

Treatment

The impact of crystal methamphetamine use on HIV-positive individuals

By Perry N. Halkitis, Ph.D.

“Crystal” is the popular street name of the pharmaceutical compound methamphetamine. The drug is a potent psycho-stimulant that has the potential to cause irreparable physical, psychological, and social damage to individuals who abuse or become dependent on this substance. Use of this illicit drug is found among all sectors of American society, is equally used by both men and women, in rural and urban settings, and across races and ethnicities. Also known as “crank,” “meth,” “Tina,” and “ice,” the drug has been abused by Americans for over 50 years.¹

Given the strong association between use of the drug and sexual risk taking, especially among gay and bisexual men where HIV is highly concentrated, concerns about the drug have extended beyond the addiction, creating the potential for a “dual epidemic.”^{2, 3, 4} For example, in 2003, *The San Francisco Chronicle* reported that over 40% of gay men in San Francisco had tried crystal methamphetamine,⁵ and that close to one-third of new HIV seroconversions occurred in men who had used the drug in the recent past. These patterns have also been noted in other large gay centers such as New York City, Miami, and Atlanta. Because of the intimate link that exists between abuse of methamphetamine and HIV sexual risk-taking, Gay Men’s Health Crisis (2004) convened task forces and implemented educational strategies to address the rising use of the drug.⁶

Effects of methamphetamine abuse

Abuse of and addiction to methamphetamine may have many pronounced effects on the user as well as the individual’s family and friends. For example, Brecht et al. (2004) found that in a sample of 350 individuals recruited from a publicly funded treatment site, 84% reported weight loss due to their methamphetamine use.⁷ Other problems included sleeplessness (78%), financial problems (73%), paranoia (67%), legal problems (63%),

hallucinations (61%), work problems (60%), violent behavior (57%), dental problems (55%) and skin problems (36%). Methamphetamine abuse complicates an individual’s life, not only causing potential for irreparable physiological damage and potential death, but also deterioration in one’s cognitive, emotional and social stability. The effect of the abuse of methamphetamine on sexual behavior can also act as a lubricator or facilitator for the transmission of HIV and other pathogens.⁸ Finally, there is abundant evidence of the cardiovascular, neurological, psychiatric, and oral complications associated with chronic use of methamphetamine.

Methamphetamine addiction and sexual risk taking

The extant literature supports the association between use of methamphetamine and the transmission of HIV, especially among gay and bisexual men. Behavioral research has documented the association between the use of methamphetamine and the heightening of sexual behavior in gay and bisexual men.^{9, 10, 11, 12, 13} Use of the drug is layered with complex behavioral and psychologically driven motivations (e.g., desire for socialization, sexual promiscuity, decreased loneliness, and depression). Such associations are also evident in non-gay populations. However, because HIV continues to permeate the gay male population more than any other in the United States, much of the behavioral research on methamphetamine use and sexual risk taking has focused on this affected group.

On average, sexual behavior under the influence of crystal is related to higher sexual risk. For example, Mansergh et al. (2006) estimated that methamphetamine use doubled the likelihood that men who have sex with men engage in unprotected receptive anal intercourse.¹⁴ Among gay men with unknown HIV

status, methamphetamine use was associated with 18 times more unprotected receptive anal intercourse in men who eventually tested HIV-positive compared to those who were HIV-negative.¹⁵ Similarly, Wong et al. (2006) delineated that methamphetamine use increased the likelihood of contracting syphilis 6-fold, and Plankey et al. (2007) indicated that there was a 1.46 increase in relative hazard for HIV seroconversion associated with methamphetamine use.^{16, 17}

Methamphetamine addiction's impact on HIV-positive individuals

Like all other behaviors which burden the bodily system, the use of methamphetamine may have particularly pronounced effects for HIV-positive individuals. This is due in part to the adulterated nature of illegally produced crystal methamphetamine, which often contains lead and may be “cut” with other materials that can be damaging to those with lower functioning immune systems. “Drug seizures show an average purity of 54%, diluted with ingredients such as baking soda, lactose, Epsom salts, quinine, mannitol, procaine, ether, insecticides, MSG, photo developer, and strychnine.”¹⁸ In addition, the impact of the drug on the cardiovascular, pulmonary, and neurological systems may be more pronounced for those who are HIV-positive.

Adverse interactive effects of HIV medications and methamphetamine have been noted, in particular, with individuals who have been undergoing treatment with the HIV antiviral, Ritonavir.¹⁹ Furthermore, methamphetamine use interferes with adherence to HIV antiviral treatments. Halkitis et al. (2002) showed that gay and bisexual men who indicated the use of methamphetamine also indicated a greater number of missed doses of their protease inhibitor treatment than those who did not indicate use of the drug (12 missed doses vs. 4 missed doses per 2 month period).²⁰ Ellis et al. (2003) demonstrated that active methamphetamine-using HIV-positive persons have higher viral loads than those who never used the drug or recently used the drug.²¹ But the impact of methamphetamine on the effectiveness of antiviral therapies may be undermined even in the presence of optimal adherence. Specifically, Ahmad (2002) indicated that even with optimal adherence, use of the drug was associated with greater HIV viral replication in the brain.²² Similarly, Gavrilin et al. (2002), and Carrico et al. (2007) documented a five-fold higher viral load among those who reported regular stimulant (including methamphetamine) use than those who did not use stimulants.^{23, 24}

One of the most pronounced effects of methamphetamine use is its impact on the neurotransmitter systems, especially those systems which control the release of dopamine. Dopamine is the neurotransmitter which creates

pleasurable feelings, and in the presence of methamphetamine use, is released at heightened rates and is not fully reabsorbed by neurons, leading to a great sense of euphoria. However, the synergistic effects of HIV and methamphetamine on the dopaminergic system may increase the HIV-positive user's susceptibility to neurotoxicity.^{25, 26} The interaction between methamphetamine abuse and HIV infection may cause alterations in the size of certain brain structures. In both cases, the changes may be associated with impaired cognitive functions, such as difficulties in learning new information, solving problems, maintaining attention, and quickly processing information.²⁷ To this end, the comorbidities of methamphetamine abuse/addiction and HIV infection result in greater impairment in this neurological system than is engendered by each condition in isolation. In a comparison of the interactive effects of methamphetamine use and HIV infection, Rippeth et al. (2004) examined the interactive effects of methamphetamine use and HIV infection on cognitive functioning.²⁸ The data demonstrated that rates of impairment to global neuropsychological functions were highest among HIV-positive methamphetamine users (58%), followed by HIV-negative methamphetamine users (40%), HIV-positive non-methamphetamine users (38%), and were lowest among HIV-negative, non-methamphetamine users (18%), indicating the synergy between HIV infection and abuse of the drug.

In addition to the interactive effects of HIV and methamphetamine use in neural systems, this comorbidity has other physiological implications resulting in the development of opportunistic infections. In one study, Tallóczy et al. (2008) found that methamphetamine directly affects the ability of the body to effectively combat infections by exerting an immunosuppressive effect on dendritic cells and macrophages.³¹ Use of methamphetamine may exacerbate the replication and inhibit the intracellular destruction of two AIDS-related pathogens—*Candida albicans*, the fungal infection that effects the gastrointestinal systems, a.k.a. “thrush”, and *Cryptococcus neoformans*, the fungus that can cause meningitis in HIV-infected individuals.

Conclusions

Data suggest that a subset of HIV-positive individuals are often users of this drug, especially gay and bisexual men.³² For the immuno-compromised person in particular, the administration of methamphetamine may have even more severe effects. In addition to exacerbating the potential for the transmission of HIV to sexual partners, the substance itself has significant effects on the biological system of the seropositive individuals, including neurological complication and associated increase in viral replication. Special attention needs to be paid to the physical and mental health of HIV-positive individuals

who are using, who are recovering from use, or are at risk for initiating the use of methamphetamine. Health care providers should be keenly aware of signs of addiction to methamphetamine, and work openly and honestly with their patients to address the detrimental effects of methamphetamine addiction.

Perry N. Halkitis, Ph.D. is Professor of Applied Psychology and Public Health and Director of the Center for Health, Identity, Behavior & Prevention Studies (CHBPS) at the Steinhardt School, New York University. He is the author of the book Methamphetamine Addiction: Biological Foundations, Psychological Factors, and Social Consequences (2009), American Psychological Association. To view references, go to www.gmbc.org/ti.html

The promise of pre-exposure prophylaxis

By Cassandra Willyard

The advent of antiretroviral cocktails in the 1990s gave HIV-positive individuals a new lease on life. The newest drugs to treat HIV infection are much cheaper, safer and easier to use than earlier generations. And that has prompted researchers to test an idea that would have been unthinkable just a decade ago; using the same drugs that doctors use to *treat* infection to instead *prevent* infection. That means giving HIV-negative adults antiretroviral medicines before they are ever exposed to HIV, an idea known as pre-exposure prophylaxis (PrEP). Scientists have already begun clinical trials to test whether the strategy can safely reduce a person's risk of contracting HIV. And the first results may be available as soon as this year.

Despite past disappointments in the field of HIV prevention, many experts are optimistic that PrEP will work. But even if the strategy proves to be effective in reducing the risk of transmission, significant hurdles remain. A once-daily antiretroviral will not be cheap, and it will not be for everyone.

Stopping infection before it starts

The idea of taking a drug to prevent disease is not novel in medicine. “The concept has been out there for a long time,” says Lynn Paxton, an epidemiologist at the U.S. Centers for Disease Control and Prevention (CDC). Physicians regularly prescribe anti-malaria pills for travelers headed to regions where malaria is endemic. The rationale is straightforward: having anti-malarial drugs in the body at the time of exposure can prevent a few stray parasites from becoming a full-blown infection.

Researchers think the same principle might apply to HIV. Antiretrovirals cannot eliminate HIV once an indi-

vidual is infected, but, if taken early enough, they may be able to stop the virus before it takes hold. “When we are treating HIV infection,” says Robert Grant, a virologist at the University of California in San Francisco, “the amount of virus is enormous. There’s HIV in the blood, in the lymph nodes, in the associated lymphoid tissue.” But at the time of transmission, often only a few virus particles are present, so the virus may be easier to block.

The two drugs being tested, tenofovir disoproxil fumarate (tenofovir) and its sister drug Truvada—a combination of tenofovir and emtricitabine — stop the virus from manufacturing a protein called reverse transcriptase. Without reverse transcriptase, HIV cannot turn its viral RNA into DNA, which means that it cannot replicate. “It is possible that these drugs would block the first round of viral replication,” Grant says. But even if they don’t, he says, they may be powerful enough stop subsequent replication, thereby staving off systemic infection.

Laying the groundwork

Researchers began talking about using antiretrovirals as an HIV prevention tool in the 1990s. In fact, a team of scientists at the University of Washington published a study as early as 1995 showing that tenofovir could prevent HIV infection in macaque monkeys when injected either two days before exposure, four hours after exposure, or a day after exposure.¹ However, at the time, tenofovir was still experimental, and the approved drugs were expensive and often toxic.

However, doctors did begin prescribing antiretroviral therapy for people who had reason to believe they’d already been exposed to HIV. The strategy, known as post-exposure prophylaxis, was aimed at health care workers who stuck themselves with infected needles. In those cases, the benefit seemed to outweigh the risk. A case-control study in the mid-1990s suggested that health workers who took AZT soon after a needle stick reduced their chances of contracting HIV by 80%.²

Still, post-exposure prophylaxis never caught on as a widespread prevention strategy. One reason is that people who contract HIV outside of the workplace often have a hard time determining when they’ve been exposed. With pre-exposure prophylaxis, no decision is necessary; the drugs are already on board when exposure occurs.

Although post-exposure prophylaxis has never been tested in rigorous randomized controlled trials, the data suggest that it works. And if post-exposure prophylaxis works, chances are pre-exposure prophylaxis will work too.

Additional indications that PrEP will be effective in curbing HIV transmission come from research on prevention of mother-to-child transmission. “There are trials in which only the baby has been given antiretrovirals after birth and it prevents infection,” Mellors says. Although

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EDITOR: NATHAN SCHAEFER

ASSISTANT EDITORS: SEAN CAHILL, JAIME GUTIERREZ

ART DIRECTOR: ADAM FREDERICKS

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it is not sexual transmission, he says, "it gives strength to the argument that this can be successful."

Furthermore, PrEP seems to provide at least partial protection against an HIV-like virus in non-human primates. Researchers at the CDC have tested the strategy in macaque monkeys, giving the animals antiretrovirals once a day and then simulating sexual exposure. They report partial protection with tenofovir, and even better protection with Truvada.^{3,4} And the latest study, presented by CDC virologist J. Gerardo García-Lerma at the Conference on Retroviruses and Opportunistic Infections in Montreal in February 2009, suggests that even intermittent antiretroviral drugs taken orally can protect against rectally transmitted infection in macaques.

The human element

Although researchers have good scientific reasons to believe that PrEP will work, they still need data from carefully controlled human studies. To date, they have completed only one human PrEP trial. The Family Health International study, which began in 2003, set out to test the safety and efficacy of pre-exposure prophylaxis among 1200 HIV-negative women in West Africa.

But the study was fraught with setbacks. The Nigerian arm closed prematurely after local investigators failed to comply with complex protocol requirements. And the study in Cameroon was halted early at the request of government officials. Ultimately, the investigators enrolled fewer participants than they had originally planned—just 936. And because incidence of HIV among these women was lower than expected, they weren't able to look at efficacy. However, the study did show that the drug appears to be well tolerated.⁵

Today at least five trials are underway, and two more are planned. Researchers hope to enroll 18,000 participants in the next several years. But they will not be looking just at high-risk women. One study tests the efficacy of PrEP among more than 2,000 injection drug users. And studies will examine the effect of PrEP among gay men. Some trials will also test the efficacy of antiretroviral-laced microbicides. Mellors says that the efficacy of the drug may vary depending on the route of transmission. According to Paxton, at the CDC, the first results should be available no later than 2010.

The fine print

Even if the trials do show that PrEP offers protection, other questions must be answered before implementation. One major concern is drug resistance. PrEP may prove to be highly efficacious, but no one believes it will provide 100% protection. And that means that at least some individuals will become infected while taking the medications. If these HIV-infected individuals continue to take their drugs, the virus can become resistant. That could jeopardize the infected individual's future treatment, and it could also lead to a larger, community-wide pool of resistance.

The two antiretrovirals being tested in the trials were chosen in part because they are least likely to spawn resistance. Still, researchers will be monitoring the trial participants closely, giving them monthly HIV tests to ensure that any participants who do become HIV-positive are taken off the medications. However, such rigorous measures may not be possible if PrEP becomes part of the prevention toolbox. Consequently, one of the goals of the trials will be to determine whether resistance is an issue.

Another concern is cost. In the world's poorest countries, the manufacturer of tenofovir and Truvada has agreed to sell the drugs at cost, which would cut the price to \$200 or \$300 a year. Yet even a few hundred dollars is more than many in the developing world could afford, so the burden will undoubtedly fall on international donors. In the developed world, the drugs can cost thousands of dollars each year. A group of researchers from Yale and Harvard concluded in March that PrEP could significantly reduce transmission of HIV among men who have sex with men in the U.S., but they added that, unless drug prices fall, the benefits would likely not justify the cost.

Yet even with these limitations, the strategy could still be a boon to HIV prevention because despite intensive research efforts, the HIV prevention toolbox is still only half full. "Any new tool we have to reduce the spread of this virus," Cates says, "is a reason for breaking out the champagne."

Cassandra Willyard is a freelance science writer in Brooklyn, NY. To view references, go to www.gmhc.org/ti.html