Perspectives

Issues in HIV Therapy in "Triple-Diagnosed" Patients

Gerald H. Friedland, MD

There is great overlap among the population of HIV-1-infected individuals who are active or former drug users and who have serious underlying mental illnesses. Challenges in treating these "triple-diagnosed" patients, particularly with regard to access and adherence to antiretroviral therapy and drug interactions, were discussed at the New York course in March by Gerald H. Friedland, MD.

Epidemiology and Comorbidity

AIDS cases associated with injection drug use account for more than one third of cases in the United States, with recent trends indicating an increase in this proportion. Data from 1997 to 1998 indicate that transmission of HIV related to injection drug use accounts for 24% to 47% of new infections. Heterosexual and perinatal exposure to HIV-infected injection drug users constitutes the major route of HIV transmission. Noninjection drug use also facilitates sexual transmission of HIV infection (eg, through disinhibition) and may be associated with factors that confound treatment of HIV infection, which can be similar to those associated with injection drug use.

The epidemiology of mental illness and HIV infection is not well characterized. However, a number of surveys conducted in the United States and Europe indicate that approximately 20% to 50% of individuals with HIV infection or AIDS have severe mental illness, including personality and mood disorders (major depression; anxiety, panic disorder, or posttraumatic stress disorder; impulsivity or personality disorder; and drug-related disorders), as well as psychoses. Injection drug users with HIV infection have been reported to have a rate

of major depression of 26% (5-times that in the general population). Other data indicate that the rate of substance abuse among the population with severe mental illness is 4% to 35% (3 to 25 times that in the general population) and that there is an HIV-seroprevalence rate of at least 2% to 8% in this population (10 to 50 times that in the general population).

Studies using the global assessment of functioning (GAF) instrument, which evaluates personality and social functioning, have indicated that scores for HIV-infected individuals are lower than those for HIV-seronegative injection drug users and fall between those for individuals not in either category and those for individuals hospitalized for psychiatric disease (Figure 1). Other studies among HIV-seropositive and -seronegative drug users who are not in drug treatment programs indicate frequencies of 41% for depression, 10% for suicide attempt, 9% for posttraumatic stress disorder, and 7% for anxiety disorder. Although no difference between HIV-seropositive and HIV-seronegative individuals for specific mental health diagnoses was observed, mental illness was significantly more common in HIV-seropositive individuals overall (39% v 23%, P=0.002).

Antiretroviral Therapy

The complex and intertwined etiologies of HIV disease, substance abuse, and psychiatric disease are associated with biologic,

behavioral, clinical, and societal factors that render effective care for the triple-diagnosed patient extremely difficult. Data from the era of potent antiretroviral therapy indicate that there have been marked decreases in rates of opportunistic illness and death in HIV infection by category of HIV transmission. However, the decrease in injection drug users has been smaller than that in other risk behavior categories (Figure 2). Centers for Disease Control and Prevention (CDC) statistics through 1997 indicate that, due to the smaller decrease in mortality in AIDS patients acquiring infection through injection drug use, these patients account for an increasing proportion of deaths in patients with AIDS (>50% in 1997). At the same time, CDC statistics show that the ongoing injection drug use-associated transmission of HIV as well as treatment benefits have resulted in a steady increase in the estimated absolute number of HIV-infected injection drug users in 1997.

Studies performed several years ago and published in 1998 (the ALIVE and Vancouver studies) indicated that only a small minority of infected injection drug users were receiving potent antiretroviral therapy. Factors associated with lack of use of antiretroviral therapy in one study included active drug use, suboptimal health care, not being in a drug treatment program, and recent incarceration. Younger age, female gender, not being in a drug treatment program, and health care
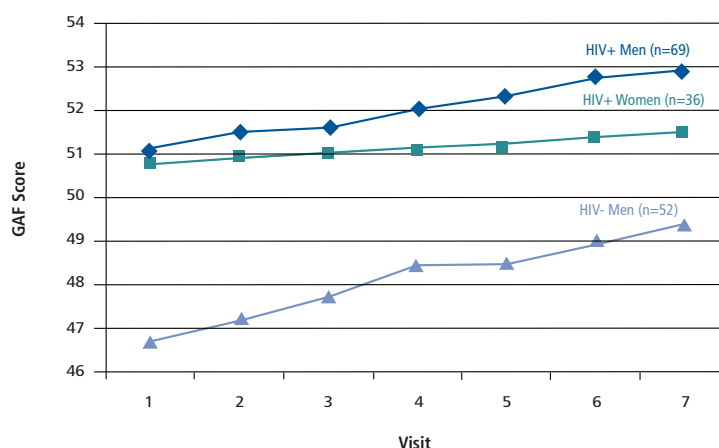
Dr Friedland is Professor of Medicine, Epidemiology, and Public Health at Yale University School of Medicine and Director of the AIDS Care Program at Yale-New Haven Hospital in Connecticut. He also serves as Chair of the annual International AIDS Society–USA course in New York City.

Figure **1.** Mean global assessment of functioning (GAF) score for injection drug users in a longitudinal study according to HIV-seropositive (HIV+) or HIV-seronegative (HIV-) status and male or female gender. Normal scores are approximately 70 or above. Adapted from Rabkin et al, *AIDS,* 1997.
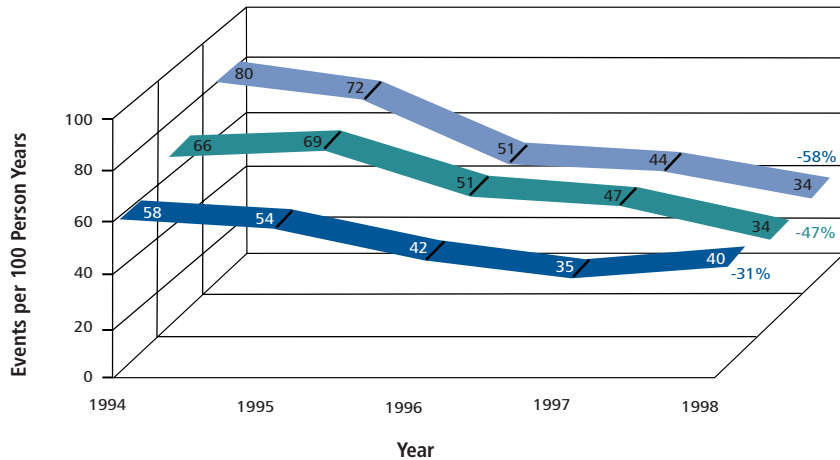
Figure **2.** Rates of opportunistic illness and death (events per 100 patient years) at a Johns Hopkins clinic according to transmission category of injection drug use (light blue), heterosexual contact (green), or male-to-male sexual contact (blue). Overall decrease in rates is shown at right. Adapted from Moore RD et al, *AIDS,* 1999.

provider expertise were associations identified in another study. More recent data from the Johns Hopkins Moore Clinic cohort (Moore et al, AIDS, 1999) indicate that although the rate of use of antiretroviral therapy among active injection drug users was approximately 60% in 1999, it remains lower than rates of use in individuals infected through homosexual or heterosexual contact.

Further, data from the Medicaid population in New York indicate that individuals with drug dependence have significantly reduced adjusted odds for receiving antiretroviral therapy, whereas drug users who are in a drug treatment program have a 40% increased likelihood of using antiretroviral therapy (Turner et al, 7th CR01, 2000). Data on the impact of severe mental illness on the rates of treatment with antiretroviral therapy are not available, although it is well known and documented that depression is a powerful predictor of poor adherence to HIV therapy. Further, having a mental health provider appears, paradoxically, to decrease likelihood of receiving antiretroviral therapy.

Recent studies by investigators at Yale have indicated that trust in the physician is the most important variable influencing acceptance of antiretroviral therapy among injection drug users, with each 1-point increase in score on the Likert scaled "Trust in Physician" instrument being associated with an 8% increase in likelihood of acceptance of antiretroviral therapy. Beliefs about medication also influence HIV therapeutics among drug users. In a recent survey, more than half of substance abuse patients "strongly agreed" or "agreed" that in using antiretroviral therapy, they were being experimented on without being told, that drug companies do not "tell bad things" about their drugs, and that there is a cure for AIDS that the government keeps quiet. Moreover, the majority of patients said they believed that antiretroviral therapy is harmful when taken with heroin, cocaine, or methadone; that they will not take therapy if they are going to get high on "street" drugs; that people "get sick and die" after starting antiretroviral therapy; and that people "get sick and die" after stopping street drugs.

The relative lack of effective drug treatment programs in the United States influences both antiretroviral use and continued transmission of HIV infection among injection drug users. Methadone may be considered one of the most successful chronic disease therapies. Its use is associated with decreased heroin use, improved quality of life, and decreased needle sharing and HIV transmission. It is estimated that only 15% to 20% of individuals eligible for opiate addiction treatment currently are receiving treatment in the United States. This is to be contrasted with countries such as Scotland, where methadone treatment is available through primary care physicians and currently is being received by 40% to 80% of the eligible population. A policy of administering methadone in the primary care setting currently is being reconsidered in the United States.

It is also important to consider broader expertise and availability of mental health treatment in traditional medical settings where patients with HIV disease are seen as well as the converse–provision of HIV expertise and therapy at mental health care sites. Co-location of treatment for all 3 comorbid conditions is the most efficient and likely most successful way of addressing the complex treatment needs of this population.

Drug Interactions

Pharmacokinetic interactions between substance abuse treatments and antiretroviral drugs, as well as drugs used for the treatment of mental illness, can affect efficacy and toxicity of and adherence to treatment for each or all of the comorbid conditions.

Methadone is metabolized by hepatic demethylation and activity of the cytochrome P450 3A4 isoenzyme system and, possibly, other CYP450 isoenzyme systems (1A2, 2C9, 2D6). The methadone derivative LAAM– has similar pharmacokinetics. With regard to pharmacokinetic interactions between methadone and nucleoside reverse transcriptase inhibitors (nRTIs), data from within- and between-subject studies indicate that the zidovudine area under the curve (AUC) concentration is increased by approximately 40% with coadministered methadone, with no change in methadone disposition observed. A crossover study of coadministered methadone and didanosine or stavudine has shown AUC decreases of 60% for didanosine and 18% for stavudine and no change in methadone levels. A recent study indicated that coadministration of abacavir and methadone produced a small but statistically significant increase in clearance (9.9-12.2 L/h), producing a decrease in methadone levels. In addition, a small but significant decrease in maximum abacavir concentration (4.4-2.9 µg/mL) was seen as was a delay in abacavir maximum time concentration (1.5-2.5 h), likely the result of the methadone effect of slowing gastrointestinal motility.

Interactions with methadone may be even more be problematic with the nonnucleoside reverse transcriptase inhibitors (NNRTIs). In a recently reported case series of 7 patients with opiate withdrawal symptoms within 8 days of starting nevirapine, the 3 subjects in whom methadone measurements were obtained had low methadone levels at the onset of symptoms. All of the patients required substantial increases in methadone dose, but only 3 responded to the increase and only

those patients continued to receive nevirapine. A recent report supports the observation of induction of increased metabolism of methadone by nevirapine and extends the findings to efavirenz. In a group of 25 stable-dose methadone patients, measurement of drug levels at baseline and after 2 and 3 weeks showed that the methadone AUC was decreased by 43% in 15 subjects receiving efavirenz and by 46% in 10 receiving nevirapine. Overall, 8 patients had opiate withdrawal symptoms after 8 days and required a mean methadone dose increase of 21.65%. The effect of methadone/ delavirdine coadministration has not been studied; however, based on what is known of delavirdine pharmacokinetics, it is hypothesized that coadministration would result in an increase in methadone levels.

Little is known about the effects of methadone on protease inhibitor pharmacokinetics. Coadministration appears to be associated with some delay in indinavir absorption, but there are yet no published reports on interactions with other protease inhibitors. No effect on methadone levels has been reported with indinavir. Ritonavir, which decreases meperidine levels and increases fentanyl levels, has been reported to decrease methadone levels, although this information is based on use of very low doses of methadone. Nelfinavir has been reported to decrease methadone levels by 30% to 50% without resulting in clinical symptoms. It is hypothesized that nelfinavir may largely affect protein-bound methadone rather than the active free drug. Available preliminary information indicates that saquinavir and amprenavir have minimal effects on methadone level. With regard to therapies for opportunistic infections, most problematic is the long-known rifampin induction of methadone metabolism, with resultant rapid opiate withdrawal. Other clinically significant interactions with opportunistic therapies have not been reported.

There is considerable likelihood of pharmacokinetic interactions between HIV therapies metabolized by the CYP450 system and commonly abused substances. Metabolic pathways of a number of abused substances are shown in Table 1. However, virtually nothing is known of the clinical effects of such interactions. The need for concern is highlighted by a recent case report in which a patient taking the amphetamine methylene dioxymethamphetamine (MDMA) experienced a prolonged amphetamine-like reaction after switching from one protease inhibitor to

Table **1.** Metabolic Pathways of Abused Substances

Drug	Metabolic Pathway (CYP Isoenzyme)
Benzodiazepines	
Alprazolam, clorazepate, estazolam, flurazepam, midazolam, triazolam	CYP450 (3A4)
Diazepam	CYP450 (3A4, 2C19)
Lorazepam	Glucuronidation
Opiates	
Buprenorphine, fentanyl, methadone	CYP450 (3A4, 2D6)
Meperidine	CYP450 (3A4?)
Propoxyphene	CYP450 (2D6)
Codeine, hydrocodone, oxycodone	CYP450 (2D6)
Heroin, hydromorphone, morphine	Glucuronidation?
Amphetamines	
Amphetamine, methamphetamine (crystal meth), methylene dioxymethamphetamine (MDMA)	CYP450 (2D6)
Others	
Dronabinol, marijuana, zolpidem	CYP450 (3A4)
Sidenafil	CYP450 (3A4)
Cocaine	Hydrolysis by plasma cholinesterase
g-hydroxybutyrate (GBH)	CYP450

Adapted from Harrington et al. *Arch Intern Med.* 1999.

ritonavir. After taking the nonsedating antihistamine g-hydroxybutyrate (GBH), the patient became comatose.

There is also very little information on potential pharmacokinetic interactions between psychiatric drug therapies and antiretroviral drugs. Although there appears to be minimal to no supporting published literature, it is suspected that interactions occur between protease inhibitors and tricyclics, selective serotonin reuptake inhibitors (metabolized via CYP450 2D6), and bupropion among the antidepressants, and benzodiazepines (metabolized by CYP450 3A4) among the anxiolytics (particularly midazolam and triazolam). No information is available on potential interactions between protease inhibitors and antipsychotics (metabolized via CYP450 1A2, 2D6), nor on potential interactions between NNRTIs or nRTIs and psychiatric drugs. Several recent

reports in small numbers of patients demonstrated increases in methadone levels when coadministered with fluvoxamine and sertraline, and less effect with fluoxetine. Although clinical indications for administration of therapies for HIV, substance abuse, and mental illness should be followed, prudence dictates that caution be taken when these drugs are administered concomitantly and that heightened awareness of possible interactions be maintained.

Interactions between antiretrovirals and substance abuse therapies are common, and interactions between antiretrovirals and psychiatric medications may also be common. The most important currently identified interactions are the effect of methadone on nRTIs and the effect of NNRTIs on methadone (and to a lesser extent the effect of protease inhibitors on methadone). Although they are difficult to

perform, pharmacokinetic studies of interactions between HIV therapies and substance abuse and psychiatric medications are essential and clinical studies in this area are urgently needed.

Conclusions

HIV disease, severe mental illness, and substance abuse frequently coexist and complicate and confound treatment efforts. More limited access to care,

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decreased provision, acceptance, and adherence to therapy, and complex and poorly studied drug interactions all contribute to limiting the benefits of potent antiretroviral therapy in populations with these comorbid conditions. As this population increases, HIV clinicians will need to increase their expertise in the management of comorbid conditions and help develop systems of care that better address the special needs of this population.

Suggested Reading

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