Dispelling the myths: HIV, ageing and the changing causes of morbidity

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Disclosures

I have received funding for membership of Data Safety and Monitoring Boards, Advisory Boards, Speaker Panels and for preparation of educational materials from the following:

- Gilead Sciences
- ViiV Healthcare
- Janssen-Cilag
Age of UK CHIC participants

UK CHIC dataset (S Jose, C Sabin)
Future projections

Future projections

2010
Median age: 44
28% >50 years

Future projections

2010
Median age: 44
28% >50 years

2030
Median age: 57
73% >50 years

Reported prevalence of common co-morbidities

- Obesity: 11%
- Osteoporosis: 5%
- Depression +/- anxiety: 24%
- Renal impairment: 15%
- Cardiovascular disease: 11%
- Type 2 diabetes: 11%
- Hyperlipidaemia: 31%
- Hypertension: 31%
Age vs. number of common co-morbidities

Ekong N. BHIVA 2018
Mean number of comorbidities:
HIV-positive: 1.3
HIV-negative: 1.0

Raised rates of:
Hypertension
MI
Peripheral arterial disease
Impaired renal function
Beliefs about ageing

- Literature abundant with studies reporting that HIV causes ‘premature ageing’ or that co-morbidities occur at an earlier age in PLWH
Beliefs about ageing

- Literature abundant with studies reporting that HIV causes ‘premature ageing’ or that co-morbidities occur at an earlier age in PLWH
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Beliefs about ageing

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- Search continues for biological mechanisms that drive this apparent increased risk
  - Residual inflammation / ‘Inflammageing’?
  - Altered gut microbiota?
  - Mitochondrial dysfunction?
  - Immunosenescence?
Beliefs about ageing

- Literature abundant with studies reporting that HIV causes ‘premature ageing’ or that co-morbidities occur at an earlier age in PLWH

In our rush to establish mechanisms, have we forgotten the basic rules of epidemiology?

- Residual inflammation? 'Inflammageing'?
- Altered gut microbiota?
- Mitochondrial dysfunction?
- Immunosenescence?
Confounding

- PLWH have very different characteristics to the general population, including increased risk of:
  - sexually transmitted infections
  - viral coinfections
  - smoking
  - recreational drug use, etc.

- Could these other factors confound associations with co-morbidities and/or bio-markers?
Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome

HIV

Co-morbidity
Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome.
Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome.

Diagram:
- Drinking wine
- Peanuts and cheese
- Weight gain
- Question mark
Co-morbidities are often multi-factorial

Confounding

- PLWH have very different characteristics to the general population, including increased risk of:
  - sexually transmitted infections
  - viral coinfections

Does HIV really cause premature ageing – or is this simply a result of unmeasured confounding?

- Could these other factors confound associations with co-morbidities and/or bio-markers?
What is being said?

PWH are increasingly dying of cancer...

It’s all due to residual inflammation / immunosenescence caused by HIV....

PWH develop comorbidities 10-15 years younger than people without HIV

HIV is causing accelerated ageing
What is being said?

PWH are increasingly dying of cancer...
Causes of death

D:A:D Merger 14 dataset

Proportion of deaths

- 1999/2000
- 2001/2002
- 2003/2004
- 2005/2006
- 2007/2008
- 2009/2011

AIDS | Liver | CVD | Cancer | Other

D:A:D Merger 14 dataset
## Deaths from cancer - Mortalité surveys

<table>
<thead>
<tr>
<th></th>
<th>Mortalité 2000</th>
<th>Mortalité 2005</th>
<th>Mortalité 2010</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reported deaths</strong></td>
<td>964</td>
<td>1042</td>
<td>728</td>
<td></td>
</tr>
<tr>
<td>Cancer-related causes of death, n (%)</td>
<td>269 (27.9%)</td>
<td>344 (33.0%)</td>
<td>262 (36.0%)</td>
<td>0.003</td>
</tr>
<tr>
<td>AIDS-related, n (%)</td>
<td>149 (15.5%)</td>
<td>134 (12.9%)</td>
<td>66 (9.3%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Non Hodgkin lymphoma</td>
<td>105 (10.9%)</td>
<td>103 (9.9%)</td>
<td>53 (7.3%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.122</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>40 (4.1%)</td>
<td>25 (2.4%)</td>
<td>11 (1.5%)</td>
<td>0.084</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>4 (0.4%)</td>
<td>6 (0.6%)</td>
<td>4 (0.5%)</td>
<td>0.848</td>
</tr>
<tr>
<td>Hepatitis-related, n (%)</td>
<td>17 (1.8%)</td>
<td>37 (3.6%)</td>
<td>31 (4.3%)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>8 (0.8%)</td>
<td>27 (2.6%)</td>
<td>19 (2.6%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>7 (0.7%)</td>
<td>6 (0.6%)</td>
<td>10 (1.4%)</td>
<td>0.279</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>2 (0.2%)</td>
<td>4 (0.4%)</td>
<td>2 (0.3%)</td>
<td>0.732</td>
</tr>
<tr>
<td><strong>Non AIDS/non hepatitis related, n (%)</strong></td>
<td>103 (10.7%)</td>
<td>173 (16.6%)</td>
<td>163 (22.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory</td>
<td>50 (5.2%)</td>
<td>65 (6.2%)</td>
<td>78 (10.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Lung</td>
<td>44 (4.6%)</td>
<td>53 (5.1%)</td>
<td>61 (8.4%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Ear, nose and throat</td>
<td>6 (0.6%)</td>
<td>12 (1.2%)</td>
<td>17 (2.3%)</td>
<td>0.056</td>
</tr>
<tr>
<td>Digestive</td>
<td>6 (0.6%)</td>
<td>13 (1.2%)</td>
<td>10 (1.4%)</td>
<td>0.342</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (0.3%)</td>
<td>11 (1.1%)</td>
<td>7 (1.0%)</td>
<td>0.282</td>
</tr>
<tr>
<td>Anal</td>
<td>6 (0.6%)</td>
<td>11 (1.1%)</td>
<td>13 (1.8%)</td>
<td>0.073</td>
</tr>
<tr>
<td>Skin</td>
<td>2 (0.2%)</td>
<td>10 (1.0%)</td>
<td>3 (0.4%)</td>
<td>0.065</td>
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<tr>
<td>Hodgkin’s lymphoma</td>
<td>12 (1.2%)</td>
<td>9 (0.9%)</td>
<td>8 (1.1%)</td>
<td>0.473</td>
</tr>
<tr>
<td>Other hematopoesies</td>
<td>5 (0.5%)</td>
<td>8 (0.8%)</td>
<td>7 (1.0%)</td>
<td>0.602</td>
</tr>
<tr>
<td>Breast</td>
<td>3 (0.3%)</td>
<td>7 (0.7%)</td>
<td>5 (0.7%)</td>
<td>0.647</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>4 (0.4%)</td>
<td>6 (0.6%)</td>
<td>2 (0.3%)</td>
<td>0.530</td>
</tr>
<tr>
<td>Other and unknown&lt;sup&gt;f&lt;/sup&gt;</td>
<td>12 (1.2%)</td>
<td>33 (3.2%)</td>
<td>27 (3.7%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Multiple&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>3 (0.4%)</td>
<td>-</td>
</tr>
</tbody>
</table>

## Deaths from cancer - Mortalité surveys

### Significant increases in proportions of deaths from:
- All cancer-related causes
- Respiratory cancers
- Lung cancers
- Ear, nose & throat cancers
- Anal cancer
- Other hemopathies
- Other/unknown cancers

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<td></td>
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</table>

Removing a cause of morbidity

Deaths from HIV causes
Deaths from non-HIV causes

40/70 (57.1%) deaths due to non-HIV causes
Removing a cause of morbidity

Deaths from HIV causes

Deaths from non-HIV causes

40/55 (72.7%) deaths due to non-HIV causes
Removing a cause of morbidity

Deaths from HIV causes
Deaths from non-HIV causes

45/60 (75.0%) deaths due to non-HIV causes
Age-standardised mortality rates

Non-AIDS mortality after HIV diagnosis

Non-AIDS mortality after HIV diagnosis

Standardised mortality ratio (SMR)

- All-cause mortality
- Non-AIDS deaths
- Non-AIDS infections
- Non-AIDS cancers
- CVD and stroke
- Liver disease
- Accident
- Suicide
- Substance misuse
- Other cancers

SMR=1

In 1st year  After 1st year

What is being said?

HIV is causing accelerated ageing. It's all due to residual inflammation.
PWH are increasingly dying of cancer. PWH develop comorbidities 10-15 years younger than people without HIV.
Several studies have examined the risk of lung cancer in the HIV-infected population (Table 1). Approximately one-half of these studies used a case-control design, whereas the other half used a longitudinal cohort approach. Of note, the average age at lung cancer diagnosis in this population was between 38 and 57 years. In contrast, the average age at lung cancer diagnosis in the general population is approximately 70 years. On a discouraging note, most of the cases were discovered in stages III or IV, and the median survival of these patients was measured in months from the time of diagnosis (Table 1).
In comparison, reported rates of falls and incontinence from the general population of community dwelling adults aged 65 years and older are 30% and 22% (for older men), respectively. Estimates of frailty depend on the definition, but using the Fried phenotype definition, estimates range from 7% (original Fried article) to 10%–14%. These data suggest that HIV-infected adults may experience similar rates of geriatric syndromes at relatively younger ages and emphasize the critical need for appropriate HIV-negative comparison groups to put these findings into further context.
Age at onset of co-morbidity

Median age at diagnosis = 67.5 years

Age at onset of co-morbidity

Median age at diagnosis = 57.5 years

### Age at onset of co-morbidity – VACS VC

<table>
<thead>
<tr>
<th>Event</th>
<th>No. events</th>
<th>Mean age diagnosis</th>
<th>Crude diff.</th>
<th>Adjusted diff.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-ve</td>
<td>308</td>
<td>56.0</td>
<td>0.2</td>
<td>-0.11</td>
<td>-0.59, +0.37</td>
</tr>
<tr>
<td>HIV+ve</td>
<td>291</td>
<td>56.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>End-stage renal disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-ve</td>
<td>688</td>
<td>59.4</td>
<td>-3.4</td>
<td>-0.46</td>
<td>-0.86, -0.07</td>
</tr>
<tr>
<td>HIV+ve</td>
<td>447</td>
<td>56.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NADC</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HIV-ve</td>
<td>2708</td>
<td>58.9</td>
<td>-1.1</td>
<td>-0.10</td>
<td>-0.30, 0.10</td>
</tr>
<tr>
<td>HIV+ve</td>
<td>1471</td>
<td>57.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV-associated cancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-ve</td>
<td>826</td>
<td>58.6</td>
<td>-2.0</td>
<td>-0.22</td>
<td>-0.52, 0.08</td>
</tr>
<tr>
<td>HIV+ve</td>
<td>732</td>
<td>56.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome.

Diagram:
- HIV
- Age
- Co-morbidity
- Arrow from HIV to Age
- Arrow from Age to Co-morbidity
- Arrow from HIV to Co-morbidity
HIV is causing accelerated ageing.
Accelerated or accentuated ageing?
Accelerated or accentuated ageing?

a) No impact of HIV on ageing

Accelerated or accentuated ageing?

Accelerated or accentuated ageing?

a) No impact of HIV on aging

b) Accelerated aging

c) Accentuated aging

Accelerated or accentuated ageing?

a) No impact of HIV on aging

b) Accelerated aging

c) Accentuated aging

d) Accelerated AND accentuated aging

Why is this important?

- Underlying aetiology and/or mechanisms differ
- Statistical approach to test for each will differ - need to consider the ‘slope’ of the association with age, as well as absolute risk of event
- Studies that claim to demonstrate ‘accelerated’ ageing, often provide little evidence to support the statement
- Difficult to differentiate between the models with a cross-sectional study
The Co-morBidity in Relation to Aids (COBRA) Collaboration

POPPY: ‘Pharmacokinetic and Clinical Observations in People over Fifty’

COBRA: clinical studies run as sub-studies of POPPY and AGEhIV:
- Collecting the extra information required
- Whilst utilising the existing infrastructure
Neuroimaging results - COBRA

Cognitive testing results - COBRA

Bio-marker age advancement - COBRA

What is being said?

It’s all due to residual inflammation/immunosenescence caused by HIV....
People living with HIV (PLWH) who are treated with effective highly active antiretroviral therapy (HAART) have a similar life expectancy to the general population. Moreover, an increasing proportion of new HIV diagnoses are made in people older than 50 y. The number of older HIV infected patients is thus constantly growing and it is expected that by 2030 around 70% of PLWH will be more than 50 y old. On the other hand, HIV infection itself is responsible for accelerated immunosenescence, a progressive decline of immune system function in both the adaptive and the innate arm, which impairs the ability of an individual to respond to infections and to give rise to long-term immunity; furthermore, older patients tend to have a worse immunological response to HAART.
CD4 and CD8 T cell senescence

CD4 and CD8 T cell senescence

CD4 and CD8 T cell senescence

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive</th>
<th>HIV-negative</th>
<th>Blood-bank donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Age (yrs), median (IQR)</td>
<td>58 (53-63)</td>
<td>59 (53-64)</td>
<td>58 (52-65)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>90</td>
<td>92.5</td>
<td>51.4</td>
</tr>
<tr>
<td>African origin, %</td>
<td>12.5</td>
<td>2.5</td>
<td>n/a</td>
</tr>
<tr>
<td>MSM, %</td>
<td>80.0</td>
<td>75.0</td>
<td>n/a</td>
</tr>
<tr>
<td>CMV+ve, %</td>
<td>95.0</td>
<td>77.5</td>
<td>22.9</td>
</tr>
<tr>
<td>Anti-CMV IgG</td>
<td>50.9 (23.5-108.6)</td>
<td>23.9 (13.8-87.8)</td>
<td>11.3 (10.2-16.8)</td>
</tr>
<tr>
<td>High avidity anti-CMV IgG</td>
<td>30.7 (13.0-57.0)</td>
<td>13.3 (8.2-39.7)</td>
<td>10.7 (10.0-13.2)</td>
</tr>
</tbody>
</table>
CD4 and CD8 T cell senescence

Bias due to confounding

- Occurs when a spurious association arises (or is hidden) due to a failure to fully adjust for factors related to both the risk factor and outcome
Inflammation markers - SMART

PLWH aged 45-76 years vs. participants in Multi-Ethnic Study of Atherosclerosis (MESA) study

Neuhaus J, et al. *J Infect Dis* 2010; **201**: 1788-1795

* Fully adjusted model includes adjustment for age, race, sex, BMI, smoking, TC/HDL ratio, diabetes, lipid-lowering drugs, anti-hypertensive drugs
Mortality – FRAM cohort

Tien PC, et al. *JAIDS* 2010; *55*: 316-322
Risk of death – SMART

Risk of death – SMART

Inflammation markers - SMART

Subset of SMART participants on ART with HIV RNA ≤400 copies/ml

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Participants 33–44 years of age</th>
<th>Participants 45–76 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Median level (IQR)</td>
</tr>
<tr>
<td>hsCRP, µg/mL</td>
<td>140</td>
<td>2.13 (0.77–5.20)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>139</td>
<td>1.89 (1.15–3.42)</td>
</tr>
<tr>
<td>D-dimer, µg/mL</td>
<td>140</td>
<td>0.21 (0.15–0.46)</td>
</tr>
<tr>
<td>Cystatin C, mg/dL</td>
<td>86</td>
<td>0.90 (0.78–0.97)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are the median level and (interquartile range [IQR]). CARDIA, Coronary Artery Development in Young Adults; Diff., difference; MESA, Multi-Ethnic Study of Atherosclerosis; NA, not available; SMART, Strategies for Management of Anti-Retroviral Therapy.
## Smoking - AGE<sub>hIV</sub>

<table>
<thead>
<tr>
<th></th>
<th>hsCRP</th>
<th></th>
<th>D-dimer</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>All participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.04 (0.80, 1.35)</td>
<td>0.79</td>
<td>0.92 (0.70, 1.22)</td>
<td>0.57</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.57 (1.16, 2.12)</td>
<td>0.004</td>
<td>1.36 (1.00, 1.85)</td>
<td>0.05</td>
</tr>
<tr>
<td>HIV-positive status</td>
<td>1.44 (1.13, 1.83)</td>
<td>0.003</td>
<td>0.64 (0.50, 0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smokers only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes smoked per day (/10)</td>
<td>1.49 (1.18, 1.87)</td>
<td>0.001</td>
<td>1.30 (1.04, 1.63)</td>
<td>0.02</td>
</tr>
<tr>
<td>HIV-positive status</td>
<td>1.24 (0.78, 1.97)</td>
<td>0.37</td>
<td>0.52 (0.32, 0.84)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Smoking

Fig. 1. Excess mortality and loss of life years. Age-specific excess mortality rates (a) and numbers of life years lost (b) in association with smoking (black bars/line) and HIV-related factors (grey bars/line) among HIV-infected men. PY, person-years.

Lifestyle factors

- In addition to smoking, several other demographic and lifestyle/behavioural factors are prevalent in PWH
  - Obesity/low exercise levels
  - Recreational drug use
  - Alcohol use
- Each is associated with raised inflammatory markers
- Each is associated with morbidity/mortality risk
- What role do these play?
Summary

- Population of people with HIV is aging:
  - Increased incidence and spectrum of age-related co-morbidities
  - When people die, increasingly dying of non-AIDS causes

- Partly to be expected, given the age and lifestyle/demographic factors that are prevalent

- Statements about HIV and ageing are often based on poor interpretation of data and/or lack of adjustment for confounders
Summary (2)

- Whilst there may be some effect of HIV, model appears to be one of accentuated rather than accelerated ageing.
- Need to focus our efforts on understanding the reasons for this – with a view to identifying appropriate interventions.
- But should also continue to focus on other modifiable risk factors, as in the general population.
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