Inflammation and Its Role in HIV Pathogenesis and Aging

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Learning Objectives

Upon completion of this webinar, learners will be able to:

• Describe the changing face of the HIV epidemic
• Describe the complexity of older adults with HIV
• List factors that contribute to unsuccessful aging
• List the main factors associated with inflammation
• Describe how to best care for aging PWH
Describe the Changing Face of the HIV Epidemic

"We just felt it was time that people saw the truth about AIDS" Kay Kirby

Photography by Therese Frare, 1990, no copyright infringement is intended

Background

The development of antiretroviral therapy (ART) for the treatment of HIV is one of the greatest achievements of modern medicine.
45% of PLWH in USA >50 years of age

https://www.cdc.gov/hiv/group/age/olderamericans/index.html
Projected Age Distribution of PWH

Describe the Complexity of Older Adults with HIV

Multi-Morbidity is Increasing

70-80% people aging with HIV (50 years and older) have at least one co-morbidity other than HIV


Accelerated Aging in PWH

Pathai et al, J of Gerontology, 2013

Includes Geriatric Syndromes

Greene JAIDS 2015
Contributes to Disability

- HAILO (observational study of ACTG A5322) evaluated 1015 participants with median age 51 years
- At least 1 IADL impairment was reported in 18%

| Table 2: Type of Impairment Present Among Participants with at Least One IADL Impairment |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Type of Impairment                             | Total (n=1015)  | % Impairment    | IADL Impairment | TIA Impairment   |
| Caring for others                              |                 |                 |                 |                 |
| Transportation                                |                 |                 |                 |                 |
| Shopping                                      |                 |                 |                 |                 |
| Laundry                                       |                 |                 |                 |                 |
| Personal care management                       |                 |                 |                 |                 |
| Self-care                                     |                 |                 |                 |                 |
| IADL impairment of daily activities            |                 |                 |                 |                 |
| Total                                          |                 |                 |                 |                 |

And Medical Cost

- Study examining Medicare expenditures for 9767 PWH aged 40+ in California in 2010
- 89.3% male, 56.9% white, 52.4% were >50 years
- Average cost $47,036 for Californian with HIV and medications account of 2/3 of that cost

List Factors that Contribute to Unsuccessful Aging
Possible Reasons for “Unsuccessful Aging” among PWH

Adapted from Deeks and Phillips, BMJ, 2009

SMART Study: Interrupting ART Increases the Risk of Heart Disease

El-Sadr, NEJM, 2006

T Cell Activation Declines with ART

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

Inflammation Can Cause Lymphoid Tissue Fibrosis

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

HIV+

High T Cell Activation Associated with Blunted CD4 Recovery

Spearman's rho: -0.40
P<0.001

Hunt et al, JID, 2003 (see also Goicoechea, JID, 2006; Gandhi, JAIDS, 2006)
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>IL-6</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 Predicts Disease in Treated HIV

- Mortality (Kuller, PLoS Med, 2008; Tien, JAIDS, 2010; Justice, CID 2012)
- Cardiovascular Disease (Duprez, Atherosclerosis, 2009)
- Cancer (Breen, Cancer Epidemiol, 2010; Borges, AIDS, 2013)
- Venous Thromboembolism (Barnes, AIDS, 2011)
- Type II Diabetes (Barnes, Diabetes Care, 2011)
- COPD (Duffy, Chest, 2011)
- Bacterial Pneumonia (Bjerk, PLoS One, 2014)
- Cognitive Dysfunction (Burdo, AIDS, 2013; Letendre CROI 2012)
- Depression (Martinez, JAIDS, 2014)
- Frailty (Erlandson, JID, 2013)

List the Main Factors Associated with Inflammation

Slide courtesy from Peter Hunt
Model of Inflammation

Low-level Viremia <20 cp/ml is Common During ART

HIV RNA Is Detectable in GUT During ART

Yukl et al. JID 2010

Yukl et al. JID 2010
HIV RNA Is Detectable in GUT During ART

80% Patients had detectable viremia

Median 3.1 copies/ml

Low-level Viremia <20 cp/ml is Common During ART
Microbial Translocation

Healthy GI tract

Damaged GI tract during HIV infection

Microbial Translocation Decreases with ART but Persists for Years

Jong et al, JID, 2009 (also Marchetti, AIDS, 2008)

Microbial Translocation is Associated with Inflammation

Perez Santiago 2013, AIDS
CMV Associated with CD8 Expansion and Inflammation in HIV Infection

Freeman, JD, 2014 (see also: Sacre, AIDS, 2011; Mudd, JD, 2014; Muzalemba, AIDS 2011 and many Gianella papers)

CD8+ T Cell Counts

- CD8+ T Cell Counts
  - CMV- (HIV+): 2.8 ± 0.9
  - CMV+ (HIV+): 3.2 ± 1.5

sTNF-R11

- sTNF-R11 (ng/mL)
  - CMV- (HIV+): 1000 ± 200
  - CMV+ (HIV+): 1500 ± 300

P = 0.002

Valganciclovir Reduces Inflammation

What can we do to reduce Inflammation?
Early ART can Greatly Reduce T Cell Activation

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

Jain et al, JID, 2013

Statins Decrease Monocyte Activation in Treated HIV Infection
(SATURN-HIV Trial)

Funderburg, 2014 CID

Diet and Exercise

- High fat or carbohydrate meal ↑ inflammation (Deopurkar, Diabetes Care, 2010).
- RCTs of exercise in elderly have been shown to:
  - Decrease inflammation (Niklas, J Am Ger Soc, 2008)
  - Increase functional status (Murfre, Geriatrics, 1992)
  - Decrease insulin resistance (Diabetes Care, 2002)
  - Improve cognitive function (Mascari, Int J Ger Psych, 2010)

- Studies in HIV?

New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Summary

• Despite optimal ART, HIV is associated with shorter life expectancy and an increase in several age-associated morbidities.
• Immune activation / inflammation persist despite ART and may predict these morbidities.
• Earlier initiation of ART decreases persistent immune activation.
• Statins, diet, and exercise may hold promise and need to be studied.
• Targeted interventions directed at the underlying causes of inflammation may hold promise
  – HIV reservoirs, co-infections/CMV, microbial translocation.

Recommendations for Patients

• Follow-up with your medical provider regularly.
  – Follow guidelines for checking and controlling vascular risk factors (cholesterol, blood pressure, diabetes).  
• Stop smoking.
• Exercise regularly, eat healthful diet, maintain healthy weight.
• Get regular cancer screening.
• Assess Polypharmacy, Safety at home, Quality of life
• Avoid or treat co-infections.
  – Viral hepatitis, syphilis, tuberculosis
  – Vaccinations
  – No current recommendations for CMV

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Question-and-Answer Period