Frailty and HIV: what is the evidence?
Disclosure

Dr Guaraldi has served as a consultant for Bristol-Myers Squibb, Abbvie, Theratecnologies, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, and ViiV Healthcare.

I’m getting old 😞
Who is frail? “I know it when I see it”

83 years old
HTN, Hyperlipidemia, prior MI

83 years old
HTN, Hyperlipidemia, prior MI
Frailty implication for clinical practice

Risk prediction

Trajectories of changes in the health status
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.

Fried, L. P. et al. (2001) The journals of gerontology 56(3)
Hypothetical age-at-diagnosis distributions of geriatric syndrome in the AIDS and general populations: Accelerated or accentuated (Premature)?

**Accelerated and Accentuated aging:** geriatric syndromes occurs earlier in persons with HIV than uninfected comparators, and more frequently.

**Accentuated aging:** geriatric syndromes occurs at the same ages in the HIV-infected population, but more often than among comparators. This configure a **Premature aging process.**

Aging Trajectories

Caveats in case comparison between HIV infected and un-infected individuals:

- Age distribution
- Gender representation
- Ethnicity representation
- Risk behaviour prevalence
- Marginalized groups representation
Pathogenesis of Frailty

**Aging Phenotypes**

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

**Evidences:**

- Multifactorial process
- Related to ageing
- Comorbidities important, but 25% of frail have no identified chronic disease
- Sarcopaenia (decreased muscle mass)
- Inflammatory markers, hormones, coagulation factors important
- 10% to 30% of frail people are obese

Reduction in functional reserve of multiple organs produce progressive deviations from a unique homeostatic system, organized in “Superaxes”, such as the immune, endocrine and bioenergetic systems which fail to obtain internal compensation and produce frailty.

Courtesy by Ferrucci L.
Frailty stratification can predict multimorbidity, geriatric syndromes, risk of institutional care, or death.
Could I predict this premature aging process?

2002

39 years old

CD4=477 cells/µL
HIV1-RNA<40 copies/mL
ABC+3TC+NEV

Heterosexual
HIV diagnosis in 1985

2013

49 years old

CD4=417 cells/µL
HIV1-RNA<40 copies/mL
ABC+3TC+NEV
Frailty recognition in clinical practice

Frailty Related Phenotype

Frailty as a deficit accumulation

Fried et al., J Gerontol Med Sc 2001

Rockwood et al. Lancet 1999;353:205-6
Frailty recognition in clinical practice

Frailty Related Phenotype

A person can be said to be frail if they have any 3 of the following features:
1. They move slowly.
2. They have a weak handgrip.
3. They have reduced their level of activity.
4. They have (unintentionally) lost weight.
5. They feel exhausted.

✓ “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 co-morbid illnesses

Frailty as a deficit accumulation

✓ Frailty can be operationalized as deficit accumulation and can be expressed in a frailty index.

✓ Can be summarised as a scale from Robust to Terminally ill

The number of deficits that an individual has
The total number of deficits considered

Fried et al., J Gerontol Med Sci 2001
Rockwood et al. Lancet 1999;353:205-6
A frailty index derived from routinely collected clinical data can offer insights into the biology of aging using mathematics of complex systems.

Valuable health deficits are clinical symptom, sign, disease, disability, or laboratory, imaging or abnormality, which 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) When considering the candidate deficits as a group, the deficits that make up a frailty index must cover a range of systems.
5) If a single frailty index is to be used serially on the same people, the items that make up the frailty index need to be the same from one iteration to the next.
Disability and co-morbidity in relation to frailty: How much do they overlap?

Olga Theou a, Michael R.H. Rockwood a, Arnold Mitnitski a,b, Kenneth Rockwood a,*

Disability and co-morbidity greatly overlap with other deficits that might be used to define frailty and add to their ability to predict mortality.
Is frailty treatable?

Fried: Yes
– Improve physical function
– Improve nutrition

Rockwood: Yes
– Ameliorate deficits
– Treat disease
– Improve physiological reserve
Factors associated with frailty-related phenotype (FRP) among HIV-positive individuals on HAART

- **HIV-related measures**
  - Longer time since diagnosis (Aging!)
  - Lower current CD4 count
  - Lower nadir CD4 count
  - Low CD4/CD8 ratio
  - Detectable viral load
  - Protease inhibitor-containing HAART regimen

- **Comorbidities**
  - Hepatitis C coinfection
  - Low BMI
  - High BMI
  - Lipodystrophy
  - Depressive symptoms
  - Cognitive impairment
  - Inflammation
  - Weak upper and lower extremities

- **Social factors**
  - Lower education
  - Current unemployment
  - Low income in past year

10,571 completed study visits from 1,946 MSM, 12% and 9% were FP+ among HIV+ and HIV− men, respectively (p = .002).

There was substantial fluctuation in expression of the FP (5%) driven by depressive symptoms, diabetes, kidney disease, hepatitis C infection, and cigarette smoking (associated with expression of the FP in elderly HIV− people).

The expression of the FP can be measured in pts HIV infection and reflect multisystem dysfunction in this population;
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>≥ 65</td>
<td>44</td>
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<table>
<thead>
<tr>
<th>CD4 cells/mm³</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
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<tbody>
<tr>
<td>≥ 500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>350 to 499</td>
<td>10</td>
<td>6</td>
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<tr>
<td>200 to 349</td>
<td>10</td>
<td>6</td>
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<tr>
<td>100 to 199</td>
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<td>10</td>
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<tr>
<td>50 to 99</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>46</td>
<td>29</td>
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<table>
<thead>
<tr>
<th>HIV-1 RNA copies/ml</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
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<tbody>
<tr>
<td>&lt; 500</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>500 to 1x10⁵</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>≥ 1x10⁵</td>
<td>25</td>
<td>14</td>
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<table>
<thead>
<tr>
<th>Hemoglobin g/dL</th>
<th>Restricted</th>
<th>VACS</th>
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<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>
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</table>

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

<table>
<thead>
<tr>
<th>eGFR mL/min</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<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>

<table>
<thead>
<tr>
<th>Hepatitis C Infection</th>
<th>Restricted</th>
<th>VACS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td></td>
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</tbody>
</table>

Tate J. et al.  IDSA 2010  Vancouver, BC October 21-24th. Poster 1136
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>Criteria</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>✗ ✓</td>
<td>✓</td>
</tr>
<tr>
<td>Validated in HIV patients</td>
<td>✗ ✓</td>
<td>✓</td>
</tr>
<tr>
<td>Is associated with aging phenotype</td>
<td>✓ ✗</td>
<td>✗</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>✗ ✓</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>✗ ✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Major caveats**

- Should not be used in pts < 65 yrs
- A Frailty Index should not include age or variables which cannot change over time
Hypothetical association between frailty, HANA and immune activation / inflammation
Hypothetical association between frailty, HANA and immune activation / inflammation
Mr. A case study

To what extent Pt Age changes 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 images.
Hypothetical association between frailty, HANA and immune activation / inflammation
A novel frailty index predicting outcomes in HIV patients

- We constructed an HIV frailty index (HIVFI) based on routine health variables.

**OBJ:** We hypothesized the HIVFI could predict multimorbidity at any age and HIV characteristics and discriminate between pts in the same age category with different mortality risk.

**Methods:** retrospective longitudinal study enrolling pts with ≥2 annual visits

**Results:** 2014 pts contributed 10816 visits, resulting in 15126 pt-years of follow-up.
- Multy-Morbidity (Mm) incidence was 23.9/1000/yr
- Mortality rate was 1.56/1000PY
List of deficits used in the HIVFI

**Clinical Diagnosis**
1. Cardiovascular disease
2. T2DM
   - Impaired fasting glucose
3. Lipoatrophy
   - Lipohypertrophy
   - Mixed form
4. Liver cirrhosis
   - NAFLD
5. Osteoporotic Fracture
   - Osteomalacia
6. Menopause / male hypogonadism
7. Hypertension
8. e-GFR

**Antropometric**
9. BMI
10. Waist
11. Visceral adipose tissue
12. Sarcopenia
13. Low bone mineral density

**Laboratory data**
15. Insulin resistance (HOMA)
16. Total cholesterol
17. LDL
18. HDL
19. TG
20. HCY
21. WBC
22. HB
23. Fib4
24. HCV+
25. HBsAg+
26. VitD insufficiency

**HIV Variables**
27. CDC group C classification
28. Cd4 nadir
29. Current CD4
30. HIV VL
31. ARV Therapy line >2

**Drugs**
32. Polyfarmacy

We excluded variables which were present <80% in each patient visits.
We excluded patients visits in which <80% of the deficit list were reported.

Linear regression between HIVFI and VACS

The third quartiles of HIVFI was chosen as Frail Cut off=0.28
Association between HIVFI and Mm at the end of follow up

Total sample: 1648 pts and 8721 visits
Median age 48 (IQR 44 – 52)
Median HIV duration 19 years (IQR 13.5 – 23.7)
Cox analysis to predict Mortality rate

In the follow-up period 25 deaths were observed
Mortality rate: 1.56/1000 PYFU
Poisson analyses to predict Mm

In the follow-up period 283 incident cases of Mm were observed
Incident rate for Mm: 23.9/1000 PYFU
Hypothetical association between frailty, HANA and immune activation / inflammation
Cox analysis to predict Mortality rate in pts with CD4>500/μL

<table>
<thead>
<tr>
<th>H.R.</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>0.92 – 1.22</td>
</tr>
<tr>
<td>Male Gender</td>
<td>0.31</td>
<td>0.07 – 1.27</td>
</tr>
<tr>
<td>Sedentary life</td>
<td>1.42</td>
<td>0.28 – 7.26</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.31</td>
<td>0.30 – 5.83</td>
</tr>
<tr>
<td>IDU</td>
<td>15.69</td>
<td>1.55 – 158.61</td>
</tr>
<tr>
<td>HIVFI (per 0.1)</td>
<td>3.22</td>
<td>1.10 – 9.42</td>
</tr>
</tbody>
</table>

Total sample: 1629 pts and 5673 visits
Median age 48.6 (IQR 45.9 – 52.9)
Median HIV duration 19 yrs (IQR 13.7 – 283.5)
ROC analyses to compare risk prediction of HIVFI and VACS for Mm in pts with CD4>500/μL
Discussion

HIVFI is a novel Index exploring aging as a cumulative deficit model.

This Index contributes to describing the complexity of aging and vulnerability in HIV pts and in predicting multimorbidity, particularly in those with effective immunovirologic responses.

Next steps

Validate Frailty in an independent dataset

Validate Frailty as an end point for ARV efficacy/success

Identify pharmacological and non pharmacological intervention capable to improve frailty

Priority research needs

Does recognising frailty improve clinical care and outcomes?
Acknowledgment

Zona S, Santoro A, Menozzi M., Mussi C., Mussini C.

Falutz J

Brothers TD, Kirkland S, Rockwood K

Thank you….and keep fit!