Ageing, comorbidities and HIV

Professor Alan Winston
St. Mary’s Hospital London
October 2016
Alan Winston Disclosure

Alan Winston has received honoraria or research grants from or been a consultant or investigator in clinical trials sponsored by Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Roche, Pfizer and ViiV Healthcare.
Healthy ageing

THE DETERMINANTS OF ACTIVE AGEING

- HIV infection
- Gender
- Economic determinants
- Health and social services
- Social determinants
- Behavioural determinants
- Physical environment
- Personal determinants
- Culture
- Life long ART

ACTIVE AGEING

Imperial College London
Concerns:

What we hear about ageing and HIV:

- Non infectious comorbidities are more prevalent and occur at younger ages in HIV-infected cohorts.
- The presence of non infectious comorbidities is due to ‘inflammaging’.
- Antiretroviral toxicities differ in older PLWH versus younger subjects.
- HIV causes premature ageing.
- Ageing changes the spectrum of HIV disease.
- HIV causes accelerated ageing.
Overview

1. Age of PLWH
2. Non AIDS Events
3. HIV Management
Age of our cohorts
Epidemiology

New diagnoses in over 50s:

1. This age group is the least likely to practice safe sex\(^1,^2\)
2. Late-life changes in the reproductive tract and immune system may enhance their susceptibility to HIV acquisition\(^1\)
3. Physicians are less likely to recommend HIV testing to older patients\(^2\)\(^-^4\)
4. Asymptomatic, older, HIV-infected individuals are less likely to seek out testing and medical care\(^2,^5\)
5. Symptomatic, older, HIV-infected individuals are more likely to attribute symptoms to other illnesses or to ageing\(^6\)

## Overview

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age of PLWH</td>
</tr>
<tr>
<td>2</td>
<td>Non AIDS Events</td>
</tr>
<tr>
<td>3</td>
<td>HIV Management</td>
</tr>
<tr>
<td>4</td>
<td>Summary and best practice management.</td>
</tr>
</tbody>
</table>
European HIV and ageing cohorts:

**Status:**
- Fully recruited and now in follow up phase
- 1300 subjects
  - 700 PLWH over 50
  - 300 controls over 50
  - 350 PLWH under 50

**Status:**
- Fully recruited and follow up phase well established
- 1200 subjects
  - 600 PLWH over 45
  - 550 controls over 45
Prevalence of co-morbidities

• Cohort study of HIV and comorbidities in The Netherlands (N=452 HIV-negative and 489 HIV-positive persons)
• Significantly more hypertension, angina, MI, liver disease, renal failure and cancer in HIV-infected subjects

Clin Infect Dis. 2014 Dec 15;59(12):1787-97
<table>
<thead>
<tr>
<th>Disease Category</th>
<th>PLWH&gt;50</th>
<th>PLWH&lt;50</th>
<th>HIV-ve &gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI, angina, narrowed blood vessels, TIA, CABG.</td>
<td>25% (76)</td>
<td>10% (14)</td>
<td>18% (18)</td>
</tr>
<tr>
<td><em>P</em>=0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson’s, vertigo, loss of consciousness, epilepsy, encephalitis.</td>
<td>11% (35)</td>
<td>8% (11)</td>
<td>5% (5)</td>
</tr>
<tr>
<td><em>P</em>=0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma, bronchitis, emphysema or COPD.</td>
<td>42% (127)</td>
<td>26% (35)</td>
<td>29% (29)</td>
</tr>
<tr>
<td><em>P</em>=0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Which co-morbidities?

Cancer
- Mammography
- Cervical PAP
- Anoscopy and PAP (MSM)
- Ultrasound and alpha-fetoprotein
- Others

Renal disease
- Risk assessment
- eGFR (aMDRD)
- Urine dipstick analysis

Liver disease
- Risk assessment
- ALT/AST, ALP
- Bilirubin

Pulmonary disease
CXR and spirometry

Bone disease
- Bone profile; calcium, PO4, ALP
- Risk assessment (FRAX in persons >40 years)
Vitamin D
- 25(OH) vitamin D

Glucose
- Oral glucose tolerance test/HbA1c

Body composition
- BMI

Haematology
- FBC
- Haemoglobinopathies
- G6PD

Neurocognitive impairment
- Screening questionnaire
Depression
- Questionnaire
Cardiovascular disease
- Risk assessment (Framingham score) in all men >40 and women >50 years without CVD
- ECG prior to ARVs in certain patients

Hypertension
- Blood pressure

Lipids
- TC, HDL-c, LDL-c and TG

EACS guideline version 7.0, October 2013; Available at:
Comorbidity by age group

US Veterans Ageing Cohort Study Virtual Cohort of 82,459 participants (HIV+ and HIV-) investigating the risk of acute myocardial infarction from 2003–2009

AMI, acute myocardial infarction; CI, confidence interval; CVD, cardiovascular disease

* Within age group P<0.05

Impact of co-morbidities

Cumulative survival for HIV-infected patients starting HAART and persons from the general population

Italian cohort

HAND prevalence by calendar year, age and level of education

CROI 2015, abstract 63
Underlying pathogenesis

Accelerated ageing phenotype has been hypothesised
# Lifestyle factors

<table>
<thead>
<tr>
<th></th>
<th>PLWH&gt;50</th>
<th>PLWH&lt;50</th>
<th>HIV-ve &gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current (%)</td>
<td>23.9</td>
<td>26.5</td>
<td>21.4</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>36.9</td>
<td>27.2</td>
<td>37.8</td>
</tr>
<tr>
<td>Never (%)</td>
<td>38.6</td>
<td>42.7</td>
<td>39.8</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current consumption (%)</td>
<td>77.8</td>
<td>73.5</td>
<td>84.7</td>
</tr>
<tr>
<td>Previous consumption only (%)</td>
<td>13.1</td>
<td>11.0</td>
<td>7.1</td>
</tr>
<tr>
<td>Units per week (if current or previous; median (range))</td>
<td>7 (0, 75)</td>
<td>3 (0, 45)</td>
<td>10 (0, 63)</td>
</tr>
<tr>
<td><strong>Recreational drugs in past 6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (%)</td>
<td>27.5</td>
<td>26.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Marijuana (%) *</td>
<td>14.7</td>
<td>12.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Methadone (%) *</td>
<td>2.6</td>
<td>10.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Mephedrone (%) *</td>
<td>9.2</td>
<td>13.2</td>
<td>5.1</td>
</tr>
<tr>
<td>Amphetamine (%) *</td>
<td>5.2</td>
<td>7.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Crystal Meth (%) *</td>
<td>3.3</td>
<td>8.1</td>
<td>5.1</td>
</tr>
</tbody>
</table>
Immunological markers
EACS Online Library. Kootstra N. Oct 22, 2015; 114943

<table>
<thead>
<tr>
<th></th>
<th>HIV+ median (IQR)</th>
<th>HIV- median (IQR)</th>
<th>P HIV+/HI V-</th>
<th>BBD median (IQR)</th>
<th>P HIV+/BBD</th>
<th>P HIV-/BBD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T cell activation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+CD38-HLA-DR+</td>
<td>2.6 (1.7-4.0)</td>
<td>1.6 (1.0-2.6)</td>
<td><strong>.001</strong></td>
<td>0.8 (0.6-0.8)</td>
<td>&lt;.001</td>
<td>.001</td>
</tr>
<tr>
<td>CD8+CD38-HLA-DR+</td>
<td>7.5 (4.5-10.8)</td>
<td>5.6 (3.3-9.7)</td>
<td>.100</td>
<td>0.4 (0.3-0.9)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>T cell senescence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+57+</td>
<td>12.1 (6.3-18.4)</td>
<td>12.2 (7.0-19.3)</td>
<td>.736</td>
<td>4.1 (3.7-4.5)</td>
<td><strong>.002</strong></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD4+CD27-CD28-</td>
<td>4.8 (1.1-8.5)</td>
<td>6.0 (1.5-12.3)</td>
<td>.485</td>
<td>0.1 (0.1-1.3)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD8+57+</td>
<td>50.6 (36.8-57.2)</td>
<td>45.1 (35.6-57.4)</td>
<td>.773</td>
<td>30.2 (19.0-31.9)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD8+CD27-CD28-</td>
<td>38.1 (24.8-46.4)</td>
<td>36.4 (22.6-50.1)</td>
<td>.802</td>
<td>16.8 (7.3-28.5)</td>
<td><strong>.002</strong></td>
<td>.014</td>
</tr>
<tr>
<td><strong>T cell exhaustion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+PD-1+</td>
<td>6.8 (5.2-10.7)</td>
<td>6.2 (3.4-8.4)</td>
<td>.106</td>
<td>3.3 (2.9-3.9)</td>
<td>&lt;.001</td>
<td>.010</td>
</tr>
<tr>
<td>CD8+PD-1+</td>
<td>19.6 (14.1-23.9)</td>
<td>16.1 (11.6-24.0)</td>
<td>.138</td>
<td>3.4 (2.8-7.5)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Conclusions:** No evidence for increased immunological ageing is found in the HIV+ compared to matched uninfected controls. Immunological ageing is increased in the HIV+ group as well as the uninfected controls when compared to blood bank donors. This illustrates the crucial importance of using appropriate controls for these studies.
## Overview

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age of PLWH</td>
</tr>
<tr>
<td>2</td>
<td>Non AIDS Events</td>
</tr>
<tr>
<td>3</td>
<td>HIV Management</td>
</tr>
<tr>
<td>4</td>
<td>Summary and best practice management.</td>
</tr>
</tbody>
</table>
Age related CD4 count gain

Gras L, et al. JAIDS 2007;45:183–92
Antiretroviral pharmacology and ageing

- Simulations at fixed age points illustrated the change in PK profiles with increasing age
- RTV AUC and patient age were significantly associated with DRV clearance

Darunavir 95% prediction intervals determined from simulations of 1000 patients aged:

(A) 25 years old
(B) 55 years old
(C) 75 years old

Dickinson L et al. 10th International Congress on Drug Therapy in HIV Infection, Glasgow 2010. Poster 184
Antiretroviral pharmacology and ageing

Adapted from Cevik M, et al EACS, Belgrade; 2011
Non ARV medication use

![Graph showing the use of different types of medications and dietary supplements among PLWH (>50), PLWH (<50), and HIV-ve (>50) with p-values: p=0.0003, p=0.06, p=0.27, p=0.56.](image)
Polypharmacy

## Overview

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age of PLWH</td>
</tr>
<tr>
<td>2</td>
<td>Non AIDS Events</td>
</tr>
<tr>
<td>3</td>
<td>HIV Management</td>
</tr>
<tr>
<td>4</td>
<td>Summary and best practice management.</td>
</tr>
</tbody>
</table>
EACS guidelines

1. All patients should be screened at regular intervals for:
   – Risk of CVD in next 10 years
   – Diabetes and dyslipidaemia
   – Neurocognitive disorders and depression
   – Cancers
   – Osteopenia/osteoporosis
   – Kidney and liver disease
   – Sexual dysfunction

2. Treatment regimens should be selected based on the patient’s risk factors and agreed among multidisciplinary teams where appropriate to avoid further comorbidities and/or drug–drug interactions

Interventional studies

REPRIEVE
Randomized Trial to Prevent Vascular Events in HIV

Participants

The REPRIEVE (A5332) trial is the first-ever large scale clinical trial to test a strategy to prevent cardiovascular disease among people living with HIV. Participants in this trial will be contributing meaningfully to the pursuit of new medical knowledge.

1. What is the purpose of the REPRIEVE trial?

The goal of the REPRIEVE trial will test a strategy to reduce the risk of cardiovascular disease—including heart attack and stroke—among people living with HIV. Previous studies have shown that HIV-infected individuals are at higher risk for cardiovascular disease than individuals without HIV.
### The future

Are we likely to see changes in prevalence of comorbidities in older PLWH?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reduction in risk factor</th>
<th>Ongoing or increasing in risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of HIV</td>
<td>Duration untreated HIV</td>
<td>Longer duration antiretroviral therapy</td>
</tr>
<tr>
<td></td>
<td>Reduced AIDS</td>
<td></td>
</tr>
<tr>
<td>Type of ART</td>
<td>Historical infective and highly toxic antiretroviral therapy</td>
<td>Unknown long term side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ageing</td>
<td></td>
<td>Increasing age and likely increase in number of co-morbidities</td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td>Recreational drug use</td>
</tr>
</tbody>
</table>

Thank you