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Basic and Clinical Research on AIDS: From the Molecule to the Patient

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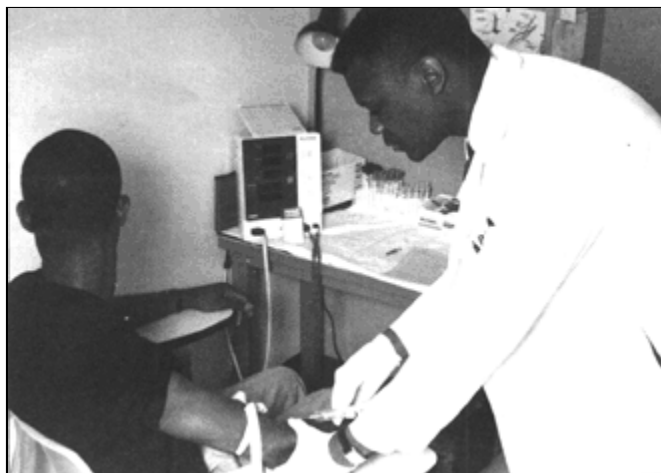
Both NIDA's basic research and clinical research programs explore ways drugs of abuse affect the spread of AIDS. Studies funded under these programs range from complex molecular-level investigations to human clinical trials.

Basic Research

Immunopharmacological research on drugs of abuse already has advanced understanding of the origin and progression of drug-related HIV infection and AIDS. This research is accumulating evidence to indicate that opiates and other drugs of abuse can suppress or enhance the immune system in laboratory animals.

Based on these findings, researchers supported by NIDA's Division of Basic Research are studying the complex interactions between the nervous system, where drugs of abuse have long been known to act, and the immune system, where recent studies show they act as well.

Several studies are exploring how opiates and other drugs modify or weaken immune defenses, alter neurotransmitter levels, and increase the potential for dementia. Neuroscientists have found that glial cells - the nonneuronal support cells of the brain and nervous system - help to modulate the immune defense against infection and are a primary focus of research after infection.



***AIDS-related health services research is a component of
NIDA's Clinical Research Program.***

Studies by NIDA-funded researchers have shown that opioids (morphine and naturally occurring morphine compounds) act on these glial cells to regulate this damage to the neurons in the brain.

One avenue of research is examining the ability of a specific protein on the surface of the HIV to activate damaging cytokines, the immune system's regulating neurotransmitters. NIDA-supported researchers have found that morphine and dynorphin, a compound similar to morphine that occurs naturally in the human body, enhance the activity of these HIV-activated cytokines to destroy human brain cells. This research holds promise for the development of therapies for HIV-related brain diseases and HIV infection, as well as for brain injuries that are aggravated by inflammation.

Basic research suggests that opioids may suppress immune function by modulating the levels of these cytokines. The effectiveness of macrophages - large cells that circulate in the blood destroying disease microorganisms - is affected by both infection and opioids, causing either an increase in the production of destructive cytokines or a decrease in the levels of beneficial cytokines.

Morphine, for example, appears to enhance the progression of infectious pneumonia by reducing the number of macrophages in pigs, whose immune systems closely resemble those of humans. In contrast, it appears that the progression of encephalitis may be slowed by opioids.

Another NIDA-funded study showed that the centrally mediated effects of morphine on the immune response in laboratory rats is markedly enhanced by psychological stress. Other studies are examining the morphine conditioning of the immune system. Enkephalins, which are endogenous opioids considered to be possible neurotransmitters, appear to be important regulators of immune responses. For example, studies show that by the presence of blood cells in a developing fetus, enkephalins may have a role in the development of immune function in fetal tissues and organs. This information could have significance for further research into the progression of disease in infants and children.

These opioid agonists (opiates and other compounds that stimulate opioid responses) characteristically stimulate immune responses. On the other hand, opioid antagonists, compounds that block the opioid response, also block the immune-suppressing actions of opioid agonists. NIDA-funded basic researchers have observed this blocking of the

action by naloxone, one of the family of opioid antagonists used to treat heroin overdoses. These findings view that opioid agonists suppress immune responses by employing typical opiate mechanisms and present ramifications for further studies of immune function and disease.

In a study of rhesus monkeys infected with simian immunodeficiency virus (SIV), an animal model for AIDS and HIV, NIDA-supported researchers have shown that opioids increase the mutation of the virus in the SIV infection. These results suggest that, in humans, this type of mutation could lead to the development of a virus that is resistant to zidovudine, or AZT, the drug most commonly used to treat AIDS patients.

For nearly 10 years, NIDA has supported longitudinal research on the natural history and progression of HIV disease in drug users.

Evidence from other studies indicates that cannabinoids, the psychoactive components of marijuana, also affect the immune response. NIDA-funded researchers are investigating how this process differs from immune system responses mediated by the central nervous system (CNS), how the immune cells differ from those in the CNS, and how cannabinoid-like compounds that occur naturally in the body act on these different systems. Other scientists have determined that one cannabinoid (THC) interferes with the ability of immune cells to target and destroy invading bacteria, fungi, and viruses.

Still other NIDA-funded basic research is examining how the abuse of nitrite inhalants depresses the immune system, thus apparently increasing abusers' risk of acquiring AIDS. The effects of abuse of anabolic steroids on the immune system are also being studied.

Clinical Research

NIDA's Division of Clinical and Services Research supports clinical studies of HIV and AIDS among drug users, including people in and out of drug abuse treatment. NIDA's multidisciplinary research program involves behavioral and biological factors associated with drug abuse and HIV infection. Current studies of HIV include disease progression, treatment of HIV-infected drug users, linkage of drug abuse treatment and primary care, relationship between HIV and other infectious diseases common among drug users, and studies of HIV in pregnant women and their infants. The goal of the clinical research program is to understand the unique characteristics of HIV and AIDS among drug users to develop better prevention and treatment strategies.

For nearly 10 years, NIDA has supported a program of longitudinal research on the natural history and progression of HIV disease in drug users. Long-term studies provide data on both the incidence and prevalence of HIV among various groups of drug users and permit researchers to define the clinical course of the disease from early infection through its long-term consequences. These studies require medical assessment and followup of complex cases, as well as also evaluating the impact of behavioral and medical interventions on the course of the disease.

Because drug users have poor access to medical care in general as well as to HIV-specific treatment, adherence to treatment regimens is often a problem, AIDS-related health services research - including drug abuse treatment, linkage of drug abuse treatment and primary care, and access and adherence to medication - is a major component of NIDA's clinical research program. Other areas of focus include barriers to medical treatment and behavioral factors associated with success or failure of treatment regimens; the impact of episodic

of drug use on treatment effectiveness; fetal and infant outcomes; and how HIV disease medications, HIV opportunistic infections, and other diseases prevalent among drug users affect HIV progression and the survival of the victim.

Development of better treatment strategies for HIV-infected pregnant women is a high priority, given that use of AZT can significantly reduce the rate of mother-to-infant HIV transmission. Opportunities exist for studies of effective treatment for drug-using women in collaboration with large national clinical studies at the National Institutes of Health. For example, through a collaborative agreement with the National Institute of Infectious Diseases at NIH, NIDA supports followup studies of a group of pregnant HIV-infected women in New York City, most of whom are drug users. Research on the role of active drug use in maternal-infant HIV transmission and the effectiveness of AZT treatment in preventing such transmission is a focus of this effort.

Suppression of the immune system, characteristic of HIV, puts infected individuals at higher risk for other diseases, including tuberculosis. NIDA is supporting a program of research on TB, one of several infectious diseases prevalent among drug users. The focus of this research includes studies of the consequences of coinfection with HIV as well as the development of better strategies to screen for TB among drug users and to improve access to and adherence with treatment. Treatment regimen adherence is critical in controlling further transmission of TB and in preventing development of treatment-resistant strains of TB.

Other current areas of HIV clinical research include studies of markers and predictors related to the virus and the immune system that are associated with rates of disease progression and survival, hepatitis C virus infection among infected and uninfected active drug users and the impact on HIV disease course, the interaction of the immune system with the virus and the impact on disease status and progression among HIV-infected children, the determination of viral strain differences that may influence the rate of disease progression, and the impact of drug injection on the activation of the immune system and the proliferation of viral strains.

NIDA-funded clinical research has contributed substantially to current knowledge about HIV infection and disease progression in populations of drug users. For example:

- Although basic research indicates that opioids can modulate (suppress or enhance) the immune response, clinical studies of HIV disease progression, as measured by decline in immune cell (CD4) counts, have not shown that immune suppression is more rapid among actively injecting polydrug (cocaine and heroin) users than among other risk groups.
- Studies of clinical manifestations and predictors of HIV disease progression among drug users found that progression to AIDS was best predicted by low numbers of immune (CD4) cells; the presence of other conditions such as candidiasis; bacterial infections including sepsis, pneumonia, and TB; and by nonuse of AZT.
- Smoking of illicit drugs increases the risk of contracting bacterial pneumonia among HIV-infected drug users who have a history of AIDS-related pneumonia.
- HIV infection appears to be associated with increased rates of endocarditis infection, a serious heart infection common among injecting drug users, but the frequency of injection apparently is not a factor.
- Although results of a skin test indicating immune suppression when testing for TB infection in HIV-infected patients have been used as a reason to initiate TB therapy, recent clinical studies of injecting drug users found that the skin-test responsiveness can fluctuate over time, bringing into question its reliability for use in treatment initiation.
- New HIV infection rates among HIV-negative drug users who remained continuously in methadone maintenance are low.

18 months were found to be six times lower than the incidence rates in comparable drug users who were on methadone treatment for the same time period.

- Studies of several laboratory markers indicative of immune status and duration of HIV infection and a relationship of these markers to the risk of developing HIV disease indicated that only low immune counts were independently related to increased risk of AIDS, that CD4 counts of less than 150 were related to immediate risk of adverse outcome, and that disease outcomes tended to occur as a progression of events (constitutional symptoms, oral candidiasis, bacterial infections, and AIDS).

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