

ANEMIA

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

Anemia is a red blood cell disorder in which there are too few red blood cells, and thus too little of the iron-containing protein called hemoglobin in the blood. Since hemoglobin is what enables the red cells to carry oxygen from the lungs to the rest of the body, sub-par levels leave the body oxygen-starved. The symptoms that may result include fatigue, weakness, shortness of breath, heart palpitations, skin pallor, and lightheadedness. But note that some people can be severely anemic with virtually no symptoms so lab testing is a must for accurate diagnosis.

Even when there are no obvious symptoms, anemia can create increased drug toxicity, increased susceptibility to infections, and reduced capacity for work and exercise. One large study found that up to three-fourths of people with clinical AIDS and around a fourth of those in less advanced disease stages may develop anemia, and that regardless of the disease stage, the risk of death is higher for those with anemia. Thus, testing to diagnose it, followed by effective treatment is a must.

Below-normal readings on blood tests—red blood cell count, hemoglobin and hematocrit—can indicate anemia. HIV-experienced clinicians recommend regular testing (at least quarterly) to screen for anemia, and immediate blood tests any time there are symptoms that might indicate this problem.

In those who are shown to be anemic, it will also be important to consider the possibility of iron deficiency. Iron is the active component of hemoglobin which is the substance that carries oxygen in red blood cells. Tests for iron deficiency include serum ferritin, serum iron and total iron binding capacity.

Hemoglobin (Hgb)—Measures the level of this protein in the blood, and thus provides a good index of the blood's oxygen-carrying capacity. In men, the normal range for Hgb is 14 to 18 grams per deciliter (g/dl); in women, 12 to 16 g/dl. Any Hgb measurement below 10 is considered severe anemia, while readings of 10 to 14 g/dl in men or 10 to 12 g/dl in women indicate moderate anemia.

Hematocrit (HCT, also called Packed Cell Volume, or PCV)—Measures the portion of blood volume made up by red blood cells. In men, the normal values are 40 to 54 percent; in women, 37 to 47 percent. HCT readings below 35 percent in men or 30 percent in women indicate severe anemia, while readings of 35 to 40 percent in men or 30 to 37 percent in women indicate moderate anemia.

Red Blood Cell Count (RBC)—Measures the number of red blood cells in one cubic millimeter of blood, as an indicator of the total body number. In men, normal values are 4.6 to 6.2 million per cubic millimeter; in women, 4.2 to 5.4 million. Lower than normal values indicate anemia.

Serum Ferritin, Serum Iron and Total Iron-Binding Capacity (TIBC)—Ferritin is a protein which binds with iron, and the resulting ferritin-iron complex serves as one of the body's main iron reserves. Although only a small amount of this complex appears in the blood, a serum ferritin level usually reflects the amount of available iron stored in the body. Serum iron measures the amount of free iron bound to a protein called transferrin. Total iron-binding capacity (TIBC) measures the amount of iron it would take to saturate all the transferrin in a certain amount of blood. By dividing the TIBC by the serum iron, the percent of transferrin that is actually saturated can be calculated.

The combination of these readings will indicate either iron deficiency or iron overload. Note that most labs have a wide reference range for serum ferritin, and the low end of normal may actually be showing inadequate iron stores. On the other hand, too much iron could indicate a level of iron storage that could be detrimental (see discussion below). Some experts believe that a range of serum ferritin from 40 to 60 would be ideal. A serum ferritin of over 80 is associated with an increased risk of cardiovascular disease. However, systemic inflammation, chronic infection, or chronic disease (all of which would characterize HIV+ people, in general) can cause increased ferritin readings which would not necessarily be indicative of iron overload. It would be important to monitor readings over time. If the ferritin remains somewhat elevated consistently over multiple readings, this might just be indicative of your chronic disease status. By countering the possibility of oxidation of the iron in the body with a plentiful supply of antioxidants, you can help lessen any cardiovascular risk that such an elevated level might otherwise confer. Interpreting these laboratory results is complex and should always be discussed with your physician.

What are the Causes?

Anemia has multiple possible causes in HIV disease, and in many people, there may be more than one factor contributing to its development.

□ Anemia is a particularly common result of infections or drugs that suppress or damage the bone marrow, the

body's red blood cell factory. Included among these infections are mycobacterial infections (*Mycobacterium avium* complex or MAC, and tuberculosis), cytomegalovirus (CMV) colitis, cryptococcal meningitis, parvovirus B-19, and fungal infections (cryptococcus, histoplasmosis, and coccidioidomycosis). Anemia also often appears with lymphoma and KS.

□ **Anemia can also be caused by HIV infection itself since the virus can impair the production of red blood cells.** It seems likely that part of the HIV effect comes via the production of cytokines (cell-produced chemicals), including tumor necrosis factor-alpha, which are known to cause bone marrow suppression. Increased TNF-alpha results in increased oxidative stress which in a vicious circle causes increased levels of TNF-alpha and so on. This may be a contributing factor in the creation of anemia, especially in those not yet on HAART.

□ **In a catch-22, the antiretroviral drugs that can suppress HIV and, thus, improve red blood cell production, may themselves suppress the bone marrow and cause anemia. Many other drugs can also contribute to the problem.** Included on a long list of possible anemia causes are AZT (either alone in Retrovir® or combined with other drugs in Combivir® and Trizivir®), ganciclovir, sulfa antibiotics, alpha interferon, hydroxyurea, pyrimethamine, pentamidine, ribavirin, and various cancer chemotherapies. Also note that alcohol is known to be bone marrow suppressive so avoiding alcohol would be wise for anyone with anemia.

□ **In addition, the high incidence of B₁₂ and folic acid deficiencies in HIV+ people can cause or contribute to anemia.** These deficiencies have also been shown to contribute to the likelihood of bone marrow suppression from AZT and other drugs, thus increasing the chance that the drugs will cause or worsen anemia. Alas, standard blood tests do not always accurately reflect these nutrient 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 some cases, B-12 deficiency can cause anemia-type symptoms that precede the appearance of red blood cell abnormalities. 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.

□ **In HIV-positive women, research has shown that iron deficiency may sometimes be the cause of anemia.** In Baltimore, the AIDS Linked to Intravenous Experiences (ALIVE) study looked at ferritin levels and hemoglobin in 197 HIV-positive women, most of whom were co-infected with hepatitis C. Researchers found that almost half (44.1 percent) were anemic, and in almost half of those cases, iron deficiency was the cause. In pre-menopausal women, the factor of monthly loss of blood during menstrual periods may contribute to such iron deficiency. In men, it is thought that iron-deficiency anemia is relatively rare.

In both men and women, it is important to remember that needless supplementation with iron is absolutely not advisable. Too many people have heard too many advertisements about "iron-deficiency anemia" and presume that iron is always needed with anemia. It absolutely is not, and there are risks with needlessly high iron intake. There has been research that indicates that too-high iron might increase HIV replication. For those coinfecting, it is important to note that researchers have seen a lack of response to interferon therapy in patients with elevated hepatic iron stores. The only time that iron supplementation should be done is when the appropriate combo of blood tests (serum ferritin and total iron binding capacity) show that iron is definitely too low. Using the blood test results to guide supplementation is crucial, both before initial supplementation with iron (in order to know if it's needed) and after supplementation (in order to know if the appropriate amount is being given).

□ **Those who have been long-term vegetarians, especially vegans who have completely avoided all animal products, are highly likely to be B-12 deficient since B-12 is only found in animal products.** It would be important for anyone with such a dietary approach to take B-12 supplementation. In addition, adding some animal protein, perhaps eggs from cage-free, organically fed hens if that fits your philosophy about animals, can really help.

□ **Last but not least, anemia has also been shown to be common in people with low incomes,** probably due to the worsening of malnutrition created when people already likely to be nutrient deficient (due to the effects of HIV infection) take in inadequate or nutrient-poor food because they simply can't afford a better diet.

What are the possible treatments?

The first must for effective treatment of anemia 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 treating any infections found, and eliminating any anemia-causing nutrient deficiencies with appropriate supplementation and a nutrient-rich diet. Supplementing with a broad range of antioxidant nutrients may also help by reducing oxidative stress in the body, and thus lowering the body's production of bone marrow-suppressive cytokines. In those not currently on antiretroviral drugs, the persistent presence of anemia would be a factor to be considered in deciding to start HAART therapy since HIV might be contributing. Where possible, choosing drugs less likely to cause anemia would be preferable.

For those currently on HAART, substitutions should be considered for anemia-causing drugs, where possible.

However, there are three caveats to this. First, it may be impossible to eliminate some of the causes. For example, although it would be appropriate to look for possible substitutions for any medication that appears likely to be contributing to this problem, there may not always be available substitutes. 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.. If the combo is otherwise working well and providing the anti-HIV benefits needed, it may be necessary to stay with those meds, while addressing the anemia with the red blood cell growth-promoting drug erythropoietin (Procrit; see below). In other cases, there may be no choice but to stick with the cancer chemotherapies or other drugs needed for treatment of particular conditions since what has been prescribed may be the best possible treatment. Again, the right approach may be to stick with those meds, but treat the anemia itself with Procrit.

Second, while HIV anemia expert Ronald Mitsuyasu, MD, of UCLA's Center for Clinical AIDS Research and Education, urges addressing all treatable causes, he notes that in the majority of cases today, no specific cause is found. So again, directly addressing the red blood cell problem itself with Procrit may be the only choice.

Third, the fact discussed above that B-12 and folic acid may be deficient despite normal-appearing lab results means that these deficiencies' possible contribution to anemia may be missed. This has led many physicians to simply do a test run of supplementation with both nutrients to see if fatigue and weakness improve. Deficiencies of other B vitamins may also contribute to anemia because they are also important for the production of red blood cells.

So an aggressive approach to anemia would include treating any identified cause, substituting for anemia-causing drugs if possible, treating HIV infection for those not currently doing so (if otherwise appropriate), supplementing with B-12 and folic acid, along with a B complex or a multivitamin that contains the whole range of B vitamins, supplementing with antioxidants, and improving the diet as much as possible. In addition, women experiencing heavier than normal blood flow during their periods may need to discuss with their physicians the possible use of drugs to help regulate menstrual flow. Where anemia cannot be eliminated by all of the above, boosting the body's production of red blood cells with erythropoietin is the best approach.

Key Therapies

Crucial nutrients.

Antioxidants. Antioxidant nutrients—including especially vitamins C and E, N-acetyl-cysteine, alpha-lipoic acid, bioflavonoids, carotenoids, and selenium—can help to reduce the oxidative stress that is common in HIV disease, and thus lower the body's production of bone marrow-suppressive cytokines. Certain antioxidants may be particularly important. For example, Vitamin E has been shown to help counter the bone marrow suppression caused by AZT and, thus, would be very important for those taking Retrovir®, Combivir®, or Trizivir®. Appropriate doses for countering oxidative stress and, thus, lessening bone marrow suppression might be vitamin E (800 to 2,000 IU daily), vitamin C (2,000 to 6,000 mg daily, spread across three 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), coenzyme Q-10 (100 to 500 mg daily), (N-acetyl-cysteine 1,500 - 2,500 mg daily), and alpha-lipoic acid (200 to 400 mg, three times daily).

B-12 and folic acid. These nutrients 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 by pills, or one to several times weekly through nasal gel or injections available by prescription) and folic acid (800 mcg daily via pills) may be useful in restoring energy and overall feelings of well-being, 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 (in either foods or pills). Since B-12 deficiency, a known cause of anemia, has been shown in many studies to be widespread in HIV disease—and researchers have noted that test results frequently do *not* accurately reflect deficiencies—supplementation with B-12 and folic acid would seem to be appropriate in anyone with fatigue or other anemia-related symptoms, or with blood signs of deficiency.

Iron. For those whose blood tests (serum ferritin and TIBC) show a need for iron, appropriate supplementation in order to return these blood test readings to the ideal range would be important. Aqueous Liver Extract by PhytoPharmica provides folic acid, B-12, and very absorbable iron, as well as a whole complex of B vitamins, and has been found to be quite useful for those needing iron supplementation for anemia.

NYBC Antioxidant Anemia Protocol:

Carotenoid Complex UltraAntioxidants x 90	3/d (1B, 1L, 1D)
Coenzyme Q-10 100mg x 50 gels	1-6/d (1B, 0-2L, 0-3D)
E, Natural Tocopherols 400IU x 250	3/d (1B, 1L, 1D)
Mineral Ascorbates C Sustained Release 1000mg x 180	3-6/d (1-2B, 1-2L, 1D)
N-acetyl-cysteine (NAC) 500mg/Lipoic 200mg/MSM 250mg Sustained Release x 90	3-6/d (1-2B, 1-2L, 2D)
Phytoflavonoid Complex UltraAntioxidant x 120	4/d (1B, 1L, 2D)
UltraProtection III & IV x 270 (iron/no iron)	9/d (3B,3L,3D)

Botanicals

Codonopsis. Practitioners of Traditional Chinese Medicine (TCM) have long used codonopsis as a primary herb in the treatment of anemia. These practitioners believe that codonopsis may help by addressing the underlying problem that seems to be at the root of most antiretroviral-related anemia: damage to the bone marrow. Phoenix naturopathic physician Kären van der Veer reports good results using a TCM product called **Marrow Plus**, a combination of codonopsis and supporting herbs. She has seen it work well for drug-induced anemia, 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. She has also used Marrow Plus preventively in people who are beginning bone marrow-suppressive drugs, especially with women (because they are generally more prone to anemia) and anyone with a history of anemia. For this, she recommends two capsules, three times daily as a way to prevent or slow the development of drug-induced anemia.

Marrow Plus 750mg x 270	9/d (3 morning, 3 afternoon, 3 evening)
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Erythropoietin (Procrit). Erythropoietin (EPO) is a protein that is normally produced by the kidneys to promote the production of red blood cells in the bone marrow. The synthetic versions are administered via subcutaneous injection and are quite effective in boosting red blood cell counts, and eliminating the symptoms of anemia. It works well to reverse anemia caused by drugs, even when the person is continuing to take them. Ronald Mitsuyasu, M.D., advises giving erythropoietin one to three times per week, even to those diagnosed with only mild to moderate anemia, as a way of maintaining hemoglobin and hematocrit at normal levels, and thus eliminating anemia symptoms. The drug can make a huge difference in quality of life, and has few side effects, although some people experience a temporary rash. Other side effects that more rarely occur are fatigue, headaches, high blood pressure, cough, fever and/or asthenia (the "blahs"). For those with uncontrolled high blood pressure, it is advised that the blood pressure be controlled before beginning EPO; for those with inadequate kidney function, it is very important to monitor blood pressure during treatment. The drug's effectiveness can sometimes be blocked by opportunistic infections that involve the bone marrow, such as disseminated MAC. Because of its high cost, some insurers are reluctant to approve its use, but it is generally reimbursed by either private insurers or Medicaid. For those without coverage for the drugs' costs, the manufacturers provide limited patient assistance programs. *In 2007, the FDA noted that the drug is often overprescribed and can have dangerous and potentially lethal side effects. If ALL other efforts to manage ANEMIA have failed, you don't have serious kidney disease, etc., this is drug to explore. If you just have fatigue NOT related to anemia, this is a drug to AVOID.*

NOTE: Both B-12 (1,000 mcg given daily in pill form, or one to several times weekly with prescription nasal gel or injections) and folic acid (800 mcg daily via pills) should be given along with Procrit because they are the *rate-limiting* step in red blood cell production. In other words, Procrit is stimulating the bone marrow to produce red blood cells but it does not provide the raw materials from which those cells are actually created. Those raw materials are the B-12 and the folic acid so if you don't have enough of them, you won't be able to build the cells. Since they are so commonly deficient in HIV disease, simply providing them along with any use of Procrit seems wise. For those shown to be iron deficient, supplementation with iron may also be needed.

Blood transfusions. In those with severe anemia, the only option may be an immediate blood transfusion to maintain the body's oxygen level. However, if at all possible, the severe deficiency state that would mandate a transfusion should be avoided. Dr. Mitsuyasu points out that transfused blood can reduce immune responses by white blood cells, decrease

production of the cytokines (cell-produced chemicals) that are used for immune cell communication, and decrease activity of two important immune system components, natural killer cells and monocytes. In addition, transfusions can result in transfusion reactions, iron overload, or transmission of blood-borne infections. As if that's not enough, studies have shown increases in viral load after infusion of as little as one unit of blood. So monitoring blood counts regularly so that anemia is caught before it ever reaches a severe stage is very important.