Soluble CD14 and D-dimer are Associated with Cigarette Smoking and Alcohol Use in HIV-infected Adults

Patricia A. Cioe[1], Jason Baker[2], John Hammer[3], Erna M. Kojic[4], Nur Onen[5], Pragna Patel[6], Christopher W. Kahler[1]

[1]Brown University, Center for Alcohol and Addiction Studies, Providence, RI; [2]University of Minnesota Medical School, Minneapolis, MN; [3]Denver Infectious Disease Consultants, Denver, CO; [4]Department of Infectious Diseases, Brown University; [5]Washington University, School of Medicine, St. Louis, MO; [6]Centers for Disease Control, Atlanta, GA

BROWN

Center for Alcohol & Addiction Studies

BACKGROUND

- Persons living with HIV (PLWH) are at increased risk for cardiovascular disease compared with uninfected adults (Gill et al., 2010; Sackoff et al., 2006; Triant et al., 2007).

- In the general population and among 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 (Baker et al., 2010; Ford et al., 2010; Kuller et al., 2008; Sandler et al., 2011).

- Cigarette smoking, a traditional risk factor for CVD, is more prevalent in this population (Glass et al., 2006).

- Smoking in PLWH has been associated with elevated risk of CV events as well as increased rates of pulmonary diseases and infections, lung cancers, and other malignancies (Clifford et al., 2012; Cockerham et al., 2010; Fris-Moller et al., 2003; Glass et al., 2006; Kaplan et al., 2007).

- Greater alcohol use is reported PLWH in the United States when compared with the uninfected population; reported rates of heavy or hazardous drinking of 5% to 33%, twice that of the general population (Galvan et al., 2002).

- High rates of heavy alcohol use in PLWH is associated with worse overall clinical outcomes, as well as increased mortality rates (Chander et al., 2006; DeLorenze et al., 2011; Samet et al., 2008).

OBJECTIVE

- To examine whether cigarette smoking and heavy alcohol use were associated with higher levels of sCD14 and D-dimer in PLWH to inform CVD prevention efforts.

- We hypothesized that cigarette smoking and heavy alcohol use would be associated with higher sCD14 and D-dimer levels.

METHODS

- The Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (the 'SUN' Study) was an prospective observational cohort study.

- 700 participants were enrolled between 2004 and 2006 in four U.S. cities.

- Plasma biomarkers (D-dimer and sCD14) were measured from cryopreserved samples from the SUN Study participants at baseline.

- Each participant completed a baseline audio computer-assisted self-interview (ACASI) to assess behavioral risk factors.

MEASURES

- **Smoking status:** Participants were asked: *Do you currently smoke cigarettes; How many cigarettes do you smoke each day;* and, *for how many years have you smoked?*

- **Heavy alcohol use:** Prior to evaluating drinking status, a standard drink of alcohol was defined as *one can or bottle of beer/wine cooler, one glass of wine, or one cocktail or shot of liquor.* Each participant was asked: *How many times during the past 30 days did you have five or more drinks (for males) or four or more drinks (for females) on an occasion?*

- **sCD14:** Measured using an ELISA-based assay (R&D Systems, Minneapolis MN).

- **D-dimer:** Measured at the Diabetes Research and Training Center Radioimmunoassay Core Laboratory at the Washington University School of Medicine; using the Roche Diagnostics, (Indianapolis IN) immunoturbidimetric assays on a Hitachi 917 analyzer.

DATA ANALYSES

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 21.0

- Descriptive statistics including means, standard deviations and proportions were calculated to describe the study sample
- Regression analyses examined associations between current cigarette smoking, heavy alcohol use (defined as more than 5 alcohol drinks on at least one day in the past month), and biomarkers of monocyte activation and altered coagulation.
- Two-tailed tests and 95% significance levels were used to test for statistical significance

RESULTS

Table 1. Demographics of Sample (N=689)

	Mean, SD		N, (%)
Mean Age, (years)	40.9 (8.9)	Race White/Caucasian Black Other	401 (58.2%) 206 (29.9%) 82 (11.9%)
CD4+ T cell count	489.8 (273.5)	Gender, male	525 (76.2%)
Years on ART	3.4 (2.6)	Taking ART	533 (77.4%)
T Chol	185 (46.6)	HIV plasma viral load <400 copies/mL	500 (72.6)
LDL	108.1 (36.4)	Current smoker	289 (43.2%)
sCD14	1188 (332.7)	Heavy alcohol use (>1 time/month)	194 (28.2%)
D-dimer	.209 (.288)	Hepatitis C antibody positive	83 (12.0%)

RESULTS

sCD14 levels were significantly associated with:

age	($r = .115$, $p = .003$)
current smoking	($t = 4.74$, $p = .000$)
currently on ART:	($t = -3.87$, $p = .000$)
CD4<200	($t = 4.17$, $p = .000$)

But did not differ by gender or race.

D-dimer levels were significantly associated with:

log10 VL	($r = .162$, $p = .000$)
heavy alcohol	($t = 2.51$, $p = .01$)
currently on ART	($t = 3.77$, $p = .00$)
gender	($x^2 = 153.76$, $p = .000$)

But did not differ by age or race.

Table 2. Predicting change in biomarker levels (N = 689)**

	sCD14 levels			D-dimer levels		
	B	95% CI	P value	B	95% CI	P value
Cigarette smoking	135.57	(84.95, 186.19)	.000	.024	(- .016, .064)	.23
Heavy alcohol use	-6.11	(-61.23, 49.013)	.828	- .038	(- .069, - .007)	.01

**controlling for age, race, current CD4, and viral load

CONCLUSIONS

- Current smoking appears to be associated with an elevated sCD14 level.

- By contrast, heavy alcohol use is associated with lower D-dimer levels.

- Smoking cessation should be encouraged by HIV care providers to improve cardiovascular risk and other all-cause mortality outcomes in PLWH.

- Further research is needed to better understand whether alcohol use confers a protective effect.