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The Impact of Substance Abuse on HIV-Mediated Neuropathogenesis in the Current ART Era

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Abstract

Approximately 37 million people worldwide are infected with human immunodeficiency virus (HIV). One highly significant complication of HIV infection is the development of HIV-associated neurocognitive disorders (HAND) in 15 – 55% of people living with HIV (PLWH), that persists even in the antiretroviral therapy (ART) era. The entry of HIV into the central nervous system (CNS) occurs within 4 to 8 days after peripheral infection. This establishes viral reservoirs that may persist even in the presence of ART. Once in the CNS, HIV infects resident macrophages, microglia, and at low levels, astrocytes. In response to chronic infection and cell activation within the CNS, viral proteins, inflammatory mediators, and host and viral neurotoxic factors produced over extended periods of time result in neuronal injury and loss, cognitive deficits and HAND. Substance abuse is a common comorbidity in PLWH and has been shown to increase neuroinflammation and cognitive disorders. Additionally, it has been associated with poor ART adherence, and increased viral load in the cerebrospinal fluid (CSF), that may also contribute to increased neuroinflammation and neuronal injury. Studies have examined mechanisms that contribute to neuroinflammation and neuronal damage in PLWH, and how substances of abuse exacerbate these effects. This review will focus on how substances of abuse, with an emphasis on methamphetamine (meth), cocaine, and opioids, impact blood brain barrier (BBB) integrity and transmigration of HIV-infected and uninfected monocytes across the BBB, as well as their effects on monocytes/macrophages, microglia, and astrocytes within the CNS. We will also address how these substances of abuse may contribute to HIV-mediated neuropathogenesis in the context of suppressive ART. Additionally, we will review the effects of extracellular dopamine, a neurotransmitter that is increased in the CNS by substances of abuse, on HIV neuropathogenesis and how this may contribute to neuroinflammation, neuronal insult, and HAND in PLWH with active substance use. Lastly, we will discuss some potential therapies to limit CNS inflammation and damage in HIV-infected substance abusers.

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Introduction

Approximately 37 million people are living with human immunodeficiency virus (HIV) worldwide, with approximately 1.8 million new infections in 2017 (1). The introduction of antiretroviral therapies (ART) has significantly reduced HIV-associated mortalities, and prolonged lifespan among people living with HIV (PLWH). HIV enters the central nervous system (CNS) within 4 to 8 days after peripheral infection, usually before a person has been diagnosed (2–4). This is mediated, in part, by the transmigration of infected peripheral blood monocytes across the blood brain barrier (BBB) (5–9). Once within the CNS, these cells can differentiate into macrophages, becoming long-lived cells and establishing a viral reservoir that persists even with effective ART (10, 11). Infected macrophages promote the infection of additional cells within the CNS including microglia, macrophages, and astrocytes, at low levels, but not neurons (12). Some studies have shown that HIV can still be detected in the cerebrospinal fluid (CSF) of PLWH on suppressive ART (4, 13–15). HIV DNA and RNA are detected in perivascular macrophages and microglia within brain tissues of HIV-infected people on ART, suggesting that these long-lived infected cells may serve as viral reservoirs in the CNS (11, 12). Additionally, viral proteins including HIV Tat, a trans activator of transcription, and HIV Nef, a negative regulatory factor, are still produced extracellularly in the CNS of PLWH, even with ART (16–18). The presence of HIV and its proteins can infect and/or activate resident CNS cells, contributing to release of viral and host inflammatory mediators and neurotoxic factors that contribute to ongoing inflammation and neuronal damage.

A significant consequence of HIV infection is HIV-associated neurocognitive disorders (HAND), with 15–55% of PLWH developing HAND even in the presence of ART (19–22). HAND is a spectrum of disorders that includes attention deficits, impaired overall executive function, motor function, working memory, learning, and speed of information processing, and dementia (23). In the pre-ART era, HIV-associated dementia was prevalent, but this form of HAND has declined significantly with the advent of ART. However, milder forms of HAND persist (23). HAND is diagnosed by a battery of neuropsychological tests and there are currently no biomarkers for diagnosis of, or treatments for, HAND. While neurons do not become infected with HIV, they are affected by viral proteins, inflammatory mediators, and neurotoxins chronically produced in the HIV-infected CNS, as well antiretrovirals, all of which contribute to neuronal damage and loss, and the development of HAND.

Substance abuse is a major comorbidity in PLWH. It may lead to the engagement of risky behaviors that facilitate HIV transmission, particularly sharing of needles, increasing the number of HIV-infected substance abusers (24). It is estimated that approximately 20% of new HIV infections are attributed to intravenous drug use, a common route of administration of substances of abuse (25). Methamphetamine (meth) and cocaine are stimulants that are abused by more than 1.5 million people in the United States (26). Additionally, there is currently a major opioid epidemic in the United States, with approximately 11 million people reported to misuse opioids in 2017 (26). Prescription opioid abuse is also on the rise and for some of these addicted individuals, difficulties in obtaining prescriptions for opioids results in their use of heroin (26). In addition, a significant number of PLWH are prescribed opioid pain medications or are addicted to heroin or prescription opioids.

Studies have shown that substances of abuse increase HIV CNS pathogenesis even in the presence of ART. Substance abuse alone, including the use of meth, cocaine, and opioids, is associated with neurocognitive impairment (NCI) (27–32). Some studies reported increased NCI in HIV-infected substance abusers when compared to infected non-substance abusers (33). However, one study reported that HAND was not associated with either cocaine or opioid use in PLWH (34). This study suggested that HAND is associated with dopamine receptor polymorphisms, indicating the importance of the dopaminergic system in HIV neuropathogenesis (34). This will be discussed in a separate section of the review. Substance abuse is also associated with poor ART adherence that may result in activation of viral reservoirs in infected individuals or HIV acquisition in people using ART for pre- and post-exposure prophylaxis (35). Some studies reported increased viral loads in the CSF of PLWH who abuse drugs that may be attributed, in part, to ART non-adherence and/or activation of HIV-infected cells (36). Serum biomarkers of inflammation including C-reactive protein are increased in PLWH who use meth and cocaine, as compared to HIV-infected non-drug users or uninfected substance abusers (37). Chronic inflammation in the periphery, mediated by translocation of microbial products, such as bacterial lipopolysaccharide (LPS), through a leaky gut epithelial barrier in PLWH, even on ART, may promote activation of peripheral monocytes and their increased migration into the CNS (38–40). A recent study reported increased monocyte activation in the peripheral blood of virally suppressed HIV-infected substance users that was not associated with ART adherence or time to ART (41). These data suggest that substance abuse contributes to increased peripheral inflammation and immune cell activation, that may result in consequent entry of monocytes, and perhaps other immune cells, into the CNS of PLWH, contributing to increased neuroinflammation, irrespective of ART. Our laboratory and others showed that a subset of peripheral mature monocytes expressing CD14, the LPS co-receptor, and CD16, the FcγRIII receptor, becomes infected with HIV, and we demonstrated that these monocytes preferentially transmigrate across a human blood brain barrier model in response to CCL2 or CXCL12, chemokines elevated in the CNS of ART treated PLWH (42–47). We also reported that $CD14^+CD16^+$ monocytes are increased in the blood of PLWH who are active substance users when compared to infected non-drug users (48). Thus, active substance use may not only increase peripheral uninfected and HIV-infected $CD14^+CD16^+$ monocytes, but also may activate this and other subgroups of monocytes, resulting in their increased transmigration across the BBB, contributing to viral entry into the CNS. This, in conjunction with reactivation of HIV in the CNS as a result of exposure of infected cells to substances of abuse, may replenish viral reservoirs and promote chronic neuroinflammation, neuronal damage and neurotoxicity in HIV-infected substance abusers, resulting in an increase in the incidence and severity of HAND.

To characterize mechanisms that facilitate HAND in HIV-infected drug users on ART, it is important to understand how substances of abuse contribute to neuronal insult. In particular, it is necessary to characterize their effects on HIV replication in the CNS and blood brain barrier (BBB) integrity, and on the entry of uninfected and HIV-infected monocytes into the brain, especially in the context of ART. The BBB tightly regulates entry of molecules and cells from the peripheral circulation into the CNS. Brain microvascular endothelial cells (BMVEC) are a major component of the BBB and these cells express surface junctional and adhesion proteins that contribute to the formation of a tight barrier and the maintenance of

BBB integrity. Astrocytes are also part of the BBB and these cells extend their end feet processes to the basement membrane of BBB vessels to interact with BMVEC which is necessary to induce BBB properties, including formation of a tight barrier (49, 50). HIV enters the CNS, in part, by the transmigration of infected peripheral mature $CD14^+CD16^+$ monocytes across the BBB (51, 52). This is a multistep process that occurs in response to gradients of chemokines including CCL2 and CXCL12 (5–9). These chemokines can induce firm arrest of monocytes, followed by the crawling and diapedesis of cells across the BBB with subsequent entry into the CNS (53). Our laboratory showed that the junctional proteins, JAM-A and ALCAM, are critical for HIV-infected $CD14^+CD16^+$ monocyte transmigration across the BBB in response to CCL2 (5). These junctional proteins are increased on HIV-infected monocytes and blocking these molecules limits monocyte transmigration in vitro (8, 54). We demonstrated that this blocking occurs even in the presence of ART (Unpublished data, Rosiris Leon Rivera). Some substances of abuse decrease endothelial junctional proteins and increase BBB permeability. This may contribute to peripheral monocyte, and perhaps T-cell, transmigration across the BBB and the entry of HIV into the CNS, leading to viral reservoir seeding and chronic neuroinflammation. Additionally, the antiretroviral drug efavirenz, a non-nucleoside reverse transcriptase inhibitor, increases permeability of human brain endothelial cell monolayers, in part through decreased tight junction proteins (55). This suggests that certain antiretrovirals may impair endothelial barrier integrity, contributing to BBB permeability. Studies need to be performed to characterize the combined effects of ART, HIV, and substances of abuse on the BBB, and their contribution to the development of HAND.

Once within the CNS, HIV-infected monocytes may differentiate into macrophages and remain as long-lived infected cells (56). Studies propose that these macrophages constitute an important CNS viral reservoir even with effective ART (57). Animal models of HIV infection include HIV-infected, ART treated humanized myeloid only mice (MoM) that are generated by injecting human hematopoietic stem cells into NOD/SCID mice (58). MoM mice are reconstituted with human myeloid and B cells, but no T-cells. Thus, MoM mice can be used to characterize the effects of HIV infection of monocytes/macrophages, in the absence of T-cells, on the pathogenesis of HIV. In a study with these mice, HIV replication is sustained in the absence of T-cells and HIV-infected macrophages are detected in multiple tissues including the brain, suggesting that these infected cells are a viral reservoir in the CNS (58). Another study with MoM mice showed that ART reduces viral load and macrophage infection with HIV. Interruption of ART resulted in viral rebound in approximately 33% of the mice indicating persistent HIV infection of macrophages even with successful ART (59). Infection of mice using EcoHIV, a chimeric HIV with replacement of gp120, the HIV envelope glycoprotein, with ecotropic murine leukemia virus (MLV) gp80, establishes infection of mouse CD4+ T-cells, peripheral and CNS monocytes/macrophages, and microglia (60). Chronically EcoHIV-infected mice develop HIV associated NCI as detected by radial arm water maze, designed to test working and spatial memory (60). To confirm further the infection of macrophages, nude mice lacking T-cells were infected with EcoHIV (60). These mice have persistent productive infection in macrophages, develop NCI, and have increased monocytes/macrophages in the brains compared to uninfected animals (60). Other studies report the presence of latently infected

macrophages in the brains of ART suppressed SIV-infected macaques (61, 62), highlighting the role of macrophages as viral reservoirs in the CNS even in the presence of suppressive ART. Additionally, latently infected peripheral macrophage reservoirs with virus capable of replication are detected in SIV-infected macaques treated with ART using quantitative viral outgrowth assays (QVOA) (63). Macrophages from these animals are able to release virus that could infect activated CD4 T-cells in culture (63).

T-cells may also contribute to HIV-mediated neuropathogenesis. In humanized mice containing only human T-cells, HIV is still detected in the brain, suggesting that T-cells may also contribute to the establishment of HIV infection in the CNS (64). CD8+ T-cells are increased in CSF of PLWH (65), with HIV specific CD8+ T-cells being present in that compartment (66). CD8+ T-cells are also associated with anti-HIV activity in the brain (67). Studies reported that depletion of CD8+ T-cells is associated with increased viral load in ART naïve (68) and ART treated SIV-infected macaques (69). These data suggest that CD8+ T-cells are important in controlling HIV in the CNS, and these cells may also contribute to ongoing neuroinflammation in PLWH.

Some studies characterized the effects of ART on neurocognitive outcomes. Treatment of mice in the absence of HIV with protease inhibitors, lopinavir and ritonavir, impairs cognition in these animals (70). In SIV-infected pig-tailed macaques, the combination of tenofovir, a nucleotide analog reverse transcriptase inhibitor, with protease inhibitors, atazanavir and saquinavir, and the integrase inhibitor, L-870812, causes neuronal injury measured by decreased synaptophysin compared to non-ART treated SIV-infected or uninfected animals (71). Cohort studies reported an association of NCI with efavirenz use in PLWH (72, 73). In vitro, treatment with antiretroviral drugs, meth, and gp120 cause a decrease in intracellular ATP in rat neurons, suggesting an effect on neuronal homeostasis (74). More studies need to be conducted to characterize the effect of ART on HAND development in PLWH who abuse drugs.

This review will highlight recent findings on the mechanisms by which substances of abuse, specifically meth, cocaine, and opioids, contribute to viral seeding and reseeding of the CNS, chronic neuroinflammation, and neuronal damage that characterize HAND. We will also describe the impact of increased CNS extracellular dopamine, induced by these substances of abuse, on the development of HAND. In addition, we will discuss some potential therapies to limit viral entry into the CNS, as well as chronic neuroinflammation in the context of substance abuse and HIV infection. Although this review will address many of the studies that were performed in the absence of ART, it is imperative for future studies to characterize the interactive effects of not only substances of abuse and HIV, but also of ART. New guidelines now recommend that ART be initiated as soon as possible after HIV infection. This early treatment of PLWH with ART may impact the mechanisms of HIV neuropathogenesis in the context of substance abuse. Although this manuscript does not have a separate section about ART and substances of abuse, we discuss effects of some antiretroviral drugs throughout the sections below and suggest potential areas of research to characterize the combined impact of HIV, ART, and substances of abuse.

Methamphetamine and HIV Overview

Approximately 1.6 million people were reported to abuse meth in the United States in 2017 (75). There are various routes of meth administration including oral and intravenous intake, or through smoking. Meth is a lipophilic stimulant with a long half-life of between 10 and 12 h. Meth readily crosses the plasma membrane of cells and can cross the BBB and enter the CNS, where it affects the dopamine reward pathway. Once in the CNS, meth exerts its effects by increasing extracellular dopamine by interacting with either dopamine transporters (DAT) or vesicular monoaminase transporter 2 (VMAT-2) (76, 77). Meth inhibits dopamine reuptake mediated by DAT in neurons, resulting in increased extracellular dopamine (76, 77). Meth also causes release of dopamine from storage vesicles in the cytoplasm of neurons by interacting with VMAT-2, and through reverse transport by DAT (76, 77). This further increases extracellular levels of this neurotransmitter that contributes to excitotoxicity and neuronal damage. Chronic meth use has been associated with NCI based on neurocognitive tests and imaging studies. The most frequently reported domains affected by meth use include memory, executive function, and motor function (29–31). One study showed that former meth users had reduced striatal dopamine transporter (DAT) density even after 3 years of abstinence when compared to controls, which may be related to axonal damage (78). Other studies also reported neuronal injury, and morphological and metabolic changes in some regions of the brains of meth users (79, 80). These studies emphasize the impact of meth alone on neuronal health, and below is a discussion of what has been reported about the interaction between meth and HIV-mediated neuropathogenesis.

Meth abuse is associated with a 1.5-fold increased risk of HIV acquisition (81). Studies reported that meth users have higher plasma and CSF HIV viral loads compared to non-meth users irrespective of ART adherence, indicating the role of meth in HIV CNS disease even in the presence of ART (82, 83). Among people with acute HIV infection, development of NCI is, in part, associated with meth use (84). Other cohort studies reported that HIV-infected meth users have an overall decline in neurocognitive performance compared to HIV-infected non-meth users, and uninfected meth users (85–87). Older PLWH on ART with a previous history of meth use have overall neurocognitive decline, especially in learning and memory, compared to non-meth using counterparts (88). Studies also examined the impact of meth and HIV on neuronal health to characterize further mechanisms mediating HAND in meth users. PLWH who chronically abused meth, have decreased expression of the neuronal marker N-acetylaspartate, indicating neuronal injury, compared to non-drug using PLWH or uninfected meth abusers (89). Similarly, in a separate study, HIV-infected meth users were shown to have decreased neuronal health and increased glial activation (82), suggesting that meth may contribute to neuron damage and development of HAND. However, another study concluded that neuronal injury is associated with HIV, and not with meth use (90). This study showed that in HIV-infected meth users, HIV RNA levels in the plasma correlates with neuronal injury (90). These studies highlight the complex interactions between meth abuse and HIV neuropathogenesis, and how both may be contributing to HAND even in the presence of ART.

Animal and in vitro studies also have been performed to characterize the impact of meth and HIV on neurocognition. In transgenic mice expressing HIV gp120, meth contributes to poor

cognitive outcomes compared to non-meth treated mice (85, 91). In transgenic mice expressing HIV Tat, escalating doses of meth results in impaired working and spatial memory compared to non-Tat transgenic mice or non-meth treated transgenic mice, suggesting cooperative effects between Tat and meth on neurocognitive functions (92). In vitro, meth increases gp120 neurotoxic effects on rat neurons, and meth and gp120 increase IL1-β and TNF-α production by rat microglia that contributes to neuronal damage (93). This part of the review will focus on the effects of meth on HIV infection, BBB integrity, monocyte entry into the CNS, macrophage, microglia and astrocyte function, and how this may all contribute to chronic neuroinflammation and neuronal damage that lead to HAND.

Methamphetamine and HIV Infection in the CNS

Meth treatment has been linked to increased HIV infection in both in vivo and in vitro studies. In SIV-infected macaques, meth does not change plasma viral load but increases virus in the brain (94). In addition, cohort studies reporting increased viral load in PLWH using meth were addressed in the previous section highlighting the contribution of meth in HIV neuropathogenesis. In vitro, meth increases HIV co-receptor CCR5 on uninfected macaque microglia, with higher expression in SIV-infected microglia (95). Meth also increases HIV replication in human microglia through downstream signaling and activation of long terminal repeat (LTR) regions of the HIV genome (96). In addition, meth induces reactivation of HIV in latently infected human microglia (96), suggesting that it may play a role in reactivation of viral reservoirs in the CNS. Meth increases HIV replication in human monocytes, and this is in part mediated by activation of the HIV LTR (97). Meth also increases HIV infection of human monocyte derived macrophages (MDM) through increased CCR5 expression (98). Additionally, a dopamine D1 receptor (D1R) antagonist blocks this effect suggesting that the effects of meth in macrophages may be mediated, in part, by activation of D1R (98). A separate study showed that meth induces large syncytia formation, augments HIV reverse transcriptase activity, and inhibits anti-HIV activity in infected human MDM through a mechanism involving D1R (99). Additionally, treatment of human MDM with meth increases HIV production as measured by p24 antigen, and this was in part due to increased galectin-1, a protein that facilitates virus-host interactions (100). Meth treatment of monocyte derived dendritic cells also increases HIV co-receptors, CXCR4 and CCR5, through modulation of dopamine D2 receptor (D2R), which in turn increases their ability to become HIV-infected (101). Meth also induces HIV replication in human neural progenitor cells (102). These cells may differentiate into latently infected astrocytes, contributing to CNS viral reservoirs. Collectively, these studies suggest that meth use may exacerbate HIV infection of CNS resident cells and may also reactivate latent viral reservoirs through various mechanisms, contributing to ongoing neuroinflammation and neurotoxicity.

Meth treatment has also been shown to increase HIV infection of T-cells. Meth pretreatment increases HIV infection of naïve and activated CD4+ T-cells, and this is proposed to be through sigma-1 receptor (103). Another study showed increased HIV replication in CD4+ T-cells, both in vitro, and in transgenic mice, through increased activation of HIV LTR (97). In contrast, high concentrations of meth inhibit HIV replication in human T-cells through upregulation of anti-HIV miRNAs suggesting that meth effects on HIV infection of, and

replication in, T-cells is concentration dependent (104). Thus, the pool of peripheral infected CD4+ T-cells available for possible transmigration across the BBB may be increased by low concentrations of meth, contributing to CNS viral seeding.

Effects of Methamphetamine and HIV on Blood Brain Barrier Permeability

Many studies examined the effects of meth by itself on BBB integrity, with an emphasis on changes in endothelial tight junction proteins. In mice, meth induces transient BBB permeability, as quantified by the passage of albumin coupled to Evans blue dye from the peripheral circulation into the brain (105). This effect is mediated, in part, by decreased tight junction proteins occludin, zona occludens-1 (ZO-1), and claudin-5 in the hippocampus (105). In studies using confluent monolayers of human brain microvascular endothelial cells (HMBVEC) in vitro as a model of the BBB, meth not only decreases tight junction proteins, but also increases polymerization of actin, inducing occludin endocytosis and disruption of barrier properties (106, 107). These results are in agreement with studies that report that meth induced ROS contributes to decreased tight junction proteins occludin and claudin-5 in rat and human BMVEC that results in increased permeability (107, 108). Meth also increases matrix metalloproteinase-9 (MMP-9) in endothelial cells that causes a transient increase in BBB permeability through cleavage of junctional proteins that maintain the integrity of the BBB (105). The effects of meth on endothelial cells of the BBB are reported to be mediated, in part, by activation of the TNF-α/NFκB pathway in BMVEC (109). Blocking this pathway inhibits increased BBB permeability in meth treated mice, as assayed by the passage of albumin-coupled dye into the brain (109). However, another study demonstrated that meth alone does not induce BBB permeability (110). In rat astrocytes, meth increases truncation of β-dystroglycan, a transmembrane protein in astrocytic end feet processes that enables astrocytes to interact with the basal lamina (111). Such effects on both endothelial cells and astrocytes may contribute to a loss of BBB integrity.

The combination of meth and HIV or its proteins can augment BBB dysfunction. In the absence of ART, BBB permeability is increased in HIV Tat transgenic mice contributing to increased numbers of perivascular macrophages (112). These results emphasize the deleterious effect of HIV on the BBB. In the context of meth with HIV, a study showed that mice treated with meth, in combination with Tat and gp120, have reduced levels of glutathione and glutathione peroxidase in the brain, suggesting increased oxidative stress (113). These animals also exhibit increased BBB permeability and decreased brain ZO-1 and occludin (113). Antioxidant treatment blocked these effects, suggesting oxidative stress as a mechanism by which HIV proteins and meth may be mediating their effects in the brain (113). In a study using cocultured HBMVEC and human astrocytes as a model of the BBB, meth and gp120 increase permeability, as measured by decreased transendothelial electrical resistance, to a greater degree than treatment with meth or gp120 alone (114). This study also showed that treatment of HBMVEC with meth and gp120 decreases ZO-1 to a greater extent than treatment with meth or gp120 alone (114). Meth in combination with Tat reduces ZO-1 in brain endothelial cell lines (110). These studies highlight the effects of meth or HIV proteins on the BBB and how in the presence of both, BBB integrity may be compromised to a greater extent than what occurs after exposure to either factor alone.

The effects of ART on BBB integrity have also been reported. The combination of protease inhibitors, lopinavir and itonavir, causes a reduction in ZO-1 and occludin, and increases matrix metalloproteinase-2 (MMP-2) in treated mice compared to controls (70). In vitro, azidothymidine and indinavir, a nucleoside reverse transcriptase and a protease inhibitor, respectively, induce ROS production by a human brain endothelial cell line (115). These data suggest that independently, meth, ART, and HIV may all be contributing to neuropathogenesis through impairing BBB tight junction protein and metalloproteinase expression. Extensive studies need to address the combined effects of ART, HIV, and meth on BBB dysfunction, and how these may contribute to HAND.

Effects of Methamphetamine and HIV on Monocyte Migration Across the Blood Brain Barrier

Studies examined whether meth facilitates immune cell entry into the CNS as a result of an increase in BBB permeability. One study determined that meth treatment alone increases monocyte transmigration across confluent monolayers of BMVEC in response to CCL2, and antioxidant treatment inhibited this effect (107). In the context of HIV infection, treatment of a BBB model of cocultured BMVEC and astrocytes with either meth or gp120 increases its permeability and transmigration of peripheral blood mononuclear cells (PBMC) in response to CCL5, with permeability and transmigration further increased by treatment with both meth and gp120 (114). With meth treatment of this BBB model, HIV-infected PBMC transmigration across the BBB in response to CCL5 is higher than that of uninfected PBMC (114). In a separate study, meth treatment of rat BMVEC monolayers results in increased migration of T-cells (116). Additionally, increased BBB permeability in mice treated with meth increases the entry of *C.neoformans* into the brain (117). These studies suggest that the extent of BBB disruption is greater with exposure to both meth and HIV or its proteins, resulting in an increase in transmigration of PBMC, monocytes, as well as pathogens across the BBB into the CNS. In vivo, meth increases the population of mature $CD14^{+}CD16^{+}$ monocyte/macrophages in the brains of SIV-infected macaques. In another study with SIV-infected macaques, meth treatment increases the population of macrophages, but not T-cells, in the brain suggesting that meth may be increasing monocyte transmigration across the BBB, resulting in increased CNS macrophages (118). This highlights the contribution of meth to monocyte/macrophage migration into the CNS and a potential mechanism that may contribute to HAND in PLWH using meth. The increased immune cell transmigration across the BBB mediated by meth may also reseed viral reservoirs and increase infection/activation of other resident cells within the CNS, contributing to chronic neuroinflammation and neuronal damage, and the development of neurocognitive impairment in HIV-infected meth users.

Effects of Methamphetamine and HIV on Macrophage, Microglia and Astrocyte Function

Meth, HIV, and functions of macrophages and microglia

Meth readily crosses the BBB, and once in the CNS it can exert its effects on resident cells, contributing to HIV neuropathogenesis. Macrophages and microglia are important for

clearing debris such as amyloid-beta and protein aggregates shown to be elevated in brains of PLWH (119). Meth treatment reduces phagocytosis by macrophages through alkalization of lysosomes, and also impairs phagocytosis of *C. neoformans* by macrophages and microglia-like cell lines (120, 121). Additionally, nucleoside reverse transcriptase inhibitors, didanosine and stavudine, impair both uninfected and HIV-infected macrophage phagocytosis (122). These data suggest that meth and some antiretroviral drugs can impair macrophage and microglia functions important for clearing debris and pathogens that may contribute to neuronal injury.

Microglia and macrophages are also involved in the CNS inflammatory response that contributes to neurodegeneration and HAND development in PLWH. In vitro, meth alone increases TNF-α in human macrophages (123), and LPS induces IL1-β, TNF-α and IL-8 in human macrophage and monocyte cell lines (123, 124). Using macrophage cell lines, meth increases IL1-β, IL-6, IL-12 and TNF-α, suggesting that it can also mediate macrophage polarization into the inflammatory M1 phenotype (125–127). In separate studies, meth alone increases TNF-α and IL-6 in a mouse microglial cell line (128), and also increases microglial activation including ROS production in mice (129). The combination of meth and gp120 increases TNF-α and IL1β by rat microglia (93). Additionally, rat microglia treated with meth and gp120 have elevated levels of nitric oxide and ROS compared to untreated microglia (93). In microglia of SIV-infected macaques treated with meth, there is increased expression of proinflammatory genes including PYCARD (Apoptosis-Associated Speck-Like Protein Containing A CARD), a component of the inflammasome, and a key mediator of inflammation (95). These studies demonstrate a contribution of meth and/or HIV in neuroinflammation. In the context of ART, one study reported increased IL1-β, IL-6, and TNF-α in brains of mice treated with lopinavir and ritonavir (70). However, raltegravir, an integrase inhibitor, in the presence of HIV, decreases TNF-α and IL-8 production below baseline in human microglia cultures (130). This suggests that some antiretrovirals may mitigate inflammatory responses in the CNS induced by HIV. More studies need to characterize the combined effects of meth, HIV and antiretrovirals on the inflammatory response by resident myeloid CNS cells.

Meth, HIV, and astrocyte function

Astrocytes are the most abundant glia cells in the CNS and are critical for maintaining brain homeostasis. The combination of meth and HIV is proposed to impair astrocyte functions, including cytokine production. Meth and HIV independently induce inflammatory cytokines in astrocytes (131, 132), and one study showed that meth or gp120 increases IL-6 in a human astrocyte cell line, with a further increase when meth and gp120 were combined (133). This suggests that the combination of these two factors may enhance neuroinflammation. In addition, meth and Tat downregulate B-catenin, a protein involved in the Wnt/B-catenin pathway, in a human astrocyte cell line (134). This effect induces senescence, and conditioned media from these astrocytes causes neuronal apoptosis due, in part, to the presence of inflammatory cytokines (135). Meth alone was shown to increase astrocyte activation, as measured by glial fibrillary acidic protein (GFAP) expression (136). Lopinavir has also been shown to increase gliosis in transgenic mice expressing HIV-1 Vpr, an accessory protein important for viral infection (137). These data suggest that meth, HIV,

and/or ART may contribute to astrocyte activation, and consequent neuroinflammation. Treatment of rat astrocytes in vitro with meth induces upregulation of inflammatory genes in a cytokine/cytokine receptor functional interaction pathway, including interleukin-1 receptor antagonist (IL1RN) and interleukin-2 receptor subunit gamma (IL2RG) (138). Meth also upregulates mitogen-activated protein kinase 5 (MAP2K5), a component of the MAPK family intracellular signaling pathway, and upregulation of MAP2K5 may be neuroprotective (138). These data suggest that meth causes transcriptional changes in astrocytes that can contribute not only to inflammation, but also to neuroprotective mechanisms.

HIV and meth have been reported to impair homeostasis in astrocytes. HIV treatment of human astrocytes induces opening of mitochondrial permeability transition pores (mPTP) that could interfere with respiratory processes (139). Meth treatment, with or without HIV, has minimal effects on mPTP opening. The expression of antioxidant proteins, including glutathione reductase, is increased in astrocytes with chronic meth exposure but elevated oxidative stress is still detected (139). In a human astrocytic cell line and human primary astrocytes, meth and HIV gp120 induce cell death by oxidative stress and increased macroautophagy (140, 141). The use of some antiretrovirals has also been associated with oxidative stress. One study reported that the combination of zidovudine (azidothymidine), ritonavir, and saquinavir induces oxidative stress in rat neuroglial cultures (71). These data suggest that meth and HIV exposure, and some ART regimens, increase the oxidative burden in astrocytes that may affect their functional capacity to maintain CNS homeostasis and regulate properties of the BBB.

Glutamate uptake is an important astrocyte function that removes excess extracellular amounts of this excitatory neurotransmitter that can induce overactivation of neurons and excitotoxicity (142). HIV alone dysregulates glutamate uptake, contributing to neuronal damage (143). One study demonstrated that the combination of meth and HIV decreases the glutamate transporter, excitatory amino acid transporter-2 (EAAT-2), and glutamate uptake by human astrocytes (144). Additionally, treatment of human astrocytes with both meth and HIV induces glutamate release by a mechanism involving gap junctions and hemichannels (145). Lopinavir decreases human astrocyte EAAT-2 and increases extracellular glutamate (137). Thus, some antiretroviral drugs, meth and HIV may inhibit the ability of astrocytes to maintain glutamate levels, resulting in neuronal insult and neuropathogenesis.

Effects of Meth on T-cell function

Many studies have examined the effects of meth on HIV infection in the CNS. Few studies have reported the effects of meth on T-cell function. In one study with ART suppressed PLWH, meth use is associated with increased CD4+ T-cell proliferation, activation and exhaustion (146). In mice, meth alters the cell cycle in antigen activated T-cells, that may decrease their proliferation as indicated by a reduction in the number of CD4+ and CD8+ T-cells (147). Meth may be mediating its effects by increasing calcium influx into T-cells which in turn increases ROS production and decreases T-cell proliferative activity after stimulation (148). These effects may all impair T-cell functions in the CNS. The role of T-cells in HIV neuropathogenesis has not been well characterized.

Cocaine and HIV Overview

Cocaine is another substance of abuse that has been associated with HIV neuropathogenesis, with approximately 2.2 million users reported in the United States (26). Cocaine is a psychostimulant that elevates dopamine in the CNS by inhibiting dopamine reuptake (149–151). Some PLWH abuse cocaine, and this is associated with poor neurocognitive performance. In one cohort, NCI in PLWH who abused cocaine is associated with ART non-adherence (152), suggesting that ART nonadherence may result in increased viral load and HAND. In contrast, PLWH using cocaine were reported to have lower CD4+ T-cell counts, and an increased viral load over time irrespective of ART (36). In another study, cocaine and HIV associate independently with HAND in a cohort of PLWH, with the majority of them prescribed ART (153). A separate report demonstrated that substances of abuse, including cocaine, do not associate with HAND (154). However, other studies reported that PLWH with a history of cocaine use or with cocaine use disorder have worse neurocognition compared to uninfected people or non-cocaine using PLWH (152, 155, 156). Based on these cohort studies, irrespective of ART adherence, cocaine use is often associated with low CD4+ T-cell count, and high viremia which may contribute to increased HIV neuropathogenesis, and development of HAND. Below we discuss some of the mechanisms by which the combination of cocaine and HIV may be contributing to the development of cognitive disorders.

Cocaine and HIV Infection in the CNS

Cocaine may contribute to HIV neuropathogenesis by increasing CNS viral load. In vivo, cocaine treatment in the bone marrow, liver, thymus (BLT) humanized mouse model induces upregulation of CCR5 on human CD4+ T-cells. These animals have increased peripheral viral load compared to controls (157). This may contribute to enhanced infection in the CNS through transmigration of infected cells across the BBB, resulting in HIV neuropathogenesis. In a severe combined immunodeficiency mouse model injected with human peripheral blood leukocytes (huPBL-SCID) infected with HIV, cocaine increases CXCR4 and CCR5 as well as viral replication in peripheral blood leukocytes (158).

The effects of cocaine on viral replication have also been characterized in vitro. Cocaine enhances HIV replication in vitro in HIV-infected PBMC (159, 160). Cocaine also increases HIV production in both human and macaque MDMs (161, 162). Cocaine induces SIV activation in latently infected macaque promonocytic cells by a proposed mechanism involving increased IL-10, a cytokine that has been reported to promote HIV infection (161). These effects are proposed to be mediated by NFκB activation, resulting in interaction of this transcription factor with HIV LTR. Cocaine treatment increases HIV infection of microglia in vitro (163). In a separate study, increased HIV expression, as measured by p24, in cultured microglia treated with cocaine was blocked by inhibitors of transforming growth factor beta 1, TGF-β1, and by sigma 1 receptor, a cocaine binding receptor, antagonists (164). Cocaine also enhances HIV replication in activated primary human CD4+ T-cells by downregulating anti-HIV miRNA and increasing HIV proviral DNA integration (165, 166). Additionally, cocaine also increases HIV infection of quiescent CD4+ T-cells (167). Another study reported that cocaine upregulates HIV infection of dendritic cells, important antigen

presenting cells, through miRNA-155 downregulation and downstream activation of HIV LTR (168). A separate study demonstrated that cocaine increases HIV transfer from dendritic cells to T-cells, further facilitating infection (169). The effects of cocaine on mediating HIV infection may contribute to establishment of viral reservoirs in the CNS, resulting in neuropathogenesis.

Effects of Cocaine and HIV on Blood Brain Barrier Permeability

Cocaine alone has been reported to impact BBB integrity. Cocaine treatment increases inter-endothelial gaps and decreases transendothelial electrical resistance in confluent HBMVEC monolayers suggesting that cocaine decreases BBB integrity (170). Some studies also examined the effects of cocaine on tight junction proteins and showed that cocaine decreases Z0–1 on BMVEC (171, 172) that may contribute to increased BBB permeability. ZO-1 is decreased, in part, through cocaine-mediated downstream signaling that increases platelet derived growth factor BB (PDGF-BB) (172). Tat has also been reported to increase PDGF-BB expression and migration of pericytes (173). This was confirmed in brain tissues of infected people with HIV encephalitis who had decreased pericytes (173). Pericytes support the integrity of the BBB, and migration of pericytes away from the BBB may contribute to its dysfunction. In the context of HIV infection, cocaine and Tat may increase PDGF-BB in the CNS vasculature and this may contribute not only to a decrease in tight junctions, but also to loss of pericytes, impacting BBB integrity. Cocaine also activates MMP-2, MMP-9 and prolidase, enzymes that degrade extracellular matrices that maintain BBB integrity (174). This consequently results in increased HBMVEC monolayer permeability (174). Tat and gp120 have also been reported to upregulate metalloproteinases (175, 176). Additionally, in a BBB model of HBMVEC and astrocytes, cocaine and Tat combined increase permeability as measured by transendothelial resistance and passage of FITC-dextran across the BBB, which is proposed to be mediated by decreased ZO-1 (177). The effects of the combination of HIV, cocaine, and ART on the BBB needs to be characterized further since some antiretrovirals have been shown to decrease metalloproteinases. Specifically, CCR5 antagonist maraviroc, and integrase inhibitors, raltegravir and darunavir, independently reduce metalloproteinases MMP-2 and MMP-9 in LPS treated rat astrocytes (178). This suggests a potential role of ART in alleviating some of the effects of HIV and cocaine on the BBB.

Effects of Cocaine and HIV on Monocyte Migration Across the Blood Brain Barrier

In vivo, cocaine increases monocyte transmigration across the BBB in mice (179). One of the key components in monocyte transmigration across the BBB is the adhesion of these cells to BBB endothelium. The effect of cocaine alone on adhesion and junctional proteins has been studied. In vivo, cocaine induces ALCAM upregulation in mouse brain microvessels, and increases the adhesion and transmigration of monocytes into perivascular regions of mouse brains (172). In vitro, cocaine increases ICAM-1 and VCAM-1 expression on HBMVEC (180, 181), and monocyte adhesion and transmigration across a BBB model of HBMVEC and astrocytes (181). Cocaine also induces TNF-α production from microglia

(182). TNF-α causes increased expression of ICAM-1 and VCAM-1 on HBMVEC (183), facilitating increased immune cell adhesion to the BBB, and consequent entry into the CNS.

Cocaine also increases adhesion and transmigration of HIV-infected, as well as uninfected, monocytes across HBVMEC monolayers (172, 174). ALCAM is upregulated on brain endothelium in PLWH with a history of substance abuse, including the use of cocaine (172). Thus, an increase in endothelial cell ALCAM by cocaine may result in increased adhesion of monocytes and T-cells to the endothelium, and increased transmigration of infected cells across the BBB. In a BBB model of cocultured human BMVEC and astrocytes, permeability and monocyte transmigration is increased to a greater extent by Tat and cocaine as compared to Tat or cocaine alone (177). The effects of Tat and cocaine on the BBB are associated with downregulation of ZO-1 and upregulation of JAM-2 on endothelial cells (177). This suggests that cocaine-mediated effects on tight junction proteins and junctional adhesion proteins increase BBB permeability and leukocyte entry into the CNS.

Cocaine mediates chemokine release that may facilitate monocyte recruitment into the CNS. PDGF-BB, that is increased by cocaine treatment of BMVEC, induces production of CCL2 from a human astrocyte cell line (184). Our laboratory showed that Tat also increases CCL2 from human astrocytes (185). Cocaine enhances CCL2 production by an HIV-infected monocytic cell line (171). Additionally, cocaine induces CCL2 from rat microglial cells through its interaction with the sigma 1 receptor, and conditioned media from these cultures increases monocyte transmigration in vitro (179). CCL2 release mediated by cocaine and/or HIV in the brain can contribute to ongoing influx of monocytes into the CNS. In addition, cocaine increases CCR2 mRNA expression in an HIV-infected monocytic cell line (171). We showed that CCR2, the only CCL2 receptor on monocytes, is essential for $CD14^{+}CD16^{+}$ monocyte transmigration across our model of the human BBB (8). We also showed that blocking CCR2 reduced the transmigration specifically of monocytes that harbor HIV (8). This indicates the importance of CCL2 in the transmigration of monocytes that carry the virus across the BBB, and increased expression of CCR2 induced by cocaine may further facilitate HIV entry into the CNS.

Cocaine also increases the secretion of CXCL10 by pericytes and conditioned media from these cultures increases monocyte transmigration across HBMVEC monolayers in vitro (186). Additionally, this same study showed that there was an overall increase in the number of macrophages in proximity to CXCL10 expressing pericytes in brains of cocaine abusers (186). A separate study showed that in a cohort of PLWH, with some of them on ART, there is elevated CCL2 and CXCL10 in the CSF of individuals with cognitive impairment compared to those with normal cognition (187). This suggests that cocaine induced CCL2 and CXCL10 may promote neuroinflammation, and monocyte recruitment that contribute to HAND.

Effects of Cocaine and HIV on Macrophage, Microglia and Astrocyte Function

Cocaine and HIV effects on macrophages and microglia

Few studies have examined the combined effects of cocaine and HIV on macrophage and microglial functions. Sigma 1 receptor and cathepsin B expression are increased in the brains of HIV-infected cocaine users compared to non-users (188). Cathepsin B, a protease that induces neuronal death, is increased in PLWH (189). These studies suggest that cocaine and HIV independently may be increasing the production of cathepsin B. In vitro, cocaine, through sigma 1 receptor, induces cathepsin B production by HIV-infected MDM (188). This may be one of the mechanisms by which cocaine and HIV both contribute to neuronal damage, and consequent HAND development.

Cocaine alone increases TNF-α and IL-6 gene expression in BV-2 microglia cell line (190). Additionally, it induces TNF-α production in a murine microglia cell line through induction of oxidative stress and activation of the TLR2 signaling pathway (191). Cocaine treatment of mouse primary microglia induces mitochondria dysfunction and an increase in mitophagy to degrade damaged mitochondria after enclosure of these organelles within autophagosomes followed by fusion with lysosomes (192). However, cocaine inhibits the fusion of mitophagosomes with lysosomes, resulting in accumulation of damaged mitochondria (192). This defect in mitophagy contributes to cocaine induced microglial activation and production of inflammatory cytokines (192). In the context of HIV, cocaine enhances IL-6 upregulation in HIV-infected MDM (193). The combined effects of cocaine and HIV on macrophages and microglia may facilitate inflammation that may result in neuronal injury.

Oxidative stress has also been implicated in cocaine and HIV neuropathogenesis. Treatment of HIV-infected MDM with cocaine induces ROS production, and downstream activation of inflammasomes (193). Treatment with both gp120 and cocaine combined induces ROS production by a human microglia cell line (163). These effects may lead to production of cytokines such as IL-1β that may cause neuronal apoptosis. Cocaine also increases HIV gp120 induced ATP use, and decreases mitochondria oxidative phosphorylation in a human microglia cell line (163). All these processes may disrupt neuronal homeostasis, contributing to neuronal loss and neurocognitive impairment.

Cocaine, HIV and astrocyte function: Cocaine and HIV independently and together induce astrocyte activation that may impair their functions. GFAP is increased in brain tissues of HIV-infected cocaine users, compared to either HIV-infected or uninfected non-cocaine users (194), and this is indicative of astrocyte activation. In another study in mice, cocaine treatment also caused upregulation of GFAP and changes in astrocyte morphology such as a decrease in size (195). This effect is also observed in vitro and in vivo in human and mouse astrocytes, and it is mediated either through mechanisms involving sigma 1 receptor or autophagy signaling (194, 196). Tat also increases GFAP in mouse astrocytes through Egr-1 upregulation (197).

Astrocyte activation by cocaine and/or HIV can lead to increased cytokine production and release of neurotoxic factors such as ROS. One study reported that cocaine and gp120 induces rat astrocyte cell death in part through increased ROS production, that leads to apoptosis (198). Cocaine and HIV proteins can also affect brain homeostasis by altering the metabolic function of astrocytes. Tat and cocaine treatment reduces lactate shuttling from human astrocytes to neurons (199). This can lead to neuronal death because lactate supply to neurons is important for their aerobic metabolism. These effects on astrocytes can all contribute to neuronal insult, and subsequent neuronal loss. ART treated PLWH are reported to have dysregulated peripheral metabolic profiles (200, 201). It is thus important to characterize these profiles and their effects on the ability of astrocytes to maintain brain metabolic functions in the context of cocaine, HIV and ART exposure.

Effects of Cocaine on T-cell function

Cocaine induces apoptosis of CD4+ T-cells from both uninfected and HIV-infected people and this is mediated by increased ROS (202). Cocaine has been reported to increase activation of CD8+ T-cells but decrease the cytotoxic phenotype of these cells upon stimulation (157). These effects in T-cells may impair their immune functions such as killing of HIV-infected cells in the CNS. More studies addressing the impact of cocaine on T-cells in the context of viral reservoirs in the CNS are needed.

Opioids and HIV Overview

Opioids are used to reduce pain, and their misuse has led to opioid use disorder, a current substance abuse epidemic in the United States. The opioid epidemic is a major public health concern with misuse or addiction to opioids, including prescription pain relievers, heroin, and synthetic opioids such as fentanyl, reported in approximately 11 million people in the U.S. (26). Intravenous use of heroin is common and needle sharing by heroin abusers contributes to HIV acquisition (24, 203). Additionally, 20–50% of PLWH are prescribed opioids, and are at risk of developing opioid use disorder compared to uninfected people. A few studies have reported that opioid dependence increases neurocognitive impairment (204, 205). The use of heroin has been associated with poor working memory and recall, suggesting that opioid abuse has detrimental effects on neurocognitive performance (154). The effects of opioids including morphine, a mu opioid receptor (MOR) agonist and a heroin metabolite, on HIV/SIV infection have been contradictory with studies reporting that opioids enhance, inhibit, or have no effect on HIV/SIV pathogenesis (206–210). These results were attributed to differences in drug usage, methods of assessing infection and disease progression, and genetic, socioeconomic, and behavioral backgrounds of study subjects. One study with SIV-infected macaques treated with morphine reported a significant number of animals develop very rapid disease progression and higher mortality rates compared to untreated infected macaques (211). There is also increased macrophage localization in perivascular regions of CNS blood vessels and within the CNS parenchyma in morphine treated infected macaques, and many of these macrophages are positive for viral gp120 as detected by immunohistochemistry (211). These data suggest that morphine enhances monocyte/macrophage infection with SIV and increases the localization of these infected cells in the CNS, contributing to SIV neuropathogenesis. In an ART naïve cohort of PLWH,

opioid use is associated with increased viral load and lower CD4+ T-cell counts (212). This study also reported that morphine treatment increases HIV replication in vitro in human MDM (212). Neurotoxicity of conditioned media from a human monocyte/macrophage cell line infected with HIV is enhanced with morphine treatment (213). Tat and morphine are also reported to increase synergistically murine neuronal dendritic pruning and cell death in vitro (214). Morphine enhances the production of neurotoxic factors by murine glial cells in Tat treated mixed murine glia neuronal cocultures, resulting in neuronal cell death (215). All these data suggest that opioid use can increase HIV infection and replication in macrophages and glial cells, and infected macrophage localization in the CNS perhaps by increasing the transmigration of peripheral uninfected and infected monocytes across the BBB. In addition, opioids can increase the neurotoxic effects of viral factors including Tat, and also increase the neurotoxicity of host factors produced by glial cells in response to HIV infection or exposure to Tat.

Opioids and HIV Infection in the CNS

Studies have addressed the effects of opioids on HIV replication. In a murine HIV infection model, morphine increases viral production in mouse hippocampus (84). In vitro, one study showed that morphine increases CCR5 and CXCR4 gene expression and enhances HIV infection of PBMC (216). High concentrations of morphine induce HIV replication in T-cells in vitro (217, 218). Morphine also decreases CD8+ T-cell anti-HIV activity, contributing to HIV pathogenesis (219). There are several potential mechanisms reported to contribute to increased HIV infection induced by morphine. In MDM, morphine increases the expression of galectin, a lectin that contributes to increased HIV infection by enhancing viral interaction with the cell membrane (220). Morphine increases HIV replication in MDM by downregulating the IFN pathway (221), and upregulating CCR5 (222, 223). In mouse microglia, morphine and Tat upregulate CCR5 that may contribute to an increase in infected glial cells and expansion of viral reservoirs in the CNS (224). In vitro, morphine promotes HIV replication in human macrophages by inhibiting the TLR9 pathway (212). Heroin increases HIV replication in macrophages by inhibiting anti-HIV miRNA and decreasing IFN expression (225). However, another study reported that morphine does not affect HIV replication in MDM but increases HIV-mediated inflammation (226). High concentrations of morphine induce HIV replication in a latently infected T-cell line, and antioxidant treatment attenuated this effect (217). These data suggest that there is a complex interaction between opioids and HIV infection of MDM, T-cells, and microglia, and such interactions may have different outcomes on HIV neuropathogenesis. These types of studies need to be repeated in the presence of ART.

Effects of Opioids and HIV on BBB Permeability

Studies examining the effects of opioids on BBB integrity reported that morphine alone does not change the permeability of HBMVEC monolayers in vitro, or the mouse BBB in vivo (227, 228). However, morphine induces PDGF-BB in HBMVEC, mediated by activation of ERK1/2, JNK, and p38 MAPK signaling pathways (229). Treatment of HBMVEC with morphine decreases ZO-1 and increases permeability as quantified by passage of FITC-dextran across HBMVEC monolayers (229). Decreased ZO-1 and increased permeability are

mediated by morphine induced PDGF-BB (229). Tat and morphine combined increase permeability of cocultured human BMVEC and astrocytes, an effect that is mediated by increased TNF-α and IL-8, and decreased ZO-1 expression (230). This suggests that opioids with HIV or HIV proteins may contribute to loss of BBB integrity that may result in the influx of monocytes and T-cells into the CNS, and ongoing neuroinflammation in PLWH. Morphine increases BBB permeability in vivo as quantified by influx of fluorescently labeled dextran into the brains of Tat transgenic mice and non-Tat expressing control mice (231). Tat transgenic mice also exhibit BBB permeability in the absence of morphine. A diffuse pattern of cytoplasmic ZO-1 immunoreactivity in brain endothelium is induced by morphine treatment of non-Tat expressing control mice and this localization is observed in Tat transgenic mice, irrespective of morphine (231). In mice given dolutegravir, abacavir, and lamivudine, morphine treatment results in lower abacavir and dolutegravir in brains of Tat transgenic mice and non-Tat control mice which correlates with increased endothelial P-glycoprotein efflux transporter induced by morphine (231). Although morphine increases BBB permeability, the penetration of specific antiretroviral drugs into the brain is inhibited (231). These data suggest that morphine induced increases in BBB permeability may enhance influx of monocytes and T-cells into the CNS of PLWH, increasing viral seeding and neuroinflammation. Morphine may also inhibit ART mediated suppression of viral load in the CNS by inhibiting penetration of specific antiretroviral drugs into the CNS.

Effects of Opioids and HIV on Monocyte Migration Across The BBB

One study showed that morphine increases ICAM-1, VCAM-1, and ALCAM on HBMVEC and this correlates with increased PBMC adhesion (228). These data suggest that opioids increase junctional proteins and adhesion molecules on the surface of BBB endothelial cells that may contribute to further recruitment of monocytes and T-cells into the CNS. Morphine and Tat treatment of astrocytes induces CCL2 production that mediates microglial chemotaxis (232). Elevated CCL2 at the BBB can also recruit monocytes and T-cells into the CNS. Morphine treated SIV-infected macaques have increased brain perivascular macrophages, with a significant number of these cells expressing viral antigens (211). These data suggest that morphine is contributing to increased transmigration of peripheral blood monocytes into the CNS (211). In another study, SIV-infected macaques treated with morphine exhibited increased migration of dendritic cells into the brain parenchyma (233). Morphine treatment of a BBB model consisting of cocultured human astrocytes and HBMVEC increases uninfected and HIV-infected PBMC transmigration to CCL5, with uninfected PBMC transmigration exacerbated with Tat cotreatment (230). Additionally, morphine increases entry of splenocytes, into the CNS of treated mice (234). Splenocytes are comprised of various immune cells including T-cells, and their increased entry into the CNS may contribute to inflammation. Streptococcus pneumoniae infection of the CNS of mice is increased by treatment with morphine and Tat (235, 236) with increased infiltration of T-cells and inflammatory monocytes into the CNS that was proposed to assist in pathogen clearance (235). These studies suggest that one mechanism by which opioids may increase HIV associated neuroinflammation and development of HAND is by increasing uninfected and infected monocyte and T-cell influx into the CNS.

Effects of Opioids and HIV on Macrophage, Microglia, and Astrocyte Function

Opioids, HIV, and macrophage/microglia function

Morphine has been reported to increase IL-6 production in HIV-infected MDM (Dave et. al., 2012). In mouse microglia, morphine and Tat upregulate TNF-α, IL-1B, and IL-6 (224). Mouse microglia also become activated, as measured by expression of the activation marker CD11b, with meth and Tat treatment (224). Morphine by itself increases production of CCL2 by human neuronal cultures but not astrocytes or microglia (237). Another study showed that morphine alone does not increase CCL2, TNF-α, IL-6 or IL-8 production by human microglia (238). However, these cytokines are increased in HIV-infected microglia treated with morphine when compared to either HIV infection or morphine treatment alone (238). Thus, increased production of inflammatory cytokines due to opioids may exacerbate immune cell influx into the CNS, neuroinflammation, and neuronal damage that may all contribute to declines in neurocognitive performance in PLWH.

Morphine, HIV and astrocyte function

The combination of morphine and HIV or Tat was reported to induce oxidative stress through production of ROS by HIV-infected human or Tat treated mouse astrocytes, and also decrease the ability of astrocytes to uptake glutamate (215, 239). Oxidative stress and excess glutamate in the CNS may result in neuronal damage that may contribute to HIV neuropathogenesis. Morphine enhances CCL2, TNF-α, and IL-8 production by HIV-infected human astrocytes (239). Morphine was also shown to induce CCL5 production by human astrocytes (240). Some studies reported a decrease in CCL2 mRNA expression in human astrocytes after morphine treatment (241), while others have shown increased IL-6, CCL2 and CCL5 production by mouse astrocytes with Tat and morphine treatment compared to Tat alone (242). This suggests that the presence of both morphine and HIV or its proteins exacerbates neuroinflammation that may contribute to CNS pathogenesis.

Dopamine and HIV Overview

Intermittent use of drugs of abuse, including meth, cocaine and opioids, significantly increases extracellular concentrations of dopamine in the CNS (243, 244), while chronic substance abuse appears to downregulate dopamine production (245). Dopamine is a catecholamine neurotransmitter that modulates many functions of the brain, including cognition, locomotion, and reward (246, 247). Drugs of abuse can interact with presynaptic DAT, preventing reuptake of dopamine by neurons (248). This contributes to increased extracellular dopamine in the CNS, and reactive oxygen species produced by oxidation of dopamine can increase oxidative stress in CNS cells and can be neurotoxic (249, 250). Tat also targets and directly inhibits DAT function (251), which may contribute to an increase in synaptic dopamine levels during the early stages of HIV infection (252). In therapy-naïve asymptomatic HIV-infected individuals, dopamine levels are increased in the CSF when compared to uninfected controls (253). This increase during the early stages of HIV infection can contribute to synaptic damage and degeneration of dopaminergic neurons. In individuals infected with HIV for long time periods, particularly in the absence of ART,

there is significant damage to dopaminergic neurons, resulting in decreased overall levels of dopamine in the CNS (254, 255). Astrocytes express dopamine receptors (256, 257) but little is known about the effects of dopamine receptor signaling on their functions, including trophic support of neurons and regulation of neuronal activity. The effects of dopamine on the ability of astrocytes to support neuronal functions in the HIV-infected CNS in the presence of ART is an area that requires further study.

Neuropathology associated with dopaminergic neuronal damage in the pre-ART era includes neuronal loss in areas of the brain innervated by dopaminergic neurons, such as the basal ganglia and the prefrontal cortex (258–260). Dopamine-rich areas of the brain in SIV-infected macaques also exhibit significant neuronal damage and loss (261). A study of brain tissues from PLWH who had HIV encephalitis and died from AIDS reported abnormal striatal dopaminergic synapses, detected by Western blot analysis of brain tissue lysates and by immunohistochemical staining of sections from the basal ganglia (262). In PLWH on suppressive ART, pathological studies on postmortem brain tissue reported less severe but detectable neuroinflammation and neuronal damage (263) and one autopsy study reported neuronal degeneration in the frontal cortex and hippocampus (264). Neuroimaging studies of brains of PLWH on suppressive ART demonstrate structural changes in frontal white matter and neuronal injury in the basal ganglia (265–267) and other studies reported structural abnormalities in white matter, increased markers of neuroinflammation, and decreased markers of neuronal integrity as detected by MR spectroscopy (MRS) (268–270). Thus, even with suppressive ART, low level chronic neuroinflammation and neuronal injury persists. Upregulation of extracellular dopamine levels in the brain of rhesus monkeys by treatment with L-DOPA or selegiline during early SIV infection increases CNS viral loads and SIV-associated neuropathology (271, 272). All of these studies suggest that abnormal dopaminergic transmission contributes to HIV neuropathogenesis in the ART era (273), and that increased extracellular dopamine during the early stages of HIV infection of the CNS can exacerbate neuronal damage.

Dopaminergic pathways in the brain, including those involved in reward processes, are targeted and damaged by HIV infection and substances of abuse (274, 275). In a mouse model in which Tat protein, under the glial fibrillary acidic protein (GFAP) promoter, is induced in the brain by doxycycline, neuropathology is similar to what is observed in PLWH (276). In this model, induced Tat expression in mouse brains decreases dopaminergic function and leads to reward deficits, contributing to increased sensitivity to subsequent meth-induced reward enhancement (277). Another study with this model reported that expression of Tat increases meth-induced locomotor sensitization, and increases microglial activation, indicative of upregulated neuroinflammation (278). Other in vitro studies demonstrated that Tat and cocaine synergistically enhance the inhibition of DAT activity, increasing extracellular dopamine to a greater degree than that induced by Tat or cocaine alone (279). These studies suggest that HIV infection may enhance the effects of substances of abuse on dopaminergic and reward pathways in the brain as well as neuroinflammation. Thus, PLWH may be more susceptible to the rewarding effects of drugs when compared to non-infected individuals. In PLWH who do become substance abusers, the levels of extracellular dopamine in the CNS, especially during the early stages of HIV infection, and

neuroinflammation are further increased after active drug use, exacerbating HIV neuropathogenesis.

The mechanisms by which increased extracellular dopamine in the HIV-infected CNS contributes to chronic neuroinflammation are not completely understood. Our laboratory reported that dopamine increases uninfected $CD14^+CD16^+$ mature monocyte transmigration across our in vitro model of the human BBB, as well as their adhesion and migration (48, 280). Using PBMC from PLWH, we also showed that these mature monocytes transmigrate in increased numbers to dopamine (48).These data suggest that increased extracellular dopamine in the CNS induced by substances of abuse contributes to HIV neuropathogenesis, in part, by increasing the influx of mature monocytes into the CNS and their accumulation in dopamine rich regions of the brain, particularly during early stages of HIV infection.

HIV/SIV DNA or RNA is detected in peripheral blood $CD14^+CD16^+$ monocytes from infected people or macaques, in the presence or absence of ART (42, 281–283). Actively or latently infected $CD14^+CD16^+$ monocytes in the periphery can transmigrate across the BBB and enter the CNS over extended periods of time in PLWH on suppressive ART, replenishing viral reservoirs when some of these cells mature into macrophages, particularly in perivascular regions of the CNS. These cells can produce infectious virus in the CNS of substance abusing PLWH who are not adherent to ART, and in individuals on successful ART, Tat and Nef can still be produced. This will result in the maintenance of low level chronic neuroinflammation that results in neuronal dendritic pruning, degeneration and cell death, contributing to the development of HAND.

Dopamine and HIV Infection in the CNS

Increased extracellular dopamine in the CNS may facilitate the infection of CNS macrophages with HIV. We reported that HIV infection of human MDM is increased by DA mediated activation of D1-like and D2-like dopamine receptors, resulting in increased viral entry (284, 285). Dopamine also increases cell surface CCR5 in the human THP-1 monocyte/macrophage cell line that is mediated by D1-like and D2-like DA receptor activation, resulting in increased infection by HIV (286). These data suggest that increased extracellular dopamine in the CNS induced by substances of abuse will increase viral load in the CNS of HIV-infected substance abusers.

Effects of Dopamine and HIV on Monocyte Transmigration Across the BBB

Peripheral blood monocytes in healthy individuals are heterogeneous with 5–10% of this population expressing CD14 and CD16 ($CD14^+CD16^+$) and the remaining 90–95% expressing only CD14 ($CD14^+CD16^-$) (287). The $CD14^+CD16^+$ mature monocyte subpopulation is increased in frequency relative to the total peripheral monocyte population in PLWH (288, 289), and we showed that this increase is significantly larger in PLWH who are active substance users (48). Our laboratory and others reported that mature $CD14^+CD16^+$ monocytes can be infected with HIV (42, 281–283, 290). We developed a method to culture human $CD14^+CD16^-$ monocytes isolated from uninfected PBMC non-adherently in media with M-CSF to expand the $CD14^+CD16^+$ mature monocyte

subpopulation. We used these cultured mature monocytes, both uninfected and HIV-infected in vitro, as well as PBMC from PLWH, in transmigration assays across our in vitro model of the human BBB, consisting of cocultured HBMVEC and human astrocytes on tissue culture inserts. We reported that uninfected and HIV-infected $CD14^+CD16^+$ monocytes preferentially transmigrate across the BBB in response to the chemokines CCL2 and CXCL12 when compared to $CD14^+CD16^-$ monocytes (5–9). Our laboratory also showed that dopamine increases the adhesion and migration of cultured uninfected $CD14^+CD16^+$ monocytes (280) and the transmigration of these cells across our BBB model (48). Dopamine-induced transmigration is mediated by activation of D1-like dopamine receptors on $CD14^+CD16^+$ monocytes and the subsequent activation of ADAM 17 (9). The transmigration across the BBB of peripheral blood $CD14^+CD16^+$ monocytes, but not T-cells, from PLWH is also increased by dopamine (48). Our preliminary data demonstrate that cultured $CD14^+CD16^+$ monocytes infected with HIV in vitro also transmigrate across our BBB model in response to dopamine at higher levels when compared to baseline transmigration to media (Figure 1). For these experiments, cultured $CD14^+CD16^+$ monocytes (10×10^6 cells/mL) were infected in vitro with HIV_{ADA} (0.5 μg/mL). After 8 hours the virus was removed by centrifugation and the monocytes resuspended at 2×10^6 cells/mL in fresh culture media (RPMI 1640 supplemented with 10% human serum and 5% FBS) with 10 ng/mL M-CSF (PeproTech, Rocky Hill, NJ) in teflon flasks. HIV-infected monocytes were cultured for an additional two days to facilitate viral infection and replication. HIV-infected monocytes (1.5×10^5 cells) were added to the top of cocultured HBMVEC and human astrocytes on tissue culture inserts in 24 well plates as previously described (48, 291), with media or 10 μM dopamine (Sigma-Aldrich, St. Louis, MO) added to the bottom of the inserts. Each transmigration condition was performed with 4 replicate cocultures. After 18 hours, transmigrated monocytes were collected from the bottom, stained for CD14 (clone M5E2, BD Biosciences, 1:12.5 dilution; San Jose, CA) and CD16 (clone 3G8, 1:10 dilution; BD Biosciences, San Jose, CA). The number of $CD14^+CD16^+$ monocytes was quantified by flow cytometry and analyzed using FlowJo software (TreeStar v.9.5.3, Ashland, OR) (Figure 1). These data suggest a potential mechanism by which drugs of abuse may be contributing to HIV-associated neuroinflammation by increasing the population of $CD14^+CD16^+$ monocytes in the peripheral circulation of PLWH, and by increasing CNS extracellular dopamine that facilitates transmigration of uninfected and HIV-infected $CD14^+CD16^+$ monocytes across the BBB, and their migration to dopamine rich areas of the CNS. This would facilitate the establishment and reseeding of viral reservoirs and contribute to the chronic neuroinflammation and neuronal damage that mediates the development of HAND. More studies of dopamine and its impact on neuroinflammation need to be performed in the context of ART.

Effects of Dopamine and HIV on Macrophage and Microglia Function

Dopamine, HIV, and macrophage function

RNA for all five dopamine receptors are detected by qRT-PCR in human MDM, with D1R and D5R RNA expressed at higher levels than the D2-like DR receptors (292). Additionally, in uninfected cells, dopamine treatment with or without LPS, increases IL-6, IL-8, CCL2, CXCL9, and CXCL10 proteins (292). Dopamine also inhibits IL-10, an anti-inflammatory

cytokine, and has no effect on TNF-α (292). In addition, dopamine induced cytokine production in MDM cultures derived from peripheral blood monocytes from PLWH on ART is similar to that of uninfected MDM (292). In mouse peritoneal macrophages, dopamine increases LPS induced IL-6, IL-10 and CXCL1, and has no effect on TNF-α (293). Dopamine-mediated activation of D1R inhibits LPS induced TNF-α and MIP-2 in mouse peritoneal macrophages (294), and also inhibits NLRP3 inflammasome activation in mouse bone marrow derived macrophages (295). In mouse peritoneal macrophages, a D1-like dopamine receptor antagonist inhibits LPS induced TNF-α and a D2-like dopamine receptor antagonist inhibits LPS induced IL-6 (296). These data suggest that extracellular dopamine in the CNS increases the inflammatory phenotype of uninfected and HIV-infected macrophages, with increased cytokine production dependent on the activation of specific dopamine receptors on these cells.

Dopamine, HIV, and microglia function

In the murine microglial BV-2 cell line and in primary murine microglia, D1R and D5R mRNA and protein are expressed at higher levels than D2R, D3R, and D4R (297). Dopamine alone does not change microglial production of IL-6 or TNF-α in the presence or absence of LPS (297). However, LPS and IFN-γ induced nitric oxide (NO) is inhibited by dopamine, and D1R-like agonists inhibit LPS induced NO (297). LPS induced phagocytic activity in BV-2 cells and primary murine microglia is inhibited by dopamine (298). Thus, dopamine may inhibit microglial production of NO, a neurotoxic factor, and microglial phagocytosis during an inflammatory response while having no effect on cytokine production by this cell type.

Potential Therapeutic Interventions to Limit HAND in the Context of ART and Substances of Abuse

HIV-infected substance users are still at a highly significant risk of developing HAND despite effective ART. There are currently no available therapies for treating meth and cocaine use disorders. Opioid substitution therapies such as methadone, a MOR full agonist, and buprenorphine, a MOR partial agonist and full agonist of kappa opioid receptor, are being used to treat opioid addiction. Very few studies have been performed to determine the effects of these drugs on HIV-mediated neuropathogenesis. It was reported that individuals taking buprenorphine have improved neurocognitive performance compared to baseline or methadone treated drug users (299–301), suggesting that this molecule may be a potential therapy for HAND in HIV-infected opioid users. Our laboratory showed that, in vitro, buprenorphine decreases adhesion of uninfected $CD14^{+}CD16^{+}$ monocytes to ICAM-1 on BMVEC, as well as their chemotaxis (302, 303). This suggests that buprenorphine may reduce monocyte recruitment into the CNS, and mitigate monocyte induced inflammation. Additionally, our unpublished data demonstrate that prophylactic treatment of EcoHIV-infected mice with buprenorphine before infection prevents the development of NCI. Additionally, these mice have decreased numbers of inflammatory monocytes in the brains (Unpublished data, Drs. Matias Jaureguiberry-Bravo & Jennifer Kelschenbach). These data suggest that in addition to its role as an opioid substitution therapy, buprenorphine can serve as potential treatment for cognitive deficits in PLWH regardless of opioid use.

A recent study used liposomal magnetic nanoformulations to deliver antiretrovirals, latency reactivating agents, and meth antagonists to latently infected human astrocytes, to target both HIV infection and meth induced effects in these cells (304). In this study, the nanoparticles did not alter the permeability of a BBB model comprised of HBMVEC and astrocytes (304). These nanoparticles crossed the mouse BBB in vivo, suggesting a potential therapeutic intervention for drug delivery into the CNS (304). Another study showed that magnetic nanoparticles containing azidothymidine 5′-triphosphate (AZTTP), the active form of zidovudine, crosses a human BBB model more effectively compared to free drug, without affecting permeability (305). These nanoparticles can also be taken up by monocytes and these cells can then transmigrate across a BBB model in the presence of a magnetic field (305). This suggests that nanoparticles may be serve as a potential intervention to increase the delivery of ART across the BBB, reducing viral reservoirs in the CNS. Due to the low penetrance of currently used antiretrovirals into the CNS, long lived HIV-infected monocyte/macrophages remain as viral reservoirs despite successful ART. In addition, low levels of ART have been detected intracellularly in these cells due to the activity of drug efflux transporters and metabolic enzymes that degrade the antiretrovirals (306). To ensure effective ART delivery into these cells, nanoparticles containing integrase inhibitor, elvitegravir, were used (306). These nanoparticles suppressed HIV replication in monocyte derived macrophages more effectively than elvitegravir alone (306). Nanoparticles may thus improve drug delivery across the BBB, as well as into macrophages, providing a potential mechanism for drug delivery, and the targeting of long-lived CNS viral reservoirs.

Our laboratory showed that adhesion molecules, JAM-A and ALCAM, are increased on $CD14^{+}CD16^{+}$ monocytes infected in vitro when compared to uninfected cells, and also on $CD14^{+}CD16^{+}$ monocytes from PLWH (7). These molecules are further increased on monocytes that specifically harbor the virus compared to those that are only exposed to, but are not infected by, the virus. These proteins mediate transmigration of uninfected and HIV-infected mature monocytes and blocking antibodies against these molecules reduce the number of monocytes that cross a BBB model, and specifically the cells carrying HIV. Cocaine has been shown to induce ALCAM on endothelial cells. Thus, ALCAM blocking antibodies can be studied to determine whether they will limit cocaine and HIV-mediated monocyte transmigration, reducing inflammation within the CNS and viral seeding. Natalizumab, an α4-integrin antibody, limits the infiltration of monocytes into the CNS of SIV-infected macaques, resulting in decreased inflammation and neuropathogenesis (307, 308). The use of blocking antibodies can thus be a potential therapy for reducing monocyte entry into the CNS that is augmented by substances of abuse. However, caution must be taken because long term use of blocking antibodies can inhibit immune surveillance in the CNS and contribute to the development of progressive multifocal leukoencephalopathy (PML), and thus the use of these drugs continuously may be detrimental and must be monitored closely.

Cocaine and meth are associated with an increase in HIV infection that is mediated by the upregulation of the CCR5 receptor. Receptor antagonists such as maraviroc, a CCR5 inhibitor, and cenicriviroc (CVC), a dual CCR2 and CCR5 inhibitor, can be used as potential therapeutics to limit HIV infection of cells within the CNS. CVC reduced chemotaxis and transmigration of monocytes from HIV-infected donors across human aortic endothelial cells

(309). Additionally, our laboratory demonstrated that CVC decreased HIV-infected $CD14^{+}CD16^{+}$ monocyte transmigration across a BBB model (8). Thus, CVC can be used not only to prevent HIV infection of monocytes by blocking CCR5, but also to reduce transmigration of these cells into the CNS by targeting CCR2. Pilot studies demonstrated improved cognitive function in PLWH who are treated with ART and maraviroc combined compared to those who only receive ART (310, 311). A single arm clinical study also reported that CVC treatment of virally suppressed PLWH is associated with improved neurocognitive performance (312).

Sigma 1 receptor is a potential target for limiting cocaine or meth-mediated effects. Cocaine and meth have been reported to interact with sigma 1 receptor on various cell types of the CNS including pericytes, astrocytes, microglia and macrophages (129, 186, 188, 313, 314). Upon interaction with sigma 1 receptor, cocaine and meth initiate inflammatory responses (314). This results in release of cytokines such as TNF-α, IL1-β, and IL6. In vitro and in vivo studies discussed in above sections showed that sigma 1 receptor antagonists attenuate these effects, and this can be one of the potential therapies for reducing the neuroinflammation and neuronal damage mediated by meth and/or cocaine. To reduce cytokines that contribute to immune cell entry into the CNS as well as neuroinflammation, antioxidants can also be examined further to reduce the effects of cocaine or meth induced ROS. Using peripheral blood from meth or cocaine users, it was reported that drug use Is associated with lower antioxidant capacities compared to non-substance users (315). This suggests that these individuals are susceptible to oxidative stress, leading to production of ROS that can damage the BBB, contributing to CNS damage. The use of antioxidants is another potential intervention to mitigate this effect. Antioxidant use such as dimethyl fumarate has been proposed to suppress HIV infection of macrophages, reduce neurotoxicity mediated by HIV-infected macrophages, as well as CCL2-mediated chemotaxis of human monocytes, in vitro (316). In a rat astroglia-like cell line, the antioxidant N-acetyl cysteine, reduces cocaine induced ROS production and cytotoxicity (317). Drugs such as fingolimod, a sphingosine-1-phosphate receptor modulator, are used to treat relapsing multiple sclerosis and fingolimod has been shown to have some inhibitory effect on astrocyte-mediated neuroinflammation (318).

Conclusion

Substances of abuse, in the context of HIV infection, contribute to BBB dysfunction, and increased endothelial adhesion protein expression, that may facilitate immune cell entry into the CNS (Figure 2A–B). Substances of abuse also facilitate HIV infection and replication that can lead to establishment and replenishment of viral reservoirs in the CNS that are difficult to eliminate (Figure 2C). Some of the functions of macrophages, microglia, and astrocytes that are important for CNS homeostasis are also impaired by HIV and substances of abuse (Figure 2D–E). Additionally, use of illicit drugs and HIV infection in the CNS can result in oxidative stress and neuroinflammation, that contribute to neuronal pruning and loss (Figure 2F–H). All of these effects may play a role in the development of HAND. Despite our understanding of the mechanisms by which substances of abuse may be affecting CNS cells, more studies need to be carried out to determine the impact of these drugs in the context of HIV and ART. Current guidelines recommend that PLWH be prescribed ART

soon after diagnosis. Thus, more cohort studies need to be performed to characterize the effects of early ART initiation, HIV, and substances of abuse in these individuals. Collectively, these studies will indicate potential therapies for limiting viral seeding and neuropathogenesis mediated by substances of abuse.

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- We describe studies demonstrating that substances of abuse exacerbate HIV neuropathogenesis
- We suggest areas for research
- We discuss potential therapies

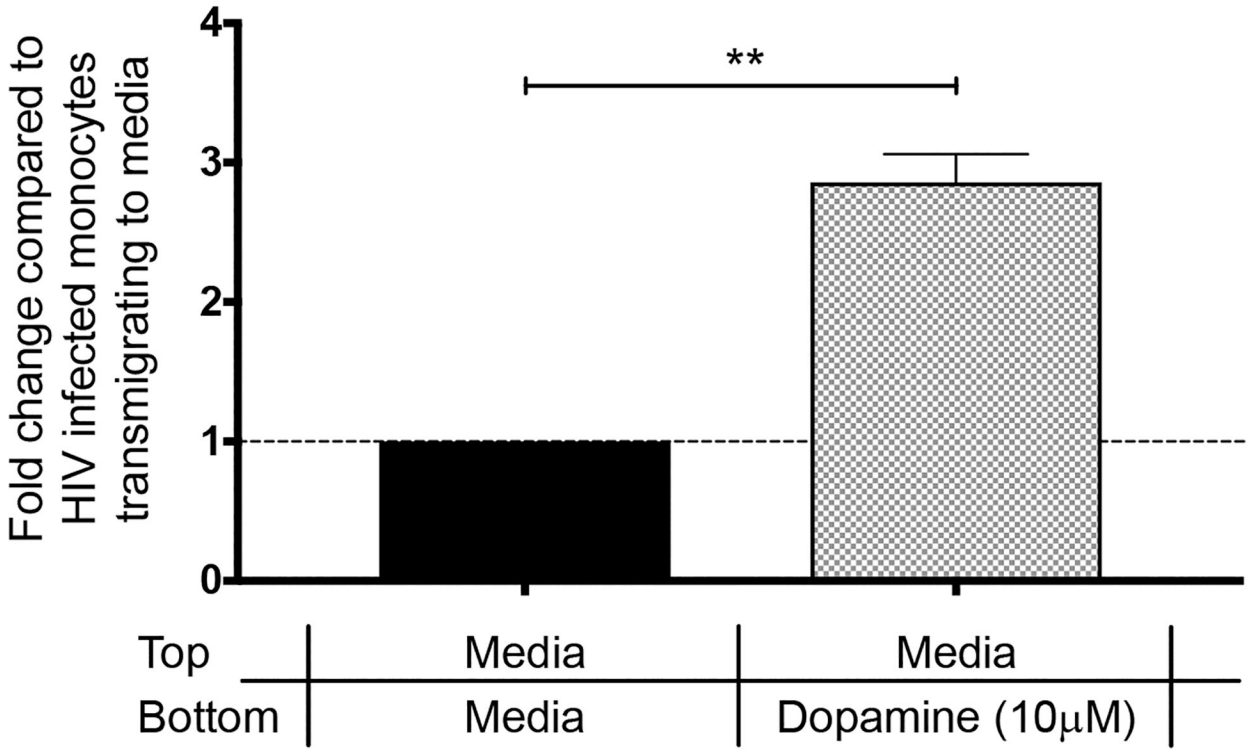

Figure 1:

Dopamine increases the transmigration across the BBB of cultured $CD14^+CD16^+$ monocytes infected in vitro with HIV. Transmigration experiments were performed with $CD14^+$ peripheral blood monocytes cultured non-adherently with M-CSF to generate mature $CD14^+CD16^+$ monocytes. These cells were infected in vitro with HIV and added to the top of our human BBB model consisting of cocultured HBMVEC and human astrocytes on tissue culture inserts in 24 well plates. Media or 10 μM dopamine was added to the bottom of the wells. After 18 hr, cells that transmigrated across the BBB were collected from the bottom of the wells and $CD14^+CD16^+$ monocytes were quantified by flow cytometry. Monocyte transmigration was expressed as fold increase over baseline (media alone), which was set to one (dotted line) for each independent donor. Data are expressed as mean ± SEM. Significance was determined by two-tailed paired Student's t test. **$p < 0.005$ (Dopamine compared to baseline); n=4 each.

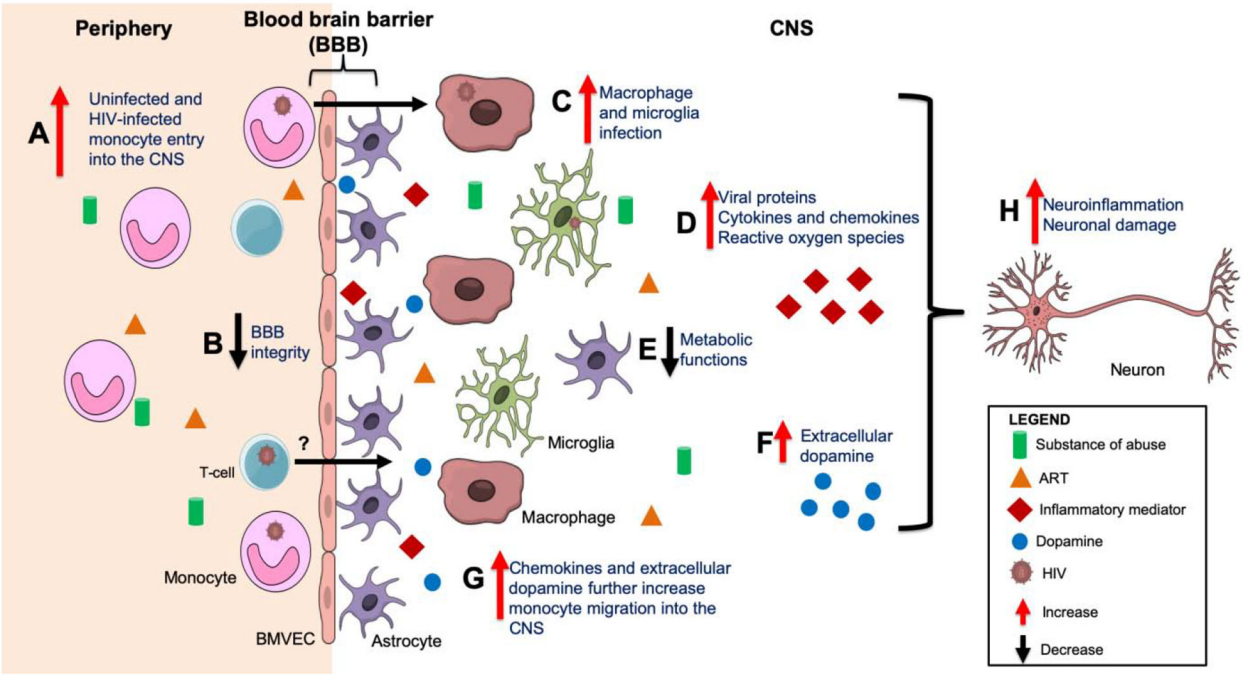

Figure 2:

Substances of abuse impact several processes of HIV neuropathogenesis leading to cognitive impairment. Methamphetamine, cocaine, and opioids contribute to HAND, in part by: **A.** Facilitating infected monocyte and perhaps T-cell transmigration across the BBB; **B.** Disrupting BBB integrity through decreased tight junction proteins, and increased metalloproteinases and adhesion molecules; **C.** Increasing HIV infection and replication in macrophages and microglia, contributing to increased viral load in the CNS; **D.** Releasing virus and/or viral proteins, and other inflammatory mediators including reactive oxygen species and cytokines; **E.** Impairing astrocyte metabolic processes and functioning that are essential for brain homeostasis; **F.** Increasing extracellular dopamine through impaired dopamine reuptake and storage mechanisms; **G.** Further recruiting monocytes due to increased chemokines and extracellular dopamine in the CNS. **H.** All of these processes (A-G) may contribute to neuronal injury, and loss, resulting in HAND.