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Hepatitis: An Overview

Contents

- * Hepatitis: An Overview
- * Co-infection with HIV and HEP C: Beyond the Basics
- * Diagnosis and Monitoring Hepatitis C Infection
- * Liver Health
- * Interferon and Beyond: Treating HEP C
- * HEP C Resources
- * CRIA News - CRIA Trials - Contributions - Masthead

About this issue

This issue of CRIA Update focuses on some of the most important concerns facing people who are co-infected with HIV and Hepatitis C. First, Irene Cerngul, MD, one of CRIA's study coordinators, offers a brief introduction to hepatitis discussing what it is and its many causes. Next, Douglas Dieterich, MD, renowned HEP C researcher, clinician and CRIA Board member, along with regular contributor Tim Horn, explore the complexities of HIV/HEP C co-infection. James Learned of Hepatitis-C Action and Advocacy Coalition (HAAC) in New York, discusses some of the ways in which HEP C is diagnosed and monitored throughout the course of disease.

To help readers understand what the treatment landscape looks like-both now and in the near future, Tim Horn has summarized much of what is known about interferon therapy, the new antiviral ribavirin, and some of the novel therapeutics in development. Finally, CRIA's Managing Editor, David Pieribone presents a common sense guide to liver health. We hope that the information in this issue, along with regular health care, will allow individuals who are co-infected with HIV and HEP C and their caregivers to better understand their disease and, with the help of their doctor, make the most appropriate treatments decisions.

Hepatitis: An Overview

By Irene Cerngul, MD

Hepatitis is a general term originating from the Greek words **hepa** meaning liver and **-titis** meaning inflammation. Inflammation of the liver can be caused by a number of things including but not limited to chemicals, toxins, drugs, viruses and autoimmune mechanisms.

A doctor can detect hepatitis in a number of ways. First upon physical examination, usually by pressing fingers into the abdomen to feel for an enlarged liver. An x-ray or sonogram (ultrasound) can also show an enlarged or shrunken liver. Laboratory (blood) tests can detect hepatitis and are discussed in the article by James Learnerd. Unfortunately these tests cannot tell the doctor the cause of the hepatitis but only that the liver is enlarged or inflamed. Symptoms of hepatitis may vary depending on the cause. One general symptom is yellowing of the skin and eyes known as jaundice. This happens when bile, a substance produced by the liver, becomes backed up into the blood instead of being excreted into the gastrointestinal track. Other symptoms that are associated with viral causes of hepatitis are discussed later in this publication.

Because the liver is responsible for breaking down and clearing toxins from the blood, individuals exposed to toxic industrial chemicals or other toxins (certain mushrooms, plants and herbs) can develop chemical hepatitis. Recovery from chemical hepatitis depends on the amount and the length of exposure to a particular toxin. In many cases, if liver damage is not severe, the liver will regenerate (regrow) damaged cells.

Drugs, like chemical toxins, are cleared through the liver and can also cause hepatitis. Alcoholic hepatitis is the most common type of drug induced hepatitis. Overdosing (taking too much) of over the counter medications such as acetaminophen (Tylenol) can also cause hepatitis. Individuals with chronic illnesses who must take lots of medications can experience hepatitis and must be monitored by their doctor.

There are many viruses that can cause hepatitis these include, B, C, D, E and G viruses. Other viruses are suspected to cause hepatitis but have not yet been named. Symptoms range from mild and inapparent to severe and sometimes fatal. Infections can be either chronic (long-term) or acute (short-term).

Hepatitis A virus (HEP A) is transmitted almost exclusively by the fecal-oral route, although gay men are at risk for sexual transmission. Travelers who visit countries without adequate sewage treatment facilities are susceptible to infection. Most infections result from contact with a household member or sex partner who has HEP A. Infection is more severe in children than adults and very rarely results in chronic infection. HEP A is rarely fatal and usually resolves within 4-6 weeks. A vaccine is available for HEP A.

Hepatitis B virus (HEP B) is transmitted by blood and blood products (including contaminated needles), sexual contact or from mother to child (vertically). A small percentage of individuals with acute HEP B infection will go on to have chronic infection and may develop cirrhosis or liver cancer. A vaccine is available for HEP B.

Hepatitis C virus (HEP C) is described in detail in the article "Co-infection with HIV and HEP C: Beyond the Basics".

Hepatitis Delta virus (HEP D) is a defective single-stranded RNA virus that requires the helper function of HEP B to replicate. HEP D virus can be acquired either as a co-infection with HEP B or as a superinfection of persons with chronic HEP B infection. Persons co-infected with both HEP B and HEP D may have more severe acute disease and a greater risk of liver damage compared with those infected with HEP B alone. For those co-infected, a greater percentage (70%-80%) go on to develop chronic liver diseases with cirrhosis as compared with those who are infected with HEP B alone (15%-30%). There is no vaccine for HEP D.

Hepatitis E virus is the major cause of enterically transmitted non-A, non-B hepatitis worldwide. It is transmitted primarily by the fecal-oral route such as fecally contaminated drinking water. Person to person transmission of HEP E appears to be uncommon. Virtually all cases of acute HEP E in the United States have been reported among travelers returning from high risk areas. Regions of the world which have high incidences of HEP E are primarily developing countries and include areas of Central America, Africa, Southeast Asia and India. When traveling to these regions of the world the best protection is to avoid drinking water (and beverages with ice) of unknown purity, eating uncooked shellfish, vegetables and unpeeled fruit. There is no vaccine for HEP E.

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Co-infection with HIV and HEP C: Beyond the Basics

By Douglas Dieterich, MD with Tim Horn

Drugs used to treat HIV and prevent opportunistic infections have had a tremendous impact on both the length and quality of life for HIV-infected people. However, as much as 50% of the HIV-infected population is now being forced to grapple with another epidemic that threatens their health: hepatitis C virus (HEP C) also known as HCV.

According to the CHORUS (Collaborations in HIV Outcomes Research-United States) database, which contains the medical records of approximately 4,000 HIV-infected patients, chronic liver failure due to HEP C has become the number one non-AIDS cause of death in HIV-infected patients.

Epidemiology

In the United States, four million people-almost 2% of the general population-are believed to be infected with HEP C; a prevalence rate four-times higher than that of HIV. According to conservative estimates, HEP C is responsible for 10,000 deaths in the U.S. every year-a number that is expected to increase to 40,000 per year by 2015.

According to national statistics, nearly one out of every two HIV-positive individuals is also infected with HEP C. In New York City, approximately 40% of the HIV-infected population is co-infected with HEP C. Looking into the future, the number of HIV/HEP C co-infected patients is likely to increase dramatically as HIV continues to spread disproportionately among injection drug users (IDUs).

The great majority of HEP C infections in the U.S.-more than 80% in the Midwest, and more than 74% in the Northeast-are HEP C types 1A or 1B, which have the unfortunate double distinction of being associated with the worst prognosis and poorest response to interferon therapy. Types 2 and 3 associated infections account for about 20% of all HEP C infections in the U.S., but are known to respond better to therapy with interferon.

Similarities Between HEP C and HIV

There are many similarities and differences between HIV and HEP C. Both are RNA viruses that, once inside a human cell, are converted to DNA and then back to RNA. However, HEP C is different in that it does not need to enter the cell's nucleus-a requirement for HIV.

Other similarities include the tests used to diagnose infection. Like the antibody test used to diagnose HIV-not only in people who think they may have been infected, but also in the nation's blood supply-a sensitive test can be used to look for the presence of HEP C antibodies. While 100% of adults who test HIV-antibody positive are definitely infected with the virus, the same may not be true for HEP C. Approximately 10% to 20% of all people infected with HEP C are able to spontaneously clear the virus from their bodies. In turn, PCR (polymerase chain reaction) technology can be used to confirm the presence of HEP C.

HEP C, like HIV, reproduces (replicates) at an extraordinarily fast rate. With HIV, the daily turnover rate is thought to be 10 billion new viruses; with HEP C, approximately 10 trillion new viruses are produced daily. Ironically, HEP C is associated with a much slower mutation rate than is seen with HIV. While most of these mutations are self-defeating to HEP C, some may cause the virus to become stronger and, quite possibly, become naturally resistant to anti-HEP C drugs.

The Clinical Course of HEP C

Approximately 80% of people infected with HEP C develop chronic infection. That is, the infection is neither eradicated nor held in check by the immune system. Some of these patients may go for many years without any symptoms of disease; most, however, will see their HEP C viral load and liver function tests (LFTs; ALT and AST) increase and experience symptoms and other tell-tale signs of disease progression. Researchers estimate that at least 20% of patients with chronic hepatitis C develop cirrhosis (liver damage) and fibrosis (scarring of the liver), a process that

usually takes 10 to 20 years. After 20 to 40 years, a smaller percentage of patients with chronic disease will develop liver cancer.

Many people with chronic hepatitis C have no symptoms of liver disease, at least not during the first several years of infection. If symptoms appear, they may include: fatigue, pain or discomfort immediately below the right-half of the rib cage, nausea, decreased appetite, and muscle and/or joint pain. In patients who have either cirrhosis or fibrosis of the liver, many of the above mentioned side effects are common, with the addition of an enlarged liver; an enlarged spleen; jaundice (yellowish skin, and eyes); muscle wasting; and ankle swelling.

There have been a number of studies demonstrating that HIV can worsen the clinical course and symptoms of HEP C disease. For example, a London-based study involving hemophiliacs demonstrated that HEP C/HIV-coinfected patients were 21-times more likely to experience liver failure than patients infected with HEP C alone. In a study conducted in Spain, up to 25% of HIV-infected IDUs had developed cirrhosis of the liver after 15 years of carrying HEP C, whereas cirrhosis only occurred in 6.5% of those who were HIV-negative. In another study conducted in the United Kingdom, liver-related deaths were almost 20-times higher than the general population among men with only HEP C infection, and an astounding 94-times higher among men with both HIV and HEP C.

The impact of HAART in helping control HEP C is questionable and is discussed in greater detail in the treatment-related article by Tim Horn.

Transmission

HEP C is spread primarily by direct contact with blood and blood products. While many people living with HEP C today were infected via contaminated blood transfusions, antibody tests initiated in June of 1992 have successfully done away with the majority of transfusion-related HEP C infections. It is estimated that 1 in 100,000 individuals will contract HEP C from a transfusion. Shared use of contaminated needles and syringes by IDUs is the most common route of transmission today. As there is no telling how long HEP C has been around, IDUs in recovery-even if they stopped using drugs many years ago-may still be infected. Also vulnerable are people who engage in high-risk sexual activity, particularly activities in which contact with blood is possible. Body piercing and tattooing is another possible transmission route. It is recommended that anyone who had a blood transfusion, injected drugs or engaged in other high-risk behavior within the last 15 years be tested for HEP C.

Cocaine users, be warned: there have been some documented cases of HEP C transmission among cocaine users who share snorting paraphernalia. As cocaine can damage capillaries in the nose, microscopic traces of blood can be deposited on the end of a straw being used to snort the drug and then passed on to the next user.

Experts recommend that individuals who are HEP C infected refrain from sharing razor blades, toothbrushes, and nail and cuticle clippers with others.

Vertical Transmission (from mother to child)

Fortunately HEP C is not easily transmitted from an infected pregnant woman to her babies. In most studies, an average of 5%(range 0% - 25%) of infants born to women with HEP C become infected. As with HIV, the risk of maternal-infant spread increases if the infected mother has a high HEP C viral load; the average rate of vertical transmission for an infants whose mother is co-infected with HIV and HEP C is 14% (range 5%-36%).

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ACRIA Board Member. Tim Horn is the executive editor of The PRN Notebook, published by Physicians' Research Network in New York.

Diagnosis and Monitoring Hepatitis C Infection

By James Learned

Learning if you have been exposed to HEP C is not so difficult, finding out if you are infected, and if so, what is going on in your body as a result of the infection can be. Ultimately you will need a number of tests to give you this important information.

To learn whether or not you have been exposed to HEP C, start with a HEP C antibody test, also known as HEP C ELISA, which looks for antibodies that your immune system produces after you are exposed. In general most individuals that are exposed to HEP C will produce antibodies eventually, unless they are severely immunocompromised. The test can be tricky. False positives show up in about one out of every four cases. If your test is negative, and you know that you are at risk, follow it up with a more specific test called a qualitative HEP C PCR to make sure (see below).

Viral Load Testing (PCR)

If you get a positive antibody test it doesn't always mean you actually have HEP C infection. About 15% of people with the antibody are not chronically (long term) infected. If you are positive, however, you will want to get a qualitative HEP C PCR (viral load) test. This test is similar to an HIV viral load test and actually looks for the virus in your blood. The qualitative PCR won't tell you how many HEP C virus particles there are in your blood sample but it will tell you whether there are any present. Even if this test comes back negative and you are at high risk, your doctor may recommend that you repeat the test in a few months since levels of the virus fluctuate. The incubation period for HEP C varies from two weeks to six months. If the PCR is negative a second time, the antibody test may have been a false positive, or you may be one of those lucky 15% whose bodies clear the infection on their own.

The second type of PCR test or viral load test is quantitative, which means it tells you how much virus is in a particular sample of blood. Most people with HEP C have viral loads anywhere between 100,000 and ten million, and sometimes higher. There's no comparison between HEP C viral loads and those for HIV. Whereas a viral load of one or two million is considered very high in HIV, the same result in HEP C isn't necessarily considered high. There is almost no information yet about how specific HEP C viral load levels relate to the likelihood of current or future liver damage. So, as with liver enzymes, don't make any decisions based solely on viral load results.

Monitoring Disease Progression

Once you are sure that you are chronically infected with HEP C, you will want to know what condition your liver is in so that you can make important treatment decisions. As your liver goes about its business, it secretes enzymes into your blood which are measured each time you get your blood work. If you're HEP C-positive, most doctors will simply monitor your liver enzymes (ALT, AST) every six months. It's a good idea to get a baseline reading, however your enzyme numbers can be affected by so many variants that they're only worthwhile for comparison purposes over time. If you're taking anti-HIV medications for example, or any medications for that matter, your liver enzymes may be on the high end as your liver works overtime to metabolize (break down) the medications. And if your liver is in really bad shape, your enzyme levels may be normal or low because your liver is too worn out to make the enzymes. Alcohol and street drugs can also significantly damage the liver, resulting in increased liver function tests. So, overall, monitoring liver enzymes isn't a useful indicator of liver damage, but can be used with other tests to tell you what state your liver is in.

Your doctor may also want to get a quantitative HEP C PCR (viral load) over time for comparison which tells you how much hepatitis C virus you have in your blood.

Liver Biopsy

You can monitor your symptoms, liver enzymes and HEP C viral load, but without having a liver biopsy, you really can't tell how your liver is doing. If you're feeling just fine, you're unlikely to jump at the chance to go through an invasive, uncomfortable, if not downright painful procedure. A liver biopsy is currently the most accurate way to measure the progression of liver damage. This is an outpatient procedure that just takes a few minutes while you're awake. A needle is inserted through your abdomen, just below your right ribs, into your liver, and a small tissue sample is taken out and examined under a microscope by a doctor called a pathologist. Because the sample is only from one part of the liver it can't tell you what's going on in other parts of your liver, but it is a useful diagnostic tool to measure the degree of inflammation, fibrosis and cirrhosis in that sample. It's particularly important and at present, necessary if you're considering treatment. Liver biopsy can be repeated to assess disease progression over time. As with any surgical procedure, preparation is required and there are risks involved. It is important to understand everything your doctor says to you about a biopsy before you undergo one.

Genotypic Tests

Of the three main HEP C genotypes (1, 2 and 3), genotype 1 is the most common in the United States, accounting for about 70% of US infections. It is also, unfortunately, the genotype least likely to respond to the treatments currently available. A genotype describes the basic genetic make-up of your particular strain of virus. Learning your genotype may give you some statistical information about how likely you are to benefit from treatment, but at this time it's still primarily a research tool.

The language used by many HEP C researchers is curious and inaccurate. When you look through the literature at studies and articles or attend research presentations, terms such as "cure," "eradication," and "PCR-negative" repeatedly come up. These words can be misleading and confusing. However, largely due to PLWAs' influence on the language of HIV and the many researchers and doctors who understand the importance of using language that reflects what's truly going on, the language of HEP C is slowly evolving. "PCR-negative" is now often replaced by "undetectable viral load"; "eradication" is most often used only when talking about that 15% or so of folks who spontaneously clear the virus from their systems after initial infection; and that loaded word "cure" appears less often now, when what is really meant is a sustained undetectable viral load.

James Learned is currently working with the Hepatitis-C Action and Advocacy Coalition (HAAC).

Liver Health

By David Pieribone

A healthy liver is important for everyone. If you are HIV positive and taking medications, your liver will be working hard to process them and keep up with all of its normal functions. If you are infected with HEP C and HIV and your liver is damaged or overly stressed by HEP C, it may be difficult for your liver to process all of your medications. It is important to do everything you can to keep your liver healthy and avoid things that harm the liver. Unfortunately, unlike other organs in the body, the liver can't let you know when it is in trouble, or often not until it is too late.

Liver Basics

The liver is located behind the lower ribs on the right side of your abdomen; it weighs roughly three pounds and is about the size of a football. Besides being one of the largest organs in your body (second only to your skin), the liver is responsible for thousands of essential body functions. Most people know that the liver processes alcohol and can be damaged by excessive drinking,

but many are unaware that the liver is also responsible for aiding other important functions such as digestion, the processing of medications and toxins, general metabolism and a healthy immune system.

The liver is involved in detoxifying just about everything that enters the body. Substances can enter the body in many different ways, (by eating and drinking, through our skin or the air we breath). Excessive alcohol and substance use can negatively affect the liver and for those with HEP C, alcohol and street drugs, can increase the chances of developing cirrhosis and liver cancer. Experts recommend that individuals with liver disease avoid street drugs and alcohol.

Avoid environmental pollutants and chemicals. Fumes from paint, paint thinners, chemical solvents, spray adhesives, insect sprays and other aerosol sources enter the body through the lungs and skin and are carried to the liver by the blood, where they must be detoxified and may damage the liver. If you use chemicals or sprays, make sure to take the manufactures suggested precautions. Avoid skin contact and breathing of chemical fumes whenever possible. Always wash your hands and any other exposed body parts after working with chemicals. Household cleaning products should be used with similar caution as they too can damage the liver.

Avoiding other hepatitis viruses is also important. Becoming infected with HEP A or B in addition to HEP C could be potentially life threatening. Ask your doctor or healthcare provider about vaccines for HEP A and B.

Because almost all medications must pass through the liver before entering the circulation system, it is important to talk to your doctor about any over the counter medications you may be taking, even if they are generally considered safe. Combining medications can be dangerous. Keep a list of all your current medications especially if you have more than one doctor, so you can remind each of them what you are taking.

Diet and Liver Health

A balanced diet is important. If your liver is stressed by disease, it is particularly important to watch your diet carefully. Although there have been no formal studies that show HEP C infected individuals can positively change the course of their disease through diet, there is some evidence that a balanced diet may help liver cells damaged by hepatitis viruses to regenerate (regrow). In general, a healthy balanced diet is one that contains whole foods from a variety of sources like fresh vegetables and fruits, beans, whole grains, and fresh meats. Avoid processed foods such as cookies, cakes, frozen dinners, packaged foods with long shelf lives and "instant" foods. Overeating can also adversely affect the liver as well as other organs because they are forced to process the additional food.

Diets that contain excessive fat, protein or carbohydrates can damage the liver. Too much protein may cause hepatic encephalopathy (mental confusion) in individuals who already have extensive liver damage. Adequate protein intake is important, however, to build and maintain muscle mass and to assist the body in repairing itself. A general rule for individuals with HEP C infection who do not have cirrhosis related encephalopathy is to eat about 0.8 grams of protein per kilogram of body weight each day. Excess carbohydrates can add to liver dysfunction and may cause fat deposits in the liver. Eating too much fat, especially processed fats and deep fried foods, can put an extra strain on the liver and may complicate laboratory tests used to monitor liver health in HEP C infected individuals.

Individuals with advanced cirrhosis may have an abnormal accumulation of fluid in the abdomen, referred to as ascities. Individuals with HEP C who have ascities usually must be on sodium (salt) restricted diets. To avoid foods high in salt, stay away from canned meats, canned vegetables and soups, cold cuts and condiments such as ketchup and mayonnaise to name a few. Be careful of fast food restaurants since most of the food they serve is very high in salt and fat.

It is best to consult your doctor or qualified nutritionist about the appropriate diet if you have liver disease. Be wary of fad diets that may not provide the body with the proper nutrition.

Vitamins are necessary for proper body functioning and good health, however megavitamins, particularly vitamins A, D, E and K are dangerous for the liver when used in large amounts. Iron supplements should not be taken unless advised by your physician. Always consult your doctor or healthcare professional before adding vitamin or mineral supplements to your diet. In addition, some herbs are toxic to the liver and should be avoided by individuals with liver problems. Herbal preparations that include the Crotalaria, Heliotropium, and Senecio plant families are toxic to the liver and should be avoided. Other herbs that are toxic include: chaparral, germander, comfrey(bush tea), mistletoe, skullcap, Jin Bu Haun, nutmeg, tansy ragwortsenna, sassafras, valerian and pennyroyal. As with all over the counter medications and therapies, it is very important to discuss herbal preparations with your doctor or healthcare provider before taking them.

Regular exercise and a stress reduction plan are also important for people with chronic illnesses and should always be included in a health plan.

David Pieribone is the Managing Editor of CRIA Update and the Director of ACRIA's Treatment Education Program.

Interferon and Beyond: Treating HEP C

By Tim Horn

Treatment for HEP C infection has finally entered the modern era. After eight years of interferon as the only treatment available for HEP C, combination therapy with a new anti-HEP C drug has become a viable option. In addition, a novel form of interferon is slated for approval and several new classes of drugs are expected to enter clinical trials soon. The following is a review of the current options available to people living with both HEP C and HIV, along with a nod to the promising future of HEP C treatment.

The Impact of HAART

While some studies have shown that HIV can cause HEP C to worsen, there has been very little success using highly active antiretroviral therapy (HAART) to control hepatitis. None of the currently available anti-HIV drugs have any impact on HEP C replication. While some researchers suggested that HIV protease inhibitors might have some kind of impact on the HEP C lifecycle, this proved similar to forcing a square peg into a round hole.

This is not to say that protease inhibitors do not have an impact on HEP C. Protease inhibitors, like HEP C, can cause liver function tests (LFTs, including AST and ALT) to increase, a sign that damage to the liver is occurring. In other words, people who are co-infected, taking protease inhibitors-and, quite possibly, non-nucleoside analogues-are at greater risk for experiencing liver problems than people only infected with HIV.

Fortunately, one study conducted at Johns Hopkins University School of Medicine found that the risk of severe liver damage among co-infected people taking protease inhibitors was low. Among people being treated with saquinavir, nelfinavir, or indinavir, the risk of serious liver damage was 6%. In co-infected people taking ritonavir, the risk increases sharply to 18%. And in a study which volunteers took both saquinavir and ritonavir, the risk was 32%.

However are these liver LFT increases necessarily bad? According to Dr. Douglas Dieterich, a hepatitis specialist in New York City, there may be more to moderate LFT increases than meets

the eye. Numerous studies have shown that antiretroviral drugs, especially when used in combination, allow the immune system to "jumpstart" itself once viral replication has been suppressed. With HIV beaten into submission, vital immune system cells in the liver are permitted to proliferate, allowing them to resume their activity against HEP C. As explained by Dr. Dieterich, such immune activity could explain the increase in LFTs.

Interferon Therapy

Interferon (IFN), whether it is used alone or in combination with ribavirin (see below), is the gold standard treatment for HEP C. There are actually two types of IFN (interferon) therapies used to treat HEP C: interferon-alpha (IFNa) and consensus interferon (Infergen). With respect to IFNa, the two most common brands prescribed for the treatment of HEP C are IFNalpha-2a (Roferon-A) and IFNalpha-2b (Intron-A). Both appear to have equal activity against HEP C and are associated with many of the same side effects. Consensus interferon combines several different types of interferon and is somewhat unique in its activity, but is associated with side effects similar to those seen with other IFNs.

There are a number of ways in which responses to interferon therapy can be determined. The first is laboratory results, specifically blood tests such as LFT (liver function test) decrease. The second is by measuring histopathologic responses, a fancy way of saying a liver biopsy, which detect the progression or reversal of physical damage to the liver (for example, cirrhosis, fibrosis, etc.). The third and, perhaps, most important response is a decrease in HEP C viral load, a measurement of how much HEP C virus is in the blood.

With respect to HIV, suppression of viral load is important to keeping T-cell counts high and the body disease free. Some researchers believe that HEP C viral load, if adequately controlled, will allow LFTs to stabilize and the liver to recover from the onslaught of infection. However, to date there is no significant evidence to back up this theory. A liver biopsy is the only sure way to know what is happening in the liver.

In terms of the effects of interferon therapy, approximately 50% of all people treated with IFNa at the standard 3 million units (MU) dose three times weekly-regardless of whether or not they also have HIV-will see their HEP C viral load decrease dramatically. However, only 20% will continue to see their HEP C viral load remain below the level of detection after completing a one-year course of therapy. But for those who do not see their HEP C viral load creep up within six months of finishing therapy, the chances of HEP C virus ever returning are slim-the virus has most likely been "eradicated" from the body.

With respect to consensus interferon, clinical trials in HIV-negative study volunteers have yielded slightly better response rates. After six months of therapy, approximately 35% of people receiving standard doses of the drug (9 micrograms three-times weekly) had undetectable HEP C viral loads, compared to 27% receiving IFNalpha-2b. After an additional six months of follow-up after stopping therapy, both drugs appeared equal in terms of sustained undetectable HEP C levels (12% for consensus interferon and 11% for IFNa).

It is important to keep in mind, however, that people who "fail" interferon therapy may still be benefiting from the drug. According to two papers published in the journal *Hepatology*, interferon therapy-regardless of whether or not biochemical, histopathological, or virological responses are seen-helps correct the ways in which the immune system responds to HEP C. This, in turn, may delay problems like cirrhosis, fibrosis, and quite possibly cancer of the liver.

According to Dr. Dieterich, there are a number of factors that may work to the advantage of co-infected people considering treatment with interferon. These include: a T-cell count above 200, a HEP C viral load less than 2 million copies low or normal body weight, a limited amount of liver fibrosis, and HEP C types other than 1a or 1b. While very few people have such favorable

factors, they do suggest that regular checkups-including important blood tests-can be advantageous in terms of figuring out when to start therapy.

Another possible factor to consider when starting therapy is the dose of interferon being used. Presently, the United States Public Health Service recommends interferon treatment for patients with increased LFTs, detectable HEP C viral load, and signs of liver damage using standard doses of IFNa (3 MU, three times weekly) or consensus interferon (9 micrograms, three times weekly). However, several studies conducted since these drugs were first approved for the treatment of HEP C seem to suggest that higher doses of interferon-or by administering the drug five or more times a week-are necessary in order to increase the likelihood of responding to treatment.

Higher doses? Don't fret. Most researchers and healthcare providers realize that there is only so high a dose of interferon before side effects become unbearable. The answer may lie in new "pegylated" formulations of the drug.

Pegylated Interferon

Pegylated interferons (Pegasys; Peg-Intron) is created by attaching a microscopic water-soluble, waxy solid called polyethylene glycol to the interferon molecules. This allows the drug to remain in the body for longer periods of time, thereby increasing the activity of interferon on HEP C. This is great news for interferon users, as it decreases the frequency of drug injections, from three-times weekly to one-time weekly.

While researchers originally hoped that pegylated versions of interferon would reduce the number and severity of side effects, this has not turned out to be the case. However, side effects associated with pegylated interferon do not appear to be any worse than those experienced by people taking standard doses of IFNa and may in fact be slightly better.

But does it actually work better than standard IFNa? Yes, according to one recent study conducted by Hoffmann-La Roche. The research showed that pegylated interferon reduced HEP C viral load to undetectable levels in 76% of HEP C-positive (but not HIV-positive) study volunteers within three months of treatment. After an additional six months of not taking the drug, 36% of patients maintained undetectable levels. Among those treated with standard interferon, 17% experienced undetectable levels of HEP C within three months of treatment and 3% maintained undetectable levels for six months following completion of therapy.

Additional trials of pegylated interferons are currently underway in the United States. FDA approval of at least one brand is expected soon.

Combination Therapy

As in HIV therapy, it only seems logical to challenge HEP C's high replication and mutation rates using combination therapy. While there really haven't been any reports concluding that HEP C can become resistant to interferon, the possibility remains. As explained in the *CRIA Update* article "Co-infection with HIV and HEP C: Beyond the Basics", HEP C-like HIV-replicates and mutates quickly. This, in turn, makes drug resistance a likely scenario.

A new treatment option is ribavirin (Rebetol), a nucleoside analog active against several viruses. Used alone, the drug is of no benefit to people with HEP C. When used in combination with interferon, however, the true benefit of ribavirin becomes apparent.

Results of two clinical trials of ribavirin in combination with IFN, both involving HIV-negative patients who had never been treated with interferon before were published in late 1998. In the first study, 832 HEP C-positive people received either standard doses of IFNa in combination with ribavirin for either 24 or 48 weeks or IFNa alone. Patients who took both drugs for a year did the

best; after stopping the combination, 43% had undetectable HEP C viral loads after six months follow-up. Among those who received only IFNa monotherapy for a year, 19% were still undetectable after six months of being off the drugs. As for the patients who only took the combination for six months, 35% had undetectable HEP C viral loads after six months being off therapy, compared to 8% among patients who received IFNa alone.

Similar results occurred in the second study. Approximately 38% of patients who took IFNa in combination with ribavirin for one year had undetectable HEP C viral loads after six months off the drugs. In those who only took the combination for six months, 31% maintained undetectable HEP C viral loads for at least six months after stopping the drugs.

Not surprisingly, combination therapy in clinical trials was associated with many of the same side effects reported in studies of interferon alone. With the addition of ribavirin, there is an increased risk of developing hemolytic anemia, a condition in which red blood cells are destroyed in the bloodstream. Hemolytic anemia is most likely to occur during the first four weeks of therapy.

Extreme caution should be used by women of childbearing years, as the drug can cause serious birth defects, especially if it is taken during the first three months of pregnancy. Women who are either pregnant or unwilling to use birth control should avoid ribavirin.

Of unique concern to HIV/HEP C co-infected patients is the fact that ribavirin may alter the ways in which AZT (Retrovir) and d4T (Zerit) are processed in the body. At least one test tube study has shown that ribavirin can reduce the activity of AZT and d4T and, interestingly, may increase the activity of ddI (Videx).

Given that ribavirin does not work by itself, it must be used in combination with interferon. Schering-Plough, the maker of ribavirin and Intron-A, currently sells them together in a boxed kit (Rebetron). While this may make a lot of sense, a number of community activists and physicians are weary of the "bundled" kit, as it prevents people with HEP C from using the ribavirin in combination with interferon types other than Intron-A. Schering-Plough's position is that since ribavirin was studied with Intron-A only, using other forms of interferon poses a safety issue. A process known as compounding, where a pharmacy can take a drug that is available on the international market and sell it for special cases, has gained a lot of attention recently. Compounding of ribavirin is currently being done, but only by a few pharmacies in the country and third party payers may not reimburse for it. The Food and Drug Administration regulates compounding and it is unclear how they will view this particular issue.

Side Effects of Interferon/Ribavirin Therapy

Chances are, if you ask someone about interferon therapy, their first response will be: "Isn't that the drug with terrible side effects?" The fact is that interferon does cause side effects. In clinical trials, some of the most common side effects-occurring in more than 10% of study participants-include: fatigue, muscle aches, headaches, nausea and vomiting, skin irritation at the site of injection, low-grade fever, weight loss, irritability, depression, mild-bone marrow suppression (low white and red blood cells), and reversible hair loss.

Most of these side effects are mild to moderate in severity and can often be managed. They are worse during the first few weeks of treatment, especially after the first injection, but usually diminish over time. Side effects such as fatigue and depression can actually escalate over time, prompting between 5% and 15% of people to drastically reduce their interferon dose or stop therapy altogether. The nocturnal (nighttime) administration of interferon may lessen the side effects since they will be occurring during sleep. Using aspirin and acetaminophen before the dose of interferon can lessen some of the side effects, **but always consult your healthcare provider before changing your medication dose time or taking any medication to control**

side effects. In many cases, antidepressants can be prescribed to help control persistent depression.

With the addition of ribavirin, there is an increased risk of fatigue and irritability. Some of the more distinct side effects that can be directly related to ribavirin include; anemia, itching, skin rash, nasal stuffiness, and cough. Of greatest concern is anemia, as ribavirin in combination with interferon can cause levels of hemoglobin-a protein used by red blood cells to transport oxygen from the lungs to the rest of the body-to decrease significantly. In some cases, this has led to heart attack and stroke. In turn, patients with a history of anemia should think twice about starting therapy with ribavirin. Under the advice of a physician, drugs used to treat anemia may be initiated to increase the red blood cells.

Beyond Interferon: A Glance at New Therapies in Development

As with HIV, researchers are rushing to develop new drugs that are unique in the way they treat HEP C infection with potentially fewer side effects. While there are numerous drugs being developed, most can be categorized into one of three types:

1. Drugs to prevent HEP C from binding to liver cells;
2. Compounds that attack viral enzymes that promote HEP C replication;
3. Drugs to bolster the immune response to HEP C.

Unfortunately, very little information is available on particular drugs in development. Most are still in the laboratory stages of development and have yet to be tested in humans.

Preventing Cellular Infection

Before the virus can infect a cell, HEP C must first successfully bind to the cell's membrane. Based on their experiences with other viruses-including rhinovirus, influenza virus, picornavirus, and, we kid you not, the Semliki Forest virus and the foot and mouth disease virus (FMDV)-researchers have stumbled upon several possible approaches that may prevent the binding of HEP C to liver cells (hepatocytes). These compounds, which include **neutralizing antibodies** and **fusion inhibitors**, are barely out of the test tube, so information about how effective they may be is extremely limited.

Viral Enzyme Targets

Once inside a cell, HEP C uses several of its own enzymes to help itself replicate. Thus, finding drugs that stop these enzymes from functioning is a primary goal for many researchers. It is likely that these drugs will be used in combination, both with interferon and each other, in clinical trials once they are available.

Protease inhibitors, as their name implies, attack the HEP C protease enzyme. Similar to HIV's protease enzyme, HEP C protease snips large strands of the virus into smaller pieces during the replication process, allowing them to form into new virus. Unfortunately, there has been very little success producing any anti-HEP C protease inhibitors although many researchers are screening possible candidates.

Helicase is another enzyme used by HEP C and is primarily responsible for unwinding the virus' RNA once it is inside a cell. As this is an important step in the lifecycle of HEP C, **helicase inhibitors** may prove to be effective treatment. Researchers have recently determined the three-dimensional structure of helicase -an important discovery for pharmaceutical companies hoping to produce compounds that will work against it.

Three other classes of drugs include replicase inhibitors, antisense molecules, and Ribozomes. **Replicase inhibitors** are being developed to halt the production of new HEP C RNA. **Antisense molecules** are receiving much attention, as they have shown to be effective for the treatment of other viral infections, such as CMV. As a potential treatment against HEP C, these drugs prevent

the virus from producing necessary proteins and prevent HEP C RNA from functioning properly. **Ribozymes** do the opposite of protease inhibitors. They cleave RNA at critical places needed by HEP C to replicate.

Immune Therapies

Over the past few years, much has been learned about the role of the immune system and its inability to control HEP C in the majority of people infected with the virus. People who are either able to clear the virus or control HEP C replication for many years have an abundance of "type 1" T-cells (Th1), while people who gradually see their HEP C viral load increase and experience liver damage mostly have "type 2" T-cells (Th2). The difference? Th1 T-cells produce vital proteins, called cytokines and chemokines, which program other immune system cells to seek and destroy HEP C-infected cells. Th2 T-cells, on the other hand, produce antibodies that can prevent necessary immune system cells from doing their job correctly. The reason for this phenomenon is not known, but one thing is for sure: Th1 T-cells are the ones to have.

According to Dr. Dieterich, one of the advantages of interferon therapy is its ability to shift the immune response in people with chronic viral infections from Th2 to Th1. Some of the other immune-based therapies slated for development include **cytokine therapies**-particularly those that boost Th1 cytokines, such as interleukin-2 (IL-2) and interleukin-12 (IL-12), and those that block Th2 cytokines, including IL-10 and tumor necrosis factor (TNF)-and therapeutic **vaccines**.

Alternative Therapies

As with other diseases that do not have a cure, there are a number of alternative therapies. Unfortunately there have been no formal studies on their effectiveness, and their safety is unknown. Be wary of products that claim a cure. When considering an alternative therapy it is always best to consult your physician. In this issue the article "Liver Health", sheds some light on how to be good to your liver and how diet can be of help.

Conclusion

While interferon therapy is by no means a panacea, there is much to be said for the newest ways in which the drug can be used to achieve HEP C eradication. In combination with ribavirin, or by administering higher doses or pegylated versions of the drug, the likelihood of achieving eradication has increased from a dismal 20% to a more favorable 40%. Still, many patients are not able achieve this desirable outcome. Thanks to recent developments that have helped researchers understand how HEP C causes disease and the tools it uses to do so, new treatments to stop the virus in its tracks are likely to follow soon.

Tim Horn is the executive editor of The PRN Notebook, published by Physicians' Research Network in New York.

HEP C Resources

ORGANIZATIONS

Alcoholics Anonymous World Services

475 Riverside Drive, 11th Floor
New York, NY 10115
1-212-870-3400

Contact to find a support group for alcoholics in your area.

American Liver Foundation

1425 Pompton Ave.
Cedar Grove, NJ 07009
1-888-4-HEP-ABC (1-888-443-7222)

This group uses research and education to prevent, treat, and attempt to cure hepatitis and other

liver diseases.

1-800-GO-LIVER (1-800-465-4837);
(Hepatitis and Liver Disease Hotline)
Hours: 9 AM-7:30 PM, Monday-Friday
Languages: English and Spanish

A great source for information and support groups.

Center for Liver Disease at the University of Miami School of Medicine

1500 NW 12th Ave., Suite 1101

JMT East

Miami, FL 33136

1-305-243-5787

8:30 AM-5 PM

Contact this center for information on hepatitis and other liver diseases or for doctor referrals.

Hep C Connection

117 Grant St.

Denver, CO 80203

1-800-522-HEPC (1-800-522-4372)

1-303-860-0800 (Colorado residents)

Call for referrals to support groups.

Hepatitis Resource Network

240 Stadium Way South

Tacoma, WA 98402

1-253-274-0928 FAX 1-253-274-1730. A non-profit organization whose goal is to increase the involvement of ID specialists in cooperation with GI specialists, in both the research and treatment of viral hepatitis.

Latino Organization for Liver Awareness

P.O. Box 842, Throgs Neck Station

Bronx, NY 10465

1-718-892-8697

Languages: English and Spanish

Hours: 9 AM-5 PM, Eastern Time

Provides counseling for people with liver disease.

Texas Liver Coalition

One Riverway

Houston, TX 77056

1-800-72-LIVER (1-800-725-4837)

1-713-626-4959 Fax: 1-713-626-4960

Offers information on hepatitis and directs patients in the Houston area to support groups.

The Hepatitis C Foundation

1502 Russett Drive

Warminster, PA 18974

1-215-672-2606 Fax: 1-215-672-1518

Hours: 9 AM-5 PM, Monday-Friday

If you are faced with hepatitis in any capacity, contact this group for support and information.

The Hepatitis Foundation International

30 Sunrise Terrace

Cedar Grove, NJ 07009

1-800-891-0707

Call to find out more about hepatitis.

WEB SITES

American Liver Foundation

<http://gi.ucsf.edu>

A Hepatitis C Resource

<http://home.texoma.net/~moreland/>

Centers for Disease Control & Prevention

www.cdc.gov

Hepatitis C

www.epidemic.org

Hepatitis Central

<http://hepatitis-central.com>

Hepatitis Doctor Home

<http://hepatitisdoctor.com>

Hepatitis Foundation International

www.hepfi.org

Hepatitis Haven

www.tiac.net/users/birdlady/hep.html

Hep-C Alert

www.hep-c-alert.org

Hepatitis Information Network

www.hepnet.com

HIV and Hepatitis

<http://www.hivandhepatitis.com>

HEP Pace

<http://www.hepatitis-c.de/hepace.htm>

WebMD

<http://my.webmd.com>

World Health Organization

www.who.int/emc/diseases/hepatitis/

CRIA NEWS

Treatment Education Technical Assistance Program Launched

CRIA is proud to announce the receipt of start up grants from the Ittleson Foundation and Glaxo Wellcome to begin a formal HIV Treatment Education Technical Assistance Program.

CRIA has been a leading provider of HIV Treatment Education for medically-underserved people living with AIDS (PLWAs) in the New York Metropolitan area since 1997. In order to reach more persons in need, CRIA has designed an initiative to leverage existing AIDS service organization staff resources to substantially expand this vital information function. The new program's goal is to teach case managers, other care providers, and peer counselors how to deliver comprehensive information on the latest treatment advances, including the critical importance of adherence, through culturally and linguistically appropriate terminology. Many thousands more PLWAs will in turn learn about their most beneficial treatment options than is currently possible. Most importantly, this is a national initiative which is aimed at rapidly proliferating HIV treatment education services in areas of the United States which have large ethnic minority and women populations.

CRIA is pleased to announce that Ayisa Kennedy was recently hired to direct this new initiative. Ayisa comes to our agency with an in-depth understanding of the many issues surrounding complex antiretroviral and prophylaxis treatments for HIV infection, and most importantly has experience in teaching these issues to both PLWAs and their caregivers.

Prior to joining CRIA, Ayisa was the Research Referral Coordinator at the Clinical Directors Network, a New York City based non-profit where she provided extensive education on HIV clinical trials. Ayisa has also long played an influential role in directing national HIV treatment policy as an active Board member of both the U.S. Department of Health & Human Services National Collaborative Group on Women and HIV and the Research Care and Treatment Committee of the Office of Women's Health.

CRIA is very excited to have someone of Ayisa's qualifications and abilities to direct this new program. We look forward to her contributions to our work to make the most effective HIV treatments available to individuals who need them most.

CRIA's Redesigned Web Page and New Address Now Online

CRIA has moved its web site address from www.aidsinfonyc.org/cria to www.criany.org to make it easier for Internet users to find and access the site.

In addition, CRIA is finalizing a major redesign of its web site. With the help of a prominent graphics designer, we now have a site with the capacity to efficiently manage our agency's rapidly growing HIV treatment education and clinical research resources on the Internet. The new site will offer the same valuable information as CRIA's old site, but in a much more logical format.

The new web site is being organized around a traditional filing system concept. Information on the agency, on each of our two core healthcare programs, and on fundraising and volunteering opportunities will now be located in their own individual web site sections. For example, users can access online copies of *CRIA Update*, of our topic specific treatment education brochures, and summaries of our monthly Community Treatment Forums within their own "file folders" in a treatment education section. Links to other HIV treatment education sites are also offered within this area. Likewise, information on clinical research, including trials enrolling, is contained within several file folders in the research section of the web site. And, for the first time, we will soon be providing materials in Spanish online.

Next to come is the CRIA Store, which will give users the opportunity to purchase unique products as a way of supporting our agency's mission.

CRIA Elects Board Members

CRIA is pleased to announce the re-election of Board Members Ross Bleckner, Jill Cadman, Charles Franchino, DC, Donald Kotler, MD, and Carlos Sandoval, Esq at our September 15th Annual Meeting. Additionally, Ross Bleckner was re-elected to the post of President, Donald Kotler, MD as Vice-President, Carlos Sandoval, Esq as Secretary, and Charles Franchino, DC as Treasurer. The long-term contributions of these five individuals have made a critical difference in the organization's research and education functions, and we look forward to their continued contribution to CRIA's activities during their next two-year term of office.

Also at the September meeting, Gary Bonasorte was elected as CRIA's newest Board Member. Gary will add a unique "insider's" perspective to the deliberations of this key advisory body. He was among the first people living with AIDS to volunteer at the agency's inception in December 1991 and later served as a staff member. His extensive knowledge of our programs, staff, and the challenges we face will be of tremendous help in the coming years.

CRIA TRIALS IN PROGRESS

Chronic Hepatitis C/HIV Co-infection Study

CRIA is collaborating with the Hepatitis Resource Network to compare the effectiveness and tolerability of daily interferon and ribavirin vs daily interferon alone for the treatment of chronic hepatitis C infection in persons who are also infected with HIV. To be eligible you must have had no previous treatment with interferon.

Fat Accumulation in the Belly (FAB) Study

Fat build-up in the abdomen may be a complication of protease inhibitor use. CRIA is conducting a pilot study on the effect of Recombinant Human Growth Hormone (Serostim®) in the treatment of truncal obesity associated with HIV infection. The protocol is designed to examine the safety and efficacy of daily human growth hormone injections over a 24-week period. An extension phase is now being conducted for patients who have completed 24 weeks of therapy to determine longer-term effects. This trial is closed to enrollment.

Metabolic Effects of Protease Inhibitors

CRIA is launching a study in cooperation with Dr. Ann Danoff, Chief of Endocrinology at Bronx-Lebanon Hospital to examine whether there is an association between short-term antiretroviral therapy (ARV) and glucose intolerance, hyperlipidemia, or body habitus changes. The trial will study HIV negative persons who have sustained needle stick injuries, before and at the conclusion of a course of ARV prophylactic therapy. This study will provide the opportunity to examine the impact of PI therapy independent of HIV infection.

Protease Inhibitor and Blood Sugar Study

CRIA is conducting a study to examine the effects of protease inhibitor use on responses to the oral glucose tolerance test (measurement of blood sugar levels after taking a drink with a high sugar content) on HIV positive persons. Participants must have been naive to protease inhibitors to participate in this study. This trial is closed to enrollment.

Topical Analgesic for Peripheral Neuropathy

This small pilot study will look at the effectiveness of a topical non-steroidal analgesic for the treatment of pain associated with peripheral neuropathy in HIV infected persons. If the results show promise CRIA plans to develop a full protocol.

Ultrase® for Diarrhea

CRIA is participating in a study of Ultrase (pancreatic enzymes) for diarrhea due to the protease inhibitor nelfinavir (Viracept®). The 12-week study, which is being conducted along with CRI New England and CRI South Florida, is open to HIV-infected persons who have been taking nelfinavir

at a dose of 1250 mg twice a day for at least two weeks and have three or more stools per day not due to any other cause. Participants will be reimbursed \$20 per visit after enrollment.

For more information on any of these studies, please call Dr. Irene Cerngul or Dr. Douglas Mendez at (212) 924-3934, or visit our Web site (www.criany.org).

FORUM UPDATE

CRIA co-sponsors monthly educational forums on AIDS research and treatment issues. Upcoming forums:

Wednesday, November 10

Update from the National Women's HIV/AIDS Conference

Wednesday, December 8

Psychological Issues and HIV Disease

Wednesday, January 12

Lipodystrophy and HIV Disease

The forums are held at 7PM in the Cronin Auditorium, 10th Floor of St. Vincent's Hospital at 11th Street and 7th Avenue, Manhattan. Forum summaries are now available on CRIA's website:

www.criany.org.

CRIA UPDATE

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CRIA is an independent, non-profit, community-based AIDS research and treatment education organization dedicated to rapidly improving the length and quality of life for people living with HIV/AIDS. CRIA studies new treatments for HIV-related diseases through its clinical research and conducts a comprehensive treatment education program. Bulk copies of *CRIA Update* are available free to agencies that provide services to people living with HIV/AIDS. For more information call Meredith Snow at 212-924-3934.

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Editor's Notes

* All material in *CRIA 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.

- *CRIA 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.

acknowledging our friends...

GENEROUS CONTRIBUTORS

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