HIV & Aging

Inflammation and Premature Aging in HIV+ People

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Professor of Pathology and Biochemistry
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
Inflammation, Atherosclerosis, and Aging

Our Colleagues:

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)
- **CVD and HIV immunology**: Sally Huber, Peggy Doyle (UVM); Alan Landay (RushU)
- **FRAM & HIV/CVD**: Carl Grunfeld et al.
- **INSIGHT/SMART**: Jim Neaton, Daniel Duprez et al.
- **HIV/CVD**: Robert Kaplan (Einstein), Matt Freiberg (UPitt), many others
- **MACS/WIHS**: Frank Pallela et al.
Outline of this Talk

• What is “inflammation”?
• What is “aging”?
• How can we view the relation of Inflammation to aging?
• Cardiovascular disease as a model of Inflammation & Aging
• HIV/AIDS & Inflammation
• Conclusions & Implications
Inflammation and the Biology of Aging

The Old View

The New View

Acute Inflammation

Chronic inflammation

HIV

“Normal”

“Inflammation”

[CRP], mg/l

0.1

1

10

100

1,000

10,000

30,100

30,000

700

600

500

400

300

200

100

0

C-Reactive Protein

Serum Amyloid A

Haptoglobin

Fibrinogen

Albumin

Transferrin

Days

Plasma Concentration (% Change)

adapted from Gitlin & Colten

inflammatory stimulus

Kushner and Rzewnicki: Acute Phase Response. In Gallin, Synderman et al., Inflammation. 1999

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Presented at the 1st Int. workshop on HIV & Aging, 4 – 5 Oct. 2010, Baltimore, USA
INFLAMMATION can be both the cause and the response to infection, dead cells, and/or damaged tissue; some forms include:

- **Homeostatic tissue remodeling** – capacity declines with age:
  - Tissue is first destroyed, then rebuilt;
  - Quality declines with age; e.g., bone density

- **Bacterial 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, liver cirrhosis, chronic kidney disease, chronic obstructive pulmonary disease, etc);
Bone Remodeling: an Example of How Remodeling Goes Wrong

- We remodel at different rates in different tissues:
  - Bone – 5-10%/year;
  - Brain – limited cellular turnover;
  - Cardiomyocytes – 1-2% /year at the age of 25, declining to half that at 75;
  - Adipocytes – 5-10%/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?

Bergmann et al., Science. 324: 98-102, 2009

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Inflammation, Atherosclerosis, and Aging

Defining Aging (not an easy task):

• ripening: acquiring desirable qualities by being left undisturbed for some time
• the organic process of growing older and showing the effects of increasing age
  wordnetweb.princeton.edu/perl/webwn

• the accumulation of changes in an organism or object over time
  wikipedia.org/wiki/Aging

Many, many sub-definitions: healthy aging, statistical aging, biological aging; interestingly, on the National Institute on Aging website, I couldn’t find a single reference to a definition of aging…..
How long should we live?
Forces that have shaped our genetic architecture


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These are “survival curves”; can we develop a similar model for the “health curve”? 

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

Interventions such as medicine, surgery, etc

Where we are

Our evolutionary lives

Where we want to be
Antagonistic Pleiotropy: at the species- and individual-level

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


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

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.

HEALTH

VASCULATURE
Provision of Nutrients
Removal of Waste
Pump function (arterial emptying)

ADIPOSE TISSUE
Energy storage
Endocrine function

PANCREAS
Digestive function
Key endocrine function

LUNG
Provision of key nutrient: O₂
Elimination of CO₂ waste

THYROID
Metabolic regulation

THYMUS
Immune Function

SKELETON
Structure
Hematopoiesis
Source of pain

KIDNEY
Elimination of waste
RAS function
Fluidic control

BRAIN
Cognitive function
Endocrine function

HEART
Pump function (arterial filling)

LIVER
Coagulation
Detoxification
COP

ADIPOSE TISSUE
Energy storage
Endocrine function

PANCREAS
Digestive function
Key endocrine function

LUNG
Provision of key nutrient: O₂
Elimination of CO₂ waste

THYROID
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Epidemiologically, chronic diseases of aging are associated with inflammation biomarkers

Incident outcomes associated with higher inflammation markers include:

• Ischemic cardiovascular events
• Heart failure & sudden death
• MetSyn & Type 2 diabetes
• Some cancers
• Dementia
• COPD
• Frailty
• Essentially all chronic diseases of old age
Inflammation biomarkers predict early mortality especially strongly in elderly men

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


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• **Cardiovascular disease as a model of Inflammation & Aging**  
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Human Aortic Atherosclerosis

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Arrows: thin cap
Asterisk: lipid pool
Atherosclerosis as a Model for Aging:

Constant lipid infiltration “mimics” constant tissue damage and cell death → chronic inflammation & fibrosis → loss of arterial function;

Vulnerable plaque: a specialized version mediated by “explosive” atherosclerosis → rupture and thrombosis
Results from TeenZzz, a substudy of the Cleveland Children’s Sleep & Health Study: Teenagers with stressful sleep disorders have increased levels of inflammatory activity

TABLE 4. Variation of CRP Levels With SDB

<table>
<thead>
<tr>
<th>AHI</th>
<th>Geometric Mean Values of CRP, mg/L*</th>
<th>Unadjusted</th>
<th>Partially Adjusted†</th>
<th>Fully Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI &lt; 1</td>
<td>0.42 (0.33–0.54)</td>
<td>0.43 (0.33–0.56)</td>
<td>0.50 (0.40–0.63)</td>
<td></td>
</tr>
<tr>
<td>AHI 1–4.9</td>
<td>0.56 (0.36–0.88)</td>
<td>0.54 (0.34–0.86)</td>
<td>0.43 (0.29–0.66)</td>
<td></td>
</tr>
<tr>
<td>AHI 5–14.9</td>
<td>1.48 (0.62–3.53)</td>
<td>1.37 (0.56–3.34)</td>
<td>0.97 (0.43–2.16)</td>
<td></td>
</tr>
<tr>
<td>AHI ≥15</td>
<td>3.11 (1.38–7.03)</td>
<td>2.73 (1.17–6.37)</td>
<td>1.66 (0.76–3.60)</td>
<td></td>
</tr>
</tbody>
</table>

*Values are geometric means (95% confidence limits) of CRP (mg/L) values in unadjusted and adjusted models.
†Adjusted for age, sex, race.
‡Adjusted for age, sex, race, BMI percentile, (BMI percentile²).

Larkin et al., Circulation. 2005;111:1978-1984

N=143;
age, 13 to 18 years;
36% black; 50% female;
wide range of SDB quantified with the apnea hypopnea index (AHI) and oxygen desaturation measures.

Scatterplot of unadjusted ln(CRP) levels (based on average of 2 measurements) by level of ln(AHI), with line indicating mean adjusted ln(CRP) and pointwise 95% CI from the GAM.

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Relationship of CRP and Atherosclerotic Lesions in Young Adults
Results from PDAY (Pathobiological Determinants of Atherosclerosis in Youth)

N = 1136; 15 to 34 years; 50% Black, 28% women; died of accidents, homicides, and suicides; were autopsied within 48 hours after death

Abdominal Aorta

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>CRP&lt;3</th>
<th>3≤CRP&lt;10</th>
<th>CRP≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>N=472</td>
<td>N=62</td>
<td>N=20</td>
</tr>
<tr>
<td>25-34</td>
<td>N=463</td>
<td>N=81</td>
<td>N=38</td>
</tr>
</tbody>
</table>

Right Coronary Artery

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>CRP&lt;3</th>
<th>3≤CRP&lt;10</th>
<th>CRP≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>N=472</td>
<td>N=62</td>
<td>N=20</td>
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<tr>
<td>25-34</td>
<td>N=463</td>
<td>N=81</td>
<td>N=38</td>
</tr>
</tbody>
</table>

Young adults with Increased markers of inflammation have increased atherosclerosis at autopsy


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CRP Guidelines

AHA/CDC Scientific Statement

Markers of Inflammation and Cardiovascular Disease
Application to Clinical and Public Health Practice
A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association

Thomas A. Pearson, MD, PhD (Co-Chair); George A. Mensah, MD (Co-Chair); R. Wayne Alexander, MD, PhD; Jeffrey L. Anderson, MD; Richard O. Cannon III, MD; Michael Criqui, MD; Yazid Y. Fadl, MD; Stephen P. Fortmann, MD; Yuting Hong, MD, PhD; Gary L. Myers, PhD; Nader Rifai, PhD; Sidney C. Smith, Jr, MD; Kathryn Taubert, PhD; Russell P. Tracy, PhD; Frank Vinicor, MD

Mean = .73 (2.07 mg/l)
N = 19100.00

National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Emerging Biomarkers for Primary Prevention of Cardiovascular Disease
NACB LMPG Committee Members: Gary L. Myers7 (Chair), Robert H.M. Christenson2 (Vice-Chair), Mary Cushman,3 Christie M. Ballantyne,4 Gerald R. Cooper,1 Christine M. Pfeiffer,1 Scott M. Grundy,5 Darwin R. Labarthe,6 Daniel Levy,6 Nader Rifai,7 and Peter W.F. Wilson8

Jacques Cenoz1 MD, Ruth MacPherson MD PhD2, Jiri Freiblich MD3, Todd Anderson MD4, Norm Campbell MD5, Andre Carpentier MD6, Patrick Couture MD7, Robert Dufour MD8, George Fowler MD9, Gordon A Francis MD9, Steven Gover MD10, Milan Gupta MD10, Robert A Hégle MD12, David C Lau MD12, Lawrence Leder MD13, Gary F Lewis MD15, Iva Lone MD15, GB John Mancini MD15, Dominic Ng MD PhD15, Glen J Pearson PhD15, Allan Sniderman MD15, James A Stone MEd PhD15, Ehsal Li MD14
CRP in the Physicians Health Study

People with increased biomarkers of inflammation have increased risk of heart attack

In meta-analyses, many markers show approximately the same predictive power.

CRP

Danesh et al., JAMA, 1998

Fibrinogen

Albumin

White Cell Count
D-dimer and Plasmin production are strong predictors of CVD events in the elderly

Fibrinolytic Markers and CHS Fatal + Non-Fatal MI

Cushman M, et al.

Cushman M, et al.

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Innate and Adaptive Immunity in Human Atherosclerosis

- Complement
- Pentraxins
  - CRP
  - SAP
  - PTX-3
- MØ TF → IIa


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Atherosclerosis as a Model for Age-Related Functional Decline: Key aspects

- **Lipid Translocation to media**
  - Driven at least in part by Mass Action; mechanism(s) uncertain

- **Lipid retention**
  - Driven at least in part by GAGs;

- **Lipid modification**
  - Driven at least in part by oxidative stress;

- **Activation of innate immunity**
  - Macs, CRP, etc

- **System in balance?**

  - **Yes:** no atherosclerosis
  - **No:** progression to activation of adaptive immunity and atherosclerosis

- **If very rapid:** explosive development of atheroma → vulnerable plaque rupture → clot & MI

- **If less rapid:** chronic development of “sclerosis” → heart failure
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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;

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

• 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.
Inflammation, Atherosclerosis, and HIV

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### SMART: Risk of death associated with biomarker at study entrance

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type of Analysis</th>
<th>&lt;25th Percentile (Reference)</th>
<th>25th–49th Percentile</th>
<th>50th–74th Percentile</th>
<th>≥75th Percentile</th>
<th>OR associated with One IQR Higher Biomarker Level after Log&lt;sub&gt;10&lt;/sub&gt; Transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>p-Value</td>
<td>OR (95% CI)</td>
<td>p-Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>hsCRP (µg/ml)</td>
<td>No.</td>
<td>16/45</td>
<td>9/42</td>
<td>20/28</td>
<td>40/55</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.0 (ref.)</td>
<td>0.7 (0.2–2.1)</td>
<td>0.50</td>
<td>2.5 (0.9–7.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Amyloid A (mg/l)</td>
<td>No.</td>
<td>11/46</td>
<td>17/35</td>
<td>28/33</td>
<td>29/56</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.0 (ref.)</td>
<td>3.4 (1.0–11.1)</td>
<td>0.04</td>
<td>3.5 (1.2–10.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Amyloid P (µg/ml)</td>
<td>No.</td>
<td>25/44</td>
<td>20/25</td>
<td>16/43</td>
<td>24/56</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.0 (ref.)</td>
<td>1.5 (0.6–4.0)</td>
<td>0.42</td>
<td>0.8 (0.3–2.0)</td>
<td>0.65</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>No.</td>
<td>8/48</td>
<td>10/41</td>
<td>26/48</td>
<td>40/29</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.0 (ref.)</td>
<td>1.0 (0.3–3.6)</td>
<td>0.98</td>
<td>4.5 (1.4–14.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>D-dimer (µg/ml)</td>
<td>No.</td>
<td>8/51</td>
<td>22/54</td>
<td>18/40</td>
<td>37/25</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.0 (ref.)</td>
<td>8.3 (1.9–36.8)</td>
<td>0.005</td>
<td>12.6 (2.4–65.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>F1.2 (pmol/l)</td>
<td>No.</td>
<td>17/29</td>
<td>21/43</td>
<td>15/43</td>
<td>31/53</td>
<td>Univariate</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.0 (ref.)</td>
<td>1.0 (0.4–2.9)</td>
<td>0.94</td>
<td>0.9 (0.3–2.6)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Adj: age, race, use of ART and HIV-RNA level, CD4+ cell count, smoking status, BMI, prior CVD, diabetes, use of BP medication, use of lipid-lowering medication, total/HDL cholesterol, co-infection with hepatitis B or C, and treatment group.

No significant interactions based on treatment.

## Inflammation, Atherosclerosis, and Aging

### Supplementary Table 1: Underlying Cause of Death for Participants in SMART+\(^\dagger\)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>DC No.</th>
<th>VS No.</th>
<th>Total No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>8.2</td>
</tr>
<tr>
<td>Cancer, excluding AIDS-defining cancers</td>
<td>11</td>
<td>5</td>
<td>16</td>
<td>18.8</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>7</td>
<td>4</td>
<td>11</td>
<td>12.9</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>4.7</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>Renal disease</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Hematological disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Digestive system disease</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>CNS disease</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Accident/violent/suicide</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>8.2</td>
</tr>
<tr>
<td>Cause unknown (unwitnessed)</td>
<td>15 (8)</td>
<td>3 (2)</td>
<td>18 (10)</td>
<td>21.2 (11.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>55</td>
<td>30</td>
<td>85</td>
<td>100.0</td>
</tr>
</tbody>
</table>

\(^\dagger\) Deaths occurring through January 11, 2006  
DC = Drug Conservation  
VS = Viral Suppression


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Inflammation, Atherosclerosis, and HIV

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• Co-morbidities are critical to understanding biomarkers and risk factors in HIV/AIDS
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 Kazazz¹, Ethan Bornstein¹, Olivier Lambotte⁵, Daniel Altmann⁶, Bruce R Blazar⁷, Benigno Rodriguez⁸, Leia Teixeira-Johnson⁸, Alan Landay⁹, Jeffrey N Martin¹⁰, Frederick M Hecht¹⁰, Louis J Picker¹¹, Michael M Lederman⁸, Steven G Deeks¹⁰ & Daniel C Douek¹

Brenchley JM, et al., Nat Med, 2006

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FRAM: CRP is high with HIV infection, but normal/low with HIV/HCV co-infection

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.

![Graph of median CRP levels by gender and HIV/HCV status.](image)

Participants were age restricted and those with recent opportunistic infections were excluded.

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

Reingold et al., J Acquir Immune Defic Syndr 48:142-8, 2008
Inflammmatory Biomarkers among Abacavir and non-Abacavir Recipients in the Women’s Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS)

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CRP results: “Return to Health”?
HIV & Aging

Outline of this Talk

• What is “inflammation”?
• What is “aging”?
• How can we view the relation of Inflammation to aging?
• Cardiovascular disease as a model of Inflammation & Aging
• HIV/AIDS & Inflammation
• Conclusions & Implications
HIV & Aging

HIV, like other chronic diseases, provides increased inflammatory stimulation (innate immunity, coagulation); unique to HIV is a dysregulation of the adaptive immune system.

Ho: the result is more accurate mimicry of aging

Are there clues for adjunctive therapeutic approaches? what works in the mildly to moderate disabled elderly? Possibly mild to moderate exercise?
Questions (1)

- HIV/AIDS appears to be associated with a generalized hyperinflammatory state that likely accelerates aging and chronic diseases of aging:
  - Question: what is/are the cause/s?
    - Increased bacterial translocation?
    - Increased chronic cell death and damage in lymphoid tissue?
    - Hypercoagulopathy?
  - Question: what is the role of ART?
    - Can it be sometimes pro- and sometimes anti-inflammatory?
    - Is it important to monitor this clinically?
  - Question: how should we think about the effect of co-infections?
    - At least, modifiers of some plasma biomarkers?
Questions (2)

• HIV/AIDS appears to be associated with a hypercoagulable state
  • Question: what is the cause?
    • Increased bacterial translocation?
    • Direct effects of the virus? And/or, of common co-infections?
  • Question: is this leading to increased CVD events?
    • If so, which type: clotting-based or atherosclerosis-based?
  • Question: is this leading to increased non-CVD, non-aids events?
Conclusions (3)

• HIV/AIDS is associated with loss of Th1 cells via loss of CD4+ cells
  • Question: while this should be anti-atherosclerotic (in our hypothesis), is this true?
  • Question: alternatively, is the effect of loss of Th1 cells swamped by the large increase in innate immunity?