The Aging Patient

Eugenia Negredo
Fundació Lluita contra la Sida
Hospital Germans Trias i Pujol
Barcelona

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## Disclosure

<table>
<thead>
<tr>
<th>Consulting, advisory boards</th>
<th>Research support</th>
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<tbody>
<tr>
<td>Gilead Sciences</td>
<td>ViiV Health</td>
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<td>Janssen Therapeutics</td>
<td>Merck</td>
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Ageing or aging is the process of becoming older.

In humans, ageing represents the accumulation of changes in a human being over time, encompassing physical, psychological and social changes.
Aging process

➢ The aging process starts at 30 years of age (the moment of maximum vitality)

➢ The probability of death increases x2 every 8 years.

➢ Ageing is among the greatest known risk factor for most human diseases.

➢ The roughly 150,000 people who die each day across the globe, about two thirds die from age-related causes.
Epidemiology
“Elderly people” in the world

2015, 2030, 2050

Número de personas de 60+ años
2015: 901m (12.3% de la población total mundial)
2030: 1,402m (16.5% de la población total mundial)
2050: 2,092m (21.5% de la población total mundial)

Aging in general population

Spain

Puente: Instituto Nacional de Estadística. Elaboración: R. Luque Revuelto
Aging in general population (Spain)

- **Progressive aging of the individual:** Life expectancy at birth:
  - men: 75.2 years of age (40 in 1900)
  - women: 82.4 years of age (42 in 1900)

- 3/5 (60%) of the elderly population are women.
  - 65 - 69 years old: 86 men / 100 women
  - >90 years: 38 men / 100 women

- **Higher male mortality:**
  1- Professional reasons
  2- Unhealthy habits (alcohol, tobacco, drugs...)
  3- Social customs (difference in years of marriage)
Aging in general population (Spain)

At 75 years of age, there is 1 widower in every 4 widows.

**Men:**
- Married
- Living at home.

**Women:**
- Widows.
- Living alone or in care centres.
Mechanisms of aging
Factors influencing aging

**INHERITANCE:**
- Main factor
- Longevity is inherited in 90%

**GENDER:** in most animals, longer longevity for females

**EXTERNAL FACTORS:**
- Diet
- Physical exercise
- Infections, radiation, drugs, ....
Aging

Loss of the function of cells and tissues

Clinical consequences

At the cellular level
- Alterations in redox cellular balance,
- Telomere shortening,
- Changes in the nuclear structure, in DNA,
- The accumulation of senescent cells in the tissues
- An accentuated inflammatory response

Aging of the organism
- Frailty
- Sarcopenia
- Increased susceptibility to infections
- Cancers
- Cardiovascular events
- Renal impairment
- Neurocognitive impairment
- Bone fractures …….
Cellular aging

Old cells + Senescent cells

- Accumulation of damage in the DNA,
  Reduction of recruitment of 53BP1 to repair the damage
- Increase of chromosomal reorganizations
- Telomere shortening

Lose the ability to proliferate

Senescence

- Ability to proliferate

Young cells

Chronic infections
  - Radiation
  - Chemotherapy
  - Drugs
  - Toxics ...

Senescent cells

Therefore, not all old cells are senescent, nor all senescent cells are old
Senescence

Lose the ability to proliferate +
Secretory phenotype
(Senescence-associated secretory phenotype, SASP)

Suppression of tumor development

Promotes the removal of senescent cells through the immune system to repair the tissues

Increasingly inefficient with age

Paradoxically...promotes the onset of tumors and aging
At the Immune System level

**Immune system**
- Innate immune system (dendritic cells, natural killers cells and monocytes)
- Adaptive immune system (B and T cells)

**Clinical and subclinical infections / exposure to antigens (inhalant allergens, food, etc.)**
- Greater susceptibility to infections, neoplasms and immunological diseases

**Differentiation process / Consecutive cell divisions**
- Shortens telomeres
  - **Immunosenescence**

**Lose the ability to proliferate**
- +
- **Secretory phenotype**
  - (Senescence-associated secretory phenotype, SASP)

**Inflamm-Aging**

As with other organs, the immune system is affected by aging, reaching an immunesenescent and proinflammatory state
HIV population
Accelerated and accentuated aging?

☐ YES ?  ☐ NO ?

Inflammation
Inflammation
Markers of inflammation may persist at elevated levels despite ART.

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

Plasma concentration of hsCRP (ng/mL)

HIV uninfected
HIV infected, untreated
HIV infected, 3 months of ART
HIV infected, 12 months of ART

* $P<0.001$ vs HIV uninfected
** $P<0.001$ vs HIV infected, untreated

Adapted from Kristoffersen US, et al. 15th CROI 2008; Poster 953.
Inflammation and HIV

HIV production and replication
ART toxicity, lipodystrophy, and traditional risk factors
Cytomegalovirus and other copathogens
Loss of regulatory cells

Inflammation
- ↑ Monocyte activation
- ↑ T-cell activation
- ↑ Endothelium adhesion
- Dyslipidaemia
- Hypercoagulation

Comorbidities
(cardiovascular disease, cancer, kidney disease, liver disease, osteopenia/osteoporosis, neurocognitive disease)

Microbial translocation

Deeks, Lewin, Havlir; Lancet 2013
Aging and HIV

- Heart disease
- Kidney disease
- Liver disease
- Osteoporosis
- Cancer
- Cognitive declines

Adapted from Vance DE. Am J Nurs 2010
Inflammation: Consequences

1. Triggers of monocyte release from bone marrow:
   - LPS or microbial translocation
   - MΦ death in tissues
   - Systemic immune activation

2. Markers/Signalling:
   - Viral proteins
   - Immune complexes
   - LPS/sCD14/TLR signalling
   - Scavenger receptors
   - Tissue factor, coagulation factors
   - Acute phase proteins

3. Correlates of neuronal damage:
   - Activated infected MΦ and microglia
   - M1 (MAC387+)/M2 (CD163+) ratio
   - Monocyte/MΦ accumulation
   - PV cuffs

4. Pathways of cardiac pathogenesis:
   - Foam cell development
   - MΦ accumulation
   - Reduced reverse cholesterol transport
   - Thickening of intima-media

5. sCD163:
   - Plasma marker of HIV activity
   - Plasma marker of nonclassified cardiac plaques
   - Plasma marker of neurocognitive impairment (HAND)
   - Immune suppressive?
   - Long 1/2 life
   - Elevated in MΦ-mediated diseases
Basic research
Genomic instability

Mitochondrial dysfunction

Payne et al. Nature genetics 2011

Telomere length

Oxidative stress

Substantial oxidative stress occurs during HIV infection.

Pommier et al. Virology 1997

Payne et al. Nature genetics 2011

Pommier et al. Virology 1997
Clinical research
This is a cross-sectional cohort study designed to compare two cohorts:

- Over50 Cohort is an ongoing prospective cohort that includes all those HIV-infected people attended in our Unit, aged 50 years old or older, who accept to participate.

- HIV-uninfected subjects, matched by age and gender, are being included from a primary care centre with a ratio 2 to 1 (2 cases, 1 control)
We are conducting a comprehensive multidisciplinary geriatric assessment including the following variables:

**MEDICAL**
- Comorbidities and age-related conditions,
- Polypharmacy and
- Drug-drug interactions
**PSYCHOLOGICAL**
- Adherence to ART (adapt SERAD, 2007)
- Depressive symptoms (GDS, 1983)
- Quality of life (adapt MOS-VIH, 1991)
- Cognitive symptoms (EACS Guidelines)
- Cognitive reserve (CRC 2011)

**FUNCTIONAL**
- Barthel and Lawton tests
- Subjects at high risk: Barber test
- Frailty.

**PHYSIOLOGICAL HABITS**
- Nutritional test
- Sleep disorders: PittsburgTest
- Urinary incontinence: Lagro-Janssen test

**Other geriatric syndromes**
- Sensorial tests: HDD (hear), visual
- Tinetti test
- Risk of falls: SSPB and Gait speed, Get up and go tests

**SOCIAL** (financial situation, isolation):
- OARS and Gijon tests

**Other evaluations:**
- Blood and urine test,
- DXA scan,
- EKG and
- Chest and lumbar spine X ray.

**Immunological characterization:**
- Immune activation,
- Immune senescence
- Inflammation markers.
Comorbidities of HIV-infected patients and controls

Currently 204 HIV and 100 controls

Analysis included:
104 HIV subjects
49 controls
Mean age 71 years

Negredo et al.  
Sent for publication
Relevant differences between HIV-infected patients and controls stratified by age

* Statistically significant differences were found between groups >70 years and no between groups ≤70 years

Negredo et al. Sent for publication
# Social and psychological parameters

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected patients (n=104)</th>
<th>Controls (n=49)</th>
<th>P values</th>
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<tbody>
<tr>
<td><strong>Social environment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor or very poor quality of life (%)</td>
<td>16</td>
<td>15</td>
<td>0.934</td>
</tr>
<tr>
<td>Unsatisfactory social environment (%)</td>
<td><strong>19</strong></td>
<td><strong>18</strong></td>
<td>0.927</td>
</tr>
<tr>
<td>Altered Barber test [elderly at risk (%)]</td>
<td>13</td>
<td>14</td>
<td>0.880</td>
</tr>
<tr>
<td>Married (%)</td>
<td><strong>73</strong></td>
<td><strong>98</strong></td>
<td>0.000</td>
</tr>
<tr>
<td>Live alone (%)</td>
<td><strong>39</strong></td>
<td><strong>14</strong></td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Psychological and cognitive alterations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive complaints %</td>
<td>26</td>
<td>13</td>
<td>0.092</td>
</tr>
<tr>
<td>Depression %</td>
<td>21</td>
<td>14</td>
<td>0.358</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
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<tr>
<td>Polypharmacy ≥5 (%)(^1)</td>
<td><strong>44</strong></td>
<td><strong>27</strong></td>
<td>0.046</td>
</tr>
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Negredo et al. Sent for publication
Most relevant differences of characteristics between HIV infected patients and controls according to the smoking habit

The same analyzes were performed stratifying subjects according to the smoking habit, to exclude tobacco as a cardiovascular risk factor.

- Among those who never smoked, significant differences were found between HIV subjects and controls with respect to the percentage of:
  - 3 or more comorbidities (58% vs 32% P=0.028);
  - lipids alteration (62% vs 25% P=0.002);
  - a trend in the cognitive complaint (24% vs 6% P=0.074).
Accelerated and accentuated aging?

☐ YES. However, ...

☐ NO

Therapeutic strategies
New treatment targets
Senescence
New treatment targets

Senescence

Table 2 | Candidate senotherapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target (or targets)</th>
<th>Target class</th>
<th>Development status</th>
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<tr>
<td>Small molecules</td>
<td></td>
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<tr>
<td>Navitoclax</td>
<td>BCL-X&lt;sub&gt;l&lt;/sub&gt; and BCL-W</td>
<td>Pro-survival proteins</td>
<td>Preclinical animal models</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Pan-receptor tyrosine kinases</td>
<td>Receptor tyrosine kinases</td>
<td>Phase II clinical trial (NCT02848131) for chronic kidney disease</td>
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</table>
Comorbidities

Polypharmacy

Functional

Social

Mental

Psychological

Geriatric syndromes

Nutrition

Hormone replacement in cases of deficiency

Exercise (Aerobic and Resistance training)

Appropriate treatment of CV RISK FACTORS

Appropriate treatment of CV RISK FACTORS

Mental Psychological

Social
Thank you