HIV and Ageing Challenges and Goals

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Conflict of Interest Disclosure

- Speaker’s bureau: Merck, ViiV, Gilead
Outline

- Risks of late presentation: greater immunosuppression; multimorbidity; frailty and cognition

- Promoting healthspan: cognitive reserve; resilience

- Successful aging
infected patients had been diagnosed with at least one cardiovascular disease, 4% with diabetes, and 2% with a non-AIDS disease, 4% had diabetes, and 2% had a non-AIDS malignancy. The model predicts that in 2030, 78% of patients will have been diagnosed with cardiovascular disease, 17% with diabetes, and 17% with malignancies.

One of the many consequences of an ageing population and increasing burden of NCDs will be an increase in polypharmacy. The model projects that in 2030, 54% of HIV-infected patients in clinical care will be taking at least one other long-term drug aside from their HIV drugs (up from 13% in 2010), and 20% of patients will be prescribed three or more co-medications (up from 5% in 2010; figure 4).

The increasing burden of polypharmacy will mainly be driven by cardiovascular drugs, in turn driven by the increasing burden of cardiovascular disease (figure 4). In the ATHENA cohort in 2010, 9% of HIV-infected patients were prescribed cardiovascular drugs. This proportion is predicted to increase to 50% in 2030, with patients prescribed both antidiabetic drugs and cardiovascular drugs expected to increase from 2% in 2010 to 7% in 2030.

The model predicts that the increasing burden of polypharmacy and NCDs could cause an increase in complications with first-line ART. We predict that the proportion of HIV-infected patients on ART who will...
Caveat

- Current epidemiologic modelling for PLWH is based on a variable mix of:
  - PLWH who survived the pre-HAART and early HAART eras
  - recently infected persons with radically different cART history and associated immuno-virologic profile

- Projections and clinical course of the latter is emerging
Realities of older PLWH

- **Late diagnosis**: HIV not considered, increased risk of heterosexual transmission (less condom use, age-related female genitalia changes, little blue pill et al)

- **Greater immunosuppression**: lower nadir CD4; more often symptomatic at presentation

- **Impaired immune recovery**: slower and more often incomplete (but more consistent cART adherence)

- **Multi-morbidity** including geriatric syndromes and under-diagnosed mental health disorders: related risks of polypharmacy and *polydoctory*

- **Lifestyle and social challenges**: stigmatization, isolation (family, friends), financial, unprepared community services
Late presentation of HIV (CD4<350): increased risk with older age and heterosexual transmission

<table>
<thead>
<tr>
<th></th>
<th>Coefficient ± SE</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>21.6 ± 56.6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Year of presentation for care</td>
<td>−0.011 ± 0.028</td>
<td>1.0 (0.94–1.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Age (by 10 years older)</td>
<td>0.23 ± 0.084</td>
<td>1.3 (1.1–1.5)</td>
<td>0.0069</td>
</tr>
<tr>
<td>Sex (0 = Female, 1 = Male)</td>
<td>0.35 ± 0.11</td>
<td>2.0 (1.3–3.1)</td>
<td>0.0021</td>
</tr>
<tr>
<td>SSA² origin (0 = No, 1 = Yes)</td>
<td>0.61 ± 0.14</td>
<td>3.4 (1.9–5.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other³ non belgian origin (0 = No, 1 = Yes)</td>
<td>0.31 ± 0.16</td>
<td>1.9 (1.0–3.4)</td>
<td>0.044</td>
</tr>
<tr>
<td>Hetetosexual⁰ mode of acquisition (0 = No, 1 = Yes)</td>
<td>0.43 ± 0.14</td>
<td>2.4 (1.4–4.1)</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

Darcis G Sci Rep 2018
Modes of HIV transmission in the elderly

SERIOR CITIZENS must practise safer sex, too, study warns

Grandma, it’s time for ‘the talk’

P.J. HUFFSTUTTER LOS ANGELES TIMES
1\textsuperscript{st} presentation in >50 yo c/w >50:
- lower nadir CD4 count
- lower proportion with CD4 count ≥350

Althoff K. AIDS Res & Ther 2010

Figure 1
Median CD4 count, and the proportion of individuals who have a CD4 count ≥350 cells/mm\textsuperscript{3}, at first presentation for HIV clinical care.
Lower nadir CD4 predicts lower “plateau” CD4 after effective cART: older PLWH at risk

![Chart showing estimated median CD4 count over time since starting antiretroviral therapy by category of pre-treatment CD4 count. Dashed lines are for non-weighted estimates (based on available data at each year of follow-up); solid lines are estimates obtained using inverse probability of censoring weighting (IPCW). N=898 patients starting antiretroviral therapy. Horizontal lines are shown at 350, 500, and 800 cells/mm$^3$.](chart.png)
Non-AIDS co-morbidities are similar to those in the general older population but occur at a younger age.

*increased risk w low nadir (<200), poor CD4 recovery (CD5 < 500), CD4/CD8 <1.0*

- Non-AIDS defining cancers
- Liver: viral hepatitis, NAFLD and ETOH-related
- Cardiovascular
- Metabolic (CVD, DLP, DM2, visceral adiposity, sarcopenia)
- Bone demineralization
- Renal
- Neurocognitive decline
Also, high rates of geriatric syndromes in PLWH: UCSF SCOPE cohort

- Frailty: 9.0%
- Hearing Impairment: 14.2%
- Mobility Impairment: 21.9%
- Difficulty ≥1 ADL: 25.2%
- Urinary Incontinence: 25.2%
- Falls: 25.8%
- Visual Impairment: 34.8%
- Depression: 40.0%
- Cognitive Impairment: 46.5%
- Difficulty ≥1 IADL: 46.5%
- Pre-frailty: 56.1%

Greene M JAIDS 2015
Increased prevalence of frailty (FP+) in PLWH c/w controls at all ages: AGEhIV Cohort

- sCD14, sCD163, D-dimer and hsCRP were not independently associated with a higher frailty category nor did they attenuate the OR of HIV-infected status significantly.
- There were no significant interactions between HIV-infected status and age or any other covariate. The final model is shown in Table 3.
- Sensitivity analyses: We repeated the model from Table 3, excluding several subgroups of HIV-infected individuals, to explore whether the observed association between HIV and a higher frailty category was caused by a certain subgroup within the HIV-infected cohort. When those HIV-infected individuals who were ART experienced before start of cART were excluded, HIV-infected status remained significantly associated with a higher frailty category (OR adjusted 1.49, 95%CI 1.10–2.02, P = 0.009).
- The relation between WHR and frailty category remained statistically significant as well (OR 1.54, 95%CI 1.23–1.92, P < 0.001). Similarly, HIV-infected status remained statistically significantly associated with a higher frailty category when individuals with a history of AIDS, or with a nadir CD4+ T-cell count (CD4+ cell count) less than 100 cells/ml were excluded.

HIV-related determinants of frailty: We explored HIV- and ART-related variables in the multivariable model including only HIV-infected individuals, adjusting for age, sex, black race/ethnicity, HCV coinfection, smoking and depression. The duration of having had a CD4+ cell count less than 200 (OR 1.14/year, 95%CI 1.00–1.30, P = 0.04) as well as the cumulative duration of exposure to protease inhibitors (OR 1.05/year, 95%CI 1.01–1.10, P = 0.01) were independently associated with a higher OR for a higher frailty category. Exposure to any other type of ART, including dideoxynucleoside analogues (D-drugs), stavudine in particular or mono- and dual ART were not

Table 2. HIV and ART-related characteristics of HIV-infected participants.

<table>
<thead>
<tr>
<th>HIV-infected</th>
<th>n = 521</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)/median (IQR)</td>
<td></td>
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<tr>
<td>Years since HIV-1 diagnosis</td>
<td>12.0 (6.1–17.0)</td>
</tr>
<tr>
<td>CD4+ cell count (cells/ml)</td>
<td></td>
</tr>
<tr>
<td>Mean value in year prior to enrollment</td>
<td>563 (433–745)</td>
</tr>
<tr>
<td>Nadir</td>
<td>180 (78–260)</td>
</tr>
<tr>
<td>Cumulative known duration of CD4+ cell count &lt; 200 (months)</td>
<td>0.8 (0–8.5)</td>
</tr>
<tr>
<td>History of AIDS</td>
<td>360 (69.5%)</td>
</tr>
<tr>
<td>Nadir BMI &lt; 20 kg/m²</td>
<td>118 (22.7%)</td>
</tr>
<tr>
<td>Using cART at enrollment</td>
<td>492 (94.4%)</td>
</tr>
<tr>
<td>Cumulative duration of exposure to ART, years</td>
<td>9.8 (4.1–14.2)</td>
</tr>
<tr>
<td>ART experienced before start of cART</td>
<td>101 (20.5%)</td>
</tr>
<tr>
<td>Exposure to dideoxynucleoside analogues, ever/duration (years)</td>
<td>232 (47.2%)/0 (0–4.44)</td>
</tr>
<tr>
<td>Exposure to protease inhibitors, ever/duration (years)</td>
<td>370 (75.2%)/2.05 (0.01–6.85)</td>
</tr>
<tr>
<td>HIV-1 viral load &lt; 200 copies/ml in year prior to enrollment (of those on cART)</td>
<td>459 (93.3%)</td>
</tr>
<tr>
<td>ART, antiretroviral therapy; cART, combination ART.</td>
<td></td>
</tr>
</tbody>
</table>
Change in biologic and chronologic age in the elderly is heterogenous: frailty may be a useful surrogate to operationalize this variability.
Physiologic aging (>80) is associated with changes in immune parameters and increased markers of chronic inflammation (immunosenescence):

- Expansion of terminally differentiated CD28-neg T cells
- Reduction of naïve Tc pool (both CD4+ and CD8+)
- Associated with CMV seropositivity
- *Inverted CD4/CD8 ratio* (<1.0)

This profile (aka Immune Risk Profile-IRP): predicts overall decreased survival in > 80 yo healthy centenarians have normal CD4/CD8 ratio
Most PLWH with durable viral suppression and CD4>350 do not achieve a normal CD4/CD8 ratio (>1.0)
Pathobiology: does the changing co-morbidity profile in aging PLWH reflect *accelerated or accentuated* aging?

- Does HIV *accelerate* specific pathways and mechanisms common to an aging phenotype (no consensus on single definition of aging)?

- Is HIV an additional risk factor for development of chronic conditions *accentuating* prevalence of disease?
Evidence supporting accelerated aging phenotype in PLWH

- **DNA methylation** patterns suggest increased biologic age of about 5 years (Gross, *Mol Cell* 2016)

- **Telomere length** in PBMCs of PLWH at all disease stages are decreased and similar to those of controls about 40 years older (Bestilny *AIDS* 2000)

- **Immune senescent cell markers** in treated PLWH similar to patterns seen in HIV-negative controls decades older (Appay *Curr Opin HIV AIDS* 2016)
Chronic inflammation \equiv idling motor
\textit{(‘cost’ of idling too long \ldots\ldots\ldots)}
Aging associated chronic diseases regulated by chronic inflammation

Inflamm-ageing

- Metabolic diseases
  - Type 2 diabetes
  - Metabolic syndrome
- Cardiovascular disease
  - Atherosclerosis
  - Stroke
  - Heart failure
- Sarcopenia & Physical impairment
- Frailty
- Neurological diseases
  - Alzheimer’s disease
  - Parkinson’s disease
- Chronic inflammatory diseases
  - Rheumatoid arthritis
  - Psoriasis
- Cancer
- Osteoporosis

Circulating levels of acute-phase proteins, cytokines, and growth factors, such as CRP, IL-6, and TNF-α, are positively associated with insulin resistance, BMI/waist circumference, circulating triglycerides, and atherosclerotic processes (66). Among individuals diagnosed with type II diabetes, it has been demonstrated that inflammation can impair insulin action, modify hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction, impair endothelial function and hormone receptor transduction. These changes in vascular function are correlated with the development of type II diabetes (70). Chronic inflammatory processes that are induced by TNF-α can contribute to insulin resistance, dyslipidemia, and cardiovascular disease (72). In animal models, TNF-α has been shown to induce bone resorption and non-tumor-induced osteopenia (71, 72). TNF-α overproduction of IL-6 contributes, through its roles as a growth factor and fuelled primarily by leukocytes and by hypoxic conditions microenvironment is characterized by the presence of an inflammatory cytokines and acute-phase proteins, which are involved in the pathogenesis of type II diabetes (73). In this in vivo model of diabetes, IL-6 plays a major role. Indeed, the overexpression of IL-6 in transgenic mice results in insulin resistance, hyperglycemia, and hyperinsulinemia (74). It has been also implicated in the pathogenesis of cancer (75). Several studies have suggested a strong association between inflammation and cancer. TNF-α is capable of stimulating osteoclastic bone resorption (IL-1, TNF-α). In addition, it seems that proinflammatory cytokines, such as TNF-α and IL-1, can enhance cancer cell proliferation and survival. For example, IL-6 promotes osteoclast differentiation and activation (IL-1, TNF-α). In this regard, it is important to note that high values of serum CRP seem to be related with reduced protein synthesis and catabolism (76, 77). Recent studies have reported that high IL-6 and CRP levels are associated with increased risk of sarcopenia (78). Sarcopenia, defined as a loss of muscle mass and strength, is a condition that predisposes to arterial stiffness and is associated with increased risk of cardiovascular disease (79). Studies have shown that high levels of TNF-α are associated with increased risk of cardiovascular disease (80). It has been demonstrated that inflammation can enhance the proliferation of smooth muscle cells and play a role in vascular remodeling (81). Inflammation is also associated with arterial stiffness and its complications (82). The major chronic diseases associated with inflammation and aging are summarized in Figure 1. Inflammation is a key regulatory process that links multiple risk factors for adverse health outcomes with inflammation role in contributing to adverse health outcomes with inflammation.

Inflamm-ageing

- Metabolic diseases
  - Type 2 diabetes
  - Metabolic syndrome
- Cardiovascular disease
  - Atherosclerosis
  - Stroke
  - Heart failure
- Sarcopenia & Physical impairment
- Frailty
- Neurological diseases
  - Alzheimer’s disease
  - Parkinson’s disease
- Chronic inflammatory diseases
  - Rheumatoid arthritis
  - Psoriasis
- Cancer
- Osteoporosis
Chronic disease and cognition in the elderly

- **Common chronic diseases** are associated with cognitive decline in the middle-aged and older persons.
- **Frailty** is associated with an increased risk of cognitive decline.
- **White matter hyperintensities** (leukoariosis) increase risk of cognitive decline.
- **Multimorbidity** leads to polypharmacy, often including drugs with high anti-cholinergic burden which are associated with cognitive decline.
PLWH are more likely to take non-ARV meds with neurocognitive adverse effects: WIHS

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>HIV Infected n visits (%)</th>
<th>HIV Uninfected n visits (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsant</td>
<td>1274 (4.3)</td>
<td>450 (3.6)</td>
<td>0.96 (0.74 to 1.24)</td>
<td>0.74</td>
</tr>
<tr>
<td>Antianxiety</td>
<td>3706 (12.4)</td>
<td>1047 (8.4)</td>
<td>1.41 (1.17 to 1.70)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>676 (2.3)</td>
<td>218 (1.7)</td>
<td>1.20 (0.86 to 1.67)</td>
<td>0.29</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>2074 (7.0)</td>
<td>903 (7.2)</td>
<td>0.93 (0.76 to 1.15)</td>
<td>0.52</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>78 (0.3)</td>
<td>34 (0.3)</td>
<td>0.79 (0.28 to 2.20)</td>
<td>0.66</td>
</tr>
<tr>
<td>Opioid</td>
<td>3420 (11.5)</td>
<td>1102 (8.8)</td>
<td>1.35 (1.15 to 1.60)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>1004 (3.4)</td>
<td>304 (2.4)</td>
<td>1.29 (0.90 to 1.86)</td>
<td>0.17</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>807 (2.7)</td>
<td>186 (1.5)</td>
<td>1.78 (1.27 to 2.50)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>2053 (6.9)</td>
<td>645 (5.2)</td>
<td>1.42 (1.17 to 1.73)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>718 (2.4)</td>
<td>316 (2.5)</td>
<td>0.87 (0.66 to 1.16)</td>
<td>0.35</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>6231 (20.9)</td>
<td>1539 (12.3)</td>
<td>1.58 (1.35 to 1.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
In the general population, modifiable risk factors at age 50 predict impaired physical function and cognitive decline 20 years later: Whitehall II Study

Modifiable risk factors:
- Physical exercise
- Depression
- Obesity
- FEV1 (tobacco)

Self-reported high physical activity is associated with lower risk of cognitive decline and prevalent dementia in older persons.
Cognitive Reserve

- Factor contributing to a weak association between neuropathologic evidence of dementia-related changes and clinical manifestations
- Initially felt to be linked to educational achievement (*sorry, but 3 PhD’s doesn’t always help*)
- Additional related factors include: occupational complexity, social participation, engagement in leisure activities
- May delay onset of clinical signs and symptoms (‘compression of cognitive morbidity’)
- Can be operationalized (no consensus)

JF
Assessment of cognitive reserve (Cognitive Reserve Index) is associated with reduced dementia prevalence in the elderly

Variables Used to Create the Cognitive Reserve Index

Components
- Education
- Socio-economic status
- Current physical activity
- Marital status
- Social participation
- Mental activities
PLWH with symptomatic HAND have lower cognitive reserve

Cognitive Reserve: composite mean z-scores: years of education; verbal IQ; highest occupation level.
Resilience

- Ability of a person to withstand or recover from functional decline after an acute or chronic health stressor
- Physical resilience focuses on maintenance or recovery of function after a biomedical challenge
- Reflects adaptive physiologic responses at the level of molecules, cells, and organs which support homeostasis
- Physical resilience is not the opposite of frailty
Variables associated with at least moderately high resilience in PLWH (50 yo, >20 yrs HIV+, nadir CD4-190)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Perception of ageing (EPSE)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cognitive self-concept</td>
<td>1.272</td>
<td>(1.105, 1.464)</td>
<td>.001</td>
</tr>
<tr>
<td>Subjective perception of time</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Subjective perception of social relationships</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Physical self-concept</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Coping strategies (Brief COPE)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Active coping</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Substance use</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Use of emotional support</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Subjective perception of time</td>
<td>1.182</td>
<td>(1.016, 1.375)</td>
<td>.030</td>
</tr>
<tr>
<td>Positive reframing</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Planning</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Humour</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Acceptance</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Self-blame</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Quality of life (NHP)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HP Total</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Energy</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Emotional status (HADS)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HADS Total</td>
<td>0.874</td>
<td>(0.793, 0.963)</td>
<td>.007</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HAD Depression</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

Results

- Mean: moderately low
- 43% > moderate to high
- 37% moderately low-moderate
- 19% low

25 Item Resilience Scale*

- Perception of ageing
- Coping strategies
- QoL
- Depression & anxiety

*Heilemann J Nursing Measurement 2003

Fumaz CR AIDS Care 2015
Is successful aging possible in PLWH?
Aging successfully with HIV is possible

No consensus on definition, WHO program evolving: includes at least avoidance of disease and disability, high cognitive and physical capacity, social engagement

Think beyond immuno-virologic control metrics
Aging successfully with HIV is possible

- Diagnose HIV early and treat rationally
- Assess and manage comorbidity risks proactively to avoid multimorbidity
- Minimize polypharmacy and review all Rx annually
- Recognize and manage risks for cognitive decline; encourage activities which contribute to cognitive reserve
- Assess functional status and adopt rehabilitation interventions to limit impairments
Aging successfully with HIV is possible

- Introduce *interdisciplinary* management principles: SW, OT, PT, pharmacist, dietician, peer and community support, geriatrician involvement

- AI: Advocate + Initiate: education and empowerment
New approach needed to manage aging PLWH

From One Syndrome to Many: Incorporating Geriatric Consultation Into HIV Care

Harjot K. Singh, Tessa Del Carmen, Ryann Freeman, Marshall J. Glesby, and Eugenia L. Siegler

Divisions of Infectious Diseases and Geriatrics and Palliative Medicine, Weill Cornell Medical College; and ACRIA, Center on HIV and Aging, New York

Clin Inf Dis 2017

EDITORIAL

Geriatric-HIV medicine: A science in its infancy

Giovanni Guaraldi and Andrea Cossarizza

University of Modena and Reggio Emilia School of Medicine, Modena, Italy

Virulence 2017
Thank you