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

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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 the general 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 in 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 Radioimmunassay 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

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.

<p>| Table 2. Predicting change in biomarker levels (N = 689)** |
|-----------------------------------------------|-------|-------|--------|</p>
<table>
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<tr>
<th></th>
<th>sCD14</th>
<th>D-dimer</th>
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<tbody>
<tr>
<td>B</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>135.57</td>
<td>(84.95, 186.19)</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>-6.11</td>
<td>(-61.23, 49.013)</td>
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**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.

This research was supported in part by grant number T32 DA016184 from the National Institute on Drug Abuse at the National Institutes of Health (Dr. Cioe).

The authors have no conflicts of interest to disclose.

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