

# Effect of endothelial activation biomarkers, including plasma angiotensin-1 and angiotensin-2, in Kenyan women initiating antiretroviral therapy

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## Abstract:

**BACKGROUND:** HIV-1-related inflammation is associated with increased levels of biomarkers of vascular adhesion and endothelial activation, and may increase production of the inflammatory protein angiotensin-2 (ANG-2), an adverse prognostic biomarker in severe systemic infection. We hypothesized that antiretroviral therapy (ART) initiation would decrease endothelial activation, reducing plasma levels of ANG-2. **METHODS:** Antiretroviral-naïve Kenyan women with advanced HIV infection were followed prospectively. Endothelial activation biomarkers including soluble intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and E-selectin, and plasma ANG-2 and angiotensin-1 (ANG-1) were tested in stored plasma samples from 0, 6, and 12 months after ART initiation. We used Wilcoxon matched-pairs signed rank tests to compare endothelial activation biomarkers across time-points, generalized estimating equations to analyze associations with change in log<sub>10</sub>-transformed biomarkers after ART initiation, and Cox proportional-hazards regression to analyze associations with mortality. **RESULTS:** The 102 HIV-1-seropositive women studied had advanced infection (median CD4 count, 124 cells/μL). Soluble ICAM-1 and plasma ANG-2 levels decreased at both time-points after ART initiation, with concomitant increases in the beneficial protein ANG-1. Higher ANG-2 levels after ART initiation were associated with higher plasma HIV-1 RNA, oral contraceptive pill use, pregnancy, severe malnutrition, and tuberculosis. Baseline ANG-2 levels were higher among five women who died after ART initiation than among women who did not (median 2.85 ng/mL [inter-quartile range (IQR) 2.47--5.74 ng/mL] versus median 1.32 ng/mL [IQR 0.35--2.18 ng/mL],  $p = 0.01$ ). Both soluble ICAM-1 and plasma ANG-2 levels predicted mortality after ART initiation. **CONCLUSIONS:** Biomarkers of endothelial activation decreased after ART initiation in women with advanced HIV-1 infection. Changes in plasma ANG-2 were associated with HIV-1 RNA levels over 12 months of follow-up. Soluble ICAM-1 and plasma ANG-2 levels represent potential biomarkers for adverse outcomes in advanced HIV-1 infection.