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Management of HIV Infection in Patients With Substance Use Problems

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Abstract

Although highly active antiretroviral therapy (HAART) has greatly reduced overall morbidity and mortality in patients with HIV, patients with substance use issues have been less likely than other patients with HIV to realize these benefits. Social obstacles (eg, lack of housing, minimal social support), and medical comorbidities (eg, mental illness, hepatitis), complicate the management of this group of patients. Not only are drug and alcohol users less likely to access medical care, initiation of HAART may be delayed due to concerns for adherence and the potential development of drug resistance. Ultimately, a multidisciplinary comprehensive approach is needed to both engage and retain this population in care. Through the integration of case management, addiction therapy, and medical treatment of HIV, we may be able to improve outcomes for patients with HIV and addiction.

Introduction

Highly active antiretroviral therapy (HAART) has greatly reduced overall morbidity and mortality in patients with HIV [1]. However, these benefits have not been distributed equally among all patient groups, and certain patients, such as injection drug users, have had relatively inferior outcomes during the HAART era [2]. The reason for this is multifold. Not only are injection drug users less likely to access medical care, but initiation of HAART may be delayed due to concerns for adherence and the potential development of drug resistance [3]. Ongoing substance use, mental health disorders, unemployment, and homelessness contribute to these patients' social instability, making routine medical care and adherence more difficult. In addition, once an addict has overcome social barriers to HIV care, comorbidities such as bacterial infections, hepatitis, mental illness, and the need for addiction treatment may complicate their medical management. This combination of social and medical obstacles to HIV treatment accounts for poorer outcomes in this population. HIV-infected patients with addiction issues need comprehensive care and cultural sensitivity: they require an engaging clinic environment with adequate resources to help them overcome the social barriers to health care, and a coordinated approach to care from health care providers experienced in the medical management of HIV, addiction, and associated comorbidities.

Providing a Framework to Overcome Personal and Systemic Barriers to Care

To better achieve treatment goals and retain patients in care, the clinician can adopt various strategies to effectively address the myriad complicated issues facing an HIV-infected patient with underlying substance use problems. Understanding the patient and systemic barriers to care is the first step toward improving health outcome in this marginalized population.

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On the patient side, there are numerous overlapping barriers to care. HIV-positive substance-using patients are more likely to have unstable housing, be involved in the legal/correctional system, and have inadequate or absent health insurance. They may also be victims of physical and sexual abuse, have suboptimal social support, poor self-efficacy, a low educational level, and suffer from health problems such as mental illness and hepatitis [4••]. Patients may also perceive stigma or have misinformation about care that hinders them from engaging in care. These challenges emphasize the need for a good patient-provider relationship wherein the patient can articulate his or her needs and the provider can coordinate the necessary services.

In addition to personal barriers, systemic and structural barriers to care are also numerous. These include accessibility of the health care facility (including hours of operation and ease of making appointments), availability of bilingual staff, access to childcare, access to social work, counselors, case management, and other relevant specialties such as addiction services, pharmacy, and psychiatry. Integration of services provided in the HIV clinic is the key to effectively and efficiently addressing these systemic barriers.

Patient-provider relationship

Patients who report positive trusting relationships with their providers and good patient-provider communication have better care utilization and better health outcomes [5]. Trust is the foundation of a therapeutic patient-provider relationship. A provider can help build trust by suspending judgment about substance use problems and having empathy for the various difficulties faced by this population. For substance users, distrust of the health care system can result from experiencing discrimination and judgment because of their addiction [6•]. Stigma and shame also serve as powerful barriers to effective communication and hinder participation in treatment.

One goal of providers should be to keep patients engaged in medical care whether or not they are actively using drugs [6•]. Although initiating addiction therapy prior to or simultaneously with HIV therapy is preferable, patients with advanced disease may need HIV treatment urgently and this should not be delayed due to ongoing substance use. Sometimes the most effective strategy is to accept ongoing substance use, but use a harm-reduction approach to provide the most effective care rather than wait for abstinence, which may never come. Providers should actively involve patients in all treatment decisions to maximize the chances of success. To achieve the overarching goal of retaining patients in care, providers should seek assistance from as many sources as necessary, including case managers, social workers, addiction specialists, and mental health care providers [7••].

Comprehensive multidisciplinary approach

Given multiple comorbid conditions and frequent triple diagnoses (HIV, substance use, and mental illness), integration of services accessed by HIV-positive substance users makes intuitive sense and has proven its efficacy in recent studies [8–10], even in a homeless, HIV-positive, substance-using population [11]. Such integration can take varied forms, and often involves a comprehensive multidisciplinary approach. Critical to this model is a case manager who serves as the link between the patient and the various services required. The case manager acts as the patient's advocate, helping the patient to navigate the medical system by assisting with practical issues (eg, health insurance and housing), and helping to prioritize medical care by directly linking the patient to substance use and mental health services. Eliminating systemic barriers to care often involves simple, practical steps such as making it easier for the patient to get to the clinic and by providing various services in one location. At least one study suggests that, with the provision of transportation, greater distance to care did not decrease the level of treatment use [12]. When feasible, colocation of services within the health care facility (eg, laboratory services, pharmacy, childcare, language interpreters) can reduce the burden faced

by the patient. In addition, referring patients to substance use treatment programs or to mental health care providers directly from the primary care/HIV clinic can result in better care utilization and health outcomes [13,14].

Integration of care

Many advances have occurred recently in integrating opiate replacement therapy (eg, buprenorphine) into HIV primary care settings [15,16]. Traditionally, HIV treatment and substance use treatment for opiate-addicted HIV-positive patients have been independent of one another. This can lead to communication difficulties among providers and subsequent attempts to coordinate care [17••].

Basu et al. [17••] describe four potential models for integration of HIV care and buprenorphine therapy: 1) a primary care model—the HIV treatment provider prescribes buprenorphine; 2) an on-site specialist model— an addiction medicine provider prescribes buprenorphine; 3) a hybrid model—an on-site specialist prescribes the initial induction therapy with buprenorphine and the HIV care provider prescribes the maintenance phase; or 4) a drug treatment model— HIV care and addiction services are provided in a substance use clinic setting. The first model may be the most appealing to patients for several reasons. First, many patients dislike the rigidity common among many outpatient substance use programs, particularly methadone maintenance treatment programs. In addition, when integrated, the coordination of HIV care and substance use care is seamless and provider conflicts can be avoided. However, as Basu et al. [17••] point out, integration of HIV care and substance use treatment has the potential to give the physician too much power in the patient-provider dynamic. In addition, HIV primary care physicians may feel overwhelmed with the added responsibilities of serving as the patient's HIV physician and addiction physician. At this time few studies are available with sufficient data to evaluate the effectiveness of offering buprenorphine in an HIV primary care setting; however, this is an exciting area of active research.

Another form of integrated care is directly observed therapy (DOT). DOT or directly administered antiretroviral therapy (DAART) can be delivered either on its own or in the context of opiate replacement therapy, such as at a methadone clinic or when receiving buprenorphine. This method has the benefit of addressing adherence with medications in addition to simultaneously treating HIV and addiction. The results of a study by Lucas et al. [18] suggest that DAART based at methadone clinics has the “potential to provide substantial clinical benefit for HIV-infected injection drug users.” The experience by Smith-Rohrberg et al. [10] suggests that high use of medical services and use of case management services in addition to DAART improve virologic outcomes. This intervention has also been shown to be effective in a randomized controlled trial that included only patients with active substance use, wherein patients receiving modified DOT (vs standard of care) had a greater likelihood of virologic suppression [19].

Clinical Management of the Patient With HIV and Substance Use Problems

In addition to overcoming the social barriers to care through a trusting patient-provider relationship and integration of clinic services, the successful management of the HIV-infected patient with addiction requires the treatment of addiction and multiple comorbidities, such as bacterial infections, hepatitis, sexually transmitted diseases, and mental illness. All these factors should be considered when initiating (or re-initiating) antiretroviral therapy in a patient with addiction, although a history of substance use or presence of other comorbidities should not preclude an individual from receiving antiretrovirals.

Substance use treatments

In general, substance (including alcohol) use should be addressed at every clinic visit. Aside from illicit drug use, alcohol is a well-known risk factor for nonadherence in HIV-positive patients [20,21]. Substance use should be discussed without alienating the patient, ideally in the context of a trusting provider-patient relationship. The clinician should keep in mind that the overarching goal is to retain the patient in medical care [6•]. Although a compassionate, nonjudgmental approach is vital, the clinician must also set limits and challenge patients when relapse or continued use is suspected [6•,22]. Addiction is a chronic relapsing illness, and the recognition of this reality by the patient and the clinician helps set realistic goals toward recovery. Identifying relapse triggers with the patient can prevent relapses; if relapse should occur, use “the opportunity to learn from what happened and to change tactics to more effectively prevent future relapse” [6•].

Treatment options—Many treatment options are available for substance users. Pharmacologic interventions include methadone, buprenorphine, and buprenorphine/naloxone combination for opiate addiction [23], and disulfiram, acamprosate, and naltrexone for alcohol addiction. New drugs are on the horizon [24]. Similar effective pharmacologic interventions for cocaine and methamphetamine use are desperately needed, but not yet available. Twelve-step programs have well-known proven efficacy in helping some users achieve periods of abstinence. Inpatient (including long-term residential) or outpatient rehabilitation programs or addiction counseling are also useful tools. Determine the patient’s readiness for these options and choose what is most appropriate for the patient at the time.

Harm reduction—Although abstinence is ideal, achieving it is often difficult for those with this relapsing illness and an often-untreated comorbid mental illness. Harm-reduction measures, including needle exchange and overdose prevention, provide an avenue for the clinician to affirm any positive step taken by the patient and to integrate health-promoting alternatives into their care [25].

HIV therapy in patients with substance use

Adherence assessment—Initially, one must consider whether the patient meets criteria for treatment according to the most recent Department of Health and Human Services guidelines, including the new recommendation of considering therapy for any patient with a CD4 count of less than 350 cells/mm³ (class AII recommendation) [26]. Once the patient and provider have agreed that it is time to start HIV treatment, an adherence assessment should be completed. Poor adherence has been associated with factors including younger age, female gender, recent incarceration, depression, and provider inexperience [3,27].

It is controversial if substance use predicts noncompliance because several earlier studies indicate that injection drug use does not predict adherence [28,29]. However, active substance use has been associated with decreased adherence to HIV medications [30]. Those who are former substance users or who are receiving addiction therapy have been shown to have adherence that is comparable to patients who have never had substance use issues [21]. If adherence is a concern, offer adherence counseling and consider DOT (see “Integration of care”).

Selecting an antiretroviral regimen—Once the decision has been made to start antiretroviral therapy, the provider, in direct discussion with the patient, should select an appropriate regimen. A thorough medication history, including both HIV-related and non-HIV medications, should be elicited. Herbal remedies, supplements, and medication allergies should be reviewed. If the patient has received antiretrovirals in the past, reviewing specific treatment dates and side effects with the help of illustrations or samples of antiretrovirals is critical. All

genotype and phenotype analyses that may have been performed should be taken into account, because certain medications may be less effective due to resistant quasiespecies of HIV. The patient should be asked to evaluate the pill burden and side effects he or she can realistically tolerate. Patients with a history of substance use may experience more medication side effects than other patients [31].

In general, once-daily antiretroviral regimens are preferable for most patients, but may not be possible given restrictions from side effects or resistance. Examples of once-daily regimens with a relatively low pill burden would be a coformulated dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) (eg, tenofovir/emtricitabine or abacavir/lamivudine) in combination with either 1) a nonnucleoside reverse transcriptase inhibitor (eg, efavirenz) or 2) a once-daily protease inhibitor (PI) such as atazanavir boosted with ritonavir (300 mg/100 mg), fosamprenavir/ritonavir (1400 mg/100 mg), or lopinavir/ritonavir (800 mg/200 mg) [32]. Other nucleoside/nucleotide reverse transcriptase inhibitors (eg, didanosine and stavudine) can be given once daily, although they are not a recommended first-line therapy. Additional protease inhibitors can be given once a day, such as saquinavir/ritonavir (1600 mg/100 mg) or indinavir/ritonavir (1200 mg/400 mg) [33], but this dosing has not been approved by the US Food and Drug Administration, may result in increased side effects, and may have decreased efficacy, especially for treatment-experienced patients.

Whatever regimen is selected, potential drug interactions should be reviewed in detail before prescribing antiretrovirals, with particular attention to p450 interactions, including those with opiate replacement therapies and antidepressants (Table 1) [34,35,36]. In addition, other comorbidities such as liver disease, renal disease, and lipid abnormalities must be taken into account because such patients need to avoid certain antiretrovirals.

Addressing comorbidities

Certain infectious comorbidities are found more commonly in people who use illicit substances, especially injection drugs, and require special mention. These include bacterial infections (eg, systemic and skin and soft tissue infections), viral hepatitis, sexually transmitted diseases, and tuberculosis.

Bacterial infections—HIV-positive injection drug users have a higher rate of pyogenic bacterial infections than their HIV-negative counterparts, such as skin and soft tissue infections, pneumonia, and endocarditis [37]. Skin and soft tissue infections are common in this population and are usually directly related to drug injection. Infections are most often caused by commensal organisms, such as *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), and streptococcal species [38]. Providers should advise their patients that if they are going to inject drugs, they need to clean the skin thoroughly before each injection, use sterile syringes for each injection, dispose of syringes properly, rotate injection sites, and avoid intramuscular injection. The practice of “skin-popping”—injecting drugs under the skin or into a muscle—places the patient at risk for abscesses, including those due to the spore-forming clostridial species that cause tetanus and botulism [39]. Therefore, patients should be counseled to avoid this practice and advised to keep their tetanus immunization current.

In addition, community-acquired pneumonia is common in HIV-positive injection drug users and may be seen at higher CD4 counts. As with all HIV-infected patients, those with a history of substance use need to be vaccinated for *Streptococcus pneumoniae* and *Haemophilus influenzae* B. Lastly, infective endocarditis is more common in injection drug users who are HIV infected, as shown in 13.8 cases (in HIV-positive patients) versus 3.3 cases (in HIV-negative patients) per 1000 person years in a Baltimore study [40]. Clinicians should have a low threshold to investigate the diagnosis of endocarditis in HIV-positive injection drug users.

Hepatitis—Due to overlapping risk factors of injection drug use and high-risk sexual behaviors, substance users are at particularly high risk for viral hepatitis. In the United States and Western Europe, approximately 25% of patients with HIV also have hepatitis C virus (HCV). Among HIV-infected injection drug users in the West, the rate of HCV infection increases to 72% to 95% [41]. HIV/HCV co-infection alters the course of both viral infections. Multiple studies have shown that HIV-infected patients have faster progression of HCV-related liver disease and that they do not respond as well as HIV-uninfected patients to standard treatment for HCV infection. In addition, in patients receiving HAART, HCV co-infection is an independent factor for decreased adherence to antiretroviral therapy [42]. Due to the risk of nonadherence and the potential for adverse drug reactions (eg, hepatic or hematologic toxicities), careful selection of a HAART regimen is essential for HCV/HIV co-infected patients.

Chronic hepatitis B infection is also common in HIV-infected substance users because they are less likely to clear acute hepatitis B virus (HBV) than HIV-negative individuals. Several antiretrovirals (lamivudine, emtricitabine, and tenofovir) used to treat HIV are also active against HBV; therefore, it is crucial to know all patients' HBV status before initiating therapy to decrease the risk of developing HBV drug resistance and to minimize toxicity. Prevention is equally as important as these treatment considerations. Individuals who have chronic HBV or HCV infection should receive prevention counseling to reduce transmission and their contacts at risk should be evaluated. In addition, hepatitis A (HAV) and HBV vaccination rates are low among HIV-infected drug users and are recommended for those who do not have antibody evidence for immunity [43]. Postvaccination antibody measurement is recommended for HBV but not for HAV.

Sexually transmitted infections—The high rate of sexually transmitted infections (STIs) among HIV-infected substance users is related to the direct influence of drugs and alcohol on risk-taking behavior, and the exchange of sex for drugs or money. Prevention counseling regarding the importance of condom use should be a routine part of clinical care in all HIV-positive patients, and is especially relevant for HIV-infected substance users. The epidemics of HIV and other STIs are intertwined because multiple sexually transmitted diseases have shown to increase the rate of HIV transmission [44]. Testing for gonorrhea, *Chlamydia* spp, *Trichomonas* spp, syphilis should be available in the clinic and should be performed regularly for high-risk patients, particularly women, who may have asymptomatic gonorrhea and chlamydial infections. Herpes simplex virus (HSV) infection is also common in patients with HIV and may have a more severe or prolonged clinical presentation. In addition, HIV-infected women are at increased risk of cervical neoplasia due to sexual transmission of human papilloma virus infection and should have routine Pap smears.

Tuberculosis—Tuberculosis is another infectious disease that is prevalent in HIV-positive substance users. Overlapping social issues homelessness, poverty, and a history of incarceration increase the risk of tuberculosis among HIV-positive substance users, and providers should perform routine tuberculosis screening in this population. For both latent and active infection, expedited treatment and DOT are recommended. Providers should be aware that drug interactions between rifampin and methadone may precipitate opiate withdrawal and that antiretrovirals may require alternate dosing.

Mental illness—In addition to infectious comorbidities, HIV-positive patients with substance use problems have a high rate of psychiatric illness [45]. The relationship between mental illness and HIV is complex and bidirectional. Having psychiatric issues is a risk factor for HIV infection, partly because of high-risk behaviors, and HIV infection can contribute to a multitude of psychiatric conditions, either secondary to the virus itself or as a complication of treatments and disease progression [46]. Screening for mental illness in HIV-infected substance-

using patients is imperative, because the triple diagnosis of HIV, drug use, and mental illness is common and further increases likelihood of delayed HAART initiation [47]. Integration of care (using a biopsychosocial model) is especially valuable for this subset of patients to maximize the concurrent treatments of HIV, mental illness, and substance use therefore improve outcomes [45].

Chronic pain management—Significant overlap occurs between those patients chronic pain issues and those with drug dependence [48], and this is particularly true in HIV-positive patients. The challenge in this group of patients is to adequately manage pain without contributing to addiction. In a comprehensive review, Basu et al. [49] recommend a stepwise approach for managing acute and chronic pain, starting with nonopioid analgesics. An underlying etiology for the pain should be sought and goals of pain therapy explicitly outlined from the start. In addition, special attention should be given to potential drug interactions between pain medications and antiretrovirals.

Conclusions

Successful management of HIV infection in patients with substance use issues is complex and involves addressing the patient's social and medical needs. It requires a supportive patient-provider relationship and a comprehensive clinical support staff to engage and retain the patient in care. The integration of services, including substance use treatment, mental health, and HIV care may result in improved health outcomes. When selecting an antiretroviral regimen in this population, special attention to adherence, once-daily antiretroviral regimens, and potential drug-drug interactions is critical. Providers also need to be aware of the multiple comorbidities that may complicate the medical care of these patients, including bacterial infections, hepatitis, STIs, tuberculosis, mental illness, and chronic pain. HIV infection and drug addiction are chronic illnesses caused by overlapping epidemics and require a comprehensive multidisciplinary approach to therapy.

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Table 1

Potential drug interactions with antiretrovirals in substance users

Antiretroviral	Interacts with	Effect	Comment
Opiate replacement			
Zidovudine	Methadone	Increases zidovudine level	May cause side effects related to zidovudine
Stavudine	Methadone	Decreases stavudine level	No dose change recommended
Efavirenz	Methadone	Decreases methadone level	May cause opiate withdrawal
Efavirenz	Buprenorphine	Decreases buprenorphine level	Not associated with opiate withdrawal
Nevirapine	Methadone	Decreases methadone level	May cause opiate withdrawal
Nevirapine	Buprenorphine	Inadequate data	
Ampranavir, nelfinavir, lopinavir, darunavir, tipranavir, ritonavir	Methadone	Decreases methadone level	Variable patient response
Atazanavir, saquinavir, ritonavir, indinavir	Buprenorphine	May increase buprenorphine levels	Need further data
Antidepressants/antipsychotics			
Protease inhibitors	TCA's	May increase TCA level	Close concentration monitoring
Lopinavir/ritonavir	Bupropion	Decreases bupropion level	May need increased bupropion dose
Ritonavir	Fluoxetine	May increase fluoxetine level	Monitor for fluoxetine side effects
Protease inhibitors	SSRIs	Some may increase, others will decrease SSRI level	Guide SSRI dose by clinical response
Efavirenz, nevirapine	Mirtazapine	Increased level of mirtazapine	Monitor
Protease inhibitors	Mirtazapine	Potential interaction	Close monitoring
Ritonavir	Haloperidol, risperidol	May increase level of antipsychotic	Monitor

SSRI—selective serotonin reuptake inhibitor; TCA—tricyclic antidepressant.

(Data from McCance-Katz et al. [34,35] and University of Liverpool [36].)