

Prevention of HIV Infection among Injection Drug Users in Resource-Limited Settings

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Injection drug use contributes to considerable global morbidity and mortality associated with human immunodeficiency virus (HIV) infection and AIDS and other infections due to blood-borne pathogens through the direct sharing of needles, syringes, and other injection equipment. Of ~16 million injection drug users (IDUs) worldwide, an estimated 3 million are HIV infected. The prevalence of HIV infection among IDUs is high in many countries in Asia and eastern Europe and could exacerbate the HIV epidemic in sub-Saharan Africa. This review summarizes important components of a comprehensive program for prevention of HIV infection in IDUs, including unrestricted legal access to sterile syringes through needle exchange programs and enhanced pharmacy services, treatment for opioid dependence (ie, methadone and buprenorphine treatment), behavioral interventions, and identification and treatment of noninjection drug and alcohol use, which accounts for increased sexual transmission of HIV. Evidence supports the effectiveness of harm-reduction programs over punitive drug-control policies.

An estimated 15.9 million persons inject drugs in 148 countries [1]; nearly three-quarters of these individuals live in low- and middle-income countries [2]. Although injection drug use directly accounts for only 5%–10% of human immunodeficiency virus (HIV) infections worldwide, this percentage increases to 30% after excluding sub-Saharan Africa [1]. The direct sharing of needles, syringes, and other injection equipment among drug users has driven HIV epidemics in eastern Europe, Southeast and Central Asia, Northern Africa, and the southern cone of South America [3, 4]. An estimated 3 million injection drug users (IDUs) are currently HIV infected, with China, the United States, and Russia currently reporting the largest numbers of HIV-infected IDUs [1].

Because injection drug use is a highly stigmatized behavior, IDUs often fall between the cracks of traditional health care systems; only ~5% of IDUs world-

wide have access to services for prevention of HIV infection [4]. Several interventions to reduce HIV transmission among IDUs have met success in a variety of settings [5], but uptake has been slow and coverage uneven among and, sometimes, even within countries. Some multilateral agencies are moving from drug-control approaches that criminalize drug users to evidence-based strategies that treat addiction as a chronic medical disease [6–8]. We review the evidence for harm reduction as prevention of HIV infection, including the promotion of sterile needle and syringe acquisition, opioid agonist therapy (OAT), and behavioral interventions to prevent HIV and other blood-borne infections among IDUs, and discuss challenges for implementation of these strategies, especially in resource-constrained settings.

THE ROLE OF SYRINGE EXCHANGE PROGRAMS IN PREVENTION OF HIV INFECTION

Contaminated injection equipment, in which HIV can remain viable for several weeks [9], quickly became the focus of early efforts to prevent HIV transmission among IDUs. Although bleach disinfection effectively inactivates HIV in vivo [10], field studies showed little

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or no effectiveness in reducing the incidence of HIV infection [11]. Rather than disinfecting used injection equipment, needle and syringe exchange programs (NEPs) provide sterile syringes to IDUs who cannot or will not cease injecting drugs. Typically, NEPs offer other health services, information, and referrals [12]. After the first NEP was introduced in 1984 in Amsterdam, several programs opened in the United Kingdom, Australia, and North America [13]. Expansion in developed countries continued through the 1990s, and more recently, NEPs have achieved success in some resource-poor settings, including Nepal, Malaysia, Vietnam, and Brazil [12, 14].

Evidence of efficacy. Multiple studies have shown that NEPs are associated with reduced risky injection behavior and incidence of HIV and other blood-borne infections [15]. A recent review summarized compelling international evidence for the effectiveness, safety, and cost-effectiveness of NEPs in reducing HIV transmission [16]. The authors concluded that, despite lack of experimental evidence, published data fulfill 6 of the 9 Bradford Hill criteria on causal inference from epidemiological studies [14, 17]. First, scientific studies demonstrated significant associations between NEPs and reduced incidence and prevalence of HIV infection and risk behaviors among IDUs [18–21]. Second, findings were replicated in multiple wealthy and resource-poor countries [8, 18–23]. Third, reductions in the prevalence and incidence of HIV infection and associated risk behaviors have occurred after NEP implementation [24–26], meeting criteria for temporality. Fourth, biological plausibility is supported by the direct link between shared injection equipment and HIV seroconversion and the absence of seroconversion with sterile needles [27, 28]. Fifth, substantive reversals of improved health behaviors occurred after NEP closure [29]. Finally, similarity between NEPs and provision of condoms for reducing sexual transmission of HIV satisfies the criterion for analogy. In the United States, a cost-effectiveness analysis revealed that optimal coverage of NEPs could have prevented 12,350 cases of HIV infection and AIDS during 1998, saving \$1.3 billion in treatment costs and saving \$34,278 per HIV infection averted—well under lifetime treatment costs for HIV-infected individuals [30].

After nearly 3 decades of extensive research, there is no convincing evidence that NEPs are accompanied by serious negative consequences [14, 31], including increased illicit drug use, crime, injection frequency, syringe sharing, inciting of drug use, recruiting of new IDUs, social network formation, or discarding of needles in public places [8]. Instead, NEPs have been associated with reductions in and cessation of injection drug use and increased enrollment in drug treatment [32–34]. Political opponents of NEPs frequently misconstrue findings that the prevalence of HIV infection is higher among NEP attendees than among nonattendees [35, 36], without recognizing that NEPs attract IDUs with a higher risk of HIV seroconversion

before they begin the program [37] and that, compared with actual NEP data, self-reports of NEP attendance may underestimate the protective effect of NEPs on the incidence of HIV infection by as much as 20% [38].

Challenges and future directions. NEPs have been implemented successfully in resource-constrained countries (ie, Nepal, Malaysia, Vietnam, Mexico, and Brazil) [14], and in prisons in at least 9 countries [39–41] and have the endorsement of multilateral institutions, including the World Health Organization (WHO). However, many nations continue to have restrictive drug-control policies that fail to distinguish between drug use and risk of HIV infection. Such policies thwart implementation and scale-up, particularly in countries dependent on foreign donor assistance that comes with conditions against harm reduction. In these settings, local law enforcement often deters NEP implementation and reduces efficacy of existing programs by challenging their legality, threatening staff, and arresting attendees [42].

One promising alternative approach to reducing the circulation of contaminated injection equipment involves improving access to sterile syringes through pharmacies. Pharmacy access is associated with reduced syringe sharing among IDUs, is highly cost-effective, and does not increase the number of discarded needles in public areas, violent crime, or other negative consequences [43, 44]. Even in settings where NEPs exist, pharmacies are a primary source of sterile syringes for many IDUs, particularly in developing countries [45–47]. Efforts to train pharmacists to be frontline educators of prevention of HIV infection are ongoing in the United States, India, Russia, and Vietnam (C. Fuller, personal communication). Research should assess the feasibility of improving pharmacy access and other programs that can serve as an alternative or an adjunct to NEPs in an effort to broaden sterile syringe coverage. Safe injection facilities have been shown to be associated with reductions in needle sharing and overdose and with increased referrals to drug treatment [48] and are operating in at least 12 countries, often in conjunction with NEPs. To our knowledge, however, safe injection facilities are not operating in low- or middle-income countries, where they could offer tremendous benefit (T. Kerr, personal communication).

THE ROLE OF OAT IN PREVENTION OF HIV INFECTION

Convincing scientific evidence supports treatment for substance use as a strategy for prevention of HIV infection for IDUs. Several decades before the HIV/AIDS epidemic emerged, OATs were developed to treat opioid dependence, a chronic medical disease involving long-lasting physiological and molecular adaptations in the brain [7]. The overall objective of OAT is to reduce consumption of illicit opioids and, in the context of prevention of HIV infection, to limit exposure to needle shar-

ing, which can lead to infection. Unlike detoxification or abstinence programs, OAT relies on regular, controlled doses of opioid agonists, with the goal of retaining patients for extended periods (ie, ≥ 6 months), allowing IDUs to stabilize and reduce their risk behaviors.

Methadone maintenance therapy is the most widely applied and researched OAT. A full opioid agonist, methadone was first developed in the late 1930s for medical use as an analgesic and subsequently became adopted in the management of opioid addiction. At an appropriate dose, methadone blocks the euphoric effects of other opioids and is associated with decreased illicit drug use. Administered orally, methadone is metabolized slowly, lasts longer than many illicit opioids, and is acceptable to many patients. Buprenorphine was recognized as an OAT >3 decades ago [49], but its application lagged behind methadone maintenance therapy [50]. As a partial opioid agonist, buprenorphine has several appealing features [51]: (1) it is less susceptible to diversion and drug abuse than are full opioid agonists, particularly when combined with naloxone, which can precipitate withdrawal symptoms if the combination is injected [52]; (2) it may be safer than other pharmacotherapies, because its effects are dose-dependent only within a limited range, rendering increased doses unproductive and reducing the likelihood of overdose [53]; (3) compared with methadone, buprenorphine is safer for HIV-infected patients receiving highly active antiretroviral therapy (HAART), because it has fewer known medication interactions [54–56]; and (4) buprenorphine is effective when administered only 3 times per week under directly observed therapy, increasing treatment compliance [57, 58]. Other pharmacotherapies, such as naltrexone (an opioid), have had mixed results [59] but may still be useful in settings where opiate agonists are illegal or otherwise unavailable, such as the Russian Federation [60].

Evidence of efficacy. There is little question regarding the efficacy of OAT with methadone and buprenorphine for treating opioid dependence and preventing HIV infection. Large-scale studies and systematic reviews have established strong associations between OAT and reduced illicit drug use, overdose, and crime and improved health and social functioning [61, 62]. Methadone maintenance therapy was approximately 3 times more effective than nonpharmacological therapies in retaining patients in treatment [62]. Buprenorphine is equally as effective as methadone in retaining patients in treatment, decreasing illicit opioid use, and reducing injection frequency [63–65]. Benefits include decreased sharing of needles, syringes, and other injection equipment [66]; reduced prevalence of HIV and other blood-borne infections; safer sexual behavior; and decreased crime [67, 68].

The consistency of findings from randomized trials and observational studies provides compelling evidence that OAT is significantly associated with reduced HIV risk behaviors, in-

cluding decreased injection frequency and lower rates of HIV seroconversion [69–72]. Some studies have also shown that OAT is associated with decreased sharing of injection equipment and reductions in unprotected sex [73–75]. OAT is highly cost-effective and feasible in culturally diverse settings, including middle- and low-income countries (ie, China, Indonesia, Lithuania, Poland, Thailand, and Ukraine) [76–78]. Furthermore, OAT benefits HIV-infected IDUs by reducing illicit drug use and improving adherence to HAART, thereby slowing HIV disease progression [79]. Drawing on this accumulated evidence, the WHO, the Joint United Nations Programme on HIV/AIDS, and the United Nations Drug Control Program endorsed OAT for prevention of HIV infection, and the WHO added methadone and buprenorphine to its list of essential medicines in 2004 [80, 81].

Challenges and future directions. Although small-scale OAT programs have been implemented in settings as diverse as China, India, Nepal, Indonesia, Iran, and Kyrgyzstan, an urgent unmet need remains, even in developed countries. Even in the United States, only 15% of drug users are engaged in drug treatment at any given time [51]. Especially in resource-poor settings, OAT is rarely available outside mental health services in major cities. Linkages are needed with services for prevention of HIV infection or other infectious diseases [61]. In developed countries, coverage must be expanded from specialty drug treatment centers to primary health care settings, where delivery of OAT has been associated with reduced HIV risk behaviors and seroconversions [82]. Reductions in drug use associated with OAT offered in prisons [83–85] warrant efforts for its expansion in detention settings.

OAT is unique among proven medical therapies in the profusion of legislative and policy requirements that govern its use; addressing this political and philosophical opposition is critical in expanding services to reach global goals for prevention of HIV infection [51, 58]. National drug-control policies—most notably, US federal regulations—have engendered criticism for ignoring scientific evidence and for hindering global expansion through restrictions on foreign aid [86]. In the Russian Federation, where the prevalence of HIV infection among IDUs may be the highest in the world, methadone and buprenorphine for OAT remain illegal [1, 6]. Despite abundant evidence, controversy persists among policy makers because of misconceptions regarding efficacy, cost-effectiveness, adverse consequences, and the perception that OAT is just replacing one drug with another. In some regions, such as Guangxi, China, forced labor camps and other compulsory treatment centers are marketed as drug treatment, despite lack of evidence on efficacy and their violation of basic human rights [87].

However, there are some legitimate concerns about OAT. When buprenorphine is offered as treatment for opioid addiction in the absence of naloxone, it can become a major drug

of abuse, as has been the case in India and Pakistan [88, 89]. In France, where high rates of buprenorphine diversion have been reported [90], other researchers contend that buprenorphine injection is the patient's response to inadequate care rather than to misuse—similar to the tendency for drug users to supplement methadone with heroin when they are severely underdosed [91, 92]. In settings where opposition to OAT persists, proposed solutions include initiating small-scale OAT to demonstrate efficacy in local contexts, educational efforts to destigmatize addiction, coherent national leadership regarding the appropriate role of OAT in prevention of HIV infection, and promoting global coordination and financial commitments [51, 93]. In progressive settings, such as Switzerland, Germany, Australia, and British Columbia, Canada, heroin substitution therapy has been evaluated [94–96], and it is part of the accepted range of treatment options in Switzerland [97].

Psychological disorders and concurrent drug use, which diminish treatment compliance and retention in therapy, pose additional challenges to OAT [98]. Psychosocial support, behavioral counseling, and contingency management have been shown to boost OAT retention and enhance progress in patients [61, 99–102]; however, these intervention components require additional funding commitments and rigorous evaluation. There is also a need for other treatment-oriented initiatives, including programs to prevent relapse, interim treatment of drug users on waiting lists [103, 104], and interventions to refer NEP attendees to receive OAT [105]. The lack of an effective pharmacotherapy for stimulants (ie, methamphetamine and cocaine) may render OAT less useful in some parts of the Americas, Europe, and Asia [106].

OTHER INTERVENTIONS

Behavioral interventions. Behavioral interventions focus on encouraging IDUs to refrain from sharing needles and other injection paraphernalia and on promoting condom use. The most successful strategies are based on multiple theories of behavior change, including social cognitive theory [107], diffusion of innovations [108], and the transtheoretical model of behavior change [109], and focus on reducing both injection and sexual risks [110]. Sexual transmission may be potentiated through the disinhibitive effects of psychoactive drugs, sex trade involvement, and increased risk of sexually transmitted infections, all of which are established cofactors of HIV transmission [111, 112]. In particular, stimulants, such as cocaine and methamphetamine, have been associated with high-risk sexual behavior [113–115]. In a recent meta-analysis of interventions aimed at reducing sexual transmission of HIV among drug users, only half of the interventions were based on behavioral theory, 6% included >1 follow-up visit, and only 12% were conducted outside the United States [110].

Behavioral interventions can reduce risk behaviors among

IDUs at the level of the individual, dyad, or social network [110]. Interventions vary, with common components including education about HIV infection, personal risk assessment, condom provision, skills training, testing and treatment for HIV and other sexually transmitted infections, and referrals to drug treatment and other health services [116]. Some incorporate community outreach or peer leaders, who are often former IDUs [117]. Although outreach can be effective in teaching IDUs to reduce needle sharing [118], a recent randomized trial of network-oriented peer educator training based in Thailand and the United States showed equivocal findings [119]. In general, outreach alone appears to have modest success at reducing sharing of injection paraphernalia or sexual risk behaviors [120].

The US Centers for Disease Control and Prevention lists 21 behavioral interventions for IDUs as having met criteria for “best evidence” [121]. Several studies and 2 systematic reviews have revealed modest efficacy of behavioral interventions in reducing sexual risk behaviors among HIV-seronegative IDUs [110, 122, 123]. More recently, interventions have focused on HIV-infected drug users to reduce sexual risk behaviors and improve adherence to HAART [124–126]. A theory-based intervention incorporating motivational interviews was successful in reducing unprotected sex among HIV-infected men who have sex with men [125] and HIV-uninfected heterosexuals [122] in the context of ongoing methamphetamine use, illustrating that harm reduction approaches can be successfully applied to behavioral interventions to reduce HIV transmission.

A growing number of evaluations have shown that couples-based interventions are more efficacious than are individual-based interventions in addressing a range of drug-related and sexual risk behaviors, including concurrent relationships, sharing needles with outside partners, and the impact of drug use on dyadic sexual expectancies, sexual communication, sexual performance, and sexual and drug-related risk behavior [127]. Future research is needed to determine whether existing behavioral approaches suffice or whether interventions require tailoring toward specific target populations, types of drugs used, and routes of administration [128]. Unfortunately, behavioral interventions found to be successful in developed countries are seldom adapted to low- and middle-income countries. Research is also needed to identify the feasibility of program components and the appropriateness of underlying theories in diverse socioeconomic and cultural settings [129, 130].

Biomedical interventions. With regard to persons who are at risk of HIV infection by means other than injection, there has been considerable discussion about use of antiretroviral medications to reduce the risk of HIV infection through reductions in HIV load. Postexposure prophylaxis (PEP) was developed to address occupational injuries related to HIV-infected patients, but its effectiveness remains an open question.

Guidelines were developed to extend this therapy to nonoccupational contexts [131]. In theory, guidelines for PEP could include IDUs; however, the complexity of the regimen is a substantial hurdle. Furthermore, virtually no studies have been reported to formally examine the PEP approach to addressing risk of HIV infection. One scenario for PEP use by IDUs involves the population of former drugs users whose use is stabilized with OAT but who experience a transient relapse. Rather than expelling the drug user from treatment, incorporating PEP could serve as a means to support treatment retention. Another approach that has been discussed vigorously for other populations is preexposure prophylaxis [132], but discussion of possible application to current or even former IDUs is virtually absent from the literature. There are many potential hurdles for implementing a PEP or preexposure prophylaxis program for drug users; these include drug use policy, which equates prevention of HIV infection as being soft on drug use, and considerations that some drug users will be noncompliant with treatment, thus implying a potential for treatment diversion. Studies are needed to examine these issues of feasibility in developing and testing programs being developed for persons other than IDUs who are at risk of HIV infection.

HAART has been shown to be highly effective in IDUs, but many IDUs do not receive testing and treatment [133]. A recent call to action has been urged for scale-up of efforts to test and treat IDUs with treatment not only for HIV infection, but also for other infections and substance use. Such interventions may prove especially efficacious in settings with a high incidence of HIV infection, where early HAART implementation could potentially reduce the incidence of HIV infection [134].

CONCLUSIONS

The prevalence of HIV infection among IDUs is increasing in countries that lack the resources or political will to mount an appropriate response [135]. For example, although surveillance of IDUs in sub-Saharan Africa is poor, existing evidence points to an increase in the injection of illicit drugs [136], and experience from Asia suggests the possibility of sub-Saharan Africa developing intertwined epidemics of injection drug use and HIV infection [137]. In addition to the high prevalence of HIV infection in sub-Saharan Africa, socioeconomic hardship and conflict are common, drug trafficking routes are expanding, and the few documented populations of IDUs—in populous countries, including Kenya and Nigeria—appear to be growing [1, 135, 138].

Decades of international data indicate that drug enforcement expenditures have not prevented the decrease in drug prices, increase in drug purity, and burgeoning of drug users. Instead, zero tolerance policy perspectives and supply-reduction programs in the “war on drugs” approach have resulted in severe unintended consequences, not limited to high incarceration

rates, stigmatization of individuals addicted to drugs, restrictions on drug treatment, and large numbers of deaths related to drug-market violence [86]. Rapid scale-up of evidence-based harm reduction interventions should be viewed as a public health imperative.

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