, and 1–3 months after ART initiation. Management is similar as in the general population	Be cognizant of drug-drug interactions when prescribing lipid-lowering medications, particularly statins with protease inhibitors.	None
Diabetes[2]	Screen at initial visit, before starting ART, and 1–3 months after ART initiation. Management the same as in the general population.	Rates of diabetes lower among individuals with HIV than among the general population.	None
Osteoporosis[2]	Baseline bone densitometry on all post-menopausal women.	Baseline bone densitometry on women 65 years of age or older, thus much later than among women with HIV.	Recommendation that HIV+ men receive routine screening at age 50.
Anemia[2]			
	CBC obtained at entry into care. No HIV-specific guidelines for definition or management of anemia.	Anemia more common among women with HIV than in the general population and closely associated with mortality regardless of CD4 count.	Anemia far more common in women than men.
Coinfection with Hepatitis C[2]			
	Test at entry into care and annual testing if risk factors persist.	High rates in baby boom generation add to the need for screening in this age group	None
Immunizations			
Zoster vaccine[572]	Do not use in individuals with CD4 count at or below 200 cells/μL. No recommendation for or against use in individuals with CD4 > 200 cells/μL.	Uncertainty re safety and efficacy of the vaccine in persons with HIV, but potential for greater benefit because of high rates of zoster and post-herpetic neuralgia in HIV+ populations.	None
Multimorbidity and polypharmacy[6367]			
	No guidelines as yet.	May need to consider multimorbidity and polypharmacy at younger ages than in general population. Impact of these conditions on HIV+ individuals requires further research.	Women may be more susceptible to impact of polypharmacy than men – requires further research.

Abbreviations: ART, antiretroviral therapy; CBC, complete blood count; CD4, cluster of differentiation 4, also known as T-helper cells (these cells mature in the *t*hymus); CVD, cardiovascular disease; HPV, human papillomavirus; HRT, hormone replacement therapy.

Table 3

Website Resources

Name of Resource	URL	Description of content
AIDSInfo	http://aidsinfo.nih.gov/guidelines	This site contains federally approved HIV/AIDS health care practice guidelines. Of key importance are the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Information about drug interactions can be found in the tables
New York State Department of Health, AIDS Institute	https://www.health.ny.gov/diseases/aids/	Excellent website containing information for patients and providers. In particular, includes a number of helpful practice guidelines.
Centers for Disease Control and Prevention, HIV site	http://www.cdc.gov/hiv/	Additional resources for patients and providers.
FRAX	http://www.shef.ac.uk/FRAX/	World Health Organization fracture risk assessment tool. The algorithms give the 10-year probability of hip fracture and of a major osteoporotic fracture.