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Associations between use of crack cocaine and HIV-1 disease progression: research findings and implications for mother-to-infant transmission

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Abstract

Recent in vitro and in vivo research has suggested that cocaine has a direct effect on the pathogenesis of AIDS. These findings are confirmed by epidemiological studies linking the use of injected, inhaled, and smoked (crack) cocaine and indicators of HIV disease progression, even among adherent users of highly active antiretroviral therapy. Recent studies of vertical HIV transmission suggest that cocaine use may play a role in mother-to-child infection via alteration of maternal immune responses, enhanced viral replication in maternal immune cells, or alterations in the immune systems of neonates or infants. The purpose of this article is to review research conducted over the past several decades on associations between use of cocaine and HIV disease progression, especially among HIV+ women, and to explore its potential relevance for understanding mother-to-infant transmission of HIV.

Introduction

Several lines of recent research suggest that cocaine may directly affect the pathobiology of HIV. Complementing these findings are epidemiological studies suggesting an independent association between cocaine use and HIV disease progression and AIDS-related mortality. The purpose of this article is to review prior research and explore its relevance for developing a better understanding of mother-to-infant transmission of HIV. To accomplish this aim, we conducted a focused review of empirical studies published in peer-reviewed journals from the 1980s through the present, using the search engines Medline, Elsevier, and Scirus. After a brief review of in vitro and in vivo studies of the effects of cocaine on the pathogenesis of AIDS, we turn to epidemiological research linking use of cocaine and indicators of HIV disease progression. Next, we review studies that support the role of cocaine in transmission of HIV infection from mother to child, concluding with recommendations for a multi-pronged research agenda to address the complex pathways in which cocaine may affect vertical transmission

Cocaine and the Pathobiology of HIV

Cocaine is associated with immune alterations in a wide variety of lymphocytes, including natural killer (NK) cells, helper T cells (CD4), and suppressor/cytotoxic T cells (CD8+) (Xu,

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Flick, Mitchel et al. 1999; Baldwin, Roth, Tashkin et al. 1998). Research summarized by Baldwin and colleagues (ibid) suggests a significant potential for cocaine to inhibit the effector functions of neutrophils and macrophages, interfering with the body's ability to defend itself against infection, as well as to suppress cytokine production, decreasing operation of important immune responses (Irwin, Olmos, Wang et al. 2007; Gekker, Hu, Sheng et al. 2006). Also well-established is the capacity of cocaine to enhance the replication of HIV in vitro (Bagasra & Pomerantz 1993; Peterson, Gekker, Chao et al. 1991; Roth, Tashkin, Choi et al. 2002). For example, cells from chronic cocaine abusers more readily support HIV replication and AIDS-defining opportunistic infections than cells from nonusers, suggesting a direct role for cocaine in the acquisition and progression of AIDS (Baldwin et al. 1998). Recently, cocaine has been shown to cause membrane permeability, facilitating endothelial transmigration of infected dendritic cells across the blood brain barrier to the central nervous system (Nair, Schwartz, Mahajan et al. 2004). Finally, there is evidence of cocaine-mediated alteration of immune responses and host resistance due to disturbances in the balance of Th1 pro-inflammatory versus Th2 anti-inflammatory cytokines and lipid bioeffectors (Cabral 2006). While intriguing, these findings remain preliminary and suggestive, with no definitive role for cocaine in the progression of HIV disease considered to be unequivocally established.

Given evidence cited above, it is not surprising that many epidemiologic studies have confirmed that cocaine users are at high risk for HIV infection and progression. However, a noteworthy minority of studies has failed to find these associations. There is also some suggestion that cocaine has differential effects on women and men, with varying implications for those who are HIV-1 seropositive. Thus, the purpose of this review is to summarize research evidence emerging in the past several decades regarding linkages between cocaine (alone or in concert with other drugs) and acquisition of HIV infection, disease progression, and mortality. Also explored will be the implications of these findings for better understanding of the role of cocaine use in mother-to-child transmission of HIV. Finally, we will propose a research agenda for the further development of the state of the science in this area.

Research on Use of Crack cocaine and other Illicit Drugs in Male and Mixed-Sex Cohorts

In this section we review studies of male and mixed-sex cohorts that examined associations between use of cocaine exclusively, or in concert with other illicit drugs and problem drinking. The research is organized chronologically, by time of follow-up, to allow the reader to follow changes that arose with the advent of highly active antiretroviral therapy (HAART) and a concomitant focus on adherence to antiretroviral (ARV) therapy.

We begin with a prospective study of the natural history of HIV conducted in a subset of 6,704 homosexual and bisexual men screened for hepatitis B in 1978 to 1980 and recruited for follow-up study in 1983 through 1992 called the San Francisco City Clinic Cohort (SFCCC) (Vittinghoff et al. 2001). The 370 SFCCC participants included in this analysis had well-documented seroconversion dates and were infected relatively early in the epidemic, with an estimated 89% seroconverting before the end of 1983. In a multivariable Cox proportional hazards model, weekly self-reported use of powder and (at later visits) crack cocaine was independently associated with all-cause mortality, controlling for age, time, and vaccine trial participation. Also significant in this model were weekly self-reported use of hallucinogens and receptive anal intercourse with ejaculation. In a second multivariable Cox proportional hazards model predicting time from seroconversion to development of AIDS, only weekly use of hallucinogens and receptive anal intercourse with ejaculation were significant. This is one of the first large-scale, prospective cohort studies to

document that increased risk of HIV disease progression and death were associated with frequent cocaine use. This association was also documented for use of hallucinogens, but not for use of other drugs and substances of abuse such as amphetamines, nitrite inhalants, marijuana, alcohol, or tobacco. The authors argued that their ability to document an AIDS cause for 75% of the deaths suggested that drug overdose and related factors were not operative, and called for further research on direct and indirect linkages between cocaine and HIV disease progression.

The next study was conducted with 633 heterosexual (54% male) injection drug users recruited in May 1986 through July 1987 from outpatient detoxification and methadone maintenance programs in San Francisco (Chaisson et al. 1989). Self-reported daily cocaine injection by blacks and Hispanics was significantly associated with being HIV+, as was all other forms of cocaine use, controlling for sex, race, heroin use, current heroin injection, number of persons sharing needles, use of shooting gallery, and number of sexual partners. Seroprevalence was actually higher for those injecting cocaine alone versus those injecting cocaine and heroin (speedballs). Cocaine use was highest among African Americans, and the association between more frequent cocaine injection and higher risk of seropositivity was found among Blacks and Hispanics but not among Caucasians. Cocaine injection was also associated with other behaviors that led to HIV infection such as using drugs in a shooting gallery and sharing paraphernalia. These authors noted that cocaine's short half-life, coupled with its highly addictive nature, could lead users to inject as many as ten or more times per day. They speculated that a greater number of injections might explain the greater likelihood of HIV infection among users of cocaine that their study had demonstrated.

In a study of 277 male and female (80%–63% male) injection drug users in Baltimore who were followed from 1988 through 1998 (Nelson et al. 2002), conversion to HIV was significantly associated with self-reported injection of cocaine alone, injection of cocaine and other drugs, more frequent injection, sharing of injection paraphernalia, and injection in a shooting gallery. Smoking and inhalation of crack cocaine were not associated with greater likelihood of HIV infection. While these factors remained consistent over time, the seroconversion incidence per 100 person-years declined significantly by 12% per year, from 4.45 in 1988–1990, to 3.35 in 1991–1994, to 1.84 in 1995–1998. These authors speculated that injection behaviors accounted for HIV seroconversion in their study population, along with sexual risk behaviors.

The next study of 3,084 patients (70% male) at an STD clinic in the Bronx was conducted during February 1988 through December 1990 to examine HIV-1 seroprevalence and risk factors (Chaisson et al., 1991). Patients were queried about their HIV risk behaviors in order to identify a group of men (n=50) and women (n=22) who denied engaging in IV drug use, sex with IV drug users, and having sex with men (males only). In multivariate analyses, among HIV-1 positive women patients without reported sexual or drug HIV risk behaviors, use of smokable freebase cocaine (crack) and prostitution were significantly related to HIV infection. Among men without reported HIV risk behaviors, crack cocaine use and a history of syphilis were associated with HIV infection. These authors speculated that both crack cocaine use and history of syphilis may be markers for having an HIV-1 infected sex partner, and identified crack users as an emerging population of importance in the heterosexual transmission of HIV-1.

In the next study, 1,967 young adults (51% male), age 18–29 years, were recruited from inner-city neighborhoods in New York, Miami, and San Francisco in January 1991 through September 1992 (Edlin et al. 1994). These included 1,137 who reported that they had smoked crack cocaine 3 or more days each week during the 30 days prior to recruitment (regular crack cocaine smokers), and 830 who said they had never smoked crack cocaine.

Excluded from the analysis were those who said they had smoked crack cocaine in the past but were not regular users in the month prior to recruitment. In a multivariable logistic regression analysis, the prevalence of HIV-1 infection was higher among regular crack cocaine smokers than non-smokers, and higher among crack cocaine-smoking women than among crack cocaine-smoking men. However, after adjusting for four sexual practices (sex work, unprotected sex work, anal sex between men, homosexual anal intercourse with 50 or more male partners), and controlling for city, race, and homelessness, HIV-1 prevalence was found to be similar among crack cocaine smokers and non-smokers. These researchers concluded that the association between regular crack cocaine smoking and HIV-1 transmission appears to occur through its link to high-risk sexual behaviors, and noted that this association is stronger among women than men. However, they also cautioned that their use of street outreach for recruitment under-represented less visible drug users, and deliberately excluded former crack cocaine smokers as well as those who used crack cocaine less frequently, which may have introduced biases to their findings.

The next study (Palepu et al. 2003) examined the impact of prior drug use on the virologic response of 578 HIV+ HAART-naïve patients (90% male) who were prescribed antiretroviral treatment between August 1996 and December 2000 as part of a population-based HIV treatment program in Vancouver, Canada. Subjects were classified as current, former, or non-injection drug users, with the type of drug not specified. The primary outcome in this study was two consecutive HIV-1 RNA levels of less than 500 copies/ml. In a multivariate analysis controlling for baseline HIV-1 RNA, duration of therapy, type of ARV therapy, adherence, and age, current injection drug users were significantly less likely to suppress their HIV-1 RNA than either non-users or former users. Moreover, there was an interaction between drug use and adherence as defined by pharmacy refill compliance. In analyses stratified by IV drug use, the adherence of former and non-users of injection drugs was significantly associated with viral suppression, while adherence of active IV drug users was not associated with suppression. These authors concluded that those who continued to inject drugs while taking HAART were less likely to suppress their HIV-1 RNA, although the explanation for this remained elusive.

A study of 1091 HIV+ individuals (81% male) participating in a Spanish multicenter study of seroconverters (Perez-Hoyos et al. 2003) examined the population effectiveness of the introduction of HAART from pre-1992 through 2000. Controlling for age, gender, transmission category, length of HAART exposure, and year, self-reported intravenous (IV) drug users had a lower likelihood of (all-cause) death than non-IV drug users, and lower reductions in the risk of progression to AIDS. The authors note that HAART was under-utilized among IV drug users compared to men who have sex with men in their cohort, and also that non-AIDS mortality was a likely factor in the low survival rate of their IV drug-using sample. Thus, they were unable to attribute a direct role to injection drug use in the progression to AIDS and all-cause mortality.

The next study examined ARV medication adherence among 85 HIV+ men and women (60% male) who were current and former opiate users in Bronx, NY and were followed from July 1998 through September 2000 (Arnsten et al., 2002). Results revealed that the strongest predictor of failure to maintain viral suppression was self-reported active use of crack and other forms of cocaine: only 13% of active cocaine users maintained viral suppression, while 46% of non-users did so. Active cocaine use and self-reported tendency to use alcohol and drugs to cope with stress were also significantly associated with lower adherence to ARV regimens. The best predictive model for viral suppression included the absence of active cocaine use, being male, and having less experience on antiretroviral medication. These authors note that theirs is the first study to quantify the impact of active

cocaine use on ARV adherence, and further argue that their results support the role of adherence as a mediator between cocaine use and disease progression.

A prospective cohort study (Webber et al. 1999) followed 222 HIV+ women and 302 HIV+ men from January 1989 through December 1996 who attended a methadone maintenance clinic to examine HIV disease progression and mortality. In this study, women were more likely than men to report smoking crack cocaine, and women were more likely to report heavy crack cocaine use, especially in the period immediately preceding an AIDS diagnosis. Men were more likely to use parenteral cocaine, heroin, and speedballs. In the multivariate analysis, crack cocaine use was associated with time to AIDS adjusting for age, symptoms, zidovudine use, tobacco smoking, other drugs of abuse, sexual risk factors, homelessness, and incarceration. When exploring associations between different AIDS defining illnesses (ADI) and different drugs of abuse, tuberculosis was found to be the most common ADI among crack cocaine users. However, there were no differences between crack cocaine users and non-users in mortality, slope of CD4 cell decline, or CD4 counts at time of AIDS diagnosis. The authors speculated that crack cocaine users who smoke tobacco might be more susceptible to respiratory infections, due to adverse effects of drug smoking and inhalation in pulmonary function and airway responsiveness in the context of immune system damage. They also suggested that use of crack cocaine along with alcohol might accelerate HIV disease progression.

The next study was designed to explore the therapeutic effectiveness of antiretroviral treatment in two time periods: before the era of protease inhibitors (1990–1995); and following HAART availability (1996–1999). Subjects were 2165 HIV+ patients at the Johns Hopkins HIV clinic in Baltimore, 70% of whom were male in the pre-HAART time period and 68% male in the HAART era (Poundstone et al. 2001). While disease-free survival time increased for both men and women from the pre-HAART to the HAART era, the increase for women was significantly smaller. Multivariable Cox proportional hazards analysis revealed that, in the HAART era, injection drug users (drug not specified) progressed to a new AIDS-related opportunistic illness (OI) or all-cause death faster than non-IDUs. These results were further explored by stratifying for initial CD4 count, which revealed that the median time to progression of HIV disease was extended in the HAART era, but the advantage for IV drug users on HAART was significantly less than for non-users taking HAART regardless of gender, race, and age. The authors noted that IV drug users were less likely than non-users to be on any type of ARV therapy, and also speculated that higher Hepatitis C infection among the former group might also hasten disease progression.

In a study of 764 HIV-1 infected patients (63% male) at the Johns Hopkins HIV Clinic followed from November 1998 through October 1999, Lucas and colleagues (2001) found that self-reported active heroin or cocaine users (via any mode of administration) were less likely to be taking HAART than former users or non-users controlling for sex, race, prior opportunistic infection, nadir CD4, and peak HIV-1 RNA. Active cocaine and heroin users also experienced smaller median reductions in viral load from baseline, and smaller median increases in CD4 lymphocyte count compared to former users and nonusers, controlling for HAART use and adherence as well as other factors. Thus, not only was active drug use associated with lower utilization of HAART and nonadherence, it also was related to inferior virologic and immunologic responses to HAART. The authors noted the importance of viewing drug use as a dynamic behavior and argued that longitudinal analysis is needed to address changes that occur in patients' illicit drug use over time when examining HIV disease progression.

In their next study of 695 HIV-1 infected patients (62% male) at the same urban HIV clinic in November 1998 through May 2001, Lucas et al. (2002) extended their notion of dynamic

patterns of substance use by focusing on a phenomenon referred to as "switching." Here, switching is conceptualized as changing from non-use of drugs or alcohol to active use of substances, and vice versa. The units of analysis in this study were consecutive pairs of study visits made by individuals, referred to as "couplets." Two types of comparisons were made: 1) couplets in which no abuse was reported at either visit compared to couplets in which participants switched from non-use to substance abuse; and 2) couplets in which drug/alcohol abuse was reported in both six-month periods compared to couplets in which subjects switched from substance abuse to non-abuse. The analysis found that switching from non-use to use was associated with lower likelihood of HAART use and adherence, and with less frequent HIV-1 RNA suppression and blunted CD4 cell increases when compared to consistent non-use. On the other hand, switching from drug/alcohol abuse to non-use was strongly associated with improvements in HAART use and adherence as well as viral suppression and immune cell reconstitution, compared with persisting drug/alcohol abuse. Building on their prior findings, the authors note that theirs is the first study to demonstrate associations between temporal changes in substance abuse behaviors and the effectiveness of antiretroviral treatment. They point out the advantages of longitudinal observation for capturing the dynamics of substance abuse and its association with HIV disease progression.

In their next study, Lucas and colleagues (2006) followed 1851 HIV+ men and women (92% male) from 1998 through 2003. Replacing the couplet method of capturing dynamic cocaine and heroin use, the research employed a time-varying measure that classified self-reported heroin or cocaine use (by any mode) at each study visit into one of four categories: 1) never, defined as no reported use of cocaine or heroin at any study visit; 2) persistent, defined as use reported at every study visit; 3) intermittent-abstinent, defined as no use reported at current study visit but use reported at prior visits; and 4) intermittent-active, defined as no use at current visit but use reported at prior visits. Multi-variable random effects regression analysis found that, compared to non-users of cocaine and heroin, persistent users had a threefold increased risk of (all-cause) death, while intermittent users during active phases had a twofold increased risk of death, controlling for age, race, sex, nadir CD4 cell count, and peak HIV-1 viral load level. Intermittent users during abstinent phases did not differ from non-users in mortality. Regarding the second measure of disease progression – OIs -- compared to non-users of cocaine or heroin, the risk of developing a new OI was significantly greater for persistent users, and for intermittent users during periods of active use. However, intermittent users during periods of abstinence were no more likely to develop a new OI than were non-users of these drugs. This was the first longitudinal study using time varying measures to demonstrate temporal linkages between cocaine and heroin use and HIV disease progression and all-cause mortality. These authors speculated that active illicit drug use (versus abstinence or non-use) could have direct or indirect biological effects that hasten disease progression. Or, they argued, their findings might also indicate that the association between drug use and disease progression is mediated by behavioral factors related to access to health care, ARV therapy, and adherence.

The next study was a prospective, longitudinal study of a mixed-sex cohort (73% male) of 222 HIV+ Miami drug users recruited beginning in March 2002 and followed monthly for 30 months through June 2008 (Baum et al. 2009). This analysis found that crack cocaine users were twice as likely to progress to CD4 cell counts less than or equal to 200 copies/ml, controlling for HAART use and other covariates. HIV-1 RNA levels over time were significantly higher among crack cocaine users independent of HAART use over time. Of all drugs tested in a multivariable analysis, (e.g., crack cocaine, marijuana, heroin, alcohol), only crack cocaine was associated with a decline over 30 months to CD4 $\leq$ 200 copies/ml. Of all poly-drug use combination tested, only crack cocaine combined with marijuana significantly increased the progression of HIV disease. In a time-varying analysis of crack

cocaine use at each study visit, with HAART use and CD4 cell count as time-varying covariates, crack cocaine use was significantly associated with higher HIV-1 RNA level over 30 months of follow-up. The authors note that theirs is the first longitudinal study to show a specific effect of crack cocaine on disease progression in a mixed gender cohort of active substance users. They argue that crack cocaine use has "multi-factorial" effects on disease progression including both direct effects and effects through reduced adherence to ARV regimens. This may include a physiological action "unrelated to HAART use that accelerates disease progression."

Our final mixed-sex cohort study was a retrospective analysis of physician-reported data on 2275 HIV+ adult patients in French Guiana followed between January 1996 and December 2007 for a median of 2.8 years (Nacher et al. 2009). Crack cocaine use was measured as both a time-varying and a time-independent variable (i.e., history of prior crack cocaine use). In two separate Cox proportional hazard analyses of untreated patients and those taking HAART, HIV-1 viral load was significantly higher among patients addicted to cocaine after adjusting for age, sex, and CD4. Patients addicted to crack cocaine were also more likely to progress to AIDS than those not using crack cocaine, controlling for age, sex, nationality, CD4, CD8, HAART use, and alcohol addiction. Crack cocaine users were more likely than non-users to develop a number of ADIs including bacterial pneumonia, pneumocystosis, oesophageal candidiasis, histoplasmosis, and cerebral toxoplasmosis. However, crack cocaine users were not more likely to experience higher all-cause mortality than non-users. Instead, those addicted to alcohol were more likely to die during the study's follow-up period. The study's authors suggest that the immunological effects of cocaine may have contributed to the significant increase in ADIs observed among addicts, along with poorer adherence among those on HAART, and/or local or regional lesions due to heat or to the respiratory complications of crack cocaine use. The absence of a link between crack cocaine addiction and death is attributed to crack addicts' weak social ties and tendency to die outside the hospital so that their deaths were not reported to physicians.

Research Finding No Association Between Cocaine Use and Disease Progression

Not every study has demonstrated a link between use of cocaine and progression of HIV disease and here we review some of the studies that failed to confirm this association. Two studies focused on the pre-HAART era. The first of these involved the Multicenter AIDS Cohort Study (MACS) (Chao et al. 2008) and included 3236 HIV-uninfected men recruited beginning in 1984 and followed semiannually through April 2003, and 481 HIV+ men who were uninfected at study baseline and seroconverted before the end of follow-up in December 1995 (the pre-HAART era). Use of cocaine (mode of administration not specified) and other drugs was a time-varying measure of use/non-use, frequency of use since last visit, and persistent use (defined as use on two consecutive visits). In mixed-effects regression analysis no clinically meaningful associations were found between use of cocaine or any of the CD4 or CD8 T cell counts, percentages, or rates of change for either HIV-infected or HIV-uninfected men. This was also true for use of marijuana, amphetamines, and poppers (the slang term for various alkyl nitrites inhaled for recreational purposes, particularly amyl nitrite and several other alkyl nitrites). Models controlled for demographics, tobacco smoking, alcohol use, sexual risk factors, follow-up time, and (for the HIV+ group) use of single or combination ARV therapy. The authors noted that their findings confirmed those done with other cohorts of MSMs, including the San Francisco Men's Health Study, and prior studies of the MACS cohort (Chaisson et al. 1995; DiFranco et al. 1996; Kaslow et al. 1989; Page-Shafer et al. 1996). They also note that despite the absence of associations between drug use and adverse effects on CD4 or CD8 T cell

parameters, this did not rule out associations with other more sensitive measures of HIV disease progression such as viral load.

The next study done in the pre-HAART era included two cohorts of injection drug users: 251 from the AIDS Link to Intravenous Experiences (ALIVE) Study (76% male); and 752 from the Italian Seroconversion Study (ISS) (70% male) (Pezzotti et al. 1999). ALIVE participants were recruited starting in 1988 and followed through December 1996, while ISS participants were recruited beginning in 1987 and followed until December 1995. Relative hazards of time to AIDS and all-cause death did not differ by duration of injection drug use, age at first injection, or year of first injection, controlling for age at seroconversion, gender and study site. When data were added from the ISS cohort's MSMs and those infected by heterosexual contact, no differences between injection drug users and non-users in progression to AIDS or all-cause mortality. These authors noted that while the ISS cohort included primarily injectors of heroin alone, ALIVE cohort members primarily alternated between cocaine and heroin, yet no cohort differences were observed to suggest a differential effect. They conclude that injection drug use had little impact on the rate of HIV progression.

The next study involved 3,342 HIV+ participants in the Swiss HIV Cohort Study (70% male) who were enrolled in September 1998 and followed semi-annually through April 1999 (Junghans et al. 1999). The probability of initiating HAART was lower among those acquiring HIV through injection drug use compared with MSMs controlling for CD4, viral load, and disease stage at baseline. In addition, the risk of progression to AIDS was similar among those who acquired HIV through injection drug use compared with MSMs, controlling for demographics, previous ARV therapy, CD4, viral load, and clinical disease stage. The authors note that a number of methodological confounds may explain the apparent inconsistency in their finding of a lower probability of HAART among those infected through IV drug use but not a higher probability of progression to AIDS among that risk group.

The next study included 3,211 HIV+ patients (71% men) with CD4 counts ≤ 500 who were recruited from the Johns Hopkins HIV Clinic beginning in January 1994 and followed through December 1998 (Moore and Chaisson 1999). The purpose of this study was to explore the impact of protease inhibitor (PI)-containing combination ARV therapy on development of OIs and all-cause mortality, while one of the control variables was HIV risk group, including those infected through injection drug use. Results indicated a decline between 1994 to 1998 in the incidence of all-cause mortality as well as each of the OIs studied, and this appeared to be due to the initiation of combination ARV treatment including PIs. Membership in the injection drug use HIV risk group did not modify this relationship. The authors mention that PI combination therapy appears to slow the rate of disease progression in a clinical cohort characterized by a history of injection drug use.

The next study examined a prospective Western European cohort (EuroSIDA study) of 7,331 HIV+ individuals (80% male) recruited beginning in 1994 and followed through the Spring of 1999 (Mocroft et al. 1999). Patients were classified as belonging to one of three HIV acquisition risk groups: homosexual, heterosexual, or IV drug user, with those reporting both homosexual and intravenous drug risks classified as homosexual. Multivariate logistic regression analysis indicated that injection drug users were less likely than homosexual men to be on HAART at time of study recruitment, and throughout the follow-up period, controlling for CD4 and other confounding factors. Among those on HAART, there were no differences by HIV exposure group in CD4 lymphocyte count response to HAART, or virologic response to HAART. After adjusting for factors related to survival, those in the IV drug use risk category showed a nonsignificant trend toward

increased risk for all-cause mortality. The authors note that their data do not allow them to control for ongoing injection drug use or HAART adherence.

The final study examined data from 1,030 HIV+ injection drug users in Baltimore's ALIVE cohort (78% male) recruited from the community beginning in 1988 and followed semi-annually through 2000 (Galai et al. 2004). The primary outcome was an AIDS-related death defined as death after an AIDS diagnosis, or as death following diagnosis of another infectious disease such as sepsis or endocarditis. This definition excluded non-HIV-related deaths such as drug overdose, trauma, or liver disease. Cox proportional hazards models found that recently active injection drug use was not associated with AIDS-related mortality when the contrast with former injection drug use. In their Discussion section, the authors report that crack cocaine use was protective against AIDS-related death (not shown in the Results section), noting that this finding was counterintuitive, and cautioning that their analysis did not compare active crack cocaine use against abstinence, but was evaluated among current and former injection drug use, and thus indicated for further study.

Reasons for Conflicting Findings in Studies of Cocaine and Disease Progression

The somewhat inconclusive findings reviewed above may be due to a number of methodological inconsistencies and variations in study design, some of which are reviewed by Kapadia et al. (2005). One likely reason for conflicting findings is the diverse populations that have been investigated. In some studies the focus was on seronegative individuals while others targeted HIV+ respondents and still others included both. Some research used community samples, others used clinical HIV populations, and still others used clinical populations being treated for addiction or STDs. A second reason for variation in findings is the fact that studies have focused on a variety of outcomes. Earlier in the epidemic, acquisition of HIV infection or seroconversion was often the outcome of focus. Later, the focus has been on disease progression measures such as immunologic outcomes assessed through CD4 cell counts, slopes, and percentages; immunologic markers such as HIV-1 RNA levels at different concentrations; progression to AIDS or the occurrence of AIDS-defining illnesses (definitions of which also varied from 1987 to the currently used 1993 CDC definition). Some of the research has focused on mortality as an outcome, and here variations have included all-cause mortality, and HIV-related mortality defined in a variety of ways but usually involving death due to AIDS-related illnesses or other OIs. A third variation is in the way that use of cocaine is defined including by mode of administration such as smoking, inhalation, or injection; as freebase crack cocaine versus powder cocaine; as a drug used alone or along with heroin; and as a drug that is one part of recreational poly-drug and alcohol use. A fourth variation is in the temporal characterization of cocaine use. Some studies did not differentiate between active and nonactive users, others used injection drug-related acquisition of HIV as a proxy for current cocaine use, and other studies used a number of different measures to capture frequency of use. A fifth variation is the manner in which studies control for confounding due to ARV treatment. Some studies did not control for use of ARV therapies, HAART, or ARV adherence, and when adherence was controlled for, it was measured in a number of ways including pharmacy refill, MEMS caps, self-report, serologic indicators, and physician report. Also absent in many analyses was the examination of longitudinal data enabling the assessment of patterns of active and nonactive drug use over extended periods of time. A sixth variation particularly relevant to the topic of vertical transmission is the representation of women in the study population, since the majority of studies included relatively small proportions of women subjects, potentially introducing biases due to under-representation. Keeping all of these methodological and design features in mind, we turn now to studies of exclusively female cohorts.

Research on Cocaine and HIV Disease Progression in Female Cohorts

The first study of interest was a prospective, multi-center study of 639 HIV-positive women recruited from four U.S. cities and followed for seven years from April 1993 through April 2000, called the HIV Epidemiology Research Study (HERS) (Rompalo et al. 2004). In a multivariate analysis, neither former self-reported injection drug use nor active injection drug use were associated with progression to AIDS or with AIDS-related mortality. However, being in drug treatment was independently associated with slower progression to AIDS, and women who were current IV drug users had faster progression to all-cause death than non-users, as did women who were former injection drug users. The authors noted that injection drug use per se did not seem to result in faster progression to AIDS and speculated that lower use of HAART among IV drug users might have accounted for the poorer outcomes that they observed among this group.

Another large multi-site cohort study called the Women and Infant Transmission Study (WITS) (Thorpe et al. 2004) included 1342 HIV+ pregnant women enrolled in 1989 and 1995 and followed for five years through June 2001 from seven pediatric and obstetric clinics located in 6 U.S. cities and Puerto Rico. This study found that hard drug use (defined as cocaine, heroin, methadone, or injecting drugs) was significantly associated with developing an AIDS-defining illness before study enrollment. Among those without an ADI prior to study entry, hard drug users were more likely than non-users to progress to an ADI and, most often, this was recurrent pneumonia or tuberculosis. However, hard drug users and non-users did not differ on other progression outcomes such as change in CD4, HIV-RNA, or all-cause mortality. The authors note that most prior studies of men finding no faster progression to AIDS among drug users than MSMs used the 1987 AIDS definition that excluded recurrent pneumonia and tuberculosis, while these were the two most common ADIs in their population of seropositive women.

A third large multi-site cohort of HIV-infected women called the Women's Interagency HIV Study (WIHS) recruited 1046 women in 1994–1995 and followed them every 6 months for seven years until 2002 (Kapadia et al. 2005). This study focused on non-injection drug use (NIDU) including non-parenteral administration of heroin, cocaine, crack, alcohol, or marijuana. This study distinguished between former and active use, and the active category was further classified as either consistent (use reported at every visit) or intermittent. Women reporting current or former use of injection drugs were excluded from this analysis. In a multivariable analysis, time to AIDS differed significantly by both pattern and type of NIDU; both current and former users showed greater likelihood of progressing to AIDS compared with never-users. Progression was also faster among users of stimulants and polydrug-users than non-users. Finally, all-cause mortality was significantly higher among former users than non-users, but not among current users of non-injection drugs. The authors note that increased susceptibility to pulmonary illness among those who use drugs non-parenterally may have accounted for the link between disease progression and NIDU.

Focusing exclusively on self-reported use of smoked crack cocaine, Cook and colleagues (2009) studied 1686 HIV+ women from the WIHS cohort who were followed semiannually from April 1996 through September 2004 to explore a number of disease progression outcomes. Examining mortality specific to AIDS, estimated survival rates at 8.2 years were 89% for non-users and 90% for intermittent users, compared to 65% for persistent crack cocaine users. In a Cox proportional hazards model, the risk of AIDS-related death was three-and-one-half times as likely for persistent crack cocaine users compared to non-users, but no different for intermittent users, controlling for CD4, HIV-1 RNA, adherent HAART use, problem drinking, and demographic features. Persistent crack cocaine users were more likely than non-users to develop a new ADI, most often bacterial pneumonia or

pneumocystis carinii pneumonia. Time-varying mixed effects random regression analyses were conducted to predict semi-annual: 1) CD4 cell counts less than 200 cells/ul; and 2) HIV-1 RNA > 100,000 copies/ml. Results indicated that, compared to non-use, persistent crack cocaine use, intermittent-abstinent, and intermittent-active use were each associated with poorer outcomes controlling for adherent HAART use, problem drinking, socio-demographic characteristics, illness duration, and baseline CD4 and HIV-1 RNA. In these models, persistent problem drinking was positively associated with disease progression defined by high viral load but not low CD4 cell count. Moreover, adherent HAART use was protective against disease progression. These results remained highly similar controlling separately for heroin use, injection drug use, hepatitis C virus co-infection, tobacco smoking, and high levels of depressive symptoms. Finally, the authors examined the effects of crack cocaine use on viral suppression and immune reconstitution among all women remaining in the cohort at the end of the follow-up period (n=1053). They found that compared with women who had never smoked crack cocaine, active users in the past 6 months and inactive users who had abstained in the past 6 months had smaller median reductions in HIV-1 RNA from peak levels, and smaller median increases in CD4 cell count from nadir levels. The authors noted that theirs was the first study to show that use of crack cocaine in a large, national cohort of HIV+ women is longitudinally associated with subsequent deterioration in immune status, failure of virologic suppression, progression to new AIDS-defining conditions, and mortality due to AIDS-related causes, even among those who reported use of HAART at 95% or more. They noted that, unlike Lucas and colleagues (2006) they did not find that progression was less likely during periods of abstinence among female crack cocaine users. This provides support for the notion that the effects of cocaine on the immune system may vary by sex, as suggested by others (Cabral 2006).

Studies of Cocaine Use and Mother-to-Infant HIV Transmission

Thus far we have reviewed research evidence demonstrating that cocaine up-regulates HIV replication, interferes with the body's ability to defend itself against infection, increases membrane permeability allowing infected cells to access the central nervous system, and impairs important immune responses. All of these documented processes suggest that cocaine may have a direct role in the acquisition of HIV infection and progression to AIDS, as well as indirect effects through behavioral and other intervening factors. Indeed, epidemiological evidence in adult men and women has documented the association of cocaine use with greater likelihood of being infected with the virus as well as experiencing seroconversion. The next logical question is whether cocaine might play a role in vertical transmission of HIV infection from mother to child, a topic to which we turn in this section.

We begin with research showing that cocaine use is a risk factor for both seropositivity and seroconversion during pregnancy. Lindsay and colleagues (1992) screened 13,469 pregnant women during July 1989 through December 1990 in Atlanta, Georgia using a case control design to identify correlates of HIV infection. They found that seropositivity was associated with a self-reported history of crack cocaine use, as well as injection drug use, controlling for age, race, education, employment, IVDU sex partner, and STDs. Chirgwin et al. (1999) studied 449 inner-city initially HIV-negative women with no history of parenteral drug use and found that those who seroconverted (n=4) were more likely to have used crack cocaine daily in the past 12 months, and 3 of these 4 were also pregnant around the time of seroconversion. Other studies confirm that use of cocaine and other illicit drugs is a risk factor for mother-to-child transmission, with up to a three-fold higher risk of vertical transmission among drug users than non-users (Rodriguez et al. 1996). There are a number of mechanisms that might explain this association, and these correspond with the three hypothesized stages of perinatal transmission reviewed by Cibulka (2006): 1) before birth by

transplacental infection; 2) during labor and delivery through exposure to maternal secretions and blood; and 3) after birth through breast feeding or other means of infection.

The use of ARV therapy during pregnancy, intrapartum, and in the postnatal period, combined with elective cesarean delivery has dramatically lowered the rate of vertical transmission from 25% to less than 2% (Brogly et al. 2007). However, transmission continues to occur even among women who have successfully suppressed the virus (Mofenson 2004; Ioannidis et al. 2001). In regard to the first phase of vertical transmission, that of transmission across the placenta, some have suggested that cocaine has immunomodulatory properties that potentiate viral replication in utero (Bulters et al. 1997). A study of 207 mother-infant sets enrolled 1986–1991 and followed for up to 4 years by Bulters and colleagues (1997) found that injection of cocaine or heroin during a woman's second and third trimester of pregnancy increased the likelihood of vertical transmission. The researchers suggested that this might be due to rapid viral replication around the time of delivery. They also speculated that cocaine use in the third trimester might directly affect the developing fetal immune system. This later notion was supported by a study showing that maternal hard drug use was associated with immunologic changes in infants in the months immediately following birth (Neu et al., 2004). In this study, HIV-exposed but uninfected infants with intrauterine illicit drug exposure had lower CD4 lymphocyte percentages over the first four months of life than infants not exposed to illicit drugs in utero, adjusting for higher natural killer cell percentage and other covariates. However, they were not more likely to develop infections once other factors were controlled.

In regard to the second hypothesized phase of transmission, that of labor and delivery, numerous studies have documented cocaine-related complications of pregnancy that are also associated with vertical transmission. For example, abruptio placentae is common among women who use cocaine and has also been associated with vertical transmission of HIV in prior research (Burns et al., 1996; Minkoff et al 1995). Wabwire et al. 1999). Drawing on data from several studies, it is estimated that the risk of transmission increases approximately 2% for every one-hour increment following membrane rupture during vaginal or non-elective cesarean deliveries up to 24 hours (International Perinatal Group 1999). Low birth weight is another complication of pregnancy common among women who use crack cocaine (Fiocchi et al. 2001) that has also been identified as a risk factor for vertical transmission (Landesman et al. 1996). For example, an international collaborative registry study identified 1202 HIV+ pregnant women with low viral load in which 44 cases of mother-infant transmission occurred (Ioannidis et al. 2001), and found in a multivariate analysis that transmission was significantly lower among infants with greater birth weight as well as those receiving ARV treatment and delivered by cesarean section. Another factor associated with vertical transmission is shedding of the virus in cervicovaginal secretions that presumably infect the infant during vaginal delivery (Biggar et al. 1996). In a study of the WIHS cohort (Neely et al. 2007), women who reported recent crack, cocaine, or injection drug use were significantly more likely than non-users to be cervical shedders of HIV-1 RNA, controlling for HAART, CD4, viral load, genital tract infections, and other confounds. A nested case-control within a randomized clinical trial of breastfeeding and formula feeding compared 92 infected infants with 187 uninfected infants (John et al. 2001) and found a highly significant association between shedding of HIV-1 provirus and mother-to-infant transmission that was independent of maternal viral load.

Finally, the last phase of vertical transmission is most commonly associated with transmission via breast-feeding and, thus, breastfeeding is not currently recommended for HIV+ mothers. However, recently, an additional risk factor was identified involving feeding infants food that was premasticated by a caregiver infected with HIV. Gaur and colleagues (2009) review the cases of three infants diagnosed at 9, 15, and 39 months in which alternate

transmission routes had been ruled out and phlogenetic analyses supported this mode of transmission. Given evidence that crack cocaine users have a greater incidence of periodontal disease and oral ephthae that can pre-dispose them to transmission (Faruque et al. 1996), HIV may be transmitted from mother to child in this manner.

Possible modes of infection in each phase of vertical transmission remain obscure but may include alteration of maternal immune responses, enhanced viral replication in maternal immune cells, or alterations in the immune systems of neonates or infants. In regard to the latter possibility, Soilleux and colleagues (2001) identified a mechanism by which HIV may be transmitted vertically across the placenta, showing that DC-SIGN, a highly efficient attachment factor for HIV-1, is present on maternal and fetal cell populations separated only by a single cell layer (the trophoblast) that is frequently breached during pregnancy especially among women who use illicit drugs or smoke tobacco (Newell 1998). Li and colleagues (2003) demonstrated that morphine enhances HIV infection of neonatal monocyte-derived macrophages (MDM) through 2 to 2.5-fold increased expression of HIV gag gene mRNA compared to untreated neonatal MDM. Li and others had previously demonstrated the greater susceptibility of neonate monocytes/macrophages to HIV infection in vitro compared to adult macrophages (Ho et al. 1992; Sperduto et al. 1993; Reinhardt et al. 1885). Thus, the up-regulation effects of morphine on both maternal and neonatal immune cells may play an important role in mother-to-child transmission of HIV. It remains to be seen whether these same effects can be duplicated for cocaine.

Conclusion: Toward a Research Agenda for Understanding Cocaine and HIV

Our findings support the need for future research on the in vitro and in vivo effects of cocaine on HIV+ women's medical outcomes and those of their children. This includes studies that shed light on the specific role of cocaine in HIV pathogenesis in neonates, infants, and adults; epidemiologic studies of morbidity and mortality among HIV-positive cocaine users and their offspring; and research on potential differences associated with type and mode of administration of cocaine, frequency and quantity of use, and patterns of abstinence and relapse.

Future in vivo and in vitro studies should build on a growing understanding of cocaine as a "multifactorial agent" as elaborated by Dhillon and colleagues' recent review of the research (2008). First, cocaine exposure leads to enhanced virus replication and immunomodulation. Second, cocaine exposure causes increased neurotoxicity leading to neuronal apoptosis or cell death. Third, cocaine breaches the blood brain barrier causing an influx of inflammatory cells into the CNS resulting in clinical and pathological abnormalities ranging from mild cognitive impairment to dementia. Finally, cocaine modulates cytokine and chemokine expression that regulates immune responses. Future research should explore these processes in relation to vertical transmission and the ongoing health of mother and child.

In addition to direct causal mechanisms, research is needed on a number of behavioral and treatment factors important in mother-to-child transmission including prenatal care, access and adherence to HAART among pregnant and nursing women, cocaine-related complications of pregnancy and delivery, smoking of crack cocaine and tobacco, and oral transmission from caregiver to infant via breastmilk and premasticated food. Only a multi-pronged research agenda will enable scientists to address the multiple pathways in which associations may indicate causal as well as spurious associations.

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