Polypharmacy in HIV: Recent Insights and Future Directions

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Abstract

Purpose of review: Update findings regarding polypharmacy among people with HIV (PWH) and consider what research is most needed.

Recent findings: Among PWH, polypharmacy is common, occurs in middle age, and is predominantly due to non-antiretroviral (ARV) medications. Many studies have demonstrated strong associations between polypharmacy and receipt of potentially inappropriate medications (PIMS), but few have considered actual adverse events. Falls, delirium, pneumonia, hospitalization, and mortality are associated with polypharmacy among PWH and risks remain after adjustment for severity of illness.

Summary: Polypharmacy is a growing problem and mechanisms of injury likely include potentially inappropriate medications, total drug burden, known pairwise drug interactions, higher level drug interactions, drug-gene interactions, and drug-substance use interactions (alcohol, extra-medical prescription medication, and drug use). Before we can effectively design interventions, we need to use observational data to gain a better understanding of the modifiable mechanisms of injury. Because sicker individuals take more medications, analyses must account for severity of illness. Because self-report of substance use may be inaccurate, direct biomarkers such as phosphatidylethanol (PEth) for alcohol are needed. Large samples including electronic health records, genetics, accurate measures of substance use, and state of the art statistical and artificial intelligence techniques are needed to advance our understanding and inform clinical management of polypharmacy in PWH.

Keywords: HIV; Polypharmacy; Drug-Drug Interactions; Drug-Gene Interactions; and Drug-Substance use Interactions

Introduction

Polypharmacy, often defined as concurrent use of five or more medications, is a growing concern among people with HIV (PWH). After antiretroviral (ARV) treatment initiation, typically requiring three ARV medications, many non-ARV medications are prescribed to address symptoms, side effects, and to treat or prevent comorbid disease. An estimated 15% to 39% of PWH are exposed to polypharmacy(1-6), with higher rates in resource rich settings and among older individuals(7). Of note, while polypharmacy is often measured as a threshold (five medications), total medication count must also be considered; each additional medication increases risk for interactions and potential adverse events.

Polypharmacy presents unique management issues for PWH(8) and clinical guidelines emphasize its importance in caring for adults with HIV(9, 10). PWH are exposed to polypharmacy a decade earlier than the general population. ARV medications interact with commonly prescribed non-ARV medications(11) and PWH may be more susceptible to medication side effects due to increased physiologic frailty. Finally, polypharmacy itself may decrease ARV adherence, threatening the patient's ability to maintain viral suppression.

Herein, we highlight recent advances based on literature published from 2017 through October 2019 on polypharmacy in PWH. Based on these studies, we discuss recent insights regarding polypharmacy among PWH including 1) prevalence; 2) associated adverse events; and 3) current recommendations. We end with a summary of key research priorities.

Prevalence of Polypharmacy Among PWH

Compared to those without HIV, PWH are more likely to be exposed to polypharmacy at younger ages, especially when non-prescription medications, complementary and alternative medicine (CAM), and extra-medical use of prescription medications (i.e., use of medications in way other than prescribed by a clinician and also referred to as "non-medical" or "misuse")(12) are included (3, 13-15). In addition to ARVs, polypharmacy among PWH is driven by non-ARV medications(3, 6, 16). We used fiscal year 2018 data from the Veterans Aging Cohort Study, a national study of all patients with HIV receiving healthcare within the Veterans Affairs Healthcare System, matched to demographically similar controls, to provide a recent snapshot (Table 1) of non-ARV polypharmacy. A comparison of prescription medications by HIV status demonstrates that many of the same medications are common in both groups and that antihypertensives, statins, antidepressants, opioid and non-opioid analgesics, erectile dysfunction medications, anticonvulsants, proton pump inhibitors, and hypoglycemic medications top the list.

Few studies have examined longitudinal patterns of polypharmacy within individuals. Ware and colleagues used data from the Multicenter AIDS Cohort Study, a cohort of men who have sex with men with and without HIV(14), to identify patterns of polypharmacy over time. Among PWH, four unique patterns of polypharmacy were identified based on an average follow-up of 12 years: non-polypharmacy (49%); slowly increasing polypharmacy (25%); rapidly increasing polypharmacy (12%); and sustained polypharmacy (14%). Among PWH, factors independently associated with increased likelihood of membership in the sustained polypharmacy compared

to non-polypharmacy group included public insurance, earlier study enrollment, having a college degree or higher, and health care visits (i.e., visits to a physician's office, emergency department or other health care clinic use). Presence of a detectable HIV viral load was associated with decreased likelihood of membership in the sustained polypharmacy group, suggesting that polypharmacy typically begins after ARV initiation, which is a hallmark of engagement in HIV care and after which attention often pivots to diagnosis and treatment of comorbidities.

Importantly, PWH commonly report use of CAM(17) and use of CAM is inconsistently captured in studies of polypharmacy. In VACS, we found that most patients reported using CAM, 60% of whom reported using vitamins and/or minerals, and 13% reported using herbs and/or herbal medicine. Similarly, data from an Australian cohort of PWH with HIV viral control (n=522), found that second to cardiovascular medications, non-prescription vitamins, minerals, and alternative therapies were the most commonly used class of medications(6).

Harms Associated with Polypharmacy Among PWH

A conceptual model of harm from polypharmacy for PWH includes independent and interacting effects of physiologic frailty, drug burden, provider distraction leading to be potentially inappropriate medications and omission of indicated medications, and a host of known and unknown drug interactions (**Figure 1**). Physiologic frailty reflects the degree to which organ system reserve capacity is lost allowing a relatively minor injury to result in disproportionate harm(18). Among both PWH and uninfected individuals, increasing polypharmacy adds to total

drug burden and inevitably increases the probability of significant two way and higher order drug interactions as well as drug-gene and drug-substance use interactions. Increasing physiologic frailty is associated with increasing polypharmacy; increasing polypharmacy can also increase physiologic frailty. All these mechanisms may contribute to risk of a host of serious adverse events including falls, delirium, pneumonia, hospitalization, and mortality.

Importantly, even if individual effects are mild, additive effects of drugs with overlapping activity can be substantial. A useful approach to quantifying cumulative harmful effects from a patient's entire medication list is to apply indices which score medications according to their activity on particular pathways. For example, geriatricians have developed several scoring systems to assess clinical manifestations of neurocognitive and functional harms associated with anticholinergic medications (19, 20). Both ARV and non-ARV medications may directly contribute to mitochondrial toxicity, microbial translocation, and immune dysfunction (21-23). Indices could be developed to summarize the level of mitochondrial toxicity, microbial translocation, and immune dysfunction conferred by cumulative exposure based on established assays. Such indices could be useful for mechanistic research on drug toxicity and to help guide ongoing medication selection in the clinical setting.

Potentially Inappropriate Medications and Medication Omissions

Polypharmacy is linked to poorer prescribing quality including over- (potentially inappropriate medications) and under- (medication omissions) prescribing. Potentially inappropriate medications refers to "'medications [that] have no clear evidence-based indication, carry a

substantially higher risk of adverse side effects or [are] not cost-effective (e.g., over-prescribing)'"(24). Neurocognitively active medications are potentially inappropriate in the setting of substantial alcohol use or among those over 65 years of age.

Under-prescribing refers to the lack of prescribing of an effective medication(25). As a patient's problem list and number of medications expands, the provider's ability to pay attention to each condition and its treatment is reduced(26). PWH are less likely to receive recommended treatments for disease prevention, such as cardiovascular disease(27, 28). This may be particularly problematic in light of increased risk for cardiovascular disease among PWH and increasing evidence of benefits from statin use that extend beyond prevention of myocardial infarction to prevention of cirrhosis and cancer (29-32). Similarly, although there is clear evidence of harms associated with substance use among PWH(33) and benefits associated with its treatment(34-37), several studies indicate that medications to address tobacco, alcohol and opioid use are grossly under-prescribed to PWH(38-41). While data support use of medications for the treatment of substance use disorders, the risks and benefits of these medications in the context of polypharmacy has not yet been rigorously evaluated. In addition, it is unclear whether polypharmacy contributes to under-prescribing of such medications. .

Drug-drug interactions

Polypharmacy increases the potential for harmful drug-drug interactions (42). Given the effects of ARVs on the cytochrome P450 system and transmembrane proteins that act as carriers of various medications, there is potential for ARVs to interact with non-ARV drugs across various

classes(43). Findings from an Italian cohort of PWH demonstrated that patients with potential

drug-drug interactions are most commonly receiving protease inhibitor-based ARV regimens

(62%), followed by non-nucleoside reverse transcriptase inhibitor- (39%) and integrase

inhibitor- (15%) based regimens (16). In this cohort, non-ARV medications associated with

concern for drug-drug interactions most commonly included anticoagulant/antiplatelet agents,

calcium channel blockers, anti-benign prostatic hypertrophy agents, anti-osteoporotic agents,

and hypnotics/sedatives. Most recently, concern has been raised regarding the potential for

ARV interactions with over-the-counter agents used to treat obesity(44) (e.g., orlistat), which

may compromise HIV viral control.

Important considerations for prescribing ARVs in the context of polypharmacy and aging have

been the subject of comprehensive and recent reviews(45). For example, one review discussed

the complexities of optimizing cancer treatment in the context of ARVs(46). In addition to

routine monitoring of organ system function and HIV biomarkers, there is growing awareness of

the importance of corrected QT (QTc) monitoring given the effects of the non-nucleoside

reverse transcriptase inhibitors, efavirenz and rilpivirine(9), which may interact with commonly

prescribed medications (e.g., antibiotics, antipsychotics). PWH were more likely than uninfected

patients to have evidence of QTc prolongation on electrocardiogram review; 29% of PWH

demonstrated evidence of QTc prolongation and 6% with extreme prolongation, a finding that

was driven at least in part by interactions with methadone(47). Importantly, drug-drug

interactions may result in a "prescribing cascade" whereby additional medications are used to

treat symptoms driven by drug-drug interactions, further exacerbating polypharmacy(16).

Data from a multisite Australian cohort of PWH with HIV viral control found that 3% of participants were taking a medication contraindicated with their ARVs(6). These combinations most commonly included protease inhibitors with statins, steroids and/or proton pump inhibitors and resulted in avoidable symptoms. In this cohort, polypharmacy was independently associated with increased risk of diarrhea (aOR [95% CI]= 1.9 [1.1, 3.0]), fatigue (aOR [95% CI]= 1.7 [1.0, 2.6]) and peripheral neuropathy (aOR [95% CI]= 3.1 [1.8, 5.2])(6).

Drug-gene interactions

As with drug-drug interactions, an increasing number of medications also increases the probability of harmful drug-gene interactions. Drug-gene interactions occur when a patient's genetic profile influences medication efficacy, tolerability, and safety(48). Such variants are likely to explain an important component of the relationship between polypharmacy and adverse health outcomes. There are now over 100 "actionable" pharmacogenetic interactions recommended for clinical management(49, 50). The best known drug-gene interactions in AARV is abacavir hypersensitivity among patients with the presence of the major histocompatibility complex (MHC) class I allele human leukocyte antigen (HLA)-B*5701(51, 52). Pharmacogenetic screening for this allele is a routine clinical practice. More recent evidence suggests that polymorphisms in the multidrug resistance protein 1 (MDR1) may predict better viral response to efavirenz-containing regimens(53). However, pharmacogenetic testing for this polymorphism and many others(54) are not yet part of routine clinical practice.

Drug-Substance Use Interactions

The current literature is limited in its study of drug-substance use interactions among PWH. Of special concern are drug-alcohol interactions because PWH continue to drink alcohol and alcohol has substantial overlapping toxic effects with neurocognitively active medications (i.e., medications with neurocognitive effects), anticholinergic medications, and medications with liver toxicity(55). We looked at concurrent use of alcohol by level of self-report and exposure to neurocognitively active and anticholinergic medications known to interact with alcohol in VACS. PWH reporting hazardous alcohol consumption were more likely than those reporting low levels of consumption to be prescribed a neurocognitive medication (73% vs. 55%) or an anticholinergic medication (29% vs. 19%). While it is important to weight the risks and benefits of prescribing these medications in the context of alcohol use, we have previously reported that these exposures are associated with more frequent hospitalization with delirium or dementia(56). Importantly, self-report of alcohol use may be subject to social desirability bias, recall bias, and/or impacted by perceptions of societal norms. We have demonstrated that a direct biomarker for alcohol exposure (phosphatidylethanol or PEth) is often positive among those reporting no current alcohol exposure and this was particularly true among individuals at greater risk of injury from alcohol(57). This finding suggests that self-reported alcohol use may be least accurate among those at greatest risk of harm from alcohol use. Since alcohol interacts widely with medication, verifying the level of alcohol exposure among those taking neurocognitively active medications, anticholinergic medications, and/or liver toxic medications would seem prudent.

Of distinct but related concern to alcohol use, is extra-medical use of prescription medications, defined as the use of medications for indications other than prescribed, in a manner other than prescribed, or without a prescription(12).. In addition to contributing to drug interactions, extra-medical use of psychoactive medications, such as prescription opioids, contributes to poor HIV outcomes, as well as addiction, overdose, and death(58). In addition, some ARV medications, particularly ritonavir for its boosting effects and efavirenz for its neuropsychiatric effects, have been used extra-medically(59).

Adverse Events Due to Polypharmacy

Recent studies heighten concern about polypharmacy. Among patients with and without HIV, non-ARV medication count (per five medications) was independently associated with a 19% increased risk of serious falls (adjusted odds ratio [aOR] [95% CI] = 1.19 [1.16, 1.22])(60). Among PWH, specific medication classes, including benzodiazepines, muscle relaxants, prescription opioids, anticonvulsants, and antiarrhythmics, were strongly independently associated with increased risk of serious falls. Similarly, we have recently reported that risk for delirium among PWH and demographically similar controls is substantially increased after exposure to neurocognitive medications and alcohol (56). In a separate set of analyses with careful adjustment for baseline severity of illness, we found that receipt of non-ARV polypharmacy was associated with a 50% increased risk of hospitalization (adjusted hazard ratio [aHR] [95% CI]= 1.52 [1.49, 1.56]) and a 43% increased risk of mortality [aHR [95%CI]= 1.43 [1.36, 1.50](3).

Data from the Boston ARCH Cohort Study, a longitudinal cohort of PWH and current substance use disorder or lifetime history of injection drug use, has also demonstrated harms associated with polypharmacy(61, 62). Of particular concern are findings that demonstrate that each additional non-ARV medication was associated with increased risk of past year non-fatal overdose (OR [95% CI]=1.07 [1.00, 1.15]), with each additional sedating medication associated with increased risk (OR [95% CI]= 1.81 [1.00, 1.39])(61). Taken together, these data suggest that polypharmacy is an important and potentially modifiable cause of multiple harms among PWH.

Medication Classes of Particular Concern among PWH

Given rising rates of opioid overdose deaths among PWH(63), the use of prescribed opioids among PWH warrants specific mention(45). It has been consistently documented that opioid prescribing alone and with other psychoactive medications is widespread among PWH receiving care in diverse settings(64, 65). A recent analysis based on a Canadian cohort found that 27% of patients were co-prescribed opioids and benzodiazepines during the study period from 1996 to 2015(66). This is concerning as prescribed opioids alone and in conjunction with prescribed benzodiazepines independently increase risk of mortality after adjusting for medication count and disease severity(67).

In addition to causing overdose(61), there is concern that prescribed opioids may contribute to infectious complications, which is particularly worrisome for PWH. Extending work based on the general population(68-70), we found that prescribed opioids increased risk of community-acquired pneumonia severe enough to warrant hospitalization(71). This risk was heightened for

opioids with known immunosuppressive (e.g., codeine, morphine) properties and with higher doses. Whether and how the observed immunosuppressive effects of prescribed opioids result in increased risk of other adverse outcomes, such as malignancy, merits investigation. In addition, enhanced efforts to decrease opioid prescribing(72) while promoting access to indicated treatments for pain(73) and opioid use disorder(74) in HIV treatment settings are urgently needed(75-77).

How can we address polypharmacy among PWH?

Critical elements to address polypharmacy among PWH include: 1) complete medication reconciliation; 2) screening, assessment and treatment of substance use; 3) assessment and ranking of medications according to risks and benefits; and 4) prioritization and planning with the patient(8). In addition, there is growing support for models of care that rely on multidisciplinary team members and clinicians. For instance, pharmacist-led evaluations of patients with evidence of polypharmacy may help promote safer and appropriate prescribing (78). Similarly, drawing from experience with addressing alcohol use among PWH which involved bringing social workers, psychologists and psychiatrists into HIV clinics(35, 36), models of care that provide on-site geriatric specialty care within HIV treatment settings may be critical. In addition, there may be a role for a "stepped care" approach. For instance, patients could be seen by a clinical pharmacist and then referred for additional services to a geriatrician as needed. Additionally, more work is needed to promote health behaviors, such as physical activity, to help prevent development of conditions associated with polypharmacy and treat symptoms that contribute to polypharmacy (80).

Key Research Priorities

Future studies should:

- Accurately catalogue use of non-prescribed medications, including CAM and other over-the-counter medications as well as extra-medical use of prescription medications, to allow for precise measurement and evaluation of the impact of polypharmacy.

- Develop indices to summarize the level of mitochondrial toxicity, microbial translocation, and immune dysfunction conferred by cumulative exposure based on established assays as measures of physiologic toxicity.

- Expand the exploration for drug interactions including drug-drug, drug-gene, and drug-substance use interactions beyond pairwise interactions in European ancestry samples. With the advent of mega biobanks around the world(81, 82), a more comprehensive approach with careful external validation is possible.

- Use direct measures of substance use, especially alcohol, when exploring adverse events resulting from drug-substance use interactions.

- As medical marijuana becomes more widely adopted as an alternative to pain management and with legislative changes, further evaluation of how marijuana contributes to polypharmacy and impacts health outcomes are needed.

Conclusion

The study of polypharmacy, among people with and without HIV infection, is in its infancy. It is critical that future research focus on differentiating which medications and which interactions are most important, warranting discontinuation among PWH. Criteria for identifying potentially

dangerous medications, such as screening tool of older people's prescriptions (STOPP), Beers,

are helpful for geriatric populations, and the Prescribing Optimally in Middle-aged People's

Treatments (PROMPT)(83) may be helpful in middle aged individuals. Criteria tailored for the

specific needs of PWH – which includes a wide age-span, with greater exposure to substance

use and even more interactive medications are needed. Until we have a better understanding

of these issues, it is difficult to design an appropriate randomized trial.

For the time being, much of this work will need to be conducted using real world, observational

data: large electronic health record datasets linked to pharmacy and genetic data,

supplemented with direct measures of alcohol and other substance use. However, drug

interactions are unlikely to comply with the typical assumptions of statistical modeling (linear

associations, normally distributed). Further, the size and complexity of this kind of data exceeds

the capacity of conventional approaches.

Expertise in "big data" must be combined with advanced statistical and artificial intelligence

techniques. Because of concerns regarding confounding by indication(3), these studies must

adequately account for severity of illness and might do well to focus on outcomes unrelated to

indications for the medications (e.g., pneumonia, delirium, falls). In the meantime, novel

interventions providing non-pharmacological treatments (e.g., exercise, smoking cessation) to

both prevent comorbidity and treat symptoms are needed. Accumulating evidence suggests

substantial harms from polypharmacy among PWH. As PWH age, these harms are likely to be

magnified. While the field has advanced, continued observational and intervention work is

needed to inform clinical practice and policies surrounding polypharmacy.

Key points: (3-5 bullets)

- Accurate medication reconciliation of prescription, over-the counter, and extra-medical medication use is essential.

- Substance use, especially alcohol use, needs to be accurately assessed and may require use of direct biomarkers.

- Indices summarizing the level of specific toxicity conferred by cumulative exposure are needed to guide research and clinical care.

Expand the exploration for drug interactions including drug-drug, drug-gene, and drug-substance use interactions beyond pairwise interactions in European ancestry samples.

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Table 1. Common Medications by HIV Status in FY 2018 in the Veterans Aging Cohort Study

Class	HIV+	Uninfected	
n	28,104	68,081	**Most Prescribed Medications**
Antihypertensives	56.8%	69.3%	lisinopril, amlodipine, metoprolol
Antilipemic agents	42.0%	50.7%	atorvastatin, simvastatin, pravastatin
Antidepressants	34.4%	37.7%	trazodone, sertraline, bupropion
Non-opioid analgesics	27.7%	32.8%	aspirin, acetaminophen
Nonsalicylate NSAIDs	25.2%	35.1%	ibuprofen, meloxiacam, naproxen
Genito-urinary agents	24.7%	29.2%	sildenafil, tadalafil, vardenafil
Opioid analgesics	22.6%	25.0%	hydrocodone, tramadol, oxycodone
Anticonvulsants	22.0%	27.7%	gabapentin, divalproex, lamotrigine
Gastric agents	21.1%	31.2%	omeprazole, pantoprazole, simethicone
Hypoglycemic agents	13.0%	23.0%	metformin, glipizide, saxagliptin

Figure 1. Conceptual Model of Harm Associated with Polypharmacy
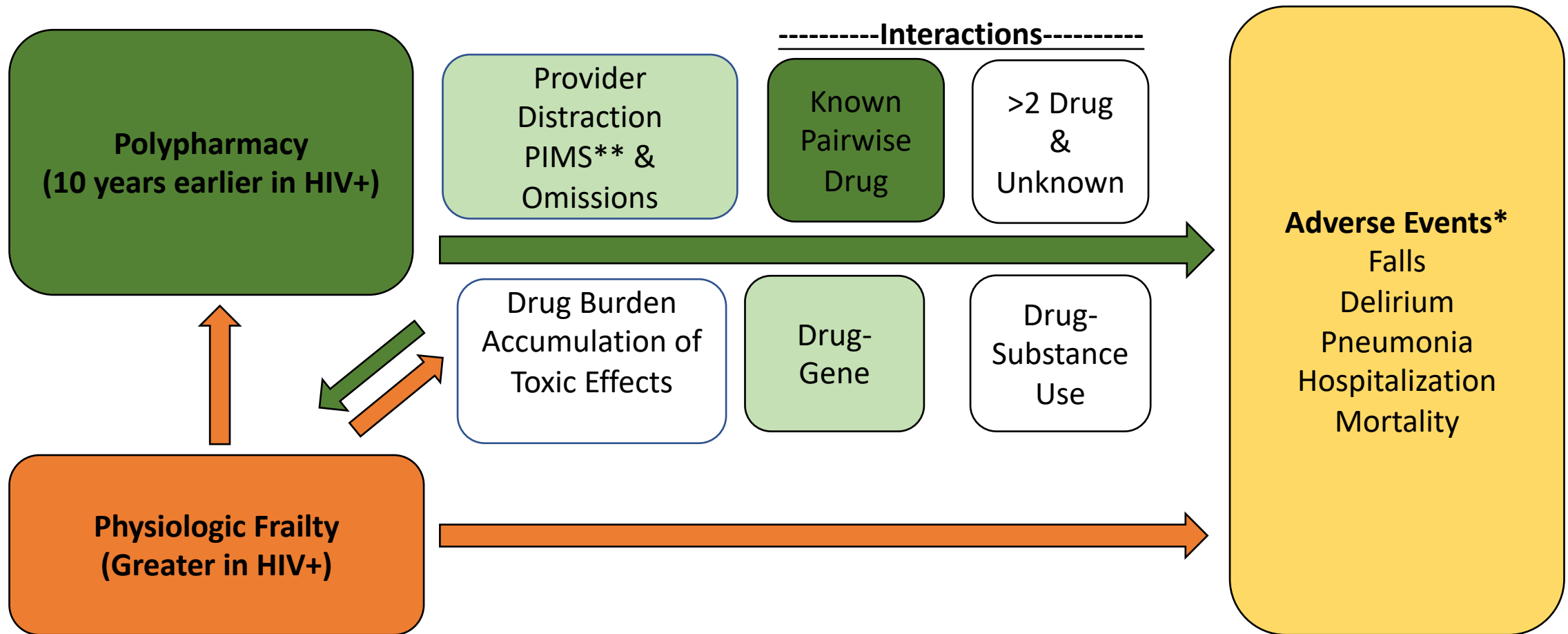
Notes: To estimate the true effect of polypharmacy, one needs to control for severity of illness to mitigate reverse causality bias or confounding by indication. The focus of current research is placed mostly on known pairwise drug interactions and some on drug-gene interactions. More research is needed on drug-gene interactions and more complex interactions, including >2 drug and drug-substance use.

*This list is not exhaustive, but includes common, well-recognized adverse events associated with polypharmacy among people with HIV.

**PIMS: Potentially Inappropriate Medications