Side Effects

Feeling Tired (Fatigue and Anemia)

Fatigue is a general term used to describe feelings of exhaustion, sleepiness, and lack of energy. It is a common problem among HIV-infected people. Fatigue is not a disease, but rather a symptom of disease. Some people suffer from isolated or periodic bouts of exhaustion. Others, however, experience chronic fatigue, which may greatly interfere with work or other day-to-day activities.

Often, HIV-positive people are told that their fatigue is either “in their heads” or an unavoidable consequence of being infected with HIV. Not only do many types of fatigue benefit from treatment or changes in lifestyle, negative health care provider attitudes about fatigue can also significantly impair the relationship between HIV-positive people and their caregivers.

It’s important to understand the very real causes of fatigue and to combat the common misconception that little can be done to treat it. If you have concerns or questions about fatigue, talk to your health care providers.

What is fatigue?
While the concept of fatigue seems obvious in everyday usage, there are several medical definitions of the term. Specialists in the field note that fatigue is multidimensional and may include:

- Physical fatigue, which refers to unusual tiredness after physical exertion;
- Mental fatigue, which is difficulty focusing on activities that require concentration;
- Motivational fatigue, which is defined as a lack of will or desire to engage in emotional or physical activities.

There are also acute and chronic types of fatigue. Acute fatigue is generally short-lived, sudden in onset, and relieved by rest. Chronic fatigue lasts a long time (usually six months or longer), may be insidious in onset, and is usually not relieved by rest.

How common is fatigue?
Among people living with HIV and AIDS, the prevalence of fatigue is quite high. In two studies, 54 and 67 percent of people reported fatigue as a symptom at some point during their course of disease. People with HIV are more likely to suffer from fatigue that interferes with their daily
activities than people not infected with the virus. One team of researchers found that when compared with persons not infected with HIV, those with HIV were more likely to be unemployed, to feel fatigued for more hours of the day, to sleep and nap more, and to have a lower level of morning alertness.

Even among people living with HIV, the prevalence of fatigue differs: those with more advanced disease (lower CD4 cell count and/or history of opportunistic infections) are more likely to experience fatigue.

What causes fatigue?
There are numerous possible causes of fatigue among persons with HIV infection. Often, a person with fatigue has several problems that can interact to cause this symptom. Here are possible causes of fatigue:

- Inadequate rest, diet, and exercise. Many people, whether they are HIV-infected or not, fail to get an adequate amount of rest and/or exercise and do not eat properly. Sleep disturbances may be associated with anxiety and depression, the use of diuretics, caffeine, alcohol, nicotine, antihistamines, decongestants, marijuana, cocaine and methamphetamines (e.g., crystal meth), or lack of exercise. Drinking too much alcohol and the use of drugs like cocaine and methamphetamines are often associated with poor diet, which can lead to anemia, liver disease, weight loss, and fatigue.

- Psychological causes. Anxiety and depression are often associated with fatigue and are also common among people with HIV. In addition to being associated with fatigue, anxiety and depression are also linked with insomnia, loss of appetite, and difficulty with concentration. Virtually every HIV-infected person goes through periods of feeling upset, worried, anxious, or depressed. Psychological causes of fatigue in HIV-infected individuals are treatable but are often overlooked.

- Alcohol, tobacco, and recreational drugs. No one knows for sure if drinking alcohol, smoking cigarettes, or doing recreational drugs speeds up HIV disease progression. However, the use of these substances is often associated with fatigue in people with HIV. While these substances may not necessarily directly cause fatigue in all people, substance abuse is often a sign—or cause—of anxiety, depression, sleep disorders, and poor diet, all of which can cause fatigue.
What’s more, alcohol and certain drugs may magnify the side effects of HIV treatments that are known to cause fatigue.

- Infections. Many of the infections associated with HIV disease can be associated with fatigue. These include viral infections such as cytomegalovirus (CMV), Epstein Barr (EBV) and Human Herpes Virus-6 (HHV-6); bacterial infections such as tuberculosis (TB), Mycobacterium avium complex (MAC) and community acquired infections such as streptococcus, staphylococcus and haemophilus. In addition, fungal and parasitic infections such as histoplasmosis, coccidiodomycosis, toxoplasmosis, Pneumocystis pneumonia (PCP) and cryptosporidiosis all have been associated with the development of fatigue. Fatigue can be the first sign of an opportunistic infection. Close attention should be given to other symptoms—such as cough, fever, and headaches—which may also point to the presence of an opportunistic infection. Anemia (low red blood cells) is quite common in people with opportunistic infections and is a frequent cause of fatigue.

- Endocrine abnormalities:
  - Adrenal insufficiency—or inadequate production of adrenal hormones—can be caused by contain HIV drugs, the HIV infection itself, or by opportunistic infections such as CMV and TB that can directly infect and damage the adrenal glands. Adrenal insufficiency can result in fatigue, chronic weight loss, decreased blood pressure, dizziness, and, ultimately, death.
  - Hypothyroidism is the term for an underactive thyroid gland—which sits inside the bottom of the neck and helps regulate the production of hormones in the body. It can cause chronic fatigue and a host of other symptoms including muscle aches, weight gain, dry hair and skin and constipation. Tests can help determine if your thyroid is functioning properly.
  - Hypogonadism—decreased testosterone production—is a common problem of HIV-infected men. Like many hormones, testosterone, which is primarily produced in the testes, helps regulate men’s moods, sexual function, nutrient metabolism, and energy levels. Approximately 45 percent of all people with AIDS suffer from low levels of testosterone, as do 25 percent of all asymptomatic HIV-infected individuals. There are several causes of low
testosterone production, including testicular dysfunction (damaged testicles, possibly due to an opportunistic infection), drug side effects (especially megestrol acetate, ketoconazole, and ganciclovir), and elevations in the adrenal hormone cortisol (which is produced in abundance during chronic infections as a normal body defense against physical stress).

- HIV treatment. Antiretroviral therapy often boosts a person’s energy level once they begin taking it. This is especially true for people who wait to start medication until their CD4 cells drop to very low levels. On the other hand, HIV medications can also lead to fatigue in some people. Retrovir (zidovudine—or AZT) can cause anemia. Another medication called Sustiva (efavirenz) can lead to sleep disturbances, which in turn can cause daytime drowsiness, tiredness and difficulty concentrating.

- Hepatitis C treatment. Today, hepatitis C treatment options are easier to manage and shorter than ever before. But fatigue is still a common symptom of the latest medications as well as a side effect of the virus.

What is anemia?
Anemia, or an abnormally low number of red blood cells, is one of the most common causes of fatigue in people with HIV. As many as 70 to 80 percent of HIV-positive people develop anemia at some time during the course of infection. Moreover, a recent report has concluded that anemia, should it not resolve, is associated with shorter survival of those living with the virus.

Red blood cells are made in the bone marrow and carry oxygen from the lungs to the rest of the body using an iron-containing protein called hemoglobin. Red blood cell production requires a natural hormone called erythropoietin and is also dependent on many other factors, including adequate sources of iron, vitamin B-12, folic acid, and trace minerals.

Certain diseases and medications can cause the number and percentage of red blood cells to fall below normal levels. When a person becomes anemic, the body tries to compensate in a number of ways. This redistribution of blood leads to the common paleness and cold sensation of people with anemia, but provides more oxygen to critical organs such as the heart, brain and muscles. Increased activity, however, produces an even greater need for oxygen in these tissues, which results in a sensation of fatigue, weakness, palpitations, shortness of breath, and other symptoms.

What causes anemia in people living with HIV?
Decreased production of red blood cells
HIV medications—as well as HIV itself—can affect the normal production of red blood cells in the bone marrow, which can result in anemia.

Inadequate hormone production may contribute to anemia. The amount of erythropoietin produced by the kidneys may not be enough to stimulate normal red blood cell production. Adrenal hormones and testosterone—other hormones known to stimulate red blood cell production—may be low in people with HIV.

Damaged bone marrow cells can also result in anemia. Red blood cells develop from immature cells in the bone marrow called erythroid progenitor cells. Toxins, such as alcohol, can directly suppress the bone marrow cells. Certain infections, like Mycobacterium avium complex (MAC), tuberculosis, fungal infections, and cytomegalovirus (CMV), can infect and destroy bone marrow cells. Non-Hodgkin’s lymphoma, a cancer associated with HIV infection, can also damage bone marrow cells and is often associated with anemia.

Many drugs used to treat HIV infection or its complications also have toxic side effects on erythroid progenitor cells that can lead to anemia. The likelihood of developing anemia when these drugs are used increases, as immune function becomes progressively impaired.

Among the drugs commonly associated with anemia are Retrovir, TMP-SMX (Bactrim, Septra), ganciclovir, dapsone, pyrimethamine, interferon and ribavirin for HCV infection, and cancer chemotherapy. It is important to remember that despite the potential side effects of these drugs, they may be essential for treatment of HIV infection or its complications, so they should not necessarily be avoided. Rather, people should be aware that side effects are a possibility and make efforts to identify and treat them.

Increased loss or destruction of red blood cells
The level of red blood cells in the body reflects the balance between their production and loss. Several processes can increase the rate of red blood cell loss in HIV-infected people. If the rate of red blood cell production does not compensate for this loss, anemia develops.

Bleeding is an obvious cause of anemia and can occur for a variety of reasons. In women, excessive menstrual blood loss can lead to anemia and iron deficiency. Certain tumors like Kaposi sarcoma and lymphoma, if they involve the intestines, can lead to bleeding. In addition, some infections of the gastrointestinal tract, such as CMV, can lead to erosions in the intestines and chronic slow blood loss. Both chronic and acute infections, severe kidney disease and malignancies can also lead to a shortened red blood cell life-span in the blood.

How do I discuss fatigue with my doctor?
There is nothing to be ashamed of or embarrassed about if you are feeling fatigued. Even though experiences of fatigue are common symptoms of an underlying complication, some health care providers may dismiss these symptoms as being unavoidable problems associated with HIV and don’t take the time to investigate further. Some may suggest that the fatigue is psychosomatic
and that what is really needed is a mental health professional, not a medical doctor. Yet, fatigue is often a sign of an underlying problem and, if evaluated properly, its cause can be determined and treated.

If you feel fatigued, tell your doctor. If you think your symptoms are dismissed too quickly, be sure to discuss the possibility of being tested for their potential causes. There’s no right or wrong way to discuss fatigue: any question or concern you have is worthy of a serious response. The only wrong thing to do is to not discuss the issue at all.

Here is a checklist of question to discuss with your doctor that may help identify other conditions that, if properly identified and treated, may help combat fatigue:

- How long has the fatigue been present?
- Did it come on suddenly?
- Are there other symptoms such as cough, fever, weight loss, or diarrhea?
- Do you feel lightheaded or dizzy when you stand up suddenly?
- Was the fatigue accompanied by signs of depression?
- Was the fatigue accompanied by signs of decreased sexual function?
- Have you ever had your adrenal hormone and testosterone levels checked?
- Did the fatigue begin when you started or switched to new medication(s)?
- Have any changes in your diet made you feel fatigued?
- Do you exercise?
- Are you having problems sleeping?
- Do you drink alcohol?
- Do you smoke?
- Do you use any other recreational drugs?

What treatments are available for fatigue?
Depending on the cause, there are several medical interventions commonly used to fight fatigue:

Hormonal/Steroid Therapy

- Testosterone: Testosterone therapy has been used to treat HIV-positive people with fatigue, decreased sex drive, and weight loss. Testosterone replacement in men with HIV has been
reported to improve energy, mood and sex drive. Replacement is usually given as a biweekly injection or via a patch.

- **Anabolic Steroids:** Testosterone is a naturally occurring anabolic steroid. Synthetic versions of anabolic steroids have been used to promote the development of lean body mass and improve energy levels. Anabolic steroids under study, in both men and women, include nandrolone (Deca Durabolin) and oxandrolone (Oxandrin). Preliminary study results have been encouraging, but researchers currently remain uncertain as to the best use of anabolic steroids in HIV. Anabolic steroids, especially oral compounds, can cause liver disease and should be used with caution. Moreover, like testosterone replacement therapy, anabolic steroids can cause virilization in women (development of ‘masculine traits’ such as thickened facial hair and voice deepening).

- **Growth Hormone:** Human growth hormone (Serostim) is another anabolic agent. Growth hormone is approved for the treatment of wasting in people with HIV/AIDS. In one 12-week study, HIV-infected people being treated for weight loss had improved energy levels after growth hormone treatment as determined by treadmill tests. Growth hormone has also been shown to increase both weight and lean body mass in people with HIV.

**Stimulants**

A few small studies are investigating the use of psycho-stimulant drugs to treat fatigue. Ritalin, Cylert Adderall, and Dexedrine are among the drugs being tried. However, these drugs contain “speed”—amphetamines, in most cases—which means that they are potentially addictive. Modafinil (Provigil) is a non-addictive stimulant used to treat narcolepsy, a neurological disorder marked by uncontrollable attacks of daytime sleepiness. It is currently being studied as an anti-fatigue treatment for HIV-positive people. Like other psycho-stimulants, modafinil is processed by the liver, which means possible drug interactions with antiretroviral (ARV) medications.

**Treat Other Infections**

Any time an infection is present, the body draws upon various energy stores (such as fat and muscle) to fuel itself. When energy stores are depleted and not replaced, energy is thrown off. For example, someone who is fighting an infection usually burns a lot more energy while at rest than someone who is healthy. Over time, energy can become depleted, causing fatigue. HIV and its complications put stress on the immune system and energy stores. Any infection or complication that causes fatigue, weight loss, fever or other symptoms should be aggressively diagnosed and
Treatment Options
Despite all the benefits offered by antiretroviral drugs and treatments for AIDS-related complications, they still have a number of undesirable side effects. Depending on the severity of symptoms, one option may be to substitute the offending drug with a similar drug that may not cause the same side effects. This is often the most desirable option, but one that is not always possible. Another option may be to lower the dose of the drug causing the side effect. However, lower doses of the drugs may be less effective and may promote drug resistance.

Blood Transfusion
Blood transfusions have long been considered to be a safe and effective way of treating anemia caused by HIV, its complications and medications. People with fatigue associated with anemia generally feel better almost immediately after receiving blood transfusions. However, blood transfusions can have drawbacks, and although they may have an immediate impact on fatigue and anemia, the benefits are usually short-lived and do not treat the underlying causes.

Erythropoietin
Procrit (recombinant erythropoietin) is a manufactured version of naturally occurring erythropoietin, which is produced by the kidneys. Erythropoietin helps stimulate bone marrow production of red blood cells, thus increasing hemoglobin levels and alleviating symptoms, such as fatigue that are associated with anemia. Procrit is manufactured by recombinant DNA technology and has the same biological effects as naturally occurring erythropoietin. Procrit can be given once, twice, or three times a week. It is given by injection, either directly under the skin or through an intravenous (IV) line. The drug is usually taken for a minimum of eight weeks, and it may take between four and six weeks for results to be seen. Procrit is most useful in people with anemia who have relatively low erythropoietin levels in their blood.

Alternative Treatments for Fatigue
While there have been many anecdotal reports suggesting alternative, non-pharmaceutical treatments are effective for alleviating fatigue, very few well-designed clinical trials have been conducted to determine whether they are safe or effective. Another problem is that it is unusual for health insurance programs to pay for alternative treatments, thus placing financial burden on the consumer.

Suggested alternative therapies for fatigue include: yohimbine and ginseng, both natural stimulants; carnitine, which mimics a muscle-building amino acid made by the body; and DHEA, a synthetic version of a naturally occurring hormone that triggers testosterone production. It is important to note that supplements containing Ma Huang (a Chinese herb)—found in ephedra alkaloid, Mormon tea, and herbal ecstasy, to name a few—has been classified as “dangerous” by the U.S. Food and Drug Administration (FDA). It can cause increases in blood pressure and irregular heartbeat.

Alternative treatments should be used carefully, considering that little is known about their
potential short-term or long-term side effects. Moreover, alternative treatments may cover-up or mask an underlying problem that is causing the fatigue.

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