INTRODUCTION

Buprenorphine and HIV Primary Care: New Opportunities for Integrated Treatment

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Drug abuse and infection with human immunodeficiency virus (HIV) are associated with high rates of morbidity and mortality, but, because of medical, social, and legal factors, opiate addiction/dependence is a major obstacle to successful treatment of disease—for example, treatment of acquired immunodeficiency syndrome (AIDS) with highly active antiretroviral therapy. In an effort to improve the opportunity for treatment of drug abuse and HIV infection, the Forum for Collaborative HIV Research, in collaboration with the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, the Centers for Disease Control and Prevention, and other agencies, presented a workshop entitled “Buprenorphine in the Primary HIV Care Setting.” Participants reviewed and discussed current issues, such as the introduction of and sources for the provision of buprenorphine in HIV primary care settings and strategies for integrating treatment of HIV-infected drug abusers, all of which are covered in this supplement.

Abuse of and dependence on opiates represents a worldwide problem associated with significant morbidity and mortality. According to the World Health Organization, almost 200 million people use an illicit drug daily [1]; an estimated 13 million people abused opiate drugs in 1999–2001 [2]. The prevalence of heroin use is greater in developed countries; 2% of youth in western Europe, Canada, and the United States have tried heroin [2]. According to the 2004 National Survey on Drug Use and Health, 110 million Americans ≥12 years of age (46% of all Americans) used at least 1 illicit drug in their lifetime [3]. Morbidity associated with opiate abuse includes the risk of contracting HIV and hepatitis C virus infections as a result of unsafe injection practices and high-risk sexual practices. The worldwide HIV infection pandemic continues at a rapid pace. Of the 40 million people estimated to be infected with HIV, 5 million were infected during 2003. In regions of the world where the infection is spreading the fastest, injection drug users and their sex partners account for most of the new infections [1]. It is estimated that 1 million people infected with HIV are living in the United States. The US Centers for Disease Control and Prevention estimates that 36% of AIDS cases in the United States are due to injection drug use or to sexual activity with an injection drug user. Of the 42,514 new cases of AIDS reported in 2004, 11,072 (26%) were associated with injection drug use.

Both drug abuse and HIV infection are associated with serious medical and health consequences, and treatments are still evolving. AIDS is currently treated with a combination regimen known as HAART. The profound suppression of HIV replication is associated with significant benefit, as reflected by reduced clinical progression and death and by improved quality of life. Because of a variety of medical, social, and legal factors, however, opiate addiction/dependence is a major obstacle to the receipt and success of HIV/AIDS treatment with HAART. Historically, the worlds of HIV/AIDS treatment and addiction treatment have not interacted or collaborated, so the infrastructure is not in place to allow for a smooth interaction. In addition, although pharmacotherapeutic agents such as methadone or the newly approved buprenorphine are available for treatment of opioid addiction, the management of combined HIV infection and opiate addiction/dependence is fraught with problems, because of conflicting drug interactions and other issues.

With these facts in mind, the members of the Forum for Collaborative HIV Research, with special support from the Health Resources and Services Administration and in collaboration with the Substance Abuse and Mental Health Services
Administration, the National Institute on Drug Abuse, the Centers for Disease Control and Prevention, and other agencies, presented a workshop entitled “Buprenorphine in the Primary HIV Care Setting” [4]. This workshop brought together experts from government agencies, the HIV and drug addiction treatment and patient communities, and industry, as well as academic researchers. The participants reviewed and discussed the opportunities resulting from the introduction of buprenorphine into the HIV primary care setting. They recommended strategies for treatment integration, examined policy issues and funding mechanisms that would enable provision of care, and developed a health services research agenda to better inform policy regarding the use of buprenorphine in the treatment of drug abuse and addiction in patients with HIV infection. To present updates on progress in these areas and to provide an opportunity to expand discussion beyond the issues presented in the 2004 workshop, the Forum for Collaborative HIV Research collaborated with the National Institute on Drug Abuse to publish this supplement to Clinical Infectious Diseases.

The supplement begins with a review by Fiellin et al. [5] of the neurobiological basis of opioid dependence, the rationale for methadone and buprenorphine treatments, and issues in prescribing these medications to patients with HIV infection. They point out that opioid dependence is a chronic and relapsing medical disorder with a well-established neurobiological basis. Opioid agonists, such as methadone and buprenorphine, stabilize opioid receptors and the intracellular processes that lead to opioid withdrawal and craving. Both agents have proved effective for the treatment of opioid dependence and could contribute to a decreased risk of transmission of HIV infection. In addition, a buprenorphine/naloxone combination appears to decrease the potential for abuse or diversion, compared with methadone. Largely because of these breakthroughs—that is, because of the availability of an effective buprenorphine/naloxone combination with a decreased potential for abuse or diversion (sold without prescription for abuse)—recent legislation now affords an unprecedented opportunity for general practitioners to offer opioid agonist treatment through their offices. Altice et al. [6] discuss the potential role of buprenorphine in the treatment of opioid dependence among HIV-infected individuals and in the prevention of HIV infection. Specifically, they discuss the emerging role of buprenorphine in (1) improving HIV treatment outcomes for HIV-infected patients, (2) achieving primary and secondary prevention, and (3) improving outcomes of HIV infection through engagement in care and access to antiretroviral therapy [7, 8] and to preventative therapies for opportunistic infections. The authors also discuss the potential benefits and pitfalls of integrating buprenorphine into HIV clinical care settings.

Reviewing the pharmacokinetic interactions between buprenorphine and antiretroviral drugs, Bruce et al. [9] state that the clinical approach to managing opioid addiction by pharmacotherapeutic means in a patient with HIV infection often dictates that the substance abuse problem be addressed first to successfully introduce long-term antiretroviral therapy. They caution that the introduction of HAART should not initiate adverse effects that would complicate the assessment of withdrawal or buprenorphine toxicity. According to Bruce et al., the optimal approach to studying antiretroviral pharmacokinetics and drug interactions remains a point of controversy, and they suggest that pharmacokinetic studies of seronegative individuals provide valuable data to guide drug development and dosage and interval selection. Furthermore, clinicians should be alert for and ready to manage such interactions. Bruce et al. recommend that researchers conduct additional pharmacokinetic studies of buprenorphine and antiretrovirals in patients who take multiple medications or who have common comorbidities (including hepatic and renal dysfunction) and then determine the effect of these interactions on clinical outcomes in this challenging patient population.

Regarding drug-drug interactions, McCance-Katz et al. [10, 11] report that, according to their recent studies of interactions between buprenorphine and antiretrovirals (the nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine and the protease inhibitors nelfinavir, ritonavir, and lopinavir/ritonavir), efavirenz produces a significant decrease in buprenorphine levels and delavirdine significantly increases buprenorphine levels. Clinically significant consequences of the pharmacokinetic interactions were not observed in association with efavirenz or delavirdine, however. Buprenorphine had no significant effect on the pharmacokinetics of antiretroviral therapies. The authors conclude that buprenorphine might be preferable to methadone for the treatment of opioid-dependent patients with HIV disease requiring efavirenz or delavirdine. There were no significant interactions between buprenorphine and the protease inhibitors nelfinavir or lopinavir/ritonavir. Ritonavir inhibited metabolism of buprenorphine, but buprenorphine did not alter the pharmacokinetics of ritonavir. Buprenorphine also did not alter the pharmacokinetics of any of the protease inhibitors. Similarly, buprenorphine did not alter the pharmacodynamics or the levels of the protease inhibitors tested. Data from these studies suggest that buprenorphine could be administered concomitantly with nelfinavir, ritonavir, or lopinavir/ritonavir to patients with HIV disease and opioid dependence, without concern for opiate withdrawal or toxicity or for adverse effects on concentrations or associated toxicities of HIV medication.

Sullivan et al. [12] point out that, in the United States, integrating HIV infection and substance abuse care optimizes outcomes for patients with both disorders. Buprenorphine provides the opportunity to integrate the treatment of HIV infection and substance abuse in one clinical setting,
yet little information exists on the models of care that will most successfully facilitate this integration. They review 4 recently implemented models for combining buprenorphine treatment with HIV primary care: (1) an on-site addiction/HIV specialist treatment model, (2) a primary care HIV physician model, (3) a nonphysician health professional model, and (4) a community outreach model. In a second article, Sullivan et al. [13] report on a 12-week pilot study investigating the feasibility and efficacy of integrating buprenorphine, along with 2 levels of counseling (brief physician management or physician management combined with drug counseling and adherence management), into HIV clinical care. The preliminary data from this trial indicate that integration is feasible, with patients experiencing good treatment retention and reductions in opioid use.

Schackman et al. [14] describe the policy and financing challenges faced by health care providers seeking to integrate buprenorphine into HIV primary care. They point out that treatments for substance abuse and HIV care historically have come from different providers, often in separate locations, and have been reimbursed through separate funding streams. Regulatory challenges include licensing and training restrictions imposed by the Drug Abuse Treatment Act of 2000 and by confidentiality regulations for records of alcohol and other drug treatment (42 Code of Federal Regulations part 2). Potential responses include the establishment of locally developed training programs and electronic medical records. Addressing the complexity of funding sources for integrated care will require administrative support, up-front investments, and federal and state leadership. A policy and financing research agenda should address gaps in evidence for the rationales behind regulatory restrictions and should include cost-effectiveness studies that quantify the “value for money” associated with investments in integrated care to improve health outcomes for HIV-infected patients with opioid dependence.

Finally, Carriere et al. [15] discuss the status of buprenorphine use in international settings. They note that the confluence of the heroin injection and HIV epidemics in many countries has increased the call for expanded access to effective treatments for both conditions. The link between injection drug use and the HIV epidemic has been particularly strong in Russia, states of the former Soviet Union, and selected areas in Asia, where opioid agonist–based maintenance therapy has generally been unavailable or has been available only in very limited settings. Buprenorphine and methadone are now listed on the World Health Organization’s Model Essential Drugs List, and each has a distinct role in expanding access to treatment for opioid dependence. France has the most extensive experience of buprenorphine treatment for opioid dependence, with ~90,000 patients receiving buprenorphine, compared with 10,000 patients receiving methadone. After buprenorphine was approved in France in 1996, the number of deaths due to overdose decreased dramatically, and buprenorphine treatment has been associated with improved access to medical care (including adherence to antiretroviral therapy). Buprenorphine diversion, which appears to be associated with several factors (including inadequate dosing, social vulnerability, and inadequate patient monitoring), may be reduced by expanding treatment options to include the formulation containing buprenorphine and naloxone (intended to discourage administration of buprenorphine by injection) as well as by including methadone treatment, if it is not already available. The need to strike a balance between maximizing treatment availability and minimizing diversion should not be allowed to compromise treatment flexibility. The growing experience with buprenorphine in many other developed countries, including the United States, Australia, Germany, and Italy, may help to delineate a wider range of treatment models and practices for the use of buprenorphine. Expanding the availability of buprenorphine and methadone is one potential approach to reducing the spread of HIV among injection drug users and to engaging those infected with HIV in medical care.

In summary, data presented at the workshop suggest that the most effective way of integrating the use of buprenorphine for the treatment of opioid dependence with the use of antiretroviral therapy for HIV infection is to bridge 2 medical fields—addiction medicine and infectious diseases—and then develop supportive policies and address research gaps. The recommendations made at the workshop are summarized in the final article of this supplement [4].

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