Aging and HIV disease: A Symbiosis.

Trevor Hawkins MD
Assoc. Clinical Professor, UNM
Medical Director, Southwest CARE Center
Santa Fe, New Mexico

Overview

- Epidemiology of HIV/AIDS in older adults
- Immune activation and immunosenescence
- Clinical considerations of HIV management in an aging patient
- Age-associated comorbidities in patients with HIV
  - Renal disease
  - Bone disease and vitamin D deficiency
  - Cardiovascular disease (CVD)
  - Neurocognitive abnormalities
  - Non-AIDS-defining malignancies

Epidemiology of HIV/AIDS in Older Adults

Growing Older: HIV and Aging

Estimated Percentage of Persons Living with HIV/AIDS Who Are 50+ by Year, 2001-2007*

By 2015, Approximately 50% of People Living With HIV Will Be ≥50 Years of Age


AIDS Cases in San Francisco: Majority ≥50 Years of Age

- Population-based surveillance registry of San Francisco
  - 95% of cases validated
- From 2006 to 2010 (people ≥50 years of age)
  - Newly diagnosed AIDS cases increased from 21% to 27%
  - AIDS-related deaths decreased from 218 to 218
- First time that the majority of people living with AIDS in San Francisco are ≥50 years of age
- Presents new challenges for research, medical care, and support services


Concurrent HIV/AIDS Among Persons Diagnosed With HIV in the US in 2006, by Age Group


Immune Activation and Immunosenescence
Impact of HIV Infection on Inflammation and Immunosenescence

**Untreated HIV infection**
- Loss of immuno-regulatory cells
- Thymic dysfunction and loss of regenerative potential
- CMV replication
- HIV replication
- Loss of gut mucosal integrity and microbial translocation

**Chronic inflammation**
- T cell maturation
- Progenitor cell exhaustion
- T cell dysfunction

**Immunesenescence and clinical disease**


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**Inflammatory Markers* in Treated HIV+ Patients vs HIV- Patients**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Unadjusted OR (4th/1st quartile)</th>
<th>P value</th>
<th>Adjusted* OR (4th/1st quartile)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>hs-CRP</td>
<td>2.0</td>
<td>.05</td>
<td>3.1</td>
<td>.02</td>
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<tr>
<td>IL-6</td>
<td>8.3</td>
<td>&lt;.0001</td>
<td>12.4</td>
<td>&lt;.0001</td>
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<tr>
<td>Amyloid A</td>
<td>2.2</td>
<td>.07</td>
<td>3.1</td>
<td>.05</td>
</tr>
<tr>
<td>D-dimer</td>
<td>12.4</td>
<td>&lt;.0001</td>
<td>41.2</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, ART, HIV RNA level, CD4+ cell count, smoking, BMI, prior CVD, diabetes, antihypertensive and/or lipid-lowering agent use, total/HDL cholesterol, Hepatitis B or C coinfection.

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**SMART: Baseline Biomarkers and All-cause Mortality**
FRAM: Sarcopenia and Central Adiposity Associated with 5 Year Mortality

Arm SM:
- Lowest Tertile: reference 0.59 (0.35, 0.99)
- Middle Tertile: 0.51 (0.25, 1.04)
- Highest Tertile: reference

Leg SM:
- Lowest Tertile: reference
- Middle Tertile: 0.92 (0.54, 1.57)
- Highest Tertile: 0.42 (0.21, 0.84)

VAT:
- Lowest Tertile: reference
- Middle Tertile: 1.77 (1.03, 3.03)
- Highest Tertile: 2.12 (1.13, 3.98)

SM=skeletal muscle
VAT=visceral adipose tissue


Telomere Length

- HIV and aging both associated with early replicative senescence marked by:
  - Low levels of CD28 markers
  - Shortened telomere levels
  - Increased mortality
  - Poor immune response
  - Faster disease progression
  - Increased IL6/TNFα

- May be mitigated by adding telomerase
  - Small molecule telomerase activators (e.g. TAT2)

Ehle R, et al. 15th CROI; Boston, MA (2008); Abst. 106.

Clinical Considerations of HIV Management in an Aging Patient

Sexual Activity in Older Americans

Adherence: Some things do get better with Age

Hinkin AIDS 2004

HIV-1 RNA <500 at 6 months: by Age

Grabar AIDS 2004

ART in Patients >50 Years Old: ATHENA National Cohort

Clinical Considerations in Aging Adults With HIV

- Older patients more likely than younger patients to present late for HIV diagnosis and care\(^1\)
- Physicians less likely to discuss HIV/AIDS and related risk factors with older patients\(^2\)
- Asymptomatic older HIV-infected individuals are less likely to seek out testing and medical care\(^3\)
- Symptomatic older HIV-infected individuals are more likely to attribute HIV-related symptoms to other illnesses or to the normal aging process\(^3\)

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HIV Risk in Older Adults: Unprotected Sexual Activity

- Use of erectile dysfunction drugs contributes to increased rates of sexual activity
- Menopause
  - No risk for pregnancy = no need for condom
- Vaginal dryness due to estrogen depletion leads to greater likelihood of trauma and increased risk of HIV acquisition


Age-Associated Comorbidities in Patients with HIV

Causes of Death In HIV+ Persons Treated With ART (1996-2006)

- Assessed deaths in 13 HIV-1 cohorts comprised of 39,727 persons
- Of 1876 deaths, definitive cause in 85%
- Non-AIDS related deaths in 56.5%

Changing Patterns of the Causes of Death in a Swiss Cohort (SHCS)

- SHCS is a prospective observational cohort
- Characteristics of participants that died from 2005-2009
- 459 deaths/9,053 participants (5.1%)

Look to the Long-Term, in Money and in HIV

Focus on Non–AIDS-Defining Illnesses

- Renal disease
- Bone disease
- Cardiovascular disease (CVD)
- Non–AIDS-defining malignancies
- Neuropsychologic abnormalities

Risk Factors Contributing to Development of Kidney Disease

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

- Nonmodifiable 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

Renal Disease Increases With Age in the General Population

Renal Function Evaluation: Complementary Ways to Monitor Kidney Function

- Serum creatinine
- Creatinine clearance (calculated by Cockcroft-Gault [CG])
- GFR (calculated by MDRD)
- 24-hour urine test
- Urinalysis
  - Dipstick to screen for albuminuria or proteinuria
- Microalbuminuria
  - 24-hour urine for albumin
  - Microalbuminuria/creatinine ratio in a spot specimen
- Proteinuria
  - 24-hour urine test for protein
  - Protein/creatinine ratio in a spot specimen


Estimating GFR: Similar Serum Creatinine Levels Do Not Mean Similar GFRs

| Plasma Creatinine: 1.4 mg/dL |

<table>
<thead>
<tr>
<th></th>
<th>White Male, 25, 210 lb</th>
<th>Black Female, 86, 115 lb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>108</td>
<td>52</td>
</tr>
<tr>
<td>MDRD</td>
<td>66</td>
<td>46</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>69</td>
<td>39</td>
</tr>
</tbody>
</table>

CKD-EPI, chronic kidney disease epidemiology collaboration. *GFR measured in mL/min/1.73 m².

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Many Potential Contributors to Decreased BMD in Patients With HIV

- Liver disease
- Premature menopause
- Hypogonadism
- Smoking
- HIV infection

- Decreased bone acquisition
- Fat deposition in marrow
- Decreased physical activity
- Decreased muscle mass
- Decreased fat mass
- Malnutrition
- Vitamin D deficiency

- Alcohol use
- Medications
  - Corticosteroids
  - Anticonvulsants
  - Nucleoside analogues/mitochondrial dysfunction
  - Protease inhibitors

- Family history
- Female sex
- Increasing age

Adapted from Glesby M et al. CID. 2003; 37(Suppl 2):S91-S95.
BMD Decreases With Age

- Male
- Female


BMD, bone mineral density.

BMD in HIV+ Persons

- Multiple studies have found increased prevalence of osteoporosis and osteopenia in HIV-infected persons compared with uninfected persons
- Meta-analysis of studies
  - 67% HIV infected persons had reduced BMD (OR 6.4)
  - 15% HIV+ had osteoporosis (OR 3.7)


- Women
- Men

Triant. JCEM. 2008

8,525 HIV-infected
2,208,792 non HIV-infected patients

0.0
1.0
2.0
3.0

30-39 40-49 50-59 60-69 70-79

Fracture prevalence

2008 US National Osteoporosis Foundation (NOF) Guidelines for DXA Screening

- Those with a history of fragility fracture
- Women ≥65 years, Men ≥70
- Postmenopausal women and men 50-70 years, if there is concern based on risk factor profile

Screening in HIV-infected Patients:

- All post-menopausal women
- Men ≥50 years
2008 US NOF Guidelines: Who to Treat

- Those with hip or vertebral fractures
- Those with BMD T-scores ≤-2.5 at the femoral neck, total hip, or spine by DXA
- Those with T-score between -1 and -2.5 (osteopenia) at above sites AND 10-year hip fracture probability ≥3% or 10-year all major osteoporosis-related fracture ≥20% based on FRAX model

* Applies to post-menopausal women and men ≥50 years

http://www.shef.ac.uk/FRAX

Management Options

- General recommendations
  - Calcium/vitamin D supplementation
  - Smoking cessation, alcohol reduction
- Rx options
  - Bisphosphonates

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Factors Affecting Risk for CVD in Patients with HIV

- Family history of CVD
- Metabolic abnormalities
  - Diabetes
  - Obesity
  - Hypertension
  - Smoking
- HIV infection
- ART
- Older age
- Male gender

Coronary Aging in HIV-Infected Patients

- **Method**: Cross-sectional study, 400 patients (mean age 48) had cardiac CT for coronary artery calcium (CAC)

- **Results**: 162 patients (40%) had increased vascular age with average of 15 years over chronological age


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Risk of MI in Patients Presenting at Least Twice to Either of Two Boston Hospitals By HIV Status

- **Results**: MI risk was 1.75 times higher for HIV-positive patients compared to HIV-negative patients

Triant et al., JCEM, 2007

* Adjusted for age, gender, race, hypertension, diabetes and dyslipidemia. Proportion of patients with hypertension, diabetes and dyslipidemia significantly higher in HIV-positive vs HIV-negative cohort

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HOPS: Attributable Risk for CVD

- **Results**: Patients with higher on-treatment CD4 cell count had lower risk of non-AIDS events, including CVD


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SMART: Changes in D-Dimer and IL-6 Levels

- **Results**: HIV viremia effect on endothelium, leading to increased tissue factors and initiation of coagulation cascade

Atherosclerosis, CVD

- Foam Cells
- Fatty Streak
- Intermediate Lesion
- Atheroma
- Fibrous Plaque
- Complicated Lesion/Rupture

Age
Gender
Hypertension
Lipid profile: LDL, HDL, Trig
T2D
Smoking
Blood pressure
Inflammation

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Multifactorial Etiology of HIV-Associated Neurocognitive Conditions

Medical conditions
- Nutritional/metabolic causes
- Vascular disease
- HCV infection
- Depression/other psychiatric conditions
- Sleep disorders

Concomitant medications and comorbidities
- Substance use
- Increased survival of HIV+ individuals
- Aging and the brain
- Alzheimer disease

HIV

ARVs

HIV Infection and Aging Independently Affect Brain Function by Functional MRI

- Method
  - fMRI in age matched persons with HIV (n=25) and without HIV (n=26)
  - Goal – changes in visual cortex due to impact of aging
  - HIV patients – med CD4 486, 60% HAART
- Results
  - HIV infection added 21 years to brain age

Ances BM. JID 2010;201:336
HIV-associated Neurocognitive Complications

- Chronic HIV infection may result in progressive neurodegenerative disease
  - Initially termed NeuroAIDS
  - More recently reclassified as HIV-associated neurocognitive disorders (HAND)
- HAND severity:
  - Asymptomatic neurocognitive impairment (ANI)
  - Mild neurocognitive disorder (MND)
  - HIV-associated dementia (HAD)

Prevalence of HAND in the Pre-AET and ART Eras

Focus on Non—AIDS-Defining Illnesses

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Neurocognitive Disorders Associated with Nadir CD4 Counts

- Multicenter cohort study (CHARTER) of 1526 pts evaluating HIV-associated Neurocognitive Disorders (HAND)
- Complex testing consistent with defined criteria used to determine HAND
  - 803 had HAND (without a substantial confounder);
  - 726 not impaired
- Multivariate analysis: Higher CD4 nadir associated with lower risk of HAND

Odds Ratios for Cognitive Impairment by CD4 Nadir

Cancer Pathogenesis

- The roots of the genesis of cancer lie in multiple mutations in proliferating cells, predominantly involving regulatory genes that affect cell cycling.
- These mutations may be provoked by chronic activation of the tissue response and here lies the potential contribution of chronic inflammation
The Burden of Cancer Among HIV-infected Persons in the US Population

- Estimate of the total number of cancers (cancer burden) in patients with AIDS as well as in HIV(+) patients without AIDS in the US
- CDC collects HIV data from US states
  - AIDS from entire country from 1991-2005
  - HIV only from 34 states 2004-2007
- NCI HIV/AIDS cancer match study

Incidence of Non-AIDS Defining Cancers Increasing in HIV+ Patients

- Incidence of cancers was increased significantly in ASD/HOPS cohort (HIV+) vs general population (HIV-):

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>SRR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>42.9 (34.1-53.3)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>21.0 (11.2-35.9)</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>14.7 (11.6-18.2)</td>
</tr>
<tr>
<td>Liver</td>
<td>7.7 (5.7-10.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>3.3 (2.0-5.3)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.6 (1.5-3.8)</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>2.8 (1.9-3.4)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.5 (1.6-3.8)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>2.3 (1.8-2.9)</td>
</tr>
<tr>
<td>Renal</td>
<td>1.8 (1.3-2.7)</td>
</tr>
</tbody>
</table>

*Standardized rate ratio (SRR) (HIV+) relative to standardized rate (SEER, HIV-)

Functional Issues with Aging and HIV

- Frailty phenotype (presence of >3 of the following)
  - Exhaustion, slowed walking speed, low activity level, weakness, and weight loss
  - Associated with poorer health outcomes
- MACS
  - A 55-year-old HIV-infected person has similar frailty as a 65-year-old HIV-negative person
- Proposed mechanisms
  - Mitochondrial dysfunction and increased number of free radicals and cytokines activate inflammatory pathways, ultimately leading to frailty.

Shiels M, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. WEAB0101.

Data for 34 U.S. States (2004-2007)
Frailty May Influence Survival Post-ARV Initiation

- Retrospective comparison of time to death and AIDS diagnoses in HIV-infected men with known date of HIV diagnosis and frailty phenotype measured within 6 months of starting ARV (n=596)
- Results unchanged when analysis restricted to ARV responders

HIV Treatment May Be Complicated by Polypharmacy

- Overlapping toxicities
- Drug-drug interactions
- Increase or decrease in drug plasma levels
- Inadequate levels of ARVs may lead to incomplete viral suppression and development of resistance
- ART-induced organ toxicities may exacerbate pre-existing age-related conditions
- Close monitoring is required to detect any emerging problems

Screening in HIV Patients

1. Start ART earlier because older patients have slower CD4 recovery and more comorbidities
   - Any CD4 count.
2. Monitor and aggressively manage CVD risk factors
   - Smoking cessation; cocaine use; BP; lipids; BS and insulin resistance; weight gain; exercise; diet; stress; depression
   - Should we measure hsCRP, D-dimer, fibrinogen levels?
   - Should HIV be a part of the Framingham equation?

Screening in HIV Patients (cont'd)

3. DXA scans and vitamin D levels
   - Should all patients with HIV over 40, over 50, have a dexascan? Most favor >50 years
   - What if there is at least 1 additional risk factor such as smoking, low BMI, white race, hypogonadism, steroid use, HCV, etc? Many favor DXA at any age in this group
   - What is the optimal vitamin D level? >30 ng/mL? >60 ng/mL? Most docs are replacing at <30 ng/mL and winging it

4. Monitor Serum Creatinine/GFR
   - UA dip for protein and glucose/spot Urine Pr/Cr ratio
   - Are these sufficient?
Screening in HIV Patients (cont'd)

5. Neurocognitive mini screens/Depression scores
   - Memory/Attention/Psychomotor speed/Construction
   - Need to eliminate the stigma of the Dx of HIV in the elderly
   - Work, retirement, remaining engaged with family and friends

6. Cancer Screening
   - All usual including vaginal PAP, breast exam and mammography, colonoscopy, DRE + PSA
   - Anal PAP ± HRA should be part of SOC
   - Cancer screening in HIV-infected patients should be considered at an earlier age than in the general population

Conclusions

- Toxicity from HAART is substantial and may be exacerbated in older patients
- Drug-drug interactions are common
- Unclear what the “ideal” HIV regimen is for older patients
- High rates of comorbidities in older HIV patients
- General routine health maintenance and screening is important
- Future research is essential for developing accurate treatment recommendations in older patients

Thank You!