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Bidirectional Associations among Nicotine and Tobacco Smoke, NeuroHIV, and Antiretroviral Therapy

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Abstract

People living with HIV (PLWH) in the antiretroviral therapy (ART) era may lose more life-years to tobacco use than to HIV. Yet, smoking rates are more than twice as high among PLWH than the general population, contributing not just to mortality but to other adverse health outcomes, including neurocognitive deficits (neuroHIV). There is growing evidence that synergy with chronic inflammation and immune dysregulation that persists despite ART may be one mechanism by which tobacco smoking contributes to neuroHIV. This review will summarize the differential effects of nicotine vs tobacco smoking on inflammation in addition to the effects of tobacco smoke components on HIV disease progression. We will also discuss biomarkers of inflammation via neuroimaging as well as biomarkers of nicotine dependence (e.g., nicotine metabolite ratio). Tobacco smoking and nicotine may impact ART drug metabolism and conversely, certain ARTs may impact nicotine metabolism. Thus, we will review these bidirectional relationships and how they may contribute to neuroHIV and other adverse outcomes. We will also discuss the effects of tobacco use on the interaction between peripheral organs (lungs, heart, kidney) and subsequent CNS function in the context of HIV. Lastly, given the dramatic rise in the use of electronic nicotine delivery systems, we will discuss the implications of vaping on these processes. Despite the growing recognition of the importance of addressing tobacco use among PLWH, more research is necessary at both the preclinical and clinical level to disentangle the potentially synergistic effects of tobacco use, nicotine, HIV, cognition and immune dysregulation, as well as identify optimal approaches to reduce tobacco use.

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Conflicts of Interest

Dr. Schnoll receives medication and placebo free of charge from Pfizer for clinical trials and has provided consultation to Pfizer, GlaxoSmithKline, and Curaleaf. Dr. Gross serves on a Pfizer Data and Safety Monitoring Board for a drug unrelated to smoking or HIV. Dr. Ashare has an investigator-initiated grant from Novo Nordisk for a drug unrelated to the current paper.

Keywords

Nicotine; Tobacco; HIV; neuroHIV; HIV-associated neurocognitive disorder; Inflammation; Immune function

Introduction

The widespread use of anti-retroviral therapy (ART) for people living with HIV (PLWH) has substantially improved life expectancy (Antiretroviral Therapy Cohort 2008), with certain sub-groups of PLWH showing a life expectancy similar to that of the general population (Samji et al. 2013). Nevertheless, the annual number of new HIV infections has remained constant, increasing the number of people living with HIV/AIDS (Hall et al. 2008; Palella et al. 1998; WHO 2019). Between 2001 and 2008, the percentage of adults in the US living with HIV who are aged 50 or older has increased from 17% to 31% and the rates of new infections among 25–29 year old increased between 2012 and 2016 (CDC 2017; Mahy et al. 2014). Thus, there is a critical need to address modifiable health risk behaviors, most notably tobacco use. Unfortunately, a study with a large nationally representative sample reported that 42% of PLWH were current smokers (Mdodo et al. 2015). Although the rate of smoking among PLWH declined by ~5% from 2009 to 2014, it was still more than 2-times greater than the rate in the general population (Frazier et al. 2018). PLWH now lose more life-years to tobacco use than to their HIV infection (Helleberg et al. 2013; Helleberg et al. 2015).

Fortunately, advances in smoking cessation research over the past several decades have led to the development of treatment models that can yield quit rates approaching 40% in smokers without HIV (Pacek and Crum 2015). Further, interest in quitting smoking is high among PLWH (Frazier et al. 2018; Pacek and Cioe 2015; Pacek and Crum 2015), particularly when HIV treatment is initiated (Vidrine et al. 2018) and when tobacco use treatment is integrated with HIV care (Pacek et al. 2017). However, PLWH may also experience unique barriers to smoking cessation. For instance, depression and deficits in cognitive function are risk factors for relapse (Hitsman et al. 2013; Loughead et al. 2015) and are more prevalent among PLWH than smokers without HIV (Heaton et al. 2015; Nanni et al. 2015). Moreover, PLWH report that nicotine dependence, concerns about cravings, weight gain, and the ability to manage stress, as well as having a social network of smokers, are barriers to smoking cessation (Cioe et al. 2018; Weinberger et al. 2018).

Several reviews have concluded that there are insufficient data to indicate that tobacco dependence interventions that are efficacious in the general population are as efficacious for PLWH (Ledgerwood and Yskes 2016; Pacek and Cioe 2015; Pool et al. 2016). Indeed, two of the most effective pharmacotherapies for nicotine dependence – nicotine patches and varenicline – appear to be less effective in PLWH compared to the general population (Ashare et al. 2019b; Humfleet et al. 2013; Mercie et al. 2018). For example, a recent randomized controlled trial of varenicline for smokers with HIV, we found that varenicline increased abstinence rates relative to placebo at end-of-treatment, but, quit rates for those treated with varenicline were lower than we see in the general population and this effect

subsided by 6 months (Ashare et al. 2019b). However, treatment utilization remains low with only 1 in 5 clinicians recommending varenicline to their patients with HIV who smoke and fewer than 4% of PLWH reporting varenicline use (Pacek et al. 2017). Moreover, while behavioral smoking cessation interventions yield moderate effects vs. standard medical care (Keith et al. 2016), no specific behavioral intervention has been identified as being uniquely effective for treating tobacco use among PLWH.

Given the high smoking rates and limited smoking cessation treatment utilization and efficacy, it is not surprising that tobacco use among PLWH has significant adverse health outcomes. It increases the risk for cancer (Altekruse et al. 2018; Reddy et al. 2017), cardiovascular disease (CVD) (Friis-Moller et al. 2003), respiratory conditions such as COPD and pneumonia (Pacek and Crum 2015), and cognitive deficits observed in HIV-associated neurocognitive disorder (HAND) (Bryant et al. 2013; Durazzo et al. 2007; Harrison et al. 2017). In the current ART era, a common feature underlying many comorbidities including HAND, is persistent inflammation that does not completely reverse with viral suppression (Butler et al. 2011; Hunt et al. 2016; Lederman et al. 2013). Thus, a shared mechanism by which tobacco smoking may exacerbate these conditions may be through tobacco's effects on inflammation (Ambrose and Barua 2004; USDHHS 2010). This review provides a brief summary of the evidence from preclinical and clinical studies demonstrating the impact of nicotine and tobacco smoking on neurocognition and inflammation in the context of HIV. The specific effects of nicotine on neuroHIV/neuroAIDS (Han et al. 2018) and the role of nicotinic receptors in HAND and inflammation (Capo-Velez et al. 2018a) have been reviewed elsewhere. The primary goal of this review is to focus on: (1) the putative paradoxical effects of nicotine (which may be neuroprotective) vs tobacco smoking (which has harmful effects) on inflammation; (2) the effects of components of tobacco smoke on HIV disease progression; (3) biomarkers of inflammation (e.g., using neuroimaging) and nicotine dependence (e.g., nicotine metabolism) that may be useful for understanding mechanisms of tobacco dependence and/or neuroHIV; (4) the interactions between ARTs and nicotine and tobacco smoking; (5) the effects of tobacco smoking on peripheral organs (lungs, heart, kidney) and subsequent central nervous system (CNS) function; and (6) the impact of alternative nicotine delivery systems (i.e., e-cigarettes) on these processes. Figure 1 depicts a proposed model for the complex relationships among HIV, nicotine/tobacco use, inflammation/immune function, and cognition. Although some of these relationships are supported by evidence reviewed below, we also include proposed relationships among these variables that require evaluation. In each section, we will review the existing evidence and will discuss gaps in the research that provide directions for future studies.

Clinical Correlates of Neurocognitive and Neuropsychiatric Comorbidities in Smokers with HIV

As mentioned above, depression and deficits in cognitive function are two known barriers to cessation or risk factors for smoking relapse (Hitsman et al. 2013; Loughead et al. 2015) that are also more common among smokers with HIV than smokers without HIV (Heaton et al. 2015; Nanni et al. 2015). Since the advent of ART, the incidence of HIV-associated dementia (HAD), the most severe form of HAND, has substantially decreased (Heaton et al.

2010; Heaton et al. 2011; Sacktor et al. 2016). Yet, mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI) persist despite ART, and 25–47% of PLWH exhibit deficits in multiple cognitive domains including memory, verbal fluency, processing speed, and executive function (Heaton et al. 2015; Sacktor et al. 2016). These cognitive deficits are associated with functional disabilities including unemployment, difficulty driving, and poor ART adherence (Doyle et al. 2013; Schouten et al. 2011; Thames et al. 2013). Importantly, abundant evidence suggests that chronic smoking increases the risk of neurocognitive dysfunction and global cognitive impairment in the general population (Durazzo et al. 2012; Paul et al. 2006; Weiser et al. 2010). Similar findings have been observed among PLWH (Bryant et al. 2013; Chang et al. 2017; Durazzo et al. 2007; Monnig et al. 2016), though not in all studies (Tsima et al. 2018). Data from our group suggests that smokers with HIV perform worse on working memory and attention tasks compared to smokers without HIV (Harrison et al. 2017). In addition, smokers with HIV have demonstrated decreased cognitive flexibility (as measured by the Wisconsin Card Sort Task) and worse decision-making (as measured via the Iowa Gambling task) compared to smokers without HIV and nonsmokers with HIV (Chang et al. 2017). In one study using data from the Multicenter AIDS Cohort Study (MACS), cumulative amount of smoking (i.e., pack-years) was associated with a greater decline in cognitive performance suggesting that even reducing smoking may reduce risk of neuroHIV (Akhtar-Khaleel et al. 2017). Moreover, nicotine withdrawal produces deficits in cognitive function (Ashare et al. 2014) that are similar to those observed in neuroHIV (Antinori et al. 2007; McArthur et al. 2010; Robertson and Yosief 2014; Woods et al. 2004) and are predictive of relapse (Culhane et al. 2008; Krishnan-Sarin et al. 2007; Patterson et al. 2010; Powell et al. 2004). Therefore, it is possible that a bidirectional relationship exists between neuroHIV and tobacco use creating a dual challenge for smokers with HIV during a quit attempt. Specifically, the cognitive deficits observed in PLWH may be exacerbated during early nicotine withdrawal, thereby making it more difficult to maintain abstinence.

Depression is another common comorbidity associated with both smoking (Forman-Hoffman et al. 2016; Hitsman et al. 2013) and HIV (Nanni et al. 2015). The prevalence of tobacco dependence among adults with depression is 3–4 times higher than that among the U.S. population (40–60% vs. 15%) (Jamal et al. 2016). Moreover, up to 43% of individuals with major depressive disorder (MDD) are daily smokers (Pratt and Brody 2010) and they are less likely to quit than those with no history of MDD (Hitsman et al. 2009; Hitsman et al. 2013; Ziedonis et al. 2008). Similarly, rates of depression are approximately 3 times higher among PLWH compared to the general population (26.5% vs. 9.1%) (Do et al. 2014). Although few studies have investigated the combined effects of smoking and HIV on depression, at least one study found that smokers with HIV reported the highest rates of psychopathology symptoms compared to smokers without HIV and nonsmokers with HIV (Chang et al. 2017). In addition to the association with both HIV and smoking, depression is also strongly associated with elevated levels of inflammation (Herron et al. 2018; Rosenblat et al. 2014) as well as deficits in cognition (Rubin and Maki 2019). Thus, the combined effects of tobacco smoking, HIV, and depression may yield synergistic effects on inflammation, which may have further consequences for neurocognition.

Differential Effects of Nicotine (NIC) vs. Cigarette Smoke Extracts (CSE) on Inflammation

Numerous studies have demonstrated that smokers exhibit elevated levels of inflammation across a variety of markers, relative to non-smokers. Tobacco-induced inflammation is believed to be one of the primary pathways by which tobacco smoking contributes to acute and chronic inflammatory diseases, including CVD, COPD, acute respiratory distress syndrome, and lung cancer (Ambrose and Barua 2004). Although this topic has been reviewed in depth elsewhere (Arnson et al. 2010; Goncalves et al. 2011; Stampfli and Anderson 2009), CRP, cytokines (e.g., IL6), markers of oxidative stress (nitric oxide), cell adhesion molecules (e.g., ICAM), and markers associated with vascular inflammation (e.g., MMP-9) have all demonstrated differences between smokers and non-smokers (Kianoush et al. 2017; McEvoy et al. 2015; Shiels et al. 2014; Sopori 2002; Tibuakuu et al. 2017). Indeed, cigarette smoke condensate upregulates pro-inflammatory cytokines including IL1α, IL1β, IL6 and IL8 *in vitro* and *in vivo*, and mRNA and protein expression levels, in a dose- and time-dependent manner (Kodidela et al. 2018; Shizu et al. 2008). Wang *et al* reported higher levels of TNFα and IL1β and lower expression of β2 adrenergic receptors in alveolar macrophages and lung tissue from rats exposed to tobacco smoke (Wang et al. 2015). Ghosh *et al* demonstrated that specific components of tobacco smoke extract activate microglia *in vitro* and *in vivo* and lead to neuronal damage (Ghosh et al. 2009). Tobacco smoke may also downregulate expression of genes involved with regulation of immune function (Spira et al. 2004). In addition, there is evidence that chronic tobacco exposure compromises the integrity of the blood-brain barrier (BBB) and increases the likelihood of monocyte transmigration into the brain and/or direct CNS exposure to tobacco constituents which, in turn, enhances the risk for neurodegeneration (Hossain et al. 2009; Manda et al. 2010b; Naik et al. 2014). This may be a particularly relevant point of synergy with neuroHIV, which is driven by myeloid cell accumulation and activation in the CNS.

There is some evidence that smoking burden (e.g., number of cigarettes smoked per day and/or number of years smoked) is associated with inflammation (Asthana et al. 2010; Kianoush et al. 2017; King et al. 2017), although others have found no relationship (Shiels et al. 2014). Importantly, former smokers exhibit lower levels of inflammation relative to current smokers (Shiels et al. 2014) and inflammation decreases following smoking cessation, particularly markers reflecting oxidative stress (King et al. 2017; Van Keulen et al. 2017). While the precise time course for reduced inflammation following cessation remains an important research question, several studies have shown a relationship between time since cessation and reductions in inflammation, with times ranging from 4 months to 20 years (Peres et al. 2017; Shiels et al. 2014; Van Keulen et al. 2017). Therefore, the adverse effects of tobacco smoking on inflammation are clearly at least in part reversible.

Despite the adverse effects of tobacco use on inflammation, nicotine alone, the main psychoactive ingredient in cigarettes, may have opposite effects (Han et al. 2018). For instance, nicotine attenuates pro-inflammatory cytokines interleukin-1β (IL1β), IL6, and tumor necrosis factor alpha (TNF)-α (Wei et al. 2015). In addition, nicotine may alter expression of genes involved with immune function, upregulating some genes (e.g., TGF-β1, IL4, CCR2, CXCR6, IL1α) and downregulating others (e.g., TNFα, CCL2, IL8, IL10, CXCR4, IRF4) (Rock et al. 2008; Yang et al. 2016). Many of nicotine's anti-inflammatory

effects occur in the CNS (Shi et al. 2009), which may contribute to nicotine's neuroprotective properties (Baez-Pagan et al. 2015; Kalkman and Feuerbach 2016; Quik et al. 2012). Specifically, nicotine binds to and activates nicotinic acetylcholine receptors (nAChRs) leading to an influx of calcium, particularly through the α7 nAChR. This activates downstream signaling cascades such as the NFκB (Yoshikawa et al. 2006), Akt and CREB signaling pathway (reviewed in Shimohama and Kawamata 2018). Nicotine has been known to modulate innate immune pathways, also through the α7 nAChR (reviewed in Cui and Li 2010). For instance, activation of α7 nAChRs suppresses abnormal activation of microglia and expression of CD14, ICAM-1, CD40, and TNFα (De Simone et al. 2005; Hamano et al. 2006; Suzuki et al. 2006), and the α7 nAChR antagonist mecamylamine reverses these effects (Hamano et al. 2006).

Components of Tobacco Smoke and HIV Disease Progression

Immunopathogenesis—In addition to nicotine, tobacco and tobacco smoke contain over 8000 compounds from different classes produced over different phases of tobacco burning (Rodgman and Perfetti 2013). These compounds include carcinogens such as 1–3 butadiene and polycyclic aromatic hydrocarbons (PAH), respiratory irritants such as acrolein and acetaldehyde, agents that increase cardiovascular risks such as cyanide, arsenic, cresols, and tar to name a few (Rodgman and Perfetti 2013). Cigarette smoke extract is comprised of various combustion products of tobacco, highly reactive free radicals, gases and heavy metals (Feldman and Anderson 2013). Tobacco smoke has also been shown to contain low levels of bacterial endotoxins that can be pro-inflammatory (Hasday et al. 1999; Larsson et al. 2012). Although increasing evidence suggests that tobacco smoking alters HIV disease progression among ART-treated individuals (Gamarel et al. 2018) and those who have not yet initiated ART (Ande et al. 2013), the exact contribution of nicotine vs. the other components of tobacco smoke extract remains elusive.

Tobacco smoking may contribute to HIV-1 replication (see Figure 2 for model). For example, smokers with HIV were found to have a higher viral load when compared to non-smokers with HIV (Ande et al. 2015; Pollack et al. 2017). This would be consistent with the fact that HIV replicates most efficiently in activated CD4+ T cells, and longstanding observations that immune activation from various causes (tuberculosis, vaccination) can enhance viral replication and/or disease progression *in vivo* (Modjarrad and Vermund 2010; Whalen et al. 1995; Yek et al. 2016). Several studies have shown that smoking enhances HIV-1 replication in alveolar macrophages, microglia and T-cells *in vitro*. Notably, HIV-1 inoculation of alveolar macrophages isolated from smokers were shown to exhibit elevated p24 antigen levels compared with macrophages isolated from non-smokers (Abbud et al. 1995). Alveolar macrophages from smokers may have increased levels of iron that contribute to increased oxidative stress (Ande et al. 2013; Boelaert et al. 1996). Oxidative stress, in turn, activates and increases HIV-1 replication via the NFκB pathway (Boelaert et al. 1996) as the long terminal repeat (LTR) region of the viral genome consists of two or more NFκB binding sites (Stroud et al. 2009). In another study, benzo(a)pyrene (BaP) from tobacco smoke was shown to enhance HIV-1 replication in primary human macrophages and U1 cells. BaP, a PAH present in tobacco smoke, induces the CYP1A1-mediated oxidative stress pathway followed by NFκB activation (Ranjit et al. 2018). Dioxin, another component

of tobacco smoke also increases HIV-1 gene expression and replication that is mediated via oxidative stress (Yao et al. 1995). Indeed, cigarette smoke condensate increases levels of CYP1A1 and CYP1B1, leading to oxidative stress, increased caspase 3 mediated apoptosis and elevated HIV-1 replication in human monocytoid cells (Rao et al. 2016). Another possible mechanism for increased HIV-1 replication associated with smoking is increased CCR5 expression. Tobacco smoke been reported to potentiate HIV-1 infection in bronchial epithelial cells by upregulating CD4 and CCR5 receptor expression (Chinnapaiyan et al. 2018). Interestingly, Zao *et al* demonstrated that tobacco smoke extract, but not nicotine alone, increased HIV-1 replication in TZM-bl and Jurkat T-cell lines (Zhao et al. 2010). These studies highlight the importance of considering both nicotine and cigarette smoke extract separately and combined in order to understand their differential effects on HIV-1 replication and pathogenesis.

In addition to the general effects on immune activation and function, tobacco use also alters these processes in the context of HIV. For instance, smokers have demonstrated a more rapid loss of CD4+ T cells during HIV-1 infection (Feldman et al. 2006). Wojna *et al* showed that among HIV-seropositive women, current smokers had a higher plasma viral load than non-smokers, and history of smoking negatively correlated with CD4+ T cell counts (Wojna et al. 2007). Valiathan *et al* showed that both HIV and smoking increase the expression of activation markers on T cells, smoking also impairs T cell function in PLWH on ART (Valiathan et al. 2014). In addition, elevated levels of microbial products in the bloodstream of smokers were associated with immune activation (Valiathan et al. 2014).

Neuropathogenesis—Besides T cells, smoking also affects dendritic cells. In fact, stimulation of human monocyte-derived dendritic cells by cigarette smoke extract inhibits the T cell priming function of dendritic cells, and skews immunity by suppressing dendritic cell-mediated Th-1 responses (Vassallo et al. 2005). Nicotine also suppresses dendritic cell-mediated T cell priming and proliferation, and reduces IFN-γ production via upregulation of PPRγ pathways (Yanagita et al. 2012). Exposure of dendritic cells to tobacco smoke promotes expression levels of pro-inflammatory chemokines including CXCL8 via oxidative stress (Vassallo et al. 2008).

As shown in Figure 2, another mechanism that might affect HIV progression in smokers includes altered blood brain barrier (BBB) permeability. A multitude of studies have demonstrated that nicotine plays a bimodal role in BBB permeability. Specifically, chronic nicotine exposure to endothelial cells increases oxidative and nitrosative stress resulting in loss of BBB integrity. In contrast, acute or chronic low dose nicotine either have no effect or prevent BBB disruption, indicating a dose-response type effect (reviewed in Feldman and Anderson 2013). Disruption of the BBB by nicotine in tobacco smoke (Hawkins et al. 2004; Manda et al. 2010a) might facilitate recruitment of HIV-1 infected macrophages and HIV progression in the CNS.

As noted above, nicotine and tobacco smoke have distinct effects on inflammation, which are also observed in the context of HIV. Steel *et al* studied the augmentative effect of tobacco smoking and ART on systemic inflammation in HIV-1 infected patients, and found significantly higher circulating levels of β2-microglobulin, cyclophilin A and RANTES

irrespective of ART status (Steel et al. 2018). Furthermore, as shown in Figure 2, the α7 nAChR, which is thought to play a role in nicotine's effects on immune pathways, has been implicated in HAND pathology as HIV-1 coat protein gp120 binds to α7 nAChR (Bracci et al. 1992). Although nicotine is shown to be neuroprotective, this effect may vary in the context of HIV. For example, pretreating human microglia with nicotine potentiates HIV-1 expression in a concentration dependent manner (Rock et al. 2008). Midde *et al* showed that transgenic rats expressing HIV-1 viral proteins (HIV-1Tg) had attenuated nicotine-induced behavioral sensitization assayed by horizontal activity following nicotine or saline administration (Midde et al. 2011). In another study, chronic nicotine exposure attenuated the effect of HIV-1 viral proteins on cognitive function as assayed by the y-maze and passive avoidance tests. They further observed differential expression of genes involved in synaptic plasticity in a brain-region specific manner that varied in HIV-1Tg and control F344 rats (Nesil et al. 2015). Yang *et al* demonstrated that HIV-1Tg rats show greater novelty seeking behavior, and that nicotine administration altered expression levels of different GABA and dopamine receptors in the ventral tegmental area (VTA), nucleus accumbens (Nac) and prefrontal cortex (PFC) of HIV-1Tg compared to control F344 rats (Yang et al. 2017). Changes in the dopaminergic and GABAergic receptor expression levels in the PFC-VTA-Nac circuit suggests changes in reward perception, goal-directed behavior and habit formation in the presence of HIV-1 proteins. Although these paradigms are useful for assessing drug effects, self-administration paradigms would be more informative as a parallel to nicotine consumption in humans.

Biomarkers

Neuroimaging Biomarkers: Nicotinic Receptors—Neuroimaging offers a powerful tool for understanding vulnerability to CNS disorders, facilitating treatment development (Borsook et al. 2006), and may therefore shed light on the mechanisms that underlie the interaction between tobacco smoking, HIV, and cognitive function. There are several techniques for studying the underlying neural effects including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). In this review, we focus on PET imaging because of its capacity to target specific receptors in the brain (i.e., nAChRs) as well as neuroinflammation. Indeed, significant technological advances in radiotracer development (i.e., the incorporation of a radioisotope into the molecular structure of an epitope that binds to a specific biologic target) and instrumentation have enabled PET brain imaging to deepen our understanding of drug abuse, including nicotine dependence. For example, the [F-18] labeled radiotracer 85380 (also known as 2[F-18]FA) targets the α4β2-nAChR subtype (Gallezot et al. 2005; Horti et al. 1998; Sullivan et al. 1996; Valette et al. 1999). Although its kinetics are suboptimal (i.e., long time to achieve homeostasis throughout the brain), quantification techniques have been developed that permit robust α4β2-nAChR measurements without invasive arterial blood sampling and labor intensive high performance liquid chromatography (HPLC) required for metabolite analysis (Kimes et al. 2008; Lotfipour et al. 2011). More recently, new radiotracers ([F-18]flubatine and [F-18] AZAN) have been developed (Deuther-Conrad et al. 2008; Kuwabara et al. 2012) that target the α4β2-nAChR and demonstrate excellent reproducibility and more desirable kinetics in human brain than 2[F-18]FA (Coughlin et al. 2018; Hillmer et al. 2016; Sabri et al. 2015; Wong et al. 2013).

Despite its limitations, 2[F-18]FA has been a valuable tool for understanding the acute effects of nicotine, the effects of smoking cessation treatments that target nAChRs, and the effects of nicotine withdrawal. Even a small amount of nicotine successfully competes for receptors (Brody et al. 2006) and does so in a dose-dependent manner. For instance, sub-cigarette nicotine doses delivered by low or de-nicotinized cigarettes showed displacement of 2[F-18]FA proportional to nicotine dose (Brody et al. 2009). Pharmacological challenge studies revealed that second hand smoke also occupies nAChRs (Brody et al. 2011). Importantly, the use of 2[F-18]FA has validated that varenicline – one of the most effective smoking cessation medications and an α4β2 nAChR agonist – occupies nAChR α4β2* *in vivo* (Lotfipour et al. 2012). More recently, a newer tracer, [F-18]flubatine, has been studied with alternative nicotine delivery systems and has shown that α4β2 nAChRs are occupied following electronic cigarette vaping (Baldassarri et al. 2018).

In addition to studying acute drug effects, PET imaging techniques are also useful for studying different states of drug dependence (e.g., nicotine withdrawal) as well as individual differences. One study found that, during nicotine withdrawal, nAChR availability, measured via SPECT (Single Photon Emission Computed Tomography) imaging, peaked one week following initiation of abstinence (Cosgrove et al. 2009). This finding was important because it suggested that nAChR receptors remained occupied by nicotine far longer than expected given nicotine's short half-life of ~2 hours (Benowitz et al. 2009). There are also individual differences in receptor availability. For example, male (vs female) smokers have greater nAChR availability after 7–9 days of nicotine abstinence (Cosgrove et al. 2012). nAChR α4β2* PET imaging has demonstrated that nAChR availability normalizes upon smoking cessation regardless of the type of treatment used (bupropion vs cognitive-behavioral therapy vs placebo) providing insight into the neural basis of effective smoking cessation treatments (Brody et al. 2013). Importantly, nAChR α4β2* availability has demonstrated utility as a predictive biomarker for successful cessation therapy. Specifically, smokers who exhibit less nAChR upregulation are more likely to maintain abstinence (Brody et al. 2014). However, there are no studies that we know of on nAChR availability in PLWH, and given the potential role for nAChRs in inflammatory processes associated with HAND (Baez-Pagan et al. 2015; Wei et al. 2015; Wittebole et al. 2007), this is a key knowledge gap and an important area for future research.

Neuroimaging Biomarkers: Neuroinflammation—In addition to radioisotopes that bind to nAChRs, ligands have been developed as a means to quantify inflammation in the brain. To date, PET probes for imaging neuroinflammation have targeted upregulation of the translocator protein (TSPO), which is thought to reflect activation of microglia (Doorduin et al. 2009; Kreisl et al. 2013; Venneti et al. 2006). First generation TSPO tracers (e.g., [^{11}C]R-PK11195) have yielded conflicting results regarding differences in binding levels between ART-treated PLWH and healthy controls, but this may be due to poor performance of the radiotracer (Garvey et al. 2014; Hammoud et al. 2005; Wiley et al. 2006). Although second generation TSPO tracers (e.g., [^{11}C]DPA-713, [^{11}C]PBR28, and [^{18}F]FEPPA) have demonstrated increased specificity (Brown et al. 2007; Chauveau et al. 2008; Endres et al. 2012; Rusjan et al. 2011), they are limited in that their ability to cross the blood brain barrier is determined by the rs6971 polymorphism in the *TSPO* gene, producing substantial inter-

individual variation in their access to brain (Guo et al. 2013; Kreisl et al. 2013). Despite these caveats, TSPO PET imaging studies have yielded important information regarding the brain regions that may be affected in HIV and nicotine dependence. For example, using the TSPO tracer [^{11}C]DPA-713, differences in binding potential between PLWH and controls were observed in white matter, cingulum, and supramarginal cortex, indicating elevated levels of neuroinflammation (Coughlin et al. 2014). Moreover, TSPO binding in the prefrontal cortex was associated with HAD, though these findings were *TSPO*-genotype dependent (Coughlin et al. 2014). In a follow-up study using [^{11}C]PBR28, Vera and colleagues (2016) found increased uptake of the TSPO tracer in PLWH compared to controls, particularly in subcortical brain regions (e.g., basal ganglia). Importantly, this study also found that higher TSPO binding was associated with worse cognitive function and peripheral markers of immune activation (e.g., lower CD4/CD8 ratio) (Vera et al. 2016). It is important to note that, in both of these studies, the findings were adjusted for *TSPO* genotype to account for differences in binding potential (Coughlin et al. 2014; Vera et al. 2016)

More recently, studies have begun to investigate the impact of tobacco use on neuroinflammation using PET imaging (for a review, see Woodcock et al. 2019). For instance, Brody and colleagues (2017) observed lower binding of the TSPO tracer [^{11}C]DAA1106, among smokers compared to nonsmokers. Moreover, higher self-reported cigarettes smoked per day was also associated with lower TSPO uptake. The authors conclude that these findings indicate that tobacco smoking results in global impairment of microglial activation, a marker of impaired inflammatory processes (Brody et al. 2017). In a follow up study, the same group investigated the effects of overnight abstinence on [^{11}C]DAA1106 binding in the brain. This study replicated the previous finding that overnight abstinent smokers exhibited lower TSPO binding compared to nonsmokers, but found no effect of nicotine withdrawal (Brody et al. 2018). Although future studies are needed to assess whether these differences persist over time, these studies demonstrate global differences in microglial activation, which may reflect impaired immune function as a consequence of chronic tobacco use.

Given some of the limitations of the TSPO ligands, newer tracers targeting different markers of neuroinflammation are being developed. Indeed, TSPO levels do not distinguish between pro- and anti-inflammatory processes (Notter et al. 2018), which, as noted above, may be critical for studying the effects of nicotine vs tobacco smoking. Moreover, TSPO is not directly involved in neuroimmune signaling and activated microglia may reflect pathophysiological processes other than neuroimmune activation (Notter et al. 2018). One promising new tracer is [^{18}F]-6-(1/2)(2-fluoro-propyl)-4-methylpyridin-2-amine ([^{18}F]NOS), which is a radiolabeled version of a reversible inducible nitric oxide synthase (iNOS) inhibitor. Nitric oxide (NO), which plays an important role in immune regulation (Alderton et al. 2001), is produced by three nitric oxide synthase (NOS) enzymes: neuronal NOS (nNOS), endothelial NOS (eNOS), and iNOS. iNOS is associated with acute and chronic inflammatory diseases including asthma and COPD (Kaneki et al. 2007; Koch et al. 2007; Lechner et al. 2005; Smith and Lassmann 2002) and is expressed on glial cells in the brain (Esplugues 2002). [^{18}F]NOS readily crosses the blood brain barrier and has good selectivity over other NOS enzymes, permitting the measurement of in vivo iNOS

expression via PET imaging (Herrero et al. 2012). Thus, [^{18}F]NOS may be a useful tool for studying neuroinflammation in future studies of HIV and tobacco use.

Although no PET imaging studies that we know of have explicitly tested the combined effects of HIV and tobacco use on neuroinflammation, a recent study utilized diffusion tensor imaging (DTI) to evaluate differences in brain microstructure (Liang et al. 2018). This study found that HIV and tobacco smoking had additive effects on diffusivity in several brain regions suggesting an increased vulnerability to white matter brain injury (Liang et al. 2018). Moreover, cognitive performance was also associated with diffusivity in some brain regions. However, the specificity of using DTI to quantify neuroinflammation is mixed given that several measures (e.g., fractional anisotropy, mean diffusivity) may also be impacted by demyelination and membrane permeability (Jones et al. 2013).

Nicotine Metabolism—An important biomarker of tobacco use is the nicotine metabolite ratio (NMR) (Allenby et al. 2016; Benowitz 2009), which reflects individual differences in the rate at which people metabolize nicotine. Nearly 70–80% of nicotine is metabolized by the P450 liver enzyme CYP2A6 (Hukkanen et al. 2005). The primary metabolite of nicotine is cotinine, which is further metabolized to 3′-hydroxycotinine (3HC). Due to the long half-life of cotinine (13–19 h), the ratio of 3HC to cotinine – the NMR – is a stable measure of CYP2A6-mediated nicotine metabolism that is independent of recent nicotine use (Benowitz and Jacob 2001; Benowitz et al. 2003). It has been validated in numerous studies as a biomarker of nicotine metabolism and has been associated with multiple smoking phenotypes in non-HIV populations (Allenby et al. 2016). Higher NMR values, which are indicative of faster nicotine clearance, are associated with smoking more cigarettes each day, greater nicotine dependence, and more several nicotine withdrawal symptoms (Allenby et al. 2016). Several studies have also demonstrated that the NMR is a viable tool for personalizing treatment for nicotine dependence to improve treatment response (Kaufmann et al. 2015; Lerman et al. 2006; Schnoll et al. 2009), including a recent large smoking cessation clinical trial using prospective NMR stratification (Lerman et al. 2015).

The NMR is influenced by both genetic and environmental factors. Genetic variation in the *CYP2A6* gene contributes to differences in enzyme activity – and therefore nicotine metabolism (Piliguian et al. 2014); https://www.pharmvar.org/). There are more than 30 known variations in the *CYP2A6* gene; some variants cause functional changes in CYP2A6 activity. Those with *CYP2A6* variants that reduce function (i.e., slow metabolizers of nicotine) are generally less nicotine dependent and more likely to quit smoking (Chenoweth et al. 2013; Gu et al. 2000; Kubota et al. 2006). There are substantial population differences in the frequencies of reduced functional variants. African-Americans are more likely to have reduced function variants compared to Caucasians (Zhu et al. 2013) and NMR values generally parallel these population differences. Moreover, estrogen levels, alcohol use, age, body mass index (BMI), and menthol exposure contribute to variation in nicotine metabolism. Overall, higher NMR is associated with being female, older, lower BMI, non-menthol smokers, and greater alcohol consumption (Allenby et al. 2016; Chenoweth et al. 2014). In addition, medications that are substrates, inhibitors, or inducers of CYP2A6 activity may also impact nicotine metabolism, such as tegafur, letrozole, and the ART medication efavirenz (discussed further below) (Tanner and Tyndale 2017).

There is emerging evidence from our group and others that HIV-infected smokers may have higher rates of nicotine metabolism compared to HIV-uninfected smokers (Ashare et al. 2019a; Earla et al. 2014). Preliminary evidence suggested that the concentration of nicotine was lower among HIV-infected smokers but concentrations of its metabolites (e.g., nornicotine and cotinine) were higher, relative to HIV-uninfected smokers (Earla et al. 2014). However, this was a small sample of only six HIV-infected smokers and 17 HIV-uninfected smokers and the authors did not specifically report the NMR. Using data from a clinical trial of varenicline for smoking cessation, we recently found that, HIV-infected smokers (n=131) had a significantly higher NMR compared to HIV-uninfected smokers (n=199) (Ashare et al. 2019a). Although we were able to match the HIV+ and HIV- groups on several key characteristics (e.g., sex, race, BMI and smoking rate), this study was still unable to determine the underlying mechanism that contributed to the faster nicotine metabolism. Follow up studies are needed to: (1) evaluate whether the HIV infection itself increases nicotine metabolism; (2) identify whether certain ARTs that are either substrates, inducers, or inhibitors of CYP2A6 contribute to changes in NMR as well as other metabolizing pathways via glucuronidation (Taghavi et al. 2017; Wassenaar et al. 2015). For instance, concentrations of the ART, efavirenz, which is a substrate of CYP2A6 (in addition to other enzymes), may be associated with variation in CYP2A6 activity (McDonagh et al. 2015); and (3) investigate the consequences of faster nicotine metabolism. Indeed, evidence that CYP2A6 variation can affect HIV pathogenesis through oxidative stress pathways (Ande et al. 2013; Jin et al. 2012) suggests that the higher NMR observed among HIV-infected smokers may have downstream effects on immune function and/or neuroHIV (for a review, see Ande et al. 2013).

Interactions between ARTs and Tobacco Smoking

Nicotine interacts with ARTs, affecting their metabolism by induction or inhibition of cytochrome P-450 (CYPs) and efflux transporters (reviewed in Kumar et al. 2015; Pal et al. 2011). Notably, CYP3A4 metabolizes most commercially available drugs including ARTs (Anzenbacher and Anzenbacherova 2001) to produce ROS that leads to oxidative stress (Ande et al. 2015; Pal and Mitra 2006; Walubo 2007). Also important in the elimination of drugs is P-glycoprotein (P-gp), an ATP-dependent transporter located in the apical membrane of mucosal cells of the gastrointestinal tract, hepatic biliary canaliculi, and proximal tubule epithelial cells. Tobacco smoking can alter the pharmacokinetics of ARTs by induction of CYP3A4 and aryl-hydrocarbon-hydroxylases (D'Arcy 1984; Rahmioglu et al. 2011). Although nicotine is primarily metabolized by CYP2A6 (reviewed above), tobacco smoking can also upregulate levels of extrahepatic CYPs, namely CYP1A1 and CYP1B1 (Ande et al. 2015; Ande et al. 2013; Kumar et al. 2015; Rao et al. 2016; Zevin and Benowitz 1999), that can result in faster clearance of specific ARTs like dolutegravir, an HIV integrase inhibitor (Zhu et al. 2018). ATP-binding cassette transporters that efflux any xenobiotic molecules including drugs are differentially regulated by tobacco smoke (e.g., ABCG2, ABCB6, ABCA13, ABCC1 and ABCC3) (Aguiar et al. 2019; An et al. 2012). Smoking and ARTs can have an additive effect on expression of CYPs and efflux transporters. A recent study by Mu *et al* showed that cigarette smoke concentrate and the ART lopinavir polarize macrophages from a pro-inflammatory-like M1 to an anti-inflammatory-like M2 phase (Mu et al. 2018). Further, this shift induced expression of drug

P-gp, CYP1B1 and CYP2A6 *in vitro*. Mathematical modeling by Irunde *et al* showed that tobacco smoking decreases efficacy of ART by inducing metabolism of ARTs by 30–70% (Irunde et al. 2017).

In addition to being a substrate of CYP2A6 (see Biomarker section above), nicotine also induces several drug-metabolizing enzymes including CYP3A4, CYP1A2, CYP2B6, CYP2E1 and UDP- glucuronosyltransferase (UGT) (Pal et al. 2011). Pal *et al* demonstrated that nicotine can induce expression of CYP3A4 and MDR1 that codes for P-gp *in vitro (Pal et al. 2011)*. Nicotine can also alter pharmacokinetics by impairing BBB integrity. Indeed, both nicotine and protease inhibitor saquinavir disrupt the BBB via their effect on endothelial cells, altering the exposure of the CNS to ARTs and other potential neurotoxins (Manda et al. 2010a; Manda et al. 2010b).

In line with the bidirectional relationship between ART and tobacco use, ARTs also potentially modulate the cholinergic system and affect nicotine metabolism. Indeed, evidence reviewed above suggests that nicotine metabolism may be increased in smokers with HIV on ART compared to smokers without HIV, suggesting a role of increased CYP expression by ART (Ashare et al. 2019a; Earla et al. 2014). For example, we recently demonstrated that individuals taking efavirenz, an ART that is metabolized in part by CYP2A6, had a higher NMR compared to those not taking efavirenz (Schnoll et al. 2019). Further, ARTs can also have an effect on the cholinergic system in the CNS. A recent study by Ekins *et al* has shown that the HIV protease inhibitor, indinavir acts as a positive allosteric modulator of α7 nAChRs at low concentrations. However, at a higher concentration, indinavir inhibits α7 nAChRs reducing synaptic transmission in the cholinergic system thus contributing to cognitive dysfunction (Ekins et al. 2017). Interactions between ARTs and the cholinergic system can contribute to pathology, especially since HIV alters expression levels of specific nicotinic receptors. The levels of α7 nAChRs have been shown to be increased by HIV *in vitro* (Delgado-Velez et al. 2015) and *in vivo* (Capo-Velez et al. 2018b). The HIV envelope glycoprotein gp120 was shown to bind to and upregulate α7 expression levels (Ballester et al. 2012). Further, α7 nAChRs may compromise the BBB (Zhang et al. 2015) and alter calcium signaling (Ramos et al. 2016), potentially exacerbating HAND neuropathology (Liu et al. 2017).

Interestingly, growing evidence suggests that single nucleotide polymorphisms (SNPs) in genes encoding for drug-metabolizing enzymes and transporters add another layer of complexity in drug-drug interactions, especially with ARTs (Berno et al. 2014; Guttman et al. 2019; Tanner and Tyndale 2017; Zanger and Schwab 2013). For example, Feldman *et al* demonstrated that a genetic variant of CYP1A1 is associated with reduced response to antiretroviral therapy selectively in HIV infected smokers (Feldman et al. 2009). The variant of CYP1A1-m1 has a higher catalytic activity and has been associated with an increase in the metabolic conversion of environmental toxins to DNA modifiers, which may stimulate HIV replication. Thus, this is further evidence of a bidirectional relationship between ARTs and tobacco use.

ARTs also contribute to neurotoxicity via various mechanisms including oxidative stress, activation of endoplasmic stress and integrated stress responses (ISR), and mitochondrial

dysfunction (reviewed in Shah et al. 2016; Yuan and Kaul 2019). In fact, some ARTs have been shown to increase neuropsychiatric symptoms (reviewed in Abers et al. 2014). For example, efavirenz has been shown to have anxiogenic (Cavalcante et al. 2017) and psychoactive effects (Gatch et al. 2013), and may produce mild increases in neuropsychiatric symptoms (Van de Wijer et al. 2019). There is also some evidence that efavirenz may have rewarding and addiction-like properties in rats (Möller et al. 2018) and humans (Grelotti et al. 2014). Thus, as depicted in Figure 3, the continuous use of ARTs might contribute to the neuropathology of HAND in the ART era, specifically for PLWH with other behavioral risk factors such as tobacco use or cigarette smoking. Given that tobacco smoking can alter expression levels of various CYPs and efflux transporters, and that ARTs can affect both nicotine metabolism and can interact with the cholinergic system, the interactions between ARTs and tobacco smoking needs to be further examined. This would not only be important to understand nicotine dependence and adherence to ARTs, but also how tobacco smoking alters HIV neuropathology.

Effects on Peripheral Organ Systems

Tobacco smoking not only increases the susceptibility to infections in the lungs and other organs (Feldman and Anderson 2013), but also affects the interaction between lungs and other organ systems including the CNS, heart and the kidneys. Several studies have demonstrated that severe pulmonary disorders such as acute lung injury or respiratory distress may be responsible for poor cognitive outcomes (Fries et al. 2005; Hopkins et al. 1999), forming the basis for the lung-brain axis (Stevens and Puybasset 2011). Further, air pollution, specifically ozone, has been linked to increased risk of several CNS disorders, mediated by the priming of microglia through the lung-brain axis (Mumaw et al. 2016). Besides ozone, tobacco smoke components can also activate microglia, potentially contributing to neuropathology of HAND (Ghosh et al. 2009). Interestingly, a study by Gao *et al* demonstrated that, whereas non-nicotine components of tobacco smoke exacerbate pathology of experimental autoimmune encephalopathy (EAE), an animal model for neuroinflammation, nicotine attenuates symptoms (Gao et al. 2014).

Tobacco smoking can also alter the epigenome in blood and alveolar macrophages, that can be associated with lung function and susceptibility to lung cancer (Armstrong et al. 2019; de Vries et al. 2018; Gao et al. 2016; Imboden et al. 2019). The lungs have been considered an anatomical reservoir for HIV, even in the era of ARTs, and HIV alters pulmonary immunology (reviewed in Almodovar 2014). This is further complicated by tobacco smoking. Chand *et al* concluded that even in the presence of ART, simian-adapted HIV (SHIV) and tobacco smoke independently and synergistically induced chronic bronchitis and pro-COPD changes in the lungs in macaques (Chand et al. 2018). How the lung-brain axis is altered in HIV remains understudied and is an important are for future investigation.

Additionally, air pollution and tobacco smoking promote cardiovascular diseases via oxidative injury and damage to mitochondria, leading to atherosclerosis (reviewed in Cole and Freeman 2009). Interestingly, tobacco smoke-induced oxidative stress activates resident immune cells in the lungs including macrophages, endothelial cells, and platelets leading to altered expression of adhesion molecules, dysfunctional smooth muscle cells and an increase

in pro-inflammatory cytokines (reviewed in Messner and Bernhard 2014). Tobacco smoking also induces the formation of advanced glycation end products (AGE) which increases oxidative stress and NFκB-mediated proinflammatory cytokines, further contributing to cardiovascular diseases (reviewed in Prasad et al. 2015). Thus, future studies should investigate how the effects of tobacco smoking on cardiovascular function interact with HIV and whether there are subsequent effects on CNS function.

Another organ system affected by tobacco use is the kidneys. Smoking is a risk factor associated with chronic kidney disease (CKD) (Hall et al. 2016; Van Laecke and Van Biesen 2017), an effect that is mediated by nicotine (Arany et al. 2016; Hua et al. 2010; Jain and Jaimes 2013). In fact, a study determined smoking as a significant risk factor for CKD within PLWH and observed a dose-response relationship between packs smoked per day and CKD within this population (Miguez-Burbano et al. 2010). Importantly, ARTs including indinavir, tenofovir, atazanavir and lopinavir have also been shown to cause renal tubular dysfunction and increase risk for CKD (reviewed in Yombi et al. 2014). A recent study exploring urine biomarkers for CKD in PLWH determined that tobacco smoking was associated with higher levels of α1-microglobulin within HIV-1 seropositive patients (Muiru et al. 2019).

Recent evidence supports an association between the microbiome and brain function, including neurodegenerative and psychiatric disorders (Kim and Shin 2018; Zhu et al. 2017). Although these relationships remain unexplored in the context of HIV-seropositive smokers, smoking may independently alter the gut biome via changes in mucus and the gut immune system (Allais et al. 2016; Capurso and Lahner 2017). Thus, the gut-brain axis is another potential mechanism linking HIV and tobacco use to neurocognitive function that warrants additional investigation. Importantly, smoking also affects the neuroendocrine or the hypothalamus-pituitary-adrenal (HPA) axis (Mendelson et al. 2005; Rohleder and Kirschbaum 2006; Tweed et al. 2012) which can alter cortisol or stress levels and mood that may be modulated by sex (Badrick et al. 2007; Mendelson et al. 2005; Torres and O'Dell 2016). Indeed, sex modulates the effects of tobacco smoking on inflammation, and can modulate risk for psychiatric disorders (reviewed in Ashare and Wetherill 2018). Thus, in addition to HIV, future studies need to consider sex and external factors, such as stress levels when planning studies of the microbiome.

Alternative Nicotine Delivery Systems

The differential effects of nicotine alone compared to combustible tobacco reviewed above may have important implications for alternative forms of nicotine delivery. This is particularly relevant in light of the dramatic rise in the use of electronic nicotine delivery systems, or ENDS (e.g., e-cigarettes, vape pens), particularly among youth and young adults (Singh et al. 2016). ENDS deliver nicotine via a liquid that is heated to form an aerosol, and thus, deliver nicotine without combusting tobacco. Because ENDS do not burn tobacco, ENDS are often perceived as less harmful than conventional cigarettes and have been proposed as part of a harm reduction approach. Although vaping is often posed as a substitute for combustible tobacco, epidemiological evidence suggests that the majority of those who vape also smoke tobacco. According to the 2016 Behavioral Risk Factor

Surveillance System (BRFSS), only 15% of current ENDS users were never-smokers compared to 54.6% who were current smokers and 30.4% who were former smokers (Mirbolouk et al. 2018). There is also emerging evidence that ENDS use is growing among PLWH. A recent survey of men who have sex with men (MSM) found that 47% of HIV+ MSM reported smoking or vaping in the last 12 months, compared to 37% of HIV- MSM. Among HIV+ MSM, 16% reported vaping and the vast majority (96%) of those who vaped, also smoked (Santos et al. 2019). While there are still relatively few randomized controlled trials of e-cigarettes to reduce tobacco smoking, a recent trial found that they increased abstinence rates compared to those who used nicotine replacement therapy (Hajek et al. 2019). However, because there is generally a lack of long-term evidence of the effects of ENDS, many practitioners, including those who provide care to PLWH, are not yet willing to recommend them to their patients who smoke as strategies for reducing cigarette consumption (Bell et al. 2017). Indeed, recent reports of lung disease associated with vaping have raised important questions about their potential adverse health effects (Henry et al. 2019; Layden et al. 2019; Maddock et al. 2019).

In light of the sharp rise in the use of ENDS, there is a rapidly growing body of research investigating the effects of aerosolized nicotine on inflammation and immune function. In fact, emerging data show that ENDS may cause inflammation similar to, yet distinct from, smoking combustible cigarettes (Hom et al. 2016; Ogunwale et al. 2017). Here, we review evidence from studies focused on markers associated with neuroHIV, including oxidative stress and cytokines (e.g., IL6) (Portilla et al. 2019; Robertson et al. 2019; Yuan and Kaul 2019). For instance, in vitro studies have demonstrated that cells exposed to ENDS vapor exhibit higher oxidative stress levels – regardless of whether nicotine was present in the vapor (Scheffler et al. 2015). However, the magnitude of the increase in oxidative stress was smaller than that observed for combusted tobacco. Exposure to ENDS vapor also increased IL6 in mice and in normal human bronchial epithelial (NHBE) cells, though this effect was specific to nicotine-containing vapor (Garcia-Arcos et al. 2016). In clinical studies, adverse effects on markers of cardiovascular disease, including oxidative stress, have been found following habitual and acute e-cigarette use among smokers (Biondi-Zoccai et al. 2019; Moheimani et al. 2017). Similar effects have been observed among non-smokers, though the effects dissipated 6 hours after inhalation (Chatterjee et al. 2019). Of particular relevance to the potential impact on neuroHIV, e-cigarette vapor may compromise the BBB through similar mechanisms as tobacco smoke (Sivandzade and Cucullo 2019). Interestingly, some studies have found that ENDS aerosol exposure increases inflammation, with or without nicotine, suggesting that the chemicals in the aerosol are sufficient to produce pro-inflammatory effects (for a review, see Shields et al. 2017). While this finding is consistent with the evidence reviewed above regarding the possible anti-inflammatory effects of nicotine, other studies have found that the effects of vaping on endothelial function and oxidative stress are driven by nicotine, not e-cigarette aerosol (Chaumont et al. 2018). Importantly, these data suggest that long-term ENDS use may impact CNS function mediated by the detrimental effects on peripheral organs (Eltorai et al. 2019), including the heart and lung.

Other parameters may be important to the inflammatory effects of ENDS including the temperature at which the aerosol is heated, the ingredients used to flavor the aerosol, and the

base constituents of e-liquids which are not contained in combustible tobacco (e.g., propylene glycol and vegetable glycerin, vitamin E). When heated, propylene glycol and vegetable glycerin produce carbonyls, including acrolein, formaldehyde, and acetaldehyde, which have adverse effects on lung and cardiovascular function (Qasim et al. 2017; Shields et al. 2017). Moreover, diacetyl, which is used in flavors such as caramel and butterscotch, and benzaldehyde, which is used in fruit flavorings, have been associated with respiratory disease and cytotoxicity (Shields et al. 2017). Although recent evidence suggest potentially harmful effects of vaping on the lungs, there is a paucity of human data on the long-term effects of ENDS use or how vaping may interact with HIV-associated inflammation. Consequently, rigorous research designed to identify the effects of ENDS use is needed.

Conclusions

Figure 1 depicts the complex and often bidirectional relationships among HIV, nicotine/tobacco use, inflammation/immune function, and cognition reviewed above. We have reviewed evidence drawing direct links between HIV and tobacco use (line c), as well as studies pointing to potential mechanisms that may account for the high smoking rates among PLWH (box e, line d). Similarly, our review provides evidence of an association between HIV and neurocognitive deficits (line b) that may be driven by chronic tobacco use (line g) and/or immune dysregulation (line a). The current review also highlighted several important biomarkers of nicotine dependence (e.g., nicotine metabolite ratio) and neuroinflammation (using novel neuroimaging techniques) that may shed light on these relationships. Additional studies are necessary at both the preclinical and clinical level to disentangle the potentially synergistic effects of tobacco use and HIV and cognition and immune dysregulation. Lastly, given the rapid rise in e-cigarettes, we suggest that future studies investigate the short- and long-term health effects of ENDS on immune function, cognition, and HIV-related disease outcomes.

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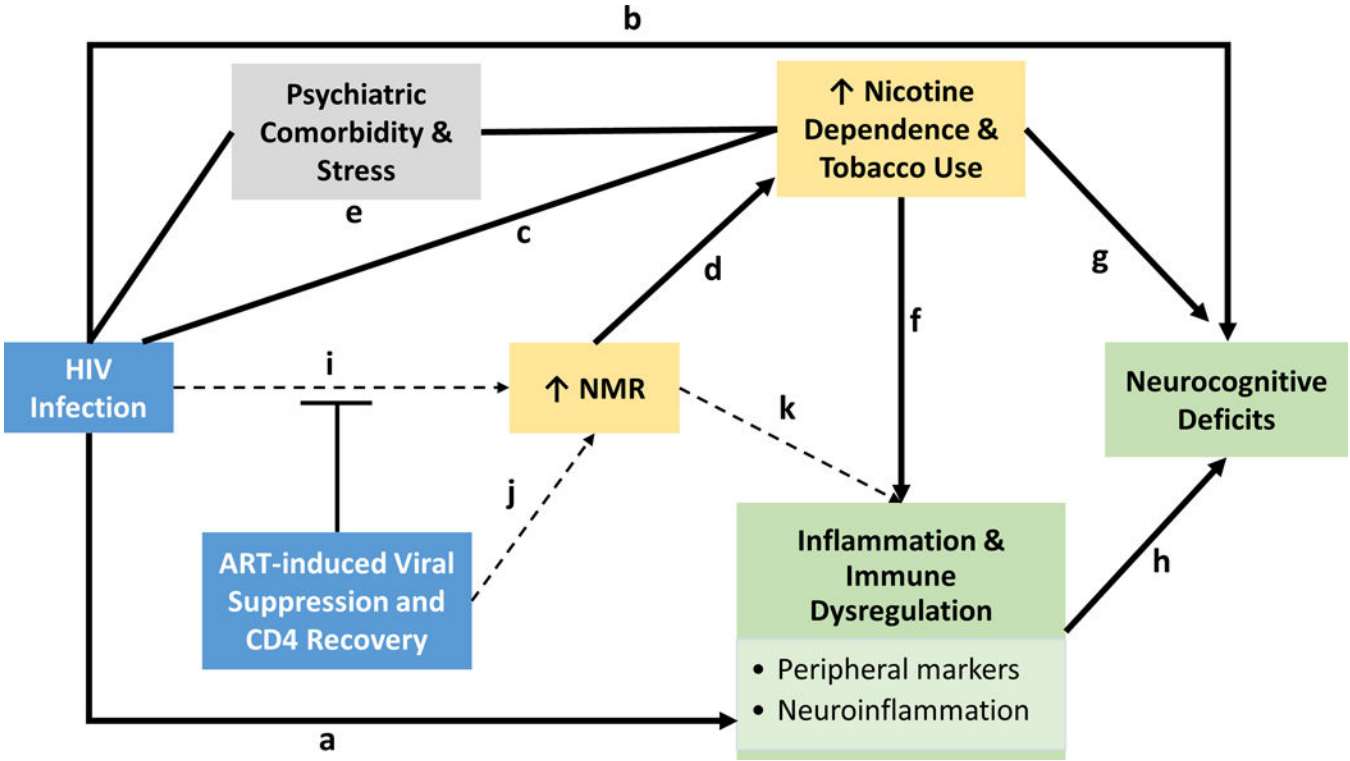

Figure 1. Proposed model of the relationships among HIV, ART, smoking, inflammation, and neurocognition.

Solid lines represent relationships supported by evidence. Dashed lines represent relationships that have not yet been studied or there is not enough evidence to make a conclusion. (a) HIV infection produces elevated levels of inflammation and immune dysregulation even among virally suppressed individuals. (b) HIV is associated with deficits in cognition function. (c) Smoking rates are significantly higher among PLWH, compared to the general population. (d) The nicotine metabolite ratio (NMR) is strongly associated with smoking behavior (i.e., faster metabolizers tend to smoke more cigarettes, are more nicotine dependent, and have less success at quitting smoking compared to slower metabolizers). (e) HIV and tobacco use are both associated with higher rates of psychiatric comorbidities, such as depression, and elevated levels of chronic stress. These factors may represent other mechanisms linking HIV and tobacco use. (f) The relationship between nicotine, tobacco smoking, and inflammation is complex, but it is well-established that smoking induces inflammation; the evidence for nicotine as anti-inflammatory is supported in some studies, but not others. (g) Similar to the relationship between tobacco use and inflammation, the relationship with neurocognition may differ for the effects of nicotine (acute nicotine use may have beneficial effects) vs. tobacco smoking (chronic use may impair cognition). (h) There is evidence that elevated levels of inflammation are associated with deficits in cognition. (i) There is some evidence that PLWH metabolize nicotine faster than those without HIV; the mechanism is not yet known and the finding needs validation in larger samples. We also hypothesize that if HIV-infection increases nicotine metabolism, then we should observe an attenuation effect once ART is initiated. (j) It is possible that the increase in NMR is due to ART effects on CYP2A6. Therefore, depending on whether a particular

ART induces, inhibits or is a substrate of CYP2A6, the direction of the effect on NMR may change. (k) We hypothesize that faster nicotine metabolism may result in higher levels of inflammation since nicotine has anti-inflammatory properties.

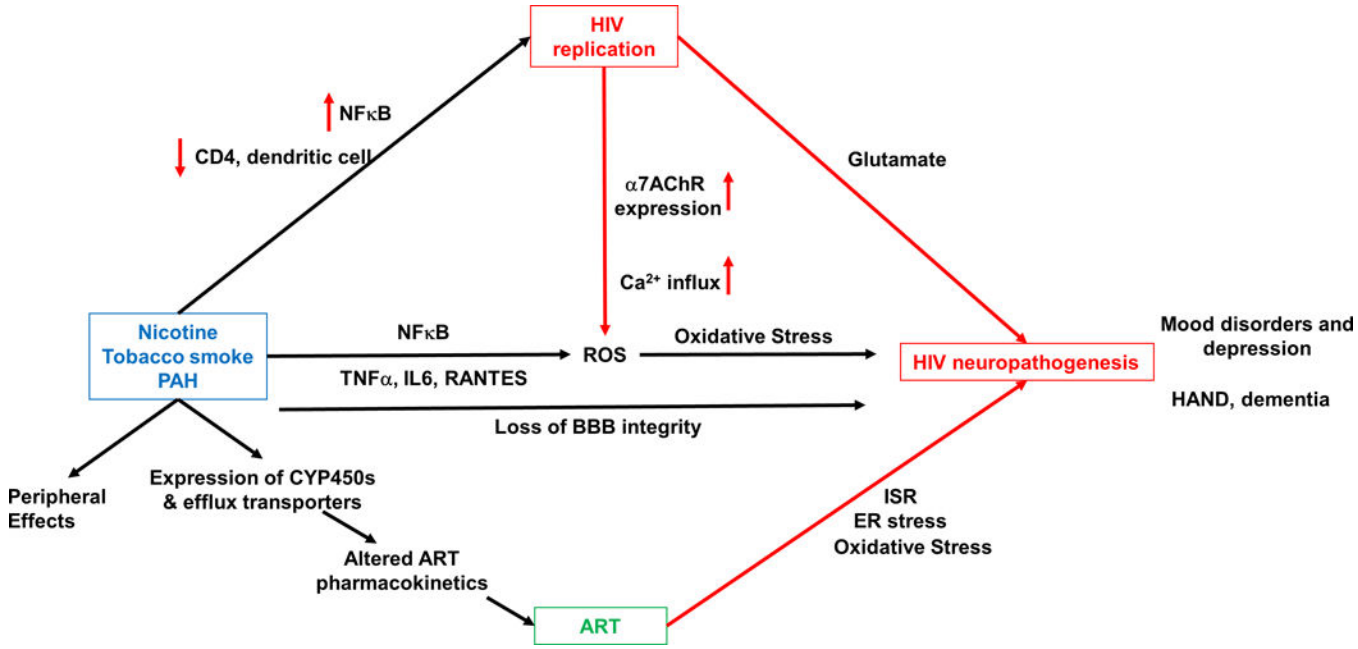

Figure 2. Proposed molecular mechanism underlying effects of tobacco smoking on HIV neuropathogenesis.

Tobacco smoke and its components increase HIV replication via increased transcription of HIV proteins mediated by NFκB pathways, and decreased function of immune cells including CD4+ T-cells and dendritic cells. In addition, tobacco smoking increases levels of pro-inflammatory cytokines and oxidative stress and leads to loss of BBB integrity, further contributing to HIV neuropathogenesis. Increased HIV replication increases oxidative stress via the α7 nAChR, that has been shown to increase expression during HIV infection. Tobacco smoking also affects the periphery including the lungs, cardiovascular system and the renal system. Importantly, tobacco smoke induces expression of cytochrome-P450s and efflux transporters, that alter pharmacokinetics, and hence the efficacy of antiretrovirals. ARTs themselves can have neurotoxic effects that are mediated by the ER stress, the integrated stress response (ISR), and oxidative stress.

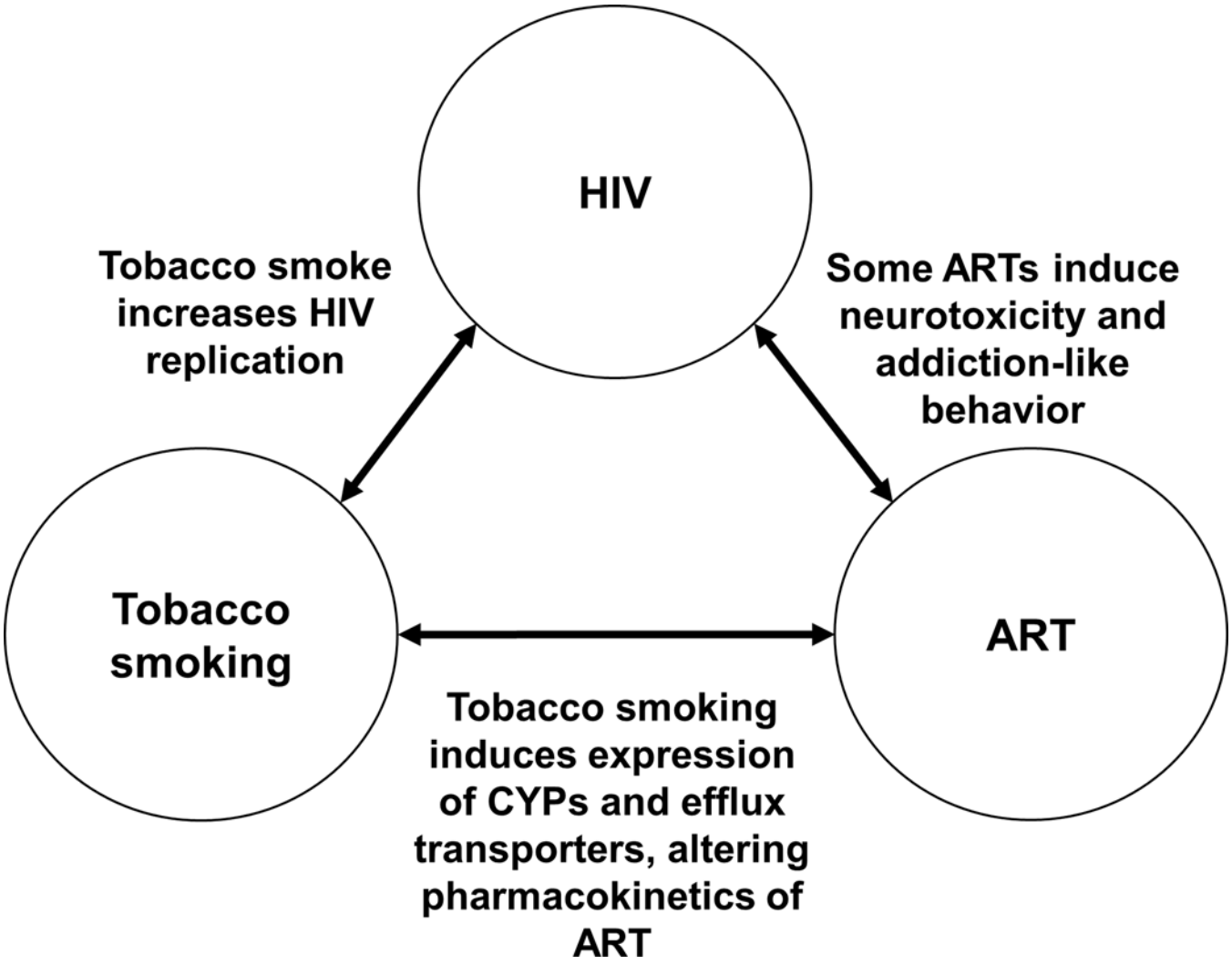

Figure 3. Interaction between tobacco smoking, HIV and antiretroviral drugs.

Tobacco smoke has been shown to increase HIV replication and decrease the efficacy of antiretrovirals (ARTs). Even though ARTs are indispensable for management of HIV, some have been shown to have neurotoxic adverse effects.