Substance Abuse and HIV: Treatment Challenges

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ABSTRACT:

Alcohol and substance abuse are common in patients with HIV infection and often complicate treatment in a number of ways. Alcohol abuse, for example, is associated with poorer adherence to antiretroviral treatment, which in turn is associated with inadequate viral suppression and the development of antiviral drug resistance. Similarly, HIV-infected patients with opioid dependence are less likely to have access to HIV clinical care, less likely to receive and adhere to antiretroviral therapy, and more likely to have rapid disease progression. Appropriate treatment of both alcohol and substance abuse can result in improved adherence to antiretroviral therapy and decreased high-risk behaviors.

Substance abuse, especially injection drug abuse, is often associated with chronic infectious diseases, including HIV infection, hepatitis B, hepatitis C, and tuberculosis. Delivery of effective treatment for these chronic conditions can be very challenging in patients who continue to abuse substances. Studies have shown that untreated substance use disorders have a negative impact on access to HIV care, HIV treatment initiation, HIV outcomes and disease progression, and adherence. Here, we discuss the impact of ongoing alcohol, cocaine, and opioid abuse on HIV disease progression and discuss unique treatment challenges in patients with HIV and substance abuse.

Alcohol abuse and HIV
The spectrum of alcohol use ranges from occasional use to alcohol dependence. Moderate drinkers make up about 35% of the general population. Men who drink more than 4 drinks a day or 14 drinks per week and women who drink more than 3 drinks a day or 7 drinks per week are considered at-risk drinkers. At-risk drinkers and those meeting criteria for alcohol abuse make up about 20% of the
population, while those meeting the criteria for alcohol dependence make up about 5% of the population.5 The prevalence of these disorders in patients with HIV infection is increased 2-4 fold compared with the general population.7-9

Alcohol abuse and dependence affect disease progression, treatment adherence, and comorbid disease severity in patients with HIV infection.10 In vitro studies have found increased viral replication in cells exposed to alcohol, suggesting that alcohol has a direct effect on disease progression.11 The association between alcohol and HIV disease progression in vivo, however, is variable. A cross-sectional study found that among patients receiving highly active antiretroviral therapy, log HIV RNA levels were significantly higher and CD4 counts were significantly lower in those with moderate and at-risk alcohol consumption compared with patients who abstained.12 However, among HIV-infected patients not receiving highly active antiretroviral therapy, there were no differences in HIV outcomes between any of the alcohol consumption groups.12

In a more recent, longitudinal study, CD4 counts were lower in HIV-infected patients who used alcohol and were not receiving HAART, but log HIV RNA levels were no different. There were no differences in CD4 counts or HIV RNA levels in patients receiving highly active antiretroviral therapy.13

The treatment of HIV infection in patients with alcohol use disorders can be challenging. Some studies suggest that alcohol abuse in treatment-naïve patients who are initiating antiretroviral therapy slows the time to viral suppression, whereas other studies suggest little impact of alcohol abuse on HIV outcomes.14,15 The impact of alcohol abuse on HIV treatment outcomes is complex, but is at least partially mediated by medication adherence.15,16

Alcohol use disorders are associated with poorer adherence to antiretroviral treatment,17,18 which in turn is associated with inadequate viral suppression and the development of antiviral drug resistance. In addition to poorer disease outcomes and medication adherence, alcohol use may negatively affect comorbid conditions. HIV-infected patients who use alcohol, especially those meeting criteria for alcohol abuse or dependence, have more depressive symptoms than their abstaining counterparts.19 Patients co-infected with hepatitis C who use alcohol are more likely to have severe liver disease.20,21

The treatment of alcohol abuse and dependence ranges from brief interventions for at-risk drinkers to specialty referral and pharmacotherapy for patients with alcohol dependence. Brief interventions consist of 10-15 minutes of counseling focused on the negative effects of drinking. Individual studies and meta-analyses have shown that brief interventions effectively reduce alcohol use in patients who are at-risk drinkers.22,23 The efficacy of a brief intervention to reduce drinking in alcohol-dependent patients is limited.

Alcohol dependence requires a more aggressive treatment approach, with the goal being complete abstinence. Successful treatment of alcohol dependence generally uses a multimodal approach often consisting of behavioral interventions, pharmacotherapy, and participation in self-help programs (such as 12-step programs). Available pharmacotherapies for alcohol dependence include disulfiram(Drug information on disulfiram), naltrexone, and acamprosate(Drug information on acamprosate). Naltrexone (Drug information on naltrexone) has been shown to decrease alcohol-induced viral replication in in vitro studies.24 Acamprosate and disulfiram are both effective in treating alcohol dependence, but little data exist on their use in HIV-infected patients.

Cocaine abuse and HIV
According to the 2007 National Survey on Drug Use and Health, about 36 million Americans, 12 years
or older, reported using cocaine and 9 million specifically reported using crack cocaine. More than 2 million (0.8%) Americans were current (past-month) users of cocaine and 610,000 (0.2%) were current users of crack. The prevalence of cocaine use in patients with HIV infection is approximately 25%. A cross-sectional study of 407 drug users in treatment facilities confirmed an association between HIV infection and use of crack cocaine.

Injecting and smoking cocaine are both known risk factors for HIV acquisition. Cocaine use negatively affects access to HIV care. In addition, cocaine impairs human macrophage and CD4 cell activity and activates HIV-1 expression in these cell types. In a large multicenter cohort study of 1686 HIV-infected women, the use of crack cocaine predicted CD4 count and viral load markers of disease progression, development of opportunistic infections, and AIDS-related mortality.

Another study showed that in HIV-infected patients, cocaine use or cocaine plus opioid use was associated with missed outpatient appointments, increased emergency department use, and lack of antiretroviral therapy. Cocaine use has also been shown to have a negative effect on medication adherence.

HIV treatment in patients with cocaine use and combined cocaine and opioid use can be especially challenging. In a pilot study of HIV-infected patients receiving buprenorphine(naloxone for opioid dependence, 33% had cocaine use at baseline and throughout treatment. There is ongoing research investigating the complex relationship between HIV infection, cocaine abuse, and opioid dependence and how this relationship affects HIV treatment.

There are no FDA-approved medications for the treatment of cocaine use. Behavioral interventions, primarily cognitive-behavioral therapy, are the mainstay of treatment and have been shown to decrease amount of use and prevent relapse. In a study of more than 1500 cocaine-dependent persons, community-based treatment decreased weekly cocaine use from 73% to 24% at 1-year follow up and to 25% at 5-year follow-up. Certain medications as well as a cocaine vaccine are being studied.

**Opioid abuse and HIV**

Injection heroin use is a direct risk factor for HIV acquisition, and roughly one-third of all HIV cases are a result of injection drug use. Although the prevalence of heroin abuse in this country has been relatively stable over the past decade, the misuse of prescription opioids has markedly increased. According to the 2007 National Survey on Drug Use and Health, about 400,000 Americans used heroin in the past year, while 12 million misused prescription opioids.

Patients with comorbid HIV infection and opioid dependence are less likely to have access to HIV clinical care, less likely to receive antiretroviral therapy, less likely to adhere to antiretroviral therapy, and more likely to have rapid disease progression. Often, treatment is delayed until active injection drug abuse has been treated, which may present a barrier to ever receiving antiretroviral therapy for many patients. AIDS-defining illnesses are more likely to develop in injection drug users, even those with access to care, than in non–injection drug-using counterparts.

The most effective treatment approach for opioid dependence involves a combination of pharmacologic and psychosocial treatments. Opioid-agonist treatments are the most common pharmacologic
options. These include methadone (Drug information on methadone), a full opioid agonist, and buprenorphine, a partial agonist at the mu opioid receptor. Nonopioid treatments are available for detoxification, while the opioid antagonist naltrexone can be used for maintenance.

Opioid-agonist treatment has been shown to be effective in HIV prevention. In a study by Metzger and associates, 155 HIV-seronegative injection drug users were followed for 18 months. Of the 152 patients receiving methadone, 3.5% became seropositive, compared with 22% of the 103 patients not in treatment. Similarly, buprenorphine has been shown to decrease behaviors that may lead to HIV infection. In a study of 166 patients receiving buprenorphine in primary care, injection drug use decreased from 37% at baseline to 7% at 24 weeks, and having sex while high decreased from 64% to 15%.

Methadone maintenance clinics provide a unique opportunity to enhance antiretroviral adherence and decrease risk behavior. One model that enhances these endpoints is directly observed therapy. Many patients who are enrolled in methadone maintenance present to the clinic daily or several times per week. Therefore, a protocol in which antiretroviral therapy is administered with methadone can improve HIV outcomes.

Co-location of HIV treatment within a methadone maintenance treatment program improves HIV outcomes. However, with the approval of buprenorphine for treatment of opioid dependence in office-based settings, co-location of treatment for opioid dependence within an HIV clinic is now possible. Buprenorphine has been shown to improve treatment adherence and HIV outcomes in HIV-infected, opioid-dependent patients. In one study, the feasibility of integrating buprenorphine into HIV clinical care was established. In this 3-month trial, CD4 counts remained stable, HIV RNA levels decreased, and opioid-positive urine toxicology decreased.

Drug-drug interactions are an important consideration when treating comorbid HIV and opioid dependence. The pharmacokinetic interactions between methadone and antiretroviral drugs have been investigated. Methadone increases the area under the concentration-time curve (AUC) of zidovudine (Drug information on zidovudine). The clinical significance of this interaction is not entirely clear, but physicians should be aware of the increased risk of zidovudine toxicity in patients receiving methadone maintenance.

The nonnucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine (Drug information on nevirapine) are known to decrease methadone blood concentrations and, therefore, may promote opioid withdrawal in patients. Interactions between methadone and some protease inhibitors have also been noted. Nelfinavir (Drug information on nelfinavir) decreases the AUC of methadone; however, this interaction does not appear to be clinically significant. Similar interactions have been noted with lopinavir (Drug information on lopinavir)/ritonavir, although some studies have noted opioid withdrawal.

Clinically significant interactions between buprenorphine and antiretroviral drugs have also been identified. Treatment with the protease inhibitor atazanavir (Drug information on atazanavir) (or atazanavir boosted with ritonavir) has been found to increase levels of buprenorphine, a cytochrome P450-3A4 substrate, and cause sedation. However, clinically significant interactions between buprenorphine and other protease inhibitors or NNRTIs have not been noted.

Conclusions
Substance abuse is commonly associated with chronic infectious diseases, including HIV. Ongoing
substance abuse has a negative impact on access to HIV care, antiretroviral therapy initiation, HIV disease progression, treatment outcomes, and adherence to antiretroviral treatment. Treatment of comorbid HIV infection and active substance use can be especially challenging. Effective treatment for opioid dependence has been established in HIV-infected patients, while treatments for cocaine dependence and alcohol abuse and dependence are still under investigation. Linkage and co-location of treatment for substance use and HIV is feasible and may be a useful strategy for some patients and providers.

References
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