Chapter 8
Substance Use Treatment in the Era of New HIV Prevention Technologies

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In December 1981, just a few months after the morbidity and mortality weekly report MMWR reported on a cluster of *pnuemocystis carinii* (PCP) cases that would later be recognized as the first wave of the AIDS epidemic, a report was published in the New England Journal of Medicine describing an outbreak of "community-acquired" PCP among 15 young men from New York City. One of the men was described as a heterosexual alcohol abuser, six were reported to be heterosexual drug abusers, six as men who had sex with men (MSM), and two as both drug users and MSM [1]. These cases had been identified at hospitals in the city during the previous two years and were among the first AIDS cases to be carefully examined. Importantly, in this first report, substance use (both injection and non-injection) was present in the majority of identified individuals, among both MSM and heterosexuals. Necessarily, the epidemiological and scientific interest of the time became sharply focused on mechanisms of transmission and strategies for preventing widespread transmission—protecting the blood supply, use of condoms, and the use of sterile injection equipment.

Prior to 1981, there was not much awareness of, or scientific interest in drug use other than at the few specialty care centers which had been established to treat the most severe forms of substance use disorders. Aside from a few studies of alcohol abuse, there were no meaningful data on the prevalence of substance use in the community or the impact of this use on public health. Researchers and clinicians working with drug users did not typically ask questions about sexual behaviors or practices that could transmit blood-borne viruses and other sexually transmitted infections. While there was much attention focused on the relationship between crime and heroin use, there was little support for drug treatment programs and little attention was paid to the link between drug use and public health. After all, only a few members of a

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few communities were affected and those who were, hidden from the public's eye. Researchers, treatment professionals, and public health agencies were unprepared to respond to the growing epidemic of HIV infection among injection drug users and their sexual partners [2]. There was little concern regarding the relationship between alcohol and non-injection drug use, sexual behavior, and viral transmission.

From the start of the AIDS epidemic, a variety of strategies have been implemented in an attempt to respond to reduce transmissions among drug users, but these efforts have been narrowly defined, are limited in scope and focused almost exclusively on injection drug use and related risks. The role of non-injection substance use in sustaining sexual transmission and inhibiting effective antiretroviral (ARV) treatment was underestimated since the first cases of HIV infection were identified.

Despite awareness of the prevalence of substance use from the earliest days of the epidemic and its direct and indirect role in transmission, substance use remains one of the greatest global challenges to effective risk reduction, access to and retention in HIV care, adherence to ARV medications, and sustained suppression of viral load. As prevention strategies have become sharply focused on "treatment as prevention", it is likely that alcohol and non-injection drug use will become more prominent components of the efforts to improve coverage and effectiveness of ARV treatment. This chapter reviews accomplishments and discusses the opportunities and challenges facing the scale-up of prevention technologies that have the potential to minimize the role of substance use in the transmission of HIV infection. Building on lessons learned from the first 30 years of the epidemic, the focus here is on maximizing the future impact of treatment interventions for harmful substance use. Three major topics will be addressed: (1) defining the challenge, (2) medication-assisted treatments for substance use disorders as prevention technologies, and (3) opportunities and challenges for scale-up.

Defining the Challenge

Current estimates suggest that there are approximately 34,000,000 people living with HIV [3]. There is some indication that the number of infected individuals has stabilized globally with new infections roughly equal to the number of deaths among HIV-infected individuals [4]. Nearly 50 % of the global burden of HIV infections is found in sub-Saharan Africa. Because most of the people in this region have been infected through heterosexual transmission, the role of substance use has not been well documented or appreciated.

The number of individuals estimated to be living with HIV infection caused by injection drug use ranges from 1 to 6 million. With significant regional variations, it is estimated that 10–25 % of infections outside of sub-Saharan Africa are attributable to injection drug use. Though monitored by AIDS surveillance systems globally, the estimate of injection-related infections is imprecise due to the illegality of the behavior, the stigma of disclosing, and a lack of interest among governments to accurately monitor injection drug use [5]. Also, given the fact that injectors are able

to be infected through unprotected sexual activity it is likely that some infections classified as injection related, are in fact sexual transmissions [6].

While estimates of the numbers of individuals who have become infected as a result of injections are imprecise, we have even less understanding of the number of individuals who are infected from risk behaviors associated with alcohol and non-injection drug use. There are no global estimates of the role of non-injection substance use in the transmission of HIV but it is likely to represent a major portion of all infections. Alcohol and illicit substance use is common globally, and it appears to be much more prevalent among individuals (and their partners) who become infected with HIV. There is increasing recognition of the role of non-injection substance use in fueling the HIV epidemic globally [7].

In studies focused on understanding heterosexual transmissions, alcohol and drug use is consistently found to be a predictor of HIV risk behavior and incident HIV infection [6, 8, 9]. Among heterosexual transmissions, alcohol use and non-injection drug use, particularly stimulant use, are commonly reported as factors associated with unprotected sexual activity [10]. Among MSM, substance use is not only more common when compared to the general population, but also recognized as a significant risk factor in explaining both HIV risk behaviors and infections [11]. In cross-sectional studies of MSM, alcohol and non-injection stimulant use are associated with HIV risk and prevalence while in prospective studies substance abuse has been found to be a powerful predictor of new infections [12, 13]. Among more than 4,000 MSM who participated in Project Explore, the largest prevention intervention trial ever conducted among HIV-negative MSM, drug and alcohol use prior to sex was found to be a stronger predictor of incident infections than unprotected receptive anal intercourse with a partner of unknown HIV status [14, 15].

From the earliest days of the epidemic, data have been available to suggest that substance use played a major role in the sexual transmission of HIV. Yet, most of the intervention literature has been focused on injection drug use and many interventions targeting sexual transmissions among heterosexuals and MSM have paid only minimal attention to substance use. This has resulted in a persistent and substantial under estimation of the role of substance use in sustaining the AIDS epidemic globally. Substance use, does not define a risk group—it is a behavior common among individuals in all risk groups and contributes not only to risk behaviors but also to access to and retention in adherence and sustained viral suppression.

Substance Use Disorders: A Chronic Disease Model

HIV prevention responses to substance use by governments and organizations tend to be rooted in how substance use itself is perceived and defined. Although not mutually exclusive, these "strategic definitions" can be seen as falling into several broad approaches—legal, harm reduction, and medical. When substance use is viewed primarily as a legal problem, prevention responses concentrate on interdiction, arrest, detoxification, and incarceration. Within this framework, people who use substances

are criminals and perceived as "weak," unable to control their behaviors. While it is true that individuals who become dependent on substances experience a loss of control, the legal responses have proven completely ineffective in both restricting access and use. A cornerstone of the criminal justice response to substance use and HIV prevention has been mandated detoxification. Harm-reduction responses view the problems associated with substance use as the health and disease consequences associated with use. From this perspective, interventions focus not on controlling drug use, but on preventing the harmful consequences caused by the use of substances. The primary harm-reduction strategies related to HIV prevention have been to ensure access to sterile injection equipment, condom distribution, and the use of methadone treatment to reduce risky injection behaviors. These strategies have been most successful in reducing the transmission of HIV among injectors when access to these services is available. Finally, medical views of the harms associated with substance use are viewed as behavioral and biological processes that need to be directly modified through evidence-based treatment strategies. Health-oriented interventions tend to focus on assisting individuals in controlling, reducing, and eliminating substance use to prevent a range of harmful health consequences and improve social functioning of the individual and those affected by their use. This approach includes behavioral interventions, counseling, and medication-assisted treatments.

While not all substance use is harmful, it is critically important to be able to identify harmful substance use when it is present. There is growing recognition that quantity and frequency of use alone are poor measures of harm. Certainly, high volume and high frequency alcohol and illicit substance use are associated with higher rates of harmful consequences, both acute and chronic. It is also true that even small or moderate amounts of substance use can be harmful, particularly in risky environments and among those with pre-existing medical conditions. Thus, the perception of substance use harm and its' assessment is a critical step in the process of determining the need for and type of response. In HIV prevention thus far, the harms associated with substance use have focused on the reuse of contaminated injection equipment. While injection drug use remains a very important behavior in the global epidemic, in communities with both medication-assisted treatments and syringe exchange programs, new injection-related transmissions have been successfully controlled. Given the greater prevalence and potential harm associated with alcohol and non-injection drug use, it will become increasingly important to understand the way in which we develop a response to substance use.

The latest revisions to the diagnostic and statistical manual (DSM5) provide a new and useful framework for classification of substance use disorders and the conceptualization of associated harms. These revisions intentionally move away from the "discrete" diagnostic categories of abuse and dependence to a classification of use as existing on a continuum of severity—mild, moderate, and severe. The severity of the substance use disorder is measured by assessing the number of symptoms present. These symptoms include: tolerance, withdrawal, more use than intended, craving for the substance, unsuccessful efforts to cut down, excessive time spent in acquisition, activities given up because of use, continued use despite negative effects, failure to

fulfill major role obligations, recurrent use in hazardous situations, and continued use despite consistent social or interpersonal problems.

In considering how best to respond to substance use disorders and the harms they cause, it's important to begin with the awareness that there are no behavioral or biological "cures" and there is increasing recognition of the genetic susceptibility of some individuals as well as the biological changes to the central nervous system that occur after prolonged use. These factors help to define substance use disorders as chronic health problems with common behavioral and biological diagnostic features and treatment responses. As the severity of substance use disorders increases, the intensity of treatment responses must also increase. While some treatments include the use of medications, all include behavior management strategies delivered via counseling interventions of various types. The most efficacious counseling strategies have been those that help individuals view their behaviors as changeable habits that can be altered by clearly identifying the behaviors that lead to use and developing strategies to achieve short term goals. These "cognitive-behavioral" strategies are non-judgmental and begin with the expectation that progress will not follow a linear trajectory. Given the biologically reinforcing properties of substance use, relapse is common, even among highly motivated individuals committed to behavior change. This is simply a characteristic of substance use disorders, and a defining characteristic of all chronic diseases.

Medication-Assisted Treatments as Biomedical Prevention Interventions

The findings from studies of medication-assisted treatments for opiate-dependent injection drug users identify agonist medication-assisted treatments as among the most powerful prevention interventions reported for any intervention with any at-risk population. The data from these studies link participation in these treatments not only to reduced risk behaviors but also to fewer new infections and they provide a clear "proof of concept" for the effective treatment of substance use as a prevention strategy. While these treatments do not cure substance use disorders, they represent powerful tools in their effective management. Using a model of chronic disease management, these agonist approaches to medication-assisted treatments address both the biological aspect of the substance use disorder and its behavioral components through counseling interventions. The findings from studies of opiate agonist treatments often referred to as opiate substitution treatment (OST), have been replicated over time and in diverse cultural and economic settings. In this chapter, we will not use the term OST for two reasons. First, one of the most common reasons for opposing the use of agonist treatments is that they merely substitute a legal medication for an illegal one and do nothing to treat the condition. Second, agonist-based medication-assisted treatments as described here are strategies for the medical management of

chronic substance use disorders and as such, much more that substitution. The consistency of these findings is impressive and reflects the fact that opiate dependence is a biological condition with important behavioral components.

Agonist medications (methadone and buprenorphine) work by activating the mu opioid receptors in the central nervous system. Unlike the direct administration of heroin, the activation by the molecules of the agonist medication is controlled, in both intensity and duration. For methadone, a pure agonist, individuals are able to achieve a stable level of activation through single daily dosing. For buprenorphine, a partial agonist, the attachment to the opiate receptor is much stronger and consequently, the medication occupies the receptor for a longer period of time, allowing for less frequent dosing. Because activation takes place through the occupation of the receptor, subsequent administration of opiates is "blocked" when dosing is appropriate. This activation effectively prevents withdrawal symptoms and sustains dependence on the medication. Symptoms of opiate withdrawal will occur when the medication is insufficient in dosage or discontinued.

Methadone

Methadone is a full opiate agonist and despite serious limitations on its availability, remains globally, the most widely used medication for the treatment of opiate dependence. Research conducted over the past 25 years provides strong evidence that methadone treatment can be an effective HIV prevention intervention. Observational and retrospective studies conducted in the USA, Australia, Europe, and more recently Asia, have consistently shown strong associations between participation in methadone treatment and reductions in the frequency of opiate use, fewer injections and injection-related HIV risk behaviors, and lower rates of HIV prevalence and incidence. Collectively these data show that patients are less likely to practice injection-related risk behaviors and become infected with HIV while they remain on methadone. Thus, the data on methadone as a protective prevention strategy are strong and widely accepted [16–18].

For ethical reasons, there are no randomized controlled trials comparing treated and untreated opiate-dependent individuals and thus there is the potential for selection bias to influence these observations. It is possible that those who enter methadone treatment have greater concern for their health and engage on less risk taking. However, the consistency of the positive findings with methadone treatment over time and across diverse settings is compelling and collectively they have been used to advocate for the expanded use of methadone maintenance as primarily an HIV prevention intervention. The support of methadone treatment as an HIV prevention intervention is most notable in eastern Europe, and Central and Southeast Asia where the dual epidemics of HIV and opiate injection began in the mid-to-late 1990s [19]. In these regions, new treatment systems were established to respond to the rapid transmission of HIV among opiate injectors. The most notable is China's enormous investment in the creation of a national methadone treatment system. In less than 10 years, over 700

clinics treating more than 160,000 patients have been established and have become the largest single drug treatment system in the world, propelled primarily as an HIV prevention strategy [20].

While the data on the impact of methadone treatment are impressive, methadone treatment alone can be expected to have only a limited impact on the global epidemic because not all individuals are at risk from opiate use and not all opiate users are appropriate for, or have access to, methadone treatment. And as discussed previously, the majority of drug-related infections are likely associated with non-injection drug use and sexual transmission. This is not to diminish the importance of methadone treatment as an HIV prevention intervention, but to acknowledge that additional treatment approaches will be needed to effectively respond to substance-related transmission. Perhaps most importantly, the data on methadone as an HIV prevention strategy provide what might be considered a "proof of concept"—effective drug treatments reduce drug use, risk behavior, and HIV transmission.

Buprenorphine

The US FDA approved buprenorphine and the combination of buprenorphine-naloxone for the treatment of opiate dependence on October 8, 2002. For several reasons, the introduction of this medication represented a significant development in the treatment of opiate dependence, particularly in the USA, because primary care providers could use it outside the highly regulated methadone system [21, 22]. Data on the HIV prevention impact of buprenorphine have begun to appear. They show significant reductions in risk behaviors using both office-based and clinic-based treatment models among adults and adolescents and are quite consistent with those of methadone maintenance treatment [21, 23–27]. While the public health impact of buprenorphine and its combination with naloxone has been impacted by their higher cost per daily dose relative to methadone, cost effectiveness studies have resulted in very favorable comparisons with methadone [28, 29]. In a randomized double-blind trial among heroin injectors in Malaysia, those assigned to buprenorphine not only reduced risk behaviors significantly but also remained in treatment longer that those assigned to naltrexone or placebo [30].

As mentioned earlier, buprenorphine has a longer period of attachment to the opioid receptor. This reduces the required frequency of administration. Thrice weekly dosing of buprenorphine–naloxone has been reported recently in an HIV prevention trial of 1,250 opiate-dependent injectors in Thailand and China [31].

Naltrexone

Naltrexone is the most widely used *antagonist* and has been available for over 25 years as a medication for the treatment for opiate dependence. As an antagonist, naltrexone works by blocking access to the mu-opioid receptor. Antagonists are non-addictive and have been found to reduce heroin use and crime for patients who

accept it (Brahen et al. 1984; Chan 1996). Naltrexone has none of the reinforcing properties of opiate agonists (methadone and buprenorphine) and in its oral form must be taken on a daily basis to maintain its blockade effect—the primary mechanism of action. Naltrexone prevents opiates from accessing and stimulating the opiate receptor and importantly, if opiate molecules are already present, naltrexone will replace them, precipitating withdrawal and this has important clinical implications. First, as an antagonist, the medication does not produce or sustain dependence. Second, the treatments for opiate use cannot begin comfortably in individuals until opiates are no longer present. For those who have recently used opiates, the initiation of antagonists will precipitate abrupt withdrawal. Consequently, the use of antagonists must begin with detoxification or, a sufficient period of abstinence.

While there is much data on the safety and efficacy of both oral and long-acting naltrexone, much less research has focused on the impact of naltrexone treatment as HIV prevention. Naltrexone is an opiate antagonist that has been available as a treatment for opiate dependence for over 25 years. Also, patients who are about to start naltrexone must be opiate free in order to avoid precipitated withdrawal on their first dose. Unless highly motivated to remain abstinent, this blockade strategy has not been effective over the long term for many opiate-dependent individuals seeking treatment [32–34].

As a result of its prohibition against the use of agonist medications, the Russia Federation has accumulated considerable experience in the use of naltrexone [35]. Addiction treatment typically begins with 7–10 days of inpatient detoxification using clonidine and other non-opioid medications followed by 2–4 weeks of rehabilitation with referral to local health centers for follow-up, but few patients keep these follow-up appointments and relapse rate are high. Family members often bring patients to treatment since the heroin problem began in the 1990s after the Soviet Union dissolved, thus many of the patients are young and live with their parents who can supervise adherence. These cultural differences likely contributed to the findings in two earlier, placebo-controlled studies where over 75 % of patients who met admission criteria enrolled, and 42–44 % of those randomized to oral naltrexone remained in treatment and did not relapse over 6 months as compared to 10–12 % of those randomized to naltrexone placebo [36–38]. Although these results were better than those seen in the US studies, adherence continued to be a problem, which led to the study of sustained-release (SR) naltrexone that is reported here. SR naltrexone is currently available in two formulations—depot injections and implants. Vivitrol® (http://www.vivitrol.com), a long-acting injectable formulation developed in the USA, was FDA approved for alcohol dependence in 2006 and for opioid dependence in 2010 based on the results of a clinical trial led by Krupitsky [39].

Non-Injection Substance Use and Sexual Risk

Risky sexual behaviors have frequently been found to co-occur with both injection and non-injection drug use, particularly with stimulant use [40–42]. Early reports

focused on substances used by MSM and cocaine use among opiate-dependent individuals in methadone treatment. There is now widespread recognition of cocaine and other stimulant use and HIV risk and incident infections. Studies from Brazil, Canada, and the USA have linked HIV risk and incidence to cocaine use (Pechanski et al. 2000). More recently, data have emerged on the elevated prevalence and incidence of HIV infection among stimulant (primarily methamphetamine) using populations in the USA, Russia, and Thailand (Shaptow et al. 2005; Koblin et al. 2005; Srirak et al. 2005; Colfax and Guzman 2006; Kozlov et al. 2006; Colfax et al. 2006). Increasing use of methamphetamine has also been reported in South Africa (Morris and Parry 2006).

HIV prevention efforts targeting stimulant users have faced significant challenges given the widespread desirability and availability of these drugs, the frequency with which they are often administered and the strong association between use and sexual activity. Although some success has been reported using psychosocial treatments for harmful stimulant use, for most, behavioral interventions alone have proven insufficient to show sustained impact on drug use and related risk behavior [43]. It is not uncommon for drug treatment programs that use a variety of behavioral intervention strategies, to report dropout rates of greater than 50 % during the first few weeks of treatment. Even patients who remain in treatment rarely achieve periods of sustained abstinence.

While medications have demonstrated efficacy for the treatment of alcohol and opiate use, there are no medications for assisting with treating stimulant use disorders. Over the past 20 years, there has been a concerted effort by the National Institute on Drug Abuse (NIDA) to support the development of new treatment agents and to test existing medications for use in the treatment of stimulant use disorders. This search is complicated by the fact that no clear pathway for central nervous system activation by stimulants has been identified. Progress has also been slowed by the general lack of interest among the pharmaceutical industry in developing medications useful in the treatment of substance use disorders. Thus far, no medications have reliably demonstrated success in reducing craving for, or use of, cocaine or other stimulants.

In the absence of efficacious medication-assisted treatments for stimulant use, psycho-social and behavioral interventions of various designs have been evaluated. Generally, multi-session psycho-social interventions directed at reducing sexual risk among substance users recruited in community settings have not shown greater efficacy than more basic educational approaches that are typically used in as control or comparison conditions [42]. Several studies, however, have reported positive findings with sexual risk reduction interventions that were delivered within drug treatment programs. A variety of intervention delivery strategies have been tested including individual and group, gender specific, and gender mixed [44–46]. However, the diversity of programs and populations makes it difficult to make broad conclusions regarding efficacy.

The delivery of sexual risk reduction interventions within drug treatment programs can be considered an example of a combination prevention strategy [47]. Using the drug treatment program as a platform for the delivery of the intervention not only makes sense but also shows signs of efficacy [43, 48]. It seems clear that sexual risk reduction is more difficult to achieve than reduction in injection risk behaviors.

Thus, in contrast to the powerful prevention impact of agonist treatments for opiate injection, few substance abuse treatment interventions have shown consistent efficacy in reducing sexual risk associated with non-injection drug use.

HIV Treatment as Prevention

With the introduction of effective HIV disease management, global HIV initiatives became focused on the scale-up of ARV treatment. Along with this scale-up came recognition of the potential for HIV treatment to have important impact on the course of the epidemic. Not only was the health of infected individuals dramatically improved but also the sustained reduction of viral load was accompanied by the potential to reduce transmission risks. There was growing consensus regarding the potential prevention impact associated with participation in ARV treatment and the achievement of sustained virologic response [49–51]. This recognition led to the development of prevention models built around engaging sufficient numbers of infected individuals in ARV treatment. This led to efforts to identify HIV positive individuals and engage them in ARV treatment. This "seek, test, and treat" model was rooted in the evidence that risk behaviors were lower among patients in HIV care and that sustained reductions in viral load were able to be achieved by the majority of adherent patients, regardless of the mode of initial infection [52].

With the growing consensus that ARV treatment was an effective prevention strategy, the findings of HPTN 052 had a powerful impact and altered the HIV prevention landscape. In this study, the protective effects of ARV medication were identified by measuring the rate of transmissions from treated individuals to their uninfected partners. Patients were randomized to start on ARV medications either when their CD4 cell counts were between 500 and 350, or when CD4 cell counts were 350 or less (the WHO recommendation for treatment initiation). The HIV incidence rate in the partners of the earlier treatment group was compared to that of partners of those who started treatment later. Only 1 of the 28 infections observed among all partners occurred in the group that initiated treatment early [53]. These dramatic findings confirmed earlier observations and placed a sharp focus on the "treatment cascade" as a framework for prevention—identifying people who are HIV infected, engaging and retaining them in HIV treatment, maintaining adherence to ARV medication, and achieving sustained suppression of viral load. Importantly, at each step of this treatment cascade, substance use inhibits success.

Despite the personal and public health benefits of ARV treatment, continued substance use has frequently been associated with poorer access to ARV treatment, slower initiation of highly active antiretroviral treatment (HAART), poorer adherence to treatment, and less success in achieving viral suppression [54–56]. There is a growing body of evidence linking substance use treatment to improved access to HIV treatment, adherence while in treatment, and sustained viral suppression. Most of this work has been reported among injection drug users in methadone or buprenorphine treatment. For example, in a prospective observational study of 231 HIV-infected

opiate using injection drug users, participation in methadone treatment was found to be a significant, independent predictor of more rapid entry into ARV treatment. Data from this study also demonstrate higher rates of adherence to HIV treatment among those in methadone treatment [57, 58].

Similarly, in a retrospective analyses of 276 HIV-positive drug injectors in France, the relationship between drug use, treatment participation, and adherence was more clearly defined [59]. The findings of this study are particularly important because those patients who continued to inject drugs, regardless of their substance use treatment participation, showed poorer rates of adherence. For patients who were in methadone or buprenorphine maintenance and not injecting drugs, adherence did not differ from patients with no history of drug use. However, for those who continued to inject adherence, it was two to three times worse, despite the fact that they were receiving agonist medications. The findings of this study were the first to identify continued injection and not merely participation in drug treatment. This same cohort produced data showing that retention in medication-assisted treatment was linked to long-term virologic suppression [60]. These data are consistent with earlier reports of poorer adherence among patients that continue substance use and improved adherence among those in drug treatment [61].

The Search for New Biomedical Tools and Strategies

As discussed earlier, harmful substance use is best viewed as a chronic medical condition requiring attention to both behavioral and biological forces that promote and reinforce continued use. While the treatment of harmful opiate use can be seen as a model for the medical management of substance use disorders and associated problems, most harmful substance use involves substances other than opiates: alcohol, stimulants, and other drugs. The biomedical treatment of these conditions is much more limited. Despite an intensive and sustained search for effective medications for cocaine and other stimulant use over the past 15 years, there is little reason for optimism that we will quickly determine the mechanism of action or develop effective treatment agents that can inhibit craving or reduce effects.

Scaling Up Prevention Strategies for Substance Users

From the earliest days of the AIDS epidemic, substance use has been known to be both a direct mode of transmission via injection and a common co-factor in sexual transmission. The primary focus of prevention science has been to stop new infections among injection drug users. While this was, and continues to be, an important mechanism of transmission and focus of prevention efforts, it has predominated the thinking about the role of substance use in the HIV epidemic and has contributed to a limited understanding of the role of substance use in sustaining the AIDS epidemic.

Even if all injection drug use ceased, substance use will remain a major factor in HIV transmission and treatment. In fact, the objectives of identifying HIV-infected individuals who are unaware of their status and engaging and retaining them in treatment will bring force to the recognition of the important role of non-injection substance use.

This chapter has focused on the consistent evidence that effective treatments for drug abuse and dependence reduce the frequency of use, risk behaviors, and infections. While these findings were observed during the first 15 years of the epidemic primarily from countries with existing drug treatment systems, more recent data provide evidence of these same impacts, particularly in countries with more recently established treatment programs and systems. The consistency of this relationship over time and across cultural settings is impressive and serves as a reminder that harmful substance use, like other chronic medical conditions, has predicable responses when treated using effective strategies.

Importantly, there is increasing evidence of the positive effects of medication-assisted treatments other than methadone. Results of interventions using buprenorphine, buprenorphine–naloxone, and naltrexone are producing findings consistent with those of methadone treatment for those who reduce their drug use. This is particularly important considering the need for multiple treatment options in communities affected by HIV and other blood-borne and sexually transmitted infections.

The current focus on treatment as prevention provides an opportunity to more fully integrate substance use screenings and interventions into the HIV treatment delivery system. This strategy significantly expands the role of effective substance abuse treatments as HIV prevention. First, the data suggest that for the most serious cases of substance use disorders (addiction) effective substance use treatments improve access to ARV treatment, adherence to those treatments, and the chances of sustained reductions in viral load.

Also, just as substance use inhibits adherence to ARV medications, it is likely to play a similar role with other prevention strategies that require regular attention. Adherence issues have become a primary concern in other biomedical prevention strategies for HIV—vaginal microbicides, pre-exposure prophylaxis (PrEP). In fact, questions of efficacy and more importantly, effectiveness, of these strategies remain unanswered mainly due to poor adherence during clinical trials testing these strategies.

Recent research has also provided strong evidence that current use of substances, not past diagnosis, mode of infection, or individual characteristics, is associated with poor adherence. Findings that medication-assisted treatments for opiate injectors reduce risk of infection with HIV have been widely promulgated. While such “low demand” interventions will undoubtedly help many dependent individuals avoid withdrawal, risk behaviors, and other negative consequences associated with dependence, it is not clear that this strategy is a very effective treatment for addiction.

Given the fact that only a small portion of drug users ever enter formal treatment, research is also needed to develop and evaluate strategies for embedding effective drug treatments in non-traditional settings where risk behaviors are common and

HIV infection is prevalent. Enormous opportunities exist for the delivery of health promoting drug treatment messages outside of drug treatment programs. New, long-acting formulations of existing medications (naltrexone and buprenorphine) offer more efficient strategies for treatment coverage and opportunities for significant advances in HIV prevention efforts.

As stated throughout this chapter, given the important role of heroin injection in propelling the spread of HIV via injection-related risk, most of the published research has involved opiate users and their treatment with methadone and buprenorphine-naloxone. The literature is quite clear that these medication-assisted treatments are effective HIV prevention strategies.

Unfortunately, comparably effective medication-assisted treatments for cocaine and other stimulant use are not currently available. While treatment strategies that do not use medications, most notably, interventions using contingency management strategies, have shown some evidence of efficacy among high-risk stimulant users, the development of a safe and effective treatment medication for stimulant abuse and dependence must remain a high priority.

Clearly, drug treatment programs play a critical role in controlling the spread of HIV and improving its treatment in many communities around the world. Still, the great majority of drug users do not have access to effective substance abuse treatments—even in countries considered to be more highly developed [67]. While the scale-up of substance abuse treatment programs remains an important priority, it is not likely that these specialty treatment programs alone will be sufficient to stop the spread of HIV infection or ensure effective ARV treatment of people who use substances. Consequently, there is both need and opportunity to scale up the screening and intervention for substance use within HIV clinics. The integration of substance use monitoring and response is necessary to maximize the success of the treatment as prevention strategy.

The role of substance use in the AIDS epidemic has never been fully recognized and goes far beyond that which is represented by injection drug use. Alcohol and non-injection substance use does not define a risk group—it is common in all risk groups not only as a factor in the direct transmission of HIV but also in inhibiting access to and retention in HIV care, adherence to ARV medication, and in the sustained suppression of viral load. As the AIDS epidemic progresses through its fourth decade, the role of non-injection substance use must move to the forefront of prevention science. While continuing efforts to control injection-related transmissions, harmful substance use must be monitored and treated in the community and in the HIV clinic. This will be necessary not only to achieve the goals of the national and global AIDS strategies but also to have any chance of eventual eradication of the virus.

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