The Immune Aspects of HIV Malignancy, Aging, and End-Organ Disease

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Disclosures

• Research Grant Support
  – Roche, Pfizer, Salix

• Consulting
  – Merck, Tobira, Bristol Myers Squibb

• Honoraria
  – Boehringer-Ingelheim, Gilead, Janssen

I will not be recommending any specific therapies for clinical use
HIV and Aging

- Changing spectrum of morbidity/mortality in modern ART era
- Does HIV cause accelerated aging?
  - Cancer as an illustrative example
- Immunologic mechanisms
- Targets for interventions

Dramatically Improved Life Expectancy in Early ART Era

Survival from Age 25 Years
N= 3,990

Late HAART Era Extended Life Expectancy
Even Further
Survival from Age 25 Years
N= 3,990

Probability of Survival
Early HAART (1997–1999)
Late HAART (2000–2005)

Age, years
25 30 35 40 45 50 55 60 65 70
0 0.25 0.5 0.75 1


Late HAART Era Patients Still Have a 10y Shorter Life Expectancy than HIV- Controls
Survival from Age 25 Years
N= 3,990

Probability of Survival
Population controls
Late HAART (2000–2005)
Early HAART (1997–1999)

Age, years
25 30 35 40 45 50 55 60 65 70
0 0.25 0.5 0.75 1


- 1,876 deaths among 39,727 patients
- Non-AIDS related deaths accounted for 50.5%

Many morbidities associated with aging also appear to be increased in treated HIV disease

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

Does HIV Cause Accelerated Aging?

I don’t care.

Cancer as an illustrative example

Risk of many - *but not all* - cancers is increased by HIV infection

Shiels, Annals Int Med, 2010
Why do HIV+ patients have a higher risk of premature mortality and many age-associated morbidities?

Many Chronic Diseases of Aging May Be Driven By Lifestyle Factors and ART Toxicity

Lifestyle (smoking, etc.)

ART Toxicity

Premature Aging

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

Many chronic diseases of aging are more common in HIV+'s, even after adjustment for ART use and lifestyle factors

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 Suppresion


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

High T Cell Activation Associated with Blunted CD4 Recovery

Hunt et al, JID, 2003 (see also Goicoechea, JID, 2006; Gandhi, JAIDS, 2006; Lederman, JID, 2011)
What are the clinical consequences of persistent inflammation and immunodeficiency during ART?

Persistently Low CD4 Counts during ART Predict AIDS and Non-AIDS Events

Baker et al for FIRST trial (INSIGHT), AIDS, 2008
Increased Risk of Non-AIDS-defining Cancers with Lower CD4 Counts during ART

Largely driven by infection-related cancers (EBV, HPV, HCV/HBV, H Pylori), 43% of all cancers

Kesselring, CID, 2011

What about inflammatory markers?
### SMART: Inflammatory Markers Strongly Associated with Mortality and CVD Events

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>All-Cause Mortality (N=85)</th>
<th>Fatal or Non-fatal CVD (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P-value</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>3.1</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>12.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amyloid A</td>
<td>3.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Amyloid P</td>
<td>1.1</td>
<td>0.78</td>
</tr>
<tr>
<td>D-dimer</td>
<td>41.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>F1.2</td>
<td>1.3</td>
<td>0.64</td>
</tr>
</tbody>
</table>


### Inflammation and T/B Cell Activation Predicts NHL (MACS)

Adjusted for age, duration HIV infection, and CD4 count

Breen, Cancer Epi Bio, 2011
Are inflammation and low CD4 count the primary drivers of cancer in HIV? Might not be that simple…

Declining KS and Lymphoma Incidence during ART

↓ pre-ART CD4 assoc. with:

↑KS
↑Lymphoma
↑HPV-related CA

Yanik for CNICS cohort, CID, in Press
Increased Risk of KS/NHL during Early ART

Are KS/NHL IRIS Events?

Jaffe for CASCADE cohort, AIDS, 2011 (see also Lanoy, Blood, 2011)

Relationship between CD4 Count and Hodgkin Lymphoma Risk is **Not** Linear

Lanoy, Blood, 2011
How do we explain an ↑ in KS/Lymphoma during early ART?

- Inflammatory markers typically decline, while CD4 counts increase…
- Must be some other mechanism
- Reversal of lymphocyte proliferative defects (i.e., take foot off the brakes)?
  - Monocyte activation?
  - IDO-1 induction?

What are the drivers of persistent inflammation during ART?
Low-level Viremia <75 copies/ml is Common During Apparent Viral Suppression on HAART

N=130

80% Patients had detectable viremia
Median 3.1 copies/ml

HIV RNA Is Also Readily Detectable in Rectal Tissue During “Suppressive” HAART

Plasma VL <40 copies/mL

N=40.
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

Brenchley et al, Nat Med,
Microbial Translocation Decreases with ART but Persists for Years

Microbial Translocation May Drive Tissue Factor Expression in HIV
Potential Mechanism for CAD Risk

- Tissue Factor expression induced by LPS in vitro
- In vivo, associated with:
  - sCD14 (marker of microbial translocation)
  - % activated CD8+ T cells
  - D-Dimer levels

Jiang et al, JID, 2009 (also Marchetti, AIDS, 2008)
Funderburg, Blood, 2009
Microbial Translocation Predicts Mortality during ART-mediated Viral Suppression
SOCA cohort

Do chronic co-infections also contribute to immune activation during ART?
CMV elicits massive immune responses even in asymptomatic HIV- individuals

Sylwester/Picker, JEM, 2005

CMV-specific T Cell Responses are Higher in HIV-infected Patients

Naeger et al, PLoS One 2010
Decreasing Asymptomatic CMV Replication with Valganciclovir Decreases Immune Activation in HIV+ Patients with CD4<350 despite ART


HIV-Mediated Immune Activation and Aging

- HIV-1 Infection
- Immunodeficiency
- Viral Reactivation (e.g., CMV)
- Innate Immune Activation (MØ/DC)
  - Microbial Translocation
  - Increased Cell Turnover and Lymphoid Fibrosis
  - Immune Exhaustion
  - Malignancy, Infections
  - Increased TF Expression and clotting
  - CAD/Stroke, Thrombosis
  - Cytokine Secretion (e.g., IL-6, TNFL)
  - “Inflam-Aging” (e.g., atherosclerosis, osteoporosis)

HIV-Mediated Immune Activation and Aging

HIV-1 Infection

*Immunodeficiency*
- Microbial Translocation
- Viral Reactivation (eg, CMV)
- TLR 7,8 Nef, gp120

*Innate Immune Activation (MØ/DC)*
- Increased Cell Turnover and Lymphoid Fibrosis
- Immune Exhaustion
- Malignancy, Infections
- Increased TF Expression and clotting
- CAD/Stroke, Thrombosis
- Cytokine Secretion (eg, IL-6, TNFL)
- “Inflam-Aging” (eg, atherosclerosis, osteoporosis)


Does Initiating ART Early Prevent Persistent Inflammation during ART?
Starting ART Early May Normalize Monocyte Activation during ART

Burdo, *JID*, 2011

See also: Vinikoor, CROI 2012, Abstract #554; Jain et al, CROI 2011, Abstract #517
What about commonly used medications with anti-inflammatory properties?

Statins May Decrease Monocyte Activation in Treated HIV Infection

SATURN-HIV Trial (n=147)
Statin Use Associated with Decreased Risk of Non-AIDS Malignancies during ART

<table>
<thead>
<tr>
<th>Event Category</th>
<th>No. of Events</th>
<th>Event Rate for Statin Users (per 100 PY)</th>
<th>Event Rate for Nonstatin Users (per 100 PY)</th>
<th>Adjusted$^a$ and Weighted$^b$ HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV events</td>
<td>62</td>
<td>0.5</td>
<td>0.4</td>
<td>0.89 (0.42–2.44)</td>
</tr>
<tr>
<td>Non-CV events</td>
<td>580</td>
<td>4.2</td>
<td>3.8</td>
<td>0.85 (0.56–1.31)</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>144</td>
<td>0.7</td>
<td>0.9</td>
<td>1.25 (0.62–2.51)</td>
</tr>
<tr>
<td>Incident diabetes</td>
<td>158</td>
<td>1.3</td>
<td>1.0</td>
<td>0.87 (0.35–2.13)</td>
</tr>
<tr>
<td>Renal events</td>
<td>135</td>
<td>1.4</td>
<td>0.7</td>
<td>0.85 (0.41–1.73)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>89</td>
<td>0.5</td>
<td>0.5</td>
<td>0.43 (0.18–0.94)</td>
</tr>
<tr>
<td>Mortality</td>
<td>143</td>
<td>0.5</td>
<td>0.9</td>
<td>0.82 (0.32–2.10)</td>
</tr>
<tr>
<td>AIDS-defining events</td>
<td>172</td>
<td>0.5</td>
<td>1.1</td>
<td>1.24 (0.44–3.52)</td>
</tr>
</tbody>
</table>

Overtom, CID, 2013 (see also: Chao, AIDS, 2011)

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.
- Needs to be confirmed in an RCT.

Diet and Exercise

• High fat or carbohydrate meal ↑ inflammation (Deopurkar, Diabetes Care, 2010).


• RCTs of exercise in elderly have been shown to:
  – Decrease inflammation (Nicklas, J Am Ger Soc, 2008)
  – Increase functional status (McMurdo, Geriatrics, 1992)
  – Decreases insulin resistance (Diabetes Care, 2002)
  – Improve cognitive function (Muscari, Int J Ger Psych, 2010)

• Studies in HIV? (Oursler, 3rd Int Workshop on HIV/Aging, 2012)

Summary

• Despite optimal ART, HIV is associated with shorter life expectancy and an increase in many – but not all- age-associated morbidities.

• Immune activation / inflammation persist despite ART and may predict many of these morbidities.
  – There may be exceptions (KS/Lymphoma “IRIS”)

• Earlier initiation of ART may decrease residual immune activation.

• Diet / exercise may improve these key pathways of interest.

• Targeted interventions directed at the underlying causes of inflammation may hold promise.
Acknowledgements

SCOPE/OPTIONS/UCSF
Steve Deeks
Jeff Martin
Hiroyu Hatano
Vivek Jain
Rebecca Hoh
Rick Hecht

CWRU
Wei Jiang
Michael Lederman
Nick Funderburg
Brial Claggett
Grace McComsey

U Minnesota
Jason Baker

NIAID/VRC
Jason Brenchley
Danny Douek

Core Immunology Lab/DEM
Elizabeth Sinclair
Lorrie Epling
Mike McCune

SFGH Cardiology
Priscilla Hsue
Amanda Schnell

UARTO
David Bangsberg
Nneka Emenyonu
Huyen Cao

R01AI100765, 1R21AI087035,
1R21AI07877, DDCF CSDA, CHRP
IDEA Award; Pfizer, Inc.; Roche, Inc.