Buprenorphine: Its Role in Preventing HIV Transmission and Improving the Care of HIV-Infected Patients with Opioid Dependence

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In the United States, ~25% of the 40,000 new human immunodeficiency virus (HIV) infections each year are secondary to injection drug use. Worldwide, there are an estimated 12.6 million injection drug users, and 10% of HIV infections (420,000 infections in 2003) are associated with this practice. Buprenorphine is a new medication used to treat opioid dependence that shows promise for reducing the rate of HIV transmission and improving the care of opioid-dependent patients with HIV infection. Although buprenorphine faces fewer clinical and regulatory barriers than does methadone, the optimal strategy for integration of office-based treatment of opioid dependence and HIV disease is an area of ongoing research. This review addresses the introduction of buprenorphine, in terms of public health, policy, and clinical implications for HIV-infected patients and for HIV care providers.

INJECTION DRUG USE IS A MAJOR AND INCREASING MECHANISM FOR HIV TRANSMISSION

Injection drug use is a significant mode of spread of HIV infection internationally [2–4]. In the United States, ~25% of the 40,000 new HIV infections each year are secondary to injection drug use [5]. Worldwide, it is estimated that there are 12.6 million injection drug users and that 10% of HIV infections are associated with injection drug use. Therefore, injection drug use directly accounted for ~420,000 new HIV infections in 2003 [6]. In addition to the direct transmission of HIV among injection drug users, injection drug use–related HIV transmission occurs through sexual contact between injection drug users, commercial sex workers, and the general population.

Countries in Central, South, and Southeast Asia and Eastern Europe are reporting HIV seroprevalence rates of 80%–90% among injection drug users [7–9]. Injection drug use is responsible for 50%–75% of cases of HIV infection in countries in Southeast Asia [10]. A recent study conducted in the St. Petersburg region of Russia revealed that from 1997 to 2001, HIV prevalence increased from 0% to 12% overall and to 33% among drug-dependent patients. It is estimated that within 5 years, 5 million Russians may be infected with HIV, with injection drug use being the major risk factor [11].

Although the link between injection drug use and HIV transmission has long been recognized in developed countries, many new cases of injection drug use–related HIV infection are occurring in developing countries. In Eastern Africa, there is emerging evidence of the significant link between injection drug use and HIV infection. The estimated prevalence of HIV infection and/or AIDS among injection drug users in Kenya is between 68% and 88%, and the areas most affected by injection drug use are the large city of Nairobi and the Coast Province towns of Mombasa, Malindi, and Lamu. Of a cohort of injection drug users in Mombasa, the majority of them were young, with 90% of them being 17–40 years old. Approximately 65% of these individuals were infected with hepatitis C virus, and 50% were positive for HIV antibody [12].

OPIOID AGONIST TREATMENT TO DECREASE HIV TRANSMISSION IN INJECTION DRUG USERS

Since the introduction of methadone into the medical treatment system in the 1960s and the recognition of the emergence of the HIV pandemic in the 1980s, research has consistently demonstrated the role of methadone in decreasing the frequency of opioid use, opioid injection, and needle-sharing events among opioid-dependent injectors. In addition, this treatment has
been associated with a decrease in the number of reports of multiple sex partners and the practice of exchanging sex for drugs or money, but appears to have a decreased effect on condom use [13, 14]. Perhaps most convincingly, research demonstrates that patients who receive methadone have lower incidence and prevalence rates of HIV infection, compared with those of injection drug users not receiving this treatment [15–17].

**BUPRENORPHINE AS A NEW TREATMENT OPTION FOR OPIOID DEPENDENT INJECTION HEROIN USERS**

Buprenorphine hydrochloride is a partial, rather than full, agonist at the mu opioid receptor with demonstrated efficacy in the treatment of opioid dependence. It has become more widely available internationally during the past 10 years and is approved for treatment of opioid dependence in 37 countries worldwide. Buprenorphine blocks exogenous opioid administration and suppresses heroin self-administration [18]. Buprenorphine treatment is more effective than placebo in decreasing illicit opioid use [19] and has demonstrated outcomes generally equivalent to those achieved by 60–100 mg of methadone [20], the low end of what is considered to be an effective dose of methadone for many patients. Recently, a panel of experts of substance abuse and HIV care produced a written proposal to the World Health Organization (WHO) for buprenorphine to be included in the WHO’s list of essential medicines [1]. Buprenorphine can be provided as a single medication (marketed as Subutex; Reckitt Benckiser) or in a 4:1 combination with naloxone (marketed as Suboxone in the United States, Australia, and New Zealand [pending]). In the United States, physicians can receive a special registration to prescribe buprenorphine by becoming certified in addiction medicine or by completing 8 h of training in the treatment of opioid dependence [21, 22].

The unique pharmacology of buprenorphine as a partial opioid agonist results in a pharmacological profile that leads to fewer withdrawal symptoms and a decreased potential for abuse, respiratory depression, or overdose [23–25]. Buprenorphine treatment is generally provided as a sublingual tablet in doses ranging from 8 to 24 mg per day [26]. Buprenorphine has poor gastrointestinal absorption but fair sublingual absorption [27] and can be provided daily or 3 times per week, according to established dosing protocols.

Four unique properties of buprenorphine’s pharmacology increase the likelihood that it will have a distinct role in the provision of opioid agonist treatment worldwide. First, buprenorphine exhibits a ceiling effect in its opioid receptor activity and thereby exhibits a greater margin of safety than full agonists, such as methadone. Second, buprenorphine has less intrinsic activity at the opioid receptor and has less (but not absent) receptor activation, compared with that of full opioid agonists that are used for treatment (e.g., methadone) or abused (e.g., heroin). This characteristic may lead to decreased diversion, although diversion of unobserved maintenance, via the injection route, has been described in regions where the medication is provided alone instead of in combination with naloxone. Third, buprenorphine can be used 3 times per week under direct observation, allowing for supervised dispensing and decreased risk for diversion [28, 29]. Finally, with respect to the care of patients receiving antiretroviral therapy, the literature indicates that there are fewer documented interactions between buprenorphine and HIV antiretroviral therapies than there are documented interactions between methadone and HIV medications [30–34].

**BUPRENORPHINE’S ROLE IN PREVENTING HIV RISK BEHAVIOR AND HIV TRANSMISSION**

The role of buprenorphine in preventing HIV risk behavior and HIV transmission has not been as systematically or rigorously evaluated as has the role of methadone. At least 13 randomized trials and observational studies have documented buprenorphine’s ability to decrease opioid use in injection drug users and in persons who administer opioids through other routes (e.g., intranasally or orally) [19, 20, 35–46].

Few of these studies, however, have reported changes in HIV risk behavior, such as changes in the frequency of injection drug use, sharing of injecting equipment, sexual behavior, overall HIV risk, or rates of HIV seroconversion. One randomized trial [47] and 1 observational study [48] have reported a decrease in the frequency of injecting, and one of these studies reported a decrease in overall HIV risk behaviors [47]. Two observational studies [49, 50] have demonstrated low rates (0.4%–0.8% over 2 years) of HIV seroconversion in patients receiving buprenorphine. A recently published randomized trial [51] revealed a significant decrease in HIV risk behavior from baseline to the end of the maintenance phase in patients receiving buprenorphine daily or 2 or 3 times per week. On an international level, the HIV Prevention Trials Network is planning a large-scale clinical trial of the efficacy of buprenorphine in HIV prevention (D. S. Metzger, personal communication).

**PROVISION OF BUPRENORPHINE IN HIV SEROPOSITIVE PATIENTS**

The majority of the literature about the use of buprenorphine in HIV-seropositive patients comes from France, where the medication has been available since 1995. Between 1995 and 1998, a prospective observational study, the Manif 2000 cohort, enrolled 467 HIV-seropositive patients who had been infected by means of injection drug use. Enrolled patients were ≥18 years old, had a CD4+ cell count of >300 cells/mm³ and no opportunistic infections, and met the Centers for Disease Control and Prevention’s (CDC’s) criteria for stage A or B. A portion of these pa-
tients were actively injecting opioids, and a subset of these patients received treatment with buprenorphine during the period that the cohort was observed. Evaluation of 167 patients in this cohort who received antiretroviral therapy for a median duration of 5.3 months revealed that the likelihood of nonadherence to these medications was highest among patients who were actively using injection drugs (58%), compared with nonadherence of persons who were former injection drug users (35%) and persons who were receiving buprenorphine treatment (22%) [52]. Active drug users not receiving treatment with buprenorphine were 5.1 times more likely to be nonadherent to their antiretroviral medication than were persons who were receiving buprenorphine (OR, 1.3–20.1) [52].

A second report regarding the same cohort revealed that HIV seropositive patients receiving antiretroviral medication with buprenorphine were able to achieve clinical outcomes, with respect to biological markers (e.g., a clinically significant increase in the CD4 cell count and a decrease in the HIV load) similar to those of patients not receiving buprenorphine, after a median of 3.7 months of exposure to the antiretroviral medications [34].

The final report of this cohort tracked treatment retention in the 114 patients who received buprenorphine during the entire follow-up period. Forty-six patients (40%) discontinued treatment during the follow-up period, with 23 patients (44%) dropping out of treatment within 9 months after the beginning of the follow-up period and 25 patients (54%) indicating reversion to injection drug use [48]. The implications of this level of treatment retention for HIV risk behavior, HIV disease status, and viral resistance patterns are not known. Notably, 32 (28%) of the 114 patients who received buprenorphine during the follow-up period reported injection misuse of buprenorphine. This practice, which is expected to be more likely associated with the buprenorphine-only preparation than it is with the buprenorphine-naloxone combination, has been reported in countries where the buprenorphine-only preparation is available.

In the United States, demonstration projects designed to incorporate the use of buprenorphine into HIV primary care are being initiated and are funded by the Health Resources Service Administration [53]. Although there are perceived barriers to the receipt of buprenorphine, including a lack of expertise, stigma, and reimbursement issues, these factors may be mitigated, especially in the United States, by the increased capacity of HIV clinics, particularly those with Ryan White funding, to provide substance abuse treatment as well as integrated counseling and psychosocial support services [54]. Finally, the use of buprenorphine as a treatment for opioid dependence in HIV-infected persons is a strategy in the domain of the CDC’s initiative to promote the prevention of HIV transmission among individuals living with HIV/AIDS [55].

**POTENTIAL AND ACTUAL MEDICATION INTERACTIONS BETWEEN BUPRENORPHINE AND MEDICATIONS USED IN PATIENTS WITH HIV/AIDS**

Although data on drug interactions between methadone and HIV medications are more extensive, the literature regarding drug interactions between buprenorphine and pharmacotherapies used in antiretroviral regimens is limited. Many medications used to treat HIV infection are metabolized via the cytochrome P450 3A4 system, the same pathway associated with buprenorphine.

A study of the interaction between buprenorphine and the nucleoside reverse-transcriptase inhibitor zidovudine (AZT) found that buprenorphine did not increase AZT concentrations and, therefore, was less likely to lead to AZT-related toxicity, in contrast to methadone, which had been found to increase AZT levels [56, 57]. In contrast, one in vitro study of the interactions between buprenorphine and the HIV protease inhibitors ritonavir, indinavir, and saquinavir revealed significant inhibition of the metabolism of buprenorphine caused by these HIV medications, which may potentially lead to significant increases in buprenorphine levels [58]. Although it is important to monitor patients for clinical sequelae, this interaction is of less concern with respect to buprenorphine, given the ceiling it exhibits for agonist effects and the decreased likelihood of adverse events, such as respiratory depression or coma. Similarly, one of the nonnucleoside reverse-transcriptase inhibitors, delavirdine, is a cytochrome P450 3A4 inhibitor and, thus, theoretically increases buprenorphine levels. The remainder of the medications in this class is considered to be composed of inducers and could theoretically decrease buprenorphine levels. A study of patients receiving buprenorphine and the nonnucleoside reverse-transcriptase inhibitor efavirenz (an inducer) concluded that these patients did not develop opioid withdrawal syndrome during the administration of efavirenz, despite decreased levels of buprenorphine in serum [59].

In addition, because of the ceiling effect on buprenorphine’s analgesic properties and its ability to block the effects of other opioids used for pain relief, patients who are receiving long-acting opioids for chronic severe pain may not be good candidates for buprenorphine treatment. This phenomenon has significant implications for patients with HIV infection. Pain disorders are more common among patients with HIV disease than among primary care patients, with the prevalence of painful syndromes ranging from 30%–97% [60]. In addition, pain is frequently undertreated in patients with HIV infection or AIDS, particularly in individuals with a history of substance abuse [61, 62]. Therefore, other medications used for treating pain, such as nonsteroidal anti-inflammatory medications, may need to be administered to HIV-infected patients receiving buprenorphine for the treatment of opioid dependence.

In managing patients who are receiving
concurrent treatment for opioid dependence and HIV infection, clinicians should be knowledgeable of potential medication interactions. Awareness of potential drug interactions between buprenorphine and HIV antiretroviral medications is important to optimize outcomes by avoiding drug interactions that may lead to suboptimal levels of HIV medication or buprenorphine and to minimize adverse events, such as toxicity or overdose. In addition, as efforts continue with the goal to integrate use of buprenorphine into HIV care, further studies will need to be undertaken to make more than theoretical statements about these interactions.

**COST AND COST-EFFECTIVENESS OF BUPRENORPHINE**

Decisions about adding buprenorphine to other treatment options for opioid dependence will necessarily include a consideration of cost and effectiveness. A recent meta-analysis comparing the efficacy of buprenorphine and methadone noted that health care payers’ choice of these 2 services may depend on their relative effectiveness and cost. There is, however, a limited literature regarding the cost-effectiveness of buprenorphine treatment [63]. Rosenheck and Kosten conducted cost analysis of buprenorphine treatment, compared with that of methadone, prior to buprenorphine’s approval or marketing [64]. They included the direct cost of the medication and its dispensation and the cost of medical and nursing personnel providing clinical care, counseling and case management services, office space, equipment, and administration, as well as cost incurred by the patient. The cost of buprenorphine in this analysis was presumed to be $4–$8 (in US dollars) per day, which is slightly less than the average cost of actual buprenorphine maintenance treatment. The researchers concluded that, in the United States, the cost of service delivery for buprenorphine would be lower than that of methadone because of a decreased need for the fixed costs incurred by an opioid treatment program.

The fixed costs of opioid treatment programs are the result of requirements imposed by federal regulations (e.g., staffing, building construction and maintenance, and the number of patient visits per year). Because these requirements do not apply to practicing physicians’ offices and fixed costs in a physician’s office can be distributed across the care of all patients, these costs are minimized with buprenorphine treatment. The hypothetical cost of the first year of treatment ranged between $3211–$6742 for buprenorphine treatment issued from a physician’s office and $5927–$8849 for methadone treatment issued from an opioid treatment program.

A second study of cost-effectiveness specifically evaluated the potential relative impact of buprenorphine therapy, with respect to HIV seroprevalence among injection drug users [63]. In this study, investigators evaluated the incremental costs, including all health care costs, and incremental effectiveness, which was measured as quality-adjusted life years (QALYs) of survival of opioid-dependent patients. The prevalence of HIV infection in the community of injection drug users was experimentally manipulated between the range of 5%–40%. Cost-effectiveness of buprenorphine treatment was evaluated at prices per daily dose that included $5, $15, and $30. The model assumed that methadone maintenance was already available in the treatment system. The authors concluded that if buprenorphine increased the number of individuals receiving opioid agonist maintenance treatment by 10% but did not, at the same time, affect the number of individuals who were receiving methadone maintenance (assuming both treatments were available), the cost-effectiveness ratios for buprenorphine therapy would be <$45,000 per QALY gained for all prices of buprenorphine for both low and high HIV-seroprevalence communities. If, however, treatment with buprenorphine resulted in a treatment expansion of 10% but half of the injection drug users were newly entering the treatment system and were patients who transferred from methadone treatment to buprenorphine treatment, the cost-effectiveness ratios in both communities were <$45,000 per QALY for the $5 and $15 medication prices and >$65,000 per QALY for the $30 medication price. The authors concluded that, at a price of ≤$5 per dose, buprenorphine maintenance was cost-effective for injection drug users among all HIV seroprevalence rates that were evaluated.

It is noteworthy that this analysis has been criticized for not being optimistic enough, because of its failure to include cost gains resulting from a decrease in overdose-related deaths, HIV treatment–related costs, and criminal behavior [65] and because it was conducted without data that reflected actual practice [66]. Also, it is worth noting, especially for resource-poor countries, that the same authors had previously demonstrated that the expansion of methadone services would have a cost-effectiveness ratio between $8200 and $10,900 per QALY. [67]

**DISCUSSION**

The introduction of buprenorphine, a new medication to treat opioid dependence that has fewer restrictions than methadone, holds promise for reducing HIV transmission and improving the care of patients with opioid dependence and HIV disease. Methadone has a long history of proven efficacy and benefits in treating opioid dependence, and the addition of buprenorphine serves to expand the treatment options with the potential for involving more physicians and office-based practices in the provision of this care. Prior to widespread adoption, a number of critical issues that encompass clinical and translational concerns must be considered.

First, will providers have adequate opportunity to prescribe this medication to high-risk populations to ensure that its HIV-prevention benefits are realized? Second, how will buprenorphine treatment
services be integrated into HIV clinical practices [68]? Third, will integrated HIV and addiction care result in improved outcomes for HIV-infected persons? Fourth, will integrated HIV and addiction care result in improved outcomes for addicted persons? Finally, are there potential medication interactions that will limit the utility of this new medication? Many of these outcomes will be addressed in ongoing and planned trials. In the meantime, office-based clinicians, for the first time in nearly 100 years, have the opportunity to provide a unique treatment to minimize the adverse impact of opioid dependence.

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