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The Challenge of Hepatitis C and HIV Co-Infection

By Damaris C. Carriero, Jennifer Lucas, Hurdley Freemantle, and Douglas T. Dieterich

The emergence of hepatitis C virus (HCV) in HIV-positive patients is an increasingly significant problem. The era of highly active antiretroviral therapy (HAART) has dramatically decreased morbidity and mortality from opportunistic diseases. The longer life span in the HIV population, however, has increased the mortality associated with underlying diseases such as HCV infection.

It is estimated that 30% of HIV-infected individuals also have HCV, totaling approximately 300,000 with co-infection in the United States. Among those infected with HIV via injection drug use (IDU), 60-90% are estimated to have HCV.

Several studies suggest that HIV accelerates HCV progression to cirrhosis and end-stage liver disease. In fact, liver disease is the leading cause of hospital admissions and death in HIV-positive patients. Antiretroviral therapy (ART) in co-infected patients increases the risk of liver toxicity. This and the potential for accelerated liver disease make it crucial to consider HCV treatment of patients with HIV. The burden of co-infection prompted the Centers for Disease Control and Prevention (CDC) to issue guidelines for HCV management in 1999.

History

Before its discovery in 1989, HCV was known as non-A, non-B hepatitis. Today, it is the most common blood-borne infection and one of the most important causes of chronic liver disease in the United States. HCV is the major cause for liver transplantation and accounts for more than 10,000 deaths each year.

Approximately 4 million Americans, or 1.8% of the U.S. population, have antibody to HCV, indicating ongoing or previous infection with the virus. Furthermore, 2.7 million people have chronic hepatitis C. The HCV epidemic peaked during the 1970s and 1980s, prior to identification of the virus and before HCV screening for blood products and organs was set in place.

Injection drug users are the largest group of people infected with HCV. African Americans and Hispanics are affected disproportionately. Individuals aged 30-49 years make up 65% of HCV infections and the majority of people who die from HCV-related disease are between 44 and 54 years of age.

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The present incidence of advanced liver disease due to HCV is on the rise, and the number of deaths from HCV is expected to increase during the next 10 to 20 years. Medical costs due to HCV-related morbidity are expected to exceed one billion dollars annually.

Transmission

Like HIV, HCV is transmitted through blood-to-blood contact. HCV, however, lives outside the body for a much longer time than HIV and therefore spreads more easily. Sharing needles for injection drugs is a very high-risk behavior.

Using sterilized needles for tattoos is very important in guarding against HIV, but it may not be enough to prevent HCV infection. The reason is that when the tattoo artist dips the needle into the ink, microscopic amount of blood from the person getting the tattoo can get into the ink. If that blood contains HCV, it is the ink and not the needle that poses the danger to the next person who gets a tattoo.

Women can pass HCV to their babies at birth, but the incidence of this is very low. Breast-feeding does not seem to increase the risk of mother-to-child transmission.

The incidence of sexual transmission of HCV seems to be low, but persons who participate in high-risk behaviors such as unprotected anal intercourse and/or those who have multiple sex partners have an increased risk of infection with HCV. At least 20% of new cases are associated with high-risk sexual behavior.

Hepatitis C and the Liver

After initial exposure to HCV, approximately 15% of infected people spontaneously clear the virus. At least 75% of patients with acute hepatitis C ultimately develop chronic infection and most of these have associated liver disease. HCV-associated liver disease develops very slowly. Many people have HCV and never even know that they are infected until it is too late. IT works silently over the years causing irreversible liver damage without any signs. The most common symptom associated with hepatitis C is fatigue.

Liver damage from HCV can lead to cirrhosis in 20 years and liver cancer in 30 years. These problems occur at a much faster rate – perhaps twice as rapidly – among those who are co-infected with HIV.

"Hepatitis" simply means inflammation of the liver. A virus that mainly infects the liver cells causes the disease. When a hepatitis virus infects a liver cell, spikes on its outer membrane (known as the "envelope") anchor to the outer surface of the liver cell. A core of viral genes is now able to pass from the envelope into the cell. Once inside, the virus can take over the normal function of the liver cell, forcing it to make more viruses. This process causes the cell to die…but not before thousands of viruses are released to infect healthy cells.

The immune system is designed to fight infection by making proteins called antibodies; a different antibody is produced for each different infection, and each type of antibody attacks only its particular virus or bacterium. Antibodies also help clear infection from the bloodstream. The antibodies our bodies produce against hepatitis C are similar to those we produce against HIV. They usually are less effective in killing off these viruses than other antibodies are in eliminating their target pathogens.

The liver is a versatile organ that plays several different and vital roles. It enables the body to use nutrients and medications and cleanse itself of toxins, acting as the body's filter. Everything we eat, drink, breathe, or inject gets filtered through the liver, which removes waste and poison from the bloodstream.

The liver is also the warehouse of the body. It stores sugar and vitamins for the body to use when necessary. The liver takes nutrients and sends them into the bloodstream so that they can be distributed to the cells that need them. The liver also helps digest and store fat, which makes it possible to keep going all day without eating each time your body needs more energy. The liver changes medicine into a form the body can handle; without the liver, medicines can't work properly. It makes proteins to build muscle, clotting factors to prevent hemorrhage, and bile to absorb nutrients and vitamins.

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Is it AIDS or is it Aging?

Considerations for Aging with HIV

By Edwin Krales

As an HIV/AIDS nutritionist and health educator, I work with many people who are over 50. I know that aging brings on medical, economic, social, nutritional and energy problems even in the absence of any disease. HIV disease creates similar problems in infected people of any age. When aging and HIV collide in a person over 50, what are the consequences? Are the problems unique to this population? If so, how are they addressed to the best advantage of the infected older person?

Contrary to what we are taught, getting older is a good thing – it means that we haven't died yet! Each aging person faces problems that are new to him or her, although the problems themselves are not new but reoccur in each generation as it ages. As people with IV continue to live longer, they will also be encountering many of the usual problems of aging.

The following is my organizational approach to many of the issues that confront a person with HIV who is getting older. It attempts to help people answer the question, "is it AIDS or aging?"

How you read this information is not important. What is important is to locate an issue that has been on your mind and see if the information can give you an idea about how to deal with it better.

Lean Tissue and Muscles Mass Loss

Habits For Years: Were you active and athletic or sedentary? The more lean tissue you have throughout life, the better you will be.
Aging: As we age tend to be less active, lose muscles and put on fat. Start exercising again today. Testosterone decreases as we age. Menopause raises related issues.
HIV/AIDS: The virus takes lean tissue when weight is regained compared to weight gain in an uninfected person.

Drug Interactions and Reactions

Habits for Years: Did you pop pills (any kind, over-the-counter, prescription, or street)? Did you use dope of any kind? Alcohol? Methadone? What was in that dope you bought in the street? What was it cut with? Does it interact with your medication? Have you told health care provider about your habits?
Aging: As we age we tend to use more medication. At what point does the negative drug interaction start? Who is paying attention? Does any one provider monitor all of our medications?
HIV/AIDS: Lipodystrophy, breast enlargement, diabetes, heart disease and osteonecrosis. Can anything help with these horrible disorders?

Eating Habits

Habits for Years: Were ketchup and mustard your vegetables? Did your vitamin C come from French fries? Were you on the SAD diet (Standard American Diet)? Were you constipated often? Did you have a hard time with certain food, such as milk? Did you know how your food was prepared? Malnutrition impairs immunity.
Aging: Idiopathic bowel disease may come from a lifelong habit of not eating enough vegetables and fruits. Our stomach acid gets weaker as we get older, making digestion less efficient and preparing the way for H. pylori and reduced amounts of Vitamin B12. Combine this with a loss of muscle tone in our GI tract and we wind up with gastro-intestinal problems.
HIV/AIDS: HIV likes to live in our gut. This has a negative impact on digestion. A low T cell count paves the way for various parasites to become established, and for H. pylori to grow in our stomachs. Combine this with a decrease in stomach acid and one of the results is we have to compete with the bacteria for the Vitamin B12 produced.

Vitamins, Mineral and Phytochemicals

Habits for Years: Did you eat enough fruits, vegetables and whole gains or take a vitamin pill? Or were you on a junk food mission? Somewhere in between?
Aging: As we age we tend not to get enough Vitamin B2, Folate, E, Selenium, protein, calories, calcium and vitamins A and D. Is there enough food at home? Do you skip meals?
HIV/AIDS: If you are HIV+ you need more vitamins B12, Folate, E, Selenium, protein calories, other B vitamins, C, Zinc and iron. Can you cook? Do you have cooking facilities? Food?

Illnesses

Habits for Years: Were you ill often? Do you have any chronic illnesses? Any structural problems? Obesity? If you are gay or bisexual, do you feel left out or guilty about being HIV+?
Aging: Cardio-vascular disease, cancer, hypertension, vision, bone and skin problems, diabetes and Kaposi's sarcoma increase as we get older.

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Battling the Enemy on Many Fronts:

Inside the Science of HIV Vaccine Development

By Angela Talley and Steven Chang

Measles, mumps, rubella, polio, diphtheria, tetanus, pertussis, pneumococcal infections, hemophilus influenza, hepatitis A, hepatitis B, chicken pox (varicella), yellow fever, smallpox…

Effective vaccines have been developed to protect against all of these diseases. Yet over 20 years after HIV was identified as the cause of AIDS, we still lack an effective vaccine for this virus which causes over 5 million new infections and 3 million related deaths worldwide each year. The struggle to develop an effective vaccine against HIV is an ongoing collaborative research effort with many roadblocks, but also one in which we make considerable progress with each new approach tested in clinical trials.

Vaccines work by teaching the body's immune system to recognize and protect against future infection. One can envision it like giving a security guard a "mug shot" of a known criminal, so if anyone walks through the front door matching the picture, security would recognize that person and radio for backup, thereby preventing the crime.

Battling on Two Fronts

There are two ways in which an effective vaccine might work to arm the body with that "mug shot" or memory for HIV. First, and considered the best outcome of HIV vaccine research, is the induction of neutralizing antibodies. By prompting the immune system to provide these HIV-specific molecules, the vaccine effectively arms the body with the "mug shot." In the event of an infection, the antibodies would bind to HIV and prevent it from infecting human cells.

Alternatively, the vaccine could aid the cells of the immune system to recognize and respond to HIV infection, which is called a cellular immune response. With the aid of the vaccine, two cell types of the immune system – CD4+ and CD8+ T-lymphocytes (Helper and Killer T-cells) – develop memory for HIV infection and then work together to recognize and destroy already infected cells. The first approach (eliciting neutralizing antibodies) aims to prevent infection while the second approach (eliciting T-cell immunity) aims to prevent progression to AIDS in the event of infection.

The difficulty in developing an HIV vaccine lies in the extreme variability of the virus, which makes it a complex target. For example, there are two basic types of HIV, HIV-1 which is causing most infections worldwide, and HIV-2, predominantly found in West Africa. Yet there are at least 9 different subtypes of HIV-1. North America and Western Europe have predominantly subtype B. India, China, South Africa have subtype C. Central Africa has a mixture of subtypes A, D, F, G, H, J, and K. With this kind of variability, it is unclear if a single vaccine would be effective against all strains worldwide.

Even within a single infected individual, HIV has the capacity to change or mutate, quickly adapting to threats like antiviral medications or the immune response itself. HIV is like the endlessly dividing broom in the classic animated film *The Sorcerer's Apprentice*, except that instead of making exact replicas of itself, HIV is an error-prone copy machine. Each copy may be a little different from its template. In this way, HIV has evolved mechanisms to avoid the immune response.

To avoid potentially neutralizing antibodies, HIV takes the main target of the antibodies and folds it up deep inside complex proteins found on the surface, called gp120 and gp41, like crumpling a grain of rice into a ball of aluminum foil; then HIV further covers itself in a shield of sugar, called glycosylation. HIV is only vulnerable to neutralizing antibodies when it is free floating in the blood and at the very moment of cell entry.

Once it infects a cell, HIV is inaccessible to the antibodies, but may then be vulnerable to the dynamic duo of CD4+ and CD8+ T-lymphocytes (Helper and Killer T-cells). To evade CD4+ and CD8+ T-lymphocytes, HIV preemptively infects and kills the CD4+ cells, depleting one of the main conductors of an orchestrated immune response. HIV then hides within some of the infected T-cells by pulling any evidence of infection below the surface. By doing so, HIV is able to hide within the infected cells, where it goes undetected by the immune defenses. There are also likely to be numerous other mechanisms that HIV has evolved to avoid the immune system that we are unaware of.

Fighting the Enemy

So, what are some of the approaches that are being tried against the elusive enemy? The goal of producing neutralizing anti-bodies will likely prove to be a greater challenge to vaccine development than a vaccine strategy based on strengthening the cellular immune response. For example, two large clinical trials

attempting to induce an antibody response by injection of copies of the gp120 surface protein have proven ineffective, because of the elusive mechanisms of HIV mentioned above. Yet ongoing research at the Vaccine Research Center of the National Institutes of Health continues to study this approach by attempting to capture the virus just as the surface protein pulls back its sugar coating and unfolds itself to reveal the site where the HIV binds to the CD4+ lymphocyte. One can envision this innovative approach as driving a wedge in the aluminum ball as it unfolds so that the neutralizing antibodies can reach their target.

While the ultimate goal continues to be prevention of HIV infection, the majority of HIV vaccines currently being tested in clinical studies are designed to achieve the next best thing, which is to prevent people from getting sick should they acquire HIV infection. These vaccines are intended to elicit the CD4+ and CD8+ T-lymphocyte response which would attack HIV-infected cells. There are three steps to this approach: first, to capture and hold the attention of the T-lymphocytes, second to teach them what HIV looks like, and finally to repeat the lesson a few times so the response endures.

Two ways to capture the attention of the T-lymphocytes are the use of adjuvants and viral vectors. Adjuvants are substances commonly added to vaccines that act like a cup of coffee to wake up the immune system and accelerate, or enhance a specific response. Some adjuvants tested in HIV vaccine trials include those used in other vaccines such as alum and Freund's adjuvant. However, researchers are increasingly turning to our bodies' own natural immune stimulants, or chemokines, such as IL-2, IL-12, interferon gamma, and GM-CSF for use as adjuvants.

Another way to draw more attention to the vaccine is to hide the lesson (the components of HIV which will stimulate the immune response) inside another virus, called a vector. Viruses being used in this way include the canarypox, adenovirus, Venezuelan equine encephalitis (VEE), and modified vaccinia Ankara (MVA), each crippled so as not to cause infection themselves. Returning to the "mug shot" analogy, this approach is like a known petty thief quickly drawing attention to himself as he walks in the door. Except, as the petty thief is surrounded by security, he points out that he is in handcuffs so couldn't possibly steal anything. Moreover, he shows them a photo of HIV and states, "If you think I'm bad, this guy's a serial killer; he's the one you really want."

Once stimulated, the immune cells are ready for the second step – or the instructions to recognize HIV. Given the variability of HIV, how can we teach the T-lymphocytes to recognize HIV so that a vaccine will be effective worldwide? The primary method to convey the message is by using DNA, which is like the instruction manual for your cells to make specific proteins. In this case the specific proteins are similar to those found on the surface of or inside HIV, including proteins called *env*, *gag*, *pol*, *nef* and *tat*. This is either injected directly as "naked" DNA or hidden inside another virus or viral vector.

Once inside the cell, production of these proteins can ultimately train the T-lymphocytes to recognize these HIV proteins. Each vaccine has its own recipe often based on one of the HIV subtypes. It could be as simple as just subtype B *gag* or as complicated as multi-subtype *env* plus subtype B *gag*, *pol* and *nef*. Finally, for most vaccines the lesson has to be repeated for it to endure, although how many times and how often remain prominent questions. Current studies adopting this approach vary, but generally include a multiple vaccination schedule, such as three vaccinations over a two-month period or four vaccinations over a six-month period.

Each of the current vaccine studies will help solve one small piece of the puzzle, such as:

- which adjuvant is the best stimulant;
- whether the DNA should be naked or packaged in adenovirus or MVA vectors;
- whether vaccine design (e.g., the lesson) should be simple or complex;
- whether changing the dosing frequency improves the response.

Alternatively, studies may reveal the path to an entirely novel approach. It is only through the true collaboration of researchers with international networks such as the HIV Vaccine Trials Network, the International AIDS Vaccine Initiative, and other similar research agencies that the piece of the puzzle may slowly be completed to speed the process of finding an effective vaccine to prevent HIV.

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Medication: Reading the Fine Print.

Lucinda K. Porter, RN, CCRC

Your doctor hands you some information about medication for hepatitis C virus infection (HCV). The information could be simple or complex, depending on the level of printed material and your ability to understand medical language. Nevertheless, even the most basic material also includes a neatly folded copy of the professional information. This is often printed on white paper in very small print. It requires training and a magnifying glass to read it.

This piece of paper is the Package Insert (PI). It is also called product or prescribing information. The Food and Drug Administration (FDA) requires all manufacturers to include this with their drugs. This article offers tips on how to crack the medical code in the PI. It will tell you what to look for, what to avoid, what to fear, and what not to fear.

If you do not have the PI, you can get a copy from your pharmacy or the Internet. It can be found under "complete prescribing information" or "information for healthcare professionals." Try to use the drug's brand name rather than its generic name for your search. For instance, Copegus® and Rebetol® are the brand names for generic ribavirin. It's like Coca Cola® and Pepsi® are the brand names for cola.

Most medications have information written specifically for patients. This will give you a broad overview of the most important information and is a good starting point. When a drug is advertised in a consumer magazine, this is what usually appears in small print on the backside of the advertisement. After you read the basic information, you may want to read the entire PI.

Using ribavirin (Copegus® and Rebetol®) as an example, let's take a PI tour. The first things you will read are the drug's trade name, generic name and manufacturer. What follows next in this case is a box with bold type. This is called black box information. This has to be predominately displayed and carries a serious message. In ribavirin's case, there are warnings about pregnancy complications and cardiac disease. If you do nothing else, read and understand every word in the black box. If any of it applies to you, do not take that drug unless your healthcare provider has adequately explained why you may take it. Not every drug has black box information.

Next is the description. This is the most complicated part and can be ignored until you are ready to tackle concepts that are more challenging. Clinical Pharmacology follows the description. This is also complicated and will be the subject of next month's Healthwise.

Clinical study information is provided next. This is the data that proves why the drug works. It may be helpful to skip this for now and then return to it after you have read the rest of the PI. You can also ask your medical provider to summarize the parts that apply to you.

The indications and usage section lists the medical conditions the drug treats. It may surprise you to learn that interferon and ribavirin were originally used for other conditions. However, the indications for the pegylated (longer acting) alfa-interferons 2a and 2b are for HCV treatment. The indications may change per FDA approval. For instance, Pegasys® is approved for treatment of hepatitis B and HIV/HCV co-infection. The shorter acting interferon Intron-A® has indications other than for HCV. Sometimes physicians will use the pegylated interferon instead. This is called an off-label use and it is legal although insurance will not always cover the drug's expense.

The contraindications and warnings sections are high priority. In contraindications, all the patients who should not take the drug are discussed. Also listed are situations in which patients can take the drug but need to be closely monitored. If the PI has a black box in the beginning, this information will be repeated in the warnings section along with additional cautions. Again, if you think information in this section applies to you, talk to your healthcare provider before you start taking the drug.

Precautions come next. This is important because it gives more information about the safety of the drug. In the PIs for Copegus® and Rebetol®, we are alerted to more possible risks. The black box information is restated and informs us about what lab tests medical providers should order before and during treatment. For example, an ECG (a simple and painless heart test) is recommended. Advice to patients is in this section, such as to drink lots of water and take medication with food.

The drug interactions section is included here. Read this section. Listed here are the drugs that are known to interact with the drug you are considering. If you are taking a drug that is on the list, tell your provider. Fortunately the list is very short for HCV drugs. Also included in the precautions section is information about special groups of people. This addresses pregnancy, nursing mothers, pediatric use (infants and children),

geriatric use (older adults) and if the drug works differently between genders.

Try to read the adverse reactions section. When you want to know the drug's side effects, go to this section. The adverse reactions section may scare you but actually its bark is worse than its bite. This is where everything that is known to have happened is listed and informs patients about the drug's risks. Look for the most common adverse reactions. Ask yourself, how common are these?

Using Copegus® as an example, you will learn that in research studies, one or more serious adverse reactions occurred in about 10% of patients. The most common life-threatening or fatal events related to this drug (when used with Pegasys®) include depression, suicide, relapse of drug abuse/overdose, and bacterial infections. This may sound frightening. The good news is that each of these events occurred at a frequency of less than 1%.

Just about everyone reported one or more adverse event. The most common of these were depression, irritability, anxiety, fatigue, headache, muscle aches, fever and chills. Again, this sounds pretty awful. However, keep in mind that if a research patient was irritable for only one day that counts as an adverse event. Just because nearly everyone reported an adverse reaction does not mean that these reactions were constant or intolerable.

Sometimes information about adverse reactions includes numbers and percentages. Looking at Rebetol® (when used with PegIntron®), we find that 31% of patients reported depression. That means that roughly 1/3 of the study patients reported at least one episode of depression. That does not tell us for how long or how severe the depression was. However, we also learn that 14% of the study patients discontinued treatment for any number of reasons. This casts a more favorable light on the 31% depression figure because no more than 14% (and probably less) of patients had depression severe enough to cause them to stop treatment.

Although percentages can be reassuring, keep in mind that these numbers were derived from clinical trial patients. Research usually uses the healthiest patients. If you are already depressed, then your risk for increased depression could be higher than the percentages listed in the PI.

Probably the best way to find out about drug side effects is to talk to other patients who have experience with that medication. Support groups are great resources for this. You can also talk to your medical provider or pharmacist and ask what sorts of feedback they are hearing from patients. Be cautious about relying on the Internet for patients' stories; negative experiences are more likely to appear than positive ones. It's important to get a full range of reports on which to base your decisions.

The final portion of the PI supplies information about overdose, discusses Dosage and Administration, states how the medication is supplied and how it should be stored. This is important to know. Peginterferons are injectable drugs that have special storage requirements. Knowledge about dosages gives you guidelines for how much medication is recommended and for how long. However, patients are unique and medications are not "one size fits all." Physicians and mid-level practitioners may prescribe different doses to different people for different reasons. If your dose differs from the printed guidelines, ask your provider to explain the reason for this.

Taking a new medication can be both frightening and exciting. Fear can be reduced when sound judgment is applied to solid information. The exciting part is that, in general, medications work well. When medications work for people living with hepatitis C, this can be good news indeed.

Further reading:

- HCSP's booklet: A Guide to Understanding Clinical Research in Hepatitis C.
- HCSP Fact Sheet: A Simple Guide to Reading an Abstract.

Ref. HCV Advocate Newsletter June 2005

HCV Advocate Launches CME Site

Announcing Web Based CME Accreditation Course: The HCV Advocate Online Education Center CME Courses are intended for physicians specializing in gastroenterology, internal medicine, and hepatology, as well as other healthcare professionals conducting research and/or providing care for individuals with diseases of the liver.

Overview: This CME course, Diagnosing HCV, is an interactive web course that provides comprehensive information on the diagnosis of HCV infection. Participants can test their knowledge of the material through study questions at the end of each section. By combining up-to-date clinical and epidemiological information this web-based training program provides a valuable educational tool to assist health professionals in the complex task of diagnosing HCV infection.

Course: Diagnosing HCV

Visit http://www.hepeducate.org for more information.

Ref. HCV Advocate Newsletter June 2005

New Data Calls Into Question the "Watch and Wait" Treatment Strategy for Hepatitis C

New Results Show Treating Early With PEGASYS[R] Combination Therapy Significantly Increases Chance of Achieving a Cure.

A study presented today at a major international medical meeting will sound a wake-up call for thousands of HCV patients who are not currently receiving treatment for their disease. New data demonstrate that patients with "normal" liver enzyme levels [alanine aminotranferase [ALT]] who are treated earlier, at a younger age, are much more likely to achieve a sustained virological response [indicative of a cure] than older patients.[i] These findings reinforce the growing body of evidence that the "watch-and-wait" treatment strategy for hepatitis C [hcv] patients may not be the most effective approach. The study was presented at the 40th Annual Meeting of the European Association for the Study of the Liver [EASL] in Paris.

"Many hepatitis C sufferers with so called 'normal' ALT levels are not receiving treatment – either because they have been told they don't require therapy or because they're choosing to wait," said Professor Gane, from Auckland and Middlemore Hepatitis Clinics and the New Zealand Liver Transplant Unit, and lead author of the study. "The results from our study confirm that not only do these patients benefit from PEGASYS combination therapy, they also experience better results when treated at an early age."

ALT is an enzyme used to estimate liver damage and, historically, hepatitis C patients with 'normal' ALT levels have not been treated due to the misconception that 'normal' levels indicated mild disease and that these patients were essentially 'healthy carriers' of hepatitis C. However, the medical community is shifting its thinking as studies reveal that the vast majority of these patients actually have some degree of liver damage and suffer a reduced quality of life compared with uninfected persons. The studies also reveal that these patients benefit from treatment with PEGASYS.[ii] At this time, PEGASYS in combination with ribavirin is the only treatment approved for these patients in Europe.

The Benefits of Treating Young

Professor Gane's study examined how a patient's age affected their chance of achieving an SVR. Investigators analysed patients aged forty and younger versus those aged over forty. Findings showed that patients treated at a younger age experienced significantly better results, regardless of genotype:

- 54% of genotype 1 patients aged forty or younger treated with 48 weeks of PEGASYS [180 mg/week] plus ribavirin [800 mg/day] achieved an SVR. In contrast, only 34% of similarly-treated patients over forty achieved an SVR.
-79% of patients forty or younger with genotype 2/3 HCV achieved an SVR following 24 weeks of the same PEGASYS combination therapy. In comparison, 69% of patients over forty achieved an SVR with this treatment regimen.

"Age is one of the few treatment success factors that a patient has some control over," said Michel Bonjour, President of SOS Hepatites-France and founding member of the European Liver Patients Association. "Patients who choose to undergo therapy early increase their chance of curing themselves of this disease. This especially holds true for those who take the initiative to educate themselves about hepatitis C, and are willing to take charge of their disease."

Today's findings regarding age are consistent with a study presented at the American Association for the Study of Liver Diseases in 2003 which showed that patients with elevated ALT levels also benefit from treatment at a younger age.[iii] Together, these studies show that age is a positive predictor of treatment success regardless of ALT levels.

Is High Patient Weight Really the Culprit?

In addition to learning more about how age affects a patient's chance of eradicating the hepatitis C virus, other factors influencing treatment success are also being carefully scrutinized. Being overweight or obese has shown in previous studies to reduce a patient's chance of achieving an SVR, irrespective of the pegylated interferon therapy used [iv],[v]. New research presented at EASL shows that poorer treatment outcomes in heavy patients is a result of an array of other patient and disease characteristics.[vi]

"Our goal is to create an accurate profile of the kind of patient that doesn't respond well to treatment, which will then help us determine how we can modify treatment strategies and ultimately, cure more patients," said Professor Mark Swain, from the University of Calgary and lead investigator of the study. "In this analysis, those with a high body weight were also more likely to be male, African American, and have cirrhosis. These are all factors that can decrease a patient's chance of achieving a cure."

Professor Swain and other researchers reviewed data from two multinational trials examining the safety and efficacy of PEGASYS combination therapy for the treatment of hepatitis C. Patients were divided into three groups: patients who weighed less than 65 kg; those weighing between 65 kg and 85 kg; and patients weighing more than 85 kg. Each group was then analyzed for additional factors that can influence response to therapy.

"Pointing the finger at a patient's weight as the culprit for poor response is too simplistic," said Professor Swain. "These results show that finding the right treatment solution will require careful consideration and research."

PEGASYS: The Right Solution for More Patients

PEGASYS is the most frequently prescribed pegylated interferon for patients infected with hepatitis C. An extensive clinical study programme has demonstrated its safety and efficacy, particularly for those with difficult-to-treat disease. The benefits of PEGASYS are derived from its unique 40 kilodalton branched PEG molecule that is irreversibly bound to the interferon, and which provides sustained viral control for patients during the full once-weekly dosing interval.

In addition to becoming the first and only treatment approved for hepatitis C patients who are co-infected with HIV, PEGASYS is also the only approved medication in the EU for hepatitis C patients with 'normal' levels of alanine aminotransferases [ALT] – a patient population previously thought not to benefit from treatment. PEGASYS monotherapy has been approved in 112 countries and PEGASYS combination therapy has been approved in 83 countries. It has also been approved in the EU, Switzerland, Hong Kong, New Zealand, Taiwan and Thailand for the treatment of chronic hepatitis B, and is the first and only pegylated interferon with this indication. Roche has recently completed enrollment for an important new study examining the effects of longer treatment duration and/or a high induction dose of PEGASYS in patients who were non-responsive to treatment with pegyinterferon alfa-2b. This study is known as REPEAT – Retreatment with PegInterferon alfa2a in Patients not Responding to prior peginterferon alfa2b/ ribavirin combination therapy.

About hepatitis C: http://www.health-kiosk.ch/start.hepa
About Roche in virology: http://www.roche-hiv.com

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Alcohol Impedes Hepatitis C Response to Therapy in HIV-Coinfected Patients

"The interactions between human immunodeficiency virus (HIV), hepatitis C virus (HCV), alcohol, and antiretroviral therapy are complex. We retrospectively assessed persons coinfected with HIV and HCV who achieved HIV suppression to <500 copies/mL and continued to take antiretrovirals for greater than or equal to 6 months," investigators in Canada report.

"Frozen plasma specimens were retrieved for quantitation of HCV RNA levels at baseline and 3, 6, and 12 months after beginning antiretroviral treatment. Median HCV RNA levels increased (0.35 log IU/mL) at month 3 (n=44). HCV RNA levels decreased to below baseline by 12 months in patients consuming <50 g of alcohol/day, whereas patients consuming greater than or equal to 50 g/day had a sustained increase (10.6 log IU/mcL) from baseline (p=.04)," said C.L. Cooper and colleagues, University of Ottawa.

"Because low levels of HCV RNA are predictive of a virological response to therapy for HCV infection, it may be advantageous to first achieve suppression of HIV RNA and then initiate treatment for HCV infection in patients coinfected with HIV and HCV."

"Excess alcohol consumption with therapy for HIV infection increases HCV RNA levels and may impede the effectiveness of this treatment strategy," researchers concluded.

Cooper and colleagues published their study in *Clinical Infectious Diseases* (Effect of alcohol use and highly active antiretroviral therapy on plasma levels of hepatitis C virus (HCV) in patients coinfected with HIV and HCV. Clin Infect Dis, 2005;41 (Suppl. 1):S105-S109). For additional information, contact C.L. Cooper, University of Ottawa, Ottawa General Hospital, Division Infectious Disease, Dept. Med, G12-501 Smyth Rd., Ottawa, ON K1H 8L6, Canada. The publisher of the journal *Clinical Infectious Diseases* can be contacted at: University of Chicago Press, 1427 E 60th St., Chicago, IL 60637-2954, USA.
Reference: Hospital & Nursing Home Week, *July 28, 2005*

Minocycline Shown to Have Protection for the Brain Against HIV

Results of a preclinical study recently published in JAMA

By Daniel S. Berger, MD

Neurological problems related to HIV disease have long been one of the most difficult complications to diagnose and treat. Before the widespread use of highly active antiviral therapy, infections and tumors of the brain were not uncommon. While we are fortunate that these severe complications are not often seen today due to better and more effective antiviral treatment, we continue to see unexpected subtle changes in cognitive functioning that include memory loss and difficulties in concentration among otherwise healthy HIV-positive individuals.

On April 26, 2005, the prestigious *Journal of the American Medical Association* (JAMA) published results of a preliminary trail of a common second-generation tetracycline against immune deficiency virus. Minocycline, a common tetracycline antibiotic used to treat acne skin problems and other infections, was administered to monkeys, investigating its possible benefit in HIV infection, specifically for neurological protection. Minocycline was chosen because of its anti-inflammatory properties, its ability to penetrate brain tissue, and its proven protection in other neurologic diseases in animals, such as multiple sclerosis, ALS and Parkinson's disease.

At the conclusion of the study, the authors observed a reduction in the cytokines (cells and proteins produced by immune system cells) associated with inflammation and the reduction in immunologic response to neurodegeneration. Also observed was a decrease in viral load levels in cerebrospinal fluid (fluid that surrounds the brain or spine) and test-tube studies revealed a reduction in virus from cultured lymphocytes and macrophages (inflammatory cells).

Because of the surprising findings of this inexpensive, safe, available antibiotic, whereas current antivirals are anything but cheap and not always effective for treating cognitive dysfunction in HIV, controversy and discussion has begun within the HIV scientific community.

Findings

The study focused on monkeys. Eleven monkeys were studied and infected with simian immune deficiency virus (SIV). SIV is a virus that is the scientific equivalent of HIV for monkeys.

Twenty-one days after infection, five monkeys were given two tablets of minocycline daily (a comparable dose used for treating humans with acne). Six other monkeys, also inoculated with SIV, were not administered the tetracycline-like treatment and were studied as a control group. During the course of the study, the monkey subjects had frequent blood tests and spinal taps for SIV testing and markers of brain inflammation. After 84 days, all monkey were humanely sacrificed for further brain pathology testing.

Among the monkeys that got the minocycline, three out of five did not develop encephalitis, and the other two had mild encephalitis. Of the untreated controls, two had severe, three moderate and one no encephalitis. Also, when studying the CSF (cerebrospinal fluid), the minocycline-treated monkeys demonstrated lower immunologic and inflammatory cytokines and had fewer signs of brain inflammation.

The authors interpreted the decrease in these markers and cytokines to mean that less virus was getting into the brain. Surprisingly, test-tube studies showed that minocycline suppresses HIV replication itself, via a reduction in HIV (and SIV) in cultures of lymphocytes and macrophages (immune and infection-fighting cells). The number of monkeys was small, but the difference was significant in terms of disease reduction, according to the study.

Further, the authors hypothesized that minocycline may not inhibit HIV replication directly like conventional antivirals, but instead may make the cellular environment "non-permissive" for the virus to replicate in.

This proposed inhibition of viral replication is nonspecific and may affect other viruses and their replication. It may also reduce the production of harmful chemicals that help mobilize cells of the immune system that cause inflammation and damage in the brain.

Interpreting the Results and Practical Implications

It would be easy to overstretch the results; however, we can't abstract data from SIV models and say that it will surely reflect HIV-infected humans. As an example, two integrase inhibitors (from Merck and from GlaxoSmithKline) that succeeded in their proof-of-concept studies in monkeys never made it past phase I or II in human HIV studies. However, the results of this well-conducted study need to be taken seriously in regards

to the potential benefit for patients with cognitive problems.

HIV-positive individuals who are not on therapy but manifest brain-related signs and symptoms should begin HAART (highly active antiretroviral therapy) without delay. Postponement of treatment can result in long-term damage and irreversible impairment in neurological functioning. The effect of antiviral drugs in reducing HIV viral load correlate highly with reduction in HIV levels in the CSF.

Antiviral drugs have been effective at slowing down or halting progression to dementia in HIV disease. Cognitive and memory problems that were once more common among individuals with HIV infection have become scarce since the emergence of HAART. From experience, however, subtle neurological problems still occur despite effective HIV therapy.

We have observed individuals on long-term therapy who have undetectable viral loads with normal or high CD4 T-cell counts who experience deterioration in their cognitive abilities, including memory, concentration and learning skills, that is out of proportion to their normal aging process. A diagnostic work-up that includes comprehensive testing of the brain and blood tests to rule out a possible opportunistic complication usually fails to show any underlying cause for a patient's cognitive deterioration.

This has been especially frustrating for physicians since there is not any proven effective way to attack this problem for our patients. A switch in treatment to antivirals with better CNS (central nervous system or brain) penetration and administering certain vitamins that are associated with improving cognitive ability have met with limited success. In these individuals, it would be potentially advantageous to have effective treatment targeted towards halting the progression in downward neurologic functioning.

Thus, in these situations where patients manifest further memory loss and deterioration in mental ability, Northstar Healthcare will begin to study these findings objectively with established cognitive testing to understand the specific changes that occur within our patients. In these patients, consideration for a trial with minocycline, to see if treatment curbs or halts their neurological deterioration, will be an option discussed after a review of findings. We will begin to collect data now, because for those individuals, we don't have the luxury of time to wait for a large institution to debate the design for a study and the years it requires to fully confirm, yea or nay, any possible benefit. The waiting may cost individuals further irreversible deterioration.

This being said, close monitoring for benefits versus side effects is needed. Long-term minocycline in patients who are infected with HIV has not been studies previously, although minocycline has been safe to use for skin problems such as acne.

As a preliminary study, there is certainly a basis here for further study in HIV-infected individuals. The investigators from Johns Hopkins should be applauded for conducting this well-designed study in macaques.

This study has other implications, not only for HIV-infected individuals, but for other neural diseases. It appears that the mechanism of action of minocycline is non-specific, so that its effect may apply to other viral infections that cause brain complications.

Additionally, the observation of minocycline's effect on lymphocyte and macrophage cultures harboring HIV provokes the possibility of examining its use in patients who harbor multi-drug HIV resistance. If other clinicians begin using minocycline in clinical practice, whether for early dementia or salvage treatment, it is hoped that objective data is collected so that we can add to our scientific understanding of this agent.

Minocycline is cheap, and generics are available; sadly this poses as an obstacle for a big-money pharmaceutical company. It makes it less likely for such a company to pump investment capital into proceeding quickly with a study and development for treatment. Who will have the resources and motivation to spend the million of dollars necessary to further out knowledge regarding minocycline's potential application for HIV or any other neural disease?

Conclusion

This appear to be a reputable groundbreaking study, having been published in JAMA, conducted at the prestigious Johns Hopkins University and supported by grants from the National Institutes of Health. It's tantalizing that an antibiotic, cheap and reasonably safe, may have far reaching applications for treatment of HIV and its associated stigmata of the brain. Patients should not rely, however, on this information to protect themselves from HIV infection nor its progression. Further study, perhaps years of investigation will probably be necessary to understand these potential implications.

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Ref. Positively Aware July/August 2005

Better Treatments and Drugs in the Pipeline

Promising research continues to move forward

By Matt Sharp

New York City's highly publicized example of a rapid progression case overshadowed most other treatment news at this year's 12th Annual Retrovirus Conference (CROI). AIDS conferences rarely provide treatment breakthroughs and sure enough, this year was no exception. In reality, however, most HIV information unfolds incrementally on the best ways to use the current therapies, and as new drug classes slowly emerge in the research pipeline. Although there are those who need newer options, the advances made in HIV are being confirmed as time goes by.

Better Treatments

Dr. Fiona Lampe from London presented data from a large joint cohort of treatment-naïve patients from England and Canada. This study shows that treatments are becoming more effective. Or are we just learning how to use them better?

The risk of reaching an initial treatment failure over a seven-year period has halved in this analysis. Still, people who were lost to follow-up or stopped therapies due to failure suggests that the treatments used today could be even simpler and less toxic.

Another large cohort from Dr. John Bartlett and colleagues at Duke University showed that treatment responses are getting better as drugs are improved. The meta-analysis collated the results of 48 weeks of data from 64 clinical trials and showed that boosted protease inhibitors and non-nucleoside reverse transcriptase inhibitors work best to bring virus levels down. Boosted PIs work best to increase CD4 cells.

Drugs in the Pipeline

There was even good news in the salvage setting for those with highly resistant HIV.

Protease Inhibitors

Use of Fuzeon in addition to the experimental protease inhibitors such as Boehringer's tipranavir or Tibotec's TMC-114 are working well for those with no treatment options.

In a 24-week analysis of the RESIST study, use of tipranavir compared to comparator protease regimens showed better results, but Fuzeon and tipranavir was the best combination in this study. Tipranavir 500 mg (two capsules) must be used with 200 mg Norvir twice daily with food.

In a subgroup analysis of TMC-114, use of Fuzeon with two nucleoside drugs showed the greatest response in lowering virus levels to less than 50 copies at week 24. The drug is boosted with a lower dose of Norvir than is used with tipranavir. The data for this drug was very impressive, showing up to 1.85 log drop in treatment-experienced patients.

Non-Nukes

TMC-278 is a non-nucleoside reverse transcriptase inhibitor that is active against resistant HIV in laboratory studies thus far. Another Tibotec compound from the DAPY class, this Phase II monotherapy, proof-of-principle study in people who have not been on treatment showed an average 1.2 log drop in HIV. The company is filling its portfolio with drugs that are made to work against both wild type and resistant HIV. Their other compound, TMC-125, is further along in development… watch for larger Phase III studies.

Maturation Inhibitors

But we are not out of the woods yet. There are still people who need new therapies from different classes due to drug resistance. And there is always room for safer, less toxic therapies.

One interesting drug target is the later "maturation" stage of HIV replication, where HIV matures and buds out of the infected CD4 cell. Panacos' compound PA-457 is the furthest along in this new class. In a randomized, controlled single dose study with different doses, the average activity seen was between .3 to .7 log drop. And while this may not sound impressive, it is only one dose, and this drug represents new hope for yet another HIV target for those who have few options. A bonus is this drug will likely only be once daily as well. The company is moving forward with further development. If all goes well, we should see this drug in larger trials by next year.

CCR5 Antagonists

There are three CCR5 antagonists running neck-and-neck down the development track in this new exciting field of research. The new drug class blocks the CCR5 co-receptor on the surface of HIV and has reached Phase II trials. Two out of the three drugs will have to be boosted with Norvir. At CROI there was information on how long the compounds block the co-receptor and how that will affect resistance. Other studies are beginning to show cross-resistance in two of the compounds,

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further complicating the problem of multi-drug regimens used in HIV. Maraviroc is the new name selected by Pfizer for their co-receptor antagonist UK-427,857.

Integrase Inhibitors

Everyone has been waiting for the integrase drugs to come to fruition, or at least show any sign that the class will work in HIV at all. Merck is farthest along in the field, even though the audience was informed at CROI that their integrase inhibitor L-870810 is being put on hold due to toxicities in a long-term dosing study of dogs. However, the study showed a hefty 1.7 log viral load drop in a controlled 10-day monotherapy trial and provides hope that the class can work once the toxicity issues are teased out. And fortunately, the company has a back-up compound in Phase II development.

A few investigational agents are being researched to target the reverse transcriptase and protease enzyme in unique ways. There is hope that these new agents will work against drug resistant virus. Stay tuned.

Gene Therapy

There were two Phase I gene therapy studies showing safety and persistence of the therapy over time. Although very new in development, it is extremely encouraging to see non-drugs move into this stage of development.

More Drug Development

New drug classes are no longer a distant wish, but are promising. According to the Treatment Action Group 2005 Antiviral Pipeline (see www.aidsinfonyc.org/tag/tx/pipeline2005.html) there are at least 28 different entry inhibitors, eight integrase inhibitors (all in pre-clinical development), four maturation inhibitors and at least 14 other drugs with various mechanisms of action in the HIV treatment research pipeline. This represents a significant new area of research into new targets to fight HIV.

Time will now only tell if some of the new classes become approved after rigorous clinical trials. There was talk at CROI that some of the new classes may actually out perform the drugs currently in use. Even though this is pure conjecture, it provides hope that there is new energy in HIV research where a few years ago there was disappointment and fear that it was stalled.

Ref. Positively Aware May/June 2005

Patients with Bleeding Disorders Can Safely Undergo Transjugular Liver Biopsy

According to a study from Canada, "prior to the introduction of virally inactivated clotting factor concentrates, the majority of individuals with congenital bleeding disorders became infected with the hepatitis C virus. Although liver biopsy is valuable in prognosis and guiding antiviral therapy, there is a reluctance to perform biopsies in this population because of the risk of hemorrhage."

"The purpose of this study was to evaluate the safety of transjugular liver biopsy, and the usefulness of evaluating liver histology in this patient population," said J.L. Shin and colleagues, University of Toronto, Western Hospital.

"Liver histopathology was assessed by the METAVIR index and compared with corrected sinusoidal pressures, platelet counts, and abdominal ultrasonography. Liver biopsy was performed at seven Canadian centers in 65 patients with hemophilia or von Willebrand's disease. Biopsies were done on an outpatient basis, followed by a 4-hr observation period in hospital.

"Normal hemostasis was maintained during the peribiopsy period, with follow-up doses of factor concentrate self administered by the patient at home. One patient (1.4%) had significant bleeding leading to readmission and red cell transfusion. Liver histology showed 14 patients (22%) had cirrhosis. Ten patients had elevated corrected sinusoidal pressures; 7 of these (70%) had cirrhosis on biopsy, and the other 3 (30%) likely had cirrhosis although histology showed stage 3 fibrosis.

"We conclude that this procedure can be safely performed on an outpatient basis. The diagnosis of cirrhosis and/or portal hypertension was made in a substantial proportion of individuals (26%), all of whom had asymptomatic liver disease," Shin and coauthors stated.

Shin and colleagues published the results of their research in *American Journal of Hematology* (A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with congenital bleeding disorders and hepatitis C: Is it safe and useful? Am J Hematol, 2005;78(2):85-93).

For additional information, contact E.J. Heathcote, University Toronto, Toronto Western Hospital, Hlth Network, 6B Fell Pavil, Rm 154, Toronto, ON M5T 2S8, Canada.

The publisher of the *American Journal of Hematology* can be contacted at: Wiley-Liss, Division John Wiley & Sons Inc., 111 River St., Hoboken, NJ 07030, USA.

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The Challenge of Hepatitis C and HIV Co-Infection - Continued

Left untreated, HCV goes on to cause damage in the form of fibrosis (scarring of the liver), cirrhosis, cancer, and liver failure. Cirrhosis can cause varices, varicose veins in the esophagus that can cause bleeding. It can lead to fluid buildup (ascites) in the abdomen. Hepatic encephalopathy (dementia) is an abnormal change in mental status caused by liver failure. Liver cancer (hepatocellular carcinoma) occurs in people with HCV in the presence of cirrhosis.

Diagnosing HCV

Liver enzymes are proteins, and persistent elevations of these enzymes indicate liver inflammation. But almost half – over 45 percent – of those infected with HCV have normal liver enzymes. Liver enzymes have no direct relationship to the condition of the liver or to serum HCV levels. Therefore, people known to be HCV-infected who have normal liver enzymes are encouraged to undergo liver biopsies to determine the exact amount of damage there is in the liver.

Liver function tests include tests for the levels of albumin, bilirubin, and platelets. Albumin is a component of blood that helps prevent swelling. Platelets aid in the clotting of blood. Bilirubin is a yellow substance that builds up in your blood as red blood cells age and break down. The liver is responsible for the breakdown of bilirubin. When the liver does not function properly and bilirubin builds up, the result is jaundice – the yellow skin that is characteristic of liver problems. Lab tests often show normal albumin, bilirubin, and platelet levels, leading to a missed HCV diagnosis.

The most reliable way to diagnose hepatitis C is through an HCV antibody test. Who should be tested? Anyone who has ever shared a needle, even one time, is at risk for infection. If you received a blood transfusion or an organ transplant before universal testing of the blood supply was initiated in 1992 you are at risk, as are people who have had long-term hemodialysis. Others at risk for infection are persons with body piercing or tattoos; healthcare workers who have been stuck with blood-contaminated needles; persons who have shared paraphernalia to snort cocaine or any other substance; persons who have shared razor blades or toothbrushes; persons who have had manicures or pedicures; and persons who have undergone electrolysis or acupuncture. Any blood on the outside of a syringe, on a tourniquet, on any surface at all, may increase your risk of exposure. So who should be tested? Just about everyone.

When you get a hepatitis C antibody test, you should be tested for hepatitis A and B (HAV and HBV) at the same time. If you test negative for antibodies to HAV and HBV, you have no protection against these infections. Ask your healthcare provider to vaccinate you against these viruses. Hepatitis A is spread through oral/fecal contact. You get it by putting something in your mouth that is contaminated with feces. It can be transmitted if someone with the virus, who doesn't wash his or her hands after going to the bathroom, touches your food. HAV is also transmitted from unclean seafood, or when water is not filtered properly. It is sexually transmitted through "rimming," or anal/oral sex. Hepatitis A can be fatal when you have HCV. HBV is transmitted sexually in much the same ways as HIV.

If you test positive for HCV, a viral load should be done to measure the amount of virus in your blood. Unlike HIV, which is measured in the thousands, HCV is measured in the hundreds of thousands to millions. Liver enzymes are measured but, as discussed above, may be normal; even if they measure five to ten times greater than normal they may still not indicate liver damage. A liver biopsy is the most effective way of diagnosing liver damage, but it is not necessary to receive treatment. You can still be treated even if your liver biopsy shows cirrhosis.

The genotype is the genetic variety of the virus. There are 6 known HCV genotypes, 1 through 6, and their relative prevalence varies by geographic location. In the United States, 75% of infected individuals have genotype 1. Patients with genotype 2 or 3 are more likely to sustain a response to therapy. Therefore it is important to know a patient's genotype in order to make recommendations about treatment.

Treatment

There is no vaccine for hepatitis C, as there are for hepatitis A and B. Effective treatment is available, however, that can help reduce the severity of this disease and decrease the death toll.

The therapy for chronic hepatitis C has advanced significantly in the last ten years. Presently, the standard of care is a 24- or 48-week course of the combination of pegylated alpha interferon (peg-interferon) and ribavirin. Interferon is a natural substance that the body makes to help defend itself against infection. It helps the body's immune response against virus and infected cells.

Ribavirin is a nucleoside analogue similar to AZT that has no independent effect against the hepatitis C virus. It essentially enables the body to utilize interferon more effectively and thereby increases the response rate by two- to three-fold. The dose of ribavirin depends on body weight. Ribavirin can cause a specific type of anemia. Individuals who are anemic may be treated before they start therapy with erthyropoietin (Procrit), a drug that stimulates the bone marrow to make red blood cells.

The development of peg-interferon revolutionized treat-

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ment of HCV. Prior to peg-interferons, standard interferons were used to treat the virus. Standard interferon was given several times weekly and provided fluctuating levels of the drug throughout the week. Peg-interferon is standard interferon that has been changed chemically by addition of a large inactive molecule of polyethylene glycol. This large molecule prolongs the life of interferon in the body. Peg-interferon is given once weekly and provides a constant level of interferon in the body. It is an injection administered subcutaneously (under the skin). More importantly, because of constant levels in the blood, peg-interferon is more active against hepatitis C and produces higher rates of sustained response. Two forms of peg-interferon have been developed and studied in large clinical trials. Peg-interferon alfa-2a (Pegasys) and peg-interferon alfa-2b (Peg-Intron) are both approved by the Food and Drug Administration (FDA). It is unknown whether these pegylated interferons differ in efficacy and tolerability, although a head-to-head comparative trial is underway.

Patients with HCV mono-infection and genotypes 2 or 3 can be treated for 24 weeks. Patients with genotype 1 need 48 weeks therapy. Studies have shown that in mono-infected patients a sustained viral response or SVR (undetectable viral load 6 months after the end of treatment) with peg-interferon and ribavirin are above 50% overall, about 80% in those with genotype 2/3, and about 45% in those with genotype one.

A number of studies have shown that interferon use in patients with cirrhosis and who are non-responders to therapy can slow disease progression. The National Institutes of Health (NIH) is sponsoring the HALT-C trial. This study is examining whether low-dose Pegasys therapy can slow or reverse disease progression for these patients.

HIV and HCV

The two viruses have many similarities and a few important differences. Both are blood-borne diseases, that is, they enter the body directly through the blood. It is much easier to get HCV through the blood than HIV. Antibody screening is the backbone of screening for both viruses. The antibody to each virus is ineffective, providing no immunity to the disease caused by the virus.

Both are RNA viruses. They produce astronomical amounts of virus each day; HIV produces approximately 10 billion new viral particles per day and HCV about 10 trillion each day. The amount of both viruses is measured by viral load. The mutation rate is much faster in HIV – 10,000 variants daily compared to 1,000 for HCV. Prior to seroconversion HCV, like HIV, is associated with extremely high viral concentrations. After seroconversion HCV concentrations are reduced, sometimes to undetectable levels. One big difference is that HIV, so far, is not curable. HCV is curable and treatment can totally eradicate this virus from the body.

In HIV-positive individuals HCV infection progresses at a faster rate than in mono-infected persons because the hepatitis C virus multiplies faster. HCV does not, on the other hand, make HIV multiply faster. The more controlled an individual's HCV is, the less strain there is on the liver and the better the prospects for effective HIV treatment. If the body can't absorb HIV medication, a possible consequence of HCV infection, then the HIV virus will start to replicate and impaired immune function with develop more rapidly.

HIV/HCV Co-Infection

Past studies of co-infected patients show they do not respond as well to interferon-based therapy as mono-infected patients. Co-infected patients with genotype 2 or 3 have a 40-60% sustained viral response, while those with genotype 1 have less than a 25% sustained viral response. Furthermore, there is no evidence that co-infected patients should receive less than 48 weeks of therapy. It has been suggested that a longer duration of therapy may improve response rates. There is an ongoing 18-month therapy trial sponsored by Hepatitis Resource Network (HRN) to study duration of treatment in co-infected individuals.

The results of three studies of pegylated interferon and ribavirin therapy in co-infected patients were presented at the 11th annual Conference on Retroviruses and Opportunistic Infections (CROI). APRICOT (AIDS Pegasys Ribavirin International Co-infection Trial) was the largest study of its kind to date and included 868 patients from 19 countries. Overall, 40% of the patients treated with Pegasys/ribavirin achieved a sustained response. This is the highest response rate ever seen in co-infected subjects. The American AIDS Clinical Trials Group (ACTG) also reported results from its much smaller study using Pegasys and ribavirin. This is the first study to compare the safety and efficacy of pegylated interferon/ribavirin with standard interferon/ribavirin in co-infected individuals. The sustained viral response with pegylated interferon/ribavirin was 27% overall versus 12% with standard interferon/ribavirin.

Finally, RIBAVIC was a study conducted in multiple centers in France using Peg-Intron and ribavirin. Overall, 27% of patients on Peg-Intron/ribavirin achieved a sustained response. Differences in rates of sustained response can be attributed to different study populations and different initial doses of ribavirin. Also, the size of the population studied affects the statistical analyses; and both the ACTG and RIBAVIC studies were much smaller than APRICOT.

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There have been questions about the use of ribavirin in HIV-positive individuals on HAART. An old study (from 1987, when ribavirin was being evaluated for its HIV effect) showed that ribavirin inhibited the effects of AZT in vitro (in a test tube). In current studies, however, it appears that ribavirin does not inhibit AZT or d4T (Zerit). HIV-RNA levels did not change when ribavirin was introduced into combination therapy in the treatment of HIV, while HCV levels dropped dramatically when ribavirin was used with interferon for the treatment of HCV.

Combination therapy leads to improvements in liver enzyme levels and a decrease in viral load. The reason for treating HCV in most cases is to prevent liver damage or keep it to a minimum. Every time your viral load is lowered, your liver has the chance to do some healing thus buying some time. Also, HCV might exacerbate the hepatotoxic effects of HAART, which provides a compelling reason for treating co-infected people aggressively.

Side Effects

There are several things one should know before beginning treatment for HIV/HCV co-infection. First, protease inhibitors can be toxic to the liver; Norvir and Crixivan are the worst offenders. Of the non-nucleoside reverse transcriptase inhibitors (NNRTIs), Viramune poses the greatest threat of liver toxicity. AZT, when used with ribavirin, can increase your risk for anemia. Ribavirin is very teratogenic; that is, it causes severe birth defects. Women who are pregnant should never take the drug. If a woman of childbearing age or her partner is undergoing treatment with ribavirin, the couple must wait at least six months after discontinuing the therapy before attempting to become pregnant. Other diseases such as arthritis, allergies, asthma, or depression may get worse during treatment with ribavirin.

Common side effects of the medications used to treat HCV include depression, irritability, insomnia, body aches, hair thinning, canker sores, abnormal thyroid function, anemia, weight loss, muscle wasting, loss of appetite, changes in taste (which can lead to poor nutrition), increased mucus production, weakness, low-grade temperature, fatigue, concentration problems, nausea, diarrhea, neutropenia (low white blood cell count), and respiratory problems. An individual may suffer from none of these effects…or from all of them.

Most of these side effects can be managed with good results. If there is a history of depression, the patient should be treated with antidepressants before starting treatment. If the patient already is on antidepressant medication, a dose increase may be necessary while on therapy. Analgesic (acetaminophen/Tylenol) and anti-inflammatory medications (ibuprofen/Advil) can help reduce aches and fever. Appetite stimulants like Marinol are helpful in maintaining and/or gaining weight. If the patient develops anemia, erythropoietin (Procrit) may be used and/or the dose of ribavirin may be decreased accordingly. Vitamin B-12 and fish oil capsules are used to treat fatigue. Inhalers are useful for breathing problems related to bronchospasms caused by interferon.

Treatment with interferon and ribavirin can be very difficult. It is important that the physician who is treating your HCV is familiar with the side effects (see above) and is able to get you through the treatment course. The treatment course for HCV can vary depending on your genotype, viral load, and stage of disease.

Looking Ahead

Hepatitis C infection is a vast area of investigation and technological advances are opening new avenues for treatment therapies. Other promising agents, including protease and helicase inhibitors, ribozymes, antisense molecules, and therapeutic vaccines are in development and may improve existing therapeutic modalities but these drugs are years away from approval.

Liver transplantation is now an accepted therapy for a number of irreversible diseases of the liver. More than 4000 liver transplants are performed in the United States annually. However, patients with HIV infection traditionally have been excluded from transplantation.

Recent statistics show that HIV-positive patients on HAART have an increased life expectancy. Therefore, HIV-positive patients with end-stage liver disease are at greater risk of dying from liver failure than from an HIV-related illness. As a result, several institutions in the United States have broadened the spectrum of patients who should be considered for transplantation to include HIV-positive individuals.

The University of Miami and the University of Pittsburgh Medical Center are at the forefront of liver transplantation for patients with HIV disease. In New York City, The Mount Sinai Hospital of Mount Sinai School of Medicine has a protocol for co-infected patients with end-stage liver disease. Patients must have undetectable HIV viral load and a CD4 count greater than 100 to meet criteria for the study.

A study published last year reviewed 16 cases of liver transplantation in HIV-positive patients. The one-year survival rate is 92% overall, equal to that seen in the

HIV-negative transplant patients. These results are encouraging and suggest that patients with HIV suffering from end-stage liver disease can benefit from and survive transplantation.

Individuals with HIV are leading longer, healthier lives since the introduction of HAART. However, the significant morbidity related to liver disease in persons co-infected with HIV/HCV impacts on many aspects of their medical care. Clinicians should encourage their patients to undergo proper and timely evaluation, and offer counseling and recommendations about treatment. The advances in HCV therapy and the improved rates of response make treatment a more viable option for many co-infected patients.

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Reference: Body Positive, XVIII, No. 1, 2005

(Continued from page 3)

Is it Aids or is it Aging? Continued

HIV/AIDS: Don't confuse AIDS-related dementia with Alzheimer's. Are opportunistic infections age-related, HIV-related, or a combination of both? End-stage liver disease is a top killer today.

Medical Issues

Habits for Years: Do you have baseline medical measurements such as: cholesterol, triglycerides, PSA, Pap smear, mammogram, sugar levels, liver enzymes, kidney function, bone density, BIA, blood pressure, eye exams, dental care, vaccines.
Aging: How have these test results changed through the years? How about macular degeneration? Glaucoma? Did you ever get baseline measurements done? Were they thought to be unnecessary or too expensive?
HIV/AIDS: How does HIV/AIDS after these test results? Have you been tested for diabetes? Bone density? CMV retinitis? Hepatitis? HIV genotype and phenotype? Ultra-sensitive viral load test?

Psycho-Social Issues and Stress

Habits for Years: Class, race, religion, sexual orientation, gender, education, neighborhood, and job all impact on how you relate to the world and how the world treats you. Do you love who you are? Do you have enough money to live?
Aging: Aging is gentler when you are rich and healthy. Stress and hypertension are exacerbated by racism in people of color. Feeling "old" is more closely related to social attitudes and personal feelings than to age.
HIV/AIDS: Are you depressed? Do you feel like a pariah and expendable in the eyes of society? Do you hide out from others? Do you feel desirable?

Sex Drive

Habits for Years: Use it or lose it. Practice safe sex all the time. Do you compare yourself or your mate to the false images in our TV commercials and magazines? Do you fall short of perfection? The entire human race falls short. Do you feel guilty about your sexual desire?
Aging: We don't describe our elders as sexy. "Dirty old man" or "little old lady" is what we say. Hormone levels do go down as we get older. Other problems may be the cause of impotence or decreased sexual interest in men. Do you feel vital and attractive?
HIV/AIDS: Hormone levels do decrease. Vaginal secretions decrease. Anemia, wasting and liver disease may add to fatigue and lack of sexual interest. Safe sex isn't important only for youngsters or people who are HIV-negative.

Smoking

Habits for Years: The longer you smoke, the worse it gets. Smoking and drinking alcohol makes the ill effects of both drugs worse.
Aging: Smoking is a systemic poison. The list of illnesses made worse by smoking gets longer every day. Stop completely, or at least cut down.
HIV/AIDS: Smoking is a great way to help the virus kill off your immune system. Stop smoking today, or at least cut down.

Ref. Body Positive Vol. XVII, No. 4, 2004
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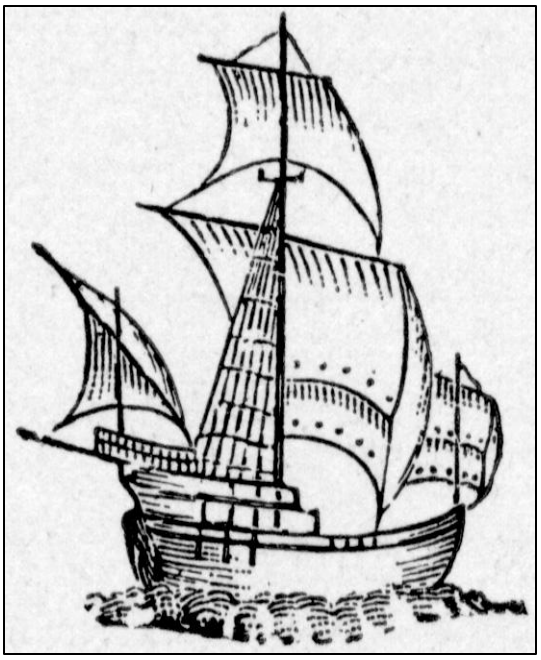

One ship drives east, and another west
With the self-same winds that blow;
'Tis the set of the sails
And not the gales,
That decides the way we go.
Like the winds of the sea are the ways of fate,
As they voyage along through life;
'Tis the will of the soul
That decides its goal,
And not the calm or the strife .

- *Ella Wheeler Wilcox, American Poet*