

LIVER DYSFUNCTION

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

Liver impairment is, alas, too common in those living with HIV and, of course, even more a problem in those coinfecting with hepatitis viruses. HIV-positive women also seem to be more prone to developing liver disease than HIV-positive men. Liver disease has emerged as a major cause of illness and death among HIV+ people. In fact, the most common cause of death at this time is liver failure.

Because the liver has so many crucial roles in the maintenance of a healthy body, any level of liver dysfunction can be problematic. One of the liver's primary functions in the body is detoxification and protection from toxins and infections. It cleanses the blood of dead cells and impurities, removes microorganisms from the circulation, and transforms toxins, including those from medications, so that they can be excreted from the body. It also manufactures enzymes and cholesterol and produces the bile necessary for emulsifying fat. It is a central storage and processing center for many nutrients, including vitamins A, E, and D. It also turns excess blood sugar into triglycerides (fats or lipids) and glycogen (a carbohydrate) and stores them for energy. Between meals, the liver converts triglycerides, glycogen, and amino acids into blood sugar in order to maintain proper levels for brain function and for meeting the body's energy needs. For obvious reasons, since the liver is required for so many crucial functions, monitoring its health and doing everything possible to support its functioning is a must.

It is always very important for HIV+ people to immediately report to their physicians any symptoms that might relate to liver damage. Included are abdominal pain, swelling (hepatomegaly, or enlarged liver), fever, nausea and vomiting, or jaundice (when the liver dysfunction results in an inability to break down bilirubin which then causes yellowing of the skin or the whites of the eyes).

Diagnosis is done initially with the results of blood tests. 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 medications. When the liver is overly stressed by this waste or damaged by various infections, the liver enzyme tests (for example, AST, ALT, and Alk Phos) done as part of your blood chemistry panel may show elevated values. You will often hear people refer to these as "liver function tests" but that term is actually misleading since most of the common lab tests are actually measuring liver cell damage, rather than liver function. They reflect the damage being done to the liver cells but do not tell you how much repair is taking place.

Unlike most other organs, the liver has a remarkable ability to repair itself. This is important when considering liver enzymes because, although there may be ongoing damage to liver cells, it is possible that the liver is able to repair this damage. The true liver function tests measure the liver's synthesis of proteins (albumin and platelets), its ability to properly break down substances (for example, bilirubin), and its ability to metabolize drugs (galactose or aminopyrine clearance).

The findings of a recent very large (more than 5,700 people) study have made it clear how important it is to pay careful attention to liver test changes and patterns over time. University of Pittsburgh researchers have reported that even mild-to-moderate elevations in the ALT and AST liver enzymes—which are experienced by up to a third of HIV+ people—are related to a risk of death that is nearly twice (1.73 times) that seen in those with mid-range normal enzyme levels. The risk of death was five times higher in those whose enzymes were two or more times the normal levels. Alas, the researchers note that elevations are usually overlooked by physicians unless they reach a point that is two to four times above the normal range.

The most common tests done to assess liver damage and function are as follows (note that reference ranges may vary slightly from lab to lab):

□ **ALT (alanine aminotransferase), also called SGPT (serum glutamic pyruvic transaminase):** This is an enzyme found primarily in the liver which is released into the blood as a result of liver damage. The normal reference range is 10 to 30 Units per milliliter (U/ml). There is a possibility of normal aminotransferase (both AST and ALT) levels in people with established cirrhosis. People with chronic hepatitis with compensated or decompensated cirrhosis may have entirely normal or even low-normal aminotransferase levels, thus giving false reassurance.

□ **Albumin:** Albumin is the most plentiful protein in the blood. It is produced primarily in the liver so albumin levels are a rough indicator of liver function. Impaired liver cells can lose their ability to produce protein so decreased albumin levels can point to liver damage. However, previously produced protein will stay in the blood for some time (its half life, the time it takes half of it to disappear, is about 20 days) so albumin levels are not a good indicator of liver function in acute liver disease (a condition that just occurred recently). Blood (serum) albumin levels are used as a component of liver disease grading systems (for example, Childs-Turcotte-Pugh or Mayo Endstage Liver Disease Score). In those with chronic hepatitis (or alcoholic liver disease or protein malnutrition), there may be a down-regulation of albumin synthesis. In those with ascites, a complication of liver cirrhosis that results in an abnormal accumulation of fluid in the abdomen there may be up-regulated albumin synthesis but blood levels will be low due to the larger volume of distribution.

□ **Alk Phos or ALP (alkaline phosphatase):** This is an enzyme found primarily in the liver and in bone. When liver cells are damaged or bone is rapidly growing (either normal or abnormal growth), large amounts of alkaline phosphatase are often released into the blood. Because the chemical structure of the enzyme differs depending upon its origin, if levels are elevated, further tests can be done to identify the subfractions (isoenzymes) and thereby determine whether the problem is with the liver or bone. The normal reference range (which varies not only between labs but also with age) ranges from 20 to 90 IU/l.

□ **AST (aspartate aminotransferase), also called SGOT (serum glutamic oxalacetic transaminase):** This is an enzyme found mainly in the liver and heart muscle which is released into the blood when either of these organs is damaged. The normal reference range is 10 to 40 international units per liter (IU/L). There is a possibility of normal aminotransferase (both AST and ALT) levels in people with established cirrhosis. People with chronic hepatitis with compensated or decompensated cirrhosis may have entirely normal or even low-normal aminotransferase levels, thus giving false reassurance.

□ **Bilirubin:** This is a brownish-yellow pigment that is a byproduct of the breakdown of hemoglobin, the oxygen-carrying molecule in red blood cells. Normally, it is sent to the liver where it is metabolized and then excreted through the bile ducts and gallbladder into the intestine where it gives the normal brown color to the stool. Before bilirubin is acted upon by the liver it's called indirect (unconjugated) bilirubin. After being metabolized by the liver, it's called direct (conjugated) bilirubin. Total bilirubin is the combination of these two. The normal reference range for total bilirubin is 0.1 to 1.2 mg/dl. If this is abnormally high, the direct and indirect components are then determined. The normal reference range for indirect (unconjugated) bilirubin is 0.1 to 1.0 mg/dl. The normal reference range for direct (conjugated) bilirubin is less than 0.3 mg/dl. If the total bilirubin in the blood is high, it is important to know how much it is conjugated because it tells your healthcare provider what process in the liver is not working normally. High amounts of conjugated bilirubin means the bile flow is blocked either inside or outside the liver. Problems inside the liver such as hepatitis, fibrosis, and cirrhosis can cause increased conjugated bilirubin. Problems outside the liver such as gallstones can also cause increased conjugated bilirubin. A high level of conjugated bilirubin in the blood can also be detected in the urine. In hepatitis, fibrosis, and cirrhosis, high amounts of unconjugated bilirubin means the liver cells are not conjugating bilirubin normally, causing it to build up in the blood. Bilirubin is not normally found in the urine but if it is, that is an indication of either liver cell damage or blockage of the flow of bile from the liver or gallbladder.

□ **BUN (blood urea nitrogen):** This is a chemical produced by the liver in the process of breaking down proteins. BUN is normally eliminated in the urine, and is most commonly measured to check how well someone's kidneys are working. If the kidneys are not working normally, the BUN level in the blood will be increased. BUN is one of the tests used to check for hepatorenal syndrome, a condition seen in those with advanced liver cirrhosis and failure in which the kidneys begin to fail because the liver is failing. If there is no kidney failure, the BUN is often lower than normal in people with cirrhosis and liver failure because the failing liver is not metabolizing proteins normally and, thus, lower than normal amounts of BUN are being produced.

□ **Bicarbonate, Chloride, Potassium, and Sodium:** These are charged particles that are among the major electrolytes in the body. Electrolytes perform many important jobs, including keeping the amount of water in your body regulated, and keeping your blood pH normal. Some people with hepatitis C, especially those with cirrhosis, hold more water in their bodies than they need, and the result can be abnormal bicarbonate, chloride, potassium or sodium levels.

□ **Calcium:** This mineral, used by the body for many things including bone formation and muscle contractions, may drop too low in those with cirrhosis because vitamin D levels become too low for proper calcium use. Alternatively, when cirrhosis leads to hepatorenal syndrome in which both the kidneys and the liver fail, the blood calcium can become elevated.

□ **GGT (gamma glutamyl transpeptidase):** This enzyme is found in all cells of the body except muscle cells, and can become elevated due to liver, biliary or pancreatic disease, heart attack (myocardial infarction), kidney (renal) disease, chronic lung disease, and/or diabetes. It must always be interpreted in the context of other enzyme results. In liver disease, GGT is often highest when bile flow is blocked either inside or outside the liver.

□ **LDH (lactic dehydrogenase):** This enzyme is found in the liver, heart, kidney, skeletal muscle, brain, and lungs. If it is elevated, it can be divided into different subfractions (isoenzymes) in order to determine which tissue is damaged. The normal reference range for total LDH is 80 to 120 IU/liter.

□ **Platelet count.** Platelets help the blood to clot, and with liver disease, there may be too low levels of platelets. Platelets, along with other markers like ALT, AST, hyaluronic acid and others have been featured in new tests that seek to evaluate the degree of *fibrosis* (or scarring) of the liver. The usual test is a biopsy, but this is an invasive, potentially dangerous and costly procedure. Fibrotest and other such bloodwork analyses may provide an alternative, particularly for either early or late stage liver disease.

Other tests that may be used for various aspects of liver assessment, especially in people living with hepatitis C, include:

□ **Alpha-fetoprotein:** This is a protein, normally found only in trace amounts in the body, which is a tumor marker for liver cancer. Since, people with chronic hepatitis C are at greater risk for developing liver cancer than are people without the virus, alpha-fetoprotein is often used to screen for the cancer in people living with hepatitis C. Elevated levels may (or may not) indicate the presence of a cancerous liver tumor.

□ **Aminopyrine:** This chemical is used to determine how well the liver is metabolizing and detoxifying substances. A single test does not give very much information, but comparing a series of tests done over a period of time can show if liver function is decreasing.

□ **Ammonia:** This chemical comes from the normal breakdown of proteins in the body and is normally found in very low levels in the blood. One potential complication of cirrhosis and portal hypertension is a condition called hepatic encephalopathy. Ammonia levels are high in hepatic encephalopathy so testing for it can help establish this diagnosis.

□ **Anti-LKM (Anti-liver-kidney microsomal antibodies), ANA (anti-nuclear antibodies), anti-SMA (anti-smooth muscle antibodies), and rheumatoid factor (RF):** These are autoantibodies, abnormal antibodies that act against your own cells. The body normally only makes antibodies against foreign substances such as bacteria and viruses, but it is estimated that more than half of all people with chronic hepatitis C have one or more autoantibodies in their blood. Checking for these is important because autoantibodies can cause additional symptoms and disease.

□ **Branched DNA test for HCV (b-DNA) and HCV PCR:** These tests are used to measure the amount of detectable hepatitis C virus in the blood. The result is called the viral load, and is often used to check the response to treatment. Just as with HIV viral loads, an undetectable reading does not mean that there is no hepatitis C virus in the blood. It just means that there is none that is detectable. The b-DNA test for hepatitis C virus is not as sensitive as the HCV PCR test. This means that the b-DNA test cannot detect as low a viral load as the HCV PCR test. It is important to remember that viral loads in hepatitis C naturally fluctuate, that not all changes in viral load are significant, and that a high viral load does not necessarily mean more symptoms.

- **Cholesterol:** Although normally thought of as a heart disease test, most of the blood's cholesterol comes from the liver, not from what we eat. The liver both produces and breaks down cholesterol, as needed. Broken down cholesterol is normally excreted into the bile, but with chronic hepatitis C, there is sometimes a blockage of bile flow either inside the liver (due to cirrhosis) or outside the liver (most often due to gallstones), as a result of which blood cholesterol rises. The more the bile flow is obstructed, the more elevated the cholesterol will become.
- **Coproporphyrin:** This is a substance normally produced in the liver and bone marrow during the process of making heme, the chemical that binds oxygen to red blood cells. When liver cell damage interferes with the production of heme, coproporphyrin can build up in the blood. Elevated levels indicate that the liver is not functioning properly to produce heme.
- **Creatinine:** Since creatinine is a waste product of muscle cell metabolism that is excreted by the kidneys in the urine, it is usually measured to check kidney function, with elevations indicating kidney problems. Since people with advanced liver cirrhosis and liver failure may develop hepatorenal syndrome, the syndrome in which the kidneys begin to fail because the liver is failing, creatinine is used to screen for this.
- **Cryoglobulins:** Some people with hepatitis C have these joined together immunoglobulins in the blood, a condition called cryoglobulinemia that can cause kidney damage.
- **Fibrinogen:** This is a protein produced by the liver that is used in the formation of blood clots when someone is bleeding. Since a failing liver cannot produce normal amounts of fibrinogen, measuring this protein is one way to determine how severely the liver is failing. Testing blood fibrinogen is also important because with too-low levels, a person may not be able to form blood clots when needed to stop bleeding.
- **Genotyping:** A genotyping test tells which of the more than 70 known strains of hepatitis virus a person has, knowledge which can be helpful in making treatment decisions because certain strains are known to be more likely to respond to treatment than others.
- **Glucose:** This test is done to determine if your blood sugar is normal. Usually done to look for problems related to diabetes, it is needed in liver disease because one of the liver's functions is to help control blood sugar. With liver damage, there can be blood sugar that is either too high or too low.
- **Glutathione:** Glutathione is produced in cells throughout the body in order to protect the cells against what is called oxidative damage, a condition that occurs when unstable molecules (usually referred to as free radicals), created initially as part of the immune response or during other body processes, cause damage to cells. It is believed that oxidative damage is one of the main ways in which hepatitis C virus damages liver cells. Glutathione prevents the unstable molecules from causing damage to cells. Measuring the amount of glutathione in the blood is one way of judging how capable your liver may be of preventing or repairing liver damage. Unfortunately, this test is very difficult to do accurately, and few labs currently provide it.
- **Hematocrit (HCT), hemoglobin (HGB), and red blood count (RBC):** Because liver disease can result in anemia, these tests are run to check for that. For details, see *Anemia*.
- **Immunoglobulins (Igs):** These are a group of proteins that act as antibodies in the body. With Igs tests, the different proteins are separated and measured. The patterns that can be seen depending on how much of each type of protein is present can suggest different types of liver problems.
- **Liver biopsy** In a liver biopsy, several tiny pieces of liver tissue are removed using a long needle that is inserted into the liver through the skin. The samples are examined with a microscope in order to determine inflammation (the presence of inflammatory cells in the liver), fibrosis (scar tissue that forms when liver cells are destroyed by the virus), and cirrhosis (wide-spread damage to the liver resulting in abnormal liver structure and function).
- **Partial thromboplastin time (PTT) and prothrombin time (PT).** These tests determine how quickly the blood is able to form a clot. Since the liver produces many of the proteins needed for blood clotting, abnormal results can indicate that normal amounts of these proteins are not being produced. Abnormal results are also a warning that if someone begins to bleed, they may not be able to form the clots needed to stop the bleeding.
- **Porphyrins.** These substances are produced in the liver and bone marrow during the process of making heme, a chemical that binds oxygen to red blood cells. Liver cell damage can interfere with heme production of heme and allow the porphyrins to build up in the blood. Testing for porphyrins shows how well the liver is functioning to produce heme.

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

The combination of these readings will indicate either iron deficiency or iron overload. Note that most labs have a wide reference range for serum ferritin, and the low end of normal may actually be showing inadequate iron stores. On the other hand, too much iron could indicate a level of iron storage that could be detrimental. Some experts believe that a range of serum ferritin from 40 to 60 would be ideal. However, systemic inflammation, chronic infection, or chronic disease (all of which would characterize HIV+ people, in general) can cause increased ferritin readings which would not necessarily be indicative of iron overload. It would be important to monitor readings over time. If the ferritin remains somewhat elevated consistently over multiple readings, this might just be indicative of your chronic disease status.

Since the liver is one of the main places where iron is stored, when liver cells are damaged, the iron is released. The amount of iron in the blood is another indicator of liver damage. Iron overload is often seen with chronic hepatitis C. Studies have shown that too much iron is tied to an increased level of liver damage. It is possible that countering the oxidation of the iron in the body with a plentiful supply of antioxidants (and thus lowering oxidative stress in the liver) may help lessen the risk of this damage. Interpreting these laboratory results is complex and should always be discussed with your physician.

□ **Total protein (TP):** Total protein is a measurement of all the proteins in the blood. Since many of these proteins are produced by the liver, the total protein measurement is one way of testing how well the liver is performing this job.

□ **Transthyretin (prealbumin):** This is a small protein produced by the liver and used to make the larger protein called albumin. Transthyretin is a sensitive indicator of how well the liver is able to produce proteins. The lower the transthyretin level is, the less well the liver is performing this job.

Note that results from some of these tests can become abnormal because of problems other than liver disease so they must be interpreted carefully. And even without abnormal readings, there can be a level of less obvious liver dysfunction. Unfortunately, without regular monitoring with appropriate liver tests, some people may remain unaware of liver disease until it reaches a point that it causes obvious symptoms, as listed above. Individual lab results must always be interpreted carefully by a physician and always in the context of all the other results.

When initial blood tests indicate liver damage, the physician will normally do a physical exam, and take a careful look at the patient's history to see what risk factors for liver damage are present. (See discussion of causes below.) If not already known, tests for hepatitis status will probably be done. When needed, further evaluation may include a liver biopsy and/or tests that provide a visual picture of the liver, including a CT scan (computed tomography), MRI (magnetic resonance imaging), or ultrasound. An ultrasound is a particularly useful noninvasive means for identifying hepatic steatosis, or fatty liver.

What are the Causes?

There are a number of possible causes of liver damage in HIV+ people, and there may be several contributing to liver problems in many people. For HIV+ people, the most common causes of liver problems are coinfection(s) with hepatitis virus(es) and use of antiretroviral drugs that can sometimes cause liver damage. Occupational exposure to toxins can contribute to liver damage, as can consumption of certain herbs that are liver-damaging. Many infections other than hepatitis viruses can also result in liver damage, including such opportunistic infections as *Mycobacterium avium* complex (MAC), tuberculosis, cytomegalovirus (CMV), or cryptosporidiosis. Excessive alcohol or recreational drug use or smoking can also contribute to or cause liver problems.

□ **Hepatitis viruses, especially chronic infection with hepatitis B or C, are a major source of liver damage in many HIV+ people.** Up to 40 percent of HIV+ people are believed to be coinfecting with hepatitis C, and hepatitis B coinfection is as high as ten percent in some HIV-positive populations. The number of reported cases of both types of coinfection is increasing. A large retrospective study of 1325 HIV+ people from 15 Italian HIV clinics found that 46.5 percent were coinfecting with hepatitis C, 4.1 percent with hepatitis B, and 8.7 percent with both hepatitis B and C. All the

people studied had been on stable HAART regimens for at least six months. Liver toxicity (ALT levels that were above the upper limit of normal) occurred in 11.1 percent of patients at six months, with most cases (7.8 percent) defined as mild (less than or equal to 5 times the upper limit of normal), but 3.2 percent of cases were severe (greater than 5 times the upper limit of normal). The rate of liver toxicity gradually increased in the two years of follow-up, reaching 12.9 percent at 24 months.

Clearly, coinfection with viral hepatitis was an important risk factor for development of liver toxicity in these HAART-takers, regardless of the specific drugs taken. At six months, liver toxicity developed in only 5.6 percent of people without hepatitis coinfection compared to 14.9 percent of those with hepatitis coinfection. Coinfection with both HBV and HCV was tied to an increased risk of liver toxicity. Other studies have also shown the increased risk for liver problems that coinfection creates, and as survival time among HIV+ people has increased due to more effective anti-HIV therapy, the risk of illness and death due to liver complications among the co-infected has risen.

□ **Deficiency of glutathione and other nutrients.** In those infected with HIV as well as those coinfecting with both HIV and hepatitis virus(es), researchers have shown that there are deficiencies of glutathione, the most important antioxidant in the liver. These deficiencies apparently begin in very early disease stages, and remain throughout the disease process(es). There are many reasons for the deficiency (discussed more in *NYBC's Basic Nutrient Protocols* and *Counteracting Inflammation* in this guide's *Introduction.*), but the bottom line is that your liver may not have enough glutathione to properly break down drugs, chemicals, and other toxins. The result can be liver damage.

This lack of glutathione can cause serious problems even in those solely infected with HIV. It may be even more problematic for those coinfecting with hepatitis C. Research has shown that there are two fundamental sources of damage to the liver in chronic hep C. One is from the infection itself, and the other is from the immune system's attempt to fight the virus. As part of the immune response, unstable molecules usually called free radicals (but also including other reactive oxygen species) are created. These molecules cause what is called oxidative stress, a condition known to be elevated in chronic viral infections. The free radicals can move very quickly through the liver, causing inflammation and scarring. Luckily, even though these damaging molecules will still be created initially, the chain reaction in which they move forward, constantly creating additional unstable molecules and damaging cells and tissues along the way can be halted with antioxidants.

Unfortunately, one of the most important antioxidants needed to halt the damage is the glutathione that is likely to be deficient. Researchers have found that the level of glutathione in the blood and the cells of people infected with HIV and/or hepatitis C is significantly depressed. The result of the inadequate glutathione is ongoing oxidative stress which researchers tell us has been shown to play a role in the progression of hep C. In fact, researchers have reported that the amount of damage caused by oxidative stress is linked to both the grade of liver fibrosis and to the overall level of liver damage. The way to help counter the oxidative stress and the damage it could cause to the liver is with a plentiful supply of glutathione and other antioxidant nutrients in the body.

□ **Many different drugs can be toxic to the liver.** This includes not only antiretroviral drugs but a long list of others. Part of the problem in avoiding drugs that may be toxic to your liver is that although universally liver-toxic substances can be identified in the laboratory, liver hypersensitivity problems are not predictable. One person may have no negative side effect from a drug, while another may develop organ failure as a result of the same drug. Hypersensitivity cannot be predicted, but there are risk factors that may increase the likelihood of such a drug reaction. Among these are multiple allergies, a history of previous adverse reactions to drugs or herbs, a history of chronic skin rashes, and chronic liver disease. With any of these, you should be aware that the possibility of adverse liver effects from drugs may be higher in you than in others.

□ **Liver injury has been shown to occur with all classes of antiretroviral therapy.** In a large (560 people) Dutch study, in the course of approximately three years after beginning HAART, eight percent developed liver enzyme levels more than ten times the upper limit of normal. Both females and those with chronic hepatitis B or C were at greater risk for enzyme increases. However, the researchers noted that in most cases, the elevations did not result in any symptoms, and resolved over time without requiring a change in the drug regimen.

Certain drugs or certain combinations of drugs may increase the risk of liver injury. This may be particularly true in those coinfecting with hepatitis. In the Italian study mentioned above (the retrospective study of 1325 HIV+ people from 15 Italian HIV clinics) it was found that 46.5 percent were coinfecting with hepatitis C, 4.1 percent with hepatitis B, and 8.7 percent with both hepatitis B and C. Researchers reported that in those without coinfection, the choice of protease inhibitor (PI) did not significantly affect liver toxicity, but in the coinfecting, the PI used was a factor influencing liver toxicity. In the coinfecting, during the first six months of HAART treatment, liver toxicity developed in 26 percent of those on ritonavir (although this figure includes those taking both full and lower doses of this drug so may be misleading), 17.3 percent of those on nelfinavir, 16.5 percent of those on saquinavir, and 11.7 of those on indinavir. These differences in liver toxicity between the different protease inhibitors disappeared at later time points but not before some people were forced to discontinue their meds (mostly those coinfecting with hepatitis C and taking ritonavir).

In another recent study of 568 HIV+ people using HAART combos that contained an NNRTI, severe liver injury was seen in 15.6 percent of those on nevirapine (Viramune) and 8 percent of those on efavirenz (Sustiva/Stocrin). In this study, the risk of liver damage was also much higher in those who were coinfecting with hepatitis C or B, with 69 percent of those with liver damage found to be coinfecting. The risk was also substantially higher in those given a combo that included a protease inhibitor along with the NNRTI. (82 percent of the liver injury cases). This is only one of many (sometimes conflicting) studies but know that making drug choices related to the possibility of liver problems is complex.

Even discontinuation of certain drugs must be carefully considered. In the Dutch study mentioned above, it was shown that in those coinfecting with hepatitis B, discontinuing the drug 3TC (Epivir®) was a risk factor for severely elevated liver enzymes. Based on this, the researchers suggested that even if 3TC-resistant HIV strains develop in such people, continued use of the drug should be considered.

Any treatment choices should only be made after considering all the latest research findings on this topic, as well as all the aspects of your medical history and current condition that may affect the likelihood of liver injury (including your coinfection status). With all that in mind, discuss all the pros and cons of various approaches with your physician. And always consider attempting to counter the toxicity of any drugs you choose with the therapies discussed below.

Some of the other drugs that may create liver toxicity, damage, or even failure at some times in some people include: acetaminophen (particularly when taken with alcohol or anti-seizure medications), alpha-methyldopa (Aldomet), amiodarone, carbamazepine, chlorzoxazone, dantrolene, diclofenac, voltaren, fluconazole or ketoconazole, flutamide, fluvastatin, hydralazine, ibuprofen, imuran, isoniazid (INH), leukotriene synthase inhibitors (asthma medications), including zafirlukast (Accolate) and zileuton (Zyflo), lovastatin, methotrexate, nitrofurantoin (Macrochantin), perihexilene maleate, phenylbutazone, phenytoin, pravastatin, quinidine, rifampin, simvastatin, sulfa medications (especially Septra or Bactrim), tacrine, tolcapone (Tasmar), and ticlid. And there are many others.

Last but not least, smoking tobacco has been tied to an increased incidence of liver cancer so nicotine should be on the list of drugs to avoid for those seeking liver protection.

☐ **Certain herbs can cause liver injury.** Included are amanita mushroom, chaparral (creosote bush, greasewood), comfrey, crotalaria (Ye Bai He), eupatorium, germander (this toxic herb is often substituted for skullcap so although skullcap itself is not toxic, it would be important to ascertain that any ingredient so identified be the real skullcap and not germander; if this is not possible, it is best to avoid either), groundsel (*Senecio longilobus*), heliotropium, Jin Bu Huan (*Lycopodium serratum*), kava, ma huang, mentha pulegium, mistletoe, pennyroyal (squawmint) oil (hedeoma pulegoides), senecio species, senna, and sophora. In addition, Chinese herbal patent medicines, tonics, elixirs and prepackaged solutions are considered quite risky, unless they are from a reputable company (such as Mayway). Ingredient labels may be inaccurate, incomplete, or mistranslated, and dangerous herbs may be contained in the mixtures. The Oriental Herbal Association lists the following as potentially lethal ingredients in patent medicines: aconite or aconitum (causes paralysis and death if not highly processed before use), acorus (causes convulsions and death), borax (triggers severe kidney damage), borneal (triggers internal bleeding and death), cinnabar or calomel (a mercury compound), litharge and minium (contain lead oxide), myiabis (can trigger convulsions, vomiting and death), orpiment or realgar (contains arsenic), scorpion or buthus (causes paralysis of the heart and death), strychnos nux vomica or semen strychni (strychnine-containing seeds that can cause respiratory failure and death), toad secretion or bufonis (can paralyze heart muscle and

lungs). For a much more complete discussion of the possible toxicity of various herbs, including a discussion of particular formulas that may contain risky ingredients, go to www.hepcchallenge.org

Since even normally beneficial herbs could cause liver damage in people who are allergic to or intolerant of them, it's always important to seek the advice of people trained in the use of herbs before adding them to your list of therapies. The best resources for this in the U.S. are usually naturopathic physicians since they have studied them in depth in their medical training. For Chinese herbs, practitioners of Traditional Chinese Medicine, often licensed acupuncturists, are usually best.

□ For people living with hepatitis, there are dangers lurking in foods and fluids that could worsen liver damage.

Alcohol is a potent toxin to the liver that can cause serious disease and death in those with no viruses. In those with hepatitis C, its intake has been tied to an increased risk of cirrhosis, a more advanced degree of liver fibrosis, and a higher rate of death. Consuming alcohol has also been associated with a decreased response to interferon therapy. Because of the widely held view that the combination of excessive alcohol and hep C accelerates the progression of liver disease, the consensus statement on the management of hepatitis C released by the National Institutes of Health in March 1997 stressed limiting alcohol consumption to no more than one drink per day. And many experts go farther, recommending total avoidance of alcohol, including even the "hidden" variety that may be found in flavored coffees and some desserts.

Another hidden danger is the large amounts of salt (sodium) contained in the standard American diet. High salt intake isn't healthy for anyone, but for those with advanced scarring of the liver (cirrhosis) it can be particularly dangerous since it can lead to an abnormal accumulation of fluid in the abdomen called ascites.

What are the possible treatments or preventive measures?

As is obvious from this review of the work it does in the body, a functional liver is critical for life. Detoxifying and repairing a damaged liver 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 therapeutic drug use. A combination of lessening the toxic load on the liver and adding those therapies that can help the liver function and repair itself may go a long way toward helping maintain its health through years of living with HIV and/or hepatitis virus(es). Please see *Detoxification in NYBC's Self Care Guide*.

Decreasing the liver's toxic load. There are many ways that you may be able to decrease the daily assault on the liver and help maintain its health. The most obvious first step is to eliminate as many sources of toxicity as possible. Cutting out recreational drugs will remove that burden from what the liver must do every day. Decreasing or, preferably, eliminating alcohol will take that source of strain off the liver. Avoiding unnecessary prescription drug use can also help. For example, antibiotics are too often prescribed at the drop of a hat. You should, of course, take them if you have a bacterial infection for which they will provide needed therapy, but they shouldn't be used for infections like colds or flus that are obviously viral, for which an antibiotic will do nothing. Cutting out chemically loaded junk foods and drinks can help to decrease the stress on your liver. Decreasing the fat content of your diet can also help. Avoiding, as much as possible, any occupational exposure to chemicals is very important. And whether in the workplace or elsewhere, try to avoid exposure to chemical fumes and vapors (such as gasoline and solvents) as well as pesticides and herbicides.

If you are taking medications that can cause liver toxicity, a careful review with your physician should be done in order to determine if there are other drugs that can be substituted for problematic ones. A review of possible drug interactions should also be done. A drug that might otherwise cause no liver problems could do so if it interacts negatively with another drug. Don't count on your physician to know every single thing you may be taking. There may be things, especially over-the-counter items, that you may not have mentioned. Asking your physician or pharmacist for a "brown bag" checkup is important to check for all possible interactions. This means that you put every single thing you're currently taking, whether it's by prescription or over-the-counter (meds, herbs, vitamins, every single thing you're consuming), into a bag which you then take to your physician and/or pharmacist so that one or both can assess the possibility of any interactions. Pharmacists are a great resource for this because most now have computerized programs that can check for such interactions. Please see the Detoxification sections in the *NYBC Self Care Guide*.

Diagnosing any possible infections. Any signs of liver damage would mandate a careful medical assessment to look at the possibility that there might be infections damaging the liver. Possibilities include viral hepatitis, MAC, tuberculosis, CMV, Epstein-Barr virus, or cryptosporidiosis.

Dietary changes. A whole foods diet that is very nutrient rich is an important foundation for any program aimed at liver support. The diet described in *NYBC's Self-Care Guide* would be an excellent beginning. However, certain dietary changes may be needed or desirable.

Increasing fiber intake may be useful. Fiber can help bind toxins in the intestines, and then speed their elimination through the bowel, thus reducing the liver's detoxification workload. By increasing your fiber intake, you may significantly decrease the demands on the liver that would otherwise occur when those toxins had to be broken down. These substances add bulk and moisture to the intestines, thereby promoting a well-formed and lubricated stool. The fibers also swell and therefore facilitates normal peristaltic action. The most commonly used of the hydrophylic fibers include: psyllium seed and husk, flax seeds, and oat bran. Each can be freely added to the diet or taken as a supplement.

Cautions: While hydrophylic fibers are beneficial for promoting elimination and cleansing, their cold and wet nature tend to have a negative effect on digestion and assimilation. To counteract this tendency, they should always be used with warming carminatives herbs such as cinnamon, ginger, or anise. Hydrophylic fibers can also decrease the absorption of conventional medications. In cases where there is a very narrow threshold regarding the effective dosage of medications or in the case of taking medications for life-threatening conditions, consult with a qualified health professional prior to using hydrophylic fibers.

Eating lots of fruits and vegetables (organic, if at all possible, in order to decrease exposure to toxic pesticides), as well as whole grains can contribute a great deal of additional fiber. Using fiber nutraceuticals like psyllium or Citrucel (citrus) or oat bran can also add to your overall fiber intake.

Consume foods that may improve liver detoxification. Citrus fruits contain a phytochemical called limonene that it is believed may boost the liver's detoxification ability. Eating oranges and tangerines and drinking orange juice (preferably the pulp-containing fresh-squeezed variety) regularly may increase your intake of limonene sufficiently to provide this help to your liver. Certain other foods contain compounds called indoles that may stimulate detoxifying enzymes in the liver. These indoles are contained in the cruciferous vegetables such as cauliflower, broccoli, cabbage, Brussel sprouts, collard greens, and kale. Increasing your consumption of these foods may also help the liver.

Consume the foods that are natural anti-inflammatories. Since inflammation in the liver causes damage, and both HIV and hepatitis increase inflammation, the idea of suppressing that inflammation is appealing. There are certainly a number of potent drugs that suppress inflammation but there are several problems with long-term use of such drugs. As noted earlier, one problem is that over-suppressing the inflammatory response might increase the risk for infections (since the inflammation is part of the immune system's way of countering infections). In addition, anti-inflammatory drugs can cause many side effects, particularly gastrointestinal bleeding. And last but not least, such drugs would be an additional burden on the liver. It would appear much less risky to use foods that have natural anti-inflammatory qualities.

Because such foods have been used for thousands of years with no apparent adverse effects on immune responses, it seems likely that long-term consumption of them would be considerably safer than long-term use of drugs. Their anti-inflammatory effects are more subtle but might still provide substantial benefit. Naturally anti-inflammatory substances are found in the following foods and seasonings:

- garlic, ginger, turmeric
- bioflavonoid- and antioxidant-rich fruits and vegetables
- omega-3 fatty acid-rich foods such as fatty fish (e.g. salmon, mackerel, sardines, tuna, cod and halibut), flaxseed, and walnuts.
- chlorophyll-containing foods such as wheat grass juice and blue-green algae.

There are also specific nutritional supplements and herbs that counteract excess inflammation and may help to lower levels of tumor necrosis factor. These include N-acetyl-cysteine (NAC), carnitine, nettle leaf extract, grape seed extract and bilberry extract, as well as a broad spectrum of all the other important antioxidants (vitamin E, vitamin C, bioflavonoid complex, carotenoid complex, selenium, coenzyme Q-10, and alpha-lipoic acid). For more detailed information on the above foods and supplements, please see *NYBC's Self-Care Guide*.

Drink (green) tea. Japanese research indicates that polyphenols, important antioxidants found in green tea may help protect the liver from toxins and also help prevent liver cancer when consumed in levels of two to four cups daily. More recent research indicates that black tea (the kind most often drunk in North America) also contains polyphenols and other important bioflavonoid nutrients. Thus, it is possible that it, too, may provide benefits to the liver.

Drink lots of pure water. Increasing the amount of water that you drink daily to truly healthful levels will help to flush the kidneys and help the body's overall purification system in ways that will help reduce the liver's workload. The best rule for determining how much water you need is simple. Take your body weight in pounds, divide that in half, and drink at least that many ounces of water daily. Unless the water in your local area is very pure, it may be best to use a water filtration system to reduce your exposure to possible toxic contaminants that could place an additional burden on the liver.

There may be additional adjustments that will be needed in those with any significant level of liver damage. Protein may sometimes need to be limited. Because adequate protein is generally so important, it's easy to jump to the conclusion that more is better. Unfortunately, with serious liver disease too much protein may be dangerous. When protein is broken down in the body, one of the byproducts is ammonia. A damaged liver cannot process ammonia as well as a healthy liver can. The result can be an overload that results in encephalopathy, a brain condition that can cause mental confusion and, in advanced stages, coma. The exact level of protein intake that is desirable for you will depend on your liver's condition. This should always be discussed with your physician who will be able to make the medical assessment necessary to determine whether protein restriction is required.

Fat intake should be kept moderately low. The standard American diet is far too high for health, in general, and may be much too high for people with liver damage. Limiting overall fat intake and completely avoiding fats that promote inflammation may be very important for people with liver problems. Fats to avoid would include all partially hydrogenated oils (and all the products made with them) and, as much as possible, polyunsaturated vegetable oils. See the full discussion on avoiding partially hydrogenated fats and choosing good fats in the section entitled *Dietary Changes in Cardiac Concerns*, and in the *NYBC Self-Care Guide*. Choline, methionine, betaine, and folic acid all help in the metabolism of fat. Methionine additionally protects against glutathione depletion, one of the primary compounds involved with the liver's antioxidant/detoxification system.

Salt restriction may be necessary. Anyone with ascites must be on a salt-restricted diet. It is estimated that every 1,000 mg of sodium consumed can result in the accumulation of 200 ml of fluid. The more the salt content of the diet can be reduced, the better the chances of avoiding this excessive fluid accumulation. Liver experts recommend limiting sodium intake to only 500 to 1,000 mg daily, with the lower end of that being preferable. This will require careful shopping and intensive food label reading. Most fast food and a large percentage of snack foods (especially chips and pretzels and crackers) are dangerously loaded with sodium, and will have to be avoided. Even foods that might otherwise be thought of as healthy can be lethally loaded with salt. For example, one cup of chicken noodle soup may contain a whopping 1108 mg of sodium, more than your whole day's allotment.

The only way to cut salt intake back is to look at all the foods eaten in a typical day, and use food labels to add up the total daily amount of sodium. Because many people with high blood pressure are placed on low-sodium diets, there are many cookbooks and dietary plans available to help you avoid salt in your home cooking. When eating out, it will be very important to try to choose dishes that don't contain large amounts of salt, and, to the greatest extent possible, ask that your food preparation is done without salt. This may mean avoiding certain pre-prepared soups or sauces, and certain ingredients that are lethally high in sodium (like soy sauce) but in many restaurants there will be menu choices that can be prepared without adding salt. And, of course, you always have control over what you do, or do not, add at the table. Hep Cers who have not developed ascites are not usually in need of severe sodium cutbacks, but are still advised to moderate their salt intake.

Another possible danger is over consumption of iron-containing foods, particularly in those with a liver biopsy showing abnormal accumulation of iron in the tissue. Iron is stored in the liver and used by the body for many different processes like building red blood cells, and as a very important part of enzymes that are involved in energy production and the manufacture of DNA, the building block of life. Many studies, however, have looked at the fact that in hepatitis C, iron appears to be much more likely to contribute to liver damage than in those who don't have hepatitis. In hepatitis C, iron can cause liver damage as a result of its ability to act as a source of free radicals, those contributors to

oxidative stress that may cause damage to liver cells that leads to inflammation and scarring. It is thought possible that a daily intake of plenty of antioxidants (as discussed below) may counter this and make iron much less problematic. However, since it is not definitively known exactly when and in whom iron will be a problem, eliminating excessive iron from your diet appears to be a good idea.

A study in India with hepatitis B or C patients showed that eating a low-iron (primarily vegetarian) diet had a significant effect in lowering blood iron levels and ALT (liver enzyme) levels, especially in those who had high iron to begin with. Although it is not a good idea to sacrifice protein for the sake of a low-iron diet (many iron-rich foods are also high in protein), it is simple enough to avoid the foods highest in iron or fortified with iron and still get enough protein. It is important to remember that although, in general, dietary iron is poorly absorbed, the iron in animal food is better absorbed (10 to 25 percent) than the iron in plant food (2 to 5 percent). Thus, if you eat a plant food and an animal food that contain the same amount of iron, the animal food will actually give your body more of this mineral. Also be aware that many processed foods are fortified with iron and, thus, can up your total daily intake. If you already have high iron levels in your liver, it may be advisable to decrease your animal protein intake and increase plant proteins. And, unless your physician has recommended supplementation because you have been diagnosed with iron-deficiency anemia, it's thought best to avoid iron nutraceuticals.

For all these reasons, it's very important to always discuss everything about your individual situation—including your health history, your lab results, the current state of your liver, any other conditions like diabetes or heart disease that may require certain dietary changes, and, for those co-infected, all aspects of both your HIV disease and your hepatitis—with your healthcare provider, and ask his or her advice on any dietary adjustments that may be needed.

Alcohol avoidance. If you're tempted, remind yourself that alcohol intake has been tied to an increased risk of cirrhosis, a more advanced degree of liver fibrosis, a higher rate of death, and a decreased response to interferon therapy. Again, because of the widely held view that the combination of excessive alcohol and hep C accelerates the progression of liver disease, the consensus statement on the management of hepatitis C released by the National Institutes of Health in March 1997 stressed limiting alcohol consumption to no more than one drink per day. And many experts go farther, recommending total avoidance of alcohol, including even the "hidden" variety that may be found in flavored coffees and some desserts. Do the best you can, and get help if you need it.

Nutrient supplementation. With all the evidence that oxidative stress is a major factor in liver damage, there is an important role for nutritional nutraceuticals that may help counter that, as well as countering the mitochondrial toxicity that may also be an important factor in liver damage. Included among the most important nutrients for liver support are antioxidants, amino acids, and fatty acids.

Of particular importance are the nutrients that work together to maintain a healthy level of glutathione in the liver (including N-acetyl-cysteine, alpha-lipoic acid, fundamental sulfur, glutamine, selenium, and vitamins C and E). These and the other important antioxidants (including the carotenoids and bioflavonoids) are needed to counter oxidative stress and help reduce liver inflammation and the accumulation of fatty tissue in the liver that could result from that. The fat cells that accumulate in this process are susceptible to damage which can lead to fibrosis (scarring) and, ultimately cirrhosis (tissue damage and cell death). Early in the process in which inflammation is created in the body, oxidative stress plays a key role. Countering this with antioxidants is one way to help avoid the inflammation that can contribute to liver damage.

Appropriate antioxidant doses might be vitamin E (800 to 1,200 IU daily), vitamin C (1,000 to 2,000 mg, three times daily with meals), bioflavonoid complex (1 capsule with each meal), carotenoid complex (1 capsule with each meal), selenium (400 to 600 mcg daily, total from all sources, including your multiple), N-acetyl-cysteine (500 mg, twice daily), coenzyme Q-10 (100 to 500 mg daily), and alpha-lipoic acid (200 to 400 mg, three times daily). (For additional information on these nutrients, see below as well as the *Introduction* to this Guide.)

Also important is supplementation with a B complex formula that contains at least 50 mg of most of the B vitamins, including riboflavin and thiamine (1 capsule with each meal) or a potent multivitamin/mineral formula that includes the whole B complex in equally potent amounts (as directed, with meals). Although there are two B vitamins that have been mentioned as being important for countering mitochondrial damage—thiamine (vitamin B-1) and riboflavin (vitamin B-2)—it should never be forgotten that the B vitamins work together, that deficiencies of several B vitamins and many other nutrients are common in HIV disease, that nutrients work as a package in the body, and that one missing link

could sabotage the effectiveness of other nutrients. For this reason, a B complex formula or a multiple containing the whole B complex should always be given in conjunction with any separate supplementation with individual B vitamins.

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

If it is not, then the over-the-counter acetyl-L-carnitine may be best since it requires lower doses for the same effect. This combination of antioxidants, B vitamins, and carnitine may greatly help to counter mitochondrial toxicity in the liver, and help to prevent the accumulation of fatty tissue:

NYBC’s Core Nutraceutical Combination for Decreasing Liver Toxicity and Enzyme Levels:

Artichoke 15% 500mg x 180	4-6/d (1-2B, 1-2L, 2D)
Lipoic Acid 100mg x 180	6+/d (2+B, 2+L, 2+D)
N-acetyl-cysteine 500mg x 200	4-6/d (1-2B, 1-2L, 2D)
Silymarin 80% 200mg x 180	3-6/d (1-2B, 1-2L, 1-2D)
Added Protection/Ultra Preventive	6/d (2B, 2L, 2D) – any potent mutli without iron

Because these nutrients are so crucial for liver support, we will provide here some expanded information on the most important of these. At the top of the list of liver-supportive nutrients are those that help to maintain optimal levels of glutathione, the most important intracellular antioxidant. Research has shown that cellular levels of glutathione go downhill as HIV disease progresses and that levels in plasma, lung fluid, and T cells are frequently deficient, even in very early disease stages. Glutathione levels are also too low in those with hepatitis C. Glutathione deficiency may result from a combination of increased oxidative stress in the body and decreased synthesis of glutathione in the liver. Proper glutathione levels are critical for proper liver function.

For people on HAART or any other medications that may be liver toxic, proper glutathione levels will be crucial since the liver uses glutathione for the detoxification of drugs. When levels of glutathione in the liver are too low, its ability to properly break drugs down may be compromised. In addition, since glutathione is a crucial counter to oxidative stress, a major source of damage to the liver, using the combination of nutrients that will ensure optimal glutathione levels may be one of the most important things that can be done to help prevent or repair liver damage.

Alpha-Lipoic Acid. Alpha-lipoic acid (ALA) is a fatty acid and antioxidant that is very important to the metabolic pathways in liver cells (the pathways used when the liver performs its important functions, including the breakdown and processing of toxins). Alpha-lipoic acid can be rapidly depleted when the liver is under stress. Although much less attention to lipoic acid has been paid in the U.S., there is a long history of its use in Europe for the treatment of liver disorders because of its apparent ability to help the liver repair itself. Since both HIV and hepatitis C induce glutathione deficiency, and that deficiency can allow the liver to become damaged by oxidative stress, alpha-lipoic acid’s effectiveness in raising cellular glutathione levels makes it very important for liver protection and repair. German researchers have found that supplementation with alpha-lipoic acid results in increases in blood levels of both glutathione and vitamin C, as well as increases in CD4 cells and decreases in the body compounds that result from oxidative stress (thus showing that the nutrient is effectively working to counter that stress).

Unlike most other antioxidant nutrients which work in either the fatty parts of the body (including the outer layers of cells) or the watery parts (including the blood), lipoic acid works in both. This helps to provide protection to cells throughout the body. It also helps to recycle and regenerate other antioxidants, including vitamins E and C, thereby helping to maintain optimal levels of these nutrients in the body. For all these reasons, many naturopathic physicians

consider lipoic acid to be one of the most important nutrients for liver support. There are many anecdotal reports from HIV+ people who have successfully used lipoic acid, usually in conjunction with NAC and other antioxidants, to reduce liver enzymes. For liver repair and general antioxidant support, doses of 200 to 400 mg, taken three times daily, preferably on an empty stomach, are appropriate.

Note: a time-released form is very important because alpha-lipoic acid has a very short half-life (the time that it takes for half the substance to disappear) in the bloodstream. By using products that release the alpha-lipoic acid gradually over time, you increase the total time that the nutrient will be available and working in the body.

Artichoke Leaf (*Cynara scolymus*): Increases flow of bile, inhibits cholesterol biosynthesis and lowers serum lipids, antioxidant, increases liver regeneration, protects liver cells from chemical damage. Specific indications include: Dyspeptic complains, nausea, vomiting, spasmodic abdominal pain, stomach ache, loss of appetite, constipation, bloating.

N-acetyl-cysteine. NAC is an amino acid whose effectiveness in raising glutathione has long been medically accepted. It is, in fact, used in the treatment of acetaminophen poisoning specifically because of its ability to raise glutathione in the liver. Studies done at Stanford University, the National Institutes of Health, and a number of European research institutes have shown that N-acetyl-cysteine (NAC) works both directly and indirectly as an antioxidant, helping to raise glutathione levels back toward normal. This makes NAC a very important component of a liver protection program. Appropriate doses for liver support would be NAC, 500 mg, taken twice daily with meals; never take NAC on an empty stomach as it can cause gastrointestinal irritation if not accompanied by food.

Milk thistle (silymarin) is at the top of most people's lists for herbal liver support. The herb commonly 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.

Researchers have reported benefits from milk thistle supplementation in those with either viral hepatitis or hepatitis caused by drugs or alcohol. There are a great many anecdotal reports from HIV+ people of success in reducing elevated liver enzymes with the use of silymarin, usually in conjunction with alpha-lipoic acid and NAC.

Based on test-tube (*in vitro*) studies, concern had been created that milk thistle might adversely affect levels of protease inhibitors in the blood via an inhibitory effect on the CYP system, which is responsible for metabolism of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). However, later research done by pharmacokinetics expert Stephen Piscitelli, Pharm.D., showed that in people there should be no concern. They looked at the interaction of milk thistle with indinavir and found that three weeks of dosing with commonly administered dosages of a commercial preparation of the herb did not significantly alter the body's exposure to indinavir. They concluded that use of milk thistle did not alter substantially the pharmacokinetics of indinavir and should not interfere with indinavir therapy. In addition, because all protease inhibitors and nonnucleoside reverse transcriptase inhibitors are metabolized at least in part through the same CYP3A4 pathway, the researchers concluded that it is unlikely that milk thistle would alter significantly the pharmacokinetics of any of these antiretroviral agents. In what might be taken as a general warning to not over-interpret test-tube studies, the researchers also noted that their study demonstrated that *in vitro* studies of herbal products may give very different results than those seen in a clinical trial. They warned that, in general, results of *in vitro* studies with herbal products should not be used as a basis for therapeutic decisions on drug interactions and should always be confirmed in a clinical trial.

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 or, depending

on your current level of drugs, perhaps continued long-term to help continually protect and regenerate the liver (especially for those on multiple drugs long-term).

Other Nutraceuticals for Liver Support:

S-adenosyl-L-methionine (SAME). SAME is an amino acid which also helps in the manufacture of glutathione in the liver. It appears to help cell membranes function normally, and assists the liver with the detoxification of drugs and other toxins. SAME can help to normalize bile secretion by the liver, a process commonly affected in chronic liver diseases. Interestingly, in several European studies of people living with hepatitis B or C, it has also been shown to help reduce jaundice, fatigue, and chronic skin irritation and itching, while also lowering liver enzymes and bilirubin levels. Dosages of SAME in these studies were either 800 mg given intravenously or 800 to 1,600 mg given orally. No side effects were reported in any of the studies with SAME in chronic liver disease.

Because SAME is expensive, another approach to gaining its benefits is to supplement with the things that the body uses to make its own SAME, including the amino acid methionine (500 mg), tri-methyl glycine (betaine, 500 mg), folic acid (800 mcg) and vitamin B-12 (1,000 to 3,000 mcg), all taken daily. Whether this would work as well as taking SAME has not been shown, but it would at least provide the building blocks for the substance.

Selenium. Selenium is a mineral that provides important antioxidant protection via the selenium-containing enzyme glutathione peroxidase. This enzyme helps the body maintain sufficient levels of glutathione in the liver and other cells, and thus may help prevent liver damage. Unfortunately, selenium levels may be too low in many people. University of Miami researchers have reported that selenium deficiencies are common in HIV+ people, and that lower levels of selenium are tied to faster HIV disease progression. Other researchers have reported that HIV+ people who are coinfecting with hepatitis C have lower blood levels of selenium compared to those who are not coinfecting. Countering this deficiency is important for several reasons.

First, it will help to maintain the levels of glutathione necessary to counter oxidative stress and the liver damage it causes. Second, selenium may also provide significant protection against the development of liver cancer, a serious risk in those living with either hepatitis B or C. In one large study that looked at the risk of developing liver cancer in 7,342 men with chronic hepatitis B or C, those with the highest levels of selenium were 38 percent less likely to develop the cancer. The researchers reported that the lowest levels of selenium were found in those with chronic hepatitis C. A very large study in China (130,471 people in an area with high rates of chronic hepatitis B and liver cancer) found that the rate of primary liver cancer dropped by one third in those who were given a selenium-containing table salt. In a sub-study, those researchers found that none of the 113 people given a selenium supplement (200 mcg daily) for four years developed liver cancer, whereas seven people of the 113 in the placebo group developed liver cancer. When the selenium supplementation was discontinued, rates of liver cancer again rose.

Current research with HIV+ people taking 400 mcg per day is being conducted at the University of Miami. While we wait for those results, it appears that in addition to providing general antioxidant protection and immune defense, selenium in doses of 200 to 400 mcg daily may provide at least some protection against the possible development of potentially fatal liver cancer in those coinfecting with either hepatitis B or C.

Vitamin C (ascorbic acid). Vitamin C is a powerful antioxidant and natural anti-inflammatory agent. Both characteristics are crucial for people with hepatitis C, since much of the damage caused by the infection comes from a combination of oxidative stress and inflammation in the liver. Vitamin C is also necessary for optimal immune function since the white blood cells that provide much of your immune response are dependent upon vitamin C for normal functioning. This makes vitamin C a crucial nutrient for control of any viral infection. NYBC uses a highly absorbable form of vitamin C called mineral ascorbates and then places the ascorbates in a pharmaceutical grade sustained release matrix so that the vitamin C is released slowly over a four hour period. This is because vitamin C is water soluble and quickly flushed from the body. Because individual needs vary widely, recommended dosages range from 1,000 to 6,000 mg or more daily (with doses spread across the day and taken with meals). (Note that amounts in excess of individual tolerance can result in gas and diarrhea; if you develop sudden watery diarrhea when you begin or increase a vitamin C dose, know that this may be the cause.).

Vitamin E. Vitamin E is an antioxidant that works in the fatty parts of the body, including in cell membranes (the outer layers of cells). It is crucial for the protection of cell membranes in the liver. Because it is a key nutrient for protection against oxidative stress, including vitamin E as part of a total approach to protecting the liver from the damage that oxidative stress can cause is very important. A number of studies have shown the potential benefit of vitamin E

supplementation for the liver. In one study of 23 people living with hepatitis C, almost half of those given 800 IU of vitamin E daily saw significant improvement of liver enzymes. The enzyme levels increased again after the vitamin E was discontinued, indicating that the nutrient was not permanently stopping the process of inflammation in the liver, but rather was suppressing the inflammation while the nutrient was being taken. Other studies have shown that vitamin E may slow the process of fibrosis by interrupting the biochemical pathway that leads to this liver scarring. For overall antioxidant defense and protection against liver damage, doses of 800 to 1,200 IU daily would seem appropriate.

Glutamine. Glutamine is an amino acid which is normally found in greater abundance in the body than any other free amino acid. Because it is crucial for many aspects of healthy body function, including maintenance of optimal antioxidant status, building and maintenance of muscle tissue, maintenance of immune function, and repair and maintenance of intestinal tissue, in those living with diseases like HIV and hepatitis B or C that demand constant immune responses and create constant oxidative stress, body supplies tend to run short. For those in need of liver protection and repair, supplementation with L-glutamine will be very important since it is needed to maintain glutathione levels. The amount of glutathione that the body can produce is initially dependent on the amount of cysteine that is available for that process (that's why cysteine is often called the "rate limiting" factor in glutathione production). However, once you've provided all the cysteine that's necessary, glutamine becomes the rate-limiting factor in the production of glutathione. Thus, in a body depleted of glutamine, glutathione production will never be optimal. Supplementing with both NAC and L-glutamine helps to guarantee that the two rate-limiting factors will always be present in the quantities needed for full glutathione replenishment. This can help to ensure that your body remains capable of properly breaking down all the drugs you may be taking with as little toxicity as possible, and has the antioxidant protection needed to help prevent liver damage. Studies have shown that supplementation with L-glutamine does, indeed, preserve liver glutathione.

Glutamine researcher Judy Shabert, M.D., believes that the very high demand for glutamine in HIV disease means that even those in early, asymptomatic disease stages may need approximately 5 to 10 grams of glutamine daily (spread across four doses and taken on an empty stomach) to provide sufficient amounts to meet all the body's needs. In those with malabsorption, wasting, and/or diarrhea, she recommends doses of 30 to 40 grams per day (spread across five doses, and taken on an empty stomach). A powdered form is best since far too many capsules would be required to reach these dosing levels. The powder can be mixed in a half a cup or so of water or juice.

There is a blood test available that can measure glutamine levels as part of an assay of amino acids in plasma. Unfortunately, blood levels can be somewhat misleading because the body will attempt to keep blood levels normal even when the level in the muscles is low. Thus, a normal blood level may not mean that the level of glutamine stored in the muscles is adequate. If the level in the blood is low, the level in the muscles is probably very low. However, despite the inadequacies of the test, Dr. Shabert believes that you could look at sequential blood levels to at least see if you are moving in the right direction. She believes that a healthy normal level is 600-700 ng/dl (*not* the lower levels that some labs list as normal; keep this in mind when assessing results). It may take some time for glutamine levels to be restored, especially in those with wasting or malabsorption. The body will have to use a lot of it to rebuild wasted muscles and/or repair the small intestine. It will need even more to boost its stores to levels adequate for maintaining optimal glutathione levels and immune function. If your initial blood level is below 600 ng/dl, Dr. Shabert recommends supplementing with L-glutamine for a month or so and then re-testing to see if the glutamine level is moving back to a healthy normal point. One company that provides an amino acid assay that includes a glutamine level is MetaMetrix.

Warning: There is no known toxicity from glutamine in those with adequate hepatic (liver) and renal (kidney) function; however, for anyone with advanced liver or kidney disease, its use should only be considered with the advice of a physician knowledgeable on this subject. Glutamine is an amino acid that must be processed by the body; for anyone with a medically necessary protein-limited diet, its use would have to be considered in light of the protein restrictions.

Carnitine. This amino acid may be particularly important for countering the development of a fatty liver (or helping to reverse that). It is also a crucial component of a protocol aimed at preventing mitochondrial toxicity in the liver. Carnitine is available in two forms: L-carnitine and acetyl-L-carnitine. There are both over-the-counter and prescription forms of L-carnitine. The brand name of the prescription form is Carnitor.

L-carnitine should be taken in doses of 1,000 to 2000 mg, three times per day. Acetyl-L-carnitine (available over the counter) should be taken in doses of 500 to 1,000 mg, twice daily. Note that acetyl-L-carnitine will release four times the amount of free carnitine into the bloodstream, compared to an equivalent dose of plain L-carnitine. Thus, the need for higher doses of L-carnitine to achieve the same effect. If insurance or Medicaid coverage for Carnitor is available, this could provide substantial savings. If it is not, then the over-the-counter acetyl-L-carnitine may be best since it requires

lower doses for the same effect. [For more information on these, see *NYBC's Basic Nutrient Protocols and Counteracting Inflammation* in this guide's *Introduction*.]

Carotenoids. Several studies have indicated that beta-carotene is another nutrient which may help prevent development of liver cancer in those suffering from cirrhosis of the liver. Decreased blood levels of beta-carotene have been found in those with either of these conditions, with the levels in those with liver cancer being the lower of the two. Researchers have suggested that supplementation with beta-carotene may help provide protection for the liver. Because it is always best to supplement with a variety of carotenoids rather than beta-carotene alone, choose a carotenoid complex (1 with each meal).

The power of nutrient combinations. Since antioxidants and other nutrients interact with each other in many positive ways, it is not surprising that the most positive results often occur in those given a combination of nutrients, rather than any single nutrient alone. In one small trial conducted at the Integrative Medical Center of New Mexico in Las Cruces, New Mexico, there were extremely impressive results in those given a comprehensive combo of antioxidants and other nutrients. Three people living with hepatitis C who had been diagnosed with moderate to severe cirrhosis were given a combination of alpha-lipoic acid (600 mg daily), selenium (400 mcg daily), silymarin (900 mg daily), vitamin B complex (100 mg twice per day), vitamin E (400 to 800 IU daily), vitamin C (1,000 to 6,000 mg daily), coenzyme Q-10 (300 mg daily), and a multiple vitamin/mineral supplement (once daily). These nutrients were chosen because of their ability to protect the liver from damage caused by oxidative stress and to interfere with the progress of the infection by supporting the immune system. The trial participants were asked to eliminate alcohol, sugar, and caffeine, decrease their meat intake to a few times weekly, increase intake of purified water to eight glasses daily, and begin a modest exercise program. The results were very impressive with significant improvements in laboratory values (for example, reductions in the ALT liver enzyme of at least 60 percent in all three patients) and even more significant improvements in overall health and well-being. After 5 to 12 months on the nutrients, all three people achieved sufficient improvement in liver function to be able to avoid the liver transplants that they had been scheduled for. According to the researcher, treatment with the combination of nutrients is a reasonable approach during the evaluation process prior to liver transplant surgery so that if there is significant improvement, surgery may be avoided. .

Other Herbs for liver support. Many herbs have been promoted as possibly boosting liver function and repair, but some have more support than others, based on the research done (mostly in Europe or China or Japan). There are many herbal liver support formulas available, with most containing one or more of the herbs discussed below.

Bupleurum Root (*Bupleurum falcatum*): A primary herb used in traditional Chinese medicine for the treatment of a wide variety of liver diseases. It contains a group of compounds known as saikosaponins which have been shown to have anti-inflammatory, immune modulating, and liver-protective effects. It is widely used in China and Japan as a primary ingredient in herbal formulas for the treatment of hepatitis. Bupleurum can rapidly cause a decrease in elevated liver enzymes. However, a number of studies have reported a tendency to return to previously elevated liver enzyme levels. Continued refinement of natural health protocols is needed to minimize the likelihood of a rebound effect.

Dandelion Root (*Taraxacum officinale*): One of the most frequently used liver supportive herbs in Europe and the US. It has cholagogue activity (meaning it stimulates bile flow from the liver), thus facilitating the liver's detoxification processes. It is specifically used for inflammation of both the liver and gallbladder and jaundice.

Glycyrrhizin. A licorice root extract known as glycyrrhizin, which comes in both capsule and sterile IV liquid forms, has been shown in studies in Japan to reduce liver inflammation, as well as having activity against hepatitis B, CMV (another possible source of liver damage), and HIV. Glycyrrhizin has been used for over forty years in Japan as a treatment for chronic liver disease. A number of studies reported in Japanese medical journals appear to show that glycyrrhizin can help detoxify the liver and help it to regenerate healthy tissue, thus reversing liver dysfunction. Japanese researchers also report that glycyrrhizin works as an anti-inflammatory and antioxidant, both of which would help counter liver damage.

However, there are important cautions for anyone considering the use of glycyrrhizin. It should definitely not be taken if you have high blood pressure, low blood potassium, a weak heart, or kidney problems. It can cause water retention and blood pressure increases that could be very serious. Both the capsule and (Dr. Rx required) IV forms are available through NYBC.

Schisandra Fruit (*Schisandra chinensis*): Schisandra is rich in a group of compounds known as lignans which have been shown to exhibit numerous beneficial effects on the liver including: protecting liver cells against the effects of toxin and viral mediated inflammation, enhancing the liver's antioxidant-glutathione defenses and regenerative capacity, and facilitating the detoxification processes of the liver. In addition it has potent adaptogenic effects which can help to reduce the negative effects of stress and treat fatigue (see Fatigue). In traditional Chinese medicine it is used for a variety of sexual dysfunctions, most notably spermatorrhea and premature ejaculation in males (see Sexual Dysfunction.)

Cautions: May modulate cytochrome P-450 enzyme systems, and therefore, may alter the effectiveness of conventional medications affected by this system. Consult a qualified health care professional when using schisandra in conjunction with conventional medications. It should be avoided during pregnancy.

Turmeric Root (*Curcumin; Curcuma longa*): Rich in a group of constituents known as curcuminoids, turmeric is a very effective anti-inflammatory, choleric (stimulates bile flow), antioxidant, and antimicrobial. Traditionally in India, it was used predominantly for digestive and liver disorders. In the west it has been used for similar purposes and additionally for the treatment of jaundice and hepatitis. Some studies have reported significant increases in CD4 and CD8s in HIV-positive subjects.

Cautions: Has blood thinning activity and may potentiate the effect of anticoagulant medications.

Traditional Chinese Medicine formulas. Because there is so much viral hepatitis in China and a long history of treating it there with herbal combinations, TCM practitioners have a great deal of information on possible therapies. There is often a combination of acupuncture with individualized herbal formulas. Since each person is considered unique in TCM and, thus, treatment approaches are generally individually designed, the best way to obtain them is through making an appointment with a practitioner of TCM. To locate such a practitioner, go to www.nccaom.org

An excellent Chinese herbal formula for hepatitis C is **Hepato C**. It has a combination of many different traditional herbs. The recommended dose is 2 to 3 capsules, twice daily, for the first 3 months. Thereafter, the dosing is changed to 2 capsules, twice daily.

Other Liver Supportive Nutraceuticals

Liver Organic Glandular: Glandulars are concentrated extracts of various raw animal glands such as thymus, thyroid, liver, spleen or adrenal cortex. While not as well known in the U.S., they are extremely popular in Europe. The idea is that consuming them results in migration of the cells to the appropriate organ to help provide replenishment to it. NYBC's glandulars are from organic cattle in New Zealand. Note: Glandulars should never be stopped suddenly, but reduced gradually in order to assure that a feedback inhibition (decreased productivity) of the gland does not occur.

Oat Bran: Oat Bran is an excellent source of soluble fiber and insoluble fiber, suitable for vegetarians. As a hot cereal, it cooks in a jiffy, is tasty and high in protein. It is also available in pill form.

NYBC and Other Nutraceuticals for Liver Health:

Mineral Ascorbates C Sustained Release 1,000mg x180	1-6+/d (0-2B, 0-2L, 1-2D)
Carotenoid Complex UltraAntioxidant x 90	3/d (1B, 1L, 1D)
Bupleurum x 100 grams	1-2 teaspoons daily in water
Curcumin 500mg x 60	6+/d (2B,2L,2D)
Dandelion x 4 oz	30-60 drops day
Dandelion root 500 mg x 100	3/d (1B, 1L, 1D)
Vitamin E 400IU x 250	1-2/d (0-1B, 1D)
Flax Seed x 12oz	3-6 grams/day
Glutamine 900mg x 180	6-12+/d (2-4B, 2-4L, 2-4D)

Glycyrrhizin 330mg x 100	3/d (1B, 1L, 1D)
Hepato-C 500mg x 100	4+d (1B, 1L, 1D)
Hepato-Detox 500 mg x 100	2/day before bed. For short-term use, 2 before and after drinking alcoholic beverages.
Liver Organic Glandular 500 mg x 125	4 - 6/d (1-2B, 1-2L, 1-2D)
Oat Bran 1,000mg x 100	3-6/d (1-2B, 1-2L, 1-2D)
SAMe 200mg x 60	4-8/d (1-2B, 1-3L, 2-3D)
Schisandra Fruit Hepa F. No. 2 x 180	6/d (2B, 2L, 2D)
Selenium 200mcg x 180	1-2/d (0-1L, 1D)

Treatment of hepatitis viruses. HIV+ people co-infected with hepatitis virus(es) should always discuss with their physicians the possibility of drug treatment to counter the viruses. There are current treatments available for both hepatitis B and hepatitis C which may provide benefit. The topic of making treatment choices is too complex for this guide but it will be very important to discuss the pros and cons of treatment with your physician, and make informed choices. Always watch for the latest news of ongoing research. We can certainly hope that research will provide ever more effective and easier treatments over time.

Juice Therapy. Fresh-squeezed vegetable juices containing the juice of carrots, green, leafy vegetables, tomatoes, beets and other nutrient-loaded veggies can help support the liver by giving it the nutrient building blocks that are used in the liver's detoxification and repair processes. The same is true for a fruit shake that you make by blending together frozen fruits (blueberries, strawberries, peaches, raspberries, mangoes, all the colorful possibilities), a banana, a few tablespoons of yogurt, and fresh-squeezed juices. Either the veggie mixture or the fruit shake will be power-packed with antioxidants and other nutrients that the liver needs so they can be a simple way to up your nutrient intake in a way that is liver supportive. For a vegetable juice, it's best to use a juicer with which the pulp of the vegetables is mostly retained. It is the pulp that contains the highest concentration of nutrients so throwing it away means you're throwing away a lot of the good. VitaMix is one of the only nationally sold brands that retains most of the pulp.

A couple of cautions should be kept in mind for anyone wanting to prepare these juice combos. First, be careful about how much beet juice you add to a vegetable juice mixture. Because beets are frequently recommended in herbal or alternative healing resources (books, encyclopedias, websites, and so on) as a liver supportive food, many people with liver problems decide to use it. The problem is that, although it's loaded with nutrients, drinking very much of it at once makes many people feel queasy and flushed (probably due to a detoxification reaction). Limit yourself to no more than an ounce of beet juice in 10 ounces or more of other vegetable juices (carrot, dark leafy greens, etc.). In addition, always properly clean vegetables and fruits, and follow food safety instructions for preparing them. (For more info on this, see *NYBC's Self-Care Guide*.)

Caution with newer drugs. Liver problems and deaths have led to several new drugs being taken off the market in the last few years, and to others having warnings added to their labels. In the rush to benefit from new drugs, particularly antiretrovirals in the case of HIV+ people needing new options, many people begin taking drugs shortly after they are approved by the FDA. The problem with that is that it is only after clinical trials are completed and drugs are approved that they begin to be used by much larger numbers of people. It may only be then that problems not seen in the clinical trials, including liver damage or failure, may emerge. For that reason, some experts recommend that patients wait a year or two before taking a newly approved drug (of any kind) unless it has important advantages over older ones. Of course, for many HIV+ people in need of antiretroviral coverage, there may not be an option to wait if they have already run through all the earlier options. But where possible, this caution about waiting to take new drugs would certainly seem advisable.

When you are taking a new drug, it is also very important to watch yourself for any symptoms and always immediately report anything new to your physician. Liver experts have said that the people who most often die from a new drug are those who continue to take it even after symptoms arise.