European Geriatric Medicine (2019) 10:199–211
https://doi.org/10.1007/s41999-018-0139-y

REVIEW

Older HIV-infected adults: complex patients (III)—polypharmacy

Samuel F. Freedman[1] · Carrie Johnston[2] · John J. Faragon[3] · Eugenia L. Siegler[4] · Tessa Del Carmen[4]

Received: 13 October 2018 / Accepted: 20 November 2018 / Published online: 6 December 2018

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 such as increased 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 tablets—and medication reconciliation/de-prescription 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 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

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 is 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 1 lists typical definitions and resources. A more comprehensive list and

✉ Eugenia L. Siegler
els2006@med.cornell.edu

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

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

3 Albany Medical Center, Albany, NY, USA

4 Division of Geriatrics and Palliative Medicine, Weill Cornell Medicine, 525 E. 68th Street, Box 39, New York, NY 10065, USA

Table 1 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

comparison of appropriateness measures can be found in Whitman et al. [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 et al. [4] distinguish between problematic (as defined in Table 1) 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 more realistic comparisons to uninfected populations, but does not reflect the frame of reference of PLWH. Fortunately, the antiretroviral therapy (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 antiretroviral (ARV) pills (among 365 PLWH) was 10 per day in 1998 compared to 3.4 per day in 2010 (among 1419 PLWH) [13]. Despite a decrease in pill burden in recent years, many patients are on single-tablet regimens, which include three 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 GEPPO cohort (aged ≥ 65) defined polypharmacy as taking five 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 8172 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, where the prevalence of HIV in those aged >=50 is 4%, the rate of polypharmacy in 411 PLWH from one clinic was 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 2). 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%

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

Table 2 (continued)

Drug class	Medication	Adverse effects	Geriatric considerations	Drug interactions
	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] Dose adjust if CrCl < 30 mL/min Dose adjust if CrCl < 50 mL/min	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]
	Alafenamide (TAF)	Headache most common side effect. < 10% of patients with abdominal pain, fatigue, malaise		
	Disoproxil fumarate (TDF)	Decreased GFR. Rare cases of acute renal failure and Fanconi syndrome Reduced BMD and increased risk for osteoporotic fracture [23]		
	Emtricitabine (FTC)	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[a]: > 2-fold risk of CVD reported in case series [26]	Cardiac risk[a] Hypersensitivity reaction	
	Zidovudine	Anemia, neutropenia Fatigue Lipodystrophy	Rarely used	
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		CNS effects and rash most common		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

Table 2 (continued)

Drug class	Medication	Adverse effects	Geriatric considerations	Drug interactions
	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	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
	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	Substrate of CYP450 system, low risk of drug interactions Concurrent PPIs contraindicated Can be given with clopidogrel without dose adjustment
	Nevirapine	Hepatotoxicity Hypersensitivity reaction	No longer used commonly	Can be given with clopidogrel without dose adjustment
	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]
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
	Lopinavir	Diarrhea HLD	"Boosted" with ritonavir	See Table III about "boosting" agents
Fusion inhibitors				

Table 2 (continued)

Drug class	Medication	Adverse effects	Geriatric considerations	Drug interactions
	Enfuvirtide Injection	Injection site reaction	Rarely used May be difficult to inject into subcutaneous tissue in thin/frail 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 key: *CYP450* cytochrome P450, *OCT2* organic cation transporter 2, *MATE1* multidrug and toxin extrusion transporter

Table references [20–22, 24, 26–29]

[a]Some studies have suggested an association between abacavir and MI. Pooled analysis suggested no increased risk, but this is still controversial [29]

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 3810 PLWH over 50-year-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 3 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 four out of the five 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 1096 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 45–65 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 1000 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

Table 3 Contraindicated medications with common HIV regimens and PKE cobicistat or ritonavir

Medication	Common regimens	Contraindicated medications
Cobicistat	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	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 (Hypericum perforatum) 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	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	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 (hypericum perforatum) HMG-CoA Reductase Inhibitors: Lovastatin, simvastatin PDE5 inhibitor sildenafil when used for the treatment of PAH Sedative/hypnotics: oral midazolam, triazolam

that the number of medications taken was significantly associated with adverse events [40]—the details of possible side effects are shown in Table 2.

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 the 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 2944 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 five studies (two abstracts and three 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, is not only likely to increase fall risk in patients, it also poses additional risk in patients with HIV who are receiving pharmacokinetic enhancers ritonavir or cobicistat. Quetiapine levels, for example, can be increased up to fivefold in patients receiving ritonavir [20, 51–55]. This is just one example of how the Beers criteria have 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 that 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 depend 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 CYP34A 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, Karnofsky 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 into 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 de-prescribing 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 3 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 and 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.

Acknowledgements Dr. Johnston receives support from NIH TL1 TR000459 and NIAID T32AI007613. Dr. Siegler receives support from Gilead Sciences, Inc. for an investigator-initiated study IN-US-311-4182.

Compliance with ethical standards

Conflict of interest Dr. Siegler receives support from Gilead Sciences for an investigator-initiated study. Dr. Faragon is on the speakers' bureaus of AbbVie, Gilead Sciences, Merck, and Janssen Pharmaceutical. Drs. Freedman, Johnston, and Del Carmen report no conflicts of interest.

Ethical approval The preparation of this review did not involve human or animal participants.

Informed consent No informed consent was required.

References

1. UNAIDS UNAIDS—AIDSinfo. http://aidsinfo.unaids.org/. Accessed 8 Oct 2018
2. CDC HIV among people aged 50 and older. https://www.cdc.gov/hiv/group/age/olderamericans/index.html. Accessed 29 Sept 2018
3. Antiretroviral Therapy Cohort Collaboration (2017) Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV 4:e349–e356. https://doi.org/10.1016/S2352-3018(17)30066-8
4. Duerden M, Avery T, Payne R (2013) Polypharmacy and medicines optimisation. Making it safe and sound. The King's Fund, London. https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/polypharmacy-and-medicinesoptimisation-kingsfund-nov13.pdf. Accessed 12 Sept 2018
5. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE (2017) What is polypharmacy? A systematic review of definitions. BMC Geriatr 17:230. https://doi.org/10.1186/s12877-017-0621-2
6. Whitman AM, DeGregory KA, Morris AL, Ramsdale EE (2016) A comprehensive look at polypharmacy and medication screening tools for the older cancer patient. Oncologist 21:723–730. https://doi.org/10.1634/theoncologist.2015-0492
7. Bushardt RL, Massey EB, Simpson TW et al (2008) Polypharmacy: misleading, but manageable. Clin Interv Aging 3:383–389
8. Burt J, Elmore N, Campbell SM et al (2018) Developing a measure of polypharmacy appropriateness in primary care: systematic review and expert consensus study. BMC Med 16:91. https://doi.org/10.1186/s12916-018-1078-7
9. Hanlon JT, Schmader KE (2013) The medication appropriateness index at 20: where it started, where it has been, and where it may be going. Drugs Aging 30:893–900. https://doi.org/10.1007/s40266-013-0118-4
10. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel (2015) American geriatrics society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 63:2227–2246. https://doi.org/10.1111/jgs.13702
11. O'Mahony D, O'Sullivan D, Byrne S et al (2015) STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 44:213–218. https://doi.org/10.1093/ageing/afu145
12. Payne RA, Abel GA, Avery AJ et al (2014) Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol 77:1073–1082. https://doi.org/10.1111/bcp.12292
13. Krentz HB, Cosman I, Lee K et al (2012) Pill burden in HIV infection: 20 years of experience. Antivir Ther (Lond) 17:833–840. https://doi.org/10.3851/IMP2076
14. Hasse B, Ledergerber B, Furrer H et al (2011) Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. Clin Infect Dis 53:1130–1139. https://doi.org/10.1093/cid/cir626
15. Guaraldi G, Malagoli A, Calcagno A et al (2018) The increasing burden and complexity of multi-morbidity and polypharmacy in geriatric HIV patients: a cross sectional study of people aged 65–74 years and more than 75 years. BMC Geriatr 18:99. https://doi.org/10.1186/s12877-018-0789-0
16. Edelman EJ, Gordon KS, Glover J et al (2013) The next therapeutic challenge in HIV: polypharmacy. Drugs Aging 30:613–628. https://doi.org/10.1007/s40266-013-0093-9
17. Gimeno-Gracia M, Crusells-Canales MJ, Armesto-Gómez FJ et al (2016) Polypharmacy in older adults with human immunodeficiency virus infection compared with the general population. Clin Interv Aging 11:1149–1157. https://doi.org/10.2147/CIA.S108072
18. Ssonko M, Stanaway F, Mayanja HK et al (2018) Polypharmacy among HIV positive older adults on anti-retroviral therapy attending an urban clinic in Uganda. BMC Geriatr 18:125. https://doi.org/10.1186/s12877-018-0817-0
19. Liverpool HIV drug interactions. https://www.hiv-druginteractions.org/checker. Accessed 29 Sept 2018
20. U.S. Department of Health and Human Services (DHHS) Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed 8 Oct 2018
21. Lepik KJ, Yip B, Ulloa AC et al (2018) Adverse drug reactions to integrase strand transfer inhibitors. AIDS 32:903–912. https://doi.org/10.1097/QAD.0000000000001781
22. Gilead Sciences (2018) Bictegravir/tenofovir alafenamide/emtricitabine [Package Insert]. https://www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf. Accessed 30 Sept 2018
23. Bedimo R, Maalouf NM, Zhang S et al (2012) Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 26:825–831. https://doi.org/10.1097/QAD.0b013e32835192ae
24. Mills A, Arribas JR, Andrade-Villanueva J et al (2016) Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 16:43–52. https://doi.org/10.1016/S1473-3099(15)00348-5
25. Mallal S, Phillips E, Carosi G et al (2008) HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 358:568–579. https://doi.org/10.1056/NEJMoa0706135
26. Marcus JL, Neugebauer RS, Leyden WA et al (2016) Use of abacavir and risk of cardiovascular disease among HIV-infected individuals. J Acquir Immune Defic Syndr 71:413–419. https://doi.org/10.1097/QAI.0000000000000881
27. Mollan KR, Smurzynski M, Eron JJ et al (2014) Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med 161:1–10. https://doi.org/10.7326/M14-0293
28. Hughes CA, Tseng A, Cooper R (2015) Managing drug interactions in HIV-infected adults with comorbid illness. Can Med Assoc J 187:36–43. https://doi.org/10.1503/cmaj.131626
29. Nan C, Shaefer M, Urbaityte R et al (2018) Abacavir use and risk for myocardial infarction and cardiovascular events: pooled analysis of data from clinical trials. Open Forum Infect Dis 5:ofy086. https://doi.org/10.1093/ofid/ofy086
30. Evans-Jones JG, Cottle LE, Back DJ et al (2010) Recognition of risk for clinically significant drug interactions among HIV-infected patients receiving antiretroviral therapy. Clin Infect Dis 50:1419–1421. https://doi.org/10.1086/652149

31. Greene M, Steinman MA, McNicholl IR, Valcour V (2014) Polypharmacy, drug–drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. J Am Geriatr Soc 62:447–453. https://doi.org/10.1111/jgs.12695
32. Holtzman C, Armon C, Tedaldi E et al (2013) Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. J Gen Intern Med 28:1302–1310. https://doi.org/10.1007/s11606-013-2449-6
33. Foisy MM, Yakiwchuk EM, Hughes CA (2008) Induction effects of ritonavir: implications for drug interactions. Ann Pharmacother 42:1048–1059. https://doi.org/10.1345/aph.1K615
34. Gellad WF, Grenard JL, Marcum ZA (2011) A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. Am J Geriatr Pharmacother 9:11–23. https://doi.org/10.1016/j.amjopharm.2011.02.004
35. Cantudo-Cuenca MR, Jiménez-Galán R, Almeida-Gonzalez CV, Morillo-Verdugo R (2014) Concurrent use of comedications reduces adherence to antiretroviral therapy among HIV-infected patients. J Manag Care Spec Pharm 20:844–850. https://doi.org/10.18553/jmcp.2014.20.8.844
36. Prosperi MCF, Fabbiani M, Fanti I et al (2012) Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. BMC Infect Dis 12:296. https://doi.org/10.1186/1471-2334-12-296
37. Huang ES, Karter AJ, Danielson KK et al (2010) The association between the number of prescription medications and incident falls in a multi-ethnic population of adult type-2 diabetes patients: the diabetes and aging study. J Gen Intern Med 25:141–146. https://doi.org/10.1007/s11606-009-1179-2
38. Erlandson KM, Allshouse AA, Jankowski CM et al (2012) Risk factors for falls in HIV-infected persons. J Acquir Immune Defic Syndr 61:484–489. https://doi.org/10.1097/QAI.0b013e3182716e38
39. Jyrkkä J, Enlund H, Lavikainen P et al (2011) Association of polypharmacy with nutritional status, functional ability and cognitive capacity over a three-year period in an elderly population. Pharmacoepidemiol Drug Saf 20:514–522. https://doi.org/10.1002/pds.2116
40. Gandhi TK, Weingart SN, Borus J et al (2003) Adverse drug events in ambulatory care. N Engl J Med 348:1556–1564. https://doi.org/10.1056/NEJMsa020703
41. Schambelan M, Wilson PWF, Yarasheski KE et al (2008) Development of appropriate coronary heart disease risk prediction models in HIV-infected patients. Circulation 118:e48–e53. https://doi.org/10.1161/CIRCULATIONAHA.107.189627
42. Deeks SG, Phillips AN (2009) HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ 338:a3172. https://doi.org/10.1136/bmj.a3172
43. Neuhaus J, Jacobs DR, Baker JV et al (2010) Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. J Infect Dis 201:1788–1795. https://doi.org/10.1086/652749
44. Freiberg MS, Leaf DA, Goulet JL et al (2009) The association between the receipt of lipid lowering therapy and HIV status among veterans who met NCEP/ATP III criteria for the receipt of lipid lowering medication. J Gen Intern Med 24:334–340. https://doi.org/10.1007/s11606-008-0891-7
45. Guaraldi G, Menozzi M, Zona S et al (2017) Impact of polypharmacy on antiretroviral prescription in people living with HIV. J Antimicrob Chemother 72:511–514. https://doi.org/10.1093/jac/dkw437
46. Portsmouth SD, Osorio J, McCormick K et al (2005) Better maintained adherence on switching from twice-daily to once-daily therapy for HIV: a 24-week randomized trial of treatment simplification using stavudine prolonged-release capsules. HIV Med 6:185–190. https://doi.org/10.1111/j.1468-1293.2005.00287.x
47. Airoldi M, Zaccarelli M, Bisi L et al (2010) One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. Patient Prefer Adherence 4:115–125
48. Fogarty L, Roter D, Larson S et al (2002) Patient adherence to HIV medication regimens: a review of published and abstract reports. Patient Educ Couns 46:93–108. https://doi.org/10.1016/S0738-3991(01)00219-1
49. Saag MS, Benson CA, Gandhi RT et al (2018) Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the international antiviral society-USA panel. JAMA 320:379–396. https://doi.org/10.1001/jama.2018.8431
50. Blanco JR, Caro AM, Pérez-Cachafeiro S et al (2010) HIV infection and aging. AIDS Rev 12:218–230
51. Zalma A, von Moltke LL, Granda BW et al (2000) In vitro metabolism of trazodone by CYP3A: inhibition by ketoconazole and human immunodeficiency viral protease inhibitors. Biol Psychiatry 47:655–661
52. Greenblatt DJ, von Moltke LL, Harmatz JS et al (2003) Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. J Clin Pharmacol 43:414–422
53. Geraci MJ, McCoy SL, Crum PM, Patel RA (2010) Antipsychotic-induced priapism in an HIV patient: a cytochrome P450-mediated drug interaction. Int J Emerg Med 3:81–84. https://doi.org/10.1007/s12245-010-0175-y
54. Pollack TM, McCoy C, Stead W (2009) Clinically significant adverse events from a drug interaction between quetiapine and atazanavir–ritonavir in two patients. Pharmacotherapy 29:1386–1391. https://doi.org/10.1592/phco.29.11.1386
55. Hantson P, Di Fazio V, Wallemacq P (2010) Toxicokinetic interaction between quetiapine and antiretroviral therapy following quetiapine overdose. Drug Metab Lett 4:7–8
56. McNicholl IR, Gandhi M, Hare CB et al (2017) A pharmacist-led program to evaluate and reduce polypharmacy and potentially inappropriate prescribing in older HIV-positive patients. Pharmacotherapy 37:1498–1506. https://doi.org/10.1002/phar.2043
57. Janssen prezcobix (darunavir and cobicistat) [Package Insert]. http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/PREZCOBIXpi.pdf. Accessed 30 Sept 2018
58. SPRINT Research Group, Wright JT, Williamson JD et al (2015) A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 373:2103–2116. https://doi.org/10.1056/nejmoa1511939
59. American Diabetes Association (2018) 11. Older adults: standards of medical care in diabetes—2018. Diabetes Care 41:S119–S125. https://doi.org/10.2337/dc18-S011
60. Bruce RD, Merlin J, Lum PJ et al (2017) 2017 HIVMA of IDSA clinical practice guideline for the management of chronic pain in patients living with HIV. Clin Infect Dis 65:e1–e37. https://doi.org/10.1093/cid/cix636
61. Lawson E, Sabin C, Perry N et al (2015) Is HIV painful? An epidemiologic study of the prevalence and risk factors for pain in HIV-infected patients. Clin J Pain 31:813–819. https://doi.org/10.1097/AJP.0000000000000162
62. Canan CE, Chander G, Monroe AK et al (2018) High-risk prescription opioid use among people living with HIV. J Acquir Immune Defic Syndr 78:283–290. https://doi.org/10.1097/QAI.0000000000001690
63. Uebelacker LA, Weisberg RB, Herman DS et al (2015) Chronic pain in HIV-infected patients: relationship to depression,

substance use, and mental health and pain treatment. Pain Med 16:1870–1881. https://doi.org/10.1111/pme.12799
64. Surratt HL, Kurtz SP, Levi-Minzi MA et al (2015) Pain treatment and antiretroviral medication adherence among vulnerable HIV-positive patients. AIDS Patient Care STDS 29:186–192. https://doi.org/10.1089/apc.2014.0104
65. CDC HIV/AIDS. https://www.cdc.gov/hiv/default.html. Accessed 29 Sept 2018
66. Cuzin L, Katlama C, Cotte L et al (2017) Ageing with HIV: do comorbidities and polymedication drive treatment optimization? HIV Med 18:395–401. https://doi.org/10.1111/hiv.12441
67. Gruta C, Goldschmidt R (2017) HIV/AIDS: implications for older adult patients. https://aging.arizona.edu/sites/aging/files/fact-sheet-pdfs/hiv_1.pdf. Accessed 29 Sept 2018
68. Burgess MJ, Zeuli JD, Kasten MJ (2015) Management of HIV/AIDS in older patients-drug/drug interactions and adherence to antiretroviral therapy. HIV AIDS (Auckl) 7:251–264. https://doi.org/10.2147/HIV.S39655
69. Silverberg MJ, Ray GT, Saunders K et al (2012) Prescription long-term opioid use in HIV-infected patients. Clin J Pain 28:39–46. https://doi.org/10.1097/AJP.0b013e3182201a0f
70. Moatti JP, Carrieri MP, Spire B et al (2000) Adherence to HAART in French HIV-infected injecting drug users: the contribution of buprenorphine drug maintenance treatment. The Manif 2000 study group. AIDS 14:151–155
71. Ruiz M, Armstrong M, Reske T et al (2014) Antiretroviral therapy at the end of life: the experience of an academic HIV clinic. Am J Hosp Palliat Care 31:475–479. https://doi.org/10.1177/1049909113494459
72. Goodkin K, Kompella S, Kendell SF (2018) End-of-life care and bereavement issues in human immunodeficiency virus—AIDS. Nurs Clin N Am 53:123–135. https://doi.org/10.1016/j.cnur.2017.10.010
73. Slomka J, Prince-Paul M, Webel A, Daly BJ (2016) Palliative care, hospice, and advance care planning: views of people living with hiv and other chronic conditions. J Assoc Nurses AIDS Care 27:476–484. https://doi.org/10.1016/j.jana.2016.02.003
74. Rhodes RL, Nazir F, Lopez S et al (2016) Use and predictors of end-of-life care among HIV patients in a safety net health system. J Pain Symptom Manag 51:120–125. https://doi.org/10.1016/j.jpainsymman.2015.08.010
75. Schwarcz L, Chen M-J, Vittinghoff E et al (2013) Declining incidence of AIDS-defining opportunistic illnesses: results from 16 years of population-based AIDS surveillance. AIDS 27:597–605. https://doi.org/10.1097/QAD.0b013e32835b0fa2
76. Lima VD, Lourenço L, Yip B et al (2015) AIDS incidence and AIDS-related mortality in British Columbia, Canada, between 1981 and 2013: a retrospective study. Lancet HIV 2:e92–e97. https://doi.org/10.1016/S2352-3018(15)00017-X
77. Stewart A, Chan Carusone S, To K et al (2012) Causes of death in HIV patients and the evolution of an AIDS hospice: 1988–2008. AIDS Res Treat 2012:390406. https://doi.org/10.1155/2012/390406
78. Wardlaw LA (1994) Sustaining informal caregivers for persons with AIDS. Fam Soc J Contemp Soc Serv 75:373–384. https://doi.org/10.1177/104438949407500606
79. Van Deventer C, Wright A (2017) The psychosocial impact of caregiving on the family caregivers of chronically ill AIDS and/or HIV patients in home-based care: a qualitative study in Zimbabwe. South Afr J HIV Med. https://doi.org/10.4102/sajhivmed.v18i1.718
80. Friedland GH, Williams A (1999) Attaining higher goals in HIV treatment: the central importance of adherence. AIDS 13(Suppl 1):S61–S72
81. Llibre JM, Hung C-C, Brinson C et al (2018) Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet 391:839–849. https://doi.org/10.1016/S0140-6736(17)33095-7
82. Aboud M, Orkin C, Podzamczer D, Boger J (2018) Durable suppression 2 years after switch to DTG +RPV 2-drug regimen: SWORD-1 and SWORD-2 studies, 22nd International AIDS Conference, Amsterdam, Netherlands, July 23–27, 2018
83. ViiV Healthcare (2016) An efficacy, safety, and tolerability study comparing dolutegravir plus lamivudine with dolutegravir plus tenofovir/emtricitabine in treatment naïve HIV infected subjects (Gemini 1). In: NCT02831673. https://clinicaltrials.gov/ct2/show/NCT02831673. Accessed 27 Sept 2018
84. ViiV Healthcare (2016) An efficacy, safety, and tolerability study comparing dolutegravir (DTG) plus lamivudine (3TC) with dolutegravir plus tenofovir/emtricitabine in treatment naïve HIV infected subjects (Gemini 2). In: NCT02831764. https://clinicaltrials.gov/ct2/show/NCT02831764. Accessed 28 Sept 2018