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An update on drug-drug interactions between anti-retroviral therapies and drugs of abuse in HIV systems

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Abstract

Introduction: While considerable progress has been made in the fight against HIV/AIDS, to date there has not been a cure, and millions of people around the world are currently living with HIV/AIDS. eople living with HIV/AIDS have substance abuse disorders at higher rates than non-infected individuals, which puts them at an increased risk of drug drug interactions.

Areas covered: Potential drug drug interactions are reviewed for a variety of potential drugs of abuse, both licit and illicit. These drugs include alcohol, cigarettes or other nicotine delivery systems, methamphetamine, cocaine, opioids, and marijuana. Potential interactions include decreased adherence, modulation of drug transporters, or modulation of metabolic enzymes. We also review the relative incidence of the use of these drugs of abuse in People living with HIV/AIDS.

Expert opinion: Despite considerable improvements in outcomes, disparities in outcomes between PLWHA who use drugs of abuse, vs those who do not still exist. It is of critical necessity to improve outcomes in these patients, and to work with them to stop abusing drugs of abuse.

Keywords

Antiretrovirals; Drug Transporters; Drugs of Abuse; HIV-1; Metabolic enzymes

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Declaration of interest

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1.0 Introduction

HIV is a global health condition with approximately 37.9 million individuals around the world living with HIV. According to the World Health Organization (WHO), 1.1 million of which are currently living with HIV in the United States with around 20,000 new cases a year [1]. Twenty-one percent of people living with HIV/AIDS (PLWHA) are unaware of their HIV status, leading to treatment delays and accelerated disease progression. While individuals with HIV live an average of 3 years without medication therapy, antiretroviral therapy (ART) has made a tremendous difference in the treatment of PLWHA since being introduced in the mid-1990s. Between 2000 and 2018, ART has increased the lifespan of PLWHA, decreased the rate of AIDs-related death by 45%, and reduced new HIV infections by 37%[1]. ART has also reduced the rate of HIV transmission from pregnant and breastfeeding women with HIV to their newborns. ART has quickly become the primary line of HIV treatment and is an essential component of care to managing HIV infections and preventing new cases.

Current HIV guidelines from the CDC establish standards of care for patients depending on their CD4 cell count, lifestyle, and adherence[2]. Because ART has been shown to reduce disease progression so significantly, all PLWHA are now recommended to receive ART as soon as possible after diagnosis, regardless of their CD4 cell count. A variety of antiretroviral medication options exist, either as a multiple tablet regimen (MTR) or a single tablet regimen (STR). While patient adherence is typically higher with STR, patients and providers may decide on MTR for a multitude of reasons, such as lower cost, wider availability, or combination flexibility. Patient adherence is a vital factor for reaching goal viral suppression levels and optimizing therapeutic outcomes[2]. Previously, it was generally accepted that adherence rates of ≥95% were necessary for patients to maintain optimal viral suppression[1]. Recent studies indicate that a lower adherence rate, potentially in the 80% to 90% range may be adequate to keep patients virally suppressed[3]. However, only 63.4% of patients studied achieved a 90%+ adherence rate [2]. Substance abuse can affect adherence in multiple ways. Occasional use can lead to increased forgetfulness, for example with a missed dose or late medication administration. Addiction can lead to a complex interplay of non-adherence risk factors that can make adherence challenging, such as increased financial burden or reduced cognitive function.

It is clear that ART is the cornerstone of HIV therapy to ensure better patient outcomes. Because these drugs are so necessary, it is important to ensure they are working to their maximum efficacy in all patients. ART medications are metabolized by many common CYP pathways in the liver, leading to multiple documented drug-drug interactions among legal medications. This metabolism may also lead to interactions with drugs of abuse. The rate of substance abuse is comparatively much higher in the PLWHA population compared to the population without HIV/AIDS, with over 80% of PLWHA reporting illegal drug use during their lifetime compared to slightly less than 50% of the individuals without HIV/AIDS. Individuals with HIV report higher than average use of legal substances of abuse, including tobacco and alcohol (both binge drinking and chronic abuse). PLWHA also reported using illegal drugs more recently than individuals without HIV with about four times as PLWHA reporting illegal drug use in the past month compared to individuals without HIV/AIDS [4].

Additionally, as these patients live longer, their likelihood of HIV/AIDS-related neurological conditions, including neuroAIDS, increases. These changes in neuropsychological and neurobehavioral function may lead to neurological impairment, increasing their likelihood of engaging in substance abuse. We propose that the potential of common metabolic pathways, particularly involving CYP enzymes (Table 1.), between ART medications and drugs of abuse can lead to decreased ART efficacy and increased toxicity, worsening patient outcomes. Because of the prevalence of substance abuse among individuals with HIV, it is important to study the interactions of ART medications with drugs of abuse to define how to adjust and improve HIV therapy and adherence to better protect the health of individuals with HIV.

2.0 Antiretrovirals and pharmacokinetics

Antiretrovirals are substrates of a variety of both drug efflux transporters and metabolic enzymes, most notably p-glycoprotein, breast cancer resistance protein, multi-drug resistance proteins, and a variety of cytochrome p450 enzymes [5]. Differences in the relative susceptibility to metabolic enzymes and transporters can influence the absorption, distribution, metabolism, and excretion of antiretrovirals. There is considerable patient to patient variability in the expression and function of these factors, as well as an active HIV infection is capable of further altering the intestinal expression of drug transporters and metabolic enzymes [6].

2.1 ART interactions with metabolic enzymes

Furthermore, as substrates of a variety of transporters and metabolic enzymes, antiretrovirals can influence concentrations of drugs given for a wide variety of diseases, as well as vice versa. Due to their requirement for pharmacoenhancement, administration of protease inhibitors or boosted elvitegravir has a high potential to interact with drugs given for cardiovascular issues, the administration of which is common in people living with HIV/AIDS [7]. There are similar concerns for a number of NNRTI medications as well. Similarly, interactions primarily related to modulation of CYP enzymes cause interactions between antiretrovirals and many medications for the treatment of tuberculosis, especially drug resistant tuberculosis [8]. There are also concerns with interactions between some antiretrovirals, including most notably efavirenz, and a variety of hormonal contraceptive methods, which can result in decreased efficacy of some contraceptive methods [9]. Notably, these interactions are primarily CYP3A4-mediated, which may then have the potential to be further affected by drugs of abuse. Similar to CYP-mediated effects of antiretroviral concentrations, P-gp can play an important role in the internalization of antiretrovirals, including atazanavir [10].

There are also potential drug-drug interactions with opioids and antiretrovirals, including boosted darunavir, elvitegravir, efavirenz, and rilpivirine, which can in some circumstances require decreasing or increasing the dose of the opioid, depending on the drug which is administered [11] [12]. CYP-mediated DDI can also occur with boosted protease inhibitors and statins, which can require decreasing the dose of the statin [11] [12]. Similar interactions can occur between antiretrovirals and the direct acting antivirals used to treat hepatitis C.

2.2 ART interactions with drug efflux transporters

Further, transporter and metabolic enzyme expression on tissue barriers in the body can be a cause of decreased concentrations in these tissue sites. Most notably, the brain represents a tissue reservoir where infected cells are capable of persisting for an extended amount of time. The blood-brain barrier represents a tight boundary which can prevent antiretrovirals or other medications from crossing into the brain environment. In addition to this tight boundary, drug efflux transporters including P-gp, BCRP, and transporters in the MRP family are present [13]. Polymorphisms in transporter expression and function can also play an important role in both efficacy and side effects [13]. In mouse models, it has been reported that P-gp inhibition can play a role in increasing brain concentrations of the protease inhibitor, atazanavir [14]. Experiments with transwell inserts supports that raltegravir is a P-gp and BCRP substrate, and suggests that alterations in expression of these transporters on the blood brain barrier may be a factor in drug distribution to these tissue sites [15].Similarly the blood-testis barrier has drug efflux transporters expressed on it, which can influence atazanavir concentrations in this reservoir [14]. In addition to P-gp, BCRP, and MRP transporters, CYP3A4 and 2D6 are expressed at the blood-testis barrier, and it has been noted that there is variable testicular tissue penetration of protease inhibitors which are substrates for the efflux transporters [16].

3.0 Alcohol

3.1 Incidence of alcohol use among PLWHA

According to the National Institute on Alcohol Abuse and Alcoholism, five drinks for men and 4 drinks for women within 2 hours are defined as binge drinking[17]. Five days or more binge drinking in one month are considered as heavy alcohol use. Both binge and heavy drinking increase the risk of alcohol use disorder (also known as unhealthy/harmful alcohol use) for individuals. Individuals with alcohol use disorder are unable to control their alcohol use which can result in unhealthy consequences[17].Alcohol use disorders are common among PLWHA[18]. Recent studies conducted in different countries showed that the prevalence of alcohol use disorder among PLWHA ranges from 14.0% to 38.4% [18–26], which was 3-times higher than the general population (5.8%−11.1%)[17] [27]. A recent meta-analysis that analyzed a total of 25 studies with more than 25,000 participants from 2010 to 2019 showed that the pooled estimated prevalence of alcohol use disorder among PLWHA was 29.8% [18]. Analysis of those studies also showed that the prevalence of alcohol use disorder in developed countries was higher (42.09%), than the developing countries (24.53%). Alcohol use disorder among PLWHA was found to be associated with increased risk of unsafe sexual behavior, decreased medication adherence, changes in HV marker CD4 counts, and unexpected interactions with antiretroviral therapy (ART) [18,20] [28]. Although physicians recommend that patients who are under ART abstain from alcohol, the majority of them do not comply[29]. Since current guidelines for ART are not personalized for patients who consume alcohol, there is a need to study the impact of alcohol use among PLWHA to help build guidelines for the drug dose adjustment of ART.

3.2 Effects of alcohol on ART adherence

Alcohol consumption has been reported to be a key cause to a lack of ART adherence among PLWHA[29]. Recent clinical studies conducted from different countries also showed the impact of alcohol use on adherence to ART[23,26] [30,31] [30]. For example, a study in Korea showed the increase in alcohol consumption was related to a decrease in adherence to ART[26]. The ratio of patients with less than 95% ART adherence for binge drinkers, hazardous drinkers, and alcohol dependents were 4.65%, 8.05%, and 27.67%, respectively. The increase in alcohol use was also found to be associated with lower adherence motivation. The low adherence ratio for hazardous drinkers and alcohol dependents were 7.47% and 12.61%, respectively. Similarly, a study from Nepal also reported the negative association between alcohol use disorder and ART adherence[23]. A higher ratio of alcohol use disorder was observed from patients who were not adherent to ART (51.1% for men, 22.7 for women), compared to those who were adherent to ART (29.6% for men, 12.5% for women). Additionally, a study from Latin America analyzed the association of alcohol use with ART adherence using a logistic regression model [31]. They showed that alcohol use was associated with a lack of ART adherence with an adjusted odds ratio of 2.46. The association between alcohol use and lack of ART adherence was also reported in a study conducted in the United States, which showed a 2% increase in odds ratio of becoming non-adherent with each additional binge drinking day among women with HIV who were adherent to ART [30].

3.3 Effects of alcohol on ART efficacy/toxicity

Although the main metabolism of alcohol in binge, chronic, or heavy drinkers is through cytochrome P450 2E1 (CYP2E1) oxidation, previous studies also showed the involvement of CYP3A4 in alcohol metabolism[32] [33] [33] [34], the enzyme responsible for the metabolism of the majority of ART drugs[35]. A recent clinical study reported the association of increased drinking behavior with lower efficacy of ART[30]. Among women with HIV who were non-heavy drinkers and adherent to ART, an unsuppressed viral load was associated with an increase of 1 drink per week. Another study from the United States also showed that the decreased ART efficacy with alcohol use was due to intermediating factors such as alcohol-ART toxicity beliefs and alcohol-ART avoidance, causing lack of adherence and ultimately detectable viral load [36]. In previous studies, protease inhibitors, which are predominately metabolized by CYP3A4, have been shown in vitro to have interaction with alcohol, leading to altered inhibition of CYP3A4 [32,37]. This may potentially represent a mechanism by which alcohol use increases metabolism of protease inhibitors. More recently, *Midde et al.* from the Kumar group also reported the in vitro effect of alcohol on ART metabolism due to alternation of the ART-CYP3A4 interaction. They reported that alcohol changed the binding of an integrase inhibitor elvitegravir, to active sites of CYP3A4, decreasing apparent half-life of elvitegravir in human microsome[38]. They also reported decreased elvitegravir intracellular concentrations and less effective HIV suppression in HIV-infected monocytes in the presence of alcohol in an in vitro system[39]. They reported that this alcohol-induced alteration of elvitegravir concentrations were associated with the induction of CYP3A4, and the drug transporters MRP1 and MDR1. The same group also reported the effect of alcohol on a protease inhibitor, darunavir, and its effect on hepatic clearance, intracellular pharmacokinetics, HIV suppression of darunavir in

liver microsomes and U1 cells[40]. They showed that alcohol decreases apparent half-life and hepatic intrinsic clearance of darunavir when alcohol was co-exposed with a commonly used pharmaco-enhancer, ritonavir. They also reported that alcohol increased viral replication in HIV-infected monocytes, while having no effect on darunavir efficacy. In addition, *Rao et al.* from the same group reported that alcohol and darunavir/ritonavir combination decreased the expression of CYP3A4 and antioxidant enzymes SOD1 superoxide dismutase 1 (SOD1) and peroxiredoxin (PRDX6) on cultured monocytes[41]. This alternation on the expression of CYP and antioxidant enzymes was associated with increased oxidative stress and cytotoxicity in monocytes. Additionally, *Jesudas et al.* showed that alcohol alone and in combination with lamivudine, a nucleoside reverse transcriptase inhibitor, enhanced hepatotoxicity and hyperlipidemia in rats. Rats receiving combined regimens with both alcohol and lamivudine showed more pronounced toxicity compared with rats received only alcohol[42]. These upregulations of metabolic enzymes due to ethanol exposure has the strong potential to decrease effective concentrations of antiretrovirals as they are administered, which may be a cause of worsened outcomes in PLWHA who drink.

In conclusion, PLWHA have an increased prevalence of alcohol use compared to the general population. This high prevalence of alcohol use, including mild, moderate, and heavy drinking, is associated with a lack of ART adherence, decrease response to ART, and increased toxicity. Thus, the screening of alcohol use and monitoring of ART adherence and drug level are recommended to improve ART outcomes among PLWHA.

4.0 Nicotine

4.1 Incidence of nicotine use among PLWHA

Smoking cigarettes is not only more common among people living with HIV/AIDS (PLWHA), but there are also lower rates of smoking cessation, as compared to the general population. A 2015 cigarette smoking prevalence study in the US reported by *Mdodo et al.* showed that 42.4% of PLWHA were current smokers while another 20.3% of patients were former smokers, whereas 37.3% had never smoked [43]. This prevalence in PLWHA is >2-times higher than the general population as only 20.6% of general adults smoked cigarettes in the United States. *Bui et al.* investigated smoking cessation among the general population and PLWHA. In 40,888 smoking patients, smoking status of 45.9% of these was reported from HIV clinics (2,675/5,825), with 17.9% of patients' status reported from non-HIV clinics (38,213/213,090) [44]. *Helleberg et al.* analyzed European and North American cohorts (N = 17,995) and reported 60% of smokers among PLWHA [45]. Since smoking may have more of an effect on life span than HIV infection [46] [45], the reduced life span among PLWHA smokers might also be attributed to smoking-induced non-HIV diseases [45] [47] [48].

Even though smoking cessation is strongly recommended in clinical settings, PLWHA who smoke are still struggling. *Mdodo et al.* reported that the smoking cessation rate was 32.4% within PLWHA, compared to 51.7% in the general population [43]. While the phenomenon is well-documented, the underlying cause is poorly understood. *Quinn et al.* recently reported that the cessation rate for treatment-adherent smokers was 35% while non-adherent

smokers' rate was 19% [49]. *Aigner et al.* believed that pain might be an obstacle for smoke cessation [50], which may also explain the adherence issue for people receiving ART.

While smoking cessation might be difficult to achieve, some researchers have used electronic nicotine delivery systems (ENDS) as a substitution for cigarettes to minimize the negative effects of combustible cigarettes. *Yingst et al.* performed a small-scale pilot study to test the acceptability of ENDS, which reported a 48% to 55% reduction ($p < 0.01$) in cigarettes per day (CPD) among the ENDS group compared to the control group [51]. *Cioe et al.* also reported similar results where CPD was reduced by more than 80% and complete transition to ENDS was observed at a rate of 36.8% [52]. Further, *Benmarhnia et al.* reported that cigarette abstinence increased from 9.6% to 15.5% with the use of ENDS [53]. However, not all clinical research supports ENDS. Although ENDS may decrease the usage of combustible cigarettes, it does not decrease the usage of nicotine [54] [55].

4.2 Effects of nicotine on ART adherence

PLWHA who smoke were reported to have a suboptimal antiretroviral treatment (ART) response, likely due in part to decreased adherence to a treatment plan. Similar to alcohol consumption, tobacco smoking is also among the top three reasons that influence negative ART adherence [56] [57] [58]. *Real et al.* reported that among non-adherent patients, 21.7% used nicotine. A similar finding was reported in China where 38.1% of patients were reported to use nicotine [57]. *Zyambo et al.'s* study with 473 patients found that ART adherence had a negative correlation with smoking relapse (HR = 0.65, 95% CI [0.49, 0.99]) [59]. *Zhang et al.* also reported smoking as the 2nd highest factor (PR = 1.30) in non-adherence [58] in U.S. women [58]. *King et al.* reported similar results among sexual minority men in the U.S. where current smokers had much lower rates of ART adherence than non-smokers. Moreover, both smoking intensity (OR = 0.36) and smoking duration (OR = 0.31) were negatively correlated with ART adherence [60]. *Pengpid et al.* reported a study in South Africa in which they found that tobacco use (OR = 2.31) was highly correlated with lack of ART adherence [61]. *Nguyen et al.* performed a study in a Southeast Asian smoking population and reported that an increase in smoking frequency (OR = 1.1) was correlated with ART nonadherence [62]. *Mai et al.* reported that suboptimal ART adherence was highly associated with smoking (coefficient = 4.19) [63]. Aye and colleagues investigated a similar topic in Myanmar, in which among patients reporting non-adherence, tobacco use was reported with an OR value at 3.22 [64].

To elucidate the role of smoking on reduced ART adherence, researchers have investigated the underlying mechanisms. It was hypothesized that nicotine usage might be an indicator of anxiety, depression, pain, stigma, or sensation-seeking [65]. These emotional experiences were reported to be associated with suboptimal adherence to ART. Hence, smoking might be a secondary indicator of an underlying psychological issue. *Esan et al.* investigated the relationship between anxiety, smoking, and ART adherence with 68 patients, and found a significant correlation between anxiety symptoms and low medication adherence [66]. *Nguyen et al.* also reported that individuals with anxiety (OR = 1.6) or reporting pain (OR = 1.9) had a higher probability of nonadherence [62]. Zeambo found that anxiety symptoms had a positive association with smoking relapse (HR = 1.55) whereas ART adherence had a

negative one [59]. *Wykowski et al.* performed a meta-analysis and found that PLWHA with anxiety had 59% higher odds of suboptimal ART adherence, compared to anxiety-free patients (OR: 1.59,) [67]. HIV-related stigma is another cause of anxiety. *Shrestha et al.* found an indirect relationship between HIV stigma and ART adherence (effect = 20.121) [68]. All of these stressors might contribute to suboptimal ART adherence [65].

4.3 Effects of nicotine on ART efficacy/toxicity

Smokers among PLWHA were reported to have suboptimal virologic suppression compared to non-smokers [69]. Such a phenomenon might result from increased HIV replication and/or decreased anti-retroviral effect from ART drugs [70]. It is well-documented that smoking negatively impacts the metabolism of ART agents [70]. Recently, *Ghura et al.* reported a potential “bidirectional” relationship between nicotine and ART drug metabolism [71]. A mathematical model predicted that smoking might induce the metabolism of antiretroviral drugs by 30% to 70%, which could result in deleterious patient outcomes [72].

Nicotine, the main addictive chemical of tobacco cigarettes, is primarily metabolized through CYP2A6 and CYP2B6 [73] [74]. In addition, long-term exposure to nicotine was reported to decrease the expression of these isoenzymes [75] [76]. As a result, patients who smoke would have different metabolism of ART drugs such as efavirenz and nevirapine which are metabolized through CYP2A6 and/or CYP2B6 [35]. On the other hand, *Zhu et al.* reported that cigarette smoking significantly upregulated the expression of CYP1A1 and 1B1 in an in vitro system. Such induction of CYPs promoted the clearance of dolutegravir [77]. Apart from the CYP superfamily, nicotine was also shown to induce UGT1A1 in a cohort of PLWHA [78]. This could then result in faster clearance rates of abacavir, raltegravir, elvitegravir, and thus result in reduced HIV suppression for smokers [79].

ART drugs have also been reported to modify the metabolism of nicotine, resulting in issues with smoking cessation and toxicity. The nicotine metabolism ratio (NMR) is a biomarker of CYP2A6 and an indicator of the nicotine clearance rate [76]. *Ashare et al.* reported a significantly higher NMR among HIV-infected smokers (0.47) than non-smokers (0.34) [76]. On the other hand, efavirenz, a commonly prescribed NNRTI to HIV patient, was reported to reduce hepatic CYP1A2 and induce CYP2A6 activity [80]. Since nicotine is metabolized through CYP2A6, smokers receiving efavirenz should have a higher NMR and may consume more cigarettes. Indeed, *Schnoll et al.* found that an increased NMR was associated with taking efavirenz ($b = 0.221$, $P = 0.010$) [81]. As a result, smokers may have a faster nicotine clearance rate and might struggle with smoking cessation. Thus, increased cigarette consumption that negatively affects ART drugs’ metabolism is likely to accelerate this vicious cycle.

In addition to tobacco products’ potential influence on isoenzymes, smoking may also increase HIV replication. *Ranjit et al.* investigated the potential effect of benzo(a)pyrene (BaP), a carcinogen in tobacco products, on HIV replication [82]. They observed in vitro that chronic BaP exposure increased HIV-1 replication by >3-fold. Moreover, increased CYP1A1 expression, which is known to metabolize BaP, was also observed. Further, the study suggested that BaP exposure reduces HIV replication via CYP1A1-mediated BaP metabolism, which subsequently induces oxidative stress and NFkB pathway [82]. *Rao et al.*

performed a similar study with cigarette smoke condensate (CSC) also reported that CSC induced CYP1A1 expression and reactive oxygen species (ROS), which resulted in HIV replication [83]. Rao's finding was also validated by *Ande et al.* in an ex vivo study using a 32 subjects. *Ande et al.* reported an increased HIV viral load in HIV positive smokers over that of non-smokers. The study also provided a correlation between increased HIV replication and oxidative stress in which oxidative stress was increased by 2-fold in HIV negative smokers as compared to HIV negative non-smokers [69]. Similar results were also reported by *Pollack et al.* from Vietnam. They reported a 1.5- to 2-fold higher occurrence of HIV viral load among HIV positive smokers who consumed 1–10 cigarettes per day [84]. In summary, tobacco smoking, through both nicotine and polyaromatic hydrocarbons such as BaP alters not only the metabolism and thus efficacy of and toxicity by ART drugs, but also enhance HIV replication via oxidative stress pathway.

5.0 Methamphetamine

5.1 Incidence of methamphetamine use among PLWHA

Methamphetamine (Meth) abuse is a common comorbidity in PLWHA and has previously been associated with a 1.5-fold increased risk of HIV acquisition [85]. In the United States alone, prevalence of meth use among PLWHA was over 9% during 2015–2016 [86]. As per the National HIV Behavioral Surveillance (NHBS) 2017 survey from Seattle, WA; Portland, OR; and Denver, CO which involved 1,602 meth users, particularly men who have sex with men (MSM), and at substantial risk of HIV, reported that meth use most likely was the cause for low oral-preexposure prophylaxis (PrEP) awareness among the risk group[87]. Similar observations were noticed in a longitudinal study of the Swiss HIV Cohort performed during 2007–2017 where use of psychostimulants, including meth, was significantly associated with unsafe sex with frequent partners, and higher prevalence of mood disorders, sexually transmitted infections, and viral infections other than HIV[88]. However, a significant increase in meth (from 0.2 to 2.4%; $P < 0.001$) use among the participants was noticed over time. Similar results were obtained in a cohort study funded by NIH/NIDA, indicating high prevalence of depression among HIV-infected MSM who were also meth users, compared to non-meth users, unemployed, as well as homeless participants[89]. A cross-sectional study performed in Iran highlighted the higher odds of emergence of viral infections, such as HIV and HCV, particularly among the meth users[90]. However, a Thai study reported a declined HIV incidence among people who inject drugs during 2005–2012 in a cohort from Bangkok. The discrepancy of HIV incidence between the countries depend on factors that likely contribute to awareness for PrEP, availability of fast HIV diagnosis and medication, and less use of sharing drug injections[91].

5.2 Effect of methamphetamine on ART adherence

Meth has long been associated with reduced/non-adherence to ART, and a failure of HIV viral suppression in the cerebrospinal fluid (CSF) that may also contribute to increased neuronal damage and cognitive disorders in both humans and in animal studies[92,93]. In previous studies, despite ART adherence, high HIV loads were reported in the plasma and CSF of PLWHA who used meth compared to non-meth users [92,94,95]. Recently, double-blind randomized clinical trial study has shown that FDA-approved antidepressant

mirtazapine reduces meth use in PLWHA. The study also reported lasting benefits of the treatment despite poor medication adherence [96]. PrEP is highly effective for preventing HIV, and is considered as an excellent preventive treatment who for those who are at high risk of acquiring HIV. A qualitative study performed in the United States reported association between poor PrEP adherence and homosexual meth users [97,98]. Meth use has been shown to increase HIV replication in both *in vitro* and *in vivo* studies [99]. However, it has been difficult to correlate direct involvement of meth and rapid progression to AIDS due to non-adherence. In the context of promoting ART adherence among PLWHA who use meth, mobile- texting based interventions are believed to enhance ART adherence and lower the frequency of meth use among drug users[100]. In contrast, Hoenigl et al., investigated the relationship between PrEP adherence and drug abuse including meth and did not find any correlation between PrEP adherence and drug abuse [101]. In a cross -sectional study focused on MSM PLWHA who used meth, Jin H et al., reported that proportion of participants with a homelessness background were associated with low probability of suppressing viral load despite ART adherence. However, estimates of adherence of ART were not accurate[102]. Lower odds of achieving undetectable viral load in HIV-infected drug/meth users were noticed compared to non-users, whereas higher odds of suppressing viral load were correlated with declining drug use over time [103].

Many factors may impact ART adherence among PLWHA who use meth. PLWHA who consumed meth within 30 days showed 50% less prevalence of nonadherence compared to lifetime HIV^+ meth users. Meth use, or potentially decreased adherence was also been associated with neurocognitive impairment including impairments in memory, speech, motor skills, executive and intellectual function, and mental awareness [104]. In contrast, a study with transgender women with HIV, Reback et al., reported that drug use of any type including meth did not impair ART adherence or achieving an undetectable viral load [103].

5.3 Effects of methamphetamine on ART efficacy/toxicity

Meth use by PLWHA was also reported to be associated with faster disease progression, immune dysfunction, neurocognitive impairment, and antiretroviral resistance [99] [105]. Sanchez et al., studied the combined effect of virus, meth, ARV such as zidovudine, nevirapine, saquinavir, and 118-D-24 in vitro and reported neuronal injury due to loss of neuronal dendrites and presynaptic terminals in cerebrocortical cells after 7-day exposure to meth and combinations of ARVs[106]. Meth is metabolized through CYP2D6, by N-dealkylation. Inhibition of CYP2D6 by ritonavir is likely to be associated with enhanced concentrations of the meth derivative MDMA toxicity[107]. Nookala et al., suggested that meth alters the binding of type II protease inhibitors such as ritonavir and indinavir to CYP3A4 in vitro, which lead to decreased metabolism of protease inhibitors, of note ritonavir[108]. Meth exposure to PLWHA receiving ART, particularly saquinavir, ritonavir, and stavudine, has been linked with toxicity and mortality of antiretrovirals or meth [109,110]. However, Jayant et al., reported that co-encapsulation of Nelfinavir and Rimcazole using nanoformulation overcome the effects of drug abuse including use of meth in HIV infection using an in vitro blood brain barrier model [111].

6.0 Cocaine

6.1 Incidence of cocaine use among PLWHA

The incidence and prevalence of cocaine use among PLWHA is typically higher than what has been found in the general population. Results from the Center for AIDS Research Network of Integrated Clinical Systems (CNICS), a prospective cohort of 10,652 PLWHA, found 11% of enrolled participants to have a co-occurring cocaine use disorder as defined by the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) criteria[112] [113]. Additional data from an annual national survey found that, among respondents, approximately 49% of PLWHA had ever used cocaine, compared to 16% of general respondents, with 14% of PLWHA meeting criteria for cocaine dependence, compared to 6% of the general respondents[4].

6.2 Effects of cocaine on ART adherence

Cocaine use among PLWHA has been repeatedly identified to negatively impact both adherence to ART as well as achieving viral suppression. A single-center study based in Vancouver, Canada, found that daily crack cocaine use to adversely impact optimal pharmacy refill adherence in one prospective study [114], while another study based in Boston, MA, found heavy cocaine use to be associated with lower rates of self-reported ART adherence [115]. This finding is consistent for HIV uninfected individuals on pre-exposure prophylaxis (PrEP) as well, with lower rates of adherence among persons using cocaine or stimulants [116] [117]. Not only does cocaine use appear to decrease rates of ART adherence, multiple studies have also shown heavy use to decrease rates of viral suppression, [118] [119], highlighting the public health impact of cocaine use among PLWHA.

The effects from cocaine use on ART adherence appears to be multifactorial. Perceived stigma and mental health disorders have previously been shown to negatively impact HIV care outcomes globally. PLWHA with cocaine use appear to have higher rates of concurrent depression [120]and stigma [121], with individuals experiencing higher degrees of anticipated substance use associated stigma having the poorest ART adherence rates. Although cognitive behavioral therapy for adherence and depression improves rates of adherence and viral suppression for most PLWHA, this unfortunately has not been shown to be the case for PLWHA with cocaine use [122]. This suggests that PLWHA who use cocaine are a particularly vulnerable population and need additional efforts to improve HIV care outcomes.

6.3 Effects of cocaine on ART efficacy/toxicity

The metabolism of cocaine appears to be at least partially mediated by CYP3A enzymes (both CYP3A4 and CYP3A5) [123], with the thought that women might be particularly more sensitive to the effects of cocaine, due to observed higher metabolic rates in women [124]. Many of the NNRTIs and PIs are metabolized by CYP3A4, suggesting a concern for potential cocaine-ART drug interactions through this metabolic pathway. As such, there is concern for toxicity when treating PLWHA with ART regimens containing NNRTIs or PIs [125] [126]. There is also growing interest in chronic inflammation and premature aging among PLWHA. Early data suggests that cocaine use among PLWHA induces telomere

shortening, potentially promoting premature aging in this population [127]. This premature aging, coupled with HIV-associated neurocognitive decline may be of considerable concern in the aging cohort of PLWHA. There is a continued need to examine the effects of cocaine use on both ART efficacy and toxicity among PLWHA.

7.0 Opioids

7.1 Incidence of opioid use among PLWHA

Opioid drug abuse, especially in PLWHA, also involves the nonmedical use of prescribed opiates such as morphine, codeine, hydrocodone or oxymorphone, and illicitly manufactured or distributed substances such as heroin, fentanyl and analogues [128]. A population-based prevalence study revealed that 26.8 million people are currently struggling with opioid use disorder world-wide. Among people who inject drugs (PWID), opioids are the most commonly used and 17.8 % of PWID are estimated to have been exposed to HIV infection world-wide [128] [129]. HIV prevalence among PWID varied across geographical regions. For instance, PWID have higher prevalence of HIV in Eastern Europe and Latin America [129] [130]. It is estimated that people who are either undiagnosed or diagnosed with HIV infection but underestimated in care are responsible for transmission of more than 90% of new HIV infection [131] [132] [133]. A recent study based on accumulated evidences suggested that prescription opioids pose infection risk, including pneumonia, especially in people living with HIV [134]. In addition, prescription opioid such as morphine appears to suppress the immune system in human and animal studies.

7.2 Effects of opioids on ART adherence

People who inject drugs and who also have HIV are less likely to adhere with ART. Azar *et al.,* reported that people injecting opioids were less likely associated with optimal level of ART adherence whereas significant enhancement in adherence of ART was reported after maintaining methadone therapy [3]. A similar finding was reported in longitudinal studies performed in Canada, by Palepu *et al.,* where patients receiving methadone maintenance therapy not only had boosted adherence and CD4 cell counts, but were also associated with suppressed HIV-1 RNA levels [3] [135]. Methadone maintenance therapy was also independently associated with lower likelihoods of opioid dependence [3]. Another longitudinal study conducted on HIV infected women in United States during 2003–2014, by Zhang and colleagues, found similar results using multivariable Poisson generalized estimating equations (GEE) regression that drug use, including opioids, was reported to have been linked with poor adherence to ART [58].

Many PLWHA with SUD have trouble with ART adherence due to use of opioids and other drugs. Anderson et al., reported reduced adherence over time in HIV-infected individuals with a history of drug dependence, including opioids [136]. Similar findings were noticed by Gonzalez A et al., based on a small scale study of 121 HIV-infected people (41 % female; *M* age = 47.00; SD = 7.1) who were also drug users despite being on opioid dependence treatment [137]. They found that medication adherence was highly associated with illicit use of substance such as opiates and cocaine. In addition, the rate of adherence on ART may depend on type or combination of drugs used before or during the treatment. For instance,

Hinkin *et al.*conducted a longitudinal study among 150 HIV-infected people to examine a link between medication adherence and drugs users. In this study they found that PLWHA who use opioids show significantly reduced ART adherence (63%), compared to non-drug users (79%) [138].

7.3 Effects of opioid on ART efficacy/toxicity

The major concern in the treatment for HIV-infected opioid users still remains the drug withdrawal side effects that lead to the occurrence of relapse, to which acute stress, renewed drug administration, treatment failure, viral resistance, and exposure to drug-associated environmental cues are firmly paired [139] [140]. The rate of relapse among people with SUD stands between 72–88% by the end of three years, despite inpatient detoxification [141]. Drug users among PLWHA routinely experience inordinate morbidity and mortality, compared to non-drug users [142]. People who inject drugs were found to be significantly less responsive to ART and viral suppression.

Synthetic opioids are structurally modified to improve the binding affinity of drug to opioid receptors such as μ-, κ-, δ- or N/OFQ-opioid receptors [143]. CYP450 isoenzymes are major enzymes involved in opioid metabolism [144] [145] [146] [147]. To a lesser extent, UDP-glucuronosyltransferases(UGTs) metabolize morphine, hydromorphone, and oxymorphone [148].Finally, UGTs are also responsible for the formation of glucuronides that are believed to be the end product of the drug metabolism [149]. Semisynthetic opioids, such as oxycodone and hydrocodone are metabolized by CYP2D6 to hydromorphone, which shows more than a 5-fold higher opioid activity than the hydromorphone. CYP3A4 is also found to be involved in the clearance of hydrocodone. In a study supported by randomized controlled trials, ART drugs such as ritonavir and lopinavir/ritonavir effectively inhibited the CYP3A-mediated N-demethylation of oxycodone, and thus increased the effects of oxycodone by 3-fold.To avoid the opioid-related adverse effects, oxycodone doses need to be regulated, especially when oxycodone is being used in clinics during anti-retroviral treatment [150]. On the other side, ritonavir decreases the effects of hydrocodone, resulting in symptoms of opioid withdrawal in human subjects [151] [152]. Fentanyl, a synthetic opioid, is metabolized by the CYP3A4 into inactive metabolites such as norfentanyl, hydroxyfentanyl and hydroxynorfentanyl. Ritovavir was shown in human trials to inhibit the metabolism of fentanyl, thereby reducing the fentanyl clearance by 67%, thus requiring precautions if using fentanyl during ritonavir treatment [150].

The possibility of resumption of drug use is common among PLWHA with SUD, which highlights the need for opioid maintenance therapy. US FDA-approved therapies for opioid maintenance include methadone and buprenorphine which can be given to HIV-infected drug users to treat opioid dependence. Gruber et al., conducted study on opioid-dependent HIV-negative people to examine drug interactions between buprenorphine and ART drug darunavir-ritonavir and fosamprenavir-ritonavir. The study showed no clinically significant pharmacokinetic or pharmacodynamic interactions between buprenorphine and used ART drugs, although there may be interactions with newer antireetrovirals since this article was originally published [151]. In contrast, darunavir and ritonavir decrease methadone levels in the plasma, causing withdrawal symptoms [151]. Other than CYP3A4, which is involved in

the metabolism of methadone and buprenorphine, CYP enzymes such as 2B6, CYP2C19, CYP2C9, and CYP2D67 also play a role in the metabolism of methadone, and 2C8 in the metabolism of buprenorphine [153] [154] [155].

The CYP3A4 inhibitors, ritonavir, nelfinavir, and nevirapine, were shown to reduce the plasma level of methadone, possibly due to involvement of CYP enzymes other than CYP3A4 [156] [153]. Heroin (diacetylmorphine) is metabolized by plasma and liver esterases to morphine, which is further metabolized by glucuronidation. High doses of ritonavir and nelfinavir resulted in faster glucuronidation of heroin. Although ARVs are also metabolized by glucuronidation, no known effects in combination with ARVs and heroin have been reported [157]. A recent study by Rodriguez et al., investigated the effect of opioid exposure on ART drugs in HIV-infected primary human astrocytes [158]. Similar to other findings, they found that emtricitabine, ritonavir, and atazanavir regimens reduced not only viral replication, but also suppressed HIV-mediated inflammatory response. The study also assessed the effect of morphine on ART related drugs in which morphine treatment neutralized the potential effects of this regimen. These effects are emerged due to loss of mitochondrial integrity and epigenetic changes [159].

8.0 Marijuana

8.1 Incidence of marijuana use amont PLWHA

Marijuana use is significantly higher among PLWHA than comparative individuals without HIV/AIDS. Based off 2005–2014 data from the National Survey on Drug Use and Health, approximately 77% of PLWHA reported lifetime marijuana use compared to 44.5% of HIV-uninfected participants[4]. The timing of illegal drug use was significantly more recent among individuals with HIV; 36% of respondents with HIV reported using any illegal drug in the past month compared to only 8.6% of the respondents without HIV/AIDS ($p<0.0001$) [4]. The percentage of males with HIV/AIDS who smoke marijuana daily has been on the rise since 1984 [160]. Marijuana use among PLWHA remained consistently higher after adjusting for demographic factors including age, sex, race/ethnicity, education, total family income (=$75,000), and marital status [4]. Data from Europe also showed higher marijuana use among PLWHA, however, the incidence of use varied from country to country [161] [162]. It is important to note that the legality of marijuana in each country is expected to affect the incidence of use, and that use in the U.S.A. will likely increase due to increasing numbers of states legalizing or decriminalizing use.

8.2 Effects on of marijuana on ART Adherence

Marijuana is conventionally accepted as having a negative impact on medication adherence. Marijuana is widely known to negatively affect memory and cognitive function, which can present a challenge for patients on complicated medication regimens. A major consideration during HIV treatment is whether a patient should take a single table regimen (STR) or a multiple tablet regimen (MTR). Both have benefits, however, STR show higher rates of adherence overall [2]. Marijuana has been shown in a longitudinal studies to negatively affect the adherence of patients to HIV treatment, particularly with STR[58]. Most literature does not evaluate if failure to adhere stems solely from the use of marijuana. Failure to

adhere may potentially result from common co-conditions, such as alcohol use and/or depressive symptoms. Marijuana's effect on adherence also seems to vary across studies when adjusting for a variety of demographics such as age and sex [4]. The frequency of marijuana use was an important consideration when evaluating medication adherence.

8.3 Effects of marijuana on ART efficacy/toxicity

Marijuana is the most commonly used illicit drug of abuse worldwide, which can cause significant efficacy and toxicity problems when combined with ART. Marijuana is an inducer of CYP 1A2 through aromatic hydrocarbon receptor activation [163]. In addition, limited data in human subjects suggest that delta-9-tetrahydrocannabinol (delta-9 THC) and cannabidiol (CBD) metabolism involves CYP3A4 and CYP2C19 enzymes[164]. These two enzymes are involved in the metabolism of multiple key ART medications, such as the non-nucleotide reverse transcriptase inhibitors (NNRTIs) and protease inhibitors, including darunavir. A combination of a CYP enzyme inhibitor and a CYP enzyme substrate could lead to much higher ART concentrations in the body than anticipated. This could lead to increased renal/hepatic demand as well as an increase in adverse drug reactions and potentially toxic results.

Marijuana use is also important to consider with ART involving pharmacoenhancers. Pharmacoenhancers, such as ritonavir and cobicistat, are medications specifically prescribed to cause a controlled drug interaction, boosting the length of time a desired ART medication is at a therapeutic level in the body by inhibiting the ART medication's metabolism[165]. These pharmacoenhancers are relied on in certain regimens to ensure ART efficacy. Because pharmacoenhancers' major role is causing drug interactions, they have a multitude of CYP enzymes that they interact with, and they could have their concentration driven up (potentially causing toxicity) or down (potentially decreasing efficacy) through concurrent marijuana use.

Additional literature has shown that marijuana was been reported to lower plasma concentrations of common ART medications, such as indinavir and nelfinavir, through an undefined mechanism Evidence suggests that the lowered plasma concentration could result from decreased intestinal absorption[164]. Many ART medications have bioavailability limitations that depend on consistent intestinal absorption. Irregular absorption can cause the ART concentration to fall below the therapeutic levels needed to maintain optimal viral suppression and prevent disease progression. The potential of marijuana use on intestinal absorption is also an important area of future study because absorption may depend on the frequency and/or level of abuse. Once this mechanism is fully defined, it may be an important factor to consider when designing dose regimens to ensure efficacy.

9.0 Conclusion

While care for PLWHA has dramatically improved over the years, for many individuals disparities in care still exist. In PLWHA who use drugs of abuse, both licit and illicit, disparities in outcomes exist for a variety of reasons. PLWHA are more likely than non-infected individuals to have substance use disorders. Drug-drug interactions due to induction

of metabolic enzyme or transporters, which can result in subtherapeutic concentrations of these drugs. This can lead to worsened outcomes in PLWHA.

10.0 Expert opinion

As previously discussed, PLWHA who have substance abuse disorders are at a higher rate of detrimental health outcomes than non-infected individuals. A key cause for this is due to the fact that there are multiple drug drug interactions that occur between ART medications and the substance the person might be taking. For instance, marijuana is a commonly used illicit drug among PLWHA and is an inducer of CYP 1A2 [163]. This is one such enzyme that is also involved in the metabolism of ART medications. The combination of a patient taking both an inducer and an inhibitor at the same time can cause serious drug toxicities, such as high levels of ART medications building up in the body. This, in turn, can lead to other issues along the line such as renal/hepatic failure and overall increase morbidity and mortality.

Alcohol use disorders are also common among PLWHA. The effects of the consumption of alcohol include decreased adherence to ART as well as drug toxicities. The enzyme that is involved in the metabolism of alcohol is CYP2E1 [35]. Consuming alcohol while taking ART has shown to cause lower efficacy of the regimen as well as increase morbidity and mortality down the line. As a result, it is imperative to discuss with the patient in depth as to whether they consume alcohol as well as the quantity and rate of consumption. Having this information on hand could help the clinician make a better decision on which ART regimen to start the patient on or even modify if there is evidence of treatment failure. Overall, the screening for alcohol usage among PLWHA is critical to improve ART effectiveness as well as health outcomes of these patients.

The combination of drug drug interactions between drugs of abuse and antiretrovirals, and drug related decreases in adherence also provides a significant concern. If antiretrovirals are taken less often than they should be, coupled with interactions resulting in lower concentrations of antiretrovirals when they are taken, there is the potential that drug concentrations may be insufficient to prevent HIV-1 replication in these individuals.

Because of the high rates of substance abuse among PLWHA, it is imperative to have a good relationship with these patients. This needs to occur so initial screening can take place prior to initiating ART. The screening for potential use of substances can take place in many different forms, such as a urinalysis or even a simple medication history discussion with the patient. There are pros and cons to each method that can include rate of turnaround time, false negatives, and even reliability. The underlying key to any method utilized for screening is to establish a sense of trust between the clinician and patient.

As new laws begin to emerge, one such thing to keep in mind is that some states might allow the legalization of marijuana. Increased access to marijuana may result in decreased effectiveness of ART among these patients. This would call for an increase in the need to understand the drug-drug interactions between ART and marijuana. There are many different types of ART available and PLWHA are not limited to only one therapy. Therefore, time and

effort are necessary to fully understand the drug interactions that can occur with each specific ART medication. It would also be useful to determine what substances of abuse PLWHA are using so therapy can be tailored to minimize interactions as well. Overall, this knowledge would help guide personalized therapy for PLWHA who also have a substance use disorder.

There is an underlying need for therapeutic measures both for substance use disorders as well as people with substance use disorder that are not willing to stop using drugs of abuse. This can include novel therapeutics or tailoring therapeutic measures to minimize drug-drug interactions. For example, during a medication history review, a clinician can identify a patient that is unable or unwilling to stop using a particular drug of abuse and use resources to determine which antiretrovirals might be the best therapeutic decision for that particular person. This may also include linking patients to non-pharmacologic interventions for stopping the use of drugs of abuse. Obtaining the help of a mental health therapist for these patients is one such example. The underlying key again is to be able to screen patients early on before they begin ART therapy, if feasible.

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Article highlights:

- People living with HIV/AIDS are more likely to use substances of abuse than non-infected individuals
- PLWHA with substance use disorders have worsened outcomes compared to PLWHA who do not use drugs of abuse
- The reasons for this are multifactorial, and include decreased adherence, modulation of drug efflux transporters, and modulation of metabolic enzymes.
- Modulations of efflux transporters and metabolic enzymes can result in altered concentrations and efficacy of antiretrovirals for the treatment of HIV-1.

Table 1.

Drugs of abuse and CYP enzymes of concern

Drug of Abuse	CYP enzyme of concern
Alcohol	2E1, 3A4
Nicotine/Smoking	2A6, 2B6
Methamphetamine	2D6
Cocaine	3A4, 3A5
Opioids	3A4, 2D6, 2B6, 2C19, 2C9
Marijuana	1A2, 3A4, 2C19