

The Linkage between Amphetamine-Type Stimulants and HIV Sexual Transmission Risk Behaviors (TRBs): A Systematic Review

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ABSTRACT

The epidemic of the *human immunodeficiency virus* (HIV) infection and its advanced stage- *acquired immunodeficiency syndrome* (AIDS) epidemic, and the illicit drug abuse epidemic are global public health issues that are intertwined on a complex psycho-social, economic, and bio-behavioral level. Based on the Monitoring the Future reports, the danger of substance abuse is significantly underestimated among many adolescents. According to recent surveys, also Americans aged 12 and older abused an illicit drug (e.g., marijuana and ecstasy) at least once during their lifetime, indicating that young adults are becoming more receptive and supportive to the effect of illicit drugs. The lack of prevention programs and inadequate public awareness may increase the risk of chronic illnesses as well as sexual transmitted diseases associated with drug abuse. A review of the literature was conducted to evaluate the link between usage of amphetamine-type stimulants (ATS) and HIV sexual transmission risk behaviors (TRBs). In total, eight articles were found to fit all inclusion and exclusion criteria. In this review, methamphetamine abuse was highly prevalent among populations

at risk for HIV infection, which was a cogent evidence to support a potential causal link between usage of ATS and HIV sexual TRBs. However, these articles had some limitations due to ethical regulations, study design, data collection methods, and generalizability of results. Future studies should aim to address these limitations by utilizing larger, more diverse population samples, and novel approaches to data collection. Confounding variables associated with both ATS and TRBs should be further explored.

Key words: amphetamines, stimulants, HIV, sexual behaviors, Drug abuse.

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INTRODUCTION

The growing epidemic of drug abuse is a major world-wide public health issue. Research involving amphetamine-type stimulants (ATS) is of particular importance due to its potential for abuse and its prevalence among illicit drug users. This group of drugs includes amphetamine and methamphetamine (commonly known as meth), as well as methcathinone, fenetylline, ephedrine, pseudoephedrine, methylphenidate and 3,4-methylenedioxy-N-methylamphetamine¹. Abuse of ATS, especially methamphetamine, has serious effects and can lead to drug-induced seizures, psychotic states and psychosis, and cognitive impairment². According to the World Drug Report 2017, Amphetamine-related disorders were ranked second to opioid-related disorders, and in 2015, the number of past-year users of amphetamines and prescriptions stimulants was ranked second to past-year users of cannabis³.

A previous study surveyed adolescents and young adults aged 14 to 20 years in an emergency department setting to evaluate associations between prescription drug misuse (PDM) and sexual risk behaviors (SRBs). The study found that adolescents who misused more than one class of prescription drugs including cannabis, stimulants, opioids, and sedatives were significantly more likely to engage in SRBs such as inconsistent condom use, multiple sexual partners, and substance use before sexual intercourse⁴. Similarly, a combined cross-sectional survey among nationally representative samples of students in grades 9 to 12 was conducted using data from the 2011 and 2013 national Youth Risk Behavior Surveys (YRBS) to assess the association between using prescription drugs for non-medical uses without a doctor's prescription and sexual risk behaviors⁵. The survey study reported that 1 in 5 US high school students engaged in non-medical substance abuse. Alcohol (68.6%), marijuana (40.3%), ecstasy (7.4%), cocaine (6.2%), methamphetamines (3.5%) were the most commonly used substances, which had a positive association with having multiple sexual partners, being currently sexually active, a lack of condom use at last sexual intercourse, and using alcohol or drugs before last sexual intercourse⁵. Comparable findings were also reported among adult populations^{6,7}.

Methamphetamine is the most commonly abused substance, after alcohol and marijuana, worldwide⁸, which could be attributed to its

low cost and longer stimulant effect compared to cocaine^{9,10}. Although the most frequently mode of administration among amphetamine abusers is smoking, methamphetamine is available in different forms (e.g., ice, oily base, liquid, pills) and can be also abused in many ways such as intranasal, intravenous, or swallowing pills^{11,12}. Crystal meth is a smokable form of methamphetamine that produces a rapid onset of action. Injection has consistently been the second most common route of administration from 1993 to 2015¹³. Methamphetamine administration causes the release of the neurotransmitters, including dopamine, norepinephrine, and serotonin that affect the cardiovascular and central nervous systems¹⁴. Due to its relatively high bioavailability, smoking crystal methamphetamine provides an advantage over intravenous injection, which is the lack of injection-related problems¹⁵. However, acute psychological effects such as increased confidence and alertness, increased energy levels and assertiveness, and a decreased sense of boredom were reported as desirable effects of methamphetamine at the first usage^{16,17}. Chronically, the methamphetamine abuse may potentially cause tremor, weakness, dry mouth, depressive symptoms and cognitive impairment^{17,18}. Additionally, previous studies investigated the relationship between the chronic abuse of methamphetamines and sexual dysfunction. The investigators reported that methamphetamines abusers may complain of inability to reach or maintain full erection as well as delayed ejaculation^{19,20}.

The HIV epidemic has continued to spread and numerous studies reported association between HIV infection and the ATS drug abuse. It should be noted that methamphetamine has been described as affecting "both physiological and psychological aspects of sexual behavior" and is commonly used to prolong sex and increase sexual satisfaction²¹. In 2005, Buchacz et al. (2005) found a 4.2% higher incidence of HIV among amphetamine users in San Francisco, California as compared to non-users²². Similarly, an increased prevalence of HIV and hepatitis C virus (HCV) in six Chinese provinces was shown to be associated with usage of ATS²³.

The interaction between HIV and drug-abuse epidemics is a complex area for research due to the multiple variables it involves. Over a third of the cases of HIV transmission in the U.S. were injection drug use-related HIV infection²⁴.

These facts support the idea that there is a relationship between injection drug use and HIV transmission. Despite the complexity involved in determining a causal relationship between HIV and illicit drug abuse, numerous studies have been conducted in an attempt to elucidate the different psycho-social, economic, and bio-behavioral associations within this field.

Despite the mounting literature that risky sexual behaviors (e.g., sexual intercourse without the use of a condom) increase the likelihood of HIV transmission²², several aspects were underreported in the present literature to firmly establish a link between TRBs and ATS usage due to different methodological approaches, the effect of different drug types, and the extent of adjusting for confounding variables. This literature review intends to benefit the development of clinical, prevention, and educational interventions for ATS abuse and HIV transmission by analyzing the existing evidence to answer the following research question; is the risk of sexual risk behaviors and HIV transmission greater for those using methamphetamine? Study limitations and recommendations for future research, along with the concluding statement were presented.

METHODS

A literature review was conducted after comprehensive keyword searches using several databases including PubMed, MEDLINE, PSYCHINFO, and EBSCOhost. In the search, different combinations of the following keywords were included: HIV, AIDS, ATS, amphetamine, methamphetamine, stimulant, sexual risk behavior, risky behavior, TRB, MSM, gay, bisexual men, heterosexual men, drug use, abuse, and motives. The above keywords were searched in combination using the Boolean operators "AND, OR, and NOT". Potential studies published in only journals written in English language during the past 10 years were identified by first screening titles and abstracts. Studies that did not address at least two of the three major subjects (ATS drug abuse, HIV, sexual TRBs) in some capacity or that concerned populations outside of the United States were excluded. Full-text articles were then assessed for eligibility and examined independently. To be eligible, studies had to be published original research. Included studies were not limited by methodology or participant demographics.

RESULTS AND DISCUSSION

Drumright et al. (2009) conducted a case-controlled study assessing the association between recent HIV infections (previous 12 months) among men who have sex with men (MSM) and use of illicit substances and erectile dysfunction medication (EDM)²⁵. The results were compared against a control group consisting of HIV-seronegative participants using generalized estimating equations (GEEs) to model the average response. The findings revealed that the association of methamphetamine or nitrites usage among the last three sexual partners and unprotected anal intercourse (UAI) was independent of case-control status (OR = 3.1, $p < 0.01$; OR = 1.8, $p = 0.01$ respectively). These results suggest that usage of methamphetamine or nitrites could increase the likelihood of UAI, which is the high-risk sexual behavior for HIV infection. Likewise, through secondary analysis of the Youth Risk Behavior Survey, Springer et al. (2007) found that lifetime methamphetamine use among U.S. high school students, both male and female, was significantly associated with six distinct sexual risk behaviors²⁶. These behaviors included "having had sexual intercourse, having had sexual intercourse before age 13, lifetime sexual intercourse experience with four or more people, no condom uses during last sexual intercourse, having been pregnant or gotten someone pregnant, and having used drugs or alcohol before last sexual intercourse". However, Drumright et al. (2009) study was not able to find out whether nitrite and methamphetamine substances had been used before participants decided to have a sexual activity or at any other time. This might overestimate the relationship between substance

abuse and the risk of HIV infection, however, the Monitoring the Future reports indicated that the danger of substance abuse is underestimated among many adolescents²⁷. Further, the study did not establish an association between HIV status and EDM use. This might be attributed to the fact that EDM may have other uses such as maintaining an erection while using a condom.

Springer et al. (2007) found that students who reported methamphetamine use were more likely to engage in high-risk sexual behavior. The study showed that the prevalence of lifetime methamphetamine use, having had sexual intercourse before the age of 13, and having sexual intercourse with multiple partners among males was comparable to females. The study strongly supports the argument about the association of amphetamine use and the risk of having unprotected sex. Moreover, the study explored several reasons behind using methamphetamine and that include enhancing the sexual experience and sexual functioning. Strikingly, a higher number of rural participants reported methamphetamine use than urban participants, nonetheless, there was lack of significant differences in the prevalence of methamphetamine use based on geographic regions. The need for future research to investigate the role of gender and geographic areas in substance abuse and sexual risk behavior is critical.

The following year, Wohl et al. (2008) identified a need to study the population demographics and methamphetamine-associated TRBs of MSM and non-MSM diagnosed with HIV/AIDS in Los Angeles County (LAC)²⁸. Using a cross-sectional survey, they found that MSM were at a higher risk of using non-injection drugs (OR = 1.8; 95% CI: 1.3, 2.5), ever having used methamphetamine (OR = 3.1; 95% CI: 2.1, 4.8), having used methamphetamine in the 12 months preceding interview (11% vs. 0.4%; Chi-square test, $p < 0.0001$), and having had anal and/or vaginal sex in the last 12 months (OR = 2.6; 95% CI: 1.8, 3.6) as compared to their non-MSM counterparts. Furthermore, 20% of all MSM reported having had 10 or more sexual partners within the preceding 12 months, and this group was four times more likely to have used methamphetamine in the past (OR = 4.0, 95% CI: 2.3, 7.2) than MSM with fewer sexual partners²⁸. Further, similar proportion of engaging in unprotected sex with a male sex partner and female sex partner was reported MSM (15%) and non-MSM (12%), respectively. In addition, MSM who reported unprotected anal intercourse with their male sex partners were more likely to use methamphetamine as compared with MSM who had never experienced methamphetamines. A key finding in this study was that a large proportion of White non-MSM reported having ever used methamphetamine (63%). This proportion was greater than that of the White MSM group (50%) despite the trend that overall the MSM group including all races reports a higher percentage of methamphetamine use. This finding could be supported by the higher prevalence of injection drug use among non-MSM lifetime methamphetamine use. The implications of this study not only supported methamphetamine abuse as a risk factor for HIV transmission through associated sexual risk behaviors (i.e., UAI and multiple sexual partners) but also showed that methamphetamine use is a behavioral issue concerning HIV-infected subgroups, despite the high prevalence of methamphetamine use among MSM. Notably, participants in Wohl et al. (2008) study who were diagnosed with HIV or those experienced disease progressions started to lessen their methamphetamine use. Further studies need to explore the psychological factors associated with this decreasing substance use.

Ober et al. (2009) also identified a lack of research concerning older, very low income MSM and the factors that led this group to use crack cocaine or methamphetamine during specific sexual encounters²⁹. Of 779 participants, 22% reported using methamphetamine during their latest sexual encounter, and 33% reported using crack cocaine. HIV positive individuals comprised 49% of the methamphetamine using group and 24% of the crack using group. Unprotected sex, having

sex in a public sex venue, having sex with an HIV positive rather than with an HIV negative partner, having exchanged sex for money or drugs, and having a higher number of sexual partners irrespective of the partner category were found to be associated with increased odds of methamphetamine use. The findings revealed that sexual risk behaviors are frequently reported among amphetamine abusers and that is potentially responsible for a higher risk of HIV transmission as compared to other stimulant abusers. The higher risk of HIV transmission associated with amphetamines use could be attributed to having higher odd of unprotected intercourse. Methamphetamine abuse was also found to be closely related to specific demographic subgroups. The study showed that abuse was higher with White non-Hispanics, HIV positive individuals, and people between the ages of 30-39²⁹. These demographic findings were consistent with those found by other studies^{25,26,28,30}.

Reports prepared by SAMHSA (2009) and PATS (2009), revealed that Americans aged 12 and older abused an illicit drug at least once during their lifetime, indicating that young adults are becoming more receptive to substance abuse^{31,32}. Among incarcerated individuals in California, methamphetamine was the second most commonly consumed substance after marijuana, but was regarded as the most problematic substance, followed by alcohol and crack. Usage of injectable drugs during the 6 months preceding incarceration was significantly associated with usage of methamphetamine (Chi-square [1, N = 806] = 75.8, $p < .001$), but injection practices (i.e. sharing of dirty syringes, cookers, cotton, or rinse water) did not differ significantly between methamphetamine users and non-users. This indicates that HIV-related sexual risk behaviors (i.e., unprotected sex) among methamphetamine users are far more challenging to the healthcare system than sharing syringes and other injection equipment. Controlling for demographic differences, methamphetamine was significantly associated with unprotected sex with a non-spouse/partner or injection drug user during the 6 months preceding incarceration ($p < 0.0001$); however, the slight difference in the number of sexual partners of methamphetamine users and non-users was not statistically significant. With the increasing prevalence of methamphetamine use, the need for establishing behavioral and drug treatment program is very essential.

Blashill et al. (2014) conducted a cross-sectional behavioral survey using an audio-computer assisted self-interviewing assessment to evaluate the association of methamphetamine use with sexual risk of HIV-transmission among HIV-positive participants³³. The participants were categorized into three relationship statuses based on the number of sexual partners. The author revealed a significant association between the relationship status and the use of methamphetamine, in which monogamous participants with only one sexual partner were less likely to use methamphetamine than monogamous participants with more than one sexual partner or those who engaged in an open relationship. Similar results were reported by Parsons et al. (2013) where substance abuse was less prevalent among gay and bisexual men who engaged in monogamous relationships as compared to those who were single or engaged in open relationships (Wald $\chi^2(3) = 8.80$, $p = 0.03$)³⁴. More important, Parson et al. (2013) study also demonstrated the key roles that life satisfaction and psychological distress play as key elements in avoiding substance abuse and sexual risk behaviors among monogamous men. Although several earlier studies did not establish the effect of life satisfaction among open and monogamous relationships^{35,36}, future efforts need to be geared towards investigating the influence of life satisfaction and psychological distress on sexual risk behaviors through using different study designs.

Blashill et al. (2014) also showed that the use of methamphetamine was a significant predictor of being susceptible to HIV-transmission risk behavior. Higher proportions of sero-discordant unprotected anal intercourse (SDUAI) were found in the “monogamous with more

than one sexual partner” (52%) and “open relationship” (42%) groups as compared to the “monogamous with one sexual partner” group (21%). Furthermore, the “monogamous with more than one sexual partner” group was almost three times more prone to engage in SDUAI compared to individuals with only one sexual partner (OR = 2.9, $p = 0.05$)³³. Non-disclosure beliefs and viral load beliefs were also associated with sexual risk behaviors in the monogamous with more than one sexual partner. It is important to note that the definition of monogamy should be accurately recognized as it may illustrate more untraditional realities about the relationship status engendered due to the fear of experiencing internalized homophobia and high levels of HIV stigma.

Concerned with elucidating causality rather than association, Hoenigl et al. (2016), studied 8,905 MSM participating in a community-based HIV screening program to determine whether starting methamphetamine lead to increased risky sexual behaviors³⁷. Due to the unethical nature of using a randomized control trial when studying methamphetamine, Hoenigl et al. (2016) utilized a retrospective cohort study. San Diego Early Test (SDET) is a self-administrated evaluation that predicts an individual's risk of acquiring HIV based on the person's sexual history. Scores were calculated for each time a participant underwent screening for HIV. SDET scores range from 0 to 10, with 10 signifying the highest risk of HIV acquisition among MSM, and are based on key risk variables of HIV sexual transmission (i.e. condomless receptive anal intercourse and number of male partners). Of the participants who tested multiple times, those who were initially grouped as “never-meth” (i.e., participants who had not used injected/non-injected methamphetamine in the previous 12 months or had never used methamphetamine) and then later grouped as “recent-meth” (i.e., participants who used injected/non-injected methamphetamine in the previous 12 months) had a significant increase in SDET scores³⁷. However, those participants who were initially categorized as “never-meth” and were later categorized as “recent-meth” during 2 or more following testing encounters did not have a significant increase in SDET scores after the initial increase. This study provides strong evidence to date that initiation of methamphetamine causes an increase in HIV sexual TRBs. Another explanation for the increased likelihood of HIV transmission among methamphetamine users could be the side effects of Methamphetamine such as dry mouth, which is suitable for HIV mucosal transmission. However, Hoenigl et al. (2016) found that stopping methamphetamine use would further decrease the number of sexual partners but it had no effect on other risk behaviors such as condomless anal intercourse or STDs. The lack of risk behavioral changes may indicate the slow recovery of methamphetamine effect.

HIV transmission is a global public health issue, as is prescription and illicit drug abuse. Unsafe injection practices (e.g. sharing needles and incorrect disposal of used sharps) are well known to increase rates of parenteral transmission of not just HIV, but also hepatitis C³⁸. However, HIV transmission has also been linked to usage of non-injectable drugs, especially amphetamine-type stimulants. This literature review analyzed many articles with the objective of clarifying this link between methamphetamine users and HIV transmission.

Numerous articles across several countries have mentioned higher rates of sexual risk behaviors such as unprotected anal/vaginal intercourse, inconsistent condom use, having sex at early age and multiple sexual partners among Amphetamine-group stimulants users or injectors compared to other drug users/injectors. Moreover, users who used CNS stimulants have been associated with increased sex drive (libido); leading to more frequent sexual activity that can potentially increase the risk of exposure to sexually transmissible infections (STIs), including HIV. Noteworthy, assessing strong relationships between amphetamine-group substance use and sexual

risk behaviors are of a particular importance but still difficult to measure indirectly. Thus, more robust research designs that examine various confounding variables are required.

A summary of the selected studies is listed in Table 1.

LIMITATIONS OF THE REVIEW

Evidence linking amphetamine-group stimulants use directly with high-risk sexual behavior that put people at risk of HIV is cogent, but not irrefutable. While a wide variety of studies were analyzed in this review, future studies can still improve upon the current literature.

Ethical concerns. All of the studies included in this review utilized observational study designs. Experimental designs are generally considered to provide stronger evidence than observational designs; however, it is ethically impossible to utilize a randomized control trial to study the effects of ATS on sexual risk behaviors. Hoenigl *et al.* (2016) and Drumright *et al.* (2009) utilized the next strongest study designs (cohort and case-controlled studies, respectively) with respect to randomized control trials. However, without an experimental randomized study, it is difficult to control for confounding variables that may have been associated with both ATS usage and sexual risk behaviors, such as depression, as acknowledged by Hoenigl *et al.* (2016).

Table 1: Comparison of Selected Studies.

Authors / Year Published	Location	Study Design	Sample Size / Participants	Relevant Findings
Blashill <i>et al.</i> , 2014	Boston, Massachusetts	Cross-sectional Audio-computer assisted self-interviewing assessment	n = 503 HIV (+) MSM who screened and/or enrolled in two HIV prevention interventions	Monogamous participants with only one sexual partner were less likely to use crystal methamphetamine than monogamous participants with more than one sexual partner or those who engaged in an open relationship.
Drumright, Gorbach, Little, and Strathdee, 2009	San Diego, California	Cross-sectional Case-control	n = 145 Cases – Recently HIV infected MSM Controls – Recently HIV-negative MSM	The association of methamphetamine or nitrites usage among the last three sexual partners and unprotected anal intercourse (UAI) was independent of case-control status.
Farabee, Prendergast, and Cartier, 2011	California, USA	Retrospective interview	n = 807 California state prison inmates with a history of substance abuse	Incarcerated meth users were significantly more likely to have injected drugs during the six months prior to incarceration and had significantly higher past six-month sex-related risks. Of those who had injected drugs, meth use was not significantly related to injection-related risks.
Hoenigl, Chaillon, Moore, Morris, Smith, and Little, 2016	San Diego, California	Retrospective survey	n = 8,905 MSM participating in a community-based HIV screening program n = 779 Male participants of the Los Angeles site of the NIDA Sexual Acquisition and Transmission of HIV Cooperative Agreement Program (SATHCAP) who reported having had at least one at least one instance of anal intercourse with men in the past six months who may or may not have also reported sexual intercourse with women	Initiation of methamphetamine significantly increased SDET scores. Continuation of methamphetamine usage did not impact SDET scores.
Ober, Shoptaw, Wang, Gorbach, and Weiss, 2009	Los Angeles, California	Cross-sectional Self-administered computerized interview	n = 927 Gay and bisexual men at a series of gay, lesbian, and bisexual (GLB) community events in New York City	Increased odds of methamphetamine usage were associated with unprotected sex, having sex in a public sex venue, having sex with an HIV positive partner, having exchanged sex for money or drugs, and having a higher number of sexual partners.
Parsons, Starks, DuBois, Grov, and Golub, 2013	New York, New York	Cross-sectional street-intercept method	n = 15,240 Male and female high school students	Substance abuse was less prevalent among monogamous relationships.
Springer, Peters, Shegog, White, and Kelder, 2007	U.S.A.	Secondary Data analysis	n = 15,240 Male and female high school students	Lifetime methamphetamine use was significantly associated with all sexual risk behaviors. MSM were at a higher risk of using non-injection drugs, ever having used methamphetamine, having used methamphetamine in the 12 months preceding interview, and having had anal and/or vaginal sex in the last 12 months.
Wohl, Frye, and Johnson, 2008	Los Angeles County, California	Cross-sectional survey	n = 683 455 MSM and 228 non-MSM diagnosed with AIDS	20% of all MSM reported having had 10 or more sexual partners within the preceding 12 months, and this group was 4 times more likely to have used methamphetamine in the past than MSM with fewer sexual partners.

Methods of data collection and temporal perspective were limitation for the study findings. Each study included collection of self-reported data or secondary analysis of previously self-reported data. Furthermore, these data sets were collected as cross-sectional or retrospective which are limited in the fact that they can only show a correlation and not determine causality. Recall and social desirability biases, as well as hesitation to truthfully disclose information regarding illicit drug use may have also negatively impacted the collected data. Lack of power was also a limitation that might affect the ability to avoid type II errors. Concerning the generalizability of findings, each of the studies reviewed considered various demographic and socioeconomic factors, most of the articles focused on populations in the northeast and western coasts of the country. Only Springer et al. (2007) sampled individuals from other regions of the country, but the mass majority of those individuals were still concentrated in these regions.

CONCLUSIONS

It is evident from this review that a correlation exists between ATS use and TRBs. These findings provide an initial description of a well-defined group of ATS users, who are at extremely high risk for HIV exposure and transmission either through injection itself or unsafe sexual behaviors. The results of this review have demonstrated the need for health programs aimed at decreasing the transmission of HIV among illicit drug abusers such as needle exchange programs and safe sex programs. Many of the limitations identified in this review can be easily addressed in future studies. Follow-up case-control or cohort studies conducted prospectively will further strengthen existing results linking ATS usage to sexual risk behaviors. Future studies should also include in their analyses possible confounding variables, such as depression, that could be associated with both ATS usage and sexual risk behaviors. Furthermore, to increase the generalizability of results, studies need to comprehensively incorporate other populations in their analyses, such as rural communities and those who engage in sex trade, through multicenter sampling across the country.

KEY MESSAGES

First, our findings suggest that methamphetamine is the second most commonly consumed substance after marijuana, especially among adolescent and school students. Secondly, measuring and preventing sexual risk behaviors (e.g., unprotected anal sex) among methamphetamine users are increasingly becoming a quiet challenge. Finally, future efforts should focus on measuring possible confounding variables, such as depression and side effects of methamphetamine, which could be indirectly associated with both drug abuse and sexual risk behaviors

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