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1 Overview

Summary and Quick Facts for HIV/AIDS

- Human immunodeficiency virus (HIV) attacks and destroys the cells of the immune system responsible for fighting infection. Without proper treatment, HIV can eventually advance to AIDS.
- This protocol reviews how HIV is transmitted and treated, along with some intriguing therapies and natural interventions that may lessen the unwanted side effects associated with traditional antiretroviral therapy.
- Combining antiretroviral therapies with a healthy diet and lifestyle may help you overcome some of the challenges associated with traditional antiretroviral therapies. The supplements described in this protocol may complement traditional medical approaches and support healthy immune cell counts as well.
- Probiotics and omega-3 fatty acids from fish oil have immune enhancing and anti-inflammatory properties that may benefit people with HIV.

What is HIV/AIDS?

Human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS) by destroying CD4+ helper T cells, thus weakening the host's immune system. When HIV invades a host cell, it integrates its viral genetic material into the cell's genome. As the viral load increases, the patient's immune system weakens, and becomes susceptible to opportunistic infection.

Thankfully, many treatment options now exist for people with HIV, and quality of life and mortality rates continue to improve. Conventional antiretroviral therapies, however, can have troubling side effects such as lipodystrophy, insulin resistance, and even diabetes and increased cardiovascular risk.

Natural interventions such as **green coffee extract** and **multivitamins** may complement antiretroviral therapy to further improve quality of life and reduce unwanted side effects.

What are the Risk Factors for HIV/AIDS?

- Exposure to contaminated body fluids:
  - Blood (eg, transfusions, sharing intravenous drug needles)
  - Semen (eg, sexual intercourse)
  - Breast milk
- Presence of sexually-transmitted diseases such as gonorrhea and chlamydia
- Uncircumcised men have a higher risk than circumcised men

What are the Signs and Symptoms of HIV/AIDS?

Note: HIV stages progress from acute, to latent, to late/advanced stages and AIDS.

Early symptoms can last a few weeks and may include:

- Headache
- Nausea
- Sore throat
- Fever
- Swollen lymph nodes
- Muscle pain
- Oral and/or esophageal sores

The latent phase may last months or even years and present no symptoms. Symptoms reappear at later stages and can include:

- Fatigue
- Night sweats
- Susceptibility to various infections

What are Conventional Medical Treatments for HIV/AIDS?

Note: Conventional treatment regimens generally combine multiple antiretroviral drugs. Some antiretroviral therapies include:

- Entry inhibitors (eg, maraviroc)
- Fusion inhibitors (eg, enfuvirtide)
- Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/ NtRTIs) (eg, abacavir)

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (eg, etravirine)
- Integrase inhibitors (eg, raltegravir)
- Protease inhibitors (eg, ritonavir)

What are Emerging Therapies for HIV/AIDS?

- *Metformin, the diabetes drug, can maintain glucose metabolism and reduce cardiovascular risk factors associated with antiretroviral therapy.
- Cytokine therapy is being researched to restore normal cytokine signaling that is essential for immunologic activity and is disrupted by HIV infection.
- Hormone restoration therapy, including growth hormone, sex hormones, and dehydroepiandrosterone (DHEA), may benefit patients with HIV.
- Attempts to create an HIV vaccine have been ongoing.

What Dietary and Lifestyle Changes Can Be Beneficial for HIV/AIDS?

- Eat a healthy, well-balanced diet to ensure adequate intake of essential nutrients
- Engage in a regular form of moderate exercise
- Avoid unhealthy lifestyle habits such as illicit drug use, smoking, and drinking alcohol excessively

What Natural Interventions May Be Beneficial for HIV/AIDS?

- ***Green coffee extract**. Extracts from green coffee beans, high in **chlorogenic acid**, suppress excess blood glucose levels; therefore, they may benefit HIV patients on antiretrovirals who develop insulin resistance or diabetes.
- **Multivitamins**. Multivitamins, including **vitamins A, B complex, C, D, and E**, have been shown to reduce the risk of HIV progression, improve pregnancy outcomes in HIV-positive mothers, and alleviate comorbidities.
- **Antioxidants**. Oxidative damage participates in the progression of HIV to AIDS. Antioxidants such as **carotenoids**, **glutathione**, **N-acetlycysteine**, **green tea**, **lipoic acid**, and **carnitine** have all been shown to benefit patients with HIV.
- **Omega-3 fatty acids**. Omega-3 fatty acid supplementation may improve lipid profiles in HIV patients.
- Other natural interventions may help promote immune system function and improve well-being for HIV patients, including **whey protein**, **selenium**, **lactoferrin**, **zinc**, **coenzyme Q10**, **reishi**, and **probiotics**.

**Metformin* and *green coffee extract* may not be a good choice for patients with malabsorption. Always speak to your doctor before adding to your treatment regimen.

2 Introduction

Quality of life for HIV/AIDS patients has *dramatically* improved in recent years with the advent of sophisticated new therapies, and scientific innovation is unraveling the mysteries of the human immunodeficiency virus at an expeditious rate. Cutting-edge treatments under investigation at the frontiers of science are redefining the discussion of HIV/AIDS and “cure” is no longer a four-letter word in the minds of some leading HIV researchers.[1]

Having identified multiple aspects pivotal in controlling HIV infection and developing antiretroviral drugs to target many of them, the scientific community has made tremendous strides in the management of latent HIV. The mortality rate for HIV-positive individuals has declined considerably and continues to do so.[2-4]

Alas, the indispensable antiretroviral drugs themselves cause a number of troubling side effects. Patients treated with long-term antiretroviral therapy usually develop, among other concerns, lipodystrophy, insulin resistance, and increased cardiovascular risk. Unfortunately, these drug-induced conditions diminish patients’ quality of life and

contribute to an increased rate of cardiovascular events and *diabetes*.[5-8]

Life Extension believes that a major gap in conventional HIV treatment regimens is the failure to aggressively manage patients' cardio-metabolic risk by using evidence-based drugs like *metformin*, and scientifically studied natural compounds like *green coffee extract* and omega-3 fatty acids from *fish oil*. Moreover, *hormone restoration therapy* appears to promote healthy fat redistribution and improve body composition in male HIV patients, and is associated with lower risk of death in HIV-positive women.

In this protocol you will learn some basics of the biology of the human immunodeficiency virus and how it destroys the immune system of its host. You will also discover a number of natural compounds that may improve your quality of life by targeting several antiretroviral drug-related side effects, and read about *avant-garde* medical therapies that aim to improve outlook for HIV patients even further in the not-so-distant future.

3 Understanding HIV/AIDS

Human immunodeficiency virus (HIV) *causes* acquired immunodeficiency syndrome (AIDS) by destroying CD4+ "helper T cells." In healthy individuals, helper T cells organize immune responses that protect the body from infection. When HIV invades the human system, it binds to co-receptors (typically CXCR4 or CCR5) on the surfaces of CD4+ cells and macrophages, and introduces viral genetic material into these cells.

Once HIV has gained entry into the host cell, viral RNA is *reverse transcribed* into viral DNA and combines with the DNA of the host cell—so as the infected cell replicates, so, too, does the virus.[9] Reverse transcription from viral RNA to viral DNA is a target for some antiretroviral drugs. As CD4+ cell levels become depleted with advancing HIV infection, viral replication within macrophages, dendritic cells, and other cell types sustains viral load.

HIV can be categorized based on its interaction with surface co-receptors during attachment and entry into host cells. Three primary entry methods comprise a large percentage of HIV cases—R5, which utilizes the receptor CCR5 to gain entry; X4, which uses the CXCR4 co-receptor; and X4R5, which uses both.[10]

Given the dependency upon these cell-surface co-receptors for entry, some strains of HIV are unable to infect individuals who harbor mutations in the gene encoding the co-receptor. These people are resistant to the subtype(s) of HIV that would normally utilize a wild-type receptor to gain entry into host cells.

In addition to attacking the immune system, HIV has the ability to escape immune attack. During cell replication, some HIV viruses mutate at such a rapid rate that they become unrecognizable to the immune system. This enables the virus to keep multiplying and also allows for further mutations. Furthermore, viral DNA that enters the chromosome of the infected cell (where it combines with the cell's own DNA by the action of the HIV-integrase enzyme) may remain in a latent state. As a result, it can remain undetected by the immune system.[9,11] This has presented a tremendous obstacle for achieving complete elimination of the disease.

As HIV continues to survive and replicate within its human host, it eventually weakens the immune system; this leaves the infected individual susceptible to opportunistic infections, including *Pneumocystis pneumonia* (PCP), tuberculosis, herpes simplex virus, and Kaposi's sarcoma.[9,12]

4 Distinguishing HIV-1 and HIV-2

The widely used term, "HIV," generally refers to HIV-1, the most prevalent form worldwide. However, two types have been identified: HIV-1 and HIV-2. Both are transmitted via the same routes,[13] both are associated with similar opportunistic infections, and both cause AIDS.[14] However, HIV-2 has a lower viral load,[14-16] is less pathogenic,[15,16] generally progresses more slowly than HIV-1,[16,17] and is mostly confined to West Africa.

The breakdown of the immune system from HIV-2 infection is less dramatic and occurs at a slower rate than it does with HIV-1.[18] Also, neutralization escape—that is, the ability to mutate and dodge an attack from neutralizing antibodies—is less common in HIV-2 infections.[19] Thus, characteristics of HIV-1 including a higher viral load, greater pathogenicity, and the ability to escape neutralization more often, contribute to its widespread prevalence.

Both types of HIV appear to have originated from simian immunodeficiency viruses (SIV) in chimpanzees (*Pan troglodytes*) and sooty mangabeys (*Cercocebus atys*; SM).[20,21] SIV are retroviruses that infect primates; certain strains of SIV are thought to have mutated into HIV and subsequently infected humans.[20,22]

5 Transmission

HIV can be transmitted via exposure to contaminated body fluids, such as blood,[23,24] semen,[23,25] or breast milk.[26-29] Potential routes of transmission include blood transfusions,[30] intravenous drug use,[24,31] and unprotected sexual intercourse[32]; HIV-infected females can transmit the virus to their children in utero,[33,34] during delivery,[34] or via breastfeeding.[35]

Anal sex is associated with a much higher risk of HIV transmission than vaginal sex. One factor that may contribute to this is that the rectum contains a thin membrane (the lamina propria) that harbors an abundance of HIV target cells—and only one layer of tissue separates these target cells from the rectal lumen.[36,37]

Although oral sex generally presents a relatively low risk of HIV transmission,[38] the risk of transmitting HIV increases if the mouth or genitals contain cuts or open sores (eg, recent dental work) that could provide an entryway for the virus.[39] Similarly, the risk of transmission during anal or vaginal sex increases in the presence of sexually transmitted diseases, such as herpes or syphilis, that produce ulcers or sores that compromise mucosal integrity, leaving the individual more susceptible to infection.[40,41] Additional risk factors include sexually transmitted infections such as gonorrhea or chlamydia, which produce genital inflammation that can weaken mucosal barriers that would normally help shield the body from infection. Gonorrhea also interferes with CD4 cell activation and proliferation, potentially increasing the opportunity for infection.[42]

Uncircumcised men are at higher risk of contracting HIV than those who are circumcised. This may be because the foreskin possesses numerous Langerhans cells, which contain a protein called Langerin. Langerin helps protect the body from HIV infection by quickly degrading the virus. However, if a viral onslaught occurs and the cells run out of available Langerin, these cells become viral transporters for infection and deliver the virus to lymph nodes. Thus, removing the foreskin diminishes the opportunity for the Langerhans cells to promote viral infection as transporters.[43,44]

6 Symptoms/Course of Disease

HIV progression comprises the acute, latent, and late/advanced stages. The acute stage comprises the first few weeks after infection, during which time the patient may experience "flu-like" symptoms including headache, nausea, sore throat, or fever[45]; other possible symptoms include swollen lymph nodes, muscle pain, and oral and esophageal sores. As HIV enters and replicates within CD4+ cells in the immune system, the viral load increases sharply, and there is a corresponding dip in the number of CD4+ cells, and an increase in CD8+ cells in the blood. During this stage, the patient is extremely infectious.

This phase usually ends a few weeks later, when the immune system is able to mount an effective response: The viral load decreases, and the number of CD4+ rises again, marking the beginning of the latent stage. At this point, the disease enters a period of clinical dormancy that could last for many years, although it can be much shorter in some patients. During this time, there may be no symptoms, and the carrier may be entirely unaware that he or she is carrying HIV. The virus, however, still continues to progress.

As CD4+ cell count decreases below 350 cells/μL, patients often develop constitutional symptoms, such as fatigue and night sweats, and become more prone to various infections. When the immune system is no longer able to fight off the infection, the advanced stage begins and is characterized by CD4+ cell counts below 200 cells/μL, the development of opportunistic infections, and a severely impaired immune system, all of which culminate into AIDS.[45]

7 Diagnosis

The diagnosis of HIV typically begins with a test that detects natural antibodies produced against the virus. If the antibody test result is positive, a more sensitive test is performed, such as a Western blot analysis or indirect immunofluorescence assay (a test that uses fluorescent compounds so that HIV antibodies present in the blood glow fluorescent green when placed under ultraviolet light).

The human body generally does not produce HIV antibodies until several weeks after infection, so if antibody tests are administered prior to that point, they may return false-negative results. This is particularly worrisome

given that people with HIV appear to be most infectious during the acute stage.[47-49] Consequently, patients with a negative test result are encouraged to be tested again three months later, as well as six months later. Virologic tests, which detect the actual virus or components thereof, are useful for identifying acute infection in patients who test negative for HIV antibodies.[50]

Current diagnostic options for detecting HIV include:

Viral Load Tests

These tests measure the quantity of HIV in the blood. Examples include the polymerase chain reaction (PCR) test, which can identify HIV by detecting its genetic material.

P24 Antigen Test

This test detects the p24 antigen, a protein produced by HIV. Detectable levels of p24 are produced during the early stages of HIV infection, making this a useful test in cases where an asymptomatic patient is suspected to have HIV (because of high-risk behaviors, for example) and tests negative for antibodies.[51]

Fourth Generation Assay

In 2010, the FDA approved a new, "fourth generation" test, called the ARCHITECT HIV Ag/Ab Combo Assay. This test detects both the p24 antigen and HIV antibodies, with the goal of facilitating early diagnosis of the infection. It has demonstrated high diagnostic sensitivity and specificity in detecting HIV.[52-54]

Nucleic Acid Tests

Nucleic acid tests (NAT) can identify HIV infection approximately 12 days before antibodies become detectable.[55] This allows for earlier detection of the virus, which could prevent the spread of the infection due to early awareness. In a study of more than 3,000 people who were tested for HIV, using NAT improved the detection yield by 23% compared with a rapid HIV test.[56]

Rapid Tests

Rapid HIV tests present an affordable option that allows for easy sample collection (eg, via oral swab or finger prick) and produces results in just 15 minutes. However, they are associated with a high rate of false-positive results. Consequently, patients who test positive with a rapid test should then be checked via a conventional HIV test to confirm the diagnosis.

Once an HIV infection has been diagnosed, key measures used for evaluation and monitoring are:

CD4+ Cell Count

This is considered the hallmark of disease progression. In healthy individuals, CD4 count usually range from 500 to more than 1,000 cells/µL; when these levels drop below 200, it is a criterion for AIDS.[57] In addition to being an indicator of disease progression, CD4 count can help to assess when to start antiretroviral therapy. A recent trial found that a combination of clinical monitoring and CD4+ cell count testing was the most effective strategy for monitoring HIV progression.[58]

The World Health Organization recommends that patients with HIV begin treatment when their CD4 count falls to ≤350 cells/µL, even if they don't have symptoms. Although, recent evidence indicates that if HIV-infected individuals initiate antiretroviral therapy sooner they are much less likely to transmit the disease to others.[59]

Viral Load

If the patient adheres to his/her medication regimen and the antiretroviral therapy is effective, the viral load will generally drop to less than 50 copies/mL in 16 to 24 weeks, depending on the level before treatment was initiated.[60] If viral load does not appear to decrease with treatment, this could be a sign of drug resistance.

Drug Resistance

These tests determine whether a strain of HIV is resistant to any anti-HIV medications. During genotypic testing, for example, the genetic structure of the HIV sample is studied for mutations that are recognized as creating HIV resistance to certain drugs. During phenotypic testing, the HIV is exposed to different concentrations of various antiretrovirals to determine resistance.

Patients who test positive for HIV should also undergo screening for other conditions that are associated with

HIV, including other sexually transmitted diseases, tuberculosis, and hepatitis B.[61]

8 Treatment

Antiretroviral Drugs

Patients today have access to an arsenal of powerful antiretroviral drugs to decrease the viral load.

Entry inhibitors. Entry inhibitors bind to CCR5 receptors on immune cells, preventing HIV from attaching to them and initiating infection. Example: maraviroc (Selzentry).

Fusion inhibitors. Fusion inhibitors block the gp41 protein on the surface of HIV, which prevents it from fusing with the host cell.[62] Example: enfuvirtide (Fuzeon).

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs). These medications interfere with HIV's ability to be imported into the DNA of healthy immune cells by limiting reverse transcription of viral RNA into viral DNA. Examples: abacavir (Ziagen), emtricitabine (Emtriva), lamivudine (Zeffix), tenofovir (Viread), zidovudine (Retrovir).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs). NNRTIs also inhibit reverse transcription of viral RNA. Examples: etravirine (Intelence), efavirenz (Sustiva), nevirapine (Viramune).

Integrase inhibitors. These medications inhibit integrase, an enzyme that facilitates the insertion of viral DNA into the DNA of infected cells.[63] Example: raltegravir (Isentress)

Protease inhibitors. These drugs inhibit protease, an enzyme that is used to help assemble HIV after it has been incorporated into host DNA. Examples: atazanavir (Reyataz), fosamprenavir (Lexiva), ritonavir (Norvir), darunavir (Prezista).

A variety of these drugs, and others, are often used in combination to manage HIV; this strategy is referred to as highly active antiretroviral therapy, or HAART. Drug regimens are typically chosen based on a number of factors, including patient tolerability, patient genetic background, and physician experience.

A Landmark Discovery

Antiretroviral drugs do not completely eliminate the virus—a patient receiving HAART can still infect others, for example, through needle sharing or sexual intercourse. However, breakthrough findings emerged in 2011 with the HIV Prevention Trials Network (HPTN) 052 clinical trial, which found that if a heterosexual with HIV initiates antiretroviral treatment early (prior to the advanced stages of the disease), this can reduce the likelihood of sexual transmission to uninfected partners by a staggering *96%*. These monumental findings suggest that, in addition to treating HIV infection, antiretroviral drugs may also *dramatically* decrease the likelihood of transmission of HIV between heterosexual partners if taken early enough. The study compared "early" participants who began antiretroviral treatment immediately at the beginning of the study, versus those who initiated treatment when their CD4+ counts fell to 250 cells/mm³ or less, or when they experienced an AIDS-associated illness.[59] As the authors carry out further research, these findings represent a groundbreaking discovery in HIV management.

Challenges of antiretroviral treatment include:

- **Drug resistance.** Combining protease inhibitors and reverse transcriptase inhibitors into drug "cocktails" has been extremely effective at decreasing viral load in patients with HIV.[64] As noted earlier, however, HIV can mutate at a rapid rate during cell replication; this can give rise to resistant strains of the virus that do not respond to treatment. Patients can mitigate this risk by adhering to their medication schedules, as non-adherence encourages the development of resistant strains of HIV. Inadequate drug treatment (ie, consisting of just one or two drugs, versus a broader combination) can also promote resistance.[65-67] Drug resistance tests, which establish whether an HIV strain is resistant to certain medications, can provide guidance for selecting optimal drug combinations for each patient and could be useful for revising combination therapies in cases where treatments begin to fail.

- **Toxicity/side effects.** A significant concern with antiretroviral drugs is their high toxicity and negative side effects, which range from nausea and diarrhea to more serious complications, including liver abnormalities and insulin resistance.[68] In many cases, a patient may not be able to tolerate one or more drugs. Moreover, these medications have been found to increase oxidative stress, overwhelming the body's antioxidant supplies. Until less toxic therapies are developed, patients can support their health by optimizing other, more controllable areas of the overall treatment package, such as engaging in moderate physical activity and maintaining optimal nutrition.

Note: Some preliminary human data indicates milk thistle extract may support liver health in HIV/HCV co-infected patients.[69] Additionally, a write-up of a single case involving a man with HIV/HCV co-infection reports eradication of both infections after two weeks of intravenous infusions of silymarin, a group of active constituents from milk thistle.[70] More studies are needed before firm conclusions can be drawn.

- **Insulin resistance and other cardio-metabolic abnormalities.** Long-term antiretroviral drug therapy has been associated with a number of metabolic side effects, including insulin resistance and diabetes.[5-7] Impaired glucose metabolism in antiretroviral-treated HIV patients, in turn, contributes to an increased risk of cardiovascular disease and other major comorbidities. In order to maintain the best quality of life, HIV patients must strive to keep these metabolic risks in check by controlling their glucose levels.

Life Extension recommends the antidiabetic drug *metformin* to maintain optimal glucose metabolism during healthy aging, as well as in various disease states.[71] Several studies suggest metformin effectively combats HAART-associated cardio-metabolic risk as well.

In a year-long trial involving 50 HIV-infected patients who had been treated with antiretroviral drugs for an average of six years and had developed metabolic syndrome, metformin treatment significantly slowed the rate of coronary artery calcification compared to lifestyle modification.[72] Moreover, metformin alone significantly improved insulin sensitivity, and, when combined with lifestyle modification, boosted levels of HDL (“good”) cholesterol.

In addition to improving insulin sensitivity, metformin also appears to promote healthy fat distribution, which is typically deregulated in HAART-treated HIV patients. A small, six-month trial in non-diabetic HIV-positive patients revealed that metformin therapy reduced abdominal fat accumulation, lowered blood pressure, and raised HDL cholesterol, supporting the cardio-protective role of the drug in this population.[73]

Studies show that though some other diabetic drugs may control insulin sensitivity in HIV patients, they do not reduce overall cardiovascular risk as effectively as metformin. In one investigation involving 37 patients, rosiglitazone tampered insulin resistance similarly to metformin, but only metformin suppressed postprandial lipemia, an independent cardiovascular risk factor.[74]

A small study published in *the Journal of the American Medical Association* found that metformin was safe and well-tolerated in HIV patients at a dose of 500 mg twice daily.[75] This trial further showed that metformin reduced visceral abdominal fat, which poses greater cardio-metabolic risk than subcutaneous abdominal fat, without affecting liver function and causing only mild gastrointestinal discomfort in some patients.

Green coffee extract has recently emerged as a powerful glucose control agent as well. Unroasted coffee beans, once purified and standardized, produce high levels of *chlorogenic acid* and other beneficial polyphenols that can suppress excess blood glucose levels. Human clinical trials support the role of *chlorogenic acid*-rich green coffee bean extract in promoting healthy blood sugar control and reducing disease risk.

Scientists have discovered that chlorogenic acid found abundantly in green coffee bean extract inhibits the enzyme *glucose-6-phosphatase* that triggers new glucose formation and glucose release by the liver.[76,77] Glucose-6-phosphatase is involved in dangerous postprandial (after-meal) spikes in blood sugar.

In another significant mechanism, chlorogenic acid increases the signal protein for insulin receptors in liver cells.78 That has the effect of increasing *insulin sensitivity*, which in turn drives down blood sugar levels.

In a clinical trial, 56 healthy volunteers, were challenged with an oral glucose tolerance test before and after a supplemental dose of green coffee extract. The oral glucose tolerance test is a standardized way of measuring a

person's after-meal blood sugar response. In subjects not taking green coffee bean extract, the oral glucose tolerance test showed the expected rise of blood sugar to an average of 144 mg/dL after a 30-minute period. But in subjects who had taken 200 mg of the green coffee bean extract, that sugar spike was significantly reduced, to just *124 mg/dL—a 14% decrease*.[79] When a higher dose (400 mg) of green coffee bean extract was supplemented, there was an even *greater* average reduction in blood sugar—up to nearly 28% at one hour.

Note: Metformin and green coffee extract may not be appropriate for patients who are experiencing malabsorption. Patients with malabsorption should consult a qualified healthcare provider before using metformin or green coffee extract.

Cytokine Therapy

Cytokines are cell-signaling proteins used by the immune system to orchestrate immunologic activity. By secreting cytokines, cells of the immune system are able to modify the number and/or activity of other immune cells throughout the body. Cytokines are needed to mediate responses to infection and injury, and to ensure hemostatic immune balance during healthy conditions. During HIV infection, however, cytokine signaling becomes irregular.[80,81]

CD8+ cytotoxic T cells are necessary to destroy HIV-infected cells, while CD4+ T-helper cells are necessary to organize defense against pathogens. In late-stage HIV, CD8+ cells become dysfunctional and CD4+ cell numbers decline dramatically, allowing HIV to replicate rampantly and impairing the body's ability to respond to infections. Thus, upon progression to AIDS, most patients succumb to opportunistic infections. Recent research suggests suboptimal production and signaling of γ-chain cytokines (IL's-2, -4, -7, -9, -15, and -21) contributes significantly to immunological failure in HIV infected patients.[81]

Armed with this knowledge, scientists have begun developing cutting-edge therapies that capitalize on the ability of exogenous recombinant cytokines to reinvigorate immune function lost to HIV infection. Currently, clinical trials with IL-2 and -7 have shown promising results,[82-84] and preliminary data with IL-15 and -21 is encouraging.[85-87] A growing body of evidence indicates that cytokines, especially in combination, may become an important tool in augmenting CD4+ cell populations and CD+8 function in HAART-treated HIV patients.

Moving forward, researchers hope to begin assessing efficacy of various combinations of recombinant γ-chain cytokines in HIV patients. Clinical trials are underway; any HIV patient interested in participating in a trial should speak with their healthcare provider(s) and visit **www.clinicaltrials.gov** to identify trials they may be eligible for.

Hormones: Striking the Right Balance

Hormones appear to have a profound impact on conditions associated with HIV.

Growth hormones. Body fat distribution disorders, including lipoatrophy (fat loss in select areas) and lipohypertrophy (fat accumulation in select areas), are common among people with HIV/AIDS.[88,89] Lipoatrophy usually occurs in the patient's buttocks, limbs, and face, whereas lipohypertrophy is characterized by visceral fat accumulations, or fat accumulations in the abdomen, mid-upper neck, mammary area, and/or above the pubic region.[88] These physical changes can have a negative impact on self-perception and quality of life. Moreover, antiretroviral drug therapy is associated with the development of these conditions, a factor that could dissuade patients from taking their medications.[88-90] Prolonged exposure to thymidine analogs, for example, particularly stavudine (d4T), is considered a risk factor for developing lipohypertrophy and lipoatrophy.[88]

This disturbance in fat metabolism, commonly referred to as "lipodystrophy syndrome," is associated with various metabolic changes, including insulin resistance and dyslipidemia (excessive amounts of fat in the blood).[88] Mounting evidence suggests growth hormone plays a role in the pathogeneses of these phenomena,[89,91,92] and numerous study findings have indicated that using hormone replacement therapy may help to combat these metabolic challenges.

In HIV-infected individuals with accumulations of abdominal fat, an independent association was found between lowered secretions of growth hormone and higher levels of fasting glucose and triglycerides. This suggests enhancing the amount of growth hormone may be beneficial for such patients.[93] Additional support for this hypothesis came from a study by Benedini and colleagues, who found that people with HIV who had syndromes of fat accumulation benefited from significant reductions in body fat, as well as increased lean tissue, following

growth hormone treatment.[94] A review of several randomized controlled trials revealed that the use of growth hormone axis drugs successfully decreases visceral fat tissue mass and increases lean body mass in people who have HIV-associated lipodystrophy.[95] A review by Leung and Glesby found that analogs of the growth hormone/growth hormone-releasing hormone axis seemed particularly effective at decreasing visceral fat tissue in patients with HIV.[96]

Testosterone. Testosterone has many important functions in the body, including its roles in fat distribution and muscle mass.[97-99] However, low testosterone levels are common in patients with HIV.[100-102]

Low testosterone levels are associated with the loss of lean body mass, lost muscle mass, and an increased incidence of wasting.[101,103] In many studies, patients with HIV who received testosterone treatment found that it helped stop the loss of lean body and muscle mass.[101] A study of HIV-infected male patients using HAART indicated that sex hormones participate in fat distribution changes, as well as insulin sensitivity, among male patients with HIV-lipodystrophy.[104]

The beneficial effects of testosterone treatment in HIV-infected patients have been reported in a number of studies. A systematic review and meta-analysis by Kong and Edmonds found that testosterone therapy increased lean body mass more than placebo, and that a greater increase occurred when the testosterone was administered intramuscularly.[105] In a review of anabolic steroids for the treatment of weight loss in people with HIV, Johns and associates found a potential relationship between the use of anabolic steroids and small increases in lean body mass and body weight. However, the authors did not formally recommend testosterone treatment due to study limitations, as well as the lack of knowledge regarding potential benefits and adverse effects of long-term anabolic steroid use, target populations for the therapy, and the best regimen.[106] In HIV-infected men with abdominal obesity and low testosterone, taking 10 grams of testosterone each day for 24 weeks corresponded with a greater reduction in total, whole body, and abdominal fat mass, as well as a more substantial increase in lean mass, compared with participants who took a placebo.[107]

DHEA. Dehydroepiandrosterone (DHEA) is an adrenal steroid hormone that exerts influence within a variety of biological systems either directly, or via its metabolites, which include androgens and estrogens. With respect to the immune system, studies have shown that the number of CD4+ cells correlates positively with serum DHEA levels, and negatively with cortisol levels in HIV patients.[108] Other data indicates antiretroviral drug therapy may cause a drop in serum DHEA levels.[109] In a study that followed 34 HIV-positive men for nearly three years, lower DHEA, and higher cortisol levels were associated with increasing lipodystrophy severity.[110]

In clinical trials, DHEA treatment has enhanced overall quality of life,[111] improved the steroid hormone profile,[112] and eased depressive symptoms[113] in HIV patients. The effects of DHEA administration on CD4+ and CD8+ levels in humans remain unclear, but DHEA treatment does not appear to result in negative outcomes in HIV trials.

Men and women who would like more information about maintaining healthy hormone levels should review Life Extension's "**Male Hormone Restoration**" and "**Female Hormone Restoration**" protocols.

Female hormone restoration. In a review of patient data from 84 cases of HIV in women older than 40, use of hormone replacement therapy was associated with a strong reduction in risk of death.[114] In fact, the risk reduction for hormone replacement therapy was as strong as that associated with antiretroviral drug use in this trial.

9 Developing a Cure

The medical community has not yet found a cure for HIV/AIDS, but a striking case from Berlin may provide valuable insights into potential treatment strategies: Due to a genetic mutation (known as CCR5-delta32), some people do not express chemokine receptor 5 (CCR5), a co-receptor for HIV, on their CD4+ cells. These individuals are naturally resistant to R5 HIV infection. In the Berlin case, a patient with leukemia and HIV received a stem cell transplant from an individual with this mutation.[115] Since the stem cell treatment, which occurred several years ago, doctors have not found any evidence of HIV. This finding has prompted further study in an attempt to replicate these results and ultimately develop a cure.

In 2011, Sangamo BioSciences announced a cell-based method for reducing HIV viral load, harnessing the potential therapeutic power of the CCR5 mutation. The process involves the temporary cessation of antiretroviral

treatment, the removal of T cells containing the CD4 receptor, and the exposure of these cells to an enzyme to knockout the gene for the CCR5 co-receptor. Following this treatment, the cells are re-introduced into the patient, where they appear to function normally. In preliminary experiments, this method has been found to boost CD4 cell counts in people with HIV and may also be useful for controlling viral load. One HIV-infected patient in these experiments was able to maintain a controlled viral load even without HAART.[116]

Numerous other investigations have been carried out to devise a cure, including attempts to produce an HIV vaccine. Kang and colleagues recently developed the SAV001 vaccine, which is now undergoing clinical trials. The SAV001 vaccine is made by genetically modifying the virus so that it is no longer pathogenic. From there, the virus undergoes further deactivation via radiation and chemical treatments. Testing this vaccine in clinical trials will take a few years, but if it proves successful, it will represent one of the greatest developments in the history of HIV/AIDS research.

10 Dietary and Lifestyle Considerations

Optimal nutrition is important for maintaining a healthy immune system and preserving overall general health. However, several factors make this a challenge for people with HIV. Weight loss and malnutrition are common due to complications such as anorexia, changes in metabolism, malabsorption, and chronic diarrhea.[117] HIV-related factors such as depression, loss of appetite, impaired taste or smell, or stomach upset (from treatment or from co-infections) may prevent affected individuals from eating enough.[117,118] Even people with HIV who consume adequate diets may experience chronic diarrhea and/or vomiting from drug treatments or opportunistic infections, leading to nutrient loss.[117] Combined, these factors can lead to nutrient deficiency, which can impair immune function and lower the body's resistance to infection.[118,119] New infections, in turn, can further impair nutritional status, creating a vicious cycle that promotes the progression of the disease.[118] Moreover, some individuals with HIV may have increased nutrient requirements for other reasons, including pregnancy, or because they are infants or growing children. These issues underscore the importance of ensuring adequate intake of vitamins and other nutrients to maintain health.

Other steps toward optimal health include maintaining a healthy lifestyle—avoiding the use of illicit drugs, alcohol, and tobacco, as well as engaging in moderate physical activity. In moderation, being active has been found to support immune function, reduce the potential for metabolic abnormalities, and decrease the risk of acute infection. It can also boost muscle mass, which may be useful for countering HIV-related lipodystrophy.[118] Regular physical activity is associated with decreased levels of skeletal muscle inflammatory proteins, as well as reductions in several other important markers of inflammation. These markers bear strong correlations with adverse conditions such as cardiovascular and metabolic diseases (eg, insulin resistance), underscoring the value of moderate physical activity. Moderate activity can also eliminate obesity. This presents additional health-related benefits, particularly since obesity is associated with impaired immune function, along with a host of other health problems.[120] Prolonged (more than 1.5 hours), high-intensity exercise is not recommended for people with HIV, as it may have an immune-suppressing effect.[121]

11 Nutrients

Given the deteriorating effects of HIV/AIDS progression on the immune system and nutrient status, it is not surprising that nutritional supplements have been shown to be extremely beneficial in patients with HIV. Taking vitamin supplements lowered the risk of HIV disease progression in several studies.[122-126] The use of vitamin supplements has also been associated with improved pregnancy outcomes in HIV-infected pregnant women,[122,127] increased appetite in HIV-infected children,[128] and better health and survival of children with HIV.[129-131]

In addition, nutritional supplements have been found to improve comorbidities associated with HIV. In HIV-infected patients being treated for tuberculosis (TB), for example, the consumption of micronutrients (vitamins A, B complex, C, and E, plus selenium) corresponded with a lower risk of TB recurrence and a significantly lower incidence of peripheral neuropathy (a side effect of TB treatment); this treatment also raised CD4+ and CD3+ counts.[132] In a recent study of children with HIV, a daily supplement of vitamins A, B complex, C, D, E, and folic acid, plus zinc, iron, and copper (at levels based on recommended daily allowances) corresponded with faster recovery from diarrheal episodes and pneumonia.[133]

Antioxidants

Antioxidants are widely known for their health benefits and may be particularly important for people with HIV. In 1985, Life Extension was among the first organizations to propose that patients with HIV/AIDS would benefit from taking high doses of antioxidants. Since then, many scientific studies have examined a wide range of nutrients and supplements for use in HIV/AIDS.

Under normal circumstances, metabolic processes in the body generate free radicals. At low/moderate concentrations, these reactive oxygen species are not harmful, but instead have a variety of beneficial functions. At high concentrations, however, they become extremely destructive. Normally, the human body keeps these levels in check by neutralizing free radicals with its own natural antioxidant defense system. However, some conditions can boost the production of free radicals and create oxidative stress—a condition in which the body's antioxidant defenses are unable to neutralize the overwhelming quantity of free radicals being produced. This can lead to cellular damage and the development of disease.[134]

HIV is associated with substantial oxidative stress,[135-142] and reactive oxygen species participate in the progression of HIV to AIDS.[139] As HIV progresses, antioxidant levels decline.[143,144] Compounding this problem further is the fact that various HIV treatments have been shown to increase oxidative stress.[141,145-147] Combined, these factors create an unhealthy environment that could be further exacerbated by the inadequate intake or poor absorption of nutrients that are commonly associated with HIV.[148,149] Antioxidant micronutrient deficiencies are common among people with HIV.[150] Reduced serum levels of vitamins E (a powerful antioxidant) have been associated with a higher risk of developing AIDS.[151]

Antioxidant supplements have been found to counteract some of the damaging effects associated with HIV. Taking supplements of vitamin E (800 IU per day) and vitamin C (1,000 mg per day) for three months lowered oxidative stress among patients with HIV and produced a trend toward a decrease in viral load.[150] High serum levels of vitamin E have been linked with a slower progression of HIV.[151] In large study in Tanzania involving 1,075 pregnant women with HIV, taking a daily multivitamin combination consisting of vitamins C (500 mg), E (30 mg), and various B vitamins and folic acid improved CD4, CD3, and CD8 cell counts and lowered the risk of fetal death, low birth weight, preterm birth, and small size for gestational age.[127]

Other antioxidants have also shown beneficial effects in people with HIV. A study involving 331 AIDS patients found that when patients received supplements including various carotenoids (natural pigments with antioxidant properties), as well as multivitamins and minerals, mortality rates were lower, and CD4 T-cell counts were higher, compared with patients who received the same supplementation without the carotenoids.[152] In HIV-infected patients following a stable HAART regimen, the use of broad-spectrum, high-dose micronutrient supplementation with antioxidants corresponded with a 24% increase in CD4 cell count.[153] Other important antioxidants that have been highlighted in the HIV literature include:

Glutathione. Glutathione is thought to be an extremely important antioxidant for HIV-infected patients, because it appears to interfere with HIV's entry into its target cells.[154] Glutathione deficiency—a common finding in HIV—is associated with compromised T-cell function and decreased survival.[155-156] Some nutrients that offer a host of health benefits also assist in the production of glutathione. One of these is N-acetylcysteine.

N-acetylcysteine. N-acetylcysteine (NAC) is of particular interest for people with HIV/AIDS, because it reinstates glutathione levels and has been found to maintain glutathione concentrations,[123,157] improve T-cell counts, and reduce viral load in patients with advanced AIDS.[157-159] In many studies, the use of NAC oral supplements has correlated with better quality of life and patient well-being.[160] A study involving 81 HIV-infected patients showed that eight weeks of oral NAC supplementation correlated with significant improvements in whole blood glutathione concentrations, as well as increased T-cell glutathione levels.[161] NAC is known for exerting antioxidant effects against the activity of glycoprotein 120 (gp120), an HIV protein that induces oxidative stress during the infection of macrophages (a type of white blood cell).[162]

Green tea. Green tea leaves contain compounds called catechins, which have powerful antioxidant properties. The most abundant catechin in green tea, epigallocatechin gallate (EGCG), has also been found to suppress HIV.[163] Kawai and colleagues found that EGCG can bind to T-cells and block the virus from attaching to them.[164] When HIV comes into contact with a helper T cell in the human body, gp120 on its surface binds to a CD4 receptor on

the surface of the T cell, ultimately leading to infection.[165] In several studies, EGCG blocked the attachment of gp120 to CD4 cells with varying degrees of inhibition.[164,166] EGCG also appears to lower the risk of HIV transmission—normally, fibrils in human sperm collect HIV viruses and deliver them to target cells. EGCG inhibits this activity and degrades the fibrils, thereby lowering transmission risk.[167] EGCG has also been found to inhibit a variety of HIV subtypes at physiologic concentrations without damaging human cells.[165] When coupled with other nutrients (vitamin C or lysine), green tea extract inhibited the production of HIV in chronically infected T cells; in latently infected cells, combining the green tea extract with vitamin C and amino acids resulted in significantly greater suppressive action than when any of the three were applied individually.[168]

Lipoic acid. This powerful antioxidant plays a central role in the defense against free radicals. It also recycles other important antioxidants, including glutathione,[169] and decreases intracellular signaling that promotes inflammation.[170] Taking a 300 mg supplement of alpha-lipoic acid three times per day for six months significantly elevated blood glutathione levels in a group of HIV-infected men and women aged 44–47 years.[171] In the lab, alpha-lipoic acid has been shown to inhibit HIV replication.[172] Its ability to scavenge reactive oxygen species has been found to block nuclear factor-kappa B, a transcriptional activator that is instrumental in the regulation of HIV gene expression.[173] In a study by Merin and associates, applying alpha-lipoic acid to cells infected with HIV completely stopped “initiation of HIV-1 induction by [tumor necrosis factor-alpha]."[174]

Carnitine (acetyl-L-carnitine). Acetyl-L-carnitine (ALC), also an antioxidant, boosts immune function and helps the body convert fat into energy. A number of studies have reported positive effects of ALC supplementation in people with HIV, especially its positive impact on the side effects of certain antiretroviral drugs. People with HIV who use the NRTIs zalcitabine, didanosine, or stavudine often experience peripheral neuropathy (peripheral nerve damage) and myopathy (muscle tissue disease). These outcomes have been observed in other NRTIs as well and can discourage patients from adhering to their medication regimens.[175] However, ALC may help to mitigate these effects.

ALC is known to be involved with peripheral nerve regeneration.[176] In a small study by Osio and associates (n=20), taking 2,000 mg of oral ALC each day for a month led to significant reductions in pain intensity scores among HIV-infected patients taking antiretroviral therapy.[177] A larger study involving 90 HIV-positive patients with antiretroviral toxic neuropathy found that taking 500 mg of ALC intramuscularly twice per day for 14 days resulted in statistically significant improvements in weekly mean pain ratings versus placebo. When these patients subsequently took 1,000 mg of oral ALC twice per day for six weeks, symptomatic improvements were observed.[178] A cohort study involving 21 HIV patients with NRTI-related neuropathy who were reviewed after receiving acetyl-L-carnitine for a mean of 4.3 years, 13 of the 16 patients who completed the study reported "very much or moderate" symptomatic improvement, and nine were pain-free.[179] Hart and associates observed that when HIV-infected patients with antiretroviral toxic neuropathy took ALC treatment, 76% of patients experienced reductions in neuropathic pain.[176] In a small study involving 21 participants, receiving 3,000 mg of ALC daily for 24 weeks corresponded with improvements in subjective pain ratings.[180] A very small review and meta-analysis of 14 studies that described various analgesics did not find a significant benefit of taking 1 gram of ALC daily in treating HIV-associated sensory neuropathy; the authors pointed out that this review was limited by the small number of eligible studies, as well as the differences in study designs and size, which made comparisons across studies difficult.[181]

Vitamins

Certain vitamins have amassed a notable amount of clinical evidence to highlight their potential supplemental value in people with HIV.

Vitamin D. Vitamin D has a multitude of important functions within the human body, including its roles in supporting proper immune function, regulating bone metabolism, and maintaining calcium and phosphorus homeostasis.[182,183] In people with HIV, vitamin D deficiency is common, as is lower-than-normal bone mineral density.[4,184-191] Additionally, people with HIV appear to be at an increased risk of osteopenia and osteoporosis.[184,190,192] In a recent review of the medical literature, McComsey and colleagues concluded that HIV infection should be regarded as a risk factor for bone disease.[193]

Deficient levels of vitamin D in HIV-infected individuals may be due to the virus itself[185,190] as well as to the effects

of antiretroviral treatment.[184,185,189,190,194-197] Tenofovir, for example, is a widely used NRTI that is associated with low bone mineral density,[198-201] as well as increased levels of parathyroid hormone (PTH). (Increased PTH levels are associated with decreased bone mineral density).[202] Non-nucleoside reverse transcriptase inhibitors (NNRTI) have also been implicated in vitamin D deficiency; one in particular—efavirenz—has been linked to low concentrations of 25-hydroxyvitamin D (the form of vitamin D that is measured to determine vitamin D status in the human body).[187,189,203]

As people with HIV continue to live longer, bone loss prevention becomes an even more prominent consideration in this aging population.[192] Some studies have shown a correlation between vitamin D status and CD4 counts,[186,203-206] while others did not find this relationship.[187,207] Interestingly, some studies that detected vitamin D deficiencies in HIV patients found that *uninfected* individuals also had low levels of vitamin D.[186,187] In the United States, vitamin D deficiency is highly prevalent in the general population, regardless of HIV status.[187]

Beta-carotene/vitamin A. Beta-carotene is a plant pigment found in colorful fruits and vegetables and is converted into vitamin A in the body. It plays important roles in human growth, vision, and its support of the immune system. In people with HIV who were given 100,000 IU of vitamin A from beta-carotene daily for four weeks, white blood cell counts rose 66%, and T-helper cells rose slightly. Six weeks after cessation of the beta-carotene treatment, the immune-cell measurements returned to pretreatment levels.[208] In a Uganda study involving 181 children with HIV, vitamin A supplementation was associated with significantly lower mortality rates, as well as improvements in chronic diarrhea and persistent cough.[129] In another study, 687 children in Tanzania with pneumonia received 400,000 IU of vitamin A at baseline, as well as four months after discharge, and, then eight months after discharge. None of the children showed any signs of vitamin A deficiency when they started treatment. Vitamin A supplementation was associated with a 49% drop in mortality and a 92% decrease in diarrhea-related deaths. Plus, AIDS-related deaths plummeted 68%.[130] In a population in South Africa that is not generally vitamin A deficient, children with HIV-infected mothers received 50,000 IU of vitamin A at ages 1 month and 3 months, 100,000 IU at 6 months and 9 months, and then 200,000 IU at 12 months and 15 months; this resulted in a significant reduction in morbidity from diarrheal disease.[131] In a U.S. study involving HIV-infected children, the use of vitamin A supplementation prior to influenza vaccination muted the increase of HIV viral load post-immunization.[209]

Kennedy-Oji and associates observed improved weight retention among South African HIV-infected women with vitamin A supplementation.[210] Conversely, vitamin A deficiency in HIV-positive women has been associated with increased mother-to-child transmission of the infection.[211] However, the potential value of vitamin A supplements in pregnant women with HIV remains questionable, particularly as some studies have indicated that vitamin A supplementation may increase the HIV load in breast milk[212] and may potentially elevate the risk of HIV transmission from mother to child.[213] A recent review of studies encompassing 6,517 women with HIV in South Africa, Zimbabwe, Malawi, and Tanzania found that vitamin A supplement use among HIV-infected pregnant women correlated with improved birth weights; although the review found no evidence that vitamin A supplements increase the risk of mother-to-child transmission of HIV, the authors pointed out the moderate quality of scientific evidence in these studies.

B vitamins. B vitamins are responsible for an array of important functions within the body, including proper functioning of the brain and immune system.[214,215] A number of reports have documented the beneficial effects of B-vitamin supplementation in people with HIV. In a study involving 281 HIV-infected patients, taking vitamin B6 (more than two times the RDA), vitamin B1 (more than five times the RDA), or vitamin B2 (more than five times the RDA) was independently associated with improved survival.[216] In 108 HIV-infected men tracked over an 18-month period, low B12 levels at the beginning of the study were significant predictors of faster disease progression (as determined by CD4 cell count); although the development of B12 deficiency corresponded with a drop in CD4 cell count, the normalization of vitamin B12 levels corresponded with higher CD4 cell counts.[217]

Additional Support

Compelling evidence has also been accumulating for the following:

Omega-3 fatty acids. Omega-3 fatty acids are essential oils—they are not made in the body and must be consumed from external sources. Their anti-inflammatory and immune-modulating capabilities make them a valuable component of general health[218]; additionally, they appear to have therapeutic value for people with HIV

who suffer from high triglyceride levels. A number of published medical reports have described changes in lipid metabolism, increased levels of serum triglycerides, and low levels of HDL cholesterol in people with HIV; moreover, combination antiretroviral treatment is reported to be a risk factor.[219-222] A combination of dieting and omega-3 supplements (6 grams per day) was found to cause a major drop in serum triglycerides and levels of arachidonic acid.[223] A small systematic review found that varying doses of omega-3 fatty acids caused significant reductions in triglyceride concentrations in people with HIV who were taking antiretroviral therapy.[224] A study involving 48 HIV-infected patients (47 males, one female) with HAART-associated hypertriglyceridemia found that a 12-week course of omega-3 fatty acids (4 grams per day) led to significant reductions in triglyceride levels compared with placebo.[225] Wohl and associates found that omega-3 fatty acids (in the form of fish oil supplements), plus dietary and exercise counseling, lowered fasting triglyceride levels in HIV-infected patients with hypertriglyceridemia taking antiretroviral medication; however, the difference was not significant compared with participants who received counseling without the fish oil supplements.[226] In other studies of HIV-infected patients with elevated triglyceride levels who were using antiretroviral therapy, omega-3 supplementation was associated with significant decreases in triglycerides.[227-229]

Whey protein. Whey protein contains all essential and nonessential amino acids, which are important for maintaining an adequate immune system response. Whey is also an important supplement to help boost the body's synthesis of glutathione, and various therapeutic benefits, including its immune-enhancing properties, make it of great interest to people with HIV.[230] In a study involving 41 HIV-infected patients, those who received 40 grams of whey protein each day benefitted from a CD4 count increase of 31 cells/µL, versus the control group, which showed a decline of 5 cells/µL over the same 12-week period.[231] Whey protein has been found to improve immune function, elevate cellular glutathione levels, and maintain muscle mass.[230,232] Although large randomized controlled trials will impart greater insights into the potential benefits of whey protein in patients with HIV, the results so far are encouraging.[233]

Lactoferrin. Lactoferrin is derived from whey protein. It has been found to inhibit viruses by binding to viral receptor sites, thus preventing the virus from infecting healthy cells.[234] *In vitro* studies show that lactoferrin is an effective inhibitor of HIV entry.[235-237] It may also effectively inhibit initial HIV infection by blocking uptake into epithelial cells and transfer from dendritic cells to CD4+ cells.[238]

One study that compared 22 asymptomatic and 45 symptomatic patients with HIV to 30 healthy control subjects found that plasma lactoferrin levels were decreased in patients infected with HIV.[239] In a six-month trial involving 22 HIV-1-infected children, oral lactoferrin caused a small decrease in viral load and an increase in CD4+ cell numbers; lactoferrin plus antiretroviral therapy was more effective than lactoferrin alone.[240]

Coenzyme Q10 (CoQ10). CoQ10 is present in all cells of the human body and is essential for proper cell function. Low levels of CoQ10 have been detected in people with HIV, and one study found that the level of CoQ10 deficiency corresponds with the stage of HIV infection.[241] CoQ10 supplementation increases a number of immune parameters, including T-cell counts,[242,243] an important consideration in HIV. A known antioxidant, it has also been found to contribute to the improvement of antioxidant defenses in HIV-infected men when administered as part of a regimen consisting of various antioxidants.[224] In a case study involving a 52-year-old man with HIV, the patient suffered from drug-related skeletal myopathy caused by zidovudine. Daily supplementation of CoQ10 led to recovery, allowing the patient to continue his HIV drug treatment.[225] Cherry and associates tested a water-soluble formulation of CoQ10 on cultured rat cells and found that it was effective in preventing neurotoxicity caused by d4T (stavudine; the HIV medication most commonly associated with neuropathy).[246] Although studies on the effects of CoQ10 in HIV are limited, findings so far highlight this as a promising area for further study.

Selenium. Selenium is required for proper immune system function[247] and facilitates a multitude of antioxidant activities in the body.[248,249] It also decreases the effect of inflammatory cytokines, which may reduce the risk of developing neurological damage, Kaposi's sarcoma (a common HIV-associated cancer), and wasting syndrome.[250] In people with HIV, selenium deficiency has corresponded with disease progression to AIDS or death.[247,250,251] Shor-Posner and colleagues found that, among HIV-infected drug users, low selenium was a significant risk factor for developing mycobacterial disease.[252] The HIV-inhibiting effects of selenium have also been observed in human cell cultures.[253,254] In human studies, selenium supplementation has been found to reduce the incidence of diarrhea and decrease the number of patient hospitalizations.[255,256]

Zinc and magnesium. On average, patients with HIV/AIDS who have low zinc levels have a higher viral load and lower T-cell counts.[257,258] A U.S. study of 231 HIV-infected adults found that taking zinc supplements every day for 18 months reduced the rate of diarrhea by more than 50% compared with placebo and lowered the risk of immunological failure by 400% (CD4 T cell counts of <200 cells/µL). However, it did not affect viral load, nor did it have an impact on mortality.[259,260] In a literature review of six human studies involving 1,009 participants, the use of zinc supplements appeared to decrease opportunistic infection among adults and children with HIV. Only the adults were found to have higher CD4 counts; no adverse events were reported for adults or children from using zinc supplementation.[261]

Some antiretroviral drugs appear to chelate magnesium post-interaction with integrase. Therefore, supplemental magnesium may ensure that magnesium levels are not depleted.[262]

Probiotics. The human gut contains naturally growing bacteria that possess an array of beneficial functions; these include their ability to provide essential nutrients to the body, break down foods that are otherwise indigestible, via fermentation reactions, for example, and prevent the growth of harmful pathogens.[263,264] However, the gut is largely compromised in patients with HIV. Acute HIV infection is marked by the dramatic depletion of CD4+ cells from the gastrointestinal (GI) tract. The GI tract is believed to be a particularly attractive target for HIV replication because the CD4 cells it contains are primarily CD4+ memory cells, which are preferential targets for HIV replication. (CD4+ "memory" cells are named as such because they "remember" antigens they previously encountered; this allows them to mount a more rapid response in subsequent encounters.) Moreover, the CD4+ cells in the GI tract express substantial amounts of CCR5—a receptor commonly used by HIV to enter and infect cells.[265,266] As HIV depletes the gut of immune cells, intestinal epithelial permeability generally increases, and the human host becomes increasingly vulnerable to microbial invasion and disease progression.[267]

Probiotics are living microorganisms that, when provided in sufficient quantities, impart health benefits. Certain strains of probiotics are associated with reduced inflammation[268-270] and permeability,[271-273] both of which are of notable interest for patients with HIV. In several studies involving people with HIV/AIDS, consuming probiotics was associated with improvements in CD4 cell counts.[274-276] More recently, Hummelen and colleagues found that adding probiotics to micronutrient-fortified yogurt did not boost CD4 cell count after one month, versus the same preparation without the added probiotics; although the added probiotics were well tolerated, and no adverse events were reported.[277] Larger clinical studies with longer follow-up periods are needed to fully assess the impact of probiotic supplementation on people with HIV, but results so far are promising.

Reishi extract. Reishi (*Ganoderma lucidum*, or lingzhi) is a mushroom native to Asia that has been a highly valued part of traditional herbal medicine for centuries.[278] It has been used to treat a wide range of health problems and promote long life, but is most commonly used as an immune-enhancing supplement.[278,279] Several studies have demonstrated reishi's immune-potentiating ability.[280] A preliminary study included five female monkeys with simian acquired immunodeficiency syndrome, caused by inoculation with a virus that is closely related to HIV, called simian immunodeficiency virus. Three of the monkeys received reishi extract and two received no treatment for one year. Treated monkeys had a higher survival rate (2/3 vs. 0/2) and the surviving monkeys experienced a decrease in viral load and less damage in lymphatic and other tissues.[281]

Reishi's active constituents include triterpene compounds and polysaccharides; these constituents are central to reishi's anti-viral and anticancer effects, as well as reishi's ability to stimulate immune cells.[282-284] Triterpenes and related compounds from reishi have been found to have specific anti-HIV-1 activity.[285-287] Reishi also contains proteins, fibers, phenolic compounds, minerals, vitamins, and other potentially beneficial constituents.[278,279] Extracts from reishi have been found in laboratory and animal studies to modulate both innate and adaptive immunity, stimulating macrophages, T cells (both CD4+ and CD8+ T lymphocytes, as well as others), B cells, dendritic cells, and natural killer cells, and altering the balance of other chemicals, called cytokines, that regulate immune cell activities.288,289 Both its antiviral and general immune-enhancing properties make reishi extract a good choice for individuals with HIV infection.

Update History

Disclaimer and Safety Information

This information (and any accompanying material) is not intended to replace the attention or advice of a physician or other qualified health care professional. Anyone who wishes to embark on any dietary, drug, exercise, or other lifestyle change intended to prevent or treat a specific disease or condition should first consult with and seek clearance from a physician or other qualified health care professional. Pregnant women in particular should seek the advice of a physician before using any protocol listed on this website. The protocols described on this website are for adults only, unless otherwise specified. Product labels may contain important safety information and the most recent product information provided by the product manufacturers should be carefully reviewed prior to use to verify the dose, administration, and contraindications. National, state, and local laws may vary regarding the use and application of many of the therapies discussed. The reader assumes the risk of any injuries. The authors and publishers, their affiliates and assigns are not liable for any injury and/or damage to persons arising from this protocol and expressly disclaim responsibility for any adverse effects resulting from the use of the information contained herein.

The protocols raise many issues that are subject to change as new data emerge. None of our suggested protocol regimens can guarantee health benefits. Life Extension has not performed independent verification of the data contained in the referenced materials, and expressly disclaims responsibility for any error in the literature.

References

†Ratings based on results of the 2025 ConsumerLab.com Survey of Supplement Users. Multivitamin rating based on results of the 2024 ConsumerLab.com Survey of Supplement Users. For more information, visit **www.consumerlab.com/survey**.

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