COMORBILITATS i ENVELLIMENT
EN PACIENTS AMB INFECCIÓ PEL VIH

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SURVIVAL FOR HIV INFECTED PATIENTS
COMORBIDITIES AND RISK FACTORS

THE PATIENT
Individual and social factors:
- Higher rate of traditional risk factors: smoking, dyslipidemia, HTN, diabetes
- Genetic factors ...

THE VIRUS
- HIV infection itself
- Ongoing inflammation despite HAART

THE TREATMENT
- Antiretroviral therapy and toxicity
Increased comorbidities are caused by:

- Low CD4+ T-cell nadir
- Coinfections (hepatitis, CMV, EBV, and HPV)
- Persistent inflammation
- Lifestyle (smoking, etc)
- Cumulative cART exposure
- Aging

CAUSES OF INCREASED COMORBIDITIES: 1. INFLAMMATION
CAUSES OF INFLAMMATION

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)

Deeks, Lewin, Havlir; Lancet 2013
CAUSES OF INFLAMMATION

- Loss of immuno-regulatory cells
- Thymic dysfunction and loss of regenerative potential
- CMV replication
- HIV replication
- Loss of gut mucosal integrity and microbial translocation

HAART

Deeks et al.
Annual Review of Medicine 2011.

Figure 1
The effect of HIV infection and its treatment on inflammation and immunosenescence.
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.
CAUSES OF INFLAMMATION

Figure 1
The effect of HIV infection and its treatment on inflammation and immunosenescence.
Arterial inflammation as measured by PET-scan:
Increased in HIV-infected patients as compared to VIH negative subjects with the same FRS
CONSEQUENCES OF INFLAMMATION

Inflammation Predicts Disease in Treated HIV Infection

- **Cardiovascular Disease** (Duprez, Atherosclerosis 2009)
- **Cancer** (Breen, Cancer Epi Bio Prev 2010; Borges, AIDS 2013)
- **Venous Thromboembolism** (Musselwhite, AIDS 2011)
- **Type II Diabetes** (Brown, Diabetes Care 2010)
- **Cognitive Dysfunction** (Burdo, AIDS 2013; Letendre CROI 2012, Abs#82)
- **Frailty** (Erlandson, JID 2013)
- **Mortality** (Kuller, PLoS Med 2008; Tien, JAIDS, 2010; Justice, CID 2012)
CONSEQUENCES OF INFLAMMATION

Markers of Inflammation and GI Dysfunction Predict Mortality

Markers of inflammation and gut barrier dysfunction predict mortality independently of CD4 count and virus load.
CAUSES OF INCREASED COMORBIDITIES: 1. INFLAMMATION

A strong acute-phase inflammatory response was required for survival; however, inflammatory responses can also promote chronic diseases.

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

Adapted from Vance DE. Am J Nurs 2010
CAUSES OF INCREASED COMORBIDITIES: 2. AGING

Image description: A bar chart showing the increase in comorbidities by age group from 2001 to 2010. The chart indicates a significant rise in comorbidities among older age groups.

References:
- CDC HIV Surveillance Report 2004 and 2011
Ageing (British English) or aging (American English) 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 change.
“Inflammation Hypothesis of Aging” supports the molecular basis of the inflammatory process as a plausible cause of the aging process.
The aging immune system is characterized by a low level chronic systemic inflammatory state, termed “InflammAging”.

This inflammatory phenotype is marked by elevated circulating levels of markers of:

- Inflammation (e.g., C-reactive protein (CRP))
- Pro-inflammatory cytokines (interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α))

It is associated with increased morbidity and mortality in older adults

**Immunosenescence**

Immunosenescence refers to the gradual deterioration of the immune system brought on by natural age advancement.

- **Thymic atrophy**
- **Decreased bone marrow production**
- **Decreased B and T cell activation and maturation** resulting in decreased humoral and cell-mediated immunity (naïve and memory cells).

  - **Increased frequency and severity of diseases** such as chronic inflammation disorders (neurodegenerative, cardiovascular...) and autoimmunity
  - **And major susceptibility to cancers and infections**
IMMUNESENESCENCE

Young Thymus:
- No Lipotoxic ‘Danger Signals’
- Inflammasome
- IL1R
- Nkp3
- ASC
- Pro-Caspase-1
- Prol-I-6

Thymic Lymphopoiesis
- Young Secondary Lymphoid organs
  - Naïve T cells
  - Effector T cells

> No T cell Senescence
> Diverse TCR repertoire

Immun-Surveillance

Aging Thymus:
- Lipotoxic ‘Danger Signals’
- Inflammasome Inhibitors
- Free Cholesterol
- Ceramides
- Caspase-1
- IL-1β
- Thymocyte Death

Thymic Atrophy
- Reduced Lymphopoiesis
- Aging Secondary Lymphoid organs
  - Naïve T cells
  - Effector T cell expansion

> T cell Senescence
> Restricted TCR Diversity

Imune Dysfunction
## HIV and AGING

<table>
<thead>
<tr>
<th>Adaptive immune response</th>
<th>Change in HIV-infected patients, compared with age-matched control subjects</th>
<th>Change in aging persons, compared with young adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive cell number</td>
<td>Normal to low</td>
<td>Normal to low</td>
</tr>
<tr>
<td>Memory cell number</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Resting activation</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Cytokine production</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>(unstimulated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD86 (costimulatory</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>ligand) expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total IgG and IgA level</td>
<td>Polyclonal increase</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>V</strong> subfamily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gene use (naive B cells)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>V</strong> subfamily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gene mutation</td>
<td>Few data</td>
<td>Normal</td>
</tr>
<tr>
<td>frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary responses</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Memory responses</td>
<td>Low to normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>T cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive cell number</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Memory cell number</td>
<td>Low</td>
<td>Normal to high</td>
</tr>
<tr>
<td>Resting activation</td>
<td>Highly increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Cytokine production</td>
<td>Low&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Low to normal&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CD28 (costimulatory</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>receptor) expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8 cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive cell number</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Memory cell number</td>
<td>Low</td>
<td>Normal to high</td>
</tr>
<tr>
<td>Resting activation</td>
<td>Highly increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Cytokine production</td>
<td>Low</td>
<td>Normal to high</td>
</tr>
<tr>
<td>CD28 (costimulatory</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td>receptor) expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senescent phenotype</td>
<td>Very high</td>
<td>High</td>
</tr>
</tbody>
</table>
PHYSIOLOGICAL PROCESS OF AGING

- Brain atrophy, decreased cerebral blood flow, decrease in neurotransmitter concentrations
- Thyroid atrophy, adrenal glands atrophy, alterations in carbohydrate, and lipid metabolism
- Decreased elasticity, alterations in the heart
- Decreased glomerular filtration rate
- Muscle atrophy, alterations in the modulation of electrolyte
- Lower bone density
- Lower gastrointestinal motility, lower hepatic blood flow, lower gastrointestinal immunity
- Lower pulmonary capacity
- Immunosenescence
CLINICAL CONSEQUENCES OF AGING

[Diagram showing the relationship between aging and various clinical consequences.]

CONSEQUENCES OF VIH/INFLAMMATION and AGING

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

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

Adapted from Vance DE. Am J Nurs 2010
CAUSES OF INCREASED COMORBIDITIES: 2. AGING

ART

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

Accumulation of changes in a human being over time

Adapted from Vance DE. Am J Nurs 2010
Accentuated

Is aging an accentuated process in HIV people?

### ACCENTUATED AGING

Overall and age-specific incidence rates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Mean Difference in Age (years)</th>
<th>Risk aIRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>-0.04 (-0.62 to 0.54)</td>
<td>1.81 (1.49-2.20)</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>-0.23 (-0.69 to 0.23)</td>
<td>1.43 (1.22-1.66)</td>
</tr>
<tr>
<td>HIV-associated cancers</td>
<td>-0.57 (-0.93 to -0.21)</td>
<td>1.84 (1.62-2.09)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>-0.45 (-0.78 to -0.12)</td>
<td>0.95 (0.85-1.06)</td>
</tr>
</tbody>
</table>

ACCENTUATED AGING

Comedications

No comedication | One comedication | Two comediations | Three comediations | Four or more comediations

% of participants

% of participants

Comorbidities

No comorbidity | One comorbidity | Two comorbidities | Three comorbidities | Four or more comorbidities

Agegroups:

<50 years: n=5761
50-64 years: n=2233
65+ years: n=450

Hasse B. et al. Clin Infect Dis 2011 53;1130-1139
Frailty is a distinct clinical entity, differing from:

- **Comorbidity** as defined by the presence of ≥2 diseases.
- **Disability** as measured by impairment in activities of daily living (ADL)

The **frailty phenotype** in older adults consists of **three or more** of the following:

- Weakness (measured by grip strength),
- Low physical activity,
- Slowed motor performance (measured by walking speed),
- Exhaustion, and
- Unintentional weight loss.
Frailty is recognized as an important clinical syndrome in old age, which:

- Results from age-related declines in physiologic reserve and complexity in resting dynamics involving multiple physiologic systems,
- Manifests by maladaptive responses to every day or acute stressors, and
- Leads to a vicious cycle towards functional decline and other serious adverse health outcomes.

This chronic condition is commonly described by two conceptual models:
- the phenotype model (frailty syndrome)
- the cumulative deficit model (frailty index). It has not been validated in HIV-infected populations.
FRAILTY PHENOTYPE

Predicts a number of serious adverse health outcomes in community-dwelling older adults, including:

- acute illness,
- falls,
- cognitive decline,
- hospitalization,
- disability,
- dependency, and
- mortality, adjusting for comorbidities.
In the Multicenter AIDS Cohort Study:

- A frailty-related phenotype of weight loss, exhaustion, slowness, and low physical activity was more common in enrollees with HIV infection compared with those who did not have HIV infection,

- It predicted mortality independently of CD4 T-lymphocyte count and viral load.

Fig. 1 The percent of study visits (and 95% confidence intervals) at which the criteria for the frailty phenotype were met, stratified by age and HIV status, October 1, 2007, to September 30, 2011, the Multicenter AIDS Cohort Study. *p < 0.05. Intraclass correlation coefficient 0.491 for HIV-infected men; 0.579 for HIV-uninfected men (reprinted with permission from Althoff KN et al. J Gerontol A Biol Sci Med Sci 2014;69A:189–198)
Factors that have been associated with frailty in HIV+ populations include:

- age,
- lower current or nadir CD4 T cell counts and
- other HIV-infection-related inflammation,
- hepatitis C co-infection,
- other comorbidities,
- depressive symptoms, and
- certain social factors (e.g., lower education, unemployment)

Is aging an accelerated process in HIV people?

ACCELERATED AGING

A prospective comparative cohort study

- Prevalence and incidence of age-associated non-communicable comorbidities (AANCC) and their risk factors in persons ≥45 yrs
- Started October 2010

- Participants:
  - HIV-1-infected: from the HIV outpatient clinic at the Academic Medical Center (Amsterdam)
  - HIV-1-uninfected: from the Amsterdam Public Health Service sexual health clinic, and the ongoing Amsterdam Cohort Studies on HIV/AIDS
## Demographic and HIV characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV neg (n=524)</th>
<th>HIV pos (n=540)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.1 (47.9-58.3)</td>
<td>52.9 (48.3-59.6)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male gender</td>
<td>85.1%</td>
<td>88.1%</td>
<td>0.15</td>
</tr>
<tr>
<td>Dutch</td>
<td>81.3%</td>
<td>72.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSM</td>
<td>69.7%</td>
<td>73.9%</td>
<td>0.125</td>
</tr>
<tr>
<td>Time since HIV-1 diagnosis (yrs)</td>
<td>12.1 (6.2-17.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CD4 count at enrollment (cells/mm³)</td>
<td>565 (435-745)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir CD4 count (cells/mm³)</td>
<td>180 (78-260)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load &gt; 200 at or within 4 mos prior to enrolment among cART-treated participants</td>
<td>1.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior clinical AIDS</td>
<td>31.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On cART</td>
<td></td>
<td>95.7%</td>
<td></td>
</tr>
<tr>
<td>• 79.1% started Rx-naive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 20.9% started ART-exp.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since ART was first initiated (yrs)</td>
<td>10.4 (4.4-14.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of viral load &lt; 200 (since last &gt; 200) (yrs)</td>
<td>5.8 (2.4 – 10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Known cumulative duration CD4 &lt; 200(mos)</td>
<td>0.8 (0.0 – 9.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median (IQR) or percentage as appropriate. P-value represents Wilcoxon Rank Sum or Chi² as appropriate.
# Comorbidity risk factors

<table>
<thead>
<tr>
<th>Smoking status currently / ever (%)</th>
<th>HIV neg (n=524)</th>
<th>HIV pos (n=540)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>currently / ever (%)</td>
<td>24.6 / 38.9%</td>
<td>32.0 / 35.0%</td>
<td>0.007 / 0.23</td>
</tr>
<tr>
<td>Smoking (packyears, smokers only)</td>
<td>15.0 (4.5-28.8)</td>
<td>22.2 (7.8-36.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe alcohol use</td>
<td>7.3%</td>
<td>4.8%</td>
<td>0.098</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily to monthly use of:</th>
<th>HIV neg (n=524)</th>
<th>HIV pos (n=540)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cannabis</td>
<td>11.6%</td>
<td>13.5%</td>
<td>0.356</td>
</tr>
<tr>
<td>cocaine</td>
<td>2.9%</td>
<td>3.7%</td>
<td>0.442</td>
</tr>
<tr>
<td>ecstasy</td>
<td>8.6%</td>
<td>4.3%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

| BMI (kg/m²)                      | 24.5 (22.8-27.0) | 24.2 (22.3-26.6) | 0.019   |
| Blood pressure systolic (mmHg)   | 133 (125-143)    | 135 (126-147)    | 0.006   |
| Blood pressure diastolic (mmHg)  | 79 (72-85)       | 81 (75-89)       | <0.001  |

Data presented as median (IQR) or percentage as appropriate. 
P-value represents Wilcoxon Rank Sum or Chi2 as appropriate.
## Age-associated Noncommunicable Comorbidity Prevalence

<table>
<thead>
<tr>
<th></th>
<th>HIV neg (n=524)</th>
<th>HIV pos (n=540)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AANCC* (%)</td>
<td>61.8%</td>
<td>69.4%</td>
<td>0.009</td>
</tr>
<tr>
<td>Number of AANCC (mean (SD))</td>
<td>1.0 (0.95)</td>
<td>1.3 (1.14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Comorbidity in relation to age

Frailty

Risk factors for (pre-)frailty
- Age
- Smoking
- Higher waist-to-hip ratio
- Chronic hepatitis C
- HIV infection

HIV-infected participants
- (Historic) BMI <20 kg/m²

K. Kooij et al; AIDS (in press)
More frailty and pre-frailty at any age in HIV+ participants

K.Kooij et al; AIDS (in press)
Comorbidity in relation to age


Mean number of AANCC
0.78 1.13 1.33 1.56 1.93 0.76 0.75 1.11 1.03 1.51
Number of participants
187 129 100 59 58 197 129 84 66 41
Comparative risk of hypertension, diabetes mellitus, renal failure, cardiovascular disease, and fracture, by age, among patients versus control subjects.

VIH, INFLAMMATION and AGING

Comorbidities
Frailty
SURVIVAL FOR HIV INFECTED PATIENTS

Based on Obel N et al. Plos One 2011
GRACIAS

Can Ruti campus, Badalona, Catalonia