Published in final edited form as:
Int J STD AIDS. 2012 August ; 23(8): 576–580. doi:10.1258/ijsa.2012.011322.

Cumulative exposure to stimulants and immune function outcomes among HIV-positive and HIV-negative men in the Multicenter AIDS Cohort Study

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SUMMARY

We examined associations between stimulant use (methamphetamine and cocaine) and other substances (nicotine, marijuana, alcohol, inhaled nitrites) with immune function biomarkers among HIV-seropositive (HIV+) men using highly active antiretroviral therapy (ART) and -seronegative (HIV−) men in the Multicenter AIDS Cohort Study (MACS). Among HIV+ men, cumulative adherence to ART (4.07, 95% CI: 3.52, 4.71, per 10 years of adherent HAART use), and recent cohort enrollment (1.38; 95% CI: 1.24, 1.55) were multiplicatively associated with increases in CD4+/CD8+ ratios. Cumulative use of methamphetamine (0.93; 95% CI: 0.88, 0.98, per 10 use years), cocaine (0.93; 95% CI: 0.89, 0.96, per 10 use years), and cumulative medical visits (0.99; 95% CI: 0.98, 0.99, per 10 visit years), each showed small negative associations with CD4+/CD8+ ratios. Among HIV- men, cumulative medical visits (0.996; 95% CI: 0.993, 0.999), cumulative number of male sexual partners (0.999; 95% CI: 0.998, 0.9998, per 10 partner years) and cigarette pack years (1.10; 95% CI: 1.02, 1.18, per 10 pack years) were associated with CD4+/CD8+ ratios over the same period. ART adherence is associated with a positive immune function independent of stimulant use, underscoring the influence of ART on immune health for HIV+ men who engage in stimulant use.

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AUTHOR DISCLOSURE STATEMENT

There are no financial conflicts of interest related to this research work.

Keywords

HIV; men; methamphetamine; cocaine; CD4+/CD8+ ratio; antiretroviral therapy; adherence; Multicenter AIDS Cohort Study

INTRODUCTION

HIV infection is associated with a decline of CD4+ cell counts, an increase of CD8+ cell counts and inversion of the ratio of CD4+/CD8+ cell ratio in the setting of increased HIV viral load. Animal and human in-vitro studies show that stimulants (cocaine and amphetamine) cause decreases in CD4+ cells, CD8+ cells and increases in HIV replication [1–3]. Even micromolar concentrations of cocaine can impair early response to stimulation of normal CD4+ cells in vitro [4]. As well, amphetamine impairs the CD8+ cell response in vitro, an essential response in the early suppression of HIV and establishment of viral set point [1].

Direct effects of substances on immune function in cohorts of HIV-seropositive (HIV+) drug users are unclear. Weekly use of hallucinogens and cocaine independently predicted HIV disease progression in an early cohort of men [5]. In data collected in a similar era (before antiretroviral therapy, ART), no associations between use of cocaine, methamphetamine, marijuana or inhaled nitrites (poppers) and measures of CD4+, CD8+ or CD4+/CD8+ ratios were found for men in the Multicenter AIDS Cohort Study (MACS) compared to non-substance users [6]. In a more recent cohort of men, weekly use of cocaine or methamphetamine corresponded with higher plasma viral RNA and immune activation after controlling for adherence to ART [7]. Among women, reported crack cocaine use corresponded with decreases in CD4+ cells, increases in HIV viral load, increased progression of AIDS-defining conditions and AIDS-related mortality events compared to non-drug users after controlling for adherence to ART [8]. As well, crack cocaine use was associated with increased progression to an AIDS diagnosis compared to users of other drugs, independent of ART in a mixed gender cohort [9].

One aspect contributing to the difficulty in finding consistent patterns of results in cohort studies may be that it is possible, even likely, that any biological association between stimulant use and biomarkers of immune function would be strongest during periods when individuals use the drugs. Ellis, et al. [10] showed significantly lower CD4+ cell counts and higher plasma viral RNA levels for methamphetamine-dependent HIV-seropositive individuals (compared to HIV-seropositive non-drug users) only when a methamphetamine-positive urine sample was collected at the same time immune biomarkers were collected.

In this report, we evaluated associations between levels of self-reported use of stimulants and of other substances (including alcohol, marijuana, poppers and cigarettes) with CD4+ and CD8+ cell counts, and CD4+/CD8+ ratio, controlling for variables known to correspond with immunological outcomes, among MACS participants, both HIV+ men receiving ART and HIV-seronegative (HIV−) men. We predicted that reported use of stimulants (cocaine and methamphetamine) would correspond with decreases in immune functioning.

METHODS

Study design and procedures

Participants were enrolled in the MACS, an ongoing prospective study of the natural and treated histories of HIV infection among homosexual and bisexual men in the United States. The study design has been described previously [11, 12]. Only methods relevant to the

present study are presented. MACS study protocols were approved by the institutional review boards of each of the participating centers. Informed consent was obtained from all participants.

MACS participants return every 6 months for detailed interviews, physical examinations, and collection of blood for laboratory testing and storage in a central repository. An interview queries medical conditions, medical treatments, sexual behavior, illegal drug use (including methamphetamine, marijuana, poppers, cocaine and crack), and cigarette and alcohol consumption since the previous visit.

Enzyme-linked immunosorbent assay with confirmatory Western blot tests were performed on all participants initially and at every semiannual visit thereafter for initially seronegative participants. T-lymphocyte subset levels were quantified by each MACS center using standardized flow cytometry [13, 14]. Adherence to ART defined according to the DHHS/Kaiser Panel guidelines [15] was categorized into four levels: 100%, 95–99%, 75–94%, and <75%, based on reported adherence to medications used since previous visit.

A prospective cohort design was used to examine associations between markers of HIV disease progress (CD4+, CD8+ and the ratio of log CD4+/CD8+) with reported use of cocaine, crack, methamphetamine, marijuana, poppers, cigarette smoking and alcohol. Because methamphetamine use was not directly assessed until visit 26 (October 1996 – March 1997) and ART was introduced in mid 1990s, we limited data to that collected between visits 26 to 46 (October 1996 – March 2007). The study population included (1) HIV-seronegative and (2) HIV-seropositive ART users who used ART continuously for at least one year. The index visit was the first visit with data available at or after visit 26 for HIV-seronegative and the first visit of two consecutive visits on ART for HIV-seropositive men.

Study sample

The sample included 2,789 male participants contributing 28,321 person-visits. The average number of observations in our study period per participant was 10 (SD=6) and the average follow-time from enrollment was 14 years (SD=9).

Primary predictor: drug use

In this study, exposure to drugs was assumed to be cumulative over the last 5 visits. That is, we assumed that the effect of drug use on the outcomes at each visit depended not only on current use, but also on previous use, but only for a period corresponding to 5 visits (2.5 years). This approach, which we named a “recovery” approach, is sensitive to exposure during periods of reported drug use and avoids prolonged carrying forward past exposures when the drug use behaviors are quiescent. This model preserves temporal associations between drug use (or drug abstinence) and immune markers, especially when these behaviors may vary across visits in the cohort.

Drug use was first calculated for each visit as the average number of reported days used per month for a one year period for methamphetamine, marijuana, poppers, and any cocaine or crack. This involved using a measure of quantity or frequency in a given time interval depending on the wording of the particular question (the weight), during a given period, typically the approximately six months between visits, normalized to a yearly basis. For example, if an individual used daily during the last six months, then his yearly average use was calculated as 30.5 days per month × 0.5 years = 15.25 days per month. For the drug use questions the weights were daily use: weight = 30.5 (times per month); weekly use: weight = 4.36; monthly use: weight=1; less often: weight = 0.33. We then computed cumulative self-reported drug use over only the five study visits previous to the current visit by summing the

previous 5 yearly averages, which proceeded longitudinally across the study period (i.e., visit 26–30, visit 27–31,…, visit 42–46).

Covariates

Demographic and behavior variables were included in the analysis to adjust for possible confounding. Age at MACS study enrollment was calculated using self-reported date of birth and was treated as a continuous covariate. Race was self-reported at enrollment and categorized as White non-Hispanic (reference group), White Hispanic, Black non-Hispanic, Black Hispanic, and “other” (predominantly mixed race). Self-reported highest level of education completed at enrollment was categorized as grade12 or less (reference group), college, and post-college graduate. Participants were classified as pre-2001 (reference group) or 2001–03 cohort to denote portions of the sample that joined MACS pre-HAART era and post-HAART era.

Additional exposure variables were measured as cumulative amounts per year. This also involved using a measure of quantity or frequency in a given time interval, depending on the wording of the particular question, normalized to a yearly basis. For example, if an individual smoked >= 1 but < 2 packs per day in the six months preceding a given visit, then his smoking pack years exposure for that visit was calculated as 1.5 (the average of 1 and 2) packs × 0.5 years = 0.75 pack years. Current exposure was calculated at each visit and cumulated over visits. Cigarette consumption was summarized as cumulative pack-years. Alcohol consumption was defined as cumulative drink-years based on number of drinks per week. Cumulative number of medical visits included all kinds of visits (e.g., doctor’s office, emergency room). Sexual behavior covariates included cumulative number of male sexual partner-years and cumulative number of unprotected receptive anal sex (URAS) partner-years. Cumulative ART-years was weighted by the reported adherence rate (weights were 1, 0.975, 0.85, and 0.375 for adherence 100%, 95–99%, 75–94%, and <75%, respectively). Because adherence data were not collected until visit 29, we carried the first adherence rate backward to visits before visit 29.

Outcome: CD4+, CD8+, CD4+/CD8+ ratio

Biomarkers of HIV disease progression were defined as CD4+ cell counts, CD8+ cell counts, and CD4+/CD8+ ratio. In order to normalize distributions for comparisons, we used the square root of CD4+ and CD8+ cell counts, and the natural log of the CD4+/CD8+ ratio.

Data analysis

A linear mixed model was used for each outcome: square root of CD4+ cell counts, square root of CD8+ cell counts, and natural log of the CD4+/CD8+ ratio. The data transformations were necessary in order to stabilize the residual variance, an assumption required by the linear mixed model. The modeling strategy examined the associations between cumulative exposure of cigarettes, alcohol, medical visits, sexual behavior, drug use, and ART on outcome variables of CD4+ and CD8+ cell counts and CD4+/CD8+ ratio. For the latter, results are presented as multiplicative (proportionate) effects. Separate analyses were conducted for the two groups in the analysis by using the SAS MIXED procedure (SAS Institute, Cary, North Carolina, USA). A random subject effect was included in each model, as well as a structure for the residual serial correlation. In all analyses, missing data were assumed to be missing at random [16]. A cross tabulation showed that participants were likely to die independent of stimulant drug use supporting this assumption (data not shown).

RESULTS

At enrollment, the cohort was mainly White, non-Hispanic with a mean age of 35 years (SD=8). Most participants (80%) completed some education following high school. About one-quarter of the study sample enrolled in the 2001–2003, post-HAART era. Comparisons of sample characteristics by study group showed HIV-seropositive ART-users had expected lower CD4+ counts, higher CD8+ counts and lower CD4+/CD8+ ratios compared to HIV- participants (Table 1). The mean cumulative exposure for HIV-seropositive ART-users was 1.8 years. HIV+ ART-users had higher cumulative mean number of medical visits compared to HIV- men (Table 2). HIV- men had a higher cumulative number of male sexual partner-years, but a lower cumulative number of unprotected receptive anal sex (URAS) partner-years compared to HIV- ART-using men. Cumulative rate of cigarette smoking was about one-half pack per year for both HIV+ and HIV- participants. The cumulative number of drink-years was higher among the HIV- men and the cumulative number of marijuana use-years was higher among the HIV+ ART-using men. The cumulative number of use-years for methamphetamine, poppers and cocaine was not statistically different between the two groups.

Among the HIV+ ART users, cumulative ART adherence was the strongest (multiplicative) predictor of improved CD4+/CD8+ ratio (4.07, 95% CI: 3.52, 4.71, per 10 adherent use years) after adjusting the other independent variables (Table 3). Significant negative associations were noted for HIV+ ART using men between CD4+/CD8+ ratios and cumulative use of methamphetamines (0.93, 95% CI: 0.88, 0.98, per 10 use years) and cocaine (0.93, 95% CI: 0.89,0.96, per 10 use years) and reported cumulative medical visits (0.99, 95% CI: 0.98, 0.99 per 10 visit years). Also HIV+ ART users who joined the cohort more recently showed significantly improved CD4+/CD8+ ratios compared to those who joined the cohort earlier (1.38, 95% CI: 1.24, 1.55). Among HIV- men, significantly positive associations between CD4+/CD8+ ratios and cumulative 10-pack-years of cigarette smoking (1.10, 95% CI: 1.02,1.18, per 10 pack years) were observed. Also among HIV- men, CD4+/CD8+ ratios declined as cumulative number of (10) medical visit-years (0.996, 95% CI: 0.993, 0.999) and number of (10) male sex partner-years (0.999, 95% CI: 0.998, 0.9998) increased. There were no differences in the relationships between any of the predictor variables and CD4+ and CD8+ cell counts (data not shown).

DISCUSSION

After adjusting for age, race and educational status and independent of other cofactors including stimulant use, 10-year increase in ART adherence corresponded with four-fold improvement in CD4+/CD8+ ratios across time among HIV+ ART-using participants in the MACS. As predicted, we found negative, small associations between reported use of cocaine or methamphetamine and CD4+/CD8+ ratios as well as cumulative rates of medical visits for HIV+ men. Among HIV- MACS participants, significant, but small associations were detected between CD4+/CD8+ ratios with cumulative medical, cumulative number of male sexual partners and cigarette pack years..

The clinical relevance of these findings for HIV-seropositive men using ART is that the unique contributions to associations of methamphetamine and cocaine with their CD4+/CD8+ ratios, while statistically significant, are small and clinically not meaningful. However, large and positive associations existed between measures of ART adherence and immune function. We know of no simple explanation why individual markers of CD4+ and CD8+ failed to be associated significantly with any of the predictors, though our solutions, even when transforming these values using logarithmic functions, was non-significant.

The model used in these analyses provided different results from an earlier report [6], which found no association with measures of CD4+, CD8+ and their ratio for MACS participants when contrasting each level of use of a range of substances (i.e., daily, weekly, monthly use) to nonuse. The analytic approach in this report, the "recovery" approach, was devised to capture associations between stimulant drugs and immune functioning over a period that minimized influence of missing observations, i.e., 5 visits or 2.5 years. The method captured associations between stimulants and immune functioning during relevant periods of use in the 6 month intervals and also allowed for the immune system to recover during periods of absence of use. In data not shown, a 2-visit cumulative model (or data over 1 year) was conducted, which yielded outcomes in which confidence intervals overlapped completely. The 5 visit model had narrower confidence intervals, providing more stable outcomes due to less missing data. In these MACS data, this "recovery" approach using a rolling 2.5 year window for analysis retains an emphasis on proximal associations between stimulant use/nonuse and immune biomarkers and observes their movement through time.

It is comforting that our findings showed expected negative associations between methamphetamine and cocaine use and immune functioning, particularly in HIV+ men. Methamphetamine [17] and cocaine [3,4] increase HIV replication in-vitro; both also show dose-response associations in frequency of use and levels of neopterin, a marker of immune activation that characterizes HIV-disease progression [18]. What is not clear is whether the large associations observed between adherence to ART and CD4+/CD8+ ratios, even in the context of stimulant use, is consistent with a recent review showing that non-injection users of a range of illicit drugs accelerated development of an AIDS defining event [19]. Indeed, while the adherence measure in our report is likely an underestimate of actual medication adherence, which implies the potential for even stronger associations between ART adherence and immune function than observed. It is of note that we found no parallel associations between stimulant use-years and CD4+/CD8+ cell ratios for HIV- men, which may imply a general capacity of the immune system to rebound from acute stimulant use-associated insults in HIV-uninfected men.

Two unexpected findings were observed in HIV- men. HIV- men who reported higher cumulative numbers of male sexual partners showed significantly lower log CD4+/CD8+ ratios. We can think of no biologic mechanism for this finding. Second, among HIV- men higher numbers of pack/years of cigarettes associated strongly with higher ratios of CD4+/CD8+. This is consistent with previous studies that have shown smoking to be correlated with an increase in CD4+ cell counts among HIV- individuals [20, 21, 22]. The lack of association of cigarette smoking on CD4+/CD8+ ratio among HIV+ ART-using individuals reflects a mixed literature, with some studies showing an association between smoking and CD4+ count decline and other studies showing no association.

Findings in this report are limited to HIV+ ART-using men with histories of stimulant use. It is possible that HIV+ ART-using men who are assayed during periods of acute use of stimulants would show stronger negative associations with markers of immune function, particularly in light of earlier work [10], that would not be detected using analyses that rely on an extensive observation period. As in any cohort study, there may be a lead-time bias such that one cannot control or measure important drug-related use events that may have occurred before participants joined the cohort.

The strongest correlate of CD4+/CD8+ ratios was cumulative ART adherence among HIV+ MACS participants. These findings provide support to clinicians who are considering the value of sustained ART regimens to maintain immune and general health functioning among HIV+ men who report stimulant use. In light of the limitations that adherence levels reported are likely underestimates, there may be clear health benefits to the immune function of

patients known by their clinicians to use cocaine or methamphetamine to access interventions that enhance ART adherence.

Acknowledgments

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers (Principal Investigators) at The Johns Hopkins Bloomberg School of Public Health (Joseph B. Margolick, Lisa P. Jacobson), Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services (John P. Phair, Steven M. Wolinsky), University of California, Los Angeles (Roger Detels), and University of Pittsburgh (Charles R. Rinaldo). The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute. UO1-AI-35042, UL1-RR025005, UO1-AI-35043, UO1-AI-35039, UO1-AI-35040, UO1-AI-35041. Website located at http://www.statepi.jhsph.edu/macs/macs.html. Additional support was provided by the National Institute of Drug Abuse through 1R01DA022936, “Long Term Health Effects of Methamphetamine Use in the MACS”, Ronald Stall, PhD., PI and 5U01DA017394-05, “HIV/STD Risk in Methamphetamine User Networks”, Steve Shoptaw, PhD., PI.

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Table 1

Baseline characteristics of MACS HIV-seronegative (SN) and HIV-seropositive (SP) ART-using participants[a]

	SN participants n=1,627	SP participants n=1,162
Age (years), median (IQR)	34.8 (28.7 – 41.0)	33.9 (28.3–39.8)
Race		
White, non-Hispanic, % (n)	66.3 (1079)	63.0 (732)
White, Hispanic, % (n)	4.7 (77)	6.1 (71)
Black, non-Hispanic, % (n)	23.8 (387)	23.2 (269)
Black, Hispanic, % (n)	0.7 (11)	1.0 (12)
Other, % (n)	4.5 (73)	6.7 (78)
Education		
Less than college, % (n)	19.2 (312)	21.2 (246)
Some college degree, % (n)	47.5 (773)	50.4 (586)
College degree or higher, % (n)	32.3 (525)	25.9 (301)
CD4 count (μL), median (IQR)[1]	919 (729 – 1145)	489 (323 – 684)
CD8 count (μL), median (IQR)[1]	521 (387 – 696)	925 (668 – 1248)
CD4/CD8 ratio, median (IQR)[1]	1.8 (1.4 – 2.3)	0.52 (0.33 – 0.77)

[a]The median CD4+ and CD8+ cell counts, and CD4+/CD8+ ratios were calculated from all visits between Visit 26 through Visit 46.

Table 2

Cohort membership and cumulative exposure of ART adherence, medical visits, sexual behaviors, cigarette, alcohol, stimulant and other drug use among the HIV-seronegative (SN) and HIV-seropositive (SP) ART-using participants, October 1996-March 2007[a]

	SN n=15,803 Mean (Min - Max)	SP n=12,518 Mean (Min - Max)
2001–2003 cohort, % (n)	23.2 (3662)	24.9 (3119)
Cumulative medication adherence (HAART-yr)	not applicable	1.8 (0 – 3.5)
Cumulative medical visits (visits)	10 (0 – 192)	21.6 (0 – 432)
Cumulative sexual behaviors (partner-yr)		
Number of male sex partners	21.0 (0 – 1101)	18.0 (0 – 1417)
Unprotected receptive anal sex	1.9 (0 – 522)	2.8 (0 – 1824)
Cumulative cigarette smoking (pack-yr)	0.4 (0 – 6.6)	0.5 (0 – 6.4)
Cumulative alcohol consumption (drink-yr)	10.6 (0 – 181)	6.9 (0 – 133)
Cumulative drug use (use-yr)		
Methamphetamine	0.2 (0 – 60.3)	0.3 (0 – 85.3)
Marijuana	3.8 (0 – 87.9)	6.0 (0 – 91.7)
Popper	1.2 (0 – 78.6)	1.4 (0 – 86.3)
Cocaine	0.4 (0 – 52.4)	0.5 (0 – 66)

[a]Data represented as mean (minimum - maximum), unless otherwise indicated. All variables are based on persons-visits. Cumulative variables are calculated over five consecutive study visits measured forward through the study period. Use-year is the number of drug use days per month for one year. For example, 1 methamphetamine use-year is equal to using one day of methamphetamine use per month for one year, or using two days of methamphetamines per month for half a year.

Table 3

Multiplicative coefficients and 95% confidence intervals from a linear mixed model of CD4+/CD8+ ratio for HIV-seronegative (SN) and HIV-seropositive (SP) HAART-using participants[a]

Exposure variables	SN Coefficient (95% CI)	SP Coefficient(95% CI)
2001–2003 cohort vs. pre-2001 cohort	0.96 (0.91, 1.01)	1.38 (1.24, 1.55) [b]
Cumulative medication adherence (10 HAART-years)	not applicable	4.07 (3.52, 4.71) [b]
Cumulative medical visits (10 visit-years)	0.996 (0.993, 0.999)	0.987 (0.98, 0.99) [b]
Cumulative sexual behaviors (10 partner-years)		
Number of male sex partners	0.999 (0.998, 0.9998) [b]	1.002 (0.99, 1.003)
Unprotected receptive anal sex	0.999 (0.998, 1.001)	0.999 (0.99, 1.004)
Cumulative cigarette smoking (10 pack-years)	1.10 (1.02, 1.18) [b]	0.87 (0.72, 1.06)
Cumulative alcohol consumption (10 drink-years)	1.00 (0.99, 1.01)	0.99 (0.97, 1.001)
Cumulative drug use (10 use-years)		
Methamphetamines	0.98 (0.95, 1.01)	0.93 (0.88, 0.98) [b]
Marijuana	1.00 (0.99, 1.01)	0.99 (0.98, 1.01)
Popper	0.99 (0.98, 1.01)	1.01 (0.98, 1.04)
Cocaine	1.01 (0.99, 1.03)	0.93 (0.89,0.96) [b]

[a] Model also includes the following variables: age, race, educational status. Cumulative variables are calculated over five consecutive study visits measured forward through the study period.

[b] $p < 0.05$