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Substance abuse, adherence with antiretroviral therapy, and clinical outcomes among HIV-infected individuals

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Abstract

Substance abuse and addiction are highly prevalent in HIV-infected individuals. Substance abuse is an important comorbidity that affects the delivery and outcomes of HIV medical management. In this paper I will review data examining the associations between substance abuse and HIV treatment and potential strategies to improve outcomes in this population that warrant further investigation. Current - but not past - substance abuse adversely affects engagement in care, acceptance of antiretroviral therapy, adherence with therapy, and long-term persistence in care. Substance abuse treatment appears to facilitate engagement in HIV care, and access to evidence-based treatment for substance abuse is central to addressing the HIV epidemic. Strategies that show promise for HIV-infected substance abusers include integrated treatment models, directly observed therapy, and incentive-based interventions.

Introduction

Injection drug use continues to be an important mode of HIV transmission worldwide and is the primary mode of transmission in Eastern Europe, Russia, and areas of Southeast Asia (Mathers et al., 2008). Substance abuse and addiction are highly prevalent in HIV-infected populations, including those where transmission of HIV is primarily sexual. Substance abuse is an important comorbidity that affects the delivery and outcomes of HIV medical management. In this paper, I will review the interaction between substance abuse and HIV treatment outcomes and discuss strategic approaches to treating this population.

Barriers to care in HIV-infected substance abusers

Substance abuse is a well documented obstacle to care among HIV-infected individuals that exerts deleterious effects at multiple levels. The neglect of social, occupational, and personal obligations is a central component of the diagnostic and statistical manual of mental disorders, fourth edition (DSM IV) definition of substance addiction (American Psychiatric Association, 1994). The addict's outlook is characteristically myopic, focused on slaking the short-term demands of addiction with increasing neglect of longer-term interests, including maintaining health. Substance abuse and addiction commonly co-occur with other factors that pose added barriers to optimal HIV treatment (box). Psychiatric comorbidity, including depression, is common among HIV-infected substance abusers (Treisman et al., 2001) and

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has been shown to be independently associated with HIV disease progression (Golub et al., 2003; Ickovics et al., 2001).

Substance abusers commonly confront stigma in their interactions with medical providers, and similarly, they are often mistrustful of the medical establishment. In a survey of primary care clinicians, 55% of those surveyed expressed negative attitudes about treating drug users while only 28% described themselves as being comfortable having drug users in their practices (Gerbert et al., 1991). Altice and colleagues found considerable mistrust of the medical establishment in a survey of 205 incarcerated drug users. 47% and 53% of those surveyed expressed agreements with the statements “HIV was made in a laboratory” and “there is a cure for AIDS, but the government is keeping it from me”, respectively (Altice et al., 2001). Patient-provider trust and communication has been found to be an important factor in healthcare disparities (Cooper, 2009).

Stages in the HIV care continuum: substance abuse-related barriers

Engagement in care and successful treatment of HIV entails progression through several steps (Figure). Movement through these steps is not unidirectional. For example, individuals who have entered care and initiated antiretroviral therapy may fail to persist in care and experience treatment lapses that result in HIV disease progression. Consequently, it is useful to envision a continuum of care for HIV-infected individuals, spanning the range from being unaware of one's HIV status to being fully engaged in HIV medical care (Cheever, 2007). A substantial body of literature shows that substance abuse is a barrier at each step in the treatment engagement process, and facilitates treatment non-persistence.

Step 1: Engagement in HIV care

HIV counseling and testing is the necessary prerequisite for engagement in care. It has been estimated that up to one quarter of HIV-infected individuals in the United States is unaware of their status (Branson et al., 2006). Consequently, the Centers for Disease Control and Prevention have taken up a campaign to promote routine HIV testing in clinical care (Bartlett et al., 2008). Soon after the advent of combination antiretroviral therapy, it was reported that this life-saving treatment was underutilized by HIV-infected drug users compared to other HIV risk groups, and that a major mediator was low levels of engagement in longitudinal treatment (Celentano et al., 1998; Celentano et al., 2001; Strathee et al., 1998).

Suboptimal engagement in care remains a major issue well into the era of highly active antiretroviral treatment. For example, a recent report examined engagement in care among HIV-infected individuals in South Carolina (Olatosi et al., 2009). Because South Carolina has mandatory name-based reporting of HIV serologic tests, CD4 cell counts and HIV RNA levels, researchers were able to assess patterns of engagement in care among 13,042 individuals who had been diagnosed with HIV and were alive in the 3 year period from 2004 to 2006. Individuals were considered to be in care if they had at least one CD4 cell count or HIV RNA measurement in each of the three years, in transitional care if they had laboratory measurements in at least one but not all three of years, and out-of-care if they had no laboratory measurements in the three-year period. The researchers found that only 35% of individuals were in care, while 25% were in transitional care and 40% were out-of-care. Compared to being in care the odds of being in transitional care and being out-of-care were increased by 29% and 65%, respectively, in injection drug users.

Step 2: Initiation of Antiretroviral Therapy

Other studies have suggested that even after substance abusers attend an HIV clinic they have poorer access to antiretroviral therapy compared to other exposure groups. A study

conducted at the Johns Hopkins HIV clinic (Lucas et al., 2001), which included 764 patients who participated in confidential interviews, found that the rate of antiretroviral therapy use was similar in individuals with no history of injection drug use and of those with a history of injection drug use who had been abstinent for more than six months. In contrast, the use of antiretroviral therapy was dramatically lower in individuals who reported active injection drug use in the previous month. Similar findings have been reported for alcohol abuse (Chander et al., 2006). It is likely that both patient factors, such as more missed clinic visits and social instability (Lucas et al., 1999), and clinician factors, such as reluctance to prescribe antiretroviral therapy to active drug users, play a role in delayed access to antiretroviral therapy in this group. However, a French study found that active drug users were less likely to be prescribed antiretroviral therapy irrespective of whether or not their medical provider perceived them as actively using drugs (Carrieri et al., 1999).

Step 3: Adherence to Antiretroviral Therapy

Once antiretroviral therapy is accepted by patients and prescribed by their clinicians, high levels of medication adherence are required indefinitely to achieve durable suppression of viral load (Paterson et al., 2000). Active drug use has been shown to reduce antiretroviral medication adherence. One group measured antiretroviral adherence with electronic pill-bottle monitors in 77 individuals with a history of drug use (Arnsten et al., 2002). The researchers found that electronically measured adherence was 68% in those who were not using cocaine compared to just 27% among participants who were using cocaine. Corroborating this dramatic difference in measured adherence, was that viral load suppression was achieved by 46% who were not using cocaine compared to just 13% of active users. Another study conducted in British Columbia, assessed differences in viral load suppression in HIV-infected injection drug users compared to other transmission risk groups. The investigators found that HIV-infected injection drug users were less likely to achieve viral suppression than non-drug users, but that this difference appeared to be completely explained by differences in medication refill adherence (Wood et al., 2003).

Step 4: Long-Term Retention to Care

After appropriate treatment is begun, management of HIV infection is a lifelong endeavor, with lapses in follow-up and treatment interruptions being common. In a cohort of HIV-infected injection drug users followed in Baltimore, 78% of participants had at least one non-structured treatment interruptions over a median follow-up of 4.5 years (Kavasery et al., 2009). Giordano and colleagues examined the number of quarters that patients attended the HIV clinic visits following antiretroviral therapy initiation in a sample of 2619 HIV-infected men in the Veterans Administration who survived at least 1 year after starting antiretroviral therapy (Giordano et al., 2007). Compared to attending the clinic in all four quarters, the relative risk of mortality (after the first year) was increased by 42%, 67%, and 95% in those who attended visits in 3, 2, or 1 quarter, respectively. In this study, inconsistent HIV clinic follow-up was strongly associated with injection drug use.

Treatment outcomes in HIV-infected drug users

Most observational studies suggest that clinical outcomes among HIV-infected individuals with a history of injection drug use are poorer than in other transmission risk groups. For example, Johns Hopkins researchers found that the rate of new AIDS defining conditions was similar between drug users and non-drug users in 1996, prior to the availability of combination antiretroviral therapy (Moore et al., 2004). In calendar years following 1996 the rate of AIDS defining conditions declined in both injection drug users and non-drug users. However, the decline was smaller in the former than the latter group. Consequently, by 2002 the relative risk of HIV disease progression was approximately twice as high in HIV-

infected drug users as in their non-drug-using counterparts. A longitudinal study in the same cohort found that, compared to non drug users, the risk for new AIDS defining conditions was increased in injection drug users only during semesters when they reported active drug use, not during semesters when they reported abstinence from drug use (Lucas et al., 2006).

Recently studies have highlighted the particularly deleterious effect of crack cocaine use among HIV-infected persons. Studies among HIV-infected women in the US (Cook et al., 2008) and HIV-infected individuals in French Guiana (Nacher et al., 2009) each found that crack cocaine use more than tripled the risk of HIV-disease progression. Another group (Baum et al., 2009) found crack cocaine use to be associated with more rapid CD4 cell decline, including a subset of individuals who were not receiving antiretroviral therapy – suggesting an independent effect of crack cocaine on HIV disease progression. Although injection drug use is generally associated with poorer HIV clinical outcomes compared to other transmission groups (Kitahata et al., 2009; Egger et al., 2002), this is not universally the case. A cohort study in British Columbia recently reported that, after adjustment for adherence, all cause and non-accidental mortality rates were similar among HIV-infected injected drug users and non-users – a finding perhaps attributable to reduced financial barriers to treatment and optimized service delivery for injection drug users in this region (Wood et al., 2008).

Strategies for improving treatment outcomes in HIV-infected patients

Several strategies have shown promise for improving engagement in treatment and treatment outcomes among HIV infected substance abusers.

Substance abuse treatment

The provision of effective treatments for substance abuse appears to facilitate engagement in HIV treatment and improved treatment outcomes in HIV-infected substance abusers. In an observational cohort study, Wood and colleagues found that the time to initiation of antiretroviral therapy was significantly faster among drug users who were receiving methadone maintenance treatment at baseline compared to drug users who were not participating in methadone maintenance (Wood et al., 2005). Several other observational studies have linked substance abuse treatment with use of antiretroviral therapy, adherence, viral suppression, and CD4 cell changes (Sambamoorthi et al., 2000; Kapadia et al., 2008; Palepu et al., 2006; Moatti et al., 2000).

The World Health Organization has endorsed the provision of opioid substitution therapy (with either methadone or buprenorphine) as part of a comprehensive package that countries should provide for injection drug users (World Health Organization United Nations Office on Drugs and Crime Joint United Nations Programme on HIV/AIDS, 2009). However, the availability of evidence-based treatment for substance abuse is woefully inadequate worldwide. For example, a recent review reported that opioid substitution therapy is unavailable in 66 countries, which are home to an estimated 34% of the global injection drug using population (Mathers et al., 2010). Moreover, even in countries where evidence-based services for injection drug users are available, supply is virtually always short of demand. In the U.S., it is estimated that methadone treatment slots are only available for less than 25% of those who need treatment, a fact that was employed with success to lobby for legislation passed in 2000 that permits physicians to prescribe schedule III medications (buprenorphine and buprenorphine/naloxone) for the purpose of treating opioid-dependent individuals (Fiellin and O'Connor, 2002).

Integrated models of HIV/substance abuse treatment

Integrated care models have resonance in the medical management of HIV because of the high prevalence of substance abuse in this population. Integrated treatment strategies have been proposed as a way to deliver care for comorbid conditions more efficiently and effectively. One randomized trial of 51 methadone maintenance patients who had at least one untreated medical condition, found that 72% of subjects assigned to receive on-site medical care in the methadone clinic attended at least two clinic visits compared to just 6% who were assigned to receive treatment at a nearby medical clinic (Umbricht-Schneider et al., 1994). Other studies have also found benefits to providing integrated substance abuse and medical treatment in selected populations (Willenbring and Olson, 1999; Weisner et al., 2001). Recently, we reported that on-site treatment of opioid-dependent participants with buprenorphine/naloxone in an HIV clinic led to improved substance abuse treatment outcomes compared to the traditional model of referring subjects to an opioid treatment program (Lucas et al., 2010). Integrated HIV and substance abuse treatment is an idea that makes sense and has long been advocated. However, historical, institutional, and reimbursement frameworks often impede the integration of medical and psychiatric services. Innovation on the policy level is needed to create incentives within the system that foster integrated care.

Directly observed therapy

The success of directly observed therapy in the treatment of tuberculosis (Chaulk and Kazandjian, 1998) sparked interest in applying this strategy to HIV infection (Lucas et al., 2002). To date, several models of directly observed therapy for HIV treatment have been assessed in randomized trials, with mixed results. Two studies recruited largely antiretroviral therapy-naïve individuals with low numbers of injection drug users (Gross et al., 2009; Wohl et al., 2006). Neither of these studies found that directly observed therapy increased rates of viral suppression compared to self-administered therapy. However, two other studies, which targeted predominantly active drug and alcohol abusers with a history of adherence problems, found evidence that directly observed therapy was efficacious compared to self-administered therapy (Altice et al., 2007; Macalino et al., 2007). Recently, a meta-analysis of randomized clinical trials of directly observed therapy found no evidence overall that directly observed therapy led to improved rates of viral load suppression compared to self-administered therapy (Ford et al., 2009). However, in subset analyses, the authors found that among studies enrolling drug users, homeless individuals, or populations at high risk for non-adherence, directly observed therapy was associated with a 31% increase in the relative rate of viral suppression (95% CI 0% to 71%). It has been proposed that directly observed therapy is likely to be of marginal benefit in unselected patient groups, but may have a role in selected populations of active substance abusers or individuals with insurmountable barriers to medication adherence (Flanigan and Mitty, 2006; Bangsberg et al., 2001). However, to be embraced in clinical care, further research is needed to define the efficacy of directly observed therapy in such high-risk groups, and to evaluate the cost-effectiveness of directly observed therapy relative to other interventions that might be used in these populations.

Incentives

Contingency management is the use of incentives to reinforce desired behaviors. In clinical trials, contingency management has frequently been shown to be effective in reducing or stopping substance abuse, particularly stimulant abuse (Stitzer and Petry, 2006). In recent years, incentive-based strategies have garnered attention for potential use in mainstream medical settings to address behaviorally mediated health problems (Loewenstein et al., 2007) including, weight loss (Volpp et al., 2008), smoking cessation (Volpp et al., 2009b), and adherence with medications. Several small clinical trials have assessed the efficacy of

incentive-based interventions for improving adherence to antiretroviral therapy (Sorensen et al., 2007;Javanbakht et al., 2006;Rosen et al., 2007;Rigsby et al., 2000). Three of these studies found that incentives for electronically-measured adherence produced statistically significant improvements in adherence during the intervention period (Sorensen et al., 2007;Rosen et al., 2007;Rigsby et al., 2000), and two studies suggested that incentive-based interventions lead to improved virologic responses (Javanbakht et al., 2006;Rosen et al., 2007). In an African study, small incentives were found to approximately double the rate at which individuals returned to learn the results of their HIV tests (Thornton, 2008).

While the use of incentives to promote engagement in HIV care and adherence with antiretroviral therapy deserves additional study, incentive-based approaches face several challenges (Volpp et al., 2009a;Schmidt et al., 2010;Marteau et al., 2009). First, some incentive-based approaches have involved large financial rewards (e.g., up to \$1200 over 12 weeks), and it is not clear if allocation of healthcare resources in this way would be feasible or advisable. Second, it may be unfair to provide rewards for a subset of individuals (e.g., those with poor adherence) while not offering incentives to others (e.g., adherent persons). However, it is costly and inefficient to reward those who would have been adherent without incentives. Finally, existing studies of contingency management approaches for antiretroviral therapy have found that adherence wanes rapidly (to levels in the control groups) when incentives were discontinued (Rigsby et al., 2000;Rosen et al., 2007;Sorensen et al., 2007), raising additional questions about the sustainability of incentive-based approaches.

Conclusions

Substance abuse is a common comorbidity in HIV-infected individuals. Current - but not past - substance abuse adversely affects engagement in care, acceptance of antiretroviral therapy, adherence with therapy, and long-term persistence in care. Substance abuse treatment appears to facilitate engagement in HIV care, and access to evidence-based treatments for substance abuse is central to addressing the HIV epidemic. However, the availability of substance abuse treatment, while variable, is inadequate in almost all settings. Continued efforts to prioritize and fund these services are needed. Integrated care models, in which coordinated substance abuse treatment and HIV care is provided in a single location, hold promise and warrant additional research. Directly observed HIV treatment may have role in selected groups of individuals with advanced HIV disease and major barriers to adherence. Incentive-based approaches have shown promise in some disease models, but face implementation and sustainability challenges.

Box1

Box. Common co-occurring conditions in HIV-infected substance abusers that adversely affect adherence and treatment outcomes

• Poverty	• Malnutrition
• Unstable housing	• Incarceration
• Depression / other psychiatric disorders	• Limited job skills / work history
• Viral hepatitis	• Sexually transmitted diseases
• Tuberculosis	• Bacterial pneumonia
• Eroded social support network	• Skin and bloodstream infections

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Figure 1. Conceptual model showing progression along continuum of engagement in HIV care. ART, antiretroviral therapy.