The Long and Winding Road of HIV Complications: Aging with HIV

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Disclosure of Financial Relationships

This speaker has the following financial relationships with commercial entities to disclose:

- Consultant: Gilead, Tibotec, Viiv – Terminated
- Speaker’s Bureau: Abbott, Boehringer, Gilead, Tibotec – Terminated

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HIV and Aging

Objectives

• Discuss the evolving complications being seen in the aging HIV population
• Improve patient education in reduction of risk factors in disease seen in the aging population
• Implement appropriate recommendations in screening and monitoring in the aging HIV population

As estimated by the CDC: The percentage of HIV infected individuals older than 50 years, in the year 2015 will be:

A. 20%
B. 25%
C. 30%
D. 40%
E. > 50%
Prevalence of HIV Infection in US

2001

- 19% > 50 year-old
- 81% < 50 year-old

2007

- 27% > 50 year-old
- 73% < 50 year-old

From: www.cdc.gov/hiv/topics/over50

Estimated Percentage of New Cases of HIV/AIDS by Age, 2005

From: www.cdc.gov/hiv/topics/over50
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

Biology of Aging in Humans

Haematopoietic stem cells experience functional decline with aging

Sahin and DePinho, *Nature* 2010

Aging of the Immune System

“Immunosenescence”

T cell characteristics that predict morbidity/mortality in the very old:

- Reduced regenerative capacity (stem cells, thymus)
- Low naïve/memory T cell ratios
- Low CD4/CD8 ratio
- Increased T cell activation
- Increased inflammatory markers (IL-6, CRP)
- Clonal expression of CD28-CD57+ T cells
- Expanded CMV specific T cell responses
- Reduced T cell proliferation

Weng N. *Immunity*, 2006;24:495-499
Cao W. *JAIDS* 2009; 50:137-147
Linton PJ. *Nat Immunol.* 2004; 2:133-139
Barrier to HIV Diagnosis in Older Adult

- Physicians are less likely to discuss HIV related risk factors with older adults
- HIV-associated symptoms and other illnesses
- Late presentation for diagnosis and care
- CDC recommendations

Patel D. Curr Inf Dis Rep 2011
Lindau ST. NEJM 2007
Gebo KA. Drugs Aging 2006
MMWR Recomm Rep 2006

Risk for Older HIV-Uninfected Adults

- National Survey of Sexual Health and Behavior (2008)
  Among all persons aged 50 years or older, condoms were not used during most recent intercourse with:
  - 91.5% of casual partners
  - 76.0% of friends
  - 69.6% of new acquaintances
  - 33.3% of transactional sexual partners

Issues Specific to Older Persons With HIV Disease

- Unprotected sex
  - No concern about pregnancy
  - “I’m too old to catch HIV”
- Delay in testing
- Limited incomes
- Immune restoration
- Comorbid illnesses
- Polypharmacy
- Insufficient data on drug interactions in older population


NIH Statement on National HIV/AIDS and Aging Awareness Day - September 18, 2010

“Older HIV-infected adults face unique health challenges stemming from age-related changes to the body accelerated by HIV infection, the side effects of long-term treatment for HIV, the infection itself and often, treatments for age-associated illnesses”

Barriers to HIV Management in Older Adults

- Age as independent predictor on clinical progression on HAART
- Significantly slower CD4 cell reconstitution
- Older patients are more susceptible to the adverse events of therapy
- Older patients have greater number of co-morbid conditions
- Viral suppression and adherence

Hinkin, CH: *AIDS* 2001; 15:1576-9
Grabar, S: *JAC*; Jan 2006; 57:4-7

Time to AIDS Diagnosis After a Diagnosis of HIV Infection in 2008 (40 States)

Survival After AIDS Diagnosis (1998-2005)

Factors of and Obstacles to Successful Aging With HIV

Successful Aging

• Length of life
  – Number of years one remains alive
  – Decreased compared to general population
  – Lower in men, IVDU, lower initial CD4 count

• Biological Health
  – How well is the interaction and function of the different systems of the body
  – Compromise of the immune system
  – Bacterial translocation and alcohol


Successful Aging

• Cognitive efficiency
  – Optimal neurological integrity
  – Cognitive decline versus same-aged peers
  – Substance use

• Mental Health
  – Emotional equilibrium
  – HIV and poor mental health
  – HIV and stigma
  – Coping with HIV while aging

Aging in HIV Infection

- Chronic inflammatory stimulation
- Bone fractures/Osteoporosis/Osteopenia
- Increase in cardiovascular disease
- Increased rates of non-AIDS associated malignancies
- Faster neurocognitive decline
- Functional decline

Polypharmacy in Older HIV-Infected Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Age Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ART medication, n (%)</td>
<td></td>
<td>&lt; 50</td>
<td>50-64</td>
</tr>
<tr>
<td>Antihypertensives (not ACE inhibitors)</td>
<td>785 (9.7)</td>
<td>300 (5.4)</td>
<td>341 (15.9)</td>
</tr>
<tr>
<td>Antihypertensives (ACE inhibitors)</td>
<td>874 (10.7)</td>
<td>311 (5.6)</td>
<td>415 (19.3)</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>1013 (12.4)</td>
<td>324 (5.8)</td>
<td>511 (23.8)</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>170 (2.1)</td>
<td>49 (0.9)</td>
<td>82 (3.8)</td>
</tr>
<tr>
<td>Insulin</td>
<td>118 (1.5)</td>
<td>39 (0.7)</td>
<td>52 (2.4)</td>
</tr>
<tr>
<td>Antiplatelets drugs</td>
<td>473 (5.8)</td>
<td>110 (2.0)</td>
<td>233 (10.8)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>792 (9.7)</td>
<td>514 (9.3)</td>
<td>240 (11.2)</td>
</tr>
</tbody>
</table>

Hasse B, et al. 18th CROI; 2011; Boston, MA. Abstract 792
Inflammation and Aging: Therapeutic Strategies

• Reduce inflammation
  – Residual HIV replication (ART intensification?)
  – Prednisone, HU, cyclosporine, mycophenolic acid
  – Chronic/persistent co-infections (HCV, CMV)
  – Microbial translocation (sevelamer, colostrum)
  – CCR5 inhibitors
  – Chloroquine (reduced PDC mediated IFNα)
  – NSAIDs (COX-2 inhibitors)

• Enhance T-cell renewal
  – GH, IL-7, stem cell transplant, perfenidone, leuprolide (Lupron®)

• Anti-aging interventions
  – Caloric restrictions
  – Sirtuin activators, Telomerase activators
  – Vitamin D, omega-3 fatty acids, sirolimus (Rapamycin®)
Treating HIV Does Not Fully restore Life expectancy

Losina et al. CID 2009

T cell activation in human immunodeficiency virus (HIV)-infected and HIV-uninfected adults

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Comorbidities Associated With Aging and HIV Infection


Diabetes Mellitus in HIV and Aging

- Incidence is higher in HIV-infected patients
- Most important prevention is to avoid excess weight gain.
- It could be related to the use of certain antiretrovirals
- Screening for glucose intolerance should be performed regularly

Summary Report from the HIV and Aging Consensus Project
JAGS 60:974-979, May2012
Cardiovascular Disease in HIV and Aging

- HIV-infected patients have greater 10-year risk of cardiovascular disease
- Higher rates of atherosclerosis independent of viral load, ARV or extent of immunodeficiency (SMART)
- Smoking
- Dyslipidemia and metabolic syndrome
- Overweight


Pathogenesis of CV Disease in HIV

van Wijk at al. *Int J Vasc Med*. 2012; ID201027
Risk Factors Contributing to Development of Kidney Disease

**Modifiable risk factors**
- Diabetes mellitus
- High blood pressure
- Kidney stones
- Inflammation (eg GMN)
- Allergic reaction to med (eg, antibiotics)
- Medications (eg, NSAIDs)
- Drug abuse
- Use of creatine, hGH testosterone

**Non-modifiable risk factors**
- Age
- Family history of kidney disease
- Trauma or accident
- Presence of other diseases:
  - HIV/AIDS, hepatitis C, lupus, sickle cell anemia, cancer, congestive heart failure

http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p7_risk_g13.htm

HIV and Age as Renal Risk Factor

- Among 2159 HIV-infected patients enrolled in ACTG studies
  - 30% of patients had low baseline glomerular filtration rate (GFR)
  - Median age was significantly higher in patients with low versus normal GFR
    - 42 versus 36 years, respectively; P<.0011

Kalayjian R. 14th CROI. 2007. Abstract 827
HIV and Age as Renal Risk Factor

• In the EuroSIDA cohort, the rate of chronic renal failure at baseline ranged from 3.5% to 4.7% depending on the method of GFR calculation
  • By multivariate analysis, age was a strong predictor of chronic renal failure at baseline
  • OR 5.47, 95% CI 4.4-6.72; \( P < .00012 \)

Mocroft A. *AIDS*. 2007;21(9):1119-1127

Bone Health in HIV and Aging

• Among HIV-infected adults up to 60% have osteopenia, and up to 15% osteoporosis
• Higher rates of fragility fractures
• Rates of fracture 60% greater on those with nadir CD4 < 200
• BMD assessment

Triant VA. *J Clin Endocrinol Metab* 2008;93(9):3499-3504
Sharma A. *AIDS*. 2010;24(15):2337-2345
BMD is Lower in HIV-Infected Older Men


Osteopenia incidence per 100 person-years at risk was 2.6 for HIV-uninfected Men and 7.2 for HIV-infected men


F/V AETC 21st Annual HIV CONFERENCE • October 26-27th, 2012 • www.FVAETC.org/Conference
Frailty in HIV and Aging

- Weakness
- Low physical activity
- Slow motor performance
- Weight loss
- Weak grip strength
- Factors associated with frailty: higher depression score, unemployment, greater comorbid conditions, past OIs


Psychiatric and Neurocognitive Disorders

- Alcohol and drug use
- Thought and mood disorders
- Depression and suicide
- Decrease memory

- UPDRS motor scores were 40.7% in HIV infected vs 15.7% in HIV-
  - Slowness of hand movement, body bradykinesia, tremor

Neurocognitive Complications in HIV

- 42% Asymptomatic Neurocognitive Impairment (ANI)
- 53% Mild Neurocognitive Disorder (MND)
- 5% HIV-associated Dementia (HAD)


Cancer in HIV and Aging

- Higher incidence among HIV-infected
  - Anal
  - Vaginal
  - Hodgkin’s lymphoma
  - Liver
  - Lung
  - Melanoma
  - Oropharyngeal
  - Leukemia
  - Colorectal
  - Renal

### Higher Cancer Risk in HIV infection

- Kaposi’s sarcoma: 199-fold
- Non-Hodgkin lymphoma: 15-fold
- Anal cancer: 55-fold
- Hodgkin lymphoma: 19-fold
- Melanoma: 1.8-fold
- Liver cancer: 1.8-fold

Silverberg MJ. *CEBP*. Dec2011 20:2551-2559

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### Cancer Screening

- Cervical cancer
- Colon cancer
- Anal cancer
- Liver cancer
- Skin cancer
- Cancer screening should be in accordance with current guidelines for the general population
Cancer Screening

- Cervical cancer
  - PAP smear upon starting care and again in six months
  - If abnormal: Colposcopy and biopsy
- Anal cancer
  - RR increases 37-fold among HIV+ men
  - RR increased 60-fold among HIV+ MSM

USPSTF, CDC, HIVMA Recommendations
Aberg JA et al. CID 2004 39(5)609-29
Frisch M et al. J NCI 2000 92(18)1500-10

Colorectal Cancer Screening

<table>
<thead>
<tr>
<th>Test</th>
<th>HIV+</th>
<th>HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal Occult Blood Test</td>
<td>43</td>
<td>5.3</td>
</tr>
<tr>
<td>Flexible Sigmoidoscopy</td>
<td>17.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Air Contrast Barium Enema</td>
<td>2.6</td>
<td>17.2</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>27.5</td>
<td>55.6</td>
</tr>
<tr>
<td>At least 1 CRC Screening Test</td>
<td>77.8</td>
<td>65.6</td>
</tr>
<tr>
<td>UTD with at least 1 CRC Screening Test Performed</td>
<td>49.3</td>
<td></td>
</tr>
</tbody>
</table>

Summary

• HIV population is aging
• Providers should ask all patients about high-risk behaviors and educate them on the risks
• Management of older HIV-infected patients may be complicated by comorbidities
• Comorbidities attributed to increasing age may overlap with morbidity from HIV disease and toxicity from ART

Summary

• Current ARV therapies are effective in reducing progression of the disease and mortality
• Life expectancy is shorter than normal despite optimal ART.
  – It appears to be predicted by lower CD4 and higher inflammation.
• Markers of inflammation and T cell activation remain higher in ART than non-HIV infected
• Early diagnosis, and probably early therapy initiation, may improve outcomes in this population