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Recent cigarette smoking and HIV disease progression: No evidence of an association

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Abstract

The association between smoking and HIV disease progression has been examined in several studies; however, findings have been inconsistent. We examined the effect of recent cigarette smoking on CD4⁺ T cell count/ μ L (CD4 count) and HIV RNA concentration (HIV viral load [VL]) among two HIV-infected cohorts with alcohol problems in Massachusetts in the periods 1997–2001 and 2001–2006 using a prospective cohort design and linear mixed models. Smoking groups were defined as: minimal or non-smokers, light smokers, moderate smokers and heavy smokers. Age, alcohol use, injection drug use, depressive symptoms, gender, annual income, and antiretroviral therapy (ART) adherence were considered as potential confounders. Among 462 subjects, no significant differences in CD4 count or viral load were found between smoking groups. Using minimal or non-smokers as the reference group, the adjusted mean differences in CD4 count were: 8.2 (95% confidence interval (CI): –17.4, 33.8) for heavy smokers; –0.1 (95% CI: –25.4, 5.1) for moderate smokers; and –2.6 (95% CI: –28.3, 3.0) for light smokers. For log₁₀ VL, the adjusted differences were: 0.03 (95% CI: –0.12, 0.17) for heavy smokers; –0.06 (95% CI: –0.20, 0.08) for moderate smokers; and 0.14 (95% CI –0.01, 0.28) for light smokers. This study did not find an association between smoking cigarettes and HIV disease progression as measured by CD4 cell count and VL.

Keywords

Cigarette Smoking; CD4⁺ T cells; Viral Load; HIV

Introduction

With the major prognostic advance of highly active antiretroviral therapy (HAART) (Palella et al., 1998; Detels et al., 1998; Crum et al., 2006), impetus to understand other potential avenues to prevent disease progression among Human Immunodeficiency Virus (HIV)-infected persons has been sought (Jia et al., 2007; Baum et al., 1995; Fawzi et al., 2004;

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Cheng et al., 2007; Cook et al., 2008). Since smoking is common among HIV-infected persons (Webb, Vanable, Carey, & Blair, 2007) (Niaura et al., 2005) its effect on HIV disease progression has merited study. Smoking can suppress the maturation of dendritic cells in the lymph nodes thereby weakening the function of CD4⁺ T cells (Robbins, Franco, Mouded, Cernadas, & Shapiro, 2008; Robbins et al., 2004). It can also affect the efficiency of peripheral blood mononuclear cells to secrete cytokines (Ouyang et al., 2000). Smoking has also been reported to up regulate the expression of Fas (cell surface molecules mediating apoptotic cell death) on peripheral blood lymphocytes, rendering them susceptible to apoptosis (Bijl et al., 2001). Other reported possible mechanisms explaining the adverse effects of smoking on immunological function have been described (Sopori & Kozak, 1998; Kalra, Singh, Savage, Finch, & Sopori, 2000), (Petersen, Steimel, & Callaghan, 1983; Silverman, Potvin, Alexander Jr, & Chretien, 1975), (Tollerud et al., 1989; Sopori, Gairola, DeLucia, Bryant, & Cherian, 1985), (Carrillo, Castro, Cuevas, Diaz, & Cabrera, 1991), (Kuniak et al., 1995), (Abbud, Finegan, Guay, & Rich, 1995).

Several epidemiologic studies have investigated the relation between cigarette smoking and the course of HIV infection yielding mixed results. Two cohort studies (Crothers et al., 2005; Conley et al., 1996) and two cross-sectional studies (Slavinsky III et al., 2002; Palacio, Hilton, Canchola, & Greenspan, 1997) found an association between smoking and development of opportunistic infections (OIs). In contrast, eight cohort studies (Webber, Schoenbaum, Gourevitch, Buono, & Klein, 1999; Stephenson et al., 1999; Coates et al., 1990; Burns et al., 1996; Eskild & Petersen, 1994; Galai et al., 1997; Craib et al., 1992; Nieman, Fleming, Coker, William, & Mitchell, 1993) and two cross sectional studies (Webb, Vanable, Carey, & Blair, 2007; Gritz, Vidrine, Lavez, Amick, & Arduino, 2004) reported a null association. One study (Royce & Winkelstein, 1990) linked smoking with an increase in CD4⁺ T cells among males although the increase was less pronounced in HIV-infected individuals.

Inconsistent results regarding the effect of smoking on HIV disease progression may in part be attributed to the differing characteristics of the study populations. Adjustment for potential confounders (e.g. alcohol use) did not consistently occur. As most previous epidemiologic studies used the incidence of OIs as a primary endpoint, we considered the other useful biological markers that might complement the observations of clinical outcomes in the examination of whether smoking accelerates HIV disease progression.

We therefore analyzed data from a prospectively assessed two cohorts of HIV-infected patients with alcohol problems to examine the association of cigarette smoking with CD4⁺ T cell count (CD4 count) and HIV viral load (VL). We hypothesized that smoking would be associated with a lower CD4 count and a higher VL.

Design and Methods

Study population

Study participants were from two longitudinal cohorts of HIV-infected persons with alcohol problems: HIV Alcohol Longitudinal Cohort (HIV-ALC) study only (1997–2001) (n=78); HIV Longitudinal Interrelationships of Viruses and Ethanol (HIV-LIVE) study only (2001–2006) (n=230); and both HIV-ALC and HIV-LIVE studies (n=154). Eligibility criteria and recruitment methods for HIV-ALC (Samet, Horton, Traphagen, Lyon, & Freedberg, 2003) and HIV-LIVE (Samet et al., 2007) were the same with follow-up visits planned every six months. Inclusion criteria included a documented HIV antibody test, a history of alcohol problems as measured by the CAGE questionnaire or a clinical investigator's assessment (Samet, Phillips, & Horton, 2004), age 18 years or older, ability to speak English or Spanish, and at least one contact person to assist with the follow-up. Exclusion criteria included

score < 21 on the 30-item Mini-Mental State Examination (M.F. Folstein, S.E. Folstein, & McHugh, 1975; Smith, Horton, Saitz, & Samet, 2006), inability to provide informed consent or answer the interview questions, and plans to move from the Boston area in the subsequent 12 months. For the current analysis, we also excluded those who did not have at least one follow-up visit. Laboratory measurements were obtained at each interview. Additional details on this population have been provided elsewhere (Samet et al., 2007; Samet et al., 1995). The study was approved by the Boston Medical Center and Beth Israel Deaconess Medical Center Institutional Review Boards.

Outcome assessment

The primary outcomes for this analysis were CD4⁺ T cell count/ μ l (CD4 count) and log₁₀ plasma HIV RNA/ ml (VL). CD4 count was determined by flow cytometry at the hospital laboratories. VL was measured using a branched-chain assay (lowest detection threshold= 75 copies/ ml) or a polymerase chain reaction (lowest detection threshold= 50 copies/ ml for ultrasensitive assay, and 500 copies/ ml for standard assay) (Pachl et al., 1995).

Exposure assessment

Information on smoking was collected at each study visit. Smoking status was categorized per Okuyemi et al. (2002) and Okuyemi et al. (2004) as follows: Minimal or non-smoker (smoked less than one cigarette per day); light smoker (smoked one to less than 10 cigarettes per day); moderate smoker (smoked 10 to less than 20 cigarettes per day); or heavy smoker (smoked 20 or more cigarettes per day). We used non-parametric local linear polynomial curves (*loess*) (Cleveland, Grosse, & Shyu, 1992) to verify that the cutoffs were reasonable for our data. We also performed a secondary, confirmatory analysis including smoking categorized based on quintiles of the distribution.

We defined a smoker as someone who answered affirmatively to the question “Do you currently smoke cigarettes?” As a secondary analysis, we defined smoking based on the subject’s reported smoking status at two successive visits. That is, the outcome at each time point was modeled as a function of smoking from the current and previous study visit, thus accounting for whether the subjects changed or maintained their recent smoking behavior. In the case of missed visits, smoking status from the last available visit was used. We categorized smoking as follows: consistent smokers (smoked in two consecutive visits); consistent minimal or non-smokers (smoked <1 cigarette per day in two consecutive visits); recent quitters (smoked in the last visit but stopped smoking in the current visit); and new/relapsed smokers (not smoked in the last visit but started or resumed smoking in the current visit). The categorization was based on data from previous studies which suggest that the effect of smoking on the immune system is acute (Tollerud et al., 1989; Hersey, Prendergast, & Edwards, 1983; Sunyer et al., 1996), with induction period of about five weeks (Thomas, Holt, & Keast, 1975) to 10 weeks (Chalmer, Holt, & Keast, 1975), and lasts for about six to 35 weeks since quitting (Thomas, Holt, & Keast, 1975; Miller, Goldstein, Murphy, & Ginns, 1982; Radloff, 1977). Since the time elapsed between the last HIV-ALC visit to the first HIV-LIVE visit was too long (range one month to 66 months) for some of the subjects enrolled in both cohorts, this secondary analysis was restricted to subjects who participated in HIV-LIVE.

Statistical analysis

We performed descriptive analyses to characterize the study population, overall and by baseline smoking status.

We applied linear mixed effects models to account for correlated measures within subjects. The models included subject-specific random intercepts and slopes, and adjusted for the

value of the outcome (i.e. CD4 count and VL) at the previous study visit. We fitted a separate model for each outcome. Graphs illustrating trajectories of HIV disease progression over time were also plotted using outcome estimates from linear mixed effects models.

Age (modeled as a continuous variable), alcohol use (≤ 2 drinks per day, $>2\text{--}\leq 4$ drinks per day, and > 4 drinks per day), current injection drug use (user vs. non-user), depressive symptoms (CESD score >23 vs. ≤ 23), gender, annual income ($>$ median (\$7,500) vs $\leq$ median), and antiretroviral therapy (ART) adherence (not on medication, on medication and adherent, and on medication but not adherent) were considered as potential confounders during analysis. The categories for alcohol use were made narrower than those suggested by Cook et al. (2009) so as to account for residual confounding. The cutoff point for depressive symptoms was determined with Radloff et al. (1977) criteria. ART adherence was measured using the AIDS Clinical Trials Group criteria (Chesney et al., 2000) and defined as a self-report of 100% adherent in the past three days (Samet, Horton, Meli, Freedberg, & Palepu, 2004). Preliminary models were fitted separately for each potential confounder. Confounders were then added sequentially in the models according to the magnitude of their effect on the association between cigarette smoking and outcome. Any potential confounder that changed the point estimate of cigarette smoking by more than 10% was included in the final model. Smoking status and all covariates with the exception of gender and age were analyzed as time-varying variables and updated at each time point. An interaction between smoking and time was included in the models and evaluated for its statistical significance. To assess whether ART modifies the effect of smoking, subgroup analyses were repeated separately for subjects not on ART and for subjects on ART and adherent to medication. Subjects who changed their ART status contributed observations to each stratum depending on the ART status of the observation.

For the primary analysis, undetectable VL was imputed as half the value of the lowest threshold of assay sensitivity. Secondary analyses evaluated the potential bias due to imputing assay values using half the limit of detection (Greenland & Lash, 2008) as follows: The undetectable assay measurements were imputed with plausible values from a logit-logistic distribution (Lesaffre, Rizopoulos, & Tsonaka, 2007) with a scale parameter of 0.8, accounting for the fact that VL values are bounded by 0. The distribution also took into account that 0 VL is unlikely as no current treatment can completely eliminate HIV. This process was repeated in 10,000 simulation runs and 95% simulation intervals (SI) were obtained. Statistical analysis was done using SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina).

Results

The cohort ($n=462$) is described in Table 1 with the following demographic characteristics: black (43%); male (77%); median age 42 years (range 21–71 years); and median annual income of \$7,500 or less. In the combined cohort, 77% (358/462) of subjects reported having smoked cigarettes within the last month before enrollment; 23% were minimal or non-smokers, 25% were light, 22% were moderate and 31% were heavy smokers. The median baseline CD4 count and viral load were 380 cells/ μ l and 1175 copies/ml respectively. The median follow-up time was 18 months for those enrolled in only HIV-LIVE, 14 months for those in only HIV-ALC, and 40 months for those in both studies. In the overall cohort, the median number of visits was seven (range: 2–14 visits). Subjects who completed the majority of study of visits had higher mean baseline CD4 count (difference=117.3; $p<0.0001$) and lower mean baseline log₁₀ VL (difference=0.35; $p=0.03$) than those who did not complete the majority of study visits. There was no significant association between baseline smoking status and whether the subject completed the majority of study visits in this cohort (chi-square=0.41; $p=0.52$). Subjects contributed 3141

observations across all follow-up visits: 827 (26%) classified as minimal or non-smokers, 696 (22%) light smokers, 772 (25%) moderate smokers and 846 (27%) as heavy smokers.

The plots in Figure 1 show the unadjusted mean CD4 count or VL over time across smoking categories. The plots suggest potential variation in mean differences in CD4 count or VL over time between smoking categories. However, the smoking-time interaction term was not statistically significant in any of the regression models and was therefore excluded from subsequent analyses.

We did not find any substantial differences in CD4 count or VL across categories of smoking (Table 2). Using minimal or non-smokers as the reference group, the adjusted mean differences in CD4 count were: 8.2 (95% confidence interval (CI): -17.4, 33.8; $p=0.44$) for heavy smokers; -0.1 (95% CI: -25.4, 5.1; $p=0.48$) for moderate smokers; and -2.6 (95% CI: -28.3, 3.0; $p=0.90$) for light smokers. For log₁₀ VL, the adjusted differences were: 0.03 (95% CI: -0.12, 0.17; $p=0.39$) for heavy smokers; -0.06 (95% CI: -0.20, 0.08; $p=0.83$) for moderate smokers; and 0.14 (95% CI: -0.01, 0.28; $p=0.06$) for light smokers.

When analysis was stratified by ART status, no clear evidence of an association between smoking with CD4 count or HIV VL was found (Table 2). We observed a small but statistically significant increase in VL for light smokers compared with minimal or non-smokers among subjects who adhered to ART (the adjusted mean difference was 0.24; 95% CI: 0.04, 0.44; $p=0.01$). However, similar associations were not observed for categories of heavier smoking.

Similarly, no substantial outcome differences were observed for subjects who switched or maintained their smoking behavior (Table 3).

Results (not shown) remained similar in analyses examining the potential bias due to the imputed assay measurements, suggesting that the unobserved values in the lower range did not have a large impact on results. Similarly, the analysis with smoking categorized based on quintiles did not alter the study findings.

Discussion

This study does not provide evidence that cigarette smoking is associated with a decrease in CD4 count or an increase in VL among HIV- infected patients. Specifically, we observed no substantial differences in CD4 count or VL between minimal or non-smokers, light smokers, moderate smokers and heavy smokers. Moreover, we found no substantial differences in CD4 count or VL when smoking status changed in two consecutive visits.

Our findings are in accordance with previous cohort studies which did not detect an association between cigarette smoking and HIV disease progression (Webber, Schoenbaum, Gourevitch, Buono, & Klein, 1999; Stephenson et al., 1999; Coates et al., 1990; Burns et al., 1996; Eskild & Petersen, 1994; Galai et al., 1997; Craib et al., 1992) when using the onset of an AIDS defining condition as a primary outcome. Our design, using CD4 count and VL as markers for HIV disease progression, is well suited for HIV cohorts with less advanced disease, fewer anticipated OIs.

Results from this study are in contrast with findings from two cohort studies which reported that smoking enhances HIV disease progression using OIs as outcomes (Crothers et al., 2005; Conley, Bush, Buchbinder, & Penley, 1996). In one of these studies CD4 counts were also examined (Conley, Bush, Buchbinder, & Penley, 1996), but not associated with smoking. As smoking may selectively affect target organs (e.g. lungs), the latter study

underscores the need to investigate biological markers of immunological dysfunction in addition to OIs in order to assess its impact on the immune system.

Although we found no evidence of a relation between smoking and HIV disease progression, we could not rule out the potential effect of smoking on CD4 cells or HIV which are not in peripheral blood. As high concentrations of smoke can get trapped in the lungs, it would not be surprising if most of the affected cells are those surrounding the lungs. For example, one study (Wewers et al., 1998) found that, compared to minimal or non-smokers, HIV-infected smokers had a significant depletion in CD4 cells in their *bronchoalveolar lavage* fluid. Analyzing samples of immunological markers derived from sites other than the peripheral blood may shed some light on the issue.

Our study was conducted using a cohort of patients with current or past alcohol problems. As alcohol drinkers tend to smoke more than non-alcohol drinkers (Collins & Marks, 1995), the choice of this cohort ensured availability of ample smokers for analysis. The selection of this cohort came with a caution in that the generalizability of its findings may be limited to a population with alcohol problems. However, given the prevalence of past alcohol problems among HIV-infected individuals, up to 40% (Samet, Phillips, & Horton, 2004), these findings would still be of importance even if not applicable to a non-alcohol affected HIV population. An interaction term between smoking and current alcohol drinking (categorized by dose) was not statistically significant in regression models.

The main strength of this study was the inclusion of assessments of changes in immunological biological markers over time using repeated measures on the same individuals. We identified the use of such methodology in only one other study (Sunyer et al., 1996) among HIV seronegative subjects in which a positive association existed between smoking and an increase in white blood cells. We performed post-hoc power calculations to assess the differences in CD4 count our study could detect with reasonably high power. While we utilized longitudinal regression methods in the analyses, for the purposes of power calculations we considered a simpler setting utilizing a single time point. Thus our estimates are conservative as the longitudinal analyses are expected to increase the study power. Assuming a standard deviation of 42 (based on our observed data at baseline), the minimum detectable difference in mean CD4 count between any two smoking groups that our sample size could detect with 80% power was 16 cells/ μ l. hence this study was adequately powered to detect effect sizes observed previously (Sunyer et al. 1996), a difference in CD4 count of 74 cells/ μ l between heavy smokers and never smokers. Other strengths included the ability to analyze short term effects of smoking initiation and cessation, information on smoking dosage and the availability of many important potential confounders.

We note Our study had limitations. First, information on cigarette smoking was self reported. Second, the number of cigarettes smoked may not necessarily reflect the amount of smoke inhaled, underestimating the actual smoking dosage.

In summary we did not find significant associations between cigarette smoking and CD4 count or VL among HIV-infected patients with alcohol problems. Future epidemiologic studies concerning the impact of smoking on HIV disease progression may provide more insight if focused on this substance's effect on specific tissues and particular immunological systems in addition to immunological markers (i.e., CD4 count and VL) in the peripheral blood.

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Figure 1.
Unadjusted mean CD4 count and VL over time

Sociodemographic and clinical characteristics of HIV-infected persons with a history of alcohol problems in two prospective cohorts stratified by baseline smoking status (n=462)

Table 1

Covariates	n (%)				Mean no. cigarettes/ smoked per day (SD) n=358
	Total n (%) n=462	Minimal or non-smokers n=104	Light smokers n=115	Mod. smokers n=100	Heavy smokers n=143
<i>Sociodemographic variables</i>					
<i>Age</i>					
≤30	22 (5)	5 (5)	6 (5)	3 (3)	8 (6)
31–40	174 (38)	34 (33)	47 (41)	43 (43)	50 (35)
>40	266 (58)	65 (63)	62 (54)	54 (54)	85 (59)
<i>Gender</i>					
Females	108 (23)	81 (78)	86 (75)	73 (73)	114 (80)
Males	354 (77)	23 (22)	29 (25)	27 (27)	29 (20)
<i>Race</i>					
Black	198 (43)	43 (41)	64 (56)	57 (57)	34 (24)
White	154 (33)	38 (37)	15 (13)	21 (21)	80 (56)
Hispanic	87 (19)	18 (17)	29 (25)	17 (17)	23 (16)
Other	23 (5)	5 (5)	7 (6)	5 (5)	6 (4)
<i>Income</i>					
>Median (\$7,500)	215 (47)	55 (53)	43 (37)	48 (48)	69 (49)
≤Median (\$7,500)	245 (53)	49 (47)	72 (63)	51 (52)	73 (51)
<i>Average no. drinks/day</i>					
0–2	381 (83)	91 (88)	93 (81)	80 (81)	117 (82)
>2–4	30 (7)	8 (8)	11 (10)	6 (6)	5 (4)
>4	50 (11)	5 (5)	11 (10)	13 (13)	21 (15)
<i>Injecting drug use</i>					
User	79 (17)	7 (7)	14 (12)	25 (25)	33 (23)
Non user	383 (83)	97 (93)	101 (88)	75 (75)	110 (77)
<i>ART status</i>					
Not on meds	173 (38)	35 (34)	34 (30)	41 (41)	63 (44)

Covariates	n (%)					Mean no. cigarettes smoked per day (SD) n=358
	Total n (%) n=462	Minimal or non-smokers n=104	Light smokers n=115	Mod. smokers n=100	Heavy smokers n=143	
On meds, not adherent	84 (18)	14 (13)	31 (27)	13 (13)	26 (18)	15.35 (11.61)
On meds, adherent	204 (44)	55 (53)	50 (43)	45 (45)	54 (38)	13.42 (8.90)
<i>Depressive symptoms</i>						
Depressed	217 (47)	35 (34)	55 (47)	48 (48)	79 (55)	15.08 (9.95)
Not Depressed	245 (53)	69 (66)	60 (52)	52 (52)	64 (45)	12.92 (8.86)
<i>Cohort</i>						
ALC-only	78 (17)	17 (16)	15 (13)	18 (18)	28 (20)	16.82 (13.30)
LIVE-only	230 (50)	58 (56)	52 (45)	52 (52)	68 (48)	13.91 (8.16)
Combined	154 (33)	29 (28)	48 (42)	30 (30)	47 (33)	13.46 (9.64)
<i>Median baseline CD4 count</i>	390	383	410	324	422	
<i>Median baseline viral load</i>	1188	388	1723	1382	1251	

¹ Minimal or non-smokers are excluded

Table 2

The association between smoking status and markers of HIV disease progression

	Mean differences in CD4 count ¹		Mean differences in HVL ²	
Smoking status	All subjects combined (n=462) ³			
	Crude [95% CI]	Adjusted [95% CI]	Crude [95% CI]	Adjusted [95% CI]
Heavy smokers	−3.2 [−27.7, 21.2]	8.2 [−17.4, 33.8]	0.18 [0.03, 0.32]	0.03 [−0.12, 0.17]
Moderate smokers	−11.7 [−36.0, 12.6]	−0.1 [−25.4, 25.1]	0.11 [−0.04, 0.25]	−0.06 [−0.20, 0.08]
Light smokers	−13.0 [−37.8, 11.9]	−2.6 [−28.3, 23.0]	0.27 [0.12, 0.42]	0.14 [−0.01, 0.28]
Minimal or non smokers	Reference	Reference	Reference	Reference
	Not on ART ^{4,5}			
Heavy smokers	24.0 [−22.4, 70.3]	27.4 [−19.7, 74.4]	−0.11 [−0.36, 0.14]	−0.09 [−0.35, 0.17]
Moderate smokers	27.7 [−18.0, 73.4]	30.1 [−16.0, 76.1]	−0.22 [−0.47, 0.03]	−0.20 [−0.56, 0.06]
Light smokers	13.8 [−30.7, 58.4]	16.0 [−28.9, 60.9]	−0.15 [−0.39, 0.09]	−0.14 [−0.38, 0.11]
Minimal or non smokers	Reference	Reference	Reference	Reference
	On ART and adhered to medication ^{4,6}			
Heavy smokers	−8.4 [−34.3, 17.5]	−6.4 [−32.4, 19.6]	0.05 [−0.14, 0.24]	0.03 [−0.16, 0.21]
Moderate smokers	−14.5 [−40.4, 11.3]	−14.2 [−40.0, 11.6]	0.05 [−0.14, 0.23]	0.01 [−0.18, 0.19]
Light smokers	−11.2 [−38.2, 15.8]	−11.4 [−38.3, 15.6]	0.25 [0.06, 0.45]*	0.24 [0.04, 0.44]*
Minimal or non smokers	Reference	Reference	Reference	Reference

¹ Adjusted analyses controlled for previous CD4+ cell count, ART status, time, and depressive symptoms² Adjusted analyses controlled for previous log10 HIV RNA, ART status, income, depressive symptoms, injection drug use, age, alcohol, time, and gender³ No. observations was 3141⁴ ART was removed in the model because we stratified on it⁵ No. subjects was 291. No. observations was 1026. Included only observations when subject was on ART.⁶ No. subjects was 363. No. observations was 1586. Included only observations when subject was on ART and adhered to medication.

* Results are statistically significant

Table 3

The association between smoking status at two successive visits and markers of HIV disease progression (n=383)¹

	Mean difference in CD4 count [95% CI]		Mean difference in HVL[95% CI]	
	Crude	Adjusted ²	Crude	Adjusted ³
Smoking Status				
New/relapsed smokers	16.87 [-6.60,60.35]	22.73 [-0.28,65.74]	-0.11 [-.41,0.19]	-0.11 [-.39,0.17]
Consistent smokers	-12.14 [-30.00,5.69]	-2.25 [-20.18,15.68]	0.18 [0.05,0.30]	0.11 [-0.05,0.26]
Recent quitters	-32.39 [-71.00,6.23]	-33.20 [-71.39,4.98]	-0.07 [-.34,0.20]	-0.04 [-0.22,0.29]
Consistent minimal or non-smokers	Reference	Reference	Reference	Reference

¹ Analysis restricted to HIV LIVE cohort. No. observations was 1974. **All p values>0.05**

² Adjusted for CD4 count at previous visit, ART status, age, time, and alcohol use

³ Adjusted for HVL at previous visit, ART status, time and depressive symptoms