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Smoking and Obesity may Partially Explain the Inflammation and Morbidity Association

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BACKGROUND

Studies in non-HIV populations have shown that inflammatory markers are mediated by body mass index (BMI), smoking and physical activity (*Marques-Vidal 2011*). In HIV populations suppressed on ART, it is unclear what is driving the levels of inflammatory markers.

High levels of IL-6, sTNFR-1 and 2 and D-dimer were associated with a non-AIDS outcome (*Tenorio JID 2014, Hunt JID 2014, Duprez 2012*).

Increased central obesity and smoking correlated with high levels of soluble inflammatory markers in HIV+ virally suppressed patients (*Krishnan CROI 2014*).

OBJECTIVE

To evaluate if each soluble inflammatory marker is independently associated with non-AIDS outcomes after adjusting for the other soluble inflammatory markers and correlates.

METHODS

Data from a previously reported case-control study: HIV+ adults from the ACTG-ALLRT cohort, antiretroviral therapy (ART) naïve, received a modern ART regimen, and were virally suppressed (<400 copies/ml) at year 1 of ART.

- Cases: myocardial infarction (MI), stroke, non-AIDS-defining malignancy, serious bacterial infection or non-accidental non-AIDS-related death after year 1 while remaining virally suppressed.
- Controls: endpoint-free follow-up time, matched for age, sex, baseline CD4+ T-cells (within ± 50 cells/mm^3), ART regimen at week 48 (whether protease-inhibitor containing or not, and whether abacavir-containing or not), and parent (initial randomized) study.

Stored plasma at year 1 was tested for interleukin-6 (IL-6), soluble CD14 (sCD14), interferon-gamma inducible protein 10 (IP-10), soluble TNF receptors (sTNFR-1, sTNFR-2) and D-dimer.

STATISTICAL ANALYSIS

Conditional logistic regression incorporating the matching factors. Odds ratios (OR) per IQR and 95% confidence intervals (CI) for each soluble inflammatory marker.

Models adjusted for other soluble inflammatory markers (singly), waist circumference (WC, cm), waist-hip ratio (WHR) and smoking (number of cigarettes/day) at year 1. WC, WHR and smoking included because correlated with soluble inflammatory markers in previous analysis and risk factors for the outcomes in the general population.

RESULTS

IL-6 was independently associated with non-AIDS outcomes after adjusting for sTNFR-1 and 2, D-dimer, IP-10 and sCD14 separately (Figure 1).

- The magnitude of the OR was attenuated by 10-15% when adjusted for D-dimer, sTNFR-1 and sTNFR-2.

In contrast, the associations for D-dimer and sCD14 were substantially attenuated (and not significant) when IL-6 was included in the model (Figure 2).

Both sTNFR-1 and sTNFR-2 remained independently associated with non-AIDS outcomes after adjusting for IL-6 (Figure 2).

- The magnitude of the OR was attenuated by 13-15%.

IL-6 was independently associated with non-AIDS outcomes in a model that included WC (or WHR) and smoking (Figure 3).

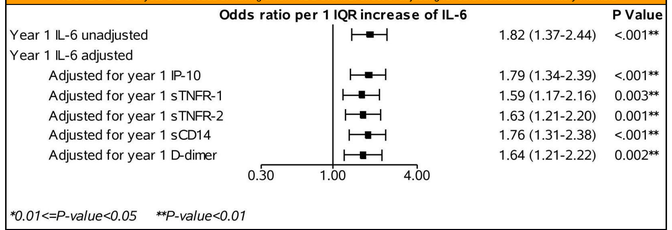
- The magnitude of the OR was attenuated by 15% (Figure 3).

sTNFR-1 and 2 were independently associated with non-AIDS outcomes after adjusting for obesity and smoking; ORs were only slightly attenuated.

TABLE 1: Selected characteristics of the study population

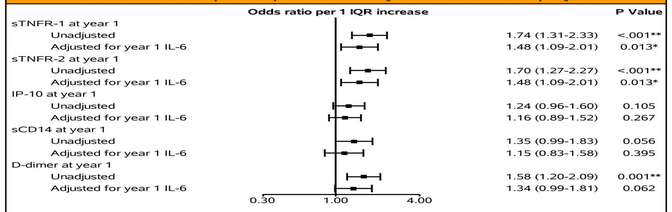
		Total (N=453)	Control (N=311)	Case (N=142)
Age at ART initiation (years)	Median (Q1, Q3)	45 (39, 51)	44 (39, 50)	46 (40, 53)
Race/Ethnicity	White Non-Hispanic	222 (49%)	148 (48%)	74 (52%)
	Black Non-Hispanic	140 (31%)	88 (28%)	52 (37%)
	Hispanic	79 (17%)	64 (21%)	15 (11%)
Sex	Male	386 (85%)	265 (85%)	121 (85%)
CD4 at ART initiation (cells/mm^3)	Median (Q1, Q3)	215 (76, 334)	221 (75, 334)	208 (87, 338)
CD4 at year 1 of ART (cells/mm^3)	Median (Q1, Q3)	386 (252, 551)	403 (266, 558)	354 (229, 503)
% with viral load <50 copies/ml at year 1 of ART		405 (89%)	277 (89%)	128 (90%)
Body mass index (BMI) at year 1 of ART (kg/m^2)	Median (Q1, Q3)	26 (23, 29)	26 (23, 29)	25 (22, 28)
Waist circumference (WC) at year 1 of ART (cm)	Median (Q1, Q3)	92 (84, 99)	92 (84, 100)	90 (85, 98)
Waist-hip ratio (WHR) at year 1 of ART	Median (Q1, Q3)	0.94 (0.89, 0.98)	0.94 (0.89, 0.98)	0.94 (0.89, 0.98)
Cigarette smoking status at year 1 of ART	Current smoker	172 (38%)	100 (32%)	72 (51%)
	Past smoker	108 (24%)	73 (23%)	35 (25%)
	Non smoker	168 (37%)	134 (43%)	34 (24%)
# of cigarettes/day (#cigs) among current smokers at year 1 of ART	Median (Q1, Q3)	10 (6, 20)	10 (5, 20)	12 (6, 20)

FIGURE 1: IL-6 at year 1 and odds of having a non-AIDS event 1: effect of adjusting for other soluble inflammatory markers



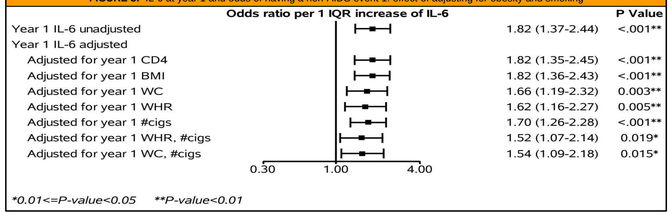
*0.01<=P-value<0.05 **P-value<0.01

FIGURE 2: Soluble inflammatory markers at year 1 and odds of having a non-AIDS event 1: effect of adjusting for IL-6



*0.01<=P-value<0.05 **P-value<0.01

FIGURE 3: IL-6 at year 1 and odds of having a non-AIDS event 1: effect of adjusting for obesity and smoking



*0.01<=P-value<0.05 **P-value<0.01

CONCLUSIONS

Among the six soluble inflammatory markers evaluated, IL-6, sTNFR-1 and sTNFR-2 measured during viral suppression appear to be robust predictors of non-AIDS outcomes; may be part of distinct pathways leading to subsequent non-AIDS outcomes.

The IL-6 association was independent of obesity and smoking; however the effect was attenuated by 15% suggesting that obesity and smoking may play a role in some IL-6 related pathways leading to an increased risk of non-AIDS outcomes. These findings further support efforts to identify the effects on residual inflammation of reducing obesity and smoking.

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