Coagulation and Morbidity in Treated HIV Infection

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Although survival has improved, predicted life expectancy still seems shorter in the HIV+ population

Many Age-associated Diseases Are More Common in Treated HIV Disease Than In Age-matched Uninfected Persons

- Cardiovascular disease
- Cancer (non-AIDS)
- Bone fractures/osteopenia
- Left ventricular dysfunction
- Lung Disease
- Liver failure
- Kidney failure
- Cognitive decline
- Frailty

Multiple factors likely explain this increased risk, including co-morbid conditions, other exposures, ARV drug toxicity

S. Deeks
Inflammation/coagulation predicts morbidity/mortality in HIV infection in “SMART”

- Interleukin-6
- D-dimers
- C-reactive protein

- Kuller et al PLOS Medicine ‘08
NWCS 329

• Nested case control study within the ACTG ALLRT cohort
• Cases (n=143): Virologically suppressed (VL < 400 copies/ml) ART-treated subjects with:
  – Non-accidental death
  – Non-AIDS morbidity
    • Myocardial infarction
    • Stroke
    • Malignancy
    • Serious bacterial infections
• Controls: 2 virologically suppressed subjects matched for:
  – Age
  – Gender and sex
  – Baseline CD4+ T-cells (within 50 cells/mm3)
  – ART regimen at week 48 (PI- or ABC-containing or not)
  – Parent study
NWCS 329 in treated HIV Infection, pre-Event Soluble Markers relate to Outcome

<table>
<thead>
<tr>
<th>Pre-event Marker</th>
<th>Odds Ratio per 1 IQR increase</th>
<th>P Value</th>
<th>OR for:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td>IL6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.58 (1.91-3.48)</td>
<td>&lt;.001**</td>
<td>20.9**</td>
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<tr>
<td>Adjusted*</td>
<td>2.48 (1.83-3.35)</td>
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<tr>
<td>IP-10</td>
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<tr>
<td>Unadjusted</td>
<td>1.49 (1.16-1.91)</td>
<td>0.002**</td>
<td>1.9</td>
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<tr>
<td>Adjusted*</td>
<td>1.42 (1.10-1.84)</td>
<td>0.007**</td>
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<td>sTNFr-I</td>
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<td></td>
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<tr>
<td>Unadjusted</td>
<td>1.99 (1.49-2.66)</td>
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<td>3.3**</td>
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<tr>
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<td>1.94 (1.45-2.60)</td>
<td>&lt;.001**</td>
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<td>sTNFr-II</td>
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<tr>
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<td>2.6**</td>
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<tr>
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<td>1.81 (1.38-2.38)</td>
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<td>Soluble CD14</td>
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<tr>
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<td>1.74 (1.29-2.35)</td>
<td>&lt;.001**</td>
<td>2.7*</td>
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<tr>
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<td>1.67 (1.23-2.27)</td>
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<td>D-Dimer</td>
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<tr>
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<td>8.4**</td>
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<td>2.38 (1.75-3.25)</td>
<td>&lt;.001**</td>
<td>8.1**</td>
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<td>CD8+ %DR+38+</td>
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<tr>
<td>Unadjusted</td>
<td>1.06 (0.88-1.28)</td>
<td>0.516</td>
<td>1.4</td>
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<tr>
<td>Adjusted*</td>
<td>0.98 (0.80-1.20)</td>
<td>0.863</td>
<td>0.8</td>
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</tbody>
</table>

**Similar findings by Hunt et al JID ‘14**

*Adjusted by CD4 count
Arteries are inflamed in treated HIV infection

Subramanian et al JAMA ‘12
Monocyte subsets can be identified by expression of CD14 and CD16

Funderburg et al. *Blood* 2012
Proportions of inflammatory and patrolling monocytes are increased in HIV disease

Funderburg et al. Blood 2012
Monocytes elaborate inflammatory mediators (IL-6, TNF, IL-18, IL-1β, IL-10) in response to microbial elements.
Tissue Factor – a cell surface protein that activates the Extrinsic Coagulation Pathway

Cell surface

Goodsell *The Oncologist* 2006
Microbial Products may drive coagulation via induction of the procoagulant Tissue Factor on Monocytes

TF MFI

No Stim 331
LPS 20ng 1194
Flagellin 1ug 2336

Funderburg et al, Blood ‘10
Inflammatory and Patrolling monocytes are enriched for the procoagulant Tissue Factor in HIV infection and in uninfected persons with Acute Coronary Syndromes.
Like LPS, oxidized LDL (but not LDL) alters inflammatory profiles of blood monocytes.
Like LPS, oxidized LDL (but not LDL) increases Tissue factor expression on blood monocytes.
Plasma levels of oxLDL are increased in HIV infection

Ox LDL - correlated to sCD14, TF levels on patrolling monocytes and Framingham Risk

Zidar, Funderbug et al
CD8 T cell homeostasis in HIV infection

- CD8 T cell expansion is characteristic of untreated HIV infection
  - and often persists after ART
- These are matured effector cells, often senescent and “exhausted” yet capable of robust inflammatory cytokine expression
- In setting of ART, expanded CD8 T cells are not HIV-reactive
  - Drivers of persistent CD8 T cell expansion in this setting are not defined
- CD8 T cell expansion and resultant low CD4/CD8 ratios predict morbid outcomes in treated HIV infection
  (Serrano-Villar et al PLOS One ’13, Lee et al JID ‘14, Serrano-Villar PLOS Pathogens ‘14)
Even with complete virologic control and CD4 T cell restoration, CD8 T lymphocytosis persists for many years.

Mann-Whitney
p=<0.0001

Carey Shive, JC Mudd unpublished
Do CD8 T cells contribute to the development of atherosclerotic plaque?

• Activated CD8+ T cell numbers in blood linked to atherosclerotic plaque in treated HIV infection (Kaplan ‘11, Longenecker ‘12)

• And are found within them (Grivel ‘11)
Circulating CD8 T cells exclusively express CX3CR1 or CCR7

JC Mudd, unpublished
CD8 T cells expressing CX3CR1 are relatively (and absolutely) expanded in treated HIV infection

JC Mudd, unpublished
CX3CR1+ CD8 T cells are enriched for protease activated receptor (PAR-1) expression and PAR-1+ cells are increased in treated HIV-infection.

PAR-1 is cleaved and activated by Thrombin.
Coagulation driven by activated monocytes may recruit and activate CX3CR1+ PAR-1+ CD8 T cells at endothelial surfaces.
Summary

• Persons with HIV infection are at increased risk for cardiovascular and other morbidities of aging: this risk is predicted by indices of coagulation and inflammation

• Monocyte subsets are inflammatory and procoagulant in HIV infection; this phenotype may be driven by microbial products translocated from the damaged gut and by inflammatory lipids

• Mature CD8 T cell numbers are expanded in HIV infection, home to endovascular sites and are linked to ART-era cardiovascular morbidities.

• Coagulation and inflammation collaborate to drive increased CVD risk in treated HIV infection.
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