*QUESTION ONE*

*"How does HIV infection affect the immune system, and specifically how do HIV-related complications, viral infection itself, hormonal imbalances, and/or medications disrupt normal pathways involving muscle and lipids?"

Areas to focus on:*

*The effect of antiretroviral therapy on insulin production and alterations of fat metabolism.*

*How vitamin D deficiency and hypogonadism contribute to the pathophys.*

*How Gonadotropin releasing hormone might do some offsetting of the degenerative processes.*

ANSWER

The effects of human immunodeficiency virus (HIV) on the immune system depend on a variety of factors, including the severity of the disease, which is measured by viral load tests. These tests detect the amount of genetic material of HIV present in the blood (typically expressed as RNA copies per mL of blood plasma). Viral load tests are often coupled with CD4+ tests however, as HIV primarily targets CD4+ cells. According to the CDC, a CD4+ count below 200 (or percentage below 14%) is criteria for the diagnosis of acquired immune deficiency syndrome (AIDS).

With the advent of antiretroviral therapy in 1987, and highly active antiretroviral therapy in 1996, the progression of HIV into AIDS has diminished and lifespans of those suffering from HIV been prolonged by 14-26 years (Lugassy, 2010).

Although these treatments clearly allow the length of one’s life to increase, they do not have a similar effect on quality. While death is delayed, the dying seems merely protracted. The combination of HIV and its treatment has an effect of calibrating the physiology for detriment, enfeebling its sufferer with a host of adverse health conditions. These include fat distribution changes (e.g., lipodystrophy syndrome), muscle wasting, and an increased risk of cardiovascular disease.

Before discussing the specific effects of HIV and its treatment on the immune system (and the consequent pathogenesis of disease states), there are important foundations I need to establish.

First, I will discuss the relevant cells of the immune system. Second, I will illustrate the pathophysiology of HIV, how infection occurs and spreads, and how it’s treated (including mechanisms of action). Then I will discuss how the combination of HIV and its treatment affects the immune system and leads to the various disease states.

**Relevant immune system cells**

The primary immune cells targeted by HIV are CD4+ cells. CD4+ cells are a type of lymphocyte, which are in turn, a type of leukocyte (white blood cell).

There are three types of lymphocytes: NK cells, T lymphocytes, and B lymphocytes. T and B cells are small lymphocytes; NK cells are large lymphoctyes.

T lymphocytes (“T” stands for thymus, which is where they mature) are divided into several types: T helper cells, cytotoxic T cells, memory T cells, regulatory T cells, gamma-delta T cells, and natural killer T cells (different from NK cells).

CD4+ (cluster of differentiation 4) is a co-receptor (a type of cell surface receptor) that is expressed on the surface of several immune cells. Cells that express CD4+ at lower levels include blood monocytes, macrophages, dendritic cells, natural killer cells, hematopoietic stromal cells, and microglial cells (in the brain). The immune cells that express the most CD4+ are T helper cells. These cells are thus referred to as CD4+ cells.

The CD4+ cells help other leukocytes, activate cytotoxic T cells (CD8+ cells) and macrophages, and secrete a variety of cytokines.

**General pathogenesis of a retrovirus**

HIV is a retrovirus. Retroviruses do not contain DNA and are thus, in order to replicate, must do so inside of a host cell. The culpable enzyme, which enables its incorporation into the host genome, is reverse transcriptase.

Reverse transcriptase is a DNA polymerase enzyme, which means it plays a role in DNA replication; making new pieces of DNA from the templates of old pieces of DNA.

The usual sequence in transcription is to synthesize RNA from DNA. In the case of a reverse transcriptase however, the enzyme reads the coding of a single strand of RNA and then creates a single strand of DNA based on that (known as “reverse transcribing”).

Then, once the first strand is done, it synthesizes the second to complete the double helix, thereafter incorporating itself into the host chromosomal DNA (U.S. Department of Health and Human Services, 2011).

What this means is that HIV is a reverse-transcribing RNA virus in which reverse transcriptase enables RNA to transcribe it into one’s DNA, and it is thereafter replicated normally by the normal DNA polymerases.

Reverse transcriptase is thus the target of many pharmacological treatments.

**General pharmacological treatments**

The most successful and widely prescribed pharmaceutical treatments of HIV are anti-retroviral drugs. Many anti-retroviral drugs are enzyme inhibitors of reverse transcriptase. Enzyme activators and inhibitors oppose each other. When an enzyme activator binds to an enzyme, it results in an increase in enzymatic activity. When an enzyme inhibitor binds to an enzyme, it decreases enzymatic activity. Inhibition can be either reversible or irreversible and there are several modes of inhibition: competitive, uncompetitive, mixed, non-competitive, and suicide (Berg, Biochemistry, 2002).

Inhibition of reverse transcriptase isn’t the only form of antiretroviral therapy. There are several classes of antiretroviral medications, classified by the phase of the retroviral lifecycle being inhibited (U.S. Department of Health and Human Services, 2011; Murphy, 1999):

*Nucleoside reverse transcriptase inhibitors (NRTIs):* these (as well as nucleotide reverse transcriptase inhibitors) inhibit reverse transcription via competitive inhibition.

[*Non-nucleoside reverse transcriptase inhibitors*](http://en.wikipedia.org/wiki/Reverse_transcriptase_inhibitor)*(NNRTIs):* these inhibit reverse transcriptase via *non-*competitive binding.

[*Protease inhibitors*](http://en.wikipedia.org/wiki/Protease_inhibitor_%28pharmacology%29)*(PIs):* these inhibit proteases, which are enzymes used by HIV in viral assembly.

*Entry (or fusion) inhibitors:* these block several targets to inhibit entry of HIV into the host cell.

*CCR5 receptor antagonists:* these bind to the CCR5 receptors on T-Cells, which is where most strains of HIV bind.

[*Integrase inhibitors*](http://en.wikipedia.org/wiki/Integrase_inhibitor)*:*these inhibit integrase, the enzyme that integrates viral DNA into the DNA of the infected cell.

**Initial infection of HIV (Klatt, 2012)**

Within the genome of HIV, there are three genes (gag, pol, and env) that code for the major proteins, and several other “accessory” genes with regulatory and other such functions.

The env gene codes for glycoproteins gp120 and gp41.

The pol gene encodes the enzymes p51 (reverse transcriptase), p11 (protease), and p32 (integrase).

The HIV virus particle contains two single strand copies of RNA covered by a protein shell (a capsid), which is covered by a viral envelope.

Exposed on the surface of that envelope is the glycoprotein gp120. Buried within the envelope is the glycoprotein gp41.

The way HIV infects its host cell is through the binding of these glycoproteins.

The first step of infection is the binding of gp120 to CD4+.

Because T helper cells express the most CD4+ on their surfaces, these are typically the cells to which gp120 binds. But it is also capable of binding to blood monocytes, macrophages, dendritic cells, natural killer cells, hematopoietic stromal cells, and microglial cells. T helper cells represent about 90% of all the infected cells in lymphoid tissues and 80% of all infected cells at the site of mucosal inoculation during primary HIV-1 infection.

The likelihood that one will contract HIV when exposed to the virus therefore depends on the number of HIV virions present in the body fluid and the number of cells present with CD4+ receptors.

When the gp120 glycoprotein binds to the CD4+ co-receptor on the surface of one of these cells, a conformational change occurs in the gp120, which exposes co-receptor binding sites.

This allows the gp120 to engage the chemokine co-receptors that also appear on the T-lymphocytes (as well as other immune cells).

This results in a conformational change of gp41, which becomes exposed when gp120 changes its confirmation.

gp41 then enables the fusion of HIV to the host cell membrane. In this fusion, a pore is opened through which the viral core gains access to the host cell.

Once the viral particle is in the host cell, it is uncoated from its envelope and its RNA is released.

A reverse transcriptase enzyme is bound to the HIV RNA. This synthesizes a double-stranded cDNA, which functions as the template for HIV integrase to insert it into host cell genomic DNA.

Mutations to chemokine coreceptors may be responsible for the observed resistance to HIV infection seen in some people. Conversely, exposure to HIV can result in an upreguation of pro-inflammatory cytokines that increases the risk of infection.

Once infected, there’s a long incubation period before signs and symptoms of the illness manifest.

**Preservation and spread of HIV virions (Klatt, 2012)**

Acutely, HIV infection upregulates immune system activity while inducing apoptosis of the infected lymphocytes, which is a primary cause of the decline in T cells seen throughout HIV infection.

The apoptosis results directly via HIV infection itself and indirectly from constant activation of the CD4+ receptor and increased production of viral proteins via CD8+ cells, B-lymphocytes, macrophages, and monocytes.

Phagocytic cells, B-lymphocytes, and dendritic cells assist in the preservation and spread of the virions as well. These cells are used as reservoirs for HIV infection (trapping and preserving the virion) and vectors for its spread. Many of these cells can become infected but not apoptose. Follicular dendritic cells inside lymphoid tissues act as the most robust storage sites for HIV virions, transmitting infection to CD4+ cells over time.

The accelerated turnover of CD4+ cells, constant re-infection, and continuous viral replication within them is important due to the short lifespan of HIV and HIV-infected host cells (compared to sites of storage such as phagocytic cells, which are relatively long lived).

Once infected, viral replication is continuous and the destruction of CD4+ cells is progressive. There is a period of “latency” before this progressive compromise of the immune system results in an inability to produce new CD4+ cells at the rate of destruction (despite hyperactive lymphocyte production). The subsequent consequence of this is failure of the immune system and the appearance of AIDS.

**Physical effects and symptoms of HIV/AIDS (Klatt, 2012)**

Clinical AIDS is defined by a CD4+ lymphocyte count below 200/µL, at which point, opportunistic infections and/or neoplasms frequently manifest.

Regarding opportunistic infections, the compromised immune system makes HIV/AIDS sufferers less resistant to bacterial organisms. The most common effect of such exposure is respiratory disease (particularly bronchopneumonia). Among autopsy studies assessing cause of death, pneumonia is often responsible for more than half of the deaths and respiratory failure in general about two thirds.

Various bacterial agents are found in soils can induce fevers, malaise, anemia, diarrhea, and a chronic cough while affecting the liver, spleen, bone, and skin (causing lesions). Gastrointestinal bacterial infections can result in diahrhea, sometimes with stool containing an abundance of leukocytes, malabsorption, and wasting syndrome. Parasites transmitted by different insects can affect the liver, spleen, lymph nodes, bone marrow, and sometimes gastrointestinal or respiratory tract. Contact with certain animals or animal products (e.g., unpasteurized milk) can result in exposure to organisms that can induce anemia and leukopenia. Unusual yeast pathogens can cause renal failure, skin lesions, and chorioretinitis. HIV infection appears to increase the likelihood of malaria when exposed to a the anopheles mosquito.

Endocrine changes also develop, including dysfunction in the thyroid, parathyroid, pituitary and adrenal glands. To illustrate one example of this, adrenal dysfunction can manifest in increases or reductions in circulating cortisol. Increases may result from adrenal stimulation caused by increases in TNF and IL-1 secretion induced by HIV-infected macrophages. Conversely, decreases to maximum cortisol levels appear in about 30% of AIDS patients and some amount of renal failure (with associated decreases in cortisol) is seen in the majority of patients who are dying with AIDS. At autopsy, malignant lymphomas are often seen in the adrenal gland and microbacterial or fungal infections commonly associate with necrosis and inflammation.

Clinical cardiac abnormalities commonly manifest. Endocarditis appears in about 5% of patients dying with AIDS. AIDS cariomyopathy is present in 10% to 30% of cases. Non-specific myocarditis is seen in about 10% of non-cocaine-using AIDS patients at autopsy. One explanation for the presence of myocardial damage is that it is potentiated by cytokines (TNF-alpha and nitric oxide synthase) released via T lymphocyte activation, itself caused by HIV. Atherosclerosis, hypercholesterolemia, hypertriglyceridemia, and insulin resistance appear to be much more frequent among patients on antiretroviral therapy.

About 20% of deaths among AIDS patients can be attributed to lesions in the central nervous system. Other neurological conditions commonly suffered include neuromuscular diseases. Robinson-Papp (2009) presents a summary of these findings.

The most common neuroligic complication of HIV is distal symmetric polyneuropathy, which affects more than half of patients with advanced HIV. Common symptoms are numbness, pain, and paresthesias. Some of this development can be traced to mitochondrial toxicity resulting from antiretroviral agents; some of it can be attributed to the secretion of neurotoxic mediators by HIV-infected macrophages; further cause may result from an apoptotic cascade of the peripheral nerve initiated by the binding of gp120 to a chemokine receptor on a Schwann cell membrane.

Other (less common) neuropathic conditions also manifest in HIV patients, including autonomic neuropathy, acute and chronic inflammatory demyelinating polyneuropathies, mononeuropathies,and polyradiculopathy.

**HIV-associated muscle wasting (Grunfeld, 1995; Gelato et al., 2007)**

Muscle wasting in HIV patients is characterized by an imbalance of muscle anabolism and catabolism. The result of this imbalance is a net loss in body mass.

HIV-associated muscle wasting was first recognized as a defining symptom of HIV/AIDS in 1987 and is often described as a type of cachexia (a vaguely defined state of malnutrition and general ill health characterized by a loss of skeletal muscle mass). Cachexia occurs in a variety of chronic conditions (e.g., cancer, sepsis, congestive heart failure, chronic obstructive pulmonary disease). The CDC created diagnostic criteria to specifically classify HIV-associated wasting:

>10% involuntary weight loss with either chronic diarrhea (two or more episodes daily for at least 30 days) or chronic weakness with at least thirty days of constant or recurring fever.

Wasting may manifest at any stage in the HIV-AIDS progression and, due to the correlation between lean body mass and muscle strength, often involves reductions to functional capacity (losing the ability to carry out normal daily tasks, such as carrying groceries). Before the advent of HAART, risk of mortality was also comparatively higher in patients suffering from wasting.

The foundation of HIV-associated wasting is related to an imbalance of caloric intake and metabolic demand. The pathogenesis of this imbalance seems to be multifactorial.

Although resting metabolism is usually related to the amount of lean body mass one has, patients suffering from HIV-associated wasting frequently exhibit higher metabolic rates during all stages of HIV infection; even when expressing normal CD4+ counts. This increased rate of catabolism is frequently paired with reductions in caloric intake and disturbances in metabolic pathways that promote anabolism and preserve muscle mass. The relative contributions of each of these factors is unknown.

Some studies show strong correlations with inadequate nutrient uptake, others show correlations with altered metabolic demands. The most probable etiology is a combination of mechanisms. I will list these possible mechanisms below:

**Caloric intake relative to energy expense (Grunfeld, 1995; Gelato et al., 2007; Glover, 2010)**

In many people with HIV-associated wasting, caloric intake has been the predominant determinant of weight change. Often, this results from anorexia induced by secondary infection.

Among people without HIV infection, caloric reductions result in reductions to resting metabolic rate to minimize the loss of weight. Among people with HIV, the elevations to metabolic rate persist despite caloric reductions.

The only official guideline that addresses this issue was published by the American Gastroenterological Association in 1996. It recommends caloric intake be increased by the use of appetite stimulants and nutritional supplements.

However, since then, nutritional countermeasures have not been consistently effective. Increased caloric intake to support the energy demands typically results in increases to fat mass in the absence of any gain in lean body mass.

One of the more promising supplemental measures was branched chain amino acids (predominantly leucine), which stimulate muscle protein synthesis through activation of mTor. Supplementally administered to people with HIV-associated wasting, these produced little effect at preserving muscle mass unless coupled with sufficient mechanical loading (exercise program). And unfortunately exercise is not commonly done due to the fatigue resulting from HIV infection, which may be a compensatory mechanism to reduce the energy deficit and thus mitigate the wasting. Maintaining normal activity levels may lead to caloric deficits. However, without activity, there are no metabolic signals to stave off atrophy.

**Cytokine dysregulation (Gelato et al., 2007)**

Patients suffering from HIV-associated wasting (usually those with disproportionate muscle wasting) often experience an excessive proliferation of pro-inflammatory cytokines, especially interleukins 1, 2, and 6, interferon gamma, and tumor necrosis factor alpha.

These cytokines typically act on protein metabolism at the local level, but IL-6 has systematic influences through its effect on the hypothalamus, which can result in appetite suppression.

At the local level, muscle protein metabolism is altered in several ways.

1. TNF-alpha and interferon-gamma activate nuclear transcription factor KB, which suppresses MyoD synthesis. MyoD, being a transcription factor that triggers myoblast differentiation, is essential for muscle repair. Through this pathway, the excessive proliferation of TNF-alpha and IFN-gamma induce a reduction in the muscle protein myosin heavy chain.
2. The increase in activation of macrophages and endothelial cells release TNF-alpha and the interferons, which activates the ubiquitinproteasome pathway of protein degradation (accomplishing this degradation through accelerated proteolysis).

**Cortisol (Glover, 2010)**

HIV-associated wasting is associated with marked elevations in cortisol, which is not a typical characteristic of non-pathological atrophy. The hypercortisolemia results in a more profound stimulation of proteolysis among muscle proteins than standard disuse atrophy.

**Myostatin (Gelato et al., 2007)**

Associations have been found between HIV-associated muscle wasting and higher levels of serum myostatin, a growth factor that inhibits myogenesis. Growth hormone is a suppressant of myostatin.

**Growth hormone–IGF axis (Gelato et al., 2007)**

GH, secreted from the anterior pituitary, stimulates protein synthesis (and consequent muscle growth). GH causes IGF-1 to be released into the blood from the liver. The IGFs (in addition to having autocrine and paracrine effects on tissues, such as prevention of proteolysis and suppression of protein degradation) mediate the effects of GH on muscle tissue.

The vast majority of IGFs are bound to IGF binding proteins in the blood, which prolong their half-life, transport them to the target tissues, and regulate their activity, potentiating or inhibiting interactions between IGFs and their receptors. The actions of IGF-1 (as well as insulin) are also mediated by the IGF-1 receptors. When IGF-1 binds to its receptor, a variety of signaling pathways are triggered, which induce cell multiplication and growth while inhibiting apoptosis.

The GH-IGF-1 axis may be disrupted by HIV infection. The glycoprotein gp120 can bind to growth hormone releasing hormone receptors in the pituitary, suppressing GH release.

Researchers frequently find patients with HIV-wasting to have reduced serum levels of IGF-1 and insulin.

**Testosterone (Gelato et al., 2007)**

Gonadal dysfunction is common among men with HIV. Although testosterone levels have not been conclucively linked to HIV-associated wasting, about a quarter of men with HIV express lower than normal amounts of testosterone. It’s possible that this is a consequence of wasting rather than a cause. However, in addition to the direct affects of testosterone administration, patients HIV-associated wasting may also benefit indirectly through its affect on the GH-IGF axis.

**Virologic factors (Gelato et al., 2007)**

Muscle amino acid metabolism may be affected by virologic factors per se in a way that promotes muscle wasting. Before the advent of HAART, relationships were found between levels of HIV RNA and losses in body mass. With the introduction of HAART, some subjects have experienced increases in muscle protein synthesis. Improving viral load profiles may thus improve metabolic conditions associated with wasting.

Correlations between CD4+ counts and lean body mass have also been found.

**Opportunistic infections (Grunfeld, 1995; Gelato et al., 2007)**

When the immune system is sufficiently compromised, a variety of opportunisitic infections (e.g., microsporidia, Cryptosporidium, Giardia lamblia, cytomegalovirus, Mycobacterium avium) can induce malabsorption of nutrients and accelerate wasting. These secondary infections may be a primary cause of rapid weight loss among many sufferers of HIV and during the recovery of body mass, fat is more efficiently gained, leading to a selective loss of lean body mass.

**Antiretrovirals (Gelato et al., 2007)**

Muscle wasting and antiretroviral use share a complex relationship. In some situations, HAART appears to diminish symptoms of wasting due to its effect on viral load and CD4+ count. In other situations, HAART appears to have no effect and in others, it appears to exacerbate wasting symptoms.

Regarding the exacerbation of symptoms, some authors (e.g., Shevits et al., 1999) have suggested HAART may increase metabolic rate due to stimulation of sympathetic nervous system activity and/or energy demands associated with the reconstitution of immune cell profiles. Further mechanisms related to specific antiretrovirals have been proposed.

**Antiretroviral-induced disruption of lipid and muscle metabolism (Scruggs, 2008; Maagaard, 2009)**

Zidovudine is a nucleoside reverse transcriptase inhibitors (NRTI; introduced in 1987). A nucleoside is a glycosylamine, which means it has a nucleobase amine group (cytosine, guanine, adenine, thymine, or uracil) bound to a carbohydrate (either ribose or deoxyribose sugar). As an NRTI, it functions as a potent inhibitor of HIV replication. For this reason, it is an integral drug in many HAART treatments.

However, patients taking zidovudine commonly experience muscle atrophy and weakness, marked by increased blood levels of creatine kinase (indicative of muscle damage). When biopsies are collected, red fibers are seen as “ragged” and structural abnormalities are found in the mitochondria. Ultimately, this mitochondrial toxicity may lead to a host of disease states.

Maagaard (2009) and Scruggs (2008) illustrate several mechanisms by which mitochondrial toxicity develops, including disruptions to mitochondrial replication and function, accelerated apoptosis, oxidative stress, and depletion of L-carnitine. I outline each mechanism below:

**Mitochondrial replication (Scruggs, 2008; Maagaard, 2009)**

Mitochondria are replicated by enzyme DNA polymerase gamma. If it’s inhibited, mitochondrial replication is inhibited, which results in a reduction of mitochondrial content.

Although the mechanism is not perfectly understood, exposure to zidovudine results in the inhibition of DNA polymerase gamma.

In vitro, this occurs through competitive inhibition.

Zidovudine gets phosphorylated by thymidine kinases to become zidovudine triphosphate. Zidovudine triphosphate then competes with the natural substrates of DNA polymerase gamma (endogenous nucleotides). When it binds to these nucleotide binding sites, DNA polymerase gamma begins to replicate the mitochondrial DNA with zidovudine phosphate in the strand. Termination of that synthesis then occurs due to a missing 3’OH group on the zidovudine phosphate molecule.

Although occurs in vitro, zidovudine triphosphate doesn’t appear to concentrate in the mitochondrial matrix and thus its capacity to inhibit DNA polymerase gamma in this way would not likely occur in vivo. Thus, other mechanisms of mitochondrial DNA depletion have been explored.

A second mechanism is the inhibition of thymidine kinases (what phosphorylates zidovudine). More specifically, TK2 is inhibited, which results in a depletion of the thymidine triphosphate pool, which reduces the levels of endogenous nucleotides, which are necessary for the replication of mitochondrial DNA.

Whatever the source of inhibition, impaired mitochondrial replication results in fewer total mitochondria, and thus a diminished capacity to produce ATP. However, several researchers (e.g., Dalakas et al., 1990; Masanes et al., 1998) have found the depletion of mitochondrial DNA to be reversible with the cessation of zidovudine administration.

**Inhibition of oxidative phosphorylation (Scruggs, 2008; Maagaard, 2009)**

Depleting mitochondrial DNA results in dysfunction of the electron transport chain. ATP production via oxidative phosphorylation is thus affected, which results in an overcompensation of glycolytic energy production and the potential for lactic academia (Cote et al., 2002).

Further effects seen in zidovudine exposure are inhibition of enzymes involved in complex I and II of the electron transport chain, a reduction of the protein subunits at complex IV (cytochrome c oxidase), impairment of ADP-ATP translocase (antiporter that enables ATP and ADP to cross the inner mitochondrial membrane), and inhibition of adenylate kinase (phosphotransferase enzyme involved in ATP formation).

The combination of these effects would result in the available mitochondria (fewer due to inhibited replication) exhibiting poorer functioning. The result of this would be a diminished capacity to produce ATP, an increased generation of reactive oxygen species, and possible leakage of electrons into the mitochondrial matrix. These in turn would lead to a cascade of further oxidative damage.

**Oxidative stress (Scruggs, 2008)**

Following exposure to zidovudine, increases in reactive oxygen species occur much sooner than depletions in mitochondrial DNA. This is characterized by a decrease in glutathione (a tripeptide that eliminates free radicals), which occurs in more oxidative environments.

Yamaguchi and colleagues found glutathione to be reduced as early as day six, and by day fifteen, glutathione levels were cut in half. Other researchers have found oxidative damage and glutathione depletion to be mitigated by vitamin A and C treatments.

Free radicals can damage (thus altering the function of) DNA as well as proteins and lipids, leading to mitochondrial and other cellular dysfunctions.

This may be a primary mechanism of mitochondrial toxicity seen in zidovudine treated patients.

**Reducing mitochondrial L-Carnitine (Scruggs, 2008)**

L-carnitine promotes the transport of long-chain fatty acids from the cytosol into the mitochondria so that they can be oxidized. Muscle tissue relies heavily on the metabolism of fatty acids to meet its energy demands.

L-carnitine must cross the plasma membrane to perform its function. It’s carried across the membrane by a sodium dependent transporter. Zidovudine is a noncompetitive inhibitor of that transporter, which reduces L-carnitine’s ability to be transported.

The result of obstructing this pathway is an accumulation of fatty acid droplets within the cytoplasm of muscle cells. This has been found in patients taking zidovudine. While this could be caused by mitochondrial DNA depletion and damage via oxidative stresses, reductions to L-carnitine seem a probable source.

When looking for reduced levels of L-carnitine, they have been found, and when treating with L-carnitine, these effects have been attenuated.

**Apoptosis (Scruggs, 2008)**

Apoptosis, which enables cells to die without disruption to the surrounding tissue, is typically very closely regulated.

It’s carried out by proteases called caspases. Caspases must be activated (from their procaspase form) by specific cell signaling cascades.

Mitochondria are among the primary regulators of apoptosis due to their ability to stimulate that cascade by releasing proteins such as cytochrome c into the cytosol of a cell.

Mitochondrial DNA depletion and mutations, overall mitochondrial dysfunction, subsequent oxidative stress, and the accumulation of fatty acids within the cell can trigger the initiation of these cascades.

**HIV infection per se (Scruggs, 2008; Maagaard, 2009)**

HIV infection on its own appears to contribute to mitochondrial toxicity (reducing mitochondrial DNA content) and result in compromised oxidative phosphorylation. Although the pathways for this aren’t as clear, the chronic hyperactivity in the immune system seems a likely candidate.

Although a hallmark of HIV infection is low CD4+ counts, lymphocyte proliferation and turnover in general becomes hyperactive. This is expressed by a 2-fold increase in proliferation/turn-over of CD4+, and a 6-fold increase in CD8+ T cells (as well as increases to B cells).

It is likely the chronic immune stimulation (largely from HIV directly) that causes the increased proliferation of CD8+ and B cells. A pro-inflammatory environment is generated, in which there is a persistent presence of not just lymphocytes but TNF-alpha, interleukins 2 and 6, and interferons alpha and gamma.

The persistent presence of pro-inflammatory cytokines and HIV proteins may induce mitochondrial apoptosis in lymphocytes. This is not seen in the muscle (without antiretrovirals); just in lymphocytes, and especially B cells, in which depleted DNA and B cell dysfunction is seen.

Mitochondrial DNA seems to be affected in specific tissues.

**Variability in mitochondrial toxicity (Scruggs, 2008; Maagaard, 2009)**

There is wide variability in the pathogenesis of mitochondrial toxicity. Some variables that may influence this variability include:

Inborn mitochondrial variants (pre-existing mutations in the DNA). This may decrease expression of mitochondrial genes (in the absence of a reduction in their DNA) and alter function accordingly.

Age (due to accumulated mitochondrial mutations). The life spans of patients taking antiretroviral drugs are often greatly prolonged.

Race/ethnicity and gender may result in varied effects through yet unidentified ways.

Various co-infections such as hepatitis B and C.

**Altered lipid metabolism (Scruggs, 2008; Maagaard, 2009)**

In addition to altered protein metabolism, the body compositions of people with HIV are also affected by altered lipid metabolism.

Patients suffering from HIV-associated wasting (usually those with disproportionate muscle wasting) often experience an excessive proliferation of pro-inflammatory cytokines, especially interleukins 1, 2, and 6, interferon gamma, and tumor necrosis factor alpha. TNF-alpha and IL-1 upregulate LDL receptor activity while increasing serum triglyceride levels. People with HIV commonly have hypertriglyceridemia.

“Futile cycling” is a common process by which fat is preserved in the presence of a higher resting metabolic rate. It describes a condition in which lipolysis occurs and fatty acids are mobilized, but instead of then being oxidized, they’re re-esterified into triglycerides and re-stored in adipocytes. Energy is wasted without consuming fatty acids as a substrate.