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Correlates of inflammatory markers after one year of suppressive antiretroviral treatment (ART)

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ABSTRACT

BACKGROUND: Elevated levels of inflammatory markers such as interleukin (IL)-6 are associated with HIV-associated non-AIDS morbidity and death. Traditional risk factors such as substance use, obesity, triglycerides, cholesterol and fasting glucose levels are likely increased in HIV+ adults, and may be causally related to inflammation. We examined the cross-sectional association between a panel of inflammatory markers, and metabolic and other risk factors in a well-treated HIV+ adult population.

METHODOLOGY: A previously described case-control study was performed on HIV+ adults enrolled in the ACTG-ALLRT cohort who were ART naïve at study entry, received a modern ART regimen, and were virally suppressed (<400 copies/ml) at year 1 of ART. This analysis examined the controls that were the event-free comparator population. Spearman correlations (unadjusted and partial) evaluated biomarkers and selected behavioral, metabolic and anthropometric factors at year 1.

RESULTS: Subjects (N=315) were 85% male; mean age was 44 years. At year 1, 59% had CD4 > 350 cells/mm3, 89% had HIV RNA ≤ 50 copies/ml. After adjusting for CD4 and other factors, levels of plasma IL-6, soluble tumor necrosis factor receptors (sTNFR)-I and II, interferon gamma inducible protein-10 (IP-10), soluble CD14 (sCD14), and D-dimer positively correlated with age (p<.0001). IL-6 positively correlated with waist circumference (r=0.22, p<.001), waist-hip ratio (r=0.15, p<.01), # cigarettes/day (r=0.19, p<.01) and fasting glucose (FG) (r=0.25, p<.001). Correlations for waist circumference, smoking and FG were significant even after adjustment for each of the other factors. IL-6 levels increased as the number of metabolic syndrome components increased (r=0.15, p<.01). sCD14 correlated with BMI (r=-0.12, p=0.03) and smoking (r=0.29, p<.001). sTNFR-I correlated with waist-hip ratio (r=0.21, p<.001) and smoking (r=0.18, p<.01). sTNFR-II correlated with waist circumference (r=0.15, p=0.01), waist-hip ratio (r=0.21, p<.001), smoking (r=0.24, p<.001), FG (r=0.14, p=0.03) and triglyceride levels (r=0.20, p<.001). None of factors examined gave significant correlations for D-dimer and IP-10.

CONCLUSIONS: As in the general population, increased age, increased central obesity and smoking are associated with increased levels of soluble inflammatory markers in HIV+ virally suppressed patients. These findings underscore the relationships between inflammation and behavioral, anthropometric and metabolic risks in treated HIV infection. Future studies should focus on determining the mechanisms for these associations, and whether the impact of inflammation on disease progression is independent of these factors.

BACKGROUND

- Elevated levels of inflammatory markers such as interleukin (IL)-6 are associated with HIV-associated non-AIDS morbidity and death, even with viral suppression on ART (*Kuller 2008, Duprez 2012, Tenorio 2013*).
- Studies in non-HIV populations have shown that inflammatory markers levels are mediated by lifestyle factors such as body mass index (BMI), smoking and physical activity (*Marques-Vidal 2011*). In HIV populations, it is unclear what is driving the levels of inflammatory markers.
- Traditional risk factors such as substance use, obesity, triglycerides, cholesterol and fasting glucose levels are likely increased in HIV+ adults, and may be causally related to inflammation.
- The objective of this analysis was to assess correlations between a panel of inflammatory biomarkers and selected demographic and metabolic covariates in a well-treated HIV-infected adult population.

METHODS

- The study population consisted of the controls from ACTG NWCS 329, which was a nested case-control study of HIV-infected individuals from the ACTG-ALLRT cohort.
- All controls were virally suppressed at year 1 and had event-free follow-up time greater than the case (events were non-AIDS morbidities and non-accidental death); controls were matched for age, sex, baseline CD4+ T-cells (+/- 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 following ART initiation was tested for: 1) IL-6 (HS600B, R&D Systems, Minneapolis, MN), 2) soluble CD14 (sCD14; DC140, R&D Systems), 3) interferon-gamma inducible protein 10 (CXCL10/IP-10; DIP100, R&D Systems), 4) sTNF-R1 (DRT100, R&D Systems), 5) sTNF-R2 (DRT200, R&D Systems), 6) D-dimer (Diagnostica Stago, Parsippany, NJ).
- Spearman correlations were used to analyze the associations between biomarkers at year 1 and selected factors.

Table 1: Selected characteristics for the study population

		Total (N=315)
Age at ART initiation	Median (10th-90th, min-max)	44 (33-65, 23-67)
Race/Ethnicity	White Non-Hispanic	150 (48%)
	Black Non-Hispanic	89 (28%)
	Hispanic	65 (21%)
Sex	Male	267 (85%)
CD4 at ART initiation (cells/mm^3)	Median (Q1, Q3)	221 (70, 331)
CD4 at year 1 of ART (cells/mm^3)	Median (Q1, Q3)	403 (271, 553)
Viral load at year 1 of ART (copies/ml)	<400	315 (100)
	<50	279 (89)
# of cigarettes/day among smokers at year 1 of ART	Median (Q1, Q3)	10 (5, 20)
Body mass index at year 1 of ART (kg/m^2)	Median (Q1, Q3)	26 (24, 29)
	BMI ≥30	63 (20%)
Waist circumference at year 1 of ART (cm) (missing for 15%)	Median (Q1, Q3)	92 (84, 99)
	>88 in women, >102 in men	67 (21%)
Waist-hip ratio at year 1 of ART (missing for 15%)	Median (Q1, Q3)	0.94 (0.89, 0.98)
	≥0.85 in women, ≥1 in men	64 (20%)
Fasting glucose at year 1 of ART (mg/dl) (missing for 26%)	Median (Q1, Q3)	90 (83, 98)
	≥ 100	51 (16%)
Fasting triglycerides at year 1 of ART (mg/dl) (missing for 27%)	Median (Q1, Q3)	152 (96, 247)
	≥ 150	119 (38%)
HDL cholesterol at year 1 of ART (mg/dl) (missing for 27%)	Median (Q1, Q3)	45 (37, 57)
	≥ 50 women, ≥ 40 men	149 (47%)
Metabolic syndrome at year 1 of ART	3 or more criteria	57 (25%)

RESULTS

- **Age positively correlated** with levels of all inflammatory markers (all p<0.0001); these correlations were significant even after adjusting for CD4 and other factors.
- **Smoking (# cigarettes per day) positively correlated with IL-6, sCD14, sTNFR1 and sTNFR2** (Figures 1-4); correlations for smoking were significant even after adjustment for each of the other factors.
- **Waist-hip ratio positively correlated with IL-6, sTNFR1 and sTNFR2** (Figures 1, 3 and 4).
- **sCD14 negatively correlated with BMI** (Figure 2); however, correlations not statistically significant (p>0.05) after adjusting for waist circumference, smoking or lipids.
- IL-6 levels increased as the number of metabolic syndrome components increased (r=0.15, p<.01).
- **HDL cholesterol negatively correlated with sTNFR1, sTNFR2 and IP-10** (Figures 3, 4 and 6), but positively with sCD14.

Figure 1: IL-6 (Spearman correlation coefficient and 95% CI)

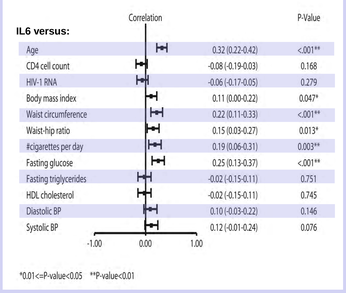


Figure 2: sCD14 (Spearman correlation coefficient and 95% CI)

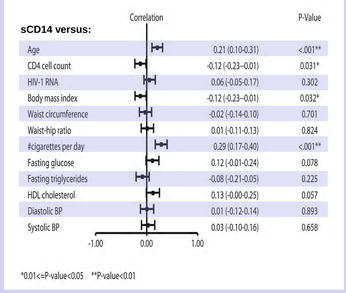


Figure 3: sTNFR1 (Spearman correlation coefficient and 95% CI)

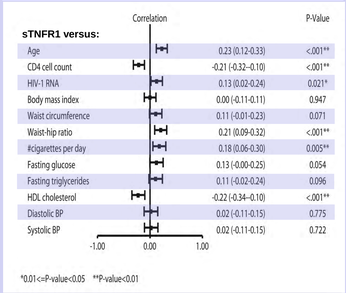


Figure 4: sTNFR2 (Spearman correlation coefficient and 95% CI)

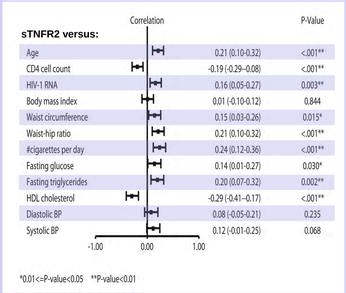


Figure 5: D-dimer (Spearman correlation coefficient and 95% CI)

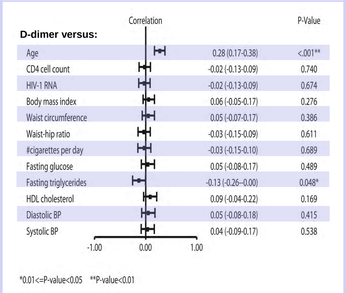
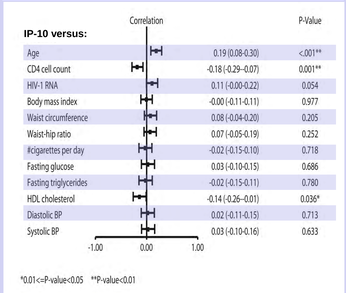


Figure 6: IP-10 (Spearman correlation coefficient and 95% CI)



CONCLUSIONS

- Increased age, increased central obesity and smoking are associated with increased levels of soluble inflammatory markers in HIV+ virally suppressed patients on ART.
- IL-6, a strong predictor of morbidity/mortality in HIV disease, is associated with a number of factors which may contribute to non-AIDS morbidity. Future studies should focus on determining how metabolic and other traditional risk factors relate to IL-6, and whether the impact of IL-6 on disease progression is independent of these factors.
- Body mass index negatively correlated with sCD14; this finding should confirmed in other studies.
- These findings emphasize relationships between inflammation, behavioral and anthropometric risks for morbidity in treated HIV infection and provide quantitative data to help in the design of interventional studies.

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