Perspective

Substance Use Disorders in HIV-Infected Patients: Impact and New Treatment Strategies

Substance use disorders — including alcohol, cocaine, and opioid dependencies — are common in HIV-infected patients. Untreated substance use disorders result in poor HIV disease treatment outcomes; however, several new treatment strategies have emerged in recent years. Combined medication and counseling therapies are effective for alcohol and opioid dependencies, and counseling treatments are effective for cocaine dependence. Office-based treatment with buprenorphine offers the opportunity for coordinated treatment of HIV disease and opioid dependence. This article summarizes a presentation by David A. Fiellin, MD, in March 2004 at the International AIDS Society–USA New York course.

Substance use is a common comorbidity with HIV infection. When untreated, substance use disorders can result in poor outcome of HIV disease treatment (Sullivan and Fiellin, *Am J Addict,* 2004). In considering the integration of substance use treatment into HIV care, it is important to recognize a number of principles of addiction medicine:

1. *Addiction is a chronic medical disorder* that includes multifactorial *genetic* components, *biologic* changes due to exposure to addictive substances, and *behavioral* components. Treatment for addictive disorders frequently must address both neurobiologic and behavioral components.

2. *Addictive substances work on common neurologic reward pathways that are highly conserved in evolution.* These pathways involve projections between the ventral tegmental area and the nucleus accumbens; in brief, most addictive substances stimulate the ventral tegmental area, resulting in release of dopamine and stimulation of the nucleus accumbens, which is experienced as euphoria or reward.

3. *Profound neurobiologic changes accompany the transition from use to abuse to dependence.* In addition to the acute response to exposure to the addictive substance, the increased intracellular cyclic adenosine monophosphate (AMP) and cellular excitation resulting from brain cell exposure results in activation of a number of intracellular pathways that leads to altered gene expression associated with craving.

4. *Detoxification does not equal treatment.* Acute detoxification alone—that is, getting the patient through the acute phase of withdrawal—typically does not result in prolonged abstinence. By analogy, treating diabetic ketoacidosis is not the same as treating diabetes. Treatment strategies for patients with substance use disorders should be considered long-term, ongoing processes. Typically, abstinence rates during acute detoxification are high and fall off dramatically at some point after treatment. The success during acute detoxification treatment should serve to suggest that rates of sustained abstinence could be improved with continuation of treatment beyond acute detoxification.

5. *Treatment outcomes are improved with increased counseling services.* This finding has been repeatedly confirmed. As an example, one study comparing patients receiving treatment with methadone alone, methadone plus standard counseling, and methadone plus enhanced counseling showed that treatment retention rates were 31%, 59%, and 81%, respectively. Urine toxicology results were negative for opiates at greater than 16 weeks in 0%, 28%, and 55% of patients, respectively (McLellan, *JAMA,* 1993).

The following reviews aspects of alcohol, cocaine, and opiate abuse epidemi-

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ology and impact on HIV care and new treatment strategies for substance abuse and dependency. Although abuse of other substances, including methamphetamines, may be seen in patients who are HIV infected, this review focuses on these 3 commonly encountered substances.

Alcohol

Epidemiologic data indicate that approximately 35% of the general population can be considered moderate alcohol drinkers. At-risk drinkers (ie, men who consume more than 2 drinks per day or more than 4 on a single occasion and women who consume more than 1 drink per day or more than 3 on a single occasion) and alcohol abusers (greater use than at-risk use) constitute approximately 20% of the population, and 5% of the population is alcohol-dependent. In the general medical-practice setting population, approximately 20% to 35% fall into at-risk and abuse categories and 5% to 10% are dependent (Fiellin et al, *Ann Intern Med,* 2000). Studies in HIV-infected populations have reported alcohol problems or alcohol use disorders in 22% to 60% of patients (Phillips et al, *J Gen Intern Med,* 2001; Petry, *Int J STD AIDS*, 1999; Cook, *J Gen Intern Med*, 2001) and rates of alcohol abuse or dependence of 12% to 41% (Lefevre, *J Gen Intern Med*, 1995; Dew et al, *Psychological Med,* 1997).

Alcohol abuse can negatively affect HIV disease and its treatment in a number of ways. Studies in vitro have indicated enhanced HIV replication with alcohol exposure (Bagasra, *Alcohol Clin Exp Res*, 1989; Cook et al, *J Investig Med,* 1997), and alcohol use is associated with decreased levels of a number of endogenous immunomodulators. Alcohol use is also associated with high-risk sexual behavior. Data from the Multicenter AIDS Cohort Study (MACS) in the pre-potent antiretroviral therapy era indicated an absence of an association between alcohol use and HIV disease progression (Kaslow, 1989). How-

Table **1.** Effect of Alcohol Use on Adherence to Antiretroviral Medication

Drinking Behavior Type		Missed dose in 24 hours	Medicines off schedule in past week
Hazardous	(n=32)	21%	53%*
Heavy	(n=17)	15%	59%*
Binge	(n=34)	17%	38%
None of above	(n=161)	12%	26%

*P<0.05. Adapted from Cook et al, *J Gen Intern Med,* 2001.

ever, studies in the potent antiretroviral therapy era have demonstrated that alcohol problems are associated with reduced adherence to antiretroviral regimens (Fabris, *J Acquir Immune Defic Syndr*, 2000; Cook, *J Gen Intern Med*, 2001; Galvan, *J Stud Alcohol*, 2002) and that alcohol consumption is associated with higher plasma HIV RNA levels and lower CD4+ cell counts. (Palepu et al, *Addiction*, 2004). Adherence to antiretroviral regimens is a critical component in maintaining optimal suppression of viral replication. An example of the effect of alcohol use on adherence is provided by the data from a study by Cook and colleagues shown in Table 1; alcohol use was associated with reduced adherence to antiretroviral medications over the prior 24 hours, and heavier use was associated with significantly poorer weekly adherence.

Treatment strategies for alcohol abuse in patients considered at-risk drinkers include brief interventions—generally, 15-minute targeted interventions provided in the office setting that focus on consequences of alcohol abuse, including the potential impact on medication adherence and biochemical damage and symptoms, and recommendations regarding appropriate and inappropriate drinking levels. A meta-analysis of 12 randomized controlled trials has shown that heavy drinkers who receive a brief intervention are twice as likely to moderate their alcohol consumption as those receiving no intervention (Wilk, *J Gen Intern Med*, 1997). In Project TREAT (Trial for Early Alcohol Treatment), performed in 64 physician offices in Wisconsin, patients receiving a 15-minute physician intervention visit with a repeat visit 1 month

later showed significant reductions in mean number of drinks during the prior 7 days, mean number of episodes of binge drinking within the prior 30 days, percentage of excessive drinking within the prior 7 days, and days of hospitalization within the prior 6 months compared with control patients not receiving the intervention (Table 2; Fleming et al, *JAMA*, 1997).

Patients meeting criteria for alcohol abuse and dependence require more intensive treatment strategies, the mainstays of which are psychosocial treatments. The main treatments are motivational enhancement therapy, cognitive behavioral therapy, and 12-step facilitation; in each of these the patient attends individual or group counseling on a weekly basis. An example of the results achieved with these approaches comes from the National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity), in which 1726 patients were randomized to one of the 3 treatments. Results with the individual treatments were very similar; pooled outcomes for outpatients and inpatients are shown in Table 3 (*J Stud Alcohol*, 1997). Overall, of patients initiating treatment from the outpatient or inpatient setting, 35% remained abstinent, 25% consumed a small amount of alcohol on at least 1 occasion, and 40% relapsed to heavy or uncontrolled drinking during the first 12 months. In the outpatient-only arm, 19% maintained complete abstinence, 35% consumed a small amount of alcohol on at least 1 occasion, and 46% had a relapse. These findings indicate that physicians can expect that many of their patients will benefit from alcohol treatment programs.

A number of pharmacologic approaches to treatment of alcohol abuse and dependence are currently available or have shown promise in clinical investigation. However, there are few available data on the use of pharmacologic treatments in HIV-infected patients. Disulfiram is a well-described medication that appears to be most effective in highly motivated patients receiving directly observed therapy. There were initial promising results with the opioid antagonist naltrexone, but more recent

Table **2.** Effect of Physician Brief Intervention in At-Risk Drinkers in Project TREAT: Baseline to 12 Months

	Baseline	12 Months
Mean number drinks, prior 7 days*		
Intervention	19.1	11.5
Control	18.9	15.5
Mean number episodes of binge drinking, prior 30 days*		
Intervention	5.7	3.1
Control	5.3	4.2
Percent drinking excessively, prior 7 days*		
Intervention	47.5%	17.8%
Control	48.1%	32.5%
Days of hospitalization, prior 6 months*		
Intervention	93	91
Control	42	146

*P<001 for intervention versus control. Adapted from Fleming et al, *JAMA*, 1997.

Table **3.** Pooled Results With Motivational Enhancement Therapy, Cognitive Behavioral Therapy, and 12-Step Facilitation in Project MATCH

	Outpatients	Inpatients
Abstinent	19%	35%
Non-abstinent	35%	25%
Relapse	46%	40%

Adapted from Project MATCH Research Group, *J Stud Alcohol,* 1997.

data suggest that it is not as effective as initial findings suggested. Acamprosate, which is widely used in Europe, tends to result in a 30% to 40% decrease in excessive drinking behavior; a large NIAAA trial combining acamprosate and naltrexone is under way. Promising results have been seen with neuroleptics such as topiramate, and odansetron has been found to be helpful in decreasing excessive drinking behavior in select patients.

Cocaine

Epidemiologic data on cocaine use in HIV-infected patients are relatively sparse. Chaisson and colleagues found that 12% of 633 heterosexual injection drug users with HIV infection were using cocaine or heroin (JAMA, 1989). More recently, Samet and colleagues (in press) found that 25% of HIV-infected patients with alcohol problems were using cocaine.

Cocaine use is a well-established risk factor for acquiring HIV infection (Chaisson, *JAMA*, 1989). The effect of cocaine use on HIV disease progression is less clear, although it is known that cocaine suppresses T-cell activity and facilitates HIV replication. It is also known that ongoing cocaine use is associated with decreased adherence to antiretroviral regimens.

Psychosocial treatments currently are the mainstay of therapy for cocaine use. Drug counseling and contingency management are the most promising counseling approaches. Results of the National Institute on Drug Abuse Collaborative Cocaine Treatment Study comparing patients receiving individual and group counseling, cognitive therapy and group counseling, supportive-expressive and group counseling, and group counseling alone are summarized in Table 4 (Crits-Cristoph, *Arch Gen Psychiatry*, 1999). These findings suggest somewhat better maintenance of abstinence with the combined individual and group counseling approach. At present, there are no established pharmacologic therapies. Early work on a potential vaccine is ongoing. Initial findings with use of disulfiram have been promising.

Opioids

Heroin use is clearly on the rise in the United States. Data from the National Household Survey on Drug Abuse indicate that 2.4 million Americans used heroin in 1997 and that there were 410,000 new users between 1996 and 1998. Prescription opioid abuse is also rising: data from the Drug Abuse Warning Network indicate that oxycodone abuse increased by 68% (from 6429 to 10,825 reports) between 1999 and 2000 and that hydrocodone abuse increased by 31% (from 14,639 to 19,221 reports) over the same period. Prescription opioid abuse with controlled-release oxycodone often occurs when the pill matrix is broken to allow the contents to be snorted or swallowed, resulting in immediate drug exposure and euphoric reward.

It is estimated that approximately 1 million Americans have heroin dependency, and 2 to 2.5 million have prescription opioid dependency. According to Office of National Drug Control Policy data for 1999, an estimated 810,000 to 1 million persons in the United States had opioid dependency, but only some 170,000 to 200,000 were receiving effective treatment strategies.

Data on the prevalence of opioid use in HIV-infected patients is largely confined to data on injection drug use. According to the Centers for Disease Control and Prevention (CDC), the number of injection drug users living with AIDS increased from 48,244 to 88,540 between 1993 and 1999 (CDC, *HIV/AIDS Surveillance Report*, 2000). It is estimated that 25% of the roughly 40,000 new HIV infections per year occur through injection drug use (CDC, *HIV Prevention Strategic Plan Through 2005*, 2001).

Opioid use is associated with poorer HIV disease treatment outcomes. Injection drug users are less adherent to antiretroviral regimens (Roca, *J Infect*, 1999; Poundstone, *AIDS*, 2001) and HIV-infected injection drug users are less likely to receive antiretroviral treatment (Celentano, *JAMA*, 1998; Strathdee, *JAMA*, 1998; Turner, *J Gen Intern Med*, 2001). Often, potent antiretroviral therapy is delayed until active opioid use is addressed. This has usually required referral of patients to off-site treatment programs; however, as discussed below, the availability of buprenorphine presents options for dependency treatment in the HIV specialty setting.

The most effective treatment strate-

Table **4.** Abstinence Outcome According to Treatment in the National Institute on Drug Abuse Collaborative Cocaine Treatment Study

Consecutive months abstinent	Individual and group counseling	Cognitive therapy and group counseling	Supportive-expressive and group counseling	Group counseling
	(n=121)	(n=119)	(n=124)	(n=123)
1	71%	54%	60%	58%
2	48%	36%	32%	42%
3	38%	23%	18%	27%

Adapted from Crits-Christoph et al, *Arch Gen Psychiatry*, 1999.

gies for opioid dependence are pharmacologic approaches combined with psychosocial treatment. (O'Connor and Fiellin, *Ann Intern Med,* 2000). Pharmacologic options consist primarily of methadone and buprenorphine; levomethadyl acetate (LAAM) is no longer available in the United States because of concerns over cardiac toxicity (QT prolongation and episodes of torsade de pointes). Figure 1 shows results of a trial comparing low- and high-dose methadone, buprenorphine, and LAAM, all combined with counseling, in patients with opioid dependence (Johnson, *NEJM*, 2000). Rates of both treatment retention and opioid-negative urine toxicology with buprenorphine treatment compare well with rates observed with high-dose methadone, which can be considered the standard treatment in this setting.

The importance of opioid dependency treatment with regard to HIV disease is illustrated by a study reported by Metzger and colleagues (*J Acquir Immune Defic Syndr*, 1993). During an 18-month follow-up of initially HIV-seronegative patients, 22% of 103 injection opioid users who were receiving no treatment became HIV-seropositive, compared with 3.5% of 152 patients receiving methadone treatment.

With regard to drug-drug interactions that may arise when treating dependency and HIV infection, there are numerous interactions between methadone and antiretroviral agents. Methadone disposition is not affected by concomitant nucleoside reverse transcriptase inhibitor treatment. However, the zidovudine area under the concentration-time curve (AUC) is reduced with concomitant treatment, and blood levels of didanosine (minimal effect with enteric formulation of didanosine) and stavudine are reduced. With regard to nonnucleoside reverse transcriptase inhibitors (NNRTIs), both efavirenz and nevirapine are associated with a 50% reduction in methadone AUC. For protease inhibitors, ritonavir, indinavir, and saquinavir inhibit methadone metabolism in vitro; however, ritonavir has no effect on methadone metabolism in vivo. Methadone concentrations are reduced by nelfinavir (40%) and lopinavir/ritonavir (32%); nelfinavir

use has not been associated with clinical opioid withdrawal symptoms, but the use of lopinavir/ritonavir has been. The interaction of methadone and atazanavir currently is being studied.

Buprenorphine. Buprenorphine is a partial agonist at the μ receptor that has a unique pharmacologic profile. The agent is characterized by a ceiling effect in intrinsic opioid activity (Figure 2), reducing the potential for respiratory depression and death associated with full agonist use. The drug has low abuse and diversion potential. The currently available formulation consists of a sublingual tablet in a 4-to-1 ratio with the opioid antagonist naloxone. The buprenorphine component is well absorbed sublingually and the naloxone component is not; if the pill is ground and injected, an opioid-dependent patient will experience an immediate withdrawal from the naloxone.

Currently, there is limited informa-

tion on drug-drug interactions between buprenorphine and antiretroviral agents. The agent undergoes N-dealkylation mediated by the cyto-chrome P450 3A4 isoenzyme, and there is thus potential for interaction with NNRTIs and protease inhibitors. Preliminary information, however, indicates that there is no decrease in buprenorphine concentrations with coadministration of efavirenz. Results from cohorts of HIV-infected patients in France, where the medication has been available since 1996, indicate that buprenorphine treatment is associated with increased adherence to potent antiretroviral therapy and that patients experience appropriate increases in CD4 + cell count and reductions in viral load while receiving this medication (Carrieri et al, *Drug Alcohol Depend*, 2000; Moatti et al, *AIDS*, 2000).

Buprenorphine was approved in October 2002 for office-based treatment of opioid dependency, including
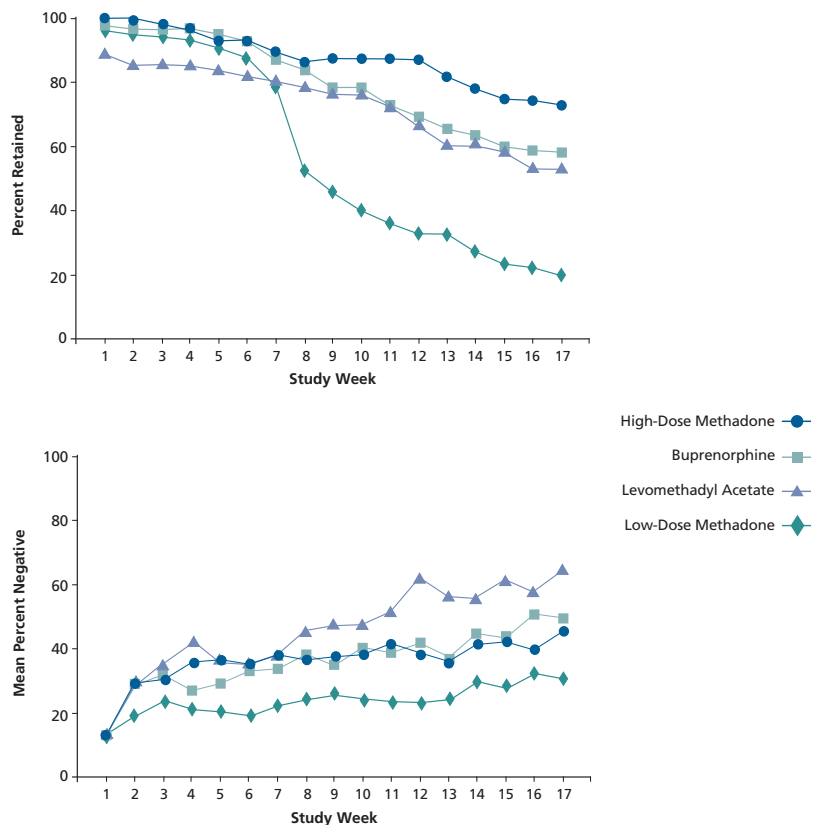

Figure **1.** Treatment retention rates (top) and opioid-negative urine toxicology results (bottom) according to treatment in opioid-dependent patients. Adapted from Johnson et al, *N Engl J Med*, 2000.
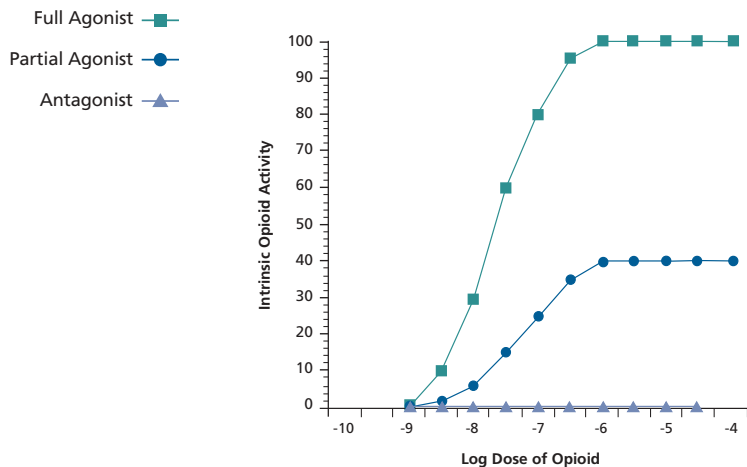
Figure **2**. Intrinsic opioid activity of methadone (full agonist), buprenorphine (partial agonist), and naltrexone (antagonist). Adapted from *Use of Buprenorphine in the Pharmacologic Management of Opioid Dependence: A Curriculum for Physicians*, 2001.

treatment in HIV specialty settings. The Drug Addiction Treatment Act of 2000 created the pathway by which physicians can prescribe buprenorphine (Fiellin and O'Connor, *N Engl J Med*, 2002).

The requirements for prescribing buprenorphine in the office setting are that it be prescribed by a licensed physician who is board certified in addiction medicine and has the capacity to refer patients for counseling. At this time, no more than 30 patients can be under the care of an individual physician or a group practice, but legislative efforts are under way to lift this restriction. The prescriber must successfully complete an approved 8-hour training. As of November 2003, there were 3159 physicians who had undergone the 8-hour training program required in the absence of certification in addiction medicine. Currently, there are approximately 3500 to 4000 physicians who have been trained, but relatively few are HIV care providers. An initiative is under way to provide training sessions targeted to HIV care providers.

Buprenorphine information, including copies of the Drug Addiction Act of 2000, waiver notification forms, a listing of buprenorphine trainings, a buprenorphine physician locator map, and frequently asked questions, can be found at http://buprenorphine.samhsa.gov. Questions about buprenorphine and training sessions can be answered

by calling 1-866-BUP-CSAT Monday through Friday, 8:30 AM to 5:00 PM Eastern time, or via email at info@buprenorphine.samhsa.gov.

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