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Older HIV-infected adults. Complex patients (III): Polypharmacy

Samuel F. Freedman, MD¹, Carrie Johnston, MD², John J. Faragon, PharmD, BCPS, AAHIVP³, Eugenia L. Siegler, MD⁴, Tessa Del Carmen, MD⁴

¹Department of Medicine, Weill Cornell Medicine, New York, New York, USA

²Division of Infectious Diseases, Weill Cornell Medicine, New York, New York, USA

³Albany Medical Center, Albany, New York, USA

⁴Division of Geriatrics and Palliative Medicine, Weill Cornell Medicine, New York, New York, USA

Abstract

Polypharmacy is a well-described problem in the geriatric population. It is a relatively new problem for people living with HIV (PLWH), as this group now has a life expectancy approaching that of the general population. Defining polypharmacy for PLWH is difficult, since the most common traditional definition of at least five medications would encompass a large percentage of PLWH who are on antiretrovirals (ARVs) and medications for other medical comorbidities. Even when excluding ARVs, the prevalence of polypharmacy in PLWH is higher than the general population, and not just in resource-rich countries. Using a more nuanced approach with “appropriate” or “safer” polypharmacy allows for a better framework for discussing how to mitigate the associated risks. Some of the consequences of polypharmacy include adverse effects of medications including the risk of geriatric syndromes, drug-drug interactions, decreased adherence, and over- and undertreatment of medical comorbidities. Interventions to combat polypharmacy include decreasing pill burden—specifically with fixed-dose combination (FDC) tablets—and medication reconciliation/deprescription using established criteria. The goal of these interventions is to decrease drug interactions and improve quality of life and outcomes. Some special populations of interest within the community of PLWH include those with chronic pain, substance abuse, or requiring end of life care. A final look into the future of antiretroviral therapy (ART) shows the promise of possible two-drug regimens, which can help reduce the above risks of polypharmacy.

Keywords

polypharmacy; geriatric; HIV; medication appropriateness; adverse drug reactions; drug interactions

Corresponding Author: Eugenia L. Siegler, MD, Division of Geriatrics and Palliative Medicine, Weill Cornell Medicine, 525 E. 68th Street, Box 39, New York, NY 10065, v: 1.212.746.1729, f: 1.212.746.4888, els2006@med.cornell.edu.

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Introduction

Worldwide, it was estimated that in 2017 approximately 6.7 million people aged 50 and older were living with HIV[1]. In 2015, approximately 47% of PLWH in the United States (US) were aged 50 and older, according to the CDC[2]. This number is expected to rise as the life expectancy of PLWH approaches that of non-infected individuals [3]. Polypharmacy, a well-described problem in the geriatric population, is a concern in the aging population of PLWH, as well. It is crucial for providers to understand the unique risks of polypharmacy within this community and how to mitigate them. This will allow for the effective treatment of HIV and medical comorbidities and the prevention of harm.

Definition

Polypharmacy denotes the prescription of multiple medications [4], but defining it is challenging; a systematic review in 2017 found 138 definitions [5]. The meaning of polypharmacy often depends upon the purpose for which the term is being used. Most commonly, a quantitative definition is used, as this is conceptually simple and supported by a literature that documents an increased risk of complications with increased number of medications [5]. A second conceptualization of polypharmacy centers around medication choice. In this case, the question is a more complicated one: irrespective of total number of medications, is each drug justified and safely administered? Table I lists typical definitions and resources. A more comprehensive list and comparison of appropriateness measures can be found in Whitman et al. (2016) [6].

Several things are noteworthy:

A quantitative definition may seem easy to measure and has the advantage of an extensive literature. Nonetheless, when viewing polypharmacy quantitatively, patients and providers may have very different perspectives. The patient may be most concerned about pill burden while the provider may be most concerned about total number of medications irrespective of dosing frequency or mode of administration. Providers may forget to ask about over-the-counter medications or complementary therapies and underestimate medication burden.

The use of multiple medications does not necessarily indicate poor prescribing but rather may merely be an indicator of multimorbidity [12]. It does not factor in medication toxicity or potency; older PLWH may meet quantitative definitions of polypharmacy merely by taking a few over-the counter medications along with their antiretroviral medication. Medication appropriateness may be a more viable construct and a more achievable goal, especially in the setting of HIV.

To that end, Duerden and colleagues (2013) [4] distinguish between problematic (as defined in Table I) and appropriate polypharmacy, which they define as “prescribing for an individual for complex conditions or for multiple conditions in circumstances where medicines use has been optimised and where the medicines are prescribed according to best evidence.” This framework is relevant to all PLWH. Age, frailty, functional and cognitive status, and multimorbidity should be considered when determining the optimal regimen.

Prevalence

For the purposes of this paper, we will use the quantitative definition of polypharmacy to evaluate prevalence. Even within this context, the prevalence of polypharmacy depends on the definition. Most studies exclude antiretroviral medications from the definition, which enables a more realistic comparisons to uninfected populations but does not reflect the frame of reference of PLWH. Fortunately, the ART pill burden among PLWH has decreased drastically over the past decades. A Canadian study showed that among PLWH of all ages, the average number of ARV pills (among 365 PLWH) was 10 per day in 1998 compared to 3.4 per day in 2010 (among 1,419 PLWH) [13]. Despite a decrease in pill burden in recent years, many patients are on single tablet regimens, which includes 3 active medications and possibly a pharmacokinetic enhancer, or “booster.”

Several studies have examined prevalence of polypharmacy in PLWH. According to the 2011 Swiss Cohort study, 14.2% of the 450 PLWH over 65 were taking at least 4 different non-ART medications [14]. An examination of polypharmacy and comorbidity in the Italian GEPPCO cohort (aged >65) defined polypharmacy as taking 5 or more non-ART medications. They found that polypharmacy was present in 37% of the HIV infected cohort compared to 24% in controls. In addition, this study demonstrated that the risk of polypharmacy increased for those greater than 75 and with longer exposure to HIV, rising to 43% for those who had been diagnosed with HIV for at least 20 years [15].

The Veterans Aging Cohort study of 7200 veterans in the US noted that among those older than 50, PLWH were taking an average of 7 medications, while uninfected counterparts were taking an average of 5. Of PLWH, 55% were taking 5 or more medications (which included ART). This likely underestimates the actual number, as only prescribed medications were counted [16]. While the prevalence of polypharmacy was much higher in this study than prior ones, it still demonstrated a higher rate of polypharmacy in PLWH than in those without HIV, even when excluding ART. When assessing what additional medications PLWH take compared to those without HIV, a Spanish study of 8,172 PLWH aged 50 years or older showed that PLWH are prescribed more CNS medications and anti-infectives, but similar amounts of cardiovascular (CV) drugs [17].

Polypharmacy is not restricted to resource-rich countries. In Uganda, a study of 411 PLWH Uganda aged >50 found the prevalence of HIV to be 4% and the rate of polypharmacy among that population to be approximately 15%. Polypharmacy was more common among those who had seen a physician and was not associated with adverse events, reflecting the possibility that polypharmacy in part may be an indicator of access to care [18].

Consequences

Even though most definitions of polypharmacy exclude ARVs, many of the negative outcomes of polypharmacy are a consequence of interactions between ARVs and medications used to treat comorbidities. The following table divides the most common ARVs by drug class and details the adverse effects, geriatric considerations, and major drug interactions (Table II). A more exhaustive list with specific drug interactions is available

online—Liverpool HIV Drug Interactions [19]. The US Department of Health and Human Services (DHHS) website contains a chart of drug interactions between ARV class and commonly prescribed medications [20].

One of the most serious consequences of polypharmacy in this population is drug interactions. In one study of PLWH that included 159 people of all ages in Liverpool, clinically significant drug interactions were recorded in 27%, with 15% of interactions potentially lowering antiretroviral concentrations. Risk of clinically significant drug interactions was significantly related to receipt of protease inhibitors. Only 36% of clinically significant drug interactions were correctly identified by physicians [30].

One can analyze drug interactions further by category (defined by Lexicomp®)—category D means to consider therapy modification while category X interactions would be completely avoided. Using these criteria, 70% of 89 PLWH aged 60 or older in a San Francisco area study had at least 1 category D drug-drug interaction (DDI), while 11% had a category X interaction. A clinical pharmacist determined 60% of interactions to be clinically significant. Approximately half of the interactions were between ART and non-ART medications, and 35% were between non-ART [31]. One study of 3,810 PLWH over 50 years old living in Liverpool showed that 7% of PLWH had at least one ARV/non-ARV combination that was contraindicated, and a third with moderate or high evidence of interaction. The medications that were most often involved included PPIs, statins, and benzodiazepines [32].

As seen in the chart above, pharmacokinetic enhancers, or “boosting” medications, such as ritonavir and cobicistat, which are strong inhibitors of CYP3A4, are among those drugs with the highest risk for interactions [33]. See Table III below for more specific interactions.

Another complication of polypharmacy is medication nonadherence. Although controversial in the literature, a systematic review of studies with rigorous designs found that 4 out of the 5 studies examined showed an association between polypharmacy and a greater risk of nonadherence [34]. Polypharmacy has been associated with decreased adherence to ART [35]. However, this is not seen universally. In the Uganda study discussed above, there was no impact on adherence or clinical outcomes [18]. Adverse events are the most frequent reason for first-line antiretroviral therapy discontinuation/switch. Among 1,096 PLWH in Italy of all ages, there was a higher rate of discontinuation of ARV secondary to side effects in older PLWH [36].

Polypharmacy increases the risk of geriatric syndromes such as falls, confusion, delirium, and cognitive decline in the general population. A study of 46,946 people of all ages in the US showed that in older individuals with diabetes, taking greater than 4 medications was associated with an increased risk of falls [37]. Another study of 395 PLWH in Colorado ages 45 to 65 determined that the odds of falling is increased by 1.7 for each comorbidity and 1.4 for each medication [38]. In the geriatric population, there is an association between impaired cognition, difficulty with daily tasks, and polypharmacy for those taking >10 medications based on 1,000 people from the GeMS Study data in Finland [39].

For other systemic side effects unrelated to the geriatric population, a study of 661 people of all ages in Boston found that the number of medications taken was significantly associated with adverse events [40]—the details of possible side effects are seen in Table II above.

Overtreatment is the underlying concern about polypharmacy. However, undertreatment is also an area of concern for PLWH who have high-risk comorbidities. For example, most models of risk for heart disease are based on risk factors that go into the Atherosclerotic Cardiovascular Disease (ASCVD) risk algorithm, which does not include other pro-inflammatory states, such as HIV [41]. The incidence of cancer, liver disease, and cardiovascular disease is higher in treated PLWH than in age matched HIV-uninfected people [42]. Furthermore, the rate of CV events is higher in untreated PLWH than in treated patients, which is likely related to higher levels of inflammation. IL-6, hsCRP, and D-dimer are three markers of inflammation that are elevated in PLWH and are associated with mortality and CV disease [43]. With this said, treated PLWH still have elevated biomarkers and have higher risk of CV events. For those on protease inhibitors, there are higher rates of hyperlipidemia, insulin resistance, and CV morbidity.

Among people in the Veterans Aging Cohort Study who met NCEP/ATP III criteria for lipid lowering therapy, HIV-infected veterans had a significantly lower prevalence for the receipt of lipid lowering therapy—approximately 60% lower as compared with HIV-uninfected veterans [44]. This shows that even when comparing standard risk factors for CV disease, PLWH were undertreated. Potential interactions between ART and lipid lowering medications may account for some of this discrepancy. When taking into account the fact that PLWH are at higher risk for CV disease in general, the rate of undertreatment is likely higher.

Interventions

Decreasing pill burden can help mitigate polypharmacy in aging PLWH. One way to do this is to encourage fixed-dose combination (FDC) tablets. However, the actual number of active medications may or may not change when these changes are made. Although previous single tablet regimens were less likely to be prescribed in those with polypharmacy possibly due to perceived risk of drug-drug interactions (Modena HIV Metabolic Clinic Cohort Study among 2,944 people of all ages) [45], two studies have shown that switching from multidrug regimen to FDC can lead to small, but statistically significant increase in adherence. A study of 43 PLWH of all ages in London showed improvement of adherence from 97.7 to 99.4% with the change to a FDC pill [46]. An Italian study of 212 PLWH of all ages showed an improvement of QoL from 68.8 to 72.7% [47]. A review found that 5 studies (2 abstracts and 3 articles) noted a statistically significant association between regimen complexity and decreased adherence [48]. These findings show that switching to or starting with FDC tablets can improve medication adherence by simplifying drug regimens.

Despite this, many PLWH may be hesitant to switch ART, especially if they have been virologically suppressed for many years. Aside from patient reservations, there are other barriers to switching medications, including time required to obtain prior authorizations (in the US) and potential for higher copays, especially with private insurance. Ideally, newer

medications will have even fewer interactions, but since PLWH may be reluctant to risk a new regimen, it is important to consider possible long-term drug interactions at initial counseling. The 2018 recommendations of the International Antiviral Society–USA Panel (IAS-USA) place FDC as preferred for most patients, specifically, combination tablets with a 2-NRTI backbone and an integrase inhibitor. The “boosted” FDC tablets with ritonavir or cobicistat are now considered first line only when regimens without them are not available [49]. In addition, these recommendations prefer TAF (when available) over TDF, given the lower likelihood of renal and bone toxicity. The DHHS guidelines, however, do not recommend one over the other [20]. There are no guidelines from IAS-USA specific for ART in older individuals despite change in pharmacodynamics/kinetics that come with aging [50]. DHHS guidelines recommend tailoring ARV drugs based on aging-associated comorbidities, such as renal or liver dysfunction and bone health, as well as consideration of drug-drug interactions [20].

Medication reconciliation is likely the most important intervention for decreasing polypharmacy or allowing for “safer” polypharmacy. This would help ensure that PLWH are not being over-prescribed unnecessary medications or under-prescribed preventive medications while simultaneously accounting for drug interactions and geriatric concerns. The two most used tools include the STOPP/START and Beers criteria [10, 11].

PLWH, especially those who are considered elderly or frail, may be eligible for de-prescription, whereby providers reduce the use of medications as patients grow older. This is particularly important when PLWH are prescribed medications that either interact or may lead to unwanted adverse events. STOPP/START and Beers criteria can be utilized to help identify medication that should be avoided or at least reduced in elderly patients [10, 11]. For example, the use of psychotropics, such as atypical antipsychotics, are not only likely to increase fall risk in patients, they pose additional risk in patients with HIV who are receiving pharmacokinetic enhancers ritonavir or cobicistat. Quetiapine, for example, can be increased up to 5 fold in patient receiving ritonavir [20, 51–55]. This is just one example of how the Beers criteria has important implications on elderly patients with HIV. In addition, a pharmacist-led study used Beers Criteria and STOPP to assess for potentially inappropriate prescribing (PIP) in older PLWH and found that targeting people with 11 or more medications had the highest yield in identifying opportunities for de-prescribing. A little over half of people were found to have a PIP, and after a pharmacist led visit, approximately 70% of participants had at least one medication discontinued; 10% had at least six medications discontinued [56].

The approval of numerous HIV FDC tablets may reduce the total number of medications a person is receiving. This should prompt HIV providers to evaluate previously selected regimens that may be changed to newer FDC tablets. For example, patients may still be receiving twice daily darunavir/ritonavir selected years ago when that was the standard of care [57]. Research has demonstrated that once daily darunavir/ritonavir or darunavir/cobicistat can be used if darunavir resistance associated mutations (RAMS) are absent [57]. This change not only reduces pill burden but also eliminates a dose of darunavir/ritonavir, which could potentially improve lipids, reduce GI adverse events and minimize drug interactions [20].

In addition, common medical issues, such as diabetes, hyperlipidemia, and hypertension need to be evaluated and addressed in all aging patients. Hemoglobin A1c and blood pressure goals may need to be adjusted to reduce the risk of falls in elderly patients. The SPRINT trial showed that more intensive blood pressure control, even in the elderly, was associated with decreased risk of many CV outcomes, but with increased risk of adverse events, including hypotension and syncope [58]. The recommendations from the American Diabetes Association for A1c goal in the elderly depends on functional status and comorbidities, though there are few data on the subject (grade C recommendations) [59]. Finally, LDL goals that require additional medications besides the use of statins may also need to be liberalized to reduce potential for toxicity.

When reviewing medications, it is important to note again that this is a cohort with higher levels of inflammation. Thus, it may be even more critical to aggressively treat comorbidities. While awaiting further studies that may change guidelines specific to those with chronic inflammation, it is important to at least ensure guideline-based CV prevention therapy.

Special populations

PLWH are at high risk for chronic pain [60]. Aging PLWH are especially vulnerable to chronic pain and opiate use [61, 62]. The treatment of chronic pain has shown to improve ART adherence [63–65]. Unfortunately, pain medications may increase both the pill burden and the risk for drug interactions/adverse drug events [66, 67]. In addition to polypharmacy, opiate use puts older adults at risk for delirium, falls and fractures, particularly in the setting of possible underlying neurocognitive deficits and low bone mineral density seen in aging PLWH [10].

A special polypharmacy consideration is the effect of ART on opiate metabolism [68]. Some NNRTIs, such as efavirenz, nevirapine, and rilpivirine may decrease methadone levels by increasing the induction of the metabolism of methadone. This can potentially cause withdrawal in people on methadone for chronic pain or opioid addiction [60, 68]. Other ART, such as ritonavir, may increase the level of opioids by inhibiting the CYP3A4 metabolism thus causing opiate overdoses [60, 68].

Substance abuse is also not uncommon among PLWH [69]. Injection drug users are more likely to be compliant with ARV if they are medically treated for their addiction [70]. The most commonly used medications to treat opiate addiction are methadone and buprenorphine. As discussed above, some ART can interact with the metabolism of methadone. This also applies to buprenorphine [60].

Another vulnerable population of PLWH at risk of polypharmacy is those near the end of life [71]. Prior to ART, HIV infection may have justified hospice or palliative care soon after diagnosis, but PLWH are now living close to the life expectancy of people without HIV [72, 73], and HIV is an infrequent primary diagnosis for hospice [63, 74]. This does not necessarily mean that people with HIV forego hospice, but that they are admitted to hospice for other life limiting illnesses [72]. The current hospice admission criteria for end-stage

AIDS include having a CD4 <25 cells/mL or viral load >100,000, an opportunistic infection, HIV-related malignancies or illnesses, Kamofsky performance status of < 50%, in addition to supporting findings such as HIV not responsive to ART, or forgoing ART [71]. This could mean that there are some who may be eligible for hospice secondary to end stage AIDS due to resistant strains. In these situations, the question of whether a person benefits from continuing ART comes in to play. Even if a PLWH is on hospice secondary to a non-HIV disease such as stroke or heart failure, the decision whether to continue ART is challenging, as currently there are no guidelines [71]. ART decreases the risks of opportunistic infections [75–77], which may lower their symptom burden and potentially decrease the caregiver's exposure to resistant strains or high viral loads. Informal caregivers have the added burden of fear of infection related to caregiving activities of PLWH [78, 79]. Continuing ART, in addition to enhancing symptom management, may also alleviate some of the fear that caregivers have regarding transmission. Despite the argument that ART should be given to help alleviate symptoms and avoid suffering from certain pain and opportunistic infections, there are situations where discontinuing ART may be necessary. Utilization of standard deprescribing techniques as described above may be helpful. Providers should evaluate the role of ART in symptom management, the risk of interactions, pill burden, and dysphagia [71].

A look into the future of ART

Initial HIV treatment regimens, which began with the first drug zidovudine in 1986, were characterized by high pill burden, side effects, and complicated dosing regimens that often resulted in decreased adherence [80]. Over the past three decades, HIV treatment has evolved greatly, now with options for one pill once a day. Any single tablet regimen is a combination therapy, typically including three to four different medications co-formulated into one tablet. As discussed previously, ease of dosing and adherence to ARV therapy have increased with single-tablet regimens and once-daily dosing schedules. Nonetheless, clinicians must consider multiple factors when selecting a single tablet that contains three to four medications within each tablet, particularly in an older population.

Ongoing research offers potential for two-drug combination regimens, notably without a protease inhibitor that may require a pharmacologic “booster.” Recently, the SWORD 1 & 2 trials evaluated the combination of dolutegravir/rilpivirine as maintenance therapy compared to “current” ARV three-drug regimens such as two NRTIs and an INSTI, NNRTI or PI. At time of enrollment, all participants had HIV-1 RNA <50 copies/mL for at least 6 months. The primary endpoint was proportion of participants with HIV-1 RNA <50 copies/mL at 48 weeks [81], and a follow-up study of 100 weeks [82]. These data show that the combination of dolutegravir/rilpivirine was non-inferior to current ARV regimens, as defined above, for ongoing viral suppression of HIV-1. Ongoing studies evaluating lipid profiles, bone mineral density, and fractures may offer further insight into the metabolic effects and potential benefits of this two-drug regimen.

There are currently no recommended two-drug regimens for initial therapy of HIV infection. However, this may change, as ongoing research is evaluating the combination of dolutegravir/lamivudine compared to a dolutegravir plus two NRTI regimen in the GEMINI

1&2 phase III clinical trials [83, 84], whose estimated completion date is March 2020. If effective, this could offer newly infected people with HIV an opportunity to initiate therapy with a novel two-drug combination free of either NNRTI or PI medications that often carry a relatively higher burden of side effects, drug interactions, and metabolic complications.

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Table I -

Select Polypharmacy Definitions and Resources

General Category	Definition	References	Advantages	Disadvantages
Quantity of medications				
	Five or more medications	[5]	Most commonly used definition	Implies that large number of drugs is wrong even if the person has multiple medical problems and is benefiting from the medications; does not take into account dosing, medication toxicities, drug interactions, or duplications
	Ten or more medications	[5]	Second most commonly used, although often with modifiers such as “hyper” or “excessive”	
Choice of medications				
	“At least one potentially inappropriate drug”	[7]	Can be difficult to accurately assess appropriateness in retrospective chart reviews	Depends upon published criteria for “inappropriate”
	“Problematic polypharmacy: where multiple medications are prescribed inappropriately, or where the intended benefit of the medication is not realized.”	[4]		
Measures of appropriateness				None specific to HIV
	12 indicators determined by an expert panel	[8]	Does not identify any particular medication as inappropriate	Unwieldy, not yet operationalized
	Medication Appropriateness Index	[9]	Easy to use; Validated; useful for over-the-counter and complementary therapies	Time consuming; incomplete
Can be used together	Beers	[10]	Widely cited, endorsed by American Geriatrics Society (AGS)	Focused on prescription drugs; sensitive, not specific
	STOPP/START	[11]	Useful in multiple settings; validated; evaluates initiation as well as discontinuation of medications	Focused on prescription drugs

Table 2

ARV adverse effects, geriatric considerations, and drug interactions by drug class

Drug class	Medication	Adverse effects	Geriatric considerations	Drug interactions
Integrase strand transfer inhibitors (INSTI)		Generally well tolerated as a class. Reports of 4–10% of patients with CNS and/or GI side effects in some series. Bictegravir with lowest side effect profile [21]		Oral absorption reduced when co-administered with calcium, aluminum or magnesium antacids, or calcium or iron supplements. If the above medications must be used, INSTI can be given while fasting 2 h before, or in some cases, given simultaneously with food [22]
	Bictegravir	Few; < 2% of patients with side effects including dyspepsia, flatulence, vomiting, abdominal pain	Not recommended with CrCl < 30 mL/min Increases tubular secretion of creatinine without changing GFR, therefore may have transient (< 4 week) increase in serum Cr	CYP3A4 substrate Should not be used with rifamycins, St. John's Wort, and anticonvulsants known to induce CYP3A4 [22] Inhibits OCT2 and MATE1 drug transporters; contraindicated with the antiarrhythmic dofetilide, as it will increase the concentration of antiarrhythmic Can increase concentration of metformin [20]
	Dolutegravir	CNS GI	Can cause sleep disturbances, headache, fatigue, malaise, altered mood, insomnia, nightmares Lowest risk of GI side effects [21]	CYP3A4 substrate Should not be used with rifampin, St. John's Wort, and anticonvulsants known to induce CYP3A4 [22] Inhibits OCT2 and MATE1 drug transporters; contraindicated with the antiarrhythmic dofetilide as it will increase the concentration of antiarrhythmic Can significantly increase concentration of metformin, consider dosage reduction for metformin
	Elvitegravir	GI upset CNS	GI side effects of nausea, vomiting and diarrhea CNS fatigue, headache, sleep disturbance	Only available co-formulated with cobicistat pharmacokinetic enhancer, therefore CYP3A4 inhibition Elvitegravir is a UGT1A1 substrate [20]
	Raltegravir	GI upset CNS	Lowest CNS side effect profile. GI side effects of nausea, vomiting and diarrhea Rare reports of myopathy and rhabdomyolysis. Avoid in patients with history of myopathy Nausea, headache, diarrhea, insomnia, depression	Lowest risk of drug interactions. Not a substrate of Cytochrome P450 system. Metabolized by UGT1A1-mediated glucuronidation Co-administration of raltegravir with drug that is inducer of UGT1A1 may reduce plasma concentration of raltegravir (i.e. rifampin)
Nucleoside reverse transcriptase inhibitors (NRTI)				Most are renally metabolized and not affected by liver dysfunction
	Tenofovir	Rare lactic acidosis and hepatic failure Also treats HBV, flare-up of HBV if tenofovir discontinued	TAF with improved GFR and hip/spine bone mineral density (BMD) compared to TDF [24]	
	Alafenamide (TAF)	Headache most common side effect. < 10% of patients with abdominal pain, fatigue, malaise	For TAF, no dose adjustment is required for patients with CrCl 30ml/min or higher. When CrCl is <30 ml/min, TAF is not recommended	Drugs which affect P-glycoprotein and BCRP will change tenofovir concentration. Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital and phenytoin will decrease concentration of tenofovir. Rifamycins and St. John's Wort also decrease concentration of tenofovir [20]
	Disoproxil fumarate (TDF)	Decreased GFR. Rare cases of acute renal failure and Fanconi syndrome	For TDF, providers should dose adjust if CrCl is <50 mL/min	

Drug class	Medication	Adverse effects	Geriatric considerations	Drug interactions
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Emtricitabine (FTC)	Reduced BMD and increased risk for osteoporotic fracture [23] Rare lactic acidosis and hepatic failure Also treats HBV, flare-up of HBV if emtricitabine discontinued 10–15% of patients report headache, diarrhea, nausea, fatigue, dizziness, abnormal dreams, abdominal pain, cough, rhinitis, rash	Dose adjust for GFR < 50 mL/min	
	Lamivudine (3TC)	Rare lactic acidosis and hepatic failure Also treats HBV, flare-up of HBV if Lamivudine discontinued Headache, nausea, malaise, fatigue, rhinorrhea, diarrhea, and cough most common side effects	Dose adjust for CrCl < 50 mL/min	
	Abacavir (ABC)	Hypersensitivity reaction, increased risk if HLA-B5701 (General prevalence ~5% of population, most common in Caucasian males) [25] Cardiac risk*: > 2-fold risk of CVD reported in case series [26]	Cardiac risk ^a Hypersensitivity reaction	Generally act as CYP450 3A4 inducers, therefore interact with Rifampin, azoles, AEDs, statins, midazolam, ergotamines and other HIV medications when used concurrently [20] Caution dosing antiplatelet agents i.e.: clopidogrel, prasugrel, ticagrelor with NNRTIs. Ticagrelor should not be given with any NNRTI
	Zidovudine	Anemia, neutropenia Fatigue Lipodystrophy CNS effects and rash most common	Rarely used	Inhibits CYP450 2C9, 2C19, and 3A4 Significant decreases in concentration of methadone, voriconazole, rifabutin Reduces concentration of clopidogrel metabolite [28], consider prasugrel for platelet inhibition
	Efavirenz	CNS effects, suicidality, rash	Mental health, specifically suicidality increased in trial data of efavirenz as initial regimen [27] Absorption improved when taken with a full meal	Substrate of CYP450 system, low risk of drug interactions Concurrent PPIs contraindicated Can be given with clopidogrel without dose adjustment Can be given with efavirenz without dose adjustment
	Rilpivirine	Poor absorption with proton pump inhibitors (PPIs)	Avoid if VL > 100 k copies/mL or CD4 < 200 cells/mm ³ Needs to be taken with food	
	Nevirapine	Hepatotoxicity Hypersensitivity reaction	No longer used commonly	
	Doravirine	Generally well tolerated. Nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, abnormal dreams possible		Cannot be given with strong CYP3A4 inducers; anticonvulsants, enzalutamide (androgen receptor inhibitor), rifampin, St. John's wort
	Etravirine	Rash, rare cases of SJS. Fat redistribution Peripheral neuropathy		Inducer of CYP3A and inhibitor of CYP2C9, CYP2C19 and P-glycoprotein Reduces concentration of active metabolite for clopidogrel, if platelet inhibitor needed consider prasugrel [20]

Drug class	Medication	Adverse effects	Geriatric considerations	Drug interactions
Protease inhibitors (PI)		Most common side effects in this class are GI and hyperlipidemia (HLD) Most commonly in “boosted” formulations	PIs may be “boosted” with pharmacokinetic enhancers ritonavir or cobicistat, which are potent CYP450 inhibitors	Ritonavir and cobicistat are CYP450 3A4 inhibitors See Table 3 for more detailed medication interactions Warfarin can be used, INR may be decreased—requires close monitoring Caution with concurrent use of Direct-Acting Oral Anticoagulants (DOACs)
	Darunavir	Skin rash Diarrhea Nausea/vomiting Headache	Dosed alone or “boosted” Often used if high resistance or in very treatment-experienced patients	See Table 3 about “boosting” agents Darunavir contains a sulfonamide moiety, use with caution in patients with sulfa allergy
	Atazanavir	Increased indirect bilirubin GI upset Kidney stones	“Boosted” with ritonavir or cobicistat	See Table III about “boosting” agents
Fusion inhibitors	Lopinavir	Diarrhea HLD	“Boosted” with ritonavir	See Table III about “boosting” agents
	Enfuvirtide Injection	Injection site reaction	Rarely used May be difficult to inject into subcutaneous tissue in thin/fragile individuals	
CCR5 antagonist	Maraviroc	Hepatotoxicity, in some cases preceded by allergic/IgE reaction		CYP450 substrate, therefore reduce dose when given with potent CYP3A4 inhibitor, increase dose when given with CYP3A4 inducer

Table III -

Contraindicated Medications with Common HIV Regimens and PKE Cobicistat or Ritonavir

Medication	Common Regimens	Contraindicated Medications
Cobicistat	<ul style="list-style-type: none"> · Elvitegravir/cobicistat/TAF/FTC · Elvitegravir/cobicistat/TDF/FTC · Atazanavir/cobicistat + ABC/3TC, TAF/FTC or TDF/FTC · Darunavir/cobicistat/TAF/FTC · Darunavir/cobicistat + ABC/3TC, TAF/FTC or TDF/FTC 	<ul style="list-style-type: none"> · Alpha 1-adrenergic receptor antagonist: alfuzosin · Antianginal: ranolazine · Antiarrhythmic: dronedarone · Anticonvulsants: carbamazepine, phenobarbital, phenytoin · Anti-gout: colchicine · Antimycobacterial: rifampin · Antipsychotics: lurasidone, pimozide · Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine · GI Motility Agent: cisapride · Herbal Products: St. John's wort (<i>Hypericum perforatum</i>) · HMG-CoA Reductase Inhibitors: lovastatin, simvastatin · Phosphodiesterase-5 (PDE5) Inhibitor: sildenafil when administered for the treatment of pulmonary arterial hypertension (PAH) · Sedative/hypnotics triazolam, orally administered midazolam
Ritonavir	<ul style="list-style-type: none"> · Atazanavir+ritonavir + ABC/3TC, TAF/FTC or TDF/FTC · Darunavir+ritonavir + ABC/3TC, TAF/FTC or TDF/FTC · Lopinavir/ritonavir + ABC/3TC, TAF/FTC or TDF/FTC 	<ul style="list-style-type: none"> · Alpha 1-adrenergic receptor antagonist: alfuzosin · Antianginal: ranolazine · Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine · Antifungal: voriconazole · Anti-gout: colchicine · Antipsychotics: lurasidone, pimozide · Ergot Derivatives: dihydroergotamine, ergotamine, methylergonovine · GI Motility Agent: cisapride · Herbal Products: St. John's Wort (<i>hypericum perforatum</i>) · HMG-CoA Reductase Inhibitors: Lovastatin, simvastatin · PDE5 inhibitor sildenafil when used for the treatment of PAH · Sedative/hypnotics: oral midazolam, triazolam