Article

Effects of Electronic Cigarette Use on Cardiovascular Disease-related Inflammatory Biomarkers in Smokers with HIV in a Switching Study in the United States

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Abstract: People with HIV (PWH) experience higher rates of cardiovascular events (CVEs) compared with the general population. A substantial body of evidence supports that select biomarkers of inflammation (soluble CD14 [sCD14], soluble CD163 [sCD163], highly sensitive C-reactive protein [hs-CRP], interleukin-6 [IL-6]), and coagulation (D-dimer) are elevated in PWH and related to increased rates of CVEs. Our previous work showed that smoking compared with nonsmoking was associated with significantly elevated sCD14, a biomarker of monocyte activation. We aimed to explore the effect of electronic cigarette (EC) provision on inflammatory biomarkers in PWH who smoked daily and then switched to an EC. Nineteen PWH were enrolled in a pilot study in which an EC and e-liquid were provided weekly or 8 weeks. Blood specimens for inflammatory biomarker analysis were obtained at baseline (BL) and at week 8. Biomarker levels were high at BL and did not differ significantly at week 8. There were small nonsignificant reductions in sCD163 and CRP levels. Non-significant increases in IL-6, D-dimer and sCD14 levels were also noted. Use of ECs for 8 weeks does not appear to significantly increase or decrease inflammatory biomarker levels in SWH. Further research with larger samples and a control group is needed.

Keywords: HIV; tobacco; electronic cigarettes; inflammation; biomarkers

1. Introduction

People with HIV (PWH) experience higher rates of cardiovascular events (CVEs), including myocardial infarction, compared with the general population (Rosenson et al., 2020). A substantial body of evidence supports that select biomarkers of inflammation (including soluble CD14 [sCD14], soluble CD163 [sCD163], highly sensitive C-reactive protein [hs-CRP], interleukin-6 [IL-6]) and coagulation (D-dimer) are elevated in PWH (Freiberg et al., 2016; So-Armah et al., 2016; Subramanya et al., 2019) and are related to increase rates of both CVEs and chronic lung disease (Kirkegaard-Klitbo et al., 2017). These markers remain elevated even in PWH who are effectively treated with ART (ART) and are virologically suppressed (Nou, Lo, & Grinspoon, 2016). Interventions to reduce levels of inflammatory markers in PWH are limited. While the Reprieve trial is examining the use of pitavastatin to reduce pro-inflammatory responses that may be drivers of CVEs in PWH (Gilbert, 2015), behavioral strategies to reduce inflammation in PWH (such as reduced cigarette smoking) have not been examined.

Importantly, persistent inflammation has been implicated as a contributor to excess mortality risk for PWH compared to those without HIV infection (Nordell et al., 2014; So-Armah et al., 2016). Persistent viremia in PWH has been associated with elevated levels of IL-6 and D-dimer, conferring a 2-3-fold increase in risk for CVEs in PWH . Highly sensitive C-reactive protein (hs-CRP) has been associated with a 2-fold increase in the rate of CVEs, , independent of other CVD risk factors. Finally, elevated sCD163 has been associated with

chronic lung disease in PWH independent of other risk factors (Kirkegaard-Klitbo et al., 2017).

Increased levels of inflammatory biomarkers, coagulation markers, and markers of monocyte activation (P. Cioe et al., 2015; Poudel, Poudel-Tandukar, Bertone-Johnson, Pekow, & Vidrine, 2020) have been associated with cigarette smoking in both PWH and smokers in the general population. Cioe and colleagues, using the Study to Understand the Natural history of HIV and AIDS in the era of effective therapy (SUN Study)(Vellozzi et al., 2009) dataset, found that among 700 participants, smoking (compared with non-smoking) was significantly associated with elevated sCD14 (P. Cioe et al., 2015). This association was independent of age, CD4 T-cell count, and HIV viral load. Smokers also had numerically higher levels of D-dimer (a marker of coagulation) compared with non-smokers, although this difference was not statistically significant (P. Cioe et al., 2015). A more recent study in smokers with HIV demonstrated that cigarettes per day (CPD), number of years smoked, and number of smoking pack-years were positively associated with concentrations of the hs-CRP biomarker (Poudel et al., 2020). A study of smokers in the general population found that current smoking was associated with higher sCD14 biomarker levels in lavage fluid from the smokers' bronchial alveolar space. They hypothesized that smoke from cigarettes activates sCD14 production by the epithelial cells in the airways, leading to higher levels of inflammation in smokers (Regueiro et al., 2009). Cigarette smoke contains numerous harmful substances that cause endothelial dysfunction and inflammation (Rigotti & Clair, 2013), so it is not surprising that these associations have been reported in smokers with and without HIV.

Although the literature on the effect of smoking cessation or reduction on biomarkers of inflammation among PWH is somewhat limited, biochemically-verified smoking cessation in the general population was demonstrated to significantly diminish D-dimer levels at both 6- and 12- months post-cessation (Caponnetto et al., 2011). In a second study (Kooij et al., 2016), investigators examined markers of inflammation (hs-CRP), immune activation (sCD14 and sCD163), and coagulation (D-dimer) in HIV-infected and uninfected never, former, and current smokers. Smoking was found to be independently associated with higher hs-CRP levels and lower sCD163 levels, and was associated with higher sCD14 and D-dimer levels at a trend level. No evidence of a differential effect of smoking in by HIV status was found (Kooij et al., 2016), and the investigators concluded that cigarette smoking was significantly and independently associated with the markers of inflammation and immune activation. Smoking status, not HIV status, was the differentiating factor in biomarker levels, with former smokers having biomarker levels similar to non-smokers, suggesting that smoking cessation is beneficial and may be associated with reduced inflammation and biomarker levels.

PWH smoke at much higher rates compared to the general population and unfortunately, many are unable or unwilling to quit smoking (Cooperman, 2016; Mdodo et al., 2015; Pacek & Cioe, 2015). Thus, smoking harm reduction approaches have been suggested to attempt to reduce the harmful health effects of smoking in this vulnerable population. Switching from combustible cigarettes (CCs) to electronic cigarettes (ECs) may represent one form of smoking harm reduction (National Academies of Sciences, 2018). Several studies have reported that smokers who switch from CCs to ECs report lower levels of CC use, fewer respiratory symptoms such as wheezing and mucus production (Cassidy, Tidey, & Colby, 2020; P. A. Cioe et al., 2020), and reduced rates of exacerbation of chronic obstructive pulmonary disease (Polosa et al., 2016). While the behavioral and health effects of switching from CCs to ECs in PWH have been reported (P. A. Cioe et al., 2020; J. Yingst et al., 2020), no studies to date have reported the effect of switching from CCs to ECs on biomarkers of inflammation and coagulation in PWH. The purpose of this secondary data analysis was to examine change over time in five cardiovascular disease-related biomarkers of inflammation (hs-CRP; IL-6; sCD14; sCD163) and coagulation (D-dimer) in smokers with HIV who switched from CCs to ECs for an 8-week period.

2. Methods

This paper describes a secondary data analysis. The primary study examined the feasibility and acceptability of EC provision for eight weeks to smokers with HIV who were not ready or not willing to quit smoking. The findings of the primary study have been previously described (P. A. Cioe et al., 2020). In this analysis, we examine whether any change in biomarkers of inflammation and coagulation occurred in smokers who switched from CCs to an EC.

Smokers with HIV were recruited from a large HIV clinic in the Northeast. Flyers were hung on study bulletin boards in the clinic and patients who were interested called the study center for screening. Eligibility criteria included: over 18 years old; smoked > 5 CPD for longer than one year; and exhaled breath CO level > 5ppm at baseline. Smokers were excluded if they had been hospitalized in the past month, had unstable angina of hypertension, had a substance use disorder other than nicotine, or were pregnant. Smokers were also excluded if they had plans to quit smoking in the next 30 days, were using smoking cessation therapy, or were using electronic cigarettes more than 2 days per week.

Twenty smokers living with HIV were enrolled in the open pilot study; one participant dropped out immediately after enrollment due to a new job and inability to attend study visits. An EC and e-liquid were provided weekly for 8 weeks to the remaining 19 participants. Participants were given two ce6 eGo-T electronic cigarette devices, which had a 3.3 volt, 1100 mAh battery with 6-10 1.5 Ohm, dual coil XL, 510-style cartomizer (SmokTech; Shenzhen, China). The electronic cigarette liquid had18 mg/ml nicotine per milliliter with a 30/70 PG/VG ratio. Participants were provided with enough e-liquid each week so that they did not run out between visits. Three flavor choices were available (Tobacco Row [tobacco], Arctic Blast [menthol], Mardi Gras [fruit]), and participants could select various flavors each week. E-liquid was manufactured by Avail Vapor (Richmond, VA) and was tested to ensure the concentration of the nicotine was accurate. Participants were encouraged to use the EC daily, whenever they would normally smoke a cigarette. Serum biomarkers of inflammation, coagulation, cigarette use, and carbon monoxide (CO) exposure were obtained at baseline (BL; prior to EC use) and at week 8 (end of e-liquid provision period). The study was approved by the Brown University Institutional Review Board and all participants signed a written informed consent to participate. Participants were compensated up to $260 for sessions completed.

2.1. Measures

2.2.1. Demographics and clinical characteristics

Age, sex assigned at birth, education level, employment status, race/ethnicity, and number of years living with HIV were obtained by self-report at baseline. Number of CPD, number of years smoked, and type of cigarette (menthol/regular) were also obtained by self-report. The most recent CD4 Tcell count and the HIV viral load were obtained from the medical record.

2.2.2. Exhaled carbon monoxide (CO) level

Participants were asked to provide an exhaled breath sample for CO measurement at the baseline and week 8 visits. A Bedfont Smokerlyzer ED50 meter (Bedfont Scientific, Haddonfield, NJ)was used for all CO measurements. Carbon monoxide is a product of cigarette combustion, and CO levels < 5 ppm are indicative of abstinence from CC use (Cropsey et al., 2014) .

2.2.3. Serum biomarkers

The following biomarkers of inflammation and coagulation were obtained: sCD14, a biomarker of monocyte activation, that is associated with tobacco use (P. Cioe et al., 2015), atherosclerosis(McKibben et al., 2015) and mortality in PWH; sCD163, a biomarker of monocyte/macrophage activation, which is independently associated with chronic lung disease in PWH; hs-CRP, an acute phase reactant, which has been linked to elevated

cardiovascular risk (De Luca et al., 2013; Koenig, 2013); D-dimer, a marker of coagulation, which has been shown to be elevated in PWH and has been associated with cardiac events (Armah et al., 2012; Baker et al., 2010; Freiberg et al., 2016; So-Armah et al., 2016); and IL-6, a biomarker of inflammation, which has been associated with increased rates of CVEs (Baker et al., 2010).

2.2.4. Biomarker collection and analysis

Venous blood samples were collected from participants at baseline (prior to EC use) and 8 weeks (at the end of the EC provision period). At each time point, two 10ml plasma samples were collected into BD Vacutainer tubes and placed on ice. Samples were centrifuged at 1700 g for 15 minutes. Using a p1000 pipette, a serum layer was aspirated from the centrifuged tube and stored in endotoxin-free cryovials at −80°C.   Enzyme-linked immunosorbent assays (ELISA) were used to quantify D-Dimer (Cat no, ab196269; abcam, Cambridge, MA), sCD14 (Cat no. DC140; R&D Systems, Minneapolis, MN), sCD163 (Cat no. DC1630; R&D Systems, Minneapolis, MN), hs-CRP (Cat no. DCRP00), and IL-6 (Cat no, HS600C)   following manufacturer instructions. For each sample, duplicate ELISA tests were performed using a GloMax® Discover Microplate Reader (Promega, Madison, WI).

3. Data Analysis

Paired samples t-tests were conducted and Cohen's D (mean difference / SD of the difference) was calculated, to examine whether markers of inflammation (IL-6, D-dimer, hs-CRP, sCD14, sCD163) improved significantly from BL to 8 weeks. Examination of skewness and kurtosis of changes in biomarkers did not indicate substantial departure from normality (West, 1995). One outlier (range = 3rd quartile + 3*interquartile range, 1st quartile – 3*interquartile) was identified for the IL-6 marker; significance did not change with or without the outlier included in analyses. Data presented in the results section include the outlier value.

4. Results

Data were collected from July to December 2018. The baseline demographic and clinical characteristics of the sample are shown in Table 1. All participants were on ART and 17 (89.5%) had an undetectable HIV viral load. During the 8-week intervention period, mean CPD was reduced by more than 80%, from 15.1±9.6 (M±SD) at baseline to 1.79±2.2 at week 8. CO levels decreased significantly from 15.7±7.6ppm at baseline to 6.7ppm (M; SD 5.6) at week 8, indicating excellent EC compliance.

Table 1. Sample Characteristics at Baseline (n=19).

Variable	Mean (SD)	Range
Age	53.6 (8.7)	32-66
Carbon Monoxide, exhaled (ppm)	15.7 (7.7)	6-32
CPD	15.1 (9.6)	6-40
Number of Years Smoked	32.9 (12.4)	7 - 50
CD4 T-cell count	765.9 (363.8)	307-1581
Years Living with HIV	21.1 (10.2)	4-38

Variable	n (%)
Type of Cigarette Smoked	
Menthol	12 (63%)
Race/Ethnicity	
Hispanic or Latino	3 (16)
Non-Hispanic White	10 (53)
Non-Hispanic Black or African American	5 (26)
Non-Hispanic Multi-Racial	1 (5)
Employment Status	
Employed, part/full-time	3 (16)
Unemployed	5 (26)
Disabled	11 (58)
Education	
Less than High School	8 (42)
High School/ Some College	9 (47)
College Graduate or Higher	2 (11)
Sex Assigned at Birth	
Female	6 (32)
Male	13 (68)

Table 2. Mean (SD) biomarker for plasma samples at Baseline, Week 8 and mean difference.

ELISA assay	Baseline Mean (SD)	Week 8 Mean (SD)	BL and W8 Mean Difference	95% CI	t	p-value
sCD14	1861198.7 (660532.9)	2197481.4 (786839.9)	336282.72	(990665.04, 318099.59)	-1.08	0.29
sCD163	883.6 (395.2)	791.4 (357.7)	-92.23	(-82.38, 266.84)	1.14	0.28
hs-CRP	3799.5 (2023.6)	3489.1 (1876.1)	-310.46	(-709.79, 1330.71)	0.64	0.53
IL-6	3.16 (2.03)	3.56 (3.73)	0.41	(-2.44, 1.62)	-0.42	0.68
D-Dimer	513.6 (327.6)	578.9 (237.7)	65.34	(-187.83, 57.16)	-1.13	0.28

Inflammatory biomarker levels were high at baseline and did not differ significantly at week 8. There were, however, small but nonsignificant reductions in mean sCD163 levels from baseline [M=883.6, SD=395.2] to week 8 [M=791.4, SD=357.7], t(1.14), p =.281, d=.26), and decreases in mean hs-CRP levels from baseline [M=3799.5, SD=2023.6] to week 8 [M=3489.1, SD=1876.1], t(.642), p =.529, d=.15). Non-significant increases in IL-6, D-dimer, and sCD14 were also noted: (IL-6: BL (M=3.16, SD=2.03), week 8 (M=3.56, SD=3.73), t(-.422), p =.678, d=.099; D-dimer: BL (M=513.6, SD=327.6), week 8 (M=578.9, SD=237.7), t(-1.125), p =.276, d=.27; sCD14: BL (M= 1861198.7, SD= 660532.9), week 8 (M= 2197481.4, SD= 786839.9), t(-1.08), p =.293, d=.26).

5. Discussion

This study evaluated changes in levels of serum biomarkers of inflammation and co-agulation in smokers living with HIV who were encouraged to switch from CCs to ECs for 8 weeks. We did not find significant changes in any of the five serum inflammatory biomarkers that we examined. We hypothesized that switching from CCs to ECs would result in a reduction in inflammatory biomarkers, based on previous work(P. Cioe et al.,

2015). While our previous work showed that current smoking compared with nonsmoking was associated with significantly elevated sCD14, there was no observable reduction in sCD14 in smokers who switched from CCs to ECs in this sample of 19 participants. There were also no reductions seen in D-dimer or IL-6 levels in our participants.

The five biomarkers selected for study have been found to be associated with higher rates of CVEs in PWH in previous studies, as described earlier. While there were small but nonsignificant reductions in sCD163 and hs-CRP seen in our sample, we also observed small, non-significant increases in IL-6, D-dimer, and sCD14. The clinical significance of these changes is unclear. While the reductions in two biomarkers may be promising as elevations in these biomarkers have been associated with higher rates of CVEs in PWH, further study in larger samples over longer periods of time is clearly needed. Previous studies have shown that smokers had increased hs-CRP, irrespective of HIV status, and increased plasma cotinine concentrations were associated with increased hs-CRP (Ahlstrom et al., 2018), so we were encouraged to see a signal indicating reductions in two of the examined biomarkers in smokers who switched to ECs. While the clinical significance of these findings remains unclear, further investigation of the potential of tobacco harm reduction for smokers who are unable or unwilling to quit is warranted. Importantly, an 8-week period of switching from CCs to ECs does not appear to significantly increase inflammatory biomarker levels in smokers with HIV.

This study has several strengths. To our knowledge, it is the first study to examine change in biomarkers of inflammation and coagulation in smokers with HIV who switch from CCs to ECs. Secondly, we used an EC and e-liquid combination that is commercially available and has been shown to deliver physiologically active nicotine doses (Hiler et al., 2017; J. M. Yingst et al., 2015). A major limitation of this study is the small sample size, limiting our ability to see significant changes in biomarker levels. Also, the 8-week duration of electronic cigarette use may have limited our findings, since the optimal period required for change in biomarker levels, related to smoking behaviors, is not known. Finally, the lack of a control group is a significant limitation.   Further study with larger samples, longer duration of EC use, perhaps several points of biomarker measurement, and a control group of smokers who continue to smoke their usual brand is clearly needed. Finally, we were not able to examine change in those smokers who made a complete switch to an EC, compared to those who became dual users (ECs and CCs), which limits our ability to fully examine the effect of EC provision on tobacco-related harms in this population. Goniewicz and colleagues (2018) have shown that exclusive EC use results in lower biomarker concentrations of nicotine and other tobacco-related toxicants compared with CC smoking (Goniewicz et al., 2018), while Stokes and colleagues showed that biomarkers of inflammation (hs-CRP, IL-6) are lower in exclusive electronic cigarette users, compared to smokers and duals users (Stokes et al., 2021). While 7 participants stopped smoking CCs by week 8, most of our participants continued to smoke at least 1-2 CPD, which may have continued to contribute to inflammation. A larger sample would allow us to examine differences in biomarkers of inflammation and coagulation in all three groups (CC smokers, dual CC/EC users, and complete EC switchers), as well.

6. Conclusion

In summary, in this small EC switch study of smokers with HIV, we found small, non-significant reductions in some key biomarkers of inflammation that have been associated with increased morbidity and mortality in PWH. This is an initial step to examine whether ECs may be beneficial as a tobacco harm reduction strategy in smokers with HIV. Further study is warranted, as tobacco harm reduction for PWH is a priority since some smokers are ambivalent about quitting smoking (P. A. Cioe, Gordon, Guthrie, Freiberg, & Kahler, 2018).   Reducing the harmful health effects of cigarette smoking by encouraging a switch to ECs may be important, either as a final step in tobacco harm reduction or as an intermediate step toward complete smoking cessation.

References

Ahlstrom, M. G., Knudsen, A., Ullum, H., Gerstoft, J., Kjaer, A., Lebech, A. M., . . . Obel, N. (2018). Association between smoking status assessed with plasma-cotinine and inflammatory and endothelial biomarkers in HIV-positive and HIV-negative individuals. *HIV Med*. doi:10.1111/hiv.12647

Armah, K. A., McGinnis, K., Baker, J., Gibert, C., Butt, A. A., Bryant, K. J., . . . Freiberg, M. (2012). HIV status, burden of comorbid disease, and biomarkers of inflammation, altered coagulation, and monocyte activation. *Clin Infect Dis, 55*(1), 126-136. doi:10.1093/cid/cis406

Baker, J., Quick, H., Hullsiek, K. H., Tracy, R., Duprez, D., Henry, K., & Neaton, J. D. (2010). Interleukin-6 and d-dimer levels are associated with vascular dysfunction in patients with untreated HIV infection. *HIV Med, 11*(9), 608-609. doi:10.1111/j.1468-1293.2010.00835.x

Caponnetto, P., Russo, C., Di Maria, A., Morjaria, J. B., Barton, S., Guarino, F., . . . Polosa, R. (2011). Circulating endothelial-coagulative activation markers after smoking cessation: a 12-month observational study. *Eur J Clin Invest, 41*(6), 616-626. doi:10.1111/j.1365-2362.2010.02449.x

Cassidy, R. N., Tidey, J. W., & Colby, S. M. (2020). Exclusive E-Cigarette Users Report Lower Levels of Respiratory Symptoms Relative to Dual E-Cigarette and Cigarette Users. *Nicotine Tob Res, 22*(Suppl 1), S54-S60. doi:10.1093/ntr/ntaa150

Cioe, P., Baker, J., Kojic, E., Onen, N., Hammer, J., Patel, P., & Kahler, C. f. t. S. S. I. (2015). Elevated Soluble CD14 and Lower D-Dimer Are Associated With Cigarette Smoking and Heavy Episodic Alcohol Use in Persons Living With HIV. *J Acquir Immune Defic Syndr, 70*, 400-405.

Cioe, P. A., Gordon, R. E. F., Guthrie, K. M., Freiberg, M. S., & Kahler, C. W. (2018). Perceived barriers to smoking cessation and perceptions of electronic cigarettes among persons living with HIV. *AIDS Care, 30*(11), 1469-1475. doi:10.1080/09540121.2018.1489103

Cioe, P. A., Mercurio, A. N., Lechner, W., Costantino, C. C., Tidey, J. W., Eissenberg, T., & Kahler, C. W. (2020). A pilot study to examine the acceptability and health effects of electronic cigarettes in HIV-positive smokers. *Drug Alcohol Depend, 206*, 107678. doi:10.1016/j.drugalcdep.2019.107678

Cooperman, N. (2016). Current research on cigarette smoking among people with HIV. *Current Addiction Reports, 3*, 19-26. doi:10.1007/s40429-016-0090-2

Cropsey, K. L., Trent, L. R., Clark, C. B., Stevens, E. N., Lahti, A. C., & Hendricks, P. S. (2014). How low should you go? Determining the optimal cutoff for exhaled carbon monoxide to confirm smoking abstinence when using cotinine as reference. *Nicotine Tob Res, 16*(10), 1348-1355. doi:10.1093/ntr/ntu085

De Luca, A., de Gaetano Donati, K., Colafigli, M., Cozzi-Lepri, A., De Curtis, A., Gori, A., . . . D'Arminio Monforte, A. (2013). The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case-control study. *BMC Infect Dis, 13*, 414. doi:10.1186/1471-2334-13-414

Freiberg, M. S., Bebu, I., Tracy, R., So-Armah, K., Okulicz, J., Ganesan, A., . . . Agan, B. K. (2016). D-Dimer Levels before HIV Seroconversion Remain Elevated Even after Viral Suppression and Are Associated with an Increased Risk of Non-AIDS Events. *PLoS One, 11*(4), e0152588. doi:10.1371/journal.pone.0152588

Gilbert, J., Fitch, KV, Grinspoon, SK. (2015). HIV-Related Cardiovascular Disease, Statins, and the REPRIEVE Trial. *Topics in Antiviral Medicine, 23*(4), 146-149.

Goniewicz, M. L., Smith, D. M., Edwards, K. C., Blount, B. C., Caldwell, K. L., Feng, J., . . . Hyland, A. J. (2018). Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. *JAMA Netw Open, 1*(8), e185937. doi:10.1001/jamanetworkopen.2018.5937

Hiler, M., Breland, A., Spindle, T., Maloney, S., Lipato, T., Karaoghlanian, N., . . . Eissenberg, T. (2017). Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience. *Exp Clin Psychopharmacol, 25*(5), 380-392. doi:10.1037/pha0000140

Kirkegaard-Klitbo, D. M., Mejer, N., Knudsen, T. B., Moller, H. J., Moestrup, S. K., Poulsen, S. D., . . . Benfield, T. (2017). Soluble CD163 predicts incident chronic lung, kidney and liver disease in HIV infection. *AIDS, 31*(7), 981-988. doi:10.1097/QAD.0000000000001432

Koenig, W. (2013). High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. *Int J Cardiol, 168*(6), 5126-5134. doi:10.1016/j.ijcard.2013.07.113

Kooij, K. W., Wit, F. W., Booiman, T., van der Valk, M., Schim van der Loeff, M. F., Kootstra, N. A., . . . Group, A. G. C. S. (2016). Cigarette Smoking and Inflammation, Monocyte Activation, and Coagulation in HIV-Infected Individuals Receiving Antiretroviral Therapy, Compared With Uninfected Individuals. *J Infect Dis, 214*(12), 1817-1821. doi:10.1093/infdis/jiw459

McKibben, R. A., Margolick, J. B., Grinspoon, S., Li, X., Palella, F. J., Jr., Kingsley, L. A., . . . Post, W. S. (2015). Elevated levels of monocyte activation markers are associated with subclinical atherosclerosis in men with and those without HIV infection. *J Infect Dis, 211*(8), 1219-1228. doi:10.1093/infdis/jiu594

Mdodo, R., Frazier, E. L., Dube, S. R., Mattson, C. L., Sutton, M. Y., Brooks, J. T., & Skarbinski, J. (2015). Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys. *Annals of Internal Medicine, 162*(5), 335-344. doi:10.7326/M14-0954

National Academies of Sciences, E., and Medicine. (2018). *Public Health Consequences of E-Cigarettes.* Retrieved from Washington, DC: https://doi.org/10.17226/24952.:

Nordell, A. D., McKenna, M., Borges, A. H., Duprez, D., Neuhaus, J., & Neaton, J. D. (2014). Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. *J Am Heart Assoc, 3*(3), e000844. doi:10.1161/jaha.114.000844

Nou, E., Lo, J., & Grinspoon, S. K. (2016). Inflammation, immune activation, and cardiovascular disease in HIV. *AIDS, 30*(10), 1495-1509. doi:10.1097/QAD.0000000000001109

Pacek, L. R., & Cioe, P. A. (2015). Tobacco Use, Use Disorders, and Smoking Cessation Interventions in Persons Living With HIV. *Curr HIV/AIDS Rep, 12*(4), 413-420. doi:10.1007/s11904-015-0281-9

Polosa, R., Morjaria, J. B., Caponnetto, P., Prosperini, U., Russo, C., Pennisi, A., & Bruno, C. M. (2016). Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respir Res, 17*(1), 166. doi:10.1186/s12931-016-0481-x

Poudel, K. C., Poudel-Tandukar, K., Bertone-Johnson, E. R., Pekow, P., & Vidrine, D. J. (2020). Inflammation in Relation to Intensity and Duration of Cigarette Smoking Among People Living with HIV. *AIDS Behav*. doi:10.1007/s10461-020-03048-0

Regueiro, V., Campos, M. A., Morey, P., Sauleda, J., Agusti, A. G., Garmendia, J., & Bengoechea, J. A. (2009). Lipopolysaccharide-binding protein and CD14 are increased in the bronchoalveolar lavage fluid of smokers. *Eur Respir J, 33*(2), 273-281. doi:10.1183/09031936.00087708

Rigotti, N. A., & Clair, C. (2013). Managing tobacco use: the neglected cardiovascular disease risk factor. *Eur Heart J, 34*(42), 3259-3267. doi:10.1093/eurheartj/eht352

Rosenson, R. S., Hubbard, D., Monda, K. L., Reading, S. R., Chen, L., Dluzniewski, P. J., . . . Colantonio, L. D. (2020). Excess Risk for Atherosclerotic Cardiovascular Outcomes Among US Adults With HIV in the Current Era. *J Am Heart Assoc, 9*(1), e013744. doi:10.1161/JAHA.119.013744

So-Armah, K. A., Tate, J. P., Chang, C. H., Butt, A. A., Gerschenson, M., Gibert, C. L., . . . Freiberg, M. S. (2016). Do Biomarkers of Inflammation, Monocyte Activation, and Altered Coagulation Explain Excess Mortality Between HIV Infected and Uninfected People? *J Acquir Immune Defic Syndr, 72*(2), 206-213. doi:10.1097/qai.0000000000000954

Stokes, A. C., Xie, W., Wilson, A. E., Yang, H., Orimoloye, O. A., Harlow, A. F., . . . Blaha, M. J. (2021). Association of Cigarette and Electronic Cigarette Use Patterns With Levels of Inflammatory and Oxidative Stress Biomarkers Among US Adults: Population Assessment of Tobacco and Health Study. *Circulation*. doi:10.1161/CIRCULATIONAHA.120.051551

Subramanya, V., McKay, H. S., Brusca, R. M., Palella, F. J., Kingsley, L. A., Witt, M. D., . . . Haberlen, S. A. (2019). Inflammatory biomarkers and subclinical carotid atherosclerosis in HIV-infected and HIV-uninfected men in the Multicenter AIDS Cohort Study. *PLoS One, 14*(4), e0214735. doi:10.1371/journal.pone.0214735

Vellozzi, C., Brooks, J. T., Bush, T. J., Conley, L. J., Henry, K., Carpenter, C. C., . . . Investigators, S. U. N. S. (2009). The study to understand the natural history of HIV and AIDS in the era of effective therapy (SUN Study). *Am J Epidemiol, 169*(5), 642-652. doi:10.1093/aje/kwn361

West, S. G., Finch, J.F., Curran, P.J. . (1995). *Structural equation models with nonnormal variables: problems and remedies.* . Newbery Park, CA: Sage.

Yingst, J., Foulds, J., Zurlo, J., Steinberg, M. B., Eissenberg, T., & Du, P. (2020). Acceptability of electronic nicotine delivery systems (ENDS) among HIV positive smokers. *AIDS Care, 32*(10), 1224-1228. doi:10.1080/09540121.2019.1687835

Yingst, J. M., Veldheer, S., Hrabovsky, S., Nichols, T. T., Wilson, S. J., & Foulds, J. (2015). Factors Associated With Electronic Cigarette Users' Device Preferences and Transition From First Generation to Advanced Generation Devices. *Nicotine Tob Res, 17*(10), 1242-1246. doi:10.1093/ntr/ntv052