HIV & obesity synergistically increase interleukin 6 but not soluble CD14 or D-dimer

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Background

- Obesity prevalence among people living with HIV (HIV+) is rising.
- HIV and obesity are associated with atherosclerosis, which is mediated by inflammation.
- Both obesity and HIV are pro-inflammatory states, but their combined association with inflammation (measured by interleukin 6, IL-6), monocyte activation (soluble CD14, sCD14), and altered coagulation (D-dimer) is unknown.
- We hypothesized that concomitant HIV infection and obesity (BMI≥30 kg/m^2) increase IL-6, sCD14, and D-dimer in the Veterans Aging Cohort Study Biomarker Cohort.

Study Design

VACS Survey Cohort
- Prospective, longitudinal study of HIV+ and HIV- participants
- Matched on age, race/ethnicity, sex, and geographic region
- Data from all VA electronic medical records
- Annual self-completed surveys on health behaviors

VACS Biomarker Cohort
- Subset of VACS survey cohort participants
- Unmatched but demographically similar HIV+ and HIV- participants
- Blood draw for measurement of IL-6, sCD14, and D-dimer

Analysis

Inclusion criteria: BMI ≥18.5kg/m^2 (underweight excluded as n=48)
Variables: Dependent: Elevated IL-6, sCD14, or D-dimer (highest quartile across all subjects); Independent: Obesity (BMI ≥30kg/m^2) and HIV status as a 4 level variable: non-obese/HIV-; non-obese/HIV+; obese/HIV-; obese/HIV+
Methods: Median biomarkers examined by obesity/HIV status; unadjusted and logistic regression models adjusted for demographics, smoking, diabetes, CVD, hypertension, lipids, liver and renal function, HCV and statin use were constructed. Sensitivity analyses excluded those with HCV, considering the known association of HCV with inflammation, and stratified by HIV-1 plasma RNA level for the HIV+ groups.

Cohort Demographics

Table 1. Characteristics of the cohort at time of biomarker measurement. Data are % of column unless otherwise indicated.

	Non-obese		Obese	
	HIV-	HIV+	HIV-	HIV+
N (% of row)	438 (19)	1232 (54)	385 (17)	245 (11)
Median age (mean, SD) years	53 (54, 9)	52 (52, 8)	53 (54, 10)	51 (51, 8)
Male	91	98	90	96
African American	71	68	63	73
Diabetes	22	17	39	38
Total cholesterol >200 mg/dL	12	9	11	11
Statin	43	46	59	56
BP ≥140/90 or anti-hypertensive meds	79	72	89	82
Hepatitis C	35	48	26	40
FIB-4 >3.25 (advanced fibrosis)	5	9	3	7
eGFR <60	7	8	12	8
Alcohol abuse diagnosis (ever)	55	40	35	34
Current smoker	55	52	38	34
Cocaine	44	37	30	33
Prevalent CVD	23	18	34	20
HIV-1 RNA >500 (HIV+ only)	-	34	-	43
CD4+ cells/mm^3 <500 (HIV+ only)	-	66	-	57

Results

Figure. Boxplots depicting median, interquartile ranges, and outliers for each biomarker by obesity/HIV status. A statistically significant difference exists between the non-obese/HIV- and obese/HIV+ groups for IL-6 (p<0.05) and sCD14 (p<0.01). No significant difference was seen between obesity/HIV status groups for D-dimer.

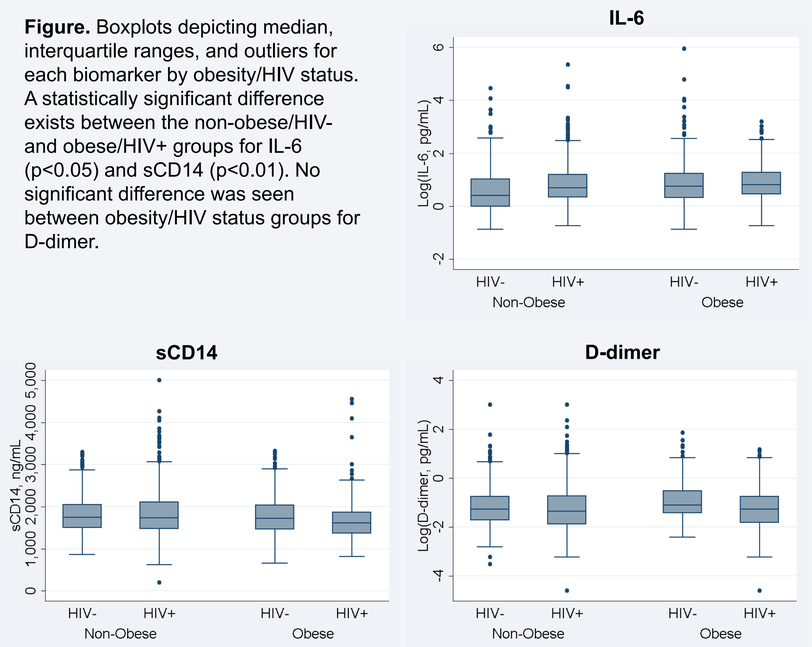


Table 2. Association between obesity/HIV comorbidity and elevated biomarkers of inflammation (IL-6), monocyte activation (sCD14), and altered coagulation (D-dimer).

Model	Weight/BMI status	Elevated biomarker (i.e highest quartile) Odds Ratio (95% Confidence Interval)		
		IL-6	sCD14	D-dimer
Unadjusted	Non-obese/HIV-	1 (ref)	1 (ref)	1 (ref)
	Non-obese/HIV+	**1.33 (1.01-1.74)**	1.15 (0.89-1.48)	1.05 (0.81-1.37)
	Obese/HIV-	**1.54 (1.11-2.13)**	0.92 (0.66-1.27)	**1.48 (1.09-2.03)**
	Obese/HIV+	**1.59 (1.10-2.29)**	**0.58 (0.38-0.87)**	0.99 (0.68-1.44)
Age, race-ethnicity adjusted	Non-obese/HIV-	1 (ref)	1 (ref)	1 (ref)
	Non-obese/HIV+	**1.39 (1.06-1.83)**	1.18 (0.92-1.53)	1.12 (0.86-1.46)
	Obese/HIV-	**1.55 (1.11-2.15)**	0.91 (0.65-1.26)	**1.54 (1.12-2.11)**
	Obese/HIV+	**1.71 (1.18-2.47)**	0.61 (0.40-0.91)	1.07 (0.73-1.56)
Fully adjusted*	Non-obese/HIV-	1 (ref)	1 (ref)	1 (ref)
	Non-obese/HIV+	1.32 (0.98-1.77)	0.97 (0.73-1.28)	1.04 (0.78-1.38)
	Obese/HIV-	**1.62 (1.14-2.30)**	0.76 (0.53-1.07)	**1.40 (1.00-1.97)**
	Obese/HIV+	**1.79 (1.20-2.67)**	**0.44 (0.28-0.68)**	0.93 (0.62-1.40)

*Adjusted for age, race/ethnicity, diabetes, cardiovascular disease, hepatitis C, FIB4, eGFR, smoking, hypertension, LDL, HDL- cholesterol, statin use, alcohol, cocaine

Table 3. Association between obesity/HIV comorbidity and elevated biomarkers of inflammation, monocyte activation, and altered coagulation, excluding those with hepatitis C.

Weight/BMI status	Elevated biomarker (i.e highest quartile) Odds Ratio (95% Confidence Interval)		
	IL-6 n=1333	sCD14 n=1343	D-dimer n=1353
Non-obese/HIV-	1 (ref)	1 (ref)	1 (ref)
Non-obese/HIV+	1.37 (0.95-1.97)	1.23 (0.88-1.74)	1.16 (0.81-1.66)
Obese/HIV-	**1.67 (1.11-2.52)**	0.77 (0.51-1.18)	**1.64 (1.10-2.43)**
Obese/HIV+	**1.85 (1.13-3.01)**	**0.53 (0.31-0.93)**	1.03 (0.62-1.71)

*adjusted for age, race/ethnicity, diabetes, cardiovascular disease, FIB4, eGFR, smoking, hypertension, LDL, HDL- cholesterol, statin use, alcohol, cocaine

Table 4. Association between obesity/HIV comorbidity and elevated biomarkers of inflammation, monocyte activation, and altered coagulation, stratified by HIV-1 RNA.

Weight/BMI status	Elevated biomarker (i.e highest quartile) Odds Ratio (95% Confidence Interval)		
	IL-6	sCD14	D-dimer
Non-obese/HIV-	1 (ref)	1 (ref)	1 (ref)
Obese/HIV-	1.60 (1.12-2.27)	0.75 (0.53-1.07)	1.38 (0.98-1.93)
Non-obese/HIV+/VL<500	1.07 (0.78-1.46)	0.88 (0.65-1.18)	0.74 (0.54-1.01)
Non-obese/HIV+/VL≥500	**1.91 (1.35-2.70)**	1.17 (0.84-1.64)	1.83 (1.31-2.56)
Obese/HIV+/VL<500	**1.91 (1.22-3.00)**	**0.47 (0.28-0.78)**	0.73 (0.44-1.19)
Obese/HIV+/VL≥500	1.61 (0.89-2.90)	**0.37 (0.18-0.77)**	1.44 (0.83-2.51)

*adjusted for age, race/ethnicity, diabetes, cardiovascular disease, hepatitis C, FIB4, eGFR, smoking, hypertension, LDL, HDL- cholesterol, statin use, alcohol, cocaine

Conclusions

- Compared with non-obese/HIV-, obese/HIV+ participants had:
  - Higher prevalence of elevated IL-6
  - Lower prevalence of elevated sCD14
  - No significant difference in elevated D-dimer
- These findings are clinically significant as all three biomarkers are associated with mortality in HIV+ and HIV- populations.
- Potential mechanisms for the unanticipated finding that sCD14 levels are lowest in obese/HIV+ participants should be explored.
- Subsequent studies should assess whether other biomarkers of inflammation, monocyte activation, and altered coagulation show similar trends.

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