Inflammation, Immune Activation and Clinical Disease in Chronic HIV infection

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Program Overview

- Living longer
- Potential impact of persistent inflammation and immune activation during HIV infection
- Age- and HIV-associated non-AIDS comorbidities
### Current Status: 90-90-90 Targets

#### Global (2016)

<table>
<thead>
<tr>
<th>Number of People Living With HIV (Millions)</th>
<th>People With HIV Who Know Their Status</th>
<th>People With HIV on Treatment</th>
<th>People With HIV Who Are Virally Suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>70%</td>
<td>53%</td>
<td>44%</td>
</tr>
</tbody>
</table>

#### Eastern and Southern Africa (2016)

<table>
<thead>
<tr>
<th>Number of People Living With HIV (Millions)</th>
<th>People With HIV Who Know Their Status</th>
<th>People With HIV on Treatment</th>
<th>People With HIV Who Are Virally Suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>76%</td>
<td>60%</td>
<td>50%</td>
</tr>
</tbody>
</table>

#### Western and Central Europe and North America (2015)

<table>
<thead>
<tr>
<th>Number of People Living With HIV (Thousands)</th>
<th>People With HIV Who Know Their Status</th>
<th>People With HIV on Treatment</th>
<th>People With HIV Who Are Virally Suppressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>85%</td>
<td>76%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Narrowing the Gap in Life Expectancy Between HIV-Positive and Uninfected Persons (1996-2011)

Kaiser Permanente Northern California (1996 to 2011): HIV-positive (n=25,768) and matched non-HIV-infected adults (n=257,600). Males (91%) and MSM (75%).

D:A:D Study:  
Trends in the Underlying Causes of Death in HIV Patients

**Overall D:A:D Cohort**

<table>
<thead>
<tr>
<th>Mortality</th>
<th>1999-2000 (n=256; 17.5/1000 person-years)</th>
<th>2009-2011 (n=627; 9.1/1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (%)</td>
<td>34%</td>
<td>22%</td>
</tr>
<tr>
<td>AIDS Related</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Liver</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>CVD</td>
<td>9%</td>
<td>23%</td>
</tr>
<tr>
<td>Non-AIDS Cancers</td>
<td>23%</td>
<td>17%</td>
</tr>
</tbody>
</table>

**Current HIV RNA <50 Copies/mL**

<table>
<thead>
<tr>
<th>Mortality</th>
<th>1999-2000 (n=72; 10.1/1000 person-years)</th>
<th>2009-2011 (n=436; 8.5/1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (%)</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>AIDS Related</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Liver</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>CVD</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Non-AIDS Cancers</td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

NA-ACCORD: Increasing Multi-Morbidity Trends Among HIV Patients Living in the US

US clinical cohorts of the NA-ACCORD (n=22,969; 2000-2009)

Multi-morbidity: ≥2 of hypertension, diabetes mellitus, chronic kidney disease, hypercholesterolemia, end-stage liver disease, non-AIDS-related cancer

Multi-morbidity prevalence from 2000 to 2009 (38% to 54%)

- High cholesterol: 18% to 20%
- Hypertension: 6% to 9%
- Hypertension with high cholesterol: 4% to 9%
- Chronic kidney disease: 0.8% to 1.6%
- High cholesterol and diabetes: 0.8% to 1.6%

NCI and CDC: Excess Burden of Cancer Among HIV-Infected Patients in the US (2010)

Retrospective analysis

Expected HIV cancer rates:
HIV/AIDS Cancer Match study

General population cancer rates:
SEER program

Excess cancer burden in the US HIV population in 2010: 54%

Nearly 65% occurred in MSM

Largest increase in NHL, Kaposi sarcoma, anal cancer, lung cancer

Largest excess occurred in those 40 to 49 years of age

Largest percentage excess in those 15 to 29 years of age

Excess or Deficit Cancer Cases Among HIV-Infected Patients in the US

<table>
<thead>
<tr>
<th>Expected Cancers (number)</th>
<th>Excess or Deficit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL (n=1645)</td>
<td>203</td>
</tr>
<tr>
<td>Kaposi sarcoma (n=912)</td>
<td>2</td>
</tr>
<tr>
<td>Lung (n=837)</td>
<td>401</td>
</tr>
<tr>
<td>Anus (n=764)</td>
<td>20</td>
</tr>
<tr>
<td>Prostate (n=574)</td>
<td>969</td>
</tr>
<tr>
<td>Liver (n=389)</td>
<td>106</td>
</tr>
<tr>
<td>Colorectum (n=357)</td>
<td>379</td>
</tr>
<tr>
<td>Hodgkin lymphoma (n=317)</td>
<td>29</td>
</tr>
<tr>
<td>Female breast (n=177)</td>
<td>303</td>
</tr>
</tbody>
</table>

SEER: Surveillance, Epidemiology, and End Results.
MACS: Frailty Phenotype in HIV-Positive MSM 50 to 70 Years of Age

- Prospective cohort of MSM (2007-2011)
  - 10,571 person-visits
  - HIV positive on ART (n=1946)
  - HIV negative (n=1048)
- Ages 50 to 64 years
  - Frailty phenotype more common in HIV-positive men versus HIV-negative men.
  - May be effect of HIV infection, ART, or both
- Further longitudinal studies are needed

Prevalence of Frailty Phenotype

Persistent Inflammation During ART: Multiple Mechanisms and Consequences

Biomarkers of Inflammation and Immune Activation

Recent data demonstrate strong associations between certain biomarkers of inflammation and morbidity and/or mortality in the setting of HIV infection.

Prospective cohort study (1996-2014) HIV suppression (n=670; 54 died)

- Residual inflammation may result from viremia below detectable levels or may represent immunologic processes that continue as a consequence of damage early in the course of infection

- High concentration of biomarkers associated with increased mortality risk in HIV-suppressed men (adjusted hazard ratio)
  
  - IL-6 (aHR: 3.5; P<0.001)
  - Soluble IL 2Rα (aHR: 3.3; P<0.001)
  - Soluble CD14 (aHR: 2.7; P<0.001)
  - Chemokine ligand 13 (aHR: 2.3; P=0.005)

aHR: hazard ratio adjusted for age, CD4 count, HBV or HCV infection, and smoking.

Marketers of Persistent Innate Immune Activation and Inflammation Predicts Morbidities Among Treated HIV Patients

- Cardiovascular disease
- Osteoporosis
- Type 2 diabetes
- Renal disease
- Lymphoma and non-AIDS-defining cancers

- Chronic obstructive pulmonary disease
- Bacterial pneumonia
- Neurocognitive dysfunction
- Depression
- Frailty

START Study: Initiation of ART in Early Asymptomatic HIV Infection

Multicontinental Study (n=4685)

HIV-positive adults
Treatment-naive
CD4 >500 cells/mm³

Primary outcome a composite outcome of 2 major components:

- Any serious AIDS-related event
  - Death from AIDS or any AIDS-defining event, Hodgkin’s lymphoma
- Any serious non–AIDS-related event
  - CVD (myocardial infarction, stroke, or coronary revascularization) or death from CVD, end-stage renal disease (initiation of dialysis or renal transplantation) or death from renal disease, liver disease (decompensated liver disease) or death from liver disease, non–AIDS-defining cancer (except for basal-cell or squamous cell skin cancer) or death from cancer, and any death not attributable to AIDS

START Study Outcomes: Composite Primary Endpoint and its Components

- Immediate ART was superior to deferral of ART both for serious and non-serious AIDS events.
- Majority (68%) of the primary endpoints occurred in patients with a CD4 >500 cells/mm³.
- Similar significant reductions were noted across all patient subgroups.
- No increase in adverse events associated with immediate versus deferred ART.

**Number of Events**

<table>
<thead>
<tr>
<th></th>
<th>Composite Endpoint</th>
<th>AIDS-Related</th>
<th>Non-AIDS Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred ART (n=2359)</td>
<td>96</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Immediate ART (n=2326)</td>
<td>42</td>
<td>14</td>
<td>29</td>
</tr>
</tbody>
</table>

- 57% Reduction ($P<0.001$)
- 72% Reduction ($P<0.001$)
- 39% Reduction ($P=0.04$)

START Study: Who Benefited the Most From Immediate ART?

Cumulative Percent With Primary Event at Month 36

Baseline Characteristics of Those Benefiting the Most

NNT: number needed to treat to prevent 1 primary event.
ARR: adjusted rate ratio (deferred-immediate ART).

Immediate ART was superior to deferred ART in asymptomatic, treatment-naïve adults with baseline CD4 $>500$ cells/mm$^3$

- Benefit seen in all subgroups, but not to the same magnitude
- Univariante analysis: Who benefited the most (higher absolute risk reduction and lower NNT)?
- Age: $>50$ years
- HIV RNA: $>50K$ copies/mL
- CD4:CD8 ratio: $<0.5$
- Framingham 10-year CHD risk score: $>10\%$

SMART Study: HIV Viremia Can Contribute to CV Risk

N=5472 HIV-infected patients with a CD4+ cell count >350mm³

No. at Risk
Treatment Interruption
2720 2070 1663 1292 1041 867 693 543 443 375 273 157
Continuous Treatment
2752 2077 1692 1307 1070 899 713 563 462 380 282 165

Major Cardiovascular, Renal, or Hepatic Disease

Hazard ratio, 1.78; 95% CI, 1.1-2.5; P=0.009

Endpoint Hazard Ratio (95%CI)* P Value
Death, any cause 1.8 (1.2-2.9) 0.007
Major cardiovascular, renal or hepatic disease 1.7 (1.1-2.5) 0.009
Fatal or non-fatal CVD 1.6 (1.0-2.5) 0.05

*Treatment Interruption vs. Continuous Treatment

Higher levels of hsCRP, IL-6, and C-dimer were significantly associated with an increased risk of **all-cause mortality**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>&lt;25th Percentile (Reference)</th>
<th>≥75th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>N (cases/controls)</td>
<td></td>
</tr>
<tr>
<td>hsCRP (μg/mL)</td>
<td>16/45</td>
<td>40/55</td>
</tr>
<tr>
<td>Univariate</td>
<td>1.0</td>
<td>2.0 (1.0-4.1)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>8/48</td>
<td>40/29</td>
</tr>
<tr>
<td>Univariate</td>
<td>1.0</td>
<td>8.3 (3.3-20.8)</td>
</tr>
<tr>
<td>D-dimer (μg/mL)</td>
<td>8/51</td>
<td>37/25</td>
</tr>
<tr>
<td>Univariate</td>
<td>1.0</td>
<td>12.4 (4.2-37.0)</td>
</tr>
</tbody>
</table>

Biomarkers of Immune Activation: The SMART Study—CRP, IL-6, D-dimer

High levels of biomarkers for inflammation and coagulation are associated with increased risk of CVD in HIV-infected patients.

- **IL-6**
  - Quartile 1 (low) (n=5037)
  - Quartile 2
  - Quartile 3
  - Quartile 4 (high)
  - Cumulative Participants With CVD Event, %
  - Time From Randomization, Months
  - \( P < 0.001 \)

- **hsCRP**
  - Quartile 1 (low) (n=5095)
  - Quartile 2
  - Quartile 3
  - Quartile 4 (high)
  - Cumulative Participants With CVD Event, %
  - Time From Randomization, Months
  - \( P < 0.001 \)

- **D-dimer**
  - Quartile 1 (low) (n=5069)
  - Quartile 2
  - Quartile 3
  - Quartile 4 (high)
  - Cumulative Participants With CVD Event, %
  - Time From Randomization, Months
  - \( P < 0.001 \)

- **Time-to-event methods were used to study associations of the baseline level of IL-6, hsCRP, and D-dimer with a CVD event**

- **IL-6** quartiles are <1.10, 1.10-1.76, 1.77-3.01, >3.01 pg/mL.
- **hsCRP** quartiles are <0.72, 0.72-1.71, 1.72-4.17, >4.17 μg/mL.
- **D-dimer** quartiles are <0.13, 0.13-0.21, 0.22-0.37, >0.37 μg/mL.

SMART and START Studies: Benefit of Immediate/Continuous ART on Disease Risk

Combined analysis of SMART and START studies (n=10,157)

AIDS events (n=123)

Serious non-AIDS events (n=244)

CVD (n=103)

Cancer (n=117)

Death (n=118)

AIDS and serious non-AIDS events (n=359)

Cancer risk reduction did not vary by type of cancer

Immune preservation through immediate and continuous ART significantly reduces the risk of AIDS and non-AIDS events

Patients with Sustained ART-Induced Viral Suppression had Lower levels of T-Cell Activation than Untreated Persons but Higher Levels than HIV-Uninfected Controls

- T-cell activation persists despite viral suppression with ART

Early immune activation after HIV infection has a strong impact on subsequent disease progression.

Theoretical Model: Impact of Nadir CD4 Count on the Root Drivers of Immune Activation in Treated HIV and Disease Manifestations

- Not all putative root drivers of the inflammatory state in treated HIV infection are likely to be active in those who initiate ART at early disease stages
- Many preferentially drive inflammation in distinct anatomic compartments
- **Primary source of measured abnormalities of systemic immune activation markers:**
  1. Nadir CD4 count at ART start
  2. HIV reservoirs in lymphoid tissues and, potentially, microbial translocation (both do not need significant pre-ART immunodeficiency to be established)
  3. Much greater diversity of sources and anatomic sites likely contributes to any elevations observed in those with very low nadir CD4 count at ART start

Further research needed

Other Contributors of Persistent Immune Activation in Treated HIV Infection

Lifestyle factors
  Smoking
  Alcohol/drug abuse
  Obesity
Coinfections

AGEhIV Cohort Study: Cigarette Smoking and Immune Activation in Treated HIV Patients

Prospective cohort study (n=1042; 2010-2012)

**HIV-infected and uninfected ≥45 years of age**
- Male (87%), MSM (72%)
- Smokers
  - Current: 32% (median 15 cigarettes/day per smoker)
  - Former: 37%
- HIV RNA <200 copies/mL in year before enrollment (94%)

Smoking was independently associated with:
- higher hsCRP levels
- lower sCD163 levels
- (borderline significance for higher sCD14 and D-dimer levels
- No differential effect between HIV-infected and uninfected persons

### Smoking and HIV Status: Association With Biomarker Levels in the Highest Quartile (adjusted OR*)

<table>
<thead>
<tr>
<th></th>
<th>hsCRP</th>
<th>sCD14</th>
<th>sCD16</th>
<th>D-dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>1.04</td>
<td>1.16</td>
<td>0.84</td>
<td>0.92</td>
</tr>
<tr>
<td>Smoking status (ref. never smoke)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1.57*</td>
<td>1.34†</td>
<td>0.62*</td>
<td>1.36†</td>
</tr>
<tr>
<td>Current</td>
<td>1.44*</td>
<td>2.11†</td>
<td>1.40¶</td>
<td>0.64‡</td>
</tr>
<tr>
<td>HIV-positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers only</td>
<td>1.49†</td>
<td>1.27†</td>
<td>0.78†</td>
<td>1.30†</td>
</tr>
<tr>
<td>Cigarette smoked per day (per 10) HIV-positive</td>
<td>1.24</td>
<td>2.08*</td>
<td>1.42</td>
<td>0.52‡</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, HCV infection, use of alcohol and recreational drugs, and waist to hip ratio.

Microbiome During Health and HIV

Gut microbes could impact HIV transmission, which leads to CD4 cell death and immune depletion, and loss of immune regulation of gut bacteria (dysbiosis); translocation of dysbiotic bacteria leads to immune activation and further HIV infection of activated CD4 cells.

ART suppresses viral replication but does not fully restore gut immunity; dysbiosis is sustained during ART and microbial translocation continues to cause chronic immune activation.

Restoring to a healthy gut may help reconstitute gut immunity and restore immune regulation of the microbiome.


HIV Is Associated With Increased Arterial Inflammation

- HIV+ individuals had signs of increased arterial inflammation, compared with noninfected controls with similar cardiac risk factors.
- Aortic inflammation in HIV+ individuals was associated with the soluble inflammatory marker, sCD163.

Arterial inflammation was significantly correlated with sCD163 levels.

HIV: Mechanisms of Atherosclerosis/MI

HIV INFECTION

IMMUNODEFICIENCY

MICROBIAL TRANSLOCATIOn

VIRAL REACTIVATION

PERSISTENT VIRAL REPLICATION

Other HIV-Associated Factors:
- Traditional CV risk factors (smoking)
- Older HIV therapies

CHRONIC IMMUNE ACTIVATION AND INFLAMMATION

INCREASED CLOTTING

ALTEDERED LIPID METABOLISM

INFLAMMATORY CELL ARTERIAL INFILTRATION

IMMUNE SENESCENCE

ATHEROSCLEROSIS & MI

Figure adapted from: Hsue PY, et al. J infect dis. 2012;205 Suppl 3:S375-382
**HIV and the Risk of Acute Myocardial Infarction**

Rates of AMI were significantly higher for HIV-positive vs uninfected veterans across 3 decades of age.

*\(p<0.05\) for HIV-infected vs uninfected veterans.


<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>80-89</th>
<th>&gt;89</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uninfected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1,175</td>
<td>6,783</td>
<td>21,866</td>
<td>19,805</td>
<td>4,209</td>
<td>1,120</td>
<td>148</td>
<td>3</td>
</tr>
<tr>
<td>AMI rates per 1,000 person-years (95% CI)</td>
<td>...</td>
<td>0.3 (0.2-0.6)</td>
<td>1.5* (1.3-1.7)</td>
<td>2.2* (1.9-2.5)</td>
<td>3.3* (2.6-4.2)</td>
<td>6.7 (4.8-9.2)</td>
<td>21.5 (12.7-36.4)</td>
<td>...</td>
</tr>
<tr>
<td><strong>Infected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>725</td>
<td>3,848</td>
<td>10,575</td>
<td>9,342</td>
<td>2,065</td>
<td>557</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>AMI rates per 1,000 person-years (95% CI)</td>
<td>...</td>
<td>0.7 (0.4-1.2)</td>
<td>2.0* (1.6-2.4)</td>
<td>3.9* (3.3-4.5)</td>
<td>5.0* (3.8-6.7)</td>
<td>10.0 (6.7-14.7)</td>
<td>13.5 (4.3-42.0)</td>
<td>...</td>
</tr>
</tbody>
</table>
Associations Between HIV Infection and Subclinical Coronary Atherosclerosis

Wendy S. Post, MD, MS; Matthew Budoff, MD; Lawrence Kingsley, PhD; Frank J. Palella Jr., MD; Mallory D. Witt, MD; XiuHong Li, MS; Richard T. George, MD; Todd T. Brown, MD, PhD; and Lisa P. Jacobson, ScD

Background: Coronary artery disease (CAD) has been associated with HIV infection, but data are not consistent.

Objective: To determine whether HIV-infected men have more coronary atherosclerosis than uninfected men.

Design: Cross-sectional study.

Setting: Multicenter AIDS Cohort Study.

Participants: HIV-infected (n = 618) and uninfected (n = 383) men who have sex with men who were aged 40 to 70 years, weighed less than 136 kg (200 lb), and had no history of coronary revascularization.

Measurements: Presence and extent of coronary artery calcium (CAC) on noncontrast cardiac computed tomography (CT) and of any plaque; noncalcified, mixed, or calcified plaque; or stenosis on coronary CT angiography.

Results: 1001 men had noncontrast CT, of whom 759 had coronary CT angiography. After adjustment for age, race, CT scanning center, and cohort, HIV-infected men had a greater prevalence of CAC (prevalence ratio [PR], 1.21 [95% CI, 1.08 to 1.35]; P = 0.001) and any plaque (PR, 1.14 [CI, 1.05 to 1.24]; P = 0.001), including noncalcified (PR, 1.28 [CI, 1.13 to 1.45]; P < 0.001) and mixed (PR, 1.35 [CI, 1.10 to 1.65]; P = 0.004) plaque, than uninfected men. Associations between HIV infection and any plaque or noncalcified plaque remained significant (P < 0.005) after CAD risk factor adjustment. HIV-infected men had a greater extent of noncalcified plaque after CAD risk factor adjustment (P = 0.026). They also had a greater prevalence of coronary artery stenosis greater than 50% (PR, 1.48 [CI, 1.06 to 2.07]; P = 0.020), but not after CAD risk factor adjustment. Longer duration of highly active antiretroviral therapy (PR, 1.09 [CI, 1.02 to 1.17]; P = 0.007) and lower nadir CD4+ T-cell count (PR, 0.80 [CI, 0.69 to 0.94]; P = 0.005) were associated with coronary stenosis greater than 50%.

Limitation: Cross-sectional observational study design and inclusion of only men.

Conclusion: Coronary artery plaque, especially noncalcified plaque, is more prevalent and extensive in HIV-infected men, independent of CAD risk factors.

Primary Funding Source: National Heart, Lung, and Blood Institute and National Institute of Allergy and Infectious Diseases.

For author affiliations, see end of text.
Imaging Atherosclerosis in HIV

759 men: 2/3 HIV+, 1/3 HIV- controls
- Noncalcified plaque (PR 1.28, CI 1.13-1.45) and coronary calcium (PR 1.13, CI 1.04-1.23) both significantly more likely for HIV+ patients

Summary/Conclusions

- Non-calcified plaque is more prevalent and extensive in HIV-infected men, suggesting increased risk for cardiovascular events.

- Men with more advanced HIV infection, as demonstrated by low nadir CD4+ T cell count and a greater number of years on HAART have a higher prevalence of clinically significant coronary stenosis > 50%.

- Additional studies are needed to identify how best to prevent progression of atherosclerosis in this unique population and correlation with future events.

- Although coronary CT angiography is not indicated as a screening test in asymptomatic individuals, these results emphasize the importance of assessing and modifying traditional cardiovascular risk factors in this population, especially in men with a history of a low nadir CD4+ T cell count.
Biomarkers of Immune Activation: 

sCD163

- CD163 is a scavenger receptor expressed exclusively on monocytes/macrophages
  - Mediates uptake of hemoglobin-haptoglobin complexes for the removal and metabolism of hemoglobin, a potent oxidant molecule
  - CD163+ macrophages have been identified in atherosclerotic lesions
  - Soluble CD163 (sCD163) levels are increased in association with macrophage proliferation and activation
Biomarkers of Immune Activation: sCD163

- sCD163 levels are significantly increased in plasma during chronic and early HIV infection\(^1\)
  - sCD163 decrease after receipt of ART, but do not completely “normalize”

Elevated sCD163 levels have been associated with noncalcified coronary plaque and neurocognitive impairment in HIV+ persons\(^2,3\)

sCD14

- Correlates with HIV infection and mortality
- Associated with carotid atherosclerosis in HIV-infected populations

Monocyte chemoattractant protein-1 (MCP-1)

- Associated with HIV infection and carotid atherosclerosis in HIV-infected individuals
- Expression is genetically determined

Elevated Levels of Monocyte Activation Markers, soluble CD14 and CD163, are associated with Subclinical Atherosclerosis in the MACS

Rebeccah A McKibben, Stephen Grinspoon, Xiuhong Li, Frank Palella, Lawrence A Kingsley, Mallory D Witt, Todd T Brown, Lisa P Jacobson, Matthew Budoff, Wendy S Post
Elevated Levels of Monocyte Activation Markers, soluble CD14 and CD163, are associated with Subclinical Atherosclerosis in the MACS

Conclusions

- Monocyte activation marker (sCD163, sCD14 and MCP-1) levels were higher among HIV-infected men, and associated with subclinical coronary atherosclerosis.

- Monocyte activation may contribute to the burden of CVD among HIV-infected men despite viral suppression.

## Developmental Considerations for Reducing Persistent Immune Activation in HIV

### Potential Investigative Options

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<thead>
<tr>
<th>Category</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologics</td>
<td>Anti-PD-1 antibodies, anti-IFN-alfa antibodies, TNF inhibitors, IL-6 inhibitors</td>
</tr>
<tr>
<td>Enhance T-cell renewal</td>
<td>Gamma-chain cytokines (IL-2, IL-7, IL-15), growth hormone</td>
</tr>
<tr>
<td>Microbial translocation</td>
<td>Rifaximin, sevelamer, prebiotics/probiotics, colostrum</td>
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<tr>
<td>Chemokine receptor inhibitor</td>
<td>Maraviroc, cenicriviroc</td>
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<tr>
<td>Anti-fibrotic agents</td>
<td>Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, keratinocyte growth factor, pirfenidone</td>
</tr>
<tr>
<td>Anti-coagulants</td>
<td>Low-dose warfarin, dabigatran, aspirin, clopidogrel</td>
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<tr>
<td>Anti-infective therapy</td>
<td>CMV, HCV/HBV, HSV, EBV</td>
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<tr>
<td>Anti-inflammatory agents</td>
<td>Chloroquine, hydroxychloroquine, NSAIDs (aspirin, mesalamine, COX-2 inhibitors)</td>
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<tr>
<td></td>
<td><strong>Statins</strong></td>
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<tr>
<td></td>
<td>Minocycline</td>
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<td></td>
<td>Methotrexate</td>
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<td></td>
<td>Thalidomide, lenalidomide, pentoxifylline</td>
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<tr>
<td>Anti-aging</td>
<td>Sirolimus, caloric restriction, omega-3 fatty acids, diet, exercise</td>
</tr>
</tbody>
</table>

Impact of Aspirin and Statin Use on Inflammation and Immune Activation

ACTG A5331

Prospective, double-blind study, healthy HIV adults on suppressive ART (n=113)

Aspirin 100 or 300 mg/day or placebo for 12 weeks

Primary outcome: change in sCD14

Aspirin had no impact on immune activation or endothelial function

Statin use and liver

Dose-dependent reduction in hepatic fibrosis progression in HCV monoinfected patients

Significant protective effect against development of cirrhosis in less severe liver disease (ALT <40 IU/L) in HIV/HCV coinfection

Reduced hepatosteatosis in HIV patients with NAFLD

Statin use and renal function

SATURN-HIV

Prospective, double-blind study, healthy HIV adults on suppressive ART with normal lipid levels

Rosuvastatin for 24 weeks reduced plasma cystatin C and slowed kidney function decline

Modulating Immune Activation With Statins
SATURN Trial (cont’d)

- 24 weeks of rosuvastatin treatment significantly reduced levels of a vascular-specific inflammatory enzyme, Lp-PLA₂
  - Lp-PLA₂ is a predictive marker for primary and recurrent CV events in the general population

<table>
<thead>
<tr>
<th>Marker</th>
<th>Statin, Percentage Change (n=72)</th>
<th>Placebo, Percentage Change (n=75)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp-PLA₂ level</td>
<td>-9.9 (-20.1 to -1.0)</td>
<td>-1.9 (-8.6 to 13.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-28 (-43 to -16)</td>
<td>3.8 (-0.7 to 17.2)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

- Conclusions: 48 weeks of rosuvastatin treatment reduced significantly several markers of inflammation and lymphocyte and monocyte activation in ART-treated subjects. Whether these favorable changes translate to a clinical benefit remains to be elucidated.

Inflammation, Immune Activation and Clinical Disease in Chronic HIV infection

Conclusions

- Inflammation is bad:
- Many types of immune activation are bad
- HIV-infected persons have more of both compared to HIV-uninfected persons, even when they are virally suppressed with cART
- It is important to isolate the effects of these from other traditional risk factors and HIV itself
- Chronic inflammation and immune activation are contributors to the risk of morbidity and mortality in HIV-infected individuals
Conclusions (cont’d)

- Paradigm shift: need to go beyond CD4 count, viral load, and AIDS-defining conditions to guide clinical care and research
- Risk assessment for important non-infectious comorbidities that are likely driven by excess inflammation and immune activation (e.g., cardiovascular disease) should be a part of routine HIV care
- Should screening for CVD risk among HIV-infected persons include selected biomarker assessment? If so, which ones?
Conclusions

Should interventions aimed at reducing morbidity and mortality risk in HIV target inflammation and immune activation? We already know that ASA, statins work in the general population to reduce CVD events.

If yes to above, how do we know that interventions aimed at reducing biomarker levels will also reduce CVD clinical events?

- One currently-enrolling NIH-funded study seeking to answer some of these questions: REPRIEVE