REVIEW

Polypharmacy in the HIV-infected older adult population

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Abstract: The prevalence of human immunodeficiency virus (HIV) infection among people older than 50 years is increasing. Older HIV-infected patients are particularly at risk for polypharmacy because they often have multiple comorbidities that require pharmacotherapy. Overall, there is not much known with respect to both the impact of aging on medication use in HIV-infected individuals, and the potential for interactions with highly active antiretroviral therapy (HAART) and coadministered medications and its clinical consequences. In this review, we aim to provide an overview of polypharmacy with a focus on its impact on the HIV-infected older adult population and to also provide some clinical considerations in this high-risk population.

Keywords: HIV, older adults, polypharmacy

Introduction: HIV, aging, and comorbidities

Acquired immunodeficiency syndrome (AIDS)-related mortality of human immunodeficiency virus (HIV)-infected people in the United States has been reduced over the years, and this trend is in large part a result of the introduction of highly active antiretroviral therapy (HAART).[1] As a result, HIV-infected individuals are living longer. By 2015, more than one-half of all HIV-infected individuals in the United States will be older than 50 years of age.[2] The prevalence of HIV in this age group is expected to be significant considering the increased life expectancy of the general population and the increased survival of HIV-infected individuals. In the general population, those who are 50 years and older are not referred to as "older adults." However, in the HIV/AIDS population, this subset of the population does carry the label "older adults." The Centers for Disease Control and Prevention applies this label and considers this subset of the population as a separate group, mainly because early in the HIV epidemic, this age group was much older than the mean age of HIV-infected patients.[2]

Studies have shown that in the current environment, where the number of HIV-infected older adults has continued to increase year after year, there has been a similar increase in the number of comorbid conditions concomitantly present in these individuals and also an increased use of medications. In one study that investigated HIV-infected individuals aged 55 years and older in New York City, 89% had one or more comorbidities, or an average of 2.4 comorbid conditions per person, and 81% received medications unrelated to HIV.[3] In that study, the most common comorbidities were hypertension, chronic obstructive pulmonary disease, and diabetes mellitus.

Additionally, it is believed that HIV infection, and quite possibly its treatment, may be contributing to the acceleration of the aging process by several years when compared

749

with those who are not infected with HIV. Dyslipidemia, dysregulation of glucose metabolism, reduced bone density and osteopenia, hypogonadism, renal and hepatic disorders, psychiatric illness, neurocognitive impairment, and coronary artery disease are all conditions likely to occur earlier in HIV-infected individuals compared with their unaffected peers.[4] Another study that compared HIV-infected veterans 50 years of age and older to non-HIV-infected veterans of similar age found that the older HIV-infected veterans had higher odds of multimorbidity.[5] This study also concluded that when compared to non-HIV infected individuals, the HIV-infected veterans experienced a more pronounced increase in disease burden (hypertension, diabetes mellitus, vascular, pulmonary, and renal disease) as well as an increase disease prevalence as they aged.

A signature collaboration group with cohorts spanning the world was formed to provide information about the prognosis of individuals starting HAART for the first time. The Antiretroviral Therapy (ART) Cohort Collaboration looked at specific causes of mortality of HIV-infected individuals who initiated HAART. They discovered that deaths classified as AIDS-related decreased with increasing duration of HAART therapy. Older age (≥50 years) was strongly associated with increased rates of non-AIDS-related malignancy and cardiovascular disease (CAD), and the cause of death least associated with age was AIDS. Furthermore, there was a marked increase in the rates of renal death in patients >60 years old. The abovementioned results further demonstrate the burden of chronic comorbid diseases in this population.

As a result of the increased average age of HIV-infected individuals since the introduction of HAART, patients are more often exposed to disease- and treatment-related morbidities, which in turn has led to an increased likelihood of polypharmacy.[6] Overall, there is not much known about the impact of aging on medication use in HIV-infected individuals; the potential for interactions with HAART and coadministered medications; and the impact of these factors on therapy tolerability and virological response.

Overview of polypharmacy

Polypharmacy can be simply defined as the concomitant use of multiple medications;[7] however, polypharmacy also has multiple definitions within the scientific literature such as the use of a large number of medications, the use of potentially inappropriate medications, medication underuse, and medication duplication.[8,9] The two most commonly cited definitions are more specific and are: (1) the use of six or more medications; or (2) the use of a potentially inappropriate drug for which the medication does not match the diagnosis.[10]

The use of multiple medications is certainly a relevant issue, especially in the older adult population. A national survey by Kaufman et al[11] found that 90% of people aged 65 and older use at least one medication per week, more than 40% of this population use five or more different medications per week, and 12% of this population use ten or more medications. Noteworthy, in the same population class, the authors found a 14% increase in fall risk with the addition of any additional medication after four drugs, regardless of drug class.[12] Studies have shown that the frequency of unnecessary or not recommended medication use is higher in patients who take many medications compared with those who take few medications.[13,14]

It is important to note some of the negative consequences as a result of polypharmacy. To start, patients taking multiple drugs for multiple chronic medical conditions have a potentially increased risk of falls,[12] drug–drug interactions (DDIs), and adverse drug events (ADEs).[15,16] ADEs and DDIs in older adults not only increase morbidity and mortality,[15] but they also are a common cause of emergency hospitalizations and represent common occurrences in both the hospital and ambulatory settings.[17,18] An example of an ADE with polypharmacy is the increased risk of serious hypoglycemia when prescribed sulfonylureas or insulin therapy with the use of five or more therapeutic classes.[19] Drug interactions can also be associated with an increased risk of toxicity. Some common interactions include combining digoxin with diuretics, resulting in digoxin toxicity including arrhythmias and hyperkalemia; the use of nonsteroidal antiinflammatory drugs and diuretics resulting in renal failure; and combinations or narcotics and antidepressants causing central nervous system depression and sedation.[20] That being said, the identification and the management of such interactions are absolutely important for delivering quality patient care.

It has been reported that ADEs are common and often preventable in older adults in the ambulatory setting. The rate of ADEs was 50.1 per 1000 person-years; 28% of ADEs were found to be preventable.[21] Field et al[22] conducted a large nested case control study in an ambulatory population and found that there was a dose–response association of ADEs with the Charlson Comorbidity Index score and number of scheduled medications. In the analysis of preventable ADEs, the dose–response relationship with comorbidity and number of medications persisted. Patients taking anticoagulants, antidepressants, antibiotics, cardiovascular drugs, diuretics, hormones, and corticosteroids were at increased risk for ADEs. Moreover, patients at greatest risk from polypharmacy were those who saw several doctors, had prescriptions filled

at multiple pharmacies, and were older adults with multiple comorbidities.[23,24]

Polypharmacy can be linked to increased costs for both the patient and the health care system. Some of the medications older patients take, including over-the-counter medications, are often not covered by health insurance or Medicare. The result can be an increased financial burden for older patients whose income generally consists of using savings from a retirement account and a fixed income such as Social Security.[25] Not surprisingly, a study that compared two groups of Medicare patients found there was a statistically significant difference in statin use when comparing those with prescription drug coverage to those without prescription drug benefits (27.4% versus 4.1%).[26]

Additionally, minor drug interactions can lead to increased clinic visits, a prescribing cascade where additional medications are given to treat new symptoms, or new lab or imaging studies. Serious adverse events from polypharmacy can lead to specialist visits, emergency department visits, and hospital admissions.[17,27,28] In a study from the 2000–2001 Medical Expenditure Panel Survey, it was found that the estimated total cost attributed to the use of potentially inappropriate medications in community-dwelling older adults was $7.2 billion.[29]

There are two approaches to evaluate potentially inappropriate medication use in older adults: the Beers criteria and the Medication Appropriateness Index. The initial Beers criteria in 1991 consisted of lists of specific drugs or drug classes that were considered inappropriate based on preexisting conditions for nursing home residents; the list was expanded to include all settings of geriatric care in 1997, 2003, and 2012.[30–33] The Medication Appropriateness Index uses ten items to assess the degree of appropriateness of a particular medication along with a three-point Likert rating scale.[34] Inappropriate medication use in the ambulatory setting has been shown to be prevalent in 65% of older adults,[35] but concomitantly, these same patients are often not prescribed potentially beneficial medications.[9]

Another problem with a large number of medications being prescribed is the increase in "pill burden," which can potentially affect compliance because patients simply get tired of taking their medications and miss doses as a result. Most of the literature that examines dosing regimens and compliance has been conducted in the HIV-infected population in which nearly perfect adherence is required to achieve and sustain viral suppression, maintain immune health, and slow disease progression.[36] Not surprisingly, literature on the relationship of regimen factors and adherence in HIV disease indicates that higher dose frequency and greater regimen complexity result in poorer adherence.[36]

Polypharmacy in HIV-infected patients

Polypharmacy is common in the HIV-infected older adult population. Marzolini et al[37] in a Swiss cohort study compared HIV-infected older adults who were aged ≥50 years with younger HIV-infected patients (aged <50) on HAART; they found that older patients were more likely to receive one or more comedications compared with younger patients (82% versus 61%, $P < 0.001$). This study also determined that older patients had more frequent potential for DDIs when compared with the younger patients (51% versus 35%, $P < 0.001$). Furthermore, HIV-infected older adults generally used a higher number of comedications and certain therapeutic drug classes more frequently when compared with the HIV-infected younger patients. Some of the drugs studied were cardiovascular drugs (53% in the older group versus 19% in the younger group), gastrointestinal medications (10% versus 6%), and hormonal agents (6% versus 3%). The potential for DDIs with HAART in the older adult group occurred mainly with cardiovascular drugs (27%), central nervous system agents (22%), and methadone (6%). It should be noted, however, that medications used in the older patient group and the younger patient group were not significantly different with respect to the effect on antiretroviral tolerability and response.[37] Another study reviewed the prevalence and risk factors for clinically significant drug interactions with HAART, and it was found that those subjects aged >42 years with more than three comorbidities and a treatment plan consisting of three or more antiretroviral agents or a protease inhibitor (PI) were at an independently increased risk of a clinically significant drug interaction.[38] It has been shown that HIV-infected patients aged 50 years or older have a better adherence rate to HAART treatment than their younger counterparts;[39–42] as a result, this can increase the likelihood of potential drug interactions.

There are currently six classes of antiretroviral medications approved for use in the United States and these include nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors (NNRTIs), PIs, integrase inhibitors, fusion inhibitors, and CCR5 antagonists.[43] Treatment with HAART has the potential for DDIs. As a class effect, PIs can inhibit cytochrome P450 3 A (CYP3 A) to varying degrees and to some extent other isoenzymes, with ritonavir (RTV) being the most potent.[44–46] RTV is used to "boost" the levels of other PIs by inhibiting their metabolism.

Inhibition of CYP450 (CYP3 A) can cause an increased plasma concentration of CYP450 CYP3 A substrates, either antiretroviral or nonantiretroviral, which has the potential for toxicity. On the contrary, NNRTIs such as nevirapine, efavirenz, etravirine, and PIs, such as lopinavir and tipranavir, are inducers of CYP3 A, which can lower the concentration of some CYP3 A substrates.[47] Interactions involving efavirenz, nevirapine, etravirine, and other medications that are metabolized through CYP450 3 A4 can lead to decreased plasma concentrations of coadministered medications, potentially leading to their decreased efficacy. Nucleoside reverse transcriptase inhibitors, maraviroc, raltegravir, and enfuvirtide do not inhibit or induce CYP450 isoenzymes, and clinically significant DDIs with these medications are uncommon.[48]

The combination of HAART and polypharmacy significantly increases the chance of adverse outcomes stemming from the potential DDIs. Some of these negative outcomes include drug toxicity, poorer HAART adherence, loss of efficacy of the coadministered medication, and virologic breakthrough.

Consequences of polypharmacy in older HIV-infected patients

The consequences of polypharmacy are significant in older adults infected with HIV. Of note, the combination of medications used to treat chronic diseases and HAART in older adults infected with HIV increases the chance for DDIs, which can lead to the loss of efficacy of medications and toxicity. Older adults are even more susceptible to drug interactions than their younger counterparts. First, older adults infected with HIV suffer from aging-related comorbid illness. Second, age-related physiologic changes affect the pharmacokinetic and pharmacodynamic properties of medications. These physiologic changes can be explained by a number of factors including patient genetics, lifestyle, and their specific environment. Simultaneously, these changes contribute to interpatient variability and may add complexity to the management of drug interactions in our older adult population. Pharmacokinetic alterations with aging alone can result in changes to both a person's body composition and to the function of drug-eliminating organs. For example, lipophilic drugs in combination with the normal age-related changes to the patient's body composition (eg, the increased proportion of fat mass with loss of lean mass and decreased total body water) tend to result in an increased volume of distribution and a prolonged half-life, whereas water-soluble drugs tend to have a decreased volume of distribution.[49]

Hepatic metabolism and renal elimination are major routes of drug clearance, including the clearance of HAART. Some age-related changes include a decline in liver and renal function, which may result in impaired drug elimination and drug accumulation.[50] Liver volume and hepatic blood flow decrease with increasing age.[51,52] This relationship needs to be taken into account when prescribing potentially hepatotoxic agents, such as the majority of PIs and NNRTIs.[53] Given the hepatotoxicity with multidrug HAART and potential interactions with other medications including lipid lower agents, over-the-counter medications, and antituberculosis therapy, it is important to monitor liver function in older adults with HIV.[54]

Additionally, on average in adults, the glomerular filtration rate decreases about 1% per year with increasing age,[55] and the methods for estimating renal function may overestimate this function in older adults by not taking their lowered relative muscle mass into account.[56] In older adults with HIV, this problem is further complicated because this population characteristically has lower muscle mass than their counterparts and often, confounding factors that can further decrease renal function – diabetes mellitus, hypertension, low CD4 cell count, race, and use of the antiretrovirals tenofovir and indinavir.[57–60] Estimating renal function is therefore even more difficult in HIV-infected older adults and affects the dosing and prescription of renally excreted medications. For example, cobicistat reduces the apparent estimated glomerular filtration rate by 15% on the initiation of treatment with this drug as a result of reduced tubular excretion of creatinine.[61,62]

Significant DDIs between HAART and various important drug classes are summarized in Table 1. The actual prevalence of ADEs and DDIs in the HIV-infected older adults is not known. Indeed, most of the studies that have been conducted with respect to antiretroviral metabolism have excluded subjects of advanced age with comorbid disease. In short, there is little data on the toxicities of antiretrovirals, especially with respect to HIV-infected older adults. More targeted research is needed.

Drug–drug interactions by system
Cardiovascular medications
CAD is one of the most common comorbidities in the aging HIV-infected population, and cardiovascular drugs are the most frequently prescribed medications in this population.[37] CAD prevalence in this population is likely due to a combination of factors including increasing age and habits such as tobacco use, as well as toxicity from HAART.[63]

Table 1 Summary of drug–drug interaction with HAART and various drug classes[4,6,48,68,135]

Drug class	PIs	Nature of interaction	Recommended adjustments	NNRTIs	Nature of interaction	Recommended adjustments
Cardiovascular medications						
HMG-CoA reductase inhibitors, statins	Mostly all PIs, (nelfinavir, fosamprenavir, ritonavir, indinavir, saquinavir, lopinavir)	Increased level of statins with potential for rhabdomyolysis	Contraindicated lovastatin and simvastatin. Dose adjustments: atorvastatin and rosuvastatin. No adjustments for pravastatin or fluvastatin	Etravirine, delavirdine, efavirenz, nevirapine	Possible decreased level of statins	Higher dose of atorvastatin or pravastatin might be needed
Digoxin	Ritonavir, saquinavir/ritonavir	Increased level digoxin and half-life	Use with caution, monitor digoxin levels, digoxin dose might need to be decreased			
Dihydropyridine CCBs	All PIs	Increase serum levels of CCBs, increasing risk of hypotension, conduction block, bradycardia	Use with caution, reduce dose of CCB, titrate carefully or avoid, monitor ECG	Efavirenz, nevirapine	Decrease CCBs serum concentrations through inhibition	Dose adjustment to steady state may be needed, titrate based on clinical response
Antiarrhythmic	All PIs, especially ritonavir boosted	Increased levels of antiarrhythmic serum concentrations	Contraindicated with ritonavir boosted PI: amiodarone, bepridil, flecainide, propafenone, and quinidine. Approach use of with caution: disopyramide, dofetilide, lidocaine, mexiletine, procainamide			
Warfarin	Interacts with most PIs	Alter S-warfarin concentrations	Monitor INR closely and adjust dose as needed. Use tipranavir with caution increased risk of bleeding	Efavirenz, nevirapine may increase or decrease levels of warfarin. Etravirine may increase levels of warfarin	Alter S-warfarin concentrations	Monitor INR closely and adjust dose as needed
Clopidogrel	Interaction is unlikely with PIs			Etravirine	May decrease formation of active clopidogrel metabolite	Avoid coadministration of clopidogrel and etravirine
Gastrointestinal medications						
H2 blockers	Boosted atazanavir, boosted atazanavir with tenofovir, unboosted atazanavir	Increased levels of H2 blocker and decreased levels of PIs – impaired absorption of drugs which require acid environment	Avoid cimetidine. Separate administration – ≥10 hours after H2 blockers	Rilpivirine	H2 blocker can decrease antiretroviral serum concentration	Give H2 blocker ≥12 hours before or ≥4 hours after rilpivirine

(Continued)

Table I (*Continued*)

Drug class	PIs	Nature of interaction	Recommended adjustments	NNRTIs	Nature of interaction	Recommended adjustments
PPIs	Boosted PIs	Altered drug levels of PIs and HAART treatment	Avoid PPI use of atazanavir, nelfinavir PPI dose should not exceed more than 20 mg/day of omeprazole if administered with atazanavir, nelfinavir PPI should be given at least 12 hours prior to HAART; PPI not recommended with unboosted atazanavir	Rilpivirine	PPI decreases effect concentration	PPI contraindicated with rilpivirine – do not coadminister
Genitourinary medications						
5-α reductase inhibitors	Minimal interactions with PIs	Dutasteride concentrations may be increased	Consider finasteride, monitor for decreased libido and erectile dysfunction			
Alpha adrenergic antagonist	Boosted PIs	Increases concentration of α-adrenergic antagonist; Increasing risk of orthostatic hypotension	Alfuzosin contraindicated, monitor tamsulosin with first dose and consider dose reduction; minimal effect with doxazosin and prazosin			
Phosphodiesterase-5 inhibitors: sildenafil, tadalafil, vardenafil	Most PIs	Increase in levels of PDE-5 inhibitors, increased risk of unsafe drop in blood pressure	Decrease dose of PDE-5 inhibitors; sildenafil: do not exceed 25 mg in 48 hours tadalafil: do not exceed 10 mg in 72 hours	Etravirine	Possible increase in levels of PDE-5 inhibitors	May need to increase dose based on clinical effect; coadministration is not recommended with avanafil
Psychiatric/neurologic medications						
Antidepressant: SSRIs	PIs	Increased levels of some SSRIs and increased levels of PIs	Monitor closely and may require lower dose of SSRI; escitalopram and citalopram are preferred SSRIs	Efavirenz, nevirapine	Decreases concentrations; nevirapine can decrease fluoxetine, efavirenz decrease sertraline	Titrate SSRI to effect, escitalopram and citalopram are preferred SSRIs
TCAs	All ritonavir boosted PIs	Increased levels of TCA which can results in orthostatic hypotension and anticholinergic side effects	Use with caution with lopinavir and ritonavir boosted PIs, monitor for adverse effects, or consider alternative antidepressant	Rilpivirine, increased concentration of TCA; efavirenz decreases sertraline dose		Avoid rilpivirine coadministration with TCA due to risk of additive QT prolongation, consider alternative antidepressant
Trazodone	Nearly all PIs	Increased level of trazodone	Monitor for CNS and cardiovascular effects, contraindicated with saquinavir			

Drug	PI	Effect	Management	NNRTI	Effect	Management
Bupropion	Lopinavir boosted and tipravnavir boosted	Decreased amount of bupropion	Titrate bupropion dose based on clinical response	Efavirenz	Decreases concentration of buproprion	Titrate buproprion dose based on clinical response
Benzodiazepine	All PIs	Increased levels of benzodiazepines alprazolam, clonazepam, diazepam, flurazepam, midazolam, triazolam	Midazolam and triazolam contraindicated with boosted PIs; can use other benzodiazepines	Efavirenz	Increases levels of midazolam, triazolam, diazepam; no data on alprazolam	Avoid use of midazolam and triazolam coadministration with efavirenz
Antimyobacterials/antifungals						
Clarithromycin	Boosted PIs, atazanavir	Increased clarithromycin concentration	Monitor for clarithromycin related toxicities, may concern alternative macrolide (azithromycin); monitor QtC; dose reduction for renal failure	Efavirenz, etravirine, nevirapine, rilpivirine	Decreased concentration of clarithromycin	Consider alternative agent, such as azithromycin, monitor for effectiveness
Rifampin	All PIs	Decreases PI concentration by greater than 75%	Do no coadminister rifampin and PIs, ritonavir increases hepatotoxicity	Efavirenz, etravirine, nevirapine, rilpivirine	Decreased NNRTIs	Contraindicated with etravirine, nevirapine, rilpivirine
Azoles	All PIs	Altered levels of azoles and PIs	Fluconazole may be better alternative but use with caution with tipranavir	NNRTIs	Alered levels of azoles and NNRTIs	Fluconazole best option, avoid others if able to
Steroids						
Budesonide (systemic, inhaled, intranasal)	All PIs	Increased glucocorticoids ad decreased PIs	Use with caution. Do not coadminister unless potential benefits of systemic, inhaled, intranasal outweigh risk of systemic corticosteroid adverse effect. Coadministration can result in adrenal insufficiency, Cushing's syndrome			
Prednisone	Boosted lopinavir	Decrease lopinavir and increased prednisolone	Use with caution. Coadministration can result in adrenal insufficiency, Cushing's syndrome			
Narcotic pain medications						
Oxycodone	Lopinavir/ritonavir	Increased levels oxycodone	Monitor for opioid-related adverse effects. Oxycodone dose reduction may be needed			
Methadone	Darunavir, lopinavir, nelfinavir, tipranavir	Decreased levels of methadone	Monitor for signs of opioid withdrawal, may require increased dose of methadone	Efavirenz, nevirapine	Decreased levels of methadone	Monitor for signs of opioid withdrawal, may require increased dose of methadone

Abbreviations: HAART, highly active antiretroviral therapy; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; HMG-CoA, 5-hydroxy-3-methylglutaryl-coenzyme A; CCB, calcium channel blocker; ECG, electrocardiogram; INR, international normalized ratio; PPI, proton pump inhibitor; PDE-5, phosphodiesterase type 5; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; CNS, central nervous system.

Prolonged treatment with HAART has been shown to be associated with an increased prevalence of hypertension in HIV-infected individuals and also with elevated blood pressure,[64] which may be seen in association with the fat redistribution/lipodystrophy syndrome.[65,66]

Hypertension is an important modifiable cardiac risk factor in HIV-infected patients; treating those who are older and on HAART can be challenging. Dihydropyridine calcium channel blockers (CCBs) have been shown to interact with HAART. Boosted PIs may increase the concentration of CCB in the serum and can potentially prolong the heart's PR interval, thus causing first-degree heart block and augment the hypotensive effect.[67] However, NNRTIs such as efavirenz and nevirapine can have the opposite effect on medication levels and have been shown to decrease CCB serum concentrations; this may require further dose adjustments to achieve a steady state.[68] Diltiazem area under the curve (AUC) is increased 125% by atazanavir; if coadministering these medications, the diltiazem dose should be reduced by 50% and electrocardiography monitoring is recommended. It is possible that other PIs increase the levels of diltiazem; therefore, they should be used with caution and the diltiazem dose adjusted to clinical response and toxicities.[68]

The antiarrhythmic agents, amiodarone and dronedarone (class 3 antiarrhythmics), are contraindicated in patients receiving PIs. As potent CYP3 A4 inhibitors, PIs have the potential to significantly reduce the metabolism of these agents and can cause serious and life-threatening adverse events. The concurrent use of lidocaine and saquinavir is contraindicated because saquinavir may increase the serum concentration of lidocaine, and therefore, its arrhythmogenic effect.[68]

Digoxin is prescribed for conditions that are common in older adults, including heart failure and atrial fibrillation with a rapid ventricular rate.[69] Between 60% and 80% of digoxin is eliminated by the kidneys.[70] Therefore, those older patients with HIV who have an increased risk of chronic kidney disease and also low body mass older patients are often subject to an increased risk of toxicity. For this reason, close monitoring of digoxin serum concentration in older HIV-infected individuals is crucial. Saquinavir/RTV increases the digoxin AUC about 49%, and this is most likely via P-glycoprotein inhibition. Given the relatively narrow therapeutic window of digoxin, caution should be exercised when these drugs are administered together.[68] It has been recommended that digoxin doses be reduced and that digoxin serum concentrations be monitored.[71]

Warfarin is known to interact with many drugs through a variety of mechanisms. NNRTIs and PIs are the antiretrovirals most likely to interact with warfarin. Among the NNRTIs, induction of warfarin metabolism is likely with nevirapine. The inhibition of warfarin metabolism can occur with efavirenz, delavirdine, or etravirine coadministration. Interactions with PIs, such as RTV, are also common.[72] Liedtke and Rathbun[43] have concluded that patients on warfarin and antiretrovirals need close international normalized ratio monitoring, and also that empiric warfarin dosage adjustments are difficult to recommend given the limited clinical evidence available and the absence of formal pharmacokinetic studies for most agents.

HAART treatment has not only been correlated with increased CAD, but also with increases in total cholesterol levels and triglyceride levels.[73] Significant DDIs have been reported between antiretrovirals and agents prescribed to treat hyperlipidemia. Simvastatin and lovastatin, which are metabolized via the cytochrome P-450 system, are contraindicated with any PI. Low-dose pravastatin, atorvastatin, or rosuvastatin are recommended. These agents can be titrated up as needed.[4] Atorvastatin should not exceed 20 mg daily when used with darunavir/RTV, fosamprenavir/RTV, saquinavir/RTV, or fosamprenavir. Atorvastatin is contraindicated with tipranavir.[74,75]

No dose adjustment is necessary for pitavastatin when used with PIs. The rosuvastatin AUC is increased 48% with darunavir/RTV and the peak concentrations to 139%; therefore, the dose of rosuvastatin must be titrated carefully and the lowest necessary dose used, along with careful monitoring for toxicities. The lipid-lowering benefits of rosuvastatin may be blunted when used in combination with darunavir/RTV.[76] Pravastatin AUC is also increased 81% by concurrent use of darunavir/RTV, requiring the use of the lowest possible dose of pravastatin and careful monitoring.[77] Additionally, efavirenz has been shown to be associated with reduced inhibition of 5-hydroxy-3-methylglutaryl-coenzyme A reductase activity during coadministration with simvastatin, atorvastatin, and pravastatin.[78]

Genitourinary medications

Benign prostatic hypertrophy (BPH) is common as men age.[79] Biopsy-proven BPH prevalence increases from 40% to 50% in men aged 51–60 years, and this rate exceeds 80% in men older than 80 years.[80] BPH has been shown to have a substantial negative effect on quality of life, with symptoms that interfere with activities of daily living.[81] Medications used to treat BPH can interact with antiretrovirals in the

aging HIV population. PIs may significantly increase concentrations of α-adrenergic antagonists such as alfuzosin. Coadministration is not recommended, given increased risk of orthostatic hypotension. Also, boosted PIs with RTV may increase the dose concentration of tamsulosin, and concurrent use is not recommended.[82] Fewer interactions are expected between PIs and other α-antagonists such as doxazosin and prazosin; however, close monitoring is recommended.

Erectile dysfunction has been reported to be a common problem in HIV-infected men. Studies have reported a prevalence rate between 53% and 71%.[83] Caution should be exerted with concomitant use of PI and erectile dysfunction drugs such as sildenafil, given the potential for PIs to increase the levels of sildenafil.[6,84] Sildenafil should be started at 25 mg every 48 hours and monitored for adverse events. The starting dose of tadalafil, also prescribed for erectile dysfunction, should be 5 mg such that it does not exceed a single dose of 10 mg in a 72-hour period. Monitoring for adverse effects of tadalafil, such as hypotension, is recommended.[85]

Gastrointestinal medications

Interactions between HAART and acid-reducing medications are common in older adults. In older HIV-infected patients treated with HAART, an increased frequency of reflux symptoms, gastroesophageal reflux disease, and *H. pylori* infection has been observed.[86] That being said, the treatment of reflux diseases can be problematic because some HAART medications require an acidic environment. The coadministration of H-2 receptor antagonists and atazanavir/RTV in HIV-infected patients has been shown to reduce the effect of atazanavir by approximately 20%. The dose of H-2 receptor antagonist should not exceed the equivalent of 40 mg of famotidine twice daily in those naïve to antiretroviral medications, or 20 mg twice daily in antiretroviral-experienced patients.[68] Atazanavir should be administered more than 10 hours after the H-2 receptor antagonist.[87] Proton pump inhibitors (PPIs) should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naïve patients. PPIs should be administered 12 hours before atazanavir/RTV. PPIs are not recommended in patients receiving unboosted atazanavir.[88] PPIs increase the AUC of saquinavir by 82%. When using these medications concomitantly, it is necessary to monitor for saquinavir toxicity.[89] Rilpivirine needs an acidic environment for absorption, and H-2 receptor antagonists as well as PPIs can decrease its absorption.[68]

Psychiatric medications

As many as 10% of adults 60 years of age or older who are seen in primary care settings have clinically significant depression.[90]

Additionally, major depressive disorder has been shown to be twice as likely to occur in patients with HIV as in those who do not have HIV infection.[91] Understandably, depression is very common in older adults with HIV. Selective serotonin reuptake inhibitors are often the prescribed treatment for depression in HIV-infected individuals,[92] and these inhibitors are believed to be better tolerated than tricyclic antidepressants (TCAs).[93] It is expected that all boosted PIs increase the levels of TCAs: the use of the lowest possible dose of the TCA and monitoring of drug levels are recommended.[68] Escitalopram and citalopram are often the preferred selective serotonin reuptake inhibitors. The AUC of paroxetine is decreased by the concurrent use of boosted darunavir and fosamprenavir,[94] and titration of the paroxetine dose based on clinical response is recommended.

Trazodone levels increase with the use of unboosted atazanavir and all boosted PIs, thereby increasing the risk for central nervous system and cardiovascular adverse events.[95] Using the lowest dose of trazodone and monitoring for adverse events is recommended. The combination of lopinavir/RTV and bupropion results in a decrease in the bupropion AUC and requires titration of the bupropion dose based on clinical response.[96]

Midazolam and triazolam are contraindicated with all PIs.[97–100] Several commonly used benzodiazepines are metabolized by CYP3 A4. These include alprazolam, clonazepam, diazepam, and flunitrazepam: CYP3 A4 inhibitors cause their levels to rise, resulting in possible toxicities such as over-sedation and central nervous system depression. RTV has been shown to increase blood levels and effects of the benzodiazepine and CYP3 A4 substrate alprazolam.[100]

Antimicrobials/antifungals

The coadministration of CYP3 A4 inhibitors results in an increased drug exposure to macrolides such as clarithromycin and erythromycin, and this can cause prolonged QTc.[101,102] QTc prolongation may lead to torsades de pointes, and older adults are particularly at increased risk for this life-threatening arrhythmia. The clarithromycin AUC can increase 94% with the concurrent use of atazanavir/RTV, thus leading to prolonged QTc; the clarithromycin dose should be reduced by 50% or an alternative antibiotic considered. The same recommendation applies for the concurrent use of clarithromycin with all other boosted PIs because they also may cause an increase in clarithromycin. Another antimicrobial to be aware of is rifampin, which is a potent inducer of both cytochrome P-450 oxidative enzymes and the P-glycoprotein transport system. Rifampin is contraindicated

with all PIs because it reduces the therapeutic response and can result in therapeutic failure or a toxic reaction.[103]

The azole antifungals have long been described as potentially arrhythmogenic drugs.[104] The coadministration with other compounds that inhibit CYP3 A4 may have an additive effect, potentially leading to arrhythmias. When boosted PIs are to be used concomitantly with itraconazole, monitoring levels of the antifungal is advised to guide dosage adjustments; high doses (>200 mg/day) of itraconazole are not recommended. Voriconazole should not be administered with boosted PIs because they decrease the voriconazole AUC. Unboosted atazanavir and fosamprenavir could possibly cause increases on voriconazole; therefore, monitoring for toxicities is necessary. Posaconazole causes increases in the AUC of atazanavir (both boosted and unboosted); therefore, patients who are receiving this combination should be monitored for atazanavir adverse events. In addition, because of decreased posaconazole exposure, coadministration with efavirenz should be avoided unless the benefit to patients outweighs the risk.[105] The use of high doses of fluconazole with tipranavir is not recommended. No dose adjustment of fluconazole is necessary with boosted atazanavir or saquinavir.

Systemic and inhaled steroids

The use of systemic, intranasal, or inhaled budesonide in combination with PIs is not recommended unless the potential benefits outweigh the risks, because this combination may result in decreased levels of PIs and an increase in glucocorticoids that can result in Cushing's syndrome.[106,107] Similarly, inhaled or intranasal fluticasone or systemic prednisone in combination with any boosted PI should be avoided, because it can result in adrenal insufficiency and Cushing's syndrome.[108] The use of dexamethasone can cause a decrease in the levels of PIs and should therefore be used with caution.

Narcotic pain medications

Opioids are often used to treat pain in older patients to improve quality of life and function. The concurrent use of lopinavir/RTV increases the oxycodone AUC 2.6-fold. A reduction in the dose of oxycodone may be needed in addition to close monitoring for adverse opioid effects that indicate it may be necessary to reduce the oxycodone dose.[109] Boosted atazanavir, darunavir, and fosamprenavir cause a 16%–18% decrease in the methadone AUC, whereas lopinavir/RTV decreases the methadone AUC 26%–53% and saquinavir/RTV decreases it 19%. As a result, the concomitant use of boosted PI and methadone may cause opioid withdrawal such that the dose of methadone may need to be increased, in particular with higher reductions in AUC.[110–113]

Osteoporosis therapies

Osteoporosis is common in HIV-infected persons and has a threefold higher prevalence compared with HIV-negative individuals.[114] The etiology of osteoporosis in HIV-infected patients is likely multifactorial, involving traditional risk factors as well as the direct effects of chronic HIV infection and antiretroviral therapy.[115] Emerging evidence suggests that the increase in the prevalence of osteoporosis in HIV-infected persons translates into a higher risk for fracture.[116,117] As a result, it likely leads to excess morbidity and mortality as the HIV-infected patient ages. Bisphosphonates are generally considered first-line therapy for persons with a history of fragility fracture and/or osteoporosis as diagnosed by dual-energy X-ray absorptiometry. Both alendronate and zoledronic acid have been shown in randomized controlled trials to significantly improve bone mineral density at the lumbar spine and total hip in HIV-infected patients treated for 96 weeks, with no known DDIs between the bisphosphonates and HAART.[118,119]

Clinical considerations for polypharmacy

A thorough review of medications is absolutely essential when managing HIV-infected older adults. It should be protocol for the health care provider to perform an annual medication reconciliation and a medication review at every visit, especially after hospital stays: hospital admission is a known risk factor for using an increased number of both appropriate and inappropriate medications.[120] Following such a protocol will help generate a complete and accurate list of active medications that is useful and readily available.

Indeed, when looking at the general population, discrepancies have been noted in the following domains: what medications patients should be taking; what medications they are actually taking; and what physicians have recorded in the patients' records.[121] Additionally, in a survey of Medicare beneficiaries, more than 35% of patients reported that they had not spoken with their doctor in the past 12 months about their different medications.[122] This should be of concern to clinical providers and provides a reason to consider changing the routine protocol.

In the ambulatory setting, there is little direct evidence to support any one method of medication review as superior to another.[123] Even so, a method that has been advocated for is the "brown bag" review. In the "brown bag" review, patients are asked to bring all their medications to the

office, including prescription medications, over-the-counter medications, vitamins, and herbal preparations. This method helps start a conversation and provides a clear picture of the patient's most up-to-date medication use.[124]

Once all of the patient's medications have been reconciled, it is helpful to review an array of issues, including: adherence to medication; the indications for medication; the effectiveness of the medication; and the patient's tolerance of the medication. Patients are often reluctant to admit to nonadherence,[125] and clues can be obtained from observing medication organization, pill counts, and refill history.[124] Barriers to nonadherence include patients' forgetting to take their pills, not believing the drug is effective, and having difficulty taking or tolerating the pills. Additionally, the cost of medications might also be limiting adherence. It may be appropriate for the clinical provider to answer questions from the patient and to reassure them concerning the effectiveness of any given medication to increase compliance.[124]

Health care providers are often hesitant to stop medications, especially if they did not initiate the treatment. The decision to discontinue a medication is multifactorial and should take into account the indication for the medication, the interaction of the medication with other prescribed medications, tolerance of the medication, and the patient's goals of care as well. Treatment targets are very often derived from studies completed in younger and healthier patients, and there is often little evidence to guide prescription in older adults with multimorbidity.[126]

To summarize, it is extremely important to have a complete and accurate medication history prior to starting additional medications (Table 2). When prescribing a new medication, health care providers should be careful to choose the drug with the highest therapeutic ratio provided efficacy is comparable, because sometimes ADEs are dose related. For example, higher doses of atypical antipsychotics were shown to cause more Parkinsonism in older adults than did lower-dosed treatment.[127] Doses should be titrated up carefully from a low starting dose in patients where pharmacodynamic or pharmacokinetic sensitivity are likely to be concerns. In certain cases, therapeutic monitoring of plasma drug concentrations may be an aid to treatment, such as for hypothyroidism.[128] However, clinical judgment is also essential in titrating drug dosages.

The prescriber should pay particular attention to avoid combinations that demonstrate known additional or synergistic toxic effects (eg, two medications with anticholinergic activity). Additionally, when multiple medications are required, such as in HIV-infected individuals, a dosing

Table 2 General considerations for managing polypharmacy in older adults

- Throughout medication history
  - "Brown Bag" asking patient to bring in all prescription, OTC, and herbal medications
    - "Teach-back" method, patient shows how taking medication
  - Determine patient adherence to medication and barriers if not adherent
    - Is the patient forgetting to take?
    - Is the pill difficult to take?
    - Is the pill costly?
    - Does the patient believe that the drug is not needed?
  - Where possible use the same pharmacy
- Indications for current medications
  - Determine if medication is on Beers List or Medication Appropriateness Index
  - Is the dosage correct?
- Review drug–drug interactions
- Determine the therapeutic ratio
  - Start low and go slow for titration up
- Good communication with other healthcare providers (physicians and caregivers)

Abbreviation: OTC, over-the-counter.

schedule should be established to clarify times of medication administration. Current evidence suggests that more efforts are needed to ensure patients receive clear and consistent information supporting safe medication use.[129,130]

Sometimes simplicity is the best solution. It may be ideal to have as few physicians as needed to address a patient's care. This move to better integrate care can help with managing polypharmacy as well as providing nonconflicting and good communications between health care providers and caregivers. A work group comprising leading researchers and clinicians across the country was formed as part of the HIV and Aging Consensus Project. The aim of this project was to recommend treatment strategies for clinicians who manage HIV-infected older adults. To address the above-mentioned concern, this work group recommended that individuals use either only one pharmacy or a pharmacy with an integrated computer network, and if possible, use a HIV-specialty pharmacy.[131] Having a clinical pharmacist assist with prescriptions can help to reduce inappropriate prescribing and thereby decrease the rate of drug-related problems.[132,133] Another method that may be helpful in managing the complex challenge of polypharmacy in HIV-infected older adults is the development of a clinic for HIV-infected patients over 50 years of age comparable to that developed in London.[134]

Conclusion

Over the last few decades, the number of HIV-infected older adults has increased significantly. Older patients

with HIV-infection have several comorbidities requiring multiple pharmacotherapies that can increase their risk of polypharmacy and related adverse events. However, little is known about the impact of aging on medication use in HIV-infected older individuals, the potential for interactions with HAART and administered medications, and the impact of this on therapy tolerability and virological response with aging. Reducing pill burden, careful titration of medications, and increasing awareness of common DDIs can prevent coadministration of potentially harmful combinations and reduce unnecessary polypharmacy-related adverse events in this population. More studies need to be conducted to assess the long-term safety and efficacy of HAART in older adults with HIV infection.

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