

# **Drug Side Effects and Other Symptoms: Helpful Tips on Countering or Preventing Them**

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Almost all drugs have the potential to cause your body problems that will create troubling symptoms. They're called drug side effects, and a few tips may help you handle them. First and foremost, you must be in touch with your body—so you're really clear on what it's experiencing and can describe it—and with your doc—so a medical judgment on the symptom can be made. Which leads us to the two most important rules: Rule #1: Tell your doc everything, from beginning to end—if a symptom appears, changes, disappears, reappears, tell Doc. Rule #2: Always apply Rule #1.

If you've talked to Doc about possible sides before starting therapy, you'll be better prepared. If there's one that might be life-threatening, you'll know what to watch for. If it's likely that this, that or the other will improve over time, it will be easier to convince yourself to stick with it if you know it may soon vanish.

Know that while the body adjusts to any new med, you may experience headaches, nausea, muscle pain or dizziness, all of which may disappear in two to six weeks. The same holds true for other, more drug-specific symptoms. As the body adjusts, symptoms may diminish or become more manageable. Always remember that you're not alone. Countless others are feeling the same thing right now. So even if the symptom seems too awful to handle long-term, talk to your co-sufferers,

soak a few shoulders if you must, and hang in there for at least six to eight weeks after a med is introduced, if you possibly can.

Also know that new side effects can appear at any time. Repeat, ANY time. Never say to yourself that you've been on this combo for three years now so what you're feeling couldn't possibly be tied to the meds. It could. And refer to Rules #1 and 2.

Regardless of the specific symptom, always seek a full diagnosis on all possible contributing causes. Yes, what you're feeling may be the med, but it could also be a hormone problem, a nutrient deficiency, an infection, depression, HIV itself or any of the countless other contributors to symptoms that are discussed below. The approach that's most likely to eliminate symptoms will address all of these, and perhaps make switching meds unnecessary.

Changing drugs is the final option. The possibilities will, of course, depend on your treatment history and current needs. But always ask Doc. If you don't, you may not find out that there is a good alternative. Doc just hasn't mentioned it because you haven't reported how troubling the symptoms are. See Rule #1.

The goal here is simple: allow you to have your cake and eat it, too. In other words, create an integrated approach that will allow you to gain the benefits that your drugs can give you, while avoiding the side effects that can make taking them so difficult. In the end, there are two potentially huge benefits to this approach. First, it can help prevent drug failure since you are much more likely to properly adhere to drugs when they aren't making you feel sick or causing symptoms that you hate. And the result of always taking your meds as directed—instead of skipping the Saturday night dose because you don't want smelly gas at the party, or the Sunday morning pills because you've been invited to brunch and don't want to be nauseated, or any other dose at any other time because you're sick of that side effect—is that you're much less likely to experience drug resistance. And that means that your meds—and their ability to save your life—may remain effective for years and years instead of months.

And last but most assuredly not least, your quality of life can be immensely improved when life-degrading symptoms are eliminated or, at least, lessened. It's all about living *well* with HIV, not just longer.

And now one last warning that you should keep in mind when you are seeking a diagnosis for any given symptom or condition. Always remember the old rule that you only find what you seek. There have been cases in which, because the person is HIV positive, the diagnostic procedures were too exclusively focused on opportunistic infections (OIs) and conditions, forgetting that HIVers are certainly also susceptible to other infections and malignancies. In some of these cases, when none of the common OIs or conditions were discovered, the symptom was then attributed to HIV disease itself and no further attempts were made at diagnosis. Then, down the line, and usually when other symptoms appeared that gave better indications of a probable diagnosis, the person was finally discovered to be suffering from something unrelated to HIV disease. Unfortunately, by that time, the condition or infection was often much more advanced and more difficult to successfully treat. In these situations, if the person had been HIV negative, the diagnosis might actually have been made sooner because the non-HIV-related possibilities would have been considered more quickly. Never forget this possibility.

And now to the nitty gritty. The most common side effects are listed below, with tips on handling them. For many of these, there will be additional info in other fact sheets devoted exclusively to a particular symptom (for example, neuropathy or diarrhea) so check the fact sheets list!

## **Appetite Loss — yuck, I don't even want to smell that food**

Loss of interest in eating can come from many different meds when they either directly suppress appetite or create changes in the sense of smell or taste which indirectly cause the disinterest. It can also occur when meds are causing nausea that makes the very thought of eating impossible (see Nausea, below). Although discontinuing the offending drug will usually quickly solve the problem, this is often not a possibility so other approaches are needed.

First, consider the other causes that might also be contributing:

- Infections and fever (treat 'em)
- Abnormal levels of hormones (especially testosterone which can be replaced if testing determines that your levels are low)
- Abnormal levels of certain cytokines (especially tumor necrosis factor which can be inhibited with either drugs or the nutrients N-acetyl-cysteine, 500 mg three times per day, and L-carnitine, 1000 mg, three times per day)
- Depression (get the treatment you need; many people lose any interest in eating when they're depressed so feeling better is a must)
- Nutrient deficiencies (particularly of zinc; try 75 mg daily). The nutrient deficiencies are one of those vicious circles: the appetite loss has caused inadequate nutrient intake, and now the lack of nutrients is causing appetite loss. The solution that's needed is usually a non-adherence to medications

## Tips for handling body distortions

Research is underway to attempt to determine exactly why lipodystrophy occurs and how to prevent or treat it so in the future there may be much better solutions. For now, therapies differ depending on the area affected and whether the problem is fat excess or loss. Numerous studies and anecdotal reports have shown that human growth hormone (Serostim) often effectively shrinks big bellies, buffalo humps and lipomas by decreasing the abnormal fat deposits, although full results may not be seen for a period of time. Because many people have a mixture of fat accumulation in some areas of the body but fat loss in others, concerns have been expressed that Serostim's stimulation of fat burning might actually worsen fat loss in the face, arms, and legs. However, this has not been reported in the studies done to date. Clearly, it will not return lost fat to the face, arms or legs, but some people have actually reported that it appears to stimulate enough muscle growth for their limbs to look better.

The standard Serostim dose of the past was 6 mg injected daily, but treatment activists have found that lower doses (1–3 mg), taken either daily or every other day, may work just as well and have the advantage of reducing or preventing the drug's possible side effects — swollen joints, carpal tunnel syndrome (numbness and pain in the wrist and hand) and higher-than-normal blood sugar levels. A number of people have reported that while they did develop joint swelling at 6 mg daily, they did *not* get it when they dropped the dose to 2 or 3 mg, either daily or every other day. And at the lower doses, they did get the positive results that they were seeking (that is, fat reduction).

It appears that the concerns about blood sugar may have been overblown. There was an interesting recent compilation of data that looked back at pre-HAART (pre-protease inhibitor) data on blood sugar changes. In a large placebo controlled study, there were only very mild, very transient elevations in blood glucose levels during treatment with Serostim, and the small increases that occurred were actually similar to what was seen with the placebo. The increases began returning toward baseline after only the first week of the study. (And since I'm diabetic, let me just add that the increases seen were so small that no diabetic would take them seriously at all. It was a truly clinically insignificant rise.)

The important thing here is that this was a study done before people were taking protease inhibitors which, as discussed more below (see *Insulin Resistance and Diabetes*), are also known to promote insulin resistance and raise blood sugar. So with the blood sugar increases that have been more recently reported, you must ask whether they are caused by the growth hormone, or by the protease inhibitor? This lookback study certainly seems to point toward the protease inhibitor as the more likely cause of the problem. Or if it is a joint result, it suggests that the PI may be the much larger contributor to the problem.

Although lower growth hormone doses are now being studied by the manufacturer for lipodystrophy treatment, Serostim is currently only approved for standard wasting, making coverage of the expensive drug dependent on the HIVer and his or her doctor reporting a 10 percent weight loss — the justification for a diagnosis of traditional wasting. You didn't hear this from me, but *suddenly remembering* such a weight loss, ahem, could be very useful.

Anabolic steroids combined with exercise can help boost "lean tissue," including muscle size, but have not been found to significantly improve the fat loss/accumulation process. In studies done to date, muscle size has increased but there have been no reductions in accumulated fat, and worrisome decreases in HDL cholesterol (the good kind) in those using oxymetholone or nandrolone. In those on oxymetholone, there were also troubling increases in liver enzymes, indicating toxicity to the liver.

Studies of exercise alone have generally shown either no benefit in terms of losing accumulated fat (in one study, four months of serious weight lifting four times weekly resulted in no fat loss) or only very small improvements (in another study, there was only two percent fat loss after four months of intensive exercise, including both strength training and aerobics).

In some areas, excess fat can be removed via liposuction (of buffalo humps or lipomas) or standard surgery (for breast reduction), though the fat sometimes returns over time, and neither approach is possible in the belly because of high hemorrhage risk.

Research is underway into the possibility that some drugs used to control diabetes (metformin and the glitazone drugs, all of which help improve insulin sensitivity) may prevent or reverse the development of fat accumulation. However, the studies done to date are relatively discouraging. In one trial, people given 850 mg of metformin, three times daily, did have small but significant (compared to placebo) drops in visceral fat (as well as in fasting glucose, insulin, and triglycerides) but the high dose caused severe diarrhea and abdominal cramps in some. And it's important to note that metformin also resulted in loss of subcutaneous fat in these people, making it inadvisable for people with lipodystrophy. In another study, a lower dose of 500 mg of metformin, twice daily, only resulted in small (not significant compared to placebo) drops in visceral fat, although those taking the drug did see significant drops in overall weight (due to the loss of subcutaneous fat), insulin levels, and diastolic blood pressure. Anyone considering metformin should be aware that it can cause lactic acidosis, a rare but potentially lethal side effect of nucleoside analogue drugs. Whether combining multiple agents (metformin and nukes) that have the potential to cause this problem would increase the overall risk of developing lactic acidosis is not clear, but be forewarned of the possibility.

As opposed to metformin's tendency to cause fat loss, the glitazone drugs (rosiglitazone and pioglitazone) are known to actually cause fat cells to be added, at least in the HIV-negative. One small pilot study of troglitazone (Rezulin) did show decreases in visceral fat combined with increases in subcutaneous fat (just what somebody with combined fat accumulation and fat wasting problems would want), along with improved insulin sensitivity and increased lean body mass. However,

troglitazone has been taken off the market due to liver toxicity, and later studies done with rosiglitazone so far have not shown improvements in either reducing visceral fat accumulation or restoring subcutaneous fat loss, although insulin levels have decreased. Additional studies are ongoing, including one that is combining metformin with rosiglitazone to see if the glitazone effects will counter the tendency of metformin to cause subcutaneous fat loss. Stay tuned.

Although there has been much discussion about the possibility that switching drugs might solve fat accumulation or fat loss problems, the majority of switch studies done to date have had discouraging results, with little if any change seen in the fat problems. Researchers have theorized that there are several possible explanations for the failure of switching to create improvements. It may be that the drug switched from is not actually involved in causing the problem(s), or that the drug is required for the creation of the problem, but not for maintaining it. It is also possible that the body change is irreversible, or that there are multiple causes of the problem(s), with the drug being switched from only one of them. It may also be that the studies done so far have been too short-term to show improvements. It will be important to watch for the results of future switch studies to improve our understanding of what may help, or alternatively what is unlikely to create improvements.

## Facial Restoration

For facial restoration (to help fill out sunken cheeks), injections of a synthetic compound of polylactic acid (New-Fill) have worked wonders. The New-Fill procedure requires several injections into each cheek, repeated three times (two to three weeks apart). In one study, 22 out of 26 people said their faces returned to normal. The change in facial appearance usually lasts for around a year to 18 months, after which another treatment is required to maintain the results. A more complete discussion of New-Fill—and its ability to restore faces lost to wasting—is in my fact sheet “Polylactic Acid Injections for Lipo-associated Facial Wasting: Yep, you can get your face back,” also available at [www.larklands.net](http://www.larklands.net).

Because New-Fill is not approved in the U.S. or Canada, it is only available to those who can afford and are willing to travel to Mexico or Europe. Attempts are ongoing to allow importation of the product into the U.S. under their “personal use” rules, but to date, the U.S. F.D.A. has blocked this. There are a handful of clinicians in the U.S. who are currently carrying out small trials. For updated information on New-Fill availability, go to [www.daair.org](http://www.daair.org).

When done by a skilled plastic surgeon, the use of fat injected into areas of lipoatrophy (fat loss) can also be effective in restoring facial appearance. The initial facial restoration usually requires only one or two treatments, but later treatments will be required to maintain the benefits. The length of time that the facial restoration remains seems to vary between individuals, with results lasting as few as 3 months in some, and as long as a year or more in others. Some plastic surgeons believe that the best overall results might come with a combination of fat and New-Fill injections but there has been little experience with this so far. There are a number of other synthetic products that have been promoted for facial restoration but it would be wise to be wary of these until clinical trials can prove (or disprove) their effectiveness, and show any potential for negative consequences.

## Mitochondrial Toxicity

Preventing body changes will require a better understanding of causes. For now, Dutch researchers theorize that nucleoside-analogue-induced damage to the mitochondria (your cells’ energy factories) may contribute to not only lipodystrophy but also neuropathy, muscle aches (myopathy), pancreatitis (See Pancreatitis, below), and lactic acidosis (a potentially lethal build-up of lactic acid in the body). Because the latter is so often fatal, experts urge anyone experiencing any of the symptoms that can indicate lactic acidosis to go for an immediate diagnostic workup. Increased blood lactate can cause a wide range of symptoms including generalized fatigue, digestive symptoms (nausea, vomiting, abdominal pain, and sudden unexplained weight loss), respiratory symptoms (rapid or labored breathing), or neurologic symptoms (including motor weakness). For anyone who appears to be experiencing lactic acidosis, experts urge immediate cessation of antiretroviral therapy. Unfortunately, symptoms may continue or worsen following discontinuation of antiretroviral therapy.

Although the Dutch researchers say that much more research is needed to confirm possible ways to counter mitochondrial toxicity, they have suggested that in the meantime it would be reasonable to try the following agents:

- antioxidants (vitamins C and E, carotenoids, selenium, alpha-lipoic acid, coenzyme Q-10, and others)
- B vitamins
- the amino acid L-carnitine (or its sulfated form L-acetyl-carnitine)

In one of the Dutch group’s studies, the following combination even reversed lactic acidosis when given intravenously twice daily:

- L-carnitine (1,000 mg) and
- B complex vitamins (in the following doses: 100 mg thiamine, 20 mg riboflavin, 100 mg niacinamide, 10 mg pyridoxine and 10 mg dexpanthenol)

Other researchers are looking at many other possibilities, and it seems likely that the problem will eventually be discovered to be multifactorial. While the research that may clarify causes and possible solutions moves forward, you may

want to hope out loud that we soon have drugs that destroy the virus, but not the body.

## Bone Death and Destruction — Holey Hips, Batman

The thigh bone's (no longer) connected to the hip bone. That could be your problem if you develop the tongue-trippingly named avascular necrosis of the femoral head, a bone disease in which a lack of blood flow results in tissue death in the top end of the thigh bone, the section that creates part of your hip. More properly termed osteonecrosis, studies from both Georgetown University and UC San Francisco have indicated that protease inhibitors may contribute to this hip-destroying problem, as well as to the occurrence of bone death in other locations. In one study, researchers reported on 18 HIVers who had been diagnosed with avascular necrosis of the femoral head since 1991. Of these, 11 had been taking protease inhibitors, and only one had any of the usual (non-HIV-related) risk factors associated with the disease. In the seven people who were *not* receiving protease inhibitor therapy, six were found to have traditional (non-HIV-related) risk factors for the disease. The differences were statistically significant, clearly suggesting that protease inhibitors increase the risk for developing osteonecrosis.

Researchers have theorized that elevated blood fats, particularly the high triglyceride levels often caused by the protease inhibitors, might be blocking blood supply to the bones, thus leading to the tissue death. Even in HIVers not on HAART, triglycerides are often too high and might be a factor in the development of the bone problems. It is also possible that there might be some direct toxicity to bone cells from protease inhibitors.

Use of corticosteroid drugs (often used long-term for treatment of inflammation caused by diseases like rheumatoid arthritis or lupus, and short-term in the treatment of infections like *Pneumocystis carinii* pneumonia or PCP), alcohol abuse, bone injury, bone infections, and scuba diving are additional risk factors for osteonecrosis because each of these can contribute to decreased blood supply to the bone. Some HIVers develop Addison's disease, an adrenal gland condition that results in reduced production of the steroid hormone called cortisol. It is usually treated with low doses of hydrocortisone (30 mg or so daily), a dosage level that is not usually thought to cause avascular necrosis but might contribute.

The hip is usually the first place that avascular necrosis of bone shows up, but it may also develop in the shoulder, knee, or hand. Common early symptoms include pain in the hip joint or groin area which may radiate down the leg to the knee, and may in some cases be quite excruciating. Some people will develop stiffness in the hip area (often particularly noticeable upon awakening), occasional aching (especially after long periods of walking or standing), and/or a decreased range of motion. With any such symptoms, getting a comprehensive physical exam is a must, followed if appropriate by an MRI scan of the bone.

If detected early on, small holes can sometimes be drilled in the bone to increase blood flow and allow new blood vessels to grow (a process called core decompression surgery), thus helping to slow worsening and reduce pain. However, there are no known curative measures that will permanently prevent a downhill slide toward bone death. If it's progressed too far in the hip bone, the only thing that works is hip replacement. While pointing out that there's nothing that's been proven by research to prevent worsening, HIV researcher Joseph Kovacs, MD, advises patients to avoid activities that could increase the pressure on the hip joint, including some weight lifting exercises, squats, running on concrete, and carrying heavy weight on the shoulders.

This type of bone death is separate from the other bone problem being seen in HIVers: osteopenia or its more advanced stage, osteoporosis. These are the gradual loss of bone tissue that occurs when the body's normal constant loss of bone cells is not equalled by constant replacement, resulting in gradually thinning and weaker bones that may become brittle and break easily. As with the avascular necrosis problems, it is not fully understood what all the causes may be, although it appears likely that both HIV disease itself and some of the drugs used to treat it may be contributing.

As to the former, HIVers are known to have abnormally high levels of proinflammatory cytokines (cell-produced chemicals that cause inflammation) as well as vitamin D deficiency, both of which could contribute to disturbed bone metabolism. In one significant study, researchers compared levels of osteocalcin, a blood serum marker for bone formation, to levels of C-telopeptide, a serum marker for bone resorption, and found that HIVers with advanced disease and high viral loads had increased levels of C-telopeptide (indicating more than usual bone loss), markedly depressed osteocalcin levels (indicating less than usual bone formation), and higher levels of pro-inflammatory cytokines. Interestingly, there was no correlation between osteocalcin and C-telopeptide levels. In the HIV-negative, these are normally in balance with each other, an indication that bone loss and growth are matched. After 24 months of HAART treatment, there was a decrease in the inflammatory cytokines and a marked rise in serum osteocalcin levels, with the result that osteocalcin and C-telopeptide levels were once again appropriately correlated. So it appears that in these people HAART had the beneficial effect of normalizing bone growth and loss processes. That's the good news.

The bad news is that at least some HAART meds, particularly protease inhibitors, have been tied to an increased incidence of osteoporosis. A Washington University study found that compared to those on non-PI regimens, HIVers on PIs were twice as likely to develop low bone mineral density (as gauged by the full-body X-ray scan called DEXA). Senior researcher Pablo Tebas, MD, and his colleagues found that 50 percent of PI takers had low bone mineral density, and more than a fifth had severe osteoporosis. Only 23 percent of those on non-PI regimens had lowered bone mineral density, and only 11 percent had severe osteoporosis, both of which were fairly close to the readings in HIV negative controls (29 percent of whom had some level of bone loss, and 6 percent severe osteoporosis). And in a vicious circle, the osteoporosis in some HIVers might actually be contributing to the development of avascular necrosis, a known complication of severe

osteoporosis.

A DEXA scan is the best way to diagnose bone mineral loss, whether it is still at the stage of osteopenia or has developed into the more severe osteoporosis. In the best of all possible worlds, all HIVers would have a baseline scan (preferably before starting HAART) that could be compared to later readings. Without a baseline scan, physicians can compare the current results with standard values based on the person's age, weight, and build, thus estimating the probable bone loss.

Until all the causes are well defined, advice on specific fixative or preventive measures will be missing. However, in the meantime, those things well-known to help prevent or reverse osteoporosis in general may certainly help. Included would be weight-bearing exercise (at least 30 minutes of walking, several times weekly would be a minimum), a nutrient-rich diet in order to ensure the presence of all the nutrients needed by bone to grow, and additional supplementation with calcium (1000 mg daily for men, and 1000-1500 mg for women), magnesium (500-1000 mg; excess magnesium can cause loose stools so watch for this), and vitamin D (800 IU daily). The latter may be particularly important. A Norwegian study found that blood levels of vitamin D-3, the natural form, were below normal in more than half of the HIVers studied, and 18 of the 54 people had undetectable levels.

In addition, natural anti-inflammatories may be useful. A number of nutrients, especially omega-3 fatty acids (found in fish oil and flaxseed oil) and ginger root (available either in capsules or as a tea that can be prepared from teabags or from fresh ginger root) may help dampen HIV-caused inflammation which, as discussed above, may be a risk factor for osteoporosis. Fish oil (2 capsules, three times daily with meals) or flaxseed oil (2 capsules, three times daily with meals) and ginger (2 capsules, three times daily with meals, or ginger tea, simmered for at least five to ten minutes and drunk three times daily) may be useful.

Hormone replacement therapy may also be important. It is clear that in postmenopausal women, hormone replacement therapy can help to prevent osteoporosis. Since HIV-positive women may go through menopause at much earlier than usual ages, the lack of appropriate hormones may contribute significantly to osteoporosis problems in a significant percentage of HIV-positive women. Another hormone important to bone health is DHEA, often too low in both men and women living with HIV. So both men and women should be tested for hormone levels, including particularly the female hormones in women, and DHEA in both sexes. Where found to be deficient, appropriate replacement could be helpful in preventing bone problems.

Last but perhaps important to consider, I'd be going way out on a limb to give any strong advice on antiretrovirals here, but based on the research discussed above, it would appear that effective HAART may help to restore proper bone metabolism and, thus, might reduce the development of osteoporosis, but that protease inhibitors might be tied to development of both osteoporosis and osteonecrosis. So....choose your meds based on all your current needs and concerns and treatment history, but keep this in mind.

## Cardiac Concerns — the pipes are clogging up

Addressing the blood fat problems—sky-high triglycerides, often combined with increased total cholesterol, increased LDL cholesterol (the bad kind), and decreased HDL cholesterol (the good kind)—that so many people on HAART are developing is crucially important to help provide longterm protection against artery damage and heart disease. There have been many reports from clinicians on serious arterial blockage and resulting angina in patients on HAART. Studies that have looked for increased incidence of heart attacks in those on HAART meds have been conflicting (with some showing increased numbers of heart attacks and others not), but since heart disease is generally slow to develop, it may simply be that no studies so far done have been able to adequately assess the increase in cardiovascular disease risk that HAART may create. Thus, it is considered highly advisable for HIVers to do everything they can to lower their risk for heart disease by quitting smoking, keeping their blood pressure under control, eating healthful diets, exercising appropriately, working to lower elevated blood fats, and, for those who are seriously overweight, working to lose the excess pounds.

It's definitely time to be concerned if:

- Your total cholesterol is greater than 250 mg/dl or 5.2 mmol/litre (SI units) on repeated measures, and
- you have an unfavorable cholesterol/HDL ratio (which is variable, depending on age and sex; age above 40 and male sex are greater risks).

Factors that would add to the concern include:

- Triglycerides are elevated.
- You have a family history of cholesterol problems or heart disease.
- You have diabetes (see "Insulin resistance and diabetes").
- You are a smoker.
- Your blood pressure is constantly elevated.
- You are overweight.
- You are an African American or Native American or Alaskan Native or Aboriginal or Hawaiian Native, as these

groups are considered to be at higher risk for the elements that increase your risk for heart disease (high blood pressure, diabetes and cholesterol).

The standard medical advice for high blood fats would usually begin with advising dietary changes to lower fat intake, but the experience of most clinicians, as well as the findings from a couple of small studies, indicate that changing what people are eating is unlikely to be of substantial benefit when HAART meds are the main cause of the problem. On the other hand, if people are on a French fry, milk-shake, cheeseburger meal plan, then this might certainly be at least contributing to the high blood fats. In such cases, aiming for less fat intake, along with increases in fruits and vegetables and whole grains, especially oats—all of which contribute soluble fiber that can block cholesterol absorption—could help. Soluble fiber sources like psyllium seed (Metamucil) or citrus fiber (Citrucel) may also be useful.

For overall cardiovascular protection, it is very important to eliminate partially hydrogenated fats from the diet. These are chemically modified fats that are found in most margarines, vegetable shortening, and a large percentage of commercial baked goods and snack foods. Everyone who cares about protecting their cardiovascular system needs to read labels and try to avoid these artery-damaging fats to the greatest extent possible. Instead, stick with the fats Mother Nature made, especially the monounsaturated fats like olive oil.

There are other lifestyle issues that should not be ignored. Smoking, stress, obesity and the couch-potato ethic are important risk factors that contribute to high cholesterol, high blood pressure and ultimately heart disease. If any of these apply to you, doing everything possible to decrease or eliminate these risks is very important.

Several switch studies have shown that blood fats that were elevated during protease inhibitor (PI) therapy fell after people switched from the PI to either nevirapine (an NNRTI) or abacavir (an NRTI). Switching to efavirenz (Sustiva) has not been shown to consistently improve blood fat levels. Thus, some so-called “PI-sparing” regimens may work better than others, although much more research will be required to determine what really may be best in this regard. It will be very important to consider the treatment history for anyone considering switching drugs, since some people may really need the protease inhibitor(s) to maintain viral control.

With high cholesterol readings, the drugs that act as cholesterol lowering agents — commonly called “statins” — are, of course, often recommended. It is encouraging that we’ve now had a number of reports on the successful use of such drugs, but the specific agents need to be chosen carefully because of the potential for drug interactions with protease inhibitors. Statin drugs help prevent the chemical conversion of fats into cholesterol, but some of these drugs use the CYP 3A4 liver enzyme pathway used by protease inhibitors while others do not. Thus, the risk of negative interactions with PIs varies considerably between the different drugs. Currently, it is thought that the most acceptable choices are pravastatin (20 to 40 mg daily) or atorvastatin (10 mg daily), with fluvastatin considered a secondary possibility. Lovastatin and simvastatin should not be given with PIs. It’s also important to be careful about interactions with herbs. The heavily promoted cholesterol-lowering herbal compound called Cholestin works similarly to the statins and may cause similar interaction problems.

Fibrates are another class of lipid-lowering drugs which may help with blood fat abnormalities. They are considered the best choice for those who have only elevated triglycerides (but no cholesterol problems). Some believe that of the available fibrate drugs, fenofibrate may be preferable to gemfibrozil because it is easier to take and may do a better job lowering elevated LDL cholesterol (the bad kind). Sometimes the two classes of fat-lowering drugs (statins and fibrates) are used together to improve effectiveness, but it is important to know that this increases the risk of muscle toxicity.

Because of interaction problems, the preference of some physicians for lowering blood fats is the B vitamin niacin (1,000 mg daily), which can lower overall cholesterol, LDL cholesterol (the bad kind) and triglycerides. Niacin actually works better than the statin drugs to raise HDL cholesterol (the good kind), although the statins do work well to lower LDL cholesterol. However, there are several potential problems with niacin.

First, a lot of people get flushing, redness, warmth and, in some people, painful stinging and itching for a period of a half hour or more after it’s taken. A sustained-release, no-flush form is much less likely to cause these problems, especially if combined with a baby aspirin taken 30 minutes before the niacin. Taking it in the middle of a meal will also help. Niaspan, 500 mg per tablet, can be taken with breakfast and dinner, and the tablet can be cut in half if even that dose causes problems.

If the dose is tolerable but insufficient for normalizing blood fats, it can be increased until good results are seen, but this increases the risk of niacin’s second important potential problem, liver toxicity. Liver function tests should be run to watch for such toxicity.

Blood glucose levels should also be monitored because niacin has the potential to affect blood sugar levels. Some experts believe that niacin’s potential to increase insulin resistance makes it inadvisable for HAART takers (since many people on HAART will develop insulin problems), and that is particularly true for anyone already showing signs of blood sugar problems.

Another important possibility for lowering triglycerides is the amino acid L-carnitine (the prescription form of which is Carnitor). Not yet studied for HAART-caused problems, it was shown in the past to be effective in normalizing HIV-elevated triglycerides when used in doses of 6,000 mg per day. It is approved for elevated blood fats in the US, although the usual dose is 3,000 mg daily, so doses higher than those usually covered might be necessary for the best results. Some doctors have found that using a combined approach with Carnitor and one of the lipid-lowering drugs can result in normalization of blood fats when drugs alone do *not* do the job, so that may be an approach worth considering.

Omega 3 fatty acids, found in fish oil and flaxseed oil, can help to lower triglyceride levels. Eating fatty fish (like

salmon, mackerel, sardines, tuna, cod, and halibut) is a tasty way to get those fatty acids, and studies of the general population (not HIV-specific) have shown reduced incidence of heart disease in those who consume several helpings of such fish weekly. However, the use of fish oils has not been studied in those with PI-caused high triglycerides so it is not known if they would work as well in this population. In addition, high doses (over 1.7 grams daily) sometimes raise insulin resistance in people with diabetes and might also have that effect in HIVers, although moderate doses appear safe in this regard.

Certain nutrients may also be very important for the prevention of heart disease.

- Magnesium, which has been found to be deficient in a significant percentage of HIVers, can help prevent arterial damage and protect the heart in doses of 500–600 mg daily. (Be reminded that too much magnesium can cause diarrhea so watch for this; check your total dosage from both your multivitamin/mineral and any additional supplements).
- Antioxidants (including vitamins E and C, bioflavonoids, selenium, coenzyme Q<sub>10</sub>, N-acetyl-cysteine and alpha-lipoic acid) and B vitamins. These nutrients help prevent the chemical changes in the blood vessels and the blood fats that are required for the fat to be deposited into the lining of the blood vessels, thus helping to prevent damage to the arteries. So even if you can't fully normalize your cholesterol readings, you can help keep it from being deposited in the blood vessels by having a plentiful supply of all these nutrients in the body.

It's also important to remember that even when blood fats can't be completely normalized, you can lower your overall heart disease risk by combining regular exercise, meditation and other stress reduction therapies, along with the nutrient supplementation.

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Heart attack warning signs:

- uncomfortable pressure, fullness, squeezing or pain in the centre of the chest lasting more than a few minutes
- pain or numbness spreading to the shoulders, neck, jaw or arms
- chest discomfort with light-headedness, fainting, sweating, nausea or shortness of breath

Stroke warning signs:

- sudden weakness or numbness of the face, arm or leg on one side of the body
- sudden dimness or loss of vision, particularly in one eye
- loss of speech or trouble talking or understanding speech
- sudden, severe headaches with no apparent cause

If you experience any of these symptoms, call your doctor or go the emergency room right away.

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## Diarrhea — the gift that keeps on giving

Diarrhea—an increase in the frequency and decrease in consistency of stools—can be caused by many antiretrovirals. This is an important side effect to keep in check, and any diarrhea that is frequent, watery or lasts for more than a couple of days should always be reported to your doctor.

The two medications most commonly reported to cause diarrhea are the protease inhibitors nelfinavir (Viracept) and ritonavir (Norvir), but many other meds may also cause this problem, including:

- indinavir (Crixivan)
- saquinavir (Fortovase)
- amprenavir (Agenerase)
- ddI (Videx EC)
- ddC (Hivid)
- d4T (Zerit)
- 3TC (alone in Epivir and also in the combination drugs Combivir and Trizivir)
- abacavir (Ziagen, ABC)
- nevirapine (Viramune)
- efavirenz (Sustiva)
- the anti-herpes drug acyclovir (Zovirax)
- many antibiotics and other meds

In other words, a large number of medications can be implicated in the problem of diarrhea. Obviously, combining these meds can make it difficult to tease out a single culprit. If the onset or sudden worsening of diarrhea is tied closely to beginning a medicine, it's a likely suspect. In some cases, the diarrhea may diminish after a period of time on the drug, but

too often it will become your longtime companion.

## Tips for handling diarrhea

If switching drugs is possible, that may be the best solution and will usually result in a quick resolution of the problem. However, since more than one cause often contributes, truly effective treatment requires aggressive diagnosis to pin down all possible factors. In addition to medicines, these can include:

- infections and parasites—check for them with aggressive diagnostic measures and treat anything found
- fat intolerance and malabsorption (very common in HIVers, even in earlier disease stages)—cut back on dietary fat and take lipase, the fat-digesting enzyme (found in the better pancreatic enzyme formulas; an excellent prescription form is Pancrecarb, made by Digestive Care, Inc.) with meals
- lactose intolerance (very common in HIVers)—eliminate or decrease dairy products and take lactase enzyme when you do consume them
- excessive sugar or caffeine—cut back on 'em
- stress—find a way to chill out (or consult with someone who can help you)

When all causes can't be eliminated, using **standard anti-diarrheal agents**, such as the following, may help relieve symptoms:

- Kaopectate
- Pepto-Bismol
- anti-motility agents (Imodium, Lomotil, tincture of opium, paregoric or opiates)
- luminal-acting agents or those that act in the intestinal passage (cholestyramine, pectin, Kaolin or fibre supplements)

Here are some other options for the runs:

- Shaman Botanicals' SB Normal Stool Formula is a tree sap extract that many HIVers have reported helps reduce or eliminate med-induced runs.
- The amino acid L-glutamine, taken in doses of 5–30 grams daily (a powdered form is best; mix it in water or juice), can both help to heal damaged intestines and reduce the diarrhea by enhancing water and sodium absorption across the wall of the small intestine.
- Friendly bacteria, such as *L. acidophilus*, may also help relieve the symptom.
- Ground flax seeds (also called flaxmeal) or flaxseed oil will also sometimes help to relieve diarrhea and heal the intestines via their natural anti-inflammatory qualities.

For diarrhea caused by protease inhibitors (PIs):

- Calcium taken in doses of 500 mg, twice per day, may work. Initially, a small study showed calcium therapy to be very effective for reducing or eliminating diarrhea caused by nelfinavir (Viracept), and since that study's publication there have been many anecdotal reports that it also works for diarrhea caused by other PIs.
- Another small study showed that a pancreatic enzyme formula (Digestive Care, Inc.'s Pancrecarb) given with meals significantly improved stool consistency in those with PI-caused diarrhea. And it also works very well to eliminate protease inhibitor-caused gas (you know, the stinky, smelly kind) and bloating.

Increasing your intake of **foods that contain soluble fiber** can help since they absorb water and expand, binding together the intestinal contents. This bulks up the stool and slows the passage of food, particularly when there is a lot of fluid in the stool. Examples of foods that contain soluble fiber include the following:

- peeled apples or apple sauce made from them
- other fruits such as apricots, peaches, pears, plums, grapes, melons, nectarines, bananas
- grains such as oatmeal, oat bran, white rice and barley
- soluble fiber supplements like psyllium (Metamucil) that you dissolve in a glass of water and drink

Fiber intake should be slowly increased to help limit the increase in intestinal gas that it can cause.

For as long as diarrhea continues, it is crucial to:

- Consume plenty of calories (eat more and make every bite count toward high-quality nutrition) and
- drink plenty of healthful liquids (water, juices, herb teas, broth and fruit juice smoothies) to replace what's being lost. Remember that **it is crucial to prevent dehydration** when you are suffering from diarrhea, regardless of the cause. Drinking lots of water daily is very important. You should consume at least a couple of quarts of water every day. Even better, divide your weight in pounds in half, and drink at least that many ounces of water daily.

With serious diarrhea, it is important to rebalance the body's electrolytes, including sodium, potassium and chloride. Drinking vegetable and fruit juices, nectars or broths (diluted with water to enhance absorption) can help. However, more concentrated sources of electrolyte minerals may be needed. Gatorade is often recommended but it is not a very concentrated source of the minerals and is also loaded with sugar, which could actually worsen the diarrhea. Pedialyte, an infant formula, is more concentrated in the needed minerals but many people don't care for its taste and it's rather expensive. Oral rehydration solutions made with rice syrup, including Infalyte and BestLyte, not only help to rebalance electrolytes but may also actually help to reduce diarrhea in some cases. The rice syrup solids actually help to slow motility (the passage of the stool contents through the intestines).

Another possibility is the use of the oral rehydration salts recommended by the World Health Organization, which are available through many pharmacies at low cost. The other inexpensive option is to mix your own solution with a teaspoon of *light* salt (which contains potassium mixed with sodium) and a quart of orange juice or apricot, peach or pear nectar (diluted with water); sweeten with a tablespoon of pasteurized honey, if desired. To add soluble fiber to this mix, dilute the nectar half and half with rice water (made by boiling four parts water and one part rice until the rice is tender, and then straining off the rice water). This rice water can also be drunk on its own as a source of both hydration and soluble fibre.

The following foods and liquids should be avoided because they can make diarrhea worse. Try to eliminate or at least cut back on these as much as possible:

- coffee and other caffeinated beverages
- alcohol
- chocolate
- fried and fatty foods
- spicy foods
- high-sugar foods or liquids

. Diarrhea is one of the most complicated of all the symptoms experienced in HIV disease. **For much more detail and discussion of appropriate diagnostic measures, see Treatment Fact Sheet #13, *Diarrhea* at [www.larklands.net](http://www.larklands.net).**

## **Fatigue — sick and tired of being sick and tired**

Fatigue—crawling out of bed feeling like you've been hit by a truck and going downhill from there—can be caused by HAART combos of any variety. Just taking all the drugs seems to wear some people's bodies out. The energy loss caused by meds will sometimes disappear after a period of time on those drugs (so you may want to consider waiting to see if the fatigue passes), and will often disappear fairly quickly if they're stopped. It seems to be an individual response—some meds may cause fatigue in you but not in your friends.

When the meds that can cause bone marrow suppression result in anemia, fatigue is highly likely. Among these are:

- AZT (alone in Retrovir and also in the combination drugs Combivir and Trizivir)
- abacavir (Ziagen, ABC)
- ganciclovir (valgan, Valcyte)
- sulfa antibiotics (Bactrim/Septra, Dapsone)
- alpha interferon (Intron-a, Peg-intron, Pegasys)
- hydroxyurea (Hydrea)
- pyrimethamine
- pentamidine
- various anti-cancer drugs (chemotherapy)

Anyone with fatigue should monitor blood counts. Anemia is experienced by more than three-fourths of those with clinical AIDS, and perhaps a fourth or more of those with less advanced disease. And treating it is critical since a very large (over 3200 people) study found that, regardless of CD4 count, the risk of death was substantially higher for those with anemia, and that recovery from the anemia, by whatever means, significantly lowered that risk.

Unfortunately, this red blood cell (RBC) problem, indicated by decreased hemoglobin, hematocrit and RBC count too often goes untreated. The result is needless fatigue and weakness, along with shortness of breath, heart palpitations, increased susceptibility to infections, and lowered quality of life. Meds are not the only anemia cause. Others include

- MAC (*Mycobacterium avium* complex)

- TB (tuberculosis)
- CMV colitis
- cryptococcal meningitis and other fungal infections
- parvovirus B19
- lymphoma
- KS (Kaposi's sarcoma)
- deficiencies of the B vitamins folic acid (folate) or B<sub>12</sub> (both of which are common in HIVers) and of iron (which is less common in men but fairly common in women)

HIV alone can also cause anemia. And that is the Catch-22—the drugs you're taking may cause it, but leaving HIV untreated will let the virus impair the production of red blood cells.

## Tips for handling fatigue

The answer for many fatigued people is **injections of recombinant human erythropoietin**, termed Epoetin alfa (sold as Procrit or Epogen), usually given three times per week, to promote the production of red blood cells. It will often resolve anemia fairly quickly (within four to six weeks, the time needed for the new red blood cells to be created), and return real energy to your life.

Because many factors can contribute to energy loss, it is important to consider that you may also have the following:

- infections — treat 'em
- inadequate nutrition — eat well and often, and take nutrient supplements
- hormonal deficiencies — test and replace any that are suboptimal; testosterone deficiency is a relatively common cause of fatigue in HIVers
- depression — get therapy and/or medication
- not enough rest — take naps and deal with insomnia
- stress — find a way to chill out (or consult with someone who can help)
- excessive recreational drug or alcohol use — ask for help
- excessive caffeine and sugar — cut back on 'em
- B<sub>12</sub> deficiency—one of the most common causes but often unsuspected because blood levels of B<sub>12</sub> may not accurately reflect the problem since it's what's in the tissues that counts, and the standard tests don't show this. So simply doing a trial run of vitamin B<sub>12</sub> supplementation for at least six to eight weeks may be best. For many people, this has been a miracle cure for HIV-related fatigue. Supplement with pills or nasal gel, 2-7 times per week or, for faster results, subcutaneous injections; the latter may be necessary for some because HIV appears to impair the parietal cells that produce the intrinsic factor needed for B<sub>12</sub> absorption; without intrinsic factor, B<sub>12</sub>, whether from food or pills, won't be taken into the body; if pills don't seem to be helping, either the nasal gel or the injections will bypass the absorption problem)

## Gas and Bloating — oops, cleared the room again

The smelly intestinal gas and abdominal bloating that any of the protease inhibitors can cause will usually disappear quickly if the offending drugs are discontinued, but often continue unabated for as long as the drugs are taken. Where discontinuation is not desirable or possible, Dennis Rosa-Re, a Florida doc with a large HIV practice, has found that taking pancreatic enzymes (one or more, taken with every meal or snack) can often eliminate the problem. Make sure to choose a brand that contains lipase, the fat-digesting enzyme, since it appears to be the key. Pancrecarb, manufactured by Digestive Care, Inc. and available by prescription, is one such brand. There are other prescription versions, such as Ultrase MT-20 (manufactured by Axcan Scandipharm), but Pancrecarb appears to work better because it also contains ingredients that help the enzymes do their work better. (Pancrecarb is not currently approved in Canada and is only available by prescription in the U.S. However, any enteric-coated pancreatic enzyme that contains a potent amount of lipase may help.)

The **amino acid L-glutamine** (5–10 grams per day) may also help by improving absorption of fat and preventing its passing into the colon undigested where it will be acted on by bacteria and create—you guessed it—stinky, smelly gas.

Not all gas comes from your medications. Conservative dietary modifications can sometimes resolve a lot of “passed gas” and bloating. Try to identify which food products cause you the most problems and moderate or eliminate them. Some of the worst culprits are broccoli, beans, garlic, onions, cabbage and tough-to-digest vegetable skins. Over-the-counter products such as Beano (a vegetable enzyme) can help by improving the digestion of such foods; take 1-4 Beano tablets with each meal that contains problem-causing foods.

## Hair loss — who pulled the rug out from over me???

Hair loss is a common experience, particularly in men as they age. When hair loss is new, rapid or severe, it is

considered abnormal. There are many medical treatments that can cause disturbing hair loss, including cancer chemotherapies and some arthritis drugs. Hair loss can also be caused by some HAART meds. The most common cause is the nucleoside analogue 3TC (alone in Epivir and also in the combination drugs Combivir and Trizivir). Many 3TC-users have reported finding clumps of hair on their pillows every morning. The protease inhibitor indinavir (Crixivan) has also been implicated in some instances of accelerated hair loss. Unfortunately, no one seems to have found a perfect solution other than switching or discontinuing the problematic drug. Even then, the return of the lost hair may be slow and incomplete.

Other causes of hair loss include:

- malnutrition, particularly low protein intake
- thyroid problems
- B complex vitamin deficiency

It is important to note that androgenic steroids, such as testosterone, are often implicated in rapid or new-onset hair loss, particularly when too-high doses are used. An evaluation of the pros and cons of testosterone for you should be considered with your doctor. In general, doses that simply replace normal levels of testosterone using through-the-skin delivery (via gels or patches) are considered best; too-high doses, especially via injections, should be avoided. For some people, minoxidil products (Rogaine) may help with hair loss, but as with all medications, check to make sure there are no possible interactions with your other drugs before taking such products.

## Headaches

Some people develop headaches as a result of drug side effects. In some cases, these will only occur during the beginning of drug therapy, and will gradually disappear over the next few weeks. In others, they may remain long-term, and the only solution may be a drug switch. Medications should be particularly suspected as a headache cause when a new drug treatment has recently been started, but note that such reactions can occur even after months of using a particular drug.

Headaches can also be a symptom of many different infections and conditions, some of which could be fatal if undiagnosed. Among the possible causes of headaches are:

- cryptococcal meningitis
- endocarditis
- syphilis
- candidiasis
- toxoplasmosis
- herpes outbreaks
- progressive multifocal leukoencephalopathy (PML)
- CMV encephalitis
- primary central nervous system (CNS) lymphoma

All headaches that are at all serious or that last for more than a few hours or that recur should be taken very seriously. If you are suffering from such headaches, run (do not walk!) to your best available neurologist or HIV specialist for a comprehensive diagnosis. It is best to *not* treat such headaches until your doctor has diagnosed the problem and told you what treatment is best. If you cover up this symptom with pain medications, you might mask what would otherwise point the way to a diagnosis of something serious. So this is a case where you should always call your doctor.

When a diagnosis is being sought, it is important to remember the old rule that you only find what you seek. There have been cases in which, because the person is HIV positive, the diagnostic procedures were too exclusively focused on opportunistic infections (OIs) and conditions, forgetting that HIVers are certainly also susceptible to other infections and malignancies. In some of these cases, when none of the common OIs or conditions were discovered, the headache was then attributed to HIV disease itself and no further attempts were made at diagnosis. Then, down the line, and usually when other symptoms appeared that gave better indications of a probable diagnosis, the person was finally discovered to be suffering from something unrelated to HIV disease. Unfortunately, by that time, the condition or infection was often much more advanced and more difficult to successfully treat. In these situations, if the person had been HIV negative, the diagnosis might actually have been made sooner because the non-HIV-related possibilities would have been considered more quickly. Never forget this possibility.

## Tips for handling headaches

One cause of headaches that is almost never suspected by doctors is magnesium deficiency, a problem that Canadian

researchers have found is relatively common in HIVers. In those who are HIV negative, it has been found that even in people who have suffered from severe headaches for many years, supplementing with **magnesium** may eliminate the problem. Supplementation with magnesium is not something that should be substituted for immediate medical attention to severe or recurrent headaches. However, if no other cause is found, keep the possibility of a deficiency in mind. Magnesium in doses of 500–600 mg per day may be required for some.

It is important to remember that if you are treating your headache, your choice of drugs should be made in the context of all the other factors currently affecting you, including:

- other drugs you are taking — because of possible interactions
- medical conditions such as liver problems — which would weigh against acetaminophen (Tylenol)
- other medical conditions such as ulcers, gastrointestinal bleeding problems or intestinal Kaposi's sarcoma, low platelets, kidney dysfunction or low serum albumin levels (common in those with wasting) — which would weigh against aspirin and other non-steroidal anti-inflammatory drugs, or NSAIDS

In general, unless any such issues make it problematic, aspirin or buffered aspirin is probably the best choice. Tylenol (acetaminophen) lowers levels of the antioxidant glutathione in the body. Since glutathione levels are already too low in HIVers, worsening this is not a good idea. In addition, the lowered levels of glutathione already present may significantly increase the chance for acetaminophen toxicity. Even in doses considered to be in the routine therapeutic range, acetaminophen can cause liver injury in certain populations with a tendency for glutathione deficiency, including HIVers. Aspirin also lowers glutathione, but to a much lesser extent.

If you are taking either aspirin or acetaminophen, the use of the following agents to help normalize glutathione levels is very important:

- N-acetyl-cysteine (NAC)
- alpha-lipoic acid
- the amino acid L-glutamine (this is also important to help keep the intestinal tract from being damaged by drugs)

Remember that long-term use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) can cause damage to the intestines and gastrointestinal bleeding. In general, only use any such meds when you absolutely need them to reduce fever, and avoid long-term use, if possible.

Other possibilities for treating some kinds of headaches include acupuncture or acupressure. The herb feverfew may also help. It contains parthenolide, an agent that reduces spasms in blood vessels in the head, and has been shown to work for both migraines and tension headaches.

## **Insulin Resistance and Diabetes — that's not the kind of sugar I like**

Protease inhibitors have been tied to an increased incidence of glucose intolerance and decreased sensitivity to insulin, the hormone that's needed for the uptake of glucose into the body's cells. When that process isn't working properly, the glucose remains in the bloodstream, creating the high blood sugar that can cause damage to the blood vessels and, ultimately, diabetes with its whole list of possible complications, including kidney failure, blindness, and cardiovascular problems from top (strokes) to bottom (amputations) and in between (heart attacks).

So far, the rate of development of diabetes is relatively low, but researchers fear it will increase over time. It's important to watch for the classic warning signs of diabetes: excessive thirst, abnormal hunger, and increased urination. With any of these, call your physician immediately so that diagnostic tests can be run.

You may be at increased risk if you:

- have a family history of adult-type diabetes
- are overweight
- live a sedentary (couch-potato) lifestyle
- are black or Aboriginal

Recent research shows that indinavir (Crixivan), amprenavir (Agenerase) and ritonavir (Norvir) (and probably all the other protease inhibitors) suppress insulin-stimulated glucose uptake by inhibiting the transport activity of the proteins that normally move glucose from the cell surface into the fat and muscle cells. The researchers, noting that other studies have shown that insulin resistance appears prior to the appearance of lipodystrophy symptoms, predict that insulin resistance may occur much earlier than has been so far reported, may be far more widespread, and may be at least one of the causes of lipodystrophy. Both this and the other theories so far proposed to explain the tie between PIs and insulin problems are complex, and additional research will be required to fine tune our understanding of this.

### **Tips for handling insulin resistance**

Substituting an NNRTI or an NRTI for a protease inhibitor has been suggested as a possible way to improve insulin sensitivity. The switch studies done to date have been somewhat conflicting but there is some evidence that switching from a protease inhibitor to either nevirapine (an NNRTI) or abacavir (an NRTI) may improve insulin sensitivity and lower glucose. Results with a switch to efavirenz have been less clear, with one study showing improvement and another not. Much more research will be required to determine what really may be best in this regard. It will be very important to consider the treatment history for anyone considering switching drugs, since some people may really need the protease inhibitor(s) to maintain viral control.

For anyone with elevated insulin levels (indicating insulin resistance) or elevated blood glucose levels, it definitely couldn't hurt to do the things that normally help to increase insulin sensitivity, including the following:

- regular progressive resistance exercise (like weight-training) and a cardio workout
- weight loss in those who are significantly overweight—obesity alone is a serious risk factor for adult-onset diabetes
- limiting sugar and refined carbohydrate intake (white starchy foods, white sugar and flour and all the foods made with them) and eating a more nutritious diet; a diet that is higher in fiber (found in whole-grain foods and fruits and vegetables) and lower in polyunsaturated fats (found in most vegetable oils and many prepared foods; it's best to stick with monounsaturated oils like olive oil) has been shown to be tied to improved insulin sensitivity in one study
- testosterone replacement therapy in men, where needed
- supplementation with a potent multiple vitamin/mineral that contains the B complex vitamins, antioxidants and minerals (especially chromium and vanadium) that help maintain normal cellular insulin sensitivity

It is important to have your blood sugars monitored regularly. If they begin to rise and lifestyle modifications or drug switches are not enough to get blood sugar under control, antidiabetic medications may be needed. Two common drugs are rosiglitazone (Avandia) and metformin (Glucophage). Studies on the use of such drugs with PI-caused insulin resistance are limited but have shown improvements. In one trial, people given 850 mg of metformin, three times daily, did have significant drops in fasting glucose, insulin, and triglycerides, along with small but significant (compared to placebo) drops in visceral fat, but the high dose caused severe diarrhea and abdominal cramps in some. ***And it's important to note that metformin also resulted in loss of subcutaneous fat in these people, making it inadvisable for people with lipotrophy (fat loss in the face, arms, legs, or buttocks).***

In another study, a lower dose of 500 mg of metformin, twice daily, resulted in significant drops in insulin levels, as well as in overall weight and diastolic blood pressure, and small (but not significant compared to placebo) drops in visceral fat. Anyone considering metformin should be aware that it can cause lactic acidosis, a rare but potentially lethal side effect of nucleoside analogue drugs. Whether combining multiple agents (metformin and nukes) that have the potential to cause this problem would increase the overall risk of developing lactic acidosis is not clear, but be forewarned of the possibility.

As opposed to metformin's tendency to cause fat loss, the glitazone drugs (rosiglitazone and pioglitazone) are known to actually cause fat cells to be added, at least in the HIV-negative, making them possibly a better choice for those who have both insulin resistance and fat loss problems. One small pilot study of troglitazone (Rezulin) showed improved insulin sensitivity, increased lean body mass, decreased visceral fat, and increased subcutaneous fat (just what somebody with combined fat accumulation and fat wasting problems would want) in those taking the drug. However, troglitazone has been taken off the market due to liver toxicity, and later studies done with rosiglitazone so far have not shown improvements in either reducing visceral fat accumulation or restoring subcutaneous fat loss, although insulin levels have decreased. Additional studies are ongoing, including one that is combining metformin with rosiglitazone to see if the glitazone effects will counter the tendency of metformin to reduce subcutaneous fat.

Most expert groups are waiting for additional research before making official recommendations on approaches to handling insulin resistance and blood sugar problems in HIVers, but the **British HIV Association now recommends the following:**

**For anyone with symptoms of glucose intolerance:**

- dietary advice and exercise
- switch PI to PI-sparing regimen (in people taking their first regimen)

**For measurable glucose intolerance (fasting glucose 101 to 115 mg/dL or two-hour glucose tolerance test 117 to 185 mg/dL) with body mass index above 25 mg/kg<sup>2</sup>, insulin above 17 mU/L, and hemoglobin A<sup>1C</sup> above 6.5 mU/L):**

- consider metformin (500 mg twice daily)
- switch off PI

**For anyone with diabetes (fasting glucose above 117 mg/dL random value or two-hour glucose tolerance test above 185 mg/dL with the same additional parameters that are listed above)**

- metformin (500 mg twice daily)

review after three months

**For anyone with body mass index 18 to 25 mg/kg<sup>2</sup> with insulin above 17 mU/L and hemoglobin A<sup>1C</sup> above 6.5 mU/L**

sulphonylurea therapy

consider metformin (500 mg twice daily)

**For anyone with body mass index below 18 mg/kg<sup>2</sup> with lipoatrophy, insulin above 17 mU/L, and hemoglobin A<sup>1C</sup> above 6.5 mU/L**

consider rosiglitazone (2 to 5 mg daily) or pioglitazone

seek clinical opinion

For the most up-to-date recommendations on how to handle glucose intolerance, go to the British HIV Association website at [www.bhiva.org](http://www.bhiva.org).

## **Kidney stones — you don't wanna know how bad this hurts**

Kidney stones can occur for many reasons and are more common in warmer climates since sweating may result in a tendency toward dehydration which, in turn, promotes the development of kidney stones. Kidney problems can occur in people taking HAART meds, especially if they drink inadequate quantities of fluids. The protease inhibitor indinavir (Crixivan) is often a culprit in the sudden onset of kidney sludge problems (so called because it's not really a stone). The sulfa drug Septra/Bactrim has also been reported to cause kidney stones.

Symptoms of kidney trouble include:

- severe pain in the lower back and sides (called flank pain or renal colic)
- difficult and painful urination
- blood in the urine
- inability to urinate

If you develop these symptoms, notify your doctor or go to your local hospital as soon as possible.

### **Tips for handling kidney stones**

Anyone taking indinavir or Bactrim or any other kidney-stressing drug, or who has a history of kidney stones, should consume at least two quarts of water daily. More specifically, divide your body weight in half, and drink that many ounces of water daily.

Other healthful fluids include:

- caffeine-free teas
- juices
- broths

Drink even more water any time you might become dehydrated — in very hot weather, when dancing or exercising, if you've got diarrhea or if you've been vomiting. And remember that alcohol and caffeine are dehydrating. That means that beverages which contain either of these not only don't count toward that fluid amount, they actually increase your need for the good fluids. So drink up and dilute the possible harmful side effects of the medications on your kidneys.

## **Liver Toxicity — Eww, I don't want to turn yellow**

Liver impairment in HIV disease is common and has many possible causes, only one of which are the meds you're taking. Many infections can result in liver damage, including not only coinfection with hepatitis viruses, but also such opportunistic infections as MAC, tuberculosis, CMV, or cryptosporidiosis. Past histories of repeated use of antibiotics, excessive alcohol, recreational drug use, and/or a nutrient-poor, chemically-loaded diet may have created a damaged liver, or at least one that's operating at less than optimal function, even before infection with HIV. Adding on top of all of that the many drugs prescribed for many HIVers, with all the liver toxicity that they can cause, makes a certain level of liver toxicity and dysfunction a frequent occurrence.

The liver uses enzymes to help it get rid of the waste produced in your body both by normal body processes and by the breakdown of drugs, alcohol, and other toxins. When the liver is overly stressed by this waste or damaged by various

infections, the liver enzyme tests done as part of your blood chemistry panel may show significantly elevated values. These liver enzyme tests include the SGOT, also called AST; SGPT, also called ALT; GGPT; alkaline phosphatase; and lactic dehydrogenase (LDH). Bilirubin is also used as an indicator of liver disease. Note that some of these can be elevated by problems other than liver disease so they must be interpreted carefully.

All HIVers, and especially those with hepatitis coinfection or who are currently on HAART, should have their liver enzymes monitored on a regular basis. However, even without elevations in these tests, there can be a level of less obvious liver dysfunction that should be addressed. Unfortunately, many people remain unaware of liver disease until it reaches a point that causes pain, swelling (hepatomegaly, or enlarged liver), fever, or jaundice (when the liver dysfunction results in an inability to break down bilirubin which then causes yellowing of the skin and/or eyes).

## Tips for handling liver toxicity

Since a functional liver is critical for life, detoxifying and repairing it can be one of the most important things you do for your long-term health, especially if you expect it to be able to handle the assault of long-term HAART use. The most obvious first step in a liver repair program is to eliminate as many sources of toxicity as possible. You may not be able to eliminate your HAART regimen, but there are other steps that may really help:

- Try to cut out recreational drugs and decrease or, preferably, eliminate alcohol.
- Make sure that you are vaccinated against hepatitis A and B.
- Avoid situations that place you at risk for hepatitis C — such as sharing needles (for drugs and tattoos) and nasal instruments used for cocaine and ketamine (sniffers, straws and bills).
- Use antibiotics only when appropriate. Many doctors tend to prescribe antibiotics at the drop of a hat and this is not a good idea if you want to avoid damaging your liver. You should, of course, take them if you have a real need, but they shouldn't be used whimsically or for an infection like a cold or flu that's obviously viral, for which an antibiotic will do nothing.
- Cut out chemically loaded junk foods and drinks, including caffeine (coffee and cola).
- Decrease the fat content of your diet.
- Check with your doctor and pharmacist to make sure that none of the supplements you are taking (particularly herbs) cause additional liver problems.

If you are taking meds that can cause liver toxicity, a careful review with your doctor should be done in order to determine if there are other meds that can be substituted for problematic ones. A review of possible drug interactions should also be done. It is always possible that drugs that would normally cause no problems when given alone might interact in a way that would cause significant toxicity. A “brown bag” checkup with your pharmacist to look at every single thing you're taking, whether it's by prescription or over-the-counter, is appropriate to check for all possible interactions. An excellent website where you can check for drug/drug and drug/food or drug/herb interactions is [www.aidsmeds.com](http://www.aidsmeds.com).

Last, but certainly not least, any indication of liver damage should immediately prompt an assessment of the possibility of any infections or cancers that can damage the liver, including:

- viral hepatitis; if hepatitis B or C are present, treatment can be considered
- MAC (*Mycobacterium avium* complex)
- TB (tuberculosis)
- CMV (cytomegalovirus)
- cryptosporidiosis
- lymphoma

In addition to removing, as much as possible, *anything* that might be stressing the liver, it is very important to **add the therapeutic agents that can help the liver to detoxify, repair and protect itself**. There are a number of potentially useful agents, listed below:

### Nutrients to Maintain Glutathione

Glutathione is the most important intracellular antioxidant and is crucially important for protecting the liver against toxicity when it goes about its task of breaking down drugs and other toxins. Taking the following **nutrients** may help to maintain or increase levels of glutathione:

- vitamin C (2–6 grams per day, in divided doses; individual tolerance for vitamin C varies greatly; amounts beyond an individual's bowel tolerance will cause gas and diarrhea so watch for this)

- N-acetyl-cysteine, or NAC (500 mg, 3 times per day; always take with food because taking it on an empty stomach can cause gastrointestinal tract irritation)
- L-glutamine (5 grams per day, increased up to 30–40 grams in those who also have diarrhea or wasting. Note that anyone with seriously compromised liver or kidney function should not take glutamine without a doctor's approval since it is an amino acid that must be processed by those organs.)
- alpha-lipoic acid (300-500 mg, twice daily; take on an empty stomach with fluids. Alpha-lipoic acid is a naturally occurring fatty acid that acts as a cellular coenzyme. It is very important to the liver cell metabolic pathways and can be rapidly depleted when the liver is under stress. It has long been used in Europe for liver regeneration where it has been shown to be effective in those with cirrhosis of the liver due to alcohol use. It appears to help boost repair when there has been either virally induced or drug-induced liver damage. It appears to be generally protective of the liver and has been shown to have a beneficial effect for those with elevated liver enzymes. Note that alpha-lipoic acid disappears from the bloodstream very rapidly, so products made in an extended-release form will last longer and work better; an excellent one is MRI's Extended Release Alpha-Lipoic Acid, available through AIDS buyers clubs.)

All of these nutrients, especially when used in combination, can help to maintain glutathione levels, even in the face of a daily assault of meds that must be broken down. Thus, for anyone with liver dysfunction or disease, their use may be very important as part of a total treatment approach.

For people with fatty livers, another important nutrient is **acetyl-L-carnitine**. Researchers say that it may help prevent mitochondrial toxicity, thus helping the body to handle fat better. Early studies of its use for non-HAART-related elevated triglycerides in HIVers did, indeed, show successful lowering of the blood fat levels. Research in animals has shown its successful use in reversal of fatty livers. The usual dosage is two capsules (500 mg each) twice daily. The alternative is Carnitor, the basic form of carnitine, available by prescription only. It is usually prescribed in doses of 3,000 mg daily (three 330-mg capsules, three times daily). Too high doses can cause diarrhea, so watch for this. Doses of plain carnitine need to be higher because the acetyl-L-carnitine releases four times as much free carnitine into the bloodstream, using equivalent doses.

### Silymarin and Other Herbs

An herb called milk thistle (*Silybum marianum*) contains the flavanolignanes silybin, silycristin, silydianin, and isosilybin which, as a group, are commonly referred to as silymarin. Silymarin has powerful effects as both an antioxidant and protector of the liver. It both protects healthy liver cells from toxic chemicals by promoting healthy cell membranes, and stimulates protein synthesis which promotes new liver cell growth, thus repairing the liver where it is damaged. Specifically, it promotes repair and regeneration of hepatocytes through the anti-inflammatory silymarin flavonoids found in the plant. These flavonoids have specificity for the liver and act in four main ways: (1) they stabilize cell membranes, acting as anti-inflammatories; (2) they stimulate RNA and DNA synthesis, enhancing regeneration; (3) they conserve glutathione peroxidase, the antioxidant enzyme so important to the liver; and (4) they stimulate enzymatic activity in the liver. There are many herbal formulas now available that contain silymarin in useful quantities. The suggested dosage for most of these is two capsules, three times per day, to be continued until liver enzymes return to normal. Many, many people have reported to me their success in reducing elevated liver enzymes with the use of silymarin, usually in conjunction with alpha-lipoic acid and N-acetyl-cysteine.

**WARNING:** Milk thistle and compounds found in milk thistle, such as silymarin, have the potential to affect levels of protease inhibitors and non-nucleoside analogues in the blood. Milk thistle and its extracts may also affect levels of other drugs that are processed by the liver. This action of milk thistle has the potential to cause side effects or weaken the activity of HIV drugs, causing them to not work effectively. For more info on the potential effect of milk thistle and silymarin on medications, see the CATIE Supplement Sheet on milk thistle available at [www.catie.ca/supple-e.nsf](http://www.catie.ca/supple-e.nsf)

### Glycyrrhizin

A licorice root extract known as glycyrrhizin has been shown in studies in Japan to reduce liver inflammation as well as having activity against herpes simplex, herpes zoster, and possibly CMV, hepatitis B, and HIV itself. It has been used for over forty years in Japan as a treatment for chronic liver disease and stomach ulcers. A number of studies reported in Japanese medical journals supposedly show that it can help detoxify the liver and help it to regenerate healthy tissue, thus reversing liver dysfunction. I say "supposedly" because the articles aren't translated and only abstracts are available in English. Japanese researchers also report that it works as an anti-inflammatory and antioxidant, helping to spare the liver from the burden of having its glutathione depleted and, thus, relieving stress on the liver. It should definitely not be taken if you have high blood pressure, low blood potassium, or a weak heart or kidney problems. It can cause water retention and blood pressure increases that could be very serious. It is available through some AIDS buyers clubs; for information, call DAAIR in New York City; 888-951-5433; or go to [www.daair.org](http://www.daair.org).

## Muscle aches and pains — ouch, that hurts.

Symptoms that can develop in the musculoskeletal system of HIVers include:

- muscle pains (myalgias)
- joint pains (arthralgias)
- muscle damage that can result in aches, pains, and weakness (myopathy)
- muscle cramping

Some of the potential culprits that cause myopathy are:

- AZT (alone in Retrovir and also in the combination drugs Combivir and Trizivir)
- d4T (Zerit) — can cause a rapid-onset very severe problem in rare cases
- other nucleoside analogues
- lipid-lowering drugs (statins)

It is thought that damage to the mitochondria caused by nucleoside analogues may be the underlying cause of myopathy in people taking these drugs. Nutrient deficiencies (especially of magnesium, a common deficiency in HIVers) may also be a factor, especially in muscle cramping. In order to distinguish between relatively minor muscle problems and what might be a severe (and even potentially lethal) problem—like the rapidly ascending muscular weakness that may be caused (although rarely) by d4T or the problems with controlling muscles that could indicate a serious neurological problem—it is very important to always call your doctor if any muscle problems develop.

Experts, as well as the manufacturer of d4T, Bristol Myers-Squibb, urge anyone experiencing any of the symptoms that can indicate lactic acidosis who also develops ascending muscular weakness to stop antiretroviral therapy immediately and see their doctor right away. Increased blood lactate can cause a wide range of symptoms. The earliest signs that lactic acid is increasing may include:

- fatigue
- nausea
- vomiting
- abdominal pain
- sudden unexplained weight loss
- shortness of breath or difficulty breathing (respiratory symptoms)
- neurologic symptoms (including difficulty moving)

Permanent discontinuation of d4T should be considered for anyone with confirmed lactic acidosis.

## Tips for handling muscle aches and pains

For the more common muscle aches and pains, discontinuing a problematic drug can often solve the problem, but that may not be an option for those in need of nukes as part of their antiretroviral combinations. Although aspirin and other over-the-counter pain medicines such as Tylenol (acetaminophen) may help counter muscle aches and pains, they don't really solve muscle problems (and do see the warnings about these meds in the "Headaches" section). Luckily, research done in Italy and at the National Institutes of Health has shown that doses of the **amino acid L-carnitine** (3,000 to 6,000 mg daily) may do so. In the small studies done, the carnitine usually reversed the myopathy and left those taking it feeling substantially better, possibly via its effects on reversing the nucleoside-analogue-caused mitochondrial dysfunction (see more complete discussion about mitochondrial toxicity in "Body Distortions"). A potentially more effective form of carnitine is L-acetyl-carnitine. The usual dosage is two capsules (500 mg each) twice daily. Doses of plain carnitine need to be higher because the acetyl-L-carnitine releases four times as much free carnitine into the bloodstream, using equivalent doses. Too high doses of carnitine can cause diarrhea, so watch for this. Note that a 3,000 mg daily dose is approved in the U.S. for elevated blood fats (hyperlipidemia) so if these are also present, you may have a justification for getting the prescription form of carnitine (Carnitor) approved for coverage.

**Magnesium supplements** (500–1,000 mg) can sometimes help to relieve muscle problems, especially muscle cramping. Epsom salts, which contain magnesium, may also help ease muscle pain and cramping when dissolved in a hot bath (mix about 3 cups of the Epsom salts with the water before climbing in).

**Quinine sulfate** taken in the evening can help some people who get night-time muscle cramps.

**Acupuncture and/or massage therapy** can help with some muscle problems. And chiropractic adjustments may also be

useful since nerve compression in the spine could be contributing to muscle spasms and pain.

Because neuropathy (nerve damage) may actually be causing some muscle problems, using the therapies suggested for neuropathy may help with some muscle problems (see “Peripheral Neuropathy”).

## **Nausea — that uneasy, queasy feeling**

Nausea—that queasiness that makes you feel like vomiting may soon follow—can be caused by many antiretrovirals (AZT, 3TC, abacavir, ritonavir, saquinavir, indinavir, and amprenavir are common causes), as well as many other drugs including Bactrim (PCP prophylaxis), and will almost always vanish when problematic drugs are discontinued. The exception can be when the liver has been damaged by the drugs since that damage can result in long-term nausea. Supporting the liver is crucial to prevent this; see *Liver Toxicity*. Since eliminating problem drugs isn’t always possible, it’s good to know that there are many things that may help reduce queasiness.

## **Tips for handling nausea**

First, consult your physician or pharmacist to determine whether taking a problematic drug at a different time could help. Some drugs need to be taken with a full meal in order to avoid nausea, while for others an empty stomach helps. If the requirements of your particular meds allow, making such adjustments can help.

Taking anti-nausea (antiemetic) drugs can often reduce or eliminate this problem. Ask your pharmacist to check for drug interactions before trying any of these over-the-counter or prescription medications. Included on a long list of anti-nausea possibilities (and there are many others if these don’t work) are:

- Gravol (dimenhydrinate)
- triethylperazine maleate (Torecan)
- prochlorperazine (Compazine; usually given in doses of 10 mg, every 6–8 hours)
- promethazine (Phenergan; given in doses of 25–50 mg, every 4–6 hours)
- trimethobenzamide hydrochloride (Tigan; usually given in doses of 100–250 mg, 3–4 times per day; can also be given via a 200-mg suppository or intramuscular injections, usually of 100–200 mg, 3–4 times per day)
- metoclopramide (Reglan; in either tablet or syrup form, usually given in doses of 10–20 mg, 3–4 times per day) \*This should not be taken with ritonavir (Norvir).
- dronabinol (Marinol; synthetic marijuana drug usually given in doses of 2.5–10 mg, 3 times per day)
- medicinal marijuana

Since med-induced nausea is particularly problematic at mealtime, anything that helps get food down is useful. The following tips may help settle your stomach:

- Eat small, frequent meals instead of two or three large ones (a full stomach makes nausea worse).
- Munch on snacks every three hours (don’t let the stomach get too empty or your blood sugar too low).
- Crunch down on dry, salty crackers or pretzels prior to eating and taking meds (salty foods are usually better to snack on than sweets).
- Sniff grated lemon peel or drink water with lemon in it just before eating.
- Chew slowly and eat in a calm, relaxed environment.
- Drink cool, carbonated beverages, especially ginger ale; the whole-foods brands that contain a potent blast of ginger — usually available in health food stores — will work better than standard varieties. Or try this simple homemade recipe: Simmer grated ginger and honey. Add a bit of lemon. Cool in the fridge and then add club soda.
- Powdered ginger root (2–3 capsules before eating) or ginger tea are natural remedies that have helped some people control nausea. Peppermint tea is another popular remedy for nausea and upset stomach.
- Substitute cool, bland, odorless foods for hot, spicy, smelly ones.
- Avoid the kitchen while food is being cooked to limit your exposure to the smells produced.

Since maintaining your food and fluid intake is crucial for health, if the nausea waxes and wanes, try to drink lots of fluids and take in lots of protein and calories when you’re feeling better, in order to make up for the times when you don’t feel like it. Try drinking supplemental drinks as an extra boost for both nutrients and fluids. If you experience recurrent vomiting, it will be very important to rebalance your electrolytes (see the suggestions in the “Diarrhea” section).

## **Neuropathy — my nerves are shot**

Peripheral neuropathy—the nerve damage that causes numbness, burning, tingling and sometimes severe pain in the hands, feet, arms and legs—is most often caused by d4T (Zerit), ddC (Hivid) or ddI (Videx), as well as metronidazole (Flagyl), thalidomide, isoniazid, vincristine, dapsone, and alcohol. Less commonly, it can also stem from 3TC (Epivir). When possible, it is extremely important that drugs causing neuropathy be stopped immediately upon the beginning of symptoms because a delay in cessation may result in permanent problems. When causative meds are stopped shortly after symptoms begin, the pain and numbness usually subside over time and are eventually completely eliminated, although that may take a number of months. However, failure to immediately cease the use of problematic drugs may greatly reduce the chances for complete reversal of symptoms. Too many people have ended up with permanent pain, numbness, and burning because symptoms weren't quickly reported to their physicians or because the physicians hesitated to take them off the drugs. Other factors can cause or contribute to neuropathy as well, such as:

- HIV itself
- diabetes
- cancer treatment
- alcohol
- cocaine
- amphetamines

Another form of neuropathy called autonomic neuropathy can cause a number of serious symptoms. Autonomic neuropathy seems to be far more prevalent in people living with HIV than is generally recognized. One study found that 13 out of 17 people tested (76.5 percent) had developed autonomic neuropathy, 11 of whom were symptomatic. The two most common symptoms caused by autonomic neuropathy are sexual dysfunction (impotence in some men), and digestive problems. A third is a potentially life-threatening effect called orthostatic hypotension where the blood pressure becomes so low that blood flow to the brain is affected. This sometimes causes fainting or weakness upon standing up. Autonomic neuropathy may also affect bladder function, causing urinary incontinence (inability to "hold it"), a symptom that can have a very debilitating impact on quality of life.

Digestive problems can occur when the nerves needed to activate the muscles to propel food out of the stomach and through the intestines are adversely affected. The result can be gastrointestinal motility problems in which the stomach fails to empty properly or food is not properly moved through the intestines. This can cause intestinal cramps, stomach discomfort, and nausea. With severe autonomic neuropathy, morning nausea that results in vomiting up the food eaten the night before may occur. A feeling of bloating and heaviness after meals is also common, as is the feeling that food sits in the stomach for long periods of time. In other words, there may be a feeling that the food eaten for lunch is still sitting in the stomach when it's time for dinner, and so on. It may also result in diarrhea.

## Tips for handling peripheral neuropathy

Both large trials with diabetics and many anecdotal reports from HIVers have shown the usefulness of nutrient supplements for preventing (preferably) or reversing peripheral neuropathy. (NOTE: what follows is a brief summary of the most important nutrient therapies; for much more in-depth information, see Treatment Fact Sheet # 12, Nutrient Therapy for Neuropathy at [www.larklands.net](http://www.larklands.net)). Most important are:

- alpha-lipoic acid (in doses of 300–500 mg, 2–3 times per day; preferably using an extended-release form like MRI's Extended Release Alpha-Lipoic Acid, available through AIDS buyers clubs)
- gamma-linolenic acid (in doses of 240 mg, twice per day; borage oil is a good source)
- L-acetyl-carnitine (LAC, in doses of 1,000 mg, taken 3 times per day)

A small British study showed that HIVers on the “d” drugs (ddC, d4T, ddI) have low levels of LAC, and that six months of supplementation improved both symptoms and nerve biopsy results, even when the “d” drugs were continued.

Also important is replenishment of magnesium, often deficient in HIVers (try 500 mg daily) and B complex vitamins, in particular, the following:

- vitamin B<sub>12</sub> (1,000 mcg, 2-7 times per week; nasal gel or injections may work better than pills due to absorption problems)
- vitamin B<sub>6</sub> (25–50 mg daily), taken with a B complex supplement, since deficiencies of these B vitamins can cause neuropathy and are common in HIVers

In addition, the nutrient protocol proposed by Dutch researchers to help address nuke-caused mitochondrial dysfunction may help (see “Body Distortions”).

Anything you do that soothes and reduces pressure on hypersensitive feet or hands can help. This includes:

- limiting walking distances
- wearing loose-fitting shoes and socks
- avoiding standing for lengthy periods
- avoiding repetitive pressure on the hands
- soaking your feet or hands in ice water on a regular basis
- raising your heels or hands off the mattress with a small pillow can help prevent increased pain while sleeping
- keeping heavy covers off of painful areas

In addition, regular exercise may help by increasing circulation to the nerves. And many swear by acupuncture or acupressure, with improvement often occurring with the first treatment, although repeated treatments may be necessary for long-term relief

The following pharmaceutical agents help some reduce pain, although they won't eliminate numbness:

- Neurontin (gabapentin) is usually the first-line therapy since it often works better for neuropathic pain than other possible meds.
- For pain that mostly occurs at night, the standard recommendation is for oral amitriptyline (Elavil, a tricyclic antidepressant), beginning with low doses in order to minimize certain side effects (dry mouth, sedation, urinary retention and low blood pressure upon suddenly sitting up or getting out of bed (orthostatic hypotension). A starting dose of 25 mg at bedtime is gradually increased to 75 mg (or as high as 100–150 mg if needed). Elavil may be particularly useful when sleep problems accompany the neuropathy because it has sedative effects.
- For predominantly daytime pain, oral nortriptyline (Pamelor) is often advised since it is less sedating, also beginning with a low dose of 10 mg per day, and gradually increasing to 30 mg, 3 times daily.

With these drugs, effective reduction of pain may not occur for up to two or three weeks, so patience is required. When one of these is not effective, another may still be.

- For occasional pain, standard anti-inflammatories such as ibuprofen (Motrin, Advil) may help with mild neuropathic symptoms.
- For more severe pain, the World Health Organization steps for treatment of pain should be used to ensure proper treatment (see below). When pain is under-treated or not treated, it may greatly increase the risk that it will become permanent.

#### **WHO's four-step approach to drug treatment of HIV-related pain:**

In general, medications should be given in the maximum tolerated doses before moving up to the next step. Where there is chronic pain, it is thought best to treat around the clock in order to prevent pain. If necessary, the usual meds can be augmented by short-acting drugs in order to treat breakthrough pain. With all these drugs, individual responses may vary and will be the best guide for proper med use.

- **Step One:** Try acetaminophen or a non-steroidal anti-inflammatory drug (NSAID). Most effective for mild pain. Possibilities include: ibuprofen, aspirin and naproxen. When one NSAID doesn't work, another might. Long-term use can cause gastrointestinal bleeding and should be avoided, if possible. People with low platelets, kidney dysfunction or low serum albumin levels (common in those with wasting) should not take NSAIDs. Those with gastric Kaposi's sarcoma should either take them with an antacid or avoid them.
- **Step Two:** If NSAIDs are not enough, try using a weak opiate derivative either alone or along with a Step One agent. Possibilities include codeine alone, codeine with acetaminophen (Tylenol), hydrocodone with acetaminophen, or oxycodone with acetaminophen.
- **Step Three:** If the above are inadequate, talk to your doctor about switching to a stronger opiate such as hydromorphone, transdermal fentanyl patches, levorphanol, morphine sulfate (intravenous), sustained-release morphine sulfate (oral) or meperidine. The minimum daily dose that affords pain relief should be used.
- **Step Four:** At any point during the preceding steps, consider adding adjuvant therapies to boost the effectiveness of the other drugs. At the top of this list, due to good effectiveness with few side effects, is the antiseizure med gabapentine (Neurontin). Other boosters include antihistamines like hydroxyzine (Vistaril); butyrophenones like haloperidol (Haldol) and pimozide (Orap); psychostimulants like methylphenidate (Ritalin), dextroamphetamine (Dexedrine) and pemoline (Cylert); amine precursors like tryptophan; selective serotonin re-uptake inhibitors such as fluoxetine (Prozac), paroxetine (Paxil) and sertraline (Zoloft); and heterocyclic and non-cyclic antidepressants like trazadone (Desyrel) and maprotiline (Ludiomil).

## Tips for Handling Autonomic Neuropathy

To treat the symptoms caused by autonomic neuropathy, there are a variety of approaches. The nutrient therapies discussed above as treatments for peripheral neuropathy may also help with the autonomic nerve problems. Having developed a very serious case of autonomic neuropathy myself (due to complications of my diabetes), I can absolutely say that an aggressive combination of nutrients resulted in very significant improvement in the digestive problems that the autonomic neuropathy had caused. I would consider doing all the nutrients discussed here (and more completely covered in Treatment Fact Sheet # 12, Nutrient Therapy for Neuropathy at [www.larklands.net](http://www.larklands.net)) to be a very important treatment component for the reversal of autonomic neuropathy. Out of the whole list, based on my personal experience, my belief is that the very most important for reversal of autonomic neuropathy are alpha-lipoic acid (500 mg, on an empty stomach, three times daily; absolutely do use an extended release form such as MRI's Extended Release Alpha-Lipoic Acid) and L-acetyl-carnitine (1000 mg, three times daily, on an empty stomach).

In addition, for those with digestive problems caused by autonomic neuropathy, the drug metoclopramide (Reglan) may provide significant help. Reglan speeds the emptying of the stomach and small intestine, thus relieving the digestive symptoms of bloating and uncomfortable fullness in the stomach. By ensuring that food moves on through the digestive tract as it is supposed to do, the use of Reglan will often not only improve digestion significantly but also eliminate the nausea and abdominal cramping that the food sitting undigested for long periods of time can cause. Reglan is available in oral form as a tablet or syrup, and in injectable form for intramuscular or intravenous use. The dosage range is from 5-20 mg, with the most common dosage for digestive problems being 10 mg, given approximately 30 minutes before each meal and at bedtime. Reglan has a sedating effect in some people so watch for this (and avoid driving if it occurs). And a very important note: in many people, Reglan eventually seems to quit working if it is used continually. The only solution seems to be saving its use for the really big meals, and not using it every time you eat. With only irregular use, it seems to continue to work.

For those with orthostatic hypotension that is caused by autonomic neuropathy, the use of elastic antiphlebotic (compression) stockings can help. These are thigh-high stockings that apply pressure to the legs in a way that helps to prevent pooling of the blood in the lower legs, thus helping to ensure normal blood flow to the head. If urinary incontinence is present, it is very important to see a urologist who can determine the cause(s) since autonomic neuropathy is only one of several potentially serious causes of this problem. There are drugs such as Hytrin or Ditropan which can help with some types of urinary incontinence.

## Nightmares and daymares and other sleep problems — can't sleep and don't want to wake up

Anxiety, mental problems, depression, nervousness, dizziness, insomnia and nightmares are all possible side effects of certain HAART drugs. The cognitive problems caused by the NNRTI efavirenz (Sustiva) can cause problems both during the day—muddled or unfocused thinking, impaired ability to concentrate, short-term memory loss, feelings of paranoia and disorientation, drowsiness, and altered moods, including euphoria, disorientation, anxiety, irritability, nervousness, and depression—and at night—insomnia and, when you get to sleep, vivid dreams and nightmares—sometimes the screaming heebie-geebe kind. Some people report feeling “stoned.” Some experience dizziness, lightheadedness, unsteadiness, or a loss of balance. Although very rare, serious psychiatric disorders have occurred in some, including severe depression, suicide attempts, aggressive behavior, delusions, paranoia and psychosis-like symptoms. Patients with a prior history of psychiatric disorders appear to be at greater risk for these serious problems. In many on efavirenz, these side effects disappear gradually after several weeks on the drug, so waiting out the problem for at least a month is advisable, if you can stand it. For others, the problems continue and stopping the drug is the only solution for those in whom the symptoms are just not bearable.

Before starting efavirenz, keep a few tips in mind. First, side effects do not always occur and vary from person to person. Your experience may be very different from that of another person's so don't program yourself to expect the worst. At the same time, be prepared for any side effects that develop. Be aware of other drugs or over-the-counter products that might increase the amount of efavirenz in your blood and, thus, increase the chance of experiencing side effects. For example, the protease inhibitor ritonavir (Norvir) can increase efavirenz levels in the blood by 20 percent. Some physicians recommend starting the drugs a few days apart. Also, taking efavirenz with a high-fat meal can increase its levels in your blood, and make potential side effects seem worse. Generally speaking, it is best to avoid recreational drugs, such as marijuana or alcohol, when starting efavirenz. Alcohol and drugs such as marijuana, cocaine, and speed, can worsen some of the CNS side effects of efavirenz. Consider beginning efavirenz on a weekend or taking a few days off from work since it may take a few days to get used to any mental changes.

Generally, taking the drug before bedtime is preferred since many of its side effects are strongest within a few hours after taking the dose. If you take it before bed, you may be able to avoid things like dizziness, impaired concentration, lightheadedness, and so on. If you find that the drug keeps you awake, taking it in the morning may be preferable. If you want to take it at night but find that sleep problems continue, try all the standard recommendations for improving sleep (see below). Some people have found that they can change their efavirenz dreams from nightmares to more pleasant dreams by

simply doing something pleasant—watching a funny TV show or reading something humorous or enjoyable—before going to bed. Hey, it's worth a try.

If nothing else works, you can ask your doc for prescription meds; see below. For many other helpful tips on using efavirenz successfully, see “Tips and Tricks on Taking Sustiva,” at [www.aidsmeds.com/drugs/SustivaTips/SustivaTips1.htm](http://www.aidsmeds.com/drugs/SustivaTips/SustivaTips1.htm). And remember: always call your doc if a particular side effect seems particularly troubling or severe.

Indinavir (Crixivan) and ddI (Videx) can cause chronic feelings of anxiety, usually low-level but sometimes more severe, in some users, and the symptom normally remains until the problematic drug is discontinued. Videx can also cause nervousness and sleeping difficulties, although these are not very common. Abacavir (Ziagen) can also cause trouble sleeping, as well as dizziness, problems which may or may not disappear after a period of a few weeks on the drug. Depression can be caused by nevirapine (Viramune) and saquinavir (Fortovase). As with efavirenz, all of the above may disappear after a period of weeks or months on the problematic drug, but may also remain long-term, with drug stopping the only solution.

For sleep problems, you can always try all the standard recommendations for increasing sleepiness and improving the likelihood that you'll fall asleep when you want to:

- Try to avoid drinking or eating anything with caffeine, sugar or alcohol for 4–6 hours before bedtime.
- Try to avoid nicotine for 4–6 hours before bedtime.
- Try to avoid strenuous exercise, bright lights and television before bedtime.
- Try relaxing before bedtime by doing peace-inducing yoga or breathing exercises, indulging in a soothing bath, or sipping calming herbal teas like chamomile.
- Try drinking a glass of warm milk. It may help since it provides a dose of tryptophan, a precursor to the chemical serotonin, which is involved in the induction of sleep.

For some people, medications may help:

- For sleep problems, standard sleep medications may help. Sedatives like Ativan (lorazepam) or Restoril (temazepam) can help many people fall asleep. Just remember that with long-term use, these drugs can be addictive so antidepressants may be a better choice. The antidepressant Serzone (nefazodone) helps some people who have difficulty remaining asleep. There are several effective, non-addictive drugs available for short-term use. Gravol (an anti-vomiting med) or Benadryl (an antihistamine) can be used safely for the occasional bout of insomnia.
- For anxiety, the standard anti-anxiety drugs may reduce that symptom, but note that such medicines are potentially addictive. Many psychiatrists believe that antidepressants are a better choice for long-term use.
- For depression, the standard antidepressant drugs may help. And remember that there are many different such meds available today so if one doesn't help, another might. If you find the side effects of a particular antidepressant troubling, know that other equally effective drugs might not have the same side effects. For example, while a number of the SSRI's (selective serotonin reuptake inhibitors, drugs like Prozac) sometimes cause loss of sex drive, the antidepressant Wellbutrin not only does NOT cause that side effect, it actually seems to increase sex drive in many.

With any such drugs, keep in mind this important caution: mixing many of these meds with herbs and/or with antiretrovirals can result in dangerous interactions. Always check with your doc and pharmacist before use.

Always remember that other causes of depression or anxiety may be contributing to your problems, including deficiencies of certain nutrients (the entire B complex, but especially B-6 and B-12) and testosterone (often deficient in both men and women HIVers and a major contributor to depression; if testing shows inadequate levels, replacement is crucial).

Don't ignore the possibility that stress may be causing you symptoms of anxiety or insomnia. At times, therapy with a good mental health therapist or psychologist can work wonders, especially if you have a lot going on in your head and your life.

## **Pancreatitis — ow, what's that pain**

Pancreatitis is an inflammation of the pancreas, the organ that secretes enzymes (that go into the gut and help you digest food) and insulin (which regulates the use of glucose, the cells' source of energy). Pancreatitis can be caused by ddI (Videx), ddC (Hivid), 3TC (Epivir), d4T (Zerit), hydroxyurea (Hydrea), and Bactrim (PCP prophylaxis), as well as by high levels of blood fats, especially the sky-high triglycerides seen in many on HAART. Elevations in the level of the enzyme amylase can indicate pancreatitis.

Pancreatitis may or may not cause symptoms such as:

- severe nausea
- vomiting

- abdominal pain

**If left untreated, pancreatitis can be fatal. If there is any suspicion of pancreatitis, it is crucial to get immediate medical attention.**

The standard North American treatment for this potentially fatal problem usually consists of immediate cessation of the problematic drug(s), along with bed rest and pain medication. However, German researchers have added another therapy that's well worth considering. Because high levels of pancreatic tissue-damaging free radicals are created in the early stages of pancreatitis, in various trials they gave selenium (intravenously, in the water-soluble form of sodium selenite), in doses of 500 mcg daily (sometimes with a first-day initial bolus of 200 mcg, followed by an additional 800 mcg given over the next 24 hours), often combined with vitamin E (1600 IU) and sometimes other antioxidants (vitamin C and N-acetyl-cysteine) immediately after a pancreatitis diagnosis. Death rates plummeted, and patients experienced faster recovery, less pain, and shorter hospital stays. Although these studies were not in HIVers, the researchers showed that these improvements occurred regardless of the cause of the pancreatitis. So immediate use of antioxidants would seem wise for anyone diagnosed with this problem, and long-term use of the nutrients might even help prevent the problem in the first place.

Last but not least, since pancreatitis may be another condition tied to mitochondrial toxicity, the use of therapies that might counter that could be of value (see discussion in *Body Distortions*).

## Skin Sins and Nail Nasties — aren't I a pretty sight

There are multiple skin problems and toenail or fingernail problems that may occur in HIVers, whether they're on or off meds. Some of the most common occurrences are skin rashes.

Rashes caused by the non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), including nevirapine (Viramune), delavirdine (Rescriptor), and efavirenz (Sustiva), the nucleoside analogue abacavir (Ziagen), and the protease inhibitor nelfinavir (Viracept) are sometimes life-threatening and always annoying. Any rash that appears after beginning any of these drugs should prompt an immediate visit to the doc, or if not available, the ER. And although most such rashes show up within the first few weeks on a drug, they may sometimes develop later so always pay attention. If ignored, such a rash could progress into a potentially fatal hypersensitivity reaction called Stevens-Johnson syndrome. Signs of hypersensitivity include:

- fever
- flu-like symptoms such as aches, pains, fatigue and headache
- with abacavir, there may be respiratory symptoms such as difficulty breathing, sore throat and a cough

## Tips for handling skin and nail problems

In general, the only solution for severe skin reactions is discontinuation of the drug causing it. Although some drugs can be tried again (rechallenged) after a rash, usually at lower starting doses, **this is not the case with abacavir which must never again be used.** The now-standard protocols for beginning with lower doses of certain NNRTIs can help prevent this. Other drugs, including ddC (Hivid) and Bactrim (PCP prophylaxis) can also cause serious rashes in some. It's best to avoid prolonged exposure to direct sunlight and to use sunscreen with at least 15 SPF when taking Bactrim/Septtra and other antibiotics because they can cause hypersensitivity to the sun.

Less serious rashes are a common occurrence that may be related to meds, although they can also be caused by many infections so a workup by an HIV-knowledgeable dermatologist is a must. The standard medical recommendation is some sort of locally applied cream, often one of the corticosteroid variety that will suppress the inflammation, but long-term use of these is considered inadvisable because of their potential for creating immune suppression when they are absorbed. Alternative practitioners have found that taking essential fatty acid supplements (several capsules daily of borage and flaxseed oils) can often help, both by resupplying the fatty acids that are deficient in many HIVers and are needed for skin health, and via their natural anti-inflammatory effects. Accompanying this with a potent multiple vitamin and mineral (to provide the vitamin E, vitamin A, zinc, and B vitamins necessary for overall skin health) can help ensure the presence of all the nutrients necessary for the skin to be at its best.

When dryness or itchiness is part of the problem, drinking plenty of fluids and applying any powerfully moisturizing cream can help. Two of the most effective are Eucerin, available over-the-counter in both cream and lotion forms, and Desitin, sold as a diaper rash cream. Colloidal oatmeal baths may also provide relief. Avoid harsh soaps that contain antibacterial chemicals and fragrances.

Cracked lips are another painful annoyance that seem to be caused most often by indinavir (Crixivan). There have been anecdotal reports of many possible solutions including: vitamin E rubbed on the lips (break open a capsule), Diprolene (a prescription cream), Micatin cream (an over-the-counter antifungal), Desitin (diaper-rash cream), bag balm (available in pharmacies) and gallons of good old water.

Another painful possibility that has been reported mostly by those taking indinavir (Crixivan) are in-grown toe nails. This may be a matter of one toenail at a time, or in some people, several toenails painfully digging in at once. In some cases,

these can be quite painful and will require surgical removal. Some people have tried doing regular pedicures to keep the nails cut back and shaped in order to help prevent them from becoming ingrown. It doesn't work for everyone but is worth a try. There have been people who simply had to discontinue the Crixivan because nothing else worked.

## Sexual Difficulties

Loss of sexual interest (decreased libido), erectile difficulties in men, and difficulties reaching orgasm in both men and women are frequently ignored side effects of some medications. Though you may blush at the idea, it is important that you refer to Rule #1 in the introduction and discuss these difficulties with your doctor, particularly if your troubles started shortly after the introduction of a new medication. Sexual difficulties have been reported in some people taking protease inhibitors, although more research is needed to show whether the drugs are really the cause of the problems.

### Tips for treating sexual difficulties

It is important to know that sexual dysfunction is rarely simply "an age-related thing," and should not be ignored. An evaluation of your testosterone level is very important in anyone experiencing a decline in sexual interest (in both men and women), erection difficulties or inability to reach orgasm. Appropriate hormone replacement can return testosterone levels to normal and remarkably reverse sexual problems. It is very important to stick to through-the-skin testosterone therapies (gels, creams or patches) because injections can shut down your own remaining testosterone production and can actually cause sexual problems down the line.

Other physical or biological problems may be responsible for lack of libido and should be considered. The following conditions can all hinder your sexual well-being, so appropriate testing to look for these is a must:

- thyroid gland disease
- elevated blood fats
- diabetes
- a form of nerve damage called autonomic neuropathy

If any of these are found, appropriate treatment of these conditions may help. With autonomic neuropathy, a nerve condition that is widespread in HIVers but often undiagnosed, much less is known about possible therapies, but the nutrient therapies for peripheral neuropathy (see *Neuropathy* in this fact sheet, as well as Fact Sheet # 12, *Nutrient Therapy for Neuropathy* at [www.larklands.net](http://www.larklands.net)) may help some people. When a physical exam and laboratory analysis of problems potentially related to sexual dysfunction appear normal, a search for other possible causes should continue.

Stress, anxiety and depression are frequently accompanied by sexual problems. These issues should be addressed and, where possible, treated through effective counselling and/or medications. If you are being treated for depression or chronic anxiety and develop sexual problems, your antidepressant may be the cause and a change in meds may be warranted. Many antidepressants provoke sexual side effects, however, some are worse than others, and one, Wellbutrin, can actually increase sexual libido. Check into this with your doctor.

Some commonsense rules to improve your chances of sexual health:

- eat well and avoid high-fat, heavy meals before sex
- cut down or quit smoking (a potent inhibitor of the sexual reflex/erection)
- cut down your alcohol consumption (a depressant in the sexual arena)
- if you are stressed, find a way to chill out (or consult with someone who can help)
- ensure that your body has enough rest to be able to pursue pleasure
- avoid the use of recreational drugs that diminish your sex drive

If troubles persist, a consultation with a urologist, sexologist or a trial of sildenafil (Viagra) may be an option. It is important to verify the safety of Viagra in conjunction with your HAART medications as certain combinations can prove dangerous. Don't even consider using Viagra without consulting with your doctor about interaction problems.

Last but not least, don't be embarrassed about your difficulties...a side effect is a side effect! And, for the last time, refer to Rule #1.

*Note: Some of the information contained in this fact sheet was included in an article published in POZ Magazine, September 2000; available at [www.poz.com](http://www.poz.com). The information here was last updated in May, 2002*

