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Women, Aging, and HIV: Clinical Issues and Management Strategies

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Abstract

Women are living longer with HIV infection. How best to manage the multiple co-morbidities and polypharmacy that are a hallmark of HIV infected individuals has not been studied.

We explore incorporating principles of gerontology, particularly multimorbidity and polypharmacy, to optimize the health of HIV infected women.

Multimorbidity and polypharmacy are important issues for HIV infected women. Incorporating a gerontologic approach may optimize outcomes until research provides more definitive answers as to how best to collaborate with HIV infected women to provide them with optimal care. A case study is used to guide the discussion.

Keywords

HIV; aging; polypharmacy; multimorbidity; gerontology

The Clinical Problem

HIV infected individuals in the United States are aging: 50% will be over the age of 50 by 2015. However, there is evidence to suggest that even with antiretroviral therapy (ART), these individuals may not have a “normal” lifespan¹ because of issues associated with HIV infection, as well as conditions commonly found in the elderly, including multimorbidity, and polypharmacy. In the general population, 20 year old men can expect to live to the age of 76. Women of the same age can expect to live to be 80 years of age. Among 35 year olds,

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men can expect to live to be 77 years of age, and women 81.² In contrast, life expectancy estimates for HIV infected individuals project that a man who initiates ART at 20 years of age will live to be 63 years old, while a woman will live to be 64 years. If they initiate ART at 35 years of age, men can expect to live to be 67 years of age, and women 68.³ These estimates may improve for individuals who initiate ART shortly after HIV diagnosis.⁴ For those with longstanding infections, however, HIV infected men may live 10-13 years less than men in the general population. HIV infected women may even more disadvantaged, losing 13 to 16 years of life compared to uninfected counterparts.

Why lifespans are shorter, and why women are particularly disadvantaged, are not well understood. HIV specific factors such as inflammation and side effects of ART likely contribute. However, issues that are common among the elderly, particularly multimorbidity and polypharmacy, likely play a role.

Multimorbidity is associated with decreased functional status and quality of life, increased adverse drug events, medical costs, disability, and mortality.⁵ Both HIV infection and older age increase the risk for multiple co-morbid conditions.^{6,7} The high prevalence of multimorbidity among HIV infected individuals has been well documented.^{5,6} Multimorbidity may be related to HIV, to immunosuppression, to antiretroviral medications, and to an increased prevalence of traditional risk factors among individuals with HIV. While little is known about multimorbidity among HIV infected women, Salter and colleagues⁶ suggest that HIV infected women may be more likely to experience multimorbidity than HIV infected men, which highlights the importance of focusing on management issues for women.

Polypharmacy has been associated with poor health outcomes, including hospitalization and mortality.⁸ In the Veterans Aging Cohort Study, 55% of HIV infected individuals over the age of 50 took five or more daily medications.⁹ Whether polypharmacy is associated with mortality independent of its association with multimorbidity is unclear. Particularly among individuals with HIV infection, polypharmacy might 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.⁹ Women may be at particular risk for the negative outcomes associated with polypharmacy because of issues related to pharmacokinetics and -dynamics which make them more vulnerable to adverse drug effects than men.¹⁰

Clinical Implications

While there is minimal information on how to manage multimorbidity and polypharmacy in HIV infected individuals, these patients are presenting to primary care (not just specialty) clinics. Disease-specific guidelines abound. However, approaching multimorbidity with individual, disease-specific guidelines can result in impractical, or even harmful, care.¹¹ We will explore the use of a framework suggested by the American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity.¹¹ Rather than a generalized, one-size-fits-all approach, the Panel suggests that providers consider the multiple problems specific to each individual, as well as individual preferences and goals, their prognosis,

multifactorial syndromes, and the feasibility of each management decision and its implementation in the context of the patient's life. Interactions between potential treatments and interventions must be considered.

Providers do not typically consider individuals between 50 and 65 years of age to be "older." However, in the context of HIV infection, given shortened lifespans and the presence of multimorbidity and polypharmacy, incorporating gerontological principles into clinical management may make sense.

We consider the implementation of the Expert Panel's guidelines using Mary's history to guide this exploration. Focusing specifically on management of women infected with HIV is important given that they may be particularly disadvantaged in terms of lifespan, and because they may be more prone to multimorbidity than HIV infected men. They may also be more susceptible to negative outcomes associated with polypharmacy. The subsequent headings match those proposed by the Expert Panel.

Identify the primary concern that brought Mary to clinic

The purpose of Mary's visit is to establish care with a new provider. Mary's current treatment plan, her comfort with the regimen, and her ability to adhere can be reviewed. Had Mary presented with a particular concern, we could focus the visit on this specific aspect of care. As Mary does not have a chief complaint, a general review of her plan of care is appropriate.

Conduct a complete review of the care plan, including a review of current medical conditions and interventions, as well as adherence/comfort with treatment plan

HIV

Mary's HIV is well-controlled. Her regimen has established efficacy,¹² but it is a twice a day regimen, and this has important, potentially negative implications for adherence.¹³ Mary states that she rarely misses her ART, although she occasionally misses evening doses when she falls asleep before taking her pills.

COPD

Mary's current forced expiratory volume (1 second) (FEV₁) is 65% of predicted. Her functional dyspnea, assessed by the Medical Research Council dyspnea scale, is a 2, indicating that she walks slower than her contemporaries on level ground because of breathlessness. Consistent inhaler use controls her symptoms, and she does not experience interference with activities that she enjoys. Her one complaint is that she used to enjoy exercising, but she is concerned that exercise might exacerbate her symptoms.

Anemia

Mary has moderate anemia that is untreated.

GERD

Mary has had GERD for years and has used a PPI for 5 years. Even with the PPI, Mary reports heartburn and regurgitation 2-3 times per week. Her heartburn improves significantly when she misses her bisphosphonate.

Osteoporosis

Mary takes a bisphosphonate to treat her osteoporosis but admits occasional nonadherence as it aggravates her GERD. She also has difficulty remembering to take a once-weekly regimen.

Mary is also Vitamin D insufficient and is treated with 1,000 IU of Vitamin D3 per day. Mary's calcium intake is very low as she is lactose intolerant. She does not take a calcium supplement because she already takes too many pills.

Osteoarthritis

Mary has had osteoarthritis in her knees for 5-6 years. Within the last 3 years, her symptoms have increased in severity, limiting her ability to move and participate in activities that she enjoys. She has been prescribed morphine which provides little relief. She has tried physical therapy which was helpful, but her insurance company limited her access to ongoing therapy. She would like to swim but is concerned that swimming would aggravate her COPD. She occasionally walks with a cane, using it more frequently over the past 6 months. She has not seen an orthopedist in several years.

Constipation

Constipation, related to chronic morphine use, poor fluid intake, a low-fiber diet, and minimal exercise is an ongoing problem, inadequately treated by the senna and colace.

Patient preferences/goals

Mary emphasizes the importance of mobility, independence and adequate pain management. Her life revolves around friends and family. She particularly enjoys spending time with her young, active grandchildren. Preservation of her cognitive function is also important. She states, "My mind is who I am:" a decline in Mary's cognitive function would entail a loss of self.

Relevant evidence regarding important outcomes

Mobility, independence, and pain management

Mary's mobility and independence are most threatened by her COPD, anemia, osteoporosis (fractures) and osteoarthritis. The latter is also the primary source of her pain.

COPD is the second most frequently encountered pulmonary condition among HIV infected individuals in the ART era.¹⁴ However, there are no studies addressing the management of COPD in HIV infected individuals. Until such evidence is available, HIV infected patients should be managed according to the guidelines established for the general population, with a

few considerations.¹⁵ First, inhaled corticosteroids in the presence of ritonavir may cause iatrogenic Cushing's syndrome as well as osteoporosis and fragility fractures.¹⁶ Secondly, because the systemic and skeletal manifestations of COPD may be exaggerated among HIV infected individuals and may be associated with greater losses in physical capacity, these individuals may experience significant benefit from pulmonary rehabilitation. Thus Mary's COPD treatment, in the context of her ART, may put her at risk for fractures and decreased mobility, but she may derive significant benefit from pulmonary rehabilitation.

Anemia has always been an important concern for HIV infected individuals.¹⁷ Currently, ART is associated with resolution of and protection against anemia. None-the-less, 30% of HIV infected individuals are mildly anemic.¹⁸ Women, Blacks, intravenous drug users, and older individuals are at greatest risk for anemia.¹⁸ Even though this is a mild anemia, it is associated with decreased survival: HIV infected individuals with anemia may experience twice the risk of death as those who are not anemic.¹⁹ Pathogenesis is multifactorial, but may be driven by the persistent inflammation that exists even with fully suppressed HIV. Poor nutrition, and all routine causes of anemia, need to be evaluated.

In the elderly general population, anemia is 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.

Osteoporosis is more common among HIV infected compared with uninfected individuals^{20,21} as are fragility fractures.^{22,23} 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 for fragility fracture found in the general population, in particular increasing age, white race, alcohol use, liver disease, corticosteroid use, current or past smoking, PPI use, body mass index, and decreased hemoglobin.^{22,24} Others have focused more on the contribution of HIV-specific factors.^{23,25} Likely the cause is multifactorial.

Pharmacologic intervention for osteoporosis must be based on absolute fracture risk, using clinical fragility fracture risk factors, and not just on T-scores. T-scores are diagnostic, not treatment, thresholds for osteoporosis and osteopenia.²⁶ FRAX®, the algorithm most commonly used to calculate fracture risk, 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). Mary's 10 year probability of a major osteoporotic fracture is 9.9%, and her risk of a hip fracture is 2.0%. She does not meet criteria for pharmacologic therapy.²⁷

Mary's osteoarthritis management does not match the recommendations put forth by the Osteoarthritis Research Society International (OARSI).²⁸ Extensive use of morphine may put Mary at risk for falls and fragility fracture,²⁹ and reliance on NSAIDs may worsen her anemia.³⁰ OARSI recommends non-pharmacologic modalities (lifestyle, exercise, pacing of activities and other measures to unload the damaged joints) as a primary focus. Referral to a

physical therapist may be helpful. Appropriate footwear might help to reduce pain, improve stability, and decrease Mary's risk for falling. Consultation with an orthopedist to evaluate the possibility of knee replacement surgery may be considered.

Cognitive function

HIV infection, morphine, and anemia may negatively impact Mary's cognitive function. HIV dementia was well-documented in the pre-ART era. While ART may have a positive effect on neurocognitive impairment,³¹ the benefits of ART for HIV cognitive disorders associated with HIV are unclear. Some have suggested the prescription of 'neuroactive ART' (at least three drugs that have good central nervous system penetrance^{32,33}) to improve cognitive function.³⁴ There is no evidence, however, that a neuroactive regimen prevents HIV-associated neurocognitive dysfunction.

Sedation and mild cognitive impairment is a common side effect of opiate use in the elderly,³⁵ and the use of opiates to treat non-malignant chronic pain is controversial, particularly if alternative therapies have not been explored.³⁶ However, pain is also an important predictor of cognitive impairment and thus must be adequately treated.³⁷ Incorporating the nonpharmacologic modalities described above for the treatment of osteoarthritis may help with pain management and decrease Mary's reliance on morphine.

As noted earlier, anemia in women is associated with decreased executive function. A full evaluation of Mary's anemia to rule out treatable causes may decrease her risk for cognitive decline.

Prognosis

Mary's lifespan may be shorter than that of someone without HIV infection. Using the VACS Index, a prognostic indicator for individuals with HIV, Mary's risk of death over the next 5 years is 19%, (<http://www.vacohort.org/welcome/vacsindexinfo.aspx>) compared to a woman of the same age with a normal hemoglobin and a CD4 count greater than 500 who has a 5 year mortality risk of 4%.

Providers need to consider how to incorporate life expectancy or prognosis into clinical decisions. These considerations are straightforward when looking at extremes: individuals with a very short life span will likely not live long enough to benefit from treatments where the benefit is not immediate, and those with a long life-expectancy will likely benefit from treatments where the benefits are long term. What to do with intermediate survival, as in Mary's case, is more difficult.

Consider interactions within and among treatments and conditions

HIV and COPD

Concurrent use of ritonavir and inhaled corticosteroids (fluticasone and possibly budesonide) may cause osteoporosis and fragility fractures,¹⁶ thus Mary's osteoporosis may, in part, be related to her medication regimen.

Osteoporosis and GERD

Bisphosphonates can aggravate reflux, and PPIs increase the risk of fracture.²⁴

Osteoarthritis and Anemia

NSAIDs increase the risk for gastrointestinal bleeding and are an important contributor to anemia, particularly in the elderly.

Weigh benefits and harms of components of the treatment plan

HIV and COPD

Both Mary's ART and her COPD treatment regimens are effective. However, given the potential interactions between Mary's ART and her COPD treatment, her provider may consider consulting with a pulmonologist and/or an HIV specialist, if she is not an expert in HIV care, to change one or both of her regimens. Determining if Mary was symptomatic when only using short- and long-acting bronchodilators would be important, as would discussing Mary's comfort with discontinuing the steroid inhaler, along with a thorough discussion of risks and benefits of the current and alternative treatment options. If Mary is willing, withdrawal of the corticosteroid under the supervision of a specialist could be considered. If discontinuing the inhaled steroid is not appropriate, consultation with an HIV specialist would be necessary to determine an alternative ART regimen.

Osteoporosis and GERD

Mary does not meet criteria for pharmacologic treatment of her decreased bone mineral density. Furthermore, the bisphosphonate aggravates her GERD and may put her at risk for a number of side effects that could threaten her health care goals, including atypical femoral fractures.³⁸ If the reflux resolves once the bisphosphonate is discontinued, no further workup or treatment is indicated. If it persists, consideration should be given to a more intensive work-up of Mary's GERD to rule out alternative etiologies. A trial of calcium-based antacids might be appropriate as it could control the reflux and provide calcium supplementation. Interactions between antacids and ART should be considered if Mary's ART regimen is changed. Discontinuing the PPI may also decrease Mary's risk for a fracture.

As falls are an important cause of hip fractures, physical therapy or a supervised exercise and balance program, in addition to her pulmonary rehabilitation, may help Mary to develop muscle and bone strength and improve her balance. Continuing her Vitamin D regimen may also decrease her risk for falls.³⁹

Osteoarthritis and pain

Mary's osteoarthritis regimen does not match guidelines that stress a combination of non-pharmacologic and pharmacologic therapies. Her participation in pulmonary rehabilitation may provide Mary with the support she needs to exercise. A referral to an orthopedist for alternative treatments for her osteoarthritis may also be helpful, as would a referral to a pain clinic.

Communicate and decide for or against implementation or continuation of intervention/treatment

Mary's revised treatment plan may include one or more of the following components. The order with which one should proceed with these modifications should be dictated by Mary's preferences taking into consideration recommendations of specialists.

1. Referral to a pulmonologist, ideally one with extensive experience managing COPD in HIV infected patients, to evaluate the possibility of tapering her inhaled corticosteroid. In addition, refer her for pulmonary rehabilitation so that she can develop her comfort with and capacity for exercise.
2. If Mary cannot be weaned off of the inhaled corticosteroid, consider alternative ART or refer to an HIV specialist. A full ART history with genotypes must be available to best consider Mary's treatment.
3. The bisphosphonate should be discontinued. Continuing Vitamin D supplementation may contribute to bone strength and decrease falls risk. Evaluate the persistence of GERD after stopping the PPI.
4. Of greater concern than bone mineral density, however, is Mary's risk for falls. Her medications (morphine), her mobility problems, Vitamin D insufficiency, and her lack of exercise may all contribute to this risk. Referring Mary to physical therapy (if pulmonary rehabilitation is insufficient or once it ends) may help to manage her pain and allow her to decrease her morphine dose. Local gyms may also have a number of water aerobics programs that might facilitate her ability to exercise, despite her osteoarthritis, and improve her pain management, strength and balance. Referring her for appropriate orthotics to provide her with greater stability while walking may also help.
5. Referral to orthopedics to determine if she is a candidate for knee replacement might provide long-term improvement in her pain.
6. Conduct a thorough evaluation of Mary's anemia, including an endoscopy and colonoscopy (if indicated). It would also be important to rule out additional causes of anemia, particularly iron deficiency secondary to NSAID use. Replacing the NSAID with acetaminophen could be considered.

Conclusions

HIV infected individuals may have a shorter expected lifespan than their uninfected counterparts. The causes of this are multifactorial, including HIV-specific effects as well as more general issues of multimorbidity, and polypharmacy. How these factors play a role in the difference in mortality by gender is not known.

How to manage multimorbidity and polypharmacy in the context of HIV infection and aging requires research, but the work already done in geriatric populations can serve as a useful starting point. There are limits, however, to this approach. Polypharmacy, in particular, is

problematic. Implementing our suggestions would bring Mary's plan of care more into line with her goals. Polypharmacy, however, would remain. At the beginning of the visit, Mary was taking 15 medications. After future consults, Mary may discontinue the budesonide/formoterol (Symbicort), the bisphosphonate, the PPI, the senna and the colace. A calcium-based antacid would be added. Mary would still be taking nine medications: polypharmacy by most definitions.⁹ Assessing patients' perspectives on whether or not they are taking too many medications is important and could be easily evaluated. A more difficult question is how to approach further reduction of polypharmacy.

While the active involvement of the patient in her care is central to this approach, cognitive impairment is a growing problem for individuals living with HIV infection. Providers need to be alert to the signs and symptoms of cognitive impairment in their patients and need to collaborate with the patient as well as specialist providers to determine when the patient is no longer able to make decisions consonant with their best interests. Identifying individuals whom the patient wants to make medical decisions for them, and incorporating these individuals into the patients' health care and decision making before the patient loses the ability to do so, is crucial. 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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Mary is a 58 year old woman diagnosed with HIV at the age of 40. In addition to HIV, Mary has a number of comorbid conditions including chronic obstructive pulmonary disease (COPD), anemia, gastroesophageal reflux disease (GERD), osteoporosis, osteoarthritis, and constipation (Table 1). She takes several prescription medications including lopinavir/ritonavir (Kaletra) + tenofovir/emtricitabine (Truvada), budesonide/formoterol (Symbicort), ipatropium, albuterol, a bisphosphonate, Vitamin D, a proton pump inhibitor (PPI), a non-steroidal anti-inflammatory (NSAID), morphine, colace, and senna. She has a fully suppressed HIV viral load (< 20 copies/ mm^3) and a CD4 count of 450 cells/mm^3 (36%). Her most recent hemoglobin was 10.5 gm/dL . Her DXA T-scores were lumbar spine -2.7 and femoral neck -2.5 . Mary's BMI is normal (21 kg/m^2). Movement is painful, and Mary reported a pain score of 8/10. She requires a cane and has help with the housework and shopping. She is cognitively intact. She presents today as a new patient, having recently moved to your area to be closer to her son. She has no complaints at today's visit.

Table 1

Mary's comorbid conditions, medications, and associated laboratory values at her initial visit, with corresponding benefits and harms of current treatment plan.

Health care condition	Associated medications	Associated laboratory/radiology/physical exam values	Benefits	Harms
HIV	Lopinavir/ Ritonavir (Kaletra) Tenofovir/ Emtricitabine (Truvada)	CD4: 450/cells/mm ³ CD4 percent: 36% HIV RNA < 20 copies/mm ³ VACS Index: 40 (5 year mortality risk 19%)	Excellent viral control	Ritonavir may interact with budesonide to increase risk for osteoporosis. BID dosing may increase risk of nonadherence
COPD	Budesonide/Formoterol (Symbicort), ipratropium, albuterol	Does not require O ₂ ; most recent FEV ₁ % predicted: 65% Medical Research Council dyspnea score: 2	Good symptom control	See above
Anemia	--	Hemoglobin: 10.5 g/dL	--	--
GERD	Proton pump inhibitor	--	Reasonable control of GERD	GERD may, be caused/aggravated by bisphosphonate. PPI may significantly increase risk of fractures
Osteoporosis	Vitamin D, Bisphosphonate	DXA T-scores Lumbar spine: -2.7 Femoral neck: -2.5 Serum 25-hydroxyvitamin D: 29 ng/ml	Adequate levels Vitamin D are important for a number of reasons	Osteoporosis may be related to combination of ART and COPD medications. (see notes for HIV) Bisphosphonates may contribute to GERD.
Osteoarthritis/ chronic pain	Morphine, NSAID	BMI 21kg/m ² Pain score: 8/10	Minimal	Morphine increases risk of falls, increases likelihood of constipation. NSAID may contribute to anemia
Constipation	Senna, Colace	--	Minimal	Additional, ineffective medications.