Physical Function & Frailty in HIV

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A “Frail” Fall
A “Fit” Fall
So many terms...
Agenda

• 1) Define the concepts of impairment, function limitations, disability, frailty and understand the significance of identification

• 2) What is currently known about the epidemiology of functional limitations and frailty in HIV

• 3) What is currently known about the pathophysiology of functional limitations and frailty in HIV

• 4) Next steps
Functional Status... the 6th vital sign?

- Tenets of care for the older adult:
  - Maintain independence
  - Prevent functional decline
  - Improve health-related quality of life

- Focus on function is a priority for the World Health Organization, the Institute of Medicine, Agency for Healthcare Research and Quality
  - US Healthy People 2020 Goal: “Improve the health, function, and quality of life of older adults”

- Rarely documented outside of nursing homes/geriatric clinics
What are we really describing?

- Classic “Disablement Model” by Nagi
- Extended by Verbrugge & Jette

Extra-individual Factors:
- Medical care & Rehabilitation
- Medications & Therapy
- External supports
- Built, physical, and social environment

Intra-individual Factors:
- Risk Factors
- Lifestyle & Behavior
- Psychosocial attributes & coping
- Activity accommodations

Pathology → Impairment → Functional Limitations → Disability

What are we really describing?

- **Impairment** = change in body function at the level of an organ or a body part
  - Physical examination, laboratory analyses, imaging
  - Examples: Hearing impairment, low muscle mass

- **Functional/Activity Limitation** = change in the ability to do something because of the impairment
  - Performance-based or self-report
  - Examples: 4-m walk, 6-minute walk distance, timed up-and-go

- **Disability** = difficulty carrying out activities in the environment
  - *Social phenomenon*
  - Self-report
  - Example: activities of daily living

Pathology → Impairment → Functional Limitations → Disability
What is “frailty”?  

• Frailty = “You know it when you see it”  
  • Dysregulation in multiple physiologic systems  
  • Associated with high vulnerability  

• How is it defined?  
  • Multiple indexes to capture  
  • Frailty index (deficit accumulation)- Rockwood Index  
  • Frailty phenotype defined by Fried (slowness, weakness, weight loss, low activity, fatigue)
Slower gait speed is associated with higher mortality

Figure 2. Predicted Median Life Expectancy by Age and Gait Speed

Studenski JAMA 2011
Frailty is associated with disability, falls, hospitalizations, and death

Table 5. Baseline Frailty Status Predicting Disability, Falls, Hospitalizations, and Death over 3 Years: Community-Dwelling Men and Women Aged 65 Years and Older, Cardiovascular Health Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratios* Estimated Over 3 Years Frail*** (Versus Not Frail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening mobility disability</td>
<td>1.50**</td>
</tr>
<tr>
<td>Worsening ADL disability</td>
<td>1.98**</td>
</tr>
<tr>
<td>Incident fall</td>
<td>1.29**</td>
</tr>
<tr>
<td>First hospitalization</td>
<td>1.29**</td>
</tr>
<tr>
<td>Death</td>
<td>2.24**</td>
</tr>
</tbody>
</table>

*Cox proportional hazards models, covariate adjusted (Ref. 17, reprinted with permission).

**p ≤ .05.

Why should we distinguish between limitations, frailty & disability?

<table>
<thead>
<tr>
<th>Health Concern</th>
<th>Implication</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional limitation</td>
<td>• High risk for disability/frailty</td>
<td>• Greatest potential to reverse with prevention/intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rehabilitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exercise, weight loss, nutrition</td>
</tr>
</tbody>
</table>

To summarize:

• Physical function impairment, disability and frailty are all important concepts in predicting outcomes
• Although *related*,
  • FRAILTY ≠ DISABILITY ≠ FUNCTIONAL LIMITATION
• Each may identify a risk for poor outcomes
  • Pathogenesis may be different
  • Treatment may be different
• Each of these are dynamic processes and intervention can prevent or reverse
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Impaired Exercise Capacity (V02) in HIV+ vs HIV-

- HIV+ had 41% lower age-adjusted V02 peak
- Older HIV+ had 26% lower exercise capacity vs younger HIV+
- 6-min walk distance only ~8% less than expected
- Older HIV+ adults have impaired aerobic capacity but maintain ability to complete day-to-day activities

- Exercise capacity can improve with training, thus is an example of a intervention to prevent a limitation from progressing to disability

Impairments in Exercise Capacity and Gait Speed

• Gait speed or 6 minute walk distance similar in HIV+ and HIV-

• V02 max, 6- minute walk distance, or gait speed worse/slower in HIV, particularly in those with AIDS
  • Mbada CE, et al. Health Qual Life Outcomes 2013

• Higher V02 peak associated with lower frequency of neurocognitive impairment
Gait speed declines faster in HIV+ vs HIV- men

Impairment on a Short Physical Performance Battery

- SPPB= 4-m walk, tandem stand, and chair rises
  - 12 possible points (highest function)

  - 33% had SPPB of 10 or less

  - 20% had SPPB of 9 or less

  - 22% had SPPB of 10 or less

- Chair stands had highest proportion of reduced performance in all 3 cohorts (nearly ½ had difficulty)
HIV and Physical Function Impairment Have Synergistic Effects on Mortality

- 12,270 person-visits (N=1627) ALIVE participants (30% with HIV)

Greene M. AIDS 2014
Impaired Balance in HIV+ Adults

• HIV+ have significantly worse performance on balance testing compared to HIV-

• 10-13% of HIV+ had difficulty with one-leg or heel-to-toe standing balance

• Impaired balance was associated with a >13-fold greater odds of recurrent falls in HIV+ adults
  Erlandson KM, et al. JAIDS 2012

www.ahrq.gov
Objective Physical Function Declines over 2 years in HIV

• 178 HIV+ adults (ANRS CO3 Aquitaine Cohort, France)
• Baseline and 2 year follow-up
• Median age 48 (IQR 43, 56); 81% men

<table>
<thead>
<tr>
<th>Test</th>
<th>Median</th>
<th>Estimated annual change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>5x sit-to-stand (s)</td>
<td>10.3</td>
<td>0.24 (0.07, 0.42)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>6 min walk (m)</td>
<td>520</td>
<td>-11 (-16, -6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10-m walk (m/s)</td>
<td>1.9</td>
<td>0.04 (0.02, 0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Timed up-and-go (s)</td>
<td>5.1</td>
<td>-0.27 (-0.34, -0.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time on 1 leg with eyes</td>
<td>16.0</td>
<td>1.49 (0.75, 2.23)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Richert L, et al. AIDS 2014
HIV-1 Infection Is Associated With an Earlier Occurrence of a Phenotype Related to Frailty

Loic Desquilbet,1 Lisa P. Jacobson,1 Linda P. Fried,2,3 John P. Phair,4 Beth D. Jamieson,5 Marcy Holloway,6 and Joseph B. Margolick,7 for the Multicenter AIDS Cohort Study

• “Frailty-Related Phenotype” (FRP) created from available subjective data in the MACS included 4 of the 5 frailty domains

• Exhaustion
  • Self-report of difficulty performing work due to physical health
• Low activity
  • Self-report of being “limited a lot” in vigorous activity
• Slowness
  • Self-report of being “limited a lot” in walking several blocks
• Shrinking
  • Self-report of unintentional weight loss >10 lbs
FRP among men with HIV

- HIV is associated with an earlier occurrence of FRP
- FRP prior to ART initiation is a predictor of AIDS/death (adjusted HR = 3.8)

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Frailty differs in prevalence across study populations

<table>
<thead>
<tr>
<th>Authors</th>
<th>Site</th>
<th>Study Population</th>
<th>Prevalence of Frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onen</td>
<td>SUN Study</td>
<td>Median age 47; 95% on ART</td>
<td>5%</td>
</tr>
<tr>
<td>Erlandson</td>
<td>Colorado</td>
<td>45-65 years; 100% on ART</td>
<td>8%</td>
</tr>
<tr>
<td>Onen</td>
<td>Wash U</td>
<td>≥18 years; 75% on ART</td>
<td>9%</td>
</tr>
<tr>
<td>Piggott</td>
<td>ALIVE</td>
<td>≥18 years; IVDU; 54% ART</td>
<td>15%</td>
</tr>
<tr>
<td>Pathai</td>
<td>Capetown</td>
<td>≥30 years; 87% on ART</td>
<td>18% ART 28% no ART</td>
</tr>
<tr>
<td>Rees</td>
<td>Arizona</td>
<td>Screened if CD4&lt;200, weight loss, neuropathy, or noncompliance</td>
<td>19%</td>
</tr>
<tr>
<td>Sandkovsky</td>
<td>Nebraska</td>
<td>n=20 of ≥ 50 years</td>
<td>20%</td>
</tr>
</tbody>
</table>

Frailty and HIV are associated with lower survival in the ALIVE Cohort

Figure 2. Survival by Frailty and HIV Status in the ALIVE cohort. Kaplan Meier Survival Curve Estimates for 2005 to December 2008. Frail- participants had a frailty score of 0–2; Frail+ participants had a frailty score of 3–5.

Frailty-related phenotype is predictive of mortality in HIV+

- Similar Adapted frailty-related phenotype derived from Veterans Aging Cohort Study participants
  - Weight loss (4 weeks), exhaustion, slowness (can’t walk a block), low activity (cannot run a short distance)

Akgun KM, et al. JAIDS 2014
Summary

• Both physical function impairments and frailty appear to occur more frequently in HIV-infected persons, particularly in those with low CD4 counts.

• Some degree of physical function limitation is common and is associated with poor outcomes.
Agenda

• 1) Define the concepts of impairment, function limitations, disability, frailty and understand the significance of identification

• 2) What is currently known about the epidemiology functional limitations and frailty in HIV

• 3) What is currently known about the pathophysiology of functional limitations and frailty in HIV

• 4) Next steps
What Contributes to Frailty or Physical Performance Limitations?

Deeks, Opening Plenary IAS, Malaysia 2013
Factors associated with frailty/functional limitations in HIV

- Colorado Cohort (n=360)
- HIV-infected men and women, ages 45-65 years
- On ART for at least 6 months with an undetectable viral load.
- All participants completed the Fried Frailty assessment and the SPPB.
- Identified the most robust (no deficits on either) and the most frail (deficits on both Fried and SBBP)
- Matched by age, gender, duration of HIV infection (N=80)
**Factors associated with frailty/functional limitations in HIV**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ T-cell activation</td>
<td>1.1</td>
<td>1.02, 1.3</td>
<td>0.02</td>
</tr>
<tr>
<td>↑ IL-6</td>
<td>1.2</td>
<td>1.02, 1.5</td>
<td>0.03</td>
</tr>
<tr>
<td>↓ Appendicular lean mass</td>
<td>1.2</td>
<td>1.1, 1.4</td>
<td>0.02</td>
</tr>
<tr>
<td>↓ Lumbar spine BMD</td>
<td>2.1</td>
<td>1.1, 4.0</td>
<td>0.02</td>
</tr>
<tr>
<td>↓ IGF-1</td>
<td>5.0</td>
<td>1.4, 20.0</td>
<td>0.02</td>
</tr>
<tr>
<td>↑ Cytomegalovirus IgG</td>
<td>4.0</td>
<td>1.2, 12.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

- Frailty was not associated with microbial translocation, immune senescence, or body fat

Factors associated with frailty in HIV

Table 2. Summary of Factors Associated With Frailty Among HIV-positive Individuals on Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>12, 13, 17, 32-34</td>
</tr>
<tr>
<td><strong>HIV-related measures</strong></td>
<td></td>
</tr>
<tr>
<td>Longer time since diagnosis</td>
<td>12</td>
</tr>
<tr>
<td>Lower current CD4 count</td>
<td>12, 13, 31-34, 44</td>
</tr>
<tr>
<td>Lower nadir CD4 count</td>
<td>12</td>
</tr>
<tr>
<td>Low CD4/CD8 ratio</td>
<td>31</td>
</tr>
<tr>
<td>Detectable viral load</td>
<td>13, 32</td>
</tr>
<tr>
<td>Longer duration of HAART</td>
<td>13</td>
</tr>
<tr>
<td>Protease inhibitor-containing HAART regimen</td>
<td>12</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C coinfection</td>
<td>33</td>
</tr>
<tr>
<td>Low BMI</td>
<td>12, 34</td>
</tr>
<tr>
<td>High BMI</td>
<td>38</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>13</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>12, 13, 32</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>12, 45</td>
</tr>
<tr>
<td>Inflammation</td>
<td>6</td>
</tr>
<tr>
<td>Weak upper and lower extremities</td>
<td>42</td>
</tr>
<tr>
<td>History of falls</td>
<td>36</td>
</tr>
<tr>
<td><strong>Social factors</strong></td>
<td></td>
</tr>
<tr>
<td>Lower education</td>
<td>12, 13, 32</td>
</tr>
<tr>
<td>Current unemployment</td>
<td>12, 35</td>
</tr>
<tr>
<td>Low income in past year</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.
Frailty: What is the contribution of HIV?

• Case-control design within the MACS Cohort
  • Frailty defined using the frailty-related phenotype (3-4 of 4 criteria)
  • Matched frail HIV+ case : non-frail HIV+ : non-frail HIV-
• Additional matching by age, visit #, HIV treatment (none, highly active ART, other ART)
• Adjusted for age, race, BMI, smoking status, hepatitis C, diabetes, dyslipidemia, and hypertension; nadir and current CD4, current detectable viral load, and type of ART (monotherapy or combination therapy).
# Frailty: What is the role of HIV?

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>HIV+ Frail vs non-Frail</th>
<th>Non-frail HIV+ vs HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ IL-6</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↑ CRP</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↑ sTNFR-1</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↑ sTNFR-2</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune</th>
<th>HIV+ Frail vs non-Frail</th>
<th>Non-frail HIV+ vs HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ T-cell Senescence</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↑ T-cell Activation</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone</th>
<th>HIV+ Frail vs non-Frail</th>
<th>Non-frail HIV+ vs HIV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ DHEA-S</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↓ Testosterone</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>↓ IGF-1</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>↑ HOMA-IR</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Erlandson KM, et al. Presented at the International Conference on Sarcopenia and Frailty, Boston 2015
All-cause mortality by FRP status in the MACS Cohort
Does Inflammation Explain the Relationship between FRP and Death?

Adjusted for:

- Univariate
- Detectable VL
- DVL, CD4+ < 350
- DVL, CD4+, IL6
- DVL, CD4+, CRP
- DVL, CD4+, TNFaR2
- DVL, CD4+, IL6, CRP, TNFaR2

Hazard ratio

1 1.25 1.5 1.75 2 2.2 2.5 3 3.5 4 4.5 5

3.53
3.09
2.69
2.6
2.47
2.42
2.3

15% reduction

\(^a\) All models, except univariate, included adjustment for black race, HCV, smoking status, BMI
Summary

• Inflammation, immune activation, and hormonal dysregulation are associated with functional limitations and frailty in HIV.

• Adjusting for inflammation among frail HIV-infected persons minimally changes the effects of frailty on mortality

• Intervening earlier may have greater impact on the trajectory
Agenda

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3) What is currently known about the pathophysiology of functional limitations and frailty in HIV

4) Next steps
Now what: #1 Define & Develop our Tools for HIV

• Many tools have been developed (and validated) in much older populations
• Ceiling/floor effects, particularly in younger populations
• Will depend on the outcome of interest (frailty vs functional limitation)
• May vary between the clinical and research setting
• Feasibility/time to complete
### Each Tool has Pro’s and Con’s

<table>
<thead>
<tr>
<th>Tool</th>
<th>Highly significant predictors (p&lt;0.01)</th>
</tr>
</thead>
</table>
| Fried Frailty         | *Psych disease*  
                         | Tobacco  
                         | *Low physical activity*  
                         | Pain  
                         | More meds/comorbidities |
| SPPB                  | *Diabetes*  
                         | *Low physical activity*  
                         | Pain  
                         | More meds/comorbidities |
| 400m walk             | *Obesity*  
                         | *Diabetes*  
                         | *Arthritis*  
                         | Pain  
                         | More meds/comorbidities |

Variables highly significant in identifying LOW function compared to HIGH function

Now what: #1 Define & Develop our Tools

• Should “frailty” in HIV be defined differently?

<table>
<thead>
<tr>
<th>Operational Definition</th>
<th>Domains</th>
<th>Objective Data in HIV</th>
<th>Proposed Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty Index</td>
<td>Cumulative deficits</td>
<td>VACS Index</td>
<td>VACS Index</td>
</tr>
<tr>
<td>Frailty phenotype</td>
<td>Weakness</td>
<td>Grip strength, Chair stand</td>
<td>Chair stands</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>Muscle mass, Obesity</td>
<td>DXA</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>V02 peak</td>
<td></td>
<td>6-MWD</td>
</tr>
<tr>
<td>Slowness</td>
<td>Short distance walk</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Low activity</td>
<td>Accelerometer</td>
<td></td>
<td>Accelerometer</td>
</tr>
</tbody>
</table>

“Cognitive frailty”

HIV-related characteristics

Slide courtesy of KrisAnn Oursler, 2014
Now what: #2 Integrate the tool in clinical & research settings

- Could be as simple & easy as a 6th vital sign done with blood pressure, heart rate, weight
- Identify those at risk of a more rapid decline so that earlier interventions can be introduced.
- Understand the impact & mechanisms of interventions.
  - Example: REPRIEVE
Now what: #3 Test Interventions

• Example: Exercise!
• 36 HIV+ and 36 HIV- sedentary men and women ages 50-70
• Cardiovascular & resistance exercise 3 times/week
Exercise for Health Aging: Main Objectives

• Primary outcome: Does moderate or high intensity exercise lead to improvements in physical function (1° = chair rise time)?

• Questions:
  • Does the ideal intensity of exercise differ between people with or without HIV?
  • Does a higher intensity of exercise lead to greater reduction in inflammation?
  • Or does more intense exercise lead to more injuries, more inflammation, and less motivation to finish?
  • Other outcomes: V02, SPPB, 1-RM, step count, QoL, depression scores, sleep
Exercise for Health Aging: Preliminary Data

Change in Exercise Tolerance

Time point

Week to Complete 10 Chair Rises (seconds)

Seconds

10 20 30

10 20 30

Entry Week 4 Week 10 Week 16 Week 22

Weeks

Weeks

ml/kg/min

20

25

30

35

40

45

1 2 3

Change in Exercise Tolerance

ml/kg/min

1 2 3

Time point

29 enrolled; 4 completed
Summary

• Physical function limitations and frailty provide a important, easy to obtain, inexpensive measure of how our patients aging with HIV are really doing

• Routinely implementing a measure of physical function or frailty in the clinical setting or research setting can:
  • Advance understanding of the underlying causes
    • HIV vs age vs other comorbidities vs lifestyle
  • Guide interventions to prevent, slow, or reverse impairments
Thank you ~ Questions?