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Drug–drug interactions between anti-retroviral therapies and drugs of abuse in HIV systems

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Abstract

Introduction—Substance abuse is a common problem among HIV-infected individuals. Importantly, addictions as well as moderate use of alcohol, smoking, or other illicit drugs have been identified as major reasons for non-adherence to antiretroviral therapy (ART) among HIV patients. The literature also suggests a decrease in the response to ART among HIV patients who use these substances, leading to failure to achieve optimal virological response and increased disease progression.

Areas covered—This review discusses the challenges with adherence to ART as well as observed drug interactions and known toxicities with major drugs of abuse, such as alcohol, smoking, methamphetamine, cocaine, marijuana, and opioids. The lack of adherence and drug interactions potentially lead to decreased efficacy of ART drugs and increased ART, and drugs of abuse-mediated toxicity. As CYP is the common pathway in metabolizing both ART and drugs of abuse, we discuss the possible involvement of CYP pathways in such drug interactions.

Expert opinion—We acknowledge that further studies focusing on common metabolic pathways involving CYP and advance research in this area would help to potentially develop novel/alternate interventions and drug dose/regimen adjustments to improve medication outcomes in HIV patients who consume drugs of abuse.

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Keywords

antiretroviral therapy; CYP; drug interactions; drugs of abuse; HIV

1. Introduction

In USA, ∼ 1.1 million people (∼ 4% of the global HIV-infected population) are infected with HIV (UNAIDS 2013). There has been a steady rate of incidence of HIV infections in USA with ∼ 50,000 new cases per year (UNAIDS 2013). As per center for disease control and prevention (CDC) guidelines for HIV care, in USA, ∼ 20% of HIV-infected patients remain unaware of their infection, and many present opportunistic infections as a primary indicator of the disease. The decline in AIDS-related death since 2005, and increase in lifespan of HIV-infected individuals, has been attributed to the successful clinical intervention employing antiretroviral therapy (ART) for HIV patients. As HIV-infected patients live longer, they are vulnerable to neuroAIDS and have higher prevalence of neuropsychological and neurobehavioral impairments [1]. This has caused an increase in the prevalence of drugs of abuse behavior. National Survey on Drug Use and Health data collected from 2005 to 2009 revealed that about one in every six individuals with HIV/AIDS has used an intravenous illicit drug in their lifetime [2]. Nearly two-thirds of the surveyed HIV-infected population have used a non-intravenous illicit drug. Moreover, ∼ 24% of the HIV-infected individuals were in need of treatment for alcoholism or other substance abuse.

Alcohol use is a common feature among HIV-infected individuals [3,4]. The prevalence of mild-to-moderate drinking is ∼ 2.5-times higher in HIV-infected population (50 – 60%) compared to general population (20 – 25%). The occurrence of heavy drinking among HIV-infected individuals has also been reported to be almost twice as compared to the general population [5]. Smoking/nicotine dependence, on the other hand, has also been recognized as a common occurrence among HIV-infected individuals with prevalence rates reported > 40% in most studies compared to ∼ 15% in general population [6-8]. From a global perspective, a significant number of HIV patients have been identified as smokers/nicotine dependent in various parts of the world [9-11]. In these studies, > 47% of participants reported to be current smokers. In addition, prevalence of smoking was found to be higher in males compared to females across these studies. Furthermore, illicit drug methamphetamine is the second most commonly abused psychostimulant worldwide and methamphetamine dependence has been identified as a common occurrence among HIV-infected individuals [12]. Similarly, cocaine use through smoking, intranasal, and injection routes has been prevalent in HIV-infected individuals for the past two decades. Data collected in early 1990s showed higher percentage of HIV occurrence amongst crack cocaine users compared to non-smokers [13]. Interview of > 1000 HIV-positive inpatients from public hospitals reported 34% crack cocaine users amongst this group [14]. High prevalence of marijuana use has also been reported among HIV-positive patients [15,16]. Finally, based on data from a cohort study in veterans, a small but significantly higher probability of opioid prescription for pain management in HIV-infected individuals, compared to non-infected individuals, has been reported [17]. In different studies evaluating prevalence of aberrant opioid usage amongst

veterans and homeless individuals with HIV infection, 13 and 37% of surveyed individuals, respectively, reported a history of opioid abuse [18,19].

Given the high prevalence of drug addiction in HIV-infected population, it is imperative to understand the effect of drugs of abuse on HIV medication. Several studies have found a strong correlation between substance abuse and non-adherence to ART in HIV patients, thereby limiting the potential benefits of ART [20,21]. In a report studying HIV-infected injection drug users on ART, lack of adherence to medication resulted in lower rates of virological suppression creating potential for an enhanced disease progression [22]. Furthermore, non-adherence to ART has been directly implicated in impaired virological responses to ART in HIV-infected patients [23]. Another study, conducted by Giordano *et al*., found inconsistent HIV clinic follow-up visits after initiation of ART as a result of injection drug use amongst HIV patients [24].

The use of these drugs, especially alcohol, tobacco, and methamphetamine, has also been shown to attribute towards lower responses to ART medication in HIV-positive patients [25]. We propose a possible involvement of CYP pathways in drugs of abuse-mediated decreased response to ART and increased toxicity, which may subsequently lead to exacerbated HIV pathogenesis and AIDS and neuroAIDS development and progression (Figure 1). CYP isozymes metabolize majority of marketed drugs including ART drugs, especially non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitor (INIs), as well as all the drugs of abuse [26,27]. The CYP-mediated common metabolic pathways might lead to potential drug–drug interactions in HIV-positive drug users who are on ART [28,29]. Recently, we have reviewed the possibility of CYP-mediated drug–drug interactions in HIV-infected substance users who are on newer classes of antiretroviral medication, including INIs and CCR5 antagonists [30]. Table 1 provides specific CYP isozymes that are known to interact with various drugs of abuse and ART drugs through metabolism, induction, and inhibition, as well as possible clinical outcomes. In this review, first we briefly discuss drug interactions among ART followed by HIV/ART interactions with drugs of abuse with respect to adherence, response, and toxicity to ART and drugs of abuse. We also discuss our opinion with regard to potential advancement in this field, which would ultimately help improve the treatment strategy of HIV-infected patients who abuse these drugs.

2. ART: pharmacokinetics and drug interactions

Since introduction in 1990s, ART has markedly improved the clinical management of HIV infection. Current antiretroviral drugs are classified into several groups based on their mode of action at various stages of HIV life cycle. Combination therapy, prescribed to HIV-infected patients, often includes drugs from different categories such as nucleoside/nucleotide reverse transcriptase inhibitors, NNRTIs, PIs, INIs, and CCR5 antagonists. Although combination therapy has improved the management of HIV and decreased progression to AIDS, it has heightened the possibility for drug–drug interactions. The two key mechanisms, which mediate most of these adverse interactions, are membrane transporters and CYPs.

2.1 ART and cell membrane transporters

Transporter proteins expressed on cell membranes are critical in facilitating the transport of substances across the cellular membrane. Although both influx and efflux roles of such transporters is required for maintaining cellular homeostasis, the effect of transporter proteins on cellular bioavailability of drug and its active metabolite is known to dictate clinical outcomes [31]. Efflux transporters such as p-glycoprotein (P-gp), multidrug resistance-associated proteins, and breast cancer resistance protein have shown to significantly affect the bioavailability of several drug molecules, including antiretroviral drugs [29].

Importantly, drugs comprising the ART regimens are not only substrates for efflux transporters but these drugs also induce or inhibit efflux transporters resulting into potential drug–drug interactions. Although inhibition of efflux proteins by antiretroviral drugs can be expected to increase the intracellular bioavailability and efficacy of ART, it can lead to adverse effects and toxicity. On the other hand, induction of efflux transporters by antiretroviral drugs can result in the sub-optimal plasma level of these drugs resulting in decreased efficacy in HIV patients.

PIs darunavir and saquinavir, for example, are known to induce the expression of P-gp and thereby reduce the bioavailability of other antiretroviral drugs prescribed as part of combination therapy [32]. On the other hand, PIs including nelfinavir, ritonavir, and nevirapine have been shown to increase the accumulation of the INI drug raltegravir possibly through a P-gp-dependent mechanism [33]. Similarly, whereas absorption and bioavailability of atazanavir are significantly reduced by tenofovir disoproxil fumarate, efflux transport of atazanavir is reported to be reduced in the presence of ritonavir [34]. Overall, based on the net effect of different antiretroviral drugs on expression and activity of efflux transporters, there is a significant chance of precipitating drug–drug interactions. Therefore, stringent clinical evaluation of newer ART and regular patient monitoring is essential to achieved desired efficacy in HIV-positive patients.

2.2 ART and CYPs

Hepatic metabolism involving CYP enzymes is the primary metabolic pathway for majority of ART drugs. Of which, CYP3A4 is the major enzyme, which metabolizes all NNRTIs and PIs, and some INIs and CCR5 antagonists. In addition, whereas several NNRTIs are CYP inducers, all PIs are known CYP inhibitors. CYP inducers enhance the rate of metabolism and decrease the bioavailability of ART, whereas CYP inhibitors enhance the bioavailability of other ART drugs leading to increased efficacy [35]. Based on this rationale, ritonavir (PI), a strong inhibitor of CYP3A4, has been a prominent part of combination therapy and widely prescribed as a booster for ART. This is the first example of positive or appropriate drug–drug interaction for the enhanced therapeutic effect in HIV-infected individuals. Similarly, cobicistat, a novel non-ART selective inhibitor of CYP3A4, has also been used for boosting plasma levels of ART drugs, including elvitegravir [36], thereby providing an alternative option for ritonavir-intolerant patients.

Although ritonavir and cobicistat boosting is associated with enhanced efficacy of other ART drugs, inhibition of CYP3A4 also increases the possibilities of inappropriate or negative drug–drug interactions leading to toxicities in HIV-infected patients [37]. This could occur as a result of increased plasma levels of other drugs such as NNRTIs or PIs, which are cytotoxic at high concentrations. Drug–drug interactions associated with approaches involving ritonavir boosting or CYP3A4 inhibition have been reviewed previously, which recommends the need for close clinical monitoring in HIV patients [38]. However, being a new drug in the ART regimen, the negative drug–drug interactions involving cobicistat-mediated CYP3A4 inhibition have not been studied yet.

Overall, the presence of multiple drugs in ART regimens, especially NNRTIs, PIs, and INIs, enhances the risk of drug– drug interactions and drug toxicity. Although involvement of common metabolic pathways comprising of CYP enzymes is one possible mechanism for such interactions, changes in expression of drug efflux transporters such as P-gp can further complicate ART for HIV-infected patients. Interactions involving multiple pathways and multiple drugs further complicate the risk of serious adverse effects in HIV-infected patients who are on ART.

3. Alcohol-ART interactions

3.1 ART adherence in alcohol users

Alcohol drinking, especially heavy drinking, is known to affect medication adherence in HIV-infected patients [39]. The CDC defines heavy drinking as 15 drinks or more per week for males and 8 drinks or more per week for females. It has been reported that patients with alcohol drinking problem are more likely to take medicine off schedule or skip dosing [40]. In separate studies, alcohol consumption has been attributed to the lack of adherence to HIV medication [41]. Therefore, several studies have emphasized the need for suitable interventions to limit alcohol use while on ART [42,43]. However, there is limited success in this area, especially with HIV-infected heavy drinkers. In addition, although heavy alcohol users, compared to non-drinkers, are four times less likely to observe positive responses to ART, there is no change in drug regimen for heavy drinkers [44]. Thus, there is an urgent need to study the impact of alcohol use on HIV population to help customize the ART regimen for drinkers.

3.2 Effect of alcohol on ART efficacy and toxicity

Heavy and light alcohol consumption, in patients on ART medication, is marked by an increased viral burden compared to non-drinking patients [45]. In addition, patients consuming heavy amounts of alcohol while on ART medication are four times less likely to achieve a positive impact on viral load. Moreover, heavy alcohol drinkers on ART are two times more likely to have their CD4 counts < 500/mm^3 than non-drinkers. Similarly, previous finding has reported increased replication of SIV in macaques following chronic ethanol consumption [46]. An increased viral load and decreased CD4 counts in HIV-infected drinkers, who are not on ART, are likely to be a direct effect of oxidative stress through CYP2E1, which has been linked to viral replication. Recently, literatures have been reviewed on examining the effect of ethanol consumption on ART and HIV progression

[47]. Alcohol metabolism is mainly regulated by CYP2E1, which is highly induced in chronic alcohol users [47-50]. Consistent with this, it has been earlier shown that ethanol induces CYP2E1, which in-turns metabolizes ethanol and produces oxidative stress and toxicity, in monocytes/macrophages and astrocytes [49,51]. However, HIV-infected drinkers, who are on ART and show decreased response to ART and increased toxicity, are likely to be through the CYP3A4 pathway as it's mainly responsible for metabolism of ART drugs [52].

A significantly higher variability in activity of hepatic CYP3A4 has been documented in HIV patients compared to control subjects suggesting a wider range of inherent drug metabolizing capacity amongst patients [53]. CYP3A4 is responsible for metabolizing all the NNRTIs and PIs, which are integral part of ART regimens [27]. In addition, NNRTIs and PIs are also known to induce the CYP3A4 protein level as well as inhibit the CYP3A4 enzyme suggesting drug–drug interactions [28]. Furthermore, chronic ethanol consumption has been shown to induce the CYP3A4 level, which may increase drug metabolism, subsequently decreasing drug efficacy and increasing drug toxicity [51,52,54]. Based on the effects of alcohol on the activity of CYP enzymes, an alteration in metabolism of ART in alcohol-dependent HIV-infected individuals has been predicted [52]. For example, chronic ethanol consumption by HIV-infected individuals has been shown to significantly affect the therapeutic steady-state plasma drug concentrations of HIV treatments including stavudine, lamivudine, and nevirapine [55]. Similarly, it has been demonstrated that ethanol interacts differentially with CYP3A4 in the presence of different types of PIs (type I: atazanavir, lopinavir, saquinavir, and tipranavir or type II PIs: indinavir and ritonavir), leading to differential effects on the IC_{50} or binding affinity of these PIs [56,57]. Type I binding occurs as a result of non-covalent binding between ligand and heme of the enzyme whereas type II binding occurs when a ligand containing strong nucleophile covalently binds to the heme of the enzyme [55]. In both the cases, they replace water molecule, which is bound to the heme of the enzyme as the sixth ligand. The altered CYP3A4 binding and inhibition of CYP3A4 activity with these PIs by ethanol may have implications on their metabolism and efficacy in HIV-infected alcohol users. In fact, the *in vitro* study has shown that 20 mM (physiological concentration) of ethanol significantly decreases the metabolism of nelfinavir by recombinant CYP3A4. Further studies with other PIs and NNRTIs are underway to examine the effects of alcohol on the metabolism and bioavailability of NNRTIs and PIs. Furthermore, there is an urgent need to examine the effects of alcohol on differential response to ART, which would help develop potentially novel interventions and apply drug–dose adjustments for HIV-infected drinkers.

4. Smoking/tobacco-ART interactions

4.1 ART adherence in smoking/tobacco users

Smoking in female HIV patients has been associated with a lower adherence to ART [58]. In another study, smoking has been identified as a critical independent predictor of non-adherence to ART in HIV-infected patients [59]. Compared to patients identified as non-smokers, smoking-associated increased levels of depression have been implicated with non-adherence to ART who continued smoking [60]. A recent study, while exploring the extent

of non-adherence to ART in HIV-infected smokers, found the extent of nicotine dependence to serve as a better predictor for non-adherence to ART [61]. This study revealed that higher levels of nicotine dependence was associated with greater extent of non-adherence to ART compared to the lower level of nicotine dependence in HIV-positive individuals.

4.2 Effect of smoking/tobacco on ART efficacy and toxicity

Literatures have been previously reviewed on the effects of tobacco use on HIV pathogenesis [62]. In brief, tobacco smoking as well as nicotine alone has shown to increase viral replication in *in vitro* systems in various cell types, such as monocytes, astrocytes, and T cells. In addition, exposure to nicotine and other cigarette constituents has been shown to induce oxidative stress, disrupt the blood–brain barrier (BBB), and result in progression of disease among HIV-infected patients. Overall, significantly higher mortality rates have been observed in HIV patients who smoke compared to non-smoking HIV-positive individuals.

Nicotine, the major constituent of tobacco smoking, is primarily metabolized by CYP2A6 (liver) and CYP2A13 (lungs) to cotinine and other minor metabolites and produce oxidative stress as well as reactive metabolites such as nitrogen-derived nitrosamine ketone [63,64]. Similarly, CYP1A1-mediated metabolism of polycyclic aromatic hydrocarbons (PAHs) is known to produce oxidative stress and reactive metabolites [65]. PAH metabolites-derived DNA adducts have been shown to stimulate HIV replication [66]. Feldman *et al*. have reported a direct association of CYP1A1 with a reduced responsiveness of ART in female smokers with HIV infection thereby implicating CYP pathways for the ineffectiveness of ART in smokers [67]. In addition, reports have shown that nicotine metabolism is relatively faster in women than men suggesting altered smoking-mediated effects in women compared with men [68]. However, the mechanism by which smoking/nicotine may reduce efficacy of ART and increase viral load is unknown. A recent finding demonstrates an increased nicotine metabolism in HIV-positive patients compared to HIV-negative individuals [69]. This finding concurrent with our recent unpublished observations, in which viral load is increased in HIV smokers than HIV nonsmokers, suggests the involvement of CYP pathway in increased viral load in HIV smokers. Similarly, an induced CYP3A4 level in HIV smokers compared with HIV nonsmokers (unpublished observation) further suggests involvement of CYP pathway in decreased efficacy of ART. These results, along with previous reports on involvement of oxidative stress in HIV disease [70,71], warrant further investigations concerning the effect of CYP pathway on metabolism of ART in HIV-positive smokers. Further studies examining contribution of CYP pathways on increased HIV-1 pathogenesis, via increased HIV-1 replication and decreased response to ART, have potential in developing a better treatment strategy for HIV-infected smokers.

5. Methamphetamine-ART interactions

5.1 ART adherence in methamphetamine users

Methamphetamine abuse in men, who have sex with men (MSM), heterosexual, and women, is associated with the increased rate of HIV infection and decreased adherence to ART drugs [72]. In particular, in an interview conducted with > 1100 HIV-positive inpatients, the prevalence of methamphetamine use and concurrent non-adherence to ART drugs was found

to be higher among HIV-infected MSM than non-MSM [73]. Importantly, as opposed to having an aggregate effect, methamphetamine was found to exhibit the day-specific effect of ART adherence [74]. Days of methamphetamine use were specifically marked by significantly higher odds of non-adherence for ART. Methamphetamine interventions often target substance use behaviors to enhance ART treatment outcomes. However, interventions may also need to address coexisting neuropsychiatric factors and cognitive impairment to improve ART medication adherence [75]. Recently, implementation of personalized interventions, including strategies such as creating focus groups and providing text reminders, has shown promising results towards improvement of ART adherence in HIV-infected methamphetamine abusers [76,77].

5.2 Effect of methamphetamine on ART efficacy and toxicity

Methamphetamine has been shown to cause peripheral toxicity as well as neurotoxicity in HIV-infected as well as uninfected population [78]. However, methamphetamine toxicity in HIV-infected individuals is further increased compared to un-infected individuals [79]. Importantly, active methamphetamine use is associated with increased viral loads and reduced ART efficacy [12]. Several pathways may contribute toward methamphetamine-mediated toxicity in the brain. For example, methamphetamine may bind to dopamine receptors and alters the levels of dopamine causing increased oxidative stress. A recent review has recently been published on this, in which, in addition to known mechanism, other mechanisms including CYP-mediated pathways have been proposed [80]. However, the mechanism by which methamphetamine further exacerbates neurotoxicity in HIV-infected patients, especially who are on ART, is not known. There is no population-based report or *in vitro* findings that suggest a decrease in response of ART in HIV-infected methamphetamine users. However, due to the involvement of CYP pathways in methamphetamine metabolism, it is worth studying the impact of methamphetamine on ART medication.

Methamphetamine is metabolized by CYP2D6 and to some extent by CYP3A4, and forms mainly amphetamine and 4-hydroxymethamphetamine in humans. Amphetamine is further metabolized to 4-hydroxymethamphetamine and norephedrine [81]. Methamphetamine-mediated metabolism is likely to increase oxidative stress that may ultimately cause toxicity [82]. As methamphetamine is also metabolized by CYP3A4, it is possible that methamphetamine induces CYP3A4, which would increase the metabolism of NNRTIs and PIs causing a decrease in response to ART drugs. Similarly, methamphetamine may also interact with CYP3A4 and compete with CYP3A4-ARTs interactions leading to a three-way methamphetamine-ART-CYP3A4 interaction. These interactions may ultimately lead to altered metabolism of ART drugs. In unpublished observations, we have shown that methamphetamine alters the binding of PIs in differential manner. For example, it increases the binding of type II PIs, ritonavir, whereas it decreases/has no effects on the binding of other PIs suggesting that methamphetamine is likely to alter the metabolism of PIs in differential manner. The need for relevant clinical evaluation of methamphetamine-induced drug–drug interactions with ART is strengthened by recent report of enhanced methamphetamine metabolism in the non-human animal model of Rhesus Macaque [83]. Hence, further studies are essential to examine the role of methamphetamine on the

metabolism and efficacy of ART drugs, especially PIs, which would ultimately help develop a better treatment strategy for HIV-infected methamphetamine users.

6. Cocaine-ART interactions

6.1 ART adherence in cocaine users

Results from MACH14 cohort, studying effects of individual drugs of abuse on ART adherence, demonstrated ∼ 11% of HIV patients are recent cocaine users [84]. A multi-center study assessing drug use among > 1100 HIV-infected jail inmates, 30 days prior to incarceration, revealed 53% individuals using cocaine [85]. Moreover, compared to other drugs of abuse, the prevalence of cocaine use was found to be highest among these HIV-infected inmates prior to incarceration.

Cocaine use amongst HIV-infected individuals has been directly linked to non-adherence to ART in various studies. Based on an electronically monitored adherence study of ART in HIV-infected individuals, active cocaine usage was associated with 41% decline in adherence to ART [86]. Continued cocaine use was attributed to decline in adherence to antiretroviral medications from 68% in non-users to 27% in active users over a period of 6-month. Similarly, a study focusing on HIV-infected black women reported lack of adherence to ART in crack cocaine users compared to non-users [87]. Results from a pilot study have suggested that counseling and video intervention lead to improved adherence to ART amongst crack cocaine users [88].

6.2 Effect of cocaine on ART efficacy and toxicity

CYP3A enzymes (CYP3A4 and CYP3A5) are partly responsible for the metabolism of cocaine [89]. In addition, reports have shown that responses to cocaine are higher in women than men, possibly due to higher metabolic rates in women [90,91]. As most NNRTIs and PIs are metabolized by CYP3A4, there is a possibility of potential cocaine–ART interactions through the CYP pathway in HIV-infected patients. Induction or inhibition of CYP3A4 by ART in HIV-patients might lead to altered metabolism of cocaine. As the metabolite of cocaine, norcocaine, is considered hepatotoxic, an altered metabolism of cocaine by antiretroviral drugs would result in severe hepatotoxicity. Overall, treating HIV-infected cocaine users with PI and/or NNRTIs in the ART regimen may result in adverse drug–drug interaction and toxicity through the CYP3A pathway [92,93]. Therefore, there is a need to examine the effects of cocaine on differential response to ART and ART-mediated toxicity, so that potentially novel interventions and/or drug dose adjustments can be developed for HIV-infected cocaine users.

7. Opioids-ART interactions

7.1 ART adherence in opioid users

Similar to other drugs of abuse, opioid misuse has been linked to decreased adherence to ART in HIV-infected individuals [94]. In this study, whereas more than half the study population reported taking prescribed opioid analgesic in the past 90 days, one-fifth of these opioid users reported opioid analgesic abuse. Importantly, treatment of opioid dependence

with opioid substitution therapy, by prescribing methadone or buprenorphine, was found to improve adherence to ART [95].

7.2 Effect of opioids on ART efficacy and toxicity

Drug interactions, as a result of altered levels of metabolic enzymes, have been reported with concomitant administration of opioids and ART [96]. NNRTIs are known to decrease the bioavailability of methadone thereby precipitating withdrawal like symptoms [97,98]. Similarly, inhibition of CYP3A4 following treatment with PIs can lead to increased oxycodone levels and toxicity [99]. Drug–drug interactions following administration of several ART drugs, in opioid users, have been reviewed previously [29]. Methadone is primarily metabolized by CYP3A4, CYP2B6, and CYP2D6, which may lead to potential methadone–ART interactions because most NNRTIs and PIs are metabolized by CYP3A4 and some NNRTIs are metabolized by CYP2B6 [100]. These drug–drug interactions may occur either as a result of induction of CYP enzymes by methadone or by inhibition of CYP3A4 by methadone. Similarly, as CYP2D6 is highly polymorphic enzymes in human, the half-life of methadone vary from 4 h (in rapid CYP2D6-metabolizing variants) to as long as 130 h (in slow/no CYP2D6-metabolizing variants) in humans [101]. This would cause varied degree of drug–drug interactions in different individuals. Similarly, oxycodone is metabolized by CYP enzymes in the liver, making it vulnerable to drug interactions [102]. Similar to methadone, some people are fast metabolizers and some are slow metabolizers of oxycodone, resulting in different half-life of oxycodone in different individuals. This may cause altered oxycodone–ART interactions in different individuals ultimately leading to decreased efficacy of ART and increased adverse effects in HIV-infected opioid users. Therefore, there is an urgent need to examine the effects of opioids, especially methadone and oxycodone, on differential response to ART and ART-and opioids-mediated toxicity. This would help to develop potentially novel drugs, as well as, drug-dose regimes for HIV-infected opioid users.

8. Marijuana-ART interactions

8.1 ART adherence in marijuana users

Marijuana use is common among HIV-infected patients. Prevalence of marijuana use has been observed to be as high as alcohol in some studies [16,103]. Critically, as observed with other drugs of abuse, marijuana use in HIV patients has been associated with lack of adherence to ART [15,85]. Furthermore, legalization of marijuana use in several states across USA is expected to exacerbate the prevalence and adverse effects of marijuana smoking amongst HIV population. This is expected to further reduce the adherence of HIV medication in HIV-infected marijuana users.

8.2 Effects of marijuana on ART efficacy and toxicity

Cannabinoids present in marijuana have been shown to significantly affect (inhibit or induce) the activity of several CYP isoforms [104]. *In vitro*, *in vivo*, and clinical observations suggest the possible interaction of marijuana constituents with CYP3A, CYP1A, CYP2C9, CYP2A6, and CYP2B6. Importantly, in comparison to other drugs of abuse, marijuana was identified as the only illicit substance that inhibited the increase in

CD4 T-cell counts associated with antiretroviral treatment in HIV patients [105]. Whereas another report has cited no significant effect of marijuana use on viral load in HIV patients [106], the study has its limitations namely, short duration of cannabis use and few participants. Cannabis use, more importantly, is associated with increased ART-related side effects suggesting possible CYP inhibitory effects [15]. A different study, however, reported that high plasma levels of delta-9-tetrahydrocannabinol, the most psychoactive ingredient of marijuana, were associated with decreased plasma concentrations of PI therapy [107]. Decreased plasma bioavailability of PI therapy is found to be in agreement with CYP induction reported in cannabinoid treated mouse [108]. Overall, given the complexity of marijuana and CYP interactions, there is a need to further examine the effects of marijuana use on CYP expression, ART pharmacokinetics, and HIV pathogenesis.

9. Conclusion

Prevalence of drug dependence and abuse in HIV-infected patients is higher than general population. Importantly, the use of recreational drugs in HIV-positive patients is associated with non-adherence to ART and subsequent failure in achieving optimal virological responses. As the CYP pathway is common to both, metabolism of ART and metabolism of drugs of abuse, this pathway plays an important role in drug interactions in HIV-infected individuals who use these substances. In addition, ability of ART drugs and drugs of abuse to induce and inhibit CYP enzymes further strengthens the importance of CYP pathways in drug interactions in HIV-infected substance users. Towards this, recent findings have demonstrated the involvement of CYP pathways in drugs of abuse-mediated decreased efficacy of ART drugs, as well as increased ART- and drugs of abuse-mediated toxicity. However, studies investigating the involvement of CYP pathway are still preliminary and additional work is needed to fully realize the impact of substance of abuse on HIV patients.

10. Expert opinion

From literature, it is apparent that increased prevalence of drug abuse in HIV-infected individuals has serious effects on their health outcomes, especially in relation to lack of adherence to HIV medication and poor virological response to ART. Therefore, newer strategies aimed at improving adherence, such as use of electronic sensor in medicine bottles, formulation of multiple drugs in single pill, and extended drug delivery strategy, have been adopted, which are showing promising results. Although health care providers and researchers play a major role in educating HIV patients and providing formulations to adhere with the medication, it is also important for the social workers and community representatives to educate these patients. It is therefore expected that in the next 5 years there will be a significant improvement in medication adherence using current as well as new strategies, which will ultimately improve clinical outcomes in HIV patients who are dependent on drugs of abuse.

In addition to improving adherence to ART, the major issue is to develop novel/additional interventions for the HIV patients who abuse alcohol, tobacco, methamphetamine, cocaine, opioids, and marijuana. There is also a need for drug dose and drug regimen adjustments for HIV patients who abuse these drugs. However, this requires additional and immediate

research on the effects of these drugs on response to ART drugs, especially on NNRTIs and PIs. As CYP pathways are involved in the metabolism of both ART (NNRTIs and PIs) and drugs of abuse (Figure 1), the role of CYP pathways in potential drug–drug interactions between ART (NNRTIs and PIs) and drugs of abuse has been discussed (Table 1). Co-administration of ART mediation and drugs of abuse has the potential for varied drug–drug interactions in HIV-infected individuals. Broadly, the drugs of abuse-and/or ART drugs-mediated induction or inhibition of CYP enzymes can lead to four different scenarios for drug–drug interactions: i)if drugs of abuse or NNRTI/PI alone as well as in combination cause induction of CYP enzymes in HIV-infected patients, this may lead to enhanced metabolism of ART. This is likely to decrease bioavailability of NNRTIs/PIs medication and attenuate/decrease the response to ART leading to increased viral load and decreased CD4 counts; ii) induction of CYP enzymes by drugs of abuse and/or NNRTI/PI followed by their increased metabolism can cause toxic accumulation of metabolites of drugs of abuse and/or NNRTI/PI leading to potential toxicity and adverse effects; iii) in HIV-infected patients, drugs of abuse and/or NNRTI/PI administration may lead to inhibition of CYP enzymes. This would decrease the metabolism of drugs of abuse and/or NNRTI/PI thereby increasing the bioavailability, which is likely to increase the efficacy of NNRTI/PI. This scenario causes positive effects on therapy and is being utilized to boost the bioavailability of ART; and iv) the inhibition of CYP enzymes by drugs of abuse and/or NNRTI/PI may cause excessive accumulation of these drugs leading to severe toxicity. Of the four scenarios, three are expected to cause inappropriate drug–drug interactions leading to suboptimal response to ART drugs and adverse events. Therefore, it is critical to examine the possible involvement of CYP pathways in drugs of abuse-mediated interactions with ART drugs, which would help develop potentially novel drugs and/or adjust drug dose and drug regimens in HIV-infected drugs users.

Recent and current studies with alcohol, tobacco, and methamphetamine have provided rationale to hypothesize that CYP pathways are likely to be involved in altering response to HIV medication through drug– drug interactions [28,54]. In particular, alcohol has been shown to interact differentially with CYP3A4 in the presence of PIs of different physicochemical properties [56,57]. Therefore, additional studies are needed to examine the effects of alcohol on the metabolism and efficacy of different PIs, which utilize *in vitro* study with primary cells, *ex vivo* study with clinical samples from HIV-infected drinkers, and *in vivo* study with HIV-infected humanized mouse. A significant progress in this direction would potentially help to find new interventions for HIV-infected drinkers and smokers. In addition, similar studies are needed to examine the role of CYP pathways in methamphetamine-, cocaine-, marijuana-, and opioid drugs-mediated altered response to HIV medication.

Psychostimulant drugs of abuse, including methamphetamine, cocaine, and nicotine, are known to cause disruption to the BBB resulting in increased permeability across BBB [109]. For example, Toborek *et al*. have demonstrated that methamphetamine exposure induces oxidative stress and disrupt BBB [110]. Based on these data, we can rationalize that, in HIV-infected drugs users, whereas the disruption of BBB would result in increased infiltration of HIV-infected monocytes and accelerate progression of neuroAIDS, the increased

permeability of BBB would also cause enhanced CNS bioavailability of NNRTI/PI. Although increased CNS bioavailability will help decrease viral load in the brain, increased accumulation of ART drugs in the brain may also cause neurotoxicity. Furthermore, CYP enzymes (CYP3A4, CYP2E1, and CYP1A1) are widely expressed in CNS and are known to be induced by xenobiotics to the levels similar to the hepatic CYP levels [111]. This is further expected to enhance drug–drug interactions and toxicity in the brain.

Other important area of future research, involving the effect of these drugs on response to ART, is examining the impact of gender- race- and polymorphism-based differences on HIV medications. There is ample evidence that CYP enzymes, which contribute to the metabolism of NNRTIs, PI, and INIs, as well as ethanol, nicotine, methamphetamine, cocaine, opioid, and marijuana carry single nucleotide polymorphisms [112]. In addition, these CYP enzymes are developmentally and hormonally regulated, and therefore, show different expressions and activities in children versus adult and men versus women. The literatures clearly show that nicotine and cocaine metabolisms are faster in women than men, which may have important implications on the treatment strategy of HIV-infected women compared to men who are tobacco and cocaine users [68,91]. Literatures also suggest significant inter-individual differences in the metabolism of many drugs of abuse, especially opioid, which are very important to study to tailor ART drugs for each group of individuals [101]. Therefore, it is critical to study the role of CYP enzymes in drugs of abuse-mediated modulation of pharmacokinetics of ART medication in these populations. In particular, it is important to study this using HIV-infected drinkers, smokers, and methamphetamine users representing population from different race, age, and sex to find the basis of inter-individual differences on the metabolism, bioavailability, and efficacy of ART drugs. The findings from these studies would provide basis for future studies that would ultimately tailor the ART drugs for men, women, children, and different ethnic groups.

Acknowledgments

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Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Mothobi NZ, Brew BJ. Neurocognitive dysfunction in the highly active antiretroviral therapy era. Curr Opin Infect Dis. 2012; 25(1):4–9. [PubMed: 22156897]

2•. NSDUH. HIV/AIDS and substance use. 2010 Statistics regarding substance abuse in HIV/AIDS patients.

3. Kresina TF, Flexner CW, Sinclair J, et al. Alcohol use and HIV pharmacotherapy. AIDS Res Hum Retroviruses. 2002; 18(11):757–70. [PubMed: 12167267]

4. Petry NM. Alcohol use in HIV patients: what we don't know may hurt us. Int J STD AIDS. 1999; 10(9):561–70. [PubMed: 10492422]

5. Galvan FH, Bing EG, Fleishman JA, et al. The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV cost and services utilization study. J Stud Alcohol. 2002; 63(2):179–86. [PubMed: 12033694]

6. Lifson AR, Neuhaus J, Arribas JR, et al. Smoking-related health risks among persons with HIV in the strategies for management of antiretroviral therapy clinical trial. Am J Public Health. 2010; 100(10):1896–903. [PubMed: 20724677]

7•. Crothers K, Goulet JL, Rodriguez-Barradas MC, et al. Impact of cigarette smoking on mortality in HIV- positive and HIV-negative veterans. AIDS Educ Prev. 2009; 21(3 Suppl):40–53. A study highlighting high prevalence of smoking among HIV-positive patients. [PubMed: 19537953]

8. Webb MS, Vanable PA, Carey MP, Blair DC. Cigarette smoking among HIV+ men and women: examining health, substance use, and psychosocial correlates across the smoking spectrum. J Behav Med. 2007; 30(5):371–83. [PubMed: 17570050]

9. Luo X, Duan S, Duan Q, et al. Tobacco use among HIV-infected individuals in a rural community in Yunnan Province, China. Drug Alcohol Depend. 2014; 134:144–50. [PubMed: 24144787]

10. Herrmann SE, McKinnon EJ, Williams LJ, et al. Use of alcohol, nicotine and other drugs in the Western Australian HIV Cohort study. Sex Health. 2012; 9(2):199–201. [PubMed: 22498169]

11. Helleberg M, Afzal S, Kronborg G, et al. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. Clin Infect Dis. 2013; 56(5):727–34. [PubMed: 23254417]

12. Ellis RJ, Childers ME, Cherner M, et al. Increased human immunodeficiency virus loads in active methamphetamine users are explained by reduced effectiveness of antiretroviral therapy. J Infect Dis. 2003; 188(12):1820–6. [PubMed: 14673760]

13. Edlin BR, Irwin KL, Faruque S, et al. Intersecting epidemics–crack cocaine use and HIV infection among inner-city young adults. Multicenter Crack Cocaine and HIV Infection Study Team. N Engl J Med. 1994; 331(21):1422–7. [PubMed: 7969281]

14. Metsch LR, Bell C, Pereyra M, et al. Hospitalized HIV-infected patients in the era of highly active antiretroviral therapy. Am J Public Health. 2009; 99(6):1045–9. [PubMed: 19372520]

15. Bonn-Miller MO, Oser ML, Bucossi MM, Trafton JA. Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. J Behav Med. 2014; 37(1):1–10. [PubMed: 23054178]

16. Newcomb ME, Ryan DT, Greene GJ, et al. Prevalence and patterns of smoking, alcohol use, and illicit drug use in young men who have sex with men. Drug Alcohol Depend. 2014; 141:65–71. [PubMed: 24907774]

17. Edelman EJ, Gordon K, Becker WC, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. J Gen Intern Med. 2013; 28(1):82–90. [PubMed: 22895747]

18. Barry DT, Goulet JL, Kerns RK, et al. Nonmedical use of prescription opioids and pain in veterans with and without HIV. Pain. 2011; 152(5):1133–8. [PubMed: 21354703]

19•. Hansen L, Penko J, Guzman D, et al. Aberrant behaviors with prescription opioids and problem drug use history in a community-based cohort of HIV-infected individuals. J Pain Symptom Manage. 2011; 42(6):893–902. Prevalence of opioid abuse in homeless HIV-positive individuals. [PubMed: 21802896]

20. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. Am J Med. 2003; 114(7):573–80. [PubMed: 12753881]

21•. Hicks PL, Mulvey KP, Chander G, et al. The impact of illicit drug use and substance abuse treatment on adherence to HAART. AIDS Care. 2007; 19(9):1134–40. Correlation between substance abuse and adherence to HAART in HIV-positive patients. [PubMed: 18058397]

22. Wood E, Montaner JS, Yip B, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. CMAJ. 2003; 169(7):656–61. [PubMed: 14517122]

23. Palepu A, Tyndall M, Yip B, et al. Impaired virologic response to highly active antiretroviral therapy associated with ongoing injection drug use. J Acquir Immune Defic Syndr. 2003; 32(5): 522–6. [PubMed: 12679704]

24. Giordano TP, Gifford AL, White AC Jr, et al. Retention in care: a challenge to survival with HIV infection. Clin Infect Dis. 2007; 44(11):1493–9. [PubMed: 17479948]

25. Mehta SH, Lucas G, Astemborski J, et al. Early immunologic and virologic responses to highly active antiretroviral therapy and subsequent disease progression among HIV-infected injection drug users. Aids Care. 2007; 19(5):637–45. [PubMed: 17505924]

26. Meyer MR, Maurer HH. Absorption, distribution, metabolism and excretion pharmacogenomics of drugs of abuse. Pharmacogenomics. 2011; 12(2):215–33. [PubMed: 21332315]
27. Anzenbacher P, Anzenbacherova E. Cytochromes P450 and metabolism of xenobiotics. Cell Mol Life Sci. 2001; 58(5-6):737–47. [PubMed: 11437235]
28••. Walubo A. The role of cytochrome P450 in antiretroviral drug interactions. Expert Opin Drug Metab Toxicol. 2007; 3(4):583–98. Review highlighting the role of CYPs in HAART metabolism and potential drug–drug interactions. [PubMed: 17696808]
29. Pal D, Kwatra D, Minocha M, et al. Efflux transporters- and cytochrome P-450-mediated interactions between drugs of abuse and antiretrovirals. Life Sci. 2011; 88(21-22):959–71. [PubMed: 20932495]
30. Rao P, Cory T, Kumar S. New antiretroviral therapies and potential drug interactions in HIV-infected drug abusers. J Antivir Antiretrovir. 2014; 6(3):86–91.
31. Shugarts S, Benet LZ. The role of transporters in the pharmacokinetics of orally administered drugs. Pharm Res. 2009; 26(9):2039–54. [PubMed: 19568696]
32. Konig SK, Herzog M, Theile D, et al. Impact of drug transporters on cellular resistance towards saquinavir and darunavir. J Antimicrob Chemother. 2010; 65(11):2319–28. [PubMed: 20817741]
33. Hashiguchi Y, Hamada A, Shinohara T, et al. Role of P-glycoprotein in the efflux of raltegravir from human intestinal cells and CD4+T-cells as an interaction target for anti-HIV agents. Biochem Biophys Res Commun. 2013; 439(2):221–7. [PubMed: 23981805]
34. Kis O, Zastre JA, Hoque MT, et al. Role of drug efflux and uptake transporters in atazanavir intestinal permeability and drug-drug interactions. Pharm Res. 2013; 30(4):1050–64. [PubMed: 23224979]
35. Zhou SF. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Curr Drug Metab. 2008; 9(4):310–22. [PubMed: 18473749]
36. Capetti A, Rizzardini G. Cobicistat: a new opportunity in the treatment of HIV disease? Expert Opin Pharmacother. 2014; 15(9):1289–98. [PubMed: 24819446]
37. Josephson F. Drug-drug interactions in the treatment of HIV infection: focus on pharmacokinetic enhancement through CYP3A inhibition. J Intern Med. 2010; 268(6):530–9. [PubMed: 21073558]
38. Jimenez-Nacher I, Alvarez E, Morello J, et al. Approaches for understanding and predicting drug interactions in human immunodeficiency virus-infected patients. Expert Opin Drug Metab Toxicol. 2011; 7(4):457–77. [PubMed: 21342079]
39. Kalichman SC, Grebler T, Amaral CM, et al. Viral suppression and antiretroviral medication adherence among alcohol using HIV-positive adults. Int J Behav Med. 2014; 21(5):811–20. [PubMed: 24085706]
40. Kalichman SC, Grebler T, Amaral CM, et al. Intentional non-adherence to medications among HIV positive alcohol drinkers: prospective study of interactive toxicity beliefs. J Gen Intern Med. 2013; 28(3):399–405. [PubMed: 23065532]
41•. Kalichman SC, Amaral CM, White D, et al. Prevalence and clinical implications of interactive toxicity beliefs regarding mixing alcohol and antiretroviral therapies among people living with HIV/AIDS. AIDS Patient Care STDS. 2009; 23(6):449–54. A study highlighting the alcohol induced lack of adherence to HAART in HIV patients. [PubMed: 19413503]
42. Parsons JT, Golub SA, Rosof E, Holder C. Motivational interviewing and cognitive-behavioral intervention to improve HIV medication adherence among hazardous drinkers: a randomized controlled trial. J Acquir Immune Defic Syndr. 2007; 46(4):443–50. [PubMed: 18077833]
43. Samet JH, Horton NJ, Meli S, et al. Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. Alcohol Clin Exp Res. 2004; 28(4):572–7. [PubMed: 15100608]
44. Miguez MJ, Burbano X, Morales G, Shor-Posner G. Alcohol use and HIV infection in the HAART era. Am Clin Lab. 2001; 20(6):20–3. [PubMed: 11480388]
45. Miguez MJ, Shor-Posner G, Morales G, et al. HIV treatment in drug abusers: impact of alcohol use. Addict Biol. 2003; 8(1):33–7. [PubMed: 12745413]
46•. Kumar R, Perez-Casanova AE, Tirado G, et al. Increased viral replication in simian immunodeficiency virus/simian-HIV-infected macaques with self-administering model of chronic alcohol consumption. J Acquir Immune Defic Syndr. 2005; 39(4):386–90. An important

study demonstrating a direct association between alcoholism and increased viral (SIV) replication. [PubMed: 16010157]

47••. Kumar S, Jin M, Ande A, et al. Alcohol consumption effect on antiretroviral therapy and HIV-1 pathogenesis: role of cytochrome P450 isozymes. Expert Opin Drug Metab Toxicol. 2012; 8(11): 1363–75. Detailed review on effects of alcohol consumption on antiretroviral therapy and HIV-1 replication. [PubMed: 22871069]

48. Ronis MJ, Huang J, Crouch J, et al. Cytochrome P450 CYP 2E1 induction during chronic alcohol exposure occurs by a two-step mechanism associated with blood alcohol concentrations in rats. J Pharmacol Exp Ther. 1993; 264(2):944–50. [PubMed: 8437134]

49•. Jin M, Ande A, Kumar A, Kumar S. Regulation of cytochrome P450 2e1 expression by ethanol: role of oxidative stress-mediated pkc/jnk/sp1 pathway. Cell Death Dis. 2013; 4:e554. A direct evidence for ethanol mediated expression of CYP2E1 and subsequent increase in oxidative stress. [PubMed: 23519123]

50. Niemela O, Parkkila S, Pasanen M, et al. Early alcoholic liver injury: formation of protein adducts with acetaldehyde and lipid peroxidation products, and expression of CYP2E1 and CYP3A. Alcohol Clin Exp Res. 1998; 22(9):2118–24. [PubMed: 9884160]

51. Jin M, Arya P, Patel K, et al. Effect of alcohol on drug efflux protein and drug metabolic enzymes in U937 macrophages. Alcohol Clin Exp Res. 2011; 35(1):132–9. [PubMed: 21039635]

52•. Flexner CW, Cargill VA, Sinclair J, et al. Alcohol use can result in enhanced drug metabolism in HIV pharmacotherapy. AIDS Patient Care STDS. 2001; 15(2):57–8. A direct evidence for the effects of ethanol on metabolism of HAART. [PubMed: 11224929]

53••. Slain D, Pakyz A, Israel DS, et al. Variability in activity of hepatic CYP3A4 in patients infected with HIV. Pharmacotherapy. 2000; 20(8):898–907. Excellent study revealing the variability in CYP3A4 activity among HIV-infected individuals. [PubMed: 10939550]

54. Weathermon R, Crabb DW. Alcohol and medication interactions. Alcohol Res Health. 1999; 23(1): 40–54. [PubMed: 10890797]

55. Bbosa GS, Kyegombe DB, Anokbonggo WW, et al. Chronic ethanol use in alcoholic beverages by HIV-infected patients affects the therapeutic window of stavudine, lamivudine and nevirapine during the 9-month follow-up period: using chronic alcohol-use biomarkers. J Basic Clin Physiol Pharmacol. 2014:1–12. [PubMed: 24468616]

56•. Kumar S, Earla R, Jin M, et al. Effect of ethanol on spectral binding, inhibition, and activity of CYP3A4 with an antiretroviral drug nelfinavir. Biochem Biophys Res Commun. 2010; 402(1): 163–7. Effect of ethanol on the metabolism of nelfinavir. [PubMed: 20937259]

57••. Kumar S, Kumar A. Differential effects of ethanol on spectral binding and inhibition of cytochrome P450 3A4 with eight protease inhibitors antiretroviral drugs. Alcohol Clin Exp Res. 2011; 35(12):2121–7. A comprehensive study assessing the effect of ethanol on CYP3A4 binding and inhibition with various protease inhibitors. [PubMed: 21682753]

58. Feldman JG, Minkoff H, Schneider MF, et al. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. Am J Public Health. 2006; 96(6):1060–5. [PubMed: 16670229]

59•. Shuter J, Bernstein SL. Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy. Nicotine Tob Res. 2008; 10(4): 731–6. Smoking mediated non-adherence to HAART in HIV-1 infected patients. [PubMed: 18418794]

60. Webb MS, Vanable PA, Carey MP, Blair DC. Medication adherence in HIV-infected smokers: the mediating role of depressive symptoms. AIDS Educ Prev. 2009; 21(3 Suppl):94–105. [PubMed: 19537957]

61. King RM, Vidrine DJ, Danysh HE, et al. Factors associated with nonadherence to antiretroviral therapy in HIV-positive smokers. AIDS Patient Care STDS. 2012; 26(8):479–85. [PubMed: 22612468]

62••. Ande A, McArthur C, Kumar A, Kumar S. Tobacco smoking effect on HIV-1 pathogenesis: role of cytochrome P450 isozymes. Expert Opin Drug Metab Toxicol. 2013; 9(11):1453–64. Review and expert opinion regarding the role of CYP in smoking-mediated changes in HIV pathogenesis. [PubMed: 23822755]

63. Bao Z, He XY, Ding X, et al. Metabolism of nicotine and cotinine by human cytochrome P450 2A13. Drug Metab Dispos. 2005; 33(2):258–61. [PubMed: 15528319]
64. Yamazaki H, Inoue K, Hashimoto M, Shimada T. Roles of CYP2A6 and CYP2B6 in nicotine C-oxidation by human liver microsomes. Arch Toxicol. 1999; 73(2):65–70. [PubMed: 10350185]
65. Puntarulo S, Cederbaum AI. Production of reactive oxygen species by microsomes enriched in specific human cytochrome P450 enzymes. Free Radic Biol Med. 1998; 24(7-8):1324–30. [PubMed: 9626590]
66. Yao Y, Hoffer A, Chang CY, Puga A. Dioxin activates HIV-1 gene expression by an oxidative stress pathway requiring a functional cytochrome P450 CYP1A1 enzyme. Environ Health Perspect. 1995; 103(4):366–71. [PubMed: 7607137]
67•. Feldman DN, Feldman JG, Greenblatt R, et al. CYP1A1 genotype modifies the impact of smoking on effectiveness of HAART among women. AIDS Educ Prev. 2009; 21(3 Suppl):81–93. Association of decreased effective of HAART in female HIV-1 infected smokers with CYP1A1 genotype. [PubMed: 19537956]
68. Johnstone E, Benowitz N, Cargill A, et al. Determinants of the rate of nicotine metabolism and effects on smoking behavior. Clin Pharmacol Ther. 2006; 80(4):319–30. [PubMed: 17015050]
69. Earla R, Ande A, McArthur C, et al. Enhanced nicotine metabolism in HIV-1-positive smokers compared with HIV-negative smokers: simultaneous determination of nicotine and its four metabolites in their plasma using a simple and sensitive electrospray ionization liquid chromatography-tandem mass spectrometry technique. Drug Metab Dispos. 2014; 42(2):282–93. [PubMed: 24301609]
70••. Pace GW, Leaf CD. The role of oxidative stress in HIV disease. Free Radic Biol Med. 1995; 19(4):523–8. Review discussing role of oxidative stress in HIV disease. [PubMed: 7590404]
71. Porter KM, Sutliff RL. HIV-1, reactive oxygen species, and vascular complications. Free Radic Biol Med. 2012; 53(1):143–59. [PubMed: 22564529]
72. Marquez C, Mitchell SJ, Hare CB, et al. Methamphetamine use, sexual activity, patient-provider communication, and medication adherence among HIV-infected patients in care, San Francisco 2004-2006. Aids Care. 2009; 21(5):575–82. [PubMed: 19444665]
73. Nishijima T, Gatanaga H, Komatsu H, et al. High prevalence of illicit drug use in men who have sex with men with HIV-1 infection in Japan. PLoS One. 2013; 8(12):e81960. [PubMed: 24339982]
74. Parsons JT, Kowalczyk WJ, Botsko M, et al. Aggregate versus day level association between methamphetamine use and HIV medication non-adherence among gay and bisexual men. AIDS Behav. 2013; 17(4):1478–87. [PubMed: 23553345]
75. Moore DJ, Blackstone K, Woods SP, et al. Methamphetamine use and neuropsychiatric factors are associated with antiretroviral nonadherence. Aids Care. 2012; 24(12):1504–13. [PubMed: 22530794]
76. Montoya JL, Georges S, Poquette A, et al. Refining a personalized mHealth intervention to promote medication adherence among HIV+ methamphetamine users. AIDS Care. 2014; 26(12): 1477–81. [PubMed: 24911433]
77. Moore DJ, Montoya JL, Blackstone K, et al. Preliminary evidence for feasibility, use, and acceptability of individualized texting for adherence building for antiretroviral adherence and substance use assessment among HIV-infected methamphetamine users. Aids Res Treat. 2013; 2013:585143. [PubMed: 24078868]
78. Cisneros IE, Ghorpade A. HIV-1, methamphetamine and astrocyte glutamate regulation: combined excitotoxic implications for neuro-AIDS. Curr HIV Res. 2012; 10(5):392–406. [PubMed: 22591363]
79. Reiner BC, Keblesh JP, Xiong H. Methamphetamine abuse, HIV infection, and neurotoxicity. Int J Physiol Pathophysiol Pharmacol. 2009; 1(2):162–79. [PubMed: 20411028]
80••. Silverstein PS, Shah A, Gupte R, et al. Methamphetamine toxicity and its implications during HIV-1 infection. J Neurovirol. 2011; 17(5):401–15. Detailed review concerning methamphetamine toxicity and effects on HIV-1 infection. [PubMed: 21786077]
81. Li L, Everhart T, Jacob Iii P, et al. Stereoselectivity in the human metabolism of methamphetamine. Br J Clin Pharmacol. 2010; 69(2):187–92. [PubMed: 20233182]

82. Cherner M, Bousman C, Everall I, et al. Cytochrome P450-2D6 extensive metabolizers are more vulnerable to methamphetamine-associated neurocognitive impairment: preliminary findings. J Int Neuropsychol Soc. 2010; 16(5):890–901. [PubMed: 20727252]

83. Earla R, Kumar S, Wang L, et al. Enhanced methamphetamine metabolism in rhesus macaque as compared to human: an analysis using a novel LCMS/MS method, kinetic study, and substrate docking. Drug Metab Dispos. 2014; 42(12):2097–108. [PubMed: 25301936]

84•. Rosen MI, Black AC, Arnsten JH, et al. Association between use of specific drugs and antiretroviral adherence: findings from MACH 14. AIDS Behav. 2013; 17(1):142–7. Study concerning prevalence of cocaine use in HIV-positive individuals. [PubMed: 22246513]

85. Chitsaz E, Meyer JP, Krishnan A, et al. Contribution of substance use disorders on HIV treatment outcomes and antiretroviral medication adherence among HIV-infected persons entering jail. AIDS Behav. 2013; 17(Suppl 2):S118–27. [PubMed: 23673792]

86••. Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. J Gen Intern Med. 2002; 17(5):377–81. Effect of cocaine use on HAART adherence in HIV-1 infected individuals. [PubMed: 12047736]

87. Sharpe TT, Lee LM, Nakashima AK, et al. Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women. J Community Health. 2004; 29(2):117–27. [PubMed: 15065731]

88. Ingersoll KS, Farrell-Carnahan L, Cohen-Filipic J, et al. A pilot randomized clinical trial of two medication adherence and drug use interventions for HIV plus crack cocaine users. Drug Alcohol Depend. 2011; 116(1-3):177–87. [PubMed: 21306837]

89. Ladona MG, Gonzalez ML, Rane A, et al. Cocaine metabolism in human fetal and adult liver microsomes is related to cytochrome P450 3A expression. Life Sci. 2000; 68(4):431–43. [PubMed: 11205892]

90. Lukas SE, Sholar M, Lundahl LH, et al. Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. Psychopharmacology (Berl). 1996; 125(4):346–54. [PubMed: 8826539]

91. Quinones-Jenab V, Jenab S. Influence of sex differences and gonadal hormones on cocaine addiction. ILAR J. 2012; 53(1):14–22. [PubMed: 23520596]

92. Pellinen P, Honkakoski P, Stenback F, et al. Cocaine N-demethylation and the metabolism-related hepatotoxicity can be prevented by cytochrome-P450 3a inhibitors. Eur J Pharmacol. 1994; 270(1):35–43. [PubMed: 8157080]

93•. Bornheim LM. Effect of cytochrome P450 inducers on cocaine-mediated hepatotoxicity. Toxicol Appl Pharmacol. 1998; 150(1):158–65. Role of cytochrome inducers in hepatotoxicity associated with cocaine use. [PubMed: 9630465]

94. Jeevanjee S, Penko J, Guzman D, et al. Opioid analgesic misuse is associated with incomplete antiretroviral adherence in a cohort of HIV-infected indigent adults in San Francisco. AIDS Behav. 2014; 18(7):1352–8. [PubMed: 24077929]

95. Roux P, Carrieri MP, Villes V, et al. The impact of methadone or buprenorphine treatment and ongoing injection on highly active antiretroviral therapy (HAART) adherence: evidence from the MANIF2000 cohort study. Addiction. 2008; 103(11):1828–36. [PubMed: 18778390]

96••. Cox S. The issues around opioid prescribing in HIV-related pain. Pain Manag. 2013; 3(5):377–85. Review of opioid use in HIV patients and possible drug–drug interactions with HAART. [PubMed: 24654871]

97. Clarke SM, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. Br J Clin Pharmacol. 2001; 51(3):213–17. [PubMed: 11298066]

98. Otero MJ, Fuertes A, Sanchez R, Luna G. Nevirapine-induced withdrawal symptoms in HIV patients on methadone maintenance programme: an alert. Aids. 1999; 13(8):1004–5. [PubMed: 10371190]

99. Nieminen TH, Hagelberg NM, Saari TI, et al. Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir. Eur J Clin Pharmacol. 2010; 66(10):977–85. [PubMed: 20697700]

100. Iribarne C, Berthou F, Baird S, et al. Involvement of cytochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. Chem Res Toxicol. 1996; 9(2):365–73. [PubMed: 8839037]

101. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002; 41(14):1153–93. [PubMed: 12405865]

102. Lofdal KCS, Andersson ML, Gustafsson LL. Cytochrome P450-mediated changes in oxycodone pharmacokinetics/pharmacodynamics and their clinical implications. Drugs. 2013; 73(6):533–43. [PubMed: 23605691]

103. Slawson G, Milloy MJ, Balneaves L, et al. High-intensity cannabis use and adherence to antiretroviral therapy among people who use illicit drugs in a canadian setting. AIDS Behav. 2014 Epub ahead of print.

104. Stout SM, Cimino NM. Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. Drug Metab Rev. 2014; 46(1):86–95. [PubMed: 24160757]

105. Montarroyos UR, Miranda DB, Cesar CC, et al. Factors related to changes in CD4+T-cell counts over time in patients living with HIV/AIDS: a multilevel analysis. PLoS One. 2014; 9:2.

106. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection - a randomized, placebo-controlled clinical trial. Ann Intern Med. 2003; 139(4):258–66. [PubMed: 12965981]

107. Kosel BW, Aweeka FT, Benowitz NL, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. Aids. 2002; 16(4):543–50. [PubMed: 11872997]

108. Bornheim LM, Everhart ET, Li JM, Correia MA. Induction and genetic-regulation of mouse hepatic cytochrome-P450 by cannabidiol. Biochem Pharmacol. 1994; 48(1):161–71. [PubMed: 8043019]

109. Kousik SM, Napier TC, Carvey PM. The effects of psychostimulant drugs on blood brain barrier function and neuroinflammation. Front Pharmacol. 2012; 3:121. [PubMed: 22754527]

110. Toborek M, Seelbach MJ, Rashid CS, et al. Voluntary exercise protects against methamphetamine-induced oxidative stress in brain microvasculature and disruption of the blood-brain barrier. Mol Neurodegener. 2013; 8:22. [PubMed: 23799892]

111. Ferguson CS, Tyndale RF. Cytochrome P450 enzymes in the brain: emerging evidence of biological significance. Trends Pharmacol Sci. 2011; 32(12):708–14. [PubMed: 21975165]

112. McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. Expert Opin Drug Metab Toxicol. 2012; 8(3):371–82. [PubMed: 22288606]

Article highlights

- Substance abuse is critical hindrance to clinical care of HIV patients.
- Drug addiction results in nonadherence to antiretroviral therapy (ART) in HIV-infected individuals.
- CYP pathways are responsible for the metabolism of all major drugs of abuse and medications, including ART.
- Induction or inhibition of CYP enzymes by either ART or drugs of abuse can cause the potential drug–drug interaction leading to adverse events.
- Decreased/abolished ART bioavailability, due to the induction of CYPs by substance abuse, may result in increased viral load and lack of response to HIV medication.
- Increased adherence to ART and novel/alternate interventions, as well as drug dose adjustments in drug users can improve the management of HIV/AIDS patients who are dependent of drugs of abuse.

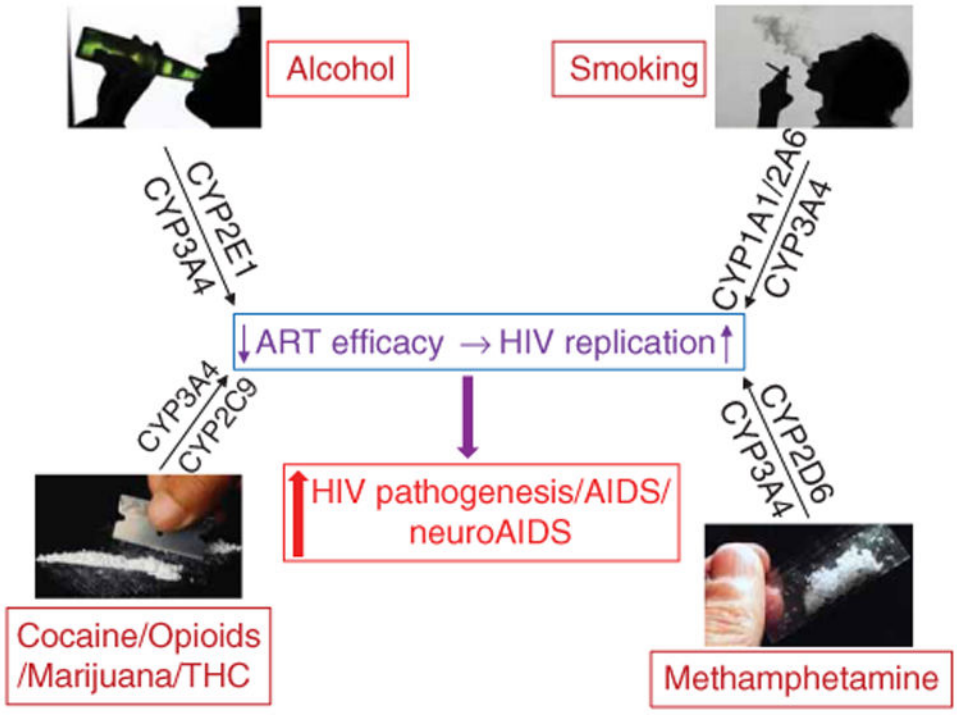

Figure 1. Effect of common drugs of abuse on efficacy of ART and progression of AIDS

Common metabolic enzymes involved in the metabolism of ART and alcohol (CYP2E1 and CYP3A4), nicotine (CYP1A1, CYP2A6, and CYP3A4), methamphetamine (CYP2D6 and CYP3A4), cocaine/opioids (CYP3A4) and marijuana/THC (CYP2C9) may result in altered bioavailability of antiretroviral drugs. Drug–drug interactions between drugs of abuse and ART drugs, mediated by CYP enzymes, may result in decreased response to ART leading to enhanced HIV replication in HIV-infected patients.

ART: Antiretroviral therapy; THC: Tetrahydrocannabinol.

Table 1

Possible clinical outcomes in HIV-positive patients as a result of interactions among drugs of abuse, ART, and CYP enzymes.

Drugs of abuse/ART	Metabolism (CYPs)	Induction (↑) Inhibition (↑)	Clinical outcome
Alcohol	2E1	↑2E1, ↑2A6, ↑↓3A4	Altered ART metabolism Increased ROS
Nicotine/tobacco	1A1, 2A6, 2A13	↑1A1, ↑2A6	Increased ROS
Methamphetamine	2D6, 3A4	↑2A6, ↓2B6	Altered ART metabolism
Cocaine	3A4	NA	NA
Opioids	3A4, 2B6, 2D6	NA	NA
Marijuana	3A4, 2C9	↑ CYP	Increased ART metabolism
		↓ CYP	Increased ART side effects
Non-nucleoside reverse transcriptase inhibitors	3A4, 2B6	↑↓3A4	Altered ART metabolism
Protease inhibitors	3A4	↑↓3A4	Altered ART metabolism
Integrase inhibitors	3A4	NA	NA

↑-Induction of CYP enzyme; ↓-Inhibition of CYP enzyme; ↑-Proposed mechanism; bold arrow (↑) represents predominant effect ART: Antiretroviral therapy; NA-data not available.