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<th>First author, year, country</th>
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<td>Ross, 2009 (1) USA</td>
<td>Common carotid artery and internal carotid artery IMT, TNF-α, hsCRP, IL-6, MLO, sVCAM-1</td>
<td>Case-control 73 HIV+, 21 HIV-</td>
<td>All biomarkers at higher level in HIV group</td>
<td>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</td>
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<td>Neuhaus, 2010 (2) USA</td>
<td>hs-CRP, IL-6, cystatin C</td>
<td>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.</td>
<td>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.</td>
<td>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</td>
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<td>Kuller, 2008 (3) USA</td>
<td>hsCRP, IL-6, amyloid A, amyloid P, D-dimer, prothrombin fragment 1p2.</td>
<td>Case-control study as part of SMART 85 HIV+ deaths 170 HIV+ ‘controls’</td>
<td>Higher levels of hsCRP, IL-6, and D-dimer at study entry significantly associated with an increased risk of all-cause mortality.</td>
<td>IL-6 and D-dimer strongly related to all-cause mortality.</td>
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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
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).

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 chemoattractant protein 1 and 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

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<td>Interagency HIV Study</td>
<td>Six semi-annual measurements: soluble sCD14, TNF-α, soluble IL-2 receptor, IL-6, IL-10, monocyte chemoattractant protein 1, D-dimer, fibrinogen, and cIMT.</td>
<td>Relative to HIV-uninfected controls, HAART-naive HIV-infected women had elevated levels of sCD14, TNF-α, soluble IL-2 receptor, IL-10, monocyte chemoattractant protein 1 and D-dimer (all P&lt;0.01). Elevated biomarker levels declined after HAART. Although most biomarkers normalized to HIV-uninfected levels, in women on effective HAART, TNF-α 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.</td>
<td>Untreated HIV infection is associated with abnormal hemostasis (eg, D-dimer), proatherogenic (eg, TNF-α), 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.</td>
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Margolick, 2012 (9) USA

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<td>MACS cohort – 602 men</td>
<td>FP+ or FP- at two consecutive study visits</td>
<td>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-.</td>
<td>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.</td>
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**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; EGF-2, Fibroblast Growth Factor; FP, Fibrinogen-related apoptosis superfamily receptors; sTRAIL,

**References**