Aging with HIV

- Increased life expectancy on ARVs. However, life expectancies still shorter than for general population
  - Especially for low CD4 and/or salvage regimens
- What is the impact of increased life expectancy on comorbidity prevalence?
- Distribution of comorbidities in HIV-infected individuals
- The impact of increased comorbidity on
  - Timing of ARV initiation
  - Appropriateness of primary care practice guidelines (e.g., colorectal cancer screening). No systematic method to predict whether guidelines developed on general population should apply to individuals with HIV

Braithwaite RS Arch Intern Med 2007;167:2361-5

Survival Trends in HIV-infected Patients Have Changed Since the Adoption of HAART


Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. N=383,862 (HIV-infected patients, n=3990; General population controls, n=379,872)

Survival From Age 25 Years

General Population
Late HAART (2000-2005)
Early HAART (1997-1999)
Pre-HAART (1995-1996)

Life Expectancy of HIV-Positive Patients

- Comparison of life expectancy of Athena cohort patients to general population (n=4174)
- Age at week 24, country of birth and stage B symptoms were associated with a higher risk of death
- Expected life years remaining at age 25 was 53.1 (44.9-59.5) for general population and 52.7 for asymptomatic HIV+ patients
- The modeled life expectancy of patient presenting at an older age and women were slightly lower than general population

General Population
Asymptomatic HIV+

Years of Life Remaining
Age at time of death

Non AIDS” Deaths More Common

<table>
<thead>
<tr>
<th>Source</th>
<th>Non AIDS</th>
<th>Leading Causes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>NY Death Certificates</td>
<td>26%</td>
<td>Alcohol/drug abuse (31%), CVD (24%), Cancer (21%)</td>
<td>Ann Intern Med 2006;145:397-406</td>
</tr>
<tr>
<td>Barcelona Death Certificates</td>
<td>60%</td>
<td>Liver (23%), Infection (14%), Cancer (11%), CVD (6%)</td>
<td>HIV Med 2007:251-8</td>
</tr>
<tr>
<td>HOPS Chart Rev.</td>
<td>63%</td>
<td>Liver (18%), CVD (18%), Pulmonary (16%), Renal (12%), GI (11%), Infection (10%), Cancer (8%)</td>
<td>J Acquir Immune Defic Syndr 2006:43:27-34</td>
</tr>
<tr>
<td>Cascade Chart Rev.</td>
<td>63%</td>
<td>Liver (20%), Infections (24%), Unintentional (33%), Cancer (10%), CVD (9%)</td>
<td>AIDS 2006; 20:741-9</td>
</tr>
</tbody>
</table>

Aging and HIV

- ART may produce chronic adverse effects
  - CHD risk increased
  - Metabolic abnormalities more common
- ART may not protect from CANCER with AGE
  - Esophageal / Lung / Rectal (HPV) / Renal / Liver
- Conditions seen at earlier age
  - Osteoporosis/ hypogonadism
Getting Older with HIV ≠ Progeria

- How did we get to the concept that HIV infection is accelerated aging?
- The immunodeficiency of HIV infection has some resemblances to the changes in the immune system seen in aging, but the consequences are strikingly different.
- HIV is an infection whose consequences to the immune system lead to an increase in specific diseases (e.g., not all cancers).

Grunfeld, C

CVD Increases with Age Framingham (1980-2003)


Comorbidity by HIV Status & Age


Common Comorbidities of Aging

Vascular Disease
Pulmonary Disease

Liver Disease*
Renal Disease*

*Note change in axis


Comorbidities associated with HIV: COPD

Crothers, K. Chest, 2006
BMI By HIV Status in VACS

![BMI By HIV Status in VACS](image)

Justice, Medical Care 2006, 44(8 Suppl 2):S13-24

---

VA Comorbidity Patterns

- As HIV-infected patients live longer prevalence of comorbidites is rising
  - 40%-70% of patients have ≥1 comorbidity
- Patterns vary by HIV status
  - HIV-infected patients more likely to have liver disease, renal disease, and multi-morbidity
  - Obesity related diseases less prevalent in HIV-infected patients.


---

VA Comorbidity Patterns

- As HIV-infected patients live longer prevalence of comorbidites is rising
  - 40%-70% of patients have ≥1 comorbidity
- Patterns vary by HIV status
  - HIV-infected patients more likely to have liver disease, renal disease, and multi-morbidity
  - Obesity related diseases less prevalent in HIV-infected patients.


---

Age Disproportionately Affects Care Resources

- 80% have at least one chronic disease
- Most common conditions
  - Arthritis, hypertension, hearing impairment, heart disease, vision impairment, orthopedic disabilities, diabetes
- The elderly make up 13% of the population but
  - utilize 30% of the prescription drugs
  - 40% of the OTC medications
- On average the elderly take 3 times more drugs than younger counterparts
- The elderly suffer 2-3 times the rate of adverse drug reactions
  - Most explainable to changes in renal and hepatic function and changes in body composition

---

Payoff Time

- **Payoff Time = Minimum time until incremental benefits > incremental harms**
  - Applies to any guideline where harms are short-term and benefits are long-term
  - Colorectal cancer screening (CRC)
    - Will vary by guideline and by patient population
  - Payoff time can be compared to life expectancy
    - If death likely before payoff time, guideline not advised
    - If death unlikely before payoff time, guideline advised

Braithwaite RS. Arch Intern Med 2007;167:2361-5; Braithwaite RS. Med Care 2009 Jun;47(6):610-7

---

Compare payoff time to life expectancy

**Case 1: 60 year-old HIV+ male on salvage ARV, CD4 count 46 severe COPD and HCV**

- Payoff time for Case 1 is 7.3 years
- Life Expectancy for Case 1 is 5.1 years
- Because life expectancy is less than payoff time (minimum time until benefits exceed harms), Case 1 is unlikely to benefit from colorectal cancer screening

Braithwaite RS. Arch Intern Med 2007;167:2361-5; Braithwaite RS. Med Care 2009 Jun;47(6):610-7

---

Compare payoff time to life expectancy

**Case 2: 60 year-old HIV+ female on 1st line ARV, CD4 count 392, DM**

- Payoff time for Case 2 is 5.7 years
- Life Expectancy for Case 2 is 15.1 years
- Because life expectancy is more than payoff time (minimum time until benefits exceed harms), Case 2 is likely to benefit from colorectal cancer screening

Braithwaite RS. Arch Intern Med 2007;167:2361-5; Braithwaite RS. Med Care 2009 Jun;47(6):610-7
Braithwaite Conclusion

- Payoff time is quantitative objective framework for predicting who will benefit
- CRC screening may not always be appropriate for HIV+ individuals
  - Low CD4
  - Salvage ARV
- May simultaneously improve quality of care and reduce resource expenditures
- May impact quality measures

Prostate Cancer: Risk?

- Association between HIV status and positive prostate biopsy in a study of US veterans (Atlanta)
  - Over a 5.5 year period, patients referred to the urology clinic (elevated PSA or abnormal DRE): markedly higher rate of prostate cancer in HIV patients when compared to HIV-negative or HIV-unknown population

  - In men receiving HAART, their age, PSA levels, clinical presentation, management, and outcome from treated prostate carcinoma does not appear to be significantly altered by HIV status.
  Pantanowitz L, BJU Int. 2008 June

Figure 1 Prevalence of neoplastic lesions in the HIV-infected subjects and control subjects. Note: These categories are not mutually exclusive since advanced neoplasia includes all patients with adenomas >=10 mm, those with adenomas of any size with villous histology or high-grade dysplasia, and individuals with adenocarcinoma.

Cancer Incidence in AIDS Patients

- Study of cancer risk in AIDS patients from 1980-2006 (N=372,364)
- Predominantly male (79%), non-hispanic black (42%), MSM (42%)
- Median age of 36 years at the onset of AIDS
- Cancer risk in years 3 - 5 after AIDS onset increased for AIDS but also Non-AIDS defining cancers

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>No. cases</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>3136</td>
<td>5321</td>
<td>5137 - 5511</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3345</td>
<td>32</td>
<td>31 - 33</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>101</td>
<td>6.6</td>
<td>5.5 - 8.9</td>
</tr>
<tr>
<td>Non-AIDS-defining cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal cancer</td>
<td>210</td>
<td>27</td>
<td>24 - 31</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>86</td>
<td>3.7</td>
<td>3.0 - 4.6</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>531</td>
<td>3.0</td>
<td>2.8 - 3.3</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>106</td>
<td>9.1</td>
<td>7.7 - 11.6</td>
</tr>
<tr>
<td>All non-AIDS related cancers</td>
<td>2155</td>
<td>1.7</td>
<td>1.5 - 1.9</td>
</tr>
</tbody>
</table>

SIR=Standardized Incidence Ratios

HIV-related Incidence Rates

Cancer Mortality in AIDS Patients

Population attributable risk among people with AIDS in the US

HIV Infection and Lung Cancer

- VA-Cohort (3,707 HIV-positive patients)
  - Predominantly male (98%), white (43%)
  - Median age 47 years
- Lung cancer risk factors
  - Smoking and drug abuse more often among HIV+
  - Similar rates of COPD
- After adjustment for smoking, risk of lung cancer higher in HIV+ patients
Geriatric Periodic Health Exam

- An assessment that is aimed at preventing, detecting and controlling specific conditions or risk factors
- The GPHE specifically addresses those over age 65 and allows detection of the common health issues that require further assessment and/or early intervention
- Targets conditions like frailty, sensory loss, cognitive impairment, depression, polypharmacy among others
- Opportunity for screening for “risky” behaviors (smoking, obesity, nutrition, medications)
- Self administered. Initial screen takes less than 30 minutes

GPHE Summary of Benefits from Chronic Disease Management

- Chronic diseases, if left untreated and undiagnosed, such as DM and depression are causally related to other diseases
- 90% DM and 80% CHD can be avoided with good nutrition, regular exercise, smoking cessation and stress management
- 20% reduction in cancer rates with daily diets high in vegetables and fruit
- Mammmography screening for 70% of women aged 50-69 would prevent 1/3 of breast cancers over a 10 yr period
- 90% of cervical cancer is preventable with regular screening
- FOBT in those aged 50-75 could reduce colorectal cancer mortality by 15-33%

Develop an HIV GPHE?

- Interprofessional screening form, patient tracking form, health questionnaire and patient information on all specific conditions
- Web tools for fracture risk and cardiac risk
- Early identification of chronic disease (case finding)
  - Diabetes
  - Thyroid Disease
  - Cancer
  - Asthma/COPD
  - Obesity
  - Coronary Heart Disease
  - Stroke
  - Arthritis
  - Osteoporosis

Using the Framingham Risk Score

- Risk Factor: Units
  - Sex: Male or Female
  - Age: Years
  - Total cholesterol: mg/dL
  - HDL: mg/dL
  - Systolic blood pressure: mmHg
  - Treatment for hypertension (only if SBP >120): Yes or No
  - Current smoker: Yes or No

- Risk Categories:
  - Low Risk
  - Moderate Risk
  - High Risk

IDSA Guidelines for Managing Lipid Disorders and CVD Risk in Patients Receiving HAART

- Obtain fasting lipid profile prior to starting antiretrovirals and within 3-6 months of starting new regimen
- Count number of CHD risk factors and determine level of risk. If ≥2 risk factors, perform 10-year risk calculation
- Intervene for modifiable nonlipid risk factors, including diet and smoking
- If above the lipid threshold based on risk group despite vigorous lifestyle interventions:
  - Consider lipid-lowering drugs
  - Consider altering antiretroviral therapy

- Serum LDL-C ≥190 mg/dL or TGs ≥500 mg/dL with elevated non-HDL-C: STATIN
- Serum TGs ≥500 mg/dL: FIBRATE
Epidemiology: MIs and Strokes Among Californians With and Without HIV

- Kaiser Permanente
- >35,000 HIV+ patients, >6 million HIV-negative individuals
- Incidence of MIs and strokes between 1996 and 2008

Hurley L, et al. 16th CROI, Montreal 2009, #710

Why the Decrease in CV Event Incidence?

- Better drugs
- More attention to lipids

Hurley L, et al. 16th CROI, Montreal 2009, #710

Increased Fracture Rate in HIV Outpatient Study Patients (HOPS)

- Comparison of HOPS cohort (n=8,456) vs National Hospital Discharge Survey and National Hospital Ambulatory Medical Care Survey (NHAMCS)
  - Adjusted for age and gender
- HOPS: 276 fractures during median 4.8 yrs follow-up
- Risk factors for fractures
  - Age >47
  - Nadir CD4+ count <200
  - HCV co-infection
  - Diabetes
  - Substance use
- Conclusion: Fracture rates higher in HIV-infected population and rate is increasing with age

Gender-adjusted rates of fracture among adults aged 25-54 years

Increased Prevalence of Vitamin D Deficiency in HIV Infection

- Retrospective seasonal analysis of Vitamin D deficiency within Swiss cohort
- Started ART in: Fall (n=108); Spring (n=103)
  - 75% men; age = 37; White = 87%; CD4+ 227; BMI = 22.9
  - ARTs: TDF - 17%; NNRTI - 20%; PI - 56%
- Conclusions
  - Vitamin D deficiency is common, but seasonal
  - Blacks are at increased risk
  - NNRTI use is a risk factor

25-OH Vitamin D Levels

- < 20 ng/ml: Deficiency
- 20-29 ng/ml: Insufficiency
- 30-60 ng/ml: Preferred

n = 57 HIV+ pts at MGH:
- 37% moderate deficiency (10-20 ng/ml)
- 10% severe deficiency (<10 ng/ml)


RISK FACTORS

- Impaired skin production
  - Inadequate sun exposure
  - Dark skin
  - Phototherapy
- Use of high SPF sunscreen (15 or more)
- Bedridden/nursing home patients
- Prolonged hospitalization
- Obesity
- Age-related decline in vitamin D production
- Season and geographic latitude > 34 N

- Dietary intake
  - Foods not fortified with vitamin D
  - No standard use of multivitamin
  - Malnutrition
  - Strict vegetarian diet
  - Medications
  - Celiac disease, CP
  - Chronic pancreatitis
  - PC, short bowel syndrome
  - Age-related intestinal resistance to 1,25(OH)2 vitamin D action

- Accelerated loss of vitamin D
  - Decreased renal 1-alpha-hydroxylation (PTH, calcium, phosphate, rhodanese)

- Impaired 25-hydroxylation

- Impaired 1-alpha-hydroxylation

- Renal failure

- Increased vitamin D turnover

- Increased vitamin D-dependent rickets type II

- Target Organs: resistance to vitamin D-dependent rickets type II (receptor deficiency)

Prevalence of Vitamin D Deficiency in 87 Subjects Initiating ART in Cleveland

84%
56%
33%

(< 32 ng/mL) (< 20 ng/mL) (< 15 ng/mL)

Brown, Antiviral Therapy, in press

Vitamin D and HIV Duration

r=0.2, p=0.07

Brown, Antiviral Therapy, in press
**Proportion of Subjects with Hypovitaminosis D (≤ 15 ng/mL)**

*Adjusted Prevalence Ratio (95% CI): 1.8 (1.2, 2.8), p=0.007

<table>
<thead>
<tr>
<th></th>
<th>Pre-ART</th>
<th>Post-ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for baseline 25(OH)D, race, season

Brown, Antiviral Therapy, in press

**Effect of D₂ 50K units q week x 8 weeks, then 50K qow**

Pietras, Arch Int Med, 2009

**Treatment of Vitamin D Deficiency**

- **Replacement**
  - Ergocalciferol (D₂) 50K units 1-2 times/week for 8-12 weeks
  - OR
  - Cholecalciferol (D₃) 2000 IU/d

- **Maintenance**
  - Ergocalciferol 50K units 1-2 times/month
  - OR
  - Cholecalciferol 1000-2000 IU/d

Rule of Thumb: 100 IU D₃/d will increase 25 OH D by 1 ng/mL

**Osteoporosis Recommendations**

- Low bone mass and osteoporosis are prevalent in HIV-infected patients
- No consensus/guidelines for screening or treatment of HIV-infected patients
  - May be reasonable to screen postmenopausal women and men > age 50; possibly those 40-50 years with risk factors
  - Calcium/vitamin D, smoking cessation, weight-bearing exercise, bisphosphonates, fall prevention

Stacy J. The NY Course 2009

**Summary**

- ARV has dramatically increased survival
  - Is HIV just another chronic disease, like diabetes?
- Increased survival has increased prevalence of non-HIV-related comorbidities
- Comorbidities may occur at Younger Age in HIV
- Increasing evidence favors starting HAART earlier
  - Benefit may be lower with age or comorbidity
- Primary care screening guidelines are often applicable to HIV patients
  - Payoff time may help to determine when particular guidelines are applicable
  - Caution we do not under screen because of wrong assumptions
  - Need to implement general medical screening and treat conditions identified