Immune Activation in Treated HIV Infection

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Life Expectancy Improving but a Gap Persists

**By pre-ART CD4 count**

- Life expectancy of patients on or starting ART in North America
- ~23,000 person-years FU
- 1,622 deaths
- Majority of HIV+ around the world still starting ART <350.

**May overestimate life expectancy**
- Excludes those out of care
- “Survivorship bias” for older patients who survived 80s and 90s.

*For 20-year old initiating ART

*Samji for NA-ACCORD, PLoS One, 2013*
Many age-associated morbidities also increased in treated HIV

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- COPD [12]
- Liver disease [7]
- Kidney disease [8]
- Cognitive decline [9]
- Non-AIDS infections [10]
- Frailty [11]

HIV and Aging — Preparing for the Challenges Ahead

Edward J. Mills, Ph.D., Till Bärnighausen, M.D., Sc.D., and Joel Negin, M.I.A.

HIV Prevalence in Sub-Saharan Africa in 2011, 2025, and 2040.

Shown are the prevalence of HIV in the population 15 to 49 years of age and in the population 50 years of age or older in sub-Saharan Africa for the year 2011 and projections of HIV prevalence in those populations in the years 2025 and 2040 with continuous scale-up of antiretroviral therapy programs. Maps courtesy of Jan Hontelez, Erasmus University, Rotterdam.
Increased Multi-morbidity in Older HIV+ Individuals (AGE$_{hIV}$)

**Morbidities:**
- CAD / MI
- HTN
- PAD
- CVD / Stroke
- COPD
- T2DM
- Renal Dz
- Non-AIDS CA
- Osteoporosis
Does HIV Cause Accelerated Aging?

Not exactly…

Cancer as an illustrative example
Risk of many - *but not all* - cancers is increased by HIV / AIDS

Strikingly similar pattern of cancer risk in RA and psoriasis...

(Smitten, Arth Res, 2008)

Adjusted for age, gender, race, calendar year, and cancer registry.

Shiels, Annals Int Med, 2010
Why do HIV-infected individuals have increased multi-morbidity / mortality?
Many Chronic Diseases of Aging May Be Driven By Lifestyle Factors and ART Toxicity

Deeks and Phillips, BMJ, 2009
SMART Study: Interrupting ART Increases the Risk of Heart Disease

<table>
<thead>
<tr>
<th>Major CVD Event</th>
<th>DC</th>
<th>VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CVD</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Non-fatal clinical MI</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Non-fatal silent MI</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>CAD requiring surgery for invasive procedure</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>All major CVD events</td>
<td>48</td>
<td>31</td>
</tr>
</tbody>
</table>

No. at Risk: 2752, 1306, 713, 379, 10 for DC; 2720, 1292, 696, 377, 10 for VS.
Many chronic diseases of aging are more common in HIV+’s, even after adjustment for ART use and lifestyle factors.

Lifestyle

ART Toxicity

Persistent Inflammation

Age-associated Morbidity

Deeks and Phillips, BMJ, 2009
An Important Clue from Nature

Sooty Mangabey
• Infect with SIV
• High Levels of Viral Replication
• No AIDS, normal lifespan
• Minimal Immune Activation

Rhesus Macaque
• Infect with SIV
• High Levels of Viral Replication
• AIDS and death
• Massive Immune Activation

Silvestri, Immunity, 2003
T Cell Activation Declines with ART

But Remains Abnormally High During ART-mediated Viral Suppression

Inflammatory markers are higher in treated HIV disease compared with HIV seronegatives, adjusted for demographics and CV risk factors.

Chronic Immune Activation May Also Cause Lymphoid Tissue Fibrosis

- Associated with low % naïve T cells and poor CD4+ T cell recovery
- May impair functional immune responses

Estes, JID, 2008; Schacker, JCI, 2002; Zeng, JCI, 2011
What are the clinical consequences of persistent immune activation and inflammation during ART?
A single measurement of IL-6 or D-dimers predicts morbidity or mortality over next decade.
Increased Arterial Inflammation in HIV

Aortic Inflammation associated with ↑sCD163 levels (monocyte activation)

Subramanian/Grinspoon, JAMA, 2012
Inflammation Predicts Disease in Treated HIV Infection

- **Mortality** (Kuller, PLoS Med, 2008; Tien, JAIDS, 2010; Justice, CID 2012)
- **Cardiovascular Disease** (Duprez, Atherosclerosis, 2009)
- **Cancer** (Breen, Cancer Epi Bio Prev, 2010; Borges, AIDS, 2013)
- **Venous Thromboembolism** (Musselwhite, AIDS, 2011)
- **Type II Diabetes** (Brown, Diabetes Care, 2010)
- **Cognitive Dysfunction** (Burdo, AIDS, 2013; Letendre CROI 2012)
- **Depression** (Martinez, JAIDS, 2014)
- **Frailty** (Erlandson, JID, 2013)
What is causing inflammation during suppressive ART?
Low-level Viremia $<75$ copies/ml is Common During Apparent Viral Suppression on HAART

N=130

Mostly reflects release of virus from infected cells without productive replication

We lack interventions that block HIV expression.

Are there indirect mechanisms by which HIV might drive persistent immune activation during ART?
Microbial Translocation ("Leaky Gut") as a Cause of Immune Activation in HIV

Disrupted Gut Epithelial Barrier
- ↑EC Apoptosis
  (Li, JID, 2008)
- ↓Tight Junctions
  (Epple, Gut 2009)

Loss of Mucosal Immunity
↓CD4+ T cells
↓Th17 cells


Brenchley et al,
Nat Med, 2006
Gut Barrier Defects and Microbial Translocation Persist Despite ART

**HIV-**

**HIV+ ART+ CD4>500**

**HIV+ ART+ CD4<350**

Persistent neutrophil infiltration in rectal mucosa during treated HIV infection in response to mucosal barrier breach

Somsouk, AIDS, 2014 (also Marchetti, AIDS, 2008; Jiang et al, JID, 2009)
Gut Barrier Dysfunction and Innate Immune Activation Predict Mortality during Suppressive ART SOCA cohort

- Microbial translocation
  - I-FABP
  - sCD14
  - IL-6
  - D-dimer
  - TNF R1
  - hsCRP

- Inflammation / Coagulation
  - % CD38+ HLA-DR+ CD8+ T Cells
  - % CD28- CD57+ CD8+ T Cells

Odds of Mortality
(4th vs. 1st Quartile)

Hunt, JID, 2014 (see also: Sandler, JID, 2011; Tenorio, JID 2014)
Do chronic co-infections also contribute to immune activation during ART?
Blocking Asymptomatic CMV Replication with Valganciclovir ↓ Immune Activation in HIV+ Patients with CD4<350 despite ART

We need larger studies of safer CMV drugs to see if this is clinically meaningful...

Valacyclovir, which has strong anti-HSV1/2 but minimal anti-CMV activity, failed to decrease immune activation (Yi et al, CID, 2013).

Hunt et al, JID, 2011
HIV-Mediated Immune Activation and Aging

IDO-1-induced Tryptophan Catabolism

- IFN-γ/IFN-α and LPS induce Indoleamine 2,3-dioxygenase-1 (IDO-1) production in DCs/MØ
- Causes tryptophan catabolism
- Kynurenine and Picolinic Acid may impair T cell proliferation
  - Maternal tolerance of fetal antigens
  - Cancer evasion of immune response
- Catabolites may be neurotoxic
  - Neurodegenerative diseases, ADC
- 3-Hydroxyanthranilic Acid (HAA) causes Th17 depletion, ↑Tregs

Kynurenine (K/T Ratio) = Marker of Tryptophan Catabolism

Favre, Mold et al, Science TM, 2010
(see also: Munn, Science, 1998; Boasso, Blood, 2007)
IDO-1 Pathway and HIV Pathogenesis
(Indoleamine 2,3-dioxygenase-1)

↑Microbial Translocation
(I-FABP, LPS) ➔ MØ / DC Activation
(sCD14, sCD163) ➔ Inflammation (IL-6, sTNFR)
T Cell Activation (CD38+DR+)
Coagulation (D-dimer)

↓Th17/Treg Ratio ➔ IDO Induction
(KT ratio) ➔ Tryptophan catabolism ➔ ↓T Cell Proliferation

↑3-HAA ➔ Morbidity & Mortality

Favre, Science Transl Med, 2010 (see also Boasso, Blood, 2007)
Higher IDO-1 Activity (K/T ratio) Predicts ↑ Mortality during ART in HIV+ Ugandans

P for Trend <0.001

Month After ART Initiation

Tertile of Baseline K/T Ratio
- 1 (<0.10)
- 2 (0.10-0.17)
- 3 (>0.17)

Are adaptive immune defects more important in resource limited settings?

CROI 2015: Lee, #317; Balagopal, #313 (Wed)

Byakwaga, JID, 2014
Kynurenine Pathway (IDO-1) Activity Declines during Suppressive ART

P for trend <0.001

Month of ART

Plasma K/T Ratio (uM/uM)

Byakwaga, JID, 2014
KT Ratio Continues to Predict Mortality during Suppressive ART (VL<400 at Month 6 of ART)

Each tertile increase in month 6 K/T ratio associated with a 2.9-fold increased hazard of death after adjusting for BMI, CD4 count, and %CD38+HLA-DR+ CD8+ T cells (P=0.042).

Byakwaga, JID, 2014
IDO-mediated Tryptophan Catabolism and Depression

McNally, CNS Spectr., 2008
HIV-associated depression may be in part mediated by IDO-induced tryptophan catabolism (and improved by ART)

**Depressive Symptoms**

<table>
<thead>
<tr>
<th>Month of ART</th>
<th>HSCL Score (affective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**Plasma Tryptophan Levels**

<table>
<thead>
<tr>
<th>Month of ART</th>
<th>Plasma Tryptophan Level (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

KT ratio and depression association appeared strongest in patients with a low protein diet (P for interaction =0.08).  

Martinez, JAIDS, 2014
What can we do to reduce immune activation?

ART is important!

Maybe even in “elite” controllers…
Negative Inflammatory Consequences in HIV Controllers

- Controllers also have:
  - ↑ Microbial Translocation (Hunt, JID, 2008)
  - ↑ Monocyte activation (Pereyra, AIDS, 2012)
  - ↑ Atherosclerosis (Hsue, AIDS, 2009; Pereyra, AIDS, 2012)
  - ↑ Lymphoid fibrosis (Sanchez, JID, 2014)
  - ↑ Hospitalizations (Crowell, JID, 2015)

- Treating controllers with ART decreases immune activation (Hatano, PLoS Path, 2013)
Early ART initiation might also be beneficial.
OPTIONS Cohort:
Early vs. Late ART Initiation

Sx of Acute HIV or Recent Seroconversion

HIV+ <6mo

- Early ART Initiate <6 mo of Infxn

HIV-

- Late ART Initiate >2 yr of Infxn
Persistently Abnormal Immune Activation
When ART Initiated during Chronic Infection

See also: Burdo, JID, 2011; Vinikoor, CROI 2012, Abstract #554

Jain et al, JID, 2013
Early ART Appears to Cause Greater Reduction in Residual T Cell Activation

Timing of ART Post-infection: Acute/Early (<6 mo) Chronic (~3y)

See also: Burdo, JID, 2011; Vinikoor, CROI 2012, Abstract #554  Jain et al, JID, 2013
Severe HIV morbidity, Baseline CD4 ≥ 500/mm³ (n=849)

- No significant interaction between Early ART and IPT
- 44% reduction in risk with Early ART
- 39% reduction in risk with IPT

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Rate /100 PY</th>
<th>aHR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO ART</td>
<td>38</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early ART</td>
<td>23</td>
<td>2.4</td>
<td>0.56</td>
<td>0.03</td>
</tr>
<tr>
<td>No IPT</td>
<td>37</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPT</td>
<td>24</td>
<td>2.5</td>
<td>0.61</td>
<td>0.056</td>
</tr>
</tbody>
</table>

aHR: adjusted Hazard Ratio (adjusted for the other strategy and for center)
Will early ART be enough to completely reverse immune activation?
Immune Activation Remains Abnormal Even in Patients Treated during Acute HIV (RV254)

- Thai study of HIV+ individuals dx very early during acute HIV infection
- Compared to high-risk HIV- controls and ART-suppressed HIV+ who initiated during chronic HIV infection

Utay, CROI 2015, #47
What can we do now to reduce the chronic inflammatory state?

Health-related Behaviors
Moderate Exercise Decreases Inflammation in Sedentary ART-suppressed HIV+ Patients (n=49)

3 Days/Wk x 12 Wks
1 hr brisk walking (n=29) + strength training (n=20)
71% completed 12 wks

Also improved:
- Weight (-3 kg)
- BMI
- Waist Circumference
- LDL
- Strength studies
- ALT

Longo, CROI 2014, Abstract #763
Impact of Smoking on Mortality May be Greater in HIV: Danish Cohort Study

Helleberg et al, CID, 2013
What about commonly used medications with anti-inflammatory properties?
Statins Decrease Monocyte Activation in Treated HIV Infection
SATURN-HIV Trial

Funderburg, JAIDS, 2015 (see also Lo, Lancet HIV, 2015; Nakanjako, Trop Med Int Health 2015)
REPRIEVE Trial Now Open

Asymptomatic HIV patients with no history of CVD and ASCVD < 7.5%

N=6500, 6 yrs

Screening and Consent

Randomization

Placebo

Pitavastatin

Intervention

N=800, 2 yrs

Mechanistic Study

Coronary plaque, vascular inflammation, immune activation

Mechanistic Primary Endpoint

CVD Death  MI  Unstable Angina  TIA & Stroke  Arterial Revasc  PAD

Clinical Primary Endpoint

Steve Grinspoon, CROI 2015, #134
Aspirin Might Decrease Monocyte Activation in Treated HIV Infection

- Uncontrolled trial of ASA 81mg x 1 week
  - HIV+ (n=25)
  - HIV- (n=44)

- Decrease in sCD14 (and T cell activation) in HIV arm.

- RCT in ACTG fully enrolled, results in time for CROI 2016

Other Commonly Used Meds with Anti-inflammatory Effects

**Enrolling trials**
- ACEI and ARB (Hatano, Utay/Lake, Baker)

**Planned trials**
- Sitagliptin (Dube/ACTG)
- Probiotics/VSL3 (Andrade/Overton-ACTG)
Biologic Interventions?

Enrolling trials

• Low-dose methotrexate (Hsue/ACTG)
• Isotretinoin (Kwon/ACTG)
• IL-1b inhibition (Hsue)
• IL-6 inhibition (Lederman/CWRU)
• Ruxolitinib (Marconi/ACTG)

Future targets

• IDO-1
• Novel CMV drugs and/or vaccines
Summary

• Despite optimal ART, HIV increases mortality and age-associated morbidities.

• Immune activation / inflammation persist despite ART and may predict these morbidities.

• Earlier initiation of ART may decrease but not completely reverse persistent immune activation.

• Exercise and smoking cessation important!

• Statins, ASA, other anti-inflammatory drugs hold promise – await clinical endpoint trials

• Targeted interventions directed at the underlying causes of inflammation may hold promise (i.e., HIV reservoirs, co-infections/CMV, microbial translocation).
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