

# Integrating Frailty and Functional Outcomes into Clinical Trials (and the Clinic)

Kristine Erlandson, MD MS

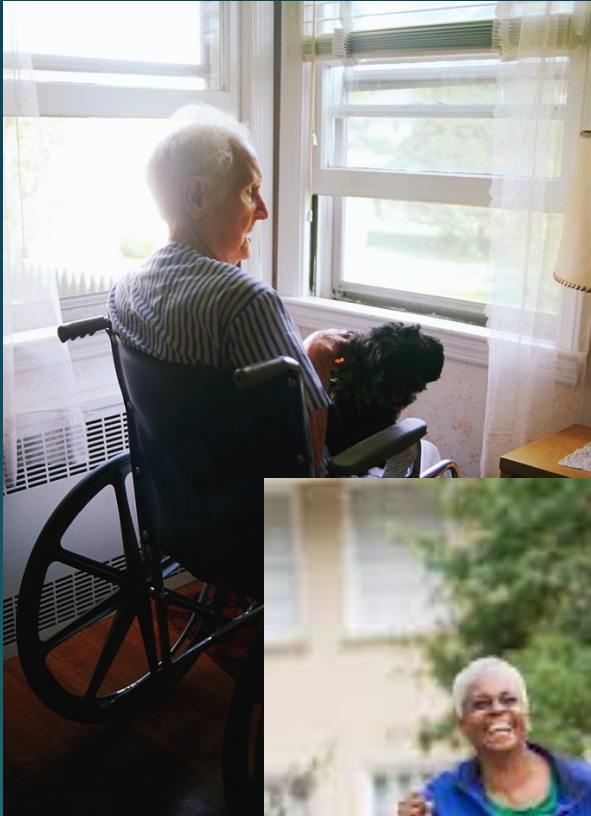
*University of Colorado, Aurora, CO. USA*

*Disclosure:* [Click to add the financial relationships you have with ineligible companies (previously defined as “commercial interests”). If you have no financial relationships, specifically note “None”]





# Ranges of Physical Function



Photograph: Howard Schatz @SchatzOrnstein 2019



Dr. Anthony Fauci, age 81

David Kirby, dying of AIDS at age 32

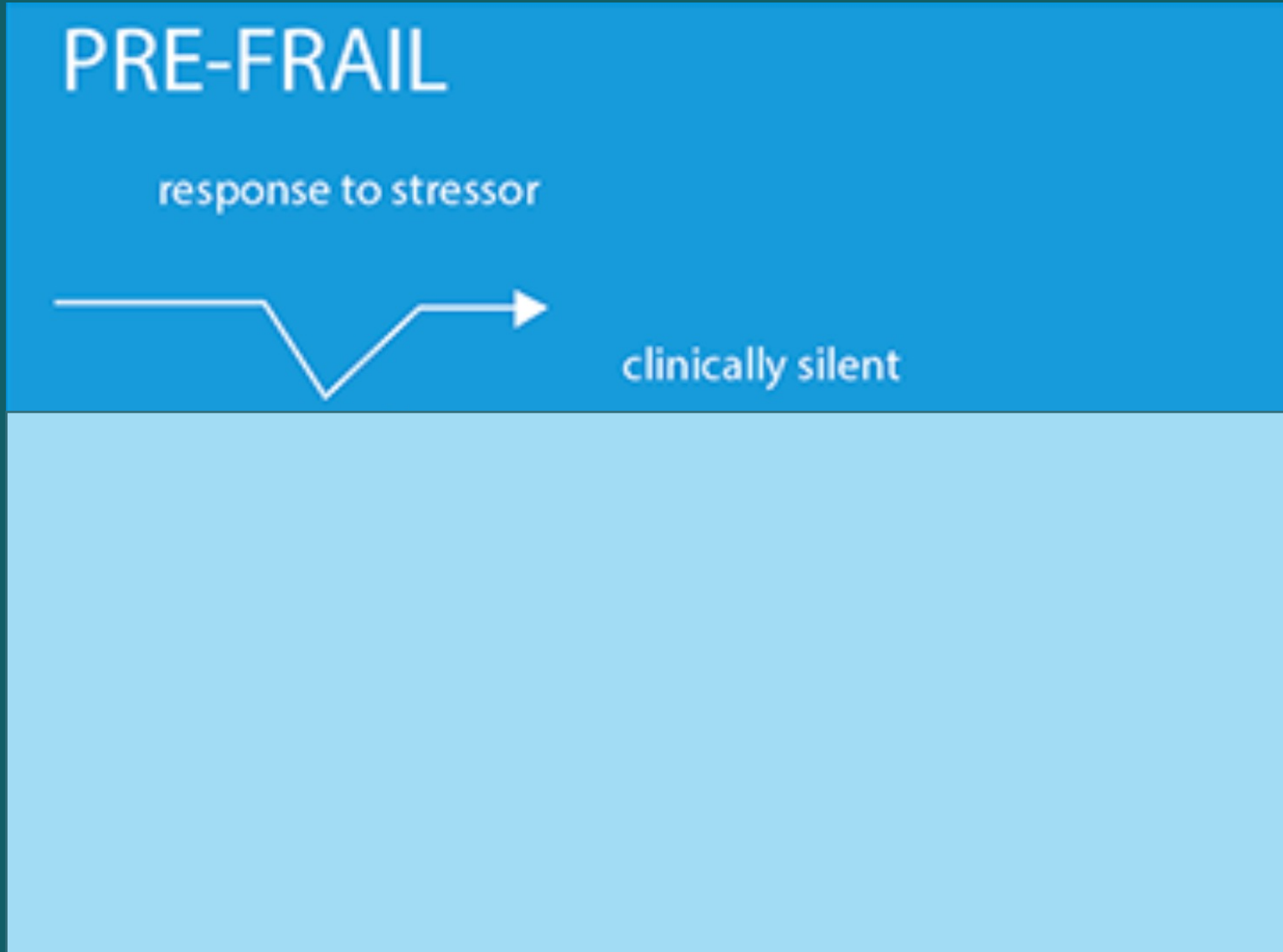
[http://www.mountsinai.on.ca/about\\_us/news/2014-news/why-have-type-1-diabetes-patients-done-so-well/](http://www.mountsinai.on.ca/about_us/news/2014-news/why-have-type-1-diabetes-patients-done-so-well/)  
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<https://rarehistoricalphotos.com/father-son-deathbed-david-kirby-1989/>  
<https://howardschatz.com/above-and-beyond-with-dr-anthony-fauci/>

# Physical Function or Functional Impairments

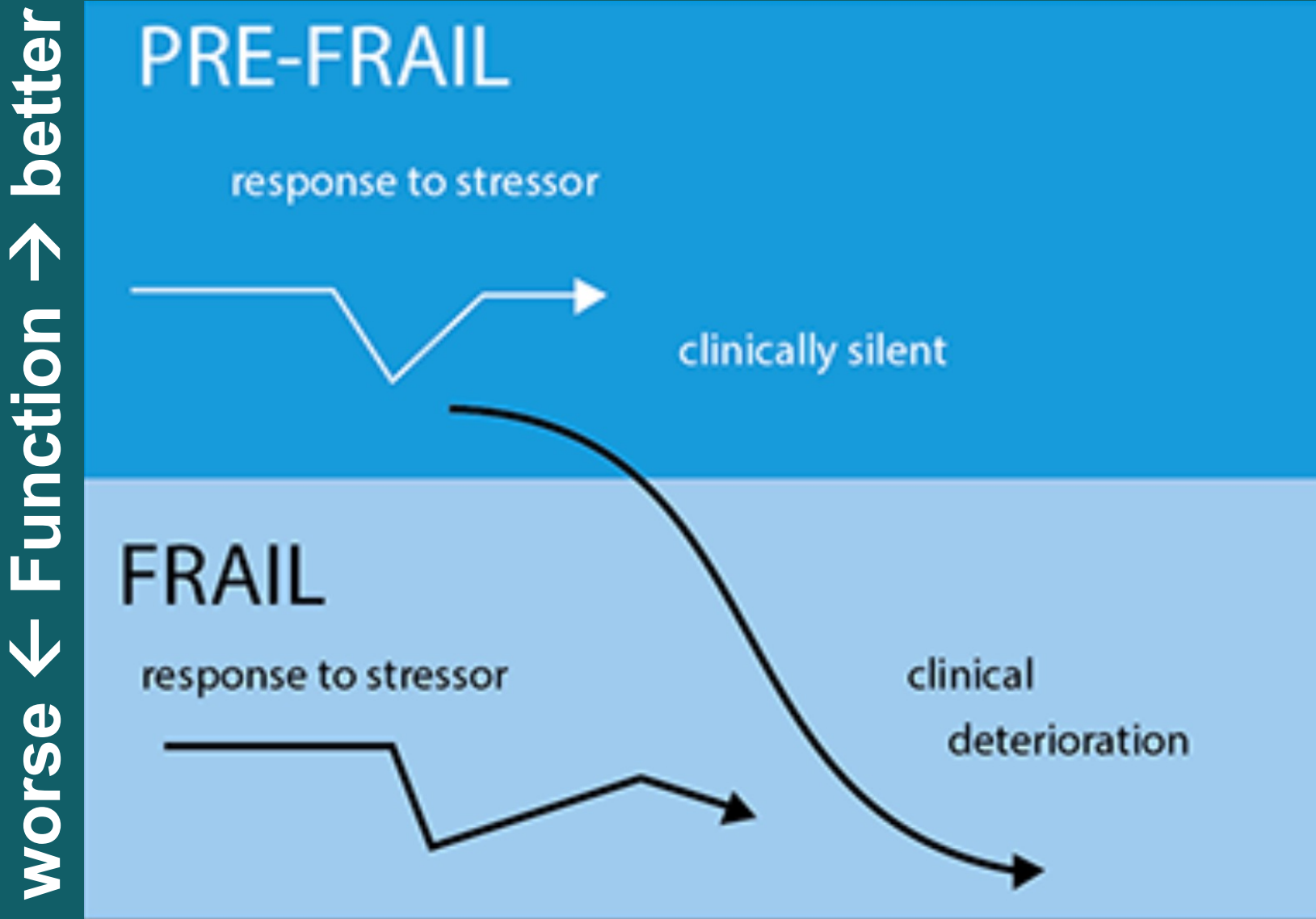
- Objective assessments or self-report
- 100s of different assessments available
- *Examples:*
  - Activities of daily living
  - Gait speed by 4-m, 400-m, or 6-minute walk
  - Short Physical Performance Battery (or its components)
  - Timed up-and-go
- “Impaired” can be defined differently: scale, cut-point, continuous

# What is Frailty?

worse ← Function → better



# What is Frailty?



# How is Frailty Defined?

## Frailty *Phenotype* (Fried)

- Reflects a *vulnerability* as result of multiple impairments:
  - Slow gait
  - Weak grip
  - Low activity
  - Fatigue
  - Weight loss
  
- Takes ~ 5-10 minutes to assess
- Requires a dynamometer
- Must be assessed prospectively
- Scored 0-5



# How is Frailty Defined?

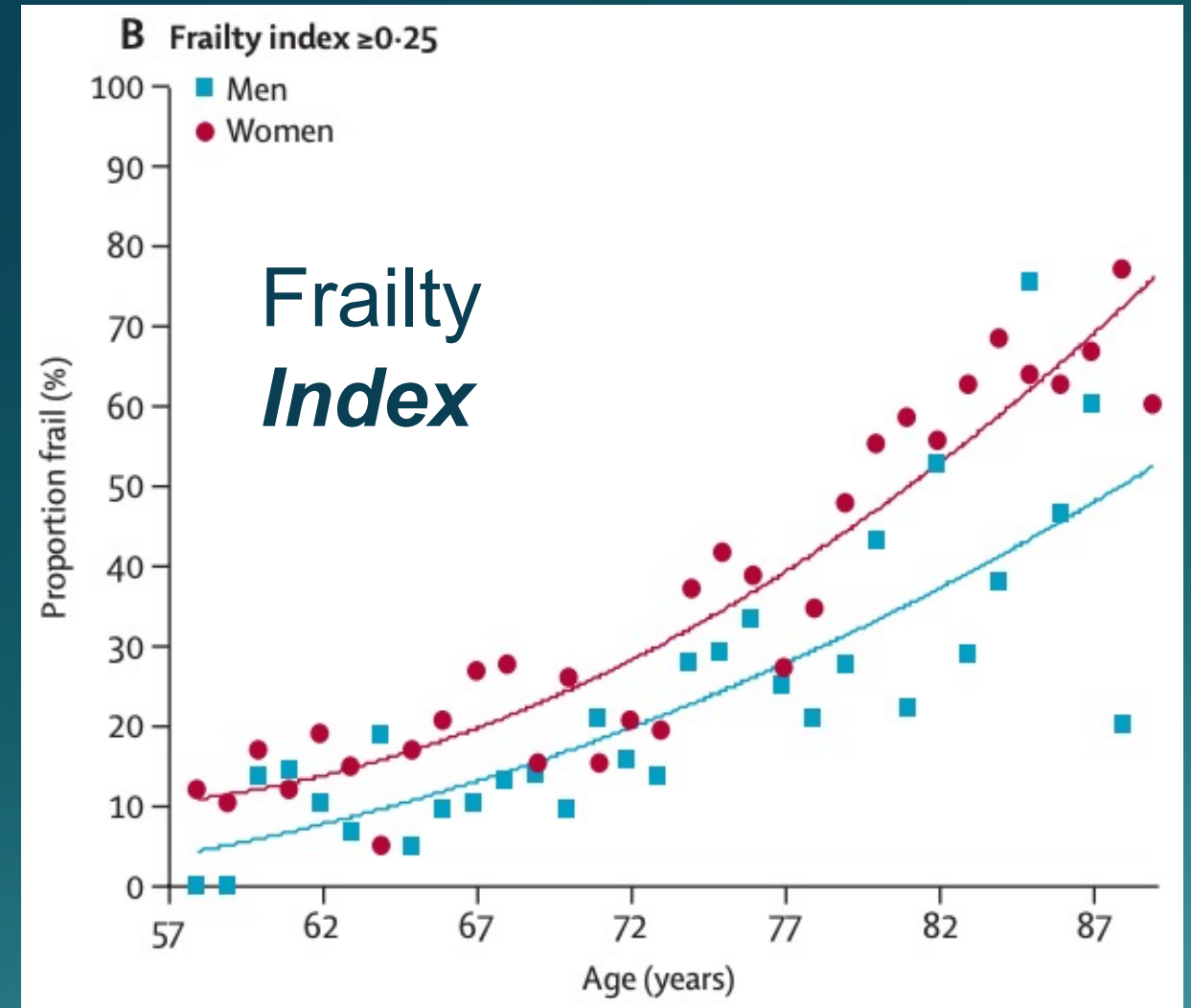
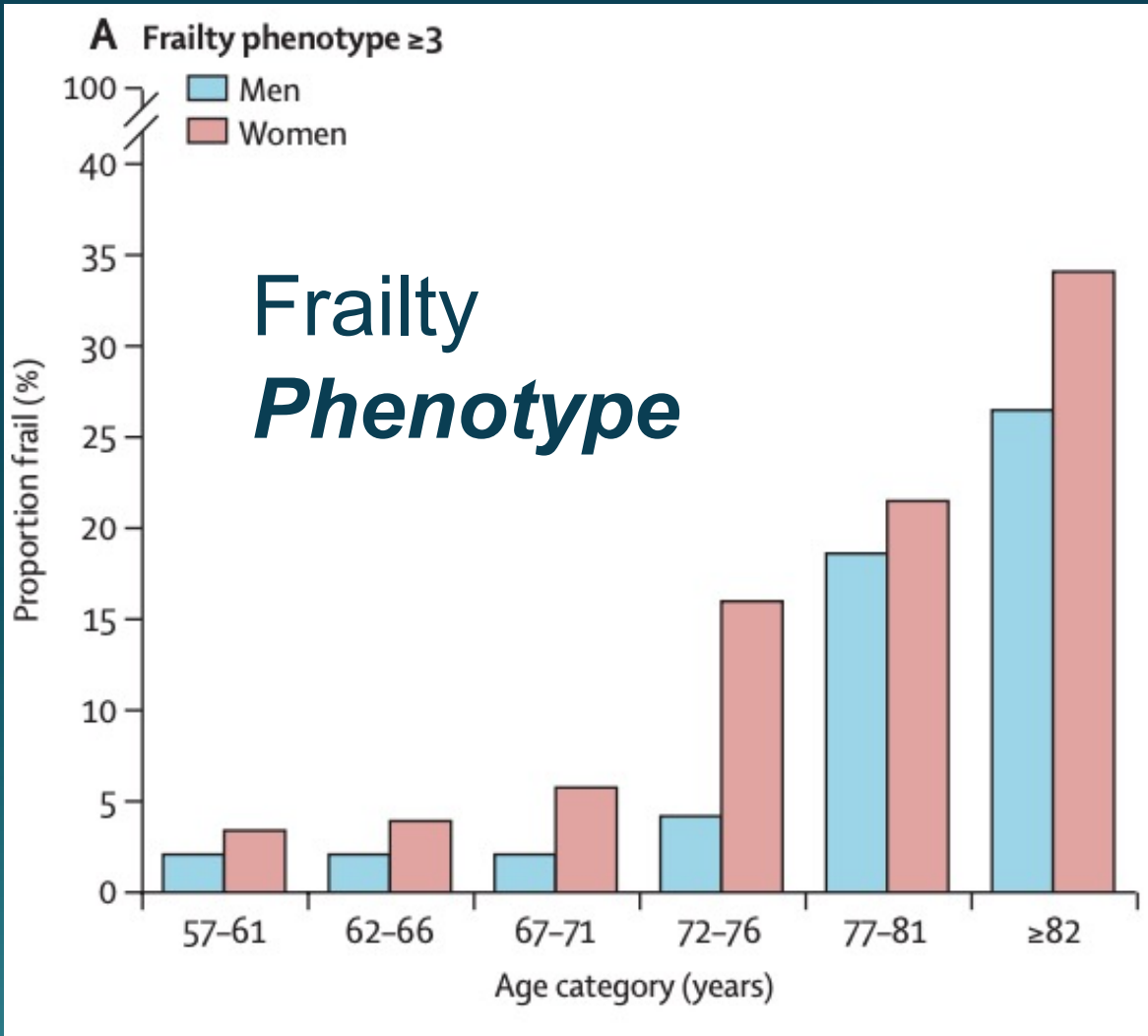
## Frailty Phenotype (Fried)

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  - Weak grip
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  - Weight loss
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## Frailty Index (Rockwood)

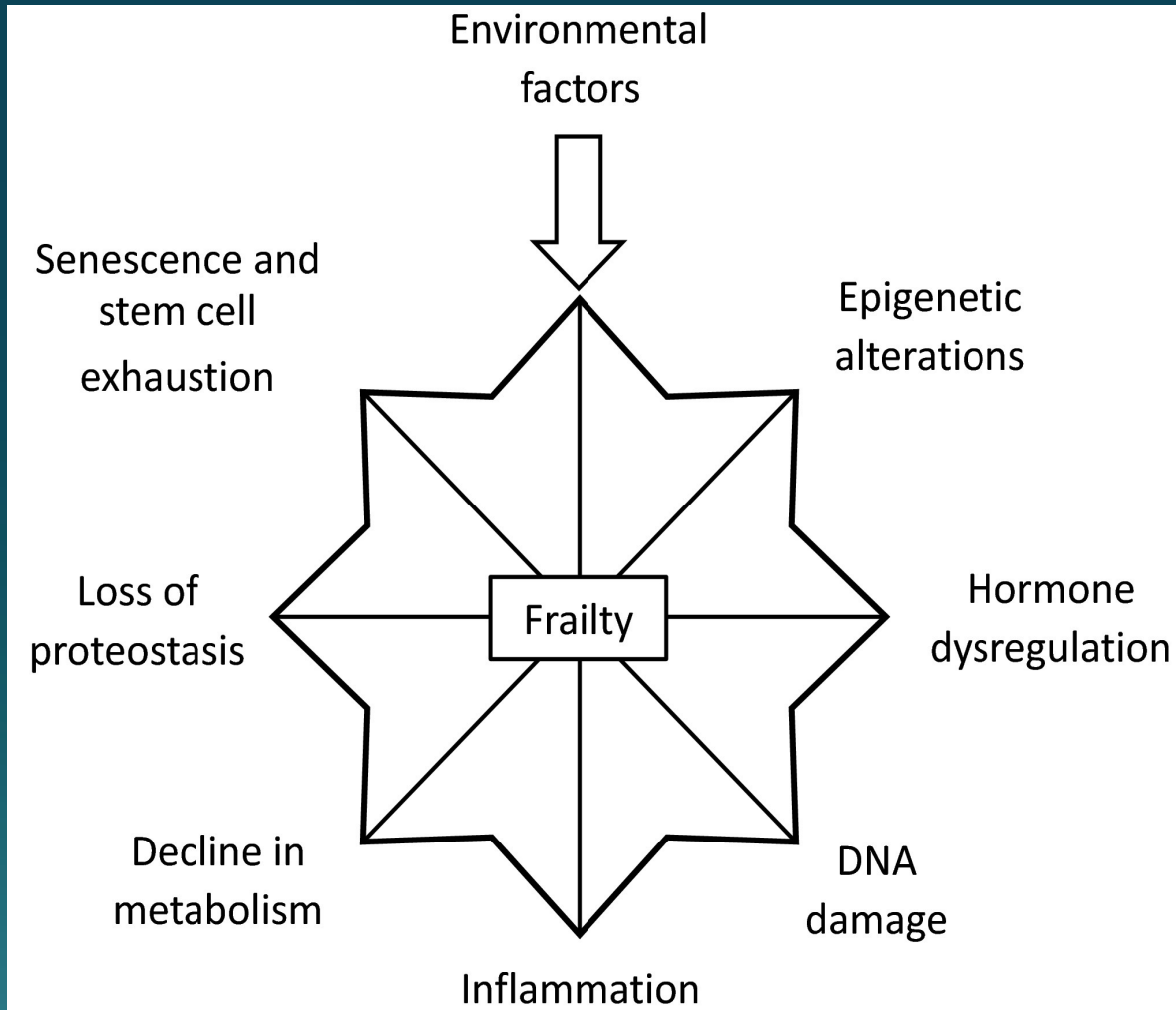
- *Accumulation of deficits*
- Variables that increase with age and are associated with health status
- Can often be derived from chart review
- Differs by cohort/health system
- Expressed as ratio of # of variables impaired/ # variables assessed
- Scored 0-1
- Veterans Aging Cohort Study Index is similar concept

# Frailty Increases with Age (HIV-uninfected)





# Why do we think about frailty and functional impairments in HIV?



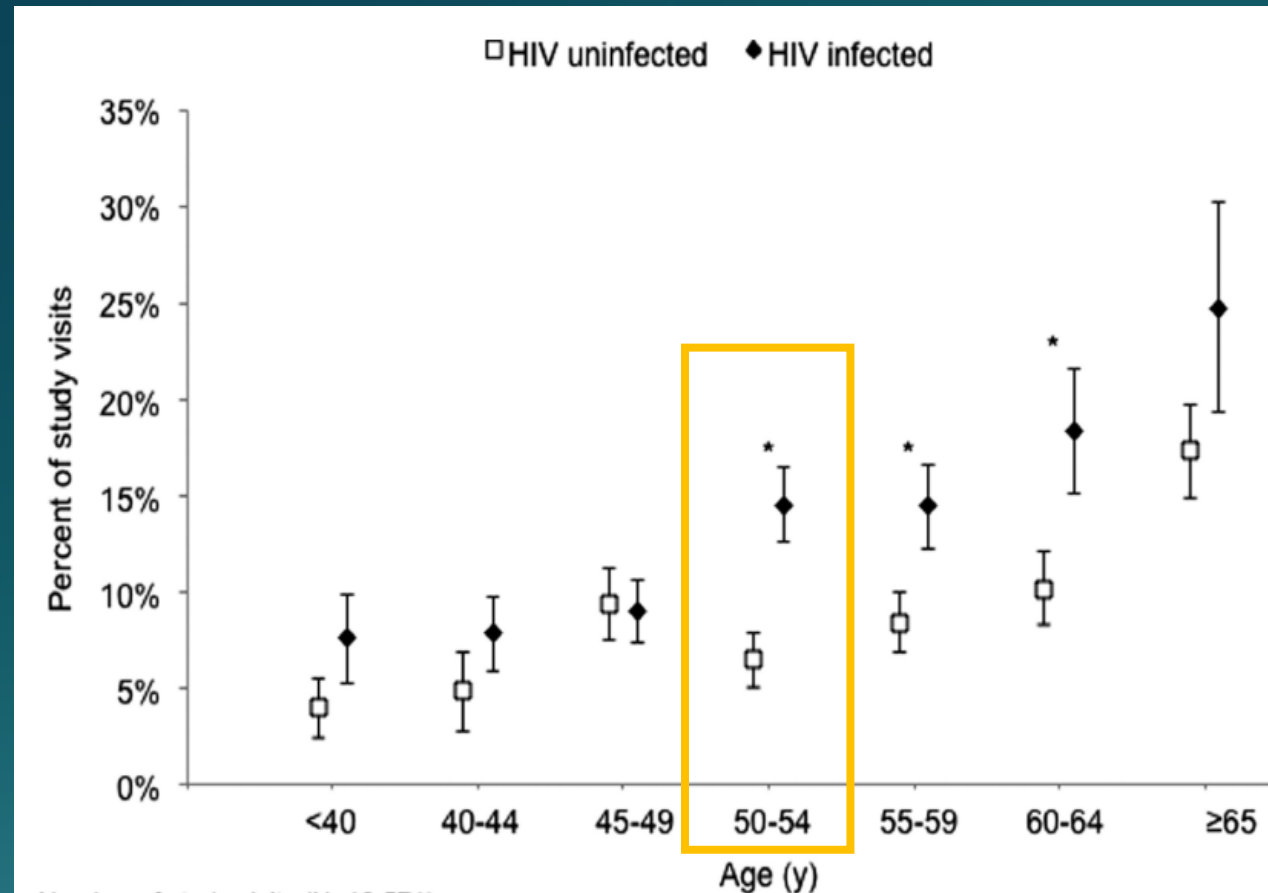
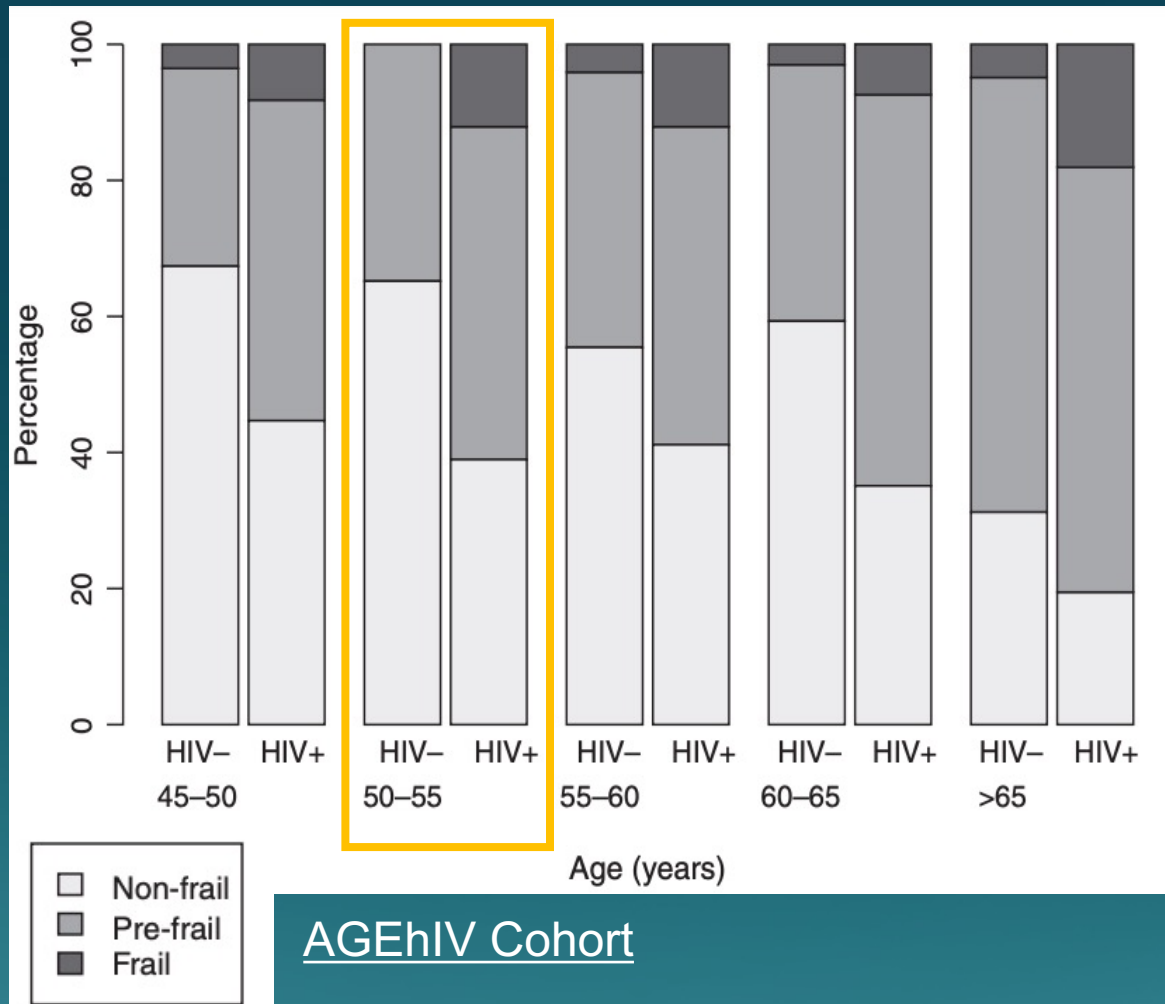
## Recent publications linking frailty to the aging pillars among people with HIV:

*Sanchez-Conde M, et al. Epigenomics 2019*  
*Shiau S, et al. Clin Infect Dis 2021*  
*Zhang, et al. Clin Epigenetics 2018*  
*Masters MC, et al. AIDS 2022*  
*De Vincentis S, et al. Euro J Endo 2021*  
*Chow DC, et al. Clin Infect Dis 2020*  
*Erlandson KM, et al. J Infect Dis 2017*  
*Johnston CD, et al. JAIDS 2021*  
*Tran T, et al. JAIDS 2022*  
*Derry HM, et al. J Geron B Psychol Sci Soc Sci 2022*  
*Edwards A, et al. Afr J AIDS Res 2020*  
*Alvarez S, et al. PLoS One 2020*  
*Sun J, et al. Clin Infect Dis 2018*  
*Margolick JB, et al. J Infect Dis 2018*  
*Tan JY, et al. J Int AIDS Soc 2021*  
*McMillan JM, et al. AIDS Patient Care STDs 2020*

# Frailty occurs earlier among people with HIV

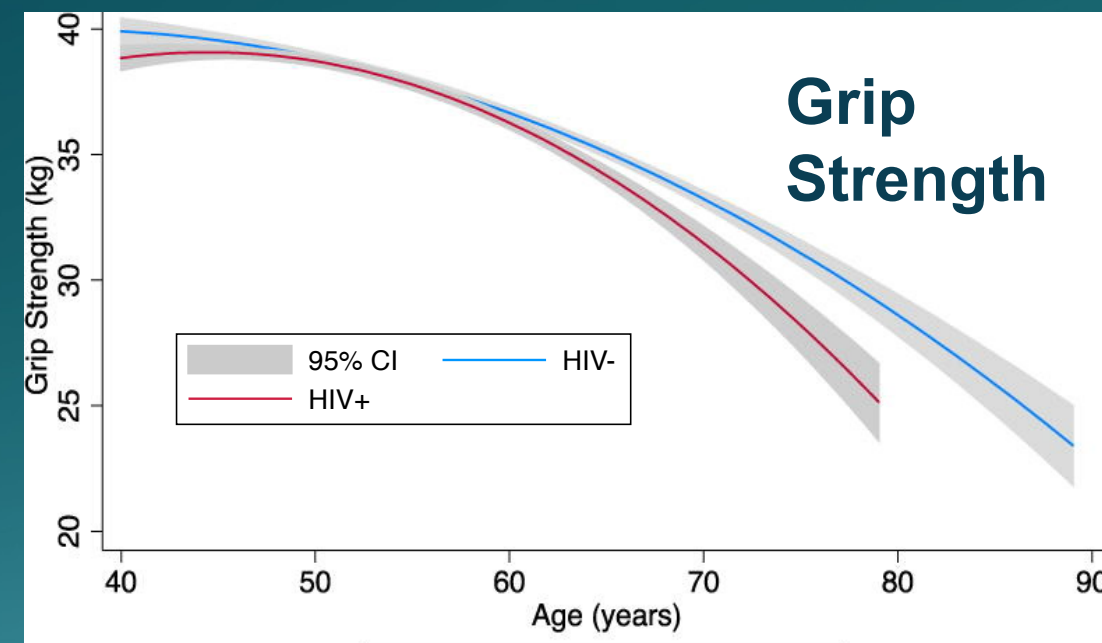
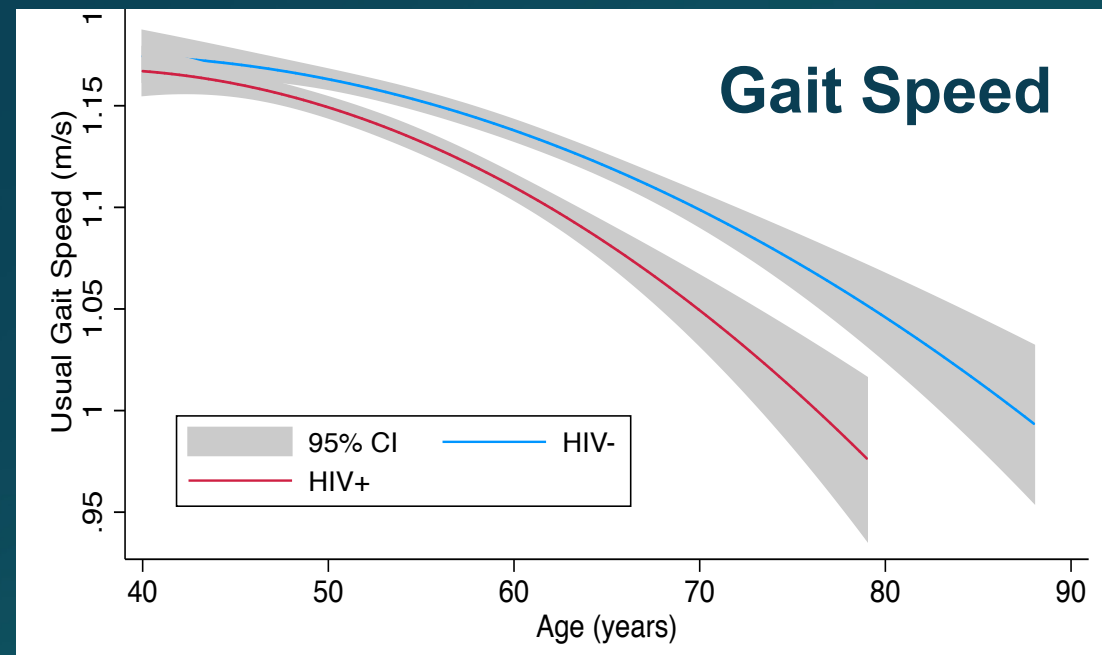
10% frail PWH vs 0 frail in controls

15% frail PWH vs 7% frail in controls



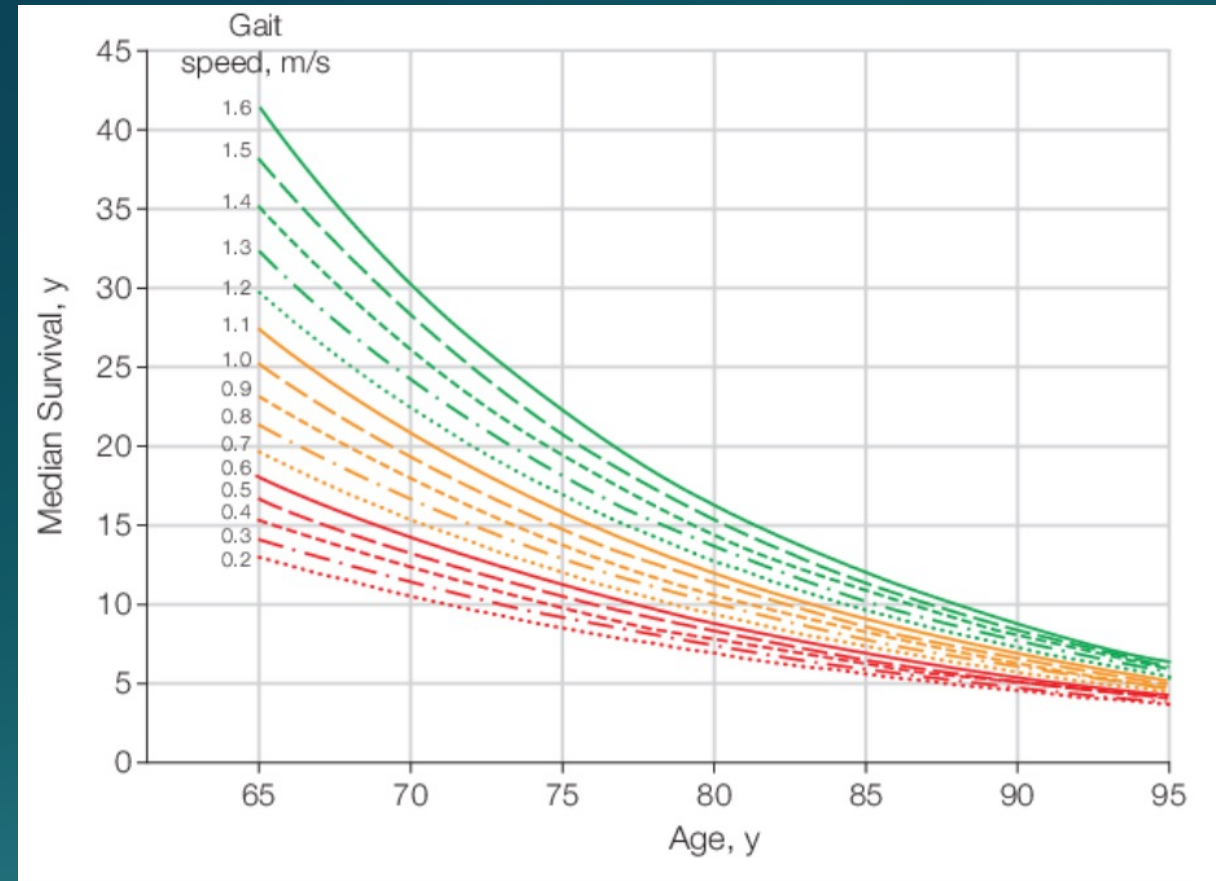
# Physical Function Impairments Greater Among Older Adults with HIV

- Greater gait speed and grip strength decline with age among PWH compared to controls



# Why are frailty and function impairment important?

- Strong association with mortality
- Major predictor of independence
- Associated with falls and fracture
- Associated with increased risk of some comorbidities

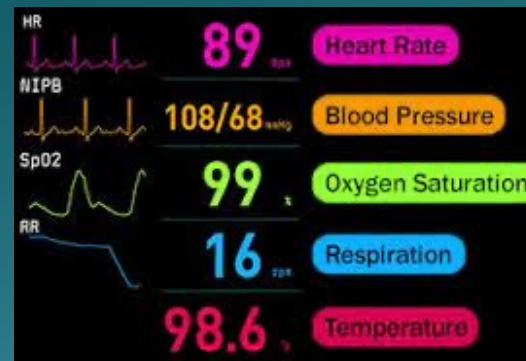
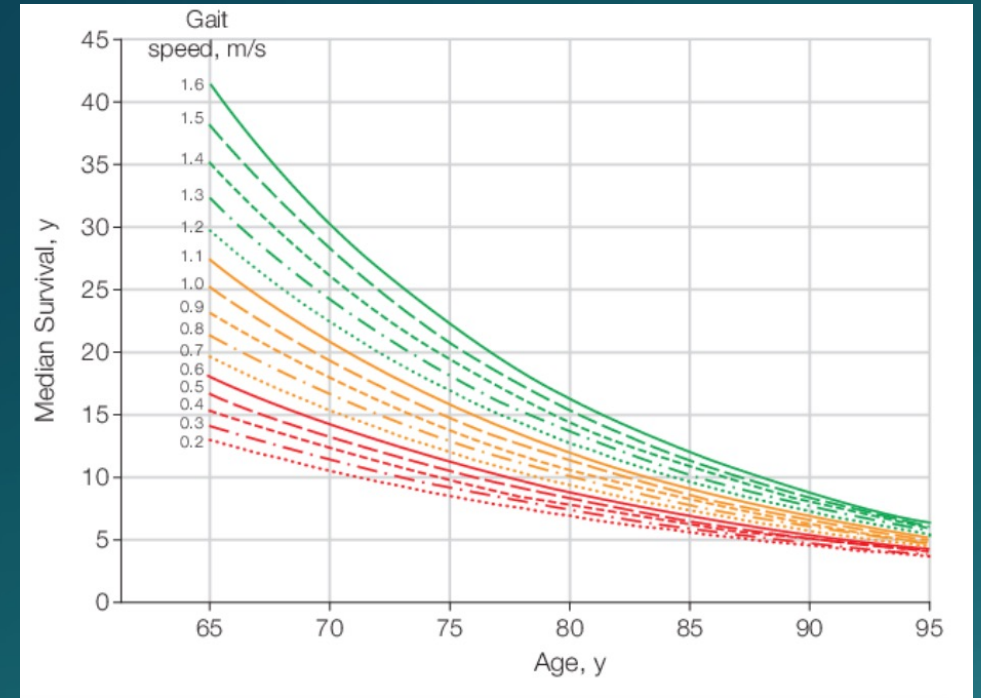


Verheij E, et al. JAIDS 2021  
Pelloquin R, et al. JAIDS 2020  
Piggott DA, et al. AIDS 2020  
Kelly SG, et al. Clin Infect Dis 2019  
Erlandson KM, et al. Clin Infect Dis 2019  
Tassiopoulos K, et al. AIDS 2017

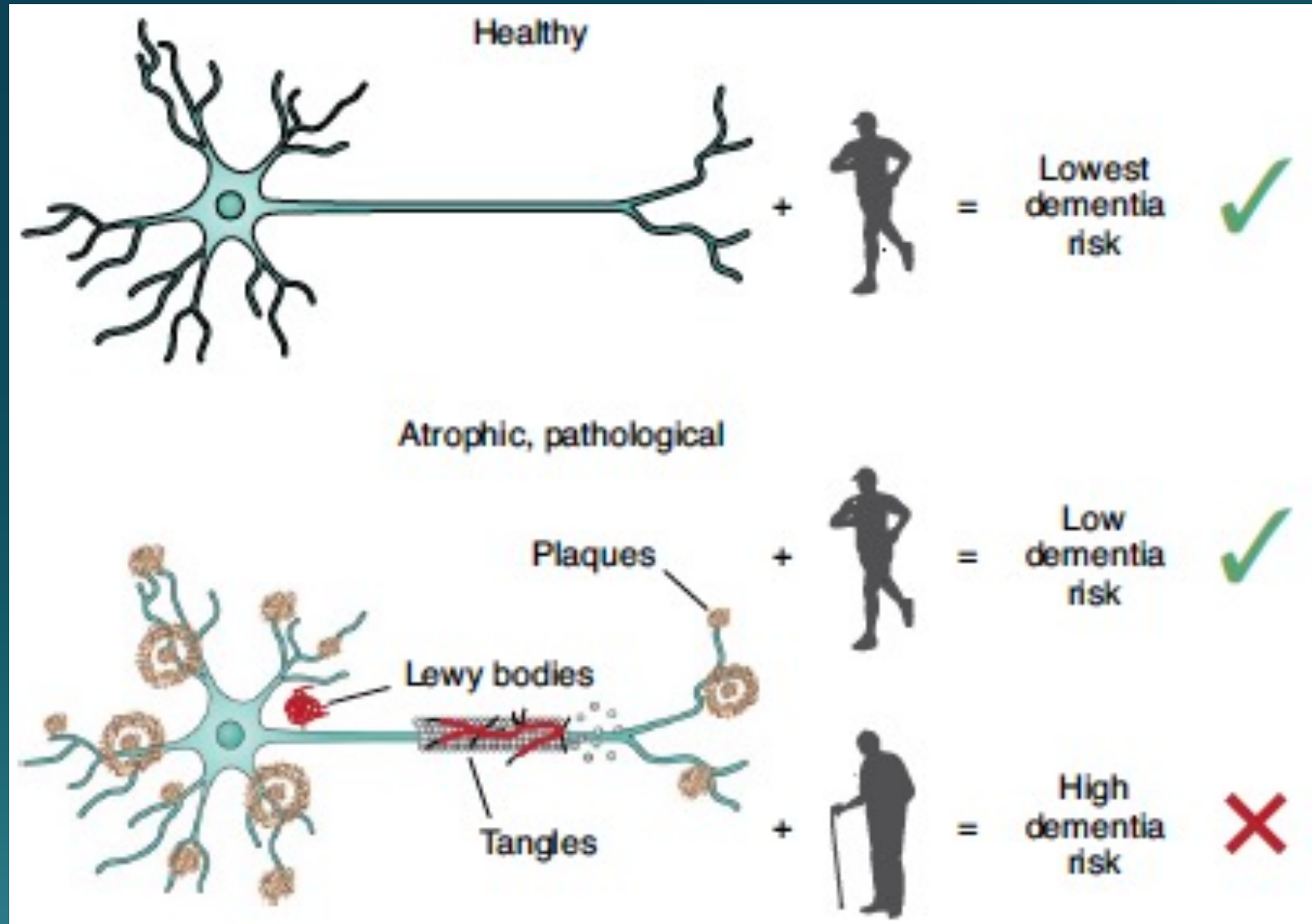


# Why are frailty and function impairment important?

- Strong association with mortality
- Major predictor of independent living
- Associated with falls and fracture
- Associated with increased risk of comorbidities
- A more informative vital sign?



# Frailty can help us understand the *expression* of disease



# How can we incorporate frailty/physical function in interventions?

## 1. Interventions that change frailty/function or the trajectory of frailty/function

- Primary or secondary outcomes

### Exercise in PWH over 12 weeks (n=32)

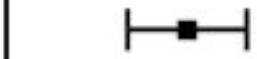
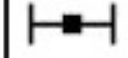
<u>Physical function</u>	<u>% Change</u>	<u>P-value</u>
Chair rise	-20 (-24, -16)	<0.01
400-m gait speed	-6 (-8, -3)	<0.01
Stair climb	-5 (-9,-2)	<0.05
Grip strength	+4 (0, 9)	NS
Bench press	+27 (22,31)	<0.01
Leg press	+16 (11,22)	<0.01
VO <sub>2</sub> max	+11 (7, 15)	<0.01

### Dasatinib/quercetin in people with IPF (n=14)

<u>Physical function</u>	<u>Change</u>	<u>P-value</u>
6-min walk distance (m)	+21.5 ± 28	0.012*
4-m gait speed (m/s)	+0.12 ± 0.2	0.024*
Timed chair-stands (s)	-2.2 ± 3	0.013*
SPPB score	+0.9 ± 1	0.003*
Grip strength (kg)	-0.6 ± 2	0.31

# How can we incorporate frailty/physical function in interventions?

1. Interventions that change frailty/function or the trajectory of frailty/ function
2. Frailty/function modifies the intervention or effect
  - Statins
    - Kutner et al. JAMA Intern Med 2015 benefits in stopping statins with advanced disease
    - Campitelli et al. CMAJ 2019 no benefit of high vs moderate dose statin in long-term care
  - Fall risk highest in PWH with both peripheral neuropathy + frailty

Variable	Odds of Falling (OR [95% CI])
Peripheral Neuropathy	
Frail vs Non-Frail	 17.7 (6.89-45.5)
Pre-Frail vs Non-Frail	 2.85 (1.48-5.47)



# How can we incorporate frailty/physical function in interventions?

- 1. Interventions that change frailty/function or the trajectory of frailty/ function**
- 2. Frailty/function modifies the intervention**
  - Statins
- 3. Improve outcomes in those who are frail**
  - “Pre-habilitation” for frail individuals before surgery

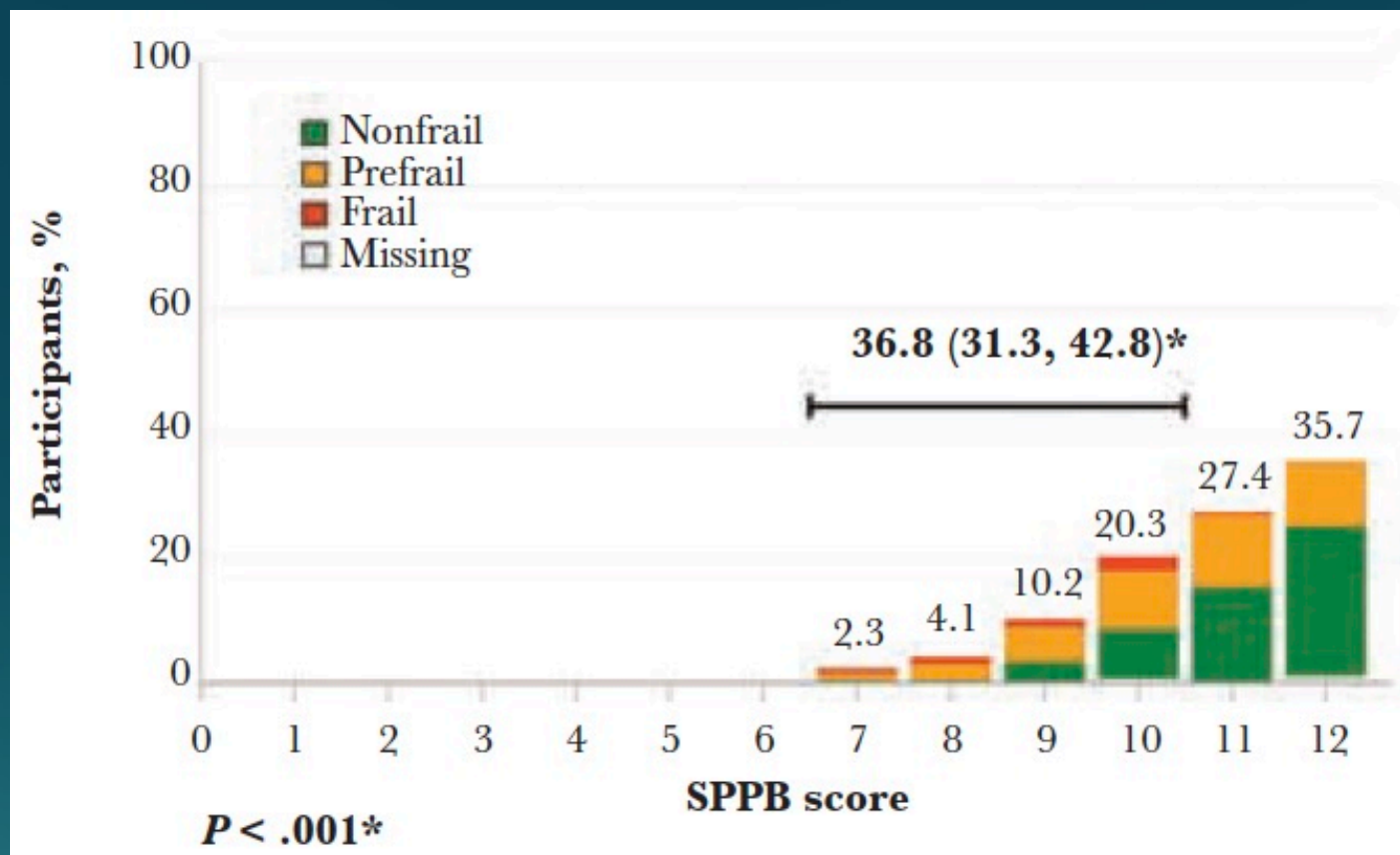
# Things to consider when incorporating frailty/functional outcomes in clinical trials

## 1. Prevalence

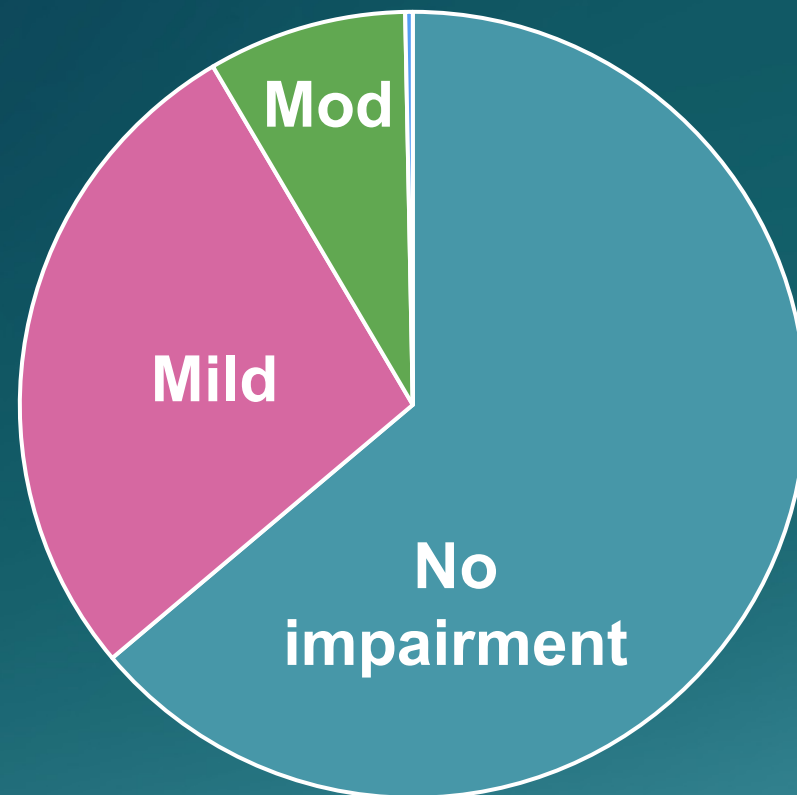
- Frailty is relatively uncommon, particularly in “younger” populations

<u>Authors</u>	<u>Study Population</u>	<u>Prevalence</u>
Onen	Median age 47; 95% on ART	5%
Erlandson	Aged 40+, 99% on ART	6%
Umbleja	Age 40+, substudy of REPRIEVE	6%
Onen	≥18 years; 75% on ART	9%
Kooij	Age 45+, 94% on ART	11%
Allavena	SEPTAVIH Study of 510 PWH aged ≥70 yrs	13.5%
Piggott	≥18 years; IVDU; 54% ART	15%

# Physical Function Impairments More Common than Frailty in PWH



## Self-reported impairment



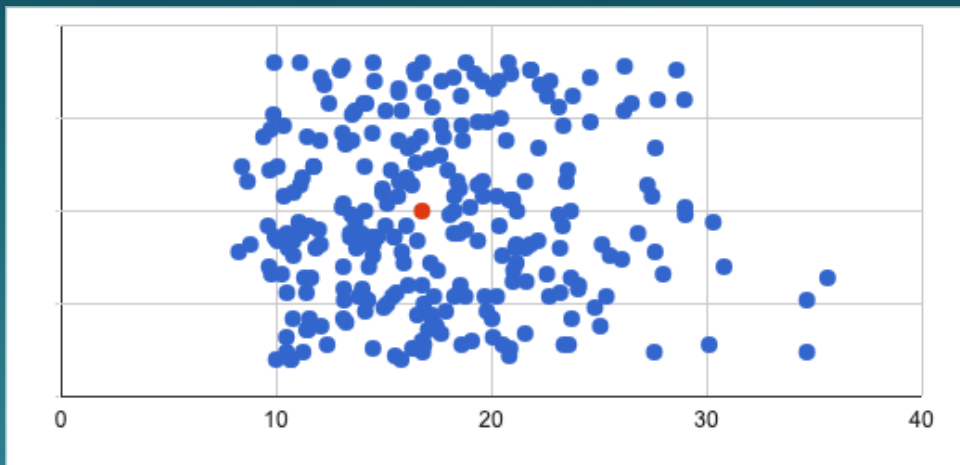
Almost 40% of low-risk middle-aged people with HIV have functional impairments

# Things to consider when incorporating frailty/functional outcomes in clinical trials

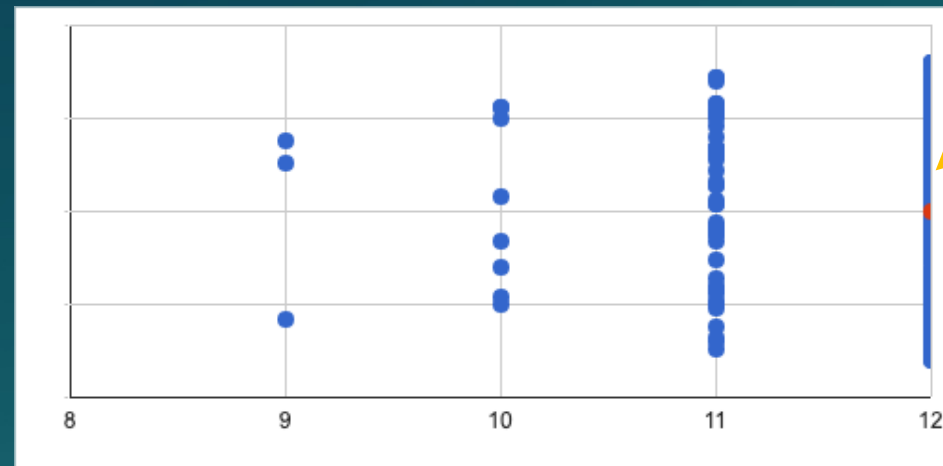
## 2. Responsiveness to therapeutic interventions

- Ceiling or floor effect?
- Can it be modified?

Time to rise from a chair 10 times



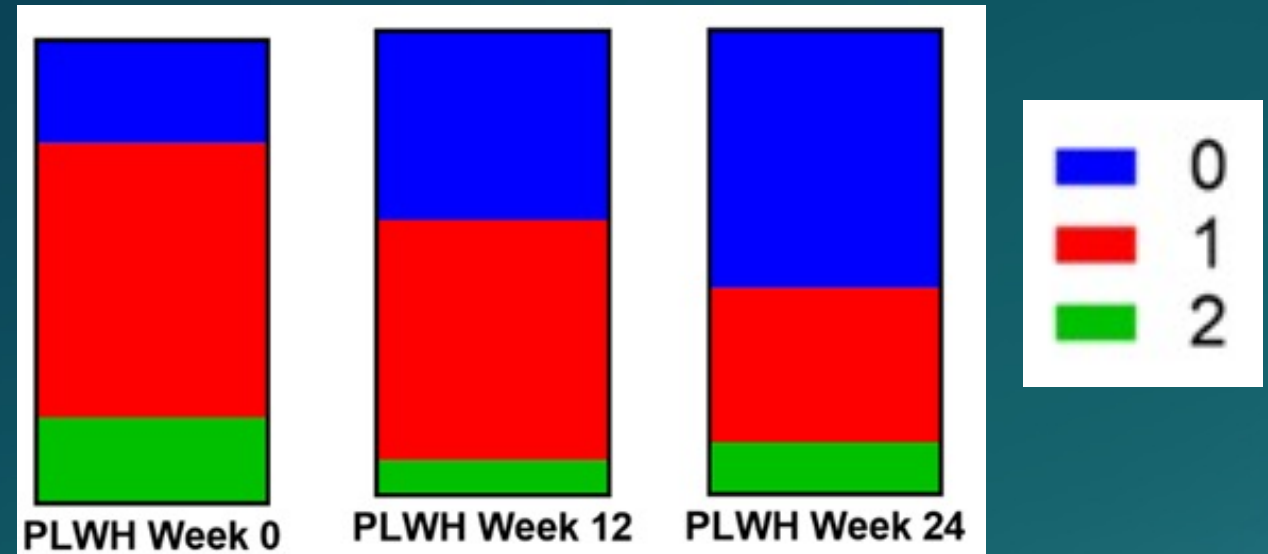
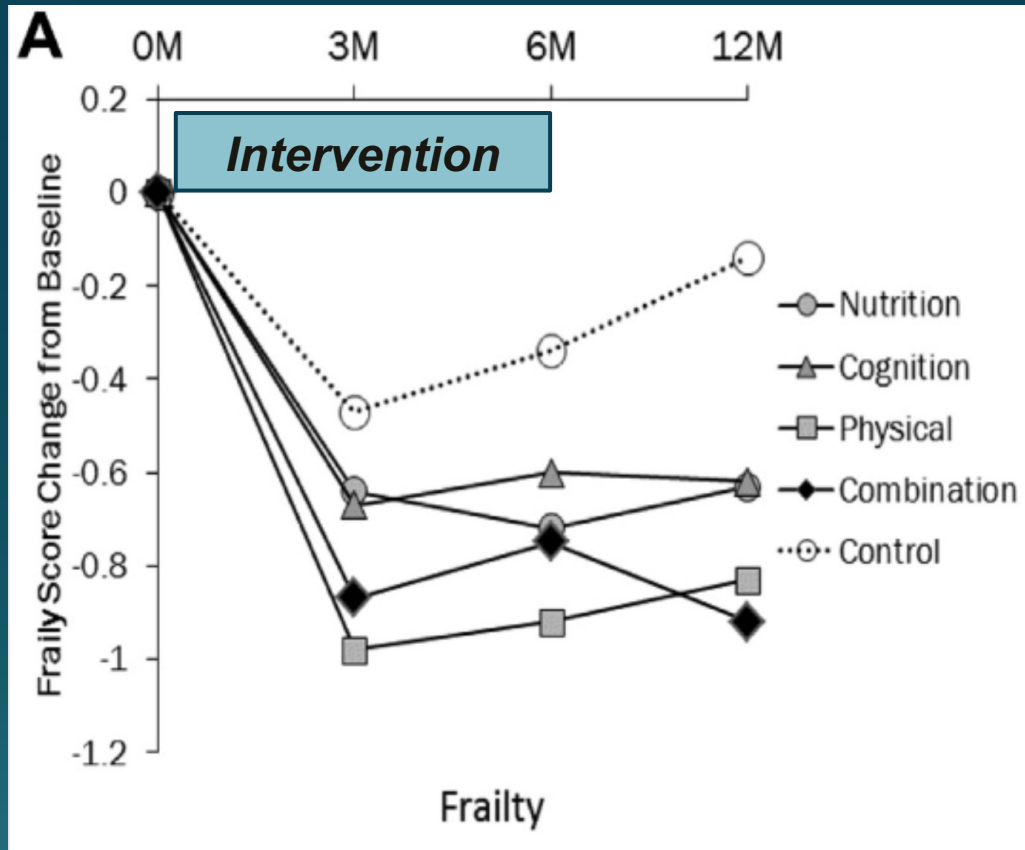
Short Physical Performance Battery



<u>Physical function</u>	<u>% Change</u>	<u>P-value</u>
Chair rise	-20 (-24, -16)	<0.01
Grip strength	+4 (0, 9)	NS



# Responsiveness to Intervention: Can frailty be modified?



- 246 pre-frail/frail adults  $\geq 65$  years
- Significant improvements in all arms vs control

# Things to consider when incorporating frailty/functional outcomes in clinical trials

## 3. Reproducibility

- Existing protocols
- Initial and ongoing training
- Ability to standardize
- Varying cut-points/components

HOME SMART PHONE APP TRAINING VIDEOS TRAINING TIPS BACKGROUND ARTICLES SPPB UTILIZATION EXAMPLES CONTACT

## TRAINING RESOURCES

The Short Physical Performance Battery (SPPB) is an objective assessment tool for evaluating lower extremity functioning in older persons. It was developed by the National Institute on Aging and is available for use without permission or royalty fees.

It is important that the SPPB be administered in a standardized manner. The videos available here, originally on a CD and now available on youtube, will provide this training. They offer background information on objective physical performance measures, how to administer the assessments, scoring of the SPPB and safety tips.

For someone new to the SPPB it would be ideal to watch all the videos in this set. Individual videos can also be watched separately. Here is the site on youtube:  
<https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.youtube.com%2Fplaylist%3Flist%3DPLIYnOnBLJyCrIV3jW7CJSWBN0ZRLLOHqY&data=02%7C01%7C%7Cb146266f264a41f6efbe08d870dbd62d%7C717009a620de461a88940312a395cac9%7C0%7C0%7C637383436798987099&sdata=qfpTbj3i11PleNRLCJMBjddoxjKckZT6om0bb941lTA%3D&reserved=0>

# Things to consider when incorporating frailty/functional outcomes in clinical trials

## 4. Logistics

- Space
- Time
- Equipment
- Participant burden

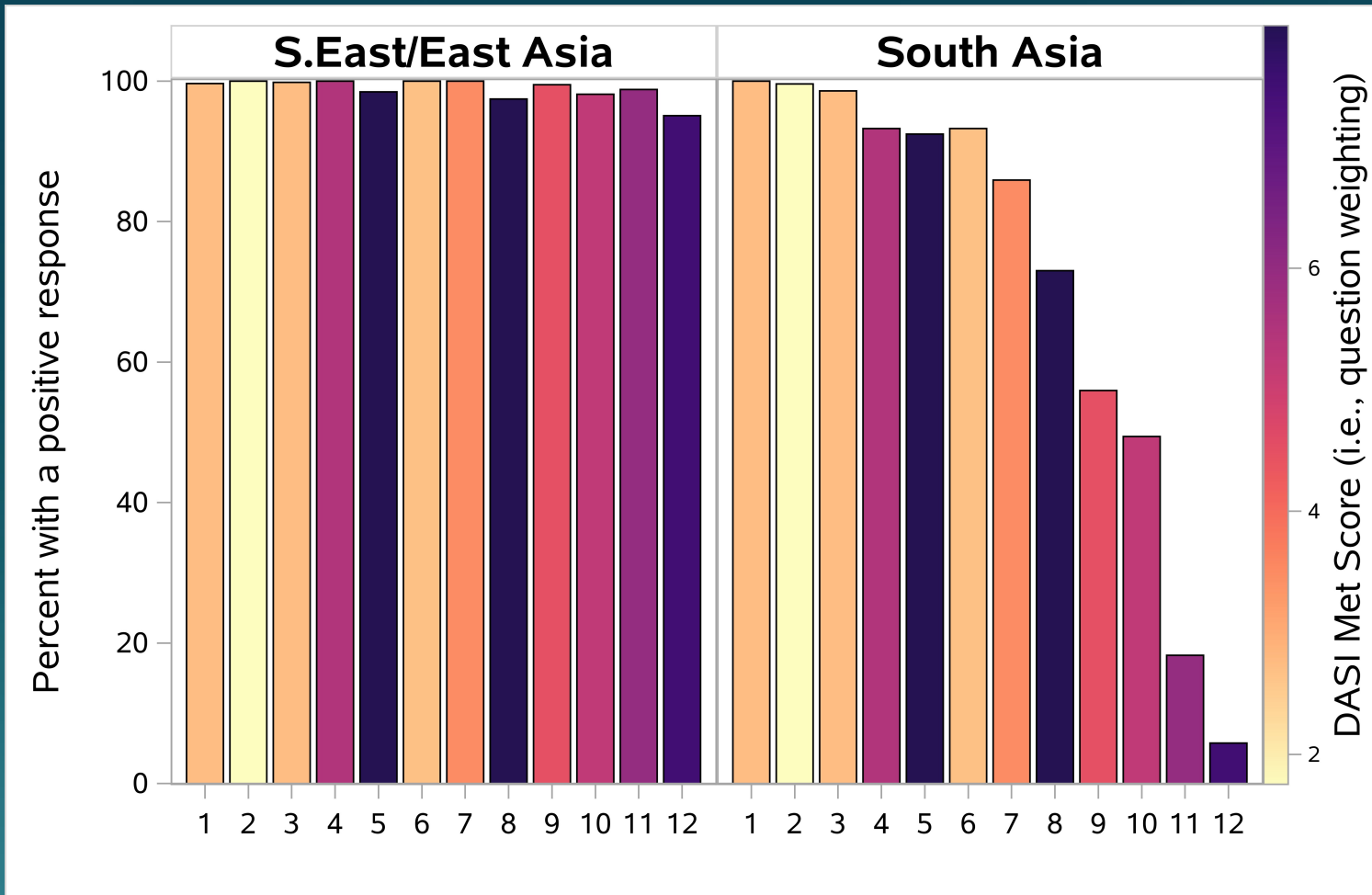
Test	Logistics
<b>Frailty Phenotype</b>	Requires dynamometer with yearly calibration, takes ~ 10 minutes
<b>SPPB</b>	Chair and 4-m space, takes ~ 10 min
<b>4-m walk</b>	Takes ~ 2 minutes; minimal space
<b>Chair rise time</b>	Takes ~ 2 minutes; only requires chair
<b>400-mw</b>	Takes 5-15 minutes; need long unobstructed hall

# Things to consider when incorporating frailty/functional outcomes in clinical trials

## 5. Participant-reported vs performance-based

- Moderately correlated
- What people **ACTUALLY** do *versus* what people **CAN** do
- Objective measures less vulnerable to external influences
- Sensitivity to change

# Things to consider when incorporating frailty/functional outcomes in clinical trials



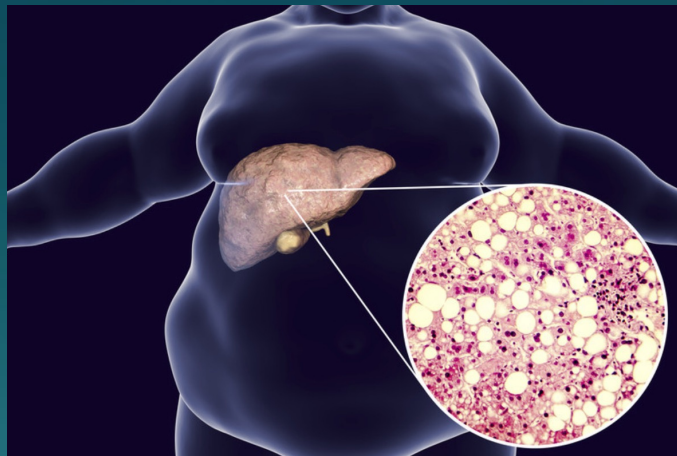
- Are regional differences in moderate-strenuous activities due to cultural context or actual impairments?



# Things to consider when incorporating frailty/functional outcomes in clinical trials

## 6. Mechanism of action

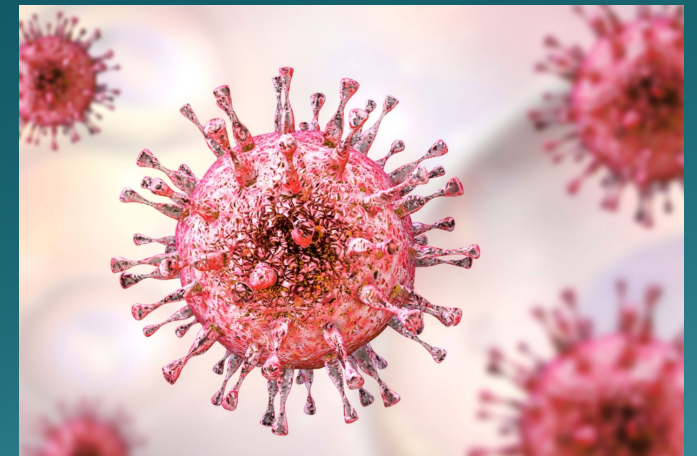
- Cardiovascular endurance vs muscle strength vs balance
- General vulnerability



Semaglutide for fatty liver



Deprescribing for polypharmacy



Letermovir in PWH

# How might we use these tests in the *clinic*?

## Frailty assessments have strengths and weaknesses<sup>2</sup>:

### Fried Phenotype

32 studies



Takes 5 to 20 min



Least feasible

Most associated with delirium

### Clinical Frailty Scale

12 studies



Takes <2 min



Most feasible

Most associated with mortality & nonhome discharge

### Frailty Index

9 studies



Takes 10 to 12 min



Largely feasible

Moderate to strong complication discrimination

### Edmonton Frail Scale

7 studies



Takes <5 min



Largely feasible

Most associated with complications

## CLINICAL FRAILITY SCALE

	<b>1</b>	<b>VERY FIT</b>	People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
	<b>2</b>	<b>FIT</b>	People who have <b>no active disease symptoms</b> but are less fit than category 1. Often, they exercise or are very active occasionally, e.g., seasonally.
	<b>3</b>	<b>MANAGING WELL</b>	People whose <b>medical problems are well controlled</b> , even if occasionally symptomatic, but often are <b>not regularly active</b> beyond routine walking.
	<b>4</b>	<b>LIVING WITH VERY MILD FRAILITY</b>	Previously "vulnerable," this category marks early transition from complete independence. While <b>not dependent</b> on others for daily help, often <b>symptoms limit activities</b> . A common complaint is being "slowed up" and/or being tired during the day.
	<b>5</b>	<b>LIVING WITH MILD FRAILITY</b>	People who often have <b>more evident slowing</b> , and need help with <b>high order instrumental activities of daily living</b> (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
	<b>6</b>	<b>LIVING WITH MODERATE FRAILITY</b>	People who need help with <b>all outside activities</b> and with <b>keeping house</b> . Inside, they often have problems with stairs and need <b>help with bathing</b> and might need minimal assistance (cuing, standby) with dressing.
	<b>7</b>	<b>LIVING WITH SEVERE FRAILITY</b>	<b>Completely dependent for personal care</b> , from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within -6 months).
	<b>8</b>	<b>LIVING WITH VERY SEVERE FRAILITY</b>	Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
	<b>9</b>	<b>TERMINALLY ILL</b>	Approaching the end of life. This category applies to people with a <b>life expectancy &lt;6 months</b> , who are <b>not otherwise living with severe frailty</b> . (Many terminally ill people can still exercise until very close to death.)

### SCORING FRAILITY IN PEOPLE WITH DEMENTIA

The degree of frailty generally corresponds to the degree of dementia. Common symptoms in **mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. In **severe dementia**, they cannot do personal care without help. In **very severe dementia** they are often bedfast. Many are virtually mute.



Clinical Frailty Scale ©2005–2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: [www.geriatricmedicine.ca](http://www.geriatricmedicine.ca)  
Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

# How might we use these tests in the *clinic*?

- Inform general care
  - Prioritize advance care planning
  - Identify patients for geriatric referral
  - Inform risk/benefit of preventive care
  - Determine frequency of clinic visits
- Treat/manage frailty
  - Referrals to appropriate resources (i.e., nutrition, physical therapy)
  - Deprescribing
- Guide treatment decisions
  - Selecting chemotherapy
  - Post-pone elective surgery
  - Determine ART?



# Is it Feasible?

- Frailty/function evaluated in many geriatric/HIV clinics
- Italian guidelines suggest screening for frailty in all PWH aged 50+
- Study evaluating the SPPB in 3 U.S. clinics found it feasible
- How do we work into the clinic flow?

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

# HRSA

Health Resources & Services Administration

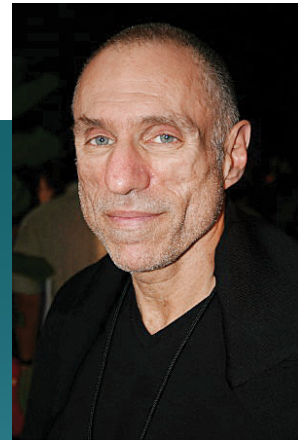
HIV/AIDS Bureau  
Division of Policy and Data

*Emerging Strategies to Improve Health Outcomes for People Aging with HIV:  
Capacity-Building Provider*

**Funding Opportunity Number:** HRSA-22-027  
**Funding Opportunity Type:** New  
**Assistance Listings (AL/CFDA) Number:** 93.928

**NOTICE OF FUNDING OPPORTUNITY**

Fiscal Year 2022



# Summary



# Acknowledgements

- Mentors and Collaborators:
  - Thomas Campbell, Todd Brown, Wendy Kohrt, Catherine Jankowski
  - AIDS Clinical Trials Group, Multicenter AIDS Cohort Study and Womens Interagency HIV Cohort (now MWCCS)
    - REPRIEVE (A5332), A5322, A5371, A5383 Teams
  - Study participants in Colorado
  - Community for vocalizing priorities

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Apply for our HIV T32!

<http://bit.ly/ColoradoHIVPostDoc>



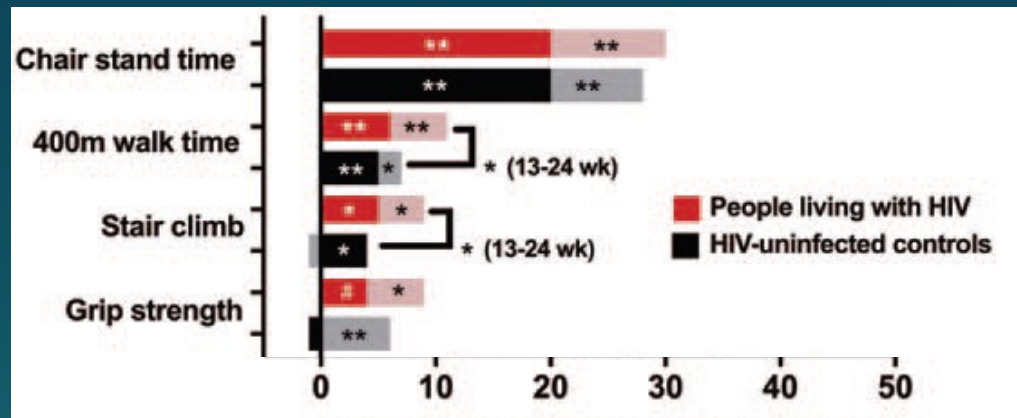
National Institute  
on Aging



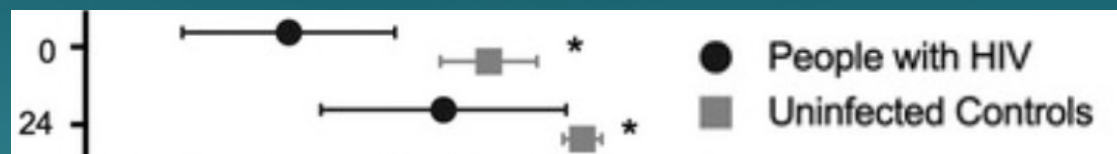
# Extra slides

# Things to consider when incorporating frailty/functional outcomes in clinical trials

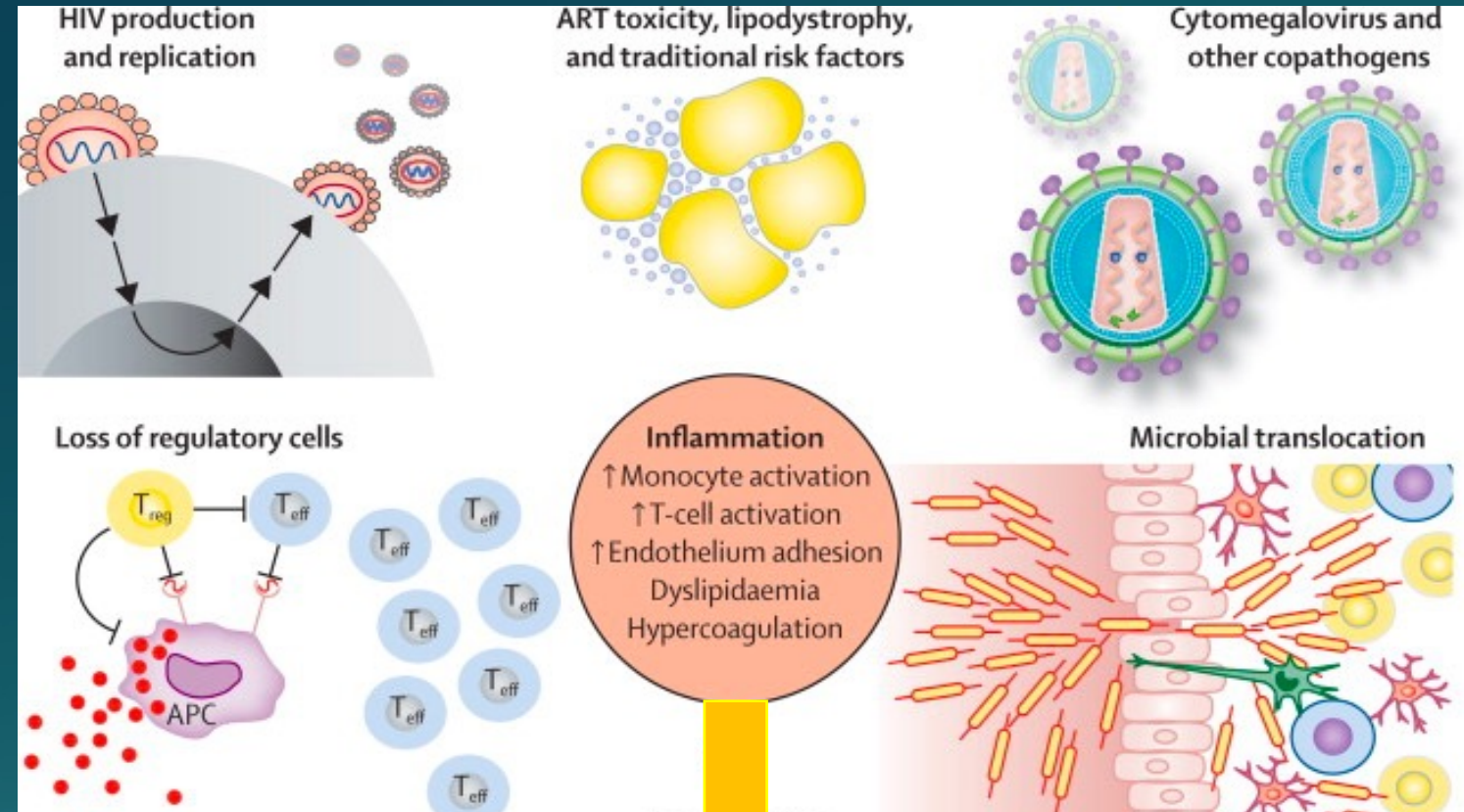
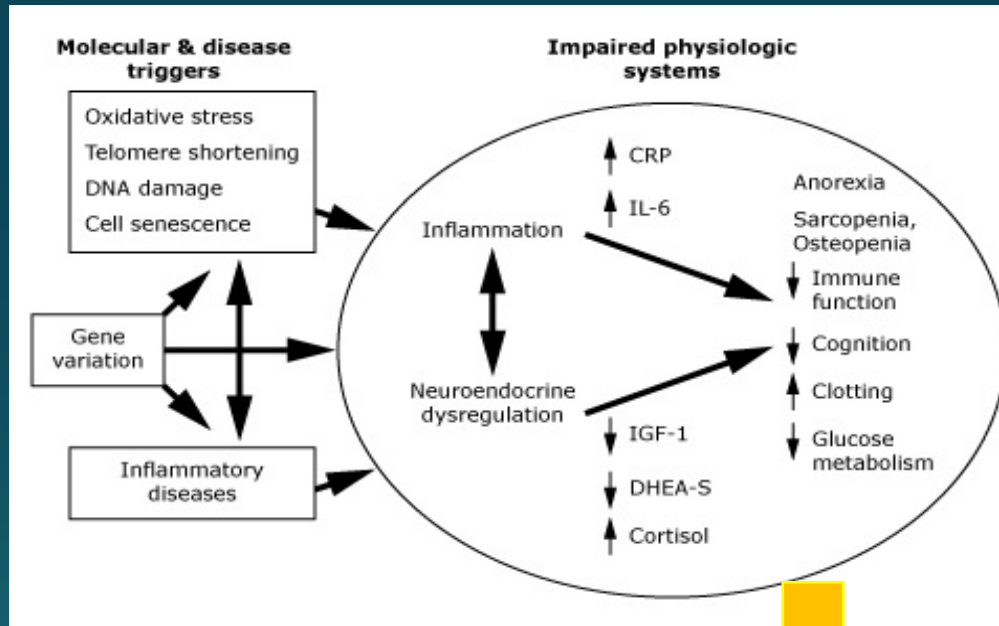
% improvement in objective measures after 24 weeks of an exercise intervention



Change in self-reported physical functioning in same intervention



# Why do we think about frailty and functional impairments in HIV?



Frailty, physical function impairments, and other complications of aging

# But what *biomarker* can I use instead?

- Biomarkers should improve risk prediction *beyond* these cheaper, readily available assessments
- In clinic, should be able to better identify a population as frail compared to the clinical tool alone, and help to better identify a care plan than the clinical tool alone
- Combine clinical assessments with biomarkers?
  - May help to identify those for whom interventions work or don't work
  - Example "biomarkers" that could complement: skeletal muscle mass by MRI or CT scans



