

Glutamine is an amino acid which is normally found in greater abundance in the body than any other free amino acid. It is crucial for many aspects of healthy body function, including maintenance of optimal antioxidant status, building and maintenance of muscle tissue, maintenance of optimal immune function, and repair and maintenance of intestinal tissue. Because it has long been classified as "non-essential"—meaning that the body can normally synthesize what it needs—little attention has been paid to its importance in HIV disease. Luckily, the work of Judy Shabert, M.D., M.P.H, is changing that. She has shown that glutamine deficiency may cause many serious problems, including inadequate antioxidant status in the body, wasting, and loss of both intestinal and immune function. Dr. Shabert points to the research showing that during the stress of infection or injury, the demand for glutamine is very high.¹ The muscles respond to this demand by releasing their stored glutamine. In fact, the rate of release of glutamine from the muscles is dramatically increased, to levels 3-4 times normal. According to Dr. Shabert, the body does this in order to provide glutamine to the intestinal tract, liver, kidneys, and immune system cells.

With the short-term metabolic stress that is created by acute infections, the body can soon return to normal rates of glutamine use. The muscle glutamine levels are quickly restored and the muscles are not damaged. Unfortunately, with the continuous metabolic stress that results from the chronic infection of HIV disease, the demand for glutamine continues and the concentration of this amino acid in the muscles falls rather rapidly. This results in a decline in the synthesis of muscle tissue and, eventually, a wasting away of the muscles. Since the muscles can no longer provide sufficient glutamine, blood levels will also stay chronically low. Only when glutamine levels are restored to normal will muscle synthesis be able to work normally in order to restore the muscle tissue. Thus, supplementation of this amino acid at levels sufficient to restore normal status in the body is vitally important. Muscle loss may be restored or, better yet, muscle wasting may be prevented in the first place. This, of course, makes glutamine crucial for the prevention of internal decline and wasting.²

In addition, glutamine is very important for the maintenance of immune function. It is the primary fuel source for lymphocytes and macrophages. These cells consume glutamine at high rates even when there are no special demands for immune system response to an infection.³ During an immune response when the immune cells have to increase in number and do their work of destroying pathogens, the rate at which glutamine is used increases dramatically. When the body's supply of glutamine runs short, immune function is compromised. Dr. Shabert notes that both the speed at which T cells mature and the proliferative responses of T cells have been shown to be positively affected by supplementation with L-glutamine. Glutamine also increases the activity of natural killer cells and improves the function of neutrophils. In addition, glutamine is critical for the immune function of the respiratory tract, the genitourinary tract, and the intestinal tract. The linings of these tracts produce secretory immunoglobulin A (sIg-A), a type of antibody which works in and on the linings to provide immune defense. Glutamine is a required nutrient for sIg-A-producing cells.

This antibody provides the primary immunological defense of the intestinal tract. Thus,

supplementation with L-glutamine may help restore sIg-A production in a way that will improve the immune defense of the gut lining and help prevent infections.⁴ It may be particularly helpful in reducing the incidence of *Candida* overgrowth in the mouth (thrush), throat (esophageal candidiasis), and lower intestinal tract. Researchers have found that decreased sIg-A levels in the saliva are tied to an increased incidence of *Candida* problems, as well as other oral opportunistic infections.⁵ L-glutamine may also help to restore the immune function of the respiratory tract. This is, of course, terribly important since so many people living with HIV experience lung infections. Anything that might boost the lungs' ability to protect themselves could have considerable benefit. In addition, adequate sIg-A production is crucial for the immune defense of the genital and urinary tracts. In a study of HIV+ women, it has been shown that secretion rates of sIg-A are sharply reduced in later disease stages.⁶ The levels of sIg-A in cervicovaginal secretions were found to be markedly lower than would be optimal for proper immune defense in the genital tract. For all these reasons, giving the body sufficient L-glutamine to help restore adequate amounts of sIg-A to the linings of the body could significantly boost immune defenses.

Glutamine is also critical for maintaining the health of the intestinal tract since it is required for the constant rebuilding of intestinal cells. The cells lining the intestine function to absorb nutrients and to block the uptake of pathogens. These cells are regenerated every 3-4 days. The energy which allows this process to occur comes from glutamine. If glutamine concentrations are low, the result is intestinal tissue atrophy and decreased absorption, with resulting lack of uptake of nutrients vital to the body's function. Glutamine is also necessary to maintain the barrier function of the intestines, the body's ability to block the uptake of pathogens, improperly digested food particles, and so on. As is readily apparent, glutamine's ability to help repair the intestines is among its most important benefits for people living with HIV.

For those on intravenous nutrition (total parenteral nutrition/TPN), it is critically important to add glutamine to the IV solution. In an extensive review article on the role of glutamine in critically ill hospitalized patients, it is suggested that supplemental glutamine in either enteral or parenteral feedings may greatly improve nutrition management and increase the speed of recovery, thus shortening hospital stays.⁷ In part, this is almost certainly due to its capacity to heal the intestines or prevent their atrophy. Dr. Shabert points out that the usual failure to replete lean tissue that is seen when standard TPN or most oral nutritional formulas are used in an attempt to address wasting is due to the fact that most such formulas fail to provide the rate-limiting amino acid for muscle tissue building, L-glutamine. [For further discussion of glutamine's importance for intestinal function, see *Chapter Nine, Treatments for Intestinal Damage*. For information on the addition of L-glutamine to TPN, see *Chapter Nine, Treatments for Weight Loss*. For information on oral formulas which contain L-glutamine, see *Chapter Three*.]

Restoring glutamine sufficiently to achieve optimal blood levels can also be critically important for maintaining the antioxidant status in the body. As discussed in the next entry, glutathione is one of the body's best antioxidant defenses against the oxidative damage of HIV disease. The reason that L-glutamine is important to maintain glutathione levels is somewhat complicated but the simple version is this. The amino acid cysteine is generally the rate-limiting factor in the production of glutathione in the body. In other words, the amount of glutathione that you can produce will be dependent on the amount of cysteine that is available for that process.

That's why N-acetyl-cysteine, discussed below, is important for glutathione synthesis. However, once you've provided all the cysteine that's necessary, glutamine becomes the rate-limiting factor in the production of glutathione. Thus, in a body depleted of glutamine, glutathione production will never be optimal. Supplementing with both NAC and L-glutamine can greatly improve the chances for full glutathione replenishment, with all the benefits that come from that. It will also help to ensure that your body remains capable of properly breaking down all the drugs you may be taking. The liver uses glutathione for the detoxification of drugs. When levels of glutathione in the liver are too low, its ability to properly break drugs down may be compromised.

Dr. Shabert believes that the combination of all these needs for glutamine results in a demand for it that is well beyond what the body can possibly provide for itself. Thus, supplementation with sufficient amounts of L-glutamine to provide the body what it needs for all these important functions is very crucial. The L-glutamine can be given either orally or intravenously to accomplish this. Glutamine normally makes up 5-8% of dietary protein so the average person eating approximately 100 grams of protein per day is getting around 5-8 grams daily. However, this level appears to be inadequate even for maintenance of glutamine levels in someone living with HIV who is asymptomatic. For someone in more advanced disease stages or in need of intestinal repair or muscle rebuilding, it is hopelessly insufficient. It appears that even those in early, asymptomatic disease stages may need approximately 10 grams per day to protect their bodies. As the disease progresses, moving toward 15 grams per day is probably appropriate. When there are already existing problems, increasing to even higher doses may be necessary.

Charlie Smigelski, R.D., a registered dietitian and researcher at Harvard University, has suggested that doses of 40 grams per day may be useful for those who need to repair the intestines or gain weight and muscle tissue. Based on his work and that of other researchers, it appears that doses of 30-40 grams per day (30,000-40,000 mg), spread out over five doses of 6-8 grams each (6,000-8,000 mg), continued for at least 7-10 days may be helpful. Lengthier periods on this higher dosage may be necessary for some, especially if the need for intestinal repair coincides with the need to restore wasted muscles. Substantial amounts of L-glutamine are necessary for both of these so when these two problems coincide, it may be necessary to continue higher dosage levels until both the intestines and the muscles are well restored. It is only when all the extraordinary demands for glutamine needed to effect intestinal and muscle repair are met that the body will be able to return to meeting day-to-day needs for maintenance of those tissues and of proper antioxidant status in the body with lower levels of L-glutamine.

There is a blood test available that can measure glutamine levels as part of an assay of amino acids in plasma. Unfortunately, blood levels can be somewhat misleading because the body will attempt to keep blood levels normal even when the level in the muscles is low. Thus, a normal blood level may not mean that the muscle level is adequate. If the level in the blood is low, the level in the muscles is probably very low. However, despite the inadequacies of the test, Dr. Shabert believes that you could look at sequential blood levels to at least see if you are moving in the right direction. She believes that a healthy normal level is above 600 nmol/ml (not the levels below 600 that some labs list as normal). Remember that it may take some time for glutamine levels to be restored. The body will have to use a lot of it to rebuild wasted muscles and/or repair the small intestine. It will need even more to boost its stores to levels adequate for

maintaining optimal glutathione levels and immune function. If your initial blood level is below 600 nmol/ml, you could supplement with L-glutamine for a month or so and then re-test to see if you're taking enough to move yourself back toward healthy normal levels. One company that provides an amino acid assay that includes a glutamine level is MetaMetrix; see *Chapter Fourteen, Nutrient Status Tests*; just remember Dr. Shabert's warning that the "normal" level on their report is actually too low; healthy normal is above 600 nmol/ml).

In general, doses of 2500-4000 mg, taken on an empty stomach 30-45 minutes before each meal and at bedtime (or any four times that your stomach is empty), can help to not only maintain intestinal function, but also to restore lean tissue (muscles), improve immune function, and maintain optimal antioxidant status in the body. Doses of 30-40 grams per day (30,000-40,000 mg), spread out over five doses of 6-8 grams each (6,000-8,000 mg) may be very helpful for those with serious intestinal damage or muscle wasting. After repair is effected and muscles are rebuilt, the lower maintenance doses are probably adequate for most people, although the need can vary among individuals. Having now worked with quite a few people who have used glutamine as part of their approach to reversing wasting, I can tell you that in a number of cases, especially those in which muscle wasting was already serious, it has taken a number of months of using 30-40 grams per day before the muscles were restored. Dr. Shabert also points out that during intensive exercise glutamine is used to restore glycogen to the muscles when they've been drained by the demands of the exercise. Thus, such exercise can increase your body's need for glutamine. Dr. Shabert suggests adding 5 grams of glutamine to your runner's bottle of liquid, and sipping it throughout the exercise period.

For those who have difficulty finding 3-5 times per day when the stomach is empty, scheduling the glutamine supplement to be taken upon arising, mid-morning, mid-afternoon, before bed, and in the middle of the night (if you wake up then anyway) will probably be best. Glutamine is available in both capsules (usually 500 mg each) and powdered form. However, in general, the powdered form is preferable since far too many capsules would be required to meet the dosage levels necessary for the best results. For those in need of higher dosages, the powdered form is a must. It will be much easier to take and is considerably less expensive than the encapsulated forms. In addition, you'd never want to take 80 gelatin capsules per day of anything. The gelatin in the capsules could cause diarrhea. With most products, each teaspoon of L-glutamine powder contains approximately 4 grams. If you're doing the higher dose of 40 g per day, this would mean taking approximately 2 teaspoons, five times per day. After the intensive therapy period, the dosage can be reduced to 3/4 to one teaspoon (3-4 grams), 3-4 times per day. The powder can be mixed in a half a cup of water or juice or, if you prefer, in a warm liquid such as soup or tea. Don't, however, add it to hot liquids. For those who can't find it locally, a mail-order source for glutamine powder is Wholesale Health, a direct buying service for obtaining supplements for people living with HIV (see *Chapter Five, Obtaining Drugs, Nutrients, & Therapeutic Agents*).

[No known toxicity. Individuals who are on protein-restricted diets because of advanced liver or kidney disease should not take glutamine without their physician's approval since it would have to be considered part of the limited amount of protein allowed. If it's taken too late in the day (around bedtime), some people feel that they have trouble sleeping, probably due to its effect on neurotransmitters. If this is a problem, skip the late dose and increase the amount in other

doses. And now to address the false rumors that have been bandied about by companies trying to sell a particular product: the purported problem with ammonia is nonsense. The rumor has been that glutamine could increase ammonia to a dangerous level in the body. This is simply not true. In some studies where high doses of glutamine were given, the ammonia levels were slightly higher in those taking glutamine than in those on placebo, but the difference was *not* significant and the levels were still within the normal range. Some companies have falsely claimed that most glutamine (not theirs, of course) breaks down rapidly and turns into ammonia when it is added to a liquid. In fact, at room temperature glutamine decreases by 0.1 % in 24 hours. When refrigerated, the process is much slower. Pyroglutamic acid, the breakdown product of glutamine, forms at less than 0.02% per day, with ammonia forming at less than 0.01 mmol/l per day. It is, therefore, quite safe to make a day's supply of glutamine, refrigerate it, and drink the liquid throughout the day. Dr. Shabert points out that when people exercise, they produce lactic acid (hydrogen ions) and that glutamine is one way that the body gets rid of these excess hydrogen ions, restoring an appropriate acid/base balance. In other words, not only is it not contributing to an imbalance in the body, it's actually part of how the body restores balance.]

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