Introduction on Comorbidities in HIV-Infected Individuals

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Agenda

• Co-morbidities: HIV+ vs HIV-
• Mortality in HIV+ patients
• Effects of ageing on HIV
• Effects of HIV on ageing
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cART is expected to improve CD4 cells and to change the natural history of HIV infection.

Hospital Clinic data, 2013

Courtesy Jose M Gatell
HIV-infected patients have a higher incidence of myocardial infarction

* Adjusted for age, gender, race, hypertension, diabetes and dyslipidaemia. Proportion of patients with hypertension, diabetes and dyslipidaemia significantly higher in HIV-positive vs HIV-negative cohort.

Greater rate of fractures in HIV-infected patients vs uninfected individuals

Population-based study
8,525 HIV-infected patients
2,208,792 non-HIV-infected patients

- All: p<0.0001
- Vertebral: P<0.0001
- Hip: p=0.001
- Wrist: p<0.0001

Triant VA et al. J Clin Endocrinol Metab 2008
Liver and kidney comorbidities more common in HIV+ patients

Liver Disease

Renal Disease
Neurocognitive impairment remains highly prevalent despite of cART

Heaton R et al. J Neurovirol 2011
Non-AIDS–defining cancer rates higher in HIV+ patients vs general population

<table>
<thead>
<tr>
<th>Cancer Type, Observed Rate per 100,000 Person-Years (95% CI)</th>
<th>ASD/HOPS (157,819 Person-Years)</th>
<th>SEER (334,802,121 Person-Years)</th>
<th>SRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal</td>
<td>51.4 (40.8-63.9)</td>
<td>1.5 (1.4-1.5)</td>
<td>42.9 (34.1-53.3)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>33.9 (18.0-57.9)</td>
<td>3.2 (3.2-3.3)</td>
<td>21.0 (11.2-35.9)</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>51.4 (40.9-63.9)</td>
<td>3.3 (3.3-3.4)</td>
<td>14.7 (11.6-18.2)</td>
</tr>
<tr>
<td>Liver</td>
<td>31.7 (23.5-41.8)</td>
<td>5.3 (5.2-5.4)</td>
<td>7.7 (5.7-10.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>88.8 (74.7-104.8)</td>
<td>67.5 (67.2-67.7)</td>
<td>3.3 (2.8-3.9)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>24.7 (17.6-33.8)</td>
<td>18.4 (18.3-18.6)</td>
<td>2.6 (1.9-3.6)</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>33.0 (24.6-43.3)</td>
<td>16.1 (16.0-16.2)</td>
<td>2.6 (1.9-3.4)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>15.2 (9.8-22.7)</td>
<td>12.2 (12.1-12.3)</td>
<td>2.5 (1.6-3.8)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>47.0 (36.9-59.0)</td>
<td>52.0 (51.7-52.2)</td>
<td>2.3 (1.8-2.9)</td>
</tr>
<tr>
<td>Renal</td>
<td>14.0 (8.8-21.1)</td>
<td>13.0 (12.8-13.1)</td>
<td>1.8 (1.1-2.7)</td>
</tr>
<tr>
<td>Prostate</td>
<td>32.7 (23.3-44.7)</td>
<td>173.5 (172.9-174.1)</td>
<td>0.6 (0.4-08)</td>
</tr>
</tbody>
</table>

ASD, Adult and Adolescent Spectrum of Disease Project; HOPS, HIV Outpatient Study; SEER, Surveillance, Epidemiology, and End Results, 1992–2003; *SRR, standardized rate ratio calculated as ASD/HOPS to SEER populations.
Comorbidities increase with age, but more common in HIV patients

Significantly more hypertension, angina, MI, peripheral vascular disease, liver dysfunction, chronic renal failure and cancer in people living with HIV

Comorbidities more common in HIV+ than in HIV-, but they do not appear earlier in HIV+. 

Results – Myocardial Infarction

**Premature aging?**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th># of events</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>56,456</td>
<td>286</td>
<td>55.3</td>
</tr>
<tr>
<td>HIV+</td>
<td>27,988</td>
<td>231</td>
<td>55.3</td>
</tr>
</tbody>
</table>

Adjusted mean difference in age: 
-0.04 (-0.62, 0.54) years

No difference in age at diagnosis by HIV status

**Greater risk?**

<table>
<thead>
<tr>
<th></th>
<th>IR per 1,000 py</th>
<th>95% CI</th>
<th>aIRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>1.31</td>
<td>(1.17, 1.47)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>2.18</td>
<td>(1.92, 2.48)</td>
<td>1.81</td>
<td>(1.49, 2.20)</td>
</tr>
</tbody>
</table>

An 81% increase in the rate in HIV+ compared to HIV-

Linear regression models to estimate the mean difference in age at diagnosis and Poisson regression models to estimate incidence rate ratios (aIRR) were adjusted for age, race, sex, body mass index, alcohol use, cigarette smoking, hepatitis C infection, anemia, diabetes, hyperlipidemia, lipid-lowering medications, hypertension, anti-hypertension medications, and statin use.

Freiberg MS et al. JAMA Intern Med 2013
Agenda

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All-cause (both AIDS and non-AIDS) mortality has decreased with cART

D:A:D Study

3,802 deaths in 49,734 HIV+ adults followed for 304,695 PY:
12.5 per 1,000 person-years

* Adjusted for: age, gender, ethnicity, mode of HIV acquisition (fixed) and HBV, HCV, smoking, diabetes, hypertension, HIV RNA, BMI, CD4 count (time-updated)

Mortality rates due to non-AIDS causes of death are higher for HIV+ persons

Health Protection Agency (England and Wales)  
Retrospective analysis 1997-2010

- 3,814 deaths in 70,914 HIV+ adults followed for 319,082 PY
- 50.2% died of non-AIDS related causes

<table>
<thead>
<tr>
<th>Crude mortality rate, 2010</th>
<th>Per 1,000 population aged 15-59</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population (all cause)</td>
<td>1.6</td>
</tr>
<tr>
<td>HIV-infected population (Non-AIDS cause of death)</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Death in HIV-infected patients on cART is due to prevalent diseases of aging

SMART / ESPRIT: causes of death in N=3,280 HIV-infected persons receiving suppressive cART with CD+ counts ≥ 350 cells/mm3

- CVD or Sudden death: 31%
- Cancer*: 19%
- Unnatural**: 18%
- Non-AIDS Infection: 10%
- Liver disease: 8%
- AIDS: 3%
- Unknown: 2%

*Non-AIDS malignancy.
**Accident, suicide or violent death.
Survival trends in HIV+ patients after widespread use of cART

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

* Viral load >49 copies/mL, CD4 <200 cells/µL, AIDS-defining disease **as defined in the Charlson comorbidity index (CCI);
† Drug abuse reported as route of HIV transmission

Obel N et al. PLoS ONE 2011
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Aging shares immunological and clinical manifestations with HIV infection

**Immunologic characteristics**
- Naïve T cells
- T cell diversity
- Memory cells
- Differentiated, senescent CD8+ T cells (e.g., CD28-CD57+)
- Telomere length
- CD16+ monocytes
- Monocyte function

**Functional immune defects**
- Replicative capacity
- Tumour surveillance
- Pathogen protection
- Chronic inflammation

**Clinical manifestations**
- Vaccine responses
- Infections
- Age-associated non-communicable diseases (e.g., CVD, non-AIDS cancers, bone/kidney disease, frailty, neurocognitive decline)

Courtesy Suzanne Crowe
Increasing proportion of older HIV+ persons

Netherlands ATHENA Cohort 1986-2010

% of patients

60 => 50-60 40-50 30-40 30 <

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%


Courtesy Peter Reiss
Older diagnosed patients usually have a more advanced HIV infection stage

COHERE Study: Baseline Virologic and Immunologic Profile by Age

Baseline HIV RNA

Baseline CD4 Count

COHERE Study Group. AIDS 2008
Older diagnosed patients have less immune recovery with effective ART

COHERE Study: Response by Baseline Age

Achieving CD4 Count >200 Cells/mm³ at 12 Months

<table>
<thead>
<tr>
<th>Age at Baseline (years)</th>
<th>13-17</th>
<th>18-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-54</th>
<th>55-59</th>
<th>≥60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>85.6%</td>
<td>86.7%</td>
<td>80.5%</td>
<td>76.3%</td>
<td>75.2%</td>
<td>73.9%</td>
<td>74.7%</td>
</tr>
</tbody>
</table>

P<0.0001 for trend

New AIDS Event At 12 Months

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<th>Age at Baseline (years)</th>
<th>13-17</th>
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<th>50-54</th>
<th>55-59</th>
<th>≥60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>4.8%</td>
<td>5.2%</td>
<td>7.0%</td>
<td>8.5%</td>
<td>9.6%</td>
<td>9.3%</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

P<0.0001 for trend

COHERE Study Group. AIDS 2008
This happens despite older patients show better virological responses

Unadjusted (blue) and adjusted (purple) relative hazards for confirmed virological and immunological responses after 1 year of ART in the different age groups.
Estimates are adjusted for year of starting cART, pre-cART CD4 and VL, AIDS, gender, origin and initial cART regimen,

COHERE 2006
Older patients have better adherence to ART.
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Smoking is twice more common in HIV+ patients than in the general population.

![Bar chart showing smoking prevalence in Spain, Australia, and USA for HIV+ individuals and the overall population.](image-url)
Smoking and aging interaction: More damage in older HIV+ than in older HIV-
Low CD4 cells are associated with AIDS and non-AIDS conditions

EuroSIDA Study

AIDS defining
Non-AIDS defining

Incidence per 1000 PYFU (95% CI)

Current CD4 count (/mm$^3$)

≤50 51-100 101-200 201-350 351-500 501-700 >700

Mocroft A et al. J Acquir Immune Defic Syndr 2010
The longer exposure to HIV&ART the higher rate and number of comorbidities

HIV Aging (HIV+ for ≥20.6 years)
HIV Aged (HIV+ for <11.3 years)
HIV negative

Adjusted for age, gender, race, and geographic area
HIV infects arterial wall and promotes atherosclerosis

- MCP-1, VCAM-1, ICAM-1
- Endotelin-1
- LDL-ox
- Foam cell
- CD4+ T
- Nef
- Tat
- Monocyte

HIV infects microglia and promotes neuronal injury

1. Activated astrocytes increase permeability of BBB and promote migration of HIV-infected monocytes.

2. HIV-infected monocytes cross the BBB and become perivascular macrophages.

3. Activated perivascular macrophages and microglia replicate HIV-1 and express neurotoxic molecules (e.g., gp120).

4. Neurotoxic molecules activate astrocytes.

5. Increase in brain concentration of glutamate and neurotoxins results in neuronal injury.

6. HIV-associated neural injury leads to AF impairment.

Courtesy Scott Letendre
Damaged gut lymphoid tissue in HIV+ patients promotes microbial translocation

Chronic endotoxemia in elderly and HIV+, not reversed by cART

HIV-

HIV+

Colon lamina propria, acute/early HIV
Red=CD4+ T cells

ART restores gut lymphoid tissue but cannot normalise it

Peripheral blood

Mucosa

Percentage of activated CD4+ T cells

AEI, untreated (N=32)

AEI, treated up to 1 year (N=7)

AEI, treated 1–3 years (N=7)

AEI, treated 3–7 years (N=8)

HIV uninfected (N=18)

AEI = acute/early HIV infected
Markers of inflammation may persist at elevated levels despite ART

N=115 HIV-infected patients
N=30 HIV-uninfected matched controls

* \( P<0.001 \) vs HIV uninfected

** \( P<0.001 \) vs HIV infected, untreated

Plasma concentration of hsCRP (ng/mL)

HIV uninfected

HIV infected, untreated

HIV infected, 3 months of ART

HIV infected, 12 months of ART

Kristoffersen US et al. HIV Med 2009
ART decreases immune activation but levels remain still high.
Switching from PI/r to raltegravir leads to lower plasma markers of inflammation

Cardiovascular biomarkers: median (95% CI) difference of percent change from baseline to W48, RAL (N = 119) minus PI/r (N = 114)

Markers of inflammation
- hsCRP
- MCP-1
- OPG
- IL-6
- IL-10
- TNF-a
- ICAM-1
- VCAM-1
- E-selectin
- P-selectin
- Adiponectin
- Insulin
- D-dimer

Endothelial dysfunction

Insulin resistance

Hyper-coagulability

Martinez E et al. AIDS 2012
Switching from enfuvirtide to raltegravir is also associated with ↓ CV biomarkers

EASIER Study

Silva E et al. J Infect Dis 2013
Statins decrease inflammation and immune activation in HIV+ patients on cART

Funderburg NT et al. J Acquir Immune Defic 2015
Summary

• The HIV infected population is ageing.
• Ageing affects the natural history of HIV, and HIV may affect the natural ageing process.
• Co-morbidities are increasingly apparent and their therapies may lead to DDIs with ART.
• Specific ART adverse effects may negatively affect co-morbidities.
• Prevention and management of co-morbidities must be an important part of routine clinical care for HIV adults.