Development of Evidence-Based Exercise Recommendations for Older HIV-Infected Patients

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Advances in antiretroviral therapy (ART) have decreased HIV-related morbidity and mortality and contributed to rapidly increasing numbers of older people living with HIV. Successful management of ART-related side effects (metabolic syndrome) and age-related comorbidities (frailty) are major challenges for patients and providers. Exercise has proven beneficial for younger HIV-infected patients, but we know little about which exercise regimens to recommend to the elderly. Our goal was to develop age-appropriate, evidence-based exercise recommendations for older HIV-infected adults (age > 50). We reviewed randomized controlled trials on the effects of physical exercise for: (a) HIV-infected young adults, (b) frail older adults, and (c) elderly individuals with metabolic syndrome. We recommend a combination of endurance and resistance exercises 3 times per week for at least 6 weeks to improve cardiovascular, metabolic, and muscle function. Further research is warranted to study the benefits and risks of physical exercise in older HIV-infected patients.

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Over the last three decades the HIV epidemic has made a remarkable transformation from a once deadly disease into a long-term manageable chronic illness. Initially, many young, energetic, and very active men and women fell ill with a difficult-to-manage disease. The introduction and continuous development of antiretroviral therapy (ART) has contributed to the dramatic decline in morbidity and mortality associated with HIV. As a result of this major medical success, people infected with HIV are growing older. In 2006, 27% of all people living with HIV in the United States were ages 50 and older (Karpiak, Shippy, & Cantor, 2006).

The everyday management of living with HIV disease today is mainly focused on coping with side effects and symptoms related to ART, but it is also related to the onset of age-related chronic health conditions such as diabetes, lean muscle loss, decline in pulmonary function, cardiovascular disease, and other conditions of aging (Beck, Rosen, & Peavy, 2001; Feigenbaum & Longstaff, 2010; Grinspoon & Carr, 2005; Sudano et al., 2006). Health behaviors such as exercise, balanced nutrition, and sufficient sleep have been identified as factors to prevent and manage age-related chronic illnesses (Hunter, McCarthy, & Bamman, 2004; Nelson et al., 2007; Sattelmair, Pertman, & Forman, 2009). Numerous investigators have published exercise recommendations for younger HIV-infected adults (Baigis et al., 2002; Hand et al., 2008; Mutimura, Stewart, Crowther,

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Yarasheski, & Cade, 2008; O'Brien, Nixon, Tynan, & Glazier, 2010; Smith et al., 2001), but little research has focused on how physical exercise might benefit older people with HIV infection (Evans, Roubenoff, & Shevitz, 1998; Oursler, Sorkin, Smith, & Katzel, 2006; Souza et al., 2008). The present review aims to develop evidence-based exercise recommendations for older adults infected with HIV by comparing exercise programs for (a) young HIV-infected adults, (b) frailty in older uninfected adults, and (c) metabolic syndrome in young HIV-infected adults. These three areas represent some of the most burdensome clinical issues for persons living with HIV: side effects from ART and HIV, the loss of lean muscle mass, and metabolic changes in glucose and fat. By taking these important areas into account, an exercise program can be constructed that is geared more specifically to the aging HIV population.

Background

Impact of HIV on Physiological Systems

HIV and cardiovascular function. Improved treatment options with combinations of ART lead to lower instances of morbidity and mortality in people infected with HIV (O'Brien, Tynan, Nixon, & Glazier, 2008). Early in the epidemic, cardiopulmonary dysfunction was found in both symptomatic and asymptomatic HIV-infected patients in the form of decreased oxygen uptake at submaximal and peak exercise levels, and a decrease in workload capability (Perna et al., 1999). Several investigators found that cardiac involvement was present in approximately 45%–65% of HIV-infected patients (Passalaris, Sepkowitz, & Glesby, 2000). Currier and colleagues (2003) demonstrated a significantly higher incidence of coronary heart disease in a younger population of men and women infected with HIV compared to subjects without HIV. Of the 1,360 subjects in the HIV-infected group, the most common cardiovascular diagnosis was coronary atherosclerosis (32%), followed by angina pectoris (24%), and myocardial infarction (22%). More recently, Triant, Lee, Hadigan, and Grinspoon (2007) found that acute myocardial infarction rates per 1,000 person-years were increased in HIV-infected (11.13) vs. uninfected patients (6.98). Cardiovascular side effects have been attributed to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs; Friis-Moller et al., 2003). Combination ART has been associated with a 26% relative increase in the rate of myocardial infarction per year of exposure during the first 4 to 6 years of taking medications compared to patients who were not exposed to combination ART. The investigators also reported that the incidence of hypertension was more common among HIV-infected patients treated with PIs, NNRTIs, or both, than in patients who had not taken ART (Friis-Moller et al., 2003).

HIV and pulmonary function. HIV infection alone impairs pulmonary function. Crothers and colleagues (2006) found that HIV-infected patients had a 50%–60% higher chance of being diagnosed with chronic obstructive pulmonary disease than uninfected patients. HIV-related pulmonary hypertension, which can decrease an individual's probability of survival by half, is becoming a common occurrence among patients (Opravil et al., 1997). Furthermore, since HIV-infected cells in the lungs are sources of HIV proteins, investigators have suggested that chronic exposure of lung endothelial cells to viral proteins is one of the most prominent explanations for lung vascular injury in HIV-infected patients (Almodovar, Cicalini, Petrosillo, & Flores, 2010).

HIV and skeletal muscle. The loss of skeletal muscle mass and lean tissue mass, known as HIV-associated wasting, is a common occurrence for HIV-infected individuals. An estimated 20% of all HIV-infected persons suffer from wasting, even with the availability of ART, and wasting has been associated with rapid disease progression and an increase in morbidity (Dudgeon et al., 2006). Zidovudine-associated myopathy was first observed early in the epidemic, when the NRTI zidovudine was widely used as a single drug therapy (Dalakas et al., 1990). These observations led to the discovery of the toxic effects of a number of NRTIs in terms of mitochondrial polymerase γ inhibition and related mitochondrial toxicity, including reduction in ATP production, loss of mitochondrial DNA, and increased reactive oxygen species production (Kohler & Lewis, 2007).

Touzet and Philips (2010) published findings in human primary skeletal myotubes treated with PIs and found that atazanavir, lopinavir, ritonavir, and saquinavir significantly increased the production of reactive oxygen species, increased endoplasmatic reticulum stress, and activated the unfolded protein response. These changes could be successfully reversed with resveratrol treatment, the compound found in grape skin and peanuts (Touzet & Philips, 2010).

HIV and metabolic function. Metabolic disorders occur frequently in HIV-infected individuals and are associated with ART. These abnormalities include body composition changes (lipoatrophy, lipodystrophy, fat accumulation), dyslipidemia (hypertriglyceridemia, hypercholesterolemia, low/high-density lipoprotein cholesterol levels), and abnormal glucose metabolism (insulin resistance, impaired glucose tolerance, diabetes mellitus; Morse & Kovacs, 2006). In patients with lipodystrophy, two primary patterns of fat redistribution occur: accumulation of central fat and loss of subcutaneous fat. Lipoatrophy, or peripheral fat wasting, is characterized by the selective loss of adipose tissue in the face, extremities, and buttocks. Both lead to a significant change in body composition, which not only affects a person's health but also takes a toll on the quality of life, as these changes may lead to stigmatization, increased stress, and reduced self-esteem (Morse & Kovacs, 2006).

Although abnormalities in lipid metabolism were first seen in HIV-infected patients before the development of ART, the introduction of PIs led to a dramatic increase in the prevalence of dyslipidemia, with rates up to 60% of irregular lipid function in patients receiving the medication (Morse & Kovacs, 2006). ART-associated dyslipidemia is distinguished by increased levels of very low–density lipoproteins and low-density lipoproteins, and reduced levels of high-density lipoproteins. Higher lipoprotein levels in plasma have been linked to the development of atherosclerosis and other complications such as myocardial infarction and peripheral vascular disease (Kramer, Lazzarotto, Sprinz, & Manfroi, 2009).

Similarly, insulin resistance and glucose intolerance have been observed since the availability of PIs, and insulin resistance has been shown to increase cardiac risk in HIV-infected patients with lipodystrophy and visceral fat accumulation (Morse & Kovacs, 2006). Grinspoon and Carr (2005) reported impaired glucose tolerance in more than 35% of HIV-infected subjects, compared to 5% in healthy control subjects matched for age and body mass index. In a longitudinal cohort study, HIV-infected men receiving combination ART were 3.1 times more likely to develop diabetes mellitus than control subjects over an observation period of 3 years (Grinspoon & Carr, 2005).

Aging

A vast amount of basic and applied aging research has focused on the physiological and functional processes of aging, thus enhancing our knowledge and understanding of factors that affect the elderly, especially the loss of functional capacities and metabolic functions (Souza et al., 2008). The aging process affects the body's ability to metabolize nutrients, which can result in poor absorption and lower levels of nutrients and maintenance of skeletal muscle in the body (Brant, 2010).

Frailty is typically associated with declining health in older adults who are identified as having one or more of the following: extreme old age, a disability of some sort, and the presence of various chronic conditions or geriatric syndromes (Durstine, Moore, & Bayles, 2003). Although several definitions have been proposed, there is currently no formal agreement on what constitutes frailty (Lally & Crome, 2007). Fried et al., (2001) have explored the concept of frailty and presented a model that provides criteria to define the condition (see Table 1). In this model, frailty was defined as a clinical syndrome in which three or more of the following criteria were simultaneously present: weight loss, exhaustion, weakness, slow walking speed, and low physical activity. Muscle atrophy, the wasting or loss of muscle tissue, is a central concept of frailty. This condition has been shown to lead to a decline in functions such as glucose regulation, hormone production, and cellular communication (Buford et al., 2010).

Frailty and HIV. Desquilbet and colleagues (2007) observed that the phenotype for frailty in older adults was comparable to the wasting syndrome that occurs in HIV infection. They found that the clinical presentation of frailty (loss of muscle mass, weight,

Table 1. Model to Define Frailty

Frailty Component	Description
Unintentional weight loss	>10-pound weight loss in previous year
Exhaustion	Self-reported exhaustion 3 or more days per week
Low physical activity levels	Men: <383 kcal/week* Women: <270 kcal/week
Slowness	Walking time/15 ft: slowest 20% (based on gender/height); cutoff approx ≥ 6–7 seconds
Weakness	Based on grip strength; lowest 20% (stratified by gender and BMI)**

* kcal/week calculated using standardized algorithm (see Fried et al., 2001).
** BMI = body mass index; see Fried et al. (2001) appendix for values.

and energy; slowed motor performance; and low physical activity) strongly resembled symptoms of the later stages of HIV infection. Multiple causal factors have been described for the onset of frailty. Increased levels of interleukin-6 (IL-6) cytokines have been associated with age-related frailty and physical decline (Desquilbet et al., 2009). HIV and aging have both been associated with progressive deficiency in CD4+ T cells, and causal factors of frailty such as continuous inflammation, oxidative stress, and endocrine and immune dysfunctions have been linked to HIV infection (Desquilbet et al., 2009). A prospective cohort study conducted by Desquilbet and colleagues (2009) identified that a decrease in CD4+ T cell count and an increase in plasma viral load were associated with a frailty-related phenotype in HIV-infected men. (See Table 2).

Table 2. ATP III Panel Clinical Definition of the Metabolic Syndrome

Risk Factor	Defining level
Abdominal obesity	Waist circumference
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/85 mmHG
Fasting glucose	≥110 mg/dL

NOTE: ATP III = third adult treatment panel.

Aging with metabolic syndrome. Metabolic syndrome is a frequent occurrence among both HIV-infected and uninfected populations in the United States. The syndrome is characterized by a clustering of central obesity, insulin resistance, dyslipidemia, and hypertension, all of which lead to a higher risk of cardiovascular disease and type 2 diabetes (Hahn et al., 2009; Stewart et al., 2005). Aging has been shown to cause an increase in general and abdominal obesity, which may also lead to various metabolic complications and cardiovascular disease risk factors (Stewart et al., 2005).

Effect of exercise on individuals with HIV and metabolic syndrome. Extensive research has documented the benefits for elderly people when they engage in regular aerobic and resistance exercise including increased cardiovascular health (increased VO_2 measures, decrease in blood pressure, decreased risk of coronary artery disease, and improved lipid profiles), decreased risk of type 2 diabetes, decreased rates of osteoporosis and osteoarthritis, and improved neuropsychological health (improved quality of sleep, cognitive function, decreased rates of depression, decreased rates of dementia; Jeon, Lokken, Hu, & van Dam, 2007; Vogel et al., 2009). Additionally, aerobic and resistance exercise has also been shown to decrease fatigue and improve quality of life (Reid et al., 2010). Research has shown that exercise also improves metabolic functions in older adults and may decrease the odds of developing metabolic syndrome (Hahn et al., 2009; Stewart et al, 2005).

Furthermore, resistance exercise in elderly people has been demonstrated to result in increased nitrogen balance, muscle mass and strength, functional capacity, and energy requirements (Bird, Hill, Ball, & Williams, 2009; Jordan, Melanson, Melby, Hickey, & Miller, 2010; Padeletti, Jelic, & LeJemtel, 2008). The use of resistance exercise in older HIV-infected patients may provide similar benefits.

Types of Exercise

Aerobic exercise. Aerobic exercise typically involves walking, running, swimming, or bicycling and is linked to beneficial changes in the body that affect cardiovascular as well as pulmonary outcomes. These include an increased plasma volume, decreased heart rate, increased stroke volume, increased cardiac output, decreased blood pressure, and increased pulmonary function (McArdle, Katch, & Katch, 2001). Aerobic capacity is objectively measured by calculating the maximal oxygen consumption of an individual (Durstine et al., 2003). Maximum oxygen consumption, or VO_2max, is defined as "the maximal capacity for oxygen consumption by the body during maximal exertion" (Wilmore & Costill, 2004, p. 707). Although VO_2max is an important physiologic indicator for the level of aerobic fitness, it may not give a true value for individuals with chronic disease or disability because these individuals are often not able to reach maximal exertion. In such cases, a measure of peak VO_2 is used to indicate exhaustion level limited by symptoms, instead of measuring exhaustion limited by oxygen supply, as in the case of VO_2max (Durstine et al., 2003).

For healthy adults ages 18–65, the American College of Sports Medicine (ACSM; 2003) recommends taking part in moderate-intensity aerobic physical activity for a minimum of 30 minutes, 5 days each week, or vigorous-intensity aerobic activity for a minimum of 20 minutes, 3 days a week (Haskell et al., 2007). The ACSM provides a useful scale for measuring exercise intensity, which may help patient self-motivation. On a scale of 0 to 10, where 0 is sitting and 10 is exertion of full effort, moderate-intensity aerobic activity rates a 5 or 6, where noticeable increases in heart rate and breathing are observed. Vigorous activity rates a 7 or 8 on the scale and should produce a large increase in heart rate and breathing (Nelson et al., 2007).

Resistance exercise. Muscle strengthening activities include weight training, weight bearing calisthenics, and other resistance exercises that incorporate all major muscle groups (Nelson et al., 2007). One method of measuring muscle strength uses one repetition maximum (1-RM), which refers to the maximum amount of weight that can be lifted at any one time during a weight lifting exercise (McArdle et al., 2001). Strength or resistance exercise is known to cause hypertrophy of muscle cells in humans (Mooren & Volker, 2005), as well as to increase muscular strength and endurance (Dudgeon, Phillips, Bopp, & Hand, 2004). Increasing strength and endurance are due to skeletal muscle adaptation to a higher workload by increasing in size, strengthening connective tissue, and improving bone density (Dudgeon et al., 2004). Currently, there are no guidelines for older patients with HIV infection as far as how often, how vigorous, or for how long one should exercise. The purpose of this review is to summarize the current evidence, use some recommendations for older uninfected patients with frailty and metabolic syndrome, and adjust for similar situations in HIV-infected patients who are affected by muscle atrophy and metabolic syndrome.

Methods

We conducted three separate searches to identify studies that met our inclusion criteria for the development of evidence-based practice guidelines for older adults with HIV. We will describe each search and the results separately.

Frail Older Adults

We searched the PubMed database for the keywords "frailty and exercise," "physical exercise and frailty," and "exercise and older frail adults," and analyzed the articles that most closely matched our criteria. We chose articles for this review if: (a) subjects were frail adults older than 65 years of age, (b) aerobic and or resistance exercise was used with physical function outcome measures, and (c) a weekly program was followed for at least 6 weeks. We identified four studies (Binder et al., 2002; Brown et al., 2000; Matsuda, Shumway-Cook, & Ciol, 2010; Seynnes et al., 2004) and compared the intervention methods and outcomes for each program. All trials were randomized and controlled with the exception of the study by Matsuda and colleagues (2010), which held a single group cohort study. In addition, we reviewed the ACSM (2003) exercise guidelines for older adults with frailty.

HIV-Infected Young Adults

A search of the key terms, "HIV and exercise," on the PubMed database yielded a total of 664 articles. The same search on CINAHL yielded 271 articles. After screening for studies that specifically addressed the issues of physiological markers in HIV-infected patients, 51 trials were selected for additional scrutiny. We chose articles for this review if: (a) subjects were infected with HIV, (b) subjects were aged 18 years and older, (c) aerobic and or resistance training was conducted, and (d) cardiopulmonary and or strength measurements were included. All ethnicities and both genders were included. After in-depth analysis, 12 studies conducted between 1998 and 2008 were included in this review. All selected studies were randomized controlled trials.

Older Adults With Metabolic Syndrome

A search of the terms "metabolic syndrome and exercise and elderly" on the PubMed database yielded 698 articles. The studies were included if: (a) subjects had metabolic problems, (b) the average age of participants was 55 years or older, and (c) aerobic and/or resistance training was conducted. Seven articles matched our initial criteria and, after further analysis, we included four in this review (Ferrara, Goldberg, Ortmeyer, & Ryan, 2006; Guiraud et al., 2010; Kemmler, Von Stengel, Engelke, & Kalender, 2009; Stewart et al., 2005). All studies were controlled and two were randomized (Kemmler et al., 2009; Stewart et al., 2005).

Results

Response to Exercise in Frail Older Adults

Aerobic and resistance exercise training can reduce physical frailty and induce significant improvements in balance, strength, and range of motion in older individuals (Brown et al., 2000). Because of the physiologic parallels and clinical signs and symptoms between aging and the premature aging phenotype of HIV disease (Desquilbet et al., 2009), we summarized four articles on exercise and frailty in the non-infected elderly (see Table 3) and adapted these exercise recommendations for older HIV patients, which will be discussed later.

Frailty and exercise in older adults. Several investigators identified aerobic and resistance exercises of various intensities that were either under direct supervision or home-based to be safe and effective to improve overall physical health and physical function in frail older adults (Binder et al., 2002; Brown et al., 2000; Matsuda et al., 2010). The level of exercise intensity varied with each study, but the general average for high intensity ranged from 70%–90%, and low intensity ranged from 30%–40% of estimated maximum heart rate, VO_2max, or 1-RM (depending on the type of exercise). High-intensity supervised exercise training can significantly improve physical function in older adults with frailty, compared to low-intensity exercised controls, which may not be enough of a stimulus to improve frailty. Seynnes and colleagues (2004) concluded that low- to moderate- intensity (40% of 1-RM) resistance training of the knee extensor muscle did not achieve the desired level of improvement in functional performance, while high-intensity (80% of 1-RM) free weight–based training was both physiologically and functionally more effective than lower-intensity exercise. Participants experienced no exercise- or testing-related injuries during the aforementioned study.

Despite positive outcomes from some of the studies, not all trials found exercise in the elderly frail population to be effective. A review article identified 20 studies that tested the functional effects of physical exercise in frail older adults, six of which did not find significant improvements ($p > .05$) in the performance measures studied (Chin A Paw, Van Uffelen, Riphagen, & Van Mechelen, 2008). In four of the six studies, patients were supervised for the entire duration of the exercise program (Baum, Jarjoura, Polen, Faur, & Rutecki, 2003; Faber, Bosscher, Chin A Paw, & van Wieringen, 2006; Miller, Crotty, Whitehead, Bannerman, & Daniels, 2006; Sullivan, Roberson, Smith, Price, & Bopp, 2007). In one study, participants were supervised for the first 3 months and unsupervised for the following 3 months (Witham et al., 2005), and the last study was home-based but had a therapist check-in weekly either by phone or by house visits (Latham et al., 2003). The authors concluded that reasons for nonsignificant results were most likely attributable not due to the lack of supervision but rather due to the higher degree of frailty of the participants, acknowledging that five of the six studies included a highly frail population (Chin A Paw et al., 2008). The ACSM (2003) has prescribed a set of exercise recommendations for frail older adults (see Table 4). Although these provide a good general guideline,

Table 3. Exercise Intervention Studies in Older Adults with Frailty

Year & Author	Population	Study Duration	Exercise Intervention (type/frequency/duration)	Outcomes
Brown et al., 2000	N1 (US, home-based) = 48 N2 (S) = 36 Physically frail elderly Mean age = 83 ± 4yrs	3 × wk for 3 mo	N1: Flexibility (NI, UE, and LE) N2: Strength (LI, UE, LE, and weight bearing)	Supervised exercise group showed a significant improvement in physical performance capacity at end of trial compared to home group ($p < .05$).
Binder et al., 2002	N1 (US, home-based) = 50 N2 (S) = 69 Community-dwelling older adults Mean age = 83 ± 4yrs	3 × wk for 9 mo	N1: Flexibility (NI, UE, and LE) N2: Flexibility (LI, UE, LE) Resistance (UE, LE) →Initially, 1–2 sets of 6–8 reps of each exercise at 65% of 1-RM. Increase to 3 sets of 8–12 reps at 85%–100% of initial 1-RM. Aerobic (treadmill, stationary bicycle, rowing machine) →Initially, 65%–70% of VO_2peak for 15 min; Gradually increase to 20–30 min with 3- to 5-min intervals of 85%–90% of VO_2peak	Training programs showed improvements in exercise group compared to control group ($p < .05$). Strength: Significant improvements in knee extensor ($p = .004$) and knee flexor ($p = .02$) torque. Endurance: Significant increase in VO_2peak (14% for men, 13% for women) in exercise group compared to unsupervised home-based training ($p = .0001$).
Seynnes et al., 2004	N1 (S, control) = 8 N2 (S) = 6 N3 (S) = 8 Frail older adults in a nursing home Mean age = 81.5 ± 1.4yrs	3 × wk for 10 wks	N1: Resistance (NI, knee extensor) N2: Resistance (LI, knee extensor) →3 sets of 8 reps; 6–8 seconds for each rep and 1–2 min of rest in between at 40% of 1-RM N3: Resistance (HI, knee extensor) →3 sets of 8 reps with 6–8 sec for each rep and 1–2 min of rest in between at 80% of 1-RM	Muscle strength improved significantly over time ($p < .0001$). Significantly higher improvement in HI group compared to LI group ($p < .001$).
Matsuda et al., 2010	N (S, home-based) = 72 (no control group) Frail older adults Mean age = 71 ± 9yrs	2 × week strength, 3 × week endurance for 6 wks	Resistance (15 to 20 min) Balance and gait (15 to 20 min) Aerobic (up to 30 min) Flexibility	After 6 weeks patients showed increase in UE and LE strength from baseline measures ($p < .001$).

NOTE: N = population; N1 = control group; N2, N3 = intervention groups; S = supervised; US = unsupervised; 1-RM = repetition maximum; UE = upper extremity; LE = lower extremity; HI = high intensity; LI = low intensity; NI = no intensity.

it is critical to take the individual's condition into consideration and adapt the exercise program to suit his or her capabilities.

Response to Exercise in Young Adults With HIV

Of the studies reviewed on the effect of exercise in younger HIV-infected adults, all 12 were randomized controlled trials that tested the effects of aerobic or resistance exercise on cardiopulmonary and/or strength changes in HIV-infected adults. Duration, intensity, sequence of exercises, and location of exercise regimens varied from study to study and included treadmill training, brisk walking, jogging, running, stair climbing, stationary cycling, ski machine training, rowing, or cross-country machine training

Table 4. American College of Sports Medicine Recommendations for Older Adults With Frailty

Modes	Intensity/frequency
Aerobic	3–5 days/week
Large muscle activities (walking, cycling, rowing, swimming)	5–60 min/session, as tolerated
Resistance	3 days/week
Free weights, weight machines, isokinetic machines, ball machines	~ 20-min session All muscle groups Start program without weight; add weight slowly
Flexibility	3 days/week
Stretching/yoga (all major muscle groups)	20–60 sec/stretch Maintain stretch below discomfort point

as part of an aerobic workout. Resistance training of the major muscle groups focused on the upper and lower extremity muscle groups, which included bench press, chest press, triceps push, seated back row, shoulder press, biceps curl, triceps extension, leg extension, leg curl, knee flexion and extension, or shoulder flexion and extension. Two of the 12 trials included aerobic as well as resistance exercises (Dolan et al., 2006; Hand et al. 2008); 6 tested aerobic exercise only (Baigis et al., 2002; Mutimura et al., 2008; Perna et al., 1999; Smith et al., 2001; Stringer, Berezovskaya, O'Brien, Beck, & Casaburi, 1998; Terry et al., 2006). Agin et al. (2001), Bhasin et al. (2000), Grinspoon et al. (2000), and Strawford et al. (1999) measured resistance exercise training alone.

Cardiopulmonary measures: Effect on VO_2max. Nine of the 12 studies included cardiopulmonary measures, all of which compared aerobic exercise intervention groups to non-exercise control groups (Baigis et al., 2002; Dolan et al., 2006; Hand et al., 2008; Mutimura et al., 2008; Perna et al., 1999; Smith et al., 2001; Stringer et al., 1998; Terry et al., 2006). Overall, these studies documented significant improvements in VO_2max in HIV-infected patients with sufficient aerobic exercise compared to sedentary controls.

Hand and colleagues (2008) found a 21% increase in VO_2max (31.6 to 39.9 ml/kg/min; $p < .01$) in the exercise compared to the control group and documented that female exercisers improved from baseline by 24%, while male exercisers improved by 20%. No significant changes occurred in the non-exercise control group ($p > .05$). Another study found that after the 6-month trial, the exercise group experienced a change of 4.7 ± 3.9 ml/kg/min in VO_2max (24.3 to 29 ml/kg/min; $p < .0001$) compared to 0.5 ± 0.3 ml/kg/min for the control group (23.9 to 24.4 ml/kg/min; $p > .05$; Mutimura et al., 2008). Dolan and colleagues (2006) showed a 1.5 ± 0.8 ml/kg/min improvement in their exercise group (16.9 to 18.4 ml/kg/min; $p < .001$) after 16 weeks, compared to a 2.5 ± 1.6 ml/kg/min drop in the control group (15.3 to 12.8 ml/kg/min; $p > .05$). Terry and colleagues (2006) demonstrated that HIV-infected individuals with hyperlipidemia improved in functional capacity after 3 months of aerobic exercise. VO_2max in the exercise and diet group showed an 8 ml/kg/min increase (32 to 40ml/kg/min; $p < .001$) compared to an insignificant increase (34 to 35 ml/kg/min; $p > .05$) in the diet-only group. According to Stringer and colleagues (1998), exercise training resulted in a significant increase of 13% in VO_2max in the heavy exercise group (1.9L/min to 2.1 L/min; $p < .01$) compared to a decrease in the control and moderate-intensity exercise groups ($p > .05$; see Table 5).

Although most studies showed significant increases in VO_2max, Baigis and colleagues (2002) and Smith and colleagues (2001) found no noteworthy improvement. Results from Baigis and colleagues (2002) suggested no major differences between VO_2max values for the exercise group (30.2 to 30.5 ml/kg/min; $p > .05$) and the control group (32 to 30.8 ml/kg/min; $p > .05$). The authors described several possible reasons for the lack of exercise improvement, which included: (a) a minimal exercise prescription of 20 minutes, 3 times per week, with increase of only intensity (there was a lack of progressive exercise incorporating intensity, frequency, and duration); (b) missed sessions that reduced frequency of exercise to an average of 2 times per week; (c) length of intervention (15 weeks) may have been too short; and (d) participants were generally fit at baseline (individuals with low level of initial fitness demonstrated most significant increase in VO_2max). Smith and colleagues (2001) found a 2.6 ml/kg/min change in VO_2max in the intervention group (34.9 to 37.5 ml/kg/min)

Table 5. HIV Exercise Intervention Studies & VO_2max Outcomes

Year & author	Population	Study duration	Exercise intervention & dose	Outcomes	VO_2max measures
Hand et al., 2008	N1 = 44 N2 (S) = 30 Mean Age = 42.4 ± 1.4 (N1) 41.2 ± 2.3 (N2)	2 × week for 6 weeks	Aerobic: 40 min (treadmill) at 50%–70% max HR Resistance: 20 min UE and LE exercise	Exercise group showed 21% increase VO_2peak compared to baseline values ($p < .01$); no difference in control group	Baseline N1: 29.4 ml/kg/min Final N1: 29.4 ml/kg/min Baseline N2: 31.6 ml/kg/min Final N2: 39.9 ml/kg/min
Mutimura et al., 2008	N1 = 50 N2 (S, group) = 50 Mean Age = 37.5 ± 6.9 (N1) 37.8 ± 5.5 (N2)	3 × week for 6 months	Aerobic: Progressive 30 min warm-up/cool-down, at 60%–75% max HR 45–60 min (jogging, running, stair climbing) Resistance: Progressive UE exercises	Exercise group showed a significant improvement in VO_2max compared to control group ($p < .0001$)	Baseline N1: 23.9 ml/kg/min Final N1: 24.4 ml/kg/min Baseline N2: 24.3 ml/kg/min Final N2: 29 ml/kg/min
Dolan et al., 2006	N1 = 20 N2 (S, HB) = 20 Mean Age = 40 ± 2 (N1) 43 ± 2 (N2)	3 × week for 4 months	Aerobic: 20-min run (First 2 weeks) at 60% max HR, 30 min at 75% thereafter Resistance: UE and LE exercises	Exercise group showed a significant improvement in VO_2max after program compared to control group ($p < 0.001$)	Baseline N1: 15.3 ml/kg/min Final N1: 12.8 ml/kg/min Baseline N2: 16.9 ml/kg/min Final N2: 18.4 ml/kg/min
Terry et al., 2006	N1 = 15 N2 (S, group) = 15 Mean Age = 39 ± 7 (N1) 36 ± 5 (N2)	3 × week for 3 months	Aerobic: 30 min warm-up/cool-down, 30 min exercise at 70%–85% max HR	Significant improvement in VO_2peak in exercise group compared to control group ($p < .001$)	Baseline N1: 34 ml/kg/min Final N1: 35 ml/kg/min Baseline N2: 32 ml/kg/min Final N2: 40 ml/kg/min
Baigis et al., 2002	N1 = 47 N2 (S, HB) = 52 Mean Age = 37	3 × week for max 15 weeks	Aerobic: 25 min (ski machine) at 75%–85% max HR	Exercise group did not show a significant improvement in VO_2max compared to control group ($p = .90$)	Baseline N1: 32.0 ml/kg/min Final N1: 30.8 ml/kg/min Baseline N2: 30.2 ml/kg/min Final N2: 30.5 ml/kg/min
Smith et al., 2001	N1 = 30 N2 (S) = 30 Mean Age = 35. 4 ± 7 (N1) 36.6 ± 6.2 (N2)	3 × week for 6 months	Aerobic: 20 min (walking/jogging), 30 min (stationary cycle, stair stepper, or cross-country machine) at 60%–80% max HR	Exercise group did not show a significant improvement in VO_2max compared to control group ($p = .09$)	Baseline N1: 31.0 ml/kg/min Final N1: 32.0 ml/kg/min Baseline N2: 34.9 ml/kg/min Final N2: 37.5 ml/kg/min
Perna et al., 1999	N1 = 10 N2 (S) = 18 Mean Age = 36.75 ± 6.27	3 × wk for 12 wks	Aerobic: 45-min intervals as 70%–80% max HR	Exercise group showed significant change in VO_2max ($p < .01$); control group did not ($p > .05$)	Baseline N1: 28.3 ml/kg/min Final N1: 26.5 ml/kg/min Baseline N2: 28.7 ml/kg/min Final N2: 32.2 ml/kg/min
Stringer et al., 1998	N1 = 8 N2 (S, moderate intensity) = 9 N3 (S, heavy intensity) = 9 Mean Age =36 ± 9	3 × week for 6 weeks	N2—Aerobic: 60 min at 80% of the LAT N3—Aerboic: 30–40 min at work rate equal to 50% of difference between LAT and VO_2max.	Vo_2max changed significantly only in heavy exercise group ($p < .01$)	Baseline N1: 2.0 L/min Final N1: 1.8 L/min Baseline N2: 2.2 L/min Final N2: 2.1 L/min Baseline N3: 1.9 L/min Final N3: 2.1 L/min

NOTE: Max HR = maximum heart rate; N1 = control group (no exercise); N2 = intervention group; HR = heart rate; N/A = not applicable; bpm = beats per min; UE = upper extremity; LE = lower extremity; S = supervised; HB = home-based; LAT = lactic acidosis threshold; ml/kg/min = milliliters/kilograms/min; L/min = liters/min.

compared to a 1 ml/kg/min increase in the control group (31 to 32 ml/kg/min; Smith et al. 2001). The study found that the change did not reach statistical significance (p = .09). The exercise intervention in this trial was similar to most other aerobic exercise studies we have reviewed. The authors noted that there was a disproportionate loss of subjects from the exercise group, which may have biased the outcomes toward the null hypothesis (Smith et al., 2001).

Effect of resistance exercise on strength. Five of the 12 studies measured the effects of resistance training on skeletal muscle strength (see Tables 6 and 7; Agin et al., 2001; Bhasin et al., 2000; Dolan et al., 2006; Grinspoon et al., 2000; Strawford et al., 1999). Most studies evaluated the effect of testosterone, protein, or androgens in their sample groups in addition to exercise (Agin et al., 2001; Bhasin et al., 2000; Grinspoon et al., 2000; Strawford et al., 1999). Our analysis was solely focused on the exercise intervention group. All five studies reached the conclusion that resistance exercise held an important role in the improvement of muscle strength and function in HIV-infected patients. In one study, the maximum dynamic muscle strength (measured by 1-RM in seven major muscle groups) for the progressive resistance exercise group increased by a range of 40.6%–95.3% (p < .001) compared to the non-exercise control group, for

Table 6. HIV Resistance Exercise Intervention Studies and Change in Muscle Strength Outcomes

Year & Author	Population	Study Duration	Resistance Exercise Intervention & Dose	Outcomes
Dolan et al., 2006	N1 = 20 N2 (S, HB) = 20 Mean age = 40 ± 2 (N1) 43 ± 2 (N2)	3 × week for 4 months	Progressive Resistance Exercise—UE & LE (knee extension, bench press, knee flexors, shoulder abduction, standing calf raises, arm curls) 3 sets of 10 reps for 2 weeks, then 4 sets of 8 reps at 60%–80% of 1-RM	Significant improvement in knee extensors, pectoralis, knee flexors, shoulder abductors, ankle plantar flexors, elbow flexors (p < .001)
Agin et al., 2001	N1 = 12 N2 (S) = 12 (Prospective study) Mean age = 38.2 ± 8.6 (N1) 41.0 ± 10.2 (N2)	20 weeks (6 week control, then Exercise 3 × week for 14 weeks)	Progressive Resistance Exercise—UE & LE (bench press, seated back row, shoulder press, biceps curl, triceps extension, leg extension, leg curl) 3 sets of 10 exercises at 8–10 reps per set with progressive increase from 50%–75% of 1-RM	Maximum dynamic muscle strength significantly increased for all seven muscle groups (p < .001)
Bhasin et al., 2000	N1 = 14 N2 (S) = 15 Mean age = 41.8 ± 2.5 (N1) 44.4 ± 3.0 (N2)	3 × week for 4 months	Progressive Resistance Exercise—UE & LE (leg press, leg curls, bench press, latissimus pulls, overhead press) 3 sets of 12–15 reps at 60% 1-RM and progressively increase to 4 sets of 4–6 reps at 70% to 90% of 1-RM	Exercise group increased muscle strength in 5 groups by 29%–36%, and thigh muscle volume significantly increased in exercise group (p = .003) compared to control group (p = .696)
Grinspoon et al., 2000	N1 = 13 N2 (S) = 14	3 × week for 3 months	Progressive Resistance Exercise—UE & LE (leg extension, leg curl, leg press, latissimus dorsi, arm curl, triceps extension) 2 sets of 8 reps at 60% 1RM and progressively increase to 3 sets of 8 reps at 80% 1-RM	Exercise had significant effect on lean body mass (p = .05) and muscle area (p < .05)

NOTE: N1= control group (no exercise); N2 = intervention group; S = supervised; UE = upper extremity; LE = lower extremity; 1-RM = one repetition maximum; HB = home-based.

which the range was 6.6%–16.9% (p = .01–.12; Agin et al., 2001). Subjects performed three sets of 10 exercises at 8–10 repetitions per set at 50% of 1-RM for the first week, and 75% of 1-RM for the remaining 13 weeks. Bhasin and colleagues (2000) found more moderate increases in muscle strength, which increased by 29%–36% in all five forms of exercise (leg press, bench press, leg curls, latissimus pulls, overhead press), compared to a –0.3% to –0.4% change in the no-exercise group.

Response to Exercise in Elderly With Metabolic Syndrome

Aerobic and resistance exercise have been shown to lower insulin resistance and decrease metabolic risk factors that cause metabolic syndrome (National Cholesterol Education Program, 2002). All of the metabolic studies included in this review found both forms of physical exercise to be beneficial to improve metabolic outcomes in the elderly (see Table 7). Kemmler

Table 7. Exercise Intervention Studies and Metabolic System

Year & Author	Population	Study Duration	Intervention	Outcome
Guiraud et al., 2010	N1 (No EX) = 8 N2 (CHD, S, AEX) = 15 N3 (No CHD, S, AEX) = 31 Men and women with Metabolic Syndrome Mean age = 57 ± 9	2 × week for ≥6 months	N1: No exercise N2: Aerobic: 40 min walking, stationary cycling, rowing at 65%–90% max HR → 1-2 additional non-supervised aerobic exercise sessions on a weekly basis	Body weight, BMI, resting diastolic blood pressure, total cholesterol, LDL-cholesterol, triglycerides decreased, and HDL-cholesterol increased in Exercise groups 1 and 2. Metabolic parameters unchanged in control group 3. MS reduced by 22% in group 1 and 25% in group 2.
Kemmler et al., 2009	N1 (US) = 33 N2 (2days/S, group; 2/days HB, US) = 32 Women with metabolic syndrome Mean age = 69.5 ± 4.3 (N1) 68.7 ± 3.4 (N2)	4 × week for 12 months	N1: Relaxation exercise (LI) N2: Aerobic: 20 min of aerobic dance exercise at 70%–85% max HR Coordination: (3–5 static and dynamic balance exercises using Thera-Band elastic belts) Resistance: Isometric strength training (1–2 sets of 10–15 isometric floor exercises)	Significant effects: total body fat (p = .0001), hip circumference (p = .0001), total cholesterol (p = .008), and HDL cholesterol (p = .036) in exercise group. The number of criteria for MS significantly decreased in exercise group.
Ferrara et al., 2006	N1 (S, group, AEX) = 19 N2 (S, group, RT) = 20 Older, overweight, and obese men Mean age = 63 ± 1	3 × week for 6 months	N1: Aerobic: 45–60 min (treadmill, running) per day at 75%–80% max HR, gradual increase. N2: Resistance: UE and LE exercise at 80% of 1-RM with 8–12 reps	VO_2max increased by 16% in the AEX group ($p < .01$) and 7% in the RT group ($p < .05$) A significant increase was seen in muscle strength after RT ($p < .05$)
Stewart et al., 2005	N1 (No EX) = 58 N2 (S, AEX/RT) = 57 Men and women with high blood pressure Mean age = 64.1 (N1) 63.3 (N2)	3 × week for 6 months	N1: No exercise N2: Aerobic: 45 min (treadmill, stationary cycle, stair stepper) at 60%–90% max HR Resistance: UE and LE exercise at 50% of 1-RM with 2 sets of 10–15 reps per exercise.	Exercise group increased peak oxygen uptake by 16% compared to control group ($p < .001$). Strength increased by 17% in exercise group. Body fat reduced by 3.5% in exercise compared to no change in control. HDL increased by a mean of 3.0 mg/dl ($p < .01$)

NOTE: Max HR = maximum heart rate; N = groups; EX = exercise; MS = metabolic syndrome; HR = heart rate; 1=RM = one repetition maximum; AEX = aerobic exercise; RT = resistance training; LI = low-intensity; CHD = coronary heart disease; LDL = low-density lipoprotein; HDL = high-density lipoprotein; HB = home-based; US = unsupervised; S = supervised.

and colleagues (2009) found that a low-volume, high-intensity program significantly lowered the severity of metabolic syndrome in elderly females with the condition. In another study, 17.7% of patients in the exercise group no longer had metabolic syndrome after 6 months, while 7.6% of participants in the non-exercise control group newly developed metabolic syndrome (Stewart et al., 2005). Similarly, as shown in Table 7, Guiraud et al., (2010) reported a 22% reduction of metabolic syndrome in the exercise group after engaging in 40 minutes of supervised aerobic training 2 times per week. Ferrara et al., (2006) conducted a study with both aerobic and resistance exercises and documented improvements in glucose metabolism and insulin sensitivity (with aerobic exercise) in older men, which could potentially reduce the risk of metabolic syndrome and type 2 diabetes.

Discussion

In order to arrive at an evidence-based exercise program to recommend for older adults living with HIV, we have summarized findings from exercise studies in young people living with HIV and in older adults living with metabolic syndrome or frailty. We have reasonable evidence for making aerobic and resistance exercise recommendations for older adults with HIV. From the review of these studies, we arrived at the following factors, which we think are critical in our recommendations to patients.

Aerobic Exercise Recommendations

We found that moderate- to high-intensity exercise leads to the most beneficial outcomes. The most common types of exercise included walking, using a treadmill, riding a stationary bicycle, swimming, cycling, stair climbing, and rowing. Based on the evidence, we recommend aerobic training at least 3 days per week for 20–40 minutes. The program should last for at least 6 weeks, as this duration has shown to result in positive outcomes (Stringer et al., 1998). In order to prevent injury and warm up major muscle groups, we recommend 5–10 minutes of stretching before and after each aerobic session. The maximal heart rate that should be achieved should be based on the age and weight of the individual and can vary from 50%–90% of the estimated maximum heart rate, with the most commonly recommended level of intensity being between 70% and 80%. We advise patients to begin at a lower intensity, incrementally increasing the level of difficulty each week according to their individual capabilities, but to aim at least for a 5% increase in intensity.

Resistance Exercise Recommendations

Following aerobic exercise, we recommend resistance training on the same day at an average of 3 days per week for at least 6 weeks. Although different muscle groups can be the focus of the training, the majority of existing programs focus on shoulder, leg, and chest muscle groups. Common exercises included knee extension, knee flexion, grip strength, shoulder flexion, chest press, seated bench press, seated row, leg press, leg curl, biceps curl, and triceps pull and extension. We recommend that the patient begin with 1–2 sets of 6–8 repetitions of each muscle group at 60% of 1-RM and gradually increase to 3 sets of 8–10 repetitions at 80%–90% of 1-RM, with a 20- to 30-second rest period in between each set. 1-RM can be difficult to gage during home-based, unsupervised exercise. We therefore suggest a scale of 1 to 10, where 1 pound can equal 10% of 1-RM and 10 pounds equals 100% of 1-RM. This can be scaled accordingly depending on the strength and ability of each patient. For example, a patient may begin with a 2-pound weight, which could equate to 10% of 1-RM, and increase progressively to a 20-pound weight, which would equal 100% of 1-RM.

Although high-intensity exercise has been shown to be beneficial for patients with HIV, it is important to take into account that intense exercise for a prolonged period of time can have a negative impact on the immune system. According to the ACSM (2003), exercise for more than 90 minutes in healthy adults can cause elevated levels of plasma concentrations of pro- and anti-inflammatory cytokines (such as interleukin-6 and interleukin-1), as well as decreases in natural killer cell function, which target HIV-infected cells in the body. The American Heart Association (2011) also provides valuable exercise suggestions for older Americans. These include staying well hydrated, wearing comfortable clothing, and choosing a safe and well-paved surface on which to exercise. Additional tips and cardiovascular disease–friendly exercises are available on the American Heart

Association Website. Too much exercise may also increase a person's susceptibility to viral and bacterial infections due to a suppressed immune system (Durstine et al., 2003). It is, therefore, important to implement an exercise program that avoids prolonged strenuous physical activity for more than 90 minutes, especially for immune-compromised individuals. Exercise for 90 minutes is a relatively high cut-off level, and this should be taken into consideration when devising a program for patients with HIV infection.

Conclusion

These evidence-based exercise recommendations for older HIV patients are the first of their kind in the absence of sufficient evidence from randomized controlled trials in this population. We have borrowed heavily from the results of studies in older adults living with frailty or metabolic syndrome and younger adults living with HIV. Combined moderate to vigorous aerobic and resistance exercise for 20–40 minutes, 3 times per week, is safe and effective in older adults and has many benefits to decrease symptom burden, decrease disease progression, and increase quality of life. Future studies are warranted in order to determine if these recommendations need to be further modified.

Clinical Considerations

- Aerobic and resistance exercise training is safe and effective and significantly improves aerobic and resistance capacity in older adults.
- Aerobic and resistance exercises should be performed at a moderate or vigorous level for at least 3 days a week.
- Prior to initiating a new exercise program, the health care provider should establish baseline pulmonary and cardiovascular health measures.
- A gradual approach to increase physical activity in HIV-infected older adults minimizes the risk of injury and increases confidence in a participant's abilities.
- Selecting a training partner or a group of training partners increases motivation and psychological well-being.

Disclosures

The authors report no real or perceived vested interests that relate to this article (including relationships with pharmaceutical companies, biomedical device manufacturers, grantors, or other entities whose products or services are related to topics covered in this manuscript) that could be construed as a conflict of interest.

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