The Role of Exercise on Those Aging with HIV

November 16, 2017

Kris Ann Oursler, MD, ScM
Director, Geriatric Research and Education
Salem VA Medical Center
Associate Professor
Virginia Tech Carilion SOM & Research Institute
Learning Objectives

I. Exercise capacity
   A. Define domains of exercise capacity
   B. Appreciate limitations in HIV-infected adults
   C. Understand biological and physiological mechanisms underlying limitations in older HIV-infected adults

II. Recognize effects of different exercise training interventions

III. Appreciate challenges in designing a durable and effective exercise training regimen in older HIV-infected adults

No financial disclosures
Primary Aging

Primary Aging is a process that occurs naturally as an organism ages. It is influenced by various factors such as inflammation, telomere shortening, immunosenescence, mitochondrial dysfunction, and lifestyle factors.

Secondary Aging

Secondary Aging is influenced by lifestyle factors such as low physical activity, obesity, smoking, and comorbidities such as metabolic disease, cardiovascular disease, pulmonary disease, cognitive loss, and cancer.

Tertiary Aging

Tertiary Aging is a stage in which the body's systems begin to decline and the risk of developing age-related diseases increases.
Exercise for Patients

Rehabilitation
- Physical Therapy
- Cardio or Pulmonary Training

Training
- Gain muscle
- Lose weight
- Healthy Aging

Slide courtesy of Kim Birkett, MPH
Exercise capacity…..
What is it and why do we care?

- Prevents and improves most age-related conditions
- Independently predicts outcomes
  - Morbidity and Mortality
  - Disability and independent living
  - Quality of life
- Domains of exercise capacity
  - Cardiorespiratory fitness
  - Strength
  - Balance
  - Flexibility
Exercise capacity declines with age in healthy adults

FIGURE 1. Age-related decreases in thigh muscle area (based on one-cut computed tomography scan), knee extensor strength (180°/s), and aerobic capacity [measured as maximal oxygen volume (VO₂ max) adjusted for fat-free mass] in 78 healthy persons who did not regularly exercise (2). The significant decline in muscle strength persisted even after normalization for leg fat-free mass (data not shown). Adapted from references 2 and 5.
1A. Cardiorespiratory Fitness

Measured by $\text{VO}_2\text{peak}$: oxygen consumption at peak exercise
VO$_2$ peak is reduced 40% in HIV-infected vs. healthy adults

Oursler, KK, AIDS Res HR 2006
Cardiorespiratory Fitness

Most common reason for reduced cardiac output is impaired diastolic function rather than impaired systolic function.

Diastolic Function:
LV relaxation
LV filling pressure
Diastolic dysfunction in HIV+

- HIV + have two-fold greater risk of diastolic dysfunction compared with HIV negative controls \(^1\)
- Clinical factors associated with diastolic dysfunction in HIV+ \(^2\)
  - Lower nadir CD4+ count
  - Elevated hsCRP level
  - Hypertension
  - Elevated fasting glucose level
- Diastolic dysfunction is associated with impaired basal myocardial insulin sensitivity in HIV + with lipodystrophy syndrome \(^3\)

---

\(^1\)Hsue PY, Circ Heart Fail. 2010;
\(^2\)Mondy KE, Gottdiener J, et al., CLID. 2011;
\(^3\)WT Cade, HIV Clin Trials 2013
HIV+ with impaired LV relaxation have lower $\text{VO}_2 \text{peak}$

Low mitral annular velocity ($E'$) is a measure of impaired LV relaxation

H. McClinic, International HIV and Aging Meeting, 2015
LV filling pressure is independently associated with VO$_2$peak in HIV +

Adjusted $R^2 = 0.35$

$p = 0.037$

H. McClinic, International HIV and Aging Meeting, 2015
Cardiorespiratory Fitness

Skeletal muscle mitochondria utilize the oxygen to produce energy.
Muscle mitochondrial enzyme activity is associated with VO\textsubscript{2}peak in HIV + and HIV -

H Ortmeyer, Physiological Reports 2016
1B. Cardiorespiratory fitness increases with aerobic exercise (AEX) training

- Training components
  - Frequency
  - Duration
  - Intensity
  - Progression: how and rate

- Types of Exercise
  - Stationary Equipment
  - Weight bearing: Functional Exercise, Calisthenics, “Cross Fit”

- Location (and level supervision)
  - Home
  - Community
  - Research Center
Exercise Intensity

**Physical Activity Spectrum**

<table>
<thead>
<tr>
<th>Sedentary Behaviour</th>
<th>Low Intensity</th>
<th>Moderate Intensity</th>
<th>High Intensity</th>
<th>HIIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.5 METS</td>
<td>1.5 – 3 METS</td>
<td>3 – 6 METS</td>
<td>&gt; 6 METS</td>
<td>90% of aerobic capacity to maximal</td>
</tr>
<tr>
<td>e.g. Sitting &amp; lying</td>
<td>e.g. slow walking</td>
<td>e.g. brisk walking</td>
<td>e.g. running</td>
<td>e.g. sprint cycling</td>
</tr>
</tbody>
</table>

**Relative Intensity**

<table>
<thead>
<tr>
<th>Intensity</th>
<th>%HRR or %VO₂R</th>
<th>%HR&lt;sub&gt;max&lt;/sub&gt;</th>
<th>%VO₂&lt;sub&gt;max&lt;/sub&gt;</th>
<th>Perceived Exertion (Rating on 6–20 RPE Scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very light</td>
<td>&lt;30</td>
<td>&lt;57</td>
<td>&lt;37</td>
<td>&lt;Very light (RPE &lt; 9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>40–59</td>
<td>64–76</td>
<td>46–63</td>
<td>Fairly light to somewhat hard (RPE 12–13)</td>
</tr>
<tr>
<td>Vigorous</td>
<td>60–89</td>
<td>77–95</td>
<td>64–90</td>
<td>Somewhat hard to very hard (RPE 14–17)</td>
</tr>
<tr>
<td>Near-maximal to maximal</td>
<td>≥90</td>
<td>≥96</td>
<td>≥91</td>
<td>≥Very hard (RPE ≥ 18)</td>
</tr>
</tbody>
</table>

MA Nimmo, 2013

Aerobic Exercise Training in HIV+ Adults

• Recent Cochrane Review and meta-analysis of AEX in HIV+ ¹
  – 24 RCTs: interventions of AEX (11) or AEX +RT (13)
  – 936 participants at completion, 73% male and on ARV (19/24 studies)
  – Most supervised and center-based
  – Safe (no change CD4 and viral load)
  – Only three compared AEX by intensity
  – Only one with nutrition component
  – No change weight, but increased lean body mass
  – NO HIV NEGATIVE COMPARISION GROUPS
  – NONE TARGET OLDER HIV+ ADULTS

• AEX ↑ 7-25% VO₂peak in younger HIV-infected adults ¹⁻⁴

AEX RCT in older HIV + men

• **Design:**
  – Twenty-two men with HIV on antiretroviral therapy, age 50+ years
  – Randomized to Mod-intensity or high-intensity aerobic training
  – 3x week for 16 weeks
  – Supervised and center-based
  – Encouraged to maintain weight (no Δ diet)

• **Mod-intensity AEX (Mod-AEX):**
  1 mile self-paced walking on indoor track

• **High-intensity AEX (High-AEX):**
  treadmill training with target of 45-60 minutes @ 70-80% HRR
  
  (heart rate reserve = (HRmax – HRrest) + HR rest)
Mod-AEX and High-AEX increase exercise endurance

Baseline 16-week

+ 11% + 12%

* p = 0.01

6-MWD, meters

Mod-AEX High-AEX

Oursler et al, Manuscript under review
Only High-AEX increases VO$_2$peak

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>16-week</th>
<th>+ 16%</th>
<th>p=ns</th>
<th>p=0.02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod-AEX</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>High-AEX</td>
<td>2.0</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

Oursler et al, Manuscript under review
Lower the VO$_2$: easier to increase
Lower the VO\textsubscript{2}: easier to increase

older HIV+

younger HIV+ (ref 2)

older HIV+

\textsuperscript{2} Lindegaard, J Clin End Metab, 2008

DP Swain, Preventive Cardiology 2005
Effects of AEX on diastolic function in younger HIV +

- 24 HIV+ adults, mean age 42 yrs
- Randomized to two groups for 4 months of:
  - Pioglitazone (PIO; 30 mg/d) alone
  - With Mod-high AEX +RT 3 x a weekly
- Basal myocardial metabolism was quantified by radioisotope tracer and PET imaging
- LV function measured by echocardiography
- PIO or PIO + Exercise
  - Did not increase basal myocardial insulin sensitivity
  - Did not improve diastolic function

WT Cade and KE Yaresheski, HIV Clin Trials, 2013
Effects of exercise on systemic inflammation

Gleeson M, 2011
Effects of exercise on inflammation in younger HIV +

• Mod-AEX + RT in 89 HIV+ adults, mean age 48 yr¹
  – No change hsCRP (even stratified by compliance)
  – Modest change VO₂peak ( 2.2 mL/kg/min, p=0.07)

• Mod-AEX with and w/o RT in 35 HIV+ adults, median age 48 yr²
  – Significant change hsCRP and biomarkers inflammation
  – 30% on a clinically Rx’ed statins (at entry and during intervention)

¹ SE Cutrono, AIDS Behav 2016
² M Bonato, BMC ID, 2017
Effect of AEX intensity on inflammation in older HIV negative adults with DM

- Participants N= 82 men and women with DM
  - 40-75 years with mean age 63 y and BMI 27-40 kg/m²
- Randomized to 4 groups:
  #1.) Sedentary controls
  #2.) Unsupervised home-based low-intensity AEX
  twice a week supervised sessions of:
    #3.) 60 min of high- AEX , 70-80% VO2
    #4). 40 min of high-AEX, 70-80% VO2 + 20 min RT
- Significant CRP reduction
  - Depended on exercise intensity
  - Inversely correlated with VO2peak
  - Despite no change in body weight

S. Balducci, Nutrition, Metabolism & Cardiovasc Dis (2010)
Effect of AEX intensity on systemic inflammation in HIV-

change from baseline
Group C $P=0.05$
Group D $P=0.0001$

Sedentary controls
Low-intensity AEX
High-AEX
High-AEX + RT

S. Balducci, Nutrition, Metabolism & Cardiovasc Dis, 2010
AEX and inflammation in HIV+: unsolved questions

Is high-intensity AEX needed to improve VO$_2$peak and systemic inflammation?

If so, HOW to do it with older HIV+ ?
Strategies for high-AEX in older HIV +

I01 RX000667 (Oursler)
T. Wamsley, ACSM Annual Meeting, 2017
Summary: AEX training in older HIV +

• What we know:
  – Feasible: safe and well-tolerated in select patients
  – Moderate and high-intensity AEX increases endurance

• What we don’t know:
  – Is there an intensity threshold to increase VO$_2$peak?
  – Best exercise strategy to modify inflammation, mitochondrial function (muscle !), and other primary aging processes
  – Impact of and need for adjunct therapy:
    → anti-inflammatory drugs
    → diet supplements
    → Visceral fat loss to reduce adipokines
2 A. Strength

• Dependent on
  – Muscle size
  – Muscle quality (Intramuscular and intermuscular fat)
  – Central activation (ability to activate available muscle)
  – Individual’s age and sex- regardless of training

• Sensitive measures with exercise equipment
  – Dynamometer: Isokinetic and Isometric force
  – Free weights/cable machines: 1 repetition maximum (1-RM)

• Functional performance measures
  – Large population based studies with normative values
  – Chair stand for lower extremity
  – Grip strength for upper extremity
## Lower extremity strength in HIV +

<table>
<thead>
<tr>
<th>Measure</th>
<th>HIV +</th>
<th>HIV Neg. Comparison</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee extensor, kg (MVC)</td>
<td>N=27 M 49 y</td>
<td>Age-predicted norm (Lindle)</td>
<td>None</td>
</tr>
<tr>
<td>Leg Press, kg (sub-max)</td>
<td>N =11 (45% M) 65 y</td>
<td>N=21 (47% M) 67 y</td>
<td>↓ HIV 45 kg p&lt;0.001</td>
</tr>
<tr>
<td>Chair stand 2 5X timed</td>
<td>N=359 (85% M) 51 y</td>
<td>Normative: SPPB scoring</td>
<td>33% impaired</td>
</tr>
<tr>
<td>Chair Stand 3 5x timed</td>
<td>N=324 (80% M) 48 y</td>
<td>Age predicted norm</td>
<td>53 % impaired</td>
</tr>
<tr>
<td>Chair Stand 4 5x timed</td>
<td>N=37 (38% M) 39 y</td>
<td>N=78 (47%) 38 y</td>
<td>none</td>
</tr>
</tbody>
</table>

Grip strength is lower in HIV+ versus HIV negative adults

Study of global AGEing (SAGE)
HIV+ adults n=181 (43 60+ yrs) ¹
HIV - adults n= 2,655 (1,405 60+ yrs)

Grip strength is lower in HIV+ versus HIV negative adults

Frailty range by BMI for men
women²

## Functional performance associated with muscle mass and insulin-like growth factor

<table>
<thead>
<tr>
<th></th>
<th>Low Function (N=30)</th>
<th>High Function (N=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat mass (kg)</td>
<td>21.2 ± 2.0</td>
<td>18.3 ± 1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>46.9 ± 1.7</td>
<td>51.6 ± 1.5</td>
<td>0.03</td>
</tr>
<tr>
<td>ASMI (kg/m²)</td>
<td>6.8 ± 0.2</td>
<td>7.8 ± 0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>99.0 ± 8.2</td>
<td>126.7 ± 6.6</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ASMI, appendicular skeletal muscle index
IGF-1, insulin-like growth factor-1

K Erlandson, JAIDS 2013
Muscle mass is lower in HIV+ men compared to healthy controls

Muscle quality decreases (intermuscular fat increases) with age in HIV + compared to HIV -

Lower density-
Higher Inter muscular fat

Fig 1. Association of thigh muscle density and age among HIV-infected (red) and HIV-uninfected (blue) men in the MACS Cohort.

J Natsa and T Brown, PLOS ONE, 2017
Intermuscular fat inversely correlates with functional performance in HIV+

Figure 2. Relationship between Physical Performance Test score and ratio of intermuscular fat (IMF) to total fat.
Sarcopenia is defined as: Low muscle mass WITH low muscle function (strength or performance)

- **Low muscle mass:** established cutoffs based on lean appendicular mass/height$^2$ by Baumgartner
- **Low function:** established cutoff for walking speed, 6-MWD, grip strength
2B. Strength training or resistance training

Helen Zechmeister, Age 81
Resistance Training in younger HIV +

- Review of exercise trials by modality
  - 11 concurrent (RT + AEX)
  - 10 RT only

- Improvements in:
  - Strength
  - Lean mass and muscle cross sectional area
  - Bone mineral density

- Targeted Interventions and outcomes
  - RT + weight loss: insulin receptors and TG metabolism in skeletal muscle for Lipodystrophy
  - RT + testosterone or GH for AIDS Wasting

1 Gomed- Neto 2013
2 O’Brien, AIDS Care, 2008
Resistance Training in *Older* HIV+ Adults

- Eleven older (60+) HIV-infected adults
  - Mean age 65 y
  - 5 Men and 6 Women
- Progressive resistance training program
  - 2x week for 1 year
  - Four free weight exercises, 3 sets each
- Results
  - Strength increased 74-122% ($p < 0.02$)
  - Improved chair stand test
  - No change in weight, lean mass or fat mass (DXA)
Resistance training combined with high-AEX increases strength in older HIV+: preliminary results

- RCT of high-AEX+ RT vs. sedentary usual care controls
- HIV+ men 50+ yrs of age on ARV

Oursler, accepted SEACSM Scientific Meeting 2018
Increased lean mass predicts increase in strength
Summary: RT in older HIV +

What we know:

1. Feasible: 2 small published studies (de Souza 2008, 2011)

2. Likely can be combined with AEX
   One preliminary report but many in younger HIV+

3. Functional performance measures have ceiling effect

4. Need to consider mediating factors of both muscle mass and quality (IMAT)
What we don’t know:

1. Best exercise strategy to modify inflammation, mitochondrial function (muscle !), and other primary aging processes

2. Impact of and need for nutritional supplements/diet $^{1,2}$
   - Quality protein intake, creatine, vitamin D

3. Impact of and need for adjuvant therapy
   - endocrine agents (androgenic steroids, growth hormone, and insulin-like growth factor-1)

2. Morley JE J Am Med Dir Assoc. 2010
3A. Balance: risk for falling and fractures

- Three sub-domains of balance: static, dynamic, and functional
- In HIV literature: assessments primarily 10 sec. tandem stand test (0-4 pts) of total possible score of 12 on Short Physical Performance Battery (SPPB)
- Formal Balance Testing
  - Clinical measures:
    - Berg Balance (BBS)
    - Dynamic Gait Index (DGI)
  - Research measures:
    - Spatial Laterality Index (SLI)
    - Center-of-pressure (COP) postural sway
Balance limitations in HIV+

- ~10% HIV+ impaired one leg or heel to toe
- Colorado Cohort: 359 HIV+ adults, 45-65 yrs, ARV, viral suppressed: Impaired tandem stand associated with recurrent falls ($\text{OR}_{\text{adj}} 15.5$ (4.6,53.0)) K Erlandson, JAIDS 2012

Pilot project UMD by A Ryan, H Ortmeyer, A Roy
Balance Battery in 5 HIV+ and 5 HIV- men

Berg Balance (BBS); Dynamic Gait Index (DGI); Spatial Laterality Index (SLI)
Center-of-pressure (COP) postural sway
3B. Exercise intervention for balance in HIV+

- 10 older HIV+ adults mean age 57 yrs
- Single arm exergame intervention: weight shifting, ankle reaching, and obstacle crossing with real-time visual and audio lower-extremity joint motion feedback
- 2x week for 45 min for 6 weeks
- Reduction in center of mass sway of 78% p=0.045
- Increased stride velocity

Flexibility?
Exercise strategies in older HIV adults are needed

- To Increase
  - Cardiorespiratory Fitness
  - Strength
  - Muscle mass and quality
  - Balance
- To determine the optimal exercise mode and intensity that targets pathogenesis of aging with HIV
- To determine role of pharmacologic adjuvants, diet, and nutritional supplements
Clinical Challenges

• Large randomized exercise interventions that can translate to durable lifestyle changes
• HIV Negative Controls?
• Address risk factors for cardiovascular disease
  – Inflammation
  – Traditional risk factors > Weight Loss
• Increase strength and muscle mass
  – Increased dietary protein

Knowledge Graph:
- Fat Mass
- Weight Loss
- Lean Body Mass
Practical Challenges

- Personal lifestyle change
- Low cost = not center-based
- Durable = feasible and fun

No unique issues identified in HIV+
- Meta-analysis of 36 RCTs
- Mean age 42 yrs, 80% male
- Overall dropout rate 29%
- Predictors of dropout
  - Low BMI and low fitness
  - Higher in AEX vs. RT
  - Not vary by mod. vs high intensity

D Vancampfort, AIDS Care 2017