Effects of progressive training in HIV/AIDS infected adults with muscle wasting

Professional assignment project

by

Lene Harstad and Elizabeth Mutubuki

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Foreword

Education is a progressive discovery of our ignorance (Will Durrant 1185-1981). Autumn 2007 saw the dawn of a new era. An era of discovery, knowledge and skill that gave rise to the systematic review you are about to read. This systematic review was written out of a desire to learn about HIV/AIDS and the role of exercise. Our prolonged gratitude goes to the following individuals and organisations who made our systematic review a success: Dr. Cia Kesselaar, Dr.Godfrey Sikipa, Helen Wiggers, HIV Vereningen, AMC hospital, VU hospital, Tafelberg library staff and friends and family whose support cannot go unmentioned.
Introduction

Physiotherapeutic relevance

According to McClure (1993), people who are living with HIV and AIDS present a new challenge to physiotherapists. Today people with AIDS/HIV live longer than they did decades ago due to the availability of highly active antiretroviral therapy (HAART). HAART has done well in terms of quantity of life however the quality of life needs further attention (WHO 2007). Once the virus interferes with a patient’s functions return to normal health is unlikely, hence the increase in prevalence and disability in the HIV infected. Hence the role of physiotherapy is changing and does not lie primarily in the treatment of respiratory disorders, neurological, musculoskeletal and pain syndromes as well as general decline in fitness and functions (Amosun 1995). The role of physiotherapy continues to change in an attempt to meet the current needs of the HIV clients but currently emphasizes on rehabilitation, prevention of secondary problems such as decreased fitness, respiratory disorders, muscle wasting, peripheral neuropathies and pain management (Irwin 1997).

Exercise which is administered by physiotherapists has been known to increase CD4 cell count, improve immunity, lead to better physical and emotional status in HIV and AIDS patients. Due to the complexities of the HIV-virus, patient supervision during exercise, by a qualified physiotherapist is often needed to ensure safety. In addition, clinical depression is the most frequently observed psychiatric disorder in patients with HIV. Therefore motivation and education on exercise by physiotherapists can yield positive results (Rabkin 1995).

HIV/AIDS is a global pandemic and physiotherapists have a role in the multidisciplinary care team for the infected persons. Billions of dollars are spent every year in treatment and research of HIV/AIDS and billions more will be spent as numbers of infected people continue to rise. Therefore knowledge of HIV/AIDS and the effect of exercise interventions enables improvement in quality of life, reduce pharmacological costs as well as understanding and management of HIV persons by healthcare workers (amongst others physiotherapists).

Personal relevance

HIV/AIDS is a global pandemic and has received a lot of attention from the media. There is no cure available for HIV/AIDS at present and focus is now placed on how to lead normal lives despite being HIV positive. As a result we feel highly motivated to become part of the team fighting against aids and improving quality of life for the infected persons. The interest is also born from the idea that anybody could contract HIV. In addition working on this thesis further improved knowledge of HIV/AIDS. For example the authors are now aware of the morning after pill administered following to exposure to the virus. The authors might not get the possibility to see or treat patients with HIV in the future, but would like to use the professional assignment project to gain more insight into the HIV infection.
GENERAL INTRODUCTION INTO HIV/AIDS

HIV infection

Human immunodeficiency virus (HIV) is a retrovirus that can lead to acquired immune deficiency (AIDS) (Sowadski 1999). AIDS is a dynamic and progressive disease that will continue to pose serious health problems well into this century (Durstine 2003). HIV selectively infects the immune system's CD4 cell, which is also called the T-helper cell. When activated, the CD4 cell divides, conquers and produces specific reactions in response to infectious agents. The CD4 cell along with the T-cytotoxic suppressor and B-cells are part of the body's second line of defence. They protect against pathogens that have slipped through the body's first line of defence, (Durstine 2003) which comprises of macrophages, neutrophils and natural killer cells. When the number of CD4 cells decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections. If untreated, eventually most HIV-infected individuals develop AIDS and die (Sowadski 1999).

The progressive clinical nature of HIV infection can be viewed in three stages. In the first stage the individual remains relatively healthy and free of symptoms. This stage may last for 10 or more years depending on the health habits maintained by the individual. During the middle stage the number of CD4 cells is moderately diminished, resulting in development of a variety of intermittent or persistent signs and symptoms that include fatigue, diarrhea, weight loss, fever and lymphadenopathy. The most advanced and severe stage of the HIV infection is AIDS. There is severe depletion of CD4 cells and presence of opportunistic infections and malignancy.

HIV - transmission

HIV is transmitted through unprotected sexual intercourse (anal or vaginal), transfusion of contaminated blood, sharing of contaminated needles, and between a mother and her infant during pregnancy, childbirth and breastfeeding (WHO 2007).

Physiological changes

HIV infected persons face many metabolic conditions that researchers have addressed with different therapies such as exercise, pharmacological and non pharmacological.

Wasting syndrome

A patient can be diagnosed with wasting if they have ,10% unintentional weight loss over 12 months; or 7.5% unintentional weight loss over 6 months; or 5% body cell mass (BCM) loss within 6 months; or  Body mass index (BMI) < 20 kg/m²; or in men: BCM < 35% body weight and BMI < 27 kg/m²; or in women: BCM < 23% body weight and BMI < 27 kg/m² according to the Treatment Guidelines for HIV-Associated Wasting, Consensus Development Panel Meeting, New York. NY (2000). In HIV wasting there is a progressive decrease in body weight consisting of decreases in both lean body mass and fat mass as well as a decrease in cross-sectional muscle area and waist circumference. The decline in physical functioning that many AIDS patients experience is directly related to weight loss and a reduction in muscle mass. Studies have shown that HIV-associated muscle wasting, when left untreated, is directly correlated with mortality.

The etiology of HIV wasting is multifactorial however it can be classified into two groups which are inadequate calorie intake or high metabolism. Key contributors that may lead to HIV-associated wasting, include diarrhea, loss of appetite, difficulty swallowing, infections, chronic fever, recreational drug use and depression. Immune response to chronic fever and infection results in an elevation of circulating cytokines such as interleukin-1 (IL-
1) and TNF-a. Elevated levels of IL-1 and TNF-a can increase the resting energy expenditure. Increased circulating cytokines further influence metabolic rates by activating the hypothalamic pituitary-adrenal axis, which leads to an increase in glucocorticoid levels. Increased glucocorticoid levels have a catabolic influence on skeletal muscle by slowing down protein synthesis and increasing protein degradation. The increased rate of protein turnover and the elevated metabolic rate can increase the resting metabolic rates and lead to accelerated depletion of energy stores. During periods of infection, when cytokine and glucocorticoid levels rise significantly, resting energy levels are further elevated and food intake drops, causing accelerated and episodic weight loss (Dudgeon 2004).

Patients lose weight and feel tired, and can be prone to more infections or other medical complications associated with HIV infection.

In addition, individuals suffering from HIV associated wasting may find tasks such as exercising, working or performing household chores difficult. The body consumes vital muscle and organ tissue (lean body mass) for energy instead of primarily relying upon the body’s stored fat. Despite the introduction of highly active anti-retroviral therapy (HAART), which extends the lives of people infected with the virus, HIV-associated wasting remains one of the principal causes of ill health in people with HIV/AIDS. Estimates of the prevalence of HIV-associated wasting range from 4 to 30% of HIV-infected individual. Today, there are three approaches to the treatment of HIV-associated wasting. These include identifying and treating the underlying cause of wasting, non-drug interventions such as improvements in diet and exercise, and use of drugs to increase appetite, build lean body mass and improve metabolism.

**Lipodystrophy syndrome**

Is a side effect of HAART which is characterized by fat accumulation in the abdomen and trunk with fat loss in the legs arm and face. HAART can increase the rate of lipid breakdown while decreasing the rate of lipid synthesis, especially in the periphery. In addition, elevation of circulating cytokine levels that accompany HIV-infection can decrease lipoprotein lipase levels resulting in a decrease in fat deposition (Dudgeon 2004).

**Anemia**

There is a 28% prevalence of anemia in HIV-infected individuals. The increase in circulating cytokines common with HIV-infection can inhibit the production of erythropoietin (EPO), which may partly explain the low EPO levels reported in HIV-infected individuals. In addition, certain medications used in the treatment of HIV-infection have been linked to development of anemia (Dudgeon 2004).

**Body cell mass**

Body cell mass (BCM) or lean body mass constitute all the metabolically active tissue of the body. It includes muscle tissue, organ tissue, intracellular and extracellular water and bone tissue. In the normal nourished individual, muscle tissue accounts for approximately 60% of the BCM, organ tissue accounts for 20% of BCM, with the remaining 20% made up of red cells and tissue cells. The BCM contains 98-99% of the body’s potassium (Agin 2001). Bioelectrical impedance analysis (BIA) is used to assess BCM depletion. BIA is portable, radiation free, inexpensive, painless, and has a high degree of accuracy (WHO 2007).

**Treatment**

Antiretroviral therapy (ART) is used to treat HIV infection by inhibiting replication of the virus. Combination of several (typically three or four) antiretroviral drugs is known as highly active anti-retroviral therapy (HAART). Treatment with HAART allows HIV-infected individuals to live a longer, healthier and more productive life than was possible at the beginning of the HIV/AIDS pandemic. However, these life-extending antiretroviral
medications often cause side effects that may adversely affect quality of life (Dudgeon 2004). Typical side effects of HAART in HIV-infected people are: anemia, bone problems, heart disease, gastrointestinal problems (anorexia and diarrhea), wasting/lipoatrophy, kidney problems, lactic acidosis and much more (WHO). Due to the side effects, medically researchers are continually seeking more effective methods to treat infected individuals (Dudgeon 2004).

HIV and exercise

For individuals who are asymptomatic, HIV infection in most cases does not alter the exercise-related physiological responses to a single session of exercise. At a more advanced stage of immunodeficiency, a decrease in exercise performance and training response has been observed. In the two last stages it has been observed a reduced exercise capacity, reduced oxygen consumption, reduced heart rate and breathing reserve (Durstine 2002).

Durstine (2002) states that exercise is safe and beneficial for most individuals infected with HIV. In HIV-positive individuals, aerobic exercise combined with strength training may result in improvements in lean body mass, oxidation and endurance capacity, cognitive and physical energy needed for daily living, psychological and coping skills, mood and physical function for a prolonged period of time. For most HIV-positive individuals, this will result in an improvement in quality of life, which may be the most important benefit of regular physical exercise for HIV-infected individuals (Durstine 2002).

Recent findings reveal that regular exercise, or sometimes just a modest increase in physical activity, can mitigate muscle protein wasting. Aerobic exercise training primarily alters mitochondrial and cytosolic proteins (enzyme activities), while progressive resistance exercise training predominantly increases contractile protein mass. Previous studies indicate that resistance exercise acutely increases the muscle protein synthetic rate more than muscle proteolysis such that the muscle amino acid balance is increased for up to 2 days after exercise. Progressive resistance exercise training increases muscle protein synthesis and muscle mass, but attenuates the increment in proteolysis that results from a single bout of resistance exercise. The cellular mechanisms that produce these adaptations are not entirely clear.
THE EFFECTS OF PROGRESSIVE RESISTANCE TRAINING IN HIV/AIDS INFECTED ADULTS WITH MUSCLE WASTING

A systematic review

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Abstract

**Background:**
Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) wasting is a condition associated with HIV infection and is defined as an involuntary loss of more than 10% baseline of body weight in combination with diarrhea, weakness or fever (O'Brien 2007). Treatment with highly active antiretroviral therapy (HAART) has increased the life span in HIV infected individuals. However both before and after the introduction of HAART, muscle wasting remains a complication of HIV and is associated with negative outcomes which include reduction in physical function (ACSM 2003). Thus strategies to develop weight and especially the metabolically active body cell mass (BCM), which is comprised primarily of muscle and viscera, remains an important goal for the management of persons infected with HIV (Sattler 1999). Moderate intensity exercise training has been shown not only to be safe but also beneficial for increasing lean muscle mass, decreasing fat mass and improving muscular strength (Dudgeon W. et.al 2006). Progressive resistance training (PRT) is a non pharmacological intervention which has been know to increase lean body mass, muscle mass and strength (Roubenhoff 1999). A better insight in the effects of PRT on muscle wasting in HIV infected individuals will enable improvement in quality of life in the HIV population, reduce pharmacological costs as well as understanding and management of PRT in HIV persons by healthcare workers.

**Objectives:** To review the effect and safety of PRT on body weight, body composition, strength and CD4 count in adults living with HIV-infection

**Hypothesis:**
PRT will increase strength and improve quality of life in HIV-infected adults.

**Methods:**

**Search strategy**
To identify studies to be included in this review a search was conducted in the following databases: MEDLINE, COCHRANE, EMBASE, SCIENCE DIRECT and GOOGLE SCHOLAR. The keywords used in the search were: HIV/AIDS, exercise, Progressive resistance training, Muscle wasting, strength, AIDS wasting and lean body mass.

**Selection criteria**
The included studies were randomized clinical trials comparing progressive resistance exercise alone or in combination with aerobic exercise to a control group or another treatment modality, performed at least three times a week and lasting for at least twelve weeks among adults (18 years or older) living with HIV/AIDS.

**Main results:**
Five articles met the inclusion criteria. The meta-analyses in this study were limited due to a variety of characteristics included in the studies which were: type of exercise intervention, exercise intensity, exercise progression, length of study, outcomes assessed, measurement tool regarding outcomes, gender and differences in baseline regarding AIDS wasting.

Main results indicated that performing PRT alone or in combination with aerobic exercise at least three times a week lasting for twelve weeks appears to be safe and may lead to significant increases in body weight, body composition and strength. These outcomes further increased when PRT was combined with pharmacological therapy.

Authors conclusions:
This systematic review suggests that progressive resistance exercise is beneficial for HIV adults with wasting conditions who can and will comply with a proper progressive resistive exercise program. Meta-analysis suggests that performing progressive resistance exercise three times a week for at least twelve weeks may lead to statistically significant improvements in body weight for adults living with HIV/AIDS. Evidence concerning effectiveness and safety of progressive resistive exercise for adults living with HIV is limited due to the small number of studies included and sample size. Further studies should aim to assess the effect of progressive resistance exercise on different stages of the HIV-infection.

Keywords: HIV/AIDS, exercise, progressive resistance training, muscle wasting, strength, AIDS wasting, lean body mass

Introduction

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) wasting is a condition associated with HIV infection and is defined as an involuntary loss of more than 10% baseline of body weight in combination with diarrhea, weakness or fever (O’Brien 2007). The wasting in HIV/AIDS is characterized by reductions in lean body mass or fat-free mass. Skeletal muscle represents between 50 and 54% of lean body mass and thus wasting results in muscle tissue breakdown. Hence decreased muscular strength, functional performance and disease progression is associated with wasting (Dudgeon 2006). Treatment with highly active antiretroviral therapy (HAART) has increased the life span in HIV infected individuals (WHO 2007). However both before and after the introduction of HAART, muscle wasting remains a complication of HIV and is associated with negative outcomes which include reduction in physical function (ACSM 2003). Thus strategies to develop weight and especially the metabolically active body cell mass (BCM), which is comprised primarily of muscle and viscera, remains an important goal for the management of persons infected with HIV. Muscle appears to be an important reservoir of substrates for the BCM. In patients with advanced HIV, muscle breakdown probably occurs to provide energy substrates for other metabolically active cells, such as intestinal and white blood cells (Sattler 1999). Depletion of energy stores occurs as a result of an increased rate of protein turn over and elevated metabolic rate caused by the combined cytokine and glucocorticoid response (Dudgeon 2006). Muscle mass is related to strength and physical activities of daily living. As muscle mass and strength decline, activities such as ambulating, stair climbing, rising from a chair, and remaining independent become progressively more difficult (Sattler 1999).

Interventions such as growth hormone, androgen therapy, anabolic steroids, testosterone, combined recombinant human growth hormone (rhGH) and insulin-like growth factor-1 have been shown to increase lean body mass and hence improve physical function and quality of life (Agin 2001). However the widespread use of these pharmacological interventions has been limited by the fact that these interventions require physician supervision, are costly and have unpleasant side effects (Agin 2001).

Moderate intensity exercise training has been shown not only to be safe but also beneficial for increasing lean muscle mass, decreasing fat mass and improving muscular strength (Dudgeon 2006).
Progressive resistance training (PRT), or the overloading of skeletal muscle, serves to increase muscular strength and muscular endurance. These functional improvements are possible because skeletal muscle adapts to load by increasing in size, strengthening connective tissue, and improving bone density. Thus, muscle is better able to perform when a stress is again introduced, and functional performance is enhanced (Dudgeon 2006). Progressive resistance training includes isotonic strengthening exercise.

PRT is a non pharmacological intervention which has been know to increase lean body mass, muscle mass and strength. Benefits of PRT have been felt in normal ageing, age frailty and arthritis (Roubenoff 1999). PRT has also been associated a cardio protective effect (Grinspoon 2000). Hence the purpose of this paper is to review the effect of PRT on muscle wasting in HIV/AIDS infected adults in an attempt to increase strength and hence improve physical function. A better insight in the effects of PRT on muscle wasting in HIV infected individuals will enable improvement in quality of life in the HIV population, reduce pharmacological costs as well as understanding and management of PRT in HIV persons by healthcare workers. In addition a pilot study will be conducted to assess whether healthcare workers adopt this approach towards muscle wasting in HIV individuals. The hypothesis is that PRT will increase strength and lean body mass in HIV infected persons.

**Methods**

**Research question**

What are the effects of progressive resistance training on HIV/AIDS infected adults with muscle wasting?

**Inclusion criteria**

**Studies:**

In this review randomised controlled trials (RCT) were included. In addition a pilot study was conducted in the form of a health questionnaire. The RCT's compared progressive resistance training alone or in combination with aerobic exercise with another treatment modality. The articles had to be written in English, Norwegian or Zimbabwean.

Participants:

HIV/AIDS infected adults 18 years and above with muscle wasting and at any stage of the infection. Women only, men only and studies including both sexes were included.

**Intervention:**

Progressive resistance training done three times a week for at least twelve weeks.

**Outcome measures:**

- **Weight measurement** - weight measures that were considered for this review included but was not limited to change in weight status (kg).
- **Body composition measurements** - Body composition measures that were considered for this review included but were not limited to: body mass index (kg/m²), lean body mass (kg), girth, skin folds (subcutaneous fat), and cross sectional muscle area (mm²). Note, for the purposes of this review, body composition was defined broadly as any outcome that contributes to the direct or indirect measurement of muscle, fat, bone or other tissues of the body.
- **Strength measurements** - Strength measures that were considered for this review included but were not limited to: strength (amount of weight able to resist in kilograms).

**Search methods for identification of studies**

To identify studies to be included in this review a search was conducted in the following databases: MEDLINE, COCHRANE, EMBASE, SCIENCE DIRECT and GOOGLE SCHOLAR. The keywords used in the search were: HIV/AIDS, exercise, Progressive resistance training, Muscle wasting, strength, AIDS wasting, lean body mass and Clinical trial in different sequences. The studies were restricted to include only articles written in English, Norwegian or Zimbabwean. Search strategy covered literature from January 1997-2007. More information was obtained by a pilot study. This was done in the form of a questionnaire which was sent to HIV/AIDS departments in different parts of the world. In addition visits to HIV/AIDS
departments were made, consisting of the Amsterdam Medish Centrum and the Vrije Universiteit in Amsterdam.

Methods of the review

From the group of studies that met the inclusion criteria, both reviewers reviewed each article independently to determine the final inclusion. From the final group of included studies, a summary was made of each article. The summary included data on study design, objective of the research, characteristics of participants included (age, gender etc.), number of participants at baseline and at the end of the study, inclusion and exclusion criteria for the participants, description of interventions (duration, frequency and level of supervision) and results (types of outcome variables used and their values at baseline and at the end of the study). Methodological quality of the studies was done by using the CONSORT checklist for randomized studies. The articles were required to check out on at least 80% of the checkpoint on this list. Group similarities at baseline were assessed.

Pilot study

In order to gather more information concerning HIV/AIDS and exercise, a pilot study was conducted in the form of a questionnaire which was sent to HIV/AIDS departments in different parts of the world. The questionnaire did contain questions regarding HIV and exercise, and was made for physiotherapists who currently or in the past were treating HIV-infected patients.

Statistical analysis

Outcomes were analyzed as continuous outcomes whenever possible. For continuous outcomes, an estimated mean difference between the mean values of the analyzed clinical trials was made. Where meta-analysis was not possible, the results were described of the individual studies.

Subgroup analyses were made whenever possible to review whether differences in groups can influence the outcome measured when performing progressive resistance exercise. Possible subgroup analyses included: males vs. females, participants with HIV wasting vs. participants without HIV wasting and participants on antiretroviral therapy vs. participants not on antiretroviral therapy.

Results

The search resulted in 1241 citations. Based on the title and the relevance to the topic, 1189 articles were eliminated. After abstract review of the remaining 50 studies, 22 articles were reviewed to determine whether they met the inclusion criteria. Out of the 22 studies reviewed, 5 articles met the inclusion criteria (Dolan 2006, Grinspoon 2000, Shevitz 2005, Agin 2001, Sattler 1999) and scored 80% or more on the consort checklist. Excluded articles were either reviews, pilot studies or supplement articles, and did not meet the inclusion criteria. Other articles were excluded because they did not include progressive resistance training.

Design of included studies

The five included articles were randomized clinical trials. Two of the five studies included a control group (Dolan 2006, Grinspoon 2000). All the five studies consisted of a non-exercising group (Dolan 2006, Grinspoon 2000, Shevitz 2005, Agin 2001, Sattler 1999). One of the five studies included a program combined of PRT and aerobic exercise (Dolan 2006). Two studies included an exercise intervention consisting of PRT only (Grinspoon 2000, Agin 2001). One of the five articles included a comparison group assessing the effect of PRT combined with testosterone therapy (Grinspoon 2000). One study included the effect of PRT in combination with whey protein (Agin 2001) and Nandrolone decanoate (Sattler 2007). All three studies (Agin 2001, Grinspoon 2000, Sattler 2007) also included a group receiving testosterone, whey protein or Nandrolone decanoate alone. All the five studies stated that the exercise intervention was supervised (Dolan 2006, Grinspoon 2000, Shevitz 2005, Agin 2001, Sattler 1999).
Table 1: Interventions

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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>PRT+Aerob</td>
<td>PRT</td>
<td>PRT</td>
<td>PRT+NA</td>
<td>PRT+Aerob</td>
</tr>
<tr>
<td>Control</td>
<td>Nandr</td>
<td>PRT+PRO</td>
<td>NA</td>
<td>PRT+Aerob+Test</td>
</tr>
<tr>
<td>group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRO</td>
<td>NA</td>
<td>OX</td>
<td>Control group</td>
</tr>
</tbody>
</table>

PRT = Progressive resistance exercise, Aerob = aerobic exercise, Nandr = Nandrolone decanoate (testosterone), PRO = Whey protein, NA = nutrition, Test = testosterone.

Participants of included studies

The participants were adults aged between 18-66 years. In addition, the participants had to be HIV-positive at any stage of the infection. Two of the five articles included only female participants (Agin 2001, Dolan 2006), one article included men only (Grinspoon 2000), and the remaining two included participants of both sexes (Sattler 1999, Shevitz 2005). Four articles included participants with AIDS/HIV related wasting. Weight loss was regarded as weight less than 90% of ideal body weight, or self reported weight loss more than 10%, (Dolan 2006, Agin 2001, Grinspoon 2000, Shevitz 2005). One article included participants with a stable weight (Sattler 1999). One article included only participants with a CD4 lymphocyte count for 50-400/mm³ at screening (Sattler 1999) and one included only subjects with a normal serum level of free testosterone (>42 pmol/L) (Grinspoon 2000).

The participants in the study made by Dolan et al. (2006) included only participants with increased hip-ratio of 0.85 or more and self-reported fat distribution.

Table 2: Number of participants Baseline

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<tr>
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</thead>
<tbody>
<tr>
<td>40 women</td>
<td>33 men</td>
<td>43 women</td>
<td>34 men</td>
<td>54 men</td>
</tr>
</tbody>
</table>

Table 3: Number of dropouts

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</thead>
<tbody>
<tr>
<td>2 Female</td>
<td>3 male</td>
<td>13 female</td>
<td>2 Female</td>
<td>0 dropouts</td>
</tr>
</tbody>
</table>

Outcomes of the included studies


Table 4: Outcomes

<table>
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<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count</td>
<td>CD4 count</td>
<td>Body weight</td>
<td>PF</td>
<td>CD4 Count</td>
</tr>
<tr>
<td>Waist Circum</td>
<td>BMI</td>
<td>BCM</td>
<td>BCM</td>
<td>LBM</td>
</tr>
<tr>
<td>BMI</td>
<td>LBM</td>
<td>Fat Mass</td>
<td>CSMA</td>
<td>Fat mass</td>
</tr>
<tr>
<td>CSMA</td>
<td>CSMA</td>
<td>Strength</td>
<td>Ab. endurance</td>
<td>Strength</td>
</tr>
<tr>
<td>Aerobic Cap.</td>
<td>Strength</td>
<td>Strength</td>
<td>Ab. endurance</td>
<td>Strength</td>
</tr>
<tr>
<td>Strength</td>
<td>QOL</td>
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</table>

BMI = Body mass index, CSMA = Cross sectional muscle area, BCM = Body cell mass, QOL = Quality of life, PF = Physical function, LBM = Lean body mass.
Results of outcome measures

In the following part six comparisons were done comparing progressive resistance training with other interventions. Many comparisons had to be made due to the fact that the included articles did compare PRT to different interventions. In some articles PRT was also combined with aerobic exercise. Each section does analyse one or more articles which include the interventions given in the headline. Whenever possible, a meta-analysis was made regarding the outcome. Whenever meta-analysis was not possible, the individual results of the studies, in each section, are presented. In each section, the outcomes in body weight, body composition, muscle strength, CD4 counts and adverse events (safety) are presented.

1.) Progressive resistance training in combination with aerobic exercise versus non-exercising control group.

PRT in combination with aerobic exercise was compared to a non-exercising control group. A non-exercising control group was defined as a group who did not receive any kind of intervention apart from placebo during the time of the study.

Two studies compared combined PRT and aerobic exercise with a non-exercising control group (Dolan 2006 and Grinspoon 2000).

A.) Body weight

Only one of the studies that compared PRT in combination with aerobic exercise to a non-exercising control group assessed body weight (Grinspoon 2000). Dolan (2006) did only refer to the participants BMI at baseline and at the end of the study.

Grinspoon (2000) found an increase in body weight of 1.7 kg for participants in the combined PRT and aerobic exercise group compared to a decrease in body weight of 0,6 kg for participants in the non-exercising control group.

B.) Body composition

Both of the two studies that included PRT in combination with aerobic exercise versus a non-exercising control group did assess body composition (Dolan 2006 and Grinspoon 2000).

Due to the fact that the studies assess different components of body composition together with different measurement tools, meta-analysis was only possible to perform regarding fat mass.

Meta-analysis of the fat mass demonstrated a decrease in 0.7 kg (95% CI: -0,2, -1,3) of fat mass for participants in the exercise groups compared to the non-exercising control groups (Dolan 2006 and Grinspoon 2000).

Individual study results – body composition:

Grinspoon (2000) found a significant increase in lean body mass (2.3 kg), arm muscle cross-sectional area (346mm²), leg muscle cross-sectional area (797mm²)and a decrease in fat-mass (-1.3 kg) for participants in the combined PRT and aerobic exercise group. There were no significant changes in the non-exercise group. Since Grinspoon (2000) included participants with wasting syndrome, the results of increase in lean body mass and body weight represents positive results.

Dolan (2006) found an increase in BMI (0.4) for the exercise group, and a decrease in BMI (-0.1) in the non-exercising control group. In the same study there was a decrease in waist circumference (-1.0 cm) in the exercise group in comparison to an increase in the non-exercise control group (1.5 cm). Total muscle area increased in the combined PRT and aerobic exercise group (6 cm²) and increased (2 cm²) in the non-exercising control group. There were no significant differences regarding p-value for treatment effect between the exercise and non-exercise control group. Since Dolan (2006) included participants with increased waist-hip ratio and changes in fat distribution, the results of a decrease in waist circumference represents favourable results.

C.) Strength

Both of the two studies that included PRT in combination with aerobic exercise versus a non-exercising control group did assess strength outcomes (Dolan 2006 and Grinspoon 2000). Due to the fact that there were some differences between
the studies regarding which muscle groups were trained and assessment of the outcomes no meta-analysis could be performed.

Individual study results-strength:
Grinspoon (2000) did not find any statistical differences in strength between the combined PRT and aerobic exercise group and the non-exercising control group. Only shoulder extension did show a significant increase in strength (3.3 kg) in the exercise group in comparison to a small increase (0.6 kg) in strength in the non-exercising control group. The fact that Grinspoon (2000) did not find statistical differences in strength could be due to the method of assessing muscle strength. Assessment of muscle strength was done by peak isometric force. A study made by Robinson (1995) found that the sensitivity to detect changes in strength was much greater for the isotonic than the isometric contraction.

Dolan (2006), which used isotonic one repetition maximum method found a statistical significant difference (p=0.001) in strength between the exercise group and non-exercising control group (7/7 variables). This study found an increase in strength by 50%-150% in the combined PRT and aerobic exercise intervention in comparison to a change of -5 %-18% in the non-exercising control group.

D.) CD4 count

CD4 count was assessed at baseline and at the end of the study in both studies including a combined PRT and aerobic exercise group versus a non-exercising control group (Dolan 2006, Grinspoon 2000).

Meta-analysis did show a non-significant increase in CD4 counts of 20.5 cells/mm³ (95% CI: 33.8) for the participants in the combined PRT and aerobic exercise group compared to an increase of 21 cells/mm³ (95% CI: 31, 11) in the non-exercising control group (Dolan 2006, Grinspoon 2000).

E.) Adverse events (safety)

Grinspoon (2000) and Dolan (2006) did describe adverse events to assess safety. Meta-analysis was not possible due to the fact that the studies discussed different events.

Individual study results-adverse events:
Grinspoon (2000) reported that no patient withdrew from the study because of an adverse event or side effect. No patients developed new prostate nodules. Three patients developed breast tenderness or gynecomastia (Two were receiving testosterone and one was receiving placebo). Dolan (2006) reported that one patient in the exercise protocol had exacerbation of asthma related to the development of bronchitis. One patient in the none-exercise group experienced chest pain at the baseline visit, but myocardial infarction and ischemia were ruled out. It was stated that none of the adverse events was related to the exercise protocol or study participation.

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<th>Table 5: Meta analysis</th>
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<tr>
<td><strong>Outcome Title:</strong></td>
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<tr>
<td>Fat mass</td>
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<tr>
<td>CD4 count</td>
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</tbody>
</table>

2.) PRT vs pharmacological therapy combined with PRT.

This part of the results presents the effect of PRT compared to pharmacological therapy combined with PRT. One out of the five studies compared PRT with a pharmacological intervention combined with PRT (Agin 2001). PRT represents the progressive resistance exercise group and PRO+PRT is the group that combined progressive resistance training and whey protein. PRO represents whey protein.

A.) Body weight

Agin (2001) found a significant increase in body weight of 1.3 kg in the group receiving PRT in combination with protein in comparison to a decrease in body weight of 0.1 kg in the group.
receiving PRT only.

B.) Body composition
Body cell mass significantly increased for both exercise groups, PRT 0.7 kg and the PRO-PRT 0.6 kg (Agin 2001).
Fat mass, measured by MRI had a non-significant increase of 0.7 kg in the PRO-PRT group and a significant decrease of 1.7 kg in the group receiving PRT only.

D.) Muscle strength
Maximum dynamic muscle strength for the exercise groups (PRT and PRO±PRT) significantly increased for all seven muscle groups trained (range of increase 40.6±95.3%, all P = 0.001).

E.) CD4 count
CD4 count was only measured at baseline (Agin 2001).

3.) Progressive resistance training versus pharmacological therapy combined with no exercise

Participants receiving PRT was compared to participants receiving pharmacological therapy in combination with no exercise intervention. Two Studies compared PRT with pharmacological therapy (Agin 2001, Shevitz 2005). Aigin (2001) compared PRT to daily consumption of 1.0 kg whey protein. Shevitz (2005) compared PRT (with nutrition) to 10 mg oxandrolone (OX) administered orally twice a day (with nutrition). Due to the fact that the two studies use different pharmacological products in comparison to PRT, no meta-analysis will be possible in this section. Results from the individual studies will be presented.

A.) Body weight

Only one of the two studies comparing PRT to pharmacological therapy with no exercise did report measurements of body weight at the baseline and end of the study (Agin 2001).
Shevitz (2005) did only refer to the participants BMI at baseline and at the end of the study.
Individual study results-body weight
Agin (2001) found a significant gain in body weight (2.3 kg) for the protein group (P=0.001) compared to a decrease in body weight (-0.1 kg) for the PRT group. This resulted in a significant difference in body weight between the protein and PRT groups (P=0.007).

B.) Body composition

Both of the studies comparing PRT to pharmacological therapy with no exercise did report measurements of body composition (Agin 2000, Shevitz 2005).

Individual study results-body composition:
Agin (2001) found significant increase in body cell mass (BCM) of 0.74 kg for the PRT group (P=0.03) and a smaller increase of 0.50 kg (p=0.07) for the protein group. The PRT group significantly increased skeletal muscle by 1.2 kg (p=0.001), with no change in the skeletal muscle (0.6 kg) seen in the protein group. The fat mass measured by MRI increased 2.5 kg in the protein group (p=0.002) and decreased in the PRT group.
Fat free mass did increase in both groups. Fat mass increased in the protein group and decreased in the PRT group.
Shevitz (2005) found a similar increase in BMI of the OX group and the PRT group. Cross-sectional muscle area increased for the PRT (5.3 cm²) and the OX group (0.35 cm²). Fat-free mass had a similar increase in both groups, 1.70 kg within the OX group compared to 1.17 kg within the PRT group.

C.) Strength

Both of the studies did include measurements of strength status at baseline and in the end of the study (Agin 2001, Shevitz 2005).

Individual study results- strength
Agin (2001) did assess the strength of the 7 muscle groups which were trained by using the 1RM method. Maximum dynamic muscle strength for the PRT group increased significantly in all 7 muscle groups. The range of increase was from 40.6 %-95.3% with a P-value less than 0.001 in all muscle groups. The range of increased strength in the protein group was of a lesser magnitude at 6.6-16.9% with a P-value of 0.01-0.12.
Shevitz (2005) did assess strength with 4 different
strength machine exercises and modified curl-ups. Improvements on all tests were far exceeded by the PRT group in comparison to the OX group. To give one example: The leg press measurement had an increase in 48 kg in the OX group in comparison to an increase in 158 kg in the PRT group. The PRT group did show an increase regarding strength in a range from 1%-42%.

D.) CD4-count

Both studies included only measurements of the CD4 count at baseline (Agin 2001, Shevitz 2005).

E.) Adverse events (safety)

Of the two studies comparing PRT to pharmacological therapy and no exercise, only Shevitz (2005) did report adverse events in the results.

Individual studies-adverse events:
In the study made by Shevitz (2005), three people developed opportunistic infections during the study, and two more were diagnosed with such conditions shortly after completing the trial. There were no deaths or serious or unexpected reactions to the study interventions. Serious liver function elevation developed in 2 study subjects and resulted in unblinding of study-drug. There were no reports of hiruitism, deepening voice, sexual dysfunction, menstrual change (among women) or gynecomastia (among men).

4.) Progressive resistance training combined with aerobic exercise versus pharmacological therapy combined with no exercise.

Participants receiving PRT in combination with aerobic exercise was compared to participants receiving pharmacological therapy in combination with no exercise intervention. One study compared PRT in combination with aerobic exercise to pharmacological therapy and no exercise (Grinspoon 2000). Grinspoon (2000) did compare PRT and aerobic exercise to intramuscular injections of testosterone enanthate (200 mg/week). Since only one study was included in this section, no meta-analysis is possible, and the results from the individual study will be presented.

A.) Body weight

Grinspoon (2000) found a significant increase in body weight (2.7 kg, P=0.01) in the testosterone group and a non-significant increase (1.7 kg) in the combined PRT and aerobic exercise group.

B.) Body composition

Grinspoon (2000) found a significant increase in lean body mass (2.3 kg), a non-significant decrease in fat-mass (-1.3 kg), a significant increase in arm muscle area (346 mm²) and leg muscle area (797 mm²) in the combined PRT and aerobic exercise group compared to significant increase in lean body mass (4.2 kg), a significant decrease in fat-mass (-2.0 kg) as well as significant increase in arm muscle area (374 mm²) and leg muscle area (1069 mm²) in the testosterone group.

C.) Strength

Grinspoon (2000) found no significant increase in strength within the combined PRT and aerobic exercise group. In the testosterone group there was a significant increase in strength regarding the shoulder extension (5.9 kg, P=0.01) and elbow flexion (3.0 kg, P=0.05) and a general significant increase in upper-extremity strength (0.7 kg, P=0.01).

D.) CD4-count

Grinspoon (2000) found an increase of 31 CD4 cells/mm³ in the combined PRT and aerobic exercise group in comparison to an increase of 8 CD4 cells/mm³ in the testosterone group.

5.) Progressive resistance training in combination with aerobic exercise versus pharmacological therapy combined with exercise.

Participants receiving PRT in combination with aerobic exercise was compared with participants receiving pharmacological therapy in combination with PRT and aerobic exercise. One study
compared PRT in combination with aerobic exercise to pharmacological therapy and exercise (Grinspoon 2000). Grinspoon (2000) did compare PRT and aerobic exercise to intramuscular injections of testosterone enanthate (200 mg/week) combined with PRT and aerobic exercise. Since only one study was included in this section, no meta-analysis is possible, and the results from the individual study will be presented.

A.) Body weight

Grinspoon (2000) found a significant increase in weight (2.5 kg, P=0.01) in the group who received testosterone in combination with PRT and aerobic exercise in comparison to a non-significant increase in weight (1.7 kg) in the PRT in combination with aerobic exercise group.

B.) Body composition

Grinspoon (2000) found a significant increase in lean body mass (2.3 kg), a non-significant decrease in fat-mass (-1.3 kg), a significant increase in arm muscle area (346 mm²) and leg muscle area (797 mm²) in the combined PRT and aerobic exercise group compared to a significant increase in lean body mass (4.6 kg), arm muscle area (638 mm²) and leg muscle area (1388 mm²), as well as a significant decrease in fat-mass (-2.9 kg).

C.) Strength

Grinspoon (2000) found no significant increase in strength within the combined PRT and aerobic exercise group. In the participants who received testosterone in combination with exercise there was a significant increase in shoulder extension (4.7 kg, P=0.01), shoulder flexion (4.7, P=0.001), dorsal flexion (3.8, P=0.5), general upper extremity strength (0.8, P=0.001) and lower extremity strength (0.5, P=0.5). There was no significant increase in strength regarding knee flexion and extension.

D.) CD4 count

Grinspoon (2000) found an increase of 31 CD4 cells/mm³ in the combined PRT and aerobic exercise group in comparison to a decrease of 27 CD4 cells/mm³ in the testosterone in combination with PRT and aerobic exercise group.

6.) Progressive resistance training combined with pharmacological therapy versus pharmacological therapy combined with no exercise.

Participants receiving PRT in combination with pharmacological therapy was compared to participants receiving pharmacological therapy only. Two studies compared PRT in combination with pharmacological therapy in comparison to pharmacological therapy only (Agin 2001, Sattler 1999). Agin (2001) compared daily consumption of 1.0 kg whey protein and no exercise to PRT combined with daily consumption of 1.0 kg whey protein. Sattler (1999) compared PRT in combination of weekly injections of nandrolone decanoate alone to weekly injections of nandrolone alone. Due to the fact that the two studies use different pharmacological products in comparison to PRT, no meta-analysis will be possible in this section. Results from the individual studies will be presented.

A.) Body weight

Agin (2001) found a significant body weight gain (3.6 kg, P=0.007) in the group receiving whey protein only. There was a non-significant increase in body weight (1.3 kg, P=0.31) in the group receiving PRT in combination with whey protein. Sattler (1999) found a significant increase in body weight (3.2 kg, P=0.001) in the group who received nandrolone only as well as in the group who received nandrolone in combination with PRT (4.0 kg, P=0.001).

B.) Body composition

Agin (2001) found a non-significant increase in body cell mass and the size of skeletal muscle (kg) in the group receiving whey protein only. In the protein-only group, there was a significant increase in fat mass (2.5 kg, P=0.002) and fat-free mass (1.4, P=0.01). In the group receiving protein in combination with PRT there was a non-significant increase in size of skeletal muscle and fat mass, but
a significant increase in body cell mass (0.61 kg, P=0.01) and fat-free mass (1.4 kg, P=0.05).

Sattler (1999) found a significant increase (P=0.001) in lean body mass (3.9 kg), body cell mass (2.6 kg), total thigh muscle area (1.5 mm²), quadriceps muscle area (0.7 mm²) and hamstrings muscle area (0.8 mm²) in the group receiving nandrolone only. The same group did show a non-significant decrease in fat mass. Regarding the group who received combined nandrolone and PRT there was a significant increase in lean body mass (5 kg), body cell mass (3 kg), total thigh muscle area (1.5 mm²), quadriceps muscle area (0.7 mm²) and hamstrings muscle area. There was a significant decrease in fat mass.

C.) Strength

Agin (2001) did assess strength of the 7 different muscle groups trained by using the 1 RM method. There was a non-significant increase in strength in the group receiving whey protein only when looking at seated back row and leg curl. Within the same group there was a significant increase in shoulder press (15.9%, P=0.02) biceps curl (16.9%, P=0.01), triceps extension (6.6%, P=0.02) and leg extension (12.6%, P=0.03). In the group receiving whey protein in combination with PRT there was a significant increase in muscle strength regarding all exercises (7/7) with a p-value of 0.001. This study found an increase of strength in a range from 40.5%-88.4% in the combined protein and PRT group in comparison a range of 6.6%-16.9% in the protein only group.

Sattler (1999) did assess strength of 7 muscle groups by using the 1 RM method, and found in the nandrolone-only group a significant increase in strength regarding all muscle groups, except from calf raises (0.006) and knee extension (0.21), and an increase in strength in a range from 8.3%-24%. In the nandrolone combined with PRT group there was a significant increase in strength regarding all muscle groups (7/7) with a P-value of 0.001. The increase in strength did range from 33%-58%.

D.) CD4 count

Agin (2005) did only assess CD4 counts of the participants at baseline. Sattler (1999) found an increase of 22 CD4 cells/mm³ in the nandrolone-only group, and a decrease of 10 CD4 cells/mm³ in the nandrolone combined with PRT group.

E.) Adverse events (safety)

Sattler (1999) found that none of the study subjects had any serious or treatment-terminating adverse events, and all reported feeling better while receiving study therapy. Only minor adverse events were documented. One patient in each group developed acneiform lesions on the chest. Lesions regressed as soon as nandrolone was discontinued. Eight patients in the nandrolone only group and four in the group assigned to PRT reported that the size of the testicles had decreased, but direct measurement of change in size was not made.

Other outcomes

Some of the articles did report individual outcomes which were only reported in one other article or not reported in the other four articles. Even though these outcomes were only reported in one article it was found interesting to include these outcomes to get a better insight in the effect of PRT on patients with HIV/AIDS.

A.) Physical functioning

Shevitz (2005) assessed the physical functioning (PF) of the participants at baseline and end of the study. PF was assessed by trained personnel verbally administering subjects the health questionnaire used in the HIV Costs and Services Utilization Study. The level of PF was measured on a 1-100 scale, with 100 representing the best functioning. In the Oxandrolone only group there was no significant change in PF (-1.0+-4.7 points, P=0.83). In the PRT group the PF improved significantly (10.4+-3.8 points, P=0.02).

B.) Costs and cost effectiveness

Shevitz (2005) compared the cost and cost effectiveness between the nutrition (NU), NU combined with OX and NU combined with PRT. Institutional costs for each intervention were
calculated by multiplying quantities of each input, times their unit costs in year 2000 prices at market value and summing the products. The NU included 12 counselling sessions, 2 food record collections and 12 weeks of canned supplements. The OX included the NU costs and the drug-cost. The PRT included NU costs with 3 months of gym fees and 36 personal training sessions. The calculated institutional cost of OX with nutrition ($3772) was greater than the cost of PRT with nutrition ($1636) or NA ($766).

C.) Quality of life

Agin (2005) assessed quality of life (QOL) in participants with HIV/AIDS at the baseline and the end of the study. QOL was assessed by the medical outcomes study survey. Following treatment, the physical activity score significantly increased for the PRT group (P=0.02), but significantly declined for the PRO subjects (P=0.01). Significant improvements in general health perceptions (P=0.03) and vitality (P=0.007) were also observed for the PRT women.

Subgroup analysis

It was not possible to complete the subgroup analyses due to the small number of studies included in the research. Some subgroup analyses were impossible to perform because all articles included one of the variables of interest. All articles included supervised exercise and all articles (except Sattler 1999) included participants with AIDS wasting. Whether the participants were taking HAART medication or not was not mentioned in any articles. The articles included both men and female only, but due to variability of characteristics among the studies subgroup analysis was not possible.

Pilot study

The pilot study was not successful because no questionnaires were returned on time, confidentiality surrounding HIV/AIDS patients and limited time for this research.

Tables – outcomes exercise groups

(PRT only or PRT in combination with aerobic exercise).

Table 6: Strength

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<tr>
<td>50%-150%</td>
<td>33%-58%</td>
<td>41%-95%</td>
<td>0%-42%</td>
<td>0%-13%</td>
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</tbody>
</table>

The possible reason for a low outcome regarding strength in Grinspoon (2000) could be due to the method of assessing muscle strength by using peak isometric force which has shown to be less reliable regarding strength measurement in comparison to isotonic contraction (Robinson 2006).

Table 7: Lean body mass (measured in kg)

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<tr>
<td>9.4%</td>
<td>6.6%</td>
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Table 8: Body cell mass (Kg)

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<tbody>
<tr>
<td>10.1%</td>
<td>4.2% (PRT+)</td>
<td>4.6% (PRT)</td>
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Table 9: Cross sectional muscle area (Cm²)

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<tr>
<td>6.2 (Quadriceps)</td>
<td>7.2</td>
<td>5.3</td>
<td>4.9 (arm)</td>
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<td>14.8 (Thigh)</td>
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<td>11 (leg)</td>
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Table 10: CD4 count (mm³)

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<td>8 cells</td>
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Discussion

The results from this review should be read carefully for many reasons.
This review is based on a small number of studies. Meta-analysis completed did include a maximum of two studies and reported on maximum 94 participants in each meta-analysis. The studies included a small number of participants at baseline, and one of the five studies had a dropout rate greater than 15%. It appears as though there is inadequate follow up data on the dropouts. Agin (2001) reports 13 drop outs, Shevitz (2005). There were only two studies which compared progressive resistance training to a non-exercising control group (Dolan 2006, Grinspoon 2000) and only two studies including an exercise intervention consisting of PRT only (Agin 2001, Shevitz 2005). To increase the level of evidence, there should have been included more studies which compared progressive resistance training to a non-exercising control group.

The studies reviewed in this review consist of participants at various stages of the HIV infection and this promotes external validity. However more attention is needed to determine the type, cause and stage of wasting to elicit the extent of physiologic changes in the HIV-infected population. No distinct connection has been made between exercise duration and the stage of HIV.

In addition, publication bias may have occurred if negative results did not make it to publication, leaving mostly small, but positive studies to include in the review.

The meta-analyses in this study were limited due to a variety of characteristics included in the studies which were: type of exercise intervention, exercise intensity, exercise progression, length of study, outcomes assessed, measurement tool regarding outcomes, gender and differences in baseline regarding AIDS wasting.

Looking at the methodological quality of the studies there was no blinding of the participants due to the type of intervention received (whey protein, exercise etc.). This could lead to bias with greater results when the participants know what that there are expectations of positive results regarding exercise. The studies did not mention whether the assessor was blinded. If the assessor was not blinded during the randomization process, this could lead to bias because he/she expect greater results from the exercise group and might assess this group differently. There was a greater interaction between the participants receiving exercise and the study investigators compared to other interventions or control group. This could lead to outcomes of increased quality of life in comparison to the participants receiving less follow up.

Even though all studies assessed outcomes regarding cross-sectional muscle area, muscle strength and body composition, only one study reported outcomes on quality of life.

Since wasting is accompanied with decreased muscular strength and functional performance (Dudgeon 2006) and as muscle mass and strength decline, disability and quality of life decreases for a HIV-infected patient (Sattler 1999), it would be important to include in the study outcome on how the participants perception of progressive resistance training was on his/her own health.

Taking into account the limitations discussed above, it will now be given a summary of the findings:

Results of meta-analysis of this systematic review indicated a non-significant decrease in fat mass among exercisers when compared to non-exercising control groups. There was also a non-significant change in CD4 count among exercisers when compared to non-exercising control groups. Showing no change in CD4 count suggests a part of safety with respect to immune status for adults living with HIV/AIDS.

Individual studies reported significant results that demonstrated some benefits of progressive resistance exercise interventions compared to non-exercise and/or pharmacological therapy. Among the four studies assessing body weight, one of the two studies comparing exercise non-exercise control group found a significant increase in body weight among exercisers (Grinspoon 2000) in comparison to control group. Comparing the four articles it was found a more significant increase in body weight regarding pharmacological therapy in
comparison to exercise, and the greatest increase in body weight was found when exercise was combined with pharmacological therapy (Agin 2001, Grinspoon 2000, Sattler 1999, Shevitz 2005). All five studies assessed body composition. In the two comparing exercise to a non-exercising control group exercise did significantly increase lean body mass and cross-sectional muscle area in addition to decrease the waist circumference in comparison to the control group (Dolan 2006, Grinspoon 2000). Analyzing the four articles comparing exercise to pharmacological therapy it was found that exercise did show a more significant increase regarding lean body mass and cross-sectional muscle area than pharmacological therapy (Agin 2001, Shevitz 2005). But greatest increase in body composition was found when exercise was combined with pharmacological therapy (Agin 2001, Sattler 1999). All five studies assessed strength. When looking at the two studies comparing exercise to a non-exercising control group, Dolan (2006) found a significantly increase in strength in the exercise group when compared to the control group. Grinspoon (2000) found no significant difference between the two groups. As stated previously, finding no significant difference could be due to the isometric method of assessing strength.

Analyzing the four articles comparing exercise to pharmacological therapy it was found that exercise did show a more significant increase in strength (Agin 2001, Shevitz 2005). But the most significant increase in strength was found when exercise was combined with pharmacological therapy (Agin 2001, Shevitz 2005). No significant changes were seen with respect to CD4 count for exercisers in the three studies assessing this outcome (Grinspoon 2000, Dolan 2006, Sattler 1999). As stated above, meta-analysis did show that there was a non-significant change in CD4 count among exercisers when compared to non-exercising control groups. The four studies assessing safety by reporting adverse events did not find any adverse events linked to exercise intervention. The adverse events presented in the study were likely due to the progression of the HIV-infection rather than the exercise interventions.

Previous studies have shown that resistance training in combination with testosterone or anabolic steroid therapy increases lean body mass. Resistance training is associated with a significant increase in HDL cholesterol level. In contrast, testosterone administration does decrease HDL cholesterol level. Concern exists over the development of abnormal lipid profiles in patients recovering from wasting, and the increased HDL cholesterol level resulting from training may benefit such patients (Grinspoon 2000). Progressive resistance training is also unique among strategies to increase lean body mass because it is associated with a cardio protective effect (Dolan 2006). Baseline data in the study made by Dolan (2006) did demonstrate that HIV women are dramatically deconditioned with respect to cardio respiratory fitness in comparison to HIV-negative women of equal age.

Error is also present when using heart rate as a measure of work rate because cardiac neuropathy is common to many HIV infected persons (Dolan 2006).

Although short term administration of testosterone or other pharmacological therapies increases muscle mass, it may be associated with adverse metabolic effect in these patients (Dolan 2006). Calculations of costs and cost effectiveness have shown that Progressive resistance exercise is more cost effective in comparison to pharmacological therapy (Shevitz 2005). It is important to include the costs regarding treatment for HIV-individuals because wasting persists as a major cause of morbidity and mortality in parts of the world where cost-effectiveness are critical.
CONCLUSION

Implications for practice

This systematic review suggests that progressive resistance exercise is beneficial for HIV adults with wasting conditions who can and will comply with a proper progressive resistive exercise program. Meta-analysis suggests that performing progressive resistance exercise three times a week for at least twelve weeks may lead to statistically significant improvements in body weight for adults living with HIV/AIDS. Individual studies indicate that performing progressive resistance exercise or a combination of progressive resistance exercise and aerobic exercise three times a week for at least twelve weeks may lead to significant improvements in body composition and strength. It also appears to be safe for adults living with HIV/AIDS as seen by no change in CD4 counts. Individual suggests that performing progressive resistive exercise or a combination of progressive resistive with pharmacological therapy three times a week for at least twelve weeks resulted in the greatest increase in body weight and composition in adults living with HIV/AIDS.

Cautious interpretation of results in this study is warranted for because the studies reviewed included outcome data only on those participants who continued to exercise and for whom there were adequate follow-up data. Characteristics of participants included in this review varied pertaining to their stage of HIV infection, age, diagnosis of AIDS wasting syndrome, and whether they were taking HAART, thus heightening the external validity of this review. Results may be relevant to individuals who may or may not be taking HAART, and thus, may be applicable to persons living with HIV in developing countries as well as developed countries. More broadly, the increasing advocacy for HIV care, treatment and support in the developing world, further supports the increasing relevance and importance of rehabilitation services for persons living with HIV in these countries.

Implications for research

Evidence concerning effectiveness and safety of progressive resistance training for adults living with HIV is limited due to the small number of studies included and sample size. Further research should include more studies and more participants to increase the level of evidence. There was no follow up for drop outs in the studies and this raises concerns about the safety of exercise among the participants that stopped exercising. Hence limits the ability to determine the effectiveness of progressive resistive exercise. The effects of coordination on strength training could also have been explored to help determine safety since a significant number of HIV/AIDS infected people have coordination problems.

This study included participants with widely ranging stages of HIV infection. Further studies should aim to assess the effect of progressive resistance exercise on different stages of the HIV-infection.

This systematic review included only studies with adults. Additional studies should assess the effect of progressive resistance exercise on HIV-infected children. It is also important for future studies to look into whether the acquired benefits are short or long term. Finally a standard measuring tool should be used and hence make comparison easier.

Acknowledgements

The authors would like to thank the contributions of the following persons:

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Helen Wiggers, working at “The Vrije Universiteit” for contributing with experience and knowledge regarding HIV and exercise.

Dr.Godfrey Sikipa for giving information regarding HIV/AIDS and being the client.
References

References of the included studies

Agin

Amosun

Dolan

Grinspoon

Irwin

Sattler

Shevitz

Additional references

Driscolla

Dudgeon

Dudgeon

Lox

McClure

Ministry of Health, Zimbabwe
Ministry of Health, Zimbabwe, Hospital Medical Officer, Mpilo Central Hospital, Bulawayo, January 1977 to June 1979.

O’Brien

Orsia
Orsia.F, Almeidaa C.D, et al, 2007. TRIPS post-

Phillips

Rabkin

Robinson

Roubenoff

Roubenoff

Robinson

Treatment Guidelines for HIV-Associated Wasting

Useh

WHO
World health organization 2007

Zinna
# Appendix

## Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Agin 2001</th>
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<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomized to PRT vs. PRT+Whey protein vs. Whey protein (3 groups).</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>43 HIV-infected women between 28-66 years with body cell mass wasting.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>PRT EXERCISE: of 7 major muscle groups. 3 sets of 8 repetitions each exercise. Week 1: Loads were 50% of baseline 1 RM. Loads increased to 75% of 1 RM. Loads were increased at least 2.5 lbs when a participant completed 10 consecutive reps for a muscle group without fatigue. Frequency: 3 times a week for 14 weeks. WHEY PROTEIN: 1 g/kg of whey protein powder for 14 weeks.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>WEIGHT AND BODY COMPOSITION: Significant increases in body weight were seen in the whey protein group. BCM significantly increased for both exercise groups (PRT and PRT+Whey protein). Skeletal muscle increased significantly in the PRT group compared to the other groups. Fat mass significantly increased in the whey protein group and significantly decreased in the PRT and PRT+whey protein group. STRENGTH: Muscle strength increased for all 7 muscle groups assessed in the PRT and PRT+whey protein from 41%-95%. HEALTH RELATED QUALITY OF LIFE: Physical activity scores significantly increased for the PRT group but significantly declined for the Whey protein groups. ADVERSE EVENTS: 1 death was reported in the PRT+whey protein group. No injuries were reported from resistance training or testing. AUTHORS CONCLUSION: Resistance exercise significantly increased BCM, muscle mass, muscle strength and quality of life in HIV-infected women with reduced BCM. Whey protein had little effect on BCM gain and combined PRT+whey protein did not increase BCM in excess of gains achieved by PRT alone.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>AUTHORS COMMENTS: No intention-to-treat analysis was performed. A control period of 6 weeks prior to interventions showed no significant differences in outcomes. The PRT+Whey protein group demonstrated a ceiling effect in the physical activity scale of the quality of life assessment.</td>
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<tr>
<td>Study</td>
<td>Dolan 2006</td>
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<tr>
<td>Method</td>
<td>Randomized to a supervised home-based program of progressive resistive training or control group (2 groups).</td>
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<tr>
<td>Participants</td>
<td>40 HIV-infected women aged 18-60 years with self report of changes in fat distribution. 20 women in the exercise group and 20 women in the control group.</td>
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<tr>
<td>Interventions</td>
<td>PRT: of 6 muscle groups. Week 1: intensity set at 60% of 1 RM, 3 sets of 10 repetitions. Week 2: intensity increased to 70% 1 RM. Week 4: 80% of 1 RM and 4 sets of 8 repetitions. AEROBIC EXERCISE: 20 min on a stationary bicycle at 60% of max HR the first 2 weeks and 75% of max HR and 30 min for remaining 14 weeks. Frequency: 3 times a week for 16 weeks.</td>
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<tr>
<td>Outcomes</td>
<td>AEROBIC CAPACITY: The exercise group showed a significantly improvement in aerobic capacity by VO2 max in comparison to the control group. STRENGTH: Increased significantly in the exercise group in comparison to the control group. BODY COMPOSITION: Total muscle area increased significantly in the exercise group in comparison to the control group. Body mass index: abdominal fat and total fat did not change between the groups. Waist circumference decreased more in the exercise group in comparison to the other group.</td>
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<tr>
<td>ADVERSE EVENTS</td>
<td>No adverse events was related to the exercise protocol or study participation.</td>
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<tr>
<td>AUTHORS CONCLUSIONS</td>
<td>A 16 week, supervised, home-based exercise regimen improved measures of physical fitness in HIV-infected women. The effects on strength were most significant, but improvements in cardiorespiratory fitness, endurance and body composition.</td>
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<tr>
<td>Notes</td>
<td>AUTHORS COMMENT: Patients assigned to exercise also reported a subjective improvement in energy and endurance on self-assessment. The use of a dedicated physiotherapist provided a consistent and supportive exercise environment and contributed to the high (96%) compliance rate in the study.</td>
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<tr>
<td>Study</td>
<td>Grinspoon 2000</td>
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<tr>
<td>Method</td>
<td>Randomized to PRT+AEROBIC vs. PRT+AEROBIC +TESTOSTERONE vs. CONTROL (3 groups).</td>
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<tr>
<td>Participants</td>
<td>54 HIV-infected males with AIDS wasting and normal level of free testosterone.</td>
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<tr>
<td>Interventions</td>
<td>AEROBIC EXERCISE: Supervised progressive strength training and constant aerobic conditioning consisting of 20 minutes aerobic exercise on a stationary bicycle at 60-70% of HR max. PRT: Week 1-2: 2 sets of 8 reps each 60% of 1 RM. Week 3-6: 2 sets of 8 reps each 70% of 1 RM. Week 7-12: 3 sets of 8 reps each 80% 1 RM. Frequency: 3 times a week for 12 weeks. TESTOSTERONE INTERVENTION: Intramuscular injection of 200 mg/wk of testosterone.</td>
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<tr>
<td>Outcomes</td>
<td>WEIGHT AND BODY COMPOSITION: Participants in the exercise only group showed significant increases in lean body mass, arm muscle area, leg muscle area, HDL cholesterol and significant decreases in AST level compared to non-exercising control group. IMMUNE INDICES: No significant response in CD4 count on viral load to exercise or testosterone therapy either alone or together as a co-intervention. ADVERSE EVENTS: No deaths were reported and reasons for withdrawal were not due to adverse events or side effects. AUTHORS CONCLUSIONS: Exercise has significant effect on lean body mass and muscle area independent of testosterone. Muscle mass and strength may further increase in response to combined exercise and testosterone therapy. Exercise was associated with an increase in HDL cholesterol whereas testosterone decreased HDL cholesterol. Exercise significantly increases muscle mass and offers cardio protective effects by increasing the HDL cholesterol in eugonadal men with AIDS wasting. Exercise may be a strategy to reverse muscle loss in this population.</td>
</tr>
<tr>
<td>Notes</td>
<td>AUTHORS COMMENT: Participants in this study were men with AIDS wasting. The goal of exercise was to increase body composition. Withdrawal rates did not differ by group. No significant effects in strength may have been attributed to the fact that strength testing was done using isometric methods which has been known to underestimate change in strength compared to one repetition maximum of isotonic training which is used in the other four studies.</td>
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### Study

<table>
<thead>
<tr>
<th>Method</th>
<th>Randomized to NA(nutrition)+placebo pills vs. NA+OX vs. NA+PRT (3 groups).</th>
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<tbody>
<tr>
<td>Participants</td>
<td>33 men and 14 women with AIDS wasting.</td>
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<td>Interventions</td>
<td>PRT: Frequency: 3 times a week for 12 weeks. Exercises for 5 muscle groups. 4 exercises performed with 3 sets of 8 repetitions and the last abdominal exercise performed 2 sets of 10 repetitions. Workload was progressively increased toward goal intensity of 80% of 1 RM.</td>
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<tr>
<td>Outcomes</td>
<td>BODY COMPOSITION: Cross-sectional muscle area did not change in the NA group, increased in the OX and PRT group. Physical function increased significantly in the PRT group.</td>
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<td>STRENGTH: Significant increases were found regarding all exercises in the PRT group.</td>
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<td>ADVERSE EVENTS: No deaths or serious or unexpected adverse reactions to the study interventions.</td>
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<td></td>
<td>AUTHORS CONCLUSION: OX and PRT induce similar improvements in body composition, but PRT improves quality of life more than nutrition or OX, particularly among patients with impaired physical function. PRT was the most cost-effective intervention, and OX was the least cost-effective intervention.</td>
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### Notes
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<thead>
<tr>
<th>Study</th>
<th>Sattler 1999</th>
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<tr>
<td>Methods</td>
<td>Randomized to PRT+Nandrolone vs. Nandrolone only (2 groups).</td>
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<tr>
<td>Participants</td>
<td>33 male participants. PRT+Nandrolone group: 17 at baseline and 15 at study completion. Nandrolone only group: 16 at baseline and 15 at study completion.</td>
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<tr>
<td>Interventions</td>
<td>PRT EXERCISE: Supervised PRT included upper and lower body weight training using free weights. PRT included warm up, 5-8 reps at 50% 1-RM for each exercise, 3 sets of 8 reps at 80% 1-RM with the final set performed to failure. Week 1: Intensity at 70% of 1-RM at baseline. End of week 2: Intensity at 80% of 1-RM. Frequency: 3 times a week for 12 weeks. NANDROLONE INTERVENTION: Weekly injections of nandrolone – 200mg in week 1, 400 mg in week 2. Dose increased to 600mg for weeks 3-12.</td>
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<tr>
<td>Outcomes</td>
<td>WEIGHT AND BODY COMPOSITION: Participants in both the combined Nandrolone and PRT group and the nandrolone-only group increased body weight significantly. The increase in lean body mass was significantly greater in the exercise group in comparison to the non-exercising group. There was a significant increase in BCM regarding both groups. Fat mass did not change in the nandrolone only group, and decreased significantly in the exercise group. Cross-sectional muscle area of the thigh increased significantly in both groups after 12 weeks. PRT did not have a greater increase than the Nandrolone only group. STRENGTH: There were significant increases in upper and lower body strength in both groups with significantly greater gains in strength in the combined PRT and Nandrolone group. IMMUNE INDICES: No significant increases in CD4 count for both intervention groups. ADVERSE EVENTS: Acne and testicular shrinkage were found in the Nandrolone groups. No participant developed urinary symptoms, breast enlargement, edema or changes in blood pressure. Other physiological measures resulted in no significant changes. AUTHORS CONCLUSIONS: Nandrolone resulted in significant increases in total weight, lean body mass, body cell mass, muscle size and strength. Increases in lean body mass and muscular strength were significantly greater with PRT.</td>
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</table>