Conceptual approaches for defining frailty phenotype in HIV

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Conflicts

I’m getting old 😞
Age distributions in patients attending the metabolic clinic from 2003 to 2011
Objective

• To review frailty conceptualization, focusing on the screening tools that have been operationalized for clinical use in HIV patients;

• To discuss whether and how the definition of frailty can inform research and clinical practice in HIV;
Mr A, 75 yrs, Heterosexual

- HIV diagnosis in 2005
- CD4 at presentation = 241 cell/µL
- At present CD4= 892 cell/µL (35.6%)
- VL < 40 copies/µL
- On ART: TDF+FTC+EFV

Chronic HBV infection
Previous NHL
Myocardial infarction (2000)
Surgery for prostate hypertrophy
T2DM, hypertension, Osteoporosis, MS
Complain sexual dysfunction

Mr. B, 75 yrs, MSM

- HIV diagnosis in 2005
- CD4 at presentation 319 cell/µL
- At present CD4= 691 (37.3%) cell/µL
- VL < 40 copies/µL
- On ART: 3TC+ABC+LPV/r

Full active life, farmer
Osteoporosis,
Regular sexual life
How can we measure aging, as a health condition?

Aging is a complex mixture of “robustness” and “frailty”
The mosaic of aging

great variability at all levels of biological organization:

- macromolecules
- organelles
- cells
- organs
- individuals
- populations


At an individual level the mosaic of aging is described by frailty
Frailty is conceptualized in relation to complexity.

Frailty is a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes.

Frailty identify an “at risk” state.
Models of Ageing across Frailty towards Polypathology and Disability

- Clinical reserve
- Frailty
- Clinical disease
  - Polypathology
  - Disability

Age
Models of Ageing across Frailty towards Polypathology and Disability

- Clinical reserve
- Frailty
- Clinical disease
- Polypathology
- Disability

Control population
Accelerated ageing

Time
Models of Ageing across Frailty towards Polypathology and Disability

- Clinical reserve
- Frailty
- Polypathology
- Clinical disease
- Disability

Age
Models of Ageing across Frailty towards Polypathology and Disability

- Clinical reserve
- Frailty
- Polypathology
- Clinical disease
- Disability

Control population
Premature ageing
Accentuated risk
Accelerated ageing

Single time point study

Age 75 yrs
Frailty implication for clinical practice

Risk prediction
Models of Ageing across Frailty towards Polypathology and Disability

- Clinical reserve
- Frailty
- Polypathology
- Clinical disease
- Disability

Events:
- Event
- Events

- Control population
- Premature ageing
- Accentuated risk
- Multiple events
- Accelerated and premature ageing

Age

- Clinical reserve
- Frailty
- Polypathology
- Clinical disease
- Disability

- Control population
- Premature ageing
- Accentuated risk
- Multiple events
- Accelerated and premature ageing

Age
Trajectories of changes in the health status

Recent minor stroke
What changed:
✓ slowness
✓ Walking stick
✓ MDD
✓ Well supported by his family

Recent Femur fracture
What changed:
✓ slowness
✓ Walking stick
✓ MDD
✓ Institutionalized (no family support)
Models of Ageing across Frailty towards Polypathology and Disability

Clinical reserve

Frailty

Polypathology

Disability

Longitudinal study

Age
Frailty implication for clinical practice

Risk prediction

Trajectories of changes in the health status
High prevalence of Co-morbidities (HANA) and Polypathology in HIV infected aging cohorts

In Modena cohort Pp on the 50’s was 20% in the AgeHIV cohort was 35%

Pp prevalence was higher in cases than controls in all age strata


Schouten J, XIX International AIDS Conference
Daily pill burden in different age strata

Pill burden including ARV

Pill burden excluding ARV

Guaraldi G. Personal communications
Synergistic Effects of HIV Infection and Older Age on Daily Functioning

Self-reported 7 IADLs (finance management, purchasing groceries, cooking, using transportation, shopping, medication management, and social activity planning)

Self-reported 5 BADLs (housekeeping/cleaning, laundry, home repairs, bathing, and dressing)

Older age may exacerbate the adverse effects of HIV on daily functioning.

Functional impairment was based on rates of unemployment and the Karnofsky Scale of Performance Status.

Lifetime major depressive disorder was arguably the most reliable predictor of adverse functional outcomes.

Early detection of functional difficulties could facilitate delivery of compensatory strategies (e.g., cognitive remediation) or assistive services.

JAIDS 2012, 61: 341-6
The aging Phenotype and the genesis of Geriatric Syndromes

Aging Phenotypes

- Changes in Body Comp
- Discrepancy energy Production/utilization
- Homeostatic Dysregulation
- Neurodegeneration

Disease Susceptibility
- Reduced Functional Reserve
- Reduced Healing Capacity
- Unstable Health
- Failure to thrive

FRAILTY

Geriatric Syndromes

- Gait Disorders
- Falls
- Disability
- Sarcopenia
- Urinary incontinence
- Cognitive impairment
- Delirium
- Sleep Disorders
- Decubitus ulcers

Courtesy by Ferrucci L.
Aging Phenotype:

1. Changes in body composition

In the general population a 60 to 85% increase of fat mass, predominantly represented by visceral adiposity (VAT), is expected between 25 and 65 years of age; in the same period there is a 20% decline of skeletal muscle mass.
Low Limb Muscle Mass and VAT are associated with 5 Year Mortality

922 HIV-infected persons

FRAM 2
1999-2004

Arm SM:
- Tertile 1
- Tertile 2
- Tertile 3

Leg SM:
- Tertile 1
- Tertile 2
- Tertile 3

VAT:
- Tertile 1
- Tertile 2
- Tertile 3

Odds Ratio (95% CI)

Lower Odds of Death

Higher Odds of Death

- Reference

0.59 (0.35, 0.99)
0.51 (0.25, 1.04)
0.92 (0.54, 1.57)
0.42 (0.21, 0.84)
1.77 (1.03, 3.03)
2.12 (1.13, 3.98)

Scherzer R, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 76.a
Activated and Central-memory Phenotype According To Clinical Lipodystrophy

CD8+CD38+T cells and CD8+CD227+T cells homeostasis alteration is associated with lipodystrophy and central fat accumulation linked with subclinical cardiometabolic diseases

Aging Phenotype:
2. Discrepancy energy production/utilization

IN VIVO MITOCHONDRIAL FUNCTION IN AGING HIV-INFECTED PATIENTS

24 older HIV-infected patients and age-matched controls were analysed with phosphorus magnetic resonance spectroscopy (31P-MRS). Spectra were obtained from gastrocnemius / soleus at rest and during recovery from brief sub-maximal exercise.

Key measures were: ATP (adenosine triphosphate) production during recovery and resting pH.

Dynamic measurement of ATP production was no different in HIV+ compared with HIV- subjects. However basal measures of ATP metabolism and pH handling were significantly perturbed in HIV+ subjects, suggestive of functional compensation for a cellular mitochondrial DNA defect.

Payne B. Poster 856 CROI 2012
Aging Phenotype:

3. Homeostasis dysregulation

Functional Impairment is Associated with Low Bone and Muscle Mass in Middle-Aged HIV-1 Infected Persons

**Obj:** to study the contribution of bone and body composition changes to physical function in 359 persons aging with HIV-1 infection.

**MM:** Low functioning \((\text{LF} : 33/141)\) and high functioning \((\text{HF})\) subjects were identified by combined deficits on Fried’s Frailty Phenotype and the Short Physical Performance Battery.

Impaired physical function among adults with HIV-1 infection was associated with low muscle mass, bone mineral density, IGF-1, and IGFBP-3.
VAT increase describes the aging anthropometric phenotype in HIV patients

1877 HIV-infected patients evaluated with VAT at the Metabolic Clinic in Modena
IGF1 median values 138.65 ± 59.73 ng/mL
Testosterone median values 523.88 ± 185.45 ng/mL

Aging related anthropometric changes are predicted by decrease IGF-1 and Testosterone plasma level

Guaraldi G., personal communication
Aging Phenotype:

4. Neurodegeneration

Resting state functional connectivity magnetic resonance imaging (rs-fcMRI) to non-invasively investigate the neurobiology of 5 functionally defined brain networks in 52 HIV+ (44% on HAART) and 52 HIV- controls.

Network composite scores were computed for five networks: default-mode network (DMN), control network (CON), salience network (SAL), dorsal attention network (DAN), and sensorimotor network (SMN).

These results suggest that HIV and aging cause similar decreases in rs-fcMRI. HIV could serve as a model for accelerated neurodegeneration within brain network connections.

Ances B, poster 493, CROI 2012
Neurologic Co-morbidities are associated with HIV infection

Excess neurologic disease was found in the categories of nervous system infections, dementia, seizures/epilepsy, and peripheral nervous system disorders, but not stroke.

HIV-positive men receiving HAART have a higher burden of neurologic disease than HIV-negative men and develop neurologic disease at younger ages.
Could I predict this premature aging process?

2002

39 years old
CD4=477 cells/µL
HIV1-RNA<40 copies/mL
TDF+FTC+NEV

2011

47 years old
CD4=715 cells/µL (+238)
HIV1-RNA<40 copies/mL
TDF+FTC+NEV
Frailty recognition in clinical practice

Frailty Related Phenotype

✓ Recognized by the presence of at least three of five particular deficits, specified as: measured slow walking speed, measured impaired grip strength, self-reports of declining activity levels, exhaustion and unintended weight loss.

✓ “pre-frail” is used when only one or two of these deficits is present.

✓ Clinically recognizable and not otherwise definable as being disabled or as having multiple comorbid illnesses

Frailty Index

✓ Is a count of health deficits which can be any clinical symptom, sign, disease, disability, or laboratory, imaging or electrodiagnostic abnormality.

✓ The more deficits which they accumulate, the greater their risk of an adverse health outcome.
Frailty-related phenotype (FRP)

- At least 3 components out of the following 5:

1. weakness (grip strength)
2. slowness (time to walk 15 feet)
3. exhaustion (self-reported)
   ✓ During the past 4 weeks, have you had difficulty performing your work or other activities (for example, it took extra effort)?
4. low physical activity level (SF-36)
   ✓ Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?
5. Unintentional weight loss (self-reported)
   ✓ During the past 4 weeks have you had difficulty performing your work or other activities (for example, it took extra effort)?

Summary of clinical trials that used frailty phenotype as research outcome

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>Population</th>
<th>Frailty assessment</th>
<th>Frailty predictors</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desquilleb L, Jacobson LP, Fried LP et al.</td>
<td>J Gerontol A Biol Sci Med Sci. 2007; 62a:1279-1286</td>
<td>MACS cohort HIV+ males ARV naïves N=245 HIV- males N=1905 Cross sectional Case control</td>
<td>At least 3 of the following 4 components: physical shrinking*, exhaustion*, low physical activity level*, slowness#</td>
<td>HIV infection (OR differed according to HIV duration) After adjustment of sex, age, ethnicity and education</td>
<td>Similar rates of frailty (3.4%) in HIV+ men older than 55 years and HIV- men (3.4%) older than 65 years</td>
</tr>
<tr>
<td>Desquilleb L, Margolick JB, Fried LP et al.</td>
<td>J Acquir Immune Defic Syndr 2009; 50:299-306</td>
<td>MACS cohort HIV+ males N=1046 Cross sectional Observational</td>
<td>At least 3 of the following 4 components: physical shrinking*, exhaustion*, low physical activity level*, slowness* # approximated using questions about difficulty in walking</td>
<td>CD4&lt;400/μL and HIV VL*&gt;50000 copies/mL (*if before 1996) Education, AIDS at visit, Age</td>
<td>Prevalence of frailty is a function of CD4 cell count CD4&gt;750/μL were protective for Fraility</td>
</tr>
<tr>
<td>Onen NF, Agbebi A, Shacham E, et al</td>
<td>J Infect 2009; 59:346-352</td>
<td>HIV+ N=445 Males 70.8% Cross sectional</td>
<td>Fraility was defined by ≥3 of 5 criteria: weight loss, low physical activity*, exhaustion*, weak grip strength and slow walking time * self reported</td>
<td>Social, number of comorbidities, past opportunistic illness, depression, low albumin.</td>
<td>Frailty prevalence=9% Urban outpatient care setting HIV infection was associated with a premature presentation of frailty Hospitalization was 5-fold longer for frail person</td>
</tr>
<tr>
<td>Terzian AS, Holman S, Nathwani N, et al</td>
<td>J Women Health 2009; 18.1965-1974</td>
<td>Women Interagency Study HIV+ women ARV N=1206 HIV- women N=573 Cross sectional</td>
<td>Frailty was defined by ≥3 of 5 criteria: weakness, slowness, self-reported physical exhaustion, unintentional weight loss, and low physical activity. Specific measures: (1) short questionnaire evaluating the ability to perform certain tasks (2) a physical activity questionnaire, (3) time gait and grip-strength tests</td>
<td>CD4&lt;100/μL</td>
<td>Severe CD4 cell depletion was an independent predictor of slowness, weakness and fraility</td>
</tr>
<tr>
<td>Margollic JB, Xiuhong Li, Detels R, et al</td>
<td>CROI 2011. P794</td>
<td>MACS cohort HIV+ males ART experienced N=1307 HIV- males N=1451 Cross sectional Case control</td>
<td>At least 3 of the following 5 components: low grip strength (&lt;20th %ile of HIV-men), low physical activity (SF-36 questionnaire), slow 4 meter walking speed (&lt;20th %ile of HIV-men), Weight loss&gt;10 lb, Exhaustion (SF-36 questionnaire)</td>
<td>Age, CD4&lt;500/μL, VL&gt;50 copies/m, ART (data not shown in the poster)</td>
<td>At age 50-70 yrs the frailty phenotype was significantly more common among HIV pos men receiving ART than among HIV neg men</td>
</tr>
</tbody>
</table>
Frailty Index

A Variables can be included in a frailty index if they satisfy the following 5 criteria:

1) The variables must be deficits associated with health status.
2) A deficit's prevalence must generally increase with age.
3) The chosen deficits must not saturate too early.
4) The deficits that make up a frailty index must cover a range of systems.
5) the items that make up the frailty index need to be the same from one iteration to the next.

VACS Index: mortality risk prediction
... and much more

The veterans Aging Cohort Study Risk Index (VACS Index) is an index composed of routinely collected laboratory values that accurately predicts all cause mortality among those with HIV infection.

Uses lab tests currently part of routine care

Identifies modifiable risk at lower test thresholds

Incorporates age, and effects of HANA and toxicity

Computation easy, can be included in lab reports and available through websites/apps

Offers approach that incorporates multifaceted HIV effects, multimorbidity, and toxicity
## VACS Index Thresholds and Weights

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50 to 64</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>44</td>
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</table>

<table>
<thead>
<tr>
<th>CD4 cells/mm³</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>350 to 499</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>200 to 349</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>100 to 199</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>50 to 99</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>46</td>
<td>29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV-1 RNA copies/ml</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>500 to 1×10⁵</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>≥ 1×10⁵</td>
<td>25</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemoglobin g/dL</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12 to 13.9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>10 to 11.9</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FIB-4</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>&lt; 1.45</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1.45 to 3.25</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td></td>
<td>25</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>eGFR mL/min</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>≥ 60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>45 to 59.9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>30 to 44.9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

| Hepatitis C Infection | 5 |

Tate J. et al.  IDSA 2010  Vancouver, BC October 21-24th. Poster 1136
The VACS Index: An internationally generalizable risk index for mortality after one year of antiretroviral therapy

AIDS 2012, 26:000–000

All-cause, five-year mortality rates by risk score

Conclusions: Among HIV-infected patients treated with ART, the VACS Index more accurately discriminates mortality risk than traditional HIV markers and age alone. By accounting for multi-organ system injury, the VACS Index may prove a useful tool in clinical care and research.
## FRP vs VACS index

<table>
<thead>
<tr>
<th></th>
<th>Frailty Related Phenotype</th>
<th>VACS Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy to perform</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Objective measure</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Validated in HIV patients</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Is associated with aging phenotype</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>Is associated with “inflammaging”</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Predict overall mortality</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Predict hospitalization</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Predict Polypathology</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Predict Neurocognitive impairment</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Predict cost for care</td>
<td>x</td>
<td>✓</td>
</tr>
</tbody>
</table>
Disability and co-morbidity greatly overlap with other deficits that might be used to define frailty and add to their ability to predict mortality.
Hypothetical association between frailty, HANA and immune activation / inflammation

Prevalence of Frailty

Immune deficiency

Immune activation

Age

Non-infectious comorbidities

AIDS associated conditions

clinical spectrum of HIV disease

surrogate markers of HIV disease

750 cells/µL

CD4+

VL

60 copies/mL

Inflammaging

(markers of immune activation, senescence and inflammatory cytokines)
Mr. A case study

To what extent Age change our clinical practice?

<table>
<thead>
<tr>
<th>Age</th>
<th>CD4</th>
<th>VL</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 yrs</td>
<td>250μL</td>
<td>73000/mL</td>
<td>Naive</td>
</tr>
<tr>
<td>45 yrs</td>
<td>650μL</td>
<td>&lt;40/mL</td>
<td>Experienced</td>
</tr>
<tr>
<td>65 yrs</td>
<td>250μL</td>
<td>73000/mL</td>
<td>Naive</td>
</tr>
<tr>
<td>75 yrs</td>
<td>650μL</td>
<td>&lt;40/mL</td>
<td>Experienced</td>
</tr>
</tbody>
</table>

The patient and his family provided consent to show these pictures
Hypothetical association between frailty, HANA and immune activation / inflammation

- Robust
- PRE-Frail
- PSEUDO-Frail
- FRAIL WITH HIV

Diagrams showing the relationship between frailty, immune deficiency, immune activation, and HIV disease markers such as VL (50 copies/mL) and CD4+ (750 cells/μL). The diagram also highlights non-infectious comorbidities and AIDS associated conditions.
Towards a Multidimensional conceptual approach to frailty

The possibility to explore a higher number of variables able to describe an HIV/AIDS specific multidimensional health status (specific vulnerability, social vulnerability, neurocognitive impairment, mood disorders, CMV viremia, …)

- Identify a broad “frailty window” in which specific interventions may reverse patient’s vulnerability
- Provide a quantitative score more suitable to assess changes across stress events and possibly effective interventions

We can take advantage of HIV specialist predisposition towards thinking about not just diseases, but the patients in whom they occur.
Towards a Multidimensional conceptual approach to frailty

Putative items/tools to be included in a multidimensional frailty index

<table>
<thead>
<tr>
<th></th>
<th>Mortality risk</th>
<th>VACS index</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Self-sufficiency</td>
<td>Instrumental Activities Of Daily Living (IADL)</td>
</tr>
<tr>
<td>3</td>
<td>Anthropometry/lipodystrophy</td>
<td>Mini Nutritional Assessment (MNA)</td>
</tr>
</tbody>
</table>
| 4 | Polypathology | Cumulative Illness Rating Scale (CIRS)  
|   |                | Pill Burden             |
| 5 | Neurocognitive/neurodegeneration | Patient health questionnaire (PHQ-9) for Depression  
|   |                | Hopkins verbal learning test-revised (learning trials) + Pegboard |
Take home messages

• Frailty in HIV care is a topic in its infancy
• Both frailty Phenotypic and Index definition have been used in HIV literature
• Frailty, assessed cross sectional and longitudinal, can predict death and clinical events in HIV infected patients.
• Pre-frailty patients are the ones who could best take advantage by intervention able to increase functional reserve at an organ level
• The possibility to explore a higher number of items able to describe an HIV/AIDS specific multidimensional health status of the patient.
Research gaps (cons)

- Built and validate a multidimensional frailty index
- ....
- Identify pharmacological and non-pharmacological intervention capable to improve frailty
- Validate Frailty as an end point for ARV efficacy/success
Priority research needs

1. Does recognising frailty improve clinical care and outcomes?
2. Does frailty inform decision around screening test?
Thank you....
...and keep fit!