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Moving HIV Pre-Exposure Prophylaxis Into Clinical Settings:

Lessons from Buprenorphine

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Introduction

Human immunodeficiency virus transmission frequently accompanies substance use. High-risk sexual behaviors done under the influence of alcohol, cocaine, methamphetamines and injection drug use contribute disproportionately to the ongoing spread of HIV.[1–3] Effective HIV prevention efforts for these individuals and their partners include expanded combination antiretroviral therapy for those who are HIV-infected, condoms, behavioral interventions including substance abuse counseling, and for those who inject drugs, the implementation of needle and syringe exchange programs, and opioid-agonist treatment,[4] including methadone and buprenorphine.[5]

Since its approval by the Food and Drug Administration in 2002, buprenorphine, an opioid-agonist medication used in the treatment of opioid-dependence, has been provided to over one million patients with an estimated 300,000 individuals (approximately 10% of those with opioid-dependence) currently receiving this treatment in a range of settings, including primary care, addiction treatment centers, and HIV clinics.[6] Data from 2009 indicates that 60% of patients used third-party insurance to cover the cost of buprenorphine while 29% were self-pay and 11% used Medicaid coverage.[7] Twenty thousand physicians from various specialties, including primary care physicians, psychiatrists, and addiction specialists, have received the training required to prescribe this treatment.[8]

Prior to the introduction of buprenorphine, physicians were prohibited from providing opioid-agonist medication to treat opioid-dependence, resulting in a general lack of knowledge, skills, and attitudes for most physicians. The introduction of buprenorphine, therefore, required a concerted effort among federal agencies and medical societies to address the training needs for this new practice in medicine. Although there is considerable practice variation in screening and treatment practices, federal guidelines recommend a comprehensive evaluation, focused physical exam and laboratories, along with treatment planning, which can take 30–45 minutes at the initial visit.[9] The duration of treatment should be tailored to the clinical response and can range from days to years,[10] and improved outcomes are associated with longer periods of treatment.[11–13] The lessons learned may help

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inform the dissemination of pre-exposure prophylaxis (PrEP) in primary care practices where people without HIV infection typically seek health care.[14]

Pre-exposure prophylaxis, which is the use of antiretroviral medication by HIV-negative patients, represents a potential strategy for HIV prevention in those with substance use disorders and those in whom the use of substances and sexual behaviors puts them at increased risk for HIV transmission. PrEP involves the use of daily oral antiretroviral therapy[14] initiated in advance of possible HIV exposure to decrease risk of HIV acquisition by uninfected individuals engaging in high-risk behaviors.[15] Evidence from clinical trials[16–18] and modeling studies[19–21] provides optimism for the potential effectiveness of PrEP among particular populations, with results of an RCT being conducted with injection drug users expected in late 2012.[22]

The successful implementation of PrEP in those with substance use disorders to reduce their risk of sexual acquisition of HIV infection will require a multipronged approach, including; (1) provision of the medication; (2) safety screening; (3) behavioral interventions; (4) integration of PrEP as part of comprehensive care; and (5) monitoring PrEP's population impact.[23] The current article outlines potential challenges to the introduction of PreP based on the experience from implementing buprenorphine, including a recent effort funded by the Health Resources and Services Administration Special Programs of National Significance to expand buprenorphine into HIV clinics, and considers strategies to address those challenges.[24]

Potential Challenges

Although the authors expect that implementing PrEP will produce patient-level challenges, such as HIV risk perception and PrEP acceptability among those with substance use disorders, the focus in the current article is on provider- and system-level factors.

Provider-Level Factors

Changing physician practice can take time. On average, there is an estimated delay of 9 years in the adoption of evidence-based medical recommendations.[25] Physicians are often slow to adopt practices, such as treatment of opioid-dependence and PrEP, which are entirely new to them, as these issues are not encountered in medical school, residency or clinical practice. Despite evidence demonstrating the efficacy of buprenorphine through RCTs,[26–29] initial uptake by providers was slower than anticipated given the prevalence of untreated opioid-dependence, for several reasons.[30–33]

First, experience with buprenorphine demonstrates that providers can be hesitant to integrate new pharmacologic interventions into their practice when they perceive the medication to be outside the domain of their specialty. This perception may result from a belief that the intervention is inconsistent with their training, clinical responsibilities and/or the demands of their practice.[34] For instance, primary care providers indicated that they would be more interested in providing buprenorphine if they received appropriate education and training.[31] Efforts to implement PrEP will likely face similar challenges as some physicians may consider antiretroviral HIV prevention to be outside the scope of their practice or requiring special counseling and educational skills they are not trained in or do not have time to provide.

Physicians often express concerns regarding safety when considering new practices in medicine. For instance, prior to its demonstrated safety,[35] some HIV treatment providers cited concern about potential interactions between buprenorphine and antiretrovirals as a barrier.[36] The implementation of PrEP will likely benefit from dissemination of information

regarding its safety and effectiveness in injection drug users and others with substance use disorders. Moreover, the challenges with medication adherence and treatment retention in patients with substance use disorders may result in provider concerns about the potential for PrEP failure and development of HIV resistance.[37]

Non-adherence and medication diversion are common, with family and friends often serving as a primary source of shared medications.[38] Although buprenorphine[34] and other controlled substance may appear to have more inherent street value than antiretrovirals provided for PrEP, provider fears of the diversion of PrEP may limit some enthusiasm for this practice.[39] Finally, providers' concerns about risk compensation, or increased HIV risk behaviors in the setting of PrEP, may prevail, despite lack of support in the literature to date.[14,16,40]

The identification of appropriate patients is central to the successful implementation of PrEP.[23] However, providers of substance use treatment in general,[41,42] and buprenorphine-prescribing providers in particular, unfortunately do not conduct routine screening for sexual risk behaviors or HIV infection,[43] despite the CDC guidelines recommending such practice.[44] The appropriate and safe implementation of PrEP will be contingent on the providers identifying and routinely monitoring[45] eligible high-risk patients informed by recent efforts.[46]

System-Level Factors

Based on experiences with buprenorphine, costs and coverage of medications will be an important additional consideration for PrEP,[33,34] likely determined by a complicated interplay among government, insurance companies, and the pharmaceutics industry.[47] Inconsistent reimbursement, limits on dose and duration and prior authorization are cited as hindrances to buprenoprhine prescribing, particularly among experienced prescribers.[33,34,48–50] Likewise, opioid treatment programs regulated by the federal government to provide methadone and buprenorphine have been slow to include buprenorphine due to a reimbursement structure that favors the provision of the less-costly methadone. Similarly, reimbursement barriers have also been cited with routine HIV testing.[51] Further, given its role for prevention and long-term use, there may be additional barriers in securing reimbursement for medications and the associated counseling and follow-up involved with PrEP, particularly when there are limited existing resources for antiretrovirals for HIV-infected patients.[52] Therefore, it is likely that coverage will be an important challenge to PrEP implementation.

Providers often cite inadequate time for a patient visit as a reason for not prescribing buprenorphine[33,34] and not providing routine HIV testing.[51] The implementation of buprenorphine has benefited from practice models that include well-trained clinical staff, often nurses, advanced practice nurses, social workers, or physician assistants, and access to essential supportive services.[32,53,54] PrEP implementation will require systems for screening for risk behaviors and appropriate HIV testing to evaluate for HIV acquisition.

Beyond patient identification, optimizing the balance between providers prescribing PrEP and PrEP candidates, including those who inject drugs, is essential. For example, as there is geographic variation in opioid use[55,56] and treatment[8] availability, there are regions with greater concentrations of at-risk populations who might benefit from PrEP. Thus, targeting the development of providers and resources in these geographic regions, generally urban areas, is appropriate. The creation of systems that support access to PrEP in rural settings, however, is also needed as an important step toward preventing widening disparities.[57] Finally, as with the prescribing of buprenorphine, a system that considers the diverse needs of the patients who may be PrEP candidates will be critical. For example, PrEP candidates may access services through a range of settings, in part related to their SES.[23]

Strategies to Address Challenges

Given the range of clinical settings, patients and providers potentially involved with the implementation of PrEP, three particular strategies for promoting the effective dissemination of evidence-based practices are relevant: (1) provide practical implementation tools and guides for the principal parties involved in PrEP; (2) create networks for learning opportunities; and (3) include monitoring and evaluation of milestones and goals.[25]

The first essential step is to provide high-quality evidence-based information for the principal parties involved in PrEP, including clinical personnel and paraprofessionals, HIV prevention service providers, potential PrEP users, policymakers, governments, advocacy groups and the media.[47] The implementation of buprenorphine was bolstered by a standard curriculum financed by federal agencies and created by leading societies in addiction medicine.[9] Given the complex needs of this patient population and the multiple components associated with PreP (e.g., HIV testing, behavioral interventions), multidisciplinary team-based approaches should be emphasized.

For example, data from the efforts to implement buprenorphine in HIV clinics showed that nonphysician team members, from a variety of backgrounds including licensed practical nurses, registered nurses, nurse practitioners, certified substance abuse counselors, health educators and pharmacists were essential in providing counseling and other services.[32] In addition, strategies for promoting routine HIV testing and manuals for medication adherence and risk-reduction counseling could be provided to promote standardized procedures. Finally, guidance on how to cover the costs associated with HIV testing, laboratory safety monitoring, counseling and antiretroviral medications will be essential.

Second, as a lack of comfort and ongoing support can serve as a major barrier to implementation of a pharmaceutic intervention,[30,31,33,50] providing accessible opportunities for training and ongoing educational support is essential. A successful model for this includes the Physician Clinical Support System-Buprenorphine (PCSS-B), a national network of physicians trained and experienced with prescribing buprenorphine, who provide training and ongoing e-mail and telephone support to other physicians interested in prescribing buprenorphine. The core components include: (1) a national network of trained and experienced physician mentors, a Medical Director and group of national experts; (2) a telephone warmline; (3) clinical guidance; (4) a website; and (5) outreach efforts to physician organizations.[8]

This infrastructure allows for accessible experts, who can provide timely support, and ongoing opportunities for learning, including in remote settings. Allowing for continuing medical education credits may further promote provider acceptance.[58] A complementary system, perhaps built on the National HIV/AIDS Clinicians' Consultation Center,[59,60] may facilitate expansion of PrEP nationally.[33] Together, these models could foster the development of a network of *PrEP specialists,* clinicians who provide services for patients in areas with increased concentrations of PrEP candidates, but who may also support the provision of care and services to those in a range of contexts (i.e., federally qualified health centers, hospital-based clinics and private practice) and in rural settings.

Developing and implementing strategies to assess the ongoing effectiveness of PrEP, similar to those that were implemented for buprenorphine, may serve to promote quality, appropriate planning and improvement in the delivery of services.[8,61–63] Important metrics should include the proportion of patients who are appropriately offered and receive PrEP; adherence and toxicities over time; changes in risk behaviors over time; HIV testing rates; and HIV seroconversions, including resistance patterns. Further, evaluations of availability of PrEP (e.g., provider uptake, antiretroviral access) will be essential. As seen with

buprenorphine, flexibility and reassessment over time are essential to ensure that adequate services are available as requests for PrEP provision by patients[64] and that adoption by physicians may increase over time.[50]

Conclusion

Although the recent data demonstrating the efficacy of PrEP provide reason for optimism, it can be anticipated that there will be important provider- and systems-level challenges to promoting PrEP's effectiveness. Learning from the implementation of buprenorphine and planning for structures that allow for clear guidance important for the principal parties involved in PrEP, continued opportunities for accessible education and trainings, and systems for ongoing evaluation and planning will enhance PrEP's chances for successful implementation.

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