

Taming HIV-Related Inflammation with Physical Activity: A Matter of Timing

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Abstract

Many sets of data indicate that HIV-infected individuals maintain a low level of chronic immune activation and inflammation even in the presence of effective antiretroviral therapy (ART). This residual immune activation seems to be associated with accelerated aging and an increased incidence of non-AIDS-defining illnesses. Several published studies suggest that physical activity is a beneficial nonpharmacological intervention to reduce chronic inflammation. However, currently available data on the potential benefits of regular physical exercises for HIV-infected individuals are limited. Nonetheless, increasing evidence suggests that the introduction of regular physical exercise in the clinical management of HIV-infected individuals may have a significant positive impact in reducing some of the long-term complications of both infection and ART. Based on a comprehensive review of the existing data, we propose that regular physical exercise should be further studied as a potential antiinflammatory, nonpharmacological approach to be used to treat HIV residual disease and non-AIDS-defining illnesses in ART-treated HIV-infected individuals.

Introduction

COMBINED ANTIRETROVIRAL THERAPY (ART) has significantly increased the average lifespan of HIV-infected individuals.^{1,2} However, this lifespan remains shorter than that of uninfected age-matched controls. In 2008, the results of the Antiretroviral Cohort Collaboration showed that the change in survival was dependent on the time of treatment initiation³; more recently, Johnson *et al.* studied 37,740 HIV-infected individual adults starting ART for the first time to estimate their average life expectancy. They found that life expectancy varied between 27.6 years for patients 20 year old and 10.1 years for those 60 year old. On the other hand, they found that the life expectancy for women was higher than for men (36.8 and 14.4 years, respectively). In addition, if baseline levels of CD4⁺ T cells are >200 cell/mm³, the life expectancy is approximately 70–80% of that of HIV-uninfected adults of the same age and sex.⁴

While ART has significantly reduced HIV-associated morbidity and mortality, lifelong treatment is associated with severe side effects and an inability to fully revert the HIV-associated immune dysfunction and chronic immune activation.^{5,6} Indeed, despite full suppression of virus replication, immune activation and inflammation are only partially

reverted by ART.^{7,8} Moreover, increasing evidence suggests that HIV-related chronic inflammation is associated with an increased risk of non-AIDS-defining illnesses, including cardiovascular, neurological, liver, and kidney disease, changes in body fat deposit, metabolic disorders, accelerated aging, and tumors.⁹ Although the relative contributions of HIV infection per se, chronic immune activation, and ART in causing non-AIDS events are still not well defined, the scientific community is exploring the use of antiinflammatory treatments (pharmacological and nonpharmacological) as part of the comprehensive prevention and treatment of HIV-associated, non-AIDS-defining illnesses.¹⁰

Impact of Non-AIDS-Related Illness on the Life Expectancy of HIV-Infected Individuals

Today, non-AIDS-related illness represents the main cause of morbidity and mortality among ART-treated, HIV-infected individuals in developed countries.¹¹ Increased life expectancy exposes HIV-infected subjects to a mix of age-related morbidities, long-time side effects of ART, and chronic low-level inflammation. A typical example of the complex situation described above is the multifactorial pathogenesis of atherosclerotic cardiovascular disease (CVD) and its high incidence

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observed in ART-treated HIV-infected individuals.^{12,13} The multifactorial pathogenesis of CVD is particularly evident in the failure of common cardiovascular risk scores (Framingham, PROCAM, SCORE) to predict and fully explain the morbidity and mortality related to heart disease in HIV-infected individuals.^{14–16} In fact, if traditional risk factors (smoking status, blood pressure, age, gender, race, and menopausal status) justify much of the cardiovascular risk, additional factors appear to contribute to the increase in cardiovascular risk observed in HIV-infected individuals, including chronic immune activation, accelerated aging, viral factors, and the adverse effects of ART.¹⁷

Significant associations between inflammation and CVD pathogenesis are well established based on large-scale clinical studies. For example, in the Women's Interagency HIV Study (WIHS), greater T cell activation was associated with subclinical arterial disease.¹⁸ Similarly, in the SMART study, baseline levels of C-reactive protein and interleukin (IL)-6, two biomarkers of inflammation, are associated with increased CVD risk.¹⁹ Moreover, in patients with undetectable viremia, high-sensitivity C-reactive protein and IL-6 levels were elevated by 38% and 60%, respectively, when compared to HIV-uninfected controls.¹⁹ In another study, plasma levels of several inflammatory and coagulopathic biomarkers, such as IL-6, D-Dimer, and highly sensitive C-reactive protein (hs-CRP), were higher in the setting of HIV infection and correlate with its clinical outcome.²⁰

If on the one hand HIV infection, ART, and host factors such as aging and chronic immune activation all contribute to the development of metabolic and cardiovascular complications, on the other hand the pathophysiology of these disorders shows some specific features in the setting of HIV infection.²¹ Recent studies have found an unexpected greater degree of subclinical coronary artery disease (CAD) with an abnormal conformation and localization of atherosclerotic plaques in asymptomatic HIV-infected individuals with no prior history of cardiovascular disease.²² In that study, d'Ettertorre *et al.* conducted a cross-sectional analysis on 55 HIV-infected individuals enrolled at the Department of Public Health and Infectious Diseases of the University "Sapienza" of Rome (Italy). The inclusion criteria were Framingham Risk Score (FRS) ≤ 10 , absence of metabolic syndrome, negative echocardiographic and ECG stress test, persistent viral suppression, and adequate recover of CD4⁺ T cells. All patients underwent dual-source computed tomography (CT) coronary angiography. Significant coronary stenosis with soft non-calcified plaques, thus requiring coronary angiography, was unexpectedly found in 16 out of 55 individuals (29.1%), with a coronary stent implant procedure performed in 8 of these 16. It was therefore concluded that increasing sets of data support the hypothesis of a relationship between HIV infection and coronary atherosclerosis independent of traditional cardiovascular risk factors, suggesting that persistent inflammation, incomplete immune reconstitution, and residual viral replication might all contribute to increased CAD in HIV-infected individuals.^{17,22–25}

The link between inflammation, virus replication, and ART can also be identified in the setting of HIV-associated metabolic diseases, in which active virus replication can cause proatherogenic elevations in serum lipids, an increase in systemic inflammation, hypercoagulation, and reduced endothelial reactivity.^{13,26} In addition, HIV-infected individuals receiving

ART may experience various metabolic complications (i.e., impaired glucose metabolism, dyslipidemia, and abnormal body fat distribution), thus potentially increasing their risk of cardiovascular disease.²⁷

The complex interactions between non-AIDS-related pathology and HIV infection are only marginally understood. For example CVD, osteopenia/osteoporosis, kidney diseases, and immune activation found a possible common denominator in vitamin D deficiency. Recent studies have revealed an association between increased inflammation markers and hypovitaminosis D during the course of HIV infection. Poudel-Tandukar *et al.* reported that the risk of increased inflammation was greater among HIV-infected individuals with a 25-hydroxyvitamin D [25(OH)D] serum level of < 20 ng/ml, and Ansemant *et al.* indicated that severe vitamin D deficiency correlates significantly with increased hs-CRP and IL-6 serum levels.^{28,29} At the same time, low vitamin D levels are also associated with a higher risk of developing osteopenia/osteoporosis, and were found to be an independent risk factor for cardiovascular disease and metabolic disorders such as insulin resistance and type 2 diabetes mellitus. Lai *et al.* found that 25(OH)D deficiency was independently associated with a > 2 -fold increase in the risk of significant coronary stenosis in a cohort of cardiovascular asymptomatic HIV-infected individuals and Szep *et al.* reported that vitamin D deficiency was independently associated with diabetes.^{30,31} Taken together, these data suggest that in HIV-infected individuals, this cardiovascular, metabolic, bone, and kidney damage is directly linked to the proinflammatory status induced by hypovitaminosis D as well as HIV-associated chronic inflammation, the direct effects of virus replication on osteoblast and osteoclast functions, and the effect of ART on bone turnover and kidney function.^{32,33}

In addition to metabolic, cardiovascular, bone, and kidney diseases, other non-AIDS-defining illnesses may be related to specific aspects of the complex immune dysfunction occurring in HIV-infected individuals. An interesting area filled with many open questions is how neurological disorders, and in particular the so-called HIV-associated neurocognitive disorders (HAND), result from the interaction among HIV, ART, and chronic immune activation. Several studies showed that the prevalence of HAND is approximately 50% in both ART-treated and ART-naive HIV-infected individuals and it is 2-fold greater in older HIV-infected individuals than in younger ones.^{34–37} These data suggest that the pathogenesis of HAND may recognize an additive or even synergistic effect of HIV infection and aging. The most important data on neurological disorders in HIV-infected individuals before and after ART were obtained studying the cohort "Central nervous system HIV antiretroviral therapy effects research" (CHARTER). These studies showed that while HIV-associated dementia has declined from 18% to $< 5\%$ of HIV-infected individuals, there is an increase of mild symptomatic neurocognitive impairment from 12% to 17% and of asymptomatic neurocognitive impairment from 20% to 28% of HIV-infected individuals.^{38,39} Along those lines, Pedersen *et al.* conducted a cross-sectional study on 61 ART-treated HIV-infected individuals with undetectable plasma viremia and found a negative correlation between the levels of immune activation and cognitive scores.⁴⁰ Overall, these data suggest that residual immune activation may be a cause of central nervous system (CNS) damage in ART-treated HIV-infected individuals.

Physical Activity and Inflammation

The role of inflammation in the pathogenesis of infectious and metabolic diseases is a relatively novel topic of investigation that has been studied using a multidisciplinary approach. As described by Mathis and Shoelson, immune metabolism is an emerging area of research which investigates the interface between immunology and metabolism. Perturbations of the multilevel interaction between metabolism and immune function can play an important role in the pathogenesis of numerous diseases, and a better understanding of this interaction may offer substantial therapeutic promise.⁴¹ The relationship between dysmetabolic conditions (such as obesity and type 2 diabetes mellitus) and immune function in the setting of a chronic low-grade inflammation is highlighted by high circulating levels of CRP, IL-6, and tumor necrosis factor. This persistent inflammation has been considered not only a risk factor but also a possible cause of pathology related to dysmetabolism such as cardiovascular disease, colon and breast cancer, depression, and dementia.^{42–44}

Physical exercise has been shown to improve the clinical course of numerous diseases by modulating both the immune system and the metabolic balance.^{45,46} It is well established that in healthy individuals, regular aerobic exercise of moderate intensity and duration is associated with a reduced incidence of metabolic diseases. In addition, exercise reduces the excess storage of fat in adipocytes and their production of inflammatory mediators, thus limiting the inflammation associated with obesity.⁴⁷ Indeed, regular aerobic exercise reduces inflammation in diseases associated with low-grade inflammation (e.g., obesity, chronic heart failure, atherosclerosis, diabetes).^{48,49} While the protective antiinflammatory effect of physical exercise is well documented, there is also evidence that physical inactivity may favor the development of low-grade systemic inflammation. This is due to the fact that sedentary behavior leads to the accumulation of visceral fat, which is accompanied by increased release of adipokines and adipose tissue infiltration by proinflammatory immune cells. This negative interplay between immune and metabolic dysfunction is associated with the development of insulin resistance, atherosclerosis, and neurodegeneration.^{50–52} For these reasons, there is growing interest in studying the effects of physical activity as a nonpharmacological tool to reduce chronic inflammation, even though the mechanisms responsible for this immune modulatory effect remain poorly understood.

Several studies have shown that regular physical exercise reduces the risk of chronic metabolic and cardiologic disease by antiinflammatory effects mainly mediated via the following: (1) reduction in visceral fat mass, (2) decreased release of adipokines, (3) increased release of cortisol and adrenaline, (4) increased production and release of IL-6, and (5) inhibition of adipose tissue infiltration by monocytes and macrophages with reduction in the circulating numbers of proinflammatory monocytes and phenotypic switching of macrophages within adipose tissue. While the inhibition of downstream proinflammatory cytokine production and the modulation of monocyte and macrophage activity as well as the related hormonal changes are effective means of reducing chronic inflammation, an excess of physical exercise can lead to excessive modulation of the immune function, which may

ultimately reduce the host defense against pathogens. This is the so-called “elite athlete paradox,” according to which the excessive antiinflammatory effect can induce partial immune suppression that makes top athletes more susceptible to common infections.^{46,51,52}

Regardless of this paradox, there is overwhelming evidence that noncompetitive sport and regular physical exercise are an essential component of a healthy lifestyle. The positive, direct effects of engaging in regular physical activity are particularly apparent in the prevention of several chronic inflammation-related diseases, including cardiovascular disease, diabetes, cancer, hypertension, obesity, depression, and osteoporosis—that is, the same illnesses that are observed in ART-treated HIV-infected individuals. It should be mentioned that another key modifiable factor affecting immune function in the general population is nutrition. While malnutrition is known to decrease immune function, excessive food intake may result in chronic low-grade inflammation.⁵³ Based on these general premises and considering that ART is unable to fully prevent the multi-organ damages associated with HIV infection and related to chronic inflammation and immune activation, the recently published clinical guidelines for HIV infection recommend physical activity as nonpharmacological treatment for individuals with dyslipidemia under ART, and as an approach to reduce symptoms of depression in HIV-infected women.^{54–57}

Potential Benefits of Physical Exercise on Non-AIDS-Defining Illness in HIV Infection: Role of a Physical Activity Program in HIV-Infected Individuals

As discussed above, regular physical activity has a protective antiinflammatory effect. However, a search for published articles on the relationship between physical exercise and immune activation during the course of HIV infection does not reveal any studies that focused specifically on this point. A more thorough examination of the available studies confirms that the current knowledge on the potential benefits of regular physical exercise in HIV-infected individuals is limited (Table 1). A recently published randomized clinical trial evaluated the impact of regular physical activity on the quality of life, body morphology, and metabolic parameters in patients with AIDS, although the issue of chronic inflammation and immune activation was not investigated.⁵⁸ In this study, patients were randomly assigned to receive a 1-h supervised gym class three times a week plus monthly nutritional counseling (intervention group) or to participate in monthly workshops to discuss the importance of physical activity and receive nutritional counseling (control group). After intervention, the exercise group showed a decrease in fat mass, resting heart rate, waist circumference, and serum glucose, as well as an increase in muscle mass, CD4⁺ T cells, metabolic markers, and maximum oxygen consumption. Similarly, the key indices of quality of life, general health, and mental health showed a statistically significant improvement in the exercise group as compared to the control group.⁵⁸

Other studies investigated the effect of regular physical activity on lipodystrophic syndrome and associated metabolic disturbances such as glucose intolerance, insulin resistance, hypertension, and dyslipidemia. In this regard,

TABLE 1. MAIN OPEN STUDIES ON HIV AND PHYSICAL ACTIVITY REGISTERED IN THE DATABASE OF CLINICAL TRIALS.GOV

<i>Title and clinical trials identifier</i>	<i>Sponsor</i>	<i>Status of the study and dates</i>	<i>Study type and study design</i>	<i>Purpose</i>
Home-Based Exercise for Management of HIV-Associated Cardiovascular Disease (NCT 01377064) ⁶³	University of South Carolina	This study is currently recruiting participants. <ul style="list-style-type: none"> • Study start date: March 2011 	Phase: 1 Study type: interventional Allocation: randomized Intervention model: parallel assignment Masking: open label Primary purpose: treatment	This study will test the feasibility of an at-home exercise program for people living with HIV/AIDS (PLWHA) and prepare for a full-scale interventional study, which may lead to a reduction in cardiovascular disease (CVD) risk among PLWHA. <ul style="list-style-type: none"> • Primary outcome: amount of physical activity • Secondary outcome: cardiorespiratory fitness
Effectiveness of Team Intervention over 12 Months in Reducing Modifiable CVD Risk Factors on Framingham 10 yr Risk Scores Outcomes in HIV-1 Subjects on Antiretroviral Therapy (NCT 01436136) ⁶⁴	Holdsworth House Medical Practice	This study is currently recruiting participants. <ul style="list-style-type: none"> • Study start date: October 2011 	Study type: interventional Allocation: randomized Intervention model: single group assignment Masking: open label Primary purpose: prevention	This is a cohort study that follows two groups of participants over a 12-month period. One group will access a team approach to care with the aim of reducing their CVD risks from a team of doctors, nurses, and health care professionals. The other group will continue to access standard care from their treating doctor. Both groups will have their CVD risk score evaluated after a 12-month period. The team care approach will involve specific tests to measure CVD risk as well as smoking cessation, exercise, and dietary advice and support, including monitoring such as blood pressure and cholesterol levels. <ul style="list-style-type: none"> • Primary outcome: percentage of patients with a reduction of Framingham risk score of at least 10% at week 52
Therapeutic Approaches to HAART-Induced Lipodystrophy (NCT 00461552) ⁶⁵	University of Texas SW Medical Center	This study is currently recruiting participants. <ul style="list-style-type: none"> • Study start date: January 2003 	Phase: 2 Study type: interventional Allocation: randomized Endpoint classification: safety/efficacy study Intervention model: single group assignment Masking: double blind (subject, caregiver, investigator) Primary purpose: Treatment	To determine the efficacy and safety of four therapeutic interventions on HAART-induced lipodystrophy. The interventions are: (1) Dietary—the effect of a high carbohydrate vs. a high cis-monounsaturated fatty acid diet. (2) The effect of aerobic exercise with dietary advice. (3) The effect of omega-3 fish oil capsules. (4) The effect of leptin therapy. These interventions are aimed at improving the metabolic complications of HAART therapy such as elevated lipids and insulin resistance or diabetes. <ul style="list-style-type: none"> • Primary outcome: fasting serum triglycerides • Secondary outcome: HDL cholesterol, LDL cholesterol, fasting serum glucose, fasting serum insulin, overall and regional adiposity
Atherosclerotic Risk and Response to Exercise Intervention in HIV+ Children (NCT 00908284) ⁶⁶	National Heart, Lung, and Blood Institute (NHLBI)	The recruitment status of this study is unknown because the information has not been verified recently. <ul style="list-style-type: none"> • Study start date: December 2008 	Study type: interventional Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: prevention	The purpose of this study is to assess cardiovascular risk factors in children infected with HIV who receive HAART medications and to determine the effectiveness of an exercise program on cardiovascular outcomes in these children. <ul style="list-style-type: none"> • Primary outcome: E-selectin, vascular cell adhesion molecule-1 (VCAM-1), P-selectin, fibrinogen, plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1), high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), adiponectin, leptin, mitochondrial DNA (mtDNA), echocardiography, flow-mediated dilation (FMD), carotid intima-media thickness (cIMT), body mass index (BMI), dual energy x-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), resting energy expenditure (REE), bone mineral density (BMD), lipid profiles, insulin and glucose strength, and fitness measures. • Secondary outcome: age, sex, HIV disease stage, CD4 counts, viral load, and type and length of antiretroviral therapies

(continued)

TABLE 1. (CONTINUED)

<i>Title and clinical trials identifier</i>	<i>Sponsor</i>	<i>Status of the study and dates</i>	<i>Study type and study design</i>	<i>Purpose</i>
Effects of an Exercise Program on Metabolic Parameters of Patients with an HIV Infection. (NCT 00910936) ⁶⁷	Charite University, Berlin, Germany	The recruitment status of this study is unknown because the information has not been verified recently. <ul style="list-style-type: none"> • Study start date: May 2009 	Phase: 2–3 Study type: interventional Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: single blind (investigator) Primary purpose: supportive care	The investigators will evaluate the effects of an endurance exercise program on the physical performance, the well being, and indicators of metabolic function in patients with an HIV infection. <ul style="list-style-type: none"> • Primary outcome: maximal oxygen uptake (VO_{2max}) • Secondary outcome: quality of life, indicators of fat metabolism, markers of inflammation
Effects of Mixed Exercise Regime and L-Carnitine Supplementation on Kinetics of Triglyceride-rich Lipoproteins in HIV Patients on HAART (NCT 00572429) ⁶⁸	University of California, Davis	This study is ongoing, but not recruiting participants. <ul style="list-style-type: none"> • Study start date: July 2008 	Study type: interventional Allocation: randomized Endpoint classification: efficacy study Intervention model: single group assignment Masking: double blind (subject, investigator) Primary purpose: treatment	This study hypothesizes that a mixed regimen of exercise (including both resistance and aerobic exercise) and L-carnitine supplementation will improve mitochondrial dysfunction in HIV/HAART patients, and therefore will alleviate dysmetabolic symptoms such as dyslipidemia and insulin resistance. In this randomized, placebo-controlled study, we will explore whether a mixed regimen of exercise, including both resistance and aerobic exercise, and L-carnitine supplementation affects lipids and remnant lipoproteins, adipokines, and insulin resistance; blood lactate levels and VO_{2max} ; and kinetics of leucine and triglyceride-rich lipoproteins among African American and Hispanic HIV-positive subjects undergoing HAART.
Strategies for the Treatment of HIV Associated Metabolic Syndrome (NCT 00399360) ⁶⁹	Massachusetts General Hospital	This study is ongoing, but not recruiting participants. <ul style="list-style-type: none"> • Study start date: December 2006 	Study type: interventional Allocation: randomized Intervention model: factorial assignment Masking: double blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: treatment	The purpose of the study is to evaluate the effects of different methods of treating HIV-associated metabolic syndrome. The groups are (1) a lifestyle modification program plus metformin (also known as glucophage), (2) lifestyle modification plus placebo, (3) metformin alone, or (4) placebo alone. The lifestyle modification program consists of nutrition and exercise sessions with the goal of improving body composition, heart health, and ways to lower the risk of developing diabetes. <ul style="list-style-type: none"> • Primary outcome: carotid intima media thickness, waist circumference, lipid levels, glucose, blood pressure • Secondary outcome: inflammatory markers, visceral adiposity, cardiorespiratory fitness, IMCL, coronary calcium score, and stenosis

ClinicalTrials.gov, <http://clinicaltrials.gov/ct2/home>

Filippas *et al.* conducted a randomized controlled trial on the effects of 6 months of aerobic and resistance exercise in HIV-infected individuals. Forty subjects were randomized into an experimental or control group. Patients included in the experimental group performed two 60-min exercise sessions per week consisting of 20 min of aerobic exercise at 60% of the maximum heart rate (HR-max) and progressing to 75% HR-max. Patients enrolled in the control group performed a walking exercise twice a week starting at 60% HR-max and progressing to 75% HR-max. The results of this study indicated that patients enrolled in the experimental group improved their self-efficacy, cardiovascular fitness, and cognitive function as compared to the control group.⁵⁹

More recently, Longo *et al.* conducted a longitudinal study on 50 ART-treated HIV-infected individuals with a sedentary life style to evaluate the effect of 12 weeks of moderate intensity exercise (i.e., brisk walking) on parameters of immune activation and metabolic profile. The program consisted of three weekly 60-min sessions of outdoor walking at 65–75% HR-max associated or not with 30-min circuit training at 65% of 1-RM (repetition maximum). At enrollment and after 12 weeks all participants were assessed by a 6-min walking test and 1-RM, DEXA, metabolic parameters (glucose, cholesterol, HDL, LDL, triglycerides, glucose, insulin, AST, ALT, γ GT, HbA_{1c}, CPK), immunovirological parameters (CD4⁺ and CD8⁺ T cells, HIV-RNA), and markers of immune activation (IL-6, D-Dimer, sCD14, and IL-18). Of note,

a significant improvement of both fitness and immune activation at the week 12 time point was found.⁶⁰

In individuals with HIV infection, as well as those with other chronic diseases, it is important to improve muscle mass to preserve muscle trophism and functional status. Sakkas *et al.* conducted a randomized double-blind, placebo-controlled study to evaluate the effect of creatine supplementation on muscle size, strength, and function in HIV-infected individuals. The study enrolled 40 HIV-infected males in a 14-week study (20 receiving creatine and 20 placebo). Treatment began with a loading dose of 20 g/day (or an equivalent number of placebo capsules) for 5 days, followed by maintenance dosing of 4.8 g/day. All subjects underwent three times-weekly supervised resistance exercise beginning at week 2 until week 14 while continuing on the assigned study medication. It was found that after 14 weeks, 1-repetition maximum strength increased in all muscle groups and that the magnitude of this increase was not greater with creatine supplementation; in the two groups phosphocreatine recovery following 15 s of maximum voluntary contraction improved significantly after progressive resistance exercise training (PRT). No effect on body composition was observed in any study group. Finally, at week 2 both insulin and HOMA-IR decreased transiently in the creatine group while there were no observed differences in lactate, glucose, or creatine kinase levels between or within groups at any time point. It was concluded that PRT is important in preventing and reversing muscle weakness and the

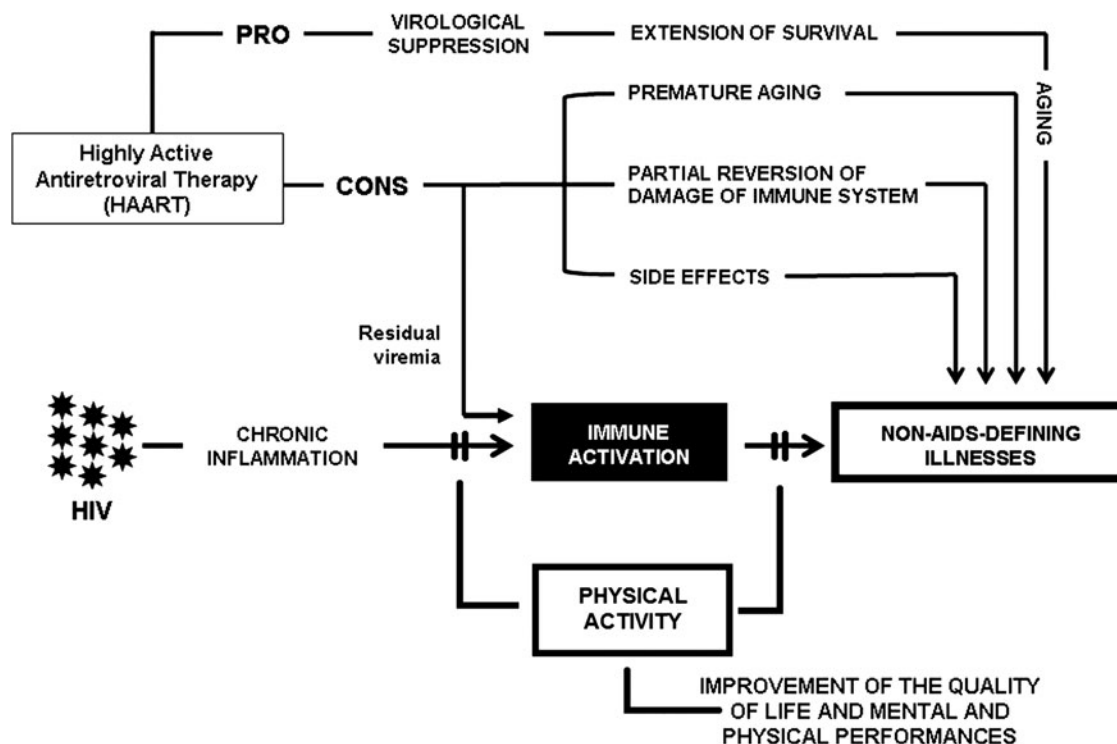


FIG. 1. Potential benefits of physical activity on chronic HIV infection. HIV-positive patients present a low level of chronic immune activation and inflammation associated with an increased incidence of non-AIDS-defining illnesses and accelerated aging. Even antiretroviral therapy can contribute to accelerated aging and to the occurrence of adverse effects, despite the undeniable benefits that it is able to give. The introduction of regular physical exercise in HIV treatment may have a significant therapeutic effect: it could reduce the impact of immune activation and non-AIDS-defining illness linked to chronic inflammation. Moreover, physical activity could generate improvements in neuropsychological function and metabolic assessment.

administration of creatine may have a beneficial aesthetic impact but does not improve physical functional capacity.⁶¹

Thoni *et al.* conducted a longitudinal study on 19 HIV-infected individuals (17 lipodystrophic and 2 dyslipidemic) to evaluate the effect of a 4-month training protocol on body composition measured by CT scan as total abdominal adipose tissue (TAT), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT). In addition, blood was collected to measure IR-HOMA, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), lactate, and pyruvate. A significant reduction of VAT leading to a reduction in total abdominal fat was observed. In addition, a positive effect of aerobic training was observed on TC, HDL-C, TG, and TG/HDL-C; in addition, cardiovascular risk at 10 years decreased from 1.12 to 0.97 throughout the study period. Based on these results, it appears that light aerobic training may have a beneficial impact on lipid disorders and central adipose accumulation in HIV-infected individuals.⁶²

The pleasure associated with physical exercises relates primarily to three main factors: the production of endorphins, the production of catecholamines, and changes in brain function. Endorphins are proteins whose effects are very similar to the opiate morphine and act through binding to specific receptors in the brain, resulting in feelings of pleasure and greater pain tolerance. The main catecholamines are epinephrine and noradrenaline. These hormones increase cardiac output, increase the release of glucose into the circulation by adipocytes and liver, and, along with endorphins, reduce anxiety and psychological stress. Indeed, physical activity is associated with alpha waves, which dominate the awake status or the time before falling asleep. The possibility of increasing these three factors by physical exercise during a lifelong drug treatment may be very important in the setting of HIV infection. In addition, physical exercise may be useful in delaying the age-related involution of the hippocampus, thus improving memory function as observed in studies conducted on the general population.

Erikson *et al.* conducted a randomized study in 100 subjects without dementia who were assigned to an aerobic exercise group and to a stretching control group. They found that the exercise intervention was effective in increasing the anterior size of the hippocampus, which contains neurons associated with spatial memory acquisition. Based on these findings, it is clear that aerobic exercise plays a neuroprotective role that can be useful both in young subjects and later in life to enhance cognition and augment brain volume.⁶³

Based on these findings, we believe that the introduction of regular physical exercise in the clinical management of HIV infection may have a significant therapeutic impact in reducing the deleterious effects of both the infection and ART (Fig. 1). Increased physical activity may result in (1) a possible decrease in immune activation with a concomitant reduction in the damage related to CVD and other non-AIDS-defining illnesses that are linked to chronic inflammation, and (2) an improvement in overall neuropsychological and metabolic function.⁶⁴⁻⁷⁰ In terms of clinical practice, it could be useful to create a network of practitioners that includes physical trainers and nutritionists to determine the appropriate level of exercises and the adequate diet for each individual patient. As these factors can have a positive impact on the patients' quality of life while also reducing the health care costs related to HIV infection, we believe that further

longitudinal studies are warranted to better assess the effects of physical exercise on disease progression, immune activation, and the size of the virus reservoir.

Acknowledgments

This work was supported by grants 40H6 and 40H8 from the Italian National Institute of Health (Istituto Superiore di Sanità-ISS).

Author Disclosure Statement

No competing financial interests exist.

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