Supplemental Table S1: Summary of studies assessing mainly inflammatory biomarkers and their association with mortality and clinical endpoints in HIV infection

First author, year, country	Biomarkers measured	Study design and population	Results	Overall conclusions
Ross, 2009 (1) USA	Common carotid artery and internal carotid artery IMT, TNF–α, hsCRP, IL-6, MLO, sVCAM-1	Case-control 73 HIV+, 21 HIV-	All biomarkers at higher level in HIV group	Hs-CRP positively correlated with carotid IMT in both groups. In the HIV+ group: sVCAM-1 positively correlated with all inflammatory cytokine levels. sVCAM-1, MLO, TNF-a all associated with internal carotid artery
Neuhaus, 2010 (2) USA	hs-CRP, IL-6, cystatin C	Individuals 45–76 years: 494 HIV+ individuals in the SMART study and 5386 uninfected participants in the MESA study. Individuals 33–44 years: hs-CRP and IL-6 levels compared in 287 HIV+ participants in the SMART study and 3231 participants in the CARDIA study.	hsCRP and IL-6 levels 55% (P=0.001) and 62% (P=0.001) higher among HIV+ group than CARDIA group. Compared with levels in MESA study participants, hsCRP, IL-6, D-dimer, and cystatin C levels were 50%, 152%, 94%, and 27% higher, respectively (P=0.001, for each), among HIV+ participants. HIV+ participants receiving HAART who had HIV RNA levels ≤400 copies/mL had levels higher (by 21% to 60%) (P= 0.001) than those in the general population, for all biomarkers.	hsCRP, IL-6, D-dimer, and cystatin C levels are elevated in persons with HIV infection Remain so even after HIV RNA levels are suppressed with HAART
Kuller, 2008 (3) USA	hsCRP, IL-6, amyloid A, amyloid P, D-dimer, prothrombin fragment 1þ2.	Case-control study as part of SMART 85 HIV+ deaths 170 HIV+ 'controls'	Higher levels of hsCRP, IL-6, and D-dimer at study entry significantly associated with an increased risk of all-cause mortality. Unadjusted ORs (highest versus lowest quartile) 2.0 (95% CI, 1.0–4.1; p= 0.05), 8.3 (95% CI, 3.3–20.8; p =0.0001), and 12.4 (95% CI, 4.2–37.0; p =0.0001), respectively.	IL-6 and D-dimer strongly related to all-cause mortality.

Sandler, 2011 (4) USA	I-FABP, LPS, sCD14, EndoCAb, and 16S (rDNA) measured in baseline plasma samples.	Nested case control from SMART study HIV+ group composed of: 74: died; 120: developed CVD; 81: developed AIDS Matched uninfected controls 2:1	Subjects with highest quartile of sCD14 levels had a 6-fold higher risk of death than did those in the lowest quartile (95% confidence interval, 2.2–16.1; P=0.001) No other marker was significantly associated with clinical outcomes. I-FABP, LPS, and sCD14 were increased and EndoCAb was decreased in study subjects, compared with healthy volunteers. sCD14 level correlated with levels of IL-6, C-reactive protein, serum amyloid A and D-dimer.	sCD14, is an independent predictor of mortality in HIV infection.
Ledwaba, 2012 (5) South Africa	Pre-ART plasma from patients with advanced HIV was used to measure hs-CRP, IL-6 and D-dimer	Nested case-control study 187 HIV+ deaths 359 HIV+ 'controls' matched on age, sex CD4 count	Median baseline biomarkers levels for cases and controls, respectively: 11.25 vs. 3.6 mg/L for hs-CRP; 1.41 vs. 0.98 mg/L for D-dimer; 9.02 vs. 4.20 pg/mL for IL-6 (all p=0.0001). Adjusted OR for the highest versus lowest quartile of baseline biomarker levels: 3.5 (95% CI: 1.9–6.7) for hs-CRP; 2.6 (95%CI 1.4–4.9) for D-dimer; 3.8 (95% CI: 1.8– 7.8) for IL-6. D-dimer and IL-6, but not hs-CRP, significantly lower at month 6 after commencing ART compared to baseline (p=0.0001)	Among patients with advanced HIV disease, elevated pre-ART levels of hs-CRP, IL-6 and D-dimer strongly associated with early mortality after commencing ART.
Armah, 2012 (6) USA	IL-6, D-dimer, and sCD14	1525 HIV+ 843 uninfected VACS participants	Elevated IL-6 in HIV+ individuals with HIV-1 RNA ≥500 copies/mL or CD4 count <200 cells/μL (OR:1.54; 95%CI: 1.14–2.09; OR, 2.25; 95% CI, 1.60–3.16, respectively) Elevated D-dimer (OR, 1.97; 95% CI, 1.44–2.71, OR, 1.68; 95%	Ongoing HIV replication and immune depletion significantly contribute to increased prevalence of elevated biomarkers of inflammation, altered coagulation, and monocyte

			CI, 1.22–2.32, respectively). Higher prevalence of elevated sCD14 in HIV-infected veterans with a CD4 cell count <200 cells/μL compared to uninfected veterans (OR, 2.60; 95% CI, 1.64–4.14).	activation. Associations persisted after restricting analysis to veterans without known confounding comorbid conditions.
Keating, 2011 (7) USA	Multiplex assays of 32 cytokines	Cross-sectional study - participants in the Women's Interagency HIV Study. HIV+ on HAART, n=17 Non-controllers*, n=14 Uninfected, n=17	Significant differences between non-controllers and uninfected participants for several markers: Elevated IP-10 and TNF-a Decreased IL-12(p40), IL-15, and FGF-2. Biomarker levels among HAART women more closely resembled the uninfected group, with the exception of TNF-a and FGF-2. Secondary analyses of combined HAART and non-controller groups: IP-10: positive correlation with viral load and negative correlation with $CD4^+$ T-cell counts. VEGF, EGF, and FGF-2: positive correlation with increased $CD4^+$ T-cell counts.	Untreated, progressive HIV infection associated with decreased serum levels of cytokines important in T-cell homeostasis (IL-15) and T-cell phenotype determination (IL-12 and increased levels of innate inflammatory mediators such as IP- 10 and TNF-a. HAART associated with cytokine profiles that more closely resembled those of HIV-uninfected women.
Kaplan, 2012 (8) USA	Six semi-annual measurements: soluble sCD14, TNF-a, soluble IL-2 receptor, IL-6, IL-10, monocyte chemoattractant protein 1, D-dimer, fibrinogen, and cIMT.	Women's Interagency HIV Study: 127 HIV+ women pre and post HAART 127 HIV-uninfected controls.	Relative to HIV-uninfected controls, HAART-naive HIV-infected women had elevated levels of sCD14, TNF-a, soluble IL-2 receptor, IL-10, monocyte chemo-attractant protein 1and D-dimer (all P<0.01). Elevated biomarker levels declined after HAART. Although most biomarkers normalized to HIV-uninfected levels, in women on effective HAART, TNF-a levels remained elevated compared with HIV-uninfected	Untreated HIV infection is associated with abnormal hemostasis (eg, D-dimer), proatherogenic (eg, TNF-a), and anti-atherogenic (eg, IL-10) inflammatory markers. HAART reduces most inflammatory mediators to HIV-uninfected levels. Increased inflammation and hemostasis are associated with

Kaplan, 2012 (8) USA	Six semi-annual measurements: soluble sCD14, TNF-a, soluble IL-2 receptor, IL-6, IL-10, monocyte chemoattractant protein 1, D-dimer, fibrinogen, and cIMT.	Women's Interagency HIV Study: 127 HIV+ women pre and post HAART 127 HIV-uninfected controls.	Relative to HIV-uninfected controls, HAART-naive HIV-infected women had elevated levels of sCD14, TNF-a, soluble IL-2 receptor, IL-10, monocyte chemo-attractant protein 1and D-dimer (all P<0.01). Elevated biomarker levels declined after HAART. Although most biomarkers normalized to HIV-uninfected levels, in women on effective HAART, TNF-a levels remained elevated compared with HIV-uninfected women (+0.8 pg/mL, P = 0.0002). Higher post-HAART levels of soluble IL-2 receptor IL-6, and D-dimer associated with increased cIMT	Untreated HIV infection is associated with abnormal hemostasis (eg, D-dimer), proatherogenic (eg, TNF-a), and anti-atherogenic (eg, IL-10) inflammatory markers. HAART reduces most inflammatory mediators to HIV-uninfected levels. Increased inflammation and hemostasis are associated with subclinical atherosclerosis in recently treated women.
Margolick, 2012 (9) USA	FP+ or FP- at two consecutive study visits	MACS cohort – 602 men 117 HIV-/FP- 20 HIV-/FP+ 393 HIV+/FP- 72 HIV+/FP+	In HIV+ FP+ men higher concentrations of IL-6, TNF-α; IL-8, IP-10, MCP-4, and TARC; and C-reactive protein Differences between FP+ and FP- HIV- men of similar magnitude but not significant CRP similar between HIV- FP+ and FP-.	Inflammatory markers had significant associations with FP in HIV+ men. Elevated IL-6, TNF-α, and CRP suggest monocyte activation. Elevation of IP-10 consistent with T-cell activation.

Abbreviations: (arranged alphabetically)

16S(rDNA), 16S ribosomal DNA; 95% CI, 95% Confidence Interval; ACGT, AIDS Clinical Trials Group; AIDS, Autoimmune deficiency syndrome; CARDIA, Coronary Artery Development in Young Adults; cIMT, carotid intima-media thickness; CSF, cerebrospinal fluid; HIV, Human immunodeficiency virus; CVD, Cardiovascular Disease; EGF, Epidermal Growth Factor; eGFR, estimated Glomerular Filtration Rate; EndoCAb, endotoxin core antibody; FGF-2, Fibroblast Growth Factor; FP, Frailty Phenotype;

References

1. Ross AC, Rizk N, O' Riordan MA, Dogra V, El-Bejjani D, Storer N*, et al.* Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy. Clinical Infectious Diseases. 2009;**49**:1119-1127.
2. Neuhaus J, Jacobs Jr DR, Baker JV, Calmy A, Duprez D, La Rosa A*, et al.* Markers of Inflammation, Coagulation, and Renal Function Are Elevated in Adults with HIV Infection. 2010;**201**:1788-1795.

3. Kuller LH, Tracy R, Belloso W, Wit SD, Drummond F, Lane HC*, et al.* Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. 2008;**5**:e203.
4. Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE*, et al.* Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection. Journal of Infectious Diseases. 2011;**203**:780-790.
5. Ledwaba L, Tavel JA, Khabo P, Maja P, Qin J, Sangweni P*, et al.* Pre-ART Levels of Inflammation and Coagulation Markers Are Strong Predictors of Death in a South African Cohort with Advanced HIV Disease. PLoS One. 2012;**7**:e24243.
6. Armah KA, McGinnis K, Baker J, Gibert C, Butt AA, Bryant KJ*, et al.* HIV Status, Burden of Comorbid Disease, and Biomarkers of Inflammation, Altered Coagulation, and Monocyte Activation. 2012;**55**:126-136.
7. Keating SM, Golub ET, Nowicki M, Young M, Anastos K, Crystal H*, et al.* The effect of HIV infection and HAART on inflammatory biomarkers in a population-based cohort of women. 2011;**25**:1823-1832.
8. Kaplan RC, Landay AL, Hodis HN, Gange SJ, Norris PJ, Young M*, et al.* Potential cardiovascular disease risk markers among HIV-infected women initiating antiretroviral treatment. 2012;**60**:359-368.
9. Margolick J, Jacobson L, Lopez J, Li X, Martinez- Maza O, Phair J*, et al.* Frailty and circulating concentrations of proinflammatory cytokines and chemokines in HIV-infected and –uninfected men in the Multicenter AIDS Cohort Study (MACS). 3rd International Workshop on HIV & Aging. Baltimore, MD, USA. 5th-6th November 2012.