MothersAgainst Meth-Amphetamine

Interaction Between Methamphetamine Use and HIV Infection
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1. Background

Methamphetamine use is associated with higher rates of all types of sexually transmitted diseases. This association is both behavioral and biochemical in nature. Methamphetamine stimulates increased sexual desire and promotes prolonged sexual encounters by delaying ejaculation. Methamphetamine use increases sexual behavior in both animals and humans. It greatly increases the dopamine response to sexual stimuli in the nucleus accumbens of rats (Fiorino 1999). Methamphetamine is also disinhibiting, which encourages promiscuous behavior and discourages the use of condoms. Genital ulcers caused by other sexually transmitted diseases increase the risk of HIV transmission (Dickerson 1996). In addition, methamphetamine is a vasoconstrictor which leads to drying of mucous membranes, both vaginal and rectal, increasing the likelihood of abrasions and the transmission of disease.

The most deadly of the sexually transmitted diseases promoted by meth use is AIDS. The incidence of new HIV infections has risen in recent years, particularly in America's coastal cities. Homosexual men from all over the nation relocate to the coastal cities in an effort to find a community. Once there they find that the harmonious community and meaningful relationships they had hoped for do not materialize. They often find themselves even lonelier than they were in the small Midwestern town they came from. While hoping to connect and make friends, they are often reduced to chance encounters in a park, often at a price. The price is more than just monetary. They often pay with their lives.

The interaction between the methamphetamine epidemic and the recent rise in sexually transmitted diseases, including HIV is not an accident, and is not confined to the homosexual community. Methamphetamine use increases the transmission of HIV, and also promotes its invasion into the immune system and central nervous system. Drug resistance is increased in situations where medication compliance is poor, and co-occurring infections like Hepatitis C also accelerate the progression of HIV disease. The mental illnesses associated with methamphetamine are exacerbated in patients who are also HIV positive, particularly depression and dementia.

The implications for public health in this nation are staggering. Our tenuous grip on the HIV epidemic is seriously threatened by the accelerating methamphetamine epidemic. As use of methamphetamine spreads across the nation, more people of all ages are exposed to 'big city' diseases with potentially devastating consequences for our collective public health.

2. Increased Transmission of HIV

Methamphetamine is a powerful aphrodisiac, and many people are using it primarily for its sexual effects. In high doses, especially smoked or injected, it causes a rapid increase in dopamine levels in the midbrain pleasure center, nucleus accumbens (Fiorino 1999). Methamphetamine stimulates sexual desire, enhances the sexual response, and reduces perception of pain, permitting a wide variety of sexual activities. Methamphetamine users report having more sex partners, engaging in sex in more types of venues, more unprotected anal intercourse with casual partners, and more esoteric sex (Rawstorne 2007). This is not just a coastal city phenomenon. Methamphetamine use among heterosexual women in rural Alabama skyrocketed between 1991 and 2008, and with it a significant increase in anonymous sex with multiple partners, often as payment to a drug dealer (personal experience as a practicing gynecologist).

Methamphetamine users were also more likely to be taking Viagra than non-users due to the loss of erectile function seen in more advanced methamphetamine addicts. These men are still experience intense sexual desire, but are unable to obtain a lasting erection, and so take Viagra to maintain an erection, or engage in receptive sex predominantly (Mansergh 2006). Both methamphetamine and Viagra use are strongly associated with HIV infection in homosexual men (Drumright 2006).

Methamphetamine users are often apathetic about their HIV status and careless about their sexual practices (Taylor 2007). Users often engage in unprotected sex which is further associated with transmission of HIV and other STD's. A longitudinal study of men who have sex with men revealed that sero-conversions were strongly related to the use of drugs before sex, high numbers of partners, and unprotected anal intercourse (Koblin 2006).

We are seeing a resurgence of all types of STD's including syphilis, gonorrhea, and AIDS particularly in drug abusing populations.

These factors are most obvious and measurable in the homosexual communities, which have seen a resurgence of HIV infection since the mid 90s (Catania 2001). Methamphetamine use is 10 - 20 times more common in homosexual men than in the population at large (Shoptaw 2006, Mimiaga 2008). Even the occasional use of methamphetamine is associated with increased unprotected and sero-discordant sexual activity – activity with persons of opposite or unknown HIV status across the nation as documented by Colfax (2005) in San Francisco and Plankey (2007) in Washington DC.

In a New York City study, methamphetamine seemed to attract a subset of hypersexual risk taking gay men who do not take precautions regardless of HIV sero-status. Equivalent rates of 'extreme' sex acts were reported while high and while sober in this meth abusing population (Halkitis 2005). Failure to disclose HIV positivity is strongly associated with methamphetamine use, and condoms are seen as obstacles to pleasure and reminders of the burden of being HIV positive (McCready 2008).

The magnitude of the associated between meth and HIV is illustrated by recent data from San Francisco. In a study of people seeking HIV testing at a San Francisco STD clinic, those who admitted to recent methamphetamine use were three times more likely to test HIV positive, and those who used methamphetamine during sexual encounters were four times more likely to test positive (San Francisco Times 2005). Among homosexuals who use IV methamphetamine, 68% are trading sex for money or drugs, and these people are

six times more likely to test HIV positive than non meth users (Bacon 2006). In the IV drug using homosexual population, 70% of men reported unprotected anal intercourse (Kral 2005) and 42% of the HIV infected men were not aware of their infection (Bacon 2006).

Methamphetamine abuse contributing to HIV transmission is commonly associated with homosexual communities, but is also seen in heterosexuals and adolescents who are also using methamphetamine primarily for its sexual effects (Springer 2008). More than 63% of adolescents who are involved with drug abuse have engaged in five or more unsafe sexual practices (Tepline 2005). Juveniles in the justice system are much more likely to engage in unsafe sexual practices, and more than 66% of them persist in doing so despite counseling and incarceration (Romero 2007). Heterosexual men are also engaging in unsafe sex under the influence of methamphetamine even when they know they are HIV+ (Purcell 2006)

Heterosexual meth using women had similarly high rates of unsafe sexual activity including multiple partners, anonymous partners, commercial sex work, and unprotected sex (Semple 2004). The prevalence of sexually transmitted disease among homosexual women is comparable to that among heterosexual women, and risk factors are similar, with number of partners and unprotected sex primary risk factors (McNair 2005). IV drug use is eight times more prevalent in homosexual women with corresponding increases in Hepatitis C and HIV risk factors (Fethers 2000).

3. General Health Effects of Methamphetamine Use

Methamphetamine use is associated with poor hygiene, crowded living conditions and increased general infection rates. Personal hygiene is often compromised as addicts become homeless or live in poverty. Methamphetamine use frequently causes loss of olfactory function as the nasal mucous membranes are compromised by near constant exposure to a potent vaso-constrictor. Nasal perforations are seen in addicts who snort the drug frequently. As the sense of smell is compromised, the addict does not realize the severity of his hygiene problem.

Methamphetamine is a powerful anorectic, and causes malnutrition in general, and vitamin deficiencies, anemia, and poor wound healing in particular. The immune system is especially vulnerable to poor nutrition, accounting for much morbidity and even mortality. Generalized weakening of immune function related to vitamin and protein deficiencies predisposes addicts to infection from a variety of sources in addition to the sexually transmitted diseases. Increased infection rates with community acquired MRSA (methacillin resistant staphylococcus aureus) are noted in methamphetamine addicts, with skin picking behavior so common it is referred to as ‘meth mites.’ Addicts also have increased rates of sinusitis and pneumonia among those who smoke the drug, and bacterial endocarditis among those who inject it.
Methamphetamine use is also associated with significant psychiatric co-morbidity as dopamine and serotonin neurotransmission is impaired. Anxiety disorders, major depressive symptoms, and bipolar spectrum are all strongly associated with methamphetamine use. Psychotic symptoms are very common among methamphetamine addicts, including persecutory delusions and frank paranoia (McKetin 2007). Severe mood and thought disorders increase the likelihood of exposure to infectious diseases, especially sexually transmitted diseases, by impairing rational decision making and

judgment. Among methamphetamine dependent gay and bisexual men, the incidence of STD's was increased in those with anxiety disorders, social phobias, bipolar disorder, and major depression (Shoptaw 2003).

3. Methamphetamine accelerates HIV progression

A single case of a rapidly progressive, multiply resistant form of HIV in a New York man who used methamphetamine lead to speculation of a super infective form of the disease spread by meth addicts (CDC 2006). And indeed, methamphetamine use is associated with one form of drug resistance in HIV, primary non-nucleoside reverse transcriptase inhibitor resistance (Colfax 2007). Gorbach in 2008 reported that methamphetamine users were four times more likely to acquire a drug resistant form of HIV. Re-infection with a different strain of HIV is a common scenario in situations where HIV + individuals are engaging in unprotected intercourse with other HIV + partners (sero-concordant sex). But viral loads have not been noted to be higher among methamphetamine users in most studies. The finding of rapid progression to clinical AIDS is more related to immune modulation directly or indirectly caused by methamphetamine.

But methamphetamine is also a potent specific immunosuppressant. Talloczy in 2007 published a series of experiments demonstrating the nature of immunosuppression associated with methamphetamine use, even at low concentrations. Methamphetamine acts biochemically as an adjuvant for HIV infection by reducing the immune response to infection both at the splenic level and in peripheral blood.

Dendritic cells in the spleen serve as the first line of defense against HIV. They recognize and internalize pathogens and subsequently activate T cells. They are also the initial targets of the HIV virus, adhering to and invading these immune cells as a first step in infection. Methamphetamine interferes with dendritic cell function on several levels. First it decreases dendritic cell expression of genes associated with chemokine regulation, cytokinesis, apoptosis and cell cycle regulation (Mahajan 2006). The clarion call for reinforcements is impaired. Methamphetamine also influences expression of two dendritic cell genes coding for adhesion related proteins (Nair 2006), which are important for defense against HIV infection. Methamphetamine thus acts as a co-factor in the invasion of HIV into the dendritic cells of the spleen.

Methamphetamine is also active at the intracellular level in the spleen, inhibiting dendritic cell function by collapsing the Ph gradient these cells use to process antigens in the lysosome. It inhibits autophagosome processing leading to an accumulation of autophagosomes and halting antigen delivery to immune cells (Talloczy 2007). Meth decreases T cell profilerative response to intact antigen, impairing the cells ability to recognize and repel an invasion. Saito confirmed in 2008 that methamphetamine reduced natural killer cell function in splenic lymphocytes, which did not recover, even with interferon treatment.

Peripherally, methamphetamine also interferes with immune function in peripheral blood. Single and repeated methamphetamine injections acutely reduced peripheral blood leukocyte counts (Saito 2008). Methamphetamine also collapses Ph gradients in peripheral blood macrophages, blocking phagocytosis in these primary immune cells concerned with clearance of bacteria. This is thought to underlie the severity of bacterial

infections such as MRSA, periodontal disease, and various forms of pneumonia in methamphetamine addicts. Methamphetamine also inhibited phagocytosis of Candida and Cryptococcus by macrophages by 40% and in fact increased proliferation of these pathogenic fungi within macrophages (Talloczy 2007) even in the absence of HIV infection.

Methamphetamine thus acts synergistically with HIV infection to cause more rapid and severe disease progression to AIDS. Animal models involving retroviruses have elucidated the effects of methamphetamine on HIV infection in humans. Methamphetamine exposure further impaired immune function in mice infected with a murine retrovirus, causing reductions in interleukin 2, interferon and cytokines in retrovirus-infected mice (Yu 2002) Methamphetamine impaired immune function in the thymus by reducing CD8 and CD4 cells, inhibiting IgM formation, impairing the proliferation of mitogen stimulated B and T cells, and inhibiting granulocyte-macrophage interactions (In 2005). Similar changes have been noted in the immune systems of HIV infected humans who abuse alcohol and cocaine (Chiappelli 2006).

4. Methamphetamine Accelerates CNS Involvement

Methamphetamine produces a massive release of neurotransmitters including dopamine, serotonin, and nor-epinephrine. As receptors are overloaded and ultimately destroyed, mood regulation is impaired resulting in symptoms of depression, anxiety, and manifestations of Bipolar Disorder. Methamphetamine is a well known neurotoxin, producing oxygen free radials in many tissues, including the central nervous system (Riddle 2006). These toxic compounds cause direct cellular damage to central areas in the brain that regulate emotion, memory, and perception. The development of psychosis and dementia is especially problematic as both can persist long into recovery and complicate treatment efforts (Yui 2000, McCann 2007).

HIV infection also affects the central nervous system with the development of AIDS Dementia in up to 60% of patients with advanced disease. Cognitive impairment is seen with loss of memory and concentration, and motor symptoms of clumsiness and abnormal gait. Development of dementia is strongly related to increased CSF viral load (Ellis 2002), decreased CD4+ counts, and poor survival, and incidence has decreased in the HAART era (Bhaskaran 2008). Progression to AIDS Dementia is significantly accelerated in patients who also use methamphetamine.

In Los Angeles, 50% of white male homosexuals testing positive for HIV are methamphetamine users (Wohl 2007). The more rapid progression of HIV in the presence of methamphetamine abuse has been noted, with more severe deterioration in immune and neurologic function. HIV infected macrophages invade the CNS early in the course of disease, causing inflammatory changes and neurodegeneration. Increased neurotoxicity in these patients is related primarily to increased inflammation independent of viral load (Vitiello 2007).

HIV infection with concurrent methamphetamine abuse results in severe and rapidly progressive HIV associated dementia with 58% of HIV+/Meth+ men showing deterioration vs 38% of HIV+ / Meth – showing impairment on neuropsychiatric testing. (Rippeth 2004). HIV infection in the brain causes encephalopathy and dementia by releasing a protein called Tat (transactivator of transcription) in the striatum (motivation

and motor control) and frontal cortex (judgment and reasoning, executive function). HIV infected individuals who also abuse methamphetamine have more severe encephalitis and more neural damage than those who do not abuse meth (Taylor 2007). Both Tat and methamphetamine activate glia (neural scar tissue) and induce cytokine production, and cytokine levels are further increased in cell preparations exposed to both. The interaction between meth and HIV resulted in increased destruction of dopaminergic terminals in the striatum of rats. (Theodore 2006)

Hippocampal (memory storage) neurons exposed to both Tat and Meth showed early evidence of neural damage at 6 hours and extensive cell death at 24 hours. These changes were associated with a dysregulated mitochondrial calcium potential (Langford 2004), increased levels of oxidative stress, inflammation, and mitochondrial damage in the frontal cortex, hippocampus and striatum (Flora 2003). Injury to these areas is strongly associated with memory loss and cognitive impairment seen in HIV + methamphetamine users (Chana 2006).

In human studies, higher viral load was strongly associated with increased cellular damage on MRS scanning (a measure of cellular metabolic function) in patients who also use methamphetamine, but significantly less in those who do not use meth (Taylor 2007). Brain metabolite MRS scanning revealed an additive effect of methamphetamine on the HIV related brain injury in the frontal lobe and basal ganglia (Chang 2005). On MRI scanning (a measure of cellular volume and structural integrity) atrophy was seen in the HIV positive patients, while significant swelling was noted in the cortical areas and striatum of HIV positive methamphetamine users, and atrophy in the hippocampus (Jernigan 2005). Lower CD4 counts were also associated with more neuropsychiatric impairment in meth using patients (Carey 2006). When HIV is poorly controlled, methamphetamine exposure results in worsening brain injury.

HIV viral control is markedly impaired in methamphetamine users, related both to the intoxicated state, and to the mental health consequences of meth use, including depression and anxiety problems. In a study of new onset HIV patients, 63% had a mental illness (including depression, anxiety, psychosis, or a personality disorder), 45% had a substance abuse disorder, and 38% had both. Those with untreated mental illness or a substance abuse disorder were in a more advanced disease state – higher viral loads and lower CD4+ counts- than those who did not have these problems (Tegger 2008). A longitudinal study showed markedly reduced HAART medication compliance in drug using patients, with a four fold greater risk of medication errors and non-compliance. Stimulant users were at greatest risk of non-compliance, particularly when they were actively using drugs and thus intoxicated (Hinkin 2007). Active cocaine users had only 27% adherence to antiviral medications, vs 68% for non-users. Consequently, only 13% of cocaine users maintained viral suppression, vs 46% in non-users (Arnsten 2002). As a result of poor compliance, drug users and patients with mental health problems such as anxiety or depression showed slower rates of virologic suppression and faster rates of virologic failure (Pence 2007). The risk of developing resistance to HAART is greatly increased in situations of late diagnosis and poor compliance with medical regimens, and these resistant strains are then transmitted to others.

The prevalence of Hepatitis C co-infection in HIV positive patients is around 30% over all (Rockstroh 2005), and between 70 and 90% among injection drug users (Lauer 2001, Sherman 2002). Not surprisingly, persons co-infected with HIV and Hepatitis C had

poorer response to HAART, higher mortality rates, and were more likely to die from HIV related causes, even with similar viral loads (Weis 2006) and CD4 counts (Anderson 2004). Hepatitis C co-infection makes HIV disease worse. Also not surprisingly, persons co-infected with HIV and Hepatitis C had increased rates of HCV persistence (95%) with a lack of CD4 T cell response during acute disease contributing to failure of early disease control (Danta 2008). Co-infected individuals who have cleared HCV spontaneously remain at risk for recurrence of Hepatitis C viremia if their CD4 counts fall (Kim 2006). HIV co-infection makes Hepatitis C disease worse. Methamphetamine use further impairs the immune response to Hepatitis C resulting in more severe liver disease and poorer response to interferon treatment (Ye 2008).

HCV is itself associated with cognitive impairment, even in the absence of cirrhosis, in one third of chronically infected persons (Perry 2008). Neuropsychological function is further impaired by concurrent Hepatitis C infection in HIV + patients (Richardson 2005, Aronow 2008). Hepatitis C infection is associated with higher levels of HIV RNA in the cerebrospinal fluid of HIV + patients, reflecting more CNS invasion by HIV (Letendre 2005). Both cognitive function and affective symptoms were adversely affected by concurrent Hepatitis C infection (Ryan 2004, Clifford 2005). Patients with concurrent HCV infection, HIV infection, and methamphetamine use were even more severely impaired with deficiencies in learning, abstraction, motor skills, information processing and delayed recall (Cherner 2005). The impact appears to be directly attributable to the viral infection since differences in biochemical measures of liver function did not explain the neuropsychological differences in the hepatitis infected persons (Morgello 2005).

5. Interventions

The opportunity for intervention in the progression of disease is significant. With the advent of HART treatments for HIV infection, more infected people are living almost full life-spans, and more of them are developing HIV related dementia. The impact methamphetamine has on HIV related dementia is substantial, and much morbidity could be prevented by reducing the meth use of HIV positive patients and high risk sexual behaviors of meth users.

Reaching the populations at risk for HIV infection has proven difficult since so many people whose sexual behavior places them at risk do not consider themselves members of the at-risk groups. Youth are increasing identifying with a homosexual lifestyle and yet do not consider themselves at risk for the diseases of the older generation of gays. Adult men who have sex with men often have a wife and kids at home, and though they participate in same-sex adventures frequently they do not consider themselves gay. Closeted homosexuals or bisexuals also are not likely to participate in HIV risk prevention programs, and are unlikely to change their behavior in response to such a program.

Concurrently IV methamphetamine and cocaine addicts often do not consider themselves IV drug abusers because they do not use heroin. IV methamphetamine addicts often do not consider themselves at risk for HIV even though 45-50% of them are HIV positive. Public perception of what constitutes a risk factor for HIV are significantly outdated (Bull 2002). Safe sex programs aiming only at self identified homosexuals miss more

than half of the at risk population, including virtually all of the IV drug abusers at risk via needle sharing.

Even among self identified homosexuals, compliance with safe sex measures is sporadic, especially among meth users. Use of party drugs' in relation to sex including methamphetamine increases risk of unprotected sexual encounters with HIV + individuals, with reliance on assumptions of sero-concordence (Purcell 2005). Unprotected sero-discordant sex is considered an act of violence among homosexuals, yet many methamphetamine users regularly engage in it. Risky behavior has escalated in the years since highly active retroviral therapy became available. HIV seroconversion is strongly associated with use of methamphetamine, poppers, and/or Viagra. It is also associated with unprotected anal insertive or receptive sex, number of partners, and complacency regarding the effectiveness of medical treatments for HIV (Schwartz 2007, Plankey 2007).

Effort to reduce unsafe sexual practices among homosexual meth using men have been disappointing. Cognitive behavioral therapy aimed at reducing unsafe sexual practices in the face of ongoing methamphetamine use improved actual behavior only minimally. Participants engaged in safe sex 25% of the time, as opposed to 18% of the time for control groups 12 months post treatment in HIV + men (Mausbach 2007). A similar study with peer-led behavioral intervention reduced unsafe sex among HIV+ men from 26% of encounters to 21% at three months post intervention (Wolitski 2005). The low rates of safe sex among these HIV+ men suggests we face a serious challenge in our attempts to control transmission of HIV.

Successful addiction treatment with contingency management, cognitive behavioral therapy, or both, was more effective in reducing sexual risk behaviors than counseling directed toward the risk factors themselves (Shoptaw 2006). Reduced methamphetamine use itself resulted in declining depression scores and reduced sexual risk behavior. This suggests that lowering methamphetamine use has a synergistic effect on reducing unsafe sex among homosexual men (Jaffe 2007). The beneficial effect on sexual risk behavior was persistent in sustained recovery. Successful drug treatment resulted in reduced sexual risk behaviors at one year followup, with fewer anonymous partners, reduced anal intercourse, and an increased sense of responsibility to disclose HIV status (Reback 2004).

Unavailability of drug treatment facilities has been a continuing problem in areas hard hit by methamphetamine, particularly in the homosexual communities. A majority of homosexual men who use methamphetamine report concern over the effects meth is having in their lives. Of 174 men surveyed at a San Diego STD clinic, 70% had tried to quit their methamphetamine use, 52% were interested in obtaining treatment, but only 12% had ever been in drug treatment (Mensa 2006). Some men feel that if they quit using meth, their sex life will be over, and they need a role model of successful recovery in order to take the first step. The vast majority deal with persistent depression and anxiety and are in need of mental health care (Mimiagra 2008). Greater availability of effective drug treatment offers our best hope of reducing HIV transmission in these populations.

Education programs that reach people where they are, physically and emotionally, are much more effective than programs that require the participant to come to a physical location, or admit something that they do not wish to acknowledge. There is some

promise in an internet based outreach program that takes advantage of the partner meeting websites that abound on the web. This is the starting point for many crystal methamphetamine related hookups, and offers a potential starting point for interventions and educational efforts (Mimiaga 2008). Specifically, posters and pictures depicting the physical degeneration common in addicts may be effective in communicating with young men who highly value their physical appearance.

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