Co-Morbidities

Dr. Mark Nelson

Chelsea & Westminster Hospital
Executive Committee of the British HIV Association (BHIVA)
“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the
Medical Assistance & Medical Education (MAME) Programs
THE GRAYING OF AIDS stories from an aging epidemic
UK CHIC – Life expectancy

Life expectancy by CD4 count compared with UK population

- LE at exact age 20 years:
  - 1996-2008
  - UK women: 61.6 yrs
  - UK men: 57.8 yrs
  - HIV+ women: 50.2 yrs
  - HIV+ men: 39.5 yrs

- 1996-99 HIV+:
  - 30.0 yrs

- 2006-08 HIV+:
  - 45.8 yrs

- Start triple ART post 2000
  - CD4 200-350: 53.4 yrs
  - CD4 100-199: 41.0 yrs
  - CD4 <100: 37.9 yrs
Countries with population aged 65 years or older exceeding 4% of the total population, Africa, 1999-2009
# Declining Fertility Rates, 1997-2009, Africa

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*Source: African Development Bank Group, Statistics Department, Social and Economic Databases*
South Africa
2000
Population: 44,846,000

South Africa
2030
Population: 58,095,000
In 2040, the number of persons over 50 years of age living with HIV is expected to be 9 million.
Ageing
Age, HIV and the Immune System

**HIV**
- CD4 lymphopaenia
- Inverted CD4:CD8 ratio
- Reduced thymic output
- Reduced naïve cells
- Shorter telomeres of CD8 cells

**Age**
- CD4 lymphopaenia
- Inverted CD4:CD8 ratio
- Reduced thymic output
- Reduced naïve cells
- Shorter telomeres of CD8 cells
What is *old*?

- > 45?
- > 50?
- > 55?
- > 60?
- > 65?
- > 75?
What is *old*?

- > 45?
- > 50?
- > 55?
- > 60?
- > 65?
- > 75?
- Older than me?
How old?

69

72
Projected Proportion of those 50+ Years of Age* Living With HIV in United States 2001-2017

US VA in 2003

As of 2008:
• San Francisco
• NY City

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Why is the HIV-infected Population Ageing?

- Decreased mortality since the introduction of HAART
- Decreased incidence of HAART failure through improved treatment options
- Improved survival benefits of HIV care
- Decreased incidence of AIDS cases and death, increased number of people living with AIDS
Why Older Persons Acquire STIs (including HIV)

• Lack of awareness of HIV risk factors
• Newly single
• Increased ease in finding new partners
• Menopause
  – No pregnancy risk, little condom use
  – Increased vaginal mucosal trauma/risk
• Unprotected intercourse: less condom use?
• Viagra: increased sex among elderly
• Lack of HIV prevention services for older persons
• Healthcare providers don’t consider seniors at risk
  – “Don’t ask, don’t tell”
• Older adults often sexually active
• Prevalence of sexual activity declined with age
• Women less likely than men to report sexual activity
• 14% men took medication to aid sexual activity
• Poor health associated with decreased sexual activity, sexual problems

HIV prevention targets the young
The Graying of HIV

HIV doesn’t care how old you are...

Think you’re too old for HIV?

Think again.

You’re never too old to think of health and Social Security. We need you to stay well.

More than 2 out of 3 people living with HIV in NYC are over 40, and 1 in 3 are over age 50.

Some say HIV’s only for young folks.

You’re dead too young to believe that nonsense.

Get tested for HIV.

Stop HIV/AIDS
Age won’t protect you from AIDS

More than 8,000 New Yorkers over 50 years old have been diagnosed with AIDS.

To prevent HIV infection:
- Use a condom every time you have sex.
- Don’t shoot drugs. Sharing works can spread AIDS.

It’s not how old you are... it’s what you do that matters.

HIV prevention is a lifelong job.

To learn more, call 1-800-541-AIDS

New York State Health Department
Persons 50+ more often present with symptomatic HIV disease

![Bar chart showing prevalence of CDC stages across different age groups.](chart.png)
Late Diagnosis and Age

• Over-representation of older persons in late presenting patients\textsuperscript{1,2}
• Physicians less likely to ask about high-risk behaviour\textsuperscript{3}
• Physicians less likely to suspect HIV\textsuperscript{4}
• Older people less likely to admit high-risk sexual activity\textsuperscript{3}
• Likely greater difficulties with differential diagnosis\textsuperscript{5}

\textsuperscript{1}Sullivan AK, et al. BMJ 2005;330;1301–02;
\textsuperscript{3}Gebo KA. Drugs Aging 2006;23(11): 897–913;
\textsuperscript{4}el-Sadr W, Gettler J. Arch Intern Med 1995;155:184–6;
\textsuperscript{5}Personal communication, M. Fisher, August 2007
...and thus more often with a lower CD4 cell count
### (a) Risk (%) at age 25

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### (a) Risk (%) at age 25

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<th>150</th>
<th>200</th>
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### (d) Risk (%) at age 55

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</table>
Emerging co-morbidities in HIV


Renal dysfunction
30% of HIV+ patients have abnormal kidney function

Reduced bone mineral density
Increased prevalence of osteoporosis or osteopenia in spine, hip or forearm: 63% of HIV+ patients

Neurocognitive dysfunction
Neurological impairment present in ≥50% HIV+ patients

Cardiovascular disease
75% increase in risk of acute MI

Cancer
Increased risk of non-AIDS-defining cancers e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal and renal

Frailty
Increased frailty phenotype if HIV infected 3-14x; Associated with CD4 count
Emerging co-morbidities in HIV

- **Renal dysfunction**
  - 30% of HIV+ patients have abnormal kidney function

- **Reduced bone mineral density**
  - Increased prevalence: 63% of HIV+ patients

- **Neurocognitive dysfunction**
  - Increased frailty phenotype if HIV infected

- **Cardiovascular disease**
  - 75% increase in risk

- **Cancer**
  - Increased risk of non-AIDS-defining cancers e.g. anal, vaginal, liver, lung, melanoma, leukemia, colorectal

- **Frailty**
  - Increased frailty phenotype if HIV infected

References:
Areas for potential preventions
T cell activation declines during long-term HAART, but remains abnormal, even after many years of viral suppression.
Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

HIV-associated fat
Metabolic syndrome

CMV
Excess pathogens

Loss of regulatory cells

HIV production
HIV replication

Co-morbidities
Aging

Microbial translocation

Excess pathogens

HIV production
HIV replication
AMI Rates in HIV Positive and HIV Negative

Cohorts (HIV+ =3851, HIV- =1,044,589) were identified in the Research Patient Data Registry. The primary outcome was AMI.

Increased Risk of Cirrhosis and ESLD due to HIV/HCV Coinfection

Histologic Cirrhosis

- Makris (UK)
- Soto (Spain)
- Pol (France)
- Benhamou (France)
- Combined

Relative Risk

- HCV Only
- HIV/HCV

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<td>Pol (France)</td>
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<td>Benhamou (France)</td>
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<tr>
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Decompensated Liver Disease

- Eyster (USA)
- Telfer (UK)
- Makris (UK)
- Lesens (Canada)
- Combined

Relative Risk

- HCV Only
- HIV/HCV

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Renal Disease Increases With Age in the General Population

BMD Decreases With Age

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

0.5% to 1.0% reduction in bone volume/year

Age and BMD are Independent Risk Factors for Hip Fracture

Kanis et al OI 2002; 13:527
## Prevalence of Reduced BMD Higher in HIV+ than HIV- Subjects

<table>
<thead>
<tr>
<th>Publication</th>
<th>Number of patients</th>
<th>Overall prevalence of reduced BMD, %</th>
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<tr>
<td></td>
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<td>HIV–</td>
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<tr>
<td>Amiel et al 2004</td>
<td>148</td>
<td>81</td>
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<td>Brown et al 2004</td>
<td>51</td>
<td>22</td>
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<td>Bruera et al 2003</td>
<td>111</td>
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<td>Dolan et al 2004</td>
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<td>Huang et al 2002</td>
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<td>80</td>
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<td>Loiseau-Peres et al 2002</td>
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<td>47</td>
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<td>Madeddu et al 2004</td>
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<td>Tebas et al 2000</td>
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<td>Teichman et al 2003</td>
<td>50</td>
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<td>Yin et al 2005</td>
<td>31</td>
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Derived from Brown TT & Qaqish RB. AIDS 2006; 20:2165-2174
Fracture prevalence in women /100 persons

Healthcare Registry study
8,525 HIV-infected patients
2,208,792 non HIV-infected patients
Fracture rates in women demonstrated

Overall comparison p=0.002

Fractures are More Common in HIV

Triant VA et al, JCEM 2008;93:3499-3504
# Age (yrs) at onset of cancer of AIDS patients and uninfected individuals

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<tr>
<th>Cancer</th>
<th>AIDS</th>
<th>GP</th>
<th>Observed difference (Years)</th>
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<td>69</td>
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<tr>
<td>Anal</td>
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<td>Larynx</td>
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<td>Lung</td>
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<td>-21</td>
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<td>Testicular</td>
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<tr>
<td>Myeloma</td>
<td>47</td>
<td>70</td>
<td>-23</td>
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</table>

Shiels et al, Ann Intern Med 2010  
A Justice, CROI 2012
Areas for potential preventions

Traditional risk factors

+
LIPIDS

DIET

Lipids

HYPTERTENSION
## Analytic Epidemiology II. Classification of Risk Factors

<table>
<thead>
<tr>
<th>Major modifiable risk factors</th>
<th>Other modifiable risk factors</th>
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<td>- High blood pressure</td>
<td>- Low socioeconomic status</td>
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<tr>
<td>- Abnormal blood lipids</td>
<td>- Mental ill health (depression)</td>
</tr>
<tr>
<td>- Tobacco use</td>
<td>- Psychosocial stress</td>
</tr>
<tr>
<td>- Physical inactivity</td>
<td>- Heavy alcohol use</td>
</tr>
<tr>
<td>- Obesity</td>
<td>- Use of certain medication</td>
</tr>
<tr>
<td>- Unhealthy diet</td>
<td>- Lipoprotein(a)</td>
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<td>- Diabetes mellitus</td>
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<th>Non-modifiable risk factors</th>
<th>&quot;Novel” risk factors</th>
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<tr>
<td>- Age</td>
<td>- Excess homocysteine in blood</td>
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<td>- Heredity or family history</td>
<td>- Inflammatory markers (C-reactive protein)</td>
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<tr>
<td>- Gender</td>
<td>- Abnormal blood coagulation</td>
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<tr>
<td>- Ethnicity or race</td>
<td>(elevated blood levels of fibrinogen)</td>
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Hypertension
Smoking

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<th>Percentage</th>
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<td>Adult Males</td>
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<td>Adult Females</td>
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<tr>
<td>Youth Males</td>
<td>29.3%</td>
</tr>
<tr>
<td>Youth Females</td>
<td>20.1%</td>
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</table>

Choose Life!
Be smart, don’t start

Cansa
Toll-free 0800 22 66 22
www.cansa.org.za
Myocardial Infarction

Adjusted for: age, sex, cohort, calendar year, antiretroviral treatment, family history of CVD, diabetes, and time-updated lipids and blood pressure assessments.
Global Prevalence of Obesity in Adult Females

With examples of the top 5 Countries in each Region (based on data available at the time)

European Region
- Turkey (Urban) 29.4%
- Scotland 28.1%
- England 26.1%
- Israel 25.7%
- Greece 25.6%

With the limited data available, prevalence's are not age standardised. Self reported surveys (marked with dots) may underestimate true prevalence.

Americas Region
- Panama 36%
- Paraguay 36%
- USA 35%
- Mexico 35%
- Barbados 31%

Eastern Mediterranean
- Kuwait 48%
- Qatar 45%
- Saudi Arabia 44%
- Palestine 43%
- Egypt 40%

Africa
- Seychelles 34.2%
- South Africa 27.4%
- Lesotho 23.7%
- Algeria 21.4%
- Mauritius 20%

South East Asia & Pacific Region
- Tonga 70%
- Samoa 63%
- Nauru 61%
- Niue 46%
- French Polynesia 44

© World Obesity Federation, 2012
Diabetes, Stroke, Sleep Apnea, Hypertension, Hyperinsulinemia, Liver Malfunction, Gall Bladder Failure, Hypertrophic Cardiomyopathy, Heart Disease, Abdominal Hernia, Bowel Cancer, Varicose Veins.
diabetes
GLOBAL PROJECTIONS FOR THE DIABETES EPIDEMIC: 2003-2025 (millions)

World
2003 = 189 million
2025 = 324 million
*Increase 72%*
Areas for potential preventions

Traditional risk factors

ART
Areas for potential preventions

Traditional risk factors

ART
Early treatment makes sense
Early treatment makes sense
Low CD4 Predicts Risk of AIDS and non-AIDS Events (DAD)

See also Weber Arch Int Med 2006, CASCADE AIDS 08, Baker AIDS 08, d'Armino Monforte AIDS 08
CHARTER: prospective observational study (N = 1525)

Risk of HIV-associated neurocognitive disorders associated with lower CD4+ nadir, but not current CD4+ cell count

- Association remained significant after adjusting for other predictors: HIV-1 RNA, age, sex, race, duration of infection

Attributable Risk Factors for Cardiovascular Disease

- Age ≥ 42 years (Median)
- Hypertension
- Tobacco Smoking
- CD4 < 500 cells/mm³
- LDL/nonHDL > goal
- HDL < 40 male or < 50 female
- Male gender
- Diabetes

Attributable risk (%)

49.2
34.4
26.7
25.6
21.5
20.9
13.1
2.4
Areas for potential preventions

Traditional risk factors

Choice of ART

ART
## Association of Toxicity with Age

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Younger age</th>
<th>Older age</th>
<th>No association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoatrophy</td>
<td></td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Lipohypertrophy</td>
<td></td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI disturbance</td>
<td></td>
<td></td>
<td>(√)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS toxicity</td>
<td></td>
<td></td>
<td>(√)</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td></td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

*Studies do not generally consider both age at starting and current age*
NRTIs and risk of MI: recent* and cumulative exposure

* recent use = current or within the last 6 months **: not shown (low number of patients currently on ddC)

#PYFU: 138,109 74,407 29,676 95,320 152,009 53,300 39,157

#MI: 523 331 148 405 554 221 139

* recent use = current or within the last 6 months **: not shown (low number of patients currently on ddC)

J Lundgren & DAD Study Group et al CROI 2009 LB abstr 44
FDA Meta-Analysis

No Association Between ABC and MI

- 26 RCTs involving ABC
  - 5028 subjects on ABC, 4840 controls
  - Average 1.62 person/years of F/U
- Overall events/subjects: 28/5628 ABC vs. 22/4840 controls (OR 1.02, 95%CI 0.56, 1.84)
- Authors conclude that the findings ‘raise significant uncertainty about the likelihood of an ABC-MI risk association’

Ding X, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 808.
Hyperlipidaemia
Exposure to Specific Protease Inhibitors and OF Risk: HAART Era

MV Model 1: Controlling for CKD, age, race, tobacco use, diabetes and BMI;
MV Model 2: Controlling for Model 1 variables + concomitant exposure to other ARVs.
Tenofovir Alafenamide (TAF)
Next Generation Prodrug of Tenofovir-increased liver, lymph concentration

TAF 10mg in E/C/F/TAF has PK comparable to TAF 25mg alone:
- COBI ↑ TAF levels ~2.2-fold

Relative to TDF 300 mg, TAF 25 mg has:
- Increased anti-HIV-1 activity in Phase 1
- Increased intracellular TFV-DP levels by ~7-fold
- Decreased circulating plasma TFV levels by ~90%
- Lower levels of TFV in kidney and bone tissue expected

1P Ruane, et al. CROI 2012; Paper # 103
2S Ramanathan, et al. IWCPHT 2012; Abstract O_13
Comorbidity in Relation to Age

THAB0205 Schouten
Comorbidity and ageing in HIV-1 infection: the AGEnIV Cohort Study
Comorbidity and ageing in HIV-1 infection: the AGE IV Cohort Study
Comparison of Daily Pill Burden in HIV+ and HIV- Subjects According to Age

Pill burden including ARV:
- < 40: 0.00
- 41-50: 4.00
- 51-60: 0.27
- > 60: 0.93

Pill burden excluding ARV:
- < 40: 0.00
- 41-50: 0.27
- 51-60: 0.88
- > 60: 0.93

all p<0.001

p=0.027
p=0.035
p<0.001
p<0.001

Pills/day

0 10 20 30 40

0 5 10 15 20 25

< 40 41-50 51-60 > 60

HIV- HIV+

HIV- HIV+
The Therapeutic Classes for Potential DDIs

Who manages the older HIV patient?

- General Physician with an interest in HIV?
  - But …. Generalists a dying breed

- Gerontologist with an interest in HIV?
  - But …. Age criteria may be difficult

- Concerted effort to re-engage with primary care?

- Joint clinics and co-management within secondary care?
Lucas Cranach: The Fountain of Youth (1546)
The Extremes: Maximum Life Span 120 years

Genesis 6: ... yet his days shall be an hundred and twenty years ... (King James Bible)
Do not regret growing older. It is a privilege denied to many.

Author Unknown
Thank you

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