INTRODUCTION
In the Strategies for Management of Anti-Retroviral Therapy (SMART) study, hepatitis B, and C co-infected participants randomized to the drug conservation (DC) arm (interrupt anti-retroviral therapy (ART) until CD4≥250/µl) group were at increased risk of non-AIDS death if their baseline plasma level of the liver fibrosis marker hyaluronic acid (HA) was elevated (>75 ng/mL), while the risk of non-AIDS death in the viral suppression (VS) arm (continued use of ART) group was considerably lower and did not depend on baseline HA level (fig. 3). The excess mortality seen in co-infected participants was not due to any particular cause(s), suggesting that interruption of ART affects multiple, and not a single, pathological process. Another biomarker sub-study within SMART showed that higher levels of the coagulation and inflammation markers D-dimer, intercellular adhesion molecule (ICAM) and high sensitivity C-reactive protein (hsCRP) at study entry were significantly associated with an increased risk of all-cause mortality (Kuller et al. PLoS Med 2008).

The findings of these different studies raise the possibility that impaired liver function is associated with activation of both inflammatory and coagulation processes, which could be further exacerbated by ART interruptions and increase the risk of death.

OBJECTIVES
1. To assess IL-6, D-dimer and hsCRP at baseline and at month 6 among all hepatitis co-infected SMART participants with known baseline HA level.
2. To examine predictors for non-AIDS death during follow-up.

HYPOTHESES
1. Hepatitis co-infected participants with existing liver impairment (as determined by elevated HA) would have higher levels of the coagulation and inflammation markers D-dimer, IL-6 and hsCRP relative to participants with normal liver function (NA) within the normal range.
2. The ability of biomarkers to predict non-AIDS death would differ by baseline HA level.

METHODS
Participants
All participants positive at baseline for HCV-RNA (HCV VL/mL) and/or HBsAg (denoted HBV), with baseline HA level and with stored plasma samples included. The study included data through the end of follow-up.

Biomarkers
D-dimer, IL-6 and hsCRP were measured in stored plasma samples at baseline and at month 6 during follow-up for all participants for Clinical Biochemistry at the University of Vermont. IL-6 was measured with Chemiluminescent Enzyme Immunosorbent Assay (CREIA), D-dimer with a KRYPTOR nephelometer, N Antiheart in Human CRP (Siemens Diagnostic), and D-dimer levels with Immunoblot development methods on the Sta-R analyzer, Leland D-Di (Diagnostic Stages).

Statistical methods
• Baseline biomarker levels were compared using Wilcoxon rank sum test.
• Percent change in biomarker level from baseline to month 6 was calculated after log transformation and adjustment for baseline level.
• Risk of non-AIDS death was estimated using Cox regression analysis adjusting for treatment group, age, gender, race, prior AIDS, baseline CD4 and RNA, radii CD4, baseline ART status, alcohol abuse and Hepatitis B status.

RESULTS
Baseline characteristics
A total of 5,472 participants enrolled in the SMART study from January 2002 - January 2006, 655 (12.0%) were HBV+ or HCV+, had HA measured at baseline and had baseline plasma samples available for biomarker analysis. There were no significant differences in baseline variables between the two randomization groups.

D-dimer, µg/mL * 0.27 (0.17 , 0.48)        0.28 (0.17 , 0.50)     0.27 (0.17, 0.49)

The interaction p-values for dichotomous HA x biomarker for non-AIDS death were 0.88, 0.89 and 0.63 for hsCRP, IL-6 and D-dimer, respectively. The results of the univariate analysis were similar.

Conclusions
• Baseline levels of IL-6 and D-dimer were significantly higher in HIV/hepatitis co-infected participants with elevated levels of the liver fibrosis marker HA.
• Intervention of ART led to increased levels of IL-6 only in participants who also had elevated HA, but unexpectedly corresponding increases in hsCRP were not observed.
• During follow-up the risk of non-AIDS death in participants with elevated baseline levels of either hsCRP, IL-6 and D-dimer was highest if HA was also elevated.

Biomarkers of Inflammation and Coagulation and Risk of Non-AIDS death in HIV/Hepatitis Coinfected Patients in the SMART Study

L Peters1, J Neaal2, D Dupree1, JD Neaton3, R Tracy4, MB Klein5, A Mosco2, J Rackstraw3, D Dore4, JD Lundgren6, for the INSIGHT SMART Study Group
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