Ageing with HIV infection

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Disclosures

• Consulting/Advisory Boards
  – Merck, Gilead, BMS, AbbVie

• Member DSMB
  – Tibotec/Janssen
I'm going to Canada for the cheap drugs.
Aging and the HIV-Infected Patient

• Epidemiology
• Natural History of HIV Infection in Older Patients
• Response to HAART in Older Patients
• Age and Comorbidities
• Management Issues in Older Patients
Proportion of HIV+ Individuals Aged 50+ in the US

FIGURE 1
Estimated percentage of the adult population (15 years and over) living with HIV which is aged 50 years or over, by region, 2012.

Source: UNAIDS.
Stage 3 (AIDS) Classifications and Deaths of Persons with HIV Infection Ever Classified as Stage 3 (AIDS), among Adults and Adolescents, 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.
Improving life expectancy in patients with HIV infection

**UK population**
- Women
- Men

**People with HIV by CD4 count (cells/mm³)**
- 200-350
- 100-199
- <100

**Life expectancy (years)**

**Age (years)**

20 25 30 35 40 45 50 55 60 65

Age is Not a Condom

Have Sex?

Age is not a condom.
Talk to your doctor about your sex life.
Get informed. Be safe. Get tested for HIV.
NYS 800-541-AIDS  NYC 800-TALK-HIV
800-541-2437  800-825-5448
Primary transmission in HIV

• Continued primary infection occurs in older people and contributes to the prevalence of infections in this age group.
• Older people are generally underserved by HIV prevention strategies
• Increasing divorce rates and greater longevity often provide opportunities for older individuals to have additional sexual partners.
• Availability of impotence treatments facilitates sexual activity among older people
• Biologic risk factors such as vaginal dryness (more common in older, postmenopausal women) may facilitate transmission
Behavioral Factors Contributing to HIV Transmission Among Older Adults

- Sexual activity
  - Unprotected sex
  - High-risk sexual partner(s)

- Drug and alcohol abuse
  - Associated high-risk sexual behavior
  - Needle sharing
  - Coexisting psychiatric illness

Risk Behaviors in HIV-Infected Adults Older Than 50 Years¹

- The Research on Older Adults with HIV Project surveyed HIV positive men and women in New York City about behaviors related to risk of HIV transmission
  - Positive behaviors: sex only with HIV-positive partners, condom use in 100% of sex acts
  - Negative behaviors: recent illicit drug use, drug use during sex

Sexual frequency among respondents aged 15 years and older in the last 30 days by age group, South Africa, 2005.

HIV and Older Adults: Obstacles to Prevention and Detection

Health Care System Obstacles

- Clinicians’ misconceptions about sexual behavior in older patients may prevent adequate assessment of HIV risk
  - In a US survey, 73% of respondents aged 57 to 64 years, 53% of those aged 65 to 74 years and 26% of those aged 75 to 85 years reported sexual activity within the past year
    - Only 38% of men and 22% of women reported having discussed sex with a physician since age 50
  - Time limits and social impediments may prevent clinicians from discussing sexual practices with older patients
  - Health care providers are less likely to discuss HIV-related risk and prevention information with older patients

Patient Obstacles

- Older people may not perceive themselves as being at risk
- Older heterosexuals may associate condoms with contraception, not disease prevention

Challenges in Diagnosing HIV in Older Patients

- Health care providers may attribute symptoms of HIV to “normal aging”\(^1\)
- HIV-associated neurocognitive impairment and other clinical manifestations misidentified as aging-associated conditions, such as\(^2\):
  - Stroke
  - Alzheimer’s disease
  - Viral pneumonia
  - Malnutrition
  - Occult malignancies

HIV Screening in Older Adults: Assessing the Benefits

- HCPs are less likely to offer HIV testing to older adults\(^1\)
- Nearly 1 in 5 HIV-positive people over the age of 50 have not been diagnosed with HIV\(^1\)
  - In many older people, HIV infection is diagnosed only when infection is advanced
- CDC recommendations: Routine screening specified in adults up to age 64\(^2\)
  - Persons aged 64 and over should be counseled to receive HIV testing if they have risk factors for HIV infection
  - Making testing routine in older patients can help open discussions between HCPs and patients
- Cost-effectiveness of screening in patients age 55 to 75 years compares favorably with that of other accepted health care interventions\(^3\)
  - In the US population, 1-time routine screening of patients age 55 to 64 years could save a total of more than 120,000 years of life among nearly 170,000 people

Issues in HIV care in older patients

• Older patients more likely than younger patients to present late for HIV diagnosis and care,
  – More likely to have been diagnosed with HIV infection while presenting with other illnesses,

• Physicians less likely to discuss HIV/AIDS and related risk factors with older patients

• Older patients have poorer routine access to HIV testing
Aging and the HIV-Infected Patient

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• Age and Comorbidities
• Management Issues in Older Patients
Age and natural history of HIV

- Immune system wanes with Age
- Older age was associated with faster progression to clinical AIDS and death (pre-HAART)
- Mixed data in HAART era
  - Some studies suggest association of age with poorer outcomes
  - Others show no effect with effective treatment
- Effect of age on Antiviral response also variable
  - Adherence may be greater in older patients
- Immune recovery may be less effective
  - Younger patients may have faster CD4 increases, although long-term data less clear
Older patients more likely to achieve HIV RNA <500 c/ml

- Kaiser Permanente study compared patients 40-49 and >50 to younger patients
- Older patients (espec >50) more likely to achieve VL <500, even when adjusting for co-morbidities
- Adherence was a major advantage for older patients

Silverberg et al, JAIDS 2007
Younger Age Associated with Better Immunologic Recovery

- Younger age, female sex, higher baseline viral load, and undetectable viral load on treatment associated with significantly greater CD4+ cell count increase
- Both naive CD4+ cell percentage and naive:memory CD4+ cell count ratio higher for younger (≤ 40 years) vs older (> 40 years) individuals \( (P < .0001 \) for both)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median Change in CD4+ Cell Count at Week 48, cells/mm³</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Age, yrs</td>
<td></td>
<td>.0005*</td>
</tr>
<tr>
<td>≤ 40</td>
<td>182</td>
<td></td>
</tr>
<tr>
<td>&gt; 40</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>.009*</td>
</tr>
<tr>
<td>Male</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>Baseline HIV-1 RNA (log_{10} copies/mL)</td>
<td>Coefficient estimate = 25</td>
<td>.0002*</td>
</tr>
</tbody>
</table>

\* Wilcoxon rank sum test.
\dagger Univariate regression.
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Changing patterns of the causes of death in the Swiss HIV Cohort

Causes of Death in Participants in the Swiss HIV Cohort Study in 3 different Time Periods, and in the Swiss Population in 2007

Years of Death of HIV+ Persons Versus Swiss Population
Interplay of time with morbidity

- Risk of “co-morbidities” increases as individuals get older
- HIV does not cause these illnesses
- However HIV and/or ART may increase the risk
HIV and Aging

- Cohort study of HIV and co-morbidities in Netherlands
  - 452 HIV- and 489 HIV+ persons
  - 12 yrs avg HIV infx, CD4 320
  - 30% prior AIDS, 91% on ART
  - Smoker: 24% HIV- vs. 32% HIV+
- >1 co-morbidity 60% HIV- vs. 71% HIV+
- Significantly more HTN, angina, MI, PVD, liver dx, CRF, and CA in HIV+

Comorbidities Occur at Similar Age but Increased Frequency in HIV-Positive Pts

- Subanalysis of Veteran’s Aging Cohort Study
  - Risk of age-related outcomes (MI, ESRD, non-AIDS defining cancers) by HIV status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Mean Difference in Age, Yrs</th>
<th>Risk aIRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>-0.04 (-0.62 to 0.54)</td>
<td>1.81 (1.49-2.20)</td>
</tr>
<tr>
<td>ESRD</td>
<td>-0.23 (-0.69 to 0.23)</td>
<td>1.43 (1.22-1.66)</td>
</tr>
<tr>
<td>HIV-associated cancers*</td>
<td>-0.57 (-0.93 to -0.21)</td>
<td>1.84 (1.62-2.09)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>-0.45 (-0.78 to -0.12)</td>
<td>0.95 (0.85-1.06)</td>
</tr>
</tbody>
</table>

*Included anal, Hodgkin’s lymphoma, liver, lung, oral cavity, and pharynx.

- Higher rate of MI, ESRD, HIV-associated cancers vs HIV-uninfected adults
- HIV-associated cancer diagnoses occurred ~ 7 mos earlier in HIV-infected adults vs HIV-uninfected adults

HIV Infection is an independent risk factor for atherosclerosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimated effect (mm)</th>
<th>Internal carotid</th>
<th>Common carotid</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td></td>
<td>0.15**</td>
<td>0.033*</td>
</tr>
<tr>
<td>Male†</td>
<td></td>
<td>0.13***</td>
<td>0.054***</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>0.17***</td>
<td>0.020**</td>
</tr>
<tr>
<td>Past smoker</td>
<td></td>
<td>0.09***</td>
<td>0.020***</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>0.12***</td>
<td>0.026***</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td></td>
<td><strong>0.16</strong>*</td>
<td><strong>0.073</strong>*</td>
</tr>
<tr>
<td>Systolic BP (per 10 mmHg)</td>
<td></td>
<td>0.05***</td>
<td>0.025***</td>
</tr>
<tr>
<td>Diastolic BP (per 10 mmHg)</td>
<td></td>
<td>-0.07***</td>
<td>-0.026***</td>
</tr>
<tr>
<td>Total cholesterol (per 10 mg/dL)</td>
<td></td>
<td>0.009***</td>
<td>0.004***</td>
</tr>
<tr>
<td>HDL (per 10 mg/dL)</td>
<td></td>
<td>-0.020***</td>
<td>-0.011***</td>
</tr>
</tbody>
</table>

*p<0.01, **p<0.001, ***p<0.0001; †There was a significant gender interaction

Grünfeld C et al. AIDS 2009
HIV and Heart disease

• Multiple studies show increased risk of MI and other ischemic CV events in HIV infected patients
  – Risk related to chronic inflammation
  – Risk related to ART – espec specific PIs and NRTIs

• However, most clinical events are seen in patients with other ‘standard’ risk factors
  – Emphasizes need for routine primary and secondary prevention
D:A:D: Recent and/or Cumulative Antiretroviral Exposure and Risk of MI

Lundgren JD, et al. CROI 2009. Abstract 44LB.

RR of recent* exposure
yes/no
95%CI
1.9
1.5
1.2
1.0
0.8
0.6
ZDV
ddI
ddC
d4T
3TC
ABC
TDF

RR of cumulative exposure/year
95%CI
1.2
1.13
1.0
1.1
0.9
1.9
1.5
1.2
1.0
0.8

*Current or within last 6 mos.
†Approximate test for heterogeneity: P = .02

Lundgren JD, et al. CROI 2009. Abstract 44LB.
New-onset diabetes increases with cumulative exposure to cART

- Prospective observational study of 33,389 patients with HIV

- Significant association between cumulative cART exposure and new-onset diabetes (relative rate per year 1.11, CI 95% 1.07–1.15 [p=0.0001])

- Older age, male sex, greater BMI, heterosexual or injection drug user, black African and other ethnicities, earlier calendar year, time-updated total cholesterol, HDL cholesterol and lipodystrophy were also associated with increased risk
BMD Changes in normal population

Relative influence on peak bone mass (men):
40% to 83% genetic
27% to 60% environmental

0.5%-1.0% reduction in bone volume/year

Risk Factors for Decreased BMD in HIV-infected Individuals

**Classic**
- Smoking
- Family history
- Increasing age
- Alcohol

**Secondary**
- Decreased physical activity
- Female sex
- Chronic diseases – weight loss
- Vitamin D Deficiency
- Hypogonadism
- Renal dysfunction
- Malnutrition/low BMI
- Medications (e.g. corticosteroids, anticonvulsants, anticoagulants)

Bone Mineral Density

**HIV**
- Direct effect on bone cells
- Immune activation

**ART**
- Direct effect on Bone cells
- Indirect effect - renal
- Immune reconstitution
Potential effects of HIV on BMD over time

Women
- Decreased total bone mass
- Increased rate of bone demineralization

Men
- Peak

Change in Bone Volume (%) vs. Age (Years)
Fracture rates higher in HIV-infected patients in HOPS Cohort vs. general population

- Fracture rate for HOPS participants (n=5826) compared with inpatient and outpatient adults aged 25–54 yrs
- HOPS participants more likely to experience fracture at fragility sites vs controls (P≤0.05) for wrist and vertebra in men and vertebra and femoral neck in women
- BMD, vitamin D data not available to assess contribution to fracture risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 47 vs &lt; 35 yrs</td>
<td>1.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Nadir CD4+ cell count &lt; 200 cells/mm³ (vs ≥ 350 cells/mm³)</td>
<td>1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Hepatitis C coinfection</td>
<td>1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>1.5</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Multivariable model obtained by backward stepwise elimination included nadir CD4+ cell count, hepatitis C, diabetes, and substance abuse, adjusted for sex and age

Other co-morbidities of Age

• Cancer
  – Cancer increasingly prevalent
  – Unclear if risk is truly increased

• Renal Disease
  – Renal function slowly declines with age (espec > 70)
  – Certain HIV drugs can affect CrCl
  – Long-term effect on renal function unknown

• Neurocognitive dysfunction
  – AIDS-associated dementia has dramatically declined
  – Mild HIV-associated cognitive impairment has not??
  – Long-term implications uncertain
Predictors of Cancer Incidence Following ART

- CNICS observational cohort study (N = 11,485) of US individuals who initiated first HIV regimen containing ≥ 3 ARVs between 1996 and 2011

- Incidence of KS in first 6 mos following ART was highest in pts with CD4+ count < 200 cells/mm³, then similar regardless of CD4+ cell count thereafter

- Incidence of all cancers decreased with changes in CD4+ cell count following ART initiation
  - In subanalysis, no impact of CD4+ cell count on incidence of non-AIDS–defining, nonvirus-related cancers

Cancer Risk and ART

- D:A:D participants followed prospectively
- Poisson regression models assessed associations between the incidence of cancer and cumulative (per year) use of cART
- Longer exposure to cART was associated with a lower risk of cancer overall (adjusted rate ratio: 0.98/year; 95%CI: 0.97-1.00; p=0.009).

MACS: Frailty Phenotype in HIV-Positive MSMs 50 to 70 Years of Age

- Prospective cohort of MSMs (2009-2010)
  - 2850 person-visits
  - HIV positive on HAART (n=1451)
  - HIV negative (n=92)
- Ages 50 to 70 years
  - Frailty phenotype more common in HIV-positive men versus HIV-negative men
    - May be effect of HIV infection, HAART, or both
- Further longitudinal studies are needed

Non-AIDS events are more common in HIV disease

Increased Comorbidities

- Low CD4 T-cell nadir
- Co-infections (hepatitis, CMV EBV & HPV)
- Cumulative cART exposure
- Ageing
- Persistent inflammation
- Lifestyle (smoking etc)

Aging and the Immune System

• Normal aging is associated with a progressive dysregulation of the immune system
  – Reduction in naïve CD4 cells
  – Reduced proliferative potential of T cells
  – Expansion of CD28⁻ CD8⁺ T cells
  – Increased production of IL-6
  – Altered monocyte function

• These changes also occur during HIV infection

• Is aging with HIV a double hit to the immune system?

Untreated HIV infection

- Loss of immuno-regulatory cells
- Thymic dysfunction and loss of regenerative potential
- Co-Infections
- HIV replication
- Loss of gut mucosal integrity and microbial translocation

HAART

- Defects in T cell regenerative potential
- Loss of immuno-regulatory function
- CMV and other copathogen levels
- Microbial translocation

Chronic inflammation / Immune activation

- Increased cell turnover and lymphoid fibrosis
- Increased TF expression and clotting
- Cytokine secretion (e.g., IL-6, TNFL)

- Immune exhaustion
- CAD/stroke, thrombosis
- “Inflam-Aging (atherosclerosis, osteoporosis)

- Malignancy

<table>
<thead>
<tr>
<th>Country</th>
<th>Life Expectancy (Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow (deprived area)</td>
<td>54</td>
</tr>
<tr>
<td>Australian Indigenous</td>
<td>59</td>
</tr>
<tr>
<td>India</td>
<td>61</td>
</tr>
<tr>
<td>Philippines</td>
<td>65</td>
</tr>
<tr>
<td>Lithuania</td>
<td>66</td>
</tr>
<tr>
<td>US</td>
<td>75</td>
</tr>
<tr>
<td>UK</td>
<td>76</td>
</tr>
<tr>
<td>Australian average</td>
<td>77</td>
</tr>
<tr>
<td>Glasgow (affluent area)</td>
<td>82</td>
</tr>
</tbody>
</table>

Lifestyle Factors

• Tobacco use
  – Increases the risk for cancers, CVD, bone loss, neurocognitive function loss
  – Highly prevalent in HIV populations
    • > 40% HIV cohorts vs 19% US population\(^1\)
      – High rates in European cohorts
      – Concern in low income countries
  – Smoking was associated with reduced response to HAART\(^2\)

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Research Priorities in HIV ageing

• Identify and test interventions to reduce the burden of chronic disease in treated HIV infection
  – Interventions to reduce inflammation, immune activation
  – To treat co-infections
  – To address end organ disease specific risk factors
  – Evaluate treatments for NCDs in HIV treated patients
Complementary, non ARV-containing, therapy: Treatment of immune dysfunction and of chronic inflammation

- Examples of strategies developed to minimize immune dysfunction and/or chronic inflammation in patients with controlled HIV replication include:
  - r-hIL-7, Maraviroc, rifaximin
  - Drugs with anti-inflammatory activity (aspirin, statins, etc.)
  - Inhibition of the TOx pathway
  - Other approaches (telomerase-based, anti-fibrosis, etc.)
Management issues in older HIV+ve patient

• **Need for regular screening and health maintenance**
  - Fasting lipids and glucose, renal function, bone disease
  - Cancer screening as would be performed in general population
  - www.europeanaidsclinicalssociety.org

• **Antiretroviral therapy**
  - Earlier initiation
  - Choice of therapy to avoid metabolic and other toxicities

• **Management of Complications and co-morbidities**
  - Prevention if possible
  - Manage other reversible factors - smoking
  - Polypharmacy - Awareness of drug-drug interactions
  - Recognition that HIV+ve patients may not respond as well
    • E.g. lipid-lowering therapy
The best thing you can do is give up smoking, drinking and fried food.

What's the second best?
Infrastructure Development

- Integrate screening and treatment of NCDs in HIV treatment programs
- HIV programs can serve as a model for managing other chronic illnesses in low and middle income settings
- Lessons learned from HIV scale-up can be applied to expansion of care for NCD in low income settings
Do not regret growing older. It is a privilege denied to many.

Author Unknown