The Status of the Aging HIV Epidemic:
Inflammation
Multimorbidity
Accentuated Aging

Stephen E Karpiak PhD
ACRIA
AIDS Community Research Initiative of America
ACRIA Center on HIV and Aging
New York University College of Nursing
New York, NY
Remember in 1989 an AIDS diagnosis meant your life span was at best 1 year.

Figure 1. Actuarial survival of patients from the time of diagnosis of AIDS.
“HIV and Premature Aging: A Field Still in Its Infancy”

- Although the hypothesis of premature aging in HIV infection is intriguing, we suggest that it remain a hypothesis—for now—and not become ingrained as a complication of HIV infection before its time.

- To mature this concept from hypothesis to fact will require more research to develop consensus definitions….

- Demonstrate potential examples of premature aging…

- A much better understanding of the normal biological process of aging.

By the end of this decade estimates show that 70% of the USA HIV infected population will be age 50 and older.

Older Adults with HIV more often die from NON-AIDS related illnesses.

Multimorbidity is the rule and not exception in this population.

Management of multimorbidity in a person with HIV is the new challenge.
Possible Causes for Increasing numbers of Non-AIDS Deaths

- The price of success: People are living long enough on ART to die of something else
- HIV disease progression
- Chronic inflammation
- ART & other drug toxicities
- No primary driver
Are HIV Infected People Aging Differently?

- Accelerated Aging
- Accentuated Aging
- Uncharacteristic Aging
What DROVE this hypothesis?

**THE COMPLICATION OF SUCCESS**

Many Age-Associated Diseases are More Common in Treated HIV Patients than in Age-Matched Uninfected Persons

- Cardiovascular disease
- Cancers
- Bone fractures; osteopenia
- Liver Failure
- Kidney Failure
- Frailty
- Reduced Immune System Function
- Depression
Are these age-related chronic conditions just **Accentuated** or/and/not **Accelerated**?

- **Accelerated risk** Condition occurs more often and at younger age among those with HIV than among HIV-uninfected comparators.

- **Accentuated risk** Condition occurs at the same age but more often in those with HIV than among HIV-uninfected comparators.

Shiels MS. Age at Cancer Diagnosis among persons with AIDS in the US. Ann Intern Med 2010
Does Clinical Data Support the Biology?

**BIOLOGY**

- Persistent inflammatory response
- Immunosenescence
- Telomere shortening
- ART Toxicities
- HIV Disease Progression
## Does Clinical Data Support the Biology?

### CLINICAL

**Increased**

- Cancer (non-AIDS)
- Cardiovascular disease
- Osteoporosis
- Liver disease
- Renal disease
- Neurocognitive disorders
- Metabolic: diabetes, dyslipidemias
- Life Span
- Frailty
Inflammation

↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

HIV-associated fat Metabolic syndrome

CMV
Excess pathogens

HIV production
HIV replication

Loss of regulatory cells

Microbial translocation

Co-morbidities
Aging
Inflammation predicts disease risk in those on ART and in the general population

- **Cardiovascular Disease**  (Baker, CROI 2013)
- **Lymphoma**  (Breen, Cancer Epi Bio Prev, 2010)
- **Venous Thromboembolism**  (Musselwhite, AIDS, 2011)
- **Type II Diabetes**  (Brown, Diabetes Care, 2010)
- **Cognitive Dysfunction**  (Burdo AIDS 2012)
- **Frailty**  (Erlandson, JID 2013)
Biomarkers Remain Elevated with Treated HIV

Among those with undetectable viral load (<400 copies/mL), hsCRP was 40% higher, IL-6 was 60% higher, and D-dimer was 49% higher, compared with controls from MESA.

Mortality RR (4th/1st QRT)

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<th>(ART-treated) HIV+</th>
<th>HIV-</th>
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<td>(SMART/ ESPRIT)</td>
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<td>D-dimer</td>
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<td>IL-6</td>
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HR adjusted for age, sex, race/ethnicity (RHS only adjusted for age and sex)

Non-AIDS morbidities are more common in HIV, even after adjustment for age, HAART exposure and traditional risk factors.

Deeks and Phillips, BMJ, 2009
Fracture Prevalence is Associated with HIV Infection: Boston Data Base

1996-2008: N = 8,525 HIV-positive / 2,208,792 HIV-negative

Women

Men

Fracture Prevalence/100 Persons

Age (years)

HIV+ HIV-

P=0.0002 (overall comparison)

P=0.0001 (overall comparison)

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Age (years)

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a Clinical care data registry from the Partners HealthCare System:
Brigham Women’s Hospital and Massachusetts General Hospital.
Triant, VA et al. JCEM. 2008;93:3499-504.
More than 50% of HIV-infected adults age 55-60 had two or more co-morbidities, higher than uninfected adults more than a decade older.
Age-dependent decline in T cell output from thymus

Naylor, K et al. J Immunol. 2005
Median Life Years at Age 20 With HIV In-Care

- '85-87: 2
- '90 to '92: 4
- '95 to '97: 24.3
- '00 to '02: 27.1
- '03 to '05: 33.2
- 06 to '10: 45.8
- 11 to '15: 50.1

ART
Stage 3 (AIDS) Classifications, Deaths, and Persons Living with HIV Infection Ever Classified as Stage 3 (AIDS) 1985–2010—United States and 6 Dependent Areas

Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting. Deaths of persons with HIV infection, stage 3 (AIDS) may be due to any cause.
Deaths of Adults and Adolescents with HIV Infection Ever Classified as Stage 3 (AIDS), by Race/Ethnicity 1985–2010—United States and 6 Dependent Areas

Note. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting. Deaths of persons with HIV infection, stage 3 (AIDS) may be due to any cause.

a Includes Asian/Pacific Islander legacy cases.

b Hispanics/Latinos can be of any race.
People Aging With HIV Have a Higher Prevalence of Comorbidities

More multimorbidity at higher age in HIV

% Number of Comorbid Illnesses 0-6+ for Each Person:
ROAH HIV + vs USA (NHANES) Age 50+

Submitted ACRIA 2015 Ambroziak, A…Karpiak, S.E.
IS THIS REALLY ALL ABOUT RISK?

Psychosocial variables that are forgotten or given at best tertiary consideration?
Tobacco use is the single most preventable cause of disease, disability and death in the United States... leading to more than 443,000 premature deaths each year.

- U.S. Department of Health and Human Services (2014)

- About 18.1% of the U.S. population smokes cigarettes and tobacco-related cancers are responsible for about 30% of cancer deaths yearly.

- Tobacco use is an individual and additive risk factor for most types of cancer, including those already disproportionally seen in the HIV+ community.
Cigarettes and Cancer

Smoking greatly increases the risk of developing tobacco-related cancers, including lung, throat, oral and esophageal cancer.

Lung cancer is the leading cause of tobacco-related cancer death in the United States, responsible for about 1 in 5 deaths or 480,000 deaths annually (2014).

The Centers for Disease Control and Prevention: Smoking & Tobacco Use
People on HIV Treatment Double Their Risk of Death by Smoking

- HIV-positive men who smoke can expect to lose almost 8 years off their life expectancy.
- Smokers with HIV were 1.94 times more likely to die than nonsmokers.
- Smokers with HIV were 6.28 times more likely to die of cardiovascular disease.
- Smokers with HIV were 2.67 times more likely to die of non-AIDS cancers when compared with nonsmokers.

Substance Use Older PLWH

- Alcohol
- Marijuana
- Pain Killers
- Cocaine
- Crack
- Heroin
- Poppers
- LSD/PCP
- Crys Meth
- Ecstasy
- Ketamine
- GHB

ROAH data – Karpiak et al. 2007
Life Style: Alcohol and CD4 Decline

The drug of choice for older adults with HIV is alcohol. Alcohol Use Accelerates HIV Progression.

**FIG. 1.** The effect of frequent alcohol use on the rate of decline of CD4$^+$ cell count to ≤200 cells/$\mu$l over 30 months was assessed in 130 participants who had a baseline CD4$^+$ cell count >200 cells/$\mu$l. Frequent alcohol use over time (two or more alcoholic drinks/day) significantly increased the decline of CD4$^+$ cell count to ≤200 cells/$\mu$l. From Cox analysis we calculated an HR = 2.91; 95% CI: 1.23-6.85, $p=0.015$. 
Healthy aging requires aggressive risk factor management, exercise and diet.
Aging Leads to Diminished Reserve

Frailty and Function

Ethnographic data….
Frailty-like syndrome occurs earlier in HIV disease (predicted by CD4 nadir)

Frail state is associated with elevated levels of immune activation
Relationship Between CD4 T-Cell Count and Prevalence of Frailty-Related Phenotype (FRP), by Calendar Period

Frailty-Related Phenotype (FRP) and Duration of HIV Infection (Pre-HAART Era)

Odds ratio [95% CI] to manifest the FRP*

- Ref: 3.4 [1.2-9.1]
- 0 - 4 years: 13.0 [6.6-25.4]
- 8 - 12 years: 14.7 [7.6-28.4]

Same FRP prevalence between a 55-year old man infected < 4 years and a >65-year old uninfected man

*Logistic regression models (GEE)

HIV-infected adults have many traditional risk factors for frailty and other geriatric syndromes, raising concerns that the real burden of disease will only become apparent late in life.

1. **Polypharmacy**
2. **Clinical Aging and Geriatric Syndromes**
   - Frailty/sarcopenia,
   - Neurocognitive decline
3. **Social isolation**

*Chang et al., Archives of Gerontology and Geriatrics, 2012*
Grand Opening: The Go-To Place On HIV And Aging
Editorial February 5, 2014 3 Comments

In the U.S. the HIV population is aging. By 2015 half of the over 1.4 million people infected with HIV will be age 50 and older. Each day 80 more people become part of this older adult group. And, 1 in every 6 new HIV diagnoses occurs in the age 50 and older population. This graying of... Continue Reading

Card For Clinicians Caring For HIV-Infected Older Adults
Science Spotlight February 5, 2014

CARD FOR CLINICIANS CARING FOR HIV-INFECTED OLDER ADULTS The Quick Reference Card for Managing Older Adults with HIV was developed out of the New York State Dept. of Health AIDS Institute Office Of The Medical Director. To obtain a copy, access www.hivguidelines.org. The AIDS Institute determined HIV and Aging as a priority over ten years ago. The number... Continue Reading
The Greying Has Just Begun: Geriatric Syndromes in HIV

**FIGURE 1.** Frequencies of geriatric syndromes. Each bar reflects the percentage of participants with each geriatric syndrome. Actual percentages are shown at the end of each bar. Horizontal axis only shown to 60%.
Is The Older Adult HIV Infected Population of Survivors Biasing the Morbidity Data of Clarifying It?

Greene et al. 2015 JAIDS 69:2  Geriatric Syndromes in Older HIV Infected Adults
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Thank you.....

- Mark Brennan-Ing, ACRIA
- Richard Havlik, MD – NIA(NIH)
- Meredith Greene, MD - UCSF
- Genie Siegler, MD - Cornell
- June Sangarlangkarn. MD – Mt Sinai

Stephen E Karpiak PhD
ACRIA
AIDS Community Research Initiative of America
ACRIA Center on
HIV and Aging
New York University
New York, NY
skarpiak@acria.org