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**RISCO CARDIOVASCULAR E OS EFEITOS DE DIFERENTES
MODALIDADES DE EXERCÍCIO TERAPÉUTICO EM PESSOAS
VIVENDO COM HIV/AIDS: UMA REVISÃO SISTEMÁTICA**

TESE DE DOUTORADO

Salvador
2013

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Tese apresentada ao Programa de Pós-graduação em Medicina e Saúde, da Faculdade de Medicina da Bahia, Universidade Federal da Bahia, como requisito para a obtenção do grau de Doutor em Medicina e Saúde.

Orientador: Profº. Drº Carlos Roberto Brites Alves

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LISTA DE ABREVIATURAS E SIGLAS

ACSM - *American College of Sports Medicine*

AHA - *American Heart Association*

AIDS - *acquired immunodeficiency syndrome*

APTA - *American Physical Therapy Association*

AVD's - Atividades de Vida Diária

ECR – Ensaio clínico randomizado

BORG - escala de percepção de esforço

HIV - *human immunodeficiency virus*

OMS – Organização Mundial de Saúde

QV – Qualidade de Vida

QVRS – Qualidade de Vida Relacionada à Saúde

RCV – Risco cardiovascular

RM – Repetição máxima

SF-36 – *Medical Outcomes Short Form Health Survey*

TARV - Terapia antirretroviral

TC – Tomografia Computadorizada

TC6 – Teste de caminhada de seis minutos

VO₂max – Consumo máximo de oxigênio.

Figura 1 - Lista de abreviaturas e siglas

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RESUMO

A terapia antirretroviral potente (TARV) tem sido associada a uma variedade de efeitos adversos, o que aumenta a incidência de distúrbios funcionais, o risco de eventos cardiovasculares e diminui a qualidade de vida (QV) em pacientes com HIV. A identificação dos riscos cardiovasculares (RCV) e as limitações funcionais podem contribuir na elaboração de estratégias de prevenção e reabilitação de pacientes com HIV. Assim, o objetivo desta tese foi identificar os RCV em pacientes com HIV/AIDS e avaliar os efeitos de programas estruturados de exercícios físicos na condição cardiovascular, funcional e QV, através de revisão sistemática da literatura. As bases de dados consultadas foram: Medline, Scielo, Lilacs, e PEDro. Foram selecionados estudos que identificassem RCV em pacientes em uso de TARV e ensaios clínicos randomizados (ECRs) que avaliaram o efeito do exercício resistido (ER), exercício aeróbico (EA) e o treino concorrente, nos desfechos composição corporal, desempenho muscular, capacidade funcional aeróbica e QV. A escala PEDro foi utilizada para avaliação da qualidade dos ECRs. Em relação ao RCV em pacientes com HIV em uso de TARV, a revisão sugere um excesso de RCV quando comparado a pessoas não infectadas. A utilização da TARV foi associada com aumento nos níveis de colesterol, triglicerídeos, acumulo de gordura visceral e disfunção endotelial. Alguns regimes TARV aumentam risco de dislipidemia, doença cardiovascular, particularmente regimes contendo inibidores de protease. ECRs individuais sugerem que cada tipo de exercício contribui na melhora de diferentes parâmetros fisiológicos e funcionais. O ER foi associado com melhora significativa nos desfechos de composição corporal e desempenho muscular, o EA foi identificado por favorecer a melhora tanto da composição corporal quanto da capacidade aeróbica e o treino concorrente foi o que apresentou resultados significativos em todos os desfechos avaliados, devendo ser a modalidade de escolha na indicação do exercício terapêutico em pacientes com HIV.

ABSTRACT

The highly active antiretroviral therapy (HAART) has been associated with several side effects, which increases the incidence of disability and the risk of cardiovascular events and decreases the quality of life (QOL) in patients with HIV. The identification of cardiovascular risk factors (CRF) and disabilities may contribute to the development of strategies for prevention and rehabilitation of patients with HIV. So, the aim of this thesis was to identify the CRF in patients with HIV/AIDS and to evaluate the effects of structured exercises on cardiovascular fitness, functional and QOL through systematic literature review. The following databases were searched: Medline, SciELO, Lilacs, and PEDro. We selected studies that identified CRF in patients using HAART and randomized clinical trials (RCTs) that evaluated the effect of resistance exercise (RE), aerobic exercise (AE) and concurrent training in body composition, muscle performance, functional aerobic capacity and QOL. The PEDro scale was used to assess the quality of RCTs. This review suggests a higher prevalence of RCV in infected compared to non-infected subjects. The use of HAART was associated with increased levels of cholesterol, triglycerides, visceral fat accumulation and endothelial dysfunction. Some schemes of antiretroviral therapy increased risk of dyslipidemia and cardiovascular disease, particularly those regimens containing protease inhibitors. Individual RCTs suggest that each type of exercise contributes to the improvement of different physiological and functional parameters. The RE was associated with significant improvement in body composition and muscle performance, the AE was associated with significant improvement in body composition, and aerobic capacity. The concurrent training presented significant improvements on all outcomes and should be the modality of choice in the therapeutic indications of exercise in patients with HIV.

1. INTRODUÇÃO

A disponibilidade da terapia antirretroviral altamente potente (TARV) teve impacto notável na morbimortalidade por AIDS, no aumento da sobrevida, na redução da incidência de doenças oportunistas e na queda das internações hospitalares. Apesar dos benefícios, eventos cardiovasculares podem estar associados ao uso da TARV em indivíduos com HIV, independente de fatores de risco clássicos.

Pacientes que antes evoluíam para o óbito agora são caracterizados como doentes crônicos com maior morbidade e incapacidades relacionadas a componentes físicos, social e psicológico da saúde. Uma variedade de alterações funcionais que comprometem a função corporal, a execução de atividade ou a participação social desses indivíduos devem ser avaliadas por profissionais de saúde. Estratégias de prevenção e tratamento como intervenções dietéticas e programas de exercício devem ser elaborados e implementados na prática clínica.

No decorrer dos anos, a prática de exercícios físicos foi vista ora como aliada, ora como deletéria no controle e tratamento de pacientes com doenças crônicas. Isso se deve, em parte, à falta de esclarecimento de alguns profissionais, que ainda nos dias de hoje resistem a prescrever exercícios físicos, com receio de agravamento do quadro. Atualmente o exercício físico é recomendado para pessoas saudáveis e com diversas condições de saúde.

O exercício terapêutico caracterizado como um programa de exercícios estruturados aplicado a pacientes com limitações funcionais, vem sendo considerado uma importante terapia complementar para promoção da saúde de pacientes com HIV. O objetivo do exercício nesta população é minimizar os efeitos deletérios, complicações decorrentes da evolução da doença, diminuir o risco cardiovascular e promover adaptação das suas limitações para o desempenho das atividades da vida diária (AVDs), bem como maximizar o bem-estar e a qualidade de vida.

Diferentes modalidades (tipos) de exercício podem ser selecionadas de acordo com os problemas encontrados. Os exercícios resistidos e aeróbicos estão sendo investigados, apresentando resultados significativos na melhora de desfechos fisiológicos e funcionais, porém são escassos os estudos que avaliaram os efeitos do exercício na qualidade de vida desta população, merecendo maior atenção.

O exercício resistido está bem definido como o mais efetivo método disponível para a melhora da força, resistência e desempenho muscular, por meio do princípio da sobrecarga. Já o exercício aeróbico promove efeitos significativos na melhora da capacidade aeróbica medida pelo consumo máximo de oxigênio (VO_{2max}). Embora diretrizes específicas para grupos especiais constituam a base para a prescrição individualizada, os componentes básicos mais comuns para todos os programas de exercício constituem a estrutura para a prescrição do programa, independente da população a que se destine.

Quando o exercício resistido e aeróbico são aplicados no mesmo paciente em uma única sessão, ele passa a ser denominado de treino concorrente ou associado. O termo concorrente está associado à concorrência demonstrada em treinos associados de exercício resistido e aeróbico numa mesma sessão. Estudos em indivíduos saudáveis demonstram que o treino concorrente pode reduzir os efeitos específicos de cada tipo de exercício, mas amplia a quantidade de desfechos fisiológicos e funcionais melhorados.

Em pacientes que apresentam comprometimentos funcionais múltiplos a combinação de modalidades diferentes de exercícios em programas de reabilitação, pode ser uma alternativa útil e complementar ao uso de medicamentos, principalmente pelos efeitos adversos gerados, podendo melhorar diferentes incapacidades, o que não seria possível com um único tipo de exercício.

Os resultados esperados desse trabalho podem ser o ponto de partida para a recomendação da incorporação de programas de exercício combinados durante o tratamento desses pacientes, que sobrevivem mais, porém com incapacidades e baixa qualidade de vida.

2. OBJETIVOS

2.1 GERAL

Comparar os efeitos de diferentes tipos de exercícios terapêuticos na condição cardiovascular, funcional e QV de pessoas com HIV/AIDS.

2.2 ESPECÍFICO

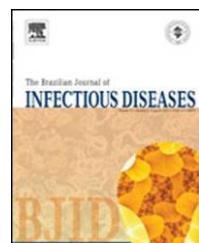
Identificar o RCV em pacientes com HIV/AIDS em uso de TARV.

3. ARTIGOS

3.1 Artigo 1: A literature review on Cardiovascular Risk in HIV infected patients: Implications for clinical management

3.2 Artigo 2: A Systematic Review of effects of concurrent strength and endurance training on the Health-Related Quality of Life and cardiopulmonary status in Patients with HIV/AIDS

3.3 Artigo 3: A systematic review on the effects of different types of therapeutic exercise on physiologic and functional measurements in patients with HIV/AIDS



1 Review article

A literature review on cardiovascular risk in human immune deficiency virus-infected patients: implications for clinical management

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article info abstract

Article history: *Introduction:* In recent years, there has been growing concern about an increasing rate of Received 23 November 2012 cardiovascular diseases in human immunodeficiency virus-infected patients, which could Accepted 8 May 2013 be associated with side effects of highly active antiretroviral therapy. It is likely that the

Available online xxx metabolic disorders related to anti-human immunodeficiency virus treatment will eventually translate into an increased cardiovascular risk in patients submitted to such regimens.

Keywords: *Objective:* To evaluate if human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy are at higher risk of cardiovascular diseases than human immunodeficiency virus infected patients not receiving highly active antiretroviral therapy, Highly active antiretroviral therapy or the general population.

Cardiovascular diseases Research design and methods: We conducted a computer-based search in representative databases, and also performed manual tracking of citations in selected articles.

Result: The available evidence suggests an excess risk of cardiovascular events in human immunodeficiency virus-infected persons compared to non-human immunodeficiency virus infected individuals. The use of highly active antiretroviral therapy is associated with increased levels of total cholesterol, triglycerides, low-density lipoprotein and morphological signs of cardiovascular diseases. Some evidence suggested that human immunodeficiency virus-infected individuals on highly active antiretroviral therapy regimens are at increased risk of dyslipidemia, ischemic heart disease, and myocardial infarction, particularly if the highly active antiretroviral therapy regimen contains a protease inhibitor.

Conclusion: Physicians must weigh the cardiovascular risk against potential benefits when prescribing highly active antiretroviral therapy. Careful cardiac screening is warranted for patients who are being evaluated for, or who are receiving highly active antiretroviral therapy regimens, particularly for those with known underlying cardiovascular risk factors. A better understanding of the molecular mechanisms responsible for increased risk of cardiovascular diseases in human immunodeficiency virus-infected patients will lead to the discovery of new drugs that will reduce cardiovascular risk in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy.

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2 Introduction

The widespread use of highly active antiretroviral therapy (HAART) – comprising protease inhibitors (PIs) and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs) combined with nucleoside reverse-transcriptase inhibitors (NRTIs)–has dramatically decreased the morbidity and mortality associated with human immunodeficiency virus (HIV) infection in the developed world.^{1,2}

Since the introduction of HAART in 1995, a significant decrease in mortality was observed in HIV-infected patients associated with a marked reduction in the incidence of opportunistic infections and certain kinds of cancers.^{3,4} However,

current evidence suggests that patients on HAART are at increased risk of developing cardiovascular disease (CVD), and recent studies reported a higher prevalence of traditional risk factors for CVD in HIV-infected patients than in non-infected controls, such as arterial hypertension, dyslipidemia, and diabetes mellitus. These abnormalities may be associated with the use of certain antiretroviral drugs.⁵

HIV infection leads to a chronic systemic inflammatory process, which is increasingly accepted as having an important role in the pathogenesis of atherosclerosis and acute cardiovascular events. HIV-infected patients have been described as presenting unique histological features of coronary artery disease, including a rapid progression of diffuse circumferential arterial lesions with proliferation of smooth muscle cells, elastic fibers, and endoluminal protrusions.⁶

HIV-infected patients with acute coronary syndrome tend to be younger, with lower high-density lipoprotein (HDL) levels, higher prevalence of smoking, and less angiographically apparent coronary artery disease, when compared to non-HIV patients, which represents a different epidemiological pattern. HIV-infected patients may have concomitant traditional risk factors for CVD such as smoking, hypertension, and dyslipidemia, but the HIV and HAART may interact with these factors and contribute to the increased incidence of CVD. The long-term benefits of HAART are remarkable, but the associated complications make the overall management of HIV-infected patients more complex and costly.⁷

Because of the dissemination of HIV infection and its potential association with CVD, some authors have proposed a routine and systematic evaluation of HIV-infected adults and children, including medical history, cardiac examination and systematic echocardiographic monitoring, since asymptomatic cardiac disease and cardiac symptoms can often be misled by secondary effects of HIV infection.⁸

The aim of this review was to evaluate if HIV-infected patients receiving HAART are at higher risk of CVD in relation to HIV-infected patients not receiving HAART and to the general population.

3 Methods

We performed a computer-based search, querying Ovid MEDLINE (1950 to July 2012), EMBASE (1980 to July 2012), and the Cochrane Central Register of Controlled Trials

Population	HIV-infected adults
Intervention	Antiretroviral therapy (when applicable)
Comparator	HIV-infected adults without antiretroviral therapy
Outcome	General population Cardiovascular Disease or Cardiovascular Risk Factors
Type of study	Randomized Clinical Trials (RCT) and Observational Studies

for original research articles published in English, Spanish and Portuguese. Medical Subject Headings (MeSH) were used as search terms when available, and keywords were used when appropriate. Terms for Anti-HIV Agents, HIV Infections, Cardiovascular Diseases, and Cardiovascular Diseases/complications were combined with a variety of MeSH terms to delimit relevant study designs and populations.

The selected outcome measures were common clinical cardiovascular outcomes (e.g. ischemic heart disease (IHD), heart failure (HF), cerebrovascular disease, acute coronary syndrome, myocardial infarction (MI) and peripheral vascular disease), or established traditional risk factors for CVD (e.g. hypertension and hypercholesterolemia).

One reviewer made the search and the initial selection of potentially relevant studies meeting the inclusion criteria and two independent reviewers selected articles that met the established inclusion and exclusion criteria. Studies were assessed for use of an appropriate source population, measurement methods of exposure and outcome, methods to deal with design-specific issues such as bias and lost to follow-up, use of analytical methods and use of statistics for primary analysis of effect. A manual tracking of citations in articles selected was also performed.

The structure of the search is shown in Table 1. Abstracts and relevant full-text articles were reviewed by one researcher.

4 Results

Design of clinical trials and subjects

The search strategy identified 205 titles, 159 of which were excluded because they did not match the source population, outcome or study design did not address the research question. Of 46 potential articles, only 26 were directly related to the main goal of this review, and two studies were added after manual search. A total of 28 articles were included in the review: four randomized clinical trials and 24 observational studies being 22 prospective cohorts and two case-control studies.

Table 2 summarizes the main characteristics and results of studies included in this review.

Evidence from the included studies indicates that exposure to antiretroviral drugs is associated with an increased rate of CVD events. HIV infection decreases good cholesterol, increases triglycerides (TG), total cholesterol (TC), and vascular inflammation.^{10,16-19,22,24,25,30} Traditional cardiovascular

risk (CVR) factors substantially contribute to the development of diastolic dysfunction (DD) in the HIV-infected patients.¹⁵

Table 2 – Study characteristics and results.

Study	Type of study	Population-follow-up	Drugs	Results	Outcomes
Coplan et al., 2003 ⁹	Prospective cohort	10,986 HIV-patients which 7951 received PI therapy – 12 months	IDV, NFV, SQV Ritonavir	RR of MI were 1.69 (0.54, 7.48) in PI-containing HAART and 1.74 (0.5, 9.0) for patients with NRTI-only regimens.	No difference in MI incidence between the PI containing or not containing groups
Llibre et al., 2006 ¹⁰	Prospective cohort	352 HIV-patients in use of 3 antiretroviral drugs – 48 weeks	Substitution of TDF by d4T	Reduction in TC (-17.5 mg/dL ; $p < 0.001$), LDL-C (-8.1 mg/dL ; $p < 0.001$) and TG (-35 mg/dL ; $p < 0.001$) at 48 weeks of follow up.	TC reduction HDL and LDL-C reduction TG reduction
Velenzuela et al., 2007 ¹¹	Prospective cohort	276 patients: 168 – HAART and PI 108 – HAART – 4 months	NS	Low CVR but higher TC and TG in the subpopulation of patients who received PI	Low CVR; higher TC and TG in the subpopulation of patients who received PI
Brothers et al., 2009 ¹²	Prospective cohort	HIV received ABC ($n = 9502$) or not ($n = 4672$) – 24 week	ABC and NS	MI were comparable among subjects exposed $n = 16$ (0.168%); or not $n = 11$ (0.235%) to ABC-containing therapy.	CAD and MI events were similar across ABC-exposed and non-ABC-exposed groups
Worm et al., 2010 ¹³	Prospective cohort	33,308 HIV-patients (D:A:D Study) – >1 year	AZT, ddI, ddC, d4T, 3TC, ABC, TDF, IDV, NFV, LPV, SQV, NVP, EFV	Recent exposure to ABC or ddI was associated with an increased risk of MI. Cumulative exposure to IDV and LPV was associated with an increased risk of MI.	Increased risk of MI associated with IDV, LPV, ddI, ABC
Cahn et al., 2010 ¹⁴	Prospective cohort	4010 HIV-patients receiving HAART for at least 1 month – 2 years	NS	The overall 10-year risk of CVD, as measured by the FRF, was 10.4 (24.7). The FRF score increased with duration of HAART.	80.2% of dyslipidemia 20.2% of metabolic syndrome
Obel et al., 2010 ¹⁵	Prospective cohort	2952 HIV-patient	ABC, AZT, d4T, ddI, 3TC	RR of MI hospitalization with ABC was 2.22 (95% CI 1.31–3.76). The risk of MI increased after initiation of ABC IRR adjusted for confounders = 2.00 (95% CI 1.10–3.64).	
Saint-Martin et al., 2010 ¹⁶	Prospective cohort	33 ATV/r > 6 months 99 ATV/r naive controls – 18 months	ATV/R Others	The CIMT course significantly decreased ($p = 0.018$) in cases at 18 months.	CIMT significantly decreased ($p = 0.018$)
Ribaudo et al., 2011 ¹⁷	Prospective cohort	1704 received ABC 3352 no ABC – 3.1 years	NS	6 years after ART initiation, 36 MI events were observed in 17,404 person-years. No evidence of an increased hazard of MI in subjects using ABC vs. no ABC was seen (over a 1-year period: $p = 0.50$; HR = 0.7 [95% CI, 0.2–2.4]).	No evidence that initial ART containing ABC increases MI risk over short-term and long-term periods
Durand et al., 2011 ¹⁸	Prospective cohort	7053 HIV-positive patients were matched to 27,681 HIV-negative patients	ABC LPV EFV	The drugs that were associated with an increased risk of AMI for any exposure were ABC OR = 1.79, lopinavir OR = 1.98, ritonavir OR = 2.29 and EFV OR = 1.83.	HIV+ were at higher risk of AMI than the general population, and several ARTs were associated with an increased risk of AMI

Table 2 (Continued)

Study	Type of study	Population-follow-up	Drugs	Results	Outcomes
Friis-Moller et al., 2003 ¹⁹	Prospective cohort	17,852 patients enrolled in DAD from nine of 11 participating cohorts	PIs, NNRTIs	Increased prevalence of elevated TC among subjects receiving an NNRTI but no PI OR = 1.79, PI but no NNRTI OR = 2.35, or NNRTI + PI OR = 5.48 compared to the prevalence among antiretroviral therapy (ART)-naïve subjects.	CVD risk factors were prevalent. With the highest prevalence among patients receiving PI, NNRTI or both of these drug classes
Choi et al., 2011 ²¹	Prospective cohort	10,931 HIV-infected patients initiating antiretroviral therapy in the Veterans Health Administration from 1997 to 2007	ABC TDF	123 cardiovascular events in 15,142 person-years of <6 months ABC use and 90 in 22,551 person-years TDF use. Incidence of any CVD event were higher in the setting of ABC use compared with TDF use or other ART (13.4 vs. 9.4 per 1000 person-years $p < 0.01$).	Recent ABC exposure was significantly associated with higher risk of atherosclerotic vascular events, and recent TDF exposure was significantly associated with HF
DAD Study Group, 2003 ²²	Prospective cohort	23,468 HIV-patients were enrolled from 11 previously cohorts	PIs NRTIs	The incidence of MI increased with longer exposure to combination antiretroviral therapy (adjusted relative rate per year of exposure, 1.26 [95 percent confidence interval, 1.12 to 1.41]; $p < 0.001$).	Combination ART was independently associated with a 26% relative increase
Silva et al., 2009 ²⁵	Cohort	HIV-positive patients	PIs NRTIs NNRTIs	DD was present in 336 (48%) of the total HIV infected population. While not statistically significant, NRTI and PI use showed a trend toward a greater prevalence in the DD group.	High prevalence of DD in HIV patients was demonstrated. Traditional CVD risk factors contributed to the DD
Triant et al., 2007 ²⁶	Prospective cohort	215 patients receiving HAART and 69 HAART-naïve patients	G A: G B: G C: G D: G E:	TC, HDL, TG and glucose were higher in the HAART group than in the non-HAART group $p < 0.001$. According to the FRS, the CVD risk was moderate to high in 11% receiving HAART.	Although the mean values for TC, HDL-c and TG were higher in the HAART group, a higher CVR was not identified in the former
Alvarez et al., 2010 ²⁷	Prospective cohort	3851 HIV and 1,044,589 non-HIV patients	PIs NRTIs NNRTIs	AMI was identified in 189 HIV and 26,142 non-HIV patients. AMI rates were increased in HIV vs. non-HIV patients 11.13 vs. 6.98 ($p < 0.001$).	AMI rates and CVR factors were increased in HIV compared with non-HIV patients
		4010 HIV patients		The overall prevalence of MS was 20.2% (812/4010). The 10-year risk of developing CVD was 10.4% (24.7). Patients with MS had higher CVD risk 22.2% vs. 7.4%, respectively, $p < 0.001$.	MS in HIV-infected patients receiving ART is comparable to populations. Patients with MS had higher estimated risk for CVD

Table 2 (Continued)

Study	Type of study	Population-follow-up	Drugs	Results	Outcomes
Kwiatkowska et al., 2011 ²⁸	Prospective cohort	72 HIV infected patients and 27 healthy individuals	PIs, NNRTIs, NRTIs	HIV infected patients show more advanced subclinical atherosclerosis in the carotid arteries (cIMT and plaques incidence). Patients treated with ARV therapy for over 5 years have a higher value of cIMT.	HIV shows significant progression of subclinical atherosclerosis and incidence of atherosclerotic plaques
D:A:D Study Group*, 2008 ²⁹	Prospective cohort	33,347 HIV-1-infected		Associations between the rate of MI and cumulative or recent use of AZT, d4T, or 3TC. Recent use of ABC or ddI was associated with an increased rate of MI relative rate 1.90 with ABC and 1.49 with ddI [p = 0.003].	There exists an increased risk of MI in patients exposed to ABC and ddI. The excess risk does not seem to be explained by underlying established CVD risk factors
SMART/INSIGHT and DAD Study, 2008 ³⁰	Prospective cohort	4544 HIV patients	NRTIs PIs	Use of ABC was associated with an excess risk of CVD compared with other NRTIs. Adjusted hazard ratios for clinical MI (n = 19), major CVD (MI, stroke, surgery for CAD, and CVD death; n = 70).	Current use of ABC was associated with an excess risk of CVD compared with other NRTIs. The drug may cause vascular inflammation, which may precipitate a CVD event
Obel et al., 2007 ³¹	Prospective cohort	3953 HIV-infected patients and 373,856 Control subjects	PIs, NNRTIs, NRTIs	In HAART period, the risk of ischemic heart disease (IHD) increase was substantially higher RR = 2.12. 1 year after receiving a diagnosis of HIV infection, RR of IHD was 2.38.	Compared with the general population, HIV-infected patients receiving HAART have an increased risk of IHD
Van Vonderen 2009 ³³	Case-control	55 HIV-patients ART, 22 HIV-patients ART naive 23 HIV-patients with LD 52 controls - NA	NS	HIV infected patients had a 0.067 mm (10.8%) greater CIMT than controls. Patients exposed to ART had similar CIMT compared with ART-naive patients but 25.9% lower DC and 21.7% lower CC of the femoral artery.	HIV infection is independently associated with C-IMT and generally increased arterial stiffness
Lang et al., 2010 ³⁴	Case-control	289 HIV-patients with history of MI 884 HIV-patients with no history of MI - 6 years	ABC, AZT, d4T, 3TC, TDF	Recent exposure to ABC was associated with an increased risk of MI (OR, 2.01; 95% CI, 1.11–3.64) Cumulative exposure to all PIs except SQV was associated with an increased risk of MI.	Short-term/recent exposure to ABC was associated with an increased risk of MI
Wand et al., 2007 ³⁵	RTC	288 ddI/d4T with EFV 305 ddI/d4T with NFV 288 ddI/d4T with EFV+ NFV - 3 years	ddI d4T EFV NFV	MS association with increased risk of CVD HR = 2.56 and was associated with an increased risk of T2DM (ATP-III: HR = 4.34; p = 0.001). Incident MS was associated with an increased risk of both CVD (ATP-III: HR = 2.73; p = 0.036) and T2DM (ATP-III: HR = 4.89; p < 0.0001).	Progression to MS

Table 2 (Continued)

Study	Type of study	Population-follow-up	Drugs	Results	Outcomes
Van Vonderen et al., 2009 ³⁶	RTC	19 HIV-patients with LPV/r plus ZDV/3TC 18 LPV/r plus NVP-3 years	LPV/r ZDV 3TC NVP	CIMT increased by 0.061 mm ($p < 0.001$) in the ZDV/3TC/LPV/r arm and by 0.044 mm ($p = 0.012$) in the NVP/LPV/r arm. Femoral artery DC and CC decreased in the ZDV/3TC/LPV/r arm and femoral DC decreased in the NVP/LPV/r arm.	CIMT and femoral artery stiffness increased after the initiation of HAART
Martinez et al., 2010 ³⁷	RTC	46 ABC/3TC 34 TDF/emtricitabine) 48 weeks	ABC 3TC TDF Emtricitabine	TC increased significantly in the ABC/3TC vs. TFV/ETB group, found no significant changes in the biomarkers ($p = 0.12$ for all comparisons)	ABC/3TC increase TCl and LDL Did not cause inflammation, endothelial dysfunction, insulin resistance
Murphy 2010 ³⁸	RTC	26 ATV/r 24 remained on PI regimen 24 weeks	ATV/r Others	Changes in the ATV/r vs. continued PI group were observed for TC (-25 vs. +1.5 mg/dL, $p = 0.009$), TG (-58 vs. +3.5 mg/dL, $p = 0.013$), and non HDL-C (-27 vs. -0.5 mg/dL, $p = 0.014$).	ATV/r improved lipid profile Did not change endothelial function, inflammatory and metabolic markers

TC, total cholesterol; HDL-C and LDL-C, high and low-density lipoprotein cholesterol; TG, triglycerides; CVR, cardiovascular risk; MI, myocardial infarction; AMI, acute myocardial infarction; FRF, Framingham risk score; CAD, coronary artery disorder; CIMT, carotid intima-media thickness; LD, lipodystrophy; MS, metabolic syndrome; 3TC, lamivudine; AZT, zidovudine; d4T, stavudine; ddC, zalcitabine; ddi, didanosine; EFV, efavirenz; IDV, indinavir; LPV, lopinavir/ritonavir; NFV, nelfinavir; NVP, nevirapine; SQV, saquinavir; TDF, tenofovir; ATV/r, atazanavir; ABC, Abacavir; ETB, emtricitabine; OPG, osteoprotegerin; ADT, adiponectin.

G A: (AZT) + (3TC) + EFV; G B: AZT + 3TC + LPV e AZT + 3TC + NFV; G C: AZT + 3TC + ATV/r; G D: (d4T) + 3TC + EFV; G E: d4T + 3TC + LPV e d4T + 3 TC + NFV e d4T + ddi + LPV (RTI) – reverse transcriptase inhibitors not specified (NS); not applicable (NA); relative risk (RR).

The use of several antiretroviral agents favors the occurrence of multiple metabolic and morphologic abnormalities, including dyslipidemia, insulin resistance, subcutaneous fat loss, visceral fat accumulation, and metabolic syndrome (MS), which are associated with an increased risk of premature atherosclerosis and MI.^{6,9,11,13,16,18,28}

HAART may also indirectly induce endothelial dysfunction.^{19,24}

HIV infection itself is an independent risk factor for acute myocardial infarction (AMI) and increase arterial stiffness. Compared with the general population, HIV-infected patients receiving HAART have an increased risk of AMI and IHD,^{18,26,31,33,36} and increase in thickness of the intima-media complex.^{28,33}

Combination antiretroviral therapy is associated with MI,^{9,13,22,29} and longer exposure to HAART and/or PIs seem to increase the risk of MI.^{29,32} HIV-infected patients using PI had slightly higher CVD risk than those using NNRTI, and slightly increased risk for patients using abacavir (ABC) or didanosine (ddI).^{18,26} Recent ABC exposure was significantly associated with higher risk of atherosclerotic vascular events, CVD, and an increased risk of MI.^{21,30,34} There exists an increased risk of MI in patients exposed to ABC and ddI within the preceding six months.²⁹

which ABC use was randomized as part of a combined antiretroviral regimen and found no association between the use of ABC and MI.⁴¹

When the outcome was the change in lipid profile, two studies showed a reduction on TC, LDL, TG,^{10,38} and two demonstrated an increase in blood lipids.^{11,37} Two studies showed an increase in CIMT,^{10,33} and one demonstrated a decrease in CIMT.¹⁶

We must be aware that the population studied in all of the reviewed studies are HIV-infected adult patients, but with different characteristics. The studied populations had different age ranges and gender; different stages of HIV infection and most of them were receiving different antiretroviral drugs regimens, which could have different effects not only in the surrogate markers of CVD risk but mainly in the incidence of CVD.

In spite of individual studies suggesting that currently available PIs could increase the CVR,^{18,26,29,32} the PI class remained a very effective class of antiretroviral drugs for HIV infection therapy. Life expectancy for HIV-infected patients has improved by 20 years for those diagnosed at age 25–33 years, and it is still improving. The HIV-infected population is becoming more susceptible to all chronic diseases that are observed in non-HIV-infected patients with the presence of additional risk factors for CVD due to infection and the treatment itself.⁴²

5 Discussion

Cardiovascular complications of HIV disease are generally late manifestations and may be related to prolonged effects of immunosuppression and a complex interplay of mediator effects from opportunistic infections, autoimmune response to viral infection, drug-related cardiotoxicity, nutritional deficiencies, and prolonged immunosuppression.³⁹

There are many ways to assess the risk of CVD and multiple risk factors can be examined, such as age, gender, body mass index (BMI), TC, LDL, TG, MS, MS, carotid intima-media thickness (CIMT). These traditional risk factors for CVD increase risk of cardiovascular events in both HIV-infected and uninfected individuals.

For HIV-infected patients the retroviral chronic infection *per se*, the use of HAART and/or at least some of the antiretroviral drugs, and lipodystrophy can be considered additional risk factors. HIV infection plays a substantial role on blood lipids disorders and can induce endothelial cells injury which leads to a local inflammatory response that could promote thrombosis, impair vessel responsiveness, and is an important factor for arterial plaque formation. HIV replication may activate endothelial surfaces directly or via up-regulation of pro-inflammatory cytokines.

Some studies suggested that even though the overall cardiovascular event rate is low, there is an excess risk of cardiovascular events in HIV-infected persons compared to non-HIV-infected individuals. Some evidence suggested that HIV-infected individuals on HAART regimens are at increased risk of dyslipidemia, IHD, and MI, particularly if the HAART regimen contains a PI. While lipid-lowering drugs are a routine strategy for CVR reduction in the general population, HIV-infected people are usually not on those drugs even when clinically indicated.⁴⁰

In this review we observed some different outcomes associated with different results. When the outcome was MI and the use of ABC was investigated, in three studies increased MI incidence was detected^{13,15,34} and in two studies there were no significant differences.^{12,17} Recently, the U.S. Food and Drug Administration (FDA) conducted a meta-analysis in

The clinical expression of cardiac involvement is variable and is affected by the stage of HIV disease, the degree of immunodeficiency, and the use of drugs to treat HIV disease or to treat or prevent opportunistic infections and neoplasms.⁴³ CVR must be considered in the overall care of adults with HIV infection. However, such risk should not influence the decision of when to initiate antiretroviral therapy, and the decision of which antiretroviral regimen to use should be made based on risk and benefit analysis that includes the clear survival benefit associated with maximal viral suppression.

HIV-infected patients confront an escalating epidemic of CVD that is comparable to that faced by the general population more than half a century ago. Stratifying risk among HIV-infected patients and devising cardiovascular preventive strategies are priorities.⁴⁴ The initial choice of ART regimen and subsequent modifications also may be considered in planning CVD prevention strategies, because the risks of inadequately treated HIV infection outweigh any increase in CVD risk that may be associated with ART, and with the understanding that uncontrolled viral infection may itself contribute to CVD risk.^{45,46}

CVD risk assessment and risk reduction are essential components of preventive medical care that are increasingly important for patients with HIV. Physicians should systematically assess their HIV-infected patients for CVR factors and should closely monitor patients receiving HAART, especially those with additional risk factors for CVD.⁴⁷

The role of the cardiologist in the evaluation and treatment of patients with HIV infection should therefore be expanded to include patients who are being evaluated for or who are receiving HAART regimens, especially those with underlying CVR. It may be important to consider traditional coronary risk profiles and to alter those that can be modified in the evaluation and continued therapy of patients with HAART.⁴⁸ It is especially important to develop simple and clear messages to educate patients about the importance of CVD prevention, the importance of identifying and treating CVD risk factors or high CVD risk, and how smoking, adverse dietary habits, and physical inactivity increase CVD risk.⁴⁹

Treatment options include the use of pharmacological and non-pharmacological methods for managing dyslipidemia and hyperglycemia, as well as considering lipid-neutral HAART regimens for their patients, especially with the availability of drugs in this class with less adverse impact on lipid profile.⁴⁷ One potential strategy to manage dyslipidemia is

switching the ARV drug that promotes the lipids increase. However, it should be taken into consideration that it depends on the availability of remaining active drugs without impact on plasma lipids. In addition, switching requires a careful evaluation of the risks of virological failure, especially for patients with previous failure to ARV regimens.

Dyslipidemic HIV/HAART patients have elevated levels of lipoprotein-associated phospholipase A2 (Lp-PLA2). The main physiological action of Lp-PLA2 is the hydrolysis of strongly inflammatory phospholipids, such as platelet-activating factor which may increase risk of CVD.^{50,51} Elevated plasma Lp-PLA2 can be reduced by an intensive diet and exercise program in patients with HIV/HAART-associated dyslipidemia.⁵¹

Current guidelines recommend dietary intervention as first line treatment for HIV dyslipidemia.^{52,53} Omega-3 supplementation has a triglyceride-lowering effect that may impact on cardiac outcomes. Triglyceride levels represent an important biomarker of CVD, because of their association with atherogenic remnant particles. The 33,308 HIV-infected included in the study of Worm et al., with elevated triglyceride levels, experienced 580 MIs over 178,835 person-years. The risk of MI increased by 67%, per doubling in triglyceride level.⁵⁴

Recently, Stradling et al. conducted a Systematic Review and Meta-Analysis which provides evidence for a comparable clinical benefit of dietary intervention or omega-3 supplementation in reducing triglycerides.⁵⁵ Diet supplementation with fish oil is prescribed when a suppression of lipid mobilization is desired. The use of antihyperlipidemic drugs should be reserved for patients at high risk of cardiovascular events.⁵⁶

Lifestyle changes (healthy diet, smoking cessation, and daily physical exercise) reduce the probability of a coronary event by up to 80% in the general population. Dietary, pharmacological interventions and exercise are established interventions to reduce metabolic changes and the relevant risk.⁵⁶

Exercise is consistently listed among the three most common complementary and alternative therapies utilized by HIV-infected persons. A training program that involves concurrent endurance and strength training must be prescribed. Exercise aerobic should be performed at a moderate intensity: from 11 to 14 on the Borg Rating of Perceived Exertion Scale, or 50–85% of peak heart rate and resistance training should focus on large muscle groups, with intensity of 60–80% of one maximal repetition and 8–12 repetitions.^{56,57}

A significant body of evidence suggests that there is a measurable increase in the risk of CVD in HIV-infected patients with varying effects from different antiretroviral drugs. In spite of studies, the impact of HIV and different HAART regimens on the risk of CVD in HIV-infected patients remains somewhat obscure. Differences in study design, endpoints, patient populations and limited follow-up in some studies prevent definitive comparisons.⁵⁸

This review has several limitations, most of them due to the varying methodologies and study designs and inherent limitations of observational studies, which makes it difficult to control for population or selection bias. Furthermore, substantial variations in study design complicate the analysis of the associations between HAART and CVD risk. Considering its descriptive purpose and the findings of this review, it seems reasonable to believe that both HIV infection and HAART have potential adverse impact on CVR factors and on the incidence of CVD.

6 Conclusion

There are many studies addressing the relationship between HAART and CVD and it is an issue still under debate. However, it is clear that this combined antiretroviral therapy remarkably decreased the overall mortality associated with HIV infection. Our review confirms that HIV-infected patients present risk of CVD, and for this reason preventive strategies should be focused on smoking cessation, increase physical exercise, and diet.

7 Conflict of interest

The authors declare no conflicts of interest.

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Review Article

A Systematic Review of Effects of Concurrent Strength and Endurance Training on the Health-Related Quality of Life and Cardiopulmonary Status in Patients with HIV/AIDS

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Purpose. To determine the effects of concurrent strength and endurance training (concurrent training) on the Health-Related Quality of Life (HRQOL) and cardiopulmonary status among HIV-infected patients, using a systematic search strategy of randomized, controlled trials (RCTs). **Methods.** A systematic review was performed by two independent reviewers using Cochrane Collaboration protocol. The sources used in this review were Cochrane Library, EMBASE, LILACS, MEDLINE, PEDro and Web of Science from 1950 to August 2012. The PEDro score was used to evaluate methodological quality. **Result.** Individual studies suggested that concurrent training contributed to improved HRQOL and cardiovascular status. Concurrent training appears to be safe and may be beneficial for medically stable adults living with HIV. The rates of nonadherence were of 16%. **Conclusion.** Concurrent training improves the HRQOL and cardiopulmonary status. It may be an important intervention in the care and treatment of adults living with HIV. Further research is needed to determine the minimal and optimal duration, frequency, and intensity of exercise needed to produce beneficial changes in the HIV-infected population subgroups.

1 INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has dramatically reduced mortality and morbidity in HIV-infected patients. On the other hand HIV-infected patients are experiencing an increasing frequency of noninfectious problems, which can significantly impair the benefits of HAART [1, 2].

Exercise training improves and maintains health and reduces the risk of chronic disease in healthy adults [3]. Exercise has been considered an important adjuvant therapy for health promotion

of patients with HIV [4, 5]. The proper exercise prescription must take into consideration the choice of exercise's type, in accordance with the objective to be achieved. This includes other important parameters such as intensity, volume, frequency, and duration of exercise [6].

Resistance training has been employed as a therapeutic tool in patients with HIV and is considered safe and effective in improving muscle strength and body composition [7, 8]. Aerobic exercise promotes a significant effect in improving

aerobic capacity, measured by maximal oxygen consumption in this population [9, 10].

Recently, the combination of two exercise modalities: concurrent strength and endurance training (concurrent training) has been employed, as recommended by the American College of Sports Medicine [11]. Participation in concurrent training has been recommended for healthy people and adults with chronic medical conditions [12].

The physiological stimuli directed to skeletal muscle as a result of strength training or endurance training are divergent in nature, due to competition in metabolic adaptation to exercise. As a consequence, its effects may be limited when compared to training, in terms of specific parameters [13, 14], but in populations with multiple functional impairments the combination of different modes of exercise is part of rehabilitation programs [15, 16].

Some studies have shown a significant improvement in components of muscle performance and endurance during concurrent training in patients with HIV/AIDS [17–19]. The impact of training on functional capacity and mainly on the HRQOL has not been well documented. In addition, there is no consensus among studies regarding the association of the exercise types, or on what is the best intensity of exercise to be prescribed for this population, with little emphasis on HRQOL. This is an open question and a barrier to a large scale use of such strategies in clinical practice.

The goal of this systematic review was to analyze the impact of concurrent strength and endurance training termed concurrent training on HRQOL and cardiopulmonary status of patients living with HIV/AIDS and discuss their implications for clinical practice.

2 METHODS

2.1. Data Sources and Searches. We performed a computerbased search querying Ovid MEDLINE (1950 to August 2012), LILACS (up to August 2012),

CINAHL (Cumulative Index to Nursing and Allied Health, 1982 to August 2012), EMBASE (1980 to August 2012), PEDro (Physiotherapy Evidence Database), and the Cochrane Central Register of Controlled Trials for original research articles published in English, Spanish, and Portuguese. We also performed a manual tracking of citations in the selected articles.

The design group included the terms randomized controlled trials, clinical trials, and controlled trials. The HIV group included the terms human immunodeficiency virus, acquired immunodeficiency syndrome, HIV, HIV infections, HIV long-term survivors, AIDS, and HIV/AIDS. The exercise group included the terms exercise, training, physical exercise, fitness, strength training, progressive resistive/resistance aerobic, aerobic training, concurrent strength and endurance training, concurrent training, anaerobic, exercise therapy, or physical training.

The outcome measures group included the terms quality of life, health-related quality of life, life expectancy, and cardiopulmonary status.

2.2. Study Selection

2.2.1.Types of Studies and Participants. We included randomized controlled trials (RCTs) comparing concurrent training with non concurrent training or with another exercise modality, performed at least two times per week and lasting at least four weeks. Studies of adults (18 years and older), regardless sexes, at all stages of infection were included.

2.2.2. Types of Interventions. The concurrent training was defined as the application of aerobic and resistance exercise in the same training session, performed at least two times per week for at least four weeks. Resistance training was defined as exercise that requires muscle contraction against resistance. Aerobic exercise was defined as a regimen containing aerobic interventions (walking, treadmill, cycling, rowing and stair stepping). Exercise programs were described with respect to

type of exercise, volume, intensity, frequency, and duration.

2.2.3. Types of Outcome Measures. Cardiopulmonary measures considered in this review included but were not limited to maximal/peak oxygen consumption (V_{O2} max/peak) (mL/kg/min), oxygen pulse (O_2 pulse), maximum heart rate (HR_{max}) (beats/min), fatigue (time on exercise), and dyspnea (rate of perceived exertion).

To assess the quality of life related to health we included in the review studies that reported HRQL through standardized and validated scales or questionnaires.

2.2.4. Data Extraction and Quality Assessment. One reviewer made the search and the initial selection of potentially relevant studies that met the inclusion criteria and two independent reviewers selected the articles that fulfill the inclusion criteria, using a standard form adapted from the Cochrane Collaboration [20] model for data extraction, considering (1) aspects of the study population, such as average age and gender, (2) aspects of the intervention performed, (sample size, type of exercise performed presence of supervision, frequency, and duration of each session), (3) follow-up, (4) loss of follow-up, (5) outcome measures and (6) results presented.

There are several scales for assessing quality of RCTs. The PEDro scale assesses the methodological quality of a study based on other important criteria, such as concealed allocation, intention-to-treat analysis, and adequacy of follow-up. These characteristics make the PEDro scale a useful tool to assess the methodological quality of physical therapy and rehabilitation trials [21].

The PEDro scale [22] is based on a Delphi list [23] and consists of 11 items. The first item is related to external validity and is generally not used to calculate the method score, leaving a score range of 0 through 10 [22]. Most trials had already been rated at least twice by trained evaluators of PEDro

database (<http://www.pedro.fhs.usyd.edu.au/>). If a trial was not included in PEDro or had not been previously rated twice, it was rated independently by two investigators. Studies were excluded in subsequent analysis if the cutoff of 4 points was not reached.

3 RESULTS

We identified a total of 98 articles with the search strategy applied to the databases MEDLINE, Scielo, AMED, Lilacs, and PEDro. These 37 items were sent to reviewers for evaluation, selection, and inclusion in the review. Twenty-six were excluded, and 11 papers met entry criterion according to reviewers. Three additional studies were excluded after retrieving the full text. Of these, 2 were RCTs that did not examine outcomes of interest to this review and one study was a duplicate of Mutimura et al. [24].

The remaining eight articles were fully analyzed and approved by both reviewers and had the extraction of data from each RCT (Mutimura et al., 2008 [24]; Hand et al., 2008 [25]; Perez-Moreno' [26]; Dolan et al., 2006 [27] Fillipas et al., 2006 [28]; Driscoll et al., 2004 [29]; Rojas et al., 2003 [30]. Rigsby et al., 1992 [31]).

Each of the papers was assessed using the PEDro scale methodology by both reviewers, with the pre-defined cutoff[4].

3.1. Characteristics of the Sample. The initial sample size for the selected studies ranged from 35 [30] to 100 [24]. The final sample ranged from 31 [31] to 97 [24], and mean age of participants ranged from 18 to 60 years. The studies included patients of both genders, but there was a predominance of males. All studies analyzed in this review included outpatients diagnosed with HIV, and the majority of these were under antiretroviral therapy.

Participants included adults infected with HIV at various stages of the disease with CD4 counts ranging from <100 to >500 cells/mm³. Also included were patients with elements of wasting syndrome

(either >5% or >10% involuntary weight loss or body weight <90% ideal body weight).

3.2. Outcomes of Included Studies

3.2.1. Cardiopulmonary Status. Stress test was used with a treadmill, stationary bike, and cycle ergometer. Submaximal tests were also used, as the Shuttle test, Kasch Pulse Recovery Test, and six-minute walk test.

3.2.2. Health-Related Quality of Life. WHOQOL-BREF and MOS-HIV health surveys were the tools used to evaluate HRQOL. Table 1 presents summary data from the 8 RCTs eligible for this systematic review.

3.3. Characteristics of Intervention Programs. The exercise intervention characteristics of included studies are provided in Table 2. The parameters used in the application of aerobic and resistance exercise have been reported in most studies, and all described the progressive nature of the training.

The duration of intervention programs with concurrent training ranged from 6 [25] to 24 weeks [24], but in most studies reviewed, the application period ranged from 12 to 16 weeks. Regarding the length of the session, there was a variation from 60 [27, 28] to 120 [29] minutes. The frequency of sessions varied from two to three times a week.

For resistance training only two studies [27, 29] specify the type of muscle contraction performed during training: the exercise was performed with concentric and eccentric contractions lasting 6 to 10 seconds, with use of machines, weight stations, and free weights in six studies, but in two, there was no description of the type of equipment used [24]. The exercise intensity was based on the extent of maximum repetition (MR), ranging from 50 to 80% of MR in most studies. One study did not report the prescribed exercise intensity [24]. The application volume of exercise ranged from 1 to 3 sets of 6–18 repetitions. The volume of exercise was not described in one study [24].

For the application of aerobic exercise, all studies reported the treadmill, bike, walking, or jogging. Except for the study of Rigsby et al. [31], all reported the criteria for progression training. In all studies the intensity was adjusted based on heart rate (HR_{max}), ranging from 45 to 80% HR_{max} .

3.4. Effects of Intervention Programs

3.4.1. Cardiopulmonary Status. Seven studies reported significant improvement in the concurrent training group compared to control group. One study did not compare the improvement intergroups, because they used a before and after evaluation [30].

In the study of Mutimura et al. [24], Shuttle's test was used to evaluate the functional capacity to predict maximum oxygen uptake (VO_{2max}). It was improved from 4.7 ± 3.9 to 0.5 ± 0.3 mL/kg per min in the intervention group compared to control ($P < 0.001$). In the study of Fillipas et al. [28], the Kasch Pulse Recovery test (which evaluates the beats per minute after 3 minutes of stepping) was used to assess the endurance, with a lower HR meaning better conditioning. HR was reduced from 19.6 ± 0.6 to 11.7 ± 2.9 in the exercise group compared to control ($P < 0.001$). In the study of Hand et al. [25], there was an improvement of 21% in VO_2 estimated in the exercise group while there was no improvement in the control group ($P < 0.001$).

Dolan et al. [27] observed an improvement (1.5 ± 0.8 versus -2.5 ± 1.6 mL/kg min $^{-1}$, $P < 0.001$) in VO_{2max} in the training group compared to control. In a study by Driscoll et al., fitness assessment was performed using the time to perform the exercise on a cycle ergometer, with a significant increase in the exercise group compared to control ($3 \pm 0.0 \pm 4$ min versus 1.1 min, $P < 0.001$). Rigsby et al. [31] also used maximum time exercise as a parameter for fitness assessment, and he observed a maximum execution time of 1388.46 ± 224.45 versus 965.91 ± 136.14 s in the exercise group and control group, respectively ($P < 0.001$).

In the study by Rojas et al. [30], a significant improvement in VO_{2max} after training was observed,

compared to baseline. Table 3 provides details of the effects of intervention programs.

3.4.2. Health-Related Quality of Life. Four researches included HRQOL outcome between the endpoints. All reported significant improvement in HRQOL of the concurrent training group compared to control group.

Mutimura et al. [24] assessed HRQOL using a short-form instrument (WHOQOL-BREF) of the WHO Quality of Life HIV (WHOQOL-HIV). The psychological (1.3 ± 0.3 versus 0.5 ± 0.1 ; $P <$

0.0001), independence (0.6 ± 0.1 versus 0.0 ± 0.0 ; $P < 0.0001$), social relationships (0.6 ± 0.2 versus 0.0 ± 0.0 ; $P < 0.0001$), HIV HAART-specific (1.4 ± 0.2 versus -0.1 ± 0.2 ; $P < 0.0001$), and QoL domains (0.5 ± 0.3 versus 0.0 ± 0.3 ; $P < 0.05$) significantly improved in the concurrent training compared to control group.

In the Perez-Moreno' et al. study [26], although statistical significance was not reached for the combined effect of group and time ($P = 0.09$), QoL significantly increased ($P < 0.01$) in the training group after the intervention period, whereas no change was observed in controls.

Table 1: Characteristics of the outcomes and results of concurrent training in the trials included in the review.

Study	Patients	Outcomes	Measures	Results		
				Aerobic capacity	HRQOL	Aerobic capacity
Mutimura et al., 2008 [24]	HIV	Aerobic capacity HRQoL	Shuttle test	WHOQOL-BREF	\uparrow $\text{VO}_{2\text{peak}}$	\uparrow QoL
Hand et al., 2008 [25]	HIV	Aerobic capacity	Graded exercise stress test	NA	\uparrow $\text{VO}_{2\text{peak}}$	NA
Perez-Moreno' et al., 2007 [26]	HIV	Aerobic capacity HRQoL	Stress test cycle ergometer	QoL	\uparrow $\text{VO}_{2\text{peak}}$	NS
Dolan et al., 2006 [27]	HIV	Aerobic capacity	Treadmill stress test TCAM6	NA	\uparrow $\text{VO}_{2\text{peak}}$ \uparrow TCAM6	NA
Fillipas et al., 2006 [28]	HIV	Aerobic capacity HRQoL	Kasch pulse recovery test	MOS-HIV	\downarrow HR	\uparrow MOS-HIV
Driscoll et al., 2004 [29]	HIV	Aerobic capacity	Submaximal stress test	NA	\uparrow ET	NA
Rojas et al., 2003 [30]	HIV/AIDS	Aerobic capacity HRQoL	Graded exercise stress test	MOS-HIV	\uparrow $\text{VO}_{2\text{max}}$ \uparrow $\text{O}_2\text{ pulse}$	\uparrow MOS-HIV
Rigsby et al., 1992 [31]	HIV	Aerobic capacity	YMCA cicle test protocol	NA	\uparrow ET \downarrow HR	NA

Table 2: Characteristics of the experimental intervention in the trials included in the review.

Study	Type exercise	Intensity/duration (wk)	Volume	Frequency ($\#$ per wk)	Time (min)	Length (wk)	Supervision
Mutimura et al., 2008 [24]	Aerobic exercise	45% $\text{HR}_{\text{max}}/3$	15 min warm-up	3	90	24	Yes
		60% $\text{HR}_{\text{max}}/6$	60 min exercise				
Hand et al., 2008 [25]	Aerobic exercise	75% $\text{HR}_{\text{max}}/15$	15 min cool-down				
		NI	NI				
Perez-Moreno' et al., 2007 [26]	Resistance exercise	50–70% HR_{max}	5 min warm-up	2	40	6	NR
		12 RM	30 min exercise 5 min cool-down				
Perez-Moreno' et al., 2007 [26]	Aerobic exercise Cycle ergometer	70–80% HR_{max}	1 set—12 reps	3	20–40	16	Yes
		10 min warm-up 20 min exercise 10 min cool-down					

	Resistance exercise	12–15 RM	1-2 set 12–15 reps	3	50	16	Yes
Dolan et al., 2006 [27]	Aerobic exercise	60% HR _{max} /2	5 min warm-up	3	35	16	Yes
	Resistive exercise	75% HR _{max} /14 60–70% MR/2 80% MR/12	20–30 min exercise 3-4 sets 8–10 reps				
Fillipas et al., 2006 [28]		60% HR _{max} /3	5 min warm-up	2			Yes
	Aerobic exercise	75% HR _{max} /3	20 min exercise				
	Resistive exercise	60% MR	5 min cool-down	30	6	6	Yes
		80% MR	3 sets				
Rojas et al., 2003 [30]	Aerobic exercise	60–80% HR _{max}	10 min warm-up	3		NR	
	Resistive exercise	60–70% MR/4 80% MR/12	25 min exercise 10 min cool-down				
Rigsby et al., 1992 [31]		60–80% HR _{max}	2 min warm-up	36	12	12	NR
	Aerobic exercise		30 min exercise				
	Resistive exercise	NI	3 min cool-down	3	24	24	NR
			1–3 sets				
			6–18 reps				

NR: not reported; maximum heart rate (HR_{max}); MR: maximal repetition; reps: repetitions.

Table 3: Effects of concurrent training on the cardiopulmonary status.

	Δ Before	– After	P value	Maximal exercise capacity	
				Mean difference (CI) for between-group comparison	P value
Mutimura et al., 2008 [24]					
Control	0.5 (0.3)	NR			
CT	4.7 (3.9)	NR		4.2 (NE)	$P < .0001$
Hand et al., 2008 [25]					
Control	0 (3.0)	NS			
CT	8.3 (3.1)	$P < .01$		NE	NE
Perez-Moreno' et al., 2007 [26]					
Control	0 (0.0)	NS		10.0 (NE)	
CT	10 (1.0)	$P < .01$			$P < .001$
Dolan et al., 2006 [27]					
Control	-2.5 (1.8)	NR			
CT	1.5 (0.8)	NR		1.0 (NE)	$P < .001$
Fillipas et al., 2006 [28]					
Control	0.6 (2.9)	NR			
CT	-19.6 (11.7)	NR		-20.2 (-25.8 to -14.6)	$P < .001$
CT	3 (0/4)	NR		3.0 (NE)	$P < .05$
Driscoll et al., 2004 [29]					
Control	0 (0/1)	NR			
CT	3 (0/4)	NR		3.0 (NE)	$P < .05$
Rojas et al., 2003 [30]					
Control	NE	NE		(NE)	(NE)
CT	2.99 (0.38)	$P < .003$			
Rigsby et al., 1992 [31]					
Control	18.18 (NR)	NR			$P < .0001$
CT	392.31 (NR)	NR		374.13 (NE)	

CT: concurrent training, NE: not estimated, NR: not reported. Data are reported as mean (SD) or as mean (95% confidence interval (CI)).

In the study of Fillipas et al. [28], and Rojas et al. [30], HRQOL was assessed using the Medical Outcomes Study HIV Health Survey (MOS-HIV). In the first study [28] HRQOL showed a between-group difference in only two out of the eleven dimensions. The experimental group improved their overall health while the control group showed slight reduction in this parameter, resulting in a between-group difference of 20.8 points (95% CI 2.0 to 39.7, $P = 0.03$). The experimental group improved their cognitive function while the control group stayed much the same; the between-group difference was 14 points (95% CI 0.7 to 27.3, $P = 0.04$).

In second study [30] six domains were assessed (health status, global quality of life, energy, physical strength, social contact, and emotional well-being); concurrent training group showed better results than controls in five domains. The only unchanged domain was social contact ($P > 0.05$).

3.4.3. Adherence to Exercise Program. Adherence to exercise is the ability to maintain a program for a certain time. In all studies a varied proportion of patients are excluded before the end of program. In this review, from 471 patients that entered the protocol, only 396 (84%) remained on study at closure.

Mutimura et al. [24] showed the lower rate of discontinuation, with only 4% of withdraw. Conversely, the study of Hand el al. [25] presented the greatest loss of patients in the exercise group,

starting with 44 and ending with 21 patients, with loss of 53.3%. The proportion of loss to exercise and control groups was 19.1% versus 11.44%, respectively.

4 DISCUSSION

This systematic review demonstrated that there is sufficient evidence to support the inclusion of concurrent training for adults living with HIV/AIDS.

It is evident that the effectiveness of concurrent training improves aerobic capacity in this population. Despite major differences in exercise prescription and duration of different programs, the aerobic capacity was significantly improved. These findings coincide with results of previous studies that found significant improvements in cardiopulmonary fitness [32, 33].

The effect of concurrent training on QOL is less clear. Only one study showed significant improvement in all domains, while two studies showed impact in specific domains, and in one study the statistical significance was not reached for the combined effect of group and time. This discrepancy can be due to intensity, frequency, and duration of the programs in the analyzed studies, which can result in a different impact on such parameters.

Physical therapists can play an important role in diagnosis and management of the physical dysfunction in HIV-infected patients [34, 35]. This systematic review suggests that concurrent exercise may be an important intervention in the care and treatment of adults living with HIV. Performing concurrent exercise for at least 60 minutes, three times per week for at least six weeks, may contribute to improvements in selected outcomes of cardiopulmonary status. These physiological adaptations to concurrent strength and endurance training may decrease functional limitations and reduce physical disability resulting from HIV infection and increase of HRQOL [35].

Intervention strategies should focus on increasing exercise, considering cessation of smoking, dietary counseling, and treatment of arterial blood hypertension and dyslipidemia [36]. Research supports the use of therapeutic exercise as an adjunct therapy in the treatment of symptoms of HIV infection [37].

The number of weekly exercise sessions should be increased until the patient can tolerate three to five sessions weekly. Aerobic exercise should be performed at a moderate intensity: from 11 to 14 on the Borg Rating of Perceived Exertion Scale, at 50% to 85% of peak heart rate, or at 45% to 85% $\text{VO}_{2\text{max}}$. Resistance training should focus on large muscle groups, such as the chest, biceps brachia, quadriceps, and hamstrings. The intensity should be moderate (set at 60 % to 80% of the one MR) and progressively increased. Overload should be selected with the level this patient can comfortably perform, 8 to 12 repetitions [17].

The role of a well-planned exercise program should therefore be emphasized and used as medical treatment among patients and health care professionals. When implementing therapeutic exercise programs for HIV-infected patients, it is recommended that programs be individualized on the basis of the functional capacity and individual symptoms presented by each patient [37, 38].

A patient participating in an exercise intervention should be monitored by a physical therapist qualified health-care provider for potential changes in their health status, especially those in more advanced stages of immunosuppression, to prevent any potential adverse events of exercise [39].

Adherence to exercise is an under researched area with regards to HIV treatment. Very few studies have been reported on the adherence of HIV patients to exercise in the clinical setting. The strongest motivators of adherence to exercise have been shown to be self-efficacy (the concept that a person is capable of performing a course of action to attain a desired outcome) and outcome expectation (the belief that specific consequences will result from specific personal actions)[40, 41].

Further research into reasons for nonadherence as well as for dropouts would be beneficial. In order to gain the most from the exercise, combined exercise programs including targeted psychological support might be the way forward[42].

Future research needs to identify which patient subgroups might benefit the most, the optimal exercise dose needed to lessen disease-related symptoms and maximize clinical benefit, and the effects with different types of programs.

Meta-analyses were not performed due to variability of characteristics of the studies pertaining to the exercise, variation among individual studies in the types of interventions the differences in endpoints, assessment instruments, and variables of exercise prescription.

5 CONCLUSION

Concurrent training is efficacious in treating disability in outpatient men who are HIV positive and showed to be a safe and beneficial intervention in the treatment. Exercise improves aerobic cardiopulmonary status and HRQOL. It may be an important intervention in the care and treatment of adults with HIV.

CONFLICT OF INTERESTS

The authors have no conflict of interests to disclose.

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A systematic review of the effects of different types of therapeutic exercise on physiologic and functional measurements in patients with HIV/AIDS

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Several studies have reported the benefits of exercise training for adults with HIV, although there is no consensus regarding the most efficient modalities. The aim of this study was to determine the effects of different types of exercise on physiologic and functional measurements in patients with HIV using a systematic strategy for searching randomized controlled trials. The sources used in this review were the Cochrane Library, EMBASE, MEDLINE, and PEDro from 1950 to August 2012. We selected randomized controlled trials examining the effects of exercise on body composition, muscle strength, aerobic capacity, and/or quality of life in adults with HIV. Two independent reviewers screened the abstracts using the Cochrane Collaboration's protocol. The PEDro score was used to evaluate methodological quality. In total, 29 studies fulfilled the inclusion criteria. Individual studies suggested that exercise training contributed to improvement of physiologic and functional parameters, but that the gains were specific to the type of exercise performed. Resistance exercise training improved outcomes related to body composition and muscle strength, with little impact on quality of life. Aerobic exercise training improved body composition and aerobic capacity. Concurrent training produced significant gains in all outcomes evaluated, although moderate intensity and a long duration were necessary. We concluded that exercise training was shown to be a safe and beneficial intervention in the treatment of patients with HIV.

KEYWORDS: AIDS; HIV Infection; Exercise; Therapeutics.

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1 INTRODUCTION

Advances in antiretroviral therapy have converted HIV infection into a chronic disease, resulting in patients with several comorbidities (1). HIV-related disability has been associated with decreased exercise capacity and impairment of patients' daily activities (2,3).

Thus, exercise training is a key strategy employed by patients with HIV or AIDS that is widely prescribed by rehabilitation professionals (4). The accumulated body of scientific evidence indicates that exercise training increases aerobic capacity, muscle strength, flexibility, and functional ability in patients with HIV or AIDS (5-7).

The exercise program should be modified according to an individual's physical function, health status, exercise response, and stated goals. The single workout must then be designed to reflect these targeted program goals, including the choice of exercises, the order of exercises, the volume (i.e., the number of repetitions, the number of sets, and the total time) of each exercise, and the intensity. Exercise intensity and volume are important determinants of physiologic responses to exercise training (6,7).

Adaptations to exercise are highly dependent on the specific type of training performed. However, there is no consensus regarding which modality and intensity are more effective in patients with HIV, making it difficult to choose the best training for this population. This issue is still an obstacle in clinical practice. A better understanding of the effectiveness and safety of exercise will enable people living with HIV and their health care providers to practice effective and appropriate exercise prescription (8).

The purpose of this report was to 1) perform a systematic review of the evidence regarding the effects of different types of exercise on health in HIV-infected patients and 2) to define the best volume, intensity, and type of exercise to achieve minimal and optimal health benefits in HIV-infected patients.

2 METHODS

This review comprised three phases. In phase 1, a database search (MEDLINE, LILACS, EMBASE, SciELO, Cumulative Index to Nursing and Allied Health (CINAHL), PEDro, and the Cochrane Library) was performed to identify relevant abstracts from up to August 2012. In the second

phase, two reviewers assessed the list of studies generated by the search strategy, using the title and abstract to determine study eligibility. Full-text copies of potentially relevant studies were then obtained for detailed examination, and in phase 3, the quality of the studies was assessed.

Data Sources and Searches

We performed a computer-based search, querying Ovid MEDLINE (1950 to August 2012), LILACS (up to August 2012), CINAHL (Cumulative Index to Nursing and Allied Health, 1982 to August 2012), EMBASE (1980 to August 2012), PEDro (Physiotherapy Evidence Database), and the Cochrane Central Register of Controlled Trials for original research articles published in English, Spanish, or Portuguese. In the search strategy, there were four groups of keywords: study design, participants, interventions, and outcome measures.

The study design group of keywords included the terms randomized controlled trials, clinical trials, and controlled trials. The participants group included the terms human immunodeficiency virus, acquired immunodeficiency syndrome, HIV, HIV infections, HIV long-term survivors, AIDS, and HIV/AIDS. The interventions group included the terms exercise, training, physical exercise, fitness, strength training, progressive resistive/resistance aerobic, aerobic training, concurrent strength and endurance training, concurrent training, anaerobic, exercise therapy, and physical training.

The outcome measures group included the terms quality of life, health-related quality of life, life expectancy, cardiopulmonary status, aerobic fitness, aerobic capacity, strength, muscle strength, body composition, health, physiologic parameters, and functional parameters.

Study Selection

Types of studies and participants. We included randomized controlled trials (RCTs) comparing exercise training with non-exercise training or with another therapeutic modality. The exercise was performed at least two times per week and lasted at least 4 weeks. Studies on adults (18 years and older), regardless of sex and at all stages of infection, were included.

Types of interventions. Resistance exercise (weight training or resistance training) was defined as exercise that requires muscle contraction against resistance (e.g., body weight or barbells). Resistance training programs were described with respect to duration, frequency, intensity, volume, rest intervals, muscle group, and supervision.

Aerobic exercise (or endurance training) was defined as a regimen containing aerobic interventions (walking, cycling, rowing, and stair stepping). Aerobic training programs were described with respect to intensity, frequency, duration, and supervision.

Concurrent training was defined as the application of aerobic and resistance exercise in the same training session.

Types of outcome measures. This systematic review was limited to key indicators of different health outcomes known to be related to exercise in HIV-infected patients. Decisions regarding what health outcomes to include in the systematic review were made by examining what outcomes were studied in previously conducted RCTs and systematic reviews on HIV. These key indicators consisted of the following:

- 1) Anthropometric characteristics, as a measure of body composition;
- 2) Muscle strength, as a measure of musculoskeletal health;

- 3) Aerobic capacity or aerobic fitness, as a measure of cardiopulmonary health; and
- 4) Physical and psychological functioning, as a measure of quality of life.

The body composition measures considered in this review included but were not limited to anthropometry, lean body mass and fat mass, body mass index [calculated as weight (kg) divided by height² (m)], and total body fat (the amount of subcutaneous fat determined using the thickness of specific skinfolds). Three trunk skinfolds (subscapular, suprailiac, and vertical abdominal) and four limb skinfolds (triceps, biceps, thigh, and medial calf); the waist circumference at the umbilicus, which is a measure of central fat (subcutaneous and visceral); and the maximum hip circumference were measured and recorded in mm. The waist-tohip ratio (WHR) was the waist circumference at the umbilicus (mm) divided by the maximum hip circumference (mm).

The musculoskeletal health measures considered in this review also included skeletal muscle mass, muscle strength, a muscle function test, the maximum torque, the maximum force, the peak torque, the peak force, and total work.

The main cardiopulmonary measures considered in this review were the maximal oxygen consumption ($\text{VO}_{2\text{max}}$ /peak) (ml/kg/min), the absolute VO_2 , oxygen pulse (O_2 pulse), the heart rate maximum (HRmax) (beats/min), the lactic acid threshold (LAT), fatigue (time on treadmill), exercise duration, and dyspnea (the rate of perceived exertion).

To assess the quality of life related to health, we reviewed studies that reported health-related quality of life based on standardized and validated scales or questionnaires.

Data extraction and quality assessment

All authors worked independently and used a standard form adapted from the Cochrane Collaboration's (9) model for data extraction, considering 1) aspects of the study population, such as the average age and sex; 2) aspects of the intervention performed (sample size, type of exercise performed, presence of supervision, frequency, and duration of each session); 3) follow-up; 4) loss to follow-up; 5) outcome measures; and 6) presented results.

There are several scales for assessing the quality of RCTs. The PEDro scale assesses the methodological quality of a study based on important criteria, such as concealed allocation, intention-to-treat analysis, and the adequacy of follow-up. These characteristics make the PEDro scale a useful tool for assessing the quality of physical therapy and rehabilitation trials (10).

Methodological quality was independently assessed by two researchers. Studies were scored on the PEDro scale based on a Delphi list (11) that consisted of 11 items. One item on the PEDro scale (eligibility criteria) is related to external validity and is generally not used to calculate the method score, leaving a score range of 0 to 10 (12). Studies were excluded in the subsequent analysis if the cutoff of four points was not reached. Any disagreements were resolved by a third rater.

Data synthesis and analysis

If the inclusion criteria were not clearly described in a particular study, the authors were contacted, and a consensus among the reviewers was obtained to decide whether the study would be part of the review. We also performed a manual tracking of citations in the selected articles.

3 RESULTS

The flow chart for our study is shown in Figure 1. In total, 59 studies were sent to the reviewers for evaluation, selection, and inclusion in the review.

After assessment, 24 studies were excluded, and 35 papers met the entry criteria. Of these, four were duplicates (studies that used the same participants), as Sattler et al. 2002 (16) used the same participants as Sattler et al. 1999 (21); Lox et al. 1996 (22) used the same participants as Lox et al. 1995 (23); Multimura et al. 2008 (37) used the same participants as Multimura et al. 2008 (36); and Fairfield et al. 2001 (45) used the same participants as Grinspoon et al. 2000(46).

The remaining 31 articles were fully analyzed and approved by both reviewers, and the data were extracted from each RCT. Each of the papers was assessed by both reviewers using PEDro scale methodology with the predefined cutoff

(4). The results of the assessment using the PEDro scale are individually presented in Table 1. Two other studies [Galantino et al. 2006 (26) and McArthur et al. 1993 (33)] were excluded because these papers did not reach the defined minimal score on the PEDro scale.

Of the 29 articles included in this review, eight were on resistance exercise compared with a control or supplementation (13,15,17-21,24), eight were on aerobic exercise (25,27,32,34) compared with a control, 11 compared concurrent training with a control group (35,36,38-44,46,47), and two compared resistance exercise with aerobic exercise (14,23).

The participants included adults infected with HIV at various stages of the disease, with CD4 counts ranging from ,100 to 500 cells/mm³. Patients with elements of wasting

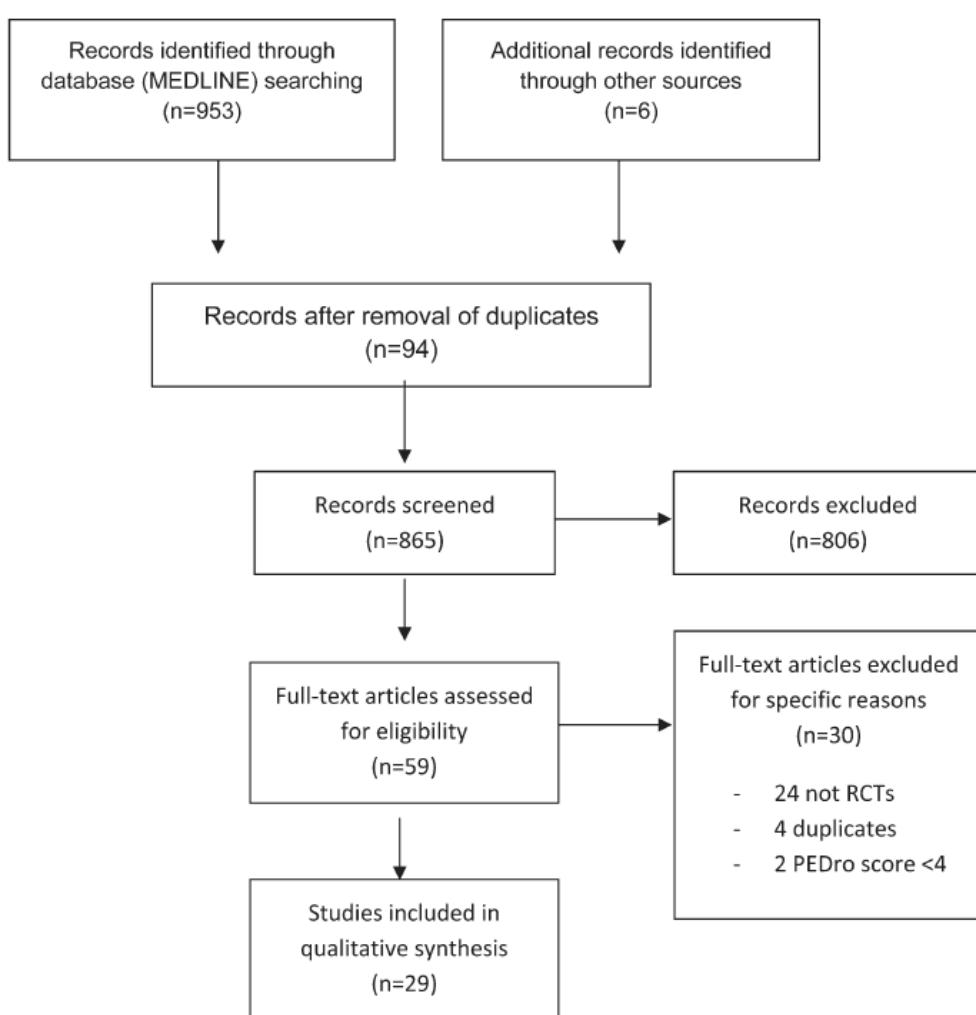


Figure 1 - Flow Diagram.

Table 1 - Study quality on the PEDro scale.

Study	1	2	3	4	5	6	7	8	9	10	11	Total
1	Sakkas et al. 2010	✓	✓	✓	✓	✓			✓	✓	✓	8
2	Lindegaard et al. 2008	✓	✓		✓			✓		✓	✓	5
3	Shevitz et al. 2006	✓	✓		✓		✓	✓	✓	✓	✓	8
4	Roubenoff et al. 2001	✓	✓		✓					✓	✓	4
5	Agin et al. 2001	✓	✓	✓	✓					✓	✓	5
6	Bhasin et al. 2000	✓			✓				✓	✓	✓	5
7	Strawford et al. 1999	✓	✓	✓	✓	✓		✓		✓	✓	8
8	Sattler et al. 1999	✓		✓				✓		✓		4
9	Lox et al. 1995	✓	✓		✓			✓		✓	✓	5
10	Spence et al. 1990	✓	✓		✓			✓		✓	✓	5
11	Terry et al. 2006	✓	✓		✓					✓	✓	4
12	Galantino et al. 2001	✓	✓							✓	✓	3*
13	Neidig et al. 2000		✓		✓					✓	✓	4
14	Smith et al. 2000	✓	✓		✓			✓		✓	✓	5
15	Baigis et al. 2002	✓	✓	✓	✓					✓	✓	5
16	Perna et al. 1999	✓	✓		✓					✓	✓	4
17	Terry et al. 1999	✓	✓		✓					✓	✓	4
18	Stringer et al. 1999	✓	✓		✓					✓	✓	4
19	McArthur et al. 1993	✓	✓								✓	2*
20	LaPerrier et al. 1990	✓	✓		✓					✓	✓	4
21	Yarakeshi et al. 2011	✓	✓		✓			✓		✓	✓	5
22	Multimura et al. 2008	✓	✓		✓			✓		✓	✓	5
23	Hand et al. 2008	✓	✓		✓			✓		✓	✓	5
24	Pérez-Moreno. 2007	✓	✓	✓	✓			✓		✓	✓	6
25	Dolan et al. 2006	✓	✓		✓					✓	✓	6
26	Filippas et al. 2006	✓	✓	✓	✓			✓	✓	✓	✓	7
27	Driscoll et al. 2004	✓	✓		✓					✓	✓	4
28	Driscoll et al. 2004	✓	✓		✓					✓	✓	4
29	Rojas et al. 2003	✓	✓		✓			✓		✓	✓	4
30	Grispoon et al. 2000	✓	✓		✓			✓		✓	✓	5
31	Rigsby et al. 1992	✓		✓						✓	✓	4

*Excluded because PEDro <4.

syndrome (either .5% or .10% involuntary weight loss or body weight ,90% of the ideal body weight) were also included. The studies included patients of both sexes, but there was a predominance of males (77%). The sample sizes, outcomes, and results of the included studies with regard to different types of exercise are summarized in Table 2.

Resistance exercise

Characteristics of the sample. The initial sample size of the selected studies ranged from 20 (13,17) to 61 (19). The final sample ranged from 20 (13,17) to 50 (15), and the mean age of the participants ranged from 18 to 60 years. All studies selected in this review included outpatients diagnosed with HIV, and most of these patients were receiving antiretroviral therapy. Four studies included patients of both sexes (13,15,17,19), six included only men (14,20-24), and one included only women (18).

Characteristics of intervention programs. The exercise intervention characteristics of the included studies are provided in Table 3. The parameters used in the application of resistance exercise were reported in most studies, and all studies described the progressive nature of the training.

The duration of intervention programs with resistance ranged from 6 (24) to 16 (14,19) weeks, but in 40% of the reviewed studies, the application period was 12 weeks. The duration of the session varied from 30 (15) to 90 (13) minutes, although in six studies, the duration was not reported. The frequency of sessions was three times per week in all studies. Only two studies (20,23) did not specify the type of muscle contraction performed during training. In the other studies, the exercise was performed with concentric and eccentric contractions

using machines, weight stations, and free weights. The exercise intensity was based on the extent of the individual's one-repetition maximum (RM), ranging from 50 to 90% of the RM in 90% of the studies. One study described the intensity as the 15RM (24).

The application volume of exercise ranged from three to five sets of six to 15 repetitions (reps). In 70% of the studies, the volume was three sets of eight reps, but only two studies reported the time interval between the series, which ranged from 60 to 120 seconds (14,21). All studies reported the application of exercises to large muscle groups of the lower and upper limbs.

Aerobic exercise

Characteristics of the sample. The baseline sample in the selected studies ranged from 20 (14) to 123 (28) people. The final sample ranged from 18 (14) to 109 (28) people, and the mean age of the participants ranged from 18 to 60 years. Three studies only included males (14,23,34), and the remaining studies included HIV-infected patients of both sexes. All studies analyzed in this review included outpatients diagnosed with HIV, and most of these patients were receiving antiretroviral therapy.

Characteristics of intervention programs. The duration of the intervention programs with aerobic exercise ranged from 6 (32) to 24 (34) weeks. In 60% of the studies, the application of the program lasted 12 weeks. The session duration was reported in all studies and ranged from 30 (29,32) to 60 (25,27,31) minutes, with an average duration of 45 min. The frequency of the program was three times per week in all studies.

Table 2 - Characteristics of the outcomes and results of the trials included in the review.

Study	Participants (M:F)	Outcomes	Outcomes			>Aerobic capacity (AC)	HRQOL	Results			
			Body composition (BC)	Muscle strength (MS)	BC			MS	AC	HRQOL	
1	Sakkas et al. 2009	HIV 43 (42:1) HIV 20 (20:0)	Body composition Muscle strength BC Muscle strength Aerobic capacity	DEXA MRI DEXA	1RM testing Isometric MVC 3RM testing VO ₂ max	NA	NA	↑ LBM	↑ RM MV/C	NA	NA
2	Lindegaard et al. 2008	HIV 50 (33:14)	Body composition Muscle strength	DEXA CSMA	Isokinetic dynamometer 1RM testing 1RM testing	TCAM6	HRQOL	↑ CSMA	↑ RM	↑ VO ₂ max	NA
3	Shevitz et al. 2005	HIV 20 (19:1)	Body composition Muscle strength	DEXA	1RM testing BC Muscle strength HRQOL	NA	SF-36	↑ LBM	↑ RM	NA	↑ SF-36 ↑ HRQOL
4	Roubenoff, 2001	HIV 43 (0:43) HIV 61 (N:N)	Body composition Muscle strength	DEXA MRI	1RM testing Anthropometric measurements	NA	MOS-HIV HRQOL	↑ LBM ↑ CSMA	↑ RM	NA	↑ MOS ↑ HRQOL
5	Agin et al. 2001	HIV 24 (24:0)	Body composition Muscle strength	DEXA MRI	Isokinetic dynamometer 1RM testing 1RM testing	NA	NA	↑ LBM	↑ RM	NA	NA
6	Basin et al. 1999	HIV 33 (33:0)	Body composition Muscle strength	BIA DEXA MRI	Anthropometric measurements	NA	NA	↑ LBM ↑ CSMA	↑ RM	NA	NA
7	Strawford et al. 1999	HIV 34 (34:0)	Body composition Muscle strength	DEXA MRI	Anthropometric measurements	NA	NA	↑ LBM	↑ RM	NA	NA
8	Sattler et al. 1999	HIV 24 (24:0)	Body composition Muscle strength	DEXA MRI	Anthropometric measurements	NA	NA	↑ LBM ↑ CSMA	↑ RM	NA	NA
9	Lox et al., 1995	HIV 42 (32:10)	Body composition Aerobic capacity	Hand-held dynamometer	Hand-held dynamometer	NA	NA	↑ LBM	↑ RM	NA	NA
10	Spence et al. 1990	HIV 60 (52:8)	Body composition Muscle strength	NA	Anthropometric measurements	NA	NA	↑ LBM	↑ RM	NA	NA
11	Terry et al. 2006	HIV 123 (89:20)	Body composition Aerobic capacity	NA	Anthropometric measurements	NA	NA	↓ BW ↓ BF ↓ WHR	NA	↑ VO ₂ max	NA
12	Neidig et al. 2003	HIV 60 (52:8)	Depressed Aerobic capacity Stress	NA	Graded exercise stress test	POMS	NA	NA	NA	NA	↑ POMS - MOS-HIV
13	Baigis et al. 2002	HIV 60 (52:8)	Aerobic capacity HRQOL	NA	Graded exercise stress test	MOS-HIV	NA	NA	NA	- VO ₂ max	NA
14	Smith et al. 2001	HIV 39 (34:5)	Body composition Aerobic capacity	NA	Graded exercise test Time on treadmill	NA	NA	↓ BMI ↓ TBF	NA	↑ TT - VO ₂ max	NA
15	Perna et al. 1999	HIV 43 (18:10)	Aerobic capacity	NA	Graded exercise test	NA	NA	↑ VO ₂ peak pulse	↑ O ₂	NA	NA
16	Terry et al. 1999	HIV 21 (14:7)	Body composition Aerobic capacity	NA	Time on treadmill	NA	NI	NA	NA	↑ treadmill time	NA
17	Stringer et al. 1998	HIV 50 (50:0)	Aerobic capacity	NA	Graded exercise test	QOL	NA	NA	NA	↑ VO ₂ max	↑ QOL
18	LaPerriere et al. 1990	HIV 97 (36:61)	Body composition Muscle strength Aerobic capacity	NA	Bicycle ergometer test	NA	NA	↑ LBM ↑ TMV	NA	↑ VO ₂ max	NA
19	Yarasheski et al. 2010	HIV 39 (34:5)	Body composition Muscle strength Aerobic capacity	DEXA	1RM testing	NA	NA	WHOQOL-BREF	NA	NA	NA
20	Multimura et al. 2008 ^a	HIV 97 (36:61)	Body composition Muscle strength Aerobic capacity	Anthropometric measurements	NA	Shuttle test	WHOQOL-BREF	↓ % BFM	NA	↑ VO ₂ peak	↑ QOL

Table 2 - Continued.

Study	Participants (M:F)	Outcomes	Outcomes				Results			
			Body composition (BC)	Muscle strength (MS)	>Aerobic capacity (AC)	HRQOL	BC	MS	AC	HRQOL
21 Hand et al. 2008	HIV 40 (30:10)	Aerobic capacity	NA	NA	Graded treadmill stress test	NA	NA	NA	↑ VO ₂ peak	NA
22 Pérez-Moreno et al. 2007	HIV 19 (19:0)	BC Strength AC HRQOL	Body mass MRI	6RM testing	Stress test Cycle ergometer	QOL	NS	↑ 6RM	↑ VO ₂ peak	NS
23 Dolan et al. 2006	HIV 38 (0:38)	Body composition	Anthropometric measurements TC DEXA	1RM testing	Treadmill stress test	NA	↑ CSMA	↑ 1 RM	↑ VO ₂ peak ↑ TCAM6	NA
24 Filipas et al. 2006	HIV 35 (35:0)	Aerobic capacity	NA	1RM testing	Kasch pulse recovery test	MOS-HIV	NA	NA	↓ HR	↑ MOS-HIV
25 Driscoll et al. 2004 ^a	HIV 25 (20:5)	BC Strength Aerobic capacity	Anthropometric measurements DEXA TC	1RM testing	Submaximal exercise stress test	NA	↑ CSMA ↓ WHR	↑ 1 RM	↑ ET	NA
26 Driscoll et al. 2004 ^b	HIV 25 (20:5)	Body composition	Anthropometric measurements CT DEXA	1RM testing	NA	NA	↓ BMI ↓ TMA	NA	NA	NA
27 Rojas et al. 2003	HIV 33 (23:10)	Muscle strength	NA	Graded exercise	MOS-HIV	NA	NA	↑ VO ₂ max ↑ O ₂ pulse	↑ MOS-HIV	NA
28 Grinspoon et al. 2000	HIV 43 (43:0)	BC Muscle strength	CT DEXA	2RM testing	NA	NA	↑ LBM ↑ CSMA	↑ 1 RM	NA	NA
29 Rigsby et al. 1992	HIV 37 (37:0)	Muscle strength	NA	2RM testing	YMCA cycle test protocol/Cycle ergometer	NA	NA	↑ 1 RM	↑ ET ↓ HR	NA

Male and female (M/F), dual energy X-ray absorptionmetry (DEXA), magnetic resonance imaging (MRI), computed tomography (CT), bioelectrical impedance analysis (BIA), lean body mass (LBM), body weight (BW), body cell mass (BCM), thigh muscle volume (TMV), percentage body fat (% BF), total body fat (TBF), waist-to-hip ratio (WHR) maximum voluntary contraction (MVC), mid-thigh cross-sectional muscle area (CSMA), 6 min walk test (TCAM6), exercise time (ET), time on treadmill (TT), health-related quality of life (HRQOL); Medical outcomes study HIV health survey (MOS-HIV); Profile of Mood States (POMS), not assessed (NA), significant improvement before and after the intervention and/or between groups ($p < 0.05$) (↑), no change (-), no improvement (N).

Table 3 - Characteristics of the experimental intervention (resistance exercise) the trials included in the review.

N	Study	Intensity (RM)	Volume	Muscle	Contraction	Frequency (x wk)	Time (min)	Duration (wk)	Supervision (yes/no)
1	Sakkas et al. 2009	80% RM	3 sets x 8 reps	Upper body	NI	3	90	12	yes
2	Lindegaard et al. 2008	50-60% RM	3 sets x 12 reps ⁴	Lower body	Concentric/Eccentric	3	45-60	16	NI
		70-80% RM	sets x 8-10 reps	Upper body	Dynamics	3	30-60	12	yes
3	Shevitz et al. 2005	80% RM	3 sets x 8 reps	Large muscles	NI	3	NI	8	yes
4	Roubenoff et al. 2001	50-60% RM	3 sets x 8 reps	Large muscles	NI	3	NI	14	yes
		75-90% RM							
5	Agin et al. 2001	75% RM	3 x (8-10) reps	NI	NI	3	NI	16	NI
6	Bhasin et al. 2000	60% RM	3 x (12-15) reps	Upper body	NI	3	NI	12	yes
		70-90% RM	4 x (4-6) reps	Lower body	NI	3	NI	7	yes
7	Strawford et al. 1999	80% RM	3 sets x 10 reps	Major muscles	NI	3	60	12	yes
8	Sattler et al. 1999	70% RM	3 sets x 8 reps	Upper body	Concentric	3	NI	12	yes
		80% RM		Lower body	Eccentric	3	NI	6	yes
9	Lox et al. 1995	60% RM	3 sets x 10 reps	NI	NI	3	NI	12	yes
10	Spence et al. 1990	15 RM	1 set x 15 reps	Bilateral	Concentric	3	NI	yes	
			3 sets x 10 reps						

RM = repetition maximum; reps = repetitions; NI = no information.

Most studies used either a cycle ergometer or combined exercise programs (such as a cycle ergometer and/or walking and/or jogging). The intensity of exercise was adjusted based on the HRmax in 70% of the studies. In one study (29), the VO₂max/peak was used, and the heart rate reserve was used in another study (23). The intensity ranged from 50 to 85% of the HRmax, 50 to 85% of the VO₂max/peak, or 50 to 85% of the heart rate reserve.

The aerobic interventions in the trials also varied according to constant compared with interval exercise and moderate compared with high-intensity exercise. Table 4 provides details on the characteristics of the intervention programs.

Outcome measures

The most commonly reported positive effects on physiologic physical performance indicators were observed in the

VO₂max/peak, resting heart rate, HRmax, and submaximal heart rate, as shown in Table 2.

Concurrent training

Characteristics of the sample. The initial sample size of the selected studies ranged from 35 (44) to 100 (36). The final sample ranged from 31 (44) to 97 (36), and the mean age of the participants ranged from 18 to 60 years. The studies included patients of both sexes, but there was a predominance of males (70%). All studies analyzed in this review included patients diagnosed with HIV, and most of these patients were receiving antiretroviral therapy.

Characteristics of intervention programs. The exercise intervention characteristics of the included studies are provided in Table 5. The duration of the intervention programs with concurrent training ranged from 6 (38) to 24 (36) weeks, but in most studies, the application period

Table 4 - Characteristics of the experimental intervention (aerobic exercise) in the trials included in the review.

	Study	Modality	Intensity/duration (wk)	Volume	Frequency (x per wk)	Time (min)	Length (wk)	Supervision
1	Lindegaard et al. 2008	NI	65% HRmax/8 75% HRmax/8	5 min warm-up 35 min IT	3	40	16	yes
2	Terry et al. 2006	Run	75-85% HRmax	15 min warm-up 30 min exercise 15 min cool-down	3	60	12	yes
3	Neidig et al. 2003	Treadmill Stationary bike Walking	50-70% HRmax	5 min warm-up 30 min exercise 5 min cool-down	3	60	12	yes
4	Braigis et al. 2002	Fitness Master ski machine	75-85% HRmax	10 min warm up 20 min exercise 10 min cool-down	3	40	15	yes
5	Smith et al. 2001	Walk or run	60-80 VO ₂ max	5 min warm-up 30 min exercise 5 min cool-down	3	30	12	yes
6	Perna et al. 1999	Treadmill Cycling exercise	60-80% HRmax	3 min exercise task 2 min recovery	3	45	12	yes
7	Terry et al. 1999	Treadmill	G1 - 60 ± 4% HRmax G2 - 80 ± 4% HRmax	NI	3	60	12	yes
8	Stringer et al. 1998	Cycle ergometer	G3 MI G4 HI	60 min IT 30-40 min IT	3	30-60	6	yes
9	Lox et al. 1995	Bicycle ergometer	50-80% HRres	5 min warm-up 24 min exercise 15 min cool-down	3	45	12	yes
10	LaPerrieri et al. 1990	Bicycle ergometer	60-79% HRmax 80% HRmax	3 min exercise 2 min recovery	3	45	24	NI

HRmax = heart rate maximum; HRres = heart rate reserve; MI = moderate intensity; HI = heavy intensity; IT = interval training; NI = no information.

Table 5 - Characteristics of the experimental intervention (concurrent training) in the trials included in the review.

N	Study	Type exercise	Intensity/duration (wk)	Volume	Frequency (x per Wk)	Time (min)	Length (wk)	Supervision
1	Yarasheski et al. 2010	Aerobic exercise cycling/treadmill	50-85% Hres	NI	3	90-120	16	Yes
		Resistance exercise	12 RM	1-2 sets 12 reps	3	90-120	16	Yes
2	Mutimura et al. 2008	Aerobic exercise	45% HRmax/3 60% HRmax/6 75% HRmax/15	15 min warm-up 60 min exercise 15 min cool-down	3	90	24	Yes
		Resistance exercise	NI	NI	3	90	24	Yes
3	Hand et al. 2008	Aerobic exercise	50-70% HRmax	5 min warm-up 30 min exercise 5 min cool-down	2	40	6	NI
		Resistance exercise	12 RM	1 set, 12 reps	2	20	6	NI
4	Pérez-Moreno et al. 2007	Aerobic exercise	70-80% HRmax	10 min warm-up 20 min exercise 10 min cool-down	3	20-40	16	Yes
		Cycle ergometer	12-15 RM	1-2 sets 12-15 reps	3	50	16	Yes
5	Filipas et al. 2006	Resistance exercise	60% HRmax/3	5 min warm-up 20 min exercise 5 min cool-down	2	30	6	Yes
		Aerobic exercise	75% HRmax/3	NI	3	50	16	Yes
6	Dolan et al. 2006	Resistive exercise	60% RM 80% RM	3 sets 10 reps	2	30	6	Yes
		Aerobic exercise	60% HRmax/2	5 min warm-up	3	35	16	Yes
7	Driscoll et al. 2004	Resistive exercise	75% HRmax/14	20-30 min exercise	3	85	16	Yes
		Resistive exercise	60-70% RM/2	3-4 sets 8-10 reps	3	25	12	Yes
8	Driscoll et al. 2004	Aerobic exercise	80% RM/12	5 min warm-up 20-30 min exercise 5 min cool-down	3	35	12	Yes
		stationary bicycle	60-75% HRmax	3-4 sets 8-10 reps	3	36	12	Yes
9	Rojas et al. 2003	Resistive exercise	75% HRmax/14	5 min warm-up 20-30 min exercise 5 min cool-down	3	24	12	Yes
		Aerobic exercise	60-70% RM/4	3 sets, 10 reps	3	50	12	NI
10	Grispoon et al. 2000	Resistive exercise	80% RM/12	10 min warm-up 25 min exercise 10 min cool-down	3	NI	12	NI
		stationary bicycle	60-70% HRmax	2-3 sets 8 reps	3	30	12	Yes
11	Rigsby et al. 1992	Resistive exercise	60-70% RM/6	30 min exercise	3	15	12	Yes
		dynamic	80% RM/6	15 min cool-down	3	2 sets, 8 reps 2 sets, 8 reps	12	Yes
		Aerobic exercise	60-80% HRmax	2 min warm-up 30 min exercise 3 min cool-down	3	36	12	NI
		Resistive exercise	NI	1-3 sets 6-18 reps	3	24	12	NI

HRmax = heart rate maximum; HRres = heart rate reserve; RM = repetition maximum; reps = repetitions; NI = no information.

ranged from 12 to 16 weeks. The duration of the session varied from 60 (40,41) to 120 (42) minutes. The frequency of sessions varied from two to three times per week, but there was a predominance of three times per week (72% of studies).

For resistance training, only two studies (40,42) specified the type of muscle contraction performed during training. The exercise was performed with concentric and eccentric contractions lasting 6 to 10 seconds with the use of machines, weight stations, and free weights in six studies, but in one study, there was no description of the type of equipment used (36). The exercise intensity was based on the extent of the RM, ranging from 60% to 80% of the RM in five studies (40-42,44,46). Three studies described the intensity as the 12RM (35,38,39), and three studies did not report the prescribed exercise intensity (36,43,47). The application volume of exercise ranged from one to four sets of six to 18 reps. The volume of exercise was not described in one study (36).

For the application of aerobic exercise, all studies reported treadmill use, bike use, cycle ergometer use, walking, or jogging. Except for a study by Rigsby (47), all studies reported the criteria for progression training. In all studies, the intensity was adjusted based on the heart rate, ranging from 45% to 80% of the HRmax. The sessions of aerobic exercise began with a warm-up period of 5 to 10 min and finished with a cool-down period of 5 to 15 min. Table 3 provides details on the characteristics of the intervention programs.

Effects of different types of therapeutic exercise

Resistance exercise training improved outcomes related to body composition, with increases in lean body mass (13,1524), mid-thigh cross-sectional muscle area (15,19,21), and bone mineral density (13-21), in addition to a reduction in body weight (14). Resistance exercise also generated muscle strength gain (13-21) but had little impact on quality of life (15-18).

Aerobic exercise training improved outcomes related to body composition, reducing body weight (25,29), total body fat (29), and the WHR (25). A significant increase was also observed in aerobic capacity, as measured by the VO_{2max} / peak (25,28-32) or time on a treadmill (29).

Concurrent training showed significant gains in body composition, with increases in lean body mass (35,46), thigh muscle volume (35), and mid-thigh cross-sectional muscle area (40,42,46). This training reduced thigh muscle adiposity (43), the percentage of body fat (36,43), and the WHR (42).

Significant increases were also observed in muscle strength (39,40,46,47); aerobic capacity, measured by the VO_{2max} / peak (37-40); exercise duration (42,47); and the distance covered in 6 min walking test (40), with a positive impact on quality of life (36,41,44). Thus, in contrast to resistance and aerobic exercise performed in isolation, concurrent training showed improvement for all evaluated outcomes.

4 DISCUSSION

The results of this review indicate that resistance training, aerobic exercise, and concurrent training are associated with improvements in body composition, muscle strength, and cardiopulmonary fitness in adults living with HIV/AIDS.

The functional impairments of a patient should determine the exercises and activities prescribed, including the mode of exercise used (48,49). The use of multiple conditioning components to address both neuromuscular strength and cardiovascular health has become an important part of most recommended exercise regimens (50).

It is important to emphasize that exercise training should be supervised by qualified professionals for the prevention of injury and to maximize the health and performance benefits (51). In 80% of the reviewed studies, the supervision of exercise by a professional was reported.

The available literature regarding the effects of exercise training in HIV is encouraging. The published trials indicate that short-term resistance exercise has physiologic benefits and positive effects on body composition and musculoskeletal health (24). Aerobic exercise directly benefits aerobic capacity (32). Concurrent training has a positive effect on body composition, aerobic capacity, muscle strength, and quality of life (38,41).

In a study by Spence et al. (24), the RM was used to evaluate muscle strength. The between-group mean values for lower-extremity muscle function were significantly different ($p<0.01$), indicating improved muscle performance in the resistance exercise group with 6 weeks of exercise. Stringer et al. (32) observed an improvement in the $\text{VO}_{2\text{max}}$ after 6 weeks of aerobic exercise. In studies by Hand et al. (38) and Fillipas et al. (41), there was an improvement in the aerobic capacity estimated in the concurrent training group, whereas no improvement was noted in the control group after 6 weeks ($p>0.01$). Individual studies also indicate that exercise training appears to be safe (52).

Incorporating both resistance and aerobic modalities into rehabilitation programs may be more effective in optimizing functional status than programs involving only one component (53-55). In people with HIV, concurrent exercise training may decrease functional limitations and reduce physical disability resulting from HIV infection and its medical treatment (56,57). Seven studies reported significant improvement in a concurrent training group compared with a control group (35,36,38-44,46,47).

In a study by Multimura et al. (36), the $\text{VO}_{2\text{max}}$ improved in the concurrent exercise group compared to the control ($p<0.001$). In a study by Hand et al. (38), there was an improvement of 21% in the VO_2 estimated in the concurrent training group and no improvement in the control group ($p<0.001$). In the study by Filipas et al. (41), the HR was reduced in the exercise group compared with the control ($p<0.001$).

Exercise prescription is based upon the frequency, intensity, and duration of training; the mode of activity; and the initial functional status. The interaction of these factors provides the overload stimulus and has been found to be effective for producing a training effect (58,59).

Determining the appropriate exercise mode depends on patient preference and safety issues regarding the stage of the disease or other conditions. The frequency, intensity, and duration are specific to the type of activity and should be tailored to the patient's ability to safely perform the activity.

A minimal intensity level is likely required to receive a benefit, although the exact value is not known and may vary from one person to another. Although the optimal intensity cannot be defined based on available information, much of the exercise that is associated with good health in published reports is at least of moderate intensity (58,60).

Resistance training should focus on large muscle groups, such as the chest, brachial biceps, quadriceps, and hamstrings. Again, the intensity should be moderate (set at 60 % to 80% of the RM) and progressively increased. Overload should be set to match the level at which a patient can comfortably perform eight to 12 reps. For people who wish to focus on improving muscular endurance, a lower intensity (i.e., 50% of the RM; light to moderate intensity) can be used to complete 15 to 25 repetitions per set, with the number of sets not to exceed two (60,61).

Aerobic exercises should be performed at a moderate intensity, from 11 to 14 on the Borg Rating of Perceived Exertion Scale, at 50% to 85% of the HRmax, or at 45% to 85% the $\text{VO}_{2\text{max}}$ /peak. The number of weekly exercise sessions should be increased until the patient can tolerate three to five sessions weekly. In total, 30 to 60 min per day is recommended, although 20 min may be beneficial in deconditioned people (60). In all studies included in this review, the session duration ranged from 30 to 60 min. Sessions should be initiated with a warm-up period and finished with a cool-down period.

The maximum duration of the intervention in the included studies was 24 weeks, with most interventions ranging between 6 and 12 weeks. Thus, the long-term effects of exercise remain unclear.

This review has several limitations, and the results should be cautiously interpreted for several reasons. The results are based on a small number of studies. The differences in endpoints, assessment instruments, and variables of exercise prescription and the limited follow-up in several studies prevent definitive comparisons and quantitative analysis.

Meta-analyses were not performed because of the variability of the characteristics of studies pertaining to exercise and variation between individual studies in the interventions, which included the type of exercise intervention, the intensity of exercise, the length of follow-up to exercise, and outcomes.

In conclusion, considerable evidence currently exists to support a role for different types of exercise in the management of HIV-infected patients. Concurrent training showed significant gains in all outcomes evaluated and is the best type of exercise in patients with disabilities resulting from HIV. Research in the field of exercise training in people with HIV should be focused on providing indications regarding evidence-based standards for exercise prescription and on careful clinical evaluation and exerciserelated risk assessment.

5 AUTHOR CONTRIBUTIONS

Gomes-Neto M, Conceição CS, Carvalho VO, and Brites C conceived the study and drafted the manuscript. Carvalho VO performed the search and the initial selection of potentially relevant studies. Gomes-Neto M and Conceição CS identified the articles in agreement with the inclusion and exclusion criteria and performed the data extraction. Brites C supervised the review process and resolved disagreements. All authors have read and approved the final manuscript.

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CONCLUSÃO

Muitos estudos avaliaram a relação entre à utilização da TARV, risco cardiovascular e doença cardiovascular, sugerindo que apesar da redução da mortalidade, existe um maior risco cardiovascular e da frequência das doenças cardiovasculares. Profissionais da saúde devem estar atentos aos riscos acumulados da doença e da utilização da TARV nesta população, elaborando estratégias de avaliação, prevenção e tratamento. Estratégias devem ser focadas na redução de problemas cardiovasculares bem como na maximização da funcionalidade e qualidade de vida.

Dentre as principais estratégias complementares ao uso da TARV, estão diminuição do tabagismo, intervenções dietéticas e a implementação de programas de exercício. As modalidades de exercício terapêutico são diferenciadas, pelo modo como o exercício é realizado, a forma de aplicação das variáveis e parâmetros de intensidade, volume, frequência e duração e nos desfechos fisiológicos e funcionais associados a cada modalidade.

O exercício resistido é associado com melhora em desfechos de composição corporal e desempenho muscular, o exercício aeróbico está associado com melhora na composição corporal e aumento na capacidade funcional aeróbica e condicionamento físico. Quando essas modalidades foram associadas numa mesma sessão de exercício (treino concorrente), estudos demonstraram melhora significativa em todos os desfechos pesquisados (composição corporal, desempenho muscular, capacidade funcional aeróbica e qualidade de vida).

Evidências consistentes suportam a segurança e o papel do exercício terapêutico, na adaptação central e periférica melhorando desfechos de saúde em pacientes com HIV. A escolha dos parâmetros de prescrição do exercício (intensidade, volume, frequência e duração), devem ser cuidadosamente selecionados e adequadamente combinados para que o resultado esperado seja alcançado.

CONSIDERAÇÕES FINAIS

A revisão sobre risco cardiovascular deve ser interpretada com cautela devido a suas limitações, dentre elas a inclusão de estudos não controlados, diferença na característica das populações em cada estudo, além da pequena quantidade de estudos de comparação de regimes diferenciados da utilização da TARV, dificultando a análise do diferente risco em diferentes regimes.

As revisões sobre a aplicação do exercício apresentam algumas limitações devido à inclusão de ensaios clínicos com pequenas populações, que apesar da qualidade metodológica, podem minimizar efeitos terapêuticos encontrados, além da diversidade dos critérios de inclusão e exclusão em cada estudo. Com populações não homogêneas, diferentes desfechos analisados e formas de avaliações desses desfechos em cada estudo, bem como a diferença nos parâmetros de prescrição dos exercícios nos estudos incluídos, não foi possível a realização de análise quantitativa (metanálise). Outra consideração importante foi a pequena duração dos estudos o que não permite a identificação dos efeitos dos programas de exercício com longa duração e follow-up.

PERSPECTIVAS DE ESTUDOS

Diante do aumento do risco cardiovascular e doenças cardiovasculares associadas à utilização da TARV, estudos experimentais devem analisar se medidas complementares como o exercício terapêutico podem reduzir de forma adicional à mortalidade nesta população.

Estudos comparativos sobre efeitos adversos da utilização de diferentes regimes de terapia antirretroviral são necessários para evidenciar as diferenças entre os regimes, incluindo os regimes atualmente aplicados.

Apesar da segurança e benefícios proporcionados pelo exercício terapêutico, novos ensaios clínicos aleatorizados são necessários para avaliar resultados de comparação de tipos, intensidades, volume diferentes, assim como programas de longa duração.