Coagulation Activation During Chronic HIV Disease

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Outline

• Clinical Complications

• Inflammation and Innate Immunity

• TF Activity and Vascular Disease

• Composition of Coagulation Factors
Incidence of Serious Non-AIDS or Death by quartiles of IL-6 and D-dimer

Sample (n=3766): Control arms of SMART/ESPRIT/SILCAAT with HIV RNA <500
Kaplan-Meier estimates of the cumulative % who experience SNA/death
Overall: 7% at 5 years.

Grund et. al. CROI 2013
D-dimer Levels Are 50% Elevated in Treated HIV Disease and Generally Stable Over Time

SMART vs. MESA in Neuhaus et al JID 2010; 201(12) and figure above unpublished data c/o J.Kovacs
HIV Infection has Several Unique Characteristics which Dramatically Increase Inflammation/Coagulation and Thereby Accelerate Vascular Disease

Deeks et al NEJM 2012
Extensive Clot Formation in Multiple Organs in SIV-infected Macaques

Plenary paper

Coagulation biomarkers predict disease progression in SIV-infected nonhuman primates

Ivona Pandrea,¹,² Elaine Cornell,³ Cara Wilson,⁴ Ruy M. Ribeiro,⁵ Dongzhu Ma,¹ Jan Kristoff,¹ Cuiling Xu,¹ George S. Hare- Richter,¹ Anita Trichel,¹,⁶ Cristian Apetrei,¹,⁷ Alan Landay,⁸ and Russell Tracy⁹

Blood. 120: 1357-1366, 2012
What is Driving Coagulation Activity Among HIV+ Patients?
Inflammation and Coagulopathy Are Intimately Linked

- Increase TF (tissue factor) expression on monocytes and endothelial cells
- Up-regulates procoagulants (e.g., FVIII) and down-regulates anticoagulants (e.g., PC)

Xu, Lupu, and Esmon in Hamostaseolgie 2010;30:5-9
Inflammation and Coagulopathy Are Intimately Linked

**Inflammation** \( \xrightarrow{\text{Coagulation}} \) **Coagulation**

- Activates inflammation through protease activated receptors (PAR)
  - Thrombin (via PAR 1,3,4)
  - TF/fVIIa (via PAR 2) stimulates pro-inflammatory cytokine production

*Cirino and Vergnolle in Current Opinion in Pharmacology 2006;6:428-434*
Enhanced Effector Function of CD8⁺ T Cells From Healthy Controls and HIV-Infected Patients Occurs Through Thrombin Activation of Protease-Activated Receptor 1


CD8⁺ T Cells

- ↑ PAR-1 on memory CD8⁺ T cells in HIV+ (among VL >50)
- Thrombin ↑ cytokine production from CD8⁺ T cells
- Thrombin ↑ chemokinesis of CD8⁺ T cells via PAR-1

Fig 2a & 4c from JID 2013;207:638
Observation #1

Both Innate and Adaptive Immunity Contribute to Coagulation Activation, which (itself) Contributes to Immune Activation and Systemic Inflammation
Tissue Factor Expression on Monocytes Associates with (A) HIV Viral Load, (B) D-dimer, (C) sCD14, and (D) LPS

A

\[ r = 0.57 \ p < 0.001 \]

\[
\begin{array}{c}
\text{HIV RNA (copies/ml)} \\
\text{\% Tissue Factor + Monocytes}
\end{array}
\]

B

\[ r = 0.27 \ P = 0.025 \]

\[
\begin{array}{c}
\text{Ddimers (ng/ml)} \\
\text{\%TF+ total monocytes}
\end{array}
\]

C

\[ r = 0.305 \ P = 0.011 \]

\[
\begin{array}{c}
sCD14 (ng/mL) \\
\text{\%TF+ total monocytes}
\end{array}
\]

D

\[ r = 0.36 \ P = 0.002 \]

\[
\begin{array}{c}
\text{LPS (pg/mL)} \\
\text{\%TF+ total monocytes}
\end{array}
\]

Slide c/o N. Funderburg; BLOOD 2010;115(2):161-167
Tissue Factor (TF) Pro-coagulant Activity on Cell-Derived Microparticles Correlates with D-dimer

- ART treatment (vs. not) lowered microparticle-TF-dependent pro-coagulant activity by 36%
- Residual MP-TF activity in treated HIV disease (n=109) associates with D-dimer, vWF & IL-6

J. Baker and N. Key, JAIDS 2013;63:367
Atherosclerosis is a Thrombotic Disease

- HIV is associated with increased vascular disease
- TF is expressed on vascular SM cells and macrophages within plaques
- Injury to vessel surfaces stimulates expression of TF
- (above) eroded plaque with superimposed thrombus (th)

Observation #2

HIV Related TF Activity Contributes to Coagulation, Mediated by Innate Immunity and Vascular Disease
General Thrombosis Model

**Net Balance of Coagulation Factors**
- age
- obesity
- warfarin
- gene mutations
- other: hepatocyte synthetic function, nutrition, antibodies

**External Forces Triggering Thrombin Generation**
- hormone treatment
- cancer pro-coagulants
- inflammation
- endotoxemia

**Inciting Events**
- e.g., trauma, stress

**Thrombosis Threshold**

**Thrombosis**

*Slide Adapted from R. Tracy*
The Effects of HIV Replication and ART

3 Complimentary Comparisons to Study the Effects of HIV Replication

A) Baseline Comparison of Untreated vs. Treated

OFF ART

Defer ART (DC)

Start ART (VS)

Randomize

Follow-up

B) Study the Effect of Starting ART

ON ART with HIV RNA <400

Stop ART (DC)

Continue ART (VS)

Randomize

Follow-up

C) Study the Effect of Stopping ART

J. Baker, K. Brummel-Ziedins. et. al. JAHA 2013
Factors Used for Modeling Thrombin Kinetics

A) Baseline Comparison: Off vs. On ART

F I I  F V  F VII  F VIII  F IX  F X  T F P I  A T  P rotein C
<0.0001 0.79 <0.0001 <0.0001 0.94 0.0002 0.03 <0.0001 0.001

Fibrinogen  vWF  Protein S (Total)  Protein S (Free)
0.13 <0.0001 <0.0001 <0.0001

J. Baker, K. Brummel-Ziedins. Et. al. JAHA 2013
Computational Modeling Indicates Viral Replication is Associated with↓Hepatocyte Protein Production and ↑Thrombin Generation

**HIV Changes in Plasma Factors:**
- ↓f-II (prothrombin)
- -- f-V
- ↓f-VII
- ↑f-VIII
- -- f-IX
- ↓f-X
- ↑TFPI
- ↓AT-III
- ↓Protein C

Observation #3

HIV Replication Increases Coagulation Potential, in part, by Decreasing Key Anticoagulants in the Context of Systemic Inflammation

HYPOTHESIS: Alterations in extrinsic pathway coagulation factors association with HIV replication are a consequence of decreased hepatocyte function
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

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**Biomarker and All-Cause Mortality Associations**

<table>
<thead>
<tr>
<th>Baseline Level</th>
<th>OR (4th/1st QRT) Univariate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer</td>
<td>12.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6</td>
<td>8.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hsCRP</td>
<td>2.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Inflammation markers after randomization to abacavir/lamivudine or tenofovir/emtricitabine with efavirenz or atazanavir/ritonavir

Grace A. McComsey\textsuperscript{a}, Douglas Kitch\textsuperscript{b}, Eric S. Daar\textsuperscript{c}, Camlin Tierney\textsuperscript{b}, Nasreen C. Jahed\textsuperscript{d}, Kathleen Melbourne\textsuperscript{e}, Belinda Ha\textsuperscript{f}, Todd T. Brown\textsuperscript{g}, Anthony Bloom\textsuperscript{h}, Neal Fedarko\textsuperscript{g} and Paul E. Sax\textsuperscript{i}

Figure 2 from: AIDS 2012, 26:1371–1385


Figure 1 from J. Baker, Thrombosis Research 2013
How are these Aspects of Coagulation Biology Influenced by Aging?
**Median Biomarker Levels by Advancing Age**

*SMART/ESPRIT participants with RNA <500 (n=3227)*

### Median Biomarker Levels

- **hsCRP** (N=2099)
- **IL-6** (N=2083)
- **D-dimer** (N=2094)

The graph shows the trend of median levels of hsCRP, IL-6, and D-dimer with advancing age. The x-axis represents the age groups (in years), and the y-axis represents the median levels of the biomarkers (in ug/mL for hsCRP and IL-6, and ug/mL for D-dimer). The data is color-coded for easy visualization.
Aging as a Pro-Coagulant State

Aging

Alterations in Coagulation Biology

Lack of Anticoag Response (inconsistent or no change)

✓ Protein C
✓ Protein S
✓ Antithrombin

Clinical Risk

• Arterial Thrombosis
• Venous Thrombosis
• Frailty Phenotype?

↑ Inflammation
✓ Fibrinogen
✓ hsCRP
✓ IL-6

↑ Procoagulant Factors
✓ FV
✓ FVIII
✓ FIX
✓ PAI-1
✓ vWF

Wilkerson & Sane, Seminars in Throm and Hemo 2002;28(6):555
HIV Related Inflammation and Coagulation as a Pathway Risk for Frailty

<table>
<thead>
<tr>
<th></th>
<th>Associated with Frailty (HIV or Gen Population)</th>
<th>Elevated Among HIV+ vs. HIV-</th>
<th>Correlated with HIV Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>✔</td>
<td>✔</td>
<td>inconsistent</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>✔</td>
<td>✔</td>
<td>NO</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>✔</td>
<td>?</td>
<td>✔</td>
</tr>
<tr>
<td>PAP complex</td>
<td>✔</td>
<td>?</td>
<td>✔</td>
</tr>
<tr>
<td>D-dimer</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Summary

• Coagulation and Inflammation are Intimately Related (esp. in HIV Disease)

• HIV Specific Factors Increase Coagulation via Ubiquitous Biologic Pathways

• HIV Infection Influences Both Pro- (TF activity, FVIII) and Anti- (AT, Protein C) Coagulant Mechanisms

• HIV Leads to Alterations in Coagulation Biology Similar to that Associated with Aging and Frailty
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  Nicholas Funderburg
  Ivona Pandrea

• INSIGHT Network
  Jens Lundgren
  Andrew Phillips
  Jacquie Neuhaus
  Deborah Wentworth
Coagulation with Thrombin Generation and Inhibition

Figure 1 from Tripodi & Mannucci, NEJM 2011;365:147