Frailty, Aging, and HIV: "Moving" Forward

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Objectives

- Review recent research addressing contributors to HIV-frailty
- Appreciate the potential impact of exercise to mitigate HIV-frailty
- Consider quantitative and qualitative findings to inform future research & clinical practice

I'm an exercise physiologist

My goal: to design exercise plans founded in science & adapted to the individual & their values

What is “frailty”?

- **Frailty = “You know it when you see it”**
  - Dysregulation in multiple physiologic systems
  - A syndrome
  - 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)
    - Objective & subjective measures

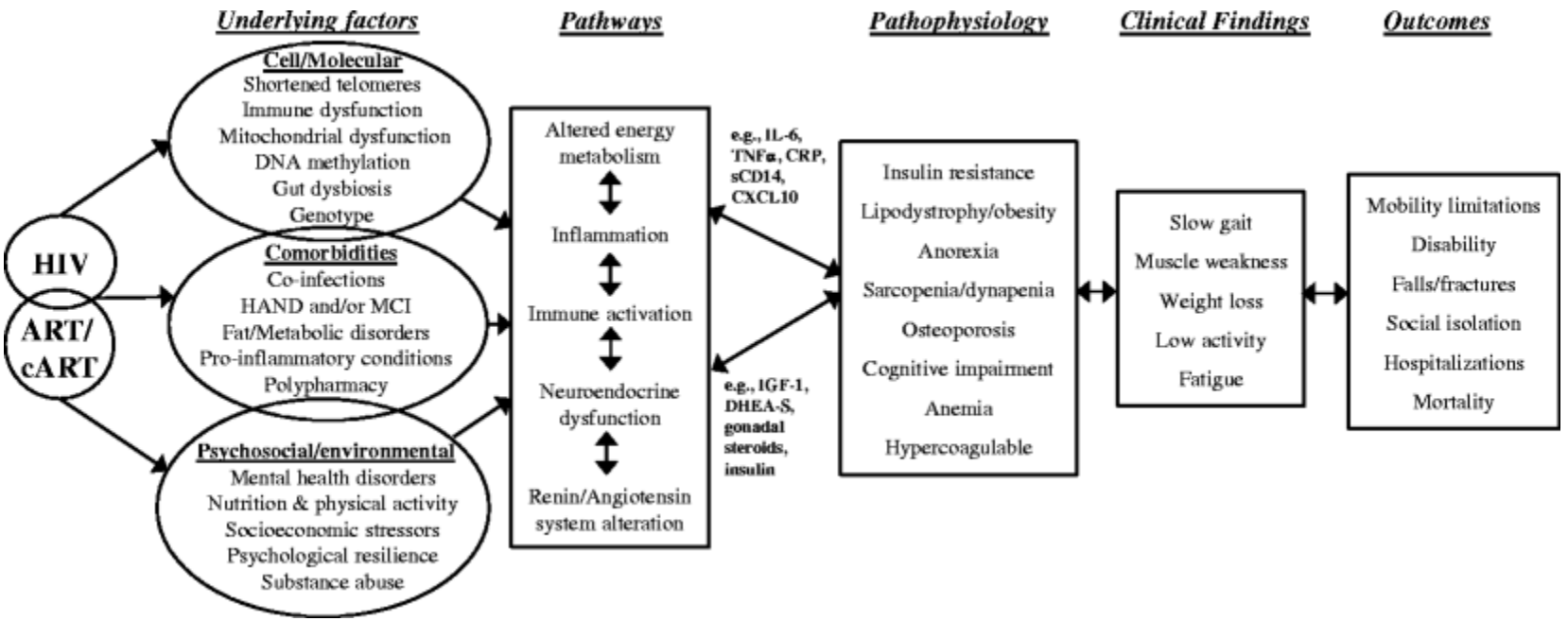
Frailty differs in prevalence across study populations

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

Onen, J Frailty Aging 2014; Erlandson, HIV Clin Trials 2012; Onen, J Infect 2009; Piggott, PLOS One 2013; Pathai, JAIDS 2013; Rees, J Vis Exp 2013; Sandkovsky HIV Clin Trials 2013

An Integrated Model of Frailty in HIV

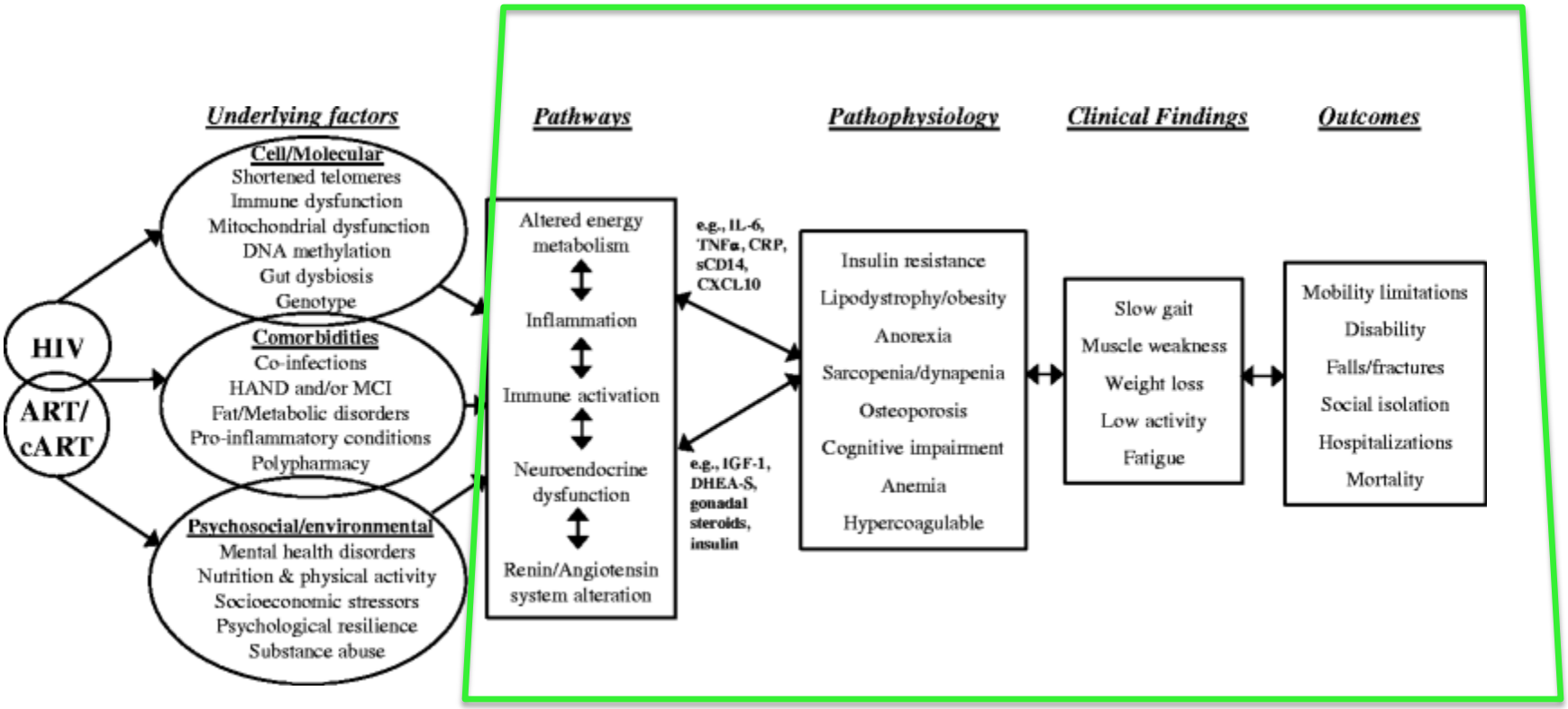
What can be acted upon to prevent or mitigate frailty?



Piggott et al, Curr HIV/AIDS Rep 2016

An Integrated Model of Frailty in HIV

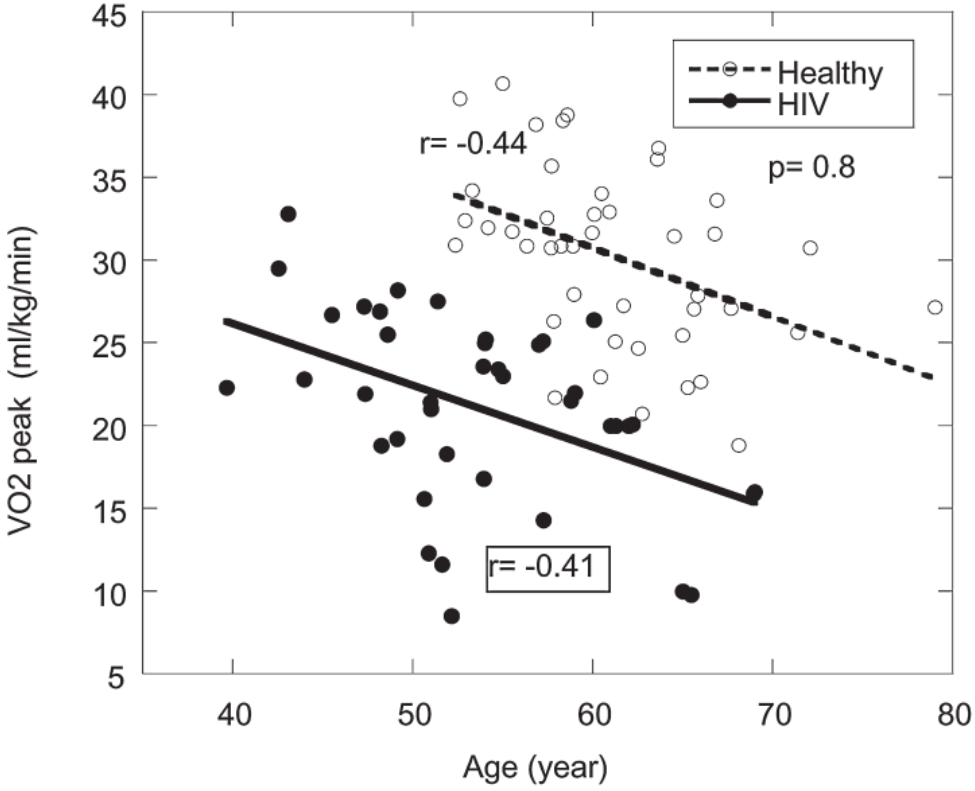
Bi-directionality – difficult to isolate mechanisms;
opportunity for interventions to impart effects on multiple levels



Piggott et al, 2016

Impaired Maximal Cardiorespiratory Capacity ($V0_2$) in HIV+ vs HIV-

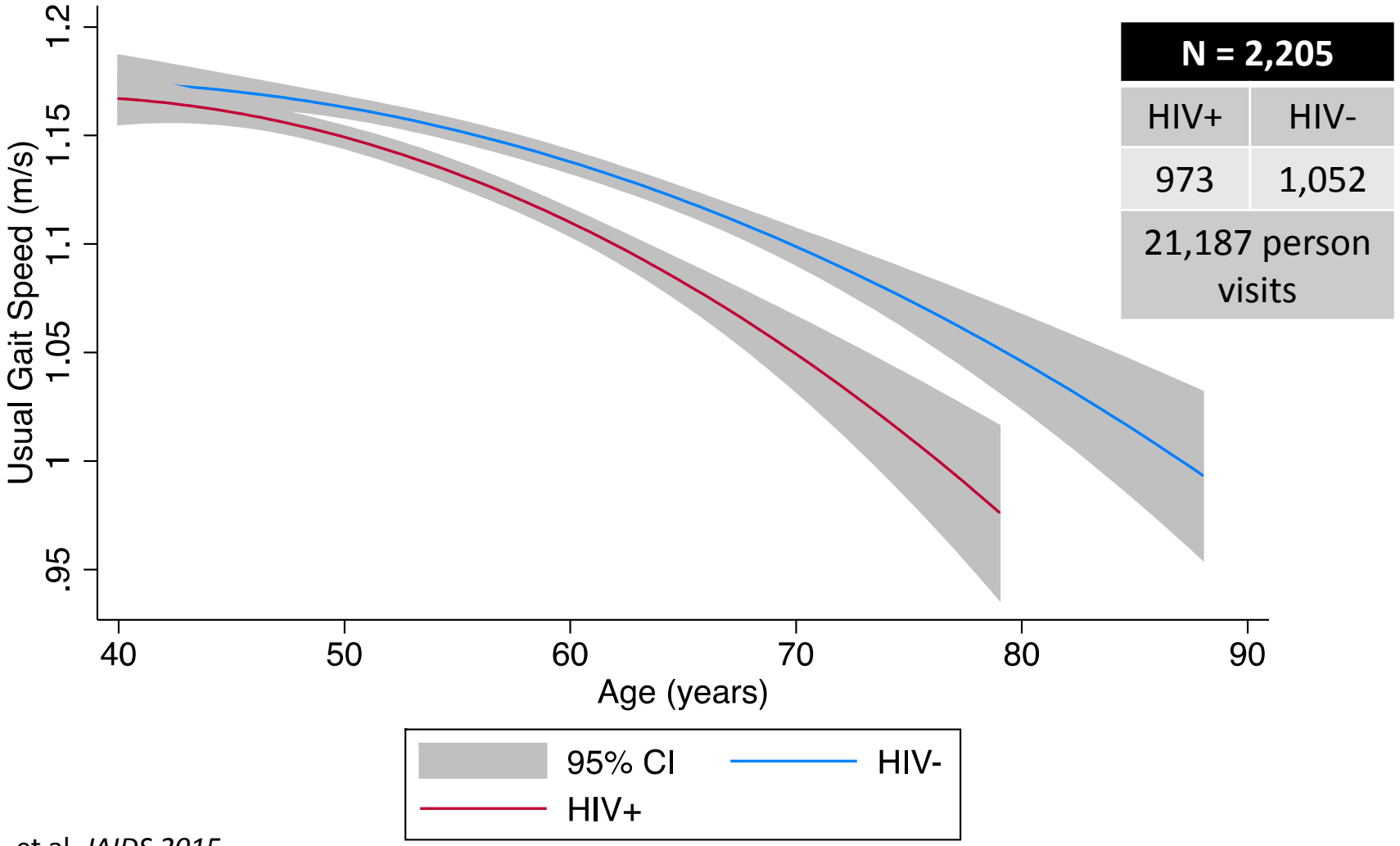
- HIV+ had 41% lower age-adjusted $V0_2$ peak
- Older HIV+ had 26% lower exercise capacity vs younger HIV+
- 6-min walk distance only ~ 8% less than expected
- Older HIV+ adults have impaired aerobic capacity but maintain ability to complete day-to-day activities



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

Oursler, et al. AIDS Res Human Retroviruses 2006.

Gait speed declines faster in HIV men

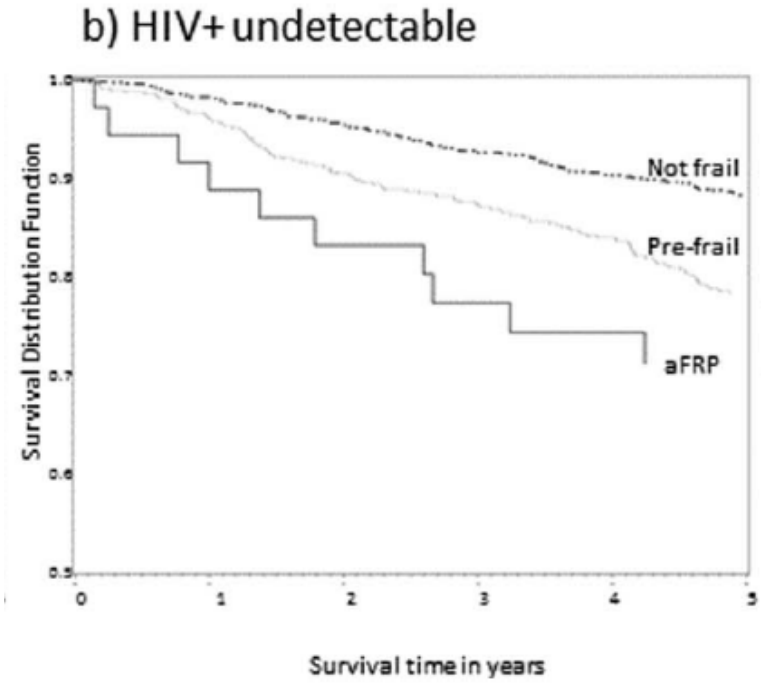


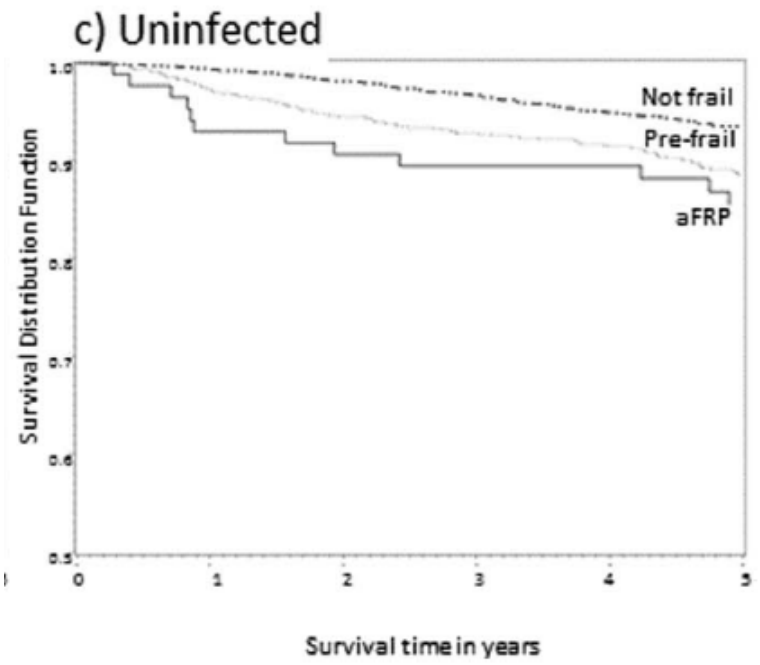
N = 2,205	
HIV+	HIV-
973	1,052
21,187 person visits	

Schrack J, et al. *JAIDS 2015*.

Frailty-related phenotype is predictive of mortality in HIV+

Weight loss (4 weeks), exhaustion, slowness (can't walk a block), low activity (can't run a short distance)

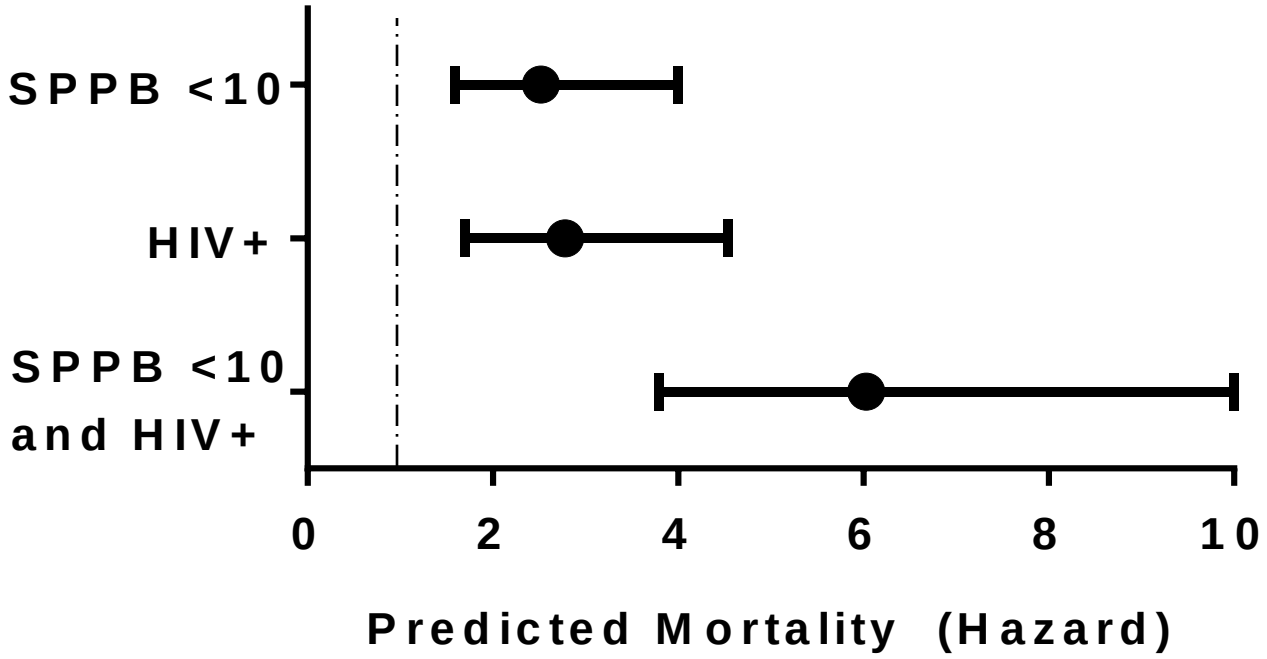




Akgun KM, et al. JAIDS 2014

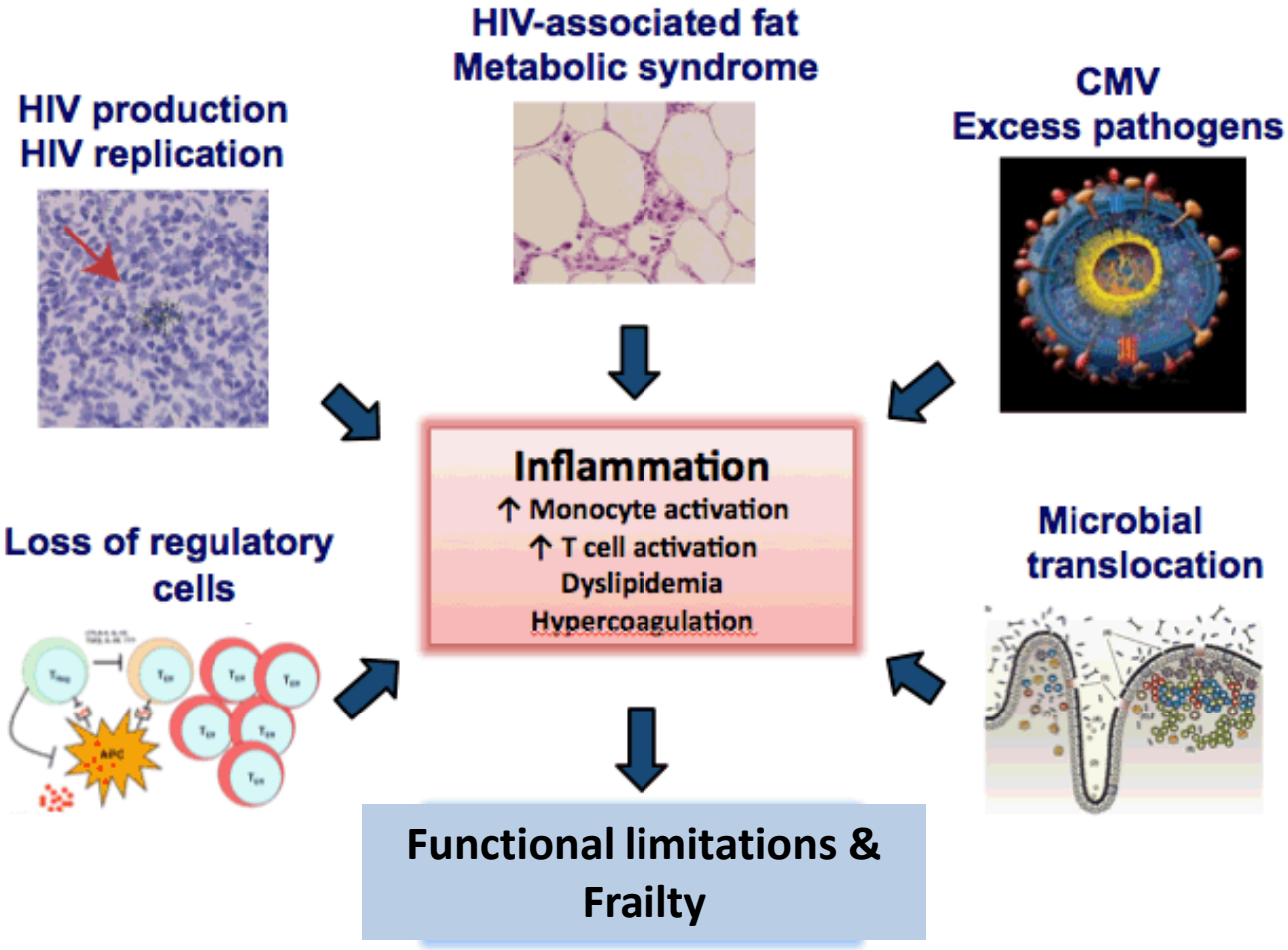
HIV and Physical Function Impairment Have Synergistic Effects on Mortality

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



Greene M. AIDS 2014

What Contributes to Frailty or Physical Performance Limitations?



Deeks, Opening Plenary IAS, Malaysia 2013

Association of inflammatory, immune, & hormonal markers with frailty in older men (Erlandson et al, in press)

- MACS includes MSM, aged 50-64 years (Althoff et al, 2014)

  Prevalence of frailty: 12% HIV+ and 9% HIV-

- Substudy of MACS cohort, 1994-2010

  Median year of assessment: 2006

- HIV-infected and high-risk uninfected men
- Frailty-related phenotype

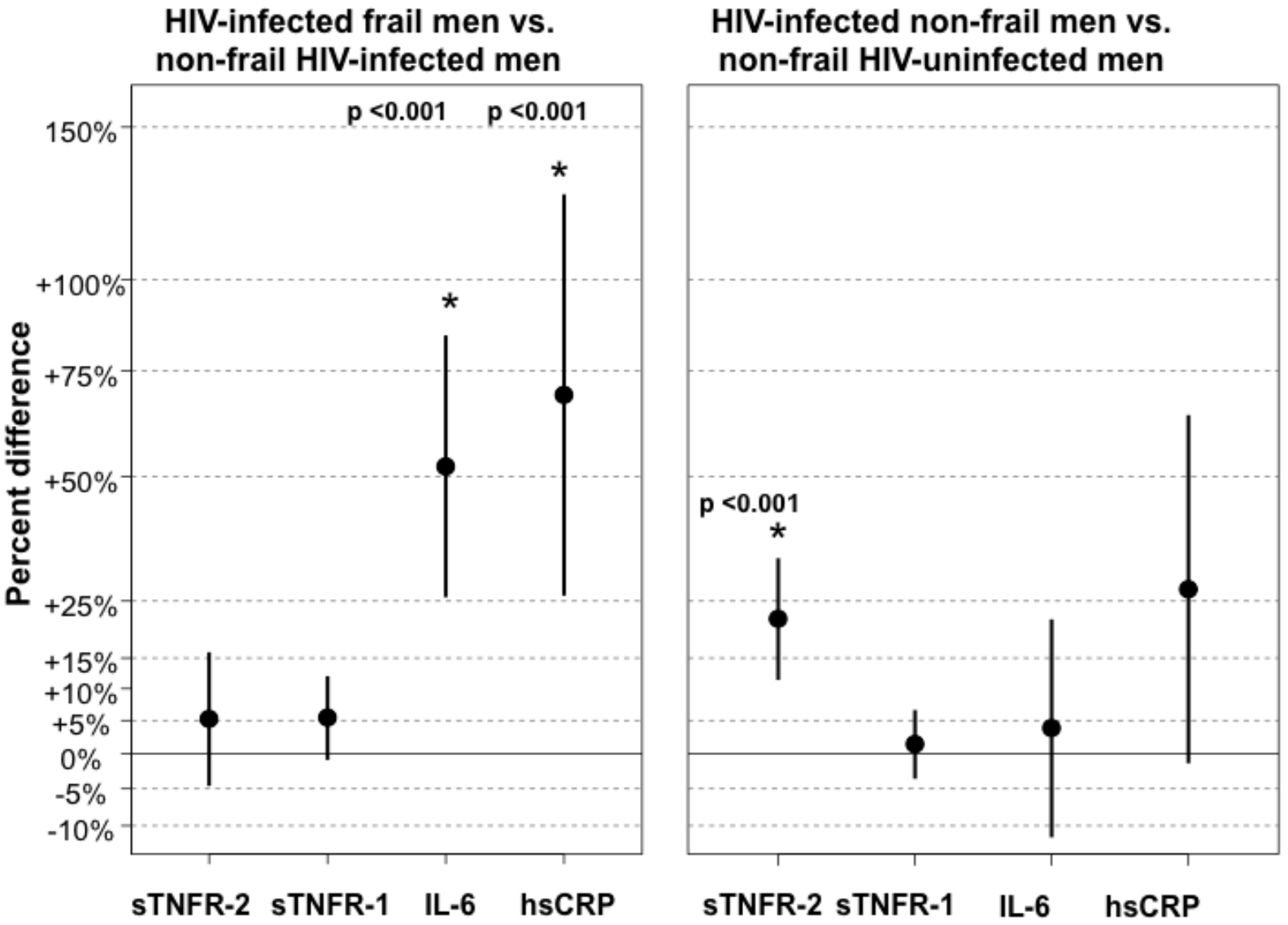
  Self-reported weight loss, exhaustion, low activity, slowness

- Frail: 2+ clinic visits w/ 3+ frailty criteria
- Non-frail: no history of any frailty criteria

	HIV-uninfected	Non-frail HIV-infected	Frail HIV-infected	
	N=150	N=141	N=155	*P*
Age, y	48.4 [41.5-53.1]	47.7 [40.4-53.0]	49.1 [41.4-53.9]	0.71
Black race, %	16.7	28.4	32.9	0.003
Hispanic, %	5.3	9.9	11	0.18
BMI, kg/m^2	25 [23.5-27.2]	25.6 [23.6-27.0]	23.9 [21.8-27.5]	0.024
Obese, %	10.7	3.7	14.9	0.004
Metabolic syndrome, %	22.7	40.4	48.4	<.001
Current smoker, %	13.3	21.3	46.1	<.001
Illicit drug use, %	63.3	53.9	61.8	0.214
Hepatitis C infection, %	1.3	4.3	17.5	<.001
Detectable viral load, %	-----	41.4	50.3	0.130
HAART, %	-----	72.3	74.8	

(Erlandson et al, in press)

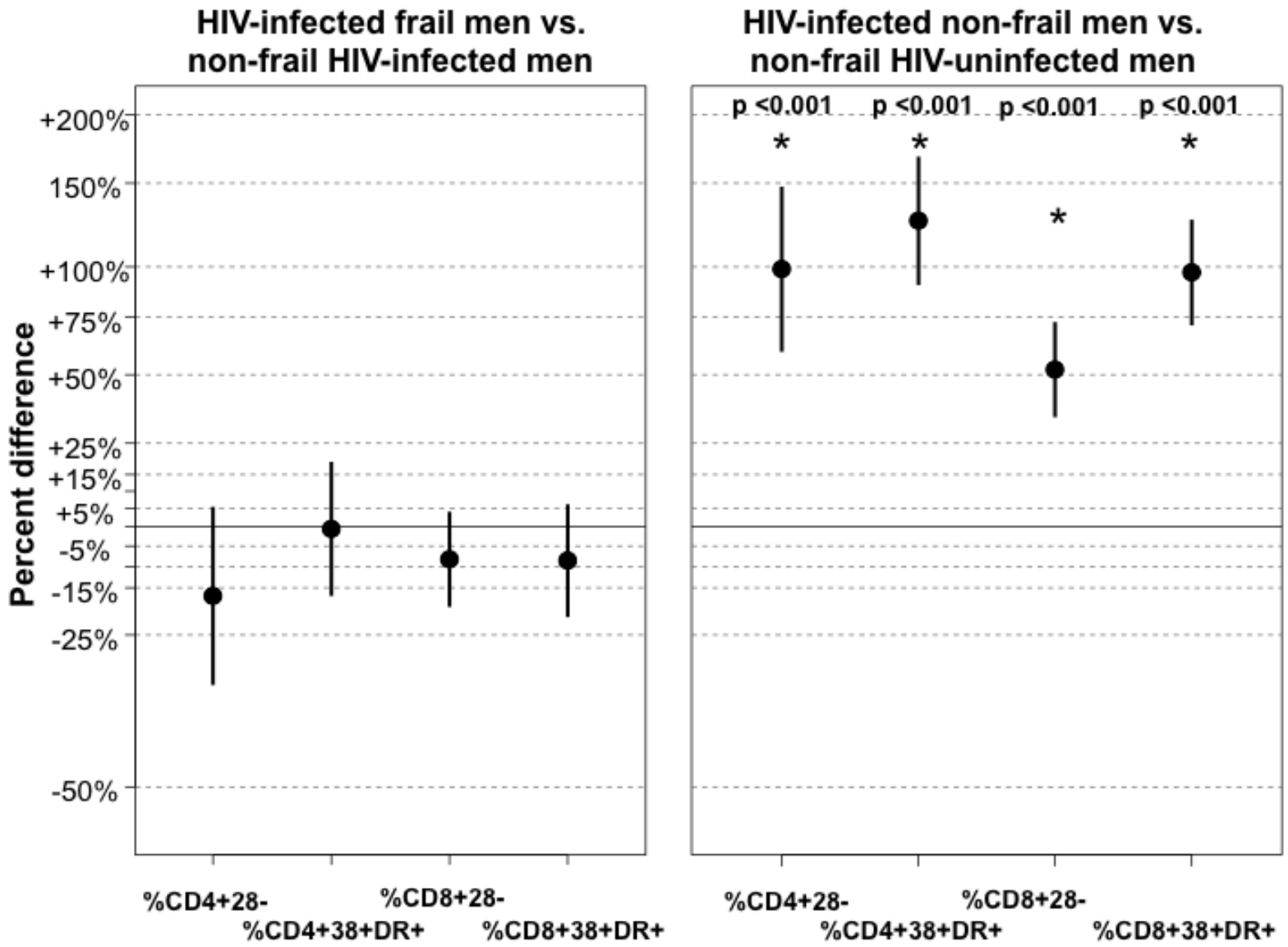
Frailty Associated with Inflammation in HIV-infected Men



Linear regression adjusted for demographic, physical & behavioral variables; HIV-related variables (e.g., CD4 nadir, HIV-1 viral load)

(Erlandson et al, in press)

HIV-infection Associated with Immune Activation & Senescence in Non-frail Men



Linear regression adjusted for demographic, physical & behavioral variables;
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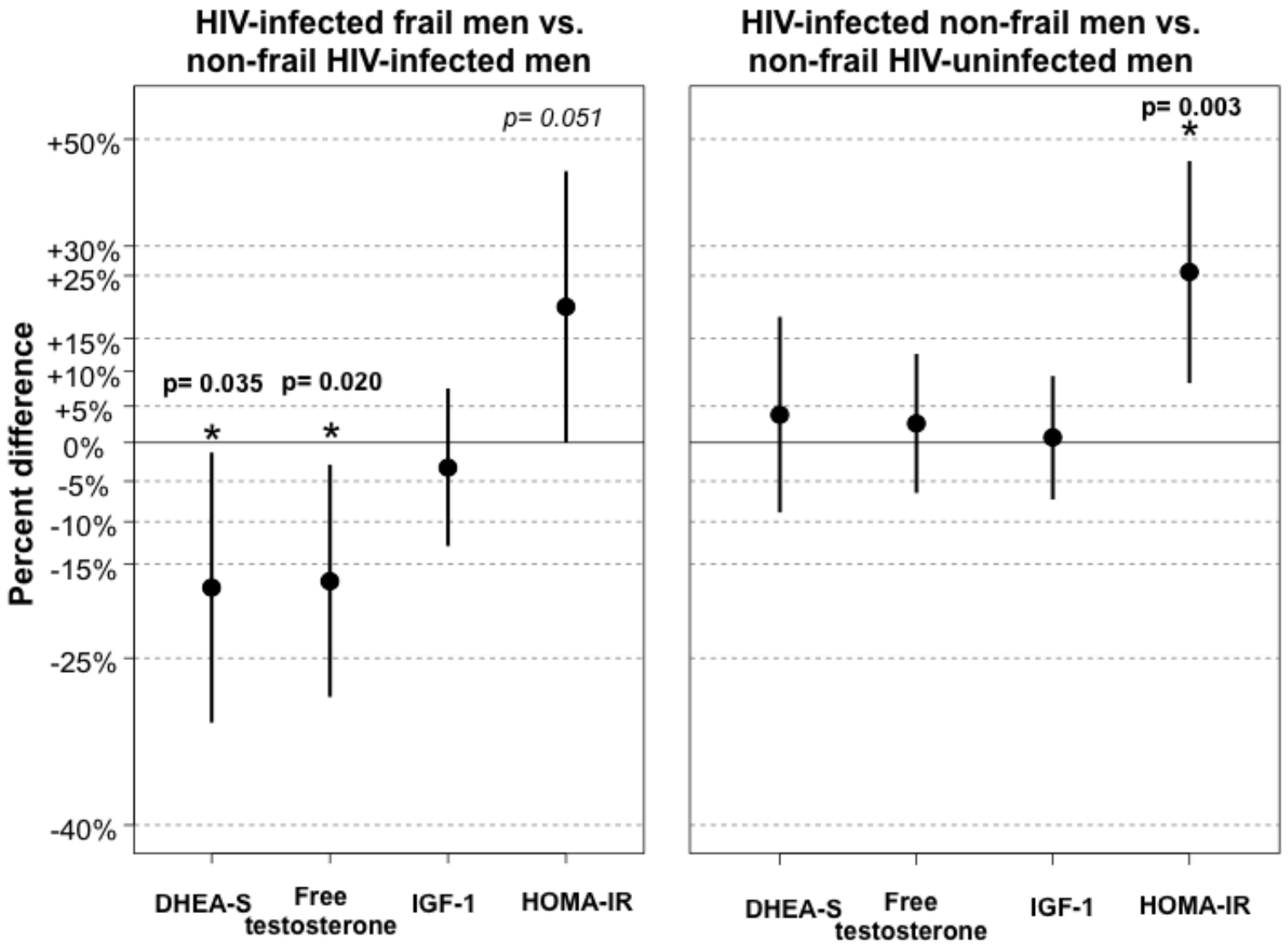
(Erlandson et al, in press)

Frailty Associated with Low DHEAS & T
HIV Infection Associated with Insulin Resistance



Linear regression adjusted for demographic, physical & behavioral variables;
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(Erlandson et al, in press)

Evidence of Multisystem Dysregulation

- HIV + frailty
  - ↑ inflammation
  - ↓ anabolic steroid hormones
  - ↑ insulin resistance
- HIV infection
  - ↑ cellular immune activation
  - ↑ immune senescence
  - ↑ insulin resistance

Independent of comorbid conditions & age

What can be done?

- Limit exposure to inflammation through lifestyle factors
- Multi-system interventions to mitigate multisystem dysregulation

(Erlandson et al, in press)

Frailty in Women Aging with HIV (Gustafson et al, 2016)

- Evaluate the complexity of frailty in women
  - Demographic & ageing-related chronic disease
  - Operationalize frailty for gender comparisons & changes over time
- Substudy of WIHS; 579 HIV- and 1449 HIV+ women
- Frail = 3+ criteria of Fried Frailty Index (0-5 scale)

	HIV – N (%)	HIV+ N (%)
FFI		
0-2	521 (90.0)	1199 (82.8)
3-5	58 (10.0)	250 (17.3)

MACS:	**9%**	**12%**

	HIV – N (%)	HIV+ N (%)
Age, years		
< 30	130 (22.5)	112 (7.7)
30-39	183(31.6)	462 (31.9)
40-49	185 (32.0)	582 (40.2)
50+	81 (14.0)	293 (20.2)

Age-adjusted Odds of Frailty in Women

Variable	OR [95% CI]
HIV status, cells/mm^3	
Negative	Reference
Positive, CD4 ≥ 500	1.14 [0.79, 1.64]
Positive, CD4 200-499	1.64 [1.16, 2.32]
Positive, CD4 < 200	2.63 [1.74, 3.99
Smoking, current/former	1.78 [1.29, 2.45]
Income < USD$12,000	1.92 [1.48, 2.49]
IV drug use	1.63 [1.23, 2.16]
BMI (kg/m^2)	0.91 [0.70, 1.18]

1. HIV+ women more likely to be frail, independent of age
2. Association between frailty and degree of immunosupression

(Gustafson et al, 2016)

Age-adjusted Odds of Frailty in HIV-infected Women

Viral load, AIDS-defining illness & chronic illness associated with frailty.

Variable	OR [95% CI]
Viral load, copies/mL	
< 500	Reference
500 – 100,000	1.28 [0.96, 1.72]
> 100,000	2.60 [1.40, 4.82]
Prior AIDS-related illness	2.35 [1.75, 3.16]

Variable	OR [95% CI]
Chronic Disease	
Hypertension	1.65 [1.27, 2.16]
Diabetes	1.52 [1.11, 2.08]
Cancer	1.48 [1.03, 2.12]
Fibrinogen-4 index	
< 1.45	Reference
1.45-3.25	1.68 [1.22, 2.31]
> 3.25	3.24 [2.07, 5.06]
eGFR, ml/min	
≥ 60	Reference
45-59.9	1.54 [0.91, 2.60]
30-49.9	4.63 [1.80, 11.95]
< 30	3.98 [1.74, 9.13]

(Gustafson et al, 2016)

Multivariate Logistic Regression Models: Frailty ≥ 3

Variable	HIV, Age	+ Demographics	+ Chronic Disease	Combined
HIV & CD4 count				
Negative	Reference			
Positive, CD4 ≥ 500	1.14 [0.79, 1.64]			
Positive, CD4 200-499	1.64 [1.16, 2.32]			
Positive, CD4 < 200	2.63 [1.74, 3.99]			
Age				
< 30	Reference			
30-39	2.48 [1.21, 5.09]			
40-49	4.53 [2.25, 9.11]			
50+	8.72 [4.29, 17.73]			
Hypertension				
FIB4 > 3.25				
eGFR 30-44.9 ml/min				

(Gustafson et al, 2016)

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Age				
< 30	Reference			
30-39	2.48 [1.21, 5.09]			
40-49	4.53 [2.25, 9.11]			
50+	8.72 [4.29, 17.73]	6.38 [3.10, 13.10]		
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Age				
< 30	Reference			
30-39	2.48 [1.21, 5.09]			
40-49	4.53 [2.25, 9.11]			
50+	8.72 [4.29, 17.73]	6.38 [3.10, 13.10]	4.84 [2.29, 10.21]	
Hypertension			1.61 [1.22, 2.13]	
FIB4 > 3.25			2.49 [1.55, 4.00]	
eGFR 30-44.9 ml/min			3.70 [1.42, 9.61]	

(Gustafson et al, 2016)

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Age				
< 30	Reference			
30-39	2.48 [1.21, 5.09]	2.32 [1.12, 4.79]	2.23 [1.08, 4.60]	2.13 [1.02, 4.43]
40-49	4.53 [2.25, 9.11]	3.54 [1.74, 7.18]	3.53 [1.74, 7.18]	2.86 [1.39, 5.88]
50+	8.72 [4.29, 17.73]	6.38 [3.10, 13.10]	4.84 [2.29, 10.21]	**3.71** [1.74, 7.92]
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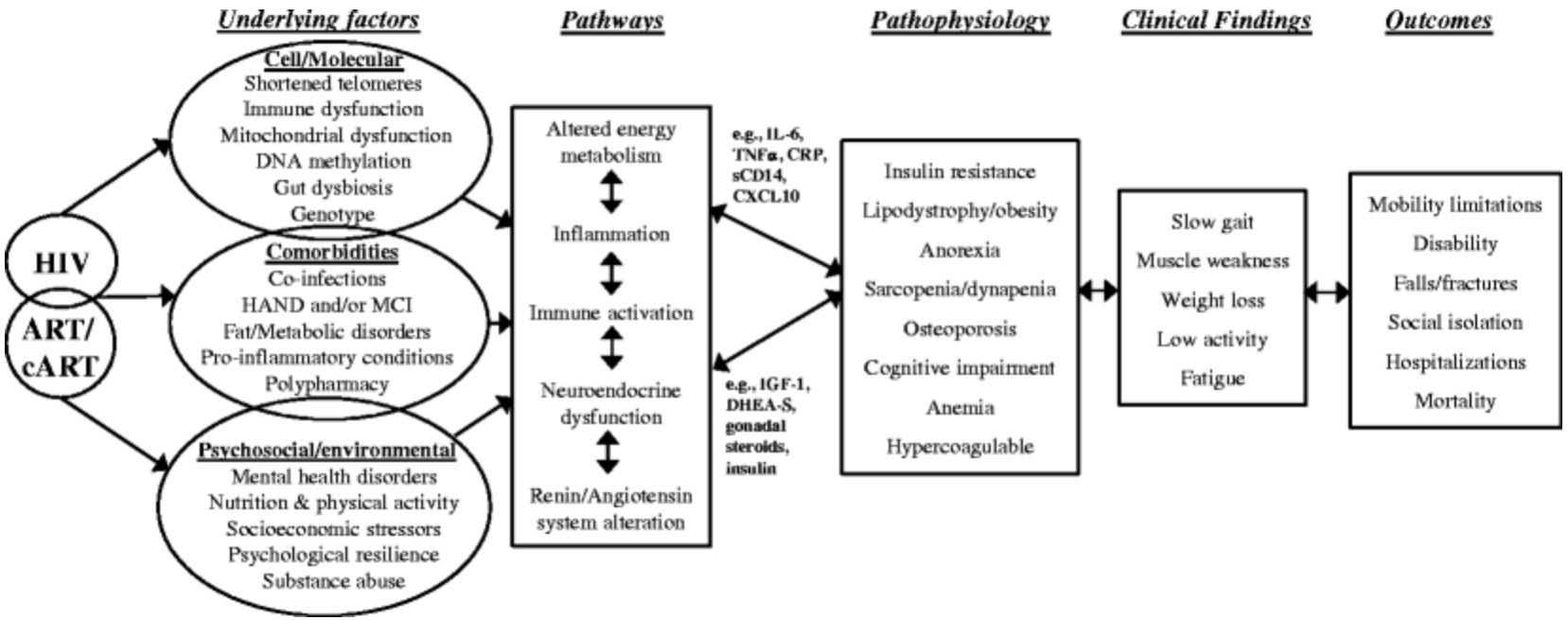
eGFR 30-44.9 ml/min			3.70 [1.42, 9.61]	**3.74** [1.37, 10.22]

(Gustafson et al, 2016)

To summarize from MACS and WIHS:

1) HIV-related factors contribute strongly to frailty.
2) Age contributes strongly to frailty; younger HIV+ adults (4th decade) have increased risk of frailty.
3) Modifiable risk factors (e.g., smoking) contribute to frailty.
4) Gender-differences in frailty are suggested.



Piggott et al, 2016

What is “frailty”?

- **Frailty = “You know it when you see it”**
  - Dysregulation in multiple physiologic systems
  - A syndrome; some HIV specificity
  - Associated with high vulnerability
- **How is it defined? Movement ability + comorbidity**
  - Multiple indexes to capture
  - Frailty index (deficit accumulation)- Rockwood Index
  - Frailty phenotype defined by Fried (slowness, weakness, weight loss, low activity, fatigue)
- **Can Frailty be Reversed?**

Nutritional, Physical, Cognitive, and Combination Interventions & Frailty Reversal Among Older Adults: A Randomized Controlled Trial (Ng et al, 2015)

- 246 Prefrail & frail adults (no HIV)
- Community dwelling
- Average age 70 y
- 61% female
- 6 month intervention
- 6 month follow-up

All interventions were effective in reducing frailty in older adults.

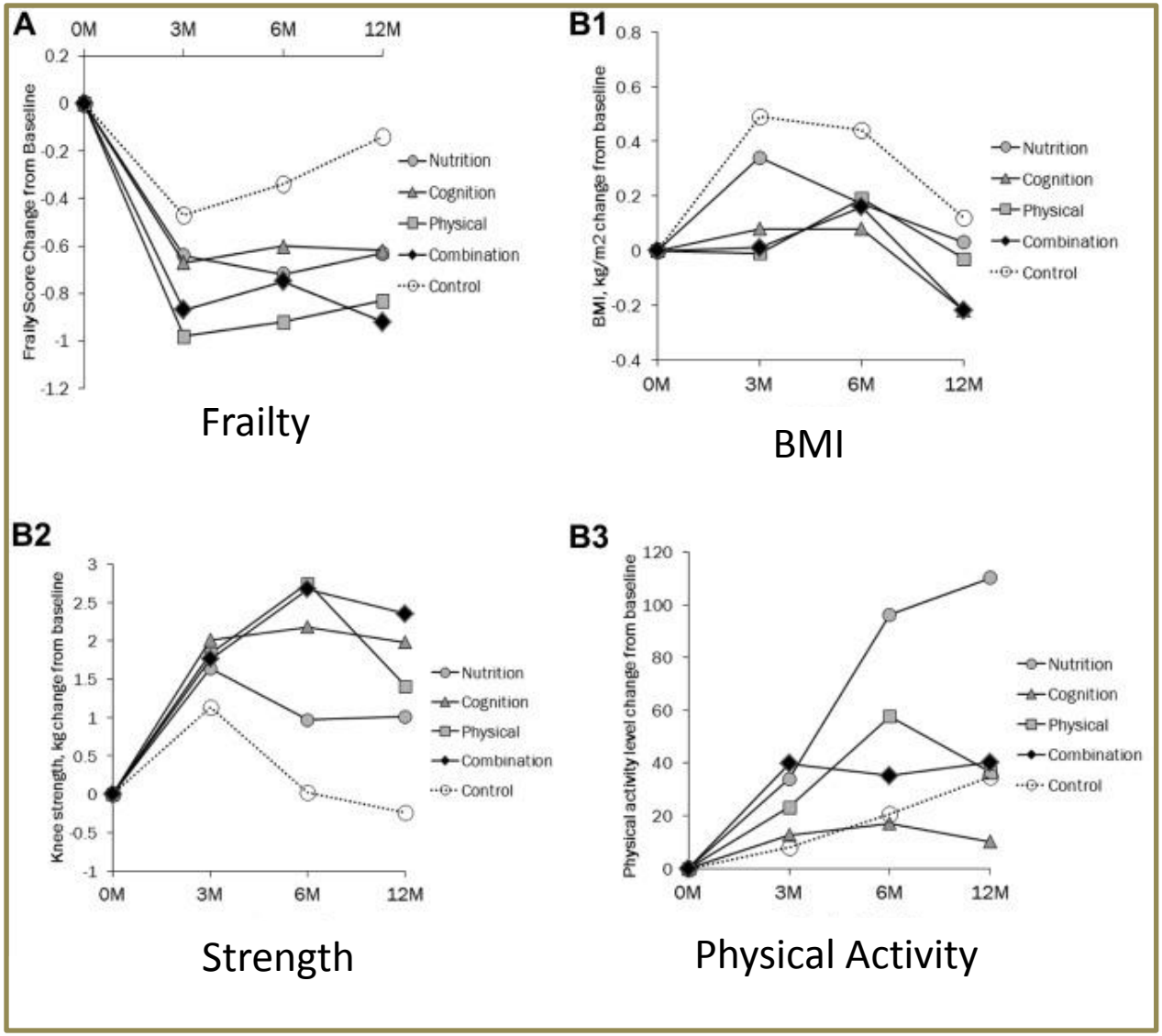


Figure. Frailty score (A) and components weights (B1), strength (B2), physical activity (B3): change from baseline.

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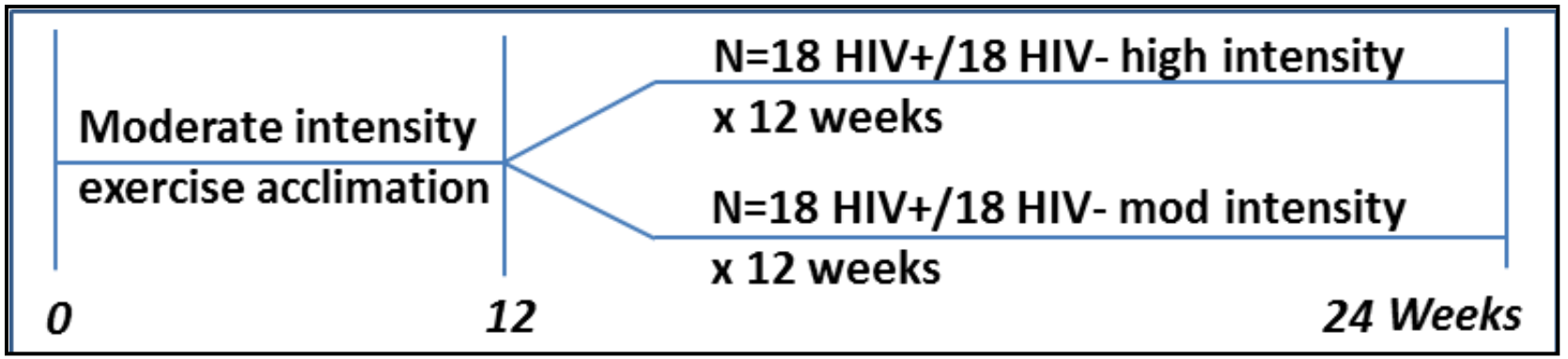
  - Dysregulation in multiple physiologic systems
  - A syndrome; some HIV specificity
  - Associated with high vulnerability
- **How is it defined? Movement ability + comorbidity**
  - Multiple indexes to capture
  - Frailty index (deficit accumulation)- Rockwood Index
  - Frailty phenotype defined by Fried (slowness, weakness, weight loss, low activity, fatigue)
- **Can Frailty be Reversed? Yes**
- **Can HIV-frailty be Reversed? Not known….yet!**

What intervention improves movement & multiple physiologic systems?

Exercise!

- 36 HIV+ and 36 HIV- sedentary men & women aged 50-70
- Cardiovascular & resistance exercise

  3 times/week



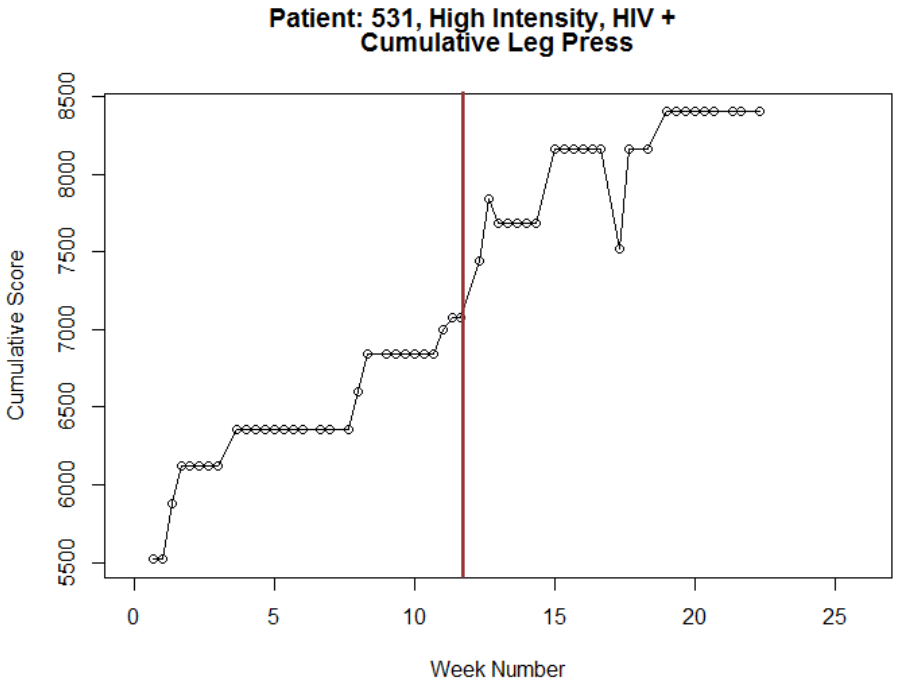
Exercise for Healthy Aging: Main Objectives

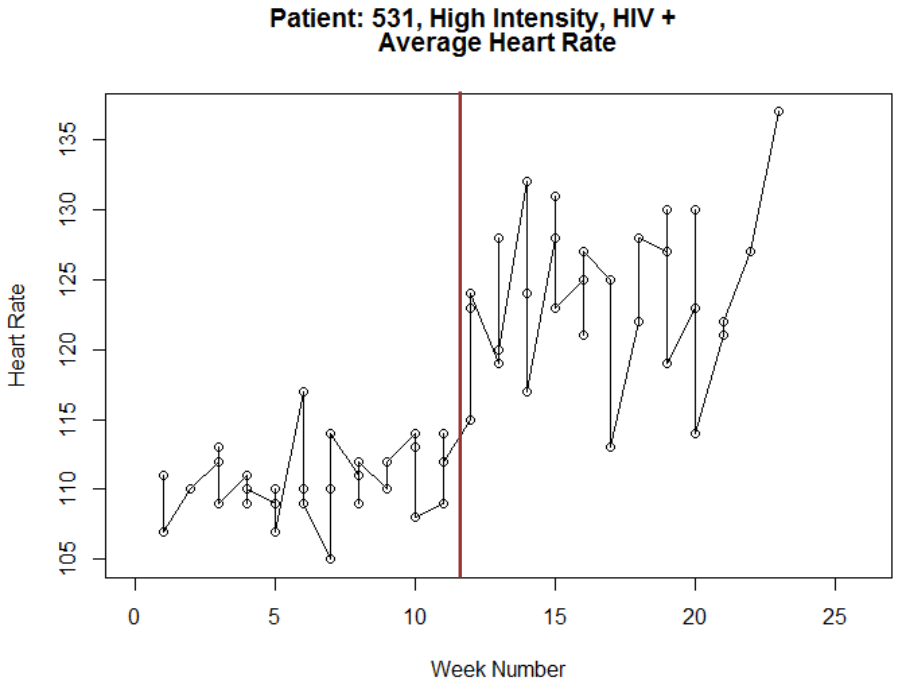
- Primary outcome: Does moderate or high intensity exercise lead to improvements in physical function (1° = chair rise time)?
- *Questions*:
  - Does the ideal intensity of exercise differ between people with or without HIV?
  - Does a higher intensity of exercise lead to greater reduction in inflammation?
  - 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

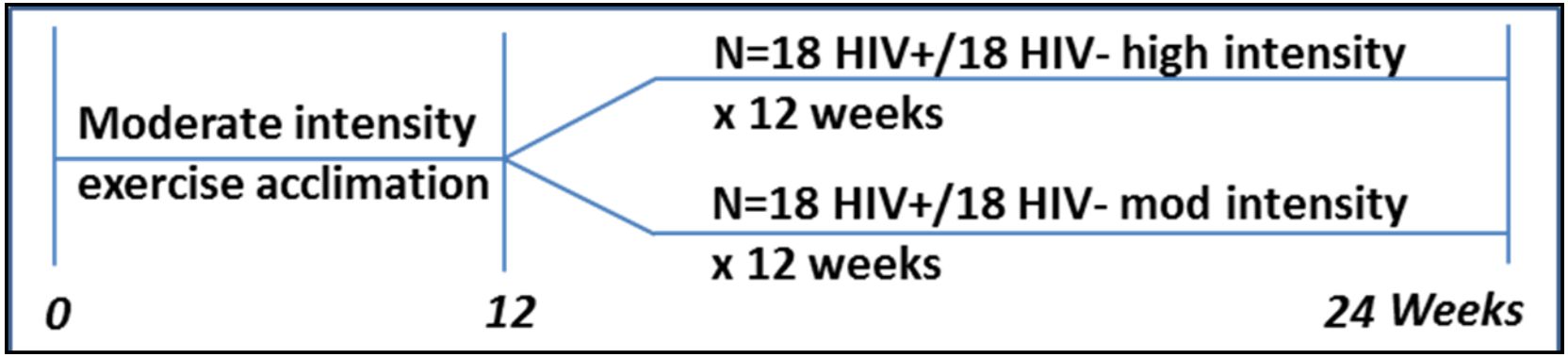
Exercise for Health Aging: Preliminary Data

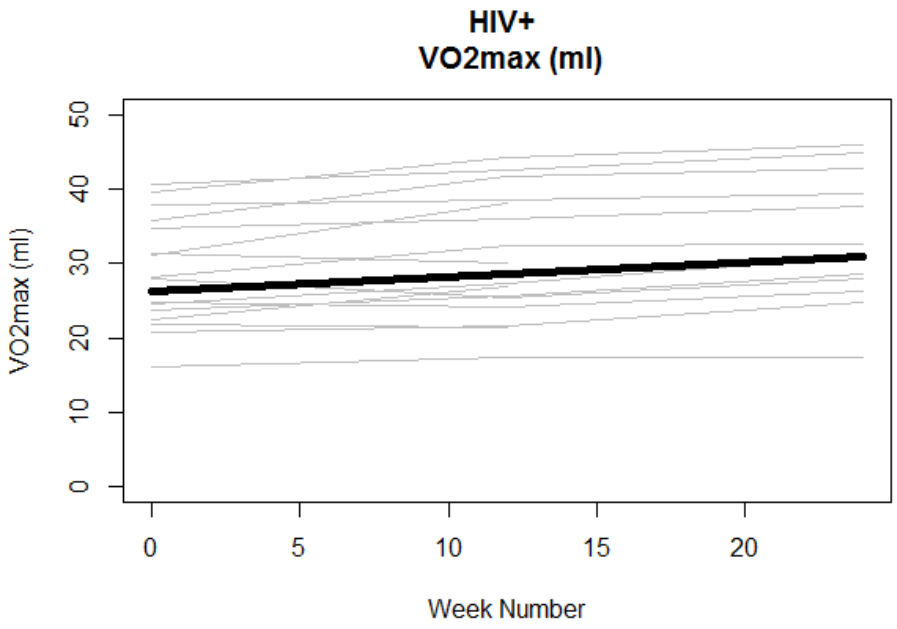
Participants Enrolled			
	HIV+	HIV-	Total
Women	4	2	6
Men	28	25	53
Age < 60	22	15	37
Age 60+	10	12	22

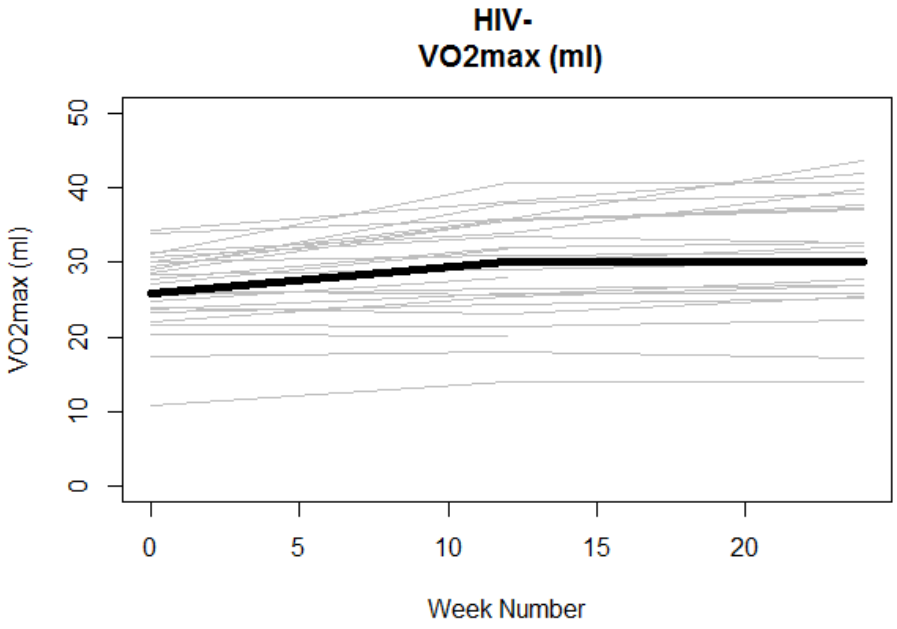
Physical Outcome Measures & Methods		
Cardiopulmonary Capacity	Treadmill walking	V02 peak, ml/kg/min
Muscle strength – upper body	Bench press	Maximal load, lbs (1-RM)
Muscle strength – lower body	Leg press	Maximal load, lbs (1-RM)
Physical Function	Chair rise, 10 repetitions	Time, sec

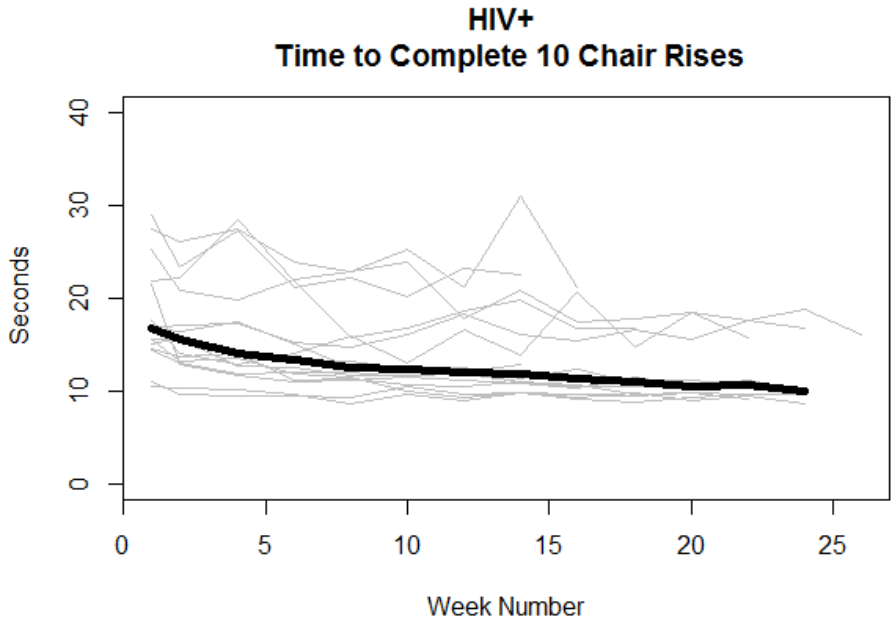

Patient: 531, High Intensity, HIV +
Cumulative Leg Press
Cumulative Score
5500
6000
6500
7000
7500
8000
8500
0
5
10
15
20
25
Week Number

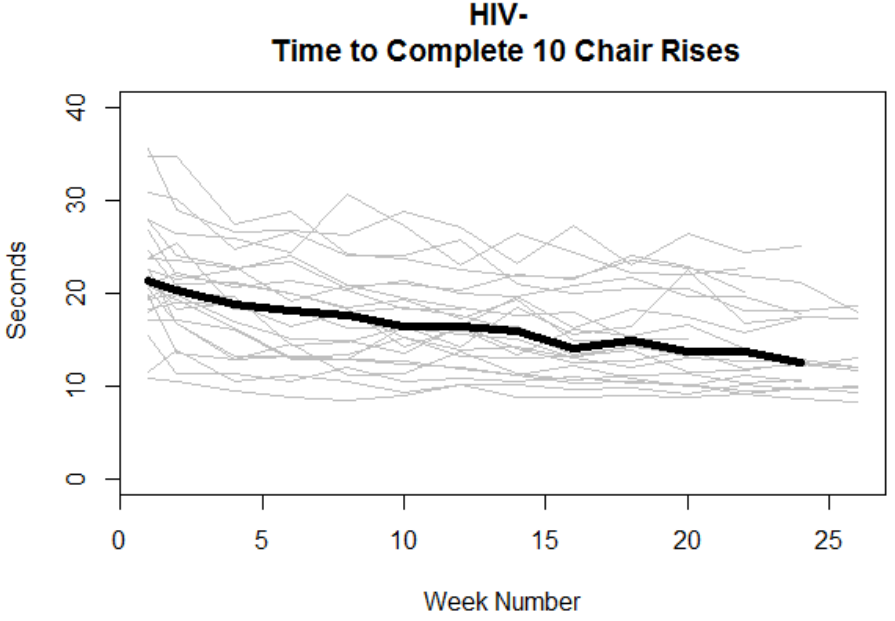

Patient: 531, High Intensity, HIV +
Average Heart Rate
Heart Rate
105
110
115
120
125
130
135
0
5
10
15
20
25
Week Number

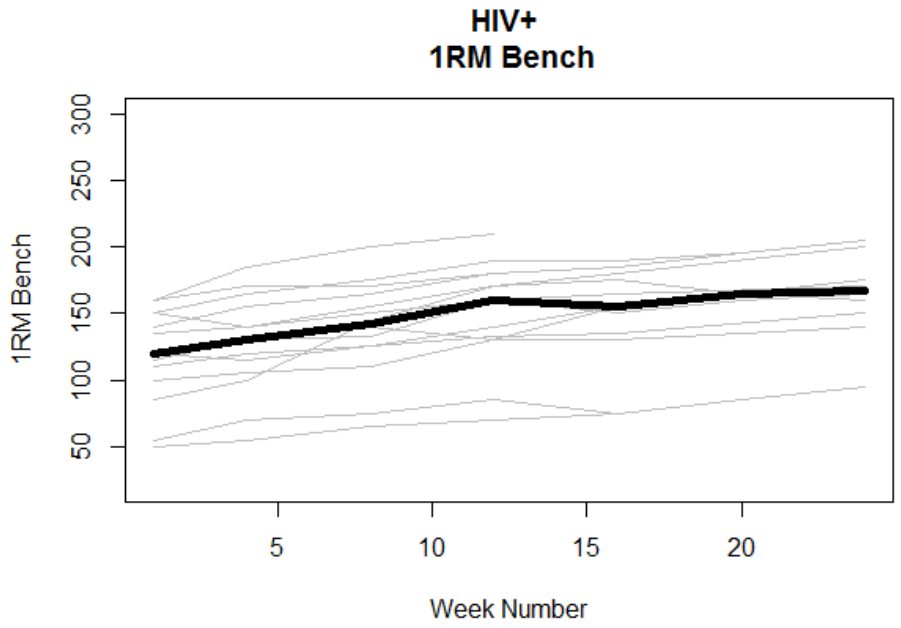

Moderate intensity
exercise acclimation
N=18 HIV+/18 HIV- high intensity
x 12 weeks
N=18 HIV+/18 HIV- mod intensity
x 12 weeks
0
12
24 Weeks

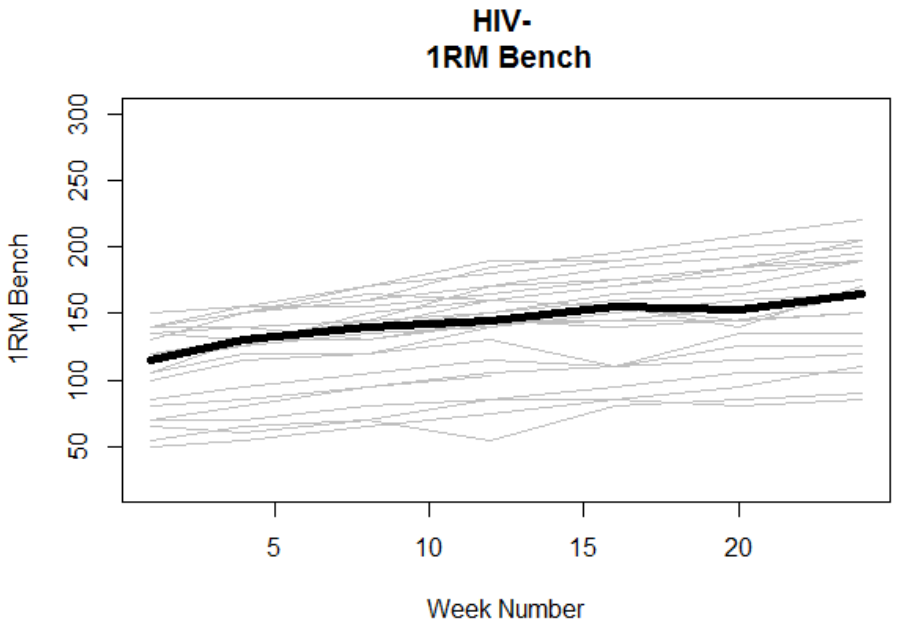

HIV+
VO2max (ml)
VO2max (ml)
0
10
20
30
40
50
0
5
10
15
20
Week Number


HIV-
VO2max (ml)
VO2max (ml)
0
10
20
30
40
50
0
5
10
15
20
Week Number


HIV+
Time to Complete 10 Chair Rises
Seconds
0
10
20
30
40
0
5
10
15
20
25
Week Number


HIV-
Time to Complete 10 Chair Rises
Seconds
0
10
20
30
40
0
5
10
15
20
25
Week Number


HIV+
1RM Bench
1RM Bench
50
100
150
200
250
300
5
10
15
20
Week Number


HIV-
1RM Bench
1RM Bench
50
100
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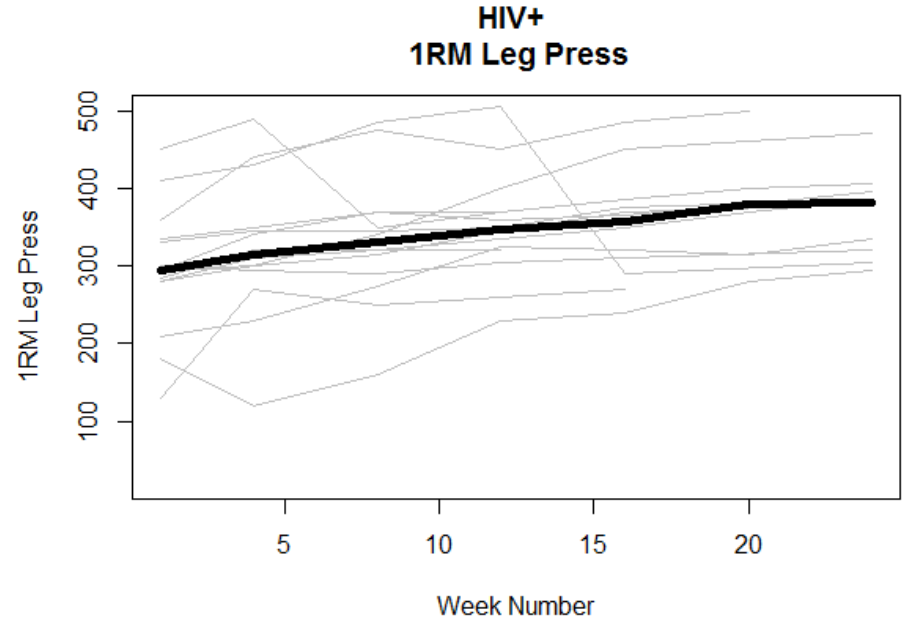
Week Number


HIV+
1RM Leg Press
1RM Leg Press
100
200
300
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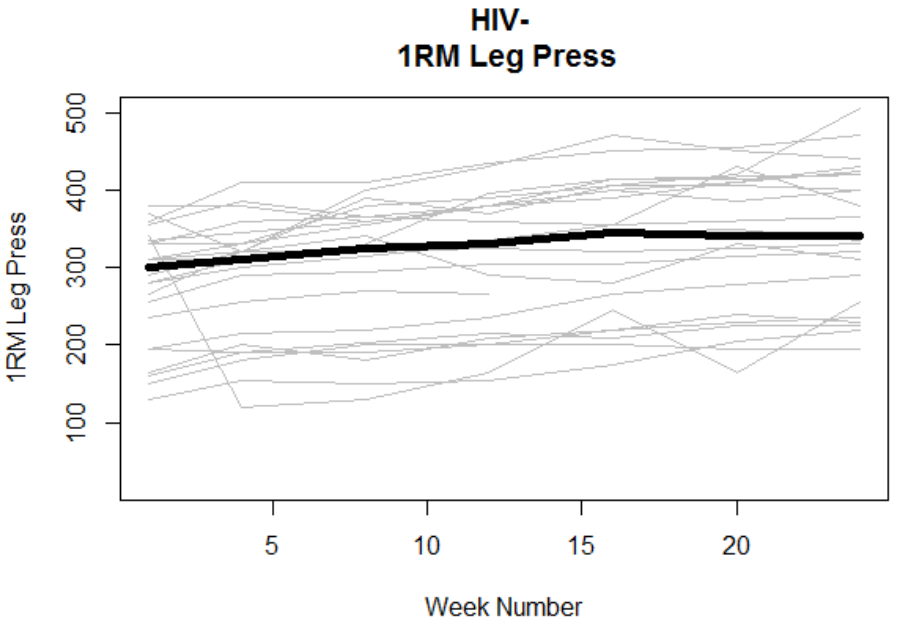
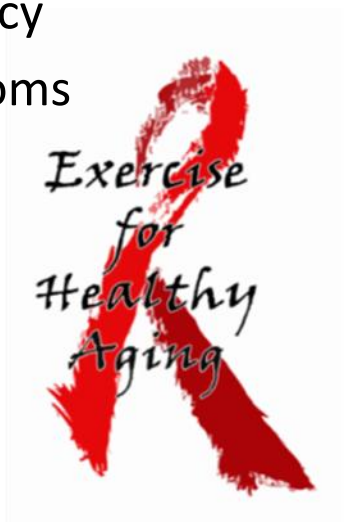
20
Week Number


HIV-
1RM Leg Press
1RM Leg Press
100
200
300
400
500
5
10
15
20
Week Number

Still to Come

- Inflammatory, hormone & Immune Markers
- IL6, sTNFR1, IGF-1, Testosterone
- Training effects & acute effects of exercise on IL6
- Physical function tests
- Epigenetic changes in skeletal muscle???

- Body Composition - DXA
- Fat-free mass
- Fat mass, visceral fat
- Quality of Life
  - Sleep quality
  - Body image
  - Exercise self-efficacy
  - Depressive symptoms



A Qualitative Study to Understand Exercise Barriers in Older, HIV-Infected Adults (n=21)

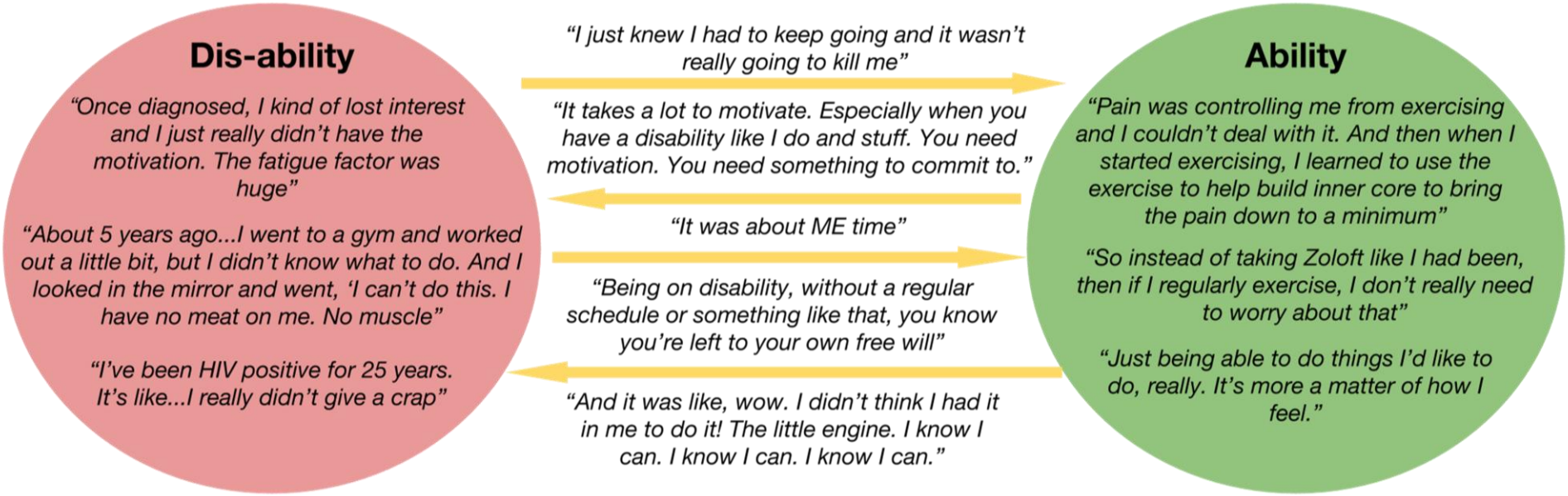
Neff, Jones, Jankowski & Erlandson (unpublished)

Participant Characteristics	
Age (Years), Mean (SD)	58 (5.2)
BMI	24.7 (2.7)
CD4 Count	570.3 (244.5)
Years Since Diagnosis	22.6 (7.0)
Years since started regularly taking HIV Meds	16.6 (6.7)
Female, N (%)	1 (4.5)
HIV-1 RNA	
<200 copies/ml	1 (4.5)
<40 copies/ml	21 (95.5)
Participant Comorbidities	
High Blood Pressure	9 (40.9)
High Cholesterol	11 (50.0)
Cardiovascular Disease (including heart attacks, stroke, or heart valve problems)	4 (18.2)
Diabetes	1 (4.5)
Depression, Anxiety, Bipolar Disorders	11 (50.0)

Participant Socio-Economic Factors N (%)	
Race	
White	15 (68.2)
Black or African American	4 (18.2)
More than 1 Race	2 (9.1)
Ethnicity	
Hispanic or Latino	2 (9.1)
Not Hispanic	19 (86.4)
Highest Level of Education	
Some High School	3 (13.6)
High School Graduate or GED	4 (18.2)
Some College or Associates Degree	6 (27.3)
Completed College or Post-College	9 (40.9)
Current Work Situation	
Unemployed	4 (18.2)
Disability	11 (50.0)
Retired	3 (13.6)
Part or Full Time	7 (31.8)

- 3 Focus groups & 3 individual interviews
- Enrolled in Exercise for Healthy Aging Study

1. Dominant Theme: HIV & aging contributed to a sense of being "disabled"
2. Dis-ability was a common barrier to exercise before joining the Healthy Aging Study
3. Self-efficacy mediates the transition from Dis-ability to Ability

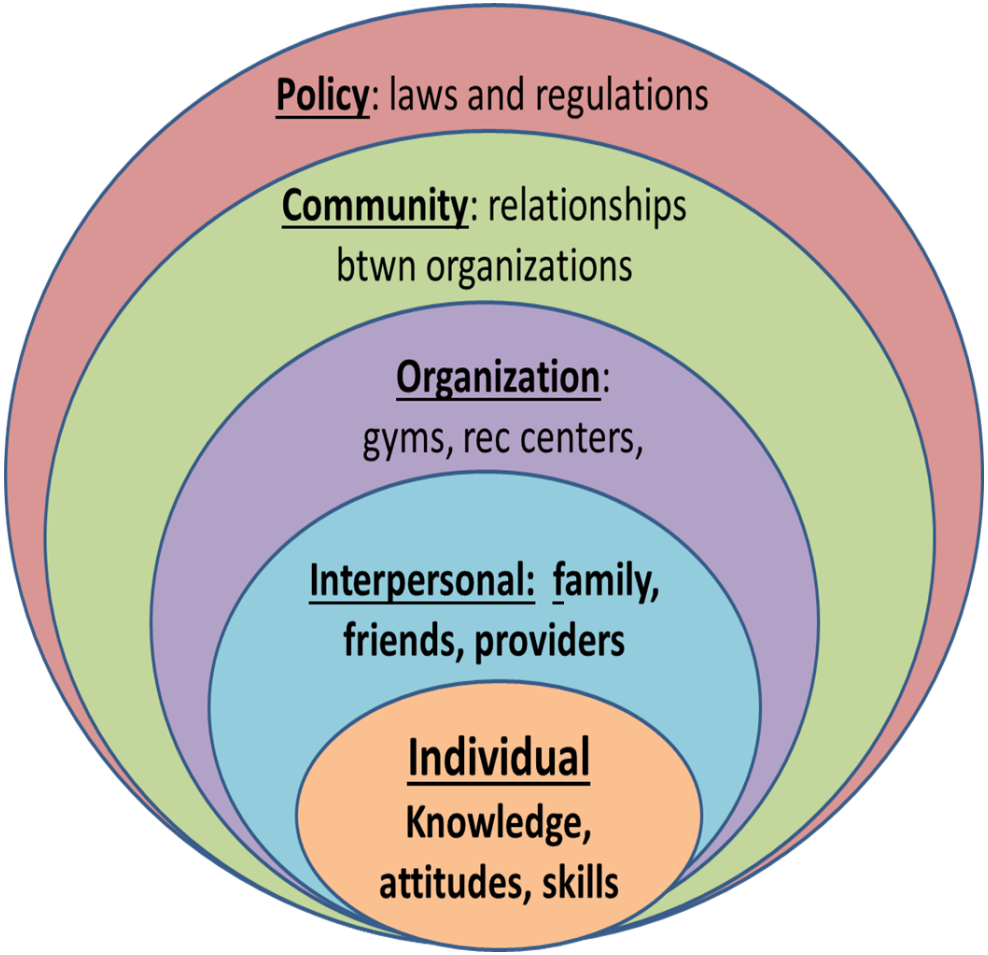


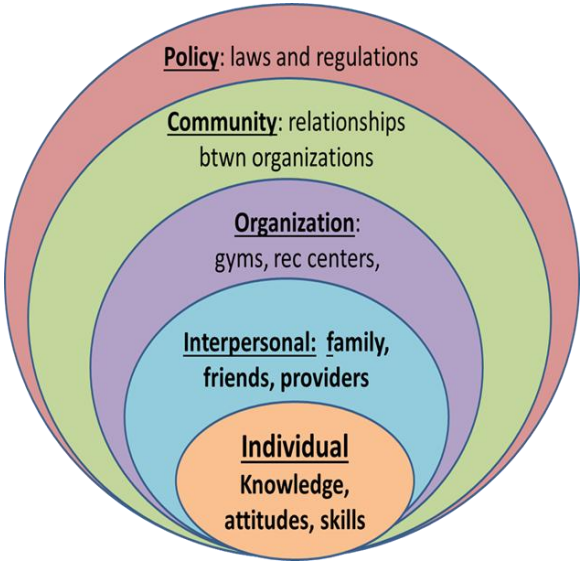
Neff, Jones, Jankowski & Erlandson (unpublished)

Second Round of Focus Groups: Persons with HIV not in The Healthy Aging Study

Table 1: Participant Characteristics		
Characteristics	**Exercise intervention (n=22)***	**HIV+ volunteers (n=29)***
Age (years)	58 (5.2)	59 (6.3)
Female	1 (4.5)	4 (13.8)
Black or African American	4 (18.2)	5 (17.2)
More than 1 Race/Unknown	3 (13.6)	4 (13.8)
Hispanic or Latino	2 (9.1)	4 (13.8)
≤ High School Education	7 (31.8)	7 (24.1)
Some College	6 (27.3)	11 (38.0)
College or post-grad	9 (40.9)	11 (38.0)
Current Work Status		
Unemployed	4 (18.2)	5 (17.2)
Disability	11 (50.0)	13 (44.8)
Retired	3 (13.6)	7 (24.1)
Full Time	2 (9.1)	4 (13.8)
Part Time	5 (22.7)	1 (3.4)
Years since HIV diagnosis	22.6 (7.0)	18.8 (8.4)
Years regularly taking ART	16.6 (6.7)	14.5 (8.6)

Social Ecological Model of McLeroy (1988) as a Framework for Understanding Physical Activity Barriers, Motivators & Facilitators in HIV-infected Older Adults





Policy: Barrier

No specific recommendations for exercise in HIV
Lack of knowledge of insurance plan benefits
Lack of food/house
Societal importance of exercise

Policy: Facilitators

Growing desire for "whole body" health/wellness
Free/discounted gym memberships
Requirements for physical activity (school, military, work, prison)
Concepts of exercise vs physical activity

Community: Barriers

Loneliness, difficulty meeting people
Homelessness or unstable housing
HIV stigma
Ageism
Lack of older, gay community

Community: Facilitators

Accountability
Social groups focused on health
Active community (Denver)
Walkable neighborhood, neighbors

Organizational: Barriers

Cost/access
Dislike for gym culture
Lack of simple gym facilities; Technology
Shared locker facilities regardless of sexual orientation

Organizational: Facilitators

Location/convenience
Cost
Age-friendly facility
Variety of exercises (dance, yoga, etc.)

Interpersonal: Barriers

Lack of exercise partner/accountability
Caregiver responsibilities
Loss of social networks to AIDS; survivors guilt
Anger
Lack of specific recommendations
Not routinely asked or avoid answering

Interpersonal: Facilitators

Accountability; partner or pet
Caregiver responsibilities
Community-shared experiences
Stages of change: turning point
Positive feedback
Relationship & recommendations of provider

Intrapersonal: Barriers

Body image: thin, lipodystrophy
No daily schedule or lack of time
Sense of disability/disease; medication burden, pain
Set-backs (hospitalizations, injuries, deaths of family)
Lack of motivation/priority
Lack of knowledge re safe exercise

Intrapersonal: Facilitators

"Me time"; priority on own health
Regular routine (vs unstructured day)
Mental & physical improvements
Confidence in safely performing
Fear of dementia/loss independence
Enjoy the activity

"stigma is placed upon people with HIV. And they look at us like if we are underweight, there is something wrong with us. If we are overweight, we don't take care of ourselves"

"I think the community…this is what we are a part of… The other big component is we are all being monitored… You get to know us. You can see us lifting the weights. You can see us when we come in. That doesn't happen in a regular gym. You walk in, you are a nobody. You are a number.."

Community: Barriers

Loneliness, difficulty meeting people
Homelessness or unstable housing
HIV stigma
Ageism
Lack of older, gay community

Community: Facilitators

Accountability
Social groups focused on health
Active community (Denver)
Walkable neighborhood, neighbors

"…having people around you that are of a similar age…you don't feel…I don't know if it's threatened or whatever, but you just feel more at ease"

"Right now I feel like there is nobody out there in this world, who is going to miss me, if I don't show up"

"When people give me that positive reinforcement of saying I'm an inspiration, that's the interesting thing is living with HIV for 30 years plus, it is nice to know somebody thinks I'm an inspiration"

Interpersonal: Barriers

- Lack of exercise partner/accountability
- Caregiver responsibilities
- Loss of social networks to AIDS; survivors guilt
- Anger
- Lack of specific recommendations
- Not routinely asked or avoid answering

Interpersonal: Facilitators

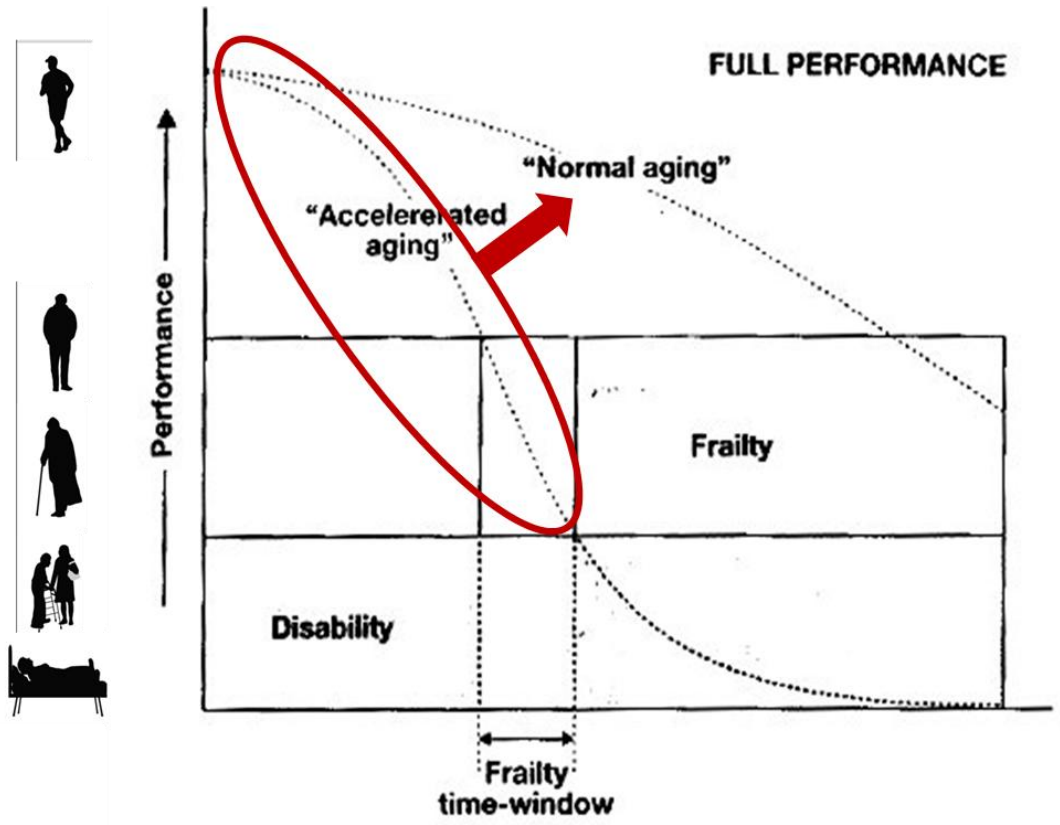
- Accountability; partner or pet
- Caregiver responsibilities
- Community-shared experiences
- Stages of change: turning point
- Positive feedback
- Relationship & recommendations of provider

Interventions aimed at promoting exercise in older adults with HIV should consider barriers & facilitators at all 5 levels of the Social Ecological Model to increase the likelihood of a successful outcome.

- Inflammation, immune activation, and hormonal dysregulation are associated with frailty in HIV.

- Intervening earlier (middle-age) may have greater impact on the trajectory

- Physiologic & psychosocial factors impact transition from dis-ability to ability



Research Directions

- Reversal of HIV-frailty – methods & magnitude
- Sex-specific frailty presentations & strategies?
- Examine physiology underpinning HIV-frailty
  - Inflammation, immune activation & senescence
  - Innate & adaptive immune system required for skeletal muscle repair (Saini et al, 2016)
  - Skeletal muscle epigenetics – HIV, exercise
- Behavioral strategies for multisystem benefits

  Physiological, clinical, psychosocial

Research Directions (con't)

- Identify barriers & facilitators of behavior change

  Stigma attached to HIV *AND* aging

- Develop welcoming exercise environment to support sustainable exercise behaviors
  - Bridge internal validity & generalizability
  - Peer coaching?
- Methods to instill exercise self-efficacy

  Support transition from dis-ability to ability

Gràcies! Preguntes?

Agraïments

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