• No Conflict of Interest
Aging and HIV Co-Morbidities:
A Challenge for Engagement in Care

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Objectives

• Understand the aging of the Immune System in the HIV population and how it relates to development of Co-morbidities
• Discuss the Epidemiology of HIV in the aging population
• Discuss the Challenges in:
  • HIV diagnosis
  • HIV care
  • Management of Co-morbidities
“Gradual change in an organism that leads to increased risk of weakness, disease, and death. It takes place in a cell, an organ, or the total organism over the entire adult life span of any living thing... Changes in organs include the replacement of functional cardiovascular cells with fibrous tissue. Overall effects of aging include reduced immunity, loss of muscle strength, decline in memory and other aspects of cognition, and loss of colour in the hair and elasticity in the skin. In women, the process accelerates after menopause.”
How old is “aging” in HIV?
Aging and Comorbidities

Common disorders in older adults

- Cardiovascular disease
- Hypertension
- Metabolic disorders, obesity
- Neurocognitive decline
- Hepatic and/or renal impairment
- Bone fractures/Osteopenia/osteoporosis
- Malignancies
The process of aging in HIV

Aging related Co-morbidities
HTN, DM, CVD, cancers, cognitive decline

Mechanisms
Persistent immune activation
Immune senescence
Microbial translocation
Chronic inflammation

Telomere length
Telomerase activity
Immune Activation in HIV-Infected Aging Women on Antiretrovirals—Implications for Age-Associated Comorbidities: A Cross-Sectional Pilot Study

Maria L. Alcaide¹, Anita Parmigiani², Suresh Pallikkuth², Margaret Roach², Riccardo Freguia³, Marina Della Negra⁴, Hector Bolivar⁵, Margaret A. Fischl⁵, Savita Pahwa⁶

- State of immune activation, immune senescence, microbial translocation, inflammation
- Biomarkers of cardiovascular disease in HIV infected post-menopausal women on ART

May 2013 | Volume 8 | Issue 5 | e63804
HIV infected post-menopausal women

<table>
<thead>
<tr>
<th></th>
<th>HIV– n=15</th>
<th>HIV+ n=27</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 (53–63)</td>
<td>56.5 (48–66)</td>
<td>0.11</td>
</tr>
<tr>
<td>Time to menopause (years)</td>
<td>15 (3–29)</td>
<td>12 (2–22)</td>
<td>0.09</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>n.a.</td>
<td>584 (144–1,144)</td>
<td></td>
</tr>
<tr>
<td>CD4 nadir (cells/mm³)</td>
<td>n.a.</td>
<td>147 (2–648)</td>
<td></td>
</tr>
<tr>
<td>HIV RNA (copies/ml)</td>
<td>n.a.</td>
<td>undetectable–80</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>13%</td>
<td>8%</td>
<td>0.61</td>
</tr>
<tr>
<td>Current illicit drug use</td>
<td>6%</td>
<td>4%</td>
<td>1.00</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.4 (21.5–38.1)</td>
<td>27.6 (20.1–38.3)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>HIV−</td>
<td>HIV+</td>
<td>P value</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>T cell activation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD38+ HLA-DR+ CD4 (%)</td>
<td>1.69±0.95</td>
<td>3.21±1.87</td>
<td>0.0313</td>
</tr>
<tr>
<td>CD38+ HLA-DR+ CD8 (%)</td>
<td>2.08±1.39</td>
<td>10.17±13.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ki-67+ CD4 (%)</td>
<td>0.39±0.22</td>
<td>0.63±0.29</td>
<td>0.0260</td>
</tr>
<tr>
<td>Ki-67+ CD8 (%)</td>
<td>0.32±0.09</td>
<td>0.34±0.18</td>
<td>0.6913</td>
</tr>
<tr>
<td><strong>T cell exhaustion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-1+ CD4 (%)</td>
<td>13.36±6.81</td>
<td>21.99±11.80</td>
<td>0.0321</td>
</tr>
<tr>
<td>PD-1+ CD8 (%)</td>
<td>16.72±9.86</td>
<td>20.50±7.34</td>
<td>0.2177</td>
</tr>
<tr>
<td><strong>T cell senescence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD28− CD57+ CD4 (%)</td>
<td>2.22±2.61</td>
<td>9.43±12.24</td>
<td>0.0390</td>
</tr>
<tr>
<td>CD28− CD57+ CD8 (%)</td>
<td>16.07±10.40</td>
<td>24.59±13.88</td>
<td>0.0481</td>
</tr>
</tbody>
</table>

Alcaide et al. PLOS ONE 2013
### Soluble markers of IA and MT

<table>
<thead>
<tr>
<th></th>
<th>HIV−</th>
<th>HIV+</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monocyte/macrophage activation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCD14 (ng/ml)</td>
<td>1,537±253</td>
<td>2,113±426</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sCD163 (ng/ml)</td>
<td>323±155</td>
<td>533±260</td>
<td>0.0043</td>
</tr>
<tr>
<td><strong>T cell activation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCD25 (ng/ml)</td>
<td>387.3±151.2</td>
<td>590.1±425.6</td>
<td>0.0423</td>
</tr>
<tr>
<td><strong>Microbial translocation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPS (pg/ml)</td>
<td>90.2±21.4</td>
<td>107.4±20.7</td>
<td>0.0221</td>
</tr>
</tbody>
</table>

Alcaide et al. PLOS ONE 2013
## Inflammatory Cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>HIV− (pg/ml)</th>
<th>HIV+ (pg/ml)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>0.89±0.17</td>
<td>1.86±0.44</td>
<td>0.0728</td>
</tr>
<tr>
<td>IL-8</td>
<td>4.38±0.52</td>
<td>6.57±1.26</td>
<td>0.1012</td>
</tr>
<tr>
<td>IL-10</td>
<td>3.31±1.58</td>
<td>19.74±4.85</td>
<td><strong>0.0124</strong></td>
</tr>
<tr>
<td>TNFα</td>
<td>7.02±1.43</td>
<td>9.58±1.23</td>
<td>0.1359</td>
</tr>
</tbody>
</table>

Alcaide et al. PLOS ONE 2013
• Tcell immune activation
• Tcell exhaustion
• Tcell senescence
• Microbial Translocation
• Soluble markers of IA
• Inflammatory Cytokines
IA and senescence are associated with low CD4

**% CD38+HLA-DR+ CD8 Tcells/CD4**

\[ R = -0.4593 \]
\[ p = 0.0315 \]

**% PD-1+ CD8 Tcells/CD4**

\[ R = -0.5085 \]
\[ p = 0.0256 \]

**% CD28-CD57+ CD4 Tcells/CD4**

\[ R = -0.5017 \]
\[ p = 0.0205 \]
Biomarkers of CVD

<table>
<thead>
<tr>
<th></th>
<th>HIV–</th>
<th>HIV+</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sVCAM-1 (ng/ml)</td>
<td>287.0±71.3</td>
<td>397.8±136.0</td>
<td>0.0073</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>100.4±28.1</td>
<td>171.5±82.9</td>
<td>0.0037</td>
</tr>
</tbody>
</table>
Biomarkers of CVD are associated with the state of immune activation and with low CD4 counts.
Despite appropriate immunological and virological response to ART:
- The immune system of HIV infected aging women is in a higher state immune activation
- The state of IA predispose them to develop CVD

IA and risk for CVD are associated with lower CD4 counts
Epidemiology of HIV in the aging population
Over one third of individuals with HIV are older than 50 years

By 2015, approximately 50% of people living with HIV will be older than 50 years of age.

Concurrent HIV/AIDS among persons diagnosed with HIV in 2006, by age group, United States.

New HIV diagnosis 2011

Challenges in HIV diagnosis, HIV care and management of Co-morbidities in the aging population
63 yo male
DM
HTN
Married for 30 years

Diagnosed with HIV infection during labs done as part of a DM research study

CD4=537, VL=90,000
Challenges in HIV diagnosis

Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

Routine voluntary testing for patients ages 13 to 64 years in healthcare settings
Challenges in HIV diagnosis

The New Invincibles: HIV Screening among Older Adults in the U.S.

Oluwatoyosi A. Adekeye¹*, Harry J. Heiman², Onyekachi S. Onyeabor², Hyacinth I. Hyacinth³

- 2009 National Health Interview Survey (NHIS)
- 12,366 adults over 50 years
- 75% had never been tested for HIV
- 84% thought they had no chances of getting HIV
- The most common reason for testing was patient request
- No difference in testing rates by race
Late or Missed Diagnosis in Older Adults

- Poor awareness of HIV risk factors (including safe sex practices)
- Lack of HIV prevention education targeting older adults
- Health care provider belief that older adults are not sexually active
- Failure of some health care providers to consider HIV infection in this patient population

CURRENT SEXUAL ACTIVITY AND RISKY SEXUAL BEHAVIOR IN OLDER MEN WITH OR AT RISK FOR HIV INFECTION


Nina A. Cooperman, Julia H. Arnsten, and Robert S. Klein

- Sexual risk behaviors among 624 men over 50 years
- In the prior 6 months:
  - 75% sexually active (48% weekly or more)
  - 50% drug use
  - 18% use condoms
  - 24% more than one sex partner
60 yo female
HIV – 23 years
Nadir CD4=23
CD4=130, RNA<20
Cervical cancer
HTN

Unable to achieve CD>200 despite adherence to medication
Baseline viral load and CD4 counts

Baseline HIV RNA

Baseline CD4 Count

Lower CD4 counts and higher VL at baseline

Almost half of the individuals over 50 years develop AIDS in less than 12 months.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Diagnosis of HIV Infection (%)</th>
<th>&lt;12 months (overall: 32.4%)</th>
<th>≥12 months (overall: 67.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>85.9%</td>
<td>14.1%</td>
<td>85.9%</td>
</tr>
<tr>
<td>20 to 34</td>
<td>76.6%</td>
<td>23.4%</td>
<td>76.6%</td>
</tr>
<tr>
<td>35 to 49</td>
<td>61.0%</td>
<td>39.0%</td>
<td>61.0%</td>
</tr>
<tr>
<td>≥50</td>
<td>53.8%</td>
<td>46.2%</td>
<td>53.8%</td>
</tr>
</tbody>
</table>

Survival after AIDS diagnosis is less if >50 years.

ART Response by Age: % of people who experience an event 12 months after ART (p<0.0001)

<table>
<thead>
<tr>
<th>Age (ys)</th>
<th>Virological response</th>
<th>Discontinuation ART</th>
<th>CD4&gt;200</th>
<th>AIDS event/death</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-29</td>
<td>50%</td>
<td>14.8%</td>
<td>86.7%</td>
<td>5.2%</td>
</tr>
<tr>
<td>30-39</td>
<td>51.6%</td>
<td>11.4%</td>
<td>80.6%</td>
<td>7.6%</td>
</tr>
<tr>
<td>40-49</td>
<td>57.5%</td>
<td>9.2%</td>
<td>76.3%</td>
<td>9.4%</td>
</tr>
<tr>
<td>50-54</td>
<td>61.4%</td>
<td>6.9%</td>
<td>75.2%</td>
<td>11.1%</td>
</tr>
<tr>
<td>55-59</td>
<td>60.3%</td>
<td>7.9%</td>
<td>73.9%</td>
<td>10.9%</td>
</tr>
<tr>
<td>&gt;60</td>
<td>61.8%</td>
<td>7.3%</td>
<td>74.7%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Total</td>
<td>53.7%</td>
<td>11.0%</td>
<td>80.1%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

CHALLENGES IN MANAGEMENT OF CO-MORBIDITIES

73 yo male
Smoker
HIV – 25 years
CD4=483, RNA<20
Nadir CD4= 190
HTN
DM
Erectile dysfunction

AMI and 3 vessel disease
VACS: Comorbidities in HIV infection


Years
- <40 (n=8522)
- 40 to 49 (n=14,561)
- 50-59 (n=7225)
- ≥60 (n=3122)

Patients (%)
### Risk of All-cause Mortality Associated with Non-fatal AIDS and Serious Non-AIDS Events among Adults Infected with HIV

Jacqueline NEUHAUS\(^1\), Brian ANGUS\(^2\), Justyna D. KOWALSKA\(^3\), Alberto LA ROSA\(^4\), Jim SAMPSON\(^5\), Deborah WENTWORTH\(^1\), and Amanda MOCROFT\(^6\) for the INSIGHT SMART and ESPRIT Study Groups

<table>
<thead>
<tr>
<th>n= 9,583</th>
<th>AIDS events</th>
<th>Non AIDS events</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence</td>
<td>16%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Cumulative mortality (6mo)</td>
<td>4.7%</td>
<td>13.4%</td>
<td>11.4</td>
</tr>
</tbody>
</table>

![Graph showing cumulative percent with death](graph.png)

Logrank = 11.86  \( p = 0.0006 \)

Non-AIDS: 422, 357, 304, 269, 233, 207, 180, 158, 140, 123, 107, 96, 83, 71, 62, 49

AIDS: 272, 253, 221, 201, 177, 156, 129, 111, 98, 83, 71, 57, 47, 39, 35, 28
### HIV Associated Non AIDS comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Cognitive decline</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Frailty</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes Mellitus type 2</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Liver Failure</td>
</tr>
<tr>
<td>Kidney Failure</td>
</tr>
</tbody>
</table>
Increased Acute Myocardial Infarction Rates and Cardiovascular Risk Factors among Patients with Human Immunodeficiency Virus


Cardiovascular Disease is more common in HIV infected patients when compared with uninfected controls and the risk increases with age.
HIV Infection and the Risk of Acute Myocardial Infarction

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Lewis H. Kuller, MD, DrPH; Melissa Skanderson, MSW;

VACS Cohort
AMI events per 1000 person-years (p<0.05)

<table>
<thead>
<tr>
<th>Age Range</th>
<th>HIV Infected</th>
<th>HIV Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 49 yrs</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td>50 - 59 yrs</td>
<td>3.9</td>
<td>2.2</td>
</tr>
<tr>
<td>60 - 69</td>
<td>5</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Adjusted for co-morbidities, substance abuse, Framingham risks

Cognitive dysfunction in HIV patients despite long-standing suppression of viremia

HAND: 69% overall in the aviremic population

ANI: Asymptomatic Neurocognitive Impairment
MND: mild neurocognitive disorder
HIV-D: HIV dementia

Nadir CD4 was associated with HAND

ANI: 27% of 84% of HAND
MND: 4% of 84% of HAND
HIV-D: 0% of 84% of HAND
Malignancies in ART treated patients

AIDS-related malignancies
- Kaposi sarcoma
- CNS lymphoma

Non-AIDS defining malignancies
- Liver
- Larynx
- Anal
- Lung

Nadir Low CD4 associated with Non-AIDS malignancies

BMD is Lower in HIV-Infected Women ≥ 40 Years of Age

Drug toxicity

Immune Activation due to HIV

Premature aging

Comorbidities HANA

Normal aging

Lifestyle

Deeks S G, Phillips A N BMJ 2009;338:bmj.a3172
Successful aging with HIV infection
Barriers and components of successful aging with HIV

- Prevention of disease & disability
- Active engagement in life
- Maximizing cognitive & physical functioning
- Spirituality within a developmental context

- Financial concerns
- Lipodystrophy/Wasting/Sarcopenia
- Fatigue
- Decreased social support
- Age-related stigma
- HIV-related stigma
- Multimorbidity
- Unhealthy lifestyle choices
- Medication side effects
- Cognitive deficits
- Suicidal ideation
- Mental illness

David E Vance
Clinical Interventions in Aging 2011:6 101-109
Summary
What we know

- HIV population is aging

- Aging of the immune system is enhanced by HIV infection despite ART

- Aging individuals engage in HIV risk behaviors but providers fail to identify those and adhere to screening guidelines

- Comorbidities attributed to increasing age overlap with morbidity from HIV disease and are predicted by lower CD4 counts
New directions: Pathogenesis

Understand the mechanisms that drive IA and aging in HIV infection (HIV reservoirs, viral co-infections, telomere length and telomerase activity,...)
New directions - Diagnosis

- Expand testing to all at risk
- PrEP in the aging population

Age is not a condom.

HIV: Know the RISKS. Get the FACTS.

HIV HAS NO AGE LIMIT.

HIV is Ageless.

Get Tested.

8th International Conference on HIV Treatment and Prevention Adherence
New directions - HIV care

- Early initiation of ART
- Strategies to improve immune recovery (intensification treatment, other immune therapies)
New directions - Comorbidities

- Guidelines for diagnosis and management of comorbidities
- Strategies to decrease inflammation and IA
- Anti-aging interventions
- Psychosocial management (HAND)

[Image of Spectrum of HIV Complications]

http://www.aoa.gov/AoARoot/AoA_Programs/HPW/HIV_AIDS/toolkit.aspx
New directions – Successful Aging

Bio-behavioral interventions to promote successful aging

HEALTHY AGING
HELPING PEOPLE TO LIVE LONG AND PRODUCTIVE LIVES AND ENJOY A GOOD QUALITY OF LIFE
OUR PATIENTS

Deborah Jones
Stephen Weiss
Michael Kolber
Allan Rodriguez
Mario Stevenson
Margaret Fischl
Suresh Pallikkuth
Anita Parmigiani
Savita Pahwa