Published in final edited form as:

J Acquir Immune Defic Syndr. 2015 December 1; 70(4): 400–405. doi:10.1097/QAI.0000000000000759.

Elevated soluble CD14 and lower D-dimer are associated with cigarette smoking and heavy episodic alcohol use in persons living with HIV (PLWH)

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Abstract

Background—Persons living with HIV (PLWH) are at increased risk for cardiovascular disease in part due to persistent inflammation and coagulation activation.

Methods—We examined whether smoking and heavy episodic alcohol use (defined as 5 or more drinks on one occasion) were associated with greater monocyte activation (sCD14) and coagulation (D-dimer) in participants in the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (the ‘SUN’ Study), a prospective observational cohort.

Results—Using regression analysis ($n = 689$), current smoking compared with nonsmoking was associated with significantly elevated sCD14 ($B = 135.57$, 95% CI (84.95, 186.19), $p < .001$); whereas heavy alcohol use compared to non-heavy use was associated with significantly lower D-dimer levels ($B = -.059$, 95% CI ($-.102$, $-.016$), $p = .007$).

Conclusions—Smoking cessation should be encouraged by HIV care providers to improve mortality outcomes from all causes of death, particularly cardiovascular disease.

Keywords

Alcohol; smoking; HIV; biomarkers; cardiovascular disease; sCD14; D-dimer

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Conflicts of Interest: The authors have no conflicts of interest to disclose.

This work was presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, MA, March 3–6, 2014.

DISCLAIMER: The findings and conclusions from this review are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

INTRODUCTION

In the United States, persons living with HIV (PLWH) are at increased risk for cardiovascular disease (CVD) when compared with the general population^{1–3}. Among uninfected persons and HIV-infected adults, biomarkers of monocyte activation (soluble CD14 [sCD14]) and altered coagulation (D-dimer) have been independently associated with increased risk for myocardial infarction, coronary heart disease, and all-cause mortality^{4–10}. Cigarette smoking, a traditional risk factor for cardiovascular disease, is more prevalent among HIV-infected adults^{11–14}. Also, PLWH tend to drink more heavily than uninfected adults in the general population, with reported rates of heavy or hazardous drinking of 5% to 33%¹⁵. Behavioral risk factors (such as smoking and alcohol use) may contribute to excess CVD and mortality risk partly through inflammation and coagulation effects, thereby further complicating the effects of HIV infection on these same pathways^{16–21}.

Prior studies have demonstrated that elevated sCD14, a marker of monocyte activation, is an independent predictor of mortality in those infected with HIV^{10,22–23}. Sandler et al. showed that HIV-infected adults with sCD14 levels in the highest quartile had a 6-fold higher risk of death compared with those in lower quartiles¹⁰. Additionally, elevated D-dimer levels have been associated with overall mortality^{8, 24}. In a study of more than 1300 HIV-infected individuals, Justice et al. found that adding D-dimer and sCD14 levels to the VACS Index improved prediction of mortality²⁵. Furthermore, elevated D-dimer has been independently associated with and predictive of incident CVD in HIV-infected persons in recent analyses^{7, 18}. Elevated D-dimer levels have been associated with vascular dysfunction, indicated by impaired small artery elasticity (a marker of early vascular disease and future clinical risk) and increased plasma markers of endothelial function⁴. In a recent prospective study, sCD14 was associated with increased carotid artery intima-media thickness²⁶; however a cross-sectional study found dissimilar results²⁷.

The presence of HIV infection itself is related to elevated levels of inflammatory biomarkers. An increased prevalence of elevated sCD14 and D-dimer levels has been associated with ongoing HIV viral replication (HIV viral loads greater than 500 copies/mL) and the degree of immunodeficiency (notably CD4 T-cell counts below 200 cells/mm³)^{22, 28–30}. To date, the effect of behavioral factors such as current cigarette smoking and heavy episodic alcohol use on sCD14 and D-dimer levels in PLWH has not been examined. In PLWH, cigarette smoking and heavy alcohol use independently have been associated with increased cardiovascular risk^{17,19}. Examining whether cigarette smoking or heavy episodic alcohol use are associated with higher levels of inflammatory biomarkers predictive of CVD risk may increase our understanding of the pathogenesis of increased CVD risk among PLWH. The purpose of this study was to explore whether behavioral factors (cigarette smoking and heavy episodic alcohol use) influence the same pathways (e.g., inflammation and coagulation) that are believed to contribute to HIV-related CVD risk in the Study to Understand the Natural history of HIV and AIDS in the era of effective therapy (SUN Study)³¹.

METHODS

The SUN study is a prospective observational cohort study of 700 HIV-infected participants enrolled from seven clinics in four US cities: Denver, CO, Minneapolis, MN; Providence, RI; and St. Louis, MO. Enrollment took place between March 2004 and June 2006.

Informed consent was obtained from all study participants, and the study was approved and has been renewed annually by the institutional review boards of all participating institutions and the CDC. The cohort and detailed study methodology have been described elsewhere³¹.

Participants

Clinic patients were eligible for enrollment if they were capable of providing informed consent, and naïve to antiretroviral therapy (ART) at the time of enrollment, or if their prior ART exposure had consisted of three nucleoside reverse transcriptase inhibitors or three drugs from at least two classes. Also, participants had to be at least 18 years of age, have documented HIV infection, have attended at least two appointments at the clinic of enrollment, and expected to live for at least two years. Patients were excluded if they were pregnant or incarcerated, expected to survive less than 2 years, or had an AIDS-defining illness, or received chemo- or immune-modulating therapy in the preceding 60 days.

Procedure

Briefly, at baseline and every 6 months thereafter, data were collected through physical examination, audio computer-assisted self-interview (ACASI), non-invasive imaging, laboratory examination and medical chart abstraction. Clinical and laboratory data, such as height, weight, CD4 lymphocyte counts and HIV viral loads, were collected and recorded at baseline. Basic demographic information and medication lists were extracted from the medical record and entered into an electronic database, using Clinical Practice Analyst software (Cerner Corporation, Kansas City, Missouri). Participants completed an ACASI at enrollment, which captured data related to employment status, adherence to ART, use of tobacco, alcohol, and recreational drugs, and sexual activity. Blood and urine specimens were also collected.

Measures

ACASI variables—A substance use history was obtained via self-report at baseline. Smoking status was assessed as *currently smoking* or *ever smoked tobacco*. Each participant was asked, “Do you currently smoke cigarettes; how many cigarettes do you smoke each day; and, how many years have you smoked”. Each participant was subsequently asked, “How many times during the past 30 days did you have five or more drinks on an occasion”, with an answer of one or more defining a *heavy alcohol month*. A drink was defined for participants as one standard drink: 1.5 fluid ounces of liquor, 5 ounces of wine, or 12 ounces of beer or wine cooler (consistent with NIAAA definitions).

Serum biomarkers—At study entry, fasting whole blood and plasma specimens were collected and shipped overnight to the CDC. All specimens were stored in liquid nitrogen at -70°C until analyzed. Soluble CD14 was measured using an ELISA-based assay (R&D Systems, Minneapolis MN). D-dimer was measured at the Diabetes Research and Training

Center Radioimmunoassay Core Laboratory at the Washington University School of Medicine, using the Roche Diagnostics, (Indianapolis IN) immunoturbidometric assays on a Hitachi 917 analyzer.

Data Analysis

Descriptive statistics including means, standard deviations and proportions were calculated to describe the study sample. Soluble CD14 was normally distributed, however, D-dimer was square root transformed to reduce skewness. Pearson correlation coefficients were used to examine associations between serum biomarkers and continuous demographic and clinical variables. Chi square analysis was used to examine categorical variables. Multiple linear regression analyses examined serum biomarker levels associations as a function of current cigarette smoking and heavy alcohol use, with non-smokers and non-heavy drinkers as the reference group, and controlling for age, race, gender, current CD4 T-cell count, HIV viral load, and Hepatitis C status. Two-tailed tests with an alpha of .05 were used to test for statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 21.0.

RESULTS

Demographic and serum biomarker data were available for 689 participants at baseline. Baseline demographic and clinical characteristics are presented in Table 1 as means $\pm$ standard deviations for continuous variables, or as proportions for categorical variables. Of the 689 participants, 292 (43%) reported having smoked cigarettes in the past 30 days and the mean number of cigarettes per day (CPD) was 13.67 (SD 9.2). One hundred ninety-four (28.9%) participants reported at least one heavy drinking day in the past month; of these, 106 (54.6%) were current smokers, while 88 (45.4%) were nonsmokers ($X^2(1) = 14.3, p < .001$). Cigarette smokers, compared with nonsmokers, were more likely to be male (72.6% vs. 27.4%, $p = .04$), have lower mean body weight (171.3 lbs. vs. 181.1, $p = .002$), have less than a high school education (17.2% vs. 8.3%, $p < .001$), have higher triglyceride levels (191.3 vs. 165, $p = .02$), and be HCV positive (9.2% vs. 4.3%, $p < .001$). Heavy alcohol users, compared with non-heavy users, were more likely to be male gender (85.1% vs. 14.9%, $p = .001$) and report MSM as their HIV transmission risk category (70.6% vs. 29.3%, $p = .004$).

The mean plasma sCD14 level in the sample was 1188.35 $\mu\text{g/mL}$ (± 332.7). Soluble CD14 levels were significantly and positively correlated with D-dimer ($r(672) = .097, p = .011$), and with age ($r(679) = .115, p = .003$). In unadjusted analyses, sCD14 levels were significantly higher for current smokers (1258.8, $SD = 360.4$) compared with nonsmokers (1133.8, $SD = 302.6$), $t(662) = -4.74, p < .001$. However, among smokers, there was not a significant correlation between CPD and sCD14 ($r = .11, p = .06$). Soluble CD14 levels were significantly higher in persons on ART at baseline (1213.9, $SD = 335.4$) compared with those not on ART (1090.1, $SD = 315.3$; $t(662) = -3.87, p < .001$), and persons with a baseline CD4 T-cell count less than 200 (1366.6, $SD = 385.4$) compared with those with a baseline count of greater than 200 (1168.1, $SD = 320.3$; $t(676) = 4.17, p < .001$). Women

had significantly higher sCD14 levels (1268.76, *SD* 344.77) compared with men (1163.66, *SD* 325.33; $t(679) = 3.52, p < .001$).

Mean plasma D-dimer level in the sample was 0.21 $\mu\text{g/mL}$ (± 0.29). D-dimer levels were significantly lower for those with heavy alcohol use in the preceding month (0.343, *SD* = 0.22) compared with no heavy alcohol use (0.395, *SD* = 0.26; $t(645) = 2.40, p = .01$). D-dimer was inversely and significantly associated with the average number of drinks per drinking day ($\rho = -0.11, p = .007$), the number of drinking days per month ($\rho = -.12, p = .002$), and the number of times per month that participants had 5 or more drinks on a drinking day ($\rho = -0.089, p = .02$). D-dimer levels were lower for those currently on ART (0.19, *SD* = 0.28) compared with those not taking ART (0.29, *SD* = 0.29; $t(653) = 3.77, p < .01$), and those with undetectable HIV viral load (0.34, *SD* = 0.25) compared with detectable viral load (0.44, *SD* = 0.25; $t(670) = -4.87, p < .001$). Women had significantly higher D-dimer levels (0.47, *SD* = 0.24) compared with men (0.35, *SD* = 0.25; $t(670) = 4.98, p < .001$). D-dimer was not associated with participant age ($r(670) = .019, p = .62$).

Using regression analyses (Table 2), controlling for age, race, gender, current CD4+ T-cell count, HIV viral load, and HCV status, current smoking was significantly associated with elevated sCD14 levels ($B = 135.57$, 95%CI [84.95, 186.19], $p < .001$), but not with D-dimer levels ($B = .023$, 95% CI [-.016, .063], $p = .24$). By contrast, heavy alcohol use (compared to non-heavy use) was associated with significantly lower D-dimer levels ($B = -.059$, 95%CI [-.102, -.016], $p = .007$), but not with sCD14 levels ($B = -6.11$, 95% CI [-61.23, 49.01], $p = .82$). Exploratory analyses indicated that there was no significant interaction between smoking and heavy alcohol use ($p = .88$ for sCD14; $p = .35$ for D-dimer).

Lastly, we dichotomized each biomarker as high versus low where “high” was defined as being in the highest quartile, with the lower three quartiles collapsed as “low”. Among smokers, 59% ($n = 98$) were classified as having high sCD14 levels, and high sCD14 remained strongly associated with current smoking status ($X^2(1) = 21.6, p < .001$). Only 24% ($n = 43$) of participants who had a heavy drinking month had high D-dimer levels and, heavy alcohol use remained associated with lower D-dimer ($X^2(1) = 3.78, p = .05$).

DISCUSSION

To our knowledge, this is the first and only study to examine the association of cigarette smoking and heavy episodic alcohol use with markers of monocyte activation and altered coagulation in a contemporary cohort of PLWH. Our results indicate that smoking was significantly associated with elevated sCD14, independent of age, CD4 T-cell count, and HIV viral load. Conversely, we found that heavy episodic alcohol use in the past month was associated with lower levels of D-dimer, a marker of thrombosis. The development of cardiovascular disease is a dynamic process, and these data may not only lend insight into the pathogenesis of CVD in PLWH but also highlight the importance of curtailing known CVD risk-related behaviors, such as cigarette smoking.

In the general population, smoking has been associated with higher levels of sCD14. Regueiro and colleagues (2009) reported that elevated sCD14 levels were detected in the

bronchial alveolar lavage fluid of smokers and postulated that cigarette smoke activated the production of sCD14 by airway epithelial cells leading to increased inflammation³². It is known that cigarette smoke contains high levels of noxious substances known to induce inflammation and endothelial dysfunction, contributing to the pathogenesis of CVD³³. Our study is the first to demonstrate that smoking in PLWH is associated with elevated sCD14 levels, adding impetus to the need for smoking cessation programs for PLWH.

Early in the HIV epidemic, elevated sCD14 levels were associated with death and a significant increase in sCD14 levels was noted in all clinical stages of HIV infection²². Notably, the elevation was more pronounced in those with an AIDS diagnosis. Soluble CD14 inversely correlated with the number of CD4 lymphocytes ($r = .66$) and a highly significant correlation was noted between sCD14 levels and HIV viral load ($r = .69, p < .001$). Immune activation, marked by elevated sCD14 levels, is a known strong predictor of HIV disease progression²³ and an independent predictor of mortality¹⁰.

More recently as PLWH achieve near normal lifespans, elevated sCD14 has been linked to an increased risk for cardiovascular events. Soluble CD14 has been linked to subclinical atherosclerosis progression²⁶, and impaired endothelial function in those on prolonged ART³⁴. Further, it has been suggested that persistent HIV-induced microbial translocation (leading to monocyte activation) contributes to arterial dysfunction and the increased CVD risk seen in individuals on long-term ART³⁴. Soluble CD14 has been independently associated with elevated blood pressure and Manner and colleagues suggest that microbial translocation may be related to the development of hypertension³⁵. While the initiation of ART has been shown to reduce sCD14 levels over time³⁶, evidence demonstrates that sCD14 levels do not normalize to levels of uninfected controls³⁷, leaving PLWH in a state of persistent immune activation. Addressing modifiable CVD risk behaviors such as smoking becomes paramount to the efforts to reduce CVD risk in PLWH.

We found that heavy episodic alcohol use was associated with significantly lower D-dimer levels. Yarnell and colleagues also found that alcohol use (to levels of greater than 230 ml per week) were associated with lower D-dimer levels, although the relationship was not statistically significant³⁸. D-dimer is a marker of activated coagulation and thrombosis and has been associated with vascular dysfunction and CVD^{4, 7}. Ingestion of moderate doses of alcohol have been shown to have little effect on coagulation factors, and D-dimer can be elevated in states of chronic inflammation such as HIV infection. Van Golde et al. found that alcohol had no effect on the coagulation pathway for 15 hours following consumption, even at dosages of 62.5 and 125 grams³⁹. Chronic moderate alcohol consumption, in general, seems to lower fibrinogen concentration while the effects on other coagulation factors remain inconclusive. Moderate alcohol consumption is considered to be protective for CVD^{40–42} and all levels of intake greater than 2.5 g/day have been shown to provide similar degrees of risk reduction for coronary heart disease outcomes. Alcohol consumption has been associated with a lower risk for coronary heart disease, with relative risk of about 0.75⁴³. The clotting/fibrinolysis system has a strong circadian rhythm with decreased fibrinolytic activity noted in the morning; also, coagulation biomarker activity is temporally related to alcohol ingestion⁴⁴ and both factors may have affected our results. The cardioprotective effects of alcohol may also be related to reduction of coagulation factors

rather than to the augmentation of factors related to fibrinolysis^{39, 45}. Finally, some of the “protective effect” of alcohol use might be due to confounding related to other health behaviors, in that moderate drinkers may tend to exercise more frequently, and in general have healthier lifestyles compared with heavy alcohol users. The interaction of alcohol, liver disease and coagulation is a complex and dynamic process and the relationship between alcohol use and biomarker activity in PLWH requires further investigation.

Although smokers in our study had numerically higher levels of D-dimer than non-smokers, this difference was not statistically significant. In healthy HIV-infected adults, biochemically verified smoking cessation has been demonstrated to significantly diminish D-dimer levels at 6- and 12- months post-cessation (but not at 2-months)⁴⁶. Studies have shown that approximately 10 years is required to see a 50% reduction in some inflammatory markers after smoking cessation, and about 20 years to reverse to levels seen in nonsmokers^{47–48}.

Our results demonstrate an effect of age and gender on biomarkers of inflammation. In our study, women had significantly higher levels of sCD14 and D-dimer compared with men, and sCD14 levels were strongly correlated with age. Other studies have found that HIV-infected women had significantly elevated plasma levels of sCD14 compared with uninfected women⁴⁹, and elevated D-dimer levels compared with HIV-infected men⁵⁰. HIV-uninfected women have also been shown to have higher mean sCD14 compared with uninfected men⁹, perhaps suggesting that aging women in general may be at increased risk for developing CVD. Some have speculated that aging HIV-infected women (who are on ART and virologically suppressed) continue to maintain a status of immune activation and subsequently are at increased risk of inflammation-related comorbidities compared with uninfected age-matched controls⁵¹.

This study has some limitations. The cross-sectional nature of the analyses precluded studying changes in biomarker levels over time and in relation to clinical outcomes. Because our smoking and alcohol data were collected at one point in time we were not able to estimate the effect of timing of cigarette or alcohol use on biomarker levels. Also, we were not able to examine causal effects of heavy alcohol use on biomarker levels. Smoking status tends to be more static, while heavy alcohol use may be more intermittent and dynamic. Lastly, our findings may have limited generalizability since the SUN study cohort was largely non-Hispanic white MSM, with a low prevalence of hepatitis C co-infection and cigarette smoking (compared with other cohorts of PLWH) and therefore may not be representative of all PLWH.

In conclusion, we found in this contemporary cohort of PLWH that current cigarette smoking appears to be associated with elevated sCD14 levels, while heavy episodic alcohol use is associated with lower D-dimer levels. Our findings support an aggressive approach in targeting traditional cardiac risk factors (such as the management of smoking cessation) for therapeutic intervention and the potential addition of biomarkers in further stratification of high-risk patients. Smoking cessation should be encouraged by HIV providers to improve cardiovascular risk and all-cause mortality outcomes among HIV-infected persons. Further

research is needed to better understand the effects of heavy episodic alcohol use on inflammation and coagulation pathways.

Acknowledgments

Sources of Funding: This work was supported by the Centers for Disease Control and Prevention contract numbers 200-2002-00610, 200-2002-00611, 200-2002-00612, 200-2002-00613, 200-2007-23633, 200-2007-23634, 200-2007-23635, and 200-2007-23636. Additional support was provided by grant number T32 DA016184 from the National Institute on Drug Abuse (Cioe), grant number K23NR014951 from the National Institute for Nursing Research (Cioe), and grant number P01 AA019072 from the National Institute on Alcohol Abuse and Alcoholism (Kahler) at the National Institutes of Health.

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Table 1

Baseline demographic, clinical, and behavioral characteristics of 689 participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy Study recruited from 2004–2006

Characteristic	
Age, years (mean $\pm$ SD)	40.9 $\pm$ 8.9
Male gender (n, %)	525 (76.2%)
Weight, lbs (mean $\pm$ SD)	176.8 $\pm$ 39.6
<u>Race/Ethnicity (n, %)</u>	
White, non-Hispanic	401 (58.2%)
Black, non-Hispanic	206 (29.9%)
Hispanic	67 (9.7%)
Other	15 (2.2%)
<u>Education (n, %)</u>	
Less than high school	82 (11.9%)
High school graduate	553 (80.3%)
Some graduate work	53 (7.7%)
<u>Transmission Risk Category (n, %)</u>	
Men who have sex with men	360 (52.2%)
<u>Laboratory Characteristics (mean $\pm$ SD)</u>	
Fasting serum total cholesterol, mg/dL	185 $\pm$ 46.6
Fasting serum LDL cholesterol, mg/dL	108 $\pm$ 36.5
Fasting serum HDL cholesterol, mg/dL	45 $\pm$ 31.7
Fasting triglycerides, mg/dL	175 $\pm$ 140.0
Hemoglobin, g/dL	14.4 $\pm$ 1.7
HIV viral load, Log10	1.38 $\pm$ 1.8
Alanine aminotransferase (ALT)	33.9 $\pm$ 25.5
<u>Clinical Characteristics</u>	
Current ART (n, %)	533 (77.4%)
Years on ART (cumulative), (mean $\pm$ SD)	3.43 $\pm$ 2.62
HIV viral load <400 copies/mL (n, %)	500 (72.6%)
Hepatitis C antibody positive (n, %)	83 (12.0%)
<u>CD4+ T-lymphocyte count (n, %)</u>	
<200 cells/mm ³	71 (10.3%)
200–500 cells/mm ³	362 (52.5%)
>500 cells/mm ³	253 (36.7%)
<u>Cigarette smoking (n, %)</u>	
Current smoker	289 (42.9%)
Ever smoked	447 (64.9%)
<u>Alcohol (EtOH) Use (n, %)</u>	
Heavy EtOH drinking day past month	194 (29%)

Table 2

Regression models of factors associated with sCD14 and D-dimer levels among 689 participants in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy Study recruited from 2004–2006.

	sCD14			D-dimer		
	Estimate	p	95% CI	Estimate	p	95% CI
Current smoking	135.57	<0.001	84.95 186.1	0.023	0.25	-0.016 0.064
CD4+ T-cell count	-0.25	<0.001	-0.34 -0.15	0.00	0.95	0.00 0.00
Undetectable VL	-36.84	0.26	-100.45 26.78	-0.11	<0.001	-0.16 -0.07
Heavy month	-6.11	0.83	-61.23 49.01	-0.06	0.007	-0.10 -0.02
Race	-10.81	0.52	-43.71 22.08	0.00	0.68	0.00 0.00
Age	4.33	0.003	1.49 7.18	0.001	0.58	-0.002 0.003

* *Heavy month* defined as five drinks on one occasion at least once in past month.