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Non-HIV Comorbidities and Exercise in German People Living with HIV.

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Table of Contents

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Abstract

The post-antiretroviral therapy era has transformed HIV into a chronic disease and non-HIV comorbidities (i.e., cardiovascular and mental diseases) are more prevalent in PLWH. The source of these non-HIV comorbidities aside from traditional risk factor include HIV infection, chronic inflammation, distorted immune activation, burden of chronic diseases, and unhealthy lifestyle like sedentarism. Exercise is known for its beneficial effects in mental and physical health; reasons why exercise is recommended to prevent and treat difference cardiovascular and mental diseases in the general population. This cumulative thesis aimed to comprehend the relation exercise has to non-HIV comorbidities in German PLWH. Four studies were conducted to 1) understand exercise effects in cardiorespiratory fitness and muscle strength on PLWH through a systematic review and meta-analyses and 2) determine the likelihood of exercising German PLWH of developing non-HIV comorbidities, in a cross-sectional study. Meta-analytic examination indicates PLWH cardiorespiratory fitness (VO_{2max} SMD = 0.61 ml·kg·min^{-1}, 95% CI: 0.35-0.88, $z = 4.47$, $p < 0.001$, $I^2 = 50\%$) and strength (of remark lowerbody strength by 16.8 kg, 95% CI: 13–20.6, $p < 0.001$) improves after an exercise intervention in comparison to a control group. Cross-sectional data suggest exercise has a positive effect on German PLWH mental health (less anxiety and depressive symptoms) and protects against the development of anxiety (PR: 0.57, 95%IC: 0.36 – 0.91, $p = 0.01$) and depression (PR: 0.62, 95%IC: 0.41 – 0.94, $p = 0.01$). Likewise, exercise duration is related to a lower likelihood of reporting heart arrhythmias (PR: 0.20, 95%IC: 0.10 – 0.60, $p < 0.01$) in German PLWH. A preliminary

recommendation for German PLWH who want to engage in exercise can be to exercise ≥ 1 time per week, at an intensity of 5 METs, with a duration ≥ 60 minutes per week.

Nevertheless, further research is needed to comprehend exercise dose response and protective effect for cardiovascular diseases, anxiety, and depression in German PLWH.

Zusammenfassung

In der Zeit seit der antiretroviralen Therapie hat sich HIV zu einer chronischen Erkrankung entwickelt und Nicht-HIV-Komorbiditäten, z.B. Herz-Kreislauf-Erkrankungen und psychische Erkrankungen, treten bei Menschen, die mit HIV leben, häufiger auf. Die Herkunft dieser Nicht-HIV-Komorbiditäten, neben den traditionellen Risikofaktoren, sind HIV-Infektion, chronische Entzündung, eine gestörte Immunaktivierung, chronische Erkrankungen und eine ungesunde Lebensweise wie Bewegungsmangel.

Bewegung ist bekannt für seine positive Wirkung auf die mentale und körperliche Gesundheit; das ist der Grund, warum Bewegung in der Prävention und der Behandlung verschiedener Herz-Kreislauf- und psychischer Erkrankungen in der Allgemeinbevölkerung empfohlen wird.

Ziel dieser kumulativen Arbeit war es, den Zusammenhang zwischen körperlicher Bewegung und nicht-HIV-Komorbiditäten bei deutschen Menschen, die mit HIV leben zu untersuchen. Vier Studien wurden durchgeführt, um 1) die Auswirkungen von Bewegung auf die kardiorespiratorische Fitness und die Muskelkraft von HIV-Infizierten durch eine systematische Übersichtsarbeit und Meta-Analysen zu verstehen und 2)

zu bestimmen, ob HIV-positive Menschen, die Bewegung treiben, entwickeln einen Nicht-HIV-Komorbiditäten.

Die metaanalytische Untersuchung zeigt, dass sich die kardiorespiratorische Fitness (VO_{2max} SMD = 0.61 ml·kg·min^{-1}, 95 % CI: 0.35-0.88, $z = 4.47$, $p < 0.001$, $I^2 = 50$ %) und Kraft (Besonders in den unteren Extremitäten 16.8 kg, 95 % CI: 13–20.6, $p < 0.001$) nach einer Trainingsintervention im Vergleich zu einer Kontrollgruppe verbessert.

Querschnittdaten deuten darauf hin, dass Bewegung eine positive Wirkung auf die psychische Gesundheit den deutschen Menschen, die mit HIV leben hat (weniger Angst und depressive Symptome) und vor der Entwicklung von Angst (PR: 0,57, 95 % IC: 0,36 - 0,91, p = 0,01) und Depression (PR: 0,62, 95 % IC: 0,41 - 0,94, p = 0,01) schützt. Ebenso geht die Dauer der Bewegung mit einer geringeren Wahrscheinlichkeit für Herzrhythmusstörungen einher, (PR: 0,20, 95 % IC: 0,10 - 0,60, p < 0,01).

Eine vorläufige Empfehlung für deutsche Menschen, die mit HIV leben und die sich sportlich betätigen wollen, kann sein, ≥ 1-mal pro Woche mit einer Intensität von 5 METs und einer Dauer von ≥ 60 Minuten zu trainieren.

Dennoch sind weitere Forschungen erforderlich, um die Dosiswirkung und die schützende Wirkung von Bewegung auf Herz-Kreislauf-Erkrankungen, Angst und Depression bei deutschen Menschen, die mit HIV leben zu verstehen.

1. Introduction

The human immunodeficiency virus (HIV) has an incidence rate of 15.6/100,000 people across Europe (European Centre for Disease Prevention and Control & WHO Regional Office for Europe., 2020). In Germany, it is estimated that 90,700 people are living with HIV (PLWH), with 2,600 new cases diagnosed by 2019 (an der Heiden M et al., 2019).

Recent data indicates that the antiretroviral drugs treatment (ART) has changed HIV clinical progression from an acute and deadly disease to a chronic disease, extending life expectancy in younger people diagnosed with HIV (Deeks et al., 2013; European Centre for Disease Prevention and Control, 2018; Gueler et al., 2017; Trickey et al., 2017).

Despite the success of ART treatment, in the post-ART era, PLWH are increasingly exposed to diverse non-HIV comorbidities like metabolic and cardiovascular diseases (Collins et al., 2020; Duffau et al., 2015; Guaraldi et al., 2011; Zicari et al., 2019). An example is that German PLWH present a higher percentage of premature cardiovascular diseases (CVDs) compared to individuals without HIV (Christensen et al., 2019). The cause of these non-HIV comorbidities are traditional CVD risk factors (e.g. age, high waist-to-hip ratio) (Schouten et al., 2014) and the role of ART and HIV chronic inflammation (Triant, 2013; Worm et al., 2010), in addition to unhealthy behaviors like smoking (Tesoriero et al., 2010) and/or physical inactivity (Schäfer et al., 2017).

Further non-HIV comorbidities in PLWH include mental health disorders, most commonly anxiety and depression, which are more prevalent in PLWH compared to the HIV-negative population (Chibanda et al., 2014; Nurutdinova et al., 2012; Remien et al., 2019; Rueda et al., 2014). In German PLWH, the prevalence of anxiety and depression has been reported at 17.4 to 24.5% and 33.9 to 37.4%, respectively (Erdbeer, 2016; Steinke, 2013). The origin of depression and anxiety has been linked to the initial HIV diagnosis, ART, the burden of living with a chronic disease, internalized stigma, limited physical activity, and greater disability related to lower quality of life (QoL) in PLWH (Blanco et al., 2019; DeJean et al., 2013; Galantino et al., 2005; Liu et al., 2018; Martin et al., 2019; Shah et al., 2016; Zareifopoulos et al., 2020).

Altogether, HIV and non-HIV comorbidities are public health concerns, not only in Europe but also in Germany, which is why for newly diagnosed HIV cases the World Health Organization (WHO) recommends aside from prompt diagnosis and ART also optimized management of comorbidities in PLWH (Lundgren et al., 2008).

Exercise is known for its positive changes in fitness (cardiovascular and strength), beneficial effects in treating CVDs, reduced anxiety and depression symptoms, and protection against CVDs, anxiety, and depression in the general population (Aylett et al., 2018; Cheng et al., 2013; Dhaliwal et al., 2013; Dinas et al., 2011; Ferraro et al., 2020; Fiuza-Luces et al., 2018; Kamody et al., 2018; Karjalainen et al., 2015; Kodama et al., 2009; Kraus et al., 2019; Nystoriak & Bhatnagar, 2018; Patel et al., 2017; Bente Klarlund Pedersen & Saltin, 2015; Rahman et al., 2018; Schuch et al., 2018, 2019; Tian & Meng, 2019; Ward et al., 2015; Yong et al., 2017; Zhang et al., 2010)

Thus, the purpose of the present publication-based dissertation was to study the relation between exercise and CVDs, anxiety, and depression in German PLWH. This work begins with a brief review of the literature pertaining to 1) HIV, 2) HIV comorbidities, 3) exercise in the prevention of CVDs, anxiety, and depression in the general population, and 4) exercise in the prevention of CVDs, anxiety, and depression in PLWH. Following the review, the aim and hypothesis of this dissertation will be presented for 4 completed studies showing: the meta-analytical effects of exercise on PLWH's fitness, both 1) cardiorespiratory, and 2) muscle strength followed by exercise as potential protective factors in cross sectional data for 3) CVDs and 4) anxiety and/or depression in German PLWH.

2. Background

2.1. Human immunodeficiency virus (HIV)

The human immunodeficiency virus is a retrovirus of the lentivirus subfamily and can be classified as HIV-1 or HIV-2. HIV-1 is the most common type, with an estimated prevalence of 36.7 million PLWH globally. (Fauci et al., 2018).

In brief, the physiological process related to the disease is as follows: the HIV gp120 molecule expressed in the virus surface couples to the cluster of differentiation 4 (CD4) molecule and the co-receptor chemokine receptor (CCR5 or CCR4) present in the T-helper lymphocytes. The virus is then integrated into the host genome with the following transcription (via transactivator of transcription "Tat" protein) and viral messenger (m)RNA production. This allows the synthesis and assembly of the HIV structural proteins in the host cell and the formation of new virus particles (via negative factor "Nef" protein) that are later released to further infect other cells, ultimately producing an immunodeficiency (T-helper lymphocytes' dysfunction and depletion). (Fauci et al., 2018; Sviridov et al., 2020).

The diagnosis of HIV is based on the demonstration of antibodies against HIV and/or the direct detection of HIV or one of its components. Commonly used is the enzyme-linked immunosorbent assay (EILSA), considered a good screening test able to detect antibodies to either HIV-1/2 with a sensitivity of 99.5%. A second confirmation with a Western blot (identifies antibodies to HIV proteins specifically: p24, gp41, and gp120) or HIV plasma RNA level has significance in corroborating the HIV diagnosis (Fauci et al., 2018).

Treatment of HIV includes counselling, psychosocial support, screening for infections/related comorbidities, and ART (cornerstone of the medical treatment). Antiretroviral drugs can be classified into four categories: 1) inhibition of the viral reverse transcriptase enzyme (RTI), 2) inhibition of the viral protease enzyme (PI), 3) inhibition of the viral entry, and 4) inhibition of the viral integrase enzyme. A combination of ART (cART) should be administered to every HIV-positive person (Fauci et al., 2018). Monitoring of the HIV infection is achieved by measuring CD4+ T-cell count and viral load. CD4+ T-cell count (performed every 3-6 months) is generally recognized as an indicator of the immunological competence of PLWH. The viral load (plasma HIV RNA levels) should be measured every 3-4 months, as it entails meaningful clinical information pertaining to therapeutic decisions about ART initiation or change. Ideally, undetectable plasma viral load should be achieved (Fauci et al., 2018).

2.2. Non-HIV comorbidities

A variety of non-communicable diseases can be seen in PLWH, either as a primary manifestation of the HIV infection due to the persistent chronic immune activation and inflammation (result of numerous features including: thymic dysfunction, persistent antigen stimulation, co-infections, and cumulative ART toxicity in PLWH), adverse effects of ART, or aging, like cardiovascular, metabolic, renal, hepatic, and mental diseases (Bastard et al., 2019; Calza et al., 2016; Dimala et al., 2016; Duffau et al., 2015; Friis-Møller et al., 2003; Guaraldi et al., 2011; Lagathu et al., 2019; Mills et al., 2012; Mondy & Tebas, 2007; Pelchen-Matthews et al., 2018; Popoola & Awodele, 2016; Schouten et al., 2014; Sviridov et al., 2020; Worm et al., 2010). Diseases that are responsible for approximately 15% of PLWH deaths in developed countries (Christensen et al., 2019; Pelchen-Matthews et al., 2018).

2.2.1 Dyslipidemia

High blood levels of low-density lipoprotein (LDL) are characteristic of the HIV infection. Low blood high-density lipoprotein (HDL) is also present in PLWH (unaltered by ART) through impairment or deficiency of liver adenosine triphosphate binding cassette subfamily A member 1 (ABCA1, a primary component in HDL formation), targeted by the HIV protein Nef or indirectly by inflammation, oxidative stress, and immune deficiency. High triglyceride (TG) blood levels are also present in PLWH due to failed transfer of triglycerides from LDL to HDL, insulin resistance, and impairment of cholesterol metabolism. ART is also linked to lipid metabolism alteration in PLWH, especially RTI and PI (Capeau et al., 2021; Lagathu et al., 2019; McGettrick et al., 2020; Sviridov et al., 2020). The prevalence of high LDL is reported to be between 14 % and 24 %, whereas for hypertriglyceridemia the reported prevalence is between 9 % and 49 %, with a reported dyslipidemia prevalence between 24 % and 63% in PLWH (Alonso et al., 2019; Capeau et al., 2021; Gelpi et al., 2018; Mathabire Rücker et al., 2018; Reinsch et al., 2011; Smit et al., 2015). In German PLWH, the reported dyslipidemia prevalence is between 24 and 33 % (Christensen et al., 2019; Ponsel, 2019).

2.2.2 Diabetes mellitus Type 2 (DMT2)

Insulin resistance and β-cell insulin secretion impairment are the reasons for this comorbidity in PLWH. The physiological process leading to an altered glucose metabolism involves: 1) cholesterol metabolism alterations that diminish β-cells' ability to regulate insulin secretion in response to blood glucose concentration, 2) Nef proteins inhibiting glucose transporter type 4 (GLUT4) in β-cells, whereas lipid rafts alter these receptors in the skeletal muscles cells, 3) dyslipidemia, 4) weight gain with truncal adiposity, and 5) use of ART (PI) (Bastard et al., 2019; Capeau et al., 2021; Sarkar & Brown, 2000; Sviridov et al., 2020). The prevalence of T2DM in PLHW is between 4 % and 15 % and is 4 times more incident in PLWH compared to the general population (Alonso et al., 2019; Capeau et al., 2021; da Cunha et al., 2020; Duncan et al., 2018; Galaviz et al., 2018; Hasse et al., 2011; Mathabire Rücker et al., 2018; Noubissi et al., 2018; Reinsch et al., 2011; Smit et al., 2015). In German PLWH, the reported prevalence is between 8.4 % and 12 % (Christensen et al., 2019; Ponsel, 2019).

2.2.3 Atherosclerosis

Dyslipidemia proatherogenic characteristics and the inflammatory state present in HIV are related to the physiological process of atherosclerosis. Furthermore, the accumulation of cholesteryl esters in macrophages and smooth muscles cells of the vessel wall, with formation of foam cells, can be triggered by ABCA1 deficiency and lipid rafts (Sviridov et al., 2020). The prevalence of atherosclerosis in PLWH has been reported at between 26 % and 58 % in PLWH (D'Ascenzo et al., 2015; Ghosn et al., 2021).

2.2.4 Cardiovascular diseases (CVDs)

This comorbidity group features distinct disorders of the heart and blood vessels as follows: coronary heart disease (CHD), myocardial infarction (MI), transient ischemic attack/stroke, heart failure (HF), hypertension (HT), heart arrhythmias, atherosclerosis, and peripheral arterial disease (PAD) (AHA, 2017; WHO, 2011). CVDs are rising in PLWH and are responsible for more than 50% of deaths in PLWH (Alonso et al., 2019; Farahani et al., 2017; Feinstein et al., 2016, 2019). The risks for developing CVDs in PLWH is associated with a mixture of HIV infection, inflammation, ART, dyslipidemia, irregular coagulation/immune activation, and traditional CVD risk factors (i.e., age, smoking, high waist-to-hip ratio, etc.) (Feinstein et al., 2019; Friis-Møller et al., 2003; Hsue & Waters, 2019; McGettrick et al., 2020;

So-Armah et al., 2020; Triant, 2013). Of note is that PLWH are at risk of developing CVDs independently of traditional risk factors due to HIV in comparison to the general population (Guaraldi et al., 2011; Schouten et al., 2014; Triant, 2013). In PLWH, the reported prevalence of CVDs is 19 % (Alonso et al., 2019) and it is estimated that by 2030, 78% of PLWH will have one CVD (Smit et al., 2015). In German PLWH, the reported prevalence of CVDs is between 13 % and 43% (Christensen et al., 2019; Ponsel, 2019).

2.2.5 Hypertension

Aside from the traditional risk factors (T2DM, dyslipidemia, high body mass index (BMI), central obesity, older age, male gender, family history of CVDs or hypertension, chronic kidney disease, and cardiovascular events), the HIV proinflammatory state (mediated by: IL-6, IL-1β, IL-23, IL-17A, and IFN-γ), induced oxidative stress (through HIV proteins: Nef, gp120, and Tat), exposure to ART, altered immune response, and altered endothelia function are also related to the presence of hypertension in PLWH (Lima et al., 2017; Masenga et al., 2019; Xu et al., 2017). The prevalence of hypertension is between 20 % and 66% in PLWH (Alonso et al., 2019; Dimala et al., 2016; Hasse et al., 2011; Mathabire Rücker et al., 2018; Reinsch et al., 2011; Smit et al., 2015; Xu et al., 2017). In German PLWH, the reported prevalence of hypertension is between 29 and 55% (Christensen et al., 2019; Ponsel, 2019).

2.2.6 Mental disorders

The burden of HIV diagnosis comes with sadness and grief, followed by the pressure of living with a chronic disease and internalized stigma. Additionally, economic instability, reduced access to health, low schooling levels, underemployment, and substance and alcohol abuse are risk factors associated with the appearance of mental disorders in PLWH (Chibanda et al., 2014; Garrido-Hernansaiz & Alonso-Tapia, 2020; Rubin & Maki, 2019; Rueda et al., 2014, 2016). Low adherence to ART has also been linked with mental disorders in PLWH

(Rubin & Maki, 2019; Yehia et al., 2015). Furthermore, mental disorders lead to disability in PLWH (Rubin & Maki, 2019).

Two of the most prevalent mental disorders in PLHW are anxiety and depression (Steel et al., 2014), which can negatively impact the 10-year risk of developing CVDs in PLWH (Park et al., 2020). Anxiety in PLWH is related to HIV symptoms aside from the mentioned psychosocial aspects (Kemppainen et al., 2013). There is also data indicating the relation of HIV Tat protein to neuron toxicity and anxiety-like behaviors in pre-clinical models (Qrareya et al., 2021). A wide array of factors influence depression in PLWH, including the psychosocial factors named above, neurological alterations (neurocognitive impairment, HIV affection to the subcortical and fronto-striatal areas, atrophy of the basal ganglia, and central nervous system (CNS) opportunistic infections) chronic inflammation (elevated inflammatory cytokine in the CNS), physical limitations (fatigue and weakness), and ART (due to postulated alteration of the serotonergic system and increase inflammatory cytokines in the CNS) (Eshun-Wilson et al., 2018). The prevalence in PLWH of anxiety is 14% to 35% and 5% to 41% for depression (Camara et al., 2020; Chibanda et al., 2014; Liu et al., 2018; Ronel et al., 2018; Tesfaw et al., 2016). In German PLWH, the reported prevalence of anxiety and depression is 9.8% to 35% and 17% to 25%, respectively (Christensen et al., 2019; Erdbeer, 2016; Steinke, 2013).

2.3. Exercise CVDs and mental disorders in the general population

Available data indicates that exercise reduces overall-cause mortality (narrowly associated with CVD mortality) in the general population when exercise is performed: one session per week with a hazard ratio HR = 0.75 (95%CI: 0.60 – 0.82), 1-2 sessions per week HR = 0.66 (95%CI: 0.62 – 0.72), and ≥ 3 times per week HR = 0.65 (95%CI: 0.58 – 0.73) compared to sedentary people (O'Donovan et al., 2017). In addition, exercise reduces about

14% of the risk of developing CHD, with a relative risk RR= 0.86 (95% CI: 0.77 – 0.96), 22% for developing stroke with a RR = 0.78 (95% CI: 0.71 – 0.85), and 23% for developing heart failure with a RR=0.77 (95% CI: 0.70 – 0.85) compared to sedentary people (Aune et al., 2020; Sattelmair et al., 2011; Wendel-Vos, 2004).

Exercise effects CVDs at different biochemical and physiological levels; exercise upregulates peroxisome proliferator-activated receptor-γ, carnitine palmitoyl transferase-1, and medium-chain acyl-CoA dehydrogenase. Exercise also stimulates GLUT4 and hexokinase cellular levels and promotes glycogenesis and glycolysis, mechanisms that ultimately decrease insulin resistance and stimulate glucose uptake. Resistance to insulin results in a lower glucose intake and increased free fatty acid (i.e. triglycerides and VLDL) release, along with transfer of cholesteryl esters from HDL to triglyceride lipoproteins, overturning transport of cholesterol from the arterial wall. In addition, insulin resistance favors endothelin-1 (promotes vasocontraction) production and formation of glycation end products (favor arterial stiffening), fostering the formation of atherosclerosis by insulin resistance, a known factor for the development of CVDs. Exercise increases HDL, reduces TG plasma concentration, and seems to lower LDL plasma levels without influencing changes in cholesterol levels (Nystoriak & Bhatnagar, 2018; Tian & Meng, 2019).

Exercise induces vasodilatation by reducing oxidative stress and inflammatory intermediates. The net cellular ROS concentration is diminished, as exercise upturns antioxidant systems. Exercise also increases endothelial nitric oxide production (favors vasodilation) in response to higher blood flow and shear stress; heart rate variability and baroreflex sensitivity through stimulating the parasympathetic pathway of the autonomous nervous system are also improved by exercise. These mechanisms are thought to be responsible for blood pressure reduction, a long-term effect of exercise (Nystoriak & Bhatnagar, 2018; Pinckard et al., 2019; Tian & Meng, 2019).

Exercise prompts adaptative morphological changes in the heart (increase in ventricular wall thickness) by cardiac myocyte remodulation, with mitochondrial biogenesis and the ability to oxidate fatty acids instead of relying on glucose for energy production, enhancing contractile function. A higher cardiac output and better systolic and diastolic performance through enhanced cardiomyocyte contraction and relaxation force and velocity are mediated by an optimized efficiency between Ca2+ channels, subsarcolemmal ryanodine receptors, sarcoendoplasmic reticulum Ca2+ ATPase, and sodium calcium exchanger activation (Nystoriak & Bhatnagar, 2018; Pinckard et al., 2019).

Exercise improves tissue oxygen delivery (enhanced vasoactive response, expansion of the intramyocardial arterioles and capillaries, along with angiogenesis of collateral arterioles), safeguarding against ischemia-reperfusion injury (especially myocardium) by preventing oxidative damage to the mitochondria, decreasing the risk of ischemia-related cardiac dysfunction or death (Nystoriak & Bhatnagar, 2018; Pinckard et al., 2019).

Blood viscosity decreases with a decline in plasma fibrinogen and erythrocyte aggregation. Exercise downregulates calcium platelet concentration and increases cyclic guanosine monophosphate in platelets, diminishing its adhesion (Pinckard et al., 2019; Tian & Meng, 2019).

Finally, exercise improves antioxidant enzymes and redox status by inactivating ERK/AMPK pathways followed by a decreased expression of IL-6, high-sensitive CRP, TNF-α, and leucocyte differentiation antigen (Pinckard et al., 2019; Tian & Meng, 2019).

In mental disorders like anxiety and depression exercise reduces the symptoms (Heissel et al., 2019). In chronically ill persons exercise reduces anxiety symptoms by distracting the diverts symptoms (inner turmoil) people with anxiety experience (Pedersen & Saltin, 2015). Lower Depression symptoms, fewer depressive episodes relapse and a reduced risk of depression are present in exercising people by giving a sensation of normality, distracting from sad thoughts, mitigating fatigue, stimulating the hippocampus and neurohormones in depressive persons (Kandola et al., 2019; Pedersen & Saltin, 2015).

2.4. Exercise and non-HIV comorbidities prevalence in PLWH

Cardiovascular and metabolic diseases can be prevented by exercise; moreover, exercise is recommended as part of their treatment in the general population (Aune et al., 2020; Ferraro et al., 2020; Fiuza-Luces et al., 2018; O'Donovan et al., 2017; Yong et al., 2017). In PLWH, there is limited data concerning the protective effect of exercise on cardiovascular and metabolic comorbidities. Multimorbidity prevalence of cardiovascular and metabolic diseases has been reported at 6% in PLWH in the US; this prevalence varies depending on the exercise levels, being more prevalent in PLWH with very low exercise levels (prevalence of 40%) compared to PLWH with moderate (prevalence of 27%) and high exercise levels (prevalence of 24%) (Willig et al., 2020; Wong et al., 2018), taking into account that PLWH tend not to engage in exercise (Schäfer et al., 2017; Vancampfort et al., 2018). However, exercising PLWH exhibit significantly different lower glycation end products and waist circumference, in addition to lower but not significantly different total cholesterol, LDL, triglycerides, and fasting blood glucose levels compared to their sedentary counterpart (Rodrigues et al., 2018). These risk factors are known to intervene in the development of atherosclerosis and cardiovascular diseases.

The REPRIEVE trial stresses the anti-inflammatory, immunomodulatory, and cardioprotective properties of statins to prevent CVDs in PLWH (Grinspoon et al., 2019).

Exercise shows the same properties and thus prevents CVDs in the general population, which is why exercise effects can be transferred to PLWH to prevent the development of CVDs.

How exercise influences mental health in PLWH is an area of current research with only early and scarce results. Metanalytic data indicates that exercise reduces anxiety and depression symptoms in PLWH compared to sedentary PLWH. However, this data comes from a small number of studies (n=10) using physical training intervention in anxious or depressed PLWH (Heissel et al., 2019) and does not examine the effect of exercise on development of these mental disorders in PLWH. This is crucial, since data from the general population indicates that low cardiorespiratory fitness is related to a higher incidence of mental health disorders HR = 1.47 (95%CI: 1.23 – 1.76), anxiety HR = 1.48 (95%CI: 1.36 – 1.60), and depression HR = 1.64 (95%CI: 1.29 – 2.08) in comparison to high cardiorespiratory fitness (Kandola et al., 2019), understanding that PLWH during their lifespans have peculiar (low) cardiorespiratory fitness (Hand et al., 2009) that can be improved by exercise (Ozemek et al., 2020; Webel et al., 2019).

2.5. Conclusion

This literature review presented the basic understanding of HIV and non-HIV comorbidities along with the scarce available data on the protective effect of exercise on cardiovascular and mental disorders in PLWH. Briefly, exercise exerts a positive effect in PLWH's basal viral disease and non-HIV comorbidities. There is limited information from previous research dealing with exercise as a protective factor in relation to HIV and non-HIV comorbidities, despite the great amount of available knowledge on exercise's effects on the general population with and without chronic diseases, which in theory can be transferred to PLWH. These limitations need to be addressed to corroborate the finding that, just like the general population and other chronic diseases, exercise has a protective effect for non-HIV comorbidities, considering that HIV by itself plays a role in the development of non-HIV comorbidities aside from the traditional risk factors that are also present in PLWH. These will undoubtedly help to improve the understanding of exercise in PLWH and its relation to non-HIV comorbidities, helping to design more specific guidelines for exercise in the context of primary and secondary non-HIV comorbidity interventions.

3. Research objectives

Exercise has been recognized as a key factor in health maintenance and treatment of chronic diseases. Previous research suggests that exercise produces positive health adaptations in PLWH. However, there are no studies investigating whether exercise prevents non-HIV comorbidities (special CVDs, anxiety, and depression in PLWH), as it does in the general population. Therefore, the major aim of the present publication-based dissertation is to understand the relation exercise has with CVDs, anxiety, and depression in German PLWH.

To this end, a systematic review and meta-analysis of exercise (aerobic and strength training) effects on PLWH was first conducted. Second, a cross-sectional study investigated whether exercise prevents CVDs, anxiety, and/or depression in German PLWH.

3.1 Summary of study aims and objectives

Studies 1-2 (Systematic review and meta-analysis): the aim was to understand exercise effects in cardiorespiratory fitness (CRF) (Study 1) and muscle strength (Study 2) on PLWH. To do so the objective was to conduct a systematic review and meta-analysis of the change (improvement or not) in CRF or muscle strength in PLWH after three training interventions: aerobic, strength, or the combination of aerobic and strength training, in comparison to control groups.

Study 3 (Cross sectional study of exercise and CVDs in German PLWH): The aim was to investigate the likelihood of reporting CVDs in relation to exercise in German PLWH. The objective was to identify if exercising German PLWH-reported CVDs prevalence was lower and if the prevalence ratio (PR) was < 1, in comparison to sedentary German PLWH-reported CVDs.

Study 4 (Cross sectional study of exercise, anxiety and/or depression in German PLWH): The aim was to investigate the likelihood of German PLWH developing anxiety and/or depression in relation to exercise. The objective was to calculate if there was a lower prevalence and a PR < 1 of anxiety and/or depression in exercising German PLWH after the HIV diagnosis in contrast to sedentary German PLWH.

Included in this publication-based dissertation is one study published as an abstract and disclosed in a conference presentation (**Study 1 - Systematic review and meta-analysis of exercise and CRF in PLWH**), along with three studies that have been accepted for publication (**Study 2 - Systematic review and meta-analysis of exercise and strength in PLWH, Study 3 - Cross sectional study of exercising and Self-Reported Cardiovascular Diseases in German PLWH, and study 4 - Cross sectional study of exercise, anxiety and/or depression in German PLWH**) in peer-reviewed journals. Further details about the journals, study-design, participants, and measurements performed in each of the studies can be found in Table 2. Thus, the following chapters will present the methods, main results, and discussion of the four studies related to the present dissertation.

Table 1. Studies presented in the publication-based dissertation

Study	Journal	Participants	Measures	Annex
1	Med Sci Sports Exerc (peer reviewed)	17 included studies (n= 617 intervention subjects)	VO_2max 6MWT distance	1
2	Plos One (peer reviewed)	13 included studies (n= 246 intervention subjects)	lifted external resistance hormones	2
3	Int. J. Environ. Res. Public Health (peer reviewed)	Female (n=31) Male (414)	Reported CVDs Exercise: frequency, intensity, and duration.	3
4	AIDS care (peer reviewed)	Female (n=33) Male (415)	Anxiety and/or depression Exercise: frequency, intensity, and duration.	4

Note. VO2max: maximal oxygen comsuption, 6MWT: six-minute walk test, CVDs: cardiovascular diseases

4. Meta-analytical Studies (1 – 2)

4.1. Meta-analytical Studies (1 - 2) methodology

The first two studies (**Systematic review and meta-analyses**) share a similar methodology summarized as follows. A literature search of randomized clinical trials (RCTs), comparing strength training alone, aerobic exercise alone or the combination of both, performed more than twice per week and for at least four weeks against a non-exercising control group (CG), was performed by two independent reviewers. The RCTs had to include participants with HIV, older than 18 years, with or without co-morbidities, and investigate CRF (maximal oxygen consumption [VO_{2max}] or 6 minutes' walk test distance [6-MWT]) and strength (lifted external resistance in kg. or lbs.) as the primary outcomes (Pérez-Chaparro et al., 2017, 2018).

Studies without any non-exercising CG were excluded, and in the case of missing relevant data in the selected RCTs the authors were contacted via email (Pérez-Chaparro et al., 2017, 2018).

The meta-analyses followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). The risk of bias and quality of the included studies were assessed using the PEDro scale (Maher et al., 2003; Moher et al., 2009). The random-effect model (Borenstein et al., 2010; DerSimonian & Laird, 1986) was used to calculate the standard mean difference (SMD) and weighted mean difference (WMD) between intervention group (IG) and CG changes from baseline and post-intervention. High-quality studies' (PEDro score ≥ 5) (Schuch et al., 2016) subgroup analyses were carried out for CRF and strength outcomes. Further subgroup analyses for muscle strength only were performed for resistance training (RT) alone, aerobic exercise combined with resistance training (AERT), upper and lower body muscles, professional supervision of exercise, performing more than 150 minutes of exercise per week, excluding active CGs, and pre-ART (before or in the year 1996 (Schuch et al., 2018, 2019). A p value equal to or less than 0.05 was considered significant. Effect size interpretation was based on (Cohen, 1992). Heterogeneity interpretations were based on I^2 statistics and 95% CI (Higgins et al., 2003). In addition, differences across subgroups were explored by calculating the Chi square (χ^2). Publication bias was assessed by the Egger test (Egger et al., 1997). For further methodological details please refer to (Pérez-Chaparro et al., 2017, 2018).

4.2. Meta-analytical Studies (1 - 2) summarized results

4.2.1 Systematic review and meta-analysis of exercise effects on CRF in PLWH (Study 1)

Eight studies (of 14 total) investigated CRF outcomes in PLWH and had a PEDro-Score ≥ 6 after quality assessment. 13 studies assessed VO_{2max} and 4 studies 6-MWT. Compared to the CG exercise improved VO_{2max} (SMD = 0.61 ml·kg·min^{-1}, 95% CI: 0.35-0.88, z = 4.47, p

< 0.001, $I^2 = 50\%$) and the 6-MWT distance (SMD = 0.59 meters, 95% CI: 0.08-1.11, z = 2.25, p = 0.02, $I^2 = 63\%$) (Pérez-Chaparro et al., 2017).

4.2.2 Systematic review and meta-analysis of exercise effects on strength in PLWH (Study 2)

Eight studies (of 13 total) investigated muscle strength outcomes in PLWH and had a PEDro-Score ≥ 5 after quality assessment. To measure muscle strength, six studies used the 1-RM test, and three studies used the peak isometric force test. Exercise improved upper-body strength by 18 kg (95% CI: 11.2–24.8, p< 0.001) and lower-body strength by 16.8 kg (95% CI: 13–20.6, p< 0.001) in PLWH compared to the CG. Long-term effects (> 4 months) of exercise also showed improved upper-body strength by 13.7 kg (95% CI: 6–21.5, p < 0.001) and lower-body strength by 16 kg (95% CI: 11.6–20.4, p < 0.001) compared to the CG. AERT prompted a greater change in upper-body strength (19.3 kg, 95% CI: 9.8–28.8, p< 0.001) than that of the main meta-analysis and when compared to RT alone (17.5 kg, 95% CI: 16–19.1, p< 0.001). In contrast, RT alone provoked a higher change in lower-body strength (29.4 kg, 95% CI: 18.1–40.8, p< 0.001) than that of the main meta-analysis and when compared to AERT (10.2 kg, 95% CI: 6.7– 13.8, p< 0.001). Exercise intervention supervised by a professional improved lower-body strength by 19.5 kg (95% CI: 13.4–25.7, p< 0.001), which was higher than the main meta-analysis. After excluding pre-ART studies, upper-body strength improved by 19.9 kg (95% CI: 12.3–27.5, p < 0.001), which was also higher than that of the main meta-analysis (Pérez-Chaparro et al., 2018).

In general, the RCTs included in the meta-analyses had a wide range of heterogeneity (I^2 between 0 to 99%) and significant differences in terms of comorbidities, training intervention, training intensities, volume sessions, total minutes/week of exercise, and strength testing for the upper and lower muscle groups (Pérez-Chaparro et al., 2018). For detailed information, please refer to the supplementary files for Studies 1 and 2.

4.3. Meta-analytical Studies (1 - 2) discussion

4.3.1 Benefits of aerobic and/or strength exercise in PLWH fitness

Exercise is well-known for its benefits for health and fitness in the general population (Ashton et al., 2020; Ihalainen et al., 2018; Kyröläinen et al., 2018; Martin-Smith et al., 2020). Previous meta-analytic data has shown the benefits of exercise in PLWH, albeit with limited data (Gomes Neto et al., 2013, 2015; O'Brien et al., 2008, 2016, 2017). Therefore, a new systematic review and meta-analysis was warranted to gain a better understanding of exercise benefits for PLWH.

Exercise increases CRF in healthy people and those with a chronic disease (Andrade et al., 2019; Aune et al., 2020; Martin-Smith et al., 2020; Tarp et al., 2019; Williams et al., 2020). The updated meta-analytic data carried out in **Study 1** (**Systematic review and meta-analysis of exercise and CRF in PLWH**) indicates that CRF in PLWH increases after an exercise intervention, demonstrated by a better VO_{2max} against the CG. The data is in line with previously available results (Gomes Neto et al., 2013, 2015; O'Brien et al., 2008, 2016, 2017). A new contribution to the field is that the distance walked in the 6-MWT also increases after an exercise intervention against the CG, indicating a better CRF in PLWH; the 6-MWT is a well-used test to estimate CRF in patients with chronic diseases and is an alternative to the direct measurement of VO_{2max}, being less expensive and easier to apply in clinical settings (Bellet et al., 2012; Parry et al., 2021; Schmidt et al., 2013). Furthermore, as previously reported by O'Brien et al. (2017), exercise only showed a trend toward increasing leg-flexor muscle strength and a non-significant improvement on lower-extremity muscle groups in PWLH. By increasing the number of newly available studies in **study 2's** meta-analysis (**Systematic review and meta-analysis of exercise and strength in PLWH**), muscle-strength outcomes of the lower extremities like the leg press (six new studies), leg flexion (six new studies), and leg extension (five new studies) were significantly improved after an exercise intervention against the CG, especially by strength training.

Overall, the results of the meta-analytical studies indicate that, as expected, exercise has the same effects on PLWH as on the general population, and on those with a chronic disease by improving aerobic capacity and muscle strength, qualities related to a better health status in the general population.

5. Cross sectional Studies (3 – 4)

5.1. Cross sectional Studies 3 - 4 methodology

Studies 3 and 4 **(Cross sectional Studies)** share a similar methodology summarized as follows. Individuals were recruited from German institutions involved in HIV/AIDS care from October 2010 to December 2012. A survey was completed in hardcopy or online. Inclusion criteria were ≥18 years of age, diagnosed with HIV, and completed exercise questionnaire. Self-reported questionnaires were used to assess exercise, QoL, HIV and ART characteristics, the presence of CVDs (Atherosclerosis, CHD, DM, dyslipidaemia, heart arrhythmia, HF, HT, MI, PAD, and stroke, before or after the HIV diagnosis), and anxiety and/or depression after the HIV diagnosis. Participants reporting a CVD who also reported a medical prescribed pharmacological treatment consistent with the disease were classified as having a CVD. The EuroQoL 5-dimensions (EQ-5D) (Cooper et al., 2017) and the medical outcome study HIV surveys (MOS-HIV) (Wu et al., 1997) were used to assess QoL. Participants scoring 2-5 on dimension #5 on the EQ-5D were classified as having depression/anxiety. The survey investigated exercise (EXC), defined as "planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness" (Caspersen et al., 1985) performed at least once a week (O'Donovan et al., 2017) for more than three months (when positive health changes usually start, i.e. CRF) (Nolan et al., 2018). Exercise duration was measured in hours per week. Exercise frequency was measured in number of sessions per week. Exercise intensity was measured in metabolic equivalents of tasks (MET) or $MET \cdot min \cdot day^{-1}$. Each reported type of sport was converted into METs according to (Ainsworth et al., 2011). Participants were categorized as exercising or sedentary (Pérez-Chaparro et al., 2021; 2021b).

The immunological parameters of cluster differentiation four (CD4) white blood cell count was a self-report question. Body mass index (BMI) was calculated after the HIV diagnosis (there was no access to clinical records). Participants who did not answer the questions about exercise frequency, duration or type were excluded from the study (Pérez-Chaparro et al., 2021: 2021b).

A prior descriptive analysis indicated a non-normal distribution of the variables. The Mann-Whitney U test or the Kruskal–Wallis test was performed to evaluated differences for continuous variables between groups. The Chi-square test with a post-hoc analysis applying the Bonferroni correction (García & Núñez, 2003) was used to evaluate group differences for ordinal and nominal variables. Fisher's exact test was chosen in cases where frequencies were less than five. A Poisson regression with robust variance was performed to calculate the prevalence ratio (PR) and 95% confidence intervals (95% CI) (Barros & Hirakata, 2003) of CVDs, anxiety, and/or depression. The relationship between CVDs, anxiety, and/or depression and the different variables in the whole sample were analyzed as follows: the relationship to anthropometric characteristics in model 1; HIV and ART characteristics in model 2; physical/mental health summary scores and the EQ-5D health state index in model 3; exercise characteristics in model 4; and exercise status (exercising and sedentary) in model 5. The significance alpha level was set to < 0.05. (Pérez-Chaparro et al., 2021; 2021b).

The study was approved by the Charité Berlin ethics committee (Protocol No. EA1/084/11). Participants' data was anonymously collected following participants' informed consent. (Pérez-Chaparro et al., 2021; 2021b). For more information, please refer to the supplementary files for Studies 3 and 4.

5.2. Cross-sectional Study 3 - Exercising and CVDs in German PLWH summarized results

The majority of German PLHW (62.8%, n = 280) reported engaging in Exercise. Exercising German PLHW had a lower proportion of CVDs. However, there was a not significant difference between groups in the prevalence of CVDs as summarized in Table 2.

Arterial hypertension was the most frequent CVD with a higher but not significant prevalence in those German PLWH engaging in exercise. Of notice is that the prevalence of one or more CVDs was higher but not significantly in exercising German PLWH. Following the HIV diagnosis, older German PLWH were significantly more likely to report dyslipidemia and heart arrhythmia. Weight and BMI were related to a higher likelihood of DM, and weight only to heart arrhythmia, CHD and reporting more than one CVD (see table 3). Dyslipidemia, arterial hypertension, atherosclerosis, and CHD likelihood was higher for every increase in years living HIV. Exercising German PLWH did not have a lower likelihood of reporting one or more than one CVD compared to sedentary German PLWH. However, exercising German

PLWH were less likely to report DM for every increase of exercise session per week and heart arrhythmias for every increase in exercise duration as described in table 3. For more information, please refer to the supplementary files for Study 3.

5.3. Cross-sectional study 3 - Exercise and CVDs in German PLWH discussion

In the post-ART era, non-HIV comorbidities, especially CVDs, are becoming more prevalent in PLWH (Alonso et al., 2019; Feinstein et al., 2019; Mathabire Rücker et al., 2018; McGettrick et al., 2020; Ryom et al., 2018), in part because PLWH have a higher coronary heart disease risk (Bergersen et al., 2004; McGettrick et al., 2020). Therefore, a prompt intervention against non-HIV comorbidities is recommend in PLWH (Feinstein et al., 2019; McGettrick et al., 2020).

Exercise is recommended for the prevention and treatment of CVDs, in particular CVDs, in the general population (Aune et al., 2020; Fiuza-Luces et al., 2018; Tarp et al., 2019). Existing information on the effects of exercise on CVDs in PLWH is scarce and, to the best of the author's knowledge, no studies have addressed whether the protective effect of exercise is transferrable to CVDs in PLWH since the pathophysiology is not comparable to that in the general population as previously rationalized.

In Study 3 (**exercise and CVDs in German PLWH)** findings show that aside from the traditional CVDs risk factors (i.e. age, body weight, and BMI), PLWH have a higher likelihood of reporting dyslipidemia, arterial hypertension, atherosclerosis, and CHD, for every increase in years living with HIV. (Pérez-Chaparro et al., 2021b).

Since PLWH are predisposed to sudden cardiac death in part due to more arrhythmias compared to non-HIV (Brouillette et al., 2019), a noteworthy outcome from this study is that

PLWH had a decreased likelihood of reporting an arrhythmia for every increase in hours of exercise per week. (Pérez-Chaparro et al., 2021b).

Table 2. *CVDs prevalence in German PLWH*

Parameter	Sedentary n = 166	Exercise n = 280	Total	X^2	df	*p* Value
Dyslipidemia, n (%)				1.12	2	> 0.05°
Pre-HIV	2 (1.2)	1 (0.3)	3			
Post-HIV	4 (2.4)	7 (2.5)	11			
Diabetes, n (%)				0.61	2	> 0.05°
Pre-HIV	1(0.6)	0	1			
Post-HIV	2 (1.2)	1 (0.3)	3			
Hypertension, n (%)				0.43	2	> 0.05
Pre-HIV	10 (6)	14 (5)	24			
Post-HIV	8 (4.8)	11 (3.9)	19			
Atherosclerosis, n (%)				5.67	2	> 0.05°
Pre-HIV	3 (1.8)	0	3			
Post-HIV	0	1 (0.3)	1			
PAD, n (%)				1.69	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	1 (0.6)	0	1			
Heart failure, n (%)				1.69	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	0	1 (0.3)	1			
Heart arrhythmias, n (%)				2.87	2	> 0.05°
Pre-HIV	1(0.6)	0	1			
Post-HIV	0	2 (0.6)	2			
CHD, n (%)				1.21	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	2 (1.2)	1 (0.3)	3			
MI, n (%)				0.17	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	2 (1.2)	3 (60)	5			
Stroke, n (%)				0.59	1	> 0.05°
Pre-HIV	0	1 (100)	1			
Post-HIV	0	0	0			

Note. Data presented in number of participants (n) and percentage (%), Chi square (χ^2), degrees of freedom (df), coronary heart disease (CHD), myocardial infarction (MI), peripheral arterial disease (PAD). Table modified from Pérez-Chaparro et al., 2021b.

The study also found that PLWH had a decreased likelihood of reporting diabetes mellitus for every increase in exercise session per week, explained by the effects of exercise in stimulating GLUT4 (inhibited by HIV Nef protein), decreasing insulin resistance, and increasing β-cell insulin secretion (impaired in PLWH) (Pedersen & Saltin, 2015; Sviridov et al., 2020).

However, a positive effect of exercise was not corroborated for other CVDs reported in German PLWH by Study 3 (**exercise and CVDs in German PLWH**). A potential reason is the persistent chronic inflammatory state and hastened aging in PLWH, factors that could attenuate the exercise effect. (Pérez-Chaparro et al., 2021b).

Since no clear evidence exists that exercise can prevent CVDs in German PLWH, further research needs to be done by means of a prospective longitudinal cohort study to elucidate whether in fact exercise can prevent CVDs in PLWH after the HIV diagnosis. (Pérez-Chaparro et al., 2021b).

5.4. Cross-sectional Study 4 - Exercise, anxiety and/or depression in German PLWH summarized results

German PLWH engaging in exercise accounted for more than half of the sample (58%, n = 450), of whom 33% started exercising after the HIV diagnosis and 25% were engaged in exercise prior to the HIV diagnosis (Pérez-Chaparro et al., 2021).

Table 3. *Risk of reporting CVDs in relation to anthropometric characteristics, HIV and ART, EXC characteristics, and exercise in German PLWH.*

Variables	Atherosclerosis pots HIV			Arterial Hypertension post HIV			Coronary heart disease post HIV			Diabetes Mellitus post HIV		
	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*
Model 1												
Age (yrs.)	0,90	0.8 - 1.1	0,43	1,00	1 - 1,1	0,21	0,80	0.7 - 1.1	< 0.01	1,10	1 - 1,2	0,64
Weight (kg)	1,00	0.8 - 1.3	0,16	1,00	0.9 - 1.1	0,82	1,20	1 - 1,3	< 0.01	1,20	1.2 - 1.4	< 0.01
BMI (kg/m^2)	0,80	0.3 - 1.6	< 0.01	1,10	0.9 - 1.4	0,14	0,80	0.5 - 1.1	< 0.01	1,10	1 - 1,1	< 0.01
Model 2												
Years since the HIV diagnosis (yrs.)	1,20	1 - 1,4	< 0.01	1,10	1 -1,2	< 0.01	1,20	1.1 - 1.5	< 0.01	1,10	1 - 1,2	0,47
Model 3												
Frequency (session · $week^{-1}$)	0,90	0.4 - 1.4	0,30	0,70	0,4 - 1	0,09	1,10	0.7 - 1.4	0,05	0,40	0,1 - 1	< 0.01
Intensity (MET · min · day^{-1})	1,00	1 – 1.1	< 0.01	1,00	0.9–1	0,02	1,00	1–1.1	< 0.01	1,00	0.9–1	0,62
Duration (hrs · $week^{-1}$)	1,00	0.9 - 1.3	< 0.01	1,00	1 - 1,2	< 0.01	1,00	0.8 - 1.3	< 0.01	1,00	0.6 - 1.3	< 0.01
Model 4												
Exercise	-	-	-	0,80	0,3 - 2	0,63	0,30	0,1 - 3	0,31	1,20	0.1 - 25.3	0,88
Sedentary	-	-	-	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Note. Prevalence ratio (PR), 95% confidence interval (95% CI), Body mass index (BMI), Exercise intensity expressed in metabolic equivalent of task (METs), reference group (Ref), Not possible to calculate (-). Table taken from Pérez-Chaparro et al., 2021b.

Table 3. *Risk of reporting CVDs in relation to anthropometric characteristics, HIV and ART, EXC characteristics, and exercise in German PLWH. (Continue)*

Variables	Dyslipidemia post HIV			Heart Arrhythmias post HIV			Myocardial infarction post HIV			> 1 Cardiovascular disease pot HIV		
	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*
Model 1												
Age (yrs.)	1,10	1 - 1,1	0,01	1,20	1 - 1,4	< 0.01	1,00	0.9 - 1.2	0,84	1,00	1 - 1,2	0,90
Weight (kg)	1,00	0.96 - 1.1	0,50	1,30	1 - 1,6	< 0.01	1,00	0.0 - 1.2	0,32	1,10	1 - 1,2	< 0.01
BMI (kg/m^2)	1,00	0.86 - 1.2	0,75	0,70	042 - 1,1	0,03	0,90	0.5 - 1.5	0,63	0,90	0.6 - 1.2	0,08
Model 2												
Years since the HIV diagnosis (yrs.)	1,10	1 - 1,1	0,02	1,00	0.9 - 1.2	0,34	1,10	1 - 1,3	0,08	1,10	1 - 1,2	0,14
Model 3												
Frequency (session · week^{-1})	1,00	0.5 - 1.3	0,81	1,60	0.90 - 2.5	< 0.01	1,00	0.7 - 1.2	0,80	1,10	0.9 - 1.2	0,06
Intensity (MET · min · day^{-1})	1,00	0.9–1	0,43	1,00	0.9–1	< 0.01	1,00	0.9–1	0,19	1,00	1–1.1	0,08
Duration (hrs · week^{-1})	1,00	0.8 - 1.1	0,53	0,20	0.1 - 0.6	< 0.01	1,20	0.9 - 1.5	0,05	1,00	0.6 - 1.3	0,72
Model 4												
Exercise	1,00	0.3 - 3.9	0,95	-	-	-	0,90	0.1 - 6.7	0,90	0,60	0.1 - 2.5	0,45
Sedentary	Ref	Ref	Ref	-	-	-	Ref	Ref	Ref	Ref	Ref	Ref

Note. Prevalence ratio (PR), 95% confidence interval (95% CI), Body mass index (BMI), Exercise intensity expressed in metabolic equivalent of task (METs), reference group (Ref), Not possible to calculate (-). Table taken from Pérez-Chaparro et al., 2021b.

Anxiety prevalence was higher in the sedentary group (21.6%) vs. the Exe group (12.7%), χ^2=6.3; df=1; p=0.01. Depression prevalence was also higher (25.8%) in the sedentary group compared to the exercise group (16.5%), χ^2=5.7; df=1; p=0.01. No significant group differences were found for comorbid anxiety and depression prevalence (14.7% vs. 12.3%) (Pérez-Chaparro et al., 2021).

The MOS-IV and EQ-5D QoL scores were significantly lower in sedentary German PLHW compared to those engaging in exercise. Exercising German PLHW had significantly fewer anxiety and depression symptoms compared to sedentary counterparts. Results are summarized in Table 4. There were no significant differences in QoL scores and the EQ-5D anxiety/depression dimension categories among depressed and/or anxious German PLWH engaging in exercise compared to sedentary ones (Pérez-Chaparro et al., 2021).

Exercising German PLHW were less likely to develop anxiety (PR: 0.57, 95%IC: 0.36 – 0.91, p = 0.01) and depression (PR: 0.62, 95%IC: 0.41 – 0.94, p = 0.01) and comorbid anxiety and depression (PR: 0.43, 95%IC: 0.24 – 0.75, p = < 0.01) compared to sedentary German PLWH. In particular, for German PLWH exercising at higher intensity (METs), this exercise characteristic conferred a lower likelihood of developing depression (PR: 0.80, 95%IC: 0.64 – 1, p = 0.04) (Pérez-Chaparro et al., 2021). For more information, refer to the supplementary files for Study 4.

Table 4. *MOS-HIV and EQ-5D questionnaires*

Parameter	Sedentary	Recreational exercise	X^2	Df	*p* value
PHSS (median, IQR)	49.5 (20.5 – 65.1)	56.7 (17.6 - 63.4)			< 0.05
MHSS (median, IQR)	44.4 (13.7 – 66.9)	51.6 (13.5 – 67.1)			< 0.05
EQ-5D HIS (median, IQR)	0.909 (0.156 – 1)	0.910 (0.127 - 1)			< 0.05
EQ-5D VAS (median, IQR)	70 (5 - 100)	85 (11 - 100)			< 0.05
Anxiety / depression (n, %)			14.6	4	0.005
no problems	67 (34.2)	129 (65.8) *			
slight problems	59 (34.4)	77 (56.6)			
moderate problems	40 (50)	40 (50)			
severe problems	21 (65.6)	11 (34.4) *			
extreme problems	3 (50)	3 (50)			

Note. Chi square (χ^2), degrees of freedom (Df), physical health summary score (PHSS), mental health summary score (MHSS), EQ-5D health state index (HSI), EQ-5D visual analog score (VAS). Dimension categories: (1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems, and (5) extreme problems. Group participants: overall n = 450; sedentary n = 190; recreational exercise n = 260. Significant differences at the 0.05 level between recreationally exercising and sedentary PLWH (*). Table taken from Pérez-Chaparro et al., 2021.

5.5. Cross-sectional study 4 - Exercise, anxiety and/or depression in German PLWH discussion.

As previously outlined, exercise produces positive physical health changes in PLWH like it does in the general population. Research indicates that exercise likewise produces positive changes in mental wellbeing in the general population (Aylett et al., 2018; Chung et al., 2017; Dziubek et al., 2016; A. Kandola et al., 2019, 2019b; Kim et al., 2019; Quiles et al., 2017; Rahman et al., 2018; Schuch et al., 2018, 2019). This is also the case in PLWH, according to a recently published meta-analysis, where symptoms of anxiety and depression were reduced in PLWH after an exercise intervention compared to a control group (Heissel et al., 2019).

Similarly, exercise prevents the development of anxiety and depression in the general population and people with a chronic disease (Chung et al., 2017; Kim et al., 2019; Schuch et al., 2018, 2019). For this reason, Study 4 (**exercise, anxiety and/or depression in German PLWH**) investigated whether these positive changes on mental health in PLWH were transferable, as according to the author's understanding, no studies investigated the preventive properties of exercise against anxiety and depression in PLWH.

In line with previously available data on the general population, exercise has a positive effect on PLWH's mental health. Study 4 (**exercise, anxiety and/or depression in German PLWH**) found that the rates of anxiety and depression were lower in physically active compared to sedentary PLWH. This is an important aspect, since anxiety and depression are related to a worse quality of life in PLWH (Bagheri et al., 2019; Ronel et al., 2018) and fewer anxiety and depression symptoms are related to a better QoL in PLWH (Heissel et al., 2019; Quiles et al., 2017). Quality of life is an important aspect in PLWH, as it has been shown to influence antiretroviral therapy (ART) success (Uthman et al., 2014), the cornerstone treatment in HIV. Altogether, results indicate that exercise can be considered a protective factor against anxiety and depression in German PLWH, enhance QoL, and positively effect mental health in German PLWH (Pérez-Chaparro et al., 2021).

6. Main dissertation discussion

The main aim of this publication-based dissertation was to investigate the relation between exercise and it´s characteristics to CVDs, anxiety and/or depression in German PLWH. Therefore, this dissertation started with studies 1 and 2 (**systematic review and meta-**

analyses) showing the benefits of aerobic and/or strength exercise in PLWH in a meta-analytical investigations, followed by studies 3 and 4 (**cross-sectional studies**) comparing exercising against sedentary German PLWH conducted to determine the prevalence and PR of reporting a CVD, anxiety and/or depression in German PLWH.

Exercise positively influences PLWH fitness status and at the same time appears to lower the likelihood of heart arrhythmias, diabetes mellitus, and positive effect mental health, as it lowers the likelihood of and protects against anxiety and depression in German PLWH. (Pérez-Chaparro et al., 2018, 2021, 2021b)

In brief, results from this publication-based dissertation support the reasoning behind recommending exercise for PLWH (Bull et al., 2020). The basic exercise recommendations (extrapolated from Studies 3 **(exercise and CVDs in German PLWH)** and study 4 (**exercise, anxiety and/or depression in German PLWH)** can include: exercise ≥ 1 time per week at an intensity of approximately 5 METs, for a duration ≥ 60 minutes per week. (Pérez-Chaparro et al., 2021, 2021b)

However, the exact exercise dose relation (frequency, amount, and duration of exercise) to prevent CVDs, anxiety, and/or depression needs to be further investigated by means of a prospective longitudinal cohort study.

6.1. Implications

Aerobic and/or strength training exercise interventions unequivocally increase CRF and muscle strength, and reduce the likelihood of anxiety, depression, and arrythmias in German

PLWH. Higher CRF and strength together with better autonomic regulation and anxiolytic and anti-depressive effects delivered by exercise can impact PLWH's daily living.

Exercise recommendations for HIV people were established only in the past year by the WHO (Bull et al., 2020). These recommendations were extrapolated from the general population and transferred to PLWH, making it the first step in standardizing type, intensity, and duration of exercise. Nevertheless, as with any other chronic disease, special attention to the disease pathophysiology and comorbidities needs to be considered to provide safe and accurate exercise guidelines suitable for PLWH.

The present publication-based dissertation results agree with the WHO's current exercise recommendations (150-300 min of moderate-intensity aerobic exercise at an intensity of 3-6 METs, or 75-150 min of vigorous-intensity aerobic exercise at an intensity > 6 METs per week, plus muscle strengthening for major muscle groups 2 or more days per week) (Bull et al., 2020). We add to these recommendations, especially for German PLWH, exercise at least once a week at an intensity of ≥ 5 METs, for a duration ≥ 60 minutes per week to attain the outlined positive health effects in German PLWH (Pérez-Chaparro et al., 2021, 2021b). This information is instrumental at the time of recommending and prescribing exercise interventions in German PLWH.

Because exercise protects against anxiety and depression in German PLW, exercise should be discussed as treatment after the HIV diagnosis if patients are characterized as sedentary or do not achieve the above-mentioned recommendations.

Finally, exercise as a protective factor against CVDs in comparison to sedentary PLWH is of great value in the treatment of non-HIV comorbidities. To clarify whether exercise diminishes the likelihood of CVDs in German PLWH, the next recommended research step should be to perform a prospective longitudinal study using objective indices measuring the amount of exercise performed and, when possible, controlling for equally gender-balanced groups and using a unique type of training.

6.2. Limitations

First, in studies 1 and 2 (**Systematic review and meta-analyses**) a wide range of heterogeneity was found, even after exploring for potential sources of heterogeneity, for the meta-analyses. In addition, the presence of a publications bias on the systematic review was stablished for chest press, leg press and leg flexion (Pérez-Chaparro et al., 2018). Second, although the sample from study 3 **(exercise and CVDs in German PLWH** and study 4 (**exercise, anxiety and/or depression in German PLWH)** was predominantly male with a distribution representative for PLWH (Reinsch et al., 2011), exercise's anti-depressive effects vary among HIV-negative females and males (Bhui & Fletcher, 2000; Zhang & Yen, 2015). Furthermore, European women with HIV are less likely to have CVDs (Pelchen-Matthews et al., 2018). Second, the assessment for non-HIV comorbidity (CVDs, anxiety, and depression) prevalence and risk factors were based on self-report measures, including retrospective evaluations. Sole reliance on self-report may therefore have increased the risk of recall and social desirability bias. Third, exercise was not objectively assessed through accelerometry or a standard validated physical activity questionnaire, such as the International Physical Activity Questionnaire (IPAQ). Rather, exercise was assessed using self-administered questions regarding exercise taking place in participants' leisure time without considering the exercise carried out during worktime. Fourth, due to the cross-sectional nature of the study, it is not possible to determine causality between variables found to be significantly associated with each other. Finally, due to the cross-sectional design, the incidence of anxiety, depression, and CVDs could not be determined, thus limiting understanding of the comorbidity trends that have emerged (Pérez-Chaparro et al., 2021, 2021b).

6.3. Summary

This publication-based dissertation demonstrates that exercise has positive effects on German PLWH's health. Exercise should be recommended after the HIV diagnosis to achieve physical (better CRF and muscle strength) and mental benefits (circumvent anxiety or depression) and potentially avoid heart arrhythmias and diabetes mellitus. A preliminary recommendation for German PLWH can be to engage in exercise ≥ 1 time per week, at an intensity of ≥ 5 METs per session, for a duration ≥ 60 minutes per week to acquire health benefits. Nevertheless, further research is needed to understand exercise-dose response and protective effects for CVDs, anxiety, and depression in German PLWH (Pérez-Chaparro et al., 2018, 2021, 2021b).

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Author's contribution

The present manuscript is designed as a cumulative dissertation. In this regard, four scientific articles have been prepared and submitted to peer-reviewed journals. All studies have been already accepted and published. According to the local doctoral degree regulations (§ 7 (4), sentence No. 2), significant contributions to the articles from the respective co-authors were acknowledged and finally confirmed by each co-author.

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Study	**Design**	**Data collection**	**Data analyses**	**Interpretation**	**Manuscript**
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Appendix

List of tables

Abbreviations

6MWT: six minutes test

95%CI: 95% confidence interval

ABCA1: adenosine triphosphate blinding cassette subfamily A member 1

AERT combination of aerobic exercise and resistance training

AIDS: acquired immunodeficiency syndrome

ART: antiretroviral therapy

BMI: body mass index

cART: combination of ART

CCR: co-receptor chemokine

CD4: cluster of differentiation 4

CG: control group

CHD: coronary heart disease

CRF: cardiorespiratory fitness

CRP: c reactive protein

CVDs: cardiovascular diseases

Df: degrees of freedom

ELISA: enzyme-linked immunosorbent assay

EQ-5D: EuroQoL 5-dimensions

ERK/AMPK: Extracellular signal-regulated kinase/ AMP-activated protein kinase

EXC: exercise

GLUT4: glucose transporter type 4

HDL: high density lipoprotein

HF: heart failure

HSI: health state index

HIV: human immunodeficiency virus

HR: hazard ratio

HT: hypertension,

I^2: Statistical heterogeneity

IFN-γ: Interferon gamma

IG: intervention group

IGF-1: insulin-like growth factor 1

IL: interleukin

IPAQ: International Physical Activity Questionnaire.

IQR: interquartile range

LDL: low density lipoprotein

MET: metabolic equivalent of task,

MHSS: mental health summary score

MI: myocardial infarction

MOS-HIV: medical outcome study-HIV survey

Nef: negative factor

PAD: peripheral vascular disease

PEDro-scale: Physiotherapy Evidence Database-Scale

PHSS: physical health summary score

PI: protease enzyme inhibitors.

PLWH: people living with HIV

PR: prevalence ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QoL: quality of life

RCTs: Randomized controlled trials

Ref: reference group

RNA: ribonucleic acid strand

RNA(m): messenger ribonucleic acid strand

ROS: reactive oxygen species

RR: relative risk

RT: resistance training

RTI: reverse transcriptase inhibitors

SMD: standardized mean differences

T2DM: Type 2 diabetes mellitus

Tat: trans-activator of transcription

TG: triglycerides

TNF-α: tumor necrosis alpha

VAS: visual analogue score.

VO_{2max}: Maximum oxygen consumption

WHO: world health organization

WMD: weighted mean difference

Z: Z-score,

χ^2: Chi-square

Supplementary papers

Study 1 Abstract conference paper

Effects Of Aerobic & Resistance Training On Cardiorespiratory Fitness In People Living with HIV. A Meta-analysis

Weblink: https://bit.ly/3BLgAM9

Study 2 Published scientific paper

Effects of aerobic and resistance exercise alone or combined on strength and hormone outcomes for people living with HIV. A meta-analysis

Weblink: https://bit.ly/3SqGJad

Study 3 Published scientific paper

Recreational exercise is associated with lower prevalence of depression and anxiety and better quality of life in German people living with HIV

Weblink: https://bit.ly/3DM1KHL

Study 4 Published scientific paper

Recreational Exercising and Self-Reported Cardiometabolic Diseases in German People Living with HIV: A Cross-Sectional Study

Weblink: https://bit.ly/3BECQqR

- Study 1 -

Effects Of Aerobic & Resistance Training On Cardiorespiratory Fitness In People Living with HIV. A Meta-analysis

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The life expectancy of people living with HIV (PLWH) is increasing due to advancements in anti-retroviral drug therapy. For this reason, PLWH are increasingly facing age-related comorbidities. Higher cardiorespiratory fitness is associated with lower risks for cardiovascular and metabolic diseases. Prior meta-analyses have focused on the effect of exercise in PLWH investigating VO2max in a small amount of available studies. This meta-analysis represents a large number of included studies and will be the first investigating the 6-Minute Walk Distance additionally.

PURPOSE: To assess the effects of aerobic exercise alone or in combination with resistance training on cardiorespiratory fitness (Maximal Oxygen Consumption (VO2max) and performance in the 6-minute walk test (6MWT) in PLWH.

METHODS: Two authors (CPC and PAZ) independently performed a systematic literature search for relevant articles in six web-based databases. Only randomized controlled trials (RCTs) were included. The Physiotherapy Evidence Database-Scale (PEDro-scale) was used to rate the quality level of the studies and to assess the risk of bias. A meta-analysis was performed and standardized mean differences (SMDs) were calculated for each outcome and assessed for heterogeneity.

RESULTS: A total of 335 articles were found. After screening, a total of 14 articles were selected with three more articles added after cross referencing, leading to a total of 17 included studies (n= 617 subjects after intervention). Only 8 of the selected studies had a PEDro-Score ≥ 6 after quality assessment. 13 studies assessed VO2max and 4 studies 6MWT. The random-effect model was used. Exercise significantly improved VO2max (SMD = 0.61 $ml \cdot kg^{-1} \cdot min^{-1}$, 95% CI: 0.35-0.88, $z = 4.47$, $p < 0.001$). After exercise intervention, 6MWT distance also increased significantly (SMD = 0.59 meters, 95% CI: 0.08-1.11, $z = 2.25$ ($p = 0.02$). Heterogeneity of VO2max and 6MWT between included studies was $I^2 = 50\%$ and $I^2 = 63\%$, respectively.

CONCLUSION: Performing aerobic exercise alone or in combination with resistance training can lead to significant improvements in outcomes of cardiorespiratory fitness (VO2max and 6MWT) in PLWH and could therefore be a protective factor for PLWH dealing with multiple comorbidities.

- Study 2 -

Effects of aerobic and resistance exercise alone or combined on strength and hormone outcomes for people living with HIV. A meta-analysis.

Effects of exercise on PLWH strength and hormones: A meta-analysis.

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Abstract

Background

Infection with human immunodeficiency virus (HIV) affects muscle mass, altering independent activities of people living with HIV (PLWH). Resistance training alone (RT) or combined with aerobic exercise (AE) is linked to improved muscle mass and strength maintenance in PLWH. These exercise benefits have been the focus of different meta-analyses, although only a limited number of studies have been identified up to the year 2013/4. An up-to-date systematic review and meta-analysis concerning the effect of RT alone or combined with AE on strength parameters and hormones is of high value, since more and recent studies dealing with these types of exercise in PLWH have been published.

Methods

Randomized controlled trials evaluating the effects of RT alone, AE alone or the combination of both (AERT) on PLWH was performed through five web-databases up to December 2017. Risk of bias and study quality was attained using the PEDro scale. Weighted mean difference (WMD) from baseline to post-intervention changes was calculated. The I^2 statistics for heterogeneity was calculated.

Results

Thirteen studies reported strength outcomes. Eight studies presented a low risk of bias. The overall change in upper body strength was 19.3 Kg (95% CI: 9.8 - 28.8, p< 0.001) after AERT and 17.5 Kg (95% CI: 16 – 19.1, p< 0.001) for RT. Lower body change was 29.4 Kg (95% CI: 18.1 – 40.8, p< 0.001) after RT and 10.2 Kg (95% CI: 6.7 – 13.8, p< 0.001) for AERT. Changes were higher after controlling for the risk of bias in upper and lower body strength and for supervised exercise in lower body strength. A significant change towards lower levels of IL-6 was found (-2.4 ng/dl (95% CI: -2.6, -2.1, p< 0.001).

Conclusion

Both resistance training alone and combined with aerobic exercise showed a positive change when studies with low risk of bias and professional supervision were analyzed, improving upper and, more critically, lower body muscle strength. Also, this study found that exercise had a lowering effect on IL-6 levels in PLWH.

Introduction

According to the Joint United Nations Program on HIV/AIDS, 17 million people living with HIV (PLWH) receive anti-retroviral drug therapy worldwide [1]. This is noteworthy because early use of combined anti-retroviral drug therapy (ART) has been shown to increase life expectancy by ~ 43.1 years [2]. Thus, human immunodeficiency virus (HIV) has changed from an acute and fatal disease into a chronic disease that comprises a greater proportion of persons older than 50 years [3].

Human immunodeficiency virus (HIV) infection affects not only the immune system [4], but also the musculoskeletal system. In particular, PLWH present pre-sarcopenia or sarcopenia [5]. Other associated muscle problems like myalgia are twice as common among PLWH, with or without receiving ART treatment [6] . Low bone mineral density (BMD) is also directly affected by HIV infection, due to the virus and/or use of ART, which stimulates osteoclastic activity and decreases osteoblast activity, affecting BMD in naive ART people [7]. These changes to the musculoskeletal system may be mediated by changes in interleukins, cortisol or testosterone[8–10] and result in a decreased capacity to carry out activities of daily life [11].

Resistance exercise training both alone (RT) and combined with aerobic exercise (AERT) is linked to improved BMD [12], muscle mass and strength maintenance, complemented by weight gain[13–15] and fewer episodes of falls [16] in the general population. These exercise benefits in PLWH have been the focus in different systematic reviews and meta-analyses [17–21]. Gomes Neto et al. [18] showed an improvement (WMD = 25.1 kg, $p < 0.001$) in knee extensor muscle strength (n= 2 studies) after AE intervention. This finding is in line with those of O´Brien et al.'s [20,21] meta-analysis showing a significant improvement (WMD = 10.5 kg 1-RM, $p < 0.001$) in knee flexion strength (n= 3 studies) after AERT intervention. However, O´Brien et al.´s [20,21] reported a non-significant improvement in other lower extremity muscle groups through resistance training combined with aerobic exercise. Subgroup analyses were only performed by O-Brien et al. [21] dealing with testosterone supplementation, with a non-significant improvement in knee flexion/extension strength (n= 2 studies). Nevertheless, these results need to be interpreted carefully because of the low number of investigated studies. Also, previous studies [22–24] have suggested that the length of the intervention and supervision by exercise professionals may moderate the benefits of exercise on physical and mental health outcomes. However, none of the previous meta-analyses have investigated whether or not longer interventions and the supervision of exercise modify the effects of exercise on PLWH.

This systematic review and meta-analysis explored the effects of exercise on body strength and hormonally levels in PLWH after resistance alone or combined with aerobic exercise intervention. Likewise, other physiological parameters (i.e. cortisol, testosterone) related to strength and HIV were analyzed. This is of importance in this systematic review, since no meta-analyses have addressed this matter to date. Finally, subgroup analysis for each exercise intervention, upper and lower body muscles, professional supervision of exercise, performing more than 150 minutes of exercise per week, and controlling for active control groups and high-quality studies (PEDro score ≥ 5) were conducted in compliance with the Cochrane meta-analysis standards.

Methods

This systematic review and meta-analysis was registered in the PROSPERO international prospective register of systematic reviews (CRD42018087004) and performed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25].

Eligibility criteria

Randomized controlled trials (RCTs) comparing resistance training alone, aerobic exercise alone or aerobic exercise in combination with resistance training against a non-exercising control group (CG) were considered for inclusion. The studies had to include participants with HIV at any stage of the infection process, older than 18 years, with or without co-morbidities, and investigate strength outcomes (lifted external resistance in kg or lbs) as the primary outcome and hormones (i.e. testosterone) related to the muscular system as secondary outcomes, in response to exercise. Aerobic exercise was defined according to the American College of Sports Medicine (ACSM) as "any activity that: uses large muscle groups, can be maintained continuously, and is rhythmic in nature" [26], and resistance training was outlined as "a form of physical activity that is designed to improve muscular fitness by exercising a muscle or a muscle group against external resistance" [27]. Both exercises had to be performed more than two times per week as described by Gomes Neto et al. [18] rather than three times per week as in O´Brien et al. [21], and for at least four weeks. Studies administering steroid supplementation to the IGs and/or CGs were excluded due to the possibility of an additional effect on muscle strength. Other forms of exercise (e.g. tai chi, qi gong) were not considered because tai chi interventions varied in the tai chi practiced forms [28] and homogeneity among the types of exercise performed by the IGs needed to be achieved.

Studies investigating two exercising groups without any non-exercising control groups were considered to be excluded because an exercising control group could lead to a significant improvement in muscle strength, resulting in a decreased ability of the intervention group (IG) to demonstrate minimal changes. Not necessarily physical activities (placebo-treated, social contact exercise recommendations, counseling, recreational activities) and very light physical activity groups, were considered to be active CGs. Groups following their usual activity and explicitly not exercising were considered to be passive CGs.

Literature search strategy for study identification

A literature search was performed using five databases (clinicaltrials.gov, PEDro physiotherapy evidence database, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science), restricted to English-language studies published up to the end of December 2017. Two reviewers (CP and PZ) individually screened and recorded the relevant citations following the above eligibility criteria and recorded them in a standard data format. After selecting the relevant citations by title, the abstracts were screened. After fulfilling both previous steps, full texts were obtained and evaluated. In case of disagreement, both authors discussed their differences until reaching an agreement. If this was not possible, a third author (AH) was consulted to determine the final decision.

Search parameters and syntax were adapted to each database's requirements. Text words and Combined Medical Subject Headings (MeSH) terms were related to exercise and physiological parameters. The search strategy is presented in Table 1.

Table 1. Systematic search strategy

Database	Combined MeSH terms and text words
PubMed	(HIV) OR (human immunodeficiency virus) AND (exercise OR exercise therapy OR physical activity OR aerobic exercise OR resistance training) AND (hormone OR testosterone OR cardiovascular OR strength OR fitness OR physiological) AND (randomized controlled trial OR randomized OR clinical trials)
Cochrane library	("HIV" OR "human immunodeficiency virus") AND ("exercise" OR "physical activity" OR "aerobic exercise" OR "resistance training" OR "exercise therapy") AND ("hormone" OR "testosterone" OR "cardiovascular" OR "strength" OR "fitness" OR "physiological" AND "randomized controlled trial")
Clinicaltrials.gov	(HIV infection HIV AND exercise AND physiologic OR muscle) and (HIV AND exercise AND cardiovascular)
PEDro physiotherapy evidence database	(HIV exercise muscle) or (HIV exercise cardiovascular) or (HIV exercise hormones)
Web of Science	(HIV AND exercise)

Data collection

Data was extracted by both reviewers (CP and PZ) independently, using a standard digital sheet form. Measuring units were independently converted by the two reviewers (CP and PZ), pounds (lbs) to kilograms (kg) and mmol/l to pg/dl. Outcomes reported as Mean ± standard error or Mean change (post minus pre) ± standard error were converted into mean ± standard deviation. In case of missing relevant data in the selected studies, the original authors were contacted via email asking for the required missing information. If two weeks passed without an answer from the author, the author was kindly reminded and the co-authors were contacted via email. If the author did not answer our emails, then the study was left out of the quantitative synthesis.

Risk of bias and quality of included studies

CP and PZ individually assessed the risk of bias and the quality of the included studies using the PEDro scale [25,29]. Every PEDro criterion had to be clearly met and described in the selected study. The PEDro scale consists of eleven criteria in which the first "criterion of eligibility" is marked with a "yes" or "no." If the study had no eligibility criteria, the study was excluded. The rest of the criteria were marked with a checkmark or a "0." The possible PEDro score range is from 0 to 10. Discrepancies on the studies' PEDro score between the two reviewers were resolved by a third author (AH). The results of the quality and risk of bias assessment of the included articles are shown in Table 2 in the Results section.

Studies with a PEDro score ≥ 5 where categorized as high-quality studies, because blinding might be difficult to achieve and maintain for various reasons and is less frequently reported in non-pharmacological treatment RCTs [30,31]. Moreover, Moseley et al. [32] investigated the number of RCTs available in the PEDro database that satisfied the blinding criteria (subject blinding, therapist blinding or assessor blinding) and found a low prevalence of blinding, with 5% using blinded therapists, 9 % blinded subjects and only 34% blinded assessors. For these reasons, the total PEDro score for RCTs involving exercise interventions can be affected and thus a PEDro score lower than six can be attained even if the other criteria are satisfied.

Statistical analysis

The random effect model [33,34] was used to calculate the weighted mean difference (WMD) between intervention and control group changes from baseline and post-intervention. When the change was not available, the change (mean pre-intervention minus mean post-intervention) and the standard deviation according to the Cochran handbook for systematic reviews of interventions [35] were calculated. Parameters were analyzed for upper and lower body strength as well as hormones. Subgroup analyses were performed for resistance training (RT) alone, aerobic exercise combined with resistance training (AERT), upper and lower body muscles, professional supervision of exercise, performing more than 150 minutes of exercise per week, excluding active CGs, pre ART-era, and high-quality studies (PEDro score ≥ 5) [23]. A p value equal to or less than 0.05 was considered significant. Interpretation of the effect size was done with the most commonly used cut-off defined by Cohen [36], d= .20 small, .50 medium and .80 large.

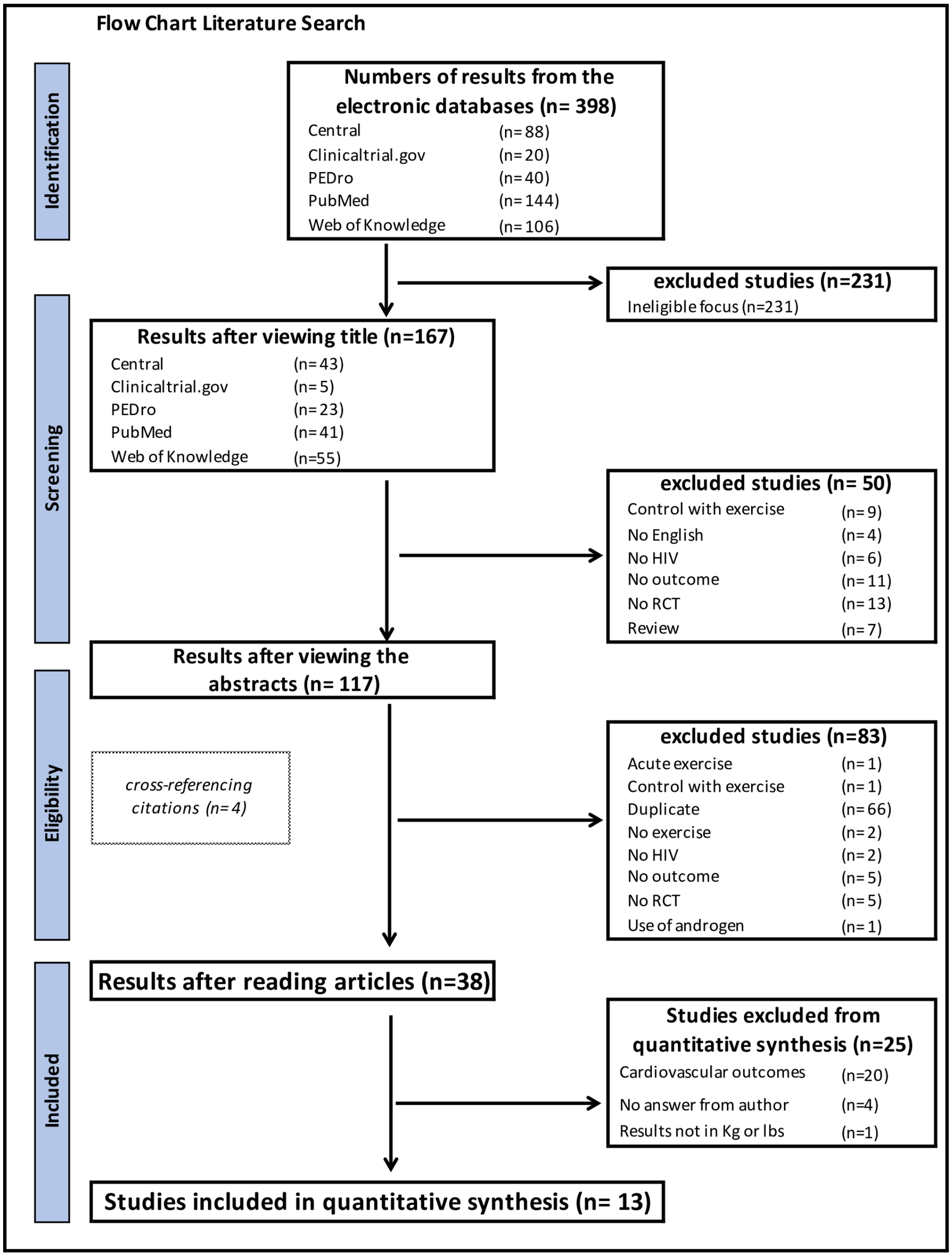
To test for heterogeneity, the I^2 statistics and 95% CI [37] was calculated. Values between 25-50% reflect low, 50%-75% moderate, and values greater than 75% reflect high heterogeneity [37]. To explore the heterogeneity, this meta-analysis looked for differences across subgroups by calculating the Chi square (χ^2). Publication bias was assessed by the egger´s test [38]. All analyses were performed using Review Manager Version 5.3 [39].

Results

Search description of selected studies

A total of 398 citations through the search criteria from the databases described in the Methods section where retrieved. After screening the titles, 231 citations were excluded due to ineligible focus. Of the remaining 167 studies, 50 were excluded for the following reasons: exercise was performed by the control group (n= 9), the language was other than English (n= 4), the intervention or control groups were partially or totally integrated with HIV seronegative participants (n= 6), the searched outcomes were not addressed (n= 11), or the citations referred to non- RCTs (n= 13) or reviews (n= 7). The remaining 117 citations were screened before full texts were acquired; 66 citations were duplicates. 51 studies' full texts were read and 17 studies had to be excluded: in one study, the intervention groups performed only one bout of exercise [40], one study's control group performed exercise [41], two studies did not investigate exercise [42,43], two studies' intervention or control groups were partially or totally integrated with HIV seronegative participants [44,45], five studies did not investigate the desired outcomes [46–50], five were not RCTs [51–55] and one study administered nandrolone [56]. In total, 34 studies from the systematic search and four studies added by cross-referencing citations met the eligibility criteria and were considered relevant for inclusion in the meta-analysis. In total, 13 studies reported strength outcomes and were included in the quantitative analysis. Of these, four studies [57–60] reported strength and hormone outcomes (See Fig. 1).

Figure 1. Search and selection of studies from the systematic review according to PRISMA



Characteristics of studies excluded from quantitative synthesis

Following our search strategy, five studies [61–65] were excluded due to incomplete data or because the requested data was not available. See excluded studies in Table S1, Information on excluded and included studies.

Description of the studies included in the meta-analysis

Of the 13 included studies, eight studies [57,60,66–71] were classified as high-quality studies (see Table 2), four studies investigated RT [57,60,66,72] and eight studies AERT [58,59,67–71,73]. The studies of Lox et al. [74] and [72] shared the same two intervention groups and results: one group performed AE alone and the other RT alone, with the exact same number of control group participants in both studies. Thus, for the purpose of analysis we decided to treat Lox et al. [74] as an AE-only intervention and Lox et al. [72] as an RT-only intervention. Passive CGs were identified in six studies [58,60,67,68,71,73] and one with no lifestyle modification [71]. Seven studies had active CGs, three studies CGs performed very low-intensity physical activity like walking or stretching [70,72,74], one study [66] applied protein supplementation 1 $g \cdot kg^{-1} \cdot day^{-1}$ to the CG, and three studies [57,59,69] administered testosterone placebo injections to the CGs. Characteristics of all the included studies can be seen in Table S1.

Characteristics of studies included in the meta-analysis

The number of participants included in the 13 studies were for the intervention group n= 249 at baseline and n= 246 post-intervention, whereas for the control group n= 1216 at baseline and n= 210 at the end of the study. Eight studies had a mean dropout rate of 10.7 ± 12.1%. Two studies reported no dropouts [60,68] and three studies [72–74] only reported participants who completed the study. The mean age for the control group was 42 ± 5.7 years and for the intervention group 42.9 ± 5.3 years. Five studies [60,66,67,69,71] included 42 women in the control group and 41 women in the intervention group. Seven studies recruited only male subjects [57–59,68,70,72,74]. Only the study by Mendes et al. [73] did not report the age and gender of the participants. The average baseline CD4 cell count was reported in 12 studies [57–60,66–72,74]. For the CGs was 432.2 ± 147.9 cells·μl^{-1} and for the IGs 431.5 ± 167 cells·μl^{-1}. Five studies included participants with health-related conditions aside from HIV [57,67,69–71]. Two studies included participants with AIDS wasting syndrome [57,59], one study lipodystrophy [67], one study low testosterone levels [57], two studies metabolic diseases [69,71] and one study included participants with functional limitations [71] .

Table 2. PEDro scale, quality assessment of included trials in the systematic review

Study	EC	I	II	III	IV	V	VI	VII	VIII	IX	X	Total
Agin D. 2001	Y	✓	✓	✓	0	0	0	0	0	✓	✓	5
Bhasin S. 2000	Y	✓	0	✓	0	0	✓	0	✓	✓	✓	6
Dolan S. 2006	Y	✓	0	✓	0	0	0	✓	✓	✓	✓	6
Dudgeon WD. 2012	Y	✓	0	✓	0	0	0	0	0	0	✓	3
Farinatti PT. 2010	Y	✓	0	✓	0	0	✓	✓	✓	✓	✓	7
Fitch K. 2012	Y	✓	0	✓	0	0	✓	0	✓	✓	✓	6
Grinspoon S. 2000	Y	✓	0	0	0	0	0	0	0	✓	✓	3
Lox CL. 1995	Y	✓	0	0	0	0	0	✓	0	✓	✓	4
Lox CL. 1996	Y	✓	0	0	0	0	0	✓	0	✓	✓	4
Mendes EL. 2013	Y	✓	0	0	0	0	0	0	0	✓	✓	3
Pérez-Moreno F. 2007	Y	✓	✓	✓	0	0	✓	0	0	✓	✓	6
Shah KN. 2016	Y	✓	✓	✓	0	0	✓	✓	0	✓	✓	7
Zanetti HR. 2016	Y	✓	0	✓	0	0	0	✓	0	✓	✓	5

EC, eligibility criteria; I: allocated randomization of subjects to groups; II: concealed allocation; III: similarities of groups at baseline; IV: blinding of subjects; V: blinding of researchers/evaluators; VI: blinding of assessors; VII: measure of at least one key outcome obtained from more than 85% of subjects initially allocated to groups; VIII: intention to treat; IX: comparison results between groups; X: measured at least one key outcome at two time points; ✓, criterion is present otherwise; 0, criterion is missing.

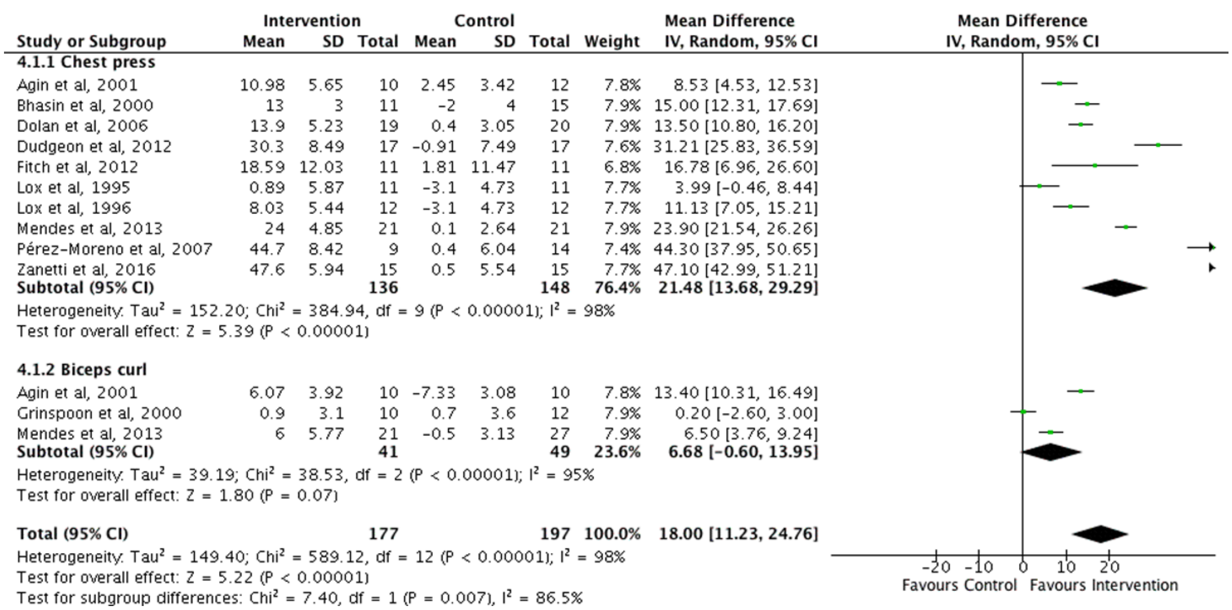
Nine studies reported strength outcomes without hormone outcomes [66–74]. Two studies [57,59] reported strength outcomes and testosterone. Three studies [57–59] reported strength outcomes and free testosterone. The study by Dudgeon et al. [58] reported strength outcomes, cortisol and insulin-like growth factor 1 (IGF-1). Two studies [58,60] reported strength outcomes and pro-inflammatory interleukins (IL-6 and IL-1β). The study by Fitch et al. [69] reported strength outcomes and c-reactive protein (CRP). Long-term effects (> 4 months) of exercise were identified on three [66,69,73] of the 13 included studies.

The 1-RM test used to measure muscle strength was reported in six studies [57,60,66,67,69,73] and the peak isometric force test was used in three studies [59,72,74]. Characteristics of all the included studies can be seen in Table S1.

Risk of bias

According to the risk of bias analysis, eight studies scored ≥ 5 in the PEDro scale, specifying a low risk of bias. Five studies presented a high risk of bias with a PEDro score < 5. See Table 2.

Figure 2. Upper body strength changes after exercise in PLWH



Changes on body strength in PLWH

All types of repetition maximum (1-RM, 3-RM, 6-RM and 12-RM) were included. No details on the type of machine used to perform the RM test was mention in the included studies. See Table S1.

Two overall meta-analyses (see Figs. 2 and 3) and 34 subgroup analyses were performed. The overall change after intervention on upper body strength in PLWH from baseline was 18 kg (95% CI: 11.2 – 24.8, $p < 0.001$) favoring the IG. Lower body strength also increased by 16.8 kg (95% CI: 13 – 20.6, $p < 0.001$) favoring the IG. Sub-analysis revealed a significant increase on lifted weight for each muscle group, favoring the IG. After long-term exercise, IG upper body strength showed a significant change 13.7 kg (95% CI: 6 – 21.5, $p < 0.001$). This was also true for IG lower-body strength with a mean change of 16 kg (95% CI: 11.6 – 20.4, $p < 0.001$), but significant changes were only for leg flexion and extension long-term exercise muscle groups (See Table 3).

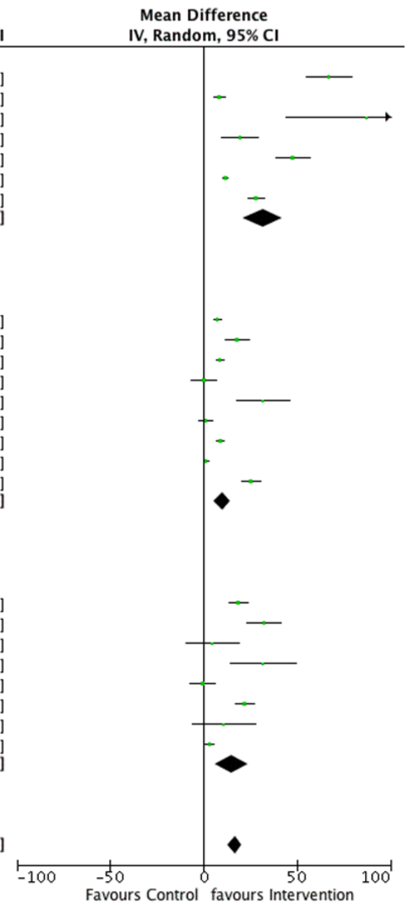
Eight studies had a PEDro score ≥ 5. This sub-analysis revealed a greater change in IG upper body strength of 22.6 kg (95% CI: 12.5 – 32.7, $p < 0.001$) and 20.1 kg (95% CI: 14.7 – 25.4, $p < 0.001$) for lower body strength, compared to the two main meta-analyses.

Aerobic exercise combined with resistance training prompted a greater change in IG upper body strength of 19.3 kg (95% CI: 9.8 - 28.8, $p < 0.001$) compared to RT alone, where the change was only 17.5 kg (95% CI: 16 – 19.1, $p < 0.001$). In contrast, RT alone provoked a higher change in IG lifted lower body weight by 29.4 kg (95% CI: 18.1 – 40.8, $p < 0.001$), while the change in aerobic exercise combined with resistance training was only 10.2 kg (95% CI: 6.7 – 13.8, $p < 0.001$). Only the study of Lox et al. (95) reported strength changes from aerobic exercise alone, with a difference after intervention in the IG of 0.9 kg, with a small effect size of 0.02 for the upper body strength and 12.8 kg with a moderate effect size of 0.59 for the lower body strength.

Professional supervision was reported for upper body strength in seven studies. Only the chest press muscle group was reported in these studies, with a significant change in the IG of 17.9 kg (95% CI: 10.5 – 25.3, p < 0.001).

Figure 3. Lower body strength changes after exercise in PLWH

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.1.1 Leg press								
Bhasin et al, 2000	72	14	11	5	16	12	3.4%	67.00 [54.74, 79.26]
Farinatti et al, 2010	9.3	6.43	19	0.8	0.26	8	5.0%	8.50 [5.60, 11.40]
Fitch et al, 2012	87.08	63.18	11	0	34.42	10	0.7%	87.08 [44.08, 130.08]
Lox et al, 1995	12.85	16.29	11	-6.65	2.92	10	3.9%	19.50 [9.70, 29.30]
Lox et al, 1996	41.14	15.44	12	-6.65	2.92	10	4.0%	47.79 [38.87, 56.71]
Mendes et al, 2013	11.7	3.82	21	0.2	0.5	27	5.1%	11.50 [9.86, 13.14]
Zanetti et al, 2016	31.4	9.2	15	3.3	1.33	15	4.8%	28.10 [23.40, 32.80]
Subtotal (95% CI)			**100**			**92**	**26.9%**	**31.75 [21.15, 42.35]**
Heterogeneity: Tau² = 169.33; Chi² = 196.36, df = 6 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 5.87 (P < 0.00001)								
5.1.2 Leg flexion								
Agin et al, 2001	8.98	3.36	10	1.73	0.08	10	5.1%	7.25 [5.17, 9.33]
Bhasin et al, 2000	18	10.87	11	0	0.3	12	4.5%	18.00 [11.57, 24.43]
Dolan et al, 2006	8.4	4.35	19	-0.3	2.17	19	5.1%	8.70 [6.51, 10.89]
Dudgeon et al, 2012	10.34	14.59	17	10.3	0.2	11	4.4%	0.04 [-6.90, 6.98]
Fitch et al, 2012	33.56	19.55	11	1.81	12.9	10	3.0%	31.75 [17.70, 45.80]
Grinspoon et al, 2000	0.8	4.1	10	-0.4	4.8	12	4.9%	1.20 [-2.52, 4.92]
Mendes et al, 2013	9	5.27	21	0.1	0.1	27	5.1%	8.90 [6.65, 11.15]
Shah et al, 2016	1.4	3.96	28	0.26	0.09	31	5.1%	1.14 [-0.33, 2.61]
Zanetti et al, 2016	25.6	10.01	15	0.3	0.21	15	4.7%	25.30 [20.23, 30.37]
Subtotal (95% CI)			**142**			**147**	**42.1%**	**9.88 [5.55, 14.21]**
Heterogeneity: Tau² = 37.00; Chi² = 146.97, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 4.47 (P < 0.00001)								
5.1.3 Leg extension								
Agin et al, 2001	20.92	7	10	2.27	3.32	10	4.8%	18.65 [13.85, 23.45]
Dolan et al, 2006	33.2	19.17	19	0.8	6.53	19	4.0%	32.40 [23.29, 41.51]
Dudgeon et al, 2012	14.29	24.73	17	9.7	13.7	11	3.0%	4.59 [-9.68, 18.86]
Fitch et al, 2012	32.2	27.07	11	0.45	12.09	10	2.4%	31.75 [14.08, 49.42]
Grinspoon et al, 2000	0	7	10	0.7	9.2	12	4.5%	-0.70 [-7.48, 6.08]
Mendes et al, 2013	21.7	11.78	21	-0.4	4.3	27	4.7%	22.10 [16.81, 27.39]
Pérez-Moreno et al, 2007	11.1	25.57	9	0.3	6.84	10	2.5%	10.80 [-6.43, 28.03]
Shah et al, 2016	3.42	6.24	28	0.25	3.28	31	5.1%	3.17 [0.59, 5.75]
Subtotal (95% CI)			**125**			**130**	**31.0%**	**14.91 [6.13, 23.69]**
Heterogeneity: Tau² = 133.28; Chi² = 98.35, df = 7 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 3.33 (P = 0.0009)								
Total (95% CI)			**367**			**369**	**100.0%**	**16.81 [13.01, 20.62]**
Heterogeneity: Tau² = 72.74; Chi² = 538.36, df = 23 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 8.66 (P < 0.00001)								
Test for subgroup differences: Chi² = 14.16, df = 2 (P = 0.0008), I² = 85.9%								



Eight studies reported a change in lower body strength under professional supervision in the IG of 19.5 kg (95% CI: 13.4 – 25.7, p< 0.001), which was higher than the main meta-analysis. See Table 3.

After excluding studies pre-ART era, performed or published before or in the year 1996 [75], a significant change in the IG's upper body strength (19.9 kg [95% CI: 12.3 – 27.5], p < 0.001) and lower body strength (15.1 kg [95% CI: 11.4 – 18.8], p < 0.001) was found, where the result for IG upper body strength was higher than that of the main meta-analysis.

Table 3. Body strength changes from baseline in PLWH

Category	*n* trials (*n* participants)	Change (kg)		Overall effect	Heterogeneity
		WMD	95% CI	Z (*p*)	I^2
Upper body strength					
Chest press	10 (284)	21.5	13.7–29.2	5.4 (< 0.00001)	98%
Biceps curl	4 (90)	6.7	-0.6–13.9	1.8 (0.07)	95%
Long-term exercise					
Chest press	3 (86)	16.4	4.8–28.1	2.8 (0.0006)	95%
Biceps curl	2 (68)	9.9	3.1–16.7	2.9 (0.004)	91%
High-quality studies					
Chest press	6 (162)	24.2	11.9–36.5	3.8 (< 0.0001)	98%
AERT					
Chest press	5 (160)	25.9	16.8–35.1	5.5 (< 0.00001)	96%
Biceps curl	2 (70)	3.4	-2.8–9.5	1.1 (0.29)	90%
RT					
Chest press	4 (102)	18.9	17.2–20.7	21 (< 0.00001)	99%
Professional supervision					
Chest press	7 (190)	17.9	10.5–25.3	4.8 (< 0.00001)	96%
Post-ART era					
Chest press	8 (238)	25	16.3–33.7	5.6 (< 0.00001)	98%
Biceps curl	4 (90)	6.7	-0.6–13.9	1.8 (0.07)	95%
Only passive controls					
Chest press	4 (145)	28.8	15.8–41.9	4.3 (< 0.00001)	98%
Lower body strength					
Leg press	7 (192)	31.7	21.1–42.3	5.9 (< 0.00001)	97%
Leg flexion	9 (289)	9.9	5.5–14.2	4.5 (< 0.00001)	95%
Leg extension	8 (255)	14.9	6.1–23.7	3.3 (0.0002)	93%
Long-term exercise					
Leg press	2 (69)	46.1	-27.7–119.9	1.2 (0.22)	92%
Leg flexion	3 (89)	10.3	5.5–15	4.2 (< 0.0001)	83%
Leg extension	3 (89)	20.9	16.7–25	9.9 (< 0.00001)	19%
High-quality studies					
Leg press	4 (101)	41.1	19.1–63.1	3.6 (0.0003)	98%
Leg flexion	6 (191)	13.5	7.4–19.7	4.3 (<0.0001)	96%
Leg extension	5 (157)	18.7	6.3–31.2	2.9 (0.003)	94%
AERT					
Leg press	3 (96)	11.6	5.4–17.8	3.7 (0.0002)	87%
Leg flexion	6 (216)	6.2	1.7–10.7	2.7 (0.007)	93%
Leg extension	7 (235)	14.4	4.2–24.5	2.8 (<0.00001)	93%
RT					
Leg press	3 (75)	47	25.2–68.9	4.2 (< 0.0001)	95%
Leg flexion	3 (73)	16.7	4.4–29	2.7 (0.008)	96%
Professional supervision					
Leg press	4 (93)	35.3	9–61.7	2.6 (0.009)	98%
Leg flexion	4 (109)	8.5	4.5–12.4	4.2 (< 0.0001)	80%
Leg extension	4 (105)	18	7.5–28.6	3.3 (< 0.0008)	77%
Post-ART era					
Leg press	6 (149)	29.9	18.5–41.4	5.1 (< 0.00001)	97%
Leg flexion	9 (289)	9.9	5.5–14.2	4.5 (< 0.00001)	95%
Leg extension	8 (255)	14.9	6.1–23.7	3.3 (0.0009)	93%
Only passive controls					
Leg press	3 (105)	15.8	7.4–24	3.7 (0.0002)	96%
Leg flexion	5 (203)	8.8	2.6–15	2.8 (0.006)	96%
Leg extension	4 (173)	15.7	1.1–30.3	2.1 (0.03)	96%

Subgroup analyses are presented in random effect model. Panel includes *n* trials (*n* participants), weighted mean difference (WMD), 95% confidence interval (95% CI), Z-score (Z) and significance (*p*) of exercise vs. control conditions. Statistical heterogeneity (I^2). AERT = aerobic exercise combined with resistance training, RT = resistance training, ART = antiretroviral therapy. Not able to calculate (NA)

Analysis of IG body strength, after excluding studies using active control groups, found a significant change for upper body strength (24.3 kg [95% CI: 12 – 36.7], $p < 0.001$) and lower body strength (12.8 kg [95% CI: 8.8 – 16.8], $p < 0.001$), although the results from the main meta-analyses were higher for lower body strength. Upper and lower body strength heterogeneity was high (> 75%) for the two main meta-analyses and all sub-analyses. See Table 3.

Hormone changes in PLWH

After screening the included studies, this meta-analysis found that three studies reported inflammatory markers (IL-6,IL-1ß, CRP) and given their relation to the muscular system they were included in the following section.

Out of the three studies that reported hormone outcomes in PLWH, two studies [58,59] had a high risk for bias with a PEDro score ≥ 5. Two studies reported testosterone [57,59], three studies free testosterone [57–59] and two studies interleukin-6 and interleukin-1ß [58,60]. All studies reported that samples were taken in a fasting state at the same time of day and in a rested state. For characteristics of the studies, please refer to Table S1.

Four overall analyses and four sub-meta-analyses were performed. There were no significant differences between IG and CG from baseline to post-intervention in PLWH for total testosterone, and the range of change was widely spread across the main meta-analyses. Likewise, free testosterone and IL-1ß also presented a non-significant change between IGs and CGs after intervention (see Table 4).

Table 4. Hormone changes from baseline in PLWH

Category	*n* trials (*n* participants)	Change		Overall effect	Heterogeneity
		WMD	95% CI	Z (*p*)	I^2
Testosterone (ng/dl)	2 (45)	40.8	-20.8–102.5	1.3 (0.19)	0%
Free testosterone (pg/dl)	3 (73)	-3	-8–2.1	1.1 (0.25)	0%
AERT	2 (50)	-3.4	-8.8–2	1.2 (0.21)	0%
Professional supervision	2 (51)	0	-11.4–11.5	0 (0.99)	0%
IL-6 (pg/ml)	2 (58)	-2.4	-2.6, -2.1	18.6 (< 0.00001)	0%
Only passive controls	2 (58)	-2.4	-2.6, -2.1	18.6 (< 0.00001)	0%
IL-1β (pg/ml)	2 (58)	-0.2	-3–2.6	0.1 (0.88)	71%
Only passive controls	2 (58)	-0.2	-3–2.6	0.1 (0.88)	71%

Subgroup analyses are presented in random effect model. Panel includes *n* trials (*n* participants), Weighted mean difference (WMD), 95% confidence interval (95% CI), Z-score (Z) and significance (*p*) of exercise vs. control conditions. Statistical heterogeneity (I^2). AERT = aerobic exercise combined with resistance training, IL = interleukin. Not able to calculate (NA)

A significant change towards lower levels of IL-6 in the IG was found, with a WMD reduction of -2.4 ng/dl (95% CI: -2.6 to -2.1, p< 0.001) (see Table 4).

Only the study by Dudgeon et al. [58] reported changes in cortisol and insulin-like growth factor 1 (IGF-1) for PLWH. After exercise intervention, lower levels of cortisol upon waking (p< 0.05) and one hour after waking (p= 0.07) were found in the IG. Overall cortisol levels prior to exercise decreased in the IG after the aerobic exercise combined with resistance training (AERT) intervention by 1.8 µg/ml (55.6 ± 24.3 to 61.2 ± 37.1, p= 0.3), while in the CG cortisol levels increased by 12.2 µg/ml (45.5 ± 22.8 to 57.7 ± 27.8, p= 0.1. IGF-1 had a non-significant increase in IGs and CGs at the end of the study, IG (pre: 128 ± 42 ng/ml; post: 132 ± 43.2 ng/m; p> 0.05) CG (pre: 118 ± 33.8 ng/ml; post: 137 ± 55.3 ng/ml; p> 0.05). C-reactive protein was reported in the study by Fitch et al. [69], where AERT exercise significantly decreased the levels of this inflammatory marker in the IG compared to the CG (−1.6 ± 0.7 vs. 0.1 ± 0.4 mg/L, p= 0.05).

Differences across subgroups

The heterogeneity was explored by looking for differences across subgroups with and without comorbidities, where studies investigating biceps curl ($\chi^2 = 6.8$, df = 1, $p < 0.05$), leg press ($\chi^2 = 36.7$, df = 1, $p < 0.001$) and leg extension ($\chi^2 = 21.4$, df = 1, $p < 0.001$) differed. A low heterogeneity was evident for leg press (0%) and moderate for leg extension (62%) in the group without comorbidities.

Biceps curl ($\chi^2 = 38.5$, df = 1, $p < 0.001$), leg press ($\chi^2 = 17,4$, df = 2, $p < 0.001$) and leg extension ($\chi^2 = 10.5$, df = 2, $p < 0.001$) differed between studies including only women or men and mixed groups. The heterogeneity was low in the female group for leg flexion (0%) and moderate for CP (75%). The heterogeneity was low in the male group for leg extension (0%). This last subgroup analysis revealed a greater change in IG lower body strength of 17.8 kg (95% CI: 13.1 – 22.4, $p < 0.001$).

Regarding the type of training, chest press ($\chi^2 = 17.4$, df = 2, $p < 0.001$), biceps curl ($\chi^2 = 8.13$, df = 1, p= 0.004) and leg press ($\chi^2 = 10.1$ df = 2, $p < 0.001$) were also different among the AE, RT and AERT groups. The heterogeneity did not change and was high for type of training ranging from 93% to 96%.

Differences between studies reporting strength intensities and not reporting strength intensities investigating chest press ($\chi^2 = 21$, df = 1, $p <0.001$) and leg press ($\chi^2 = 9.1$, df = 1, p= 0.003) were found. A low heterogeneity was evident for studies reporting no strength intensity for leg extension (0%).

Differences between weekly volume sessions (the number of RT sets, times the number of training session per week: < 5, 5 – 9, ≥ 10 times per week) investigating chest press ($\chi^2 = 18.4$, df = 2, $p <0.001$) and leg flexion ($\chi^2 = 8.5$, df = 2, p= 0.01) were found. The heterogeneity did not change and was high in the weekly volume sessions subgroup analysis ranging from 79% to 99%).

Differences between the minutes of physical activity per week in total investigating chest press (χ^2 = 15.1, df = 2, p <0.001), leg press (χ^2 = 6.2, df = 1, p= 0.01), and leg extension (χ^2 = 7, df = 2, p= 0.03) were found. A moderate heterogeneity of the studies investigating chest press for the subgroup performing 180 min/week of exercise was evident for leg extension (64%). A moderate heterogeneity for the subgroup performing 240 to 270 min/week was found for leg press (68%) and leg extension (67%).

The strength tests used in the studies indicated that the chest press (χ^2 = 17.4, df = 2, p < 0.001), biceps curl (χ^2 = 6.8, df = 1, p= 0.009), leg press (χ^2 = 13, df = 2, p= 0.002), leg flexion (χ^2 = 128 df = 2, p < 0.001) and leg extension (χ^2 = 37.6, df = 1, p < 0.001) differed among the studies. The heterogeneity was high for chest press (81%) when strength was assessed by the peak force test and moderate for leg extension when strength was assessed by the 1-RM method. Heterogeneity was low for leg flexion (0%) and leg extension (0%) in the group that used other methods to asses muscle strength (3-RM, 6-RM, 12-RM or by a hand-held dynamometer) (see Table 5).

Discussion

The main results of this meta-analysis suggest that aerobic exercise combined with resistance training or resistance training alone has a positive effect on muscle strength and levels of IL-6 in PLWH.

New in this meta-analysis is the inclusion of 13 studies reporting changes in strength, testosterone and inflammatory markers in PLWH. Moreover, separate analyses of the main outcomes for RT alone and AERT, studies with a low risk of bias, professional supervision and the exclusion of active control groups were performed.

Table 5. Sub-group differences

Category	*n* trials (*n* participants)	Change (kg)		Overall effect	Heterogeneity	Difference	
		WMD	95% CI	Z (*p*)	I^2	χ^2	(*p*)
Comorbidities							
CP with	4 (110)	22.2	11.7 – 32.8	4.12 (< 0.0001)	96%	0.02	0.88
CP without	6 (174)	21	9 – 32.9	3.4 (0.0006)	98%		
BC with	1 (22)	0.2	-2.6 – 3	0.14 (0.89)	NA	6.8	0.009
BC without	2 (90)	9.9	3.1 – 16.7	2.9 (0.004)	91%		
LP with	2 (44)	68.5	56.7 – 80.3	11.39 (< 0.00001)	0%	36.7	<0.00001
LP without	5 (148)	22.3	13.1 - 31.5	4.77 (< 0.00001)	96%		
LF with	5 (163)	9.4	3.4 – 15.4	3.1 (0.002)	94%	0.06	0.81
LF without	4 (126)	10.5	3.9 – 17.1	3.11 (0.002)	94%		
LE with	5 (159)	5.2	2.9 – 7.5	4.4 (<0.00001)	92%	44.5	<0.00001
LE without	3 (96)	19.3	15.8 – 22.7	11 (<0.00001)	62%		
Gender							
CP women	2 (61)	11.2	6.4 – 16.1	4.5 (<0.00001)	75%	4	0.14
CP mixed	2 (52)	32.3	2.6 - 62	2.1 (0.03)	97%		
CP males	5 (129)	20.9	9.6 – 32.3	3.6 (0.0003)	97%		
BC women	1 (20)	13.4	10.3 – 16.5	8 (< 0.00001)	NA	38.5	<0.00001
BC males	1 (22)	0.2	-2.6 - 3	0.1 (0.89)	NA		
LP mixed	2 (31)	53.6	-3.7 – 110.8	4.4 (<0.0001)	86%	0.3	0.57
LP male	4 (93)	35.4	9 – 61.7	2.6 (0.009)	98		
LF women	2 (58)	7.9	6.4 – 9.4	10.3 (<0.00001)	0%	1.2	0.55
LF mixed	3 (110)	18.7	-1.5 - 39	1.8 (0.07)	98%		
LF male	3 (73)	6.3	-4.3 – 16.9	1.2 (0.25)	91%		
LE women	2 (58)	25	11.5 – 38.4	3.6 (0.0003)	85%	17.9	0.0001
LE mixed	2 (80)	16.1	-11.8 – 43.9	1.1 (0.26)	90%		
LE male	3 (69)	1.4	-4.3 – 7.2	0.5 (0.62)	0%		
Type of training							
CP AE	1 (22)	4	-0.5 – 8.4	1.8 (0.08)	NA	20	<0.0001
CP AERT	5 (160)	25.9	16.8 – 35.1	5.5 (<0.00001)	96%		
CP RT	4 (102)	20.4	4.5 – 36.3	2.5 (0.01)	99%		
BC AERT	2 (70)	3.4	-2.8 – 9.5	1.1 (0.29)	90%	8.1	0.004
BC RT	1 (20)	13.4	10.3 – 16.5	8.5 (<0.00001)	NA		
LP AE	1 (21)	19.5	9.7 – 29.3	3.9 (<0.0001)	NA	10.1	0.006
LP AERT	3 (96)	11.6	5.4 – 17.8	3.7 (0.0002)	87%		
LP RT	3 (75)	47	25.2 – 68.9	4.2 (<0.0001)	95%		
LF AERT	6 (216)	6.2	1.7 – 10.7	2.7 (0.007)	93%	2.5	0.12
LF RT	3 (73)	16.7	4.4 - 29	2.7 (0.008)	96%		
LE AERT	7 (235)	14.4	4.2 . 24.5	2.8 (0.006)	93%	0.6	0.4
LE RT	1 (20)	18.7	13.8 – 23.4	7.6 (<0.00001)	NA		

Category	*n* trials (*n* participants)	Change (kg)		Overall effect	Heterogeneity	Difference	
		WMD	95% CI	Z (*p*)	I^2	χ^2	(*p*)
Strength training intensity							
CP 50-90%	6 (175)	14.8	9.7 – 19.8	5.7 (<0.00001)	92%	21	<0.00001
CP unknow	3 (87)	40.9	30.9 – 50.9	5.7 (<0.00001)	91%		
LP 50-90%	5 (141)	35.7	22.3 – 49.2	5.2 (<0.00001)	97%	1.1	0.29
LP unknow	1 (30)	28.1	23.4 – 32.8	11.7 (<0.00001)	NA		
LF 50-90%	6 (172)	9.4	5.9 – 12.9	5.2 (p<0.00001)	86%	0.1	0.76
LF unknow	2 (89)	13.1	-10.6 – 15.5	1.1 (0.28)	99%		
LE 50-90%	5 (149)	19.9	9.3 – 30.4	3.7 (0.0002)	91%	9.1	0.003
LE unknow	2 (87)	3.2	0.7 – 5.8	2.5 (0.01)	0%		
Weekly volume sessions							
CP < 5	1 (34)	31.2	25.8 – 36.6	11.3 (<0.00001)	NA	18.4	0.0001
CP 5 – 9	6 (166)	20.6	19.2 – 22	28.9 (<0.00001)	98%		
CP > 10	2 (62)	18.2	15.7 – 20.7	14.4 (<0.00001)	99%		
LF < 5	1 (28)	0.04	-6.9 - 7	0.01 (0.99)	NA	8.5	0.01
LF 5 - 9	6 (162)	13.7	7.6 – 19.7	4.4 (<0.00001)	94%		
LF > 10	1 (38)	8.7	6.7 – 15.4	5 (<0.00001)	NA		
LE < 5	1 (28)	4.6	-9.7 – 18.9	0.6 (0.53)	NA	2.6	0.28
LE 5 - 9	4 (101)	16.7	5.4 – 28	2.9 (0.004)	91%		
LE > 10	2 (57)	22.9	1.9 – 43.9	2.1 (0.03)	79%		
Minutes week							
CP 180	4 (90)	9	4.9 – 13.2	4.3 (<0.0001)	64%	15.2	0.0005
CP 240-270	3 (109)	32.8	21.4 – 44.3	5.6 (<0.00001)	95%		
CP 360	1 (39)	13.5	10.8 – 16.2	9.8 (<0.00001)	NA		
BC 180	2 (42)	6.1	4.1 – 8.2	5.8 (<0.00001)	97%	0.04	0.84
BC 240	1 (48)	6.5	3.8 – 9.2	4.7 (<0.00001)	NA		
LP 180	3 (64)	44.5	17.6 – 71.4	3.2 (0.001)	91%	6.2	0.01
LP 240-270	2 (75)	10.2	7.3 – 13.1	6.9 (<0.00001)	68%		
LF 180	3 (63)	9.5	1.3 – 17.7	2.2 (0.02)	90%	0.7	0.71
LF 240	2 (78)	5.1	-3.5 – 13.7	1.2 (0.24)	82%		
LF 360	1 (38)	8.7	6.5 – 10.9	7.8 (<0.00001)	NA		
LE 180	3 (63)	15.1	-1.1 – 31.5	1.8 (0.07)	92%	7	0.03
LE 240-270	3 (95)	14.1	2.1 – 26.2	2.3 (0.02)	67%		
LE 360	1 (38)	32.4	23.3 – 41.5	7 (<0.00001)	NA		
Strength test							
CP 1-RM	6 (181)	20.9	11.3 – 30.4	4.3 (<0.0001)	98%	17.4	0.0002
CP peak force	2 (46)	7.6	0.6 – 14.6	2.1 (0.03)	81%		
CP other	2 (57)	37.6	24.8 – 50.5	5.7 (<0.00001)	89		
BC 1-RM	2 (68)	9.9	3.1 – 16.7	2.9 (0.004)	91%	6.8	0.009
BC peak force	1 (22)	0.2	-2.6 - 3	0.1 (0.89)	NA		
LP 1-RM	4 (122)	41.1	21.1 – 61.1	4 (<0.0001)	98%	13	0.002
LP peak force	2 (43)	33.7	6 -61.4	2.4 (0.02)	94%		
LP other	1 (27)	8.5	5.6 – 11.4	5.7 (<0.00001)	NA		
LF 1-RM	6 (180)	14.4	9.6 – 19.1	6 (<0.00001)	92%	28	<0.00001
LF peak force	1 (22)	1.2	-2.5 – 4.9	0.6 (0.53)	NA		
LF other	2 (87)	1.1	-0.3 – 2.5	1.5 (0.14)	0%		
LE 1-RM	4 (127)	24.1	18 – 30.3	7.7 (<0.00001)	63%	41.3	<0.00001
LE peak force	1 (22)	-0.7	-7.5 – 6.1	0.2 (0.84)	NA		
LE other	3 (106)	3.4	0.9 – 5.9	2.6 (0.009)	0%		

Subgroup analyses are presented in random effect model. Panel includes n trials (n participants), Weighted mean difference (WMD), 95% confidence interval (95% CI), Z-score (Z) and significance (p) of exercise vs. control conditions. Statistical heterogeneity (I^2). Subgroup differences are tested by the Chi-square (χ^2) and significance (p). Not able to calculate (NA)

Muscle strength

As previously stressed by Gomes-Neto et al. [18], aerobic exercise and resistance training programs have limited benefit on muscle strength in healthy people. Nonetheless, two previous meta-analyses have reported positive changes after AERT intervention in muscle strength in PLWH [18,21]. However, these changes were restricted only to chest press, biceps curl, and leg extensors, with no changes to the leg flexors [21]. Our results indicated that both RT alone and AERT exercise has a significant positive effect on increasing upper and lower body muscle strength in PLWH. This study highlighted that the results were significantly higher after excluding studies with a high risk of bias over upper and lower strength.

Of importance here is that after different sub-meta-analyses were performed, lower strength increased more after RT alone or if the exercise was supervised by an exercise professional (exercise scientist, physiotherapist or certified trainer [23]). Upper strength increased more after AERT intervention, excluding active CGs and in studies carried out during the ART era.

Of special importance is the significant positive change in the leg press, leg flexors and leg extensors (see Table 3). The data contrasts with that of O´Brien et al. [21] who reported only a trend toward increasing leg flexor muscle strength and a non-significant improvement on other lower extremity muscle groups in LPWH. This difference in results might be due to the increased number of included studies in the meta-analyses for lower body strength in comparison to O´Brien et al. [21]. In detail, for leg press six further studies [57,60,68,72–74], for leg flexion six further studies [57,58,60,66,71,73] and for leg extension five further studies [58,66,70,71,73] were included. It is important to remark that in the study of Dudgeon et al. [58], the intervention group exercised less than three times per week, an exclusion criterion in the study by O'Brien et al. [21]. See Table S1.

This meta-analysis tried to have a more homogeneous IG by grouping the IGs according to the amount of time (more or less than 150 minutes per week) dedicated to exercise. Due to complex differences in the types of training (progressive resistance training, continuous resistance training, AERT), the use of free weights, color-coded therapeutic bands or multi-training exercise machines, alongside great differences in exercise intensity (refer to Table S1, Information on excluded and included studies), no differences in strength compared to the main results were found.

The clinical relevance of muscle strength increases in PLWH has not yet been established. Gomes-Neto et al. [18] discussed how an increase of 40% in muscle strength likely represents a clinically meaningful strength gain. On the other hand, for O´Brien et al. [21] a clinically important change was an improvement of 2 kg for upper body and 5 kg for lower body strength. Nevertheless, no statement can be made, about the clinically relevant change due to the different possible biases in our study (i.e. types of training, exercise intensity, strength testing) and because our focus was not the standard error of measurement (SEM) and the small real difference (SRD) values of the upper and lower body strength tests.

The high degree of heterogeneity (I^2> 75%) found among the meta-analyses might be the result of differences in the associated comorbidities (i.e. insulin resistance, HCV and altered testosterone levels), gender (only women were evaluated), and strength testing procedures (1-RM test, 3RM, 6-RM, 12-RM or peak isometric force). Furthermore, the number of participants in the included studies as well as the number of studies included in each of the meta-analyses can contribute to this high heterogeneity. Thus, caution is advised when interpreting the results.

Hormones

Testosterone levels are associated with muscle strength and physical performance in healthy men [76]. This meta-analysis found no significant changes in testosterone and free testosterone levels after the exercise interventions (see Tables 4), perhaps due to differences in the testing methods, the number of included studies and, more importantly, because this secondary outcome was extracted from studies mainly reporting changes in muscle strength.

High levels of IL-6 are related to T-cell failure [77], a greater risk of losing 40% of muscle strength [76] in the aging population, and a 1.3 times higher chance of presenting with a CVD [78]. Thus, strategies directed towards controlling levels of IL-6 may be helpful in PLWH. This meta-analysis, found a significant change of lower levels of IL-6 after exercise intervention in the studies of Dudgeon et al. [58], where only males participated in an AERT intervention, and Zanetti et al. [60], where a mixed-gender intervention group performed only RT (see Table 4), supporting exercise as an alternative to reduce levels of IL-6 in PLWH.

No changes in IL-1β levels were found. This data is in agreement with Peake et al. [79], who reported that even though AE and RT increase muscle and leucocyte cells' gene expression of IL-1β, the release of this interleukin is highly regulated and thus changes in plasma may not be observed.

Limitations

The high degree of heterogeneity found in the meta-analyses was considered to be the result of a combination of various differences among the studies included in the quantitative analysis. Associated comorbidities in PLWH included coinfection of the hepatitis C virus [70,71], unhealthy habits like smoking, drinking or the use of hallucinogenic drugs [67,69,70] and other diagnosed chronic pathologies [57,67,69,71]. Gender, type of training, strength performance testing, active or passive control groups and the number of participants in each analysis was also uneven among the studies. After exploring some potential sources of heterogeneity, such as the exercise characteristics (exercise intensity, volume and weekly frequency). We were able to reduce the heterogeneity from high to low or from high to moderate in some cases. However, a high heterogeneity was still observed for most analyses. This heterogeneity can be attributed to the lack of power of the I^2 statistic when looking to small number of studies. (80-82). For these reasons, the results of this meta-analysis warrant attention when interpreted.

Other limitation was the presence of publications bias on the systematic review. According to the egger´s test, there ar publication bias for the meta-analyses: chest press (bias = 10.6, 95%CI: 6.3 – 14.9, $p < 0.001$), leg press (bias = 7, 95%CI: 2.7 – 11.4, $p = 0.009$) and leg flexion (bias = 7.4, 95%CI: 0.6 – 14.1, $p = 0.03$).

Regarding the clinical relevance of muscle strength in PLWH, the question remains, whether a value lower or higher than 40% could reflect a better cut-off point.

Implications for research

After the above studies were evaluated in this meta-analysis, some concerns, pertinent for further RCTs involving exercise interventions in PLWH were raised. From a methodological standpoint, when possible, equally balanced groups in terms of gender, use of a unique type of training and blinding of evaluators could all increase the quality of future RCTs and decrease the risk of bias. Additionally, more studies investigating changes in testosterone and inflammatory markers (IL-6 and IL-1β) to establish the effect of RT alone or AERT on hormones in PLWH are needed.

Conclusion

Resistance training alone or combined with aerobic exercise showed a positive change after studies with a low risk of bias and professional supervision were analyzed, improving upper and, more critically, lower body muscle strength. This meta-analysis also reported that exercise had a lowering effect on IL-6 levels in PLWH.

Key considerations

- Both RT alone and AERT have a significant positive effect on increasing upper and lower body muscle strength in PLWH.
- Lower body strength increases more if exercise is supervised by a professional.
- Exercise is an alternative to reduce levels of IL-6 in PLWH.
- Taken together, exercise plays a fundamental role in HIV treatment to improve upper and lower body muscle strength in PLWH.

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- Study 3 –

Recreational Exercising and Self-Reported Cardiometabolic Diseases in German People Living with HIV: a cross-sectional study

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Abstract

Exercise is known for its beneficial effects on preventing cardiometabolic diseases (CMDs) in the general population. People living with the human immunodeficiency virus (PLWH) are prone to sedentarism, thus raising their already elevated risk of developing CMDs in comparison to individuals without HIV. The aim of this cross-sectional study was to determine if ex-ercise is associated with reduced risk of self-reported CMDs in a German HIV-positive sample (n = 446). Participants completed a self-report survey to assess exercise levels, date of HIV diagnose, CD4 cell count, antiretroviral therapy, and CMDs. Participants were classified into exercising or sedentary conditions. Generalized linear models with Poisson regression were conducted to assess the prevalence ratio (PR) of PLWH reporting a CMD. Exercising PLWH were less likely to report a heart arrhythmia for every increase in exercise duration (PR: 0.20: 95% CI: 0.10 – 0.62, $p < 0.01$) and diabetes mellitus for every increase in exercise session per week (PR: 0.40: 95% CI: 0.10 – 1, $p < 0.01$). Exercise frequency and duration are associated with a decreased risk of reporting an arrhythmia and diabetes mellitus in PLWH. Further studies are needed to elucidate the mechanisms underlying exercise as a protective factor for CMDs in PLWH.

Keywords: HIV, exercise, cardiovascular diseases, metabolic disease, sedentary.

Introduction

Life expectancy of younger people diagnosed with HIV is approximately 54 years [2]. This reduced life expectancy can be attributed to the increased prevalence of CMDs as described in European PLWH (3.7% to 5%) [3], including German PLWH compared to individuals without HIV (12.8% vs. 10.4%, $p < 0.01$), with premature onset and higher prevalence of CMDs in PLWH older than 40 years [4].

The incidence of CMDs can be explained by traditional risk factors (e.g., age, high waist-to-hip ratio, symptomatic HIV) [5], and the role of ART and HIV chronic inflammation [6,7]. In addition, health behaviors like smoking [8] and/or physical inactivity [9] are highly prevalent in people with HIV [10].

Conversely, exercise is beneficial for preventing CMDs in the general population [11]. Specifically, cross-sectional studies have found that exercise has a protective factor against hypertension (odds ratio (OR) = 0.49, 95% CI: 0.29 - 0.84 to OR = 0.92, 95% CI: 0.87 - 0.98) and diabetes (OR = 0.46, 96% CI: 0.25 - 0.86 to OR = 0.87, 95% CI: 0.80 - 0.95) [12,13], and people performing exercise ≥ 150 minutes per week are 42% less likely to have a cardiovascular disease [14].

Recent meta-analyses indicate that exercise has a beneficial effect on PLWHs' physical health (including increased aerobic [15] and strength [16] capacity), favoring a better cardiorespiratory fitness (CRF) [17]. In contrast, physical inactivity is associated with the development of hypertension (prevalence ratio (PR) = 1.46, 95% CI: 1.03 -2.06, p = 0.03) and diabetes mellitus (PR = 1.71, 95% CI: 1.12 - 2.62, p = 0.01) in PLWH [18].

Exercise is recommended to prevent or treat CMDs in the general population. Data on the protective effect of exercise intensity, frequency, and duration on CMDs in German PLWH is scarce. The aim of this study was to investigate the role exercise has in reported CMDs in German PLWH. The objectives of this study were to 1) assess the differences in comorbidities between two groups of PLWH (sedentary = Sed and exercising = Exe) and 2) calculate the PR of reporting a CMD among the two groups in relation to self-reported: anthropometric characteristics (age, weight, BMI); number of years living with HIV; exercise characteristics (intensity, frequency, duration); and exercise status (Sed vs. Exe).

Materials and Methods

This cross-sectional study was based on data from The HIBES study [19]. Individuals were recruited from various German institutions involved in HIV/AIDS to minimize the recruitment bias. Participants were recruited from (1) The official AIDS-offices (Germany-wide), (2) the Academy Waldschlösschen e.V., (https://www.waldschloesschen. org/de/), (3) Medical care facilities in Berlin and Germany who specialize in HIV and AIDS, (4) The consortium of HIV and AIDS specialized physicians (DAGNÄ) (https://www.dagnae.de/), and (5) The Competence Network HIV/AIDS. The study was conducted from October 2010 to December 2012 over a 26-month period in both rural and urban areas of Germany. Questionnaires were freely available for individuals to complete either in hardcopy or online format. Inclusion criteria were: ≥18 years of age, diagnosed with HIV, and completed the exercise questionnaire. The survey assessed self-reported HIV and ART characteristics (years with HIV, CD4 cell count, and current ART: Truvada, Trizivir, Kivexa, Combivir, Atripia, or no combination), and the self-reported presence of a CMD (comparable to the GEDA 2014/2015-EHIS questionnaire [20]). Specifically, participants were asked to indicate yes or no if they had a CMD in addition to the HIV; if the answer was affirmative, participants were asked to mark a box if they had one or more of the following CMDs: atherosclerosis, arterial hypertension, coronary heart disease (CHD), diabetes mellitus (DM), dyslipidemia, heart arrhythmia, heart insufficiency, myocardial infarction (MI), peripheral arterial disease (PAD), and stroke, before or after the HIV diagnosis. Participants were also asked to report any medication they were taking in relation to the CMD. To ensure the diagnosis was made by a medical doctor, only CMDs with the correct pharmacology treatment were considered to be valid. The survey in-vestigated regular exercise defined as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” [21] performed at least once a week [22] for more than one year. If the answer was affirmative, participants were asked to report the exercise type, time period, frequency, and duration. The length of exercise practice was measured in years. Exercise frequency was measured in number of sessions per week (sessions·week^{-1}). Each reported type of sport was con-verted into metabolic equivalent of task (METs) to measure exercise intensity according to Ainsworth et al. [23] and expressed as MET·min·day^{-1} [24]. The duration of each exercise session was measured in hours per week-(hrs·week^{-1}). Details concerning intensity, du-ration and frequency assessments can be found in [19]. Exercise frequency, intensity, and duration were divided in tertiles. Participants were categorized into two groups: 1) Exe: participants who performed exercise more than 12 months before completing the survey and 2) Sedentary: participants who never performed exercise, before completing the survey.

The immunological parameters of cluster differentiation four (CD4) white blood cell count were a self-report question (participants were asked to check a box with different CD4 values: < 200, 200-499 and > 500 cell/µL, according to the Center for Disease Control (CDC) [25]. Years living with HIV was calculated based on the year of HIV diagnosis and the time they answered the survey. Body mass index (BMI) was calculated from self-reported weight and height after the HIV diagnosis. Participants who did not answer the questions about exercise frequency, length of time, or type were excluded from this study.

Statistical analysis

A prior descriptive analysis including the Kolmogorov–Smirnov and Shapiro–Wilk tests, indicated a non-normal distribution of the variables. The Mann-Whitney U test was performed to evaluate any differences in age (yrs.), height (cm), weight (kg), body mass index (BMI = kg·m$^{2-1}$), years living with HIV (yrs.), exercise frequency (days per week^{-1}), exercise intensity

(MET·min·day^{-1}), and exercise duration (hrs. per week^{-1}) between the groups. The Chi-square test with a post-hoc analysis applying the Bonferroni correction [25] was used to evaluate the differences between the groups in terms of gender, CD4 cell count category according to the CDC [25], exercise frequency, intensity, and duration tertiles, and prevalence of CMDs before and after the HIV diagnosis. Fisher's exact test was chosen in cases where one or more frequencies were less than five. A Poisson re-gression with robust variance was performed to calculate the PR and 95% confidence intervals [26,27] of CMDs. The relationship between a CMDs after the HIV diagnosis and the different variables was analysed as follows: the relationship to anthropometric characteristics (age, weight, and BMI) adjusted for years living with HIV in model 1; to number of years living with HIV, adjusted for age, weight and BMI in model 2; to exercise characteristics (intensity, frequency, duration) adjusted for age, weight and BMI and diabetes mellitus in model 3; and to the current exercise status (exercising vs. sedentary) adjusted for age, weight and BMI and diabetes mellitus in model 4. The significance level of alpha was set to < 0.05. Data are presented as median and interquartile range (IQR, 1st quartile - 3rd quartile) unless otherwise indicated. All statistical analyses were performed using the statistical package SPSS version 26 (IBM Corp., Armonk, NY, USA).

Results

The Exe group was significantly younger, and the proportion of females was lower compared to the Sed group. The Sed group had a greater proportion of participants with a CD4 cell count < 200 cell/µL, whereas a greater proportion of PLWH in the Exe had a CD4 cell count > 500 cell/µL. Characteristics of the cohort are shown in Table 1.

Table 1. Cohort characteristics.

Parameter	Overall n = 446	Sedentary n = 166	Exercise n = 280
Gender			
Female, n (%)	31 (7)	17 (10.2)	14 (5) *
Male, n (%)	414 (92.8)	148 (89.2)	266 (95) *
Other, n (%)	3 (0.2)	1 (0.6)	0
Age (yrs.), m (SD)	44(10)	46(11)	43 (9) *
Height (cm)	180 (150 - 198)	178 (156 - 197)	180 (150 -198)
Weight (kg)	77 (50 - 178)	77 (50 - 138)	77 (52 - 178)
BMI ($kg \cdot m^{2-1}$)	23.7 (15.7 - 63)	23.8 (15.7 - 41.6)	23.6 (17 - 63)
Years with HIV	8 (1 - 32)	7 (1 - 32)	8 (1 - 32)
ART			
Yes, n (%)	412 (92.4)	150 (90.4)	262 (93.6)
No, n (%)	34 (7.6)	16 (9.6)	18 (6.4)
CD4 cell count category			
Unknown, n (%)	44 (9.9)	17 (10.2)	27 (9.6)
> 500 cell/µL, n (%)	264 (59.2)	82 (49.4)	182 (65) *
200 – 499 cell/µL, n (%)	108 (24.2)	48 (28.9)	60 (21.4)
< 200 cell/µL, n (%)	30 (6.7)	19 (11.4)	11 (3.9) *

Data presented in median and interquartile range (IQR), number of participants (n) and percentage (%). Patient self-reported: antiretroviral treatment (ART), CD4 cell count expressed in cell per microliters ($cell \cdot \mu L^{-1}$). Significant differences at the 0.05 level between PLWH performing exercise or not (*).

Exercise in PLWH

The proportion of PLWH who reported not being engaged in exercise was 37.2%. The greater proportion of exercising PLHW did so with frequency between 2 -3 $days \cdot week^{-1}$, with an intensity of ≥ 103 $MET \cdot min \cdot day^{-1}$, and total duration greater than 4 $hrs \cdot week^{-1}$, as summarized in Table 2.

CMD in PLWH

Overall, 8.5% of participants reported one or more CMD after the HIV diagnosis. Of these 38 participants, 79% (n = 30) reported one CMD, 16% (n = 6) reported two CMDs, and 5% (n =

2) reported three CMDs. The Exe group reported a non-significant higher pro-portion of CMDs (65.8%) compared to the Sed group (34.2%). No differences were found between groups for the reported prevalence of any specific CMD before or following the HIV diagnosis, as reported in Table 3.

Table 2. Cohort exercise characteristics.

Exercise Characteristics	**n = 280**
Frequency (days · week^{-1})	
< 2	33 (11.8)
2 – 3	169 (60.3)
> 3	78 (27.9)
Intensity (MET · min · day^{-1})	
≤ 103	99 (35.3)
104 - 190	86 (30.7)
> 190	95 (34)
Time (hrs.· week^{-1})	
< 2	59 (21.1)
2 - 4	99 (35.4)
> 4	122 (43.5)

Data presented in total number of participants and percentage (%).

Risk of reporting a CMD after the HIV diagnosis

For every increase in years living with HIV, PLWH were more likely to report arterial hypertension, atherosclerosis, CHD, and dyslipidemia. PLWH were less likely to report arrhythmias for every increase in hours of exercise and diabetes mellitus for every increase in exercise session per week. No relation between the reported type of ART treatment and reported CMD was found, (see Table 4).

Table 3. Cardiometabolic diseases after the HIV diagnosis

Parameter	Sedentary n = 166	Exercise n = 280	Total	χ²	df	*p* value
Dyslipidaemia, n (%)				1.12	2	> 0.05°
Pre-HIV	2 (1.2)	1 (0.3)	3			
Post-HIV	4 (2.4)	7 (2.5)	11			
Diabetes, n (%)				0.61	2	> 0.05°
Pre-HIV	1(0.6)	0	1			
Post-HIV	2 (1.2)	1 (0.3)	3			
Lipodystrhopia, n (%)				0.08	1	> 0.05
Post-HIV	4 (2.4)	8 (2.8)	12			
Hypertension, n (%)				0.43	2	> 0.05
Pre-HIV	10 (6)	14 (5)	24			
Post-HIV	8 (4.8)	11 (3.9)	19			
Atherosclerosis, n (%)				5.67	2	> 0.05°
Pre-HIV	3 (1.8)	0	3			
Post-HIV	0	1 (0.3)	1			
PAD, n (%)				1.69	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	1 (0.6)	0	1			
Heartfeilure, n (%)				1.69	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	0	1 (0.3)	1			
Heart arrhythmias, n (%)				2.87	2	> 0.05°
Pre-HIV	1(0.6)	0	1			
Post-HIV	0	2 (0.6)	2			
CHD, n (%)				1.21	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	2 (1.2)	1 (0.3)	3			
MI, n (%)				0.17	1	> 0.05°
Pre-HIV	0	0	0			
Post-HIV	2 (1.2)	3 (60)	5			
Stroke, n (%)				0.59	1	> 0.05°
Pre-HIV	0	1 (100)	1			
Post-HIV	0	0	0			
One or more CMD, n (%)						
Pre -HIV	15 (9)	15 (5.3)	30	2.24	1	> 0.05
Post-HIV	13 (7.8)	25 (8.9)	38	0.16	1	> 0.05
More than one CMD, n (%)						
Post-HIV	4 (2.4)	4 (1.4)	8	0.56	1	> 0.05

Data presented in number of participants (n) and percentage (%), Chi square (χ^2), degrees of freedom (df), coronary heart disease (CHD), myocardial infarction (MI), peripheral arterial dis-ease (PAD), Fisher's exact test (°).

Table 4. Risk of reporting a cardiometabolic disease in relation to anthropometric characteristics, HIV and ART, exercise characteristics, and exercise in German PLWH

Variables	Atherosclerosis pots HIV			Arterial Hypertension post HIV			Coronary heart disease post HIV			Diabetes Mellitus post HIV		
	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*
Model 1												
Age (yrs.)	0,90	0.8 - 1.1	0,43	1,00	1 - 1,1	0,21	0,80	0.7 - 1.1	< 0.01	1,10	1 - 1,2	0,64
Weight (kg)	1,00	0.8 - 1.3	0,16	1,00	0.9 - 1.1	0,82	1,20	1 - 1,3	< 0.01	1,20	1.2 - 1.4	< 0.01
BMI (kg/m^2)	0,80	0.3 - 1.6	< 0.01	1,10	0.9 - 1.4	0,14	0,80	0.5 - 1.1	< 0.01	1,10	1 - 1,1	< 0.01
Model 2												
Years since HIV diagnosis (yrs.)	1,20	1 - 1,4	< 0.01	1,10	1 -1,2	< 0.01	1,20	1.1 - 1.5	< 0.01	1,10	1 - 1,2	0,47
Model 3												
Frequency (session · week^{-1})	0,90	0.4 - 1.4	0,30	0,70	0,4 - 1	0,09	1,10	0.7 - 1.4	0,05	0,40	0,1 - 1	< 0.01
Intensity (MET · min · day^{-1})	1,00	1 – 1.1	< 0.01	1,00	0.9–1	0,02	1,00	1–1.1	< 0.01	1,00	0.9–1	0,62
Duration (hrs · week^{-1})	1,00	0.9 - 1.3	< 0.01	1,00	1 - 1,2	< 0.01	1,00	0.8 - 1.3	< 0.01	1,00	0.6 - 1.3	< 0.01
Model 4												
Exercise	-	-	-	0,80	0,3 - 2	0,63	0,30	0,1 - 3	0,31	1,20	0.1 - 25.3	0,88
Sedentary	-	-	-	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Prevalence ratio (PR), 95% confidence interval (95% CI), Body mass index (BMI), Exercise intensity expressed in metabolic equivalent of task (METs), reference group (Ref), Not possible to calculate (-).

Table 4. Risk of reporting a cardiometabolic disease in relation to anthropometric characteristics, HIV and ART, exercise characteristics, and exercise in German PLWH (continue)

Variables	Dyslipidaemia post HIV			Heart Arrhythmias post HIV			Myocardial infarction post HIV			> 1 Cardiometabolic disease pot HIV		
	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*
Model 1												
Age (yrs.)	1,10	1 - 1,1	0,01	1,20	1 - 1,4	< 0.01	1,00	0.9 - 1.2	0,84	1,00	1 - 1,2	0,90
Weight (kg)	1,00	0.96 - 1.1	0,50	1,30	1 - 1,6	< 0.01	1,00	0.0 - 1.2	0,32	1,10	1 - 1,2	< 0.01
BMI (kg/m^2)	1,00	0.86 - 1.2	0,75	0,70	042 - 1,1	0,03	0,90	0.5 - 1.5	0,63	0,90	0.6 - 1.2	0,08
Model 2												
Years since HIV diagnosis (yrs.)	1,10	1 - 1,1	0,02	1,00	0.9 - 1.2	0,34	1,10	1 - 1,3	0,08	1,10	1 - 1,2	0,14
Model 3												
Frequency (session · week^{-1})	1,00	0.5 - 1.3	0,81	1,60	0.90 - 2.5	< 0.01	1,00	0.7 - 1.2	0,80	1,10	0.9 - 1.2	0,06
Intensity (MET · min · day^{-1})	1,00	0.9–1	0,43	1,00	0.9–1	< 0.01	1,00	0.9–1	0,19	1,00	1–1.1	0,08
Duration (hrs · week^{-1})	1,00	0.8 - 1.1	0,53	0,20	0.1 - 0.6	< 0.01	1,20	0.9 - 1.5	0,05	1,00	0.6 - 1.3	0,72
Model 4												
Exercise	1,00	0.3 - 3.9	0,95	-	-	-	0,90	0.1 - 6.7	0,90	0,60	0.1 - 2.5	0,45
Sedentary	Ref	Ref	Ref	-	-	-	Ref	Ref	Ref	Ref	Ref	Ref

Prevalence ratio (PR), 95% confidence interval (95% CI), Body mass index (BMI), Exercise intensity expressed in metabolic equivalent of task (METs), reference group (Ref), Not possible to calculate (-).

Discussion

More than the half of the participants (62.8%) in this study reported engaging in exercise at the time of assessment. These results are comparable with other studies in this field, including a Swiss HIV cohort [9], where the prevalence of physical inactivity was 44%. Furthermore, 38% of the exercise group in the current sample reported spending 2 to 3 days·week^{-1} engaging in exercise. These results are compatible with Schäfer et al.'s study [9] whereby 14% of their sample exercised 3-4 times per week.

The incidence of CMDs in the current sample, could be explained by the HIV-related side effects and ART treatment linked to dyslipidaemia, glycaemic alterations, and a chronic inflammatory state [6,29,30]. In this context, the CHD and MI prevalence in this study population is not surprising as PLWH have a Framingham CHD risk score >20% [31]. Furthermore, the prevalence of hypertension in this study (9.6%) is consistent with the prevalence rate of 7.9% reported in Silveira et al. [18] Brazilian sample of PLWH.

A noteworthy outcome from this study is that PLWH had a decreased likelihood of reporting an arrhythmia for every increase in hours of exercise per week. This is of importance since PLWH are predisposed to sudden cardiac death in part due to more arrhythmias (such as prolonged QTc intervals: 1.6 to 4 times more in PLWH compared to non-HIV) [32]. The reason for the increased arrhythmias arises from medications used to treat opportunistic infection in PLWH capable of prolonging QTc [32]. Another source of arrhythmias is an electrolyte disturbance in cases of gastrointestinal opportunistic infections. There is also evidence that the HIV virus has a primary relation with arrhythmias as Torsades de Pointes in the context of QTc prolongation has been described in PLWH, even in the absence of drugs or electrolyte alterations [32]. Additionally, PLWH taking ART have a lower heart rate variability (HRV) compared to the general population that could increase the risk of arrhythmias [33]. Exercise increases HRV (is associated with a better autonomic balance) in PLHW [34], by improving vagal tone to the heart and at the same time regulating sympathetic tone, that prevents against malignant arrhythmias [35]. Nevertheless, it is important to stress that high aerobic fitness in older adults could have a pro-arrhythmic effect [36].

We also found that PLWH had a decreased likelihood of reporting diabetes mellitus for every increase in exercise session per week, explained by the effects of exercise in stimulating GLUT4 (inhibited by HIV Nef protein), decreasing insulin resistance, and increasing β-cell insulin secretion (impaired in PLWH) [11,37].

Limitations

Some limitations need to be considered. First, although a notable strength was the large sample size (n=516 PLWH), the sample might not be nationally representative given the sample was predominantly male, with a distribution representative for PLWH in more economically developed countries [38] and taking into consideration that European women with HIV are less likely to have CMD [3]. Second, the assessment for HIV and CMDs prevalence and risk factors were based on self-report measures, including retrospective evaluations, whilst access to participants' medical records were not available; sole reliance on self-report may therefore have increased the risk of recall and social bias. Third, exercise was not objectively assessed through accelerometry or a standard validated physical activity questionnaire, such as the International Physical Activity Questionnaire (IPAQ). Rather, exercise was assessed using self-administered questions regarding exercise taking place in participants' leisure time without considering the exercise carried out during worktime. Fourth the statistical models were not adjusted by participating institutions due to the nature of anonymous assessment, and no mathematical correction or adjustment was made for multiple comparisons, acknowledging that for the risk of reporting a CMD after the HIV diagnosis as summarized in Table 4 the statistically significant findings were at $p < .01$. Furthermore, due to the cross-sectional nature of the study, it is not possible to determine causality between variables found to be significantly associated with each other. Finally, due to the cross-sectional design, the CMDs incidence could not be determined, thus, limiting understanding of the comorbidity trends which have emerged.

Implications for research

Exercise is prescribed in cases of CMDs for its health benefits [11,39]. The role of exercise as a protective factor against CMDs in comparison to physical inactivity in PLWH is of great value in the treatment of CMDs. Due to the cross-sectional study design, a comprehensive evaluation between exercise and inactivity and their corresponding as-sociations with CMDs in PLWH could not be fully determined. Hence, the next step in research should be based on prospective longitudinal designs (with a higher sample size and accurate CMDs objective indices collection) to further delineate the protective mechanisms of exercise in reducing the risk of CMDs in PLWH, using both validated exercise questionnaires and objective indices measuring the amount of exercise performed and impact on fitness levels.

Implications for practice

Notwithstanding the study limitations, the findings shed some light on the benefits of exercise as a primary prevention intervention, focusing on the risk factors for CMDs in PLWH, as recommended by the European AIDS clinical society [40]. Indeed, exercise is a well-known protective factor against CMDs deaths (HR 0.69, 95% CI: 0.43 – 1.12) and all-cause mortality (HR 0.64, 95% CI: 0.52 – 0.79) in the general population [41]. Moreover, in PLWH, recent meta-analyses have shown that exercise significantly improved aerobic capacity, resulting in a better oxygen consumption and 6-Minute walk distance [15], as well as strength, where resistance exercise alone or in combination with aerobic exercise improved upper and lower muscle strength [16]. Hence the value of exercise in a primary lifestyle intervention program for PLWH should be considered to decrease the risk for CMDs, following existent exercise guidelines [40] i.e., intensity in METs (moderate: 5.6 - 6 METs), time (≥ 150 min) and frequency (at least 1 session·week^{-1}) [22].

Conclusion

The promotion of exercise is warranted to facilitate improvements in cardiovascular and metabolic health in PLWH. However, further studies are needed to elucidate the mechanisms pertaining to exercise as a protective factor in PLWH against CMDs.

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- Study 4 –

Recreational Exercise is associated with lower Prevalence of Depression and Anxiety and better Quality of Life in German People Living with HIV.

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Abstract

Sedentarism is a risk factor for depression and anxiety. People living with the human immunodeficiency virus (PLWH) have a higher prevalence of anxiety and depression compared to HIV-negative individuals. This cross-sectional study (n = 450, median age 44 (19 – 75), 7.3 % females) evaluates the prevalence rates and prevalence ratio (PR) of anxiety and/or depression in PLWH associated with recreational exercise. A decreased likelihood of having anxiety (PR=0.57; 0.36-0.91; p = 0.01), depression (PR=0.41; 0.36-0.94; p=0.01), and comorbid anxiety and depression (PR= 0,43; 0.24-0.75; p=0.002) was found in exercising compared to non-exercising PLWH. Recreational exercise is associated with a lower risk for anxiety and/or depression. Further prospective studies are needed to provide insights on the direction of this association.

Keywords: HIV; depression; anxiety; exercise

Introduction

The most common mental disorders in people living with HIV (PLWH) are depression and anxiety (Steel et al., 2014). This is of importance because mental health disorders negatively affect PLWH's quality of life (QoL) and antiretroviral therapy (ART) success (Uthman et al., 2014).

PLWH are 50% less likely to meet the physical activity recommendations than HIV-negative individuals (Vancampfort et al., 2018), which might be explained by the higher prevalence of physical comorbidities related to the chronic inflammatory state in HIV (Ceccarelli et al., 2013; d'Ettorre et al., 2011), disabilities (Myezwa et al., 2018) and fatigue (Barroso et al., 2014).

Sedentary PLWH report worse mental well-being and lower QoL scores compared to the physically active PLWH (O'Brien et al., 2016). Physical activity (PA) is related to reductions in anxiety and depression symptoms and serves as a protective factor for depression and anxiety in non-HIV population (Schuch et al., 2018, 2019), given that PA influences mood, cognitive functions, and depression symptoms (Basso & Suzuki, n.d.). It also effects the central nervous system (Firth et al., 2018; Kandola et al., 2019) and HIV chronic inflammation/oxidative stress (d'Ettorre et al., 2011; Ivanov et al., 2016). Meta-analyses have further shown significant improvements in fitness (including aerobic capacity and strength) in exercising vs. sedentary PLWH (Pérez et al., 2017, 2018). This suggests that planned, structured and repetitive PA done to improve or maintain fitness, may be beneficial in preventing anxiety and/or depression in PLWH.

To date, there is no published data on recreational exercise as a protective factor for depression and/or anxiety in PLWH. Therefore, the aim of the present study was to a) assess the likelihood of PLWH experiencing anxiety or depression and b) QoL, in relation to recreational exercise.

Methods

Individuals were recruited from German institutions involved in HIV/AIDS care. Questionnaires were completed in hardcopy or online format. Inclusion criteria were: ≥18 years of age, diagnosed with HIV. Self-reported questionnaires were used to assess exercise, QoL, HIV and ART characteristics, and the presence of anxiety and/or depression. The EuroQoL 5-dimensions (EQ-5D) (Cooper et al., 2017) and the medical outcome study-HIV survey (MOS-HIV) (Wu et al., 1997) were used to assess QoL. Participants scoring 2-5 on dimension #5 on the EQ-5D were classified as having depression/anxiety. The survey investigated regular recreational exercise (RE) defined as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (Caspersen et al., 1985) performed at least once a week for at least three months (Pollock et al., 1998). To determine exercise time, participants were asked whether they were currently performing exercise or had performed exercise in the past. The time length of exercise practice was measured in years. Exercise frequency was measured in number of sessions per week. Exercise intensity was measured in metabolic equivalents (METs), and each reported type of sport was converted into METs according to (Ainsworth et al., 2011). Each exercise session duration was measured in hours per week. Participants were categorized into recreational exercising (i.e., performed RE in the past and were also still performing RE and/or never performed RE and started regular RE at least once a week in the last 3 months, prior to study and sedentary (individuals who never performed exercise or used to perform recreational exercise more than 3 months, before completing the survey) PLWH.

The immunological parameters of cluster differentiation four (CD4) white blood cell count was a self-report question. For the total ART duration, participants indicated the year they commenced ART. Age commencing ART was calculated based on the year of HIV diagnosis and the total time under ART. Body mass index (BMI) was calculated after the HIV diagnosis (there was no access to clinical records). Participants who did not answer the questions about exercise frequency, duration or type were excluded from this study. For more study information, refer to method’s supplementary material and (Zech et al., 2020).

Statistical analysis

A prior descriptive analysis indicated a non-normal distribution of the variables. The Mann-Whitney U test evaluated differences for continuous variables between the two groups (physically active X sedentary). The Chi-square test with a post-hoc analysis applying the Bonferroni correction (García & Núñez, 2003) was used to evaluate group differences for ordinal and nominal variables. Fisher's exact test was chosen in cases where frequencies were less than five. A Poisson regression with robust variance was performed to calculate the prevalence ratio (PR) and 95% confidence intervals (95% CI) (Barros & Hirakata, 2003) of anxiety and/or depression. The relationship between depression or anxiety and the different variables in the whole sample were analyzed as follows: the relationship to anthropometric characteristics (age, height, weight, BMI) in model 1; HIV and ART characteristics in model 2; physical/mental health summary scores and the EQ-5D health state index in model 3; exercise characteristics in model 4; and to exercise status: exercising and sedentary in model 5. Model 3 to 4 were adjusted for years living with HIV. The significance alpha level was set to < 0.05. Data are presented as median and interquartile range (IQR, 1st quartile – 3rd quartile) unless otherwise indicated. All statistical analyses were performed using SPSS (IBM Corp., Armonk, NY, USA).

Ethical aspects

The study was approved by the ethics committee of the Charité Berlin (Protocol No. EA1/084/11). Participant's data were anonymously collected following participants informed consent.

Results

In the RE group the anxiety prevalence was 33 (12.7%), the depression prevalence was 43 (16.5%), and the prevalence of comorbid anxiety and depression was 32 (12.3%). For sedentary PLWH, the anxiety prevalence was 41 (21.6%), depression was 49 (25.8%), and comorbid anxiety and depression was 28 (14.7%). A significant difference between groups for anxiety (χ^2=6.3; df=1; p=0.01) and depression (χ^2=5.7; df=1; p=0.01) emerged, with prevalence rates being higher for sedentary PLWH. No significant group difference was found for comorbid anxiety and depression.

Table 1. Cohort characteristics

Parameter	Overall	Sedentary	Recreational exercise
	n = 450	n = 190 (42%)	n = 260 (58%)
Gender			
Female, n (%)	33(7.3)	23 (69.7)	10 (30.3) *
Male, n (%)	415 (92.2)	165 (39.8)	250 (60.2) *
Other, n (%)	2 (0.4)	2 (100)	0
Age (yrs.)	44 (19 – 75)	45 (22 -75)	43 (19 - 69)
Height (cm)	180 (150 – 198)	178 (155 - 197)	180 (150 -198)
Weight (kg)	77 (32 - 178)	75.5 (32 - 138)	77 (52 - 178)
BMI (kg·m^{2-1})	23.5 (9 – 63.1)	23.4 (9 – 41.7)	23.5 (17 – 63.1)
Years with HIV	8 (1 – 32)	7.5 (1 - 31)	8 (1 - 32)
Years with ART	5.5 (0-29)	6 (0 - 29)	5 (0 - 23)
CD4 cell count category			
Unknown, n (%)	39 (8.7)	15 (38.5)	24 (61.5)
> 500 cell/µL, n (%)	272 (60.7)	106 (39)	166 (61)
200 – 499 cell/µL, n (%)	110 (24.6)	51 (46.4)	59 (53.6)
< 200 cell/µL, n (%)	27 (6)	16 (59.3)	11 (40.7)
Missing	2	2	0
Exercise			
Started after HIV dx, n (%)	-	-	149 (33%)
Started before HIV dx, n (%)	-	-	111 (25%)

Data presented in median and interquartile range (IQR), number of participants (n), and percentage (%). Patient self-reported: antiretroviral treatment (ART), CD4 cell count expressed in PLWH affected by anxiety and depression

QoL, anxiety, and depression

An analysis in depressed and/or anxiety PLWH engaging in RE or sedentary activities revealed no differences in QoL scores and the EQ-5D anxiety/depression dimension categories. Data is displayed in Table 2.

Discussion

The objective was to investigate the relationship between RE and the prevalence of anxiety and/or depression, and QoL in PLWH. The rates of anxiety and depression were lower, QoL scores were better in exercising compared to sedentary PLWH. These findings are in line with previous research in HIV negative (Schuch et al., 2018) and HIV-positive (Heissel et al., 2019). The prevalence for comorbid anxiety and depression did not differ between groups. This accords with previous cross-sectional studies with a reported prevalence between 8.1% (Camara et al., 2020) and 25% (Tesfaw et al., 2016) in PLWH explained by the impact that a chronic disease (like HIV) has on depression and anxiety (DeJean et al., 2013). Notably, no differences were found in the severity of anxiety and/or depression between exercising and sedentary depressed and/or anxious PLWH.

The reduced depression/anxiety symptoms (Table 3) and better QoL in exercising PLWH, may be attributed to different pathways in the physiopathology of depression and anxiety. Exercise can increase brain-derived neurotrophic factor (BDNF) circulating concentrations (lowered in depressed individuals (Kandola et al., 2019) and anxiety (Castrén & Kojima, 2017). In PLWH, a chronic inflammatory state is present (d'Ettorre et al., 2011) and pro-inflammatory markers identified as a cause of depression and anxiety (Renna et al., 2018), are downregulated by exercise (Kandola et al., 2019). Oxidative stress connected to HIV (Ivanov et al., 2016), and

ART elevates reactive oxygen species (ROS) in PLWH (Popoola & Awodele, 2016). Depression and anxiety are associated with oxidative stress (Hovatta et al., 2010; Black et al., 2015), and regular/long-term exercise produces an adaptive response to ROS by upregulating the production of antioxidant enzymes and enzymes that repair ROS damage (Kandola et al., 2019). Finally, exercise stimulates the parasympathetic nervous system activity (reduced in people with anxiety), ultimately regulating anxiety symptoms (Stubbs et al., 2017).

Table 2. MOS-HIV and EQ-5D questionnaires

Parameter	Sedentary	Recreational exercise	χ^2	Df	*p* value
PHSS	49.5 (20.5 – 65.1)	56.7 (17.6 - 63.4)			< 0.05
MHSS	44.4 (13.7 – 66.9)	51.6 (13.5 – 67.1)			< 0.05
EQ-5D HSI	0.909 (0.156 – 1))	0.910 (0.127 - 1)			< 0.05
EQ-5D VAS	70 (5 - 100)	85 (11 - 100)			< 0.05
Anxiety / depression			14.6	4	0.005
Category 1	67 (34.2)	129 (65.8) *			
Category 2	59 (34.4)	77 (56.6)			
Category 3	40 (50)	40 (50)			
Category 4	21 (65.6)	11 (34.4) *			
Category 5	3 (50)	3 (50)			

Number of participants (n), Chi square (χ^2), degrees of freedom (df), physical health summary score (PHSS), mental health summary score (MHSS), EQ-5D health state index (HSI), EQ-5D visual analogue score (VAS). Each dimension has five categories: 1) no problems, 2) slight problems, 3) moderate problems, 4) severe problems, and 5) extreme problems. Group participants: overall n =450; sedentary n =190; Recreational exercise n =260. Significant differences at the 0.05 level between recreational exercise and sedentary PLWH (*). Please refer to results supplementary material for dimension #1-4 of the EQ-5D.

Lower QoL scores in sedentary compared to exercising PLWH (Table 2), may be related to health/physical limitations (i.e., frail PLWH (Blanco et al., 2019), that hinder aptitude to perform exercise or, alternatively, discontinued exercise due to worse HIV-status.

Table 3. Risk of anxiety and depression in relation to anthropometric characteristics, HIV and ART, RE characteristics, and RE after the HIV diagnosis in PLWH.

Variables	Depression			Anxiety			Anxiety & depression		
	PR	95% CI	*p*	PR	95% CI	*p*	PR	95% CI	*p*
Model 1									
Age (yrs.)	1.01	1 - 1.03	0.03	1.01	1 - 1.03	0.4	1.02	0.99 – 1.04	0.05
Weight (kg)	1.12	0.95 - 1.32	0.11	1.24	1 - 1.45	0.04	1.22	0.98 – 1.52	0.06
BMI ($kg·m^{2-1}$)	0.71	0.41 - 1.17	0.64	0.14	0.34 - 1	0.05	0.52	0.26 – 1.05	0.08
Model 2									
Years since the HIV diagnosis (yrs.)	1.04	0.97 - 1.11	0.16	1.05	1 - 1.11	0.1	1	0.90 – 1.10	0.88
Years under ART (yrs.)	1	0.92 - 1.09	1	0.96	0.89 - 1.03	0.05	1	0.91 – 1.16	0.67
CD4 cell count ($cell·µL^{-1}$)	1	0.99 - 1	0.67	1	0.99 - 1	0.36	1	0.99 - 1	0.86
Model 3									
PHSS score	0.99	0.96 – 1.01	0.31	0.98	0.95 – 1.02	0.2	0.96	0.94 – 1	0.02
MHSS score	0.94	0.92 – 0.97	0.001	0.94	0.91 – 0.96	0.001	0.96	0.93 - 0.99	0.007
EQ-5D health index	0.30	0.08 – 1.13	0.01	0.26	0.06 – 1.15	0.02	0.22	0.04 – 1.31	0.03
Visual analog health score	0.98	0.97 – 0.99	0.001	0.98	0.97 – 0.99	0.001	0.98	0.97 – 1	0.03
Model 4									
Frequency ($session·week^{-1}$)	1.14	0.93 - 1.37	0.06	1.06	0.83 - 1.31	0.5	1	0.73 – 1.31	0.97
Intensity (METs)	0.80	0.64 – 1	0.04*	0.85	0.66 - 1.1	0.15	0.88	0.65 – 1.2	0.38
Duration ($hrs·week^{-1}$)	0.95	0.87 - 1.03	0.17	0.98	0.89 - 1.06	0.59	0.98	0.87 – 1.08	0.69
Model 5									
Exercise	0.62	0.41 – 0.94	0.01	0.57	0.36 – 0.91	0.01	0.43	0.24 – 0.75	0.002
Sedentary	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Prevalence ratio (PR), 95% confidence interval (95% CI). CD4 cell count expressed in cells per microliter ($cell·µL^{-1}$), Exercise intensity expressed in metabolic equivalents (METs), reference group (Ref). (*) this relation disappeared after controlling for years living the HIV diagnosis.

Limitations

Although a strength was the sample size (N=450), it was not nationally representative due to the convenience sampling, and although predominantly male with a distribution representative for PLWH (Reinsch et al., 2011), exercise anti-depressive effects vary among HIV-negative females and males (Bhui & Fletcher, 2000; Zhang & Yen, 2015). A self-report assessment was used; this may have increased the risk of memory and social desirability bias. Quantification of RE was not assessed through accelerometry or a validated PA questionnaire.

Conclusion and implications for practice

A lower likelihood of experiencing depression and/or anxiety was found in exercising PLWH. Exercise anxiolytic and anti-depressive effect is instrumental in informing exercise lifestyle interventions for PLWH to enhance their QoL. Exercise guidelines to control and adjust intensity, time, and frequency of exercise should be followed to prevent the occurrence of anxiety and/or depressive symptoms.

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