# Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women

Judith A. Cook[a], Jane K. Burke-Miller[a], Mardge H. Cohen[b], Robert L. Cook[c], David Vlahov[d], Tracey E. Wilson[e], Elizabeth T. Golub[f], Rebecca M. Schwartz[e], Andrea A. Howard[g], Claudia Ponath[h], Michael W. Plankey[i], Andrea Levine[j] and Dennis D. Grey[a]



**Background:** Longitudinal associations between patterns of crack cocaine use and progression of HIV-1 disease are poorly understood, especially among women. This study explores relationships between crack use and HIV-1 disease outcomes in a multicenter cohort of infected women.

**Methods:** Subjects were 1686 HIV-seropositive women enrolled at six US research centers in the Women's Interagency HIV Study. Approximately 80% were non-white and 29% used crack during the study period. Cox survival and random regression analysis examined biannual observations made April 1996 through September 2004. Outcome measures included death due to AIDS-related causes, CD4 cell count, HIV-1 RNA level, and newly acquired AIDS-defining illnesses.

**Results:** Persistent crack users were over three times as likely as non-users to die from AIDS-related causes, controlling for use of HAART self-reported at 95% or higher adherence, problem drinking, age, race, income, education, illness duration, study site, and baseline virologic and immunologic indicators. Persistent crack users and intermittent users in active and abstinent phases showed greater CD4 cell loss and higher HIV-1 RNA levels controlling for the same covariates. Persistent and intermittent crack users were more likely than non-users to develop new AIDS-defining illnesses controlling for identical confounds. These results persisted when controlling for heroin use, tobacco smoking, depressive symptoms, hepatitis C virus coinfection, and injection drug use.

**Conclusion:** Use of crack cocaine independently predicts AIDS-related mortality, immunologic and virologic markers of HIV-1 disease progression, and development of AIDS-defining illnesses among women.



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From the [a]Department of Psychiatry, University of Illinois at Chicago, the [b]Core Center and Stroger (formerly Cook County) Hospital, Chicago, Illinois, the [c]College of Public Health and Health Professions, University of Florida, Gainesville, Florida, the [d]New York Academy of Medicine, New York, the [e]Department of Preventive Medicine and Community Health, State University of New York Downstate Medical Center, Brooklyn, New York, the [f]Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, Maryland, the [g]International Center for AIDS Care and Treatment Programs, Mailman School of Public Health, Columbia University, New York, the [h]Department of Clinical Pharmacy, University of California at San Francisco, San Francisco, California, the [i]Department of Medicine, Georgetown University Medical Center, Washington, District of Columbia, and the [j]City of Hope, Duarte, California, USA.

Correspondence to Judith A. Cook, PhD, Center on Mental Health Services Research and Policy, Department of Psychiatry, University of Illinois at Chicago, 1601 W. Taylor St, 4th Floor M/C912, Chicago, IL 60612, USA.

Tel: +1 312 355 3921; fax: +1 312 355 4189; e-mail: cook@ripco.com

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## Introduction

Recent research suggests that cocaine may directly affect the pathobiology of HIV by causing immune alterations in different lymphocytes such as helper T cells (CD4), suppressor/cytotoxic T cells (CD8), and natural killer (NK) cells [1]. Studies [2] show that cocaine interferes with the body's ability to defend against infection by inhibiting the effector functions of neutrophils and macrophages and by suppressing cytokine production, decreasing operation of important immune responses. Cocaine also enhances the replication of HIV *in vitro* [3]. Cells from chronic cocaine users more readily support HIV replication and development of AIDS-defining opportunistic infections than cells from non-users, suggesting a direct role for cocaine in the acquisition and progression of AIDS [2]. 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 [4]. There is also evidence of cocaine-mediated alteration of immune responses and host resistance due to disturbances in the balance of Th1 proinflammatory versus Th2 anti-inflammatory cytokines and lipid bioeffectors [3].

Epidemiologic research confirms that crack users are at high risk of HIV infection and progression [5,6]. In a prospective study of HIV-seropositive drug users, crack use was significantly associated with progression to AIDS [7]. A study of HIV-positive current and former drug users found that active cocaine use was the strongest predictor of failure to maintain viral suppression; 13% of active users maintained suppression versus 46% of non-users [8]. In a prospective cohort study, compared with non-users and former users, active cocaine and heroin users experienced smaller median reductions in HIV-1 RNA and smaller median increases in CD4 cell count from baseline, controlling for antiretroviral exposure, adherence, and sociodemographic factors [9]. Compared with non-users, the risk of AIDS-related opportunistic conditions was greater for persistent users and intermittent users during periods of active use, with no difference during periods of abstinence [10].

Mixed results characterize studies of drug users in exclusively female cohorts in the United States. In a multicenter cohort of HIV-positive women, injection drug use was not associated with progression to AIDS [11]. Another large multisite cohort study found that hard drug use (i.e., cocaine, heroin, methadone, or injection drugs) was significantly associated with AIDS-defining illnesses, but not with change in CD4 cell count, HIV-RNA, or mortality [12]. In a third multisite cohort of HIV-positive women, non-injection drug use was associated with time to AIDS-defining event but not with AIDS-related mortality [13].

Although suggestive, these studies and others focusing on injection drug use do not uniformly demonstrate a link between illicit drug use and HIV-1 disease progression [14–17]. Possible reasons include diverse definitions of illness progression, failure to differentiate between active and non-active users, and lack of distinction between mortality due to AIDS versus non-AIDS causes [17]. Other reasons include lack of controls for HAART use and adherence, and inadequate follow-up periods. We addressed all of these issues by examining patterns of crack use and their association with four distinct measures of HIV/AIDS disease progression in a multicenter cohort over an 8.5-year period during the HAART era.

## Methods

### Study population

The Women's Interagency HIV Study (WIHS) is a prospective cohort study of HIV disease progression among 2058 HIV-positive women at six consortium centers: Brooklyn, New York; Bronx, New York; Chicago, Illinois; Los Angeles, California; San Francisco/Bay Area, California; and Washington, District of Columbia. Our analysis includes biannual observations from 1 April 1996 (commercial availability of protease inhibitors) to 30 September 2004.

We analyzed data from cohort members completing two or more study visits (not necessarily consecutive). All women provided institutional review board approved written informed consent for research participation and use of their medical records. Analyses were adjusted for covariates identified in prior research as being associated with illicit drug use, HIV disease progression, and mortality both in the WIHS cohort [13,18,19] and other cohorts [9–12,14–16]. These included age, race/ethnicity, education, income, baseline HIV-1 RNA and CD4 cell count, year of HIV diagnosis, and study site. We also controlled for problem drinking because of research reviewed by Cabral [3] showing that cocaine in combination with alcohol places individuals at increased risk of infection with a number of pathogens, due to additive or synergistic effects resulting in impaired immune function.

### Measurements

The first marker of disease progression was time-varying CD4 T lymphocyte levels of less than 200 cells/μl. The second was time-varying HIV-1 RNA greater than 100 000 copies/ml. Lymphocyte subsets were determined using flow cytometry at laboratories participating in the AIDS Clinical Trials quality assurance programme. Plasma HIV-RNA levels were measured using a nucleic acid sequence based amplification technique (Organon Teknika Co., Durham, North Carolina, USA). Third, newly acquired AIDS-defining illnesses were identified

through medical record review using a case file abstraction protocol for participants' primary and specialty care records described elsewhere [20], along with respondent self-report. Conditions were defined according to the Centers for Disease Control and Prevention AIDS definition excluding the criterion of low CD4 cell count [21]. Cause of death was obtained from death certificates and the National Death Index, local death registries, hospital records, physician reports, and information from friends/relatives. Deaths were classified as AIDS-related if the cause was an AIDS-defining illness, or if the stated cause was organ failure or non-specific infection and the CD4 cell count was below 200 cells/μl, using procedures described elsewhere [22].

At each study visit, women reported how often they took their regimens as prescribed during the past 6 months. Responses were classified as taking all drugs as prescribed at least 95% of the time versus less than 95%. This cutoff was based on past adherence research showing that HIV-1 RNA loads of less than 400 copies/ml occurred 80% of the time in patients with antiretroviral adherence of at least 95% [23]. The construct validity of this measure is supported by WIHS research finding statistically significant relationships between adherence self-reports and subsequent virologic and immunologic parameters [24]. For analysis, women were classified at each study visit as reporting HAART with at least 95% adherence versus all others (i.e., non-adherent HAART use, other antiretroviral therapy use, and no therapy use).

Biannually, respondents reported the occurrence and frequency of alcohol and crack use in the past 6 months. Using National Institute on Alcohol Abuse and Alcoholism guidelines for women, at-risk drinking was defined as 8 or more drinks per week, and binge drinking as 4 or more drinks per day. Occurrence of either in the past 6 months was classified as problem drinking.

Following Lucas *et al.* [10], four patterns of use were constructed and a value was assigned to the women's reports for each visit, separately for crack and for alcohol use: intermittent use with current abstinence (crack use or problem drinking reported previously with abstinence reported at the current visit), intermittent but currently active use (use reported at current visit but not all previous ones), persistent use (use reported at every visit), and non-use (no reports of crack or problem drinking).

### Statistical analysis

Time to AIDS-related death and time to AIDS-defining illness were each examined using Kaplan–Meier survival analysis to test for differences in survival and hazard function according to patterns of crack use. Data from women with non-AIDS-related mortality were retained in the analysis until the date of death, when they were right-censored. Women lost to follow-up were censored at their last interview date. We used the Cox proportional hazards model to examine whether different patterns of crack use were associated with mortality and with AIDS-defining illnesses controlling for illness duration, baseline immunologic and virologic factors, use of HAART at greater than or equal to 95% adherence, sociodemographic characteristics, and study site. We used random effects logistic regression analysis (MIXOR) [25] to examine the effects of different crack use patterns on CD4 cell count and HIV-1 RNA level controlling for the same covariates. Random effects analysis modeled intrasubject associations as a Gaussian process representing an individual's propensity to develop an outcome indicating virologic, immunologic, or clinical disease progression. Two random effects, for intercept and slope, fit the data better than one random effect.

## Results

Data from 1686 women were analyzed: 1203 (71.4%) were categorized as non-users, 429 (25.4%) as intermittent users, and 54 (3.2%) as persistent users of crack. Their characteristics are presented in Table 1.

There were 419 deaths during the follow-up period: 197 (47.0%) were AIDS-related, 138 (33.0%) were non-AIDS-related, and 84 (20.0%) were indeterminate. Time to death was assessed with a Kaplan–Meier function (Fig. 1). The estimated survival rates at 8.2 years (3000 days) were 89% for non-users, 90% for intermittent users, and 65% for persistent users (log-rank test = 6.6, $P < 0.05$). In a Cox proportional hazards model (Table 2) adjusting for age, race, income, education, problem drinking, adherent HAART use, CD4 cell count less than 200 cells/μl at baseline, HIV-1 RNA level more than 100 000 copies/ml at baseline, illness duration, and study site, compared with that for non-users, the risk of AIDS-related death was significantly higher for persistent users (hazard ratio = 3.61, $P < 0.001$), but not for intermittent users.

Of the total group of 1686 women, 543 (32.2%) were found to have a newly acquired AIDS-defining illness during the follow-up period. Significantly higher proportions of intermittent users (42.0%, $n = 180$) and persistent users (38.9%, $n = 21$) reported a new illness during this time period than did non-users (28.4%, $n = 342$) (chi-square = 27.6, $P < 0.001$). The most frequently reported AIDS-defining illnesses were bacterial pneumonia ($n = 98$, 18% of all cases), pneumocystis carinii pneumonia ($n = 52$, 10%), herpes simplex virus, non-pulmonary ($n = 49$, 9%), esophageal candidiasis ($n = 48$, 9%), cryptosporidiasis ($n = 30$, 6%), dementia/encephalopathy ($n = 27$, 5%), wasting syndrome ($n = 27$, 5%), and tuberculosis ($n = 20$, 4%). Among these, persistent and/or intermittent users were significantly

**Table 1. Characteristics of 1686 HIV+ women in a multisite cohort according to longitudinal patterns of crack use (1996–2004)[a].**

| Variable | Nonusers ($n=1203$) | Intermittent users ($n=429$) | Persistent users ($n=54$) | Chi square/ANOVA significance[b] | Linear trend significance |
|---|---|---|---|---|---|
| African–American | 600 (50%) | 305 (71%) | 36 (67%) | *** | *** |
| Hispanic/Latina | 331 (28%) | 60 (14%) | 12 (22%) | *** | *** |
| White/other | 272 (23%) | 64 (15%) | 6 (11%) | ** | *** |
| Less than high school education at baseline | 414 (34%) | 179 (42%) | 33 (61%) | *** | *** |
| Baseline income ≤$12 000/year | 651 (55%) | 334 (78%) | 46 (85%) | *** | *** |
| Age in years at baseline | 36.5 (8.3) | 37.4 (6.6) | 38.0 (7.9) | NS | – |
| Baseline CD4 cell count (cells/μl) | 364 (264) | 433 (305) | 257 (194) | *** | – |
| Baseline CD4 <200 cells/μl | 338 (29%) | 91 (22%) | 20 (40%) | ** | ** |
| Baseline CD4 percentiles | | | | | |
| 25th | 175 | 227 | 70 | | |
| 50th | 328 | 374 | 274 | | |
| 75th | 508 | 564 | 366 | | |
| Baseline HIV-1 RNA level (copies/ml) | 89424 (344409) | 54815 (157806) | 205160 (373550) | ** | – |
| Baseline HIV-1 RNA >100 000 (copies/ml) | 164 (15%) | 52 (13%) | 18 (37%) | *** | NS |
| Baseline HIV-1 RNA percentiles | | | | | |
| 25th | 4000 | 4000 | 4250 | | – |
| 50th | 8100 | 8950 | 38 000 | | |
| 75th | 53 250 | 44 000 | 265 000 | | |
| Baseline $\log_{10}$ HIV-1 RNA | 4.05 (0.93) | 4.01 (.090) | 4.53 (1.04) | ** | ** |
| Baseline $\log_{10}$ HIV-1 RNA percentiles | | | | | |
| 25th | 3.60 | 3.60 | 3.63 | | – |
| 50th | 3.91 | 3.95 | 4.58 | | |
| 75th | 4.73 | 4.64 | 5.42 | | |
| Year of HIV+ diagnosis | 1991 (2.5) | 1991 (2.8) | 1991 (2.5) | NS | *** |
| Ever reported HAART | 903 (75%) | 307 (72%) | 17 (32%) | *** | *** |
| HAART adherence ≥95% at all reports | 346 (29%) | 69 (16%) | 4 (7%) | *** | *** |
| Baseline problem alcohol use[c] | 123 (10%) | 114 (27%) | 17 (32%) | *** | *** |
| Number study visits completed | 12 (6) | 13 (5) | 6 (6) | *** | – |
| Date of first study visit (month/year) | 8/96 | 9/96 | 9/96 | ** | – |
| Follow-up time (months) | 86 (20) | 85 (18) | 66 (33) | *** | – |
| Deceased during study (all-cause mortality) | 278 (23%) | 104 (24%) | 37 (68%) | *** | *** |

ANOVA, analysis of variance; NS, not statistically significant.
[a]Values are expressed as frequency (%) for discrete variables and as mean (standard deviation) for continuous variables.
[b]For discrete variables, significance refers to chi-square and linear by linear associations, for continuous variables, to analysis of variance.
[c]Problem alcohol use is defined as more than 8 drinks per week and/or at least 4 drinks per day.
**$P<0.01$.
***$P<0.001$.
Source: Women's Interagency HIV Study: 1994–2004.

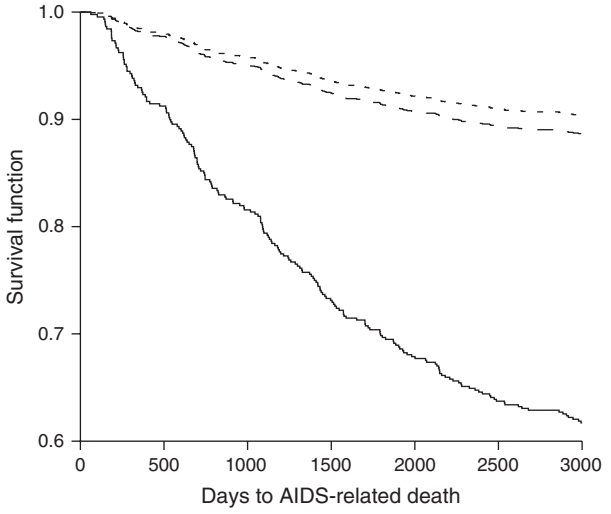


**Fig. 1. Survival by patterns of crack use in a cohort of HIV-1 infected women.** Compared with non-users (dashed line) and intermittent users (dotted line), days to death for persistent crack users (solid line) were significantly shorter and survival rates significantly lower ($P<0.05$).

more likely than non-users to report bacterial pneumonia (chi-square = 18.8, $P<0.001$), tuberculosis (chi-square = 16.6, $P<0.01$), and esophageal candidiasis (chi-square = 6.4, $P<0.05$). Time to new AIDS-defining illness was assessed in the three groups with a Kaplan–Meier function (Fig. 2). The average days to illness or censoring was 2592 days for non-users, 2305 days for intermittent users, and 2211 days for persistent users (log-rank test = 27.5, $P<0.001$). In a Cox proportional hazards model (Table 2) the risk of AIDS-defining illness was significantly higher for intermittent crack users (hazard ratio = 1.57, $P<0.001$) and consistent users (hazard ratio = 1.65, $P<0.05$) than for nonusers, adjusting for all covariates.

Figures 3 and 4 present the unadjusted proportions over time by pattern of crack cocaine use of women with CD4 cell count less than 200 cells/μl, and HIV-1 RNA more than 100 000 copies/ml. Throughout most of the study period, those reporting persistent crack use had higher viral load and poorer immune function, whereas those reporting no use had the lowest HIV-1 RNA levels and

**Table 2. Cox proportional hazards models of effects of patterns of crack use on AIDS-related mortality and AIDS-defining illnesses, $N = 1686$: Models control for study site.**

| Variable | Dependent variable: AIDS-related mortality (200/1686 = 11.9%) hazard ratio | Dependent variable: newly acquired AIDS-defining illness[a] (543/1686 = 32.2%) hazard ratio |
|---|---|---|
| Crack use | *** | *** |
| Intermittent | 0.93 | 1.57*** |
| Persistent | 3.61*** | 1.65* |
| Problem drinking[b] | ** | |
| Intermittent | 0.54** | 1.05 |
| Persistent | 0.38 | 0.69 |
| HAART and ≥95% adherent | 0.52** | 1.13 |
| CD4 lymphocyte count <200 cells/μl at baseline | 5.70*** | 1.05 |
| HIV-1 RNA >100 000 copies/ml at baseline | 2.46*** | 0.94 |
| Year of HIV+ diagnosis | 0.99 | 1.05** |
| African–American | 1.44 | 0.90 |
| Latina | 1.16 | 1.01 |
| Low income (<$12 000 per year) | 1.27 | 1.06 |
| Less than high school education | 1.16 | 1.10 |
| Age (10 year increments) | 1.04 | 1.01 |

[a]Defined in accordance with the Centers for Disease Control and Prevention 1993 clinical surveillance conditions, excluding the criterion of low CD4 cell count (CDC, 1993).
[b]Problem drinking defined as at least 8 drinks per week and/or binge drinking at least 4 drinks per day.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
Source: Women's Interagency HIV Study: 1994–2004.



best immune health, with intermittent crack users falling in between.

Table 3 presents the results of a time-varying random regression analysis of the effects of persistent and intermittent crack cocaine use on women with CD4 cell counts less than 200 cells/μl and HIV-1 RNA more than 100 000 copies/ml. Across both models, persistent crack use, intermittent-active, and intermittent-abstinent crack use were significantly associated with HIV disease progression, controlling for adherent HAART use, problem drinking, women's sociodemographic characteristics, study site, illness duration, baseline viral load (in the CD4 model), and baseline CD4 cell count (in the

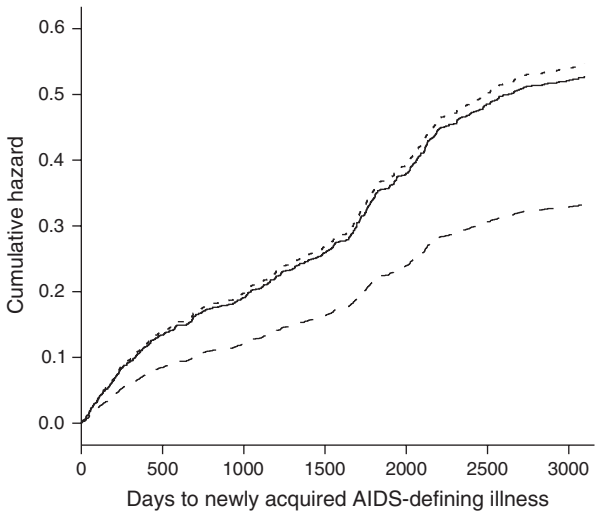


**Fig. 2. Time to newly acquired AIDS-defining illness by patterns of crack use in a cohort of HIV-1 infected women.** Compared with non-users (dashed line), days to illness for intermittent users (dotted line) and persistent crack users (solid line) were significantly shorter and hazard rates significantly higher ($P < 0.001$).

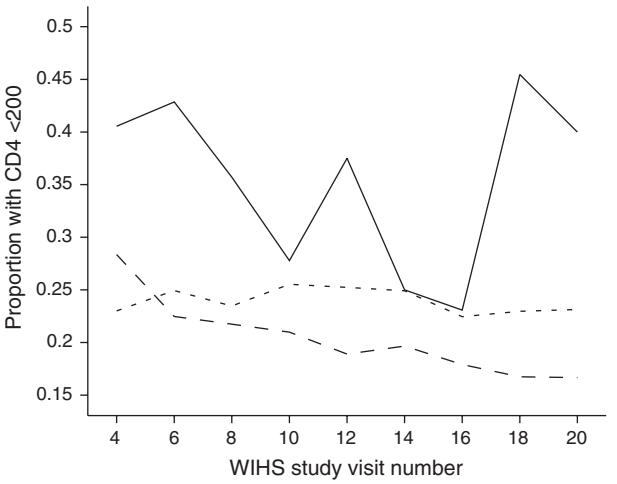


**Fig. 3. Unadjusted proportions of women with CD4 lymphocyte count less than 200 cells/μl over 18 semi-annual study visits.** Non-users (dashed line) had generally lower proportions, whereas persistent users (solid line) typically had the highest proportions, with intermittent users (dotted line) falling in between.

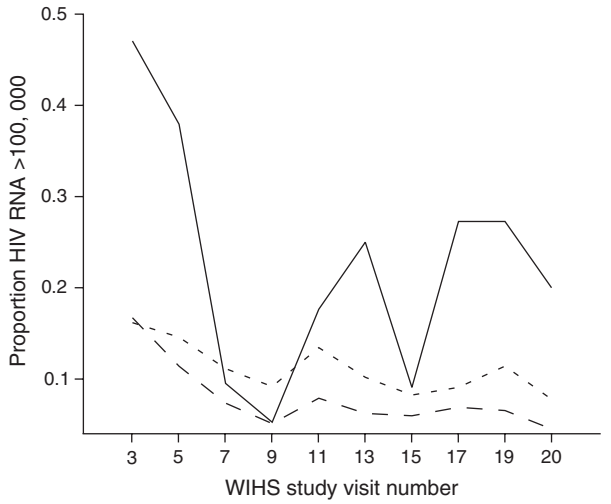


**Fig. 4. Unadjusted proportions of women with HIV-1 RNA viral load more than 100 000 copies/ml over 18 semiannual study visits.** Non-users (dashed line) had consistently lower proportions, whereas persistent users (solid line) generally had the highest proportions, with intermittent users (dotted line) falling in between.

viral load model). Persistent problem drinking was positively associated with disease progression defined by high viral load but not low CD4 cell count. In both models, adherent HAART use was protective against disease progression.

We tested five additional covariates that could account for the relationship between crack use and disease progression, with the same models used in the Cox proportional hazards and random regression analyses. Results (not shown) remained highly similar controlling, separately, for heroin use, injecting drug use, tobacco smoking, hepatitis C virus coinfection, and depressive symptoms (using the Center for Epidemiologic Studies-Depression Scale clinical cutoff of 16) [26]. The only exceptions were for intermittent-abstinent crack use, which became non-significant in the viral load models when controlling for smoking and for depression.

Finally, to explore the impact of crack use on immune reconstitution, we conducted a supplementary analysis of associations between patterns of use (non-use, inactive use, and active use) and immunologic response. Following Lucas *et al.* [9], for all women remaining in the cohort at the end of the study period ($n = 1053$), we defined change in HIV-1 RNA ($\log_{10}$ copies/ml) as the difference between the most recent viral load and peak HIV-1 RNA level, and change in CD4 cell count as the difference between the most recent and nadir CD4 lymphocyte counts. We found that the median reduction in HIV-1 RNA level was highest in non-users, at 1.7 $\log_{10}$ copies/ml, compared with 1.4 $\log_{10}$ copies/ml in inactive crack users and 1.0 $\log_{10}$ copies/ml in active users ($F = 4.94$, DF = 2/1035, $P < 0.01$). The median CD4 cell count increase was highest in non-users, at 161 cells/μl, compared with 123 cells/μl in inactive

**Table 3. Random regression analysis of effects of time-varying patterns of crack use on markers of HIV disease progression, $N = 1686$: Models control for study site.**

| Variable | Dependent variable: time-varying CD4 cell count <200 cells/μl estimate[a] | Dependent variable: time-varying HIV-1 RNA >100 000 copies/ml estimate[a] |
|---|---|---|
| Intercept | 1.87 | −1.00 |
| Time (study visit number) | 0.05*** | 0.03*** |
| Crack use | | |
| Crack use intermittent – abstinent | 0.67*** | 0.45** |
| Crack use intermittent – active | 0.98*** | 0.58*** |
| Crack use – persistent | 0.82** | 2.24*** |
| Problem drinking[b] | | |
| Problem drinking intermittent – abstinent | −0.18 | −0.22 |
| Problem drinking intermittent – active | 0.08 | −0.01 |
| Problem drinking – persistent | −1.08 | 1.91* |
| CD4 lymphocyte count <200 cells/μl at baseline | – | 2.21*** |
| HIV-1 RNA >100 000 copies/ml at baseline | 2.60*** | – |
| Year of HIV+ diagnosis | −0.09*** | −0.04 |
| HAART ≥95% adherence | −1.10*** | −2.13*** |
| White | – | – |
| African–American | 0.24 | 0.16 |
| Latina | 0.69*** | −0.16 |
| Low income (<$12 000 per year) | 0.20** | 0.26** |
| Less than high school education | −0.10 | 0.22 |
| Age (10 year increments) | 0.42*** | −0.05 |

[a]Effect shown as unstandardized parameter estimate in which negative sign indicates that outcome was less likely and positive sign indicates that outcome was more likely.
[b]Problem drinking defined as at least 8 drinks per week and/or binge drinking at least 4 drinks per day.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
Source: Women's Interagency HIV Study: 1994–2004.

users, and 100 cells/μl in active users ($F = 6.99$, DF = 2/1035, $P < 0.01$). In multivariate linear regression models (not shown), active and inactive crack use remained significant after adjustment for race/ethnicity, use of HAART, HAART adherence 95% of time, prior HAART exposure, nadir CD4 cell count, and peak HIV-1 RNA level. Here, compared with non-users, active and inactive crack users had smaller median reductions in HIV-1 RNA from peak levels, and smaller median increases in CD4 cell count from nadir levels. These results confirm that inferior virologic and immunologic responses are associated with both active and inactive use of crack.

## Discussion

Ours is the first study to show that use of crack cocaine in a large, national cohort of HIV-positive women is longitudinally associated with subsequent deterioration in immune status, failure of virologic suppression, development of AIDS-defining conditions, and mortality due to AIDS-related causes, even among those who reported adhering to HAART regimens 95% of the time or more. Likely confounds such as heroin use, injection drug use, tobacco smoking, hepatitis C virus coinfection, and depression do not appear to account for these significant associations. Unlike prior research on a predominantly male sample [10], we did not consistently find that progression was less likely during periods of abstinence among female crack users, providing support for the notion that effects of cocaine on the immune system may vary by sex, as others have suggested [3].

Even in the face of this evidence, our analysis does not conclusively demonstrate that crack use causes AIDS-related morbidity and mortality. We have not ruled out other processes that could account for these associations, such as greater sexual risk taking, poorer diet and nutrition, substandard living conditions, and other unknown confounders.

Our findings suggest that a multipronged research agenda is needed to understand the effects of crack cocaine on HIV disease progression. In-vivo studies can illuminate the specific role of the drug in HIV pathogenesis [2]. In-vitro research, such as the human lymphocyte/severe combined immunodeficient (huPBL/SCID) mouse model [1], can shed light on how cocaine upregulates HIV and also acts as a cofactor in HIV pathogenesis [4]. In-vitro studies of peripheral blood samples from crack users can examine alterations in T cell and dendritic cell subsets, immune function, cytokine and chemokine expression, indicating predisposition to HIV infection. Studies of alveolar macrophages from the lungs of chronic crack users can help to understand impaired cytokine production [2] and how intrapulmonary accumulation of contaminants may promote chronic lung diseases [17]. However, neither in-vivo nor in-vitro research can control for the complex interactions that occur in human beings with repeated exposure to crack over time, necessitating rigorous, large-scale epidemiologic studies of morbidity and mortality among HIV-positive and at-risk users, and potential differences associated with frequency, quantity, and mode of administration [17].

Although prior research highlights difficulties crack users confront in using the medical care system [27], this was not true in our cohort. At their last interview, 100% of participants reported seeing a healthcare provider in the past 6 months: 93% said they saw the same healthcare provider consistently, including 94% of persistent crack users. Related to this are the findings of a recent study of HIV-positive African–Americans in which women crack users reported more positive relationships with their physicians than did male crack users [28]. The use of HAART in the WIHS cohort is significantly related to higher satisfaction with both medical care and healthcare providers [29]. This is a foundation on which to build care delivery models that are effective in engaging and retaining women crack users. One recommendation is that women using crack receive sustained follow-up with periodic reevaluations of therapy regimens to promote greater use of and adherence to HAART [30]. Another suggestion is colocation of rapid HIV testing, risk reduction counseling, HIV therapies, psychiatric and substance abuse treatment, and other services to promote successful engagement and seamless access to multiple interventions [30,31]. Finally, the importance of cultural competence is paramount, calling for diversity in clinical staff, attention to patient–provider communication, and sensitivity to the multiple vulnerabilities faced by these women [32,33].

One caveat to our findings is the non-representativeness of our longitudinal cohort, limiting the generalizability of our results. Another study limitation is use of self-report rather than urine or toxicology screening to measure crack cocaine exposure. The same is true for self-reported measures of alcohol use, HAART use, and adherence, which may be subject to distortion due to recall errors or positive response bias. Study intervals were lengthy, number of time-points varied by participant, and respondents entered the study at different stages of illness. The use of death certificates and other administrative records to establish AIDS-related deaths, and reliance on case record review to identify AIDS-defining illnesses also introduced measurement error into our dependent variables. Finally, without direct measures of pathobiology, the effect of crack on disease progression can only be assessed using proxy variables.

The challenges involved in treating crack addiction are well documented and include high rates of treatment dropouts, treatment repeaters, and relapse [34]. This suggests the need for models that acknowledge crack

users' diverse levels of readiness for change and recognize that work can be done, even with women who are not yet ready to alter their behavior or are just beginning to consider doing so. Helping individuals move from precontemplation to readiness for change requires approaches that are assertive and 'strengths-based' [35], building on low-income, minority women's intrinsic resources such as resilience and 'street smarts' [27,35]. Finally, culturally competent care is needed to promote the trust necessary for personal risk taking that accompanies willingness to change through addiction treatment and commitment to antiretroviral regimens [33,36].



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J.A.C. originated the study, supervised the data analyses and interpretation, and led the writing. J.K.B.-M. and D.D.G. conducted and interpreted the data analyses. All of the authors helped to conceptualize ideas, interpreted findings, and reviewed drafts of the article.

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