Published in final edited form as:

Curr Opin HIV AIDS. 2014 July ; 9(4): 317–324. doi:10.1097/COH.0000000000000069.

Substance Use in Older HIV-Infected Patients

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Abstract

Purpose of the Review—Substance use may persist throughout the life course and has a substantial impact on health outcomes globally. As HIV-infected individuals are disproportionately impacted by substance use and living longer, it is critical that providers and researchers alike understand the impact of substance use on older, HIV-infected patients and potential treatment options. To this end, we conducted a review of the literature focusing on the most commonly used substances to outline the epidemiology, health consequences, treatment options and latest research relevant to older, HIV-infected patients.

Recent Findings—Substance use impacts older, HIV-infected patients with regards to HIV-related and non-HIV related outcomes. Counseling strategies are available for marijuana and stimulant use disorders. Brief counseling is useful alongside medications for alcohol, tobacco and opioid use disorders. Many medications for alcohol, tobacco, and opioid use disorders are safe in the setting of antiretroviral therapy. Unfortunately, few interventions targeting substance use in older, HIV-infected patients have been developed and evaluated.

Summary—As older, HIV-infected patients continue to experience substance use and its related health consequences, there will be a growing need for the development of safe and effective interventions which address the complex needs of this population.

Keywords

HIV; substance-related disorders; older adults

Introduction

Substance use contributes to significant morbidity and mortality worldwide and is an important cause of disability and the main cause of premature deaths[1, 2]. Since substance use often persists over time at sustained high levels[3], its impact extends across age groups[2]. Substance use disorders are more common among HIV-infected patients than those without HIV; this pattern remains true among younger and older populations alike[4]. For example, an analysis of 6,351 patients with a mean age of 50 years old from the

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Disclosures

Dr. Fiellin has received honorarium from Pinney Associates for serving on external advisory boards monitoring the diversion and abuse of buprenorphine.

Veterans Aging Cohort Study (VACS) found that HIV-infected patients more commonly reported past year problematic drug use, cocaine/stimulant use, opiate/heroin use and marijuana use compared to demographically matched uninfected patients[4]. Substance use was common across substances with approximately 20% of the cohort reporting past year cocaine use, 52% reporting current tobacco use, 10% reporting past year opioid use, and 30% reporting past year marijuana use. Prevalence rates are likely to vary depending on the specific characteristics of the population. A multi-site study of older, HIV-infected patients with depressive symptoms found that 25% had self-reported substance use in the past 60 days, with common self-reported use across all substances: cocaine 48%; marijuana 48%; and other drugs, including opioids and benzodiazepines 44% [5].

Therefore, we conducted the current review to examine the literature on the epidemiology, health consequences, treatment options and recent advances for the most commonly used substances as it pertains to aging, HIV-infected patients. When possible we selected articles that focused on substance use among those aging with HIV. Since there were few studies with such a focus, we also include key studies that address the epidemiology and treatment of substance use in non-elderly individuals with HIV-infection and older individuals without HIV-infection.

Alcohol

Alcohol use is common among HIV-infected individuals. Unhealthy alcohol use includes at-risk drinking, heavy episodic (binge), and alcohol use disorder (formerly alcohol abuse or dependence)[6]. Eight to 12% of HIV-infected patients are at-risk drinkers [7, 8]. The lifetime prevalence of alcohol use disorder in patients with HIV ranges from 22% to 60% [9–12]. While the prevalence of unhealthy alcohol use among older HIV-infected individuals appears to be similar to that of HIV uninfected comparators, there is limited data on this topic [13, 14]. Among HIV-infected individuals, unhealthy alcohol use is associated with adverse health effects including poor adherence to combined antiretroviral treatment (cART), liver injury and risky sexual activity [15–18]. Treatment options for unhealthy alcohol use depend upon the specific diagnosis. Lower levels of unhealthy use such as at-risk drinking may respond to brief interventions. More severe diagnoses, such as alcohol use disorder, require specialized counseling (e.g. motivational enhancement therapy) and/or medications (e.g. naltrexone).

Recent longitudinal data from the Health and Retirement Study demonstrated that compared to abstainers, older individuals who maintained alcohol consumption at low-risk levels were less likely to develop functional limitations [19]. This finding was true among 50–64 year olds, and those who were older than 65. Interestingly, however, the authors did not find more functional limitations among those with persistent high-risk drinking. Findings from another large cohort of older patients demonstrated an increased risk of all-cause mortality among those who met criteria for an alcohol use disorder or scored greater than 8 on the Alcohol Use Disorder Identification Test (AUDIT) [20]. Consumption of more than 14 drinks per week was associated with a hazard ratio for mortality of 2.6 (95% CI, 1.2–5.5).

Recent treatment research relevant to those aging with HIV include a meta-analysis published for the United States Preventative Services Task Force supporting the efficacy of brief multi-contact counseling interventions for individuals with at-risk or heavy episodic drinking[21]. A trial of a brief multi-contact intervention used primary care provider brief advice to reduce drinking followed by a health educator's telephone follow up at 2, 4 and 8 weeks[130]. This study was conducted in individuals over the age of 55 years and demonstrated that at 3 months the proportion of patients who decreased their drinking to below at-risk levels was greater in the intervention than a control condition (odds ratio 0.4, 95% CI, .22–.76). Although similar declines were seen in reports of drinks in the last seven days and heavy drinking at 3 months, there was no effect of the intervention at 12 months revealing the potential need for “booster” counseling sessions. The most recently available medications to treat alcohol use disorders are a monthly injectable formulation of naltrexone and oral acamprosate. A recent evaluation of naltrexone in HIV-infected individuals prescribed naltrexone demonstrated that it is rarely associated with clinically significant changes in hepatic enzymes[22]. Recent controlled trials of off-label use of gabapentin and varenicline have demonstrated improved drinking outcomes suggesting a potential role for these, or similar medications in the future[23, 24].

Tobacco

Depending on the specific characteristics of the population, between 31 to 84% of HIV-infected patients smoke[25]. There is growing attention to the use and impact of tobacco among HIV-infected patients, though not specifically among older populations. Results from one single-site study (n=60) found that while patients were concerned about the negative health effects and costs associated with smoking, the majority felt that smoking helped them relax and manage their anxiety, anger and depression[26]. Notably, 27% believed that smoking would help increase their T-cell count[26]. While some studies have found an association between smoking and an increase in T-cell count[7, 8], subsequent studies have not[9, 10]. For example, data from the Multicenter AIDS Cohort Study (MACS) demonstrated evidence of a smoking-induced leukocytosis among uninfected individuals, though this effect was lost among those infected with HIV for at least 3 years[8]. The most recent study addressing this question did not find an association between recent smoking levels and CD4 cell count change among a cohort of HIV-infected patients with alcohol problems. This lack of an association persisted in a secondary analysis assessing the impact of changes in smoking behaviors over time and CD4 cell count[9]. Given the overall negative health impact of cigarette smoking, patients should be educated that the potential for smoking-induced leukocytosis should not motivate smoking behaviors.

Just as HIV is increasingly recognized as an independent risk factor for non-AIDS defining conditions, such as lung cancer[31], smoking similarly confers an increased risk to numerous negative health consequences. These include pulmonary complications, cancer, cardiovascular disease, fragility fractures and impaired immune response to antiretroviral therapy[32, 25, 33–37, 30]. Most important is the impact of smoking on mortality. A recent report from the Danish HIV Cohort Study found that HIV-infected current smokers experienced over a 5-fold increased risk of non-AIDS related deaths compared to never-

smokers, driven by cancer and cardiovascular disease-related deaths. Furthermore, smoking was associated with a greater number of lost life-years than HIV infection[38].

Smoking is often inadequately addressed and prioritized in health care settings despite its adverse impact[26, 39, 40]. Data from the general population demonstrate that benefits of quitting smoking are evident regardless of age[41]. While effective treatment strategies in the general population and older populations specifically integrate counseling and pharmacotherapy[42–44], there have been only a limited number of treatment trials in HIV-infected populations[32, 45–49]. A large-scale trial compared the efficacy of a cell phone counseling-based smoking cessation intervention which occurred over 3 months plus access to a hotline to treatment as usual targeting a HIV-infected population (n=474). At 3 months, those assigned to the intervention were 4.3 (95% CI= 1.9, 9.8, $p<0.001$) times more likely to report past 7-day abstinence[50]. The differences in the groups, however, had diminished by 6 and 12 months ($p>0.05$)[51].

The data on the efficacy and safety of pharmacotherapy for tobacco dependence in the setting of antiretroviral agents and in HIV-infected patients are currently limited[52, 32, 53]. A recent preliminary non-randomized 12-week study in which all participants received telephone counseling and either varenicline or nicotine replacement therapy found that varenicline was associated with a greater odds of abstinence compared with nicotine replacement therapy. Adverse events associated with varenicline included nausea, sleep problems and mood disturbances and one person reported suicidal ideation; this did not vary based on whether patients were receiving antiretroviral therapy[54]. Results from a separate drug-company sponsored, multi-center open label pilot trial found that these adverse events were common, with 17% discontinuing the medication. There was no significant change in viral load and CD4 counts increased over the 24 weeks[55].

Non-Opioid Prescription Medications

Roughly 25% of prescription medications are prescribed to older individuals. Older individuals have a high prevalence of agitation, anxiety, insomnia, pain and other symptoms that can result in the prescription of controlled substances such as benzodiazepines, other sedative hypnotics, and stimulants. Non-medical use of prescription controlled substances can include behaviors such as using higher than prescribed doses, using for longer than intended or for an indication other than prescribed, hoarding, using medications that were not prescribed to the individual, and using medications along with other mood altering substance such as marijuana or alcohol[56, 57]. Non-medical use is also seen in individuals with a diagnosis of a drug use disorder (e.g. benzodiazepine use disorder). Non-medical use of prescription drugs is as common as marijuana use among those older than 60 and seen in 1.2% of this population in the US[58]. US-based emergency department visits for prescription drug abuse by those over 50 years of age rose by 159% between 2004 and 2009, with 32% of visits resulting from anti-anxiety and insomnia medications[59].

Benzodiazepines are among the most frequently prescribed medications in the US and alprazolam is the most commonly prescribed psychiatric medication[60]. Prolonged prescription (> 4 weeks) of benzodiazepines and use of doses greater than 10 mg per day of

diazepam equivalents may be associated with the development of dependence[57]. Risks of long-term benzodiazepine prescription in older patients beyond development of physical dependence include cognitive impairment, falls, and fractures[61]. In addition, abrupt cessation and/or rapid tapering of long-term benzodiazepines among older patients can precipitate acute deterioration in mental status secondary to withdrawal symptoms, which may be difficult to diagnosis[62]. Recent systematic reviews and meta-analyses that have looked at benzodiazepine discontinuation in general populations and older adults have demonstrated success including decreased benzodiazepine use (risk ratio 2.04, 95% CI 1.48 to 2.83) through brief interventions in the form of a letter to the patient from their prescriber instructing the patient on how to reduce their benzodiazepine dose and provision of a support group[63, 64]. Similarly, the addition of brief interventions and psychological counseling to gradual dose reduction was found to be superior to usual care or gradual dose reduction alone in a meta-analysis looking at benzodiazepine discontinuation[65]. Non-medical use of stimulant prescription medications appears to be low among older patients, perhaps due to decreased dopamine in the aging brain[66].

An emerging area of prescription drug misuse of particular importance to HIV providers is the report of increased diversion and nonmedical use of antiretroviral medications for their psychoactive properties[67–69]. Efavirenz in particular, may have a distinct hallucinogenic effect similar to LSD, and there are reports of its abuse alone and in combination with other psychoactive substances[67, 70]. In addition, ritonavir, an inhibitor of CYP2D6, is reported to heighten the psychoactive effects of methamphetamine and ecstasy[68].

Marijuana

Approximately 13.1 million people are cannabis dependent globally[71]. Marijuana is the most commonly used illicit substance in the US and roughly 4.6 million people over age 50 report marijuana use, translating to roughly 6% of this age group. Over the last decade, increases in marijuana use in adults aged 50 to 54 and those aged 55 to 59 appear to be largely due to the aging of the baby boom birth cohort[72]. The prevalence of marijuana use increases when perceived risk of use decreases. Over the past 16 years, 18 US states and the District of Columbia have legalized medical marijuana and 2 states have legalized recreational marijuana use; which may translate to a decrease in perceived risk of marijuana use. HIV-infected, individuals, in particular, report health benefits from smoked marijuana. In a sample of over 250 HIV-infected individuals recruited from public health clinics, 23% reported marijuana use in the previous month[73]. Reported benefits of marijuana smoking among HIV-infected individuals include improved mood, decreased anxiety, improved appetite, decreased nausea and decreased pain[74, 73]. Marijuana's reported effect on decreasing nausea may be associated with improved adherence to antiretroviral medications[75]. Among the aging population, marijuana's potential to decrease intraocular pressure is considered another therapeutic benefit[76]. Among HIV-infected women, use of marijuana is common and often used for medicinal purposes[77]. Despite potential benefits of smoked marijuana, certain health effects need to be considered. Although acute marijuana inhalation results in bronchodilation with a forced expiratory volume in one second (FEV₁) increase of 0.15–0.25L, and minimal airflow obstruction has been noted at low levels of chronic marijuana exposure; higher levels of marijuana exposure are associated with reports

of cough, phlegm production, wheeze and with measures of airflow obstruction[78, 79]. Also of concern for the aging HIV population, marijuana may increase the likelihood of lung cancer. HIV-infection, itself, increases the risk of lung cancer and this risk is increased with cigarette smoking[31, 80]. A 40-year cohort study noted a 2-fold increased risk of lung cancer among chronic, habitual marijuana smokers after adjustment for tobacco smoking, alcohol use, respiratory conditions and socioeconomic status[81], and other studies have suggested an association between marijuana smoking and precancerous changes in the lungs[82]. Although a distinct relationship between marijuana smoking and lung cancer among HIV-infected patients has not been definitively noted, biologic plausibility suggests that this combination may in fact pose an increased risk.

Additional health concerns exist related to marijuana's effect on cognition. This is of particular concern in aging HIV-infected individuals given the impact of other potential offending agents on cognition in this population. Although data is inconclusive regarding marijuana's effect on cognition[83, 84], it appears that heavy marijuana use beginning in adolescence is more likely to lead to IQ decline, even after cessation of marijuana use[83].

Because some HIV-infected and other patients report benefit from marijuana relating to its anti-emetic, mood and pain relieving properties, and many of the adverse effects of marijuana result from smoke inhalation, investigation into alternatives have been conducted. A recent placebo-controlled, within-subject study evaluated the tolerability and efficacy of oral dronabinol vs. smoked marijuana across a range of behaviors in HIV-infected marijuana smokers. The results of this study suggested that both dronabinol and marijuana increased daily caloric intake and body weight in a dose-dependent fashion[85], however, how this translates into meaningful clinical outcomes is yet to be determined.

Treatment options for marijuana use disorder have generally relied on counseling strategies. However a recent double-blind placebo-controlled trial of N-acetylcysteine plus contingency management and brief counseling shows promising results in adolescents and is now being investigated in other populations[86].

Heroin and Prescription Opioids

According to data from the US National Survey on Drug Use and Health between 1979 and 2002, the mean age of individuals reporting injection drug use (IDU) ever increased from 26 to 42 years, with roughly 60% of all persons with IDU between 35–49 years[87]. Heroin is the primary drug used via the injection route. Several studies have confirmed that despite aging and forays into treatment for opioid use disorders, older adults continue to struggle with the relapsing and remitting nature of the disease and comorbid physical and mental health conditions often complicate treatment[88]. In addition to concerns over injection heroin use, the non-medical use of prescription opioids is also a major public health concern, especially in North American and Australia. In addition to poor screening for IDU and prescription opioid misuse in older HIV-infected adults, clinicians often fail to educate this population regarding ongoing risky behaviors.

Ongoing IDU negatively affects treatment outcomes among HIV-infected individuals despite the advent of combined antiretroviral treatment[89–91]. However, opioid agonist

treatment of opioid use disorders with methadone or buprenorphine in HIV-infected individuals can lead to decreased viral transmission and improved treatment outcomes. Roughly 10% of patients receiving opioid agonist treatment are over 50 years.

Certain treatment-related issues may be particularly concerning in older HIV-infected individuals with multiple comorbidities and use of multiple medications[92]. For methadone treatment, clinicians must consider potential for QTc prolongation as well as drug-drug interactions[93, 94]. For both naltrexone and buprenorphine treatment, concerns over hepatotoxicity have been expressed in the literature but emerging data in HIV-infected individuals suggest the likelihood of clinically significant hepatic enzyme elevation with either of these medications is low[95, 96]. A recent multi-site study investigating the use of buprenorphine in HIV-infected opioid-dependent patients found that buprenorphine treatment resulted in improved cART initiation, improved CD4 lymphocyte counts, and decreased illicit opioid use[97, 98]. Other studies have noted the feasibility of implementing buprenorphine treatment into HIV clinical care and found that additional counseling above and beyond routine physician management was unlikely to improve treatment outcomes[99, 100].

Stimulants

Stimulant use is common among HIV-infected patients, particularly among men who have sex with men[101]. Recent data from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) found that 9% of HIV-infected patients reported amphetamine use, and 9% reported crack-cocaine use[102]. Another recent study focused specifically on HIV-infected men who have sex with men, however, found higher rates of self-reported stimulant use with methamphetamine and cocaine use reported by 21% and 17% of patients, respectively[101]. While older patients are less likely to report stimulant use[102, 103], it is cause for concern due to the myriad of negative health effects associated with their use. These include antiretroviral medication non-adherence[104, 102], HIV disease progression[105–108], neurotoxicity[109, 110], and cardiovascular complications[111, 112]. In addition, stimulant use has been associated with increased sexual risk behaviors, contributing to ongoing HIV transmission[113]; findings which extend to older men[114]. Treatment hinges on behavioral interventions, such as contingency management[115] and cognitive behavioral therapy[116] as there are currently no effective pharmacologic treatments[117–120].

Several medications and a vaccine strategy are under active investigation as potential treatment options for stimulant use disorders[121–126]. A recently published double-blind, randomized, placebo-controlled 12-week trial found that topiramate was more effective than placebo at increasing the mean weekly proportion of cocaine nonuse days among cocaine dependent patients[123]. In a separate trial, topiramate combined with extended-release mixed amphetamine salts, compared to placebo, was found to promote abstinence among cocaine dependent adults[126]. Compared to placebo, topiramate was also found to reduce use and relapse among patients with amphetamine addiction, though it was not found to promote abstinence[124].

Multi-Substance Use

Multi-substance use is common (e.g. tobacco and alcohol use) and is associated with negative health effects including poorer drug treatment outcomes and HIV-related outcomes; medical and psychiatric comorbidity; and important social consequences, such as criminal activity[127, 4]. Also, multi-substance use increases the likelihood of substance-medication interactions, specifically with ART[92, 128].

A latent class analysis of VACS data revealed that 25% of HIV-infected patients were current high consequence, multi-drug users. In addition to active injection and non-injection drug use, these individuals were more likely to report current unhealthy alcohol use, poor quality of life scores, and have medical and psychiatric disease[4]. Data from CNICS found that 10% of patients had multi-substance use[102]. In multivariate models, men, those with a detectable HIV viral load, greater antiretroviral nonadherence, major depression, drug treatment, and HIV sexual risk behaviors, specifically unprotected anal intercourse, and those with a higher number of anal or vaginal sex partners, were more likely to have multi-substance use[102]. Increasing age was the one factor identified as being associated with a decreased odds of multi-substance use. Effective treatment interventions for these individuals are likely to require comprehensive services, which address substance use, HIV, psychiatric illness and underlying coping strategies[102, 5].

Conclusion

Substance use impacts the overall health of older, HIV-infected patients with regards to both HIV and non-HIV related outcomes. Accordingly, efforts aimed at optimizing care along the HIV-treatment cascade, will benefit from improved screening, linkage to and retention in treatment for substance use across the life-span of HIV-infected patients.

In addition our review highlights the need for improved treatments for substance use and data demonstrating the safety and effectiveness of interventions for older, HIV-infected patients. Novel treatment approaches, which are comprehensive in nature and integrated into HIV clinics[129, 97], are likely to be most successful. Research focused on designing and testing interventions focused on the unique needs of older, HIV-infected patients is needed.

Acknowledgments

EJ Edelman was supported by NIDA K12 (1K12DA033312-01A1) grant during the conduct of this work.

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Bullet Points

- Substance use is prevalent among HIV-infected patients and appears to persist among older, HIV-infected individuals.
- The epidemiology and impact of substance use among older, HIV-infected populations remains largely unknown.
- Counseling strategies are the mainstay of treatment for marijuana, stimulant use disorders, and brief versions are important co-treatments for alcohol, tobacco and opioid use disorders.
- Existing data suggest that currently approved pharmacotherapies for alcohol, tobacco, and opioid use disorders are for the most part safe in the setting of antiretroviral therapy.
- New data suggest a potential role in the future for gabapentin and varenicline for alcohol use disorders; N-acetylcysteine for marijuana use disorders; and topiramate for cocaine and amphetamine use disorders.