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Not Just the Needle: The State of HIV Prevention Science among Substance Users and Future Directions

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Abstract

Successes in preventing HIV transmission among substance using populations have focused primarily among injection drug users, which have produced measurable reductions in HIV incidence and prevalence. By contrast, the majority of substances used worldwide are administered by non-injectable means, and there is a dearth of HIV prevention interventions that target non-injecting substance users. Increased surveillance of trends in substance use, especially cocaine (including crack) and methamphetamine in addition to new and emerging substances (e.g., synthetic cannabinoids, cathinones and other amphetamine analogs) are needed to develop and scale-up effective and robust interventions for populations at risk for HIV-transmission via sexual behaviors related to non-injection substance use. Strategies are needed that address unique challenges to HIV prevention for substance users who are HIV-infected and those who are HIV-

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uninfected and at high risk. We propose a research agenda that prioritizes: (1)) combination HIV prevention strategies in substance users; (2) behavioral HIV prevention programs that reduce sexual transmission behaviors in non-treatment seeking individuals; (3) medical and/or behavioral treatments for substance abuse that reduce/eliminate substance-related sexual transmission behaviors; and (4) structural interventions to reduce HIV incidence.

HIV prevention research on substance using populations has focused primarily on people who inject drugs (PWID). Scale-up of proven combination HIV prevention strategies that include syringe exchange programs (SEPs) and opioid substitution therapies (OST) effectively and significantly curtail HIV incidence among PWID. Around the world, however, most substances of use and abuse (e.g., cocaine/crack, heroin, prescription medications, amphetamine-like stimulants (ATS), amyl nitrites, cannabis, alcohol, tobacco) are administered through routes of administration other than injection (e.g., snorting, smoking, inhaling, ingesting, rectal insertion). These forms of substance use apply to a much larger proportion of the general population than injection drug use, affecting virtually all HIV risk groups and all regions of the world. These licit and illicit substances of use and abuse are a dynamic part of the world economy and are available in even the most conservative societies.

Not Just the Needle

Strategies for HIV prevention among PWID do not translate well to non-injectors. First, the most important HIV transmission route among non-injectors is sexual and not linked to route of drug administration. Second, since the nature and frequency of substance use among non-injectors varies widely (e.g., sporadic use, binging, daily use) they may not identify as ‘substance users’ and may not be reached by venue-based HIV prevention interventions that typically target PWID, such as SEPs and OST. Moreover, non-injection substance use occurs in various contexts that confer HIV transmission risks and involves unique subgroups (e.g., LGBT, street youth, sex workers, low income migrant workers), which complicates omnibus prevention efforts. Adding complexity, both injection and non-injection substance users who are HIV-positive can transmit infection, which among non-substance users can be prevented using antiretroviral treatment (ART).[1] Data are needed to inform whether this strategy is viable for active substance users who may have difficulty adhering to ART regimens. Finally, policymakers, leaders in civil societies and even some substance users debate whether non-injection substance use warrants focus in HIV prevention above and beyond evidence-based interventions (EBI) used by all persons at risk. We present the literature regarding this issue and advocate for a research agenda to guide HIV prevention efforts among all populations of substance users, including non-injectors.

Non-injection Substance Use and Transmission of HIV and other STIs

Some forms of non-injection substance use, particularly stimulant use, confer elevated rates of HIV transmission, due to their association with high-risk sexual behaviors.[2] Cocaine and ATS can increase sexual arousal[3,4] and promote high-risk sexual behaviors among users.[3] Stimulants are frequently a drug of choice among MSM[5] and female sex workers (FSWs). Other non-injected substances also associated with sexual HIV transmission include alcohol,[6] volatile nitrates, and some prescription drugs.[7] Due to its worldwide availability, alcohol misuse is increasingly recognized as a significant factor associated with HIV sexual risk behaviors in both MSM[8] and heterosexuals.[9] There are no studies showing independent associations between cannabis use and elevated HIV transmission risks.[10]

Tools for Preventing HIV Transmission in Non-Injecting Substance Use

Epidemiology & Surveillance

There is a compelling need for better data on HIV incidence attributable to non-injection substance use. Substance use often involves two or more substances that may be co-administered (i.e., polypharmacy)[11] or used within the same time frame, which complicates measurement and an understanding of contextual influences of substance-related HIV risks. These realities underscore the need for event-level data and surveillance approaches that are flexible and time-sensitive. Studies that focus on HIV risks related to non-injection substance use often rely on estimates of relative risks. By contrast, little attention has been focused on attributable risks at the individual and population level, which would yield the number of HIV infections that could be averted if specific forms of substance use were reduced or eliminated (i.e., etiologic fractions). Such studies require prospective data collected from large samples reporting varying levels and types of substance use. For example, in Project EXPLORE and the Multisite AIDS Cohort Study, both large studies of MSM, substance use, particularly stimulant use, was shown to account for 28% and 33%[12,13] of new HIV infections, respectively.

Interventions

HIV prevention science has overwhelmingly focused on behavioral interventions to reduce HIV transmission behaviors. Behavioral interventions, often consisting of brief individual or multi-session group interventions, have shown efficacy in reducing drug and/or sexual transmission behaviors compared to a standard of care or to baseline risk behaviors.[14] Substance users are less likely, however, to reduce sexual risk behaviors compared with drug risk behaviors.[14] The lack of evidence-based programs for sexual behaviors related to non-injection substance use is striking. Notable exceptions exist for female crack cocaine users,[15] or heterosexual[16] and MSM methamphetamine users.[17] Interventions are especially needed that reduce substance use-related HIV risks in groups that have high HIV prevalence (e.g., MSM, sex workers, street youth, migrant workers).

Behavioral drug treatments including contingency management (CM) and cognitive behavioral therapies have shown reductions in sexual risks and methamphetamine use among MSM in outpatient treatment.[18] No medications are approved to treat stimulant dependence, which is unfortunate. Among individuals who inject opioids, treatment using OST can reduce HIV incidence.[19] While medications are approved for alcohol dependence, none show efficacy in reducing sexual HIV risk behaviors. Future HIV prevention strategies should consider SBIRT (Screening, Brief interventions, and Referral to drug Treatment) in venues high-risk substance users frequently attend, such as STD clinics.[20]

Recent advances offer new biomedical approaches to HIV prevention, such as HIV treatment as prevention (TasP) and as a prevention strategy for HIV-uninfected populations as pre-exposure prophylaxis (PrEP)[21] or post-exposure prophylaxis (PEP). With the potential use of these new therapies, there are concerns about adherence to ART,[5,22] engagement in care, and continued risk behaviors among substance users that dampen the political will for assessing these strategies. Yet the effect of stigma is significant and measureable: in the United States and Canada, injection *and* non-injection drug users were less likely than non-drug users to have access to ART.[23] One recent study found that offering PEP in combination with CM was feasible and acceptable among methamphetamine-using MSM.[24] Overall, little research has evaluated acceptability, feasibility, and efficacy of TasP, PrEP or PEP with substances users, independent of needle use. Surveillance studies rarely include biomarkers of HIV disease status or substance use among substance users, which leads to under-estimates of prevalence.

Non-injection substance users, particularly stimulant users, often encounter multi-level risk environments that prevent access to HIV and drug treatment. These include gender inequalities, intimate partner violence,[25] stigma, discrimination, incarceration, homelessness, lack of health insurance, and coerced treatment. Effective structural interventions are also needed to address these substance related HIV risks that range in scope and unit of analysis. These include changes in drug possession laws, increased access to drug treatment, and interventions at the venue-level (e.g., safer inhalation facilities, prison settings) and community-level (e.g., school-based interventions). The need for research on the influence of regional drug policies (e.g., supply control efforts, criminal sanctions on drug possession and use, and prescription monitoring systems) is palpable. Drug policies differ according to the needs, resources, and culture of the region; while most were created with the intention of enhancing public good,[26] these often carry major unintended consequences to the public health.[27] Research into structural level changes within the health care system also is of high priority. In the U.S. President's National HIV/AIDS Strategy, HIV prevention is organized at the system level in order to optimally influence the outcomes toward HIV prevention among HIV-positive individuals, including substance users (seek, test, treat, retain).

New Substances and Emerging Groups at Risk

Shifting patterns of substance use and the ways and contexts in which they are used present a moving target for HIV prevention. In countries where HIV incidence among PWID has declined, HIV transmissions among substance users have shifted from injection to sexual behaviors. In Brazil and the southern cone of Latin America, cocaine injection was prevalent in the late 1980s and early 1990s, but subsequently declined with rises in crack use.[28] In Thailand, since the late 1990s, declining heroin injection has been replaced by wide-spreading methamphetamine smoking.[29] South Africa is also experiencing a methamphetamine epidemic, with most users reporting non-injection routes of administration.[30] Other countries in sub-Saharan Africa have witnessed emerging epidemics of heroin and cocaine use, and their impact on HIV incidence within the context of high HIV prevalence in the general population is unknown.[31] Changes in ways substance use influences HIV transmission behaviors across broad geographic areas underscore the vital need for rapid surveillance assessment and response, with an increased use of biomarkers that target HIV subtypes and medication resistance.

New compounds are being derived from parent substances of abuse, altered sufficiently to avoid laws on drug possession and distribution.[32] Their use is on the rise.[33] These include synthetic cannabinoids, cathinones (e.g., "bath salts") and other amphetamine analogs, which are marketed to youth. Whether these substances are associated with elevated HIV transmission risks is unknown. Among non-injection substance using youth, engagement in HIV risk behaviors is high, especially among those who are MSM and street-involved.[34] Evidence is accruing that shows school attendance is protective against HIV[35] and substance use.[36] Little is known about substance-related risks or their mitigation in youth who drop out of school, are orphaned or who do not work.

Gaps in Knowledge

- Can HIV-positive substance users adhere to ART and experience the TasP benefit? When offered as part of HIV prevention, ART can prevent HIV transmission in HIV serodiscordant couples when started early[1] and reduces HIV transmission in HIV-negative MSM.[21] Yet, substance users were systematically excluded from "proof-of-concept" trials that established initial efficacy of combination HIV

prevention strategies due to concerns over potential medication adherence problems.

- What data exist on HIV in high risk subgroups of substance users, including users of non-injection substances, from racial/ethnic groups and in regions where substance use, homosexuality or sex-work are illegal that can guide high-impact prevention studies? There is a compelling need for data from low and middle-income countries that have ongoing generalized HIV epidemics (e.g., Sub-Saharan Africa, South and Southeast Asia) or emerging epidemics (e.g., Central Asia).
- What medications or behavioral therapies are effective for treating substance use that might reduce HIV-related transmission behaviors? In contrast to OST, effective medications for alcoholism have modest effect sizes and there are no medications for stimulant drugs. As more effective medications are developed, efforts to assess these for reducing drug-related sexual risk behaviors should be prioritized.[37]
- What structural interventions can be implemented to reduce HIV transmissions among users of injection and non-injection substances within settings of criminal justice or of primary care services?

The Way Forward

An evidence-informed strategy to guide HIV prevention in non-injection substance users draws heavily from the successes of combination HIV prevention in non-substance users and from declines in HIV transmission among PWIDs from using the combination of SEPs, OSTs and ART.

We propose a rational plan of HIV prevention research for substance users addressing the following:

Epidemiology

In most high-income countries, links between non-injection substance use and HIV transmission behaviors are well described. There is need for evidence describing associations between these factors, particularly in regions where cultural and religious sanctions exist against substance use, homosexual behaviors, street youth and women. An increased emphasis on biomarkers of HIV incidence and substance use is vital.

Combination Prevention Approaches in Non-Injection Substance Users

There is a crucial need to conduct studies that advise implementation of combination prevention approaches (e.g., PrEP, TasP, PEP) in substance users. Strategies of TasP remain unproven among injection and non-injection substance users who are HIV-positive, which is of highest priority. Combination HIV prevention strategies of PrEP and PEP in HIV-negative substance users at high-risk also merit consideration. Recognizing that no medication can be effective if it remains in the bottle, efforts to quantify and address potential problems with medication adherence in substance users, including structural and behavioral approaches are important. Testing of depot formulations of ART medications specifically in non-injection substance use would carry high impact. There is a concomitant need for combination HIV prevention research that addresses co-occurring infections in substance users, particularly hepatitis C, tuberculosis and STIs.

Substance Use-Related Risk Reduction Strategies

Sexual behaviors are the principal risk for HIV transmission among non-injection substance users, and studies that develop potent substance use reduction tools, including medication

and behavioral approaches, can reduce risk behavior. However, it is unknown to what extent HIV incidence can be reduced.

Future Directions

To significantly reduce HIV incidence among individuals who engage in non-injection substance use and sexual risk behaviors, scientists and policymakers need to set aside personal biases about substance use, sexual behaviors and cultural attitudes that promote abstinence as the only goal, recognizing that even modest decreases in substance use and related sexual risks may reduce harms and hence be associated with impressive etiologic fractions. While condoms are effective against HIV transmission, rising HIV incidence in high risk subgroups of substance users are unlikely to be reversed without additional prevention strategies, such as combination prevention, structural interventions and interventions to reduce substance use. In prior work,[38] we noted the need to overcome "addictophobia" to continue gains in HIV prevention with PWIDs. Future success in HIV prevention for non-injection substance users will rely on the ability to marshal the scientific and political will to allocate resources to reduce HIV transmissions in groups whose sexual risk behaviors are associated with substance use—and not just the needle.

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