

Management of HIV/AIDS in older patients—drug/drug interactions and adherence to antiretroviral therapy

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Abstract: Patients with human immunodeficiency virus (HIV) are living longer with their disease, as HIV has become a chronic illness managed with combination antiretroviral therapy (cART). This has led to an increasing number of patients greater than 50 years old living successfully with HIV. As the number of older adults with HIV has increased, there are special considerations for the management of HIV. Older adults with HIV must be monitored for drug side effects and toxicities. Their other non-HIV comorbidities should also be considered when choosing a cART regimen. Older adults with HIV have unique issues related to medication compliance. They are more likely than the younger HIV patients to have vision loss, cognitive impairment, and polypharmacy. They may have lower expectations of their overall health status. Depression and financial concerns, especially if they are on a fixed income, may also contribute to noncompliance in the aging HIV population.

Keywords: HIV, aging population, management issues, drug interactions, medication adherence

Introduction

Human immunodeficiency virus (HIV) infection in the United States (US) has evolved from an illness that was the leading cause of death among young adults in the early 1990s to a chronic disease. HIV continues to cause significant morbidity, but, increasingly, patients with access to potent combination antiretroviral therapy (cART) are healthier and living normal life spans. Patients over 50 years old are commonly considered “older adults” in HIV literature, owing to management considerations that are unique to this group of patients as they age. In 2010, older Americans greater than 55 years old comprised approximately 20%, or 217,000, of the people living with HIV in the US. The CDC estimates that by 2015, greater than 50% of individuals infected with HIV in the US will be over 50 years old.¹

The aging of the HIV population in the US was addressed by medical leaders in both HIV and geriatrics subspecialties, resulting in a consensus document in 2012 that provided strategies for caring for the older HIV-infected individual.¹ The authors did not call this document a guideline in view of the paucity of evidence in the aging HIV population. The “graying” of the HIV epidemic has brought new challenges. No longer are HIV medical providers purely focused on how to prevent progression to AIDS and death in infected individuals. HIV caregivers are more engaged in comprehensively managing patients and selecting cART that maximizes the quality of their patients’ lives as they age. Both HIV infection and the drugs used to treat HIV are believed to contribute to increased comorbidities among older HIV-infected individuals.²

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Multiple comorbidities that include osteoporosis, diabetes, cardiovascular disease, cancer, hyperlipidemia, and chronic renal disease are common among the older patient living with HIV, which can be exacerbated and sometimes caused by cART.

This review will focus on antiretroviral therapy in the aging HIV patient, including when to start cART, how to minimize side effects, and exacerbation of preexisting comorbidities by careful choice of antiretroviral drugs, and review of common drug–drug interactions between antiretroviral agents and other drugs commonly used in individuals over 50 years. Strategies to maximize adherence to cART will also be discussed.

HIV screening and initiation of cART in older patients

HIV screening

Both the Centers for Disease Control (CDC) and the United States Preventive Services Task Force (USPSTF) guidelines on HIV screening recommend screening for those under 65, but make no recommendation for those >65 years.^{3,4} As a group, older patients may be less forthcoming with risk factors for HIV, will likely benefit more than the average HIV-infected individual from early diagnosis and treatment, and transmission can be reduced in this population with routine screening.¹ For these reasons, the authors of the HIV and Aging consensus document strongly recommend that all adults >65 years who have never been tested for HIV be screened.

Older patients are less likely than younger patients to be screened for HIV infection.⁵ Many primary caregivers believe their patients over 50 are unlikely to be at risk for HIV.⁶ Older individuals do become infected, and between 2006 and 2009, 11% of new diagnosis in the US occurred in individuals over 50 years.⁷ Failure to screen for HIV in older persons likely contributes to late disease presentation and more rapid progression to AIDS.⁸ Rates for older African Americans are 12 times higher than rates for older whites, and 70% of older infected HIV women are African American or Hispanic/Latina. These health disparities are higher than what is seen in the younger HIV-infected population in the US.^{9–11}

Initiation of cART

The Department of Health and Human Services (DHHS) guideline on use of antiretroviral agents in HIV-1-infected adults and adolescents recommends treatment for everyone who is able to commit to treatment and understands the importance of adherence.¹² Adherence to treatment is crucial for long-term success. Therapy is strongly recommended for

those with CD4 counts of 500 cells/mm³ or less and encouraged for those with CD4 counts >500 cells/mm³. The START trial randomized patients with CD4 counts over 500 cell/mm³ to either initiate cART or defer treatment until CD4 dropped to 350 cells/mm³ or less. The study's primary end points were any AIDS-related event, serious non-AIDS related events, or death. The study was discontinued in May of 2015 after an interim analysis revealed that patients in the immediate treatment group had a hazard ratio of 0.28 for serious AIDS-related events and 0.61 for non AIDS-related events.¹³

Older patients have similar virologic responses to cART when compared with younger adults, with both groups attaining similar reduction of HIV serum viral levels <50 copies/mL on appropriate cART.^{14,15} However, older patients are less likely than younger individuals to have full immune reconstitution following cART and initiating therapy at higher CD4 counts is more likely to preserve long-term immune function.^{14–16} We therefore recommend therapy for all older HIV infected adults regardless of CD4 count.

Ongoing viral replication is important to consider in patients who are considering deferring HIV therapy. The DHHS guidelines, even prior to release of the START study data recommended cART in individuals with high CD4 cell counts despite their low risk of opportunistic infections based partially on growing evidence that HIV viremia is associated with development of non-AIDS-defining diseases including cardiovascular disease, kidney disease, liver disease, neurologic complications, and malignancies. Additional evidence has shown that the higher the viral load, the faster the progression to AIDS and death independent of CD4 count.¹⁷ The EuroSIDA collaboration evaluated the importance of viral load on rates of AIDS and non-AIDS-related events in individuals with CD4 >350 cells/mm³. Even relatively low levels of viral replication were associated with increased adverse effects. Individuals with viral loads between 500 and 9,999 copies/mL had a 61% higher rate of non-AIDS-related events, when compared with those with viral loads of <500 copies/mL.¹⁸ The HIV and Aging Consensus Project document states that HIV-infected persons over age 50 who have a CD4 cell count greater than 500 cells/mm³ should be considered for cART, and a viral load >50,000 copies/mL would favor initiation of therapy.¹ As with younger patients, they must be committed to taking their medication daily before initiating a cART regimen. Treatment fatigue can also be a factor in the older patient, and this must be assessed regularly during treatment, to ensure compliance.

cART in this population also has the benefit of reducing transmission within the community.¹⁹ Studies have shown

that patients in this age cohort are less likely to use condoms, are less likely to discuss sexual activity with their physicians than younger patients, and they have little knowledge regarding risks for HIV transmission.^{1,12,20–22} Older women who are sexually active with an HIV-infected partner may also be at higher risk of acquiring HIV due to physiologic changes in the vagina.

The DHHS guideline and the HIV and Aging Consensus Project both strongly recommend cART for patients with rapidly declining CD4 counts (eg, >100 cell/mm³ decline in prior 12 months).^{1,12} Both strongly recommend cART in all patients with HIV-associated nephropathy regardless of CD4 count, and in individuals coinfecting with hepatitis B. Patients coinfecting with hepatitis B need a cART program active against both viruses, and this is easily accomplished by using Truvada (coformulated tenofovir and emtricitabine) as the backbone of the combination program.

HIV genotypic drug resistance testing should be obtained at the initial diagnosis of HIV, even if antiretroviral therapy is not immediately planned. Transmission of drug-resistant HIV strains occurs and resistance testing should be used to choose a potent cART regimen with a high chance of achieving viral suppression.^{23,24} Resistant viruses are generally less fit than wild type viruses (those without resistant mutations) and detectable presence of resistant clones tends to decline with time, frequently to levels below the limit of standard resistance tests, so early genotype testing is recommended.²⁵

Selection of cART

The DHHS guidelines recommend cART with two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active drug for treatment-naïve HIV-infected persons with fully susceptible virus. The third active drug can be a nonnucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI/r), or an integrase inhibitor (INSTI) (Table 1).

Selection of which antiretroviral drugs to use for an individual patient is complex, requiring consideration of individual comorbidities, drug–drug interactions, insurance and affordability, patient preferences, and likelihood of adherence to a particular program. In older patients, there is a greater likelihood of preexisting comorbidities. They are also more likely to be taking both over-the-counter and prescription medications for other chronic illnesses. Treating patients with a resistant virus or changing a failing program becomes even more complicated, and the choice of antiretroviral medications should be guided by the resistance profile, with other issues playing a less prominent role.

Table 1 DHHS recommended and alternative cART programs for treatment naïve patients

Recommended Regimens	
Integrase (INSTI) based cART	
DTG/ABC*/3TC (co-formulated as Trimeq)	
DTG + TDF/FTC	
EVG/cobi/TDF/FTC (co-formulated as Stribild) (only if pre-treatment est crcl \geq 70 ml/min)	
RAL + TDF/FTC	
Protease Inhibitor (PI) based cART	
DRV/r + TDF/FTC	
Alternative Regimens	
Nonnucleoside reverse transcriptase inhibitor (NNRTI) based cART:	
EFV/TDF/FTC (co-formulated as Atripla)	
RPV/TDF/FTC (co-formulated as Complera) (only for pre-treatment viral load $>$ 100,000 copies/ml and CD4 $>$ 200 cells/mm ³)	
Protease Inhibitor (PI) based cART	
ATV/cobi + TDF/FTC (only if pre-treatment estimated crcl \geq 70ml/min)	
ATV/r + TDF/FTC	
DRV/cobi + ABC*/3TC	
DRV/r + ABC*/3TC	
DRV/cobi + TDF/FTC (only if pre-treatment estimated crcl \geq 70ml/min)	

Notes: *ABC should not be used unless individual is confirmed to be HLA-B*5701 negative. Data from Panel on Antiretroviral Guidelines for Adults and Adolescents. Initiating antiretroviral therapy in treatment-naïve patients. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. Available from: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>. Section accessed May 6, 2015.¹²

Abbreviations: DHHS, Department of Health and Human Services; cART, combination antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; EFV, efavirenz; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; PI, protease inhibitor; ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; INSTI, integrase; DTG, dolutegravir; ABC, abacavir; 3TC, lamivudine; EVG, elvitegravir; RAL, raltegravir; RPV, rilpivirine.

Adverse effects and drug interactions with cART in older patients

Adverse drug effects

With aging, hepatic and kidney function typically decline, suspected at least in part due to loss of functional tissue of these organs as a result of aging. The decline in kidney function was 0.75/mL/min/year in one study,²⁶ and liver function decline has been demonstrated in pharmacokinetic studies that show altered metabolism.²⁷ As a result, older patients will often have increased drug exposure and consequently increased adverse effects.^{28,29} Most clinical studies of antiretroviral therapy have not included patients over 50 years old and have not yet evaluated adverse effect rates in older patients versus younger cohorts. The therapeutic window between an effective drug level and a toxic level for many drugs is often reduced in the older population owing to increased drug sensitivity associated with aging,

Table 2 Commonly used antiretroviral therapy and associated adverse effects

Protease inhibitors		
Atazanavir (ATV)	Indirect hyperbilirubinemia	Cholelithiasis
Reyataz	PR interval prolongation: first-degree symptomatic AV block reported Hyperglycemia Fat maldistribution	Nephrolithiasis Renal insufficiency Serum transaminase elevations Hyperlipidemia (especially with RTV boosting) Skin rash
Darunavir (DRV) Prezista	Skin rash (10%): DRV has a sulfonamide moiety; Stevens–Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and erythema multiforme have been reported	Hepatotoxicity Diarrhea, nausea Headache Hyperlipidemia Serum transaminase elevation Hyperglycemia Fat maldistribution
Ritonavir (RTV) Norvir	GI intolerance, nausea, vomiting, diarrhea Paresthesia (circumoral and extremities) Hyperlipidemia (especially hypertriglyceridemia) Asthenia Hepatitis	Taste perversion Hyperglycemia Fat maldistribution Possible increased bleeding episodes in patients with hemophilia
Nonnucleoside reverse transcriptase inhibitors		
Efavirenz (EFV)	Rash	False-positive results with some cannabinoid and benzodiazepine screening assays reported
Sustiva	Neuropsychiatric symptoms Increased transaminase levels Hyperlipidemia	Teratogenic in nonhuman primates and potentially teratogenic in humans Hepatotoxicity
Rilpivirine (RPV) Edurant	Rash Depression, insomnia, headache	
Etravirine (ETR) Intelence	HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure, have been reported	Nausea Rash, including Stevens–Johnson syndrome
Nucleoside reverse transcriptase inhibitors		
Lamivudine (3TC) Epivir	Minimal toxicity	Severe acute exacerbation of hepatitis may occur in HBV coinfecting patients who discontinue 3TC
Tenofovir Disoproxil Fumarate (TDF)	Renal insufficiency, Fanconi syndrome, proximal tubulopathy Osteomalacia, decrease in bone mineral density	Severe acute exacerbation of hepatitis may occur in HBV coinfecting patients who discontinue TDF
Viread	Potential decrease in bone mineral density	Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Zidovudine (ZDV) Retrovir	Bone marrow suppression: macrocytic anemia or neutropenia Nausea, vomiting, headache, insomnia, asthenia Nail pigmentation Lipoatrophy Myopathy	Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life threatening toxicity) Hyperlipidemia Insulin resistance/diabetes mellitus
Abacavir (ABC) Ziagen	Hypersensitivity reaction: patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC. Rechallenge is not recommended Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, or fatigue or respiratory symptoms such as sore throat, cough, or shortness of breath	Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies
Emtricitabine (FTC) Emtriva	Minimal toxicity Hyperpigmentation/skin discoloration	Severe acute exacerbation of hepatitis may occur in HBV coinfecting patients who discontinue FTC
Integrase inhibitors		
Dolutegravir (DTG)	Insomnia	HSRs including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported
Tivicay	Headache	
Elvitegravir (EVG)	Nausea Diarrhea Elevated cholesterol	

(Continued)

Table 2 (Continued)

Raltegravir (RAL)	Nausea	CPK elevation, muscle weakness, and rhabdomyolysis
Isentress	Headache	Rash, including Stevens–Johnson syndrome, HSR, and toxic epidermal necrolysis
	Diarrhea	
	Pyrexia	
CCR5 antagonists		
Maraviroc (MVC)	Abdominal pain	Hepatotoxicity, which may be preceded by severe rash or other signs of systemic allergic reactions
Selzentry	Cough	Orthostatic hypotension, especially in patients with severe renal insufficiency
	Dizziness	
	Musculoskeletal symptoms	
	Pyrexia	
	Rash	
	Upper respiratory tract infections	

Notes: Data from Panel on Antiretroviral Guidelines for Adults and Adolescents. Initiating antiretroviral therapy in treatment-naïve patients. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. Available from: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>. Section accessed October 28, 2014.¹²

Abbreviations: AV, atrioventricular; GI, gastrointestinal; HBV, hepatitis B virus; HLA, human leukocyte antigen; MI, myocardial infarction; HSR, hypersensitivity; CPK, creatine phosphokinase.

which further heightens the need to monitor for toxicity and adverse effects in this patient population.³⁰ Common adverse effects are listed in Table 2 for our commonly used first-line antiretroviral agents.

Prevention of adverse drug reactions is particularly crucial in managing the older patient with HIV. In a study of hospitalizations to an internal medicine unit, where the mean age of patients hospitalized was 69 years, Samoy et al³² found that 25% of hospital admissions were due to adverse medication events and 70% were deemed preventable. Of those admissions, 35% were due to adverse drug reactions, 24% were due to improper drug selection, and 26% were attributable to dosing errors. Additional studies have shown 27% of adverse drug events in the elderly to be preventable in ambulatory settings and 42% in long-term care settings.^{33,34} While these study populations were not solely HIV patients, it highlights the need for care providers to be aware of the potential for adverse drug events in this older population to prevent potential errors.

Successfully preventing adverse drug events in the elderly HIV patient is a multifaceted approach that requires appropriate cART selection, making appropriate cART dose adjustments for impaired organ function, and minimizing drug interactions. It is important to select HIV medications that minimize toxicity and to routinely monitor for adverse drug effects. For instance, efavirenz is best avoided in a patient at fall risk because dizziness is common when initiating efavirenz. Furthermore, given the decrease in hepatic and renal function in the elderly, organ clearance estimations are important, and drug dosing should be adjusted accordingly (see Table 3). For instance, a 70-year-old (43 kg) female

patient with a serum creatinine of 1.1 who has been on Kaletra (lopinavir 200 mg/ritonavir 50 mg), 2 tablets, and Combivir (zidovudine 300 mg/lamivudine 150 mg), 1 tablet twice daily for 9 years, is receiving too high a dose of lamivudine based on an estimated creatinine clearance of 32 mL/min. Thus, if this regimen is continued, Combivir should be changed to its individual components of zidovudine and lamivudine, with the lamivudine dose adjusted to 150 mg daily.

Drug interactions

Drug interactions can be severe and warrant close attention to the cART medication regimen selected for HIV treatment and the medication regimen for non-HIV indications. Ritonavir and cobicistat, both cytochrome P450 3A4 inhibitors, are currently utilized to boost levels of PIs and the INSTI elvitegravir. They have mixed inducer/inhibitor effects on different cytochrome P450 pathways and should be closely evaluated when added to non-HIV medication regimens.¹²

Understanding metabolic pathways for commonly used cART can help lend insight into potential drug interactions for our currently recommended first-line HIV agents (Table 3). When data for a specific drug combination are lacking, the metabolic pathways should be reviewed, and the need for dose adjustment and monitoring should be determined with the consultation of a pharmacist or provider with expertise in HIV therapy management. Additionally, the effect of drugs on transporter systems such as P-glycoprotein should be reviewed for potential interaction. Furthermore, the available studies of drug interactions usually consist of healthy young patients with minimal or limited comorbid conditions

Table 3 Description of the metabolic pathways, interaction potential, usual daily dose, and dose adjustment recommendations for renal/hepatic impairment for commonly utilized antiretroviral therapy

Medication generic name (abbreviation) Brand name	Metabolism/elimination/ potential for interactions	Usual daily dose	Dose in renal insufficiency	Dose in hepatic impairment
Protease inhibitors				
Atazanavir (ATV) Reyataz	CYP3A4 inhibitor and substrate, CYP 2C8 (weak inhibitor), UGT1A1 inhibitor	300 mg once daily with boosting agent (RTV 100 mg or COBI 150mg)	No dosage adjustment for patients with renal dysfunction who do not require HD ARV-naïve patients on HD: ATV 300 mg + RTV 100 mg once daily ARV-experienced patients on HD: ATV or RTV/r not recommended	Child-Pugh Class B: 300 mg once daily Child-Pugh Class C: not recommended RTV boosting is not recommended in patients with hepatic impairment (Child-Pugh Class B or C) Mild-to-moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: not recommended
Darunavir (DRV) Prezista	CYP3A4 inhibitor and substrate, CYP 2C9 inducer	ARV naïve or no DRV mutations: DRV 800 mg + boosting agent (RTV 100 mg or COBI 150 mg), otherwise DRV 600 mg + RTV 100 mg twice daily As a PI-boosting agent: 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI used
Ritonavir (RTV) Norvir	CYP3A4 > 2D6 substrate; potent 3A4, 2D6 inhibitor Inducer of CYP1A2, CYP 2C8, CYP2C9, CYP2C19, and UGT1A1	600 mg once daily, given before bedtime on an empty stomach 25 mg once daily (take with a meal)	No dosage adjustment necessary	No dosage recommendation, use caution in patients with hepatic impairment Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Nonnucleoside reverse transcriptase inhibitors				
Efavirenz (EFV) Sustiva	Substrate of CYPs 2B6, 2A6, and 3A4. Inhibits: 2C9, 2C19, 3A4. Induces: 3A4, 2B6	200 mg twice daily	No dosage adjustment necessary	No dosage adjustment necessary
Rilpivirine (RPV) Edurant	CYP3A4 substrate	200 mg once daily	No dosage adjustment necessary	Child-Pugh Class C: no dosage recommendation
Etravirine (ETR) Intencef	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	300 mg once daily or 150 mg twice daily	No dosage adjustment necessary	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Nucleoside reverse transcriptase inhibitors				
Lamivudine (3TC) Epivir	Renal excretion: 70%		CrCl (mL/min) 30–49 15–29 5–14 <5 or on HD On dialysis days, take dose after dialysis	Dose 150 mg q24h 1×150 mg, then 100 mg q24h 1×150 mg, then 50 mg q24h 1×50 mg, then 25 mg q24h

Tenofovir disoproxil fumarate (TDF) Viread	Renal excretion – primary route of elimination	300 mg once daily	CrCl (mL/min) 30–49 10–29 < 10 and not on HD on HD On dialysis days, take dose after dialysis	Dose 300 mg q48h 300 mg twice weekly (every 72–96 hours) No recommendation 300 mg q7 days	No dosage adjustment necessary
Zidovudine (ZDV) Retrovir	Metabolized to azidothymidine glucuronide. Renal excretion of azidothymidine glucuronide	300 mg twice daily	CrCl (mL/min) < 15 or HD On dialysis days, take dose after dialysis	Dose 100 mg tid or 300 mg once daily	No dosage recommendation
Abacavir (ABC) Ziagen	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites: 82%	300 mg twice daily or 600 mg once daily	No dosage adjustment necessary		Child-Pugh Score 5–6: 200 mg twice daily (use oral solution) Child-Pugh Score > 6: contraindicated
Emtricitabine (FTC) Emtriva	Renal excretion: 86%	200 mg oral capsule once daily or 240 mg (24 mL) oral solution once daily	CrCl (mL/min) 30–49 15–29 < 15, HD, CAPD On dialysis days, take dose after dialysis	Capsule 200 mg q48h 200 mg q72h 200 mg q96h	No dosage recommendation
Integrase inhibitors					
Dolutegravir (DTG) Tivicay	UGT1A1-mediated glucuronidation Minor contribution from CYP3A4	50 mg once daily or 50 mg twice daily	No dosage adjustment necessary		Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: not recommended
Elvitegravir (EVG)	CYP3A4 substrate; UGT1A1 substrate	150 mg or 85 mg daily (depending on concomitant ART/formulation)	No dose adjustment necessary for renal function. The dosing form of Stribild (which contains EVG/COBI/TDF/FTC) should not be initiated when CrCl < 70 mL. Stribild should be discontinued if CrCl declines to < 50 mL/min		Mild-to-moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: not recommended
Raltegravir (RAL) Isentress	UGT1A1-mediated glucuronidation	400 mg twice daily	No dosage adjustment necessary		Mild-to-moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: no recommendation
CCR5 antagonists					
Maraviroc (MVC) Selzentry	CYP3A4 substrate	Usual dose 300 mg twice daily. With strong CYP 3A4 inhibitors: 150 mg twice daily With strong CYP3A4 inducers: 600 mg twice daily	CrCl < 30 mL/min or on HD Without Potent CYP3A inhibitors or inducers: 300 mg bid; reduce to 150 mg bid if postural hypotension occurs With potent CYP3A inducers or inhibitors: not recommended		No dosage recommendations Concentrations will likely be increased in patients with hepatic impairment
Pharmacokinetic enhancer					
Cobicistat (COBI), Tybost	CYP3A4 substrate; Inhibitor of CYP3A4 and CYP2D6	150 mg once daily	With TDF: not recommended starting with a CrCl < 70 mL/min. Use not recommended if CrCl < 50 mL/min. Without TDF: no dose adjustments necessary		Child-Pugh Class A-B: No adjustment necessary. Child-Pugh Class C: No data available

Notes: Data from Panel on Antiretroviral Guidelines for Adults and Adolescents. Initiating antiretroviral therapy in treatment-naïve patients. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. Available from: <http://aidsinfo.nih.gov/contentfiles/guidelines/AdultandAdolescentGL.pdf>. Section accessed May 26, 2015.

Abbreviations: HD, hemodialysis; CrCl, Creatinine clearance; ARV, antiretroviral.

or organ compromise. Thus, these conclusions may not accurately transfer to an older population who may experience more adverse reactions due to poorer organ function and more complex medication regimens.

The DHHS Adult HIV treatment guidelines¹² provide extensive drug interaction tables for specific antiretroviral agents when combined with other medications. We have summarized some of the interactions, monitoring, and adjustment approaches highlighted in the DHHS guidelines that are more relevant in the older HIV population (Table 3). Primary literature data and expert clinical HIV advice should be sought for complicated patients with multiple complicated drug interactions that affect different metabolic pathways. Additional drug interactions might be found at <http://www.hiv-druginteractions.org>.³¹

Acid suppression therapy/polyvalent cations

Certain cART medications are dependent on an acidic environment in the stomach for adequate absorption. Appropriate absorption ensures therapeutic levels that maintain viral suppression and reduce the risk of resistance development. Atazanavir and rilpivirine (found in the coformulated tablet of Complera) are especially dependent on stomach acid for absorption, they require food for absorption and avoidance of acid suppression therapy. Proton pump inhibitor (PPI) use is contraindicated with rilpivirine. In some circumstances, histamine receptor blockers, low dose PPI, and oral antacids (eg, magnesium hydroxide, calcium carbonate) may be used in combination with these agents, but strict timing of drug administration to separate the medications is required and close follow-up of viral response is necessary. In general, it is best to avoid acid suppression therapy with atazanavir or rilpivirine to prevent this issue.

The oral antacid agents often contain polyvalent cations such as calcium and aluminum. These and other polyvalent cations (iron supplements, magnesium, zinc) can inhibit absorption of the INSTIs by chelation in the stomach. It is usually required to space administration times when both agents are used together.

Anticoagulation

Warfarin is metabolized via CYP3A4 and 2C9. Use of PI/r's can increase warfarin levels and bleeding risk. Dose adjustment of warfarin with close monitoring of INR is necessary with concomitant use. By a similar metabolic mechanism, rivaroxaban levels are increased in the setting of PI/r use. Given the increased levels of rivaroxaban and

increased bleed risk, concomitant use should be avoided. When used concomitantly with warfarin, efavirenz has been shown to both increase and decrease warfarin levels and INR. While the cause is not specifically elucidated, this variable effect is likely multifactorial. It may be related to different pharmacogenomic profiles of metabolic enzymes related to efavirenz and warfarin metabolism and the mixed induction/inhibition effect of efavirenz on CYP3A4.¹² When efavirenz is used concomitantly with warfarin, close warfarin dose adjustment and INR monitoring for therapeutic effect is recommended. Being relatively new, cobicistat has less clinical data available. However, it has notable CYP3A4 inhibition,³⁵ making it important to closely monitor warfarin dosing and INR if concomitant use is necessary. Additionally, concurrent use of rivaroxaban and cobicistat is not recommended given its CYP3A4 inhibition.

Antidepressants

The combination of darunavir/ritonavir has been shown to decrease levels of paroxetine by approximately 40% and sertraline by about 50%. Efavirenz will also decrease sertraline levels by 40%, and levels of bupropion by 50%.¹² In the setting of combined use of the aforementioned combinations, doses of these antidepressants should be titrated on the basis of clinical response.

All current first-line PI/r combinations will increase levels of trazodone,¹² necessitating the use of the lowest possible dose of trazodone with close monitoring for CNS adverse effects (ie, sedation, confusion) and cardiovascular effects (ie, hypotension, bradycardia). In general, tricyclic antidepressants (TCAs) should be avoided in the older patient given that they are highly anticholinergic, sedating, and can cause orthostatic hypotension.³⁶ Current PI/r's will increase levels of TCAs, increasing risk of problematic anticholinergic side effects. If combined use is necessary, the lowest dose possible should be initiated with titration based on clinical response. Cobicistat would also be anticipated to have a similar effect on trazodone and TCAs, and doses should be adjusted accordingly.

Benzodiazepines

Benzodiazepines (BZDs) should generally be avoided in patients 65 years and older owing to the increased sensitivity to BZDs in this population and increased risk of cognitive impairment, delirium, falls, and fractures.³⁶ When use is required, however, it is pertinent to note that those BZDs metabolized through CYP3A4 (eg, alprazolam,

diazepam, midazolam, triazolam) have notable interaction with all PI/r's and cobicistat. Midazolam and triazolam should never be concurrently used with PI/r's or cobicistat given the severe toxic degree of BZD drug level increase and half-life extension. Midazolam and triazolam are also contraindicated with efavirenz use due to expectations of elevated levels. Alprazolam and diazepam are also best avoided with concomitant PI/r, cobicistat, or efavirenz. If benzodiazepine use is necessary, selection of an agent that is not metabolized predominantly via CYP450 enzymes would be prudent. Lorazepam's metabolism involves glucuronidation, making it a more appropriate choice when concomitant use with PIs, cobicistat, or efavirenz is necessary.¹²

Steroids

PI/r's and cobicistat pose unique challenges in the setting of steroid use, as they inhibit steroid metabolism via CYP3A4 and can drastically increase levels of prednisone and other steroids. This can increase the risk of drug-induced Cushing syndrome and adrenal suppression. Close monitoring and dose adjustment must be employed if concurrent therapy is required. Systemic accumulation has been documented even with inhaled steroids such as budesonide and fluticasone.^{12,37,38} Beclomethasone should be used if an inhaled steroid is needed in the setting of PI/r or cobicistat therapy, as beclomethasone has significant metabolism via routes other than CYP3A4.

This accumulation effect holds true even for intra-articular steroids such as triamcinolone, prednisolone, and methylprednisolone. If steroid injections are required, the DHHS guidelines recommend changing from a PI/r to an alternative that would not affect steroid metabolism, such as an INSTI.

Uniquely, dexamethasone has the effect of inducing metabolism of protease inhibitors, and use should be avoided and an alternative steroid selected if a patient is on PI/r therapy. Dexamethasone would also be expected to induce the metabolism of efavirenz, etravirine, and rilpivirine, and concurrent use with these drugs should be avoided when alternative steroids may be used. Rilpivirine use with dexamethasone for more than one dose is contraindicated.¹²

Statin therapy

Atorvastatin, simvastatin, and lovastatin are metabolized via cytochrome P450 3A4, and increased serum levels are expected when used with all PI/r's or cobicistat. The

combination of lovastatin or simvastatin with PI/r therapy or cobicistat is contraindicated in view of the degree of statin elevation. When atorvastatin or rosuvastatin is used with ritonavir-boosted darunavir or atazanavir, utilize the lowest statin dose possible, and titrate carefully with close monitoring for myopathy. The dose of atorvastatin should not exceed 20 mg when used with darunavir/ritonavir, and the dose of rosuvastatin should not exceed 10 mg when used with atazanavir/ritonavir.¹² Pravastatin is not extensively metabolized by cytochrome P450. Pravastatin undergoes glucuronidation with biliary and renal excretion. Thus, this is typically the preferred statin used with concomitant protease inhibitor therapy to avoid risk of toxicity.

The NNRTIs (with the exception of rilpivirine) tend to have an opposing effect on statins by inducing their metabolism. Efavirenz and etravirine will lead to decreased levels of atorvastatin and simvastatin, often requiring dose titration upward for lipid responses. Efavirenz will also significantly decrease pravastatin levels by about 40%, whereas etravirine is not expected to affect pravastatin or rosuvastatin levels.¹²

Opiates

Antiretroviral therapy can have differing effects on opiate metabolism owing to the varied metabolic pathways of these agents and the mixed induction/inhibition profiles of certain cART agents. PI/r's will decrease methadone levels 16%–50% via induction of metabolism.^{12,39} Efavirenz will decrease methadone levels by approximately 50%. If one of these is utilized with methadone, close monitoring for withdrawal is necessary with titration of methadone as appropriate. Interestingly, cobicistat has not been shown to have a significant effect on methadone levels,⁴⁰ and dose adjustments of methadone are not recommended by DHHS with concomitant use. Methadone can increase levels of zidovudine by up to 43%, necessitating close monitoring of zidovudine-related adverse effects (ie, anemia, bone marrow suppression).

Ritonavir and the other PI's inhibit CYP3A4 metabolism of opiates such as oxycodone and fentanyl. In contrast, efavirenz has the potential to increase metabolism via CYP3A4 induction. Careful initial opiate dose adjustment should be made in the setting of these interactions, patients monitored closely, and doses titrated accordingly. This is particularly crucial with protease inhibitors as overdoses can occur, leading to CNS side effects and respiratory depression.

PDE5 inhibitors

All PDE5 inhibitors used for erectile dysfunction are metabolized via CYP450 and will need dose adjustment if

on protease inhibitor or cobicistat therapy.¹² Avanafil is not recommended for use with protease inhibitors, cobicistat, or NNRTIs. All others (sildenafil, tadalafil, vardenafil) will require dose and/or frequency reduction to prevent toxicity (hypotension, headache, etc) with protease inhibitor or cobicistat use.

Comorbidities and management issues

Confounding the decrease in drug elimination rates due to reduced hepatic and kidney function, the older HIV patient population has more comorbidities that require consideration when choosing a cART regimen.

Psychiatric illness

Older HIV patients have a higher rate of anxiety and depression as compared with the non-HIV population.^{1,41} In view of the significant risk of drug interactions with BZDs, the consensus document recommends prescribing selective serotonin reuptake inhibitors (SSRIs) for the treatment of anxiety. Postmarketing data has shown aggressive reactions, agitation, delusions, paranoia, and psychosis associated with efavirenz use.¹² Suicidal ideation has also been seen in those with uncontrolled depression. Efavirenz is contraindicated in patients with uncontrolled depression, and should be used with caution in those with controlled symptoms or a history of depressive episodes.

Cardiovascular disease

Cardiovascular disease occurs at a younger age in HIV patients and has become a leading cause of death among the HIV-infected population in the US. The inflammation associated with untreated HIV infection and adverse effects of cART, including dyslipidemia and metabolic disorders, is

contributing. However, other risk factors appear to be similar to those in the general population including elevated LDL, smoking, diabetes mellitus, and hypertension.⁴²

Cardiovascular-related disease and events are more prevalent in older HIV patients.¹ Early data suggested abacavir was associated with an increased rate of cardiovascular events, but recent research does not document an elevated risk as compared with other NRTIs.^{43,44} Multiple HIV drugs are associated with increased lipid levels (Table 4).¹²

To reduce cardiovascular disease risk factors in HIV patients >50 years, close monitoring of lipids every 3–6 months should be completed and lipid-lowering drugs prescribed to control LDL. Drug interactions with statins need to be closely monitored. All older HIV patients who have tobacco dependence should be advised to quit and offered counseling. Diabetes should be managed per guidelines, and exercise and weight loss encouraged. HIV cART should be prescribed to reduce the accumulative inflammatory effects of viral replication.^{45,46}

Osteoporosis

Patients with HIV are more likely to have a low bone density and higher rates of bone fracture than uninfected patients.^{1,47} HIV-specific risk factors associated with osteoporosis include some cART medications, particularly tenofovir, and chronic immune activation. Additional risk factors include vitamin D deficiency, hypogonadism, reduced weight, and smoking.^{1,48} These risk factors should be investigated and treated.

Kidney disease

Chronic kidney disease (CKD) is more common in HIV-infected patients than in non-HIV-infected patients. Since the advent of cART, HIV-associated nephropathy has declined. However, there has been an increase in CKD that is related to comorbidities such as diabetes and hypertension and to the nephrotoxicity of HIV medications, particularly tenofovir.^{49,50} Atazanavir is associated with crystalline formation leading to abrupt changes in kidney function. Renal function should be evaluated at the time of initial diagnosis with measurement of creatinine, estimated glomerular function rate (eGFR), and urinalysis.⁴⁶ In patients with underlying kidney disease at baseline, tenofovir can still be administered if the creatinine clearance is greater than 10 mL/min or if they are receiving hemodialysis. However, the decision to administer tenofovir for the benefit of HIV control in the setting of chronic kidney

Table 4 cART medications associated with increased hyperlipidemia

NRTI class

Abacavir (including combination pill Epzicom and Trizivir), stavudine, zidovudine (including combination pill Combivir and Trizivir)

NNRTI class

Efavirenz (including combination pill Atripla)

PI class^a

Lopinavir (including combination pill Kaletra), saquinavir, ritonavir, indinavir, nelfinavir, fosamprenavir

Stribild

Notes: ^aAtazanavir and darunavir are also associated with hyperlipidemia, but to a lesser extent as compared with the other PIs.

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; cART, combination antiretroviral therapy.

disease should be weighed closely against the risk of worsening renal function.

Renal function monitoring is recommended every 3–12 months, depending on the patient's baseline renal function and antiretroviral regimen.¹² No recommendations for monitoring were specifically identified in the HIV and Aging consensus document; however, older individuals with HIV are more likely to be sensitive to drug side effects or interactions that result in a decline in kidney function.¹ For this reason, kidney function monitoring every 3 months in older HIV patients should be considered.

If renal dysfunction is present, dose adjustment of the NRTIs, with the exception of abacavir, is required. Stribild should not be started if creatinine clearance is <70 mL/min, and must be stopped if <50 mL/min. Dose adjustment of maraviroc may also be required with creatinine clearance <30 mL/min.

Malignancy and chemotherapy

AIDS-defining malignancies, which include Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer, are declining while non-AIDS-defining cancers (NADCs) are increasing.⁵¹ Older individuals with HIV are at increased risk of NADCs including anal cancer, Hodgkin's lymphoma, hepatocellular cancer, skin cancers, cancers of the head and neck, and lung cancer.¹ When an HIV patient is diagnosed with malignancy, interprofessional communication is essential. The cART medications will typically require modification. In some cases, cART might be held or stopped due to the patient's overall prognosis.

Multiple chemotherapy drugs undergo metabolism via CYP450 enzyme pathways, leading to interaction with PI/r's, NNRTIs, and cobicistat. Given the narrow therapeutic window for most chemotherapy, this can be problematic for managing combined therapy. The NRTIs and INSTIs, raltegravir and dolutegravir, usually have minimal interaction with most chemotherapy agents. Medication adjustment in this setting would best be completed with the assistance of a pharmacist, experienced in HIV therapeutics and chemotherapy management.

Liver disease and chronic hepatitis

HIV-infected individuals have a higher rate of chronic hepatitis B and hepatitis C infection as compared with the general population. Coinfected patients are at increased risk for progression to cirrhosis. Additionally, in the cART era, both alcoholic liver disease and nonalcoholic steatohepatitis (NASH) are increasing in the HIV population. These patients are also at risk for medication toxicity from their antiretroviral treatment.⁵²

All HIV patients should be screened for viral hepatitis and have baseline liver function tests at the time of their HIV diagnosis. Liver functions tests (LFTs) should be monitored every 3–6 months, and any unexplained rise in LFTs should be investigated. For patients with well-controlled HIV infection and progression to end-stage liver disease, liver transplantation is an option.⁵³

Patients with chronic hepatitis B and HIV coinfection require two antiviral drugs that are effective against hepatitis B. The choices include the antiretroviral NRTI medications tenofovir, with either emtricitabine or lamivudine. For simplicity, most patients receive Truvada, a coformulated tablet containing tenofovir and emtricitabine as the dual nucleoside cART backbone.

Medication adherence strategies

Adherence to optimal antiretroviral regimens is crucial to successful HIV management. Some studies suggest that cART adherence is actually improved in the older population.^{29,54,55} The higher adherence seen in older HIV patients is likely due to familiarity with medication usage for chronic diseases and increased awareness that treatment of HIV requires a high level of medication adherence.⁵⁵ Many HIV patients over 50 years old have had friends or partners who passed away from infections associated with HIV/AIDS, particularly during the height of the epidemic when treatment options were limited, and this emotional experience has shaped their desire to maintain control of this disease.

Despite data suggesting more favorable adherence to prescribed cART regimens in older HIV patients, vision loss, cognitive impairment, limitations in health literacy, complex regimens with increased number of medications, medication cost, depression, and decreased expectations of health status can all negatively impact adherence.^{56–58} Additionally, older HIV patients with a history of drug abuse may continue to have drug dependence issues that negatively impact adherence. Thus, adherence should be closely monitored in our older HIV patients in order to maximize success, limit viral resistance, and enhance outcomes.

Optimizing compliance is of utmost importance for clinicians providing care to the older patient with HIV. Not effectively assessing cART compliance can lead to unnecessary therapeutic alteration of an otherwise well-tolerated and convenient cART. Studying compliance can be challenging, and outcome measures can be difficult to compare because of differing study methodology, but many interventions have been shown to enhance medication compliance in the elderly:

Table 5 Approaches to enhance compliance with antiretroviral therapy

1. Targeted antiretroviral medication education (written and oral) in accordance with the patient's level of health literacy to include: indication for their cART, expectations with therapy and response to therapy, administration requirements, and anticipated side effects (helpful fact sheets can be found on <http://www.aidsinfonet.org/categories>)⁶⁰
2. Targeted education regarding the importance of compliance/adherence for control of HIV (a helpful patient fact sheet can be found on http://www.aidsinfonet.org/fact_sheets/view/405)⁶¹
3. Medication organizing devices (pill organizers, pillboxes, unit dose packaging, blister packaging, etc)
4. Reminder devices: calendars, medication checklists, smartphone apps, alarms
5. Incorporation of medication taking with patient's daily routine and/or selection of appropriate ART that minimizes adverse effects that disrupt daily routine
6. Involvement of family members, significant others, and caregivers when able

Abbreviations: cART, combination antiretroviral therapy; ART, antiretroviral therapy.

Reminder prompts (phone call reminders, videoconference call reminders), education and instruction on medication (pharmacist oral instruction/education, written handouts), dose administration simplification tools (pillboxes, unit dose packaging, pillbox fills), simplifying medication regimen (less pills, reduced dosing frequency), and involving a pharmacist in medication review, education, and providing care.^{56,58}

The more interventions and focus provided on adherence, the higher the chance of success (Table 5). However, every patient is different in their approach to medication taking, and any interventions should be patient-focused and tailored to the individual patient rather than generalized. Tailoring interventions has been shown to be more successful.⁵⁹ For example, some patients are not good candidates for weekly pillboxes owing to the manual dexterity required for filling and loading, or the perceived sense of aging associated with using a pillbox. However, they are quite content to use unit dose packages with preloaded medications and cell phone alarms to remind them of dosing times. Every patient will be different, and a multifaceted tailored approach to addressing adherence in the older patient has been shown to be successful.⁵⁸

Summary

cART is highly effective at preventing morbidity and mortality from HIV. HIV medication therapy in older individuals is often complex, and the decision of when to start, what to start, and when to stop medication should

involve all aspects of the individual patient and not only their HIV resistance pattern. The aging HIV population is at an increased risk of drug-related complications and exacerbation of non-HIV comorbidities, which must be considered when choosing a cART regimen. Most older patients will benefit from cART, but it is crucial that they are prepared and ready to be adherent to therapy. Occasionally, the risk of nonadherence may offset the benefits of early initiation of therapy. Incorporating the patient's values and preferences into shared decisions regarding regimen selection, adherence interventions, and care management will lead to the best chance of successful care for older HIV-infected patients.

Disclosure

The authors report no conflicts of interest in this work.

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