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**Dr. Dieckhaus Written Comprehensive Examination Question**

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**How does HIV 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?** In answering the question, areas to focus on include the effect of antiretroviral therapyon insulin production and alterations of fat metabolism. How does vitamin D deficiency and hypogonadism contribute to the pathophysiology of the disease process? How does Gonadotropin releasing hormone attenuate some of the degenerative processes of the disease process?

**Introduction**

The effect of Human Immunodeficiency Virus (HIV) on the immune system depends on a variety of factors, including the severity of the illness, which is measured by viral load tests. Viral load tests detect the amount of genetic material of HIV in the blood (typically expressed as RNA copies per milliliter of blood plasma). These tests typically come paired with CD4+ tests however as CD4+ cells are the primary targets of HIV. According to the CDC, a CD4+ count below 200 is one of the criteria for diagnosis of Acquired Immunodeficiency Syndrome (AIDS).

The course HIV takes (and its progression into AIDS) was radically altered with the advent of antiretroviral therapy in 1987 and highly active antiretroviral therapy (HAART) in 1996. These pharmacological interventions have extended the average lifespan of people with HIV by 14-26 years (Lugassy, 2010). However, despite the positive influence on lifespan, antiretroviral treatment does not elicit a similar effect on quality. The combination of HIV and its treatment often has an effect of calibrating one’s physiology for detriment, enfeebling its sufferer with a host of adverse health conditions. These include the alteration of protein and lipid metabolism which manifests in disease states such as muscle wasting and lipodystrophy (Klatt, 2012).

The purpose of this answer is to discuss how the metabolic pathways are altered by HIV and its treatment while focusing on the disruptions involving muscle and lipids. Before I can address these however, there are some important foundations I must first establish. These include the relevant cells of the immune system, how HIV infection occurs, how it spreads, and how it is treated. The physiological explanations for these will help me illustrate how the normal pathways involving muscle and lipids are disrupted.

**Relevant cells of the immune system (Source: Berg, 2002)**

CD4+ cells are the primary targets of HIV. CD4+ cells are a type of lymphocyte and lymphocytes are in turn a type of leukocyte (i.e., white blood cell).

There are three classes of lymphocytes: T cells, B cells, and natural killer (NK) cells. The NK cells are regarded as large lymphocytes while the T and B cells are regarded as small lymphocytes.

T cells can be further divided into T helper cells, cytotoxic T cells, regulatory T cells, memory T cells, gamma-delta T cells, and natural killer T cells (different from NK cells).

CD4+ cells are the T helper cells. CD4+ (i.e., cluster of differentiation 4) is a type of co-receptor (a cell surface receptor) appearing on a variety of immune cells, including blood monocytes, macrophages, cytotoxic T cells (i.e., CD8+ cells), NK cells, and microglial cells (in the brain).

T helper cells are referred to as CD4+ cells because they’re the immune system cell that expresses the most CD4+. Their function is to help other leukocytes, activate CD8+ cells and macrophages, and release a variety of cytokines. The specific cytokines will be discussed in detail later.

**General pathogenesis of a retrovirus (source: Klatt, 2012)**

HIV is a retrovirus. Retroviruses lack DNA and are thus unable to replicate outside of a host cell. The culpable enzyme enabling the replication of a retrovirus (following access to the host cell) is reverse transcriptase. Reverse transcriptase is a DNA polymerase enzyme. DNA polymerase enzymes facilitate the assembly of new pieces of DNA from the templates of old pieces of DNA. The usual course of transcription is to begin with DNA and then manufacture RNA. In reverse transcription however, the process begins with RNA followed by the manufacturing of DNA. HIV is a reverse transcribing RNA virus in which reverse transcriptase (aided by enzymes such as integrase) enables its integration into the host genome. Reverse transcriptase is thus a common target of pharmacological treatments.

**General pharmacological treatments of HIV (source: Department of Health and Human Services, 2011)**

HIV is predominantly treated with antiretroviral medications. These are enzyme inhibitors. Inhibition can take on a variety of forms (e.g., competitive, non-competitive, uncompetitive, mixed, and suicide) and can be reversible or irreversible. While reverse transcriptase is a common target of these medications, there are other enzymes that the drugs may affect instead. The mode of action of these therapies is based on the phase of the retroviral lifecycle being targeted. The classes of antiretroviral medications are as follows:

*Nucleoside (or nucleotide) reverse transcriptase inhibitor*. These are competitive inhibitors of reverse transcriptase. A common drug in this class is zidovudine (introduced in 1987). The effects of zidovudine on protein and lipid metabolism will be discussed in detail later.

*Non-nucleoside reverse transcriptase inhibitor*. These are non-competitive inhibitors of reverse transcriptase.

*Protease inhibitor*. These inhibit proteases, which are enzymes used by HIV in viral assembly.

*CCR5 receptor antagonist*. CCR5 receptors are expressed on T cells and are a primary target for HIV to bind before it integrates itself into the host cell.

*Entry (or fusion) inhibitor*. These inhibit a variety of targets which combat the fusion of HIV to the host cell.

*Integrase inhibitor*. These inhibit integrase, which is an enzyme used by HIV to integrate its genomic information into the genome of the host cell.

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

The HIV genome consists of several “accessory” genes (which have regulatory and other such functions) and three genes that code for the major functional proteins (gag, pol, and env). The proteins I’ll be discussing as related to the initial infection of HIV are coded for by pol and env.

Pol codes for p51 (reverse transcriptase), p11 (protease), and p32 (integrase). These three proteins were mentioned in the previous section as targets of antiretroviral medications.

Env codes for the glycoproteins gp120 and gp41. These glycoproteins are responsible for the binding that the remaining antiretroviral medications target.

The viral particle of HIV contains two single strands of RNA covered in a protein shell (a capsid), which is in turn covered in a viral envelope. Exposed on the surface of that envelope is the glycoprotein gp120. Buried within the envelope is gp41.

Gp120 is what binds to the CD4+ co-receptor on the T helper cell (or any other immune cell that expresses a CD4+ receptor). The likelihood that infection will thus take place depends on the concentration of HIV virions and CD4+ cells present.

Once gp120 binds to the CD4+ receptor, that gp120 undergoes a conformational change which exposes co-receptors, allowing it to engage with the chemokine receptor (also present on the T cells). At the same time, gp41 undergoes conformational changes which expose it and enable it to fuse with the host cell. In this fusion, a pore is opened through which the viral core gains access to the host cell, after which the RNA uncoats its viral envelope. A reverse transcriptase is attached which facilitates the assembly of a double-stranded cDNA, which integrase then uses as a template for integration into the host genome. At this point HIV infection has taken place.

The resistance to HIV infection found in some people has been proposed to be related (at least in part) to variations found in the chemokine receptors. If specific variations have a reduced likelihood for binding, susceptibility to HIV infection is reduced. However, when HIV is introduced, there is usually an influx of cytokines which increases the likelihood that exposure will eventuate in infection.

Following infection, there is a period of incubation before any disease states manifest.

**Preservation and spread of HIV (source: Klatt, 2012)**

Phagocytic cells, B cells, and dendritic cells function as storage sites for HIV. These “warehouse” cells are important due to the short lifespan of HIV itself and HIV-infected T cells. Compared to T cells, immune cells such as macrophages experience relatively long lives following HIV infection. Macrophages are especially important as vectors for the spread of HIV and manifestation of disease states due to their effect on one’s cytokine profile (which I will discuss later). The most robust storage sites are the follicular dendritic cells in the lymphoid tissue. These are also important to the preservation and systemic spread of HIV during the period of latency between initial infection and manifestation of symptoms.

The short lifespans of HIV- infected T cells lead to a continuous decline in count. Although proliferation is also increased (a 2-fold increase is commonly seen in CD4+ cells and a 6-fold increase in CD8+ cells), the destruction eventually overtakes proliferation and the turnover favors decline. When CD4+ cells are reduced below 200, this is one of the criteria for the diagnosis of clinical AIDS. A variety of physical effects manifest at this stage.

**Physical effects of HIV infection (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

When the immune system reaches a threshold of compromise, many bacterial agents can no longer be tolerated and a variety of opportunistic infections result. The most common and lethal of these affect the respiratory tract. In autopsy studies, more than half of the deaths are typically attributed to bronchopneumonia while some form of respiratory failure appears in more than two thirds.

Respiratory failure isn’t the only effect however. The sources of bacteria are varied and can come from soils, contact with animals or animal products (e.g., unpasteurized milk), or from resident bacteria in the gastrointestinal tract. Additionally, people with more advanced HIV can become more susceptible to the transmission of parasites from insects (e.g., malarial transmission from the anopheles mosquito).

The organs and body systems affected by this are varied and include the skin, bone marrow, lymphatic system, liver, kidneys, spleen, respiratory, and gastrointestinal tracts. The symptoms that manifest are even more varied, a minimal list of which includes lesions on the skin, malaise, a chronic cough (and other more severe respiratory tract infections), anemia, neoplasms, and gastrointestinal complications which can result in malabsorption of nutrients and chronic diarrhea (sometimes containing an excess of leukocytes). The development of gastrointestinal disorders is one explanation for the development of muscle wasting.

Endocrine changes also develop, seen commonly in the thyroid, parathyroid, pituitary, and adrenal gland. One example of this is adrenal dysfunction (or pituitary dysfunction which affects the adrenal gland through the hypothalamic-pituitary-adrenal axis). Adrenal dysfunction in patients with HIV can result in either elevated or reduced serum cortisol.

Elevations to cholesterol are more commonly seen and arise from HIV-infected macrophages releasing an excess of tumor necrosis factor alpha (TNF-alpha) and interleukin-1, which have stimulatory effects on the adrenal gland. Regarding reductions to cortisol levels, about 30% of AIDS patients are found to have reduced maximal cortisol levels and the majority of people dying with AIDS have some amount of kidney failure (with associated adrenal dysfunction). And at autopsy malignant lymphomas commonly appear in the adrenal gland.

The summation of these effects (the bacterial infections, changes to endocrine function, etc.) result in characteristic symptoms of HIV/AIDS, including alterations to muscle protein metabolism (i.e., muscle wasting) and changes to lipid metabolism (i.e., lipoatrophy or lipodystrophy).

**HIV-associated wasting (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

HIV-associated muscle wasting is characterized by an imbalance of anabolism and catabolism, which leads to a net reduction in lean body mass. It was first identified as a common occurrence in HIV/AIDS in 1987 and is usually described as a state of cachexia (a vaguely defined state of malnourishment and general ill health characterized by a loss of muscle mass).

People with HIV aren’t the only demographic to experience wasting (e.g., sepsis, cancer, chronic obstructive pulmonary disease, congestive heart failure), but the CDC has established criteria to specifically classify HIV-associated muscle wasting:

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

Wasting can manifest at any stage in HIV-AIDS and is not inherently linked to CD4+ count (although some authors have found correlations; particularly before the advent of HAART). Also before the advent of HAART, wasting among people with HIV-AIDS was closely correlated with mortality. However, since pharmaceutical treatments have become widespread, these relationships have become much more complicated (and will be addressed later).

Due to the relationship between muscle wasting and strength, it’s frequently associated with a compromise of normal daily functioning (such as the ability to carry groceries up stairs) and thus is central to many clinical investigations. Despite the abundance of literature however, what is known about the etiology is still limited. It seems to be multifactorial and related to an imbalance of nutrient uptake and metabolic demands, compounded by altered metabolic pathways involving protein and lipids. The relative contribution of each of these is unknown, but I will discuss each of the proposed mechanisms individually.

**Reductions to caloric intake (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

Several authors have proposed that the primary cause of HIV-associated muscle wasting is anorexia caused by secondary infection. Among people who are not affected by a pathological state, reductions in total caloric intake typically result in reduced metabolic demands as the body attempts to maintain bodyweight. In people with HIV however, these reductions to metabolic demand do not usually appear, which results in wider discrepancies of the energy balance (basal metabolic rate remains high despite a lower caloric intake).

The only guideline that seems to have been published that addresses this comes from the American Gastroenterological Association in 1996. They propose that appetite stimulants and nutritional supplements be used to mitigate this discrepancy in energy balance. However, all the nutritional countermeasures that have been investigated since then have yielded discouraging results (or very inconsistent when encouraging).

One of the more promising supplements was branched chain amino acids (BCAAs). These (especially leucine) stimulate the anabolic cascade mTor, which should lead to better outcomes in muscle repair, remodeling, and general maintenance. However, for BCAAs to sufficiently work, some amount of mechanical signaling (i.e., exercise) appears to be necessary. Unfortunately, a symptom of HIV-AIDS is often extreme malaise, which may be a protective mechanism, limiting the overall discrepancy in energy balance by reducing metabolic output. Without this output however, the possible effects of BCAAs (and other such stimulators of cell signaling cascades) do not yield as favorable of results.

Overall, as a person with HIV experiences a phase of weight loss, a considerable portion of that weight comes from proteins and particularly skeletal muscle proteins. This is a possible result of cytokine dysregulation, hypercortisolemia, or a number of other variables I will discuss in the following sections.

During the reconstitution of one’s weight, fat is much more efficiently gained, which ultimately leads to a selective loss of muscle protein even after a return to baseline weight has been achieved.

**Cytokine dysregulation (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

HIV infection is often accompanied by a hyper-proliferation of pro-inflammatory cytokines, especially interleukins 1, 2, and 6, TNF-alpha, and interferon gamma. Most of these have effects at the local level of protein metabolism, but some systemic effects are exhibited as well.

An example of a systemic effect is the influence of interleukin 6 on the hypothalamus which can result in appetite suppression (thus contributing to the explanation of muscle wasting found in the previous segment).

Regarding protein metabolism at the local level, I present two examples:

1. TNF-alpha and interleukin 1 stimulate nuclear transcription factor KB. Nuclear transcription factor KB inhibits MyoD synthesis. MyoD synthesis is required for the differentiation of myoblasts, which are critical to the repair and remodeling of muscle tissue. Without MyoD, there is a prominent loss in the muscle protein myosin heavy chain.
2. HIV-infected macrophages and endothelial cells release TNF-alpha and the interleukins, which stimulate the ubiquitinproteosome pathway. The ubiquitinproteosome pathway accomplishes degeneration of muscle tissue via accelerated proteolysis.

**Hypercortisolemia (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

As I described in the section titled “Physical effects of HIV infection”, adrenal dysfunction commonly occurs. Although a considerable number of people with AIDS experience reductions to maximal circulating cortisol, adrenal dysfunction much more frequently occurs in the direction of hypercortisolemia. This occurs when HIV-infected macrophages release an excess of TNF-alpha and interleukin 1, which stimulate the adrenal gland to produce more cortisol.

When compared to non-pathological disuse atrophy, people who are not experiencing atrophy due to a pathological state do not experience a marked increase in cortisol, and thus their muscle proteins are better preserved. The hypercortisolemia may be a contributing factor to the selective loss of muscle proteins during the periods of weight loss.

**Myostatin (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

Myostatin is an extracellular cytokine with regulatory roles in muscle protein metabolism through its effect on cell signaling cascades. Myostatin has an inhibitory effect on cascades that promote the expression of myogenesis genes and it facilitates cascades that promote the expression of atrogenes (genes involved in atrophy).

Increased serum levels of myostatin have been found in people with HIV and particularly those with wasting syndromes. However, more research needs to be done before it can be identified as a cause of the altered protein metabolism found in wasting.

A myostatin-related pathway with a larger history of investigation is growth hormone. Growth hormone has a variety of effects on the body; one of them is the suppression of myostatin.

**Growth hormone–Insulin-like growth factor axis (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

Growth hormone (GH), released from the anterior pituitary, has a broad range of anabolic and anticatabolic effects. Beyond its suppression of myostatin, GH stimulates the release of insulin like growth factor (IGF) into the blood stream from the liver (IGF-1 especially).

IGF-1 has a variety of autocrine and paracrine effects (including the inhibition of proteolysis and thus preservation of muscle tissue) but one of its relevant roles is to regulate the effects of growth hormone. Regarding its anabolic effects, most IGF in circulation is bound to one of six IGF binding proteins. These prolong the half-life, transport it to the target tissues, and either facilitate or inhibit binding with the IGF receptors (which also have a regulatory effect on IGF action). When IGF binds to its receptors, cell signaling cascades are triggered which inhibit proteolysis and promote protein synthesis.

The GH-IGF axis may be inhibited by HIV as gp120 (the glycoprotein on the surface of the HIV viral envelope which I discussed in detail in “Initial infection of HIV”) binds to growth hormone releasing hormone receptors in the pituitary and inhibits the subsequent release of growth hormone (and thus the release of IGF-1). Researchers have found people with HIV to have reduced levels of IGF-1 in the blood.

**Gonadotropin releasing hormone and the sex hormones (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

Gonadotropin releasing hormone is released from the hypothalamus and is what stimulates the release of follicle stimulating hormone and lutenizing hormone from the pituitary. These have important roles in the sex hormone cascade which is commonly interrupted in people with HIV. Among women, estrogen levels are commonly affected and among men, hypogonadism is a frequent occurrence and may be a causal factor of altered muscle protein metabolism.

About a quarter of men with HIV express lower than normal levels of testosterone. Whether this is a cause of muscle wasting or caused by muscle wasting is not known, but testosterone plays a critical role in one’s anabolism. For this reason, numerous researchers have investigated the effect of supplemental testosterone (enough to warrant a Cochrane review meta-analysis on testosterone administration for HIV sufferers. The individual studies (as well as the meta-analysis) have yielded favorable results in the reconstitution of muscle mass. In addition to the direct effects of testosterone, patients receiving testosterone (or any of its precursors, beginning in the hypothalamus) may benefit from its facilitation of the GH-IGF axis.

**Virologic factors (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

Before the advent of HAART, viral load and CD4+ counts were found to be associated with muscle wasting and altered protein metabolism. Higher viral loads and lower CD4+ counts were correlated with more extreme wasting. With the inception of antiretroviral treatment, some of these patients were able to regain lean body mass. However, this does not describe all findings predating HAART and does not address possible HAART related effects that may exacerbate metabolic abnormalities. What the relationships with virologic factors may have been is a surrogate measure for opportunistic infections.

**Opportunistic infections (sources: Grunfeld, 1995; Gelato et al., 2007; Glover 2010)**

As I described in “Physical effects of HIV infection”, a compromised immune system (much more common in the era predating HAART) reduces one’s resistance to bacteria found in soils and contact with animals and in foods and resident in the gastrointestinal tract. While the effects are varied, the malabsorption and chronic diarrhea present a possible explanation for the previously-discussed relationship between virologic factors and muscle wasting. In the post-HAART era, people with HIV can more successfully stave off such infections with proper treatment. That treatment carries its own inherent risks however.

**Antiretroviral treatment (source: Shevits et al., 1999)**

One explanation for how antiretroviral treatment may exacerbate wasting is its effect on basal metabolic rate. In the section titled “Reductions to caloric intake” I described how there is a metabolic discrepancy brought about by reduced calorie intake in combination with chronically elevated basal metabolism. This chronic elevation to basal metabolism can be attributed (at least in part) to antiretroviral medication via activation of the central nervous system and reconstitution of a healthier immune profile (hyper-proliferation of immune cells carries a metabolic expense).

Other authors have investigated more specific pathways by which antiretroviral treatments promote symptoms such as muscle wasting and lipodystrophy through altered metabolic pathways. One of the most thoroughly researched drugs in this regard is zidovudine.

**Zidovudine’s effects on muscle and lipid metabolism (Scruggs et al., 2008; Maagard et al., 2009)**

Zidovudine is a nucleoside reverse transcriptase inhibitor, meaning it inhibits reverse transcription via competitive inhibition. Although in cases of extreme immune system compromise, it may help reconstitute immune system profiles (and thus combat the associated detriments), it is commonly blamed for metabolic disturbances.

When muscle biopsies are collected, red fibers are seen as “ragged” and mitochondrial defects are observed (reductions to mitochondrial content as well as abnormalities to proteins). These effects are typically resolved with cessation of zidovudine treatment.

The causes of the metabolic disturbance have been well researched and I will present each of them individually.

**Mitochondrial replication and content (Scruggs et al., 2008; Maagard et al., 2009)**

Mitochondria are replicated by DNA polymerase gamma. If DNA polymerase gamma is inhibited, mitochondrial replication is inhibited and mitochondrial content is thus affected. Although the mechanism is not entirely clear, zidovudine inhibits DNA polymerase gamma. In vitro, this occurs by competitive inhibition.

Zidovudine gets phosphorylated by thimadine kinases to form zidovudine triphosphate. Zidovudine triphosphate competes with the natural substrates of DNA polymerase gamma (endogenous nucleotides). When it binds to the nucleotide binding sites, DNA polymerase gamma initiates replication of mitochondrial DNA but stops due to the missing 3’OH in the zidovudine phosphate molecule.

While this is observable in vitro, it’s possible that, in vivo, the zidovudine will not concentrate in the mitochondrial matrix and thus another explanation would be needed. One such explanation addresses the inhibition of thimadine kinases (the enzymes that phosphorylate zidovudine) by zidovudine. If these are inhibited (especially TK2), the result is a reduction in the thimadine triphosphate pool, which has an effect on endogenous nucleotides, all of which is necessary for mitochondrial replication.

Whatever the mechanism, depleted mitochondrial DNA results in reduced mitochondrial content and thus impaired metabolism (which can manifest in a variety of ways).

Cessation of zidovudine has resulted in a reversal of this effect.

**Inhibition of oxidative phosphorylation**

In addition to the depleted mitochondrial DNA, the electron transport chain (ETC) is also affected. Zidovudine inhibits enzymes at complex I and II of the ETC, reduces the protein subunits at complex IV (cytochrome c oxidase), impairs ADP-ATP translocase (antiporter enabling the transport of ATP and ADP across the inner mitochondrial matrix), and inhibits adenylate kinase (enzyme involved in ATP assembly).

The impaired functioning of the mitochondria (fewer due to depleted mitochondrial DNA) potentially results in an overreliance of glycolytic metabolism, subsequent lactic acidosis, and an excess of oxygen reactive species being generated.

**Oxidative stress (Scruggs et al., 2008; Maagard et al., 2009)**

Oxidative stress is marked by a reduction in available glutathione, a tripeptide involved in the clearance of oxygen reactive species. This reduction is seen much sooner than the depletions to mitochondrial DNA, which implies damage and inhibition to the enzymes in the ETC occur independent of the DNA depletion. Reductions to glutathione have been seen by day six of zidovudine exposure and by day fifteen, may be cut in half. Treated with antioxidants (e.g., vitamins A and C), there have been positive findings, but the oxidative damage may still result in further deterioration (see section on apoptosis).

**Insulin sensitivity/resistance**

Many researchers, such as Tien (2008), have investigated glucose tolerance based on the length of nucleoside reverse transcriptase inhibitor exposure, reporting longer exposures to equate to poorer tolerance. However, other researchers, such as Heidigan (2005), have characterized other variables that may contribute to the poor insulin sensitivity found in HIV patients.

One variable is acidosis. Higher levels of lactate can affect insulin signaling and subsequent glucose uptake. In studies in which lactate is administered, the researchers find inhibition of glucose uptake. When nucleoside reverse transcriptase inhibitors such as zidovudine are seen to compromise mitochondrial replication and the functioning of oxidative phosphorylation, the lactic acidosis that results may be an explanation for the findings of Tien (2008).

A related possibility is the effect of oxidative stress (seen in zidovudine treatment). Oxidative damage can reduce levels of adiponectin, which is a hormone with functions that help clear glucose. Low serum adiponectin has been identified as an independent risk factor for diabetes and the metabolic syndrome (see also Renaldi et al. 2009).

One final possibility is the hyper proliferation of interleukin 1. As I’ve described in several other sections, interleukin 1 is released in excess by HIV-infected macrophages. One effect of its hyper-proliferation I have not previously described is its toxic effect on the beta cells in the pancreas

**L-Carnatine (Scruggs et al., 2008; Maagard et al., 2009)**

Muscle metabolism relies heavily on the oxidation of fatty acids. L-carnatine facilitates the transport of long chain fatty acids from the cytosol into the mitochondria where they may be oxidized. In order for L-carnatine to carry out this task, it must first cross the plasma membrane. L-carnatine is carried across this membrane by a sodium-dependent transporter. Zidovudine is a non-competitive inhibitor of that transporter. Thus, exposure to zidovudine would reduce the amount of fatty acids available for oxidation. When this occurs, fatty acid droplets built up in the cytoplasm. This can have further detrimental effects (see section on apoptosis). While these fatty acid droplets could possibly be induced by mitochondrial DNA depletion or oxidative damage, reductions to the availability of L-carnatine is a probable source. Furthermore, when looking for depleted levels of L-carnatine, they have been found. And when treating with L-carnatine, these effects have been attenuated.

**Apoptosis (Scruggs et al., 2008; Maagard et al., 2009)**

Apoptosis allows isolated cells to die without affecting other cells in the local environment. It is typically a very well-controlled process. Apoptosis is carried out by proteases called caspases, which must be activated from their pro-caspase form by specific cell signaling cascades. Mitochondria are among the primary regulators of apoptosis due to their ability to initiate those cascades by releasing proteins such as cytochrome c into the cytosol. If mitochondrial DNA is depleted, or oxidative phosphorylation is compromised resulting in oxidative stress, or if fatty acids accumulate in the cytoplasm, mitochondria can initiate apoptosis.

**Variability in infection and course of physical effects (Scruggs et al., 2008; Maagard et al., 2009)**

There is wide variability in the susceptibility for infection and the course HIV-AIDS takes once infected. Several explanations for this are inborn variations in receptors such as the chemokine receptors (discussed in the section “Initial infection of HIV”) or in the mitochondria. Age may influence both of these variables as well through factors such as the accumulation of genetic mutations in the mitochondria. Among people already infected with HIV, the additional time to develop these mutations is made possible by the lengthening effect of HAART on one’s lifespan. Gender may also influence the manifestations of disease states (see section titled “Gonadotropin releasing hormone and the sex hormones”). Race and ethnicity may influence susceptibility and resistance to metabolic alterations in yet unidentified ways. And one final explanation may be vitamin D levels.

**Vitamin D**

Although early research estimated the prevalence of vitamin D deficiency among people with HIV to be higher than those without HIV, many researchers find no difference and others still find people with HIV to have lower rates of deficiency than those without HIV (Dao et al., 2011). However, people with HIV who are deficient are often seen to experience worse health outcomes. Viard et al. (2011) illustrates a possible mechanism:

Kidney damage (common in AIDS patients; see “Physical effects of HIV infection”) and certain antiretroviral medications (such as non-nucleoside reverse transcriptase inhibitors) inhibit the bioactivation of vitamin D. This bioactivation is critical to carry out its functions. The functions of vitamin D include regulatory effects on cell growth and metabolism as well as immune system functions (CD4+ and CD8+ have vitamin D receptors). If vitamin D bioactivation is impaired, people with HIV may thus experience an earlier onset of detriments or different courses of deterioration.

**Altered lipid metabolism (Scruggs et al., 2008; Maagard et al., 2009)**

There are two hallmark pathways of altered lipid metabolism in people with HIV.

First, the hyper-proliferation of cytokines (particularly TNF-alpha and interleukin 1) up-regulates LDL receptor activity while also increasing serum triglyceride levels, which leads to hypertriglyceridemia and the poor cholesterol profile that predisposes people with HIV to cardiovascular disease.

Second, there is a metabolic pathway experienced by people with HIV called futile cycling. In futile cycling, triglycerides undergo lipolysis, are mobilized into the blood, but are not oxidized. Instead, they’re re-esterified and put back into storage as triglycerides. Calories are consumed in this process, but no fat is oxidized. Thus the “futile” expense of calories. This is one more mechanism that can increase the basal metabolic rate in people with HIV while favoring a selective use of proteins as the energy substrates.

**In summary**

HIV infection is not characterized by a single course of deterioration, but the progressive compromise of a variety of organs and body systems. What begins with the binding of gp120 to a CD4+ co-receptor may be likely to end in respiratory failure, but there is a very broad array of opportunistic conditions that can cause demise and the in-between phase is commonly characterized by severe disruptions to muscle and lipid metabolism. This can result from the compromised immune system, hormonal imbalances, the virus itself, and its treatment. The purpose of this answer was to illustrate the most common ways in which these metabolic disruptions develop.