

WHITE BLOOD CELL AND PLATELET DECREASES

What's the Problem, and How Do You Diagnose It?

White blood cells (leukocytes) provide the body's cellular immune response. They are formed from your bone marrow throughout your life from basic stem cells which, influenced by cytokines (cell-produced chemicals), eventually grow into various types of blood cells. There are many white blood cell subsets, including dendritic cells, granulocytic cells (neutrophils, basophils, and eosinophils), lymphocytes (T cells, B cells, and natural killer cells), mast cells, megakaryocytes (cells from which platelets are derived), and mononuclear cells (monocytes and macrophages). As anyone reading this no doubt knows, the white blood cells most talked about with HIV disease are the lymphocytes, particularly T cells and natural killer cells. Support for these cells comes from suppressing the virus and supporting the immune system. [For a discussion of this, see this guide's Introduction.] In terms of the other white blood cells, the problem which most commonly needs to be addressed is a lowered level of neutrophils, key infection fighting cells. Many people also develop lowered levels of platelets (thrombocytes), the disc-shaped structures which are formed in the megakaryocytes and then released in clusters to help blood clot.

Neutropenia (low neutrophils) is estimated to affect 8 percent of asymptomatic HIV+ people, 10 to 30 percent of those with early symptomatic disease, and up to 75 percent of those in later disease stages. As can be seen by these numbers, its severity tends to parallel the course of HIV disease, worsening with disease progression. Thrombocytopenia (low platelets) is estimated to affect 13 percent of asymptomatic HIV+ people, and may ultimately affect 30 to 60 percent of all HIV+ people. Unlike neutropenia, neither the occurrence nor the severity of thrombocytopenia necessarily correlates with disease stage.

In people with low neutrophils, there is a likelihood of increased susceptibility to infections but no obvious symptoms. A blood test called a white blood cell differential shows what proportion of your white blood cells are made up of each of the different types of cells. Although values may vary from lab to lab, a normal neutrophil count will be approximately 47 to 77 percent. On a lab report, this will usually be listed as SEGS or polys (polymorphonucleocytes or PMN).

In people with low platelets, the skin may have black and blue spots (ecchymosis) or tiny freckle-like red spots (petechiae). There may be a tendency toward bruising easily and nose bleeds. The gums may bleed more easily when you brush your teeth. In some cases, the spleen may become enlarged. Rarely, there may be gastrointestinal blood loss. Although values may vary from lab to lab, a normal platelet count is from 150,000 to 400,000 platelets per cubic millimeter of blood. In some HIV+ people, the count can be severely depressed. A platelet count below 50,000 would be of definite concern. Platelets less than 20,000 create a serious risk of abnormal bleeding and would mandate an aggressive approach to diagnosis and treatment.

A particular type of platelet problem called thrombotic thrombocytopenic purpura (TTP) causes a purpling of the skin due to low platelet levels that cause blood clotting problems, along with fever, hemolytic anemia, elevated blood levels of urea and other nitrogenous compounds, neurological dysfunction, and kidney insufficiency. Confusion is a common symptom.

The condition called idiopathic thrombocytopenic purpura (now also called immune thrombocytopenic purpura) or ITP can also result in low levels of platelets and resulting problems with uncontrolled bleeding. ITP can often be successfully treated with intravenous immune globulin (IVIG) although the increase in platelets achieved usually only lasts two to four weeks.

What are the Causes?

There are several possible causes for lowered neutrophils and platelets in HIV disease, and in many people, there may be more than one factor contributing to the decreases.

Neutropenia commonly results from the use of bone marrow suppressive drugs, and may also stem from drug-induced mitochondrial toxicity. Drug-induced neutropenia can be related to direct cytotoxic effects (the drug damages or destroys the cells), immunologic mediators (the drug may induce abnormal cytokine responses or balance), and/or the effects of vitamin depletion on the bone marrow (the drug adversely affects nutrient status). Most often, the neutrophil bashers are antiretroviral meds, as well as drugs used to treat opportunistic infections and cancers. Of the antiretrovirals, the most common causes of neutropenia are the nucleoside analogue AZT (found alone in Retrovir® and in the combination drugs Combivir® and Trizivir®) and the cellular inhibitor hydroxyurea (Droxia, Hydrea). However, with long-term use, the mitochondrial toxicity caused by any or all of the nucleoside analogues can contribute to bone marrow suppression and resulting neutropenia. [For a full discussion of mitochondrial toxicity, see the **Mitochondrial Support and Protection Against Oxidative Stress** section of this **Introduction**, and the Mitochondrial Toxicity section of the **Comprehensive Goals/Self-Care Guide**.]

Other possible neutrophil-decreasing drugs that are fairly commonly used in HIV disease are Bactrim (used for

treatment or prevention of PCP) and ganciclovir (used for treatment or prevention of CMV). A long list of other drugs not specific to HIV disease can also result in neutropenia.

Low platelets are sometimes also caused by drugs. There are many drugs that can suppress platelets including bone-marrow suppressive antiretrovirals, cancer chemotherapies, anti-inflammatory meds (phenylbutazone, aspirin), quinidine, thiazide diuretics, meprobamate, antibiotics (sulfonamides, penicillin), and others.

HIV can directly or indirectly cause low platelets and may contribute to low neutrophils. HIV may directly suppress platelet production by infecting megakaryocytes and indirectly suppress production by causing alterations in the production of cytokines (cell-produced chemicals) and growth factors needed for proper platelet production and function. Research has shown that HIV infection may induce macrophages to produce more of a chemical called macrophage-derived chemokine (MDC) which appears to alter the function of platelets. HIV may also cause platelets to be targeted by anti-platelet antibodies, a process that results in what is termed immune destruction. The result is immune thrombocytopenic purpura (ITP). With ITP, it appears that the platelets have become coated with proteins from HIV and are, thus, recognized as foreign invaders by the immune system when they pass through the spleen. The immune system then targets them for destruction. There can also be non-immune destruction with thrombotic thrombocytopenic purpura (TTP). It is thought that TTP may result from the blood vessel damaging effect of HIV proteins. Destruction of platelets may also occur as the result of infections or fevers which reduce the life span of platelets.

However, based on recent findings, it appears that decreased production of platelets may be much more likely to be the cause of low platelets in HIV+ people than increased destruction. Researchers have reported that decreased platelet survival time, a common occurrence in non-HIV+ people with low platelets which suggests increased destruction, does not appear to generally occur in HIV+ people.

HIV may also indirectly suppress neutrophil production, possibly because HIV infection results in deficiencies in the production of the G-CSF (granulocyte colony-stimulating factor) needed to boost neutrophil production when neutrophils drop too low.

Deficiencies of vitamin B-12 or folic acid can cause neutropenia or thrombocytopenia. Since these nutrients are necessary for building blood cells and deficiencies, especially of B-12, are common in HIV disease, this may be a contributing factor in many cases of low neutrophils or platelets. The presence of nutrient deficiencies can both directly affect the bone marrow's ability to produce cells and indirectly create a heightened likelihood of damage from drugs. It has been shown that low levels of either B12 or folic acid can increase the likelihood of bone marrow toxicity from AZT.

It is important to remember that standard blood tests do not always accurately reflect B-12 deficiencies. Researchers point out that B-12 deficiency is present in a significant percentage of HIV+ people, but does not always cause the red blood cell changes that physicians look for as a sign of deficiency. In addition, because the standard blood test reflects only what's in the bloodstream and not what is in the body's cells, a reading that appears normal may not truly reflect the body's status.

Certain infections or cancers can cause decreased neutrophils or platelets. For this reason, diagnostic workups to establish the cause(s) of these problems will include looking for fever or other signs of infection, and for swollen lymph glands or other signs of lymphoma.

What are the possible treatments?

The first must for effective treatment of any neutrophil or platelet problem is identification of all the possible contributing causes, to the greatest extent possible, followed by elimination of as many of these as possible. This would include checking drug lists to see if any are being used that could be suppressing the bone marrow, and conversely considering the use of antiretrovirals if it appears that HIV is a major cause of the problem. Considering the possibility of nutrient deficiencies would also be important. In addition to antiretroviral therapy, ITP can often be successfully treated with intravenous immune globulin (IVIG), although the benefits are not usually long-term. Standard treatments for TTP include plasma transfusions, plasmapheresis, and, if nothing else works, high-dose steroids or other immunosuppressive agents. Regardless of the other treatment(s) being considered, it is recommended that anyone living with severe hemophilia who has a platelet count that drops below 50,000/mcl be given prophylactic infusions of clotting factor three times per week until such time as other treatments can improve the count.

Key Therapies

For Both Neutrophil and Platelet Support

Starting or changing drug therapy. It has been shown that effective HAART often results in dramatic increases in platelet counts. For those with serious platelet problems, this may be the most important therapy. On the other hand, checking to see if any drugs being taken could be contributing to decreased neutrophils or platelets would also be important. Where possible, switching any potentially problematic meds to others less likely to cause the problem(s) would be ideal.

There is one important caveat, however. Although it would seem appropriate to look for possible substitutions for any drug that appears likely to be contributing to decreased levels of either neutrophils or platelets, there may not always be available substitutes. In cases of neutropenia, this may be a particular problem for people who are very treatment experienced with HAART meds. They may have become resistant to many previously used drugs, and might well be on the only combo currently available to them. Some people may also be intolerant of protease inhibitors or NNRTIs because of the symptoms that they cause. If the current nuke-containing HAART combo is otherwise working well and providing the anti-HIV benefits needed, it may be necessary to stay with those meds, if possible, while attempting to address the neutropenia with G-CSF (discussed below) and the nutrients that provide mitochondrial support.

When nukes must be continued to maintain viral control, it might be advisable to try to use the drugs that may be the least likely to cause mitochondrial dysfunction, and thus lessen the risk that the antiretrovirals will contribute to neutropenia. In general, it is thought that d4T (Zerit®), ddC (Hivid®), AZT (alone in Retrovir® and also in the combination drugs Combivir® and Trizivir®), and ddI (Videx®) have the greatest potential for mitochondrial toxicity, while 3TC (Epivir®), abacavir (Ziagen®), and tenofovir (Viread®) are less likely to cause the problem. However, it is important to note that most of the evidence in support of this ranking has been derived from in vitro (test tube) research so whether this will actually be the case in HIV+ people is not perfectly known.

B-12, folic acid, and other nutrients. A number of nutrients are needed for proper bone marrow function. Re-supplying the body with all the nutrients commonly deficient in HIV+ people, including particularly B12, folic acid, and zinc, is very important. A potent B complex formula or multivitamin should also be included as there are a number of different B vitamins critical to proper bone marrow function. Note that B-12 and folic acid should always be given together since taking folic acid alone could prevent the blood cell changes that might otherwise indicate B-12 deficiency. Doses of B-12 (1,000 mcg given daily via pills, or one to several times weekly through prescription nasal gel or injections) and folic acid (800 mcg daily via pills) may be useful, even when tests don't indicate obvious deficiencies. The injections or nasal gel forms of B-12 bypass absorption problems that may be present in many HIV+ people due to problems with the parietal cells that produce the intrinsic factor that is needed for absorption of B-12 consumed orally.

Therapy with **vitamin C** may help normalize platelets in some people. In one long-ago study, a dose of 10,000 mg daily resulted in normalization of platelet levels and restoration of normal homeostasis in most of those given the vitamin. When the vitamin C was discontinued, platelet levels decreased again to undesirable levels. When the vitamin was begun again, the platelets again went back up to normal. This study was small and no followup research was done, but for those with low platelets, a trial of vitamin C therapy might be worthwhile.

Alkylglycerols from shark liver oil have provided some positive results increasing white blood cell counts in Scandinavian studies. A minimum of 1,000mg three times per day up to 2000mg three times per day may be beneficial.

Treatment of infections or cancers. If any infection or cancer known to cause suppression of neutrophils and/or platelets is diagnosed, treatment of these will be important. However, in some cases, the treatments might themselves be problematic, in which case concomitant use of G-CSF is often very useful.

For Neutrophils

G-CSF (Neupogen). Granulocyte Colony Stimulating Factor is normally produced by the body to stimulate the development of granulocytes. It works by stimulating the immature cells of the bone marrow to reproduce and mature. Use of the synthetically engineered Neupogen will dramatically increase white blood cell counts in almost all recipients (98 percent in one study), in an average of only two days. The most widely prescribed dose of G-CSF is 5 micrograms (mcg) per kg of body weight per day. In some cases, such as bone marrow transplant, higher doses are used. The dose is usually individually adjusted to avoid overstimulating the production of neutrophils. The effect of the drug is dose-related—with larger doses bringing higher white blood cell counts, but only temporary, with drops back to pre-treatment levels after the drug is discontinued. Neutrophils are the most common cells produced with use of G-CSF. In addition to increasing the number of neutrophils, their function is also restored with the drug. Researchers have found that neutrophils are dysfunctional in HIV+ people, with function worsening with disease progression. Thus, the G-CSF-induced restoration of neutrophil function is very important for the control of bacterial and fungal infections. Studies have shown a very significantly reduced incidence of bacterial infections in those given the drug.

G-CSF works whether decreased neutrophils are the result of HIV or of drug side effects. Perhaps of most importance, it has been clearly shown that the use of G-CSF will allow the continuation of bone marrow suppressive antiretroviral drugs or drugs used to treat opportunistic infections or cancers when those drugs might otherwise have had to be discontinued. Thus, potentially lifesaving therapy can be continued in effective doses by concomitant use of G-CSF.

Neupogen is usually given via subcutaneous injections but can also be given via an intravenous infusion. There

are usually only mild side effects with its use. The most common is bone pain which occurs in about a fourth of those given the drug, and is more severe in those given higher doses or who are given the drug intravenously. The bone pain can usually be controlled with mild pain relievers. Other side effects attributed to the drug in studies include fever and elevated liver enzymes. Because G-CSF is a growth factor, it may stimulate the growth of malignant cells in tumors, particularly those of the bone marrow.

Mitochondrial Support. Doing everything possible to help prevent mitochondrial damage may help to prevent (or prevent worsening of) and possibly even reverse (at least partially) neutropenia. Based on the research done to date, the most important nutrients for this would be a broad spectrum of antioxidants, the B complex, and the amino acid L-carnitine.

The most important antioxidants would include vitamin E (800 to 2,000 IU daily), vitamin C (1,000 to 2,000 mg, three times daily with meals), bioflavonoid complex (1 capsule with each meal), carotenoid complex (1 capsule with each meal), selenium (400 to 600 mcg daily, total from all sources, including your multiple), N-acetyl-cysteine (500 mg, three times daily), coenzyme Q-10 (100 to 500 mg daily), and alpha-lipoic acid (200 to 400 mg, three times daily). (For additional information on these nutrients, see *NYBC's Core Nutrient Protocols* and *Counteracting Inflammation* in this guide's *Introduction*.)

Also important is supplementation with a B complex formula (1 capsule with each meal) or a potent multivitamin/mineral formula that includes the whole B complex (as directed, with meals). Although there are two B vitamins that have been mentioned as being important for countering mitochondrial damage—thiamine (vitamin B-1) and riboflavin (vitamin B-2)—it should never be forgotten that the B vitamins work together, that deficiencies of several B vitamins and many other nutrients are common in HIV disease, that nutrients work as a package in the body, and that one missing link could sabotage the effectiveness of other nutrients. For this reason, a B complex formula or a multiple containing the whole B complex should always be given in conjunction with any separate supplementation with individual B vitamins.

Also crucially important is the amino acid carnitine. Carnitine is available in two forms: L-carnitine and L-acetyl-carnitine. There are both over-the-counter and prescription forms of L-carnitine. The brand name of the prescription form is Carnitor. L-carnitine should be taken in doses of 1,000 to 2000 mg, three times per day. L-acetyl-carnitine (available over the counter) should be taken in doses of 500 to 1,000 mg, twice daily. Note that L-acetyl-carnitine will release four times the amount of free carnitine into the bloodstream, compared to an equivalent dose of plain L-carnitine. Thus, the need for higher doses of L-carnitine to achieve the same effect. If insurance or Medicaid coverage for Carnitor is available, this could provide substantial savings.

If it is not, then the over-the-counter L-acetyl-carnitine may be best since it requires lower doses for the same effect. [For more information on these, see *NYBC's Core Nutrient Protocols* and *Counteracting Inflammation* in this guide's *Introduction*.]

Codonopsis. Practitioners of Traditional Chinese Medicine (TCM) have long used codonopsis as a primary herb in the treatment of white blood cell decreases. These practitioners believe that codonopsis may help by addressing the underlying problem that seems to be at the root of most antiretroviral-related neutropenia: damage to the bone marrow. Some naturopathic physicians report good results using a TCM product called Marrow Plus, a combination of codonopsis and supporting herbs. It seems to work well for drug-induced neutropenia, whether the causative drugs are antiretrovirals or cancer chemotherapies. The Marrow Plus is often helpful even when the drugs are continued long-term. The standard dose is three to four capsules, three to four times daily. Marrow Plus has also been used to prevent or slow the development of drug-induced neutropenia in people who are beginning bone marrow-suppressive drugs. For this, the recommended dose is two capsules, three times daily.

NYBC Supplements for Low White Blood Cells:

B12 1,000mcg x 250	chew 1/day
Mineral Ascorbates C 1,000mg x 180	10/d (3B, 3L, 4D)
Folic Acid 800mcg x 250	1/day
Marrow Plus 750mg x 270	12-16/d (3-4B, 3-4L, 3-4D+)

For Platelets

IVIg. Intravenous immune globulin preparations (IVIg) can be very useful when immediate restoration of platelets is needed. Infusion of gamma globulin (400 mg/kg per day for 4 to 5 days) will rapidly raise the platelet count in 70 to 90

percent of recipients, but the effect is often only temporary, usually lasting from two to three weeks. Fewer than ten percent of IVIG recipients have a sustained benefit. For that reason, this costly therapy is usually limited to those with immediate bleeding problems, or those who need to have a rapid platelet increase prior to surgery.

Anti-D (anti-RH) antibody. A particular type of human immune globulin, Rho(D) immune globulin, also called anti-D antibody therapy (Ortho's RhoGAM or RH Pharmaceutical's WinRho SD), is FDA-approved for ITP in HIV+ people. This product contains concentrated antibodies that bind to the Rh antigen on red blood cells. With anti-D antibody therapy, platelet counts rise temporarily in about 75 percent of recipients, usually within one to two days, and usually remain elevated for around a month. The drug has a sustained effect in fewer than ten percent. This treatment will not work in those who are Rh-negative or who have had the spleen removed. It can result in some reduction of red blood cells, although not usually enough to be problematic.

Platelet transfusions. In emergency situations where bleeding is occurring or there is a need for surgery, platelet transfusions can be given.

Other possibilities

Alpha interferon. Alpha interferon has been shown in several studies to bring about at least partial platelet restoration in around two-thirds of those treated, although complete restoration is not common. One study indicated that it may be only a temporary improvement in most, although the length of time that the improvement lasts varies widely. The therapeutic effect lasted for as little as 19 days in one person to as long as 100 days in another. Standard dosing is 3 million units given subcutaneously three times weekly. The flu-syndrome side effects of alpha interferon treatment would make long-term continuation unacceptable to most people.

Corticosteroid drugs. The standard approach of the past was to treat lowered platelets with corticosteroid drugs such as prednisone. However, because of the research showing the lack of long-term improvement in most people, and the significant risk of development of infections with long-term use of such immunosuppressive drugs, this therapy is not generally considered advisable, if it can be avoided. However, for those in immediate need of platelet restoration, a short course of corticosteroids is effective in 40 to 80 percent of recipients.

Spleen removal or radiation. Because platelets coated with antibodies are mostly cleared from the body by macrophages residing in the spleen and liver, when platelet levels remain dangerously low despite other treatments, some physicians recommend removal of the spleen (splenectomy). This does often result in increases in platelet levels but the levels often decline again within a few months. In addition, removal of the spleen creates an increased risk of infections that has led some researchers to term splenectomy "hazardous" for HIV-infected people. Thus, it would seem wise to avoid this, if at all possible. A somewhat less drastic approach is radiation of the spleen. Low doses of radiation (total doses of around 900-1,000 centigrays administered over a month's time) have resulted in immediate improvement in about 70 percent of those receiving the radiation, although long-term improvement only occurs in around 40 percent. It does allow the spleen to remain at least partially functional so, where nothing else works, it might be preferable to removal of the spleen.