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Tobacco smoking effect on HIV-1 pathogenesis: role of cytochrome P450 isozymes

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Abstract

Introduction—Tobacco smoking is highly prevalent among the HIV-1-infected population. In addition to diminished immune response, smoking has been shown to increase HIV-1 replication and decrease response to antiretroviral therapy, perhaps through drug–drug interaction. However, the mechanism by which tobacco/nicotine increases HIV-1 replication and mediates drug–drug interaction is poorly understood.

Areas covered—In this review, the authors discuss the effects of smoking on HIV-1 pathogenesis. Since they propose a role for the cytochrome P450 (CYP) pathway in smoking-mediated HIV-1 pathogenesis, the authors briefly converse the role of CYP enzymes in tobacco-mediated oxidative stress and toxicity. Finally, the authors focus on the role of CYP enzymes, especially CYP2A6, in tobacco/nicotine metabolism and oxidative stress in HIV-1 model systems monocytes/macrophages, lymphocytes, astrocytes and neurons, which may be responsible for HIV-1 pathogenesis.

Expert opinion—Recent findings suggest that CYP-mediated oxidative stress is a novel pathway that may be involved in smoking-mediated HIV-1 pathogenesis, including HIV-1 replication and drug–drug interaction. Thus, CYP and CYP-associated oxidative stress pathways may be potential targets to develop novel pharmaceuticals for HIV-1-infected smokers. Since HIV-1/TB co-infections are common, future study involving interactions between antiretroviral and antituberculosis drugs that involve CYP pathways would also help treat HIV-1/TB co-infected smokers effectively.

Keywords

cytochrome p450; HIV-1; nicotine; oxidative stress; smoking/tobacco

1. Introduction

HIV-1 infection is a global pandemic that affects 34 million people worldwide, among which, sub-Saharan Africa accounts for 67% of this population [1]. Recent reports reveal that the HIV-1 infection is highly prevalent among pregnant women in Africa [2], and this increases pediatric infections due to mother-to-child transmission [3]. However, the majority of African populations do not have access to effective treatment to circumvent the increase in transmission. The co-infection by hepatitis C virus (HCV) in HIV-1-infected individuals is highly prevalent in the USA (25% co-infected individuals) [4]. Similarly, HIV-1 infection is also known to be associated with an increased risk of acquiring *Mycobacteria tuberculosis* (TB) infection in sub-Saharan Africa [5]. The advent of highly active antiretroviral therapy (HAART) has not only decreased the mortality rates substantially among individuals living with AIDS [6], but has also significantly decreased the incidence of HIV-1-associated dementia (HAD) [7]. However, the incidence of HIV-1-associated neurocognitive disorders (HAND), especially the milder form, has actually increased, perhaps due to central nervous system (CNS) toxicities mediated by HAART [8, 9]. Consumption of drugs of abuse, such as alcohol, tobacco, cocaine, methamphetamine and marijuana, has also been shown to exacerbate HIV-1 pathogenesis by accelerating the incidence and progression of HAND/HAD [10].

Tobacco-related deaths are the highest among addictive substances, and tobacco-associated deaths are estimated to increase from 3.0 million in 1990 to 8.4 million in 2020 [11]. Further, according to the World Health Organization (WHO) predictions, smoking related deaths though are not as severe as predicted by National Institute of Drug Abuse (NIDA), but will account for about 8 million annually by 2030 [12]. Furthermore, tobacco use is projected to account for 9% of global disability-adjusted life years by 2020, which would make it the world's single largest health problem [13]. In the USA, the prevalence of cigarette smoking in the HIV-1-infected population is 50 – 70% [14] compared to 15 – 20% in the general population [15], which further increases the risk of smoking-related health problems in this group. For example, HIV-1-infected smokers show decreased immune responses, poorer responses to antiretroviral therapy (ART) and greater risk of virological rebound, compared to HIV-1-infected non-smokers [16]. Several *in vivo* and *in vitro* studies have shown that smoking/nicotine is associated with decreased immune responses [17–19], increased inflammation [17, 20, 21], increased oxidative stress [22, 23] and increased numbers of opportunistic infections [21]. Several *in vitro* studies have shown that smoking/nicotine enhances HIV-1 replication in alveolar macrophages [24], microglia [25] and T cells [26]. However, the mechanism by which smoking or nicotine increases HIV-1 replication is largely unknown. As an exception, a report suggests that iron and oxidative stress are possible mechanisms of enhanced production of HIV-1 by alveolar macrophages in cigarette smokers [27].

Tobacco constituents are known to be metabolized by different isozymes of cytochrome P450 (CYP), and this leads to the generation of reactive metabolites and reactive oxygen species (ROS) in various organ systems such as, liver, lung, esophagus and brain [28–30]. In view of the fact that ROS is known to play an important role in HIV-1 pathogenesis, the authors propose a novel pathway involving the role of CYP enzymes in oxidative stress-mediated HIV-1 pathogenesis in tobacco users.

In this review, the authors discuss the possible role of CYP pathways in tobacco/nicotine-mediated effects in HIV-1/AIDS with respect to: i) the effect of smoking on HIV-1 pathogenesis, ii) the general mechanism of smoking-mediated oxidative stress and toxicity, iii) the potential role of the CYP pathway in tobacco/nicotine-mediated oxidative stress in HIV-1 model systems, iv) conclusions and v) an expert opinion on this subject.

2. Role of smoking on HIV-1 pathogenesis

A recent study conducted on the assessment of the mortality rates among AIDS patients has revealed that the risk of death is twice as high among smokers in the HIV-1-infected population than the non-HIV-1-infected population [31]. In part, this could be because smoking is known to increase the prevalence of other viral infections such as human papilloma virus (HPV) leading to the risk of cervical cancer in HIV-1 seropositive women [32]. Similarly, the incidence of emphysema is also reported to occur earlier and at an increased level among HIV-1-infected smokers than in non-HIV-1-infected smokers [33]. There is an evidence from the literature suggesting that smoking is associated with decline in CD4 cell counts in the HIV-1-infected population, despite of the higher baseline CD4 cell counts observed among smokers than nonsmokers [34]. However, the role of smoking in the progression to AIDS is unknown. Recent reports from the literature have also demonstrated the toxic effects of the tobacco constituents, nicotine and nicotine-derived nitrosamine ketones (NNK) in neurons, microglia and white blood cells, which are exposed to the virus or viral proteins [28, 35]. For example, the treatment with NNK to mouse microglial cells and *in vivo* injection of mouse with NNK showed an increase in ROS, as well as an increase in the levels of proinflammatory cytokines [28]. In addition, a multisite longitudinal study for up to 7.9 years using 924 women has shown that tobacco smoking negates the effect of HAART medication in relation to CD4 recovery [16]. However, the mechanism of tobacco-mediated toxicity and decreased efficacy of HAART is largely unknown.

Limited studies have addressed the effects of smoking on cognitive function and neurological disorders in the HIV-1-infected individuals with controversial findings [36]. Of relevance, it has been reported that chronic nicotine exposure can lead to the disruption of the blood–brain barrier (BBB) integrity, which may enhance the exposure to HIV-1-infected monocytes, tobacco constituents and antiretroviral drugs [37]. The exposure of these agents to CNS may exacerbate neuroAIDS and neurodegenerative diseases [37]. Another report from an observational cross-sectional study conducted in 56 women (36 HIV-1-infected and 20 non-HIV-1-infected) suggests that there is no correlation between smoking and cognitive dysfunction [36] in the HIV-1-infected population. Collectively, the available evidence suggests that there is an increase in smoking-mediated HIV-1 pathogenesis among individuals with HIV-1/AIDS and patients may benefit from the development of novel

therapeutic agents and/or drug dose adjustments that can be used to treat HIV-1-infected smokers effectively.

3. Mechanism of tobacco smoking mediated toxicity: role of CYP

The role of CYP enzymes has not been studied in context with smoking/nicotine and HIV-1 pathogenesis. However, there are several elegant studies that show the involvement of CYP2A6, CYP2A13, CYP1A1 and CYP1B1 in smoking/nicotine-mediated toxicity leading to various types of cancers and hepatic toxicity [38, 39]. The majority of tobacco constituents, including nicotine, are metabolized and/or activated by CYP enzymes to generate ROS and/or reactive metabolites, NNK [40]. ROS and reactive metabolites are known to cause DNA damage, lipid peroxidation and protein oxidation that leads to cell toxicity [41]. Nicotine, the major constituent of tobacco, is predominantly metabolized by liver CYP2A6 and lung-specific CYP2A13 to cotinine (75%) and other metabolites (15%) [29, 39, 42, 43]. In addition, CYP2A6 and CYP2A13 are involved in the metabolic activation of tobacco-specific nitrosamines into reactive compounds that lead to liver and lungs toxicities [44]. Other tobacco constituents, such as polyarylhydrocarbons (PAH) are mainly activated by CYP1A1 and CYP1B1 [45, 46] that leads to the formation of reactive metabolites, which has been shown to be associated with oral toxicity [46]. Furthermore, a study comprising 600 patients has demonstrated that CYP1A1 is a risk factor in oral cancer among smokers [45]. Based on the fact that CYP pathways play a critical role in smoking-mediated cell/organ toxicity, there is a critical need to explore the involvement of CYP pathways in smoking/nicotine-mediated HIV-1 pathogenesis.

4. Potential role of CYP in tobacco/nicotine-mediated oxidative stress and toxicity in HIV systems

In the following sections, we discuss whether CYP enzymes, especially those that are related to tobacco/nicotine, are expressed in monocytes/macrophages, lymphocytes, astrocytes and neurons (Figure 1). We then discuss the role of CYPs in tobacco/nicotine-mediated oxidative stress in these cells, and their possible link to HIV-1 pathogenesis and neuroAIDS. Finally, we identify the future course of investigation in this area of research.

4.1 Monocytes/macrophages

Monocytes/macrophages are considered to be one of the major cellular targets of HIV-1 and are thought to function as important viral reservoir [47]. Compared to activated CD4⁺ T lymphocytes, macrophages are more resistant to the cytopathic effect of HIV-1 and survive HIV-1 infection for extended periods of time [48, 49]. Furthermore, infiltration of macrophages into the brain results in spreading of the virus to resident glia, including perivascular macrophages, microglia and astrocytes [50–52]. Migration of HIV-1-infected monocytes through the BBB is thought to be one of the major mechanisms responsible for the neuropathogenic effects of HIV-1, such as HAD and HIV-1 encephalitis (HIVE) [53, 54]. Investigations to study the effect of tobacco/nicotine in monocytes/macrophages *in vivo* are therefore clinically relevant.

The major nicotine-metabolizing CYP2A6 mRNA and protein are expressed in U937 monocytic cell line [55]. A comparison between the levels of CYP2A6 mRNA in U937 cells and previously reported hepatocytic cells demonstrated that the level of CYP2A6 mRNA is similar in both the cells [56–58]. More importantly, the relative levels of the mRNA of CYP2A6 are much higher than the other CYP enzymes, including the mRNA of CYP1A1 and CYP1A2 [56, 59]. A relatively high abundance of CYP2A6 in U937 cells is intriguing and suggests further investigation on its role in HIV-1-infected smokers. Other investigations in macrophages derived from the U937 monocyte cell line have shown that nicotine is metabolized to cotinine and NNK by CYP2A6, a finding that was later confirmed using a CYP2A6 selective inhibitor, tryptamine [60]. In addition, it has been demonstrated that the metabolism of nicotine by CYP2A6 results in the generation of ROS [60]. To study the role of CYPs in smoking-mediated oxidative stress, *ex-vivo* experiments using peripheral blood monocytic cells from human cohorts (smokers and non-smokers, HIV-1-infected smokers and HIV-1-infected non-smokers) are underway. Since oxidative stress has been linked to increased HIV-1 replication in human primary macrophages *in vitro* [61], we hypothesize that CYP2A6-mediated nicotine metabolism and resultant oxidative stress may be a mechanism for the increase in viral replication among HIV-1-infected smokers. This hypothesis is also supported by the fact that alcohol-mediated oxidative stress through CYP2E1 pathway increases the replication of another deadly virus, HCV [62, 63]. In one of these studies, it has been shown that CYP2E1-mediated alcohol metabolism, which produces ROS, increases the replication of HCV in hepatic cells and decreases the antiviral action of interferon [62]. The study involving the role of CYP2A6 and other tobacco/nicotine-metabolizing CYPs in oxidative stress and HIV-1 pathogenesis in monocytes/macrophages of HIV-1-infected smokers and non-smokers is underway.

In addition to CYP2A6, CYP2E1 and CYP3A4 are abundantly expressed in U937 monocytic cell lines [56]. Furthermore, CYP2E1 and CYP3A4 (mRNA and protein) are both induced by alcohol by approximately two fold in U937 cells [56]. CYP3A4 is mainly involved in the metabolism of ART drugs, non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) [64]. Thus an altered level of CYP3A4 in the HIV-1 model systems by agents, such as alcohol and other medications, is expected to affect the response to ART drugs, especially NNRTI and PI.

4.2 Lymphocytes

Smoking has been shown to be associated with a reduction in CD4⁺ T cells [34] and an increase in mortality in HIV-1-infected individuals [31, 65], but the mechanism for smoking-mediated effects on lymphocytes is unknown. From these studies it appears that tobacco constituents, especially nicotine, decrease immune response possibly by altering cytokines and chemokines in these cells. In addition, other studies have shown that nicotine toxicity in lymphocytes is mediated through superoxide anion formation [66]. It has been further shown that the ROS generated in lymphocytes, by smoking, results in the oxidation of lipids, protein and DNA. It also decreases the levels of antioxidant enzymes (GST and SOD) [66]. This finding is further supported by the fact that DNA fragmentation in lymphocytes is mediated by oxidative stress resulting from nicotine [67]. Earlier study using quantitative RT-PCR showed that CYP1A1 mRNA is present at very low levels in human

blood lymphocytes [68]. Furthermore, this study demonstrated that CYP1A1 mRNA is induced 20-fold by 2,3,7,8-tetrachlorodibenzo-p-dioxin in lymphocytes. Since the residual levels of tobacco/nicotine-metabolizing CYP enzymes (CYP1A1, CYP1A2 and CYP2A6) are extremely low in lymphocytes, a study involving recombinant expression of these enzymes was performed to examine the role of these enzymes in lipid peroxidation through CYP pathways [69]. The results showed that these CYP enzymes increased lipid peroxidations by 2.1-fold, suggesting their role in oxidative stress. Further, a recent report showed that CYP2A6 is significantly induced in peripheral blood lymphocytes of lung cancer patients, suggesting that the expression of CYP2A6 could potentially be used to predict environment-induced disease and toxicity in humans [70]. However, there is nothing known about the expression of CYP2A6 or other tobacco/nicotine-metabolizing CYPs in the lymphocytes of HIV-1-infected smokers or nonsmokers. Studies are underway to investigate the role of CYP pathway in smoking-mediated HIV-1 pathogenesis in peripheral blood lymphocytes.

4.3 Astrocytes

Despite of the fact that HAART therapy increases the life span of HIV-1-infected individuals, the neurological complications, such as HAND, continue to be a source of significant morbidity. This is increasingly important, because since HIV-1-infected individuals live longer, this trend is expected to continue [71]. Astrocytes, the most abundant glial cells in the brain, which are important to protect the integrity as well as nourishment of neurons, play a major role in the pathology of HAND [72]. Astrocytes are also known to be infected by HIV-1, though to a lesser extent compared to microglia [73]. In addition, viral proteins and cytokines released by HIV-1-infected microglia are known to damage astrocytes [72], which may ultimately lead to HAND. It has been shown that HIV-1 protein gp120 induces proinflammatory cytokines/chemokines such as IL-6, IL-8 and CCL5 in SVGA astrocytic cell lines and primary astrocytes [74–76]. The expression of these cytokines/chemokines is regulated through the nuclear factor-kappa B-dependent (NF- κ B) pathway [74–76]. In these studies, the involvement of NF- κ B in the regulation of the inflammatory cytokines/chemokines was shown using specific chemical inhibitors, as well as siRNA of NF- κ B pathway.

Nicotine has been shown to increase BBB permeability by modulating tight junction proteins [77]. Since BBB integrity is critical to prevent the development of HAND, smoking could enhance the development and progression of these disorders through the effect of nicotine on the BBB. It has been reported that a decreased uptake of methyllycaconitine (a selective antagonist for the nicotinic acetylcholine receptor $\alpha 7$ subtype), in chronic nicotine exposed rodent models, is due to diminished blood–brain passive diffusion of compounds with very low extraction rates [78]. Hence it is vital to understand the interactions of smoking and HAART with the BBB, which may affect the pharmacokinetic profile of these drugs leading to decreased efficacy and increased toxicity.

Recent investigations have shown that the relative abundance of CYP1A1 mRNA is 36% and CYP2A6 mRNA is 56% compared to the mRNA of other CYP enzymes that were detectable in SVGA astrocytes [79]. In addition, CYP3A4 that is responsible to metabolize

NNRTI and PI is also expressed in SVGA astrocytes [79]. In addition, this study demonstrated that acute nicotine treatment at 1 μ M induces CYP1A1 and CYP2A6 at both mRNA and protein levels [79]. Furthermore, the study showed that nicotine metabolism is mediated by CYP2A6, resulting in the formation of cotinine and NNK, and the generation of ROS. These findings in astrocytes are similar to that observed in monocytes/macrophages, suggesting a critical role of CYP2A6 in nicotine-mediated oxidative stress and perhaps toxicity in astrocytes. Further studies are needed to examine the role of other CYP enzymes in toxicity mediated by other tobacco constituents in astrocytes, as well as the role of CYP in tobacco-mediated HIV-1 pathogenesis.

4.4 Neurons

There is very limited information on the effects of smoking on HAND. A recent report has shown that genetically expressed HIV-1 viral proteins in rats attenuate nicotine-induced behavioral sensitization, which is associated with altered cAMP response element binding protein and extracellular regulated kinase signaling pathway in mesocorticolimbic system [80]. *In vitro* and *in vivo* studies reveal that NNK is known to cause neuroinflammation in brain [28]. NNK activates microglia and astrocytes to induce proinflammatory cytokines/chemokines with subsequent neuronal damage [28]. In addition, NNK treatment increases phosphorylation of inflammatory signaling molecules such as NF- κ B, ERKs, JNK and p38 MAPK in the brains of BALB/c mice [28]. Since HIV-1 gp120, a major viral protein, induces proinflammatory cytokines in astrocytes [74–76], NNK-mediated neuroinflammation could further aggravate HAND.

Another nicotine metabolizing enzyme, CYP2B6, is expressed in both astrocytes and neurons [81]. An earlier report has shown that rat CYP2B1 (homologous to human 2B6) is induced by nicotine in the brain, however, in this case, induction is not mediated through nicotinic acetyl choline receptors (nAChRs) [82]. Similarly, the level of CYP2B6 is increased in the brains of smokers compared to nonsmokers, specifically in cerebellar purkinje cells and hippocampal pyramidal neurons [81]. Similarly, a study in African green monkeys shows the induction of CYP2B6 in the brain, but not in hepatic cells following chronic nicotine treatment [83]. An increased level of CYP2B6 in smokers could lead to an altered metabolism of CYP2B6 substrates. For example, CYP2B6 metabolizes nicotine and also activates NNK, which may lead to increased oxidative stress and damage [84]. In addition, CYP2B6 metabolizes an important HAART drug, efavirenz, which may cause tobacco–HAART interaction. Further studies are needed to examine the role of CYP enzymes in tobacco/nicotine-mediated neuropathogenesis and tobacco–HAART interactions in neurons.

5. Conclusions

Although smoking is highly prevalent in HIV-1-infected individuals and it is known to increase mortality [31, 65], studies related to the effects of smoking on HIV-1 pathogenesis are very limited. Therefore, there is an urgent need to investigate the complexities of these pathways that are responsible for decreased immune responses, increased HIV-1 replication, and increased AIDS related conditions in HIV-1-infected smokers. Recent findings, as

described in Section 4, suggest that CYP plays an important role in smoking mediated effects on HIV-1 model systems, such as monocytes/macrophages, lymphocytes, astrocytes and neurons. In addition, it is known that smoking decreases the efficacy of HAART, especially NNRTI and PI, which may also involve the CYP pathway. CYPs are the major drug metabolizing enzymes for HAART, nicotine and drugs used to treat opportunistic infections such as TB. A differential expression of CYP enzymes may alter the pharmacokinetic profiles of these drugs, including efficacy and toxicity. Therefore, it is imperative not only to examine the role of smoking on the CYP pathways, but also the impact of smoking on drug–drug interactions. Future studies in the following areas are necessary: i) investigation of CYP pathway in HIV-1-infected smokers, especially the CYP enzymes by which tobacco-mediated oxidative stress enhances HIV-1 replication in macrophages, astrocytes and neurons, ii) a similar study with women and diverse ethnic groups who have CYP2A6 and CYP2B6 polymorphisms, which would provide an opportunity for personalized medicine in the future, iii) an investigation in HIV-1-infected patients co-infected with TB/hepatitis who receive HAART and/or anti-tubercular drugs that are metabolized through the CYP pathway, iv) studies to determine the role of smoking on the immune system in HIV-1 infection, v) clinical trials to identify potent CYP inhibitors as therapeutic agents that block nicotine-mediated HIV-1 replication and vi) investigation of the role of the CYP pathway in the combined effect of alcohol and nicotine on oxidative stress-mediated HIV-1 replication because alcohol consumption is common among smokers and appears to follow a similar CYP pathway (CYP2E1) [59].

6. Expert opinion

This review highlights the first evidence we are aware of to examine a link between nicotine-induced CYP-mediated (2A6 and others) oxidative stress and increased HIV-1 pathogenesis in HIV-1-infected smokers (Figure 1). Our approach explores the *in vitro* effect of nicotine/tobacco on lymphocytes, monocytes/macrophages and astrocytes as well as an *ex vivo* study involving lymphocytes and monocytes/macrophages of peripheral blood mononuclear cells (PBMC) obtained from HIV-1-infected smokers. This is clinically relevant, because smoking is common among HIV-1-infected individuals and smoking/nicotine has been shown to enhance HIV-1 replication in alveolar macrophages [24], microglial cells [25] and T cells [26]. Furthermore, oxidative stress is known to enhance nicotine-mediated HIV-1 replication in alveolar macrophages and monocyte-derived macrophages [27, 61]. However, little is known about the mechanism/pathways by which nicotine or other constituents of smoking exert its effect on these cells.

We propose that tobacco/nicotine, or its metabolites, enhance HIV-1 replication in monocytes/macrophages through CYP pathway (Figure 2). This is supported by the fact that CYP2A6 induces oxidative stress in monocytes/macrophages on nicotine metabolism [60]. These findings suggest a fruitful new area of study to explore the role of CYP2A6 in nicotine metabolism and oxidative stress in HIV-1 replication in HIV-1-infected smokers. Furthermore, it provides an opportunity to explore the use of selective inhibitors to prevent nicotine/tobacco-mediated oxidative stress and reduce HIV-1 replication. In addition to CYP2A6, several CYP enzymes, such as CYP1A1 and CYP2A13, are expected to metabolize or activate other tobacco constituents (PAH, NNK, benzopyrene) into pro-

carcinogens and produce oxidative stress in monocytes/macrophages, lymphocytes, astrocytes and neurons (Figure 1). Therefore, examination of the role of these CYP enzymes would further aid in development of novel pharmaceuticals using selective inhibitors of these CYP enzymes. It is possible that specific anti-oxidants, such as vitamin C, vitamin E, melatonin and taurine, which are very effective in alleviating oxidative stress mediated damage in alcoholic liver disease [85], could also reduce nicotine/tobacco-mediated HIV-1 pathogenesis.

Smoking is frequently associated with alcohol consumption, which is even more prevalent in HIV-1-infected population [86]. In reference to this, recent findings have shown that ethanol induces CYP2A6 and CYP2E1 in U937 monocytes/macrophages [55, 56]. Furthermore, CYP2A6 and CYP2E1 are induced by oxidative stress-mediated protein kinase C/-mitogen-activated kinase/-nuclear factor-erythroid2-related factor 2 (PKC/MEK/Nrf-2) [55] and protein kinase C/-c-Jun N-terminal kinase/-specificity protein 1 (PKC/JNK/SP1) pathways, respectively, in U937 monocytes/macrophages [87]. Thus, these pathways can be potential therapeutic targets in HIV-1-infected smokers, especially who also consume alcohol. It is likely that the contribution of CYP2A6 in nicotine-mediated effects on HIV-1 replication will be further increased in alcohol users. Similarly, it is possible that the increased level of CYP3A4 in these cells, as well as in the liver, will increase the metabolism of ART (NNRTI and PI) and this leads to a decrease in bioavailability and efficacy of ART drugs in alcohol users (Figure 3). An increase in the metabolism of ART drugs is also expected to increase drug toxicity in these cells. Therefore, examination of tobacco-alcohol interaction and their impact on HIV-1 replication and response to ART drugs through CYP2A6 and CYP3A4 pathways in liver, lymphocytes, monocytes, astrocytes and neurons is imperative (Figure 3). The findings from these studies would help to develop potentially novel pharmaceuticals and/or to find an optimal drug dose to treat HIV-1-infected smokers who also drink alcohol.

HIV-1-infected individuals are prone to TB [88]. The mortality of co-infected individuals is four times greater in TB patients with HIV-1 infection compared to patients with TB alone [89]. In a recent study conducted to determine the risk factors in HIV-1/TB co-infected patients, smoking was found to have a significant relationship with TB [90]. The occurrence of TB also increases the chance of adverse effects through CYP-mediated drug-drug interactions. The rifampicin class of antibiotics, for example, is the most effective in treating TB, but it is known to induce CYP3A4 by up to 20-fold in hepatocytes, thus decreasing the bioavailability of most NNRTI and PI. Therefore, there is a substantial risk of drug-drug interaction between the TB drugs and ART. In addition, since CYP3A4 is highly expressed in monocytes/macrophages and astrocytes [56, 64, 79], such interactions may occur in HIV-1-infected cells, which are targets of ART drugs. This hypothesis is further supported by a recent report that there is an increase in viral load in the patients who receive anti-retroviral and anti-TB drugs concomitantly [91, 92]. The management of the therapy in co-infected patients could be enhanced by proper understanding of a three-way tobacco-TB drugs-ART interactions in these patients. Therefore, it is imperative to study these interactions using recombinant CYP3A4 enzymes, as well as in hepatocytes, monocytes/macrophages, lymphocytes, astrocytes and neurons (Figure 3). These interactions are expected to decrease the efficacy of ART drugs, which may increase HIV-1 replication and exacerbate HIV-1 pathogenesis and neuroAIDS.

In addition to CYP3A4-mediated tobacco-ART interaction, CYP2B6 may also be involved in this interaction. A study has shown that cigarette smoke extract (CSE) causes induction of CYP2B6 through activation of human constitutive androstane receptor (hCAR) in hepatocytes [93]. Interestingly, CYP2B6 is involved in the metabolism of a NNRTI, efavirenz, and it has been reported that polymorphisms in either CYP2B6 or hCAR may lead to reduced adherence to efavirenz containing therapy [94]. Since efavirenz is the most common NNRTI of ART regimens, it is important to study interaction between smoking and efavirenz in hepatocytes, as well as HIV-1 systems (monocytic, lymphocytic, astrocytic and neuronal cells). This interaction may further increase CYP2B6 induction, which may lead to a decrease in bioavailability and efficacy of efavirenz in HIV-1-infected smokers.

The Immune Reconstitution Inflammatory Syndrome (IRIS) occurs in a sub-set of HIV-1-infected patients who undergo HAART and also receive anti-microbial therapy during HAART for a co-infection, such as TB. Such patients undergo a unique and exuberant recovery characterized clinically by an inflammatory syndrome which is excluded by a typical drug reaction. In a recent study by Worodria *et al.* [95], a total of 21% of 254 HIV-1/TB co-infected patients developed TB-IRIS within 2 weeks of starting HAART. It occurs in between 8 and 43% of co-infected patients and causes significant patient morbidity [96]. The mechanism of the phenomenon is poorly understood, but appears to involve the regulation and activation of CD38⁺, CCR5⁺ and CD4 T cell subsets [97] and the production of Th-1 cytokines [98] that result in granulomatous inflammation. Currently, there is no diagnostic test to predict IRIS, but it is important to note the potential cross-talk between the above cytokine producing cells and CYPs induced in PBMCs in smokers.

Tobacco/nicotine causes CYP-mediated oxidative stress [60] as well as inflammation through the release of inflammatory cytokines in monocytes/macrophages and astrocytes [99]. These findings suggest that there is a cross talk between CYP and cytokines in HIV-1-infected patients, which may occur through a common pathway in these cells. This hypothesis is strengthened by the fact that nicotine activates CYP1A1 in macrophages, which releases cytokines that further activate T-lymphocytes leading to chronic inflammation [99]. Furthermore, IL-6, an important proinflammatory cytokine, has been shown to be involved in the regulation of CYP3A4 [100]. Thus, the cross talk between CYP and cytokines is very important to study within the context of HIV-1 pathogenesis and especially IRIS.

In conclusions, smoke extract/nicotine is known to enhance HIV-1 replication in both T cells and macrophages, and therefore, it would be expected to exacerbate HIV-1 pathogenesis leading to accelerated disease progression. This article puts forward a novel hypothesis where CYP enzymes would be involved in increased oxidative stress that will in turn accelerate HIV-1 replication. We believe that further studies using *in vivo/ex vivo* human samples from HIV-1-infected nonsmokers and smokers will substantiate the role of CYP pathway in HIV-1 pathogenesis and neuroAIDS. These studies, if successful, will provide a novel and additional target for drug development for effective treatment of HIV-1 infected smokers.

Acknowledgments

Declaration of interest

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100. Williams JF. Cytochrome P450 isoforms. Regulation during infection, inflammation and by cytokines. *J Fla Med Assoc*. 1991; 78(8):517–519. [PubMed: 1720447] •• Alteration of the levels and activity of Cytochrome P450 enzymes by the cytokines released during infection and inflammation

Article highlights

- Tobacco smoking is highly prevalent in HIV-1-infected individuals. Tobacco/nicotine is associated with decreased immune responses, increased inflammation, increased oxidative stress and opportunistic infections, and perhaps increased HIV-1 replication, decreased response to antiretroviral drugs and increased progression to AIDS.
- CYP2A6 plays a major role in nicotine metabolism resulting in the formation of reactive metabolites and oxidative stress which causes carcinogenesis. CYP2A6 is also expected to play an important role in tobacco/nicotine-mediated HIV-1 pathogenesis.
- CYP2A6 is regulated by oxidative stress-mediated PKC/MEK/Nrf2 pathway by alcohol, which is significant in context of co-consumption of alcohol and tobacco that is highly prevalent in HIV-1-infected populations.
- TB is highly prevalent in HIV-1-infected populations and IRIS is a common co-morbidity of TB and HIV-1 therapy that may be mediated through tobacco–TB drugs–ART drugs interactions involving CYP pathway.
- The current findings provide strong evidence of the role of CYP pathway and oxidative stress in HIV-1 pathogenesis and drug–drug interactions. Thus, future studies are needed in the development of improved therapeutic interventions for HIV-1-infected individuals who are addicted tobacco smokers, as well as co-infected with TB.

This box summarizes key points contained in the article.

Figure 1. Cells or organs that are involved in tobacco/nicotine metabolism or activation in context to HIV-1 infection
 The metabolism and/or activation of tobacco/nicotine may be involved in the toxicity of lymphocytes, monocytes/macrophages, microglia, astrocytes and neurons causing HIV-1 pathogenesis and neuroAIDS.

Figure 2. The proposed mechanistic pathway involving the role of CYP enzymes in nicotine metabolism and/or activation of tobacco constituents, especially nicotine, which may lead to HIV-1 pathogenesis

Figure 3. Proposed strategy to study tobacco/rifampicin, tobacco/ethanol and tobacco/rifampicin/ethanol interactions and their effects on ART using recombinant CYP3A4 enzyme, HIV-infected macrophages and astrocytes, as well as hepatocytes and neurons

These interactions may additively/synergistically enhance expression of CYP3A4 enzyme leading to increased metabolism of ART thereby decreased bioavailability and efficacy of ART. A decrease in the response to ART may eventually increase HIV-1 pathogenesis. In this case ART represents only PI and NNRTI.