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# Brain Abnormalities in HIV and Stimulant Users: Interventions and Prevention

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## Abstract

The session, "HIV and other Infectious Diseases," was chaired by Dr. Jacques Normand, Director of the AIDS Research Program of the U.S. National Institute on Drug Abuse. The two presenters (and their presentation topics) were: Dr. Linda Chang ("Neural Correlates of Cognitive Deficits and Training Effects on Brain Function in HIV-infected Individuals") and Dr. Steven Shoptaw ("HIV Prevention in Substance Users").

### Keywords

Stimulant use; HIV prevention; brain abnormalities; neurocognitive disorder

## 1. Introduction

In this session, both presenters discussed the HIV related issues among stimulant users, with Dr. Chang focusing on brain abnormalities among HIV-infected stimulant users and Dr. Shoptaw focusing on HIV prevention.

## 2. Presentations

Dr. Linda Chang is a professor of medicine (Neurology) at the University of Hawaii's John A. Burns School of Medicine. Dr. Chang reported that despite effective viral suppression with antiretroviral medications, approximately 50% of HIV-infected individuals continue to show neurocognitive deficits, especially in working memory and attention. She demonstrated in her presentation how the various multimodal brain imaging studies can be used to evaluate the neuropathophysiological changes in HIV patients. For example, proton magnetic resonance spectroscopy ($^1$H MRS) studies demonstrated elevated myoinositol levels but lower levels of glutamate [1–3], which suggested excess neuroinflammation, whereas functional MRI studies showed compensatory changes, as well as lower cognitive reserve, suggesting premature aging in HIV patients [4]. The degree of neuroinflammation

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and lower cognitive reserve were often related to the severity of cognitive deficits measured on neuropsychological tests in these HIV-infected individuals. HIV-infected individuals with the *APOE* 4 gene, a major risk factor for Alzheimer's disease, also showed greater brain atrophy, and the *APOE* 4 gene also renders them particularly vulnerable to cognitive deficits [5]. After using intensive computerized working-memory training in HIV patients, preliminary data from Dr. Chang's laboratory show that these patients may improve their cognitive function and that their functional MRI showed normalization of the abnormal brain networks after training. Dr. Chang and colleagues further demonstrated that the LXMIA genetic polymorphism also may predict the level of improvements from working-memory training effects. Ongoing studies will further evaluate how neuroinflammation may be related to cognitive function after cognitive training in these HIV-infected individuals.

Dr. Steven Shoptaw is executive director of the UCLA Center for Behavioral and Addiction Medicine, and professor in both the Department of Family Medicine and Department of Psychiatry and Biobehavioral Sciences at UCLA. Dr. Shoptaw's talk focused on HIV prevention efforts that have stemmed new infections among substance users, particularly among injection drug users, due to the scaling-up of interventions that target HIV-positive substance users and reduce harm (syringe exchange programs), provide treatment (opioid substitution therapies), and ensure quality HIV medical care (access to antiretroviral therapy). Yet most substances used around the world are administered via non-injection methods and there are only a handful of HIV prevention interventions that target non-injecting substance users at risk for HIV transmission. HIV incidence rates are high among subgroups of HIV-negative substance users, including men who have sex with men (MSM), female sex workers, street youth, and itinerant laborers. Attributable fractions of new infections due solely to substance use that would otherwise guide intervention development and implementation are available only for MSM substance users. There is existing evidence for using a combination of HIV prevention strategies in both HIV-positive and HIV-negative substance users. Studies of users of stimulants and alcohol show ways that drug-dependence treatment can function as HIV prevention in reductions of drug use and of concomitant sexual risk behaviors. Structural interventions (policies for criminal justice and health care settings) may offer cost-effective strategies to reduce HIV transmission in substance users. Greater detail of this presentation can be found in Shoptaw (2013) in this Special Issue.

## 3. Discussion

There were several questions discussed.

1. Why do most studies on neurocognitive impairments among HIV patients focus on stimulant use such as methamphetamine or cocaine?

   First, stimulant drugs are one of the major categories of drugs abused by this population. Second, like HIV, stimulant drugs may be neurotoxic to the dopaminergic system, which in turn may lead to impairments in attention and working memory. Since attention and working memory are necessary for almost all cognitive tasks, the additive and synergistic effects of HIV and stimulant drugs have the greatest impact on neurocognitive deficits in this population.

2. Have we looked at anti-inflammatory drugs such as marijuana to see if they can help reduce adverse effects on cognitive functioning caused by HIV?

   Marijuana use is even more prevalent than stimulant use in this population. Dr. Chang's laboratory has started to examine the effect of marijuana on the immune system among HIV patients. To her surprise, instead of anti-inflammatory effects, they have seen higher levels of peripheral inflammatory markers such as activated monocytes (CD14/CD16) in these patients [6]. However, using proton spectroscopy, they found that while HIV and marijuana users each showed unique patterns of neurometabolite abnormalities, HIV patients who used marijuana show normalization of the lower brain glutamate in the frontal white matter, which indeed suggests less neuroinflammation in that brain region, but they had even lower glutamate in the striatum, suggesting greater inflammation or neuronal dysfunction [7]. Therefore, the peripheral and central effects of marijuana may be different, and the different brain regions are affected differently. She suspects that when one smokes marijuana, it is not just THC that enters the body because there are almost 200 other compounds in marijuana. This may be similar to the observation that nicotine is neuro-protective, but smoking tobacco cigarettes is not healthy for your lungs, and even in the brain, tobacco smoking may not be neuro-protective for all brain regions since one is exposed to more than just nicotine from tobacco smoke.

3. How big is the impact of their neurocognitive deficits on everyday life?

   The majority of HIV patients in Dr. Chang's studies are not able to work because of HIV-associated neurocognitive disorder (HAND). There are a lot of data showing that HAND severely impacts the functioning of these patients, which could be due to the fact that the cognitive impairment renders it difficult for them to manage the demands of a job.

4. Is it morally and ethically correct to divert antiretroviral therapy (ART) medications to HIV-negative people for prevention when there is insufficient coverage of HIV-positive people globally?

   The response was that there are different ethics depending upon the level of resources available to a country. For instance, in the United States and other developed nations, it is morally (and perhaps ethically) wrong that there should be any person living with HIV who is without access to ART. The question of whether there is available medication is not a relevant one in developed nations.

5. Are the measurement and definition of HIV risk behaviors adequate?

   Risky sexual practices (e.g., without condom use) and needle-sharing may not always increase the risks for HIV infection or transmission if, say, the persons involved do not have HIV or only clean needles are used. The constructs of HIV risky behaviors have not been very precise and, therefore, are not very useful. Future research should identify biomarkers that can be more objective and useful.

6. How do we know if it is HIV that enhances substance abuse, and not something preexisting?

It could be that these patients are genetically susceptible to these problems (i.e., more prone to risk-taking behaviors), and that is the reason why they start abusing substances or become addicted. A recent brain imaging study suggests the possibility of pre-morbidity in stimulant users of amphetamines since their non-amphetamine using siblings also showed the same brain abnormalities [8]. However, in that study, many of the non-drug using siblings were tobacco smokers. Since nicotine is a form of stimulant too, and they had similarly enlarged striatal brain structures as their stimulant abusing siblings, which could have resulted from the stimulant use, rather than the enlargement as a premorbid phenotype. Therefore, Dr. Chang believes that longitudinal studies are needed to evaluate the changes over time in relation to the progression of the disease (e.g., drug use or HIV infection). Translational research using animal models that can verify the clinical observation will also be useful to test the hypotheses.

**7.** What is the connection between cognitive enhancement and drug-use reduction?

While we clearly can enhance cognitive functioning, enhancing cognition may not cause a reduction in drug use. Some suggest that the anti-inflammatory and neuroprotective effects of memantine may help address substance use. Others suggest that methamphetamine users do many other risky activities besides their use methamphetamine. When methamphetamine is taken out of the person's activities, something else needs to replace or fill the void, so helping patients improve their cognitive functioning so that they can engage in normal activities could be a way to prevent methamphetamine use.

## REFERENCES


1. Chang L, Ernst T, Witt M, et al. Relationships among cerebral metabolites, cognitive function and viral loads in antiretroviral-naïve HIV patients. NeuroImage. 2002; 17:1638–1648. [PubMed: 12414302]
2. Chang L, Ernst T, Witt M, et al. Persistent brain abnormalities in antiretroviral-naïve HIV patients before and 3 months after HAART. Antivir Ther. 2003; 8:17–26. [PubMed: 12713060]
3. Ernst T, Jiang CS, Nakama H, et al. Lower brain glutamate is associated with cognitive deficits in HIV patients: a new mechanism for HIV-associated neurocognitive disorder. J Magn Reson Imaging. 2010; 32:1045–1053. [PubMed: 21031507]
4. Chang L, Yakupov R, Jiang C, et al. Lower cognitive reserve in the aging human immunodeficiency virus-infected brain. Neurobiol Aging. 2013; 34:1240–1253. [PubMed: 23158761]
5. Chang L, Andres M, Sadino J, et al. Impact of *APOE*ε4 allelle, age and HIV on cognitive function and brain atrophy: antagonistic pleiotropy and premature brain aging. Neuroimage. 2011; 58:1017–1027. [PubMed: 21803164]
6. Munsaka, S.; Andres, M.; Feger, U., et al. Cannabinoid receptor expression on peripheral blood mononuclear cells of HIV subjects and marijuana users by flow cytometry. 17th Society of NeuroImmune Pharmacology Conference; April 7–9th, 2011; Clearwater, FL.
7. Chang L, Cloak C, Yakupov R, et al. Combined and independent effects of chronic marijuana use and HIV on brain metabolites. J NeuroImmune Pharmacol. 2006; 1:65–76. [PubMed: 18040792]
8. Ersche KD, Jones PS, Williams GB, et al. Abnormal brain structure implicated in stimulant drug addiction. Science. 2012; 335(6068):601–604. [PubMed: 22301321]