HIV in people who use drugs 5

Amphetamine-group substances and HIV

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This is the fifth in a Series of seven papers about HIV in people who use drugs

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Amphetamine-group substances are used worldwide and are more prevalent than either cocaine or opioids. We reviewed published reports about amphetamine-group substances and did a meta-analysis of randomised controlled trials of behavioural interventions for their use. Most research was done in developed countries. Many, but not all, studies show an association between amphetamine-group substance use and risk of HIV infection. Much use of amphetamine-group substances is non-injection and is associated with increased HIV risk, particularly in men who have sex with men. The structural, social, interpersonal, and personal factors that link to amphetamine-group substance use and HIV risk are poorly understood. 13 studies, with a cumulative sample size of 1997 individuals, qualified for the meta-analysis. Overall, high-intensity behavioural interventions were moderately effective in reducing use of amphetamine-group substances (effect size 0·28, 95% CI 0·13–0·44). We did not find conclusive evidence that behavioural interventions as a group are more effective than are passive or minium treatment for reduction of amphetamine-group substance use or sexual risk behaviours. The search for effective, scalable, and sustainable interventions for amphetamine-group substance use, including pharmacotherapies, should be supported and encouraged.

Introduction

Amphetamine-group substances are synthetic compounds that are used worldwide, often in populations with high prevalence and incidence of HIV infection. Amphetamine-group substances include amphetamine (rINN amfetamine), methamphetamine (rINN metamfetamine), and their derivatives, such as methcathinone, fenetylline, and methylphenidate, but

Key messages

- The contribution of amphetamine-group substances to the global HIV epidemic cannot be quantified, and the contribution of non-injection use of amphetamine-group substances to the HIV epidemic has been understudied. Improved efforts are needed to quantify and monitor the extent to which amphetamine-group substances are used, and the role of amphetamine-group substances in the HIV/AIDS epidemic, especially in developing countries.
- The natural history of amphetamine-group substance use needs to be established in different populations, including predictors of initiation, episodic versus heavy use, development of dependence, and cessation.
- Greater understanding is needed of the developmental, psychological, social, and environmental factors contributing to amphetamine-group substance use and sexual risks and other harms related to amphetamine-group substances. Most research has focused on men who have sex with men in developed countries, and little is known about how these factors interact to contribute to sexual risk taking in other populations.
- The prevalence of other drug use among users of amphetamine-group substances needs quantification, and the contribution of specific patterns and combinations of amphetamine-group substance use with other drugs to risk of HIV infection needs to be established.
- Rigorous trials of behavioural and pharmacological interventions for amphetamine-group substance use are needed with drug-related and HIV-related biological outcomes. The focus must be on scalable and cost-effective interventions. Findings of our meta-analysis showed that as a group, high-intensity interventions reduced use of amphetamine-group substances, but we recorded no significant evidence that high-intensity interventions or other behavioual interventions reduced sexual risk behaviour.
- Users of amphetamine-group substances need to be provided with evidence-based, culturally competent substance-use treatment and care, combined with HIV treatment and prevention for people with or at risk of HIV infection.

Search strategy and selection criteria for the narrative review

The narrative section of this report does not lend itself to traditional systematic review methodology. We searched PubMed, Embase, PsycInfo, and EBSCO databases with general or specific terms for the drugs that we examined (eg, "amphetamine", "methamphetamine", "stimulant", "dextroamphetamine", "d-amphetamine", "methylamphetamine", "desoxyn", "desoxyephedrine", and "methcathinone") with the components: behavioural and biological endpoints of interest, including "HIV", "HIV risk", "HIV progression", "AIDS", "AIDS mortality", "sexual risk", "behavioral risk", "STDs", "condom use", "unprotected sex", and "sex partners"; populations and geographical regions of interest, such as "MSM", "gay and bisexual men", "commercial sex workers", "homeless", "IDU", "youth", "women", "South Africa", "Thailand", "Ukraine", and "Australia"; and interventions, inclusive of "cognitive behavioral therapy", "relapse prevention", "contingency management", "pharmacologic interventions", "pharmacotherapy", "substance use treatment", "dependence treatment", "precursor regulation", and "harm reduction." We selected relevant published reports, including reports by governments, policy institutes, and non-governmental organisations, on the basis of our knowledge and experience. Emphasis was placed on inclusion of studies published within the past 3 years, but earlier studies that were highly relevant were also considered. We restricted the review to documents published in or translated into English.

exclude the class of ecstasy-type stimulants.[1] Use of amphetamine-group substances is implicated in HIV transmission, with data supporting the hypothesis that in some populations, the effects of amphetamine-group substances result in increased risk taking, such as unprotected sex, sex with many partners, and lengthened sexual episodes.[2] Most documented use of amphetamine-group substances linked to risk of HIV infection is non-parenteral and episodic, emphasising the need for drug treatment and HIV prevention programmes to address the needs of users of amphetamine-group substances who do not inject.[2,3] People who remain in treatment for amphetamine-group substance use have reduced use of these substances and HIV-related risk behaviour.[4,5] However, we show in our meta-analysis that few rigorous, randomised controlled trials have assessed the efficacy of behavioural interventions for reduced amphetamine-group substance use or sexual risk behaviour. Additionally, most interventions focus on heavy users, and few result in reduced incidence of HIV infection or sexually transmitted diseases compared with control conditions. We report present patterns of amphetamine-group substance use, interpret the contribution of amphetamine-group substance use to HIV-related risks, systematically review and meta-analyse interventions for amphetamine-group substance use, and identify knowledge gaps.

Prevalence of amphetamine-group substance use

Amphetamine-group substances are the most widely used subgroup of amphetamine-type stimulants, and are more prevalent than either opioids or cocaine.[1] 16–51 million people worldwide used amphetamine-group substances at least once in 2007. Although prevalence of amphetamine-group substance use might be stabilising in some western countries, use is increasing in east and southeast Asia and the Middle East (panel 1).[1] Amphetamine-group substances can be snorted, smoked, injected, or used rectally. By contrast with opioids, most use of amphetamine-group substances is non-injection, although the proportion of users of amphetamine-group substances reporting injection varies substantially by region and risk population (eg, men who have sex with men, heterosexual people, commercial sex workers).[23–25] Despite the apparent widespread use of amphetamine-group substances, there are few reliable epidemiological data about the distribution of amphetamine-group substance use in general and specific populations.[1,24] Regions in which amphetamine-group substance use might be increasing have a scarcity of data on the extent of the problem. Often the best available data are from developed countries and therefore are not generalisable to developing countries.[26] This gap in data on amphetamine-group substance use is also present in populations at risk for HIV infection. Probability-based samples are not available for most regions, but in the USA and Australia, amphetamine-group substance use is far more prevalent in men who have sex with men than in the general population.[11,21,22,27] In some regions, use of amphetamine-group substances is particularly common in people with HIV infection.[28,29] Use of amphetamine-group substances is also of concern in other vulnerable populations, including homeless people, those with unstable housing, and incarcerated populations.[30,31]

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Manufacture and supply

Unlike opioid or cocaine precursors, which can be grown only in regions with suitable climate and soil, amphetamine-group substances can be manufactured anywhere with access to the appropriate ingredients. The most common precursors for methamphetamine production include ephedrine or pseudoephedrine.[13] Either phenylpropanolamine or phenylacetic acid can be used to synthesise amphetamine. In Europe, benzyl methyl ketone (BMK; 1-phenyl-2-propapone) is mainly

Panel 1: Diversity of amphetamine-group substance use worldwide

Africa

- South Africa: increasing prevalence of use of methamphetamine, locally known as Tik; spike in treatment related to amphetamine-group substance use in Cape Town[6]
- Uganda: use of Khat, a plant containing amphetamine-like compounds, associated with increased sexual desire[7]

Americas

- Brazil: lifetime prevalence of amphetamine-group substance use in urban areas doubled from 2001 to 2005; use of amphetamine-group substances documented among truckers and commercial sex workers engaging in unprotected sex[1,8]
- Canada: amphetamine taken during survival sex work in cohort of street youths[9]
- Colombia: in 2004–05, the prevalence of amphetamine-group substance use for the previous year in secondary school students was seven times higher than was that in the general population[1]
- Mexico: increasing methamphetamine production and distribution, accounting for 70–90% of supplies to USA; in Tijuana, methamphetamine use documented with transactional sex[1,10]
- USA: disproportionately high use of methamphetamine in men who have sex with men[11,12]

Eastern Mediterranean

- Jordan: substantial increase in presence of fake fenethylline or Captagon tablets adulterated with amphetamine in illicit drug market[1]
- Saudi Arabia: site of a quarter of all amphetamine seizures worldwide[1]

Europe

- Czech Republic: highest reported prevalence of methamphetamine use in Europe; pervitin, a homemade methamphetamine variant, is usually injected[13,14]
- Estonia: increase in injection of amphetamine coincided with reductions in heroin supplies in the region; HIV prevalence of 27% in injectors of amphetamine[15]
- Norway: largest number and greatest volume of methamphetamine seizures in Europe[13]
- UK: methamphetamine use among men who have sex with men with high-risk sexual behaviours in London[16]
- Ukraine: stimulant injection of home-brewed amphetamine-group substances; rising HIV prevalence associated with injection of amphetamine-group substances[17,18]

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Southeast Asia

- Indonesia: methamphetamine use independently associated with HIV status in urban men who have sex with men[19]
- Thailand: methamphetamine ingested in pill form locally known as yaba; high rates of methamphetamine use associated with sexually transmitted infections[1,20]

Western Pacific

- Australia: increase in crystal methamphetamine use among substance users and men who have sex with men; local production and importation of amphetamine-group substances is increasing[1,21,22]
- Japan: injection was most common route of administration in a sample of users of amphetamine-group substances in an outpatient treatment centre[23]
- New Zealand: restrictrions on over-the-counter precursors of amphetamine-group substances has led to smurfing (shopping at several pharmacies to circumvent pill precursor restrictions)[1]

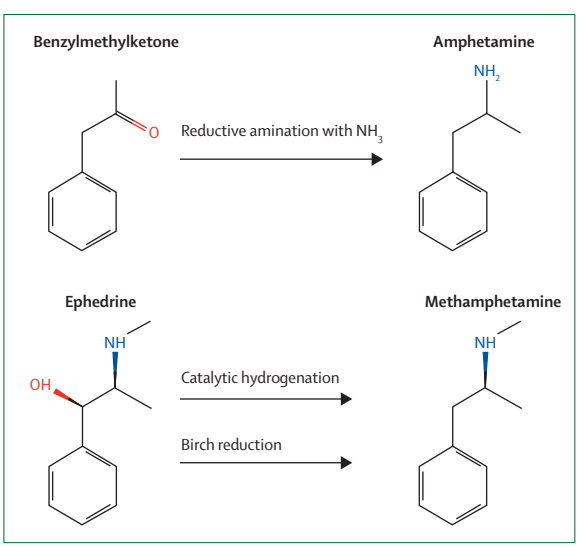

Figure 1: **Chemical structure of amphetamine, methamphetamine, and their precursors[32]**
Structures sourced from the PubChem Project.

For the **PubChem Project** see http://pubchem.ncbi.nlm.nih.gov

used to synthesise amphetamine, but elsewhere BMK is used to manufacture methamphetamine (figure 1).[1] The wide availability and low cost of these precursors, coupled with the simple manufacturing process, has probably contributed to the escalation of amphetamine-group substance use worldwide. Amphetamine-group substances are manufactured in more than 60 countries.[1] In 2007, an estimated 230–640 metric tons of amphetamine-group substances were manufactured, with seizures of 44 metric tons.[1] Regions with particularly high manufacturing and trafficking include southeast Asia, Russia, Mexico, and Australia.[1,21,33] In addition to illicit manufacture, substantial quantities of prescription amphetamine-group substances are diverted to recreational use and abuse.[34,35]

Natural history of amphetamine-group substance use

Few data are available on the proportion of people starting to use amphetamine-group substances who progress to heavy use or dependence.[24] The social determinants of starting and continuing amphetamine-group substance use still need to be established in most populations, although social norms and homophobia have been implicated in contributing to high rates of amphetamine-group substance use among men who have sex with men.[36] Despite a growing interest in identification of biomarkers for abuse of amphetamine-group substances, little research has been empirically replicated. Several candidate genes have been identified as associated with the response to amphetamine: acute responses to amphetamine (ie, increased euphoria) have been associated with polymorphisms in transporter genes for dopamine (*SLC6A3*), norepinephrine (*SLC6A2*), and serotonin (*SLC6A4*).[37–39] In a 10-year study on the trajectory of substance use, Hser and colleagues[40] reported that use of amphetamine-group substances can persist long term but, by comparison with opioids, most amphetamine-group substance use remains moderate. Social users and functional users of amphetamine-group substances have been characterised.[41] Social users share amphetamine-group substances to enhance interpersonal interaction.[42] By contrast, functional users have utilitarian motives: they take amphetamine-group substances to complete a specific task.[41] Motivations of functional users of amphetamine-group substances are varied and include the desire to lose weight, improve mood, enhance work performance, and counter fatigue.[41,43,44]

The chemical structure of methamphetamine might affect dependence severity—for example, users of the crystalline form were significantly more likely to be dependent than were those using other forms of the drug.[45] In a US national survey in people who reported using amphetamine-group substances within the past month, only 22·3% met the criteria for stimulant dependence.[27] But although heavy use and dependence might occur in a small proportion of users of amphetamine-group substances, the individual and public health consequences of amphetamine-group substance use should not be underestimated. In many countries, users of amphetamine-group substances account for a substantial proportion of substance users presenting for treatment; data for selected countries are shown in figure 2.[1]

Risk of HIV infection

The HIV-related risks associated with amphetamine-group substance use are well documented in epidemiological and clinical studies. Findings suggest that use of amphetamine-group substances increases susceptibility to HIV infection through many behavioural and biological pathways.

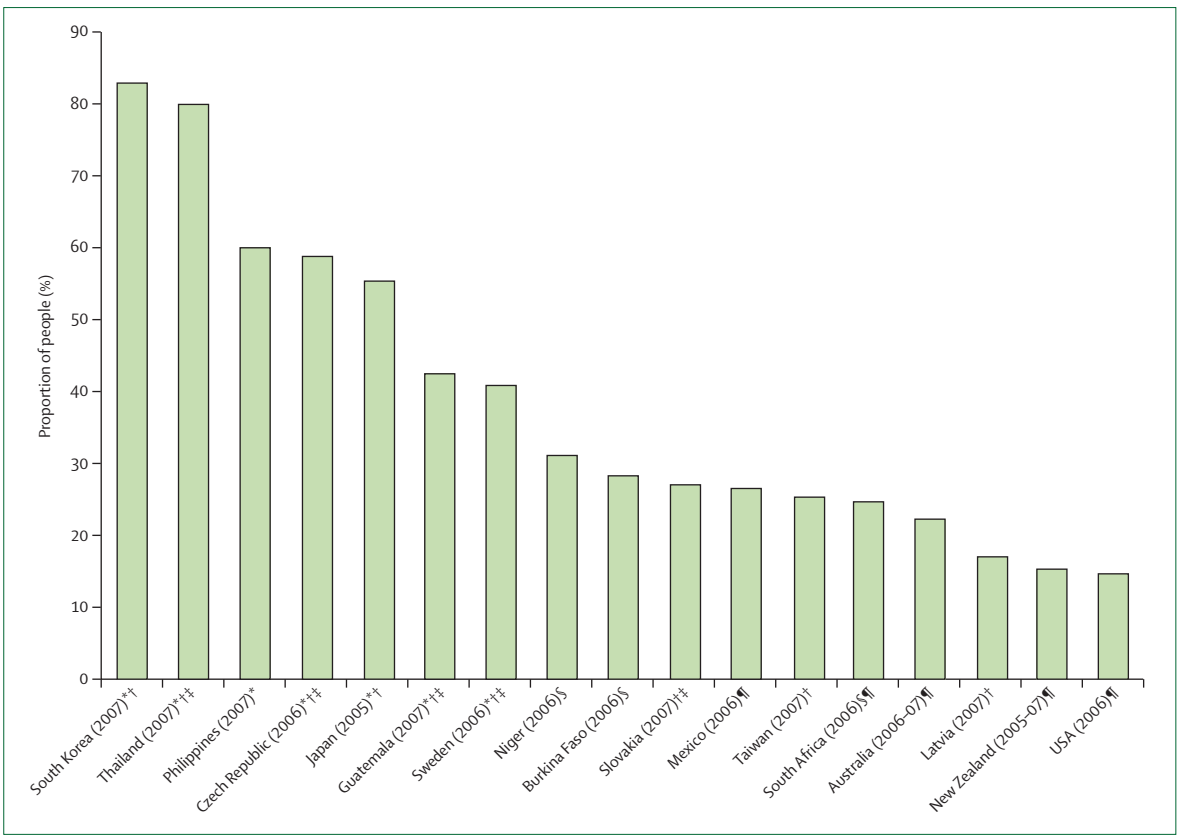

Figure 2: **Countries in which a high proportion of drug abusers in treatment report amphetamine-group substances as main drug of abuse**
Data are adapted from UN Office on Drugs and Crime report[1] for countries in which abusers of amphetamine-group substances constitute more than 14% of substance users reported in treatment. Dates of data collection are noted in parentheses. *Amphetamine-group substances are the most widespread illicit drug abused. †Inpatient treatment centre. ‡Outpatient treatment centre. §Data are for amphetamine-type stimulants, which could include drugs with hallucinogenic properties, such as ecstasy. ¶Publicly funded treatment centre.

Sexual risk behaviour

Amphetamine-group substances are especially relevant to the HIV epidemic because they are often used in a sexual context to enhance and prolong sexual pleasure and to reduce sexual inhibitions (panel 2).[46–48] High risk of HIV infection is associated with heavy use of amphetamine-group substances and, importantly, with intermittent (less than weekly), episodic (during specific social events or with specific sexual partners) use of amphetamine-group substances, suggesting that these patterns also make a substantial contribution to HIV transmission.[49] Independent associations of amphetamine-group substance use and HIV-related risk behaviour have been widely reported in men who have sex with men, heterosexual adults, young people, and other populations at risk for HIV infection.[50–52] Use of amphetamine-group substances is independently associated with behavioural outcomes that are directly related to HIV exposure, such as unprotected anal or vaginal sex, and sex with many partners.[50,53–55] These associations are not limited to cross-sectional data. For instance, in one longitudinal analysis, methamphetamine use was positively associated with unprotected sexual behaviour at four timepoint assessments.[56] Some,[3,50,53] but not all,[57] event-level analyses (ie, analysis of whether drug use occurred just before or during sexual episodes) also show independent associations between amphetamine-group substance use and sexual risk behaviour. Use of amphetamine-group substances is also associated with contextual factors for risk, such as having sex in a public venue, meeting partners in a bathhouse, exchanging money or drugs for sex, and having an early sexual debut.[51,53,55] Intensity and frequency of amphetamine-group substance use also affect sexual risk—for example, binge users of methamphetamine report having more unprotected vaginal sex than do non-binge users.[54]

Evidence linking amphetamine-group substance use directly with high-risk sexual behaviour is strong, but not irrefutable. In some studies, independent associations between risk behaviour and amphetamine-group substance use have not been identified.[24] Also, publication bias could favour studies reporting positive associations. The positive independent associations between amphetamine-group substance use and sexual risk do not confirm causality and could be confounded

***Panel 2:* Thoughts from a recovering crystal methamphetamine addict (Jan 14, 2010)**

"My name is John. I am 49 years old. On the surface there were no outstanding environmental factors that would have predicted my crystal meth addiction.

New Year's Eve was when I discovered meth; it was placed in my juice. For the next several months I used meth intermittently. But in short time I had moved from snorting meth to smoking it. I equate my meth use and fall, in a way, as an elevator on the 37th floor of a high rise in the financial district, where I worked, to the basement, in four years.

I would get high and then in a 24 hour period, I would have multiple partners. It could be either multiple partners at the same time playing or it could be four, five, six, seven, eight, nine, ten, fifteen partners over a 24 hour period, and it might be five, six, seven days that I would be out doing meth and having sex. Within three months I was infected with HIV. I had tested negative for the previous nine years, every six months.

Rather than deal with this life-threatening issue (being newly HIV positive), I used it to justify using meth and having more sex. All other parts of my life took a back seat to speed and sex. Then I began to inject meth. Just when I thought I had hit bottom, shooting speed became my way of picking up a shovel and digging me into a deeper hole of addiction.

When I first started using I was a successful corporate executive, owned my own home, had the golden retriever, and drove the nice car. In short order, everything fell apart. I ended up homeless and moved back in with my parents.

I had the ability to get clean for two or three months at a time, but then would slip. But my slips weren't a day or two; my slips would be another three months out. By far the biggest challenge in my life was getting the speed off my back and figuring how to do it because it was so intertwined with sex. The first six months of my sobriety I could count on my one hand the number of times I had sex.

My addiction to crystal meth lasted 6 years. Since getting sober, and because of a lot of hard work and help, I have been blessed with a life I never thought I'd ever live again. Meth once controlled my life. But I am living proof that it doesn't have to."

by many factors, including personality characteristics (eg, sensation seeking or the desire to escape from stressors), and social and sexual networks.[58,59] As for substance use generally, the social contexts of amphetamine-group substance use and expectancies about its effects could be an underlying source of risk.[60] Ethical concerns about the harmful effects of amphetamine-group substances might preclude long-term randomised studies to prove definitive causality. However, in a short-term placebo-controlled study of intravenous methylphenidate, sexual desire significantly increased in both healthy participants and stimulant abusers.[61]

Impairment in decision making and other cognitive deficits are also postulated to contribute to increased risk in users of amphetamine-group substances.[62] The possible deleterious effects of abuse of amphetamine-group substances, especially methamphetamine, on cognition, brain functioning, and decision making have received much attention. The effects of the quantity and duration of amphetamine-group substance use on long-term functioning has been debated at length. Brain imaging studies of adults who use methamphetamine show structural and metabolic abnormalities, but the clinical implications of these findings have not yet been established.[63,64] Methamphetamine abusers perform significantly worse than do controls on measures of executive function, attention, learning, and memory.[62,65] As a result, some researchers view methamphetamine abuse as a cause of impairments of cognitive functioning and related neural mechanisms. However, these important findings have limitations. For example, in many studies, the performance of methamphetamine abusers was compared with that of individuals using no drugs. Since most methamphetamine abusers also use and abuse other drugs (panel 3), the effects of other drug use on cognitive performance has been difficult to disentangle. This situation makes the available data difficult to interpret and suggests that future research should use control groups with individuals who use methamphetamine exclusively.

Association of amphetamine-group substance use with HIV and other sexually transmitted infections

In studies dating back to the late 1980s, use of amphetamine-group substances was associated with HIV prevalence and new diagnoses of HIV infection.[77,78] This association has also been identified with other sexually transmitted infections,[79] mostly in cohorts from developed countries, but emerging evidence suggests that such associations also exist in other regions.[20,80] Although these associations are often attributed to increased risk behaviour linked to amphetamine-group substance use, some longitudinal studies report an independent association of amphetamine-group substance use and HIV seroconversion even after controlling for many behavioural risks. For example, in the EXPLORE trial[70] of men who have sex with men, methamphetamine use independently increased the risk of HIV seroconversion after controlling for number of sex partners, use of other specific substances, unprotected sex, and other variables. Similarly, in the Multicentre AIDS Cohort Study,[81] methamphetamine use was independently associated with greater risk for HIV seroconversion. The reasons for these independent associations remain speculative, but they could be due to unmeasured behavioural factors including prolonged sexual activity or increased trauma during sex while under the influence of amphetamine-group substances, poor recollection of self-reported events, sexual network factors, or potential direct effects of amphetamine-group substances on immune function.[46,58]

Whether the immunological effects of amphetamine-group substances directly contribute to HIV infection remains an area of continued investigation and debate. Several in-vitro studies suggest that certain neurological and physiological factors linked to methamphetamine use

can affect susceptibility to HIV infection and the development of AIDS-related pathology.[82,83] These data provide evidence to support the concept that methamphetamine might be a cofactor for enhancement of HIV infection and replication, although the clinical ramifications remain to be established.[84]

Injection of amphetamine-group substances

Most use of amphetamine-group substances worldwide is not by injection, but injection of amphetamine-group substances still has an important, but difficult to accurately quantify, role in harms and complications related to amphetamine-group substances.[24] Injectors use amphetamine-group substances more frequently, are more likely to be dependent, and, in men who have sex with men, are more likely to report sexual risk than are users of methamphetamine who do not inject.[85,86] In a Thai study, daily injection of methamphetamine was reported by a third of injecting drug users.[87] In samples of injecting drug users, injectors of amphetamine-group substances are more likely to be younger and male, and men are more likely to report sex with other men, than are injectors of other drugs.[25,88] Findings from some, but not all, studies show that methamphetamine injectors are more likely to report injection risk behaviour, a same-sex partner, and non-fatal overdose, and have higher HIV prevalence than do injectors of other drugs.[89–93] Futhermore, injection of amphetamine-group substances has been implicated in HIV transmission in some countries, such as Ukraine (panel 4).

Interventions for users of amphetamine-group substances

To adequately address use of amphetamine-group substances, a combination of multilevel approaches (eg, individual, group, community, and policy) might be needed, including those that address risk of HIV infection. Programmes to prevent and treat amphetamine-group substance use should aim to decrease the number of new users, keep harm to users to a minimum, reduce morbidity and mortality, and lower incidence of HIV infection.[4] We review a variety of interventions, focusing on those most relevant to HIV prevention.

Structural and policy strategies

The general complexities of structural and policy interventions to address substance use, including interventions that address criminalisation, drug demand, supply, and trafficking are covered in detail in other reports in this Series.[96,97] With respect to specific issues around amphetamine-group substances, precursor regulation merits special attention here. Synthetic ingredients are needed for production of amphetamine-group substances so precursor regulation could, theoretically, reduce supply more effectively than it does for agriculturally derived substances such as cocaine, opiates, and cannabis (marijuana). Regulatory measures for amphetamine-group substances focused on bulk precursor diversion from industry, and imposed tight regulations on consumer pharmaceuticals containing ephedrine. Recent efforts have focused on prevention of diversion of over-the-counter formulations containing pseudoephedrine.[1] Data suggest, however, that precursor regulation might have restricted effects.[98] Various precursor regulations in the USA and Canada had mixed results: stores were stopped from selling over-the-counter ephedrine-containing products and had to monitor the amount of ephedrine in individual purchases; Canada's precursor regulations were associated with a 13–15 point increase in methamphetamine purity.[98] In Ukraine, home and small-scale production of amphetamine-group substances continues despite precursor regulation.[17] As regulation of precursor chemicals in wealthy destination

Panel 3: Association of amphetamine-group substances and other drugs with HIV infection

Amphetamine-group substances have a well documented association with sexual risk, but several other substances have also been associated with sexual risk behaviour, although the strength of evidence varies. Crack and powder cocaine have a long association with sexual risk in many populations.[66] Cannabis (marijuana) and club drugs, including methylenedioxymethamphetamine (rINN methylenedioxy-methamfetamine [ecstasy]), ketamine, and gamma-hydroxybutyrate, are used in variety of communities worldwide, but the evidence for independent associations of these drugs with sexual risk behaviour is less compelling than is that for stimulants.[12,67] Amyl nitrates and nitrites (poppers), frequently used during anal sex, are strongly associated with HIV transmission even after controlling for unprotected sex behaviour.[68,69] The correlation of alcohol with risk behaviour is highly variable and dependent on the amount consumed, population studied, and social and cultural context.[70,71]

The association of drug use with HIV infection is further complicated by the fact that many different drug combinations are often used together or sequentially. Although identification of a specific substance to establish risk of HIV infection is logical from a statistical perspective, treatments might need to address polydrug use to reduce risk of HIV infection and drug-related harm. Use of amphetamine-group substances with various classes of other substances can be particularly challenging and seems to be the rule rather than the exception.[72,73] In Malaysia, users of amphetamine-group substances take nimetazepam to induce sleep after binge sessions.[74] Benzodiazepine use in regular users of amphetamine-group substances has also been recorded in Australia.[75] Crystal methamphetamine use has increased in regular users of ecstasy in Australia, and users of crystal methamphetamine reported increased injecting drug use and heroin use.[73] In the USA and Canada, cocaine, ecstasy, ketamine, sildenafil, and heroin have each been reported to be taken with amphetamine-group substances.[9,76]

Panel 4: Injection of amphetamine-group substances in Ukraine

The risk of HIV infection from illicit amphetamine-group substance use has become an issue of increasing concern in eastern Europe, especially in Ukraine, where rates of HIV infection are some of the highest in the region. An estimated 0·7–2·3% of the adult population (aged 15–49 years) is infected with HIV; in 2006, 45% of all new HIV infections were attributable to injecting drug use.[18] Prevalence of HIV infection is high in injectors of amphetamine-group substances, and needle sharing and sexual risk are increased in stimulant injectors compared with opioids injectors, with women who use stimulants at particularly high risk.[94] Stimulants are most often produced and used by home-brewers, and include active ingredients of amphetamine, methamphetamine, and cathinone; products are known as vint, jeff, and boltushka.[17] Cathinone is an inexpensive, weak stimulant with little psychoactive effect when taken orally, so users typically inject the drug intravenously to obtain increased effects. Interventions for Ukrainian injectors are associated with reduced sexual and injection risks, although which strategies are most effective is unclear.[95] Some researchers have postulated that declines in infrastructure and social conditions, including increased unemployment and decreased capacity of medical and social services, have exacerbated Ukraine's drug-related epidemic of HIV infection.[17]

markets becomes more stringent, responsibility for policing of chemical diversion and manufacture of synthetic drugs, and for management of harms from synthetic drug use, are likely to shift increasingly to other countries, many of which have restricted capacity to manage such problems. For example, the tightening of regulations for purchase of methamphetamine precursors in countries with high consumption rates (eg, USA and Japan) has led to a corresponding increase in production of amphetamine-group substances in nations with historically low rates of consumption, including Mexico and Indonesia.[1]

Notably, broad public campaigns have been implemented to address the risks associated with use of amphetamine-group substances. In New York City, social marketing campaigns about the negative aspects of amphetamine-group substances elicited discussion and controversy, but had mixed and unintended results (eg, causing cravings of amphetamine-group substances).[99] Other campaigns have emphasised an empowerment or risk-reduction approach to avoid amphetamine-group substance use.[100] On the internet, websites provide information about amphetamine-group substances and HIV, and many provide a forum for present and former users to share their stories and approaches to dealing with amphetamine-group substances. Although unproved, these peer-education approaches could increase awareness about the risks of amphetamine-group substances. Funding for rigorous assessments of the effectiveness of social marketing and the development of internet-based intervention programmes are needed.

Needle and syringe exchange programmes

As shown by Degenhardt and colleagues' review in this Series,[96] needle exchange programmes have high effectiveness for reduction of HIV transmission.[101] Injectors of amphetamine-group substances should be offered comprehensive needle exchange services. Injectors of amphetamine-group substances are often less likely to engage and access these services than are opioid injectors, and might have different needs for social and other support services.[24,89] These findings point to the need for further tailoring of needle exchange and drug treatment programmes to address both sexual risk and injection-related harms that could be unique to users of amphetamine-group substances.

Testing and treatment for HIV and other sexually transmitted infections

In view of the high rates of sexual risk associated with amphetamine-group substances, routine testing for HIV and other sexually transmitted infections should be offered to users. Although the optimum interval for testing in such populations has not yet been established, screening every 3–6 months seems prudent in settings with high incidence or prevalence of HIV and other sexually transmitted infections. Testing could be increased by integration with treatment services for amphetamine-group substance use, but outreach efforts to test users of amphetamine-group substances not accessing treatment programmes are also likely to be important. Partners of users of amphetamine-group substances should be contacted and encouraged to test at regular intervals.

Few data are available on use of antiretroviral therapy (ART) in users of amphetamine-group substances who are infected with HIV. As discussed by Wolfe and colleagues in this Series,[102] in repeated studies substance users have adhered to ART with resulting declines in HIV-associated morbidity and mortality. A concern regarding ART is the episodic nature of amphetamine-group substance use in some populations: patterns of intermittent binge use of amphetamine-group substances could, if accompanied by lapses in adherence to ART, cause drug resistance to develop. In small studies restricted mainly to men who have sex with men, users of amphetamine-group substances with HIV infection report lower adherence to ART than do individuals who do not use amphetamine-group substances.[29] Methamphetamine use is associated with increased primary resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI) in people with recent HIV infection or infection of unknown duration, although the clinical and public health implications of these findings have yet to be established.[103,104] In a qualitative study, men who have sex with men reported purposive non-adherence:

men planned medication vacations before use of amphetamine-group substances to prioritise sex, prolong or focus on their drug high, or avoid mixing ART with amphetamine-group substances due to fears of possible harmful interactions.[105] Although these data are provocative, clinical experience suggests that use of amphetamine-group substances should not be a contraindication to ART. Instead, clinicians should work with the patient to carefully consider adherence patterns, along with the other risks and benefits of ART, and decide whether to start ART. Ideally, these conversations and subsequent monitoring of viral loads and medications will include encouragement to reduce use of amphetamine-group substances, and referral to treatment for amphetamine-group substance use.

Pharmacological interventions

No approved pharmacotherapies are available for amphetamine-group substance use. Development of pharmacological interventions for opioid and nicotine dependence has been advanced at least in part because the neurobiological mechanisms mediating reinforcement are fairly well understood. By contrast, the neuronal mechanisms of action for amphetamine-group substance use are more complicated, which has probably contributed to the slow progress in drug development. This continuing search has mirrored the discouraging results of trials of pharmacotherapies for cocaine use.[106] Amphetamine-group substances increase monoamine (dopamine, norepinephrine, and serotonin) activity, so most trials have focused on drugs that change monoaminergic function. A large number of candidate drugs has been assessed in double-blind, placebo-controlled trials.[107] None has shown efficacy for reduction of amphetamine-group substance use and many trials are limited by a variety of factors, including small sample sizes and poor retention. No rigorous studies have assessed the effectiveness of substitution treatment for dependence on amphetamine-group substances, a curious omission in view of the fact that replacement therapies for opioid dependence are effective treatments. Several case reports have indicated that oral amphetamine has promise for reduction of amphetamine use, but these data are pending rigorous assessment.[108] Naltrexone, an opioid antagonist, shows promise as a potential treatment for amphetamine dependence, with significant reductions in amphetamine use compared with placebo in a recent trial.[109] Although the mechanisms by which naltrexone produced these effects remains unclear, the investigators speculated that the treatment blunted the subjective and mood-altering effects of amphetamine.[109,110] These encouraging results await confirmation from additional studies.

Behavioural therapies

Engagement in treatment for amphetamine-group substance use is associated with declines in use of these substances and HIV risk behaviour, reinforcing the need to provide treatment options.[111–113] Which behavioural approaches are most effective in which populations remains largely unanswered, and the long-term efficacy of such interventions is questionable. Outcomes of behavioural interventions for amphetamine-group substance use are similar to those for other stimulants such as cocaine; however, very few users of amphetamine-group substances report accessing treatment, which usually occurs in the setting of traditional drug programmes.[27,114,115]

Research into treatment for amphetamine-group substance use has followed the same course as for other substances: the focus has been on treating active users, rather than on primary prevention. In most cases, withdrawal from amphetamine-group substances is not marked with objectively measurable physical symptoms—unlike with opioids—and so behavioural interventions have generally focused on the psychological and social reasons for use rather than on addressing symptoms of physical withdrawal.[116] Treatment relies heavily on behavioural and psychosocial approaches, including cognitive behavioural therapy, relapse prevention, and contingency management.[5] Interventions are largely adapted from programmes developed for other substance-use disorders and many are abstinence based. Most interventions have focused on dependent and heavy users of amphetamine-group substances; very few interventions address the treatment and HIV prevention needs of episodic users of amphetamine-group substances who might not be appropriate candidates for traditional treatment programmes. Innovative programmes integrating syringe access with other harm-reduction strategies, or treating hard-to-reach users of amphetamine-group substances outside of treatment centres, have been piloted and evaluated, but their effectiveness remains unknown.[117,118] Risk-reduction approaches have also been tested in randomised controlled trials and they reduced sexual risk behaviour in specific populations, although rates of follow-up are low.[119,120] Most behavioural interventions are for use individually or in groups, and have been tested in users of amphetamine-group substances in developed countries. An exception is a network-oriented intervention trial done in young Thai people, which led to similar reductions in use of amphetamine-group substances, sexual risk, and incidence of sexually transmitted infections in the two study groups (peer-education network intervention *vs* life-skills condition; panel 5).[123]

Generally, behavioural interventions are resource intensive, and their cost-effectiveness—as is the case for most interventions for amphetamine-group substance use—has typically not been evaluated. Even if behavioural interventions are shown to be cost effective, implementation barriers remain. For instance, the matrix model intervention is a combination of individual and group therapy rooted in cognitive behavioural and psychoeducational theory; this intervention needs

Panel 5: Drug use in Thailand

Methamphetamine use in Thailand has been of epidemic proportions since the mid-1990s, and has mainly been in adolescents and young adults. The most widespread drug of abuse in the country, methamphetamine from Burma, has been regarded as a principal threat to Thailand's national security.[121] In response, Thailand waged aggressive, widespread criminal justice campaigns targeting drug users. The government's 2003 war on drugs resulted in more than 2200 documented killings and was met with worldwide condemnation from human rights organisations.[122] The campaign was revived in February, 2008.

Despite the criminal justice approach, the persistent widespread availability of methamphetamine has continued to allow young people to experiment with the drug. In our intervention trial with more than 1000 Thai citizens aged 18–25 years,[123] methamphetamine had been used for several reasons: as a coping mechanism in response to family strife or boredom; as a solution to the demanding balance of work, school, and family obligations; and as a perceived way to be accepted by peers. The start, continuation, and relapse of methamphetamine use are heavily affected by peers. As one 20-year-old man said: "I had seen it [methamphetamine] used so many times with my friends. I just wanted to try it—I am a teenager of course." Thus, sustainable interventions to reduce harm need to incorporate the role of peers to change permissive norms surrounding methamphetamine use.[123]

Methamphetamine negatively affects users' lives, including interpersonal relationships, productivity, probability of arrest, and susceptibility to HIV or other sexually transmitted infections. Methamphetamine use was linked to sex and sexual risk behaviours in young people by enhancing sexual desire and sexual energy for men and women. The concomitant rise of methamphetamine use in young people coupled with changing norms around premarital sex, a general lack of awareness about vulnerability to HIV or other sexually transmitted infections, and a scarcity of open discussions about safe sex, resulted in low rates of condom use and high rates of sexually transmitted infections. Reduction of methamphetamine use in young Thai people needs comprehensive approaches that address the context of young people and the realities of sex, and methamphetamine policy needs to shift from a criminal justice approach to a public health approach.[124]

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See Online for webappendix

56 sessions and significantly reduces use of amphetamine-group substances at 6 months, but not at 12 months.[125] The balance between the need to treat a disorder that is often chronic and relapsing versus the cost and sustainability of the intervention is a central issue for treatment of amphetamine-group substance use.

Meta-analysis

Search strategy and selection criteria

We did a systematic review and meta-analysis to assess the consistency, quality, comparability, and efficacy of behavioural interventions for reduction of amphetamine-group substance use and HIV-related risk behaviours. To our knowledge, no meta-analysis has focused only on populations using amphetamine-group substances. With the assistance of a professional reference librarian, we searched Embase, PubMed, and PsychInfo for studies about amphetamine-group substances (amphetamine or methamphetamine), users of amphetamine-group substances, and interventions for amphetamine-group substance use (behavioural therapeutic approaches), and for studies with a randomised controlled design. Strings of search terms used in different databases are available on request. Two independent reviewers (G-MS and PC) screened abstracts against predetermined eligibility criteria. Eligible studies had: a randomised, experimental design with at least one treatment group receiving a behavioural intervention and at least one control or comparison group; a sample using amphetamine or methamphetamine; sufficient reported data for calculation of effect size (or author provided appropriate data in response to our inquiries); and measured at least one of the dependent variables of interest at the end of treatment—eg, use of methamphetamine or amphetamine by self-report or urinalysis, and sexual risk behaviours (such as number of partners, frequency of condom use, and number of events of unprotected sex). We excluded citations of single-group studies, quasi-experimental studies, or studies using duplicate datasets or secondary reports. We also excluded reports that were deemed to be inconsistent with the criteria by both reviewers. For example, studies were excluded if they did not assess outcomes of interest,[126] did not report data that were essential for the meta-analysis,[125] or did not disaggregate data on users of amphetamine-group substances from users of other substances.[127] Citations that were repeat retrievals from across databases were also excluded. We resolved reviewer disagreements on study eligibility by full-text reviews and discussion; ties were broken by a third reviewer (GC). We also reviewed the reference lists of retrieved reports for potentially relevant studies.

Data abstraction and outcomes

Two reviewers (G-MS and PC) independently extracted data to calculate effect sizes by use of a standardised form (protocol described in webappendix p 1). We aimed to provide a quantitative aggregate measure of the trials' overall performances on two outcomes: use of amphetamine-group substances and HIV-related sexual risk behaviours. Pooled effect sizes were

calculated for four comparisons: (1) the overall efficacy of behavioural interventions versus passive or minimum treatment on amphetamine-group substance use; (2) the overall efficacy of high-intensity or adjunctive behavioural interventions (eg, gay-specific cognitive behavioural therapy ["gay-specific" is the term used by the studies included in the meta-analysis], or contingency management as an adjunct to cognitive behavioural therapy) versus active treatment on amphetamine-group substance use; (3) the overall efficacy of behavioural interventions versus passive or minimum treatment on sexual risk behaviours; and (4) the overall efficacy of high-intensity or adjunctive behavioural interventions versus active treatment on sexual risk behaviours.

Statistical analysis

We calculated standardised mean differences for individual pair-wise comparisons with Cohen's d,[128] and pooled effect sizes by use of fixed-effects and random-effects models in STATA (version 11.0). We weighted effect size estimates with the inverse-variance method during pooling. We truncated the extreme sample sizes (ie, Winsorised) during weighting by use of a cutoff of 80 people for each of the intervention and comparison groups, similar to other meta-analyses.[129] We did subgroup analyses to assess potential moderators, and checked for homogeneity with Q and I^2 statistics. We used the Begg and Egger tests to assess publication bias. To avoid invalid comparisons, we did a separate meta-analysis for interventions that were tested against different comparison types: we modelled studies with comparison groups receiving passive or minimum treatment separately from studies with comparison groups receiving active treatment (eg, another type of behavioural treatment).[130]

Findings

13 studies qualified for inclusion in the meta-analysis (figure 3): seven were from the USA, four from Australia, and two from Thailand (table). One study[111] contributed two independent pair-wise comparisons. Study size ranged from 20 to 864 participants, and participants were either dependent on amphetamine-group substances (six studies) or regular methamphetamine users (seven studies). Most participants were men; three studies were done exclusively in men who have sex with men. Two studies were done in groups with comorbid psychiatric disorders. The duration of follow-up for trials ranged from 8 weeks to 12 months.

The first comparison modelled the overall efficacy of behavioural interventions versus passive or minimum treatment for reduction of amphetamine-group substance use, and included 622 participants (302 *vs* 320; figure 4). Heterogeneity across the studies was not significant (p=0·672, I^2=0%). The pooled effect size favoured behavioural interventions for reduction of amphetamine-group substance use, but not significantly so. No evidence for publication bias was detected (p=0·88 from Begg's test; p=0·96 from Egger's test; subgroup analyses are shown in webappendix pp 2–3).

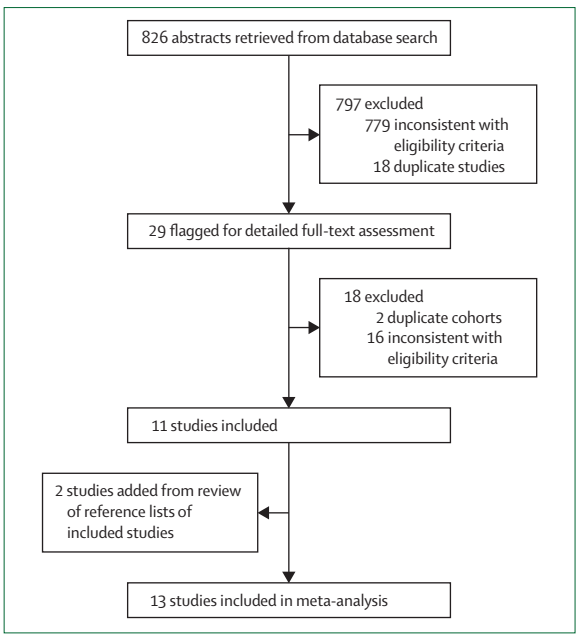

Figure 3: **Selection of studies for the meta-analysis**

The second comparison modelled the overall efficacy of high-intensity or adjunctive behavioural interventions versus active treatment for reduction of amphetamine-group substance use, and included 1375 participants (680 *vs* 695; figure 5). The pooled effect size favoured high-intensity behavioural interventions for reduction of amphetamine-group substance use (effect size 0·28, 95% CI 0·13–0·44). I^2 (32·2%) and Q statistic (p=0·182) suggested that the assumption of homogeneity across the studies was not violated. No evidence for publication bias was detected (p=0·88 from Begg's test; p=0·70 from Egger's test). Subgroup analyses comparing active interventions versus high-intensity interventions showed reduced use of amphetamine-group substances with both gay-specific cognitive behavioural therapy (0·52, 0·22–0·82) and contingency management (0·31, 0·09–0·53; webappendix p 4).

The third comparison modelled the overall efficacy of behavioural interventions versus passive or minimum treatment for reduction of sexual risk behaviours, and included 390 participants (189 *vs* 201) from two studies.[119,120] The pooled effect size favoured behavioural interventions for reduction of sexual risk behaviours, but was not significant (0·04, 95% CI –0·18 to 0·26; webappendix p 5). No evidence for publication bias was recorded (p=0·317 from Begg's test).

The fourth comparison modelled the overall efficacy of high-intensity or adjunctive behavioural interventions versus active treatment for reduction of sexual risk

	Country	Intervention group*	Comparison group*	Age (years)	Proportion of men	Study population	Retention	Treatment frequency and duration†	Comparison	Outcomes analysed
Baker et al (2006)[131]‡§	Australia	Motivational interviewing+CBT (n=11)	Self-help booklet (n=9)	28·83 (10·27)	78%	Regular user of amphetamine-group substances (at least weekly use); comorbid psychiatric disorders	93·1% at 15 weeks	Ten sessions, 15 weeks	1	Use of amphetamine-group substances (primary)
Baker et al (2005)[113]	Australia	CBT (n=48)	Self-help booklet (n=54)	30·22 (7·83)	63%	Regular user of amphetamine-group substances (at least weekly use)	72·4% at 5 weeks	Two or four sessions, 5 weeks	1	Use of amphetamine-group substances (primary)
Baker et al (2001)[132]	Australia	CBT (n=24)	Self-help booklet (n=28)	32·72 (8·76, intervention) *vs* 30·57 (8·57, control)	62%	Regular user of amphetamine-group substances (at least monthly use)	81·3% at 6 months	Two or four sessions, 6 months	1	Use of amphetamine-group substances (primary)
Baker et al (2002)[133]‡§	Australia	Motivational interviewing (n=13)	Information (n=9)	30·05 (10·65, intervention) *vs* 30·05 (9·77, control)	75% (intervention) *vs* 75% (control)	Regular user of amphetamine-group substances (at least weekly use); comorbid psychiatric disorders	70·0% at 3 months	One session	1	Use of amphetamine-group substances (primary)
Srisurapanont et al (2007)[134]	Thailand	Behavioural intervention (n=17)	Education (n=19)	16·88 (1·45, intervention) *vs* 16·83 (1·69, control)	88% (intervention) *vs* 92% (control)	Dependent on amphetamine-group substances (by DSM-IV)	75% at 4 weeks	Two sessions, 2 weeks	1	Use of amphetamine-group substances (primary)
Mausbach et al (2007)[119]	USA	Fast-lane behavioural intervention (n=93¶)	Diet and exercise (n=89¶)	36·2 (9·9, intervention) *vs* 36·0 (9·5, control)	72% (intervention) *vs* 63% (control)	Recent user of amphetamine-group substances (at least twice in the past 2 months and once in the past 30 days)	57·6% at 6 months	Four sessions, 4 weeks	1 and 3	Sexual risk (primary), use of amphetamine-group substances (secondary)
Mausbach et al (2007)[120]	USA	Edge behavioural intervention (n=96¶)	Diet and exercise (n=112¶)	37·42 (7·11, intervention) *vs* 36·76 (7·58, control)	100%	Recent user of amphetamine-group substances (at least twice in the past 2 months and once in the past 30 days); men who have sex with men	61% at 4 months	Five sessions, 5 weeks	1 and 3	Sexual risk (primary), use of amphetamine-group substances (secondary)
Shoptaw et al (2008)[135]	USA	Gay-specific CBT (n=40)	Gay-specific social support therapy (n=32)	38·1 (7·1, intervention) *vs* 36·0 (8·1, control)	100%	Abuser of amphetamine-group susbstances (treatment seeking); men who have sex with men	62·5% (intervention) *vs* 50% (control) at 16 weeks	48 sessions, 16 weeks	2 and 4	Use of amphetamine-group substances (primary), sexual risk (secondary)
Shoptaw et al (2005)[111]‖	USA	Gay-specific CBT (n=40)	CBT (n=40)	37·5 (5·8)	100%	Dependent on amphetamine-group substances (by DSM-IV); men who have sex with men	80% at 6 months	48 sessions, 16 weeks	2 and 4	Use of amphetamine-group substances and sexual risk (primary)
Shoptaw et al (2005)[111]‖	USA	Contingency management+CBT (n=40)	Contingency management (n=42)	37·5 (5·8)	100%	Dependent on amphetamine-group substances (by DSM-IV); men who have sex with men	80% at 6 months	48 sessions, 16 weeks	2 and 4	Use of amphetamine-group substances and sexual risk (primary)
Roll et al (2006)[136]	USA	Contingency management+ treatment as usual (n=51)	CBT (n=62)	29·8 (8·3, intervention) *vs* 31·3 (7·9, control)	43% (intervention) *vs* 52% (control)	Abuser of or dependent on amphetamine-group substances (by DSV-IV)	54·9% (intervention) *vs* 37·1% (control) at 3 months	24 sessions, 12 weeks	2	Use of amphetamine-group substances (primary)
Peirce et al (2006)[137]‡§	USA	Contingency management+usual care (n=18)	Usual care (n=11)	40·7 (7·8)	69%	Dependent on amphetamine-group substances (by DSM-IV)	66% at 12 weeks	24 sessions, 12 weeks	2	Use of amphetamine-group substances (primary)
Shoptaw et al (2006)[138]	USA	Contingency management+ placebo+CBT (n=54)	Placebo+CBT (n=55)	31·3 (6·7, intervention) *vs* 33·3 (7·3, control)	61% (intervention) *vs* 61% (control)	Dependent on amphetamine-group substances (by DSM-IV)	50·7% at 12 weeks	36 sessions, 12 weeks	2	Use of amphetamine-group substances (primary)
Sherman et al (2009)[123]‡§	Thailand	Peer-education network intervention (n=431¶)	Life skills condition (based in cognitive behavioural psychology; n=433¶)	19·41 (1·83)	74%	Recent user of amphetamine-group substances (at least three times in the past 3 months)	90% at 3 months	Seven sessions, 3 months	2 and 4	Use of amphetamine-group substances (primary), sexual risk (secondary)

Data for age are mean (SD). CBT=cognitive behavioural therapy. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders (4th edition). *Sample sizes are for after treatment or at the closest point after treatment; combined sample sizes for individual studies are not equal to cumulative sample sizes for separate meta-analysis comparisons because the frequency of missing data varies by comparison outcome, and data imputation was used in some original analyses. †Papers reported different operational measures for variable. ‡Data on users of amphetamine-group substances provided by authors of report. §Subset of users of amphetamine-group substances. ¶Windsorised to sample size of 80 individuals during weighting. ‖Contributed two independent pair-wise comparisons.

Table: **Studies included in the meta-analysis**

behaviour, and included 1063 participants (532 *vs* 531) from four pair-wise comparisons in three studies.[111,123,135] The pooled effect size did not favour high-intensity behavioural interventions for reduction in sexual risk behaviours, and was not significant (–0·12, 95% CI –0·33 to 0·09; webappendix p 6). No evidence for publication bias was recorded (p=0·17 from Begg's test; p=0·08 from Egger's test).

Discussion

We did not identify conclusive evidence that overall, behavioural interventions are more effective than is passive or minimum treatment for reduction of amphetamine-group substance use or sexual risk behaviours. Conversely, our results indicated that overall, high-intensity behavioural interventions are more effective for reduction of amphetamine-group substance use than are active interventions given alone. Moreover, the subgroup of high-intensity behavioural interventions with adjunctive contingency management were also more effective than was active treatment for reduction of amphetamine-group substance use. This finding portends to the usefulness of economic incentives for reduction of substance use, and is broadly consistent with results from meta-analysis of similar interventions among other populations using substances.[139] Our findings regarding the subgroup of high-intensity interventions with gay-specific cognitive behavioural therapy are limited to trials done in one municipality and should be interpreted with caution. However, these findings do lend support for adaptation of behavioural therapies with culturally appropriate components for this specific subpopulation.

We do not have a clear understanding of why the effect size recorded for behavioural interventions versus passive or minimum treatment was smaller than that for high-intensity behavioural interventions versus active treatment. The generally higher dropout rates of the studies in the second comparison (four studies had follow-up of 37–66% of participants after treatment) could point to attrition and self-selection bias. Additionally, the effect sizes in the first comparison were all calculated from self-reported measures of substance use, whereas in six of the seven studies in the second comparison, measurements of substance use were based on urinalysis. Self-reported outcomes are more susceptible to information or social desirability bias, or both, whereas use of a biological marker could support the validity of the effect size in the second comparison.

Our meta-analysis comparisons show promising results in favour of high-intensity or adjunctive behavioural interventions to reduce use of amphetamine-group substances, but not sexual risk behaviour. However, our analysis has certain caveats. We explored only the efficacy of interventions after treatment or at the closest timepoint after treatment and therefore do not know how effective behavioural interventions will be long term.

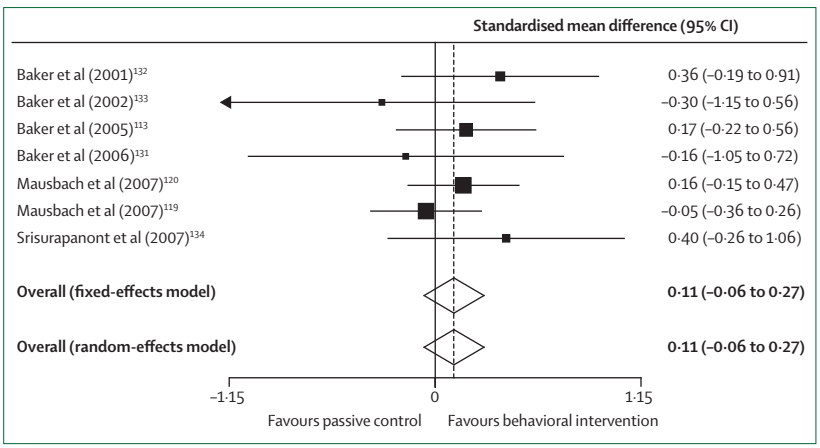

Figure 4: **Meta-analysis comparison one—efficacy of behavioural interventions versus passive or minimum treatment for reduced use of amphetamine-group substances**
Treatments compared in each study are shown in the table.

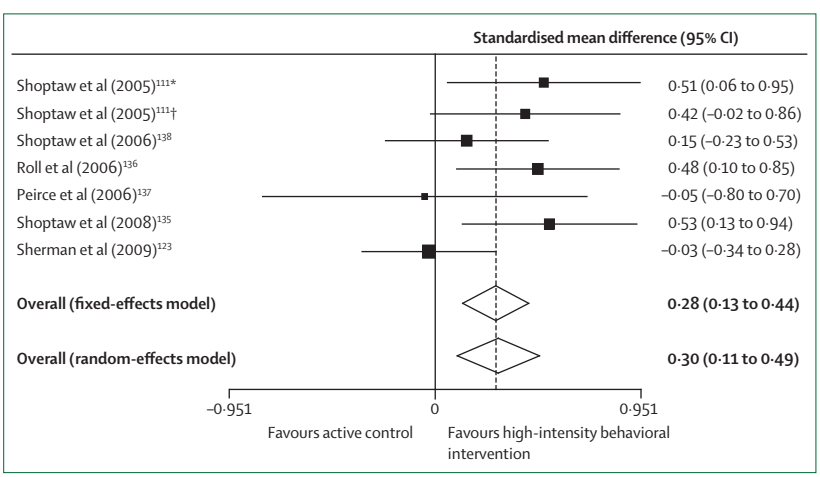

Figure 5: **Meta-analysis comparison two—efficacy of high-intensity or adjunctive behavioural interventions versus active treatment for reduced use of amphetamine-group substances**
Treatments compared in each study are shown in the table. *Gay-specific cognitive behavioural therapy versus cognitive behavioural therapy. †Contingency management plus cognitive behavioural therapy versus contingency management.

Furthermore, only one of our eligible studies included an endpoint for sexually transmitted infections. Unfortunately, because none of the trials we analysed compared high-intensity interventions against passive or minimum treatment, we were not able to assess which of the two interventions is superior for reduction of amphetamine-group substance use and sexual risk behaviour. Additionally, we noted a marked deficit in the diversity of populations studied: only two studies were done in developing countries; samples were predominantly men; and several studies focused on dependent users. Our results emphasise the need for more rigorous development and testing of interventions in diverse populations of users of amphetamine-group substances. Despite these limitations, the moderate overall effect size of high-intensity interventions is encouraging and provides some indication that behavioural therapy is a

worthwhile approach for reduction of amphetamine-group substance use. Our findings suggest that in the absence of effective brief interventions, high-intensity behavioural interventions should be prioritised and made available to achieve maximum reductions in amphetamine-group substance use, although costs and sustainability should also be considered.

Conclusions

Patterns and frequency of amphetamine-group substance use, routes of administration, psychological factors, social structure, local HIV epidemiology, and host-specific immunological and genetic factors have complex and often intersecting roles in amphetamine-group substance use and in the contribution of amphetamine-group substance use to HIV risk. In populations using amphetamine-group substances, simple interventions such as testing for HIV and other sexually transmitted infections should be widespread and prioritised, particularly if HIV infection is prevalent and incidence of infection is substantial. Global efforts must be made to integrate, coordinate, and evaluate HIV testing and care strategies with treatment for amphetamine-group substance use.

Our findings reinforce the need to develop and rigorously test additional interventions to address both amphetamine-group substance use and sexual risks associated with different patterns of use, from episodic use, to abuse, to severe dependence. Additionally we were were unable to identify any rigorously evaluated primary prevention interventions. The fairly small number of studies eligible for our meta-analysis is a concern, particularly because of the heavy reliance on these approaches for treatment of disorders related to amphetamine-group substances.[5] Present behavioural interventions for use individually and in groups have limitations. In the short term, people reduce their use of amphetamine-group substances and self-reported HIV risk behaviour; however, reductions are often seen in several trial groups, making quantification of the effect of a specific intervention difficult. Most interventions are done in drug-treatment settings in people actively seeking treatment and therefore do not engage most active users. Interventions have generally been targeted towards drug-dependent populations, leaving a void with respect to which strategies could effectively reduce HIV risk behaviours in the larger populations of episodic users of amphetamine-group substances. Many questions remain about the long-term efficacy of specific interventions for reduced use of amphetamine-group substances, and which interventions are most appropriate for particular populations. Also, most trials use behavioural endpoints as a marker for risk of HIV infection, but whether these interventions reduce rates of HIV infection is unknown. Many trials have follow-up of far fewer than 70% of participants, calling into question the validity of results. However, despite these shortcomings, we showed that treatment with high-intensity interventions is beneficial. In view of the severity and number of harms associated with amphetamine-group substance use, these behavioural approaches should be provided. Future research is needed to develop behavioural interventions that are efficacious for reduction of sexual risk, and HIV and other sexually transmitted infections.

Harm-reduction strategies in needle exchange programmes are clearly effective, but whether these strategies reduce HIV infections associated with substance-related sexual behaviour has yet to be proven in most populations. An overall harm-reduction approach is endorsed for treatment of substance users, but with respect to HIV prevention, there are crucial differences between injection-related risks and sexual risks linked with substance abuse. For injectors, use of a clean needle and injection paraphernalia obviates risk of HIV infection, but the user can still have the reward of using the drug. By contrast, when substances are used to decrease sexual inhibitions, or enhance or facilitate sex, the issue is raised as to whether users can consistently reduce their HIV-related risk behaviour while under the influence of amphetamine-group substances such that rates of HIV infection are reduced. Although we have described some studies in which risk-reduction approaches reduced risk behaviour, the effectiveness of such approaches has yet to be confirmed.

Additionally, substance use and sexual risk taking do not occur in isolation: substance use in populations at risk of HIV infection often occurs in the setting of other conditions that could contribute to both substance use and sexual risks, including depression and other mental health disorders, stigma, and violence.[140,141] The syndemic nature of these conditions could create an additive effect on sexual risk behaviours in substance users,[142] such that these underlying factors might account for the difficulty with which sustained reduction of sexual risk behaviours is achieved. Attention should be paid to these co-occurring conditions to reduce substance use and sexual risk behaviours.[140]

The absence of effective pharmacological interventions for amphetamine-group substance use is a major treatment gap. Scientific research is needed to fully understand the mechanisms of action of amphetamine-group substances, and drug-development efforts should focus on development and testing of compounds which target specific receptors or pathways related to amphetamine-group substance use. Rigorous drug-screening trials could offer an efficient mechanism for identification of promising candidates for efficacy trials. Drug-development efforts should be coordinated to harness resources, avoid duplication of effort, and improve the chances of success.

Adequate resources for epidemiological assessment and intervention research are needed, but alone they are not enough; undertaking of comparative effectiveness and cost-effectiveness studies is imperative. Although

further testing of intensive, proof-of-concept interventions might be warranted, careful consideration must be paid to the scale-up and sustainability of interventions. Even the most efficacious interventions have restricted applications in societies that do not invest substantial resources into scale-up and evaluation of effectiveness.[143] Furthermore, the direct input and perspectives of users of amphetamine-group substances must inform such efforts to ensure that they succeed.

Contributors

GC conceived and designed the analyses with assistance from G-MS; EV also contributed to the design of analyses. G-MS and PC extracted data. GC, G-MS, PC, EV, and CH reviewed, analysed, and interpreted data. GC was main author of the report; and G-MS, PC, AP, SK, and CH drafted parts of the report. GC critically revised the report with assistance from G-MS, PC, EV, AP, SK, and CH.

Steering committee

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Conflicts of interest

We declare that we have no conflicts of interest.

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