Liver Health, Hepatitis & HIV

We realize that this issue of ACRIA Update might cause unease for some of our readers – yet more viruses to worry about, the possibility that anti-HIV drugs could affect the liver, and lots of unfamiliar words, many of them beginning with “hepa.” But, we know that the following discussion can be important to your health. Liver problems have become a part of living with HIV for many people, so we’ve included tips on keeping your liver healthy, questions to ask your provider, tests to request, results to monitor, and symptoms of liver problems to watch out for. Perhaps the most helpful hint we can offer as you read on is that “hepa” means liver. For example, hepatitis means inflammation of the liver, whether the cause is alcohol, toxins, or a viral infection like hepatitis B or hepatitis C. Similarly, hepatologists are liver specialists, something that’s hepatotoxic can be harmful to the liver, hepatocellular carcinoma is a type of liver cancer, etc. Still kind of intimidating, perhaps, but not having information is often harmful. We thank the writers who contributed to this issue of ACRIA Update, especially Joan Warner and Jeff Gustavson for sharing their personal journeys through fear to become active participants in their health care.

Best wishes for a good summer.

J Daniel Stricker, Editor in Chief

Antiretrovirals & Liver Toxicity: How Big A Concern?

by Bertrand Toulouse & James Learned

The benefits of combination therapy that have led to dramatic decreases in opportunistic infections and AIDS deaths over the past several years are accompanied by drawbacks, not the least of which is drug side effects. Some of these side effects are hepatotoxic – the scary sounding term for something that can harm the liver.

Even when their health is failing, many people put off treatment, fearing that antiretrovirals will automatically result in irreversible liver damage. Most anti-HIV drugs are processed primarily by the liver, so the fear isn’t irrational. But every drug is different; each class of antiretrovirals works differently; and the condition of each person’s liver can differ depending on factors such as co-infection with hepatitis B or C, previous or current alcohol use, age, sex, genetics – lots of things.

There are still many unknowns about the effects of antiretrovirals on the liver, but there’s a lot we do know. If combination therapy makes sense for you clinically and you’re worried about your liver, understand your personal risk factors, know what symptoms to watch out for, and – most importantly – carefully monitor liver function while on therapy to help you avoid the possibility of liver damage but still experience the benefits of treatment.

Many studies have looked at the prevalence and causes of liver toxicity in people on combination therapy. Results show that all three classes of antiretrovirals used to treat HIV infection are associated with different kinds and degrees of hepatotoxicity:

• Some nucleoside analogues (also called nucleoside reverse transcriptase inhibitors or NRTIs) can cause a very rare but potentially life-threatening side effect – lactic acidosis – that is sometimes accompanied by liver problems.
• Non-nucleoside reverse transcriptase inhibitors (NNRTIs), especially Viramune (nevirapine), can cause severe liver inflammation (clinical hepatitis).
• Protease inhibitors (PIs), mainly Norvir (ritonavir), have been associated with varying degrees of liver damage, particularly in people co-infected with chronic hepatitis B or C.

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Ampligen and HAART: Protocol AMP 719

This trial will study the effects and safety of adding Ampligen to HAART and see if it helps to lower viral load.

Adults with a CD4 count over 300, and a viral load between 500 and 30,000 may be eligible for this study. The first 10 people in the trial will receive infusions of Ampligen twice a week, and take HAART. Later groups will either receive infusions at entry or receive them 6 months later.

The study will last 48 weeks during which time participants will make 21 visits to ACRIA. All blood tests, study visits and study drugs will be provided at no charge to the participants. Once enrolled in the study, there will be a reimbursement of $25 per visit to cover lost time from work, transportation costs and/or meals.

For more information, call Dr. Douglas Mendez at 212-924-3934, ext. 126.

Ampligen and Treatment Interruptions: Protocol AMP 720

This trial will study whether Ampligen can extend the time people can interrupt HAART, before viral load rebounds.

Adults who are taking HAART, and who have a CD4 count over 400 and viral load below 50, will take HAART and receive infusions of Ampligen, or take HAART without Ampligen, for 2 months. Then, HAART will be stopped and viral load will be checked weekly. If viral load rises above 5,000, HAART will be restarted. If viral load drops below 50 for 2 months, HAART will be stopped again. This pattern will continue for the rest of the study. People who don’t receive Ampligen can take it after 14 months.

The study will last approximately 128 weeks during which time participants will make 128 visits to ACRIA. All blood tests, study visits and study drug will be provided at no charge to the participants. Once enrolled in the study, there will be a reimbursement of $25 per visit to cover lost time from work, transportation costs and/or meals.

For more information, call Dr. Douglas Mendez at 212-924-3934 ext 126

Editor's Notes

- All material in ACRIA Update is presented for educational and informational purposes only, and is not intended as medical advice. All decisions regarding one’s personal treatment and therapy choices should be made in consultation with a physician.
- ACRIA Update refers to all drugs by both their commercial and scientific names upon their first reference in an article. Thereafter in the article, they will be identified with the name by which we feel they are most commonly known, either commercial or scientific.
Antiretrovirals & Liver Toxicity  (continued from first page)

In most of the studies discussed below, severe liver toxicity is defined as an elevation of the liver enzymes ALT (alanine aminotransferase) and/or AST (aspartate aminotransferase) to levels greater than 5 times the upper limit of normal. Although useful as a way to classify reactions to medications, it’s important to realize that liver enzyme levels don’t necessarily correlate with the degree of liver cell damage. Enzyme levels can be normal in people with severe liver disease and abnormal in people with diseases that don’t affect the liver.

Nucleoside Analogues
The side effects of nucleoside analogues are fairly well known because this class of drugs has been around the longest. Recently, more attention has been paid to their effect on the liver. Numerous studies have implicated the NRTIs as damaging mitochondria, the “powerhouses” inside cells that convert nutrients into energy. Mitochondrial damage can affect many parts of the body, including muscle, nerves, the heart, and the liver. A disruption in mitochondrial energy supply can also result in an increase in lactic acid levels in the blood. If lactate levels get very high, a rare condition called lactic acidosis occurs, which is often accompanied by liver abnormalities—elevated enzymes, fatty liver (hepatic steatosis) and acute inflammation.

For someone currently on or thinking about beginning therapy, one question to consider is which NRTIs are more likely to cause high lactate levels and, possibly, liver toxicity. Researchers from the University of California at San Diego looked at 2,144 patients who were taking NRTIs from July 1998 through September 2001 to see how often symptoms that could lead to lactic acidosis (symptomatic hyperlactatemia) occurred and to identify which NRTI combinations were most often responsible. Symptomatic hyperlactatemia was defined as having at least one symptom—fatigue, nausea, vomiting, abdominal pain, loss of appetite, difficulty breathing or elevated ALTs—and high lactate levels in the blood.

Eighty-one patients (only 4%) met the definition, and most of them were on combinations that included two NRTIs. The risk of developing symptomatic hyperlactatemia doubled with each additional NRTI used in a regimen. A substantially higher risk was seen in people whose regimens included Zerit (d4T) plus Videx (ddI) or Zerit plus Ziagen (abacavir), particularly compared to the relatively low risk for people taking combinations that included AZT plus Epivir (3TC). These results reinforce concern that Zerit—especially when used in combination with Videx—could lead to mitochondrial damage and potential liver injury.

“Liver enzyme levels don’t necessarily correlate with the degree of liver cell damage.”

Gilead Sciences, the manufacturer of the nucleoside analogue, Viread (tenofovir), conducted a test tube (in vitro) study to evaluate the effect of Viread and each available nucleoside analogue on the mitochondrial DNA of liver cells, muscle cells, and kidney cells. Hivid (ddC) caused the most damage, followed by Videx, Zerit, and, to a lesser degree, AZT, Epivir, Ziagen, and Viread. These results are generally consistent with the toxicities seen in human studies, but it’s important to remember that what happens in the test tube may not reflect what happens in the body.

Many small studies and case reports suggest that mitochondrial damage is more likely to occur the longer you’re on treatment, sometimes within several months, but often after a number of years. The relationship between lactic acidosis and liver damage is unclear. In some cases, liver damage seemingly caused by mitochondrial toxicity is not accompanied by lactic acidosis. The liver rarely lets us know when it’s in trouble, and the symptoms of lactic acidosis are notoriously non-specific. Blood tests, including those that check lactic acid and bicarbonate levels, can help confirm the presence of lactic acidosis, and regular liver function tests are particularly important if you’re on treatment.

Non-Nucleosides
Among the non-nucleoside reverse transcriptase inhibitors (NNRTIs) – Rescriptor (delavirdine), Sustiva (efavirenz) and Viramune (nevirapine) – Sustiva and, particularly, Viramune have been shown to cause liver damage in some people.

Viramune received a lot of unflattering attention early last year when a South African study was stopped prematurely at week 48 because of two deaths caused by liver failure. The trial, called FTC-302, was comparing FTC (emtricitabine), an investigational NRTI, to Epivir in combinations that included Zerit and either Viramune or Sustiva. Both deaths occurred in women who were on Viramune. Of the 468 people enrolled (59% were women), severe liver toxicity occurred in 17% of those taking Viramune and in none of those taking Sustiva. Only one-third of the people with liver toxicity also had the rash that commonly occurs with NNRTI drugs. One of the women who died had experienced a rash but wasn’t advised to stop her medications until almost two weeks had passed. Other than being on Viramune, the only significant predictive factor for developing severe liver toxicity in this study was female sex. Women were twice as likely as men to experience liver toxicity. Three-quarters of the cases occurred within the first month on therapy, and the rest occurred later in the course of treatment.

A study published in AIDS in July of last year reported on 610 individuals who started combinations that included Viramune between September 1997 and May of 2000 in Barcelona and London. Almost half of the participants were co-infected with hepatitis C. In this study, liver damage was defined as an increase
In ALT or AST levels at least three times higher than the patient’s measurement before beginning treatment. This occurred in 76 participants (12.5%), but only thirteen (2%) had to stop Viramune because of the liver toxicity. Seven of the thirteen experienced symptoms of clinical hepatitis, which improved once they switched to a different regimen. The risk of liver damage increased with longer time on therapy, and only half of the cases of clinical hepatitis occurred during the first two months on treatment. The researchers concluded that people who had been on any antiretroviral therapy for longer periods of time, were co-infected with hepatitis C, or had elevated ALT levels before starting therapy were at higher risk of developing liver damage while on Viramune and, perhaps, on any other three-drug regimen.

Liver enzyme elevations or liver inflammation occur in as many as one out of four people who take Viramune, but it only rarely causes clinical hepatitis. If liver problems develop, they usually happen during the first three months on the drug, although at least one-third of people who experience liver problems develop them later.

Researchers in Madrid looked at plasma levels of Viramune in 33 people who developed elevated liver enzymes. They found significantly higher drug levels in this group compared to those whose enzymes weren’t elevated, suggesting a correlation between higher plasma drug concentrations and liver toxicity. This might help explain the higher rates of liver toxicity in women compared to men. Weight, body mass and hormones affect drug metabolism. It’s possible that differences in these areas could lead to higher drug levels in women.

The Impact of Viral Hepatitis

A study published in Hepatology in January compared the occurrence of severe liver toxicity in 568 people on regimens that included either Viramune or Sustiva. Almost half of the study participants (43%) were co-infected with hepatitis C, and a much smaller 7.7% had hepatitis B. Severe liver toxicity occurred in almost 16% of those on Viramune and 8% of those on Sustiva. Again, most of the liver toxicities were detected after the participants had been on treatment for more than three months. Liver toxicity was much more likely to occur in people co-infected with hepatitis B or C and whose regimens included a protease inhibitor. Some good news – although hepatitis C co-infection was a significant risk factor, the majority of co-infected participants (84%) did not experience severe liver damage.

Researchers from the San Francisco Community Health Network looked back at the effect of antiretrovirals on the livers of co-infected individuals who were seen at their clinics between mid-1996 and mid-2000. The findings were presented at the 9th Conference on Retroviruses and Opportunistic Infections in February. Of more than 3,000 patients whose results were available, 39% were hepatitis C co-infected and 9% had chronic hepatitis B. The researchers found that Viramune was the only antiretroviral associated with increased liver enzymes in individuals co-infected with viral hepatitis, particularly hepatitis B. Interestingly, people taking a protease inhibitor had decreased liver enzyme levels overall. Sadly, the researchers also found that patients with hepatitis C were prescribed antiretrovirals less often than those who weren’t co-infected, even when CD4 count, viral load, liver enzyme levels and other factors between the two groups were similar.

Some studies contradict findings of NNRTI liver damage. One of the most interesting, published in JAIDS in April 2002, comes from the New York University School of Medicine. Researchers looked for liver toxicity in 272 patients – almost all men – who were on combinations that included an NNRTI. Only three patients experienced severe liver toxicity. There were no significant changes in liver enzymes in patients taking Viramune compared to those taking Sustiva or Rescriptor. Although co-infection rates were relatively low in this group (12% had hepatitis C and 9% had hepatitis B), co-infection was not associated with a significant increase in liver enzymes.

Much of these data might tempt you to steer clear of this class of drugs altogether, but the NNRTIs, particularly Viramune and Sustiva, are extremely useful to many people as part of combinations that successfully lower viral load, keep CD4 cells climbing, and help the immune system regain its strength. If you begin Viramune or Sustiva, have your liver enzyme levels checked before starting the drug and monitor liver function regularly. If symptoms of liver problems develop (fatigue, lack of appetite, weakness or nausea), call your doctor right away. The drug may need to be stopped and not restarted after symptoms clear.

Protease Inhibitors

Researchers at John Hopkins University sought to determine which antiretroviral drugs posed the greatest risk of liver toxicity and to establish the role of chronic hepatitis B or C infection in the development of liver toxicity. As part of their study, they followed 211 people who received protease inhibitor (PI)-based combinations between January 1996 and January 1998. Over half of the patients were co-infected with hepatitis C. Less than 3% had chronic hepatitis B. Severe liver toxicity occurred in about 10% of the participants. The highest incidence was observed in people on Norvir (ritonavir), which was associated with 48% of all cases of severe hepatotoxicity. There were no significant differences in liver damage incidence in the other treatment groups. Again, most co-infected participants (88%) didn’t experience severe liver damage, which led the authors to conclude that, although co-infection is certainly a risk factor, PIs should not be withheld from people who are co-infected.

The higher likelihood of developing liver damage while on Norvir was confirmed in a study published in JAIDS in January. The cleverly named LIVERHAART Group determined the frequency of liver toxicity in 1,325 people in Italy, more than half of whom were co-infected with chronic hepatitis B, C or both. After six months on PI-based regimens, 11% (147 patients) experienced some degree of hepatotoxicity. The liver damage was mild in almost 8% of the patients and severe in just over 3%. The percentages were about the same even after one and two years on treatment. Only thirty
Keeping Your Liver Healthy

The liver is the largest internal organ and is responsible for some 500 bodily functions. It processes almost everything we ingest, breathe, or absorb through the skin. It plays an important role in digestion and metabolism, regulating the production, storage, and release of sugar, fats, and cholesterol. The liver produces a variety of important proteins, including enzymes, hormones, blood proteins, clotting factors, and immune factors. Finally, the liver plays a role in detoxification. It filters infectious organisms, alcohol, heavy metals, drugs, and other poisons from the blood, and also processes and eliminates toxic byproducts of normal metabolism.

Liver Damage
Because the liver performs so many vital functions, liver damage can impact almost all body systems. As the liver sustains damage, normal tissue can become fibrous (fibrosis), fatty (steatosis), and scarred (cirrhosis). Symptoms of liver disease may include fatigue, loss of appetite, nausea, vomiting, abdominal pain, and jaundice (yellowing of the skin and whites of the eyes). When the liver becomes too heavily damaged, it can no longer carry out its normal functions, a condition known as decompensated cirrhosis. Scar tissue may block the normal flow of blood through the liver, causing stretched and weakened blood vessels in the esophagus and stomach and internal bleeding. Reduced production of blood proteins may lead to fluid accumulation in the abdomen and easy bleeding or bruising. Inability to process metabolic byproducts may lead to a buildup of bilirubin, causing jaundice, and other poisons from the blood, and also processes and eliminates toxic byproducts of normal metabolism.

Liver Monitoring
If you have hepatitis, you should be monitored regularly to determine the extent of liver damage, whether treatment is indicated, and how well treatment is working. Regular liver function tests are also important if you are taking antiretroviral regimens for HIV in order to detect liver damage that may occur as a side effect of many drugs.

Liver damage may be indicated by high levels of liver enzymes including alanine transaminase (ALT, normal level 0-48 IU/L), aspartate transaminase (AST, normal level 0-42 IU/L), alkaline phosphatase (AP, normal level 35-125 IU/L), and gamma-glutamyl transpeptidase (GGT, normal level 30-60 IU/L). Other liver function tests include bilirubin (normal level 0-1.3 mg), albumin (normal level 3.2-5.0 g), and prothrombin time (a measure of blood clotting). Abnormal liver function tests do not always indicate liver damage. You could have high liver enzyme levels but little or no liver damage, or normal liver enzyme levels despite serious damage. A liver biopsy is a better tool for determining the extent of liver damage. A high level of alphafetoprotein (AFP) may – but does not always – indicate the presence of hepatocellular carcinoma (HCC), a type of liver cancer that occurs more often in people with cirrhosis. If you are being treated for hepatitis B or C – or HIV – your blood cell count should be monitored regularly, since low counts can be a side effect of many drugs.

Maintaining Liver Health
Whether or not you have existing liver diseases, you can take several steps to keep your liver healthy. These include getting regular medical care; avoiding alcohol, recreational drugs, and toxic substances; eating a healthy diet; engaging in moderate exercise; and taking measures to manage stress and fatigue.

Alcohol, Drugs, and Toxins
Heavy alcohol consumption can cause liver damage on its own, and is known to speed up liver disease progression in people with hepatitis B or C. It is not yet known whether light or moderate alcohol consumption is harmful to the liver. Many experts recommend that if you have hepatitis – and especially cirrhosis – you should not drink alcohol at all.

Certain prescription and over-the-counter medications, recreational drugs, herbal remedies, and vitamin and mineral supplements can be toxic to the liver (hepatotoxic), especially when taken in high doses or used in combination. Drug toxicity is more likely if you have existing liver disease. A damaged liver may have more difficulty processing medications, potentially leading to more serious drug side effects. Several anti-HIV drugs – in particular some of the protease inhibitors and non-nucleosides – are associated with increased liver enzyme levels and other signs of liver toxicity. Be sure to tell your healthcare providers about all drugs, herbs, and supplements you are using so they can be on the lookout for possible drug interactions.

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Hepatitis C & Co-infection: An Overview

As more people with HIV are living longer, co-infection with hepatitis C virus (HCV) has emerged as a significant concern. Serious illness and death from hepatitis C-related liver disease are increasing in HIV-positive people. In the United States, about one-third of people with HIV are co-infected with HCV; the rates vary by area because up to 90% of people who get HIV through injection drug use are also infected with HCV.

Before the hepatitis C virus was identified in 1988, doctors knew that some people had a type of viral hepatitis that they called non-A, non-B (NANB). Initially, NANB hepatitis wasn’t considered a serious health concern, but after many years, some people with NANB hepatitis began to develop serious liver problems. A small RNA virus – hepatitis C – turned out to be the culprit in most cases.

Transmission

HCV is transmitted by direct blood-to-blood contact. In other words, transmission happens when the blood from an infected person’s body directly enters another person’s body. HCV is tiny and can live in blood for weeks outside of the body. Most new infections are from the use of shared injection equipment – cookers, cotton, water and syringes. As many as 90% of people who have ever shared injection drug equipment are infected with HCV.

Since July of 1992, the U.S. blood supply has been screened for HCV, but anyone who received a blood transfusion or used blood products such as clotting factor before that time may have been infected with HCV.

Sexual transmission of HCV, though rare, is possible. Unprotected sexual acts that involve blood can increase the risk of HCV infection.

The risk of mother-to-child transmission of HCV during labor and delivery is about 6%, although the risk can be as high as 25% if the mother also has HIV.

Sharing tattooing needles and inkwells, unsterilized piercing equipment, and, less commonly, straws used to sniff drugs and personal care implements such as toothbrushes, manicuring equipment, and razors can result in HCV infection.

Health care workers who have had occupational exposure to blood are at risk for HCV.

Acute HCV Infection

Only about three out of ten people have symptoms immediately after infection. These symptoms can include:

- Pain in the right upper belly,
- Dark urine and pale feces,
- Jaundice (yellowing of the skin, the whites of the eyes and under the nails),
- Depression, and/or
- Flu-like symptoms such as fever, stiff or achy joints, nausea and loss of appetite leading to weight loss, headaches and fatigue.

About one out of seven people has a strong immune response that clears the infection two to six weeks after infection. Unfortunately, clearing the virus doesn’t make you immune to HCV re-infection. If the infection clears, the antibodies to HCV remain in your blood, but the actual virus doesn’t. It may be harder for HIV-positive people to clear HCV infection because the immune system isn’t as strong.

Antibody Testing & Viral Load

In 1999, HCV was categorized as an opportunistic infection because of the potentially serious health consequences of living with two chronic viral infections. Due to the overlap in modes of transmission between the two viruses, it is recommended that people with HIV undergo HCV antibody testing. Most people who have been infected with HCV will develop antibodies within three months. If your antibody test is positive, a viral load test can diagnose current HCV infection.

Chronic HCV Infection

HCV usually progresses very slowly, so a person might not develop any serious liver damage until 10 to 50 years after infection – if they’re going to develop serious damage at all. Most of our information about HCV disease progression comes from studies of people without HIV. Based on those studies, about 25 out of 100 of people with HCV will never have any symptoms or liver problems. Forty to 50 will experience some symptoms and liver damage (mild liver scarring called fibrosis) that will affect their quality of life, the most common symptoms being fatigue and depression. About 20 out of 100 will develop serious liver scarring (cirrhosis), and only 1% to 4% of people with cirrhosis will eventually develop liver cancer. At most, that’s one person out of 100.

Qualitative viral load testing can confirm whether virus is present in a blood sample. The test will find virus if there’s more than 50 to 60 copies in the sample, but it can’t tell you the amount of virus in your blood. A quantitative viral load test does measure the amount of virus in a blood sample (the test can find any amount above 600 copies per ml). Qualitative testing is usually used to confirm or rule out chronic HCV infection because it’s cheaper and more sensitive. HCV viral load will show up two weeks to six months after infection. If your qualitative viral load test doesn’t find any virus, re-testing six months later is recommended to confirm or rule out current HCV infection. If the second viral load test still doesn’t detect any HCV, either the antibody test result was a false positive or the initial infection may have cleared.

If the HCV antibody test is negative, many medical providers recommend HCV viral load testing – either qualitative or quantitative – as a follow up for people whose immune systems are weak and/or have symptoms of liver disease (persistently high liver enzymes, fatigue or liver pain). A damaged immune system may just be too worn out to make antibodies.

Does HIV Make HCV Worse?

HCV disease may progress more rapidly in people with HIV. Studies conducted prior to the use of HAART (Highly Active AntiRetroviral Therapy) showed that HIV could speed up HCV disease (continued on page 8)
Fumbling Towards Health

In the fall of 1987, at the age of 25, I went to be tested for HIV. In the elasticized lengthening of time between then and Halloween when I would get my results, I had convinced myself that my test would come back negative and that I would get on with my life. I was unprepared to hear the words that I was HIV-positive and reacted with a sort of disassociative dance, as if I were watching all this from outside, shocked but disconnected. After a couple of cathartic phone calls to people close to me, I retreated into a certain level of denial and went three and a half years before seeking medical attention for HIV.

One direct message I finally heard was that if you had less than 200 CD4 cells, you should go on prophylaxis against PCP so as not to die a needless death. In the Spring of 1991, I finally saw a doctor who ran a series of tests. I found out that I was hepatitis B surface antibody positive, core antibody negative, meaning that I was exposed to HBV at some time in the past, but had controlled it. I was also positive for something called non-A, non-B hepatitis, which would later be recharacterized as hepatitis C. Whatever: A disease without a name. I chose to ignore it. My CD4 cells came back in the mid-300s.

A year later, I began a series of monotherapies, expanding in 1994 to dual therapy, and then in early 1996 to triple therapy. Each of these regimens usually followed the same pattern - a rise and then subsequent fall in CD4 cells. When viral load became more widely available, it was clear I wasn’t reaching anything approaching maximum viral suppression. In the summer of 1996, when the virtual cure was announced at the International AIDS Conference in Vancouver, I was virologically failing my second protease inhibitor-containing regimen.

I took two six-month long structured treatment interruptions hoping that in the absence of selective pressure provided by antiretrovirals, my HIV might revert to wild type and subsequently respond to medicine. After the second STI, in January of 2001, I started a new regimen. My viral load plummeted and after a few months was just over 200 copies. But I felt really wiped out. The reason for my fatigue was later be recharacterized as hepatitis C. Whatever: A disease without a name. I chose to ignore it. My CD4 cells came back in the mid-300s.

Within a little more than a month, my HIV was undetectable for the first time ever. But my CD4 cells kept falling to an all time low in January 2002 of 129. Even more frustrating, though, my fatigue was really taking over. I was sleeping most of the time, and had become unpredictably bitchy - easily upset and angry out of all proportion to things that ticked me off. My poor boss! I decided that even though the study wanted me to take interferon for a year, my quality of life had fallen so low, I would discontinue at 24 weeks, since participation in any clinical trial is always voluntary. I told the study coordinator that I was willing to be followed, but not to stay on HCV treatment. Within 12 weeks, my HCV returned to detectable levels, but my liver enzymes have only come back to twice the upper limit of normal and have remained steady for several months. My HIV remains undetectable, and my CD4 cells have roughly returned to baseline, in the 500s.

Most importantly, within two weeks of stopping the interferon, I felt much more like myself. I made the right decision for me, even though it didn’t lead to a sustained virologic response. Would I do alpha interferon again if I needed to? I’ll drive off that bridge when I come to it.

Jeff Gustavson is an HIV and HCV positive activist who lives and swims in San Francisco.
Hepatitis C & Co-infection (continued from page 6)

progression. But HAART’s boost to the immune system may help to slow down HCV-related liver damage.

Co-infected people usually have higher HCV viral loads than people with HCV alone, but much controversy remains about HCV disease progression in co-infection. Long-term follow-up is needed to help provide more answers about HIV’s role in HCV disease progression. Several other factors also play a role: alcohol consumption, general liver health before HCV and HIV infection, which infection you got first, age, overall immune health, access to care and the quality of care received, drug use, and use of HAART.

Does HCV Make HIV Worse?
A recent Swiss study showed that co-infected people had a higher risk of progression to AIDS and death despite the use of HAART, implying that HCV may be a co-factor in HIV disease progression. Several studies have shown that co-infected people do not gain as many CD4 cells after beginning HIV treatment compared to those with HIV alone. A Spanish study, for example, found that after two years of HAART, co-infected people gained an average of 53 CD4 cells, while those with HIV alone gained an average of 111 CD4 cells. A study at Johns Hopkins followed a group of co-infected people from January of 1996 until June 2000 and saw similar results. In addition, the Hopkins study found that co-infected people with CD4 cell counts between 50 and 200 progressed to death more quickly than those with HIV alone. However, other studies of co-infected people have not seen a difference in survival rates. Since so many factors can contribute to both HIV and HCV disease progression, further research is needed to confirm whether HCV does make HIV disease worse.

Monitoring HCV
Statistics about the chance of developing liver damage from HCV can’t give you specific information about your individual HCV disease progression. There are several tests available that provide information about the condition of your liver. While these tests aren’t a crystal ball, the results can help you recognize changes over time and make treatment decisions.

Many people are used to looking at an HIV viral load test as a predictor of disease progression. HCV viral load testing won’t provide this information. The amount of virus in your blood can’t predict how much liver damage HCV has caused or the likelihood of liver damage in the future. An average HCV viral load ranges between two and five million copies – much higher than in HIV. This can be scary if you’re used to seeing much lower viral load results and associating them with changes in your health. HCV viral load testing is primarily used before and during treatment to determine how likely you are to respond or are responding to HCV medications.

Liver Function Testing
Our liver cells die periodically and are replaced with new ones. When liver cells are damaged or dying, liver enzymes (called AST and ALT) seep into the bloodstream. Liver enzyme levels can be higher than normal for many reasons. This is often a sign that the liver is working hard to break down HIV medications, alcohol, street drugs or other medications. Enzyme levels often go up and down with HCV, and if your liver is damaged, it may be too worn out to make them. Although liver enzyme testing can’t predict HCV disease progression, it’s a useful tool; it can help you measure your response to HCV treatment and/or changes in your diet and use of alternative or complementary therapies. (See “Keeping Your Liver Healthy” on page 5 for a discussion of other important measurements of liver function.)

Genotypic Testing
Genotypic testing looks at the genetic makeup of an individual’s virus. It identifies which type of HCV you have. There are at least six different HCV genotypes. Genotype 1 is the most common in the United States – about 75% of people with HCV in the U.S. have genotype 1. Genotype doesn’t predict disease progression, but it is the single most important predictor of your response to HCV treatment. Genotypes 2 and 3 respond much better to treatment than genotype 1. Some people with genotypes 2 and 3 may need only six months of HCV treatment, although some medical providers recommend that people with co-infection complete a year of HCV treatment regardless of genotype.

Other Predictors of Treatment Response
Besides your HCV genotype, your immune health may influence your response to HCV treatment. The higher your CD4 cell count, the better your response to HCV treatment is likely to be. HCV treatment is not as effective in people with less than 200 CD4 cells. The condition of your liver can also impact response to HCV treatment. People without cirrhosis tend to have better responses to treatment, although HCV treatment can prevent cirrhosis from worsening. An HCV viral load under 2 million copies and lower body weight or body mass index are also associated with better response to treatment. In addition, people under 40, especially women, have a better response to treatment.

Ultrasound & Biopsy
Ultrasound testing uses sound waves to get a picture of the liver. The test is not invasive, but the information it provides about the condition of your liver is limited.

Liver biopsy, an outpatient procedure, is the most accurate way to identify the extent and cause(s) of liver damage. A needle is inserted quickly through the abdomen, under the ribs on your right side, and a very small liver tissue sample is removed. An ultrasound can be used to guide the biopsy to areas where liver damage is present and to lower the already small risk of puncturing other organs. Liver biopsy can be painful. If you’re concerned, ask your doctor about pain management options. In rare cases (less than 1%), a biopsy can cause internal bleeding or death. Results from a liver biopsy are graded between 0 (no fibrosis or inflammation) and 4 (serious scarring that impairs liver function).
Treatment: Interferon & Ribavirin

Currently, the standard of care for HCV is a combination of two drugs: interferon and ribavirin. Interferon, a protein made in small amounts by the body, literally interferes with a virus’s ability to infect cells. HCV therapy uses much larger amounts of synthetic interferon than the body naturally produces. Standard interferon is given as an injection three times a week. Early last year, a new formulation of the drug called pegylated interferon was approved by the Food and Drug Administration. Pegylation is a process that attaches a small molecule to interferon to maintain steady levels in the body for a longer period of time. Pegylated interferon is injected once a week.

Ribavirin capsules are taken twice a day. Like several anti-HIV drugs, ribavirin is a nucleoside analogue, although it has no effect against HIV. Adding ribavirin to interferon produces much better results than interferon alone. Dosing of either or both drugs may need to be adjusted during treatment to help manage side effects. It may be best to try to treat side effects before lowering the dose of either interferon or ribavirin – if the dose is too low, the treatment won’t be as effective. (See sidebar below)

Side effects are different for each person who uses a drug. Both versions of interferon can cause side effects that range from uncomfortable to life threatening. These include flu-like symptoms such as weight loss and fatigue as well as mild hair loss, thyroid problems and low white blood cells and platelets. Interferon can also produce a rapid heartbeat and, in rare cases, heart attacks. Interferon can also cause sleeplessness, mood swings, irritability, and depression – sometimes resulting in suicidal thoughts or even attempts. Side effects of ribavirin include shortness of breath, stuffy nose, sinusitis, coughing, itchiness, diarrhea and anemia. There may also be a risk of mitochondrial toxicity (damage to the power plants of cells) if ribavirin is used with other nucleoside analogues. In rare cases, this could lead to a very serious condition called lactic acidosis. (see article on page 1)

Both interferon and ribavirin can cause serious birth defects. Men and women must wait six months after completing treatment before trying to conceive a child.

Currently, there’s one brand of pegylated interferon available, Schering-Plough’s PEG-Intron. Hopefully, within a year, the Food and Drug Administration will approve Hoffman-LaRoche’s brand of pegylated interferon, Pegasys. Some states’ Medicaid and AIDS Drug Assistance Programs (ADAPs) cover standard interferon and/or pegylated interferon. Schering-Plough offers a Peg-Intron patient assistance program for people who are uninsured and with low incomes. Hopefully, when Roche’s Pegasys is approved, it will also be available through a patient assistance program.

HCV Treatment: What It Can Do

There are different ways to measure how a person has responded to HCV treatment. Some differences in treatment response have been seen in co-infected people compared to people who are infected with HCV alone, while other studies have shown similar responses. Treatment usually lasts for one year, although continuing interferon therapy for 18 months is being studied as a possible way to halt or slow down liver damage and improve the condition of a person’s liver. Usually, treatment will be discontinued after six months if you continue to have a detectable HCV viral load because you’re extremely unlikely to clear the virus even if you continue treatment for a year. Recent studies show that viral load might be used earlier in the course of treatment to predict response. More definitive information about the best time to use HCV viral load testing as a predictor of response to treatment will be helpful to people who are making tough decisions about continuing treatment.

Sometimes HCV treatment is evaluated by measuring the amount of HCV in your blood after you’ve finished treatment. This is called an end of treatment response (ETR). Unfortunately, an ETR doesn’t mean that you’ll remain free of HCV. A sustained virologic response (SVR) — no detectable virus six months after finishing treatment — is a much more reliable indicator of long-term viral clearance. The likelihood of achieving a SVR after a year of HCV treatment with standard interferon plus ribavirin for mono-infected people with genotype 1 is about 28%. When pegylated interferon is used with ribavirin, SVR rates for mono-infected people with genotype 1 range from 30% to 50%. In mono-infected people with genotypes 2 and 3, after six months to one year of treatment with standard interferon and ribavirin, the SVR rate is about 60%, and the SVR rate rises to about 75% with pegylated interferon and ribavirin.

(continued on page 14)
The Other Hepatitis: The ABCs of HBV

Hepatitis B has been nothing short of a global-health catastrophe – approximately two billion people in the world today have, at some point in their lives, been infected with the hepatitis B virus (HBV). Of these, 400 million people have chronic hepatitis B, which remains the leading cause of liver cancer and kills more than one million people around the world each year. Closer to home, the U.S. Centers for Disease Control estimates that 80,000 people were infected with HBV in 1999 (the most recent available data) and that there are more than one million people living with chronic hepatitis B in the U.S., resulting in 5,000 deaths every year from cirrhosis of the liver and/or liver cancer.

The ultimate irony is that hepatitis B is a preventable disease. Vaccines are available and are more than 90% effective in preventing infection. While the number of new HBV infections has decreased in the United States and in other countries where the vaccine is available, there is still much work to be done to prevent what is now the ninth leading cause of death worldwide. At the same time, there is much more to learn about how best to manage and treat people who are infected with HBV, particularly those with chronic infection and those living with both hepatitis B and HIV.

Hepatitis B and Hepatitis C: Similarities and Differences

As discussed in this issue of ACRIA Update, hepatitis means inflammation of the liver – the most common cause being infection with one of five viruses: hepatitis A, B, C, D, or E. All of these viruses can cause short-term (acute) disease with symptoms lasting several weeks. Like the hepatitis C virus (HCV), HBV can also cause long-term (chronic) infection in which the patient never gets rid of the infection. If untreated, chronic HBV or HCV infection can be life-threatening, and the risk of serious liver problems is higher in people who are co-infected with HIV.

Technically speaking, HBV is quite different from HCV. HBV is a hepatitis virus, meaning that it contains DNA. It infects liver cells (hepatocytes) in both humans and animals (HBV is the only hepadnavirus to infect humans). While HCV also infects liver cells, it contains RNA and belongs to the flavivirus family, which includes a few viruses known to cause some unsavory tropical infections, most notably dengue and yellow fever.

HBV is also much easier to transmit than HCV. Whereas HCV is almost always spread through the exchange of blood (i.e., injection drug users who share equipment), HBV can spread through many of the same activities as HIV:

- unprotected sex (including oral sex);
- sharing of unsterile needles; from mothers to their babies either before or during delivery; accidental puncture from contaminated needles, broken glass, or other sharps; contact between broken or damaged skin and infected body fluids.

HBV and HCV also differ in the ways they cause liver disease. HCV is a cytopathic virus, which means that it causes direct damage to liver cells. HBV, on the other hand, is a noncytopathic virus, meaning that it does not permanently damage the liver cells it infects. Ironically, it is the immune system, not the HBV itself, that ends up damaging the liver in its efforts to clear the virus from the body.

Chronic hepatitis B is also faster in its progression than chronic hepatitis C. In people with chronic HCV infection, it can take up to 20 years for cirrhosis of the liver to occur and more than 30 years for even more serious complications to develop, such as liver cancer. In people with chronic HBV infection, cirrhosis can occur in as few as four to five years, with a significant risk of cancer occurring within ten years after infection.

Acute Hepatitis B

After HBV enters the body, it can take six weeks for the acute phase of HBV infection to officially begin and for symptoms to develop. However, HBV does not affect all people in the same way. Approximately 70% of people do not experience any noticeable symptoms of infection. Of the remaining 30%, most experience typical symptoms of hepatitis, which usually last a few weeks but can sometimes take more than a year to subside completely. A very small percentage (0.1% to 0.5%) of people with HBV develop severe (fulminant) hepatitis, which can lead to serious illness and death if not treated immediately.

Among the typical symptoms of acute HBV infection are fatigue, appetite loss, nausea, vomiting, joint and muscle pain, itchy skin, headache, swollen lymph nodes, sensitivity to light, sore throat and a runny nose. Acute HBV can also result in a rash on the face, buttocks, and limbs. After a few weeks of these symptoms, jaundice can occur – a yellowing of the skin and the whites of the eyes. Urine may also become dark and stools can appear pale. If these symptoms occur, they usually last for at least four to eight weeks.

Complete recovery from acute hepatitis B infection depends on the ability of the immune system to control the virus. If it is successful, HBV antigens – proteins produced by the virus, such as HBsAg and HBeAg – eventually become undetectable in the bloodstream and are replaced by specific antibodies produced by the immune system: anti-HBs and anti-HBe. Once these antibodies appear, the virus can no longer be detected in the

“Ironically, it is the immune system, not the HBV itself, that ends up damaging the liver in its efforts to clear the virus from the body.”
body and the liver eventually normalizes. (Note: A third antigen, HbcAg [the “core” antigen], can only be detected in liver cells and always results in the production of anti-HBc core antibodies, which are detectable in the blood.)

**Chronic hepatitis B**

Most adults with healthy immune systems are capable of clearing the HBV virus within six months after the infection first establishes itself. There are, however, the unfortunate few who simply aren’t able to mount the immune response needed to eliminate the infection – approximately 5% of healthy adults who are infected with the virus go on to experience chronic hepatitis B. In children and individuals with compromised immune systems – such as the elderly and HIV-positive people – chronic infection rates are much higher. More than 90% of babies infected with the virus at birth, because their mothers had HBV, go on to develop chronic hepatitis B. Children who are infected with the virus between the ages of one and five have a 25% to 50% chance of developing chronic hepatitis B.

So what is chronic hepatitis B? For diagnostic purposes, chronic hepatitis B simply means that HBsAg – the HBV surface antigen – has overstayed its welcome, lingering in the bloodstream for longer than six months after infection. This indicates that the virus is still present in the liver. Most people with chronic hepatitis B also have detectable amounts of the HBeAg antigen in their blood, which often means that HBV is not only present, but actively reproducing in liver cells. This can spell trouble on two levels. First, active HBV replication can provoke the immune system to cause greater damage to the liver in its efforts to keep hepatitis B viral load in check. Second, it means that the person harboring the virus is extremely infectious and can easily transmit the virus to others.

As mentioned above, it is the immune system – not the virus itself – that causes inflammation of the liver. Simply put, the immune system recognizes the virus as foreign and will attempt to do everything in its power to rid the body of the infection. This results in “flares” of the immune system – brief periods of intense immune activity to prevent HBV from reproducing and to kill liver cells that have either been infected or damaged by the virus. A person with chronic hepatitis B often has between two and four flares a year, which usually last several days to a few weeks. These flares are often effective against the virus, resulting over time in the loss of the HBeAg antigen and the gain of the anti-HBe antibody. However, it can take many flares over the course of several years for this crucial antigen-to-antibody shift to occur. It is during these flares that the immune system causes the greatest amount of damage to the liver.

Most people with chronic hepatitis B infection have no symptoms in the early stages. The most common early symptoms include fatigue and right upper abdominal discomfort. Occasionally, during flares, there may be symptoms similar to those seen during acute hepatitis B. People who have developed cirrhosis are more likely to have symptoms. As liver disease progresses, complications of cirrhosis and liver failure may occur, including jaundice, ascites (accumulation of fluid in the abdomen), variceal bleeding (bleeding from blood vessels in the esophagus, stomach, or intestines), leg edema, and encephalopathy (mental confusion due to the accumulation of toxic metabolic products that cannot be cleared by the liver).

It’s estimated that 20% to 35% of patients with chronic hepatitis B will go on to develop cirrhosis of the liver. However, the most accurate way to interpret the risk of cirrhosis is on an annual basis. According to one Italian study, for every year that the HBeAg antigen remains positive in the bloodstream, there is a 6% chance of developing cirrhosis (rates in other studies have varied from 2% to 12%). In other words, after five years of chronic hepatitis B infection, provided that HBeAg remains positive, the risk of developing cirrhosis would be approximately 30%. After ten years, the risk would increase to 60%, and so on.

(continued on next page)
Liver cancer, technically called hepatocellular carcinoma, is more likely to occur in men with chronic HBV infection (as opposed to women) and develops in approximately 25% of all patients with cirrhosis. But liver cancer can also occur in patients with chronic hepatitis B who don’t develop cirrhosis. In one study conducted in Asia, approximately 15% of patients with chronic hepatitis B without cirrhosis went on to develop liver cancer. And in a study conducted in Africa, roughly 40% of noncirrhotic chronic hepatitis B patients developed liver cancer, usually within one or two decades of becoming infected with the virus.

The HIV Question
Until recently, there has been little information – and very little research – regarding the effects and treatment of HBV in HIV-positive people. This should come as no surprise, given that HIV-associated deaths were most commonly tied to “classic” AIDS-related complications rather than chronic HBV disease. Thus, for many years chronic hepatitis B was of little concern. But with the significant survival gains ushered in by combination antiretroviral therapy, fewer HIV-positive people are dying of typical AIDS diseases, such as MAC or PCP. Many are now living long enough to see their slow-brewing liver disease become a major health concern.

Although only a small percentage of otherwise healthy adults infected with HBV go on to experience chronic hepatitis B, this is not the case in HIV-positive adults: roughly 25% of HIV/HBV-co-infected patients develop chronic infection. What’s more, a number of reports have suggested that as HIV disease progresses, the immune response to HBV gradually decreases or is sometimes lost. Some patients experience a relapse of infection, marked by the loss of anti-HBs and the return of HBsAg positivity. Other co-infected patients experience gradual declines in anti-HBs activity, sometimes at the expense of increased hepatitis B viral load and HBsAg levels.

It is not entirely understood what impact HIV has on the severity of chronic HBV infection. There have been a number of reports demonstrating that patients infected with both viruses have higher HBV viral loads and more cirrhosis, regardless of immune system status. There are also data from studies suggesting that HIV-positive people with chronic hepatitis B are more than twice as likely as their HIV-negative counterparts to experience liver failure, thus requiring a liver transplant – a life-saving treatment option that is not without controversy (see article on page 18).

Treating Chronic Hepatitis B
While it is usually not necessary to treat acute hepatitis B – taking it easy and avoiding alcohol remain the best possible remedies – it is often necessary for patients with chronic hepatitis B to consider treatment.

It’s safe to say that neither of the currently available treatments for chronic HBV infection – interferon-alpha (Intron A) and lamivudine (Epivir-HBV) – are perfect. Interferon-alpha has been approved for more than a decade. At doses of 5 million units (MU) every day or 10 MU three times a week for six months – doses that are much higher than those used to treat chronic hepatitis C – using interferon alone is associated with HBeAg clearance in up to 40% of otherwise healthy HIV-negative patients and HBsAg clearance in up to 15% of patients. However, the drug is associated with significant side effects including fever, muscle aches, thyroid problems, bone marrow damage, and a litany of psychiatric symptoms. What’s more, the drug must be used cautiously in patients with cirrhosis, as it may heighten the immune response to the virus and lead to severe liver damage. For patients co-infected with HIV and HBV, interferon has been disappointing. Many do not respond to therapy and, given the increased risk of side effects in this group of patients, interferon is a less-than-ideal choice. (Pegylated interferon, an approved treatment for chronic hepatitis C, has not yet been studied for the treatment of chronic hepatitis B.)

GlaxoSmithKline’s lamivudine (Epivir), first approved for the treatment of HIV in the mid-1990s, was awarded a second FDA approval for the treatment of chronic HBV infection in December 1998. The dose of lamivudine typically used to treat chronic HBV is 100 mg once a day, compared to the 150 mg twice a day schedule used for HIV.

Unlike interferon, lamivudine has no direct effect on the immune response to HBV. It does, however, have a profound impact on HBV viral load and, in three randomized phase III studies, was associated with a loss of HBeAg after a year of therapy in 17% to 33% of chronically infected patients. Moreover, progression of cirrhosis decreased in all patients who received lamivudine.

Given that lamivudine has far fewer side effects than interferon, healthcare providers have come to depend heavily on this drug. But it’s important to use it cautiously. If the drug is stopped abruptly or not taken correctly, HBV viral load can rebound and cause a flare of the immune system. This can cause a person with chronic hepatitis B to become ill and, as discussed above, may result in liver damage.

As in HIV, HBV resistance to lamivudine can and does occur. Used as monotherapy, approximately 40% of people taking lamivudine develop HBV resistance to the drug within one year. After four years of lamivudine use, approximately 70% have HBV strains resistant to the drug. While these findings suggest that lamivudine monotherapy is somewhat limited, they also suggest that HBV resistance to lamivudine develops much more slowly than it does with HIV. And even when HBV resistance to lamivudine does occur, the drug still appears to be helpful in keeping HBV viral load low and in slowing the progression of liver disease.

The threats of flares and lamivudine resistance are particularly important for HIV-positive people to consider. When the time comes to use lamivudine to treat both HIV and HBV, it is necessary for patients with chronic hepatitis B and their healthcare providers to remember both viruses when making treatment decisions. For example, if a drug-resistance test shows that lamivudine is no longer working against HIV – which would usually prompt someone to switch the drug – it may be useful to continue using lamivudine to treat chronic hepatitis B. Stopping the drug early may not only result in a...
flame, but could prematurely end lamivudine’s anti-HBV benefits.

**The Hope of Combination Therapy**

Researchers evaluating treatments for chronic hepatitis B have learned a valuable lesson from those studying anti-HIV therapies: that combination therapy is likely the best approach, given the impact of drug resistance. Unfortunately, the results of two-drug anti-HBV combinations in clinical trials have been mixed. In one international trial combining lamivudine with interferon-alfa in chronically infected patients who had already attempted interferon monotherapy, those who received the dual regimen responded similarly to those who received lamivudine monotherapy. However, in two other studies, HbeAg seroconversions to anti-HBc after a year of treatment were much more common in patients receiving a combination of interferon-alfa and lamivudine (29%), compared to those receiving either interferon monotherapy (19%) or lamivudine monotherapy (18%).

The next step is to evaluate three-drug regimens in clinical trials. At the present time, however, this is something of a problem, given that only two drugs are currently approved for the treatment of chronic hepatitis B. New drugs must be developed and approved if three-drug regimens are to become feasible options. There are a number of drugs in various stages of development, including several nucleoside/nucleotide analogues that target HBV’s DNA polymerase protein, which is similar to HIV’s reverse transcriptase enzyme. Three of the nucleoside analogues furthest along in development are famciclovir (GlaxoSmithKline), which is already approved for the treatment of herpes, entecavir (Bristol-Myers Squibb), and emtricitabine (Triangle Pharmaceuticals). There is also adefovir dipivoxil (Gilead Sciences), the nucleotide analogue that did not pan out as a treatment for HIV, but is enjoying a good showing in clinical trials involving patients with chronic hepatitis B. Tenofovir dipivoxil, another nucleotide analogue from Gilead Sciences that is approved for the treatment of HIV, also has activity against HBV and is expected to enter clinical trials soon.

These new agents – and there are several more of them in earlier stages of development – are being studied as monotherapy and in various combinations, both with each other and with approved therapies (interferon-alfa and lamivudine). Unfortunately, it is still too early to tell how safe and effective anti-HBV regimens containing three (or more) drugs are for patients with chronic hepatitis B. Even if these drug combinations prove to be more effective than currently available options, the question remains of when to initiate treatment, and for how long, in order to achieve the best possible outcome with the fewest side effects possible. This is especially true for patients co-infected with both HIV and HBV who may face the daunting task of combining two different combinations of drugs – this could easily exceed six antiviral drugs being taken at one time – to effectively battle both viral infections. Thus, amid the hope of emerging options, there are numerous fundamental questions that have yet to be addressed.

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**Keeping Your Liver Healthy (continued from page 5)**

Because the liver processes toxins, it is important to avoid substances that may harm the liver. Avoid exposure to toxic liquids and fumes including solvents, paint thinners, and pesticides. It is necessary to use such chemicals, work in a well-ventilated area, cover your skin, and wear gloves and a protective face mask.

**Diet and Exercise**

A healthy, well-balanced diet is important for all people, with or without hepatitis or HIV disease. Such a diet is low in fat, cholesterol, and sodium, high in complex carbohydrates, and has adequate protein. Drinking enough fluid is also important – eight glasses of water per day is often suggested. Many experts recommend that people with liver damage avoid raw or undercooked shellfish (which may contain infectious organisms or toxins), processed or preserved foods (which may contain chemical additives), fruits and vegetables treated with pesticides, caffeine, and chocolate. High doses of vitamin A, vitamin D, iron, and niacin can be toxic to the liver. In some cases, people with advanced cirrhosis may be advised to limit their consumption of protein. Many people with hepatitis – as well as those with HIV disease – experience loss of appetite, nausea, vomiting, and diarrhea, sometimes as side effects of drugs. It may be helpful to eat small, frequent meals or snacks rather than three large meals each day, and to avoid spicy or fatty foods.

Regular aerobic exercise can improve overall fitness and may help reduce fatigue, stress, and depression. Most people with liver disease can safely engage in moderate exercise, but strenuous exercise may lead to a flare-up of symptoms. People with advanced cirrhosis should be cautious about exercising. If you have hepatitis or HIV disease, consult your healthcare provider before starting an exercise program.

**Alternative and Complementary Therapies**

In addition to pharmaceutical drugs, many people use alternative and complementary therapies for hepatitis. Some find that a combination of conventional and alternative modalities is more effective than any single type of treatment. Herbs often suggested for chronic hepatitis B or C include milk thistle (silymarin), licorice root (glycyrrhizin), bupleurum, phyllanthus, and schisandra. Herbal remedies should be treated like drugs, since they may have side effects and can interact with conventional medications. Many herbs can be toxic to the liver, including chaparral, germander, kava kava, pennyroyal oil, and plants that contain pyrrolizidine alkaloids. Nutritional supplements suggested for hepatitis include vitamin C, vitamin E, selenium, glutathione, N-acetyl-cysteine, alpha lipoic acid, bile acids, coenzyme Q10, lecithin, s-adenosylmethionine (SAM-e), and thymic factors. Some people report that acupuncture helps relieve their (continued on next page)
Keeping Your Liver Healthy (continued from previous page)

symptoms and improve their overall sense of well-being. Inform all your healthcare providers about any herbs, supplements, or other alternative therapies you are using.

Hepatitis A and B Vaccines
Hepatitis A and hepatitis B can be more severe in immunocompromised people and in people with existing liver damage. Most experts recommend that if you have HIV or hepatitis C, you should receive vaccines to prevent these diseases if you haven’t already had them. Today, children in the U.S. routinely receive the hepatitis B vaccine as infants or teenagers. A combination hepatitis A/hepatitis B vaccine is available. There is no vaccine for hepatitis C yet.

General Wellness
Living with a chronic disease can be stressful, and fatigue is a problem for many people with hepatitis or with HIV disease. Stress management, good time management, and measures to reduce fatigue can help improve your quality of life. Be aware of your limits and try not to overexert yourself. Alternate strenuous activities with more restful ones. Take naps as needed and get an adequate amount of sleep at night. Many people find it helpful to use a daily planner to make activity schedules. Meditation – a method of relaxation and clearing and focusing the mind – may also help reduce stress. Therapy with a psychologist or social worker may be beneficial, and peer support groups can offer a safe space to discuss emotional issues and develop strategies for coping with chronic illness.

While living with liver disease can be challenging, there are things you can do to keep your liver as healthy as possible. You and your healthcare providers can work as a team to keep your disease under control, manage your symptoms, and maximize your quality of life.

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Hepatitis C & Co-infection (continued from page 9)

Even if a person does not achieve an SVR, HCV treatment can improve the condition of the liver tissue by giving the liver a break. Improvements in liver tissue (histological response) can be measured by liver biopsy before and after treatment. People who reduce and maintain low liver enzymes after treatment may have gained benefit from treating HCV.

New Treatments For HCV
Although current HCV treatment options are severely limited, several new treatments are in development – drugs to reduce or slow fibrosis, drugs to boost the effect of ribavirin, a therapeutic vaccine, immunomodulators, HCV protease inhibitors and several new interferons, both standard and pegylated. Some of these are in very early stages of development; others are further along in the process. Hopefully, within the next three to five years, people will have more treatment options.

Which To Treat?
Many doctors would treat HCV first in someone with a CD4 count above 500. The rationale behind this is the higher likelihood of a good response to HCV treatment and the possibility of “wiping out” HCV, leaving your liver in better condition to deal with HIV medications, some of which can be hard on the liver.

Other doctors believe that if HIV infection is controlled with HAART, HCV will also remain controlled. Guidelines for when to start HIV treatment in co-infected people don’t exist yet. People with less than 200 CD4 cells are at greater risk of developing HCV-related cirrhosis, so keeping your immune system as healthy as possible is an important part of HCV care. Of course many people don’t find out that they have HIV until their CD4 cell counts are already low. Unless your liver has been seriously damaged by HCV, most doctors would try to boost the CD4 count above 200 before beginning HCV treatment. Interferon can cause a temporary drop in CD4 cells, which could put people with low counts at risk for developing certain opportunistic infections. A lower CD4 count may also add more preventive medications to your drug regimen, increasing the risk of drug interactions and possible stress on the liver.

Working with Medical Providers
Part of making the treatment decision is learning about your and your liver. Having a list of questions for any doctor you consult can help you select one that’s right for you involves collecting information. Although some HIV doctors may be knowledgeable about HCV, consulting a liver specialist – a gastroenterologist or hepatologist – can be very helpful. Different doctors have different philosophies about which tests are most important and about when to treat HCV (and HIV). Having a list of questions for any doctor you consult can help you.

If you’re working with more than one doctor, get copies of your lab results and medical records. Make them available to both doctors and do everything in your power to make them talk to each other!

Making Treatment Decisions
Without long-term follow up information on people with co-infection or treatment guidelines for co-infection, making treatment decisions can be confusing. A conference to revise the out-dated National Institutes of Health 1997 HCV treatment guidelines and add guidelines for co-infection took place in June. (A link to the guidelines can be found in this article at www.acria.org.) These guidelines will help you and your medical provider begin a discussion about the right treatment strategy for you, including how often you want to monitor your liver enzymes and HCV viral load, whether or not to have a liver biopsy, and all the potential risks and benefits of HCV treatment.

Tracy Swan, an HIV treatment activist, works at ACRIA as a treatment educator.
Hepatitis G: The Nice Virus?

Throughout the course of the AIDS epidemic, many co-factors have been investigated as possible causes of faster disease progression. But recent studies have suggested that there may be a co-factor that actually benefits people with HIV.

The hepatitis G virus (HGV, also known as GB virus C) is commonly found in people co-infected with HIV and hepatitis C. HGV, first identified in 1995, is a blood-borne virus that doesn’t seem to cause liver disease or have any effect on hepatitis C, although its long-term effects are unknown. But researchers soon began noticing the effect of HGV on HIV infection.

A study from Japan published in 1998 found that HIV-positive people with hemophilia who were also HGV-positive had slower HIV disease progression than those who were HGV-negative, although the results were not statistically significant. Another 1998 study from England found that people with HIV were less likely to clear HGV than those who were HIV-negative, but did not look at the effect of HGV on HIV infection. Then, a study published in 1999 found slower HIV disease progression in 23 people who were also HGV-positive compared to those who were HGV-negative. A study from Japan published in 2000 found that HGV infection benefited people with HIV – for people with hemophilia and HIV, the risk of progression to AIDS was 40% lower if they were also HGV-positive, regardless of age, viral load, CD4 count or CCR5 genotype.

Last September, two studies published in The New England Journal of Medicine received considerable attention. The first study, from Iowa City, followed 362 people with HIV from 1993 to 2000. Among the 17% who tested positive for HGV, survival was significantly longer, even in those on HAART. The researchers also found slower progression to AIDS, higher CD4 counts and lower HIV viral loads in people co-infected with HGV. More surprisingly, those with higher HGV viral loads had lower HIV viral loads, although a higher HGV viral load was not associated with higher CD4 counts.

The second study, from Germany, followed 197 people with HIV from 1993 to 2000. Among the 17% who tested positive for HGV, survival was significantly longer, even in those on HAART. The researchers also found slower progression to AIDS, higher CD4 counts and lower HIV viral loads in people co-infected with HGV. More surprisingly, those with higher HGV viral loads had lower HIV viral loads, although a higher HGV viral load was not associated with higher CD4 counts.

A study presented at February’s Conference on Retroviruses and Opportunistic Infections looked at the disease history of 80 asymptomatic injection drug users with HIV from 1989 to 1997. Seventeen people were positive for HGV, and were comparable to those without HGV in terms of HIV viral load, CD4 count, years since HIV infection, and time on antiretrovirals. But at the end of follow-up, those with HGV had a better AIDS-free survival rate, lower viral loads and higher CD4 counts than those who were HGV-negative. The most striking finding was that 73% of the HGV-positive group had viral loads below 400, compared to only 39% of the HGV-negative group.

More importantly, this study proposed a new theory as to how HGV infection might slow HIV disease progression. It found that Th1 cytokines (IL-2 and IL-12) remained stable only in the HGV-positive group, and that Th2 cytokines (IL-4 and IL-10) rose only in the HGV-negative group. The authors suggest that HGV may interfere with the classic shift from a Th1 to Th2 pattern that is seen in many people with disease progression.

What does this mean for people with HIV? Nothing right now. No one is suggesting that anyone with HIV attempt infection with HGV, since the long-term effects of that infection are unknown. In addition, these studies only show an association between HGV infection and slower HIV disease progression – we don’t know if it’s actually HGV that is causing the slower progression or if there’s something else that people with HGV have in common. However, a German study that looked at receptor mutations known to slow HIV disease progression (CCR5, CCR2, and SDF1) found no differences between people with and without HGV, and concluded that HGV infection was an independent predictor of better survival and slower disease progression.

If HGV does slow HIV disease, we don’t know how it does this – is it acting as an antiviral or is it stimulating the immune system to better respond to HIV? The in vitro results would seem to indicate that HGV is somehow able to inhibit HIV replication, but more research is needed to find the answer. If we can find out exactly what, if anything, HGV infection does to people with HIV, it could lead to new treatment strategies and entirely new approaches to slowing HIV disease progression. Stay tuned.

Mark Milano is a longtime AIDS treatment activist and a treatment educator at ACRIA.
patients (2.3%) had to stop treatment because of liver toxicity.

All protease inhibitors used in the study increased liver enzymes, but not in everyone and not all to the same degree. In descending order, the following PIs or dual-PI combinations caused severe liver damage: Norvir 11.7%, Norvir plus Fortovase (saquinavir) 11.6%, Fortovase 3.7%, Crixivan (indinavir) 1.3%. Viracept (nelfinavir) 0%, and Norvir plus Crixivan 0% (only five patients were on this combination). Liver damage occurred most often in people co-infected with viral hepatitis. Of particular interest, people with hepatitis C who didn’t respond to antiretroviral therapy after a year on treatment had the highest rates of liver toxicity. The LIVERHAART Group’s data suggest that Norvir is more hepatotoxic than other PIs only during the first six months on treatment.

Results of other recent studies somewhat contradict the common belief that PIs cause liver damage. Researchers from Ottawa looked back at 66 HIV/HCV co-infected patients who were on single or dual-PI regimens and found that Norvir was as well tolerated by the liver as any other PI, whether used as the single PI or as one of two PIs in a combination. Eight of the 66 patients (12%) stopped treatment because of hepatotoxicity, but the rates were the same whether the patients were on Norvir or not. Another study of 692 HIV-positive individuals in Thailand who were on a variety of regimens showed that liver damage was rare in people who were on PI-based regimens, even when Norvir was used.

Liver Toxicity in the Adult AIDS Clinical Trials Group
To get a sense of how often antiretroviral-related liver toxicity occurs and which drugs or combinations may be most responsible, researchers from the National Institutes of Health looked back at the data on 10,611 participants in twenty-one adult AIDS Clinical Trials Group (ACTG) studies from 1991 to 2000. Because of the years covered, the various drugs and treatment strategies ran the gamut from NRTI monotherapy to combinations that included an NNRTI, a PI and two NRTIs. Overall, 662 (6.2%) of the patients experienced severe liver damage. Varying and somewhat surprising rates of liver damage occurred on all of the treatment regimens: 7.4% in people taking just one NRTI, 4.9% on dual-NRTI therapy; 8.2% on NNRTI-based triple therapy, and 5% on PI-based triple therapy. Of the people who experienced liver toxicity, just over one-quarter stopped their medications. Forty-two of the 10,611 trial participants died of liver failure, although whether these deaths were directly related to antiretroviral use or other factors such as viral hepatitis is unclear.

In Summary
These and other studies identify many factors that may increase the risk of antiretroviral liver toxicity: obesity, preexisting liver disease such as hepatitis B or C, age greater than 50, alcohol use, diabetes, and interactions between antiretrovirals, herbs, and over-the-counter and other prescription drugs. Several theories, possibly interrelated, have been proposed to explain the connections between antiretrovirals and liver problems:

- Mitochondrial toxicity related to the use of some NRTIs may lead to liver enlargement and/or fatty liver. Unless the drug is stopped, severe liver damage and liver failure is possible.
- NNRTIs, especially Viramune, can raise liver enzymes, possibly causing serious liver toxicity. This toxicity is often, though not always, accompanied by the hypersensitivity skin reaction experienced by up to 16% of people taking the drug. Careful monitoring of your liver enzymes while on any NNRTI, especially during the first three months, is important.
- Depending on the state of your liver, co-infection with hepatitis B or C may predispose you to further liver damage once antiretrovirals are introduced.
- Heavy alcohol use is toxic to the liver. A damaged liver may have trouble metabolizing antiretrovirals properly, which could lead to more severe liver injury – inflammation, high liver enzymes and, possibly, antiretroviral levels that are too low to do their job.
- Most medicinal products – pharmaceutical drugs, herbs, hormones, and over-the-counter medications – are partly or totally processed by the liver.
- Know what you’re taking and discuss them with your healthcare providers to avoid interactions and the possibility of liver toxicity.
- As the immune system restores itself, increases in CD4 cells can cause flare-ups of infections. Immune reconstitution syndrome, as it’s sometimes called, can particularly affect people co-infected with hepatitis C or, especially, hepatitis B, as new immune responses harm liver cells.

Numerous studies have shown varying rates of liver toxicity associated with antiretrovirals – individually, by class, and in combination. Exactly how antiretrovirals affect the liver still isn’t fully understood. More data are needed from controlled clinical trials to clarify which individual drugs and risk factors can contribute to liver toxicity in people with HIV. How often the liver damage is irreversible is also unclear, although most people who stop the drug that’s causing the problem see their liver enzymes return to normal levels.

There’s no doubt that combination therapy has prolonged the lives of thousands of people with HIV. In a small but significant number of people, the drugs used can also cause liver damage. Learning as much as you can, monitoring liver function regularly, being aware of potential symptoms, and, possibly, managing metabolic or other viral conditions before starting HIV treatment may be the best ways to avoid antiretroviral-associated liver problems.

Bertrand Toulouse is a Treatment Advocate at AIDS Project Los Angeles and has been involved in HIV treatment issues for six years.

James Learned is ACRIA’s Treatment Education Director and editor of ACRIA Update.
The Battle Between Fear & Freedom

When I was diagnosed HIV+ in 1990, my only thought was, “What do I need to do to stay alive?” The first and foremost thing I had to do was to free myself from my use of illegal drugs. That wasn’t easy for a person like myself who had been a substance user/abuser for most of my adult life. But I was able to move from every day, all day drug use to sobriety by way of a harm reduction technique – a methadone program.

Life was like new for me after joining the program. I began to see myself as alive and truly involved in life. I was able to keep up with my bills and still have some money to spend. I found myself setting goals, paying more attention to my eating habits (no longer living off of Little Debbie’s cakes and 25¢ water juices), and even playing paddle ball again. Everything seemed to be going great.

I even put at the back of my mind an arrest that I hadn’t answered up to. There’s an old saying: “If you play with fire, you must pay the price.” And pay I did. A knock on the door in May 1995 forced me back to reality. It was the warrant squad coming to get me. I felt as though my world just collapsed. Little did I know that this incarceration would enlighten me to a condition that I might not have known about until it was too late.

I was diagnosed with hepatitis C while I was in a correctional facility in upstate New York. I thought to myself, “My God, HIV and hepatitis C – what does all this mean?” I didn’t have a clue and I was scared to death. I had picked up a brochure in the medical office about the hepatitis B vaccine, so I asked the doctor about it. He told me that there were different hepatitis and there was nothing that he could give me for my hepatitis C. He said that I should just eat right and do some exercise. So that’s what I tried to do for the remainder of my stay.

Being incarcerated at the age of 51 took quite a toll on me. I didn’t think that I was going to make it home alive. But I did – and alive I want to stay. I could hardly wait to see an outside doctor and learn about my co-infection. Upon my release, I found a good doctor and established a working relationship with him. Monitoring my liver enzymes was a top priority, along with tracking my HIV viral load and CD4 counts. Sometimes my liver enzymes were a little high, but not high enough for me to even think about hepatitis C treatment. Things seemed to be going rather well, and I was feeling good once again.

For some of us it always seems to take a jolt back to reality to make us move forward. This time it was my good friend Juan, whose hepatitis C had progressed to end stage liver disease. As if it were yesterday, I remember the words he spoke to me when he knew that the end was near. “Please don’t do like I did and not pay attention to your liver. Please go to the doctor and find out where you’re at before it’s too late.” Six weeks later he died. On top of the incredible sense of loss I felt, I was scared to death.

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After awhile I found myself very busy, volunteering and being active in my community. I began to miss medical appointments. I was neglecting myself.

So now I monitor my liver enzymes on a regular basis, every two or three months. Sometimes they’re up a little and sometimes they’re not.

With so much talk about HIV medications and liver failure, I’m in a constant battle with myself – should I or should I not take my HIV meds? Sometimes I don’t know which way to go.

At the age of 62, my CD4 count has hovered below 200 ever since I had a bout with hepatitis A in 1997. (Why wasn’t I ever offered the hepatitis A vaccine?) But my HIV viral load is undetectable, so I waver between taking the meds and not taking them.

To add insult to injury, I recently had my gall bladder removed, and the surgeon who did my operation had a chance to take a close look at my liver. He informed me that my liver is very badly damaged. So I’ve made an appointment with a liver specialist to get more information and talk about my options. It’s time for me to take more control. I’m tired of being scared to death.

Joan Warner is the health educator at Osborne Association in the Bronx and a member of ACRIA’s Community Advisory Board.
Is Transplant An Option?

As more people with HIV live longer these days, liver disease is becoming a larger health threat than the usual opportunistic infections. In the emotionally charged world of organ transplantation, giving livers to HIV-positive people has been controversial.

Michelle Roland, MD, an Assistant Professor of Medicine in the UCSF Positive Health Program at San Francisco General Hospital, notes that before people with HIV began doing so much better, “it was felt that it didn’t make sense to take a very scarce resource and allocate that resource to a patient population that wasn’t likely to benefit from it for very long. As fewer people [in the U.S.] die from traditionally defined opportunistic infections, they’re developing the complications of hepatitis B and C, including end stage organ failure. There’s an increasing need to consider the safety and efficacy of organ transplants.”

Also, according to Dr. Roland, since HIV itself “is a disease of immunosuppression, there has been substantial concern that the post transplant immunosuppression might cause acceleration of HIV disease progression.” Nevertheless, some immunologists wonder if suppressing the generalized activation of the immune system might even be beneficial to people with HIV, although no study has yet shown this.

Dr. Roland sees many patients with end stage liver disease. She says, “Transplant is not the right option for a lot of people. It’s a very personal decision. They have to ask themselves, ‘Do I want to step into this high-tech medical intervention with all these potential complications and have the possibility of the end of my life being in an intensive care unit?’”

Another big question for transplants in HIV-positive people is how to pay. Some third party payers have declared that they need proof that transplants work for people with HIV, which is a Catch 22 – you can’t prove it if no transplants are done because no one will pay. A pilot study was started at UCSF called the Migden HIV Transplant Initiative when State Assemblywoman Carole Migden and AIDS activist Jeff Getty were able to secure a large California state appropriation. “At the same time,” Dr. Roland says, “we pulled together a group of transplant centers across the country to develop a common protocol to learn as much as we could as fast as we could while sharing clinical experiences along the way.” One goal of the study is to develop clinical practice guidelines. An investigator-initiated grant application was submitted to the National Institutes of Health. The expense of the clinical costs (not the surgical costs) will likely have to be borne by insurers or the patients themselves.

At the 9th Conference on Retroviruses and Opportunistic Infections in February, Dr. Roland presented data on 41 HIV-positive transplant recipients who would have been eligible for the UCSF protocol (no history of opportunistic infections and fully suppressed or suppressible virus). Half of them had received livers and the other half kidneys. Half of these patients had a follow up of at least 279 days and were compared with one-year survival data collected by the organization that monitors transplants. The HIV-positive recipients fared almost as well as people who were HIV-negative. HIV viral load remained relatively controlled and there were only two opportunistic infections. A 15-year-old boy had CMV esophagitis and hepatitis C recurrence with a relatively high T-cell count and died. Another recipient had Candida esophagitis that responded very quickly to treatment.

However, eight patients who did not meet the eligibility criteria for the protocol didn’t fare so well. There were two cases of PML and one case of MAC. This is the justification for the rather strict entry requirements for the study. Dr. Roland will give an update on how people are doing at the International AIDS Conference in Barcelona in July.

There are plans to open up the protocol gradually to people with a history of opportunistic infections and, possibly, detectable viral load, once safety and efficacy have been demonstrated in the more conservatively chosen patients.
New Directory of HIV Trials Available

ACRIA’s Spring 2002 edition of HIV/AIDS Clinical Trials: A Directory for New York State is now available for people living with HIV and their care providers. In addition to providing the most comprehensive listing available of enrolling HIV trials within the New York metropolitan area, the directory offers valuable information on the clinical trials process and patient assistance programs. Unfortunately, ACRIA’s AIDS Institute funding for this project only allows us to print 5,000 copies of the directory, almost all of which had been distributed by the end of May. However, copies should be available to the public at medical facilities and other agencies offering care to people with HIV throughout New York State. The publication can also be read in its entirety in PDF format on ACRIA’s web site and through a searchable online database at www.acria.org.

ResPAC Meeting for Behavioral Science Held

The Research Policy Advisory Committee for New York State (ResPAC) held its second group meeting on April 4th at amfAR’s offices – this time to discuss research priorities for HIV behavioral issues. Chief among the discussion was identifying studies that could bring about better prevention strategies for a variety of at-risk populations. Findings from this meeting, as well as those from the previous meeting on epidemiology research, will be available to the public on ACRIA’s web site later this year. ACRIA wants to particularly thank Beatrice Krauss, Executive Director of Hunter College’s Center on AIDS, Drugs and Community Health, for her leadership on this project as chair of the behavioral research group.

ACRIA Provides Technical Assistance in Detroit

ACRIA recently began an HIV treatment education technical assistance initiative in the Detroit area. Twenty-six non-medical service providers and community members, representing fourteen Michigan organizations, participated in a multi-day training conducted by ACRIA staff in January. We have continued to provide follow-up support to participants since, including a follow-up training in May, to help members of the Detroit community develop lasting HIV treatment education programs and incorporate community-based treatment education into the provision of social services.

Southeastern Michigan is one of four regions outside of New York State to participate in ACRIA’s national technical assistance program to date. We offer comprehensive, on-site training to help participants develop and expand the practical skills and treatment knowledge needed to educate and counsel people living with HIV. ACRIA has made a sustained commitment to each community to ensure that program participants receive ongoing support to become and remain effective HIV treatment educators. Thanks to a major grant from Ortho Biotech, ACRIA will be able to offer this service in two additional areas of the country during the next year.

This is looking for new COMMUNITY ADVISORY BOARD members.

ACRIA’s Community Advisory Board (CAB) fosters partnership between the education staff and the local community impacted by HIV/AIDS. Involving community members in the development of our education programs ensures that community values and cultural differences are respected in ACRIA’s educational work.

Community Advisory Board members meet every other month, review program materials and help us identify education needs.

For more information about the CAB or if you are interested in volunteering at ACRIA, please call Mark Milano at (212) 924-3934, ext. 123.
generous contributions

The following persons, corporations and organizations made major donations between March 16, 2002 and June 12, 2002 to support ACRIA’s research and education efforts:

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Thoughtful donations in memory of the following remind us of what is at stake in the fight against AIDS:

Barry Binkowitz, MD
Mary Lou Liddick
Clark D. Moore
Carl Parisi
Steven Wright

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