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Recreational Drug Use and T Lymphocyte Subpopulations in HIV-uninfected and HIV-infected Men

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Abstract

The effects of recreational drugs on CD4 and CD8 T cells in humans are not well understood. We conducted a longitudinal analysis of men who have sex with men (MSM) enrolled in the Multicenter AIDS Cohort Study to define associations between self-reported use of marijuana, cocaine, poppers and amphetamines, and CD4 and CD8 T cell parameters in both HIV-uninfected and HIV-infected MSM. For the HIV-infected MSM, we used clinical and laboratory data collected semiannually before 1996 to avoid potential effects of antiretroviral treatment. A regression model that allowed random intercepts and slopes as well as autoregressive covariance structure for within subject errors was used. Potential confounders adjusted for included length of follow-up, demographics, tobacco smoking, alcohol use, risky sexual behaviors, history of sexually transmitted infections, and antiviral therapy. We found no clinically meaningful associations between use of marijuana, cocaine, poppers, or amphetamines and CD4 and CD8 T cell counts, percentages, or rates of change in either HIV-uninfected or -infected men. The regression coefficients were of minimum magnitude despite some reaching statistical significance. No threshold effect was detected for frequent (at least weekly) or continuous substance use in the previous year. These results indicate that use of these substances

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does not adversely affect the numbers and percentages of circulating CD4 or CD8 T cells in either HIV-uninfected or -infected MSM.

Keywords

marijuana; cocaine; poppers; recreational drug use; T cells; HIV infection

1. Introduction

Experimental studies have shown that commonly used recreational drugs such as marijuana, cocaine, poppers, and amphetamines have immunomodulatory properties[Baldwin et al., 1998;Klein et al., 1998;Pellegrino and Bayer, 1998;Dax et al., 1991;James, 1999;Kubera et al., 2002;Nunez-Iglesias et al., 1996]. Altered T cell responses to immune challenges such as mitogens, alloantigens, and bacterial infections with exposure to these substances have been observed *in vitro* and in animal models[Domingues-Junior et al., 2000;Freire-Garabal et al., 1991;Klein et al., 1998;Klein et al., 2004;Kubera et al., 2002;Pellegrino and Bayer, 1998;Dax et al., 1991]. However, the impact of exposure to recreational drugs on the function and number of T cell subsets in humans remains unclear.

Cross-sectional studies have reported varied T lymphocyte profiles in habitual marijuana [Wallace et al., 1988;Wallace et al., 1994] and cocaine users[Ruiz et al., 1994;Ruiz et al., 1998]. In a study that analyzed comparable groups of marijuana smokers, tobacco smokers, cocaine smokers and nonsmokers, it was found that marijuana use was associated with significantly higher percentages of CD4 cells in the peripheral blood, after controlling for age and gender[Wallace et al., 1994]. However, this study did not find a dose-response relationship with amount of marijuana smoked. Ruiz and colleagues[Ruiz et al., 1994] compared circulating T cell subsets among cocaine-positive and cocaine-free patients admitted to the emergency room. All groups were free of HIV or other infections. They found that the percentages of CD4 T cells were significantly reduced in the cocaine-positive groups. However, a more recent study by the same group did not confirm this finding[Ruiz et al., 1998].

Prospective studies have also reported diverse findings. Ascher and colleagues[Ascher et al., 1993] found no significant differences in the rate of decline in CD4 T cells with increasing drug use (including marijuana, cocaine, nitrite inhalants and amphetamines) in either HIV-uninfected or –infected men. Thorpe and colleagues[Thorpe et al., 2004] also found that hard drug use (including powder cocaine, crack cocaine, heroin, and other opiate use at baseline, in the past year, or any time during the study) did not influence CD4 percentages or HIV RNA level in HIV infected women. In contrast, Larrat et al.[Larrat et al., 1996] and Siddiqui et al. [Siddiqui et al., 1993] reported cocaine use to be associated with a greater decline in CD4 cell count in HIV-infected men and women. The inconsistent findings may be due to differences in the levels of substances used in the study populations, the statistical models employed, and uncontrolled confounding.

In this study, we examined the association between use of marijuana, cocaine, poppers (nitrite inhalants), and amphetamines and CD4 and CD8 T cell parameters in HIV-uninfected and -infected men in the Multicenter AIDS Cohort Study (MACS). We examined the levels and rates of change in CD4 and CD8 T cell profiles as a function of drug use at baseline and during the study taking into account frequency and duration of use to explore possible dose-response relationships and threshold effects.

2. Methods

2.1. Study Population

The MACS is an ongoing cohort study of the natural and treated histories of HIV-1 infection in men who have sex with men (MSM) that initiated enrollment in 1984[Detels et al., 1989;Kaslow et al., 1987]. Sites are located in Chicago IL, Baltimore MD/Washington DC, Pittsburgh PA, and Los Angeles CA. The study had three recruitment periods: (1) April 1984 to March 1985, during which 4,954 predominately white men were enrolled; (2) April 1987 to September 1991, during which 668 ethnically more diverse men were enrolled; and (3) October 2001 to August 2003, during which 1,350 men, primarily African-American and Latino, were enrolled. The present study was based on the first and second recruitments. Every 6 months, the men in the MACS complete an interviewer-administered questionnaire and a physical examination. The interview requests information on demographic characteristics, behaviors (e.g., sexual practices, recreational drug use, tobacco smoking, alcohol drinking), and medical history (e.g., AIDS-related symptoms and medications prescribed). Blood is collected at each visit for virologic, serologic, immunologic and other laboratory measurements, and for a repository of serum, plasma, and peripheral blood mononuclear cells.

For the analysis of HIV-uninfected men, 3,236 such men who made more than one HIV-seronegative study visit were included. Follow-up started at the first study visit, and ended at the last HIV seronegative visit during the study period, loss-to-follow up, or April 2003, whichever came first. The maximum follow-up time for men in this analysis was 18 years. For the analysis of HIV-infected men, we used men who were uninfected at baseline but acquired HIV before 1996. This cutoff date was chosen to avoid the effects of highly active antiretroviral therapy. 481 men provided data for this analysis. Follow up started at the first HIV seropositive visit and ended at the time of death, loss-to-follow up, or by the end of 1995. The maximum follow-up for HIV-infected men was 11 years.

2.2. Statistical Analysis

To model the repeated measurements of CD4 and CD8 T cell subpopulations, we performed mixed effects linear regression using the PROC MIXED procedure in SAS version 8 (Statistical Analyses System Inc, Cary, NC). The following four measurements were examined as outcomes of interest: CD4 cell count, CD8 cell count, CD4 cell percentage among all lymphocytes, and CD8 cell percentage. For men who HIV seroconverted during the study follow-up, data obtained from the last seronegative visit were excluded from the analysis to avoid effects due to very early HIV infection, when the men might have been HIV infected but not yet antibody positive. Distributions of CD4 and CD8 T cell counts were slightly skewed and were normalized by natural logarithmic transformation. Use of marijuana, cocaine, poppers and amphetamines was first modeled as binary variables (use vs. no use since last visit). To look for possible threshold effects and dose-response relationships, substance use was further modeled by frequency of use: no use (reference), monthly or less frequent use, and weekly or more frequent use. We also examined the effect of long-term exposure, defined as reported drug use on two consecutive study visits.

To visually examine the distributions and trajectories of CD4 and CD8 T cell parameters by drug use behaviors, we constructed the profile plots[Chambers JM et al., 1983] on repeated random samples of 20 subjects, box plots[Tukey, 1977] and empirical summary plots[Weiss RE, 2005] stratifying by (1) no drug use vs. drug use at any time during the study period; (2) no baseline drug use vs. baseline drug use; and (3) no drug use or use at < 50% of the visits vs. drug use at ≥50% of the visits. Univariate associations between covariates of interest (including recreational drug use and potential confounders) and CD4 and CD8 T cell parameters at baseline were analyzed using linear regression. In modeling the fixed effects, we

used a hybrid model that allowed randomly varying intercepts and slopes and an autoregressive covariance structure for within-subject errors. As suggested by previous studies[Taylor JMG et al., 1994;Taylor and Law, 1998], this model fitted the data better than a model that only included random effects.

Substance use and potential confounders were modeled as time-varying exposures. For analysis of HIV-uninfected men, potential confounders assessed included: age, race, education, tobacco smoking, alcohol use, number of male sexual partners, receptive anal intercourse (yes vs. no), follow-up time, and lifetime history of sexually transmitted infections (STI scores were based on one point for each of hepatitis, gonorrhea, herpes, genital/anal warts and scabies, and ranged from 0 to 5). For analysis of HIV-infected men, the above confounders were assessed, as well as use of single or combination antiretroviral therapy. We also fit models with baseline covariates and interaction terms between baseline drug use and follow-up time to estimate the association between baseline drug use and rate of change in T cell parameters over time. Finally, we fit models with continuous drug use in the past year (time-varying exposures) to examine the potential threshold effect of continuous use. Transformed residuals using Cholesky factorization were used to examine model fit by inspecting the residual plot of rescaled residuals and predicted value[Fitzmaurice GM et al., 2004].

3. Results

3.1. HIV-uninfected Men

During the study period, 50,048 person-visits were made. The average number of observations per participant was 15 and the average follow-up time was 10 years. At baseline, the cohort was mostly white and middle-aged, most had a college degree, and substance use was common: 59% used marijuana, 27% used cocaine, 58% used poppers, and 16% used amphetamines. The distributions of CD4 and CD8 cell counts and percentages at baseline are presented in Table 1. Despite moderate within-individual fluctuation, average CD4 and CD8 lymphocyte profiles were stable over time. Those who used any of the four substances at baseline or any time during the study had a higher average CD4 cell count throughout the follow-up period. Longitudinal CD4 cell counts stratified by baseline drug use and HIV-serostatus are shown in Figure 1; the effect of baseline drug use was minimal.

We did not find any association between use of marijuana, cocaine, poppers, and amphetamines and any of the four outcomes examined that appeared to be of a clinically meaningful magnitude in either the baseline univariate analysis (data not shown) or the longitudinal multivariable analysis (Table 2, HIV-uninfected. Data not shown for CD4 and CD8 cell percentages). Although use of poppers was significantly associated with lower CD4 cell count, the size of the effect was tiny, even the strongest effect (for weekly or more frequent use) amounting to only a 4 percent reduction relative to who did not use poppers. We also did not observe clinically meaningful associations between baseline substance use and the rate of change (slope) of the CD4 and CD8 cell counts or percentages over time (data not shown). Analysis of continuous use of recreational drugs in the previous two study visits did not strengthen these associations (Table 2).

As previously reported[Park et al., 1992], smoking one pack of cigarettes or more per day was associated with an approximately 10% increase in mean CD4 cell count (data not shown). The Cholesky rescaled residuals appeared to be randomly distributed around zero for all models, suggesting reasonable fit to the data.

3.2. HIV-infected Men

The 481 men who seroconverted before 1996 contributed a total of 4,735 person-visits from seroconversion to 1996, with an average of 10 observations per men and an average follow-up of 5 years. The demographics, substance use, sexual behaviors, and distribution of CD4 and CD8 T cell counts and percentages at the first seropositive visit are shown in Table 1. As in the HIV-uninfected men, substance use was common in this group: 61% used marijuana, 30% used cocaine, 58% used poppers, and 17% used amphetamines. Empirical summary plots showed that while average CD4 cell count and percentage declined over time, average CD8 cell count increased after seroconversion. As in the seronegative population, those who used any of the four substances at the first seropositive study visit or any time during follow-up had a higher average CD4 cell count compared to those who did not use these substances (Figure 1).

In the univariate analysis at baseline, use of marijuana, poppers and amphetamines was associated with higher CD4 cell count. Use of poppers was also positively associated with CD4 cell percentage and inversely associated with CD8 cell percentage. Tobacco smoking was associated with a higher CD4 cell count, while non-white race and alcohol use were inversely associated with CD4 cell count and percentage.

Again, we did not find any clinically meaningful adverse associations between use of marijuana, cocaine, poppers, or amphetamines and any of the four outcomes examined in the longitudinal multivariable analysis (Table 2, HIV-infected men. Data not shown for CD4 and CD8 cell percentages). Baseline substance use was also not associated with a faster decline in CD4 cell count and percentage, or a steeper increase in CD8 cell count and percentage. Analysis of the continuous use of these substances in two consecutive study visits yield stronger associations for CD4 cell count than those observed with use in the past 6 months (except for continuous use of poppers), but none of these associations were statistically significant (Table 2, HIV-infected men).

Tobacco smoking was positively associated with CD4 cell count. The Cholesky rescaled residuals against the predicted values appeared to be randomly distributed around zero for all models, suggesting reasonable model fit.

4. Discussion

In this cohort, we did not find any clinically meaningful associations, adverse or otherwise, between use of marijuana, cocaine, poppers, or amphetamines and T cell counts and percentages in either HIV-uninfected or HIV-infected men. We also did not observe any threshold effect by frequency of use or duration of use (at least not with weekly or more frequent use or continuous use in the past year). Due to the large number of measurements, the study detected some differences that were statistically significant, but these were trivial and no consistent or meaningful differences in the rates of change of CD4 and CD8 T cell parameters over time by baseline recreational drug use status were found.

These findings are consistent with previous reports that recreational drug use was not associated with HIV disease progression in MSM[Chaisson et al., 1995;Di Franco et al., 1996;Kaslow et al., 1989;Page-Shafer et al., 1996]. A lack of association was also observed among injection drug users[Chaisson et al., 1995;Vlahov et al., 1998]. A randomized, placebo controlled trial among HIV-infected persons found no short-term (21 days) effect of marijuana smoking on immune phenotypes, including the proportion of CD4 and CD8 T cells (naïve or memory), B cells and natural killer cells[Bredt et al., 2002]. Our prospective study, together with a previous epidemiologic analysis[Ascher et al., 1993], did not find short-term or long-term adverse effects of use of marijuana on CD4 cell count. Although an adverse effect of use of cocaine on

CD4 cell count has been suggested by others[Larrat et al., 1996;Siddiqui et al., 1993], this association was not observed in our study, even in those who used cocaine weekly or more frequently.

Our observation of the upward trajectories of average CD8 cell count after HIV seroconversion is consistent with previous findings from MACS[Margolick et al., 1995]. The observed positive association between tobacco smoking and CD4 cell count was previously reported by Park and colleagues[Park et al., 1992], who found that the effect of tobacco smoking on CD4 cell count was non-specific, maximal in HIV-uninfected men, and lost three years after seroconversion. In our analysis, tobacco smoking was associated with approximately 6% ($p<0.01$) and 7% increase ($p=0.04$) in mean CD4 cell count in HIV-uninfected and HIV-infected men. A clear dose-response relationship was observed only in HIV-uninfected men. Smoking had very little effect on CD4 cell percentages, as previously reported[Park et al., 1992;Corre F et al., 1971;Friedman GD et al., 1973].

Our study was subject to several potential limitations, including uncontrolled confounding, potential bias caused by missing data and non-random loss to follow-up (e.g. dropout due to death or advanced disease), and potential bias induced by multicolinearity between drug use. To evaluate whether those who used the four substances were more likely to have missing T cell measurements, we used logistic regression to model the association between substance use and the odds of having missing data on CD4 and CD8 cell counts. For HIV-uninfected men, 22% of the study visits had missing CD4 and CD8 T cell measurements since the study protocol did not dictate their measurement on all HIV seronegatives throughout the study. We found that use of substances was associated with a lower likelihood of having missing CD4 and CD8 T cell measurements. However, the majority of missing for these men should be considered random and was a result of the study protocol (i.e., only a random sample of the HIV-seronegatives were assayed for CD4 and CD8 cell measurements). In HIV-infected men, substance use was not associated with the likelihood of missing data. Furthermore, only 5% of the HIV-seropositive study visits were missing CD4 or CD8 T cell measurements, which is unlikely to cause substantial bias. To evaluate the degree of sensitivity of our results to the effects of potential non-random loss to follow-up, we performed joint modeling for longitudinal CD4 cell measurements and survival data using loss-to-follow up as events[Elashoff et al., 2007;Henderson et al., 2000]. This showed that our results were not sensitive to this potential source of bias. To assess the impact of multicolinearity on our estimates, we examined the regression coefficients for use of a particular substance adjusting for potential confounders but not use of the other three substances. We found similar estimates for each of the four substances in this sensitivity analysis, suggesting that the validity of our results was not substantially affected by multicolinearity. Despite these limitations, our study has substantial strengths: a longitudinal design and measurements of immunological variables at approximately six-month intervals, as well as adjustment for multiple potential confounders. Furthermore, in the analysis of HIV-infected men, we only included incident HIV seroconverters, thereby avoiding any systematic differences in duration of infection between those who used recreational drugs and those who did not as might have been the case in previous studies.

In conclusion, we did not find evidence that use of marijuana, cocaine, poppers, or amphetamines adversely affects CD4 or CD8 T cell parameters in HIV-uninfected or -infected men. Although the circulating numbers of CD4 and CD8 T cells do not appear to be significantly affected by use of these substances, these findings do not preclude the possibility that substance use may adversely affect the functional properties of T cells.

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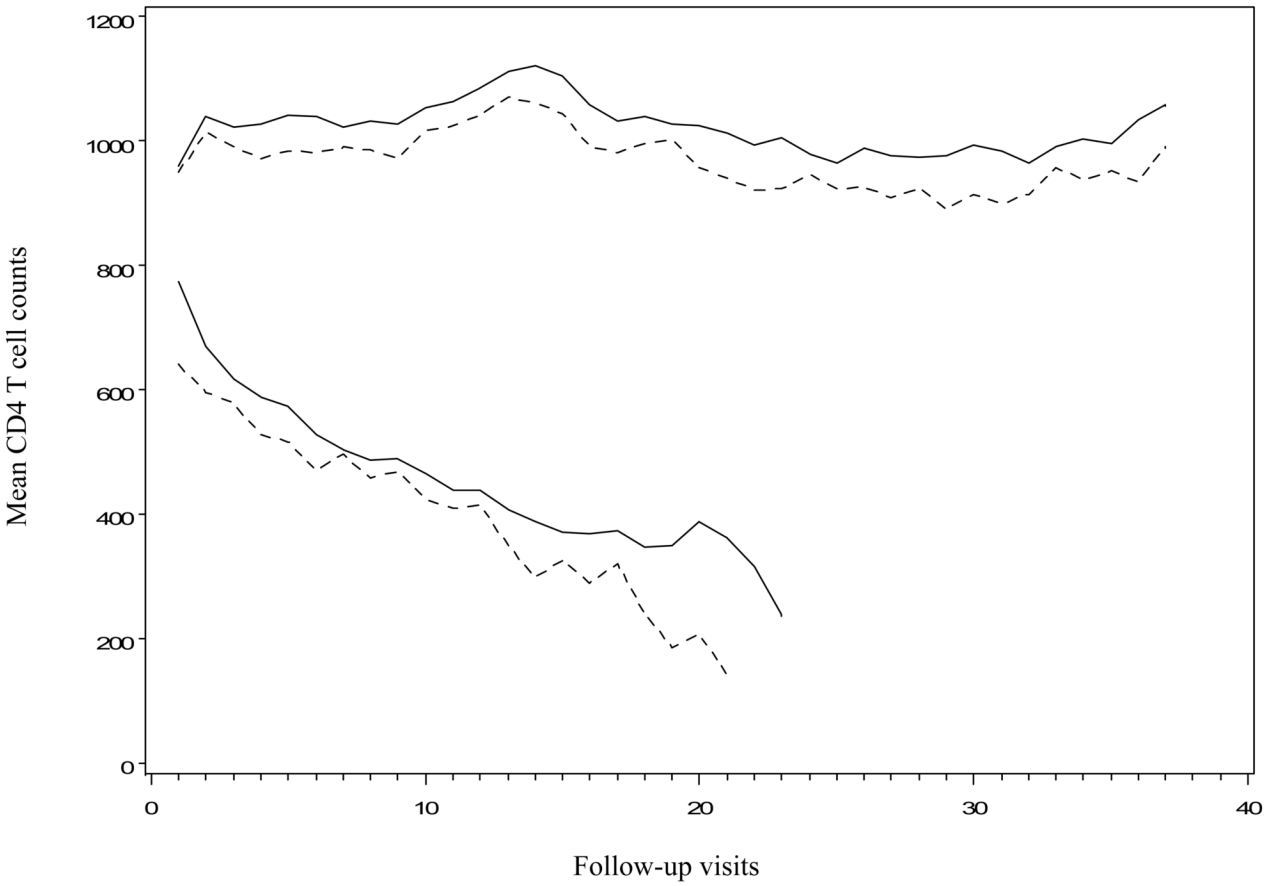

Figure 1.

Mean CD4 T cell counts over time by HIV infection status and baseline substance use status. Upper solid line: HIV-uninfected men who used marijuana, cocaine, poppers, or amphetamines at baseline (first study visit). Upper dashed line: HIV-uninfected men who did not use marijuana, cocaine, poppers, or amphetamines at baseline (first study visit). Lower solid line: HIV-infected men who used marijuana, cocaine, poppers, or amphetamines at baseline (first HIV-seropositive visit). Lower dashed line: HIV-infected men who did not use marijuana, cocaine, poppers, or amphetamines at baseline (first HIV-seropositive visit).

Note: Follow-up visits occurred every 6 months. First follow-up visit is the first study visit for HIV-uninfected men and the first HIV-seropositive visit for HIV-infected men.

Table 1

Baseline* demographics, substance use, sexual behaviors, and CD4 and CD8 T cell parameters.

	HIV-uninfected men n=3,236	HIV-infected men n=481
	Number (%)†	
Age	32.9 (27.9/38.7)**	34.0 (29.2/39.5)**
Race		
White	2957 (91.4)	435 (90.4)
Non-white	277 (8.6)	46 (9.6)
Education		
Less then college degree	1252 (38.7)	233 (49.0)
College degree or higher	1947 (60.2)	243 (51.1)
Use of marijuana in the past six months		
Did not use	1322 (40.9)	189 (39.5)
Monthly or less frequent	1269 (39.2)	179 (37.5)
Weekly or more frequent	642 (19.8)	110 (23.0)
Use of cocaine in the past six months		
Did not use	2370 (73.2)	336 (70.2)
Monthly or less frequent	803 (24.8)	131 (27.4)
Weekly or more frequent	55 (1.7)	12 (2.51)
Use of poppers in the past six months		
Did not use	1350 (41.7)	200 (41.8)
Monthly or less frequent	1267 (39.2)	169 (35.4)
Weekly or more frequent	612 (18.9)	109 (22.8)
Use of amphetamines in the past six months		
Did not use	2713 (83.8)	345 (83.3)
Monthly or less frequent	449 (13.9)	54 (13.1)
Weekly or more frequent	62 (1.9)	14 (3.4)
Tobacco smoking in the past six months		
No	2057 (63.6)	283 (59.0)
Yes	1179 (36.4)	197 (41.0)
Alcohol drinking in the past six months		
No	231 (7.1)	51 (10.6)
≦ 2 times/week	1861 (57.5)	226 (47.0)
>2 times/week	1084 (33.5)	203 (42.3)

	HIV-uninfected men n=3,236	HIV-infected men n=481
	Number (%)†	
Number of lifetime sexual partners	102 (37/351)**	190 (55/503)**
Number of male sexual partners in the past six months	5 (2/12)**	5 (2/12)**
Receptive anal intercourse in the past six months		
No	1104 (34.1)	107 (22.5)
Yes	2089 (64.6)	369 (77.5)
Sexually transmitted infection score		
0	899 (27.8)	56 (11.7)
1	987 (30.5)	127 (26.6)
2	759 (23.4)	155 (32.5)
3	408 (12.6)	95 (19.9)
4	139 (4.3)	38 (8.0)
5	18 (0.06)	6 (1.3)
CD4 cell count (μL)	891.0 (691.0/1149.0)**	700.0 (511.5/906.0)**
CD8 cell count (μL)	560.0 (412.0/748.0)**	774.5 (563.0/1089.0)**
CD4 cell percentage (among all lymphocytes)	43.0 (37.0/49.0)**	34.3 (28.0/42.0)**
CD8 cell percentage (among all lymphocytes)	27.0 (21.6/33.0)**	39.0 (31.0/47.0)**

* Baseline was first study visit for HIV-uninfected men, and first HIV seropositive visit for HIV-infected men.

** Median (25^{th}/75^{th} percentile).

† Percentage may not add up to 100% due to missing values.

Table 2

Recreational drug use and CD4 and CD8 T cell count in HIV-uninfected men and HIV-infected men.

	HIV-uninfected men*		HIV-infected men**	
	Log CD4 cell count	Log CD8 cell count	Log CD4 cell count	Log CD8 cell count
	Coefficient‡ (95% CI)		Coefficient‡ (95% CI)	
Use of Marijuana†				
Any use	**−0.01 (−0.02, −0.00)**	−0.00 (−0.01, 0.00)	0.04 (−0.02, 0.10)	−0.01 (−0.05, 0.02)
-Monthly or less frequent	**−0.01 (−0.02, −0.00)**	−0.00 (−0.01, 0.00)	0.04 (−0.01, 0.10)	−0.01 (−0.04, 0.03)
-Weekly or more frequent	−0.00 (−0.01, 0.01)	−0.01 (−0.02, 0.01)	0.01 (−0.06, 0.09)	**−0.05 (−0.10, −0.0)**
-Continuous use in the past year	−0.01 (−0.02, 0.00)	−0.01 (−0.02, 0.01)	0.07 (−0.00, 0.14)	0.01 (−0.03, 0.05)
Use of Cocaine†				
Any use	−0.00 (−0.01, 0.01)	**0.01 (0.00, 0.03)**	0.04 (−0.03, 0.10)	0.01 (−0.03, 0.05)
-Monthly or less frequent	−0.00 (−0.01, 0.01)	**0.02 (0.00, 0.03)**	0.04 (−0.02, 0.10)	0.02 (−0.02, 0.06)
-Weekly or more frequent	0.01 (−0.02, 0.04)	0.01 (−0.03, 0.04)	−0.01 (−0.16, 0.15)	−0.07 (−0.17, 0.03)
-Continuous use in the past year	0.01 (−0.00, 0.02)	**0.02 (0.01, 0.04)**	0.07 (−0.02, 0.16)	0.00 (−0.05, 0.06)
Use of Poppers†				
Any use	**−0.02 (−0.03, −0.02)**	−0.01 (−0.02, 0.00)	0.04 (−0.01, 0.09)	0.01 (−0.02, 0.04)
-Monthly or less frequent	**−0.02 (−0.03, −0.01)**	−0.01 (−0.02, 0.00)	0.03 (−0.02, 0.08)	0.01 (−0.02, 0.04)
-Weekly or more frequent	**−0.04 (−0.05, −0.02)**	**−0.02 (−0.03, −0.01)**	0.07 (−0.01, 0.15)	0.03 (−0.02, 0.08)
-Continuous use in the past year	**−0.02 (−0.02, −0.01)**	**−0.01 (−0.02, −0.00)**	0.00 (−0.06, 0.07)	−0.02 (−0.06, 0.02)
Use of Amphetamines†				
Any use	**−0.03 (−0.04, −0.01)**	−0.00 (−0.02, 0.02)	0.00 (−0.09, 0.09)	0.03 (−0.03, 0.08)
-Monthly or less frequent	**−0.03 (−0.04, −0.01)**	−0.00 (−0.02, 0.02)	0.02 (−0.07, 0.11)	0.03 (−0.03, 0.09)
-Weekly or more frequent	−0.01 (−0.05, 0.03)	−0.02 (−0.06, 0.03)	−0.09 (−0.27, 0.09)	0.03 (−0.08, 0.15)
-Continuous use in the past year	−0.01 (−0.03, 0.01)	−0.01 (−0.04, 0.01)	0.05 (−0.08, 0.19)	0.06 (−0.02, 0.14)

*Model includes the following variables: follow-up time, age, race (white vs. non-white), education (no college degree vs. college degree), alcohol drinking (≤ 2 times per week vs. >2 times per week), tobacco smoking (no smoking vs. <1 pack per day vs. ≧1 and <2 pack per day vs. ≧2 pack per day), receptive anal intercourse (yes vs. no), sexually transmitted infections score, and higher number of male sexual partner (>6 in the past 6 months).

** Model includes the above potential confounders and single and combination antiretroviral therapy.

† Reference group: no use.

‡ A 5% difference in original scale for CD4 and CD8 cell count is equivalent to a coefficient of 0.05 or -0.05 in the log scale; a 10% difference is equivalent to a coefficient of 0.10 or -0.10 in the log scale.

§ Bold font: p-value < 0.05.