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## ELEVATED LEVELS OF INTERLEUKIN-6 AND D-DIMER ARE ASSOCIATED WITH AN INCREASED RISK OF DEATH IN PATIENTS WITH HIV

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**BACKGROUND:** In SMART, CD4-guided intermittent antiretroviral treatment (ART) as compared to continuous ART resulted in an increased risk of cardiovascular disease (CVD) and of all-cause mortality, the latter primarily due to non-AIDS diagnoses. To explore reasons for these increased risks, we evaluated four inflammatory (high sensitivity-C reactive protein [hsCRP], interleukin-6 [IL-6], amyloid A, and amyloid P) and two coagulation (D-dimer and prothrombin fragment 1+2 [F1.2]) markers that have high laboratory and biological reproducibility and that have been associated with mortality and CVD in the general population.

**METHODS:** Patients with CD4+ count  $>350$  cells/mm<sup>3</sup> were randomized to viral suppression (VS) (continuous ART) ( $N=2,752$ ) or to drug conservation (DC) (CD4-guided intermittent ART) ( $N=2,720$ ). To assess the short-term effect of intermittent ART on the biomarkers, stored plasma samples at baseline and one month after randomization for a random subset of DC ( $N=249$ ) and VS ( $N=250$ ) patients were analyzed. In addition, a nested case control study was carried out in which two controls were matched (age, gender, country, date of randomization) to each death ( $N=85$ ) and case of CVD ( $N=136$ ). Adjusted odds ratios (ORs) for the 4<sup>th</sup> versus 1<sup>st</sup> quartile of each biomarker at baseline were estimated using logistic regression.

**RESULTS:** IL-6 and D-dimer levels increased by 30% and 16%, respectively, one month after randomization in the DC group and changed little in the VS group (5% and 0%) ( $P<0.0001$  for treatment difference for each biomarker). For DC patients, increases in IL-6 and D-dimer after one month were related in a graded manner to the increases in HIV RNA at month 1 ( $P<0.0001$  for each biomarker). IL-6 and D-dimer determined at baseline were strongly related to mortality with ORs greater than 12 for those in 4<sup>th</sup> versus 1<sup>st</sup> quartile. Associations with CVD were more modest and were significant for IL-6

and amyloid P. ORs are summarized in the table below.

<b>Biomarker</b>	<b>All Case Mortality</b>			<b>Fatal or Non-Fatal CVD</b>		
	<b>OR</b>	<b>95%CI</b>	<b>P-value</b>	<b>OR</b>	<b>95%CI</b>	<b>P-value</b>
hs-CRP	3.5	1.5-8.1	0.004	1.6	0.8-3.1	0.20
IL-6	12.6	4.3-37.4	<0.0001	2.8	1.4-5.5	0.003
Amyloid A	2.3	0.9-5.5	0.08	1.6	0.9-2.9	0.12
Amyloid P	1.1	0.5-2.4	0.90	2.8	1.4-5.3	0.002
D-dimer	13.3	4.4-40.3	<0.0001	2.0	1.0-3.9	0.06
F1.2	1.4	0.6-3.5	0.45	0.8	0.4-1.6	0.56

Associations of baseline levels of the biomarkers with all-cause mortality and with CVD were similar for DC and VS patients.

**CONCLUSIONS:** ART interruption results in significant increases in IL-6 and D-dimer. Elevated levels of D-dimer and IL-6 identify a subgroup of HIV-infected patients at high risk of death in both treatment groups. Increases in IL-6 and D-dimer may explain, in part, the increased risk of mortality and CVD in the DC group.

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