The Role of Substance Abuse in HIV Disease Progression: Reconciling Differences from Laboratory and Epidemiologic Investigations

Farzana Kapadia,[1] David Vlahov,[1] Robert M. Donahoe,[2] and Gerald Friedland[3]

[1]Center for Urban Epidemiologic Studies, New York Academy of Medicine, New York, New York; [2]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia; and [3]AIDS Program, Yale School of Medicine, Yale New Haven Hospital, New Haven, Connecticut

From the onset of the HIV/AIDS epidemic, the use of licit and illicit drugs has been investigated for its potential impact on HIV disease progression. Findings from a large number of laboratory-based studies indicate that drug abuse may exacerbate HIV disease progression; however, epidemiological studies have shown mixed results. This article presents a review of findings from both laboratory-based and epidemiologic investigations. In addition, we provide a careful evaluation of methodological strengths and limitations inherent to both study designs in order to provide a more nuanced understanding of how these findings may complement one another.

From the onset of the HIV/AIDS epidemic, the impact of licit and illicit drug use on HIV disease progression has been a focus of investigation. Initial research investigated the link between the use of amyl nitrates, or "poppers," to enhance sexual pleasure, and behaviors associated with the use of these drugs and HIV infection [1, 2]. Following identification of HIV as the etiologic agent of AIDS, AIDS-related research shifted toward understanding differences in the AIDS incubation periods and whether drug use influenced progression to AIDS or survival. These epidemiological inquires were supported by evidence from laboratory studies suggesting that certain drugs of abuse had immunosuppressive properties in vivo , and thus, could theoretically hasten progression to AIDS among illicit drug users. With the availability of potent antiretroviral therapies, such as HAART, questions regarding equal access, adherence, and development of resistance to HAART among illicit drug users were examined, as well as whether the concomitant use of drugs of abuse (e.g., heroin, cocaine, crack cocaine, marijuana, and alcohol) or drugs for treatment of drug abuse (methadone) and HAART could produce negative side effects. (Hereafter, the phrase "drug use" refers to both these categories of drugs.)

Laboratory studies examining the relationship between drug use and HIV disease progression suggest that distinct patterns or types of drug use affect immunologic components that, in turn, influence HIV disease progression. These studies have included in vitro and animal model experiments in which researchers were able to manipulate key drug-use and disease parameters to examine the discrete influences of individual drugs on HIV infection and its progression. Epidemiologic investigations have attempted to approximate laboratory findings; yet because of the long incubation period for clinical AIDS, these analyses used various intermediate outcome measures, such as $CD4^+$ T cell decline, functional immune markers, HIV load, constitutional symptoms of HIV infection, and neurological manifestations of HIV infection. Given the limitations inherent in conducting observational research, these studies were not always able to demonstrate in the more complex, human, homeostatic

Received 6 January 2005; accepted 6 June 2005; electronically published 22 August 2005.

Reprints or correspondence: Dr. Farzana Kapadia, Center for Urban Epidemiologic Studies, New York Academy of Medicine, 1216 Fifth Ave., New York, NY 10029 (fkapadia@nyam.org).

Clinical Infectious Diseases 2005; 41:1027–34

1058-4838/2005/4107-0017$15.00

environment those results found in controlled laboratory settings. In fact, results from epidemiological studies suggest that the effects of drug use on HIV infection may be harmful or protective, and, in some cases, equivocal [3].

The purpose of this report is to provide an overview of laboratory and epidemiologic studies that examined the effects of drug use on HIV disease progression. An examination of the key aspects of the various study designs may shed light on the differences in the findings of laboratory-based and epidemiological investigations. We begin with a summary of laboratory studies, organized by individual drugs of abuse, followed by a review of epidemiologic evidence organized by outcome of interest. We conclude with a discussion of the strengths and methodological limitations of each study design as well as recommendations for future investigations.

IN VITRO AND ANIMAL STUDIES

A number of laboratory studies have observed the effects of licit and illicit drug use on cellular functioning, immune alterations, and viral replication. These studies not only examined the effects of individual drugs, but also mimicked acute onset of drug use and withdrawal-like symptoms under conditions simulating recent HIV seroconversion. Consequently, results from these studies have provided information on possible mechanisms through which drug use may influence HIV disease progression.

Heroin and opiates. The influence of heroin and other opiate-derived substances on immune system functioning are well documented [3]. This class of drugs adversely affects several integral immune processes, including the proper functioning of T and B lymphocytes [4–7], the production of antibodies [8], and the cytotoxicity of natural killer (NK) cells [9, 10]. Heroin use may also induce apoptosis of macrophages [11], stimulate increases in serum immunoglobulin levels [12, 13], and cause DNA damage to peripheral lymphocytes [14]. Certain leukocytes express μ, δ, and κ opioid receptors that facilitate binding of opiate molecules to these immune cells [15–17]. Interestingly, the ability to bind to these receptors can produce opposing effects on HIV expression. For example, μ receptor activation stimulates HIV expression in monocytic cells [18], whereas κ receptor activation inhibits HIV expression in these cells [19, 20]. Opiate effects may also be mediated through secondary alterations to neural pathways, such that the impact of opiates in vivo may be mediated through direct and indirect impact on the immune system [21]. Finally, morphine has also been shown to activate latent HIV infection in neuroblastoma cell cultures; this is an important finding because human tissue that can host latent HIV, such as the brain, may be irreparably damaged among opiate users [22].

Animal studies provide a unique perspective on the in vivo effects of opiates on host immune functioning and HIV disease progression. A study by Donahoe et al. [23] found continuous opiate administration retarded the progression of simian immunodeficiency virus disease, but Chuang et al. [24] noted greater simian immunodeficiency virus disease progression after opiate injection. These contradictory results were attributed to differences between the 2 study designs [3]. First, the Donahoe study used a less virulent strain of simian immunodeficiency virus (smm9) than the strain used in the Chuang model (mac239). Second, compared with the Donahoe model, the Chuang study administered about one-half the amount of opiate per injection cycle, thereby creating withdrawal-like conditions. This is an important distinction because structured opiate withdrawal resulting from reduced frequency or disruption of continuous opiate injection may affect the proper functioning of both immune and viral activities. Similarly, a structured discontinuation of opiate administration in the Donahoe model also precipitated increases in the number of circulating T cells infected with simian immunodeficiency virus.

It appears that continuous opiate exposure may assist in balancing circulating levels of naive and activated T cells, whereas the stress associated with irregular patterns of drug administration fosters imbalances in immune cell levels [3, 25]. Further evidence supporting this hypothesis was presented by Veyries et al. [26], who found daily morphine administration to mice did not exacerbate infection with Friend murine leukemia virus (FMLV). However, this protective effect was attenuated during discontinuation of morphine administration, and actually led to increased viral load. Other studies also reported increased immunosuppression in animal models after a structured withdrawal from or intermittent administration of opiates [27, 28].

Cocaine, crack cocaine, and other stimulants. As reviewed by Baldwin et al. [29], cocaine disrupts immune functioning by modulating the distribution of lymphocytes, including neutrophils, NK cells, helper T cells, $CD4^+$ T cells, and cytotoxic T cells. In vitro studies have reported increased HIV replication in PBMCs treated with cocaine, compared with untreated PBMC cultures [30, 31], and recently, mouse models used to examine the effects of cocaine on HIV showed significant increases in circulating HIV load [32]. Of note are in vitro investigations of alveolar macrophages (the main class of leukocyte responsible for phagocytosis of bacteria in the lungs) from nonsmoking individuals, compared with alveolar macrophages obtained from active tobacco, marijuana, and cocaine smokers [29]. Alveolar macrophages obtained from individuals who smoked marijuana or cocaine exclusively and did not report injecting drugs were less able to eliminate *Staphylococcus aureus* bacteria and to suppress growth of tumor cells, compared with alveolar macrophages from nonsmokers [33]. Cocaine and crack cocaine smoke may also be directly associated with respiratory AIDS conditions, either directly, by its effect

on the lungs of individuals who smoke, or indirectly, by its association with other contaminants that, in combination, produce worse outcomes.

Marijuana. δ^9-Tetrahydrocannabinol (THC) is a lipophilic compound found in marijuana plants and is responsible for producing the major psychoactive effects associated with marijuana use [34]. For example, when certain cell types, such as alveolar macrophages, are exposed to THC in high concentrations, THC can disrupt cellular membrane activities that regulate antiviral and antibacterial functions [35–38]. Recent research also indicates that the mechanism for THC expression may be the binding of THC to cannaboid receptors (CB1 and CB2) on immune cells that express these receptors [39]. Early studies examining the effect of THC on viral and bacterial infections involved animal models of mice and swine [35, 36, 40]. These studies reported greater immunosuppression among mice and swine infected with herpes simplex virus and exposed to THC [40]. In addition, exposure to THC may also alter host resistance to retroviruses such as FMLV. In 1991, Specter et al. [41] noted decreased lymphocyte activity and NK cell cytotoxicity in mice that were infected with FMLV and then exposed to THC 2 to 4 weeks later.

Alcohol. The principal component of alcohol, ethanol, is water soluble and, to some degree, fat soluble; as a result, ethanol can cross cell membranes and alter immune responsiveness and host resistance to infection. In vitro studies and experimental animal models have shown that ethanol intake increases susceptibility to HIV infection by suppressing proper lymphocyte response to HIV [42, 43]. Bagasra et al. [44] reported increased viral replication in cultures of HIV-infected PBMCs obtained from subjects exposed to alcohol for 3 days, compared with those from individuals who did not consume alcohol. Furthermore, several animal models used to examine the impact of chronic alcohol consumption on retroviral infections in mice have also shown an immunosuppressive effect after alcohol administration [45, 46].

EVIDENCE FROM EPIDEMIOLOGICAL STUDIES

Early epidemiologic investigations of HIV-seropositive individuals who are also injection drug users (IDUs) suggested that drug use could hasten progression to AIDS [47]. In conjunction with earlier laboratory research, these results prompted further epidemiologic investigation. Consequently, epidemiologic studies sought to examine various aspects of drug use, intermediate markers of disease progression, and different stages of HIV disease. To date, results from large cohort studies of HIV-seropositive individuals in the United States and in Europe present mixed findings on the effects of drug use and HIV disease progression as measured by immunologic status, viral replication, and time to AIDS and death among drug users.

Immunologic Progression

Injection drug use. Data from the ALIVE study [48, 49] comparing T cell decreases between IDUs with seroprevalent infection and IDUs with recent seroconversion found the median rate of decrease in absolute numbers (and percentages) of $CD4^+$ cells among those with seroprevalent infection was 8 cells/mm^3 (0%) per 6 months, with a median follow-up of 18 months, compared with 55 cells/mm^3 (1.9%) per 6 months for individuals with recent seroconversion, with a median follow-up of 12 months [50]. This rate of decline did not differ by IDU status at baseline (active vs. inactive IDU), and was gradual, and not attributable to use of antiretroviral therapy. A subsequent investigation comparing HIV-seropositive IDUs and men who have sex with men (MSMs) reported a slightly lower, but not statistically different, rate of $CD4^+$ cell decline among IDUs [51]. This difference was thought to be related to the longer duration of HIV infection among MSMs. A study by Pezzotti et al. [52] examined $CD4^+$ cell decline among individuals with recent seroconversion with longer follow-up and found a continued pattern of no difference according to IDU status (active or inactive IDU) and according to exposure risk group (including IDUs, MSMs, and persons infected via heterosexual contact).

Drug use patterns. The Donahoe model suggests that by maintaining an opiate dependency, withdrawal and its negative side effects are avoidable, and, in the long term, may help to retard progression to AIDS. Conversely, a poorly maintained dependency increases withdrawal stresses and may hasten progression to AIDS. Recognizing that differential drug use patterns play a role in HIV disease progression, Lyles et al. [53] examined the impact of episodes of withdrawal, frequency of drug use, binge use, and overdose on $CD4^+$ cell decline between consecutive visits. Unlike analysis of laboratory findings, this analysis indicated that different patterns of drug use had no effect on $CD4^+$ cell decline observed over 6-month intervals. Inferences from this analysis are limited, given that the HIV-seropositive drug users in the cohort were all IDUs with a history of polydrug use and had seroprevalent HIV infection, which may bias estimates of progression to AIDS [54] unless analytic techniques, such as adjusting for $CD4^+$ to control for the duration of infection, are applied [55].

Drug type. Krol et al. [56] attempted to mimic laboratory findings by examining the effect of use of specific drug types on $CD4^+$ cell decline among IDUs with recent HIV seroconversion. Their findings suggested that in a modest subset of subjects, including heroin-only users, heroin use was associated with more rapid $CD4^+$ T cell decline than among cocaine or polydrug users; however, this effect was transient. Given that the mode of heroin use was injection, the investigators noted that injection itself or behaviors associated with injection of drugs, such as needle sharing, could offset the risk of immu-

nologic decline associated with the specific drug used. Nonetheless, by focusing on recency of drug use and recency of HIV infection, these investigators were able to examine the impact of drug use on HIV disease progression in a manner that may reconcile differences between in vitro and cohort studies.

Incubation Period for AIDS

As early as 1990, Weber et al. [57] reported a higher relative risk of progression to AIDS among persistent IDUs (RR, 1.78; 95% CI, 1.20– 2.67) compared with former IDUs; later studies suggested that progression to AIDS did not differ according to continued drug use status [58, 59] or frequency of injection drug use [60]. A study of IDUs in Amsterdam found that IDUs who reported more instances of borrowing used injecting equipment (>99 times and 10–99 times) between 1980 and the baseline interview had lower relative hazards of progression to AIDS (RH, 0.44; 95% CI, 0.22–0.88 and RH, 0.19; 95% CI, 0.03–0.37, respectively) than did those who reported fewer instances of borrowing used injection equipment (<10 times) [61]. Rather than suggesting that these findings advocated the borrowing of injection equipment, the investigators theorized that IDUs' behaviors may offset risk for HIV disease progression posed by injection drug use itself. Specifically, these findings suggested that needle sharing may increase alloantigenic stimulation, and hence, heighten a tolerance response to needle sharing that could, in turn, affect host response to HIV disease progression [3].

Studies that have investigated drug use by route of administration have found significant differences in the spectrum of AIDS-defining illnesses reported among noninjection drug users (NIDUs) and those reported among IDUs. In a case-control study comparing HIV-seropositive drug users with bacterial pneumonia with those without bacterial pneumonia, Caiaffa et al. [62] found self-reported smoking of illicit drugs, including marijuana, cocaine, or crack, was the only behavioral factor significantly associated with reports of bacterial pneumonia as an AIDS-defining illness (OR, 2.24; 95% CI, 1.03–4.89). In addition, a study of HIV disease progression among IDUs recruited from a methadone maintenance program noted a significant association between cocaine and/or crack cocaine smoking and reports of pulmonary AIDS illnesses, such as tuberculosis [63]. These findings are consistent with in vitro studies indicating decreased alveolar function in individuals who reported exclusively smoking cocaine and/or crack cocaine.

Mortality

Analysis of mortality risk according to cause of death indicates that IDUs have a substantially higher pre-AIDS mortality related to overdose, suicide or homicide, and accidents, compared with other exposure risk groups [64–66]. In a study by Hendriks et al. [67], IDUs were more likely to progress from seroconversion to death, compared with MSMs; however, examination of mortality among those who survived long enough to develop an AIDS-defining illness shows no differences in survival between IDUs and MSMs. This lack of difference in survival between exposure risk groups has also been reported in other studies [68, 69].

Drug Use and HIV Disease Progression in the HAART Era

As the availability and use of potent antiretroviral therapy increases, attention has recently been directed toward identifying and understanding potential interactions or toxicities arising from the concomitant use of methadone, an opiate used to treat heroin dependence, and antiretroviral medications [70]. These studies have examined antiretroviral therapy by specific class of HIV medication because of the different effects that the different classes may have on the metabolic pathway of methadone [70]. Specifically, methadone is metabolized by the cytochrome P450 system and is excreted via urine or bile. Drugs that act as inducers of this system cause faster metabolism of methadone, and drugs that act as inhibitors of this system prevent proper methadone metabolism [70].

Nucleoside reverse-transcriptase inhibitors (NRTIs) do not impact the cytochrome P450 system, so studies focusing on interactions between NRTIs and methadone have not found clinically significant effects of these medications on methadone levels [71–73]. The most important interactions are those related to nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors. One study found that both efavirenz and nevirapine were potent inducers of P450 enzymes and decreased methadone levels by 43% and 46%, respectively [74, 75]. Decreased levels of methadone can lead to opiate withdrawal and reduce efficacy of antiretroviral treatments if medication regimens are not adhered to, and subsequently increase the risk for antiretroviral resistance. Use of amprenavir, nelfinavir, or lopinavir-ritonavir has shown significant decreases in methadone levels among individuals using methadone. Whereas amprenavir use may result in mild symptoms of opiate withdrawal, nelfinavir use is not associated with opiate withdrawal symptoms because of the lack of effect on free, rather than total, methadone levels [76, 77]. Use of the lopinavir-ritonavir combination was associated with significant reductions in methadone levels and increased reporting of opiate withdrawal symptoms [78]. This was shown to be due to the lopinavir, which acts as a potent inducer of methadone metabolism; use of ritonavir alone had no significant effect on methadone metabolism. A recent study also indicates a lack of pharmacokinetic interaction between atazanavir and methadone [79].

Epidemiologic studies examining the relationship between drug use and HIV disease progression among patients starting HAART show mixed results [80–83]. Findings from the

EuroSIDA [80] and Swiss HIV Cohort studies [81] indicate no significant difference in HIV disease progression among IDUs, compared with MSMs or heterosexually active individuals receiving HAART. However, a study restricted to IDUs reported lower HAART-induced viral load suppression among active IDUs, compared with former users and nonusers (0.8 $\log_{10}$ copies/mL vs. 1.6 $\log_{10}$ copies/mL in former users and 1.7 $\log_{10}$ copies/mL in nonusers) [82]. These findings were significantly associated with lack of use of and adherence to HAART among active IDUs, compared with former users and nonusers (34% vs. 17% in former users and 24% in nonusers) [82]. Regarding mortality, Poundstone et al. [83] found that disease-free survival among IDUs, compared with NIDUs, was lower in the HAART era than in the era before the advent of HAART [83]. These findings raise the question of whether higher mortality rates among drug users are the result of access [84] and adherence [85] to HAART, rather than effects of the drug use per se. In a recent report, dramatic improvement in survival was identified in IDUs in analyses of data from before and from after 1996 [86]; the implications of these findings are that treatment can be effective in persons who have used illicit drugs and that the decision to offer antiretroviral therapy should not be based on prior drug use status.

Neurological Outcomes

In addition to affecting immune system activity, drugs of abuse are also able to target cells of the nervous system and exacerbate neurological dysfunction in drug users. Analyses that included neurological examination and longitudinal neuropsychological testing of HIV-seropositive and HIV-seronegative IDUs found no differences in outcomes of neuropsychological test batteries, after accounting for age and education [87–90]. However, these studies involved only asymptomatic HIV-infected individuals and could not examine the neuropsychological effects of drug use on late-stage HIV infections. One such report that supports this hypothesis is from the Edinburgh cohort [91], which is comprised predominantly of heroin users and initiated during the onset of the HIV epidemic. Among cohort members whose deaths were caused by HIV-related conditions, autopsies revealed that opiate users were significantly more likely to have had HIV encephalitis, compared with MSMs. Further research is required to determine whether these effects are attributed to the direct effects of drug use or the additional indirect effects of access to both drug treatment and antiretroviral therapy.

METHODOLOGICAL ISSUES IN EPIDEMIOLOGIC STUDIES

Although epidemiological research suggests that the impact of drug use on HIV disease progression is mixed, an evaluation of study methodologies may shed light on how these results complement those of laboratory studies. First, the use of MSMs as an external comparison group to IDUs is problematic because differences between these groups in the risk factors for HIV disease progression may offset the risk associated with drug use alone. Specifically, MSMs tend to be white, of higher socioeconomic status, report higher rates of sexually transmitted infections, and have higher frequency of noninjection drug usage (e.g., inhaling amyl nitrates, smoking marijuana, and inhaling cocaine), whereas IDUs tend to be predominantly African American, of lower socioeconomic status, and report higher levels of cutaneous or bacterial infection that may act as cofactors in HIV disease progression. Second, IDUs are more likely to experience non–AIDS-related mortality from overdose, violence (i.e., homicide and suicide), and accidents, and in many cases, these deaths may occur prior to an AIDS diagnosis. In addition, higher morbidity among IDUs may also preclude enrollment of IDUs who are more ill in research studies. Consequently, IDUs who do participate in epidemiologic studies may be healthier or better able to manage their drug use, and thus, progress to AIDS or death less rapidly. These selection biases are difficult to avoid, but must be sufficiently addressed to prevent incorrect conclusions. Finally, IDUs are often recruited from methadone maintenance programs, drug detoxification programs, or other clinical settings [63, 92, 93] and may be at various stages of drug use.

Measurement of drug use requires greater refinement to fully capture the spectrum of drug use behaviors. Detailed information is required on different means of administration (e.g., sniffing, snorting, and smoking), especially given the increasing number of findings from both in vitro and epidemiologic studies indicating a greater propensity for respiratory AIDS infections among individuals who report smoking cocaine or crack cocaine. Data on use of specific drugs would allow for greater ability to understand the individual impact of each type of drug, as well as approximate results obtained from in vitro and animal model experiments. The inclusion and identification of individuals at different stages of drug use (i.e., those who recently initiated taking drugs and inconsistent and chronic users) in cohort studies of drug users may also improve our understanding of drug effects on HIV disease progression.

Additionally, the inclusion of participants with seroprevalent HIV infection presents a significant limitation to many epidemiologic investigations. Individuals enrolled in cohort studies of HIV infection are often unaware of the date that they acquired HIV infection; consequently, the time of seroconversion is also unknown. In these situations, accurate information regarding duration of infection is largely unavailable or based on best-guess estimates derived from an individual's recall of their first positive HIV serum test result. As most in vitro and animal model studies report on the impact of drug use on seroincident HIV infection, duration of drug use can be evaluated for its long-term effect on HIV disease progression, even

though duration of infection may act as a confounder in epidemiologic studies and bias estimates of effect.

CONCLUSIONS AND FUTURE DIRECTIONS

Although laboratory studies have been critical in isolating potential pathways by which drug use may impact immunologic and virologic outcomes, epidemiologic studies have attempted to translate these findings into larger, biologically complex, and clinically relevant systems. Consequently, neither the laboratory nor epidemiologic study designs may be wholly discounted or, alternatively, considered as a gold standard. Rather, this overview indicates that these 2 types of studies provide complementary information and should draw from one another to move research in this field forward.

Taken together, findings from laboratory and epidemiologic studies indicate that the relationship between drug use and HIV disease progression may be mediated by several key factors, including immunologic and virologic conditions affecting host susceptibility, underlying comorbidities among drug users, use of antiretroviral therapy, and viral strain, as well as pharmacodynamic aspects of drug use, such as the pattern and type of drug administration and the route of administration. Current research also indicates that few eligible IDUs in the United States are receiving antiretroviral medication, despite indication for treatment [84]. Consequently, a better understanding of the effects of drug use on access to, utilization of, and adherence to antiretroviral medication is warranted, because it is unclear whether these differences are due to structural barriers (reluctance of clinicians), personal barriers (avoidance of care until symptoms become manifest), or both. As access to antiretroviral therapy has improved, attention has shifted toward understanding those factors associated with suboptimal adherence to therapy and development of infection resistant to antiretrovirals. In addition, the impact of the use of illicit drugs such as heroin and cocaine on the brain in late-stage HIV infection has received limited attention, and research to address this issue is urgently needed. In summary, information gathered from both laboratory and epidemiological studies should be used to inform future research. Specifically, the development of in vitro study conditions and animal models that more closely approximate real-world HIV infection and disease progression in humans are necessary. At the same time, epidemiological studies need to explore the effects of different characteristics of drug use and drug users to refine the understanding of the role of use of specific drugs in modulating HIV disease progression.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References

1. Haverkos HW, Kopstein AN, Wilson H, Drotman P. Nitrite inhalants: history, epidemiology, and possible links to AIDS. Environ Health Perspect **1994**; 102:858–61.
2. Duesberg P, Rasnick D. The AIDS dilemma: drug diseases blamed on a passenger virus. Genetica **1998**; 104:85–132.
3. Donahoe RM, Vlahov D. Opiates as potential cofactors in progression of HIV-1 infections to AIDS. J Neuroimmunol **1998**; 83:77–87.
4. Wybran J, Appelboom T, Famaey JP, Govaerts A. Suggestive evidence for receptors for morphine and methionine-enkephalin on normal human blood T lymphocytes. J Immunol **1979**; 123:1068–70.
5. Tubaro E, Borelli G, Croce C, Cavallo G, Santiangeli C. Effect of morphine on resistance to infection. J Infect Dis **1983**; 148:656–66.
6. Peterson PK, Sharp B, Gekker G, Brummitt C, Keane WF. Opioid-mediated suppression of cultured peripheral blood mononuclear cell respiratory burst activity. J Immunol **1987**; 138:3907–12.
7. Bryant HU, Bernton EW, Holaday JW. Morphine pellet-induced immunomodulation in mice: temporal relationships. J Pharmacol Exp Ther **1988**; 245:913–20.
8. Guan L, Townsend R, Eisenstein TK, Adler MW, Rogers TJ. Both T cells and macrophages are targets of kappa-opioid–induced immunosuppression. Brain Behav Immun **1994**; 8:229–40.
9. Shavit Y, Depaulis A, Martin FC, et al. Involvement of brain opiate receptors in the immune-suppressive effect of morphine. Proc Natl Acad Sci U S A **1986**; 83:7114–7.
10. Carr DJ, Gebhardt BM, Paul D. Alpha adrenergic and mu-2 opioid receptors are involved in morphine-induced suppression of splenocyte natural killer activity. J Pharmacol Exp Ther **1993**; 264:1179–86.
11. Singhal PC, Sharma P, Kapasi AA, Reddy K, Franki N, Gibbons N. Morphine enhances macrophage apoptosis. J Immunol **1998**; 160: 1886–93.
12. Nath A, Hauser KF, Wojna V, et al. Molecular basis for interactions of HIV and drugs of abuse. J Acquir Immune Defic Syndr **2002**; 31(Suppl 2):62–9.
13. Ansari AA. Drugs of abuse and HIV—a perspective. J Neuroimmunol **2004**; 147:9–12.
14. Madden JJ, Wang Y, Lankford-Turner P, Donahoe RM. Does reduced DNA repair capacity play a role in HIV infection and progression in the lymphocytes of opiate addicts? J Acquir Immune Defic Syndr **2002**; 31(Suppl 2):78–83.
15. Mellon RD, Bayer BM. Evidence for central opioid receptors in the immunomodulatory effects of morphine: review of potential mechanism(s) of action. J Neuroimmunol **1998**; 83:19–28.
16. Bidlack JM. Detection and function of opioid receptors on cells from the immune system. Clin Diagn Lab Immunol **2000**; 7:719–23.
17. McCarthy L, Wetzel M, Sliker JK, Eisenstein TK, Rogers TJ. Opioids, opioid receptors, and the immune response. Drug Alcohol Depend **2001**; 62:111–23.
18. Peterson PK, Gekker G, Schut R, Hu S, Balfour HH Jr, Chao CC. Enhancement of HIV-1 replication by opiates and cocaine: the cytokine connection [review]. Adv Exp Med Biol **1993**; 335:181–8.
19. Chao CC, Gekker G, Hu S, et al. Kappa opioid receptors in human microglia downregulate human immunodeficiency virus 1 expression. Proc Natl Acad Sci U S A **1996**; 93:8051–6.
20. Peterson PK, Gekker G, Lokensgard JR, et al. Kappa-opioid receptor agonist suppression of HIV-1 expression in $CD4^+$ lymphocytes. Biochem Pharmacol **2001**; 61:1145–51.
21. Weber RJ, Pert A. The periaqueductal gray matter mediates opiate-induced immunosuppression. Science **1989**; 245:188–90.
22. Squinto SP, Mondal D, Block AL, Prakash O. Morphine-induced transactivation of HIV-1 LTR in human neuroblastoma cells. AIDS Res Hum Retroviruses **1990**; 6:1163–8.
23. Donahoe RM, Byrd LD, McClure HM, et al. Consequences of opiate-dependency in a monkey model of AIDS [review]. Adv Exp Med Biol **1993**; 335:21–8.

24. Chuang RY, Chuang LF, Li Y, Kung HF, Killam KF Jr. SIV mutations detected in morphine-treated *Macaca mulatta* following SIVmac239 infection. Adv Exp Med Biol **1995**; 373:175–81.
25. Donahoe RM. Multiple ways that drug abuse might influence AIDS progression: clues from a monkey model. J Neuroimmunol **2004**; 147: 28–32.
26. Veyries ML, Sinet M, Desforges B, Rouveix B. Effects of morphine on the pathogenesis of murine Friend retrovirus infection. J Pharmacol Exp Ther **1995**; 272:498–504.
27. Rahim RT, Adler MW, Meissler JJ Jr, et al. Abrupt or precipitated withdrawal from morphine induces immunosuppression. J Neuroimmunol **2002**; 127:88–95.
28. Weber RJ, Gomez-Flores R, Smith JE, Martin TJ. Immune, neuroendocrine, and somatic alterations in animal models of human heroin abuse. J Neuroimmunol **2004**; 147:134–7.
29. Baldwin GC, Roth MD, Tashkin DP. Acute and chronic effects of cocaine on the immune system and the possible link to AIDS. J Neuroimmunol **1998**; 83:133–8.
30. Bagasra O, Pomerantz RJ. Human immunodeficiency virus type 1 replication in peripheral blood mononuclear cells in the presence of cocaine. J Infect Dis **1993**; 168:1157–64.
31. Peterson PK, Gekker G, Chao CC, Schut R, Molitor TW, Balfour HH Jr. Cocaine potentiates HIV-1 replication in human peripheral blood mononuclear cell cocultures: involvement of transforming growth factor–beta. J Immunol **1991**; 146:81–4.
32. Tashkin DP. Evidence implicating cocaine as a possible risk factor for HIV infection. J Neuroimmunol **2004**; 147:26–7.
33. Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. Am J Respir Crit Care Med **1997**; 156:1606–13.
34. Klein TW, Friedman H, Specter S. Marijuana, immunity and infection. J Neuroimmunol **1998**; 83:102–15.
35. Cabral GA, Mishkin EM, Marciano-Cabral F, Coleman P, Harris L, Munson AE. Effect of delta 9-tetrahydrocannabinol on herpes simplex virus type 2 vaginal infection in the guinea pig. Proc Soc Exp Biol Med **1986**; 182:181–6.
36. Cabral GA, Lockmuller JC, Mishkin EM. Delta 9-tetrahydrocannabinol decreases alpha/beta interferon response to herpes simplex virus type 2 in the B6C3F1 mouse. Proc Soc Exp Biol Med **1986**; 181:305–11.
37. Watzl B, Scuderi P, Watson RR. Marijuana components stimulate human peripheral blood mononuclear cell secretion of interferon-gamma and suppress interleukin-1 alpha in vitro. Int J Immunopharmacol **1991**; 13:1091–7.
38. Zheng ZM, Specter S, Friedman H. Inhibition by delta-9-tetrahydrocannabinol of tumor necrosis factor alpha production by mouse and human macrophages. Int J Immunopharmacol **1992**; 14:1445–52.
39. Klein TW, Newton C, Larsen K, et al. The cannabinoid system and immune modulation. J Leukoc Biol **2003**; 74:486–96.
40. Mishkin EM, Cabral GA. Delta-9-tetrahydrocannabinol decreases host resistance to herpes simplex virus type 2 vaginal infection in the B6C3F1 mouse. J Gen Virol **1985**; 66:2539–49.
41. Specter S, Lancz G, Westrich G, Friedman H. Combined immunosuppressive activities of delta-9-tetrahydrocannabinol and murine retrovirus. Adv Exp Med Biol **1991**; 288:135–41.
42. Dingle GA, Oei TP. Is alcohol a cofactor of HIV and AIDS: evidence from immunological and behavioral studies. Psychol Bull **1997**; 122: 56–71.
43. Kresina TF, Flexner CW, Sinclair J, et al. Alcohol use and HIV pharmacotherapy. AIDS Res Hum Retroviruses **2002**; 18:757–70.
44. Bagasra O, Whittle P, Kajdacsy-Balla A, Lischner HW. Effects of alcohol ingestion on in vitro susceptibility of peripheral blood mononuclear cells to infection with HIV-1 and on CD4 and CD8 lymphocytes. Prog Clin Biol Res **1990**; 325:351–8.
45. Watson RR, Odeleye OE, Darban HR, Lopez MC. Modification of lymphoid subsets by chronic ethanol consumption in C57Bl/6 mice infected with LP-BM5 murine leukemia virus. Alcohol Alcohol **1992**; 27:417–24.
46. Wang Y, Watson RR. Chronic ethanol consumption prior to retrovirus infection alters cytokine production by thymocytes during murine AIDS. Alcohol **1994**; 11:361–5.
47. DesJarlais DC, Friedman SR, Marmor M, et al. Development of AIDS, HIV seroconversion, and potential co-factors for T4 cell loss in a cohort of intravenous drug users. AIDS **1987**; 1:105–11.
48. Vlahov D, Anthony JC, Munoz A, et al. The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of methods and characteristics of participants. NIDA Res Monogr **1991**; 109:75–100.
49. Vlahov D. Epidemiologic studies of illicit drug use as a cofactor for HIV progression. In: Program and abstracts of the National Institute on Drug Abuse conference, held in association with the XIV International AIDS Conference (Barcelona, Spain). Bethesda, MD: National Institute on Drug Abuse, **2003**:264.
50. Margolick JB, Munoz A, Vlahov D, et al. Changes in T-lymphocyte subsets in intravenous drug users with HIV-1 infection. JAMA **1992**; 267:1631–6.
51. Margolick JB, Munoz A, Vlahov D, et al. Direct comparison of the relationship between clinical outcome and change in $CD4^+$ lymphocytes in human immunodeficiency virus-positive homosexual men and injecting drug users. Arch Intern Med **1994**; 154:869–75.
52. Pezzotti P, Galai N, Munoz A, Vlahov D, Rezza G. Declino dei linfociti $CD4^+$ dopo la sieroconversione: uno studio longitudinale su 941 soggetti. Giornale Italiano dell' AIDS **1994**; 5:93–100.
53. Lyles CM, Margolick JB, Astemborski J, et al. The influence of drug use patterns on the rate of $CD4^+$ lymphocyte decline among HIV-1-infected injecting drug users. AIDS **1997**; 11:1255–62.
54. Alcabes P, Pezzotti P, Phillips AN, Rezza G, Vlahov D. Long-term perspective on the prevalent-cohort biases in studies of human immunodeficiency virus progression. Am J Epidemiol **1997**; 146:543–51.
55. Phillips AN, Lee CA, Elford J, Janossy G, Kernoff PB. The cumulative risk of AIDS as the CD4 lymphocyte count declines. J Acquir Immune Defic Syndr **1992**; 5:148–52.
56. Krol A, Flynn C, Vlahov D, Miedema F, Coutinho RA, van Ameijden EJ. New evidence to reconcile in vitro and epidemiologic data on the possible role of heroin on $CD4^+$ decline among HIV-infected injecting drug users. Drug Alcohol Depend **1999**; 54:145–54.
57. Weber R, Ledergerber B, Opravil M, Siegenthaler W, Luthy R. Progression of HIV infection in misusers of injected drugs who stop injecting or follow a programme of maintenance treatment with methadone. BMJ **1990**;301:1362–5.
58. Disease progression and early predictors of AIDS in HIV-seroconverted injecting drug users. The Italian Seroconversion Study. AIDS **1992**; 6: 421–6.
59. Pezzotti P, Galai N, Vlahov D, Rezza G, Lyles CM, Astemborski J. Direct comparison of time to AIDS and infectious disease death between HIV seroconverter injection drug users in Italy and the United States: results from the ALIVE and ISS studies. AIDS Link to Intravenous Experiences. Italian Seroconversion Study. J Acquir Immune Defic Syndr Hum Retrovirol **1999**; 20:275–82.
60. Rompalo AM, Shah N, Margolick JB, et al. Evaluation of possible effects of continued drug use on HIV progression among women. Int J STD AIDS **2004**; 15:322–7.
61. Mientjes GH, van Ameijden EJ, van den Hoek AJ, Goudsmit J, Miedema F, Coutinho RA. Progression of HIV infection among injecting drug users: indications for a lower rate of progression among those who have frequently borrowed injecting equipment. AIDS **1993**; 7: 1363–70.
62. Caiaffa WT, Vlahov D, Graham NMH, Astemborski J. Drug smoking, *Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus–seropositive injection drug users. Am J Respir Crit Care Med **1994**; 150:1493–8.

63. Webber MP, Schoenbaum EE, Gourevitch MN, Buono D, Klein RS. A prospective study of HIV disease progression in female and male drug users. AIDS **1999**; 13:257–62.
64. Prins M, Veugelers PJ. Comparison of progression and non-progression in injecting drug users and homosexual men with documented dates of HIV-1 seroconversion. European Seroconverter Study and the Tricontinental Seroconverter Study. AIDS **1997**; 11:621–31.
65. Prins M, Hernandez A, I, Brettle RP, et al. Pre-AIDS mortality from natural causes associated with HIV disease progression: evidence from the European Seroconverter Study among injecting drug users. AIDS **1997**; 11:1747–56.
66. Prins M, Sabin CA, Lee CA, Devereux H, Coutinho RA. Pre-AIDS mortality and its association with HIV disease progression in haemophilic men, injecting drug users and homosexual men. AIDS **2000**; 14:1829–37.
67. Hendriks JC, Satten GA, van Ameijden EJ, van Druten HA, Coutinho RA, van Griensven GJ. The incubation period to AIDS in injecting drug users estimated from prevalent cohort data, accounting for death prior to an AIDS diagnosis. AIDS **1998**; 12:1537–44.
68. von Overbeck J, Egger M, Smith GD, et al. Survival in HIV infection: do sex and category of transmission matter? Swiss HIV Cohort Study. AIDS **1994**; 8:1307–13.
69. Chaisson RE, Keruly JC, Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. N Engl J Med **1995**; 333:751–6.
70. Gourevitch MN, Friedland GH. Interactions between methadone and medications used to treat HIV infection: a review. Mt Sinai J Med **2000**; 67:429–36.
71. McCance-Katz EF, Rainey PM, Jatlow P, Friedland G. Methadone effects on zidovudine disposition (AIDS Clinical Trials Group 262). J Acquir Immune Defic Syndr Hum Retrovirol **1998**; 18:435–43.
72. Rainey PM, Friedland G, McCance-Katz EF, et al. Interaction of methadone with didanosine and stavudine. J Acquir Immune Defic Syndr **2000**; 24:241–8.
73. Rainey PM, Friedland GH, Snidow JW, et al. The pharmacokinetics of methadone following co-administration with a lamivudine/zidovudine combination tablet in opiate-dependent subjects. Am J Addict **2002**; 11:66–74.
74. Clarke SM, Mulcahy FM, Tjia J, et al. Pharmacokinetic interactions of nevirapine and methadone and guidelines for use of nevirapine to treat injection drug users. Clin Infect Dis **2001**; 33:1595–7.
75. Clarke SM, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. Br J Clin Pharmacol **2001**; 51:213–7.
76. McCance-Katz EF, Farber S, Selwyn PA, O'Connor A. Decrease in methodone levels with nelfinavir mesylate. Am J Psychiatry **2000**; 157: 481.
77. McCance-Katz EF, Rainey PM, Smith P, et al. Drug interactions between opioids and antiretroviral medications: interaction between methadone, LAAM, and nelfinavir. Am J Addict **2004**; 13:163–80.
78. McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. Clin Infect Dis **2003**; 37:476–82.
79. Friedland GH, Andrews L., Argawala S., et al. Lack of an effect of atazanavir on steady-state pharmacokinetics of methadone in chronically treated subjects. In: Program and abstracts of the International Symposium on HIV and Emerging Infectious Disease (Toulon, France). **2004**:289.
80. Mocroft A, Madge S, Johnson AM, et al. A comparison of exposure groups in the EuroSIDA study: starting highly active antiretroviral therapy (HAART), response to HAART, and survival. J Acquir Immune Defic Syndr **1999**; 22:369–78.
81. Junghans C, Low N, Chan P, Witschi A, Vernazza P, Egger M. Uniform risk of clinical progression despite differences in utilization of highly active antiretroviral therapy: Swiss HIV Cohort Study. AIDS **1999**; 13: 2547–54.
82. Lucas GM, Cheever LW, Chaisson RE, Moore RD. Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection. J Acquir Immune Defic Syndr **2001**; 27:251–9.
83. Poundstone KE, Chaisson RE, Moore RD. Differences in HIV disease progression by injection drug use and by sex in the era of highly active antiretroviral therapy. AIDS **2001**; 15:1115–23.
84. Celentano DD, Galai N, Sethi AK, et al. Time to initiating highly active antiretroviral therapy among HIV-infected injection drug users. AIDS **2001**; 15:1707–15.
85. Wood E, Montaner JS, Yip B, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. CMAJ **2003**; 169:656–61.
86. Vlahov D, Galai N, Safaeian M, et al. Effectiveness of highly active antiretroviral therapy among injection drug users with late-stage human immunodeficiency virus infection. Am J Epidemiol **2005**; 161: 999–1012.
87. Concha M, Graham NM, Munoz A, et al. Effect of chronic substance abuse on the neuropsychological performance of intravenous drug users with a high prevalence of HIV-1 seropositivity. Am J Epidemiol **1992**; 136:1338–48.
88. Selnes OA, McArthur JC, Royal W III, et al. HIV-1 infection and intravenous drug use: longitudinal neuropsychological evaluation of asymptomatic subjects. Neurology **1992**; 42:1924–30.
89. Concha M, Selnes OA, Vlahov D, et al. Comparison of neuropsychological performance between AIDS-free injecting drug users and homosexual men. Neuroepidemiology **1997**; 16:78–85.
90. Selnes OA, Galai N, McArthur JC, et al. HIV infection and cognition in intravenous drug users: long-term follow-up. Neurology **1997**; 48: 223–30.
91. Bell JE, Brettle RP, Chiswick A, Simmonds P. HIV encephalitis, proviral load and dementia in drug users and homosexuals with AIDS. Effect of neocortical involvement. Brain **1998**; 121:2043–52.
92. Lucas GM, Gebo KA, Chaisson RE, Moore RD. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. AIDS **2002**; 16:767–74.
93. Webber MP, Schoenbaum EE, Gourevitch MN, Buono D, Chang CJ, Klein RS. Temporal trends in the progression of human immunodeficiency virus disease in a cohort of drug users. Epidemiology **1998**; 9: 613–7.