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Review Article

The Impact of Addictive Drugs on HIV Immunopathogenesis

Xiaochun Li[1], Wenwen He[2], Yifang Wen[3], Binhua Ling[4], Lishomwa C. Ndhlovu[5], Amanda Wagner[6], Azizul Haque[7], Jingjing Wang[8], Danielle Macedo[9], Ren Lang[10], Aimee McRae-Clark[6], Lei Huang[11], Wei Jiang[7,12] and Davide Amato[13*]

[1]The Sixth People's Hospital of Xinjiang, Antiviral Treatment Center for HIV/AIDS, China
[2]The Sixth People's Hospital of Xinjiang, Clinical Laboratory Center, China
[3]The Sixth People's Hospital of Xinjiang, Hepatitis Treatment Center, China
[4]Department of Microbiology and Immunology, Tulane University School of Medicine, USA
[5]Department of Infectious Diseases, Weill Cornell Medical College, USA
[6]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, USA
[7]Department of Microbiology and Immunology, Medical University of South Carolina, USA
[8]Department of Immunology, Flinders University, South Australia
[9]Department of Physiology and Pharmacology, Faculty of Medicine, Universidade Federal do Ceará, Brazil
[10]Department of Hepatobiliary Surgery, Beijing Chaoyang Hospital, China
[11]Treatment and Research Center for Infectious Diseases, The 302 Hospitals of PLA, China
[12]Department of Medicine, Medical University of South Carolina, USA
[13]Department of Neurosciences, Medical University of South Carolina, USA

[*]Address Correspondence to Davide Amato, E-mail: amatod@musc.edu

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Abstract

Substance Use Disorder (SUD) is associated with neurocognitive disorders as well as with alterations of the immune system function. Different addictive drugs exhibit differences in neurocognitive performance and immune response against inflammation. In HIV disease, SUD is associated with increased HIV susceptibility and infection, HIV replication, blunted $CD4^+$ T cell reconstitution under viral suppressive Antiretroviral Therapy (ART), perturbations of immune system and accelerated HIV-associated neurologic disorders (HAND). To date, extensive studies have been done to understand high incidence of HAND in HIV disease, but the exact mechanisms are not completely understood, especially of long term ART and viral suppression settings. We have reviewed work on the impact of addictive drugs on HAND in HIV immunopathogenesis.

Keywords: HIV; Substance use disorder; $CD4^+$ T cells; Neurocognition; HAND; Antiretroviral therapy

Highlights

- Substance use disorder is associated with neuroinflammation and neurocognitive disorders.
- In HIV disease, addictive drug abuse is associated with increased HIV susceptibility and infection.
- Bacterial product translocation is a potential mechanism through with substance of abuse can aggravate HIV impact on overall clinical course and brain function.
- The use of animal models can be fundamental to gain insight into the mechanisms underlying HIV and neurocognitive disorders comorbidity.

Introduction

HIV-Associated Neurocognitive Disorder (HAND) persists in people living with HIV infection (PLWH) despite viral suppression by ART [1-4]. Brain abnormalities are observed in 30%-50% of PLWH and are known to be driven partly by systemic neuroinflammation [5-11]. In PLWH, impaired amygdala responses were associated with increased neurocognitive symptoms such as depression, anxiety, and reduced emotional awareness. Reduced putamen size was associated with impaired motor function in HIV.

The most commonly abused addictive drugs by HIV-infected individuals include cannabis,

Cocaine, morphine, methamphetamine, heroin, and amphetamine. The use of addictive drugs is associated with increased incidence of HIV infection, neurocognitive disorders, HIV replication, morbidity and mortality compared to non-HIV drug users and HIV-infected non users [1-4]. Currently, most patients in the US receive viral suppressive Antiretroviral Therapy (ART) treatment to suppress viral replication and control disease progression. However, Substance Use Disorders (SUD) in HIV patients could be

a main factor underlying low adherence to ART treatment, uncontrolled viremia, and increased chronic inflammation may account for blunted $CD4^+$ T cell reconstitution [5-8]. Thus, HIV infected individuals with comorbid addictive drug use disorders may characterize a distinct subgroup of patients who will suffer a more severe clinical course [9-13]. To date, extensive studies have been done to understand high incidence of HIV Associated

Neurologic Disorders (HAND) in HIV disease, but the exact mechanisms are not completely understood, especially of long term ART and viral suppression settings.

The Impact of Addictive Drug on HIV Viral Replication

It is challenging to study the impact of addictive drugs on immune perturbations in HIV as several confounding factors are involved (e.g., ART treatment adherence and viral replication levels). ART treatment adherence and viral replication levels are often related to addictive drug abuse, suggesting a mechanism of addictive drug mediated immune perturbations and faster disease progression in HIV [14,15]. Moreover, factors including single or multiple drug use, duration of drug use, and route of drug use contribute to drug associated disease progression. Previous studies showed that both substance abuse and heightened levels of T cell activation are associated with poor $CD4^+$ T cell recovery under ART in HIV disease; and drug use associated low adherence to ART treatment and loss of virology control mainly account for poor immune reconstitution in these patients [16-20]. Nevertheless, previous studies show that treatment of cocaine, cannabis, or opiates impacts HIV viral replication using animal models or using human cells in vitro [21-23]. Notably, treatment with 200 mg/L-1000 mg/L of cocaine results in $CD4^+$ T cell death in vitro, implies that cocaine may have a direct role in poor $CD4^+$ T cell recovery and uncontrolled HIV replication [24]. In addition, increased susceptibility to HIV infection and HIV reservoir have been observed in cultured brain cells treated with cocaine [25,26]. Thus, SUD is associated with loss of viral control, accelerated disease transmission and progression, mortality, and morbidity.

The Impact of Addictive Drug on Systemic Immunities in HIV Disease

It is critical to study the impact of addictive drugs on systemic immune perturbations in HIV disease under viral suppressive ART treatment. Previous investigations have shown that HIV-infected patients with SUD have poor $CD4^+$ T cell recovery, accelerated disease progression, and mortality [6,27]. Monocyte and macrophage activation play a key role in persistent immune activation and inflammation, as well as increased incidence of cardiovascular diseases in HIV and neuro HIV infection [28-31]. Soluble CD163 and CD14 can be produced by monocytes in response to LPS stimulation [7,8,32-37]. SUD is associated with increased plasma levels of soluble CD163 and CD14, suggesting cell activation and oxidative stress of monocytes or macrophages [32-35]. Studies from Brenchley group and our group show that HIV/SIV infection results in intestinal barrier impairment, systemic bacterial product translocation, and as a consequences of cell activation, apoptosis and persistent inflammation [38-41]. HIV has been reported to have a direct effect on epithelial cells; HIV Tat and gp120 proteins decrease tight junction (claudin 1, 2, 4, occludin and ZO-1) protein expression using human primary cells and cell lines in vitro [42,43].

The activation of monocytes or macrophages may result from increased gut permeability and microbial translocation in drug users in HIV disease. Some factors have the potential to affect the microbial translocation and cell activation, the route of drug use and microbiome. Ingestion of drug most likely affects the intestinal tract; inhalation of drug most likely affects lung and respiratory tract; and vascular injection of drug most likely affects the whole system. The translocated bacterial products may also play a role in cell activation, as some inflammatory strain of bacterial products may promote heightened inflammation and non-inflammatory or commensal strain of bacterial products may inhibit inflammation. Nonetheless, the exact mechanisms on how drug abuse mediated $CD4^+$ T cell decline, persistent immune activation and inflammation even in HIV-infected patients with long term viral suppressive ART treatment remain unclear.

The Impact of Addictive Drug on Neuro-impairment in HIV Disease

There are about one third of ART-treated HIV-infected patients who exhibit HAND under viral suppressive ART treatment [44]. This may occur via alteration of blood brain barrier by addictive drugs abuse allowing faster replication of HIV virus infection in the brain [45]. Cocaine has been shown to induce macrophage and microglia activation directly, resulting in neuro-inflammation and neurotoxicity and uncontrolled HIV viral replication [46,47]. Moreover, increased intestinal and blood brain barrier permeability has been reported in cells or animals after treatment with cocaine, opioid, and morphine [48]. However, decreased blood brain barrier permeability has been reported in rat models after treatment with cannabis [49]. Because of permeable barriers, microbial translocation promotes cell activation, migration and induce pro-inflammatory cytokine (e.g., TNF-α) production, resulting in the activation of microglia, astrocytes, and perivascular macrophages and neuroinflammation. Furthermore, the cytokines and chemokines (e.g., IL-6, MCP-1, MIP-1) produced by these activated CNS cells recruit circulating lymphocytes to CNS and induce in neuronal injury [50]. Importantly, microbial TLR-related proinflammatory cytokines such as IL-17a, IL-10, IL-6, IL-8, TNF-α, IP-10, MIP-α, and IL-12/IL-23p40 are increased in the CNS in patients with neuro-cognitive impairment [44,51]. These cytokines can be produced by microglia and astrocyte activation in response to TLR4 ligation and are associated with HIV HAND without being further stratified by use of a particular drug [52-56]. Moreover, plasma levels of soluble CD163 and CD14 are associated with neurocognitive disorders in HIV diseas-

es, another evidence of monocyte activation in response to bacterial products [57-59]. These lines of evidence strongly suggest that the host defense to foreign antigens may play a double edged role: They are essential to control invading pathogens, but the perturbed systemic or CNS immune responses could be harmful.

Associated brain cell markers such as Neurofilament Light chain protein (NFL) in Cerebrospinal Fluid (CSF) has been shown association with neuronal injury in HIV patients especially with dementia [44]. In ART naïve patients, plasma level of NFL is directly associated with CSF NFL level, indicating a potential non-invasive biomarker for HAND in HIV [44]. In addition, S100B is a calcium binding protein in astrocytes and may associate with neurodegeneration; quinolinic acid, a neuroexcitotoxic metabolite of L-tryptophan, has been found to increase in HAND HIV patients [44,60]. Increased inflammation and acute phase proteins Creative Protein (CRP) and amyloid A (SAA) is associated with HIV patients with cocaine abuse and increased neuro-inflammation [61].

Neuro-HIV Animal Models

Neuro-HIV animal models have been critical for investigating causality and mechanisms of neuro-HIV disease pathogenesis, evaluating novel therapies along with the interaction of virus with neuroimmune responses and behavior [47,62-64]. Potential confounding factors can be evaluated using animal models including food, gene, environmental, and socio economic factors. HAND includes HIV-Associated Dementia (HAD) Asymptomatic Neurocognitive Impairment (ANI) and Milder Neurocognitive Disorder (MND) [65]. HAD exhibits irreversible neuronal impairment and neurodysfunction; whereas ANI and MND may have reversible physiological and neurodisorders [66]. The incidence of HAD is significantly decreased after introduction of ART treatment, and ANI and MND are the most prevalent neurodisorders in ART treated HIV disease [65,66]. Notably, there are about 50% HIV-infected population who have HAND despite ART treatment. HIV-infected patients with HAND exhibit mild learning and/or memory disturbances, consistent with data from HAND animal models [47, 62-67]. Therefore, HAND animal models can help to evaluate behavioral performance similar to neurocognitive disorders in HIV patients. Furthermore, neuro histopathological parameters may not present in ANI and MND, which rely on both neuropathological parameters and behavioral assessments. It is important to have a window of plasticity when animal models are used to evaluate a novel treatment to reverse neurological impairments such as memory performance.

In animal models memory can be quantified and assessed using the Object Recognition Test (ORT), which evaluates the ability to remember and recognize a previously presented object and discriminate it from a new one. There will be a new object if the animal has a successful memory retention [68,69]. Thus HAND animal models can be used to characterize learning and memory, as well as the alteration of brain cellular activity and cognition. The limitation of the HAND mouse model is that they cannot perfectly represent HIV patients with HAND. However, they serve as an excellent preclinical model for novel treatment and for pathogenetic studies. Notably, a reliable marker of human HAND and autopsy studies are critical for us to define a more precise model. Our goal is to eliminate HIV reservoir and HIV infection in the brain. The HAND animal models may be applied to investigate other diseases with neuro-cognitive disorders.

Discussion

In summary, drugs of abuse combined with HIV infection accelerate systemic immune perturbations and neurological disorders leading to increase mortality and morbidity. Animal models are warned to be a suitable approach to characterize the underlying mechanisms of HIV-SUD comorbidity.

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