



## **Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents**

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## **HIV and People Who Use Illicit Drugs (Last updated March 27, 2012; last reviewed March 27, 2012)**

### ***Treatment Challenges in People with HIV Who Use Illicit Drugs***

Injection drug use is the second most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate [i.e., poppers]). The most commonly used illicit drugs associated with HIV infection are heroin and stimulants (e.g., cocaine and amphetamines); however, the use of club drugs has increased substantially in the past several years and is common among individuals who have HIV infection or who are at risk of HIV infection. The association between club drugs and high-risk sexual behavior in men who have sex with men (MSM) is strongest for methamphetamine and amyl nitrate; this association is less consistent with the other club drugs.<sup>1</sup>

Illicit drug use has been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection because depression is one of the strongest predictors of poor adherence and poor treatment outcomes.<sup>2</sup> Treatment of HIV disease in people who use illicit drugs can be successful, but this group presents special treatment challenges. These challenges may include the following: (1) an array of complicating comorbid medical and mental health conditions; (2) limited access to HIV care; (3) inadequate adherence to therapy; (4) medication side effects and toxicities; (5) the need for substance abuse treatment; and (6) drug interactions that can complicate HIV treatment.<sup>3</sup>

Underlying health problems in people who use injection and/or noninjection drugs result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis (TB), skin and soft tissue infections, recurrent bacterial pneumonia, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in people with HIV who use illicit drugs than in people who use illicit drugs and do not have HIV, due in part to respiratory, hepatic, and neurological impairments associated with HIV infection.<sup>4</sup> Success of antiretroviral therapy (ART) in people with HIV who use illicit drugs often depends on clinicians becoming familiar with and managing these comorbid conditions and providing overdose prevention support.

People with HIV who use illicit drugs have less access to HIV care and are less likely to receive ART than other populations.<sup>5-6</sup> Factors associated with low rates of ART use among people who use illicit drugs include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and health care providers' lack of expertise in HIV treatment.<sup>5-6</sup> The typically unstable, chaotic life patterns of many people who use illicit drugs; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence.<sup>7</sup> The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and people who use illicit drugs.<sup>8-9</sup> The first step in provision of care and treatment for these individuals is to recognize the existence of a substance use problem. It is often obvious that the problem exists, but some patients may hide these problem behaviors from clinicians. Assessment of a patient for a substance use disorder should be part of routine medical history taking and should be done in a professional, straightforward, and nonjudgmental manner.

## ***Treatment Efficacy in Populations of People Who Use Illicit Drugs***

Although people who use illicit drugs are underrepresented in HIV therapy clinical trials, available data indicate that efficacy of ART in people who use illicit drugs—when they are not actively using drugs—is similar to that seen in other populations.<sup>10</sup> Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use per se.<sup>11</sup> Providers need to remain attentive to the possible impact of disruptions caused by drug use on the patient both before and while receiving ART. Although many people who use illicit drugs can sufficiently control their drug use for a long enough time to benefit from care, treatment for substance use disorders is often necessary for successful HIV management.

Successful HIV treatment requires close collaboration with treatment programs for substance use disorders and proper support and attention to this population's special multidisciplinary needs. HIV care sites should be accommodating, flexible, and community-based, with experience in managing a wide array of needs for people who use drugs. HIV care sites must also have experience in developing effective strategies to promote medication adherence.<sup>9</sup> These strategies should include, if available, the use of adherence support mechanisms such as modified directly observed therapy (mDOT), which has shown promise among people with HIV who use illicit drugs.<sup>12</sup>

## ***Antiretroviral Agents and Opioid Substitution Therapy***

Compared with people receiving ART who do not use illicit drugs, people who use illicit drugs are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal (GI), and hematologic disorders are highly prevalent among people who use injection drugs. These comorbid conditions should be considered when selecting antiretroviral (ARV) agents in this population. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended-release naltrexone are commonly used for management of opioid dependence in patients with HIV.

**Methadone and Antiretroviral Therapy.** Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur.<sup>13</sup> These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. Patients and substance abuse treatment facilities should be informed of the likelihood of this interaction. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved.

**Buprenorphine and Antiretroviral Therapy.** Buprenorphine, a partial  $\mu$ -opioid agonist, is administered sublingually and is often coformulated with naloxone. It is increasingly used for opioid dependence treatment. Compared with methadone, buprenorphine has a lower risk of respiratory depression and overdose. This allows physicians in primary care to prescribe buprenorphine for the treatment of opioid dependency. The flexibility of the primary care setting can be of significant value to patients with HIV and opioid addiction who require ART because it enables one physician or program to provide both medical and substance abuse services. Limited information is currently available about interactions between buprenorphine and ARV agents.<sup>13-14</sup> Findings from available studies show that the drug interaction profile of buprenorphine is more favorable than that of methadone.

**Naltrexone and Antiretroviral Therapy.** A once-monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid

detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP450 enzyme system and is not expected to interact with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).<sup>15</sup>

Currently available pharmacokinetic (PK) interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine can be found in [Tables 19a-d](#). Effective communication between HIV care providers and drug treatment programs is essential to prevent additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported.<sup>16</sup>

## Summary

It is usually possible over time to support most people with HIV who actively use drugs such that acceptable adherence levels with ARV agents can be achieved.<sup>17-18</sup> Providers must work to combine all available resources to stabilize someone who actively uses drugs in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment and needle and syringe exchange programs, strategies to reduce high-risk sexual behavior, and harm-reduction strategies. A history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to those who do not use drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include need for supportive clinical sites, linkage to substance abuse treatment, and awareness of the interactions between illicit drugs and ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

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