A View on the Role of Inflammation in Chronic Diseases and Aging

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University of Vermont College of Medicine

With respect to inflammation & aging:
“Yep, son, we have met the enemy and he is us!”
Pogo to Porky (as written by Walt Kelly), 1971

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HIV & Aging

Outline of this Talk

• A Perspective on Inflammation and Inflammation Biomarkers
• A Perspective on Chronic Disease & Aging
• Can We Learn about Aging from HIV?
• A few “Conclusions”
HIV, Inflammation, and Aging

“Inflammation”

CRP

----------IL-6----------

Innate Immunity  Adaptive Immunity

Coagulation/Thrombosis

D-dimer

Biomarkers are available; many other aspects, but we have focused on these
Inflammation, Inflammatory Mediators and Aging

• INFLAMMATION:
  • Homeostatic tissue remodeling – capacity declines with age:
    • Tissue is first destroyed, then rebuilt;
    • Quality declines with age; e.g., bone density
  • Bacterial/viral defense – capacity declines with age:
    • Inflammation components kill microorganisms, then clean up the residue;
    • Immunosenescence leads to increased vulnerability with age;
  • Wound repair – capacity declines with age:
    • similar to remodeling, but more aggressive “rebuilding”;
    • rebuilt tissue not of the same quality as the starting tissue – often fibrotic;
    • Chronic low-level “wound repair”: response to continued low-level insult:
      • the rebuilt tissue is often fibrotic and not as functional contributing to loss of organ function; many examples:
        • Atherosclerosis (lipid infiltration)
        • Liver cirrhosis (e.g., alcohol)
        • Chronic obstructive pulmonary disease (e.g., smoking)
        • etc
Bone Remodeling: an Example of How Remodeling Goes Wrong

Note decline in Bone Mass Post-40 YO

- We remodel at different rates in different tissues:
  - Bone, liver, fat – 5-10%/year;
  - Brain – limited cellular turnover;
  - Cardiomyocytes – 1-2% /year;
  - Skin epithelial cell – frequent; lifespan of a cell ~2-4 weeks;
- In bone, initially this yields improved bone; later, in life worse bone;
- What is the cause of this loss in remodeling efficiency? Many candidate mechanisms…..

Bergmann et al., Science. 324: 98-102, 2009
Age-Related Cardiorespiratory Fitness (CRF) Changes in Women and Men

Changes are expressed in metabolic equivalents (METS) (A) and as a percentage of peak CRF (B).


Slide courtesy Lew Kuller
How long should we live?
Forces that have shaped our genetic architecture

Rectangularization of the “Health Curve” (aka the compression of morbidity) is the “Holy Grail” of Aging Research: “Live long and die fast”
HIV & Aging

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• A few “Conclusions”
Humans as integrated organisms: a decline in one system affects all
Is vascular decline of particular importance?

“Longevity is a vascular question, which has been well expressed in the axiom ‘a man is as old as his arteries.’
To a majority of men, death comes primarily or secondarily through this portal.” William Osler, 1892.
Both Innate and Adaptive Immunity are Involved:

Plus other components of the Innate Immune System such as:

- Complement
- Pentraxins
  * CRP
  * SAP
  * PTX-3
- MØ TF → IIa
People with increased biomarkers of inflammation have increased risk of heart attack.

CRP in the Physicians Health Study


Laboratory for Clinical Biochemistry Research
University of Vermont
Associations of factor VIIIc, D-dimer, and plasmin–antiplasmin with incident cardiovascular disease and all-cause mortality

Aaron R. Folsom,1* Joseph A.C. Delaney,2 Pamela L. Lutsey,1 Neil A. Zakai,3,4 Nancy S. Jenny,4 Joseph F. Polak,5 and Mary Cushman3,4 for the Multiethnic Study of Atherosclerosis Investigators

**TABLE II. Hazard Ratio and 95% Confidence Interval for Study Endpoints by Quartile of D-Dimer, MESA, 2000–2006**

<table>
<thead>
<tr>
<th>Outcome model</th>
<th>D-dimer quartiles</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>≤0.13 µg/mL</td>
<td>0.14–0.20 µg/mL</td>
<td>0.21–0.37 µg/mL</td>
<td>&gt;0.37 µg/mL</td>
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</tr>
<tr>
<td>Total CVD</td>
<td>Events</td>
<td>56</td>
<td>51</td>
<td>98</td>
<td>102</td>
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<tr>
<td></td>
<td>Person-years</td>
<td>8516</td>
<td>6230</td>
<td>7251</td>
<td>6804</td>
</tr>
<tr>
<td>Crude</td>
<td>1.00 (Reference)</td>
<td>1.25 (0.85–1.83)</td>
<td>2.07 (1.49–2.87)</td>
<td>2.29 (1.66–3.18)</td>
<td></td>
</tr>
<tr>
<td>Age, sex, and race adjusted</td>
<td>1.00 (Reference)</td>
<td>1.01 (0.69–1.49)</td>
<td>1.41 (1.00–2.00)</td>
<td>1.29 (0.90–1.85)</td>
<td></td>
</tr>
<tr>
<td>Age, sex, race, and risk factor(1) adjusted</td>
<td>1.00 (Reference)</td>
<td>0.92 (0.62–1.35)</td>
<td>1.30 (0.92–1.84)</td>
<td>1.08 (0.75–1.55)</td>
<td></td>
</tr>
<tr>
<td>Also adjusted for IL-6, fibrinogen, and CRP</td>
<td>1.00 (Reference)</td>
<td>0.87 (0.59–1.28)</td>
<td>1.20 (0.84–1.70)</td>
<td>0.95 (0.65–1.39)</td>
<td></td>
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<tr>
<td>Hard CHD</td>
<td>Events</td>
<td>32</td>
<td>36</td>
<td>68</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Person-years</td>
<td>8575</td>
<td>6267</td>
<td>7329</td>
<td>6866</td>
</tr>
<tr>
<td>Crude</td>
<td>1.00 (Reference)</td>
<td>1.55 (0.96–2.49)</td>
<td>2.51 (1.65–3.82)</td>
<td>2.80 (1.84–4.25)</td>
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<tr>
<td>Age, sex, and race adjusted</td>
<td>1.00 (Reference)</td>
<td>1.24 (0.76–2.00)</td>
<td>1.69 (1.09–2.62)</td>
<td>1.55 (0.98–2.44)</td>
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<tr>
<td>Age, sex, race, and risk factor(1) adjusted</td>
<td>1.00 (Reference)</td>
<td>1.11 (0.69–1.81)</td>
<td>1.53 (0.98–2.38)</td>
<td>1.27 (0.80–2.01)</td>
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<tr>
<td>Also adjusted for IL-6, fibrinogen, and CRP</td>
<td>1.00 (Reference)</td>
<td>1.05 (0.64–1.71)</td>
<td>1.41 (0.90–2.21)</td>
<td>1.11 (0.69–1.79)</td>
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<tr>
<td>Total Mortality</td>
<td>Events</td>
<td>21</td>
<td>34</td>
<td>58</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Person-years</td>
<td>8796</td>
<td>6479</td>
<td>7533</td>
<td>7124</td>
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<tr>
<td>Crude</td>
<td>1.00 (Reference)</td>
<td>2.21 (1.28–3.30)</td>
<td>3.26 (1.98–5.37)</td>
<td>5.79 (3.61–9.28)</td>
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<tr>
<td>Age, sex, and race adjusted</td>
<td>1.00 (Reference)</td>
<td>1.69 (0.97–2.92)</td>
<td>1.98 (1.18–3.31)</td>
<td>2.75 (1.66–4.55)</td>
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<tr>
<td>Age, sex, race, and risk factor(1) adjusted</td>
<td>1.00 (Reference)</td>
<td>1.62 (0.94–2.81)</td>
<td>1.91 (1.14–3.21)</td>
<td>2.57 (1.54–4.27)</td>
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<tr>
<td>Also adjusted for IL-6, fibrinogen, and CRP</td>
<td>1.00 (Reference)</td>
<td>1.48 (0.85–2.58)</td>
<td>1.70 (1.00–2.87)</td>
<td>2.14 (1.27–3.61)</td>
<td></td>
</tr>
</tbody>
</table>

* Body mass index, systolic blood pressure, antihypertensive medications, LDL and HDL cholesterol, statin use, usual alcohol intake, smoking status, cigarette pack-years, exercise, and glycemia status.

Epidemiologically, chronic diseases of aging are associated with inflammation biomarkers

Incident outcomes associated with higher inflammation markers include:

- Atherosclerosis
- Acute & Chronic CVD (MI, CHF, SCD)
- MetSyn & Type 2 diabetes
- Some cancers
- Dementia
- COPD
- CKD
- Frailty
- Essentially all chronic diseases of old age

Inflammation is a Foundational Biological Process
Inflammation biomarkers predict early mortality especially strongly in the elderly

Cardiovascular Health Study: N ~2500 men >65 years at baseline
The outcome is CVD mortality within 3 years of baseline

HR ~ 20

CRP Quartiles
FGN Quartiles
Inflammatory Cytokines Go Up with Age

InChianti: Information on inflammatory markers, cardiovascular risk factors, and diseases was collected in 595 men and 748 women sampled from the general population (age, 20-102 years)

CRP and Fibrinogen go up with age

But go up much less in models which assume a low risk profile and no major co-morbidities, especially CVD
Cellular Epidemiology

• We’re using molecular epidemiology extensively, and will continue to do so;
• However, the limitations are clear:
  – Specificity for particular tissue/pathway;
  – Sensitivity in easily obtained biospecimens;
  – Choices are many and hugely covariate;
• Cellular epidemiology allows for:
  – Increased specificity (not perfect, since it \textit{ex vivo})
  – Dynamic interrogation;
  – Potentially increased sensitivity;
Ho: T Helper bias towards Th1 cells is associated with atherosclerosis; the Multi-Ethnic Study of Atherosclerosis (MESA)

- 45 to 84 years old, free of clinically apparent CVD
- **1000 individuals** randomly selected in exam 4, 2006 - 2007
  - 57% women, 46% Caucasian, 10% Asian American, 21% African American, and 23% Hispanic
- Cellular epidemiology including T Helper bias
## MESA Inflammation: Prediction of T Cell Indices

<table>
<thead>
<tr>
<th>Variable (increment)</th>
<th>%CD4 Coef.</th>
<th>%CD4 P value</th>
<th>%Th1 Coef.</th>
<th>%Th1 P value</th>
<th>%Th2 Coef.</th>
<th>%Th2 P value</th>
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</thead>
<tbody>
<tr>
<td>Age (10 yr increase)</td>
<td>ns</td>
<td>-0.86</td>
<td>&lt;0.005</td>
<td>ns</td>
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<tr>
<td>Sex (male vs female)</td>
<td>-3.17</td>
<td>&lt;0.005</td>
<td>1.12</td>
<td>&lt;0.05</td>
<td>ns</td>
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<tr>
<td>Race (vs European American)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian American</td>
<td>-7.73</td>
<td>&lt;0.001</td>
<td>0.09</td>
<td>ns</td>
<td>0.31</td>
<td>&lt;0.01</td>
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<tr>
<td>African American</td>
<td>-9.01</td>
<td>&lt;0.001</td>
<td>1.08</td>
<td>ns</td>
<td>0.33</td>
<td>&lt;0.001</td>
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<tr>
<td>Hispanic American</td>
<td>-4.34</td>
<td>&lt;0.001</td>
<td>0.78</td>
<td>ns</td>
<td>0.10</td>
<td>ns</td>
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<tr>
<td>Season (vs Winter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Spring</td>
<td>0.16</td>
<td>ns</td>
<td>1.44</td>
<td>&lt;0.05</td>
<td>ns</td>
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<tr>
<td>Summer</td>
<td>-7.39</td>
<td>&lt;0.001</td>
<td>3.03</td>
<td>&lt;0.01</td>
<td>0.53</td>
<td>&lt;0.001</td>
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<tr>
<td>Fall</td>
<td>-0.23</td>
<td>ns</td>
<td>0.35</td>
<td>ns</td>
<td>0.25</td>
<td>&lt;0.001</td>
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<tr>
<td>CMV (vs 0.0 EU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1 – 99.9 EU/ml</td>
<td>-4.84</td>
<td>&lt;0.001</td>
<td>4.02</td>
<td>&lt;0.001</td>
<td>ns</td>
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<tr>
<td>100 – 199.9 EU/ml</td>
<td>-4.48</td>
<td>&lt;0.005</td>
<td>7.94</td>
<td>&lt;0.001</td>
<td>ns</td>
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<tr>
<td>200 – 299.9 EU/ml</td>
<td>-7.35</td>
<td>&lt;0.001</td>
<td>9.30</td>
<td>&lt;0.001</td>
<td>ns</td>
<td></td>
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<tr>
<td>IL-6 (pg/ml)</td>
<td>-1.19</td>
<td>&lt;0.01</td>
<td>0.50</td>
<td>&lt;0.05</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Model R²</td>
<td>0.15</td>
<td></td>
<td>0.21</td>
<td></td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Median (SD)</td>
<td>40 (10)</td>
<td></td>
<td>16 (8)</td>
<td></td>
<td>0.85 (0.8)</td>
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</tbody>
</table>
# MESA Inflammation: Prediction of Atherosclerosis

<table>
<thead>
<tr>
<th>Variable (increment)</th>
<th>Ln CAC (n=552)</th>
<th>cIMT-common (n=905)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coef.</td>
<td>P value</td>
</tr>
<tr>
<td>Age (10 yr increase)</td>
<td>0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race (vs European American)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian American</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Hispanic American</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sys blood pressure (10 mmHg)</td>
<td>ns</td>
<td>0.02</td>
</tr>
<tr>
<td>dia blood pressure (10 mmHg)</td>
<td>ns</td>
<td>-0.02</td>
</tr>
<tr>
<td>BMI (5 kg/m$^2$)</td>
<td>ns</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking (vs never smoker)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>0.39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Current</td>
<td>0.61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cell-based analytes</td>
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<td></td>
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<tr>
<td>%Th1 (10%)</td>
<td>0.25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>%Th2 (1%)</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Model $R^2$</td>
<td>0.17</td>
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</table>
HIV & Aging

Outline of this Talk

• A Perspective on Inflammation and Inflammation Biomarkers
• A Perspective on Chronic Disease & Aging
• Can We Learn about Aging from HIV?
• A few “Conclusions”
Does HIV accelerate the decline in health associated with aging?
Inflammation, Atherosclerosis, and HIV

Inflammation & HIV/AIDS – four points:

• Despite being an “immunodeficiency” disease, HIV/AIDS is an inflammatory disorder;

• Inflammation is associated with risk of death from all causes not just AIDS-related;

• HIV is associated with long-term decreased adaptive immunity;

• Co-morbidities are critical to understanding biomarkers and risk factors in HIV/AIDS
A. Percentage difference in the levels of hsCRP and IL–6 in HIV–infected study participants 33–44 years of age vs. the general population.

B. Percentage difference in the levels of hsCRP, IL-6, D-dimer, and cystatin C in HIV-infected study participants 45–76 years of age vs. the general population

Cumulative Deaths Over Time by D-dimer Quartile

**SMART/ESPRIT control arms with HIV RNA <500 at entry (n=3227)**

Inflammation, Atherosclerosis, and HIV

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• HIV is associated with long-term decreased adaptive immunity;

• Co-morbidities are critical to understanding biomarkers and risk factors in HIV/AIDS
## Cause of Death in CHS vs SMART

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>CHS</th>
<th>SMART, unadj</th>
<th>SMART, adj*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD/Stroke</td>
<td>33</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>non-AIDS Cancer</td>
<td>19</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5</td>
<td>3.3</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>60</td>
<td>46</td>
</tr>
</tbody>
</table>

* Adjusting = remove AIDS, Substance abuse, Violent/suicide
Inflammation & HIV/AIDS – four points:

• Despite being an “immunodeficiency” disease HIV/AIDS is an inflammatory disorder;

• Inflammation is associated with risk of death from all causes not just AIDS-related;

• HIV is associated with long-term decreased adaptive immunity

• Co-morbidities are critical to understanding biomarkers and risk factors in HIV/AIDS
HIV Replicates in Lymphoid Tissues
Possible reservoir for virus.....
Inflammation, Atherosclerosis, and Aging

Microbial translocation is a cause of systemic immune activation in chronic HIV infection

Jason M Brenchley¹, David A Price¹, Timothy W Schacker², Tedi E Asher¹, Guido Silvestri³, Srinivas Rao⁴, Zachary Kazzaz¹, Ethan Bornstein¹, Olivier Lambotte⁵, Daniel Altmann⁶, Bruce R Blazar⁷, Benigno Rodriguez⁸, Leila Teixeira-Johnson⁸, Alan Landay⁹, Jeffrey N Martin¹⁰, Frederick M Hecht¹⁰, Louis J Picker¹¹, Michael M Lederman⁸, Steven G Deeks¹⁰ & Daniel C Douek¹
The CD8+ T cell response to just two CMV proteins (pp65 and IE) was approximately 6% during long-term therapy, which was over twice that seen in HIV-seronegative persons.

CMV-specific CD4+ T cell responses followed the same trends, but the magnitude of the effect was smaller.

Conclusions/Significance: Long-term successfully treated HIV infected patients have remarkably high levels of CMV-specific effector cells. These levels are similar to that observed in the elderly, but occur at much younger ages.
Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses

Priscilla Y. Hsue\textsuperscript{a}, Peter W. Hunt\textsuperscript{b}, Elizabeth Sinclair\textsuperscript{c}, Barry Bredt\textsuperscript{c}, Arlana Franklin\textsuperscript{a}, Maudi Killian\textsuperscript{c}, Rebecca Hoh\textsuperscript{b}, Jeffrey N. Martin\textsuperscript{b,d}, Joseph M. McCune\textsuperscript{c}, David D. Waters\textsuperscript{a} and Steven G. Deeks\textsuperscript{b}

**Fig. 2. Carotid IMT and CMV-specific T-cell responses in HIV-infected subjects.** Carotid IMT is plotted against the percentage of CMV-specific CD8 T cells for HIV-infected subjects (black circles) and uninfected controls (gray circles). The black line represents the linear prediction from an unadjusted linear regression model. Among all participants, for every 10-fold increase in the percentage of CMV-specific T cells, there was a 14% increase in carotid IMT ($P < 0.001$).
In Immune Biology:
Infection with *cytomegalovirus* but not herpes simplex virus induces the accumulation of late differentiated CD4+ and CD8+ T-cells (CD-28-) in humans. Derhovanessian E, et al.

Inflammation & HIV/AIDS – four points:

- Despite being an “immunodeficiency” disease HIV/AIDS is an inflammatory disorder;

- Inflammation is associated with risk of death from all causes not just AIDS-related;

- Inflammation is associated with decreased lymphoid organ function (chronic low-level “wound repair”);

- Co-morbidities may be critical to understanding biomarkers and risk factors in HIV/AIDS
The health of the liver may be critical to our understanding of a liver-mediated biomarker such as CRP.

A “return to health” process might simultaneously:

- Lower inflammation and thereby **lower** the biomarker;
- But also return the liver to health and **raise** the production of the biomarker.

**FIGURE 1. Median CRP levels by gender and HIV/HCV status.**

Participants were age restricted and those with recent opportunistic infections were excluded.
Thrombosis Risk Factor Model

**Coagulation Balance**
*Mix of pro- & anti-coagulant factors*
- Genes
  - Anticoagulant deficiencies
  - Factor V Leiden
  - Prothrombin 20210A
- Age, Obesity
- Warfarin
- Other causes of “coagulant imbalance” (e.g., nutrition, synthetic function, antibodies)

**External Forces**
*Direct causes of thrombin generation*
- Previous VTE
- Cancer pro-coagulants
- Varicose Veins
- Hormone Treatments
- Endotoxemia

**Prophylaxis**

**Thrombosis Risk**

**Triggering Events**
- Pregnancy (intrinsic)
- Surgery & trauma (extrinsic)
- Immobilization & blood stasis; e.g. air travel (extrinsic)

**Thrombosis Threshold**

**Blood Clot** (e.g., VTE)
SMART Design Facilitates Randomized Comparisons of Starting/Stopping ART
(via subgroups defined by ART use at study entry)

On ART with HIV RNA <400 (Treated HIV Infection)  
N=500

Randomize

Stop ART (DC)  
Continue ART (VS)

Comparison at 2 months
Coagulation Biomarkers: Untreated vs. Treated
Coagulation Biomarkers: Untreated vs. Treated

B) Month 6 Comparison (DC-VS): off vs. starting ART

* <0.05
† <0.01

% Diff. at Mo. 6 Between Participant’s Deferring (DC) vs. Starting (VS) ART

D-dimer, PAP, Fibrinogen, Factor V, Factor VII, Factor VIII, vWF, sTM, ATIII, Protein C, Protein S (Total), Protein S (Free)

Pro-Coagulant Markers

Anti-Coagulant Markers

J. Baker and R. Tracy CROI 2011 (#811)
Coagulation Biomarkers: Untreated vs. Treated

B) Month 2 Comparison (DC-VS): stopping vs. on ART

% Diff. at Mo. 2 Between Participant’s Stopping (DC) vs. Continuing (VS) ART

D-dimer  PAP  Fibrinogen  Factor V  Factor VII  Factor VIII  vWF  sTM  ATIII  Protein C  Protein S (Total)  Protein S (Free)

Pro-Coagulant Markers

Anti-Coagulant Markers

* <0.05
† <0.01

J. Baker and R. Tracy CROI 2011 (#811)
Simulated Thrombin Generation

A) Baseline

B) Off versus Starting ART

C) Stopping versus On ART

Coagulation and thrombin generation in liver disease prior to end-stage disease: increased thrombin production

Tripodi & Mannucci, NEJM 2011;365:147

D-dimers
HIV & Aging

Outline of this Talk

• A Perspective on Inflammation and Inflammation Biomarkers
• A Perspective on Chronic Disease & Aging
• Can We Learn about Aging from HIV?
• A few “Conclusions”
HIV & Aging

Our Working “Inflammation Hypothesis” of Aging:

• First, with age, quality remodeling gives way to poor remodeling (a form of inflammation);
  • This “baseline” aging is driven by evolutionary biology; there are many possible mechanisms:
    • loss of telomeres and/or loss of stem cells;
    • somatic buildup of mtDNA mutations;
    • somatic buildup of nuclear DNA damage;
    • Increased generation of proinflammatory senescent cells;
  • Overall rate affected by genetics: some age faster than others;
Second, specific exposures can accelerate organ-specific aging:
- Alcohol $\rightarrow$ liver fibrosis
- Chronic infectious burden $\rightarrow$ immunosenescence
- Hyperlipidemia $\rightarrow$ vascular sclerosis
- Smoking $\rightarrow$ pulmonary fibrosis
- New: Life-long extreme exercise $\rightarrow$ cardiac fibrosis (J Appl Physiol, 2011)

Because we’re “integrated organisms” accelerated aging in each organ affects the whole system; i.e., there is a heterodynamic decline of integrated physiology (homeostenosis);

These rates are also affected by genetics;
HIV & Aging

- **Third**, most organ-specific damages also accelerate this overall process through a generalized increased in inflammation mediators;
  - e.g., atherosclerosis activates coagulation which in turn increases the inflammatory milieu

- There are some exposures of special public health importance:
  - Caloric excess $\rightarrow$ fat deposition and increased inflammatory response capacity $\rightarrow$ accelerated decline;
  - Lack of exercise $\rightarrow$ many metabolic effects on adiposity, blood pressure, lipids, etc $\rightarrow$ accelerated decline;

- Ultimately unless a single organ’s dysfunctionality prevails, homeostenosis leads to multi-organ failure and death
HIV, like other chronic diseases, provides increased inflammatory stimulation (innate immunity, coagulation); unique to HIV is a dysregulation of the adaptive immune system

$H_0$: the result is more accurate mimicry of aging

Are there clues for adjunctive therapeutic approaches? Which therapies work in the mildly to moderately disabled elderly? Possibly mild to moderate exercise?
INVITATION AND CALL FOR ABSTRACTS

2nd International Workshop on HIV & Aging
Renaissance Baltimore Harborplace Hotel, Baltimore, MD, USA
27 – 28 October 2011

Organizing Committee:
Charles Boucher, MD, PhD
Erasmus University Rotterdam, the Netherlands
William Enshier, MD
IASIA, Gaithersburg, MD, USA
Charles Flexner, MD
Johns Hopkins University School of Medicine, Baltimore, MD, USA
Scott Letandra, MD
University of California, San Diego, CA, USA
Jules Levin, MS
NAIAP, New York, NY, USA
Jonathan Behaprio, MD
Sheba Medical Center, Tel Aviv, Israel
Russell Tracy, PhD
University of Vermont, Burlington, VT, USA
Side Bar: GWAS in MESA

MESA 1000 (MESA Inflammation)
EA – 375        AA – 170
Hispanic – 216    Chinese - 94

Variables
Log %Th1    Log %Th2    %CD4

GWAS
Only genotyped SNPs; ~750k

University of Vermont:
Peter Durda
Peggy Doyle

University of Virginia:
Joe Mychaleckyj
Ani Manichaikul
Steve Rich

University of Washington
Bruce Psaty
Dick Kronmal
Acknowledgements

University of Vermont:
  Peter Durda
  Peggy Doyle

University of Virginia:
  Joe Mychaleckyj
  Ani Manichaikul
  Steve Rich

University of Washington
  Bruce Psaty
  Dick Kronmal
Percent CD4 Cells Results
Percent CD4 Cells EA

\[ \lambda = 1.01 \]
Percent CD4 Cells EA
EA Pct CD4
Top Hit for EA Percent CD4 Cells

- rs4693051 is in an intron on the Chrm 4 gene Stearoyl-CoA desaturase 5 (SCD5)

- SCD5 has been associated with two pathways
  - Biosynthesis of unsaturated fatty acids
    - T cells have unique FA metabolism among lymphocytes
  - PPAR signaling pathway
    - PPAR-gamma signaling is critical in T cells
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Technical Staff</th>
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</thead>
<tbody>
<tr>
<td>Ted Bovill, MD</td>
<td>Lourdes Bielsa</td>
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<tr>
<td>Mary Cushman, MD, MS</td>
<td>Melissa Floersch</td>
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<td>Peggy Doyle, PhD</td>
<td>Nicole Gagne</td>
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<tr>
<td>Sally Huber, PhD</td>
<td>Florence Keating</td>
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<tr>
<td>Nancy Jenny, PhD</td>
<td>Jessica Lanzer</td>
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<tr>
<td>Michael Lewis, MD</td>
<td>Rebecca Marin</td>
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<td>Russ Tracy, PhD</td>
<td>Mohamad Moussawi</td>
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<td>Neil Zakai, MD</td>
<td>Sarah Nightingale</td>
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<td>Danielle Parent</td>
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<td>Angela Patnoad</td>
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<td>April Perry</td>
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<td>Cheryl Powden</td>
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<td>Julie Prytherch</td>
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<td>Brian Roberts</td>
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<td>Cathy Tilley</td>
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<td>Julia Valliere</td>
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<td>Mary Ellen Walker</td>
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<th>Unit Administrators</th>
<th>Supervisory Staff</th>
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<tbody>
<tr>
<td>Pamela Burton</td>
<td>Elaine Cornell</td>
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<td>Angela Jacobs</td>
<td>Lab Coordinator</td>
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<td>Rebekah Boyle</td>
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<td>Asst Lab Coordinator</td>
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<tr>
<td></td>
<td>Peter Durda</td>
</tr>
<tr>
<td></td>
<td>DNA Lab</td>
</tr>
<tr>
<td>Variety of students, post-docs,</td>
<td>Dean Draayer, PhD</td>
</tr>
<tr>
<td>visiting scientists, etc</td>
<td>IT/IS</td>
</tr>
<tr>
<td></td>
<td>Patrick Daunais</td>
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<td></td>
<td>QA/QC</td>
</tr>
</tbody>
</table>

**Focus:**

assay development; molecular & genetic epidemiology; clinical trial support, murine models of heart disease
Inflammation, Atherosclerosis, and Aging

We are collaborating with many investigators in the CVD and HIV fields; in particular for today’s talk:

• CVD epidemiology: Nancy Jenny, Mary Cushman (UVM); Lew Kuller (UPitt); Bruce Psaty, Dick Kronmal (UWash)
• Molecular immunology & coagulation/fibrinolysis: Sally Huber, Peggy Doyle, Kathleen Brummel-Ziedens (UVM); Alan Landay (RushU)
• SIV in primates: Ivona Pandrea (UPitt), Alan Landay (RushU)
• HIV-CVD Consortium: Robert Kaplan (Einstein), Matt Freiberg (UPitt), Steve Deeks & Priscilla Hsue (UCSF), many others
• The FRAM Study: Carl Grunfeld et al. (UCSF)
• VACS: Amy Justice, Matt Freiberg, others
• The NIAID INSIGHT Network/SMART/ESPRIT: Jim Neaton, Jason Baker, Daniel Duprez et al. (UMinn)
• The MACS/WIHS: Frank Palella (Northwestern), Wendy Post, et al.
FIGURE 1. The factor loading pattern of metabolic, inflammatory, and hemostatic variables related to insulin resistance syndrome in 322 non-diabetic adults aged 65–100 years, Cardiovascular Health Study, 1989–1990. The 21 intercorrelated variables load on seven uncorrelated factors, which are represented by the large ellipses. While the seven factors are uncorrelated, there are four variables that have factor loadings ≥0.40 on more than one of the factors; these variables lie in the regions of overlap between ellipses. F1-2, prothrombin fragment 1-2; FPA, fibrinopeptide A; PAI-1, plasminogen activator inhibitor-1; BP, blood pressure; D-dimer, fibrin fragment D-dimer; PAP, plasmin-α2-antiplasmin; CRP, C-reactive protein; FVIIIc, factor VIIIc; HDL-C, high density lipoprotein cholesterol.

Dramatically Increased VTE Rates with Aging

Note how rates start to increase post-40 yo.

Survivorship and/or competing risks?
Two Concepts

• Immune Landscape
• Cellular Senescence
The CD8⁺ T cell response to just two CMV proteins (pp65 and IE) was approximately 6% during long-term therapy, which was over twice that seen in HIV-seronegative persons.

CMV-specific CD4⁺ T cell responses followed the same trends, but the magnitude of the effect was smaller.

Conclusions/Significance: Long-term successfully treated HIV infected patients have remarkably high levels of CMV-specific effector cells. These levels are similar to that observed in the elderly, but occur at much younger ages.
Inflammation, Atherosclerosis, and Aging

Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses

Priscilla Y. Hsue\textsuperscript{a}, Peter W. Hunt\textsuperscript{b}, Elizabeth Sinclair\textsuperscript{c}, Barry Bredt\textsuperscript{c}, Arlana Franklin\textsuperscript{a}, Maudi Killian\textsuperscript{c}, Rebecca Hoh\textsuperscript{b}, Jeffrey N. Martin\textsuperscript{b,d}, Joseph M. McCune\textsuperscript{c}, David D. Waters\textsuperscript{a} and Steven G. Deeks\textsuperscript{b}

Fig. 2. Carotid IMT and CMV-specific T-cell responses in HIV-infected subjects. Carotid IMT is plotted against the percentage of CMV-specific CD8+ T cells for HIV-infected subjects (black circles) and uninfected controls (gray circles). The black line represents the linear prediction from an unadjusted linear regression model. Among all participants, for every 10-fold increase in the percentage of CMV-specific T cells, there was a 14% increase in carotid IMT ($P < 0.001$).

Table 1. SASP factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Senescence Inducer</th>
<th>High increase (4+ fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM-CSF</td>
<td>OIS (RA5, MD5), D5OIS (XRA), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ, PrECs, BPH1, RWPE1, PC3</td>
</tr>
<tr>
<td>GROa</td>
<td>OIS (RA5, MD5), D5OIS (XRA, BLEX), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ, PrECs, BPH1, RWPE1, PC3, prostate fibroblasts (PSC7, PSC31, and PSC32)</td>
</tr>
<tr>
<td>GROa,β,γ</td>
<td>OIS (RA5, MD5), D5OIS (XRA, BLEX), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ, PrECs, BPH1, RWPE1, PC3</td>
</tr>
<tr>
<td>IGFBP-7</td>
<td>OIS (BRAF)</td>
<td>+ melanocytes</td>
</tr>
<tr>
<td>IL-1α</td>
<td>OIS (RA5, MD5), D5OIS (XRA, BLEX)</td>
<td>+ IMR-90, HCA2, PrECs, BPH1, RWPE1, PC3</td>
</tr>
<tr>
<td>IL-6</td>
<td>OIS (RA5, D5OIS (XRA), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ, PrECs, BPH1, RWPE1, PC3</td>
</tr>
<tr>
<td>IL-7</td>
<td>OIS (RA5), D5OIS (XRA), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ</td>
</tr>
<tr>
<td>IL-8</td>
<td>OIS (RA5, MD5), D5OIS (XRA, BLEX), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ, PrECs, BPH1, RWPE1, PC3, prostate fibroblasts (PSC7, PSC31, and PSC32)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>OIS (RA5, D5OIS (XRA), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ, PrECs, BPH1, RWPE1, PC3</td>
</tr>
<tr>
<td>MCP-2</td>
<td>OIS (RA5, D5OIS (XRA, BLEX), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ</td>
</tr>
<tr>
<td>MMP-1a</td>
<td>OIS (RA5, D5OIS (XRA, BLEX), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ, hepatic myofibroblasts</td>
</tr>
<tr>
<td>MMP-1</td>
<td>OIS (RA5, D5OIS (XRA, BLEX), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ</td>
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<tr>
<td>MMP-10</td>
<td>OIS (RA5, D5OIS (XRA, BLEX, ETOP), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ</td>
</tr>
<tr>
<td>MMP-3</td>
<td>OIS (RA5, D5OIS (XRA, BLEX), REP</td>
<td>+ IMR-90, HCA2, WI-38, BJ</td>
</tr>
</tbody>
</table>
Downward Spirals....

Adaptive Side

- Chronic Infection e.g., CMV, HIV
- Occupation of “immunologic landscape”
- Large fraction of TCR repertoire
- Large fraction of CD28- cells
  - Apoptotic-resistant
  - Non-proliferative
  - “Senescent”

Innate Side

- Chronic Inflammation
- Chronic Diseases Aging
- Adiposity

Genes

Surrogates: IMT, CAC, etc

Increased cancer, infectious disease
Antagonistic Pleiotropy: at the species- and individual-level

• **Thrifty Genotype (species-level; genomic):** genes evolved under conditions of caloric scarcity, might be harmful under conditions of caloric plenty.
  

• **Thrifty Phenotype (individual-level; epigenomic):** Metabolic capacity programmed under conditions of caloric scarcity, might be harmful under conditions of caloric plenty.
  
Inflammation, Atherosclerosis, and Aging

Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection

Lewis H. Kuller¹, Russell Tracy², Waldo Belloso³, Stephane De Wit⁴, Fraser Drummond⁵, H. Clifford Lane⁶, Bruno Ledergerber⁷, Jens Lundgren⁸, Jacqueline Neuhaus⁹, Daniel Nixon¹⁰, Nicholas I. Paton¹¹, James D. Neaton⁹*, for the INSIGHT SMART Study Group

¹ University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, ² University of Vermont, Burlington, Vermont, United States of America, ³ Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, ⁴ Saint-Pierre Hospital, Brussels, Belgium, ⁵ National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia, ⁶ National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, United States of America, ⁷ University Hospital, Zurich, Switzerland, ⁸ University of Copenhagen, Copenhagen, Denmark, ⁹ University of Minnesota, Minneapolis, Minnesota, United States of America, ¹⁰ Virginia Commonwealth University, Richmond, Virginia, United States of America, ¹¹ Medical Research Council Clinical Trials Unit, London, United Kingdom
Strategies for Management of Anti-Retroviral Therapy (SMART)

**Study Design & Flow Diagram for Case-Control Study & Random Sample**

**5,472 HIV-infected Patients with CD4+ Cell Counts >350 cells/mm³**

**Drug Conservation (DC) Group**
- n=2,720
- [Stop or defer ART until CD4+ cell count declines to below 250 cells/mm³; then treat to increase CD4+ cell counts > 350 cells/mm³; then use episodic ART based on CD4+ cell count.]
- 55 deaths; 45 with unknown vital status

**Virologic Suppression (VS) Group**
- n=2,752
- [Use ART to maintain viral load as low as possible irrespective of CD4+ cell count by changing ART when the viral load is not suppressed.]
- 30 deaths; 47 with unknown vital status

**Status on January 11, 2006 (Study Modification)**

**Nested case-control study:**
- 85 deaths and 170 controls (99 DC and 71 VS) with baseline specimens matched on country, age (+/-5 years), gender and date of randomization (+/- 3 months)

**Follow-up specimens available for 74 deaths and 141 controls+**

**499 with results:**
- 249 DC and 250 VS

---


Laboratory for Clinical Biochemistry Research
University of Vermont
SMART Case – Control Study

<table>
<thead>
<tr>
<th>Sampling Point</th>
<th>Biomarker</th>
<th>Deaths, Median (25th, 75th %ile)</th>
<th>Controls, Median (25th, 75th %ile)</th>
<th>Difference after Log$_{10}$</th>
<th>p-Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study entry$^b$</td>
<td>hsCRP (µg/ml)</td>
<td>4.26 (2.12, 7.49)</td>
<td>2.14 (0.84, 5.68)</td>
<td>0.21 (0.07)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>Amyloid A (mg/l)</td>
<td>4.75 (2.80, 9.06)</td>
<td>3.65 (1.90, 8.08)</td>
<td>0.10 (0.06)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Amyloid P (µg/ml)</td>
<td>58.8 (43.1, 82.3)</td>
<td>67.8 (48.8, 94.1)</td>
<td>−0.08 (0.03)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>IL-6 (pg/ml)</td>
<td>3.80 (2.72, 7.20)</td>
<td>2.31 (1.51, 3.33)</td>
<td>0.29 (0.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>D-dimer (µg/ml)</td>
<td>0.49 (0.27, 1.16)</td>
<td>0.26 (0.17, 0.45)</td>
<td>0.35 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>F1.2 (pmol/l)</td>
<td>344.0 (245.8, 565.8)</td>
<td>351.4 (255.5, 533.4)</td>
<td>0.01 (0.04)</td>
<td>0.81</td>
</tr>
<tr>
<td>Latest level$^c$</td>
<td>hsCRP (µg/ml)</td>
<td>5.26 (2.19, 19.3)</td>
<td>2.00 (0.78, 4.80)</td>
<td>0.47 (0.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Amyloid A (mg/l)</td>
<td>6.88 (2.40, 16.7)</td>
<td>3.35 (2.00, 6.75)</td>
<td>0.28 (0.08)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Amyloid P (µg/ml)</td>
<td>57.7 (34.9, 78.5)</td>
<td>67.3 (49.6, 88.1)</td>
<td>−0.09 (0.03)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>IL-6 (pg/ml)</td>
<td>7.84 (3.08, 15.5)</td>
<td>2.72 (1.60, 4.39)</td>
<td>0.45 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>D-dimer (µg/ml)</td>
<td>0.70 (0.34, 1.64)</td>
<td>0.34 (0.22, 0.63)</td>
<td>0.39 (0.07)</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>F1.2 (pmol/l)</td>
<td>339.5 (260.6, 463.7)</td>
<td>321.1 (218.8, 507.4)</td>
<td>−0.01 (0.04)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

- Cases generally higher than Controls;
- Levels increased in Cases but not in Controls;
- Compared to healthy reference groups, the baseline values tended to be high, especially in Cases, but not extraordinarily so. For example:
  - CRP tertile cut points are 1 ug/ml and 3 ug/ml
  - D-dimer values are generally < 0.4 ug/ml

Biomarker, CD4+ Cell Count Change, and HIV-RNA Level Change 1 mo after Randomization

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>DC Group, Mean (SD) or %</th>
<th>VS Group, Mean (SD) or %</th>
<th>Average Difference (SE)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP (µg/ml) (log_{10})</td>
<td>0.02 (0.41)</td>
<td>0.00 (0.41)</td>
<td>0.02 (0.03)</td>
<td>0.63</td>
</tr>
<tr>
<td>Amyloid A (mg/l) (log_{10})</td>
<td>0.03 (0.38)</td>
<td>0.01 (0.38)</td>
<td>0.00 (0.03)</td>
<td>0.88</td>
</tr>
<tr>
<td>Amyloid P (µg/ml) (log_{10})</td>
<td>-0.02 (0.20)</td>
<td>0.01 (0.20)</td>
<td>-0.03 (0.01)</td>
<td>0.05</td>
</tr>
<tr>
<td>IL-6 (pg/ml) (log_{10})</td>
<td>0.12 (0.30)</td>
<td>0.01 (0.34)</td>
<td>0.08 (0.02)</td>
<td>0.0005</td>
</tr>
<tr>
<td>D-dimer (µg/ml) (log_{10})</td>
<td>0.09 (0.31)</td>
<td>-0.03 (0.31)</td>
<td>0.11 (0.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>F1.2 (pmol/l) (log_{10})</td>
<td>-0.04 (0.34)</td>
<td>-0.03 (0.27)</td>
<td>-0.02 (0.02)</td>
<td>0.44</td>
</tr>
<tr>
<td>CD4+ cell count (cells/mm³)</td>
<td>-104 (180)</td>
<td>18 (188)</td>
<td>-130 (16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change in HIV-RNA (copies/ml) (log_{10})</td>
<td>1.17 (1.37)</td>
<td>-0.31 (0.97)</td>
<td>1.46 (0.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV-RNA ≤400 copies/ml at 1 mo (%)</td>
<td>16.7</td>
<td>67.1</td>
<td>-50.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Change in Log10 D-dimer (lg/ml) from Baseline to 1 mo According to HIV-RNA Level at 1 mo for Participants in the DC Group with an HIV RNA level 400 Copies/ml or less at Baseline

Similar for IL-6

Increased tissue factor expression on circulating monocytes in chronic HIV infection: relationship to in vivo coagulation and immune activation

*Nicholas T. Funderburg,1 *Elizabeth Mayne,2 Scott F. Sieg,1 Robert Asaad,1 Wei Jiang,1 Magdalena Kalinowska,1 Angel A. Luciano,1,3 Wendy Stevens,2 Benigno Rodriguez,1 Jason M. Brenchley,4 Daniel C. Douek,5 and Michael M. Lederman1

Figure 1. Exposure of human monocytes to TLR ligands, but not to IL-6, increases surface expression of the procoagulant TF. Whole blood was obtained from HIV-uninfected subjects and was exposed to LPS (50 ng/mL), flagellin (10 μg/mL), or IL-6 (30 μg/mL) for 3 hours. Surface expression of TF was measured on CD14+ monocytes by flow cytometry. (A) Gating strategy. (B) Representative histograms. (C) Summary data.

Funderburg et al., Blood, 2009
FRAM: ART may affect inflammation biomarkers

Association of antiretroviral therapy with fibrinogen levels in HIV-infection

Erin Madden, Grace Lee, Donald P. Kotler, Christine Wanke, Cora E. Lewis, Russell Tracy, Steven Heymsfield, Michael G. Shlipak, Peter Bacchetti, Rebecca Scherzer, and Carl Grunfeld

SMART/DAD: Some evidence for risk from particular ART

Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients

The SMART/INSIGHT and the D:A:D Study Groups*

Table 3. Hazard ratio for developing each cardiovascular outcome for patients in the Viral Suppression arm of SMART, according to type of nucleoside reverse transcriptase inhibitor currently used.

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Number of events</th>
<th>Abacavir no didanosine</th>
<th>Didanosine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
</tr>
<tr>
<td>CVD, major</td>
<td>70</td>
<td>1.63 (0.96–2.76)</td>
<td>1.80 (1.04–3.11)</td>
</tr>
<tr>
<td>Clinical MI</td>
<td>19</td>
<td>4.22 (1.41–12.6)</td>
<td>4.25 (1.39–13.0)</td>
</tr>
<tr>
<td>CVD, minor</td>
<td>58</td>
<td>2.83 (1.61–4.97)</td>
<td>2.70 (1.51–4.83)</td>
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<tr>
<td>CVD, expanded definition</td>
<td>112</td>
<td>1.84 (1.22–2.76)</td>
<td>1.91 (1.25–2.92)</td>
</tr>
</tbody>
</table>

Adjustment is for:

- age
- Sex
- Race
- baseline HIV-RNA
- smoking status
- prior CVD
- Diabetes
- BP-lowering drugs
- hepatitis B or C virus infection
- baseline CD4 cell count
- baseline use of NNRTI
- baseline use of protease inhibitors.

**WHIS/MACS: However, results from WIHS/MACS were not consistent…**

HAART-associated reductions in D-dimer and IL-6 were apparent regardless of ABC use and were correlated with HIV RNA reductions.

Table 3. Changes in plasma biomarker levels from pre-HAART to on-HAART by abacavir exposure and cohort among (A) all 508 patient pairs and (B) 184 persons who were ART-naïve at HAART initiation.

<table>
<thead>
<tr>
<th></th>
<th>Change from Pre-HAART Visit</th>
<th>Adjusted Difference of Change</th>
<th>p-value$^1$</th>
<th>Change from Pre-HAART Visit</th>
<th>Adjusted Difference of Change</th>
<th>p-value$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-ABC HAART</td>
<td>ABC HAART</td>
<td></td>
<td>Non-ABC HAART</td>
<td>ABC HAART</td>
<td></td>
</tr>
<tr>
<td><strong>hsCRP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACS</td>
<td>19%</td>
<td>33%</td>
<td>4%</td>
<td>-1%</td>
<td>-6%</td>
<td>6%</td>
</tr>
<tr>
<td>WIHS</td>
<td>21%</td>
<td>16%</td>
<td>-2%</td>
<td>41%</td>
<td>3%</td>
<td>-3%</td>
</tr>
<tr>
<td>Combined</td>
<td>21%</td>
<td>22%</td>
<td>-1%</td>
<td>20%</td>
<td>4%</td>
<td>-20%</td>
</tr>
<tr>
<td><strong>D-dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACS</td>
<td>-23%</td>
<td>-41%</td>
<td>-24%</td>
<td>-38%</td>
<td>-57%</td>
<td>-23%</td>
</tr>
<tr>
<td>WIHS</td>
<td>-19%</td>
<td>-20%</td>
<td>7%</td>
<td>-28%</td>
<td>-26%</td>
<td>-8%</td>
</tr>
<tr>
<td>Combined</td>
<td>-20%</td>
<td>-28%</td>
<td>-7%</td>
<td>-33%</td>
<td>-40%</td>
<td>-7%</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACS</td>
<td>-29%</td>
<td>-27%</td>
<td>7%</td>
<td>-32%</td>
<td>-63%</td>
<td>-15%</td>
</tr>
<tr>
<td>WIHS</td>
<td>-2%</td>
<td>2%</td>
<td>3%</td>
<td>8%</td>
<td>-17%</td>
<td>-38%</td>
</tr>
<tr>
<td>Combined</td>
<td>-12%</td>
<td>-9%</td>
<td>-9%</td>
<td>-12%</td>
<td>-38%</td>
<td>-21%</td>
</tr>
</tbody>
</table>

$^1$From linear mixed models of log-transformed on-HAART to pre-HAART ratios with random effect terms for each pair adjusted for ABC HAART exposure, age, calendar year, time between baseline and index visits, smoking, BMI, HDL, CD4 cell count, HIV RNA, and cohort.

$^2$From linear mixed models of log-transformed on-HAART to pre-HAART ratios with random effect terms for each individual adjusted for ABC HAART exposure, age, calendar year, time between baseline and index visits, smoking, BMI, HDL, CD4 cell count, HIV RNA, and cohort for WIHS (124 observations for 105 individuals) and combined models (204 observations for 184 individuals). Models for MACS were adjusted for the same factors but did not include random effects terms (80 observations for 79 individuals).

Palella F, et al., In Press, 2010
HIV Infection

In the chronic phase, characterized by increased innate immunity and coagulation, and decreased adaptive immunity.

Early *in situ* CD4⁺ cell death → lymphoid inflammation & fibrosis (e.g., HA) → loss of 2° lymphoid tissue function

- Loss of GALT function → ↑ microbial translocation → ↑ endotoxemia & coagulant activity (e.g., D-dimer) → ↑ thrombosis
- Loss of general lymph node function → ↓ immune surveillance → ↑ cancers and infections (e.g., CMV)

Other aspects of HIV infection such as cryptic virus repositories

Systemic Pro-inflammatory Cytokininemia (e.g., IL-6)

HAART:
- ? Direct effect of drugs
- “Return to Health”

Liver disease:
- Hep.B/C; possibly HIV
- Alcohol

Biochemical effects:
- ↑ Hepatic biomarkers (e.g., CRP)
- ↑ Coagulation (e.g., D-dimer)
- ↓ Plasma lipids

↑ Chronic diseases:
- Atherosclerosis
- Diabetes
- Osteoporosis
- COPD
- Dementia
Inflammation, Atherosclerosis, and Aging

Inflammatory Biomarkers among Abacavir and non-Abacavir Recipients in the Women’s Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS)

Frank J. Palella Jr MD, Stephen J. Gange PhD, Lorie Benning MS, Lisa Jacobson ScD, MS, Robert C. Kaplan PhD, Alan L. Landay PhD, Russell P. Tracy MD, Richard Elion MD
Northwestern University Feinberg School of Medicine, Chicago, IL; Johns Hopkins University, Baltimore, MD; Albert Einstein College of Medicine, New York, NY; Rush University Medical Center, Chicago, IL; University of Vermont, Burlington, VT; George Washington University, Washington, DC.

Figure 1. Study Design

ABC Exposed

Enrollment Pre-HAART 1st HAART Report 1st Reported ABC use as part of HAART

180 MACS 328 WIHS

"Pre-HAART"

180 MACS 328 WIHS

"On-HAART"

Propensity score matched index visit

ABC Unexposed

Enrollment Pre-HAART 1st HAART Report No ABC use as part of HAART

180 MACS 328 WIHS

180 MACS 328 WIHS
SMART/DAD: Some evidence for risk from particular ART

Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients

The SMART/INSIGHT and the D:A:D Study Groups*

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>(1) Abacavir, no didanosine (n = 175)</th>
<th>(2) Didanosine (n = 116)</th>
<th>(3) Other NRTI (n = 500)</th>
<th>Percentage differencea (1) vs. (3) (P-value)</th>
<th>Percentage differencea (2) vs. (3) (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>hsCRP (µg/ml)</td>
<td>2.99 (1.27–6.46)</td>
<td>2.24 (1.01–4.81)</td>
<td>2.33 (0.96–5.31)</td>
<td>17.4 (0.14)</td>
<td>27.1 (0.02)</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>2.52 (1.67–3.67)</td>
<td>2.33 (1.42–3.67)</td>
<td>2.23 (1.36–3.74)</td>
<td>15.0 (0.04)</td>
<td>16.2 (0.02)</td>
</tr>
<tr>
<td>Amyloid A (mg/l)</td>
<td>3.50 (1.80–6.90)</td>
<td>3.40 (2.05–6.67)</td>
<td>3.57 (1.90–6.77)</td>
<td>3.0 (0.71)</td>
<td>15.0 (0.14)</td>
</tr>
<tr>
<td>Amyloid P (µg/l)</td>
<td>67.6 (51.5–88.1)</td>
<td>62.5 (48.3–81.3)</td>
<td>64.5 (50.8–86.2)</td>
<td>4.1 (0.27)</td>
<td>7.3 (0.07)</td>
</tr>
<tr>
<td>D-dimer (µg/ml)</td>
<td>0.27 (0.17–0.61)</td>
<td>0.27 (0.17–0.51)</td>
<td>0.27 (0.15–0.49)</td>
<td>13.9 (0.12)</td>
<td>6.2 (0.49)</td>
</tr>
<tr>
<td>F1.2 (pmol/l)</td>
<td>327 (243–513)</td>
<td>307 (221–475)</td>
<td>352 (256–527)</td>
<td>2.0 (0.77)</td>
<td>4.9 (0.41)</td>
</tr>
</tbody>
</table>

Percentage differences are adjusted for:
- age (46 years), sex (27% females), Race
- smoking (37% current smokers)
- CVD history (3% with such a history)
- diabetes (10% with such a history)
- use of blood pressure (29%) & lipid meds (23%)
- CD4+ cell count & HIV-RNA level
- hepatitis status, BMI
- the use of NNRTIs (48%) and protease inhibitors (e.g. 13% on lopinavir)

Study Entry CRP and IL-6 were Higher with ABACAVIR

Table 2. Median (interquartile range) levels of six preselected biomarkers at study entry and percentage difference between the abacavir and didanosine groups and the other nucleos(t)ide reverse transcriptase inhibitors group: 791 patients on nucleos(t)ide reverse transcriptase inhibitors at study entry.

SMART/DAD: In the Viral Suppression arm, CVD was higher with ABACAVIR

Table 3. Hazard ratio for developing each cardiovascular outcome for patients in the Viral Suppression arm of SMART, according to type of nucleos(t)ide reverse transcriptase inhibitor currently used.

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Number of events</th>
<th>HR (95% CI) Univariable</th>
<th>HR (95% CI) Multivariable b,c</th>
<th>HR (95% CI) Univariable</th>
<th>HR (95% CI) Multivariable b</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD, major d</td>
<td>70</td>
<td>1.63 (0.96–2.76)</td>
<td>1.80 (1.04–3.11)</td>
<td>0.98 (0.41–2.35)</td>
<td>1.06 (0.43–2.58)</td>
</tr>
<tr>
<td>Clinical MI</td>
<td>19</td>
<td>4.22 (1.41–12.6)</td>
<td>4.25 (1.39–13.0)</td>
<td>2.13 (0.41–11.0) g</td>
<td>1.89 (0.35–10.2)</td>
</tr>
<tr>
<td>CVD, minor e</td>
<td>58</td>
<td>2.83 (1.61–4.97)</td>
<td>2.70 (1.51–4.83)</td>
<td>0.98 (0.34–2.85)</td>
<td>1.03 (0.35–3.03)</td>
</tr>
<tr>
<td>CVD, expanded definition f</td>
<td>112</td>
<td>1.84 (1.22–2.76)</td>
<td>1.91 (1.25–2.92)</td>
<td>0.83 (0.40–1.75)</td>
<td>0.86 (0.40–1.85)</td>
</tr>
</tbody>
</table>

Adjustment is for:
- age
- Sex
- Race
- baseline HIV-RNA
- smoking status
- prior CVD
- Diabetes
- BP-lowering drugs

- hepatitis B or C virus infection
- baseline CD4 cell count
- baseline use of NNRTI
- baseline use of protease inhibitors.

Table 4. Hazard ratio for developing cardiovascular disease (expanded definition, see legend to Table 3 for definition) for patients in the Viral Suppression arm of SMART according to the presence of five or more cardiovascular disease risk factors and the presence of ischemic abnormalities on an electrocardiograph at study entry, according to type of nucleos(t)ide reverse transcriptase inhibitor currently used.

<table>
<thead>
<tr>
<th>Variable at study entry stratified for</th>
<th>Abacavir, but no didanosine</th>
<th>Interaction P-value</th>
<th>Didanosine</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of five or more CVD risk factors&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
<td>3.06 (1.59–5.89)</td>
<td>0.10</td>
<td>0.85 (0.24–3.04)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.34 (0.74–2.41)</td>
<td></td>
<td>0.92 (0.35–2.40)</td>
</tr>
<tr>
<td>Ischemic abnormality&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes</td>
<td>3.11 (1.55–6.26)</td>
<td>0.50</td>
<td>1.40 (0.45–4.32)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.59 (0.87–2.90)</td>
<td></td>
<td>0.62 (0.19–2.06)</td>
</tr>
</tbody>
</table>

Adjustment is for:

- age
- Sex
- Race
- baseline HIV-RNA
- smoking status
- prior CVD
- Diabetes
- BP-lowering drugs
- hepatitis B or C virus infection
- baseline CD4 cell count
- baseline use of NNRTI
- baseline use of protease inhibitor

CV lesions can only be observed in pathogenic SIVagm infection of PTMs (b, c, e, g, i, k, m, n, o, q, r, s, t) but not in nonpathogenic infection of AGMs (a, d, f, h, j, l, p)
HIV & Aging: lessons from Non-Human Primates

Pandrea et al., CROI, 2009; manuscript in preparation

Laboratory for Clinical Biochemistry Research
University of Vermont
HIV & Aging: lessons from Non-Human Primates

Pig-Tailed Macaques

African Green Monkeys

Pandrea et al., CROI, 2009; manuscript in preparation
Experimental administration of LPS to Chronically SIVagm.sab-Infected AGMs Results in Significant Increase in Viral Replication and D-dimer levels

Pandrea et al., CROI, 2009; manuscript in preparation
Changes in microbial translocation in SIVagm-infected monkeys

Rhesus macaques

\[ 0.0493 \]

NS

NS

NS

Pigtailed macaques

\[ <0.0001 \]

\[ 0.0026 \]

\[ 0.0002 \]

\[ <0.0001 \]

AGMs

\[ NS \]

\[ NS \]

\[ NS \]

Pandrea et al., CROI, 2009; manuscript in preparation
Pathogenic SIV infection (PTMs and RMs) associate significant increases of both MT (sCD14) and hypercoagulopathy (2D-Dimer). Nonpathogenic SIV infections of AGMs do not associate such changes

Pandrea et al., CROI, 2009; manuscript in preparation