

## **NIDA FY18 Priorities**

Project Title: Unsolicited Investigator-Initiated Research

NIDA supports high priority domestic and international research relevant to drug abuse (injection and non-injection) and HIV. This research focuses on vulnerable populations who tend to be underserved and not engaged by health care services. Use of illicit and licit drugs, often in the context of polysubstance abuse continues to be a major factor in driving HIV incidence and in adversely impacting HIV treatment success. NIDA's research seeks to prevent HIV acquisition and transmission associated with use of injection paraphernalia and/or high-risk sexual behavior in the context of substance use. In addition, NIDA seeks to improve the HIV continuum of care by improving access, linkage to treatment services, adherence, long-term retention, and durable viral suppression. Another priority is reduction and mitigation of HIV-associated coinfections and comorbidities associated with HIV/AIDS among substance users.

To improve individual health and reduce HIV transmission to the community, NIDA supports studies of the seek, test, treat, and retain paradigm (STTR), which seeks out hard-to-reach substance using populations, tests them for HIV, links them to treatment and retains them in care. As recently highlighted in the White House's "National HIV/AIDS Strategy for the United States Update to 2020," treatment for substance use disorders is an efficient HIV prevention intervention that has been shown to increase adherence to HAART. Research on substance abuse treatment as a component of HIV prevention including studies combining substance abuse and AIDS treatment to enhance adherence and retention, are significant component of NIDA's HIV/AIDS research. NIDA's HIV/AIDS research program includes studies that integrate substance abuse treatment (including licit substances such as alcohol and tobacco as well as opioids, methamphetamine, cocaine, marijuana, club drugs) in order to prevent new infections and reduce comorbidities. NIDA also supports research on the natural/treated history, epidemiology, etiology and pathogenesis, prevention, and treatment of HIV/AIDS and AIDS-related co-infections (e.g., hepatitis C virus (HCV), other sexually transmitted infections (STIs)) and other comorbid conditions (e.g., neurologic, cardiovascular). In addition, as new HIV therapies come on line, NIDA will support studies of the effectiveness of such new therapies among drug using populations. In order to be better able to explore multiple issues relating to HIV in substance using populations, NIDA has enhanced its portfolio of cohort studies, adding MSM cohorts and continuing IDU cohorts, and facilitating harmonization across cohorts. Another research area supported by NIDA is basic research; this includes the use of animal models (including model development) and in vitro systems to study the role of drugs of abuse in HIV/AIDS etiology and pathogenesis; including a major focus on neuroAIDS and research on eradication of HIV reservoirs in the CNS. Research on genetics (host and viral genetic factors), epigenetics, proteomics, and systems biology are major areas of focus of this program; included in this basic research program are studies that examine the effects of drugs of abuse on HIV reservoirs, HIV latency, and other cure-related topics. Because HIV/AIDS associated with substance abuse knows no national boundaries, NIDA supports international research to reduce the intertwined epidemics of HIV/AIDS and substance use. NIDA also participates in collaborative efforts with other Institutes and Agencies in order to leverage resources and conduct complementary research in areas such as HIV and aging, HIV and the CNS, HIV persistence, HIV and HCV co-infection.

NIDA supports initiatives to enhance dissemination of research findings, develop and distribute state-of-the-art treatment and prevention guiding principles. NIDA disseminates the results of important medical discoveries resulting from NIDA funded research initiatives. The NIDA utilizes multiple media platforms,

including TV, radio, Web, portable communication devices, print, and social media, to reach both scientific and lay audiences. NIDA sponsors and supports a myriad of meetings, conferences, and workshops each year that bring together scientific experts to discuss critical scientific issues and develop recommendations, or research agendas.

Project Title: Promoting Linkage and Retention in HIV Care and Durable Viral Suppression

The cascade (or continuum) of HIV care model has been adopted as a major prevention tool and is used by the National AIDS Prevention Strategy to measure progress in preventing HIV transmission. Gardner et al. (CID 52, 793-800, 2011) calculated that only 19% of the HIV infected population in the U.S. had undetectable viral loads. Most recent CDC calculations (MMWR 63/47 Nov. 28, 2014) based on their surveillance data and the medical monitoring project estimate that 30% of HIV infected individuals in the U.S. had undetectable viral loads in 2011. In order for Treatment as Prevention to be effective in eliminating AIDS in a generation, the U.S. will have to greatly improve this number. Increased attention has been focused on HIV testing in order to reduce the number of HIV+ unaware of their infection; and that number has decreased to about 18%. Skarbinski et al. (JAMA Int. Med., 2015) reported that 91.5% of new transmissions are due to those who are either unaware that they are HIV+ (30% of new infections) or are diagnosed but not retained in care (61% of new infections). While technologies enable individuals to learn their HIV status within minutes and testing can be performed in a variety of settings the next critical steps in the care cascade are linkage to care and engagement in long-term treatment. Given the critical need to identify and successfully treat those with substance use disorders NIDA supports research on linkage and engagement in care through major priority initiatives addressing the Seek, Test, Treat, and Retain (STTR) paradigm. Data from ongoing NIDA funded studies on stages of the cascade are able to be analyzed across studies because of resources devoted to harmonizing STTR data.

Especially vulnerable groups include youth and minorities. Continuum of HIV care data reveal major differences between youth and adults. Consistent antiretroviral use and virologic suppression among adolescents and young adults are low, with estimates that under 10% of all HIV+ youth are suppressed compared to about 30% of adults. At every step of the HIV cascade of care, youth and minorities are less engaged than the general population. African Americans tend to be diagnosed later than Caucasians. African American MSM account for disproportionate numbers of new HIV cases. Knowledge of HIV status is less common and despite comparable rates of ever receiving HIV testing, frequency of testing is lower and diagnosis of HIV is more likely to occur in the context of HIV-attributable symptoms. Incidence is high among minority MSM under age 25 and lack of awareness of HIV infection is common in this age group. For young minority MSM, stigma and discrimination associated with drug use and HIV are cited as deterrents to testing and seeking HIV treatment. It is essential that youth and minorities be engaged in testing, linkage to care, and retention in ARV therapy for treatment as prevention to succeed at the population level.

Factors associated with successful strategies for maintaining long term retention in care and achieving require further research. Studies have highlighted how relatively few HIV+ are retained in care (Fleishman et al. JAIDS 60, 249-59, 2012; Hall et al. JAIDS 60, 77-82, 2012). In both studies African Americans, younger patients, IDU had worse retention. Fleishman et al. using data from the multi-site HIV Research Network from 2001 to 2009 found that only 21% of all patients established HIV care, met retention criteria in every year, and were not lost to follow-up. Hall et al. analyzed CDC data from people living with HIV (PLWH) in 13 areas in the U.S. in 2009. Less than half of PLWH had laboratory evidence of ongoing clinical care and only two thirds established care within one year after diagnosis. Another CDC study (Crepaz et al. Clin Infect Dis. 2016 Jun 29.) of those in care in 2011 and followed 2012-2013 showed that only two-thirds exhibited durable viral suppression; one third had high viral load burden and were at risk of onward transmission of HIV. A community based study of IDU indicated that lapses in care were associated with issues related to health

care access but that failure to maintain suppressed viral load was associated with social and behavioral factors including alcohol and crack cocaine use (Westergaard et al., 2013). Initiating ART was found to be the strongest correlate of retention in care in a multi-site study of retention in care of patients within one year of their initial care visit (Tedaldi et al., 2014).

Retention in care frequently involves multiple cycles of an individual cycling in and out of care and is prevalent among substance users. The concept of “churn,” the analysis of the pattern of aggregate measures of retention patterns over time at a population level, may be useful in identifying intervention targets for a particular group in order to tailor retention interventions to a particular population—interventions targeted to substance users who have cycled in and out of care multiple times may require additional components vs. interventions for those newly diagnosed and entering treatment for the first time. Studies of a number of strategies have been undertaken to increase retention in care such as use of peer navigators, case management, incentives, use of technology such as cell phone reminders, but many issues remain in how to best develop and implement these strategies individually and in combination. For example, while peer navigation has been adopted in many studies, there is no agreement on the elements that should be included in peer navigation, and peer navigation may not be as effective in drug abusers as others.

Retention in care is also a broader health care issue for all chronic diseases, and it is possible that strategies employed for other conditions can be adapted to HIV. Re-engagement in care of patients who have dropped out of care is a related issue which has also received little attention. Given that substance users may experience HIV treatment interruptions because of life events that they are more likely to encounter such as incarceration, loss of stable housing, it is important that studies be directed toward locating and re-engaging those who have dropped out of treatment.

Project Title: Developing Comprehensive Interventions for Substance using MSM

MSM continue to be disproportionately affected by HIV. CDC's current estimates indicate that HIV diagnoses among MSM are 44-86 times greater than for other men, and 40-77 times that of women in the US. In addition to ongoing transmission among MSM in the US, MSM have emerged as a population at considerable risk for HIV in parts of Asia, epidemics have re-emerged in parts of Europe, and HIV among MSM communities in Africa is beginning to be identified. Substance abuse is common among MSM in the US and, increasingly in international regions such as Asia, and is associated with elevated risk of acquisition or transmission of HIV through risky sexual behaviors. Methamphetamine use, in particular, has been identified as a driver of risk among MSM, in part because of its motivational effects on behavior. Other stimulant use is common, particularly cocaine and crack, as well as the use of "club drugs" (e.g., ecstasy), and alcohol; poly-substance use is common.

Although PrEP has been demonstrated to be an effective prevention tool among high-risk MSM, specific research is needed on PrEP uptake and effectiveness in MSM who abuse drugs. The impact of the new long acting ART for PrEP and as a tool for facilitating more efficient TasP needs to be investigated. Priority research includes development and testing of interventions that tailor elements of the Seek, Test, Treat and Retain paradigm of HIV prevention to the social context of MSM, including effective outreach strategies to encourage sexually active substance-using MSM to receive routine and repeated screening for HIV to allow for early diagnosis and treatment and linkage to integrated treatment settings for HIV infection which can effectively address multiple risks related to substance use and sexual behaviors. The development of more effective adherence approaches which utilize real time biomedical and behavioral interventions for substance using MSM are needed. Models of HIV care targeted to achieving long-term retention to ensure sustained viral suppression and risk mitigation which include management of infectious and non-infectious HIV co-morbidities common in substance-using MSM require additional research.

As the US AIDS epidemic has evolved; ethnic/racial minorities, particularly African-Americans and Latinos bear an increasingly disproportionate share of new HIV infections and people living with HIV. While new infections have remained relatively stable, there has been an increased incidence of HIV among men who have sex with men (MSM), which is being driven by increases in young MSM who are members of ethnic/racial minority groups, particularly young, Black MSM. In 2016, CDC released projections of the lifetime risks of acquiring HIV, which suggested that if current HIV diagnoses rates persist, about 1 in 2 black men who have sex with men (MSM) and 1 in 4 Latino MSM in the United States will be diagnosed with HIV during their lifetime.

NIDA has had an ongoing program addressing vulnerable populations in the U.S., but it is now placing increased emphasis on research on youth and young Black/African-American men who have sex with men (YBAAMSM). Sexual networking patterns, sexual mixing patterns, and concurrent STI may be significant contributors to the dissemination of HIV among Black/African Americans, particularly within defined geographic areas. While an increasing number of HIV prevention interventions targeting African-American MSM with evidence of efficacy have become available recently, substance use among MSM, particularly stimulant abuse, remains a barrier to implementing effective HIV prevention strategies among the drug using MSM community.

There is a continuing need for new and novel interventions, that can be combined with efficacious interventions (e.g., pre-exposure prophylaxis, post-exposure prophylaxis) to better address the heightened risk of transmission and acquisition among substance abusing minority MSM. Substance use, particularly stimulant abuse, has been a barrier to adherence to HIV medications. Studies are needed in MSM to determine whether substance use interferes with the effective use of medication-based pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). High risk MSM who also engage in injection risk behavior may be important targets for PrEP because PrEP has also been shown to be efficacious in preventing injection related HIV transmission as well as sexual transmission. This priority supports the development of comprehensive, multidisciplinary approaches that focus on the interdependent nature of sexual and substance use risk, as well as effects of substance use on adherence to antiretroviral treatment (ART) for HIV treatment and for prevention (including PrEP and TasP).

Project Title: Screening, Prevention, and Treatment of Comorbidities and Coinfections in Substance Users

Comorbidities:

Consistent with the NIH HIV/AIDS research priorities, the proposed NIDA's priority supports research on co-morbidity associated with HIV among substance abusing populations in domestic and international settings. This research will include the study of physiological/biochemical systems, including, but not limited to: (a) cardiovascular, renal, hepatic, endocrine, neurologic consequences of drugs of abuse and HIV, respiratory/pulmonary consequences of smoked drugs and HIV, excess mortality among HIV treated drug users, and premature aging in HIV infected substance abusers; (b) development of integrated medical/therapeutic interventions for drug abuse and HIV associated diseases; (c) studies of pharmacokinetic/pharmacodynamics drug-drug interactions between drugs of abuse, medications for drug addiction and other co-morbid conditions, and current or potential new HIV/AIDS antiretroviral and HCV antiviral medications.

Cohort studies have demonstrated that drugs of abuse such as cocaine accelerate HIV disease progression and enhance comorbidities, e.g., cardiovascular, metabolic disorders, and neurologic effects. An important focus of NIDA research are studies aimed at understanding the mechanisms of HIV neuropathogenesis and the effects of drugs of abuse on CNS disease progression. While the era of cART has greatly reduced HIV associated dementia, the prevalence of HIV associated neurocognitive disease has increased as the numbers of PLWH increase. A better understanding of neuroAIDS in drug using populations may lead to more effective therapies.

Co-infections:

Although, NIDA supports research on HIV-related co-infections including TB and STIs, the predominant co-infection research need among substance abusers is Hepatitis C and HIV coinfection; Globally it has been estimated that approximately two million are infected with both HIV and HCV. HIV and HCV share routes of acquisition and transmission, predominantly through injection drug use but also via sexual transmission. In IDU cohort studies in the US, Europe and Asia reports of up to 90% prevalence of HIV/HCV co-infection are common. Sexual transmission, often in the context of stimulant abuse, is occurring mainly among MSM: HCV infection is six to eight-fold more likely to occur in HIV infected MSM than in MSM who are HIV negative. HIV and HCV also share racial and ethnic disparities in infection rates, including substantially higher rates among African Americans in the US. Incidence rates of HIV and HCV are increasing among young white adults (15 to 30 years of age) living in rural and suburban areas who are transitioning from prescription opiate abuse to opioid injection. is

In the U.S., deaths from HCV now exceed those due to HIV. Because HIV co-infection influences HCV disease progression through increased HCV replication, lower rates of HCV clearance, and increased risk of fibrosis progression, untreated HCV/HIV co-infection has emerged as a major threat to the survival of co-infected individuals. New direct acting antivirals (DAAs) can cure HCV infection, but lack of awareness of HCV infection, poor access to both ART, which can attenuate liver disease progression, and DAAs remain serious issues for both IDU and MSM, particularly African American MSM. Bundling rapid HCV point-of-care antibody testing and as needed follow-up testing for detection of HCV RNA with HIV testing and ongoing infection

status monitoring is a potentially scalable and cost effective strategy to identify HIV/HCV co-infection. To this end, studies are needed to develop combined HCV and HIV testing outreach in venues accessed by high-risk populations, such as substance use disorder (SUD) treatment programs, STD clinics, and criminal justice settings. Research using a seek, test, treat, and retain approach for HIV/HCV co-infection is needed to maximize components of the care cascade and develop integrated models which include testing, treatment, care and risk reduction prevention into primary care, SUD treatment programs and other health service venues. . As new therapeutic agents become available for both HIV and HCV, testing for interactions with other medications used to treat substance abuse, as well as abused substances, is important in order to ensure treatment effectiveness. Because of the critical role that substance abuse plays in morbidity and mortality related to HIV/HCV disease, NIDA is conducting priority research aimed at breaking down barriers to accessing HIV/HCV coinfection screening, treatment, and prevention services.

Project Title: Implementation Science Research

Development of efficacious interventions to prevent and treat HIV in substance using populations which can be successfully utilized in diverse settings remains a critical priority. Because drug abuse is stigmatized and often dealt with punitively rather than from a public health perspective, implementation science research may be particularly useful in identifying barriers and testing possible solutions for HIV/AIDS interventions. The goal of this implementation research priority is to determine how best to provide a comprehensive, integrated mix of high quality, sustainable, cost-effective interventions to reduce substance abuse related HIV risk behavior, prevent HIV transmission and acquisition, and mitigate the consequences of HIV infection.

While advances in HIV prevention and treatment make it now possible to look forward to a generation without AIDS, understanding how to evaluate local epidemiologic data and then develop programs to meet local needs for combination, integrated HIV prevention and treatment is critical. There is no one size fits all; prevention must be tailored to local conditions and resources. Epidemiologic data are needed to guide prevention efforts, but reliance on national or state-wide data may not capture local conditions and/or may not be available in many resource poor settings. Utilization of local data regarding HIV and substance use can provide sentinel data to efficiently target prevention efforts. In addition, it is important to assess the local social, economic, and policy environments in which substance use related HIV risk behavior and HIV transmission occur which will affect the choice of interventions. Evaluation of resources available for HIV prevention and modeling different scenarios can help to determine the most cost-effective approach for a given setting. The constituents of comprehensive prevention and treatment for substance use related HIV and the integration of biomedical, behavioral and social/structural components will also vary. To further enhance this prevention approach, this initiative calls for integrating as well as combining interventions. Integration would be more than co-localization of services—it would aim to use the same team to deliver a variety of HIV interventions. For example, ART, drug abuse treatment, treatment for HIV-related co-infections and risk reduction counseling could be provided by the same staff that provides linkages to housing and other assistance.

To date, several promising integrated behavioral and biomedical treatments and approaches have shown positive outcomes in decreasing the rate of new HIV infections, promoting greater adherence to HIV treatment and overall medical management, improving engagement and retention in HIV care, and reducing substance abuse. However, there remains a large gap regarding translation from research models into combination approaches for HIV in the context of substance use that are effective in “real world” settings, such as front-line community based organizations, substance abuse treatment venues and other direct providers of clinical care. Maximizing adherence in the broadest sense is key to effective implementation. Specifically, this initiative seeks to explore mechanisms to successfully transfer and sustain efficacious integrated combination preventive and treatment interventions (e.g., targeting use of and adherence to ART, screening and risk reduction, engagement and long-term retention in HIV care, and overall medical management for co-morbid conditions, such as substance use, mental health impairments, Hepatitis C, TB) for at-risk and HIV+ populations in real-world practice settings. This may include investigating the optimal settings and approaches for intervention delivery (primary care, urgent care and/or specialized care settings, home) as well as a structured analysis of local community resources to understand the capacity needed to deliver the optimal “dose” of required HIV treatment. In short, it is critical to understand how evidence-based

HIV interventions are transported into and maintain their potency in real-world community-based practice settings (e.g., ERs, primary care, criminal justice settings, drug treatment etc.).

This NIDA priority supports research on ART as HIV prevention and improving the continuum of care by focusing on local level data. Identifying HIV-infected substance users earlier in the course of their infection and, engaging and retaining them in care to achieve viral suppression. Initiating care earlier in the course of HIV infection, fostering long-term retention in care, and pursuing re-engagement in care for those who drop out are crucial to maximizing prevention opportunities, preserving the efficacy of first-line ART, and improving individual and population health outcomes. This includes testing of models to optimize coverage of HIV care services, comparing models of HIV service provision and adherence/retention support, delineating key issues that result in suboptimal HIV clinical outcomes identifying appropriate portals for HIV testing and identifying social and structural barriers as well as individual-level barriers to improve ART initiation and retention. The HIV continuum of care varies by population (age, gender, type of drug use, etc.) and geographic region (as granular as neighborhood differences within a city); it is important to tailor HIV programs to specific drug using populations within local communities.

Substance abuse treatment (both medication-assisted treatment (MAT) and behavioral therapy) as HIV prevention is unavailable or of limited availability in many settings. Studies are needed to optimize substance abuse treatment in order to increase adherence to ART, retention in care, viral suppression, and improve HIV treatment success including quality of life indicators. Long-lasting opioid pharmacotherapy with depot naltrexone—Intramuscular injection of extended release naltrexone can be used as a once a month treatment. In countries that do not allow opioid substitution therapy (OST), the use of agonists to treat opioid addiction, this medication assisted therapy offers an alternative. This therapy may also be beneficial in situations where adherence is an issue, health care staff are limited, or where patients have to travel long distances to reach caregivers. In addition, long-acting buprenorphine implants are a new treatment for opioid abuse. How to best implement long-acting buprenorphine implants among HIV+ opioid abusers will have to be studied since insertion and removal of implants requires surgical procedures performed by those with special training and may limit the settings in which this treatment can be employed. It will be important to determine whether patients remain in treatment and to what extent they reduce their HIV transmission and/or engage and are retained in HIV care including durable adherence to ART.

Project Title: Transformative Research

NIDA Director's Avant-Garde Award Program for HIV/AIDS Research: In FY08, NIDA introduced the Avant-Garde award to encourage cutting edge, high-risk, high payoff HIV/AIDS research that has the potential to open new avenues of research and/or have broad public health impact by leading to new breakthroughs in HIV/AIDS prevention and treatment interventions for substance users. It uses the DP1 mechanism; the same mechanism as the NIH Director's Pioneer award. This ongoing program selects 2-3 awardees each year. Several Avant-Garde awardees are conducting studies that are highly relevant to efforts towards a cure by focusing on strategies that may lead to new therapies to control or eliminate HIV. Among the funded projects are: studies of HIV reservoirs and latency, systems biology of immune reconstitution, proteomics of virus-host interactions, HIV transmission between cells, development of a mouse model containing human genes that regulate replication, pathogenesis, and immunity, public health approaches to prevention that combine behavioral/social science data with phylogenetic information to intervene in network transmission, and new therapeutic approaches suited to treat infections in populations with limited access to health care. Treatment as prevention in injection drug users was one of the projects funded in 2008, and several significant papers have resulted from this award, and the work is continuing under an Advancing Exceptional Research on HIV/AIDS award. In 2013 NIDA developed the Advancing Exceptional Research on HIV/AIDS award that utilizes an R01 mechanism and complements the Avant-Garde DP1. It supports research by individual and multiple principal investigators and is an ideal mechanism to support continuation of the research begun under the DP1 award or new, innovative projects. In 2015, NIDA initiated the Avenir Award Program for research on Substance Abuse and HIV/AIDS, which uses the DP2 mechanism to support highly creative, early stage investigators (ESI). Avenir awards to date have ranged from studies of host and viral genetics to prevention in the hard-to-reach.

Project Title: Training, Infrastructure, and Capacity Building

Humphrey Fellowship Program: The Humphrey program is a partnership with the U.S. Department of State to support a unique training program for midcareer drug abuse professionals; some of NIDA's Humphrey fellows have an interest in HIV/AIDS. In addition, NIDA participates in the national Humphrey Fellowship seminar and has organized sessions focusing on HIV/AIDS and invited participation of fellows from Emory Humphrey Program, which has an HIV/AIDS concentration. Through contacts with NIDA staff, further interactions between foreign HIV/AIDS researchers and U.S. investigators have been facilitated.

A-START: To facilitate the entry of newly independent and early career investigators into the area of AIDS research, NIDA has developed the AIDS-Science Track Award for Research Transition (A-START) mechanism. This program supports feasibility studies using the R03 mechanism and providing up to \$100,000 direct costs for two years to facilitate the entry of new investigators into drug abuse and HIV/AIDS research.

Research Training: This program supports research efforts through institutional training research grants (T32), pre-doctoral (F31), post-doctoral (F32) mechanisms, as well as through collaborations with FIC. The NIDA Research Education Program for Clinical Researchers and Clinicians (R25) also supports careers as clinical researchers, clinicians/service providers, or optimally, a combination of the two and includes HIV/AIDS as a topic of interest. To increase the numbers of underrepresented minorities in research careers in drug abuse research, including HIV/AIDS, NIDA supports a program of diversity supplements at the pre-doctoral, post-doctoral, and investigator level to train minority investigators in HIV/AIDS research. In addition NIDA co-funds the FIC international HIV training grant program and capacity building. The purpose of all of these programs is to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation's biomedical and behavioral research agenda in the areas of substance abuse and HIV/AIDS.

Project Title: Research Towards a Cure: Role of substances of abuse in the pathogenesis of HIV and effects on HIV latency, reservoirs, and persistence

Numerous in vivo and ex vivo studies have demonstrated diverse effects of drugs of abuse on cells of the immune system and on immune function. NIDA supports cohort studies in diverse groups of drug users (IDU, non-IDU, different primary drugs of abuse) that enable cure studies. Studies in animal models have also shown effects of drugs of abuse on HIV pathogenesis. It is also important to determine how cycles of drug abuse and drug withdrawal affect HIV pathogenesis, latency, reservoir size and persistence. NIDA has an ongoing portfolio of research directed at understanding the mechanisms of HIV neuropathogenesis and the effects of drugs of abuse on HIV in the CNS. In addition, understanding the mechanisms underlying CNS HIV infection is important to understanding the brain as a potential reservoir of HIV infection. CNS is a major focus of NIDA's research as are studies on the effects of drugs of abuse (including nicotine and alcohol and drug combinations) on reservoirs throughout the body, e.g., gut and lung.

CNS reservoirs may serve as a barrier to cure strategies, in part, because many therapeutic drugs do not penetrate the blood brain barrier. Drugs of abuse are known to exacerbate the role of HIV in the CNS for example; the deleterious synergistic effects of methamphetamine and HIV on CNS structure and function are well established. Drugs of abuse have been shown to increase HIV transcription in cells of the CNS. Amphetamine induces HIV transcription in human CNS microglial cells, and cocaine enhances HIV transcription in primary human macrophages in culture. In addition, drugs of abuse have been shown to exert epigenetic effects in the CNS. These interactions may have implications for the establishment of latency within cells in the CNS, for reactivation, and for maintenance of HIV reservoirs within cells of the CNS. HIV enters the brain early in infection and replicates and evolves within the CNS. In the CNS, HIV may actively, persistently, or latently infect perivascular and meningeal macrophages, microglia, and astrocytes. HIV is not uniformly distributed throughout the brain, highest viral loads are found in basal ganglia where drugs of abuse act through dopaminergic transmission. To understand the brain as an HIV reservoir, it will be important to establish which cell types harbor replication competent virus and to quantify this in different brain regions.

Project Title:

Trans-NIH HIV Collaborations

In order to leverage HIV resources and promote the integration of substance use related bio-behavioral research into high-priority NIH HIV initiatives, NIDA co-funds multiple trans-NIH IC programs. These include the MACS, WIHS and PHACS cohorts, the ATN, HPTN, and ACTG clinical trials networks, the IeDEA network, the CFAR program, the Martin Delaney Collaboratory for HIV Cure, and the FIC international HIV training and capacity building grant programs.