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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; Drug-Substance use Interactions

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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.

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REFERENCES

1. Ware D, Palella FJ, Jr., Chew KW, Friedman MR, D'Souza G, Ho K, et al. Prevalence and trends of polypharmacy among HIV-positive and -negative men in the Multicenter AIDS Cohort Study from 2004 to 2016. PLoS One. 2018;13(9):e0203890. [PubMed: 30204807]
2. Guaraldi G, Malagoli A, Calcagno A, Mussi C, Celesia BM, Carli F, et al. 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. 2018;18(1):99. [PubMed:

29678160] *Reports on high prevelance of multimorbidity and polypharmacy in a large sample of older patients with and without HIV in Italy.

3. Justice AC, Gordon KS, Skanderson M, Edelman EJ, Akgun KM, Gibert CL, et al. Nonantiretroviral polypharmacy and adverse health outcomes among HIV-infected and uninfected individuals. AIDS. 2018;32(6):739–49. [PubMed: 29543653] **Using data from the Veterans Aging Cohort Study, this study demonstrates dose response effects of increasing count of non-ARV medications on risk of hospitalization and mortality among patients with and without HIV. These effects were independent of severity of illness.
4. Milic J, Russwurm M, Cerezales Calvino A, Brañas F, Sánchez-Conde M, Guaraldi G. European cohorts of older HIV adults: POPPY, AGEhIV, GEPPO, COBRA and FUNCFRAIL. European Geriatric Medicine. 2019;10(2):247–57.
5. Ssonko M, Stanaway F, Mayanja HK, Namuleme T, Cumming R, Kyalimpa JL, et al. Polypharmacy among HIV positive older adults on anti-retroviral therapy attending an urban clinic in Uganda. BMC geriatr. 2018;18(1):125. [PubMed: 29843635] *Cross-sectional study of PWH over 50 years old attending an outpatient clinic in Uganda; demonstrates that polypharmacy is prevalent and associated with recent hospitalization in sub-Saharan Africa.
6. Siefried KJ, Mao L, Cysique LA, Rule J, Giles ML, Smith DE, et al. Concomitant medication polypharmacy, interactions and imperfect adherence are common in Australian adults on suppressive antiretroviral therapy. AIDS. 2018;32(1):35–48. [PubMed: 29135584] *Using data from an Austrialian cohort of PWH, polypharmacy, medications with potential interactions, and associated adverse effects are described.
7. Livio F, Marzolini C. Prescribing issues in older adults living with HIV: thinking beyond drug-drug interactions with antiretroviral drugs. Ther Adv Drug Saf. 2019;10:2042098619880122. [PubMed: 31620274]
8. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC. The next therapeutic challenge in HIV: polypharmacy. Drugs Aging. 2013;30(8):613–28. [PubMed: 23740523]
9. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. 2018.
10. Guaraldi G, Marcotullio S, Maserati R, Gargiulo M, Milic J, Franconi I, et al. The Management of Geriatric and Frail HIV Patients. A 2017 Update from the Italian Guidelines for the Use of Antiretroviral Agents and the Diagnostic Clinical Management of HIV-1 Infected Persons. The Journal of frailty & aging. 2019;8(1):10–6. [PubMed: 30734825]
11. Hughes CA, Tseng A, Cooper R. Managing drug interactions in HIV-infected adults with comorbid illness. Cmaj. 2015;187(1):36–43. [PubMed: 25225224]
12. Larance B, Degenhardt L, Lintzeris N, Winstock A, Mattick R. Definitions related to the use of pharmaceutical opioids: extramedical use, diversion, non-adherence and aberrant medication-related behaviours. Drug Alcohol Rev. 2011;30(3):236–45. [PubMed: 21545553]
13. Kong AM, Pozen A, Anastos K, Kelvin EA, Nash D. Non-HIV comorbid conditions and polypharmacy among people living with HIV age 65 or older compared with HIV-negative individuals age 65 or older in the United States: A retrospective claims-based analysis. AIDS Patient Care and STDs. 2019;33(3):93–103. [PubMed: 30844304]
14. Ware D, Palella FJ, Chew KW, Friedman MR, D'Souza G, Ho K, et al. Examination of Polypharmacy Trajectories among HIV-Positive and HIV-Negative Men in an Ongoing Longitudinal Cohort from 2004 to 2016. AIDS Patient Care and STDs. 2019;33(8):354–65. [PubMed: 31369298] **This study identifies and determines predictors of longitudinal patterns of polypharmacy among patients with and and without HIV.
15. Ruzicka DJ, Imai K, Takahashi K, Naito T. Greater burden of chronic comorbidities and co-medications among people living with HIV versus people without HIV in Japan: A hospital claims database study. Journal of Infection and Chemotherapy. 2019;25(2):89–95. [PubMed: 30396821]
16. Ranzani A, Oreni L, Agro M, van den Bogaart L, Milazzo L, Giacomelli A, et al. Burden of Exposure to Potential Interactions Between Antiretroviral and Non-Antiretroviral Medications in a Population of HIV-Positive Patients Aged 50 Years or Older. JAIDS-Journal of Acquired Immune Deficiency Syndromes. 2018;78(2):193–201.

17. Halpin SN, Carruth EC, Rai RP, Jennifer Edelman E, Fiellin DA, Gibert C, et al. Complementary and Alternative Medicine Among Persons living with HIV in the Era of Combined Antiretroviral Treatment. AIDS and Behavior. 2018;22(3):848–52. [PubMed: 28733920]

18. Justice ACT JP Strengths and Limitations of the Veterans Aging Cohort Study Index as a Measure of Physiologic Frailty. AIDS Res Hum Retroviruses. 2019.**Review on the application of the Veterans Aging Cohort Study Index.

19. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatr. 2015;15:31. [PubMed: 25879993]

20. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. J Am Geriatr Soc. 2015;63(1):85–90. [PubMed: 25597560]

21. Wang F, Roy S. Gut Homeostasis, Microbial Dysbiosis, and Opioids. Toxicol Pathol. 2017;45(1):150–6. [PubMed: 27895265]

22. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. J Med Toxicol. 2014;10(1):26–39. [PubMed: 23963694]

23. Serpa JA, Rueda AM, Somasunderam A, Utay NS, Lewis D, Couturier JP, et al. Long-term Use of Proton Pump Inhibitors Is Associated With Increased Microbial Product Translocation, Innate Immune Activation, and Reduced Immunologic Recovery in Patients With Chronic Human Immunodeficiency Virus-1 Infection. Clin Infect Dis. 2017;65(10):1638–43. [PubMed: 29020215]

24. Chang CB, Chan DC. Comparison of published explicit criteria for potentially inappropriate medications in older adults. Drugs Aging. 2010;27(12):947–57. [PubMed: 21087065]

25. Lipton HL, Bero LA, Bird JA, McPhee SJ. The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing. A randomized controlled trial. Med Care. 1992;30(7):646–58. [PubMed: 1614233]

26. Moen J, Norrgard S, Antonov K, Nilsson JL, Ring L. GPs' perceptions of multiple-medicine use in older patients. J Eval Clin Pract. 2010;16(1):69–75. [PubMed: 20367817]

27. Burkholder GA, Tamhane AR, Salinas JL, Mugavero MJ, Raper JL, Westfall AO, et al. Underutilization of Aspirin for Primary Prevention of Cardiovascular Disease Among HIV-Infected Patients. Clin Infect Dis. 2012;55(11):1550–7. [PubMed: 22942209]

28. Freiberg MS, Leaf DA, Goulet JL, Goetz MB, Oursler KK, Gibert CL, et al. 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. 2009;24(3):334–40. [PubMed: 19127386]

29. Nixon DE, Bosch RJ, Chan ES, Funderburg NT, Hodder S, Lake JE, et al. Effects of atorvastatin on biomarkers of immune activation, inflammation, and lipids in virologically suppressed, human immunodeficiency virus-1-infected individuals with low-density lipoprotein cholesterol <130 mg/dL (AIDS Clinical Trials Group Study A5275). J Clin Lipidol. 2017;11(1):61–9. [PubMed: 28391912]

30. Oliver NT, Hartman CM, Kramer JR, Chiao EY. Statin drugs decrease progression to cirrhosis in HIV/hepatitis C virus coinfected individuals. AIDS. 2016;30(16):2469–76. [PubMed: 27753678]

31. Toribio M, Fitch KV, Sanchez L, Burdo TH, Williams KC, Sponseller CA, et al. Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV. AIDS. 2017;31(6):797–806. [PubMed: 28252528]

32. Riedel DJ, Jourdain G. Potential impact of statins on cancer incidence in HIV-infected patients. AIDS. 2014;28(16):2475–6. [PubMed: 25265231]

33. Helleberg M, May MT, Ingle SM, Dabis F, Reiss P, Fatkenheuer G, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. AIDS. 2015;29(2):221–9. [PubMed: 25426809]

34. Fiellin DA, Weiss L, Botsko M, Egan JE, Altice FL, Bazerman LB, et al. Drug treatment outcomes among HIV-infected opioid-dependent patients receiving buprenorphine/naloxone. J Acquir Immune Defic Syndr. 2011;56 Suppl 1:S33–8. [PubMed: 21317592]

35. Edelman EJ, Maisto SA, Hansen NB, Cutter CJ, Dziura J, Deng Y, et al. Integrated stepped alcohol treatment for patients with HIV and liver disease: A randomized trial. J Subst Abuse Treat. 2019;106:97–106. [PubMed: 31540617]
36. Edelman EJ, Maisto SA, Hansen NB, Cutter CJ, Dziura J, Deng Y, et al. Integrated stepped alcohol treatment for patients with HIV and alcohol use disorder: a randomised controlled trial. Lancet HIV. 2019;6(8):e509–e17. [PubMed: 31109915]
37. Mercie P, Arsandaux J, Katlama C, Ferret S, Beuscart A, Spadone C, et al. Efficacy and safety of varenicline for smoking cessation in people living with HIV in France (ANRS 144 Inter-ACTIV): a randomised controlled phase 3 clinical trial. Lancet HIV. 2018;5(3):e126–e35. [PubMed: 29329763] *Supports use of varenicline to address tobacco use disorder among PWH.
38. Wyse JJ, Robbins JL, McGinnis KA, Edelman EJ, Gordon AJ, Manhapra A, et al. Predictors of timely opioid agonist treatment initiation among veterans with and without HIV. Drug Alcohol Depend. 2019;198:70–5. [PubMed: 30878769]
39. Williams EC, Lapham GT, Shortreed SM, Rubinsky AD, Bobb JF, Bensley KM, et al. Among patients with unhealthy alcohol use, those with HIV are less likely than those without to receive evidence-based alcohol-related care: A national VA study. Drug Alcohol Depend. 2017;174:113–20. [PubMed: 28324813]
40. Shuter J, Salmo LN, Shuter AD, Nivasch EC, Fazzari M, Moadel AB. Provider beliefs and practices relating to tobacco use in patients living with HIV/AIDS: a national survey. AIDS Behav. 2012;16(2):288–94. [PubMed: 21301950]
41. Vijayaraghavan M, Yuan P, Gregorich S, Lum P, Appelle N, Napoles AM, et al. Disparities in receipt of 5As for smoking cessation in diverse primary care and HIV clinics. Prev Med Rep. 2017;6:80–7. [PubMed: 28271025]
42. Halloran MO, Boyle C, Kehoe B, Bagkeris E, Mallon P, Post FA, et al. Polypharmacy and drug-drug interactions in older and younger people living with HIV: The POPPY study. Antivir Ther. 2019;24(3):193–201. [PubMed: 30700636]
43. Gervasoni C, Formenti T, Cattaneo D. Management of Polypharmacy and Drug-Drug Interactions in HIV Patients: A 2-year Experience of a Multidisciplinary Outpatient Clinic. AIDS Rev. 2019;21(1):40–9. [PubMed: 30899119]
44. Cattaneo D, Giacomelli A, Gervasoni C. Loss of control of HIV viremia with OTC weight-loss drugs: a call for caution? Obesity. 2018;26(8):1251–2. [PubMed: 30070075]
45. Freedman SF, Johnston C, Faragon JJ, Siegler EL, Del Carmen T. Older HIV-infected adults: complex patients (III)—polypharmacy. European Geriatric Medicine. 2019;10(2):199–211. [PubMed: 31983932]
46. Olin JL, Klibanov O, Chan A, Spooner LM. Managing Pharmacotherapy in People Living With HIV and Concomitant Malignancy. Ann Pharmacother. 2019;53(8):812–32. [PubMed: 30770025]
47. Myerson M, Kaplan-Lewis E, Poltavskiy E, Ferris D, Bang H. Prolonged QTc in HIV-Infected Patients: A Need for Routine ECG Screening. J Int Assoc Provid AIDS Care. 2019;18:2325958219833926. [PubMed: 30907255]
48. Mallayasamy SP SR. Chapter 8 - Pharmacogenomic Considerations in the Treatment of HIV Infection: Academic Press; 2019.
49. Chanfreau-Coffinier C, Hull LE, Lynch JA, DuVall SL, Damrauer SM, Cunningham FE, et al. Projected Prevalence of Actionable Pharmacogenetic Variants and Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users. JAMA Netw Open. 2019;2(6):e195345. [PubMed: 31173123]
50. Administration UFD. Table of pharmacogenomic biomarkers in drug labeling [cited 11.4.2019]. Available from: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling.
51. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002;359(9308):727–32. [PubMed: 11888582]
52. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359(9312):1121–2. [PubMed: 11943262]

53. Frasco MA, Mack WJ, Van Den Berg D, Aouizerat BE, Anastos K, Cohen M, et al. Underlying genetic structure impacts the association between CYP2B6 polymorphisms and response to efavirenz and nevirapine. AIDS. 2012;26(16):2097–106. [PubMed: 22951632]
54. Aceti A, Gianserra L, Lambiase L, Pennica A, Teti E. Pharmacogenetics as a tool to tailor antiretroviral therapy: A review. World J Virol. 2015;4(3):198–208. [PubMed: 26279982]
55. Moore AA, Whiteman EJ, Ward KT. Risks of combined alcohol/medication use in older adults. Am J Geriatr Pharmacother. 2007;5(1):64–74. [PubMed: 17608249]
56. Akgun KMKS, Tate JP, et al.:, editor Potentially inappropriate medications increase delirium more in HIV+ than uninfected. Annual American Delirium Society (ADS) Conference; 2019; Boston
57. Eyawo O, McGinnis KA, Justice AC, Fiellin DA, Hahn JA, Williams EC, et al. Alcohol and Mortality: Combining Self-Reported (AUDIT-C) and Biomarker Detected (PEth) Alcohol Measures Among HIV Infected and Uninfected. J Acquir Immune Defic Syndr. 2018;77(2):135–43. [PubMed: 29112041]
58. Lemons A, DeGroote N, Perez A, Craw J, Nyaku M, Broz D, et al. Opioid Misuse Among HIV-Positive Adults in Medical Care: Results From the Medical Monitoring Project, 2009–2014. J Acquir Immune Defic Syndr. 2019;80(2):127–34. [PubMed: 30383590] *National data on extra-medical opioid use among PWH engaged in care and demonstrates that extra-medical opioid use is associated with worse HIV-related outcomes (adherence, viral suppression and risk behaviors).
59. Davis GP, Surratt HL, Levin FR, Blanco C. Antiretroviral medication: an emerging category of prescription drug misuse. Am J Addict. 2014;23(6):519–25. [PubMed: 24102874]
60. Womack JA, Murphy TE, Rentsch CT, Tate JP, Bathulapalli H, Smith AC, et al. Polypharmacy, Hazardous Alcohol and Illicit Substance Use, and Serious Falls Among PLWH and Uninfected Comparators. J Acquir Immune Defic Syndr. 2019;82(3):305–13. [PubMed: 31339866]
61. Kim TW, Walley AY, Heeren TC, Patts GJ, Ventura AS, Lerner GB, et al. Polypharmacy and risk of non-fatal overdose for patients with HIV infection and substance dependence. J Subst Abuse Treat. 2017;81:1–10. [PubMed: 28847449]
62. Kim TW, Walley AY, Ventura AS, Patts GJ, Heeren TC, Lerner GB, et al. Polypharmacy and risk of falls and fractures for patients with HIV infection and substance dependence. AIDS Care. 2018;30(2):150–9. [PubMed: 29034725]
63. Bosh KC,N; Dong X; Lyss S; Mendoza M; Mitsch AJ, editor Opioid overdose deaths among persons with HIV infection, United States, 2011–2015, Abstract #147. CROI; 2019; Seattle, WA.
64. Becker WC, Gordon K, Edelman EJ, Kerns RD, Crystal S, Dziura JD, et al. Trends in Any and High-Dose Opioid Analgesic Receipt Among Aging Patients With and Without HIV. AIDS Behav. 2015.
65. Silverberg MJ, Ray GT, Saunders K, Rutter CM, Campbell CI, Merrill JO, et al. Prescription long-term opioid use in HIV-infected patients. Clin J Pain. 2012;28(1):39–46. [PubMed: 21677568]
66. Parent S, Nolan S, Fairbairn N, Ye M, Wu A, Montaner J, et al. Correlates of opioid and benzodiazepine co-prescription among people living with HIV in British Columbia, Canada: A population-level cohort study. International Journal of Drug Policy. 2019;67:52–7. [PubMed: 30897373]
67. Weisberg DF, Gordon KS, Barry DT, Becker WC, Crystal S, Edelman EJ, et al. Long-term Prescription of Opioids and/or Benzodiazepines and Mortality Among HIV-Infected and Uninfected Patients. J Acquir Immune Defic Syndr. 2015;69(2):223–33. [PubMed: 26009831]
68. Wiese AD, Griffin MR, Schaffner W, Stein CM, Greevy RA, Mitchel EF Jr., et al. Opioid Analgesic Use and Risk for Invasive Pneumococcal Diseases: A Nested Case-Control Study. Ann Intern Med. 2018.
69. Wiese AD, Griffin MR, Schaffner W, Stein CM, Greevy RA, Mitchel EF, et al. Long-acting Opioid Use and the Risk of Serious Infections: A Retrospective Cohort Study. Clin Infect Dis. 2019;68(11):1862–9. [PubMed: 30239630]
70. Dublin S, Walker RL, Jackson ML, Nelson JC, Weiss NS, Von Korff M, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. J Am Geriatr Soc. 2011;59(10):1899–907. [PubMed: 22091503]
71. Edelman EJ, Gordon KS, Crothers K, Akgun K, Bryant KJ, Becker WC, et al. Association of Prescribed Opioids With Increased Risk of Community-Acquired Pneumonia Among Patients

With and Without HIV. JAMA Intern Med. 2019.**Using data from the Veterans Aging Cohort Study, this study demonstrates that prescribed opioids increase risk of pneumonia, with greater effects with higher doses and immunosuppressive opioids among patients with and without HIV.

72. Bruce RD, Merlin J, Lum PJ, Ahmed E, Alexander C, Corbett AH, et al. 2017 HIVMA of IDSA Clinical Practice Guideline for the Management of Chronic Pain in Patients Living With HIV. Clin Infect Dis. 2017;65(10):e1–e37. [PubMed: 29020263]
73. Merlin JS, Westfall AO, Long D, Davies S, Saag M, Demonte W, et al. A Randomized Pilot Trial of a Novel Behavioral Intervention for Chronic Pain Tailored to Individuals with HIV. AIDS Behav. 2018;22(8):2733–42. [PubMed: 29340913]
74. Edelman EG, Geliang;, Omar Audrey; Becker William C; Chan Philip A; Cornman D; Dziura JD; Esserman D; Fiellin LE; Morford K; Oldfield BO; Tetrault JM; Yager J; Muvvala S; Fiellin DA, editor Implementing medication treatment of opioid use disorder in HIV clinics: Baseline results from the WHAT-IF? study 11th Annual Conference on the Science of Dissemination and Implementation in Health; 2018; Washington, D.C.
75. Tsui JI, Walley AY, Cheng DM, Lira MC, Liebschutz JM, Forman LS, et al. Provider opioid prescribing practices and the belief that opioids keep people living with HIV engaged in care: a cross-sectional study. AIDS Care. 2019:1–5.**Cross sectional study of 41 HIV providers demonstrating suboptimal adherence to guidelines for prescribing long-term opioid therapy, higlighting a need for interventions to address this problem.
76. Carroll JJ, Colasanti J, Lira MC, Del Rio C, Samet JH. HIV Physicians and Chronic Opioid Therapy: It's Time to Raise the Bar. AIDS Behav. 2019;23(4):1057–61. [PubMed: 30519904]
77. Colasanti J, Lira MC, Cheng DM, Liebschutz JM, Tsui JI, Forman LS, et al. Chronic Opioid Therapy in People Living With Human Immunodeficiency Virus: Patients' Perspectives on Risks, Monitoring, and Guidelines. Clin Infect Dis. 2019;68(2):291–7. [PubMed: 29860411]
78. McNicholl IR, Gandhi M, Hare CB, Greene M, Pierluissi E. A Pharmacist-Led Program to Evaluate and Reduce Polypharmacy and Potentially Inappropriate Prescribing in Older HIV-Positive Patients. Pharmacotherapy. 2017;37(12):1498–506. [PubMed: 29023938]
79. Greene ML, Tan JY, Weiser SD, Christopoulos K, Shiels M, O'Hollaren A, et al. Patient and provider perceptions of a comprehensive care program for HIV-positive adults over 50 years of age: The formation of the Golden Compass HIV and aging care program in San Francisco. PLoS ONE. 2018;13(12).
80. NIH Research Portfolio Online Reporting Tools (RePORT). Effect of exercise training on inflammation and function in HIV infected veterans (#5I01RX000667–06) [10.16.2019]. Available from: https://projectreporter.nih.gov/project_info_description.cfm?aid=9924244&icde=47014784&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=.
81. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779. [PubMed: 25826379]
82. Gaziano JM, Concato J, Brophy M, Fiore L, Pyarajan S, Breeling J, et al. Million Veteran Program: A mega-biobank to study genetic influences on health and disease. J Clin Epidemiol. 2016;70:214–23. [PubMed: 26441289]
83. Cooper JA, Ryan C, Smith SM, Wallace E, Bennett K, Cahir C, et al. The development of the PROMPT (PRescribing Optimally in Middle-aged People's Treatments) criteria. BMC Health Serv Res. 2014;14:484. [PubMed: 25410615]

Key points:

- 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.

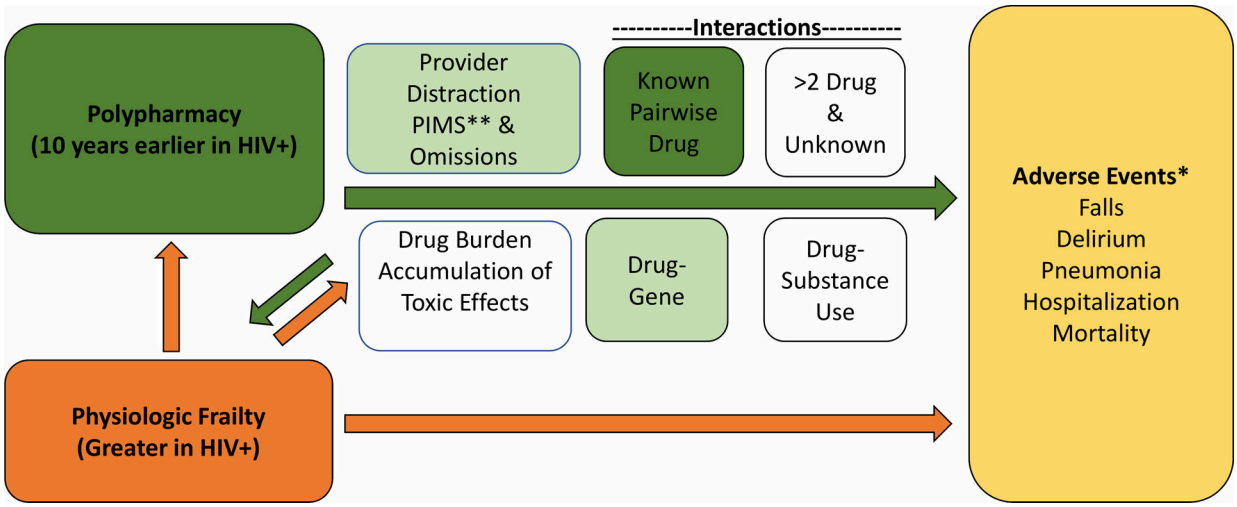

Figure 1. Conceptual Model of Harm Associated with Polypharmacy

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

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