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Managing Those Important Unimportant Side Effects

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There is a perception that if you don't have one of the major side effects of HCV treatment, like severe depression, or unresponsive anemia or neutropenia, that you should be able to get through the treatment. Side effects? Well buck up!

In fact, it's the daily grind of the cumulative, "minor" side effects that leads many treated patients to throw up their hands in dismay and decide that the cure is worse than the disease. That is a shame. Although the expectation that you can feel marvelous while taking interferon and ribavirin is unrealistic, for almost everyone those feared side effects are manageable enough to be kept to a tolerable, dull roar.

Probably what feeds our inadequacies in side effect management is that there are potentially so many different problems in so many differ-

ent patients that a cookie cutter approach doesn't work. It takes a lot more time to understand and manage the many different systemic side effects than it does, for instance, to prescribe erythropoietin for anemia. And time, sadly, is what many medical caregivers fail to provide.

However, if you as a patient are aware of some basic side effect strategies, and inform yourself about the many potential options for managing the unpleasant nonsense that doesn't respond to those, you will be able to advocate for yourself if you need more help. In today's revolving door medical system you may need to take control of your treatment. In other words, the most important strategy for managing those side effects is being informed.

One more point, before we begin to discuss

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some of the specific side effects. If you expect HCV treatment to be the worst thing that you have ever gone through, your expectations will be fulfilled. That is a fact. However, if you look upon it as a necessary but possibly arduous path to a long, healthy life, the experience will be much more tolerable. Did you ever need to walk up a long, steep hill? Did it help to constantly remind yourself how unpleasant it was? Of course not.

Indeed, we liken HCV treatment to running a marathon. And you would not run a marathon without preparing yourself, both physically and mentally. Start managing your side effects before you start the medications. Get yourself in better shape. Start eating a good healthy diet and drinking lots of water. Gather a circle of family and friends that can help support you—and don't forget to tell them that you may be an unpleasant jerk for awhile, but not to take it personally!

Here are some approaches to help you manage some of those "unimportant" side effects that are so important.

Flu-Like symptoms

You will get through these. Believe it. Everyone worries about the initial fevers, muscle aches, and joint pains, and they are most definitely unpleasant. But guess what? The more serious flu-like symptoms at the start of your treatment won't be your main problem, because they will be at their worst in the first few weeks when you are still motivated and have a pretty good attitude. Then they usually taper down to a mild daily unpleasantness that consists of fatigue and aches and blahs. That is the kind of thing that will piss you off, like a faucet dripping at night. Some people continue to have extra problems for the first day or two after their interferon injections, and time their injections on weekends so they can get more rest. But most feel kind of run down, to a greater or lesser extent, through the course of the therapy.

What can you do for these symptoms? The most important word is this: water. Time and time again, experience shows that water is the most effective intervention for those flu-like symptoms. Interestingly, no one knows why it works, but we do know that you need a lot: 15-20 8 oz glasses daily is the usual recommendation. Roughly a gallon—so make sure you locate ahead of time all of the bathrooms near your daily and nightly haunts. Don't like water? Give it a try and you will: it will really help you feel better.

A couple of other points. Soda is not water. Don't even think about it. And keep the hydration going regularly during the day by keeping a bottle of water with you, but taper off a bit in the evening so you can sleep through the night. The insomnia may be bad enough, without having to get up all the time.

Other things that you can use are Tylenol and ibuprofen. Moderate quantities of these, no more than 2 grams of Tylenol or 1600 mg of ibuprofen per day, are almost always fine for patients with hepatitis C, but run it by your doctor.

Here's another thing you don't want to hear. Exercise, unfortunately, is also important. I, myself, have never wanted to exercise either when I have had the flu and so I understand the reluctance. However, a modest amount of exercise is always helpful and you will feel better afterwards. Because it is really hard to get motivated to exercise, this is where discipline needs to come in. Just as you make a decision to take your shots and pills on schedule because they are important, you should also schedule a little exercise program as a required part of your treatment regimen. Not an hour of power walking and weight training, but just stroll around the block every day at 2, something like that. Do not allow yourself to get in the mode of considering it optional.

Nausea

A lot of people have some nausea here and there but it is usually mild and manageable and we have

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never had to stop a patient's treatment because of it. As you might guess, ribavirin is the usual culprit, but some of the other things you take, like ibuprofen, add to it. There are some reasons you may be getting nauseated. The ribavirin can be irritating to the stomach, increasing the acid or allowing the usual amount to cause more burning. Sometimes this keeps the stomach from emptying normally, and if it doesn't want to go down then unfortunately it will probably want to come up. A couple of simple things you can try are spreading out the ribavirin pills over the day, and taking antacids or an over-the-counter anti-acid medication, like Pepcid AC, Tagamet, or Zantac. There are stronger anti-ulcer medications you can get from your doctor, like Prevacid or Protonix, and there are anti-nausea medications like promethazine or Compazine that can work wonders for some people.

Insomnia

One of the main reasons people feel so lousy on the treatment is that they don't sleep well. Think about how you have felt after a few nights of getting no sleep. Tired, irritable, stressed out: sound familiar? Insomnia from interferon is not uncommon, whether you are administering it to yourself or whether your natural levels are high because you have a bug. If you do develop significant insomnia, it is important to try to do something about it before you become so exhausted that you throw in the towel. Everyone knows that there are lots of sleeping pills, but despite this it can be surprisingly tricky to find the right one.

First: don't forget the exercise, and if you take a nap during the day don't make it too long. An easy thing to try for sleeping is one or two capsules of over-the-counter Benadryl, which works for a lot of people, but remember that it can make your mouth extra dry when you are on interferon. After this you are pretty much dependent on your doctor for help. For their potential extra psychiatric benefit, we like using the sedating antidepressant-type medications, like amitriptyline, trazodone, Seroquel, or low dose Remeron. Any of these can make you too groggy, and so you may need to keep shopping. The new (expensive) short acting sleeping pills called Sonata and Ambien can be useful, as can the short-acting benzodiazepine sleeping pills like temazepam, but their effects tend to wear off and they can be addictive. Interestingly, sometimes these latter medications are too short acting if the insomnia is severe, and that is another reason we prefer the antidepressants. The important thing is this: don't give up, be a pest if you need to. You need to sleep if you are to finish this treatment successfully.

Hair loss

First: you will not go bald. Second: your hair WILL return to its previous luxuriant state. Third: occasion-

ally there can be some interesting temporary effects, like straightening of tight curls, making us wonder if there would be a market for interferon shampoo. The reality is that your hair will thin and look dry. You probably won't like the way it looks, but the problem will be more noticeable to you than to anyone else. There's no way to stop this, but using soft brushes, mild shampoo, and minimizing blow-drying can help. Shorter styles may look better. There is also a shampoo made for chemotherapy patients called Nioxin, sold only in salons, which you can try.

Rash

If there is a patient on hepatitis C treatment that hasn't had some sort of skin problem, send them my way. Everyone, it seems, gets something. There are bumps, blotches, and hives that mysteriously appear, disappear, then reappear elsewhere. Most people get itchy red skin from the dryness. The stuff you've had before, like psoriasis or lichen planus, may blossom. And those interesting "interferon spots" at the sites of injection itch, burn, stay discolored for months, and have everyone worried that they have a flesh-eating illness. The bottom line is that this stuff will screw up your skin. Most people pay a lot of money for fancy creams and emollients, many of which moisturize initially but actually draw moisture out of the skin. As it turns out, the best treatment for the dry itchy skin is Vaseline. What you are looking for is kind of a Saran Wrap effect, not a greased pig thing. Get yourself moisturized in the shower or tub. Then take dab of the Vaseline, rub it between your palms, and then apply a very thin coating over your dry areas to seal the moisture in. Once or twice a day should be good. For the mystery blotches, you can start with over-the-counter hydrocortisone cream, which usually isn't strong enough, then graduate up to stronger steroid-based creams or ointments like triamcinolone, applied before the Vaseline. Oh, another thing: if you itch, scratch with an ice cube. It helps numb the itch while you scratch it, and you won't rip your skin to shreds.

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Drugs and the Liver

Liz Highleyman

Many drugs—estimated at nearly 1,000—can harm the liver. These include prescription and over-the-counter medications, illicit recreational drugs, and herbal remedies. In the worst cases drug toxicity can cause acute liver failure, necessitating a liver transplant or causing death. In fact, drug toxicity is the leading cause of acute liver failure, and liver toxicity (hepatotoxicity) is the most common reason drugs are withdrawn from the market. Although severe drug-related liver injury is rare, the risk is higher in people with chronic hepatitis B or C.

How Drugs Damage the Liver

After most oral medications are ingested, they are carried in the bloodstream from the intestines to the liver, where they are metabolized, or broken down into active chemical components and byproducts (metabolites). Some of these metabolites are toxic to the liver. Eventually the byproducts are excreted in the bile (which is eliminated in the feces) or the urine. The chemical changes are carried out by enzymes in the liver (not to be confused with the liver enzymes—such as ALT and AST—measured in liver function tests). A family of enzymes called the cytochrome P450 (CYP450) system plays a major role in drug metabolism; a few of these enzymes—CP3A4, CYP2D6, and CYP2C9/10—process most common prescription drugs.

Interactions can occur when one drug (or herb, or even food product such as grapefruit juice) speeds up or slows down the metabolism of another. If a substance inhibits CYP450 enzymes, drug processing is slowed and drug levels in the body may rise too high, causing intensified toxicities and side effects. If it induces CYP450 enzymes, drug metabolism is accelerated and drugs may be eliminated too quickly, causing concentrations to fall to ineffective levels. If multiple drugs are metabolized by a shared processing pathway, there may be a "bottleneck" as they compete for the same CYP450 enzymes.

Some drugs (such as acetaminophen, or Tylenol) are harmful to the liver at predictable doses. Most others (such as isoniazid, used to treat tuberculosis) are more unpredictable or "idiosyncratic," and cause liver damage only occasionally in susceptible people. Some drugs kill liver cells (hepatocellular necrosis) and cause acute liver injury. Several others (such as erythromycin and certain steroid hormones) can cause impaired bile flow, or cholestasis. Still others can cause chronic liver damage, cirrhosis, allergic or hypersensi-

tivity reactions, fat buildup in the liver (steatosis), immune reactions, or damage to hepatic blood vessels. Some may even cause liver tumors.

Who is at Risk for Hepatotoxicity?

Different individuals process drugs at varying rates: some are slow metabolizers, while others are rapid metabolizers. These differences are largely genetic; for example, some people have less CYP450 enzymes than others. Pharmacogenetic tests that determine how well specific people can metabolize drugs may soon be widely available. Other factors—such as smoking cigarettes, drinking alcohol, and eating certain foods—can also affect drug metabolism. Research suggests that women are more likely to experience drug-related hepatotoxicity, perhaps because they have a lower average body weight. Also, children and elderly people tend to metabolize drugs more slowly. Because of these variations, a drug dose that is appropriate for one person may be too high or too low for another.

People with existing liver disease—for example, due to hepatitis B or C or heavy alcohol consumption—are more likely to experience drug-related liver toxicity. People with damaged livers may have inadequate levels of CYP450 enzymes, and those with impaired blood flow through the liver may break down drugs less efficiently. For this reason, people with liver disease sometimes need lower than normal medication doses.

Symptoms of Liver Toxicity?

Severe liver toxicity can result in rapid, acute liver failure, which may lead to encephalopathy (brain dysfunction), impaired blood clotting, coma, and death. But most cases of liver toxicity are less serious. The most common symptom of hepatotoxicity is elevated levels of liver enzymes, including ALT and AST, which leak into the bloodstream when liver cells are damaged. People who take drugs that are processed by the liver often have slightly elevated liver enzymes, but levels two or more times the upper limit of the normal range (0-48 IU/L for men and 0-42 IU/L for women) are cause for concern. Levels five times or more the upper limit of normal (grade 3 toxicity) indicate severe liver toxicity. However, liver enzyme levels are not a foolproof indicator of hepatotoxicity, since some people can experience drug-induced liver damage without having dramatically increased ALT or AST levels.

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Mild-to-moderate hepatotoxicity is often asymptomatic, but some people may experience nausea, diarrhea, loss of appetite, fatigue, itching (pruritus), muscle and joint aches, or abdominal pain. Drug toxicity that causes cholestasis can lead to elevated levels of bilirubin, a pigment released when the liver breaks down red blood cells. This can cause jaundice (yellowing of the skin and whites of the eyes), dark urine, and pale stools. Often it can be hard to distinguish drug-related liver toxicity from other types of liver damage, since the symptoms and diagnostic test results may be so similar.

In order to diagnose drug-induced hepatotoxicity, it is important to consider when liver enzyme elevations or other symptoms occur relative to when a drug is started. Symptoms typically appear within days or weeks after starting a new drug and often stabilize over time. But in some cases (for example, with isoniazid and certain antibiotics) liver toxicity can develop after a longer period—up to several months—on a medication. The surest way to determine if a drug is the cause of liver-related symptoms is if the symptoms subside when the drug is stopped and worsen again if it is restarted.

Drugs & Herbs Cause Hepatotoxicity

Many different drugs are known to cause liver toxicity. Acetaminophen is the one of the leading causes of acute liver failure, responsible for more than 50,000 emergency room visits and some 100 deaths in the U.S. each year. Liver cell death occurs when the liver's normal drug-processing pathway is overwhelmed and a toxic byproduct called NAPQ1 is produced. Usually severe hepatotoxicity occurs when people take twice the normal dose or more, but some individuals are susceptible to liver damage at lower doses; liver toxicity is especially likely when the drug is used with alcohol. N-acetylcysteine, which replenishes a natural protein called glutathione, is an antidote to acetaminophen poisoning.

Many anti-HIV drugs are associated with liver toxicity—a cause for concern among people coinfecting with HIV and hepatitis B or C. All classes of anti-HIV drugs have been linked with liver toxicity. The non-nucleoside reverse transcriptase inhibitor nevirapine (Viramune) can cause liver inflammation and elevated liver enzyme levels. One South African trial found that women taking nevirapine were twice as likely as men to experience liver-related side effects; two women in the study died due to liver failure. Protease inhibitor drugs are most often associated with liver problems, especially ritonavir (Norvir). A study by researchers at Johns Hopkins University found that the risk of liver toxicity was five times greater in people taking this drug. Ritonavir plays a major role in drug interactions.

Because it induces certain CYP450 enzymes, it can cause rapid metabolism and low levels of many other drugs. On the other hand, because it has a high affinity for the CYP3A4 enzyme, ritonavir can cause elevated levels of other drugs that also compete for processing by this same enzyme. But this effect is not always bad: small amounts of ritonavir are now often added to other protease inhibitors to raise their blood levels and allow lower doses to be used. Careful drug selection can help prevent hepatotoxicity. The newer protease inhibitors nelfinavir (Viracept) and atazanavir (Reyataz, not yet approved) may be the best options for coinfecting people. Importantly, most people—including those coinfecting with HBV or HCV—do not experience serious liver problems due to anti-HIV drugs. With an increasing number of antiretroviral medications available, most coinfecting people can be successfully treated for both HIV and viral hepatitis.

For many other conditions as well, there are a variety of drugs to choose from and the most hepatotoxic ones can often be avoided. For example, the anti-diabetes drug troglitazone (Rezulin) was taken off the market in March 2000 due to severe liver toxicity, including nearly 90 reported cases of liver failure and 60 deaths; two newer drugs for type 2 diabetes—rosiglitazone (Avandia) and pioglitazone (Actos)—are safer for the liver. Other drugs pulled from the market by the FDA due to concerns about liver toxicity include the pain medication bromfenac (Duract), the diuretic ticrynafen (Selacryn), and the arthritis drug benoxaprofen (Oralflex). The antidepressant nefazodone (Serzone)—associated with more than 50 reports of liver injury, including 11 deaths—has been withdrawn in Europe and consumer advocates have asked the FDA to ban it in the U.S. as well, saying it is no more effective than other similar drugs. Advocates have also asked the FDA to withdraw the arthritis drug leflunomide (Arava).

But some drugs, even though they cause liver toxicity, remain on the market because they have important benefits and there are no equally effective safer medications. The antibiotic trovafloxacin (Trovan) is still available—despite several cases of acute liver injury leading to transplants or deaths—for people with life-threatening bacterial infections. Isoniazid is one of the drugs most often associated with liver toxicity, but it is still used to prevent and treat tuberculosis. For some conditions—such as seizures—many of the effective drugs can cause hepatotoxicity.

In addition to drugs, some nutritional supplements can cause liver toxicity, as can many herbs, herbal teas, and patented traditional Chinese herbal formulas. Although some herbs are beneficial to the liver, others are highly toxic. There have been numerous reported cases of liver failure and death associated with certain herbs. For

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example, in March 2002 the FDA issued a warning about kava kava, and sale of the herb is banned in France, Germany, and Switzerland. People interested in using herbs—especially if they have liver disease—should consult a knowledgeable practitioner.

Some Drugs Associated with Liver Toxicity:

- amiodarone (Cordarone), heart arrhythmia
- azathioprine (Imuran), rheumatoid arthritis
- carbamazepine (Tegretol), seizures
- chlorpromazine (Thorazine), antipsychotic
- cyclophosphamide (Cytosan), cancer chemotherapy
- diclofenac (Voltaren), arthritis
- diltiazem (Cardizem), angina and high blood pressure
- felbamate (Felbatol), seizures
- ketoconazole (Nizoral), fungal infections
- methotrexate (Rheumatrex), arthritis, cancer chemotherapy
- methyldopa (Aldomet), high blood pressure
- nitrofurantoin (Macrochantin), urinary tract infections
- pemoline (Cylert), attention deficit disorder
- phenytoin (Dilantin), seizures
- tacrine (Cognex), Alzheimer's disease
- ticlopidine (Ticlid), reduce blood clotting, prevent strokes
- tolcapone (Tasmar), Parkinson's disease
- valproic acid, seizures
- zafirlukast (Accolate), asthma
- zileuton (Zyflo), asthma

Some Supplements Associated with Liver Toxicity:

- iron
- niacin in high doses
- vitamin A in high doses

Some Herbs Associated with Liver Toxicity:

- bush tea • chaparral
- coltsfoot • comfrey

- Crotalaria species • ephedra (Ma Huang)
- germander • Gordolobo yerba tea
- groundsel • Heliotropium species
- Jin Bu Huan • kava kava
- Mate tea • mistletoe
- pennyroyal oil • pyrrolizidine alkaloids
- sassafras • Senecio species
- senna • skullcap
- valerian

Preventing Liver Toxicity

Ideally, drug-related liver problems should be discovered when drug candidates are tested. However, because animals and humans metabolize drugs differently, sometimes liver toxicity is not seen in animal studies. Drug candidates are often withdrawn from consideration due to hepatotoxicity in early human clinical trials. But in other cases, severe liver toxicity is so rare that it does not show up in clinical trials. For example, no cases of liver failure were reported in trials of trovafloxacin that included some 7,000 participants. Liver toxicity may only become apparent after a drug is approved and used by larger numbers of people.

If possible, people with chronic hepatitis B or C should avoid taking drugs associated with liver toxicity. Often effective alternative medications are available that can be used instead. In some cases, it may be possible to reduce the risk of liver problems by using lower drug doses. But sometimes people need a medication known to cause hepatotoxicity. Individuals taking such drugs—especially if they have existing liver disease—should have their liver function (including ALT, AST, and bilirubin levels) monitored regularly. This is especially important when starting a new medication. Because alcohol can increase the risk of drug-related liver injury, avoid or reduce alcohol consumption. Finally, it is important to tell your doctor and all other healthcare providers about any prescription drugs, over-the-counter medications, recreational drugs, herbs, or nutritional supplements you are using. If hepatotoxicity is discovered early, liver damage usually can be halted and the liver can recover.

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HCV Advocate, May 2003

An Artificial Liver Device—A Potential Breakthrough in the Management of Acute Liver Failure

Alan Franciscus, Editor-in-Chief, HCV Advocate

Acute liver failure is a potentially fatal condition that affects about two thousand people in the United States each year. The majority of cases of liver failure usually develop over many years and are the outcome of prolonged insult to the liver either by a virus (chronic hepatitis B or hepatitis C) or by toxin or alcohol abuse. On the contrary, acute liver failure can develop in a very short period, days or months as in the example of Tylenol (acetaminophen) overdose.

Persons diagnosed with acute liver failure have only a small chance of recovery and survival, but a new technology that has been used to develop an artificial liver may bring hope for end-stage liver disease patients whose options are otherwise limited to a liver transplant. Donor livers are in grave shortage in the United States and patients in acute liver failure may have to wait months or even years for a compatible donor organ with often a negative outcome during the wait.

The new technology is known as ELAD which stands for extracorporeal liver device. The technology has been developed by VitaGen located in La Jolla, California. It is the first technology of its kind and actually integrates functioning human liver hepatocytes (liver cells) into the process. The human hepatocytes help assist and support the exhaustive work of the patient's damaged and failing liver. This new ELAD technology is the first liver assist system that utilizes hepatocytes from humans rather than pigs.

The ELAD device will be undergoing many clinical tests in the coming months. It is hoped that this device will serve in the future as a bridge to successful transplantation. The ELAD device is a closed system that joins to a patient through a catheter inserted into the main vein in the neck. After the blood is initially filtered, the residual plasma is funneled through cartridges in the device where hepatocytes (human liver cells) help accomplish much of the liver's critical functions, such as energy storage and regulation, bile production, blood detoxification and the production of clotting factors and many essential proteins. The filtered blood and ELAD-treated plasma are then returned to the patient.

Investigators are very optimistic of the role that the ELAD device will play in managing acute liver failure in the future. The liver has a remarkable ability to regenerate itself so if the patient in acute liver failure can be sustained early on, it is feasible that they may not need

liver transplantation and may recuperate without any substantial liver problems, including chronic liver disease.

The ELAD is not yet FDA approved in the United States but an initial phase clinical trial conducted in Great Britain and the United States showed hopeful results. In the initial trial, almost 92% of patients who had been selected at random to receive treatment with the ELAD achieved either a successful bridge to transplantation or full recovery. In the comparative control group of patients who received only current standard care, only 42% achieved the same positive outcome. In an analysis of overall results in twenty-five patients, including those not listed for transplantation, 81% improved on the device compared to only about 50% of those in the control group. VitaGen will now need to conduct a subsequent clinical trial to test ELADs with a primary objective of evaluating overall effectiveness, safety and tolerability and a secondary objective of evaluating appropriate inclusion/exclusion criteria and system performance with regard to specific endpoints. This next trial in ELADs overall development plan will be conducted in about forty patients.

Currently there are no effective therapies for patients with acute liver failure so this new technology brings hope and could potentially save many lives.

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HCV Advocate, July 2003

Bone Loss and HCV

Liz Highleyman

Bone loss (osteopenia and osteoporosis) is one of the many conditions associated with chronic hepatitis B or C, although it is not yet clear why liver damage—and viral liver disease in particular—leads to bone destruction. Researchers have reported widely varying rates of bone loss in people with liver disease, with most finding that it is worse in people with more advanced liver damage. By keeping your HCV under control through effective treatment, therefore, you may be able to reduce your risk of osteopenia and osteoporosis. In addition, there are other steps you can take—ranging from exercise to medication—to help prevent or treat bone loss.

What is Bone Loss?

Bone loss refers to loss of minerals from the bones. As the bones become more porous and brittle, they are more likely to break, or fracture. Bone mineral depletion is a “silent” condition, and usually has no symptoms. Bone loss encompasses two related conditions:

Osteopenia: a more mild condition characterized by moderate loss of bone mineral density.

Osteoporosis: a more serious condition in which a more substantial amount of bone is lost.

Bones are made up of cells embedded in an intracellular scaffolding, or matrix, made up largely of minerals. Bones are constantly being “recycled,” or remodeled. Cells called osteoclasts dissolve bone and allow the minerals to be re-absorbed, while cells called osteoblasts build new bone. Normally, these two processes are in balance. But sometimes bone is destroyed faster than it can be rebuilt, causing overall bone mineral density to decrease.

What Causes Bone Loss?

Many different factors can contribute to bone mineral loss. Osteopenia and osteoporosis are most often associated with older people—particularly postmenopausal women—and, indeed, people start to lose about 0.5–1.0% of their bone tissue per year after age 35. But in addition to the demineralization that normally occurs with aging, various diseases,

dietary deficiencies, medications, and lifestyle factors can also increase the risk of bone loss.

Research has shown that progressive liver disease is associated with accelerated bone loss. For example, Sif Ormarsdottir and colleagues reported in the January 2002 issue of the *European Journal of Gastroenterology and Hepatology* that people with higher Child-Pugh cirrhosis scores had more bone loss in their spines and hipbones than those with lower scores, and that higher bilirubin levels were associated with greater bone loss. A study reported at the 2001 AASLD conference found that about three-quarters of people with end-stage liver disease (ESLD) had either osteopenia or osteoporosis, and that people with viral hepatitis were five times more likely to have bone loss compared with those who had liver disease due to other causes. Likewise, Elizabeth Carey and colleagues from the Mayo Clinic found that people with ESLD related to HCV had lower bone mineral density than people with alcoholic liver disease. At the 2002 EASL conference, Ingolf Schiefke and colleagues reported decreased bone mineral density even in non-cirrhotic people with hepatitis B or C, with higher rates in HCV-infected people compared with HBV-infected people.

It is not completely understood how liver dysfunction in general, or viral liver disease in particular, contributes to bone loss, but there are a several theories; many researchers believe multiple factors may interact. People with chronic disease (of any sort) often have abnormal levels of hormones, immunoglobulins (antibodies), and intercellular messenger chemicals. Low levels of the sex hormones—testosterone and estrogen—are known to predispose people to bone loss, while elevated levels of certain cytokines can promote destruction of bone by the osteoclasts. In people with advanced liver disease, the damaged liver may not be able to produce enough insulin-like growth factor 1 (IGF-1), a hormone that stimulates the osteoblasts to build more bone. Thyroid and parathyroid dysfunction in people with hepatitis may also play a role in bone loss.

Several medications have been linked to bone loss. Long-term use of steroids, particularly the glucocorticoids (e.g., prednisolone, hydrocortisone) is one of the major risk factors. Drugs from this family are often

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given after a transplant to prevent rejection of the new organ. This is one reason why people who have received a liver transplant are at high risk for bone fractures. Some studies have shown that people taking ribavirin to treat hepatitis C are more likely to develop osteopenia and osteoporosis, but other researchers have not found an elevated risk. Likewise, in recent years there have been increasing—but conflicting—reports that anti-HIV medications (both protease inhibitors and nucleoside analogs) may be associated with bone mineral loss, a concern for people coinfecting with HIV and viral hepatitis. Some researchers believe that both ribavirin and the nucleoside analogs may contribute to bone loss through mitochondrial toxicity and lactic acidosis (a high level of acid in the blood), which may cause important minerals to be leached out of the bones.

Other risk factors for bone demineralization include alcohol use, tobacco smoking, lack of exercise (especially being bedridden for long periods), race (Caucasians and Asian have higher rates of bone loss, while African-Americans have lower rates), and nutritional deficiencies—notably calcium and vitamin D. People with chronic diseases may be malnourished or suffer from wasting, in which case there may not be enough nutrients to build strong bones, or minerals may be leached out of the bones to provide for the normal needs of the body. Vitamin D deficiency in particular is very common in people with ESLD. In addition to the harm it can do to the liver, even a moderate amount of alcohol is strongly linked to osteopenia. Finally, the tendency to lose bone is genetic, and people who have stronger, denser bones when they are young are less likely to develop osteopenia and osteoporosis later on.

Preventing and Treating Bone Loss

Fortunately, there are several steps you can take to prevent or minimize bone loss. The first line of defense is a healthy lifestyle: avoid tobacco smoking and alcohol use, get adequate amounts of calcium and Vitamin D, and exercise regularly. Good calcium sources include dairy products, soy products, beans, fish with bones, and green vegetables. Some people with advanced liver disease may need supplements, but consult your doctor or a nutritionist because excess vitamin D can be toxic to the liver. (Vitamin D can also be safely absorbed through the skin during exposure to the sun.) Regular weight-bearing exercise—such as weight lifting, walking, and climbing stairs—is

one of the best ways to maintain strong bones. But some exercises that are good for cardiovascular health (such as swimming) do not strengthen the bones.

Medications including alendronate (Fosamax) and risedronate (Actonel) help restore bone mass and are approved by the FDA for treating osteoporosis. Supplements of calcitonin, a natural chemical that helps regulate bone remodeling, have been shown in some studies to reduce the risk of bone fractures. Until recently, many post-menopausal women were routinely prescribed hormone replacement therapy (HRT) to prevent osteoporosis. But since a large study revealed in July 2002 that HRT can increase the risk of breast cancer, heart attacks, and strokes, use of hormones solely to maintain bone health is no longer recommended. However, supplemental testosterone may be used in men and women who have low hormone levels (hypogonadism).

Much remains to be learned about bone loss in people with hepatitis B or C. In the meantime, getting treated for HBV or HCV (if appropriate for you) and making certain lifestyle changes can improve your overall health while helping minimize bone damage. Until more is known, ask your doctor about getting a baseline DEXA (dual energy x-ray absorptiometry) bone density measurement and regular bone density screenings, especially if you have other risk factors for osteopenia and osteoporosis.

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HCV Advocate, July 2003

Molluscum Contagiosum

I'm including this article because I think MC can sound more frightening than it is. I've found these lesions on my arms and simply scratch them off. My doctor suggests that we have a lot more important things to deal with regarding our health and quality of life, and that dermatological abnormalities are not uncommon with HIV people. It is important to state that MC is different from a newly emerging staph infection called Staphylococcus aureus. Staphylococcus aureus causes nasty-looking boils, deep abscesses, and wide-spreading surrounding inflammation, which has proved impervious to common anti-biotics.

What is it?

Molluscum contagiosum (MC) is a common skin problem caused by a viral infection in the top layers of the skin. MC causes one or more lesions or bumps on the skin and looks something like warts or pimples. It is a common problem in children but can also occur in adults.

MC is caused by the molluscum contagiosum virus (MCV), a member of the poxvirus family. It can be spread through skin-to-skin contact, especially during sexual activity that involves friction and skin irritation. MCV is more likely to cause skin lesions in people with compromised immune systems, although many adults with healthy immune systems can develop MC.

MC does not progress to more serious diseases, such as cancer. However, MC skin lesions can be bothersome and disfiguring.

What are the symptoms?

MC looks like small flesh-colored or pink dome-shaped bumps. They are usually shiny in appearance, and each bump typically has a small indentation in the peak of its dome. The bumps usually form in clusters, notably on the thighs, buttocks, groin and lower abdomen, and may occasionally appear on the external genital and anal region and on the face and eyelids.

MC lesions can cause itching or tenderness in the area, but in most cases the lesions cause few problems. Untreated lesions can last from two weeks to five years.

People with compromised immune systems, including those infected with HIV, can experience severe MC lesions, so-called giant lesions, and often have a much wider spread of lesions.

How is molluscum contagiosum diagnosed?

Very often, a healthcare professional can diagnose MC simply by looking at the bumps. Sometimes, a specimen needs to be collected from one of the bumps for further analysis. Collecting a specimen is relatively painless, and results from the laboratory are often available within a week.

How is molluscum contagiosum treated?

While MC lesions can go away on their own, treatment is often recommended. Treating MC reduces the risk of lesions traveling to other parts of the body and helps to prevent transmission to others.

The treatments used for MC are similar to those used to manage warts caused by the human papillomavirus, or HPV. These include:

Topical medications: Topical gels and creams -- such as podophyllum, trichloroacetic acid (Tri-Chlor®), cantharidin (Verr-Canth™), tretinoin (Avita™, Retin-A®), tincture of iodine, silver nitrate, or phenol -- can be applied directly to the MC lesions. Some of these medications can be applied at home while others need to be applied by a healthcare provider, often a dermatologist.

Surgical options: These include cryotherapy (applications of liquid nitrogen to freeze MC lesions), laser treatment, curettage (scraping of MC lesions), and electrocautery (an electric needle used to remove MC bumps). These procedures are always performed in a doctor's office, often by a dermatologist.

Oral medications: Some oral medications that can be prescribed are griseofulvin (Fulvicin®) and cimetidine (Tagamet®). Griseofulvin is actually approved to treat certain fungal infections, but it has also been shown to treat MC lesions. Cimetidine can be used to treat MC lesions, particular if the

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VIRxSYS to Initiate Phase I Clinical Trials

For Innovative Treatment of HIV/AIDS-New Experimental AIDS Treatment

Aims to Thwart Development of Disease in Infected Individuals by Turning HIV Against Itself

VIRxSYS Corp., a private biotechnology company focused on the development of novel genetic medicines and vaccines for the treatment and management of serious diseases such as HIV/AIDS and cancer, announced today that it will initiate Phase I clinical trials for the genetic treatment of HIV/AIDS. The trials will involve the first-ever use of a lentiviral vector in humans called VRX496, whereby HIV is genetically turned against itself in a clinical setting. The therapeutic goal is to show in human trials what has been demonstrated in the laboratory and in small animals. In the laboratory, the VIRxSYS vector repeatedly showed extremely high delivery efficiency to CD4 T cells (immune cells) significant inhibition of HIV replication and ability to thwart wild-type HIV's (wt-HIV) tendency to create resistance to the treatment via mutation. In small animals, safety and non-toxicity of the VIRxSYS vector were also demonstrated.

The Phase I clinical trials are expected to begin in the next 90 days at the University of Pennsylvania's School of Medicine and will involve HIV infected patients, who have failed two consecutive combination anti-retroviral drug therapy regimens. The treatment involves the removal of T cells from patients infected with HIV, treating these immune cells with the HIV lentiviral vector and then reintroducing them back into the patient. The trials are being led by University of Pennsylvania's Drs. Rob Roy MacGregor, principal investigator and Carl H. June, co-investigator, both leaders in the fields of T cell transplantation and infectious diseases.

VIRxSYS' HIV lentiviral vector technology is a radically different approach to HIV treatment. Instead of developing newer classes of HIV replication blockers, VIRxSYS has developed a gutted version of HIV, called VRX496, by taking out the components that foster its replication and cause disease and inserting instead an anti-HIV 'antisense' payload that destroys the genetic material of HIV. This vector is then added to the CD4 T cells of an HIV-infected patient to enable that patient's T cells to inhibit HIV replication and resist their destruction by HIV. VRX496 resides in these CD4 T cells in a dormant state until the infectious wt-HIV invades the cell. Upon infection and then subsequent activation of that cell, wt-HIV attempts to reproduce itself. This in turn triggers VRX496 replication that ultimately destroys the wt-HIV genetic material and prevents its replication. The goal of the VIRxSYS treatment approach is to reverse and potentially cure individuals with HIV/AIDS by creating an 'army' of VRX496-enabled CD4 T cells in the patient's body that permanently suppresses HIV infection and restores the body's immune system.

Additional information is available at VIRxSYS' web site at <http://www.virsys.com> and at Signature Capital's web site at <http://www.sigcap.com>.

PRNewswire, February 14, 2003

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area becomes inflamed or itchy.

Can molluscum contagiosum be prevented?

The molluscum contagiosum virus, which causes MC, can be hard to avoid, given that it is spread by skin-to-skin contact. The best tip is to avoid touching or brushing up against a partner's MC lesions.

If you do get MC, you should avoid touching the lesion and then touching another part of the body -- or another person -- without washing your hands. This can help prevent the lesions from spreading.

Also, keeping the immune system healthy is the best way to prevent MC lesions, even if you are exposed to the molluscum contagiosum virus. This means keeping viral

load low and T-cells high using anti-HIV drug treatment and by adopting a healthy lifestyle.

Are there any experimental treatments in development for molluscum contagiosum?

There may be new treatments being developed for the treatment of MC lesions and the molluscum contagiosum virus. If you would like to find out if clinical trials of new MC treatments are being conducted, there is an interactive web site run by amfAR, the American Foundation for AIDS Research. Another useful service for finding clinical trials is AIDSinfo.nih.gov, a site run by the U.S. National Institutes of Health. They have "health information specialists" you can talk to at their toll-free number at 1-800-HIV-0440 (1-800-448-0440).

Being Alive, March/April 2003

Complementary Corner

Interest in nutritional health products stems from a number of observations. These include documented nutritional/vitamin deficiencies even in early stages of HIV infection and malnutrition associated with increased risk of HIV disease progression. There is great controversy, however, over whether or not using supplements is always a good idea and if it provides benefits in the long run. There has also been long-standing interest in complementary and alternative medicine (CAM) approaches to managing HIV infection and various conditions associated with HIV. The CAMs most commonly used by people living with HIV are not drugs, herbs or other pharmacologic agents, but rather things like meditation, massage, energy healing, acupuncture and the like. The following article contains summary highlights of studies of nutritional health products and CAM approaches in the setting of HIV presented at the World AIDS Conference in Barcelona.

Selenium and HIV

Several studies have suggested that deficiencies in selenium are associated with HIV disease progression. A small study of 24 children and a larger study of 125 adults living with HIV concluded that those with selenium deficiencies were at a greater risk for HIV disease progression and death. Whether or not selenium supplementation would make a difference, however, is not known, nor did the study clearly determine whether selenium deficiency was a cause or an effect of disease progression.

Observations of selenium toxicity have been noted among people using selenium supplements. This led to warnings noting that unusual diets and vitamin supplements are the most common causes of selenium toxicity in the United States. The US RDA of selenium is generally 55mcgs. The Institute of Medicine has proposed that The maximal daily intake of selenium before causing toxic effects is roughly 400mcgs for adults.

A study conducted at the University of Miami compared the use of selenium supplementation (200µg/day) to placebo in 259 people living with HIV (147 men, 112 women). Information about CD4+ cell count, viral load and other parameters were collected at the initial study visit and then every six months thereafter for two years. While investigators concluded otherwise, it was not clear that selenium supplementation decreased the risk of hospitalization.

In a related study, investigators examined blood levels of selenium in the 112 women receiving anti-HIV therapy and looked for correlations between selenium levels and the risk for pre-cancerous cervical cells (*cervical dysplasia*). While selenium levels were lower in women who developed cervical dysplasia, supplementation made no difference in the risk of developing cervical dysplasia.

In another related presentation, investigators provided

information on the impact of selenium supplementation on CD4+ cell count increases. It appears that those receiving supplements were more likely to have slightly higher CD4+ cell count increases, but problems with data reporting leave it unclear what other factors may have impacted these increases. Investigators note that heroin use appears to decrease general nutritional status and is associated with lower levels of selenium, but no information on the distribution of heroin users in the supplement vs. placebo group were provided.

In short, the most that can be concluded from these reports is that it remains unknown if selenium supplementation offers any beneficial or harmful effects, whatsoever. Risks for cervical dysplasia appear slightly increased when selenium levels are lower, but supplementation does not appear to lessen this risk. Well-designed research is critical to evaluating the potential benefits (and risks) of selenium supplementation.

Vitamin A (Beta Carotene and Retinoids) and HIV Drug Interactions

Deficiencies in vitamin A (retinol and its precursor, beta-carotene) have been associated with advanced HIV disease. As in many similar situations, it is unclear if the deficiencies are a cause or effect of disease progression. It also remains unclear if supplementing vitamin A with retinoids or beta-carotene is helpful for people with HIV beyond correcting the deficiency. Moreover, questions remain as to whether or not vitamin A supplements cause vitamin-drug interactions. A team in Canada set out to evaluate whether or not a variety of forms of vitamin A supplements interact with the p450 enzyme system. This system is important for the breakdown and use of many anti-HIV drugs. Things that interact with the p450 system are highly likely to have interactions with anti-HIV drugs, particularly protease inhibitors, as well as with drugs to prevent and treat some opportunistic infection.

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The Canadian team evaluated six different vitamin A (beta-carotene) supplement products (four tablets and two liquid filled soft gel capsule products). All of the products tested had lower beta-carotene content than what was indicated on the label. One product had ten-fold less beta-carotene than what was advertised.

All of the constituents of vitamin A (retinal, retinol, retinate and beta-carotene) as well as all of the products tested had moderate (45 to 65%) to strong (65 to 100%) inhibitory effect on the p450 enzyme system. Therefore, these products have a very strong likelihood of interacting with anti-HIV drugs. Studies, in people as opposed to the laboratory, to look at the impact of taking vitamin A supplements (like beta-carotene) in combination with anti-HIV medications, are needed to understand the extent and impact these findings.

Vitamin Supplements and HIV in Women (Implications for Everyone)

A study in Tanzania, Africa of the use of multivitamins among HIV-positive pregnant women showed that multivitamin supplementation led to decreases in death of the unborn child (fetal death), increases in birth weight and decreases in pre-term births. While these findings were encouraging, trends were noted that children born to HIV-positive moms who received multivitamins during pregnancy were more likely to be infected with HIV. Because of this observation, another study was initiated in Kenya to examine the impact of daily multivitamin supplementation (or placebo) among 400 women who weren't pregnant and evaluate their impact on vaginal and cervical shedding of HIV.

Women received either a daily multivitamin or placebo for six weeks. The use of multivitamins was associated with slightly higher CD4+ and CD8+ cell counts and no overall changes in HIV levels in the blood. However, multivitamin use was associated with increases in vaginal shedding of HIV, with about 1/2 log higher levels of HIV in vaginal swabs among those receiving multivitamins.

Researchers speculate that the use of daily multivitamins among women is unlikely to protect women from HIV infection and may increase the likelihood that they will transmit HIV to others.

Another study found that vitamin A deficiencies in the blood were associated with increased vaginal shedding of HIV during pregnancy, increased HIV in breast milk, higher rates of mother-to-child HIV transmission, lower

CD4+ cell counts and more rapid HIV disease progression. These observations come from studies in the third world where dietary vitamin A deficiencies are notable and marked, regardless of HIV status. The same team that conducted the study of multivitamins noted above evaluated the use of vitamin A supplementation or placebo in 400 Kenyan women who were not pregnant and examined a variety of viral and immune parameters.

Women received either vitamin A (10,000 IU delivered as retinyl palmitate) or placebo, daily for six weeks. The dose of vitamin A used is the dose recommended by the World Health Organization for correcting symptomatic vitamin A deficiencies in women of childbearing potential. The study found that vitamin A supplementation had no effect (positive or negative), whatsoever, on vaginal shedding of HIV, blood levels of HIV, CD4+ or CD8+ cell counts compared to placebo. These observations held true even among women with notable vitamin A deficiencies at the start of the study (about 59% of the women). These findings suggest that while vitamin A deficiencies may be associated with poorer outcomes in mother-to-child HIV transmission and poorer outcomes of HIV disease in general, supplementation is unlikely to address these problems.

The women in these studies were not receiving anti-HIV therapies and thus the results are perhaps most relevant to settings where anti-HIV therapies are not available and/or to individuals who choose not to use them in conjunction with supplement approaches. Whether the increase in vaginal shedding of HIV associated with multivitamin supplements would be controlled with the concurrent use of anti-HIV therapy remains unknown.

Vitamin E, Vitamin A and Anti-HIV Therapies

Previous reports have suggested that vitamin E levels are decreased in people living with HIV and low levels of vitamin E in the blood have been associated with increased risk of HIV disease progression. Researchers in the United Kingdom sought to evaluate vitamin E levels among 33 people before and six weeks after starting anti-HIV therapy and compare them to levels observed in healthy HIV-negative people.

Investigators found that prior to starting anti-HIV therapy, vitamin E levels were lower among people with HIV compared to healthy HIV-negative people. Contrary to previous reports, people with HIV who had AIDS had slightly *higher* vitamin E levels (24µmol/l) compared to people with HIV who did not have AIDS (19µmol/l). After six weeks of anti-HIV therapy, vitamin E levels normal-

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ized among people with HIV (28µmol/l) compared to HIV-negative people with vitamin E levels measured six weeks after the start of study (26µmol/l).

Vitamin A levels were also evaluated before and six weeks after starting anti-HIV therapies. No differences were observed in vitamin A levels either before or after starting anti-HIV therapy. Moreover, vitamin A levels were in normal healthy ranges, roughly equivalent to those observed in HIV-negative individuals, both before and after six weeks of anti-HIV therapy use. Further, no differences were observed in vitamin A levels between healthy HIV-positive people and those with AIDS.

This study suggests that for people taking anti-HIV therapy, vitamin E supplementation is likely not necessary. Moreover, vitamin A deficiencies were not noted with HIV infection, regardless of stage of disease. It remains unknown if vitamin E supplementation among people not on anti-HIV therapy will provide benefits.

Nutrition and Exercise to Manage Lipodystrophy

A group in New York conducted a small study to evaluate the impact of individualized nutrition and exercise advice (delivered by a registered dietitian in accordance with recommendations by the American Heart Association) on lipid levels in people with HIV experiencing lipid elevations associated with the use of anti-HIV therapy. Twenty-five people were enrolled in the study (1 Asian, 10 African Americans, 7 Hispanics and 7 white/non-Hispanic), which included 10 women and 15 men.

Nutritional and exercise advice had little to no impact on lipid levels. Virtually no changes were seen in cholesterol levels (either HDL or LDL cholesterol). There were slight decreases in triglyceride levels, but not to healthy target levels defined by the National Cholesterol Education Program. While only a small study, the investigators propose that nutrition and exercise advice

alone are unable to improve lipid abnormalities seen in people on anti-HIV therapy.

There are several limitations to this study that may confound conclusions. One is the relatively small size of the study. Another is that dietary assessments were not conducted (while people were given advice on nutrition and exercise, it's unknown if they actually followed the advice). Despite underwhelming results from this study, improving nutrition and exercise habits and routines will likely benefit a person's general overall health even if it has apparently little effect on lipid profiles.

Managing Side Effects of Anti-HIV Therapy with Acupuncture

Acupuncture is an ancient Chinese healing art, involving placing small, fine needles at various points through the skin. These points are believed to conduct an energy, called *qi*, between the surface of the body and internal organs. Putting fine needles in various points is believed to direct this energy and promote healing and balance. Acupuncture is sometimes used with Chinese herbal remedies, though not always. A Boston study evaluated acupuncture as a treatment for digestive side effects associated with anti-HIV medications.

The study included 26 people who were taking anti-HIV medication and experiencing digestive side effects of therapy. Half received symptom-specific acupuncture for three weeks and half received non-specific acupuncture for three weeks. At the end of three weeks the groups switched modes of acupuncture therapy.

Preliminary results were presented on the effect of symptom-specific and non-specific acupuncture for nausea, excessive gas and loss of appetite associated with the use of anti-HIV therapy.

Side Effect	% reporting symptom after <i>symptom-specific</i> acupuncture treatment	% reporting symptom after <i>non-specific</i> acupuncture treatment
Nausea	25%	37%
Excessive gas	50%	63%
Appetite Improvements (only includes those reporting lack of appetite at study entry)	85%	58%

These results suggest that symptom-specific acupuncture may be more effective than non-specific acupuncture in managing digestive side effects of anti-HIV therapies. Of note, adherence to anti-HIV therapies improved following symptom-specific treatment (80%) compared to non-specific treatment (68%). Current plans are to expand the pilot study to see if these results hold true in a larger and more diverse group of people.

PI Perspective, January 2003

Re-Infection: Is it a Concern for People Living with HIV?

Re-infection is a term used to describe a new or secondary infection by a virus that has already infected a person. In most viral diseases, re-infection with the same virus doesn't occur because once the immune system conquers the original viral infection, it creates immunity against that virus. Re-infection occurs almost constantly, however, in some types of infection, such as the cold or flu viruses, because each new version of those new viruses is substantially different from the last. This is why a person may develop immunity to the flu strain that is common in one year, but still be at risk from the strain that becomes dominant the next year.

The question of re-infection with HIV has long been debated. There is no theoretical reason to think re-infection isn't possible, since the immune system never fully conquers the initial HIV infection. Still, many people, including many physicians, clung to the hope that re-infection with HIV either does not happen or that it only happens rarely. This view is the basis of the belief held by some HIV-positive people that having sex or sharing needles with another HIV-infected person poses little or no risks. Many if not most virologists, however, have long believed that re-infection is both possible and perhaps even likely. What is not known are the individual short- and long-term clinical consequences (which may vary from person to person for wholly unknown reasons).

For many years, there were no clear cases of re-infection presented at scientific conferences, but this did not mean such re-infection wasn't occurring. Instead, we know that finding and documenting cases of re-infection is extraordinarily difficult, if for no other reason than that no structured program has looked for them. Finding a case of re-infection has largely been a matter of chance. Yet, several observations over the years support the notion that re-infection is possible, including observations of sex workers in Africa infected with several different recombined "clades" of HIV as well as detailed genetic analysis of a few people's virus suggesting that re-infection was possible. This research is very difficult to conduct. Perhaps the only simple example of re-infection is in western Africa, where people are routinely found who carry both HIV-1 and HIV-2. At the very least, this proves that having HIV-1 does not protect a person from infection with HIV-2.

Recently, there has been considerable media attention about a few well documented cases of suspected re-infection with two versions of HIV-1. The most interesting case, presented by Dr. Bruce Walker, was the re-

sult of an almost accidental observation. While researching the effects of Structured Treatment Interruption (STI) in some newly infected volunteers, Walker's team was intrigued by one particular case in which the volunteer responded well to two initial cycles of STI. After each, the person's viral load remained undetectable for several months without treatment. Shortly after a third STI, however, the viral load remained low for only a brief period and then suddenly soared upward. The team wondered what made things different this time? After conducting extensive genetic analysis, they found their answer: the volunteer had become infected with a second, slightly different strain of HIV. Most striking, and discouraging, was that the genetic makeup of the new infection differed by only 12% compared to the original infection. Despite this small difference, the second infection had completely escaped control by the immune system, breaking through the suppression achieved against the original virus. This discovery, while important enough in regards to re-infection, also had discouraging implications for vaccine development, suggesting that as little as 12% variation between viruses might be enough to make a vaccine fail.

Several questions remain in regards to re-infection. Will re-infection lead to more rapid disease progression? Will re-infection with HIV result in transmission/acquisition of drug-resistant HIV that will limit a persons' anti-HIV treatment options? Both of these concerns are theoretically possible, and both have now been demonstrated in case studies. Currently there is not a large amount of data to assess the actual risk to the individual. Although only a little data currently exists and it is extremely difficult to gather more, it does not lessen the real potential for re-infection or its consequences.

There are several reasons why people living with HIV would want to maintain safer sex activities. While the clinical implications of re-infection remain unknown (and will likely be unknown for many years to come), there is some evidence of harm and no evidence of harmlessness. We also know for certain that safer sex does protect against many blood-borne infections that are major causes of life-threatening diseases and death in people with HIV. These likely include CMV, some forms of hepatitis virus, genital herpes, possibly the JC virus (cause of a particularly destructive condition known as PML), to name a few.

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State of Mind: Grief, Depression and Your Immune System

by Tony Zimbardi, PsyD

Many of us have an innate sense of a "mind/body" connection and how life's stresses, (which include adjusting to constant loss), over time can directly affect our health, especially for those of us living with HIV. Therefore, it's important for all of us to understand the difference between experiencing grief versus the symptoms of anxiety, stress and/or clinical depression. If you remember nothing else, remember this, expressing emotions can be a very healthy thing, because generally you are in touch with and expressing your feelings as sad as they may be. Chronic grief (experiencing multiple losses) on the other hand, can turn into clinical depression and this, over time, can cause an immune response, or more appropriately a lack of immune response, which can be detrimental to your health.

In her book [Heavenly Hurts, Surviving AIDS-Related Deaths & Losses](#), author [Sandra Jacoby Klein](#) describes normal grief as responding to comfort and support. She goes on to describe how even when one is in the process of their experiences of grief, one can also openly express anger and sorrow; And, one is still able to experience moments of enjoyment in life. Depression, on the other hand, does not accept support, may be evidenced by irritability (rarely anger), has generalized feelings of guilt and exhibits a pervading sense of hopelessness.

Based on her work at UCLA, Dr. Margaret E. Kemeny lectures on the immune system, her research indicates that individuals regularly expressing their emotions related to traumatic experiences showed a higher immune cell response and helper T-cell proliferation. Those studies also indicated that this led to fewer visits from the study participants to their health care providers than those studied who were not expressing and experiencing their emotions. So, the message is that expressing "normal and healthy grief" can be beneficial to the immune system. Chronic grief, however (such as that which comes from dealing with prolonged HIV progression, loss of a child, loss of members of one's friends or fellow support group members) is another story. Chronic grief left untreated can lead to clinical depression and a decline in immune functioning. So how can we help the immune system during a particularly rough period? Well, the good news is treatment is available, such as entering cognitive/behavioral therapy and support groups. Research has shown that both have the power to affect immune functioning.

Kemeny's data suggested that the individuals who progressed fastest from being asymptomatic to receiving an AIDS diagnosis were those who believed they would get sick and die of AIDS. Hence, the phrase "Unrealistic Optimism" was coined in acknowledgment of those who seemed to have an attitude that they would not become ill despite evidence to the contrary. It is notable that this work was done prior to the availability of protease inhibitors.

In the 1989 article "The Transformative Power of Grief," author J. Schneider explains that when we experience the loss of a loved one, we have a three-fold task before us.

1. We must acknowledge the loss.
2. We must experience and express the pain.
3. We must "get beyond" the loss, this meaning to reestablish a new life that reflects the absence of the beloved.

Klein offers several suggestions as well:

1. Seek support from friends or counselors who are capable of simply asking the following question: "What would be most helpful for you at this time?" Sound too simple? Just try it with a friend who has suffered a recent loss.
2. Surround yourself with individuals who can allow you to talk about all the multiple losses.
3. For those of us experienced in grief, to teach others and share our experiences when appropriate. What that means is not to make their time to talk about their grief, your time to talk about your grief, but rather to share or acknowledge a similar situation and how you were able to get through it.

Kemeny suggests that there are four major life themes that effect outcomes for those dealing with grief, loss, stress and their affects on the immune system. These themes are:

The motivational realm. This means finding meaning in one's traumatic experience. Her work concluded that most people typically find meaning through giving and receiving love; being creative; realizing the preciousness of life and finding their

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Oral Surgery: HIV Infection does not Affect Hemophiliac's Complication Risk

"Dental extractions and other oral surgical procedures, including local analgesic injections, potentially can cause problems in hemophiliac and HIV infected persons," however, "there are few data on treatment results in HIV-infected hemophiliacs compared with non-HIV-infected hemophiliacs," according to a recent study from England.

"The oral surgery treatment results in 48 patients with special needs, including HIV-infected hemophiliacs, non-HIV-infected hemophiliacs, HIV-infected non-hemophiliacs, and a group with other medical problems were therefore studied" by C Scully and colleagues, University College of London. "Around 20% of the hemophiliacs developed post-oral surgical complications, which was not significantly different whether or not they were HIV-infected," they found. "However, complications were less frequent (8%) in HIV-infected non-hemophiliacs or other patients with special needs."

"Although the patient groups are not large, it would appear that hemophiliacs had more postoperative complications but that the presence of HIV infection had no notable influence on treatment outcome," the researchers concluded.

Scully and colleagues published their study in the International Journal of Oral and Maxillofacial Surgery (Complications in HIV-infected and non-HIV-infected hemophiliacs and other patients after oral surgery. Int J Oral Maxillofac Surg, 2002; 31 (6):634-640).

The contact person for this report is C. Scully, University College of London, Eastman Dental Institute of Oral Health Care Science, 256 Grays Inn Road, London WC1X8LD, UK.

To subscribe to the International Journal of Oral and Maxillofacial Surgery, contact the publisher: Churchill Livingstone, Journal Production Department, Robert Stevenson House, 1-3 Baxters Place, Leith Walk, Edinburgh, EH13AF, Midlothian, Scotland.

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[Http://www.NewsRX.net](http://www.NewsRX.net)

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spirituality; And, staying engaged with life (doing volunteer work or setting new personal goals such as art classes or going back to school for vocational rehabilitation).

Stress Management. Understanding the detrimental effects of chronic stress, which is often evidenced by disengagement from life and a defeated attitude which can lead to immune suppression.

One's belief system. It seems that those who were quick to anger, have a negative view of life and a basic "cynical mistrust" towards others were those who characteristically had the highest mortality rate.

The social realm. Having just one confidante, meaning having at least one person you can "really talk to," leads

to higher immune function and lower mortality rates.

So, now you know that it's okay to be an "unrealistic optimist," just tell those well meaning individuals who might suggest you're simply in "denial" ...phooey. And remember too, that if nothing else, stay engaged in life. Whether you're HIV+ or HIV negative, being a part of all the madness is what keeps us human, and apparently, keeps us quite healthy too.

Tony Zimbardi, Psy.D., is an HIV+ licensed psychotherapist in private practice in the Hollywood Hills. He is the former Mental Health Chair on the Los Angeles County Commission on HIV Health Services and former Board President of Being Alive, LA. He can be reached at 323.851.1304. *Being Alive, March/April 2003*

Social Security Continuing Disability Reviews (CDRs)

Jacques Chambers

Whether you are collecting Social Security Disability (SSDI) or Supplemental Security Income (SSI), your medical records will be reviewed periodically to see if you are still disabled enough for benefits to continue.

Generally, for people receiving disability benefits due to HIV, Social Security only reviews your file every five to seven years. However, due to the improved treatments for HIV, Social Security is reviewing HIV cases more carefully than in the past and may start reviewing some more frequently.

When it's time for a CDR, you will be sent one of two forms:

- Short Form CDR (SSA-455-OCR-SM)
- Long Form CDR (SSA-454-BK)

The "right" way to fill them out depends on which form of CDR you are sent.

The short form (SSA-455-OCR-SM) is only two pages long and is read by computer (OCR stands for optical character reader). Since it is sent primarily to beneficiaries who have a low probability of medical improvement, this is probably the form you will receive.

This is good in that the short form assumes you are still disabled unless you give them reason to question that. A human only looks at the short form if the computer kicks it out for one reason or another. If it isn't sent to a human for further review, then your benefits continue uninterrupted.

Assuming you are still disabled and your condition has not measurably improved, there are some things you can do to see that the computer accepts the form without sending it for further review:

- Fill out the form exactly as instructed. Use a box for each letter or number. If the boxes run out, stop, even if it's mid-word.
- No new information. The goal of this form is to simply confirm the information they already have, so you don't want to include any changes, not even

administrative changes such as an address change on this form. New information will cause the form to be kicked out for human review.

- Use original diagnosis. Under "Reason for Last Visit," use the same diagnosis for which you were approved.

The long form (SSA-454-BK) is ten pages and is very similar to the original forms that you filled out when you first applied for Social Security Disability. It primarily asks for the names and addresses of all your providers. They will obtain your medical records directly from them.

This form not only goes to people whose condition is expected to improve, it is also sent to people whose short form was "kicked" by the computer, and is randomly sent to people as part of a trial or study that Social Security may be conducting.

The long form should be filled out just as thoroughly and completely as when you initially applied for disability benefits. On this form, it is important to note any changes in your medical condition, especially new infections, symptoms or diagnoses. Make sure your doctors are alerted to the review and that they submit new medical records since your last review promptly.

Be sure to make copies of the completed CDR, including the short form before sending it in. This will facilitate the next review when it comes.

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Being Alive, January/February 2003

Hepatitis G

The Nation: Common Virus is Said to Slow HIV Help Combat Infections, Some See Deliberate Infections by Doctors Coming Soon. Others Urge Caution.

Los Angeles Times, February 14, 2003

Byline: Thomas H. Maugh, II, Times Staff Writer

New studies confirm that an innocuous and relatively common virus can prolong the survival of AIDS patients, researchers said here Thursday.

People who had HIV, the virus that causes AIDS, and were co-infected with the virus, called GBV-C, were 2.5 times more likely to survive than those who were not co-infected during an 11 year evaluation period, epidemiologist Carolyn Williams of the National Institute of Allergy and Infectious Diseases told the 10th Conference on Retroviruses and Opportunistic Infections.

The time is nearing when physicians will deliberately infect HIV and AIDS patients with the virus to determine how beneficial it really is, said Jack Stapleton of the University of Iowa. The discovery could also lead to new drug treatments for HIV infections, he said.

Recent studies have shown that GBV-C has infected humans for millions of years, but the virus was not actually identified until 1995, when two teams of molecular biologists isolated it.

The Abbott team called the new virus GB virus C because it was genetically similar to the hepatitis C virus, while Genelabs called hepatitis G. Although both names are now used, GBV-C is now used more commonly because the virus does not seem to infect the liver or cause any other adverse symptoms in humans. It is transmitted sexually, through blood products and from mother to infant at birth.

Between 1% and 2% of US blood donors are actively infected with GBV-C, and another 13% to 18% have antibodies indicating a previous infections. As many as 40% of HIV-positive individuals have an active infection, however.

Stapleton reported in September 2001 that co-infection with GBV-C increased survival of HIV-positive individuals by about 50%, but subsequent studies have given less encouraging results.

To examine the problem more carefully, a team headed by Williams examined stored blood serum samples col-

lected in the ongoing Multi-center AIDS Cohort Study. The group tested samples from 271 men collected an average of 12 to 18 months after an HIV diagnosis and found that 39% of them had an active GBV-C infection.

An initial examination of medical records coming about 11 years after the initial diagnosis had indicated no survival benefit from the co-infection.

Puzzled, they tested serum samples collected six years after the initial diagnosis and found that 12 of the men who were originally infected with GBV-C had cleared the infection. Ten of those 12 had died by 11 years after diagnosis.

When the team reanalyzed the data, they found that 75% of those who were persistently infected by GBV-C were still alive after 11 years, compared with only 39% of those who were not persistently infected.

"That's a pretty strong beneficial effect," Williams said.

But she cautioned that researchers should not rush into deliberate infections because of the experience with the 12 people who cleared the infection, who were more likely to die than those who had never been infected by GBV-C. Stapleton, meanwhile, studied the virus in the test tube to try to understand how it works. He reported here that the virus binds to the CCR-5 receptor on the surface of white blood cells called T-cells, the same receptor that is used by HIV to enter the cells. That binding limits the amount of HIV that can enter the cell.

GBV-C "doesn't prevent infection by HIV, but it slows replication," he said. The GBV-C infection also increases the production of various chemokines, proteins that mobilize and activate white blood cells to fight infections. "There are multiple mechanisms by which it helps the HIV-positive," he concluded.

Hepatitis G Virus Prolongs Survival of AIDS Patients

Genelabs Technologies, Inc. (GNLB) said that a presentation at the 10th Conference on Retroviruses and Opportunistic Infections in Boston confirmed that GB virus C (GBV-C, also known as hepatitis G virus or HGV) prolonged survival of people infected with

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the human immunodeficiency virus (HIV), which causes AIDS.

This presentation confirms two studies that were published in the *New England Journal of Medicine* on September 6, 2001, showing that patients infected with both HIV and GBV-C had a reduced mortality rate compared to those only infected with HIV.

Genelabs scientists first discovered this virus, which is transmitted by blood and other bodily fluids, while seeking to identify what was then an unknown hepatitis virus. Patents covering the HGV genome, peptides and their uses have issued to Genelabs. Companies such as Chiron Corporation, Ortho Diagnostics and Boehringer Mannheim (now Roche Diagnostics) have licensed diagnostic applications from Genelabs. Genelabs retains all other commercial rights to its discovery of HGV, including therapeutic and vaccine applications of the virus.

The oral abstract, "Persistent GBV-C Virus Type C Infection is Associated with Decreased Risk of Death in HIV-seroconvertors in the Multicenter AIDS Cohort Study," was presented by Carolyn Williams, acting chief, Epidemiology Branch, National Institute of Allergy and Infectious Diseases. The research was conducted in collaboration with Jack T. Stapleton of the University of Iowa. The University of Iowa team continues to elaborate the mechanism of interaction between HGV and HIV under a research-use license from Genelabs.

"Despite significant efforts made by Genelabs and others around the world, HGV infection has not been associated with any significant disease. It is therefore very encouraging that the findings reported may have implications for the development of new treatments for HIV infection," stated Irene A. Chow, PhD, chairman, and chief executive officer of Genelabs. "We are collaborating with Stapleton in his cutting-edge work on how infection with HGV may be beneficial to HIV patients."

Since the discovery of the virus, Genelabs has collaborated with academic researchers and government institutions, investigating the pathology of infection with HGV and has granted non-exclusive research-use licenses to assess the impact of HGV on survival of patients infected with HIV.

The virus has been reported to be found in approximately 2% of all blood donated in the US, in 15% of people infected with hepatitis C, and as high as 40% of people infected with HIV. Because of the potential

importance of observations showing improved survival for HIV patients who also have an HGV co-infection, Genelabs has research licenses available at no cost to academic institutions interested in further scientific research in this area.

Hepatitis Weekly, March 17, 2003

(Continued from page 15)

Reinfection Continued

Ultimately people living with HIV need to consider this information and make informed decisions about safer sex for themselves. In the early 1980s many did not want to believe that HIV was caused by unsafe sex. Many people have dearly paid the price for that belief. The optimal outcome here is for people not to fight against data and shy away from acknowledging the potential consequences of re-infection. Some people will come to a conclusion that it's better to be safe than sorry. Others will choose the risk of being sorry rather than safe and will continue to participate in unsafe sex with positive partners. What matters most is that people make a conscious decision based on the available information.

PI Perspective, January 2003

25 Things You Should Have Learned By Now

1. If you're too open-minded, your brains will fall out.
2. Don't worry about what people think, they don't do it that often.
3. Going to church doesn't make you a Christian, any more than standing in a garage makes you a car.
4. Never ask a barber if you need a haircut.
5. Artificial intelligence is no match for natural stupidity.
6. My idea of housework is to sweep the room with a glance.
7. Not one shred of evidence supports the notion that life is serious.
8. It is easier to get forgiveness than permission.
9. For every action, there is an equal and opposite government program.
10. If you look like your passport picture, you probably need a trip.
11. A friend will bail you out of jail. A true friend will be sitting next to you in jail saying, "Wow! Wasn't that FUN!"
12. A conscience is what hurts when all of your other parts feel good.
13. Eat well, stay fit, die anyway.
14. Men are from earth. Women are from earth. Deal with it.
15. No man has ever been shot while doing the dishes.
16. Never underestimate the power of stupid people in large groups.
17. Opportunities always look bigger going than coming.
18. We have Meetings because none of us is as dumb as all of us.
19. Junk is something you've kept for years and throw away two weeks before you need it.
20. There is always one more imbecile than you counted on.
21. Experience is a wonderful thing. It enables you to recognize a mistake when you make it again.
22. By the time you can make ends meet, they move the ends. Or....Every time you make your mark, somebody paints the wall.
23. Thou shalt not weigh more than thy refrigerator.
24. Someone who thinks logically provides a nice contrast to the real world.
25. If you must choose between two evils, pick the one you've never tried before.

If you have anything to add to the lighter side of life, we want to hear from you. Email HACA at hacacares@aol.com. We look forward to hearing from you.

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**The Archer strikes the target,
Partly by pulling,
Partly by letting go.**