293

Inflammatory Biomarker Changes after Antiretroviral Treatment (ART) Initiation

Angelidou K [1], Hunt PW [2], Tenorio AR [3], Landay AL [4], Wilson CC [5], Rodriguez B [6], Deeks SG [2], Bosch RJ [1], Lederman MM [6]

[1] Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA; [2] San Francisco General Hospital, University of California, San Francisco, CA; [3] ViiV Healthcare, RTP, North Carolina, NC; [4] Department of Medicine, Rush University Medical Center, Chicago, IL; [5] University of Colorado Hospital, Aurora, CO; [6] Case Western Reserve University School of Medicine, Cleveland, OH

Konstantia Angelidou
Harvard T.H. Chan School Of Public Health
651 Huntington Avenue
FXB 519
Boston, MA 02115
617-432-2524
kangelid@sdac.harvard.edu

BACKGROUND

Elevated levels of inflammatory biomarkers are associated with HIV-associated non-AIDS morbidity and death, even with viral suppression on antiretroviral therapy (ART) (*Kuller 2008, Duprez 2012*).

Inflammatory cytokine levels pre- and one year post-ART were associated with incident non-AIDS events after one year in a nested case-control study of ACTG A5001 of well-treated HIV-infected adult population (*Tenorio 2014*).

OBJECTIVES

- To evaluate changes in inflammatory biomarkers after ART initiation.
- To evaluate if changes in inflammatory biomarkers are associated with non-AIDS events, independently and after adjusting for correlates.

METHODS

HIV-infected adults from the ACTG 5001 cohort, ART-naïve, who received ART regimen, and were virally suppressed (<400 copies/mL) at year 1 of ART.

- **142 cases:** non-accidental non–AIDS death, myocardial infarction (MI) stroke, non–AIDS malignancy, serious bacterial infection after year 1 while remaining virally suppressed.
- **302 matched controls:** endpoint-free follow-up time, matched for age, sex, baseline CD4+ T-cells (within 50 cells/mm^3), ART regimen at week 48 (whether protease-inhibitor containing or not, and whether abacavir-containing or not), and parent (initial randomized) study.

Stored plasma from pre-ART (Y0), year 1 (Y1) and at the visit preceding an event was tested for inflammatory biomarkers: interleukin-6 (IL-6), soluble CD14 (sCD14), soluble TNF receptors (sTNFR-1, sTNFR-2) and D-dimer.

STATISTICAL ANALYSIS

Unadjusted and partial Spearman correlations evaluated among controls the associations between levels and changes of inflammatory biomarkers with pre-ART factors: HIV-1 RNA (VL), CD4, CD4:CD8 ratio, CD8, age, waist-hip ratio (WHR).

Conditional logistic regression analysis was used to study the associations of inflammatory biomarker changes at year 1 and at a pre-event time with non-AIDS events. Odds ratios (OR) per IQR and 95% confidence intervals (CI) for each inflammatory biomarker were computed.

Multivariable models adjusted for CD4 count, Hepatitis B/C, IV drug use, waist-hip ratio (WHR), diabetes, hypertension, anti-hypertensive or lipid lowering agents, smoking, family history of MI *(Krishnan CROI 2014)*

RESULTS

Cases: Median pre-ART age was 46 years; 85% were male; median Y0 CD4 208 cells/mm^3 and VL 64,847 copies/mL
Controls: Median pre-ART age was 44 years; 85% were male; median Y0 CD4 215 cells/mm^3 and VL 64,371 copies/mL

Biomarker changes

Figure 1: Changes from baseline to Y1

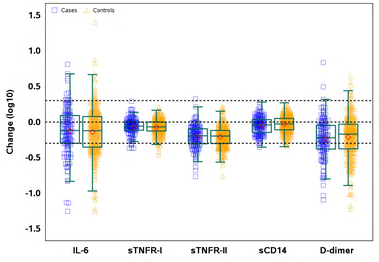
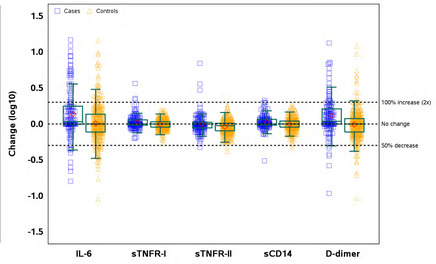


Figure 2: Changes from Y1 to pre-event time



Summary

Biomarker levels for Controls:

Higher biomarker levels at Y0 and Y1 (except for Y1 D-dimer) correlated with higher Y0 VL (p<0.05) and lower Y0 CD4 (p<0.05)

Biomarker changes Y0 to Y1:

All biomarkers declined (p<0.0001) for cases and controls (Figure 1)

Controls: Correlations (p-values) of pre-ART factors with changes in inflammatory biomarkers

Pre-ART factors	Changes of Inflammatory Biomarkers: Y1 – Y0 (controls)				
	IL-6	sTNFR-I	sTNFR-II	sCD14	D-dimer
HIV-1 RNA	**-0.17 (0.002)**	**-0.32 (<0.001)**	**-0.36 (<0.001)**	**-0.42 (<0.001)**	**-0.28 (<0.001)**
CD4	**0.27 (<0.001)**	**0.40 (<0.001)**	**0.39 (<0.001)**	**0.43 (<0.001)**	**0.41 (<0.001)**
CD4:CD8 ratio	**0.22 (<0.001)**	**0.39 (<0.001)**	**0.43 (<0.001)**	**0.41 (<0.001)**	**0.40 (<0.001)**
CD8	0.10 (0.08)	0.08 (0.16)	-0.04 (0.44)	0.06 (0.30)	0.06 (0.30)
Age	-0.06 (0.30)	-0.07 (0.26)	**-0.13 (0.02)**	**-0.12 (0.04)**	**-0.12 (0.03)**
Waist-hip ratio	-0.01 (0.88)	-0.10 (0.11)	-0.06 (0.32)	**-0.20 (0.002)**	**-0.17 (0.01)**

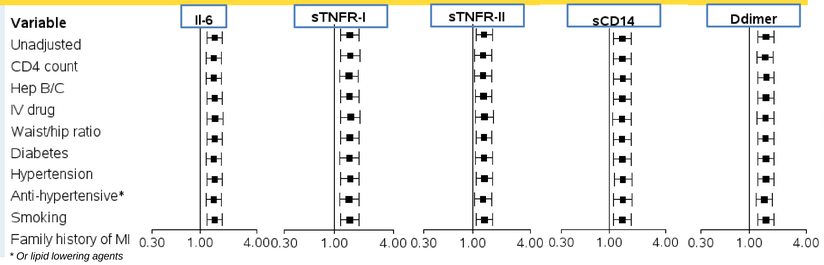
Y0 to Y1 declines were greater for:

- high Y0 VL (p<0.002)
- low Y0 CD4 (p<0.001)
  - even after Y0 VL adjustment
- low Y0 CD4:CD8 (p<0.001)
  - even after Y0 VL adjustment
- older participants for sTNFR-II, sCD14 and D-dimer (p<0.04)
- those with higher WHR for sCD14 and D-dimer (p<0.01)

Association between risk of event and changes of biomarkers from year 1 to the visit preceding the event (Figure 3)

Though higher Y1 levels for all biomarkers were significantly associated with incident non-AIDS events (cases vs. controls), greater declines in biomarkers at Y1 showed no significant associations.

Cases, had significantly greater increases than controls from Y1 to the visit preceding the event (p<0.02). Univariate and adjusted findings were similar (OR per 1 IQR increase are presented in Figure 3).



CONCLUSIONS

- **Inflammatory biomarkers decreased after 1 year of ART** (Figure 1; consistent with Wada 2015) **and subsequently remained mostly stable in controls** (Figure 2)
- **Greater increases in cases prior to a non-AIDS event may reflect subclinical disease processes**
- **Controls with greater pre-ART viral load levels or lower pre-ART CD4 levels had higher biomarker levels at year 1 after ART initiation while also experiencing the greater biomarker declines in the first year of ART**
- **Results support earlier initiation of ART in HIV-infected adults since low pre-ART CD4 result in higher year 1 biomarker levels**

REFERENCES

- Kuller LH, Tracy R, Belloso W, et al. **Inflammatory and coagulation biomarkers and mortality in patients with HIV infection.** PLoS Med 2008; 5:e203
- Duprez DA, Neuhaus J, Kuller LH, et al. **Inflammation, coagulation and cardiovascular disease in HIV-infected individuals.** PLoS One. 2012;7(9):e44454.
- Tenorio AI, Zheng Y, Bosch R, et al. **Soluble markers of inflammation & coagulation, but not T-cell activation, predict non-AIDS-defining morbid events during suppressive antiretroviral therapy.** J Infect Dis. 2014; 210 (8):1248-59
- Krishnan S, Bosch RJ, Rodriguez B, et al. **Correlates of inflammatory markers after one year of suppressive antiretroviral treatment.** Presented at the 21th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, MA, March, 2014.
- Wada NI, Jacobson LP, Margolick JB, et al. **The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation.** AIDS 2015, 29:463-471

ACKNOWLEDGMENTS

We would like to thank the ALLRT participants and protocol team, the ACTG clinical trial sites that enrolled and followed the participants, and the ACTG. This work was supported by grants from the National Institute of Health UM1 AI068636 to MML and ALL, U01 AI068634 to YZ, RJB and SK, K24 AI069994 to SGD, AI36219 to MML, R21 AI087035 to PWH, and U01 AI069471 to ART