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Baseline cigarette smoking status as a predictor of virologic suppression and CD4 cell count during one-year follow-up in substance users with uncontrolled HIV infection

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Abstract

Cigarette smoking is prevalent in people living with HIV/AIDS (PLHIV) who abuse alcohol and/or illicit substances. This study evaluated whether smoking is predictive of virologic non-suppression (>200 copies/mL) and low CD4 count (<200 cells/mm³) during 1-year follow-up in medically hospitalized, substance-using PLHIV recruited for a multi-site trial. Smoking status was assessed with the Heaviness of Smoking Index (HSI). Analyses revealed that, controlling for baseline differences and adherence to antiretroviral therapy, non-smokers (n=237), compared to smokers scoring in the medium-to-high range on the HSI (n=386), were significantly more likely to achieve viral suppression (OR=1.50, 95% CI 1.02, 2.20). There was a significant smoking-by-time interaction for CD4 cell count ($\chi^2(1)=4.08$, $p<.05$), with smokers less likely to have low CD4 count at baseline and 6-month follow-up, but more likely to have low CD4 count at 12-month follow-up. The results suggest that smoking may play a role in immunological functioning in HIV-infected substance users.

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Compliance with Ethical Standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Keywords

Tobacco; HIV; substance abuse; virologic suppression

INTRODUCTION

Cigarette smoking is prevalent in people living with HIV/AIDS (PLHIV) (1–3) and has been found to be significantly associated with viral load and CD4 cell count in some (4–7), but not all studies (8, 9). Evidence that smoking increases viral load through a direct biological effect (10–13) suggests the importance of providing smoking-cessation treatment as part of HIV care. However, two key confounds, which could largely account for the poorer immunological functioning observed in PLHIV who smoke, have been identified. First, there is evidence that cigarette smoking is associated with lower adherence to antiretroviral therapy (ART) (14, 15), which could account for the observed poorer immunological functioning. Second, some research has found that substance use (16), including the use of opioids (17, 18), cocaine (19, 20), and alcohol (21, 22), is associated with accelerated HIV progression and is more prevalent in smokers (1, 23) and, thus, could help account for the association.

It is therefore important that clinical research control for these potential confounds when evaluating the association between cigarette smoking and immunological functioning in PLHIV, as done in studies by Feldman et al. (5) and Hile et al. (4). Feldman and colleagues conducted a multi-year longitudinal study in a sample of women with HIV and found that, in analyses controlling for ART adherence, substance use, and other potential confounding factors, ART was less effective in improving immunological functioning in cigarette smokers than non-smokers as assessed by viral load and CD4 cell count (5). Of interest, cigarette smokers initially had higher CD4 cell counts than non-smokers but this changed during the course of ART treatment such that smokers had significantly lower CD4 cell counts than non-smokers at follow-up (5). In a recently completed, large (N=14,000), retrospective chart review by Hile and colleagues (4), analyses controlling for the receipt of ART, the use of other substances, and other potential confounds, revealed a significant association between cigarette smoking and low CD4 cell count (<200 cells/mm³) and viral non-suppression (> 200 copies/mL).

To our knowledge, a similar analysis has not been conducted in a sample of PLHIV specifically selected for active substance use. The present paper reports findings from a secondary analysis of the National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) CTN-0049 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01612169): NCT01612169) dataset, a trial which tested interventions to reduce viral load in a sample of hospitalized PLHIV using substances (24). This secondary analysis was designed to test our hypothesis that, in substance-using PLHIV, baseline smoking status would predict unsuppressed viral load (> 200 copies/mL) and low CD4 cell count (<200 cells/mm³) during the 12-month follow-up period when controlling for other substance use and ART adherence.

METHODS

Study Design

Details of CTN-0049 are provided elsewhere (24). The study was an intent-to-treat, 3-group randomized controlled trial with follow-up visits at 6- and 12-months post-randomization; the primary outcome was viral suppression at 12 months post-randomization. Participants were recruited from 11 study sites and randomly assigned in a 1:1:1 ratio to receive: 1) 6 months of patient navigation, 2) 6 months of patient navigation plus financial incentives, or 3) treatment as usual. Patient navigation included up to 11 sessions of care coordination with case management and motivational interviewing with the goal of increasing linkage to substance use disorder treatment and HIV care. Financial incentives (up to \$1160) were provided for increased engagement in HIV care and substance use disorder treatment, reduced substance use, and improved HIV outcomes. Treatment as usual participants received the site's standard intervention for linking patients to outpatient HIV care and substance use disorder treatment. Hospital staff, including social workers, case managers, attending physicians, and infectious diseases consultants, were typically responsible for scheduling an outpatient HIV care appointment. The most common practice for linkage to substance use disorder treatment was written referral. Participants were reimbursed up to \$210 for completing research-related activities.

Participants

Participants were recruited from 11 hospitals located in the following U.S. cities: Atlanta, Georgia; Baltimore, Maryland; Boston, Massachusetts; Birmingham, Alabama; Chicago, Illinois; Dallas, Texas; Los Angeles, California; Miami, Florida; New York, New York; and Philadelphia and Pittsburgh, Pennsylvania. Eligible participants were at least 18 years of age, English speaking, medical inpatients with HIV infection who signed a medical record release. To be eligible, participants were required to: 1) self-report, or have medical record documentation of, any illicit opioid (e.g., including misuse/abuse of prescription opioids), illicit stimulant, or heavy alcohol use as determined by the Alcohol Use Disorders Identification Test (AUDIT-C) (25) within the past year; 2) meet one of the following requirements: had an AIDS-defining illness; had a CD4 cell count less than 350 cells/mm³ at their most recent screen and a viral load of > 200 copies/mL within 6 months; or had a CD4 cell count within 12 months that was 500 cells/mm³ or less and their viral load was more than 200 copies/mL (or their viral load was unknown with clinical indicators that the patient was likely to have a detectable viral load); 3) had functional status of 60 or higher on the Karnofsky performance scale; and 4) lived in the area of the site and provided locator information.

Measures

All measures included in this secondary analysis were obtained at baseline and 6- and 12-month follow-up. At baseline, cigarette smoking status was assessed using the Fagerström Test for Nicotine Dependence (26, 27) modified to include "Do you currently smoke cigarettes?" as an initial question. Participants who responded "no" to the initial question were scored as non-smokers. Smoking severity for those responding "yes" was assessed with the Heaviness of Smoking Index (HSI), which is comprised of two items (time to first

cigarette after waking; number of cigarettes per day) from the Fagerström Test for Nicotine Dependence (26, 27). The HSI score has a range of 0–6, with cut-offs for low (0–1), medium (2–4), and high (5–6). Viral load and CD4 cell count were measured by local laboratories. HIV medication adherence was measured by self-report as the percentage of pills taken in the last 30 days (28); “high adherence” was defined as self-reporting taking 90% of prescribed ART. Illicit substance use was assessed using the substance module of the Addiction Severity Index (29, 30). Alcohol use was assessed with the AUDIT-C (25).

Data analysis

The present secondary analysis was not specifically outlined in the parent trial (CTN-0049) but was delineated prior to being conducted. The CTN-0049 trial included 801 randomized participants. Past research suggests that effects of smoking on viral load and CD4 cell count may not be found in light smokers (31). Hence, the present analyses compared participants self-reporting no smoking at baseline (n=237) to participants scoring in the medium-to-high range on the HSI (n=386). The remaining 178 CTN-0049 participants (who were light smokers) were excluded from the analyses. Demographic characteristics of the smoking and non-smoking groups were compared using Pearson’s chi-square, t-tests, and the Wilcoxon test. We then used Generalized Estimating Equation (GEE) models to evaluate whether there was a difference in rates of follow-up across the smoking groups. GEE was also used to evaluate the associations between smoking status and the outcomes of unsuppressed viral load (> 200 copies/mL) and low CD4 cell count (<200 cells/mm³) at the 6th and 12th month follow-up. Variables showing significant differences across smoking status in the descriptive analyses, the CTN-0049 treatment arm (i.e., patient navigation, patient navigation plus incentives, or treatment as usual), baseline low CD4 cell status, baseline viral suppression status, and ART adherence were included in the GEE model as control variables. As reported in the study results, the groups did not significantly differ in the proportion of missing data; all observed data were included in the analyses such that participants with missing data at a particular time point had only that time point excluded from the analysis. Analyses were performed using SAS statistical software (Version 9.3; SAS Institute, Cary, NC). All tests were performed at a significance level of 0.05.

RESULTS

Sample Characteristics

Table I provides participant characteristics as a function of baseline smoking status. The 623 participants were approximately 44 years of age, 68% were male, and 72% were African American. A greater proportion of smokers, compared to non-smokers, were female, had a lower level of educational achievement, and were less likely to be employed. A greater proportion of smokers, compared to non-smokers, used illicit drugs, including both stimulants and non-stimulants. At baseline, non-smokers were more likely to have a low CD4 cell count and to have met lifetime criteria for an AIDS defining illness relative to smokers. These differences were controlled for in the analyses. The results of a GEE analysis revealed no statistically significant group differences on proportion of missing data across the two follow-up times ($\chi^2(1)=2.4$, $p=0.12$). At 6-month follow-up, 88.9% of smokers and 88.6% of non-smokers completed the visit. At 12-month follow-up, 82.1% of

smokers and 83.1% of non-smokers completed the visit. Frequency counts revealed little change in smoking status between baseline and 12-month follow-up, with 3.84% of baseline smokers becoming non-smokers and 6.47% of baseline non-smokers scoring in the medium/high range of the HSI at 12-month follow-up.

Viral Load Suppression

The results of a GEE analysis revealed a statistically significant effect for baseline smoking status across both follow-up time points (OR=1.50, 95% CI 1.02, 2.20) and a non-significant smoking-by-time interaction effect ($\chi^2(1)=1.17$, $p=0.28$) on viral load suppression. As can be seen in Figure 1, more smokers were not virally suppressed at the 6- and 12-month follow-up assessments than non-smokers.

Low CD4 Count

The results of the GEE analysis revealed a non-significant effect for baseline smoking status (OR=0.83, 95% CI 0.48, 1.41) and a statistically significant baseline smoking-by-time interaction effect ($\chi^2(1)=4.08$, $p<0.05$) for low CD4 cell count over the 12-month follow-up. As can be seen in Figure 2, a higher proportion of non-smokers, relative to smokers, met criteria for low CD4 count at baseline and 6-month follow-up, but at 12-month follow-up this reversed with more smokers meeting criteria for low CD4 count.

DISCUSSION

This secondary analysis of the CTN-0049 dataset tested the hypothesis that, in PLHIV who use substances, baseline smoking status would predict poorer virologic and immunological response as measured by lack of viral load suppression (> 200 copies/mL) and low CD4 cell count (<200 cells/mm³) during a 12-month follow-up period when controlling for ART adherence, other substance use, and other potential confounding factors. Consistent with our hypothesis, baseline smoking status was a significant predictor of not achieving virologic suppression during follow-up, with smokers being less likely to be suppressed at 6- and 12-month follow-up. For low CD4 cell count, there was a significant smoking-by-time interaction, with smokers more likely to have high CD4 cell count at baseline and 6-month follow-up but more likely to have low CD4 cell count at 12-month follow-up. The latter finding is consistent with a study by Feldman and colleagues (5) which found that female PLHIV smokers were healthier than non-smokers initially but, over the course of ART, non-smokers evidenced significantly greater benefits as reflected in both CD4 cell count and viral load compared to smokers.

In the current era of ART, smoking in PLHIV is associated with significant morbidity and mortality (32–36), with a recent study estimating that the risk of death associated with smoking is greater than 60% for PLHIV (37). The potential mechanisms accounting for the worse outcomes are unclear and may include lower ART receipt/adherence and the impact of other substance use (4). The present study adds to evidence from clinical studies finding an association between cigarette smoking and immunologic response when controlling for ART adherence and other substance use (4, 5). However, other research evaluating this potential association has failed to find a significant effect for smoking on viral load and CD4 cell

count. For example, no evidence of an association between HIV progression and smoking was found in a sample of PLHIV who had a history of alcohol abuse (9). The discrepant findings may reflect the impact of factors that have not been assessed. For example, there is evidence that oxidative stress, which is an imbalance between reactive oxygen species and antioxidant defense, may play a role in HIV progression (10, 38–41). While cigarette smoking is associated with a significant increase in oxidative stress (42–45), not all smokers evidence an increase (45). Hence, the negative impact of smoking on immunological function in PLHIV may, for example, be limited to those experiencing a significant increase in oxidative stress resulting from cigarette smoking.

In addition to the potential negative impact on immunological functioning, cigarette smoking is a significant concern due to its prevalence in PLHIV. An estimated 40 – 60% of PLHIV smoke (46), a rate two to three times higher than the general population (47). Of the 801 participants randomized into CTN-0049, 70.4% reported being cigarette smokers; this elevated rate is consistent with the greater prevalence of smoking in substance using patient populations (48). The interventions tested in CTN-0049 were designed to engage the participants in substance use disorder treatment. Unfortunately, smoking-cessation is not a priority in most substance use disorder treatment programs (49) and, not surprisingly, very few of the participants in the present study stopped smoking between baseline and 1-year follow-up (3.84%). A recent review revealed that there has been limited research on effective smoking-cessation interventions for PLHIV and noted the importance of addressing this research gap (50). The present findings serve to reinforce the importance of addressing this gap in future research.

The present study has several strengths and a few limitations. First, the parent trial was conducted at 11 sites, which enhances the generalizability of the results, and included a relatively large sample of substance-using PLHIV. A limitation is that the findings are correlational in nature and, thus, cause and effect determinations cannot be made. In addition, smoking may be related to other potential confounding factors that could not be accounted for in the models; these factors could include baseline differences that, while controlled for in the model, could still impact the outcomes of interest. Another limitation is the use of self-report, which is open to social desirability and other biases, for both smoking status and level of ART-adherence.

In conclusion, the results of this exploratory analysis suggest that smoking may play a role in immunologic response in HIV-infected substance users. Future research to replicate this finding and to delineate the potential mechanisms by which smoking may affect HIV progression seems warranted.

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Figure 1. Proportion of participants not virally suppressed (>200 copies/mL) $\pm$ SE (model implied) as a function of baseline smoking status and time.

Figure 2.
Proportion of participants with low CD4 cell count (<200 cells/mm³) $\pm$ SE (model implied)
as a function of baseline smoking status and time

Table 1
Participant demographic and baseline characteristics as a function of baseline smoking status

	Non-smoker (N=237)	Smoker ^a (N=386)	Total (N=623)	Group Analysis Statistic ^b	P value
Age, mean (SD), years	44.1 (10.7)	44.2 (9.7)	44.1 (10.1)	T=-0.14	0.8864
Gender, female	65 (27.4)	136 (35.2)	201 (32.3)	$\chi^2=4.10$	0.0430
Race/ethnicity				$\chi^2=6.04$	0.1096
African American	170 (72.3)	277 (71.8)	447 (72.0)		
Caucasian	21 (8.9)	56 (14.5)	77 (12.4)		
Hispanic	29 (12.3)	36 (9.3)	65 (10.5)		
Other	15 (6.4)	17 (4.4)	32 (5.2)		
Education				$\chi^2=27.63$	<0.0001
<High school	72 (30.4)	182 (47.2)	254 (40.8)		
High school, GED	78 (32.9)	130 (33.7)	208 (33.4)		
>High school	87(36.7)	74 (19.2)	161 (25.8)		
Marital status				$\chi^2=3.41$	0.1814
Married or cohabitating	27 (11.4)	49 (12.7)	76 (12.2)		
Separated/divorced/widowed	46 (19.4)	97 (25.1)	143 (23.0)		
Never married	164 (69.2)	240 (62.2)	404 (64.8)		
Employment status				$\chi^2=20.05$	0.0002
Working	43 (18.1)	27 (7.0)	70 (11.2)		
Unemployed	78 (32.9)	143 (37.0)	221 (35.5)		
Disabled	105 (44.3)	204 (52.8)	309 (49.6)		
Other status	11 (4.6)	12 (3.1)	23 (3.7)		
Substance use eligible ^c					
Alcohol use eligible	140 (59.1)	220 (57.0)	360 (57.8)	$\chi^2=0.26$	0.6104
Drug use eligible	150 (63.3)	325 (84.2)	475 (76.2)	$\chi^2=35.43$	<0.0001
Stimulant use	139 (58.7)	301 (78.0)	440 (70.6)	$\chi^2=26.45$	<0.0001
Non-stimulant use	125 (52.7)	277 (71.8)	402 (64.5)	$\chi^2=23.21$	<0.0001
Currently take antiretrovirals	101 (55.5)	169 (56.0)	270 (55.8)	$\chi^2=0.01$	0.9204
High ART adherence ^d	41 (17.5)	50 (13.0)	91 (14.7)	$\chi^2=2.35$	0.1257

	Non-smoker (N=237)	Smoker ^a (N=386)	Total (N=623)	Group Analysis Statistic ^b	P value
AIDS defining illness	113 (48.9)	142 (37.9)	255 (42.1)	$\chi^2=7.16$	0.0074
HIV viral load ^c	60.5 (13.6–228.0)	53.7 (6.7–218.2)	55.5 (7.8–221.9)	W=70129.50	0.3691
HIV viral load >200 copies/mL	211(89.0)	347 (89.9)	558 (89.6)	$\chi^2=0.12$	0.7311
CD4 count <200 cells/mm ³	171 (72.2)	248 (64.2)	419 (67.3)	$\chi^2=4.16$	0.0413
CTN-0049 Treatment arm				$\chi^2=3.73$	0.1550
Patient navigation	83 (35.0)	122 (31.6)	205 (32.9)		
Patient navigation+ financial	67 (28.3)	138 (35.8)	205 (32.9)		
Treatment as usual	87 (36.7)	126 (32.6)	213 (34.2)		

Note: Where not specifically indicated, numbers represent number (%).

^aSmoker=Participants scoring in the medium-to-high range on the Heaviness of Smoking Index;

^bT= t test value; W=Wilcoxon two-sample test statistics value.

^cTo be substance use eligible the patient had to be alcohol-use eligible (Alcohol Use Disorders Identification Test (AUDIT)-C score of 3 for women and 4 for men) or drug-use eligible (used stimulants or opiates within the past 12 months);

^dSelf-report taking 90% of prescribed ART;

^eMedian (Q25–Q75).