

Crystal methamphetamine use and antiretroviral drug resistance:

A pilot study of behavioral and clinical correlates

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The prevalence of recreational crystal methamphetamine use and related emergency room admissions are on the rise across the United States,^{1,2} accompanied by a curious media sometimes quick to sensationalize the trend, other times to isolate its impact on specific social groups (eg, gay and bisexual men, circuit party attendees).^{3,4} According to the World Health Organization (WHO), amphetamines are the second most commonly used and abused controlled substances, after cannabis. More than 35 million people regularly abuse these substances.^{1,5}

Even episodic or intermittent use of methamphetamines is associated with risky sexual practices likely to transmit HIV, such as unprotected anal intercourse (UAI) with serodiscordant sex partners.⁶ To the chagrin of public health scholars, crystal methamphetamine use has exploded concurrently with two other disconcerting trends: first, an increase in new HIV infections, particularly within the gay dance “circuit” and, on average, among an older cohort of gay men (eg, the average age of a newly infected gay man in New York in

2005 is around 40 years)⁷⁻¹³ and second, a rise in antiretroviral (ARV) drug resistance within already-infected individuals.¹⁴ Antiretroviral drug resistance is a primary cause of treatment failure, is connected with neurological damage, and is linked to increased mortality.¹⁵⁻²⁰ It therefore behooves researchers interested in treatment efficacy and group health to inquire into the relationship between crystal methamphetamine (ab)use and ARV drug resistance.

The crystal methamphetamine use-HIV infection-ARV drug resistance nexus is troubling. This is perhaps nowhere more pronounced than for communities of men who have sex with men (MSM), which are already encumbered by the persistence of risky sexual practices, including a resurgence of UAI and other activities associated with HIV transmission.^{9,21,22} Crystal methamphetamine use is often a culprit during seroconversion. One Los Angeles study found that 61% of gay and bisexual men seeking treatment for crystal methamphetamine dependence were infected with HIV.¹ A recent San Francisco study also found that HIV incidence among methamphetamine users was statistically higher than among non-users, with users at least three times as likely as nonusers to

be HIV-positive.²³ These studies, along with others, suggest that crystal methamphetamine use is a common co-morbidity among HIV-positive individuals, whose viral loads also increase in its presence.¹⁴

Crystal methamphetamine-using seropositive individuals are at greater risk for ARV drug resistance, a relationship that is attributable to one or more of three causal mechanisms, of which two are clinical and one is behavioral.

- **Cellular suicide.** Crystal methamphetamine use stimulates the secretion of tumor necrosis factor (TNF), a cytokine whose levels are already high in HIV-positive individuals. High levels of TNF trigger a biochemical pathway that leads to cellular suicide, a condition known as *apoptosis*. In HIV-positive people, crystal methamphetamine boosts TNF levels, which can induce CD4 apoptosis. This facilitates increased viral replication and thus reduced ARV effectiveness.
- **Metabolism rates.** Crystal methamphetamine can alter ARV drug absorption and breakdown, expediting elimination of ARV drugs via metabolic pathways as a result of drug-drug interactions.

Accelerated metabolism of ARV drugs lowers bloodstream levels to below the threshold required to manage the virus. This can increase viral loads, prompting the onset of resistance. Indeed, this is precisely what a recent San Diego study found: crystal methamphetamine-using seropositive individuals on highly active antiretroviral therapy (HAART) experienced higher viral loads than those on therapy who either had never tried crystal methamphetamine or who had been clean for at least 30 days.

- **Adherence.** There is a behavioral link between crystal methamphetamine and ARV drug resistance through methamphetamine's association with inadequate adherence to dosing schedules. In other words, crystal methamphetamine use can impair adherence. Sporadic adherence contributes to ineffective inhibition of viral replication and thus the onset of ARV drug resistance.¹⁴

In addition to compromised HAART effectiveness, the HIV-crystal methamphetamine nexus may also produce potentially fatal effects. In the human body, CYP2D6 is a liver enzyme that metabolizes both methamphetamines and protease inhibitors (PIs). Some PIs—especially ritonavir (RTV) and delavirdine (DLV)—have a greater affinity for this enzyme than do methamphetamines. When taken together, CYP2D6 will metabolize the PI before it will metabolize crystal methamphetamine. Delayed metabolizing of crystal methamphetamine allows levels in the bloodstream to rise to dangerous levels, especially in the brain—a 3- to 10-fold increase—which can result in fatal overdose.^{1,17}

Although research on the clinical and behavioral mechanisms of ARV drug resistance is growing, the above discussion demonstrates the need for continued investigation. This article reports the results of a pilot study that is part of a larger project exploring the correlates of ARV drug resistance.

Methods

Sampling strategy. Participants in the present study comprise a purposive sample of 38 physicians who are members of the International Association of Physicians in AIDS Care (IAPAC), a Chicago-based non-profit medical association that represents a professional membership of more than

12,000 physicians and other health care providers in more than 103 countries. Physician-members were surveyed at the IAPAC North American Sessions 2005, held June 3-4, 2005, in Chicago. This IAPAC-sponsored study is part of a larger, longitudinal study on the behavioral and clinical correlates of ARV drug resistance.

Instrument and statistical analyses. Physicians were asked to complete a 45-item questionnaire that contained a series of questions pertaining to their HIV-positive patients. Questions were clustered into five themes:

- physician's practice and patient profile;
- medication, adherence, resistance;
- illicit drug use;
- psychiatric symptoms; and
- sexual activity.

Two-tailed, Pearson's product-moment correlations were computed across items for behavioral and clinical cofactors. Because analyses were conducted on a small, purposive sample, results should be interpreted as indicating trends that signal the need for further investigation.

Results

Physician practice and patient profile.

On average, 60% of IAPAC physician-members' patients are HIV-infected; 55% are gay men. Five percent of the physicians see one to five HIV-positive patients per week; 21% see six to 10 per week; 29% see 11 to 20 per week; 24% see 21 to 50 per week; and 21% see more than 50 HIV-positive patients per week. Seventy-six percent of HIV-positive patients are on HAART. Forty-five percent of the patients are on an RTV-containing regimen, 3% on a DLV-containing regimen. At the time of the survey, 55% had undetectable viral loads, 20% were resistant to just one ARV drug, and 30% to multiple ARV drugs. Fifty-two percent of patients self-report to their physicians that they have missed taking their medications in the past month. The number increases to 70% for the past six months. The majority of patients cite reasons such as "forgot" and "traveling" for the missed doses. The second and third most common reasons for missing doses include physical side effects and the disruptive nature of controlled substances, respectively.

Physicians report extensive and varied illicit drug use by their patients. Crystal methamphetamine was the most commonly

ingested drug for 11% of the patients. Forty-six percent of these patients reported using another controlled substance beside crystal methamphetamine. Of this group, 62% most commonly ingested alcohol, 21% most commonly ingested cocaine, 12% an erectile dysfunction medication, and 11% marijuana. The sixth most commonly ingested drug was ecstasy, followed by gamma hydroxybutyrate (GHB) and ketamine, respectively. The physicians indicated that they believe 23% of their patients are habitual users of one or more controlled substances. Eleven percent of patients self-report taking an ARV "drug holiday" specifically because of illicit drug use. Only one third of the patients were described as being "very well informed" about the relationship between drugs and HIV.

Patients reported to their physicians a variety of socio-sexual behaviors. Fifteen percent of patients used Internet-based services to arrange sex, 13% had visited a bathhouse, and 8% had attended a circuit party. Eleven percent of patients self-report *insertive* UAI in the past six months; 8% report *receptive* UAI. Twenty-one percent of those who reported any type of UAI said they were using crystal methamphetamine at the time the UAI occurred. Another 32% of patients were high on another substance, and 53% of patients had consumed alcohol prior to or during the sexual encounter. Physicians believe that slightly more patients are "very well informed" about the relationship between drugs and sex (43%) than are very well informed about the relationship between such drugs and HIV (33%).

Crystal methamphetamine and resistance: Behavioral risk factors. Crystal methamphetamine use at one point in time increases the likelihood of future use. Crystal methamphetamine use in the past week is positively correlated with use in the past month ($r=0.975$, $P<0.001$), use in the past three to six months ($r=0.833$, $P<0.001$), and use in the past 12 months ($r=0.908$, $P<0.001$). The use of crystal methamphetamine is associated with a series of risk factors connected to ARV drug resistance. For example, those who report crystal methamphetamine as their most commonly ingested drug within the past month show a trend for missing a medication dose in the past month ($r=0.417$, $P<0.085$). Crystal methamphetamine users also participate in high-risk lifestyles.

Those who used crystal methamphetamine in the past week, month, or 12 months were more likely to have gone to a bathhouse ($r=0.387$, 0.374 , and 0.422 , respectively; $P<0.05$) and circuit party ($r=0.667$, 0.657 , 0.613 , respectively; $P<0.001$).²⁴ Crystal methamphetamine use is also connected to incidences of UAI. Those who used crystal methamphetamine in the past week, past month, and past 12 months were more likely to engage in insertive UAI ($r=0.662$, 0.626 , 0.541 , $P<0.001$) and receptive UAI ($r=0.792$, 0.729 , 0.640 , $P<0.001$), two high-probability HIV transmission-related sexual behaviors.

Crystal methamphetamine and resistance: Clinical risk factors. The survey instrument did not solicit specific information on TNF, metabolism, or CYP2D6. Results on the clinical aspect of the crystal methamphetamine/resistance relationship are therefore limited. Results do, however, suggest that those who used crystal methamphetamine in the past three to six months were also likely to be on an RTV-containing regimen ($r=0.335$, $P<0.028$), which exacerbates the likelihood of a fatal drug-drug interaction. Those patients who self-report crystal methamphetamine as their most commonly ingested drug show a trend for being resistant to multiple ARV drugs ($r=0.446$, $P<0.083$). The most substantively noteworthy finding, however, is that crystal methamphetamine use in the past week, month, three to six months, or 12 months is not correlated with having an undetectable viral load ($r=0.014$, $P<0.939$; $r=0.071$, $P<0.697$; $r=-0.001$, $P<0.995$; and $r=-0.028$, $P<0.879$, respectively). If the counterfactual is true, then those who do not report crystal methamphetamine use are likely to be those for whom HAART is effective and vice versa.

Discussion

It should be noted that results stem from a pilot study of 38 physicians attending the IAPAC North American Sessions 2005. Results are not intended to be definitive and generalizable without qualification, but rather suggestive of the viability of a potential behavioral and clinical relationship between crystal methamphetamine use and ARV drug resistance. The intent is to document trends and relationships to motivate further inquiry.

Results reveal that clinical and behavioral pathways undergird the relationship between crystal methamphetamine use

and ARV drug resistance. The still-nascent literature emphasizes the role of inadequate adherence as a critical behavioral factor responsible for resistance. Study results are confirmatory. The possibilities for addiction are in place as patients who report using crystal methamphetamine at one point in time are also likely to report future use. Addiction concerns aside, crystal methamphetamine users are more likely to engage in a number of HIV-transmittable sexual behaviors such as insertive and receptive UAI. These findings are especially troubling in light of the fact that crystal methamphetamine users are more likely to visit bathhouses and attend circuit parties, where there may be an overall high prevalence of seropositive patrons and riskier sexual practices. The public health threat is exacerbated given that: (1) seropositive individuals exhibit a less cautious sexual profile,⁸ (2) crystal methamphetamine-using seropositive individuals are less likely to be adherent to their ARV regimen (which then increases the likelihood of ARV drug resistance),²⁵⁻²⁶ and (3) crystal methamphetamine-using seropositive individuals on HAART are likely to have higher viral loads.¹⁴

Study results corroborate the role played by behavioral and clinical factors in the relationship between crystal methamphetamine and ARV drug resistance. Although instrument limitations precluded testing for the direct or indirect role played by ARV drug metabolism, neurological damage, or apoptosis, results did reveal that those individuals who reported using crystal methamphetamine in a variety of different time periods were not likely to have undetectable viral loads. If the reverse is also true (ie, that those who do not use crystal methamphetamine are statistically more likely to have undetectable viral loads), then there is further evidence for a clinical relationship between crystal methamphetamine use and ARV drug resistance. Much more research is required into this important and growing area of public health concern. ■

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