National Institute on Drug Abuse
FY08 Priorities

Title of Project: Drug Abuse and HIV Prevention
Area of Emphasis: 5
Plan Objective(s): 1A, 1B, 5A, 5C, 5D, 7A, 7B
SIC: M50%, I20%,
Mechanism: RPGs/Centers/Other
New or Expansion: CR/EXP/NEW
Co-Funding: possibly NIAID, NIMH, NIAAA, NICHD
Roadmap Area (if applicable):

Project Descriptions:
These priorities include new, continuing, and expanded research to prevent the intertwined HIV and drug abuse epidemics and their associated health and social consequences. Of critical interest are studies that address both the acquisition (i.e., primary prevention) and transmission (i.e., secondary prevention) of HIV among drug abusers. Over the past two decades NIDA's prevention research efforts (e.g., outreach, drug abuse treatment) have focused on injection drug use, which has led to significant decreases in the number of new AIDS cases associated with this transmission category. Given the sustained importance of sexual transmission in new HIV infections, new HIV prevention research questions of great public health relevance have emerged. That is, "How much of a role does non-injection drug use play in facilitating sexual transmission of HIV?" and "What are the mechanisms involved?" and "What strategies are needed to prevent drug-related sexual acquisition and transmission of HIV?" NIDA's ongoing secondary HIV prevention research priorities also include the development and testing of interventions to improve and maintain adherence to ART and OI treatment medications among drug users, including those in high risk groups and environments such as criminal justice settings; linking HIV prevention to drug treatment and prevention services; and cost-benefit and cost-effectiveness evaluations of interventions. A major new priority area is the expansion of HIV Testing and Counseling in drug abusing populations. These areas of research are more fully described below.

A) Secondary Prevention: HIV education, testing and counseling, and referral to treatment
CDC estimates that one quarter of the persons living with HIV in the U.S. do not know that they are infected. This puts them at greater risk for transmitting HIV. It also makes it likely that they will not receive treatment early in their disease; many do not learn their serostatus until they receive a diagnosis of AIDS. Mounting evidence suggests that starting antiviral therapy earlier, i.e., at higher CD4 counts, is more likely to lead to normalized CD4 counts and virologic suppression and slower disease progression. Advances in HIV testing technology (rapid testing) make it possible to give HIV-seronegative and provisional HIV-seropositive results in a single visit so that it is now much more likely that those who are tested will receive the results of testing. Despite increased emphasis on HIV education, testing, counseling, and referral to treatment as important elements in HIV prevention, there is relatively little information about how to optimize each phase of the process for drug abusing populations. For example, racial and ethnic minority populations are most affected by IDU-associated AIDS. Minorities are disproportionately affected by AIDS. Data indicate that minorities are less well-informed about the benefits of HIV treatment, and racial and ethnic minorities experience delays in linkage to care following HIV diagnosis. Emphasis will be given to how to best incorporate education, testing and counseling, referral to HIV/AIDS treatment into sites such as drug treatment and outreach facilities and social institutions (e.g., prisons, churches); assessing structural and individual barriers to testing and accessing care; addressing concerns of ethnic, racial, and other minorities about stigmatization. In light of the fact that a large proportion of HIV infected

people pass through correctional facilities in a given year (e.g., 20% to 26% of all people living with HIV in 1997); this initiative will give special emphasis to correctional settings and other criminal justice institutions. Given the current disproportional rates of HIV infections among minorities it is anticipated that 70% of study participant will be minorities. Therefore the SIC minority code for this priority is 70% (i.e., M70%).

B) HIV/AIDS Health Disparities Among African Americans: Over the past 20 years, empirical findings have shown that HIV prevention interventions are effective in reducing behavioral risks for HIV/AIDS, as evidenced by declines in the incidence of HIV among many risk groups. There are disparities in the effectiveness of these prevention interventions, however, as indicated by the disproportionate prevalence and incidence of HIV/AIDS in the African American population. Although African Americans comprise about 12-13% of the U.S. population, they account for a growing number of HIV/AIDS cases. For example, among females, the majority (over half) of all new cases of HIV/AIDS occur among African Americans. In light of the scope and magnitude of this problem, NIDA proposes to develop and evaluate comprehensive strategies to decrease HIV transmission and to improve access to treatment as well as treatment options and treatment outcomes in order to address the disproportionate burden of HIV/AIDS among the African American population. Special emphasis will be given to focusing increased attention to sexual transmission and acquisition among heterosexuals and MSM minority populations. The proposed research initiatives will encourage investigators to develop new primary (i.e., prevent acquisition) and secondary interventions (i.e., prevent transmission) that target minority drug using populations. These include interventions that address the co-occurrence of other STDs, hepatitis, and psychiatric disorders; and interventions that consider the role of culture, family, contextual/environmental factors. Social factors such as characteristics of social, drug use, and sexual networks in facilitating transmission and acquisition of HIV will also be studied. This priority focuses on minorities, the SIC is 80% (i.e., M80%).

C) HIV/AIDS Prevention within Drug Abuse Treatment: While effective drug abuse treatments, in and of themselves, reduce HIV risk behaviors and transmission, these treatments do not typically focus on preventing HIV risk and do not address sexual transmission very effectively. Presumably, integrating targeted HIV risk-reduction interventions into treatment could improve HIV risk outcomes for highly vulnerable populations. This research priority will support research to develop, modify, and/or test behavioral interventions to reduce HIV risk behavior among drug using populations in drug abuse treatment programs. Specific research areas of interest include: 1) the development and testing of new age-appropriate behavioral HIV risk reduction interventions based on research findings from basic behavioral, cognitive, and social epidemiology; or based on clinical theories of behavior change, intervention, etc.; 2) the adaptation and testing of behavioral interventions developed for other target problems (*e.g.,* impulsiveness, ADHD, conduct disorder) to HIV risk reduction among drug users in treatment. Given the unique nature of the risks of HIV among women who abuse drugs, this priority will also address the pressing need to develop targeted HIV risk-reduction interventions for women in drug treatment. The proposed research priority will also support the development and evaluation of HIV prevention strategies within pharmacotherapeutic drug abuse treatment programs. Given that a substantial proportion of patients in drug treatment are minorities, the SIC Minority code is M40%.

D) HIV/AIDS Prevention within Drug Abuse Prevention among Youth: In the US, women, youth, and minorities account for growing proportions of new HIV/AIDS cases in both rural and urban areas and among drug users, cases are increasingly linked to sexual exposure. Thus, it is important that youth be a major focus of research efforts examining prevention of drug abuse and HIV/AIDS. In many areas of the world, adolescents and young adults represent the component

of the population at greatest risk for HIV infection and young females are often at highest risk. This priority will support domestic and international research on drug-related HIV/AIDS epidemiology and prevention among general population and highly vulnerable youth (including minority youth, status offenders, non-institutionalized youth in the juvenile justice system, youth who are incarcerated or under supervision of the criminal justice system, and youth in foster care, on the street, runaways, or victims of sexual abuse). The initiative will support drug abuse prevention research to better reduce health risking sexual behaviors in adolescents and young adults. This priority will also encourage researchers to examine the effects of drug abuse prevention interventions on reducing both HIV transmission and acquisition.

E) Prevention of HIV/AIDS and Other Co-morbid Conditions among Substance Abusing Individuals Involved in the Criminal Justice System. This priority focuses on supporting new research to prevent further spread of HIV and to treat HIV/AIDS among diverse drug-using individuals involved in the criminal justice system at all levels including community-based diversion programs, drug courts, jails, prisons, and those re-integrating in the community after release from prison or jail. Drug users returning to their communities following incarceration are at particularly high risk of relapse to drug use and risky sexual behaviors associated with the spread of HIV/AIDS and other infectious diseases. Many of these individuals experience difficulty in accessing medical care. For these reasons, novel HIV/AIDS interventions need to be integrated within the criminal justice system. In addition, community-based interventions are needed to more efficiently link drug users transitioning from prison or other criminal justice system involvement to HIV/AIDS interventions. NIDA is encouraging new approaches for making HIV/AIDS prevention and treatment interventions more responsive and adaptive to the needs of drug users in and/or transitioning from the criminal justice system. Researchers are encouraged develop, test, and evaluate interventions that target both HIV transmission (i.e., HIV+) and acquisition (i.e., HIV-). Given the over representation of minorities in the criminal justice system the SIC code for minorities is M50%.

F) International HIV Prevention: Given that drug users and their sexual partners are one of the fastest growing segment of HIV/AIDS cases in many parts of the world, NIDA is encouraging researchers to evaluate innovative, culturally relevant, contextually appropriate drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings; identify and compare common and unique elements of effective HIV/AIDS prevention and treatment interventions, and adapt, and test these elements in a variety of social and cultural contexts; design, implement and assess the effectiveness of combined behavioral and biomedical HIV intervention models in and across different socio-cultural and geographic contexts; and develop innovative methodologies for the application, implementation, and cost-effectiveness analysis of prevention and treatment interventions. Given that this priority area focuses on international HIV prevention initiatives, the SIC code for International is I100%.

G) Assessment of the Public Health Impact and Effectiveness of Interventions: This initiative has short-term and longer-term goals which include, but are not limited to: 1) characterizing and forecasting the epidemiology of HIV/STI infections within and across different drug-using and non-drug-using populations; and 2) characterizing the influence of macro-level factors – that is, social, physical, health, environmental, and their interaction on multiple risk behaviors, behavioral changes, new patterns of drug use, and changes in the incidence and prevalence of HIV and co-infections; and 3) analyzing the benefits and cost effectiveness of different HIV prevention strategies, HIV/AIDS treatment, health services organizational models to improve access, utilization, availability, financing, and cost-effectiveness for HIV and its co-occurring conditions.

H) Dissemination of HIV Prevention Research: This program will support research on factors influencing the dissemination of research findings on substance abuse and HIV infections to prevention programs, facilities and clinics that address these problems. The program will stimulate research on the array of influences, and their interaction, that beneficially affect the adoption of valid HIV prevention and drug abuse prevention research findings into clinical practice, and promote the development of an empirical base on the effectiveness of knowledge dissemination interventions. There is a need for research on strategies for moving evidence-based practices into broader use in clinical care, and for examining the factors that, adversely or beneficially, influence the adoption of current state of the art practices into clinical practice and policy. The initiative will support research on: (1) the factors that beneficially or adversely affect the adoption of evidence-based HIV prevention and drug abuse prevention interventions into clinical practice and health care service systems; (2) test of alternative approaches to dissemination of effective interventions; (3) promote of the development of an empirically-supported knowledge base on the effectiveness and applicability of knowledge dissemination interventions; and 4) test the utility of alternative dissemination strategies for service delivery systems targeting rural, minority, and/or other underserved populations.

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FY08 Priorities

Title of Project: Drug use and HIV/AIDS Treatment
Area of Emphasis: 3
Plan Objective(s): 1B, 3C, 3D, 5B, 5C
SIC: M30%, I10%
Mechanism: RPGs
New or Expansion: New/CR/EXP
Co-funding: possibly NIAID, NIMH, NIAAA, NIDDK, NICHD
Roadmap area: multi- and interdisciplinary research teams

Program Description:
These priorities include new, continuing, and expanded research to develop better therapeutic regimens, limit development of drug resistance, promote adherence, and make treatment more accessible for drug abusing populations. NIDA supports domestic and international research on treatment of HIV/AIDS and co-occurring infections such as hepatitis C, TB, STIs among drug abusers. This research program includes studies to: 1) develop and test interventions to improve and maintain adherence to ART and OI treatment medications among drug users, including those in high risk groups and environments; 2) link and integrate treatment services for drug abuse, HIV, and co-occurring infections and conditions; 3) understand drug interactions among drugs of abuse or medications used in the treatment of addiction (e.g., methadone, buprenorphine) and medications to treat HIV infection and HCV infection; 4) investigate the development of viral resistance linked to non-compliance and/or treatment failure; 5) conduct basic research on host factors relevant to development of new therapies for HIV in drug abusers, e.g., research on opiate/CCR5 cross-desensitization is relevant to the development of CCR5 antagonists; and 6) conduct functional genomics studies of HIV infection in drug abusers, including those co-infected with HCV.

A) Adherence to HIV/AIDS Treatment Regimens. Antiretroviral therapy has dramatically reduced the morbidity and mortality of infection due to HIV/AIDS. It is important to understand the extent to which HIV + drug users adhere to their HIV medications and the role that substance abuse may have on adherence. This research priority will focus on improving our understanding of antiretroviral drug adherence among HIV-positive substance abusers. This research will encourage studies that address the interaction between abuse of particular drugs of abuse or combinations of drugs of abuse with individual and environmental factors to influence adherence, e.g., it has been suggested that stimulant abuse is associated with poor adherence. Understanding the effects and interactions of clinical, behavioral, neurocognitive, social, and environmental factors on the attitudes, beliefs, and motivations of substance abusers toward antiretroviral adherence will ultimately help in the development of improved behavioral and therapeutic interventions for antiretroviral adherence among drug users across the stages of HIV infection and disease. NIDA also proposes to support research on the effectiveness of pharmacological approaches, behavioral interventions, and other methods to facilitate adherence to HART regimens among drug users. Moreover, NIDA will encourage researchers to develop better methods to assess adherence to treatment regimens across a variety of affected populations domestically and internationally.

B) HIV/AIDS Treatment for Adolescents and Young Adults; Implications of Drug Abuse: This initiative will support domestic and international research that examines the intersection of HIV, HAART, and drug use in the context of biology, cognition and behavior unique to the developmental period of adolescence and young adulthood. Research areas include: (1) studies

on the effects of drug use including nicotine, marijuana, inhalants, abused prescription drugs, stimulants, cocaine, opiates, and club drugs on HIV disease progression and treatment during adolescence and young adulthood, (2) studies to examine the effects of substance use and abuse on HIV medication and treatment adherence for youth living with HIV, and (3) studies to examine the effects of combined exposure to HIV, HAART, and drugs of abuse on cognitive, emotional, and social development, behavior (including risk-taking behaviors associated with HIV/AIDS), psychiatric, psychological and neurological conditions, educational and vocational outcomes, health and development. Given that a large proportion of infected individuals are minorities, the SIC code for minorities is M40%. Moreover, given that many of the youth infected with HIV are in foreign countries, the International SIC code is I30%.

C) Pharmacogenetics and Pharmacoepidemiology of Drug Interactions

Research is needed on pharmacokinetic and pharmacodynamic drug-drug interactions among drugs of abuse and medications used in the treatment of addiction (e.g., methadone, buprenorphine) and medications to treat HIV infection and HCV infection and other co-occurring infections and disorders**.** Studies have shown that there can be interactions among various classes of antiretroviral and anti-infective drugs (e.g., PIs, NNRTIs, NRTIs, or combinations [HAART]) and drug abuse treatments, e.g, methadone, resulting in adverse consequences. The variability in outcome of drug therapy may be contingent upon multiple factors, including the patient's medical history, nutritional status, disease severity, viral variant, ethnicity, gender, age, etc. Pharmacogenomic research has shown that many cytochrome P450 genes have polymorphisms that directly contribute to varying metabolism of antiretroviral agents, and have a large impact on drug interactions among drugs of abuse, drug addiction medications, and medications for mental disorders. Research is needed to determine the incidence and prevalence of such interactions, underlying genetic contributions to drug interactions, and the effect of drug-drug interactions on adherence to antiretroviral therapies in those addicted or being treated for addiction.

D) Linking and Integrating Treatment for HIV and HCV and Other Co-morbid Conditions with Drug Abuse Treatment Services.

Drug abusers with HIV/AIDS frequently have co-morbid conditions such as hepatitis C (HCV), hepatitis B (HBV), tuberculosis, sexually transmitted diseases, and mental health disorders. Programs that offer comprehensive, accessible services as well as improved outreach and referral strategies are needed to optimally engage drug-using populations in care. The U.S. healthcare system does not provide coordinated care for HIV infected drug abusers, and issues of access to care and coordination of care are particularly relevant for underserved and minority drug abusing populations. For example, incorporation of HCV-related services in drug treatment units that treat intravenous drug users and provide HIV-related services is limited. Research is needed to: 1) identify the organizational factors that limit provision of coordinated drug abuse treatment, HIV, HCV, and other services; 2) identify the behavioral and social support needed by drug abusers in order to engage in treatment and adhere to treatment regimens; and 3) evaluate innovative approaches to treatment coordination such as use of nurses to monitor and support treatment or integrating mental health assessment and treatment to improve HIV /co-infection treatment success rates. Studies are also needed on how best to stage the introduction of medications to treat drug abuse, HIV, and HCV and to explore different medication combinations. Coordinated treatment settings could also provide a unique opportunity to integrate HIV prevention with service provision, and studies are needed on how best to accomplish this. Research is also encouraged on health services organizational models to improve accessibility, availability, utilization, financing, and cost-effectiveness of services for treating HIV and co-occurring conditions among diverse risk groups and to improve the diffusion of evidence-based treatment and prevention technologies for HIV and co-occurring

conditions. Given that a large proportion of co-infected individuals are minority members, the Minority SIC code is M40%.

National Institute on Drug Abuse
FY08 Priorities

Title of Project: Epidemiology and Natural History of HIV/AIDS Among Drug Using Populations
Area of Emphasis: 1
Plan Objective(s): 1A, 1B, 1C, 2B, 3C, 5A, 5B, 5C
SIC: I60%
Mechanism: RPGs
New or Expansion: New/CR/EXP
Co-funding: NIAID, NIMH, NIAAA, NIDDK, NICHD
Roadmap area: multi- and interdisciplinary research teams

Project description:
These priority areas include new, continuing, and expanded research on drug abuse, HIV/AIDS, and the health and social consequences associated with these intertwined epidemics. The proposed natural history and epidemiologic studies will improve monitoring of epidemic trends, following of changing clinical manifestation of HIV disease and co-morbid conditions, and measure the effects of treatment regimens (i.e., antiretroviral and substance abuse) in drug using populations. Of critical interest are studies that advance knowledge of the changing behavioral and social epidemiology of drug abuse, HIV/AIDS, and other infectious diseases; the natural history of HIV/AIDS and co-infections among injection and other drug users and their sexual partners; and the changing social, environmental, and behavioral contexts of risk among drug users, their sexual partners, and among high-risk groups that bridge HIV and AIDS-related co-infections to lower risk populations. The spectrum of research covered by these priorities will help to elucidate our understanding of the HIV transmission dynamics and disparate health effects of drug use and HIV/AIDS among diverse population groups and their communities.

A) International Studies on HIV/AIDS and Other Infections in Drug-Using Populations.
This is a continuation and expansion of an ongoing international initiative to foster cross-national and international HIV research and research training collaborations related to HIV/AIDS and other infectious diseases among drug using populations, and their sexual partners. HIV/AIDS associated with drug use continues to expand globally. This is particularly true in Eastern and Central Europe, Asia, and Southeast Asia. In Russia, for example, data suggest that drug abuse is driving 90% of the HIV epidemic, which has been fueling a multi-drug resistant TB epidemic, high rates of STIs, and viral hepatitis. In Asia, in the Golden Triangle area, molecular epidemiologic studies indicate the development of new recombinant HIV subtypes, reflecting the intersection of the IDU and heterosexual epidemics. HIV/ HCV co-infection is a widespread and increasing problem, as demonstrated by rates of HCV infection in HIV-infected drug users surpassing 80% in some areas of Southeast Asia and China. This priority will encourage investigators to: (a) develop systematic epidemiological approaches for monitoring changes and patterns in transmission of HIV and other infections associated with drug use; (b) researchers are also encouraged to assess the impact of HIV prevention interventions on the dynamic of the HIV epidemics; and (c) characterize the risk networks, environmental contexts, and dynamic interactions between rapid behavioral and social changes, including natural and man-made disasters (e.g., famines, wars) and the spread of infectious diseases among new and vulnerable drug-using populations (e.g., migrant populations) utilizing observational, molecular, medical and behavioral methodologies. Moreover, researchers will be encouraged to develop and evaluate the relative efficiency of novel epidemiological methods for obtaining HIV accurate incidence data in cost efficient manners for possible use in resource poor countries. For example, the use of cross-sectional studies that use new sampling procedures (e.g., Respondent

Driving Sampling) combined with newly available detuned assays (e.g., Calypte BED Assay) to obtain representative incidence rates among hard to reach populations, can not only provide more timely and accurate estimates then the traditional longitudinal study approach used to estimate incidence but it can also represent substantial cost savings. This priority area focuses on international project, so the SIC code for International is I100%.

B) Methodology. Initiatives in this area will seek new research that addresses methodology and measurement issues in diverse drug-using populations, issues in studying sensitive risk behaviors, issues of ethics in research, issues related to confidential data and the protection of research subjects, and issues in developing interdisciplinary, multi-method, and multilevel approaches to natural history and epidemiological research. Also of importance are approaches that integrate behavioral and social science research with biomedical, physical, or computational science research or engineering. NIDA is encouraging collaborations among researchers to promote molecular epidemiology studies using existing drug abuse cohorts. The many cohorts of drug abusers that have been used in primarily behavioral studies are a resource for conducting studies on the transmission, establishment, and spread of HIV infection in diverse populations. For example, these cohorts could be used for genetic studies of host factors such as chemokine and chemokine receptor variants that affect resistance and susceptibility to HIV infection and alter disease progression. Related initiatives will support cohort development utilizing observational, medical and behavioral methodologies in areas of high prevalence to study the natural and treatment history of HIV and HIV/hepatitis co-infection among drug users. It has long been recognized that HIV transmission among drug users depends on multiple factors, including the reservoir of infectious disease, the characteristics and distribution of HIV risk behaviors among drug users and their social networks, as well as environmental and social factors. Mathematical models that integrate these and other parameters of drug abuse and disease (e.g., co-infections, mental health disorders) are critical for understanding and predicting different trajectories of the epidemic across populations and their communities. These models also help inform the design and testing of HIV prevention interventions for optimal cost-effectiveness in reaching risk groups at different phases of the epidemic curve to avert the spread of new infections. NIDA supports the development of new mathematical and simulation studies of drug abuse and infectious disease transmission. Topics of interest include, but are not limited to: 1) characterization and forecasting of the incidence of HIV and other sexually transmitted infections (STIs) among different drug-using populations; 2) analysis of the cost-effectiveness of behavioral HIV prevention interventions for drug users relative to different model-based assumptions; 3) assessments of the benefits, costs, and consequences of antiretroviral and other medications for HIV-infected drug users in and out of the drug treatment setting; and 4) estimations of disease transmission dynamics relative to changing patterns of drug abuse, background seroprevalence levels, intervention-induced changes in risk behaviors, and the consequences of relapse or continuing HIV risk behaviors following participation in behavioral interventions. This priority area will support the development and refinement of epidemiological methods for studying sensitive risk behaviors in diverse settings. It will also encourage research on ethics and ethical issues that arise in studies of drug abuse and HIV/AIDS, especially in the international context. Other methodological issues relate to the collection and handling of confidential data and the protection of research subjects. So of the proposed modeling areas will involve international populations. The International SIC code for this priority is I40%.

National Institute on Drug Abuse
FY08 Priorities

Title of Project: Drug Abuse Related HIV/AIDS and Its Consequences
Area of Emphasis: 2
Plan Objective(s): 1A, 1B, 2B, 2E, 2F, 2G, 3C, 3D, 3H, 5A, 5B
SIC: M20%, I20%
Mechanism: RPGs
New or Expansion: New/CR/EXP
Co-funding:
Roadmap area: multi- and interdisciplinary research teams

Project Description:
These priorities include new, continuing, and expanded research to better understand how HIV infection is established and maintained and the bases for HIV-associated profound immunodeficiency and severe clinical complications. Such priorities include basic behavioral research of the mechanisms underlying the effects of drug abuse on the valence of positive reinforcement as well as negative reinforcement and punishment and how this influences the likelihood of engaging in HIV risk behaviors. NIDA research on etiology and pathogenesis of HIV/AIDS studies IDU and non-IDU drug abusers, human cells in culture, and animal models of HIV to understand the role of drug abuse and drugs of abuse, e.g., opioids, cocaine, and methamphetamine, on: 1) the transmission, establishment, and spread of HIV and coinfections such as HCV; 2) the medical and health consequences of HIV and HIV/HCV coinfection; 3) the toxicities and long term complications of combined therapy for drug abuse and HIV or HIV/HCV co-infection.

A) HIV/AIDS Models: To enhance understanding of the mechanisms involved in cell injury and death in the immune, nervous, and other organ systems affected by HIV, NIDA is supporting studies to increase the number of animal models available for studies of HIV-like infection in combination with drug administration, including further development and validation of a mouse model (Potash et al., 2005) employing a chimeric virus that holds promise for studies of systemic HIV infection, antiviral immune responses, and neuroinvasiveness and the development and validation of a Chinese rhesus macaque model of SIV. A particular focus is the development and validation of in vitro and animal models that allow the concurrent study of HIV, SIV or other lentivirus infection in the brain and specific patterns of chronic or acute drug exposure. In vitro studies with established cell cultures and primary human cell cultures, including neurons and glial cells as well as neural precursor cells, are being used to explore interactions of HIV, drugs of abuse and their receptors, and chemokines and their receptors. Mechanistic studies of these interactions and their cellular and molecular bases may lead to new therapies for HIV such as treatment modalities to slow progression of neuroAIDS.

B) Health and Development of Children Affected by HIV/AIDS and Drug Abuse: This new initiative will support international research to examine the cognitive, emotional, and social development, health, and psychosocial functioning of children and adolescents affected by the dual epidemics of substance abuse and HIV/AIDS. Worldwide it is estimated that almost 14 million children under the age of 15 years have lost one or both parents to AIDS. There are millions more children affected by the virus and its medical and psychosocial consequences vis-à-vis parents, caregivers, siblings, partners, friends, and neighbors who are living with HIV/AIDS. Affected youth may experience psychosocial and economic stresses associated with caring for a person with a chronic illness, or with grieving a parent or loved one who is dying or deceased. Children of women infected through drug use risk behaviors may experience multiple

challenges related to parental illness and to drug abuse. Non-IDU substance abuse can also impact families living with HIV/AIDS. Substance abuse in families may impact caregiver's abilities to monitor their children, can be associated with negative developmental outcomes for children and may result in the separation of the substance using caregivers and their child. In international settings there is a dearth of information on the children of IDUs and non-IDU substance abusers with HIV/AIDS. Qualitative and quantitative research is needed to understand how substance use affects these families and child outcomes directly (e.g., care giving) and indirectly (e.g., prenatal care, adherence to medication). This information can guide future interventions to improve the quality of life for these children. In addition, by understanding the health, development, and psychosocial functioning of affected children and adolescents we can learn which children may be vulnerable to developing substance abuse and other HIV risk behaviors in the future. Such knowledge will inform future initiatives aimed at preventing the dual epidemics of substance abuse and HIV in subsequent generations. Given that the majority of children affected by the HIV/AIDS pandemic are in foreign countries, this priority the International SIC code for this priority area is I80%.

C) Drug Abuse Effects on HIV Risky Behaviors: This priority will focus on disentangling the relative contribution of drug intoxication and/or the role of various patterns of drug abuse (i.e., class of abused drug, chronic versus acute or intermittent use, including withdrawal state) on HIV risk behaviors. That is, NIDA will develop various initiatives to further our understanding of effects of drug abuse on the valence of positive reinforcement as well as negative reinforcement and punishment and how this influences the likelihood of engaging in HIV risk behaviors. As part of these initiatives, NIDA will ensure that neurobehavioral studies of how drugs of abuse and drug abuse (dependent state or withdrawal) affect decision making by modulating the processing of rewarding and aversive stimuli. These initiatives will also highlight the importance of studying these phenomena during critical stages of human development.

Specific areas of interest include: 1) <u>Drug abuse, risky decision making and HIV/AIDS</u>. A fundamental question that drives research on decision making is why do people who are presented with the same options make different choices? And why do people choose options that are not in their best long-term interests? Moreover, what is the role of drug intake and alcohol intoxication on decision making? Effective HIV/AIDS prevention and treatment for alcohol and drug abusers would benefit from research on decision making. Despite a wealth of anecdotal reports and limited empirical data, there remains a great deal to be learned about the cognitive/behavioral processes and the neurobiological mechanisms that mediate the interactive effects of alcohol and drug abuse, risky decision making and HIV/AIDS. NIDA is interested in developing an interdisciplinary research portfolio that will study the role of drug abuse on HIV transmission and acquisition. Such a portfolio will integrate economics, psychology and neuroscience to elucidate the complex interrelationships among drug abuse, risky decision making and HIV/AIDS. Research on the role of emotion, expectancies, attitudes, impulsivity, and stress on the interaction among these factors is needed. Hypothesis driven research and modeling approaches will help to guide empirical testing and are encouraged. Both laboratory based research and investigations in naturalistic settings are critically important and should be integrated into a single proposal where it is feasible; 2) <u>Adolescence: Development of HIV risky behaviors and effects of substance abuse</u>. A great deal to be learned about the cognitive/behavioral processes and the neurobiological mechanisms that 1) lead to risky behavior and 2) mediate the interactive effects of alcohol and drug abuse, biobehavioral mechanisms and HIV/AIDS. Using both human and animal models, significant differences between adolescents and adults in these processes have been demonstrated. For example, higher death rates are seen during adolescence in multiple species, apparently related to increased risk-taking behaviors. Adolescent male rats show much stronger conditioning to novelty and social rewards than do adult rats, and alcohol seems to enhance social behavior in adolescent rats while decreasing it in

the adults. This initiative will support research to increase understanding of developmental processes and trajectories of HIV risky behaviors, and in turn, the effects of these risky behaviors (e.g., drug use) on the further development of those processes and trajectories. Adolescence is a crucial time for developing self regulatory capacities and decision making skills as this developmental period is marked by changing social roles, greater responsibilities and decreased adult supervision. Recent discoveries in the area of developmental neuroscience have provided accumulating evidence for a shift from decisions driven by activation of subcortical pathways to top-down control mechanisms with age. The relatively immature neurobehavioral systems for cognitive control, emotion regulation and decision making skills in adolescents are likely related to the risk-taking behavior and higher rates of substance use occurring in this developmental period. Of critical interest are studies that advance knowledge of adolescent cognitive and affective development in high-risk groups that may lead to a greater incidence of HIV risky behaviors and/or drug use. Also of critical interest is advancing knowledge of how drug use influences cognitive and affective development, and decision making skills in these high risk groups. Improved understandings of these developmental processes are likely to have implications for primary/ secondary prevention and adherence to HIV treatments.

D) Liver Disease in HIV and HCV co-infected Drug Abusers and Role of HIV/HCV Co-infection in Other Health Outcomes.

The advent of HAART therapy has had profound changes on morbidity and mortality associated with HIV disease and co-infections. For example liver disease has increased as a cause of morbidity and mortality among those co-infected with HIV and HCV. Many injection drug users (IDUs) are co-infected with both HIV and hepatitis C (HCV); co-infection rates range from 50 to 90 percent. Progression of liver disease is more rapid in co-infected individuals than with those infected with HCV only. The mechanisms by which HIV increases the rate of progression of HCV liver disease are not understood and further research is needed to understand the mechanisms by which HIV modulates host immune responses to HCV in drug abusers. Research is also needed on the effects of HCV/HIV co-infection on other health outcomes. For example, recent studies have shown that HCV augments cognitive deficits associated with HIV infection and methamphetamine abuse. Studies are needed on the effects on liver function of combined pharmacotherapies for drug abuse, HIV, and HCV and how best to integrate drug abuse treatment, HIV treatment, and HCV treatment. Given that a large proportion of co-infected individuals are minority members, the Minority SIC code is M40%

E) Cardiovascular Effects Including Sub-clinical Atherosclerosis

Human studies have demonstrated that cocaine and HIV are associated with clinical cardiovascular disease. Studies in animal models of HIV have confirmed additive effects of cocaine and viral infection on cardiac function. Studies in young, African-American cocaine abusers have shown that HIV infection, cocaine use, or both contribute to sub-clinical atherosclerosis as measured by coronary artery calcification. Further research is needed to understand the pathogenesis of cardiovascular dysfunction in HIV infected cocaine abusers. Studies are also needed to determine whether gender, race or ethnicity are associated with increased cardiovascular disease in HIV infected drug abusers. In light of the high prevalence of drug abuse and cardio vascular diseases among African Americans, the Minority SIC code for this priority area id M40%.

F) NeuroAIDS: In the era of HAART, the incidence of neurological complications of HIV infection has been reduced somewhat, but their prevalence remains high. The nature of the neurological effects associated with HIV infection has also changed somewhat; a milder form of CNS dysfunction, minor cognitive motor disorder (MCMD), is now seen more frequently. The incidence of HIV-associated dementia (HAD) has been reduced, but its prevalence has increased because more people are living longer with HIV. In the era of

HAART, the pattern of HAD is much more variable in severity and clinical features and in -temporal progression. Drug abusers are a significant proportion of those infected with HIV, and studies have demonstrated that drug abuse can exacerbate neuroAIDS. In Edinburgh, a higher prevalence of HIV encephalitis was found in IDUs (polydrug users who abused opiates) compared to homosexuals, and greater microglial activation was found in the brains of drug users with HIV encephalitis compared to non-drug users. Chronic methamphetamine use has been demonstrated to exacerbate cognitive deficits seen in HIV-infected persons and to produce enhanced neurotoxicity. Relevant issues include effects of drug abuse on HIV entry into the brain, viral replication and spread within the brain, initiation of immune and inflammatory responses, and the interaction of viral and cellular proteins within brain-resident cells. A combination of in vitro, animal and human neuroscience and neuroimmunology research is needed to explore the underlying basic mechanisms of chronic HIV-associated neurological diseases in the context of drug abuse, particularly with respect to neuroinflammation, changes in blood brain barrier permeability, glial activation or dysfunction, neurotoxicology, neuroprotection, and drug-drug interactions**.** Further research is needed to: understand how drugs of abuse and medications to treat addiction affect blood-brain barrier integrity and cell phenotype, leukocyte trafficking, HIV/SIV neuroinvasion, viral replication, and/or progression of neurologic disease. Studies using structural, functional and/or neurochemical imaging studies, or other types of clinical or basic neuroscience studies, are needed to identify brain regions and systems that exhibit relatively greater or lesser sensitivity to HIV infection as well as to assess the impact of co-occurring substance abuse on disease progression, including neuropsychological or cognitive impairment, and/or response to antiviral treatment of HIV in the context of drug abuse.

G) Resistance to Antiretroviral Drug Therapy: It is critically important to understand how drugs of abuse or medications to treat drug abuse, or their withdrawal, affect the outcome of antiretroviral therapy. For example, there are data that indicate that continued methamphetamine use decreases the effectiveness of HAART therapy leading to increased viral loads. This could potentially lead to the development of antiretroviral drug resistance. To stimulate research in this area, NIDA has encouraged virologists, immunologists, and infectious disease specialists to partner with researchers conducting epidemiology studies.

National Institute on Drug Abuse
FY08 Priorities

Title of Project: Training, Infrastructure, and Capacity Building
Area of Emphasis: 6
Plan Objective(s): 6A, 6B
SIC: M10%
Mechanism: Training
New or Expansion: CR
Co-funding: NIAID, NIMH, NIAAA
Roadmap area: multi- and interdisciplinary research teams

A) Institutional Research Training in the areas of Drug Abuse and Infections: Drug abuse and related co-infections are associated with a significant morbidity/mortality among drug abusers. Much research is needed to determine underlying pathophysiology of medical/clinical/health consequences of substance abuse and infections and how these may vary with population subgroups (e.g., women, youth, and minorities). However, it is apparent that there remains a substantial need for clinicians/researchers trained, for example, in the fields of cardiology, endocrinology, hepatology, neurology, and others, to be able to work with drug addicts and carry out research on various aspects of drug addiction and HIV/AIDS and other infections, including sexually transmitted infections.

This program will support research efforts through institutional training research grants (T32), pre-doctoral (F31), post-doctoral (F32) and short-term training grants to train clinician/researchers from the biomedical and clinical fields to conduct research on drug abuse and co-occurring viral and bacterial infections such as HIV, hepatitis C, TB, STDs and other bacterial infections. The program will support eligible institutions of higher learning to develop or enhance research training opportunities for individuals, selected by the institution, who are training for careers in specified areas of biomedical, behavioral, and clinical research, specific/relevant to drug abuse and infections. The purpose of this program 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 infections. Accordingly, this program will support predoctoral, postdoctoral, and short-term research training experiences. This training program will be used as the primary means of supporting graduate and postdoctoral research training in the area of substance abuse and infections. It will use a combination of institutional training grants and individual fellowships to ensure a continuing supply of well-trained scientists prepared to conduct cutting-edge health-related research on drug abuse and infections at institutions of higher learning. The program will support the following types of training: predoctoral training will lead to a Ph.D. degree or a comparable research doctoral degree and that it will emphasize fundamental training in areas of biomedical and behavioral sciences; postdoctoral research training will be for individuals who have received a Ph.D., D.V.M, D.D.S., M.D., or a comparable doctoral degree from an accredited domestic or foreign institution. Research training at the postdoctoral level will emphasize specialized training to meet national research priorities in the biomedical, behavioral, or clinical sciences. In addition, short-term (8-12 weeks) research training for health-professional students will include short-term predoctoral positions reserved specifically to provide full-time, health-related research training experiences during the summer or other "off-quarter" periods. Such positions will be limited to medical students, dental students, students in other health-professional programs to provide such students with opportunities to participate in biomedical and/or behavioral research in an effort to attract them into the fields of substance

abuse and infections. This priority area will sustain the same level of support for minority applicants as it has in the past. That is, the SIC Minority Code is M15%.

B) A/START To facilitate the entry of early career investigators into the area of AIDS research, NIDA is focusing on newly independent investigators who have not previously been supported by an R01 grant who are ready to launch their careers. The challenge for early career scientists is to obtain preliminary data related to the intersection of HIV/AIDS and drug abuse. This program will support feasibility studies to facilitate the entry of new investigators into the areas of clinical and basic neuroscience, pathogenesis, epidemiology, treatment, and prevention related to drug abuse and AIDS research. In this way it is anticipated that new careers in HIV/AIDS research in drug abuse will be established. It is hoped that this process will facilitate and encourage the development of appropriate and fundable R01 grant applications by early career investigators subsequent to generating preliminary data supported by an A-START grant. Funding would be limited to direct costs for one-two years of up to $175,000 and would be non-renewable.

C) Infrastructure Development

The global HIV epidemic continues to expand. UNAIDS estimates that during 2004 nearly 5 million adults and children became infected with HIV worldwide – about 14,000 new infections each day. The epidemic is driven primarily by behaviors: heterosexual intercourse is the predominant mode of transmission in most countries while intravenous drug use is important in Asia, South East Asia, Central Europe and Eastern Europe. Prevention efforts are of critical importance for slowing the epidemic, and the availability of local behavioral and social scientists are of critical importance for successful prevention efforts. In order to increase capacity and capability of those counties most affected by HIV through drug abuse NIDA plans to collaborate with NICHD, NIMH, FIC, and NCCAM to encourage partnerships between skilled foreign investigators and U.S. This collaborative initiative would use the R24 grant mechanism to support proposed projects. Moreover, NIDA intends to continue collaborating with NIAID's HIV Networks to facilitate strengthening the research infrastructure of foreign research institutions.