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IL-6 and D-dimer levels are associated with vascular dysfunction in patients with untreated HIV infection

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In the Strategies for Management of AntiRetroviral Therapy (SMART) study, higher baseline levels of the inflammatory cytokine interleukin-6 (IL-6) and the thrombotic marker D-dimer were strongly associated with mortality risk (cardiovascular disease [CVD] and non-CVD related).1 In that report, authors speculated activation of tissue factors and endothelial surfaces may be driving elevations in IL-6 and D-dimer levels. In this pilot study of persons with untreated HIV infection, we explore the relationship between IL-6 and D-dimer with the following measures of vascular dysfunction: large and small artery elasticity (LAE and SAE, respectively) and plasma markers of endothelial function (E-selectin and soluble intercellular adhesion molecule-1 [sICAM-1]).

HIV-infected participants had not taken ART in the previous year, and had no known CVD. Arterial elasticity was assessed via pulse waveform analysis of the diastolic decay curve (model HDI/PulseWave CR-2000, Eagan, MN). Biomarker levels were measured at the Laboratory for Clinical Biochemistry Research at the University of Vermont. Details of these methods and the study protocol have been reported.2 3

To consider the combined influence of IL-6 and D-dimer, a joint mortality risk score was also generate according to the weighted contribution of each biomarker for risk of death in SMART.4 The joint mortality risk score was obtained from SMART data using a conditional logistic regression model that considered both IL-6 and D-dimer (each $\log_{10}$ transformed) for outcome of all-cause mortality. The joint mortality risk score was calculated by solving for the logit formed with the estimated parameters from SMART and

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the $\log_{10}$ transformed values of IL-6 and D-dimer from the current study. Higher values of this score were associated with a higher risk of death in SMART. Data were analyzed by use of R statistical software (version 2.8.1; http://www/cran.r-project.org).

Characteristics of the 32 HIV-infected participants who were enrolled have been previously reported.2 3 Mean (SD) age was 40 (9.6) years and body mass index was 26 (5.1) kg/m^2. Twenty-eight (88%) were male, 19 (59%) were current smokers, 11 (34%) with hepatitis C co-infection, 2 (6%) with diabetes mellitus, and 2 (7%) had a prior AIDS clinical event. Mean CD4 count was 391 (182) cells/mm^3 and HIV RNA level was 4.15 (0.73) $\log_{10}$ copies/mL.

The median (IQR) values for IL-6, D-dimer, and the joint mortality risk score were 1.79 (1.34–4.88) pg/mL , 0.39 (0.19–0.60) μg/mL, and 0.47 (0.33–0.74), respectively. Mean values for each surrogate measure of vessel function (untransformed) and HIV RNA level ($\log_{10}$ transformed) are reported by quartile of IL-6 and D-dimer (table1). Higher levels of IL-6 (4^{th} versus 1^{st} quartile and as continuous variable in spearman rank correlations) tended to associate with impaired SAE and higher levels of sICAM-1 and E-selectin. A similar patter was seen when comparing markers of vascular dysfunction with D-dimer levels, though a significant association was only consistently present for E-selectin. LAE and CD4 count (data not shown) did not vary by IL-6 or D-dimer levels. For comparisons using the joint (IL-6/D-dimer) mortality risk score, the associations with markers of vascular dysfunction (SAE, sICAM-1 and E-selectin) became more pronounced.

In summary, we show that higher IL-6 and D-dimer levels among persons with untreated HIV infection are associated with vascular dysfunction, indicated by higher endothelial biomarkers and impaired small artery elasticity (SAE)—a marker of early vascular disease and future clinical risk. Findings from SMART suggest that non-AIDS related mortality may be a consequence of greater inflammation (IL-6) and thrombotic activity (D-dimer) in persons with HIV infection.1 Levels of IL-6 and D-dimer and estimates of artery elasticity (LAE and SAE) are being ascertained in a subset of participants in the ongoing Strategic Timing of Antiretroviral Therapy (START) trial, and will provide valuable insight into the mechanisms driving vessel dysfunction and early vascular disease in persons with HIV infection. Future research should consider the role of HIV-mediated endothelial injury as a contributor to both CVD- and non-CVD-related mortality in the current era.

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Table 1

Markers of Vascular Dysfunction and HIV RNA by Quartile of IL-6, D-dimer, and Joint (IL-6 / D-dimer) Risk Score

	Quartile of IL-6				Comparison of Quartiles (4th vs. 1st)		Spearman's Rank Correlation	
Surrogate Marker	**1st**	**2nd**	**3rd**	**4th**	**Percent (%) Difference***	***p*-value**	**R**	***p*-value**
LAE (mmHg/mL × 10)	16.5	15.7	18.2	15.1	−9.90	0.50	−0.14	0.45
SAE (mmHg/mL × 100)	8.2	6.3	6.7	5.6	−37.8	0.03	−0.33	0.06
sICAM-1 (ng/mL)	252	397	424	554	77.1	0.07	0.34	0.05
E-selectin (ng/mL)	32.0	33.6	60.8	65.7	86.4	0.02	0.57	0.001
HIV-RNA ($\log_{10}$ copies/mL)	4.0	4.1	4.1	4.4	11.3	0.08	0.26	0.15
	Quartile of D-dimer Level							
	1st	**2nd**	**3rd**	**4th**				
LAE (mmHg/mL × 10)	15.6	16.1	17.6	16.2	2.1	0.90	0.18	0.34
SAE (mmHg/mL × 100)	8.0	6.7	6.5	5.7	−33.9	0.12	−0.27	0.13
sICAM-1 (ng/mL)	275	452	277	601	94.8	0.05	0.29	0.11
E-selectin (ng/mL)	27.9	49.6	41.3	70.7	138.2	0.001	0.54	0.001
HIV-RNA ($\log_{10}$ copies/mL)	4.1	4.5	3.5	4.4	5.9	0.48	0.06	0.73
	Quartile of Joint (IL-6 / D-dimer) Mortality Risk Score							
	1st	**2nd**	**3rd**	**4th**				
LAE (mmHg/mL × 10)	15.6	17.6	16.9	15.5	−2.1	0.89	−0.06	0.74
SAE (mmHg/mL × 100)	8.5	7.1	5.6	5.5	−41.5	0.02	−0.42	0.02
sICAM-1 (ng/mL)	256	391	352	628	114.5	0.01	0.41	0.02
E-selectin (ng/mL)	30.0	39.4	50.0	72.7	130.5	0.001	0.67	<0.001
HIV-RNA ($\log_{10}$ copies/mL)	4.0	4.1	4.1	4.3	7.1	0.33	0.25	0.17

*Percent differences were obtained by exponentiating the $\log_e$ transformed means.