UNIVERSITÀ DEGLI STUDI DI MILANO

Scuola di Dottorato in Scienze Morfologiche,
Fisiologiche e dello Sport
Dipartimento di Scienze Biomediche per la Salute

Dottorato di Ricerca in Scienze dello Sport
Settore scientifico/disciplinare: MDF/02
Ciclo XXVII

Tesi di Dottorato di Ricerca

A pilot study of brisk walking in sedentary cART-treated patients

Matteo Bonato
Matr. n. R09691

Tutor: Prof. Giampiero Merati
Coordinatore: Prof. Livio Luzi

Anno Accademico 2013-2014

Abstract

Antiretroviral treatments (ART) have dramatically reduced HIV infection mortality, transforming HIV infection into a chronic disease requiring life-long treatment. Sadly, treatment is associated with a number of metabolic, cardiovascular, osteoarticular, renal and central nervous system toxicities. Moreover, Chronic HIV infection is associated with low-level inflammation and increased risk of chronic diseases and mortality. As a result, long-term treated patients may present with increased risk of cardiovascular and cerebrovascular disease, lypodystrophy, early diabetes, kidney failure, osteoporosis and cognitive impairment. These toxicities imitate age-associated comorbidities. Indeed, long-term HIV infection and ART use appear to predispose patients to premature aging and accelerate the risk of these comorbidities.

In the general population the risk of cardiovascular and metabolic conditions can be reduced by lifestyle interventions, such as dietary adjustments, exercise, smoking cessation, and by pharmacological approaches. Similar general and pharmacological measures are also indicated in HIV persons and anti-hypertensive and lipid-lowering drugs are frequently used in association with ART.

Among lifestyle measures, exercise, involving both aerobic and strength training, is associated with reduction of cardiovascular events in the normal population. In older persons regular physical activity has been shown to lower overall mortality, risk of coronary heart disease, colon cancer, diabetes, obesity and of developing high blood pressure; to improve mood and relief of symptoms of depression, quality of life and functioning. In addition to prevent these morbidities, physical activity is also effective in treating cardiovascular disease, high blood pressure, high cholesterol, chronic lung disease, diabetes, obesity, and osteoarthritis.

There is evidence that exercise is also useful in people with HIV infection. Although

studies have differed for design (controlled vs. single arm), sample size (up to 20 subjects per group), type of activity (aerobic vs. strength vs. both), training frequency (2-3 session a week), duration (weeks-few months), most have shown, with aerobic exercise, a reduction of abdominal and total body fat, total cholesterol, triglycerides, BMI, hip circumference, and increases in HDL. In contrast, strength exercise, either alone, or in association with aerobic exercise, seems to be associated with increased fat free mass and of muscle strength.

The general objective was to study the effects at 12 weeks of supervised moderate aerobic exercise (walking) with/without strength training in patients with HIV infection on chronic ART. Ultimately, we aim to validate an exercise approach to propose for prevention and treatment of ART-

For this reason a pilot study enrolling cART-treated, sedentary persons with metabolic complications in a 12-week protocol, consisting of three sessions per week of 60 min brisk walking with (strength walk group) or without (walk group) 30 min circuit-training, was proposes.

Assessments at baseline and week 12 (W12) included body morphometrics and total body dual-energy X-ray absorptiometry; lipid and glucose blood profile; plasma level of high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), D-dimer, interleukin-18 (IL-18), soluble CD14 and myostatin, and CD38 and HLA-DR expression on CD4+ and CD8+ T-cells were done.

Forty-nine patients were enrolled and 35 (71%) completed the program: 21 in the walk and 14 in the strength-walk group. Median adherence to the training sessions was 67%. At W12, significant improvements were observed of body mass index, waist and hip

circumference, and total and LDL cholesterol, with no change differences between training groups. Overall, significant reductions were observed in hsCRP, IL-6, D-dimer, IL-18 and myostatin level, and of CD8+/CD38+/HLA-DR+ cell frequencies. HsCRP and CD8+/CD38+/HLA-DR+ frequency decreased significantly in both training groups; IL-6 and D-dimer in the walk group only and myostatin in the strength-walk group only.

Brisk walking, with or without strength exercise, can improve lipid profile and inflammatory markers in chronic HIV infection.

Keywords. Immune activation, inflammatory markers, exercise, physical activity, cART, cholesterol

Contents

PART TWO
Review of the exercise interventions in people living with HIV infection

PART THREE
A pilot study of brisk walking in sedentary cART-treated patients

REFERENCES

APPENDIX

PART ONE
General Introduction

Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) is a lentivirus (a subgroup of retrovirus) that causes the acquired immunodeficiency syndrome (AIDS), a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells.

HIV infects vital cells in the human immune system such as helper T cells (specifically CD4+ T cells), macrophages, and dendritic cells.

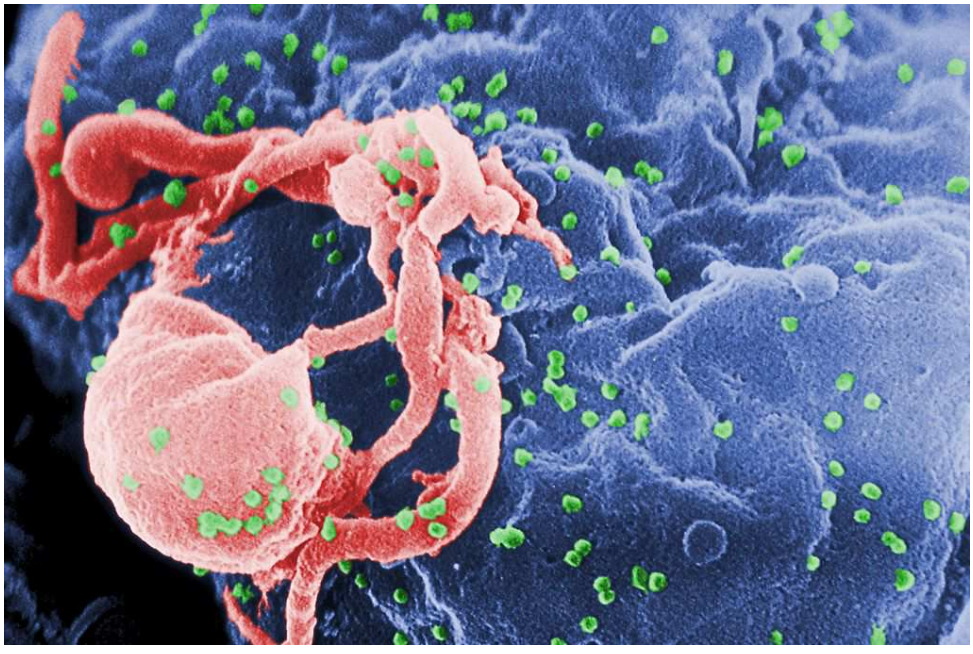

Figure 1. Scanning electron micrograph of HIV-1 budding, in green, from cultured lymphocyte (Centres for Disease Control and Prevention's Public Health, modified)

HIV infection leads to low levels of CD4+ T cells through a number of mechanisms, including apoptosis of uninfected bystander cells, direct viral killing of infected cells, and killing of infected CD4+ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections.

Virology

HIV is the cause of the spectrum of disease known as HIV/AIDS. HIV is a retrovirus that primarily infects components of the human immune system such as CD4+ T cells, macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells.

HIV is a member of the genus Lentivirus, part of the family Retroviridae. Lentiviruses share many morphological and biological characteristics. Many species of mammals are infected by lentiviruses, which are characteristically responsible for long-duration illnesses with a long incubation period. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors. Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system. Alternatively, the virus may be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew.

Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was originally discovered (and initially referred to also as LAV or HTLV-III). It is more virulent, more infective, and is the cause of the majority of HIV infections globally. The lower

infectivity of HIV-2 as compared with HIV-1 implies that fewer people exposed to HIV-2 will be infected per exposure. Because of its relatively poor capacity for transmission, HIV-2 is largely confined to West Africa.

Pathophysiology

After the virus enters the body there is a period of rapid viral replication, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million-virus particles per millilitre of blood.

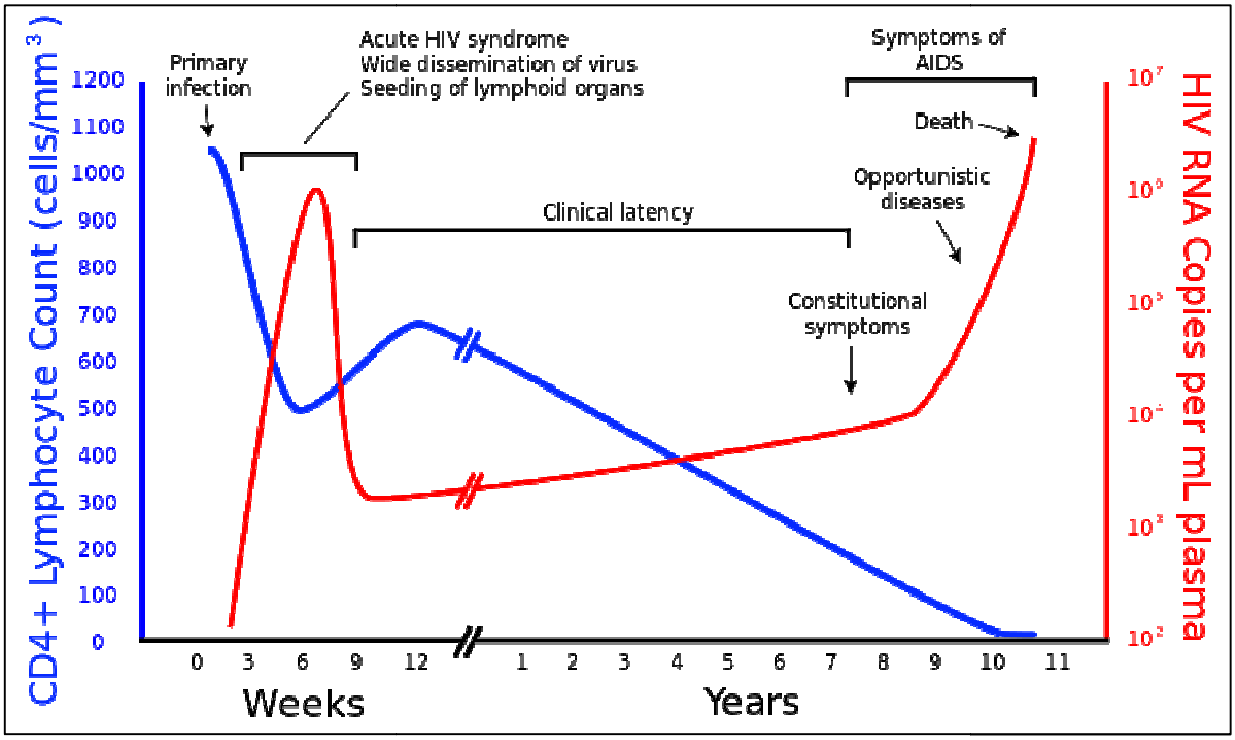

Figure 2. A generalized graph of the relationship between HIV copies, viral load, and $CD4^+$ counts over the average course of untreated HIV infection.

CD4+ T cell count (cells per µL)

HIV RNA copies per mL of plasma

This response is accompanied by a marked drop in the numbers of circulating CD4+ T cells. This acute viremia is associated in virtually all people with the activation of CD8+ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The CD8+ T cell response is thought to be important in controlling virus

levels, which peak and then decline, as the CD4+ T cell counts rebound. A good CD8+ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.

The pathophysiology of AIDS is complex. Ultimately, HIV causes AIDS by depleting CD4+ T helper lymphocytes. This weakens the immune system and allows opportunistic infections. T lymphocytes are essential to the immune response and without them; the body cannot fight infections or kill cancerous cells. The mechanism of CD4+T cell depletion differs in the acute and chronic phases.

During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for CD4+ T cell depletion, although apoptosis may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in CD4+ T cell numbers.

Although the symptoms of immune deficiency characteristic of AIDS do not appear for years after a person is infected, the bulk of CD4+ T cell loss occurs during the first weeks of infection, especially in the intestinal mucosa, which harbours the majority of the lymphocytes found in the body. The reason for the preferential loss of mucosal CD4+ T cells is that a majority of mucosal CD4+ T cells express the CCR5 co-receptor, whereas a small fraction of CD4+ T cells in the bloodstream do so.

HIV seeks out and destroys CCR5 expressing CD4+ cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase. However, CD4+ T cells in mucosal tissues remain depleted throughout the infection, although enough remain to initially ward off life-threatening infections.

Continuous HIV replication results in a state of generalized immune activation persisting throughout the chronic phase. Immune activation, which is reflected by the increased activation state of immune cells and release of pro-inflammatory cytokines, results from

the activity of several HIV gene products and the immune response to ongoing HIV replication. Another cause is the breakdown of the immune surveillance system of the mucosal barrier caused by the depletion of mucosal CD4+ T cells during the acute phase of disease.

This results in the systemic exposure of the immune system to microbial components of the gut's normal flora, which in a healthy person is kept in check by the mucosal immune system. The activation and proliferation of T cells that results from immune activation provides fresh targets for HIV infection. However, direct killing by HIV alone cannot account for the observed depletion of CD4+ T cells since only 0.01–0.10% of CD4+ T cells in the blood are infected.

A major cause of CD4+ T cell loss appears to result from their heightened susceptibility to apoptosis when the immune system remains activated. Although new T cells are continuously produced by the thymus to replace the ones lost, the regenerative capacity of the thymus is slowly destroyed by direct infection of its thymocytes by HIV. Eventually, the minimal number of CD4+ T cells necessary to maintain a sufficient immune response is lost, leading to AIDS.

Sings and symptoms

Acute infection

Acute HIV infection, primary HIV infection or acute sero-conversion syndrome is the second stage of HIV infection. It occurs after the incubation stage, before the latency stage and the potential AIDS succeeding the latency stage.

During this period (usually days to weeks post-exposure) many individuals develop an influenza or mononucleosis-like illness called acute HIV infection, the most common symptoms of which may include fever, lymphadenopathy, pharyngitis, rash, myalgia, malaise, mouth and oesophageal sores, and may also include, but less commonly,

headache, nausea and vomiting, enlarged liver/spleen, weight loss, thrush, and neurological symptoms. Infected individuals may experience all, some, or none of these symptoms. The duration of symptoms varies, averaging 28 days and usually lasts at least a week.

Because of the nonspecific nature of these symptoms, they are often not recognized as signs of HIV infection. Even if patients go to their doctors or a hospital, they will often be misdiagnosed as having one of the more common infectious diseases with the same symptoms. As a consequence, these primary symptoms are not used to diagnose HIV infection, as they do not develop in all cases and because other more common diseases cause many. However, recognizing the syndrome can be important because the patient is much more infectious during this period.

Latency

A strong immune defence reduces the number of viral particles in the blood stream, marking the start of secondary or chronic HIV infection. The secondary stage of HIV infection can vary between two weeks and 20 years. During this phase of infection, HIV is active within lymph nodes, which typically become persistently swollen, in response to large amounts of virus that become trapped in the follicular dendritic cells (FDC) network. The surrounding tissues that are rich in CD4+ T cells may also become infected, and viral particles accumulate both in infected cells and as free virus. Individuals who are in this phase are still infectious. During this time, CD4+ CD45RO+ T cells carry most of the proviral load. A small percentage of HIV-1 infected individuals retain high levels of CD4+ T-cells without antiretroviral therapy. However, most have detectable viral load and will eventually progress to AIDS without treatment. These individuals are classified as HIV controllers or long-term nonprogressors (LTNP). People who maintain CD4+ T cell counts

and also have low or clinically undetectable viral load without anti-retroviral treatment are known as elite controllers or elite suppressors (ES).

AIDS

The symptoms of AIDS are primarily the result of conditions that do not normally develop in individuals with healthy immune systems. Most of these conditions are opportunistic infections caused by bacteria, viruses, fungi and parasites that are normally controlled by the elements of the immune system that HIV damages. These infections affect nearly every organ system.

People with AIDS also have an increased risk of developing various cancers such as Kaposi's sarcoma, cervical cancer and cancers of the immune system known as lymphomas. Additionally, people with AIDS often have systemic symptoms of infection like fevers, sweats (particularly at night), swollen glands, chills, weakness, and weight loss. The specific opportunistic infections that AIDS patients develop depend in part on the prevalence of these infections in the geographic area in which the patient lives.

History of HIV/AIDS

AIDS was first clinically observed in 1981 in the United States. The initial cases were a cluster of injecting drug users and homosexual men with no known cause of impaired immunity who showed symptoms of Pneumocystis carinii pneumonia (PCP), a rare opportunistic infection that was known to occur in people with very compromised immune systems. Soon thereafter, an unexpected number of homosexual men developed a previously rare skin cancer called Kaposi's sarcoma (KS). Many more cases of PCP and KS emerged, alerting U.S. Centers for Disease Control and Prevention (CDC) and a CDC task force was formed to monitor the outbreak.

In the early days, the CDC did not have an official name for the disease, often referring to it by way of the diseases that were associated with it, for example, lymphadenopathy, the disease after which the discoverers of HIV originally named the virus. They also used Kaposi's sarcoma and Opportunistic Infections, the name by which a task force had been set up in 1981. At one point, the CDC coined the phrase "the 4H disease", since the syndrome seemed to affect Haitians, homosexuals, haemophiliacs, and heroin users. In the general press, the term "GRID", which stood for gay-related immune deficiency, had been coined. However, after determining that AIDS was not isolated to the gay community, it was realized that the term GRID was misleading and the term AIDS was introduced at a meeting in July 1982. By September 1982 the CDC started referring to the disease as AIDS.

In 1983, two separate research groups led by Robert Gallo and Luc Montagnier independently declared that a novel retrovirus may have been infecting people with AIDS, and published their findings in the same issue of the journal Science. Gallo claimed that a virus his group had isolated from a person with AIDS was strikingly similar in shape to other human T-lymphotropic viruses (HTLVs) his group had been the first to isolate. Gallo's group called their newly isolated virus HTLV-III. At the same time, Montagnier's group isolated a virus from a person presenting with swelling of the lymph nodes of the neck and physical weakness, two characteristic symptoms of AIDS. Contradicting the report from Gallo's group, Montagnier and his colleagues showed that core proteins of this virus were immunologically different from those of HTLV-I. Montagnier's group named their isolated virus lymphadenopathy-associated virus (LAV). As these two viruses turned out to be the same, in 1986, LAV and HTLV-III were renamed HIV.

Origin of HIV

Both HIV-1 and HIV-2 are believed to have originated in non-human primates in West-central Africa and were transferred to humans in the early 20th century. HIV-1 appears to have originated in southern Cameroon through the evolution of SIV (cpz), a simian immunodeficiency virus (SIV) that infects wild chimpanzees (HIV-1 descends from the SIVcpz endemic in the chimpanzee subspecies Pan troglodytes troglodytes).

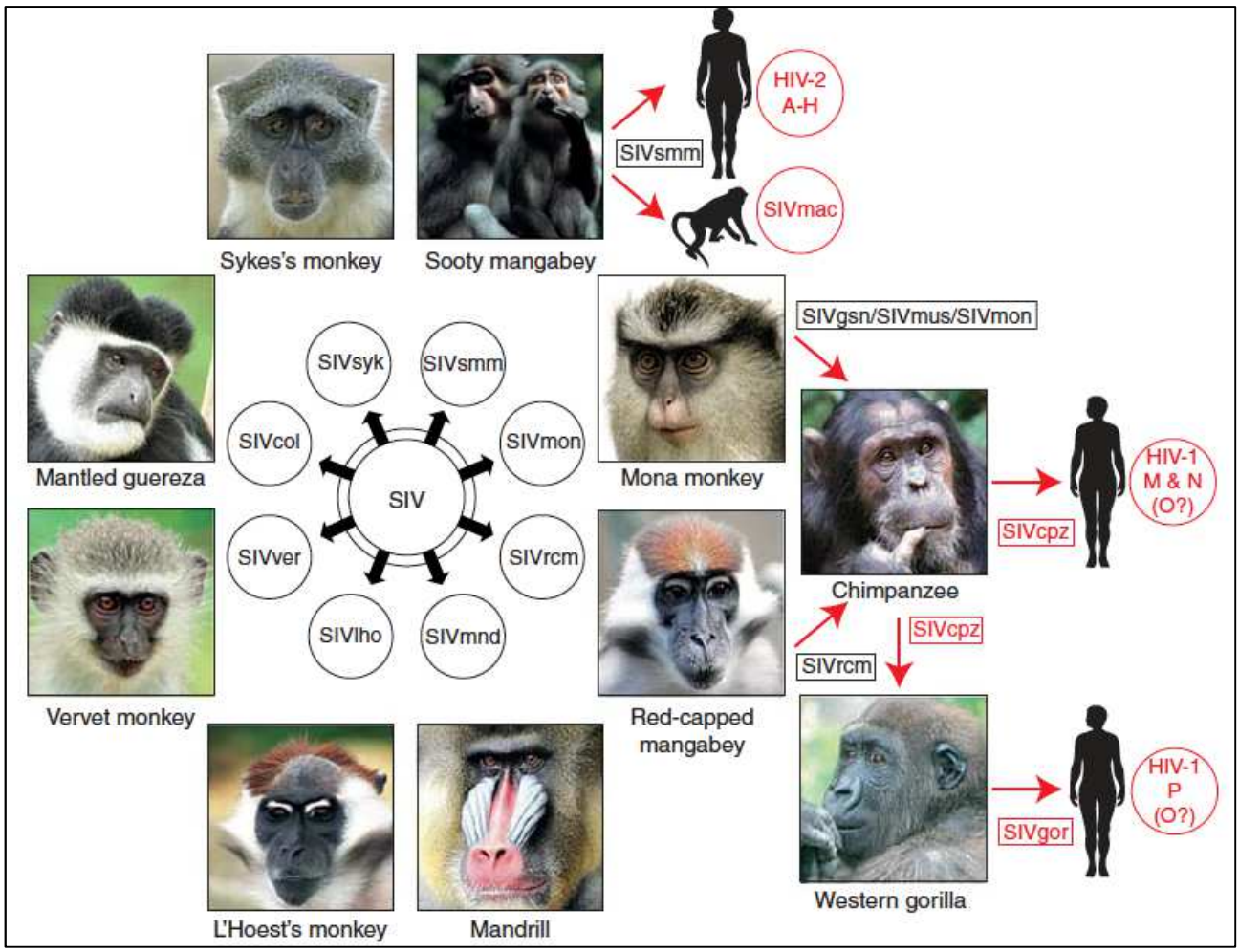

Figure 3. Origins of human AIDS viruses, old world monkeys are naturally infected with more than 40 different lentiviruses, termed simian immunodeficiency viruses, SIVs, with a suffix to denote their primate species of origin. Several of these SIVs have crossed the species barrier to great apes and humans, generating new pathogens. Known examples of cross-species transmissions, as well as the resulting viruses, are highlighted in red.
(From Sharp & Hahn, 2011, modified)

The closest relative of HIV-2 is SIV (smm), a virus of the sooty mangabey (Cercocebus atys atys), an Old World monkey living in coastal West Africa (from southern Senegal to

western Côte d'Ivoire). New World monkeys such as the owl monkey are resistant to HIV-1 infection, possibly because of a genomic fusion of two viral resistance genes. HIV-1 is thought to have jumped the species barrier on at least three separate occasions, giving rise to the three groups of the virus, M, N, and O.There is evidence that humans who participate in bushmeat activities, either as hunters or as bushmeat vendors, commonly acquire SIV. However, SIV is a weak virus which is typically suppressed by the human immune system within weeks of infection. It is thought that several transmissions of the virus from individual to individual in quick succession are necessary to allow it enough time to mutate into HIV. Furthermore, due to its relatively low person-to-person transmission rate, SIV can only spread throughout the population in the presence of one or more high-risk transmission channels, which are thought to have been absent in Africa before the 20th century.

Specific proposed high-risk transmission channels, allowing the virus to adapt to humans and spread throughout the society, depend on the proposed timing of the animal-to-human crossing. Genetic studies of the virus suggest that the most recent common ancestor of the HIV-1 M group dates back to circa 1910. Proponents of this dating link the HIV epidemic with the emergence of colonialism and growth of large colonial African cities, leading to social changes, including a higher degree of sexual promiscuity, the spread of prostitution, and the accompanying high frequency of genital ulcer diseases (such as syphilis) in nascent colonial cities. While transmission rates of HIV during vaginal intercourse are low under regular circumstances, they are increased many fold if one of the partners suffers from a sexually transmitted infection causing genital ulcers. Early 1900s colonial cities were notable due to their high prevalence of prostitution and genital ulcers, to the degree that, as of 1928, as many as 45% of female residents of eastern Kinshasa were thought to have been prostitutes, and, as of 1933, around 15% of all residents of the same city had syphilis.

An alternative view holds that unsafe medical practices in Africa after World War II, such as unsterile reuse of single use syringes during mass vaccination, antibiotic and anti-malaria treatment campaigns, were the initial vector that allowed the virus to adapt to humans and spread.

The earliest well documented case of HIV in a human date back to 1959 in the Congo. The virus may have been present in the United States as early as 1966, but the vast majority of infections occurring outside sub-Saharan Africa (including the U.S.) can be traced back to a single unknown individual who became infected with HIV in Haiti and then brought the infection to the United States some time around 1969. The epidemic then rapidly spread among high-risk groups (initially, sexually promiscuous men who have sex with men). By 1978, the prevalence of HIV-1 among homosexual male residents of New York and San Francisco was estimated at 5%, suggesting that several thousand individuals in the country had been infected.

Transmission

Only certain fluids—blood, semen (cum), pre-seminal fluid (pre-cum), rectal fluids, vaginal fluids, and breast milk—from an HIV-infected person can transmit HIV. These fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the bloodstream (from a needle or syringe) for transmission to possibly occur. Mucous membranes can be found inside the rectum, the vagina, the opening of the penis, and the mouth.

HIV does not survive long outside the human body (such as on surfaces), and it cannot reproduce. It is not spread by: air or water, insects, including mosquitoes or ticks, saliva, tears, or sweat.

There are cases where HIV was transmitted orally, so it's not completely without risk to have HIV-infected semen, vaginal fluid or blood in mouth. However, oral sex is considered

a low risk practice. The virus can't survive well in the mouth (in semen, vaginal fluid or blood), so the risk of HIV transmission through the throat, gums, and oral membranes is lower than through vaginal or anal membranes.

There is no documented case of HIV being transmitted by spitting, casual contact like shaking hands or sharing dishes, closed-mouth or “social” kissing, toilet seats.

Having an undetectable viral load greatly lowers the chance that a person living with HIV can transmit the virus to a partner, but there is still some risk. “Viral load” refers to the amount of HIV in an infected person’s blood. An “undetectable viral load” is when the amount of HIV in a person’s blood is so low that it can’t be measured. Antiretroviral therapy (ART) reduces a person’s viral load, ideally to an undetectable level, when taken consistently and correctly. However, a person with HIV can still potentially transmit HIV to a partner even if they have an undetectable viral load, because:

HIV may still be found in a person’s genital fluids (e.g., semen, vaginal fluids). The viral load test only measures virus in a person’s blood.

A person’s viral load may go up between tests. When this happens, they may be more likely to transmit HIV to partners.

Sexually transmitted diseases (STDs) increase viral load in a person’s genital fluids.

Sexual intercourse

Anal and vaginal intercourses are high-risk activities. In the penis, vagina and anus, HIV may enter through cuts and sores (many of which would be very small and hard to notice), or directly through the mucus membranes.

Sharing injection needles or works

Sharing needles or other materials used for injecting are considered a high-risk practice. Injection needles can pass blood directly from one person to another if you share them. If

a person with HIV injects with a needle then shares it with another person, the second person is at very high risk for getting HIV.

Mother-to-child

Mother to child transmission is now rare in the US and other developed countries because pregnant women who are HIV-positive are normally given medications to prevent the fetus from getting infected. However, it is possible for an HIV-infected mother to pass the virus directly before or during birth, or through breast milk. Breast milk contains HIV, and while small amounts of breast milk do not pose significant threat of infection to adults, it is a risk for infants.

Prevention

Sexual contact

Consistent condom use reduces the risk of HIV transmission by approximately 80% over the long term. When a couple in which one person is infected uses condoms consistently, the rate of HIV infection is less than 1% per year. There is some evidence to suggest that female condoms may provide an equivalent level of protection. Application of a vaginal gel containing tenofovir (a reverse transcriptase inhibitor) immediately before sex seems to reduce infection rates by approximately 40% among African women. By contrast, use of the spermicide nonoxynol-9 may increase the risk of transmission due to its tendency to cause vaginal and rectal irritation. Circumcision in Sub-Saharan Africa "reduces the acquisition of HIV by heterosexual men by between 38% and 66% over 24 months". Based on these studies, the World Health Organization and UNAIDS both recommended male circumcision as a method of preventing female-to-male HIV transmission in 2007. Whether it protects against male-to-female transmission is disputed and whether it is of benefit in developed countries and among men who have sex with men is undetermined.

The International Antiviral Society; however, does recommend for all sexually active heterosexual males and that it be discussed as an option with men who have sex with men. Some experts fear that a lower perception of vulnerability among circumcised men may cause more sexual risk-taking behaviour, thus negating its preventive effects. Programs encouraging sexual abstinence do not appear to affect subsequent HIV risk. Evidence for a benefit from peer education is equally poor. Comprehensive sexual education provided at school may decrease high-risk behaviour. A substantial minority of young people continues to engage in high-risk practices despite knowing about HIV/AIDS, underestimating their own risk of becoming infected with HIV. Voluntary counselling and testing people for HIV does not affect risky behaviour in those who test negative but does increase condom use in those who test positive. It is not known whether treating other sexually transmitted infections is effective in preventing HIV.

Pre-exposure

Treating people with HIV whose CD4 count ≥ 350cells/μL with antiretrovirals protects 96% of their partners from infection. This is about a 10 to 20-fold reduction in transmission risk. Pre-exposure prophylaxis (PrEP) with a daily dose of the medications tenofovir, with or without emtricitabine, is effective in a number of groups including men who have sex with men, couples where one is HIV positive, and young heterosexuals in Africa. It may also be effective in intravenous drug users with a study finding a decrease in risk of 0.7 to 0.4 per 100 person years. Universal precautions within the health care environment are believed to be effective in decreasing the risk of HIV. Intravenous drug use is an important risk factor and harm reduction strategies such as needle-exchange programmes and opioid substitution therapy appear effective in decreasing this risk.

Post-exposure

A course of antiretrovirals administered within 48 to 72 hours after exposure to HIV-positive blood or genital secretions is referred to as post-exposure prophylaxis (PEP). The use of the single agent zidovudine reduces the risk of a HIV infection five-fold following a needle-stick injury. As of 2013, the prevention regimen recommended in the United States consists of three medications—tenofovir, emtricitabine and raltegravir—as this may reduce the risk further. PEP treatment is recommended after a sexual assault when the perpetrator is known to be HIV positive, but is controversial when their HIV status is unknown. The duration of treatment is usually four weeks and is frequently associated with adverse effects-where zidovudine is used, about 70% of cases result in adverse effects such as nausea (24%), fatigue (22%), emotional distress (13%) and headaches (9%).

Mother-to-child

Programs to prevent the vertical transmission of HIV (from mothers to children) can reduce rates of transmission by 92–99%. This primarily involves the use of a combination of antiviral medications during pregnancy and after birth in the infant and potentially includes bottle feeding rather than breastfeeding. If replacement feeding is acceptable, feasible, affordable, sustainable, and safe, mothers should avoid breastfeeding their infants; however exclusive breastfeeding is recommended during the first months of life if this is not the case. If exclusive breastfeeding is carried out, the prevision of extended antiretroviral prophylaxis to the infant decreases the risk of transmission.

Vaccination

As of 2012 there is no effective vaccine for HIV or AIDS. A single trial of the vaccine RV 144 published in 2009 found a partial reduction in the risk of transmission of roughly 30%,

stimulating some hope in the research community of developing a truly effective vaccine. Further trials of the RV 144 vaccine are ongoing.

Diagnosis

HIV tests are used to detect the presence of the human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), in serum, saliva, or urine. Such tests may detect antibodies, antigens, or RNA.

Tests used for the diagnosis of HIV infection in a particular person require a high degree of both sensitivity and specificity. In the United States, this is achieved using an algorithm combining two tests for HIV antibodies. If antibodies are detected by an initial test based on the ELISA method, then a second test using the Western blot procedure determines the size of the antigens in the test kit binding to the antibodies. The combination of these two methods is highly accurate (see below).

HIV antibody tests are specifically designed for routine diagnostic testing of adults; these tests are inexpensive and extremely accurate.

Window period

Antibody tests may give false negative (no antibodies were detected despite the presence of HIV) results during the window period, an interval of three weeks to six months between the time of HIV infection and the production of measurable antibodies to HIV seroconversion. Most people develop detectable antibodies approximately 30 days after infection, although some seroconvert later. The vast majority of people (97%) have detectable antibodies by three months after HIV infection; a six-month window is extremely rare with modern antibody testing. During the window period, an infected person can transmit HIV to others although their HIV infection may not be detectable with an antibody test. Antiretroviral therapy during the window period can delay the formation of antibodies

and extend the window period beyond 12 months. This was not the case with patients that underwent treatment with post-exposure prophylaxis (PEP). Those patients must take ELISA tests at various intervals after the usual 28-day course of treatment, sometimes extending outside of the conservative window period of 6 months. Antibody tests may also yield false negative results in patients with X-linked agammaglobulinemia; other diagnostic tests should be used in such patients.

Three instances of delayed HIV seroconversion occurring in health-care workers have been reported, in these instances, the health-care workers[16] tested negative for HIV antibodies greater than 6 months postexposure but were seropositive within 12 months after the exposure. DNA sequencing confirmed the source of infection in one instance. Two of the delayed seroconversions were associated with simultaneous exposure to hepatitis C virus (HCV). In one case, co-infection was associated with a rapidly fatal HCV disease course; however, it is not known whether HCV directly influences the risk for or course of HIV infection or is a marker for other exposure-related factors.

ELISA

The enzyme-linked immunosorbent assay (ELISA), or enzyme immunoassay (EIA), was the first screening test commonly employed for HIV. It has a high sensitivity.

In an ELISA test, a person's serum is diluted 400-fold and applied to a plate to which HIV antigens have been attached. If antibodies to HIV are present in the serum, they may bind to these HIV antigens. The plate is then washed to remove all other components of the serum. A specially prepared "secondary antibody" — an antibody that binds to human antibodies — is then applied to the plate, followed by another wash. This secondary antibody is chemically linked in advance to an enzyme. Thus the plate will contain enzyme in proportion to the amount of secondary antibody bound to the plate. A substrate for the enzyme is applied, and catalysis by the enzyme leads to a change in colour or

fluorescence. ELISA results are reported as a number; the most controversial aspect of this test is determining the "cut-off" point between a positive and negative result.

Western blot

Like the ELISA procedure, the western blot is an antibody detection test. However, unlike the ELISA method, the viral proteins are separated first and immobilized. In subsequent steps, the binding of serum antibodies to specific HIV proteins is visualized.

Specifically, cells that may be HIV-infected are opened and the proteins within are placed into a slab of gel, to which an electrical current is applied. Different proteins will move with different speeds in this field, depending on their size, while their electrical charge is levelled by a surfactant called sodium lauryl sulphate. Some commercially prepared Western blot test kits contain the HIV proteins already on a cellulose acetate strip. Once the proteins are well separated, they are transferred to a membrane and the procedure continues similar to an ELISA: the person's diluted serum is applied to the membrane and antibodies in the serum may attach to some of the HIV proteins. Antibodies that do not attach are washed away, and enzyme-linked antibodies with the capability to attach to the person's antibodies determine to which HIV proteins the person has antibodies.

There are no universal criteria for interpreting the western blot test: The number of viral bands that must be present may vary. If no viral bands are detected, the result is negative. If at least one viral band for each of the GAG, POL, and ENV gene-product groups are present, the result is positive. The three-gene-product approach to western blot interpretation has not been adopted for public health or clinical practice. Tests in which less than the required number of viral bands are detected are reported as indeterminate: a person who has an indeterminate result should be retested, as later tests may be more conclusive. Almost all HIV-infected persons with indeterminate western blot results will develop a positive result when tested in one month; persistently indeterminate results over

a period of six months suggests the results are not due to HIV infection. In a generally healthy low-risk population, indeterminate results on western blot occur on the order of 1 in 5,000 patients. However for those individuals that have had high-risk exposures to individuals where HIV-2 is most prevalent, Western Africa, an inconclusive western blot test may prove infection with HIV-2.

The HIV proteins used in western blotting can be produced by recombinant DNA in a technique called recombinant immunoblot assay (RIBA).

Rapid or point-of-care tests

Rapid antibody tests are qualitative immunoassays intended for use in point-of-care testing to aid in the diagnosis of HIV infection. These tests should be used in conjunction with the clinical status, history, and risk factors of the person being tested. The positive predictive value of Rapid Antibody Tests in low-risk populations has not been evaluated. These tests should be used in appropriate multi-test algorithms designed for statistical validation of rapid HIV test results.

If no antibodies to HIV are detected, this does not mean the person has not been infected with HIV. It may take several months after HIV infection for the antibody response to reach detectable levels, during which time rapid testing for antibodies to HIV will not be indicative of true infection status. For most people, HIV antibodies reach a detectable level after two to six weeks.

Although these tests have high specificity, false positives do occur. A lab using the western blot should confirm any positive test result.

Interpreting antibody tests

ELISA testing alone cannot be used to diagnose HIV, even if the test suggests a high probability that antibody to HIV-1 is present. In the United States, such ELISA results are not reported as "positive" unless confirmed by a Western Blot.

The ELISA antibody tests were developed to provide a high level of confidence that donated blood was NOT infected with HIV. It is therefore not possible to conclude that blood rejected for transfusion because of a positive ELISA antibody test is in fact infected with HIV. Sometimes, retesting the donor in several months will produce a negative ELISA antibody test. This is why a confirmatory Western Blot is always used before reporting a "positive" HIV test result.

Rare false positive results due to factors unrelated to HIV exposure are found more often with the ELISA test than with the Western Blot. False positives may be associated with medical conditions such as recent acute illnesses and allergies. A rash of false positive tests in the fall of 1991 was initially blamed on the influenza vaccines used during that flu season, but further investigation traced the cross-reactivity to several relatively non-specific test kits. A false positive result does not indicate a condition of significant risk to health. When the ELISA test is combined with Western Blot, the rate of false positives is extremely low, and diagnostic accuracy is very high (see below).

HIV antibody tests are highly sensitive, meaning they react preferentially with HIV antibodies, but not all positive or inconclusive HIV ELISA tests mean HIV infects the person. Risk history, and clinical judgement should be included in the assessment, and a confirmation test (Western blot) should be administered. An individual with an inconclusive test should be re-tested at a later date.

Accuracy of HIV testing

The specificity rate given here for the inexpensive enzyme immunoassay screening tests indicates that, in 1,000 HIV test results of healthy individuals, about 15 of these results will be a false positive. Confirming the test result (i.e., by repeating the test, if this option is available) could reduce the ultimate likelihood of a false positive to about 1 result in 250,000 tests given. The sensitivity rating, likewise, indicates that, in 1,000 test results of HIV infected people, 3 will actually be a false negative result. However, based upon the HIV prevalence rates at most testing centres within the United States, the negative predictive value of these tests is extremely high, meaning that a negative test result will be correct more than 9,997 times in 10,000 (99.97% of the time). The very high negative predictive value of these tests is why the CDC recommends that a negative test result be considered conclusive evidence that an individual does not have HIV.

Of course, the actual numbers vary depending on the testing population. This is because interpreting of the results of any medical test (assuming no test is 100% accurate) depends upon the initial degree of belief, or the prior probability that an individual has, or does not have a disease. Generally the prior probability is estimated using the prevalence of a disease within a population or at a given testing location. The positive predictive value and negative predictive value of all tests, including HIV tests, take into account the prior probability of having a disease along with the accuracy of the testing method to determine a new degree of belief that an individual has or does not have a disease (also known as the posterior probability). The chance that a positive test accurately indicates an HIV infection increases as the prevalence or rate of HIV infection increases in the population. Conversely, the negative predictive value will decrease as the HIV prevalence rises. Thus a positive test in a high-risk population, such as people who frequently engage in unprotected anal intercourse with unknown partners, is more likely to correctly represent

HIV infection than a positive test in a very low-risk population, such as unpaid blood donors.

Many studies have confirmed the accuracy of current methods of HIV testing in the United States, reporting false-positive rates of 0.0004 to 0.0007 and false-negative rates of 0.003 in the general population.

Management of HIV/AIDS

Antiviral therapy

Current HAART options are combinations (or "cocktails") consisting of at least three medications belonging to at least two types, or "classes," of antiretroviral agents. Initially treatment is typically a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside analogue reverse transcriptase inhibitors (NRTIs). Typical NRTIs include: zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC).[124] Combinations of agents which include a protease inhibitors (PI) are used if the above regimen loses effectiveness.

When to start antiretroviral therapy is subject to debate. The World Health Organization recommends antiretrovirals in all adolescents, adults and pregnant women with a CD4 count less than 500/µl with this being especially important in those with counts less than 350/µl or those with symptoms regardless of CD4 count. This is supported by the fact that beginning treatment at this level reduces the risk of death. The United States in addition recommends them for all HIV-infected people regardless of CD4 count or symptoms; however it makes this recommendation with less confidence for those with higher counts. While the WHO also recommends treatment in those who are co-infected with tuberculosis and those with chronic active hepatitis B. Once treatment is begun it is recommended that it is continued without breaks or "holidays". Many people are diagnosed only after treatment ideally should have begun. The desired outcome of treatment is a long term

plasma HIV-RNA count below 50 copies/mL. Levels to determine if treatment is effective are initially recommended after four weeks and once levels fall below 50 copies/mL checks every three to six months are typically adequate. Inadequate control is deemed to be greater than 400 copies/mL. Based on these criteria treatment is effective in more than 95% of people during the first year.

Benefits of treatment include a decreased risk of progression to AIDS and a decreased risk of death. In the developing world treatment also improves physical and mental health. With treatment there is a 70% reduced risk of acquiring tuberculosis. Additional benefits include a decreased risk of transmission of the disease to sexual partners and a decrease in mother-to-child transmission. The effectiveness of treatment depends to a large part on compliance. Reasons for non-adherence include poor access to medical care, inadequate social supports, and mental illness and drug abuse. The complexity of treatment regimens (due to pill numbers and dosing frequency) and adverse effects may reduce adherence. Even though cost is an important issue with some medications, 47% of those who needed them were taking them in low and middle-income countries as of 2010 and the rate of adherence is similar in low-income and high-income countries.

Specific adverse events are related to the antiretroviral agent taken. Some relatively common adverse events include: lipodystrophy syndrome, dyslipidemia, and diabetes mellitus, especially with protease inhibitors. Other common symptoms include diarrhea, and an increased risk of cardiovascular disease. Newer recommended treatments are associated with fewer adverse effects. Certain medications may be associated with birth defects and therefore may be unsuitable for women hoping to have children.

Treatment recommendations for children are somewhat different from those for adults. The World Health Organisation recommends treating all children less than 5 years of age; children above 5 are treated like adults. The United States guidelines recommend treating

all children less than 12 months of age and all those with HIV RNA counts greater than 100,000 copies/mL between one year and five years of age.

Opportunistic infections

Measures to prevent opportunistic infections are effective in many people with HIV/AIDS. In addition to improving current disease, treatment with antiretrovirals reduces the risk of developing additional opportunistic infections. Adults and adolescents who are living with HIV (even on anti-retroviral therapy) with no evidence of active tuberculosis in settings with high tuberculosis burden should receive isoniazid preventive therapy (IPT), the tuberculin skin test can be used to help decide if IPT is needed. Vaccination against hepatitis A and B is advised for all people at risk of HIV before they become infected; however it may also be given after infection. Trimethoprim/sulfamethoxazole prophylaxis between four and six weeks of age and ceasing breastfeeding in infants born to HIV positive mothers is recommended in resource limited settings. It is also recommended to prevent PCP when a person's CD4 count is below 200 cells/uL and in those who have or have previously had PCP. People with substantial immunosuppression are also advised to receive prophylactic therapy for toxoplasmosis and Cryptococcus meningitis. Appropriate preventive measures have reduced the rate of these infections by 50% between 1992 and 1997.

<u>Pulmonary</u>

Pneumocystis pneumonia (PCP) (originally known as Pneumocystis carinii pneumonia) is relatively rare in healthy, immunocompetent people, but common among HIV-infected individuals. It is caused by Pneumocystis jirovecii.

Before the advent of effective diagnosis, treatment and routine prophylaxis in Western countries, it was a common immediate cause of death. In developing countries, it is still

one of the first indications of AIDS in untested individuals, although it does not generally occur unless the CD4 count is less than 200 cells per µL of blood.

Tuberculosis (TB) is unique among infections associated with HIV because it is transmissible to immunocompetent people via the respiratory route, and is not easily treatable once identified. Multidrug resistance is a serious problem. Tuberculosis with HIV co-infection (TB/HIV) is a major world health problem according to the World Health Organization: in 2007, 456,000 deaths among incident TB cases were HIV-positive, a third of all TB deaths and nearly a quarter of the estimated 2 million HIV deaths in that year. Even though its incidence has declined because of the use of directly observed therapy and other improved practices in Western countries, this is not the case in developing countries where HIV is most prevalent. In early-stage HIV infection (CD4 count >300 cells per µL), TB typically presents as a pulmonary disease. In advanced HIV infection, TB often presents atypically with extrapulmonary (systemic) disease a common feature. Symptoms are usually constitutional and are not localized to one particular site, often affecting bone marrow, bone, urinary and gastrointestinal tracts, liver, regional lymph nodes, and the central nervous system.

Gastrointestinal

Esophagitis is an inflammation of the lining of the lower end of the oesophagus (gullet or swallowing tube leading to the stomach). In HIV-infected individuals, this is normally due to fungal (candidiasis) or viral (herpes simplex-1 or cytomegalovirus) infections. In rare cases, it could be due to mycobacteria.

Unexplained chronic diarrhoea in HIV infection is due to many possible causes, including common bacterial (Salmonella, Shigella, Listeria or Campylobacter) and parasitic infections; and uncommon opportunistic infections such as cryptosporidiosis,

microsporidiosis, Mycobacterium avium complex (MAC) and viruses, astrovirus, adenovirus, rotavirus and cytomegalovirus, (the latter as a course of colitis).

In some cases, diarrhoea may be a side effect of several drugs used to treat HIV, or it may simply accompany HIV infection, particularly during primary HIV infection. It may also be a side effect of antibiotics used to treat bacterial causes of diarrhoea (common for Clostridium difficile). In the later stages of HIV infection, diarrhoea is thought to be a reflection of changes in the way the intestinal tract absorbs nutrients, and may be an important component of HIV-related wasting.

Neurological and psychiatric

HIV infection may lead to a variety of neuropsychiatric sequelae, either by infection of the now susceptible nervous system by organisms, or as a direct consequence of the illness itself.

Toxoplasmosis is a disease caused by the single-celled parasite called Toxoplasma gondii; it usually infects the brain, causing toxoplasma encephalitis, but it can also infect and cause disease in the eyes and lungs. Cryptococcal meningitis is an infection of the meninx (the membrane covering the brain and spinal cord) by the fungus Cryptococcus neoformans. It can cause fevers, headache, fatigue, nausea, and vomiting. Patients may also develop seizures and confusion; left untreated, it can be lethal.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease, in which the gradual destruction of the myelin sheath covering the axons of nerve cells impairs the transmission of nerve impulses. It is caused by a virus called JC virus which occurs in 70% of the population in latent form, causing disease only when the immune system has been severely weakened, as is the case for AIDS patients. It progresses rapidly, usually causing death within months of diagnosis.

AIDS dementia complex (ADC) is a metabolic encephalopathy induced by HIV infection and fuelled by immune activation of HIV infected brain macrophages and microglia. These cells are productively infected by HIV and secrete neurotoxins of both host and viral origin. Specific neurological impairments are manifested by cognitive, behavioural, and motor abnormalities that occur after years of HIV infection and are associated with low CD4+ T cell levels and high plasma viral loads.

Prevalence is 10–20% in Western countries but only 1–2% of HIV infections in India. This difference is possibly due to the HIV subtype in India. AIDS related mania is sometimes seen in patients with advanced HIV illness; it presents with more irritability and cognitive impairment and less euphoria than a manic episode associated with true bipolar disorder. Unlike the latter condition, it may have a more chronic course. This syndrome is less frequently seen with the advent of multi-drug therapy.

Tumors

People with HIV infections have substantially increased incidence of several cancers. This is primarily due to co-infection with an oncogenic DNA virus, especially Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpes virus (KSHV) (also known as human herpesvirus-8 [HHV-8]), and human papillomavirus (HPV).

Kaposi's sarcoma (KS) is the most common tumour in HIV-infected patients. The appearance of this tumour in young homosexual men in 1981 was one of the first signals of the AIDS epidemic. Caused by a gamma herpes virus called Kaposi's sarcoma-associated herpes virus (KSHV), it often appears as purplish nodules on the skin, but can affect other organs, especially the mouth, gastrointestinal tract, and lungs. High-grade B cell lymphomas such as Burkitt's lymphoma, Burkitt's-like lymphoma, diffuse large B-cell lymphoma (DLBCL), and primary central nervous system lymphoma present more often in HIV-infected patients. These particular cancers often foreshadow a poor prognosis.

Epstein-Barr virus (EBV) or KSHV cause many of these lymphomas. In HIV-infected patients, lymphoma often arises in extra nodal sites such as the gastrointestinal tract. When they occur in an HIV-infected patient, KS and aggressive B cell lymphomas confer a diagnosis of AIDS.

Invasive cervical cancer in HIV-infected women is also considered AIDS-defining; it is caused by human papillomavirus (HPV).

In addition to the AIDS-defining tumours listed above, HIV-infected patients are at increased risk of certain other tumours, notably Hodgkin's disease, anal and rectal carcinomas, hepatocellular carcinomas, head and neck cancers, and lung cancer. Some of these are causes by viruses, such as Hodgkin's disease (EBV), anal/rectal cancers (HPV), head and neck cancers (HPV), and hepatocellular carcinoma (hepatitis B or C). Other contributing factors include exposure to carcinogens (cigarette smoke for lung cancer), or living for years with subtle immune defects.

Interestingly, the incidence of many common tumours, such as breast cancer or colon cancer, does not increase in HIV-infected patients. In areas where HAART is extensively used to treat AIDS, the incidence of many AIDS-related malignancies has decreased, but at the same time malignant cancers overall have become the most common cause of death of HIV-infected patients.[30] In recent years, an increasing proportion of these deaths have been from non-AIDS-defining cancers.

Other infections

People with AIDS often develop opportunistic infections that present with non-specific symptoms, especially low-grade fevers and weight loss. These include opportunistic infection with Mycobacterium avium-intracellulare and cytomegalovirus (CMV). CMV can cause colitis, as described above, and CMV retinitis can cause blindness.

Penicilliosis due to Penicillium marneffei is now the third most common opportunistic infection (after extra pulmonary tuberculosis and cryptococcosis) in HIV-positive individuals within the endemic area of Southeast Asia.

An infection that often goes unrecognized in people with AIDS is Parvovirus B19. Its main consequence is anaemia, which is difficult to distinguish from the effects of antiretroviral drugs used to treat AIDS itself.

Epidemiology

Globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012. An increase from previous years as more people are receiving the life-saving antiretroviral therapy. There were 2.3 (1.9–2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. At the same time the number of AIDS deaths is also declining with 1.6 (1.4–1.9) million AIDS deaths in 2012, down from 2.3 (2.1–2.6) million in 2005. As this report reveals, striking gains have been made towards many of the 2015 targets and elimination commitments, although significant challenges remain (UNAIDS 2013).

prevalence countries have generally been favourable over the last decade, recent surveys in several countries in sub□Saharan Africa have detected decreases in condom use and/or an increase in the number of sexual partners. Efforts to reduce transmission related to sex work and men who have sex with men remain insufficient, as evidence by recent trends in prevalence among these groups.

However, prospects for strengthening prevention efforts have never been more promising, as a series of highly effective biomedical prevention tools have emerged in recent years to buttress the prevention benefits of behavioural and structural approaches. Momentum accelerated in 2012 towards the scale-up of one such biomedical intervention – voluntary medical male circumcision.

Prevention efforts continue to bear fruit, with the number of new HIV infections among adults in low- and middle-income countries in 2012 being 1.9 million (1.6–2.3), which was 30% lower than in 2001. Declining rates of new HIV infections in 26 low- and middle-income countries are a testament to these efforts. Reductions in new infections among adults since 2001 primarily represent a reduction in sexual transmission, although the declining trend in the global number of new HIV infections among adults needs to be accelerated if the 2015 target is to be reached.

While challenges persist in preventing new infections, opportunities to dramatically lower HIV incidence have never been more promising. In recent years, evidence has emerged that antiretroviral therapies can reduce the risk of HIV transmission by as much as 96%,1 voluntary medical male circumcision by approximately 60%,2,3,4 pre-exposure antiretroviral prophylaxis by more than 40% among men who have sex with men5 and 49% among people who inject drugs.

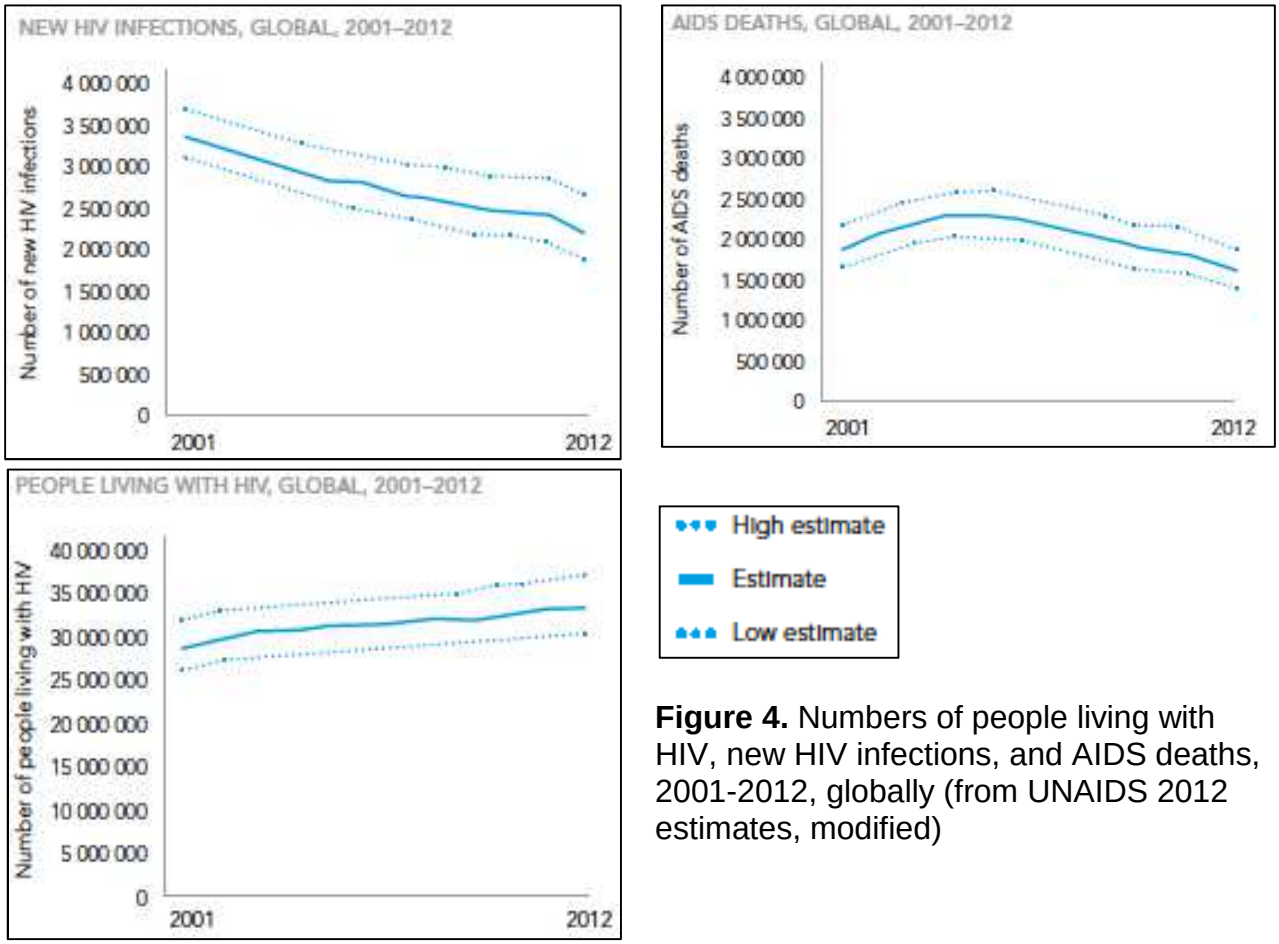

Figure 4. Numbers of people living with HIV, new HIV infections, and AIDS deaths, 2001-2012, globally (from UNAIDS 2012 estimates, modified)

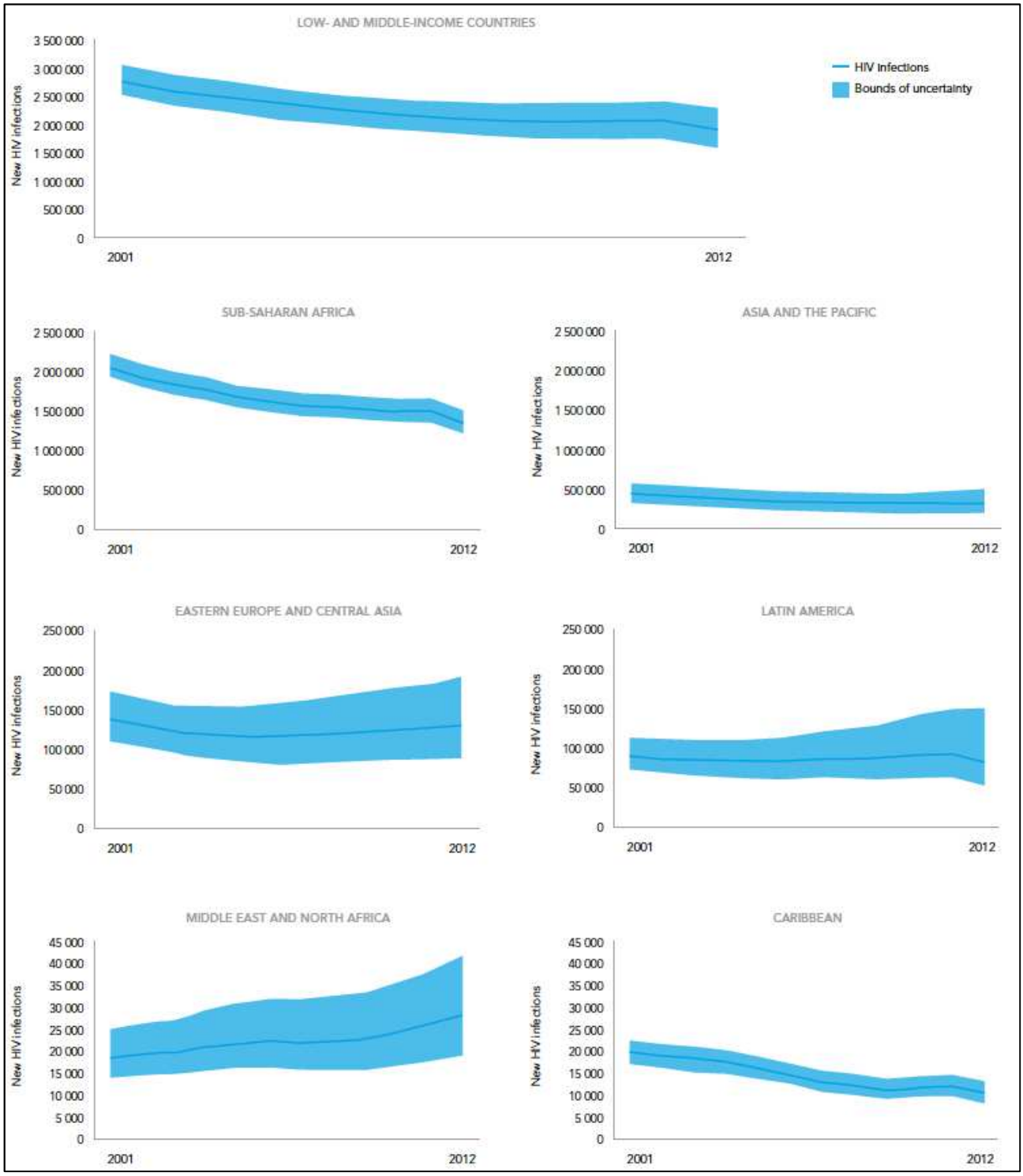

Figure 5. New HIV infections among adults in low- and middle-income countries, by region, 2001–2012 (from UNAIDS 2013 estimates, modified)

PART TWO

Review of exercise interventions in people living with HIV infections

Introduction

The introduction of a combined Antiretroviral Therapy (cART) in 1996 has reduced the morbidity and mortality associated with Human Immunodeficiency Virus (HIV) (Palella et al., 1998; Collaboration ATC, 2008) becoming in this way a chronic disease.

Globally, an estimated 35.3 (32.2–38.8) million people were living with HIV in 2012. There were 2.3 (1.9–2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. At the same time the number of AIDS deaths is also declining with 1.6 (1.4–1.9) million AIDS deaths in 2012, down from 2.3 (2.1–2.6) million in 2005. As of December 2012, an estimated 9.7 million people in low- and middle-income countries were receiving antiretroviral therapy, an increase of 1.6 million over 2011. That brings the world nearly two-thirds of the way towards the 2015 target of 15 million people accessing antiretroviral treatment. Under the 2010, 61% (57–66%) of all persons eligible for HIV treatment in low- and middle-income countries had obtained antiretroviral therapy in 2012. Taking into account the 875.000 people receiving antiretroviral therapy in high-income countries, a total of 10.6 million people were receiving antiretroviral therapy as of December 2012 (WHO, 2013).

Despite these impressive results, several questions still wait for an answer and several issues are still under debate. Furthermore, the emergences of new comorbidities that may be partly associated with cART therapy and partly with HIV itself represent a new problem in medical practice.

Abnormal lipid and glucose metabolism and fat redistribution with central lipohypertrophy and peripheral lipoatrophy, are common among cART-treated patients (Carr et al., 1998; Grinspoon et al., 2005). Moreover, osteoporosis and osteopenia are also increased (Grund et al., 2009).

Medications may ameliorate some cART-related complications, but their use is associated with financial cost and potential toxicities. For these reason, safe, effective and non-pharmacological interventions are needed to prevent and manage the side effect of medications and chronic inflammation seen in HIV-infected patients.

In addition, HIV is now a chronic illness in patients with continued treatment access and excellent long-term adherence. Since cure is not yet possible, treated people have to maintain lifelong adherence and face the risk of delayed drug toxic effects (Palmisano & Vella, 2011).

The aim of this review was to examine the effects of aerobic, resistance and combined exercise training on a variety of outcome markers, including body composition, metabolic profile, inflammatory markers and bone mineralisation in HIV infected people living with cART therapy. Based on literature findings, we suggest general models of intervention as practical guidance for prescribing an effective exercise protocols for this particular population.

Methods

Studies for this review article were identified via a systematic search on the electronic database of PubMed (www.pubmed.gov) including these major keywords: HIV/AIDS, physical activity and exercise training. In addition to computer investigation, we use previous review articles and references from original articles. Studies including aerobic, resistance and combined exercise training in people living with cART therapy published from January 1996 to November 2014 were selected. The following inclusion criteria were

chosen: (1) patients no in cART therapy; (2) other exercise intervention; (3) review articles; (4) studies that gave only psychological outcomes; (5) studies that described only the study design and baseline measurements; (6) case studies. Non-English language publication, unpublished studies, abstracts and conference proceeding were excluded. The studies are presented in chronological order. The main categories of information include: (1) first author and year; (2) number of subject at baseline, sex and presence of control group; (3) the type of exercise, length of training period, duration of session, frequency of session per week, intensity and volume of exercise; (4) number and percentage of drop-out; (5) results of the studies according to outcome measures. The initial search identified 72 citations. Two independent reviewers screening the titles and the abstracts reduced these to 21 studies after elimination of duplicates and application of the inclusion and exclusion criteria. These studies were finally analysed and the findings were divided based on outcome measures including: (1) body composition; (2) metabolic profile; (3) inflammation; (4) bone mineralisation.

Results

The initial search identified 72 citations (Figure 6). Two independent reviewers screening the titles and the abstracts reduced this to 21 studies after elimination of duplicates and application of the inclusion and exclusion criteria. These studies were finally analysed and the results were divided for: (1) body composition; (2) metabolic profile; (3) inflammation; (4) bone mineralisation.

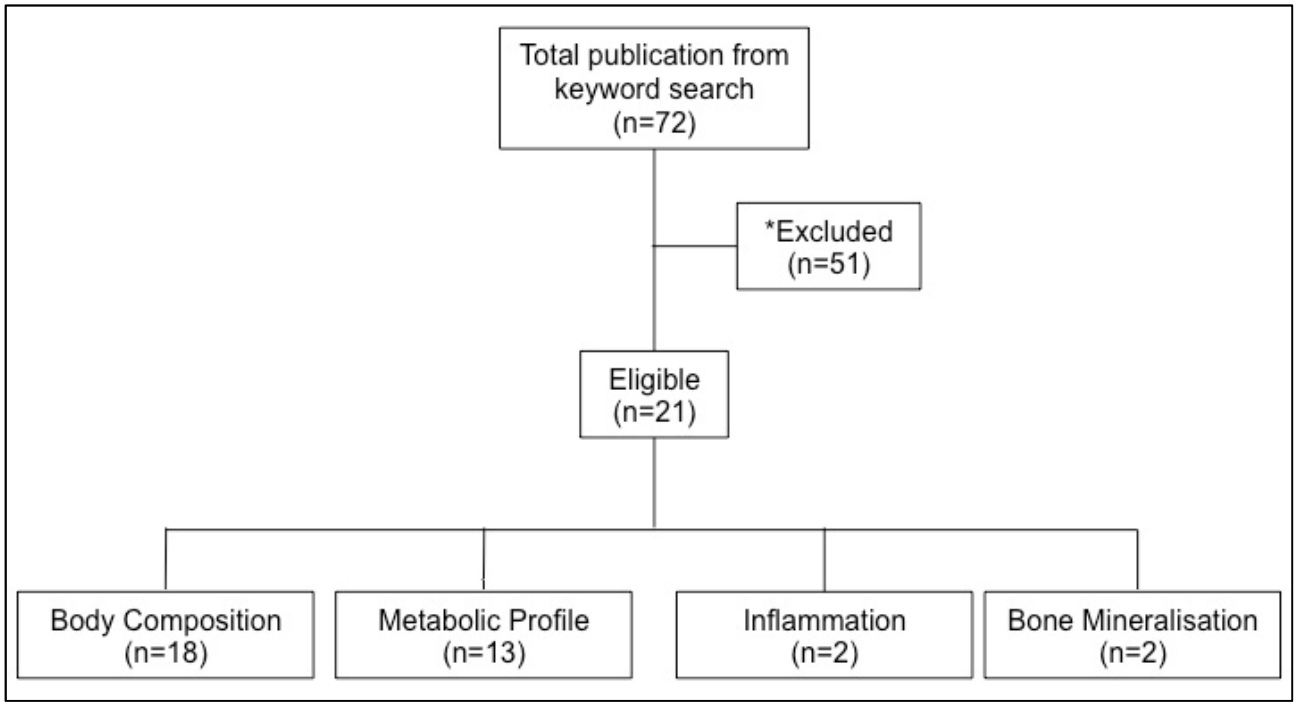

Figure 6. Flowchart of literature search. *Reason for exclusion: patients no in cART therapy (n=23); other exercise intervention (n=1); review (n=21); psychological outcomes (n=3); study design (n=2); case study (n=1).

Physical fitness outcomes

In Table 1, are shown 21 trials that met the inclusion criteria. Fourteen studies were randomized controlled trial (Agin et al., 2001; Roubenoff et al., 2001; Driscoll et al., 2004a/b; Terry et al., 2006; Dolan et al., 2006; Hand et al., 2008; Lindegaard et al., 2008; Gomes et al., 2010; Farinatti et al., 2010; Souza et al., 2011; Dudgeon et al., 2012; Broholom et al., 2013; Ezema et al., 2014), whereas seven studies have no control group (Roubenoff et al., 1999; Yarashesky et al., 2001; Thoni et al., 2001; Engelson et al., 2006; Robinson et al., 2007; Ahmad et al., 2014; Garcia et al., 2014).

Eight trials included participants of both sexes (Roubenoff et al., 2001; Thoni et al., 2002; Driscoll et al., 2004a/b; Therry et al., 2006; Robinson et al., 2007; Hand et al., 2008; Souza et al., 2011), three studies included only women (Agin et al., 2001; Engelson et al., 2006; Dolan et al., 2006), six trials included only men (Roubenoff et al., 1999; Yarasheski et al., 2001; Lindegaard et al., 2008; Dudgeon et al., 2011; Broholom et al., 2013; Ahmad

et al., 2014) and 3 trials not reported the sex of participants (Gomes et al., 2010; Farinatti et al., 2010; Ezema et al., 2014; Garcia et al., 2014).

The total number of participants was 687, and the number of dropouts was 162 (24%).

Ten trials used combined exercise training (Roubenoff et al., 1999; Driscoll et al., 2004a/b; Dolan et al., Robinson et al., 2007; Hand et al., 2008; Gomes et al., 2010; Farinatti et al., 2010; Dudgeon et al., 2014; Garcia et al., 2014), four studies used aerobic training (Thoni et al., 2002; Terry et al., 2006; Ezema et al., 2014; Ahmad et al., 2014) and five studies used resistance training (Agin et al., 2001; Yarasheski et al., 2001; Roubenoff et al., 2001; Engelson et al., 2006; Souza et al., 2011). Furthermore, only one proposed the comparison between aerobic and resistance training (Lindegaard et al., 2008; Broholom et al., 2013).

The duration of the training program ranged from 6 weeks to one year, the frequency of training session varied from 2 to 4 per week.

Regarding the aerobic training activity all studies performed continuous exercise training with the duration from 20 to 45 minutes mainly performed indoor with stationary bike or treadmill. On the other hand the studies of Lindegaard et al. (2008) and Broholom et al., 2014, subjects have to complete an interval-training program.

The parameters to monitor the intensity of training between the various studies are different. The majority of the studies used the calculation of the maximal heart rate (HR_{max}) using the 220-age or the 208-(0.7*age) formula, ranging the intensity from 60 to 80% of HR_{max} (Driscoll et al., 2004a/b; Engelson et al., 2006; Terry et al., 2006; Dolan et al., 2006; Dudgeon et al, 2012). Four ranged the intensity of the training session it from 60 to 80% of $\dot{V}O_{2\,max}$ (Robinson et al., 2007; Lindegaard et al., 2008; Broholom et al., 2014; Garcia et al, 2014) and Hand et al (2008) used instead the 50-70% of $\dot{V}O_{2\,peak}$. In particular, the study of Thoni et al. (2002) used the intensity corresponding to the ventilatory threshold

measured during $\dot{V}O_{2\,max}$; the studies of Farinatti et al. (2010) and Gomes et al. (2010) used a workload associated with an heart rate of 150 beats per minutes (BPM) to avoid possible exercise-induced immunodepression; and the study of Ezema et al. (2014) used the 60-75% of heart rate of reserve. A different approach was used by the study of Ahmad et al., 2014, who train the subjects with a one-year individual marathon running plan, so with different distances and intensities among the training sessions. Finally, the study of Roubenoff et al (1999) not reported the intensity of the training sessions.

Regarding the resistance-training program all studies used free weight, exercises machines and bodyweight exercises, using the 3 set of 8-12 repetition or the circuit training methods.

The majority of studies used the one-repetition maximum (RM), measuring directly the maximal amount of weight that could be lifted one time by the target muscle group (Roubenoff et al., 1999; Agin et al., 2001; Yahasheski et al., 2001; Roubenoff et al., 2001; Driscoll et al., 2004a/b; Engelson et al., 2006; Dolan et al., 2006; Robinson et al., 2007; Garcia et al., 2008). The studies of Hand et al. (2008), Lindegaard et al. (2008) and Broholom et al. (2014) estimate the maximal load using the 3RM test, instead the study of Farinatti et al. (2010) and Gomes et al. (2010) estimate the maximal load using the 12RM. Using these methods the intensities were scheduled from 50 to 80% of RM. On the contrary, the study of Souza et al. (2011) used adjusted submaximal loads and the study of Dudgeon et al. (2012) scheduled the exercises adjusting the load so that subjects were able to perform 12 repetitions.

For assessing the improvement in the physical fitness six studies assessed it directly using a ramp protocol until volitional exhaustion (Thoni et al., 2002; Terry et al., 2006; Lindegaard et al., 2008; Broholom et al., 2013; Ahamad et al., 2014; Garcia et al., 2014). Furthermore, three studies (Robinson et al., 2007; Hand et al., 2008; Ezema et al., 2014)

used the modified Bruce protocol that estimated $\dot{V}O_{2\,peak}$ the total time spent on treadmill that was subsequently placed into the gender specific equations that have been validated for estimating $\dot{V}O_{2\,peak}$ from treadmill time during the Bruce Protocol. Moreover, the studies of Engelson et al. (2006) and Dudgeon et al. (2012) estimated the $\dot{V}O_{2\,max}$ from a modified stress test using the Balke and the Keytel protocol respectively.

Two studies used submaximal exercise stress test to measure the grade of physical fitness of the patients. The study of Dolan et al. (2006) used a submaximal exercise stress test based on the American College of Sports Medicine equation for estimation of $\dot{V}O_{2\,max}$ during cycle ergometer, and in addition assesse the functional status with a 6-Minutes Walking Test (6MWT) at baseline and at the end of the study. The study of Farinatti et al. (2010), instead, used a 3-stage cycle ergometer protocol. A different approach was used by Souza et al. (2011), which submitted to two functional tests that included an assessment of a timed 2.4-meter walk at a normal pace and a timed test of five repetitions of rising from a chair and sitting down (sit-standing).

Finally four studies did not report any measure of aerobic fitness (Roubenoff et al., 1999; Driscoll et al., 2004a/b; Gomes et al., 2010).

Author	Subjects	Intervention	Drop out	Outcomes
Roubenoff et al. 1999	14 men No control group	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on treadmill or cycle ergometer, intensity NR. – Resistance: the major muscle groups of the legs, back and arm (1 hour at 80% 1RM)	4 subjects (28%)	↑ Leg Press (p<0.02) ↑ Leg Extension (p<0.03) ↑ Chest Press (p<0.005)
Agin et al. 2001	37 women Prospective, randomized, controlled trial 12 Protein supplementation Vs. 12 Progressive resistance training Vs. 13 Combined treatment	Frequency: 3 sessions/week Duration: 14 weeks Exercise: – Resistance: 3 sets of 8-10 rep at 75% 1RM for 7 major muscle groups Protein supplementation: 1.0 g/kg/day of undenatured bovine derive whey protein powder	7 subjects (19%)	Whey protein ↑ Bench press (p=0.02) ↑ Shoulder press (p=0.02) ↑ Biceps curl (p=0.01) ↑ Triceps extension (p=0.02) ↑ Leg extension (p=0.03) ↔ Seated back row, leg curl Exercise treatment ↑ Bench press (p<0.001) ↑ Seated back row (p<0.001) ↑ Shoulder press (p<0.001) ↑ Biceps curl (p<0.001) ↑ Triceps extension (p<0.001) ↑ Leg Extension (p<0.001) ↑ Leg curl (p<0.001) Combined treatment ↑ Bench press (p<0.001) ↑ Seated back row (p<0.001) ↑ Shoulder press (p<0.001) ↑ Biceps curl (p<0.001) ↑ Triceps extension (p<0.001) ↑ Leg Extension (p<0.001) ↑ Leg curl (p<0.001)
Yarasheski et al. 2001	18 men No control group	Frequency: 4 sessions/week Duration: 24 weeks Exercise: Resistance: 3 upper-body/4 lower-body done 1-1.5 h/d, at 75-85% 1 RM, exercises not clearly stated	None	↑ RM in all six exercises (23-38%, p<0.001)

Roubenoff et al. 2001	20 men and 5 women 6 with AIDS wasting vs 19 No AIDS wasting	Frequency: 3 sessions/week Duration: 8 weeks Exercise: Resistance: 3 sets of 8 reps, double leg press, leg extension, seated chest press, seated row (50% 1-RM first session, 60% second session, and 75%-80% for remain sessions)	None	No wasting ↑ Chest press, Leg press, Leg extension Upper back (0.01>p>0.0001) Wasting ↑ Chest press, Leg press, Leg extension Upper back (0.01>p>0.0001)
Thoni et al. 2002	12 men and 5 women No control group	Frequency: 2 session/week Duration: 16 weeks Exercise: Endurance: 45 min on cycle ergometer at HR corresponding to ventilatory threshold	2 subjects (10%)	↑ VO_{2max} ($p<0.005$)
Driscoll et al. 2004 (a, b)	20 men and 5 women Prospective, randomized 19 metformin and exercise vs 18 metformin only	Frequency: 2 sessions/week Duration: 12 weeks Exercise: combined – Endurance: 20 min on cycle ergometer for 2 weeks at 60% of HR_{max} and 30 min at 75% of HR_{max} for 10 weeks. – Resistance: 3 sets/10 rep, hip extension, lateral pull down, knee extension, elbow flexion, knee extension, chest press (60% 1RM first two weeks, 70% 1RM third and fourth week, 80% rest of weeks) Metformin treatment: 500 mg twice a day, with an increase at 850 mg twice a day after two weeks.	12 subjects (33%)	Study one Metformin and exercise subjects ↓ Waist-to-hip ratio (p=0.026) ↓ Abdominal CT subcutaneous adipose tissue fat (p=0.049) ↑ Mid-thigh CT leg muscle area (p=0.015) ↑ CT anterior thigh muscle attenuation (p=0.04) ↔Weight, BMI, DEXA total fat, abdominal CT visceral adipose tissue area, CT visceral adipose tissue area subcutaneous adipose tissue fat ratio
Engelson et al. 2006	39 women No control group	Frequency: 3 sessions/week Duration: 12 weeks Exercise: combined with diet – Endurance: 30 min on treadmill 70-80% HR_{max} – Resistance: 3 sets/8-10 rep, 10 exercises for 7 major muscle groups, – Diet: 5024-kJ hypo energetic	21 subjects (54%)	↑ Pectoral ($p<0.0001$) ↑ Latissimus dorsi ($p<0.0001$) ↑ Quadriceps ($p<0.0001$) ↑ Time to fatigue (p=0.0015) ↓ RPE (p=0.03)
Terry et al. 2006	26 men and 16 women Randomized controlled trial 21 Endurance and diet	Frequency: 3 sessions/week Duration: 12 week Exercise: – Endurance: 30 min running at 70-85% HR_{max}	12 subjects (29%)	↑ VO_{2max} (Exercise and diet) ↔ VO_{2max} (Diet only)

	vs 21 Stretching, relaxation program and Diet	Daily caloric intake of 30 kcal/kg of body weight for women and 40 kcal/kg of body weight for men, with a protein intake of 2.0 g/kg of body weight for women and 2.5 g/kg of body weight for men.		
Dolan et al. 2006	40 women 20 exercise 20 Non-exercise	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on cycle ergometer, 60%HR_{max} 1-2 wk and 30 min, 75% HR_{max} 3-16 wk – Resistance: 3 sets of 10 rep 60% 1RM for weeks 1 and 2; 4 sets of 8 rep at 70%1RM for week 3 and 4; 4 sets of 8 rep at 80%1RM for weeks 5 and 16 (knee-hip extension, bench press, knee flex, lat-raise, stand calf, arm curl)	1 subject (5%)	↑ VO2max (p<0.001) ↑ Submaximal bike exercise time (p<0.001) ↑ Strength (p<0.001) ↑ 6MWT distance (p=0.009) ↑ Knee extensors (p<0.001) ↑ Pectoralis (p<0.001) ↑ Knee flexors (p<0.001) ↑ Shoulder abductors (p<0.001) ↑ Ankle plantar flexors (p<0.001) ↑ Elbow flexors right/left (p<0.001)
Robinson et al. 2007	8 men and 1 women No control group	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on treadmill at 70-80% $V'O_{2max}$ – Resistance: 2 sessions a week, 1 set of 8 to 10 repetitions at 60-80% 1-RM (lat pull down, seated row, shoulder press, bench press, leg press, calf press, seated leg curl)	4 subjects (56%)	↔VO2max (p=0.08) ↑ Strength, sum of increase of increases in 1RM for all seven resistance exercises (p=0.04)
Hand et al. 2008	30 men and 10 women Randomized controlled trial 30 Exercise 40 control	Frequency: 2 sessions/week Duration: 6 weeks Exercise: combined – Endurance: 30 min at 50-70% $V'O_2$ peak – Resistance: 20 min at 60% 3-RM	34 subjects (46%)	↑ Time to fatigue (p<0.001) ↑ Estimated VO2max (p<0.001) ↓ % Functional aerobic impairment ↑ Peak heart rate during exercise stress test ↓ HR at submaximal absolute workload
Lindegaard et al. 2008	20 men Randomized controlled trial 10 Endurance vs 10 Strength	Frequency: 3 sessions/week Duration: 16 weeks Exercise: – Endurance: 35 min of interval training on treadmill (8wks at 65% of $V'O2_{max}$, 8 wks of 75% $V'O_{2max}$) – Resistance: 3 sets of 8-12 rep at 50-80% 3RM (leg curl, pull-down, seated leg press, chest press, seated rows, leg extension,	2 subjects (10%)	Endurance training ↑ VO2max (p=0.0046) ↑ 3RM for six muscle groups (p=0.0044) Strength training ↔VO2max, 3RM for six muscle groups

		abdominal crunch, back extension)		
Gomes et al. 2010	29 subjects Randomized controlled trial 19 Exercise group 10 Control group	Frequency: 3 sessions/week Duration: 12 weeks Exercise: combined – Endurance: 30 min at 150 bpm (treadmill/ cycloergometer) – Resistance: 3 sets/12 rep 60-80% 12RM (leg press, horizontal supine, leg extension, low rowing, abdominal flexion) – Flexibility: 3 sets at 30 sec/exercise (trunk, hip, knee, shoulder and elbow)	None	Physical fitness outcomes not reported
Farinatti et al. 2010	27 subjects (gender not defined) Randomized controlled trial 19 Exercise 8 Control	Frequency: 3 sessions/week Duration: 12 weeks Exercise: combined – Endurance: 30 min on cycle ergometer at 150 bpm – Resistance: 3 sets of 12 rep at 80% of 12RM (leg press, bench press, knee extension, seated bilateral row, abdominal sit-ups) Flexibility 2 sets 30 sec major joint	None	↑ Flexibility ($p<0.05$) ↑ Leg press ($p<0.05$) ↑ Seated bilateral row ($p<0.05$) ↓ HR at workload ($p<0.05$)
Souza et al. 2011	18 men and 18 women Randomized controlled trial 14 Exercise with HIV 22 Control without HIV infection	Frequency: 2 sessions/week Duration: 48 weeks Exercise: Resistance: 3 sets of 8-12 rep with adjusted sub-maximal loads (leg press, seated row, lumbar extension, chest press, seated abdominal)	4 subjects (11%)	↓ Sit-Standing ($p<0.001$) ↑ Walking 2.4.m ($p<0.001$) ↑ Leg press ($p<0.001$) ↑ Chest press ($p<0.001$) ↑ Lumbar extension ($p<0.001$) ↑ Seated row ($p<0.001$) ↑ Seated abdominal ($p=0.003$)
Dudgeon et al. 2012	111 men Randomized controlled trial 52 Exercise 59 Control with HIV	Frequency: 2 sessions/week Duration: 6 weeks Exercise: combined – Endurance: 30 min on treadmill or cycle ergometer at 60-75% HR_{max} Resistance: circuit training for 12 rep (upper and lower body exercises)	35 subjects (32%)	Physical fitness outcomes not reported
Broholom et al. 2013	20 men Randomized controlled trial 10 Endurance	Frequency: 3 sessions/week Duration: 16 weeks Exercise: – Endurance: 35 min of interval training on treadmill (8wks at 65% of $V'O2_{max}$, 8 wks of	2 subjects (10%)	Endurance training ↑ VO2max ($p=0.0046$) ↑ 3RM for six muscle groups ($p=0.0044$) Strength training

	vs 10 Strength	75% V'O_{2max}) – Resistance: 3 sets of 8-12 rep at 50-80% 3RM (leg curl, pull-down, seated leg press, chest press, seated rows, leg extension, abdominal crunch, back extension)		↔VO2max, 3RM for six muscle groups
Ezema et al. 2014	33 subjects with HIV Randomized controlled trial 17 Exercise 16 Control	Frequency: 3 sessions/week Duration: 8 weeks Exercise: Endurance: 2 weeks for 45 min at 60-79% HRR; 6 weeks for 60 at 60-79% HRR (treadmill)	3 subjects (9%)	↑ VO2max
Ahmad et al. 2014	12 men No control group	Individual marathon running plan – First week 3/wk for 3-4 hours, 60-70%HRmax (improve aerobic metabolism) – 4 months, 3/wk for 6 hours, 70-80% HRmax (economization of metabolism and cardiovascular system) – 7 months 3/wk for 10 hours (introduction of 3x2000m rec 800 m relaxed pace) – 2 weeks before marathon, tapering, 60-70%HRmax	4 subjects (33%)	After 4-month ↑ Maximal velocity ($p<0.05$) ↑ Anaerobic threshold velocity ($p<0.05$)
Garcia et al. 2014	10 subjects No control group	Frequency: 3 sessions/week Duration: 20 weeks Exercise: combined – Resistance: circuit training, 1-4 wks (1circuit, 12 rep at minimal load); 5-12 wks (2 circuits, 15 rep at 40%1RM); 13-20 wks (3 circuits, 15 rep at 60% 1RM), ½ squat, bench press, 45° leg press, sit-ups, seated row, leg curl, shoulder press, triceps pulley, biceps curl, seated calf raise, abdominal crunches – Endurance: walking, 1-4 wks (30 min free); 5-12 weeks (30 min at 60%V'O_{2max}); 13-20 (30 min at 75%V'O_{2max})	None	↑ Abdominal ($p<0.01$) ↑ VO2max ($p<0.005$) ↑ Squat ($p<0.008$) ↑ 45° leg press ($p<0.02$) ↑ Seated row ($p<0.02$) ↑ Triceps extension ↔Push-ups, bench press, leg curl, shoulder press, biceps curl, calf raise

Table 1. Physical fitness outcomes.
Legend: VO_{2max}: Maximal Oxygen Consuption; VO_{2peak}: Peak Oxygen Consuption; HR_{max}: Heart Rate Max; HRR: Heart Rate of Reserve; RM: Repetition Maximum.

Body composition outcomes

In Table 2 shows the main findings from 18 interventional longitudinal studies that met the inclusion criteria. Eleven studies were randomized controlled trials (Agin et al., 2011; Roubenoff et al., 2001; Driscoll et al., 2004a/b; Terry et al., 2006; Dolan et al., 2006; Lindegaard et al., 2008; Farinatti et al., 2010; Souza et al., 2011; Dudgeon et al., 2012; Ezema et al., 2014), whereas seven studies had no control group (Roubenoff et al., 1999; Yarashesky et al., 2001; Thöni et al., 2002; Engelson et al., 2006; Robinson et al., 2007; Ahmad et al 2014; Garcia et al; 2014).

Seven trials included participants of both sexes (Roubenoff et al., 2001; Driscoll et al., 2004a/b; Terry et al., 2006; Souza et al., 2011; Thoni et al., 2002; Robinson et al., 2007), three studies included only women (Agin et al., 2001; Dolan et al., 2006; Engelson et al., 2006), five trials included only men (Lindegaard et al., 2008; Dudgeon et al., 2012; Roubenoff et al 1999; Yarasheski et al., 2001; Ahmad et al., 2014) and 3 trials not reported the sex of participants (Farinatti et al., 2010; Ezema et al., 2014; Garcia et al., 2014). The total number of participants was 566, and the number of dropouts was 124 (22%).

Nine trials used combined exercise training (Roubenoff et al 1999; Driscoll et al., 2004a/b; Engelson et al., 2006; Dolan et al., 2006; Robinson et al., 2007; Farinatti et al., 2010; Dudgeon et al., 2012; Garcia et al., 2014), four studies used aerobic training (Thoni et al., 2002; Terry et al., 2006; Ezema et al., 2004; Ahmad et al., 2014) and four studies used resistance training (Agin et al., 2001; Yarasheski et al., 2001; Robinson et al., 2007; Souza et al., 2011). Furthermore, only one proposed the comparison between aerobic and resistance training (Lindegaard et al., 2008).

The protocols had a median duration of 16 weeks with a median frequency of 3 sessions per week. Regarding the aerobic training activity all studies performed continuous exercise training with the duration ranging from 20 to 45 minutes mainly performed indoor with cycle

ergometer (4) or treadmill (4). Moreover, the studies of Terry et al., 2006, and Garcia et al., 2014 trained subject with running or walking without specifying how the training was performed. Finally, Ahamad et al., 2014 trained their subjects with a one-year individual running plan.

The parameters chosen to define and monitor the intensity of aerobic training between the various studies varied. The majority of the studies used the calculation of HR_{max} using the 220-age (Fox et al., 1971) or the 208-(0.7*age) (Tanaka et al., 2001) formula, ranging the training intensity from 60 to 80% of HR_{max} (Driscoll et al., 2004a/b; Engelson et al., 2006; Terry et al., 2006; Dudgeon et al, 2012). Three studies measured directly the maximal oxygen consumption ($\dot{V}O_2$max), and then setting the intensity of the training session from 60 to 80% of $\dot{V}O_2$max (Robinson et al., 2007; Lindegaard et al., 2008; Garcia et al, 2014). In particular, the study of Thoni et al. (2002) used the intensity corresponding to the ventilatory threshold measured during the $\dot{V}O_2$max incremental test; the study of Farinatti et al. (2010) used a workload associated with an heart rate of 150 BPM to avoid possible exercise-induced immune-depression; and the study of Ezema et al. (2014) used the 60-75% of heart rate of reserve (HRR, HR_{max} – HR at rest) (Fletcher et al., 2001). A different approach was used by the study of Ahmad et al., 2014, who trained the subjects with a one-year individual marathon running plan, so with different distances and intensities among training sessions. Finally, the study of Roubenoff et al (1999) did not report the intensity of the training sessions.

Regarding the resistance-training program all studies used free weight, exercises machines and bodyweight exercises, using the 3 set of 8-12 repetition or the circuit training methods.

The majority of studies used the one-RM, measuring directly the maximal amount of weight that could be lifted one time by the target muscle group (Roubenoff et al., 1999;

Agin et al., 2001; Yahasheski et al., 2001; Roubenoff et al., 2001; Driscoll et al., 2004a/b; Dolan et al., 2006; Robinson et al., 2007; Garcia et al., 2008). The studies of Lindegaard et al. (2008) and Farinatti et al. (2010), estimate the maximal load using the 3RM test and the 12RM respectively. On the contrary, the study of Souza et al. (2012) used adjusted submaximal loads. Using these methods the intensities were scheduled from 50 to 80% of RM.

For assessing the body composition parameters Dual Energy X-ray Absortiometry (DEXA), Computer Tomography (CT), and Magnetic Resonance Imaging (MRI) were used. In addition one study used also skinfold thickness for the estimation of the body density and percentage of body fat by the formulas of Durnin and Womersley and Siri, respectively.

The influence of exercise training on body weight and Body Mass Index (BMI, kg · m2) was not supported by strong evidence; in fact only two studies reported their reduction (Engelson et al., 2006; Terry et al., 2006). These parameters were obviously affected by the exercise type in particular resistance training caused an increase of fat free mass in six studies (Agin et al., 2001; Yarasheski et al., 2001; Roubenoff et al., 2001; Lindegaard et al., 2008; Dudgeon et al., 2012; Garcia et al., 2014).

On the other hand, nine studies reported a reduction of the parameters related to fat mass (Roubenoff et al 1999; Agin et al., 2001; Thoni et al., 2001; Driscoll et al., 2004a/b; Engelson et al., 2006; Terry et al, 2006; Robinson et al., 2007; Lindegaard et al., 2008) and five studies reported a reduction of morphometric parameters such as waist-to-hip ratio (Driscoll et al., 2004a/b; Terry et al., 2006), circumferences (Engelson et al., 2006; Dolan et al., 2006) and skinfolds thickness (Engelson et al., 2006).

Author	Subjects	Intervention	Drop-out (nr)	Outcomes
Roubenoff et al. 1999	14 men No control group	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on treadmill or cycle ergometer, intensity NR. – Resistance: the major muscle groups of the legs, back and arm (1 hour at 80% 1RM)	4 subjects (28%)	↓ Total Body fat by DEXA (p<0.01) ↓ Trunk Fat by DEXA (p<0.03) ↔ Weight, lean mass
Agin et al. 2001	37 women Prospective, randomized, controlled trial 12 Protein supplementation Vs. 12 Progressive resistance training Vs. 13 Combined treatment	Frequency: 3 sessions/week Duration: 14 weeks Exercise: – Resistance: 3 sets of 8-10 rep at 75% 1RM for 7 major muscle groups Protein supplementation: 1.0 g/kg/day of undenatured bovine derive whey protein powder	7 subjects (19%)	Protein Supplementation ↑ Body weight (p=0.001) ↑ Fat mass by MRI (p=0.002) ↑ Fat mass by DEXA (p=0.001) ↑ Fat free mass by DEXA (p=0.01) ↔Body cell mass by TBK, skeletal muscle by MRI Exercise treatment ↓ Body cell mass by TBK (p=0.03) ↑ Skeletal muscle by MRI (p<0.001) ↓ Fat mass by MRI (p=0.02) ↓ Fat mass by DEXA (p=0.06) ↓ Fat free mass by DEXA (p=0.05) ↔ Body weight, Body cell mass by TBK Combined treatment ↑ Body cell mass by TBK (p=0.01) ↑ Fat free mass by DEXA (p=0.05) ↔ Body weight, skeletal muscle by MRI, fat mass by MRI, fat mass by DEXA
Yarasheski et al. 2001	18 men No control group	Frequency: 4 sessions/week Duration: 24 weeks Exercise: – Resistance: 3 upper-body/4 lower-body done 1-1.5 h/d, at 75-85% 1 RM, exercises not clearly stated	None	↑ Body weight (<0.001) ↑ Whole body lean mass (p<0.005) ↑ Trunk lean mass (p=0.02) ↑ Arms lean mass (p=0.001) ↑ Thigh muscle area (p<0.005) ↔Total intramuscular fat area, leg lean mass, whole body, trunk, arms, legs fat mass, trunk-to-appendicular fat ratio
Roubenoff et al. 2001	20 men and 5 women 6 with AIDS wasting	Frequency: 3 sessions/week Duration: 8 weeks	None	Wasting ↑ Fat free mass (p<0.05)

	vs 19 No AIDS wasting	Exercise: – Resistance: 3 sets of 8 reps, double leg press, leg extension, seated chest press, seated row (50% 1-RM first session, 60% second session, and 75%-80% for remain sessions)		No wasting ↑ Fat free mass ($p<0.05$)
Thoni et al. 2002	12 men and 5 women No control group	Frequency: 2 session/week Duration: 16 weeks Exercise: – Endurance: 45 min on cycle ergometer at HR corresponding to ventilatory threshold	2 subjects (10%)	↓ Total abdominal adipose tissue by DEXA ($p=0.0005$) ↓ Visceral adipose tissue by DEXA ($p=0.004$) ↔Weight, BMI, fat free mass, fat mass, subcutaneous abdominal adipose tissue, subcutaneous abdominal adipose tissue visceral adipose tissue ratio:shrink
Driscoll et al. 2004 (a, b)	20 men and 5 women Prospective, randomized 19 metformin and exercise vs 18 metformin only	Frequency: 2 sessions/week Duration: 12 weeks Exercise: combined – Endurance: 20 min on cycle ergometer for 2 weeks at 60% of HR_{max} and 30 min at 75% of HRmax for 10 weeks. – Resistance: 3 sets/10 rep, hip extension, lateral pull down, knee extension, elbow flexion, knee extension, chest press (60% 1RM first two weeks, 70% 1RM third and fourth week, 80% rest of weeks) Metformin treatment: 500 mg twice a day, with an increase at 850 mg twice a day after two weeks.	12 subjects (33%)	Study one Metformin and exercise subjects ↓ Waist-to-hip ratio ($p=0.026$) ↓ Abdominal CT subcutaneous adipose tissue fat ($p=0.049$) ↑ Mid-thigh CT leg muscle area ($p=0.015$) ↑ CT anterior thigh muscle attenuation ($p=0.04$) ↔Weight, BMI, DEXA total fat, abdominal CT visceral adipose tissue area, CT visceral adipose tissue area subcutaneous adipose tissue fat ratio
Engelson et al. 2006	39 women No control group	Frequency: 3 sessions/week Duration: 12 weeks Exercise: combined with diet – Endurance: 30 min on treadmill 70-80% HR_{max} – Resistance: 3 sets/8-10 rep, 10 exercises for 7 major muscle groups, – Diet: 5024-kJ hypo energetic	21 subjects (54%)	↓ Weight ($p<0.0001$) ↓ BMI ($p<0.0001$) ↓ Waist circumference ($p=0.0003$) ↓ Chest circumference ($p<0.0001$) ↓ Biceps skinfold ($p=0.04$) ↓ Abdominal skinfold ($p=0.01$) ↓ Thigh skinfold ($p=0.04$) ↓ Skeletal muscle by MRI ($p=0.035$) ↓ Visceral adipose tissue by MRI ($p<0.0001$) ↓ Subcutaneous adipose tissue by MRI

				(p<0.0001) ↓ Total adipose tissue by MRI (p<0.001) ↓ Fat mass by DEXA (p<0.0001) ↓ Total body potassium (p=0.02) ↓ Body cell mass (p=0.02) ↔Waist-hip ratio, mid-arm circumference, thigh circumference, triceps skinfold, visceral/subcutaneous adipose tissue ratio by MRI, lean mass by DEXA, total body water, intracellular water,
Terry et al. 2006	26 men and 16 women Randomized controlled trial 21 Endurance and diet vs 21 Stretching, relaxation program and Diet	Frequency: 3 sessions/week Duration: 12 week Exercise: – Endurance: 30 min running at 70-85% HR_{max} Daily caloric intake of 30 kcal/kg of body weight for women and 40 kcal/kg of body weight for men, with a protein intake of 2.0 g/kg of body weight for women and 2.5 g/kg of body weight for men.	12 subjects (29%)	In both groups: ↓ Weight (p=0.005) ↓ BMI (p<0.003) ↓ Waist-to-hip ratio (p<0.0001) ↓ Body density (p<0.0001) ↓ Body Fat (p<0.0001)
Dolan et al. 2006	40 women 20 exercise 20 Non-exercise	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on cycle ergometer, 60%HR_{max} 1-2 wk and 30 min, 75% HR_{max} 3-16 wk – Resistance: 3 sets of 10 rep 60% 1RM for weeks 1 and 2; 4 sets of 8 rep at 70%1RM for week 3 and 4; 4 sets of 8 rep at 80%1RM for weeks 5 and 16 (knee-hip extension, bench press, knee flex, lat-raise, stand calf, arm curl)	1 subject (5%)	↓ Waist circumference (p=0.03) ↓ Total muscle area (p=0.02) ↓ Total muscle attenuation (p=0.03) ↔BMI, total fat, subcutaneous adipose tissue, visceral adipose tissue
Robinson et al. 2007	8 men and 1 women No control group	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on treadmill at 70-80% $V'O_{2max}$ – Resistance: 2 sessions a week, 1 set	4 subjects (56%)	↓ Total fat by DEXA (p<0.05) ↓ Trunk fat by DEXA ↔Visceral fat area, subcutaneous fat area, total lean tissue by DEXA, trunk lean tissue by DEXA, limb fat by DEXA.

		of 8 to 10 repetitions at 60-80% 1-RM (lat pull down, seated row, shoulder press, bench press, leg press, calf press, seated leg curl)		
Lindegaard et al. 2008	20 men Randomized controlled trial 10 Endurance vs 10 Strength	Frequency: 3 sessions/week Duration: 16 weeks Exercise: – Endurance: 35 min of interval training on treadmill (8wks at 65% of V'O2$_{max}$, 8 wks of 75% V'O$_{2max}$) – Resistance: 3 sets of 8-12 rep at 50-80% 3RM (leg curl, pull-down, seated leg press, chest press, seated rows, leg extension, abdominal crunch, back extension)	2 subjects (10%)	Endurance training ↔Body weight, total lean mass, total fat mass, trunk fat mass, limb fat mass Strength training ↓ Body weight (p<0.05) ↑ Total lean mass (p<0.05) ↓ Total fat mass (p<0.05) ↓ Trunk fat mass (p<0.05) ↓ Limb fat mass (p<0.05)
Farinatti et al. 2010	27 subjects (gender not defined) Randomized controlled trial 19 Exercise 8 Control	Frequency: 3 sessions/week Duration: 12 weeks Exercise: combined – Endurance: 30 min on cycle ergometer at 150 bpm – Resistance: 3 sets of 12 rep at 80% of 12RM (leg press, bench press, knee extension, seated bilateral row, abdominal sit-ups) – Flexibility 2 sets 30 sec major joint	None	↔Body mass, BMI
Souza et al. 2011	18 men and 18 women Randomized controlled trial 14 Exercise with HIV 22 Control without HIV infection	Frequency: 2 sessions/week Duration: 48 weeks Exercise: – Resistance: 3 sets of 8-12 rep with adjusted sub-maximal loads (leg press, seated row, lumbar extension, chest press, seated abdominal)	4 subjects (11%)	↔Body mass, BMI
Dudgeon et al. 2012	111 men Randomized controlled trial 52 Exercise 59 Control with HIV	Frequency: 2 sessions/week Duration: 6 weeks Exercise: combined – Endurance: 30 min on treadmill or cycle ergometer at 60-75% HR$_{max}$ – Resistance: circuit training for 12 rep (upper and lower body exercises)	35 subjects (32%)	↑ Total lean tissue mass (p<0.001) ↔Body mass, BMI, fat mass, % total body fat, % trunk fat, % arm fat, %leg fat, arm/leg/trunk lean tissue mass
Ezema et al.	33 subjects with HIV	Frequency: 3 sessions/week	3 subjects	↔BMI

2014	Randomized controlled trial 17 Exercise 16 Control	Duration: 8 weeks Exercise: – Endurance: 2 weeks for 45 min at 60-79% HRR; 6 weeks for 60 at 60-79% HRR (treadmill)	(9%)	
Ahmad et al. 2014	12 men No control group	Individual marathon running plan – First week 3/wk for 3-4 hours, 60-70%HRmax (improve aerobic metabolism) – 4 months, 3/wk for 6 hours, 70-80% HRmax (economization of metabolism and cardiovascular system) – 7 months 3/wk for 10 hours (introduction of 3x2000m rec 800 m relaxed pace) – 2 weeks before marathon, tapering, 60-70%HRmax	4 subjects (33%)	After for months of training ↔BMI
Garcia et al. 2014	10 subjects No control group	Frequency: 3 sessions/week Duration: 20 weeks Exercise: combined – Resistance: circuit training, 1-4 wks (1circuit, 12 rep at minimal load); 5-12 wks (2 circuits, 15 rep at 40%1RM); 13-20 wks (3 circuits, 15 rep at 60% 1RM), ½ squat, bench press, 45° leg press, sit-ups, seated row, leg curl, shoulder press, triceps pulley, biceps curl, seated calf raise, abdominal crunches – Endurance: walking, 1-4 wks (30 min free); 5-12 weeks (30 min at 60%V'O_{2max}); 13-20 (30 min at 75%V'O_{2max})	None	↑ Percentage of lean mass (p=0.007) ↑ Total lean mass (p=0.05) ↔Total mass, percentage of fat mass, total fat mass, BMI

Table 2. Body composition outcomes

Legend: VO_{2max}: Maximal Oxygen Consuption; VO_{2peak}: Peak Oxygen Consuption HRmax: Heart Rate Max; HRR: Heart Rate of Reserve; RM: Repetition Maximum; wks: weeks; TBK: Total Body Potassium Counting; MRI: Magnetic Resonance Imaging; DEXA: Dual Energy X-Ray Absortiometry; BMI: Body Mass Index; CT: Computer Tomography

Metabolic profile outcomes

In Table 3, shows the results of the 13 interventional longitudinal studies that met the inclusion criteria. Eight studies were randomized controlled trial (Driscoll et al., 2004a/b; Terry et al., 2006; Dolan et al., 2006; Lindegaard et al., 2008; Souza et al., 2011; Broholom et al., 2013; Ezema et al., 2014), whereas five studies had no control group (Yarasheski et al., 2001; Thoni et al., 2002; Robinson et al., 2007; Ahmad et al., 2014; Garcia et al., 2014).

Six trials included participants of both sexes (Thoni 2002; Driscoll et al., 2004a/b; Terry et al., 2006; Robinson et al., 2007; Souza et al., 2011), one studies included only women (Dolan et al., 2006), four trials included only men (Yarasheski et al., 2001; Lindegaard et al., 2008; Broholom et al., 2014; Ahmad et al., 2014) and two trials did not reported the sex of participants (Ezema et al., 2014; Garcia et al., 2014). The total number of participants was 333, and the number of dropouts was 59 (17%).

Five trials used combined exercise training (Driscoll et al., 2004a/b; Dolan et al., 2006; Robinson et al., 2007; Garcia et al., 2014), four studies used aerobic training (Thoni et al., 2002; Terry et al., 2006; Ezema et al., 2014; Ahmad et al., 2014) and two studies used resistance training (Yarasheski et al., 2001; Souza et al., 2011). Furthermore, two studies proposed the comparison between aerobic and resistance training (Lindegaard et al., 2008; Broholom et al., 2013).

The protocols had a median duration of 16 weeks with a median frequency of 3 sessions per week.

Regarding the aerobic training activity all studies performed continuous exercise training with the duration ranging from 20 to 45 minutes mainly performed indoor with cycle ergometer (three) or treadmill (four). In addition, the studies of Roubenoff et al, 1999 and Dudgeon et al., 2012 used both training methods. Moreover, the studies of Terry et al., 2006, and Garcia et al., 2014 trained subject with running or walking without specifying

how the training was performed. Finally, Ahamad et al., 2014 trained their subjects with a one-year individual running plan.

The parameters chosen to define and monitor the intensity of training between the various studies were different. Five studies used the calculation of the HR_{max} using the 220-age (Fox et al., 1971) or the 208-(0.7*age) formula, and then setting the intensity from 60 to 80% of HR_{max} (Driscoll et al., 2004a/b; Terry et al., 2006; Dolan et al., 2006; Ahmad et al., 2014). Four studies measured directly the $\dot{V}O_2$ max, ranging the intensity of the training session from 60 to 80% of $\dot{V}O_2$ max (Robinson et al., 2007; Lindegaard et al., 2008; Broholom et al., 2014; Garcia et al., 2014). In particular, the study of Thoni et al. (2002) used the intensity corresponding to the ventilatory threshold measured during the VO2max incremental test, and the study of Ezema et al. (2014) used the 60-75% of HRR (Fletcher et al., 2001). A different approach was used by the study of Ahmad et al., 2014, who trained the subjects with a one-year individual marathon running plan, so with different distances and intensities among training sessions.

Regarding the resistance-training program all studies used free weight, exercises machines and bodyweight exercises, using the 3 set of 8-12 repetition or the circuit training methods.

The majority of studies used the 1-RM, measuring directly the maximal amount of weight that could be lifted one time by the target muscle group (Yarasheski et al., 2001; Driscoll et al., 2004a/b; Robinson et al., 2007; Garcia et al., 2014). The studies of Lindegaard et al. (2008), Brohlom et al. (2013) and Farinatti et al. (2010), estimate the maximal load using the 3RM test and the 12RM respectively. On the contrary, the study of Souza et al. (2012) used adjusted submaximal loads. Using these methods the intensities were scheduled from 50 to 80% of RM.

The metabolic parameters were assessed by standard laboratory analysis. The influence of exercise training on blood lipids was not supported with strong evidence, only four studies reported a reduction of triglycerides (Yarasheski et al., 2001; Thoni et al., 2002; Lindegaard et al., 2008; Ahmad et al., 2014). Surprisingly, the study of Lindegaard et al (2008) reported a reduction of this parameter in the subjects that performed the resistance training and not the endurance protocol. In addition the study of Ahmad et al., (2014), which trained the subjects for one year with a individual marathon training program observed a reduction of triglycerides after 4 months of training but not on the marathon day after a tapering period. Moreover, only two studies reported a reduction of total cholesterol (Thoni et al., 2008; Lindegaard 2008). In particular the study of Lindegaard et al. (2008), observed this reduction in the group, which performed the endurance training. Furthermore, only the study of Lindegaard et al. (2008) observed a reduction of LDL-cholesterol for both groups of training, instead three studies reported an improvement of HDL-cholesterol (Thoni et al., 2002; Lindegaard et al., 2008; Garcia et al., 2014).

The same can be said for the insulin parameters. In fact only the study of Driscoll et al., (2004b) reported a reduction of fasting insulin, but the exercise program was supported by a Metformin treatment for 500 mg twice a day, with an increase at 850 mg twice a day after two weeks. A different approach was used by the study of Broholom et al., (2013) where HIV-infected patients with lipodystrophy have decreased insulin-stimulated glucose uptake in skeletal muscle and defects in insulin-stimulated phosphorylation of Aktthr308. Endurance and strength training increase insulin-stimulated glucose uptake in these patients, and the muscular training adaptation was associated with improved capacity for phosphorylation of glucose by HKII, rather than changes in markers of insulin signalling to glucose uptake or glycogen synthesis.

Author	Subjects	Intervention	Drop out	Outcomes
Yarasheski et al. 2001	18 men No control group	Frequency: 4 sessions/week Duration: 24 weeks Exercise: Resistance: 3 upper-body/4 lower-body done 1-1.5 h/d, at 75-85% 1 RM, exercises not clearly stated	None	↓ Serum Triglycerides (p=0.022) ↔Total cholesterol, HDL-c, LDL-c, Insulin, C-peptide, proinsulin, glucagon
Thoni et al. 2002	12 men and 5 women No control group	Frequency: 2 session/week Duration: 16 weeks Exercise: Endurance: 45 min on cycle ergometer at HR corresponding to ventilatory threshold	2 subjects (10%)	↓ Total cholesterol (p=0.005) ↑ HDL-c (p=0.01) ↓ Triglycerides (p<0.003) ↓ Total cholesterol HDL-c ratio (p=0.0007) ↓ Triglycerides HDL-c ratio (p=0.003) ↔LDL-c, glucose, insulin, IR-HOMA
Driscoll et al. 2004 (a, b)	20 men and 5 women Prospective, randomized 19 metformin and exercise vs 18 metformin only	Frequency: 2 sessions/week Duration: 12 weeks Exercise: combined – Endurance: 20 min on cycle ergometer for 2 weeks at 60% of HR_{max} and 30 min at 75% of HRmax for 10 weeks. – Resistance: 3 sets/10 rep, hip extension, lateral pull down, knee extension, elbow flexion, knee extension, chest press (60% 1RM first two weeks, 70% 1RM third and fourth week, 80% rest of weeks) Metformin treatment: 500 mg twice a day, with an increase at 850 mg twice a day after two weeks.	12 subjects (33%)	Study one Metformin and exercise subjects ↓ Waist-to-hip ratio (p=0.026) ↓ Abdominal CT subcutaneous adipose tissue fat (p=0.049) ↑ Mid-thigh CT leg muscle area (p=0.015) ↑ CT anterior thigh muscle attenuation (p=0.04) ↔Weight, BMI, DEXA total fat, abdominal CT visceral adipose tissue area, CT visceral adipose tissue area subcutaneous adipose tissue fat ratio
Terry et al. 2006	26 men and 16 women Randomized controlled trial 21 Endurance and diet vs 21 Stretching, relaxation program and Diet	Frequency: 3 sessions/week Duration: 12 week Exercise: – Endurance: 30 min running at 70-85% HR_{max} – Daily caloric intake of 30 kcal/kg of body weight for women and 40 kcal/kg of body weight for men, with a protein intake of 2.0 g/kg of body weight for women and 2.5 g/kg of body weight for men.	12 subjects (29%)	In both groups: ↓ Glucose (p=0.05) ↔ Systolic and diastolic blood pressure, triglycerides, total-C, HDL-C
Dolan et al. 2006	40 women 20 exercise	Frequency: 3 sessions/week Duration: 16 weeks	1 subject (5%)	↔Systolic and diastolic blood pressure, total-C, triglycerides, LDL-C, HDL-C, fasting

	20 Non-exercise	Exercise: combined – Endurance: 20 min on cycle ergometer, 60%HR_{max} 1-2 wk and 30 min, 75% HR_{max} 3-16 wk – Resistance: 3 sets of 10 rep 60% 1RM for weeks 1 and 2; 4 sets of 8 rep at 70%1RM for week 3 and 4; 4 sets of 8 rep at 80%1RM for weeks 5 and 16 (knee-hip extension, bench press, knee flex, lat-raise, stand calf, arm curl)		glucose, 2-h glucose
Robinson et al. 2007	8 men and 1 women No control group	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on treadmill at 70-80% $V'O_{2max}$ – Resistance: 2 sessions a week, 1 set of 8 to 10 repetitions at 60-80% 1-RM (lat pull down, seated row, shoulder press, bench press, leg press, calf press, seated leg curl)	4 subjects (56%)	↔Total-C, LDL-C, HDL-C, triglycerides, beta-cell function, insulin sensitivity.
Lindegaard et al. 2008	20 men Randomized controlled trial 10 Endurance vs 10 Strength	Frequency: 3 sessions/week Duration: 16 weeks Exercise: – Endurance: 35 min of interval training on treadmill (8wks at 65% of $V'O2_{max}$, 8 wks of 75% $V'O_{2max}$) – Resistance: 3 sets of 8-12 rep at 50-80% 3RM (leg curl, pull-down, seated leg press, chest press, seated rows, leg extension, abdominal crunch, back extension)	2 subjects (10%)	Endurance training ↓ Total-C (p=0.0023) ↑ HDL-C (p<0.0001) ↓ LDL-C (p=0.0001) ↓ Fat free acid (p=0.017) ↔Glucose, insulin, triglycerides Strength training ↑ HLD-C (p=0.0068) ↓ LDL-C (p=0.04) ↓ Triglycerides (p<0.001) ↓ Fat free acid (0.008) ↔Glucose, insulin, total cholesterol
Souza et al. 2011	18 men and 18 women Randomized controlled trial 14 Exercise with HIV 22 Control without HIV infection	Frequency: 2 sessions/week Duration: 48 weeks Exercise: Resistance: 3 sets of 8-12 rep with adjusted sub-maximal loads (leg press, seated row, lumbar extension, chest press, seated abdominal)	4 subjects (11%)	↓ Fat glycaemia (p=0.037) ↔Total-C, HDL-C, LDL-C, triglycerides,
Broholom et al.	20 men	Frequency: 3 sessions/week	2 subjects	Effect of insulin on HIV patients

2013	Randomized controlled trial 10 Endurance vs 10 Strength	Duration: 16 weeks Exercise: – Endurance: 35 min of interval training on treadmill (8wks at 65% of V'$O2_{max}$, 8 wks of 75% V'O_{2max}) – Resistance: 3 sets of 8-12 rep at 50-80% 3RM (leg curl, pull-down, seated leg press, chest press, seated rows, leg extension, abdominal crunch, back extension)	(10%)	↑ Phosphorylation of Akt^{thr308} (p<0.0001) ↑ Ratio of $AS160^{thr624}$/AS160 (p<0.001) ↑ Ratio $GSK3B^{ser9}$/GSK3B (p<0.05) ↑ Phosphorylation GS (p<0.0001) ↑ GS activity as % of I-form (p<0.0001) ↑ GS activity as fractional velocity (p<0.0001) ↔GS total activity Endurance ↑ Phosphorylation of Akt^{thr308} (p<0.0001) ↓ pGS (site 3a+b)/ GS (p<0.01) ↔Ratio of $AS160^{thr624}$/AS160, Ratio $GSK3B^{ser9}$/GSK3B Strength ↑ Phosphorylation of Akt^{thr308} (p<0.0001) ↓ Ratio of $AS160^{thr624}$/AS160 (p<0.001) ↑ Ratio $GSK3B^{ser9}$/GSK3B ↑ pGS (site 3a+b)/ GS (p<0.0001)
Ezema et al. 2014	33 subjects with HIV Randomized controlled trial 17 Exercise 16 Control	Frequency: 3 sessions/week Duration: 8 weeks Exercise: Endurance: 2 weeks for 45 min at 60-79% HRR; 6 weeks for 60 at 60-79% HRR (treadmill)	3 subjects (9%)	↓ Diastolic blood pressure ↔Systolic blood pressure
Ahmad et al. 2014	12 men No control group	Individual marathon running plan – First week 3/wk for 3-4 hours, 60-70%HRmax (improve aerobic metabolism) – 4 months, 3/wk for 6 hours, 70-80% HRmax (economization of metabolism and cardiovascular system) – 7 months 3/wk for 10 hours (introduction of 3x2000m rec 800 m relaxed pace) – 2 weeks before marathon, tapering, 60-70%HRmax	4 subjects (33%)	After four months of training ↓ Triglycerides (p<0.05) ↔LDL-C, HDL-C Marathon day ↔LDL-C, HDL-C, triglycerides, glucose
Garcia et al. 2014	10 subjects No control group	Frequency: 3 sessions/week Duration: 20 weeks Exercise: combined – Resistance: circuit training, 1-4 wks	None	↑ HDL-C (p=0.04) ↔Glucose, insulin, HOMA-IR, total-C, triglycerides, VLDL-C, LDL-C

		(1circuit, 12 rep at minimal load); 5-12 wks (2 circuits, 15 rep at 40%1RM); 13-20 wks (3 circuits, 15 rep at 60% 1RM), ½ squat, bench press, 45° leg press, sit-ups, seated row, leg curl, shoulder press, triceps pulley, biceps curl, seated calf raise, abdominal crunches – Endurance: walking, 1-4 wks (30 min free); 5-12 weeks (30 min at 60%V'O_{2max}); 13-20 (30 min at 75%V'O_{2max})		

Table 3. Metabolic profile outcomes

Legend: VO_{2max}, Maximal Oxygen Consuption; VO_{2peak}, Peak Oxygen Consuption; HRmax, Heart Rate Max; HRR, Heart Rate of Reserve; RM, Repetition Maximum; wks, weeks; TBK, Total Body Potassium Counting; MRI, Magnetic Resonance Imaging; AUC, Area Under the Curve; GS, Glucose Sintetase, HDL-C, high-density lipoprotein, LDL-C, low-density lipoprotein; VLDL-C, very low-density lipoprotein; Akt^{thr308}, Phosphorylation of Aktthr308; $AS160^{thr624}$/AS160, Phosphorylation of AS160thr642 related to total AS160 protein expression; $GSK3B^{ser9}$/GSK3B, Phosphorylation of GSK3bser9 related to total GSK3b protein expression; GS: Activity measures of glycogen synthase.

Inflammation outcomes

In Table 4, shows the results of the only 2 interventional longitudinal studies that met the inclusion criteria (Lindegaard et al., 2008; Dudgeon et al., 2012). Both studies included male patients that were subsequently randomized. The total number of participants was 131, and the number of dropouts was 37 (28%).

The study of Lindegaard et al. (2008) proposed an exercise intervention for 16 week at 3 sessions a week, but made a comparison between endurance and resistance training program. The endurance program was performed indoor on treadmill, and consisted of 35 minutes of interval training at 65-75% of $\dot{V}O_2$max. The endurance program was performed with machines at an intensity of 50-80% of 3RM.

On the contrary, the study of Dudgeon et al. (2012) proposed an exercise intervention for 6 weeks of combined exercise training 2 sessions a week. The aerobic training program was performed indoor on treadmill or stationary bike for 30 minutes at 60-75% of HR_{max} measured by 220-age formula (Fox et al., 1971). In addition, the resistance training was made with the circuit training method with adjusted intensity that allowed subjects to perform 12 repetitions.

Lindegaard et al. (2008) reported that the endurance-training program reduced the values of high-sensitivity C-reactive protein (hsCRP), Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin-6 (IL-6) and Interleukin-18 (IL-18). In addition the subject that performed the strength-training program reported a reduction only in IL-18, and not in the other parameters evaluated.

On the contrary, the study of Dudgeon et al. (2012), reported only a reduction in salivary cortisol, whereas no variation were detected in all the other parameters such as IL-6, interleukin-1- β (IL-1-β), soluble tumour necrosis factor receptor II (sTNFrII), insulin-like growth factor-1 (IGF-1), insulin-like growth factor-binding protein 3 (IGFBP-3), growth hormone (GH), cortisol, testosterone .

Generally, cART-controlled chronic HIV infection is associated with increased inflammation and coagulation, and higher plasma levels of hsCRP, IL-6 and D-dimer strongly predicted higher overall mortality and cardiovascular events. However, the anti-inflammatory effect of exercise in HIV infection has been rarely addressed in clinical studies. Reductions of hsCRP, IL-6, TNF-□ and IL-18, a cytokine released by adipocytes and other cell types, were observed in a 16-week study of aerobic or resistance training performed at variable intensity (Lindegaard et al., 2008), but no of IL-6 after 6 weeks of aerobic plus resistance moderate intensity exercise (Dudgeon et al., 2012). Looking these encouraging results we suggest that are needed more studies that assess the anti-inflammatory effect of exercise in HIV infection.

Author	Subjects	Intervention	Drop out	Outcomes
Lindegaard et al. 2008	20 men Randomized controlled trial 10 Endurance vs 10 Strength	Frequency: 3 sessions/week Duration: 16 weeks Exercise: – Endurance: 35 min of interval training on treadmill (8wks at 65% of V'$O2_{max}$, 8 wks of 75% V'O_{2max}) – Resistance: 3 sets of 8-12 rep at 50-80% 3RM (leg curl, pull-down, seated leg press, chest press, seated rows, leg extension, abdominal crunch, back extension)	2 subjects (10%)	Endurance training ↓ hsCRP ($p<0.0001$) ↓ TNF-alpha ($p=0.009$) ↓ IL-6 ($p=0.01$) ↓ IL-18 ($p=0.029$) Strength training ↓ IL-18 ($p<0.0001$) ↔hsCRP, TNF-alpha, IL-6,
Dudgeon et al. 2012	111 men Randomized controlled trial 52 Exercise 59 Control with HIV	Frequency: 2 sessions/week Duration: 6 weeks Exercise: combined – Endurance: 30 min on treadmill or cycle ergometer at 60-75% HR_{max} – Resistance: circuit training for 12 rep (upper and lower body exercises)	35 subjects (32%)	↓ Salivary cortisol after exercise ($p<0.05$) ↔IL-6, IL-1, sTNFrII, IGF-1, IGFBP-3, growth hormone, cortisol, salivary testosterone

Table 4. Inflammatory outcomes

Legend: VO_{2max}, Maximal Oxygen Consuption; VO_{2peak}, Peak Oxygen Consuption HRmax, Heart Rate Max; HRR, Heart Rate of Reserve; RM, Repetition Maximum; wks, weeks; hsCRP, high-sensitivity C-Reactive Protein; TNF-alpha, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; IL-18, Interleukin-18; IGF-1, Insulin-like Growth Factor 1; IGFBP-3, Insulin-like growth factor-binding protein 3

Bone mineralisation outcomes

In Table 5, shows findings from the 2 interventional longitudinal studies that met the inclusion criteria (Roubenoff et al., 1999; Engelson et al., 2006). Both studies had no control group. The study of Roubenoff et al. (1999) enrolled only male subjects, whereas the study of Engelson et al. (2006) only female patients. The total number of participants was 53, and the number of dropouts was 25 (47%).

Both trials used the combined exercise training with the duration of 16 (Roubenoff et al., 1999) and 12 weeks (Engelson et al., 2006), at 3 sessions a week. Regarding the aerobic training activity all studies performed continuous exercise training with the duration of 20 (Roubenoff et al., 1999) and 30 minutes (Engelson et al., 2006) mainly performed indoors with stationary bike or treadmill. The study of Roubenoff et al. (1999) did not report the intensity of exercise; instead Engelson et al. (2006) scheduled the exercise at 70-80% of HR_{max} calculated by the 220-age formula (Fox et al., 1971).

Regarding the resistance-training program all studies used free weight, exercises machines and bodyweight exercises, using the 3 set of 8-12 repetition or the circuit training methods. Both studies used the 1-RM method for assess the intensity of the resistance exercises.

The parameters of bone mineralisation were assessed by DEXA. Neither study reported variations in bone mineral density and bone calcium. BMC, Z- e T-score not assessed

Author	Subjects	Intervention	Drop out	Outcomes
Roubenoff et al. 1999	14 men No control group	Frequency: 3 sessions/week Duration: 16 weeks Exercise: combined – Endurance: 20 min on treadmill or cycle ergometer, intensity NR. – Resistance: the major muscle groups of the legs, back and arm (1 hour at 80% 1RM)	4 subjects (28%)	↔Bone mineral density by DEXA
Engelson et al. 2006	39 women No control group	Frequency: 3 sessions/week Duration: 12 weeks Exercise: combined with diet – Endurance: 30 min on treadmill 70-80% HR_{max} – Resistance: 3 sets/8-10 rep, 10 exercises for 7 major muscle groups, – Diet: 5024-kJ hypo energetic	21 subjects (54%)	↔Bone calcium, bone mineral density by DEXA

Table 5. Bone mineralisation outcomes
Legend: VO_{2max}, Maximal Oxygen Consuption; VO_{2peak}, Peak Oxygen Consuption HRmax, Heart Rate Max; HRR, Heart Rate of Reserve; RM, Repetition Maximum; wks, weeks; DEXA, Dual Energy X-Ray Absortiometry.

Discussion

The wide spread introduction of cART for HIV infection had dramatically decrease HIV-morbidity and mortality (Palella et al., 1998; Collaboration ATC, 2008) becoming in this way a chronic disease. Despite marked increases in life expectancy, mortality rates among HIV-infected persons remain 3-15 times higher than those seen in the general population (Guaraldi et al., 2011). Although, some of excess mortality observed among HIV-infected persons can be directly attributed to illnesses that occur as a consequence of immunodeficiency, more than half of the deaths observed in recent years among cART-experienced HIV-infected patients are attributable to non-infectious comorbidities (Guaraldi et al., 2011). These include cardiovascular diseases, hypertension, bone fractures, renal failure, and diabetes mellitus, diseases that in the general populations often coexist and are associated with advancing age (Guaraldi et al., 2011).

Regular physical activity and exercise are associated with numerous physical health benefits in the general population. In fact, all-cause mortality is delayed by regularly engaging in physical activity; this is also the case when an individual increases physical activity by changing from a sedentary lifestyle or a lifestyle with insufficient levels of physical activity to one that achieves recommended physical activity levels. Exercise and physical activity decrease the risk of developing cardio-vascular diseases (CVD), stroke, type-2 diabetes and some form of cancer (e.g. colon and breast cancers). Exercise and physical activity lower blood pressure; improve lipoprotein profile; C-reactive protein and other CVD biomarkers; enhance insulin sensitivity, and play an important role in weight management. Of particular relevance to older adults, exercise preserves bone mass and reduces the risk of falling.

Several studies were conducted to assess the benefits an exercise intervention in people living with HIV infections treated with cART. The most investigated parameters concerned

the body composition and metabolic profile outcomes. Moreover, the inflammatory and bone mineralisation outcomes were also assessed.

Physical fitness outcomes

None of the examined papers investigated directly the decrease the risk of developing cardio-vascular diseases following a program of physical activity. On the other hand, nine studies assessed the level of physical fitness measuring directly of estimating the $\dot{V}O_2$ max, that is an important indicator of the functionality of the cardiorespiratory system. In particular eight studies reported an improvement of $\dot{V}O_2$ max (Thoni et al., 2002; Terry et al., 2006; Dolan et al., 2006; Hnd et al., 2008; Lindegaard et al., 2008; Brohlom et al., 2013; Ezema 2014; Garcia et al., 2014) and one did not detected any variation in $\dot{V}O_2$ max (Robinson et al., 2007). Relationship, between cardiorespiratory fitness, biological risk factors and clinical health outcomes tend to parallel those for physical activity: apparently health middle-aged and older adults with greater cardiorespiratory fitness at baseline, and those who improve fitness over time have a lower risk of all-cause and CVD mortality and morbidity. A decreased risk of clinical events is also associated with greater cardiorespiratory fitness in individual pre-existing disease. Generally, cardiorespiratory exercises reduces several cardio-metabolic disease risk factors, although the magnitude of effects is modest, varies according to individual and exercise program characteristics, and a change in one cardio-metabolic risk factors apparently occurs independently of a change in another (Garber et al., 2011). Favourable improvements in hypertension, glucose intolerance, insulin resistance, dyslipidaemia and inflammatory markers have been reported in middle aged and older persons exercising within the volumes and quality of exercise recommended here, even during weight regain (Garber et al., 2011). The benefits of exercise on cardio metabolic risk factors are acute (lasting hours to days) and chronic,

highlighting the value of regular exercise participation on most days of the week (Garber et al., 2011).

Body composition outcomes

Eighteen studies analysed how exercise training affected the parameters of body composition in this population.

Several aspects were analysed in order to assess the efficacy of exercise intervention on body composition outcomes. In addition to the general morphometric parameters such as weight, BMI, circumferences and skinfold thickness, was also determined the differences in fat mass and fat free mass using DEXA.

Principally, was observed a reduction of the fat mass and an improvement of fat free mass following a period of physical activity. On the other hand this, was not observed for weight and BMI because these parameters were obviously affected by the exercise type in particular resistance training caused an increase of fat free mass.

In the general population physical exercise is generally play an important role in the weight management looking for a reduction of body composition parameters. In the domain of body composition outcomes overall and abdominal obesity are associated with increased risk of adverse health outcomes whereas greater fat free mass is associated with a lower risk of all-cause mortality (Garber et al., 2011).

Metabolic profile outcomes

Thirteen studies analysed how exercise training affected the parameters of metabolic profile out comes in this population.

From a clinical standpoint, a remarkable observation was the general reduction of total cholesterol, the reduction of LDL cholesterol. Total, HDL and LDL cholesterol are each independent strong predictors of CVD in the general population and elevated LDL is the

primary target for cholesterol-lowering therapy. While high intensity aerobic exercise is followed by favourable cholesterol alterations, the influence of moderate intensity aerobic and of resistance training is not clearly evidence-supported. Only a few studies have examined the effects of exercise on blood lipids in HIV infection, with inconsistent outcomes, likely resulting from large variability of populations and exercise interventions.

Inflammatory outcomes

Only two studies how exercise training affected the parameters of inflammatory outcomes in HIV-infected patients, with one study that reported a general reduction on the parameters of chronic inflammation.

Broad systemic immune activation is characteristic of untreated HIV infection. A robust activation and inflammatory state are seen during acute infection, which is often reflected clinically ad “viral syndrome”. These clinical manifestations typically resolve ad markers of inflammation attenuate but still remain relatively and persistently elevated. Inflammatory and coagulation indices are typically and persistently elevated during untreated therapies. Whit application of cART therapy these markers improve but persistent immune activation, inflammation and coagulation abnormalities persist.

In the general population a prolonged inflammatory state has detrimental health effects and predispose of both disability and mortality even in the absence of clinical diseases. On the other hand lifestyle behavioural interventions, including changes in food dietary/intake and physical activity, may have clinically significant benefits for improving inflammation over the long term (Beavers et al., 2010). Observational data from large population cohort studies consistently show an association between physical activity and inflammation. Moreover, data from intervention studies designed to examine the effects of exercise training on inflammation reflect less consistent findings than the data from observational

studies. Finally, cross sectional evidence showing that a higher volume of physical activity is associated with a lower systemic inflammation.

Bone mineralisation outcomes

Only two studies how exercise training affected the parameters bone mineralisation in HIV-infected patients, but they did not report variation in the bone mineralisation outcomes.

Osteoporosis is common in human immunodeficiency virus (HIV)–infected populations and is likely to become an important cause of morbidity and mortality as the HIV-infected population ages (Walker & Brown 2012). Data are emerging that suggest the increased risk of osteoporosis translates into a higher risk of osteoporosis-related fracture. In a population-based study at a large US healthcare system, the period prevalence of fractures of the spine, hip, and wrist, sites commonly associated with osteoporosis was 60% higher in HIV-infected men and women compared with HIV-uninfected persons (Walker & Brown 2012). Similar results have been found in the Veterans Aging Cohort Study and HIV Outpatient Study. Early detection of osteoporosis, prior to the clinical presentation of fracture, and institution of appropriate treatment can decrease the burden of osteoporosis-associated fractures in HIV-infected persons. HIV-infected patients are also at increased risk for osteonecrosis of the hip and other bones.

The causes of bone complications have not been fully elucidated but could be related to establish osteoporosis risk factors (i.e. smoking, opiate use, alcohol use), to the HIV infection per se or to the effect of antiretroviral drugs (in particular, protease inhibitors—PIs and tenofovir—TDF) (Torti et al., 2011).

Like in the general population, and in particular in post-menopausal women, physical activity could play an important role for improve bone mineralisation also in HIV-infected patients.

Conclusions

According to our literature search, this is the first review that divided the effect of exercise intervention looking at different outcomes in people living with HIV infection treated with cART. Although our conclusions are useful, there are several limitations when interpreting these findings. For example we include trials with and without control groups, whereas other methodological differences on exercise protocol, the large variability of populations and different exercise interventions may confound the conclusions. Furthermore, the heterogeneity of the level of physical fitness, state of HIV infection, possible other medications may considerably influence the final results.

PART THREE

A pilot study of brisk walking in sedentary cART-treated patients

Aim of Study

Physical activity delays all-cause mortality in the general population and reduces the risk of cardiovascular disease (CVD), stroke, type-2 diabetes and some types of cancer (Garber et al., 2011). These diseases are associated with chronic inflammation, which is characterized by activation of inflammatory signalling pathways with abnormal production of cytokines and other mediators (Hotamisligil, 2006). Observational studies of large population cohorts consistently showed an association between physical inactivity and low-grade systemic inflammation and interventional studies a reduction of inflammatory markers following exercise (Beavers et al., 2010).

Chronic inflammation is also a predominant feature of treated HIV infection (Lederman et al., 2013; Deeks et al., 2013).

Compared to age-matched HIV-negative subjects, persons with chronic HIV infection are at higher risk to develop non-AIDS related chronic diseases (Guaraldi et al., 2013), and several studies have shown an association between chronic inflammation and higher cardiovascular risk and overall mortality (Kuller et al., 2008; Duprez et al., 2012).

We hypothesized that, like in the general population, physical exercise could decrease inflammation in HIV infection. We designed a pilot study of moderate physical activity, consisting of brisk walking, with or without strength exercise, with the objective to assess its effects on metabolic parameters and inflammatory markers in treated HIV-infected persons.

Material and methods

Study design

This was a 12-week pilot study, which enrolled sedentary HIV-infected patients receiving combination antiretroviral treatment (cART). Inclusion criteria were: age ≥18 years; cART for ≥6 months; sedentary lifestyle, defined as physical activity for <2 days per week for <20 minutes per session; either evidence of lipodystrophy or of at least one of the Adult Treatment Panel III definition criteria of the metabolic syndrome (NCEP, 2002).

Exclusion criteria included any disease requiring hospitalization in the 6 weeks before enrolment; medical conditions contraindicating exercise as established by a sport medicine specialist; inability to walk at brisk pace; current substance or alcohol abuse. San Raffaele Hospital Ethical Committee approved the study. Written informed consent was obtained from all study participants.

Participant screening and protocol

Subjects were screened for eligibility by an infectious diseases specialist (SB, PC) and a sport medicine specialist (GM), after performing electrocardiogram at rest and during sub-maximal cycle ergometer test. Patients who met the above inclusion criteria and with no contraindications to exercise were offered to either join the ‘walk’ group, consisting of brisk walking only, or the ‘strength-walk’ group, where each walking session was preceded by a strength exercise session.

Groups of 10-15 subjects trained three times a week for 12 weeks in the periods March-July, 2011 and 2012. The walking sessions were performed outdoor for 60 min at an intensity of 65-75% of maximal HR (HRmax), (Tanaka et al., 2001). Each subject was equipped with a personal HR monitor (Polar FT4, Polar Electro 2011, Kempele, Finland) with an acoustic warning if HR was below or exceeded the predetermined range. Mean HR (HRmean) was recorded during each session, with values captured every 5 seconds.

Strength exercise was carried out before walking in a gym by circuit training, including crunch, lat machine, chest press, leg press, leg extension, sitting calf. Each exercise was repeated 12 times for three sets at 65% of 1-Repetition Maximum Test (1-RM).

Professional coaches (MB, GP, ALT) followed all the sessions providing technical instruction, supervision and encouragement. Participants received generic dietary advice. Study variables were assessed at baseline (BL) and at the end (W12) of the program.

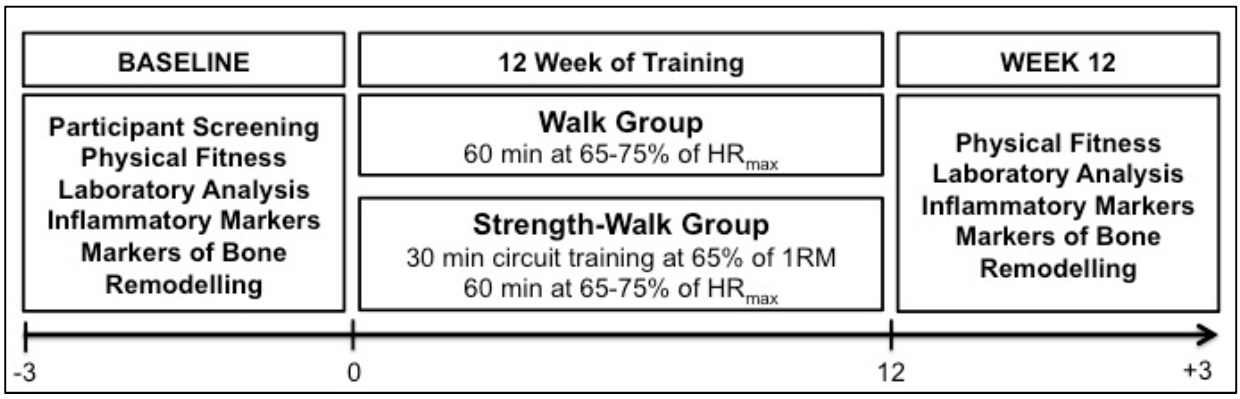

Figure 8. Flowchart of the study.

Physical Fitness Evaluation

6 Minutes Walking Test (6MWT). Participants were instructed to walk as fast as possible for six minutes on a 400 m outdoor athletic track (ATS, 2002). HRmean was recorded during the test, blood lactate concentration was assessed before and 3 minutes after 6MWT (Lactate ProTM, Arkray KdK, Japan), and the Rating of Perceived Exertion (RPE) (Borg, 1998) before and at the end of 6MWT.

Strength measurements. 1-RM test assessed the maximal load lifted in one repetition, and the 30-seconds crunch test the number of crunches performed in 30 seconds.

Body composition

Anthropometric variables included weight, body mass index (BMI), waist, hip, and thigh circumference on dominant side. Total and % fat mass at arms, limbs, trunk and as total body was measured by dual-energy X-ray absorptiometry (DEXA)(Lunar Prodigy, version 8.8, GE Medical Systems, Madison, WI). Superficial and visceral fat was measured by ultrasonography at the periumbilical skin-point (Schwenk, 2002).

Laboratory analysis

Blood examination included complete blood count; standard biochemical exams with fasting total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, insulin, HbA1c; CD4+ and CD8+ T-cell counts, HIV-1-RNA plasma level (Abbott RealTime HIV-1 assay). The Homeostatic Model Assessment (HOMA)-I and the Veterans Aging Cohort Study Risk (VACS) indexes were calculated (Justice et al., 2013).

Inflammatory markers

Soluble markers. Soluble biomarkers were measured in cryopreserved plasma samples, drawn at BL and W12, by commercially available enzyme-linked immunosorbent assays according to manufacturers' recommendation. These included high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and soluble CD14 (sCD14)(R&D Systems, Minneapolis, MN), D-dimer (Asserachrom, Diagnostica Stago, Asnieres-Sur-Seine, France), interleukin-18 (IL-18)(Medical and Biological Laboratories, Nagoya, Japan) and myostatin (Cusabio Biotech, Wuhan, China).

Flow cytometry for cell-activation markers. T-cell activation was measured on cryopreserved peripheral blood mononuclear cells isolated by Ficoll-Paque gradient from

EDTA-anticoagulated whole blood. After thawing and PBS-washing, 3 x 105 cells were stained using phycoerythrin (PE)-conjugated anti-HLA-DR, PE-cyanin red 5.1-conjugated anti-CD38, Alexa Fluor 647-conjugated anti-CD3, fluorescein isothiocyanate-conjugated anti-CD4 or anti-CD8 (BD-Biosciences, San Diego, CA). CD38+ and HLA-DR+ cells were gated from the CD3+/CD4+ or CD3+/CD8+ cells on a 2-dimensional dot plot. Analyses were performed by FACSCalibur with CellQuest software (BD-Biosciences) and results reported as percentages of CD3+/CD4+ and CD3+/CD8+ T-cells expressing both HLA-DR and CD38.

Statistical Analysis

Quantitative variables were expressed as median and 25-75% interquartile (Q1-Q3). Changes between BL and W12 were assessed by Wilcoxon matched-pairs signed rank test, BL values and % change differences between groups by Mann-Whitney test, and correlations of continuous variables by the Spearman's test. Statistical analysis was performed using Graph Pad Prism Software, version 6.0 for Macintosh (Graph Pad Software, San Diego, CA). Level of significance was set at 0.05.

Results

Patient disposition and baseline characteristics

Fifty-nine subjects underwent a screening visit and 49 were enrolled: 29 in the walk group and 20 the strength-walk group. Fourteen subjects dropped out and were not included in the analyses (Figure 9). Fourteen subjects stopped the activity after a median of 5 weeks (range, 2-7) because unable to handle family or work commitments (walk group, n=5; strength-walk group, n=5); medical problems unrelated to the study (walk group, n=2; strength-walk group, n=1); "exercise too hard" (walk group, n=1). Thirty-five subjects were evaluated at W12, including 21 in the walk group and 14 in the strength-walk group.

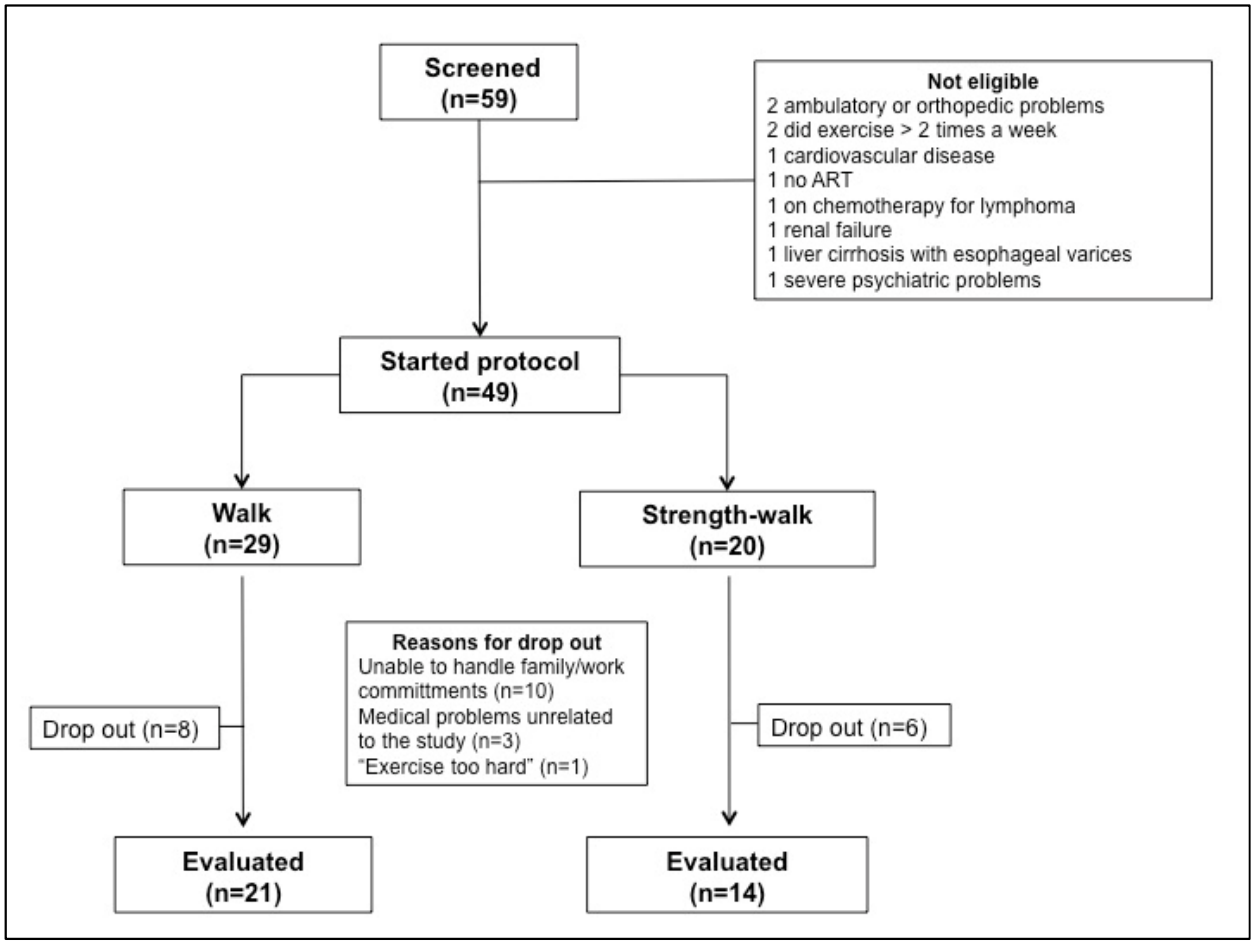

Figure 9. Of 59-screened patients, 49 were enrolled and 35 completed the study. Fourteen subjects stopped the activity after a median of 5 weeks (range, 2-7) because unable to handle family or work commitments (walk group, n=5; strength-walk group, n=5); medical problems unrelated to the study (walk group, n=2; strength-walk group, n=1), "exercise too hard" (walk group, n=1)

BL patients' characteristics are shown in Table 6. Except from gender, there was no difference between the two training subgroups in demographic and clinical variables. Because all women trained in the walking group, post-exercise changes were also separately analysed according to gender.

	All (n=36)	Walk (n=21)	Strength-Walk (n=14)
Demographics			
Male gender[a]	26, 74%	12, 57%	14, 100%
Age (years, median, Q1-Q3)	48 (44-54)	48 (43 (54)	49 (44-54)
Caucasian race	35 (100%)	21 (100%)	14 (100%)
Risk Group			
Ex-intravenous drug users	8 (23%)	7 (33%)	1 (7%)
Men-having-sex-with-men	21 (57%)	7 (33%)	13 (93%)
Heterosexual infection	6 (17%)	6 (29%)	0
Vertical infection	1 (3%)	1 (5%)	0
HIV infection variables			
AIDS-defining events	9 (25%)	7 (33%)	2 (14%)
Nadir CD4+ T-cells/µL (median, Q1-Q3)	94 (37-197)	80 (34-140)	188 (77-258)
CD4+ T-cells/µL (median, Q1-Q3)	577 (406-726)	485 (374-686)	624 (527-740)
VL<40 c/mL	34 (97%)	21 (100%)	13 (93%)
Hepatitis C virus coinfection	4 (11%)	4 (19%)	0
VACS Index	12 (5-19)	16 (6-24)	9 (0-12)
Smoking and Treatments			
Smokers	8 (23%)	6 (29%)	2 (14%)
NRTI+Protease inhibitor	14 (40%)	7 (33%)	7 (50%)
NRTI+NNRTI	11 (31%)	7 (33%)	4 (29%)
Other ART regimens	10 (28%)	7 (33%)	3 (21%)
Beta blockers[b]	6 (17%)	5 (24%)	1 (7%)
Other anti-hypertensive drugs[b]	5 (14%)	2 (10%)	3 (21%)
Statins[b]	10 (29%)	4 (19%)	6 (42%)
Fibrates[b]	2 (6%)	0	2 (14%)

Inclusion criteria			
Lipodystrophy	35 (100%)	21 (100%)	14 (100%)
≥1 metabolic syndrome criterion	32 (91%)	3 (14%)	0
Blood triglycerides 150 ≥ mg/dL	14 (40%)	8 (38%)	6 (42%)
Blood HDL-C ≤ 40 (m) or ≥50 (w) mg/d	12 (34%)	9 (43%)	3 (21%)
Blood glucose 50 ≥ 100 mg/dL	1 (3%)	0	1 (7%)
Waist ≥ 102 (m) or ≥ 88 cm (women)	10 (28%)	8 (38%)	2 (14%)
SBP ≥ 150 or DBP ≥85 mmHg	12 (34)	7 (33%)	5 (36%)

Table 6. Participants characteristics at baseline. Values are expressed as number of patients (%) where no otherwise indicated.
a. Walk vs. strength-walk, p=0.005.
b. Chronic treatment, with no changes during the training period or the 6 weeks before training.
Legend: VACS, Veterans Ageing Cohort Study; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non nucleoside reverse transcriptase inhibitors; m, men; w, women; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Physical Fitness

Performance during the training sessions. Median overall adherence to the sessions was 67%. Participants walked a median distance of 122 km in 12 weeks (5040 m each session) at a median exertion of 66% HRmax (Table 7). Participants in the strength-walk group walked longer distances than those in the walk group, both in each session and as a total. No different performances were observed between women and men within the walk group (Table 8).

	All (n=35)	Walk (n=21)	Strength-walk (n=14)
Adherence (%)	67 (58-75)	61 (56-72)	69 (63-79)
HRmean (%HRmax)[a]	66 (62-75)	66 (58-73)	70 (63-86)
Walked distance/session (m)	5040 (4380-5500)	4740[b] (3535-5390)	5330[b] (4980-5700)
Total walked distance (km)	122 (84-146)	105[c] (73-139)	136[c] (121-155)

Table 7. Participants performance during the 12 weeks of training. Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test. (a) The median HRmean value was calculated for each participant through all her/his walking sessions, to derive the median HRmean value of all participants (b) Walk vs. strength-walk group, p=0.027 (Mann-Whitney test). (c) Walk vs. strength-walk group, p=0.029 (Mann-Whitney test). HR, heart rate.

	Walk (n=21)	**Women (n=9)**	**Men (n=12)**
Adherence (%)	61 (56-72)	58 (54-65)	66 (61-82)
Total walked distance (Km)	105 [b] (73-139)	76 (67-123)	107 (88-181)
Walked distance/session (m)	4740 [c] (3535-5390)	4000 (3445-5330)	4755 (4388-5400)
HR_{mean} (% of HR_{max}) [a]	66 (58-73)	66 (63-77)	63 (56-68)

Table 8. Participants performance during the 12 weeks of training. Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test.
a. The median HRmean value was calculated for each participant through all her/his walking sessions, to derive the median HRmean value of all participants
b. Walk vs. strength-walk group, p=0.027 (Mann-Whitney test)
c. Walk vs. strength-walk group, p=0.029 (Mann-Whitney test)
Legend: HR, heart rate.

6MWT**.** At W12 6MWT, participants walked for a significantly longer distance compared to BL both in the overall sample and in the two subgroups (Figure 10), in parallel with significant increases of HRmean, HRmax and delta lactate (Table 9). The distance improvement from BL did not differ between subgroups and between women and men. Overall, better distance improvement correlated with higher adherence (r=0.580; p=0.0003) and longer walked distance (r=0.555; p=0.0005) during the 12 weeks of training.

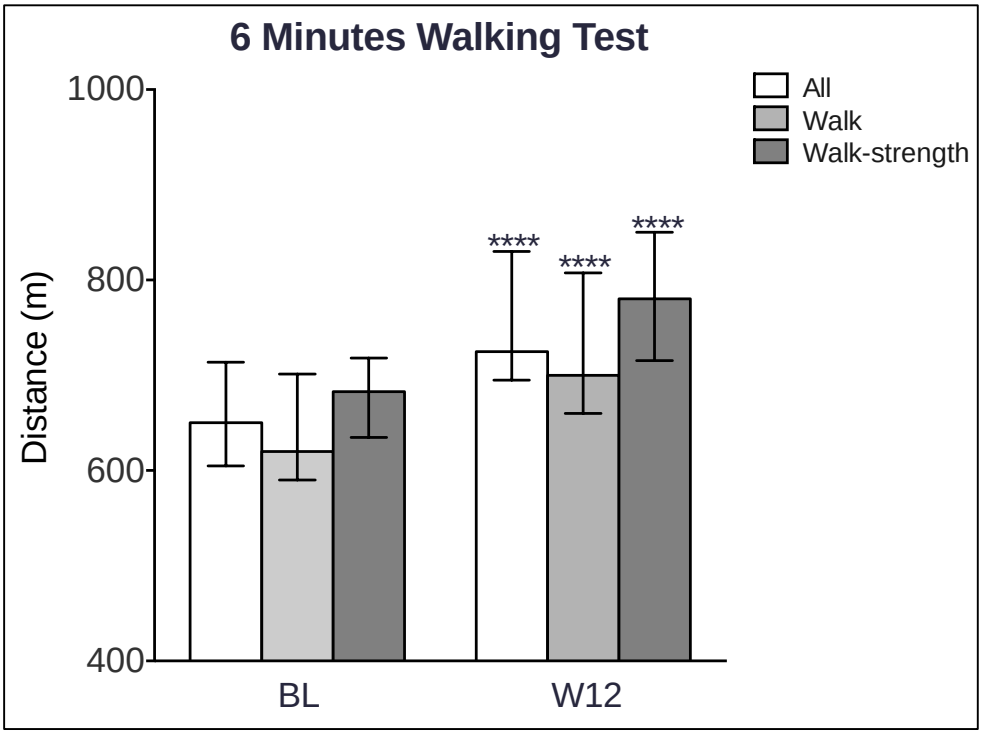

Figure 10. Comparison of participants' performance during the 6MWT. Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test (****p<0.0001).

	Women (n=9)			Men (n=12)		
	BL	**W12**	**p**	**BL**	**W12**	**p**
Distance (m)	620 (577-712)	697 (614-775)	0.002	625 (591-705)	717 (695-816)	0.004
HR_{mean} (bpm)	127 (119-148)	138 (118-164)	n.s	113 (99-119)	122 (110-144)	0.002
HR_{mean} (%HR_{max})	73 [a] (68-85)	80 (67-91)	n.s	62 [a] (59-79)	69 (67-81)	0.002
$\Delta[La^-]$(mmol/L)	0.5 (0.2-3.7)	1.2 (0.5-3.7)	n.s	0.8 (0.1-1.7)	3.4 (1.9-6.1)	0.003
Δ RPE	0.5 (0.0-1.8)	0.0 (0.0-0.5)	n.s	0.8 (0.1-2.0)	1.8 (0.6-2.5)	n.s

Table 9. Physical fitness values by the 6 Minutes Walking Test (6MWT) at baseline (BL) and week-12 (W12) in the walk group divided by gender. Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test.

a. At BL, women had higher %HR_{mean} than men (p=0.021, Mann-Whitney test)

Legend: HR, heart rate; $\Delta[La^-]$, difference in lactate blood concentration between before and after 6MWT; Δ RPE, difference in Rate of Perceived Exertion between before and after 6MWT.

1-RM and 30-seconds crunch tests. In the strength-walk group, training was followed by improvement of all strength exercises (Figure 11).

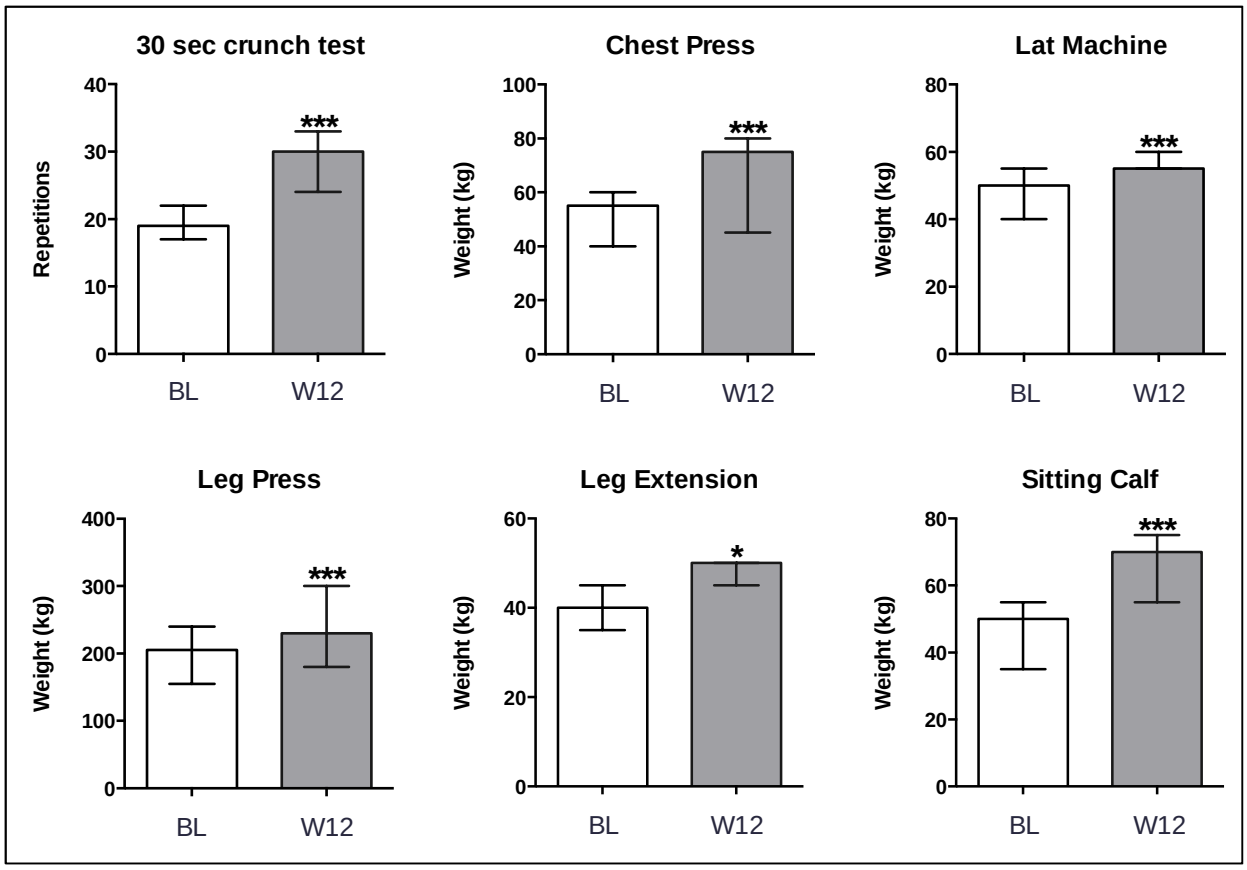

Figure 11. Comparison of participants' performance during the 1RM of the exercises of the circuit training. Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test (*p<0.05; ***p<0.001).

Body composition

Significant reductions were observed of weight, BMI and waist and hip circumference in the whole group. Weight, BMI reduction, hip and waist circumference reductions were maintained in the walk group, but none in the strength-walk group (Figure 12). Within the walk group, neither BMI nor waist circumference was significantly reduced when women and men were analysed separately (Table 11).

No significant changes were observed of total or % fat by DEXA, or of superficial, visceral or total fat by ultrasonography (Table 10 and Table 11).

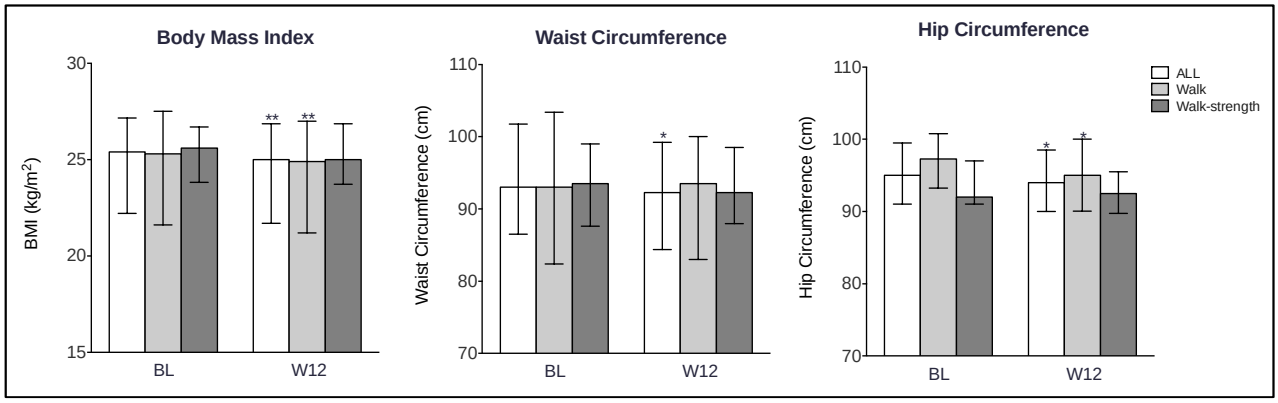

Figure 12. Comparison of participants' variations in Body Mass Index, waist and hip circumference. Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test (*p<0.05; **p<0.01).

1

2 *Laboratory examinations*

3 At W12, significant reductions were observed of total and LDL cholesterol in the whole
4 sample. Both were decreased also in the walk group, and LDL cholesterol in the strength-
5 walk group (Figure 13 and Table 10). Changes from BL did not differ between groups. No
6 cholesterol improvement was observed in women (Table 11).
7 Among 25 statin-untreated patients, total, LDL, and also HDL cholesterol improved
8 significantly both in the overall sample and in the walk group, and both total and LDL
9 cholesterol were decreased in the strength-walk group (Table 12). No significant changes
10 were observed of the other laboratory examinations (Table 10 and Table 11).

11

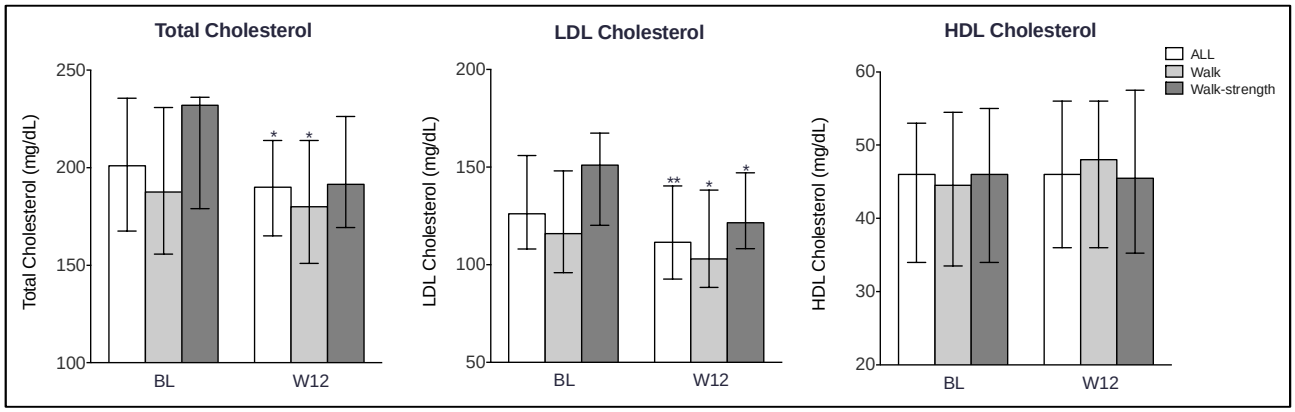

Figure 13. Comparison of participants' variations in Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol. Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test (*p<0.005; **p<0.01).

12

Inflammatory markers

Soluble and cell inflammatory markers were examined in a total of 25 and 16 patients, respectively. Overall, we observed significant decreases of all soluble markers, except for sCD14, and of the proportion of CD8+/CD38+/HLA-DR+, but not of CD4+/CD38+/HLADR+ cells (Figure 14). HsCRP and the proportion of CD8+/CD38+/HLA-DR+ decreased significantly in both walk and strength-walk groups; IL-6 and D-dimer in the walk group only and myostatin in the strength-walk group only. Changes from BL did not differ between training groups. Significant IL-6 and D-dimer reductions were also observed in women (Table 11). We neither observed significant intercorrelations between changes of inflammatory markers, nor between inflammatory markers and other variables changes, except for a more marked decrease of myostatin in participants who walked longer total distances during training (r=-0.340, p=0.032, Spearman's correlation).

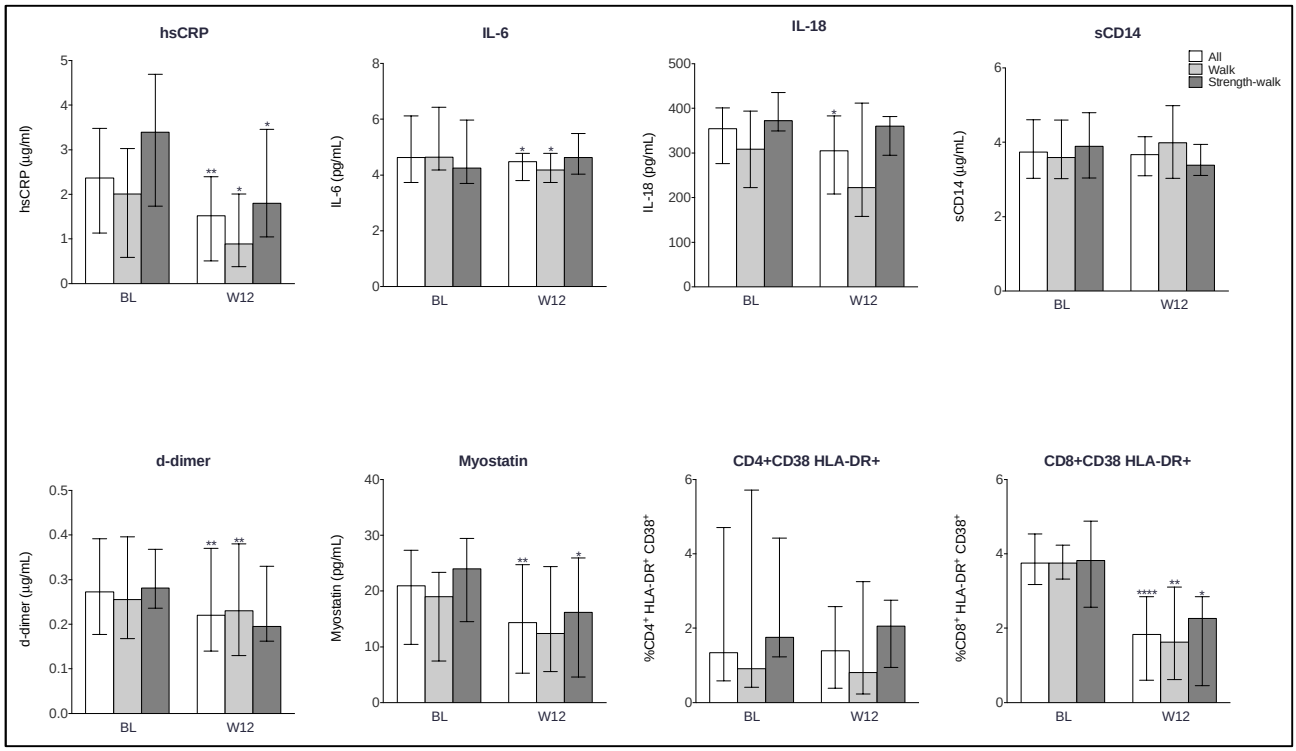

Figure 14. Soluble and cell inflammatory markers at baseline (BL) and week-12 (W12). Twenty-five patients were evaluated for soluble markers (walk, n=15; strength-walk, n=10), and 16 for cell markers (walk, n=10; strength-walk, n=6).
For each group, first and second columns represent values at BL and W12, respectively. Horizontal bars indicate median and Q1-Q3 values. HsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; IL-8, interleukin-18; sCD14, soluble CD14.

	All (n=35)			Walk (n=21)			Strength-Walk (n=14)		
	BL	**W12**	**p value**	**BL**	**W12**	**p value**	**BL**	**W12**	**p value**
Physical fitness									
6 Minute Walking Test									
Distance (m)	642	730	<0.0001	620	700	<0.0001	684	792	<0.0001
	(605-715)	(695-830)		(590-701)	(660-807)		(634-724)	(714-850)	
HR_{mean} (bpm)	119	137	<0.0001	118	128	0.0003	121	138	0.004
	(107-132)	(116-152)		(107-135)	(116-154)		(107-133)	(116-153)	
HR_{mean} (%HR_{max})	69	73	<0.0001	69	71	<0.0001	69	75	0.0005
	(63-75)	(63-75)		(59-75)	(63-83)		(63-75)	(68-79)	
$\Delta[La^-]$(mmol/L)	0.9	1.9	n.s	0.8	1.2	n.s	1.0	3.3	n.s
	(0.2-2.2)	(0.5-4.1)		(0.0-2.3)	(0.5-2.6)		(0.6-2.1)	(0.7-4.5)	
Δ Rate of Perceived Exertion	1.0	0.5	n.s	0.5	0.5	n.s	1.0	0.5	n.s
(RPE)	(0-1)	(0-2)		(0.0-2.0)	(0.0-0.2)		(0.0-1.0)	(0.2-2.0)	
1-Repetition Maximum	n.a.	n.a.		n.a.	n.a.				
Crunch (number)	n.a.	n.a.		n.a.	n.a.		20 (17-22.0)	30 (23-34)	0.0002
Lat machine (kg)	n.a.	n.a.		n.a.	n.a.		50 (44-55)	58 (55-61)	0.0002
Chest press (kg)	n.a.	n.a.		n.a.	n.a.		55 (48-61)	78 (60-80)	0.0007
Leg extension (kg)	n.a.	n.a.		n.a.	n.a.		40	50	0.014

							(39-45)	(45-51)	
Leg press (kg)	n.a.	n.a.		n.a.	n.a.		207 (146-242)	240 (187-300)	0.002
Sitting calf (kg)	n.a.	n.a.		n.a.	n.a.		53 (43-55)	70 (59-75)	0.0004
Body Composition									
Anthropometrics									
Weight (kg)	75	72	0.0003	75	71	0.0001	76	74	n.s
	(65-80)	(64-78)		(63-80)	(60-77)		(71-81)	(71-79)	
BMI (kg/m^2)	25.8	25.6	0.004	25.3	24.9	0.0098	25.8	25.0	n.s
	(22.2-27.5)	(22.2-27.2)		(21.6-27.5)	(21.2-27.0)		(24.1-26.9)	(23.9-27.0)	
Waist Circumference (cm)	93	92	0.05	93	94	0.046	94	92	n.s
	(86-102)	(84-100)		(82-103)	(83-100)		(88-100)	(88-99)	
Hip Circumference (cm)	95.0	94.0	0.04	97.3	95.0	n.s	92.0	92.0	n.s
	(91.0-99.5)	(90.0-99.5)		(93.8-101.5)	(90.0-101.0)		(91.0-99.0)	(89.0-97.0)	
Leg Circumference (cm)	53.0	53.0	n.s	53.0	52.0	n.s	53.5	53.0	n.s
	(49.4-56.8)	(49.0-55.7)		(47.5-56.0)	(48.0-55.0)		(50.6-57.8)	(50.0-57.5)	
DEXA									
Arm Fat (kg)	1.7	1.7	n.s	1.7	1.7	n.s	1.4	1.6	n.s

	(1.2-2.5)	(0.9-2.6)		(1.3-3.0)	(0.9-2.7)		(0.7-1.9)	(0.9-2.6)	
Arm Fat (%)	22.4	23.3	n.s	24.3	26.5	n.s	21.2	21.3	n.s
	(15.4-29.3)	(11.2-31.4)		(16.8-35.6)	(11.7-35.5)		(13.8-26.7)	(11.2-25.9)	
Leg Fat (kg)	3.3	3.4	n.s	3.3	3.1	n.s	3.4	3.5	n.s
	(2.2-5.6)	(2.4-6.4)		(2.2-6.1)	(1.8-7.9)		(2.5-5.3)	(3.1-6.1)	
Leg Fat (%)	17.5	17.1	n.s	18.5	19.1	n.s	16.8	15.6	n.s
	(11.1-26.4)	(11.5-25.9)		(12.3-28.1)	(9.1-20.4)		(9.5-27.2)	(11.5-24.3)	
Trunk Fat (kg)	11.9	11.6	n.s	13.4	14.2	n.s	10.9	11.4	n.s
	(8.4-15.4)	(7.1-15.9)		(6.4-16.2)	(5.4-16.0)		(9.1-12.4)	(7.7-12.1)	
Trunk Fat (%)	30.8	31.8	n.s	30.9	34.6	n.s	30.4	30.2	n.s
	(24.2-38.9)	(22.2-38.9)		(21.9-39.9)	(20.9-40.1)		(25.5-36.3)	(23.1-35.3)	
Tot Fat (kg)	17.7	17.7	n.s	19.6	20.8	n.s	16.9	17.5	n.s
	(12.1-22.3)	(10.0-23.5)		(11.0-28.1)	(9.4-26.5)		(12.7-18.5)	(11.2-18.6)	
Tot Fat (%)	25.1	25.8	n.s	25.7	26.9	n.s	24.7	24.3	n.s
	(19.7-36.40)	(15.5-32.7)		(191.1-38.3)	(15.3-38.0)		(22.1-32.9)	(16.9-30.9)	
Trunk-to-Limb Fat Ratio	1.7	1.7	n.s	1.6	1.6	n.s	1.8	1.8	n.s
	(1.2-2.1)	(1.1-2.5)		(1.1-1.8)	(1.1-1.9)		(1.1-2.8)	(1.2-2.8)	

Ultrasonography									
Superficial Fat (mm)	17.0	16.0	n.s	18.0	18.7	n.s	12.0	13.0	n.s
	(11.8-28.2)	(12.0-30.3)		(12.4-29)	(13.0-32.5)		(8.0-23.5)	(9.0-18.0)	
Visceral Fat (mm)	60.0	64.0	n.s	59.0	61.0	n.s	68.0	69.0	n.s
	(52.5-75.5)	(49.8-77.8)		(46.5-70.0)	(38.5-69.5)		(57.0-83.0)	(61.0-90.0)	
Total Fat (mm)	82.0	80.0	n.s	83.5	81.0	n.s	81.5	80.0	n.s
	(70.3-97.5)	(72.5-99.5)		(70.3-102.8)	(59.0-101.5)		(68.0-93.5)	(77.0-99.0)	
Laboratory examinations									
Haemoglobin (mg/dL)	14.8	14.5	n.s	15.1	13.0	n.s	14.6	14.6	n.s
	(13.7-16.3)	(13.0-15.5)		(13.6-16.3)	(14.4-15.5)		(14.1-16.7)	(13.6-15.6)	
WBC (10^{-9}/L)	5.8	5.8	n.s	5.5	5.4	n.s	6.4	6.2	n.s
	(5.1-6.9)	(4.9-6.9)		(4.8-6.4)	(4.4-6.3)		(5.4-6.9)	(5.4-7.6)	
PLT (10^{-9}/L)	195	198	n.s	195	199	n.s	209	191	n.s
	(168-254)	(168-248)		(168-238)	(160-228)		(162-279)	(170-269)	
Creatinine (mg/dL)	0.83	0.82	n.s	0.8	0.8	n.s	0.9	0.9	n.s
	(0.76-0.92)	(0.71-0.94)		(0.7-0.9)	(0.6-0.9)		(0.8-1.0)	(0.8-1.0)	
AST (U/l)	23	19	n.s	23	20	n.s	22	19	n.s
	(16-29)	(16-33)		(15-32)	(14-34)		(15-27)	(17-31)	

ALT (U/l)	36	31	n.s	33	30	n.s	38	32	n.s
	(22-53)	(22-44)		(22-53)	(20-43)		(21-57)	(26-46)	
Total Cholesterol (mg/dL)	196	186	0.018	190	180	0.042	217	191	n.s
	(163-236)	(162-215)		(157-229)	(151-214)		(174-237)	(165-232)	
HDL-Cholesterol (mg/dL)	46	47	n.s	47	48	0.012	46	45	n.s
	(34-54)	(36-56)		(36-53)	(37-55)		(33-56)	(35-59)	
LDL-Cholesterol (mg/dL)	124	108	0.002	121	103	0.025	147	121	0.031
	(106-155)	(93-139)		(98-151)	(88-138)		(119-164)	(106-144)	
Triglycerides (mg/dL)[b]	143	131	n.s	142	112	n.s	137	165	n.s
	(111-201)	(93-200)		(101-222)	(80-205)		(107-210)	(121-283)	
Glucose (mg/dL)	85	82	n.s	85	81	n.s	86	82	n.s
	(78-92)	(79-93)		(74-92)	(79-92)		(80-93)	(78-93)	
Insulin (mg/dL)	11.8	13.0	n.s	10.2	13.8	n.s	13.1	10.3	n.s
	(7.9-16.5)	(8.0-16.9)		(5.8-17.0)	(6.6-17.2)		(9.9-15.2)	(8.6-18.8)	
HOMA-Index	2.8	2.7	n.s	2.3	2.8	n.s	3.0	2.3	n.s
	(1.6-3.4)	(1.7-4.1)		(0.9-3.7)	(1.2-4.1)		(2.1-3.3)	(1.8-5.0)	
HbA1c (%)[a]	5.3	5.5	0.040	5.2	5.3	n.s	5.5	5.5	n.s
	(5.1-5.8)	(5.3-5.6)		(5.0-5.7)	(5.1-5.6)		(5.3-5.9)	(5.5-6.0)	
CD4+ T-cells/µL	577	559	n.s	485	557	n.s	642	587	n.s
	(407-726)	(445-715)		(365-686)	(365-684)		(527-740)	(481-796)	

CD8+ T-cells/µL	821	747	n.s	766	743	n.s	916	747	n.s
	(652-914)	(566-975)		(581-872)	(632-950)		(783-1349)	(561-1090)	
VACS index	12	12	n.s	16	17	n.s	9	10	n.s
	(5-19)	(0-21)		(6-24)	(3-22)		(0-12)	(0-18)	

Table 10. Phyisical fitness, body composition and laboratory values at baseline (BL) and week-12 (W12). Values are expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test. HR, heart rate; □[La-], difference in lactate blood concentration between before and after 6MWT; Δ RPE, difference in Rate of Perceived Exertion between before and after 6MWT; BMI, body mass index; DEXA, Dual-energy X-ray absorptiometry; HOMA, Homeostasis Model Assessment; VACS, Veterans Ageing Cohort Study.

	Women (n=9)			Men (n=12)		
	BL	W12	p	BL	W12	p
Body composition						
Anthropometry						
Weight (kg)	65 (54-79)	62 (53-76)	n.s	77 (69-82)	72 (63-81)	0.004
BMI (kg/m^2)	24.7 (21.5-28.7)	24.0 (21.3-28.5)	n.s	25.3 (21.6-27.5)	24.9 (21.2-27.0)	n.s
Waist circumference (cm)	93.0 (82.0-106.0)	98.0 (80.0-100.0)	n.s	93.0 (82.5-102.5)	92.0 (84.0-99.0)	n.s
Hip circumference (cm)	100.0 (90.0-110)	100.0 (90.0-107.0)	n.s	97.0 (94.0-98.0)	95.0 (90.0-98.0)	n.s
Leg circumference (cm)	54.0 (48.0-59.0)	55.0 (47.0-56.0)	n.s	53.0 (44.0-55.0)	51.5 (48.3-53.8)	n.s
Ultrasonography						
Superficial fat (mm)	29.0 (16.0-36.5)	24.5 (14.3-37)	n.s	17.5 (12.0-19.9)	18.7 (12.0-30.5)	n.s
Visceral fat (mm)	59.0 (37.0-68.5)	52.5 (36.8-69.0)	n.s	59.0 (51.0-99.0)	65.0 (44.5-74.0)	n.s
Total Fat (mm)	83.0 (60.0-100.5)	76.0 (53.0-106.3)	n.s	84.0 (70.0-118.0)	85.0 (68.5-101.5)	n.s
DEXA						
Arm Fat (kg)	3.1 (1.3-3.9)	2.4 (1.1-3.3)	n.s	1.7 (0.6-2.5)	1.7 (0.4-2.5)	n.s
Arm Fat (%) [a]	38.5 (22.2-48.7)	38.7 (22.7-48.5)	n.s	20.0 (8.1-29.0)	20.1 (8.7-30.6)	n.s
Leg Fat (kg)	5.6 (3.1-9.8)	7.9 (2.9-10.4)	n.s	2.9 (2.1-4.1)	2.5 (1.0-4.1)	n.s
Leg Fat (%) [a]	24.5 (16.8-39.9)	21.2 (14.5-39.8)	n.s	14.4 (9.8-21.2)	17.5 (7.4-27.7)	n.s
Trunk Fat (kg)	15.4 (6.4-19.6)	12.1 (7.8-17.2)	n.s	13.3 (4.6-15.9)	14.2 (4.1-15.9)	n.s
Trunk Fat (%)	35.1 (26.7-49.8)	38.2 (28.0-42.1)	n.s	26.8 (14.2-37.2)	27.3 (14.5-40.0)	n.s

Tot Fat (kg)	27.8 (11.4-34.9)	22.9 (12.7-32.1)	n.s	18.6 (9.3-22.3)	20.8 (5.8-21.9)	n.s
Tot Fat (%) [a]	39.7 (26.9-48.1)	36.0 (26.3-46.0)	n.s	23.6 (13.1-30.4)	25.3 (11.0-31.1)	n.s
Trunk-to-limb % fat ratio	1.3 (1.1-1.8)	1.5 (1.1-2.1)	n.s	1.7 (1.4-2.0)	1.6 (1.0-2.3)	n.s
Laboratory exams						
Haemoblobin (mg/dL) [a]	13.1 (11.9-14.2)	13.0 (12.0-14.0)	n.s	16.2 (14.9-16.4)	15.1 (14.2-15.9)	n.s
WBC (10-9/L)	5.1 (4.6-8.1)	5.3 (4.4-7.0)	n.s	5.6 (5.1-5.9)	5.5 (4.3-6.3)	n.s
PLT (10-9/L)	215 (169-294)	195 (174-271)	n.s	188 (155-230)	200 (125-220)	n.s
Creatinine (mg/dL) [a]	0.67 (0.64-0.77)	0.65 (0.58-0.69)	n.s	0.84 (0.78-0.92)	0.81 (0.75-0.94)	n.s
AST (U/l)	20.0 (9.0-22.0)	19.0 (12.5-31.0)	n.s	29.0 (18.0-51.0)	22.0 (14.0-37.0)	n.s
ALT (U/l)	25.0 (18.0-36.0)	23.0 (16.0-36.0)	n.s	47.0 (22.0-66.0)	42.0 (26.0-70.0)	n.s
Total Cholesterol (mg/dL)	180 (156-287)	197 (155-239)	n.s	196 (155-227)	180 (150-201)	n.s
HDL (mg/dL)	51 (41-72)	55 (44-63)	n.s	37 (32-51)	37 (31-48)	n.s
LDL (mg/dL)	112 (88-158)	94 (92-191)	n.s	119 (94-149)	104 (78-128)	0.045
Triglycerides (mg/dL)	95 (59-210)	102 (73-114)	n.s	158 (123-258)	148 (87-260)	n.s
Glucose (mg/dL)	81 (71-92)	79 (75-89)	n.s	85 (78-97)	88 (80-93)	n.s
Insulin (mg/dL)	8.1 (5.8-16.2)	13.6 (5.6-23.0)	n.s	13.8 (5.4-17.4)	14.3 (7.2-16.7)	n.s
HOMA index	1.6 (1.0-3.9)	2.8 (1.0-4.6)	n.s	2.8 (0.8-3.8)	2.9 (1.5-3.9)	n.s
HbA1c (%)	5.1 (5.2-5.9)	5.3 (5.3-5.6)	n.s	5.1 (5.0-5.6)	5.4 (5.0-5.6)	n.s
CD4+ T cells/µL [a]	646 (428-898)	566 (426-855)	n.s	435 (335-570)	548 (315-630)	n.s
CD8+ T cells/µL	698 (550-862)	842 (674-1005)	n.s	776 (615-893)	696 (502-884)	n.s

VACS	15 (10-28)	21 (11-22)	n.s	16 (6-18)	16 (0-18)	n.s

Table 11. Body composition and laboratory values at baseline (BL) and week-12 (W12) in the walk group divided by gender.
Values as expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test.
a. At BL, women had higher % of fat in the arm (p=0.015), leg (p=0.034) and as total (p=0.017), lower haemoglobin (p=0.002) and creatinine levels (p=0.008), and higher CD4 cell counts (p=0.009)(Mann-Whitney test).
BMI, body mass index; DEXA, Dual-energy X-ray absorptiometry; HOMA, Homeostasis Model Assessment; VACS, Veterans Ageing Cohort Study.

	All (n=25)			Walk (n=17)			Strength-Walk (n=8)		
	BL	**W12**	**p**	**BL**	**W12**	**p**	**BL**	**W12**	**p**
Total Cholesterol (mg/dL)	202 (178-235)	193 (173-214)	0.003	190 (157-229)	180 (151-214)	0.042	234 (202-236)	194 (191-232)	0.010
HDL-C (mg/dL)	47 (36-55)	48 (39-56)	0.016	47 (36-53)	48 (37-55)	0.012	49.0 (41.8-60.5)	53.0 (46.0-64.0)	n.s
LDL-C (mg/dL)	147 (110-161)	121 (93-146)	0.002	121 (98-151)	103 (88-138)	0.025	156 (147-172)	144 (121-150)	0.002

Table 12. Values of cholesterol at baseline (BL) and week-12 (W12) in patients untreated with statins. Values are expressed as median (Q1-Q3). W12 values were compared to BL values by the Wilcoxon matched-pairs signed rank test.

Discussion

This pilot study explored the efficacy of three days per week, 12-week program of brisk walking, with or without strength exercise, on metabolic and inflammatory markers in sedentary cART-treated persons with metabolic complications. We observed, in parallel with improvement of physical fitness and of some morphometric measures, substantial improvements of cholesterol profiles and inflammatory markers. Many of the changes were observed in both training groups and, within the walk group, most changes did not differ substantially between women and men.

From a clinical standpoint, a remarkable observation was the general reduction of total cholesterol, the reduction of LDL cholesterol in both training groups, and the increase of HDL among statin-untreated participants. Total, HDL and LDL cholesterol are each independent strong predictors of CVD in the general population and elevated LDL is the primary target for cholesterol-lowering therapy (Stone et al., 2014). In HIV-infected persons, higher total and lower HDL cholesterol were independently associated with CVD (Friis-Møller et al., 2010). While high intensity aerobic exercise is followed by favourable cholesterol alterations, the influence of moderate intensity aerobic and of resistance training is not clearly evidence-supported (Tambalis et al., 2009).

Only a few studies have examined the effects of exercise on blood lipids in HIV infection, with inconsistent outcomes, likely resulting from large variability of populations and exercise interventions (Fillipas et al., 2010; O'Brien et al., 2010; Lindegaard et al., 2008). Our findings, indicating that moderate exercise may reduce blood cholesterol in HIV infection, support exercise interventions prior to use of cholesterol lowering drugs (Stone et al., 2014).

In contrast, we observed no improvement in glucose or insulin level. Functional tests in the general population and HIV-positive patients showed that exercise improves insulin resistance, but often without changes of glucose, insulin or glycate haemoglobin level

(Lindegaard et al., 2008). It is thus possible that, at the exercise intensity of this protocol, blood static markers did not accurately reflect exercise-induced benefit on glucose control.

Because the HRmean during the training session was set in the so-called fat-burning zone, the observed weight reductions were not unexpected. However, BMI and waist circumference reductions were less marked in the strength-walk group, likely resulting from increase of muscle mass, and thus of total weight, following strength exercise. In addition, there was no significant change in body fat by DEXA or ultrasounds examination. Since we prescribed no specific diet, the limited effect of exercise on body fat might reflect an unbalanced caloric intake following exercise. It is also possible that 12 weeks of brisk walking was not sufficient to reduce visceral fat, similar to what observed in obese subjects with type-2 diabetes or dyslipidaemia, likely resulting from a reduced capacity of fat oxidation (Ohkawara et al., 2007; Kelley et al., 1994). Remarkably, also HIV-negative patients with different chronic conditions experienced favourable and consistent effects of exercise on metabolic or inflammatory markers, primarily hsCRP, despite no effect on weight loss (Beavers et al., 2010).

cART-controlled chronic HIV infection is associated with increased inflammation and coagulation (Neuhaus et al., 2011; Lederman et al. 2013; Deeks et al., 2013), and higher plasma levels of hsCRP, IL-6 and D-dimer strongly predicted higher overall mortality and cardiovascular events (Kuller et al., 2008; Duprez et al., 2012). Beyond cART, a number of interventions are in use, e.g., statins, or proposed, to treat inflammation (Klatt et al., 2013). However, the anti-inflammatory effect of exercise in HIV infection has been rarely addressed in clinical studies. Reductions of hsCRP, IL-6, TNF-□ and IL-18 were observed in a 16-week study of aerobic or resistance training performed at variable intensity (Lindegaard et al., 2008), but no of IL-6 after 6 weeks of aerobic plus resistance moderate intensity exercise (Dudgeon et a., 2012). Our study showed substantial reductions of

hsCRP, IL-6, D-dimer, IL-18 and myostatin following 12-weeks of moderate intensity exercise.

In HIV-negative subjects, longitudinal studies have demonstrated exercise-induced changes of plasma inflammatory markers. These have largely focused on hsCRP and IL-6, showing more marked reductions in subjects with higher baseline levels, but no or low effect in healthy persons (Beavers et al., 2010; Nimmo et al., 2013). A small number of studies of old healthy and diabetic subjects have shown plasma reductions of IL-18, a cytokine released by adipocytes among other cell types (Kohut et al., 2006; Kadoglou et al., 2006), whereas myostatin expression in muscle tissue was found to be reduced in obese elderly following aerobic exercise (Ryan et al., 2013). No information is available on the effect of exercise on D-dimer levels, although levels of other coagulation markers have improved following exercise (Lockard et al., 2007). Our findings extend previous observations on the effect of exercise on plasma hsCRP, IL-6 and IL-18 to patients with HIV infection and following moderate exercise. In addition, we disclose a beneficial effect of exercise on plasma D-dimer and myostatin, a myokine secreted by the muscle during exercise. Myostatin may represent a homeostasis marker in HIV infection, because its inhibition increases muscle mass and, according to recent studies, also bone mass, while reducing fat tissue (Buehring et al., 2013). In contrast to the above markers, we did not observe changes of sCD14, a microbial translocation marker and independent predictor of mortality in chronic HIV infection (Sandler et al., 2011). Similarly, plasma levels of lipopolysaccharide (LPS) were not reduced by 16 weeks of endurance or strength interventions (Trøseid et al., 2014). Thus, effects on microbial translocation seem unlikely to mediate exercise-induced inflammatory alterations.

The frequency of CD8+/CD38+/HLA-DR+ activated T-cells decreased significantly following exercise in both training groups. The effect of physical exercise on T-cell activation is unknown, with no change shown by one study in HLA-DR expression on

CD3+ or CD8+ T-cells in HIV-negative elderly following exercise [34]. Unlike soluble markers, CD8+ T-cell activation is considered a poor predictor of mortality in treated HIV infection (Hunt et al., 2014). Recently, higher proportions of CD8+/CD38+ cells have been reported in patients with visceral fat accumulation (Guaraldi et al., 2013) and of both CD4+ and CD8+ CD38+/HLA-DR+ cells in women with subclinical carotid artery disease (Kaplan et al., 2001). However the predictive value of T-cell activation in non-AIDS comorbidities remains controversial (Tenorio et al., 2014). Our findings suggest that decreased T-cell activation may contribute to mediate exercise-induced health benefit, although the clinical significance of these observations remains to be established.

The interpretation of the effect of different exercise programs on inflammatory markers was limited by the small sample size of training groups. For the same reason, comparison of inflammatory changes between women and men within the walk group was not possible. Of note, however, reductions of hsCRP and CD8+/CD38+/HLA-DR+ cells were observed in both training groups, likely reflecting high sensitivity of these markers to exercise. Although we could not well dissect the effects of aerobic versus strength exercise, we observed that IL-6 and D-dimer did not improve in the strength-walk group. Similarly, a program of strength exercise alone did not improve plasma hsCRP or IL-6 in a previous study of HIV-infected subjects (Lindegaard et al., 2008). It is thus possible that resistance and aerobic exercise affect inflammation in different ways (Beavers et al., 2010, Lindegaard et al., 2008). We also observed a selective reduction of myostatin in the strength walk participants, which may either suggests a specific effect of strength exercise on myostatin expression, or reflect the greater total exercise load in this training group.

Two main mechanisms have been suggested to mediate the effect of exercise on inflammation in the general population. First, the reduction of fat mass following physical activity may promote an anti-inflammatory environment via reduced infiltration of immune cells in the adipose tissue and release of adipokines, including pro-inflammatory cytokines

(Van Gaal et al., 2006). In addition, contracting skeletal muscle secretes molecules with immune modulatory effects, including the so-called myokines, most notably IL-6, which mediates metabolic changes during exercise. While single bouts of exercise induce an increase of IL-6 and other cytokines, regular exercise with repeated bouts may induce an anti-inflammatory environment, with lower basal levels of inflammatory markers over time (Lederman et al., 2013). Compared to the general population, inflammation in HIV infection may be caused or enhanced by specific conditions, including persisting low-level HIV replication, chronic co-infections, and ART induced altered lipid and metabolic profiles (Nimmo et al., 2013), suggesting that additional mechanisms may mediate and perhaps enhance the effects of exercise on inflammation.

This study has some limitations. First, we did not include a non-exercise control group. However, there were no changes of medications, including lipid-lowering drugs, in the weeks before or during the training period, which may have affected study outcomes. Second, assignment to either training protocol was not randomized, but subject's own decision, because groups exercised in different places at different day times. While this favoured recruitment of participants, it resulted in an unbalanced women distribution between training groups. Also, the relatively small sample size of subgroups, and consequent low statistical power, did not allow drawing firm conclusions on efficacy of different exercise programs. Finally, dietary intake was not restricted, which also might have affected study outcomes. In conclusion, brisk walking was associated with significant improvement of soluble and cell inflammatory markers and cholesterol profile in sedentary patients with HIV infection and metabolic problems. This pilot study provides potentially relevant information for the design of larger controlled studies of moderate physical exercise as treatment of HIV-related chronic immune activation.

REFERENCES

Agin D, Gallagher D, Wang J, Heymsfield SB, Pierson RN Jr, Kotler DP. Effects of whey protein and resistance exercise on body cell mass, muscle strength, and quality of life in women with HIV. AIDS. 2001 Dec 7;15(18):2431-40.

Ahmad B, Glufke K1, Grau M1, Sandig D2, Rockstroh J3, Vogel M3, Wasmuth JC3, Bloch W1, Brixius K1. Influence of endurance training and marathon running on red cell deformability in HIV patients. Clin Hemorheol Microcirc. 2014;57(4).

Anuurad E, Semrad A, Berglund L. Human immunodeficiency virus and highly active antiretroviral therapy-associated metabolic disorders and risk factors for cardiovascular disease. Metab Syndr Relat Disord. 2009;7(5):401–410.

American Toracic Society (ATS) Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166:111-7.

Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. Clin Chim Acta 2010; 411:785-93.

Borg, G. A. (1982). Psychophysical bases of perceived exertion. Medicine and Science in Sports and Exercise, 14, 377 – 381.

Borg G. Borg's perceived exertion and pain scales. Champaign, IL: Human Kinetics, 1998.

Broholm C, Mathur N, Hvid T, Grøndahl TS, Frøsig C, Pedersen BK, Lindegaard B. Insulin signaling in skeletal muscle of HIV-infected patients in response to endurance and strength training. Physiol Rep. 2013 Aug;1(3).

Buehring B, Binkley N. Myostatin – The Holy Grail for muscle, bone, and fat? Curr Osteoporos Rep 2013; 11:407-14.

Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet. 1998;351(9119):1881–1883.

Collaboration ATC. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008;372:293–299.

Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet. 2013; 382:1525-33.

Dolan SE, Frontera W, Librizzi J, Ljungquist K, Juan S, Dorman R, Cole ME, Kanter JR, Grinspoon S. Effects of a supervised home-based aerobic and progressive resistance training regimen in women infected with human immunodeficiency virus: a randomized trial. Arch Intern Med. 2006 Jun 12;166(11):1225-31.

Driscoll SD, Meininger GE, Lareau MT, Dolan SE, Killilea KM, Hadigan CM, Lloyd-Jones DM, Klibanski A, Frontera WR, Grinspoon SK. Effects of exercise training and metformin on body composition and cardiovascular indices in HIV-infected patients. AIDS. 2004 Feb 20;18(3):465-73.

Driscoll SD, Meininger GE, Ljungquist K, Hadigan C, Torriani M, Klibanski A, Frontera WR, Grinspoon S. Differential effects of metformin and exercise on muscle adiposity and metabolic indices in human immunodeficiency virus-infected patients. J Clin Endocrinol Metab. 2004 May;89(5):2171-8.

Dudgeon WD, Jaggers JR, Phillips KD, Durstine JL, Burgess SE, Lyerly GW, Davis JM, Hand GA. Moderate-Intensity Exercise Improves Body Composition and Improves

Physiological Markers of Stress in HIV-Infected Men. ISRN AIDS. 2012 Dec 11;2012:145127.

Duprez DA, Neuhaus J, Kuller LH, et al.; INSIGHT SMART Study Group. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS One 2012; 7:e44454.

Engelson ES, Agin D, Kenya S, Werber-Zion G, Luty B, Albu JB, Kotler DP. Body composition and metabolic effects of a diet and exercise weight loss regimen on obese, HIV-infected women. Metabolism. 2006 Oct;55(10):1327-36.

Ezema CI, Onwunali AA, Lamina S1, Ezugwu UA, Amaeze AA, Nwankwo MJ. Effect of aerobic exercise training on cardiovascular parameters and CD4 cell count of people living with human immunodeficiency virus/acquired immune deficiency syndrome: a randomized controlled trial. Niger J Clin Pract. 2014 Sep-Oct;17(5).

Farinatti PT, Borges JP, Gomes RD, Lima D, Fleck SJ. Effects of a supervised exercise program on the physical fitness and immunological function of HIV-infected patients. J Sports Med Phys Fitness. 2010 Dec;50(4):511-8.

Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation. 2001 Oct 2;104(14):1694-740.

Fox SM 3rd, Naughton JP, Haskell WL. Physical activity and the prevention of coronary heart disease. Ann Clin Res. 1971 Dec;3(6):404-32.

Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, et al.; DAD study group. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil 2010; 17:491-501.

Fillipas S, Cherry CL, Cicuttini F, Smirneos L, Holland AE. The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a systematic review of randomised controlled trials. HIV Clinical Trials 2010; 11:270-82.

Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al.; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011; 43:1334-59

Garcia A, Fraga GA, Vieira RC Jr, Silva CM, Trombeta JC, Navalta JW, Prestes J, Voltarelli FA. Effects of combined exercise training on immunological, physical and biochemical parameters in individuals with HIV/AIDS. J Sports Sci. 2014;32(8):785-92.

Global report: UNAIDS report on the global AIDS epidemic 2013. “UNAIDS / JC2502/1/E”- Revised and reissued, November 2013

Grinspoon S, Carr A. Cardiovascular risk and body fat abnormalities in HIV-infected adults. N Engl J Med. 2005;352(1):48–62.

Grund B, Peng G, Gibert CL, et al. Continuous antiretroviral therapy decreases bone mineral density. AIDS (Lond). 2009;23(12):1519–1529.

Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. Premature agerelated comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis 2011; 53:1120-6.

Guaraldi G, Luzi K, Bellistrì GM, Zona S, Domingues da Silva AR, Bai F, et al. CD8 Tcell activation is associated with lipodystrophy and visceral fat accumulation in antiretroviral therapy-treated virologically suppressed HIV-infected patients. J Acquir Immune Defic Syndr 2013; 64:360-6.

Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 14:860-7

Hunt PW, Sinclair E, Rodriguez B, Shive C, Clagett B, Funderburg N, et al. Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection. J Infect Dis. 2014 Apr 21. [Epub ahead of print]

Justice AC, Modur SP, Tate JP, Althoff KN, Jacobson LP, Gebo KA, et al. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. J Acquir Immune Defic Syndr 2013; 62:149-63.

Kadoglou NP, Iliadis F, Angelopoulou N, Perrea D, Ampatzidis G, Liapis CD, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. Eur J Cardiovasc Prev Rehabil 2007; 14:837-43.

Kelley DE, Simoneau JA. Impaired free fatty acid utilization by skeletal muscle in noninsulin-dependent diabetes mellitus. J Clin Invest 1994; 94:2349-56.

Klatt NR, Chomont N, Douek DC, Deeks SG. Immune activation and HIV persistence: implications for curative approaches to HIV infection. Immunol Rev 2013; 254:326-42.

Kohut ML, McCann DA, Russell DW, Konopka DN, Cunnick JE, Franke WD, et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. Brain Behav Immun 2006; 20:201-9.

Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med 2008; 5:e203.

Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. Advances in immunology 2013; 119:51 83.

Lindegaard B, Hansen T, Hvid T, van Hall G, Plomgaard P, Ditlevsen S, Gerstoft J, Pedersen BK. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-infected patients with lipodystrophy. J Clin Endocrinol Metab. 2008 Oct;93(10).

Lockard MM, Gopinathannair R, Paton CM, Phares DA, Hagberg JM. Exercise traininginduced changes in coagulation factors in older adults. Med Sci Sports Exerc 2007; 39:587-92.

Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. Diabetes Obes Metab 2013; 15 Suppl 3:51-60.

O'Brien K, Nixon S, Tynan AM, Glazier R. Aerobic exercise interventions for adults living with HIV/AIDS. Cochrane Database Syst Rev 2010; 8:CD001796.

Ohkawara K, Tanaka S, Miyachi M, Ishikawa-Takata K, Tabata I. A dose-response relation between aerobic exercise and visceral fat reduction: systematic review of clinical trials. Int J Obes (Lond) 2007; 31:1786-97.

Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and among patients with advanced human immunodefi ciency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338(13):853–860.

Palmisano L, Vella S. A brief history of antiretroviral therapy of HIV infection: success and challenges. Ann Ist Super Sanita. 2011;47(1):44-8.

Robinson FP, Quinn LT, Rimmer JH. Effects of high-intensity endurance and resistance exercise on HIV metabolic abnormalities: a pilot study. Biol Res Nurs. 2007 Jan;8(3):177-85.

Roubenoff R, Weiss L, McDermott A, Heflin T, Cloutier GJ, Wood M, Gorbach S. A pilot study of exercise training to reduce trunk fat in adults with HIV-associated fat redistribution. AIDS. 1999 Jul 30;13(11):1373-5.

Roubenoff R, Wilson IB. Effect of resistance training on self-reported physical functioning in HIV infection. Med Sci Sports Exerc. 2001 Nov;33(11):1811-7.

Ryan AS, Li G, Blumenthal JB, Ortmeyer HK. Aerobic exercise + weight loss decreases skeletal muscle myostatin expression and improves insulin sensitivity in older adults. Obesity (Silver Spring) 2013; 21:1350-6.

Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, et al; INSIGHT SMART Study Group. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis 2011; 203:780-90.

Schwenk A. Methods of assessing body shape and composition in HIV-associated lipodystrophy. Curr Opin Infect Dis 2002; 15:9-16.

Souza PM, Jacob-Filho W, Santarém JM, Zomignan AA, Burattini MN. Effect of progressive resistance exercise on strength evolution of elderly patients living with HIV compared to healthy controls. Clinics (Sao Paulo). 2011;66(2):261-6.

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129 (Suppl 2):S1-45.

Tambalis K, Panagiotakos DB, Kavouras SA, Sidossis LS. Responses of blood lipids to aerobic, resistance, and combined aerobic with resistance exercise training: a systematic review of current evidence. Angiology 2009; 60:614-32.

Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol 2001; 37:153-6.

Tenorio AR, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B3, Hunt PW, et al. Soluble markers of inflammation and coagulation, but not T-cell activation, are predictors of non-AIDS-defining morbid events during suppressive antiretroviral treatment. J Infect Dis. 2014 May 1. [Epub ahead of print]

Terry L, Sprinz E, Stein R, Medeiros NB, Oliveira J, Ribeiro JP. Exercise training in HIV-1-infected individuals with dyslipidemia and lipodystrophy. Med Sci Sports Exerc. 2006 Mar;38(3):411-7.

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106:3143-421.

Thöni GJ, Fedou C, Brun JF, Fabre J, Renard E, Reynes J, Varray A, Mercier J. Reduction of fat accumulation and lipid disorders by individualized light aerobic training in human immunodeficiency virus infected patients with lipodystrophy and/or dyslipidemia. Diabetes Metab. 2002 Nov;28(5):397-404.

Torti C1, Mazziotti G, Soldini PA, Focà E, Maroldi R, Gotti D, Carosi G, Giustina A. High prevalence of radiological vertebral fractures in HIV-infected males. Endocrine. 2012 Jun;41(3):512-7.

Trøseid M, Ditlevsen S, Hvid T, Gerstoft J, Grøndahl T, Pedersen BK, Nielsen SD, Lindegaard B. Reduced trunk fat and triglycerides after strength training are associated with reduced LPS levels in HIV-infected individuals. J Acquir Immune Defic Syndr 2014; 66:e52-4.

Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006; 444:875-80.

Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. Cold Spring Harb Perspect Med. 2011 Sep;1(1)

Walker Harris V, Brown TT. Bone loss in the HIV-infected patient: evidence, clinical implications, and treatment strategies. J Infect Dis. 2012 Jun;205 Suppl 3:S391-8.

Yarasheski KE, Tebas P, Stanerson B, Claxton S, Marin D, Bae K, Kennedy M, Tantisiriwat W, Powderly WG. Resistance exercise training reduces hypertriglyceridemia in HIV-infected men treated with antiviral therapy. J Appl Physiol (1985). 2001 Jan;90(1):133-8.

SITOGRAPHY

Averting HIV and AIDS: http://www.avert.org

Associazione NADIR onlus: http://www.nadironlus.org

Anlaids onlus: http://www.anlaidsonlus.it

APPENDIX

Side Scientific Production

Papers

Peer-review Journals

Bonato M, Maggioni MA, Rossi C, Rampichini S, La Torre A, Merati G. Relationship between anthropometric or functional characteristics and maximal serve velocity in professional tennis players. J Sports Med Phys Fitness. 2014 Jul 7. [Epub ahead of print]

Piacentini MF, Comotto S, Guerriero A, Bonato M, Vernillo G, La Torre A. Does the junior IAAF athletic world championship represent a springboard for the success in the throwing events? A retrospective study. J Sports Med Phys Fitness 2014;54:410-6

Bonato M, Rampichini S, Ferrara M, Benedini S, Sbriccoli P, Merati G, Franchini E, La Torre A. Aerobic training program for the enhancements of HR and VO2 off-kinetics in elite judo athletes. J Sports Med Phys Fitness. 2014 Oct 30. [Epub ahead of print]

Pugliese L, La Torre A, Pavei G, Bonato M, Porcelli S. Cardiovascular and metabolic responses at rest and to exercise during 48 hour of head-out immersion: a case report. Sport Sci Health (2011) 6:51-66

Under review on peer reviewed journals

Bonato M, Longo V, Galli L, Bossolasco S, Pavei G, Bertocchi C, Cernuschi M, Balconi G, Lazzarin A, Merati G, La Torre A, Cinque P. A pilot study of brisk walking in sedentary cART-treated patients: benefits on soluble and cell inflammatory markers. HIV medicine.

Pugliese L, Porcelli S, Bonato M, Pavei G, La Torre A, Maggioni AM, Bellistri G, Marzorati M. Effects of manipulating volume and intensity training in master swimmers. International Journal of Sport Physiology and Performance

Pizzuto F, Bonato M, Vernillo G, La Torre A. Piacentini MF. Dropout rate of the World Junior Championship finalists for middle and long distance events. European Journal of Sports Science

No peer review journals

Arcelli E, Bianchi A, Tebaldini J, Bonato M, La Torre A. Energy Production in the 800m. News Studies in Athletics, 27:3; 1, 2012.

Guerriero A, Comotto S, Bonato M, La Torre A, Piacentini MF. Tasso di abbandono fra i lanciatori finalisti dei campionati mondiali juniores. Atleticastudi 3-4/2011

La Torre A, Bonato M. Riconoscere il Talento. Sport&Medicina, 3, maggio-giugno 2012

Arcelli E, Sassi F, Bonato M. L'intervento dei tre meccanismi energetici negli 800 metri dell'atletica leggera. Nuova Atletica n. 233-234 (2012)

Bravin M, Bonato M, Vago P. Il nuovo sistema di giudizio nel pattinaggio di figura su ghiaccio. SdS/Scuola dello Sport Anno XXXI n. 95 (2012)

Lanzieri L, Bonato M. MyAgonism. Agonisti si diventa: un social netsporting potrebbe facilitare l'avvicinamento allo sport? SdS/Scuola dello Sport Anno XXXII n.97 • 2013

Pugliese L, Bosio D, Benis R, Bonato M, La Torre A. Il core training in pratica. Esercizi e progressioni di base per l'allenamento del core. SdS/Scuola dello Sport Anno XXXII n.97 • 2013

Pizzuto F, Comotto S, Bonato M, La Torre A, Piacentini MF. Tasso di abbandono fra i mezzofondisti finalisti dei campionati mondiali juniores. Atletica Studi, Anno 44, n 1-2 gennaio-giugno 2013.

Bonato M, Gobbo S, Invernizzi PL, La Torre A. La capacità di reazione motoria e i fattori che la influenzano. SDS/Scuola dello Sport, Anno XXXIII n.102, 2014

Congress Experience

Invited Oral Presentation

12th April 2014. Benefits of moderate intensity training in HIV infected patients. Sport & University Forum, organised by Università degli Studi di Milano

Bonato M, Bossolasco S, Galli L, Pavei G, Testa M, Bertocchi C, Galvano E, Balconi G, Lazzarin A, Giampiero M, La Torre A, Cinque P. Brisk walking as moderate aerobic exercises, increases bone density in cART-treated persons. 6° workshop nazionale CISAI.

Oral Presentations

Bonato M, Bossolasco S, Galli S, Pavei G, Merati G, La Torre A, Cinque P. Increases of bone density in cART-treated persons after 12 weeks of brisk walking. Sport Sci Health (2012) 8 (Suppl 1): S1-S70.

Bonato M, Bossolasco S, Galli L, Mandola S, Pavei G, Testa M, Bertocchi C, Galvano E, Balconi G, Lazzarin A, Merati G, La Torre A, Cinque P. Brisk walking increase bone mineral density in cART-patients. European College of Sport Sciences, 27-29 June 2013, Barcelona (Spa).

Pugliese L, Armellini D, Bonato M, La Torre A. Physical fitness and academic performance in high-scholl students. Sport Sci Health (2013) 9 (Suppl 1): S1-S94

Bonato M, Longo V, Pavei G, Bossolasco S, Balconi. G, Rubinacci A, Testa M, Bertocchi C, Galvano E, Lazzarin A, Merati G, La Torre A, Cinque P. A 12-week program of moderate intensity exercise reduces plasma myostatin in HIV-infected subjects. Sport Sci Health (2013) 9 (Suppl 1): S1-S94.

Longo V, Bonato M, Galli L, Bossolasco S, Pavei G, Passeri L, Merati G, Lazzarin A, La Torre A, Cinque p. Brisk Walking Improves Inflammatory Markers in cART-Treated

Patients. Conference on Retroviruses and Opportunistic Infections, 3-6 March 2014, Boston (USA).

Bonato M, Longo V, Bossolasco S, Pavei G, Galli L, Merati G, La Torre A, Cinque P. A Pilot study of moderate physical activity in HIV-infected persons receiving anti-HIV dugs: benefits on soluble and cell markers of inflammation. Book of Abstracts of the 19th Annual Congress of the European College of Sport Science – 2nd - 5th July 2014, Amsterdam – The Netherlands. ISBN 978-94-622-8477-7.

Bonato M, Longo V, Bossolasco S, Pavei G, Merati G, La Torre A, Cinque P. Benefits of briskwalking on soluble and cell markers of inflammation in HIV-infected persons receiving anti HIV drugs: a pilot study. Sport Sci Health (2014) 10 (Suppl 1).

Poster Presentations

Bonato M, La Torre A, Bossolasco S, Pavei G, Merati G, Galli L, Cinque P. The practice of fitwalking® in people with HIV infection receiving antiretroviral treatment. 3rd National Congress at Scuola Italiana delle Scienze Motorie e Sportive 29th Sept – 1st Oct 2011, Verona (Italy).

Bonato M., Bossolasco S., Galli L., Pavei G., Cernuschi M., Cuomo M., Lazzarin A., Merati G., La Torre A., Cinque P. Moderate aerobic exercise in cART-treated persons improved metabolic markers and increases bone density. 4° Italian conference on AIDS and Retroviruses, 2012, Naples (Italy).

Merati G, La Torre A, Bonato M, Pavei G, Bossolasco S, Galli L, Cinque P. Parasympathetic tone and its adaptations to aerobic training (Fitwalking®) in HIV patients on anti-retroviral theraphy. American College of Sport Medicine Congress, 2012, San Francisco (USA).

Porcelli S, Pugliese L, Rejc E, Pavei G, Bonato M, La Torre A, Marzorati M, Marconi C. Did Popeye® know something about nitrates? American College of Sport Medicine Congress, 2012, San Francisco (USA).

Bonato M, La Torre A, Bossolasco S, Pavei G, Merati G, Galli L, Cinque P. What are the benefits of physical exercise in people living with HIV infection? European College of Sport Sciences Congress, 4th-7th Jul 2012, Bruges (Bel).

Nonis D, La Torre A, Bonato M, Gerzevic M. Exercise intensity and inflammation markers during an ultra-cycling event: a case study. Sport Sci Health (2012) 8 (Suppl 1): S1-S70.

Pugliese L, Bonato M, Bellistri G, La Torre A, Marzorati M, Maggioni M, Parisi A, Pigozzi F, Porcelli S. High-volume and high-intensity training in master swimmers. Sport Sci Health (2012) 8 (Suppl 1): S1-S70.

Bonato M, Bossolasco S, Galli L, Pavei G, Testa M, Bertocchi C, Galvano E, Balconi G, Lazzarin A, Merati G, La Torre A, Cinque P. Moderate aerobic exercise (brisk walking) increases bone density in cART-treated persons. J Int AIDS Soc. 2012 Nov 11;15(6):18318

Bonato M, Bossolasco S, Galli L, Pavei G, Testa M, Bertocchi C, Galvano E, Balconi G, Lazzarin A, Merati G, La Torre A, Cinque P Moderate aerobic exercise (brisk walking) increases bone density in cART-treated persons. 11th International Congress on Drug Therapy in HIV, 11-15 November 2012, Glasgow (Gbr).

Porcelli S, Bellistri G, Pugliese L, Bonato M, La Torre A, Maggiorni MA, Massoni M, Marzorati M. Effect of low-volume high-intensity training on performance in master swimmers. European College of Sport Science Congress, 26th-29th June 2013, Barcelona (Spa).

Bonato M, Rospo G, Merati G, La Torre A, Agnello L Autonomic nervous systems chenges during 21 half-marathon in 21 days: a case report. Sport Sci Health (2013) 9 (Suppl 1): S1-S94.

Bonato M, Rampichini S, Benedini S, Ferrara M, Sbriccoli P, Merati G, La Torre A. High intensity interval training for the enhancement of the aerobic fitness in elite judo athletes. Sport Sci Health (2013) 9 (Suppl 1): S1-S94.

Pavei G, Porcelli S, Rejc E, Bonato M, Marzorati M, La Torre A, Pugliese L. Effects of nitrate supplementation on repeated performance in healthy subjects. Sport Sci Health (2013) 9 (Suppl 1): S1-S94.

Brentel E, Pavei G, Bonato M, La Torre A. Physical should be taught by “squadre” or “classic” methods? The students’ opinion. Sport Sci Health (2013) 9 (Suppl 1): S1-S94.

Benis R, Vignati S, La Torre A, Bonato M, Pugliese L. A Pilot study for the prevention of lower limbs injuries in youth female basketball players. Book of Abstracts of the 19th Annual Congress of the European College of Sport Science – 2nd - 5th July 2014, Amsterdam – The Netherlands. ISBN 978-94-622-8477-7

Bonato M, Papini L, La Torre A. Analysis of men world marathon record. Sport Sci Health (2014) 10 (Suppl 1).

Bonato M, Pagani C, Piacentini MF, La Torre A. Dropout rate of the finalists of the IAAF world junior Championship: analysis of the middle-long distance events. Sport Sci Health (2014) 10 (Suppl 1).

Awards

Conferimento della menzione d'onore al Premio Internazionale Edoardo Mangiarotti con la seguente motivazione:

"*Dottorando presso il Dipartimento di Scienze Biomediche per la Salute, ha catalizzato gli sforzi e le esperienze della Scuola di Scienze Motorie dell'Università degli Studi di Milano, in collaborazione con il Dipartimento di Malattie Infettive dell'Istituto Scientifico San Raffaele, creando un programma di attività fisica per sieropositivi e malati di AIDS. Un progetto che aiuta il fisico degli ammalati a reagire meglio alle cure, e soprattutto, permette loro di socializzare*".

ACKNOWLEDGEMENTS

I will write the acknowledgements in my native language, so that everyone can understand.

Questa tesi è frutto di 3 anni intensi di lavoro e ritengo quindi doveroso ringraziare tutti quelli che hanno contribuito alla riuscita di questo lungo percorso.

Innanzitutto, un doveroso ringraziamento alla mia famiglia, alla mamma Renata e al babbo Max che in questi anni, partendo dalla Laurea Triennale, mi hanno sempre supportato e sopportato in questo cammino guidandomi e spronandomi a dare il meglio per raggiungere i miei obiettivi. Sappiate che ho sempre cercato di dare il mio meglio, cercando di mettere a frutto i vostri insegnamenti al fine di essere sempre all'altezza delle vostre aspettative. Un ringraziamento ulteriore ai miei nonni Giglio, Emilia, Giuseppe e Giuseppina, anche se non siete qui oggi, vi porto sempre nel mio cuore.

Un immenso grazie a tutte le cavie che hanno partecipato a questo studio, grazie di esservi buttati con entusiasmo in questa pazza idea e per aver portato a termine con successo il programma di allenamento.

Data la complessa organizzazione di questa ricerca un sentito ringraziamento a tutti quei scienziati motori e ormai dottori, Marta Ferrario, Simona Mandola, Stefano Pozzi, Gianluca Rospo, Giorgio Spadola, Clizia Torriglia, i quali mi hanno aiutato nella gestione del protocollo di ricerca e allenamento sul campo. La loro serietà e professionalità è stata fondamentale per la riuscita di questo lavoro.

Grazie a tutto il gruppo di ricerca del Dipartimento di Malattie Infettive dell'Istituto Scientifico San Raffaele, Valeria Longo, Simona Bossolasco e Laura Galli per i loro preziosi consigli medico-scientifici che mi hanno permesso di imparare un sacco di nuovi argomenti di questo mondo che a prima vista sembrerebbe molto lontano da quello sportivo.

Una menzione speciale Paola Cinque, leader di questo gruppo di ricerca, per avermi guidato in questi anni. E' stata lei, ormai 4 anni orsono, ad avere questa pazza idea e senza i suoi consigli questo lavoro non sarebbe stato possibile. Grazie davvero per avermi accolto e guidato infondendomi sempre la giusta carica per continuare a far del mio meglio nonostante le numerose difficoltà che durante questo cammino abbiamo incontrato.

Un grande ringraziamento va a tutti i colleghi, ormai diventati amici, dell'istituto di Scienze Motorie di via Colombo, Susanna, Luca, Gianluca e il prof. Merati, grazie a loro, la fisiologia dell'esercizio è davvero più semplice.

Il più grande ringraziamento va al Prof. Antonio La Torre, mio mentore e professore fin dalla laurea triennale in Scienze Motorie, un vulcano d'idee e opportunità e grazie a lui poiché durante la laurea specialistica mi ha spronato a seguire questo argomento. Non smetterò mai di ringrazialo poiché ha sempre creduto in me e nelle mie capacità incoraggiandomi sempre anche nei momenti più difficili. In questi anni è stato per me un grande esempio a cui mi sono ispirato al fine di cercare di far coincidere tutti gli impegni che mi si presentavano.

Un abbraccio forte a tutti gli amici che mi sono stati vicino in questi anni condividendo il difficile mondo della ricerca, Letizia, Lucrezia, Beppe, Matthew, Simone dott. Porcelli, Fabio, Jacopo, Luca Bonfanti, il mitico Cavag, Damiano e Alessio. Andare in giro con voi per i vari convegni è sempre uno spettacolo!!

Grazie anche a Silvia, per essermi stata vicino in questi ultimi davvero difficili mesi, rincuorandomi e incoraggiandomi sempre con grande dolcezza.

Last but not least un ringraziamento e un pensiero davvero speciale per Gas e Lori, miei compagni di studi alla triennale e in questo dottorato, ma soprattutto veri amici.
Eravamo 3 pischellini rampanti della laurea specialistica con tanta curiosità e voglia di imparare. Ne abbiamo davvero combinate di tutti i colori scientificamente parlando e (soprattutto) anche non. Ormai i nostri aneddoti sulle nostre avventure stanno quasi diventando leggenda!!
Se mi guardo indietro, vedo tutto il percorso che abbiamo fatto e sono davvero onorato di averlo condiviso con voi!!